Edited by
Boy Cornils and Wolfgang A. Herrmann

WILEY-VCH

Aqueous-Phase Organometallic Catalysis

Second, Completely Revised
and Enlarged Edition

GREEN CHEMISTRY

Aqueous-Phase Organometallic Catalysis

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Aqueous-Phase Organometallic Catalysis

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Second, Completely Revised and Enlarged Edition

WILEY-VCH Verlag GmbH & Co. KGaA

Editors

Prof. Dr. Boy Cornils
Kirschgartenstraße 6
65719 Hofheim
Germany

Prof. Dr. Dr. h.c. mult. Wolfgang A. Herrmann
Anorganisch-Chemisches Institut
der Technischen Universität München
Lichtenbergstraße 4
85747 Garching
Germany

Library of Congress Card No: applied for
A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

Printed in the Federal Republic of Germany
Printed on acid-free paper

Typesetting, printing and binding
Konrad Triltsch
Print und digitale Medien GmbH
Ochsenfurt-Hohestadt

ISBN 3-527-30712-5

Preface to the Second Edition

Very recently, some colleagues noticed a statement in one of the monthly columns about the state-of-the-art that “in organic chemistry reactions employing the solvent water are still rare [1]” – which is true and untrue at the same time: certainly, water-based conversions are scarce compared to those in the great majority of other solvents. But whoever was sensitive enough to recognize the tremendous possibilities of aqueous-phase catalysis would never ignore the increasing number of publications concerning this field of activity, the progress which has taken place during recent years, and the breakthroughs which have been brought about following these activities.

So it is a great pleasure for us to announce the second edition of our book *Aqueous-Phase Organometallic Catalysis* – in such close proximity to the first edition in 1998. Responsible for this are on the one hand the dramatic successes of industrial realization: production figures are now close to 1 MM tons per year in various applications (with hydroformylations, at approximately 800 000 tpy, in a senior position). On the other hand, the long overdue in-depth occupation with the scientific basis, the exploratory work with the various possibilities of this “immobilization with the liquid support water”, and the exploitation of the immense variability of the method in chemical respects (regarding central atoms and ligands) create an atmosphere of overwhelming interest in this technique.

Thus the sections of this revised edition have been enlarged to different extents. For instance, in respect of the scientific fundamentals and taking into account that the role of water in organometallic conversions is not only purely as a solvent but as a strongly coordinative polar reagent. It contributes considerably to the formation of polar or ionic intermediates or to oxidative additions to lower-valent transition metal complexes (thus explaining the strong pH dependence of many aqueous-phase catalyzed reactions). The work on different central atoms of catalytically active complexes and the search for alternative, highly specialized ligands – including chiral ones – has extended considerably the scope of aqueous-phase organometallic catalysis together with knowledge about coordination catalysis.

The same is true for the application of water-soluble catalysts for quite a bunch of basic organometal-derived chemical reactions ranging from hydrogenations or

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ISBN: 3-527-30712-5

hydroformylations to more “exotic” applications such as water-based enantioselective Diels–Alder reactions or kinetic resolutions. It also includes improvements and alternative answers for the chemical reaction engineering of aqueous-phase catalyzed conversions.

Last but not least, the success of aqueous-phase catalysis has drawn the interest of the homogeneous-catalysis community to other biphasic possibilities such as organic/organic separations, fluorous phases, nonaqueous ionic liquids, supercritical solvents, amphiphilic compounds, or water-soluble, polymer-bound catalysts. As in the field of aqueous-phase catalysis, the first textbooks on these developments have been published, not to mention Joó’s book on *Aqueous Organometallic Catalysis* which followed three years after our own publication and which put the spotlight on Joó’s special merits as one of the pioneers in aqueous biphasic catalysis. Up to now, most of the alternatives mentioned are only in a state of intensive development (except for one industrial realization: that of Swan/Chematur for hydrogenations in $scCO_2$ [2]) but other pilot plant adaptations and even technical operations may be expected in the near future.

This second edition is based mainly on the state-of-the-art as described in the published literature up to the year 2003. To make things easier and to avoid errors, parts of the second edition are revised and updated, rather than rewritten. Thus, in some cases the order of the references is unchanged and new references are added without renumbering the existing ones (or substitute existing refs. by new items). The numbering of structures, equations, etc., was changed if necessary.

Once more we have to express our thanks not only to the authors and coauthors of the volume but also to the team at Wiley-VCH at Weinheim, especially Mrs. Claudia Grössl, for the production and their endless patience, and Dr. Elke Maase, the publishing editor. As with all our books, Mrs. Diana Boatman from Redhill, Surrey (UK), served as freelance copy-editor and was an invaluable help during the difficult process of completion. The Munich research group, especially PD Dr. F. E. Kühn, is acknowledged for scientific and technical assistance.

Hofheim and München
January 2004

Boy Cornils
Wolfgang A. Herrmann

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[1] *Nachr. Chem.* **2003**, *51*(5), 516.

[2] B. Cornils, W. A. Herrmann, R. Schlögl, C.-H. Wong, *Catalysis from A to Z*, 2nd Edition, Wiley-VCH, Weinheim, **2003**, p. 746.

Preface to the First Edition

This book describes homogeneously catalyzed reactions under two major boundary conditions: the catalysts employed are *organometallic* complexes that are used in the *aqueous phase*. In this respect the book is restricted to one area of homogeneous catalysis and therefore – though substantially expanded and more detailed – to one special area of our previous book, *Applied Homogeneous Catalysis with Organometallic Complexes* (VCH, Weinheim, Germany, 1996).

The subject of the book is the use of water-soluble organometallic catalysts for chemical reactions. These catalysts are so far the sole successful means of implementing the idea of *heterogenization* of homogeneous catalysts by *immobilizing* them with the aid of liquid supports. They thus solve the cardinal problem of homogeneous catalysis, which lies in the expensive separation of catalyst as well as product that is inherent in the system: the catalyst used in the homogeneous phase is separated by simply decanting the aqueous catalyst phase from the organic phase of the substrates and reaction products. Since all attempts to heterogenize homogeneous catalysts by immobilizing them on solid supports ("anchoring") have to varying degrees been unsuccessful, only the use of homogeneous catalysts in aqueous solution and thus on liquid supports ("biphase operation") leads to a neat, inexpensive solution to the problem that conserves resources and is therefore environmentally friendly.

This book is restricted essentially to *aqueous*-phase catalyses and thus to one area of the more comprehensively defined two-phase catalyses. This restriction to the most recent and successful development of homogeneous catalysis takes account of the rapid technical advances in the process concept first described by Manassen et al. in 1973, which was followed in rapid succession in the 1970s by hesitant basic work and in 1984 by the first commercial implementation. This unusual sequence – industrial implementation in a 100 000 tonnes per year oxo plant for the hydroformylation of propylene **before** years of time-consuming basic research to determine mechanistic, kinetic and other data – demonstrates clearly the great leap forward that this process development represented in the field of homogeneous catalysis and in solving the central problem mentioned earlier. Since then

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ISBN: 3-527-30712-5

other processes employing homogeneous catalysis have been converted to an aqueous two-phase procedure.

The development work intensified worldwide in various research groups in the years following the first commercial implementation at Ruhrchemie AG in Oberhausen. The obvious course of action was to let colleagues and specialists themselves report on their developments. This led to the formation of the international circle of contributors from the USA, France, the United Kingdom, China, Italy, Japan, India, Hungary and Germany which gives first-hand reports on its work.

One focus of the book is the hydroformylation process, the process involved in the first commercial implementation of aqueous-phase catalysis with its detailed descriptions of fundamental laws, special process features, and the present state of the art. Further focal points of the book are basic research on the complex catalysts (central atoms, ligands) and on the influence of the reaction conditions, solvents, and co-solvents, and a survey of other aqueous two-phase concepts and of proposed applications, with experimental examples and details. Environmental aspects are also considered.

We are sure that the outline chosen and the wide range of contributions from the authors give a multifaced and informative picture of the present state of developments in the field of aqueous two-phase catalysis, which presents not only the principles and accounts of the latest applications but also many aspects of spin-offs and alternative processes.

This description of ideas and process developments appears to us to be highly important for an appreciation of the potential of aqueous biphase catalysis. The familiar assessment of the most important aspects of heterogeneous and homogeneous catalysis demonstrates that only in a solution of the problem of continuous separation of catalyst and product, such as becomes possible with the processes involving aqueous immobilized catalysts, in the key to further progress found. Only *homogeneous* catalysts that can be handled without problems will give us scientists and developers confidence that the clear and sure mechanistic understanding of their mode of action and the possibility of easy variability of steric and/or electronic properties can be transferred to other immobilized, and thus easy-to-handle, catalysts. More optimistically, it is hoped that this will apply especially to those heterogenized catalysts that basically are derived from tailor-made homogeneous catalysts.

The sharp line of demarcation between homogeneous and heterogeneous catalysis would thus be blurred and the possibility opened up of combining in one species the advantages of homogeneous catalysts and none of the disadvantages of heterogeneous catalysts: heterogenized homogeneous catalysts would lead to equally advantageous results as homogenized heterogeneous catalysts – the long-awaited dream of catalysis research would be fulfilled!

We thank the team at WILEY-VCH, especially Mrs. Diana Boatman, Dr. Anette Eckerle, and Mrs. Claudia Grössl for their cooperation during preparation of this book and for helpful technical assistance.

Dipl.-Chem. Kolja Wieczorek is acknowledged for preparing all formulas, figures, and schemes; Dipl.-Chem. Thomas Weskamp for the total index.

Frankfurt-Höchst and München
Spring, 1998

Boy Cornils
Wolfgang A. Herrmann

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Contributors

Prof. Dr. Jacques Augé
Université de Cergy-Pontoise
5, mail Gay-Lussac
Neuville-sur-Oise
F-95031 Cergy-Pontoise/France
Tel: + 33/1 342 57051
Fax: + 33/1 342 57067
E-mail: jacques.auge@chim.u-cergy.fr

Prof. Dr. Manfred Baerns
Institut für Angewandte Chemie
Berlin-Adlershof e. V.
Rudower Chaussee 5
D-12484 Berlin/Germany
Tel: + 49/30 6392 4444
Fax: + 49/30 6392 4454
E-mail: mbaerns@aol.com

Dr. Helmut Bahrmann
Celanese GmbH/Werk Ruhrchemie
Postfach 13 01 60
D-46128 Oberhausen/Germany
Tel: + 49/208 693 2201
Fax: + 49/208 693 2291

Prof. Dr. Arno Behr
Universität Dortmund
Fachbereich Chemietechnik
Lehrstuhl für Technische Chemie A
Emil-Figge-Str. 66
D-44227 Dortmund/Germany
Tel: + 49/231 755 2310
Fax: + 49/231 755 2311
E-mail: arno.behr@bci.uni-dortmund.de

Prof. Dr. Matthias Beller
Leibnitz-Institut für Organische Katalyse
an der Universität Rostock
Buchbinderstr. 5–6
D-18055 Rostock/Germany
Tel: +49/381 466 9313
Fax: +49/381 466 9324
E-mail: Matthias.Beller@ifok.uni-rostock.de

Dr. Bhalchandra M. Bhanage
Division of Materials Science and Engineering
Hokkaido University
Kita 13 Nishi 8, Kita-ku
Sapporo 060-8628/Japan
Tel: +81/11706 6597
Fax: +81/11706 6594
E-Mail: bhanage@proc-ms.eng.hokudai.ac.jp

Dr. Claudio Bianchini
Istituto per lo Studio della Stereochimica
ed Energetica dei Composti
CNR di Coordinazione
Via J. Nardi, 39
I-50132 Firenze/Italy
Tel: + 39/55 243 990/24 5990
Fax: + 39/55 247 8366
E-mail: bianchini@fi.cnr.it

Dr. Sandra Bogdanovic
Booz Allen Hamilton
Lenbachplatz 3
D-80333 München/Germany
Tel.: +49/89 545 250
Fax.: +49/89 545 25 500

Prof. Dr. Armin Börner
Universität Rostock
Fachbereich Chemie
Albert-Einstein-Str. 3a
D-18059 Rostock/Germany
Tel.: +49/381 466 6931/350
Fax: +49/381 466 9324
E-mail: armin.boerner@ifok.uni-rostock.de

Prof. Dr. Mario Bressan
Universitá G. D'Annunzio
Dipartimento di Scienze
Viale Pindaro 42
I-65127 Pescara/Italy
Tel: + 39/85 453 7548
Fax: + 39/85 453 7545
E-mail: bressan@sci.unich.it

Dr. Henry R. Bryndza
DuPont Nylon
Experimental Station, Bldg. 302
P.O. Box 80328
Wilmington, Delaware 19880-0302/USA
Tel: + 1/302 695 3761
Fax: + 1/302 695 9084
E-mail: Bryndza@esvax.enet.duPont.com

Prof. Dr. Raghunath V. Chaudhari
National Chemical Laboratory
Pune 411 008/India
Tel: + 91/2025 893 163
Fax: + 91/2025 893 260
E-mail: rvc@ems.ncl.res.in

Prof. Dr. Peter Claus
Technische Universität Darmstadt
Institut für Technische Chemie und
Makromolekulare Chemie
Petersenstr. 20
D-64287 Darmstadt/Germany
Tel: +49/6151 16 5369
Fax: +49/6151 16 4788
E-mail: claus@ct.chemie.tu-darmstadt.de

Prof. Dr. Boy Cornils
Kirschgartenstr. 6
D-65719 Hofheim/Germany
Tel: +49/6192 23502
Fax: +49/6192 23502
E-mail: boy.cornils@t-online.de

Prof. Donald Darensbourg
Texas A&M University
Department of Chemistry
PO Box 30012
College Station, Texas 77892-3012/USA
Tel: +1/979 845 5417
Fax: +1/979 845 0158
E-mail: djdarens@mail.chem.tamu.edu

Prof. Dr. Mark E. Davis
Chemical Engineering
California Institute of Technology
Pasadena, California 91125/USA
Tel: + 1/626 395 4251
Fax: + 1/626 568 8143
E-mail: mdavis@cheme.caltech.edu

Prof. Dr. Eckehard V. Dehmlow
Universität Bielefeld
Fakultät für Chemie
Universitätsstr. 25
D-33615 Bielefeld/Germany
Tel: + 49/521 106 2051
Fax: + 49/521 106 6146
E-mail: Dehmlow@post.uni-bielefeld.de

Dipl.-Chem. Robert W. Eckl
morphochem AG
Gmundener Str. 37 – 37a
D-81379 München/Germany
E-mail: robert.eckl@morphochem.de

Dr. Carl D. Frohning
Celanese GmbH/Werk Ruhrchemie
Postfach 13 01 60
D-46128 Oberhausen/Germany
Tel: + 49/208 693 2419
Fax: + 49/208 693 2291
E-mail: Frohning@cityweb.de

Prof. Dr. Robert H. Grubbs
Division of Chemistry
and Chemical Engineering
California Institute of Technology
Pasadena, California 91125/USA
Tel: + 1/626 395 6003
Fax: + 1/626 564 9297
E-mail: rhg@its.caltech.edu

Prof. Dr. Brian E. Hanson
Virginia Polytechnic Institute
and State University
Department of Chemistry
College of Arts and Sciences
Blacksburg, Virginia 24061-0212/USA
Tel: + 1/540 231 7206
Fax: + 1/540 231 3255
E-mail: hanson@vt.edu

Dr. John A. Harrelson, Jr.
DuPont Nylon
Experimental Station, Bldg. 302
P.O. Box 80328
Wilmington, Delaware 19880-0302/USA
Tel: + 1/302 695 3761
Fax: + 1/302 695 9084

PD Dr. Peter Härter
Technische Universität München
Anorganisch-chemisches Institut
Lichtenbergstr. 4
D-85747 Garching/Germany
Tel: +49/89 2891 3099
Fax: +49/89 2891 3473
E-mail: peter.haerter@ch.tum.de

Prof. Dr. Wolfgang A. Herrmann
President of the
Technische Universität München
Arcisstr. 21
D-80333 München/Germany
Tel: + 49/89 2892 2200
Fax: + 49/89 2892 3399
E-mail: sekretariat.ac@ch.tum.de

Dr. Dietmar Hoff
Rheinchemie
Paul-Ehrlich-Str. 10
D-67122 Altrip/Germany
E-mail: dietmar.hoff@rheinchemie.com

Prof. Dr. István T. Horváth
Eötvös University
Department of Chemical Technoloy
and Environmental Chemistry
Pázmány Péter sétány 1/A
H-1117 Budapest/Hungary
Tel: +31/1 2090590
Fax: +31/1 2090607
E-mail: istvan.t.horvath@hit-team.net

Prof. Dr. Zilin Jin
State Key Laboratory of Fine Chemicals
Dalian University of Technology
116012 Dalian/China
Tel: + 86/411 467 1511
Fax: + 86/411 363 3080
E-mail: hpcuo@mail.dlptt.ln.cn

Prof. Dr. Ferenc Joó
University of Debrecen and
Hungarian Academy of Sciences
P.O. Box 7
H-4010 Debrecen/Hungary
Tel: +36/52 512 900
Fax: +36/52 512 915
E-mail: jooferenc@tigris.klte.hu

Prof. Dr. Philippe Kalck
Ecole Nationale Supérieure
des Ingénieurs en Arts Chimiques
et Technologique (ENSIACET)
118, Route de Narbonne
F-31077 Toulouse Cedex 04/France
Tel: +33/562 885 690
Fax: +33/562 885 600
E-mail: Philippe.Kalck@ensiacet.fr

Dr. Paul C. J. Kamer
University of Amsterdam
Institute for Molecular Chemistry
Inorganic Chemistry & Homogeneous
Catalysis
Nieuwe Achtergracht 166
NL-1018 WV Amsterdam
The Netherlands
Tel: + 31/20 525 6495/6454
Fax: + 31/20 525 6456

Dr. Agnes Kathó
University of Debrecen and
Hungarian Academy of Sciences
P.O. Box 7
H-4010 Debrecen/Hungary
Tel: +36/52 512 900
Fax: +36/52 512 915
E-mail: katho@tigris.klte.hu

Prof. Dr. Shu Kobayashi
Graduate School of Pharmaceutical
Sciences
The University of Tokyo
Hongo, Bunkyo-ku
Tokyo 113-0033/Japan
E-Mail: skobayas@mol.f-u-tokyo.ac.jp

Dr. Christian W. Kohlpaintner
Chemische Fabrik Budenheim
Rheinstr. 27
D-55257 Budenheim/Germany
Tel: +49/6139 89495
Fax: +49/6139 89464
E-mail: ckohlpaintner@budenheim-cfb.com

Dr. Jürgen G.E. Krauter
Degussa AG
Rodenbacher Chaussee 4
D-63457 Hanau-Wolfgang/Germany
E-mail: juergen.krauter@degussa.com

PD Dr. Fritz E. Kühn
Technische Universität München
Anorganisch-chemisches Institut
Lichtenbergstr. 4
D-85747 Garching/Germany
Tel: + 49/89 2891 3105
Fax: + 49/89 2891 3473
E-mail: fritz.kuehn@chem.tum.de

Dr. Emile G. Kuntz
CPE-LYON – Laboratoire
d'Electrochimie Analytique
43, Bd du 11 Novembre 1918
F-69616 Villeurbanne/France
Tel: + 33/472 448 478
Fax: + 33/472 448 479

Prof. Dr. Gábor Laurenczy
Institut de Chimie Minerale et
Analytique
Batiment de Chimie (BCH)
CH-1015 Dorigny Lausanne/Suisse
Tel: +41/21693 9858
Fax: +41/21693 9865
E-mail: gabor.laurenczy@epfl.ch

Prof. Dr. Piet W. N. M. van Leeuwen
University of Amsterdam
Institute for Molecular Chemistry
Inorganic Chemistry & Homogeneous
Catalysis
Nieuwe Achtergracht 166
NL-1018 WV Amsterdam
The Netherlands
Tel: + 31/20 525 5419
Fax: +31/20 525 6422
E-mail: pwnm@anorg.chem.uva.nl

Prof. Dr. Walter Leitner
Lehrstuhl für Technische Chemie
und Petrolchemie
RWTH-Aachen
Worringer Weg 1
D-52056 Aachen/Germany
Tel: +49/241 802 6480
Fax: +49/241 802 2177
E-mail: leitner@itmc.rwth-aachen.de

Prof. Dr. André Lubineau
Laboratoire de Chimie Organique
Multifonctionnelle
Université de Paris-Sud
Bat. 420
F-91405 Orsay/France
Tel: + 33/169 157 233
Fax: + 33/169 154 715
E-mail: lubin@icmo.u-psud.fr

Dr. David M. Lynn
Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125/USA
Tel: + 1/626 395 6003
Fax: + 1/626 564 9297

PD Dr. Stefan Mecking
Albert-Ludwigs-Universität
Institut für Makromolekulare Chemie
Stefan-Meier-Str. 31
D-79104 Freiburg/Germany
Tel: +49/761 203 6304
Fax: +49/761 203 6319
E-mail: stefan.mecking@makro.uni-freiburg.de

Dr. Andrea Meli
Istituto per lo Studio della Stereochimica
ed Energetica dei Composti
CNR di Coordinazione
Via J. Nardi, 39
I-50132 Firenze/Italy
Tel: + 39/55 243 990 245 990
Fax: + 39/55 247 8366

Prof. Dr. Eric Monflier
Université d'Artois
Faculté des Sciences J. Perrin/
Laboratoire de Physicochimie des
Interfaces – CRUAL
Rue Jean Souvraz – Sac postal 18
F-62307 Lens/France
Tel: + 33/321 791 715
Fax: + 33/321 791 717
E-mail: monflier@univ-artois.fr

Prof. Dr. André Mortreux
Université des Sciences et Technologies
de Lille
Ecole Nationale Supérieure de Chimie
de Lille
B.P. 108
F-59652 Villeneuve d'Ascq Cédex/France
Tel: + 33/320 434 993
Fax: + 33/320 436 585
E-Mail: andre.mortreux@enac-lille.fr

Prof. Dr. Antonino Morvillo
Università di Padova
Dipartimento di Chimica Inorganica
Via Marzolo 1
I-35100 Padova/Italy
Tel: + 39/49 827 5156
Fax: + 39/49 827 5161

Prof. Dr. Günther Oehme
Institut für Organische Katalyseforschung
an der Universität Rostock e. V.
Buchbinderstr. 5–6
D-18055 Rostock/Germany
Tel: + 49/381 466 930
Fax: + 49/381 466 9324
E-mail: guenther.oehme@ifok.uni-rostock.de

Prof. Dr. Tamon Okano
Department of Materials Science
Faculty of Engineering
Tottori University
Tottori 680/Japan
Tel: + 81/857 31 5260
Fax: + 81/857 31 0881
E-Mail: okano@che.tottori-u.ac.jp

Prof. Dr. Hélène Olivier-Bourbigou
Institut Français du Pétrole
1–4 Avenue de bois Préau
F-92852 Rueil-Malmaison Cédex
France
Tel: + 33/1 475 26779
Fax: + 33/1 475 26055
E-mail: helene.olivier-bourbigou@ifp.fr

Dr. Yücel Önal
Technische Universität Darmstadt
Institut für Technische Chemie und
Makromolekulare Chemie
Petersenstr. 20
D-64287 Darmstadt/Germany
Tel: +49/6151 16 3766
Fax: +49/6151 16 4788
E-mail: oenal@ct.chemie.tu-darmstadt.de

Dr. Cesar G. Ortiz
Texas A&M University
Department of Chemistry
PO Box 30012
College Station, Texas 77892-3012
USA
Tel: +1/979 845 5417
Fax: +1/979 845 0158

Prof. Dr. Georgios Papadogianakis
University of Athens
Department of Chemistry
Industrial Chemistry Laboratory
Panepistimiopolis – Zografou
GR-15771 Athens/Greece
Tel: + 30/1 728 4235
Fax: + 30/1 724 9103
E-mail: papadogianakis@chem.uoa.gr

Prof. Dr. Peter J. Quinn
King's College London
Section of Biochemistry
Campden Hill
GB-London W8 7AH/Great Britain
Tel: + 44/171 333 4408
Fax: + 44/171 333 4500
E-mail: p.quinn@kcl.ac.uk

Dr. J.N.H. Reek
University of Amsterdam
Institute of Molecular Chemistry
Homogeneous Catalysis
Nieuwe Achtergracht 166
NL-1018 WV Amsterdam
The Netherlands
Tel: +31/20 525 6437
Fax: +31/20 525 6422
E-mail: reek@science.uva.nl

Dr. Claus-Peter Reisinger
Business Development
Exatec LLC
31220 Oak Creek Drive
Wixom, Michigan 48393/USA
E-Mail: www.exatec.biz

Dr. Stefan Rossenbach
Bergische Universität
Gauss-Str. 20
D-42047 Wuppertal

Dr. Ana M. Santos
Technische Universität München
Anorganisch-chemisches Institut
Lichtenbergstr. 4
D-85747 Garching/Germany
Tel: +49/89 2891 3102
Fax: +49/89 2891 3473
E-mail: ana.kuehn@ch.tum.de

Dr. Marie-Christine Scherrmann
Laboratoire de Chimie Organique
Multifonctionelle
Université de Paris-Sud, Bat 420
F-91405 Orsay/France
Tel: +33/1691 54719
Fax: +33/1691 54715
E-mail: mcscherr@icmo.u-psud.fr

Dr. Marcel Schreuder Goedheijt
Dinosynth, Room FP 2045
PO Box 20
NL-5340 H Oss/The Netherlands
Tel: +31/412 668 395
Fax: +31/412 662 521
E-mail: marcel.Schreudergoedheijt@dinosynth.com

Dipl.-Chem. Ernst Schwab
Albert-Ludwigs-Universität
Institut für Makromolekulare Chemie
Stefan-Meier-Str. 31
D-79104 Freiburg/Germany
Tel: +49/761 203 6295
Fax: +49/761 203 6319
E-mail: schwabe@fmf.uni-freiburg.de

Dr. Aaron M. Scurto
Lehrstuhl für Technische Chemie
und Petrolchemie
RWTH-Aachen
Worringer Weg 1
D-52056 Aachen/Germany
Tel: +49/241 802 6453
Fax: +49/241 802 2177
E-mail: ascurto@itmc.rwth-aachen.de

Prof. Dr. Roger A. Sheldon
Delft University of Technology
Department of Organic Chemistry
and Catalysis
Julianalaan 136
NL-2628 BL Delft/The Netherlands
Tel: + 31/15 278 2675
Fax: + 31/15 278 1415
E-mail: R.A.Sheldon@tnw.tudelft.nl

Prof. Dr. Denis Sinou
Université Claude-Bernard Lyon I
CPE Lyon
Laboratoire de Synthèse Asymétrique
U.M.R. U.C.B.L./C.N.R.S. 5622
43, Bd du 11 Novembre 1918
F-69622 Villeurbanne Cédex/France
Tel: + 33/472 446 263
Fax: + 33/472 448 160
E-mail: Denis.Sinou@univ-lyon.fr

Prof. Dr. Othmar Stelzer †
Formerly:
Bergische Universität Wuppertal

Dr. Martine Urrutigoity
Ecole Nationale Supérieure des
Ingénieurs en Arts Chimiques et
Technologique (ENSIACET)
118, Route de Narbonne
F-31077 Toulouse Cedex 04/France
Tel: +33/562 885 703

Prof. Dr. Dieter Vogt
Eindhoven University of Technology
Schuit Institute of Catalysis STW 3.29
PO Box 513
NL-5600 MB Eindhoven
The Netherlands
Tel: +31/40 247 2730
Fax: +31/40 245 5054
E-mail: d.vogt@tue.nl

Yanhua Wang
State Key Laboratory of Fine Chemicals
Dalian University of Technology
116012 Dalian/China

Ernst Wiebus
Celanese GmbH/Werk Ruhrchemie
Postfach 13 01 60
D-46128 Oberhausen/Germany
Tel: + 49/208 693 2459
Fax: + 49/208 693 2041
E-mail: Ernst@Wiebus.de

Dr. Noriaki Yoshimura
Chemical Research Laboratory
Kuraray Co., Ltd.
2045-1 Sakazu, Kurashiki
710 Okayama/Japan
Tel: + 81/86 423 2271
Fax: + 81/86 422 4851

Dr. Xiaolai Zheng
State Key Laboratory of Fine Chemicals
Dalian University of Technology
Dalian 116012/China
Tel: + 86/411 467 1511
Fax: + 86/411 363 3080

1

Introduction

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

1
Introduction

Boy Cornils, Wolfgang A. Herrmann

> "For it is one thing to invent a basically correct process, another to introduce it in industry".
>
> "Denn [eines] ist es, ein prinzipiell richtiges Verfahren zu erfinden, ein anderes, es in die Industrie einzuführen."
>
> *Hermann Ost* [1]

Well disposed critics think that heterogeneous catalysis [2] is still at a stage of blindly groping empiricism and therefore at the level of a "black art" [3]. This statement, which has not remained uncontradicted [4], is in complete unison with the result of a comparison of heterogeneous with homogeneous catalysis (cf. Table 1 [5]).

Echoing the above criticism, the comparison under "variability of steric and electronic properties" and "mechanistic understanding" showed an advanced understanding of elementary steps in homogeneous catalysis. Yet Table 1 also lists the major industrial disadvantage of homogeneous catalysis: the immense difficulty of catalyst recycling, which is responsible for the fact that about 80% of catalytic reactions still employ heterogeneous catalysts and only 20% involve homogeneous catalysts. This is because it is inherently difficult to separate the molecularly dissolved homogeneous catalyst from the reaction products and any unconverted reactants in which the catalyst is likewise dissolved at a molecular level. Particularly, homogeneous organometallic catalysts while being recycled/worked-up, e.g., by using distillation or chemical techniques, suffer from thermal or chemical stress. Table 2 shows this and in detail in a comparison of homogeneous two versions of heterogeneous catalyses [6 b].

Tables 1 and 2 immediately suggest as a practical solution that a "heterogenization" of homogeneous catalysts, i.e., the immobilization or anchoring of dissolved catalysts on immobile, solid supports, may be a way of transferring many of the advantages of heterogeneous catalysis to homogeneous systems. In theory, a heterogenized (immobilized) homogeneous catalyst should behave like a heterogeneous catalyst and solve the problem of catalyst recycling, provided the attend-

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Tab. 1 Homogeneous versus heterogeneous catalysis [6].

	Homogeneous catalysis	*Heterogeneous catalysis*
Activity (relative to metal content)	High	Variable
Selectivity	High	Variable
Reaction conditions	Mild	Harsh
Service life of catalysts	Variable	Long
Sensitivity toward catalyst poisons	Low	High
Diffusion problems	None	May be important
Catalyst recycling[a)]	Expensive	Not necessary
Variability of steric and electronic properties of catalysts	Possible	Not possible
Mechanistic understanding	Plausible under random conditions	More or less impossible

[a)] *Catalyst recycling* has to be distinguished from *catalyst (or catalytic) cycle*. While "catalyst recycling" describes the way in which a catalyst is formed, employed, separated or deposited, made-up, and regenerated or recovered, "catalyst cycle" is the visual interpretation of a complex reaction mechanism by subdividing the overall reaction into a series of ad- and desorption steps (with heterogeneous catalysts) or arranging the intermediates of a homogeneously catalyzed reaction in a logical sequence to form a closed cycle. This gives rise to the well-known catalytic cycles of homogeneous catalysis (cf. a multitude of examples in the course of the following chapters) [38 a–c].

ant diffusion problems – the significant disadvantage of heterogeneous catalysis – prove tolerable.

Since solving this recycling problem is essential for the high-volume processes of homogeneous catalysis (for hydroformylation especially: annual output was about 6.5 million tonnes in 1996 [7]; this figure has now augmented to 9.2 MM tpy [7 b]), legions of scientists have published innumerable papers demonstrating ways of achieving heterogenization by the anchoring of homogeneous catalysts. Many of the sometimes very ingenious methods tried to date (including poly- or copolymerization of catalytically active and polymerizable monomers, functionalization of suitable supports and introduction of catalytically active constituents, precipitation of metals, or impregnation of suitable supports with active catalyst precursors, etc. [8, 9]) did indeed lead to initially active, "heterogenized" catalysts. However, it was also found that, despite coordination-capable support groups and covalent bonds, all these catalysts have only a finite on-stream life due to the leaching which starts from the first minute of use. This leaching always affects not only the (usually costly) central atoms but also the (frequently more costly) ligands of homogeneous metal complex catalysts. The economic need to recover them more than offsets the saving due to simplified recycling. Whistling in the dark is not problem-solving: at present, despite sporadic news of success, there is no economical process for heterogenizing homogeneous catalysts of large industrial processes.

Tab. 2 Catalyst removal in homogeneous and heterogeneous catalysis [6 b].

	Homogeneous catalysis	***Heterogeneous catalysis***	
		Suspension	***Fixed bed***
Separation	Filtration after chemical decomposition; Distillation Extraction	Filtration	No separation problems
Additional equipment required	Yes	Little	No
Catalyst recycling	Possible	Easy	Not necessary
Costs of catalyst losses	High	Minimal	Minimal
Catalyst concentration in product	Low	High	–

There is little mileage in looking for ostensibly more and more effective ligands and better and better optimization of support and catalyst precursor to ensure, on the one hand, adequate immobilization on the support (sufficient stability of the covalent bond between support matrix and central atom) and, on the other, adequate mobility for the catalytically active catalyst constituents (sufficient lability of the ligand sphere of the metal atom). All the results so far allow only the conclusion that the heterogenizing techniques used had to remain unsuccessful. The reason for this is that the various catalyst species undergo changes in spatial configuration as they pass through the catalytic cycle typical of a homogeneous process. The constant "mechanical" stress on the central atom ↔ ligand bonds and the constant change in the bond angles and lengths ultimately lead also to a weakening of the central atom ↔ support bond. This is conveniently demonstrated using the hydroformylation catalyzed by heterogenized cobalt carbonyls as an example (Fig. 1). The catalyst passes through the two forms of a trigonal-bipyramidal and of a tetrahedral cobalt carbonyl, which overstresses and weakens the heterogenizing bond Co ↔ support.

A more elegant and ultimately more successful solution is the idea, probably first articulated and systematized by Manassen [10], although Papadogianakis and Sheldon [11] mistakenly credit Bailar [9], of an immobilization with the aid of a "liquid support". In 1972 Manassen suggested

> "... the use of two immiscible liquid phases, one containing the catalyst and the other containing the substrate ..."

and hence the general form of biphase catalysis, which constitutes a logical development of the work in "molten salt media" (known today as "ionic liquids"; this term used to refer to high-melting, inorganic salts or salt mixtures [12]) described by Parshall [13]. Interestingly, the inventors of Shell's SHOP process, who had already worked on soluble, homogeneous complex catalysts in a biphase system

$$Co_2(CO)_7\ \text{support} + H_2 \rightleftharpoons 2\ HCo(CO)_3\ \text{support} + CO$$

$$HCo(CO)_3\ \text{support} \rightleftharpoons HCo(CO)_2\ \text{support} + CO$$

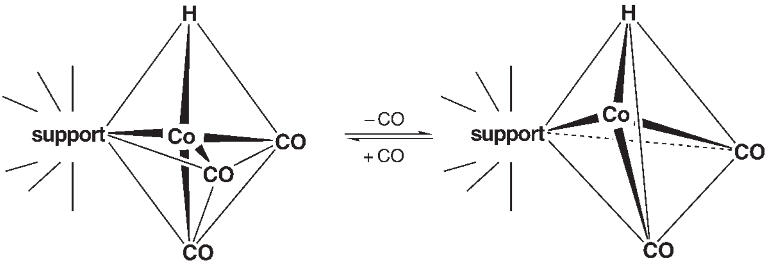

Fig. 1 Extreme configurational changes of cobalt carbonyls in the course of the catalytic hydroformylation cycle.

some years earlier [14], cited the special method without particular emphasis, judging by the wording in the first patents. Shell seems not to have been aware immediately that it had laid its hands on the key to the novel technology of homogeneous catalysis by means of immobilized catalysts on liquid supports – albeit not water (cf. Section 7.1).

The basic principles of biphase catalysis is accordingly that the homogeneous catalyst is in solution in one of the phases and the reaction products are located in a second phase which is immiscible with the catalyst phase – “heterogeneous” – and are therefore easy to separate off (see below).

The specific form of aqueous biphase catalysis was very significantly stimulated by the work of Joó and Beck at Debrecen (in relation to hydrogenation especially [15]; cf. Section 6.2) and Kuntz at Rhône–Poulenc (hydroformylation, telomerization [16] cf. Section 6.1.1), following Manassen’s work, which was then unfortunately merely theoretical. Three years after the first edition of this book Joó’s work about “Aqueous Organometallic Catalysis” appeared in 2001 [39]. Quite unusual, in “A personal look at the history of aqueous organometallic catalysis” he took down on record his important share of the development of this new field of activity. We all know Joó as the earliest pioneer and can now acknowledge that his first publications appeared simultaneously (but somewhat hidden among Hungarian journals) to that of Manassen et al. [40]. Therefore, the ideas were developed independently from each other and leave Joó as a man of merit within the historical assessment. The mentioned book of Joó, by the way, is meritorious because it focusses especially on the hydrogenation as a well suitable application of aqueous-phase catalysis. Remarkably, the fundamental papers of Joó and Kuntz created little interest and only found a wider echo in academic research once Ruhrchemie AG had managed to achieve industrial scale-up of aqueous biphase catalysis in an oxo process (cf. Section 6.1 [17]). In a drastic departure from the normal pattern, here basic research lagged considerably behind industrial research and application.

Reviews, even recent ones, tend to concentrate more on the state of basic research than on that of the large-scale industrial processes [11, 18], and curiously there are reviews appearing even now which fail to cite the contributions made by industry (see [19]!). In addition, it has to be mentioned as typical of this very recent development of homogeneous catalysis that considerable areas of the art and of its advances are chronicled in patents. Anyone who knows of the reluctance of basic researchers to read patents knows what this means for the current awareness amongst workers in basic research on biphasic catalysis.

In a technology involving two liquid phases, one of which contains the metal complex catalyst in solution, the idea of using water as one of the phases is not necessarily obvious. Hydroformylation, in 1972 – the time of Manassen's idea – the most important application of homogeneous catalysis, utilized cobalt catalysts, whose handling sensitivity ruled out an aqueous phase. Or, as P. Cintas [20] wrote,

> "At first, the idea of performing organometallic reactions in water might seem ridiculous, since it goes against the traditional belief that most organometallics are extremely sensitive to traces of air and moisture and rapidly decompose in water."

This is all the more surprising as the history of the oxo process actually prescribed the use of aqueous catalysts and catalyst precursors (aqueous cobalt salts as precursors of the earlier "Diaden" process [21], the at least partially aqueous cycle of the BASF and Kuhlmann process [22 b], or the cleavage of solvent-soluble by-products and heavy ends of the oxo process with the aid of water-dissolved metal salts [22 c, 23]).

The advantage of using water is that it is easy to separate from organic products, as indicated by Manassen in a continuation of the above quotation [10]:

> "The two phases can be separated by conventional means and high degrees of dispersion can be obtained through emulsification. This ease of separation may be particularly advantageous in situations where frequent catalyst regeneration is required".

Figure 2 illustrates the enormous importance of the biphase technique for homogeneous catalysis: the aqueous catalyst solution is charged in the reactor with the reactants A and B, which react to form the solvent-dissolved reaction products C and D. C and D are less polar than the aqueous catalyst solution and are therefore simple to separate from the aqueous phase (which is recycled directly into the reactor) in the downstream phase separator (decanter).

The advantage of the "liquid support" water and of its high affinity for the metal complex catalyst is evident. The catalyst is heterogenized with respect to the organic reaction products C and D and therefore can not only be separated from the products in the "other phase" (possibly including unconverted reactants A and B), but also immediately thereafter starts a new cycle of the catalytic cycle process. Aqueous biphase catalysis is therefore – intentionally – located between heterogeneous and homogeneous catalysis, as illustrated in Figure 3. Special attention

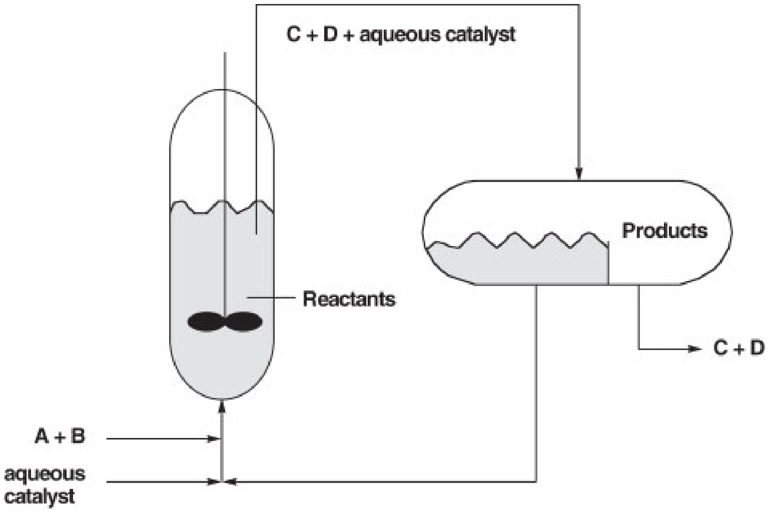

Fig. 2 Principle of biphase catalysis illustrated for the reaction A + B → C + D.

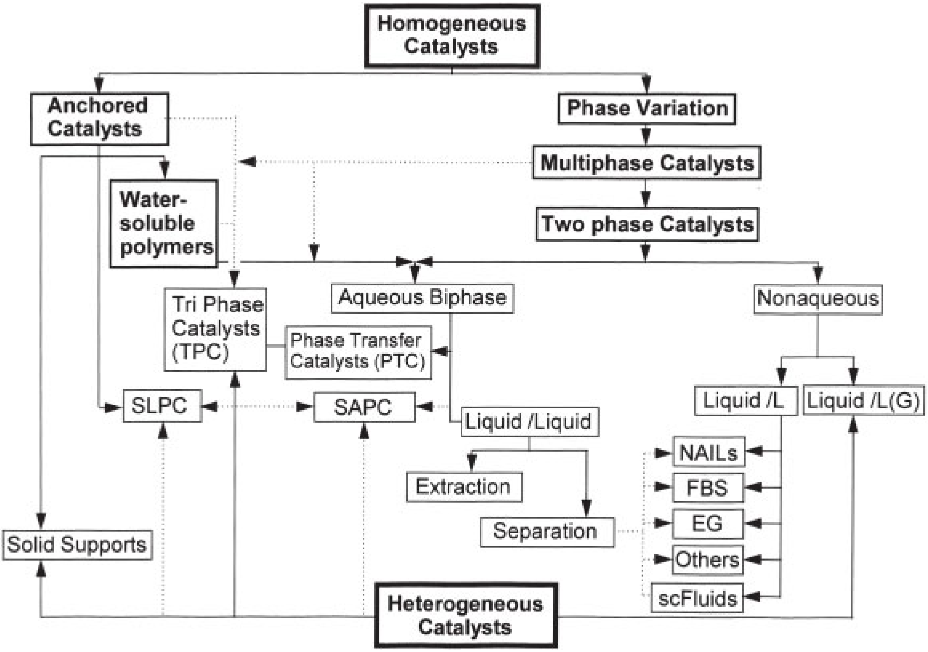

Fig. 3 Positioning of aqueous biphase catalysis: different approaches according to the variation of the application phase of catalysts. FBS, fluorous biphase system (cf. Section 7.2 [24]; PEG, polyethylene glycol cf. Sections 4.6.3 and 6.1.3.2; SAPC, and SLPC, cf. Section 4.7). NAIL, non-aqueous ionic liquids. (cf. Section 7.3).

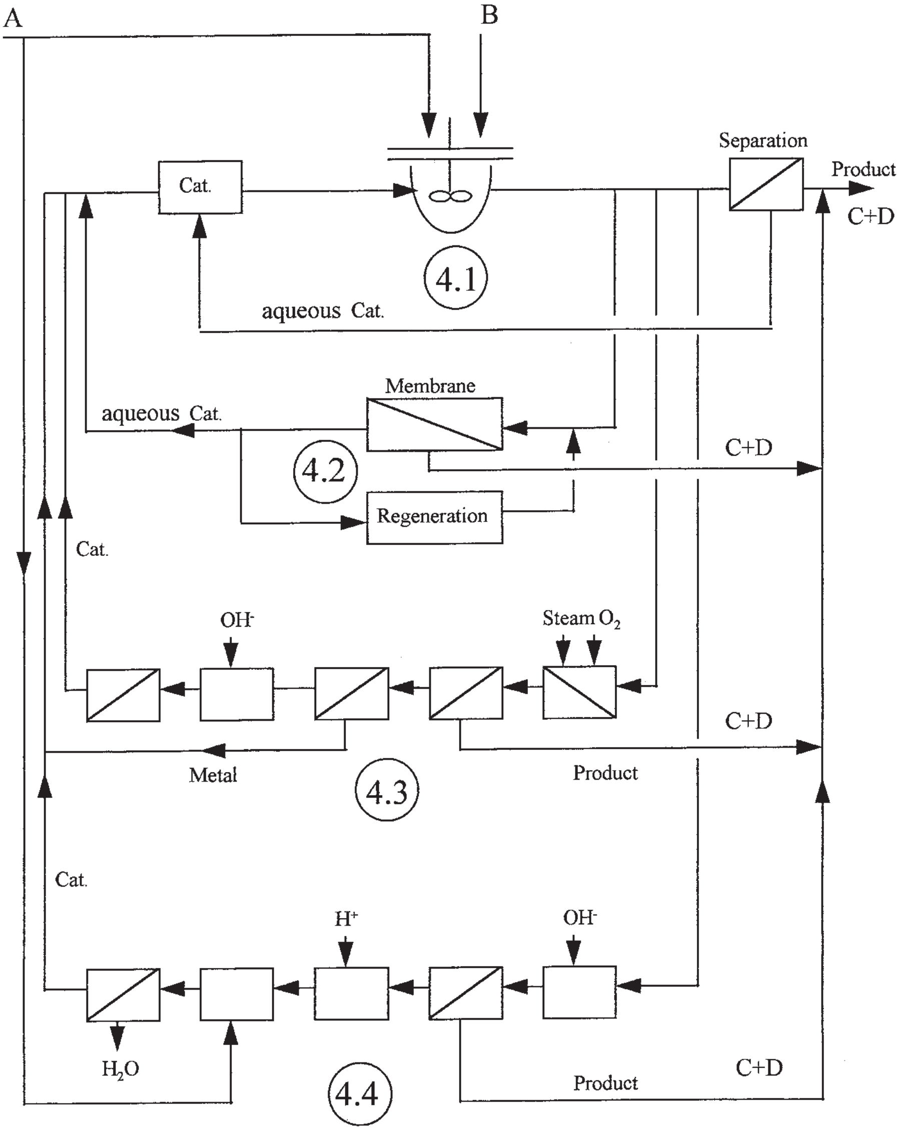

Fig. 4 The different methods of separation and recycling of oxo catalysts for the reaction A + B → C + D. (4.1) Aqueous biphase operation; (4.2) membrane technique; (4.3) thermal methods; (4.4) chemical treatment [22a].

may be drawn to the somewhat confusing and ambiguous use of the terms "homogeneous" and "heterogeneous" in the context of homogeneous/heterogeneous catalysis and homogeneous/heterogeneous phase variation: the catalytic system works homogeneously despite heterogeneous phase variation.

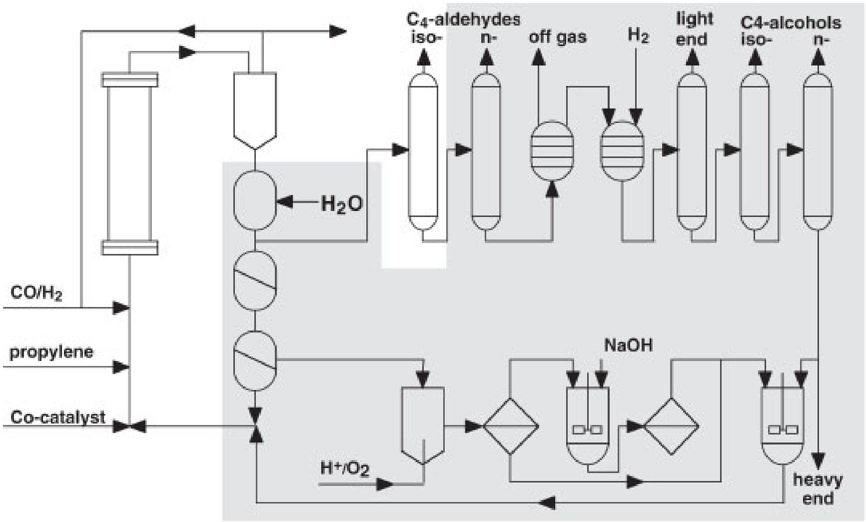

Fig. 5 Schematic flow sheet of a "classic" oxo process (known earlier as the Ruhrchemie process [22a]). Those parts of the process and equipment which are dispensed with in the RCH/RP process are stippled [17e].

The immobilization of the homogeneous catalyst with the aid of water as liquid support leads to appreciable technical simplifications, as illustrated in Figure 4 for the recycling of the catalyst of an industrial hydroformylation process (A = olefin, B = CO/H_2, C and D = butyraldehydes) [22a, 25].

For the overall process of hydroformylation, the lower expense of aqueous biphase catalysis compared with the "classic" process can easily be projected at about 50% of capital expenditure costs [17e]. Figure 5 illustrates the significant simplifications and savings in a comparison of the two process variants.

Table 2 predicts that, of the biphase processes, the aqueous version will attain particular importance because of the many advantages of water as the support. As a solvent, water has numerous anomalies (e.g., density anomaly, the only non-toxic and liquid "hydride" of the non-metals, pressure-dependence of the melting point, dielectric constant), and its two- or even three-dimensional structure is still not well understood (cf. Sections 2.1–2.3). Some of the known properties are listed below:

(1) Polar and easy to separate from apolar solvents or products; polarity may influence (improve) reactivity.
(2) Nonflammable, incombustible.
(3) Widely available in suitable quality.
(4) Odourless and colourless, making contamination easy to recognize.
(5) Formation of a hexagonal two-dimensional surface structure and a tetrahedron three-dimensional molecular network, which influence the mutual (in)solubility significantly; chaotropic compounds lower the order by H-bond breaking.

(6) High Hildebrand parameter, as unit of solubility of non-electrolytes in organic solvents.
(7) A density of 1 g/cm^3 provides a sufficient difference from most organic substances.
(8) Very high dielectric constant.
(9) High thermal conductivity, high specific heat capacity and high evaporation enthalpy.
(10) Low refractive index.
(11) High solubility for many gases, especially CO_2.
(12) Formation of hydrates and solvates.
(13) Highly dispersible and high tendency toward micelle formation, stabilization by additives.
(14) Amphoteric behavior in the Brønsted sense.
(15) Advantageous influence on chemical reactivity.

Besides its positive influence on reactivity (entry 15, [26]), the properties of water which are of direct significance for the aqueous two-phase processes are in particular the physiological (entries 2, 4), economic (1, 3, 6), ecological/safety (2, 4), technical (1, 6, 7, 9, 11, 12, 13) and physical properties (1, 5, 6, 8, 10, 12, 14). The various properties have multiple effects and are mutually reinforcing. For instance, water, whose high Hildebrand parameter [27] and high polarity have an advantageous effect on organic reactions (such as hydroformylation) [26], has a sufficiently high polarity and density difference from organic (reaction) products to allow separation of the phases following the homogeneously catalyzed reaction.

On the other hand, the high solubility for many compounds and gases – possibly augmented by solvate, hydrate, or hydrogen bond formation – facilitates reactions within the two-phase system. The chaotropic properties of many chemical compounds prevent the H_2O cage structures necessary for the formation of solvates, and facilitate the transfer of apolar molecules from both non-aqueous and aqueous phases. Between 1998 and the year of publication of the second edition a series of surveys about modern solvents in organic synthesis, including water, were published, thus indicating the new role of alternative (or no) solvent [41]. Some work deals with the application of *supercritical* water (sc water; [42, 50 f]) or even in a combination of $scCO_2$ (cf. Section 7.4) and water; in which case the schematic representation of the experimental set-up in Figure 6 (hydroformylation of 5-norbornene-1-*endo* carboxylic acid-2-methyl ester) is quite similar to Figure 2 [42 f]. The similarity of both Figures 2 and 6 and the simplicity of the experimental equipment indicate the elegance of the various biphasic processes.

Water does not ignite, does not burn, is odorless and colorless, and is ubiquitous: important prerequisites for the solvent of choice in catalytic processes. The dielectric constant or the refractive index can be important in specific reactions and their analytical monitoring. The favorable thermal properties make water

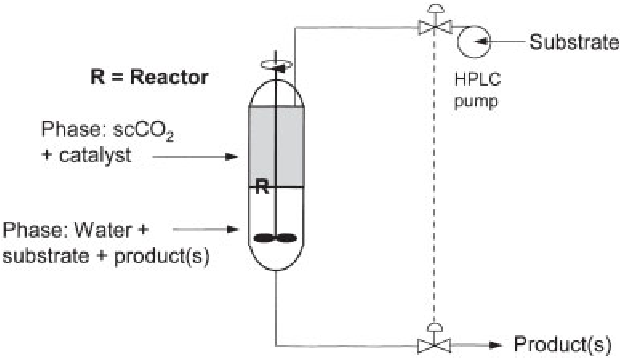

Fig. 6 Principle set-up for the hydroformylation in a system $scCO_2$/water.

doubly exploited as mobile support and as heat-transfer fluid, which is industrially exploited in the RCH/RP process (cf. Section 6.1.1) [17e–h].

The decisive advance for aqueous biphase technology was to leave behind traditional ways of thinking and move from organically and hence homogeneously soluble to heterogeneous and water-soluble hydroformylation catalysts with the aid of water-soluble ligands [16a]. This water solubility meant more than the change in the ligand sphere (CO → L, e.g., phosphines) and hence the replacement of the "classic" oxo catalyst $HMe(CO)_4$ by those of the type $HMe(CO)_nL_m$ and also more than the switch of the central atoms (Co → Rh). Water not only dissolves the catalyst, but also acts as a moderator [22, 26]; this represents the decisive difference in relation to the chemical reaction of the hydroformylation process and the process control of the reaction. The "standard ligand" of aqueous biphase catalysis, triphenylphosphine trisulfonate (TPPTS, 3,3′,3″-phosphinidynetris[benzenesulfonic acid], trisodium salt; cf. Section 3.2.1), has particular significance here. To what extent the replacement of TPPTS by new ligands in the catalyst system has repercussions for the management of the aqueous biphase reaction will depend on their nature and possibly also the addition of additives and auxiliaries (cf. Sections 4.1–4.7; for acronyms cf. Section 3.2).

The prevalent view is that the feed olefins of the aqueous biphase technique require a certain minimum solubility in the aqueous catalyst phase for adequate conversion. The reactivity differences in hydroformylation between, for example, propene and octene are readily explained by the solubility differences between the two olefins (Figure 7) [28, 29]. This is also the basis of the many proposals for solubilizing solvents or cosolvents, which are meant to make possible the reaction of higher and hence less water-soluble olefins in the bulk of the catalyst solution. In Figure 8, the two possibilities for the hydroformylation of propene (a liquified gas under reaction conditions) and syngas are shown.

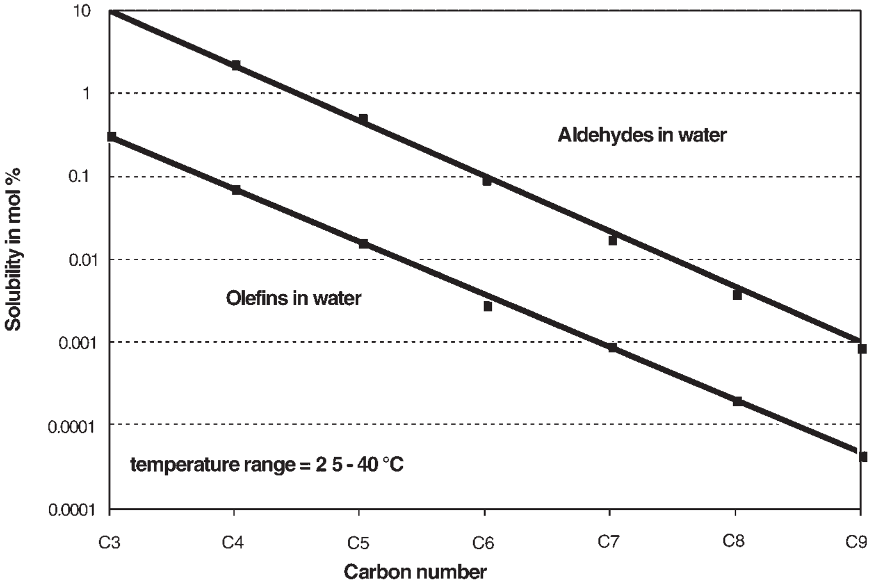

Fig. 7 Solubility of olefins [30, 31 a] and of the aldehydes obtained therefrom by hydroformylation in water [31 b, c].

On the one hand the reaction can occur in the bulk of the liquid phase: the gaseous reactants have already become uniformly distributed in the liquid phase owing to the rapid mass transport somewhat before the actual and slower, chemical reaction commences. This model A contrasts with the idea of a relatively rapid chemical reaction as opposed to mass transport.

The fact that the gaseoues reactants react very quickly means that, in practice and according to model B, the reaction takes place at the phase boundary or in an interfacial layer with a relatively small thickness [30, 32]. The latter has been proven which – via process modeling on the basis of appropriate kinetic models – made possible a more optimal reactor and mixing design [43]. Additionally, there is much (industrially initiated) work underway to check the addition of counterions or surface active ligands (Sections 3.2.4 and 3.2.6) or to test measures which increase the widths of the interfacial layers or the consequences of micelle/vesicle-forming devices (Section 4.5) [45]. The dependence of the reactivity of aqueous systems on the solubility of the reactants in the aqueous catalyst solutions is of appreciable importance for the problem of universal applicability (cf., e.g., Sections 4.1, 4.2, 6.1.3.2, and Chapter 7).

Using water as the solvent has not only the advantage of having a "mobile support" and hence of a *de facto* "immobilization" of the catalyst while retaining a homogeneous form of reaction, but also has positive repercussions on the environmental aspects of hydroformylation (cf. Section 5.2 and remarks on p. 338).

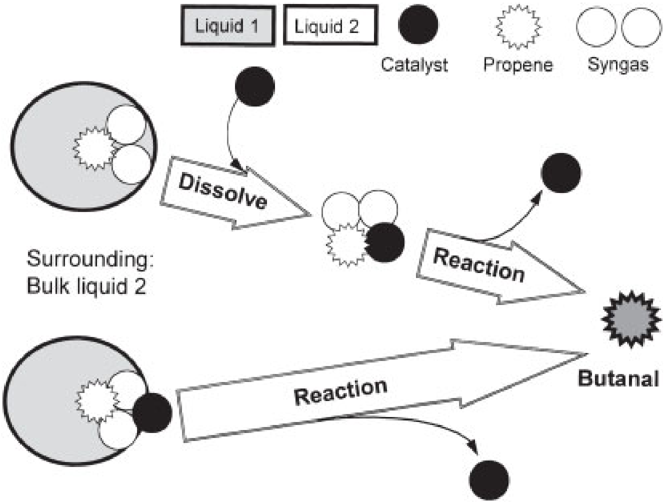

Fig. 8 Comparison of model A (above: reaction in the bulk of the liquid) and model B (below: reaction at the interfacial boundary).

Aqueous biphase processes will become more important in the future because of the immense advantages of this version of homogeneous catalysis. Dimerizations, telomerizations, hydrocyanations, aldolizations, Claisen condenstaions, and the great diversity of C–C coupling reactions are or will become targets, in addition to the syntheses already utilized now. Work in this area is described in Section 6. In anticipation, Table 3 gives an overview about some very recent publications dealing with biphasic catalytic reactions [44]. Nearly all catalytically relevant transition metals (and mixtures thereof) are involved. Some of these publications will be dealt with in Section 6.16 (Other Recent Exampels).

Systematic studies on the oxo process in particular have shown the vast improvements which can be achieved through variation of the ligands [33]. The comparison of the standard TPPTS ligand of aqueous biphase technology with new ligands such as BISBIS, NORBOS, or BINAS shows up distinct differences. The hydroformylation results so far demonstrate that different requirements such as highest possible activity, highest *n*/iso ratio (ratio between linear [l or *n*-] and branched [b or *iso*-] compounds), lowest required Rh concentration, or lowest excess of ligands (in all cases BINAS $\gg$ TPPTS) may be achieved by different ligands, thus indicating bright prospects for future tailor-made oxo catalysts in biphasic operation (Figure 9 and Section 3.2).

During the course of the last years, asymmetric/enantiomeric reactions more and more play an increasing role (cf. Section 6.11). Recent publications range from enantioselective hydrogenations [45 m, 47 j, r, 51 a] or asymmetric hydroformylations [51 b] to cyclopropanations, Diels–Alder reactions, or oxidative kinetic resolutions [46 d, 49 c, 51 c, d].

Tab. 3 Recent publications about aqueous-biphasically catalyzed reactions.

Type of reaction/Metal involved	***Refs.***
Additions or alkyl boronic acids to alkynyl aza-compounds	[56 c]
Aldolization/Sc, In, Cu, Ln	[46 a–d]
Alkylation/K, Pd, all-organic 1)	[46 e, f; 50 l]
Allylation/Ru, Pd	[46 d; 49 b]
Amination/Pd	[46 g]
Carbonylation/Pd, Rh	[46 h–l]
Cyanation/Pd, Ln	[46 m, n]
Cycloaddition, cyclotrimerization/Co	[46 o, p; 49 v]
Epoxidation/W, Re, Mn	[46 q–u]
Hydration/Au, Pt, Rh	[46 v; 49 y; 50 b]
Hydroaminomethylation/Rh–Ir	[46 w]
Hydrocarboxylation/Pd	[46 h; 47 a–e; 50 d]
Hydrodesulfurization/Ru, Rh	[47 f, g]
Hydrogenation/Ru, Rh, Pd, Ir, Pt–Pd	[45 d, m; 47 h–t; 50 m; 56 a, d]
Hydrosilylation/Pt	[47 u]
Isomerization/Ni	[47 v, w]
Metallo-Ene reactions	[56 b]
Metathesis/Ru, In	[47 x–z; 48 a]
Oligomerization/Pd, Al	[47 c; 48 b–f]
Oxidation/Ru, Pd, Os, W, Mn	[48 g–l; 50 a, e, h]
Phenol synthesis/Fe	[48 m]
Polymerization/Cu, Ti, Ni, Pd, Rh, Co	[48 n–r]
Syntheses of various heterocycles/Rh, Ni	[48 s; 50 c, k]
Telomerization/Pd, Ni	[48 t–v]
Thiolysis/In	[48 w]
Wacker reaction/Pd	[48 x]
Water-gas shift reaction/Ru	[49 t]
Examples for name reactions:	
• Barbier-type allylation/In, Sn	[48 y, z]
• Claisen rearrangement/Al	[49 a]
• Diels–Alder/Si, Cu	[46 d; 49 c; 50 j]
• Friedel–Crafts/Sc	[49 d]
• Grignard/Sn, Sn–Rh	[49 e]
• Heck/Pd	[49 f–i; 50 g]
• Kharasch/Pd	[49 j]
• Mannich/Zn	[46 d]
• Michael/Sc, Ag	[46 d; 49 k]
• Pauson–Khand/Rh	[46 x]
• Reformatsky/Zn	[49 l]
• Sharpless/Os	[49 m–o; 50 i]
• Suzuki/Pd	[49 p, q, x]
• Ullmann/Pd, Rh, Ni	[49 u, w]
• Wittig/all-organic a)	[49 r]

a) All-organic (or organic or organo) catalysts, cf. [49 s].

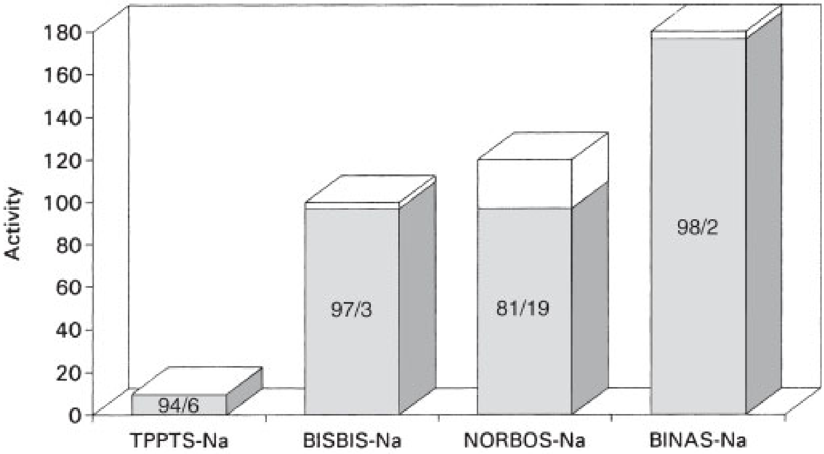

Fig. 9 How do ligands of aqueous oxo catalysts compare with each other? Oxo catalyst $HRh(CO)L_3$, with L = TPPTS, BISBIS, NORBOS or BINAS [33].

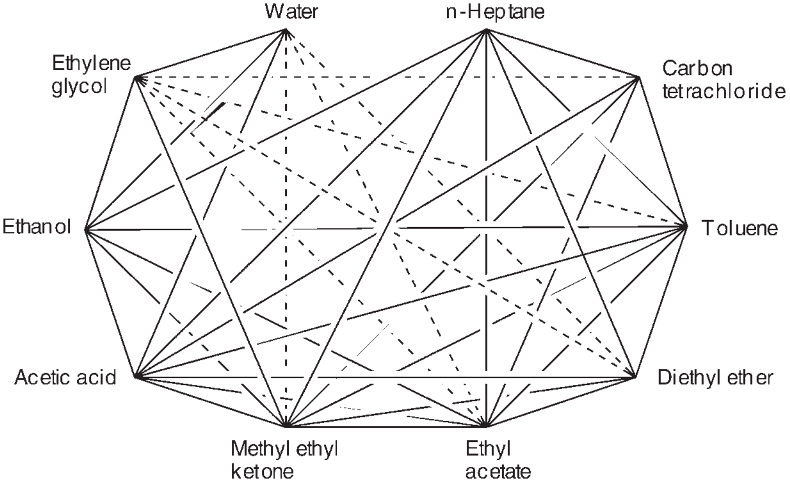

Fig. 10 Miscibility of organic solvents. —— miscible in all proportions; – – – – – limited miscibility; · · · · · little miscibility; no line, immiscible.

The use of biphase processes, starting from aqueous biphase catalysis, is only just beginning. As well as the versions which have been mentioned, other immiscible solvent mixtures will be used (depending on the requirements of the reactions or of the homogeneous catalysts), chosen on the one hand, according to the principle of "like dissolves like" ("Similia similibus solvuntur," as the alchymists used to say) in respect of the catalyst solvent and, on the other, according to fundamental nonmiscibility studies, similarly to the miscibility diagram (Figure 10) [34].

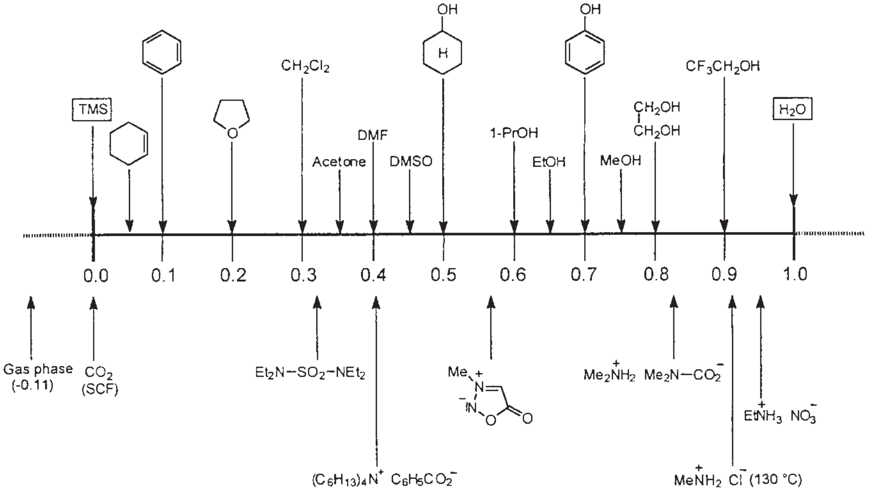

Fig. 11 Empirical polarity values E_T^N.

Now, informations about the behavior of the solvation capability (solvation power, E_T^N) of various solvents from nonpolar, aprotic tetramethylsilane (TMS; $E_T^N = 0.000$) to water ($E_T^N = 1.000$) are available (cf. Figure 11) [54].

This graph gives a selection of 14 (out of approx. 360) usual solvents above the basis line and 7 exotic solvents (ionic liquids included) below. The 14 compounds include (from left to the right: increasing solvent polarity) apolar, aprotic solvents (such as TMS, cyclohexene, or benzene), bipolar solvents (such as acetone, DMF, or DMSO), and eventually bipolar, protic solvents (cyclohexanol, ethanol, phenol, 2,2,2-trifluoroethanol). Using the E_T^N values numerous solvent-dependent processes may be correlated by far better than with the physical values of the solvents alone. This is true because the E_T^N values include specific cross interactions as well.

Some condensed papers [17i, k, 38c, 39, 43b, 46d, 47u, 48n, 49t, 52a–k] review the fundamentals, the applications, the reaction engineering aspects, and the limitations of aqueous-phase homogeneous catalyses and the special role of water. Interestingly, some authors still describe the use of water in aqueous-biphasic operation as disadvantageously because “the detection in case of leakage” is supposed to be difficult and “water shows no incineration of bleed streams”. Although the industrial attractiveness of, e.g., the aqueous-biphasic catalyzed Ruhrchemie/Rhône-Poulenc hydroformylation process, speaks for itself, the “misunderstandings” still remain since the early days of scientific discussion about aqueous-biphasic processes starting 1994 at the 1994 NATO Advanced Workshop on “Aqueous Organometallic Chemistry and Catalysis” [18c]. But generally, the time delay between the original idea from the academia [15], the industrial realization of this technique [17] (following initial experimental work by Kuntz, then at Rhône-Poulenc [16]) and only after at least 10 years of successful economic operation the cata-

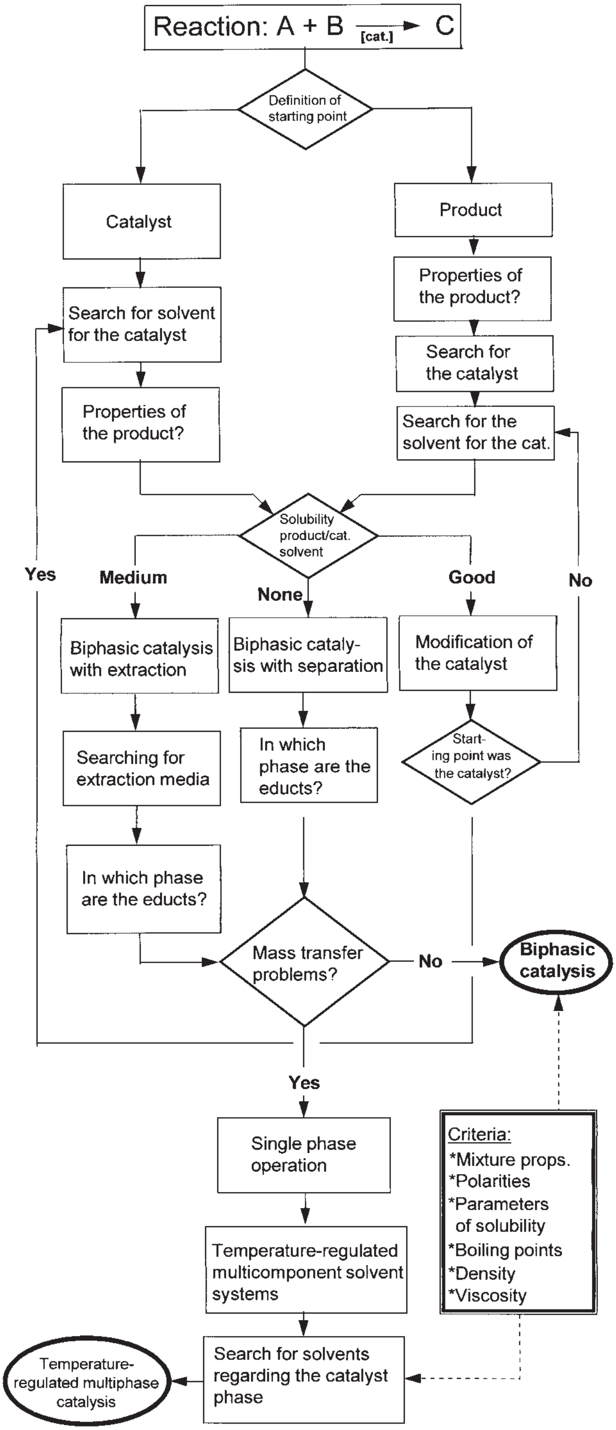

Fig. 12 Decision-making for multiphase reactions in respect to their catalyst, phase, and solvent.

lytic community started more detailed scientific studies [17i]. Nowadays, the academia proposes supports for the decision-making of catalyst recycling in the case of different catalysts, products, and differently polar solvents (see Figure 12) [55].

The role of aqueous-biphasic catalysis as a fundamental technique of “green catalysis” (or more specified: of “green chemistry”) is underlined by a multitude of publications [48i, 53].

Section 7 reviews non-aqueous biphase processes and their variations. Sections 4.5 and 4.6 deal with micellar systems and various applications of phase transfer catalysis in relation to aqueous biphase catalysis. Interestingly, biphase techniques are also being utilized from the other side, that of heterogeneous catalysis [35].

It is likely that the spread of biphase processes [36] will increase the proportion of homogeneously catalyzed reactions and hence the importance of homogeneous catalysis in general. It will then also be possible to demonstrate in full the great advantages of homogeneous catalysis over the rather empirical methods of heterogeneous catalysis and answer Heinemann’s 1971 question, “Homogeneous and heterogeneous catalysis – common frontier or common territory?” [37], clearly in favor of the homogeneous version.

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2
Basic Aqueous Chemistry

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

2.1
Organic Chemistry in Water

André Lubineau, Jacques Augé, Marie-Christine Scherrmann

2.1.1
Introduction

Water is a natural solvent. Molecular interactions and biochemical transformations in living systems mostly occur in an aqueous environment. Nevertheless, the use of water as a solvent in modern synthetic chemistry had practically disappeared when the role of highly polar organic solvents endowed with solvation properties was recognized. The lack of water-solubility of organic compounds, along with the water-sensitivity of some reagents or reactive intermediates, prevented chemists from thinking about water as a solvent for organic synthesis. Its use was rediscovered in the 1980s when Breslow [1 a], and Kuntz for organometallic catalyzed reactions [1 b], showed that the rate of the cycloaddition of cyclopentadiene with methyl vinyl ketone in water was enhanced by a factor of more than 700 compared with the reaction in isooctane [1]. Since this seminal contribution, there has been an upsurge in interest in using water as the solvent, not only to enhance the reaction rates but also to perform organic reactions that would otherwise be impossible, or to elicit new selectivities. Several reviews have been devoted specially to such a use [2–8, 104], which nevertheless does not exclude the possibility of further catalyzing the reactions with Lewis acids [9, 10].

Among the main advantages of using water as the solvent are the following:

- as the most abundant liquid that occurs on Earth, water is very cheap and more importantly it is not toxic, so it can be used in large amounts without any associated hazard;
- in water-promoted reactions, mild conditions can be sufficient and yields and selectivities can therefore be largely improved;
- water-soluble compounds such as carbohydrates can be used directly without the need for the tedious protection–deprotection process;
- water-soluble catalysts can be re-used after filtration, decantation or extraction of the water-insoluble products [1 b–f].

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A remarkable feature of water-promoted reactions is that the reactants only need to be sparingly soluble in water, and most of the time, the effects of water occur under *biphasic* conditions. If the reactants are not soluble enough, co-solvents can be used as well as surfactants. Another possibility for inducing water-solubility lies in grafting a hydrophobic moiety (a sugar residue or carboxylate, for instance) onto the hydrophobic reactant.

This contribution encompasses the main concepts supporting the origin of the reactivity in water, along with some applications in organic synthesis with the exception of transition-metal-catalyzed reactions, which are fully described in Section 2.2.

2.1.2
Origin of the Reactivity in Water

The combination of a small size and a three-dimensional hydrogen-bonded network system is responsible for the complexity of the structure of water, which results in a large cohesive energy density (550 cal/mL or 22 000 atm), a high surface tension and a high heat capacity. These three attributes give water its unique structure as a liquid, and give rise to the special properties known as hydrophobic effects, which play a critical role in the folding of biological macromolecules, in the formation and stabilization of membranes and micelles, or in the molecular recognition processes such as antibody–antigen, enzyme–substrate, and receptor–hormone binding. Since Breslow's discovery that the Diels-Alder reaction, which is known as insensitive to solvent effects, can be dramatically accelerated in aqueous solution, special attention was focused on the origin of the aqueous acceleration. Breslow suggested that hydrophobic packing of the reactants is likely to be responsible for the rate enhancement of Diels-Alder reactions [1a, 2]. Of interest was the observation of good correlations between solubilities of the reactants and Diels-Alder rate constants [11]. This influence of hydrophobic effects on solubilities, reaction rates, and selectivities could be interpreted by the use of prohydrophobic and antihydrophobic additives [12]. In 1986, Lubineau assumed that a fundamental issue is the high cohesive energy of water; he postulated then that a kinetically controlled reaction between two non-polar molecules for which $\Delta V^{\ddagger}$ is negative must be accelerated in water [13]. The importance of the cohesive energy density to Diels-Alder reactions and Claisen rearrangements, both displaying a negative activation volume, was demonstrated by Gajewski [14, 15].

By measuring standard Gibbs energy of transfer from organic to aqueous solvents, Engberts and co-workers showed that enforced hydrophobic interaction due to a decrease in the overall hydrophobic surface area during the activation process plays an important role in the rate acceleration in water [16]. This effect was considered to be a consequence of the high cohesive energy density of water [6] and should be expressed in terms of pressure (cohesive pressure), but one must avoid any confusion with the internal pressure of water, which is small compared with other solvents [17].

Employing a self-consistent reaction field model, Cramer and Truhlar concluded that the hydrophobic effect is always accelerating in aqueous Claisen rearrangements, even if most of the activation stems from polarization contributions to the activation energy [18].

The importance of hydrophobic effects was recently emphasized in Monte-Carlo simulated Diels-Alder reactions, especially when both reactants are non-polar; when one of the reactant is a hydrogen-bond acceptor, enhanced hydrogen-bonding interaction and hydrophobic effect contribute equally to the rate enhancement [19]. With methyl vinyl ketone as dienophile model in Diels-Alder reactions, computed partial charges displayed greater polarization of the carbonyl bond in the transition state and consequently enhanced hydrogen bonding to the transition state; on the basis of Monte-Carlo simulations [20] and molecular orbital calculations [21], hydrogen bonding was proposed as the key factor controlling the variation of the acceleration for Diels-Alder reactions in water. Monte-Carlo simulations showed enhanced hydrogen bonding to the oxygen in the transition-state envelope of water molecules for Claisen rearrangements as well [22].

Such an enhanced hydrogen-bonding effect was invoked to explain the experimental differences of reactivity between dienophiles in some Diels-Alder reactions [23, 24] and to understand the acceleration in water of the retro Diels-Alder reaction, a reaction with a slightly negative activation volume [25].

In summary, the acceleration in water of reactions between neutral molecules arises from:

- an enforced hydrophobic effect, especially when apolar reactants are involved;
- a charge development in transition states, especially when one of the reactant is a hydrogen donor or acceptor.

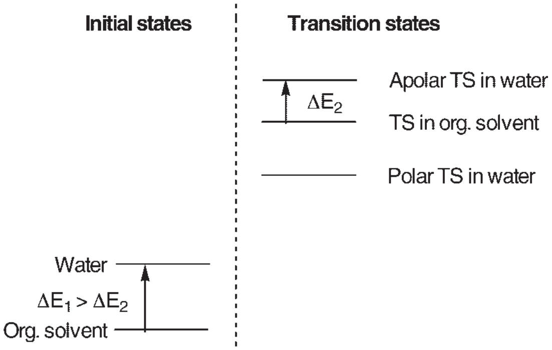


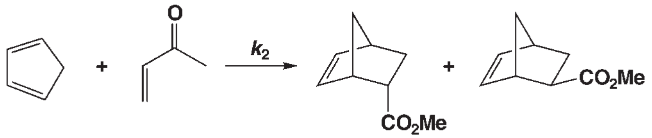
Fig. 1 Destabilization of the reactants and, to a smaller extent, of the transition states in water versus organic solvents.

In both cases a negative volume of activation is expected. Both contributions (hydrophobic effects and polarity) could be active in the same reaction (Figure 1), which means a greater destabilization of the hydrophobic reactants in the initial state than in the transition state, and a greater stabilization of a more polar transition state.

2.1.3
Pericyclic Reactions

2.1.3.1
Diels-Alder Reactions

In this pioneering work [1a], Breslow studied the kinetics of the cycloaddition between cyclopentadiene and methyl vinyl ketone (Eq. (1) and Table 1). The implication of the hydrophobic effect in Diels-Alder reactions was extensively supported by the effect of cyclodextrins [26] and additives, such as lithium chloride (salting-out agent) or guanidinium chloride (salting-in agent), which respectively increases or decreases the rate of the reaction [27].

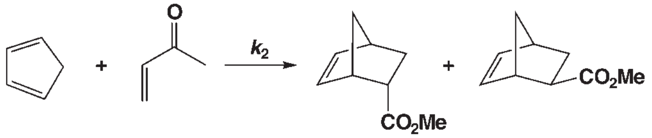


(1)

Tab. 1 Effect of different solvents according to Eq. (1).

Solvent	*10^5 k_2 [$M^{-1}s^{-1}$]*	*Solvent*	*endo/exo*
Isooctane	5.94	Cyclopentadiene	3.85
Methanol	75.5	Ethanol	8.5
Water	4400	Water	22.5
4.86 M LiCl in H_2O	10800		
4.86 M $(NH_2)_3CCl$ in H_2O	4300		
β-Cyclodextrin [10 mM]	10900		
α-Cyclodextrin [10 mM]	2610		

By measuring the rate constant of the cycloaddition between cyclopentadiene and dimethylfumarate, Schneider [28] demonstrated the importance of solvophobic effects, quantified by solvophobic power (S_p) values [29], which originate from the standard free energy of transfer of alkanes from the gas phase to a given solvent. Such a sensitivity of Diels-Alder reactions to solvent hydrophobicity depends, however, on the nature of the reagents [30] and is more pronounced for the reactions with a more negative activation volume [31]. Evidence for presence of en-



(2)

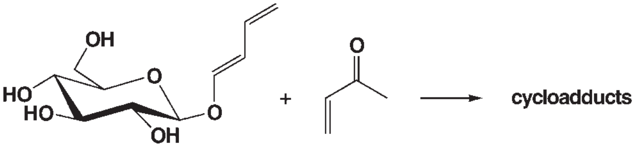
Tab. 2 Influence of solvents on Eq. (2).

Solvent	***10^5 k$_2$ [M^{-1}s^{-1}]***	***ΔH$_{act}$ [kJ mol^{-1}]***	***ΔS$_{act}$ [J mol^{-1} K^{-1}]***
Methanol	75	38.0 ± 1.0	-173.9 ± 3.4
Water	4400	38.0 ± 1.7	-140.9 ± 5.0

forced hydrophobic effects was provided from the study of rate constants and activation parameters of Diels-Alder reactions in aqueous solutions [16].

By measuring activation parameters (Eq. (2) and Table 2), it has been shown that the cceleration arises from a favorable change of activation entropy, which is an indication of the implication of the hydrophobic effect [32]. Concentrated aqueous carbohydrate solutions (glucose and saccharose for instance) have been shown to accelerate the Diels-Alder reaction. The acceleration is even greater than that observed with saturated β-cyclodextrin solution (Eq. (3) and Table 3) [32].

Another aspect of the influence of water as the solvent in Diels-Alder reactions is the higher *endo* selectivity observed by comparison with organic solvents (Table 1). The Diels-Alder reaction has a negative activation volume (ca. $-30\ cm^3 mol^{-1}$) and of the two possible transition states, the *endo* one is the more



(3)

Tab. 3 Acceleration of Eq. (3) by various carbohydrate solutions.

Additive	***10^5 k$_2$ [M^{-1}s^{-1}]***	***ΔH$_{act}$ [kJ mol^{-1}]***	***ΔS$_{act}$ [J mol^{-1} K^{-1}]***
None	28.5	40.0 ± 0.6	-178.8 ± 2.1
Methanol	8.5	33.6 ± 0.8	-211.1 ± 2.6
LiCl (2.6 M)	57.8	39.3 ± 1.7	-175.1 ± 5.4
Glucose (2.6 M)	45	39.2 ± 0.3	-177.4 ± 1.1
Ribose (2.6 M)	35	36.7 ± 1.5	-188.3 ± 4.9
Glucose (3 M)	61.3		
Saccharose (2 M)	74.9		
Satd. β-cyclodextrin	40.2		

compact. In the cycloaddition between ethyl maleate and cyclopentadiene, the *endo* selectivity was directly correlated with solvophobicity power [26], but in the cycloaddition between methyl acrylate and cyclopentadiene, the endoselectivity results were accounted for by means of a two-parameter S_p/E_T model [31]. Unlike Schneider's results [26], solvophobic (S_p) and polar (E_T) contributions, including hydrogen-bonding ability of the solvent, showed similar relative importance [33]. It is worth noting that the difference in compactness between the *endo* and the *exo* transition states of the ethyl maleate–cyclopentadiene cycloaddition ($\Delta\Delta V^{\neq} = 0.82\ \mathrm{cm^3\,mol^{-1}}$ is greater than that for the methyl acrylate–cyclopentadiene cycloaddition ($\Delta\Delta V^{\neq} = 0.62\ \mathrm{cm^3\,mol^{-1}}$), which could explain the greater hydrophobic influence of the former reaction [31].

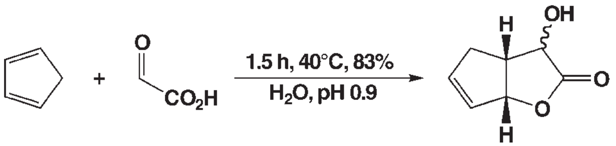
A recent improvement in the rate of the aqueous Diels-Alder reaction came with the use of Lewis acid in aqueous media. The first study deals with the Diels-Alder reaction between cyclopentadiene and a bidentate dienophile. A large acceleration can be achieved by the combined use of copper(II) nitrate as a catalyst and water as a solvent [10, 34]. Lanthanide and scandium triflates [9, 35] as well as indium trichloride [36] were found to catalyze the Diels-Alder reaction in water.

The aqueous Diels-Alder reaction has been widely exploited at the preparative level since the first studies of Breslow. Two reviews [4, 6] were in part devoted to this aspect. In order to increase the water-solubility, dienes have been attached at the anomeric position of a carbohydrate. The sugar moiety, which induces chirality, can easily be removed after the cycloaddition either via acidic or enzymic hydrolysis [37].

2.1.3.2
Hetero Diels-Alder Reactions

Aqueous aza Diels-Alder reactions were first described in cycloadditions of iminium salts and dienes [38]. Likewise, iminium salts derived from amino acids react in excellent yields in aqueous medium [39]. Such an aqueous aza Diels-Alder reaction was found to be catalyzed by lanthanide(III) trifluoromethanesulfonates [40].

An aqueous solution of glyoxylic acid reacts with cyclopentadiene to provide α-hydroxy-γ-lactones (Eq. 4); the more acidic the solution, the faster the reaction [41].



(4)

Such an aqueous hetero Diels-Alder reaction, which was extended to other dienes [42], was applied in various syntheses, including sesbanimides A and B [43], carbovir [44], mevinic acids [45], aristeromycin and carbodine [46], ketodeoxyoctulosonic acid (KDO) and analogs [47], and sialic acids [48]. Pyruvaldehyde, glyoxal, and even ketones like pyruvic acid also react with dienes in water [42].

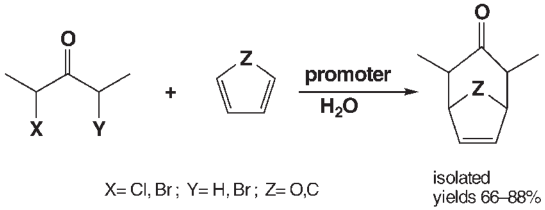
The influence of a low pH on the rate of reaction was also observed in the hetero Diels-Alder of di(2-pyridyl)-1,2,4,5-tetrazine with substituted styrenes [49].

2.1.3.3
Other Cycloadditions

An unusual influence of water on the rate of 1,3-dipolar cycloadditions was first observed when 2,6-dichlorobenzonitrile *N*-oxide was allowed to react with 2,5-dimethyl-*p*-benzoquinone [50]. Likewise, bromonitrile oxide, generated in water at acidic pH, gave cycloadducts efficiently with water-soluble alkenes and alkynes [51]. In highly aqueous media remarkable accelerations for the cycloaddition of phenyl azide to norbornene were observed [52].

Whereas cycloaddition of azomethine ylids were usually conducted with careful exclusion of water, it was recently shown that the cycloaddition in water–tetrahydrofuran solution of stabilized ylids derived from ethyl sarcosinate with several dipolarophiles can occur in excellent yields [53].

The cycloaddition of α,α'-dibromo (or dichloro) ketones with furan (or cyclopentadiene) gave very good yields when the reaction was conducted in pure water with iron powder. Furthermore, in the presence of triethylamine as the base, monobromo (or chloro) ketones react to furan (or cyclopentadiene) in water to afford the corresponding cycloadducts in near-quantitative yields (Eq. 5). In both cases, 2-oxyallyl cation, the formation of which is favored in water, was considered as the reactive intermediate [54].

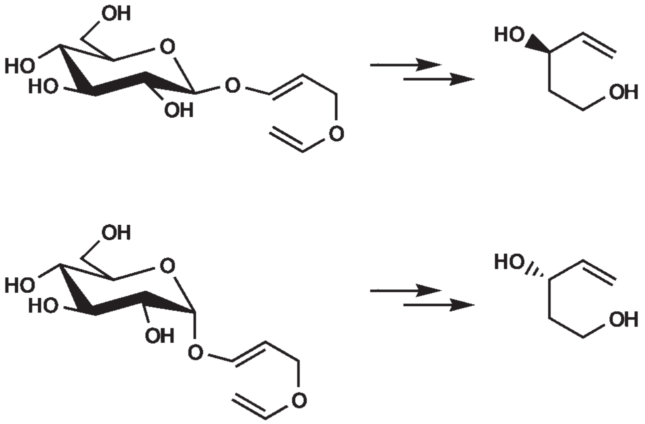


(5)

2.1.3.4
Claisen Rearrangements

The Claisen rearrangement, which displays a negative activation volume, is also accelerated in water. Thus, the non-enzymatic rearrangement of chorismate to prephenate occurs 100 times faster in water than in methanol [55]. The accelerating influence of water as a solvent on the rate of the Claisen rearrangement has been largely demonstrated on various substrates in organic synthesis [56]. Although otherwise impossible, the Claisen rearrangement of fenestrene was performed with success in mixed aqueous media [56].

The aqueous rate-enhanced Claisen rearrangement of glycoorganic compounds was shown to proceed in excellent yields [57]. The water solubility of the reactants was induced by grafting a free sugar onto the allyl vinyl ether moiety; moreover, the sugar functioned as a chiral template and gave highly crystalline diastereomers which were easily separable to yield pure enantiomers after enzymic hydrolysis. This method allows the preparation of either enantiomerically pure (*R*)- or (*S*)-1,3-diol (Scheme 1).

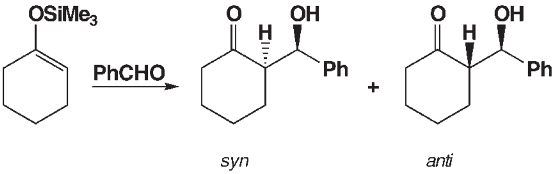


Scheme 1

2.1.4
Carbonyl Additions

2.1.4.1
Aldol-type Reactions

The Mukaiyama reaction is an aldol-type reaction between a silyl enol ether and an aldehyde in the presence of a stoichiometric amount of titanium chloride. The reaction, which displays a negative volume of activation, could be performed without acidic promoter under high pressure [58]. In this case, the major product is the *syn* hydroxy ketone, not as for the $TiCl_4$-promoted reactions which lead mostly to the *anti* addition product. Since the *syn* or *anti* selectivity is the result of two transition states with different activation volumes ($\Delta V^{\neq}_{\mathrm{syn}} < \Delta V^{\neq}_{\mathrm{anti}}$), it was of great interest to investigate the aldol reaction in water. Indeed, the reaction of the silyl enol ether of cyclohexanone with benzaldehyde in aqueous medium was shown to proceed without any catalyst and under atmospheric pressure, with the same *syn*



(6)

Tab. 4 Influence of solvents on Eq. (6).

Solvent	*Temp. [°C]*	*Time*	*Conditions*	*Yield [%]*	*syn* : *anti*
CH_2Cl_2	20	2 h	1 eq. $TiCl_4$	82	25 : 75
CH_2Cl_2	60	9 d	10 000 atm.	90	75 : 25
H_2O	20	5 d	stirring	23	85 : 15
H_2O/THF (1 : 1)	20	5 d	stirring	45	74 : 26
H_2O/THF (1 : 1)	55	2 d	ultrasound	76	74 : 26

selectivity as under high pressure (Eq. (6) and Table 4). This is an indication of the implication of hydrophobic effects during the activation process [13]. Taking account of the competitive hydrolysis of the silyl enol ether, this aqueous reaction is remarkable. The method was extended to other carbonyl compounds, such as formaldehyde, substituted benzaldehydes and α,β-unsaturated aldehydes and ketones [59].

To improve the yields and therefore the scope of this aqueous aldolization, the use of lanthanide triflates as water-tolerant Lewis acids was recommended [9, 60]. After completion of the reaction nearly 100% of the catalyst is recovered from the aqueous layer and can be re-used quite easily. Other water-tolerant Lewis acids, including indium chloride [61] and tris(pentafluorophenyl) boron [62], were proposed as catalysts in the aqueous aldol reaction.

The Henry reaction is an aldol-type reaction between a nitroalkane and an aldehyde in the presence of a base. Since basic reagents are also catalysts for the aldol condensation, the nitroaldol reactions must be strictly controlled. An interesting alternative lies in the use of surfactants to perform the reaction in an aqueous medium [63]. The Reformatsky reaction, which involves α-haloketones and aldehydes, can be mediated by zinc, tin or indium in water; in the latter case the proportion of undesirable reduction products could be strongly reduced [64].

Considerable rate enhancements have been observed when water is used as solvent compared with alcoholic or hydrocarbon media for Mannich reactions, i.e. condensations of ketones with secondary amines in the presence of formaldehyde [65]. Allylsilanes [66] and allylstannanes [67] in aqueous media were used in organic synthesis under Mannich-like conditions. More recently, Kobayashi reported the catalysis of the reaction of vinyl ethers with iminium salts by ytterbium triflate in tetrahydrofuran–water mixtures [68].

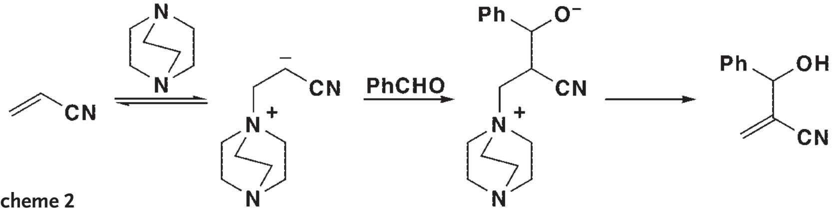
2.1.4.2
Michael-type Reactions

The use of water as a solvent in the conjugate addition of 1,3-diketones was reported earlier [69] and applied more recently in organic synthesis [70]. Ytterbium triflate turned out to be an efficient catalyst for the Michael addition of various β-ketoesters to β-unsubstituted enones [71].

A huge acceleration of the Michael reaction of nitroalkanes with methyl vinyl ketone was mentioned when going from non-polar organic solvents to water. The hydrophobic effect could be at least to some extent involved, since additives, such as glucose or saccharose, accelerate the reaction even more [72]. Cetyltrimethylammonium chloride as an amphiphilic species which can influence the hydrophobic interactions was found to promote the Michael reaction of various nitroalkanes with conjugated enones in dilute aqueous solutions of sodium hydroxide [73].

There is a remarkable effect of water as the solvent on the rate of the conjugate addition of amines to α,β-unsaturated nitriles. The lack of apparent reactivity of α,β-unsaturated esters comes from the reverse reaction, which is particularly accelerated in water [74].

A related reaction known as Baylis–Hillman reaction, which also has a large negative activation volume, was found to be greatly accelerated in water, compared with usual organic solvents. The first step is the conjugate addition of a tertiary amine (1,4-diazabicyclo[2.2.2]octane; DABCO) to acrylonitrile (Scheme 2) which is fast in water. The second step, which is rate-determining, is accelerated via a process wherein the hydrophobic effect could be involved. Other structured solvents also enhance the Baylis–Hillman reaction, but to a small extent [75].

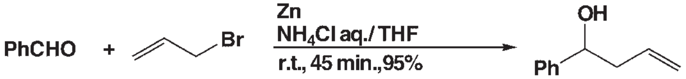


Scheme 2

2.1.4.3
Allylation Reactions

The allylation of aldehydes via organotin reagents displays a negative activation volume [76]. As a matter of fact, the allylation of benzaldehyde with diallyltin dibromide is accelerated by addition of water [77]. The reaction was extended to various aldehydes and ketones and to various allylic organotin dichlorides [78] or tetraallyltin in acidic aqueous medium [79]. With scandium triflate as a catalyst, tetraallyltin [80] or tetraallylgermane [81] react smoothly in mixed aqueous solvents providing high yields of the corresponding homoallylic alcohols.

Since the observation that allylation of carbonyl compounds could be mediated by tin in aqueous medium [77], there has been an intensive development of the Barbier-type allylation reaction in water. Three metals were particularly investigated: zinc, tin, and indium. In the aqueous zinc-promoted allylation, allylzinc species are considered unlikely. The initiation of the reaction could be attributed to the formation of an allylic radical anion on the metal surface; this radical surface could then react with the carbonyl compound to give an alkoxide radical, which could add an electron and form the alcohols [82]. Allyl bromide or even chloride reacts with aldehydes and ketones in the presence of commercial zinc powder in a mixture of tetrahydrofuran and saturated ammonium chloride aqueous solution (Eq. 7) [83].



(7)

By contrast, tin- and indium-promoted allylation reactions might involve organometallic intermediates, since preformed organotin and organoindium are highly reactive toward aldehydes in aqueous medium [84]. The tin-mediated allylation reaction requires either acidic conditions, metallic aluminum as an additive [77], or ultrasonic waves [85]. When applied to carbohydrates, the sonoallylation proceeded with useful diastereoselectivity (*threo* selectivity) and made it possible to prepare higher-carbon sugars from water-soluble substrates directly in aqueous ethanol without protection [86].

A major improvement was realized with the use of indium, a metal with a very low first ionization potential (5.8 eV) which works without ultrasonic radiation even at room temperature [87]. As the zero-valent indium species is regenerated by either zinc, aluminum, or tin, a catalytic amount of indium trichloride together with zinc, aluminum [88], or tin [89] could be utilized in the allylation of carbonyl compounds in aqueous medium. The regeneration of indium after its use in an allylation process could be readily carried out by electrodeposition of the metal on an aluminum cathode [90]. Compared with tin-mediated allylation in ethanol–water mixtures, the indium procedure is superior in terms of reactivity and selectivity. Indium-mediated allylation of pentoses and hexoses, which were however facilitated in dilute hydrochloric acid, produced fewer by-products and were more diastereoselective. The reactivity and the diastereoselectivity are compatible with a chelation-controlled reaction [84, 91]. Indeed, the methodology was used to prepare 3-deoxy-D-galacto-nonulosonic acid (KDN) [92, 93], *N*-acetylneuraminic acid [93, 94], and analogs [95].

2.1.5
Oxido-reductions

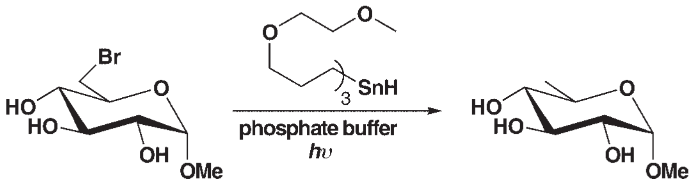
2.1.5.1
Oxidations

Oxidation reactions have often been conducted in water using water-soluble oxidants such as potassium permanganate, sodium periodate, and sodium (or calcium) hyperchlorite. Moreover, many oxidations can be performed in aqueous conditions using peroxy acids such as *meta*-chloroperbenzoic acid (MCPBA) or *meta*-peroxyphthalic acid (MPPA), or with hydroperoxides in the presence of transition metals. Thus, peroxybenzoic acid and MCPBA quickly epoxidize olefins in good yields in aqueous hydrogen carbonate [96]. Although the epoxidation of polyolefinic alcohols in organic media is usually not regiospecific, good regio- and stereoselectivities are observed when using hydroperoxides in water in the presence of transition metals [97]. Likewiese, polyolefinic alcohols are epoxized regioselectively by monoperoxyphthalic acid when controlling the pH of the medium [98].

2.1.5.2
Reductions

Apart from sodium borohydride, which is frequently used in water or water–alcohol mixtures to reduce ketones or aldehydes selectively, water is rarely used as the solvent in reductions, because of incompatibility with most reducing agents. However, samarium iodide reduction of ketones, as well as alkyl and aryl iodides is accelerated in water [99]. Likewise, the α-deoxygenation of unprotected aldonolactones is efficient when the SmI_2–tetrahydrofuran–water system is used [100].

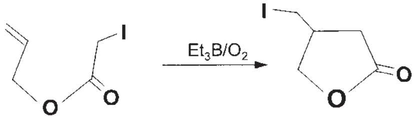
A water-soluble tin hydride was used to reduce alkyl bromides in a phosphate buffer in the presence of a radical initiator or light (Eq. 8) [101]. The more available tributyltin hydride, albeit insoluble in water, was successfully used as the reducing agent with or without a detergent as a solubilizing agent [102].



(8)

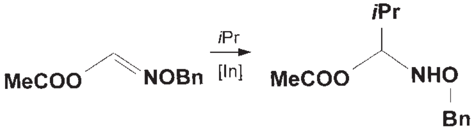
2.1.6
Radical Reactions

Although significant solvent effects have been observed for radical reactions in water, the use of aqueous medium for this type of chemistry remains, nowadays, rare. Some published work has been recently rewieved [105]. Oshima's group has reported a remarkable improvement for the triethylborane-mediated radical cyclisations reactions of allyliodoacetates to butyrolactones (Eq. 9) [106, 107].



(9)

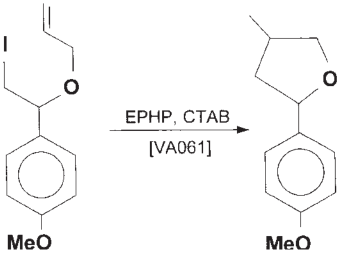
Later the same group reported that α-bromo carbonyl compounds could be added to terminal alkenes [108] or coupled with allylgallium [109] through intermolecular radical reactions still initiated with triethylborane. Another remarkable example was reported by Miyabe et al. They described the indium [110] or triethylborane [111]-mediated radical addition of alkyl iodide to electron deficient C=N bond and C=C bond in water (Eq. 10).



(10)

The use of water soluble radical initiator 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA061), water soluble chain carrier 1-ethylpiperidium hypophosphite (EPHP), and surfactant cetylammonium bromide (CTAB) allowed the C–C bond forming radical reactions of highly hydrophobic substrate in water (Eq. 11) [112].

Similarly, the use of CTAB and EPHP in presence of 4,4′-azobis(4-cyanovaleric acid) (ABCVA) promoted the indium-mediated radical addition to β-substituted cconjugated alkenes in water. This method produced 1,4-addition products to α,β-enones while the classical allylindium reagents lack generally of regioselectivity [113].



(11)

2.1.7
Outlook

The origin of specific reactivity in water lies both in the high cohesive energy density of water and in its ability to form hydrogen bonds. Radical or ionic reactions with a negative volume of activation can be facilitated in aqueous solutions. Water can be used with co-solvents in two-phase or one-phase systems, or with additives which enhance the hydrophobic effects (concentrated solutions of structure-making salts, sugars, etc.), the polarization of transition states (water-tolerant Lewis acids in catalytic amounts), or the solubility of reactants (surfactants). Smooth conditions are then possible, even for the more energy-demanding reactions. At high temperatures and pressures, dramatic changes occur in the physical properties of water, so that it can act as an acid–base bicatalyst, which could have ecological applications in recycling, regeneration, disposal and detoxification of chemicals [103].

The understanding of aqueous chemistry should favor the discovery of new selective transformations with benign environmental impacts.

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2.2
Organometallic Chemistry in Water

Wolfgang A. Herrmann, Fritz E. Kühn

2.2.1
Introduction

Water plays a fundamental role in coordination chemistry. Not only do many, if not all, metals bind water molecules to fill up their coordination sphere; it has been through the kinetics of water-exchange processes at metal ions that the basics of the theory of coordination chemistry have been conveyed [1]. By way of contrast, relatively little is known of aqueous organometallic chemistry, because of the notorious lability of organometallics toward water. It has to be noted, however, that in the recent years the organometallic chemistry of water is gaining increasing attention particularly with water as the polar phase in multiphase systems, as can be seen in the appearance of an increasing number of original articles and several review articles on this field [2]. This section focuses on the key features of water in both aspects, i.e., coordination and organometallic chemistry.

2.2.2
Water as a Solvent and Ligand

Water as a *solvent* offers opportunities as compared with organic solvents. It favors ionic reactions because of its high dielectric constant ($\varepsilon_{25^\circ} = 78.5$) and the ability to solvate cations as well as anions. Beyond that, water is the ideal solvent for radical reactions since the strong O–H bonds (enthalpy 436 kJ/mol) are not easily attacked [1 g]. Furthermore water displays particularly high enthalpy changes during the solid-liquid ($\Delta H_{\text{melt}} = 6.003$ kJ/mol) and particularly the liquid-gaseous ($\Delta H_{\text{vap}} = 40.656$ kJ/mol) transfer, since the phase transfers are associated with the formation or breaking of hydrogen bridges. Additional advantages of water as a solvent are its high heat capacity, its strong pressure dependency of the viscosity, and the high cohesive energy density (c.e.d. = 2.303 kJ/cm^3) [2].

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Tab. 1 Rates of water exchange of hexaquo metal complexes.

Metal	***Rate [sec^{-1}]***	***Electron configuration***
Cr^{2+}	7×10^9	d^4
Cr^{3+}	3×10^{-6}	d^3
Mn^{2+}	3×10^7	d^5
Fe^{2+}	3×10^6	d^6
Fe^{3+}	3×10^3	d^5
Co^{2+}	1×10^6	d^7
Ni^{2+}	3×10^4	d^8
Cu^{2+}	8×10^9	d^9
Rh^{3+}	4×10^{-8}	d^6

Classified as a *ligand* for metal ions, water has decent crystal field splitting properties, standing between oxygen-bound anions and nitrogen donors such as pyridines in the spectrochemical series:

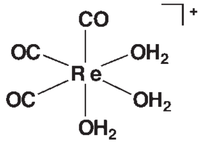
$$I^- < Br^- < Cl^- < F^- < OH^- < CH_3CO_2^- < \text{oxalate} < \mathbf{H_2O} < \text{pyridine} \approx NH_3 < NO_2^- < CN^-, CO, CNR$$

The water molecule is a good σ-donor ligand, while π-backbonding is negligible. For this reason, higher-valent transition metals form the more stable metal complexes, but the nature of the metal by itself is important, too (Table 1).

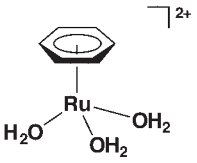
For first-row metals (+ 2), an extra destabilization due to electrons in e_g orbitals accounts for a ligand labilization. This effect is commonly referred to as “crystal field activation energy” (CFAE) [1 a–c].

From these properties it is concluded that low-valent metals do not favor water in the ligand sphere. Not that $Cr(CO)_6$ is a stable compound because of the outstanding π-backbonding of carbon monoxide, while $\{Cr(H_2O)_6\}$ does not exist – quite contrary to the common $[Cr(H_2O)_6]^{3+}$. On the other hand, trivalent chromium does not form the (hypothetical) cationic carbonylchromium complex $\{Cr(CO)_6]^{3+}\}$. This is, in short, one major reason why so little is known about typical organometallic water complexes.

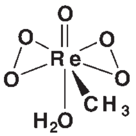
Few organometallic aquo complexes have been isolated in substance. Examples are the carbonylrhenium(I) and (π-benzene)ruthenium(II) complexes **1 a** and **1 b**, respectively, and their congeners **1 c–e** [3–6]. They are of course soluble in water and can be used as convenient starting materials for complexes exhibiting the respective organometallic backbones, e.g., the $[Re(CO)_3]^+$ cation from **1 a** which is otherwise available only with difficulty [6]. The synthesis of aquo complexes from metal carbonyls proceeds via photolysis from the anhydrous parent compounds. The air-stable (!) rhenium complex **1 a** is conveniently generated from $[ReO_4]^-$ or $[ReOCl_4]^-$ and $[BH_3 \cdot \text{solvent}]$ in the presence of carbon monoxide [5 a, b]. It is an outstanding precursor of products like $[L_3Re(CO)_3]^+$, with L = N- or P-donors.



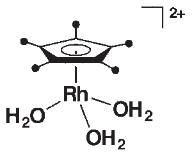
1a



1b



1c



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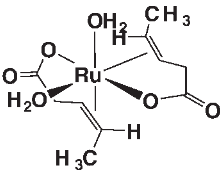
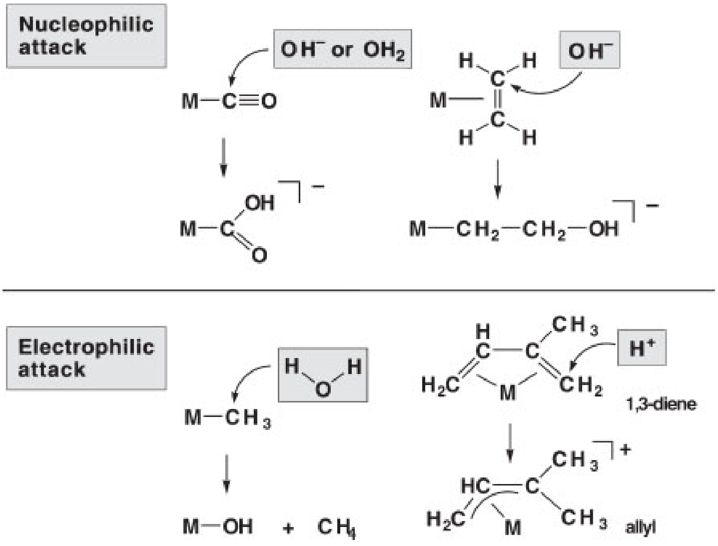


1e

2.2.3
Organometallic Reactions of Water

Metal–carbon (M–C) bonds are thermodynamically unstable with regard to their hydrolysis products. Water can attack M–C bonds either by proton transfer (H^+, electrophilic reaction) or via the oxygen (OH_2 or OH^-, nucleophilic reaction). Examples are shown in Scheme 1. Ligands such as carbon monoxide and ethylene are activated toward nucleophilic attack upon coordination to (low-valent) metals, e.g., Pd^{2+}. A number of C–C-bond forming reactions derive from this activation. Allyl ligands are generated by proton attack to the terminal 1,3-diene carbon



Scheme 1 Basic reactions of organometallic compounds in aqueous systems.

groups (Scheme 1). In other cases, protonation of heteroatoms of metal-attached ligands is followed by elimination steps; for example, the allyl alcohol ligand $H_2C{=}C(CH_3)CH_2OH$ (η^2) is converted by $H[BF_4]$ into the allyl cation $[H_2CC(CH_3){=}CH_2]^+$, which is a standard route of making metal-allyl complexes [3].

High bond polarity yields increased reactivity with water. Thus, $Al(CH_3)_3$ and $In(CH_3)_3$ hydrolyze quickly. $Sb(CH_3)_3$ and $Sn(CH_3)_4$ are inert because of low bond polarity and efficient metal shielding (electron pair at Sb, coordination number 4 at Sn). $Si(CH_3)_4$ is water-stable (low bond polarity, good steric shielding), while SiH_4 hydrolyzes quickly due to inefficient shielding and nucleophilic attack, probably via 3 d orbitals of the silicon.

However, metal hydrides hydrolyze only if they are ionic or coordinatively unsaturated. For example, NaH (ionic) instantaneously extrudes hydrogen upon contact with water whereas the covalent hydrides $Mn(CO)_5H$ $(\eta^5\text{-}C_5H_5)Fe(CO)_2H$, and $(\eta^5\text{-}C_5Me_5)ReH_6$ remain unchanged.

Since the M–R bond is normally polarized toward an anionic organyl group ($R^{\delta-}$), a metal hydroxide forms along with the respective hydrocarbon from metal alkyls (Eq. 1).

$$\overset{\delta+}{M}-\overset{\delta-}{R} + H_2O \longrightarrow M-OH + R-H \tag{1}$$

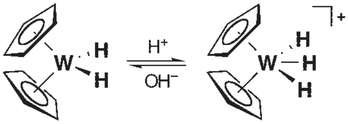
$$2\ M-OH \longrightarrow M{=}O + H_2O-M \tag{2}$$

$$2\ M-OH \longrightarrow M-O-M + H_2O \tag{3}$$

$$2\ Re_2(CO)_{10} + 4\ H_2O \xrightarrow[-\ 8\,CO]{h\nu} [(CO)_3Re\,OH]_4 + 2\,H_2 \tag{4}$$

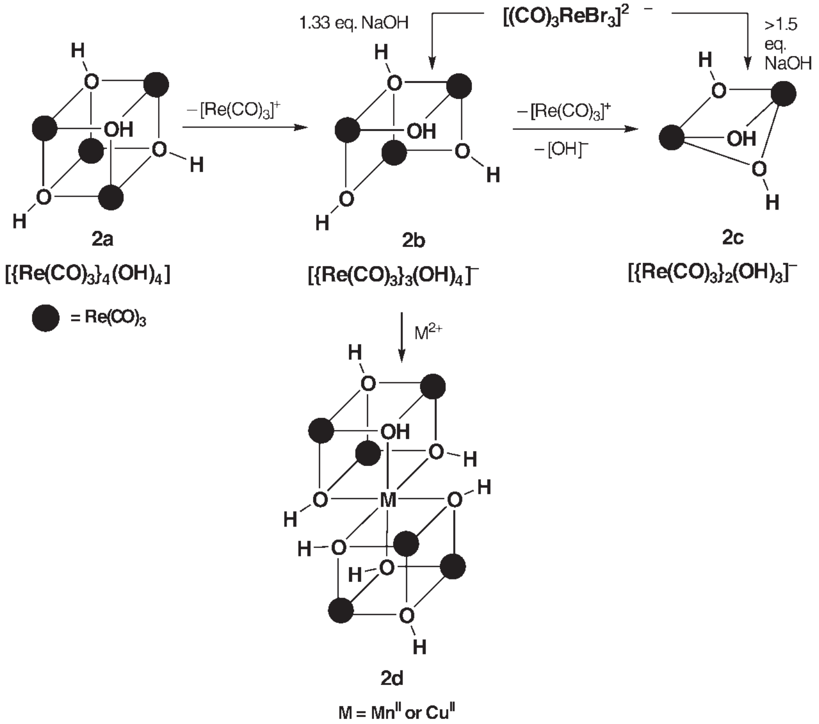
Follow-up products may include metal oxides, be it in a mononuclear or in a di- and oligonuclear form (Eqs. 2–4). The tetranuclear rhenium(I) complex formed by photolysis (Eq. 4) has a cubane-type structure [7]. Related complexes **2a–d** were made according to Scheme 2 [8].

Since many organometallics behave as Lewis bases due to electron-rich metals, protonation is a common reaction. For example, the tungsten hydride **3** undergoes reversible protonation at the metal, forming the water-soluble cationic hydride **4** (Eq. 5). In nickelocene **5**, a 20e$^-$ complex, protonation occurs at the π-bonded cyclopentadienyl ligand; the intermediate **6** has a stable, isolable counterpart in the fully methylated derivative. Consecutive loss of cyclopentadiene forms the cation **7**, which adds to unchanged nickelocene forming the tripledecker sandwich **8** (Scheme 3).

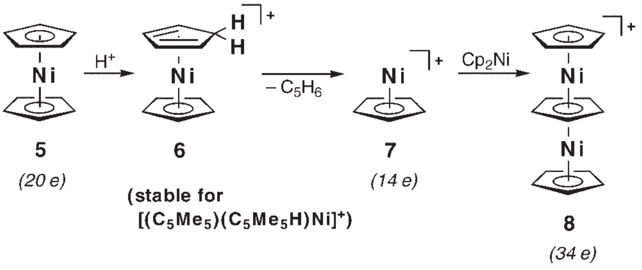


3 **4**

(5)



Scheme 2 Organometallic hydroxy complexes from hydrolysis and aggregation reactions.



Scheme 3 Protonation of an electron-rich ligand of an organometallic complex.

Suffice it to say that pronouncedly oxophilic metals such as the rare-earth elements are particularly sensitive to water. There are numerous cases where an oxo ligand has been introduced by accidental moisture present under the conditions of reaction [9]. There is good reason for chemistry of this type of metals to be performed under scrupulous glove-box conditions.

There are also cases where the *ligand* reacts with water (Section 2.2.6). Organic phosphanes, for example, may show up as phosphane oxides under certain circumstances (cf. Eq. 6). The oxidant is not always obvious in these cases, but it can be water.

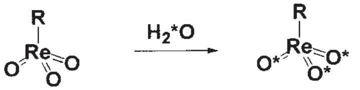
$$L_nRh-P(C_6H_5)_3 + H_2O \longrightarrow O{=}P(C_6H_5)_3 + \ldots \tag{6}$$

Strong metalla-acids undergo protonation of water to form the corresponding anion; $HCo(CO)_4$ is such an example (Eq. 7).

$$(CO)_4Co-H + H_2O \longrightarrow [(CO)_4Co]^- + H_3O^+ \tag{7}$$

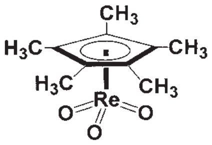
There are cases where the M–C bonds withstand cleavage. The organorhenium (VII) oxide **9a** (pentamethyl[cyclopentadienyl]trioxorhenium) does not exchange its terminal oxo ligands with water, while the sterically less hindered and more electron deficient cyclopentadienyl trioxorhenium **9b** exchanges its oxo ligands slowly [10]. The water-soluble (ca. 30 g/L) methyltrioxorhenium(VII) (MTO) **10** [5] exchanges its oxo ligands quickly with water (Eq. 8) [10a–f] and it has been assumed that it possibly forms octahedral water adducts prior to undergoing aggregation to "polymeric MTO". Mainly steric but also electronic reasons are likely to account for this difference between the organorhenium(VII) oxides **9a,b** and **10**. MTO is also an example of a water-stable metal organyl: even in boiling water, only few of the methyl groups are lost (as methane) after several hours [5, 11a,e]! The reaction product of MTO with excess hydrogen peroxide, a highly reactive and catalytically active organometallic bisperoxo complex (**11**) can be stabilized – among other possibilities – and isolated with a coordinating water molecule (Eq. 9) [6e, 12]. The behavior and reaction chemistry of MTO in water is described in more detail in Section 6.4.3.

Water can also *oxidize* organometallic complexes. For example, the platinum(IV) complex cation $[(C_6H_5)_2Pt(OH)]^+$ is generated from divalent platinum by water [13].

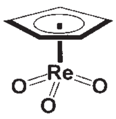


(8)

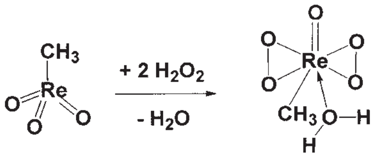
R = CH_3; C_5H_5 *O = ^{17}O



9a

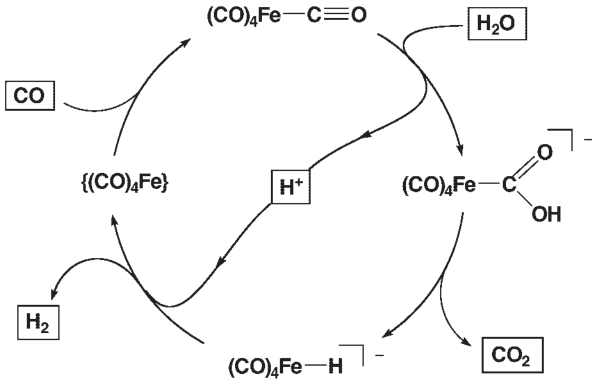


9b



(9)

10 **11**



Scheme 4 The mechanism of the water-gas shift reaction (cf. [14] and references cited therein).

2.2.4
Catalytic Reactions with Water

2.2.4.1
Water-gas Shift Reaction

A famous example is the water-gas shift reaction [14]. Efficient catalysts are late transition metals such as iron, e.g. $Fe(CO)_5$ [14].

Mechanistically, attack of water (hydroxide) occurs at the carbonyl ligands, with the catalytic cycle depending on the formation and lability of metallacarboxylic acids (Scheme 4). This reaction can interfere with typical CO reactions such as hydroformylation (C–C-bond formation) [15].

2.2.4.2
Wacker–Hoechst Acetaldehyde Process

Water is also involved as a substrate in the Wacker–Hoechst acetaldehyde process based on a partial, selectie oxidation of ethylene [16]. According to Eq. (10), it is necessary to form the new C–O bond starting from ethylene (*trans*-stereochemistry), while the oxygen of Eq. (11) regenerates the catalyst ($Pd^0 \rightarrow Pd^{2+}$), but does not oxidize the ethylene as suggested by the net Eq. (12). Metal attachment of ethylene is the prerequisite to make it accessible to nucleophilic attack by water (cf. Section 6.4.2).

$$CH_2{=}CH_2 + H_2O + PdCl_2 \longrightarrow CH_3{-}C({=}O)H + 2\,HCl + Pd \tag{10}$$

$$Pd + {}^1\!/_2\,O_2 + 2\,HCl \longrightarrow PdCl_2 + H_2O \tag{11}$$

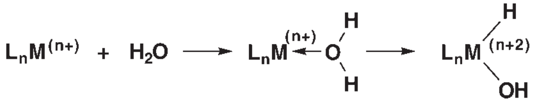
$$CH_2{=}CH_2 + {}^1\!/_2\,O_2 \longrightarrow CH_3{-}C({=}O)H \tag{12}$$

2.2.4.3
Olefin Hydration

Otherwise, water has not been exploited as a cheap building block in catalytic reactions. Note, for example, that the highly desired *anti*-Markovnikov addition of water to α-olefins forming α-alcohols still awaits efficient catalysis (Eq. 13) [15]. Very probably, an oxidative addition will activate the water for the nucleophilic attack at the (metal-bound) alkene (Eq. 14) [3].

$$R{-}CH{=}CH_2 + H_2O \longrightarrow R{-}CH_2{-}CH_2{-}OH \qquad (13)$$

anti-Markownikoff addition



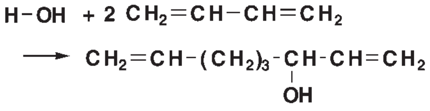
$$L_nM^{(n+)} + H_2O \longrightarrow L_nM^{(n+)}\leftarrow OH_2 \longrightarrow L_nM^{(n+2)}(H)(OH) \qquad (14)$$

2.2.4.4
Hydrodimerization

Hydrodimerization is a special case of telomerization, where a (solvent) molecule A–B (the telogen, e.g., H_2O) reacts with n molecules of an unsaturated molecule M (the taxogen) to yield oligomers or polymers of relatively low molecular mass (Eqs. 15 and 16). An important special case is the Kuraray 1-octanol process resulting from the products of Eq. (17) by subsequent hydrogenation. This industrially relevant reaction includes hydrodimerization of 1,3-butadiene [17]. Efficient catalysts are palladium–phosphine complexes, e.g., Pd^{2+}/TPPMS (TPPMS = $P(C_6H_4\text{-}m\text{-}SO_3^-Na^+)(C_6H_5)_2$). Little is as yet known on mechanisms.

$$A{-}B + n\,M \longrightarrow A{-}(M)_n{-}B \qquad (15)$$

$$H{-}OH + n\,M \longrightarrow H{-}(M)_n{-}OH \qquad (16)$$



$$H{-}OH + 2\,CH_2{=}CH{-}CH{=}CH_2 \longrightarrow CH_2{=}CH{-}(CH_2)_3{-}CH(OH){-}CH{=}CH_2 \qquad (17)$$

[+2,7-Octadienol (1)]

Telomerizations provide an opportunity to make functionalized organic products from simple, abundant precursor molecules, e.g., butadiene and water; see also Section 6.9.

2.2.5
Water-soluble Metal Complexes

Following the pioneering work in the area of biphasic catalysis [18], a steady demand for water-soluble and, at the same time, water-compatible metal complexes has been recognized. Despite a broad array of solubilizing ligands (Section 3.2.1), sulfonated derivatives of ligands containing aryl groups have proven most successful, mostly because of the outstanding solubility in water. Notably, the standard tris(*m*-sulfonatophenyl)phosphine $[P(C_6H_4\text{-}m\text{-}SO_3^-Na^+)_3$; TPPTS] has a solubility of ca. 1.1 kg/L upon which the success of the catalyst system Rh/TPPTS depends in biphasic, aqueous hydroformylation [19] (cf. Section 6.1).

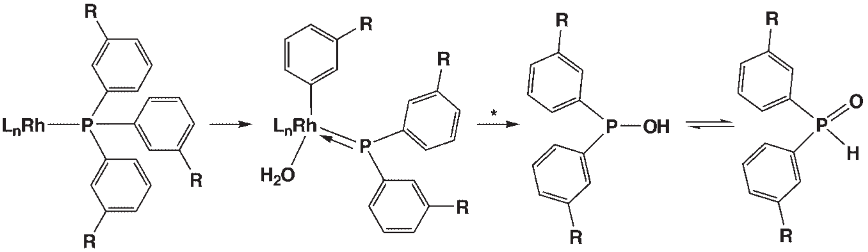
Numerous ionic organometallics, e.g., $Na[Re(CO)_5]$ or $[(\eta^5\text{-}C_5H_5)Fe(CO)_2\text{-}\{P(C_6H_5)_3\}]^+I^-$, are soluble in water and can be precipitated by large counterions (e.g., $[P(C_6H_5)_4]^+$, $[B(C_6H_5)_4]^-$, $[(C_6H_5)_3P{=}N{=}P(C_6H_5)_3]^+$). Basic ions such as $[Re(CO)_5]^-$ give hydrido complexes upon protonation, e.g., $HRe(CO)_5$.

2.2.6
Perspectives

Organometallic entities display a variety of reactions with water, following their commonly observed thermodynamic instability. However, in many cases, kinetic barriers prevent these reactions from occurring, making organometallics seemingly stable toward water and, often, even toward protic aqueous acids and toward hydroxide. Even in cases where highly charged metal ions coordinate water, further degradation of the (organic) ligand sphere does not necessarily occur. Striking examples are the organorhenium(VII) oxide CH_3ReO_3, a series of alkylmercury compounds (e.g., $[(CH_3)_3Hg]^+$), and the well-known methylcobalamin. Also, hydrated alkylchromium and alkylcobalt complexes are known [1d]. Therefore, water is much more compatible with organometallic compounds than has previously been assumed. We note that organic chemistry in water is just beginning to gain wider attention, too [2, 20].

Specific reaction modes arising from the reactivity of water have to be taken into account. Consider, for example, the sulfonated hydroformylation catalyst **12**, which undergoes slow but significant P–C bond cleavage (Scheme 5). The resulting phosphinidene intermediate **13** can react with water to give the phosphinous acid **15** via tautomerization of the hydroxyphosphine **14** [19a]. Thus, one must be aware of oxygenated (side)products when working with aqueous organometallics. The field is far from being fully explored.

Supercritical water (the critical point of water is reached at $T = 374.2\,^\circ C$ and $p = 22.1$ MPa) offers opportunities in selectivity for organometallic reactions. The behavior of supercritical water is in several aspects, e.g. heat capacity, viscosity, dissociation constant, etc., quite different from water under normal conditions. This be-



12 13 14 15

R = SO_3Na

Scheme 5 P—C bond cleavage at rhodium(I) hydroformylation catalysts in aqueous medium; see text. * Loss of the rhodium-containing entity.

havior change is due to the loss of hydrogen bridging. The dielectricity constant, for example, changes from 78.5 to 6.0 in supercritical water and becomes quite similar to the dielectricity constants of some organic solvents, such as tetrahydrofuran ($\varepsilon_{\mathrm{THF}} = 7.4$). Several applications of supercritical water have been reported [21] during the recent years. An example is the cyclotrimerization of certain alkynes, which is very selective for benzene derivatives in supercritical water at 374 °C [22]. Organometallic, water-soluble anticancer reagents, normally in the context of amino acid ligands, are also appearing more frequently in the literature now [23]. Important C—C coupling reactions, such as the Heck- and Suzuki-reaction have been successfully transferred to aqueous media recently [24], the use of polymer-fixed homogeneous catalysts which can be disperged in aqueous phase is also becoming more widespread and a particularly interesting development is the use of surface or polymer-anchored catalysts, which are reversibly released into the aqueous solution only in certain defined temperature intervals [25].

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2.3
Characterization of Organometallic Compounds in Water

Gábor Laurenczy

2.3.1
Introduction

It is generally known that the majority of organometallic compounds are stable only in the absence of water, and many of them can be synthesized only under rigorously dry conditions. Although in most cases H_2O acts destructively on organometallics, in some cases the organometallic compounds resist water.

The growing importance of aqueous organometallic chemistry is well demonstrated by the increasing number of publications in this field: both catalytic applications in industrial processes and fundamental research requirements justify this explosion [1–5, 65]. In this section a general overview is given to characterize compounds containing metal–carbon bonds in aqueous solutions. Nowadays pressure has become one of the common parameters used in several laboratories to help improve understanding of structures and processes: this is an additional variable besides temperature, concentration, pH, solvents, ionic strength, etc. Special attention will be given to the pressurization of organometallic systems in water. There are two completely different subsections: the first deals with the effect of the high hydrostatic pressure on organometallics and the second concerns characterization of reactions involving pressurized gases with aqueous organometallics.

2.3.2
General Survey

Nuclear magnetic resonance (NMR) spectroscopy has proven to be the most versatile technique to study organometallic compounds both non-aqueous and aqueous solutions [6, 7]. To explore all the possibilities of ^1H NMR one has to either work in D_2O as solvent or use a water signal suppression technique. Proton chemical shifts can give information about the structure. Generally, protons bound to carbons coordinated to a metal center show a low-field shift, about 1–4 ppm, compared with the metal-free environment. Metal hydrides usually have negative

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

chemical shifts, sometimes down to -40 ppm. In a paramagnetic environment chemical shifts can be very large; the resonances are broadened and sometimes are not even detectable. Substituting protons by deuterium can have a dramatic effect on the rest of the ^{1}H NMR spectrum: since ^{2}H nuclei have a spin value of 1, so the multiplicity of the resonances increase. ^{13}C is naturally one of the most widely used nuclei to elucidate structure and dynamic behavior of organometallic compounds. ^{13}C NMR is applied both when the natural abundance and for compounds enriched in ^{13}C during the synthesis. ^{13}C nuclei have a spin of 1/2, $^{1}J(C,H)$ couplings giving direct information on the number of H atoms linked to the carbon: the CH signal is a doublet, the CH_2 is a triplet and the CH_3 gives a quartet in a ^{13}C spectrum. The $^{1}J(C,H)$ coupling constants are about 250, 160 and 125 Hz in the alkynes, alkenes, and alkanes, respectively. Protons can be decoupled to simplify ^{13}C spectra. In aqueous solution ^{17}O NMR gives the possibility of studying water exchange and dynamic behavior of organometallic aquo complexes. Having a spin of 5/2, the ^{17}O signals are broad and the observed chemical shifts are between 1500 and -250 ppm referenced to the bulk water. The presence of other NMR-active nuclei in the compounds (^{31}P and ^{19}F having a spin of 1/2, ^{14}N and ^{2}H having a spin of 1) and sometimes the metal atoms (^{103}Rh, ^{59}Co, ^{195}Pt, etc.) extend the available information via NMR spectroscopy. To move to a higher magnetic field can simplify the strongly coupled spectra, because chemical shifts in hertz increase with the magnetic field but the coupling constants stay the same (in hertz). Measuring spin–lattice or longitudinal relaxation times, T_1, can help to distinguish between classical dihydrides and molecular hydrogen complexes, the latter having much shorter T_1 values. To resolve difficult structures two-dimensional NMR or special pulse sequences can sometimes be useful. Intramolecular exchange processes can broaden NMR signals, giving further possibilities for determining structures in solution. From variable-temperature NMR spectra the activation enthalpies and entropies of these dynamic processes can be calculated.

Infrared (IR) spectroscopy is particularly helpful to study organometallic compounds [8, 9] especially carbonyl complexes. This is also true in aqueous solutions, although one has to take into consideration the water absorbances in the IR spectral region. The CO stretching vibrations are intense and characteristic of the chemical environment. In the case of several carbonyls in the same molecule, the intensity ratios give structural information and can help to distinguish isomers. In water the useful spectral domain is limited by solvent absorbances and one must use a shorter optical pathlength and compensate for water absorbance.

In the UV-visible spectra of organometallic compounds the spectral bands generally are large and less specific absorbances, due either to the transition metal or to the ligands in the compounds. So optical spectroscopy is used to study kinetic processes, to follow fast reactions (stopped-flow method), or to determine equilibrium constants. UV–visible spectra of the organometallic compounds are frequently studied for photochemical purposes. Preparative-scale photolysis has proven to be a valuable synthetic technique in organometallic chemistry, and also in water [10]. Ligand substitution reactions are often accelerated by UV light.

The acidity of the coordinated water in organometallic aquocomplexes varies over a large range. In aqueous solutions pH potentiometry is one of the most precise methods of determining the acid dissociation constants, K_a, for the organometal ions. Several stable oxidation states of the transition metal ions in organometallic compounds can exist in water. Cyclic voltammetry gives information on the reversibility of the oxidation/reduction processes.

Crystallography, chromatographic techniques, mass spectrometry, and elemental analysis complement the direct and non-destructive methods used to study the organometallic compounds *in situ* in aqueous solutions. In the majority of the cases it is generally accepted that crystallization from aqueous solutions does not change the basic structures, compositions, or bonding orders. However, it is not always the case for bonding distances and angles. One has to be very careful when using crystallographic results to explain structures, reactions, catalysis, or kinetic behavior in solution. Incontestable and independent evidence is necessary that the structure of the studied compounds is the same in aqueous solution as in the solid state.

Computation completes more and more experimental results to explain, interpret, and predict structures, reactivities, and to contribute to the better understanding of reaction mechanisms. The powerful computers and software now available (density functional theory, ab-initio and molecular dynamic calculations, etc.) give calculated parameters closer and closer to the experimental values.

2.3.3
Effect of High Hydrostatic Pressure on Aqueous Organometallic Systems

Since the late 1960s pressure has become a common and important variable in the study of chemical kinetics and equilibrium [11–13, 66]. High-pressure techniques have been developed for the majority of physicochemical methods (NMR, IR, and UV–visible spectroscopy, electrochemistry, etc.), generally up to 200 MPa (= 2000 bars) pressure [14, 15]. Applications for organometallic aqueous systems are shown here.

$$RT \ln(k/k_0) = -\Delta V^{\ddagger} P \tag{1}$$

The pressure dependence of a rate constant, k, is given by Eq. (1) where $\Delta V^{\ddagger}$ is the volume difference between the volume of the transition state and the volume of the reactants. Generally the pressure dependence of $\ln k$ is linear, and the compressibility of the transition state can be neglected. Symmetric reactions like solvent exchange are especially suited to the study of the effect of pressure on the reaction rate, since the reaction volume, ΔV^0, is 0. Since there is no change formation or cancelation during this reaction, the activation volumes determined give direct information about the transition state. In the case of complex formation or non-symmetric ligand-exchange reactions, only the complete volume profile (activation volumes for the forward and for the reverse reaction, reaction volume) allow mechanistic conclusions.

Water exchanges on $[Ru(\eta^6\text{-}C_6H_6)(H_2O)_3]^{2+}$ and on $[Os(\eta^6\text{-}C_6H_6)(H_2O)_3]^{2+}$ [16] were studied by variable-pressure ^{17}O NMR spectroscopy. A home-built high-pressure ^{17}O probehead was used with a Bruker CXP-200 spectrometer up to 200 MPa [17]. The exchange rates (Eq. (2), M = Ru or Os) were in the slow-exchange domain on the NMR timescale, so the rate constants at different pressures were determined from the line broadening of the water signals of the diamagnetic complexes: low-frequency shifts at $\delta -73.4$ ppm for M = Ru and $\delta -66.6$ ppm for M = Os (the organometallic aquo ions were enriched previously in $H_2{}^{17}O$).

$$[M(\eta^6\text{-}C_6H_6)(H_2O)_3]^{2+} + 3\,H_2O^* \rightleftharpoons [M(\eta^6\text{-}C_6H_6)(H_2O^*)_3]^{2+} + 3\,H_2O \quad (2)$$

The slightly positive activation volume values for $[Ru(\eta^6\text{-}C_6H_6)(H_2O)_3]^{2+}$ and for $[Os[\eta^6\text{-}C_6H_6)(H_2O)_3]^{2+}$ show that the water exchange takes place via an interchange mechanism. The same technique, high-pressure ^{17}O NMR [18], was applied to study water exchange on $[Rh(Cp^*)(H_2O)_3]^{2+}$ and $[Ir(Cp^*)(H_2O)_3]^{2+}$ [19], where Cp* = pentamethylcyclopentadienyl anion; on $[Pt(L)(H_2O]^+$ arylplatinum complex [20], where $L = C_6H_3(CH_2NMe_2)_2$-2,6, a terdentate *N,C,N′*-chelating monoanionic ligand, and on $[Ru(H_2O)_5(CH_2{=}CH_2)]^{2+}$ [21]. From the experimental results it was concluded that the water exchange in the triaqua species follows an interchange mechanism with the M–O(water) bond breaking being rate-controlling. In the case of $[Pt(L)(H_2O)]^+$ the large negative activation volume ($\Delta V^{\neq}_{kex} = -9.2 \pm 1.0\ cm^3\,mol^{-1}$) indicates an associative model of activation for the water exchange. The positive volumes obtained for the axial and equatorial water exchange reactions on $[Ru(H_2O)^{eq}_4(H_2O)^{ax}(CH_2{=}CH_2)]^{2+}$ are in accordance with a dissociative activation mode for the exchange process.

A high-pressure stopped-flow technique [22] was applied to study the complex formation reactions between $[Pt(L)(H_2O]^+$ and N_3^- or tmtu, where $L = C_6H_3(CH_2NMe_2)_2$-2,6 [23] or *N,N*-dimethylbenzylamine and pyridine-3-sulfonic acid [24], tmtu = *N,N,N′,N′*-tetramethylthiourea. The large negative activation volumes found for the forward and reverse reactions ($\Delta V^{\neq}$ values are between -10.1 and $-12.4\ cm^3\,mol^{-1}$) are evidence for the operation of an associative activation mode for the substitution.

Methyltrioxorhenium, one of the most versatile organometallic catalysts [25–28], hydrolyzes very slowly in dilute aqueous solution. This reaction was studied as a function of pressure by a spectrophotometric method [29]. The hydrolytic reaction (Eq. 3) was followed at 268.5 and 227.0 nm, where the absorbance changes were maximal and it was found the reaction has the experimental rate law described by Eq. (4).

$$CH_3ReO_3 + OH^- \longrightarrow CH_4 + ReO_4^- \tag{3}$$

$$-\,d(CH_3ReO_3)/dt = k\,[OH^-][CH_3ReO_3] \tag{4}$$

An UV–visible–near-IR high-pressure optical unit [30] equipped with pillbox cells [31] was used for the kinetic experiments. Here the observed small negative activation volume does not necessarily indicate an associatively activated reaction pathway. Indeed, the $\Delta V^{\neq}$ determined is a composite one, as it includes the activation volume of the rate-determining step and the unknown reaction volume. Attempts to perform the reverse reaction, the synthesis of CH_3ReO_3 from CH_4 (200 MPa) and ReO_4^-, failed, so the hydrolysis of CH_3ReO_3 seems to be irreversible.

The pressure dependences of formation, homolytic and heterolytic fission of chromium–carbon bonds in aqueous solutions were investigated for the $[(H_2O)_5CrR]^{2+}$ complexes, where R = different alkyl groups [32–34]. The reactions (Eqs. 5 and 6) were followed by spectrophotometry [35], the alkyl radicals being generated *in situ* by pulse radiolysis [36].

$$[Cr(H_2O)_6]^{2+} + \bullet R \rightleftharpoons [(H_2O)_5CrR]^{2+} + H_2O \tag{5}$$

$$[(H_2O)_5CrR]^{2+} + H_2O \longrightarrow [(H_2O)_5CrOH]^{2+} + RH \tag{6}$$

The determined activation volumes for complex formation ($\Delta V^{\neq}$ in $cm^3\,mol^{-1}$, between + 3.4 and + 6.3 for the different alkyl groups) and the large volumes of reaction support a dissociative interchange mechanism for $[(H_2O)_5CrR]^{2+}$ formation. Similar reactions were studied for the $[(H_2O)_2ML]$ transition metal complexes with the $\cdot CH_3$ radical, where L = nitrilotriacetate (nta) for M = Co(II) and Fe(II); 1,4,8,11-tetraazacyclotetradecane (cyclam) for M = Ni(II) [37–39]. The activation volumes calculated for the $[ML(H_2O)(CH_3)]$ complex formation, $\Delta V^{\neq}$, and the suggested mechanisms are in accordance with those found for the water exchange on these aquo ions.

The acidolysis reaction of dimethylmercury as a function of pressure [40] was studied in aqueous medium, in dilute HCl and HBr solutions (Eq. (7), X = Cl or Br) by a conductivity technique [41]. The volumes of activation, $\Delta V^{\neq}$, were measured to be -22.0 and $-37.0\ cm^3\,mol^{-1}$ for X = Cl and Br, respectively.

$$(CH_3)_2Hg + HX \rightleftharpoons (CH_3)HgX + CH_4 \tag{7}$$

As an explanation of the large negative values the authors suppose that the activated complexes are much more polar than the reactants and the solvation term contributing to the volume of activation is larger than the contributions arising from breakage or formation of covalent bonds on the reacting species in the transition state.

2.3.4
Aqueous Organometallics with Pressurized Gases

Reactions of organometallic compounds with pressurized gases in water are becoming more and more important for industrial applications (cf. Section 6.1). High pressure increases the dissolved gas concentration according to Henry's law. It has a twofold effect, thermodynamic and kinetic. The higher concentration of the dissolved compound shifts equilibrium toward product formation, increasing the yield. Higher concentrations accelerate the second- and higher-order reactions, and in the case of parallel reactions help to increase the formation of the desired product. Applications of pressurized gases in aqueous organometallic systems are described here.

The synthesis [42] of one of the simplest organometallic aquo ions, $[Ru(CO)(H_2O)_5]^{2+}$, was carried out under 5.0 MPa CO pressure in a 10 mm sapphire NMR tube [43] (Eq. 8). The $[Ru(H_2O)_6]^{2+}$ was previously enriched with 10% $H_2{}^{17}O$, so the reaction was followed simultaneously by ^{13}C and ^{17}O NMR spectroscopy. During the reaction the disappearance of the ^{17}O signal of the $[Ru(H_2O)_6]^{2+}$ at −192 ppm and the appearance of two new resonances in a 1:4 ratio (at −29.3 ppm and −154.8 ppm) were observed, corresponding to the water molecules axial and equatorial to the CO in $[Ru(CO)(H_2O)^{ax}(H_2O)_4^{eq}]^{2+}$. At the same time the ^{13}C NMR spectrum shows the growth of a new signal at 205.5 ppm due to the coordinated CO, next to the signal of the free CO (187.0 ppm). The FT-IR spectra [44] of $[Ru(CO)(H_2O)_5]^{2+}$, measured in a high-pressure IR cell, shows the characteristic stretching frequency at 1971 cm^{-1} due to the coordinated CO (the free-CO frequency in water appears at 2134 cm^{-1}). Further substitution of H_2O by CO in $[Ru(CO)(H_2O)_5]^{2+}$ is very slow [60, 62]. The water exchange on the resulting complexes, *cis*-$[Ru(CO)_2(H_2O^{eq})_2(H_2O^{ax})_2](tos)_2$, $[Ru(CO)_3(H_2O)_3](ClO_4)_2$ and on $[Ru(CO)(H_2O^{eq})_4(H_2O^{ax})](tos)_2$, as well as the ^{17}O exchange between the bulk water and the carbonyl oxygens have been studied by ^{17}O NMR spectroscopy. The water exchange of equatorially and axially coordinated water molecules follow an I_d mechanism. The X-ray crystallographic structures of $[Ru(CO)(H_2O)_5](tos)_2$ and *cis*-$[Ru(CO)_2(H_2O)_4](tos)_2$ have been determined.

$$[Ru(H_2O)_6]^{2+} + CO \longrightarrow [Ru(CO)(H_2O)_5]^{2+} + H_2O \qquad (8)$$

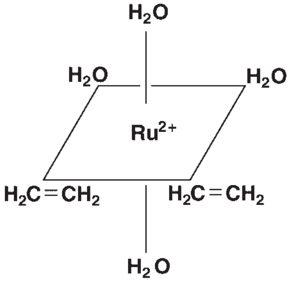
Several olefin complexes of the Ru(II) aquo ion [45–47] and of the other Ru complexes [48, 49] have been synthesized and characterized in the ring-opening metathesis polymerization (ROMP; cf. Section 6.13) or olefin isomerization reactions. The simplest olefin complex of Ru was also observed, isolated, and characterized under ethylene pressure [50]. A $H_2{}^{17}O$-enriched aqueous solution of $[Ru(H_2O)_6]^{2+}$ was pressurized with ethylene and mixed. The reaction (Eq. 9) was followed by ^1H, ^{13}C, and ^{17}O NMR spectroscopy.

$$[Ru(H_2O)_6]^{2+} + CH_2{=}CH_2 \longrightarrow [Ru(CH_2{=}CH_2)(H_2O)_5]^{2+} + H_2O \quad (9)$$

After 6 h the ^{17}O NMR spectra showed the complete loss of resonance at −192 ppm due to the hexaaqua Ru(II). At the same time new signals appeared corresponding to $[Ru(CH_2{=}CH_2)(H_2O)_4^{eq}(H_2O)^{ax}]^{2+}$. After 18 h of mixing the NMR spectra show the substitution of a second water molecule (Eq. 10).

$$[Ru(CH_2{=}CH_2)(H_2O)_5]^{2+} + CH_2{=}CH_2 \longrightarrow [Ru(CH_2{=}CH_2)_2(H_2O)_4]^{2+} + H_2O \quad (10)$$

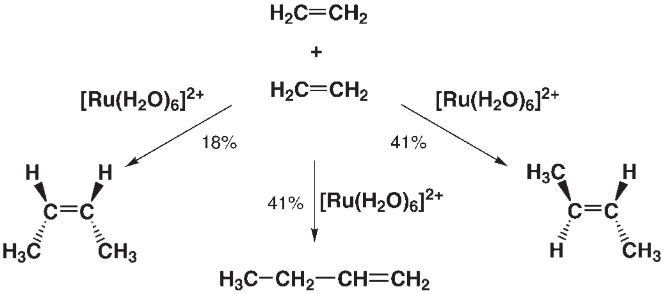
The ^1H, ^{13}C and ^{17}O NMR signals characteristic for the *cis*-$[Ru(CH_2{=}CH_2)_2(H_2O)_4]^{2+}$ cation (Structure **1**) are ^1H: at 3.81 ppm (free $CH_2{=}CH_2$ at 5.46 ppm).



1

After three days on mixing, an organic phase was formed above the aqueous solution. The analysis of this new phase showed the presence of free butenes: *cis*-2-butene (18%), *trans*-2-butene (41%) and 1-butene (41%). This aqueous catalytic dimerization of ethylene is not stereoselective (Scheme 1), all possible butenes, except for 2-methylpropene, being formed. No higher oligomers were detected, probably due to the low solubility of butenes in aqueous solutions and to the lack of their coordination to Ru(II). Besides $[Ru(CH_2{=}CH_2)(H_2O)_5]^{2+}$ and *cis*-$[Ru(CH_2{=}CH_2)_2(H_2O)_4]^{2+}$, no more highly substituted Ru(II) complexes were isolated or detected.

The catalytic activity of the HRh(CO)[P(*m*-$C_6H_4SO_3Na)_3]_3$ complex [51] was checked in aqueous solution up to 20.0 MPa CO : H_2 (1 : 1) pressure [52, 53]. The high-pressure NMR spectra of HRh(CO)[P(*m*-$C_6H_4SO_3Na)_3]_3$ show the characteristic chemical shifts and infrared resonances. This complex does not show any further substitution of phosphine ligands by CO. The catalytic activity in hydroformylation reactions of the similar $HRh(CO)(PPh_3)_2$ complex in toluene has been proven to be linked to the coordinatively unsaturated $HRh(CO)_2(PPh_3)$ and $HRh(CO)(PPh_3)_2$ species. The absence of the further-substituted complexes explains the lower catalytic activity and the higher selectivity towards *n*-aldehydes. The HRh(CO)[P(*m*-$C_6H_4SO_3Na)_3]_3$ complex is successfully applied as an aqueous catalyst in industrial hydroformylation processes [54–57].



Scheme 1

Aqueous solutions of ruthenium clusters $[Ru_3(CO)_{12-x}(P\{m\text{-}C_6H_4SO_3Na\}_3)_x]$, where $x = 1$, 2 or 3; and $[H_4Ru_4(CO)_{11}(P\{m\text{-}C_6H_4SO_3Na\}_3)]$, as catalyst precursors, were used in the hydrogenation of non-activated alkenes [61]. Each cluster displays catalytic activity under moderate conditions (60 bar H_2 pressure, $T = 333$ K) with turnovers up to 500.

Ligand substitution on $M(CO)_5L$ complexes, where M = Mo or W and $L = P(m\text{-}C_6H_4SO_3Na)_3$ or PPh_3, were studied under 3.4 MPa CO pressure in water and a water–THF (1:1) mixture [58]. The reactions (Eq. 11) were followed *in situ* by infrared spectroscopy in a reactor cell [59] between 388 and 423 K.

$$M(CO)_5L + CO \longrightarrow M(CO)_6 + L \tag{11}$$

Under constant CO gas pressure the kinetics of the substitution reaction can be described by a first-order rate law. The calculated activation enthalpies and entropies for the $P(m\text{-}C_6H_4SO_3Na)_3$ ligand are quite similar to those determined for the analogous processes involving the unsulfonated PPh_3 ligand: $\Delta H^{\ddagger}$/kcal mol^{-1} ($\Delta S^{\ddagger}$/eu) is 31.8 (−0.73) for M = W, $L = P(m\text{-}C_6H_4SO_3Na)_3$, 32.6 (−1.4) for M = W, $L = PPh_3$, 28.8 (−4.2) for M = Mo, $L = P(m\text{-}C_6H_4SO_3Na)_3$ and 30.5 (0.17) for M = Mo, $L = PPh_3$ in water/THF (1:1) solvent.

Recently it has been shown that the water-soluble cluster cations $[(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2Ru_3(\mu_3\text{-}O)(\mu_2\text{-}H)_3]$ and $[(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2Ru_3(\mu_3\text{-}O)(\mu_2\text{-}OH)(\mu_2\text{-}H)_2]$ are highly active in the catalytic hydrogenation of benzene to cyclohexane in aqueous solutions [63, 64]. Mass spectroscopy, NMR, and modelling support the hypothesis that the substrate molecule is incorporated in the hydrophobic pocket spanned by the three arene ligands in these clusters, suggesting the catalytic reaction to occur within these host–guest complexes without the substrate being coordinated to a metal centre [63].

2.3.5
Concluding Remarks

Many organometallic compounds are astonishingly stable in protic media and in aqueous solution. There is an increasing interest in the use of water as solvent for industrial organic reactions. The main advantages are the ease of separation processes as well as economic and ecological considerations. In aqueous solution or in a two-phase system homogeneous catalytic organic syntheses involve organometallic compounds. Structural information on the catalysts leads to better understanding of the reaction mechanism, to improve the yield and the selectivity. Non-destructive analytical methods play a key role in this respect. Although a very great number of catalytic organic syntheses have been studied under high gas pressures in autoclaves, the majority of investigations have dealt only with the reaction products when the reaction was complete, after the release of pressure, and analyzed them mainly by chromatographic methods (HPLC, GC). As has been shown, the availability of non-destructive *in situ* methods allows these reactions to be followed in detail. As can be realized, multinuclear NMR plays a predominant role in this field. New organometallic aquo ions have thus been synthesized, isolated, and characterized.

Techniques applying high hydrostatic pressure have proven to be one of the most powerful methods to obtain information about the reaction mechanisms and about the transition state. These techniques were used to study water exchange on organometallic aquo ions by variable-pressure ^{17}O NMR. The activation volumes, $\Delta V^{\ddagger}$, have shown whether bond breaking or bond making is the rate-determining step in the exchange reaction.

These examples confirm that water as a solvent offers a number of variations to the possibilities offered by organic solvents in organometallic reactions and underline the importance of the analytical methods to characterization of organometallic compounds in water. There is still a huge potential for the use of water as the solvent of choice for homogeneous or biphasic catalysis.

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3
Catalysts for an Aqueous Catalysis

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

3.1
Variation of Central Atoms

3.1.1
Transition Metals

Donald J. Darensbourg, Cesar G. Ortiz

3.1.1.1
Introduction

The use of water as a suitable medium for catalysis has received much attention in recent years [1]. The increasing interest in this field stems from obvious economic and safety considerations. From an industrial point of view, an aqueous medium translates into waste reduction costs as well as the potential recovery of the catalyst via a biphasic process. The latter process is the foundation of the Ruhrchemie/Rhône-Poulenc hydroformylation of alkenes, where, in 1998, it was reported to produce approximately 10% of the world's C_4–C_5 aldehyde capacity [2]. Furthermore, replacing flammable, carcinogenic, and explosive organic solvents with water leads to a safer working environment (cf. Section 5.2).

One of the largest beneficiaries of water utilization has been organic chemistry (through the use of organometallic catalysts; cf. Sections 2.2 and 2.3). Historically, an unsuccessful reaction could be attributed to water contamination. Ironically, recent discoveries have shown that the presence of water is advantageous as enhanced rates and better stereoselectivity are sometimes obtained [3]. Our contribution to this edition focuses on transition metals in aqueous catalysis. Great advances in this field have been made since the first edition of this book was released in 1998 [1 b]. Herein, we wish to highlight some of these developments. The framework of this chapter will be similar to that employed in the first edition.

Water solubilizing of the metal center can be achieved in two general ways:

(1) Coordination of water-soluble ligands has been the most attractive route. These ligands range from traditional sulfonated phosphines to those utilizing nitrogen donors which are capable of hydrogen bonding to the surrounding aqueous environment.

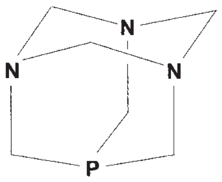
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

(2) Direct interaction of water molecules at the metal center can lead to a water-soluble complex. As will be shown, addition of organic moieties to such water-coordinated complexes affords more labile water molecules. This in turn leads to potential active sites for substrate binding in the corresponding catalysts.

3.1.1.2
Water-soluble Catalysts by Virtue of Water-soluble Ligands

The most well known water-soluble ligands used in aqueous catalysis today are based on tertiary phosphines. Their neutral donating nature can effectively stabilize the metal center throughout catalytic processes. In addition, they participate in reduction of the metal center; for example, in carbon–carbon bond formation reactions typical group 10 metals, M^{+2}, are reduced to the active M^0 species. Common tertiary phosphines are usually made water-soluble by sulfonation, although carboxylate [4], ammonium [5], and phosphonium salts [6] and hydrolic [7] groups are effective alternatives. Other common water-soluble ligands include those incorporating nitrogen-based donors such as 1,3,5-triaza-7-phosphaadamantane (PTA) (Structure **1**) [8].



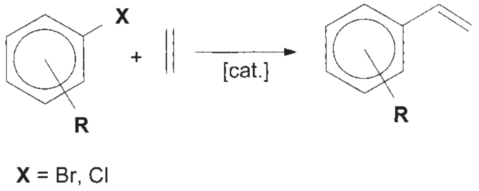
1

Since the initial discovery and application of the *meta*-monosulfonated triphenyl phosphine (TPPMS) [9] much success in aqueous catalysis has been achieved via the use of the further sulfonated derivatives such as TPPDS [10] and TTPTS [11] (cf. Sections 3.2.1 and 6.1.1). Upon surveying the literature, one encounters an array of applications of metal-catalyzed reactions involving these water-soluble ligands. Herein, we wish to focus on three fundamental reactions that illustrate how a number of metals may be used to achieve (1) carbon–carbon bonds, (2) hydrogenation, and (3) hydroformylation of unsaturated compounds. Through the years several transition metals have been found to be more active than others for a specific transformation. For example, group 10 metals, specifically palladium, have had a great impact in the field of carbon–carbon bond formation, while rhodium is heavily relied upon in the hydroformylation of lower molecular weight alkenes.

3.1.1.2.1
Carbon–Carbon Bond Formation (CCBF)

Carbon–carbon bond formation (CCBF) reactions lie at the heart of organic synthesis, and rely heavily on group 10 metal catalysts. Historically, such catalysts were designed for organic media, as they were based on aromatic, hydrophobic tertiary phosphines [12]. However, because of the hydrophilic nature of organic products (especially those in natural synthesis) and the hydrophobic nature of these traditional catalysts (e.g., Pd[PPh_3]$_4$), water-soluble catalyzed CCBF reactions would increase efficiency by bypassing time-consuming protection/deprotection steps. With this in mind, implementation of small, water-soluble phosphines in catalysis has led to effective coupling of various organic substrates in aqueous media.

With regard to CCBF reactions, no metal has had a greater impact than palladium. Apart from the favorable economic standpoint, this metal has been shown to mediate a variety of coupling reactions. In the palladium-catalyzed [13] Heck reaction using TPPMS, the coupling of various aryl halides with alkenes was achieved by Kiji [14] and Calabrese [15]. In the former report, styrene derivatives were successfully synthesized in moderate to quantitative yields via the coupling of various aryl halides with ethylene (Eq. 1). As is typical for these types of reactions, the best results are obtained using a water/acetonitrile solvent system. Additionally, using Pd(TPPMS)$_3$ as a catalyst, the Suzuki coupling of various aryl halides with boronic acids was accomplished (Eq. 2) [15].



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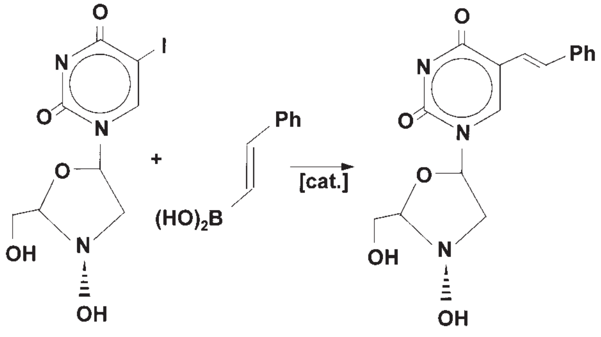
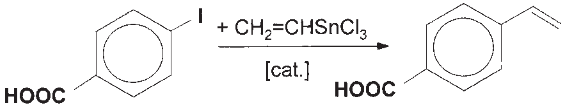


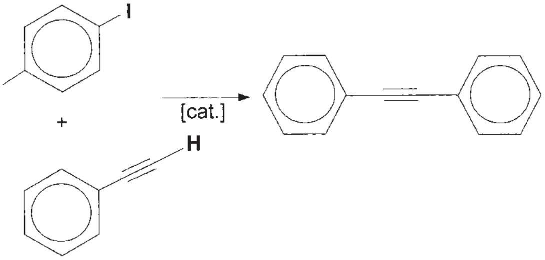
(2)

In this manner, unprotected nucleosides can be coupled to boronic acids in moderate yields. In the Stille coupling reaction, the palladium catalyst formed *in situ* from $PdCl_2$ and four equivalents of TPPMS was used effectively to couple various aryl halides with R groups on $RSnCl_3$ (Eq. 3) [16]. The use of this catalyst improved the yield and reproducibility compared to the use of $PdCl_2$ alone. The Sonogashira coupling of alkynes with aryl halides is an additional route for the formation of sp–sp^2 bonds. The use of this water-soluble phosphine with Pd(OAc)$_2$



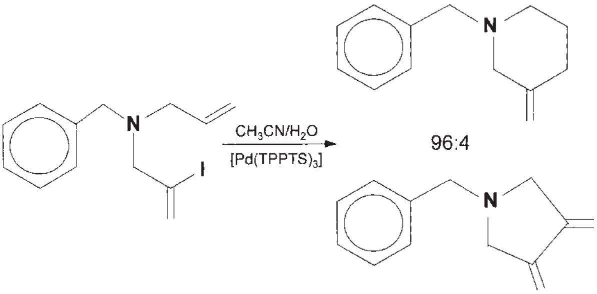
(3)

was also shown to couple many terminal acetylenes effectively with aryl halides, with yields being quantitative in some instances (Eq. 4) [15]. The use of the doubly sulfonated triphenylphosphine, TPPDS, in catalysis (using Pd[TPPDS]$_3$) has been studied to a lesser extent. An example of its use includes the Heck reaction of iodobenzene with methyl acrylate [17]. This report indicates that TPPDS is comparable to TPPMS and TPPTS in product yield and palladium leaching (cf. also Section 6.6).



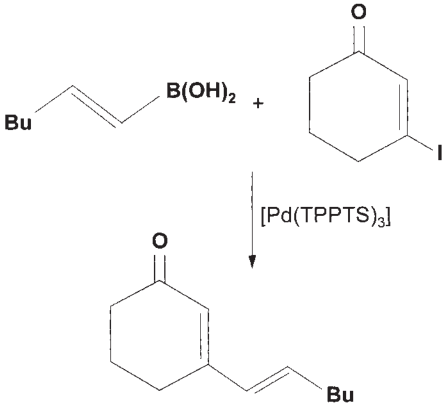
(4)

Coordinating the triply sulfonated analog, TPPTS, to palladium has led to improvements in CCBF reactions. For example, Genêt previously reported the selective intramolecular Heck-type reaction of various substrates to produce the cyclized product in good yield (Eq. 5); intramolecular Heck coupling [18]. One of the most important features of the Pd(TPPTS)$_3$ catalyst involves the regioselectivity associated with the reaction. For these types of reactions, carried out in organic media, the *exo* product is usually favored. However, with the use of this catalyst, the *endo* species was the predominant product.



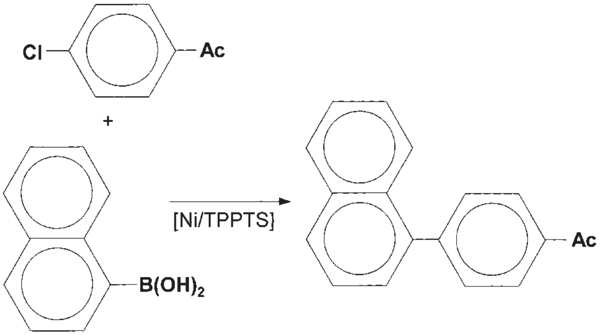
(5)

The use of this catalyst in Suzuki coupling reactions has also been successful. The coupling of various aryl halides with alkenyl borates and boronic acids has been achieved to afford products in good yields (Eq. 6) [19]. One of the advantages of this system concerns the mild reaction conditions that are employed. There have been very few reports involving nickel as the metal center in CCBF. In one



(6)

report, an array of boronic acids were coupled with various aryl chlorides using a $NiCl_2$(dppe)/TPPTS catalysts [20]. This report is of importance due to the use of aryl chlorides that were less reactive than the corresponding bromides and iodides (Eq. 7). In addition, the catalyst was not poisoned by sulfur-containing substrates, allowing these functionalized substrates to be used. As illustrated in Eq. (7), yields up to 99% were reported for the naphthalene boronic acid derivative. In a separate report, Arai and workers developed a Ni/TPPTS catalyst immobilized on an ethylene glycol film on a silica support [21]. This heterogeneous catalytic system was found to couple iodobenzene effectively with various terminal alkenes in the presence of an inorganic base such as potassium acetate. At 140 °C, deactivation was minimal after 20 recycling cycles. The coupling of two distinct alkynes for the formation of unsymmetrical butadiynes is an ongoing challenge due to the competing homocoupling. However, using the catalyst prepared *in situ* from $Pd(OAc)_2$/TPPTS, unsymmetrical butadiynes were synthesized in good yields under moderate conditions with very little or no production of homocoupled products (Eq. 8) [22]. Typically, Cu^I is added as a promoter, however, in this instance, no promoter was necessary.



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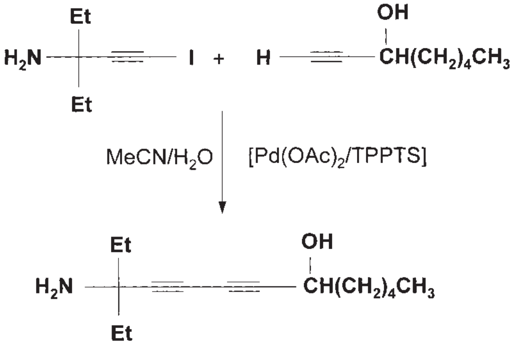
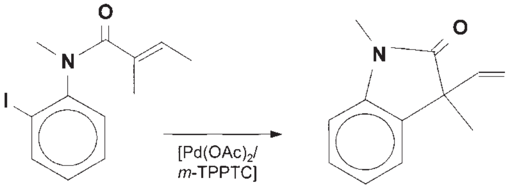


(8)

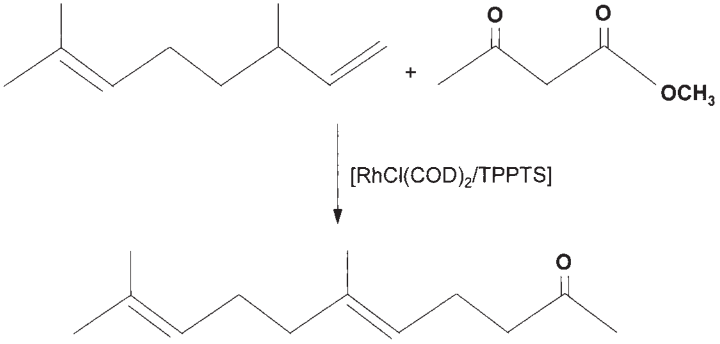
The catalyst was also shown to be effective for the production of indolic and furanic derivatives by sp^2-sp coupling of aryl halides and alkynes followed by intramolecular cyclization. Again, mild reaction conditions (i.e., 25 °C) were employed and no Cu^I promoter was needed.

Another example using palladium as the metal center involves the use of a carboxylic phosphine, which was effective in the intra- and intermolecular Heck reaction of a dimethyliodo derivative and of iodobenzene, respectively, with ethyl acrylate [23]. For the intramolecular reaction, the cyclic amide was produced in nearly quantitative yields using mild reaction conditions (Eq. 9). A comparison with the TPPTS system reveals the *m*-TPPTC (*m*-triphenylphosphine tricarboxylic acid [Li salt]) analog to be a more efficient system. After one hour of reaction, a 60% conversion was observed compared to approximately 45% with the TPPTS system.



(9)

The examples utilizing other metals for CCBF of organic substrates are very limited. The cyclopropanation of alkenes and diazoacetates has been achieved through the use of a ruthenium-based catalyst employing the chiral bis(hydroxymethyldihydrooxazolyl)pyridine ligand [24]. This catalyst was the first active system found utilizing an aqueous or protic medium for this process. Additionally, enhanced enantioselectivities and yields were observed with the addition of water. Rhodium has also been shown to be effective in carbonyl additions and conjugated additions of various substrates using phenyltin derivatives in water under an air atmosphere [25]. In the commercial synthesis of geranyl acetone, a Rh/TPPTS (21 : 1) catalyst is used to effectively mediate the nucleophilic addition of myrcene to methyl acetoacetate (Eq. 10) [26]. The advantages of this system are the ease of product separation along with its provision of exclusive 1 : 1 additions with high regioselectivity.



(10)

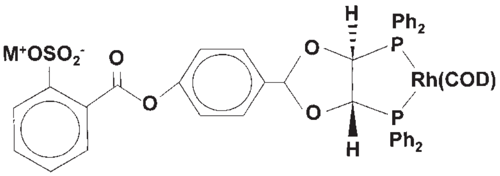
3.1.1.2.2

Hydrogenation

Hydrogenation of unsaturated organic substrates with stereo control is of current interest to many research laboratories worldwide. Such selectivity is crucial to areas such as natural product synthesis, and the use of water as a solvent is ideal due to the hydrophilic nature of many of these reagents. Additionally, the heterolytic cleavage of H_2 in water is energetically favored when compared to that in organic solvents, and with the aid of a transition metal catalyst the process can occur readily. There are numerous reviews related to this subject, and a more in-depth overview is provided elsewhere in the text [1, 27]. As with CCBF reactions, the most widely employed phosphines for this process have been the sulfonated derivatives, TPPMS [9] and TPPTS [11] (see Sections 6.2 and 6.3). Historically, hydrogenations have been accomplished with the aid of metals from the platinum group, most often Ru, Rh, Ir, Ni, and Pd. Substrates which may be reduced by hydrogen include simple alkenes, aldehydes, ketones, arenes, nitroaromatics, and other unsaturated molecules.

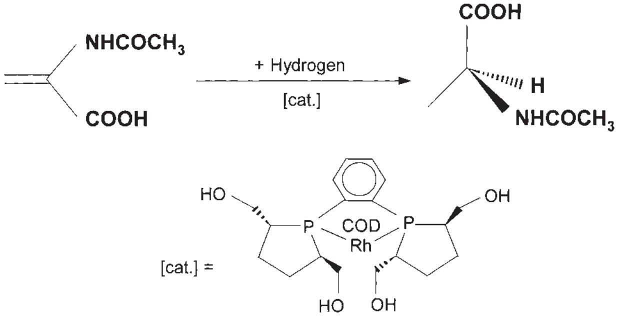
The reduction of simple alkenes has been accomplished by several metal catalysts. One example involves the use of $RhCl_3$ and TPPTS to generate the active catalyst *in situ* utilizing a biphasic water system to yield products in quantitative yields [28]. An important attribute of this catalyst involves its selective nature as the more accessible double bonds are readily saturated and internal double bonds are unaffected. The reduction of 1-hexene has also been achieved through the use of a tungsten-based catalyst, $[W(CO)_3(CH_3CN)(TPPTS)_2]$, where approximately 90% conversion was obtained at 100 °C [29]. As with many other catalytic systems, the order of activity decreases with substrates containing internal double bonds or unsaturation near steric hindering groups. The water-soluble, heterocyclic PTA (cf. Structure **1**) has also been found to be an effective ligand in aqueous catalysis when coordinated to various metals [8]. The $[RhCl(PTA)_3]$ catalyst was found to reduce *trans*-cinnamaldehyde to 3-phenylpropionaldehyde selectively with turnover frequencies on the order of 82 h^{-1} at 50 °C [30a–c]. Using the methylated derivative of PTA, the $[RhI(CO)(Me\text{-}PTA^+I^-)_3]$ catalyst selectively reduces the C=C double bond in *trans*-cinnamaldehyde using a biphasic medium under 0.1 MPa of H_2 [31]. From these studies, it was concluded that this system is comparable to the aforementioned nonmethylated derivative.

As previously mentioned, the introduction of chiral centers to organic substrates via enantioselective hydrogenation is of great interest for industrial processes, especially those dealing with pharmaceuticals, agrochemicals, fragrances, etc. The majority of research conducted in this field generally deals with the use of enamide- and ester-substituted alkenes due to the fact that coordination of a heteroatom to the metal center is required in order to produce one enantiomer selectively. There are numerous examples of prochiral water-soluble phosphines that have been used to enantioselectively hydrogenate alkeneic substrates effectively. Börner and co-workers recently reported the hydrogenation of methyl-(Z)-α-acetamidocinnamate utilizing a chiral sulfonated diphosphine ligand (Structure **2**) [32].



2

The [Rh(COD)(**L**)$^+BF_4^-$ catalyst was found to produce the (R) product in 70.5% *ee*. A polyhydroxydiphosphine (BASPHOS; Structure **3**) ligand was also found to effectively hydrogenate 2-acetamidoacrylic acid to render the (S) product in 99.6% *ee* (Eq. 11) [33].



(11)

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Additionally, a Rh(I) dissacharide system has also been used to hydrogenate dehydroamino acids and their esters asymmetrically in water and in a biphasic aqueous/organic medium [34]. In one example, α-acetamidocinnamate was completely reduced (100% conversion), rendering the (S) product in 90% *ee* in one hour using 1 mol% of the catalyst in water. Other ligand frameworks coordinated to Rh(I) and Ru(I) have appeared through the years, such as Vries' sulfonated BDPP [35] and sulfonated BINAP [36], respectively. Although rare, iridium-based catalysts have been used in hydrogenations. Crabtree and co-workers have demonstrated the hydrogenation of allylbenzene using a biphasic water/allylbenzene medium with $[(COD)Ir(PPh_3)Py]PF_6$ and the poly(ethylene glycol)-bound complex, PEG-$(OC_6H_4PPh_2)$-[Ir], as the catalysts [37]. The former exhibited a maximum TOF of 62 h^{-1} while the latter proved to be less active, with a TOF on the order of 23 h^{-1}.

A wide array of catalytic systems have been investigated to reduce aliphatic and aromatic aldehydes such as crotonaldehyde, propionaldehyde, citral, and benzaldehyde. Using ruthenium as the metal center, Basset and co-workers have developed a series of water-soluble catalysts for the hydrogenation of propionaldehyde [38]. $[RuCl_2(TPPTS)_3]$, $[HRu(OAc)(TPPTS)_3]$, $[RuH_2(TPPTS)_4]$, and $[HRuCl(TPPTS)_2]$ were all found to be very active at 100 °C. Furthermore, the reactions can be carried out under milder conditions with the addition of salts such as NaI; for example, enhanced rates and selectivities were observed at 35 °C. The effect of adding $ZnCl_2$ to the $[RuCl_2(TPPTS)_3]$ system has been studied recently by Bajaj and co-workers [39]. A maximum of 50% conversion with exclusive cyclohexane production was observed with the use of $ZnCl_2$ in the hydrogenation of benzene. Darensbourg and co-workers have reported the use of a ruthenium/PTA complex ($[RuCl_2(PTA)_4]$) with formate, as the hydrogen source, to reduce benzaldehyde to benzyl alcohol with turnover frequencies of 22 h^{-1} at 80 °C [30a, b]. The biphasic medium employed allowed for catalyst recycling without significant loss of activity.

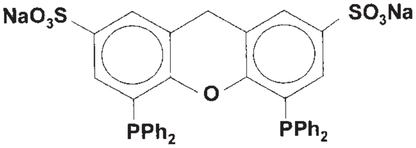
A challenge in this area involves the partial reduction of aldehydes in the presence of C=C functionalities since aldehyde groups are easier to hydrogenate than carbonyls. A suitable substrate for investigation is *trans*-cinnamaldehyde, which if fully reduced will be converted to 3-phenylpropanol. Intermediate products leading to this species may be 3-phenyl-2-propenol (from first reducing the C=O group), and 3-phenylpropionaldehyde (from saturation of the C=C bond). Numerous catalytic systems have appeared throughout the years, yielding different product distributions. Examples of such systems include $[RuCl_2(CH_3CN)/TPPMS]$ [40] and $[\{OsCl_2(TPPMS)_2\}_2]$ [41], which exclusively form 3-phenyl-2-propenol. The former system produces the product in the presence of Na_2SO_4 with high conversion while the osmium system was found to be less active. A palladium-based system, $[PdCl_2(TPPTS)_2]$, was also found to be active for this type of reduction [42]. The catalyst was found to produce predominantly 3-phenylpropanal under basic conditions in the presence of Na_2CO_3, with high conversions. The hydrogenation of unsaturated aldehydes to their respected unsaturated alcohols has also been reported with the use of *cis*-$RuCl_2(PTA)_4$ [43]. In one of the earlier studies, Bényei and Joó utilized $RuCl_2(TPPMS)_2$, $RhCl(TPPMS)_3$, and $IrCl(CO)(TPPMS)_2$ as catalysts for the hydrogenation of benzaldehyde [44]. The most active species was found to be the ruthenium-based system, whereas the iridium catalyst's performance was much poorer. Selectivities associated with several of these systems are highly dependent on the pH of the medium. In general, acidic solutions tend to cause the reduction of the C=C group while basic solutions lead to the hydrogenation of the carbonyl moiety. These effects are all due to the formation of different catalytic species, which selectively affect one functionality over another [45].

3.1.1.2.3
Hydroformylation

Without a doubt, the most successful demonstration of aqueous catalysis has been the hydroformylation of low molecular weight terminal alkenes. The use of an aqueous biphasic medium to separate catalysts from products for this process was first envisioned by Kuntz at Rhône-Poulenc; this eventually led to the development of a water-soluble rhodium catalyst [46] (cf. Section 6.1.1).

The active catalyst, $HRh(CO)(TPPTS)_3$, has several advantages over other catalytic systems, such as supported cobalt systems [47]. First, the completely water-soluble nature of the catalyst allows for the reaction to take place *exclusively* in the aqueous phase, leading to no appreciable metal leaching. Additionally, the active catalyst is based on rhodium, a very active metal for hydroformylation as was previously illustrated by Wilkinson's catalyst [48]. Water has very favorable economic and safety properties over traditional organic solvents. Of course, the very distinct chemical and physical properties of water with respect to organic compounds (i.e., aldehyde products in hydroformylation) makes it an ideal solvent to facilitate separation of products from the precious catalyst (see Section 5.2). Finally, the catalyst is relatively robust and not sensitive to sulphur- or oxygen-containing compounds, adding yet another economic advantage, as monomers do not need be purified to a great extent [2]. Today, this process is responsible for the production of many terminal aldehydes [49]. Combined with the plant operating in Oberhausen, Germany, now owned by Celanese AG (the former Ruhrchemie AG) and South Korea, approximately 800 000 tons/year of butyraldehyde is currently manufactured by this process.

The years following the initial discovery of the Rh(I)/TPPTS process have led to the development of new and improved biphasic catalytic systems which are mainly based on rhodium as the metal center. However, it is worth noting that although many of these systems have been found to exhibit either enhanced activity or *n*/*i* selectivity (or both) compared to the aforementioned process, other factors, such as degradation of the ligand, have impeded their implementation in industry. For example, the sulfonated diphosphine BISBIS (cf. Structure **2**; Section 3.2.2) chelated to Rh^I exhibited higher activites and productivities than the Rh/TPPTS system [50]. In addition, the *n*/*i* ratio was also improved while utilizing a BISBIS/Rh ratio that was 12 times lower than that of TPPTS/Rh system. Other examples of rhodium catalysts are those incorporating BINAS [51] (cf. Structure **11**; Section 3.2.1), NORBOS [51 a, c], and 2,7-bis($SO_3^-Na^+$)-XANTHPOS [52] as the water-soluble ligands (**4**).



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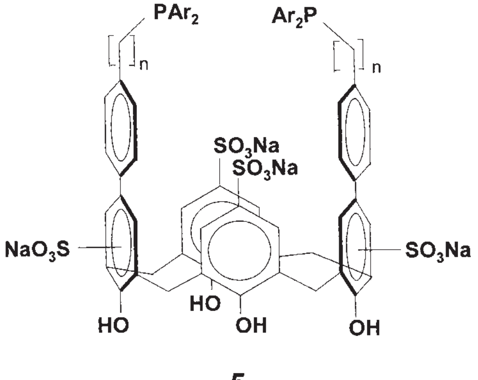
The [Rh]-BINAS system was found to produce *n*-butyraldehyde with a TOF of 10 000 h^{-1} with 99 : 1 *n*/*i* selectivity. This increase in activity and selectivity over the traditional Rh/TPPTS system (i.e., 95 : 5 *n*/*i* selectivity) illustrates the effects on the electronic and steric properties of the ligand. In addition, although the phosphine/rhodium ratio was much lower for the BINAS than the TPPTS system (6.8 : 1 vs. 80 : 1 for BINAS and TPPTS, respectively), easier degradation and the higher prize of BINAS has led to a continued use of TPPTS in industry (cf. Chapter 1).

Other water-soluble monodentate ligands coordinated to rhodium and used for this purpose include $P(CH_2OH)_3$ [53] and PTA [8]. The former was found to effectively convert 1-pentene to hexanal utilizing a benzene/water biphasic solvent system at 100 °C under 4 MPa of syngas. For the latter, $ClRh(CO)(PTA)_2$ was found to effectively convert 1-hexene to 1-heptanal and 2-heptanal in 53 and 41% yield, respectively, with an average TOF of 162 h^{-1} at 60 °C under 3 MPa of syngas [31, 54].

The hydroformylation of higher molecular weight substrates has been a challenge in aqueous catalysis due to the substrates' less soluble nature in water. Several techniques have been developed to facilitate hydroformylation. These techniques can be classified in four categories, depending on the nature of the catalyst and/or ligands or auxiliaries added to the reaction mixture: (1) surfactants, (2) surfactant phosphines, (3) inorganic salts, and (4) microemulsions. The aim of each is to create suitable micelles in which the reaction can take place. There are many critical issues to consider in each of these processes, such as size and charge of the micelle. In the hydroformylation of 1-dodecene with ClRh(TPPTS)(BISBIS) and cetyltrimethylammonium bromide, the corresponding aldehyde was produced with a TOF on the order of 740 h^{-1} with a regioselectivity for the linear aldehyde of 96.5% [55]. Using $ClRh(TPPTS)_3$ in conjunction with a variety of surfactants was also reported to enhance catalytic activity [56]. To illustrate briefly the use of surfactant phosphines, the hydroformylation of 1-octene and 1-decene was accomplished by the use of a rhodium phosphacalix[4]arene (**5**) in which catalysis occurs within the hydrophobic interior of the ligand, affording high conversions with good yields [57].

Additionally, PEO-DPPPA (**6**) was used with $RhCl_3 \cdot 3\,H_2O$ to convert 1-decene to the corresponding aldehydes with greater than 95% conversion even after the water layer was recycled 20 times [58].



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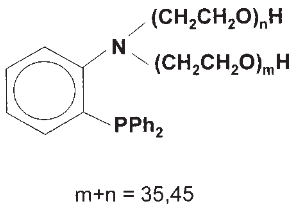


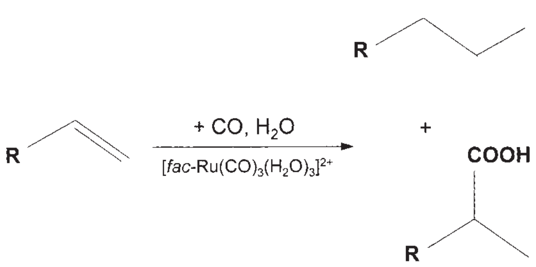
6

The use of other metals for this process in aqueous medium is rare. One example involves the use of a cobalt catalyst, $[Co(CO)_3(Ph_2PCH_2CH_2N\{CH_3\}_3)_2]_2(PF_6)_2$, which was found to effectively hydroformylate 1-hexene in water [59]. Unfortunately, little selectivity was observed as only a 4.6 : 1 *n*/*i* ratio was obtained. Hydroformylation of ethene and propene was also achieved through the use of the ruthenium catalyst, $[Ru_3(CO)_9(TPPMS)_3]$ [60]. In the hydroformylation of propene, this catalyst exhibited TONs on the order of 490 in water. Also, increasing the temperature from 100 to 120 °C favored the formation of *n*-butyraldehyde. Other catalytic systems such as $Fe(CO)_4(TPPMS)$ were nearly inactive, while activity increased slightly with the use of $Co_2(CO)_8$/TPPMS.

3.1.1.3
Water-soluble Catalysts through Water Coordination

Water solubility of all the aforementioned catalysts was due to the hydrophilic nature of ligand. In a second class, the aqueous nature originates from direct interaction of water molecules with the metal center [61]. Although this area of aqueous catalysis is not as extensive, there are several representative examples illustrating its importance and potential, as well as the variation of the metal center. One of the earlier examples involved the hydrogenation of maleic and fumaric acids with $[RhCl_n(H_2O)_{6-n}]^{3-n}$ and $[RuCl_n(H_2O)_{6-n}]^{3-n}$ [62]. These simple catalysts revealed key mechanistic information that is applicable to many other systems, such as the requirement of alkene complexation prior to H_2 activation. After this important discovery, many advances have been made in the areas of hydrogenation and polymerization reactions using these types of catalysts.

Although partial water solubility is owed to PTA, the water-soluble ruthenium catalyst, $[Ru^{II}(H_2O)_3(PTA)_3](tos)_2$, was found to effectively hydrodehalogenate organic halides [63]. The TON of the catalyst, prepared from $[Ru^{II}(H_2O)_6](tos)_2]$ and PTA, was on the order of 90 mol product/mol catalyst, making it a less effective system when compared to $[\{\textit{fac}\text{-Ru(CO)}_3(\text{TPPMS})_2\}_2]$. Another interesting species is the $[\textit{fac}\text{-Ru(CO)}_3(\text{H}_2\text{O})_3]^{2+}$ complex, which was been shown to hydroxycarbonylate alkenes in a purely aqueous solvent environment (Eq. 12) [64]. The alkyl intermediate, $[\textit{fac}\text{-Ru(C}_2\text{H}_5)(\text{CO})_2(\text{H}_2\text{O})_3]^+$, quickly inserts CO, leading to the formation of the acyl derivative, $[\textit{fac}\text{-Ru(C\{O\}C}_2\text{H}_5)(\text{CO})_2(\text{H}_2\text{O})_3]^+$. Raising the temperature allows for the release of propionic acid with a TOF of 15.4 h^{-1}.



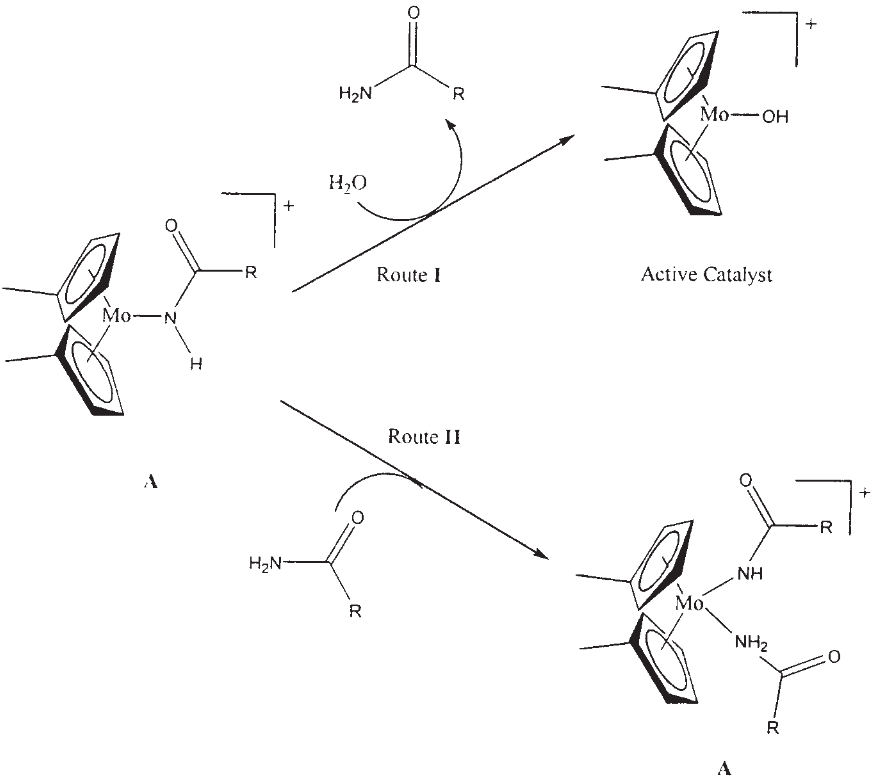
(12)

In the hydration of nitriles, $[(\text{MeCp})_2\text{Mo(OH)(H}_2\text{O)}]^+$ effectively converted several different nitriles to the corresponding amides [65]. One of the main drawbacks of this system involves product inhibition; that is, higher activities resulted with the use of lower initial substrate concentrations (Scheme 1).

As Scheme 1 illustrates, part of the proposed catalytic cycle involves intermediate **A** which can either trap H_2O (route **I**) to release the amide and regenerate the catalyst, or become inactive by product coordination (route **II**). A positive note involves the regioselectivity of the catalyst as only the C≡N position is hydrated when bifunctional substrates, such as acrylonitrile, are used. At 75 °C, $\text{CH}_2{=}\text{CHC(O)NH}_2$ was produced exclusively with no detectable amounts of $\text{HOCH}_2\text{CH}_2\text{C}{\equiv}\text{N}$ and $(\text{N}{\equiv}\text{CCH}_2\text{CH}_2)_2\text{O}$, which are drawbacks of other processes [66].

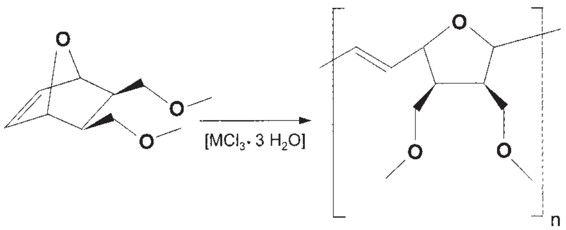
Because water-soluble catalysts containing water molecules as ligands behave differently at various pH values due to different catalytic species, a pH-dependent study was conducted on the hydrogenation of carbonyl compounds promoted by the iridium catalyst, $[\text{Cp*Ir}^{\text{III}}(\text{H}_2\text{O})_3]^{2+}$ [67]. At a pH of 2.7 (at which $[\text{Cp*Ir}^{\text{III}}(\text{H}_2\text{O})_3]^{2+}$ dissolved in water), the complex is monomeric. However, raising the pH to 3.2 and in the presence of a hydrogen donor (i.e., HCOONa) the dinuclear, active catalyst, $[(\text{Cp*Ir}^{\text{III}})_2(\mu\text{-H})(\mu\text{-OH})(\mu\text{-HCOO})]^+$, is formed. TOFs were found to be higher for cyclic aldehydes than for their straight chain analogs.

The development of living ring-opening metathesis polymerization (ROMP; cf. Section 6.10) catalysts was greatly influenced by the initial use of hydrated late transition metal salts. In the aqueous polymerization of 7-oxanorbornene derivatives, RuCl_3 and $[\text{Ru(H}_2\text{O)}_6]^{2+}$ were found to produce polymer with the latter having a smaller induction period [68]. A key intermediate and product in the reaction is the alkene adduct, $[\text{Ru(H}_2\text{O)}_5(\text{alkene})]^{2+}$ with the use of RuCl_3 and



Scheme 1 Key intermediates in the hydration of nitriles using $[(MeCp)_2Mo(OH)(H_2O)]^+$.

$[Ru(H_2O)_6]^{2+}$. Therefore, using $RuCl_3$ first involves the reduction of the metal center to afford the alkene Ru^{2+} complex. ROMP reactions have also been reported with the use of $IrCl_3 \cdot 3\,H_2O$ and $OsCl_3 \cdot 3\,H_2O$ in water [69]. The hydrated $RuCl_3$ salt remains the most active catalyst still, affording yields of up to 95% with a higher M_W in the ROMP of *exo,exo*-5,6-bis(methoxymethyl)-7-oxabicyclo[2.2.1]hept-2-ene than is given by the iridium (2% yield) and osmium (95% yield) salts (Eq. 13).



(13)

A description of the evolution of ROMP catalysts involving these metal hydrates can be found in the literature [70].

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3.1.2
Lanthanides in Aqueous-phase Catalysis

Shū Kobayashi

3.1.2.1
Introduction

Lewis acid-catalyzed reactions have been of great interest in organic synthesis because of their unique reactivities and selectivities, and for the mild conditions used [1]. Although various kinds of Lewis acid-promoted reactions have been developed and many have been applied in industry, these reactions must be carried out under strictly anhydrous conditions despite the general recognition of the utility of aqueous reactions [2]. The presence of even a small amount of water stops the reaction, because most Lewis acids immediately react with water rather than with the substrates and decompose or deactivate, and this fact has restricted the use of Lewis acids in organic synthesis.

Yet lanthanide trifluoromethanesulfonates (triflates), including scandium and yttrium triflates, were recently found to be stable Lewis acids in water, and many useful aqueous reactions using lanthanide triflates as catalysts have been reported. Lanthanides have a larger radius and specific coordination number than typical transition metals. They have been expected to act as strong Lewis acids because of their hard character and to have strong affinity toward carbonyl oxygens [3]. Among these compounds, lanthanide trifluoromethanesulfonates (lanthanide triflates) were expected to be one of the strongest Lewis acids because of the strongly electron-withdrawing trifluoromethanesulfonyl group, but their hydrolysis was postulated to be slow on the basis of their hydration energies and hydrolysis constants [4]. In fact, unlike most metal triflates, which are prepared under strictly anhydrous conditions, lanthanide triflates have been reported to be prepared in aqueous solution [5–7]. Many synthetic reactions using these triflates as catalysts have been developed [8].

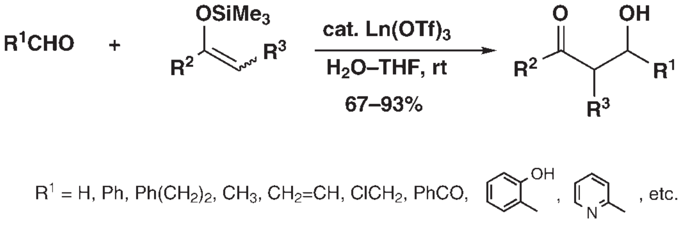
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

3.1.2.2
Aldol Reactions

Formaldehyde is a versatile reagent as one of the most highly reactive C_1 electrophiles in organic synthesis [9, 10] and *dry* gaseous formaldehyde has been required for many reactions. For example, the titanium tetrachloride ($TiCl_4$)-promoted hydroxymethylation reaction of a silyl enol ether was carried out by using trioxane as an HCHO source under strictly anhydrous conditions [11, 12]. Formaldehyde/water solution could not be used because $TiCl_4$ and the silyl enol ether reacted with water rather than with HCHO in that aqueous solution.

It was found that the hydroxymethylation reaction of silyl enol ethers with commercial formaldehyde solution proceeded smoothly when lanthanide triflates were used as Lewis acid catalysis (Eq. 1) [7, 13]. The reactions were first carried out in commercial formaldehyde solution THF media.



(1)

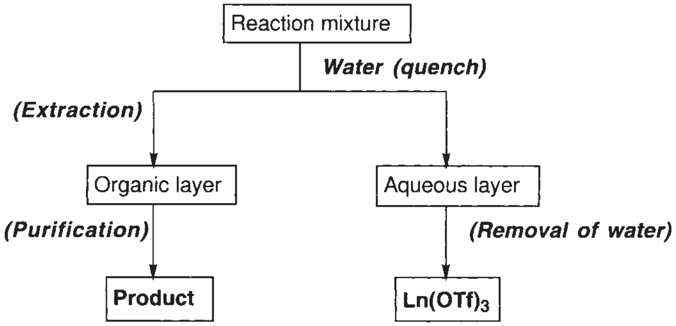
R^1 = H, Ph, Ph(CH$_2$)$_2$, CH$_3$, CH$_2$=CH, ClCH$_2$, PhCO, , , etc.

Ln = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

Lanthanide triflates were effective for the activation of aldehydes other than formaldehyde [13–15]. The aldol reaction of silyl enol ethers with aldehydes proceeds smoothly to afford the aldol adducts in high yields in the presence of a catalytic amount of scandium triflate ($Sc(OTf)_3$), ytterbium triflate ($Yb(OTf)_3$), gadolinium triflate ($Gd(OTf)_3$), lutetium triflate ($Lu(OTf)_3$), etc., in aqueous media (water/THF). Diastereoselectivities are generally good to moderate. One feature in the present reaction is that water-soluble aldehydes, for instance, acetaldehyde, acrolein, and chloroacetaldehyde, can be reacted with silyl enol ethers to afford the corresponding cross-aldol adducts in high yields. Some of these aldehydes are commercially supplied as aqueous solutions and are appropriate for direct use. Phenylglyoxal monohydrate also works well. It is known that water often interferes with the aldol reactions of metal enolates with aldehydes and that in the cases where such water-soluble aldehydes are employed some troublesome purifications including dehydration are necessary.

3.1.2.2.1
Recovery and Re-use of the Catalysts

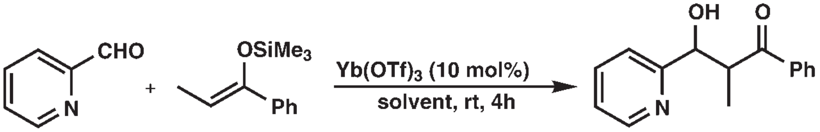
Lanthanide triflates are more soluble in water than in organic solvents such as dichloromethane. Very interestingly, almost 100% of the lanthanide triflate is quite



Scheme 1 Recovery of the catalyst.

easily recovered from the aqueous layer after the reaction is completed and it can be re-used. The reactions are usually quenched with water and the products are extracted with an organic solvent (for example, dichloromethane). Lanthanide triflates are in the aqueous layer and only removal of water gives the catalyst which can be used in the next reaction (Scheme 1). It is noteworthy that lanthanide triflates are expected to solve some severe environmental problems induced by mineral acid- or Lewis acid-promoted reactions in the industrial chemistry [16].

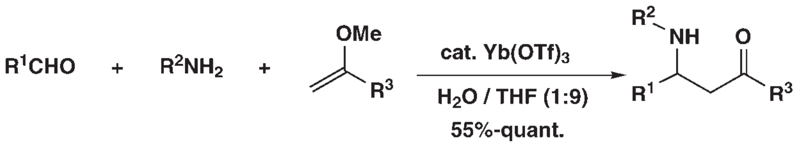
The aldol reactions of silyl enol ethers with aldehydes also proceed smoothly in water/ethanol/toluene [17]. The reactions proceed much faster in this solvent than in water/THF (Eq. 2). Furthermore, the new solvent system involves continuous use of the catalyst by a very simple procedure. Although the water/ethanol/toluene (1 : 7 : 4) system is one phase, it easily becomes two phases by adding toluene after the reaction is completed. The product is isolated from the organic layer by a usual work-up. On the other hand, the catalyst remains in the aqueous layer, which is used directly in the next reaction without removing water. It is noteworthy that the yields of the second, third, and fourth runs are comparable with that of the first run.

 (2)

3.1.2.3
Mannich-type Reactions

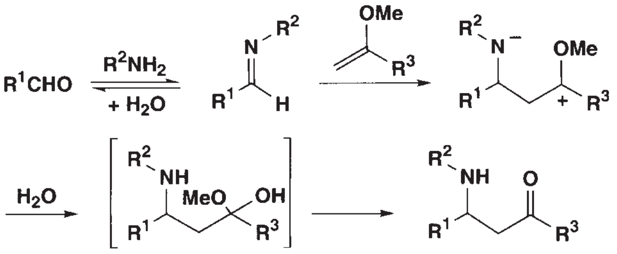
The Mannich and related reactions provide one of the most fundamental and useful methods for the synthesis of β-amino ketones. Although the classical protocols include some severe side reactions, new modifications using preformed iminium salts and imines have been developed [18]. These materials however, are often hygroscopic and are not stable at high temperatures. The direct preparation of β-amino ketones from aldehydes is desirable from a synthetic point of view.

Mannich-type reactions between aldehydes, amines, and vinyl ethers proceed smoothly using $Ln(OTf)_3$ in aqueous media [19] (Eq. 3). Commercially available formaldehyde and chloroacetaldehyde aqueous solutions are used directly and the corresponding β-amino ketones are obtained in good yields. Phenylglyoxal monohydrate, methyl glycoxylate, an aliphatic aldehyde, and an α,β-unsaturated ketone also work well to give the corresponding β-amino esters in high yields. Other lanthanide triflates can also be used; in the reaction of phenylglyoxal monohydrate, *p*-chloroaniline, and 2-methoxypropene, 90% ($Sm(OTf)_3$), 94% ($Tm(OTf)_3$), and 91% ($Sc(OTf)_3$) yields are obtained. In some Mannich reactions with preformed iminium salts and imines, it is known that yields are often low because of the instability of the imines derived from these aldehydes or because troublesome treatments are known to be required for their use [20]. The present method provides a useful route for the synthesis of β-amino ketones.



(3)

A possible mechanism for the present reaction is shown in Scheme 2. It should be noted that dehydration accompanied by imine formation and successive addition of a vinyl ether proceed smoothly in aqueous solution. Use of lanthanide triflate, a water-tolerant Lewis acid, is key and essential in this reaction.

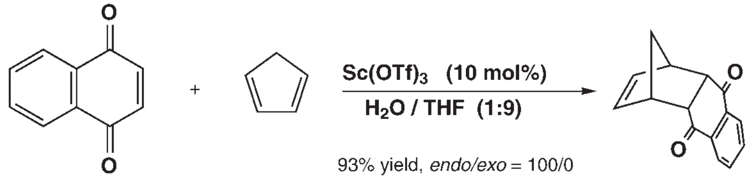


Scheme 2 A possible mechanism of Mannich-type reactions.

3.1.2.4
Diels–Alder Reactions

Although many Diels–Alder reactions have been carried out at higher reaction temperatures without catalysts, heat-sensitive compounds in complex and multistep syntheses cannot be employed. While Lewis acid catalysts allow the reactions to proceed at room temperature or below with satisfactory yields in organic solvents, they are often accompanied by diene polymerization and excess amounts of the catalyst are often needed to catalyze carbonyl-containing dienophiles [21, 22].

It was found that the Diels–Alder reaction of naphthoquinone with cyclopentadiene proceeded in the presence of a catalytic amount of a lanthanide triflate in H_2O/THF at room temperature to give the corresponding adduct in a 93% yield (Eq. 4) [23].



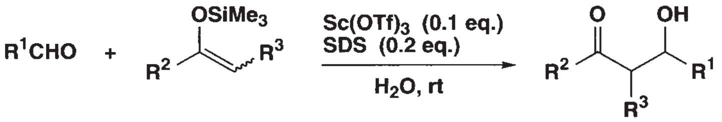
(4)

3.1.2.5
Micellar Systems

3.1.2.5.1
Aldol Reactions

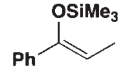
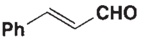
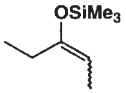
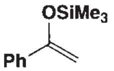
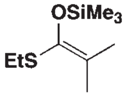
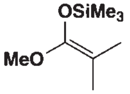
Quite recently, it has been found that scandium triflate (Sc(OTf)$_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes can be successfully carried out in micellar systems [24]. While the reactions proceeded sluggishly in pure water (without organic solvents), remarkable enhancement of the reactivity was observed in the presence of a small amount of a surfactant (cf. Section 4.5).

Lewis acid catalysis in micellar systems was first found in the model reaction of the silyl enol ether of propiophenone with benzaldehyde. Although the reaction proceeded sluggishly in the presence of 0.2 equiv. Yb(OTf)$_3$ in water, remarkable enhancement of the reactivity was observed when the reaction was carried out in the presence of 0.2 equiv. Yb(OTf)$_3$ in an aqueous solution of sodium dodecylsulfate (SDS, 0.2 equiv., 35 mM), and the corresponding aldol adduct was obtained in a 50% yield. In the absence of the Lewis acid and in surfactant (water-promoted conditions) [11], only 20% yield of the aldol adduct was isolated after 48 h, while a 33% yield of the aldol adduct was obtained after 48 h in the absence of the Lewis acid in an aqueous solution of SDS. The amounts of the surfactant also influenced the reactivity, and the yield was improved when Sc(OTf)$_3$ was used as a Lewis acid catalyst. Judging from the critical micelle concentration, micelles would be formed in these reactions, and it is noteworthy that the Lewis acid-catalyzed reactions proceeded smoothly in micellar systems [25].



(5)

Tab. 1 $Sc(OTf)_3$-catalyzed aldol reactions in micellar systems.

Aldehyde	*Silyl enol ether*	*Yield [%]*
PhCHO	 1	88[a]
	1	86[b]
	1	88[c]
HCHO		82[d]
PhCHO		88[e]
PhCHO		75[f,g]
PhCHO		94
PhCHO	 2	84[g]

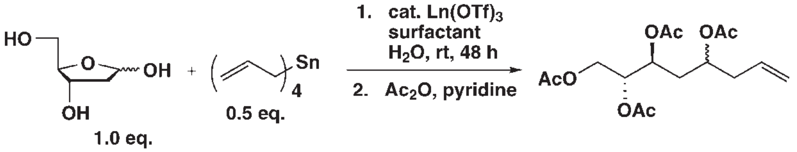
[a] *Syn/anti* = 50/50.
[b] *Syn/anti* = 45/55.
[c] *Syn/anti* = 41/59.
[d] Commercially available HCHO aq. (3 ml), **1** (0.5 mmol), $Sc(OTf)_3$ (0.1 mmol), and SDS (0.1 mmol) were combined.
[e] *Syn/anti* = 57/43.
[f] $Sc(OTf)_3$ (0.2 equiv.) was used.
[g] Additional silyl enolate (1.5 equiv.) was charged after 6 h.

Several examples of $Sc(OTf)_3$-catalyzed aldol reactions in micellar systems are shown in Table 1 and Eq. (5). Not only aromatic, but also aliphatic and α,β-unsaturated aldehydes, react with silyl enol ethers to afford the corresponding aldol adducts in high yields. Formaldehyde/water solution also works well. It is exciting that ketene silyl acetal **2**, which is known to hydrolyze very easily even in the presence of a small amount of water, reacts with an aldehyde in the present micellar system to afford the corresponding aldol adduct in high yields.

3.1.2.5.2
Allylations of Aldehydes

It was also found that the allylation reactions of aldehydes (cf. Section 6.8) with tetra-allyltin proceeded smoothly in micellar systems using $Sc(OTf)_3$ as a catalyst

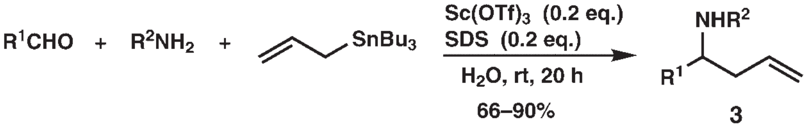
[26]. Utilities of organometallic reagents are now well recognized in organic synthesis, and a variety of organometallics have been developed to achieve unique reactivities as well as selectivities [27]. In general, however, most organometallic reagents are hygroscopic and therefore they are deactivated or decomposed in the presence of even a small amount of water, which sometimes limits their use in organic synthesis. On the other hand, the allylation reaction of 2-deoxyribose (an unprotected sugar) was found to proceed smoothly in water under the influence of 0.1 equiv. of $Sc(OTf)_3$ and 0.2 equiv. of SDS (sodium dodecylsulfate) by using tetra-allyltin (0.5 equiv.) as an allylating reagent (Eq. 6) [28]. The reaction proceeded sluggishly without the Lewis acid (surfactant only) or without the surfactant (Lewis acid only). It is noted that the sugar reacted smoothly without protecting any hydroxyl groups in this system, and that the reaction proceeded smoothly in water without using any organic solvents. Several examples of the allylation reactions were examined, and in all cases they were successfully carried out in micellar systems to afford the corresponding homoallylic alcohols in high yields. With regard to the stoichiometry of an aldehyde and tetra-allyltin, it was found that 0.25 equiv. of tetraallyltin was enough to achieve high yields of the homoallylic alcohols. Either SDS or TritonX-100 could be used as a surfactant. Not only aromatic but also aliphatic and α,β-unsaturated aldehydes reacted with tetra-allyltin to afford the corresponding allylated adducts in high yields. Under the present reaction conditions, salicylaldehyde and 2-pyridinecarboxaldehyde reacted with tetra-allyltin to afford the homoallylic alcohols in good yields. Unprotected sugars other than 2-deoxyribose also reacted directly to give the adducts, which are intermediates for the synthesis of higher sugars [29], in high yields.



(6)

3.1.2.5.3
Three-component Reactions of Aldehydes, Amines, and Allyltributyltin

The reaction of imines with allyltributyltin provides a useful route for the synthesis of homoallylic amines [30]. The reaction is generally carried out in the presence of a Lewis acid in organic solvents under strictly anhydrous conditions [31], because most imines, Lewis acids, and the organotin reagents used are hygroscopic and decompose easily in the presence of even a small amount of water [32]. It was found that three-component reactions of aldehydes, amines, and allyltributyltin proceed smoothly in micellar systems using $Sc(OTf)_3$ as a Lewis acid catalyst (Eq. 7) [33]. The reaction of benzaldehyde, aniline, and allyltributyltin was chosen as a model, and several reaction conditions were examined. While the reaction proceeded sluggishly in the presence of $Sc(OTf)_3$ without SDS or in the presence of SDS without $Sc(OTf)_3$, a 77% yield of the desired homoallylic amine (Structure **3**) was obtained in the coexistence of $Sc(OTf)_3$ and SDS. A satisfactory yield was obtained when 0.2 equiv. $Sc(OTf)_3$ and 35 mM (0.2 equiv.) SDS were used and the reaction was carried out at room temperature (rt) for 20 h [34]. No homoallylic alcohol (an adduct between an aldehyde and allyltributyltin) was produced under these conditions.



(7)

The present three-component reactions of aldehydes, amines, and allyltributyltin proceeded smoothly in water without using any organic solvents in the presence of a small amount of $Sc(OTf)_3$ and SDS, to afford the corresponding homoallylic amines **3** in high yields. Not only aromatic aldehydes but also aliphatic, unsaturated, and heterocyclic aldehydes worked well. It is known that severe side reactions occur to decrease yields in the reactions of imines having α-protons with allyltributyltin [30]. It should be noted that aliphatic aldehydes, especially unbranched aliphatic aldehydes, reacted smoothly under these conditions to afford the homoallylic amines in high yields. In all cases, no aldehyde adducts (homoallylic alcohols) were obtained. It was suggested that imine formation from aldehydes and amines was very fast in the presence of $Sc(OTf)_3$ and SDS [19], and that the selective activation of imines rather than aldehydes was achieved using $Sc(OTf)_3$ as a catalyst [35].

3.1.2.6
Asymmetric Catalysis in Aqueous Media

Catalytic asymmetric aldol reactions have emerged as one of the most powerful carbon–carbon bond-forming processes affording synthetically useful, optically active β-hydroxy carbonyl compounds [36]. Among them, chiral Lewis acid-catalyzed reactions of aldehydes with silyl enol ethers are one of the most promising methods. Although several successful examples have been developed since 1990 [37], most of the reactions have to be conducted at low reaction temperatures (e.g., $-78\,^{\circ}C$) in aprotic anhydrous solvents such as dry dichloromethane, toluene, and propionitrile.

While $Ln(OTf)_3$ are the first metal salts which were found to catalyze aldol reactions of aldehydes with silyl enol ethers efficiently in aqueous media, it has been difficult to realize asymmetric versions of $Ln(OTf)_3$-catalyzed reactions in such media. Recently, the first example of this type of reaction using chiral bis-pyridino-18-crown-6 (Structure **4**) has been developed (Eq. 8) [38]. In the reaction of benzaldehyde **5** with water–ethanol (1/9), the cation size of rare earth metal triflates including $Ln(OTf)_3$ strongly affected the diastereo- and enantioselectivities of the

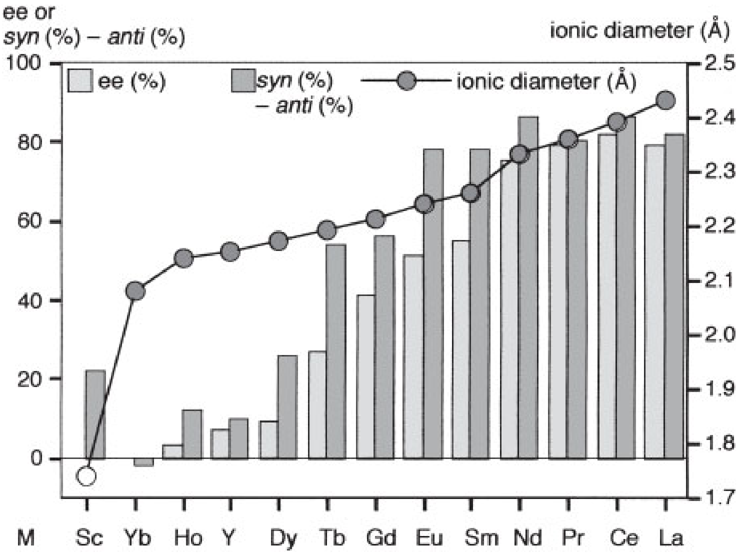
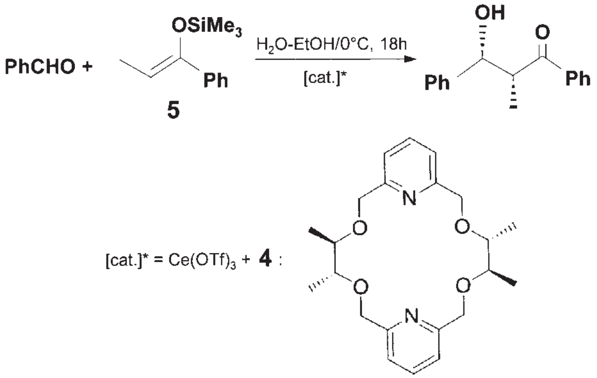


Fig. 1 Enantio- and diastereoselectivities in the aldol reaction using rare earth metal triflates and ionic diameters (eight-coordination for Sc, nine-coordination for other metals) of the metal cations (M^{3+}). *ee:* ((2*R*,3*R*)% – (2*S*,3*S*)%); yields: 49–95%.

aldol adducts as shown in Figure 1. For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high, while the smaller cations such as Sc and Yb showed no enantioselection.



(8)

A study on the reaction profile of the asymmetric aldol reaction catalyzed by $Pr(OTf)_3$ with **4** revealed that his crown ether-type chiral ligand did not significantly reduce the activity of the metal triflates. This retention of the activity even in the presence of the crown ether containing oxygen and nitrogen atoms in a key to realize the asymmetric induction in this asymmetric aldol reaction in aqueous me-

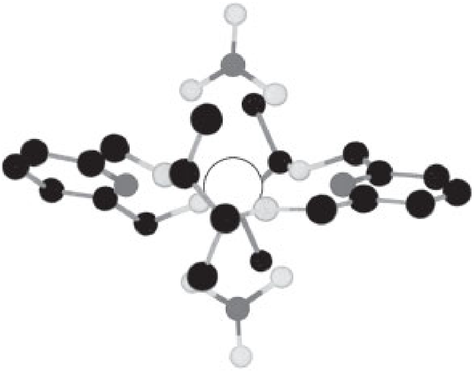


Fig. 2 X-ray structure of $Pr(NO_3)_2 \cdot \mathbf{4}$ moiety of $[Pr(NO_3)_2 \cdot \mathbf{4}]_3[Pr(NO_3)_6]$.

dia. The X-ray structure of $[Pr(NO_3)_2 \cdot \mathbf{4}]_3[Pr(NO_3)_6]$ shows that Pr(III) cation is located in the center of the crown ring (Figure 2). The use of a chiral multidentate ligand such as the crown ether is a versatile concept for catalytic asymmetric reactions in aqueous media.

3.1.2.7
Conclusions

Lanthanide triflates are stable Lewis acids in water and are successfully used in several carbon–carbon bond-forming reactions in aqueous solutions. The reactions proceed smoothly in the presence of a catalytic amount of the triflate under mild conditions. Moreover, the catalysts can be recovered after the reactions are completed and can be re-used. Lewis acid catalysis in micellar systems will lead to clean and environmentally friendly processes, and it will become a more important topic in the future. Finally, catalytic asymmetric aldol reactions in aqueous media have been attained using $Ln(OTf)_3$–chiral crown ether complex as a catalyst.

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3.2
Variation of Ligands

3.2.1
Monophosphines

Othmar Stelzer (†), Stefan Rossenbach, Dietmar Hoff

3.2.1.1
General Features, Scope, and Limitations

A great deal of the development of catalysts with unprecedented activities and selectivities within the last decade has been achieved by a systematic modification of suitable phosphorus ligands bearing functionalities and elements of chirality in their backbones or peripheries. It was already recognized, however, in the early stages of this development that these homogeneous processes suffer from the difficulties of separating the catalysts from the products. This problem has been solved in an elegant manner using strongly hydrosoluble catalysts in immiscible aqueous/organic two-phase systems following a proposal by Manassen [1a]. The water-solubility of the catalysts employed in aqueous two-phase catalysis can be achieved by appropriate modification of the phosphine ligands with polar groups such as SO_3^-, COO^-, NMe_3^+, OH, etc. First attempts to carry out transition metal catalyzed reactions using water-soluble phosphine ligands date back to 1973 [1b]. The monosulfonated derivative of Ph_3P had already been synthesized in 1958 [1c], and the well-known standard ligand TPPTS (trisulfonated triphenylphosphine) was reported by Kuntz in 1975 [2]. The development of new types of hydrosoluble phosphine ligands with "tailor-made" structures for highly active and selective two-phase catalysts is an ongoing challenge to chemists working in this field. Aspects of the topic under review have been covered in the literature by review articles [3–6] and monographs [7].

In this section catalysts containing monophosphines for aqueous-phase catalysis will be presented, the influence of ligand variation on catalyst activity being emphasized. Syntheses of hydrophilic monodentate phosphine ligands will be discussed very briefly. Reference to catalysts containing other ligands (see Sections 3.2.2 to 3.2.6) is made only where appropriate.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

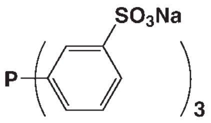
3.2.1.2
Anionic Phosphines

3.2.1.2.1
Phosphines Containing Sulfonated Aromatic and Aliphatic Groups

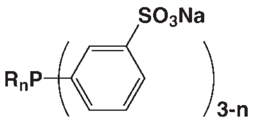
Ligand Syntheses

Water-soluble phosphines of this type reported in the literature so far are collected as Structures **1**–**6**. Direct sulfonation of the neutral "mother phosphine" with oleum, introduced originally by Kuntz in 1975 [2] for the preparation of TPPTS (**1a**), is still the most important procedure; it has also been used for the syntheses of an extended series of TPPTS-type catalyst ligands, e.g., **1b** (R = Ph [8], C_6H_{13} [9]), **1c** (R = alkyl, *c*-Hex; R′ = Me, OMe [10]), **1d** (R = 4-F-C_6H_4 [11]), **1e** [12]. Sulfonated tris (ω-phenylalkyl)phosphines **5a** [13] and their *p*-phenylene analogs **5b** [14] as well as the bicyclic phosphine **4** [15] were obtained in an analogous manner. Triaryl phosphines containing activated aryl groups, e.g. the dibenzofuran system, can be sulfonated with concentrated sulfuric acid under mild conditions (**1g**) [123]. The kinetics of PPh_3 sulfonation have been investigated by Lecomte and Sinou [16a]. The selectivity has been studied by Chaudhari [16b].

The formation of phosphine oxides, which is a serious disadvantage inherent to this synthetic procedure [17], may be suppressed by addition of boric acid to the reaction mixtures [18]. Alternative synthetic routes have been developed using either nucleophilic phosphination of sulfonated fluorobenzenes, e.g., F-C_6H_4-2-SO_3K, F-C_6H_4-4-SO_3K, F-C_6H_3-2,4-$(SO_3K)_2$, in superbasic media (DMSO/KOH) or Pd-catalyzed P–C coupling of sulfonated bromo- or iodoaromatic compounds with PH_3 or primary and secondary phosphines. The scope of these synthetic strategies is rather broad; the *p*-isomer of TPPTS (**2a**) [19a–d], higher and even secondary (R = H, R′ = Ph) sulfonated phosphines **2b**, **2c**, and **3** [20a] as well as the disulfonated dibenzophosphole **1f** [19e] are accessible. The phosphines **2b**, **2c** (R, R′ = Ph) have been obtained by reaction between Ph_2PK or Ph_2PCl with Li or K 4-chlorobenzenesulfonate or *o*-lithiated lithiumbenzenesulfonate, respectively [21b, 22]. A multistage low-yield synthesis has been published for the methyl derivative **1b** (R = Me; $n = 1$) [23]. Alkylation of the alkali metal phosphides R_2PM (M = Li, Na, K) or $RPLi_2$ with sultones [24–26] or ω-haloalkyl sulfonates [27] affords the sulfonated benzyldiphenylphosphine **5c**, phenylsulfonatoalkylphosphines **6a**, **6c**, and the peralkyl derivative **6b** [22b, 27, 28]. Highly water soluble aminomethylphosphines containing sulfonyl groups (**6d**) are accessible by condensation of $P(CH_2OH)_3$ with 3-(*N*-butylamino)propanesulfonic acid sodium salt and *N*-methyltaurine, respectively [124].

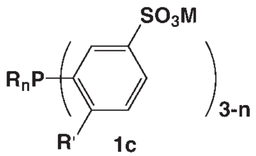


1a (TPPTS)



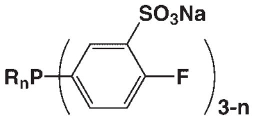
1b

R = Ph; n = 1, 2 (TPPDS, TPPMS); R = Me; n = 1; R = C_6H_{13}; n = 1



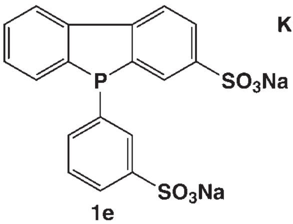
1c

R = Me, Et, Pr, Bu, Cy; R'= Me, OMe; n = 0-2

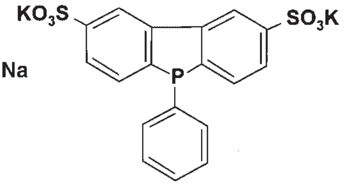


1d

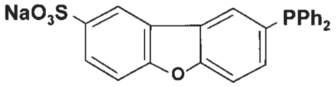
R = 4-F-C_6H_4; n = 0–2



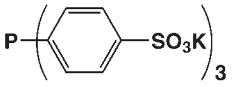
1e



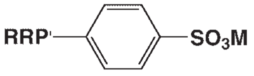
1f



1g

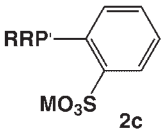


2a



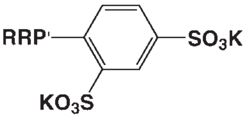
2b

R = R' =Ph, 3-Py; R = H; R'= Ph; R = 2-Py; R'= 4-SO_3K-C_6H_4; M = Li, Na, K



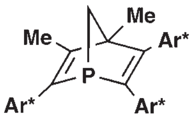
2c

R =R'=Ph; M = Li, K; R = H; R'=Ph; M = K, Na



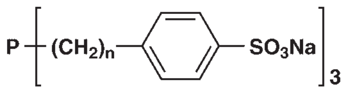
3

R = R'= Ph, 3-Py;
R = H; R'= Ph, Ar*;
R = 2-Py, Ph; R'= Ar*;
R = CH_2Ph, nBu; R'= Ar*;
R = CH_2Ph; R'= Mes;
Ar* = 2,4-$(SO_3K)_2C_6H_3$

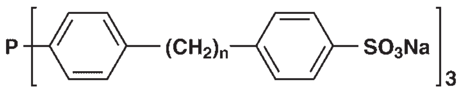


4

Ar* = 4-SO_3Na-C_6H_4 (NORBOS)



5a (n = 1–3, 6)

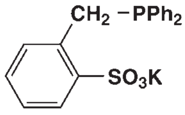


5b (n = 3, 6)

Water-soluble phosphines containing sulfonated aryl and alkyl side chains.

Catalysts Containing Sulfonated Aromatic Phosphines as Ligands

Ruthenium complexes of TPPTS and TPPMS [29–32] have been employed as catalysts or catalyst precursors for the hydrogenation of α,β-unsaturated carbonyl compounds in biphasic systems ([29–33], cf. Section 6.2). Dimeric structures **7**, **8** were assigned to the catalyst complexes $[RuX(\mu\text{-}Cl)(TPPMS)_2]_2$ (X = H, Cl) on the basis of NMR studies [30]. The regioselectivity toward the production of α,β-unsaturated alcohols is greatly enhanced on going from the homogeneous medium (using Ph_3P as the ligand) to the biphasic system using the TPPMS or TPPTS catalysts $[RuCl(\mu\text{-}Cl)L_2]_2$ [30]. While TPPMS is acting as a surface-active agent, TPPTS behaves more like an electrolyte [29]. In acidic solution formation of phosphonium salts, e.g., **9**, was observed if the $RuCl_3 \cdot 3\,H_2O$/TPPTS catalyst system was used



5c

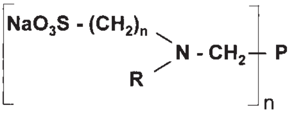
$R_2P{-}(CH_2)_n{-}SO_3M$

6a (R = Ph; n = 2-4; M = Li, Na, K)

6b (R = Et; n = 2; M = Na)

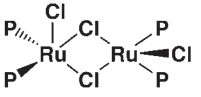
$Ph[P{-}(CH_2)_4{-}SO_3Na]_2$

6c



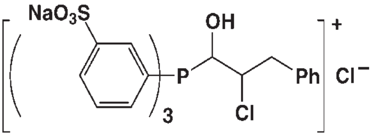
6d

(R = *n*Bu, Me; n = 2,3)

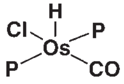


7 (P = TPPMS)

8 (P = TPPMS)

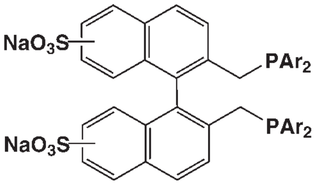


9

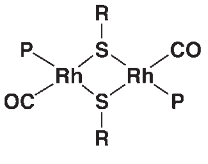


10

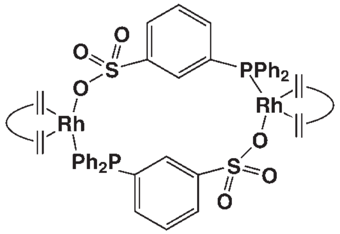
(P = TPPMS)



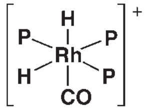
11 (Ar = 4-C_6H_4-SO_3Na)



12 (P = TPPTS; R = tBu)



13



14 (P = 5a)

Structure of catalysts, ligands and intermediates.

[32]. In Rh-catalyzed hydrogenation of activated olefins, phosphonium salt formation obviously promotes the formation of the catalytically active species [34 a] by consuming free phosphine [34 b]. This reaction may lead to severe phosphine loss and may account in part for the large excess phosphine requirement in related catalytic processes. The hydrogenation of unsaturated aldehydes can be directed to either the allylic alcohols or the saturated aldehydes by proper choice of the metal (Ru, Rh) [33]. TPPMS complexes of osmium, OsH_4L_3, $OsHCl(CO)L_2$ and $[OsCl(\mu\text{-}Cl)L_2]_2$, have also been found to be active catalysts for hydrogenation of α,β-unsaturated aldehydes [30]. A monomeric structure **10** was assigned to the hydrido complex $OsHCl(CO)L_2$. In Ru-catalyzed propionaldehyde hydrogenation the complexes $[RuCl(\mu\text{-}Cl)L_2]_2$, $RuH(X)L_3$ ($X = Cl$, I, OAc) and H_2RuL_4 ($L = TPPTS$) have been employed, the real catalyst being H_2RuL_3 [35]. Complexes prepared by ligand exchange between $RuCl_2(Ph_3P)_3$ and TPPTS have been used in aqueous solution for hydrogenation of D-mannose with molecular hydrogen and by transfer hydrogenation [36].

The technically most important biphasic process in the Ruhrchemie/Rhône-Poulenc hydroformylation of propene using the *in situ* Rh(I) catalyst $HRh(CO)(TPPTS)_3$ [6, 37]. Its formation from $Rh(CO)_2(acac)$ and TPPTS in a syngas atmosphere has been studied in detail [38, 39]. The BINAS-Na (**11**)/Rh catalyst showed an outstanding performance in propene hydroformylation [15]. Binuclear thiolato bridged rhodium complexes **12** have been used in 1-octene hydroformylation as precatalysts [41]. For details of the hydroformylation, cf. Section 6.1 [15, 40, 41].

Rh(I) catalysts containing TPPTS-type ligands with electron-withdrawing groups in the aromatic rings show higher n/i selectivity in hydroformylation reactions. Thus *para*-fluorinated derivatives of TPPTS and TPPDS (**1 d**), which are weaker bases and stronger π-acids than TPPTS and TPPDS [42], in 1-hexene hydroformylation gave n/i selectivities of 93 : 7, compared with 86 : 14 for the non-fluorinated ligands [11]. The application of aqueous two-phase catalysis in hydroformylation of longer-chain olefins is hampered, however, in most cases by their low solubility in water. This problem has been overcome by using phosphine ligands like **5 b**, showing a more pronounced surface-active character than TPPTS. Light-scattering experiments [43] on aqueous solutions of catalysts obtained from $(acac)Rh(CO)_2$ and **5 b** ($n = 6$) (L/Rh ratio = 2 : 1) indicated the presence of aggregates (micelles) with a hydrodynamic radius of ca. 19 Å. In hydroformylation of *n*-octene an average TOF of 160 was measured for **5 b**, compared with 90 for TPPTS, the n/i ratio (at L/Rh = 2 : 1) being much better [14]. This was attributed to micelle formation providing a hydrophobic pocket for binding the olefin. Reaction rate and selectivity increase with ionic strength of the solution, since added salt promotes the formation of micelles [44]. For a detailed discussion of stability and structure of complex catalysts containing highly sulfonated ligands, e.g., $HRh(CO)(TPPTS)_3$, the role of the "spectator" cations (Li^+, Na^+, K^+, Cs^+, Al^{3+}) has to be considered [45]. One of the 2^9 possible ligand conformations in $RhH(CO)(TPPTS)_3$ derived from the solid-

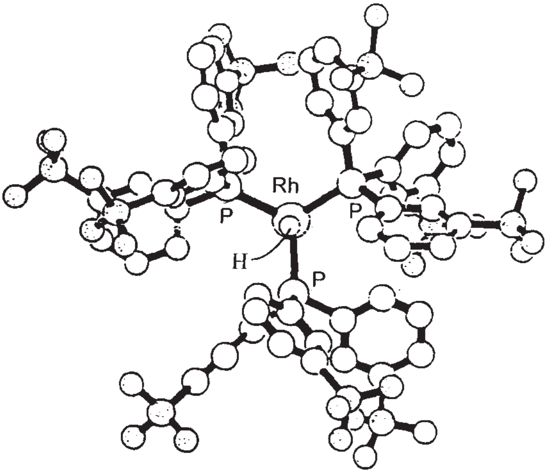


Fig. 1 Representation of $HRh(CO)(TPPTS)_3$.

state structure of $HRh(CO)(PPh_3)_3$ with the *meta*-SO_3^- groups being as far apart on average as possible is shown in Figure 1.

High ionic strengths stabilize the hydration sphere by minimizing the electrostatic repulsions between the sulfonate groups. As a consequence the dissociation energy for TPPTS with formation of the active species $\{HRh(CO)(TPPTS)_2\}$ will be increased, thus lowering the activity of the catalyst. In agreement with this reasoning a value of 30.6 or 22.4 $kcal\,mol^{-1}$ has been calculated for the barrier of exchange at high or low ligand and complex concentration, respectively [44]. The decrease in phosphine dissociation rates in the complexes *cis*-$Mo(CO)_4L_2$ ($L = \{(Na^+$-kryptofix-221$)_3[P$-$(C_6H_4$-*m*-$SO_3^-)_3]\} > PPh_3 \geq$ TPPTS) is in line with this, showing the stabilizing effect of the alkali-metal cations. For the tri-anionic cryptated and encapsulated TPPTS containing $P(C_6H_4$-*m*-$SO_3^-)_3$ a cone angle $-$ 30% greater than that of PPh_3 was estimated [46] in agreement with the value of 170° as determined from the X-ray structure of $(Na^+$-kryptofix-221$)_3[(CO)_5W{-}P(C_6H_4$-*m*-$SO_3^-)_3]$ [47]. Using PH_3 as the model phosphine, the PH_3 gas-phase dissociation energies for $HRh(CO)(PH_3)_3$ have been calculated at different theoretical levels, being 19.4 or 22.7 ($kcal\,mol^{-1}$) for HF or MP2 optimized geometries [48]. The agreement of the calculated with the experimental value for the PPh_3 complex (20 ± 1 $kcal\,mol^{-1}$) [49] might be the result of a fortuitous error cancellation.

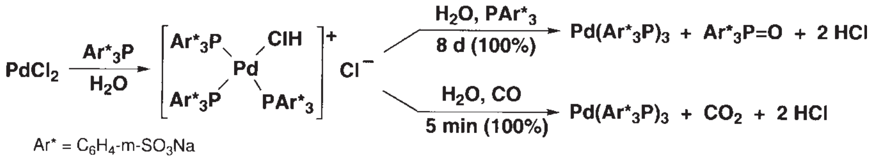
The surface-active character of sulfonated phosphines, e.g., TPPMS (**1b**, $n = 2$), was already noted in 1977 by Wilkinson et al., who also commented on the participation of the SO_3^- groups in the coordination of these ligands to transition metals in catalyst complexes (**13**) [50]. Rh complexes of **1b** (TPPDS) have been employed as catalysts in hydroformylation of olefins in biphasic media [21a]. The *p*-isomer **2b** ($Ph_2P{-}C_6H_4$-*p*-SO_3K) was, however, much more reactive in the presence of a surfactant (lauric acid) [21b]. Rh catalysts using TPPMS have been employed in the Union Carbide process of hydroformylation of higher olefins combining a homogeneous catalytic process in polyalkene glycols and an aqueous biphasic recovery of the catalyst [51, 52]. Problems in Rh/TPPTS-catalyzed hydroformylation arising from the insolubility of the olefin in water can be solved at least in part by addition of co-solvents [41, 53], quaternary phosphonium salts or by performing the reaction in micellar systems which can be created by addition of tensides to the organic/aqueous phase [54, 55] (cf. Sections 3.2.4 and 4.5). Alternatively, supported aqueous-phase catalysis (SAPCs; cf. Section 4.7) may be employed, which, with two recent exceptions [56], has been limited to the use of TPPTS. Replacing TPPTS by the more basic weakly surface-active ligand **1b** ($R = C_6H_{13}$) provided no improvement in the activity of the SAP Rh catalyst in C_8–C_{12} alkene hydroformylation, however [9]. On the other hand, excellent space-time-yields in rhodium-catalyzed hydroformylation of higher olefins with TPPTS have been achieved by use of static mixers [125].

Catalysis of 1-octene hydroformylation in biphasic systems by $[Rh(cod)Cl]_2$-TPPTS can be dramatically enhanced by addition of lipophilic phosphines, e.g., Ph_3P. The rate enhancement by the “promoter ligands” is believed to be the result of an increasing local concentration of the catalytic species at the interface [57]. Mixed-ligand complexes $HRh(CO)(TPPTS)_{3-x}(Ph_3P)_x$ prepared separately from HRh(CO)(TPPTS) and Ph_3P are likely not to be catalyst precursors.

Rh(I) complexes such as $RhCl(TPPMS)_3 \cdot 4\,H_2O$, $Rh(cod)Cl(TPPMS) \cdot H_2O$, $[Rh(cod)(\mu_2\text{-}Ph_2P{-}C_6H_4\text{-}3\text{-}SO_2{-}O)]_2$ catalyze oligomerization of alkynes (propynoic acid, arylacetylenes); this has been studied only very recently in terms of biphasic catalysis. The Rh(I) complex $[Rh(cod)(\mu_2\text{-}Ph_2P{-}C_6H_4\text{-}3\text{-}SO_2{-}O)]_2$ already reported by Wilkinson et al. [50] promotes the conversion of phenylacetylene to 1,2,4- and 1,3,5-triphenylbenzene under biphasic conditions (toluene/water) [58].

Palladium complexes of TPPTS and TPPMS have been employed extensively as catalysts for carbonylation, hydroxycarbonylation, and C–C cross-coupling reactions (cf. Section 6.6). Hydroxycarbonylation of bromobenzene in biphasic medium using $Pd(TPPTS)_3$ as catalyst yields benzoic acid, which remains in the aqueous phase, thus avoiding the direct recycling of the catalyst [59]. The formation of $Pd(TPPTS)_3$ from $PdCl_2$ and TPPTS in aqueous solution has been studied in detail by ^{17}O, $\{^1H\}^{31}P$, and ^{35}Cl NMR spectroscopy. The complex $[PdCl(TPPTS)_3]^+Cl^-$ obtained initially is reduced by excess TPPTS, TPPTSO being formed. A more attractive synthesis of $Pd(TPPTS)_3$ involves the facile reduction of $[PdCl(TPPTS)_3]^+Cl^-$ with CO (Scheme 1) [60].

Using $Pd(TPPTS)_3$ as a catalyst, 5-hydroxymethylfurfural could be carbonylated chemoselectively in water to yield 5-formylfuran-2-acetic acid. Replacement of TPPTS by ligands containing fewer SO_3Na groups (TPPDS, TPPMS, **1d**, $n = 1$) gives rise to a dramatic drop in catalytical activity [61]. The $Pd(OAc)_2$/TPPTS mixture widely applied as catalyst for sp–sp and sp^2–sp C–C coupling reactions without a Cu(I) promoter spontaneously affords a palladium(0) complex “$Pd(TPPTS)_n$”



Scheme 1 Formation of $Pd(TPPTS)_3$.

[62]. Using $PdCl_2(TPPMS)_2$ as catalyst, benzyl chloride could be carbonylated to form phenylacetic acid in 93% yield. The reaction is accelerated by addition of surfactants [63].

The X-ray structure of $Pd(TPPMS\text{-}K)_3(H_2O)_4$ obtained by reductive phosphination of K_2PdCl_4 with TPPMS has been determined [64 a]. $Pd(TPPMS)_3$ is a highly efficient catalyst for C–C coupling reactions between aryl and heteroaromatic halides with aryl- and vinylboronic acids and alkynes in biphasic systems and single-phase aqueous media [64]. This catalyst system using either TPPMS or TPPDS is also active in Stille-type coupling reactions (cf. Section 6.6) between organohydroxotin complexes $K_n[RSn(OH)_{3+n}]$ or organotin trihalides and aryl halides [65, 66]. Water-soluble $ArPdL_2I$ complexes ($L = TPPMS$, **2b** ($R = R' = Ph$) [19, 21 b, 22 a], which may be envisaged as intermediates in these reactions, have been isolated [22 a]. Pd(0) complexes formed in the $TPPTS/Pd(OAc)_2$ system have been employed as catalysts for the syntheses of polynuclear aromatic compounds by cross-coupling reactions [67]. The same catalyst was employed for the substitution of allylic substrates with carbon- and heteronucleophiles under mild conditions [68]. A catalyst mixture of $[Rh(cod)Cl]_2$ and TPPDS gives excellent yields in coupling reactions of arylboronic acids to olefins in aqueous media employing SAPCs [126].

Using a catalyst mixture of $Pd(OAc)_2$ and TPPTS, TPPMS or **1c** ($R' = Me$, $n = 0$) [69–72] in a molar ratio of about 1:5, telomerization of butadiene to octadienol could be achieved with high efficiency in micellar systems formed by addition of surfactants (cf. Section 6.9). Surprisingly, butadiene conversion and octadienol selectivities were not affected significantly by the hydrophilicity of the phosphines. Selectivity reached an unprecedented value of 97% with **1c** ($R' = Me$, $n = 0$), employing $C_{12}H_{25}NMe_2$ as surfactant precursor. This was interpreted in terms of the steric effects on the ligands, the cone angles increasing significantly within the series Ph_3P (145°), TPPMS (151°), TPPTS (166°), and **1c** ($R' = Me$, $n = 0$) (194°) [46]. The Pd/TPPTS catalyst has been very recently employed in the reductive carbonylation of nitroaromatic compounds in aqueous biphasic systems proceeding in a highly selective manner and tolerating reactive functional groups [73]. For the reduction of nitroaromatic compounds with molecular hydrogen the complex $Rh(CO)Cl(TPPTS)_2$ was used as catalyst [74].

Ni(0) complexes of TPPTS have been employed as catalysts for the hydrocyanation of dienes and unsaturated nitriles (cf. Section 6.5). Product linearity and catalyst lifetimes can be improved if the catalysis is performed in a xylene/water biphasic system by using TPPTS as co-catalyst [75]. The Ni(0)/TPPTS complexes employed may be obtained by electrochemical reduction of $Ni(CN)_2$ in water in presence of TPPTS [76].

Dual metal Rh/Ir/TPPTS catalysts have been employed in the hydroaminomethylation of 1-pentene with synthesis gas ($CO:H_2 = 1:5$) and ammonia in an aqueous two-phase system [127]. With this catalyst system good *n*/*i*-selectivities and a rapid hydrogenation of the imine to amine have been observed. Both primary and secondary amines can be formed with high selectivity by variation of the olefin : NH_3 ratio.

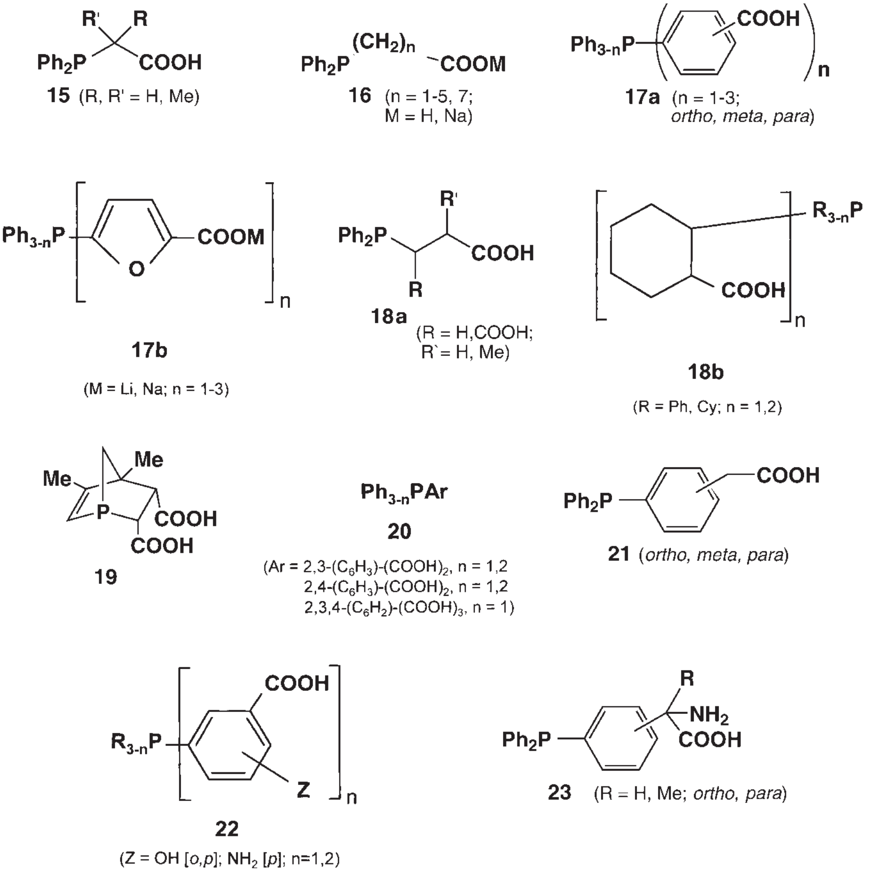
Catalysts Containing Electron-donating Phosphines with Sulfonated Alkyl Side Chains

Rhodium(I) complexes $HRh(CO)L_3$ of alkali-metal phenylphosphinoalkylsulfonates (L = **6a**, $n = 3, 4$; **6c**) have been used as catalysts for hydroformylation of higher olefins (e.g., *n*-1-tetradecene) in methanolic solution. The catalyst could be recovered with loss of activity by extraction of the isolated product with water. Using the bis-sulfonated ligand **6c** instead of monosulfonated **6a** more than half of the aldehyde was reduced to the alcohol [25]. The electron-donating water-soluble phosphines **5a** have been used to generate aqueous catalysts with $Rh(CO)_2(acac)$ for hydroformylation of 1-octene, its conversion increasing with increasing *n*. On reaction of **5a** (L) with $Rh(CO)_2(acac)$ complexes Rh(acac)(CO)L are formed initially, which with dihydrogen give $HRh(CO)L_3$. These complexes, which are stable for L = TPPTS, decompose via oxidative addition of water to yield $[H_2Rh(CO)L_3]^+OH^-$, to which the dihydride structure **14** has been assigned [77]. Zwitterionic cobalt(I) complexes $Na_5[Co(CO)_3L_2]$ obtained from $Co_2(CO)_8$ and the electron-donating water-soluble phosphines **5a** (L) are precatalysts in aqueous biphasic and SAP systems, giving almost exclusively the aldehyde [78]. Palladium(II) complexes $PdCl_2L_2$ of **5c** (L) and **6a** (L) have been proposed as catalysts for the hydrodehalogenation of allyl and benzyl halides using potassium formate as hydrogen source in a biphasic water/heptane system. The selectivity (allylbenzene vs. propenylbenzene) was controlled to a larger extent by different surfactants than by variation of the ligands [79]. The complexes formed from bis(dibenzylideneacetone)palladium and the electron-rich $Et_2PCH_2CH_2SO_3Na$ (**6b**) are effective catalysts for telomerization of conjugated dienes [28].

3.2.1.2.2
Phosphines Containing Carboxylated Aromatic Groups and Side Chains

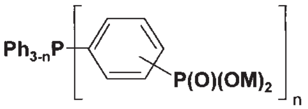
Ligand Syntheses

Structures **15–23** are hydrophilic phosphine ligands bearing carboxylic groups. In contrast to their alkali-metal salts, the free acids show only moderate solubilities in water. The ligands **15–17a** have been obtained by standard preparative methods



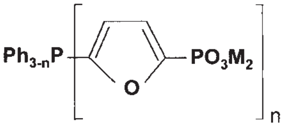
Carboxylated phosphines.

comprising alkylation and arylation of alkali-metal organophosphides in organic solvents (THF, DME, dioxane) [80–82]. Improved synthetic procedures based on the nucleophilic phosphination of fluorobenzoic acids [83] or Pd-catalyzed P–C coupling reaction of bromo- and iodobenzoic acid with primary or secondary phosphines [20] are known. These methods are of broad applicability and can be used also for the syntheses of multiply functionalized phosphinocarboxylic acids (**20**, **22**) including the diphenylphosphinophenylacetic acids (**21**) and the novel phosphine ligands containing amino acid moieties (**23**) [84]. Phosphines of type **16** ($n = 2$) have been obtained by oxidation of hydroxyalkylphosphine–borane complexes with chromic anhydride in sulfuric acid following by decomplexation with NEt_2H [85]. Schumann and co-workers published a multistage synthesis for the ligands **17a** [86]. The novel bicyclic carboxylated phosphine **19** was obtained using the [4 + 2] dimer of 3,4-dimethyl-2*H*-phosphole as a starting material [87]. Free-radical or base-catalyzed addition of secondary phosphines or phosphine–borane



24a

(M = Et, H, Na [*o*,*m*,*p*]; n = 1-3)

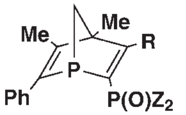


24b

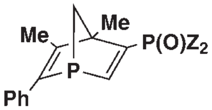
(M = Li, Na; n = 1,2)

$R_2P-(CH_2)_n-P(O)(OM)_2$

25 (M = Me, Et, iPr, H, Na; R = Ph, Et; n = 1-3, 6, 10, 12)



26 (Z = NEt_2, OEt, OH, ONa; R = Ph, H)



27 (Z = NEt_2, OH, ONa)

Phosphonated phosphines.

complexes to unsaturated carboxylic esters followed by saponification gave the mono- and dicarboxylated phosphines **18a** and **18b** [88]. A new type of water-soluble phosphines bearing furyl groups has been described by Mathey. The carboxylated and phosphonated furyl-phosphines **17b** and **24b** (see Section 3.2.1.2.3) are accessible via a three step synthesis [128].

Catalysts Containing Carboxylated Phosphines as Ligands

Compared with their sulfonated analogs, phosphine ligands containing carboxylic acid moieties have been much less investigated as catalyst components, although some of them (e.g., Ph_2PCH_2COOH, **15**) have already been applied at an early stage in the Shell Higher-olefin Process (SHOP; cf. Section 7.1) [89], the first large-scale industrial biphasic but non-aqueous catalytic process.

The surface-active rhodium(I) complexes obtained by ligand exchange between $RhCl(Ph_3P)_3$ and long-chain ligands of type **16** were found to be effective catalysts for hydrogenation of olefins and polybutadiene in aqueous and non-aqueous biphasic media. Terminal olefins were hydrogenated much faster than internal ones. An unusual enhanced reaction rate was observed for the internal double bond in 2-pentene and 3-pentene nitriles [90]. Rh(I) complexes of the amphiphilic ligands of type **17a** ($n = 1$, *para*) have shown to be active catalysts in 1-octene hydroformylation. They could be separated from the product by basic extraction into water and re-extraction after neutralization into a new batch of *n*-octene with toluene [91]. Preliminary experiments of van Leeuwen and co-workers [92] have shown, however, that this ligand in its protonated form with $Rh(CO)_2(acac)$ produces complexes that are insoluble in all common solvents and water at variable pH values. They were of low activity in hydroformylation of *n*-octene due to formation of polymeric rhodium carboxylate structures. The binuclear thiolato-bridged Rh(I) complex $[Rh(CO)(\mu\text{-}SPh)(\mathbf{17a})]_2$ containing the carboxylated ligand **17a** ($n = 1$, *meta*) catalyzes trimerization of propynoic acid or phenylacetylene in aqueous or biphasic medium (toluene/water), trimesic (38%) and trimellitic acid (62%) or 1,2,4- and 1,3,5-triphenylbenzene (22%, 5%) being formed [58].

3.2.1.2.3
Phosphines Containing Phosphonated Aromatic Groups and Alkyl Side Chains

Ligand Syntheses

The water-soluble phosphonate-functionalized phosphines **24a** ($M = Na$, $n = 1$) have been obtained by halogen–metal exchange on bromophenyldiphenylphosphines with *n*BuLi followed by reaction with diethylchlorophosphate and subsequent hydrolysis [93]. An alternative more generally applicable synthesis of phosphines of type **24a** ($n = 1$, 3) comprises the nucleophilic phosphination of fluorophenylphosphonic esters or amides with metal phosphides [94]. Triphenylphosphine derivates of type **24a**, bearing one and two phosphonato groups ($n = 1$, 2), have also been synthesized in high yields by consecutive Pd-catalyzed P–C coupling reactions [94a]. ω-Alkylphosphonate-functionalized phosphines **25** are accessible by reaction of $Li{-}CH_2P(O)(OiPr)_2$ with $BrPPh_2$ ($n = 1$), alkylation of Ph_2PLi and Ph_2PH with ω-bromoalkylphosphonates ($n = 2$, 3, 6, 10, 12) [27, 95, 129a] and by addition of Ph_2Ph on vinyldiethylphosphonate ($n = 2$) [129a]. The synthesis of the bicyclic phosphines **26** and **27** is based on the [4 + 2] cycloaddition of ethynyl phosphonates or phosphonamides to 1-phenyl-3,4-dimethylphosphole [96]. Hydrolysis with HCl or de-ethylation with Me_3SiBr followed by hydrolysis gave the free acids in all cases; neutralization with NaOH yielded the sodium salts.

Catalysts Containing Phosphonated Phosphines as Ligands

The cationic palladium(II) complex $[Pd(\mathbf{24a})_3Cl]^+$ of the *para*-isomer of **24a** ($M = Na$) catalyzes the carbonylation of benzyl chloride in basic medium to give phenylacetic acid in high yields. The Pd(0) complex $[Pd(\mathbf{24a})_3]$, formed by reduction of $[Pd(\mathbf{24a})_3Cl]^+$ with CO, is asumed to be the catalytic species [93] (see Scheme 1). Palladium complexes of ligands related to **24a** ($M = Na$) have also been employed in aqueous ethylene glycol phases as catalysts for Suzuki-type C–C cross-coupling reactions for the syntheses of substituted biphenyls (cf. Section 6.6) [97].

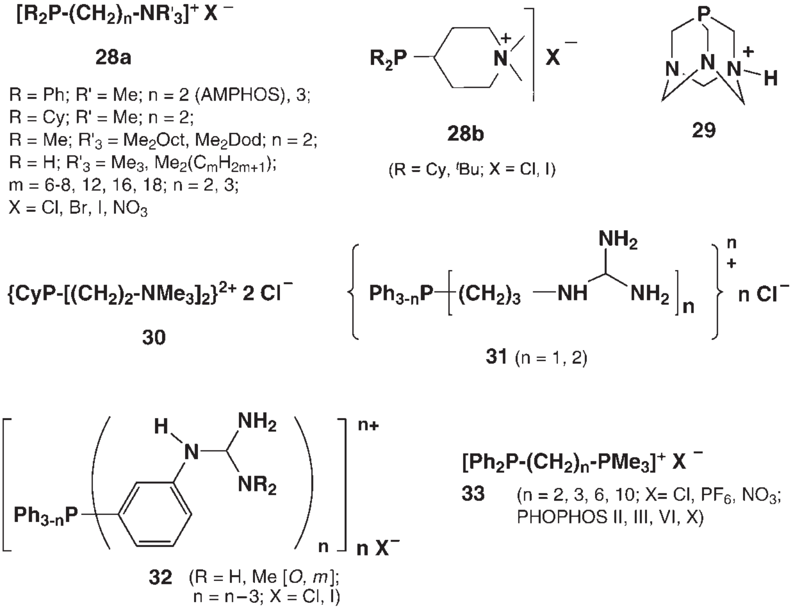
In aqueous two-phase hydroformylation of 1-octene and 1-dodecene the amphiphilic ligands of type **25** ($n = 10$, 12) have been shown to form Rh catalysts that are superior to Rh/TPPTS systems [129]. The bicyclic ligands **26** were considered to be of interest as substitutes for TPPMS in the new oxo process developed by Union Carbide for the hydroformylation of higher olefins using *N*-methylpyrrolidone or polyalkylene glycols as solvents [7, 51, 52]. Rh(I) complexes $[Rh(\mathbf{26})_2]^+$ [96] showed, however, a very poor performance as catalysts in biphasic systems for hydrogenation and hydroformylations in contrast to non-functionalized 1-phosphanorbornadiene [98]. This was explained by formation of P,P(O) chelates blocking the catalytic cycle. This hypothesis was confirmed by the pronounced activity of analogous Rh(I) complexes obtained from **27** (Z = ONa) for which P(O) chelation is not possible for steric reasons.

3.2.1.3
Cationic Phosphines

3.2.1.3.1
Ligand Syntheses

The synthesis of AMPHOS, the prototype of cationic phosphines, known for almost 20 years, requires intermediate protection of the phosphorus in $Ph_2P{-}(CH_2)_2{-}NMe_2$ by oxidation or coordination to a transition metal before *N*-quaternization [99, 100]. In the case of the ligands **28a**, **28b**, and **30**, borane was used as the protecting group.

Thus, starting with tBu$_2$P(H)BH$_3$, Cy$_2$P(H)BH$_3$ and CyP(H$_2$)BH$_3$ base-assisted aminoalkylation, *N*-quaternization and *P*-deprotection with morpholine gave **28a**, **28b** or **30** (R = *t*Bu, Cy) [101]. Further AMPHOS analogs could be obtained without using a protecting group by two-phase protected selective *N*-quaternization and subsequent *P*-alkylation of primary phosphines $H_2P{-}(CH_2)_n{-}NR_2$ [102]. Phosphines **33** bearing terminal phosphonium groups are accessible by quaternization


$[R_2P\text{-}(CH_2)_n\text{-}NR'_3]^+ X^-$

28a

R = Ph; R' = Me; n = 2 (AMPHOS), 3;
R = Cy; R' = Me; n = 2;
R = Me; R'$_3$ = Me$_2$Oct, Me$_2$Dod; n = 2;
R = H; R'$_3$ = Me$_3$, Me$_2$(C$_m$H$_{2m+1}$);
m = 6-8, 12, 16, 18; n = 2, 3;
X = Cl, Br, I, NO$_3$

28b

(R = Cy, ^{t}Bu; X = Cl, I)

29

$\{CyP\text{-}[(CH_2)_2\text{-}NMe_3]_2\}^{2+}\ 2\ Cl^-$

30

31 (n = 1, 2)

32 (R = H, Me [*O*, *m*]; n = n−3; X = Cl, I)

$[Ph_2P\text{-}(CH_2)_n\text{-}PMe_3]^+ X^-$

33 (n = 2, 3, 6, 10; X= Cl, PF$_6$, NO$_3$; PHOPHOS II, III, VI, X)

Cationic phosphine ligands.

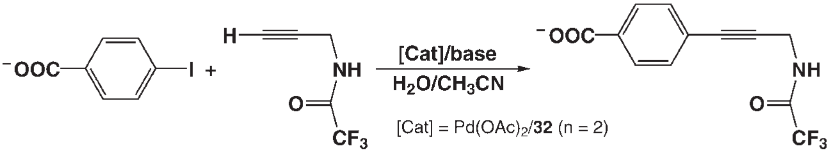
of PMe_3 with ω-chloroalkyl-diphenylphosphines or alkylation of $LiPPh_2$ with ω-halogenoalkylphosphonium salts $[X{-}(CH_2)_n{-}PMe_3]^+X^-$, respectively [103].

Ligands **31** and **32** containing guanidinium moieties constitute a novel type of cationic phosphine ligand showing extreme solubilities in water. The guanidinium groups were introduced into the corresponding aminoalkyl- and aminoarylphosphines by addition of cyanamides $R_2N{-}CN$ (R = H, Me) or 1*H*-pyrazole-1-carboxamidine [104]. The phosphines of type **32** have also been synthesized by Pd-catalyzed P–C coupling reaction of *p*- and *m*-iodophenylguanidines with Ph_2PH or $PhPH_2$, respectively [20b,c].

3.2.1.3.2
Catalysts Containing Cationic Phosphines as Ligands

Rhodium(I) and cobalt(0) complexes of AMPHOS, $[(nbd)Rh(AMPHOS)_2]^{3+}$ and $[Co(CO)_3(AMPHOS)]_2(PF_6)_2$, were already being used in the early 1980s for the hydrogenation and hydroformylation of maleic and crotonic acid or styrene and 1-hexene in water or aqueous biphasic systems [99, 105]. The lower effectiveness of the Co catalyst was attributed to the lighter metal's proclivity to oxidation and phosphine dissociation. Binuclear thiolato-bridged Rh(I) complexes, $[Rh(CO)(AMPHOS)(t\text{BuS})]_2^{2+}2[BPh_4]^-$ are highly active catalysts for the hydrogenation of unsaturated alcohols and acids [106]. Water-soluble Rh(I) complexes of monoprotonated 1,3,5-triaza-7-phosphaadamantane (PTA), $[Rh(PTA)_2(PTAH)Cl]Cl$ (PTAH = **29**), have been used as catalysts for the regioselective reduction of unsaturated to saturated aldehydes with sodium formate in an aqueous biphasic system or dihydrogen in presence of ethanol as co-solvent [107]. The P-basicity of PTA and PTAH is believed to be similar to that of triarylphosphines, but the cone angles are smaller [108]. The cyclohexyl analog of AMPHOS (**28**, R = Cy) is less electron-donating than the corresponding ligand bearing an SO_3^- instead of an NMe_3^+ group. Their Ru complexes $L_2Cl_2Ru{=}CHPh$ (L = **28**) initiate ring-opening metathesis polymerization (ROMP) of 7-oxanorbornenes and ring-closing metathesis (RCM) of acyclic dienes in water, methanol, and aqueous emulsions (see also Section 6.10) [101].

Palladium complexes of AMPHOS (**28**, $R'_3 = Me_3$ and Me_2H; X = Cl) are suitable catalysts for telomerization of butadiene and isoprene in biphasic systems in the presence of CH_3OH/CH_3ONa. Conversion rates and selectivities are altered only very little upon catalyst recycling, the results obtained for butadiene comparing favorably with those obtained for TPPTS [109]. The cationic phosphines **28a**, **b**



(1)

$P(CH_2\text{-}OH)_3$

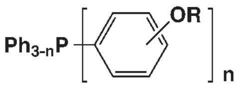
34

$Ph_{3\text{-}n}P[\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}(CH_2\text{-}CH_2\text{-}O)_m\text{-}R]_n$

35a (R = H, Me; m = 1-3; n = 1, 2)

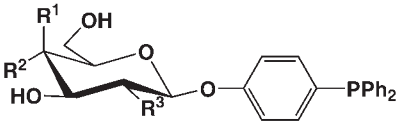
$Ph(R)P\text{-}CH_2\text{-}CH_2\text{-}O\text{-}(CH_2\text{-}CH_2\text{-}O)_2\text{-}R'$

35b (R = Oct; R' = H, Me)



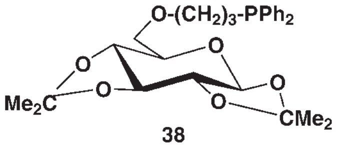
36

R = H, $(CH_2\text{-}CH_2\text{-}O)_mH$;
n = 1-3; m = 8-25)

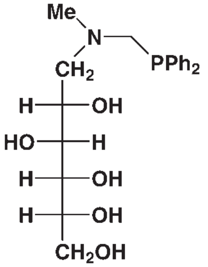


37

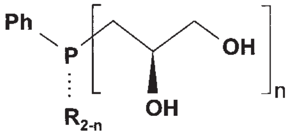
R^1 = H; R^2 = OH; R^3 = NHAc;
R^1 = OH; R^2 = H; R^3 = OH;
R^1 = H; R^2 = OH; R^3 = OH



38



39a



39b

(n = 1: R = H, Ph, Me and 4-C_6H_4-SO_3Na;
3-C_6H_4-[NH-C(NH_2)(NR_2)])

Nonionic water-soluble phosphines.

(R = *t*Bu) show excellent reactivity in palladium-catalyzed Suzuki-type C–C coupling reactions of arylbromides in aqueous solvents at room temperature [101 b]. A comparative study of the alkyl- and arylguanidinium phosphines **31** and **32** including TPPTS in the palladium-catalyzed Castro–Stephens C–C coupling reactions between *p*-iodobenzoate and (trifluoroacetyl)propargylamine has shown **32** to be of superior activity (see Eq. 1) [104]. Copper(I) iodide promotes the conversion rates but is not vital to these reactions. The Pd complex formed from $Pd(OAc)_2$ and TPPTS barely exceeds the $Pd(OAc)_2$-catalyzed background reaction.

Rh complexes of composition $[Rh(nbd)(\mathbf{33})_2]^+X^-$ containing the phosphonium phosphines **33** (PHOPHOS II, III, VI, X) have been shown to be very active catalysts for the biphasic hydrogenation of *n*-hexene and maleic acid in water [103, 110]. A definite chain length effect was observed, the system where $n = 6$ being the most active. The biphasic systems containing longer chain ligands are not well behaved as catalysts since they are prone to formation of stable emulsions which are quite difficult to break.

3.2.1.4
Nonionic Water-soluble Phosphines

3.2.1.4.1
Ligand Syntheses

Water-solubilization of organometallic catalysts is preferably performed by introduction of anionic or cationic functional groups into the phosphine ligands. The concept of attaining water-solubility by incorporation of hydroxylic groups into the ligand periphery has attracted much less attention. Large-scale syntheses for **34** [111] based on K_2PtCl_4-catalyzed addition of aqueous formaldehyde to PH_3 or decomposition of commercially available $[P(CH_2OH)_4]^+Cl^-$ have been published recently [112]. Ligands of type **35a** have been obtained by addition of $Ph_{3-n}PH_n$ to ethylene glycol monoallyl ethers [113]. Chiral ligands of this type, e.g. **35b**, showing unprecented η^3-mode bonding to transition metals, were prepared by Mathieu and co-workers [114]. The hydroxyphenylphosphines **36** are accessible by multistage syntheses [115] or by making use of the Pd-catalyzed P—C coupling reaction employing iodophenols as starting materials [20]. Ethoxylation of mono-, di- and tris-*p*-hydroxytriphenylphosphines with ethylene oxide yields polyether-substituted triphenylphosphines (PETPPs) designed for use in micellar [54, 116] and thermally regulated [117] phase-transfer catalysis. Ligands whose water-solubility is inversely dependent on temperature were first reported by Bergbreiter et al. [118]. This subject will be discussed in more detail in Sections 3.2.4, 4.5, and 4.6.3.

Ligands incorporating the diphenylphosphine moiety into sugar structures have been reported by a number of authors [119]. This subject has been reviewed by Blaser [120]. In most cases, however, the hydroxyl functions were fully (e.g., **38**) or at least in part protected, the solubilities of these ligands (especially those of the acetonides) in water being low [113]. By two-phase glycosidation of acetyl-protected halopyranoses with *p*-hydroxyphenyldiphenylphosphine at ambient temperature and subsequent O—Ac deprotection the aryl-β-*O*-glycosides of glucose, galactose, and glucosamine (**37**) could be obtained [121]. Temperature-dependent partition coefficients in the system water/ethanol/di-*n*-butyl ether indicate thermally reversible solvation for **37** ($R^1 = H$, $R^2 = OH$, $R^3 = NHAc$). The sugar phosphines **39a** have been synthesized by a Mannich-type condensation involving hydroxymethyldiphenylphosphine and sugars which incorporate the amine function [122]. The reaction of primary or secondary phosphines with enantiopure (*S*)- or (*R*)-glycidol in superbasic media (KOH/DMSO) leads to chiral hydroxylated phosphines **39b**. By reaction of **39b** ($n = 1$, $R = H$) with fluorophenylsulfonate or *m*-iodophenylguanidine chiral hydroxylated phosphines with additional guanidinium or sulfonate groups have been synthesized [130].

3.2.1.4.2
Catalysts Containing Neutral Phosphines as Ligands

Homoleptic Ni(0) and Pd(0) complexes of **34**, $M[P(CH_2OH)_3]_4$, have been reported [112]. The rhodium complexes, e.g., *trans*-$RhCl(CO)[P(CH_2OH)_3]_2$, are relatively active catalysts for the water-gas shift reaction [108]. The catalytic activities and n/i selectivities of Rh(I) complexes $HR(CO)_nL_m$ of 3-hydroxyphenyldiphenylphosphine (L = **36**; R = H; $n = 1$) and unmodified Ph_3P in *n*-octene hydroformylation in organic solvents (toluene) are comparable [92]. Within the new catalyst recycling approach, which is not solely restricted to water but can switch between an organic and aqueous phase by varying the pH of the system, the ligand **36** could not be employed, however, because of its weekly acidic character [91]. The Pd complexes obtained from the sugar phosphines **37** and $Pd(OAc)_2$ turned out to be catalytically more active in Heck-type and Suzuki-type C–C coupling reactions than those formed with TPPTS. This was attributed to the higher catalyst concentration of the organic phase in the case of **37**. The concept of thermally regulated phase-transfer catalysis has been successfully applied to the biphasic hydroformylation of *n*-1-dodecene using Rh(I) complexes of **36** (L; R = $(CH_2CH_2O)_mH$; $n = 1-3$) of composition $HRh(CO)L_3$ obtained by reaction of the ligands with $Rh(CO)_2(acac)$ in a syngas atmosphere [116, 117].

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3.2.2
Diphosphines and Other Phosphines

Marcel Schruder Goedheijt, Paul C. J. Kamer, Joost N. H. Reek,
Piet W. N. M. van Leeuwen

3.2.2.1
General

Tertiary phosphines represent the major class of ligands used in homogeneous catalysis to stabilize metal centers in low oxidation states (cf. Section 3.2.1). Recent developments in the field, for example, rhodium-catalyzed hydroformylation in the organic phase have shown that the selectivity of the reaction is greatly enhanced toward the production of linear aldehydes [1, 2, 50] upon replacement of monodentate ligands for bidentate ligands, often at the expense of activity. The next logical step to deal with the problem of product separation is the conversion of chelating diphosphines into water-soluble derivatives. A powerful strategy to obtain water-soluble ligands for organometallic catalysis is the attachment of ionic or polar substituents. This is usually done by introducing sulfonate groups, either by direct sulfonation or at an earlier stage in the synthesis of the diphosphine. Other classes of water-soluble diphosphines include diphosphines with quaternized aminoalkyl or aminoaryl groups, diphosphines with hydroxyalkyl or polyether substituents, carboxylated diphosphines, and amphiphilic diphosphines (cf. Sections 3.2.2.2 – 3.2.2.7). Chiral diphosphines will not be discussed here (see Section 3.2.5).

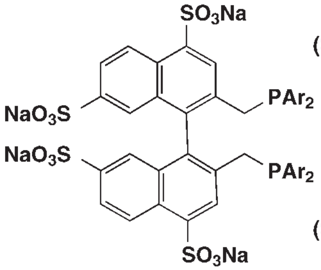
3.2.2.2
Diphosphines – Introduction of Sulfonate Groups by Direct Sulfonation

As already outlined in Section 3.2.1, several water-soluble monophosphines, such as TPPTS, have been synthesized by controlled sulfonation in oleum. In the same way several diphosphines have been sulfonated (Structures 1 – 5). Although the number of chiral diphosphines reported is ever increasing, the number of sulfonated achiral diphosphines remains limited and includes BINAS-8 (**1**) [3, 4] and BISBIS (**2**) [5], both of which contain an aromatic bridge between the two phosphi-

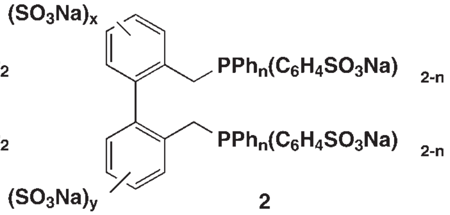
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

no moieties, and the alkyl-bridged bidentates 1,2-bis[di(3-sulfonatophenyl)phosphino]ethane (**3**) [6] and 1,3-bis[di(3-sulfonatophenyl)phosphino]propane (**4**) and some analogues [51]. Sulfonated analogous of Xantphos have also been prepared using this strategy and these water-soluble ligands form rhodium complexes that are very selective in the hydroformylation of alkenes [52].



1 Ar = C_6H_4-*m*-SO_3Na



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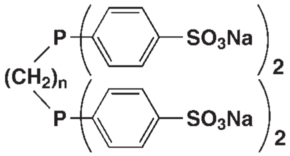
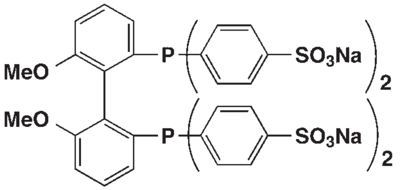


3 n = 2
4 n = 3



5

The precise control of the number and position of the sulfonate groups remains a challenge. The concentration of SO_3 and reaction temperature have a major effect on the degree of sulfonation [3]. The best results are obtained when the SO_3 concentration is ± 25–40% and the temperature is not allowed to rise above room temperature. Oxidation of phosphorus may be avoided using a method recently developed by Herrmann et al., which makes use of a superacidic medium derived from orthoboric acid and anhydrous sulfuric acid [8a]. In that manner, BINAP was sulfonated almost without formation of phosphine oxides (≤ 3 mol%). The isolation of the sulfonated ligands is often difficult, but by successive extraction with methanol, to remove inorganic salts, and subsequent filtration, the diphosphines are obtained in appreciable purity. The more economical method (and obligatory for industrial use) is extinction with tertiary amines [8b]. A more recent strategy to isolate the sulfonated diphosphines, involves the precipitation of the sulfonated ligand prior to neutralization, a procedure which simplifies scale-up [53].

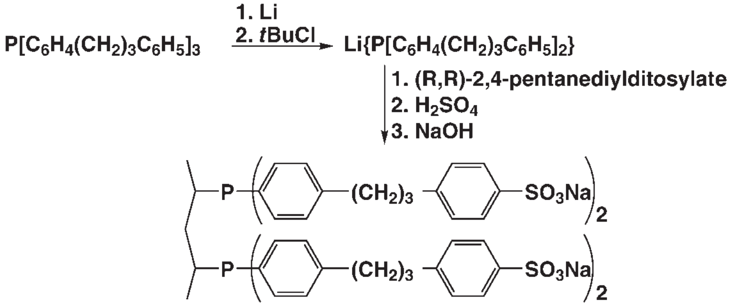
The diphosphines **1** and **2** were tested as ligands in the rhodium-catalyzed *biphasic* hydroformylation of propene. Both catalysts were found to exhibit higher activities and gave rise to higher *l*/*b* ratios [4] than TPPTS. Furthermore, it was shown that displacement of the *biphenyl* unit of **2** by a *binaphthyl* unit in **1** leads to an increase of the catalytic activity which was ascribed to electronic effects. In addition, the steric effect of the binaphthyl unit was proposed to cause higher *l*/*b* ratios.

The alkyl-bridged diphosphine **3** was also tested as a ligand for hydroformylation in the *biphasic* process, but it was found to be not very active [9]. The use of previously described ligands in catalysis will be discussed in more detail in Chapter 6.

3.2.2.3
Introduction of Sulfonate Groups During Synthesis

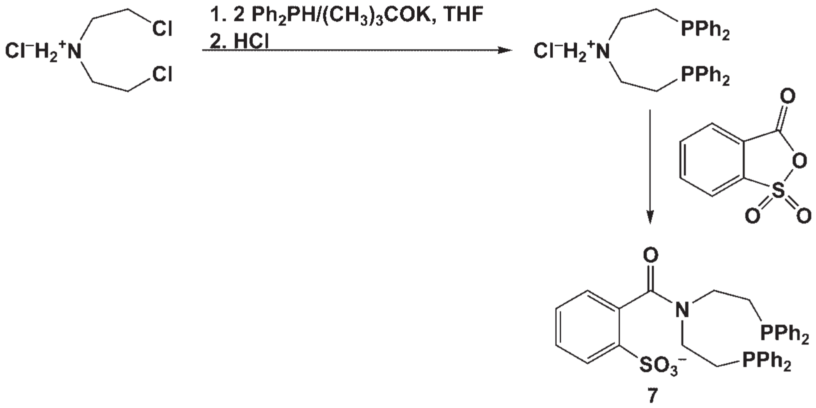
Sulfonate groups can also be introduced during the course of the diphosphine synthesis. For example, as shown in Scheme 1, the surfactant sulfonate derivative of bis(diphenylphosphino)pentane is formed by reaction of $Li\{P[C_6H_4(CH_2)_3C_6H_5]_2\}$ with (*R*,*R*)-2,4-pentanediylditosylate and subsequent sulfonation with sulfuric acid [10]. Here, the phenyl group that is not attached directly to phosphorus is less deactivated for sulfonation.

The tetrasulfonated product **6** is formed in high yield after 6 h. The ^1H and ^{13}C NMR spectra were consistent with sulfonation in the *para* position; that is, only the AA′BB′ pattern of the signals expected for *para* substitution in an aromatic ring is observed in the ^1H NMR spectrum. Diphosphine **6** was used in the asymmetric hydrogenation of prochiral olefins in a two-phase system consisting of water and dichloromethane or ethyl acetate. The *ee* values varied from 18 to 75%. From dynamic light-scattering experiments it was shown that **6** forms aggregates with a radius of 25 Å in aqueous solutions that are 0.01 M in **6** and 0.25 M in NaCl, though its suggested surface-active character has only a minor influence on its catalytic activity. Furthermore, its activity decreased when a salt, such as Na_2HPO_4, was added, which is not surprising because there is no excess of phosphine present to form micelles at high ionic strength. Also, in other systems it has been observed that high ionic strength, inhibiting micelle formation, has the effect of decreasing the activity in two-phase system with a poorly water-soluble substrate.



6

Scheme 1 Synthesis of the surfactant sulfonate derivative of 2,4-bis(diphenylphosphino)pentane.

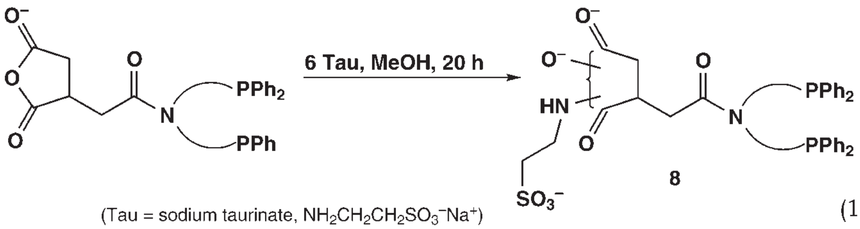


Scheme 2 Reaction of bis[2-(diphenylphosphino)ethyl]amine · HCl with *o*-sulfobenzoic anhydride.

In the same way as has been described for **6**, *chiral* tertiary arylphosphines, such as the atropisomeric tetrasulfonate (*R*)- or (*S*)-MeO-BIPHEP-TS **3** were prepared [11] (cf. Section 3.2.5).

Functionalized diphosphines which carry sulfonic acid groups in one or more side chains are also known. This class of compounds has mainly been developed by Whitesides and co-workers [12–14]. For example, acylation of bis[2-(diphenylphosphino)ethyl]amine, which was first prepared by Sacconi et al. [15], with *o*-sulfobenzoic anhydride in the presence of HCl afforded the water-soluble diphosphine **7** in high yield (Scheme 2) [14]. It was found that **7** is highly soluble in water, although the complex **7** · Rh(I)nbd$^+$Tf$^-$ (nbd = norbornadiene, Tf = triflate) was only sparingly soluble. This was ascribed to coordination of the sulfonic acid group to rhodium, resulting even in a decrease of activity when used as a homogeneous hydrogenation catalyst. Related effects have been observed with sulfonated triphenylphosphine complexes [16].

Another example published by Whitesides and co-workers is the preparation of diphosphine **8** using sodium taurinate as the sulfonate donor. Diphosphine **8** and its metal complexes appeared to be highly water-soluble, with a concentration in aqueous solution of ± 0.3 M (pH 7.0, 25 °C) [13]. In the same way, several other diphosphines were synthesized.

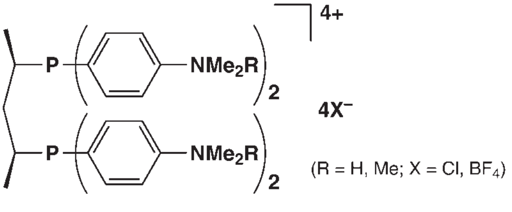


(Tau = sodium taurinate, $NH_2CH_2CH_2SO_3^-Na^+$) (1)

The corresponding rhodium complexes L · Rh(I)nbd$^+$Tf$^-$ (L = diphosphine) were prepared *in situ* and appeared to form homogeneous solutions in water, although in some cases formation of micelles was observed, especially at higher temperatures. Not only were these cationic rhodium complexes shown to be catalytically active in homogeneous hydrogenation reactions in water using several substrates, such as unsaturated carboxylic acids, but also they may catalyze the water-gas shift reaction [13].

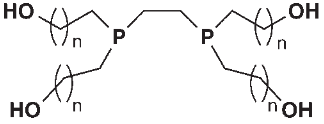
3.2.2.4
Diphosphines with Quaternized Aminoalkyl or Aminoaryl Groups

Quaternization of nitrogen atoms of aminoalkyl or aminoaryl diphosphines opens up another route to water-soluble diphosphines (cf. Section 6.1.5). One of the first (chiral) diphosphines that has been synthesized by this method was shown to be very soluble in water [54], which stimulated several others to use similar procedures to prepare chiral water-soluble diphosphines [55]. Before quaternization, the phosphorous atom has to be protected either by oxidation (e.g., with hydrogen peroxide) or by coordination to a metal. Subsequent reduction or decomplexation then affords the water-soluble diphosphine. For example, Tóth and Hanson have synthesized the *chiral* diphosphine **9** with *p*-trimethylaniline substituents opposite phosphorus [17]. Stelzer and co-workers used a strategy involving a palladium catalyzed P–C coupling reaction to introduce water-soluble groups in (di)phosphine ligands [56], which can be used to prepare guanidinium modified (di)phosphines (cf. Section 3.2.1) [57].



(R = H, Me; X = Cl, BF$_4$)

9

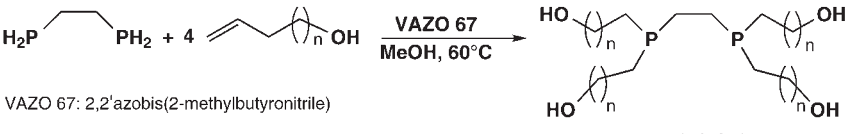


10 n = 0
11 n = 2
12 n = 3
13 n = 4

3.2.2.5
Diphosphines with Hydroxyalkyl or Polyether Substituents

Investigations into water-soluble hydroxyalkyl-substituted phosphines were first carried out by Chatt et al. [18]. Klötzer et al. reported the synthesis of 1,2-bis[di(hydroxymethyl)phosphino]ethane (**10**, $n = 0$; DHMPE) [19], and Boerner and co-workers synthesized several *chiral* bis(phosphines) bearing hydroxyl groups [20].

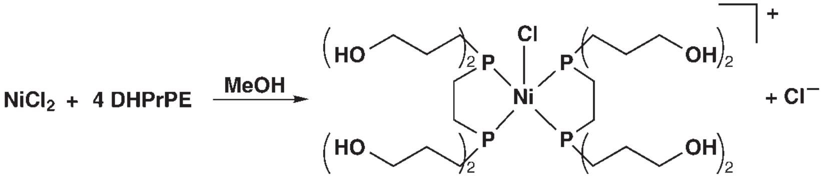
The synthesis of 1,2-bis(di(hydroxyalkyl)phosphino)ethane were alkyl is propyl (**11**, $n = 2$, DHPrPE), butyl (**12**, $n = 3$, DHBuPE) or pentyl (**13**, $n = 4$, DHPePE) was described [21 a]. They were synthesized by the well-known reaction [22] between an olefinic alcohol and 1,2-bis(phosphino)ethane under free-radical conditions in good yields (Eq. 2).



VAZO 67: 2,2'azobis(2-methylbutyronitrile)

(2)

To demonstrate the potential use of these ligands in aqueous catalysis, several metal complexes were prepared and characterized. For example, the reaction of **11** with $NiCl_2$ in a 2 : 1 ratio in methanol gave an orange product identified as $Ni(DHPrPE)_2Cl$ (**14**; Eq. 3). The structure of **14** was confirmed by X-ray crystallography (Figure 1). As expected, due to its cationic nature it is highly water-soluble (> 0.5 M). In the same way, complexes similar to **14** were synthesized from **12** and **13** with $NiCl_2$. Both complexes were found to be highly water-soluble as well (> 0.5 M), which was determined by monitoring the solubility of the ligand in the presence of $NiCl_2$. For example, the solubility of the DHPePE (**13**) ligand is $\pm$ 0.002 M in water, whereas the solubility in the presence of 0.5 equiv. of $NiCl_2$ increases the solubility of the ligand to > 0.5 M. The solubility of the metal complexes in water can be attributed to the hydrophilic hydroxyl groups, which surround the outside of the complexes, but even more to the charges on the molecules.



(3)

14

Besides Ni(II) complexes, Ru(III), Rh(I) and Rh(II) [21 b] complexes were prepared with these ligands which also appeared to be highly water-soluble. The sodium sulfonate analog of **11**, DSPrPE in which OH is replaced by SO_3Na, was synthesized [21 b] and was shown to be highly soluble in water (1.5 M). Rh(I) complexes with DSPrPE were demonstrated to hydrogenate alkenes completely with a higher selectivity and activity than a similar system prepared with TPPTS.

Pringle and co-workers found that formaldehyde adds readily to primary diphosphines, without the need for a catalyst, to give bidentate, water-soluble diphosphine ligands with bis(hydroxymethyl)phosphino groups [23].

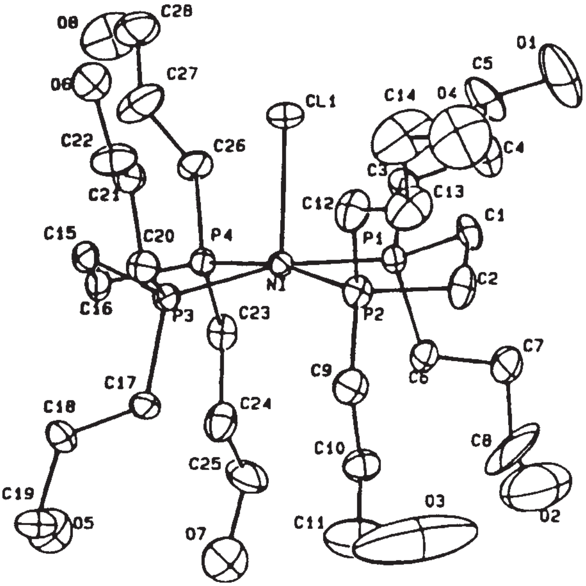
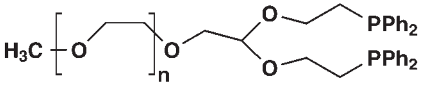


Fig. 1 X-ray crystal structure of Ni(DHPrPE)$_2$Cl$_2$ (**14**). Reproduced by the permission of the American Chemical Society (© 1997 American Chemical Society).

Substituting a phosphine with a polyether chain may also make the phosphine water-soluble. However, diphosphines of the type **15** (Structures **15**–**17**) are only soluble in water when $n > 15$ [24]. This type of materials can also be used to prepare thermally responsive catalysts [58]. Other examples related to **15** are the class of compounds **16** (cf. Section 3.2.2.3; $n = 12$, 16, 110) and **17** ($n = 18$) [12, 25]. The number n gives the average value of the "degree of polycondensation". So far, these polyether-based diphosphines have mainly been used in asymmetric hydrogenation of prochiral substrates such as α-acetamidocinnamic acid where *ee* values vary from 11 to 91% depending on the reaction medium and ligand used (cf. Section 4.6.3).



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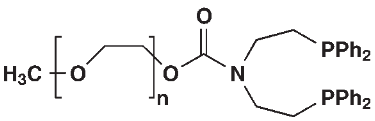

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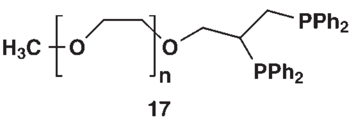

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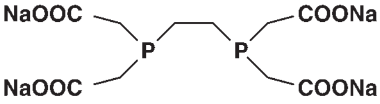
3.2.2.6
Carboxylated Diphosphines

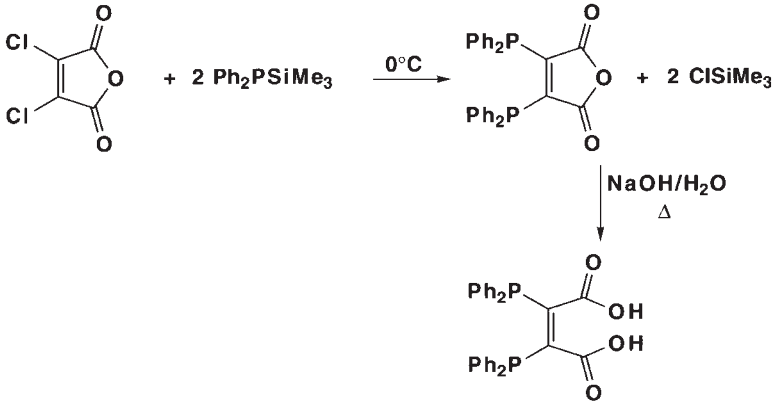
Phosphines with carboxylic groups were some of the earliest water-soluble phosphines investigated [26]. The group of Podlahová prepared a diphosphine, the phosphine analog of ethylenediaminetetraacetic acid, which is obtained as a monohydrate of the tetrasodium salt (**18**) [26]. Jegorov and Podlahová recently published a short review on the catalytic uses of these carboxyalkylphosphines [27].



18

Van Doorn developed a water-soluble diphosphine based on 2,3-bis(diphenylphosphino)maleic anhydride, which was converted into the biscarboxylic acid **19** with sodium hydroxide (Scheme 3) [28 a]. The compound was also described by Tyler and co-workers in 1993 [28 b].

An advantage over other methods for the preparation of water-soluble phosphines is that diphosphine **19** could easily be purified by extraction followed by crystallization from diethyl ether. The structure of **19** was confirmed by X-ray crystallography. The ligand is readily soluble in aqueous solution at pH 5 or higher. For example, the solubility is > 1 M at pH 7. At this pH the ligand is deprotonated. To demonstrate the utility of **19** in aqueous organometallic chemistry, solutions of several water-soluble complexes, such as $(cpCOOH)_2W_2(CO)_6$, were irradiated in the presence of the ligand. This resulted in the disporportionation of the metal



19

Scheme 3 Synthesis of the water-soluble diphosphine **19** based on 2,3-bis(diphenylphosphino)maleic anhydride.

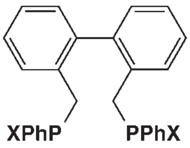
complex (Eq. 4), which proceeds analogously to the reaction of $cp_2M_2(CO)_6$ (M = Mo or W) and dppe (1,2-bis(diphenylphosphino)ethane) in benzene solution [29]. So far, the ligand has not been used for catalytic purposes.

$$[(\mathrm{CpCOO^-})_2\mathrm{W_2(CO)_6}]^{2-} + \mathrm{L_2}^{2-} \xrightarrow[\mathrm{H_2O,\ pH\ 10}]{h\upsilon} [(\mathrm{CpCOO^-})_2\mathrm{W^{II}(CO)_2(L_2{}^{2-})}]^{2-} + [(\mathrm{CpCOO^-})_2\mathrm{W^{0}(CO)_3}]^{2-} + \mathrm{CO} \tag{4}$$

$\mathrm{L_2}^{2-}$ = deprotonated **19**

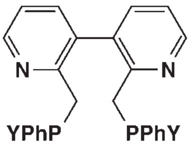
3.2.2.7
Amphiphilic Diphosphines

Another approach to water-soluble phosphines with the emphasis on metal recycling was reported by van Leeuwen and co-workers [30]. They have synthesized a number of diphosphines that, when coordinated to rhodium, form complexes having an amphiphilic character. The ligands synthesized are based on BISBI and Structures **20**–**22**, and hydroformylation (for example) can be conducted in a homogeneous (organic) phase [30a]. After it has been used in the hydroformylation of olefins the catalyst can be removed by acidic extraction. It was established that these novel diphosphines form active and highly selective catalysts. This amphiphilic approach, i.e., rhodium recycling abased on the extraction and re-extraction principle, will be discussed in more detail in Section 7.5.



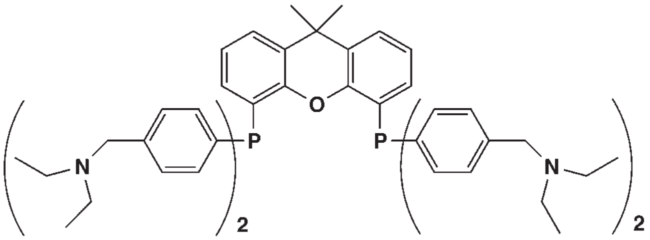
20

X = Py or 4-diethylaminomethylphenyl



21

Y = Py or Ph



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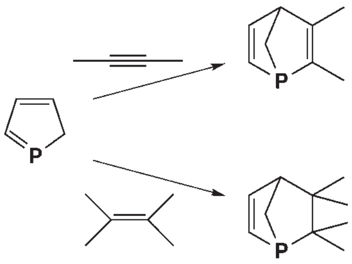
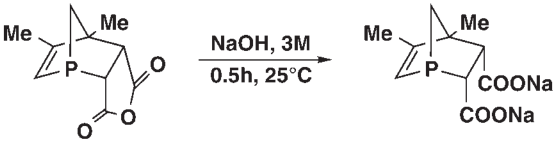


Scheme 4 Bicyclic phosphines based on 2*H*-phospholes.

3.2.2.8
Other Phosphines

Water-soluble mono- and diphosphines represent the major class of phosphines used in aqueous-phase homogeneous catalysis. However, some new types of water-soluble phosphines have been developed, including phosphines containing sugar substructures [31] or phosphonate chains [32], and chiral sulfonated phosphines for the asymmetric hydrogenation of dehydropeptides [33] and phosphines with amino acid moieties [59].

A different class was developed by Mathey et al. [34], who described a simple route for the synthesis of bicyclic phosphines with phosphorus atoms at the bridgehead from transient 2*H*-phospholes (Scheme 4) and water-soluble analogues **23**. These phosphines showed a significant activity in the rhodium-catalyzed hydrogenation [34] and hydroformylation [35] of olefins. In view of the growing academic and industrial interest in bisphasic catalysis, water-soluble versions of these phosphanorbornadienes represent a further logical development, if cheap enough. Mathey et al. extended the synthesis to water-soluble bicyclic phosphines starting from 3,4-dimethyl-2*H*-phosphole, which was reacted with maleic anhydride to give the 2*H*-phosphole-maleic anhydride [4 + 2] *endo* cycloadduct. Upon treatment with sodium hydroxide, this cycloadduct was converted into the sodium salt (**23**) of 3,4-dimethyl-1-phospha-2-norbornene-5,6-dicarboxylic acid, which proved to be very soluble in water (> 300 g/L) (Eq. 5). From NMR experiments it was shown that both carboxylate groups are on the *endo* side. The diacid, obtained when **23** is treated with 3 M hydrochloric acid, slowly loses water to regenerate the anhydride.



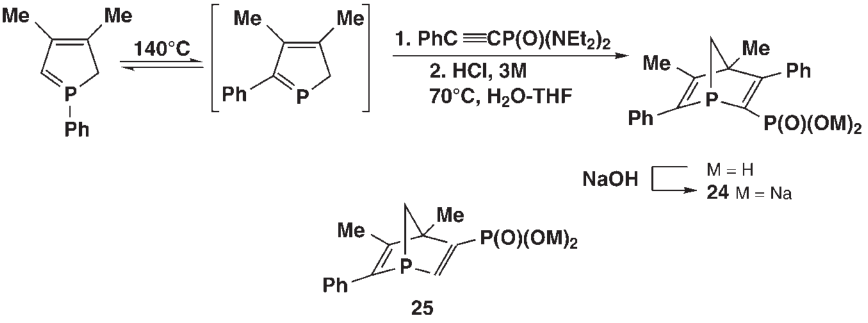
23

(5)

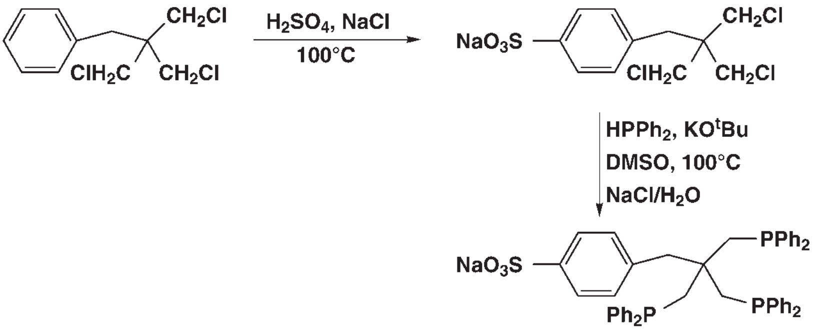
In line with the so-called NORBOS ligand, which shows an outstanding activity in the biphasic hydroformylation of propene [4], Mathey and co-workers developed several phosphanorbornadienes functionalized with phosphonate or phosphonamide groups [36]. For example, reaction of 2-phenyl-3,4-dimethyl-5*H*-phosphole, which was obtained by thermal isomerization of 1-phenyl-3,4-dimethylphosphole, with various (phenylethynyl)phosphonic acid derivatives produced phosphanorbornadienes having a phosphoryl group at C_2 (Scheme 5). Upon acid hydrolysis they could be converted into the corresponding phosphonic acid, of which the sodium salt (**24**) (after treatment with sodium hydroxide) is moderately soluble in water (20 g/L). Because of this low solubility, **24** was potentially of some interest as a substitute for the sodium salt of triphenylphosphinemonosulfonic acid, which is used in the proposed new oxo process developed by Union Carbide for the hydroformylation of higher olefins [37].

Various $[RhL_2]^+$ complexes of the functionalized phosphanorbornadienes used in the hydrogenation of 1-methylcyclohexene. However, the results were poor, which contrasts with the high activity observed for the nonfunctional 1-phosphanorbornadiene [38]. Poor results were also observed in the hydroformylation of 1-hexene catalyzed by $[Rh(CO)_2Cl]_2^+ \cdot 2\,L$, where L is **24**. These results were ascribed to a detrimental effect of the α-P(O) groups (formation of P,P(O) chelates), which block the catalytic cycle. This hypothesis was confirmed by using **25** (see Scheme 5) as a ligand, since in this case the hydrogenation proceeds quantitatively. The improvement is less impressive for the hydroformylation of 1-hexene, although it was found that **25** gave higher yields and rates than **24**. As expected, in this case the potential P(O) chelation has a less significant effect on the catalysis.

Besides the well-known applications of water-soluble phosphines, e.g., in hydroformylation, water-soluble catalysts may have significant advantages for electrochemical processes in which the much lower resistance of aqueous solutions compared with that of organic solutions would improve the energy efficiency of the process. It is known that the electrochemical reduction of carbon dioxide to carbon



Scheme 5 Synthesis of phosphanorbornadienes having a phosphoryl group.



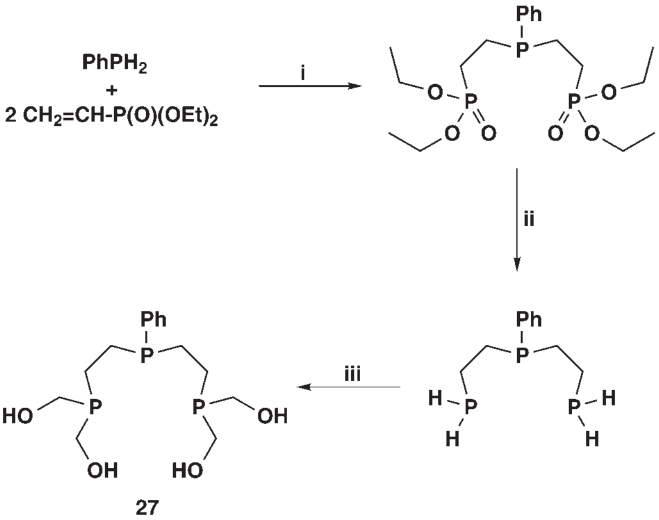
26

Scheme 6. Synthesis of SULPHOS (**26**).

monoxide in acidic acetonitrile or DMF solutions is catalyzed by [Pd(triphosphine)(solvent)]$(BF_4)_2$ [38]. These complexes exhibit interesting catalytic properties, such as high turnover rates and high selectivities (under appropriate reaction conditions). To study the effect of an aqueous environment on the rates and selectivities of these catalysts, various water-soluble triphosphine complexes of the type [Pd(triphosphine)(CH_3CH)]$(BF_4)_2$ were prepared by DuBois et al. [38]. Hydroxyl, phosphonate, or amines were used as water-solubilizing groups. The synthetic strategy used extends previous work on monodentate [31] and bidentate [39] ligands. As concluded from kinetic studies carried out in DMF solutions, the mechanism for the carbon dioxide reduction is the same as that proposed for complexes without water-soluble functional groups. In addition, the ligands may have applications in other catalytic processes in which water-solubility is an important feature.

Bianchini et al. [40] synthesized another water-soluble triphosphine, $NaO_3S(C_6H_4)CH_2C(CH_2PPh_2)_3$, the so-called SULPHOS (**26**; Scheme 6). This ligand is a TRIPHOS ligand [41] with a hydrophilic tail attached to the bridgehead carbon atom. It has been developed to facilitate catalyst separation in biphasic but aqueous systems. The synthesis involves the treatment of benzyltris(chloroethyl)methane with concentrated sulfuric acid at 100 °C, which results in the regioselective *para* sulfonation of the phenyl ring. Reaction of $NaO_3S(C_6H_4)CH_2C(CH_2Cl)_3$ with $KPPh_2$ in DMSO at 100 °C gives **26**. The complexes (**26**)Rh(cod) and (**26**)Rh$(CO)_2$ were used in biphasic catalysis as hydrogenation and hydroformylation catalysts respectively. Typical of the (**26**)Rh$(CO)_2$ catalyst system is that when methanol is used as a solvent, mainly alcohols are formed during the hydroformylation of higher olefins (*e.g.*, 1-hexene) whereas rhodium catalysts usually only produce aldehydes (e.g., the Rh/TRIPHOS system [41 a]).

Recently, Katti et al. developed the new water-soluble triphosphine $PhP[CH_2CH_2P(CH_2OH)_2]$ (**27**; Scheme 7) [42]. This triphosphine, upon interaction with [Rh(cod)Cl]$_2$ under biphasic (water/dichloromethane) conditions, produces a



Scheme 7 Synthesis of water-soluble triphosphine **27**.
Reagents: (i) $KOBu^t$, thf; (ii) $LiAlH_4$, Et_2O; (iii) HCHO, EtOH.

water-soluble rhodium(I) complex in which the rhodium center is tripodally coordinated *via* the PPh and $P(CH_2OH)_2$ functionalities, as established by NMR spectroscopy. The presence of PPh and $P(CH_2OH)_2$ groups of disparate basicities makes it unusual in comparison with the traditional triphosphines (e.g., TRIPHOS: $PhP(CH_2CH_2PPh_2)_2$). They suggested that the different basicities in **27** may aid the development of catalytically useful transition metal complexes in which the weaker of the two different M–P bonds may be reversibly cleaved in the presence of a substrate molecule.

The following topics have not been considered in this section: metal complexes of sulfonated 2,2′-bipyridine [43] and alizarin [44], water-soluble porphyrins and cyclopentadienyl ligands [45], and metal complexes of sulfonated phenanthroline derivatives [46]. Also *P,N*-bidentate phosphines [47], of which coordination properties await further study, have not been discussed here.

In conclusion, monophosphines are still the most widely investigated and applied water-soluble phosphines (e.g., TPPTS in the Ruhrchemie/Rhône-Poulenc process [48]). However water-soluble diphosphines and other phosphines, such as triphosphines, are currently under investigation; chelating diphosphines, for example, show significantly improved regioselectivity in hydroformylation and may have other advantages over monophosphines. The combination of recent successes of newly developed diphosphines and the success of the Ruhrchemie/Rhône-Poulenc process have led to the development of a range of new water-soluble di- and triphosphines. They might be applicable if cheap enough under industrial conditions [49].

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3.2.3
Ligands or Complexes Containing Ancillary Functionalities

Philippe Kalck, Martine Urrutigoity

Since the early preparation of TPPMS by Chatt and co-workers [1] in 1958 and the spectacular properties of TPPTS discovered by Kuntz in 1975 [2, 3], many complexes have been prepared, most of them in situ, containing in addition to the water-soluble phosphines other ligands required for catalysis, such as hydride, carbon monoxide, alkene, etc.

This section deals with complexes containing a main phosphorus ligand and ancillary organo- or water-soluble groups which make it possible either to tune the metal coordination sphere or to graft the complex onto various supports.

3.2.3.1
Complexes Containing at Least Two Classical Functionalities

Because of their great capacity of water-solubility, a large proportion of the research has been directed toward the sulfonated phosphines. Nevertheless, it is obvious that other hydrophilic functionalities can be introduced on phosphines. Adapting the kind and the number of hydrophilic groups, it is thus possible to have a better control of the water-solubility of the complex thus formed by this way.

3.2.3.1.1
Phosphanorbornadiene Phosphonate

As an introduction, it is of interest to report the special influence of the position of a functionality, taking as an example the phosphonation of 1-phosphanorbornadiene **1** [4]. This molecule has shown very good properties as a ligand for transition-metal catalyzed hydrogenation [5] and hydroformylation [6] of alkenes.

Therefore, the influence of the substituents on the water-solubility has been studied. For this purpose, a phosphonate group was introduced, leading to ligand **2**. This ligand is quantitatively extracted from water-saturated toluene and it is a good substitute for the sodium salt of triphenylphosphinomonosulfonic acid, which is operating the new hydroformylation process of higher olefins developed

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

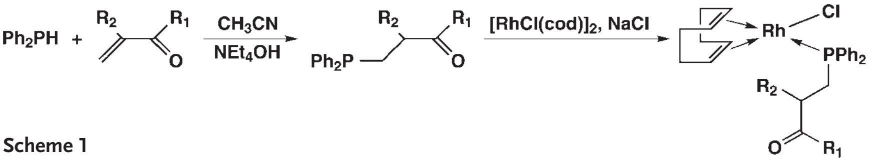
ISBN: 3-527-30712-5

by Union Carbide [7]. That molecule was used in the hydrogenation of (*Z*)-α-(*N*-acetamido)cinnamic acid. The results were poor compared with those obtained with the unsubstituted phosphanorbornadiene **1** [5]. In order to find a basis for the hypothesis that the inhibition of the catalytic cycle was due to P,P(O) chelate formation, molecule **3** was synthesized. Although the solubility of the sodium salt of molecule **2** was only 20 g/L, the solubility of the corresponding salt of **3** was 230 g/L. Used in catalysis, it allowed the quantitative hydrogenation of the substrate.

1 $R_1 = R_2 = Ph$
2 $R_1 = -P(O)(ONa)_2$, $R_2 = Ph$
3 $R_1 = H$, $R_2 = -P(O)(ONa)_2$

3.2.3.1.2
Complexes Containing at Least Two Functionalities

A few years ago, Patin and co-workers reported the synthesis under mild conditions of a series of ligands obtained from the mixture of Ph_2PH and an activated alkene in the presence of a small amount of tetraethylammonium hydroxide (Scheme 1) [8], and observed, when the olefin is very hygroscopic, that some phosphine oxide is produced. During complexation with rhodium, oxidation is avoided using an Rh(I) dimer as a precursor. The synthetic reaction is shown in Scheme 1 and the various complexes obtained are listed in Table 1.



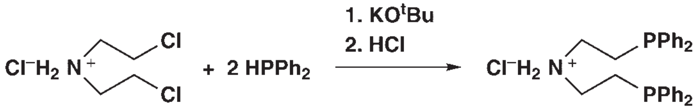
Scheme 1

Tab. 1 Listing of the various R_1 and R_2 substituents in Scheme 1.

R_1	*R_2*
$-NHC(CH_3)_2CH_2SO_3-NEt_4^+$	$-H$
$-OCH_2CH_2N^+(CH_3)_3I^-$	$-H$
$-OCH_2CH_2N^+(CH_3)_2CH_2CH_2SO_3^-$	$-CH_3$
$-OCH_3$	$-CH_2CO_2CH_3$
$-NHC(CH_2OH)_3$	$-H$
$-OCH_2CH_2N(CH_3)_2$	$-H$
$-OH$	$-CH_2CO_2H$

Grubbs and his group described an elegant method to prepare water-soluble alkylidene ruthenium complexes active in metathesis and containing the ligands $Cy_2P(CH_2CH_2NMe_3^+,Cl^-)$ or Cy_2P(*N*-methylpiperidinato chloride) [63, 64]. An interesting H/D exchange in protic media has been observed on the alkylidene moiety and this experimental fact opens the way to metathesis of biological substrates [65].

Generally, polydentate phosphines are synthesized by sequential introduction of phosphine units into a precursor [9]. Nevertheless, Whitesides and co-workers proposed a synthetic route by which diphosphine **4** is obtained in situ, as shown in Eq. (1) [10–12].



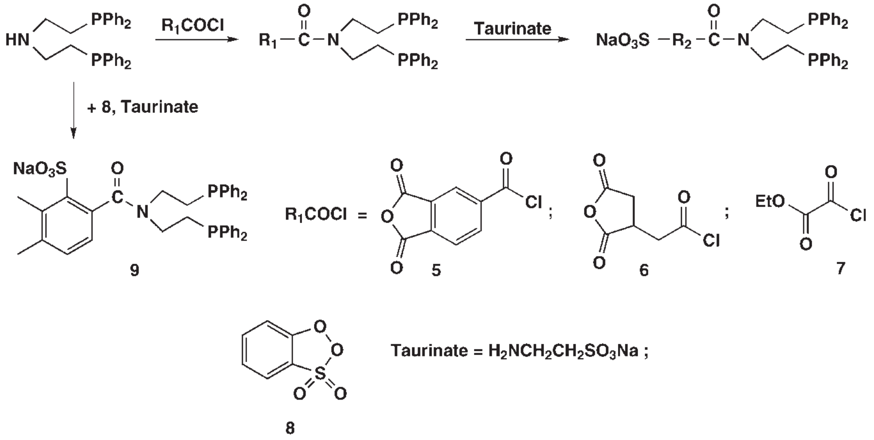
4

(1)

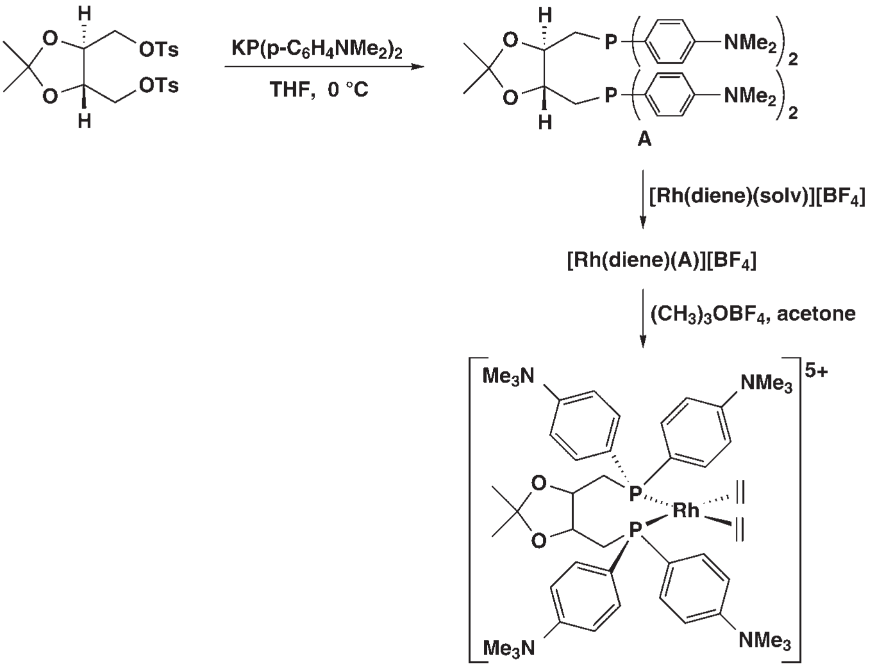
From this molecule, it became possible to synthesize easily various ligands containing complex frameworks, and different functionalities. Once acylated by acid chlorides, like molecules **5**, **6**, and **7** of Scheme 2, it reacts with sodium taurinate, $H_2NCH_2CH_2SO_3Na$. Complex **4** can also condense with sulfonic acid **8** in order to obtain **9**.

To extend Whiteside's method, it is possible to synthesize ligands containing hydroxyl, ether, or carboxyl groups [13], e.g. acid chlorides or anhydrides containing poly(ethylene glycol), poly(ether) or poly(hydroxyalkyl) chains. In Scheme 3 [12], the use of this method to synthesize water-soluble derivatives of the DIOP ligand is displayed [14, 15].

Smith and co-workers reported the synthesis of a new triphosphine ligand via formylation of $PhP(CH_2CH_2PH_2)_2$ [16, 17]. From $[Rh(cod)Cl]_2$ (cod = cyclooctadiene) or $[Pt(cod)Cl_2]$, the authors formed tripodally-coordinated complexes of Rh(I) and Pt(II) (**10** and **11** in Scheme 4 [16]).



Scheme 2



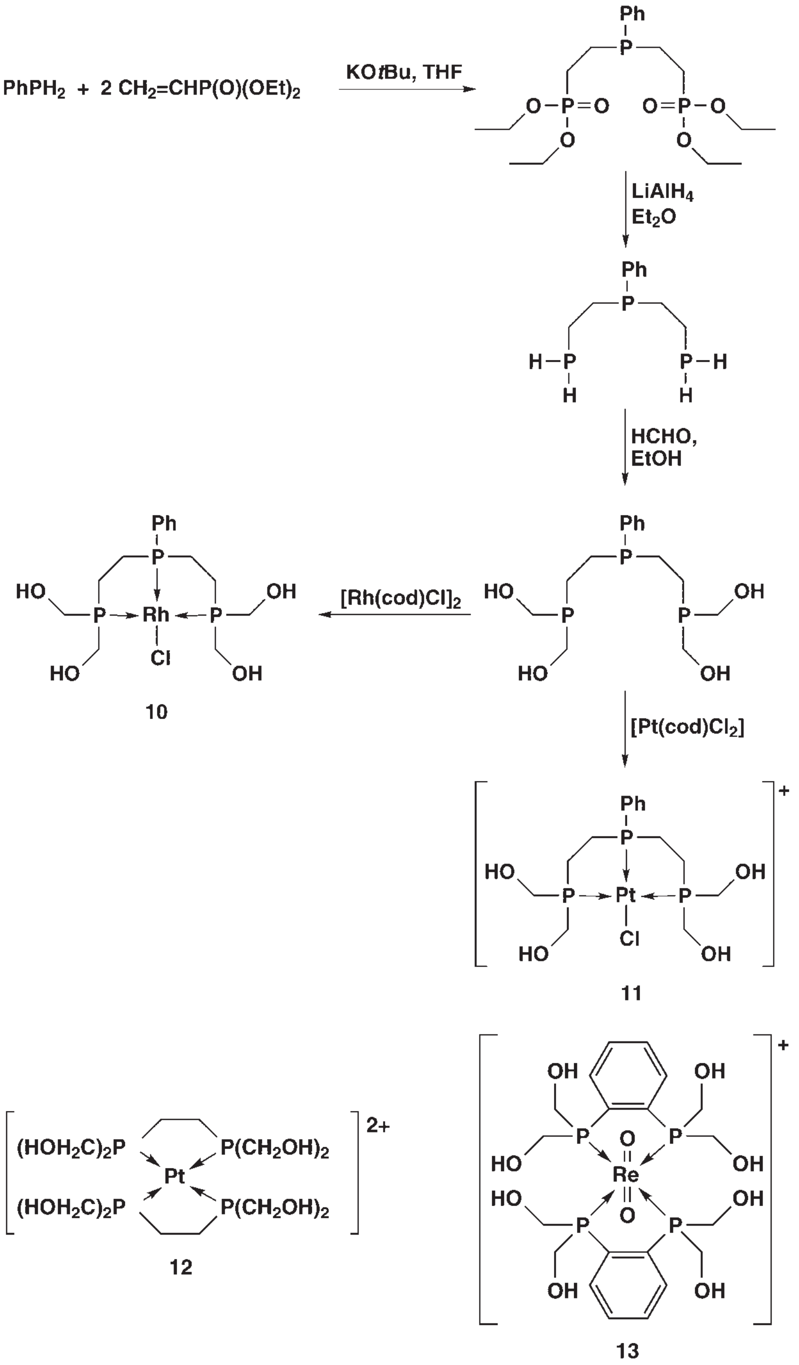
Scheme 3

In a recent review [66] devoted to hydrogenation reactions in aqueous media, Dwars and Oehme have listed various water-soluble mono- and diphosphine ligands bearing hydrophilic substituents which, in addition to the classical sulfonato or carboxylato groups, are hydroxy, ammonium, guanidinium, amine and polyether groups. Similarly, Bischoff and co-workers have phosphorylated various diphosphine ligands, many of them having the BINAP framework, and used the resulting mono- or diphosphonates to perform biphasic hydroformylation with Rh(I) precursors [67, 68].

3.2.3.2
Cationic Complexes

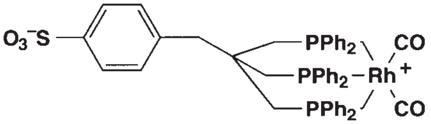
There are a few complexes containing more or less hydrophilic ligands which induce very high solubilities in water. For example, Sreenivasa Reddy et al. studied new ligands as in structures **12** and **13** [18–20]. The authors studied and characterized different complexes of palladium, rhenium, and platinum.

Water-solubility does not always depend solely upon the water-solubility of the functionalized ligand itself; it can also arise from specific water–metal interactions. The literature reports cationic as well as zwitterionic complexes [21–24]. These systems are not yet well known and some complexes can behave in an unexpected way. Thus, it has been reported that the SULPHOS–rhodium complex **14**

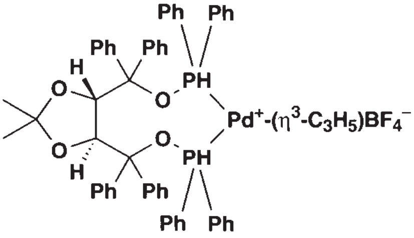

PhPH2 + 2 CH2=CHP(O)(OEt)2
KOtBu, THF
LiAlH4
Et2O
HCHO,
EtOH
[Rh(cod)Cl]2
10
[Pt(cod)Cl2]
11
12
13

Scheme 4

is not soluble in water but it is soluble in light alcohols or in 1 : 1 (v/v) alcohol–water mixtures even if each molecule is a zwitterion [21]. In the same way, complexes such as **15** with limited water-solubility and stability have been characterized and their reactivity has been studied [23, 24]. Even if authors did not mention it, the low solubility in water seems not to be a drawback for catalytic purposes.



14

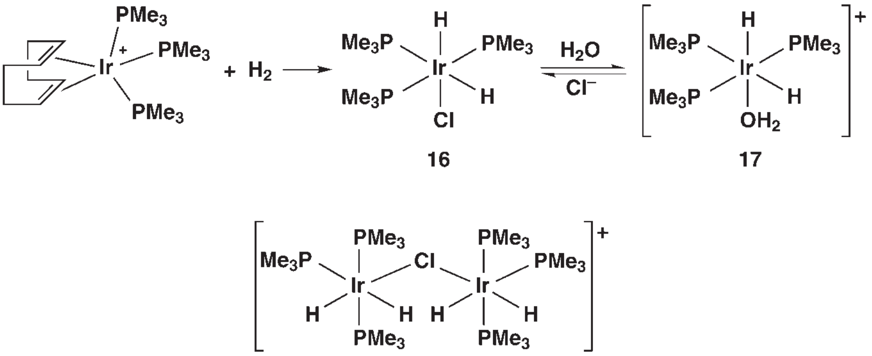


15

The chemistry of complexes containing cationic iridium has been studied by Merola and co-workers. Among all the complexes described in the literature, they reported the complex *cis,mer*-$(Me_3P)_3IrH_2Cl$, whose aqueous chemistry looks very rich [25]. It resulted from the oxidative addition of H_2 to $[Ir(cod)(PMe_3)_3]Cl$ [26]. From ^1H and ^{31}P NMR measurements, they showed that two different species are formed upon dissolution in water. One species is the cationic aquo complex [*mer,cis*-$(Me_3P)_3IrH_2(OH_2)$] **17** and the other one is the dinuclear cation **18** (Scheme 5).

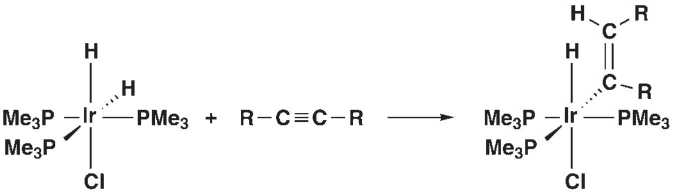
It was also demonstrated that both **16** and **17** are in equilibrium, which involves loss or gain of chloride ligand. Compound **16** is very reactive toward alkenes and alkynes in water, whereas it is absolutely unreactive in organic solvents. The reaction which takes place with alkynes is shown in Eq. (2).

In catalysis, **16** showed very good activity for the hydrogenation of alkynes and alkenes to alkanes or ketones to alcohols (cf. Section 6.2).



16 **17**

Scheme 5 **18**



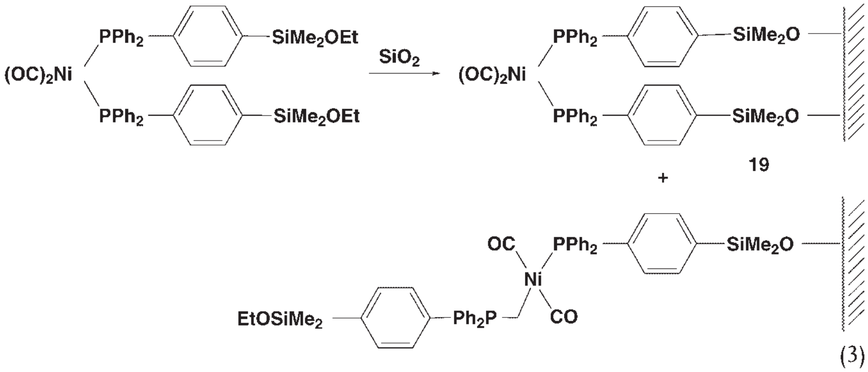
(2)

3.2.3.3
Immobilization on Silica Supports

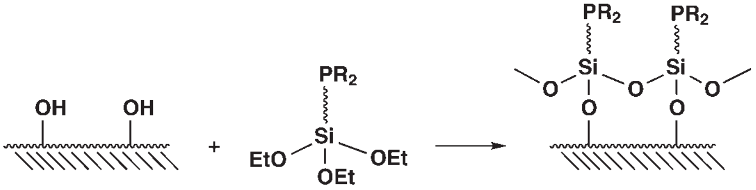
In order to combine all the advantages of both homogeneous (great activity and high selectivity) and heterogeneous catalysis (ease in separating catalyst from the medium), much work has been done with the aim of binding the active metal centers to organic polymers or inorganic oxides. Silica is certainly the most widely studied support in surface organometallic chemistry because it resists elevated temperatures and most solvents. These properties contribute greatly to enhance the lifetime and deactivation resistance of the catalyst. It is convenient to include the work done using silica with a thin film of water on its surface and generally called supported aqueous-phase catalysis (SAPC; see Section 4.7).

In 1992, Mercier and co-workers studied the chemoselective hydrogenation of several α,β-unsaturated aldehydes using, among other methods, SAPC [27, 28]. The catalysts were synthesized by adding a solution of a Ru-TPPTS complex to silica gel, resulting in two catalysts: $RuCl_2(TPPTS)_3/SiO_2$ and $RuH_2(TPPTS)_4/SiO_2$. Like Davis et al. [29–31], the authors assumed that the immobilization is due to strong interactions between the sulfonated groups and the silanol functions inside a thin surface water film (cf. Section 4.7). The kinetics of the reaction are largely governed by the transfer of the reactants from the organic to the aqueous phase and modeling has been established [69]. Other supports have been developed in order to improve this transfer phenomena [70, 71].

The catalyst immobilized in this way is often leached from the support during the reaction because of the oxidation of the ligand and above all because of insufficiently strong bonds or interactions [32–38]. There are two synthetic routes to obtain strong immobilization: (a) silica was phosphinated, then treated by the appropriate precursor although phosphine exchange was described as tedious and difficult to control, or (b) the complex was first coordinated by a bifunctional phosphine, then linked to silica [36]. This method allows good characterization of the complex before linking. In this latter method, one uses the weakly acidic properties of a silica surface and the silane condensation reactions of donor molecules containing terminal trialkoxy groups. Because of the flat surface of silica, the ligands act as anchors leading to a robust, densely packed, single layer of transition metal centers maintained either in water or in the interfacial region and soluble in the reaction medium. Behringer started from the monoalkoxy phosphine $PPh_2(C_6H_4)SiMe_2OEt$, which forms just one siloxane bridge, to graft a dicarbonylnickel onto a support (Eq. 3) [35].



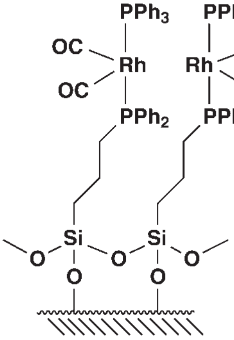
(3)



(4)

One can exclusively obtain species **19** grafted by the two phosphine chains when DIPHOS in very dilute solutions of toluene is added dropwise to a silica suspension at room temperature. Petrucci used the same approach but started from a trialkoxyphosphine (Eq. 4) [37], or reacted an amine with a terminal alcohol containing a phosphine [37, 38].

An example is provided by complex **20**. Placed in an acidic medium, the reaction can easily be carried out in biphasic conditions.



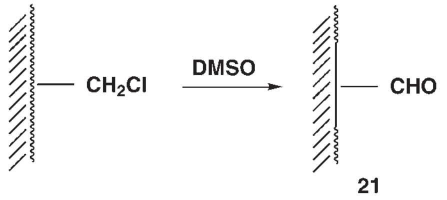
20

3.2.3.4
Macromolecular Ligands or Supports

3.2.3.4.1
Polymers

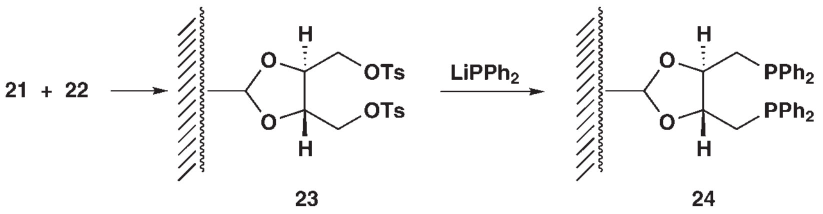
Using polymers was one of the very first methods in order to heterogenize the catalyst in a homogeneous catalytic reaction. Thus, thanks to these supports, the catalyst acquires the property of insolubility while maintaining its catalytic performance [39–42]. Some authors synthesized phosphonated resins, such as polystyrene, and used them as a ligand in several rhodium and platinum complexes. Thus, hydrogenation [43, 44], hydrosilylation [45], and hydroformylation of olefins were catalyzed.

Other authors have described the use of the previously seen framework [39]. The grafting of the DIOP ligand (Eqs. 5–7) onto a Merrifield resin was performed by treatment of the insoluble aldehyde **21** with the (+)-diol **22** of the DIOP, leading to the ditosylate **23**. This product was then treated with lithium diphenylphosphide, affording the desired phosphinated resin **24**, which contains 0.5 meq/g of phosphorus functions. The reaction with $[RhCl(C_2H_4)_2]_2$ gave an insoluble complex that may be used further in catalysis.



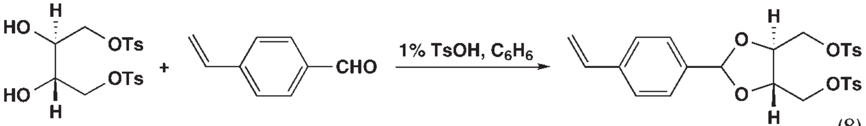
(5)

(6)



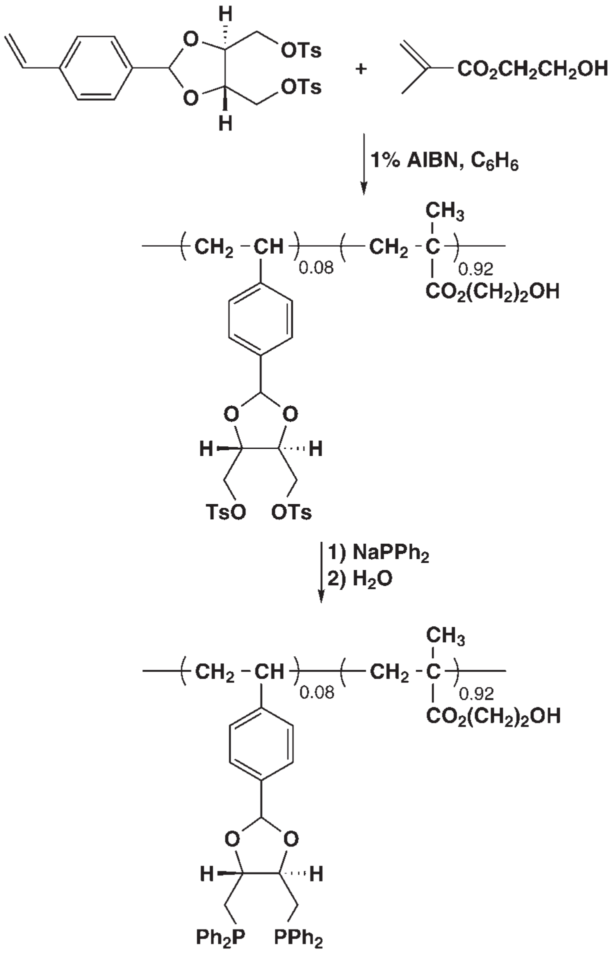
(7)

The second procedure is related to a copolymerization reaction [40]. Reacting (−)-1,4-ditosylthreitol with 4-vinylbenzaldehyde afforded a styryl monomer (Eq. 8). When this monomer (8% w/w) copolymerized at 70 °C with hydroxyethyl methacrylate (HEMA) in the presence of azobisisobutyronitrile (AIBN), the polymer formed was then treated with sodium diphenylphosphide (Scheme 6). The rhodium complex was obtained by reaction with [$RhCl(C_2H_4)_2]_2$.



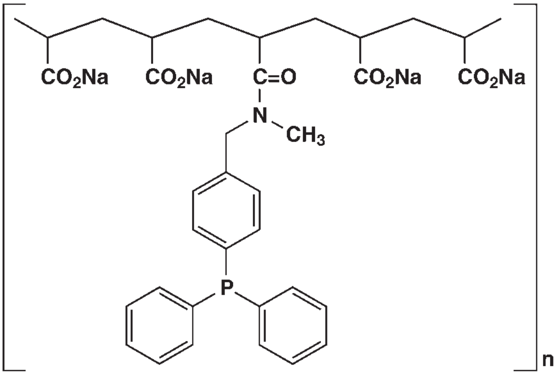
(8)

Although these authors used the supported catalyst only in benzene for the grafted polymer, and in polar solvents for the copolymer, it is obvious that these catalysts can be used in water: the copolymer is indeed insoluble but the active part is water-soluble.

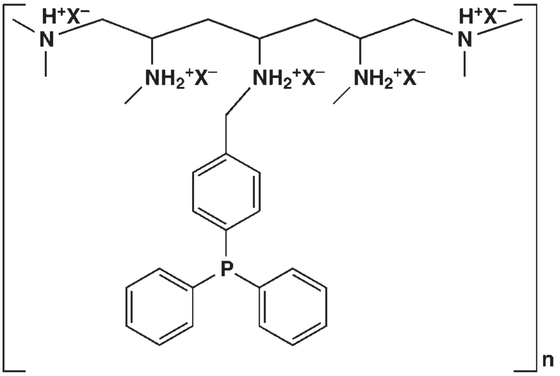


Scheme 6

Some years ago, Malmström et al. synthesized water-soluble metal phosphine complexes based on water-soluble polymers [41]. In order to have solubility in both an acidic and a basic medium, they prepared two different water-soluble polymers. For the first, they made methyl [4-(diphenylphosphino)benzyl]amine (PNH) react with poly(acrylic acid) (PAA) using dicyclocarbodiimide (DCC) as the coupling agent, under strict exclusion of oxygen (**25**). For the second, they reacted (4-carboxyphenyl)diphenylphosphine with polyethylene imine (PEI) at room temperature (**26**). The reduction by sodium borohydride was made in situ, followed by the addition of methanesulfonic acid and diethyl ether. Then, the methanesulfonic salt of phosphinated polyethylenimine was precipitated.



25 **PAA-PNH**



26 **PEI-PNH**

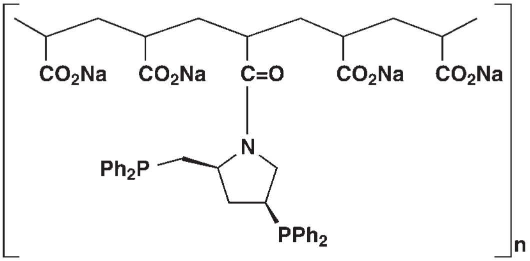
The main characteristics of both polymer-based phosphines are listed in Table 2. In both cases, water-solubility can be varied changing the phosphine groups to carbonyl or nitrogen ratios. To warrant a high solubility, these ratios were kept at ca. 5 for PAA and ca. 7 for PEI during all the experiments. More recently, an extension of this concept to chiral ligands was reported. (2*S*,4*S*)-4-diphenylphosphino-2-

Tab. 2 Comparison of various phosphines grafted onto polymers [41, 42].

Polymer	*PAA–PNH*	*PEI–PNH*	*PAA–PPM*
COO^-/P or N/P ratio	5	7	5
P or N content [%]	3.2	2.6	3.6
Water-solubility [mg L^{-1}]	165	260	115
pH dependence	pH ≥ 7	pH ≤ 6	–

diphenylphosphinomethylpyrrolidine (PPM) was acylated by PAA, using DCC [42]. Results are given in Table 2.

The reaction of an aqueous solution of PAA–PPM (**27**) with $[Rh(nbd)_2][CF_3SO_3]$ (nbd, norbornadiene) led to the *cis*-phoshino complex $[(PAA{-}PPM)Rh(nbd)][CF_3SO_3]$. Stirring an aqueous solution of this complex for 10 min under an H_2 atmosphere gave the solvato complex $[(PAA{-}PPM)Rh(H_2O)_2]^+$. $[Rh(nbd)_2][CF_3SO_3]$ was used for the hydrogenation of (*Z*)-2-acetamidocinnamic acid in water and in water–ethyl acetate. Results are given in Table 3.



27 PAA-PPM

Tab. 3 Enantiomeric excesses obtained in various solvents for the hydrogenation of (*Z*)-2-acetamidocinnamic acid [42].

Solvent	*pH*	*t* [min]	*Rh/alkene*	*Yield* [%]	*ee* [%]
H_2O	8.26	120	1:35	> 97	56
H_2O/EtOAc	7.00	50	1:83	> 97	74
MeOH	–	–	1:100	100	93

3.2.3.4.2
Dendrimers

Most of the phosphines used in enantioselective catalysis possess a chiral backbone terminated by two diphenylphosphino groups (cf. Chapters 3.2.2 and 3.2.5). The chiral information is transmitted from the ligands to the metallic center via ordering of benzene rings [46]. Owing to the size of these groups, a long-distance effect is forbidden in spite of their great effectiveness. Therefore, it is of interest to use the dendrimers model in order to increase the size of the optically active phosphines. Dendrimers are spherical polymers with a highly symmetrical structure [47–49]. Thanks to internal cavities and functional end groups, dendrimers possess unusual properties. Grafting terminal P(III) phosphine groups at the periphery of the P(V) dendrimer, it becomes possible to cover its surface with metal complexes.

To ensure a strong chelation effect on the metal center, the backbone of the ligand must contain a PCH_2CH_2P framework. The dendrimer is built up by successive branchings, the final layer containing an enantiomerically pure compound; as this compound can easily be changed, such a method appears to be very flexible. Because of the space-filling nature of the ligands, chiral information is forced toward the center of the catalyst, which was called by Brunner the "pocket of the catalyst," i.e., the place where the enantioselective reaction occurs.

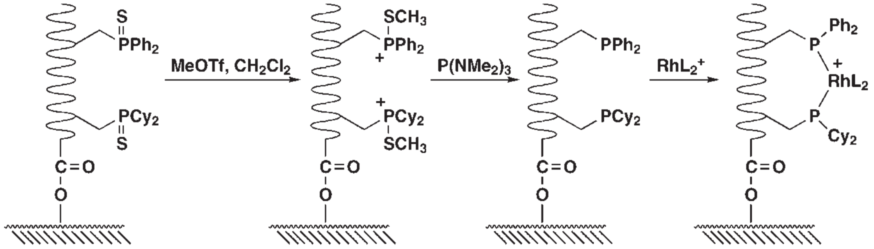
From a menthyl-based diphenyl ligand, a complex containing the $Rh(cod)^+$ residue was, for instance, easily obtained. This complex is soluble in toluene, pentane, and hexane; the ion pair Rh^+/PF_6^- is surrounded by a kind of "membrane" of menthyl groups whose hydrophobic sides are oriented toward the exterior, leading to the solubility in hydrocarbons. The presence of the Rh^+ cation and the PF_6^- anion suggests to us that this complex should be quite suitable for a biphasic catalysis. Indeed, water-soluble dendritic phosphonated ligands have been recently prepared by introduction of hydrophilic amine or sulfonic acid groups at the periphery. These ligands introduced in the coordination sphere of rhodium exhibit high activity for the biphasic hydroformylation of styrene and 1-octene [72].

A potentially attractive generation of dendritic architectures, mostly bearing carbohydrate entities, has appeared and will provide a useful pool of hydrophilic ligands [73, 74]. In such a way ferrocene-containing carbohydrate dendrimers open future prospects [75].

3.2.3.4.3
Peptides

For several years, the use of peptides in organometallic chemistry has been a growing area. The synthesis of peptides containing phosphine ligands opens new prospects for transition metal coordination chemistry. Indeed, it becomes possible to have a better control over the reactivity of the metal and to fix it in various membranes [50, 51].

In order to prevent formation of the unwanted phosphine oxide, the usual synthetic procedure is to convert phosphine to phosphine sulfide, the deprotection by Raney nickel restoring the phosphine. However, such a treatment [50] appeared inappropriate for the reduction of a large number of ligands [51]; then a new homogeneous reducing method was reported in which the sulfide-containing peptides remain attached to the polymer on which they are synthesized [52]. Phosphine sulfide is methylated by trifluoromethanesulfonate to give the phosphonium



Scheme 7

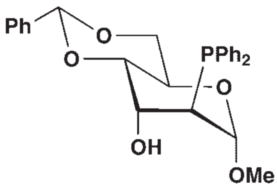
salt, which is treated with tris(dimethylamino)phosphine in order to remove the sulfur atom, giving the expected bis(phosphine) (Scheme 7) [51]. It is assumed that, as the peptides possess an α-helical secondary structure [53] and the phosphine-containing amino acids lie in the i and $i + 4$ positions on the same side of the α-helical structure, the phosphines are able to bind a metal. This bis(phosphine) is treated with $[Rh(nbd)_2][ClO_4]$ to give the desired complex, whose structure is not yet well known: it may be an α-helical peptide coordinated to rhodium by two phosphorus atoms, or one rhodium atom linked to two different peptides, or both structures at the same time. The authors assume that it is probably the last possibility which exists in the system.

This complex was tested as a catalyst precursor for the hydrogenation of an enamide in an experiment which showed a 100% conversion in spite of a low *ee* ranging from 4 to 9%.

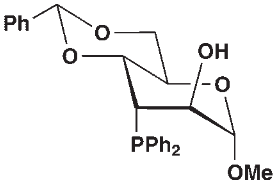
To demonstrate how powerful this method is, Gilbertson and Wang synthesized libraries of phosphines containing peptides, coordinated them to rhodium, and tested the corresponding precursors in asymmetric hydrogenation of enamides [76]. Although the enantiomeric excesses are still moderate (35–40%) the best solvent is water and this approach has proved its viability.

3.2.3.4.4
Sugars

Unexpected ligands were synthesized from sugars for asymmetric catalysis by Shi and co-workers [54]. They bound the phosphorus atom of a phosphine to a carbon atom in a system of pyrano rings (see **28** and **29**). The aim was to coordinate this chiral ligand with gold for medicinal applications. They reported synthesis and characterization of a series of gold(I) complexes whose general formula is [Au(P′)X], where P′ is for example methyl 4,6-*O*-benzylidene-2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside (2-MBPA, **28**) and X is a chlorine atom or pyridine-2-thiol. The authors assumed that the complex [Au(2-MBPA)Cl], which presents a chelate structure where the hydroxyl oxygen O(3) is bound to gold, gives rise to the release of HCl and then to the hydrolysis of the molecule. They also showed by crystallographic measurements that, for the phosphine ligands, the donor ability toward gold(I) decreases in the order DBP > DMPP > 2-MBPA > PPh_3 > PCy_3. Moreover, a cytostatic activity has been discovered for several glucose-ferrocenyl derivatives [77]; presumably such water-soluble ligands containing a ferrocenyl framework could also be used in catalysis.



28 2-MBPA



29 3-MBPA

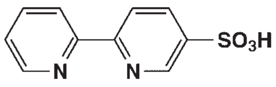
Following the original systems found by Selke et al. [78] who synthesized phenyl β-D-glucopyranoside containing vicinal diarylphosphinite ligands, which were coordinated to rhodium for asymmetric hydrogenation of dehydroamino acids in water, this strategy was extended to various polyhydroxyphospholanes. They were essentially built from mannitol moieties and cationic rhodium complexes. They were subsequently prepared to increase the solubility in water and they display excellent catalytic activity for the hydrogenation of dehydroamino acids, too [79]. An extension to the α,α-trehalose-derived phosphine–phosphinite (TREHAPPN) ligand and to the corresponding [(TREHAPPN)Rh(cod)]BF_4 complex has been reported [80].

Recently, such diphosphine ligands bonded to sugar have been adapted to a cyclodextrine. The synthesis was focused on a diphosphite framework, and the new ligand coordinated to rhodium. The resulting precursor is active for the enantioselective hydrogenation of dimethyl itaconate into (*R*)-(+)-methylsuccinate (*ee* = 84%), and moderately active for the hydroformylation of 1-octene [81]. Although the complexes were used in organic solvents, provided the phosphite would be changed with a nonhydrolyzable phosphine ligand, the concept deserves interest because a cyclodextrine presents its own solubility in water.

3.2.3.5
Ligands not Containing Phosphorus

3.2.3.5.1
Nitrogen-containing Ligands

The literature about ligands not containing phosphorus is scarce. Most of the articles report nitrogen-containing ligands, especially substituted bipyridine and ethylene diamine *N,N,N′,N′*-tetraacetic acid (EDTA), and were recently reviewed [12]. The most commonly used functionalities are sulfonate and carboxylic acid groups. The first functionalization consists of various mono- and disulfonated bipyridines, like the structures **30**–**32**. Formic or acetic acid is usually introduced on bipyridine (**33**), aniline and above all ethylenediamine. The most commonly used ligand in this chemistry is EDTA, and the synthesis of EDTA-containing complexes has been detailed in a recent review [55]. The chemistry of EDTA–ruthenium species was widely studied, especially by Taqui Khan and co-workers [56, 57]. They investigated the hydroformylation reaction catalyzed by $[Ru(EDTA)]^-$ and observed a poor selectivity for allyl alcohol but a satisfactory linearity starting from 1-hexene. They showed that the rate-determining step was the hydride transfer to the coordinated alkene.



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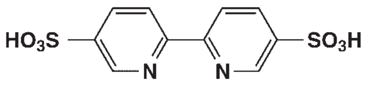

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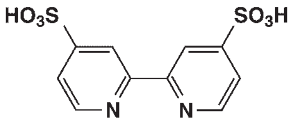

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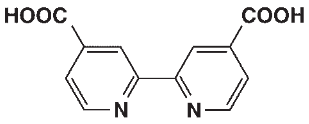


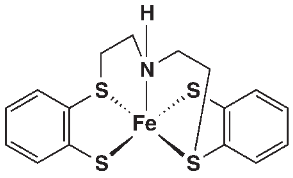
33

New pyrazolyl ligands containing an aminomethyl group, in position 4, have been coordinated to rhodium(I) and show a good solubility in water, presumably because the ammonium group does not interact with the metal center. The resulting complexes have been characterized and, in our opinion, they are good candidates for biphasic catalysis [82], such as 1,2,4-triazol-2-ium-5-ylidene complexes of Rh(I), Ir(I), Ni(0), Ni(II), Pd(II), and Hg(II) [83]. Due to their ionic character, these carbene complexes are extremely soluble in water.

3.2.3.5.2
Sulfur-containing Ligands

Studying iron models for the FeMo cofactor of FeMo nitrogenases, Sellmann et al. isolated iron complexes with sulfur ligands [58, 59]. Generally, complexes such as **34**–**36** are only soluble in organic solvents like CH_2Cl_2, THF, DMSO, or DMF.

They succeeded in rendering them water-soluble by introducing carboxylic acid functions. These iron or ruthenium complexes become water-soluble when the carboxylic groups are deprotonated. Various complexes of iron and ruthenium can be obtained according to the method developed. An example is given in Eq. (9) [58].



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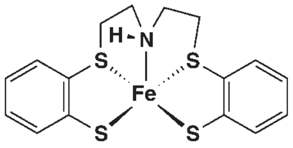

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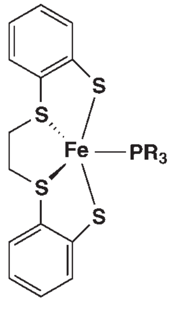

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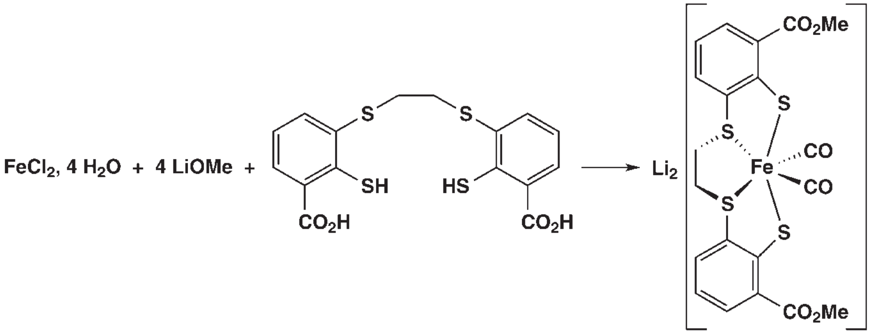


(9)

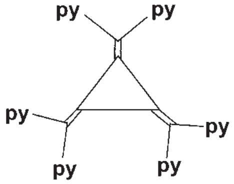
The dinuclear rhodium complex containing the water-soluble TPPTS ligand and the bridging *t*-butylthiolato ligands [$Rh_2(\mu\text{-}S^tBu)_2(CO)_2(TPPTS)_2$] was shown to be an active catalyst of the hydroformylation of alkenes [60]. This complex can also use the CO/H_2O couple to combine the water-gas shift reaction and the hydroformylation reaction under moderately acidic conditions [61]. This compound and a cationic complex containing two aminothiolato bridges, [$Rh_2(\mu\text{-}SCH_2CH_2CH_2NHMe_2)_2(CO)_2(TPPTS)_2]Cl_2$, catalyze more or less rapidly the hydroformylation of heavy alkenes in the presence of ethanol as co-solvent in order to increase the transfer between the organic and aqueous phases [62].

Interesting chiral water-soluble aminosulfonamide ligands containing a phenylsulfonic acid substituent have been synthesized and engaged directly with a ruthenium precursor to reduce enantioselectively aromatic ketones to the corresponding alcohols [84]. As concluded by the authors, these ligands should be evaluated in biphasic catalysis.

3.2.3.6
Additional Perspectives

In the recent literature, some papers deal with interesting ligands which, even they have not yet used in biphasic systems and thus could be considered as out of the scope of this chapter, draw new tendencies for elaborated water-soluble systems.

In addition to calixarenes which have been made water-soluble as new inverse phase-transfer catalysts [85], novel ligands have been designed, based on a cyclopropene moiety bearing pyridyl substituents and called [hexakis(2- or 3-pyridyl){3}-radialene] **37**. A metallosupramolecular chemistry is envisioned by the authors and the solubility in water and their stability offer innovative perspectives [86].



37

(py = 2- or 3-pyridyl)

At the opposite of the molecular chemistry described until now, nanoparticles are reminiscent of heterogeneous catalysts. However, these colloid-derived materials have been shown to catalyze efficiently in water coupling reactions which have been previously described in pure homogeneous systems. For instance, poly(*N*-vinyl-2-pyrrolidine)-stabilized palladium nanoparticles promote the Suzuki cross-coupling in aqueous media with high yields (see also Section 6.6) [87].

Single-wall or multi-wall carbon nanotubes have been functionalized with amino-acids, so that these nanomaterials can be solubilized in water and through all the lateral organic chains act as a multidentate ligand [88].

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3.2.4
Tenside Ligands

Georgios Papadogianakis

3.2.4.1
Introduction

Organometallic catalysis in aqueous/organic two-phase systems combines the inherent advantages of homogeneous catalysts (high activity and selectivity) with the facile catalyst separation which is the great advantage of heterogeneous systems, thus affording both economic and environmental benefits [1]. The highly water-soluble $RhH(CO)(TPPTS)_3$ complex catalyst (TPPTS = triphenylphosphine trisulfonate), for example, is applied in the Ruhrchemie/Rhône-Poulenc (RCH/RP) biphasic process for the hydroformylation of propene with a capacity of 800 000 t/a (debottle-necked) butyraldehyde (cf. Section 6.1.3.1). Other lower olefins such as 1-butene can also be hydroformylated with acceptable rates according to the RCH/RP process [2]. However, Rh/TPPTS catalysts exhibit low catalytic activity in the hydroformylation of higher olefins, due to the much lower solubility of such olefins in water. The reaction rates decrease dramatically with increasing C-number of the olefin. For example, 1-hexene is hydroformylated with conversions up to 22% [3] whereas the highly water-immiscible 1-tetradecene gives only traces of C_{15}-aldehydes [4].

Several concepts have been suggested to increases the rates in aqueous-phase catalytic conversion of higher substrates such as addition of conventional surfactants [3, 5] (cf. Sections 4.5 and 6.1.5), counter (inverse)-phase transfer catalysis using β-cyclodextrins [6] (cf. Section 4.6.1), addition of promoter ligands, e.g. PPh_3 [7], or co-solvents (cf. Section 4.3). However, addition of “foreign compounds” militates against the facile catalyst separation and purification of the products and increase the costs as well.

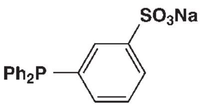
A particularly elegant approach to circumventing the solubility problem is to generate transition metal complexes from tenside phosphines which combine both the inherent properties of a ligand (appropriate steric and electronic environment) and a surfactant in one molecule, and to use them as catalysts in micellar systems.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

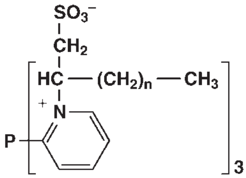
ISBN: 3-527-30712-5

3.2.4.2
Tenside Phosphines and Amines

The term “tenside” is synonymous with surfactant (surface-active agent), amphiphilic or amphipathic; it is *not* synonymous with detergent (often used interchangeably with “surfactant”), which is a substance capable of cleaning and contains, inter alia, surfactants. A surfactant is composed of a nonpolar hydrophobic (lipophilic) region, usually an elongated alkyl group called the tail, and a polar hydrophilic (lipophobic) portion (the head). It therefore has both pronounced hydrophobic and hydrophilic properties. Depending on the charges of their polar head groups, tensides are conveniently divided into anionic, cationic, zwitterionic (amphoteric), or nonionic. Surfactants are adsorbed at the interfaces of aqueous/organic two-phase systems, leading to a reduction of the interfacial tension. The term “hydrophile–lipophile balance” (HLB), according to Griffin [8], expresses the relative simultaneous attraction of a surfactant in the aqueous and nonpolar organic phases. The HLB value is an empirical number in the range from 1 (oleic acid) to 40 (sodium dodecylsulfate, SDS) where the low values indicate solubility in the nonpolar solvents and the high values solubility in water [8, 9c]. When surfactants are dissolved in water they have the characteristic property of assembling into molecular aggregates called micelles (cf. Section 4.5) above a certain concentration termed the critical micelle concentration (CMC) [9]. Structures **1**–**38** depict the tenside ligands used so far in organometallic catalysis in aqueous media. Surfactant phosphines containing sulfonate or polyether functionalities are the tenside ligands most frequently used to impact surface activity to transition metal complexes applied as catalysts in hydroformylation or hydrogenation reactions. Tenside phosphines bearing carboxylic, phosphonium, phosphate, amine [52, 63],

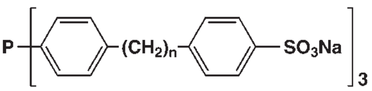


1



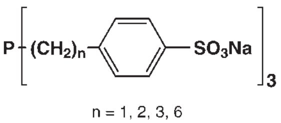
$n = 0, 3, 5, 7, 9, 11$

2



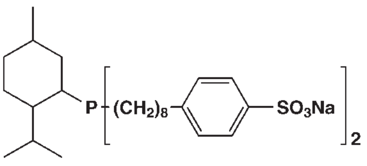
$n = 3, 6$

3



$n = 1, 2, 3, 6$

4

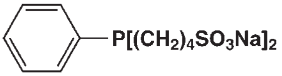


5

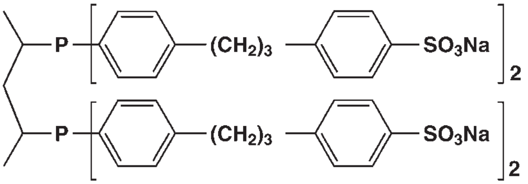
$R_2P(CH_2)_nSO_3Na$

R = Ph, menthyl, cyclohexyl
$n = 2, 3, 4, 5$

6



7

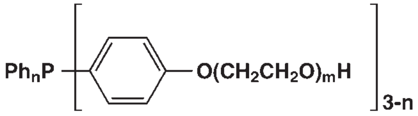


8

$Ph_nP[(CH_2)_x(CH_2CH_2O)_mR]_{3-n}$

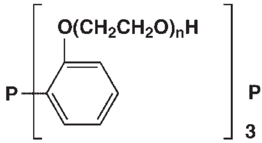
n = 0, 1, 2; x = 0, 1; m = 1, 2, 3, 12, 16; R = Me, Bu

9



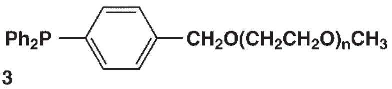
n = 0, 1, 2; m = 3–25

10

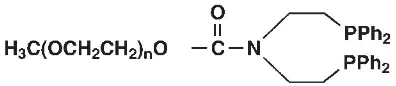


n = 3–14

11

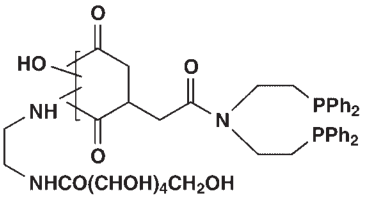


12

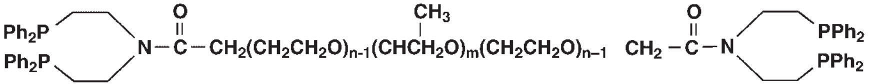


n = 12, 16, 110

13

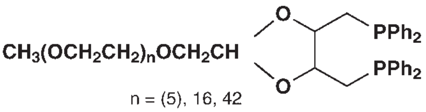


14



n = 11; m = 34

15



n = (5), 16, 42

16

$Ph_2P(CH_2)_nCOOH$

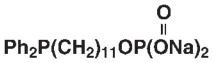
n = 1, 2, 3, 4, 5, 7, 9, 11

17

$[Ph_2P(CH_2)_nPMe_3]^+$

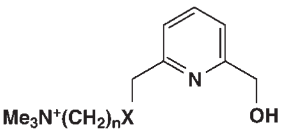
n = 2, 3, 6, 10

18



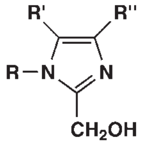
$\mathrm{Ph_2P(CH_2)_{11}O\overset{O}{\overset{\|}{P}}(ONa)_2}$

19



n = 2, 10, 11; X = CONH, S

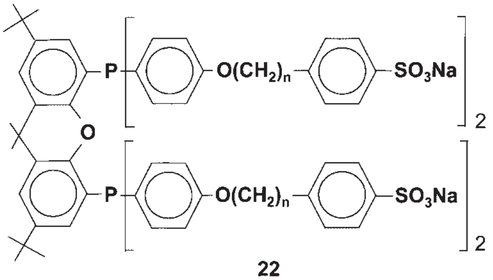
20



R = $C_{16}H_{33}CH(OSO_3Na)CH_2$, $C_{12}H_{25}$

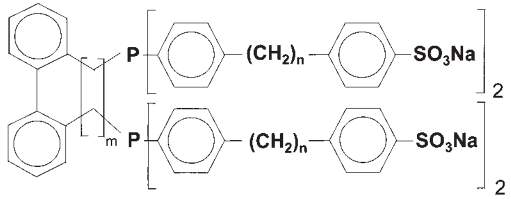
R'= H, CH_2OH; R''= H, $CH_2S(CH_2)_2SO_3Na$

21



22

n = 0, 3, 6



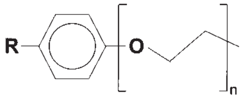
23

m = 0, 1; n = 0, 3, 6, 10

sulfonamide [53], calix[*n*]arene [59], amide [61], sulfate [64], and phosphonate moieties [65, 66] have also been used as ligands in hydroformylation and hydrogenation experiments. Furthermore, other classes of surfactant ligands, namely tenside phosphites (e.g., **29**), phosphine oxides (**30**), and amines or other *N*-containing compounds (**20**, **21**, **27**, or **33**) have been applied as modifiers in transition metal-catalyzed hydroformylation and hydrolysis reactions [10, 54–57].

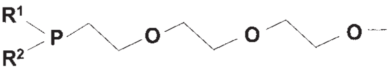
3.2.4.3
Hydroformylation Reactions Catalyzed by Transition Metal Surfactant–Phosphine Complexes

The fact that water-soluble sulfonated phosphines may combine the properties of a ligand and a surfactant in the same molecule was first mentioned in 1978 by Wilkinson et al. [11] in their study of the hydroformylation of 1-hexene using rhodium and ruthenium catalysts modified with TPPMS (triphenylphosphine mono-



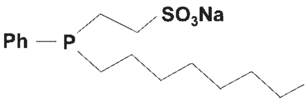
24

R = 2,2,4,4-tetramethylbutyl-; *n*-nonyl;
n = e.g.,1,2,5,12,13.
R^1/R^2 = Ph/Ph; Ph/-$(CH_2)_2$-SO_3Na

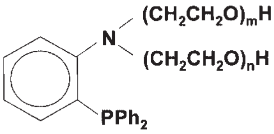


25

R^1/R^2 = Ph/Ph; Ph/methylbutyl-;
Ph/octyl; Ph/-$(CH_2)_2$-SO_3Na

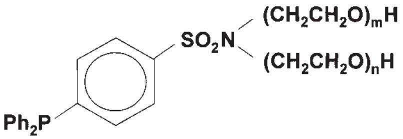


26



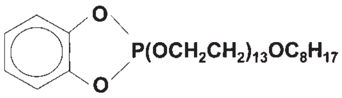
27

m+n = 35, 45

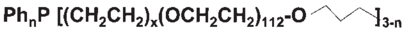


28

m+n = 17, 25, 34



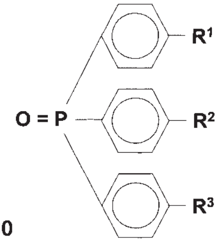
29



$Ph_nP\ [(CH_2CH_2)_x(OCH_2CH_2)_{112}\text{-}O\ \ ]_{3-n}$

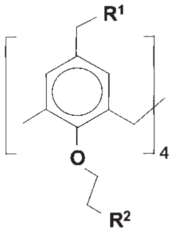
31

x = 0, 1; n = 1,2



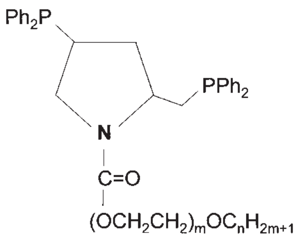
30

R^1/R^2R^3 = -$(OCH_2CH_2)_xOH$/ -$(OCH_2CH_2)_yOH$/ -$(OCH_2CH_2)_zOH$;
x+y+z = N; N = 20, 22, 30, 45
$R^1=R^2=R3$ = -$(OCH_2CH_2)_6OH$
R^1/R^2R^3 = H/-$(OCH_2CH_2)_{25}OH$/H
R^1/R^2R^3 = H/*ortho*-$CH_2(OCH_2CH_2)_nOH$/H; n = 18, 25



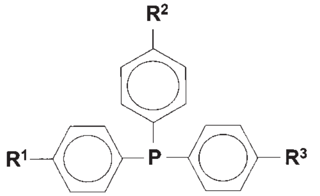
32

R^1/R^2 = -PPh_2/ -$O(CH_2CH_2O)_nCH_3$
R^1/R^2 = -$O(CH_2CH_2O)_nCH_3$ /-PPh_2



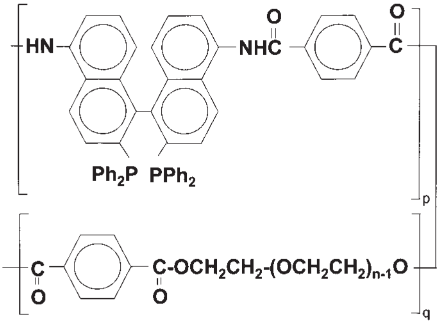
33

m = 4, 10, 16, 23; n = 1, 12

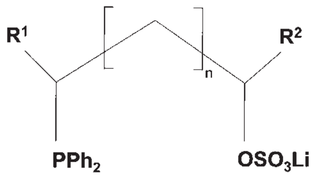


34

$R^1/R^2/R^3$ = + Ph/-$mC_6H_4SO_3Na$/-$mC_6H_4SO_3Na$
$R^1/R^2/R^3$ = + Ph/-$mC_6H_4SO_3Na$/H
$R^1/R^2/R^3$ = + Ph/+ Ph/-$mC_6H_4SO_3Na$
$R^1/R^2/R^3$ = H/H/p-$CH_2N[(CH_2)_2\text{-}NEt_2]$

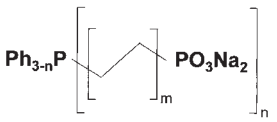


35



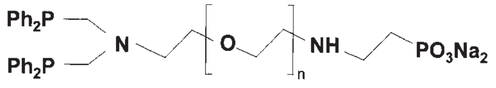
36

n = 0, 1, 2; R^1 = H, Me; R^2 = H, Me



37

n = 1, 2; m = 1, 3, 5, 6



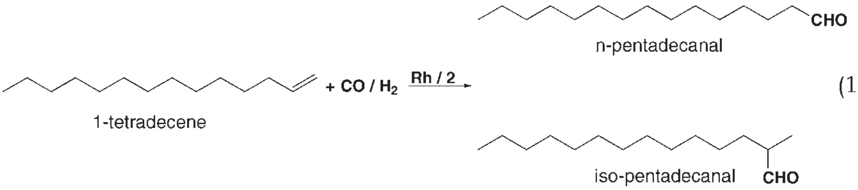
38

n = 1, 2, 3

sulfonate; **1**) in an aqueous/organic two-phase system. The authors [11] noted that under all conditions employed using Rh/TPPMS catalysts some orange color was present in the organic phase after the reaction, indicating leaching of rhodium, probably due to the low HLB value of TPPMS. Quite recently, surface tension measurements of TPPMS and TPPTS (the corresponding trisulfonate) in a water/

toluene two-phase system provided evidence for surface activity of TPPMS which gives rise to a lower interfacial tension between the two phases (15.05 dyn cm^{-2}) whereas TPPTS behaves as an electrolyte (51.23 dyn cm^{-2}) [12]. Rh/TPPMS catalysts generated from the potassium salt of TPPMS were active in the biphasic hydroformylation of 1-hexene and 1-dodecene to afford aldehyde yields as high as 86% and 66%, respectively [13]. However, the authors have not discussed the question of the carry-over of rhodium from the aqueous to the organic phase [13].

The first water-soluble system specifically designed to combine both functions of a ligand and a surfactant in one molecule and applied in transition-metal-catalyzed conversions of highly water-insoluble substrates in micellar systems is the zwitterionic tenside trisulfoalkylated tris(2-pyridyl)phosphine, **2** ($n = 0$, 3, 5, 7, 9, 11) [4, 14, 72, 74]. Turnover frequencies (TOF) up to 340 h^{-1} were achieved in the micellar hydroformylation of 1-tetradecene to pentadecanals, according to Eq. (1), using Rh/**2** catalysts at 125 °C, by fine tuning of the hydrophilic/lipophilic properties of the tenside system **2** [4, 14]. In sharp contrast, Rh/TPPTS catalysts gave only traces of pentadecanals under the same biphasic conditions.



(1)

The conversions in the micellar Rh/**2**-catalyzed hydroformylation of 1-tetradecene increased with increasing length of the nonpolar hydrocarbon tail of the surfactant **2** up to a maximum for 8 C-atoms ($n = 5$) achieving a conversion of 79% within 3 h. A further increase in nonpolar chain length resulted in a decrease in conversion (C_{10} and C_{12} gave 72% and 39%, respectively). With high HLB values, i.e., a shorter nonpolar tail in the range of 3 to 10 C-atoms ($n = 0-7$) the Rh/**2** catalyst was quantitatively recovered by simple phase separation. In contrast, lower HLB values, namely a longer tail with 12 or 14 C-atoms ($n = 9$, 11), very stable emulsions were formed which did not break into a desired two-phase system even after standing for one year at room temperature.

In order to rationalize the effect whereby the activity in the Rh/**2**-catalyzed hydroformylation of 1-tetradecene goes through a maximum as a function of the tail length of the surfactant **2**, the model of simplified spherical (Hartley) ionic micelle [9 a–c] (Figure 1) was proposed [14, 15]. The core of the micelle is probably composed of the hydrophobic tail of the tenside phosphine **2** where 1-tetradecene is solubilized (Figure 1, stippled part).

Surrounding the core is the Stern layer where the charged head groups (SO_3^-) of the surfactant **2** are located together with the counterions (Na^+) in a compact region a few angstroms wide. The rhodium atom of the catalyst is probably located

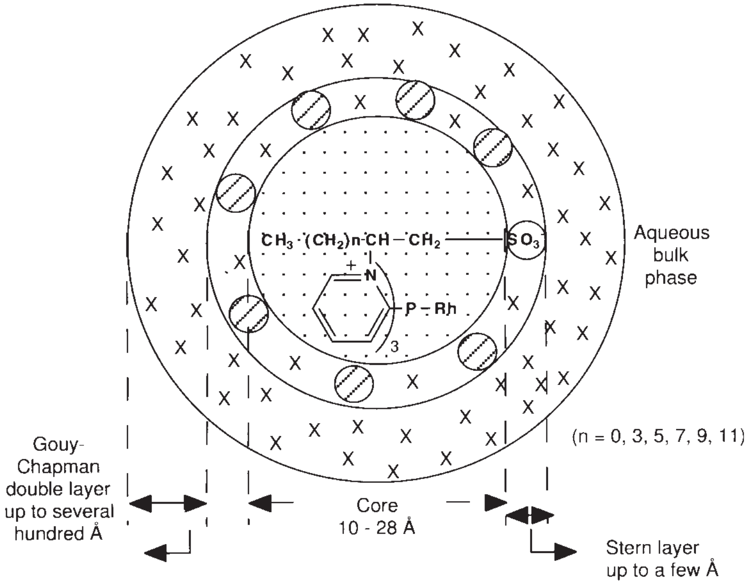


Fig. 1 Representation of a simplified model of a spherical (Hartley) ionic micelle containing the Rh/**2** catalyst. The solubilized 1-tetradecene in the core (stippled area), the tail of the tenside ($CH_3(CH_2)_nCHCH_2^-$), the head (SO_3^-), the counter ions (Na^+, OH^-, depicted as X) schematically indicate their relative locations and not the relationship to their molecular size, distribution, number, or configuration.

on the polarity gradient between the Stern layer and the core of the micelle. The situation of the Rh should depend on the HLB value, i.e., on the tail length of the system **2**. The surfactant **2** with eight C-atoms ($n = 5$) apparently possesses the optimum length for solubilizing 1-tetradecene efficiently, and therefore maximum activity is observed in the hydroformylation reaction. In contrast, when $n < 5$ the ligand **2** is probably too short to solubilize the olefin and when $n > 5$ the Rh is probably located far from the polarity gradient between the Stern layer and the core of the micelle, which gives rise to a drop in the catalytic hydroformylation activity [4, 14]. The Rh/**2**-catalyzed hydroformylation of 1-tetradecene may, alternatively, proceed in “wet micelles” [16], which are water-permeated, porous micellar structures, or in reversed (inverse) micelles [9a, 17, 18], where the polar head groups of **2** form an aqueous interior while the hydrophobic tails are in contact with the olefin exterior bulk phase.

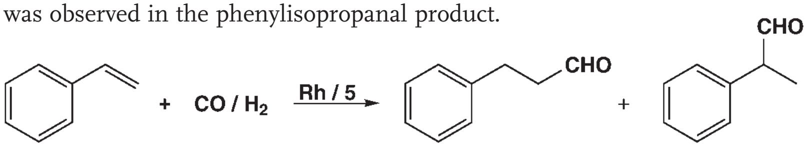
The anionic tenside phosphines **3**, **4**, and **5** [19–26] were used as ligands to impart surfactant properties to rhodium and cobalt catalysts in hydroformylation reactions of higher olefins in aqueous media. The aggregation of the system **3** ($n =$ 3, 6) and **5** was investigated with dynamic light-scattering experiments at different ionic strengths of the solution by addition of NaCl [19]. It was assumed that if the relationship of the SO_3^- groups to the P-atom of the system **3** is pyramidal, then a tetrahedral array of four ligands **3** form a small spherical micelle with the P-atom comprising its core [19, 27]. Hydroformylation reactions of 1-octene were carried out using rhodium catalysts modified with the surfactant ligand **3** ($n = 3$, 6) dissolved in an aqueous methanol solution ($MeOH/H_2O = 1:1$) to give C_9-aldehydes and nonanols (alcohols up to 10%) [19, 20]. At a ligand/Rh ratio of 10 : 1 the TOF obtained with **3** ($n = 3$) was 335 h^{-1} and with **3** ($n = 6$) 360 h^{-1}. Under the same conditions using Rh/TPPTS catalysts, however, the TOF obtained was 260 h^{-1} [20]. When this biphasic reaction occurred in water instead of aqueous methanol the reaction rates were clearly diminished, using both Rh/**3** and Rh/TPPTS catalysts [19, 22]. Rhodium catalysts derived from the electron-donating surfactant ligand **4** have been used in the hydroformylation of 1-octene and in the presence of a conventional tenside, namely the sodium salt of dodecylbenzenesulfonic acid (0.5 wt.%) in a 1-octene/nonane/methanol/water (60 : 34 : 50 : 56) mixture [23]. At low ligand/Rh ratios in the range 2–4, the conversion increased with increasing number of methylene groups in the ligand **4**; with Rh/**4** ($n = 6$) the conversion of 1-octene achieved was 85% (TOF = 28 h^{-1}) [23].

Cobalt complexes generated from the tenside ligand **4** ($n = 1$, 2, 3, 6), namely $Na_5[Co^+(CO)_3(\mathbf{4})_2]^{5-}$, have been used as catalysts for the biphasic hydroformylation of 1-hexene and 1-octene [24]. The products obtained were almost exclusively aldehydes (4–38%) and there was very little (0.4–3%) or no alcohol formation [24]. This contrasts with the expected products for the phosphine-modified cobalt hydroformylation catalysts in conventional organic solvents which are alcohols. The *n*/iso ratios of the aldehydes using the $Na_5[Co^+(CO)_3(\mathbf{4})_2]^{5-}$ catalysts was low (1.1–2.5) [24] and never approached that expected for a phosphine-modified cobalt catalyst in organic media (7.3) [1 c]. However, the reaction rates and the selectivity are dependent on the ligand **4**/Co ratio and no leaching of cobalt was observed into the organic phase [24].

The amphiphilic diphosphines (**22**) [44, 45] were used as modifiers to Rh catalysts for the hydroformylation of 1-octene in biphasic systems. Dynamic light-scattering experiments of aqueous solutions of the tenside xanthphos derivatives ($n =$ 3, 6; cf. Section 7.5) showed aggregates with average hydrodynamic radii of 63 and 67 nm, respectively. The small radius of the ligand itself (2 mm) indicates that this ligand does not form aggregates. Transmission electron microscopy (TEM) studies of the tenside ligand **22** ($n = 0$, 3, 6) show that the compound forms vesicles of sizes varying from 50 to 250 nm spontaneously in aqueous solution, whereas **22** with $n = 0$ again does not form aggregates. Rh complexes, ligand-modified with $n = 0$, 3, 6, were used as catalysts for the micellar hydroformylation of 1-octene under aqueous-biphase conditions at various temperatures. The TOF achieved with **22**/$n = 3$, 6 were considerably higher than with **22**/$n = 0$. At higher temperatures of 120 °C the activity of the mentioned Rh/**22** catalyst system proved that under these conditions 1-octene is slightly soluble in the aqueous phase, even in the absence of aggregates. In four consecutive recycling experiments, the TOF and the high selectivity (an *n*/*i* ratio of the aldehydes of 97 : 3–99 : 1) remain stable [44].

The water-soluble surfactant phosphines **3** and **23** [45–47] bearing the pendant sulfonates $-[(C_6H_4(CH_2)_n-p\text{-}C_6H_4SO_3Na]$ were introduced to modify transition metal complexes used as catalysts in micellar media. Rh complexes generated from the ligands **3** ($n = 3$, 10) and **23** were also used for the hydroformylation of 1-octene and 1-tetradecene in aqueous/organic systems. TOFs up to 450 h^{-1} and selectivities of 89% to 1-nonanal were observed using Rh/**3**, compared to TOFs of 220 h^{-1} and selectivities of 78% with Rh/TPPTS [46]. Sulfonates **3** exhibit higher activities than **23** [46].

Rhodium complexes modified with the tenside chiral phosphine **5** were used as catalysts in the hydroformylation of styrene, according to Eq. 2, in an aqueous/organic two-phase system [19, 26]. The TOFs achieved with the surfactant catalyst Rh/**5** were higher (245 h^{-1}) compared with the Rh/TPPTS system (100 h^{-1}) [26]. The *n*/iso ratios of the aldehydes were about 0.6 with Rh/TPPTS and ca. 0.4 with the Rh/**5** system. Although the phosphine **5** is chiral, virtually no optical activity was observed in the phenylisopropanal product.



(2)

Styrene n- iso-
Phenylpropanal

The sulfonated phosphine system **6** [28–30] was also described as possessing surfactant properties [28]. However, **6** and **7** have only been applied in the hydroformylation of 1-tetradecene in methanol followed by biphasic separation of the catalyst after treatment with water [30].

Rhodium complexes generated from the poly(ethylene glycol)-functionalized phosphine **9** ($n = 1$, $x = 0$, R = Me, Bu), which should behave as a nonionic surfactant and be able to induce micelle formation, have been used as catalysts in the hydroformylation of 1-dodecene in an aqueous/organic two-phase system [31]. The conversion of 1-dodecene was 80% and the *n*/iso ratio 60 : 40, with no carry-over of the rhodium catalyst into the organic phase. The Rh/**9** ($n = 1$, $x = 0$, R = Me, Bu) catalyst remained active after one recycle step [31].

The novel polydentate tenside phosphines **24**–**26** containing polyether chains were prepared in order to modify Rh and Ru complexes used as catalysts in various aqueous-biphase reactions [48–51]. Hydroformylations of 1-octene were carried out using Rh and the surfactant ligands from the **24** and **26** series [51]. All Rh catalysts containing ligands with medium or long polyether chains exhibit poorer conversions than Rh/TPPTS. In contrast, the conversions with shorter polyether ligands were significantly higher. The higher activity of the ligands of the **24** series can probably be attributed to leaching of rhodium from the aqueous to the organic phase (indicated by the intense coloration of the organic phase after the reaction observed only in the experiments performed with the compounds with $R^1/R^2 = Ph/-(CH_2)_2SO_3Na$) [51].

A novel concept in the field of hydroformylation of higher olefins consists in the use of rhodium catalysts modified with the nonionic surfactant phosphines **10**, **11**, **27**, **28**, and **29**, which become organic-soluble on heating above a critical-temperature cloud point (T_p) and on cooling back to room temperature become water-soluble again, providing for higher rates and a quantitative catalyst separation by simple decantation [32, 52–55, 67–69, 75] (cf. Section 4.6.3). An advance in this field is Jin's "thermoregulated phase-transfer catalysis" using nonionic surfactant phosphines **10** [70, 71]. More details are given in Section 4.6.3.

Rhodium complexes modified with polyether phosphine oxides according to the Structure **30** were used as catalysts for the hydroformylation of 1-decene and oleyl alcohol in micellar aqueous-biphase systems [56, 57].

The surfactant phosphines containing poly(ethyleneoxide) **31**, sulfonate **47**, amine **34** (with $R^1/R^2/R^3 = H/H/{-}CH_2{-}N[(CH_2)_2{-}NEt_2]_2$, sulfate **36**, and phosphonate **37** moieties were used as tenside ligands to modify Rh catalysts for the hydroformylation of higher alkenes such as 1-hexene, 1-octene, 1-decene, and 1-dodecene in aqueous/organic two-phase systems [58, 62–65].

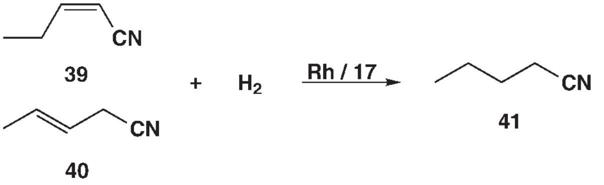
The concept of organometallic catalysis in micellar systems is compared by several writers [15, 33, 34] with the concept of heterogeneous catalysis on solid surfaces since the solubilization of the reactants in the core of the micelle containing catalytically active sites can be compared with adsorption on surfaces and the number of micelles to surface area (cf. Section 4.5).

3.2.4.4
Hydrogenation Reactions Catalyzed by Transition Metal Surfactant–Phosphine Complexes

Biphasic hydrogenation reactions of cyclohexene using Rh/TPPMS catalysts in a dimethylacetamide/H_2O mixture demonstrated that this reaction does not take place at the interface. Thus, doubling of the volume of the aqueous phase gave rise to an increase in the reaction rate. If this reaction were an interfacial reaction, the rates would not depend on the volume of the aqueous phase [35]. In contrast, the rates in the Ru/TPPMS-catalyzed biphasic hydrogenation of cyclohexene [36] were dependent on the rate of stirring (0–1000 rpm), indicating interfacial catalysis.

Rhodium complexes generated from the water-insoluble carboxylated surfactant phosphine **17** ($n = 3, 5, 7, 9, 11$) were used as catalysts in the micellar hydrogenation of α- and cyclic olefins, such as 1-octene, 1-dodecene, and cyclohexene, in the presence of conventional cationic or anionic tensides such as cetyltrimethylammonium bromide (CTAB) or SDS and co-solvents, e.g., dimethyl sulfoxide [15]. After the reaction the catalyst was separated from the organic products by decantation and recycled without loss in activity. There is a critical relationship between the length of the hydrocarbon chain of the ligand **17** and the length and nature of the added conventional surfactant, for obtaining maximum reactivity. For example, maximum efficiency was observed in the micellar hydrogenation of cyclohexene at 50 °C using rhodium catalysts modified with the ligand **17** possessing a C_5 or C_7 chain in the presence of the anionic surfactant SDS. In contrast, using the cationic tenside CTAB, the ligand with a C_5 chain was almost inactive but became active again in the presence of dodecyltrimethylammonium bromide. However, the C_9 ligand shows the same behavior with anionic (SDS) and cationic (CTAB) tensides [15]. Rh/**17** catalysts exhibit higher rates with linear than with cyclic olefins.

Rhodium catalysts modified with the sodium salt of the surfactant phosphines **17** ($n = 5, 7$) exhibited high catalytic activity in the hydrogenation of higher α-olefins such as 1-octene and 1-decene at 50 °C in an aqueous/organic two-phase system without any addition of conventional tensides [37]. Using the ligand **17** with a chain length of six C-atoms ($n = 5$) the rhodium catalysts were more efficient than with a tail of eight C-atoms ($n = 7$). For example, the TOFs achieved in the hydrogenation of 1-octene were 1880 h^{-1} with the Rh/**17** ($n = 5$) compared with 460 h^{-1} with the Rh/**17** ($n = 7$) catalyst [37]. With both catalysts the α-olefins were hydrogenated much faster than internal olefins. Unusually high reaction rates (up to TOF = 7920 h^{-1}) were obtained in the hydrogenation of the internal double bonds in *cis*-2-pentenenitrile (**39**) and *trans*-3-pentenenitrile (**40**), both giving valeronitrile (**41**) when catalyzed by the sodium salt of the surfactant Rh/**17** system (Eq. (3) and Table 1) [37].



(3)

That the hydrophobic chain length of tenside ligands has a significant effect on the catalyst activity in micellar systems was further demonstrated in the biphasic hydrogenation of 1-hexene using rhodium catalysts generated from the cationic surfactant phosphonium phosphines **18** ($n = 2, 3, 6, 10$) [38]. The Rh/**18** with a chain length of six C-atoms was the most active catalyst; ca. 90% of 1-hexene were hydrogenated (with 10% isomerization) at 25 °C. The catalytic activity of the Rh/**18** system decreased with the chain length n in the order $6 > 10 > 3 > 2$ [38a]. Using Rh/**18** catalysts with longer-chain ligands, very stable emulsions were formed which were quite difficult to break [38a].

Tab. 1 Rh/**17** ($n = 5,7$)-catalyzed hydrogenation of **39** and **40**.

Substrate	*Rh/17*	*TOF (h^{-1})*
39	$n = 5$	7920
39	$n = 7$	6800
40	$n = 5$	1980
40	$n = 7$	1760

Hydrogenation of unsaturated membrane lipids, for modulation of membrane fluidity, is facilitated by water-soluble catalysts in aqueous media, thus rendering organic solvents such as THF or DMSO, which are necessary for penetration of the membrane with conventional organic-soluble complex catalysts, superfluous (cf. Section 6.8). For example hydrogenation of dioleoylphosphatidylcholine dispersions catalyzed by rhodium complexes modified with the surfactant phosphate phosphine ligand **19** and TPPMS were carried out at 37 °C and 1.2 atm H_2 in aqueous media [39]. Under these mild reaction conditions, isomerization of the oleoyl group to an elaidoyl moiety is followed by hydrogenation of the elaidoyl functionality. Rhodium catalysts modified with either **19** or TPPMS exhibit similar behavior in this reaction [39].

Whitesides and co-workers [40] synthesized the nonionic surfactant phosphines **9** ($n = 2$; $x = 0$; $m = 12, 16$; R = Me), **12**, **13**, **14** and used them as ligands in rhodium-catalyzed hydrogenation of water-immiscible starting materials such as cyclohexene in a two-phase system.

The inverse temperature dependence of the water-solubility of nonionic tenside phosphines at the T_p was applied by Bergbreiter et al. [41] in the hydrogenation of allyl alcohol using water-soluble rhodium catalysts modified with the "smart ligand" **15** in aqueous media. In this case, on heating the sample to 40–50 °C the reaction stopped but on cooling to 0 °C hydrogenation was resumed in the aqueous phase (cf. Section 4.6.3).

The anionic tenside chiral diphosphine **8** was used to generate rhodium catalysts for the hydrogenation of the prochiral olefin (*Z*)-2-(*N*-acetamido)cinnamic acid methyl ester in micellar ethyl acetate/H_2O two-phase systems [42]. The yield (100%) and enantiomeric excess (69%) were considerably higher than those observed with the tetrasulfonated bis(diphenylphosphino)pentane (32% yield and 20% *ee*) and the reaction time was shorter (1.5 versus 20 h) [42].

The asymmetric diphosphine **16**, used in rhodium-catalyzed enantioselective hydrogenation reactions [43], should exhibit surfactant properties due to the poly(ethylene glycol) functionality. The behavior of **16** in water (insoluble when $n = 5$ and water-soluble with $n = 16$) is typical for nonionic surfactant diphosphines and analogous to that of **13**, which shows increasing water-solubility with increasing molecular mass [40b].

Ruthenium complexes generated from the amphiphilic phosphines **24** (see also Section 7.5) were used for the selective hydrogenation of 3-methyl-2-butenal (prenal) to 3-methyl-2-butenol (prenol) in isopropanol/water mixtures [49]. High conversions of up to 100% and selectivities of 90–96% were achieved with ligands of the type **24** containing long polyether chains [49].

The nonionic surfactant, the chiral diphosphine **33**, was used to modify Rh catalysts for the hydrogenation of the prochiral alkene (*Z*)-methyl α-acetamidocinnamate in aqueous and organic media [60]. Only in water did the catalyst Rh/**33** give the expected increase in enantioselectivity (91% *ee*) [60].

The new amphiphilic polyethylene-bound BINAP ligand **35** was used to generate Ru catalysts for the asymmetric hydrogenation of 2-(6-methoxy-2-naphthyl)-acrylic acid to naproxene [61]. The enantioselectivity in the biphasic decreased from 77 to 88% compared to the methanolic system [61].

Thermoregulated phase-separable Ru/**10** catalysts ($n = 6$) were applied for the hydrogenation of styrene to give ethylbenzene with yields up to 99.5% [75]. The catalyst was separated from the reaction mixture and re-used ten times without loss of activity [75].

3.2.4.5
Carbonylation Reactions Catalyzed by Transition Metal Surfactant – Phosphine Complexes

The tenside phosphines **38** ($n = 1, 2, 3$) containing amino and phosphonate moieties were used as ligands to impart surfactant properties to Pd catalysts for the carbonylation (cf. Section 6.5) of benzyl chloride to phenylacetic acid under aqueous-biphase conditions [66]. The recovery of the Pd/**38** catalyst after the carbonylation reaction, however, was only 85 – 92%.

3.2.4.6
Concluding Remarks and Future Prospects

Organometallic catalysis in micellar systems using transition metal complexes generated from tenside ligands is a particularly attractive approach for circumventing the solubility problem of highly water-immiscible starting materials encountered in catalysis in aqueous media. Higher reaction rates combined with facile catalyst separation and recycling can be achieved by fine tuning of the HLB value of the surfactant ligand. Hence, we conclude that catalysis in micellar microheterogeneous systems has considerable potential for further applications in the synthesis of fine chemicals.

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3.2.5
Chiral Ligands

Wolfgang A. Herrmann, Robert W. Eckl, Fritz E. Kühn

3.2.5.1
Introduction

The growing demand for chiral precursors and products has reinforced academic efforts to control enantioselectivity in homogeneous catalysis. The application of chiral ligands coordinated to catalytically active transition metals has proven to be the most successful way to achieve such asymmetric transformations. A plethora of chiral ligands have been synthesized and applied in catalysis in the past three decades. In aqueous-phase catalysis the advantage of catalyst recovery becomes even more significant if, besides precious metals, costly ligands are employed and recycled. Further support for the efforts toward asymmetric aqueous phase catalysis may be seen in the very limited success of heterogeneous catalysts in enantioselective reactions since the great number of catalytically active species in most cases leads to a drop in selectivity.

The majority of chiral ligands for asymmetric catalysis in a homogeneous phase consists of tertiary phosphines, and this is also true for aqueous-phase catalysis. This section concentrates on the different approaches to achieve solubilization of these ligands in water.

3.2.5.2
Sulfonated Chiral Phosphines

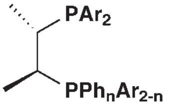
(Di)phosphines containing chiral backbones equipped with diphenylphosphino-substituents are the most successful and best-investigated chiral ligands in asymmetric homogeneous catalysis. Thus, a variety of chiral water-soluble ligands were prepared by direct sulfonation of these phosphorus ligands under conditions similar to those for the synthesis of achiral sulfonated phosphines.

Sinou et al. prepared several water-soluble derivatives of chiral 1,2-, 1,3- and 1,4-diphosphines. The sulfonated counterparts **1**–**4**, respectively, of (*S*,*S*)-CHIRAPHOS [1a], (*S*,*S*)-BDPP, (*S*,*S*)-CDB, and *R*-PROPHOS [1b] are shown. Except for

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

the latter case, all diphosphines can be obtained tetrasulfonated by treating the precursors with sulfuric acid containing 20% SO_3 for 2–5 days with subsequent neutralization and workup [2]. Unexpectedly, sulfonation of *R*-PROPHOS could only be extended to give a mixture of tetrasulfonates (55%), trisulfonates (35%), and phosphine oxides (10%) under optimized conditions. Nevertheless, yields of highly water-soluble products are generally quantitative and analysis was carried out mainly by $^{31}P\{^1H\}$NMR and a special HPLC technique referred to as "soap-chromatography" [2, 3a]. Phosphines **1**–**4** were successfully applied in asymmetric hydrogenation of carbon–carbon, carbon–oxygen, and carbon–nitrogen double bonds under two-phase conditions with up to 89% *ee* (cf. Section 6.2). In almost all cases re-use of the catalysts did not lower the enantioselectivity of the products obtained. Asymmetric hydroformylation of styrene using rhodium complexes of tetrasulfonated **3** or tetrasulfonated **4** has been reported [3b]. The use of sulfonated, water-soluble biphenyl-type ligands for the rhodium-catalyzed asymmetric hydroformylation of styrene has also been described [3c].



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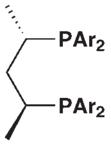

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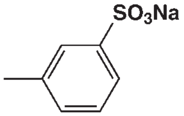

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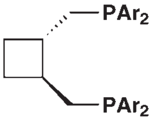

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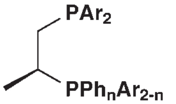

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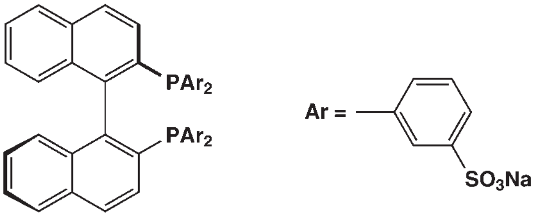
Some striking features were observed in the performance of these ligands, depending on the degree of sulfonation. Mono-, di- and trisulfonation of the diphosphines mentioned above gives rise to formation of diastereomers because of different configurations of the phosphorus atoms. Hence, the use of tetrasulfonated derivatives should give the highest enantioselectivity. However, a mixture of mono-, di- and trisulfonated (*S*,*S*)-BDPP gave higher optical yields compared with fourfold-sulfonated **2**. On the other hand there was no change in enantioselectivity between a mixture of partially sulfonated (*S*,*S*)-CHIRAPHOS and tetrasulfonated **1** when compared in the same reaction.

The dependence of the degree of sulfonation was also studied by the Vries and co-workers [4]. A remarkable effect was observed in the hydrogenation of acetophenone *N*-benzylimine. While the use of monosulfonated (*S*,*S*)-BDPP in an EtOAc/H_2O mixture gave the corresponding amine with 94% *ee* in a very fast reaction, only 2% *ee* was achieved when the disulfonated ligand was applied. Furthermore, application of the unsulfonated phosphine in the same solvent mixture gave no reaction at all and in homogeneous methanol solution only 65% *ee* could be attained. As was shown by HPLC and NMR analysis, the monosulfonated ligand and its Rh complexes contained equal amounts of two epimers and the high enantioselectivity was attributed to a single kinetically superior species formed during catalysis. On the other hand, the reaction probably takes place in the organic phase, since the same optical yield was found in a run that was performed in neat ethyl acetate.

BINAP, one of the most outstanding ligands in asymmetric hydrogenation, was also converted into a water-soluble diphosphine by direct sulfonation. Davis et al. reported that treatment of a solution of (*R*)-BINAP in concentrated sulfuric acid with fuming sulfuric acid (40 wt.% SO_3) gives a mixture of a tetra- and a penta- or hexasulfonated compound after three days at 10 °C [5], the major species (85%) being the tetrasulfonated derivative **5**. The by-product was assumed to carry one or two additional sulfonate group(s) on the naphthyl ring(s) but their presence was believed not to affect the enantioselectivity since interaction of the four phenyl groups of a diphosphine with the substrate is generally presumed to control chiral recognition.



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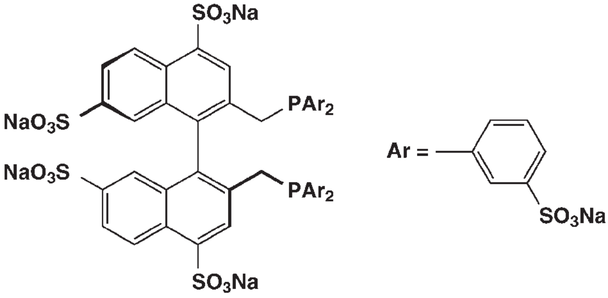
Indeed catalysts prepared from several batches of sulfonated ligand with different ratios of major to minor species showed similar activity and selectivity in Rh-catalyzed hydrogenation of 2-acetamidoacrylic acid. No loss in enantioselectivity was observed in comparison with reactions using the unsulfonated ligand in organic solvents. Ruthenium(II) complexes of sulfonated BINAP proved to be even more efficient. 2-Acetamidoacrylic acids and methylenesuccinic acid can be hydrogenated with up to 85% and 90% *ee* in alcoholic solvents [6]. Although the optical yield decreased in most cases when the reaction was performed in neat water, some of the substrates were reduced with almost identical enantioselectivities compared with the unsulfonated parent system. The ligand was also applied in Ru-catalyzed, asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid to (*S*)-naproxen [7]. Impregnation with [Ru(BINAP-4-SO_3Na)(benzene)Cl]Cl of a controlled-pore glass (CPG) yields an efficient SAP catalyst whose activity and enantioselectivity were found to be very sensitive to the amount of water present on the surface. The limit in enantioselectivity of the hydrated SAP catalyst was restricted to about 77% *ee*, which resembles the performance of the organometallic catalyst in neat water (80% *ee*). In anhydrous methanol, however, enantiomeric excesses up to 90% can be achieved. An explanation for this effect can be found in the rapid hydrolysis of the ruthenium–chloro bond in the presence of water, which was shown to be responsible for the decrease in optical yield. As a consequence, highly polar ethylene glycol was successfully used as a substitute for water in the SAPC system. Thus, enantioselectivities could be extended to about 95% *ee* at a reaction temperature of 3 °C and proved to be dependent on the ethylene glycol loading in the triphasic system. With ethyl acetate as the organic phase, reasonably high rates were observed and recycling of the catalyst is possible without leaching of ruthenium at a detection limit of 32 ppb.

Another sulfonated derivative of BINAP was mentioned in a patent of Takasago International Corporation [8]. Cationic complexes of ruthenium and or iridium with this ligand – sulfonated on the 5- and 5′-positions of the naphthyl rings – are claimed to affect asymmetric hydrogenation of olefins, ketones, and imines.

The diphosphine ligand NAPHOS (2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthalene) proved to be an efficient ligand for hydroformylation reactions due to its large “natural bite angle” [9]. Direct sulfonation of enantiopure *S*-NAPHOS with oleum with addition of boric acid [10 a] yields the eightfold-sulfonated species *S*-(−)BINAS-8, **6** (80–90% yield), accompanied with small amounts of seven- and sixfold-functionalized derivatives as highly water-soluble sodium salts. Application in Rh-catalyzed two-phase hydroformylation of styrene furnishes the corresponding branched aldehyde with good regioselectivity but optical yields are lower (18% *ee*) than in the conventional monophase technique (34% *ee*) [10 b]. Stirring BIFAP at 20 °C for 88 h with 5% SO_3 in H_2SO_4 gives enantiopure BIFAPS (**7**) almost quantitatively, although performing the reaction at 50 °C in sulfuric acid leads to a racemic product [11].



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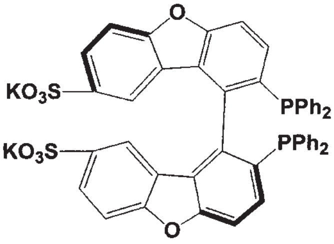
Diphosphine diversity was also exploited by atropisomeric biphenyl ligands. An interesting approach toward water solubilization was disclosed for one of these BINAP-type diphosphines (Scheme 1, MeOBIPHEP-S) [12] (cf. Section 3.2.1). The indolylsulfonyl group withstands the Grignard reaction and phosphine oxide reduction and is readily cleaved under mild alkaline conditions to yield the fourfold *p*-sulfonated diphosphine.



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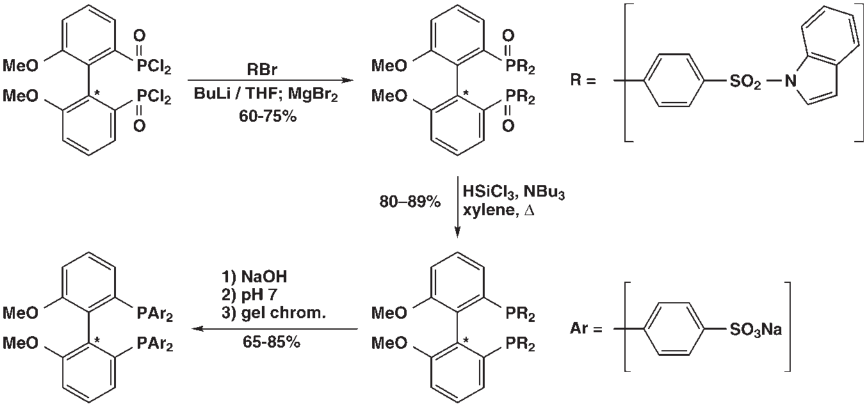
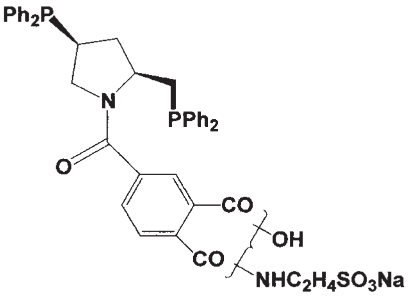
Promising results were achieved in hydrogenation experiments with Rh(I) and Ru(II) complexes derived from MeOBIPHEP-S. Hydrogenation of methyl acetoacetate and geraniol was accomplished with 93% and 98% *ee* in methanol and in an ethyl acetate/water two-phase system, respectively. Moreover, reduction of triethylammonium salts of two different unsaturated acids in water was performed with high S/C ratios (1000 to 10000 : 1) and with *ee* values up to 99%.

An additional access to chiral sulfonated phosphines was also described [13a, b]. The method is based on the acylation of chiral hydroxyphosphines with commercial *o*-sulfobenzoic anhydride and was demonstrated on a number of diphosphines based on the DIOP skeleton (Eq. 1). The chelating properties of the diphosphines were studied by preparation of cationic rhodium complexes. The presence of the *o*-sulfobenzoate group is thought not to influence the catalytic properties. Chiral phosphines containing a sulfonate group (e.g., **8**) were also obtained from BPPM by acylation with trimellitic anhydride followed by treatment with sodium taurinate [13c].



Scheme 1



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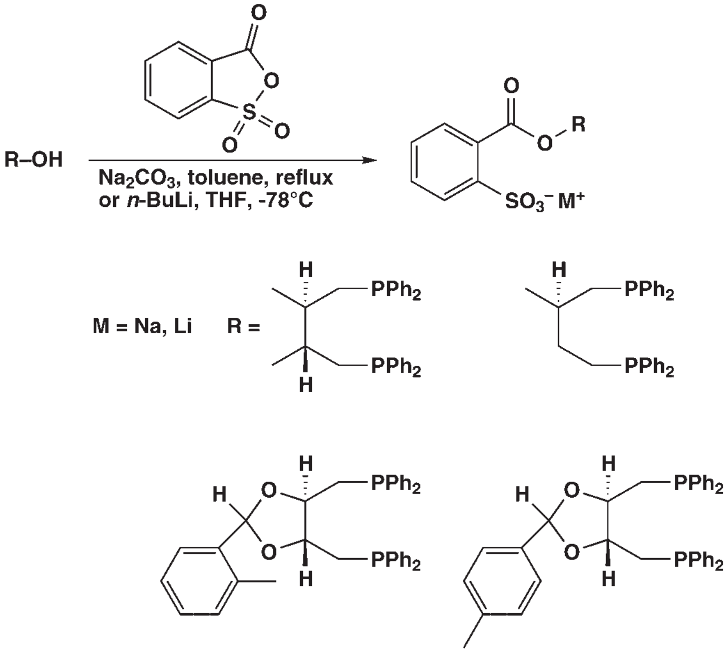
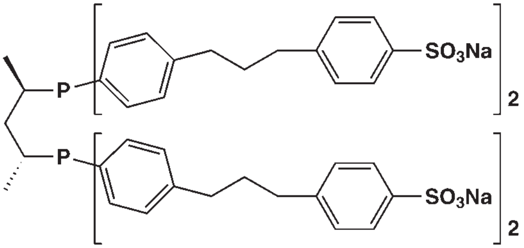


(1)

Stelzer and co-workers reported a number of chiral water-soluble secondary phosphines [14], prepared by nucleophilic phosphination of primary phosphines with fluorinated aryl sulfonates in the superbasic medium DMSO/KOH. Further reaction with alkyl halides gives bidentate tertiary phosphines with P-chirality, but only racemic versions have been reported so far. Hanson et al. introduced so-called surface-active phosphines into asymmetric aqueous-phase catalysis. One of the main problems inherent to two-phase catalysis is the often very low miscibility of the substrates in the aqueous phase. Insertion of long alkyl chains between phosphorus atoms and phenyl groups in sulfonated phosphine ligands has been proven to increase reaction rates in the Rh-catalyzed hydroformylation of 1-octene [15]. This concept was extended to a number of chiral ligands, i.e., the monodentate bis(8-phenyloctyl) (1*R*,3*R*,4*S*-(−)menthyl) phosphine and the corresponding *p,p*-disulfonated phosphine by sulfonation under mild conditions. The latter ligand was applied in two-phase hydroformylation of styrene; higher activity was achieved compared with a TPPTS catalyst under similar conditions. Nevertheless, virtually no enantioselectivity was observed with this monodentate phosphine.

The preparation of chelating surface-active diphosphines proved to be more successful. The BDPP analogue *R,R*-(**9**) was synthesized by lithiation of tris[*p*-(3-phenylpropyl)phenyl]phosphine, reaction with (*R,R*)-2,4-pentane-diylditosylate and subsequent sulfonation with concentrated sulfuric acid [16]. Hydrogenation of the prochiral olefin (*Z*)-2-(*N*-acetamido)cinnamic acid ester in a two-phase system (ETOAc/H_2O) with Rh complexes derived from *R,R*-(**9**) was accomplished with identical selectivity compared with the unsulfonated BDPP and improved reactivity compared with BDPPTS (**2**).



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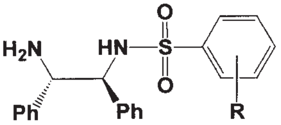
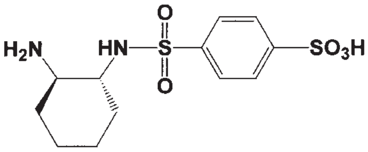


R = *p*-SO_3H (**10**)
R = *o*-SO_3H (**11**)

A surface-active equivalent of BINAP was also prepared recently [17]. According to the new preparative route to BINAP that was previously developed, di[*p*-(3-phenylpropyl)phenyl]phosphine was coupled with the ditriflate of 2,2′-binaphthol (2,2′-bis(trifluoromethanesulfonyloxy)-1,1′-binaphthalene) in a Ni-catalyzed reaction. Again, sulfonation of the diphosphine thus obtained with concentrated H_2SO_4 yields a water-soluble ligand tetrasulfonated on the terminal phenyl groups in the *para* position. Only the racemic version of the diphosphine has been synthesized so far; in biphasic hydroformylation of 1-octene its activity was equal to or less than that of TPPTS.

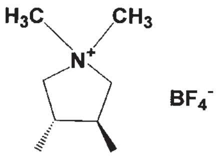
It should be noted, that water soluble chiral sulfonated diamines (**10**–**12**), analogs of Noyori's (1*S*,2*S*)-*N*-(*p*-polylsulfonyl)-1,2-diphenylethylenediamine and Knochel's (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diaminocyclohexane, containing an additional sulfonic acid group have been synthesized recently [18].



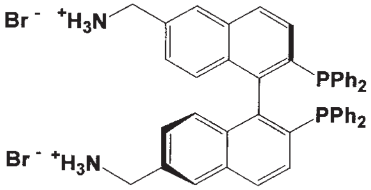
12

3.2.5.3
Other Water-soluble Chiral Ligands

Among the other accesses to chiral water-soluble ligands, the introduction of a quaternary ammonium group is one of the most studied. Nagel et al. reported on the preparation of diphosphine **13** by quaternization of (3*R*,4*R*)-3,4-bis(diphenylphosphino-1-methylpyrrolidine) with Me_3OBF_4 after protecting the phosphorus through complexation to rhodium [19].



(R,R)-13



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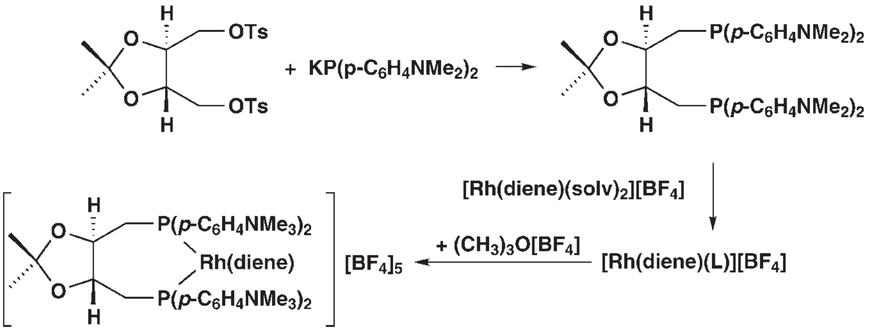
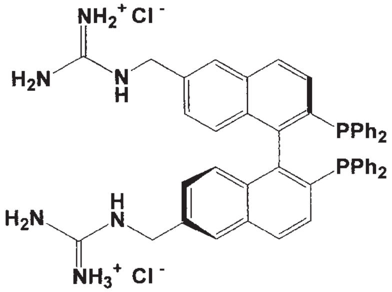
Tóth and Hanson synthesized a number of tetra-amine functionalized diphosphines and achieved a very high water-solubility by methyl quaternization of their rhodium complexes. As outlined in Scheme 2 a new *p*-dimethylamino derivative of DIOP was prepared by standard procedures and quaternized with Meerwein's salt, $[(CH_3)_3O][BF_4]$, after complexation to rhodium [20a]. Coordination of the ligand prevents alkylation of the phosphorus atoms.



Scheme 2

In the same way, cationic complexes of amine derivatives of BDPP and CHIRAPHOS were prepared which showed unlimited solubility in water and negligible solubility in common organic solvents. They were used in asymmetric hydrogenation of dehydroamino acids and provided modest to high enantioselectivities [20b]. The presence of the dimethylamino group in the DIOP derivative resulted in a reversal in the observed dominant product antipode, which was attributed to a change in the preferred ligand conformation.

BINAP analogs bearing amino quaternized ammonium functions were simultaneously prepared by the groups of Lemaire and Genêt [21]. Lemaire et al. obtained the hydrobromide form of diamo-BINAP **14** or 6,6′-di(aminomethyl)-BINAP by treatment of this diaminophosphine with aqueous hydrobromic acid [21a]. Genêt et al. prepared the diguanidinium BINAP ligand **15** by reaction of diam-BINAP with *N*,*N*′-di-Boc-*N*″-triflylguanidine followed by addition of hydrochloric acid in methanol [21b].



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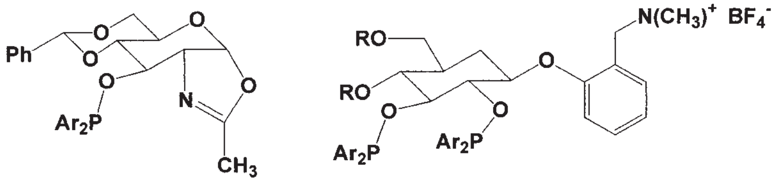
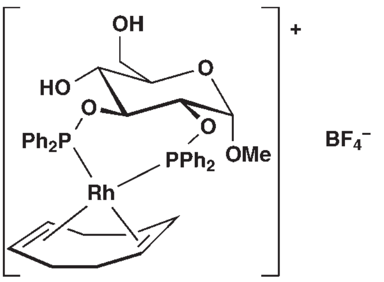


Ar = $C_6H_4\text{-}CH_2N^+(C_2H_5)_2CH_3$ BF_4^- (16a) Ar = 3,5-di(methyl)phenyl (16b)

Furthermore, a phosphinite-oxazoline ligand **16a** and a bisphosphinite ligand **16b** bearing quaternary ammonium groups were prepared starting from natural D-glucosamine and 2-(hydroxymethyl)phenyl β-D-glucopyranoside, respectively, the last synthetic step being a quaternization of the corresponding amine with Me_3OBF_4 [22].

Nonionic, asymmetric polyoxy-1,2- and -1,4-diphosphines, analogs of Prophos and DIOP have been prepared [23a, b], as well as a chiral polyether phosphite ligand derived from (*S*)-binaphthol [23c] and PEG-BINAP [23d] through polycondensation of 5,5′-diamino-BINAP, polyethylene glycol, and terephthalic chloride.

Various research groups took advantage of the chirality and hydrophilicity of sugar backbones for the synthesis of various water-soluble nonionic ligands. While investigating the influence of tensides and micelles upon asymmetric hydrogenation of enamide substrates in water, Oehme, Selke, and co-workers synthesized the water-soluble carbohydrate phosphinite complex **17**, having free hydroxy groups in the 4 and 6 positions of the hexoside [24]. The compound provided increased enantioselectivity in the presence of a variety of surfactants and polymerized micelles. The catalytic results suggest that the phosphorus–oxygen bonds in the phosphinite are stable toward hydrolysis.



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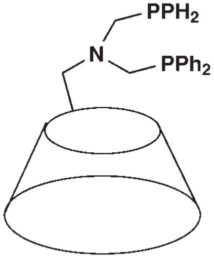


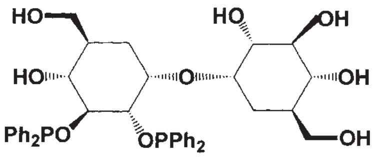
18

Reetz et al. prepared β-cyclodextrin-modified diphosphine **18** and a series of derivatives by phosphinomethylation of the corresponding amino-substituted cyclodextrin precursors [25]. The ligands were used in biphasic hydroformylation of 1-octene and competitive hydrogenation of 1-alkenes, with rather poor results. The chiral cavity in the backbone might achieve molecular recognition of certain prochiral substrates and thus provide enantioselectivity in the products.

Diphosphinites **19** and **20** derived from α,α- and β,β-trehalose were also prepared [26], since the trehaloses are known to be more water-soluble than ligands based on monosaccharides. Additionally, chiral tetrahydroxydiphosphines **21** and **22**, analogs of DUPHOS, were synthesized from D-mannitol in good yields [27].

Carboxylate groups were used in many cases to achieve water-solubilization of simple achiral phosphines. With the synthesis of the water-soluble polymer shown in Eq. (2) this methodology was extended into the field of chiral ligands [28a]. Acylation of the diphosphine (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidone (PPM) with poly(acrylic acid) (PPA) yields the hydrophilic macroligand PAA–PMM [28a, b] and PAA–pyrphos [28c].

Some other nonionic ligands based on carboyhdrates were synthesized by Beller et al. [29]. Glycosidation of glucose, galactose, and glucosamine with *p*-hydroxyphenyldiphenylphosphine yields water-soluble phosphines of the general type **23** (R_1, R_2 = H or OH; R_3 = NHAc or H), which were applied in two-phase Heck and Suzuki reactions. Due to the monodentate character and the remote chiral centers, asymmetric induction with this type of ligand should be negligibly low.



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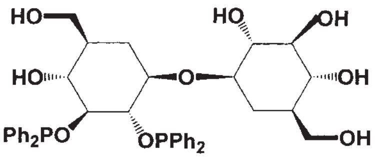

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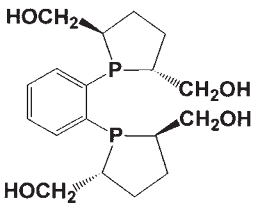

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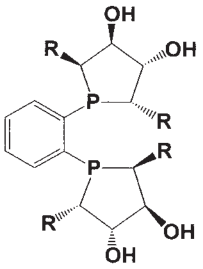
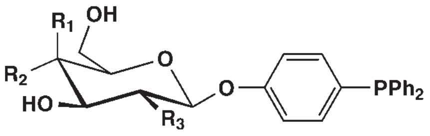


R = CH_3, C_2H_5 **(22)**



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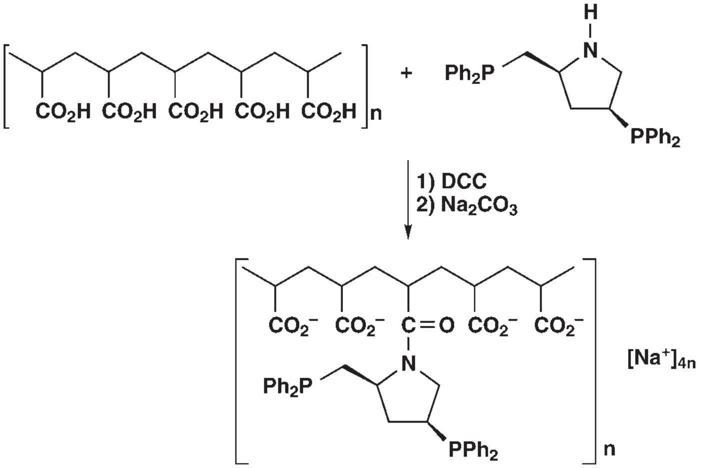
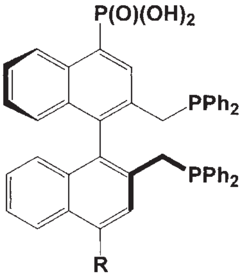


(2)

Mono- and bisphosphorylated BINAP derivatives of composition **24** have been reported quite recently. The sodium salts of the phosphonic acid derivatives are soluble in water [30].



R = H, P(O)(OH)$_2$ (24)

3.2.5.4
Conclusions

It is evident by now that enantioselective catalysis in water is a potentially rich area of research in aqueous-phase catalysis. Progress in this field is strongly dependent on the design and synthesis of tailormade, water-soluble ligands. Despite the fact that in most cases enantioselectivity in biphasic systems is decreased, some of the results mentioned are very encouraging with respect to activity, selectivity, and catalyst recovery. Beyond that, the solvent water with its intrinsic properties often makes it possible to follow different reaction pathways.

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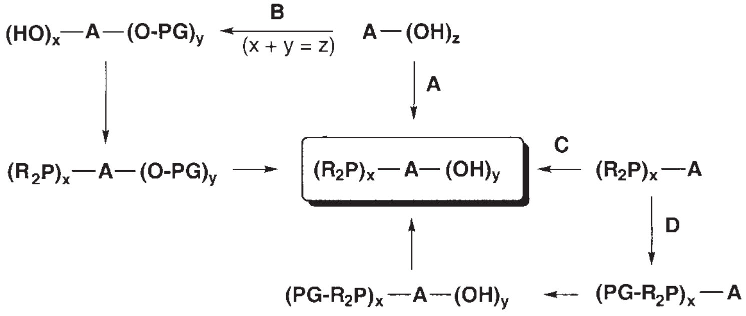
3.2.6
Other Concepts

3.2.6.1
Hydroxyphosphines as Ligands

Armin Börner

Apart from sulfonate, carboxylate and ammonium groups, hydroxy groups incorporated in phosphorus ligands also increase the solubility of the catalyst in water. Several members of this large class of ligands have been described and were tested in catalysis preferentially in organic solvents but also in water. Particular attention has been given to the special effect of the hydroxy group acting as a hemilabile ligand or establishing secondary interactions with a suitable substrate [1].

A large range of methods for the preparation of achiral and chiral hydroxyphosphines have been described in the literature [2]. In Scheme 1 important strategies for the synthesis of the target compounds are summarized. It is known, that common phosphines, particularly alkylphosphines, can easily be prepared by conversion of alcoholic groups into an appropriate leaving group (mesylate, tosylate, etc.), followed by substitution of the latter by phosphide (pathway A). Therefore, achiral and chiral polyols represent one of the main sources of hydroxyphosphines. In particular the chiral pool provides a plethora of starting compounds



PG = Protective group
A = Alkyl, Aryl etc.

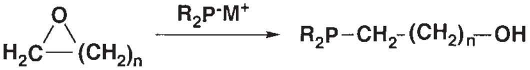
Scheme 1 Pathways for the synthesis of hydroxyphosphines.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

e.g., carbohydrates and hydroxy acids. The crucial problem of this approach arises from the selective conversion of a limited number of hydroxy groups into phosphine groups without touching the others. In several cases the protection of hydroxy groups is inevitable (pathway B). In general, due the high sensitivity of trivalent phosphorous only in a few instances can hydroxyphosphines be directly derived from phosphines (pathway C). In most cases prior protection of the phosphine groups is necessary for the incorporation of the hydroxy group. Moreover, several hydroxyphosphines are prone to oxidation, which may affect subsequent purification reactions. In all these cases protection of the phosphine as phosphine–borane adducts has been shown to be advantageous (pathway D) [3].

Simple hydroxyphosphines can be prepared conveniently by the ring-opening reaction of cyclic ethers with phosphides (Eq. 1) [4].

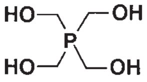


n = 1, 2, 3, 4
M = Li, Na, K

(1)

Phosphine and hydroxy groups emerge simultaneously and therefore subsequent reaction with the air-sensitive hydroxyphosphine can be avoided. The structure of the cyclic ether determines in each case the distance separating functional groups in the product; this means epoxides form 1,2-hydroxyphosphines, 1,3-products can be produced by the employment of oxetanes [5], etc. Problems may be caused by the formation of regio- and stereoisomeric byproducts during the ring-opening step by application of internal nonsymmetric cyclic ethers [6].

As shown by Katti et al. the nucleophilic addition of PH_3 or primary phosphines to formaldehyde or other carbonyl compounds affords polyhydroxyphosphines **1–5** [7]. The utility of such ligands for the formation of water-soluble transition



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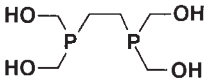

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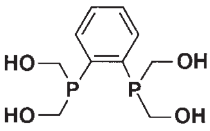

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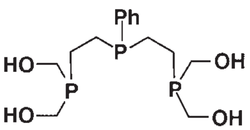

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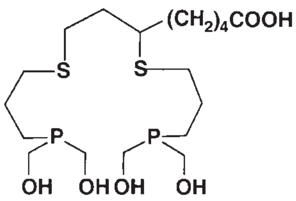
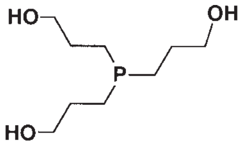


5

metal complexes was evidenced in several cases [8]. It should be noted that besides the phosphorus(III) atom hydroxy groups also can coordinate to soft transition metals [9]. This hemilabile coordination may significantly affect the catalytic behavior of *P*-ligands bearing hydroxy groups [1].



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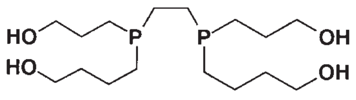
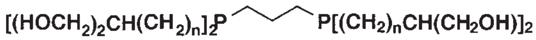


7

By addition of PH_3 or 1,2-ethylenediphosphine to allyl acetate [10] or allyl alcohol, 1,3-polyhydroxyalkylphosphines **6** and **7** can be prepared [11].

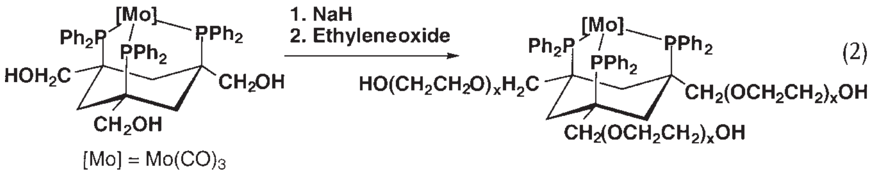
Related 1,3-polyhydroxyphosphines **8** and **9** were synthesized by Lindner et al. by photochemical addition of 1,3-propylenediphosphine to the relevant alkenes [12]. Pd(II) complexes of the new ligands were successfully employed for the copolymerization of CO and ethylene in water.

8 (n = 1-8)



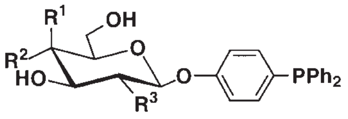
9 (n = 3-6)

On the way to water-soluble polyether phosphines Mayer and co-workers synthesized a tripodal polyhydroxyalkylphosphine ligand in a three-step synthesis starting from the relevant hydroxyphosphine (Eq. 2) [13]. The most interesting feature of this approach is the protection of the phosphine groups as a $Mo(CO)_3$ complex during the synthesis.



(2)

Carbohydrates represent one of the most versatile tools for the synthesis of *P*-ligands bearing hydroxy groups [2, 14]. Thus, Beller et al. used *β*-*O*-glycoside ligands **10** bearing a phenylphosphine group as aglycones for the Pd-catalyzed Suzuki coupling and Heck reaction in an aqueous two-phase system [15].

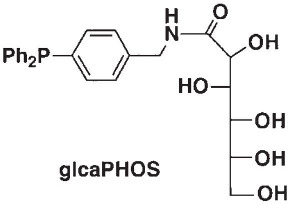


$R^1 = H$, $R^2 = OH$, $R^3 = NHAc$
$R^1 = OH$, $R^2 = H$, $R^3 = OH$
$R^1 = H$, $R^2 = OH$, $R^3 = OH$

10

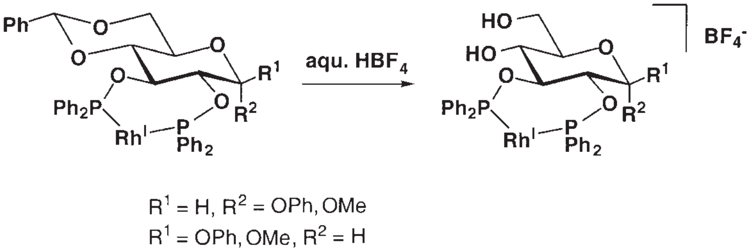
In comparison to the application of TPPTS, with ligands of type **10** improved catalyst activities and yields were observed. These effects were rationalized by the higher catalyst concentration in the nonpolar phase.

Similarly superior results in comparison to the application of sulfonated phosphine ligands were achieved in the Pd-catalyzed biaryl coupling of arylboronic acids in aqueous media by use of the ligand glcaPHOS **11** [16]. The phosphine was prepared in a single step by the condensation of D-glucono-1,5-lactone with *p*-diphenylphosphinobenzylamine.



11

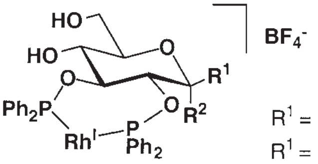
Selke et al. advantageously used rhodium(I) for the protection of acid-labile phosphinite groups in order to cleave an benzylidene acetal in the backbone of carbohydrate bisphosphinite ligands (Eq. 3) [17].



(3)

The cationic catalyst precursors bearing two hydroxy groups were subsequently tested in the asymmetric hydrogenation of *Z*-acetamidocinnamic acid derivatives in water. Strong effects upon the enantioselectivity were noted, depending on the orientation of the hydroxy groups at the pyranose (besides D-glucose derivatives of D-galactose were also used). By addition of amphiphiles the enantioselectivity could be considerably enhanced in comparison to the reactions in a water blank.

Ohe and Uemura investigated the asymmetric hydrogenation of several enamides and itaconic acid in water in the presence of Rh(I) catalyst based on disaccharide (e.g., trehalose) diphosphinite ligands **12** [18]. When sodium dodecyl sulfate (SDS) was used as an additive the amount of the catalyst could be significantly reduced. Simultaneously the enantioselectivity in the product was enhanced.

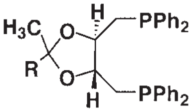


$R^1 = H, R^2 = 1\text{-}\alpha\text{-D-glucopyranose}$

$R^1 = 1\text{-}\beta\text{-D-glucopyranose}, R^2 = H$

12

Evidence for a synergistic effect of internal hydroxy groups and amphiphiles on the Rh-catalyzed asymmetric hydrogenation in water was given by Selke and Börner. Thus, incorporation of a single hydroxy group in the DIOP-analog ligand **13** increased the enantioselectivity by up to 70% *ee* in comparison to the blank experiment [19].

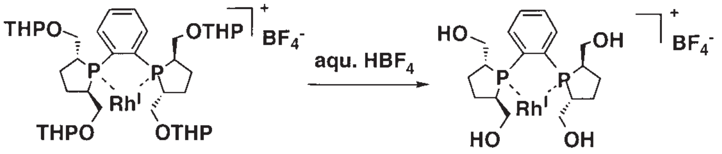


13: R = CH_2OH

DIOP: R = CH_3

Such an effect was absent in the trial with the parent ligand (DIOP). It is noteworthy that the enantioselectivity achieved under optimized conditions distinctly exceeded that in pure methanol.

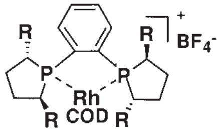
A chiral tetrahydroxydiphospholane named BASPHOS was prepared by Holz and Börner by hydrolysis of four THP-acetal groups in a corresponding Rh^I complex (Eq. 4) [20]. In comparison to the strongly related Et-DuPHOS-Rh precatalyst the four hydroxy groups increased the water solubility of the complex by a factor of four (Structure **14**) [21].



THP = 2-Tetrahydropyranyl

(4)

In the asymmetric hydrogenation of acetamidoacrylate in water with this cationic $(HO)_4$-BASPHOS catalyst (*S*)-*N*-acetyl alanine was obtained in quantitative yield and in more than 99% *ee*. Noteworthy is the unusually short time necessary in or-



solubility in H_2O

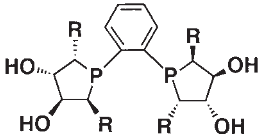
R = CH_2CH_3: 17.5 mg/l

R = CH_2OH: 62.4 mg/l

14

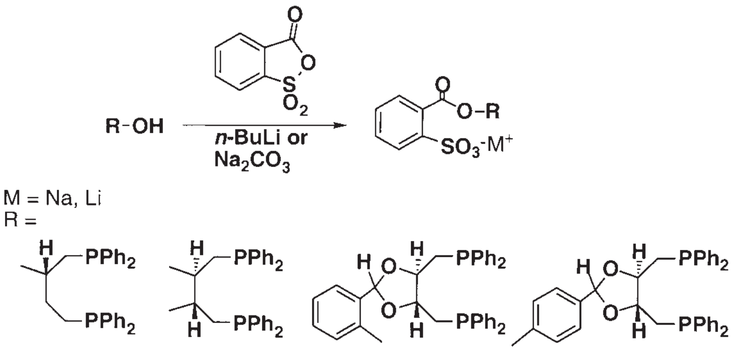
der to get complete conversion of the substrate. Later, RajanBabu and co-workers succeeded in the preparation of the free ligand, $(HO)_4$-BASPHOS, by removal of bulky silyl OH-protective groups with an acidic resin in anhydrous methanol [22]. This method was revealed to be more advantageous than the cleavage of HO-protective groups with acids in aqueous solutions affording mainly phosphonium salts [23].

Polyhydroxyphospholanes of the RoPHOS type [24] were prepared by Zhang and co-workers [23, 25]. With the ethyl-substituted ligand **15b** in the Rh(I)-catalyzed asymmetric hydrogenation of itaconic acid in a water/methanol mixture as solvent 100% conversion and > 99% *ee* were achieved.



15a: R = Me
15b: R = Et

It should be finally noted that hydroxyphosphines can be converted under very smooth conditions into sulfonated phosphines by acylation with *o*-sulfobenzoic anhydride, as shown by Börner et al. (Eq. 5) [26]. With this methodology in hand the severe conditions commonly used for the incorporation of sulphonate groups in phosphines can be avoided. Acid-labile functional groups like acetals survive under these conditions. In comparison to the parent hydroxyphosphines the water solubility of the relevant Rh catalysts was strongly enhanced [27]. In the asymmetric hydrogenation of prochiral olefins, moderate enantioselectivities were achieved.



(5)

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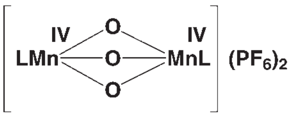
3.2.6.2
Amines and Polyoxometallates as Ligands

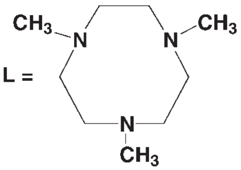
Wolfgang A. Herrmann, Claus-Peter Reisinger

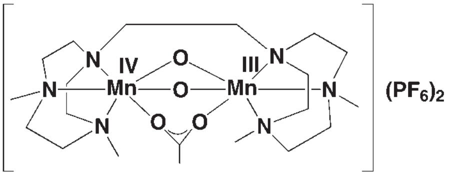
Apart from the aforementioned concepts for water-soluble catalysts, there are some new trends for ligands and catalysts that promise to facilitate their utilization in water. These concepts include nonionic donor ligands, water-soluble polymers (cf. Section 7.6) and inorganic polyoxometallates as redox-active ligands and/or complex ions in homogeneous aqueous-phase catalysis.

Neutral amine ligands are often applied with transition metals in higher oxidation states in polar solvents. This concept combined with the resistance of amines against oxidative conditions led to the development of novel bleaching catalysts (Structures **1**–**3**) for washing powders by Unilever [1].

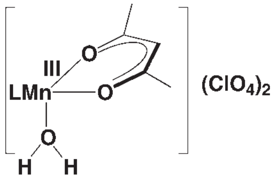


1





2



3

This class of binuclear compounds [2] with tripodal 1,4,7-trimethyl-1,4,7-triazacyclononane ligands [3] was originally reported by Wieghardt and co-workers [4]. The manganese(IV) complexes exhibit rather unusual structural and physical properties [5], combined with superior bleaching activity at room temperature (rt). The oxidizing agents are either hydrogen peroxide or peroxyacetic acid, generated by tetraacetylethylenediamine (TAED) in European detergent powders. Unligated “free” manganese salts show high instability as detergents, resulting in the forma-

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ISBN: 3-527-30712-5

tion of brown stains on textiles due to precipitation, while oxo- and acetato-bridged manganese complexes with 1,4,7-trimethyl-1,4,7-triazacyclononane combined with hydrogen peroxide show the highest activity at pH 10.

Bleaching is a complex process consisting of different oxidation reactions involving manifold substrates, such as arenes and fatty acids. Thus, investigations of the epoxidation of 4-vinylbenzoic acid (a water-soluble alkene) with $H_2{}^{18}O_2$, as a model reaction, gave a product with 100% ^{18}O, suggesting that the oxygen of the epoxide is derived from hydrogen peroxide, and not from water. The optimum pH for epoxidation was established to be around 8, whereas the optimum pH for bleaching of tea-stained test cloths (commercially available as BC-1 cloths) was found to be around pH 10. Thus it appears that catalytic epoxidation and fabric bleaching involve different mechanisms [6].

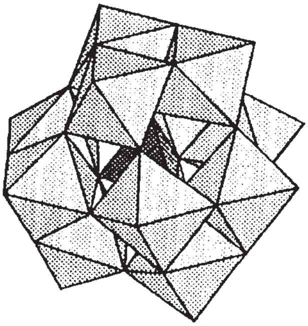
A comparative study of the bleaching performance of complexes **1**–**3** with hydrogen peroxide as a function of pH revealed that compounds **1** and **3** show higher activities at $pH < 9.5$ and compound **2** demonstrates much better results at $pH > 9.5$. This difference in behavior appears to be related to the generally higher stability of the mixed-valence Mn species under catalytic conditions [6] and it may suggest that catalytic fabric bleaching involves mononuclear species at $pH < 9.5$ and binuclear species above this pH.

In the field of catalysis with heteropolyacids (HPAs) and related polyoxometallate systems, large-scale processes such as oxidation of methacrolein, hydration of olefins, and polymerization of tetrahydrofuran have been developed and commercialized [7].

They have outstanding properties which are of great value for catalysis, such as strong Brønsted acidity [8], ability to catalyze reversible redox reactions under mild conditions [9], and high solubility in water [10]. In most applications, they are used as acid, redox, and bifunctional catalysts in homogeneous and heterogeneous systems.

HPAs are polyoxometallates incorporating anions (heteropolyanions) having metal–oxygen octahedra as the basic structural units [11]. Among a wide variety of HPAs, those belonging to the so-called Keggin series have the most importance for catalysis, being the most stable and easily accessible. They include heteropolyanions (HPANs) $XM_{12}O_{40}^{x-8}$, where X is the central atom (Si^{4+}, P^{5+}, etc.), x is the oxidation state, and M is the metal ion (Mo^{6+}, W^{6+}, V^{5+}, etc.). These HPANs are composed of a central tetrahedron XO_4 surrounded by 12 edge-sharing metal–oxygen octahedra MO_6 (Figure 1) [12].

Despite the utilization of polyoxometallates as Brønsted acid catalysts in organic synthesis [13], the most important application is the palladium-catalyzed Wacker oxidation of ethylene to acetaldehyde in aqueous phase. Under standard conditions ($PdCl_2$, $CuCl_2$, O_2, HCl), chlorine ions are corrosive and produce chlorinated by-products (mainly from $CuCl_2$); these conditions are not suitable for the oxidation of higher olefins, such as 1-butene to methyl ethyl ketone. For this reason



$[PO_4Mo_{12}O_{36}]$

Fig. 1 Structural pattern of polyoxymolybdates (HPANs).

HPANs with $PdSO_4$ are applied, instead of $PdCl_2/CuCl_2/HCl$ as a chlorine-free reoxidizing agent with molecular oxygen. Mixed molybdovanadophosphoric heteropolyanions $[PMo^{6+}_{12-n}V^{5+}_{n}O_{40}]^{(3+n)-}$ ($n = 2-6$) [14] and dodecamolybdophosphoric homopolyanion $[PMo_{12}O_{40}]^{3-}$ [15] are used preferentially for the oxidation of ethylene and 1-butene with superior selectivity. The reaction proceeds in an acidic aqueous solution at a pH of 0.5–2.0 and can be represented by Eqs. (1–3):

$$C_2H_4 + Pd^{2+} + H_2O \longrightarrow CH_3CHO + Pd^0 + 2\,H^+ \tag{1}$$

$$Pd^0 + HPAN + 2\,H^+ \longrightarrow Pd^{2+} + H_2(HPAN) \tag{2}$$

$$H_2(HPAN) + 0.5\,O_2 \longrightarrow HPAN + H_2O \tag{3}$$

In general, homogeneous catalysts based on HPANs consist of complex equilibrium mixtures of polyanions of different compositions with products of the degradative dissociation of the heteropolyanion. All these species can function as the active form or as ligands of a transition metal complex [16]. The HPAN + Pd(II) and HPAN + Rh(I) systems are also used in carbonylation, hydroformylation, and hydrogenation reactions [17]. Other redox systems based on HPANs are also known. Their second component is Tl(III)/Tl(I) [18], Pt(IV)/Pt(II) [19], Ru(IV)/Ru(II), or Ir(IV)/Ir(III) [20].

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4

Catalysis in Water as a Special Unit Operation

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

4.1
Fundamentals of Biphasic Reactions in Water

Yücel Önal, Manfred Baerns, Peter Claus

4.1.1
Introduction

Catalytic biphasic reactions, including their aqueous variants, are widely used for the catalytic synthesis of organic products. Catalysts, various types of water-soluble ligands, synthetic uses, industrial applications, and their advantages over conventional homogeneously catalyzed reactions are well documented (e.g. [1–3]). Table 1 presents few examples of reactions performed in an aqueous gas/liquid–liquid medium with a homogeneous complex catalyst soluted either in the aqueous phase or organic phase.

However, knowledge of the physicochemical fundamentals of catalytic biphasic reactions, their kinetics, and mass-transfer processes related to reactions where a gas phase and a second (aqueous) or even a third (organic) phase are present lags behind the successful development of industrial processes such as, for example, the hydroformylation of propene using a water-soluble Rh–TPPTS catalyst (cf. Section 6.1).

Only for reactions that are usually homogeneously catalyzed in the liquid phase, and carried out in the absence of a second or even third phase, i.e., a gas or an immiscible liquid, are the procedures known required for kinetic analysis (e.g. [17–20]). In two-phase systems in which the catalytic reaction takes place in the liquid phase between a liquid reactant and gaseous reactants the quantitative analysis can be more complicated because the gaseous reactions have to be transferred over the gas–liquid boundary layer into the liquid phase. In this situation the reaction engineering prediction of the reactor performance can be performed easily as long as the rate of transfer of the gasous reactants into the liquid phase is fast compared with the intrinsic catalytic reaction according to Eq. (1) [21].

$$\frac{r_i}{k_l a c_i^*} < 0{,}1 \tag{1}$$

Under these circumstances it can usually be assumed that the liquid-phase concentrations of the gaseous reactants correspond to gas–liquid thermodynamic equilibrium described by Henry's law (Eq. 2).

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Tab. 1 Examples of gas–liquid–liquid catalytic reactions.

Reaction	*Catalyst*	*Category*	*Refs.*
Hydroformylation of propylene to butyraldehyde	Rh-TPPTS or Rh-BISBIS	G-L-L/water soluble catalysis	[4, 5]
Hydroformylation of 1-hexene to heptaldehydes	Rh-TPPTS	G-L-L/water soluble catalysis	[5]
Hydroformylation of 1-octene to nonaldehydes	$[RhCl(1,5\text{-cod})]_2$/ TPPTS	G-L-L/water soluble catalysis	[6–8]
Hydroformylation of 1-dodecene to tridecaldehydes	$RhCl(CO)(TPPTS)_2$	G-L-L/water soluble catalysis	[9]
Hydroformylation of allyl alcohol	$HRh(CO)(PPh_3)_3$	G-L-L/organic phase catalysis	[10]
Selective hydrogenation of α-β unsaturated aldehydes	Rh-TPPTS or Ru-TPPTS	G-L-L/water soluble catalysis	[11]
Oligomerisation of α-olefins (SHOP process)	$Ni\text{-}(C_5H_5)_2PCH_2COOH$	G-L-L/organic phase catalysis	[12, 13]
Carbonylation of isobutyl phenyl ethyl alcohol to ibuprofen (Boots–Hoechst process)	$Pd(PPh_3)_2Cl_2$	G-L-L/organic phase catalysis	[14]
Oligomerisation of terminal alkynes	Rh/water soluble phosphines	G-L-L/water soluble catalysis	[15]
Regioselective hydrogenation of sorbic acid	$[RuCl_2\{P[(CH_2)_3OH]_3\}]_2$	G-L-L/water soluble catalysis	[16]

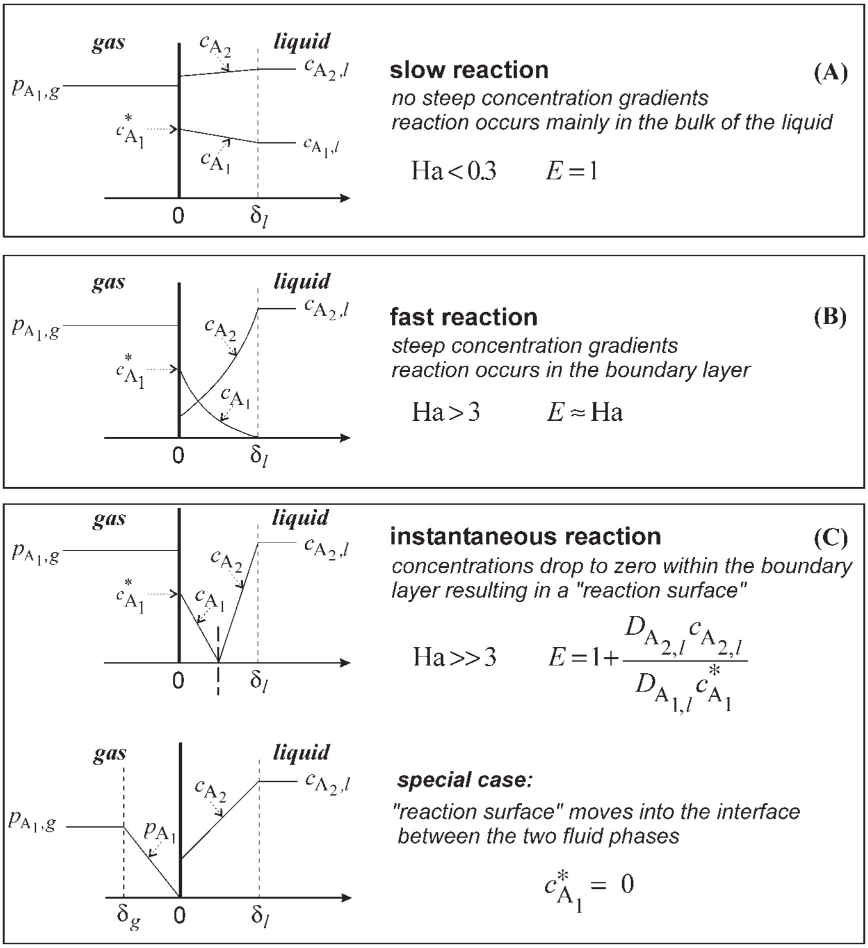
$$p_i^* = H_i c_i^* \tag{2}$$

By contrast, if the assumption of the rate-limiting catalytic reaction is not valid, reaction engineering modeling is no longer trivial. The situation may become even more complicated if a second liquid phase (e.g., water) is present: either this second phase may serve as the reaction space containing the catalyst while the product as well as a part of the reactants exist in the first liquid phase, or it may function as a solvent into which a desired intermediate is extracted from the reacting liquid phase. Thus, for a kinetic analysis of a homogeneous catalytic reaction in a multiphase chemical reactor it is necessary to combine several pieces of information (i.e., about intrinsic kinetics of the homogeneous catalytic reaction, mass transfer between the phases, the effect of the hydrodynamic conditions on mass transfer, and hydrodynamics within the reactor affecting the residence time distribution in continuous operation) in a suitable reactor model. In this section, the required of kinetics and the mode of operation of biphasic reactions in water are considered, with the emphasis on problems which follow from chemical engineering aspects of gas–liquid–liquid reactions.

4.1.2
Gas/Liquid-phase Reactions

In homogeneously catalyzed gas/liquid-phase reactions the overall reaction rate is determined by the actual chemical reaction rate and by mass transfer processes [1 b]. Depending on the magnitude of the rates of the catalytic reaction and of the transfer rate of the gaseous reactants, severe concentration gradients may exist near the gas–liquid interface. These phenomena are shown in Figure 1 for the reaction

$$A_{1,g} + A_{2,l} \rightleftharpoons P_1 \tag{3}$$



slow reaction (A)
no steep concentration gradients
reaction occurs mainly in the bulk of the liquid

$\mathrm{Ha} < 0.3 \qquad E = 1$

fast reaction (B)
steep concentration gradients
reaction occurs in the boundary layer

$\mathrm{Ha} > 3 \qquad E \approx \mathrm{Ha}$

instantaneous reaction (C)
concentrations drop to zero within the boundary layer resulting in a "reaction surface"

$$\mathrm{Ha} >> 3 \qquad E = 1 + \frac{D_{A_{2,l}} c_{A_{2,l}}}{D_{A_{1,l}} c^*_{A_1}}$$

special case:
"reaction surface" moves into the interface between the two fluid phases

$$c^*_{A_1} = 0$$

Fig. 1 Concentration profiles in gas and liquid for a chemical reaction influenced by mass transfer in the liquid phase at various ratios of the reaction rate to the rate of mass transfer. D = binary diffusions coefficient.

As can be easily derived from the concentration pattern, the reaction takes place either mainly in the bulk of the well-mixed liquid phase or in the liquid-phase boundary layer. In reactions which occur in the bulk of the liquid phase, the concentration of gaseous educts decreases only within the interfacial layer (thickness δ) to the concentration $c_{\mathrm{A}_1,l}$ by physical diffusion processes. Only in the case of mass transport processes that are fast relative to the reaction rate is the latter proportional to the $c_{\mathrm{A}_1,l}$ in the liquid phase. If the catalytic reaction is fast enough a "reaction surface" may develop within the boundary layer which may even move into the interface itself and, thus, neither the bulk of the liquid nor the liquid-phase boundary layer is utilized any more for the reaction. A simple approach in order to determine the regime of the overall reaction rate can be performed by comparison of the intrinsic kinetics with the rate of mass transfer according to Table 2 [22].

Tab. 2 Controlling regimes and criteria for mass transfer in gas-liquid reactions [22].

Criterium	*Controlling regime*
$\frac{r_A}{k_l a c_A^*} < 0{,}1$	Kinetic control
$\frac{c_{B,l}}{\nu c_A^*} >> \frac{r_A}{k_l a c_A^*} > 0{,}1$	Fast reaction with significant reaction within the liquid film
$\frac{r_A}{k_l a c_A^*} \approx 1$	Diffusion control
$\frac{r_A}{k_l a c_A^*} \approx \left(1 + \frac{c_{B,l}}{\upsilon c_A^*}\right)$	Instantaneous reaction regime

The use of these criteria requires an experimentally measured point value for the reaction rate, the solubility of gas phase reactant and an estimation of gas to liquid mass transfer coefficient $k_l a$. Some correlations for calculating $k_l a$ values in different multiphase reactor systems are presented in Table 3.

From a chemical point of view it is obvious that not only the overall rate but also the selectivity towards a desired product is affected by these phenomena if a complex reaction network exists. If concentration gradients near the gas–liquid interphase are detrimental to good selectivity, they have to be avoided. This can be done by increasing the rate of transfer of the reactants or by lowering the rate of the catalytic reaction; the former is achieved by engineering means such as increasing the interfacial area per unit volume or/and increasing the rate of transfer per unit interfacial area by influencing the fluid dynamics (e.g., by stirring). The rate of the catalytic reaction may be reduced by decreasing the concentration of the catalyst, by diluting the reactants, or by lowering the temperature.

Tab. 3 Empirical correlations for the mass transfer coefficient $k_l a$.

Reactor	*Correlation*	*Refs.*
Mechanically agitated batch reactor	$\frac{k_l a d_l}{D} = 0.06\left(\frac{d_l^2 N\varphi_L}{\mu_L}\right)^{1,5}\left(\frac{d_l N^2}{g}\right)^{0,19}\left(\frac{\mu_L}{\varphi_L D}\right)^{0,5}\left(\frac{\mu_L \mu_g}{\sigma_L}\right)^{0,6}\left(\frac{N d_l}{u_g}\right)^{0,32}$	[23]
Mechanically agitated batch reactor	$k_l a = 0.32\ N^{1,16} d_I^{1,98} u_g^{0,32} V_L^{-0,52}$	[24]
Mechanically agitated batch reactor	$k_l a = 1.48 \cdot 10^{-3} N^{2,18}\left(\frac{V_g}{V_L}\right)^{1,88}\left(\frac{d_l}{d_T}\right)^{2,16}\left(\frac{h_1}{h_2}\right)^{1,16}$	[25]
Bubble column reactor	$k_l a = \frac{14.9\mathrm{gf}}{\mathrm{u_g}}\left(\frac{u_g \mu_L}{\sigma_L}\right)^{1,76}\left(\frac{\mu_L^4 g}{\varphi_L \sigma_L^3}\right)^{-0,284}\left(\frac{\mu_g}{\mu_L}\right)^{0,243}\left(\frac{\mu_L}{\varphi_L D}\right)^{-0,604}$ $f = 1.0$ for non electrolytes	[26]
Jet loop reactor	$k_l \approx 4.6 \cdot 10^{-2}\,\mathrm{cm/s}$ for $u_g = 0.4 - 0.6\,\mathrm{cm/s}$ $a = 5.4 \cdot 10^3 u_g^{0,4}\left(\frac{P}{V_L}\right)0.66$	[27]

To derive the overall kinetics of a gas–liquid-phase reaction it is required to consider a volume element at the gas–liquid interface and to set up mass balances including the mass transport processes and the catalytic reaction. These balances are either differential in time (batch reactor) or in location (continuous operation). By making suitable assumptions about the hydrodynamics and, hence, the interfacial mass transfer rates, in both phases the concentration of the reactants and products can be calculated by integration of the respective differential equations either as a function of reaction time (bath reactor) or of location (continuously operated reactor). In continuous operation certain simplifications in setting up the balances are possible if one or all of the phases are well mixed, as in a continuous stirred tank reactor; thereby the mathematical treatment is significantly simplified.

Therefore, it is necessary to determine the influence of mass transfer to or from the above-mentioned interfaces on the conversion, leading to expressions for the flux of a reactant across the interface and for the overall reaction rate. After balancing the disappearance of the components A_1 and A_2 at, for instance, the gas–liquid interface by analogy with the treatment of the rate of chemical reactions and pore diffusion in heterogeneous catalysis, the overall reaction rate is given by Eq. (4) [18].

$$r_{eff} = a\frac{\mathrm{Ha}}{\tanh \mathrm{Ha}}\,\frac{p_{1,g} - \dfrac{H_1 c_{1,l}}{\cosh \mathrm{Ha}}}{\dfrac{RT}{k_{1,g}} + \dfrac{H_1}{k_{1,l}}\,\dfrac{\tanh \mathrm{Ha}}{\mathrm{Ha}}} \tag{4}$$

For analysis of such coupled fluid/fluid systems it is useful to distinguish between three regimes of the reaction rate (see Figure 1) which are characterized by different values of the Hatta number Ha (Eqs. 5 and 6) and the enhancement factor E (see below).

$$\mathrm{Ha} = \frac{1}{k_{1,l}} \sqrt{\frac{2}{n+1} k_{n,m} D_{A_1,c} c_{A_1}^{n-1} c_{A_2}^{-m}} \tag{5}$$

$$\mathrm{Ha} = \frac{1}{k_{1,l}} \sqrt{k D_{1,l}} \quad \text{(first-order reaction)} \tag{6}$$

The mass exchange rate between two phases during the course of the chemical reaction is compared with that for purely physical absorption. The ratio of these two rates (Eq. 7) is known as the enhancement factor E for mass transfer on the liquid side during the course of a chemical reaction:

$$E = \frac{J_{\mathrm{A\,(with\ reaction)}}}{J_{\mathrm{A\,(without\ reaction)}}} = \frac{\dfrac{\mathrm{Ha}}{\tan \mathrm{Ha}} \left[1 - \dfrac{c_{1,l}}{c_1^*} \dfrac{1}{\cosh \mathrm{Ha}} \right] k_{1,l} c_1^*}{k_{1,l}(c_1^* - c_{1,l})} \tag{7}$$

For slow reactions ($\mathrm{Ha} < 0.3$) the rate of mass exchange through the fluid/fluid interface is not enhanced by the chemical reaction, which mainly takes place in the bulk of the reaction (catalytic) phase, and E becomes approximately 1 [18].

Under conditions of $0.3 < \mathrm{Ha} < 3$, the rate of mass exchange is enhanced by the chemical reaction ($E > 1$), and in the case of $\mathrm{Ha} > 3$, A_1 and A_2 react so fast that the reaction proceeds only in the boundary layer ($E = \mathrm{Ha}$). Thus equation (4) for the overall rate of reactions is reduced to Eq. (8).

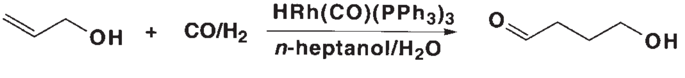
$$r_{\mathrm{eff}} \approx a \frac{p_{1,\mathrm{g}}}{\dfrac{\mathrm{RT}}{k_{1,\mathrm{g}}} + \dfrac{\mathrm{H}_1}{k_{1,1}\mathrm{Ha}}} \tag{8}$$

A theoretical analysis to evaluate the mass transfer effects quantitatively for a hyperbolic form of the intrinsic kinetics of a homogeneous catalytic reaction has been developed [28], covering all the regimes of a gas–liquid reaction in the presence of a homogeneous catalyst, and thus leading to quantitative prediction of mass transfer effects on the kinetics of this operation mode. Assuming a gaseous reactant A, an organic liquid-phase reactant B and a homogeneous catalyst C, two cases have to be considered, namely that (1) the reaction is assumed to occur either in bulk liquid, or (2) the reaction of A occurs completely in the film. For the second case the concept of a generalized Hatta number is used to obtain an approximate analytical solution for the enhancement factor. Plots of E vs. Ha at various values of the parameters are given [28]. In the former case a transition in the regimes of absorption with changes in Ha is indicated, which, with respect to the homogeneous catalyzed reaction, reflects a change in the concentration of the catalyst.

4.1.3
Gas/Liquid/Liquid-phase Reactions

In gas–liquid reactions, the liquid phase contains the homogeneous catalyst together with the liquid reactant and the dissolved gaseous reactant. To perform gas–liquid–liquid reaction, in the biphasic (liquid–liquid) mode it is essential that the solubility of the homogeneous catalyst in one of the two liquid phases is negligible. By using water-soluble ligands, homogeneous metal complex catalysts are dissolved in the aqueous phase where the catalytic reaction can take place (see below). In these aqueous biphasic liquid systems, different situations are possible which would have to be considered in any quantitative treatment. On the one hand, for example, the gaseous reactants are dissolved in the catalyst-containing aqueous phase where they react to form an immiscible product which is only soluble in the organic liquid phase. The gaseous reactants are transferred into the catalyst-containing phase either directly from the gas phase and/or from the liquid phase, in which they may be soluble, too. On the other hand, the gaseous reactants are soluble in only one liquid phase. This requires that the catalytic liquid takes place at the liquid–liquid interface only, i.e., the products, again soluble only in one of the two phases, are formed in the boundary layer or in the phase boundary interface for the case of an instantaneous reaction (Ha $\gg 3$).

These processes are still not fully understood and need further elucidation. In the case of the homogeneously catalyzed hydroformylation of olefins according to Ruhrchemie/Rhône-Poulenc, the reaction products are completely insoluble in the aqueous phase which contains the water-soluble catalyst ($[HRh(CO)(TPPTS)_3]$). By contrast, if the homogeneous catalyst is not soluble in water but in an organic liquid, the biphasic homogeneously catalyzed reaction may also occur in the organic phase. For instance, in the case of biphasic hydroformylation of allyl alcohol (Eq. 9), the educt and the reaction products are water-soluble but the catalyst is present in the organic phase [9]. Furthermore, in some cases the second liquid phase is formed during the catalytic reaction itself (e.g., in the SHOP process of Shell [1]).



(9)

In all the above-mentioned cases conversion can only take place when the components are transferred to the catalytic phase or at least to the interface in which the reaction proceeds. The transport from one phase to the other(s) requires a driving force, i.e., the existence of concentration gradients. The principal steps of a homogeneously catalyzed gas–liquid–liquid reaction (10) are shown schematically in Figure 2, where the reaction product P_1 is formed by the reaction between a gaseous reactant A_1 and reactant A_2 from the organic liquid phase in presence of a second phase, i.e., an aqueous liquid phase which contains the water-soluble catalyst. Moreover, it is assumed that both liquid phases are immiscible. In such a scenario two cases can be distinguished: (i) aqueous droplets containing the dissolved catalyst are dispersed in a continuous organic liquid phase, if the aqueous phase hold-up is smaller than the organic phase hold-up, and, (ii) the organic liquid phase is dispersed in a continuous aqueous phase which contains the water-soluble catalyst if the organic phase hold-up is smaller than the aqueous phase hold-up.

$$A_{1,g} + A_{2,l} \xrightarrow[\text{aqueous biphase}]{\text{homogeneous catalyst}} P_1 \tag{10}$$

Several steps influencing the overall rate of the reaction and the selectivity of a desired product have to be considered; they are outlined in Table 4. It is important to note that steps (e) and (f) cannot be separated from each other in either case because, in general, the transport from the interfaces occurs *simultaneously* with the catalytic reaction.

From the above qualitative discussion it can be clearly derived that at least four important factors, namely interphase mass transfer, solubility, thermodynamic phase equilibria, and intrinsic kinetics must be considered during quntitative analysis of gas–liquid–liquid reactions (Figure 3).

Thus, in the scenario shown above the various equations for the overall rate may be obtained, depending themselves on, for example, the types of catalst and water-

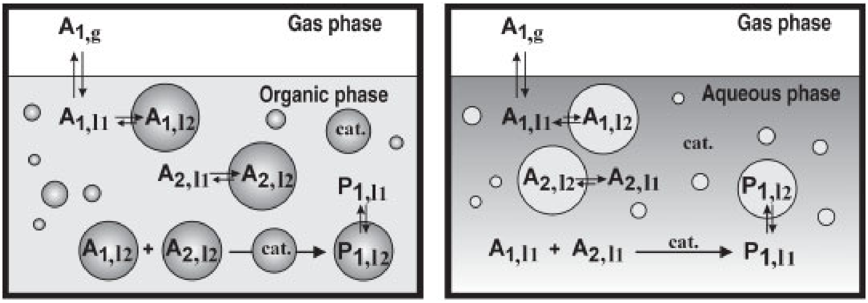


Fig. 2 Two features of the principal steps of mass transfer and chemical reaction during a homogeneously catalyzed gas–liquid–liquid reaction (aqueous biphasic mode). A_1 = gasous reactant; A_2 = liquid reactant; P_1 = reaction product. Aqueous droplets containing the dissolved catalyst are dispersed in a continuous organic liquid phase (left); the organic liquid phase is dispersed in a continuous aqueous phase which contains the water-soluble catalyst (right).

Tab. 4 Dependence of sequence of steps in an aqueous biphasic catalytic reaction on the mode of operation.

Step	*Case I: Aqueous droplets containing the dissolved catalyst are dispersed in a continuous organic liquid phase*	*Case II: Organic liquid phase is dispersed in a continuous aqueous phase which contains the catalyst*
(a)	Transport of a gaseous reactant (A_1) from the bulk of the gas phase to the gas/organic liquid interface	Transport of a gaseous reactant (A_1) from the bulk of the gas phase to the gas/aqueous catalyst interface
(b)	Transport of A_1 through the gas/organic liquid interface	Transport of A_1 through the gas/aqueous catalyst interface
(c)	Transport of A_1 into the bulk of the organic liquid	Transport of A_1 into the bulk of the aqueous catalyst phase[a]
(d)	Transport of both dissolved A_1 and liquid reactant (A_2) from the organic phase to the organic/aqueous interface	Transport of liquid reactant (A_2) from organic droplets to the organic/aqueous interface
(e)	Transport of $A_1$and A_2 from the organic/aqueous interface to the aqueous catalyst phase	Transport of A_2 from the organic/aqueous interface to the aqueous catalyst phase
(f)	Homogeneously catalyzed reaction of dissolved A_1 and A_2 to product (P) in the aqueous phase	Homogeneously catalyzed reaction of dissolved A_1 and A_2 to products (P) in the aqueous phase
(g)	Transport of water-immiscible P from the aqueous to the organic phase	Transport of water-immiscible P from the aqueous to the organic liquid phase

[a] In the presence of an organic liquid, further transport to the gas/organic liquid interphase and into the bulk of the organic liquid.

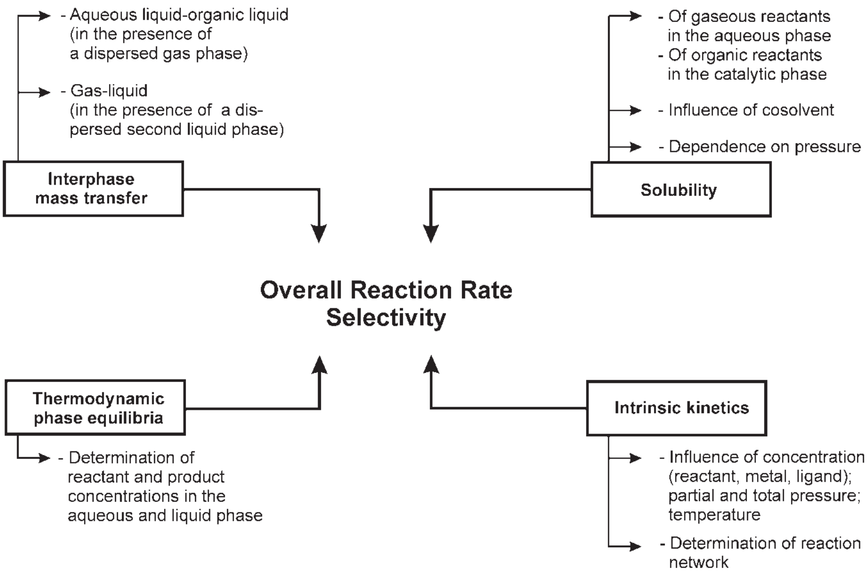


Fig. 3 Factors controlling gas–liquid–liquid reactions (aqueous biphasic mode).

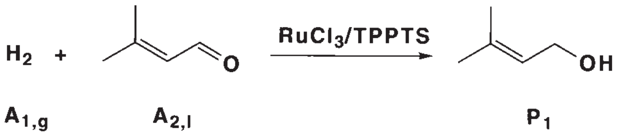
soluble ligands, solvents, surface-active compounds, phase equilibrium properties and the extent of gas–liquid and liquid–liquid resistances.

The droplet size of the dispersed aqueous and organic liquid phase is affected by the liquid properties and the reactor type. For instance, in the case of reaction (9) given above between $A_{1,g}$ and $A_{2,l}$ in a homogeneous catalyst-containing aqueous phase, the enhancement of gas-to-water mass transfer rates by a dispersed organic phase can be described with a new mass transfer theory without any additional parameter adjustment, the so-called film variable holdup (FVH) model [29]. This model takes into account the distribution of organic and continuous aqueous phase near the gas–liquid interface and explains quantitatively the influence of hold-up, droplet diameter, and permeability of the organic phase on the observed enhancement. Experimental data have been presented on the enhancement of O_2 mass transfer into an aqueous Na_2SO_3 solution in a stirred cell, due to the presence of a dispersed liquid 1-octene phase. Also the experimental data for O_2 mass transfer enhancement in hexadecane and for CO_2 mass transfer enhancement due to toluene droplets can be reasonably well described; this indicates that in different liquid–liquid systems the dispersed phase distribution is similar for different organic droplets in water.

A generalized theoretical model based on the film theory was also developed for the calculation of the enhancement factor for the simultaneous absorption of two gases coupled with a complex reaction mechanism in liquid phase, in which the rate is negative-order with respect to one of the gases and first order with the other [40]. This phenomenon is typically observed in hydroformylation reactions, where the reaction rate is first order with respect to hydrogen partial pressure and negative order with respect to CO. Practical implications of this analysis have been illustrated with the hydroformylation of 1-hexene. Thereby, an expression for the enhancement factor E_{CO} has been derived, which is applicable irrespective of the regime of absorption.

The very low solubility of organic reactants in the catalytic phase often gives rise to a drastic decrease of the effective reaction rate. This drawback of gas–liquid–liquid reactions has been overcome by adding a co-solvent. In the case of 1-octene hydrogenation which was performed in semibatch operation and by using $[RhCl(cod)_2]$/TPPTS as water-soluble catalyst, the water/1-octene co-solvent equilibrium was estimated by a combination of the UNIFAC group distribution method and the UNIQUAC equation in order to select a convernient co-solvent [30]. Ethanol, *n*-propylamine, or ethylene glycol enhances the 1-octene concentration in the aqueous phase considerably without losing catalyst in the organic phase. Furthermore, it was shown that the hydrogen solubility in the aqueous catalytic phase increases according to Henry's law (2), with increasing hydrogen pressures up to 10 MPa. Then, initial kinetics, derived without any gas–liquid and liquid–liquid mass transfer limitations, showed first-order reaction rates with respect to dissolved hydrogen and 1-octene in the aqueous phase. Finally, by measuring time-dependent concentrations together with the thermodynamic liquid–liquid model, which makes it possible to calculate the concentrations of reactants and products in the aqueous catalytic and organic phases, complete kinetics of parallel hydrogenation and isomerization were analyzed [30].

Several of the factors of Figure 3 controlling the activity and selectivity of the biphasic selective hydrogenation of α,β-unsaturated aldehydes to allylic alcohols, for instance, 3-methyl-2-butenaldehyde to 3-methyl-2-buten-1-ol (Eq. 11) with ruthenium-sulfonated phosphine catalysts were investigated [11], such as the effect of agitation speed and the influence of aldehyde, ligand, and metal concentrations. Under optimized reaction conditions, where gas–liquid mass transfer was not rate-determining, the kinetic equation (Eq. 12) was found to apply. A zero-order dependence with respect to the concentration of the α,β-unsaturated aldehyde was found.



(11)

$$r = k\,c_{\mathrm{Ru}}\,c_{\mathrm{H_2}} \tag{12}$$

Gas–liquid–liquid reaction engineering was studied by Purwanto and Delmas [8] during hydroformylation of 1-octene by [Rh(cod)Cl_2]/TPPTS catalyst in a batch reactor at pressures between 1.5 and 2.5×10^3 kPa and temperatures of 333 and 343 K. As also shown for olefin hydrogenation [30], the concentration of 1-octene in the aqueous phase was increased by using a co-solvent (e.g., ethanol) which gave rise to an enhancement of the reaction rate of hydroformylation [8, 31]. Ternary diagrams of the octene–water–ethanol system have been established with the UNIFAC prediction. An equilibrium of the quaternary mixture of water–ethanol–octene–octane was also calculated using PROPHY software of ENSIGC. The interaction parameters in UNIFAC were calculated from the Magnussen parameters. By addition of the co-solvent, the solubility of hydrogen and carbon monoxide also increased. Kinetic studies showed that the reaction is first-order with respect to 1-octene and catalyst concentrations. The reaction rate was enhanced by hydrogen partial pressure and at low CO partial pressures, whereas inhibition was observed at high CO pressures. This dependence on CO partial pressure was typical of hydroformylation kinetics in homogeneously catalyzed reactions with a Rh complex catalyst. A semi-empirical kinetic model (Eq. 13) based on initial reaction rates obtained during this study was used to describe the overall rate of the 1-octene hydroformylation:

$$r = \frac{k\,c_{\mathrm{octene}}\,c_{\mathrm{H_2}}\,c_{\mathrm{CO}}\,c_{\mathrm{cat}}}{[1 + K_{\mathrm{H_2}}c_{\mathrm{H_2}}][1 + K_{\mathrm{CO}}c_{\mathrm{CO}}]^2} \tag{13}$$

Tab. 5 Parameters of Eq. (13) obtained for the kinetics of the hydroformylation of 1-octene at two temperatures [8].

Parameter	***T* = 333 K**	***T* = 343 K**
$k \times 10^{-5}$ [$m^9 kmol^{-3} s^{-1}$]	1.571	7.441
$K_{H_2} \times 10^{-2}$ [$m^3 kmol^{-1}$]	1.967	2.185
$K_{CO} \times 10^{-2}$ [$m^3 kmol^{-1}$]	1.133	1.886

The parameter values obtained by an optimization routine are given in Table 5. Furthermore, it was observed that, if PPh_3 was added to the organic liquid phase (toluene) during hydroformylation, the rate was increased by a factor up to 50 [32].

Kinetics of the 1-octene hydroformylation in aqueous biphasic media with the complex catalyst [RhCl(1,5-cod)Cl]$_2$/TPPTS was also reported in [7]. Thereby, the reaction rate was also described by a mechanistic model (Eq. 14) assuming the addition of the olefin to the active catalyst to be the rate limiting step.

$$r = \frac{k_2\, c_{\text{octene}} c_{H_2} c_{CO} c_{\text{cat}}}{1,0 + K_{H_2} c_{H_2} + K_{CO} c_{H_2} c_{CO} + K_{\text{cat}} c_{CO}^2} \tag{14}$$

Kinetics of the hydroformylation of propylene using RhCl(CO)(TPPTS)$_2$/TPPTS complex catalyst in aqueous system was studied by an orthogonal experimental design analyzing the influence of temperature total pressure, molar ratio H_2/CO, partial pressure of propylene, molar ratio Rh:TPPTS, and the catalyst concentration on the initial reaction rate [33].

The relative importance of certain reaction conditions on the hydroformylation rate and the optimal set of factor levels were determined by margin and variance analysis. Experimental data could be described by an empirical, a semi-empirical, and a mechanistic rate model assuming the addition of propylene to the active catalyst species as the rate limiting step (see Table 6).

The kinetics of the above-mentioned biphasic hydroformylation of allyl alcohol (see Eq. 9) was described by the rate Eq. (15) [10], which shows the inhibition of the reaction rate by the partial pressure of carbon monoxide.

$$\mathrm{r} = \frac{k\, c_{C_3H_5OH} c_{H_2} c_{\text{cat}}}{[1 + K_{CO} c_{CO}]^3} \tag{15}$$

4.1.4
Place of Reaction in Aqueous Biphasic Systems

With respect to the location where homogeneously catalyzed biphasic reactions occur, two main conclusions can be drawn from the experimental observations sketched above: in such cases where the reaction rate is accelerated by co-solvents and other solubility promoters (e.g., EtOH), it has been concluded that the bulk of the liquid is the reaction place [10, 30]. This seems to be confirmed by the observed decrase in reactivity of olefins as starting compounds for hydroformylation with their decreasing solubility [1]. Chaudhari et al. [6] studied aqueous biphasic hydroformylation of 1-octene in a mechanically agitated batch reactor assuming the aqueous bulk as the site of reaction. Kinetic analysis have been developed in the regime of gas to liquid mass transfer limitation by performing the hydroformylation at a low stirring velocity. True reaction kinetics of the hydroformylation of 1-octene has been coupled to a pseudo-homogeneous gas–liquid–liquid model based on Higbie's penetration theory, which takes into account the presence of a dispersed organic phase. The effects of the main parameters, stirrer speed, and organic phase hold-up have been discussed.

By contrast, the increase in the reaction rate and control of the selectivity in biphasic system observed with the use of surfactants or other surface-active compounds [34–36] (for "promotor ligand" see [32]) indicate an increase in the liquid–liquid interfacial area, and it has therefore been speculated that the latter seems to be the reaction site [32].

To answer the fundamental question of where the reaction takes place in RCH/RP's process, Cornils and co-workers [37] conducted relatively simple batch calorimetric experiments at various pressures, temperatures, stirrer speeds, and concen-

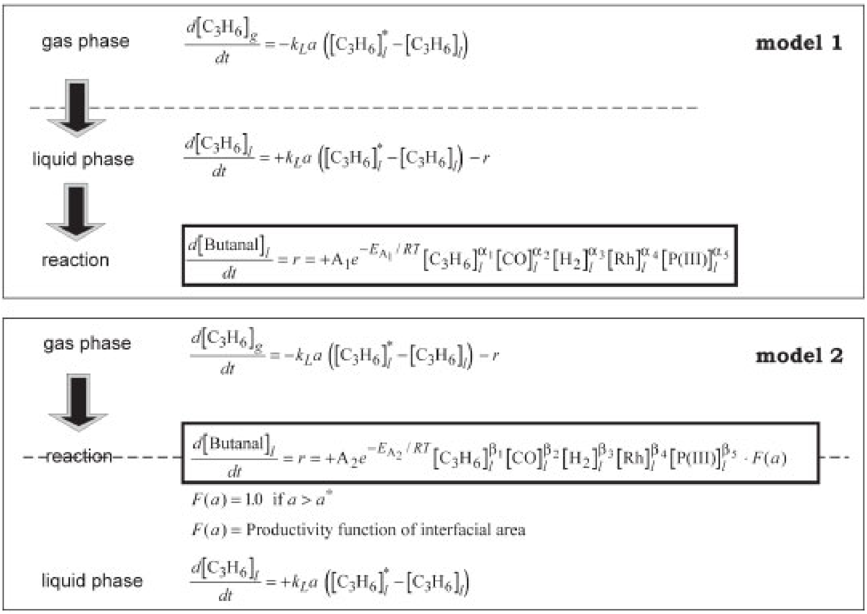


Fig. 4 Kinetic models for the RCH/RP process by Cornils and co-workers [37].

trations, using catalyst solutions from the large-scale plants at Oberhausen, together with reaction modeling. Two kinetic models were tested, namely one for a reaction in the bulk water phase (model 1) and another for a reaction at the phase interface (model 2) (Figure 4).

By comparison between the calculated and measured pressure and heat flux vs. time curves it was shown that the site of this hydroformylation reaction could not be the bulk of the liquid. Only the assumption of a reaction in the liquid boundary layer at the gas–liquid interface gave satisfactory agreement of the data under all experimental conditions. Thus, on this basis scale-up rules for the aqueous biphasic hydroformylation and appropriate kinetic models can be developed for optimal reactor design. The principle of both models applied to the general equation (Eq. 10) is shown in Figure 5.

However, reaction modeling will be more complex, for instance in the case of hydroformylation of higher olefins, if co-solvents or surfactants, i.e., additional liquid phase(s), are present in the reaction mixture.

Macro-kinetics of biphasic hydroformylation of 1-dodecene catalyzed by water-soluble catalyst $RhCl(CO)(TPPTS)_2$ has been investigated in the presence of the cationic surfactant cetyl trimethyl ammonium bromide (CTAB) assuming the liquid–liquid interphase as the site of reaction by Zhang et al. [9]. The objective of the cationic surfactant, which is located at the liquid–liquid interphase of the solvent mixture with dispersed organic phase, is the attraction of the water-soluble catalyst with negative charge to the interphase by electrostatic interaction. As a consequence, the coordination with olefin in the organic phase proceeds more easily (as shown in Figure 6).

This formation of ordered an assembly of micelles results in a higher rate of hydroformylation and increased selectivity to the linear aldehyde. Effects of operation

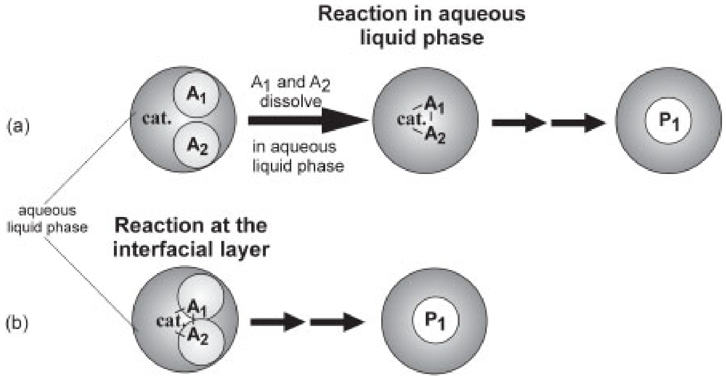


Fig. 5 Principle of two alternative models for aqueous biphasic reactions. (a) Reaction in the bulk of the aqueous liquid phase (must be preceded by diffusion from the gas into the liquid phase). (b) Reaction in the interphase region.

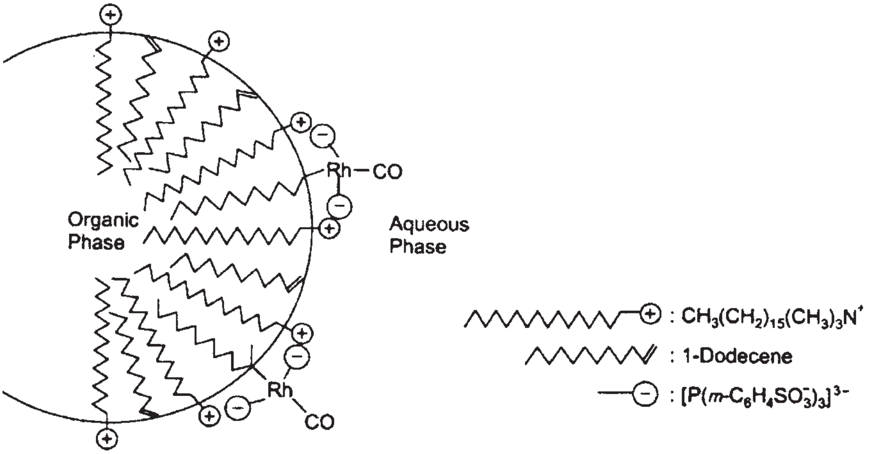


Fig. 6 Biphasic hydroformylation at the liquid–liquid interface with CTAB for oil-in-water dispersion [9].

variables on the reaction rate and the *n/iso*-ratio of the corresponding aldehyde were conducted by an orthogonal experimental design. The optimal reaction conditions were suggested by margin and variance analyses of experimental data showing, that above all the volume ratio of organic phase to aqueous phase has the most important effect on the reaction rate. An analysis of mass transfer of gaseous reactants to the liquid phase indicated that gas–liquid mass transfer rate was still a controlling factor in some cases. An empirical kinetic equation was developed after correcting the effect of mass transfer, which is presented by Eq. (16).

$$r = 2.5485 \cdot 10^{17} \exp\left(\frac{-8533}{T}\right)\left(p^{*}_{\mathrm{H_2}}\right)^{0.59}\left(p^{*}_{\mathrm{CO}}\right)^{0.52} c_{\mathrm{cat}}^{0.32} c_{\mathrm{dodecene}}^{0.41} c_{\mathrm{CTAB}}^{2.91}\left(\frac{c_{\mathrm{Ligand}}}{c_{\mathrm{Rh}}}\right)^{-0.74}\left(\frac{V_{\mathrm{Org}}}{V_{\mathrm{Aq}}}\right)^{-1.66} \tag{16}$$

By combining the homogenous catalytic mechanism with interfacial reaction and assuming the addition of olefin to the active catalyst species as the rate-controlling step, a semi-empirical kinetic model could also be proposed, which was also in good agreement with the experimental data.

In the case of another biphasic variant, namely phase-transfer-catalyzed reactions (cf. Section 4.6.1; e.g., [38]), mass transfer rates of ionic intermediates between the aqueous and organic phases, their phase and partition equilibria, as well as the reaction rate in the organic phase, have to be analyzed to model the overall reaction rate. Finally, the dynamics of liquid–liquid phase transfer reactions, which are a part of multiphase reactions as shown above, can be described by a new phase-plane model [39] based on the two-film theory.

Tab. 6 Rate models describing the hydroformylation of propylene using RhCl(CO)(TPPTS)$_3$/TPPTS complex catalyst [33].

Approach	***Rate model***
Empirical	$r = A_0 \exp\left(\frac{-E_A}{R_G T}\right) p^{\alpha}_{H_2} \cdot p^{\beta}_{CO} \cdot p^{\chi}_{P} \cdot c^{\varepsilon}_{Rh} \cdot c^{\phi}_{L}$
Mechanistic	$r = \frac{k_1 c_{H_2} c_{CO} c_p c_{Rh}}{k_2 + k_3 c_{H_2} + k_4 c_{CO} + k_5 c_{H_2} c_{CO} + k_6 c_p + k_7 \frac{c^2_{CO}}{c_L} + c_{H_2} c_L}$
Semi-empirical	$r_0 = \frac{A_0 \exp\left(\frac{-E_A}{R_G \mathrm{T}}\right) p_{H_2} \cdot p_{CO} \cdot p_p \cdot c_{Rh}}{(1 + k_1 p_{H_2})(1 + k_2 p_{CO})^2 (1 + k_3 p_p)^2 (1 + k_5 c_L)^3}$

In future, a complete quantitative analysis on the basis of chemical reaction engineering principles of homogeneously catalyzed gas–liquid–liquid reactions is needed to improve known aqueous biphasic reactions as well as to find new, highly active and selective homogeneous catalysts for organic synthesis.

Notation

a	interfacial area per unit volume	$[\mathrm{m}^{-1}]$
A_0	Arrhenius parameter	
ci	concentration of species i	$[\mathrm{kmol\,m^{-3}}]$
c^*_i	concentration of species i at phase equilibria	$[\mathrm{kmol\,m^{-3}}]$
d_I	impeller diameter	$[\mathrm{m}]$
d_T	tank diameter	$[\mathrm{m}]$
D_{ik}	binary diffusion coefficient	$[\mathrm{m^2\,s^{-1}}]$
E	enhancement factor	$[-]$
E_A	activation energy	$[\mathrm{J\,mol^{-1}}]$
g	acceleration due to gravity	$[\mathrm{m^2\,s^{-1}}]$
h_1	height of the first impeller from bottom	$[\mathrm{m}]$
h_2	height of the liquid	$[\mathrm{m}]$
H_i	Henry coefficient	$[H_i = p_{A_{1,g}} c_{A_1}]$
Ha	Hatta number	$[-]$
J_i	diffusion flow density	$[\mathrm{mol\,m^{-2}\,s^{-1}}]$
k	rate constant (dimensions depend on kinetics)	$[\mathrm{m}^{3(n-1)}\,\mathrm{kmol}^{-(n-1)}\,\mathrm{s}^{-1}]$
k_i	mass transfer coefficient	$[\mathrm{m\,s^{-1}}]$
N	speed of agitation	$[\mathrm{rev\,s^{-1}}]$
n, m	reaction orders	$[-]$

P	power consumption	$[\mathrm{W}]$
p_i	partial pressure	$[\mathrm{Pa}]$
r	reaction rate	$[\mathrm{kmol\,m^{-3}\,s^{-1}}]$
r_{eff}	effective reaction rate	$[\mathrm{kmol\,m^{-3}\,s^{-1}}]$
R	gas constant	$[8.314\ \mathrm{J\,mol^{-1}\,K^{-1}}]$
T	temperature	$[\mathrm{K}]$
u_g	superficial gas velocity	$[\mathrm{m\,s^{-1}}]$
V	volume	$[\mathrm{m^3}]$
δ	film thickness	$[\mathrm{m}]$
φ	density	$[\mathrm{kg\,m^{-3}}]$
λ	distance of reaction plane from interface	$[\mathrm{m}]$
μ	viscosity	$[\mathrm{kg\,m^{-1}\,s^{-1}}]$
σ	surface tension	$[\mathrm{N\,m^{-1}}]$
υ	stoichiometric coefficient	$[-]$
F	fluid	
g	gas	
i	component (e.g., $i = 1, 2$ or A, B ...)	
l	liquid	

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4.2
Technical Concepts

Arno Behr

4.2.1
Reaction Systems

A general problem in homogeneous reactions with organometallic catalysts is the question of how to separate the catalysts from the products after the reaction is completed. In aqueous-phase catalysis this problem can become the most critical point in the technical realization of a process. One advantage of aqueous-phase chemistry is the fact that often more or less nonpolar starting chemicals are used which form a second organic phase. That means that the reaction system consists of two immiscible or partly miscible phases which can be used for the separation of catalyst and products. To obtain a better and more complete insight into this separation technique, the general Eq. (1) will be considered, in which the starting materials A and B react to give the products C and D. This reaction is carried out in the presence of the solvent water (or a similar strongly polar solvent or solvent mixture) and with the help of an organometallic catalyst, which may be polar or nonpolar.

$$\mathrm{A} + \mathrm{B} \xrightarrow[\text{water}]{\text{cat.}} \mathrm{C} + \mathrm{D} \tag{1}$$

In Table 1 different variations are listed, depending on whether the starting compounds A and B or the products C and D and the catalyst are soluble in the aqueous phase (a) or in the nonpolar organic phase (o). In the last column of this Table a first evaluation is made of the possibility of separating the catalyst from the product chemicals (which may be mixed with unreacted starting compounds).

Entries 1 and 6 of Table 1 are the two cases of “homophase” homogeneous catalysis, either in aqueous or in organic solution. The evaluation (in view of catalyst separation) is negative, because in accordance with the definition of homogeneous reactions the catalyst is dissolved in the reaction medium and cannot be separated directly from the products.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Tab. 1 General concept of aqueous-phase organometal-catalyzed reactions (acc. to Eq. 1).

Entry	*Solubility*[a)]					
	A	***B***	***C***	***D***	***Catalyst***	***Evaluation***[b)]
1	a	a	a	a	a	–
2	a	a	a	a	o	+
3	a	a	o	o	a	+
4	a	a	o	o	o	–
5	o	o	o	o	a	+
6	o	o	o	o	o	–
7	o	o	a	a	a	–
8	o	o	a	a	o	+
9	o	a	a	a	a	–
10	o	a	a	a	o	+
11	o	a	o	o	a	+
12	o	a	o	o	o	–
13	a	a	o	a	a	–
14	a	a	o	a	o	–
15	o	o	o	a	a	–
16	o	o	o	a	o	–

a) a = soluble in aqueous phase; o = soluble in organic phase.

b) – low possibility of product separation; + good possibility of product separation.

Entries 2, 3, 5, 8, 10, and 11, however, are judged positive, because neither product (C or D) dissolves the catalyst. These estimations do not guarantee that all of these types of reactions can be carried out in a reasonable manner, however.

Entry 2, for example, comprises the reaction of aqueous-soluble compounds using a nonpolar catalyst. It is questionable whether this reaction really works because of the bad distribution of the catalyst in the reaction system. In this case it can be better to add a further nonpolar solvent which dissolves the catalyst, thus forming a true liquid–liquid two-phase system (LLTP).

The opposite of entry 2 is the phase combination of entry 5, a fully organic reaction in the presence of an aqueous phase which contains the catalyst. This type of reaction system is the most often used for the technical realization of aqueous-phase organometallic-catalyzed reactions, for instance in the oligomerization of ethylene using the SHOP process (cf. Section 7.1) or in the Ruhrchemie/Rhône-Poulenc process (cf. Section 6.1.1) of propene hydroformylation (see also Section 4.2.2).

An interesting variant of entry 5 is entry 11, in which one of the educts is a polar and the other a nonpolar reactant yielding organic products. Once again the catalyst is in the aqueous phase and thus easily separated from the products. This technique is used in the telomerization of butadiene with water (Kuraray process; cf. Section 6.7) and the telomerization of butadiene with ammonia (see Section 4.2.2).

As already discussed with entry 2, all the aqueous-phase reactions of Table 1 can in principle be carried out as two-phase reactions by adding a second, nonpolar, solvent. The question of catalyst separation is not influenced by this solvent addition, but a second solvent can effectively control the selectivity of the reaction.

If a consecutive reaction (Eq. 2) is investigated, the initially formed organic product C will enter the organic solvent phase almost completely, thus disabling the consecutive reactions yielding products D or E. Consequently by this technique product C is formed with high selectivity.

$$\mathrm{A + B \xrightarrow{cat.} C \xrightarrow[+\,A]{cat.} D \xrightarrow[+\,A]{cat.} E} \qquad (2)$$

4.2.2
Technical Realization: Variations

Table 2 gives a brief overview of the industrially realized aqueous-phase organometallic-catalyzed reactions, together with some related reactions which are still un-

Tab. 2 Important examples of polar-phase organometallic-catalyzed reactions.

Company or University	*Reaction* [a]	*Catalyst*	*Solvent*	*Refs.*
Shell (SHOP)	Oligomerization of ethene (7.1)	Ni	1,4-Butanediol	[1–9]
Ruhrchemie/ Rhône-Poulenc	Hydroformylation of olefins (6.1)	Rh	Water	[10–20]
Rhône-Poulenc	Co-oligomerization with myrcene (6.10)	Rh	Water	[21–23]
Rhône-Poulenc	Hydrogenation of unsaturated aldehydes (6.2)	Ru	Water	[24–27]
DuPont	Hydrocyanation of pentenenitrile (6.5)	Ni	Ionic liquids	[28]
Kuraray	Telomerization of butadiene with water (6.7)	Pd	Water/solfolane	[29–44, 75–79]
University of Dortmund	Telomerization of isoprene with water	Pd	Water	[45–48]
University of Dortmund	Telomerization of butadiene with CO_2	Pd	Water	[49–55]
University of Aachen	Telomerization of butadiene with NH_3	Pd	Water	[56, 57]
University of Aachen	Telomerization of butadiene with phthalic acid	Pd	Acetonitrile	[58, 59]
University of Aachen	Dimerization of butadiene	Pd	DMSO	[58, 59]

[a] Cf. Section indicated in parentheses.

der development. The list includes not only water systems but also systems with polar solvents which have much in common with the aqueous-phase reactions.

The most important process worldwide is the "Shell higher-olefin process" (SHOP) in which ethylene is oligomerized to higher-molecular-mass, linear, α-olefins. The nickel-catalyst, containing a phosphorus/oxygen chelate ligand, is dissolved in the polar solvent 1,4-butanediol, which is not miscible with the α-olefins. Two big plant with a total capacity of 1 Mio. $t\,y^{-1}$ are built in Geismar (USA) and Stanlow (UK).

The most important process with the solvent water is the hydroformylation of propene to butyraldehydes, known as the Ruhrchemie/Rhône–Poulenc process. This reaction is catalyzed by a rhodium complex containing the water-soluble ligand triphenylphosphane trisulfonate (TPPTS). The aldehydes are formed with an annual capacity of approx. 300 000 t.

All other industrial applications are still on a smaller scale. The Kuraray telomerization of butadiene with water is carried out at 5000 t/y^{-1} (see Section 6.7); the Rhône-Poulenc reactions have been developed into bulk processes. The investigations at the Universities of Dortmund and Aachen (Germany) are still on the laboratory or miniplant scale.

All the examples given in Table 2 make use of the same decisive advantage to recycle the homogeneous transition metal catalyst by applying the LLTP system. However, the technical realization of the catalyst recycle can be carried out in very different ways [60]. There are a number of possibilities:

Products and catalyst must be separated. This can be done by methods which either separate the *product* or the *catalyst* from the residue.

The separation methods can be varied: simple *separation* of two liquid phases, *extraction* with an additional extractant, or chemical *treatment* with additional bases and acids.

In all cases a reaction and a separation step are combined. Reaction and separation can be done in the same unit, *i.e.*, *simultaneously*, or in separate units, i.e. *successively*.

In total – by combining all the variations listed above – there are 12 cases to be distinguished:

- simultaneous or successive reaction and product separation
- simultaneous or successive reaction and product extraction
- simultaneous or successive reaction and product treatment
- simultaneous or successive reaction and catalyst separation
- simultaneous or successive reaction and catalyst extraction
- simultaneous or successive reaction and catalyst treatment

In the following, these variants will be discussed in more detail, always looking at the same general reaction (Eq. 1). In this discussion some basic flow schemes will be presented which contain in some cases two different solvents, one polar (e.g., water) and one nonpolar. For reasons of simplicity in these cases it is assumed that the expected products are organic nonpolar compounds, that means we consider only entries 3–6, 11 and 12 in Table 1. Of course, analogous considerations apply if the products are polar compounds, i.e., in the case of entries 1, 2, and 7–10 in Table 1. In these cases the terms "polar" and "nonpolar" in the flow scheme have to be exchanged.

4.2.2.1
Reaction with Product Separation

The easiest technique to combine catalysis in a polar medium with product separation is shown in Figure 1. Both operations are done in the same unit at the same time. The nonpolar product phase is deposited from the polar catalyst phase and can be separated at the top of the reaction column. The SHOP oligomerization of ethene works in this way. The catalytic phase, consisting of 1,4-butanediol and nickel catalyst, always remains in the reaction unit. In the technical plant the reaction takes place not in only one reactor but in a series of tanks. This is so that the heat of reaction may be removed by water-cooled heat exchangers which are placed between the different reactor tanks. The flow scheme of the SHOP process is shown in Section 7.1.

A variant of this technique is "supported aqueous-phase catalysis" (SAPC), in which the polar catalyst phase is heterogenized on a solid support [61–68]. The principle of this technique is shown in Figure 2. The organometallic complex, e.g.,

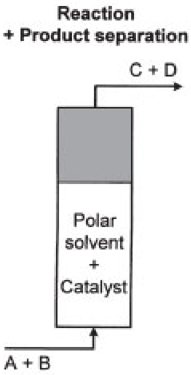


Fig. 1

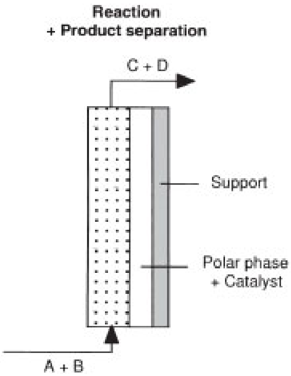


Fig. 2

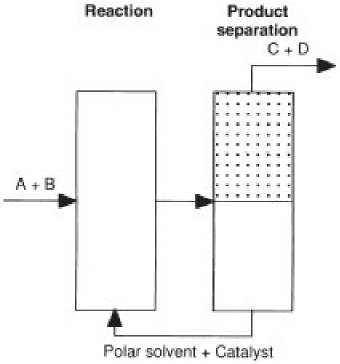


Fig. 3

Fig. 1 Simultaneous reaction and product separation (two liquid phases).
Fig. 2 Simultaneous reaction and product separation (liquid nonpolar phase, heterogenized polar phase).
Fig. 3 Successive reaction and product separation.

rhodium with triphenylphosphine sulfonate ligands, is dissolved in an aqueous solution which is fixed onto a hydrophilic support, e.g., controlled-pore glasses on surface-modified silica. The advantage of this method lies in the easy handling of the homogeneous catalyst, very similarly to a solid heterogeneous catalyst. However, no industrial application of SAPC is known so far (cf. Section 4.7).

Figure 3 shows a technical modification of the general principle illustrated in Figure 1; while in Figure 1 the two liquid phases are separated during the reaction, but in Figure 3 these steps are divided into two different units. As in the Ruhrchemie/Rhône–Poulenc process of propene hydroformylation, in this industrial application the reaction steps and the separation step are divided. The reaction takes place in a continuously stirred tank reactor, while the phase separation is carried out in a decanter.

4.2.2.2
Reaction and Product Extraction

The appropriate process described so far use only an aqueous catalyst solution, and no additional organic solvent is necessary. In the processes described in this section an organic nonpolar solvent is used as product extractant. Hydrocarbons, chlorinated hydrocarbons, or ethers are often chosen as nonpolar solvents.

Figure 4 shows simultaneous reaction and product extraction, also called "*in situ* extraction." The reaction of A and B runs in the reactor which contains the polar (e.g., aqueous) catalyst phase. The nonpolar extractant absorbs the organic products which are separated from the polar catalyst phase in the following separation step. The procedure is more costly because a further distillation is necessary in a third unit to separate the products from the low-boiling extractant, which is then recycled to the reactor.

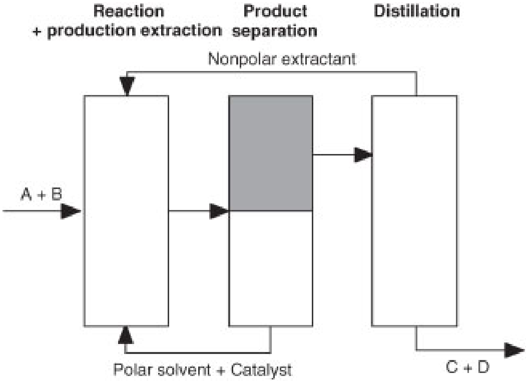


Fig. 4 Simultaneous reaction and product extraction.

For this technique some examples are given in the literature. Baird [69, 70] describes the hydrogenation and the hydroformylation of olefins applying this two-phase system. The aqueous phase contains the soluble rhodium catalyst which is formed from norbornadienylrhodium chloride and AMPHOS nitrate ($Ph_2PCH_2CH_2NMe_3^+NO_3^-$); the organic phase contains solvents such as methylene chloride, diethyl ether, or pentane, or the olefin, e.g., 1-hexene. This system is very favorable because only traces of rhodium (0.25 ppm) move into the organic layer, and the aqueous catalyst phase could be re-used in the reaction with little or no loss of activity, even after expsoure to air.

An interesting new example is the two-phase telomerization of butadiene with ammonia, yielding octadienylamines [57]. When this reaction is carried out in homogeneous one-phase solution, a great amount of primary, secondary and tertiary amines is formed [56]. With the two-phase techniques using water, and toluene or pentane as the second phase, the consecutive reactions (Eq. 2) can be almost completely avoided, and the primary octodienylamines are the only main products. This reaction has not yet been realized industrially.

An important alternative is the successive reaction and product extraction procedure shown in Figure 5. First the reaction of A and B is carried out in a single polar homogeneous phase containing the catalyst. Downstream, the products are extracted with a nonpolar solvent or solvent mixture. In the third unit, the distillation, the low boiling extractant is distilled off and recycled to the extraction unit. Two examples will demonstrate the practicability of this concept.

Butadiene can be dimerized to 1,3,7-octatriene in the presence of the catalyst $Pd(PPh_3)_4$ and the alcohol $PhC(CF_3)_2OH$ (Eq. 3). This reaction is carried out favorably in the solvent acetonitrile. Then the product octatriene is extracted with isooctane while the catalyst and the alcohol remain in the acetonitrile phase, which is recycled to the reactor. Finally, the isooctane is distilled off from the dimer. In a continuously working miniplant, 3 kg of octadiene/g Pd could be produced [58, 59].

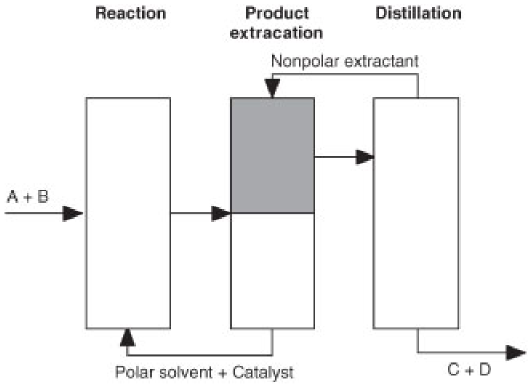
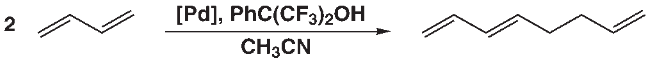


Fig. 5 Successive reaction and product extraction.



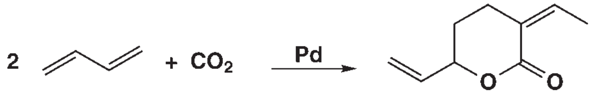
(3)

The second example is the telomerization of phthalic acid with butadiene yielding bis(octadienyl) phthalates, which can then be hydrogenated to the bisoctyl phthalates which may be used as plastic softeners. The catalyst is formed from palladium bis(acetylacetonate) and tris(*p*-methoxyphenyl)phosphite in the polar solvent dimethyl sulfoxide. Once again the extraction can be carried out with isooctane [58, 59].

A third example is the Kuraray process [29–44, 75–79].

The method shown in Figure 5 only works if the polar solvent (e.g., water) dissolves the catalyst completely and the nonpolar extractant dissolves only the product. Solvent and extractant must form a perfectly separable biphasic system. However, there are extractants which of course dissolve the products in good yields, but which dissolve also the solvent of the reaction. In that case, no proper biphasic system can appear. The solution of this problem is the – costly – distillation of the solvent before the extraction step.

In Figure 6 this principle is demonstrated for the telomerization of butadiene with carbon dioxide yielding a δ-lactone (Eq. 4). The reaction is carried out in a homogeneous acetonitrile solution using a palladium catalyst. After distillation of the acetonitrile in the second unit, the product/catalyst mixture is treated with the extractant, 1,2,4-butanetriol, which dissolves the product but not the catalyst [55]. The catalyst is then recycled to the reactor in a small amount of the liquid product. The main quantity of the lactone is separated from the extractant by a second distillation step.



(4)

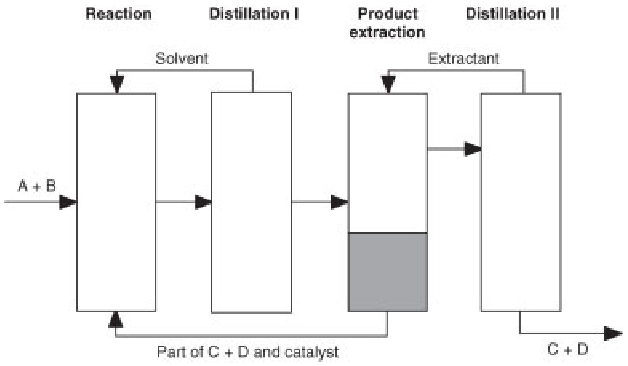


Fig. 6 Successive reaction and product extraction (after solvent distillation).

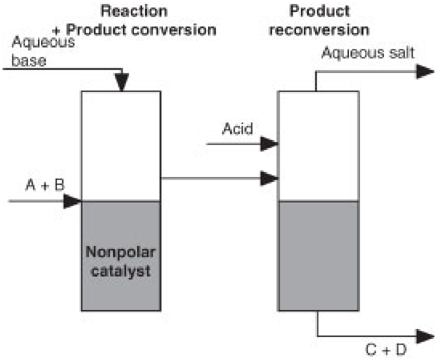


Fig. 7 Simultaneous reaction and product treatment.

4.2.2.3
Reaction and Product Treatment

An interesting concept is to synthesize an organic nonpolar product with the help of a nonpolar organometallic catalyst and to convert this nonpolar product into a polar one. In sum, the catalyst and the product phase can be separated (entry 8 in Table 1), thus enabling the required catalyst recycle. An example of this chemical conversion is the synthesis of a nonpolar long-chain carboxylic acid which is then transformed into the polar carboxylate salt by addition of an aqueous base solution. This product treatment can be performed principally during the reaction (Figure 7), thus absorbing the product continuously into the aqueous phase. In a second unit the polar product, e.g., the carboxylate salt, is reconverted into the nonpolar product, the carboxylic acid, and the product and the aqueous salt solution can be separated in a decanter. This salt solution is one of the disadvantages of this and related separation technique using chemical product treatment.

An alternative to the simultaneous reaction and product conversion shown in Figure 7 is the successive reaction and product treatment in Figure 8. This sequence of three units comprises the reactor for the homogeneously catalyzed reaction, the separator of polar product and nonpolar catalyst phase, and the separator for nonpolar product and aqueous salt solution. An example for this case will be given in Section 6.12 (Fat Chemicals).

4.2.2.4
Reaction and Catalyst Separation

In Section 4.2.2.1 cases are described in which the catalyst stays in the reactor because of the liquid–liquid two-phase technique (LLTP). In other cases only one liquid phase occurs and attention is turned especially to the removal of the catalyst. This removal

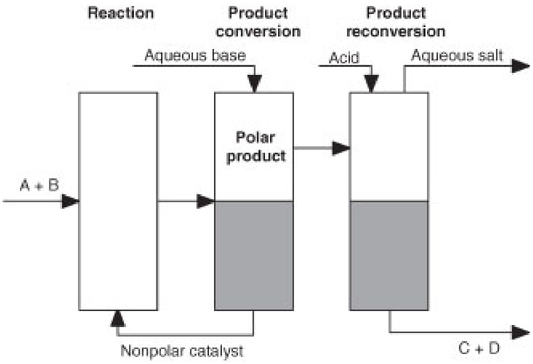


Fig. 8 Successive reaction and product treatment.

can be achieved by using the membrane technique shown in Figures 9 and 10. Special polyamide and polyimide membranes are able to separate transition metal complexes from smaller organic molecules [71–73]. The separation by membrane will be most effective if the difference in size between complex and organic molecules is as large as possible. Therefore, this technique is particularly useful if the reaction is catalyzed by complexes with macromolecular ligands [74] (cf. Section 4.4).

In Figure 9 the simultaneous reaction and catalyst separation by membrane has been described. In one part of the reactor a catalyst is dissolved which cannot pass the membrane which is installed in the reactor. Here the starting chemicals A and B form the products C and D in a homogeneous catalyst solution. The products are able to pass through the membrane, perhaps together with a certain amount of the solvent. In the second unit, the distillation step, this solvent is recycled to the reactor and the products are isolated at the bottom of the distillation column.

Figure 10 shows a similar arrangement, but reaction and catalyst separation now occur in different units. The reaction is succeeded by the membrane separation step, which is then followed by the distillation unit. The products C and D

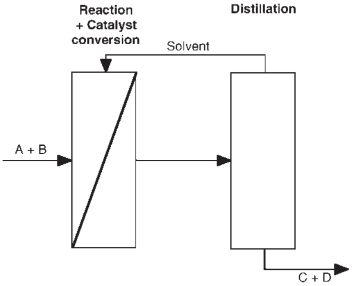


Fig. 9 Simultaneous reaction and catalyst separation (via membrane).

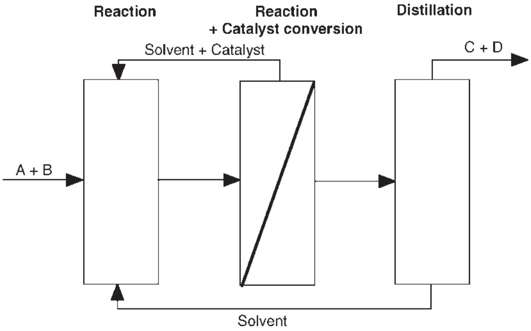


Fig. 10 Successive reaction and catalyst separation (via membrane).

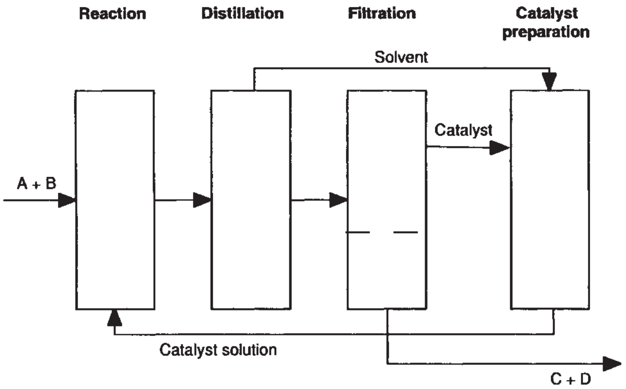


Fig. 11 Successive reaction and catalyst separation (via solvent distillation and catalyst filtration).

leave the distillation at the top of the column and the solvent leaves at the bottom. Of course, the contrary is also conceivable, depending of the boiling points of products and solvent.

Besides catalyst separation by membranes, there is also the possibility of separating the catalyst via filtration after the catalyst has been precipitated. One interesting application is given by Fell and co-workers [83]. They describe the hydroformylation of higher-molecular-mass olefins with a rhodium/phenylsulfonatoalkylphosphine catalyst which is soluble both in methanol and in water. Figure 11 shows the principle of the separation: the reaction is first carried out in homogeneous methanol solution. After distillation of the methanol, the rhodium catalyst is precipitated and filtered off (or centrifuged) in a third unit. The products C and D, in the given example the higher-molecular-mass aldehydes, pass the filter. In a fourth unit the catalyst solution is prepared again by dissolving the solid catalyst in the solvent methanol.

4.2.2.5
Reaction and Catalyst Extraction

In Section 4.2.2.2 some processes are described in which the organic products are separated – simultaneously or successively – by extraction with a nonpolar extractant. In the cases presented in this section, not the product but the catalyst will be extracted and recycled to the reactor. Theoretically, this can be done simultaneously in the reactor, as shown in Figure 12. However, this arrangement is highly unfavorable, because it means that the catalyst is taken away from the reaction medium during the catalytic conversion. The successive variant, shown in Figure 13, makes much more sense: the reaction is first carried out in the reaction unit, then the catalyst is extracted by an extractant which does not dissolve the products C

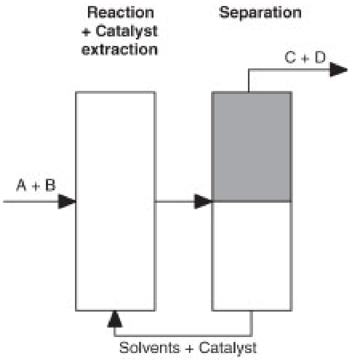


Fig. 12 Simultaneous reaction and catalyst extraction.

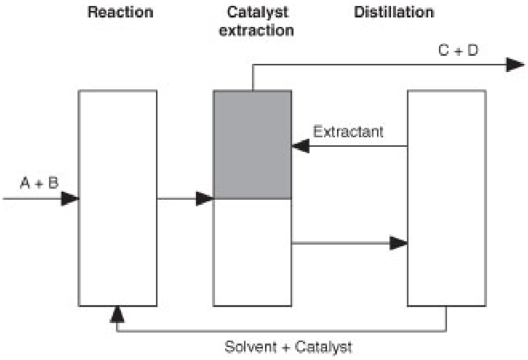


Fig. 13 Successive reaction and catalyst extraction.

and D. Thus, the products can be removed, and the extractant and the catalyst solution are separated in a distillation step.

The crucial point of this method is the complete separation of the extractant (containing the catalyst) and the products. One example, where this problem could be solved, is shown in Figure 14, the hydroformylation process of higher olefins proposed by Union Carbide at the beginning of the 1990s [80–82]. The reaction is carried out as a homogeneous catalytic process using the solvent *N*-methylpyrrolidone (NMP). The catalyst is then extracted by addition of water: the rhodium catalyst containing the water-soluble ligand monosulfonated triphenylphosphine (TPPMS) goes almost completely into the NMP/water phase, and the nonpolar aldehydes form the second phase. In this way C_7- and C_{15}-aldehydes may be produced with the final effluent being lower than 20 ppb in rhodium. However, the expenditure to regenerate the catalyst solution is considerable: first, the water is partly distilled from the catalyst solution in vacuo, then a further catalyst-drying vaporizer is required until the catalyst can be recycled to the oxo reactor.

Another way to hydroformylate higher olefins and to extract the catalyst afterwards is described by Fell and co-workers [83–85]. They use a similar method to that described in Figure 11, but the catalyst is not precipitated and filtered off, but it is extracted with water.

The general flow scheme for this alternative is shown in Figure 15. After the homogeneous reaction, catalyzed for instance by a rhodium catalyst containing triphenylphosphine monosulfonic acid as complex ligand, the solubilizer methanol is distilled off. The catalyst system now becomes insoluble and is separated by extraction with water in the third unit. The products C and D, in this case the aldehydes, can be separated as the second liquid phase. After evaporation of the aqueous catalyst solution to dryness (unit 4) the catalyst is dissolved in the solvent methanol for a new reaction step (unit 5).

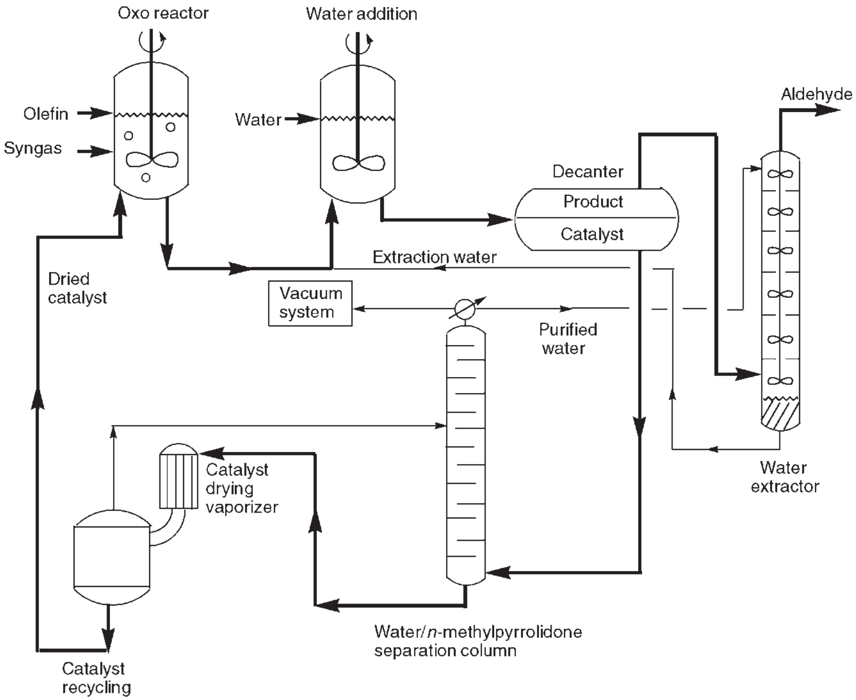


Fig. 14 Hydroformylation of higher olefins [81].

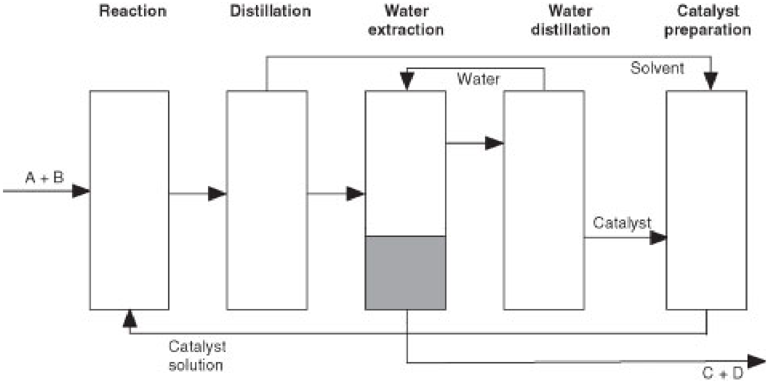


Fig. 15 Successive reaction and catalyst extraction (after solvent distillation).

4.2.2.6
Reaction and Catalyst Treatment

In Section 4.2.2.3 examples are given where the product is treated with bases and acids to enable the separation of the product. In this section analogous cases will

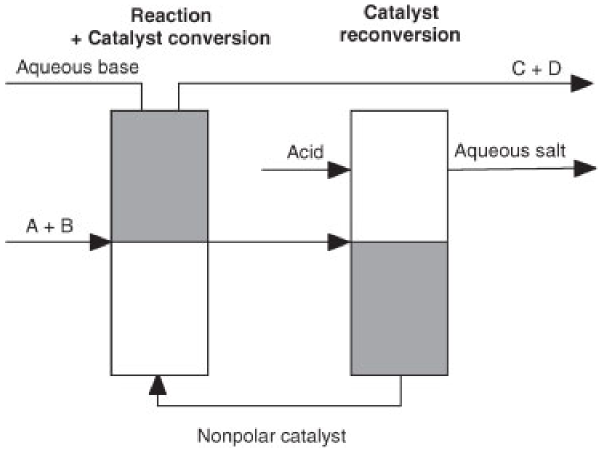


Fig. 16 Simultaneous reaction and catalyst treatment.

be considered in which, however, the catalyst is treated in such a way that it can be removed and recycled.

The principal flow scheme of a simultaneous reaction and catalyst treatment is shown in Figure 16. However, once again this technique seems not to be favorable, because during the conversion the nonpolar catalyst is removed from the organic reaction phase by the addition of a base.

It makes more sense to separate the two units as shown in Figure 17, the successive reaction and catalyst treatment. First, the reaction is carried out as a homogeneously catalyzed conversion using a nonpolar solvent and a nonpolar catalyst. In the second unit, the nonpolar catalyst is converted into a polar one by adding

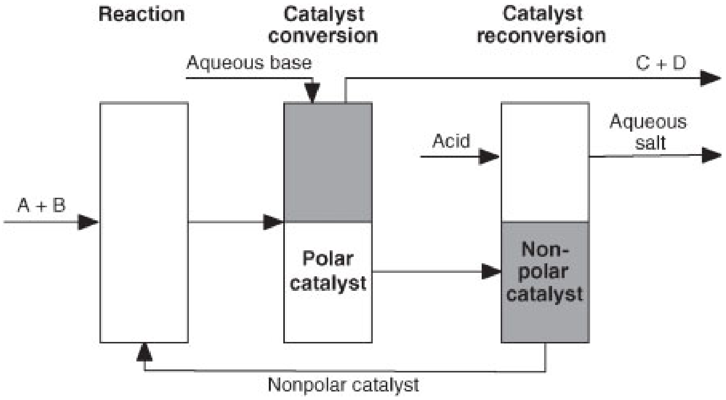


Fig. 17 Successive reaction and catalyst treatment.

an aqueous base. Finally, in the third unit, the polar catalyst is reconverted into a nonpolar one which can be recycled to the reactor. The main question remains, of how a catalyst can be converted from nonpolar to polar and vice versa. The answer is to use metal complexes with anionic ligands which contain a cationic counterion such as ammonium. When it has some higher-molecular-mass alkyl substituents, both this alkylammonium cation as well as the whole complex will be soluble in a nonpolar solvent such as toluene. If after the reaction an aqueous base such as a sodium hydroxide solution is added in excess, the ammonium counterion will be exchanged by the sodium cation, thus yielding a water-soluble complex (cf. Section 6.1.4). Of course, this process can be reversed by adding an acid and new ammonium ions.

4.2.3
Reaction Engineering Aspects

The reaction engineering aspects of liquid–liquid reactions have been well studied ([86–88], cf. Section 4.1). The performance of these reactions depends on the hydrodynamics of the dispersion, the mixing of the two fluid phases, the interface mass-transfer steps, the phase equilibria and kinetics of the reactions involved.

Some of the examples presented in Section 4.2.2 are, however, not only restricted to the two liquid phases discussed, but contain in addition a further gas phase [89]. For instance, in hydroformylation a water-gas phase exists, in oligomerizations an ethylene phase and in telomerizations a butadiene phase. For these gas–liquid–liquid systems there is so far only a limited amount of published information on the reaction engineering aspects [90]. One exception is the study of 1-octene hydrogenation using a rhodium/TPPTS catalyst [91], in which both thermodynamics and kinetics have been investigated in some detail. The same group also studied the hydroformylation of 1-octene [92].

Some further special technical aspects should be mentioned. The intensive mixture of the two liquid phases is an important condition for obtaining high reaction rates. This mixing can be achieved in bubble columns, tray columns or in stirred-tank reactors. In the few publications on industrially realized two-phase reactions the stirred tank reactor is always cited, but without detailed information on the stirring device. One further possible way to increase the mass transfer between the two liquid phases is by the influence of sonification. Cornils et al. applied this technique in the hydroformylation of hexene or diisobutene and found a considerable increase in the turnover numbers [93]. Another possibility for increasing the mass transfer may be by the use of microemulsions and micellar systems [94], which can be reached by addition of certain surfactants. This aspect is discussed in Sections 3.2.4 and 4.5. The separation of catalyst compounds in two-phase systems in combination with membranes has been studied recently by Müller and Bahrmann [95].

4.2.4
New Developments

Since the first edition of this book a great number of articles have been published in which the different techniques to separate the catalyst from the products via two liquid phases were applied. Some general review articles in books and journals about multiphase homogeneous catalysis, catalyst recycling and fluid–fluid systems have been published [96–102]. Other review articles concentrate on aqueous organometallic chemistry and catalysis [103–108], on biphasic systems with ionic liquids [109, 110], or on fluorous solvents [111, 112] (cf. Sections 7.2, 7.3).

In particular, the concepts of biphasic catalysis were used in telomerization (Section 6.9), oligomerization (Section 6.12), hydrogenation (Section 6.2), and hydroformylation (Section 6.1) reactions. Therefore these reactions will be considered in the following sections in some more detail and thus complement the appropriate Chapters as far as technical concepts are concerned.

4.2.4.1
Telomerization

Recently, a nice example has been studied in which biphasic catalysis was not only used for catalyst recycling but also to increase the selectivity of the catalytic reaction. In the telomerization of butadiene with the bifunctional nucleophile ethylene glycol both monotelomers and ditelomers can be formed [113, 114]. When the reaction is carried out in a single liquid phase, for instance in tetrahydrofurane with a catalyst formed from palladiumbis-acetylacetonate and triphenylphosphine, the monotelomers are formed in a maximum yield of 60% with more than 20% of ditelomers as byproducts. When palladiumcarbene-complexes were used, the mono/di-ratio switched to 1 : 3, thus increasing the formation of the ditelomer. However, if the monotelomers are the favored products, for instance for the production of detergents, no sufficient reaction control by choice of the ligand was possible so far.

This problem can be solved by using biphasic catalysis: In aqueous biphasic systems using a Pd catalyst with the TPPTS ligand the monotelomers were obtained in 84% yield with more than 95% selectivity and traces of the ditelomers only. This highly increased selectivity can be explained by the *in situ* extraction effect: The monotelomer is only poorly soluble in the aqueous catalyst phase and forms a separate organic phase thus preventing a further reaction to the ditelomer. This biphasic reaction permits, too, an elegant catalyst recycling: The aqueous catalyst phase could be recycled six times without any important loss of activity, when a small loss of the ligand TPPTS because of oxidation to the corresponding oxide is supplemented simultaneously. After six runs a total turnover number of 9000 could be realized.

The technical realization of telomerizations is not very well investigated. In a recent paper the telomerization of isoprene with methanol was studied in detail and different concepts of realization were proposed both for single phase operation as well as for biphasic catalysis [115]. One possible alternative proved to be the biphasic telomerization with an aqueous methanolic solution as catalyst phase, followed by distillation of unreacted isoprene and methanol, then finally extracting the telomers from the aqueous layer with isoprene. The second alternative for the product separation is without any extraction step and uses only phase separation and distillation steps.

Further work was done in the telomerization of butadiene with carbon dioxide yielding a α-lactone in good yields [116–118]. For the catalyst recycle the successive extraction of the product with 1,2,4-butanetriol was proposed and investigated in detail. Mortreux et al. studied the telomerization of butadiene with sucrose which could also be carried out efficiently in water–organic medium in the presence of Pd salt and TPPTS [119]. Mono- and dioctadienylether were selectively obtained using aqueous sodium hydroxide/isopropanol mixtures.

4.2.4.2
Oligomerization

A new concept in biphasic catalysis is the use of temperature-dependent multicomponent solvent (TMS) systems which is a real alternative concept for catalyst recycling [120, 121] (cf. also Section 4.6.3). The common aqueous two-phase technique has the problem that reactants might have no or only a low solubility in the polar catalyst phase. In a right mixture of solvents this problem can be solved. The best mixture of solvents is a multicomponent system which forms a single phase during the reaction at higher temperatures and forms two different phases after the reaction at lower temperatures. These TMS consist of three solvents, a polar solvent S1, a non-polar solvent S2, which is not miscible with S1 and a third semipolar solvent S3 which is miscible with S1 and S2 and which acts as a solubilizer. Typical polar solvents S1 are water, ethylene glycol or alkylene carbonates, typical non-polar ones S2 are cyclic or non-cyclic aliphatics, typical semipolar solvents S3 are dioxane or anisole. An example for this new technique is the cooligomerisation of conjugated linoleic acid methyl ester with ethene [122]. In this rhodiumchloride-catalyzed reaction internal branched oleochemicals can be synthesized which may be useful as biodegradable lubricants. When this reaction is carried out in a common biphasic system, for instance in a mixture of the unpolar fatty compound and the polar solvent glycol which contains the polar catalyst, then mass transport problems restrict the yield of cooligomers to only 9%. When using a TMS system, for instance a mixture of oleo compound, propylene carbonate and dioxane, then the reaction proceeds in two hours with 99% conversion and 97% yield. By this technique the turnover frequency TOF could be increased from 2 up to 220 h^{-1}.

A somewhat similar technique was discovered by Bergbreiter et al. [123]. He found that biphasic solvent systems exhibit an increase in phase miscibility at elevated temperature if special soluble polymers are added (cf. also Section 7.6). An elegant option is to fix the catalyst on this soluble polymer. For example, he used poly(*N*-isopropylacryl amide) derivatives which are able to bound phosphine ligands coordinated to a Pd catalyst. High yields in Heck- and Suzuki-couplings can be obtained and the catalyst can be recycled (cf. also Section 6.6).

Other biphasic C–C bonding reactions were carried out with fluorous solvents, for instance Suzuki- and Sonogashira-couplings [124] or ethene or propene oligomerizations [125, 126]. Further new solvent systems use ionic liquids for the linear dimerisation of 1-butene to octenes [127] or the hydrovinylation of styrene with a combination ionic liquid/supercritical carbon dioxide [128] (cf. Section 7.4).

4.2.4.3
Hydrogenation

As could be expected, a large number of applications of the biphasic reaction system was investigated in hydrogenation chemistry (see Section 6.2). One typical example is the hydrogenation of the δ-lactone – already described in the chapter telomerization – to ethenylheptenoic acid which can be the basis of interesting plasticizers [114, 129]. The cleavage of the δ-lactone ring was achieved by a two-phase hydrogenation with a water-soluble and *in situ* rhodium-phosphine catalyst. The catalyst-containing aqueous phase could be recycled five times without loss of activity. High conversions (100%) of the δ-lactone were attained because of the good solubility of this reagent in water.

Most of the other biphasic hydrogenations use also water as polar medium [130–145]. Interesting variations are the use of aqueous micellar media [146] (see also Section 4.5) and the hydrogenation in aqueous media with Rh complexes which were deposited on aluminophosphate molecular sieves [147]. Other groups employed biphasic systems with fluorous solvents [148–151] or ionic liquids [152–153].

4.2.4.4
Hydroformylation

Various papers describe the aqueous biphasic hydroformylation for simple olefins as well as for functionalized olefins or dienes [154–174] (cf. the Section 6.1). In recent work [175], the synthesis of *n*-nonanal by consecutive isomerization and hydroformylation reactions of *trans*-4-octene has been described. The catalyst used was the *in situ* combination of $Rh(acac)(CO)_2$ and the chelate phosphite BIPHEPHOS. Performing the reaction in propylene carbonate the selectivity to *n*-nonanal could be raised up to 95%. If after the reaction the product is extracted with dodecane, the propylene carbonate phase could be recycled in five runs without any loss of activity and selectivity to *n*-nonanal. The solvent system propylene carbonate/dodecane can be transferred into a temperature-dependent multicomponent solvent system (TMS) if a third semi-polar solvent is added, for instance toluene. In this case, conversions of *trans*-4-octene of $> 99\%$ and selectivities of 98% to *n*-nonanal could be observed [176].

Another interesting technique to solve the problem of mass transport in biphasic reactions was developed by Fell and Jin, the catalysis with so-called thermoregulated phase transfer ligands [177–185] (details see Section 4.6.3). In the examples given so far, a "smart solvent" system controlled the phase behaviour of the reaction mixture. Lemaire et al. have found that also polyether-functionalized chiral mono- or diphosphites are active in thermoregulated conversion [186]. The hydroformylation of styrene yields conversions of 99%, *n*/*i*-ratios of 85/15 and an enantioselectivity of up to 25%. A recycling of the catalyst proved to be possible, however, with a certain leaching of the rhodium catalyst.

A further technique to overcome the mass transport limitations in biphasic catalysis is the method to work in micellar [187] or reverse micellar [188] systems, that means to enhance the surface area decisively via addition of surfactants. Renken found higher reaction rates and selectivities than in non-micellar systems and could hydroformylate also olefins with a long hydrocarbon chain up to C_{16} (see also Section 4.5).

Another method is the hydroformylation with the addition of water soluble dendrimers which gave high activity and selectivity in the hydroformylation of 1-octene and styrene [189]. Cyclodextrins can also be used to enable a strong exchange between the two layers [190]. In addition, hydroformylation has been tested in fluorous biphasic systems with good results, however, very special fluorocopolymer-supported arylphosphines had to be prepared [191].

4.2.4.5
Other Reactions

Furthermore, a vast number of organometallic catalyzed reactions can be performed in a biphasic manner thus proving that also uncommon reactions may be worth to be investigated in liquid/liquid systems. For instance, Braddock describes the atom economic nitration of aromatics in a two-phase process [192]. Nitration of aromatics leads usually to excessive acid waste streams and the classical Lewis acid catalysts such as boron trifluoride are destroyed in the aqueous quench after the reaction thus making any recycle impossible. In the method of Braddock the ytterbium triflate catalyst is solved in the aqueous phase and can be recycled by a simple evaporative process. Monflier and Mortreux [193] investigated the nickel catalyzed isomerization of olefins, for instance allylbenzene, in a two phase system yielding good yields of *cis*- and *trans*-methylstyrene.

Hydrodehalogenation of aliphatic or benzylic halides were catalyzed by water soluble ruthenium phosphine complexes in the presence of sodium formate as hydrogen donor [194]. Hydroxycarbonylations could also be performed with high palladium catalyst activities in biphasic systems [195–197].

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4.3
Side Effects, Solvents, and Co-solvents

Brian E. Hanson

4.3.1
Introduction

The concept of biphasic catalysis requires that the catalyst and product phases separate rapidly to achieve a practical approach to the recovery and recycling of the catalyst. It is obvious that simple aqueous/hydrocarbon systems form two phases under nearly all operating conditions and thus provide rapid product-catalyst separation. Ultimately, however, the application of water-soluble catalysts is limited to low-molecular-mass substrates which have appreciable water-solubility. The problem is illustrated by the data in Table 1, which gives the solubility of some simple alkenes in water at room temperature [1]. Although hydrocarbon (alkene)-solubility in water increases at higher temperature, most alkenes do not have sufficient solubility to give practical reaction rates in catalytic applications. The addition of salts further decreases the solubility of hydrocarbons in water. Substrate solubility in water is a significant issue and it is no accident that so-far the practiced and proposed commercial applications of water-soluble catalysts for hydroformylation are limited to propene and butene.

The addition of co-solvents to the aqueous phase has been investigated extensively as a means of improving the solubility of higher olefin substrates in the cat-

Tab. 1 Alkene solubility in water at 298 K [1].

Alkene	*Solubility [ppm]*
1-Pentene	148
1-Hexene	50
2-Heptene	15
1-Octene	2.7 [a]
2-Octene	2.4 [a]
1-Decene	0.6 [a]

[a] Data in 0.001 M HNO_3.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Tab. 2 Distribution of methanol and hydrocarbon (mole fraction) between the methanol-rich phase and the hydrocarbon-rich phase.

Hydrocarbon	*T [K]*	X_{methanol} *(in olefin-rich phase)*	$X_{\text{hydrocarbon}}$ *(in methano-rich phase)*
Hexane	287	0.215	0.188
Heptane	295	0.147	0.095
1-Heptene	295	0.140	0.142
Octane	300	0.136	0.063
Decane	295	0.090	0.028
1-Dodecene	274	Not reported	0.013

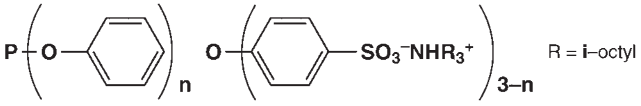
alyst-containing phase. Although data are difficult to find for the appropriate ternary systems, the effect on substrate solubility of a simple additive such as methanol is illustrated by the solubility of hydrocarbons in methanol alone.

Methanol forms a biphasic system with many simple hydrocarbons, as seen in Table 2. However, the hydrocarbon solubilities in methanol are orders of magnitude greater than in water alone [2]. The effect of methanol addition to aqueous solutions of hydrocarbons is then to increase the solubility of the hydrocarbon.

4.3.2
Hydroformylation

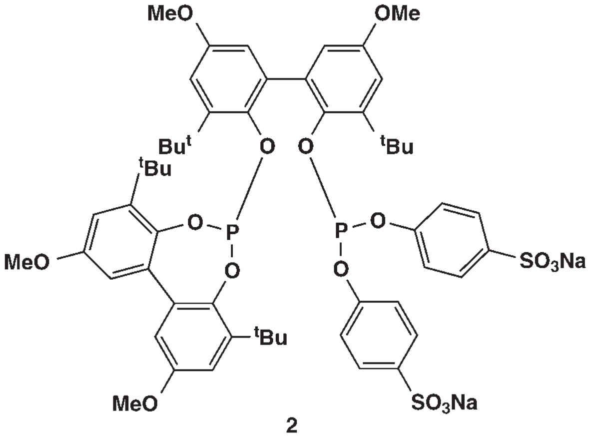
Biphasic reaction conditions can be achieved within a wide range of operating conditions with respect to co-solvents. The most common co-solvents are the lower alcohols; the purpose is to improve substrate solubility and as a consequence to increase reaction rate. Recent work with ethanol as a co-solvent shows that this is very effective at improving reaction rates [3]. It is estimated for example that the solubility of 1-octene in a 50 : 50 mixture of ethanol and water is 10^4 times greater than in water alone [3]. In a comparison of several co-solvents – ethanol, methanol, acetone, and acetonitrile – it was found that ethanol was the most effective at improving reaction rates in the two-phase hydroformylation of 1-octene [4]. Generally, though, the use of co-solvents in hydroformylation reactions with Rh/TPPTS catalysts is not advisable, because of diminished reaction selectivity and the possibility of acetal formation (see below).

When the alkali-metal cation of a sulfonated phosphine or phosphite is replaced by ammonium ion it is possible to devise applications in nonaqueous solvents. Alkylammonium salts of TPPTS were reported in the first patents of Kuntz [5] and catalytic examples were given in which water alone was the solvent. More recently Fell et al. prepared a series of sulfonated phosphites including the example shown below, **1** [6], and examined these in a variety of solvents for the hydroformylation of tetradecene. Catalytic results are reported with acetone and acetophenone as the solvents; the yield of linear aldehydes among all aldehyde products is as high as 88%.



1

Chelating biphosphites (cf. Section 3.2.2) which apparently are hydrolytically stable, were also reported by Fell et al. [6]. Similar ionic phosphites were reported by Abatjoglou and Bryant; an example is shown below, compound **2** [7]. The bisphosphites are reported to be hydrolytically stable, but the applications shown for the ionic ligands are limited to nonaqueous solvents such as 2,2,4-trimethyl-1,3-pentanediol and poly(ethylene glycol) [7].



2

Monosulfonated triarylphosphines, for which TPPMS is the prototypical example, have good solubility in polar organic solvents. A variety of monosulfonated phosphines, including TPPMS, with several different metal cations as the counterion have been examined in the hydroformylation of propene, butene and octene [8]. The solvent composition is reported to be a mixture of texanol and carbowax. The catalysts showed excellent selectivity to linear aldehydes, up to 96% depending on the reaction conditions [8].

Fell et al. describe the hydroformylation of tetradecene in methanol alone as the solvent. Since the standard ligand for two-phase catalysis, the sodium salt of TPPTS, is not soluble in methanol, the authors used the ligand $Ph_2P(CH_2)_4SO_3Na$. Good activities were observed although reaction selectivity to linear products was typically 70% and a relatively high proportion of alcohol products were observed [9]. Acetal formation is a possible side reaction when alcohols are used as the sol-

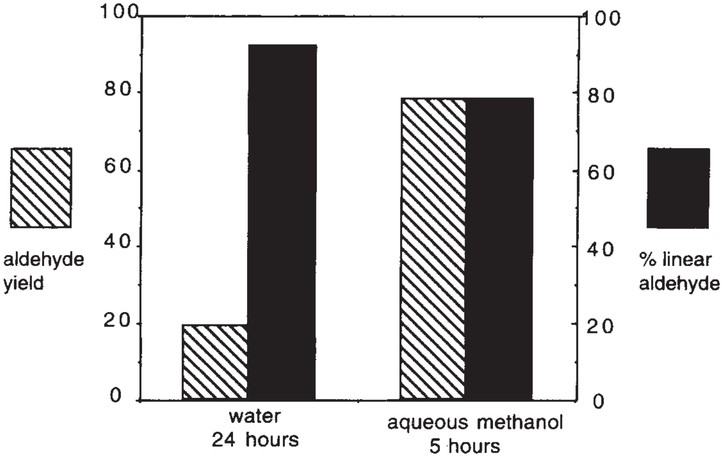


Fig. 1 Comparison of 1-octene hydroformylation in water and aqueous methanol. The reaction time in water was 24 h; the reaction time in 50% aqueous methanol was 5 h [10, 11].

vent for hydroformylation catalysis. The authors reported that this side reaction is minimized when the solution is made alkaline by the addition of a strong base such as LiOH [9].

As noted above, the addition of alcohols improves the reaction activity in the two-phase hydroformylation of higher olefins with Rh/TPPTS catalysts. Reaction selectivity, however, is diminished if the operating conditions are otherwise similar. This is illustrated in Figure 1, which compares the conversion and selectivity of 1-octene hydroformylation over the $(acac)Rh(CO)_2/TPPTS$ catalyst in water alone and 50% aqueous methanol as the solvent [10, 11]. Selectivity can be improved in the aqueous methanol system when ligands other than TPPTS are used, as for example with ionic phosphites of the type **1** cited above. These ligands differ significantly from TPPTS in that they are expected to be amphiphilic in character; the ionic portion is hydrophilic while the rest of the ligand is relatively hydrophobic.

A similar effect on activity and selectivity is observed upon addition of co-solvents to the dimeric rhodium hydroformylation catalyst, $[Ru_2(\mu\text{-S-}^t\text{Bu})_2(CO)_2\text{-}(TPPTS)_2]$ [12]. Specifically, there is an inverse relationship between solvent solvophobicity [13] and the log of the n/iso ratio of the aldehyde products for the hydroformylation of 1-octene. The catalyst is most selective to linear products in water.

In general, amphiphilic phosphines show both better activity and selectivity than TPPTS when compared in aqueous/solvent mixtures as the reaction medium. The series of phosphines, $P[(C_6H_4)/(CH_2)_n(C_6H_4SO_3Na)]_3$, $n = 3, 6, 10$ has been compared with TPPTS for the hydroformylation of 1-octene in aqueous methanol [11, 14]. In the schematic representation of the ligand with $n = 10$ (compound **3**), hydrogen atoms are omitted for clarity.

3

Phosphine **3** has good solubility in both water and methanol. A comparison of **3** and TPPTS for the rhodium-catalyzed hydroformylation of 1-octene in aqueous methanol is shown in Figure 2 [14]. At all ligand/rhodium ratios studied, the amphiphilic phosphine shows both better activity and selectivity than TPPTS. The improved selectivity is attributed to diminished inter- and intra-ligand ionic repulsions with the greater distances between sulfonate groups in complexes of the amphiphilic ligands.

Aqueous-phase hydroformylation is dependent on both the pH of the aqueous solution and the ionic strength of the solution. Typical reaction conditions reported in patents show rhodium concentrations of approximately 0.05 M with the appropriate concentration of TPPTS to give the desired ligand/rhodium ratio. Buffers are typically added to control the pH. In the original patents the pH was buffered to approximately 7 [5]. As result of the added salts, the aqueous medium for catalysis has a very high solution ionic strength ("salt effect"). High solution ionic strength may play a role in stabilizing Rh/TPPTS complexes. In particular, $HRh(CO)(TPPTS)_3$ has a net charge of -9 due to the sulfonate groups on the TPPTS ligands. Stabilization of the ionic charge in this complex and in catalytic intermediates may contribute to the high selectivity of aqueous-phase catalysts

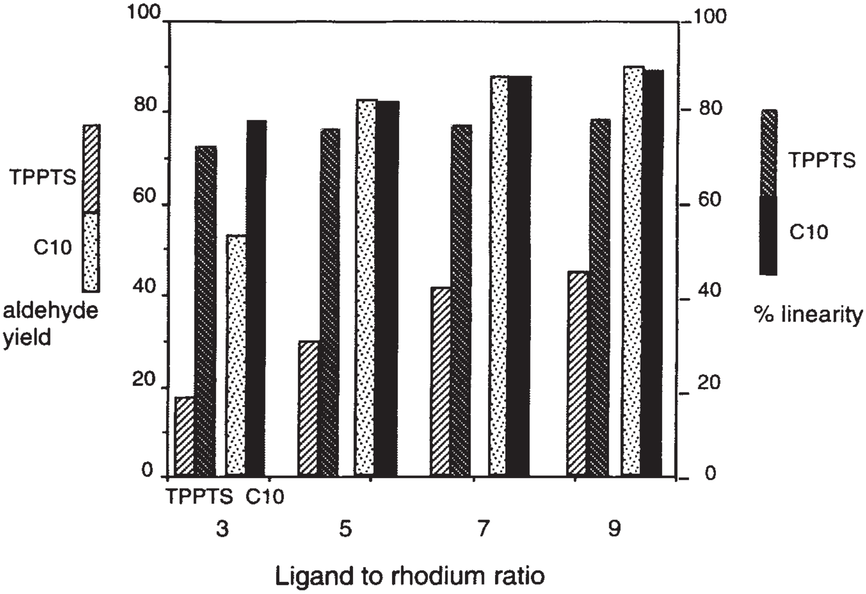


Fig. 2 Comparison of TPPTS and C10-TS, **3**, for 1-octene hydroformylation under two-phase reaction conditions [14].

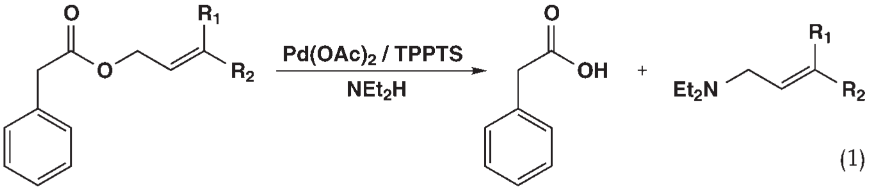
toward linear products [15, 16]. This is consistent with the trend in selectivity with solvent solvophobicity noted above [12].

In more recent patents, examples are given that demonstrate that the formation of aldol condensation products and heavy ends is pH-dependent; specifically, condensation products are inhibited at relatively low pH. For example, propene hydroformylation at a reaction pH of 5.9 leads to a total of 1.2 wt.% C_8 and higher products. In contrast, when the reaction was repeated at a pH of 6.9, the C_8 higher products formed from condensation reactions comprised 7.5 wt.% of the reaction mixture [17]. A higher proportion of linear products was observed at the lower pH as well. It has been noted also that the presence of CO_2 inhibits aldol condensation [18]. This may be a pH effect as well, since aqueous solutions of CO_2 are acidic.

4.3.3
Hydrogenations and Other Catalytic Reactions

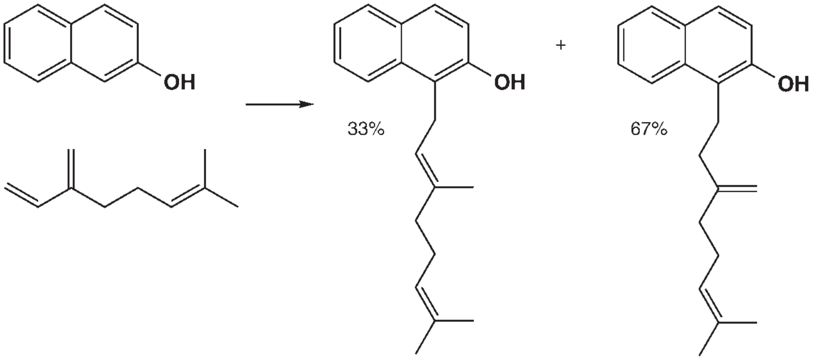
Co-solvents also play a rate-enhancing role in two-phase hydrogenation reactions. In the two-phase hydrogenation of cyclohexene with a catalyst prepared *in situ* by the hydrogen reduction of $RhCl_3 \cdot 3H_2O$ in the presence of monosulfonated triphenylphosphine, TPPMS, the rate of hydrogenation was observed to be dependent on the co-solvent [19]. Lower alcohols, methanol plus ethanol, were superior to co-solvents such as acetone plus THF. At the co-solvent concentrations used, the system remained biphasic. The increase in activity was attributed to improved olefin solubility in the aqueous/co-solvent phase compared with water alone as the solvent. It was further observed that the addition of salts decreased the reaction rate, presumably by decreasing olefin solubility, while the addition of surfactants had little net effect on reaction rate.

In the deprotection of phenylacetic allyl esters over $Pd(OAc)_2$/TPPTS catalysts, it was noted that the reaction medium plays a role in determining reaction selectivity. The reaction is shown below in Eq. (1). When the reaction is performed homogeneously in CH_3CN/H_2O as the solvent, the allyl substituents with $R_1 = R_2 = H$; $R_1 = Ph$, $R_2 = H$; $R_1 = R_2 = Me$ are all substituted [20, 21]; the first in the series is the fastest to react. In contrast, when the reaction takes place under biphasic conditions in C_3H_7CN/H_2O, only the simple allyl ester, $R_1 = R_2 = H$, is cleaved. When two allylic esters are incorporated into a single molecule the allyl ester can be selectively substituted under two-phase reaction conditions.



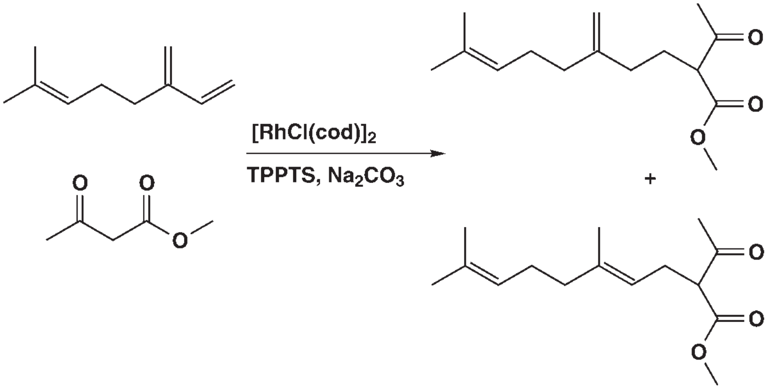
(1)

The alkylation of phenols with isoprene and isoprene derivatives can be catalyzed over rhodium complexes of TPPTS [22]. In the case where the isoprene derivative is myrcene, methanol is added to the reaction mixture. The apparent benefit is to increase reaction rates with the highly water-soluble myrcene substrate. The alkylation of 2-naphthol with myrcene is shown in Eq. (2). In 2 h at 100 °C in aqueous methanol a 40% conversion of myrcene is observed (160 turnovers).



(2)

Similarly, the reaction of isoprenes with methyl acetylacetate can be accomplished over rhodium complexes of TPPTS [23]. The example with myrcene is shown in Eq. (3). In this case rates are also increased upon addition of methanol. For example, in water alone as the solvent 174 turnovers of myrcene are observed in 1 h at 90 °C, whereas 297 turnovers are observed under otherwise identical conditions in water/methanol (75 : 25). No difference in reaction selectivity is observed in the presence of methanol. In both cases the selectivity to the isomeric products shown in Eq. (3) is 99%.



(3)

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4.4
Membrane Techniques

Helmut Bahrmann, Boy Cornils

Membranes, i.e., microporous separation layers in the form of thin films, can be used for selecting separation of substances (liquids) differing in particle sizes (e.g., colloids) and, under some circumstances, in molecular weight. For homogeneous catalysis, this means the possibility of separating reactants and reaction products from the catalysts (and possibly also their decomposition and aging products) [1, 23]. In this respect, membrane techniques are employed simply as a substitute for the phase separation step in homogeneous aqueous catalysis. In conventional homogeneous catalysis, membrane and membrane processes are regarded as alternatives to techniques for the otherwise inherently difficult separation of catalyst and products, e.g., immobilizing the homogeneous species by "anchoring" it to supports ("heterogenization") [2, 3]. In this context the term "membrane reactor" refers to the fundamental part of this device: the membrane, acting either as a catalyst or a physical barrier. Thus, the following different applications may be distinguished:

- as a catalytically active membrane (catalytically active sites incorporated in or on the surface of membranes) – this describes catalytic membrane reactors (CMRs) [4];
- as "selective" membranes which allow a selective removal of product from the catalyst–reactant/product mixture;
- a membrane through which reactants and products can pass while the dissolved homogeneous catalyst is retained [2].

"Liquid membranes" [5] are in the transition to micellar systems (cf. Section 4.5).

In most cases the membrane material serves as a classification for reviews and surveys [6–9]. The "selectivity" of membranes is based on the pore size and various properties of the membrane material such as hydrophilicity or hydrophobicity, thus giving the ability, depending on the particle size, to recover soluble catalysts either by reverse osmosis or by ultrafiltration. In the case of ultrafiltration, the molecular weight of the catalyst has to be increased by suitable methods such as deri-

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Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

vatization (cf. Section 6.1.5, re-immobilization [10, 11]) or coupling to soluble polymers (Section 7.5) [1]. Examples of the combination of various homogeneous catalytic processes and membrane techniques are compiled in [2, 11, 12]. In all cases, membrane separation of catalyst from product or of catalyst from reactant + product offers a gentle mechanical method without any thermal or chemical stress due to, for example, distillation or persistent effects of chemicals.

This is exactly the overall target when membrane techniques are combined with two-phase operations. However, since the basic task of separating catalyst from product has already be achieved by the phase separation (decantation) step in the two-phase processes, additional membrane processes can enhance the further work-up of the homogeneous catalyst, especially continuous, simultaneous, and *in situ* workup ("makeup"). Membrane processes are particularly suitable here for separating the intact complex catalyst from its components (such as precursors, ligands, decomposition products (e.g. [13]), catalyst poisons) or accompanying substances (e.g., high-boiling condensation products, solvents, additives). Catalysts of the biphasic reaction can also be chemically modified (by coupling, introducing other cations, or tenside ligands [14], etc.; cf. Section 6.1.5) to alter their molecular weight and thus improve their ease of separation using a given membrane. In addition, Exxon patents (e.g. [15]) refer to the suitability of the membrane processes for removing the water-soluble catalyst in the presence of surfactants, which are reported to increase the reaction rate of reactants that are sparingly soluble in water (cf. Section 6.1.3.2).

The principal task of membrane separation components within two-phase aqueous homogeneous catalytic processes is therefore to perform fine separation of undesirable constituents of the catalyst or substances accompanying the catalyst, while the phase decantation has already performed the coarse separation of catalyst from product (or residual starting material) [16]. It is therefore generally useful to place the membrane separation processes in a catalyst recycling sidestream, and parallel to the main stream, as the schematic diagram in Figure 1, variant 1.1 shows. This means that the membrane treats only a portion of the entire catalyst stream to be recycled, and so is subjected to a lower loading and lasts longer.

In variant 1.2, which is the subject of patent claims by Exxon in particular [12, 15, 17, 18], the entire stream flows through the membrane stage, giving rise to considerably higher loadings of the membrane material. The membrane treatment of the mainstream of the organic phase may be advisable, if the preseparation by decantation is still convenient and only traces of the aqueous phase have to be separated.

In both variants, steps must be taken to ensure that the pressure and temperature conditions upstream and downstream of the membrane do not differ substantially from the standard conditions. Otherwise, deviations in conditions can lead to the complex catalysts breaking down or denaturing, resulting in recycled catalysts differing in behavior from fresh catalyst.

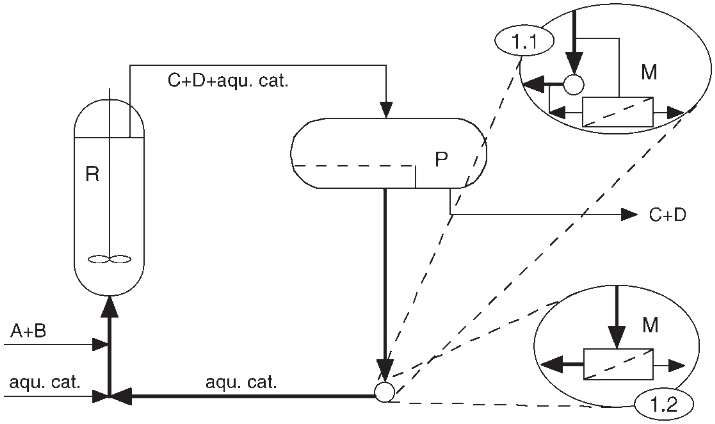

Fig. 1 Membrane processes as a constituent of aqueous two-phase homogeneous catalytic methods for the reaction $A + B \rightarrow C + D$ (R = reactor; P = decanter; M = membrane separation): 1.1, sidestream membrane separation; 1.2, mainstream membrane separation.

The relatively difficult experimental conditions explain why preference is given to membrane steps in technically and economically significant aqueous catalysis processes (e.g., oxosynthesis [12, 15–22]), and why it is chiefly industrial companies that have developed them (Hoechst [6, 22], Exxon [12, 15, 17, 18], BP [20], ICI [21], or Enichem [13]). Progress in this field is largely documented by patents. There is considerable scope for further development, because combination of membrane separation processes with homogeneous aqueous catalysis should be an interesting advance with improved activity and catalyst service life without the need for (costly) auxiliaries. A likely development is the connection of a simultaneous continuous makeup membrane stage in a sidestream to the circuit recirculating the aqueous catalyst solution stream.

Further developments are still being made in membrane materials and membrane modules. There are reports, in particular, of hydrophobic membranes made of polyolefins, crosslinked polyolefins, polyamides, polyaramids, poly(vinylidene fluoride), PTFE, polyimides, and suchlike.

Since the first edition some reviews (and lots of patents) about the application of membranes and membrane reactors have been filed and published (for example [24]). Mostly, special aspects were in the foreground of investigations (such as the interplay of micelles or microemulsions and membranes, interfacial phenomena, three phase emulsion/solid heterogenization, or the properties of metal-based membranes [25]).

Membrane and membrane reactors have not been used in the industrial practice but find some application as modern separation technique [26] or in laboratory work about the application of chemzymes [27] or for enzymatic syntheses [28].

Interestingly, membrane and membrane reactors for aqueous-phase conversions are not an outstanding topic for the specialists discussing “sustainable” or “green” catalysis [24 c].

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4.5
Micellar Systems

Günther Oehme

4.5.1
Introduction

Micelles, vesicles, and related species are supramolecular assemblies in a colloidal dimension [1]. This aggregation is based on amphiphilic molecules carrying a hydrophilic headgroup and a hydrophobic tail. Amphiphiles with a special structure can be surface-active agents (surfactants, detergents), which assemble in aqueous or nonpolar media [2]. A new proposal is to call surfactants “synkinons” (in analogy to synthons) and the aggregation by nonbonded forces “synkinesis” [3]. A simplified relationship between surfactant structure and the morphology of the aggregate is illustrated in Figure 1.

Aqueous micelles are thermodynamically stable and kinetically labile spherical assemblies. Their association–dissociation process is very fast and occurs within milliseconds. The actual order is less than shown in Figure 1. Driving forces for the formation of aqueous micelles or vesicles are the solvation of the headgroup and the desolvation of the alkyl chain (“hydrophobic effect”). Because of the rapid exchange of surfactants, the core of the micelle contains a small percentage of water molecules. Aqueous assemblies are preferentially stabilized by entropy, and reverse micelles by enthalpy [4]. The actual formation of micelles begins above a certain temperature (Krafft’s point) and above a characteristic concentration (critical micelle concentration, CMC). Table 1 shows a selection of typical micelle-forming surfactants and their CMCs.

The hydrophilic “headgroup” is either charged (cationic, anionic, zwitterionic) or strongly polar (e.g., a polyether chain) and the hydrophobic (lipophilic) tail is usually a chain containing aromatic and aliphatic groups. Extremely hydrophobic properties were observed with perfluorinated alkyl groups [5].

Because of a very high polarity gradient between surface and core, micelles can enclose different organic species out of the surrounding aqueous phase [6]. This incorporation can be described by an equilibrium constant as a basis for kinetic

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Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

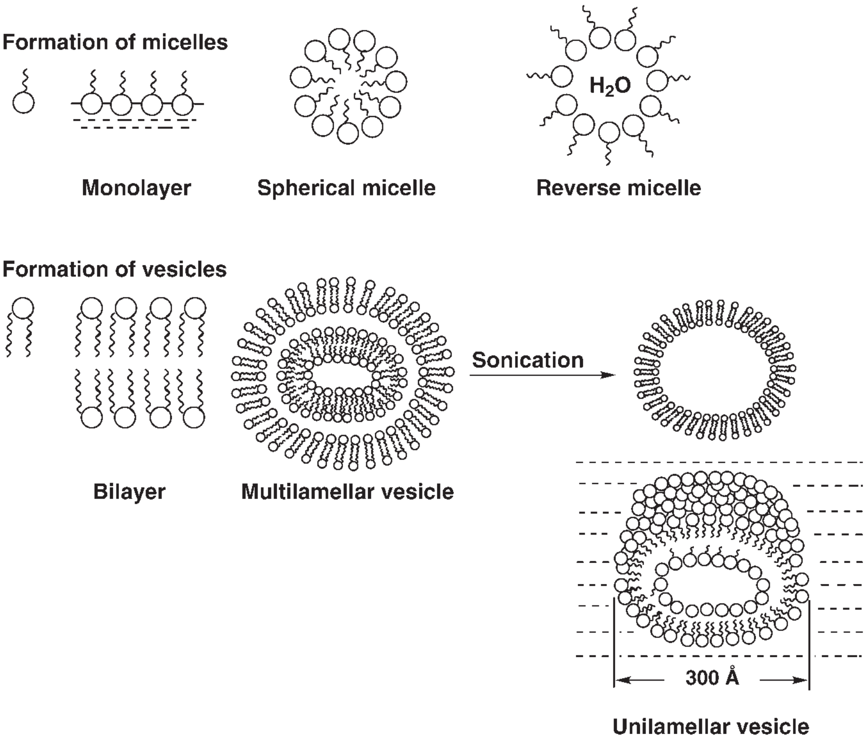
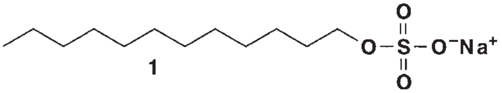
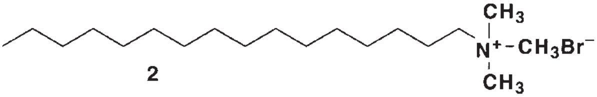
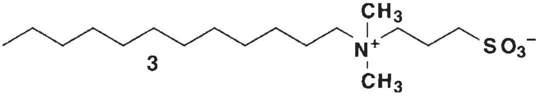
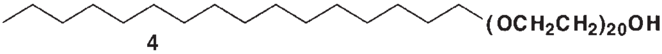


Fig. 1 Principle of self-organization of different types of amphiphiles (all the sketches are idealized).

Tab. 1 Typical micelle-forming surfactants and their CMC values (with Structures **1** to **4**).

Surfactant	*CMC [mol L^{-1}]*
 **1**	**(SDS)** 8.1×10^{-3}
 **2**	**(CTABr)** 9.2×10^{-4}
 **3**	**(DDAPs)** 1.2×10^{-3}
 **4**	**(Brij 58)** 7.7×10^{-5}

treatments. Encapsulation of reactants in micelles often enhances or inhibits the reaction rates. Any reaction promotion has been called "micellar catalysis".

In an early review Morawetz [7] discussed three types of micellar catalysis:

- The surfactant forms the micelle and reacts as reagent.
- The interaction between the reacting species and the micelle influences the rate of reaction.
- The micelle carries catalytically active groups and acts as a catalyst.

Most reactions influenced by micelles are related to the second type [8].

As mentioned above, surfactant micelles in water as medium create a special environment from high to low polarity. According to Brown et al. [9] the rate enhancement of organic reactions in micelles can be a combination of the following effects:

- There is a medium effect because of the lower dielectric constant in comparison with water.
- The reaction transition-state is stabilized by interaction with the polar headgroup.
- Reactants are concentrated by interacting with the micelle surface or due to incorporation. Thus the rate of bimolecular reactions should be increased. Surfaces of ionic surfactant micelles are more acid or more basic than the surrounding water phase.

Because of the hydrophobic core and a polar headgroup there are certain similarities between micellar and enzymic catalysis, but the lifetime of a micellar assembly is very short and there is no organization of catalytic and anchor groups as there is in enzymes. As a result, the enhancement of activity and enantioselectivity is much lower. Although formation and dissociation of micelles are very fast processes, some reactions occur with a high selectivity. Analogy between micellar catalysis and enzymic catalysis is also confirmed by a similar kinetic treatment. All kinetic models presuppose an interaction of the reactants with aggregated but not with dissociated surfactants. Detailed kinetic treatments are given in various reviews [10]. Certainly, there is no information about the morphology of surfactant aggregates in the presence of reactants. The existence of spherical micelles depends on the temperature, the concentration of surfactants, and the concentration of other solutes, e.g., salts. The transition from micelles to rods and even to vesicles of different shapes was observed. Nevertheless, it is very helpful to create micelles and most effects on the reaction rate and selectivity are observed near the CMC [11].

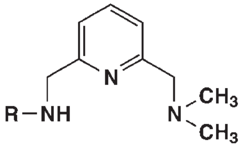
It is also noteworthy that micelle-forming surfactants may solubilize organic compounds sometimes in a very low concentration of the surfactant (still above the CMC). This embedding depends on the charge of surfactant and the charge of reactant. Only hydrophobic reactants may permeate into the hydrophobic core. Important for good solubilization properties is the hydrophile–lipophile balance (HLB) of the surfactant because sufficient water-solubility is required [12] (cf. Section 3.2.4). The transfer of a catalytic reaction into a micelle represents a case of microheterogenization. The suitability of micellar solutions as reaction media in dependence on the structure of surfactants and environmental influences is discussed in a review by Taşcioğlu [13].

4.5.2
Hydrolytic Reactions in Micelles

Nucleophilic reactions in micelles with water as reagent have been investigated as models of enzymic reactions. The enhancement of the reaction rate as well as the stereoselectivity of the reactions was studied. Typical substrates were activated esters of amino acids [14], carboxylic acids [15], and phosphoric acid [16], and typical catalysts were surface-active peptides with histidine as active component.

Kinetic resolution of racemic esters was determined. Brown et al. [17] and Moss et al. [18] gave explanations for the stereoselectivity. As a rule the effect of chiral inert micelles on the stereoselectivity is not important, but the use of chiral functional surfactants as catalysts sometimes gave unexpected effects. Surprisingly, nonfunctional amphiphiles as co-surfactants can improve the stereoselectivity enormously. One example given by Ueoka et al. [19] was that the saponification of D,L-*p*-nitrophenyl *N*-lauroylphenylalaninate with the tripeptide *Z*-Phe-His-Leu-OH as catalyst in assemblies of bis(tetradecyl)dimethylammonium bromide ($2\,C_{14}Br$) gave almost pure L-*N*-dodecanoylphenylalanine upon addition of 7–20 mol% of the anionic surfactant sodium dodecylsulfate (SDS; **1**). A structural change of the vesicle into a rodlike or cylindrical micelle could be a possible explanation. Hydrolytic reactions are not favored in aqueous complex catalysis but there is an interest in finding models for the cytalytic effects in metalloenzymes [20].

In a series of papers Tonellato, Tecilla, Scrimin, and co-workers [21] gave examples of highly active complexes with amphiphilic or hydrophilic ligands (Structures **5**–**8**) for the cleavage of various esters. Sometimes the rate is very drastically increased in comparison with the reaction in pure water (over a half-millionfold). These lipophilic ligands change into amphiphiles upon complexation with Ni(II), Cu(II), Zn(II), or Co(II), respectively. A comparison of amphiphiles and non-amphiphiles (methyl instead of dodecyl or hexadecyl chains) gave significant differ-



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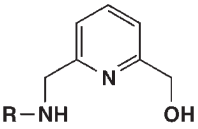

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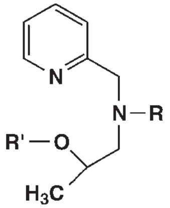

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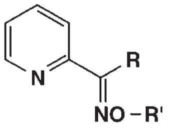

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R = CH_3, C_nH_{2n+1}
R′= H, CH_3
n = 8, 12, 13, 16

ences in rates and selectivity. The use of optically active ligands led to a moderate kinetic resolution of racemic α-amino acid esters [22]. Best results were obtained with bilayer-forming cationic co-surfactants in the gel state. In principle, the kinetic resolution of a racemic mixture of activated α-aminoesters appears feasible [23].

It is noteworthy that metallomicelles of Ni(II) complexes with long-chain *N*-alkylated ethylenediamine ligands catalyze the epimerization of aldoses in an aqueous dispersion [24]. A reexamination of the effect of metallomicelles on the hydrolysis of phosphate and carboxylate esters was given by Scrimin et al. [25]. Acceleration in second-order reactions are often to interpret as a local concentration increase of the reactants. The catalytic effect of metallosurfactants in enzyme-related reactions has been investigated by Nolte's working group [26], also carefully considering the assembly structure [27]. The wide field of artificial enzymes was recently reviewed by Murakami et al. [28].

4.5.3
Oxidation Reactions in Micelles

As pioneering work in micellar catalysis, Menger et al. [29] in 1975 described two reactions: the oxidation of piperonal to the corresponding carboxylic acid by means of $KMnO_4$ and the saponification of trichloromethylbenzene to benzoic acid, both in the presence of cetyltrimethylammonium bromide (CTABr, **2**). In these experiments the authors observed improved yields attributable to surfactant assemblies. The surfactant-supported oxidation of organic compounds with inorganic reagents has been developed into a useful method [30]. An enantioselective oxidation of 3,4-dihydroxy-L-phenylalanine catalyzed by an *N*-lauroyl-L-(or -D-)histidine-Cu(II) complex was submitted by Yamada et al. [31]. Using CTABr co-micelles, appreciable enantioselectivity was observed. Simon and co-workers [32] synthesized a series of amphiphilic copper(II)–amine complexes. These annelides exhibited oxygen activation [33] but no catalytic activity.

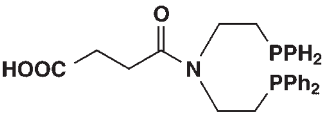
Shinozuka and co-workers [34] developed bleomycin model complexes bearing long alkyl chains. The multidentate amine ligand contains imidazole and shows high oxygen-activating capacity.

Recently, Rabion et al. [35] described a methane oxygen model, i.e., the oxidation of cyclohexane with *tert*-butyl hydroperoxide catalyzed by an iron complex in aqueous micelles. The favored surfactant was cetyltrimethylammonium hydrogen sulfate and the following complexes have been used: $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$ and $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(BPIA)_2]^{3+}$ with TPA = tris[(2-pyridyl)methyl]amine and BPIA = bis[(2-pyridyl)methyl][2-(1-methylimidazolyl)methyl]amine. The investigated reaction does not occur in a biphasic aqueous system without surfactant. A biomimetic system of cytochrome P450 in a micellar medium (cf. Section 6.15) was investigated by Monti et al. [36]. The authors found in the epoxidation of styrene with NaOCl a significant influence of the type of surfactant: cetylpyridinium chloride promoted the reaction more than cetyltrimethylammonium bromide. An explanation could be a specific non-covalent interaction between catalyst, substrate, and surfactant.

4.5.4
Complex-catalyzed Hydrogenation in Micellar Media

Homogeneous hydrogenation is a typical example of the activation of small molecules by transition metals (cf. Section 6.2). The state-of-the-art has been reviewed in a series of articles and books [37]. A great number of transition metals are able to activate hydrogen but Co, Rh, Pd, Ru, and Pt are preferentially used. A special position in the asymmeric (enantioselective) hydrogenation is taken by rhodium and ruthenium complexes [38]. In the early investigation of homogeneous hydrogenation, water was strictly avoided as solvent except in experiments with the water-soluble complex of the potassium hydridopentacyanocobaltate, $K_3[HCo(CN)_5]$. By using a micellar medium, Reger and Habib [39] tried to stabilize this hydrido complex and even to influence the regioselectivity by the partial hydrogenation of conjugated dienes. The authors could observe stabilization of the catalyst but no alteration in the product distribution. Using the same catalyst but having atropic acid or the corresponding esters as substrate, Ohkubo et al. [40] found some acceleration in presence of micelle-forming reagents.

With the introduction of water-soluble phosphine ligands [41] and their application in complex catalysts in biphasic and phase-transfer systems, the influence of amphiphiles could be expected but the results were not really encouraging [42]. Quinn and Taylor [43] reported on selective hydrogenation in phospholipid bilayer membranes and Nuzzo et al. [44] described the rhodium complex of **9** as active exclusively in the presence of SDS.



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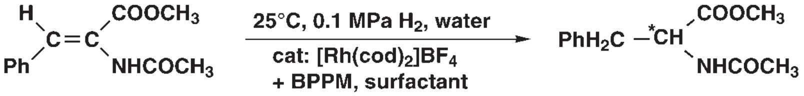
It also seems to be noteworthy that in the presence of phospholipids the nitrogen reduction catalyzed by an artificial nitrogenase system is very selectively enhanced [45]. Ding et al. [46] gave examples of the use of chiral amphiphilic ligands in hydrogenation reactions but directed attention to their application in biphasic systems. Usually, the presence of water causes loss of activity and, in the case of enantioselective hydrogenation, loss of enantioselectivity [47].

Surprisingly, in the hydrogenation of unsaturated amino acid derivatives catalyzed by a chiral rhodium complex in water, these disadvantages are overcome by the addition of micelle-forming surfactants [48]. The mixture was solubilized by

Tab. 2 Hydrogenation with different types of surfactants (Rh/surfactant/substrate = 1 : 20 : 100).

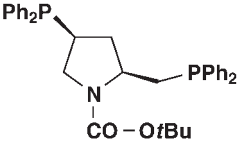
Surfactant	*t/2 [min]*	*Optical yield [% ee (R)]*
None: in water (methanol)	90 (2)	78 (90)
Anionic: sodium dodecyl sulfate (SDS)	6	94
Cationic: cetyltrimethylammonium hydrogen sulfate (CTA · HSO_4)	5	95
Zwitterionic: *N*-dodecyl-*N,N*-dimethyl-3-ammonio-1-propanesulfonate	5	93
Nonionic: decaoxyethylene hexadecyl ether (Brij 56)	7	95

addition of a relatively small amount of surfactant, became yellow and consumed hydrogen [49]. Activity and enantioselectivity are comparable with the results obtained in methanol as standard solvent and in some cases the enantioselectivities were even higher than in organic solvents. Table 2 and Eq. (1) show selected examples with different amphiphiles.



(1)

All types of surfactants promote the reaction but only the hydrogen sulfate was active in the case of the cationic amphiphiles. No influence was found for the anions tetrafluoroborate or triflate. The most favorable chiral ligand was BPPM (**10**), described by Achiwa [50], but even DIOP (4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan) [51] and Ph-*β*-glup-OH (phenyl 2,3-*O*-bis(diphenylphosphino)-*β*-D-glucopyranoside) [52] show the effect. A micellar effect was also observed with phosphinites derived from *α*,*α*- and *β*,*β*-trehalose as ligands [53]. The increase of activity and enantioselectivity depends on the concentration of the surfactant. There is a sudden increase near the CMC of the surfactant which might be an indication of the existence of micelles [11].



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The enhancement of enantioselectivity cannot be an effect of solubility because water-soluble substrates gave enhanced activities but no enantioselectivity increase [54]. Acylation of PPM ((2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine) with the chlorocarbonic ester of alkyl polyoxyethylene ethers (Brij; **4**)

Tab. 3 Chiral induction by optically active surfactants (for conditions see Table 2).

Surfactant	***Catalyst: [Rh(cod)$_2$]BF$_4$ + BDPD***[a]	
	t/2 [min]	***Optical yield [% ee]***
Derived from amino acids:		
N-palmitoyl-L-Pro-Na	6	3 (*S*)
N-palmitoyl-D-Pro-Na	16	2 (*R*)
N-palmitoyl-L-Pro-L-Pro-Na	10	8 (*S*)
N-palmitoyl-D-Pro-D-Pro-Na	12	7 (*R*)
N-palmitoyl-D-Pro-L-Pro-Na	8	3 (*R*)
Derived from carbohydrates:		
Tetradecyl-β-D-maltoside	40	6 (*R*)
Dodecyl-β-D-maltoside	23	6 (*R*)
Derived from cholesterol:		
Cholesteryl (β-sodiumsulfonato)propionate	11	8.5 (*R*)

[a] BDPD = $Ph_2P(CH_2)_4PPh_2$; (bis(diphenylphosphino)butane).

leads to water-soluble or amphiphilic (that means in water as colloids dispersible) ligands. Complexation of these ligands to rhodium(I) leads to chiral metallomicelles which successfully catalyze the hydrogenation in methanol and even in water [55].

It is difficult to determine the location of the reactants in micelles. Both substrate and catalyst have to be located very close. Chiral induction by optically active surfactants, with the catalyst optically inactive, might indicate the location. Table 3 summarizes selected results with different types of chiral surfactants.

The induction is quite low, less than 10% *ee*, but the use of dipeptides containing two prolines of identical configuration causes amplification of the optical induction, whereas the acylated amino acid directs the induction when dipeptides with prolines of opposite configuration are being used [56]. This characteristic is true even for carbohydrate amphiphiles [57].

The most likely region for the reaction should be the transition between polar headgroup and hydrophobic chain ("palisade layer" [58]), which is also discussed by Monflier [59].

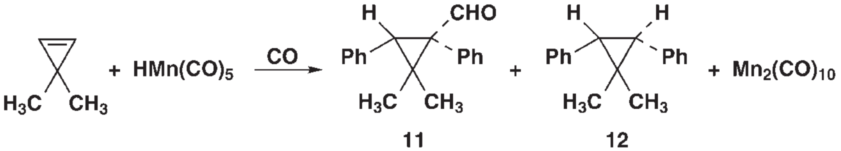
Other indications about the intramolecular reaction were concluded from **p**ulsed field **g**radient **s**pin **e**cho-NMR (PGSE-NMR) measurements [60]. This method gives informations about the incorporation of the substrate into the micelle and enabled the measurement of an average diffusion coefficient of the catalyst below and above the CMC.

The low chiral induction due to optically active surfactants in micelles could be a result of the low kinetic stability of micelles. It could be shown that micelle-analogous dendrimers as models for stabilized micelles gave significant higher inductions ($>$ 50% *ee*) in the asymmetric reduction of ketones compared to supramolecular aqueous micelles ($<$ 10% *ee*) [61].

4.5.5

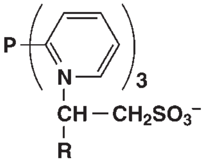
Carbon–Carbon Coupling Systems

One of the most important industrial reactions catalyzed by transition metal complexes is hydroformylation. Discussion of new aspects and developments are given in a review [62]. Milestones for this reaction are the development of water-soluble phosphines (Rhône-Poulenc [63]) and the first application as ligands by Ruhrchemie [64]. Gradually, a liquid/liquid biphasic system originated, which contained the catalytic acting complex in the water phase. It is difficult to work with higher olefins than propene because the water-solubility of educts and products is extremely low. Many proposals have been made in order to improve the solubility of the catalyst in the olefinic phase (cf. Section 6.1). It should be possible by addition of hydrophobic cations to anionic groups in the water-soluble ligands [65]. A hydroformylation in presence of micelle-forming surfactants was proposed by Dror and Manassen [66]. They did not find any indication of selectivity enhancement but there was clearly a stabilization of the catalyst. A comparable result was noted by Quinn and Taylor [43], who used phospholipid bilayers (vesicles) in water. The catalyst did not work in organic solvents but gave acceptable activities and regioselectivities in aqueous bilayer assemblies. Matsui and Orchin [67] investigated the stoichiometric reaction of $HMn(CO)_5$ with cyclopropenes which led to aldehyde and cyclopropane (Eq. 2).



(2)

In 1991 Fell and Papadogianakis provided an example of hydroformylation with surface-active phosphine ligands **13** [68].



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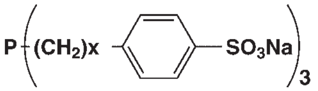
Some years ago, Hanson and co-workers started a program of rhodium-catalyzed hydroformylation with various surface-active phosphine ligands (Structures **14–16** [69]). In their ligand models the phosphorus is bound to the hydrophobic part.

As a new development, van Leeuwen and co-workers used ligands with amphiphilic properties in acid media for hydroformylation, but these phosphines are hardly able to form micelles [70]. Chinese authors [71] investigated the influence



x = 1, 2, 3, 6

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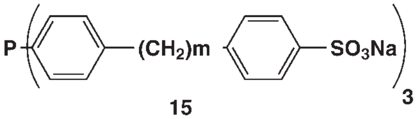

m = 3, 6

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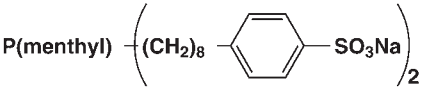

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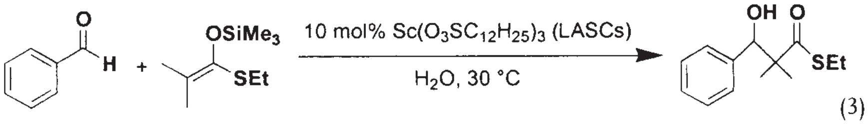
of CTABr on the biphasic hydroformylation of 1-dodecene with the water-soluble catalyst [RhCl(CO)(TPPTS)$_2$] [TPPTS = P(m-$C_6H_4SO_3Na$)$_3$] and found an acceleration of the reaction rate and an increase of aldehyde linearity. No indication is given for the recycling of the catalyst.

Some other C–C bond coupling reactions in micellar systems should be mentioned here. Monflier et al. [72] described, in both papers and patents, the telomerization of 1,3-butadiene into octadienol in a micellar system by means of a palladium–phosphine catalyst. Water-soluble and amphiphilic phosphines have been used and the surfactants were widely varied. The authors have shown that the promoting effect of surfactants appeared above the CMCs of the surfactants, and they conclude that micellar aggregates were present in the reaction mixture. Cationic, anionic, and nonionic surfactants gave this micellar effect but the combination of the highly water-soluble TPPTS and the surfactant dodecyldimethylamine hydrocarbonate was found to be best. A speculation about the location of reactants shows that the reaction probably occurs in the interface between the micellar pseudophase and water.

Sinou and co-workers [73] studied the influence of different surfactants on the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in presence of potassium carbonate as base and non-water-soluble chiral ligands. Best results in activity and enatioselectivity ($> 90\%$ *ee*) were observed with 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as ligand and cetyltrimethylammonium hydrogen sulfate as surfactant in aqueous medium. Water-stable Lewis acids as catalysts for aldol reactions were developed by Kobayashi and co-workers [74]. An acceleration of the reaction was indicated in presence of SDS as anionic surfactants. An additional promotion could be observed by combination of Lewis acid and surfactant (LASCs = Lewis acid-surfactant-combined catalysts) as shown in Eq. (3). Surfactant the anion of dodecanesulfonic acid.

In the same manner Engberts and co-workers used the copper(II) salt of SDS as catalyst in a Diels–Alder reaction of 3-(p-substituted phenyl)-1-(2-pyridyl)-2-



(3)

propen-1-ones with cyclopentadiene in water as medium and observed a spectacular enhancement of the reaction rate [75].

Surfactant-supported polymerization reactions are not included in this report.

4.5.6
Some Examples of Reactions in Reverse Micelles and Microemulsions

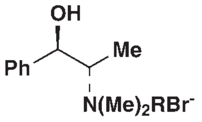
Reverse micelles are formed by association of polar headgroups of amphiphiles with colloidal drops of water in an organic medium. A favored surfactant seems to be AOT (sodium-di[2-ethylhexyl]sulfosuccinnate) but SDS and tetraalkylammonium salts have also proved to be useful. Like aqueous micelles, reverse micelles exist in highly diluted systems.

A microemulsion is a multicomponent (3–4 components) system, e.g., water in hydrocarbon (water/oil) or hydrocarbon in water (oil/water), surfactant, and co-surfactant, and generally it exists only in small concentration ranges. Nevertheless, the capacity for reactants and variability of solubilization properties are high and of practical interest [76]. On the basis of microemulsions Menger and co-workers developed a method for an economical environmental cleanup of chemical warfare contamination [77]. As an example of organometallic catalysis in a microemulsion, Beletskaya [78] performed palladium-catalyzed C–C coupling reactions in aqueous medium with a very high content of surfactant.

An acceleration was observed in the hydrogen-transfer reaction from 1,2-cyclohexanedimethanol to (*E*)-4-phenyl-3-butene-2-one in toluene catalyzed by [RuCl((*S*)BINAP)(benzene)]Cl (2 mol%; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) and SDS (6 mol%) [79]. The surfactant is essential for the enhancement of catalytic activity and the authors proposed the existence of reverse micelles.

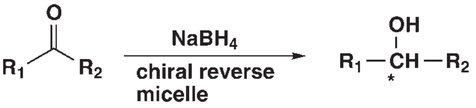
It was shown by Buriak and Osborn [80] that non-micelle-forming anions improved the enantioselectivity of an imine hydrogenation catalyzed by rhodium complexes in the same way as reverse micelles. Complexation of the sulfate or sulfonate anion with the catalyst appears to be responsible for the enhancement of the enantioselectivity. The very strong dependence of the product chirality on the structure of the anion is discussed. Finally, a long-chain ephedrinium salt **17** as surfactant, should be mentioned.

Several ketones are reduced by $NaBH_4$ in a reaction of the type shown in Eq. (4). A maximum of 17.2% *ee* could be observed with $R^1 = Ph$ and $R = {}^tBu$, which is noteworthy for optical induction from the micelle [81].



17

R = ethyl, octyl, dodecyl, hexadecyl



(4)

Interesting new experiments of CH-activation in *n*-heptane and methylcyclohexane were communicated by Elsevier and co-workers [82]. The authors used a reverse micellar system containing Na_2PtCl_4 in D_2O, AOT and the substrate. CH/CD exchange occurs in the methyl groups under mild conditions (80 °C) regioselectively.

4.5.7
Perspectives

Micelles, vesicles, and other self-organized assemblies are interesting microreactors for a series of complex-catalyzed reactions. The solubilization of reactants in water, and the achievements in rate and selectivity enhancement, are sometimes unexpectedly high, but the main problem has been the separation of products, amphiphile, and catalyst after the reaction. One of the older arguments against the application of micelles is the low capacity for reactants, but there are some examples in which small concentrations of amphiphiles led to sufficient effects [83]. The challenge of catalyst recycling still remains. One solution should be the immobilization of micelle-like structures on polymers. Such polymers are well investigated and discussed as polysoaps in a series of reviews [84]. A first proposal to use polymers like micelles was made by Brown and Jenkins in 1976 [85].

For the first time Regen [86] used amphiphilic polymers in phase-transfer catalysis. Flach et al. [87] synthesized a variety of different amphiphilized polymers with organic and inorganic backbones for use in asymmetric hydrogenation. The simplest type is an admicelle [88]; this means that the surfactant (SDS) is adsorbed on alumina, thus forming a bilayer on its surface, which is stable against washing with water or other polar solvents. Best results have been observed with highly crosslinked organic ion exchange resins and inorganic ion exchanger. Polyether-surfactants bound to silica were also suitable as medium in the asymmetric hydrogenation of amino acid precursors with chiral rhodium complexes in water.

In analogy to admicelles, Milstein and co-workers [89] adsorbed the amphiphilic complex [Rh(4,4′-diheptadecyl-2,2′-bipyridine)(1,5-hexadiene)]$^+PF_6^-$ on hydrophobic or hydrophilic porous glass particles and observed a high catalytic activity and selectivity under the conditions of a Langmuir-Blodgett film for the hydrogenation of acetone in aqueous medium. The complex was almost inactive in solution.

Thus, interesting new aspects using of surfactants in aqueous complex catalysis can be found, but at present there is no industrial application. On the other hand there is still potential, worth investigating in functional surfactants (amphiphilic complexes which are useful in both polar organic solvents and water), with surfactants with large HLBs which are consequently soluble in the water phase in biphasic systems with an extremely nonpolar organic phase (e.g. in hydroformylation and telomerization processes), and finally with immobilized micelle-like polymers as outlined above. In cases of unusual effects in activity and selectivity, industrial application might be advantageous despite the costly separation process.

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4.6
On the Borderline of Aqueous-phase Catalysis

4.6.1
Phase-transfer Catalysis

Eckehard Volker Dehmlow

4.6.1.1
General Overview, Fundamentals, and Definitions

Most organic substrates are hardly soluble in water, or miscible with it, whereas the appropriate reagents may be situated in an aqueous layer. Depending on their structure, organometallic catalysts can be present in either phase. The necessary transport often causes inefficient reaction rates. As detailed in other sections, the situation may be rectified by one of the following:

- use of a solvent mixture in which all species are (somewhat) soluble,
- increasing the interfacial area by fine dispersion, rapid stirring, emulsification, ultrasonification or the like,
- application of detergents and utilization of micellar processes, or
- modification of catalyst ligands to make the active species water-soluble.

Phase-transfer catalysis (PTC) has a different approach. In its archetypical version, the chemical reaction is located in the organic phase of a two-phase mixture. A catalytic amount of a quaternary ammonium salt QX is present. Catalyst cation Q^+ transfers an anionic species Y^- from the aqueous to the organic phase via extraction as a ion pair. The resultant ionized, but undissociated, salt QY is solvated much less in the organic layer than it would be under aqueous conditions. It therefore reacts very fast, and the anion Z^- (generated in the reaction) pairs with Q^+ to be transported to the interphase for a ion exchange of Z^- for Y^-. Regenerated QY returns to the depth of the organic phase for the next reaction cycle. Altogether the action of the phase-transfer (PT) catalyst is twofold, causing anion phase transfer and activation of the anion by removal of most of the hydration shell. Typically a limited number of water molecules are co-extracted with QY into an organic phase (Eqs. 1–3).

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

$$\text{organic phase:} \quad [QY] + R\text{-}Z \longrightarrow R\text{-}Y + [QZ] \qquad (1)$$

$$\text{phase boundary:} \quad [QX] + Y^{-}{}_{(aq.)} \rightleftharpoons [QY] + X^{-}{}_{(aq.)} \qquad (2)$$

$$[QZ] + Y^{-}{}_{(aq.)} \rightleftharpoons [QY] + Z^{-}{}_{(aq.)} \qquad (3)$$

$Q^+ = NR_4^+$, PR_4^+, metal$^+$(crown), metal$^+$(cryptand)

This so-called "liquid/liquid phase-transfer catalysis" is what most chemists associate with the term: the extraction of a vital anionic species from the aqueous phase to the organic one, either by an onium salt or with the help of a crown ether or cryptand. Its application to metal organic catalysis will be described below. First it should be stressed, however, that the concept of "PTC" is much wider in scope and comprises numerous variants:

- The second phase can be a solid ("solid/liquid PTC") – or even a gas.
- Cations can be extracted from water to the organic phase by appropriate catalysts. This method is utilized in quite a number of organometallic applications.
- Various uncharged species (including metal oxides and Lewis acids) can be made organically soluble by complexation with some type of catalyst.
- Finally, extraction of the important reactive species can be executed in the opposite direction, from organic phase to water. This is called "inverse phase-transfer catalysis." Catalysts for such processes are mostly cyclodextrins or modified derivatives thereof. Relatively few applications of this type of PTC have been published. Whereas the present section is concerned only with the organic phase as the location of the proper chemical reaction, important contributions of inverse PTC toward organometallic catalysis are detailed in Section 4.6.2.

A comprehensive introduction to PTC may be found in recent monographs [1–3] and these as well as a symposium volume contain specific chapters on organometallic applications [4, 5]. Other short reviews are also available [6–8].

As stated above, anion extraction of the most common type (water to organic layer) is executed by quaternary ammonium or other onium cations or by crown-ether-masked metal cations. To be useful, at least two factors have to be met:

- The PTC cation must be sufficiently lipophilic. There is an increase in extraction constants E_{QX} (Eq. 4) of 10^{10} for any given QX when changing Q^+ from $N(CH_3)_4^+$. Tetrabutylammonium chloride or bromide, for instance, has a good balance of extractabilities for many organometallic applications.

$$E_{QX} = [\text{conc. } QX]_{org} / [\text{conc. } Q^+]_{aq} \bullet [\text{conc. } X^-]_{aq} \qquad (4)$$

- The original catalyst anion X^-, the reagent anion Y^-, and the anion Z^- generated in the reaction compete for the small catalytic concentration of Q^+ present. If Z^- is much more lipophilic than Y^- it will pair up with Q^+ and thereby encumber the catalytic effect ("catalyst poisoning"). Thus, the conversion will proceed

> properly only if the *relative* extractability of Y^- is better than that of Z^-. This condition is found in most organometallic applications. Extraction constants for many anions are tabulated in [1, 2]. These might help to get a feeling for new examples. QX values can vary by several powers of ten when Q^+ is kept constant and X^- is changed.

The kinetics of a PTC reaction can be very simple if anion transfer is fast relative to the intrinsic rate of the chemical reaction, and cases of pseudo first-order behavior are known. On the other hand, things can be very complicated if phase transfer is rate-limiting and special effects (e.g., competitive extraction, pH influences, complex stabilities, solubility limits, etc.) intervene. An extensive discussion of all possibilities and limiting rate laws has been published [1, Chapter 3].

Several fundamentally different ways of using PTC as a tool for organometallic catalysis can be distinguished, and some of these will be exemplified now with actual cases.

4.6.1.1.1
Solubilization by Complexation

Transition metal cations can be made organically soluble by complexation with a crown ether, a poly(ethylene glycol) or its dimethyl ether (an open crown) or tris(3,6-dioxaheptyl)amine (TDA-1, an open cryptand, **1**). TDA-1 is very hydrophilic and is most useful for the solubilization of solid salts. On the other hand, it also forms complexes with some metal carbonyls. Alternatively, a very lipophilic anion (for instance stearate) can make a salt "organic." Finally, some other special ligand (e.g., a bipyridine-*N*,*N'*-dioxide derivative) can be used. In all these cases positively charged species are brought into the organic phase for reaction.

$$N(CH_2CH_2OCH_2CH_2OCH_3)_3$$

1 (TDA-1)

4.6.1.1.2
Extraction of an Anionic Complex Salt

It can be shown that very many transition metal halides MX_n react with QX to form salts Q_mMX_{m+n}. For copper(I), for instance, the following simple salts and clusters have been characterized: NBu_4CuCl_2, NBu_4CuBr_2, $NBu_4Cu(CN)_2$ [9], $[NBu_4]_2Cu_2I_4$ [10], and $[MeNEt_3]_3Cu_6Br_9$ [11]. Other known ones include $NBu_4Ag(CN)_2$ [12] and NBu_4PdCl_3 [13].

Cerium(IV) presents an interesting case. The useful oxidant ceric ammonium nitrate (CAN) can be extracted from an aqueous solution as a complex salt $[NBu_4]_2[Ce(NO_3)_6]$ into hexane. Ceric ammonium sulfate, however, being a true double salt, cannot be transferred by a QX catalyst [14]. In an actual catalytic oxidation procedure, naphthalene is converted into naphthoquinone in a water/hexane two-phase system. CAN is added in a substoichiometric amount to the aqueous phase together with excess ammonium peroxidisulfate (the actual oxidant) and a small amount of $AgNO_3$ (catalyzing the reoxidation Ce(III) → Ce(IV)) and NBu_4HSO_4 (PT catalyst). The water phase is acidified by sulfuric acid, and the oxidation proceeds at 55 °C. The reoxidation of Ce(III) occurs in the aqueous layer. It should be noted that there are three catalysts present in the system altogether: CAN, NBu_4HSO_4, Ag^+. It can be shown that the process becomes still faster and more efficient when a fourth catalyst, sodium dodecylsulfate as micellar catalyst, is added [14]!

4.6.1.1.3
Catalytic Transport from Aqueous Phase

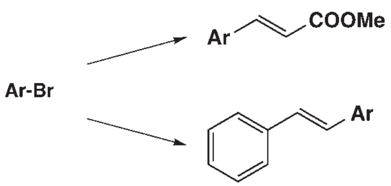
In a third mechanistic possibility the transition metal catalyst remains in the organic phase all the time and is regenerated therein. Here the PT catalyst transports a different reagent to the reactive site from the water phase. A simple case in point is the oxidation of substituted (deactivated) toluenes to benzoic acids in dichloroethane/water by hypochlorite, catalyzed by organically dissolved RuO_4. OCl^- is extracted by NBu_4^+. No oxidation occurs in the absence of the PT catalyst, and the ruthenium precipitates as black RuO_2 [15]. Numerous, more complicated examples involve the reactions of metal carbonyls. In a reduction of nitrobenzene derivatives by carbon monoxide (1 bar), for instance, the catalytic reducing species $[HRu_3(CO)_{11}]^-$ is generated from $Ru_3(CO)_{12}$ at the interphase with 5 M NaOH. The PT catalyst ($PhCH_2NEt_3Cl$, "TEBA") carries it into the depths of the organic phase [16].

These principles of phase transfer catalysis allow manyfold applications in organometallic chemistry and, indeed, numerous studies have been published. The following sections concentrate on five subfields that have come to a certain maturity but quite a few other types have been explored.

4.6.1.2
Aqueous Organic-phase Heck and Other Cross Couplings under Phase-transfer Catalysis Conditions

It has been known for some time that the addition of tetrabutylammonium bromide or chloride to Pd(0) triphenylphosphine complexes enhances their stability and activates them for reactions at the same time [17]. It was tempting therefore to use the salts simultaneously as PT catalysts. Indeed, quite a number of such organometallic reactions can be accelerated in the presence both of salts QX and of *solid* inorganic bases such as potassium carbonate (solid/liquid PTC).

Zhang and Daves reported that water-containing solvents (H_2O/EtOH, 1:1) are more effective than conventionally used solvents (DMF, acetronitrile) in certain Heck couplings of iodoheterocycles and glycals or other cyclic enol ethers in the



Scheme 1

presence of NBu_4Cl [18]. This was corroborated by Jeffery for the coupling of iodobenzene and methyl acrylate. This reaction could even be performed in neat water with 0.05 equiv. $Pd(OAc)_2$with potassium carbonate or sodium carbonate as a base and 1 equiv. of a tetrabutylammonium salt as PT catalyst. Here it did not matter whether the NBu_4 counterion was chloride, bromide, or even hydrogensulfate [19]. The reaction proceeds even in the absence of triphenylphosphine. Such purely aqueous Heck couplings are conducted at room temperature, but some authors recommend acceleration by microwave irridation [87]. The Jeffery group found, however, that even trace amounts of water brought in with the various tetrabutylammonium salts were detrimental to the same reaction when performed in DMF or acetonitrile solvents. In these cases the presence of molecular sieves as dehydrating agent was recommended [20].

Again in water as medium, styrene and acrylic acid were coupled with aryl bromides or iodides using K_2CO_3 as a base, NBu_4Br as a PT agent and $PdCl_2/P(o\text{-Tol})_3$ as an organometallic catalyst (Scheme 1). Isolated yields were mostly in the order of 70–90% [21].

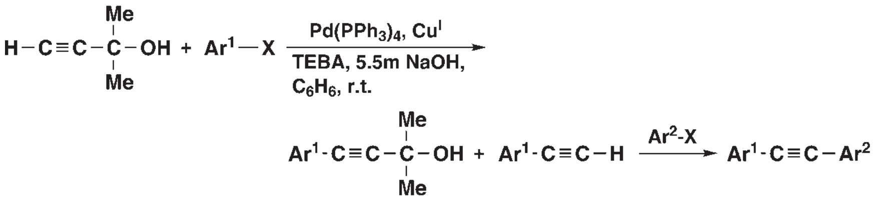
This methodology was extended very recently to the “ligandless” Suzuki type coupling of aryl bromide and substituted arylboronic acid in water [86].

Chloro- or bromoarenes undergo an Ullmann-like reductive homocoupling to the respective biphenyls in the presence of PEG-400 (PT catalyst) and a trimetallic catalyst consisting of 4% Pd, 1% Pt, and 5% Bi on carbon with either hydrogen, formate and water, or zinc and water. Simple dehalogenation, a side reaction, can be minimized (Eq. 5).

$$2\ \text{Ar-X} \xrightarrow[\text{[Cu]}]{} \text{Ar-Ar} + \text{CuX}_2 \tag{5}$$

Cross couplings of vinyl halides with alkynes to give enynes were also performed in benzene/10% aqueous sodium hydroxide in the presence of $Pd(PPh_3)_4$, CuI and TEBA at room temperature [22, 23]. This was extended to couplings of vinyl bromide and ethinyl thiophenes (Eq. 6) [24] and to the alternative combina-

(6)



Scheme 2

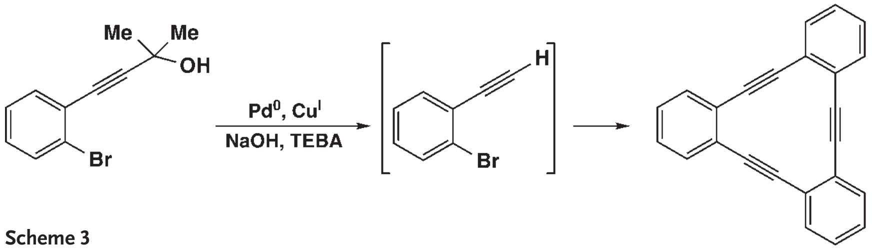
tion of 2-halothiophene and propyne [25]. The coupling of terminal alkynes and aryl halides in acetonitrile/water/NEt_3 with $Pd(OAc)_2$ and triphenylphosphine is accelerated strongly by the Pt catalyst NBu_4HSO_4 [89], Eq. (7).

$$\text{Ar-X + HC}\equiv\text{C-Ar}' \xrightarrow[\text{[M}_3\text{]}]{} \text{Ar-C}\equiv\text{C-Ar}' + \text{MX} \tag{7}$$

Rossi's group [26] pioneered a very elegant one-pot procedure for multistep couplings of two aryl or heteroaryl halides to a central acetylene unit that is partially masked in the beginning and becomes unmasked in due course: the first aryl halide is coupled with 2-methyl-3-butyn-2-ol at room temperature under PT conditions in benzene/5.5 M aqueous NaOH. TEBA is the PT agent, and a mixture of $Pd(PPh_3)_4$ and copper(I) iodide are the organometallic catalysts. The coupling product may be isolated, and the yield is often very high. More conveniently, however, the reaction mixture is charged thereafter with the second (different or identical) aryl halide and heated for up to 40 to 50 h at 80 °C. Fragmentation of acetone and a second coupling occur in moderate to good yields ([26], Scheme 2). For an experimental variant of this procedure cf. [90].

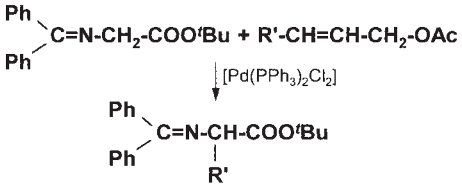
Applications of this method include among others the preparation of unsymmetrical diaryldiynes [27] and of 1,4-bis[2-(4′,4″-dialkoxyphenyl)ethenyl]benzenes for polymer [28] and liquid-crystal synthesis [29]. Such one-pot "acetylene double couplings" are also possible between (substituted) 6-bromoazalenes and substituted bromobenzenes [30], and even macrocyclic polyenepolyynes have been made in this way ([31, 32], Scheme 3).

These recently described applications deserve short special mention; (1) 2,3-disubstituted norbornenes were prepared by a three-component-one-pot coupling of



Scheme 3

aryl halides, norbornadiene, and arylacetylenes (masked in the form of alkynols as in Scheme 4) with TEBA and $Pd(PPh_3)_2Cl_2/CuI$ and aqueous NaOH [91]. (2) *N*-Diphenylmethylene)glycine *tert*.-butylester was C-alkylated with numerous allylic acetates in the presence of Pd(0), various phosphine or phosphite ligands, aqueous KOH, and PT catalysts (see Eq. 8).



$$\mathrm{Ph_2C{=}N\text{-}CH_2\text{-}COO^tBu + R'\text{-}CH{=}CH\text{-}CH_2\text{-}OAc} \xrightarrow{[\mathrm{Pd(PPh_3)_2Cl_2}]} \mathrm{Ph_2C{=}N\text{-}CH(R')\text{-}COO^tBu} \qquad (8)$$

Using chiral cinchona alkaloid derived PT catalysts (but achiral phosphines!), new amino acid derivatives were obtained in enantiomeric *ee*s up to 96% [92]. (3) The unusual coupling of four molecules sketched above was accomplished in high yield with Pd(0)/bis(dibenzylideneacetone) as metal and NBu_4Br as PT catalyst in aqueous $NaOH/CH_2Cl_2$ at room temperature.

$$\mathrm{Ar\text{-}X + HNR^1R^2} \xrightarrow[{[\mathrm{Pd(Pt[(^tBu)_3]_2]}}]{} \mathrm{Ar\text{-}NR^1R^2} \qquad (9)$$

As by-product, diynes R–C≡C–C≡C–R were formed [93]. (4) Finally, the amination of aryl bromides and chlorides with aliphatic and aromatic amines turned out to be possible in toluene/aq. KOH with $Pd(Pt[^tBu)_3]_2)$ and CTABr at 90 °C [94].

4.6.1.3
Hydrogenations Mediated by Phase-transfer Catalysts

Very convenient aqueous/organic hydrogenations can be executed at room temperature with H_2 at atmospheric pressure with rhodium trichloride and Aliquat 336 (technical-grade methyltrioctylammonium chloride). QX extracts the rhodium salt from the aqueous layer as $Q^+RhCl_4^-$. Hydrogenation occurs after an induction period. This can be shortened by pretreatment of the complex with a little H_2 and substrate before the proper hydrogenation [33]. It is believed that addition of a first substrate molecule to the rhodium takes place during this pretreatment. In the absence of the PT catalyst, metallic rhodium separates within minutes and the rate of hydrogenation is much lower. The metal complex is stabilized further by the addition of trialkylamines. The actual hydrogenation catalyst is homogeneous. It can be re-used for subsequent hydrogenations of different substrates. The structure of the active species is only speculative [34]. The extracted ion pair $Q^+RhCl_4^-$ is somewhat hydrated and, as a matter of fact, a dried solution becomes totally inactive. Deuterium labeling indicates, however, that the water hydrogen atoms do not participate in the hydrogenation [33, 34].

Extensive work showed that this methodology can be applied to many hydrogenations: alkenes or alkynes [33], substituted benzene → substituted cyclohexane [33, 34], deuterium exchange [34], selective reduction of polycyclic aromatics [35, 36], selective double-bond reduction in the presence of nitro groups (e.g., $PhCH{=}CHNO_2 \rightarrow PHCH_2CH_2NO_2$) [37], and reduction of double bonds in α,β-unsaturated esters and carbonyls [38, 39].

Rhodium(III) complexes $L_2Rh(H)Cl_2$ ($L =$ tricyclohexylphosphine or triisopropylphosphine) were also shown to be excellently suited to a PTC-mediated hydrogenolysis of chloroarenes. The solvent mixture was 40% aqueous NaOH/toluene, and TEBA was the PT catalyst. Functional groups such as OR, CF_3, COR, COOH, and NH_2 were compatible with the $C{-}Cl \rightarrow C{-}H$ process [40].

Quite a different catalyst and technique were used by Wilkinson and co-workers for the hydrogenation of benzylideneaniline in water/diethyl ether. The water-soluble complex salt $[Rh(PPh_3)_2(cod)]PF_6$ was extracted by Triton X-100, a non-ionic detergent [41].

A unique application comprises a facile hydrodehalogenation (hydrogenolysis) of aromatic compounds in 15% KOH with a heterogeneous Pd/C catalyst and Aliquat 336 as PT catalyst [42]. The latter results in a marked rate enhancement in many cases. The ease of halide removal falls from iodide through chloride to fluoride. It is believed that the lipophilic Q^+ promotes the transport of the halide ion produced, from the Pd site to the alkaline aqueous phase.

Alper's group discovered a ring hydrogenation of variously substituted aromatics and heteroaromatics at 1 bar pressure in a mixture of a buffer (pH 7.4–7.6) and hexane. Acetophenone gave acetylcyclohexane as the major product; phenol led to cyclohexanone and cyclohexanol. Use was made of the dimer of chloro(1,5-hexadiene)rhodium as metal catalyst and cetyltrimethylammonium bromide or tetrabutylammonium hydrogensulfate as PT catalyst [43]. The constituents of the buffer were not important, only the pH applied. Reactions in the absence of the PT catalysts were much slower, but it is difficult to understand their role in the reaction apart from the stabilizing effect on the metal complex catalyst.

The hydrogenation catalyst $K_3[Co(CN)_5H]$ can be prepared easily from $CoCl_2$ and KCN with gaseous hydrogen. Its stability and usefulness is improved vastly by the presence of a PT catalyst for hydrogenation in benzene/dilute aqueous NaOH. TEBA and tetramethylammonium chloride are recommended by the Reger group as catalysts [44, 45], but more lipophilic onium salts might be even better. Japanese workers use dodecyldimethyl(α-methylbenzyl)ammonium chloride [46]. The method allows transformations such as styrene → saturated ketones [44, 45], and conjugated dienes → *E*-monoenes (main products) in 1,4-additions [44, 45].

4.6.1.4
Biphasic Transfer Hydrogenations

For the simplest form of such reactions, palladium on charcoal is the catalyst and aqueous formate the hydrogen donor. Interfacial transport of formate is facilitated by an organophilic counter ion, and for the present purpose a triethylammonium ion is mostly used [48, 49].

Applications include these conversions: alkyne → *Z*-alkene [48], aromatic nitrocompound → aniline derivative [48], aromatic ketone → aromatic nitrocompound aniline derivative [48], aromatic ketone → hydrocarbon [48], and selective reduction of one nitro group in dinitroaromatic compounds [49]. A similar method was also applied for the reductive coupling of aryl halides or heteroaryl halides to yield biaryls or biheteroaryls, respectively [50, 51]. Aqueous sodium formate was used together with either a QX (cetyltrimethylammonium chloride, cetyltributylphosphonium bromide, TEBA), or a neutral or anionic surfactant instead. The alkyne → (*Z*)-alkene transfer hydrogenation was also performed with sodium phosphinate, NaH_2PO_2, as hydrogen donor, TEBA as phase-transfer agent, and Pd/C catalysts that were modified by Hg or Pb salt additions [52].

A somewhat different approach toward formate/QX transfer extraction and hydrogenation was taken by Blum and Sasson [53–56]. They started out by using $RuCl_2(PPh_3)_3$ for aldehyde → alcohol and unsaturated ketone → saturated ketone and $RhCl(PPh_3)_3$ for ketone → alcohol reductions at 20–80 °C [53–55]. A kinetic investigation showed a dependence on structure and concentration of the onium salt (among other factors). The observed activation energy suggested that the process is both chemical rate- and diffusion-controlled [54]. Hydrogenolysis of aryl bromides was possible under similar conditions with $PdCl_2(PPh_3)_2$ plus additional PPh_3 at 100 °C [56]. In these studies, the efficiency of various onium salts was compared: TEBA < PBu_4Br < NBu_4HSO_4 < Aliquat 336 < hexadecyltributylphosphonium bromide < tetrahexylammonium hydrogensulfate. Thus, the most lipophilic ammonium salt, predicted to be the best extractant for formate by phase-transfer catalysis theory, is the best suited agent.

There is yet another transfer/PTC hydrogenation method for the reduction of ketones to alcohols: here 2-propanol in dilute NaOH is the reductant, a QX is the phase-transfer agent, and $HFe_3(CO)_{11}^-$ (generated *in situ* from $Fe_3(CO)_{12}$) is the metal catalyst [57].

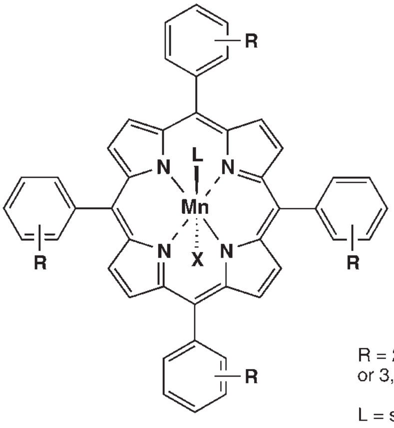
4.6.1.5
Aqueous/Organic-phase Oxidations Mediated by Metal and PT Catalysts

Aqueous hydrogen peroxide is one of the cheapest and most convenient oxidants. It can be extracted into organic media with an onium salt QX as a complex $[QX \cdots H_2O_2]$ [58]. Patents describe oxidations of alkenes in the additional presence of heavy metal oxides [59]. OsO_4, MoO_3, and H_2WO_4 give mainly *trans*-diols and epoxides; V_2O_5, Cr_2O_3, and TiO_2 lead mostly to allylic alcohols, and α,β-unsaturated ketones. Styrene can be transformed into benzaldehyde with $RuCl_3$/QX/H_2O_2 at $pH < 4$ [60], and the side chains of aromatics are oxidized to ketones or tertiary alcohols under similar conditions [61]. In these experiments, the PT catalyst has a threefold role: extraction of both H_2O_2 and $RuCl_3$, and stabilization of Ru(III) against reduction. When the ratio QX/$RuCl_3$ is less than 8:1, metallic ruthenium is precipitated. Aqueous *tert*-butyl hydroperoxide can be used as a cheap oxidant in conjunction with $CuCl_2$, CuCl or even powdered copper, and a PT catalyst (NBu_4X) for allylic and benzylic substrates. Alcohols give ketones or aldehydes, and hydrocarbons yield mixed *tert*-butyl peroxides as main products in most cases. The PT catalyst is thought to extract intermediate Cu(OH)Cl [95].

The situation becomes quite different when hydrogen peroxide is used to generate certain peroxo anions. As a matter of fact, many information exists on oxidations by aqueous H_2O_2 with homo- or hetero-polyanion redox carriers and a QX as carrier cation source. The anions ($PMo_{12}O_{40}^{3-}$; $PW_{12}O_{40}^{3-}$; $PW_4O_{16}^{3-}$; $Mo_7O_{24}^{6-}$; $PNiW_{11}O_{39}^{5-}$; SiRu $(H_2O)W_{11}O_{39}^{5-}$ and others) are formed *in situ* in some cases; in others they are brought into the reaction mixture as previously prepared catalyst salts. They are oxidized to peroxo anions in the aqueous layer (or at the interphase) prior to extraction.

The relevant literature in this subfield is too voluminous to be detailed here. Overviews are available [62], and only a few recent references to the newest publications are given below. Oxidations of the following types have been performed: alcohol → ketone [63]; aldehyde → acid; alkene → diol or epoxide [64–67]; alkene → aldehyde, acid; 1-alkyne → ketoaldehyde and acid (1 C-atom shorter); internal alkyne → α,β-epoxyketone; vic-diol → 1,2-diketone [68] or hydroxyketone [69]; amine → amine oxide [70]; aromatic amine → nitrosobenzene, nitrobenzene, azoxybenzene [71].

Aqueous sodium hypochlorite is another low-priced oxidant. Very efficient oxidative systems were developed which contain a *meso*-tetraarylporphyrinato-Mn(III) complex salt as the metal catalyst and a QX as the carrier of hypochlorite from the water phase to the organic environment. These reactions are of interest also as cytochrome *P*-450 models. Early experiments were concerned with epoxidations of alkenes, oxidations of benzyl alcohol and benzyl ether to benzaldehyde, and chlorination of cyclohexane at room temperature or 0 °C. A certain difficulty arose from the fact that the porphyrins were not really stable under the reaction conditions. Several research groups published extensively on optimization, factors governing catalytic efficiency, and stability of the catalysts. Most importantly, axial ligands on the Mn porphyrin (e.g., substituted imidazoles, 4-substituted pyridines and their *N*-oxides), **2** increases rates and selectivities. This can be demonstrated most impressively with pyridine ligands directly tethered to the porphyrin [72]. Secondly, 2,4- and 2,4,6-trihalo- or 3,5-di-*tert*-butyl-substituted tetraarylporphyrins are more stable. Thirdly, the pH has a strong influence: at pH 12.7 only QOCl (extracted from the aqueous phase with Aliquat 336, for instance) is present as primary oxidant in the organic medium. At pH 9.5–10.5, however, HOCl is the oxidizing species in the nonaqueous environment. The reaction proceeds in this case without the presence of a phase-transfer catalyst [73]. Under optimal conditions the reactions can be over after a few minutes at 0 °C. Iron porphyrins proved to be less active for the present purpose. Regio- and stereochemistry of the Mn porphyrin/PT catalyst-mediated epoxidations of dienes and terpenes differed from those found for the epoxidation methods. A certain influence of the nature of the axial ligand on reaction results was also observed [74–76]. The actual oxidant is considered to be a Mn(V) oxo species, but the rate-determining step is still in doubt. Overviews of the extensive literature are available [2, 3, 77].



R = 2,4-dihalo or 2,4,6-trihalo
or 3,5-di-tert-butyl

L = substituted imidazole or pyridine

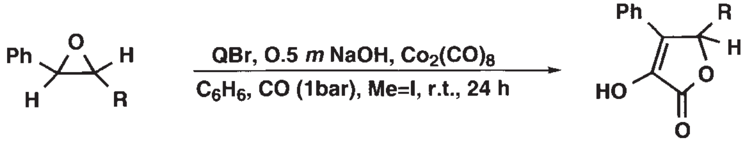
2

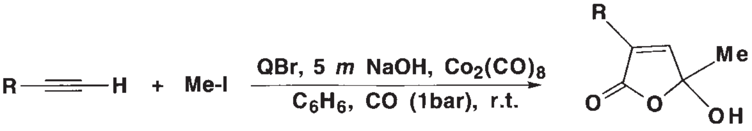
Potassium hydrogenperoxysulfate has been used alternatively to hypochlorite as primary oxidant in phosphate buffer (pH 6–7)/dichloromethane with the Mn porphyrin/tetraalkylammonium chloride system at room temperature. Very fast alkene epoxidations and hydroxylations of hydrocarbons (cyclohexane, adamantane, decalins, etc.) were observed. Methoxybenzenes were also oxidized [78].

4.6.1.6
Aqueous/Organic-phase Carbonylations

Carbonylations of a great many different compounds have been performed by CO, a catalytic amount of various metal carbonyls, 0.3–6 M NaOH, and a phase-transfer catalyst. Typical reactions occur at atmospheric pressure and often at room temperature. The literature in this field is very voluminous, but more or less extensive overviews are available up to the early 1990s [1–4, 6, 7], and further results are emerging continuously.

$$\text{Ar-X} + \text{Me-I} \xrightarrow[\text{C}_6\text{H}_6\text{, CO (1bar), 20 h, r.t.}]{\text{QBr, 50\% NaOH, Co}_2\text{(CO)}_8} \text{Ar-COOH} + \text{Ar-CO-Me} \qquad (10)$$


(11)


(12)

Benzyl, allyl, vinyl, and aryl, but also some aliphatic, halides have been transformed into carboxylic acids (Eq. 10). Under other conditions, couplings with CO to give symmetrical or unsymmetrical ketones were possible. Epoxides yielded unsaturated hydroxy acids, and α-oxo-butyrolactones (Eq. 11), couplings of alkynes and alkyl halides gave hydroxybutenolides (Eq. 12) and other more complex conversions could also be realized.

The carbonylation of a benzyl halide in the presence of iron pentacarbonyl to give a phenylacetic acid may serve to exemplify the interaction of a metal carbonyl, carbon monoxide, PT catalyst, aqueous sodium hydroxide, and the substrate [79]. $Fe(CO)_5$ is attacked by QOH at the interphase, and the species formed is extracted into the depths of the oganic phase, where it reacts with CO and benzyl halide (Eqs. 13 and 14). This new anion **3** is the actual catalyst. It reacts with a second benzyl halide to give a non-ionic intermediate **4** (Eq. 15). By insertion of CO and attack of QOH, **4** is decomposed to the reaction product under regeneration of **3** (Eq. 16). Thus, the action of the PT catalyst is twofold. Firstly it transports the metal carbonyl anion. More important seems to be its involvement in the (rate-determining) decomposition step. A basically similar mechanism was proposed for cobalt carbonyl reactions [80], which have been modified somewhat quite recently (see below).

Most published PT-assisted carbonylation reactions were executed with $Co_2(CO)_8$, others with $Fe(CO)_5$ as indicated above, or with $Ru_3(CO)_{12}$, Pd complexes, $Ni(CN)_2$,

$$\text{Fe(CO)}_5 + 2\,\text{QOH} \longrightarrow \text{Q}_2[\text{Fe(CO)}_4] + \text{CO}_2 + \text{H}_2\text{O} \qquad (13)$$

$$\underset{\mathbf{2}}{\text{Q}_2[\text{Fe(CO)}_4]} + \text{CO} + \text{ArCH}_2\text{X} \longrightarrow \underset{\mathbf{3}}{\text{Q[ArCH}_2\text{–CO–Fe(CO)}_4]} + \text{QX} \qquad (14)$$

$$\text{Q[ArCH}_2\text{–CO–Fe(CO)}_4] + \text{ArCH}_2\text{X} \longrightarrow \underset{\mathbf{4}}{\text{ArCH}_2\text{–CO–Fe(CH}_2\text{R)(CO)}_4} + \text{QX} \qquad (15)$$

$$\text{ArCH}_2\text{–CO–Fe(CH}_2\text{R)(CO)}_4 + \text{QOH} + \text{CO} \longrightarrow \text{ArCH}_2\text{COOH} + \text{Q[ArCH}_2\text{COFe(CO)}_4] \qquad (16)$$

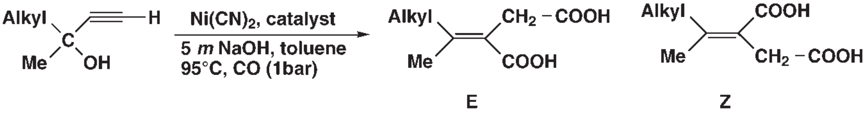
and cobalt salts. The catalytically active species $Q[Ni(CN)(CO)_3]$ generated from nickel cyanide is much less hazardous than the very poisonous nickel carbonyl itself.

Research trends of the last few years highlight applications to more involved systems either from the substrate/product side or from the catalyst side. Furthermore, a deeper insight into underlying mechanism is intended. Thus, reductive carbonylation of dibromocyclopropanes was performed in toluene/5 M KOH with syngas (CO/H_2, 3 : 1) at elevated temperature (90 °C) using a mixture of $CoCl_2$, KCN, and $Ni(CN)_2$ for the metal catalyst and PEG-400 as PT catalyst which was much more efficient than a quaternary ammonium catalyst [81]. 1,1-Dibromo-2-phenylcyclopropane furnished a 72% yield of 2-phenylcyclopropanecarboxylic acid (1 : 1 *cis*/*trans* mixture).

The same set of metal and PT catalyst and reaction conditions was used for a reductive carbonylation of 1-alkynes giving mostly branched acids [82] (Eq. 17).

$$\text{R–C} \equiv \text{C–H} \longrightarrow \text{R–CH(CH}_3\text{)–COOH} \qquad (17)$$

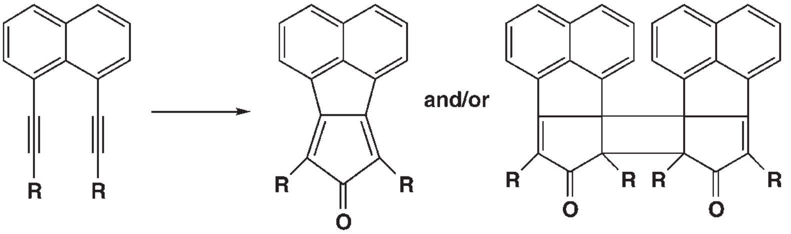
Poly(ethylene glycol)s (PEGs) substitute for onium salts as PT catalysts occasionally. There are cases where yields vary with the catalyst, but in one reaction the stereochemical outcome is influenced: nickel cyanide catalyzes double insertion of CO into alkynols (5 M NaOH, 95 °C) furnishing the acids shown in Eq. (18). When a NR_4X is the PT agent, the major products have *Z* geometry, and if PEG-400 is present, *E* geometry prevails [83].



Catalyst:		E	Z
	NR_4X	5–15%	85–95%
	PEG-400	65–90%	10–35%

(18)

Again using PEGs as PT catalysts, the Alper group reinvestigated the carbonylation of benzyl halides in the presence of $Co_2(CO)_8$. They were able to characterize and investigate η^1-benzyl, η^3-benzyl, and (η^1-phenylacetyl) cobalt carbonyls as intermediates, and arrived at an elaborate mechanistic cycle [84].



(19)

Another recent development is the preparation of polycycles that are difficult to make, by utilizing the extraction of rhodium chloride from water with Aliquat 336 for reductive ring-forming carbonylations (Eq. 19) [85].

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4.6.2
Counter-phase Transfer Catalysis

Tamon Okano

4.6.2.1
Introduction

The phenomena accompanying interphase transfer of chemical materials are universally observed in biological systems. A number of carriers and various transportation methods are used and the selective transportation of materials contributes to controlling the biochemical reactions *in vivo*. In synthetic chemistry, however, the carriers as well as the methods are very limited. Phase-transfer catalysts (PTCs; cf. Section 4.6.1) such as crown ethers or onium salts are limited to the transportation of anions from an aqueous or solid phase into an organic phase; nevertheless, the PTCs contributed to the development of synthetic chemistry. The most important point is that these catalysts have enabled the biphasic reactions of lipophilic molecules with inexpensive inorganic salts and at the same time facilitated the separation of products.

Use of inorganic salts and easy separation are also important problems in catalytic reactions involving transition metal complexes. It is well known that the PTCs greatly accelerate the organic reactions catalyzed by anionic metal complexes which are water-soluble, owing to their easy extraction [1, 2] (Figure 1). However, the most important transition metal catalysts in homogeneous system consist of phosphine complexes, which are commonly lipophilic. Altough PTCs are applicable to such catalytic reactions of hydrophobic substrates with inorganic salts [2a], they have no effect on the separation of the phosphine complexes and the products.

New tools for such biphasic reactions are inverse- or counter-phase transfer catalysts, which are able to transport lipophilic molecules from the organic phase into the aqueous phase. An advantage of the inverse- or counter-PTC is its applicability to reactions not only with ionic salts but also with non-ionic reagents soluble in water. Such carriers were first reported by Mathias and Vaidya and by us in 1986 [3, 4], and three types of carriers are known at present. Mathias and Vaidya found that pyridine derivatives react with acid halides in the organic phase to form the pyridinium salts, which transfer into the aqueous phase [3]. This catalysis was

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

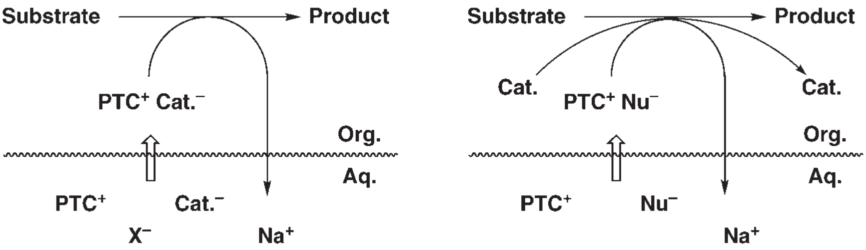


Fig. 1 Mechanisms for metal-catalyzed reactions using phase-transfer catalysts: phase-transfer catalyst and anionic metal catalyst (left); phase-transfer catalyst and lipophilic meta catalyst (right).

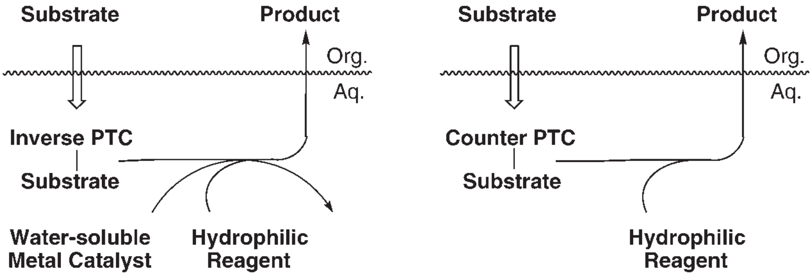
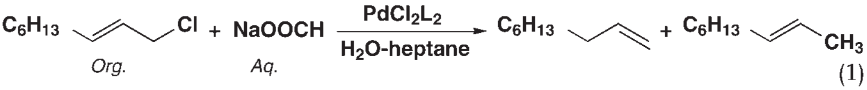


Fig. 2 Mechanisms for inverse- and counter-phase transfer catalyses: mixed system of inverse PTC and water-soluble metal catalyst (left); counter-phase transfer catalyst (right).

named "inverse-phase transfer catalysis". As catalysis of this type, i.e., pyridine derivatives [5] and sulfides [6], are able to transport only alkyl and carboxylic acid halides, their application to organometallic reactions has not been reported.

The other type of inverse-PTCs are cyclodextrins, which are capable of forming water-soluble inclusion compounds with organic molecules with their lipophilic cavities. Owing to the absence of limitations of the functional groups of organic substrates on this transportation, the cyclodextrins are applicable to biphasic reactions using water-soluble metal catalysts (Figure 2). For example, Wacker oxidations [7, 8], deoxygenations [9, 10], and hydroformylations [11, 12] have been reported. However, inhibition of the catalytic activity due to complexations of metal catalysts with cyclodextrins is observed in some cases [8, 9, 11]. Another defect is a steric limitation on the transportation of the substrates due to the cavity size.

The inverse-PTCs with no steric limitations are hydrophilic phosphine complexes, which are able to transport the lipophilic substrates capable of forming complexes with transition metals. These hydrophilic phosphine complexes differ essentially from the other inverse-PTCs in that they have the functions of both inverse-PTCs and transition metal catalysts by themselves. Therefore we named these catalysts "counter-phase transfer catalysts" [4].



(1)

Tab. 1 Reduction of an allyl chloride (Eq. 1).

Catalyst	*Yield [%]*	
	$C_6H_{13}CH_2CH{=}CH_2$	$C_6H_{13}CH{=}CHCH_3$
1	82	17
$PdCl_2[P(n\text{-}Bu)_3]_2$	20	3

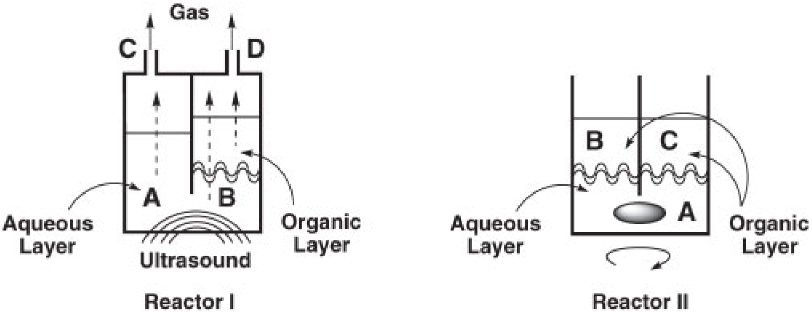
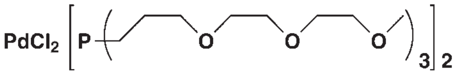


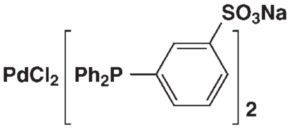
Fig. 3 Partitioned reactors.

4.6.2.2
Mechanism of the Counter-phase Transfer Catalytic Reaction

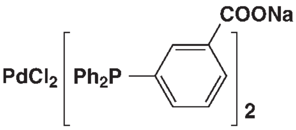
It is difficult to verify the counter- or inverse-phase transfer catalysis strictly, because the catalyst more or less acts as a surfactant as well as a normal PTC [13]. However, it should be a positive proof of the counter-PTC to ascertain that the aqueous phase is where the products are formed.



1



2

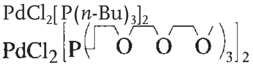


3

The reduction of allyl chlorides and acetates with sodium formate is efficiently catalyzed by hydrophilic phosphine complexes (Structures **1**–**3**) under water–hep-

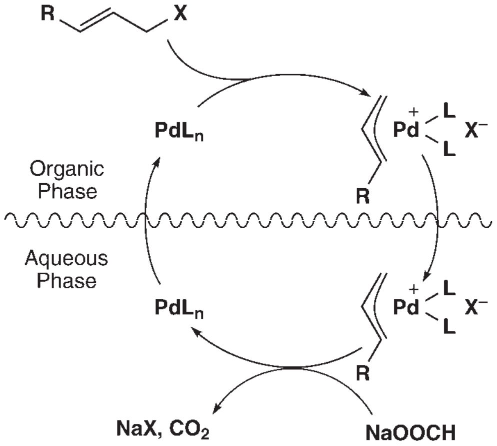
$$\underset{\textit{Org.}}{\mathrm{CH_2{=}CHCH_2OAc}} + \underset{\textit{Aqu.}}{\mathrm{NaOOCH}} \xrightarrow[\mathrm{H_2O\text{-}Heptane}]{\mathrm{PdCl_2L_2}} \underset{\mathrm{Gas}}{\mathrm{CH_2{=}CHCH_3}} \uparrow \qquad (2)$$

Tab. 2 Conversion of allyl acetate (Eq. 2).

Catalyst	*Yield of C_3H_6 [%]*	*Source of C_3H_6 [aq.:org.]*
$PdCl_2[P(n\text{-}Bu)_3]_2$	38	12:88
	55	98:2

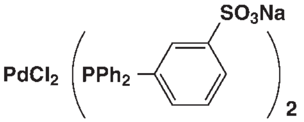
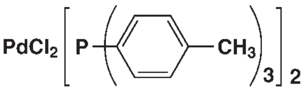
tane two-phase conditions [4]. The catalytic activity of **1** is higher than that of $PdCl_2(PBu_3)_2$ (see Eq. (1) and Table 1). In order to ascertain the phase where the product is formed, the reduction of allyl acetate to form gaseous propene was carried out in a partitioned reactor as shown in Figure 3 (Reactor I). Part A is charged with an aqueous solution of catalyst and sodium formate, and a heptane solution of allyl acetate is placed in part B. The propene gas evolved from part A of the aqueous layer is collected from outlet C, and the gas from the heptane layer, the interface, and part B of the aqueous layer is collected from outlet D. As the volume ratio of the aqueous solution in part A to that in part B is known, the amount of gas from each phase can be calculated. Reduction with a hydrophobic catalyst, $PdCl_2(PBu_3)_2$, causes evolution of the gas mostly from the heptane layer and/or the interface, whereas reaction with **1** leads to propene gas evolution mostly from the aqueous layer (see Eq. (2) and Table 2).

Though the polyether phosphine is capable of acting as a normal PTC [14], this result indicates that the hydrophilic complex transports the allyl acetate from the heptane phase into the aqueous phase and catalyzes the reduction to propene with sodium formate in the aqueous phase [4] (see Scheme 1).



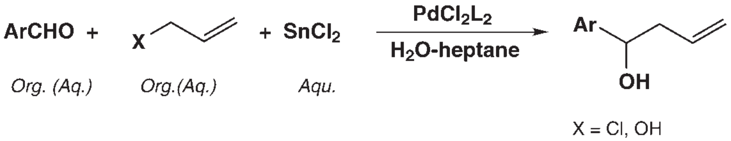
Scheme 1

Tab. 3 Biphasic allylation of aldehydes with allyl compounds and $SnCl_2$.

Catalyst[a]	*Aldehyde*	*Allyl compound*	*Yield [%]*
	PhCHO	$CH_2{=}CHCH_2Cl$	98
	PhCHO	$CH_2{=}CHCH_2OH$	98
	p-$NaOOCC_6H_4CHO$	$CH_2{=}CHCH_2Cl$	95
	p-$NaOOCC_6H_4CHO$	$CH_2{=}CHCH_2OH$	93
	PhCHO	$CH_2{=}CHCH_2Cl$	5
	PhCHO	$CH_2{=}CHCH_2OH$	17
	p-$NaOOCC_6H_4CHO$	$CH_2{=}CHCH_2Cl$	16
	p-$NaOOCC_6H_4CHO$	$CH_2{=}CHCH_2OH$	8

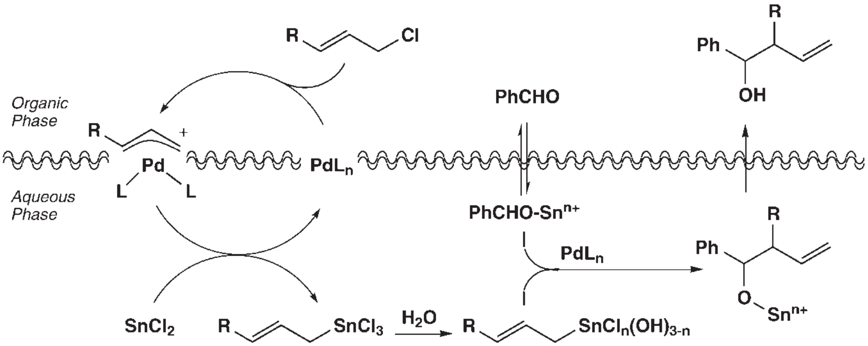
[a] $PdCl_2L_2$ (0.1 mmol): $PhCHO:CH_2{=}CHCH_2Cl:SnCl_2 = 1:100:200:300$, H_2O (10 mL), heptane (10 mL), 35 °C, 7 h.

Palladium-catalyzed allylation of aldehydes with allyl compounds and stannous chloride in DMF or DMSO (Table 3) is a synthetically important reaction [15]. However, the normal PTCs might be inefficient for this class of reaction, because it is difficult to transport stannous chloride. The use of $PdCl_2(TPPMS)_2$ (**2**) enables us to achieve the carbonyl allylation under biphasic conditions [16]. Though **2** does not function as a normal PTC, its reactions give the allylated products in excellent yields even in a heptane–water two-phase system (see Table 3). One of the palladium-requiring steps in this allylation is the reaction of allyl compounds with stannous chloride to form allyl stannic compounds [15]. In the absence of aldehyde, the consumption rate of allyl chloride in the heptane phase is much faster in the reaction with **2** than with $PdCl_2\{P(p\text{-}C_6H_4CH_3)_3\}_2$. This result suggests that the high efficiency of the hydrophilic catalyst is attributed to the fast transfer of allyl chloride from the organic phase into the aqueous phase via a hydrophilic π-allyl–palladium complex. In the presence of bentaldehyde (in part B, Figure 3), the carbonyl allylation with allyl chloride (in part C) in the partitioned Reactor II gives about half of the product in part B and another half in part C. This result indicates that the product is not formed in the organic phase or the interface but in the aqueous phase. The proposed mechanism for the carbonyl allylation is depicted in Scheme 2.



(3)

The counter-phase transfer catalysis via π-allyl–palladium complexes exhibits an unusual solvent effect [16]. Both the reduction with sodium formate and the car-



Scheme 2

bonyl allylation are faster in heptane than in toluene or anisole, whereas the efficiency of normal PTCs is generally higher in polar organic solvents than in nonpolar solvents. This inverse solvent effect is probably ascribed to a faster transfer of the π-allyl–palladium complexes from the heptane phase into the aqueous phase than that from the toluene or anisole phase. The use of nonpolar solvents is favorable for the separation of catalysts.

4.6.2.3
Counter-phase Transfer Catalytic Reactions

The biphasic reactions are essentially slow compared with the homogeneous reactions. However, some of the slow biphasic reactions are considerably improved by the use of the counter-PTCs, keeping the advantage of easy separation of the catalysts.

The biphasic carboxylation of allyl halides with NaOH and CO (Eq. 4) is quite fast even in the absence of PTCs; nevertheless, the use of normal or counter-PTCs is beneficial to the reaction [17, 18]. The selectivity as well as the reactivity is improved by the use of **2** instead of $PdCl_2(PPh_3)_2$ in the biphasic carboxylation of cinnamyl chloride [19]. The solvent effect on the carboxylation with **2** is analogous to those on the reduction of allyl compounds and the carbonyl allylation as shown in Figure 4 [16]. The carboxylation in toluene or in chloroform forms considerable amounts of the dimer (**7**) (Table 4). The initial CO absorption rate in dioxane is the fastest, but large amounts of cinnamyl alcohol and the ether (**6**) are formed. This fact indicates that simple nucleophilic substitutions occurred significantly in a solvent that was miscible with water like dioxane. Though the carboxylation of cinnamyl chloride forms various products, simple acidification of the separated aqueous solution, which contains the sodium carboxylate and the catalyst, gives almost pure cinnamic acid, because the sulfonated phosphine complex is soluble even in the acidic aqueous solution.

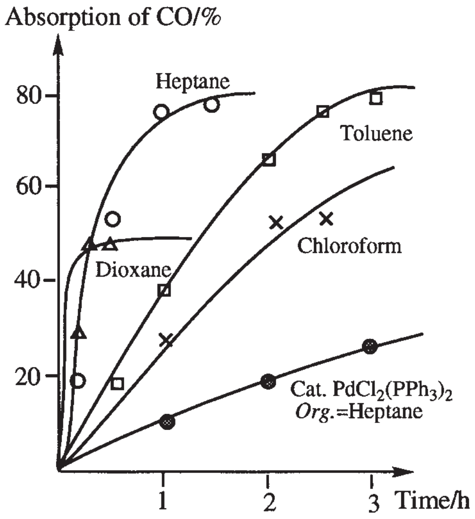
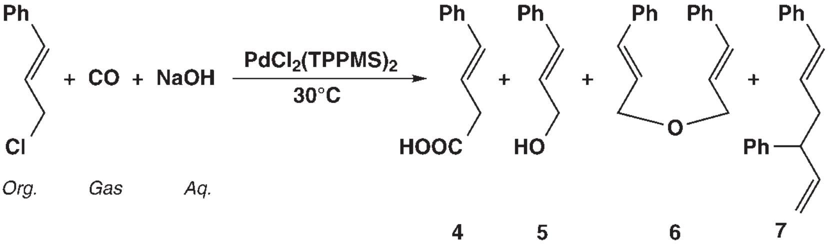


Fig. 4 Rate of CO absorption for carboxylation of cinnamyl chloride.

Tab. 4 Biphasic carboxylation of cinnamyl chloride with CO and NaOH.

Organic phase	*Time [h]*	*Conversion [%]*	*Yield [%]*		
			4	*5 + 6*	*7*
Heptane	1.5	83	57	18	25
Toluene	4	95	53	7	40
Chloroform	2.5	95	40	18	40
Dioxane	0.5	66	40	45	15

$PdCl_2\{PPh_2(m\text{-}C_6H_4SO_3Na)\}_2$ (0.05 mmol) : $PhCH_2{=}CHCH_2Cl$: NaOH = 1 : 100 : 1000, heptane (10 mL), H_2O (50 mL).



(4)

The hydrophilic palladium complex (**2**) was also a good catalyst for the carboxylation of benzyl halides under heptane–water two-phase conditions [20]. Benzyl chloride and bromide give phenylacetic acid in high yields under mild conditions (Eq. 5). However, the biphasic carboxylation with $PdCl_2(PPh_3)_2$ is very slow, and gives a considerable amount of benzyl alcohol. The addition of a normal PTC such as Bu_4NBr improves the catalytic activity of $PdCl_2(PPh_3)_2$ [16, 21]. However, the acceleration effect is poor, and the normal PTC is ineffective in retarding the formation of benzyl alcohol. Though the carboxylation with $PdCl_2(PPh_3)_2$ in ethanol is very fast, a large amount of benzyl alcohol is formed by the nucleophilic substitution. These results indicate that the water-soluble transition metal complex is very effective in retarding non-metal-catalyzed side reactions of organic substrates susceptible to nucleophilic substitution.

$$\mathrm{PhCH_2X + CO + NaOH \xrightarrow{PdCl_2(TPPMS)_2} PhCH_2COOH} \tag{5}$$

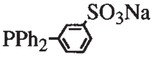
The biphasic carboxylation shows an unexpected induction period. Interestingly, the addition of sodium phenylacetate shortens the induction period, and at the same time accelerates the reaction rate [22]. The other additives, such as sodium heptanesulfonate, Bu_4NBr, and $n\text{-}C_{18}H_{35}(OCH_2CH_2)_7OH$, are also effective. As the carboxylate and the sulfonate do not have the function of a normal PTC, these may as surfactants. The surfactants, however, have no effect on the reaction with the lipophilic catalysts $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$, suggesting that they do not act on the benzyl halides but on the hydrophilic catalyst.

Aryl iodides can also be carboxylated with NaOH and CO at atmospheric pressure in the presence of **2** under biphasic conditions, and give aryl carboxylic acids in high isolated yields [16] (Eq. (6) and Table 5). The normal PTCs are not very effective in accelerating the carboxylation [23]. This may be ascribable to the poor extractability of hydroxy anion [24].

$$\mathrm{PhI + CO + NaOH \xrightarrow[H_2O\text{–}organic\ solvent]{PdCl_2L_2} PhCOOH} \tag{6}$$

It is well known that the normal PTCs are effective for the biphasic cyanation of aryl halides with cyanide salts using hydrophobic catalysts [25]. However, a simple application of hydrophilic catalysts results in failure. The cyanation with **2** requires

Tab. 5 Biphasic carboxylation of phenyl iodide catalyzed by $PdCl_2L_2$.

L	*Organic phase*	*Isolated yield [%]*
	Heptane	88
	Toluene	84
	Anisole	81
	Dioxane	90
	Heptane	5
	Anisole	2
	Anisole + Bu_4NBr (1 mmol)	24

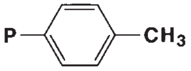
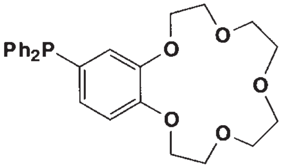
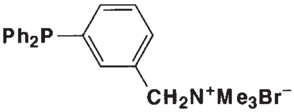
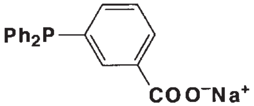
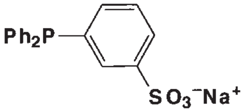
$PdCl_2L_2$ (0.1 mmol) : L : PhI : NaOH = 1 : 5 : 100 : 250, CO (1 bar), H_2O (10 mL), organic solvent (10 mL), at 50 °C for 4 h.

$NaBH_4$ and zinc chloride (Eq. 7) [16]. These additives are necessary for reduction of the catalyst precursor and for prevention of deactivation of the catalyst by excess cyanide anion in the aqueous phase, respectively. As the use of zinc chloride in a Zn/CN molar ratio of more than 0.25 : 1 is required, the active cyanide source may be tetracyanozincate or zinc cyanide [26]. The efficiency of the counter-PTC in the heptane–water system exceeds that of the mixed catalyst system of lipophilic catalyst and normal PTC, though the cyanide anion is easily extractable by the normal PTCs (Table 6).

$$\mathrm{ArI} + \mathrm{NaCN} \xrightarrow[\mathrm{ZnCl_2{-}NaBH_4}]{\mathrm{PdCl_2(TPPMS)_2}} \mathrm{ArCN} \tag{7}$$

Carboxylated phosphine complex **3** is active for the cyanation, though this hydrophilic complex is inferior to **2** as a counter-PTC. As the cyanide anion is easily extractable, a phosphine complex having an ammonium group or a crown ether, which is insoluble in water [27], is also efficient for the cyanation. The catalytic efficiency is higher than that of the mixed system of lipophilic catalyst and normal

Tab. 6 Biphasic cyanation in the presence of various phosphine complexes.

Phosphine (L)	*Catalyst*[a]	*Additive*	*PhCN [%]*
	$PdCl_2L_2$	$NaBH_4$	0
	$Pd_2(dba)_3$ – 4 L	Bu_4NBr (1 mmol)	4
	$Pd_2(dba)_3$ – 4 L	n-$C_7H_{15}SO_3Na$ (1 mmol)	1
	$PdCl_2L_2$	$NaBH_4$	1
	$Pd_2(dba)_3$ – 8 L		25
	$PdBr_2L_2$	$NaBH_4$	12
	$Pd_2(dba)_3$ – 8 L		24
	$PdCl_2L_2$	$NaBH_4$	22
	$PdCl_2L_2$	$NaBH_4$	99

[a] $PdCl_2L_2$ (0.2 mmol) – $NaBH_4$ (0.4 mmol) or $Pd_2(dba)_3 \cdot CHCl_3$ (0.1 mmol) – L (0.4 mmol), NaCN (13 mmol), $ZnCl_2$ (5 mmol), heptane (10 mL), water (10 mL), reflux, 1 h.

PTC, owing to the proximity effect caused by the conjunction of metal catalyst and normal PTC. However, the hydrophilic complexes are superior to the doubly functional catalysts in the cyanation.

4.6.2.4
Concluding Remarks

Although the highly water-soluble catalysts such as polysulfonated phosphine complexes have the advantage of easy separation of catalyst from products, these catalytic reactions, especially using highly lipophilic substrates, are not so fast as in homogeneous systems [28, 29]. To improve the catalytic efficiency, the addition of inverse-PTCs, surfactants [30], and co-solvents [31] has been attempted. However, these additives are not beneficial to the separation. Recently, some of the water-soluble phosphine complexes with reduced hydrophilicity, including amphiphilic catalysts (see Section 7.4), have been recognized to be more effective than the highly hydrophilic catalysts. These low-hydrophilicity complexes are still easily and satisfactorily separable from the biphasic reaction mixtures [29, 32, 33]. Several mechanisms for these reactions have been proposed.

Biphasic hydroformylation with Rh-TPPTS (cf. Section 6.1) catalyst is markedly enhanced by the addition of PPh_3. The proposed mechanism is that the promoter ligand binds to the highly water-soluble catalyst, thereby increasing the catalyst concentration at the interface [29]. The use of phosphines having long alkyl chains and ionic groups also shows improved rates for the hydroformylation of liquid olefins [8, 32–35]. As sulfobetaine derivatives of tris(2-pyridyl)phosphine are surface-active, the high efficiency of their complexes is interpreted in the same way [32]. Some emulsification is observed in the biphasic hydroformylation using carboxylated phosphines, $PPh_2(CH_2)_nCO_2Na$ [33]. Dynamic light-scattering experiments show that sulfonated phosphines, $P[C_6H_4(CH_2)_n\text{-}p\text{-}C_6H_4SO_3Na]_3$, aggregate in aqueous salt solutions, though no stable emulsion is formed under biphasic reaction conditions [35]. The measured hydrodynamic radius for the catalyst solution is consistent with isolated molecules of the Rh–phosphine complex. The authors speculate that the two ligands of the Rh complex can mimic a small micelle which provides a hydrophobic pocket for binding olefins near the Rh center. The sulfonated phosphines TPPMS [33] and TPPTS [35] do not form emulsions. In the counter-phase transfer catalytic reactions as mentioned above, obvious emulsification is not seen.

The aim of the most studies on the water-soluble phosphines is to find separable, active, and selective catalysts. The water-soluble catalysts are additionally useful for the reactions of hydrophobic substrates with inorganic salts. So far, amphiphilic solvents or mixed catalyst systems of normal PTCs and normal transition metal complexes have been used for some reactions. Though the mixed system enables the easy separation of inorganic salts from the reaction mixture, the separation of the metal catalyst is still difficult. Another problem of the mixed system is its slow rates, especially in reactions with poorly extractable anions such as the hydroxy anion. In the mixed system, the activated intermediate formed from an organic substrate and a metal complex reacts with the anionic reagent extracted by a normal PTC in the organic phase (see Figure 1). The concentrations of both species are ordinarily low, depending on the amounts of both catalysts, the reactivity of the metal catalyst, and the extractability of the anion. These conditions result in slow reaction rates and serious noncatalytic side reactions owing to a higher concentration of the substrate than that of the activated intermediate in the organic phase. These defects are diminished by means of chemical modification of the phosphine ligand with crowns or onium groups. However, neither the chemical binding nor the simple addition of phase-transfer catalysts has an effect on the separation of catalysts and products.

In such reactions as are described above, the counter-PTCs exhibit high efficiency and high selectivity, which arise from the concerted performance of their double function as an inverse-PTC and as a metal catalyst. The high efficiency is ascribed to the absence of any unnecessary transportation of substrates, because the carrier molecule itself is the metal catalyst. All of the transported substrates are able to react with reagents in the aqueous phase. The high selectivity is attributed to the specified transportation of the activated substrates by the metal catalyst from the organic phase into the aqueous phase in which the nucleophiles exist. The specific transportation is very effective in retarding the side reactions of any organic substrates susceptible to nucleophilic substitution, such as allyl halides and benzyl halides. The most important advantage is the easy separation of catalyst and products. Even if the product and the catalyst both exist in the aqueous layer, the product could be isolated, because the sulfonated phosphine complexes as well as polyether complexes have a high affinity for water over a wide range of pH. It is also beneficial to the separation that the catalytic efficiency of the counter-PTCs is higher in nonpolar solvents than in polar solvents.

Although counter-phase transfer catalysis has not yet attracted much attention, it is a very promising method for solving some of the problems of organometallic catalyses. Since transition metal complexes are capable of interacting with a wide variety of organic compounds, great development of counterphase catalysis is expected.

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4.6.3
Thermoregulated Phase-transfer and Thermoregulated Phase-separable Catalysis

Zilin Jin, Yanhua Wang, Xiaolai Zheng

4.6.3.1
Introduction

Over the past decade, increasing interest has been focused on the chemistry of water-soluble transition metal complexes and two-phase catalysis [1, 2]. One reason for this is the stimulating introduction of triphenylphosphine trisulfonate (TPPTS) and aqueous/organic two-phase systems to the rhodium-catalyzed hydroformylation of propene in Ruhrchemie/Rhône–Poulenc's process in 1984 [3]. However, the use of water as the second phase suffers from its drawbacks, especially when the water-solubility of the organic substrates proves too low. In this case, an undesirable reaction rate may arise due to a severe mass-transfer phenomenon. A variety of tentative approaches, including the addition of cosolvents, surfactants [4, 5], or "promoter ligands" [6], and the design of a "fluorous biphase system" (FBS) [7] and its variation [8], have been reported in order to ensure that the hydroformylation of extremely water-immiscible higher olefins may be smoothly carried out in the two-phase system. From the view-point of industrial development, however, the utilization of "foreign additives" will inevitably increase the difficulty of product separation, yet FBS would have to deal with the possible environmental impact of fluorinated solvents being employed.

Over the past few years, a novel catalytic system based on the nonionic water-soluble phosphine-modified rhodium complexes has been successfully applied to the aqueous/organic two-phase hydroformylation of higher olefins [9, 10]. With polyoxyethylene chains as the hydrophilic group in the molecular structure, the ligands demonstrate a special property of inversely temperature-dependent water-solubility similar to that of the nonionic surfactants. As a result, the rhodium catalysts are soluble in the aqueous phase at a lower temperature and could transfer into the organic phase at a higher temperature. A catalyst which is capable of transferring between the aqueous phase and the organic phase in response to temperature changes is called a "thermoregulated phase-transfer catalyst" and a homogeneous catalytic process effected by a thermoregulated phase-transfer catalyst is

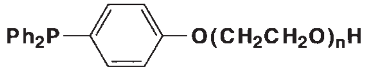
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

called “thermoregulated phase-transfer catalysis” (TRPTC) [11]. Conspicuously, the concept of TRPTC as a “missing link” could not only provide a meaningful solution to the problem of catalyst/product separation, but also extricate itself from the limitation of low reaction rates of water-immiscible substrates. Thus, the scope of application of two-phase catalysis could be greatly broadened. More recently, another novel biphasic catalytic system termed as thermoregulated phase-separable catalysis (TPSC) based on the critical solution temperature (CST) of nonionic phosphine ligand PETPP ($P\text{-}[p\text{-}C_6H_4O(CH_2CH_2O)_nH]_3$) is presented [26]. Additionally, the hydroformylation of higher olefins and hydrogenation of styrene catalyzed by the thermoregulated phase-separable transition metal complex with PETPP as the ligand will also be discussed.

4.6.3.2
Thermoregulated Phase-transfer Catalysis with Nonionic Water-soluble Phosphines

It is well known that the water-solubility of nonionic surfactants with polyoxyethylene moieties as the hydrophilic group is based on the hydrogen bonds formed between polyether chains and water molecules. The solubility of this type of surfactant decreases with a rise in temperature, and their aqueous solutions will undergo an interesting phase separation process (a miscibility gap) on heating to a lower critical solution temperature – the “cloud point”. A reasonable explanation attributes this phenomenon to the cleavage of hydrogen bonds. In addition, it is worth mentioning that such a process is a reversible one since the water-solubility could be restored on cooling to a temperature lower than the cloud point [12].



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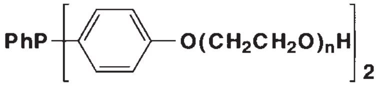

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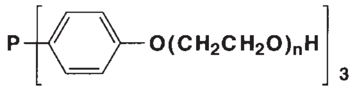

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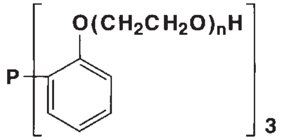

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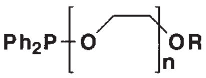

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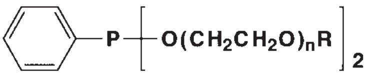

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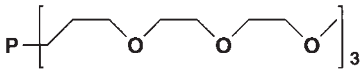

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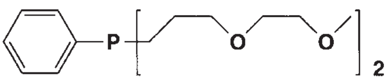

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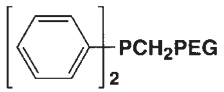

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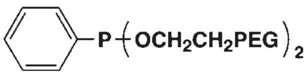

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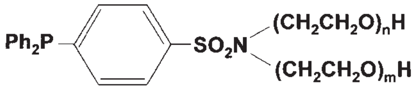


11

In view of the principles described above, a series of nonionic surface-active water-soluble phosphines **1**–**6**, **11** by introducing polyoxyethylene moieties to organophosphines [9–11] have been described. Results indicate that the ligands are appropriately soluble in water if the average number of ethylene oxide units per molecule exceeds ($N \geq 8$). As shown in Table 1, the ligands reveal the clouding property pertaining to typical nonionic surfactants. Moreover, the cloud points could deliberately be controlled by adjusting the ratio of hydrophobic to hydrophilic groups in the molecule.

Several papers involving the synthesis of polyether-bound phosphines have been published previously. Okano et al. prepared tertiary phosphines **7** and **8** by Grignard reactions [14], and Harris et al. synthesized high-molecular-weight phosphines **9** and **10** through the functionalization of poly(ethylene glycols) (PEGs)

Tab. 1 Cloud points of nonionic water-soluble phosphines with polyoxyethylene moieties [11, 13].

Ligand	*End group (R)*	*n*	*N* a)	*Cloud point [°C]*
1	H	8	8	26
1	H	16	16	52
1	H	25	25	75
2	H	7	14	55
2	H	10	20	71
3	H	6	18	95
5	n-C_5H_{11}	16	16	48
5	n-C_8H_{17}	16	16	43
5	n-$C_{12}H_{25}$	16	16	39
6	n-C_5H_{11}	8	16	50
6	n-C_5H_{11}	16	32	66
6	n-$C_{12}H_{25}$	8	16	30
6	n-$C_{12}H_{25}$	16	32	60
11	–	–	25 b)	57

a) $N =$ average no. of ethylene oxide units per molecule of ligand.

b) $N = n + m$.

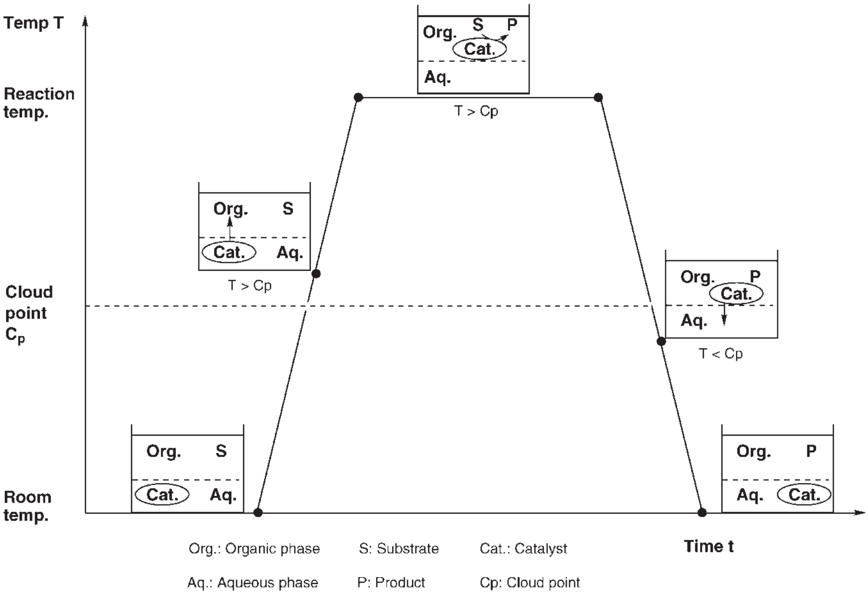


Fig. 1 General principle of thermoregulated phase-transfer catalysis. The *mobile* catalyst transfers between the aqueous phase and the organic phase in response to temperature changes.

[15]. Though not claimed by the authors, these ligands could hardly have a cloud point, since not enough hydrophobic groups are present in the molecules.

Based on the inversely temperature-dependent solubility of phosphines modified with polyoxyethylene chains, TRPTC has been proposed, and applied to the aqueous/organic two-phase reaction system [11]. The general principle of TRPTC is depicted in Figure 1.

The thermoregulated phase-transfer function of nonionic phosphines has been proved by means of the aqueous-phase hydrogenation of sodium cinnamate in the presence of Rh/**6** ($N = 32$, $R = n\text{-}C_5H_{11}$) complex as the catalyst [16]. As outlined in Figure 2, an unusual *inversely* temperature-dependent catalytic behavior has been observed. Such an anti-Arrhenius kinetic behavior could only be attributed to the loss of catalytic activity of the rhodium complex when it precipitates from the aqueous phase on heating to its cloud point. Moreover, the reactivity of the catalyst could be restored since the phase separation process is reversible on cooling to a temperature lower than the cloud point.

The analogous phenomenon was first reported by Bergbreiter et al. [17, 18]. In the presence of phosphorus-bonded block copolymers of ethylene oxide and propylene oxide as ligands ("smart ligands"), rhodium-catalyzed hydrogenation of maleic acid or allyl alcohol in the aqueous phase would show the same anti-Arrhenius reactivity.

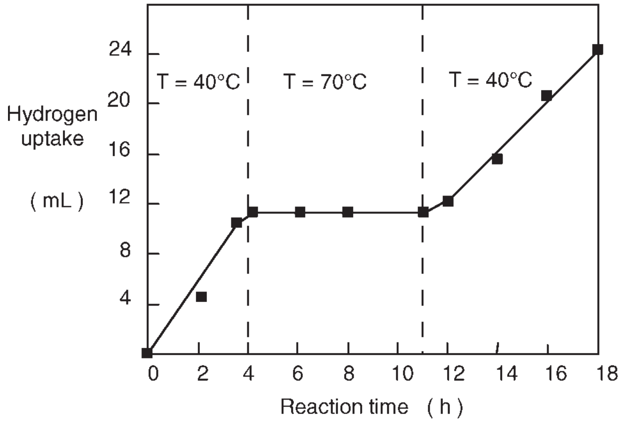


Fig. 2 Atmospheric-pressure hydrogenation of sodium cinnamate using Rh/**6** ($N = 32$, $R = n\text{-}C_5H_{11}$) as the catalyst in water at different temperatures. The cloud point of the catalyst is 64 °C. Anti-Arrhenius kinetic behavior results due to the inversely temperature-dependent water-solubility of the nonionic phosphine [16].

Obviously, the existence of such an unusual temperature-dependent phenomenon provides fundamental support of TRPTC. By introducing an extra *organic* phase containing a water-immiscible substrate into the reaction system, the catalyst being precipitated from the aqueous phase on heating to its low critical solution temperature would transfer into the organic phase, thus ensuring that the reaction takes place in the same – "homogeneous" – phase.

4.6.3.3
Hydroformylation of Higher Alkenes Based on TRPTC

Hydroformylation of higher alkenes with water-soluble catalysts is difficult to achieve (cf. Section 6.1.3.2). For example, the Rh/TPPTS complex, a perfect catalyst used in the two-phase hydroformylation of propene to generate butanol in the RCH/RP process, if applied to the hydroformylation of 1-hexene only gave conversions as low as 16–22% [4].

Thermoregulated phase-transfer catalysis, however, could be successfully put into effect for the hydroformylation of higher olefins in aqueous/organic two-phase media [11]. As shown in Table 2, various olefins have been converted to the corresponding aldehydes in the presence of nonionic phosphine-modified rhodium complexes as catalysts. An average turnover frequency (TOF) of 250 h^{-1} for 1-dodecene and 470 h^{-1} for styrene have been achieved. Even the hydroformylation of oleyl alcohol, an extremely hydrophobic internal olefin, would give a yield of 72% aldehyde [19]. In comparison, no reaction occurred if Rh/TPPTS complex was used as the catalyst under the same conditions.

Tab. 2 Two-phase hydroformylation of olefins catalyzed by nonionic phosphine-modified rhodium complexes [10, 19].

Olefin	*Ligand Na*	*N* [a)]	*P/Rh*	*P [Mpa]*	*T [°C]*	*Yield [%]*	*n/i ratio*	*TOF [h^{-1}]*
1-Hexene	**3**	18	5	5.0	100	85	2.0	–
1-Octene	**3**	18	5	5.0	100	88	2.8	–
1-Dodecene	**3**	18	5	5.0	100	84	1.8	250
Styrene	**1**	25	12	3.0	80	94	0.5	470
p-Chlorostyrene	**1**	25	12	3.0	80	92	0.6	460
p-Methoxystyrene	**1**	25	12	3.0	80	95	0.5	480
Cyclohexene	**1**	25	5	6.0	120	82	–	140
Oleyl alcohol	**1**	16	5	6.0	120	72	–	70

a) N = average no. of ethylene oxide units per molecule of ligand.

The recycling effect of the thermoregulated phase-transfer catalyst was also examined. Aqueous phase containing the Rh/**3** ($N = 18$) catalyst after phase separation was re-used five times in the hydroformylation of 1-dodecene. Almost no loss in the reactivity was observed [10]. It should be pointed out that leaching of rhodium into the organic phase might difficultly be diminished to less than the ppm level by means of a single-phase separation. Fortunately, further washing of the organic phase with water could significantly reduce the rhodium loss to such an extent that the industrial requirement might be met.

Approaches in which surfactants [5, 20] and surface-active water-soluble phosphines [21, 22] are used to accelerate the reaction rate of hydroformylation in the two-phase system have been reported by several research groups. Surface-active materials tend to make it possible for hydrophobic higher olefins to "*enter*" the aqueous phase through micellar solubilization (cf. Section 4.5). As far as nonionic phosphines with polyoxyethylene chains as the hydrophilic group are concerned, micellar solubilization and other surface activities should hardly have played a decisive role at the temperature of hydroformylation (usually higher than 100 °C), since these ligands are designed to have a cloud point lower than 100 °C and would precipitate from the aqueous phase at those high hydroformylation temperatures.

The concept of TRPTC provides a reasonable explanation for the satisfactory catalytic reactivity of Rh/nonionic phosphine complexes in the case of the two-phase hydroformylation of higher olefins. At a temperature lower than the cloud point, a nonionic phosphine-modified rhodium catalyst would remain in the aqueous phase since the partition of the catalyst between water and a nonpolar aprotic organic solvent strongly favors the aqueous phase. On heating to a temperature higher than the cloud point, however, the catalyst loses its *hydrate shell*, transfers into the organic phase and then catalyzes the transformation of alkenes to aldehydes. As soon as the reaction is completed and the system cools to a temperature lower than the cloud point, the catalyst regains its hydrate shell and returns to the aqueous phase [11]. It deserves to be emphasized that the reaction site of TRPTC is the organic phase rather than the aqueous phase or the aqueous/organic interface. Thus, even the reaction of extremely water-immiscible substrates could be smoothly carried out.

It has been reported that the rates of hydroformylation decrease in the order 1-hexene $>$ 1-octene $>$ 1-decene in the classical aqueous/organic two-phase system, whereas the rates are almost identical in the homogeneous organic system [23]. Interestingly, in the hydroformylation of a mixture of equimolar 1-hexene and 1-decene in the presence of Rh/**1** ($N = 25$) complex as the catalyst, roughly the same reaction rates at various conversion levels have been observed [19]. This phenomenon further verified the conclusion that the organic phase is the reaction site of TRPTC.

4.6.3.4
Thermoregulated Phase-separable Catalysis

4.6.3.4.1
Critical Solution Temperature (CST) of PETPP in Organic Solvents

Till now, there have been many studies on the solubility of nonaqueous solutions of ionic surfactants. On the other hand, information on *non*ionic surfactant solutions is still scarce. Kon-no et al. [27] studied the effect of temperature on the solubility of α-monoglycerol esters of C_{11}–C_{17} fatty acids in benzene. Such solubility behavior has also been observed by Matin and Pink [28] for zinc soaps in various organic solvents. The solubility increases slowly as the temperature is raised. Within a narrow temperature range, the solubility begins to increase very rapidly. The temperature at which the abrupt change in the solubility occurs is called the critical solution temperature (CST).

In order to investigate whether the nonionic phosphine ligands also possess the behavior of CST, the solubilities of PETPP ($P\text{-}[p\text{-}C_6H_4O(CH_2CH_2O)_nH]_3$) (Structure **3**) in organic solvents were measured [29]. The results are shown in Figure 3. The curves in Figure 3 indicate that there exists an inflection point from which the solubility of PETPP in toluene increases sharply, i. e., the phosphine ligand PETPP indeed exhibits the property of CST in toluene. In addition, the effect of N ($N = 3n$) in PETPP on the CST in toluene also has been examined. With increasing N, the CST of PETPP in toluene increases slightly. However, the increase of solubility with the increase of temperature in contrast to ionic surfactants is much less for the system under study. This may probably be due to the distribution of n in PETPP, which was prepared by ethoxylation.

It is known that in conventional homogeneous catalysis, one usually has to abandon the advantages of phase separation in catalyst recovery and product puri-

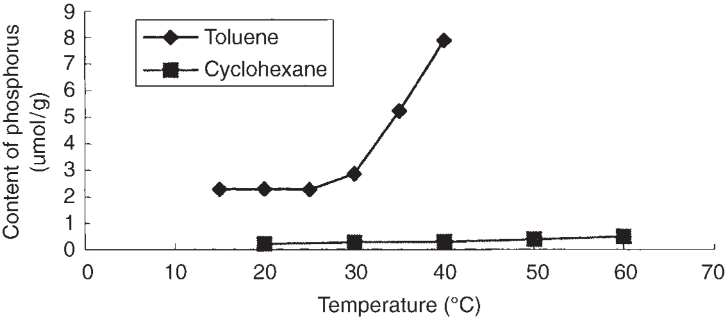


Fig. 3 Solubility of PETPP in organic solvents.

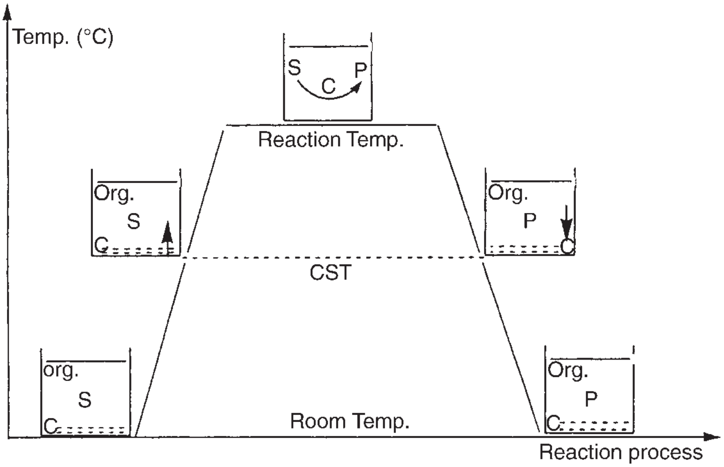


Fig. 4 General principle of TPSC: C, catalyst; CST, critical solution temperature; Org., organic solvent; P, product; S, substrate; Temp., temperature.

fication for the sake of higher or more controllable catalyst activity and selectivity. To combine the merits of high activity and the easier separation of catalyst from product in one catalytic process, herein, a novel biphasic catalysis termed as thermoregulated phase-separable catalysis (TPSC) was proposed based on the critical solution temperature of nonionic phosphine ligand.

The general principle of TPSC is illustrated in Figure 4. At room temperature ($T <$ CST), the catalyst is insoluble in organic solvent and the organic phase is colorless. When heating to $T >$ CST, the catalyst would be soluble in organic solvent and the whole system turned to be homogeneous with a brown yellow color. At the reaction temperature ($T >$ CST), the reaction proceeds homogeneously. After completion of the reaction and on cooling to the room temperature ($T <$ CST), the catalyst would precipitate out from the organic phase, which now contains the products. Thus, by decantation products could be easily separated from the catalyst. The TPSC system described above is a combination of the advantages of homogeneous with those heterogeneous catalysis: high activity and simple catalyst/product separation.

4.6.3.4.2
Applications

The strategy of TPSC (using nonionic phosphines with the property of CST as ligand to separate, recover and reuse a homogeneous catalyst) was firstly applied in the hydroformylation of higher olefins [30] (Table 3).

Table 4 indicated the recycling efficiency of PETPP/Rh complex in the hydroformylation of 1-dodecene. By convenient decantation, the catalyst could be easily isolated from organic phase and directly reused in the next reaction runs. After eight recycles, almost no loss in reactivity has been observed.

Further applications of TPSC have been attempted in the hydroformylation of cycloolefins, cyclohexene being a model substrate (Eq. 1). The experimental results indicate that the catalytic activity of PETPP/Rh complex is higher than that of the

Tab. 3 Hydroformylation of various higher olefins catalyzed by the PETPP/Rh complex.[a]

Entry	*Olefins*	*Reaction temperature [°C]*	*Conversion [%]*	*Yield of aldehyde [%]*
1	1-Hexene	100	95.5	95.5
2	1-Octene	100	96.5	92.6
3	1-Dodecene	130	95.8	93.7

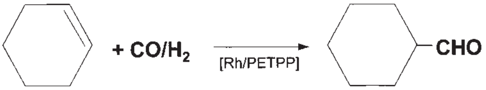
[a] Reaction conditions: $P = 4.0$ MPa ($CO/H_2 = 1:1$), P/Rh = 13, [Rh] = 4.73×10^{-6} mol/ml, PETPP ($N = 18$), $t = 6$ h, toluene 2 ml, $V_{olefin} = 1$ ml.

Tab. 4 The recycling efficiency of the PETPP ($N = 18$)/Rh complex catalyst hydroformylating 1-dodecene.

NOS of recycling	*Conversion [%]*	*Yield of aldehyde [%]*
1	95.8	93.7
2	95.0	92.4
3	95.6	94.6
4	95.2	93.5
5	95.7	94.3
6	95.8	92.6
7	95.8	94.0
8	95.6	93.2

$T = 130$ °C, all the other conditions cf. Table 3.

reported $Co_2(CO)_6(PBu_3)_2$ complex [31] and is comparable to that of the Wilkinson catalyst. Moreover, the catalyst also exhibits better recycling efficiency [26].



(1)

More recently, the application scope of thermoregulated phase-separable transition metal complex with nonionic phosphine ligand has been expanded from hydroformylation to hydrogenation, and the central metal varied from Rh to Ru. The first experimental study is the hydrogenation of styrene catalyzed by thermoregulated phase-separable $Ru_3(CO)_{12}$/PETPP complex catalyst. Under the conditions of $p_{H_2} = 2.0$ MPa, $T = 90\,^\circ C$, catalyst/substrate (mol/mol) = 1/1000, 3 hours, the $Ru_3(CO)_{12}$/PETPP complex catalyst exhibited good activity (Table 5). Compared with other catalysts, $Ru_3(CO)_{12}$/PETPP complex showed the same catalytic activity compared to the lipophilic $Ru_3(CO)_9(TPP)_3$, while the hydrophilic $Ru_3(CO)_9(TPPTS)_3$ and $Ru_3(CO)_9(TPPMS)_3$ are less active (Table 6).

In order to test the recycling efficiency of Ru/PETPP complex, the catalyst was separated by simple decantation and directly re-used. After ten reaction runs, the yield of ethylbenzene is still over 95%.

Tab. 5 Effect of temperature on the hydrogenation of styrene catalyzed by $Ru_3(CO)_{12}$/PETPP[a)].

Temperature [°C]	*Conversion [%]*	*Yield [%]*	*TOF [h^{-1}]*
90	100.0	99.5	332
80	93.7	93.1	310
70	60.4	60.1	200
60	40.1	40.0	133

a) Reaction conditions: $p_{H_2} = 2.0$ MPa, substrate/catalyst = 1000:1 (molar ratio), $t = 3$ h.

Tab. 6 Effect of different P/Ru catalyst on the hydrogenation of styrene.[a)]

Catalyst	*Conversion [%]*	*Yield [%]*	*TOF [h^{-1}]*
$Ru_3(CO)_9(TPP)_3$	96.6	95.8	319
$Ru_3(CO)_9(TPPMS)_3$	76.8	76.4	255
$Ru_3(CO)_9(TPPTS)_3$	48.2	48.0	160
$Ru_3(CO)_{12}$/PETPP	100.0	99.5	332

a) Reaction conditions: $T = 90\,^\circ C$, for the other conditions see Table 5.

4.6.3.5
Conclusions

Although the development of the aqueous/organic two-phase catalysis has only occurred more than 20 years since its emergence [24], crucial advantages of this methodology have been proved as it overcomes the immanent problem of catalyst/product separation associated with homogeneous catalysis. Compared with classical aqueous/organic two-phase catalysis, the process of TRPTC is more "*homogeneous*" to some extent because the catalyst and substrate would remain in the same organic phase at the reaction temperature. TRPTC is also quite different from FBS [5]. While the initial fluorous/organic biphase of FBS becomes a *single phase* at an appropriate higher temperature, TRPTC would maintain the aqueous/organic *two-phase* system throughout the reaction. It is the *mobile* catalyst that transfers between two phases without any additive in response to temperature changes.

The introduction of TRPTC to the aqueous/organic two-phase hydroformylation of higher olefins is free from the shortcomings of classical two-phase catalysis, in which the scope of application is more or less restrained by the water-solubility of the organic reactants. Obviously, the core of TRPTC is to use nonionic water-soluble phosphines with the property of clouding. Therefore, to design and prepare ligands with higher catalytic reactivity at lower cost will be a main topic in the scientific research and industrial exploitation of this strategy in the future. Just as Cornils remarks in this connection [25]: "since the agent responsible for the merger and subsequent separation of the phases is the appropriately custom-designed ligand itself, there is no call for investing extra effort in the removal and recycling of a foreign additive, and this must therefore be regarded as a promising avenue for further exploration on a commercially realistic scale."

The concept of CST of nonionic tensioactive phosphine ligand PETPP has been primarily applied to the hydroformylation of higher olefins and hydrogenation of styrene. Credit goes to high reactivity, efficient separation, recovery, and recycling of the catalyst. TPSC thus combines the advantages of homogeneous and heterogeneous catalysis. The TPSC process provides not only a method for hydroformylation of higher olefins or hydrogenation of styrene, but also a novel approach for the homogeneous catalysis. In addition, there are also a number of other potential advantages that are likely to receive increasing attention. For example, compared with the aqueous/organic biphasic catalysis, TPSC is more suitable for the catalytic process when the catalyst or substrate are sensitive to water.

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4.7
Transitions to Heterogeneous Techniques (SAPC and Variations)

Mark E. Davis

4.7.1
Introduction

It is obvious that the diversity of catalytic chemistry that can be accomplished in aqueous phases by organometallic catalysts is burgeoning. Specific and newer details of the expanding field of catalysis in water can be found elsewhere in this book and in a special issue of the *Journal of Molecular Catalysts A* [1]. Here a concept is presented for converting known homogeneous catalytic systems that operate in aqueous media into heterogeneous analogues.

Comprehensive reviews of immobilization (heterogenization) techniques are available (e.g., [2]). In principle, immobilization may be achieved in one of several ways: physical adsorption or chemisorption of a metal complex onto a support; entrapment of metal complexes via *in situ* synthesis within zeolites; dissolution of a metal complex in a nonvolatile solvent; and dissolution of a metal complex in a nonvolatile solvent that is adsorbed onto the surface of a support, i.e., as a supported liquid phase (SLP) [3]. The first three methods have not yet provided a commercially viable heterogeneous catalyst. In general, the immobilized systems never approach the combined activity/selectivity performance levels of their homogeneous counterparts and tend not to retain the metal complexes for a sufficiently long time ("leaching"). Dissolution of the metal complex has been successfully applied, as exemplified by the hydroformylations of propene of Union Carbide (hydrocarbon solvent) [4] and Ruhrchemie [5] after a laboratory development by Rhône-Poulenc (aqueous solvent) [6]. Both of these processes employ homogeneous catalysis; however, the reactants (propene, CO, H_2) and products (butanals) enter and leave as separate phases. The drawback of these immobilization methods is that they are not applicable for liquid-phase reactants/products that are miscible with the nonvolatile solvent phase.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

4.7.2
The SAPC Concept of Immobilization

Although there is a vast literature on heterogenization of homogeneous catalysts, there is no successful commercialization of a solid catalyst that is an immobilized homogeneous catalyst. The primary reason for this is the lack of simultaneous high activity, high selectivity, and no leaching of active material. In order to convert a catalytic material into a commercially viable catalyst, these and other factors must all be optimized simultaneously. Thus, for an immobilized homogeneous catalytic material to have the opportunity to become a commercial catalyst, it must show high activity, selectivity, and enantioselectivity (if the reaction is chiral), without leaching.

A new immobilization method designed specifically to convert liquid-phase reactants has been developed [7, 8]. The catalytic materials consist of a thin film that resides on a high-surface-area support, such as controlled-pore glass or silica, and is composed of a hydrophilic liquid and a hydrophilic organometallic complex (see Figure 1).

Initially, water was used as the hydrophilic liquid and these catalysts are therefore denoted as supported aqueous-phase catalysts (SAPCs) [7–10]. Subsequently, we expanded this concept to other hydrophilic liquids such as ethylene glycol and glycerol [11]. Reactions of liquid-phase, hydrophobic organic reactants take place at the film–organic interface. SAP catalysis differs significantly from SLP catalysis in that the latter is used for gas-phase reactants whereas the former is specifically designed for liquid-phase substrates. Additionally, with SLP catalysis, the reaction proceeds homogeneously in the supported film while in SAP catalysis it occurs at

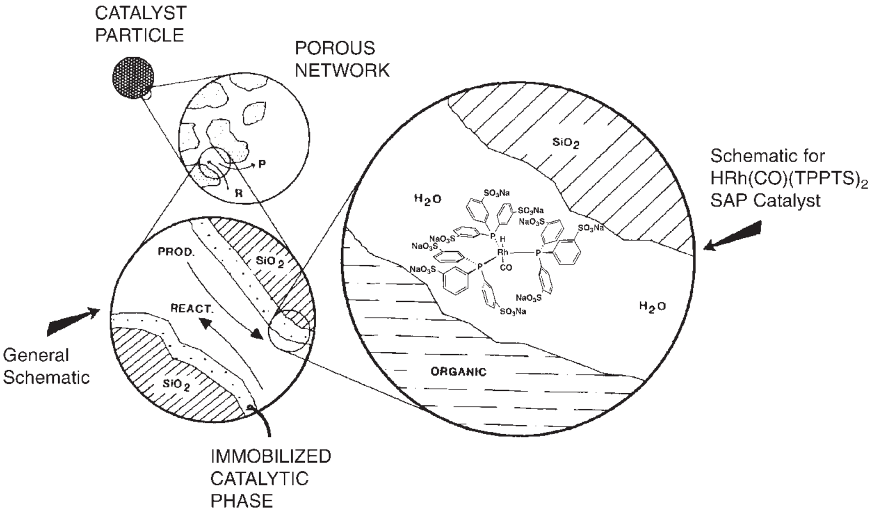


Fig. 1 Schematic illustration of a supported aqueous-phase catalyst.

the interface. Like many metals contained in biological systems, such as magnesium in chlorophyll or iron in hemoglobin, the hydrophilic catalysts contain ligands that ensure the hydrophilic properties while the environment at the metal center can remain essentially hydrophobic in character. Thus, the key is to impart hydrophilic properties to an organometallic complex that is known to be a homogeneous catalyst in organic media by modifying its ligands. The hydrophilic complex is supported on a hydrophilic solid to create a large interfacial area between the catalytic species and the organic reactants. The hydrophilicity of the ligands and the support creates interaction energies sufficient to maintain the immobilization. Thus, these catalysts are designed to conduct reactions efficiently at interfaces.

The proof of the concept of this type of catalysis was primarily obtained using hydroformylation as the test reaction. The commercial water-soluble rhodium hydroformylation catalyst (cf. Section 6.1.1) is used as the active organometallic complex. An SAP catalyst was created as follows: a controlled-pore glass, e.g., CPG-240 (mean pore size, 24.0 nm) was impregnated with $HRh(CO)[P(m\text{-}C_6H_4SO_3Na)_3]_3$ and $P(m\text{-}C_6H_4SO_3Na)_3$ (TPPTS). After the complex and excess ligand had been deposited, the water content of the solid was approximately 3 wt.%. Water was then added to the catalyst. For details of the catalyst preparations and analyses, see [7, 8]. The rhodium-based SAP catalysts were used to hydroformylate liquid-phase olefins. For example, oleyl alcohol was hydroformylated with the SAP catalysts at 100 °C with 50 bar $CO + H_2$ ($CO:H_2$, 1:1). Extensive work was performed to show that rhodium is not leached into the organic phase. Elemental analysis of the organic phase for rhodium shows no detectable amounts, with a sensitivity of 1 ppb. Additionally, no reactivity is observed from the organic filtrate when it is tested for hydroformylation or hydrogenation activity (it is important to note that the filtrate must be obtained at the reaction temperature in order to eliminate the possibility of precipitation upon quenching the reaction medium). Since neither oleyl alcohol or its hydroformylation products are water-soluble, these reactivity results prove that rhodium is immobilized and that the reaction occurs at the organic–aqueous film interface. Finally, if the rhodium complexes are supported on various CPGs with different surface areas, the conversions obtained are proportional to the interfacial area in the reactor.

Horváth conducted several other interesting experiments with rhodium SAPCs (Table 1) [12]. Clearly, the water-solubility of the olefins does not limit the performance of the SAPCs since the TOFs (turnover frequencies) are essentially independent of olefin carbon number. This has been shown to be true also for carbon numbers as high as 17 [13]. Additionally, Horváth conducted experiments aimed at observing rhodium loss into the organic phase. He concluded that the SAPC does not leach catalytically active rhodium species under hydroformylation conditions. Another critical test for leaching was performed by Horváth. He conducted a 38 h continuous-flow experiment in a trickle-bed reactor and showed no loss of rhodium by elemental analysis. Thus, the combined data from all work shows that

Tab. 1 Hydroformylation of a 1 : 1 : 1 mixture of 1-hexene, 1-octene, and 1-decene with aqueous and organic soluble rhodium complexes and an SAPC (adapted from [12]).

Product	***TOF[a) $[s^{-1}]$***		
	Biphasic[b)	***SAPC[c)***	***Organic[d)***
Heptanals	0.0047	0.12	0.46
Nonanals	0.0014	0.12	0.50
Undecanals	0.0003	0.11	0.50

a) TOFs are estimated from conversions specified at various reaction times. Values are only estimates since the levels of conversion in some cases were very high.

b) $HRh(CO)[P(m\text{-}C_6H_4SO_3Na)_3]_3$ in water. $T = 125\,°C$, $P = 58$ bar.

c) SAP catalyst containing $HRh(CO)[P(m\text{-}C_6H_4SO_3Na)_3]_3$ in water. Olefins were contained in hexane solvent. $T = 100\,°C$, $P = 51$ bar.

d) $HRh(CO)[P(C_6H_5)_3]_3$ in hexane. $T = 100\,°C$, $P = 51$ bar.

there is significant evidence to conclude that the SAPCs do remain immobilized and that the reaction occurs at the interface as designed.

For long-term stability, the SAPC must remain assembled. To test for this type of stability, it was investigated whether the components can self-assemble. The rhodium complex $HRh(CO)(TPPTS)_3$, TPPTS and water were loaded into a reactor with cyclohexane and 1-heptene. The reactor was pressurized with approx. 70 bar $H_2 + CO$ ($CO : H_2$, 1 : 1) and heated with stirring to 100 °C. A second experiment was carried out in a manner similar to the one previously described except that CPG-240 was added also. The components of the SAPC self-assemble to form an SAPC and carry out the hydroformylation reaction [13]. Upon termination of the reaction, the solid collected contained $HRh(CO)(TPPTS)_3$ and TPPTS. This test indicates that, under the conditions of the experiment, the individual components of the SAPC are more stable assembled in an SAPC configuration than separated. Therefore, the reverse, i.e., the separation of the solution and complex from the support, is not likely to happen under reaction conditions.

The water content of $HRh(CO)(TPPTS)_3$-based SAPCs has a great influence on their performance. For example, when 1-heptene is hydroformylated, the TOF increases by two orders of magnitude when the water content of the catalyst increases from approx. 2.9 wt.% to approx. 9 wt.% (Table 2).

Tab. 2 Hydroformylation of 1-heptene. $P = 7$ bar, $H_2/CO = 1 : 1$, $T = 75\,°C$ [13].

Catalyst	***TOF $[s^{-1}]$***	***E_a $[kJ\,mol^{-1}]$***
$HRh(CO)(TPPT)_3$–SAPC (≈ 2.9 wt.% H_2O)	0.0002	≈ 75
$HRh(CO)(TPPTS)_3$–SAPC (≈ 9 wt.% H_2O)	0.02	≈ 40

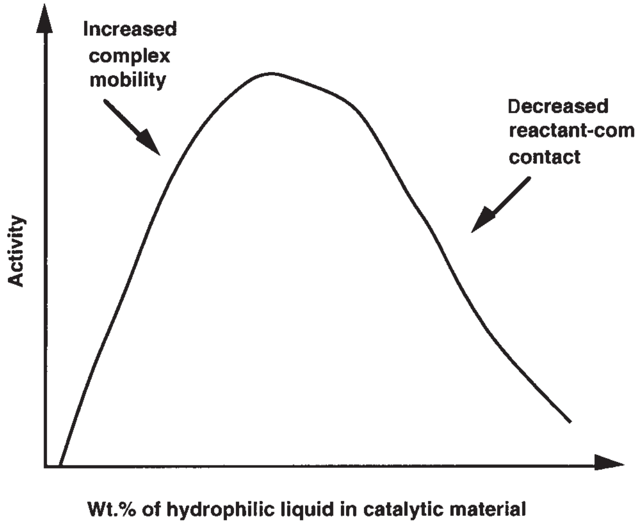


Fig. 2 Schematic illustration of the activity of the immobilized catalyst as a function of the amount of hydrophilic liquid in the film.

What is interesting from these results is that, whereas the activity is dramatically affected by the water content, the selectivity does not change. Thus, at the low water content, the activity is low and the apparent activation energy (approx. 75 kJ mol^{-1}) is the same as that obtained from $HRh(CO)[P(C_6H_5)_3]_3$ in organic solvent. As the water level increases, the activity increases to almost that obtained from $HRh(CO)[P(C_6H_5)_3]_3$ in toluene. It is surprising that the reaction rate is so high in view of the fact that the observed activity is most probably limited by mass transport (implied from observed activation energy). If too much water is added to the SAP catalyst the activity declines [8]. Thus, a bell-shaped curve describes the activity dependence on water (Figure 2).

This dependence has been noted by others as well [14, 15]. The increase in activity was suggested by use to be due to increase complex mobility (observed by NMR techniques) [7, 8]. ^{31}P NMR spin relaxation times do decline with increasing water content in SAP catalysts and the spin relaxation time at the optimal water loading is near that of the organometallic complex in water [16]. Thus, it is not unreasonable to suggest that the loss in activity as the catalyst is dried is due to the restrictions of the motion in the organometallic complex. As the water content becomes large, there is also a loss in activity. This decline is most probably due to losses in contacts between reactants and the organometallic complexes because of the lessening of interfacial area (the maximum water content would be that which fills the pore space and allows no contact with the hydrophobic organic phase). It is clear that one of the disadvantages of the SAPC concept is the sensitivity to water content in the film. Horváth reported that water is lost from the SAPC over

Tab. 3 Catalyst types and reactions successfully used in the supported aqueous-phase configuration.

Catalyst type	*Reaction*	*Refs.*
Rh, TPPTS	Hydroformylation	[7, 8, 12–15, 18]
Co, TPPTS	Hydroformylation	[19]
Pt, Sn, TPPTS	Hydroformylation	[20]
Pd, Cu	Wacker oxidation	[21]
Pd, TPPTS	Allylic alkylation	[22]
Ru, TPPTS	Hydrogenation	[17]
Rh, TPPTS	Olefin isomerization	[23]
Pt, Sn, chiral ligand	Asymmetric hydroformylation	[24]
Rh, chiral ligand	Asymmetric hydrogenation	[24]
Ru, BINAP–4 SO_3Na	Asymmetric hydrogenation	[10, 11]

the 38 h reaction conducted in the trickle-bed reactor and that the activity of the catalyst did vary over this time period [12]. Additionally, Fache et al. noticed that Ru–TPPTS–SAP catalysts lost activity upon recycling when hydrogenating α,β-unsaturated aldehydes [17]. In both of these studies, water-saturated solvents were not used. It is therefore expected that the water content and thus the activity of the SAP catalysts would vary with time on stream or batch number. For long-term stability, the water content of an SAPC must be carefully controlled.

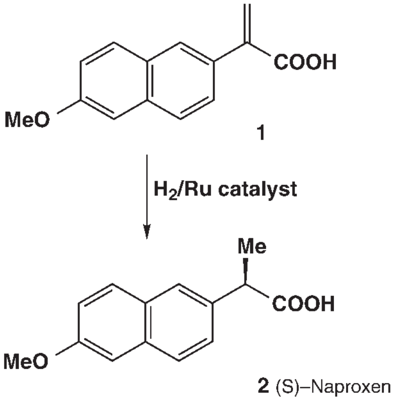
The foregoing discussions show that the SAPC immobilization concept does reveal the desired properties of activity and selectivity with no catalyst leaching. Table 3 provides a summary of the catalytic materials/reactions reported using this immobilization technique.

4.7.3
Example of Rational Catalyst Design Strategy

After several years of work devoted to proving the concept of SAP catalysis, it was attempted to show that this class of heterogeneous catalyst could be prepared by design. In order to provide convincing evidence that this could be done, we chose to design and prepare a heterogeneous, asymmetric catalyst – which we believed to be the most difficult class of heterogeneous catalyst to prepare. Next, the successful design of such a catalyst is described.

It was known that ruthenium complexes of BINAP were efficient homogeneous catalysts for the asymmetric reduction of dehydronaproxen (**1**) to naproxen (**2**) (see Eq. 1) [25, 26].

This important and difficult reaction was used to test the design procedure. We followed the design steps listed in Table 4 except that initially we did not use ethylene glycol but rather water as the hydrophilic liquid for the immobilized film, i.e., an SAP-type catalyst. Implementation of the design sequence began by developing



(1)

Tab. 4 Steps in a route to the rational design of immobilized homogeneous catalysts.

Step	***Example*** *(from [11])*
1. Identify homogeneous reaction and catalytic material of interest.	Asymmetric hydrogenation to produce naproxen by Ru–BINAP catalytic material.
2. Convert hydrophobic ligand to hydrophilic ligand.	BINAP converted into sulfonated BINAP (BINAP–4 SO_3Na).
3. Prepare hydrophilic catalytic material.	Ru–BINAP–4 SO_3Na.
4. Immobilize hydrophilic catalytic material in a thin film of hydrophilic liquid on a high-surface-area hydrophilic solid.	Ru–BINAP–4 SO_3Na in ethylene glycol film on a controlled-pore glass support.
5. Conduct reaction.	Synthesis of naproxen.

a water-soluble analogue of BINAP using direct sulfonation [27] and created an SAPC comprising a ruthenium(II)–sulfonated BINAP complex [10]. The catalyst revealed good activity and no leaching of the active component and gave an *ee* of approx. 70%. For comparison, the *ee* values from homogeneous reactions using neat methanol as solvent were greater than 95%. Thus, the SAPC gave poorer *ee* values, and it was shown that this was due to the presence of water. Water hydrolyzed a Ru–Cl bond in the organometallic complex and lead to the reduction in *ee* [10]. Thus, the final step in the catalyst preparation was to replace water with another hydrophilic liquid that would preserve the Ru–Cl bond. This step was not anticipated and was therefore not included in the original design procedure. The substitution of water by ethylene glycol completed the catalyst construction (see Figure 3) and the reactivity results from this catalytic material are listed in Table 5. The heterogeneous, asymmetric catalyst produced naproxen in 100% yield with an *ee* of 96% and with no catalyst loss at approximately one-third the rate of homogeneous reaction.

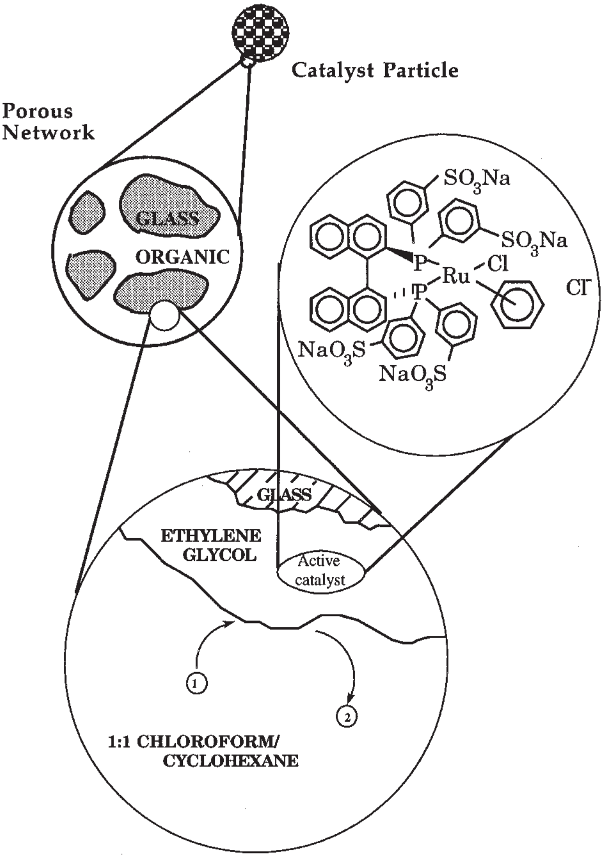


Fig. 3 Schematic diagram of the designed heterogeneous catalyst (left) for the reaction shown in Eq. (1). (Adapted from [11]).

In order to show that this procedure is not specific to the synthesis of naproxen, the asymmetric hydrogenation of β-ketoesters was investigated. Like the asymmetric hydrogenation to produce naproxen, the asymmetric hydrogenations of β-ketoesters by Ru–BINAP complexes were known to provide *ee* values above 95% [28, 29]. Using the procedure outline in Table 4 and armed with the knowledge that water should cause a loss in *ee* heterogeneous, asymmetric catalysts using Ru–BINAP–4SO_3Na complexes with ethylene glycol and glycerol were formulated (for comparison). Table 6 shows the results of hydrogenating ethyl butyrylacetate at 85 °C (Eq. 2). The heterogeneous catalysts gave *ee* values that were within experimental error (approx. 2% *ee*) of the *ee* obtained from the homogeneous reaction. Also and as now expected, the *ee* from the SAPC was lower.

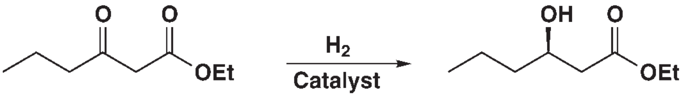
Tab. 5 Reaction results for the hydrogenation of **1** to yield naproxen (from [11]).[a]

Solvent	*TOF [h^{-1}]*	*ee [%]*
1:1 $CHCl_3$/cyclohexane[b] (heterogeneous catalyst)	40.7	88.4
1:1 $CHCl_3$/cyclohexane[b] (heterogeneous catalyst)	–	95.7[c]
MeOH (homogeneous catalyst)	131.0	88.2
MeOH (homogeneous catalyst)	–	96.1[d]

[a] Chiral catalytic material = [Ru(benzene)(BINAP–4 SO_3Na)Cl]Cl.
[b] No ruthenium found in the reaction filtrate at a detection limit of 32 ppb.
[c] Reaction temperature = 276 K.
[d] Reaction temperature = 277 K.

Tab. 6 Hydrogenation of ethyl butyrylacetate by homogeneous and heterogeneous catalysts at 85 °C and 60 bar H_2. The *ee* values are reported at 100% conversion (from [30]).

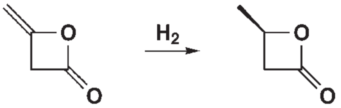
Catalysis	*ee [%]*
Homogeneous (methanol solvent)	97
Heterogeneous (ethylene glycol)	95
Heterogeneous (glycerol)	94
SAP (water)	83



(2)

4.7.4
Suggested Reactions for Implementation of Design Concepts

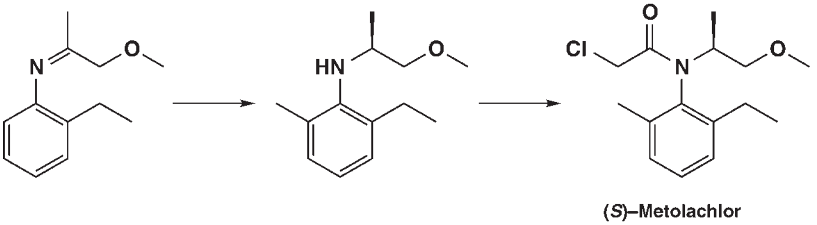
The design strategy outlined here is general and should be applicable to the development of other chiral and achiral heterogeneous catalysts. For example, in the area of chiral hydrogenations two reaction chemistries that could greatly benefit from the use of a heterogeneous asymmetric catalyst are: (1) the asymmetric hydrogenation of diketene; and (2) the asymmetric hydrogenation of imines. The efficient conversion of diketene **3** to its chiral lactone **4** (Eq. 3) could allow for low-cost production of polyhydroxybutyrate-type biodegradable polymers [28, 31].



3 **4**

(3)

Currently, these polymers are obtained via fermentation [31]. The Ru–BINAP type of catalysts have shown good selectivities and *ee* values for the asymmetric reduction of diketene [28, 29] and an immobilized version of the catalyst could be easily designed. The asymmetric reduction of imines to chiral amines has also been accomplished by homogeneous catalysts. Balkos et al. have hydrogenated imines with rhodium complexes of sulfonated bdpp ((–)(2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane) with *ee* values exceeding 90% [32]. Using this information the design of a heterogeneous catalyst for imine reduction is obvious and an important reaction for application of such a catalytic material would be the preparation of (*S*)-Metolachlor (Eq. 4). *S*-Metolachlor is an herbicide of which more than 10 000 tons^{-1} are produced, making it the largest-scale product to be prepared by asymmetric hydrogenation.



(4)

Although the aforementioned examples involve only asymmetric hydrogenation, it is likely that the rational design strategy outlined here should provide a route to the design of a class of heterogeneous catalytic materials. However, skillful choice of the reaction system will be necessary. For example, reactions that provide large changes in hydrophilicity between reactants and products will most probably not be amenable to the immobilization procedure outlined here.

4.7.5
Outlook

Although SAP catalysts and their non-aqueous analogues have been reported only for less than a decade, it is clear that the reaction chemistries that can be accomplished in this configuration continues to burgeon. This method of immobilization has proven effective and as the realm of water-soluble organometallic catalysts expands, so can the field of SAPCs and its variants. Scientifically and in special, Delmas and his collegues still work on this topic [33]. It is hoped that economic proof will follow.

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5
Aqueous Catalysts for Environment and Safety

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

5.1
Water-soluble Organometallics in the Environment

Wolfgang A. Herrmann, Fritz E. Kühn

5.1.1
Introduction

The focus of this book is on water as a solvent and reactant in organometallic chemistry. Although there are still a number of laboratory curiosities in this field, striking examples of industrial applications highlight the recent development and point toward a promising future. With the new recognition of aqueous organometallic chemistry, environmental aspects are coming into view that deserve further research or re-examination. A particularly important aspect, related both with naturally occurring processes in a broad variety of organisms and the toxicity of certain metal-alkyl species is the biological methylation. Particularly in the recent years a significant amount of examinations on the stability of metal alkyl compounds in biological systems and their generation through biological processes has been published.

5.1.2
Biological Methylation

The term biological methylation, usually contracted to "biomethylation", refers to an enzymatic transfer of a previously formed methyl group from a donor atom to an acceptor atom within a living organism. The enzymes, which control such transfers are called methyltransferases. In principle, biomethylation is equivalent to enzymatic transmethylation occurring in cells. As far as it is known, enzymatic transmethylations occur in all organisms. Biomethylations of carbon, nitrogen, oxygen or sulfur atoms are used regularly by these organisms as part of their metabolism [1]. Genetic and cancer research are fields, in which enzymatic transmethylations have gained increasing interest in recent years, and terms such as hypomethylation and hypermethylation are used quite frequently in these research areas [2]. Among the compounds involved in biomethylation are also several metal species. Most severely examined among them are mercury and tin complexes. It

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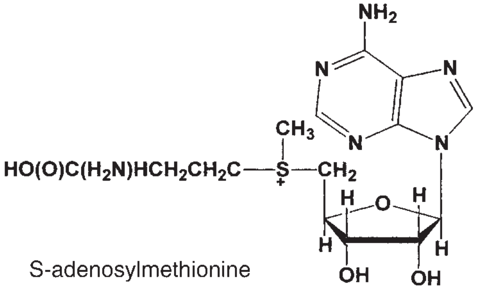
should be emphasized, however, that biomethylation is by far not limited to organometallic complexes of these latter metals [3].

The largest number of elements, especially metals, are methylated primarily by bacteria, usually in sediments or soils. Algae, fungi and yeasts methylate metalloids and nonmetals (arsenic, antimony, chalkogens), the halogens undergo methylation primarily in seaweeds and in marine kelps. Plants and animals have been much less investigated as biomethylating systems than unicellular organisms, but appear to be more limited in the scope of their biomethylation [3b].

Introduction of methyl groups onto atoms generally enhances the solubility in lipids and usually decreases solubility in water. One obvious chemical consequence of methylation is a change in the ability of the acceptor moiety to form complexes with other ligands or to bind to surfaces. Therefore, biomethylation may significantly change the biological activity of the acceptor moiety, often expressed in a change of its toxicity. Accordingly, biological methylation is a process that converts inorganic, often harmless compounds, e.g., Hg^{2+}(aq), into highly toxic methylated species, e.g., CH_3Hg^+. Poisonings and death resulting from methylated mercury and arsenic derivatives have provided the major impetus for research on biomethylation [3].

During the course of biomethylation the methyl group is most likely transferred as a bridging intermediate rather than a free entity. Such an intermediate is assumed to form during an associative mechanism [4]. The methyl group may be electrophilic (cationic), radical or nucleophilic (anionic), depending on the specific donor moiety. A broad variety of methyl transfer reactions are therefore possible. Besides the two biological donors, methylcobalamin (see below) and *S*-adenosylmethonine (**1**) nonenzymatic transmethylation is also possible in the natural environment, probably also very important for the formation and decomposition of metal methyl compounds [3b].



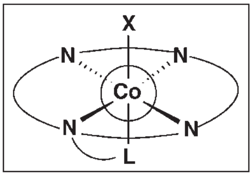
S-adenosylmethionine

1

5.1.3
Cobalamines – Organometallics in Nature

With the possible exception of the redox enzymes cytochrome P-450 (iron) and the methanogenic bacterial cofactor F-430 (nickel) [5–7], the cobalamines are the only naturally occurring organometallics featuring σ-bonds between a transition metal (cobalt) and carbon ligands. Vitamin B_{12}, which can be found in the human body in amounts of 2–5 mg, is a derivative bearing a cyano group in place of the metal-attached ligand X (Structure **2**). It is effective against several forms of anemic diseases of animals, e.g., "bush disease," "coast disease," and "salt sickness."

- X = CN (**2a**): Vitamin B_{12}
- X = Adenosyl (**2b**): Coenzyme B_{12}



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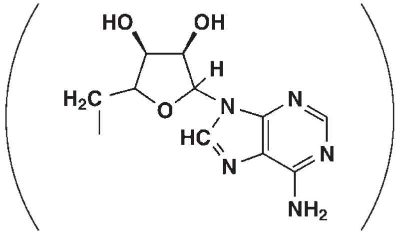
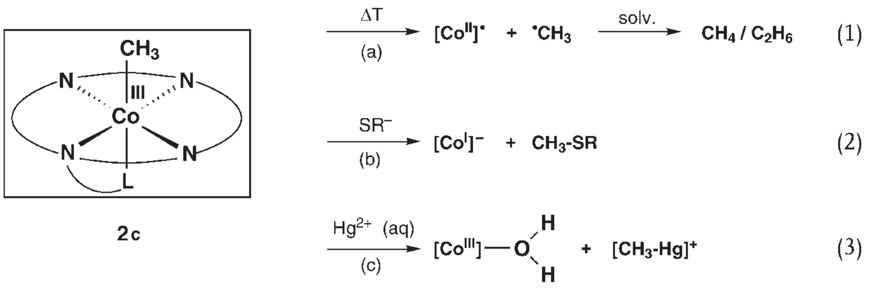


- X = CH_3 (**2c**): Methyl-cobalamin
- L = benzimidazole derivative (*N*-coordination)

Vitamin B_{12} (**2a**) participates in the aqueous-phase biosynthesis of purine and pyrimidine bases, the reduction of ribonucleotide triphosphates, the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A, the biosynthesis of methionine from homocysteine, and the formation of myelin sheath in the nervous systems.

Methylcobalamin (**2c**) can be isolated from microorganisms. Its largely covalent Co–CH_3 bond undergoes all three possible types of reactions, namely homolysis, carbonium-ion transfer, and carbanion transfer (Scheme 1), thus including reduction and oxidation of cobalt, respectively. Thermal degradation of cobalamin preferentially yields methane and ethane as radical-type reaction products (cf.



Scheme 1 Reaction of methylcobalamin in aqueous media; (a) and (b) reduction of cobalt, (c) redox-neutral reaction (CH_3^- transfer: Co(III) → Hg(II)).

Scheme 1, reaction (a)). The carbonium ion $[CH_3]^+$ is transferred from **2c** to sulfides and sulfhydryl ions forming methylmercapto derivatives (cf. Scheme 1, reaction (b)). The CH_3 group of **2c** is available as an anion in the presence of metal cations (cf. Scheme 1, reaction (c)).

Coenzyme B_{12} catalyzes the 1,2-shift of alkyl groups (isomerase reaction) in hydrocarbons. An extensive chemistry was based on the reactivity aspects, where cobalamins acted as model systems, mainly in the work of Schrauzer et al. [8].

Much of this chemistry depends on the redox processes. The strongly reducing, anionic cobalt(I) species, the so-called B_{12s} form, seems to play the central role in the catalytic reactions of the coenzyme B_{12}. Methylcobalamin (**2c**) is very similar to cyanocobalamin (**2a**) in its geometry and ligand properties [8–10]. Methylcobalamine is the second major biomethylating agent besides *S*-adenosylmethionine (**1**). Heavy elements usually undergo biomethylation from one of these two biological donors. Since methionine can be converted to **1** both important biomethylating agents are closely linked.

There is a considerable demand for research on organometallic species generated in living organisms (cf. Section 6.15). Apart from the analogies with the chemistry of vitamin B_{12}, hardly any research has been concluded in this area.

5.1.4
Organoarsenic and Organotin Compounds

Prominent examples of toxic methylated metal ions are $[(CH_3)_2As]^+$ und $[(CH_3)_3Sn]^+$ [11]. The former is generated in rooms, which were painted with dyes such as Schweinfurter Grün, a copper(II) acetate-arsenate(III), $Cu(CH_3CO_2)_2 \cdot 3\,Cu(AsO_2)_2$. The death of the French emperor Napoleon I has been associated to a gradual poisoning because of the Schweinfurter Grün-painted rooms he particularly liked and inhabitated, especially during his last years on the island of St. Helena [12]. The pioneering work of F. Challenger on arsenic volatilization by the fungus *Scopulariopsis brevicaulis* arose from numerous cases of arsenic poisonings and first introduced the concept of biomethylation [13]. Challenger formulated a mechanism (now usually named “Challenger mechanism”) to describe the biomethylation of arsenic: in biological systems arsenate ions (As(V)) would be reduced to arsenite (As(III)). At the pH levels found in most living organisms, arsenite exists primarily as $H_2AsO_3^-$ and the methylation reaction is given in Eq. (4). The methyl donor $RRSCH_3^+$ is compound **A** [14].

$$As(O)OH)_2^- + RR'SCH_3^+ \longrightarrow CH_3As(O)OH)_2^- + RR'S \qquad (4)$$

Arsenic can undergo successive methylations, with each methyl transfer being preceded by reduction of arsenic(VI) to arsenic(III). Intermediate methylarsenic(III) species have been detected *in vivo* and may be a carcinogenic risk factor

[15]. In organisms mixtures of methylarsenicals are usually found, with the relative concentrations of the compounds varying substantially. The primarily metabolite in vertebrates is the cacodylate ion. It is excreted in urine. Microorganisms frequently generate and emit gaseous trimethylarsine. It has been reported that some invertebrates are able to generate the $(CH_3)_4As^+$ ion [16], making arsenic the only element reported to date that is able to accept four methyl groups during biomethylation. It is unlikely, however, that pentamethylarsenic, also being a long known compound [17], forms under biological conditions.

Investigations of the environmental biomethylation of tin compounds originated on the widely use of water-soluble stannonium compounds as biocidal reagents, especially in wood treatment (e.g., antifouling paints). The release of these compounds into natural waters and sediments with subsequent accumulation by invertebrates, such as shellfish, has posed potentially serious health problems [18]. Like arsenic and some other elements (selenium, tellurium) tin can undergo successive methylations. Tetramethyltin was one component of a mixture of volatile gases formed in anaerobic digestion of sewage sludge [19]. Note that tetramethyltin, $(CH_3)_4Sn$, is extremely poisonous because it reacts with water to form a water-soluble cation (cf. Eq. 5).

$$(CH_3)_4Sn \quad + \quad H_2O \longrightarrow [(CH_3)_3Sn]^+ OH^- \quad + \quad CH_4 \qquad (5)$$

Organotin compounds find wide application in agriculture. The advantage of the mostly used triorganyltin compounds is their excellent selectivity for lower organisms; in addition, their inorganic degradation products are not toxic. Examples of tin-based agrochemicals are $(n\text{-}C_4H_9)_3SnOH$ and $(C_6H_5)SnOAc$.

5.1.5
Organomercury Compounds

Several organomercury compounds of formula CH_3HgX are water-soluble, which makes them very poisonous to organisms [20]. They dissociate according to Eq. (6).

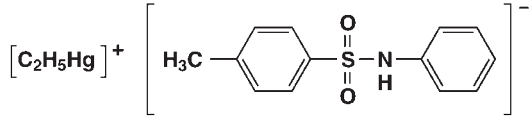
$$CH_3HgX \xrightarrow{(H_2O)} [CH_3Hg(H_2O)]^+ \ X^- \qquad (6)$$

The biological methylation of mercury (e.g., from weathering, volcanism, fossil fuels, chloralkali electrolysis) is effected by microorganisms that utilize methylcobalamin (**2c**); see Section 5.1.2.

The water-soluble organometallic **2** is the only natural product able to transfer the methyl group as a carbanion (cf. Eq. 7). As a soft Lewis acid (in the classification of Pearson), the methylmercuronium ion $[CH_3Hg]^+$ is soluble in the presence of hard bases such as $[NO_3]^-$ or $[SO_4]^{2-}$. In turn, soft bases such as (organic) sulfides thus make it lipophilic and enable its uptake by living organisms.

$$CH_3 — [Cob] + Hg^{2+} \xrightarrow{(H_2O)} H_2O \rightarrow [Cob]^+ + \underset{\mathbf{3}}{CH_3Hg^+} \qquad (7)$$

The catastrophy of Minamata in Japan (1953–1960), with 55 people killed and more than 1200 poisoned, for the first time focused attention on the environmental consequences of water-soluble organometal species. In this particular case, it was mercury-containing waste water that had access to marine organisms [3a, 20]. Fish, particularly, accumulates mercury, up to 250 ppb. In another case (Iraq, 1970–1971), the seed disinfectant ethylmercury *p*-toluenesulfonic anilide (**4**) had been applied to wheat and caused severe poisoning of consumers.



4

Organomercury compounds derive their toxicity from their solubility in both aqueous and lipophilic systems. They primarily affect the central nervous system. The reversible ionic/covalent bonding in organomercury compounds distributes them in the body. Thus, water-soluble species such as **3** are converted in the stomach into lipophilic **5** (cf. Eq. 8) $X = [NO_3]^-$, etc., where they are then absorbed.

$$\underset{\mathbf{3}}{CH_3HgX} + Cl^- \xrightarrow{(H_2O)} \underset{\mathbf{5}}{CH_3HgCl} + X^- \qquad (8)$$

Fixation to pyrimidine bases containing SH groups, such as uracil and thymine, is thought to explain the mutagenic effect of organomercurials.

5.1.6
Other Metal-alkyl Complexes in the Environment

Selenium was among the first elements to be investigated for its environmental importance and has an extensive biochemistry, in which biomethylation plays an important part [21]. Methylselenium compounds occur in many organisms and adenosylselenomethionine can form in cells [22]. The methylating ability of the seleno compound may be greater than that of **A**. Selenium biomethylation proceeds *via* the Challenger mechanism in analogy to its arsenic counterpart. It should be noted, however, that the chemical differences between selenium and arsenic may result in significantly different metabolic products [3b].

Tellurium biomethylation also occurs via the Challenger mechanism. However, it is not yet clear whether or not the same enzymes are used as in the case of selenium. Generation of volatile dimethyltelluride occurs by fungal action on telluride salts, through anaerobic disgestion of sewage sludge and by action of the facultative anaerobe *Pweudomonas fluorescans* on tellurite and tellurate salts [19, 23].

Evidence has been presented that suggests that $(CH_3)_2Po$ might be formed in the presence of bread mold and PoO_2 added to a culture treated with seaside sediments probably gave rise to the same compound [24]. ^{210}Po occurs in nature as a part of the ^{238}U decay series and has a half live of 138,4 days while ^{208}Po and ^{209}Po have somewhat longer half live (2.9 years and 102 years, respectively).

The formation of methyl antimony compounds by biomethylation has been confirmed only recently [25], despite the fact that methyl antimony compounds have been found in natural waters before [3a]. The research on alkylated antimony compounds in biological environments got an initial impetus from the examinations on the possible role of trimethylstibine as contributor to the sudden infant death syndrome [26].

Trimethyl bismuth occurring in the environment was detected in several environmental sources [27]. Biomethylation of bismuth very likely involves non oxidative methyl transfer, suggesting that **2c** is the most likely methyl source.

No anthropogenic sources for methyl germanium compounds are known. However, mono- and dimethylgermanium compounds have been found in natural waters with an uniform level of ca. 16 ng/L [28]. Tetramethyl germane was detected in geothermal gases and, most notably, a trimethyl germanium complex was found in human urine after consumption of germanium containing fish [29]. The methyl germanium species must therefore originate from biomethylation.

Organic lead compounds have been introduced into the environment as pollutants, e.g. the fuel additive (anti knocking agent) tetraethyl lead, making it difficult to establish a biogenic origin of related compounds. However, methyl lead compounds, e.g. $(CH_3)_4Pb$ have been discovered under environmental conditions, which are in accord with the biomethylation of lead [30]. In a comparative study, bioactive sediments methylated mercury, tin and lead substrates. Mercury underwent methylation ca. 10000 times faster than tin and lead, but lead was methylated more readily than tin [31].

Methyl thallium species have been discovered in natural water quite recently but thallium was reported to undergo biomethylation *in vitro* already more than two decades ago [32]. While the total thallium levels in oceans and lakes vary between 1.6 and 20.1 ng/L, levels exceeding 1000 ng/L have been found in industrial waste waters [33]. The proportion of $[(CH_3)_2Tl]^+$ to total thallium ranged up to 48%. The stability of the monomethyl derivatives varies in the order mercury(II) $>$ thallium(III) $\gg$ lead(IV) $\gg$ bismuth(V) [3b].

Monomethyl cadmium complexes were found in seawater and in arctic ice melts, where they reach levels of 1.2 ng/L (48% of total cadmium) [34]. Polar bacteria generate monoethyl cadmium species along with trimethyl lead compounds [30b]. It seems that cadmium undergoes biomethylation under conditions similar to that necessary for mercury. This means that complex **1c** would be the methyl donor.

Nickel biomethylation seems to occur only in methanogenic bacteria. However, methane generation plays a prominent role in terrestrial ecology and occurs over virtually the entire earth [3b]. Methanogenesis has been extensively under investigation and nickel is a required trace element for the methanogenic Archaea [35]. During this process, a methyl group bonded to nickel is converted to methane.

5.1.7
Perspectives

Water-soluble organometallic complexes should be developed further as reagents for alkyl- and aryl-group transfer processes. The example of cobalamin shows that nature exploits metal–carbon σ-bonds in aqueous systems for biomethylation processes. The increasing interest in biomethylation arises not only from concerns about the further fate of human induced metal containing compounds in the environment, but also from the need to recycle semiconducting compounds (electronic waste) and other materials containing elements that might undergo biomethylation. Biomethylation will furthermore be increasingly employed for the remediation of polluted soils and waters.

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5.2
Environmental and Safety Aspects

Boy Cornils, Ernst Wiebus

5.2.1
Introduction

A comprehensive review [1] summarizes the environmental status of processes using catalytic conversion in water, and – more especially – several very recent comments highlight the main environmental features of Ruhrchemie/Rhône-Poulenc's (RCH/RP's) novel oxo process as a prototype of an aqueous biphasic technique [2]. Based on two-phase catalysis with water-soluble catalysts, this has now been used successfully for almost 20 years [3]. Astonishingly, in the early days of academic research (following far behind the industrial utilization; cf. Section 1) the importance of water as a "liquid support" of the thus immobilized homogeneous catalysts was underestimated and not undisputed.

Jiang and Sen, in a paper on water-soluble Pd(III) catalysts and their use in manufacturing CO/ethylene copolymers wrote [4]:

> "The use of water as a reaction medium in place of organic solvents is of great interest from the standpoint of environmentally benign synthesis of organics and polymers since the use of the former would significantly decrease harmful emissions, as well as cut costs associated with solvent recycling,"

whereas the organizers of a NATO Advanced Research Workshop on *Aqueous Organometallic Chemistry and Catalysis* (comprising the absolutely top level of academic researchers) took a more cautious view [5]:

> "Environmentally benign synthetic processes may also favor water as a solvent [...] though this question is not completely free of ambiguity."

This view, quoted from the concluding discussion of the NATO symposium [5c], is based on the disputed opinion that water as a solvent must be a bad thing because it has no inherent odor and therefore can disappear unnoticed (!) in the event of a leak. On the other hand, Papadogianakis et al. [1] mention

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

"... Organometallic catalysis [...] affording both economic and environmental benefits."

Interestingly, some authors still describe the use of water in aqueous-biphasic operation as disadvantageously because "the detection in case of leakage" is supposedly difficult and "water shows no incineration of bleed streams" [2 m]. Although the industrial attractiveness of, e.g., the aqueous-biphasic catalyzed Ruhrchemie/Rhône-Poulenc hydroformylation process, speaks for itself, the "misunderstandings" still remain since the early days of scientific discussion about aqueous-biphasic processes starting 1994 (and that was 10 years after the beginning of economic operation in 1984!) at the mentioned NATO Advanced Workshop. But generally, the time delay between the original idea from the academia, the industrial realization of this technique (following initial experimental work by Kuntz, then at Rhône-Poulenc; for the history cf. Section 6.1.1) and only after at least 10 years of successful economic operation the catalytic community started more detailed scientific studies (cf. also the introductory Chapter). Nowadays, the academia proposes supports for the decision-making of catalyst recycling in the case of different catalysts, products, differently polar solvents, etc.

The divergence of opinion surrounding "aqueous chemistry" and two-phase catalysis makes two things very clear: firstly the need to provide more detailed information on the extremely favorable environmental potential of this type of process using catalysts dissolved in water; and, secondly, the frequently criticized fact (cf. Chapter 1 "Introduction" of this book and [6]) that universities are far behind industrial users in their knowledge of the subject and make up for this deficiency by gleaning information from industry. Only now, when two-phase catalysis is becoming a focus of university research, does willingness to accept the arguments and experience of industry seem to be on the increase – almost 15 years after industry set out on this environmentally beneficial, important, and advantageous path.

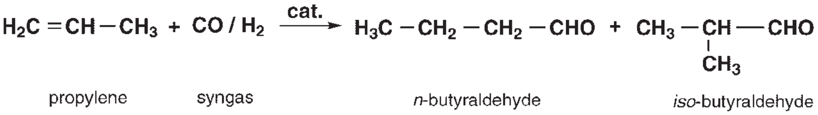
5.2.2
The Ruhrchemie/Rhône-Poulenc (RCH/RP) Process

The Ruhrchemie/Rhône-Poulenc oxo process has been reviewed repeatedly (cf. Section 6.1 and [2, 3, 6]). This two-phase hydroformylation process using catalysts dissolved in water, and also the scientific work on this subject untertaken by universities, have resulted in hundreds of publications and patents [7] and extensive experience with the first large-scale implementation.

It is probably no coincidence that the interest of the scientific world in biphasic hydroformylation, as the only process so far to be used industrially, lags far behind the industry's activities, although technical implementation normally follows the pure (not the applied) scientific results.

The advances in two-phase homogeneous catalysis can be demonstrated very easily, taking the hydroformylation reaction as a large-scale, economic example.

The advantages of homogeneous over heterogeneous catalysis are numerous, notably gentle reaction conditions, defined species of catalyst, the possibility of modifying the coordination sphere by varying the central atoms or ligands, and – as a consequence – high activity and selectivity. The disadvantage of homogeneous oxo catalysts, namely the difficulty of separating the catalyst from the reaction products after reaction has so far been overcome only by using complicated recycling processes [8a] or, taking UCC's low-pressure oxo process (LPO [9]) as an example, by thermal-stressing process steps. An oxo-active catalyst, dissolved in water but nevertheless highly active, extends the scope of hydroformylation and considerably simplifies process engineering, especially with regard to the environment [8b]. As the catalyst is soluble in the most readily available "solvent," namely water, and the reactants and products formed are soluble in the organic phase, this allows the catalyst to be separated very easily as a "mobile phase" by decantation and simple separation of the two phases ("two-phase" or "biphase process"). Although acting homogeneously, the oxo catalyst is located in a heterogeneous phase and is thus "heterogenized" or "immobilized". A suitable idea for a process presented by Kuntz [10] has been adopted and developed since 1982 by Ruhrchemie AG ([2d] and references therein) into an industrial-scale operation. Taking propene hydroformylation as an example (Eq. 1), the RCH/RP oxo process has been producing a total of 5 MM tons of *n*-butanyraldehyde (as well as less than 4% isobutyraldehyde) since 1984.



$$H_2C{=}CH{-}CH_3 + CO/H_2 \xrightarrow{cat.} H_3C{-}CH_2{-}CH_2{-}CHO + CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CHO \qquad (1)$$

Production of more than 3 million tonnes of *n*-butanal demonstrates the strength of the aqueous-phase oxo concept, as do some other applications of two-phase homogeneous catalyst systems such as Shell's SHOP process (two-phase but not aqueous; cf. Section 7.1) or variations by Rhône-Poulenc [11], Montedison [12], Kuraray ([13] and Section 6.9), or Hoechst [14] manufacturing higher olefins, vitamin precursors, telomers, or fine chemicals.

The triumph of water-soluble catalysts in homogeneous catalysts follows the laborious work involved in the development of water-soluble ligands (cf. Section 3.2 and [7]). Logically, the above-mentioned foreword to the NATO workshop [5] continues:

> "The design and synthesis of aqueous transition-metal catalysis requires broad knowledge of organometallic chemistry in water as well as of the physical and chemical properties of water itself. Water is now regarded as a unique solvent for certain stoichiometric and catalytic reactions involving organometallic compounds. Because of its highly polar, protic nature, water strongly influences the acid–base behaviour of solutes, the formation and disruption of ion-pairs and hydrogen bonds, and the extent of hydrophobic interactions. These effects often

> lead to unexpected reaction rates and selectivities, but the phenomena are still not fully understood."

The details and backgrounds of RCH/RP's developments have been described elsewhere, especially with respect to the highly sophisticated catalyst system [2d, 3, 15]. Kuntz's work on trisulfonated triphenylphosphine (TPPTS [2d, 10]) and the industrial improvements developed by Ruhrchemie eventually laid the foundation for the subsequent successful commercialization. TPPTS is an ideal ligand modifier for the oxo-active $HRh(CO)_4$. Without any expensive preformation steps, three of the four CO ligands can be substituted by the readily soluble ($1100\ g^{-1}$) nontoxic (LD_{50}, oral $> 5000\ mg\,kg^{-1}$) TPPTS, which yields the hydrophilic oxo catalyst $HRh(CO)[P(3\text{-sulfophenyl-Na})_3]_3$ (cf. Section 6.1). TPP*M*S and TPP*D*S (the appropriate TPP mono- and disulfonates) maintain their importance, except for industrial applications, alongside TPPTS because the different degrees of sulfonation permit fine adjustment of the hydrophilic/hydrophobic ratio of the catalysts during biphase operation. Recently other authors have described an oxo process employing TPPMS [16]. The flow diagram of the RCH/RP process is shown in Section 6.1.3.1.

Because of the solubility of the Rh(I) complex in water and its insolubility in the oxo products, the oxo unit is essentially reduced to a continuous batch reactor followed by a phase separator (decanter) and a stripping column. Propene and syngas are added to the stirred, noncorrosive catalyst solution in the reactor (for an explanation see Section 6.1.3). After reaction the crude aldehyde passes to the decanter and, while being degassed, is thus separated into the aqueous catalyst solution and the organic aldehyde phase. The catalyst solution exchanges heat and produces process steam in the heat exchanger and is replaced by the same amount of water (not catalyst solution!) dissolved in the crude aldehyde and is returned to the oxo reactor. The crude aldehyde passes through a stripping column in which it is treated with countercurrent fresh syngas and, if necessary, is freed from unreacted olefin. No side-reactions occur which decrease the selectivity or yield of the crude aldehyde, since this stripping of the aldehyde is carried out in the absence of the oxo catalyst, a distinctive feature of RCH/RP's process. The crude aldehyde is fractionally distilled into *n*- and *iso*butanal in a conventional aldehyde distillation unit. The reboiler of this "*n*/iso column" is designed as a heat-absorbing falling film evaporator incorporated in the oxo reactor, thus providing a neat, efficient method of recovering heat by transferring the heat of reaction in the reactor to cold *n*-butanal, which subsequently heats the *n*/iso column. The preferred hydroformylation temperature is 110–130 °C and is therefore used for the production of process steam. Whereas other oxo processes are steam "importers", the RCH/RP process including the distillation of *n*-/isobutanol exports steam.

The catalyst is not sensitive to sulfur or other oxo poisons, which is another environmental advantage. Together with simple but effective decanting, which allows the withdrawal of organic and other by-products at the very moment of separation, accumulation of activity-decreasing poisons in the catalyst solution is prevented. Therefore no special pretreatment or even purification steps are necessary. This reduces the environmental burden still further. For a considerable time the oxo units at Ruhrchemie were supplied with syngas derived from coal produced by the TCGP (Texaco coal-gasification process, in Ruhrchemie/Ruhrkohle's version). In some cases this can be an important factor as far as local resources are concerned. Since syngas from widely differing sources created a highly suitable link to hydroformylations, the biphase process is best for environmentally undemanding techniques.

The oxo catalyst $[HRh(CO)(TPPTS)_3]$, its formation from suitable precursors, and its operation are described in Section 6.1.3 (see [2]). The reaction system is self-adjusting – an important consideration for safety reasons – and thus control analyses are needed only at prolonged intervals. Owing to the high degree of automation, only two employees per shift supervise two oxo units with a total capacity of currently over 400 000 tons y^{-1}. The design obviates the need for certain equipment (e.g., feed and cooling pumps); the on-stream factor of the whole system exceeds $>98\%$. Typical reaction conditions, crude product compositions of the RCH/RP process averaged out over a 20-year period, and a discussion of selectivities and activities are given in Table 3 of Section 6.1.3.1.

The high selectivity toward the sum of C_4 products is a special feature of two-phase operation and results from the availability of water during hydroformylation [17].

The high selectivity toward C_4 products (a maximum of 1% of higher-boiling components, "heavy ends", are formed relative to butanals) makes fractional distillation after aldehyde distillation unnecessary, reduces expenditure, and thus also minimizes the environmental load. The manufacture of the by-products becomes part of the 2-EH (2-ethylhexanal) process since the heavy ends consist mainly of 2-ethyl-3-hydroxyhexanal, which, during downstream processing, is also converted to 2-EH. This (and the avoidance of butyl formates) is the reason for the considerable simplification of the process flow diagram compared with other process variants (see Figure 1).

As described earlier, as process steam permits economic heat management, the utilization of that part of the heat of reaction not used for *n*/iso separation is neat, saves energy, and is thus environmentally more benign. The consequences of the adjustable propene conversions and rhodium management (including losses) in respect of this heterogenized catalyst and for process factors are given elsewhere [2] together with comparative manufacturing costs. These show a crucial reduction of 10% in costs compared with other modern low-pressure oxo processes with their relatively complex operation. This demonstrates the favorable nature of the two-phase reaction system. Evidence of these advantages is apparent from the licences taken out for the process for commercial hydroformylation of butenes, and

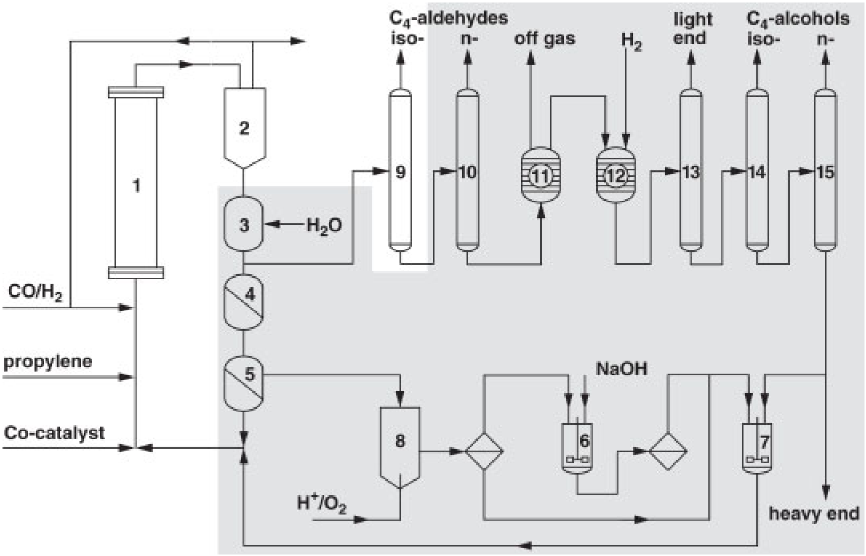


Fig. 1 Schematic flowsheet of a conventional oxo process [2 a]. The process steps superfluous RCH/RP's process are marked. 1, Oxo reactor; 3, decobalter; 2, 4, 5, separators; 6–8, Co catalyst make-up; 9, 10, butyraldehyde distillation; 11, by-product cracking; 12, hydrogenation; 13–15, butanol distillation.

for additional new plants [15, 18], which will increase the total production figures to approx. 800 000 tons y^{-1}.

5.2.3
Crucial Environmental Improvements

The fundamental advance represented by the RCH/RP process (as a prototype of a biphasic technique) in terms of the environment, conservation of resources, and minimization of environmental pollution can be demonstrated by various criteria and proved very convincingly by means of the environmental factor, *E* [19] (which is far more suitable and constructive than Trost's "atom efficiency" [20]). Sheldon defined the *E* factor as the ratio of the amount of waste produced per kilogram of product and specified the *E* factor for every segment of industry (Table 1).

As expected and shown in Table 2, this environmental quotient for conventional oxo processes (cobalt catalyst) and the production of the bulk chemical *n*-butyraldehyde is actually about 0.6–0.9, depending on the definition of the term "target product". This range indicates that the by-product isobutyraldehyde (see Eq. 1) occurring with conventional oxo processes is further processed by a number of producers (e.g., to neopentyl glycol [2,2-dimethylpropane-1,3-diol] or isobutyric acid)

Tab. 1 Environmental acceptability: the *E* factor [19].

	Product tonnage	***By-products/product ratio, w/w***
Oil refining	10^6-10^8	0.1
Bulk chemicals	10^4-10^6	$< 1-5$
Fine chemicals	10^2-10^4	5–50
Pharmacueticals	10^1-10^3	25–100 +

Tab. 2 *E* factors for oxo processes.

	By-products/product ratio, w/w	
	Isobutyraldehyde as product	***Isobutyraldehyde as by-product***
Co: high-pressure process	> 0.6	> 0.9
Rh: Ruhrchemie/Rhône-Poulenc	< 0.04	< 0.1

so that the isobutyraldehyde thus becomes the target product and the *E* factor then falls from 0.9 to 0.6. Strictly speaking, this observation is included in Sheldon's wider assessment, according to which the *E* factor is refined and becomes the "environmental quotient" *EQ*, depending on the nature of the waste. Since such quotients "are debatable and will vary from one company to another and even from one production to another" [19] they will not be discussed here. The crucial point is that, on the same basis (taking into account all by-products, including those produced in ligand manufacture, etc.) that gives conventional oxo processes an *E* factor of 0.6–0.9, this factor falls to below 0.1 in the RCH/RP process: an important pointer to the environmental friendliness of the new process (Table 2).

The low *E* factor (< 0.04) indicates that the utilization of material resources is improved more than tenfold: according to Sheldon's assessment [19] production of the bulk chemical *n*-butyraldehyde is classified alongside the highly efficient mineral-oil refining processes.

Whereas this important quotient is calculated solely from the product spectrum, process simplifications are a consequence of combining the rhodium catalyst with the special two-phase process. Compared with the conventional oxo processes and with other variants which include thermal separation of the oxo reaction products from the catalyst, the procedure is considerably simplified (see Figure 1).

Figure 1 demonstrates impressively that in the RCH/RP process most of the equipment commonly used for conventional oxo processes is not required. Items 10–15 in particular are superfluous because of the higher selectivity of conversion with Rh catalysts (also expressed in the *E* factor), whereas the efficient catalyst feed with the two-phase procedure obviates the need for items 3–8. It is therefore

Tab. 3 Environmentally important values for the RCH/RP process.

	Old Co high-pressure process	*RCH/RP Rh low-pressure process*
Selectivities		
– toward C_4 products [%]	93	> 99
– toward C_4 aldehydes [%]	86	99
Products other than *n*-butyraldehyde [%]	31	< 5
n/i ratio	80 : 20	93–97 : 7–3
Manufacturing costs	140	100
Capital expenditure costs	> 1.9	1
Waste water volume	70	1
Energy consumption figures		
– Steam	82	-6.5 (steam exporter)
– Power	> 2	1
– Syngas compression	1.7	1
Reaction conditions		
– Pressure [bar]	300	< 50
– Temperature [°C]	150	120
E factor	0.6–0.9	0.04– < 0.1

not surprising that a comparison of capital expenditure for the old Co high-pressure process with that for the RCH/RP process, showing that it is at least 1.9 times higher for the conventional oxo process, favors the new process.

The conservation of energy resources with the RCH/RP process is dramatic. Note should be taken of the much milder reaction conditions and of the fact that the RCH/RP process is an energy exporter because of an intelligent, integrated, heat network (an unusual occurrence for conventional oxo processes – including Rh processes with triphenylphosphine as ligand). Furthermore, the steam consumption figures for the old Co process are very much higher than those for the Rh process and power consumption was twice as high as that of the RCH/RP process: both of these factors represent an environmental burden. The compression costs alone for the required syngas are 1.7 : 1 (old Co process compared with RCH/RP process). The volume of waste water from the new process is 70 times lower than that from the Co high-pressure process – convincing evidence of the environmentally benign process (Table 3). Other consumption figures for the new process are correspondingly lower than those for the older Co high-pressure process.

No consideration has yet been given to the special technology of the RCH/RP process. The solubility in water of the oxo catalyst, and the fact that the resultant separation of the catalyst from the reaction product proceeds very quickly, mean that to all intents and purposes the catalyst does not leave the oxo reactor and its immediate surroundings. This is an important reason why the low Rh losses are in the ppb range. The reduced probability of leaks also increases effectiveness and safety.

The "solvent" water reliably averts the risk of fire inherent in the old Co process as a result of leaking, highly flammable, metallic carbonyl. The reaction system with its "built-in extinguishing system" reliably prevents such fires, and the painstaking measuring and monitoring procedure necessitated by the valuable catalyst metal rhodium, accompanied by constant simultaneous balancing of the RCH/RP process, permits any leaks from the aqueous system to be detected much earlier than was ever possible with the expensive mass and liquid balance of the old Co process. This also applies to the cooling system, in which any leak from the falling film evaporator would be noticed after a loss of only a few ppm of rhodium.

The solvent, water, is available instantly everywhere, and there is no need here to go into the special advantages of this polar solvent in respect of the process characteristics and its chemical effects [17, 21, 22]. It is not odor-free: because of its residual solubility for *n*-butyraldehyde it is as certain to be detected by the sensory/olfactory organs as are the product streams of other oxo processes. This is also the reason for the weakness of the criticisms leveled against water as a catalyst carrier (and quoted at the beginning) for being undetectable owing to the lack of odor.

5.2.4
Conclusions

Taking all the criteria into consideration, the RCH/RP biphasic oxo process is probably the soundest variant in terms of the environment; it is a "green" process which, in addition to environmental compatibility, has the advantage of being extremely cost-effective. The process is also "good-natured" from the handling aspect and thus inherently safe, as already emerged during development with a scale-up factor of $\gg 1:10\,000$ [2 f]. The process has great development potential, whether in terms of varying the ligand TPPTS (and thus the activity and selectivity of the conversion [2] as well as the possibility of achieving asymmetrical hydroformylations), or in terms of other starting olefins. The adoption of the aqueous two-phase reaction [2 d, 3] for hydroformylation in particular, and for other homogeneously catalyzed processes in general, shows the striking and unequaled advantages of this special neat type of "immobile" catalyst and its "heterogenization" by the catalyst carrier, water, as a result of which it is handled in similar fashion to a heterogeneous catalyst. This affects costs as well as environmental compatibility. The Ruhrchemie/Rhône-Poulenc process is on stream since 1984. Since then (and during the manufacture of 5 MM tons of *n*-butyraldehyde), the various plants experienced no serious accident which could be attributed to the use of water as the "mobile support".

The advantages of avoiding by-products, and of successful waste management, are further good points of the process which ultimately lead to higher cost-effectiveness as a result of better environmental compatibility and less downtime. This is further proof that in the long term the most effective processes are all likely to be the environmentally sound ones. The aqueous-biphasic process is thus a typical example for a “green process” using the “green catalyst” in that respect that “cleaner technologies” or “soft chemistry” are involved in the unideological meaning of the word [23]. Aqueous biphasic processes support sustainable developments (although the latter expression ought to be more precise), and the well-known question “So you think your process is green – how do you know?” (Glaxco [24]) is not adequate because of the high portion of production-integrated environmental protection [25] which is incorporated.

Among the homogeneously catalyzed processes the aqueous biphase variants will be in the forefront.

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6
Typical Reactions

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

6.1
Hydroformylation

6.1.1
Development of the Commercial Biphasic Oxo Synthesis

Boy Cornils, Emile G. Kuntz

6.1.1.1
History of Biphasic Catalysis

The history of biphasic homogeneous catalysis starts with Manassen's statement [1]:

> "... the use of two immiscible liquid phases, one containing the catalyst and the other containing the substrate, must be considered. The two phases can be separated by conventional means and high degrees of dispersion can be obtained through emulsification."

Roughly at the same time (in contradiction to a misleading publication by Papadogianakis [2]) and parallel to work done by Joó [3] and others [4], one of us (EK, then at Rhône-Poulenc) devoted time and effort to starting practical work on biphasic catalysis with organometallic catalysts (especially hydroformylation), developing the biphasic principle and the current well-known standard ligand triphenylphosphine trisulfonate (TPPTS, cf. Section 3.2.1).

These efforts have to be considered against an "official" background which Parshall [5] described as follows: "There was some use of transition-metal carbonyls in catalytic reactions of CO, but soluble catalysts played only a minor role in industry" (which even at that time was not correct [6b]), and "... the discovery that had the greatest impact on technology was recognition of the catalytic merit of rhodium complexes," thus indicating that only a few homogeneously catalyzed processes were commercialized before the early 1970s (among them hydroformylation with Co catalysts) and only some of them used precious metals as the catalyst base [7]. Examples were

1. the Pd/Cu catalytic system used for the oxidation of ethylene to acetaldehyde (Wacker–Hoechst process) [8];

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2. the production of 1,4-hexadiene by codimerization of ethylene and butadiene catalyzed by rhodium trichloride (the scale of the production was not mentioned and the catalyst cycle was not published [9]);
3. Monsanto's processes to yield acetic acid via methanol carbonylation [10] or a chiral L-DOPA precursor via hydrogenation of substituted cinnamic acids [11].

In the field of homogeneous catalysis, the late 1960s and early 1970s saw the discovery and utilization of catalytic systems involving metals associated with phosphorus compounds and their use in oxo syntheses. After the discovery of zerovalent metal complexes in 1957 by Quin and in 1958 by Malatesta and Cariello [12], the Wilkinson school of thought opened up a new field of rhodium chemistry by applying the remarkable catalytic properties of triphenylphosphine (TPP)-substituted Rh carbonyls [$HRh(CO)(TPP)_3$] in the hydrogenation and hydroformylation of olefins [13]. The important Wilkinson complex stimulated a rapid expansion in the chemistry of the lower-oxidation-state complexes. Thus, the progress made in the area of homogeneous catalysis includes processes such as the low-pressure, highly selective hydroformylation of lower olefins on a laboratory scale since 1976 using TPP-modified Rh-carbonyls with excess TPP (commercialized by Union Carbide, Celanese, and BASF; the name "LPO" – low-pressure oxo – stems from BP [14]); the oligomerization and functionalization of dienes; the telomerization of butadiene with water to octadienols; the hydrocyanation of olefins and dienes to adiponitrile; the hydrogenation, isomerization and dimerization of olefins; and miscellaneous reactions in fine chemistry [15].

In 1970, the discovery of these new organo-soluble catalysts based on Rh, Pd, or Pt was generally considered unfeasible for industrial processes because of the prohibitive price of the metals involved. However, the hgh activity and productivity of these catalysts made possible production levels of 100 000 $t\,y^{-1}$ with only a few dozen kilograms of precious metals needed as inventory by each single plant. Thus, the amount of precious metal involved represents only a minor part of the investment and the manufacturing costs, i.e., the price of the metal was not an important factor in the production unit cost, provided that its usage occurred without any loss. In 1972 this hypothesis was confirmed by Monsanto and its commercialization of the important process to generate acetic acid by methanol carbonylation [16].

Uncertainty still attended the handling of "commercial" quantities of precious-metal catalysts. Another point in question was the technique to be used for separating the products from the expensive catalysts, i.e., for solving the imminent problem of homogeneous catalysis, and for developing new catalyst recovery systems. One possibility for solving the separation problem mentioned was distillation, which however causes thermal stress of the products to be separated and – more seriously – of the residual catalyst. The other way was decantation as a consequence of a biphasic operation. In the oxo technique in particular, a biphase process for the homogeneously catalyzed work-up of formic acid esters by cracking with aqueous sodium formate solutions as catalyst has been employed since 1967 [17] by one of us (BC at Ruhrchemie). According to Manassen's proposal, decantation of catalyst and product meant that homogeneous catalysts dissolved in a liquid other than the organic phase to be separated. Water in particular would allow acceptable partition coefficients [18].

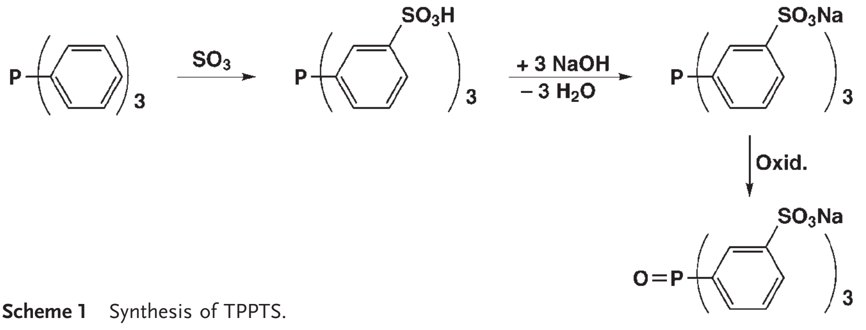
The principle of technically feasible two-phase catalysis with water, alongside Manassen's [1] theoretical considerations, was conceived in 1973, taking the hydroformylation of propene as an example. The metal-complex catalyst solubilized in water by a hydrophilic ligand converts the starting material into the reaction products, which can be separated from the catalyst by simple phase decantation. During the hydroformylation of propene it is important that the butyraldehyde (in which water is slightly soluble [3% at 20 °C]) does not extract the hydrophilic complex from the water-soluble catalytic system. It was obvious that on the one hand the best hydrophilic substitute for the proven TPP as a ligand for a water-soluble complex catalyst would be the sodium salt of an appropriate TPP sulfonate, which is thermally very stable. According to Wilkinson and Joó, monosulfonated triphenylphosphine (TPP*M*S, with a carbon/sulfonate ratio of 18 : 1) would be slightly foamy, extractable, and thus too organophilic (or hydrophobic) [3, 4 d]. It therefore proved essential to use the nondetergent, highly water-soluble (and thus hydrophilic), trisulfonated triphenylphosphine (TPP*T*S, C/sulfonate ratio 6 : 1) which is not extractable by an organic medium, notably not by water-saturated butyraldehyde [19].

6.1.1.2
Basic Work and Investigations by Rhône-Poulenc

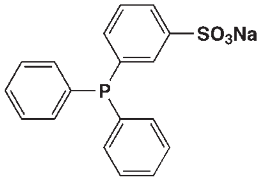
Following initial studies in 1974 the preparation of TPPTS was carried out via the sulfonation of TPP with "oleum" (i.e., concentrated sulfuric acid containing 20% by weight of SO_3) at 40 °C in one day. After hydrolysis and neutralization by NaOH, an aqueous solution of sodium sulfate and a mixture of different P compounds – consisting mainly of TPPTS and the corresponding P-oxide ("TPPOTS") as key chemical species – were obtained (Scheme 1) [20].

Crude TPPTS fractions contained TPPTS and TPPOTS in ratios of roughly 55 : 45. Today's much improved commercial procedures [21, 59] yield TPPTS/TPPOTS ratios of 94 : 6 under appropriate conditions, even in the crude material. Under suitable conditions even the less preferable mono- and the disulfonated species (TPP*M*S and TPP*D*S) can be formed in addition to TPP*T*S (Structures **1**–**3**).

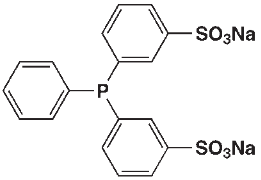
From 1974 onwards the scope of different reactions using biphasic catalyst systems, preferably with precious metals, was tested in laboratory-scale experiments. Among these were butadiene hydrodimerization, hydrogenation of acrylonitrile or cyclohexene, hydroformylation of propene, and some other conversions to fine



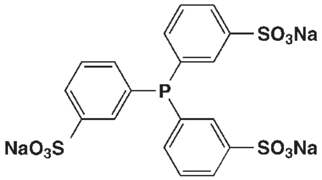
Scheme 1 Synthesis of TPPTS.



1
TPPMS



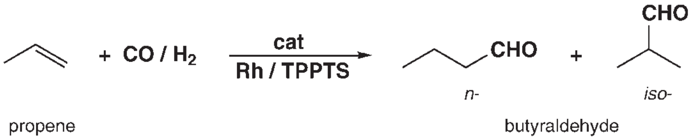
2
TPPDS



3
TPPTS

chemicals. Even during this initial stage of experimental work it was shown that only a small fraction of the precious metals (much less than 0.1 ppm Rh in the case of hydrogenation or hydroformylation) is leached by the organic phase. To be protected against Joó‘s and Beck’s results on the hydrogenation of pyruvic acid to lactic acid with aqueous solutions of Ru or Ph catalysts and TPPMS [3], Rhône-Poulenc (RP) filed different patent applications on the results achieved so far, taking into consideration the first laboratory results, RP’s interest in various product lines, and the economic importance of the invention [19]. Thus a series of patent applications protected three different main fields of interest [20], which included hydroformylation, hydrocyanation, and diene conversions.

Although RP was not an oxo producer, the excellent laboratory results with the biphasic system compared with conventional Co-based processes were regarded as providing an important opportunity. Taking the propene hydroformylation to *n*-butyraldehyde with a TPPTS ligand-modified rhodium catalyst as an example (Eq. 1), savings of up to 20% of propene and of syngas could be envisaged [20]. Although the reaction conditions in terms of activity, productivity, and selectivity were



(1)

roughly optimized by using TPPTS instead of TPPMS or TPPDS for hydroformylations, hydrocyanations, or diene conversions [20b,c, 21] the stability of the aqueous catalyst system, the commercial design of a biphasic oxo unit, and the influences of the different reaction variables – all under conditions of a continuous process – remained unknown.

Continuing the research on the reactivity of dienes with biphasic catalytic systems, Morel and Mignani discovered that the Rh/TPPTS functionalization of dienes in the 4-position has beneficial efforts [22]. With other asymmetrical dienes such as myrcene and the addition of, for example, ethyl acetoacetate, interesting regioselectivities of 99% for the desired isoprenic compounds were achieved [23, 24]. A couple of subsequent reaction steps, based on TPPTS from Ruhrchemie, thus convert geranylacetone to vitamin E [25].

6.1.1.3
Investigations by Ruhrchemie AG

Following earlier contacts Ruhrchemie AG (RCH), now a part of Celanese AG, and Rhône-Poulenc joined forces in 1982 to develop a *continuous* biphase hydroformylation process for the production of *n*-butyraldehyde from propene.

On the basis of the ideas documented in RP's applications, RCH used its own expertise with the biphasic catalytic cracking process [17] and its long experience in converting laboratory-scale syntheses to commercial processes – as Ost [26] observed as long ago as 1907: "It is one thing to discover a process that is right in principle but a very different thing to introduce it on the industrial scale." In transferring processes to the economic scale, Ruhrchemie was successful in many cases, e.g., with the Fischer–Tropsch synthesis [27], the Co-based oxo reaction (invented at RCH by Otto Roelen [6]), the UHMW variant of Ziegler-type HDPE [28], the Texaco coal gasification process [29], etc. In the case of biphasic oxo synthesis, appropriate agreements defined the tasks for RP (support) and RCH (R & D, engineering, production, licencing, and marketing and distribution agreements). Between 1982 and 1984, in a period of less than 24 months, RCH developed and tested a completely new process for which no prototype was available. Using a scale-up factor of 1:24 000 the first production unit employing the "Ruhrchemie/Rhône-Poulenc oxo process" went on stream in July 1984 with an initial capacity of 100 000 tons per year (see Section 6.1.3) [30].

Because of Ruhrchemie's commitment and status as an important oxo producer, development was thus primarily driven by product and commercial considerations. It was not until the 1990s that further development became science-driven, including especially all the scientific research work currently being conducted at universities as a result of the successful implementation of the RCH/RP process.

All the development tests included the full work-up of the reactants, side-streams and products, reflecting the characteristics of the biphasic system, the

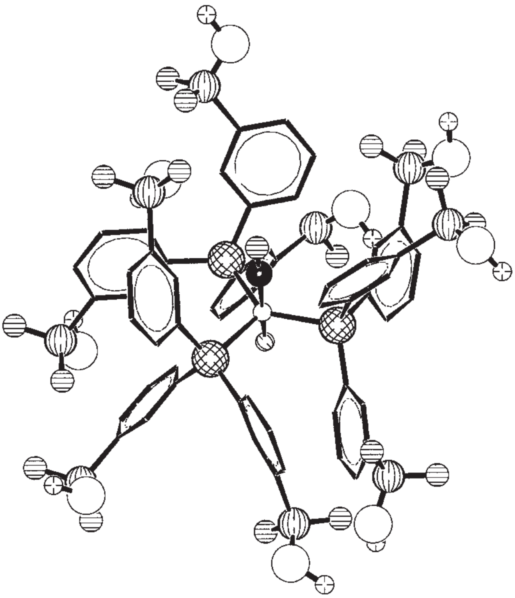


Fig. 1 [Rh(CO)(TPPTS)$_3$], the water-soluble catalyst of the RCH/RP process.

testing of reaction parameters, the dynamic responses of both the reactor and the catalytic system, product qualities, etc. [31].

The heart of the new process is the new catalyst [HRh(CO)(TPPTS)$_3$] (Figure 1). Apart from the handling of the new catalyst system with a water-soluble species, a virtually new design of a hydroformylation process had to be prepared, involving much detailed work. Most of the solutions and numerous important variants have been patented. This detailed work focused on the special aspects of the process flow chart as indicated in Figure 2 [61].

The sensitive areas of the process include the reactor and its environment (reactor, separation, control units, cooling devices, off-gases), olefin and syngas feed, preparation of the catalyst (including central atom, ligands, accompanying salts, and modifiers) and catalyst recycling (including catalyst separation from different sources and catalyst recycling at different levels). For all of the sensitive areas marked, various solutions were developed by RCH.

Some of the conditions of the new process were based on RP's patents but all had to be adjusted to the rougher operation conditions of a commercial plant, to different qualities and purities of commercially available reactants (olefins, syngas, catalyst precursors), to a normal operation of 8760 h y^{-1}, and to the fine-tuned relationships between, e.g., temperatures, pressures/partial pressures, concentrations of various organic and inorganic components in different phases, mass and heat transfer, and flow conditions of a continuous process [32]. The economics of cool-

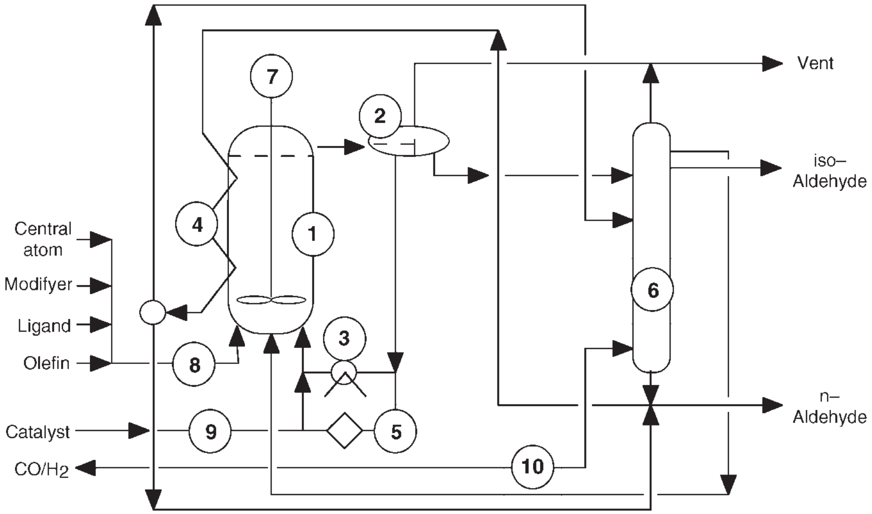


Fig. 2 General design of the biphasic hydroformylation process: focal points of R & D work as indicated. (1) Reactor; (2) decantation; (3, 4) heat recovery and steam generation; (5) Rh recycle; (6) distillation; (7) control units; (8, 10) feed; (9) catalyst.

ing and heat recovery and the utilization of unreacted substrates in off-gases or vents are of special importance [33]. In contrast to the literature [34], a combination of a low-pressure oxo stage and a subsequent high-pressure stage proved to be more convenient than vice versa [33 c].

Detailed work undertaken for the first time on this technique, which is mainly described in patents and therefore little known, has focused on special reaction conditions and special measures (even within extreme limits) which are based on the biphasic character of the conversion such as pH values, addition of CO_2, salt effects and solution ionic strengths, catalyst modifiers, spectator effects, or ultrasonic devices, etc. [35]. The measures mentioned allowed a considerably simplified process to be used compared with other oxo processes (basically consisting of a stirred tank reactor and a decanter), this being a consequence of the biphasic concept of RCH/RP. These relationships ensure a smooth, stable operation yielding high selectivities to *n*-butyraldehyde (cf. Section 6.1.3.1). The specific load of the system may be altered very unequivocally by varying the temperature, pressure, partial pressures, and concentrations (catalyst, ligands, and salts).

In contrast to other low-pressure processes, the purification of syngas is not critical [36]. Surprisingly, the presence of carbon dioxide in the syngas acts as a selectivity improver [35 c], a similar effect to the one described later by Rathke and Klinger [37]. The oxo units at Oberhausen have also been supplied with syngas from a TCGP (Texaco coal gasification plant) without any problems [29]. Although the RCH/RP process is best suited to the conversion of lower olefins to the appropriate aldehydes (ethylene through pentenes) higher olefins may be converted using special precautions (cf. [38, 39 c, 60]) or special ligand developments [40].

There was no prototype for the behavior and the lifetime of the biphase catalytic system and catalyst recycling. Intensive research work has been conducted to identify the optimal sets of operating conditions to ensure maximum efficiency and lifetime of the catalytic system. The advantages over other low-pressure processes are that the catalyst is on a "short circuit" around the reactor (ensuring fewer losses) and that because of mechanical separation of catalyst and product no thermal stress occurs. The catalyst may be regenerated within the reaction system using chemical or mechanical means [41]. Recycling by working-up the precious metal content as an ultimate solution is exceptional [42]. The losses of catalyst, a factor of major importance figuring in catalytic systems containing precious metals, are $< 10^{-9}$ g Rh/kg *n*-butyraldehyde. Other methods of recovering Rh from oxo crudes [43, 44 a] or distillation residues [45] are also being investigated.

The catalyst $[HRh(CO)(TPPTS)_3]$ (see Figure 1) is prepared from suitable precursors, which contain the central atom and the ligand. The catalyst can be preformed or may be prepared *in situ* [46]. The preparation of TPPTS is not as simple as it seems: many misinterpretations concerning catalytic strength, behavior, extractabilities, cluster or colloid formation, etc., can be explained by unsuitable methods of ligand syntheses and purification [39, 59]. For special purposes TPPTS may be modified [47]. These modifications of the original sulfonated phosphines result in, for example, different solubilities, re-immobilization [48], etc. Very different levels of phase behavior and thus various degrees of immobilization may be adjusted.

The search for water-soluble ligands other than TPPTS is a focal point of present academic and industrial work. In cooperation with Professor Herrmann of the Technical University of Munich and others, the R & D department of Ruhrchemie has focused on special water-soluble phosphines [49], phosphites [50], and other catalysts [48, 51, 52], and the most suitable way to manufacture them. The application of external or internal solubilizers may be recommended [44, 53]. Appropriate complexes with other central atoms can be used for other syntheses [54].

Although commercial emphasis has been on propene hydroformylation, other starting olefins include higher-molecular-mass substrates; see, e.g., [33 d, 38 a–d, 40, 44 b, 52, 55].

6.1.1.4
The RCH/RP Process as the Final Point of Development

As mentioned earlier, the first commercial oxo plant using the Ruhrchemie/Rhône-Poulenc biphasic process went to stream in 1984 [30] and has been reviewed recently [56, 61]. Water-soluble catalysts offer significant advances in homogeneous catalysis: the "heterogenization" of the catalyst in a second, immiscible liquid phase ("liquid support") immobilizes the catalyst phase, thus combining the advantages of heterogeneous catalysis (e.g., long lifetime, easy separation of product from catalyst) with those of the homogeneous mode, e.g., defined species of catalyst, gentle reaction conditions, high activity, and high selectivity.

The Ruhrchemie plant reacts propene and syngas and yields *n*-butyraldehyde as the desired product besides less than 4% isobutyraldehyede. The basic flow diagram of the 800 000 $\mathrm{t\,y^{-1}}$ units is shown in Section 6.1. A smaller unit converts butenes. Additional plants are under construction.

In comparison with other oxo processes the procedure is much simpler and many steps in the original process are superfluous (cf. Section 5) [57]. The actual oxo catalyst is simply made within the oxo unit by reacting suitable Rh salts with TPPTS of appropriate quality without any additional preformation step. The reaction system is self-adjusting; the on-stream factor of the whole system is $> 98\%$. Typical reaction conditions and performances on a 14-year average are given in [56, 57].

The successful implementation of the biphasic oxo process as *the* prototype of a homogeneous aqueous catalyst system will have different consequences for hydroformylation reactions as described in Chapter 3 (development of new ligands) and Chapter 4 (solvents, co-solvents, micellar techniques) and Section 6.1.3.2.

The suitability of the homogeneous aqueous catalysts and thus the scope of application in general will be extended in commercial or pilot-plant operation to other central atoms and reactions such as Heck reactions and other carbonylations (with Pd), hydrogenations (Pd, Pt, Rh, Ir), formation of water-soluble polymers (Pd), vinylations, metathesis conversions (Ru), Suzuki couplings, etc. (cf. Section 6.6).

A recent NATO workshop on aqueous homogeneous catalysis [58] summarized the situation:

> "A very important practical and environmentally beneficial aspect of the use of a separate aqueous phase in catalytic reactions producing water-insoluble products is the potential for relatively easy and complete recovery of water-soluble catalysts. This could lead to the elimination of further steps for removal of traces of heavy metal from the product and to considerable savings."

Reality shows this to be true.

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6.1.2
Kinetics

Raghunath V. Chaudhari, Bhalchandra M. Bhanage

6.1.2.1
Introduction

Biphasic catalysis using water-soluble metal complexes has been the most significant development in recent years to facilitate commercially viable separation of homogeneous catalysts from the reaction products. It is well known that several attempts to heterogenize the homogeneous catalysts, which include polymer anchoring, supported liquid-phase catalysis [1], and use of organometallic catalysts on mineral supports [2, 3], have not led to industrially viable alternatives. However, biphasic catalysis, in which water-soluble organometallic catalysts are contacted with the immiscible organic phase containing reactants and products with or without gaseous reactants in a multiphase system (gas–liquid–liquid) has proved to be the most attractive alternative to the conventional homogeneous catalysts. It was after the work of Kuntz [4] on the synthesis of triphenylphosphine trisulfonate (TPPTS) ligand and its application in the hydroformylation of olefins that the research on water-soluble catalysis gained momentum. The concept has been proven on a commercial scale in the Ruhrchemie/Rhône-Poulenc process for the hydroformylation of propene to butyraldehyd [5]. The role of different water-soluble ligands, their synthesis and stability as well as other means of intensifying these gas–liquid–liquid catalytic reactions have been extensively studied and the subject has been reviewed by Kalck and Monteil [6], Herrmann and Kohlpaintner [7], Cornils [5, 8], and Beller et al. [9] among others. Herrmann and Kohlpaintner [7] have shown that Rh complexes with other water-soluble ligands, such as BISBIS (sulfonated (2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl) and NORBOS, give exceptionally high activities and *n*/*i* ratios. Uses of cationic [10], non-ionic [11], and surface-active [12] phosphines as water-soluble ligands have also been proposed. A Rh catalyst prepared with a surface-active ligand such as a sulfobenzene derivative of tris(2-pyridyl)phosphine gives a 70% yield of the aldehyde products in hydroformylation of tetradecene [13]. Of all catalyst systems studied, Rh–TPPTS is the most suitable and commercially proven catalyst system for biphasic hydroformylation.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Several modifications of the water-soluble catalysts using co-solvents (cf. Section 4.3 and [14]), micelle forming reagents (Section 4.5 and [15]), super-critical CO_2-water biphasic system (cf. Section 7.4 and [16]), SAPC (Section 4.7 and [17]), and catalyst binding ligands (interfacial catalysis) [18, 24] have been proposed to overcome the lower rates observed in biphasic catalysis due to poor solubilites of reactants in water. So far endeavors were centered on innovating novel catalyst and development of the existing systems. However, limited information is available on the kinetics of biphasic hydroformylation.

Besides development of new catalysts and ligands, the understanding of the overall kinetics of biphasic catalytic reactions is an equally important aspect in the evolution of an economical process. In the case of hydroformylation of olefins using water-soluble catalysis, the rate of reaction will be governed by several factors, which include dissolution of CO, H_2 and olefins in organic and aqueous (catalyst) phases, the solubility of these components, their partition coefficients, and the intrinsic kinetics of the reaction occurring in the aqueous phase (cf. Section 4.1). The most important of these is the knowledge of kinetics, which is also essential to understanding of the reaction mechanism and elucidation of the rate-controlling step.

The aim of this contribution is to present a review of the current status of the kinetics of hydroformylation of olefins using water-soluble catalysis. Kinetic studies for various reaction systems and the role of ligands, pH, co-solvents, and surfactants are discussed.

6.1.2.2
Kinetics Using Water-soluble Catalysts

Hydroformylation of olefins using water-soluble catalysis in an example of a gas–liquid–liquid catalytic reaction in which reaction of two gaseous reactants (carbon monoxide and hydrogen) with gaseous or liquid-phase olefin occurs in the presence of a water-soluble catalyst in liquid–liquid dispersion. The reaction of dissolved gases and olefins occurs in the aqueous ("bulk") phase or organic–aqueous interface. The understanding of the overall rate of hydroformylation is important in this multiphase catalytic system, which depends on gas–liquid and liquid–liquid mass transfer, the solubility of gas-phase reactants in the organic and aqueous phases, the liquid–liquid equilibrium properties and intrinsic kinetics of the reaction in the aqueous phase. In addition the dispersion characteristics of the droplets, the droplet size and the bubble size can also influence the rate of reaction. Depending on the fractional hold-up of the aqueous phase, it will be either a continuous aqueous phase with dispersed organic droplets or a dispersed aqueous phase in a continuous organic medium. The coupled influence of mass transfer with chemical reaction is expected to be quite different in these two situations. Below, the current status of development of the kinetics of hydroformylation in two-phase systems is reviewed.

6.1.2.2.1
Kinetic Studies Without Any Additives

The hydroformylation of 1-octene using a water-soluble Rh–TPPTs catalyst in a biphasic medium was studied in the absence of any additive or co-solvent by Bhanage [19]. These experiments were carried out under conditions such that the aqueous phase containing Rh–TPPTS catalyst was dispersed in the continuous organic phase consisting of 1-octene and toluene. The results indicated absence of hydrogenation products and the selectivity to hydroformylation was greater than 98%, with the *n*/*i* ratio in the range 1–2 : 1. The aqueous Rh complex catalyst was found to retain its activity even after 10 recycles, indicating negligible deactivation. The effect of the concentration of catalyst precursor, TPPTS, and 1-octene, and of the partial pressure of CO and hydrogen, was studied in a temperature range of 353–373 K. The rate of reaction was found to be first order with respect to catalyst concentration. This was explained as a consequence of oxidative addition of hydrogen to acyl carbonyl rhodium species as the rate-determining step [20]. The reaction rate was found to be 0.7th order with CO partial pressure in contrast to the CO inhibition observed for homogeneously catalyzed hydroformylation [21].

For a water-soluble catalyst, the concentration of dissolved carbon monoxide in the aqueous phase is very low compared with that in the organic phase; hence, formation of a dicarbonyl Rh species [$(RCO)Rh(CO)_2(TPPTS)_2$], which is believed to be responsible for a negative-order dependence [20], is not very likely. Therefore, this difference in trends is not truly due to any change in the reaction mechanism. In the homogeneous catalytic reaction, the rate varies linearly with carbon monoxide pressure in the lower region and only beyond a certain pressure of CO is the inhibition in the rate observed. The 1-octene concentration dependence of the rate of hydroformylation showed an apparent order of 1.7 (Figure 1), but this was due to an inappropriate account of the solubility variation with changes in 1-octene concentration. Bhanage [19] has shown that if the variation in solubility is accounted for, the rate of reaction shows first-order dependence on 1-octene concentration.

The form of rate model described by Eq. (1) was found to represent the data satisfactorily. This model is derived from the well-known mechanism of hydroformylation [20] assuming addition of hydrogen to acyl rhodium species as a rate-determining step:

$$R = \frac{kK_1\,K_2\,K_3\,A\,B\,C\,D}{1 + \alpha B} \tag{1}$$

where A = partial pressure of hydrogen [MPa]
B = partial pressure of carbon monoxide [MPa]
C = concentration of catalyst [lmol m^{-3}]
D = concentration of olefin [lmol m^{-3}]
k = reaction rate constant
K_1, K_2, K_3, α = constants

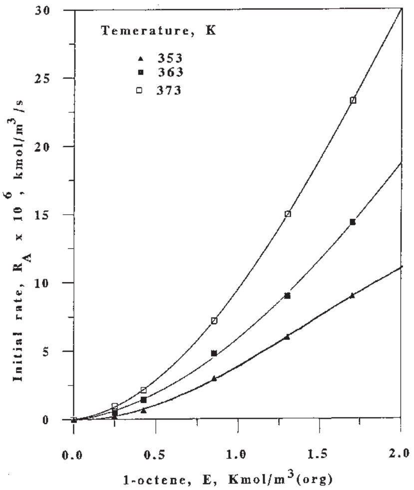

Fig. 1 Effect of concentration of 1-octene on the rate of hydroformylation of 1-octene [19].

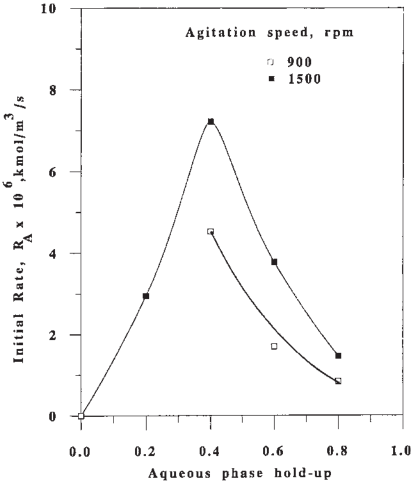

Fig. 2 Effect of aqueous-phase hold-up on the rate of hydroformylation of 1-octene [19].

The effect of aqueous phase hold-up on the rate of reaction for 900 and 1500 rpm is shown in Figure 2.

At 1500 rpm, the rate vs. ε_{1a} (aqueous phase hold-up) shows a maximum. For kinetic control, the rate is expected to vary linearly with catalyst loading. However, in a case where the reaction occurs essentially at the liquid–liquid interphase, it would depend on the liquid–liquid interfacial area even though liquid–liquid mass transfer is not rate-limiting. For $\varepsilon_{1a} > 0.4$, phase inversion occurs and the interfacial area would be determined by the dispersed phase, which would be the organic phase. Since, for $\varepsilon_{1a} > 0.5$, ε_1 will decrease with an increase in ε_{1a}, a reduction in liquid–liquid interfacial area is expected. Hence, the observed results of a decrease in the rates with an increase in ε_{1a} indicate a possibility of interfacial reaction rather than a bulk aqueous-phase reaction [5]. For $d_L < 0.3$ mm, a very large interfacial area ($a_1 = 6\,\varepsilon_1 d/d_1$) in the range $(4-5) \times 10^4$, l/m is likely to exist compared with the volume of the aqueous phase.

Hydroformylation of ethylene using a water-soluble Rh–TPPTS catalyst system has been investigated [22] using a toluene–water solvent system at 353 K. The effect of TPPTS concentration on rate passes through a maximum of at a P/Rh ratio of 8 : 1. The effect of the catalyst precursor concentration on the rate of reaction first increases and above a certain concentration it remains constant. The effect of aqueous-phase hold-up shows a maximum in the rate ($\varepsilon_{1a} = 0.4$). The apparent reaction orders for the partial pressure of hydrogen and ethylene were found to be 1 and zero respectively. A strong inhibition in the rate with an increase in P_{CO} was observed.

Herrmann et al. [23] have reported the hydroformylation of propene using a Rh–BISBIS catalyst system in a continuous reactor. The activity of this catalyst was 45.5 mol g^{-1} min^{-1}, three times higher than that of Rh–TPPTS catalyst (15 mol g^{-1} min^{-1}). The *n*/*i* ratio also improved from 94 : 6 (TPPTS) to 97 : 3 (BISBIS). They have also studied the hydroformylation of 1-hexene at 5 MPa CO/H_2 pressure and in the temperature range 395–428 K, and observed that the activity increased from 0.73 to 10.73 when the temperature was raised from 396 to 428 K whereas the *n*/*i* ratio decreased from 97 : 3 to 94 : 6. They have tested the catalyst stability after 16 h of continuous hydroformylation. Cornils et al. [24] have shown that hydroformylation of propene using Rh–TPPTS catalyst operates under conditions of significant gas–liquid mass transfer resistance. A detailed analysis of the engineering aspects supported with experimental validation is necessary to understand the critical scale-up issues. Kinetics of hydroformylation of styrene using a biphasic HRhCO(TPPTS)$_3$ catalyst [25] showed that the rate was first order with respect to catalyst loading, H_2, CO and styrene concentrations. The rate was found to be limited by transport of styrene from organic to aqueous phase under certain conditions.

The development of supported aqueous-phase catalysis (SAPC) opened the way to hydroformylating hydrophobic alkenes such as oleyl alcohol, octene, etc. (cf. Section 4.7 [17]). SAPC involves dissolving an aqueous-phase HRh(CO)(TPPTS)$_3$ complex in a thin layer of water adhering to a silica surface. Such a catalyst shows a significantly high activity for hydroformylation. For classical liquid–liquid systems, the rate of hydroformylation decreases in the order 1-hexene > 1-octene > 1-decene; however, with SAP catalysts, these alkenes react at virtually the same rate and the solubility of the alkene in the aqueous phase is no longer the rate-determining factor [26].

6.1.2.2.2
Effect of Co-solvents on Biphasic Hydroformylation Reactions

It has been reported that use of a suitable co-solvent increases the concentration of the olefin in water (catalyst) while retaining the biphasic nature of the system. It has been shown that using co-solvents like ethanol, acetonitrile, methanol, ethylene glycol, and acetone, the rate can be enhanced by several times [27, 28]. However, in some cases, a lower selectivity is obtained due to interaction of the co-solvent with products (e.g., formation of acetals by the reaction of ethanol and aldehyde). The hydroformylation of 1-octene with dinuclear $[Rh_2(\mu\text{-SR})_2(CO)_2(TPPTS)_2]$ and $HRh(CO)(TPPTS)_3$ complex catalysts has been investigated by Monteil et al. [27], which showed that ethanol was the best co-solvent. Purwanto and Delmas [28] have reported the kinetics of hydroformylation of 1-octene using $[Rh(cod)Cl]_2$–TPPTS catalyst in the presence of ethanol as a co-solvent in the temperature range 333–353 K. First-order dependence was observed for the effect of the concentration of catalyst and of 1-octene. The effect of partial pressure of hydrogen indicates a fractional order (0.6–0.7) and substrate inhibition was observed with partial pressure of carbon monoxide. A rate eqution was proposed (Eq. 2).

$$R = \frac{k\,A\,B\,C\,D}{(1 + K_1 A)(1 + K_2 B)^2} \tag{2}$$

where K_1, K_2 = constants

The kinetics of hydroformylation of 1-octene using $[Rh(cod)Cl]_2$ as a catalyst precursor with TPPTS as a water-soluble ligand and ethanol as a co-solvent was further studied by Deshpande et al. [14]. In this case the aqueous phase was continuous and the organic phase was in the form of dispersed droplets. The organic phase consisted of 1-octene in octane and the aqueous phase consisted of Rh/TPPTS along with the co-solvent ethanol. The effect on the initial rate of reaction of the concentration of catalyst and of 1-octene, and of the partial pressures of hy-

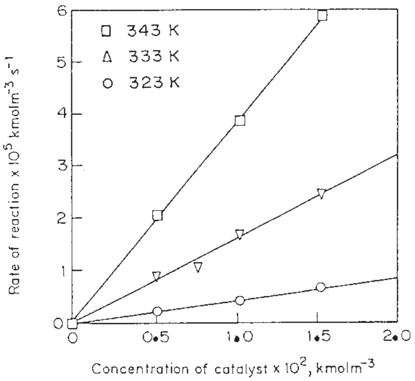

Fig. 3 Effect of catalyst concentration on the rate of hydroformylation of 1-octene using ethanol as a co-solvent [14].

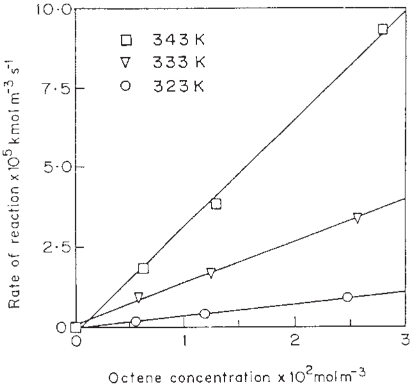

Fig. 4 Effect of 1-octene concentration on the rate of hydroformylation of 1-octene using ethanol as a co-solvent [14].

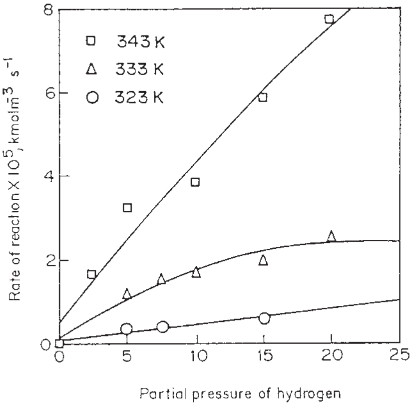

Fig. 5 Effect of partial pressure of hydrogen on the rate of hydroformylation of 1-octene using ethanol as a co-solvent [14].

drogen and carbon monoxide, in a temperature range of 323–343 K and at a pH of 10 was studied. The rate of reaction was found to be first order with respect to catalyst concentration (Figure 3) and 1-octene concentrations (Figure 4).

Since the catalytic cycle involves individual stoichiometric steps leading to formation of products and regeneration of catalyst, it is more meaningful to have a mechanistic rate model to predict the observed trends. In this respect a rate model (Eq. 3) derived according to the mechanism assuming addition to olefin to $HRh(CO)_2(TPPTS)_2$ to be the rate-controlling step was found to fit the data exceedingly well. The activation energy was found to be 15.7 kcal mol^{-1}.

$$R = \frac{k_2\,A\,B\,C\,D}{1 + k_1A + k_2AB + k_3B^2} \tag{3}$$

where k_1, k_2, k_3 = constants

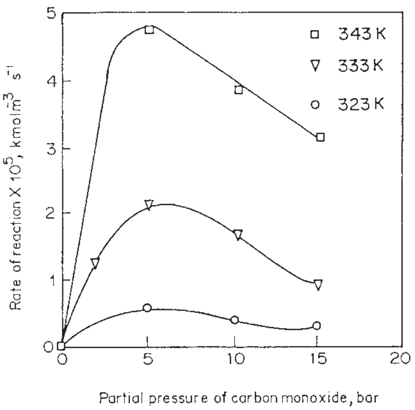

Fig. 6 Effect of partial pressure of carbon monoxide on the rate of hydroformylation of 1-octene using ethanol as a co-solvent [14].

Kinetics of hydroformylation of styrene using HRhCO(TPPTS$)_3$ catalyst in a biphasic system with various co-solvents was investigated by Nair [25]. He reported that 50% aqueous (*v*/*v*) *N*-methyl pyrrolidone (NMP) solution showed much better performance in comparison to ethanol as a co-solvent due to its non-reactive nature towards the aldehyde products. The rate was found to increase by seven times compared to that in the absence of any co-solvent. Kinetic study at 373 K revealed that the rate was first order dependent with catalyst concentration, fractional order with CO and first order tending to zero order with styrene concentration.

6.1.2.2.3
Effect of pH on the Rate of Biphasic Hydroformylation

The pH of the aqueous catalyst phase or addition of salt shows a strong influence on the rate of reaction and the *n*/*i* ratio of the aldehyde products [29]. Smith et al. [30] have reported a drop in the activity when the pH of the reaction medium was reduced from 6.8 to 5 for an Rh/AMPHOS nitrate catalyst system (AMPHOS = 1-*N*,*N*,*N*-trimethylamino-2-diphenyl phosphinoethane, iodide). Hydroformylation of 1-tetradecene with a water-soluble Rh–NABSDPP (NABSDPP: Na–butyl sulfonated diphenylphosphine) catalyst gave poor rates in acidic pH (2.5 to 6) medium. A seven- to eightfold increase in the rates was obtained when the pH was increased from 6 to 10 [31]. A detailed investigation into the kinetics of hydroformylation of 1-octene with an Rh/TPPTS catalyst system using ethanol as a co-solvent has been reported by Deshpande et al. [32] for various pH values. The rate increased by two- to fivefold when the pH increased from 7 to 10, while the dependence of the rate was found to be linear with olefin and hydrogen concentrations at both pH values. The rate of hydroformylation was found to be inhibited at higher catalyst concentrations at pH 7, in contrast to linear dependence at pH 10 (Figure 7). The effect of concentration of carbon monoxide was linear at pH 7, which is different from

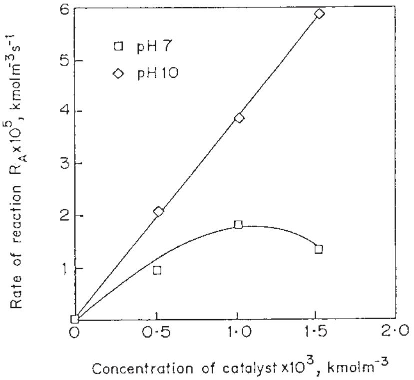

Fig. 7 Effect of catalyst concentration on the rate of hydroformylation of 1-octene at different pH [32].

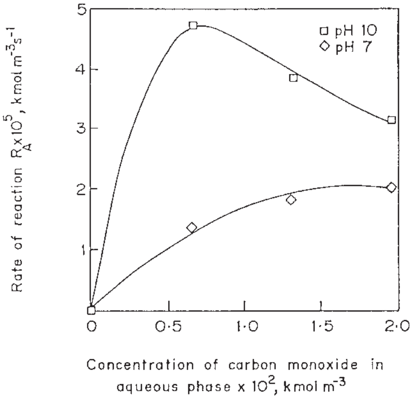

Fig. 8 Effect of partial pressure of carbon monoxide on the rate of hydroformylation of 1-octene at different pH values [32].

the usual observation of a negative-order dependence. At pH 10, substrate-inhibited kinetics was observed with respect to CO (Figure 8).

6.1.2.2.4
Effect of Surfactant Addition

The addition of various surfactants and micelle forming agents on the biphasic hydroformylation of olefins was also considered as a tool for enhancement of the reaction rate. The relation between the extent of emulsification of the reaction mixture and the performance of hydroformylation reaction was also investigated. Mass transfer effects in biphasic hydroformylation of 1-octene in the presence of cetyltrimethylammoniumbromide (CTAB), was studied by Lekhal et al. [33]. A mass-transfer model based on the Higbie's penetration theory was proposed to predict the rate of hydroformylation in a heterogeneous gas–liquid–liquid system under gas–liquid mass transfer limitations. Biphasic hydroformylation of 1-dodecene in the presence of various micelle-forming agents with aqueous [$RhCl(CO)(TPPTS)_2$] catalyst was studied by Li et al. [34]. Solubility of 1-dodecene was enhanced in the presence of mixed micelles due to decrease in the critical micelle concentration (CMC), and higher conversion and selectivity were observed in the mixed micellar solution compared to that for a single micelle type. For biphasic hydroformylation of 1-dodecene in the presence of CTAB, Yang et al. [35] reported several agitator configurations for improving the mixing, dispersion and interphase mass-transfer. The following form of empirical macro-kinetic equation was found to represent the initial rate data as well as the n/i ratio of aldehydes (Eq. 4).

$$R = k\,N^m {C_{CTAB}}^n D^p \left(\frac{V_O}{V_W}\right)^q \tag{4}$$

In another report a semi-empirical rate equation has been proposed combining mechanisms of homogeneous and interfacial parameters for biphasic hydroformylation of 1-dodecene with water-soluble Rh-complex catalyst [36].

6.1.2.2.5
Role of Catalyst-binding Ligands

In a report Chaudhari et al. [18] have shown that the rate of biphasic hydroformylation can be enhanced severalfold by using a catalyst binding ligand which facili-

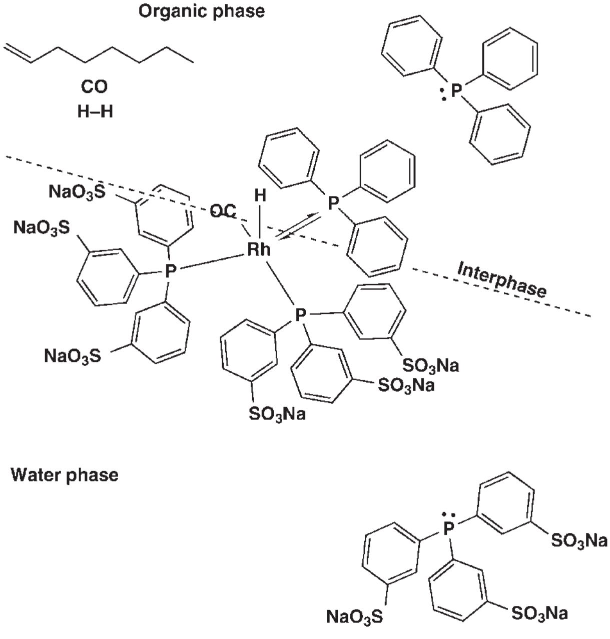

Fig. 9 A schematic representation of interfacial catalysis.

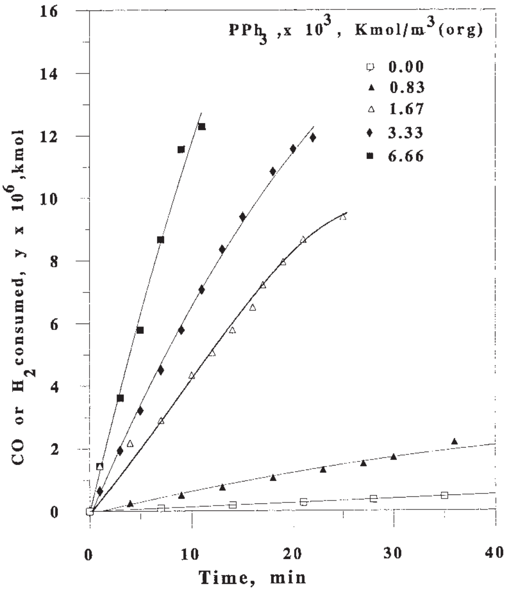

Fig. 10 Effect of catalyst binding ligand on the rate of hydroformylation of 1-octene [18].

tates interfacial catalytic reaction. This approch involves the use of a ligand that is insoluble in the aqueous, i.e., catalyst phase but has a strong affinity for the metal complex catalyst. The interaction of the ligand and the catalyst takes place essentially at the liquid–liquid interface (Figure 9); thus the concentration of the catalytic species will be enriched at the interface where it can access the reactants present in the organic phase, in significantly higher concentrations with respect to the aqueous phase [5]. This results in a dramatic increase in the rate of such a biphasic catalytic reaction, as indicated by experimental data on the hydroformylation of 1-octene using an Rh–TPPTS complex catalyst with triphenylphosphine as a catalyst binding ligand [18].

The rate of the reaction was enhanced by 10–50 times in the presence of catalyst binding ligands when compared with the biphasic hydroformylation reaction (Figure 10). This concept has also been demonstrated in reverse for the hydroformylation of water-soluble olefin (allyl alcohol) and organic phase containing catalyst, $HRh(CO)(PPh_3)_3$. In this case the catalyst is present in the organic phase, whereas the catalyst binding ligand (TPPTS) is added to the aqueous phase.

The effect of reaction parameters, such as the concentrations of catalyst and olefin and the partial pressures of CO and hydrogen, on the rate of reaction has been studied at 373 K [19]. The rate varies linarly with catalyst concentration, olefin concentration, and partial pressure of hydrogen. Typical substrate-inhibited kinetics was observed with the partial pressure of carbon monoxide. Further, a rate equation to predict the observed rate data has been proposed (Eq. 5).

$$R = \frac{k\,A\,B\,D}{(1 + K_1 B^2)(1 + K_2 E)} \tag{5}$$

where E = concentration of olefin
K_1, K_2 = constants

It is important to note that the kinetic trend were completely opposite for cases with and without catalyst binding ligand for carbon monoxide. Since, under conditions of interfacial catalysis, a higher CO concentration is accessible to the catalytic species, substrate inhibition is observed.

6.1.2.3
Concluding Remarks

A review of the kinetics of hydroformylation using water-soluble Rh complex catalysts demonstrates that the rate behavior varies significantly for biphasic catalytic reactions depending on the ligands, additives, and co-solvents. Particularly, the kinetics with respect to CO shows variation for different systems. A major limitation to the rate of biphasic hydroformylation is the solubility of the olefin in the aqueous catalyst phase. Using co-solvent, catalyst binding ligands and SAPC, the rates are enhanced significantly. Although sufficient information on the intrinsic kinetics is now available, further studies on understanding of the role of gas–liquid and liquid–liquid mass transfer, and the influence of dispersed-phase hold-up and drop size, and phase equilibrium properties, is necessary. Interface mass transfer parameters and gas–liquid–liquid hydroformylation conditions also need to be investigated.

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6.1.3
Reaction of Alkenes

6.1.3.1
Lower Alkenes

Carl D. Frohning, Christian W. Kohlpaintner

6.1.3.1.1
Introduction

Although olefins with variable chain lengths have been successfully hydroformylated in aqueous two-phase reactions, a distinction between lower and higher olefins is reasonable. The solubilities of ethylene (C_2), propene (C_3) and C_4 alkenes, herein referred to as lower olefins, in the aqueous catalyst phase is high enough to assure chemical reaction without phase transfer limitations. Olefins with chain lengths greater than C_4 show significantly lower solubilities, thus making special means necessary to overcome phase transfer limitations (see Section 6.1.3.2).

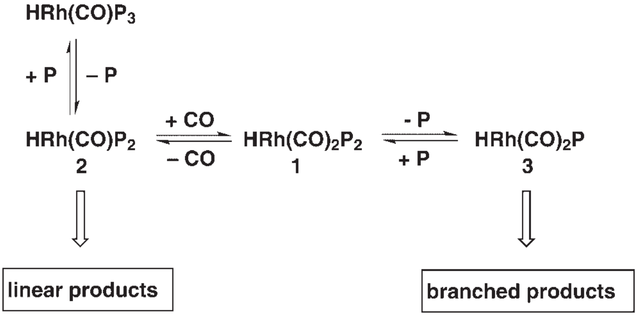
The following contribution will describe the basics of aqueous two-phase hydroformylation as they apply to C_3 and C_4 alkenes. The focus will be on TPPTS (cf. Section 3.2.1) as a ligand and rhodium as the active metal center, e.g., the complex $HRh(CO)(TPPTS)_3$ [1]. Emphasis will be put on the commercial applications and the basic description of the processes.

6.1.3.1.2
Mechanism

The mechanism of the oxo reaction has been extensively studied in the past. A comparative study of both commercially applied oxo catalysts $HRh(CO)(TPP)_3$ (TPP = triphenylphosphine) and $HRh(CO)(TPPTS)_3$ was performed by Horváth [2]. The latter, water-soluble catalyst is considered to react according to the dissociative mechanism. However, remarkable differences exist in the catalytic activity and the selectivity of the organic- and water-soluble catalysts. The latter shows much lower specific activity but an increased selectivity to linear products in the hydroformylation of propene. From an Arrhenius plot it is concluded than the dissociation energy of TPPTS from $HRh(CO)(TPPTS)_3$ is about 30 ± 1 kcal/mol

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5



Scheme 1 Initial equilibria forming the active catalyst species; P = TPP or TPPTS.

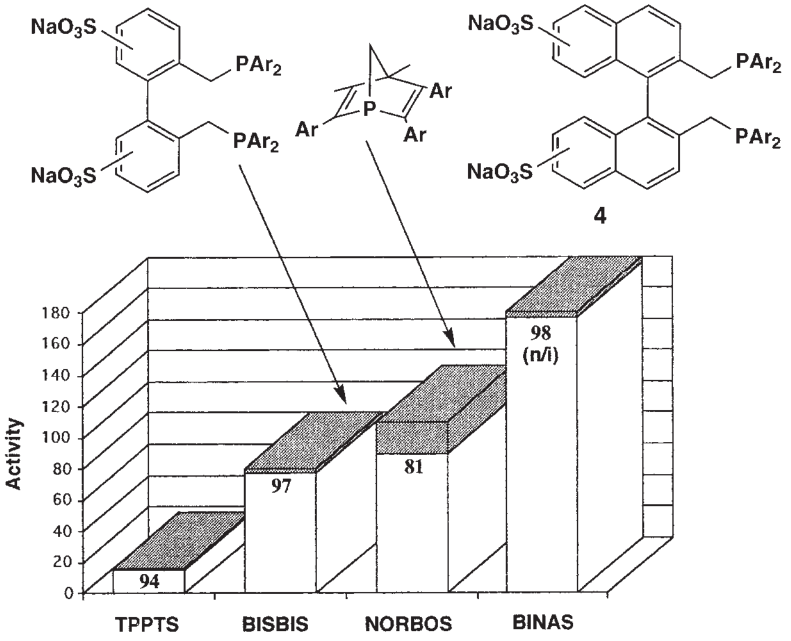
(1 kcal/mol = 4.18 kJ/mol). Compared with the dissociation energy of TPP from $HRh(CO)(TPP)_3$ (19 ± 1 kcal/mol [3]) the difference is greater than 10 kcal/mol, thus explaining the lower catalytic activity at comparable reaction conditions. Additionally it was shown that $HRh(CO)(TPPTS)_3$, in contrast to its organic-soluble derivative, does not form $HRh(CO)_2(P)_2$ (P = TPPTS; **1**) at syngas pressures up to 200 bar. By dissociation of either carbon monoxide or TPPTS the unsaturated species $HRh(CO)(TPPTS)_2$ (**2**) and $HRh(CO)_2(TPPTS)$ (**3**) are generated, which are responsible for the formation of linear or branched aldehydes (Scheme 1). As $HRh(CO)(TPPTS)_2$ is formed by dissociation of TPPTS from $HRh(CO)(TPPTS)_3$, and $HRh(CO)_2(TPPTS)$ is obtained through an equilibrium reaction from $HRh(CO)_2(TPPTS)_2$, the observed increased selectivity to linear products becomes explicable.

6.1.3.1.3
Kinetics

Limited data are available for the kinetics of the oxo synthesis with $HRh(CO)(TPPTS)_3$. The hydroformylation of 1-octene was studied in a two-phase system in the presence of ethanol as a co-solvent to enhance the solubility of the olefin in the aqueous phase [4]. A rate expression was developed which was nearly identical to that of the homogeneous system, the exception being a slight correction for low hydrogen partial pressures (Eq. 1).

$$R_0 = k\frac{[\text{octene}]_0[\text{cat}][H_2][CO]}{(1 + K_{H_2}[H_2])(1 + K_{CO}[CO])^2} \qquad (1)$$

The lack of data is obvious and surprising at a time when the Ruhrchemie/Rhône-Poulenc process has been in operation for more than 20 years. A rigid reaction rate model, established under idealized conditions, becomes complex and complicated when it is transferred to the hydroformylation of lower olefins under conditions relevant to the industrial practice, as the mass transfer phenomena involved in a triphasic system (gas–liquid–liquid) in large reactors have to be taken



P/Rh	80	7	14	7

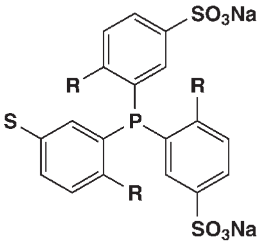
Fig. 1 Comparison of water-soluble phosphines in the continuous hydroformylation of propene. Activity = [mol (*n* + *iso* aldehyde)]/[g atom (rhodium) × min]; Ar = *m*-$C_6H_4SO_3Na$; for NORBOS Ar = *p*-$C_6H_4SO_3Na$.

into account. The resulting algorithm in general is limited to a narrow bandwidth of operating conditions, thereby diminishing the applicability and reliability of this type of models. The substitution of rigid models by data-driven models (e.g. so-called artificial neural networks) is under consideration for some years, showing first promising results.

6.1.3.1.4
Recent Developments

In order to develop highly active and selective catalysts for propene hydroformylation, several ligands based on biphenyl or binaphthyl structures were synthesized and have been applied in the oxo synthesis [5]. The results are summarized in Figure 1 showing activity and selectivity of these ligands compared with TPPTS. A mixture of six-, seven- and eightfold sulfonated NAPHOS, called BINAS (**4**), together with rhodium is the most active water-soluble oxo catalyst known today. Even at very low phosphine to rhodium (P/Rh) ratios, n/i selectivities of 98 : 2 are achieved.

A challenge in synthesizing new water-soluble ligands is the direct functionalization of new or previously known organic phosphines. The plethora of functionalized phosphines available today have been categorized and discussed in [6]. In the particular case of sulfonated phosphines the introduction of the sulfonato group is extremely difficult as the phosphines tend to oxidize during treatment with oleum (sulfur trioxide dissolved in concentrated sulfuric acid) and require special synthesis methods [26]. Some information about special phosphines such as **5**–**7** and special manufacturing conditions is given in [7] (cf. Section 3.2.1).



5 S = H, R = H
6 S = SO_3Na, R = CH_3
7 S = SO_3Na, R = OCH_3

6.1.3.1.5
Commercial Applications

The industrial hydroformylation of short-chained olefins such as propene and butenes is nowadays almost exclusively performed by so-called LPO (low-pressure oxo) processes, which are rhodium-based. In other words, the former high-pressure technology based on cobalt has been replaced by the low-pressure processes, which cover nearly 80% of total C_4 capacity due to their obvious advantages (cf. [8]). Nevertheless, some cobalt processes are still in operation for propene hydroformylation, for example as second stages in combination with a low-pressure process serving as the first stage [8, 9].

Two basic variants for LPO processes exist: the homogeneous processes, i.e., the catalyst and the substrate are present in the same liquid phase; and the two-phase process (Ruhrchemie/Rhône-Poulenc process, RCH/RP) using a water-soluble catalyst. The homogeneous processes dominate the field by far (Table 1), a consequence as much of their early development as of the licencing policy for the two-phase process. Both types of processes use rhodium as catalyst metal in combination with a suitable phosphine as ligand. More precisely, the ligand is triphenylphosphine (TPP) in both cases, applied as such in the homogeneous case and in its water-soluble (sulfonated) variant (TPPTS) in the RCH/RP process. Some phosphine ligands have also gained commerical importance for LPO processes recently [27], and no metal other than rhodium has been successfully applied commercially in this technology.

Tab. 1 Capacities for C_4 products by various processes (excluding 2-EH).

Process	***Catalyst***	***Capacity [× 1000 t]***	***Share [%]***
Union Carbide	Rh	3040	46
BASF	Rh	900	14
Celanese	Rh	890	13
Mitsubishi	Rh	680	10
Eastman	Rh	610	9
Leuna/Neftekhim	Co	425	7
Shell	Co	75	1
Subtotal		6620	100
Unknown/not disclosed		230	
Total		6850	

About 75% of the *n*-butyraldehyde generated is converted into 2-ethylhexanol, which is almost completely consumed as a phthalate ester, e.g., in plasticizers for PVC. The remainder of the butyraldehydes are either used as such for chemical synthesis, converted to acids or amines, or – more important today – hydrogenated to the butanols which are either directly sold as solvents or are further converted into acrylate esters, glycol ethers, butyl acetate, and butyl amines.

6.1.3.1.6
Economic and Ecological Aspects

The RCH/RP process has been in operation for more than 13 years now. The water-soluble catalyst $HRh(CO)(TPPTS)_3$ combines the advantages of a homogeneous catalyst (high activity, high selectivity) with those of a heterogeneous one (catalyst/product separation, cf. Section 1). These advantages, in addition to a highly efficient recovery of process heat, lead to a superior technology which also results in a cost advantage compared with the classical homogeneous processes. In Table 2 a comparison of the RCH/RP process with a process using a homogeneous rhodium catalyst is given [10, 11]. As can be seen, the RCH/RP process has its strengths in the efficiency of material usage (raw materials, energies, and by-product credits)

Tab. 2 Cost comparison of RCH/RP process vs. classical Rh process.

	RCH/RP	***Rh-based***
Raw materials	88.9	89.0
Energy costs	1.5	9.7
Credits (isobutyraldehyde, *n*-butanol)	– 7.7	– 11.4
Sum = material costs	82.7	87.3
Fixed costs + license fee	17.3	22.1
Manufacturing costs	100.0	109.4

along with smaller fixed costs due to the ease of operation. The overall cost advantage is estimated to be roughly 10% compared with the standard processes.

The ecological benefits of this modern process are clear and can be summarized as follows:

- usage of water as a nontoxic, nonflammable solvent;
- efficient usage of C_3 raw material (propene);
- high selectivity toward the desired products;
- energy consumption minimized, e.g., net steam exporter!
- efficient recovery of catalyst (loss factor $= 1 \times 10^{-9}$);
- ligand toxicity is not critical (LD_{50} (oral) > 5 g/kg);
- environmental emissions almost zero;
- excellent atom economy.

Along with other water-based reactions the RCH/RP process has been reviewed recently with respect to its environmental attractiveness, by Sheldon [12]. Overall the RCH/RP process is, besides a technical success, an outstanding example of the impact of modern technology on economy and ecological aspects at the same time.

6.1.3.1.7
C_3 Process Description

Ruhrchemie AG was the first to seize upon the idea of applying a water-soluble rhodium catalyst and thus commercialize a process which has been elaborated on a laboratory scale by Rhône-Poulenc earlier [13, 14]. It took only two years of intensive research to develop the technical concept and to erect the first plant, which went on-stream in 1984 [15]. By 1987 the second unit was already built and today the total capacity for *n*-butyraldehyde amounts to more than 350 000 tons per year [16, 17]. An additional plant for the production of *n*-pentanal from *n*-butene was brought on-stream in 1995 (see Section 6.1.3.1.8).

Basically, the requirements for a process using an aqueous catalyst phase are the same as for the homogeneous processes. The reaction of propene, hydrogen, and carbon monoxide takes place in the aqueous catalyst solution or at the phase boundary. The second, organic, layer is formed by the reaction product, e.g., butyraldehydes. Intimate contact between the catalyst solution and the gaseous reactants has to be provided by intensive gas dispersion at the bottom of the reactor together with sufficient stirring. The two liquid phases form an intimate admixture (emulsion) upon stirring which occupies most of the reactor volume, leaving only a small headspace as an internal reservoir for the gaseous reactants. A heating/cooling device is necessary in order to enable start-up of the reactor and to control the exothermic hydroformylation reaction (about 28 kcal/mol or 118 kJ/mol). Finally, the mixture of liquid and gaseous products has to be withdrawn from the reactor, products and catalyst have to be separated, and the latter has to be recycled.

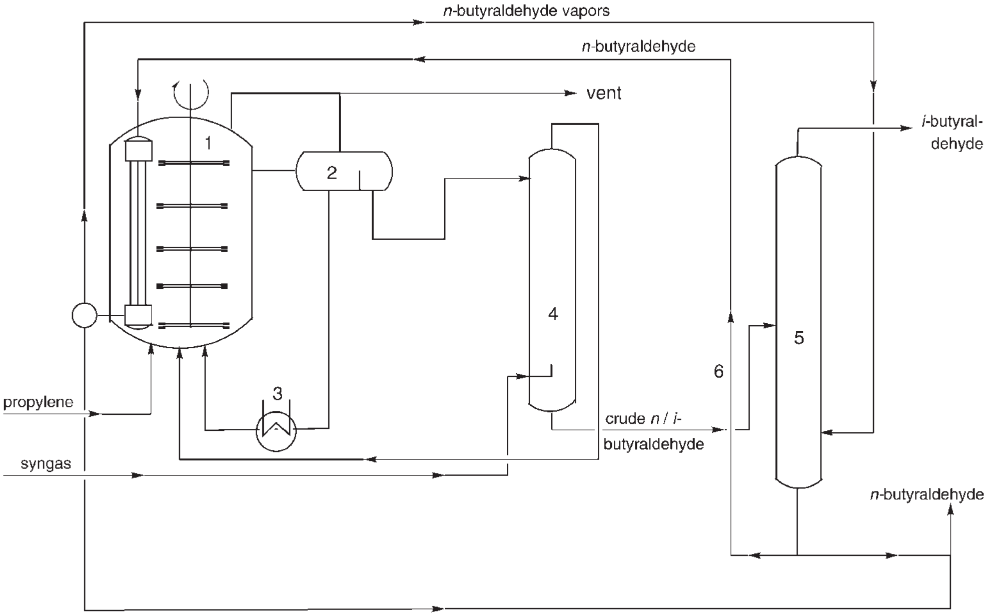


Fig. 2 Ruhrchemie/Rhône-Poulenc process (RCH/RP): flow diagram.

A simplified scheme of the RCH/RP unit is presented in Figure 2 [1, 10, 11]. The reactor (1) is essentially a continuous stirred tank reactor equipped with a gas inlet, a stirrer, a heat exchanger and a catalyst recycle line. Catalyst and reactants are introduced at the bottom of the reactor. Vent gas is taken from the head of the reactor and from the phase separator. Control of the liquid volume inside the reactor is simple: the liquid mixture composed of catalyst solution and aldehydes leaves via an overflow and is transferred to a phase separator (2), where it is partially degassed. The separation of the aqueous catalyst solution (density of the catalyst solution $\approx$ 1100 g/L) and the aldehydes occurs rapidly and completely, favored by the difference in densities (density of aldehyde layer $\approx$ 600 g/L due to dissolved gases). The catalyst solution passes a heat exchanger and produces process steam that is consumed in downstream operations. Some water is extracted from the catalyst solution by its physical solubility in the aldehydes (about 1.3% w/w) which may be replaced before the catalyst solution re-enters the reactor.

The most ingenious part of the RCH/RP process is the subsequent stripping column (4). From the raw organic phase coming from the phase separator and entering at the top of the stripping column, the dissolved reactants are removed by a fresh synthesis gas countercurrent stream. The pressure inside the stripping column is kept slightly higher than the pressure in the reactor, e.g., no additional mechanical compression or heating is necessary to recycle unconverted reactants.

Tab. 3 RCH/RP process: typical data.

	Range	***Typcial value***
Reaction conditions		
Temperature [°C]	110–130	120
Pressure [bar]	40–60	50
CO/H_2 ratio	0.98–1.03 : 1	1.01
Propene conversion [%]	85–99	95
Propene purity [%]	85–99.9	95
Product composition [%]		
Isobutyraldehyde	4–8	4.5
n-Butyraldehyde	95–91	94.5
Isobutanol	< 0.1	< 0.1
n-Butanol	0.5	0.5
Butyl formates	Traces	Traces
Heavy ends	0.2–0.8	0.4
Selectivity to C_4 products [%]	> 99	> 99.5
Selectivity to C_4 aldehydes [%]	99	99
n/*i* ratio	93 : 7–97 : 3	95 : 5

The resulting crude aldehydes are virtually free of propene as well as propane and contain only minimum amounts of dissolved synthesis gas. The head gas from the stripping column is fed back into the reactor.

The crude aldehydes are split into *n*- and isobutyraldehyde in the distillation column (5). The heat required is supplied by the hydroformylation itself: the re-boiler of the distillation is a falling film evaporator which is incorporated in the synthesis reactor using *n*-butyraldehyde as the heat carrier. This system is clearly advantageous over the classical hydroformylation processes, as the RCH/RP process not only efficiently uses the heat of reaction but is a net steam exporter. The favorable combination of stripping column, distillation, and heat recovery system is closely linked with the properties of the catalyst solution. The raw aldehydes are virtually free of ingredients of the catalyst solution, thus avoiding any of the well-known side reactions which take place in the presence of even traces of catalyst during thermal treatment. The fact that highly reactive *n*-butyraldehyde may be used as a heat-transfer medium well unterlines this statement.

The active catalyst species $HRh(CO)(TPPTS)_3$ is generated during the start-up of the reactor. Rhodium is introduced in any suitable form, e.g., as acetate or as a salt of another organic acid. The resulting solution, with a rhodium concentration in the range 200–350 ppm, is brought to reaction temperature under synthesis gas pressure, leading to the formation of the active yellow complex. No induction period is observed when the reaction is started immediately by adding propene and synthesis gas after the reaction temperature of about 120 °C has been reached, making start-up and close-down operations extremely easy. Some typical data for the hydroformylation of propene are summarized in Table 3 [8].

6.1.3.1.8

C_4 Process Description

It is an intrinsic characteristic of the oxo reaction – not only in the presence of aqueous catalyst solutions – that the reaction rate in comparable conditions declines with increasing chain length of the olefin (see Section 6.1.3.2). This fact is attributed, *inter alia*, to the decreasing solubility of higher olefins in the aqueous catalyst solution, which correspondingly leads to low olefin concentrations and thus reduced reaction rates [18]. There are not too many options to overcome the problem: increase in temperature (with a negative impact on long-term ligand stability and *n*/*i* ratio), increase in rhodium concentration (cost factor), or addition of substances improving the solubility of the olefins (complicating the simple basic process). For the hydroformylation of *n*-butene a slight increase in rhodium concentration is sufficient to ensure appreciable space-time yields at industrially relevant conditions.

The cheapest source of *n*-1-butene is "raffinate II", a C_4 cut from which butadiene (by extraction) and isobutene (by conversion into methyl *t*-butyl ether) have been removed. The remaining mixture of C_4 hydrocarbons contains about 50–65% of *n*-1-butene, the remainder consisting of *cis*/*trans* *n*-2-butene and saturated butanes. A high concentration of *n*-1-butene in the raffinate is desirable for obvious reasons. On the other hand, the price for "raffinate II" is directly proportional to its content of *n*-1-butene. Therefore it is an unconditional requirement for the process to be compatible with different concentrations of *n*-1-butene in the feedstock.

The most valuable product of C_4 hydroformylation is *n*-pentanal, whereas the isomers 2-methylbutyraldehyde and 3-methylbutyraldehyde are less in demand and lower in value. A catalyst with high selectivity should not catalyze the hydroformylation of 2-butene and should coonvert 1-butene predominantly to *n*-pentanal. Both requirements are fulfilled by the Rh/TPPTS system [19]. However, despite the high regioselectivity in hydroformylation, a side reaction occurs which diminishes the overall selectivity. Under reaction conditions, parallel to the hydroformylation reaction part of the *n*-1-butene is isomerized to *n*-2-butene, which is not hydroformylated in the presence of Rh/TPPTS under regular reaction conditions.

The choice of reaction temperature depends on several aspects. High temperatures favor the activity of the catalyst system and increase the partial pressure of *n*-1-butene (b.p. $-6.1\,^\circ C$) but have a negative impact on the long-term ligand stability. As a compromise a reaction temperature 5–10 °C higher than in the hydroformylation of propene is acceptable. Also, with respect to the partial pressure of *n*-1-butene the overall pressure is lower: about 40 bar has been proven suitable. The stripping column, as the central unit in the process, deserves special attention: in order to remove dissolved butenes and butane completely from the oxo crude a balance between temperature and pressure conditions has to be established. The process design corresponds to the rCH/RP process for the hydroformylation of propene, e.g., by slight adjustment of the conditions propene as well as *n*-1-butene may be processed in the same unit [19].

6.1.3.1.9
Deactivation Phenomena

A commercially applied rhodium/phosphine catalysts deactivate with time for different reasons and in several ways. Most obvious is a decline in activity, as it directly reduces the unit capacity and frequently also leads to increased materials consumption as unconverted olefins have to be vented. The reasons are found in the rhodium inventory: there are always some losses which decrease the rhodium concentration in the reaction medium, either by carry-over with the products during thermal (distillative) separation from the catalyst (homogeneous systems), or by being swept out with the products from the two-phase system. Although these losses normally are in the parts-per-billion range with respect to the rhodium concentration in the products, they may well accumulate to substantial losses if the lifetime of the catalyst charge exceeds years. In most kinetic expressions for the reaction rate the rhodium concentration is of or close to first order, thus directly influencing the reaction rate. On the other hand, the formation of inactive rhodium species may leave the rhodium inventory virtually unchanged, although the catalyst loses activity. Finally, the formation of modified phosphines has been proven to occur under reaction conditions, e.g., TPPTS can be converted to propyldi(sulfophenyl)phosphine (PDSPP), which acts as a stronger electron donor than TPPTS, thus occupying coordination sites on the rhodium [6].

The deactivation mechanism for TPPTS has been elucidated in some detail. The primary idea of *ortho* metallation of the phenyl ring has been abandoned in the meantime as it definitely plays no role. Instead the deactivation is initiated by the oxidative insertion of the rhodium metal into the P–C bond of the triphenylphosphine ligand. An analogous mechanism to that of the TPPTS degradation has been outlined for the homogeneous system with TPP as ligand [20].

In continuous operation consecutive phosphorus-containing products are formed which also influence the activity of the rhodium center and thus contribute to the catalyst deactivation. One of the main degradation products from TPPTS is the sodium salt of *m*-formylbenzenesulfonic acid, which indicates the insertion of the rhodium atom into the P–C bond. The arylrhodium species in which rhodium has replaced one phosphorus atom presumably exists as a phosphido-bridged dimer which is inactive. This compound may subsequently be converted to a series of consecutive products, e.g., alkyl-diarylphosphines, which act as catalyst poisons.

Besides the degradation reactions, all phosphines are oxidized by traces of oxygen which are always present in the olefins introduced. Synthesis gas, generated mainly by partial oxidation of hydrocarbons, may well contain small amounts of

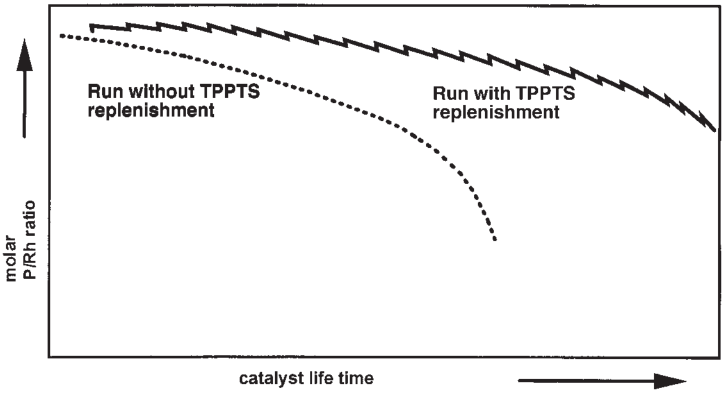


Fig. 3 Characteristic course of ligand concentration vs. operating time in the RCH/RP process.

oxygen which are removed by special gas purification systems. Nevertheless, oxidation also plays a role in the losses of ligand in long-term operation. A certain concentration of "active" ligand, e.g., phosphorus in the oxidation state + III, is necessary to ensure stability of the rhodium and a sufficiently high *n*/*i* ratio; maintenance of this concentration, which is achieved best by adding small portions of ligand over the whole run. The ligand concentration vs. operating time relationship follows a characteristic course which is depicted in Figure 3.

At the very beginning, it was noticed that some sulfur dioxide together with sulfur-containing components was swept out with the butanals formed, causing partial poisoning of the catalysts in the subsequent hydrogenation steps. The source of the sulfur dioxide is clearly identified today: during sulfonation of TPP with oleum, i.e., in the presence of a surplus trioxide, some of the TPP is oxidized to TPPO, yielding sulfur dioxide as reduced product, which in part is preserved in the neutralized catalyst solution. The problem was resolved by treating the acidic aqueous solution of TPPTS with some inert gas (nitrogen, carbon dioxide) thus leading to complete removal of the sulfur dioxide [28].

The TPPTS catalyst system is not sensitive toward sulfur and most of the other common poisons for hydroformylation catalysts. One reason is the continuous withdrawal of organic and other by-products with the product phase and the vent stream from the decanter (see Figure 2), avoiding the accumulation of poisons in the catalyst solution.

6.1.3.1.10
Outlook and Future Developments

The hydroformylation of propene and butene in the presence of an aqueous catalyst phase has proven successful for 13 years now. The hydroformylation of propene, especially, has acquired merit from the very beginning in 1984 and has encountered virtually no problems, even in large-scale units. Comparison with other hydroformylation processes based on the conventional homogeneous principle has shown some distinct technical and economical advantages [1, 10, 11].

- Phase separation is an elegant and efficient method to recover catalyst and oxo crude.
- Space-time yields in biphasic and homogeneous processes are on a comparable level.
- The *n*/*i* ratio is very high (95 : 5) and can be shifted if desired.
- Losses in rhodium and TPPTS are negligible.
- The absence of thermal strain reduces the formation of high-boiling by-products.
- The technical equipment is extremely simple and reliable.
- A process-integrated energy usage system operates (net energy exporter).
- There is high overall selectivity with respect to propene input.
- There are no environmental emissions.

However, despite the cited advantages in the hydroformylation of propene and butene, it has to be admitted that the biphasic system nears its limits when olefins with increasing chain lengths are considered. Due to the decreasing solubility of the olefins in the aqueous catalyst phase, the reaction rate slows down (cf. Section 6.1.3.2).

Several proposals have been published to solve this problem, e.g., by using polyether-substituted triphenylphosphines [21–23]. This type of phosphines show inverse-temperature dependence of their solubility in water that enables them to act as thermoregulated phase transfer ligands [24]. So far little is known about their applicability in technical operation. One the other hand, the homogeneous systems are also facing problems with long-chain olefins, but at a different process stage: whereas the hydroformylation still proceeds acceptably, the recovery of the oxo crude by distillation from the catalyst residue generates by-products and destroys the catalyst or the ligand, respectively. These facts explain the remanence of "ancient" cobalt hydroformylation processes for the hydroformylation of C_6–C_{10} olefins until a convenient solution has been found for one or the other variant. It may be noted that Celanese operates a ligand-modified homogeneous rhodium catalyst for hydroformylation of C_6 and C_8 olefins very successfully at its Bay City (TX, USA) plant.

The extension of the biphasic principle to higher olefins may be accomplished by changing the ligand [25] from TPPTS, e.g., to bisphosphines, some of which have already been proven to be valuable tools to increase the specific activity combined with high *n*/*i* selectivity [5]. Increasing the specific (better: intrinsic) activity of rhodium in the aqueous two-phase system may be coupled with understanding of the relevant mass transport phenomena. In this case the role of the phase boundaries as a potential barrier for the chemical reaction will have to be carefully analyzed.

As a whole one may state that the potential of the biphasic system has not been fully elucidated so far, and there is still a broad field for research activity with this simple but highly efficient technique.

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6.1.3.2
Higher Alkenes

Helmut Bahrmann, Sandra Bogdanovic, Piet W. N. M. van Leeuwen

6.1.3.2.1
Introduction

The Ruhrchemie/Rhône-Poulenc [1] process for the hydroformylation of short-chain alkenes such as propene and butene (cf. Section 6.1.3.1) combines a facile catalyst recycling with high selectivity and sufficiently high conversion rates to provide a commercially viable large-scale manufacturing process for butyraldehyde [2] and valeraldehyde [3]. Higher alkenes ($> C_8$) are not suited for the RCH/RP process as run in Oberhausen.

The hydroformylation of higher alkenes with five or more carbon atoms accounts for about 25% of the world-wide capacity of oxo products. Commercial hydroformylation processes based on phosphine-modified rhodium catalysts, such as the low-pressure oxo (LPO) process of the Union Carbide Corporation, are only known for alkenes with a maximum carbon atom number of 8 [4]. Processes with higher alkenes encounter problems due to the thermal sensitivity of the respective aldehydes [5], which cannot be isolated from the homogeneous reaction mixture by distillation. Cobalt-based processes [6] yield primarily less thermally sensitive alcohols. Therefore about 90% of higher oxo products are manufactured by processes using unmodified or trialkylphosphine-modified cobalt catalysts. For this reason a biphasic process for the hydroformylation of higher alkenes with more selective rhodium catalysts, which allows for a catalyst recycling by phase separation, would be highly desirable. So far, however, no catalytic system has been found which yields sufficiently high conversion rates and yet brings about a complete catalyst separation by decantation.

There have been many approaches to overcome the problem of low space-time yields in biphasic reaction systems with rhodium and other metals, such as the Ruhrchemie/Rhône-Poulenc process. Concerning two-phase hydroformylation of higher alkenes in an aqueous–organic reaction system, the different approaches can be categorized as follows:

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

1. The use of water-soluble ligands with amphiphilic properties which will either improve the solubility of the higher alkenes via formation of micelles or increase the reaction rate by preferential concentration of the catalyst complex close to the interface of the aqueous and the organic phase [7–10] (see Section 3.2).
2. Modification of the Ruhrchemie/Rhône-Poulenc system with co-solvents such as polar, alcoholic solvents or by use of detergent cations or modified cyclodextrins [11] to enhance the mutual solubility or mobility of the components across the phase boundary.
3. Increasing the surface area of the phase boundary by mechanical methods, such as ultrasound or cavitron.
4. The principle of thermoregulated phase-transfer catalysis (TRPTC), originally developed by Bergbreiter et al. [12], which has been applied to two-phase hydroformylation by Fell, Jin and co-workers [13], which is based on a temperature-controlled switch of the catalyst system from the aqueous phase to the organic phase (see Section 4.6.3).
5. Immobilization of unmodified rhodium catalyst (i.e., without ligands) in the aqueous phase by using polymeric or oligomeric water-soluble supports [14].
6. Supported aqueous-phase catalysis (SAPC) (see Section 4.7) [15].

Non-aqueous approaches toward two-phase hydroformylation have been demonstrated by Horváth et al. [16] with the use of a fluorous biphasic system containing a rhodium catalyst bearing partially fluorinated “ponytail” ligands, and Olivier and Chauvin [17] with TPPMS and TPPTS dissolved in nonaqueous ionic liquids (see Sections 7.2 and 7.3).

In this section, we will report on investigations in the two-phase hydroformylation of higher alkenes with aqueous Rh–TPPTS catalyst systems. The overview on the present state of the art in two-phase hydroformylation will be confined to those investigations which are not covered by the respective original authors in this book.

6.1.3.2.2
Two-Phase Hydroformylation of Higher Alkenes with Rhodium/Triphenylphosphine Trisulfonate (TPPTS) as Catalyst System

The Unmodified Ruhrchemie/Rhône-Poulenc Process

Whereas various studies have been published dealing with new water-soluble ligands and their effects on the hydroformylation of higher alkenes, only little data are available in the academic literature on the Rh–TPPTS catalyst system, especially without any additives. This section will provide some information on the effect of various reaction parameters (pressure, P/Rh ratio, rhodium concentration, alkene chain length, etc.) in the two-phase hydroformylation of higher alkenes with the aqueous catalyst system Rh–TPPTS. The alkene *n*-1-hexene was most thoroughly investigated. The results in the tables are average values from 3 to 30 single experiments (standard conditions; $T = 125\,^{\circ}\mathrm{C}$, $p = 25$ bar, Ru concentration = 300–400 ppm, P/Rh ratio = 80–100 : 1, reaction time = 3 h).

Preparation of the Basic Catalyst $HRh(CO)(TPPTS)_3$ [18]

There are several methods for the preparation of the active hydroformylation catalyst $HRh(CO)(TPPTS)_3$. In analogy to its homogeneous counterpart [19], it is possible to synthesize the catalyst directly from $RhCl_3$ and TPPTS under syngas pressure. However, purification of the resulting material has been found to be a problem since chloride ions bind strongly to the rhodium center and form less active mixed rhodium complexes. Thus, in general, water-soluble rhodium acetate was used as a starting material in the so-called “preforming” reaction. The relative consumption of P(III) and Rh (on a mol/mol basis) was investigated in a series of experiments on the preforming reaction using different amounts of rhodium and TPPTS. It was shown that despite the use of Schlenk technique the amount of P(III) consumed strongly depends on the absolute concentration of phosphorus and rhodium (see also [20]) and approaches a value of 4–7 mol P(III)/mol Rh at high catalyst concentrations.

The Relationship Between Solubility of Linear α-Olefins in Water and the Reaction Rate under Ruhrchemie/Rhône-Poulenc Conditions

If the conditions of the Ruhrchemie/Rhône-Poulenc process are applied to linear α-alkenes (LAOs) with 5–12 carbon atoms, the space-time yield of the hydroformylation reaction decreases with increasing chain length of the substrate. Table 1 summarizes the results of the batchwise hydroformylation of LAOs different at 30–80 bar syngas pressure.

The conversion vs. time diagram (Figure 1) illustrates the dependence of the reaction rate on the chain length of the alkene. The reaction proceeds according to first-order kinetics, i.e., the consumption rate of the substrate alkene is proportional to the concentration of the substrate.

Figure 2 depicts the first-order rate constants and the solubility of the respective terminal alkenes in pure water at $125\,^{\circ}\mathrm{C}$ according to a quantiative model of Brady et al. [21]. Obviously, there is a marked dependence of the reaction rate on the solubility of the alkenes in hot water. It has to be kept in mind that the catalyst phase is a concentrated solution of Na–TPPTS in water whose solubility for alkenes should be lower than that of pure water (“salt effects”).

Obviously, the reason for the low space-time yields of the biphasic hydroformylation reaction is in some way related to the low solubility of the higher alkenes in the catalyst phase. However, this finding does not necessarily imply that the catalytic reaction takes place in the bulk phase of the catalyst solution (concerning kinetics, see [22] and Section 6.1.2).

Tab. 1 Variation of α-alkenes.

	Pressure [bar]	*Yield [%]*	*n/iso Ratio*	*$Rh_{org.\ phase}$*	*Rate constant [min^{-1}]*
1-Pentene	30	49	96:4	0.05	0.0038
1-Hexene	30	31	98:2	< 0.05	0.0021
1-Octene	30	9	98:2	< 0.05	0.00053
1-Decene	30	2	100:0	< 0.03	0.00011
1-Dodecene	30	0	n. d.[a]	< 0.05	0
1-Pentene	50	75	96:4	< 0.03	0.0077
1-Hexene	50	39	97:3	< 0.03	0.0028
1-Octene	50	8	95:5	< 0.03	7.83×10^{-5}
1-Dodecene	30	< 1	n. d.	< 0.05	$< 5.58 \times 10^{-5}$
1-Pentene	80	73	94:6	0.05	0.0073
1-Hexene	80	36	96:4	< 0.5	0.0025
1-Octene	80	8	95:5	< 0.5	0.00046
1-Decene	80	3	94:6	< 0.03	0.00015
1-Dodecene	80	< 1	n. d.	< 0.5	$< 5.58 \times 10^{-5}$

[a] n. d. (not determined).

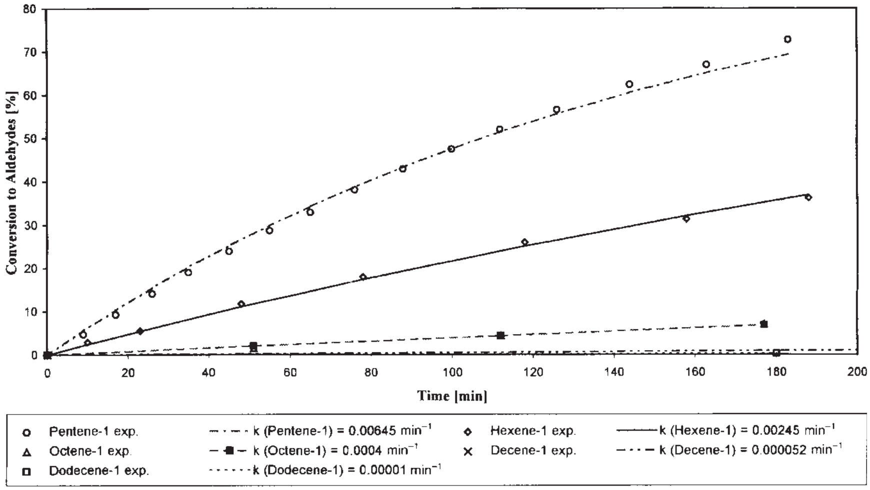


Fig. 1 Dependence of reaction rate on chain length of alkenes.

The Influence of the Reaction Pressure

Two-phase hydroformylation of alkenes is an example of the development of a low-pressure oxo process operating at a syngas pressure of 20–50 bar. As can be seen in Table 2, the conversion rate seems to reach a maximum between 30 and 80 bar in the hydroformylation of *n*-1-hexene. By increasing the syngas pressure from 25 to 270 bar the *n*/*iso*-ratio decreases from 98:2 to 92:8. Whereas the increase of

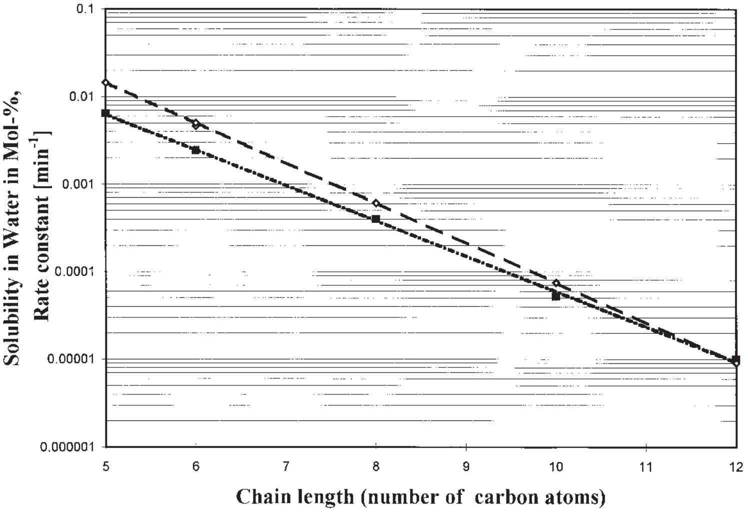


Fig. 2 Solubility of alkenes in water (■) and rate constants (◇) vs. chain length.

Tab. 2 Variation of the pressure in the hydroformylation of 1-hexene.

	Pressure [bar]				
	25	***30***	***50***	***80***	***270***
Conversion [%]	18	31	34	35	20
n/iso ratio	98:2	98:2	97:3	96:4	92:8

the conversion rate at medium pressure cannot yet be explained, the decrease of the *n/iso* ratio is probably due to the formation of a sterically less hindered rhodium dicarbonyl complex.

The Influence of the Phosphine/Rhodium Ratio

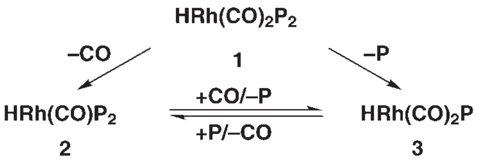
In the biphase hydroformylation of 1-hexene the conversion rate strongly depends on the phosphorus to rhodium ratio (P/Rh ratio). An increase of the P/Rh ratio from 50:1 to 100:1 and to 150:1 results in a decrease of the conversion from 33% to 18% and to 9% respectively (Table 3). This may be due to the shift of the **1**, **2** and **3** (Scheme 1). At higher phosphine concentrations the formation of the catalytically active species is suppressed. Furthermore the “salt effect” is much more pronounced in the aqueous catalyst solution than in homogeneous organic systems.

Otherwise a high ligand concentration has a positive influence on the *n/iso*-ratio. This was rationalized by Horváth et al. [23] by a shift of the equilibrium between complexes **2** and **3**.

Tab. 3 Variation of P/Rh ratio.

	P/Rh ratio				
	0	***20:1***	***50:1***	***100:1***	***150:1***
Conversion [%]	25	(27)[a]	31–35 (27)	18 (20)	9
n/iso ratio	38:62	(80:20)	97:3 (89:11)	98:2 (92:8)	98:2
Rh concn. [ppm]	100	(400)	400 (400)	400 (400)	400

[a] Values in brackets are true for 270 bar pressure.



Scheme 1

The TPPTS ligand exhibits a higher dissociation energy compared with the TPP ligand due to hydrogen bond formation in aqueous solution. At a higher pressure level of 270 bar the influence of the P/Rh ratio on the selectivity toward linear aldehyde formation is much more pronounced because the CO as a ligand can complete better with the phosphine ligands. In the absence of phosphine ligands, the *n/iso* ratio is as low as 40 : 60.

Variation of the Rhodium Concentration

In the hydroformylation of *n*-1-hexene the rhodium concentration was varied at a low P/Rh ratio of 20 : 1 to 40 : 1. By increasing the rhodium concentration from 50 to 400 ppm, the conversion rate rises from 33 to 44% under standard conditions. This relatively minor effect must be due to the fact that a high rhodium concentration implies a high concentration of Na–TPPTS, which has a negative effect on the solubility of 1-hexene in the aqueous phase (salt effect). On the other hand, the salt effect shifts the equilibrium of the rhodium complexes toward the phosphine-rich complex **2**. Hence, the *n/iso* ratio is improved substantially.

Tab. 4 Variation of Rh concentration.

	Rh concentration [ppm]		
	50	***100***	***400***
Conversion [%]	33	36	44
n/iso ratio	86:14	90:10	96:4
P/Rh ratio	23	38	33

Variation of the Volume Ratio of Catalyst Phase to Olefin Phase

In the hydroformylation of *n*-1-hexene under standard reaction conditions the amount of catalyst solution was varied (Table 5). Clearly, by using large amounts of catalyst solution the conversion rate can be improved from 22% up to over 70%.

Tab. 5 Variation of the volume ratio of catalyst solution/alkene phase.

	***TPPTS: n*-1-hexene**					
	1:5.1	***1:3.4***	***1:1.7***	***1:0.6***	***1:0.15***	***1:0.09***
Conversion [%]	4	7	10	22	66	71
n/iso ratio	97:3	97:3	98:2	98:2	98:2	98:2
Rh–TPPTS solution [mL]	130	174	261	391	478	478
n-1-Hexene [mL]	663	592	444	235	72	43
Activity [mol aldehyde/mol Rh per min]	1.1	1.2	0.9	1.0	0.74	0.50

Variation of Alkali Cations

In a series of experiments the counterion of TPPTS was varied. With K^+, Cs^+, Li^+, NH_4^+ no significant differences with respect to the catalyst performance were observed as compared with the sodium salt of TPPTS.

Comparison of TPPTS and TPPDS

By substituting TPPTS for the less water-soluble TPPDS (triphenylphosphine disulfonate, cf. Section 3.2.1) the conversion rate is increased significantly from 12% to 36%, i.e., by a factor of 3 at a low P/Rh-ratio. Whereas the leaching of rhodium into the organic phase remains unchanged, the leaching of TPPDS into the organic phase increases by a factor of 10. Therefore the use of a TPPDS-derived catalyst system cannot be considered a viable alternative for the two-phase hydroformylation of higher alkenes. Higher leaching rates of both rhodium and TPPMS (triphenylphosphine monosulfonate) have been reported by Russel et al. [25]. A synergistic effect of TPPTS and TPPDS on the regioselectivity was also observed by Chen et al. [50, 59]. The ratio of linear/branched aldehyde rose from 6.5 (without TPPDS) to 22.3 ([TPPTS]/[TPPDS] = 2:1).

pH Value

During the hydroformylation of higher alkenes under the Ruhrchemie/Rhône-Poulenc conditions the pH value is controlled and adjusted between 5.5 and 6.2 [26]. In discontinuous operation it drops by almost one pH unit from approximately 6.5 at the beginning of the reaction to pH 5.5–6 at the end of the reaction. According to our investigations the pH shift is due to the formation of carbon dioxide, formed via the water-gas shift reaction (WGSR), which is also promoted by rhodium TPPTS complexes but to a lower extent [27].

Isomerization of Terminal Alkenes to Internal Alkenes

The Rh/TPPTS catalyst system is only applicable to the hydroformylation of terminal linear alkenes. With branched or internal alkenes as substrates only very low conversion rates are achieved. Exceptions include strained cyclic alkenes such as cyclopentene and norbornene, which are hydroformylated at moderate rates under Ruhrchemie/Rhône-Poulenc conditions.

Thus, the isomerization of linear α-alkenes to internal alkenes during the hydroformylation reaction is an unwanted side reaction since internal alkenes accumulate in the reaction mixture. Table 6 summarizes the selectivity with respect to isomer formation in the two-phase hydroformylation of 1-pentene at different pressure levels. It is concluded that the isomerization can be suppressed most effectively by employing higher pressures.

Tab. 6 Isomerating hydroformylation of *n*-1-pentene.

	Pressure		
	30	***50***	***80***
Conversion [%]	48	75	73
Isomerization [%]	7.11	7.72	5.57
Selectivity toward isomerization [%]	14.8	10.3	7.7
n/iso ratio	98:2	96:4	95:5

Improvement of Mass Transfer by Mechanical Aids

Since the mass transfer seems to be the limiting factor in the two-phase hydroformylation of higher alkenes under Ruhrchemie/Rhône-Poulenc conditions, an improvement of the mixing of the two phases can be a measure to improve the space-time yields. The possibilities have been evaluated.

The Cavitron

The cavitron [28] is a dispersing unit or shock-wave reactor with a throughput of 8–30 $m^3 h^{-1}$ and an installed power of 25–60 kW. High shear forces are induced by an optimized rotor/stator system with passage gaps at the rotor and stator. The gaps are filled with material which is centrifugally accelerated by the rotor to the next row of gaps. Similarly to ultrasound, alternating pressure fields are generated.

The cavitron device was used to study the conversion rate of *n*-1-hexene hydroformylation under biphasic conditions. Under standard reaction conditions, but at a lower pressure of 10 bar, a conversion of 17% (*n/iso* ratio 99:1) was reached in this unit compared with 12% in a regular stirred autoclave.

Ultrasound

Ultrasound denotes sound waves with a frequency of more than 20 kHz. In the field of two-phase catalysis ultrasound can be used to create stable emulsions and extremely large liquid–liquid phase boundaries. Special dipping oscillators provide a source of ultrasound in autoclaves. When the reaction mixture is exposed to ultrasonic vibration under stirring [29], the conversion rate of 1-hexene hydroformylation is increased by a factor of 2 under standard conditions.

Modification of the Rh/TPPTS System Using Additives

Alcohols

Table 7 shows that the reaction rate can be extremely enhanced by the addition of lower alcohols. The highest increase in rate was achieved with methanol. In contrast to literature data [30], the effect of ethanol is less pronounced and *n*-butanol shows no effect. If 20 wt.% of methanol are added to the alkene phase, a conversion of 90% is achieved under standard reaction conditions. The selectivity with respect to *n*-aldehyde formation drops from 98 to 92%. Formation of acetals as well as aldols can be kept below 1% if the pH is adjusted to 10.

Tab. 7 Addition of alcohols as co-solvent.

		Ethanol	*Methanol*	*Methanol*
Amount of added alcohol [% rel. to alkene]	–	7	7	20
Conversion [%]	22	37	54	92
n/iso ratio	98:2	97:3	95.5:4.5	92:8
Activity [mol ald./mol Rh per min]	1.0	2.9	4.6	8.3
Productivity [g ald./mL catalyst soln. per h]	0.030	0.069	0.108	0.180

Anionic Detergents

In order to increase the conversion rate, anionic detergents (2.5 wt.% relative to the catalyst solution) were added. A variety of anionic detergents, such as the sodium salts of fatty acids, alkylsulfonic acids, α-olefin sulfonates, fatty alcohol sulfates, fatty alcohol polyglycol ethers, alkylphenol ether sulfates, alkylphosphonic acids, and salicyclic acid, however, do not show any activating effects. Additionally, anionic detergents tend to produce foams and emulsions and in many chases phase separation is made impossible.

Counterion Modification [31]; TPPTS Modified with Cationic Detergents

By addition of 2.5% of a typical cationic detergent such as benzyltrimethylammonium (BTMA) to the catalyst phase under standard conditions, conversion could be increased by 45–60% [32]. Different anions such as benzenemonosulfonate, chloride, or sulfate do not have any effect (Table 8). A variation of the chain length

Tab. 8 Addition of cationic detergents.

Cationic detergent T1	***Conversion [%]***	***n/iso ratio***	***Rate of increase***[a]	***Remarks***
[BTMA][$C_6H_5SO_3$][b]	31	98 : 2	1.55	
[BTMA][I]	32	98 : 21.60		
[BTMA][Cl]	30	98 : 2	1.50	
[BTMA][SO_4]	30	98 : 2	1.50	
[BTMA][F]	29	98 : 2	1.45	
[$C_{12}H_{25}N(CH_3)_3$][CH_3OSO_3]	29	95 : 5	1.45	
[$C_{14}H_{29}N(CH_3)_3$][CH_3OSO_3]	43	95 : 5	2.15	
[$C_{16}H_{33}N(CH_3)_3$][CH_3OSO_3]	32	95 : 5	1.60	Foaming
[$C_{20}H_{41}C_{22}H_{45}N(CH_3)_3$][$CH_3OSO_3$]	–	–	–	Strong foaming

Hydroformylation conditions: according to standard conditions. T1-added tenside: 2.5%, relative to catalyst solution.

[a] Relative to 20% conversion.

[b] BTMA, benzyltrimethylammonium.

Tab. 9 Use of detergent cations with TPPTS.

Detergent cation	***Conversion [%]***	***n/iso ratio***	***Rate of increase***[a]	***Remarks***
[$(CH_3)_4N$]	19	98 : 2	–	
[$C_6H_5N(CH_3)_3$]	27	98 : 2	1.35	
[$HOCH_2{-}CH_2N(CH_3)_3$]	44	98 : 2	2.20	
[BTMA][b]	82	94 : 6	4.10	
[$(C_4H_9)_4N$]	90	80 : 20	4.50	
[$(C_{12}H_{25})(C_2H_5)N(CH_3)_2$]	97	77 : 33	4.85	Difficult phase separation

[a] Relative to a conversion of 20%.

[b] BTMA, benzyltrimethylammonium.

of the alkyl group R of the detergent ammonium cation $[RN(CH_3)_3]^+$ shows the strongest effect in the typical detergent region with C_{14}. Similar results have been reported by Chen et al. [33]. At this conversion level, the *n/iso* ratio remains at 95 : 5. With even higher alkyl chains ($C_{16}–C_{20}$) the effect is less pronounced and phase separation becomes difficult due to foaming. Cations of the type $[R_2N(CH_3)_2]^+$ do not show any rate enhancement and exhibit strong foaming properties.

If all sodium cations of Na–TPPTS are substituted by detergent cations [34], extremely high conversions of up to 100% can be achieved. In this case, the selectivity regarding *n*-aldehyde decreases to 77% (Table 9).

A further optimization could be achieved by only exchanging part of the sodium cations with detergent ammonium cations. An exchange of 7 to 30% of the sodium cations was found to be sufficient to reach good results in terms of conversion and selectivity [35]. Instead of ammonium cations, phosphonium cations can also be used successfully [36].

^{31}P NMR evidence suggests a strong interaction of one TPPTS with three cetyltrimethylammonium cations at CTAB concentrations that exceed the critical micelle concentration. Selectivity in the rhodium/TPPTS-catalyzed hydroformylation reaction decreases at high CTAB concentrations. This may be due, in part, to the association of TPPTS with CTAB. The addition of cetyltrimethylammonium bromide to TPPTS/rhodium hydroformylation catalysts has a complicated effect on reaction activity and selectivity. In water alone as the solvent, high CTAB concentration leads to the formation of emulsions and reaction selectivity drops. In aqueous alcoholic solvents selectivity also drops but the effect appears to be due to the solvent composition. Emulsion formation is minimized and initial reaction activity goes through a maximum at a CTAB/TPPTS ratio of 3 [51]. A light-scattering study has been reported [52]. The results demonstrate that the acceleration of 1-dodecene hydroformylation in biphasic catalytic system in the presence of CTAB can be attributed to: (1) binding of $RhCl(CO)(TPPTS)_2$ and TPPTS to cationic micelle interface, which led the rhodium catalyst to concentration greatly on the interface of micelle; (2) 1-dodecene solubilization in micelle, which is favorable for alkene coordination with rhodium catalysts (cf. also Section 4.5).

Chen [53] reported that the formation of micelle was not only favorable for the reaction acceleration, but also favorable for the increase of linear aldehyde ratio in products. The key factor of the enhancement of reaction rate was the richness of rhodium catalyst in the interlayer with the static electricity attraction between active rhodium anion species and cationic end of surfactant.

Poly(ethylene Glycol) and Poly(ethylene Glycol) Derivatives as Rate-enhancing Additives

Poly(ethylene glycol) (PEG) of a medium molecular mass (400 – 1000) as an additive to the catalyst phase of the process greatly enhances the conversion rate under standard reaction conditions. Table 10 summarizes the results for the hydroformylation of the higher alkenes with and without addition of the specified amount of PEG. In contrast to the addition of methanol or ethylene glycol, the leaching of PEG into the organic phase remains at a very low level (< 0.1 wt.%). Similarly there is virtually no increase in the leaching of rhodium or Na – TPPTS into the organic phase. The phase separation after the reaction is fast and as straightforward as in the classical Ruhrchemie/Rhône-Poulenc process. The modification of the catalyst phase with PEG, however, leads to a slight decrease of the *n/iso* ratio. The amount of PEG added to the catalyst phase has to be adapted to the olefinic substrate. A variety of water-soluble phosphine and phosphite ligands with phase-transfer ability based on functionalized polyethylene oxide has been synthesized. The corresponding rhodium complexes showed high catalytic activity in hydroformylation of higher alkenes. The complexes combine properties of a catalyst and a

Tab. 10 Hydroformylation in the presence of PEG.

	Pressure [bar]	*PEG-400 [wt.%]*	*Oxoproducts formed [%]*	*n/iso ratio*	*Leaching of rhodium [ppm]*
1-Pentene	50	0	75	96:4	0.03
1-Pentene	50	12	85	95:5	0.08
1-Hexene	50	0	39	97:3	0.03
1-Hexene	50	16	71	95:5	0.05
1-Octene	50	0	8	95:5	0.05
1-Octene	50	35	63	83:17	0.11
1-Dodecene	80	0	>1	99:1	0.03
1-Dodecene	80	35	13	75:25	0.03

phase-transfer agent within the same molecule [55]. TPPTS hydroformylation in the presence of crown ether was also reported [56].

Interfacial Catalysis

The idea of promoter ligands which are exclusively dissolved in the organic phase of a biphasic reaction mixture was put forward by Chaudhari et al. [37]. The two-phase hydroformylation of 1-octene with $HRh(CO)(TPPTS)_3$ was accelerated by a factor of 10–50 by addition of triphenylphosphine (TPP). At the phase boundary, complexes of the general formula $[HRh(CO)(TPP)_{3-x}(TPPTS)_x]$ are formed via ligand exchange reactions. According to Chaudhari these complexes preferentially concentrate close to the phase boundary of the aqueous/organic reaction mixture, giving rise to the term "interfacial catalysis".

However, it can also be argued that the TPP simply enhances the solubility in the organic phase of the mixed rhodium complexes that are formed, just as rhodium complexes with TPPDS or TPPMS instead of TPPTS do. In addition, it has to be considered that the promoter ligand TPP will stay in the crude aldehyde mixture after phase separation and will have to be separated by a distillation step.

Interfacial kinetics of biphasic hydroformylation of 1-dodecene catalyzed by water-soluble rhodium complex have been studied by a combined numerical and experimental approach [54].

In order to hydroformylate heavy alkenes at adequate reaction rates while maintaining a water-compatible catalyst in the aqueous phase, Kalck et al. have examined the effect of small amounts of triphenylphosphine on the water-soluble complexes $[Rh_2(CO)_2(\mu\text{-S}^t\text{Bu})_2(TPPTS)_2]$ and $[RhH(CO)(TPPTS)_3]$. It has been demonstrated that the reaction occurs in the organic phase; an exchange of phosphine restores the starting [58].

Modified Cyclodextrins as Phase-transfer Catalysts

A different approach toward the improvement of the mass transfer of higher alkenes into the aqueous TPPTS phase has been suggested by Mortreux and co-workers [39, 60]. By using chemically modified cyclodextrins, inverse micellar systems are obtained which show largely increased space-time yield in the two-phase hydroformylation of 1-decene. According to the authors, the effect is due to the solubility of the alkylated cyclodextrins in both the organic phase and the aqueous phase (cf. Sections 4.5 and 4.6.1). The formation of inclusion complexes between the different components of the system was also discussed on the basis of NMR experiments. The results indicate that the chemically modified cyclodextrins must not be considered only as inverse phase-transfer catalysts but also as compounds which, by trapping the water soluble ligand, can modify the equilibria between the different catalytic species. Heavy terminal alkenes can be hydroformylated at a significant rate by using the water-soluble catalyst precursor $[Rh_2(\mu\text{-}S^tBu)_2(CO)_2(TPPTS)_2]$ and β-cyclodextrin or its dimethylated form as phase-transfer agent. A gradual supramolecular organization in the interphase was proposed by Kalck for the rhodium complex, its solvation sphere and cyclodextrin [61]. Calixarenes have been successfully used for the same purpose [62].

Protein-rhodium Complexes

The water-soluble complex derived from $Rh(CO)_2(acac)$ and human serum albumin (HSA) proved to be efficient in the hydroformylation of several alkene substrates [63]. The chemoselectivity and regioselectivity were generally higher than those obtained by using the classic catalytic systems like TPPTS–Rh(I). Styrene and 1-octene, for instance, were converted in almost quantitative yields into the corresponding oxo-aldehydes at 60 °C and 70 atm ($CO/H_2 = 1$) even at very low $Rh(CO)_2(acac)$/HSA catalyst concentrations. The CD technique was useful for demonstrating the Rh(I) binding to the protein and to give information on the stability in solution of the catalytic system. Some other proteins have been used to replace HSA as complexing agent for Rh(I). The results were less impressive than those obtained using HSA and their complexes with Rh(I) which were much less stable.

Water-soluble Dendrimers

Four water-soluble dendritic phosphonated ligands were first synthesized based on poly(amidoamine) (PAMAM) (generation 3 with 32 cascade end groups), with the hydrophilic amine or sulfonic acid groups on the surface of the dendrimer. Their Rh(I) complexes were used as the catalysts in the two-phase hydroformylation of styrene and 1-octene. The results showed that these new water-soluble dendritic catalysts exhibited high catalytic activity [64].

6.1.3.2.3
Other Water-soluble Phosphines

BINAS and BISBIS

Special chelating ligands, such as BINAS (sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthylene) [40, 41] and BISBIS (sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl) [42], were found to be very useful ligands for the two-phase hydroformylation of higher alkenes. Under standard conditions with BINAS a relatively high conversion of 36% is achieved (Table 11). In the presence of only 0.24 wt.% of tetradecyltrimethylammonium BINAS in the catalyst phase, the conversion rate rises to 77% (3 h) or 84% (6 h). In addition it should be mentioned that no decrease of the excellent *n/iso* ratio of 99 : 1 is observed with BINAS, as opposed to TPPTS.

A high selectivity toward linear aldehydes at a low P/Rh ratio could also be achieved with sulfonated fluorophosphine [tris(*p*-fluorophenyl)phosphine] [43].

Dinuclear rhodium(I) complexes with TPPTS, containing thiolato bridging ligands in aqueous phase, were found to be transformed into the monomer $HRh(CO)(TPPTS)_3$ under reaction conditions [44].

Recycable catalysts based on Rh complexes and xanthene diphosphine ligands were used in the hydroformylation of 1-octene. Amphiphilic diphosphines spontaneously form aggregates that are remarkably stable at elevated temperatures and are specially suitable for the aqueous two-phase catalytic process. The observed TOF in the hydroformylation of 1-octene using ligands that form vesicles was up to 14 times higher compared to ligands that do not form aggregates [65]. Electron microscopy experiments showed that these ligands and their complexes form vesicles in H_2O if the hydrophobic part of the ligand is large enough. The formed aggregates are stable at elevated temperatures (90 °C), and their presence leads to a significant enhancement of the solubility of 1-octene in aqueous solution. Furthermore, recycling experiments show that the TOF and the high selectivity toward the more valuable linear aldehyde remains the same in four consecutive runs. The

Tab. 11 Comparison of TPPTS and BINAS.

	No additive		$C_{14}Me_3N$ cation		
	BINAS [a]	TPPTS	BINAS [a]		TPPTS
	3 h	3 h	3 h	6 h	3 h
Additive [%]	–	–	0.24		0.86
Rate of conversion [%]	36	22	77	84	74
n/iso rate	99:1	98:2	99:1	99:1	91:9

P/Rh ratio 15:1.

[a] Relative to the whole catalyst solution.

aggregates stay intact during the recycling and the active Rh complex is retained in the H_2O-phase quantitatively [66].

Two new phosphines, tris[*p*-(10-phenyldecyl)phenyl]phosphine and 2,2′-bis{di}[*p*-(10-phenyldecyl)phenylphosphinomethyl]-1,1′-biphenyl were successfully synthesized and sulfonated in H_2SO_4. The resulting water soluble surface active phosphines were applied to the rhodium catalyzed hydroformylation of higher alkenes. It is found that these two ligands are not only excellent for octene hydroformylation, but catalyze tetradecene hydroformylation under biphasic conditions as well. Rates and selectivities are superior to TPPTS-modified rhodium catalysts under the same reaction conditions [68].

Nonionic tensioactive water-soluble phosphines that act as ligands for rhodium-catalyzed hydroformylation of higher alkenes under biphasic conditions have been tested, too. Phosphines discussed are $P\text{-}[p\text{-}C_6H_4(OCH_2CH_2)_nOH]_3$ ($n=18$, 25) and $Ph_2P\text{-}[p\text{-}C_6H_4(OCH_2CH_2)_nOH]$ ($n=16$, 25). The rhodium catalyst combined with these ligands gave an average turnover frequency of 182 h^{-1} for 1-hexene. More importantly, recovery and reuse of catalyst is possible because of the inverse temperature-dependent water solubility of the phosphines [69].

Phosphonated Ligands

New and efficient routes to modify phosphines with phosphonic acid groups have been developed. Phosphonate-phosphines showed high solubilities in water and were used to immobilize rhodium catalysts in the aqueous phase of biphasic systems. In the two-phase hydroformylation of propene, some of the novel catalysts showed activities and regioselectivities similar to those of Rh/TPPTS. Amphiphilic Rh/phosphonate-phosphine catalysts were found widely superior to Rh/TPPTS in the hydroformylation of 1-octene (see Section 3.2.1) [67].

6.1.3.2.4

The Combination of Triphenylphosphine Monosulfonate (TPPMS) and Polar Solvents

Several processes for the hydroformylation of higher alkenes have been suggested on the basis of the water-soluble ligand TPPMS. In contrast to TPPTS, which is almost exclusively soluble in water, TPPMS can be used in both aqueous and polar organic media.

Recently, Abatjoglou et al. from the Union Carbide Corporation (UCC) presented a homogeneous process for the hydroformylation of higher alkenes, combined with an aqueous two-phase catalyst recovery [45]. The key discovery is that alkali-metal salts of monosulfonated triphenylphosphine form reverse micelles in organic media in the presence of certain solubilizing agents which are stable under the reaction conditions. These systems can easily be induced to separate into a nonpolar product phase and a polar catalyst phase, thereby providing the catalyst recovery typical of two-phase reactions. The separation of the micelles can be accomplished by either raising the temperature or cooling the reaction mixture. In the case of *N*-methylpyrrolidine (NMP)-solubilized systems the addition of water brings about a sharp separation into an organic phase and a catalyst phase. The product phase, however, has to be extracted with water to eliminate traces of catalyst components completely.

Fell et al. recently published a simplified version of the above-mentioned process design of UCC in which the hydroformylation reaction of 1-tetradecene is performed homogeneously with a Rh/Li-TPPMS catalyst system in the presence of methanol. When the methanol is distilled off after almost complete conversion, the catalyst complex precipitates and can be separated by filtration or extraction with water [46].

The idea of using monosulfonated or monocarboxylated triphenylphosphines in a biphasic reaction medium in the presence of amphiphilic reagents has already been patented, in 1981, by the Johnson–Matthey Corporation. However, the recycling of the catalyst complex published in this patent was not complete so that no technical process could be established in those early days of two-phase hydroformylation [47].

6.1.3.2.5
Outlook

What are the major challenges for the two-phase hydroformylation of higher alkenes?

The most important applications of higher oxo products are plasticizer alcohols in the C_8–C_{11} range and synthetic detergent alcohols in the C_{12}–C_{18} range, with a worldwide consumption of 1.5 million tons [48] and 1.2 million tons in 1995, respectively. Compared with cobalt, rhodium as catalyst metal is favorable with respect to the raw material economy and the energy balance in the hydroformylation of higher alkenes. A biphasic hydroformylation process would bear the advantage that the long-chain aldehydes can be separated from the catalyst simply by phase separation. For alkenes above C_{10} the crude aldehyde cannot be separated from the unreacted alkene by distillation. Therefore such a process would be required to achieve complete conversion in continuous operation.

Since the major raw materials for higher plasticizer alcohols are internal alkenes from polygas units (e.g., diisobutene, tripropenes), this marked requires the development of even more efficient biphasic catalyst systems for internal and branched alkenes.

Scientifically, another major challenge is the development of a biphasic hydroformylation process for internal alkenes combining isomerization and hydroformylation of linear internal alkenes and affording predominantly terminal hydroformylation products. Such a technology would be of primary interest for the fine chemical and the detergent alcohol markets. For organic solvents several systems have been reported recently that will give terminal products starting from internal alkenes, based on phosphines [70] or phosphites [71]. A two-phase reaction for cobalt has also been reported [72]. For new palladium catalysts the preferred way for carrying out the reaction seems to be a one-phase catalysis followed by a two-phase separation [73].

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6.1.3.3
Functionalized Alkenes

Eric Monflier, André Mortreux

6.1.3.3.1
Introduction

Hydroformylation or oxosynthesis is a well-known homogeneous, transition metal catalyzed reaction which has known considerable and continuous development since its discovery by Otto Roelen in the laboratories of Ruhrchemie AG in 1938 [1]. This reaction, which can be considered as the addition of a formyl group and hydrogen to a double bond, has been successfully applied in the industrial context by using two basic processes: the homogeneous process where the rhodium or cobalt catalyst and the substrate are in the same phase (Shell, UCC, BASF, RCH processes) [2] and the aqueous/organic biphasic process where the water-soluble rhodium catalyst and the organic compounds are in two different phases (Ruhrchemie/Rhône-Poulenc process) [3].

Application of the homogeneous process is not limited to simple alkenes like propene, butene, octene, or nonene. Indeed, a plethora of functionalized alkenes can be converted to aldehydes by using this technology [4]. For instance, BASF and Hoffmann–La Roche have developed new approaches for the vitamin A synthesis which involves the hydroformylation of 1,2-diacetoxy-3-butene and 1,4-diacetoxy-2-butene, respectively [5]. Arco has commercialized a process to obtain 1,4-butanediol which requires a step in which allyl alcohol is hydroformylated to 4-hydroxybutyraldehyde by using Kuraray technology [6]. The latter company has also described some attractive routes for producing cyclic products by hydroformylation [7]. So, hydroformylation of 3-methyl-3-butenol and 3-butenol give rise to 2-hydroxy-4-methyltetrahydropyran and 2-hydroxytetrahydropyran, respectively.

Although the broad applicability of the hydroformylation in homogeneous medium has been demonstrated without ambiguity, the scope of *biphasic* catalysis for the hydroformylation of functionalized alkenes remains to be investigated. Indeed, there are relatively few examples in the literature related to hydroformylation of such substrates. Furthermore, most of the work described so far has been devoted to the hydroformylation of δ-functionalized alkenes (the functional group is not di-

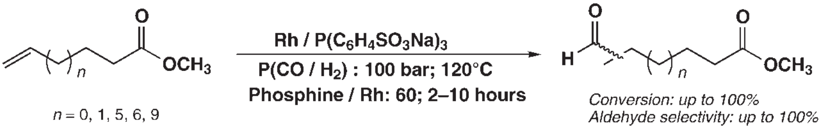
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

rectly branched on the double bond but on an alkyl chain of the alkene, as in the case of 7-octen-1-al or linoleic alcohol) and little attention has been given to the hydroformylation of α-functionalized alkenes (functional group directly branched on the double bond). The results described in the academic and patent literature for these two classes of alkenes will be discussed separately. Although some interesting results have been reported [8], hydroformylation of water-soluble alkenes in two-phase systems with water-insoluble catalysts such as $HRh(CO)(P(C_6H_5)_3)$ is far beyond the scope of this section and will not be discussed here.

6.1.3.3.2
Biphasic Hydroformylation of δ-Functionalized Alkenes

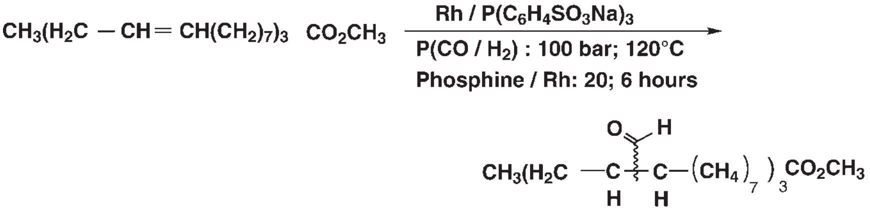
From a regio- and chemoselectivity point of view, the behavior of this class of alkenes is very similar to that observed with unfunctionalized alkenes in biphasic medium. As expected for a biphasic medium, the catalytic activities are comparable with or lower than those observed under similar homogeneous conditions, and strongly dependent on the water-solubility of the alkene. Addition of solubilizing agents is often necessary for high-molecular-mass alkenes. For instance, low-molecular-mass ω-alkenecarboxylic acid methyl esters such as methyl 4-pentenoate can be hydroformylated efficiently in biphasic systems whereas methyl esters of higher ω-alkenecarboxylic acids such as methyl 13-tetradecenoate require the presence of surfactants (Eq. 1) [9].



(1)

The best results in terms of activity have been obtained with cationic surfactants such as octadecyltrimethylammonium bromide. The normal to branched (*n*/iso) aldehydes ratio was found to be very dependent on the nature of the surfactant. For example, methyl 9-decenoate hydroformylation gave methyl 11-formylundecanoate with an *n*/iso aldehydes ratio of 6.1 : 1, 4.0 : 1, 2.3 : 1 and with anionic, amphophilic, and cationic surfactants, respectively. Interestingly, hydroformylation of this substrate has also been achieved successfully with inverse-phase transfer catalysts such as chemically modified β-cyclodextrins. In this approach, the cyclodextrin forms an inclusion complex with methyl 9-decenoate and transfers the alkene into the aqueous phase. Under optimal conditions, the aldehydes are obtained in a 100% yield and in an *n*/iso aldehydes ratio of 2.3 : 1 [10].

The use of cationic surfactants also makes it possible to apply the concept of biphasic catalysis in oleochemistry. For instance, the Johnson–Matthey company has reported that oleic acid methyl ester or linoleic acid methyl ester can be hydroformylated in micellar media using a water-soluble rhodium complex of monocarboxylated triphenylphosphine as catalyst [11]. Hydroformylation of linolenic acid methyl ester has also been described recently. Interestingly, with this triunsaturated fatty acid ester, the triformyl derivative selectivity can reach 55% [12] (Eq. 2).

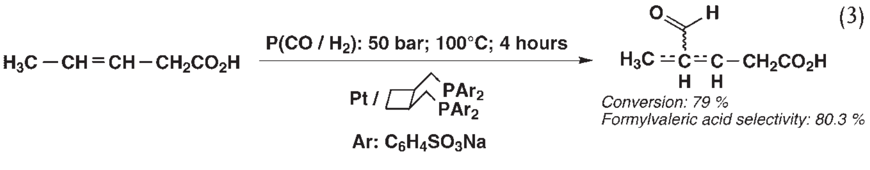


Conversion: 100%
Triformyl selectivity: 55% (2)

Hydroformylation of the water-insoluble oleyl alcohol into formylstearyl alcohol has also been successfully achieved with a 96.6% yield by using a rhodium/trisulfonated triphenylphosphine complex dissolved in an aqueous film supported on a high-surface-area silica gel (cf. Section 6.1) [13]. This supported catalyst has also been used to perform the hydroformylation of allyl 9-decenyl ether and 3-methyl-2-(2-pentenyl)-2-cyclopenten-1-one (*cis*-jasmone). However, with the latter substrate, the aldehyde yields did not exceed 38% [14].

In the course of a continuous search for new strategies to produce Nylon monomers, the DSM company has described an attractive approach for the synthesis of adipic acid or 6-aminocaproic acid precursors. Indeed, in a recent patent, this company has claimed the hydroformylation of 3-pentenoic acid into 5-formylvaleric acid in biphasic medium (Eq. 3). With a water-soluble platinum complex of tetrasulfonated *trans*-1,2-bis(diphenylphosphinomethylene)cyclobutane as catalyst, the selectivity for 5-formylvaleric acids reached 62% [15]. The same catalytic system allows also the hydroformylation of *trans*-3-pentenenitrile with 91.4% selectivity.

(3)



Conversion: 79 %
Formylvaleric acid selectivity: 80.3 %

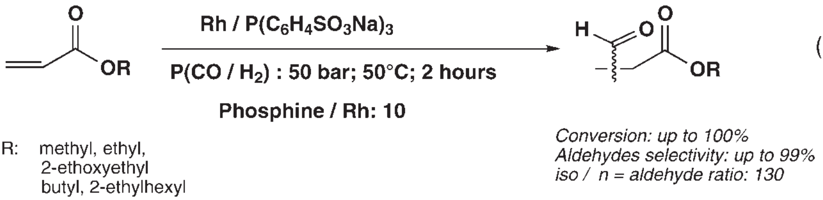
Recently, rhodium/poly(enolate-*co*-vinyl alcohol-*co*-vinyl acetate) catalysts have been developed for the biphasic hydroformylation of aliphatic alkenes and applied to the selective hydroformylation of functionalized alkenes [16]. Although the conversions were low (< 25%), excellent selectivities for the hydroformylation of *n*-butyl vinyl ether and methyl 3,3-dimethylpenten-4-onate can be achieved with such water-soluble polymer-anchored rhodium catalysts. For instance, the hydroformylation of methyl 3,3-dimethylpenten-4-onate gives only the linear aldehyde.

As far as is known, the only industrial application of the water-soluble catalyst for the hydroformylation of δ-functionalized alkenes has been developed by Kuraray [17]. In this process, 7-octen-1-al is hydroformylated into nonane-1,9-dial, a precursor of nonene-1,9-diol, by using a rhodium catalyst and the monosulfonated triphenylphosphine as water-soluble ligand in a 1:1 sulfolane/water system. At the completion of reaction, the aldehydes are extracted from the reaction mixture with a primary alcohol or a mixture of primary alcohol and saturated aliphatic hydrocarbon (cf. Section 6.9).

6.1.3.3.3

Biphasic Hydroformylation of α-Functionalized Alkenes

As reported above, a literature survey shows that the hydroformylation of this class of alkene has been scarcely investigated. Indeed, these studies have been devoted exclusively to the hydroformylation of arylic esters such as methyl acrylate, ethyl acrylate, butyl acrylate, 2-ethoxyethyl acrylate, and 2-ethylhexyl acrylate (Eq. 4) [18–21]. Most attention has been focused on the hydroformylation of methyl acrylate to 2-formylpropanoate ester since the latter is used extensively for the synthesis of pharmaceuticals and may also be considered as a potential source of methyl methacrylate [18].



(4)

In contrast with the first class of functionalized alkenes, immobilization of the catalyst in aqueous phase results in an enhancement of the catalytic activity [19]. Indeed, it has been observed that the hydroformylation rates of arylic esters having high solubility in water were much higher in biphasic systems than those observed under comparable homogeneous conditions. Except for 2-ethylhexyl acrylate, the initial rate was increased by a factor of 2.4, 12, 2.8, and 14 for methyl, ethyl, butyl, and 2-ethoxyethyl acrylate, respectively (see Figure 1) [20]. One of the most intriguing features is that the hydroformylation rates for ethyl and butyl acrylates in biphasic medium were respectively higher than and comparable with those observed with methyl acrylate. Actually, the water-solubilities of ethyl and butyl acrylates (18.3 and 2.0 g L^{-1} at 20 °C, respectively) are lower than that of methyl acrylate (59.3 g L^{-1} at 20 °C).

The peculiar enhancement of the catalytic activity in biphasic medium for the hydroformylation of the water-soluble acrylates seems to be due to the physical and chemical properties of water [21]. Indeed, it is assumed that water stabilizes

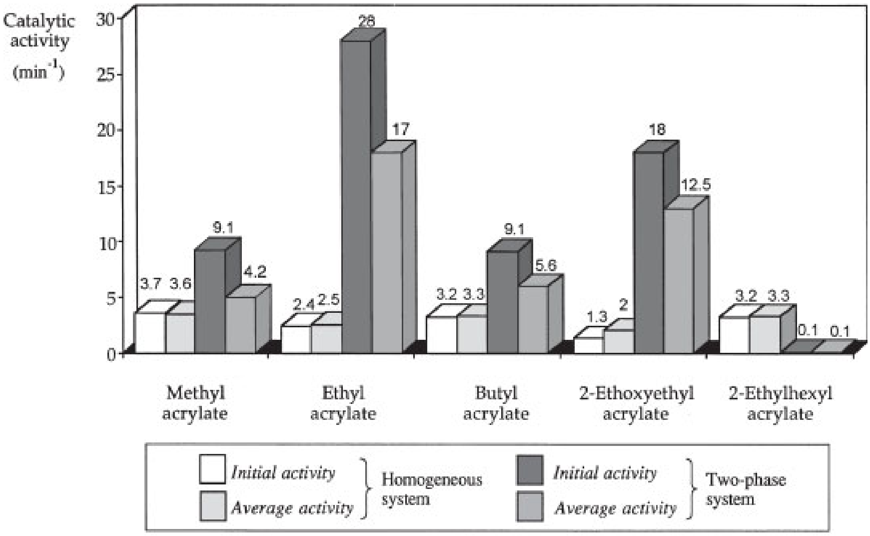
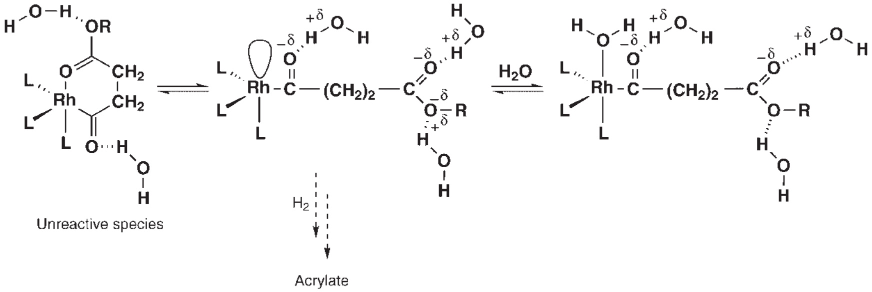


Fig. 1 Initial and average catalytic activities for the hydroformylation of various acrylates in homogeneous and biphasic systems. $Rh(acac)(CO)_2$, 0.2 mmol; phosphine, 2 mmol; substrate, 100 mmol; toluene, 40 mL; water for biphasic medium, 30 mL; T: 50 °C, p_{CO/H_2}: 50 bar.

the catalytic species by hydrogen bonding. For instance, it has been proposed that the equilibrium between chelated and nonchelated rhodium complexes is shifted toward the reactive nonchelated species by the formation of hydrogen bonding between water and the carboxyl group of acrylate, which makes oxidative addition of hydrogen easier (see Scheme 1).

The decrease in the activity with 2-ethylhexyl acrylate is more familiar and can be attributed to low mass transfer between aqueous and organic phases due to the very poor solubility of this acrylate in water. As a matter of fact, it must be noticed that the hydroformylation of this substrate can be achieved by using an aqueous-phase supported rhodium catalyst [20] or inverse-phase transfer catalysts such as



Scheme 1 Equilibrium between chelated and nonchelated rhodium complexes in water.

chemically modified cyclodextrins [22]. Owing to the formation of inclusion complexes between an appropriately modified cyclodextrin and the 2-ethylhexyl acrylate, the catalytic activity can be up to 30 times higher than those observed with an aqueous-phase supported rhodium catalyst and 50 times higher than those observed without cyclodextrin. Thus, in the presence of per(2,6-di-*O*-methyl)-β-cyclodextrin and a Rh/TPPTS catalyst, 2-ethylhexyl acrylate conversion and selectivity to aldehydes reached 100% and 99%, respectively.

More surprising is the unprecedented observation that immobilization of the rhodium/water-soluble phosphine catalyst on a wet silica gel yields an extremely active supported aqueous-phase catalyst for the hydroformylation of a series of acrylic esters [20]. Thus, under optimized conditions, an initial turnover frequency of 4300 h^{-1} was observed for methyl acrylate hydroformylation, compared with 545 h^{-1} in a water–toluene biphasic system and 225 h^{-1} in a homogeneous system. It has been found that the water content, the surface area, and the chemical nature of the solid support play a major role in the activity of the catalyst, whereas the pore diameter has almost no influence. The possibilities of separating the catalyst easily from the reaction medium and recycling it in further experiments were also studied. Unfortunately, a decrease of ca. 10–20% in the catalytic activity was observed between each recycling experiment. This decrease was attributed mainly to the leaching of the rhodium into the organic phase and the gradual dehydration of the silica.

6.1.3.3.4
Conclusion

The behavior of functionalized alkenes depends strongly on the proximity of the functional group relative to the double bond to be hydroformylated. The few examples described so far reveal that most of the principles used for the hydroformylation of unfunctionalized alkenes can be applied. However, unusual results can be observed with α-functionalized alkenes, i.e., with acrylates. The formation of reactive nonchelated species has been suggested as an explanation of this behavior. Such a phenomenon should probably be generalized to other alkenes bearing functional groups in a suitable position, but experiments still remain to be done under biphasic conditions to confirm this hypothesis.

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6.1.4
Re-immobilization Techniques

Helmut Bahrmann

6.1.4.1
Introduction

Recent developments in hydroformylation [1–5] were mainly influenced and accelerated by the introduction of functionalized ligands [6–10] which enable the formation of aqueous two-phase or other biphasic catalysts [14]. Normally, the functionalization is affected by the introduction of sulfonic, carboxylic, or ammonium groups which are connected with alkali or alkaline-earth cations as counterions. If ammonium cations are used, the substituents of the nitrogen have an extreme influence on the properties of the functionalized ligands. Using trisulfonated triphenylphosphine (TPPTS) [11, 12] anions the whole system shifts from a water-soluble ("biphasic") to an insoluble ("monophasic") system by minor variations of the alkyl groups and substitution by hydrogen in the counterions (Figure 1) [13].

The chemistry and separation technique of the insoluble ("monophasic") system are outlined in more detail below mainly for the hydroformylation, mostly on the basis of TPPTS.

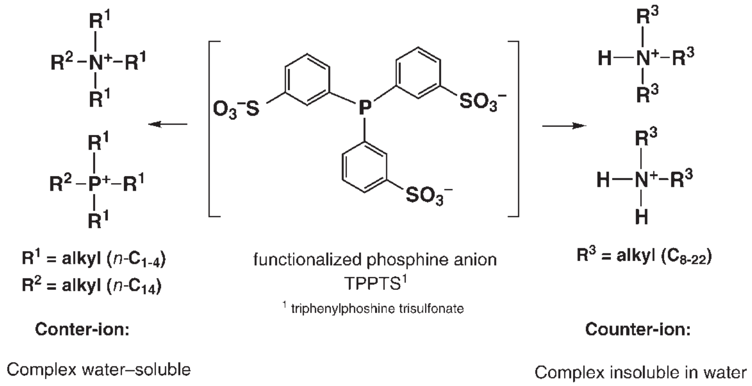


Fig. 1 Influence of cations on the properties of TPPTS salts.

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

6.1.4.2
Water-insoluble, Re-immobilized Liphophilic Ligands and Their Separation by Membrane Technique

The water-insoluble ammonium ligands are prepared from available water-soluble sodium salts according to Eq. (1). By introducing different amines in solvents, the sodium cations of the sulfonates can be exchanged in the presence of sulfuric acid. Sodium hydrogensulfate as a by-product can be removed smoothly by phase separation. This re-immobilization technique may also be extremely useful in the separation of salts from raw sulfonation mixtures within the preparation of sulfonated phosphines [12]. According to Eq. (1) many variations are possible, for example in the amines, functionalized phosphorus ligands, acids, solvents, and preparation procedures. The variability of the monoamines is demonstrated in Table 1.

$$\underset{\substack{\text{Immobilized ligand}\\ \text{for biphasic aqueous}\\ \text{catalysis}}}{P(R^1\text{-}SO_3Na)_3} \xrightarrow[-\ NaHSO_4]{NR_3,\ H_2SO_4,\ \text{toluene}} \underset{\substack{\text{Re-immobilized}\\ \text{ligand for monophasic}\\ \text{organic catalysis}}}{P(R^1\text{-}SO_3HNR_3)_3} \qquad (1)$$

In all cases the P(III) yield (transition into the organic phase) is sufficient. For amines with higher molecular masses the pH value is generally lower. Perhaps because of the large distance between the amine groups, the multifunctional amines do not tend to polymerize as do the lower amines (see below).

Tab. 1 Ligand preparation with variation of amines.

Entry	*Amine*	*Mol. mass*	*Temp. [°C]*	*pH*		*Addition of i-C_3H_7OH*	*P(III) content of phases [%]*	
				Start	*End*		*Lower aqueous*	*Upper organic*
1	Triisooctylamine	353.7	20		3.5	–	0.0	100
2	Methylditallowamine	513.6	60	7.3	3.5	+	0.8	100
3	Distearylamine	522.0	65	7.7	2.6	+	0.0	100
4	Methyldistearylamine	536.0	60	9.0	3.6	+	–	93.9
5	Jeffamine M 600	600.0	20	10.0	1.8	–	1.6	88.6
6	Tricetylamine	690.3	20	7.5	3.5	–	6.6	98.7
7	Tristearylamine	740.8	60	5.7	1.0	–	0.6	87.0
8	Tri-*n*-octadecylamine	774.5	75	6.8	1.0	–	1.8	90.6
9	Triicosylamine	858.6	75	6.8	0.0	–	1.1	95.5
10	Tridoicosylamine	942.8	80	3.5	0.1	–	–	94.3
11	Jeffamine D 2000	2000	20	9.7	3.6	+	8.9	88.0
12	Jeffamine T 3000	3000	20	9.0	3.6	+	–	93.2
13	Jeffamine D 4000	4000	20	9.5	3.4	+	16.0	73.0

Solvent, 2.7 g toluene/g amine; source of phosphorus, TPPTS, 0.33 mol/mol amine; acid, sulfuric acid.

Normally, as outlined above, the “triacidic acid” TPPTS was combined with “monobasic amines” as bases. Dibasic amines such as 1,3-diaminopropane yield highly crosslinked polymeric materials, whereas other diamines such as Thancat CD® $[(CH_3)_2NCH_2CH_2]_2O$ or 3,4,8,9-Bis(dimethylaminomethylene)tricyclodecane result in the formation of water-soluble ligand salts.

Replacing the “triacidic acid” TPPTS by the disulfonated TPPDS in combination with TCD-diamine (tricyclodecane diamine), a salt partly soluble in toluene and soluble in THF was formed. The same is true with *N*,*N*′-dimethyl-TCD-diamine instead of TCD-diamine. These salts may be useful in water-free (although biphasic) operation. Under special circumstances even the olefin for the further catalysis may serve as a solvent itself. This concept was successfully realized with dicyclopentadiene (DCP).

In some cases, it is desirable and necessary to use phosphines with low basicity such as phosphites. In order to prepare ionic phosphites of the same structure as mentioned above, the preparation procedure [15] can be modified as outlined in Eqs. (2) and (3).

$$(OH)_n{-}R^1{-}(SO_3Na)_m \xrightarrow[-\ NaHSO_4]{NR_3,\ H_2SO_4,\ toluene} (OH)_n{-}R^1{-}(SO_3HNR_3)_m \tag{2}$$

$$3\ (OH)_n{-}R^1{-}(SO_3HNR_3)_m \xrightarrow[-\ 3\ HZ]{PZ_3,\ T} P[O{-}R^1(OH)_{n-1}(SO_3HNR^3)_m]_3 \tag{3}$$

Z = Hal, OR
$R^1 = C_6H_6$, x = 6-(n+m)

The technique is described in more detail in [38].

6.1.4.3
Separation and Use of Water-insoluble Ammonium Ligands in Hydroformylation

Whereas, on the one hand, in hydroformylation with water-soluble ligands the catalyst can be separated easily after the reaction by simple phase separation, the conversion of higher olefins is normally poor and suffers from the reduced miscibility of both phases by restricted mass transfer. This can be overcome by different supplementary methods (cf. Sections 4.6.3 and 6.1.3.2, and Chapter 7). In addition, the very active and useful phosphite ligands must be excluded from the aqueous phase due to hydrolysis. On the other hand, high conversion rates can be reached even with branched unreactive olefins using conventional homogeneous ligands in “homophasic” operation, but separation of the catalysts may be a problem, especially with high-boiling substrates, which cannot be distilled.

By using water-insoluble ammonium ligands, the advantages of both catalyst systems (easy separation under mild reaction conditions and high conversion rate) can be combined while avoiding their disadvantages. Thus, hydroformylation with

Tab. 2 Ligand testing by hydroformylation: ionic phosphites versus triphenylphosphine (TPP).

	Triphenylphosphine (TPP)		***TPPpS–TIOA salt*** [a]	
P/Rh ratio [mol/mol]	***40 : 1***	***80 : 1***	***40 : 1***	***80 : 1***
Conversion [%]	81	83	71	70
n/iso ratio	72 : 28	72 : 28	83 : 17	87 : 13

Reaction conditions: olefinic feedstock, *n*-1-tetradecene; pressure, 50 bar; Rh concentration, 20 ppm; temperature, 125 °C; reaction time, 3 h; solvent, acetone.

[a] Triisooctylamine salts of *p*-sulfonated phosphorous acid triphenyl ester.

ionic phosphites (e.g., the triisooctylamine salt of sulfonated phosphorous acid triphenyl ester, TPPpS–TIOA salt, Table 2) was introduced by Fell and Papadogianakis [16]. As compared with TPP, the TPPpS–TIOA salt offers a significantly better ratio of linear/branched compounds (l/b, or *n*/iso, ratio). For the separation and recycling of the water-insoluble ammonium salt ligands and Rh complexes, two different methods have been proved their worth, i.e., the phase separation by pH change after reaction and the separation of the catalyst system by membrane filtration.

6.1.4.3.1
Phase Separation by pH Change After Reaction

In this case the potential functionality of the ligands is applied to induce a phase transition of ligands and Rh complexes and subsequent phase separation by a pH change after the reaction at room temperature under mild conditions. The principle is outlined in Eqs. (4) and (5):

$$\mathrm{P(R'SO_3HNR_3)_3} \xrightarrow{\text{NaOH (aq.)}} \mathrm{P(R'SO_3Na)_3} + \text{amine} \tag{4}$$

and thus

$$\underset{\text{organic phase}}{[\mathrm{Rh}]_{\mathrm{org}}} \xrightarrow{\text{NaOH (aq.)}} \underset{\text{aqueous phase}}{[\mathrm{Rh}]_{\mathrm{aq}}} + \underset{\text{organic phase}}{\text{amine}} \tag{5}$$

By changing the pH value the water-insoluble ammonium salts are reconverted into water-soluble sodium sulfonates. The phosphine and the Rh catalyst are thus transferred to the aqueous phase. They can easily be separated from the organic product. A process scheme is outlined in Figure 2.

As can be seen from Figure 2 the resulting aqueous catalyst phase can be further used in the biphase catalyst system (such as the RCH/RP process [5 g]) or may be re-immobilized in a regenerator with fresh H_2SO_4/amine for the next catalyst cycle. The amine content of the organic phase can be separated by distillation and recycled again by treatment with recycled sulfonated phosphine and sulfuric acid.

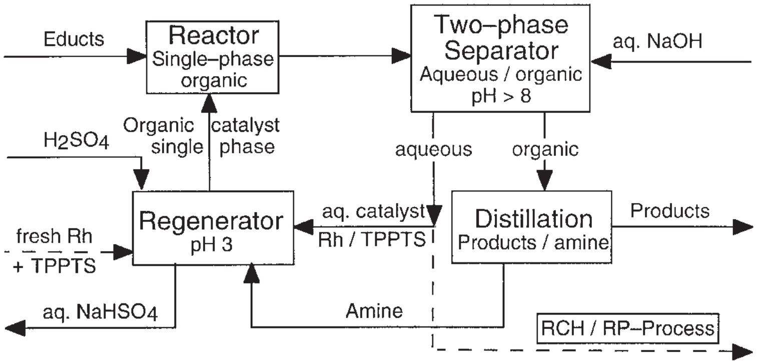


Fig. 2 Catalyst recycling by pH-induced phase separation.

Using this procedure a variety of different olefinic compounds and structures (cycloaliphatic, internal, functionalized) have been tested with the triisooctylamine/TPPTS salt [17, 38]. Since fairly good results have been obtained by hydroformylation of oleyl alcohol, the catalyst separation and recovery were investigated successully in more detail on a pilot-plant scale [18, 19].

6.1.4.3.2
Separation of the Catalyst by Membrane Filtration

The formation of salts according to Figure 2 is environmentally disadvantageous. Thus, a separation of the catalyst system (Rh complexes as well as an additional excess of stabilizing ligands) by membrane filtration ought to be the best way to overcome this and other disadvantages. The state-of-the-art is characterized by the transition from reverse osmosis (RO) conditions (high pressures, 50–100 bar), low flow rates (1–4 L/m^{2}h), and a solute rejection of about 80–95% [20–27] to ultrafiltration (UF) at lower pressures (2 bar), higher flow rates (20 L/m^{2}h), and a satisfying metal retention ($>$ 95%) [28–30].

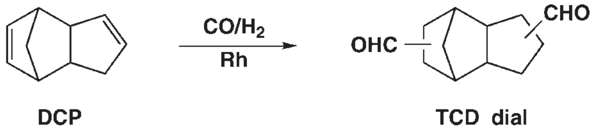
6.1.4.3.3
Other Developments

The challenge to enable a good retention for both metal complexes and free ligands requires

- the development of new membranes resistant to organic liquids with a narrow cut-off in a molecular-mass (M) range between 1000 and 10 000;
- an oxo raw material with a high process development and market potential;
- the choice and development of appropriate ligands (M 1000–10 000).

At the beginning the first requirement was not fulfilled, because experiments with commercially available membranes showed insufficient resistance to organic products, especially against oxo products. Later, a new polyaramide membrane

(UF-PA-5 from Hoechst AG) with outstanding properties, which meet all the requirements, was available [31]. The second requirement was met with the decision to use tricyclodecane dialdehyde ("TCD-dial") from the hydroformylation of dicyclopentadiene (DCP). TCD-dial is the starting product for TCD-diamine, which is a speciality chemical used as a curing agent for epoxy resins (Eq. 6) [37].



(6)

DCP is normally hydroformylated using unmodified Rh catalysts yielding high TCD-dial contents under disastrous Rh recycling conditions. It was found that on hydroformylating DCP an ammonium salt modified phosphine Rh catalyst can also be used.

The third requirement was achieved by the use of the "re-immobilized catalysts" which enable a fine tuning of the size of the ligands by variation of amines due to their modular ionic structure. Since the development of effective and efficient ligands is costly and exceeds the value of the transition metals, it becomes necessary to separate and recycle the ligands, too. Moreover, the structure of the re-immobilizing ligands makes it possible to remove phosphine oxides and other poisons during economical operation by a simple washing procedure. In the final treatment of the ligand, normally all of the ligand is lost, whereas in the case of ionic ligands the ammonium backbone can be re-used.

First results in membrane filtration with a polyaramide membrane and conventional Rh/TPP catalysts were unsatisfactory, even with the Rh complex itself ($M < 1000$). Only the use of the re-immobilized catalyst with a higher molecular mass (> 3000) showed an encouraging Rh retention of 96% as compared with 50% with TPP [32].

Mutual Optimization of Hydroformylation and Membrane Filtration Step

This mutual optimization could be achieved via variation of amines and the P/Rh ratio as well as by introduction of chelating ligands. A variety of amines was tested with TCD-dial with respect to conversion and selectivity to dialdehyde, as well as to the separation data in the subsequent membrane separation step. Figure 3 shows the unit used and in Table 3 some results are outlined. The results are discussed intensively in [38].

In Table 3 the retention of amines is also stated. This is because in the course of the investigations traces of amine were always found in the permeate. This is a result of a very-low-temperature-dependent dissociation of the ammonium salts into amine and free acid during the hydroformylation reaction according to Eq. (7).

$$P(C_6H_4SO_3\text{–}HNR_3^+)_3 \longrightarrow P(C_6H_4SO_3H)_3 + 3\ NR_3 \qquad (7)$$

Tab. 3 Hydroformylation of dicyclopentadiene and membrane separation of the catalyst system (with variation of amines).

Amine	*Mol. mass [M]*	*Conver-sion [%]*	*Selectivity, dialdehyde/ monenal*	*P(III)/Rh ratio*[a)]	*pH value after reaction*	*Permeate amount [% of input]*	*Permeate flux [L m^{-2} h^{-1}]*	*Retention [%] of*		
								[Rh]	*Ligand [P]*	*Amine [N]*
Triisooctylamine	353.7	99.7	99 : 1	74	–	5–15	65–64	89.3	69.8	16.5
Methylditallowamine	513.6	99.6	92 : 8	41	4.0	11	71–	91.9	95.0	76.4
Distearylamine	522.0	98.4	97 : 3	72	4.0	66	67–61	97.5	96.1	78.3
Methyldistearylamine	536.0	99.4	95 : 5	63	4.3	5–10	82–77	97.1	94.3	
Jeffamine M 600	600.0	98.8	40 : 60	51	3.3	23	9	99.7	98.7	63.9
Tricetylamine	690.3	98.7	96 : 4	78	–	22	44–	95.0	90.0	73.3
Tri-*n*-octadecylamine	774.5	98.5	91 : 9	84	–	53	68–49	93.0	87.0	88.7
Triicosylamine[b)]	858.6	99.0	95 : 5	103	–	22	57–59	98.9	95.9	88.3
Tridoicosylamine[b)]	942.8	99.7	90 : 10	–	–	48.8	44–29	96.5	94.7	81.9
Jeffamine D 2000	2000	98.1	69 : 31	7.6	4.0	29	23–22	99.5	89.4	93.9
Jeffamine T 3000	3000	98.4	63 : 37	3.9	6.2	56	45–31	99.7	97.7	91.4

Hydroformylation conditions: solvent, about 50% toluene; phosphorus source, TPPTS, 0.33 mol/mol amine; pressure 270 bar; Rh concn., 60 ppm; P/Rh ratio, 100 : 1, reaction temperature, 130 °C; reaction time, 4 h.

Membrane separation conditions: feed, reaction product of hydroformylation of dicyclopentadiene; solvent, about 50% toluene; membrane, UF-PA-5/PET 100 from the former Hoechst AG; overflow, ≈ 200 L h^{-1}; separation temperature, 40 °C; pretreatment of membranes in water at 80 °C for 10 min; transmembrane pressure, 10 bar.

[a)] After reaction.

[b)] Precipitation of the ligand below 40 °C.

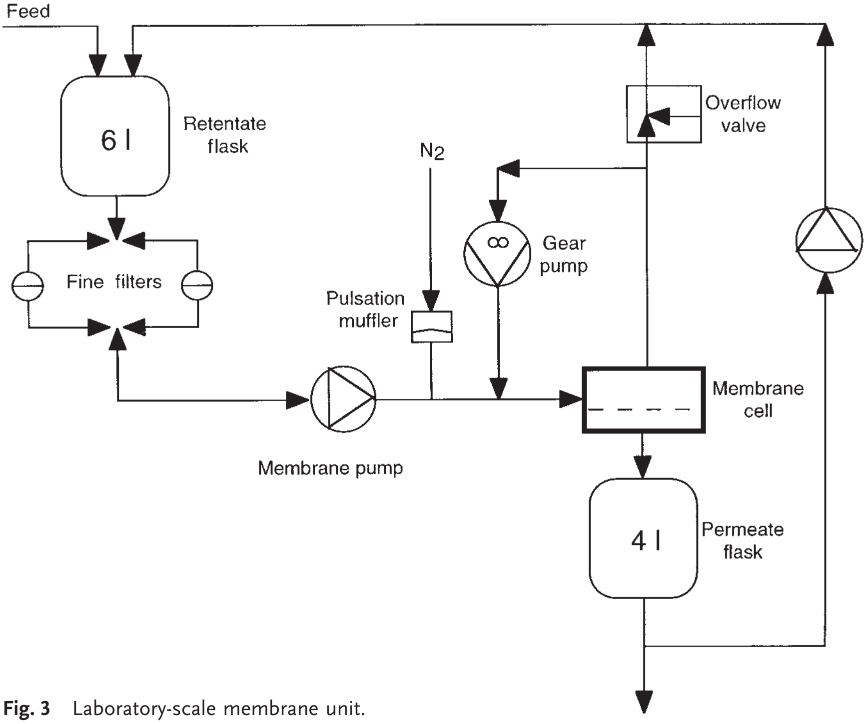


Fig. 3 Laboratory-scale membrane unit.

In order to stabilize the ammonium salts it was necessary to allow the presence of some free amines. With respect to this additional requirement, an ideal system must have the same good retention for amines as well as for the rhodium and the ligands. In this light the choice of distearylamine could only be regarded as a good compromise between hydroformylation and membrane separation data. Thus, further optimization work was done by hydroformylation of DCP or propene respectively with the Rh–distearyl amine/TPPTS catalyst system.

Test runs with low P/Rh ratios and Rh concentrations while hydroformylating DCP showed excellent membrane separation results but decreasing activity data. This failure in the optimization approach of the hydroformylation and membrane separation step without regard to long-term stability again underlines a basic problem in catalyst development, the coincidental consideration of different contradictory circumstances. A second series with a high P/Rh ratio of 100 was performed with the same catalyst system and butyraldehyde from the hydroformylation of propene as feed.

This replication series (for details cf. [38]) showed overall excellent results in the hydroformylation as well as in the membrane separation step. With a high P/Rh ratio no deactivation was observed. The activity of the catalyst remained sufficient and high amounts of permeate with stable flow rates of 10 to 12 $\mathrm{L\,m^{-2}h}$ in the

Tab. 4 Recycle series with Rh-distearylamine-1,3-bis(disulfonatophenyl)phosphinopropane catalyst.

Hydroformylation			*Membrane filtration*				
Conversion [%]	*n/iso ratio*	*No of recycles*	*Retention [%]*			*Flow rate* $[\mathrm{L\,m^{-2}\,h^{-1}}]$	
			Rh	*P [total]*	*N*	*1st stage*	*2nd stage*
93.9	55 : 45	0	96.4	80.9	60.3	92–59	119–75
85.4	56 : 44	1	97.7	88.8	58.7	82–54 a)	112–72
88.6	55 : 45	2					

Hydroformylation conditions: feed, propene, 270 bar; temperature, 125 °C; P/Rh ratio, 2 : 1; reaction time, 2 h; Rh concn., 20 ppm; membrane separation conditions: feed, butyraldehyde; membrane type, UF-PA-5/PET 100 from the former Hoechst AG; pressure, 15 bar; temperature, 40 °C; amount of permeate, 1st stage, 91–84%; 2nd stage, 95–92%.

a) Addition of 0.4 mmol P(III) of ligand to the permeate of the first stage.

critical first stage could be achieved. Obviously, traces of amine in the system catalyze the formation of some high boiling components.

Whereas, on the one hand, a sufficiently high excess of ligands is required for the stabilization of the catalyst system, on the other hand, this high excess of ligands leads to limitations, which depend on the physical properties of such an excess (“salt effect” of the ligands). This, in turn reduces the permeate flow rate and the permeate amount of the membrane filtration.

These contradictory effects with monodentate phosphines may be overcome by the use of bidentate ligands. Chelating ligands as strong complexing agents generally do not need a high excess of free uncomplexed ligands for the stabilization of the active catalyst complex. They make it possible to perform the hydroformylation reaction at a lower P/Rh ratio. Table 4 shows first results with an ammonium salt of simple functionalized chelating ligands, the distearylamine/1,3-bis(disulfonatophenyl)phosphinopropane salt and butyraldehyde from the hydroformylation of propene as feed.

Generally, retention data were somewhat poorer, but very high flow rates could be achieved. On the basis of these results, an increase of the flow rate from 10–12 up to 30–50 $\mathrm{L\,m^{-2}\,h^{-1}}$ by a factor of 3–4 could be reached. Additionally, the amount of ligand could be reduced by a factor of 50 and the Rh concentration by a factor of 2–3.

Membrane Techniques on a Pilot-plant Scale [33]

Finally, the separation of the Rh–distearylamine/TPPTS catalyst system by membranes was successfully tested on pilot-plant scale with crude aldehyde from the hydroformylation of DCP. The unit was continuously operated over a period of 12 weeks. No decrease in permeate flux and catalyst activity was observed. In contrast to laboratory-scale results, the Rh concentration must be increased to 100 ppm in order to obtain a selectivity of $> 90\%$ of dialdehyde. The recirculation rate of Rh was established at 99.2% and of the ligand up to 98%. The permeate flux was roughly 10 $\mathrm{L\,m^{-2}\,h^{-1}}$. Most of the loss of ligand was due to traces of oxygen.

6.1.4.4
Separation of Phosphine Oxides and Other Degradation Products

The special functionality of the ionic phosphines enables a continuous catalyst make-up. Phosphine oxides and other degradation products can be separated from phosphine oxide by simple extraction with a dilute aqueous sodium hydroxide solution. The concentration of the aqueous sodium hydroxide and the extraction temperature have a tremendous influence on the extraction data. At low concentrations (0.01%) only the water-soluble sodium phosphine oxides and some benzenesulfonic acid sodium salt (a degradation product of TPPTS) are extracted into the aqueous phase selectively, whereas at higher concentrations above 0.05% some of the phosphine is discharged, too. This simple selective separation of phosphine oxides and degradation products in continuous operation can enhance the lifetime of the catalyst system. The amount of aqueous NaOH can be adjusted to the degradation rate, which is much lower than the extraction rate. An adequate amount of NaTPPTS may be added together with the aqueous NaOH for generation of new ammonium salts from the amine, which will be formed by this procedure (see Eqs. 4 and 5).

If higher concentrations of aqueous sodium hydroxide (15%) are used, all of the re-immobilized ligands and the rhodium complex can be extracted into the aqueous phase. This can thus be submitted to the oxidative treatment for Rh recovery according to [34–36]. In this way, 92–95% of the Rh content may be recovered. The amine content of the organic phase was used again by treatment with fresh sulfonated phosphine and sulfuric acid. In the subsequent hydroformylation the same results were actually observed.

6.1.4.5
Further Developments

Because of their salt-like structure, the quaternary ammonium salts enable a selective continuous separation of phosphine oxides and degradation products during the hydroformylation reaction and thus a prolongation of catalyst life-time [38]. The amine backbone can be re-used. The finally recovery of valuable metal, anions, or cations is possible by simple neutralization reactions.

Additionally, other types of ligands could be used which have the right molecular mass to make possible sufficient retention in the subsequent membrane separation step.

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6.2
Hydrogenation

Ferenc Joó, Ágnes Kathó

6.2.1
Introduction

Hydrogenation constitutes a most important class of homogeneously catalyzed reactions for several reasons. Therefore, ever since the discovery of the catalytic properties of $[Co(CN)_5]^{3-}$ and of $[RhCl(PPh_3)_3]$, hydrogenation has been *the* prototype reaction of homogeneous catalysis by transition metal complexes, leading to such important discoveries as, for example, the processes of enantioselective production of L-DOPA and naproxen [1]. The number of papers, patents, and reviews on homogeneous hydrogenation is enormous and this reaction is treated in detail in chapters of important series of books and in independent monographs.

Having learned that much about the kinetics and mechanisms of homogeneous hydrogenations in the past 60 or so years, is there anything special in hydrogenations in *aqueous systems*? The answer is “yes,” and it lies in the distinct properties of water as contrasted with those of non-aqueous (mostly, but not exclusively, organic) solvents (cf. Sections 2.2 and 2.3).

Being a highly polar solvent, water is *not* a good medium in which to dissolve molecular hydrogen and the usual substrates of catalytic hydrogenations, mostly apolar organics. Conversely, its immiscibility with many of the common organic solvents makes possible the realization of hydrogenation processes in biphasic solvent systems, allowing easy and efficient isolation of products and recovery of catalysts. It is important to note that, although many biphasic reactions are known with water as one of the solvents, in the following we restrict our discussion to cases where the reaction takes place in the aqueous phase. Relation of aqueous-phase organometallic catalysis to phase-transfer catalysis is discussed in Section 4.6.1.

A specific value of water as solvent lies in the fact that there are catalysts (such as $K_3[Co(CN)_5]$) and substrates (e.g., carbohydrates) which do not dissolve in common nonpolar organic solvents. In the special cases of hydrogenations in living systems, although the constituent lipids are soluble in organic solvents, use of an aqueous medium is essential to preserve the integrity of the cell membranes (cf. Section 6.15).

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Limited solubility of molecular hydrogen, organic substrates, and products has an important effect on the mechanism of hydrogenations [2]. However, water itself may also affect the formation of catalytically important intermediates by influencing acid/base equilibria of transition metal hydrides, protonation reactions, and formation of hydrogen bonds. Inorganic salts, too, may have a significant effect on the kinetics of hydrogenation ("salt effect;" cf. Section 4.3) – such phenomena are seldom observed in purely organic solutions.

Solubility of the catalysts in water can be due either to their *overall* charge, such as with $[\mathrm{Rh(cod)}(\widehat{\mathrm{L\,L}})]^+$ (cod = 1,5-cyclooctadiene, $\widehat{\mathrm{L\,L}}$ = a chelating diphosphine) or to their water-soluble ligands. Frequently, derivatives of well-known tertiary phosphines (modified by sulfonation, carboxylation, etc.) serve as such ligands; however, some of the phosphines used in water-soluble hydrogenation catalysts (e.g., 1,3,5-triaza-7-phosphaadamantane) have no analogs able to dissolve in apolar organic solvents (see Chapter 3 for details).

Catalytic hydrogenation in aqueous solutions is discussed in several general overviews [3–12]. In this section, a cross-section of the field is given, with just some examples of catalysts and reactions.

6.2.2
Mechanisms and Catalysts of Hydrogenations in Aqueous Solution

6.2.2.1
Basic Mechanisms of Dihydrogen Activation

Obviously, there is a great deal of analogy between the mechanisms of hydrogen activation and hydrogenations in aqueous and non-aqueous systems. In principle, H_2 may react with a suitable transition metal complex, $[ML_n]$, in several ways (Eqs. 1–4).

$$H_2 + [ML_n] = [(H_2)ML_n] \tag{1}$$

$$H_2 + [ML_n] = [H_2ML_n] \tag{2}$$

$$H_2 + [ML_n] = [HML_n]^- + H^+ \tag{3}$$

$$H_2 + 2[ML_n] = 2[HML_n] \tag{4}$$

Reaction (1) may precede both (2) and (3), and (3) may follow either (1) or (2), or their combination.

The chemistry of transition metal dihydrogen complexes, such as formed in Eq. (1) is in the focus of very intensive studies [13, 14] and such complexes were shown to be involved in the mechanism of several hyrogenation processes [15]. Despite this fact, their role in aqueous-phase hydrogenations is largely unexplored, although examples of water-soluble (or water-stable) dihydrogen complexes are known [16, 17]. Reaction (1) does not involve the change of the oxidation state of the central metal ion and may offer a more probable pathway for hydrogen activation (via subsequent deprotonation) in the case of catalysts where oxidative addition (Eq. 2) would seem unfavorable, especially in H_2O. A suspected example is the enzyme hydrogenase containing a Ni(II) metal center [18, 19].

Oxidative addition of H_2 to low-valent metal centers, such as Rh(I) or Ir(I), results in formation of transition metal dihydrides (Eq. 2); well-characterized dihydrides are known [16, 17] and play important role in hydrogenation cycles [15].

Equation (3) depicts direct formation of a monohydrido complex from H_2 and ML_n, although the reaction is likely to proceed via deprotonation of a dihydrogen complex or that of a transition metal dihydride. Such deprotonations are obviously facilitated by the presence of sufficiently strong bases (either H_2O itself, or the bases dissolved in it).

The hydrides of radical nature, formed for example in reaction (4), are less frequently encountered in aqueous-phase catalyzed hydrogenations, despite the fact that water is an ideal solvent for free radicals in terms of its unreactivity [24]. The best-known organometallic hydrogenation catalyst acting via this route in aqueous solutions is $[Co(CN)_5]^{3-}$.

Simple thermodynamic calculations [12] show that, while in the gas phase, homolytic bond dissociation of H_2 requires much less energy (436 kJ mol^{-1}) than the heterolytic split to H^+ and H^- (1674 kJ mol^{-1}), the reverse is true for aqueous solutions (423 kJ mol^{-1} vs. 156 kJ mol^{-1}). The high hydration energies of H^+ (− 1090 kJ mol^{-1}) and H^- (− 435 kJ mol^{-1}) compared with the very low value for atomic H (− 4 kJ mol^{-1}) explain the difference. Although these enthalpy values cannot be directly related to the activation of H_2 by metal complexes (Eqs. 1–4), they clearly show the potentially very large contribution of solvation to the driving force of the overall reaction; the heterolytic split of H_2 is clearly more preferred in the case of water than in nonpolar organic solvents.

6.2.2.2

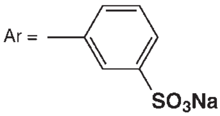
Water-soluble Hydrogenation Catalysts with Tertiary Phosphine Ligands

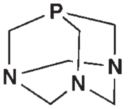
A wide variety of water-soluble tertiary phosphines have been prepared and used in aqueous hydrogenations in combination with the metal ions from the platinum metals group; examples are shown as Structures **1**–**19**. Most of the fundamental, general studies on catalytic hydrogenation used *sulfonated* arylphosphines because of their availability, stability, and good solubility in water in a wide pH range. A facile way of their characterization in the solid state has recently been reported [151]. For the same reason, phosphonato-phosphines, e.g., $Ph_2P(CH_2)_2PO_3Na_2$, have been getting increased attention [152, 153].

In general, coordination chemistry of water-soluble phosphine complexes and their reaction with dihydrogen show many similarities to reactions of their water-insoluble analogs. Active hydrogenation catalysts or catalyst precursors, such as

Ph_nPAr_{3-n}

1 n = 2; TPPMS
2 n = 0; TPPTS

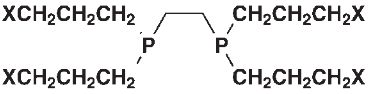




4

$[Ph_2PCH_2CH_2NMe_3]^+$
3 AMPHOS

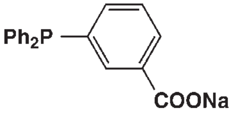
$P[CH_2CH_2O(CH_2CH_2O)_nCH_2CH_2OCH_3]_3$
5 n = 33



6 X = OH
7 X = SO_3Na

$Ph_2P–(CH_2)_n–COONa$

8 n = 5 **HEXNa**
9 n = 7 **OCTNa**



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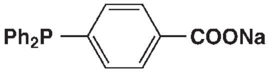

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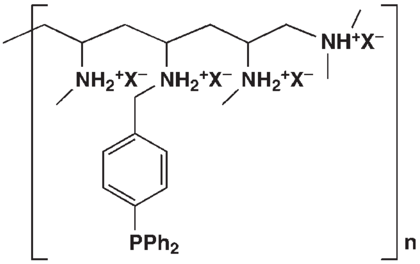
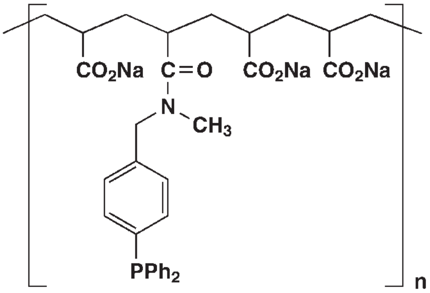
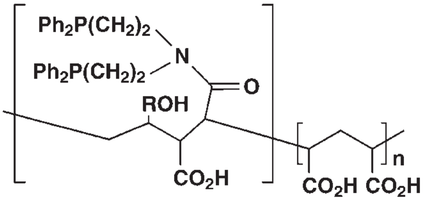


12 PEI–PNH



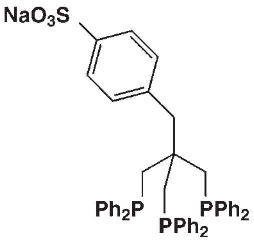
13 PAA–PNH



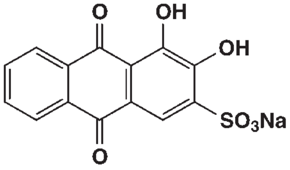
MA – MVE
n = 10, **14**
n = 12, **15**
n = 15, **16**

$Ph_2P(CH_2CH_2O)CH_2CH_2PPh_2$

17, n ~ 2000



SULPHOS **18**



QS **19**

$[RhCl(TPPMS)_3]$ [25], $[HRu(OAc)(TPPMS)_3]$ [26], or $[Rh(cod)(BDPP_{TS}]^+$ ($BDPP_{TS}$, Structure **28**) [27], can be prepared by familiar procedures, either from reduction of hydrated salts by an excess of the ligand (as to TPPMS and TPPTS cf. Section 3.2.1) (Eq. 5), or by substituting labile ligands on the metal center Eq. 6). In several cases exchange of a PPh_3 ligand for TPPMS or TPPTS in tetrahydrofuran is driven to completion by the insolubility of the product in THF [28] (e.g., Eq. 7). With tertiary phosphine complexes the most common way of activation of dihydrogen is its homolytic splitting by oxidation addition, as in Eq. (8)). The further fate of the resulting dihydrides is pH-dependent and formation of monohydrido complexes by dehydrochlorination or proton dissociation can be observed [29].

$$\mathrm{RhCl_{3aq} + 4\,TPPMS + H_2O = [RhCl(TPPMS)_3]_{aq} + 2\,H^+ + 2\,Cl^- + TPPMSO} \tag{5}$$

$$\mathrm{[Rh(cod)(MeOH)_2][ClO_4] + BDPP_{TS} = [Rh(cod)(BDPP_{TS})][ClO_4] + 2\,MeOH} \tag{6}$$

$$\textit{trans}\text{-}\mathrm{[IrCl(CO)(PPh_3)_2] + 2\,TPPMS} = \textit{trans}\text{-}\mathrm{[IrCl(CO)(TPPMS)_2] + 2\,PPh_3} \tag{7}$$

$$\mathrm{[RhCl(TPPMS)_3] + H_2 = [H_2RhCl(TPPMS)_3]} \tag{8}$$

Aqueous organometallic catalysis, however, is not a mere duplication of what had already been observed in organic solvents, and indeed, special effects of the aqueous solvent can be encountered (see examples in Section 6.2.3).

Activation of dihydrogen by oxidative addition is facilitated by complexes with low-valent metal centers; water itself may add oxidatively to the same metal ions (Eq. 9). Reductive elimination of HCl results in the formation of hydroxorhodium(I) derivatives (Eq. 10). Indeed, prolonged treatment of $[RhCl(PPh_3)_3]$ or $[RhCl(cod)]_2$ with an excess of TPPTS in aqueous solvents gives high proportions of $[Rh(OH)(TPPTS)_3]$ [23]; this compound may also be formed by direct Cl^-/OH^- exchange. An unwanted consequence of such redox and hydrolytic reactions is the degradation of the catalysts. Even in the most carefully deoxygenated water as solvent, a considerable proportion of phosphine oxide was formed upon dissolution of $[RhCl(TPPTS)_3]$ under an inert atmosphere [30]. Phosphine oxidation is more pronounced with the more basic PTA [31]. Obviously, formation of hydroxo complexes is facilitated by increasing the pH of the solution. Under hydrogen, some of the complexes undergo phosphine degradation to give colloidal metals, oxides, or hydroxides [32–34]. $[Pd(OH)_2(TPPMS)_2]$, which catalyzes the hydrogenation of alkynes and dienes to monoenes in aqueous solutions at ambient conditions, gave phosphide-bridged clusters and finally $[Pd(OH)_2]$ [32].

$$\mathrm{[RhCl(TPPTS)_3] + H_2O = [HRhCl(OH)(TPPTS)_3]} \tag{9}$$

$$\mathrm{[HRhCl(OH)(TPPTS)_3] = [Rh(OH)(TPPTS)_3] + H^+ + Cl^-} \tag{10}$$

Many transition metal hydrides are sufficiently acidic to undergo proton dissociation in the presence of bases or in solvents of suitable solvation power; a thorough analysis of the phenomenon is given in [36]. Water itself can act as a base and, as discussed in Section 6.2.2.1, solvation (hydration) of H^+ is accompanied by an extraordinarily high negative enthalpy change. Consequently, formation of monohydrido complexes can often be observed without the need for an external base. Whereas in benzene solutions formation of $[HRuCl(PPh_3)_3]$ takes place only in the presence of an added base (B) such as 1,8-diaminonaphthalene ("proton sponge") or triethylamine (Eq. 11), reactions of $[RuCl_2(TPPMS)_2]_2$ in water are spontaneous (Eqs. 12–14).

$$[RuCl_2(PPh_3)_3] + H_2 + B \rightarrow [HRuCl(PPh_3)_3] + HB^+ + Cl^- \tag{11}$$

$$[RuCl_2(TPPMS)_2]_2 + 2H_2 \rightleftharpoons [HRuCl(TPPMS)_2]_2 + 2H^+ + 2Cl^- \tag{12}$$

$$[RuCl_2(TPPMS)_2]_2 + 2H_2 + 2TPPMS \rightleftharpoons 2[HRuCl(TPPMS)_3] + 2H^+ + 2Cl^- \tag{13}$$

$$[RuCl_2(TPPMS)_2]_2 + 4H_2 + 4TPPMS \rightleftharpoons 2[H_2Ru(TPPMS)_4] + 4H^+ + 4Cl^- \tag{14}$$

In addition to the temperature and phosphine excess, the positions of equilibria (12)–(14) depend critically on the pH of the solution. The number of protons produced during hydrogenation of $[RuCl_2(TPPMS)_2]_2$ with or without an excess of TPPMS was determined [37]. Below pH 3 the major species is $[HRuCl(TPPMS)_3]$, whereas $[H_2Ru(TPPMS)_4]$ becomes dominant in neutral and basic solutions; in the pH 3–7 range there is a mixture of hydrides present.

A very important conclusion arises, in that meaningful kinetic results can be obtained only in limited pH ranges, and this should be kept in mind when choosing reaction conditions. In addition, a change in the solution composition brings about changes in the rates and selectivities of the catalyzed reactions (see also Section 6.2.3.2).

It has been known for some time that polar solvents accelerate the activation of dihydrogen, as was found with $[HCo(CN)_5]^-$ [38] and $[RhCl(PPh_3)_3]$ [39]. A recent study revealed the same phenomenon, a very large rate increase, *in aqueous* solution [40]. In both dimethyl sulfoxide (DMSO) and water as solvents, the oxidative addition of H_2 to *trans*-$[IrCl(CO)(TPPMS)_2]$ yielding *trans*-$[H_2IrCl(CO)(TPPMS)_2]$ could be described by the rate law given by Eq. (15), which is identical with what had been found earlier for the reaction of *trans*-$[IrCl(CO)(PPh_3)_2]$ with H_2 in toluene or DMSO.

$$\text{rate} = k[\textit{trans}\text{-}IrCl(CO)(TPPMS)_2][H_2] \tag{15}$$

In DMSO, the second-order rate constants, k_{DMSO}, were the same (1.3 ± 0.02 and $1.2 \pm 0.02\ M^{-1}s^{-1}$) for both the TPPMS and the PPh_3 complex. However, in water *trans*-$[IrCl(CO)(TPPMS)_2]$ reacted much faster, with $k_{water} = 12 \pm 3\ M^{-1}s^{-1}$. (For comparison, the corresponding rate constant in toluene was as low as $0.26 \pm 0.07\ M^{-1}s^{-1}$, i.e. a change of solvent from toluene to water brought about a 50-fold increase.) Such a great increase should be a consequence of water favoring a polar transition state, and a pseudo-five-coordinate molecular hydrogen complex is suggested as a likely intermediate. The existence of water-stable dihydrogen complexes [16], the examples of preferential η^2-H_2 versus H_2O binding in $[W(CO)_3(PR_3)_2L]$ ($L = \eta^2$-H_2 or H_2O) [17], and the hydrogenation of acetone to 2-propanol catalyzed by $[Os(NH_3)_5(H_2)]^{3+}$ [41] do, indeed, support the hypotheses on the role of molecular hydrogen complexes along the reaction coordinate in homogeneously catalyzed aqueous hydrogenations.

$[RuCl_2(TPPMS)_2]_2$ is an active catalyst for the hydrogenation of water-soluble alkenes, such as maleic, fumaric, and crotonic acids, in aqueous solutions [26]. A thorough kinetic study of crotonic acid (CA) hydrogenation was undertaken. The rate law derived is given by Eq. (16):

$$-\frac{dn[H_2]}{dt} = \frac{kK[Ru]_0[CA]_0[H_2]}{1 + K[CA]_0 + K^*[TPPMS]} \qquad (16)$$

where K and K^* are the equilibrium constants for reactions (17) and (18).

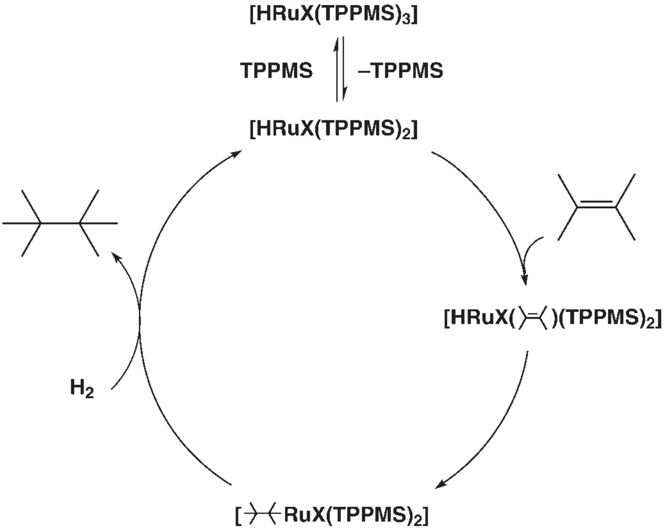
$$[HRuCl(TPPMS)_2] + CA \xrightleftharpoons{K} [(HCA)RuCl(TPPMS)_2] \qquad (17)$$

$$[HRuCl(TPPMS)_2] + TPPMS \xrightleftharpoons{K^*} [HRuCl(TPPMS)_3] \qquad (18)$$

This rate law is identical with that found for the hydrogenation of maleic acid in DMF solutions catalyzed by $[RuCl_2(PPh_3)_3]$ [12]. Similar studies with an $[HRu(OAc)(TPPMS)_3]$ catalyst showed the same kinetic characteristics and again, this was analogous to the hydrogenation of 1-alkenes in benzene with $[HRu(OAc)(PPh_3)_3]$ as catalyst [12]. For both TPPMS complexes, a simple mechanism accounted for all the kinetic observations (Scheme 1).

In aqueous/organic biphasic medium the reaction rate for the hydrogenation of linear and cyclic alkenes with several Ru(II) complexes including $[HRuCl(TPPMS)_2]_2$, $[HRuCl(TPPMS)_2(L)_2]$ and $[HRuCl(TPPTS)_2(L)_2]$ (L = aniline or tetrahydroquinoline) followed the order: linear C_2–$C_6 \geq$ linear C_7–$C_{10} >$ cyclic alkenes $\ggg$ branched alkenes [54]. This reactivity pattern is similar to the case of alkene hydrogenations with $[HRuCl(PPh_3)_3]$, i.e., the least-substituted double bonds are hydrogenated the fastest.

Taking all these observations together, it could be concluded, therefore, that neither the sulfonation of the phosphine ligand nor the replacement of an organic solvent by water had any effect on the reaction mechanism of alkene hydrogenation by Ru(II)–phosphine catalysts.



Scheme 1

Hydrogenation of maleic, fumaric, and crotonic acids in water, catalyzed by [RhCl(TPPMS)$_3$], led to somewhat different conclusions [35]. The reaction was studied in the 30–60 °C temperature range and the pH was set by the substrates (approximately 2.5). With respect to the concentration of the catalyst and substrate and to the partial pressure of H_2, the reaction showed the same behavior as [RhCl(PPh$_3$)$_3$] in hydrogenation of 1-alkenes [42]. Surprisingly, however, an excess of the phosphine ligand did not affect the rate of hydrogenation of maleic and fumaric acids and the corresponding rate law was that in Eq. (19):

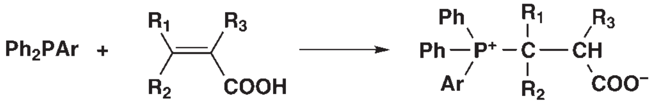
$$-\frac{dn[H_2]}{dt} = \frac{k^*K^*[Rh]_0[MA]_0[H_2]}{1 + K^*[MA]_0} \tag{19}$$

where K^* is defined as the equilibrium constant for reaction (20) and MA is maleic acid.

$$[RhCl(TPPMS)_3] + MA \overset{K^*}{\rightleftharpoons} [(MA)RhCl(TPPMS)_2] + TPPMS \tag{20}$$

In contrast to the case of maleic and fumaric acids, hydrogenation of crotonic acid was sharply inhibited by an excess of TPPMS – again, behavior analogous to that of [RhCl(PPh$_3$)$_3$] in hydrogenation of alkenes.

Taking the facile reaction of [RhCl(TPPMS)$_3$] with H_2 (Eq. 8), the kinetic data suggest a mechanism analogous to the familiar one of alkene hydrogenation with [RhCl(PPh$_3$)$_3$] [42]. Whether the reductions of maleic, fumaric and crotonic acids proceed via the “unsaturate route” or the “hydride route” was not established, but this would not effect the overall kinetics.



(21)

Ar = C_6H_4-*m*-SO_3Na

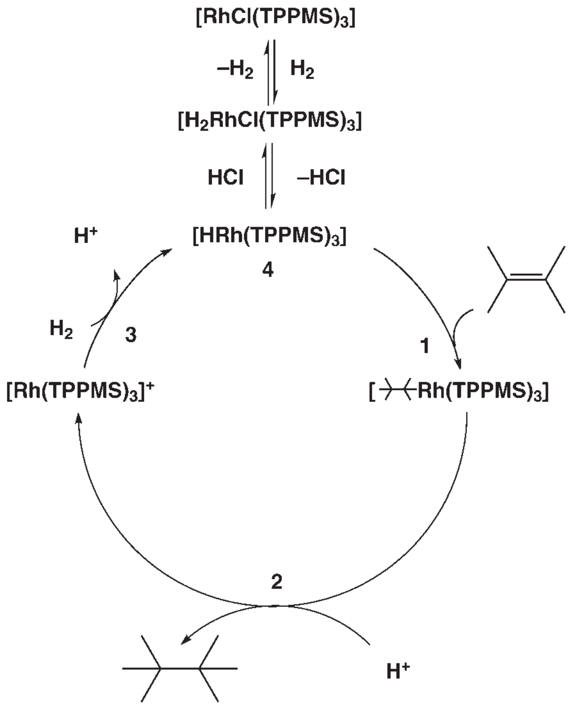
According to the mechanism, excess of the phosphine ligand should inhibit the reaction, and this was indeed observed in crotonic acid hydrogenation. However, as was discovered well after the cited kinetic studies, more-activated alkenes, such as maleic and fumaric acids, react instantaneously with TPPMS in acidic aqueous solutions to yield alkylphosphonium salts (Eq. 21) [43]. When used as a substrate, maleic or fumaric acid is present in high excess relative to the catalyst, and therefore fast phosphonium salt formation will remove any free phosphine ligand with no appreciable change in the [substrate]/[catalyst] ratio; consequently, no inhibition by TPPMS of the hydrogenation of activated alkenes is observed. In the hydrogenation of maleic acid this side reaction even helps the rhodium complex to enter the catalytic cycle: under hydrogen 18% of the TPPMS was ripped off the metal center as the corresponding phosphonium salt [43]; this results in an average composition of $[RhCl(TPPMS)_{2.5}]$. On the other hand, phosphonium salt formation by TPPMS or TPPTS and crotonic acid is sluggish [44] and will not interfere with the kinetics of hydrogenation.

Another aspect of catalysis by Rh(I)–phosphine complexes is shown by proton production in the reaction of $[RhClP_3]$ complexes (P = TPPMS, or PTA, **4**) with H_2 [29]. This can be accounted for by dehydrochlorination (Eq. 22) or by deprotonation (Eq. 23) of the primary product, $[H_2RhClP_3]$, especially in the presence of excess phosphine. Although proton production could be unambiguously measured, neither [42], $[HRhP_4]$ (P = PTA) was only recently detected by NMR spectroscopy [169]. In a closely related biphasic system, formation of $[HRh(PPh_3)_4]$ was assisted by stirring a benzene solution of $[RhCl(PPh_3)_3]$ + PPh_3 with an aqueous solution of Et_3N; up to 85% of Cl^- was found in the aqueous phase [45].

$$[H_2RhClP_3] + P \rightleftharpoons [HRhP_4] + H^+ + Cl^- \qquad (22)$$

$$[H_2RhClP_3] \rightleftharpoons [HRhClP_3]^- + H^+ \qquad (23)$$

A catalytic cycle for alkene hydrogenation, involving a monohydridorhodium(I) catalyst, $[HRhL_n]$, is shown in Scheme 2. For the protonation step, H^+ originates in the solvent, and when D_2O is used in place of H_2O deuterated products do, indeed, arise [29]. Moreover, since step is hindered, while step is facilitated by decreasing $[H^+]$, a nonlinear effect of pH may arise. In fact, with the $[RhCl(PTA)_3]$ catalyst, a sharp maximum in the hydrogenation rate of crotonic acid, as well as of allyl alcohol, was observed as a function of pH [46], furnishing kinetic evidence for



Scheme 2

the intermediacy of monohydrides in [$RhClP_3$]-catalyzed hydrogenations in aqueous solutions.

The aqueous hydrogenations catalyzed by [$RuCl_2(TPPMS)_2$] and [RhCl-(TPPMS)$_3$] show that, while a general similarity between the hydrogenations catalyzed by analogous hydro-soluble and organo-soluble complexes may be expected, one has to be aware of the decisive influence that an aqueous environment may exert on the reaction mechanisms.

Among the Rh complexes with ammonium-substituted alkylphosphines, [$Rh(nbd)(AMPHOS)_2]^{3+}$ (nbd, norbornadiene; AMPHOS, **3**) proved to be an active catalyst for hydrogenation of various alkenes in water, in methanol, or in aqueous/organic two-phase systems [47]. The kinetics of maleic acid hydrogenation was studied in detail and was found to be very similar to that of alkene hydrogenations catalyzed by [$Rh(nbd)(PPh_3)_3]^+$, although the rate were rather low due to the low solubility of H_2 in water. With 1-hexene as substrate, isomerization to internal hexenes was also observed. Similar observations were made with phosphonium phosphines, [$Ph_2P(CH)_nPMe_3]^+$, as ligands [48]. In the hydrogenation of 1-hexene the rate varied with the ligand chain length in the order of n $6 > 10 \geq 3 > 2$. Interestingly, the Rh(III) dihydride prepared with AMPHOS underwent a fast reductive elimination of H_2 in water, even under an H_2 atmosphere (Eq. 24), and no hydride species could be detected in the aqueous solutions by NMR spectroscopy.

$$[RhH_2(AMPHOS)_2(solvent)_2]^{3+} \rightarrow [Rh(AMPHOS)_2(solvent)_2]^{3+} + H_2 \qquad (24)$$

There are only a few examples of hydrogenations catalyzed by complexes with hydroxyalkylphosphines in purely aqueous solutions [48], a nice example being the selective hydrogenation of 2,4-hexadienoic (sorbic) acid to *trans*-3-hexenoic acid in a water-heptane biphasic system with a $[Ru(CO)(Cp^*)\{P(CH_2CH_2CH_2OH)_3\}][CF_3SO_3]$ ($Cp = \eta^5\text{-}C_5Me_5$) catalyst [49]. A large family of chelating hydroxyalkylphosphines, such as **6**, was prepared and [Rh(**6**)$_2$]Cl was shown to hydrogenate 1-hexene in a biphasic system with rather low TONs ($5\ h^{-1}$) [50]. In contrast, water-soluble rhodium(I) complexes of tertiary phosphine ligands with polyether chains such as **5** showed moderate to high activity in hydrogenation of allyl alcohol [51]. Carboxyalkyl- and carboxyarylphosphines served as ligands in Rh(I)-catalyzed hydrogenation of alkenes in aqueous/organic biphasic systems [52] (see also Section 6.2.3.1).

Macromolecular water-soluble phosphine ligands offer the potential to catalyst recovery via membrane ultrafiltration or solubility manipulations by adjustment of the pH or the temperature [154, 155]. Types of such ligands include phosphines with long-chain polyether substituents [53], phosphinated polyethylenemine (PEI–PNH, **12**) [55, 56], poly(acrylic acid) (PAA–PNH, **13**) [55–57] derivatives and phosphinated maleic anhydride/methyl vinyl ether (MA–MVE, **14**–**16**) copolymers [58]. The catalytic performance of rhodium(I) complexes prepared with these macromolecular ligands was characterized in hydrogenation of water-miscible, as well as of water-insoluble, substrates (allyl alcohol, 1-buten-4-ol, acrylic acid, 4-propenoic acid and 1-hexene, respectively) under mild conditions. PEI–PNH derivatives are soluble in acidic solutions whereas PAA–PNH derivatives dissolve in basic solutions. In case of the MA–MVE-based Rh(I) complex, a rather small drop of pH from 7.5 to 5.0 was sufficient for complete precipitation of the catalyst, which could be re-used with only a small loss of activity [58]. The solubility of the rhodium(I) complex with the polyether–phosphine ligand **17** in water shows an unusually steep inverse dependence on temperature; catalytic amounts can be easily dissolved and used for hydrogenation of allyl alcohol at 0 °C, whereas at 40–50 °C the hydration shell of the ligand is lost and the catalyst is precipitated [53].

Space constraints do not allow description of all the imaginative efforts to prepare, characterize, immobilize, and recover water-soluble transitional metal–phosphine complexes as hydrogenation catalysts. Further examples can be found in [11] and in [7]. For the mechanism of asymmetric hydrogenation of alkenes and that of the hydrogenation of aldeyhydes, see Section 6.2.3.

6.2.2.3
Complexes of Ligands with Donor Atoms Other Than Phosphorus(III)

$RuCl_3$.aq and $RhCl_3$.aq were among the first catalysts of hydrogenation in aqueous solution [59, 60]. Spectrophotometric experiments revealed the formation of an Ru(II)–alkene complex prior to the heterolytic activation of H_2 ("unsaturated route" of hydrogenation).

Several complexes of copper, silver, ruthenium, rhodium, and cobalt, randomly exemplified by cupric acetate, silver acetate, $[RuCl_4(bipy)]^{2-}$, $[HRh(NH_3)_5]^{2+}$, and cobaloximes (bisdimethylglyoximatocobalt compounds), have been found to catalyze hydrogenations in aqueous solutions, and were studied in considerable detail [12]. Although important for the early research into homogeneous catalysis in general, and the activation of H_2 in particular, these catalysts did not gain synthetic significance. A recent study has demonstrated that ruthenium(II) carbonyl carboxylate complexes of the type $[Ru_2(CO)_4(OAc)(\overset{\frown}{N\,N})_2]^+$ and $[Ru(CO)_2(OAc)_2(\overset{\frown}{N\,N})]$ ($\overset{\frown}{N\,N}$ = bidentate nitrogen donor, such as for example 2,2′-bipyridine or 1,10-phenanthroline) catalyze the hydrogenation of alkenes, alkynes, and ketones in partially or fully aqueous solutions [61]. Hydrogenations were run with TOFs in the 20–200 h^{-1} range.

The hydridopentacyanocobaltate anion is readily formed under mild conditions from $Co(CN)_2$ and KCN under H_2 (Eqs. 25 and 26). The resulting complex is an active catalyst for hydrogenation of a variety of unsaturated substrates but the catalysis suffers from several drawbacks [12, 62] (rapid "aging" of the catalyst, and the necessity of using highly basic aqueous solution (see Section 6.2.3).

$$Co(CN)_2 + 3\,KCN \rightleftharpoons K_3[Co(CN)_5] \tag{25}$$

$$2\,K_3[Co(CN)_5] + H_2 = 2\,K_3[HCo(CN)_5] \tag{26}$$

The mechanism of alkene hydrogenation by $[HCo(CN)_5]^{3-}$ was worked out in very fine details [62, 63]. *Activated* alkenes add across the Co–H bond with formation of an intermediate Co–alkyl species or with generation of a radical pair. Both pathways require further reaction with an additional $[HCo(CN)_5]^{3-}$to yield the product alkane. Reaction of $[Co(CN)_5]^{3-}$ with H_2 completes the catalytic cycle.

Carbonyl complexes of transition metals or anionic carbonylmetallates, such as $[Fe(CO)_5]$, $[Co(CO)_4]^-$, or $[Rh(CO)_4]^-$, are usually not very efficient at activating molecular hydrogen in aqueous systems; however, they do even catalyze reductions with $CO + H_2O$ mixtures [11]. In most cases an aqueous base is needed as solvent, although there are a few examples of such reactions in acidic solutions, too. The explanation lies according to Eq. (27) in the reaction of metal carbonyl with OH^-, e.g. reaction (26). The resulting hydrides can react with alkenes similarly to the case of $[HCo(CN)_5]^{3-}$. Indeed, $[HCo(CO)_4]^-$ is a thoroughly studied hydrogenation catalyst capable of reducing alkenes and even aromatics [12]; however, its use for *hydrogenations* in aqueous solutions did not generate much interest. It should be noted here that hydrogenations using CO + H_2O as reductant proceed through one-electron steps, and therefore match the preferred one-electron reduction steps of certain substrates, such as nitro compounds (see also Section 6.2.3.4).

$$[M_n(CO)_m] + OH^- \rightleftharpoons [HM_n(CO)_{m-1}]^- + CO_2 \tag{27}$$

Arene hydrido clusters of Rh and Ru are moderately active catalysts of hydrogenation of simple alkenes [64, 65]. Upon hydrogenation in aqueous solution $[(\eta^6\text{-}C_6H_6)_2Ru_2Cl_4]$ gives the hexahydrido cluster, $[Ru_2(\eta^6\text{-}C_6H_6)H_6]^{2-}$, which catalyzed fumaric acid hydrogenation. No kinetic studies are known concerning the activation of H_2, in contrast to the case of $[Ru(\eta^6\text{-}C_6H_6)(CH_3CN)_3]^{2-}$, where it was established [66] that hydrogen activation takes place both on a monohydridic and a dihydridic pathway, depending – *inter alia* – on the proton solvation power of the solvent.

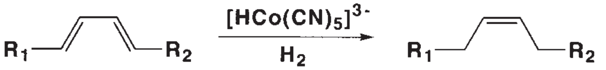
Pd(II), Pt(II) and Rh(III) complexes of certain ligands with extended conjugated π-electron systems act as very efficient catalysts for hydrogenation of alkenes and nitro compounds and hydrogenolysis of organic halides. 1-Phenylazo-2-naphthol [67] and indigosulfonic acid [68], but particularly 1,2-dioxy-9,10-anthraquinone-3-sulfonic acid (Alizarin Red, QS) [69], were used in studies on such reactions. By EPR and NMR spectroscopy as well as by kinetic measurements it was established that these complexes delocalize the extra electron originating from reaction with H_2 on the ligand, from which it is eventually transferred to the substrate (peripheral mechanism of electron transfer) [70]. $[Pd(QS)_2]$ found extensive use in biomembrane hydrogenations [71] (see Sections 6.2.3 and 6.15).

6.2.3
Typical Reactions

6.2.3.1
Hydrogenation of Compounds with C=C and C≡C Bonds

Hydrogenation of simple alkenes often serves as a test reaction to characterize the catalytic performance of new hydrogenation catalysts, and only in relatively few cases was it employed for straightforward synthetic purposes. In aqueous solutions the most widely employed substrates for catalyst characterization are unsaturated carboxylic acids (such as maleic, fumaric, crotonic, and itaconic acids), alcohols (i.e., allyl alcohol) and sodium 4-styrenesulfonate, while in two-phase hydrogenations α-alkenes (1-hexene, 1-octene), cyclohexene, and styrene are the conventional targets of catalytic reduction. These reactions will not be discussed here in detail.

Hydridopentacyanocobaltate(II), $[HCo(CN)_5]^{3-}$, is a catalyst of choice for selective hydrogenation of conjugated dienes and polyenes to monoenes; unactivated alkenes are totally unreactive [12, 62, 63]. In general, hydrogenation proceeds with 1,4-addition of H_2 (Eq. 28). Because of the insolubility of dienes in water, such reactions are carried out in aqueous/organic biphasic systems. The possibilities for modification of the catalyst by ligand alteration are very restricted but various additives, such as KCN, KOH, lanthanide salts, cyclodextrins, phase-transfer, and micellar agents, are known to influence the selectivity of $[HCo(CN)_5]^{3-}$-catalyzed reactions.



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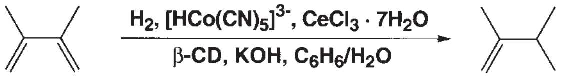


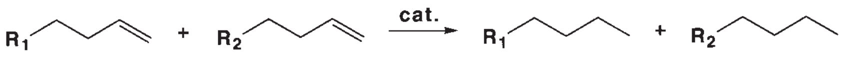
(29)

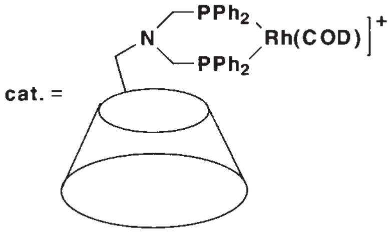
In benzene/water biphasic systems a variety of dienes were hydrogenated in the presence of β-cyclodextrin (β-CD) and La, Ce, and Yb salts [72]. 2,3-Dimethyl-1,3-butadiene gave 2,3-dimethyl-1-butene with 100% yield and 97% selectivity, representing a reduction with *1,2-addition* of hydrogen (Eq. 29). In this β-cyclodextrin acted as a *reverse*-phase transfer agent, assisting the diene to enter the aqueous phase; equally selective reactions could be achieved by using poly(ethylene glycol)s, such as PEG-400.

Reaction of $[HCo(CN)_5]^{3-}$ with activated alkenes, such as α,β-unsaturated acids, produces free-radical intermediates (see also Section 6.2.2.3), and therefore hydrogenation of these substrates is often characterized by low yields and numerous side-products. In the presence of β-CD the yield of acrylic acid hydrogenation increased to 81% [73]. Both neutral (Brij 35) and ionic (SDS, CTAB) micellar agents were shown to increase the rate of hydrogenation of cinnamic acid as a result of an increased local concentration of the substrate within the micelles [74] (cf. Section 4.5).

Rhodium(I) complexes, prepared from $[Rh(cod)_2][BF_4]$ and from amphiphilic, β-CD modified diphosphines, were used as catalysts for the competing hydrogenation of 4-phenyl- and 4-cyclohexyl-1-butene in two-phase water/substrate mixtures (Eq. 30) [75].

In all cases the catalyst favored the phenyl derivative; chemoselectivity was in the 80–90% range. The β-CD unit selectively incorporates the phenyl ring and this assists the transport of the substrate from the organic into the aqueous phase. Formation of such a host/guest molecular complex keeps the alkene double bond at a suitable distance to interact with the Rh–phosphine catalyst. Both effects increase the rate of hydrogenation of 4-phenyl1-butene.



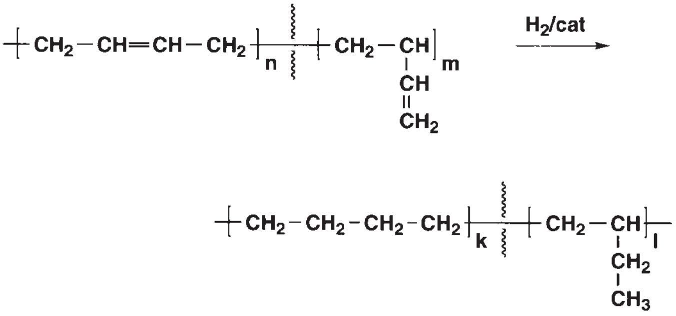


(30)

Hydrogenation of polymers results in better thermal and oxidative stability, and several attempts were made to employ homogeneous catalysis for this purpose. An ABS copolymer was reduced in the form of an aqueous emulsion with neutral and cationic Rh(I) complexes. The slightly water-soluble cationic complex was more efficiently built into the micelles of the anionic detergents used for polymer solubilization and this resulted in better conversions, e.g., 70% in contrast to 20% with [$RhCl(PPh_3)_3$] [76].

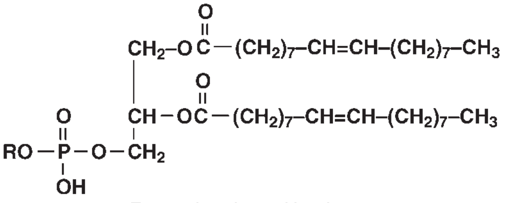
A detailed study of hydrogenation of several alkenes and polybutadiene was undertaken using the catalysts [$RhCl(HEXNa)_2]_2$ and [$RhCl(OCTNa)_2]_2$ (HEXNa and OCTNa, Structures **8** and **9**) [52] with or without an added solvent (toluene). With both catalysts the terminal alkenes were hydrogenated much faster than the internal ones, and this was also reflected in the preferential hydrogenation of the pendant vinyl units (products of 1,2-addition) in polybutadiene versus the internal double bonds (from 1,4-polymerization) (Eq. 31). Internal double bonds in 2-pentene- and 3-pentenenitriles were hydrogenated unusually fast compared with simple alkenes such as 1-octene, with no concomitant reduction of the nitrile group.

A very special application of homogeneous hydrogenation of alkenes in aqueous solution is the catalytic modification of lipid membranes, either in model systems (liposomes) or in living cells (cf. Section 6.15) [77–80].



$$\left[\mathrm{CH_2{-}CH{=}CH{-}CH_2}\right]_n\left[\mathrm{CH_2{-}\underset{\underset{\underset{CH_2}{\|}}{CH}}{\underset{|}{CH}}}\right]_m \xrightarrow{H_2/cat} \left[\mathrm{CH_2{-}CH_2{-}CH_2{-}CH_2}\right]_k\left[\mathrm{CH_2{-}\underset{\underset{\underset{CH_3}{|}}{CH_2}}{\underset{|}{CH}}}\right] \qquad (31)$$

Polar lipids, such as the one depicted as Structure **20**, form aggregates (liposomes) in aqueous solutions with single or multibilayer structures. Biomembranes are bilayer arrangements of various lipids incorporating a large number of other components, such as proteins, carbohydrates, etc. Therefore the target of hydrogenation is a very complex, microheterogeneous structure, with uneven molecular and spatial distribution of the unsaturated substrate (lipids) mixed with potentially reducible or potentially inhibitory "additives" (e.g., quinones and proteins, respectively).



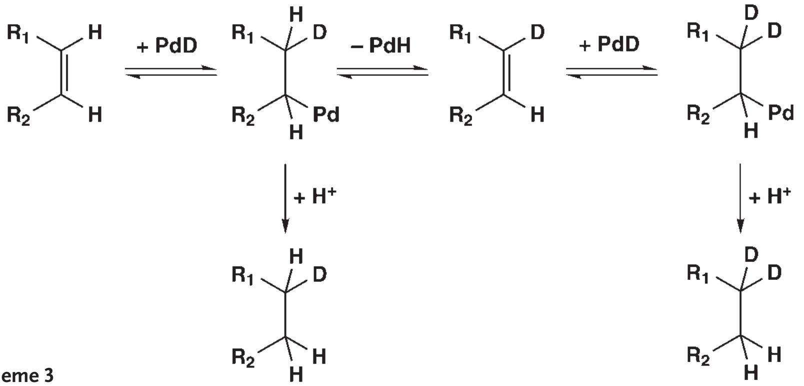
R= $-CH_2CH_2N(CH_3)_3$; $-CH_2CH_2NH_2$

20

All kinds of selectivity of hydrogenation are important here, notably chemoselectivity (polyunsaturated versus monounsaturated lipids, unsaturated fatty acids versus quinones), regioselectivity (terminal versus internal alkeneic units), and stereochemical selectivity (*cis*- versus *trans*-fatty acid units). An ideal catalyst is able to reach particular membranes in various compartments of the cell ("targeting"), does not effect transformations other than hydrogenation, efficiently reduces the unsaturated fatty acid units at low temperatures (0–40 °C) in an aqueous environment, can be totally removed from the cell after the reaction is completed, and has no "self-effect," such as toxicity.

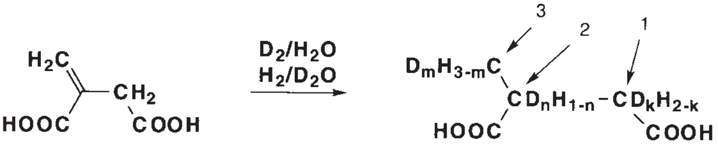
Although $[RhCl(TPPMS)_3]$ and $[RuCl_2(TPPMS)_2]_2$ could be used in some of the studies, the most investigated homogeneous catalyst for biomembrane hydrogenation is $[Pd(QS)_2]$ [80]. Following appropriate pretreatment [71], this catalyst will hydrogenate 10–100 mL of cell suspensions with 10^5–10^6 cells mL^{-1}, at room temperature and 1 bar H_2 in a few minutes, bringing about 10–30% saturation of all C=C bonds. The small amounts of unsaturated lipids in such samples (usually in the micromolar range) and the similarly low catalyst loadings ensure that only a few catalyst turnovers are required to attain reasonable conversion of the substrate.

Deuteration of membrane lipids is a useful method for studying thermotropic gel-to-liquid crystalline phase transitions of the bilayer membrane structures [81]. In the reduction of dioleoylphosphatidylcholine liposomes with D_2 in H_2O as solvent and $[Pd(QS)_2]$ as catalyst, it was observed that a considerable proportion of products with nonsymmetric deuteration, i.e., having $-CD_2-CH_2-$ units instead of the expected $-CHD-CHD-$ units, was formed [82]. A very probable explanation of this finding is in the *reversible* formation/β-hydrogen elimination of a Pd–alkyl intermediate, as shown in Scheme 3.



Scheme 3

In hydrogenations with H_2 in D_2O the product showed only –CHD– stretches in the infrared. This observation excludes a fast H/D exchange on Pd, and implies a monohydridic mechanism of hydrogenation. With the same catalyst in an aqueous (D_2O) solution, itaconic acid is reduced under H_2 to yield multiply deuterated methylsuccinic acid having 1.97 deuterons at C3, 0.66 at C2 and none at C1 (Eq. 32) [83]. On the other hand, in an H_2O/ethyl acetate biphasic solvent mixture, the catalyst prepared *in situ* from $[Rh(cod)Cl]_2$ and TPPTS catalyzed the reduction (with D_2) of dimethyl itaconate with deuterium incorporation at C3 (2.06), C2 (0.78) *and* at C1 (0.18) [84]. Similar results were obtained in toluene/methanol (1 : 1) with the Rh(I)–BPPM cationic catalyst [85]. Again, these findings could be explained by a fast *β*-elimination from the intermediate Rh(I)–alkyl.



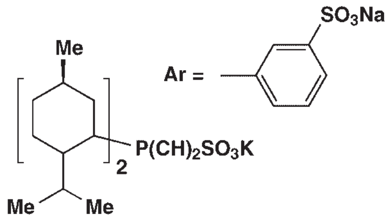
(32)

Whereas in case of liposomes the nonsymmetric deuteration of the alkeneic bond in the unsaturated fatty acids could be assisted by the liquid “cage” around the catalyst, in the homogeneous solution of itaconic acid or its esters multideuteration is facilitated by the coordination of the carboxylic group or the ester carbonyl [84].

No specific study on the homogeneous hydrogenation of acetylenes in aqueous systems has appeared [86, 87]. Lignin phenols were hydrogenated to the corresponding cyclohexanols with Ru-sulfonated triphenylphosphine catalysts resulting in inhibition of the ligand-induced yellowing of lignin and lignin-rich wood pulps [156].

Although there are several important industrial syntheses based on enantioselective homogeneous hydrogenation of prochiral alkenes and catalyzed by platinum metal complexes [1], at present none of them is practiced in aqueous or biphasic systems. In addition to the solubility problems, the main reason is that reaction rates and enantioselectivities in water are often much inferior than those of analogous systems using purely organic solutions. Nevertheless, due to the intensive research that has been done, the possibilities of large-scale applications are slowly emerging.

Several representatives of the widely studied tertiary phosphine ligands for enantioselective hydrogenation in aqueous solutions are shown as Structures **21**–**39**. It is seen that the most successful ligands in this field do have their water-soluble, mostly sulfonated, derivatives [7, 11]. In case of acid-sensitive compounds, solubility in water could be achieved by attaching dimethylamino substituents to the parent arylphosphines and by their further protonation or quaternization. Monophosphines, such as **21** [88], played a minor role in comparison with the chelating diphosphines. Water-soluble phosphine–phosphinite ligands (L) were obtained from trehalose and used as components of with [Rh(cod)(L)[BF_4]] catalysts for the enantioselective hydrogenation of enamides [157].



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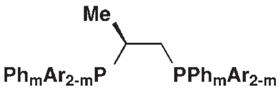
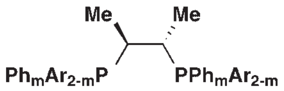
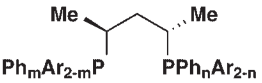


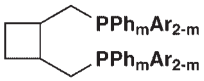
m = 0, **22**



m = 0, **23**

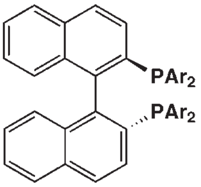


m = 2	n = 2	BDPP,	**24**
m = 2	n = 1	$BDPP_{MS}$,	**25**
m = 1	n = 1	$BDPP_{DS}$,	**26**
m = 0	n = 1	$BDPP_{TRS}$,	**27**
m = 0	n = 0	$BDPP_{TS}$,	**28**

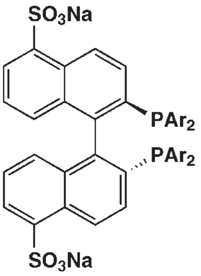


m = 0, **29**

Similarly to the purely organic solutions, the most widely studied alkeneic substrates are (*Z*)-α-acetamidocinnamic and (*Z*)-α-acetamidoacrylic acids and their salts. The corresponding methyl and ethyl esters are often studied in aqueous/organic biphasic systems, one of the organic solvents most often employed being ethyl acetate.



30 BINAP$_{TS}$



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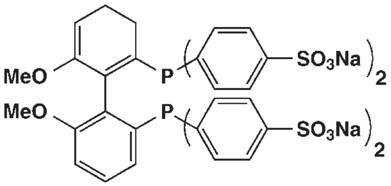
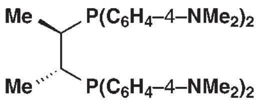


32 MeO-BIPHEP-S



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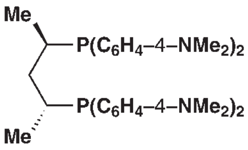

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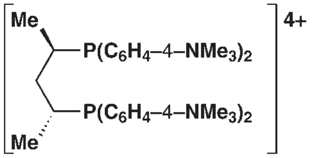

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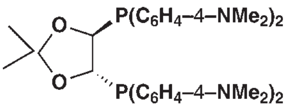

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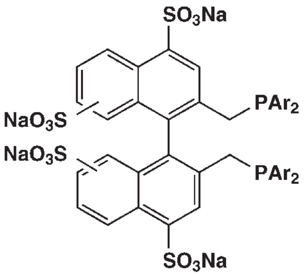
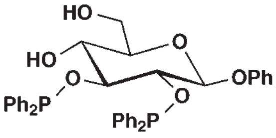


38 BINAS



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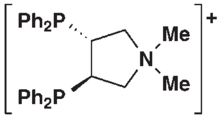

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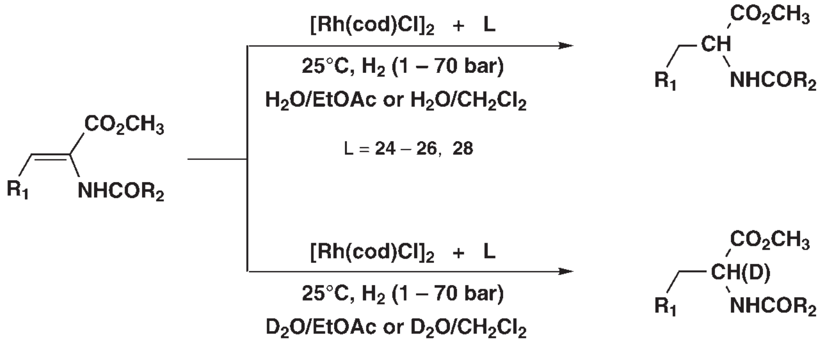


Scheme 4 $R_1 = H, Ph; R_2 = CH_3, C_2H_5$

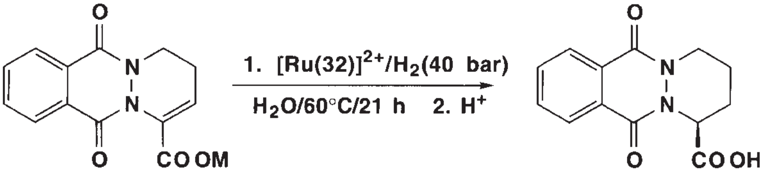
Prochiral enamides and dehydropeptides were biphasically hydrogenated with enantiomeric excess (*ee*) up to 88% with Rh(I) complexes of the chiral, sulfonated derivatives of PROPHOS, CHIRAPHOS, cyclobutane-DIOP, and BDPP, **22**–**29** (Scheme 4) [27, 89]. Using D_2O instead of H_2O, hydrogenation of methyl (*Z*)-α-acetamidocinnamate, (*Z*)-α-benzamidocinnamate, and (*Z*)-α-acetamidoacrylate with a $[Rh(cod)Cl]_2$ + phosphine catalyst (phosphine: **23**–**26**, **28**) resulted in the regiospecific deuteration at the carbon atom that is α to the amide and the ester groups (maximum incorporation of D was 76%). The results were interpreted in terms of a fast $[Rh]{-}H \rightleftharpoons [Rh]{-}D$ exchange on the σ-rhodium monohydride intermediate, although protonation (with H^+ or D^+) of the same intermediate could not be ruled out [90].

Quaternization of the ligand (3*R*,4*R*)-3,4-bis(diphenylphosphino)-1-methylpyrrolidone, bound in the complex $[Rh(cod)L]^+$, (L = **39**) yielded a highly active and selective catalyst for hydrogenation (*Z*)-α-acetamidocinnamic acid; (*S*)-*N*-acetylphenylalanine was obtained in 88–96% enantiomeric excess [91]. The 4-dimethylamino derivatives of CHIRAPHOS (**33**), BDPP (**34**, **35**) and DIOP (**36**) showed similarly high activities and enantioselectivities (up to 97% *ee*) for the reduction of (*Z*)-α-acetamidoacrylic acid either in aqueous slurries or in biphasic systems [92].

Stepwise substitution in the phenyl rings of phosphines such as BDPP creates new diastereomeric pairs due to chirality on phosphorus. In a detailed investigation into the hydrogenation of (*Z*)-α-acetamidocinnamic acid, its methyl ester and dimethyl itaconate, the catalyst was prepared from $[Rh(cod)Cl]_2$ plus 2 equiv. of (2*S*,4*S*)-BDPP or its mono-, di-, tri-, or tetrasulfonated derivative (**25**–**28**) [93].

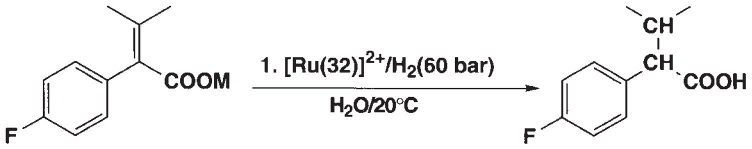
As a result, in the case of the enamides the enantioselectivity gradually decreases with the degree of sulfonation. Conversely, only in case of the monosulfonated phosphine, as ligand, was a moderate enantiomeric excess of (*R*)-methylsuccinic acid diemethyl ester obtained. (The effect is more pronounced in hydrogenation of imines; see Section 6.2.3.2.) It should be noted that the catalyst with $BDPP_{MS}$ is *not* soluble in water and moves to the organic phase during the reaction. Interestingly, the degree of quaternization of the tetrakis(4-dimethylamino) derivatives of BDPP and CHIRAPHOS did not influence the enantioselection in hydrogenation of enamides [92, 94]. Ru(II)–diphosphine catalysts are usually more robust than the related Rh(I)–diphosphine complexes, and more and wider applications of ruthenium complexes can be expected. E.g., the water-soluble variant of the highly successful Ru(II)–BINAP catalysts has been prepared using 5,5′-disulfonato-BINAP, **31** [95], and tetrasulfonated (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP$_{TS}$, **30**) [96, 97]. In water, [*R*u(R-BINAP$_{TS}$)Cl$_2$] catalyzed the hydrogenation of (*Z*)-α-acetamidocinnamic and (*Z*)-α-acetamidoacrylic acid with 87.7% (*R*) and 68.5% (*R*) *ee*, respectively. With respect to the hydrogen pressure the water-soluble catalyst showed the same behavior as the parent [Ru(BINAP)Cl$_2$] (a sharp decline of *ee* with increasing p_{H_2} [97]).

Several new, water-soluble atropisomeric diphosphines in the biphenyl series, such as (*S*)-(+)- and (*R*)-(−)-MeO-BIPHEP tetrasulfonate (**32**), were prepared and used as components of Ru(II)- and Rh(I)-based hydrogenation catalysts [98]. Several C=C unsaturated substrates (enamides, unsaturated acids) could be hydrogenated biphasically with high rates and enantioselectivities (Eqs. 33 and 34). In some cases high substrate/catalyst ratios could be used (up to 10 000 : 1), a strong requirement for practical applications [99].



(33)

M = Et_3NH	substr/cat	10 000	98% yield, > 99% ee
M = Na	substr/cat	2000	99% yield, > 99% ee



(34)

M = Et_3NH	substr/cat	1000	84% ee
M = Na	substr/cat	1000	80% ee

One of the attractive features of the Ru(II)-based catalysts described above is that the enantioselectivities obtained in aqueous solution are usually close to those which can be observed using organic solvents; in some cases even an increase in the *ee* was observed when methanol or ethanol was replaced by water [97]. However, this is not the general case with the various Rh(I)–chiral diphosphine catalysts, where more often than not a significant drop of *ee* is seen when running the reactions in water instead of an organic solvent [105].

So far no complete equilibrium and kinetic investigation has been published which could allow the analysis of the reaction mechanism of an aqueous enantioselective hydrogenation with the precision reached by Halpern et al. in their seminal studies [100, 101]. Nevertheless, some general facts and observations are worth discussing.

The enantioselection in certain catalytic hydrogenations is very dependent on the pressure of H_2 which, in turn, determines the equilibrium concentration, $[H_2]_{sat}$, of H_2 in the solution. A thorough recent analysis [2] of solubility and mass-transfer processes has shown, that it is the availability of dissolved H_2 in the solution, rather than $[H_2]_{sat}$, which influences the enantioselectivity, and the former is determined by the relation between the chemical and the mass-transfer rates. The solubility of hydrogen in water is 8×10^{-4} M, which is about 20% of the solubility in MeOH, 3.8×10^{-3} M (both at 20 °C, 1 bar total pressure [102]). It follows that working in an aqueous solution is equivalent to using methanolic reaction mixtures under reduced pressure of H_2, and that reactions in which the enantioselectivity is known to be pressure-sensitive (such as those described in [92] and in [97]) cannot be strictly compared at the same partial pressure of dihydrogen. The limited solubility of H_2 may influence the chemoselectivity, too (reduction vs. isomerization of alkenes) [103].

In a systematic study of solvent effects (cf. Section 4.3) on the catalytic hydrogenation of dehydro-amino acids, a good linear correlation was found between the enantioselectivity parameter, log (%S/%R), and the solvofobicity parameter, S_p [104], of the solvents; water fits this relationship well [105]. In the case of a given substrate and a given catalyst, this correlation may also reflect the solubility of H_2 in the solvents under study.

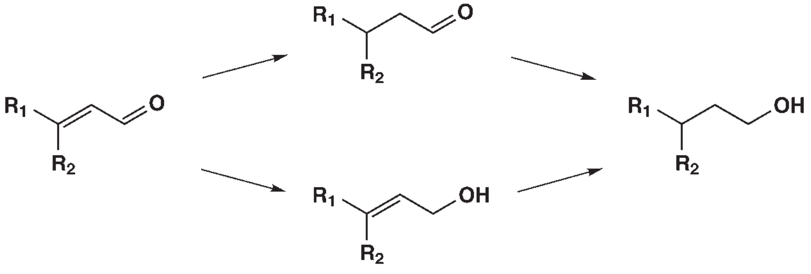
Many of the substrates are only slightly soluble or “insoluble” in water, i.e., their equilibrium concentration in saturated solutions is very low [106]. In an aqueous/organic two-phase mixture, the concentration of the substrate in the aqueous phase is lowered even further by its distribution between the phases. Addition of amphiphiles not only increases the chemical rate by the well-known solubilization phenomenon but may dramatically influence the enantioselectivity, too [158]. A striking example of such an effect was observed with the [Rh(Me-α-glup-OH)(cod)][BF_4] catalyst (**37**), containing a phosphinated methyl-α-D-glycopyranoside ligand. On addition of sodium dodecylsulfate (SDS) the half-time ($t_{1/2}$) of the hydrogenation of (Z)-methyl-α-acetamidocinnamate was shortened from 390 min to 6 min together with an increase of enantioselectivity from 83.4% to 97.1% *ee* [106]. Similar improvements in the reaction rate and enantioselectivity were found with using carbohydrate-derived amphiphiles [107], but the chirality of these latter compounds did not contribute significantly to the overall increase of the *ee* [108]. The effect of amphiphiles is also dependent on the pH of the aqueous reaction mixtures [159]. The use of surface-active, chiral, tertiary phosphine ligands, such as $P[C_6H_4(CH_2)_3C_6H_4SO_3Na]_3$ eliminated the need for an additional amphiphile. With the catalyst prepared *in situ* from this phosphine and $[Rh(cod)Cl]_2$, (*Z*)-methyl-α-acetamidocinnamate was hydrogenated in water/ethyl acetate at a higher rate and better selectivity than with the unmodified, analogous phosphine BDPP [109]. Micellar effects are discussed in detail in Section 4.5.

6.2.3.2
Hydrogenation of Compounds with C=O and C=N Bonds

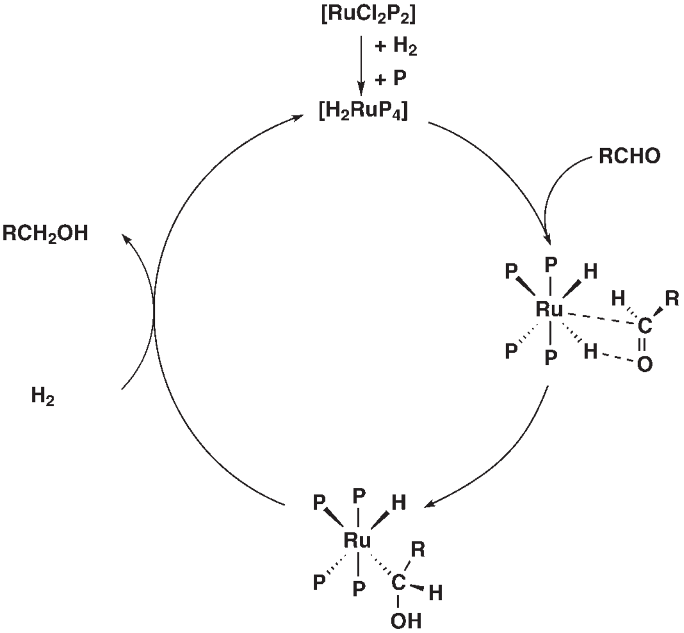
One of the most desirable chemical transformations is the aqueous selective hydrogenation of α,β-unsaturated aldehydes to the corresponding allylic alcohols (Scheme 5). There are only a few Rh, Ru, and Ir complexes capable of catalyzing this reaction [110, 111].

Several water-soluble ruthenium complexes, with P = TPPMS, TPPTS or PTA ligands, catalyze the selective reduction of crotonaldehyde, 3-methyl-2-butenal (prenal), and *trans*-cinnamaldehyde to the corresponding unsaturated alcohols (Scheme 5) under relatively mild conditions [109–118, 127]. Chemical yields are often close to quantitative in reasonable times (from minutes to a few hours) and the selectivity toward the allylic alcohol is very high ($> 95\%$), except for the carbonyl complexes $[HRuCl(CO)P_3]$ where the highest proportion of cinnamyl alcohol in the product mixture was around 30% [118]. With all three phosphine ligands TPPMS, TPPTS and PTA, the reactions are genuine two-phase processes and the catalyst-containing aqueous phase can be cleanly separated from the organic phase of the product mixture.

Both aliphatic and aromatic unsaturated aldehydes were reduced exclusively to unsaturated alcohols by hydrogen transfer from aqueous sodium formate in a two-phase system with or without an organic solvent. The reactions proceeded smoothly with either $[RuCl_2(TPPMS)_2]$ [119, 120] or $[RuCl_2(PTA)_4]$ catalyst [116, 117]. Although the procedure is particularly suited for smaller-scale laboratory preparations, the inorganic by-product ($NaHCO_3$) arising from the process makes it inacceptable on the industrial scene.



Scheme 5 e.g. $R_1 = R_2 = Me$; $R_1 = Ph$, $R_2 = H$



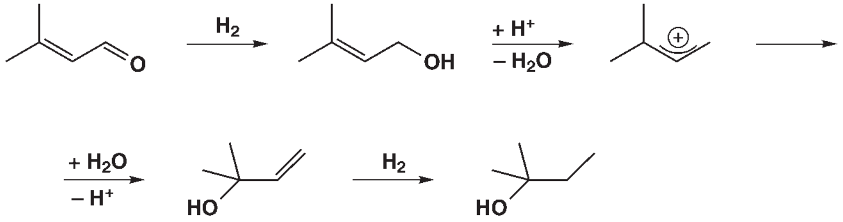
Scheme 6

P = TPPMS, TPPTS

Much effort was devoted to exploring the mechanism of this selective reduction by varying the catalyst precursor [115] and reaction parameters [113], such as catalyst concentration, hydrogen pressure, temperature, and concentration of excess phosphine and of other additives. Strikingly, no phosphine inhibition was observed, either in the hydrogenation or in the hydrogen-transfer reduction of aldehydes [113, 120], and in some cases an excess of TPPTS or TPPMS ligand even increased the rate of reduction [120]. While this latter effect may be related to the surface activity of TPPMS [118], the explanation will not hold for TPPTS, which has no surfactant properties [118].

The most likely catalytic species for RCHO reduction is [H_2RuP_4] (P = TPPTS, TPPMS, PTA), either prepared separately [22, 121] or formed *in situ* from the various precursors (precatalysts). However, it has not been determined unambiguously whether this complex loses a phosphine ligand before entering the catalytic cycle and coordinating the substrate, or reacts directly with the aldehydes by nucleophilic attack of one of the hydride ligands on the carbonyl oxygen. The lack of phosphine inhibition seems to support this latter suggestion (Scheme 6).

Unfortunately, most of the aldehyde reduction experiments were run in unbuffered solutions. Exceptions are the hydrogen-transfer reductions [117, 120], where the HCOONa/$NaHCO_3$ mixture has a fairly constant pH of 8; and the hydrogena-



Scheme 7

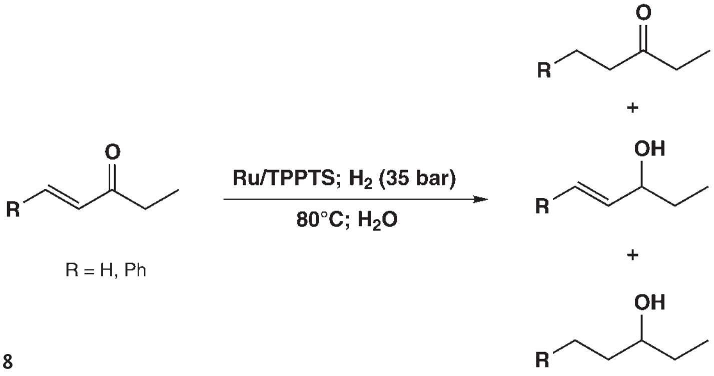
tion of prenal, where a phosphate buffer of pH 7 was used to prevent acid-catalyzed formation of *tert*-amyl alcohol (Scheme 7) [113].

As discussed in Section 6.2.2.2, the equilibrium between the various ruthenium hydride species, first of all between [$HRuClP_3$] and [H_2RuP_4], is critically influenced by the pH of the solutions, which – in the absence of a suitable buffer – are always slightly acidic, especially when the catalyst is prepared *in situ* by reducing hydrated $RuCl_3$ with an excess of the phosphine ligand. This effect may not be obvious in reduction of a saturated aldehyde, but will determine the selectivity in hydrogenation of unsaturated aldehydes. Differences in the pH of the reaction mixtures may be the cause of some apparent contradictions in the literature, such as the case of prenal hydrogenation [113, 115].

Hydrogenation of propionaldehyde, catalyzed by various ruthenium–TPPTS complexes, was dramatically influenced by the addition of certain salts [122, 123]. Whereas in the absence of salts there was no reaction at 35 °C and 50 bar H_2, in the presence of NaI TOFs of more than 2000 h^{-1} were determined. This was lowered to 300 h^{-1} when the sodium cation was selectively sequestered by a cryptant (4,7,13,16,21-pentoxa-1,10-diazabicyclo[5.8.8]tricosane). Obviously, the larger part of the "salt effect" belonged to the cation. It was concluded that electrophilic assistance by Na^+ facilitated C-coordination of the aldehyde and formation of a hydroxyalkyl intermediate.

It is noteworthy that in a homogeneous organic solution, i.e., where the catalyst and the substrate aldehyde are contained in the same phase, pronounced substrate inhibition is observed [124]. When running the reaction in a two-phase aqueous/organic mixture the solubility of aldehyde is not high enough to bring about such an inhibitory effect, and large quantities of the substrate residing in the organic phase as a reservoir can be hydrogenated. Other reactions leading to catalyst deactivation are the formation of 1-hydroxyalkylphosphonium salts [125] and of arene-ruthenium(II) complexes [121].

Water-soluble rhodium(I) complexes with TPPTS, TPPMS, and PTA ligands, such as [$RhCl(TPPTS)_3$], are capable of hydrogenating aldehydes, although their catalytic activity is inferior to the ruthenium complexes discussed above [116]. In sharp contrast to the ruthenium(II)-based catalysts, in reactions of *unsaturated* al-



Scheme 8

dehydes rhodium(I) complexes preferentially promote the reduction of C=C double bonds, although the reactions are not completely selective [31, 113, 116].

In line with the expected low reactivity of osmium(II) complexes [126], $[OsCl_2(TPPMS)_2]$, $[OsH_4(TPPMS)_3]$, and $[OsHCl(CO)(TPPMS)_2]$, hydrogenated cinnamaldehyde at lower rates (and selectivities from 60 to 90%) than the analogous ruthenium(II) catalysts [127].

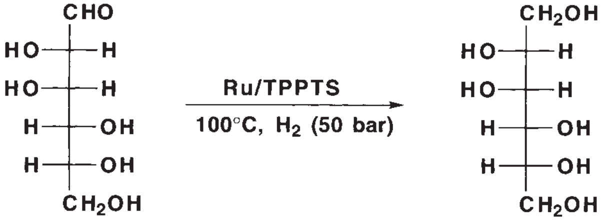
In general, hydrogenation of ketones is less facile and less selective than the reduction of aldehydes. Of the complexes $[RuCl_2(TPPTS)_2]_2$, $[HRuCl(TPPTS)_3]$, and $[H_2Ru(TPPTS)_4]$, the last one proved to be the most active catalyst in hydrogenation of 2-butanone, cyclohexanone and benzylacetone [115]. Under the same conditions, all three catalysts were rather selective towards the formation of the saturated ketone in hydrogenation of *trans*-4-hexen-3-one (Scheme 8), yielding only 2% to 7% of 3-hexanol. However, addition of strong alkali (LiOH or KOH) promoted reduction of the C=C function as well, probably by facilitating enolization, and as much as 76% of the saturated alcohol was formed.

Benzylideneacetone was hydrogenated in biphasic systems using toluene, dichloromethane or tetrahydrofuran as organic solvents, and $[RuCl_2(TPPTS)_2]_2$ and $[H_2Ru(TPPTS)_4]$ as catalysts. Very similar results were obtained with $[HRu(\eta^6\text{-}C_6H_6)(CH_3CN)][BF_4]$ as catalyst for hydrogenation of benzylideneacetone and cyclohex-1-en-2-one [66].

Ketones with functional groups facilitating enolization and/or coordination to the catalyst can be hydrogenated more smoothly. 2-Ketoacids, such as pyruvic and 2-ketoglutaric acids, were reduced by $[HRuCl(TPPMS)_3]$, $[RhCl(TPPMS)_3]$, and $[RhCl(PTA)_3]$ [26, 35, 46], while 4- or 5-ketoacids proved unreactive. More importantly, ethyl and methyl acetoacetate were hydrogenated with Ru(II)/5,5′-disulfonato-BINAP (**31**) and Ru(II)/MeO–BIPHEP–S (**32**) with 91% *ee* and 93% *ee*, respectively [95, 98].

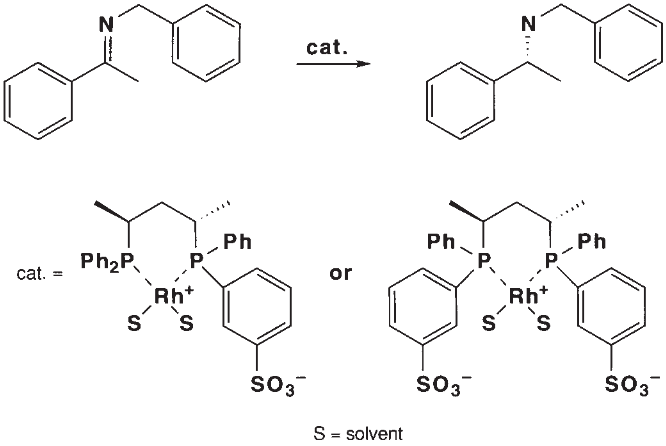
A rhodium complex prepared *in situ* from $[Rh(cod)Cl]_2$ and (1*R*,2*R*)-*N*,*N*′-dimethyldiphenylethylenediamine catalyzed the hydrogenation of methyl phenylglyoxylate with low enantioselectivity in water and in H_2O/MeOH mixtures. However, in water/methanol (30:70) solvent, in the presence of cyclodextrin, 50% *ee* was obtained, which is the same as in methanol itself [128]. The organometallic aqua complex $[Ir(Cp^*)(H_2O)_3]^{2+}$ served as a suitable catalyst precursor for the hydrogenation of water-soluble aldehydes, ketones, and alkenes [160]. The reaction showed a characteristic pH-dependence: above pH 4 the Ir(III)-complex was deprotonated to yield the catalytically inactive dinuclear compound, $[\{Ir(Cp^*)\}_2(\eta\text{-}OH)_3]^+$. $[\eta^6\text{-}C_6Me_6)Ru(bipy)(H_2O)]^{2+}$ (bipy = 2,2′-bipyridine) was found active in the hydrogenation of various ketones by hydrogen transfer from aqueous sodium formate [161]. In hydrogen transfer reductions of acetophenone derivatives in aqueous or biphasic systems 96% *ee* were obtained with $[Ru(p\text{-cymene})Cl]_2$ + (*S*)-proline amides [162, 163], 94% *ee* with $[Cp^*MCl_2]_2(M = Rh, Ir)$ + water-soluble aminosulfonamides [164], and 84% *ee* with phosphonated chiral *N,N*′-dimethyl-1,2-diphenylethane-1,2-diamine ligands [165].

Synthetic transformations of carbohydrates have enormous practical value because of their availability in large quantities from renewable sources. The first example of hydrogenation of a carbohydrate (fructose) in aqueous solution, catalyzed by $[HRuCl(TPPMS)_3]$ under mild conditions (60 °C, 1 bar total pressure) originates from 1977 [26]. Under the same conditions, the simplest ketose, 1,3-dihydroxyacetone, was rapidly reduced. Efficient hydrogenation of the epimeric aldoses D-glucose and D-mannose was achieved with $[HRuCl(TPPTS)_3]$ catalyst at 100 °C and 50 bar H_2 yielding D-sorbitol and D-mannitol (Eq. 35) – D-mannose being more reactive, as expected [129]. Addition of NaI accelerated the reduction of both aldoses by a factor of 6, most probably with the same mechanism as discussed before in connection with hydrogenation of propionaldehyde [123]. In a similar study fructose (obtained in the hydrolysis of inulin) was hydrogenated using a Ru(II)/TPPTS catalyst [166].



(35)

Enantioselective hydrogenation of imines in aqueous systems generated much research interest, partly because of the practical value of the product amines, partly due to the unusual kinetic observations. Imines, such as *N*-benzylacetophenoneimine, are relatively stable to hydrolysis, and could be reduced either in a water/ethyl acetate two-phase solvent mixture [93, 130, 131], or in a benzene–AOT–water reverse micellar solution (AOT = bis(2-ethylhexyl)sulfosuccinate). With catalysts, prepared from $[Rh(cod)Cl]_2$ and the products of the stepwise sulfonation of



(36)

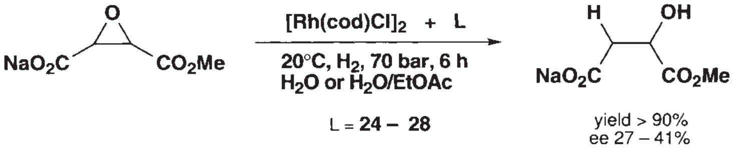
BDPP (**25**–**28**), the highest rate and enantioselectivity were obtained with the monosulfonated ligand (**25**) [93, 130, 131]; the effect is very pronounced. It should be noted that the Rh/**25** catalyst is insoluble in water and during catalysis it moves to the organic phase, where it is supposed to have the structure shown in Eq. (36).

In the same reaction, the [Rh(NBD)(BDPP)]$^+$ catalyst showed an enantioselectivity (*ee*) of 68% both in neat methanol and in benzene. Formation of reverse micelles by AOT (0.05 M) and varying amounts of water in the benzene solution increased the selectivity to 82% *ee* (at $w = [H_2O]/[AOT] = 5$); addition of further increments of H_2O resulted in a decrease of the enantiomeric excess [132]. Note that the 14% increase in the *ee* was induced by an *achiral* additive; this implies changes in the reaction mechanism rather than in the structure of the catalytically active species (about the background cf. [132]). The high enantioselectivity, achieved with the Rh(I)/monosulfonated BDPP catalyst (with no external RSO_3) in the hydrogenation of itaconic acid and imines [93, 130, 131], may be the result of a similar coordination of the sulfonate group of the phosphine itself – a warning to bear in mind the possible effects of $-SO_3$ coordination when using sulfonated ligands.

6.2.3.3
Hydrogenolysis of C–O, C–N, C–S, and C–Halogen Bonds

Various water-soluble palladium complexes are active in the hydrogenolysis of C–O and C–N bonds, involving allylic substrates either with molecular H_2 or with other hydrogen sources such as formates or amines. Hydrogenolysis of allyl acetate with $[PdCl_2L_2]$ (L = **1**, **5**, **10**) catalyst proceeded smoothly in a heptane/aqueous sodium formate two-phase mixture at 80 °C yielding propene [133]. The catalyst, formed *in situ* from $[Pd(OAc)_2]$ and TPPTS, could be used for the selective removal of allylic protecting groups. With careful choice of the amount of the catalysts and of the reaction conditions, distinction between such closely related protecting groups as dimethylallylcarbamates and allyloxycarbonates was achieved. Conversely, allyloxycarbamates could be selectively deprotected with the same catalyst system in the presence of a dimethylallyl carboxylate group [134, 135]. The use of per(2,6-di-*O*-methyl)-β-cyclodextrin strongly accelerated the deprotection of water-insoluble allylic substrates [167].

Asymmetric hydrogenolysis of sodium *cis*-epoxysuccinate leads to malic acid derivatives which are useful building blocks in natural product synthesis. This reaction was catalyzed by $[Rh(cod)Cl]_2 +$ chiral sulfonated BDPP ligands from the stepwise sulfonation of BDPP (Eq. 37) [136]. At 20 °C and 70 bar H_2 pressure the chemical yields exceeded 90% and the *ee* varied between 34% ($BDPP_{MS}$, **25**) and 26% ($BDPP_{TS}$, **28**). In contrast to the hydrogenation of prochiral imines the enantioselectivity of the hydrogenolysis of *cis*-epoxysuccinate decreased monotonically with the increasing number of sulfonate groups in the ligands. This may be the consequence of the good solubility of the ligand in the aqueous phase where the catalysis takes place. In a closely related reaction, racemic sodium *trans*-phenylglycidate was hydrogenolyzed with kinetic resolution. Using (*S*,*S*-$BDPP_{TS}$ as ligand, the hydrogenolysis of the (2*R*,3*S*)-epoxide enantiomer was preferred, yielding a product mixture rich in (2*R*)-2-hydroxy-3-phenylpropionate.



(37)

A rare example of C–O bond scission in aqueous solution is the deoxygenation of allylic alcohols catalyzed by $[HCo(CN)_5]^{3-}$ [137]. When the two-phase reaction was carried out in the presence of β-cyclodextrin it yielded *trans*-alkenes selectively whereas, with no cyclodextrin added, a mixture of *cis*- and *trans*-alkenes was formed. In a typical example, reaction of 2-hexen-1-ol yielded 91% *trans*-2-hexene and 4% 1-hexene.

The removal of sulfur from petroleum is commonly achieved by hydrogenation on heterogeneous catalysts (hydrodesulfurization, or HDS process). For biphasic processes cf. Section 6.3 [138, 139].

Hydrogenolysis of the C–halogen bond is an important reaction both from preparative and from environmental points of view. $[HCo(CN)_5]^{3-}$ was studied in detail as a catalyst for reductive dehalogenations of organic halides, which proceed according to Eqs. (38) and (39). The results of the early experiments are summarized in [12].

$$[Co(CN)_5]^{3-} + RX \rightarrow [Co(CN)_5X]^{3-} + R^{\cdot} \tag{38}$$

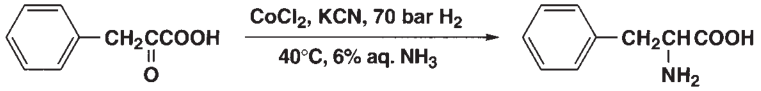
$$[HCo(CN)_5]^{3-} + R^{\cdot} \rightarrow [Co(CN)_5]^{3-} + RH \tag{39}$$

Allylic chlorides can be dehalogenated with aqueous sodium formate in a heptane/water solvent mixture with $[PdCl_2L_2]$ catalysts ($L =$ various sulfonated phosphines) [133]. $[RuCl_2(TPPMS)_2]_2$ and $[Ru(H_2O)_3(PTA)_3]^{2+}$ proved effective catalysts for hydrogenolysis of a variety of organic halides [140], including CCl_4, $CHCl_3$, 1-hexyl and cyclohexyl halides and benzyl chloride by hydrogen transfer from aqueous sodium formate at 80 °C (Eq. 40). Initial turnover frequencies as high as 1000 h^{-1} were determined, the catalysts showing activity far superior to the analogous system [141] employing $[RuCl_2(PPh_3)_3]$. Under the same conditions, chlorobenzene was completely unreactive (cf. Section 6.14).

$$CCl_4 + HCOO^- + OH^- \rightarrow CHCl_3 + Cl^- + HCO_3^- \qquad (40)$$

6.2.3.4
Miscellaneous Hydrogenations

Hydrogenation of nitro compounds can be achieved with $[HCo(CN)_5]^{3-}$ as catalyst; however, in many cases (especially with nitroarenes), products of reductive dimerization, i.e., azo and hydrazo compounds, are formed instead of the expected amino derivatives [12]. Ketoximes and oximes of 2-oxo acids are hydrogenated to amines [142]. 2-Amino acids can be prepared in high yields by reductive amination of 2-oxo acids in an aqueous NH_3 solution (Eq. 41) [143].



(41)

Catalytic hydrogenation of chloronitroaromatics is often accompanied by dehalogenation. Importantly, in DMSO-containing water, the $[Pd(OAc)_2] +$ TPPTS catalyst hydrogenated 5-chloro-2-nitrophenol to 5-chloro-2-aminophenol with outstanding selectivity [168].

Anilines can be obtained from nitroarenes under water-gas shift (WGS) conditions (Eq. 42).

$$PhNO_2 + 3CO + H_2O \rightarrow PhNH_2 + 3\,CO_2 \qquad (42)$$

In most cases such reactions are conducted in strongly alkaline aqueous solutions [144] or in the presence of amines [145, 146]. $[Rh_6(CO)_{16}]$, $[Rh_{12}(CO)_{30}]^{2-}$ and $[Rh_5(CO)_{15}]^-$, formed *in situ* in the reaction mixture, are among the most active catalysts [147]. However, addition of a strong base to solutions of $[Rh(CO)_4]^-$ (with K^+, Cs^+, or $(PPh_3)_2N^+$ cation) diminishes the catalytic activity in the hydrogenation of nitrobenzene to aniline with $CO + H_2O$ [148]. Recently it was disclosed that the catalysts prepared from $PdCl_2$ and TPPTS or multiply-sulfonated BINAP

(BINAS, **38**) catalyzed the selective reduction of nitroarenes to anilines at 100 °C under 120 bar CO [149].

A similarly selective reduction of nitroarenes was achieved under WGS conditions by using $[Ru_3(CO)_{12}]$ in the presence of certain amines, such as diisopropylamine, piperidine, dibutylamine, and triethylamine [146]. Importantly, the latter reaction yielded no unwanted H_2 as by-product from a concomitant WGS reaction.

Hydrogenation of carbon dioxide can be achieved in aqueous solutions, too [150, 170].

Recent research in the application of supercritical (sc) fluids and ionic liquids (IL) as solvents in homogeneous catalysis (see Sections 7.3 and 7.4), opened the way to the development of biphasic water/$scCO_2$ [171, 172] and water/IL [173] systems for the hydrogenation of various substrates, e.g., alkenes, aldehydes, etc. with water-soluble catalysts. The catalytically highly active, versatile and robust transition metal–*N*-heterocyclic carbene complexes [174] have also been applied for hydrogenation reactions [175]. Given that water-soluble complexes with *N*-heterocyclic carbene ligands are known [176], catalytic applications in aqueous systems are also foreseen.

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6.3
Hydrogenation and Hydrogenolysis of Thiophenic Molecules

Claudio Bianchini, Andrea Meli

6.3.1
Introduction

With the advent of stricter pollution laws concerning sulfur in gasoline and diesel oil, an outburst of research on the hydrodesulfurization (HDS) process is currently pervading chemical laboratories worldwide. In the HDS process (Eq. 1), sulfur is removed from fossil materials upon treatment with a higher pressure of H_2 (35 – 170 bar) in the presence of heterogeneous catalysts at high temperature (300 – 425 °C) [1].

$$C_xH_yS + 2\,H_2 \longrightarrow C_xH_{y+2} + H_2S \qquad (1)$$

With the existing HDS technology, the sulfur contents in gasoline can only with difficulty be reduced to the marketing limit ($\leq$ 60 ppm) without drastic changes in the octane and cetane rating, especially when the cracking and coking naphthas come from fossil materials containing large amounts of thiophenic molecules. These comprise an enormous variety of substituted thiophenes, benzo[*b*]thiophenes, and dibenzo[*b,d*]thiophenes as well as other fused-ring thiophenes, all of which are generally less easily disulfurized over heterogeneous catalysts than any other sulfur compound in petroleum feedstocks (e.g., thiols, sulfides, and disulfides). In addition to the inherent refractoriness, it is now apparent that each category of thiophenes may undergo HDS through a distinct mechanism [1]. As a consequence, specific catalysts for each type of thiophene should be developed for the deep desulfurization of refined fuels as these may contain different distributions of thiophenic contaminants. A problem of this type cannot find a general solution as HDS reactors in refineries are commonly fed with petroleum feedstocks of various natures. Moreover, the design of an heterogeneous catalyst for the degradation of a specific substrate, in trace amounts and in the presence of similar substrates, is an arduous task, certainly much more demanding than tailoring a soluble homogeneous catalyst for an analogous action. It is probably for all of these reasons

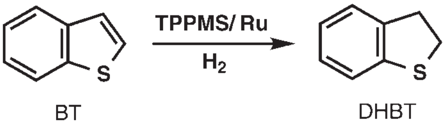
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

that the HDS of thiophenes and other organosulfur compounds catalyzed by water-soluble metal complexes is attracting increasing interest from petrochemical industries [2], especially in relation to the development of catalysts for improving gasoline quality once the major part of the sulfur has already been eliminated by hydrotreatment on conventional heterogeneous catalysts. Over the last few years, in fact, aqueous biphase catalysis has made impressive progress, particularly as regards its application to large-volume reactions [3].

6.3.2
Hydrogenation Reactions

Researchers at INTEVEP SA (Ven) have recently shown that the regioselective hydrogenation of benzo[*b*]thiophene (BT) to dihydrobenzo[*b*]thiophene (DHBT) (Eq. 2) can be performed in a 1:1 water/decalin mixture using an *in situ* catalyst system formed by addition of an excess of either *m*-monosulfonated triphenylphosphine (TPPMS) or trisulfonated triphenylphosphine (TPPTS) to various Ru(II) precursors [2a]. It is believed that the catalytically active species is a mononuclear Ru(II) complex with chloride and hydride ligands.

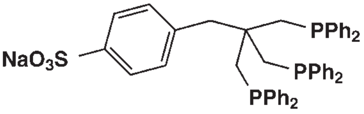


(2)

Interestingly, the rate almost quadruples if nitrogen bases such as quinoline (Q) or aniline are used as co-catalysts. This kinetic effect may be due to several beneficial actions by the nitrogen bases on either the catalyst (faster formation and/or better stabilization) or the phase system (stabilization of the emulsion, improved solubility of BT in water). The quality of the emulsion seems to be of particular importance as shown by the fact that TPPTS, which is a worse surfactant than TPPMS, also gives worse catalytic results. Other nitrogen bases such as acridine, tetrahydroquinoline (THQ), piperidine, and triethylamine give lower conversions to DHBT as compared with analogous reactions co-catalyzed by aniline or quinoline.

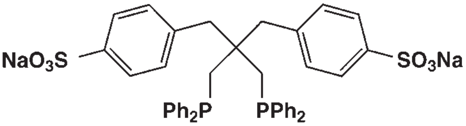
The tolerance of the Ru/TPPMS or TPPTS systems toward organic nitrogen bases has also allowed their use as catalysts for the hydrogenation of Q/BT mixtures in which Q kinetically favors the hydrogenation of BT [2a]. This result is quite surprising as it is generally observed that the presence of nitrogen compounds in fuel feedstocks inhibits HDS reaction over heterogeneous catalysts [1a, f].

More recent work on the hydrogenation of thiophenic molecules catalyzed by water-soluble metal complexes is pursuing the use of polyphosphine ligands (cf. Section 3.2.2). These studies follow the success obtained with the tridentate phosphine MeC $(CH_2PPh_2)_3$ (TRIPHOS), which forms rhodium and iridium catalysts for the hydrogenation, hydrogenolysis, and desulfurization of various thiophenic substrates in homogeneous phase [4–7]. The two-water-soluble chelating polyphosphines $NaO_3S(C_6H_4)CH_2C(CH_2PPh_2)_3$ (NaSULPHOS, Structure **1** [8] and $(NaO_3S(C_6H_4)CH_2)_2C(CH_2PPh_2)_2$ (Na_2DPPPDS; Structure **2**) [9] have already proved to be effective ligands for the formation of transition metal complexes capable of catalyzing both the hydrogenation and hydrogenolysis of thiophenic substrates.



NaSULPHOS

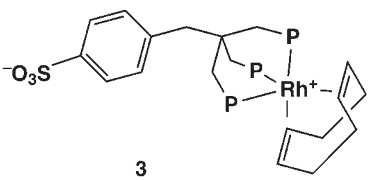
1



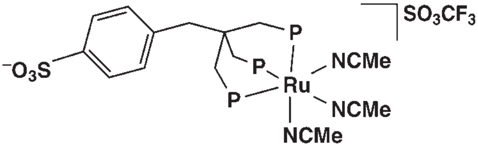
Na_2DPPPDS

2

The triphosphine **1** is the water-soluble version of TRIPHOS and was initially developed to study, in association with rhodium, the liquid-biphase hydrogenation and hydroformylation of alkenes [8]. The Rh catalyst employed in these reactions, e.g., the zwitterionic Rh(I) complex (SULPHOS)Rh(cod) (**3**), has recently been used as catalyst precursor for the hydrogenation of BT to DHBT in biphase systems comprising water and methanol as polar phase and *n*-heptane as hydrocarbon phase [10]. Although the catalyst system is very robust and can tolerate relatively drastic reaction conditions for a long time (30 bar H_2, 200 °C), the catalytic activity is quite modest (TOF $\simeq$ 2). Increased catalytic efficiency has been obtained by substituting Ru for Rh. Under comparable conditions (30 bar H_2, BT/Ru ratio 100 : 1), the tris(acetonitrile) complex $[(SULPHOS)Ru(MeCN)_3]SO_3CF_3$ (**4**) catalyzes the regioselective hydrogenation of BT to DHBT in H_2O–MeOH/*n*-heptane with a TOF of ca. 40 already at 100 °C [11]. The addition of MeOH to water may be necessary to enhance the mutual solubility and mobility of the components across the phase boundary. Analogously to the TPPMS/ and TPPTS/Ru systems developed earlier, both the Rh and Ru complexes **3** and **4** have proved effective catalyst precursors for the hydrogenation of Q to THQ, thus showing that the hydrodenitrogenation (HDN) of fossil fuels may also be pursued by aqueous-biphase catalysis.

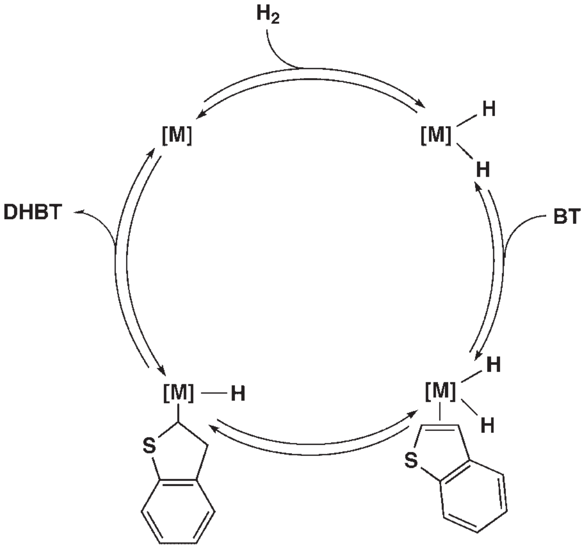


3



4

Unlike the tripodal ligand **1**, the chelating diphosphine **2** forms rhodium and ruthenium catalysts (by simple reaction with the corresponding hydrated trichlorides) that catalyze the hydrogenation of BT in water/hydrocarbon biphase systems



Scheme 1

with no need for alcohol co-solvents [11]. The catalytic activity is generally lower than that with the tridentate ligand **1**, however.

In summary, BT can be hydrogenated in liquid biphase systems using water-soluble catalysts with transition metals belonging to the family of the HDS promoters such as Ru and Rh [12]; the ruthenium catalysts are generally more efficient than those with rhodium, a finding that is consistent with heterogeneous HDS reactions [1]. The fact that all the reported studies involve BT is most probably attributable to the pronounced "olefinic" character of the C_2-C_3 bond that favors hydrogenation pathways [4]. Moreover, the reduction products of BT are easier to handle. This, however, does not exclude the application of aqueous biphase catalysis to thiophenes or dibenzothiophenes, for which homogeneous processes have already been developed [5, 7]. Although no mechanistic study of aqueous hydrogenation reactions of BT has ever been reported, it is very likely that the reactions comprise the usual steps of H_2 oxidative addition, hydride transfer to η^2-C_2, C_3-coordinated BT to form dihydrobenzothienyl species, and reductive elimination of DHBT to complete the cycle (Scheme 1) [13].

6.3.3
Hydrogenolysis Reactions

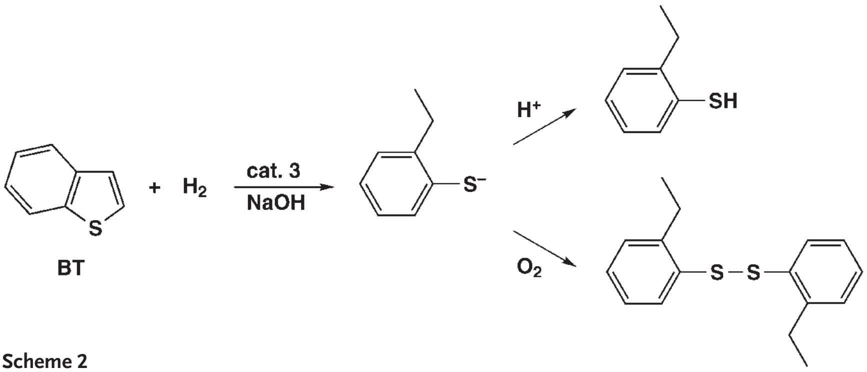
The catalytic conversion of thiophenic substrates to the corresponding thiols (hydrogenolysis) (Eq. 3) is a reaction of much relevance in the HDS process as the thiols can subsequently be desulfurized over conventional HDS catalysts with greater efficiency and under milder reaction conditions than those required to accomplish the HDS of the thiophene precursors [1]. This aspect is particularly important for fused-ring thiophenes because the conventional catalysts can desulfurize the corresponding thiols without affecting the benzene rings necessary to preserve a high octane number.

$$C_xH_yS + H_2 \longrightarrow C_xH_{y+1}SH \qquad (3)$$

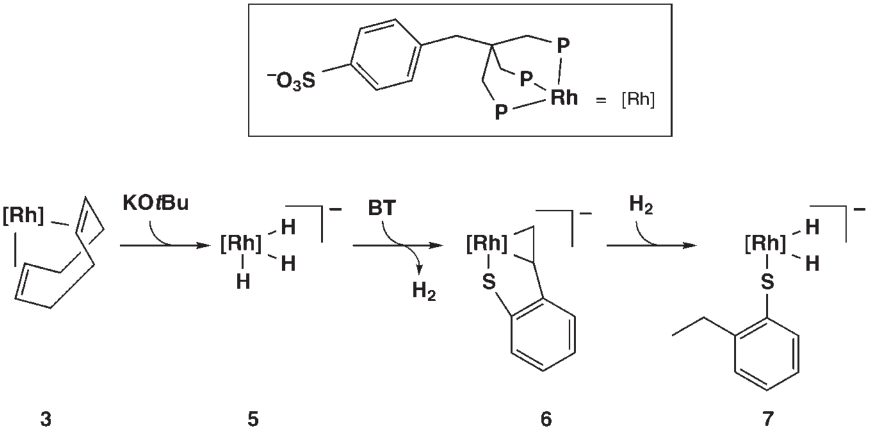
The hydrogenolysis of various thiophenes (thiophene, benzo[*b*]thiophene, dibenzo[*b*,*d*]thiophene, dinaphtho[2,1-*b* : 1′,2′-*d*]thiophene) has been achieved in homogeneous phase with the 16e$^-$ catalyst [(TRIPHOS)RhH] [4–7, 13 d]. This can be generated from appropriate TRIPHOS/Rh precursors by either thermal elimination of H_2 [4, 6, 14] or base-assisted heterolytic splitting of H_2 [7–10]. Depending on the thiophenic substrate, it has been observed that the addition of strong Brønsted bases (NaOH, KO*t*Bu) to the catalytic mixtures may increase the reaction rate by as much as tenfold [7]. Besides generating M–H moieties in a reductive manner (e.g., $[M]^{n+} + H_2 + \text{base}^- \rightarrow [M - H]^{(n-1)+} + \text{base} - H$), the base serves to speed up the catalysis rate by aiding the elimination of the thiol product from the metal center, i.e. the rate-determining step for the hydrogenolysis reactions assisted by [(TRIPHOS)RhH] [4] (Eq. 4).

$$\text{(TRIPHOS)Rh(H)}_2\text{SR} + \text{NaOH} \longrightarrow \text{[(TRIPHOS)RhH]} + \text{NaSR} + H_2O \qquad (4)$$

The application of the "strong base" method to liquid biphase hydrogenolysis reactions has provided quite interesting results using the SULPHOS complex **3** as catalyst precursor, BT as substrate and NaOH as base [10]. In a typical reaction in H_2O–MeOH/*n*-heptane (BT/NaOH/**3** = 100 : 100 : 1, 30 bar H_2), all the substrate is selectively transformed into 2-ethylthiophenol sodium salt (ETPNa; the production of DHBT is generally less than 1%) (Scheme 2). At 200 °C, however, appreciable decomposition of the catalyst has been observed to give metal particles that are responsible for heterogeneous HDS of BT to ethylbenzene and H_2S.



Scheme 2

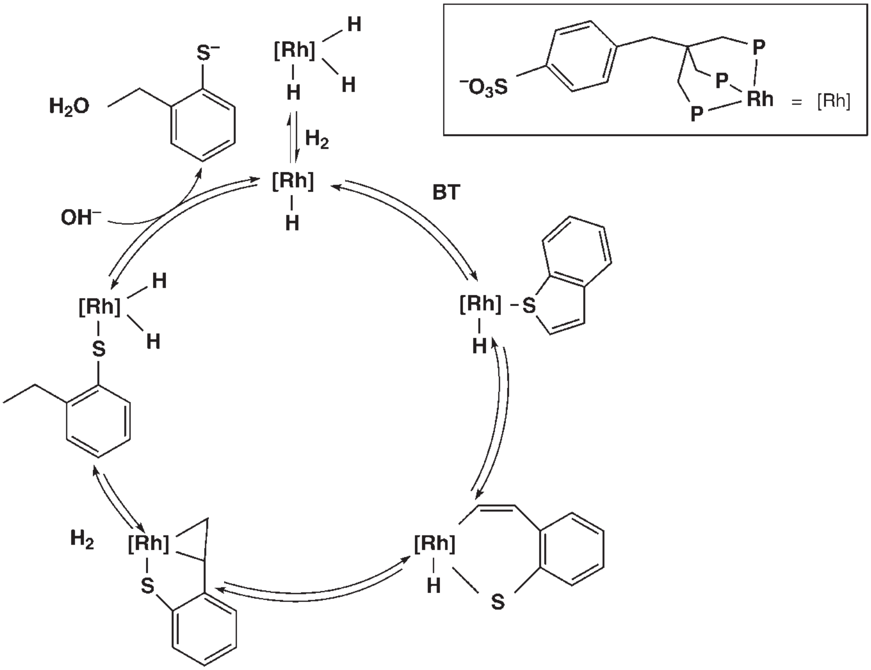


Scheme 3

When all the BT has been consumed, the hydrogenolysis product accumulates in the polar phase as Na[*o*-S(C_6H_4)C_2H_5] leaving the hydrocarbon phase completely desulfurized and also devoid of any rhodium. The hydrogenolysis product can also be separated as the disulfide [*o*-S(C_6H_4)C_2H_5]$_2$ if the polar phase is exposed to air oxidation. Alternatively, the reaction mixture can be acidified under an inert atmosphere and the thiol extracted from the polar phase with *n*-heptane so as to leave the complexed rhodium in the polar phase for use in a further catalytic run. Due to the inherent surfactant properties of SULPHOS metal complexes [8], very efficient emulsions are obtained and the hydrogenolysis rates are independent of the stirring rate in the 650–1800 rpm range as well as of the addition of surfactants. Methanol, however, is a necessary co-solvent to ensure the mutual solubility and mobility of the components across the phase boundary.

The effect of the H_2 pressure and of the substrate, catalyst, and base concentrations on the conversion rate of BT has been studied. The hydrogenolysis reactions are first-order in both the catalyst and BT concentration. They are also first-order in the base concentration as long as the NaOH/BT ratio is lower than or equal to 0.6 : 1. For greater concentrations of base, the rates tend to flatten because the high ionic strength of the polar phase disfavors the mixing of the phases as well as the diffusion of BT. The hydrogenolysis rates increase linearly also with the H_2 pressure in the range from 5 to 30 bar. Above 30 bar, the rates decrease due to the formation of increasing equilibrium concentrations of the trihydride complex [(SULPHOS)RhH_3]$^-$ (**5**) ([10, 15]; cf. Scheme 3).

The trihydride **5** is the first Rh compound to be formed upon hydrogenation of the precursor **3** in the presence of KO*t*Bu. The Rh(I) catalytically active species [(SULPHOS)RhH]$^-$, generated by thermal elimination of H_2 from **5**, then reacts with BT to give the C–S insertion 2-vinylthiophenolate complex [(SULPHOS)-



Scheme 4

$Rh(\eta^3\text{-}S(C_6H_4)CH{=}CH_2)]^-$ (**6**), which can be isolated as the potassium salt. As in monophase systems [4], **6** would form by regioselective insertion of rhodium into the C_2–S bond from BT, followed by intramolecular hydride migration to the α-carbon atom of a metallathiacycle intermediate [14, 16]. Reaction of **6** with H_2 finally yields the (2-ethylthiophenolate)dihydride complex $[(SULPHOS)Rh(H)_2(o\text{-}S(C_6H_4)\text{-}C_2H_5)]^-$ (**7**).

The catalysis cycle proposed for the opening and hydrogenation of BT to ETPNa does not diverge much from those previously reported for the hydrogenolysis of BT to 2-ethylthiophenol [4, 13 d] and of thiophene to 1-butanethiol [7] catalyzed by [(TRIPHOS)RhH]. The mechanism illustrated in Scheme 4 involves the usual steps of C–S insertion, hydrogenation of the C–S-inserted BT to 2-ethylthiophenolate, and base-assisted reductive elimination of the thiol to complete the cycle.

At variance with the homogeneous reactions with [(TRIPHOS)RhH] in which the base simply accelerates the catalytic process, in the biphase reactions the presence of NaOH is mandatory for catalysis to occur. This is most probably because the concentration of BT in the polar phase is too low to promote effectively the elimination of the thiol product. A similar dependence of the reaction rate on Brønsted bases has been observed for the homogeneous hydrogenolysis of thiophene by TRIPHOS/Rh catalysis, and was attributed to the weak nucleophilic properties of thiophene [7].

Unlike the hydrogenation of BT to DHBT, the substitution of (SULPHOS)Ru for (SULPHOS)Rh in the base-assisted hydrogenolysis to ETPNa seems to decrease the conversion rate. Preliminary results with the tris(acetonitrile) complex **4** show that the transformation of the substrate does not exceed 10% of that obtained with comparable Rh catalysts in analogous conditions [11]. This poor activity is attributed to the formation of stable μ-OH ruthenium species rather than to the minor propensity of (polyphosphine)Ru(II) moieties to catalyze the hydrogenolysis of thiophenes. As a matter of fact, good conversion and selectivity of BT to ETPNa are being observed in water/*n*-hexane using Ru(II) catalysts with the water-soluble diphosphine Na_2DPPPDS [9, 11].

6.3.4
Future Developments

If business pull has played the dominant role in the innovation process by which HDS has led to a doubling of the catalytic activity of conventional heterogeneous catalysts over the last 20 years, environmental push will largely contribute to drive future research efforts aimed at developing more efficient technologies for sulfur removal form crude oil. Emerging technologies of great interest are aqueous biphase catalysis and its variations such as supported liquid-phase catalysis [17]. The introduction of aqueous biphase techniques to industrial HDS will require an enormous amount of research work to be particularly directed to the synthesis of water-soluble catalysts containing inexpensive metals (Fe, Co, Ni, Ru) and endowed with specific characteristics such as inherent emulsifying attributes and great thermal and chemical stability.

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6.4
Oxidations

6.4.1
Partial Oxidations

Roger A. Sheldon, Georgios Papadogianakis

6.4.1.1
Introduction

The main difficulty in discussing oxidation reactions within the context of aqueous-phase organometallic catalysis is to define the frame of reference. Metal-catalyzed hydrogenations, carbonylations, hydroformylations, etc., involve transition metals in low oxidation states coordinated to soft ligands, e.g., phosphines, as the catalytically active species and organometallic compounds as reactive intermediates. Performing such reactions in aqueous/organic biphasic media generally involves the use of water-soluble variants of these ligands, e.g., sulfonated triarylphosphines. In contrast, catalytic oxidations involve transition metals in high oxidation states as the active species, generally coordinated to relatively simple hard ligands, e.g., carboxylate. Reactive intermediates tend to be coordination complexes rather than organometallic species.

Water often has an inhibiting effect on catalytic oxidations, owing to strong coordination to the hard metal center hampering coordination of a less polar substrate, e.g., a hydrocarbon (cf. Section 2.1). Coordination of complex nitrogen- and/or oxygen-containing ligands can lead to the generation of more active oxidants by promoting the formation of high oxidation states. For example, in heme-dependent oxygenases and peroxidases the formation of active high-valent oxoiron complexes is favored by coordination to a macrocyclic porphyrin ligand. Hence, the frame of reference has been limited to systems in which the reaction takes place in the aqueous phase with two types of catalyst: transition-metal complexes of water-soluble ligands and transition-metal salts/complexes in micellar systems.

The vast body of literature is devoted to catalytic oxidations of carbohydrates, which by necessity are performed in water but generally involve the use of hetero-

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

geneous noble-metal catalysts or simple metal salts [1]. These oxidations, as well as the use of phase-transfer agents to solubilize inorganic oxidants, e.g. H_2O_2, NaOCl or metal catalysts in an organic phase [2] have been excluded from this section. Although such systems have considerable synthetic utility they fall outside the scope of the present discussion. One example of a catalytic oxidation which takes place in water and involves organometallic intermediates in the palladium-catalyzed oxidation of alkenes to the corresponding ketones (Wacker process). This reaction is discussed in the following section (Section 6.4.2) and will not be dealt with here.

Just as with hydrogenations, hydroformylations, etc., a major reason for performing catalytic oxidations in water is to provide for facile recovery of the catalysts, by simple phase separation, from the product which is in an organic phase. However, many examples of catalytic oxidations in water involve water-soluble substrates and/or products. In this case catalyst recovery can be facilitated by using polymeric water-soluble ligands (see below) in conjunction with separation with an ultrafiltration membrane [3] or by other measures.

6.4.1.2
Water-soluble Ligands

Much of the research devoted to catalytic oxidations mediated by metal complexes of water-soluble ligands falls into the category of biomimetic oxidations. Hence, water-soluble porphyrins and the structurally related phthalocyanines have been widely used (see Figure 1 for examples).

For example, the cobalt(II) complex for phthalocyanine tetrasodium sulfonate (PcTs) catalyzes the autoxidation of thiols, such as 2-mercaptoethanol (Eq. 1) [4] and 2,6-di(*t*-butyl)phenol (Eq. 2) [5]. In the first example the substrate and product were water-soluble whereas the second reaction involved an aqueous suspension. In both cases the activity of the Co(PcTs) was enhanced by binding it to an insoluble polymer, e.g., polyvinylamine [4] or a styrene–divinylbenzene copolymer substituted with quaternary ammonium ions [5]. This enhancement of activity was attributed to inhibition of aggregation of the Co(PcTs) which is known to occur in water, by the polymer network. Hence, in the polymeric form more of the Co(PcTs) will exist in an active monomeric form. In Eq. (2) the polymer-bound Co(PcTs) gave the diphenoquinone (**1**) with 100% selectivity whereas with soluble Co(PcTs) small amounts of the benzoquinone (**2**) were also formed. Both reactions involve one-electron oxidations by Co(III) followed by dimerization of the intermediate radical ($RS^{\bullet}$ or $ArO^{\bullet}$).

$$2\,RSH + 1/2\,O_2 \xrightarrow{CoPcTs} RSSR + H_2O \qquad (1)$$

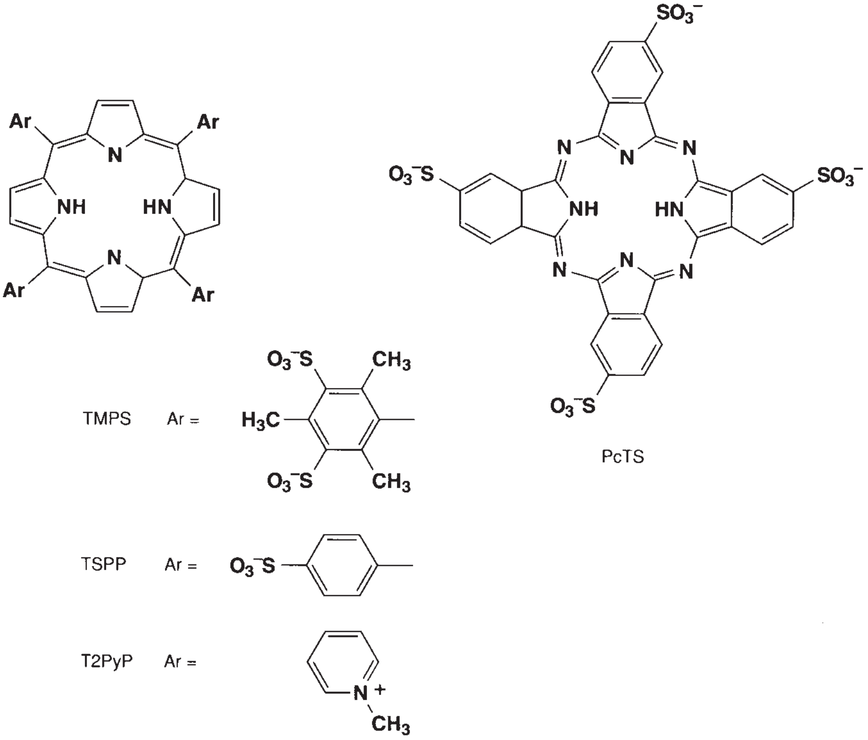
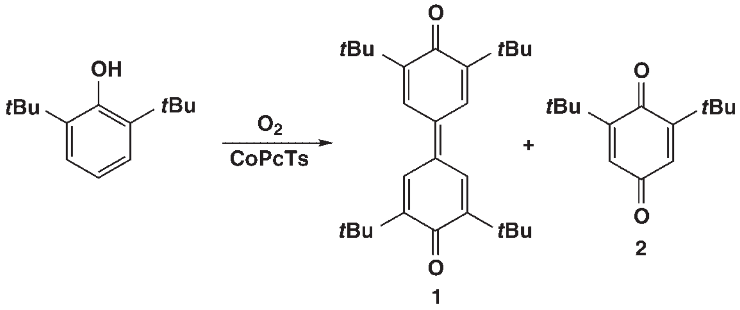
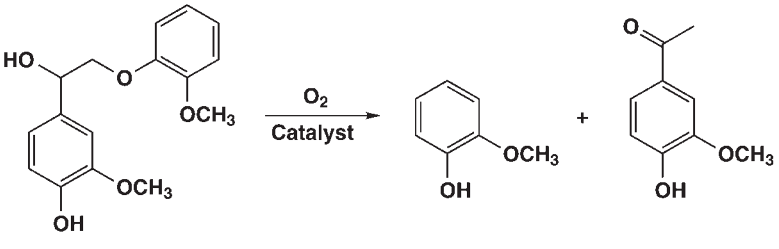


Fig. 1 Water-soluble porphyrins and phthalocyanines.



(2)

Much of the research on water-soluble metalloporphyrins and metallophthalocyanines stems from the interest in their use as catalysts in environmentally friendly O_2-based delignification of wood pulp in paper manufacture. Conventional processes involve the use of Cl_2 or ClO_2 as oxidants and produce effluents containing chlorinated phenols. For example, Wright and co-workers [6] oxidized lignin model compounds such as **3** with O_2 (Eq. 3) in the presence of Na_3-Fe(III)(PcTS), Na_3Co(III)(TSPP) and Na_3Rh(III)(TSPP) catalysts. The latter gave the highest rates and selectivities.

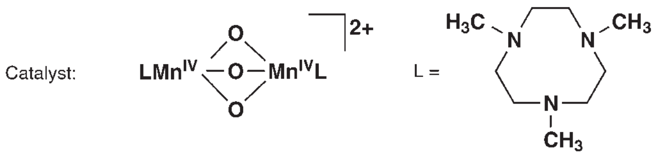


3 **4** **5** (3)

Similarly, Hampton and Ford [7] studied the Fe(PcTS)-catalyzed autoxidation of 3,4-dimethoxybenzyl alcohol as a model for delignification. They concluded, however, that the catalyst degrades too fast to be useful for delignification. In this context it is worth mentioning that water-soluble polyoxometallates such as $PV_2Mo_{10}O_{40}^{5-}$ have also been used as catalysts for delignification with O_2 [8]. Fe(PcTS) [9] and Fe(TMPS) [10] have also been examined as catalysts for the oxidative destruction of chlorinated phenols in waste water, using H_2O_2 or $KHSO_5$ as the oxidant. For example, 2,4,6-trichlorophenol underwent facile oxidation to 2,6-dichloro-1,4-benzoquinone with Fe(PcTS)/H_2O_2 [9] or Fe(TMPS)/$KHSO_5$ [10]. Similarly, Fe(III) and Mn(III) complexes of T2MPyP catalyzed the oxidation of phenols with $KHSO_5$ [11].

Water-soluble manganese complexes of 1,4,7-trimethyl-1,4,7-triazacyclononane (**6**) and related ligands are highly effective catalysts for low-temperature bleaching of stains [12]. Polyphenolic compounds were used as appropriate models for tea stains. The same complexes were shown to catalyze the selective epoxidation of styrene and 4-vinylbenzoic acid with aqueous H_2O_2 (Eq. 4) in aqueous MeOH or water, respectively. However, large amounts of H_2O_2 (10 equiv.) were required, indicating that considerable nonproductive decomposition occurs. Subsequently, it was shown that nonproductive decomposition of the hydrogen peroxide could be largely suppressed by the addition of oxalate [13] or ascorbic acid [14] as cocatalysts, or by anchoring the ligand to a solid support [15]. More recently, the use of glyoxylic acid methyl ester hemiacetal as a cocatalyst was shown to afford an even more effective epoxidation catalyst, enabling high conversions with only a 30% excess of H_2O_2 [16]. Interestingly, the corresponding *cis*-diols were observed as byproducts in many cases and a concerted mechanism via a manganese(III)-*cis*-diol complex was proposed to explain their formation. The binuclear manganese complex of **6** also catalyzed the oxidation of benzylic alcohols, to the corresponding benzaldehydes, with aqueous hydrogen peroxide [17].

(4)



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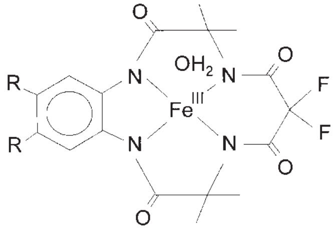
Collins and co-workers [18] have developed a series of iron(III) complexes of macrocyclic tetradentate nitrogen ligands, so-called TAML oxidant activators, with greatly enhanced stability towards oxidative and hydrolytic degradation (Structure **7**). They are efficient, water-soluble activators of hydrogen peroxide, over a broad pH range, with a wide variety of potential applications, e.g., to replace chlorine bleaching in the pulp and paper industry, and for use in water effluent treatment in the textiles industry. Applications in organic synthesis have, as yet, not been explored.



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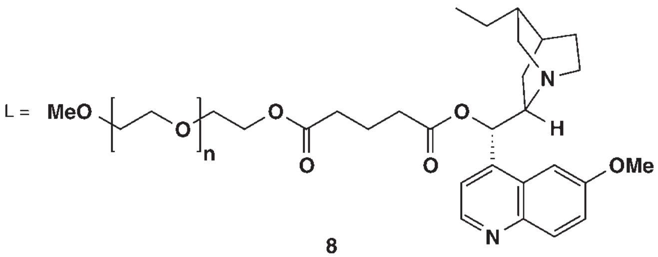
A noted earlier, coordination of transition-metal ions to water-soluble polymers can allow for facile catalyst recovery, by ultrafiltration, from water-soluble substrates and/or products. For example, Han and Janda [22] used an osmium complex of the water-soluble polymeric chiral ligand **8** as a catalyst for the asymmetric dihydroxylation of alkenes in aqueous acetone (Eq. 5). However, they suggested that the catalyst should be recovered by precipitation with methylene chloride. Obviously the use of an ultrafiltration membrane for catalyst separation would be far more attractive.

(5)



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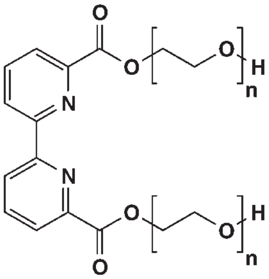
A variant on this theme is to attach a transition-metal complex of a “smart” polymer, the solubility of which can be dramatically influenced by a change in a physical parameter, e.g., temperature [23] (cf. Sections 4.6 and 4.7). Catalyst recovery can be achieved by simply lowering or raising the temperature. For example, block copolymers of ethylene oxide and propene oxide show an inverse dependence of solubility on temperature in water [24]. Karakhanov et al. [25] prepared water-soluble polymeric ligands comprising bipyridyl (bipy) or acetylacetonate (acac) moieties covalently attached to poly(ethylene glycol)s (PEGs) or ethylene oxide/propene oxide block copolymers **9** and **10**.



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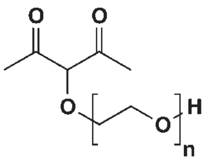

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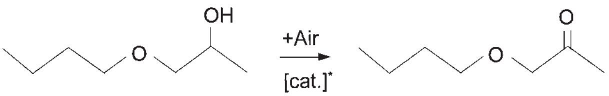
Iron(III) and cobalt(II) complexes of these polymeric ligands were found to be effective catalysts for the oxidation of cyclohexane and ethylbenzene with H_2O_2 or O_2 in biphasic media. The authors proposed that the oxidation takes place inside polymer micelles which can be regarded as microreactors. However, no recycle experiments were performed to ascertain the stability of these catalysts. *A priori* one would expect acetylacetonate ligands to undergo facile degradation under oxidizing conditions.

Recently, we described [19–21] the use of a water-soluble palladium(II) complex of sulfonated bathophenenthroline (**11**) as a stable, recyclable catalyst for the aerobic oxidation of alcohols in a two-phase aqueous-organic medium (e.g., Reaction 6). Reactions were generally complete in 5 h at 100 °C/30 bar air with as little as 0.25 m% catalyst. No organic solvent is required (unless the substrate is a solid) and the product is easily recovered by phase separation. The catalyst is stable and remains in the aqueous phase, facilitating recycling to the next batch.



(6)

A wide range of primary and secondary alcohols were oxidized with turnover frequencies ranging from 10 to 100 h^{-1}, depending on the structure and the solubility of the alcohol in water (since the reaction occurs in the water phase the alcohol must be at least sparingly soluble in water). Secondary alcohols afforded the corre-

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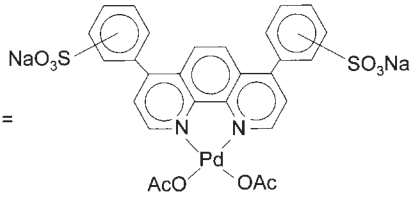

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sponding ketones in > 99% selectivity in virtually all cases studied. Primary alcohols afforded the corresponding carboxylic acids via further oxidation of the initially formed aldehyde, e.g., 1-hexanol afforded 1-hexanoic acid in 95% yield. It is important to note that this was achieved without the necessity to neutralize the carboxylic acid product with one equivalent of base. When the reaction was performed in the presence of 1 mol% of the stable free radical, TEMPO (2,2,6,6-tetramethylpiperidinoxyl) over-oxidation was suppressed and the aldehyde was obtained in high yield, e.g., 1-hexanol afforded hexanal in 97% yield.

Compared to most existing systems for the aerobic oxidation of alcohols the Pd-bathophenanthroline system is an order of magnitude more reactive, requires no organic solvent, involves simple product isolation and catalyst recycling, and has broad scope in organic synthesis.

6.4.1.3
Concluding Remarks

Important advances have been made in the last few years in the design of water-soluble, oxidatively stable ligands. In combination with appropriate metal ions they afford stable, water-soluble catalysts for oxidations with dioxygen or hydrogen peroxide in aqueous-organic biphasic systems. Up till now, synthetic applications have generally been limited to alkene epoxidations with hydrogen peroxide (Mn) and aerobic oxidation of alcohols (Pd). These methodologies constitute green alternatives – clean oxidants, no need for organic solvents, facile product separation and catalyst recycling – for traditional oxidations. In the future we expect that these methodologies will be further applied in organic synthesis. In particular, iron complexes offer significant advantages from both an economic and environmental viewpoint.

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6.4.2
Wacker-type Oxidations

Eric Monflier, André Mortreux

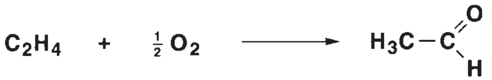
6.4.2.1
Possibilities of Wacker-type Oxidations

With oxo synthesis, Wacker-type oxidations of alkenes is one of the older homogeneous transition-metal-catalyzed reactions [1]. The most prominent example of this type of reaction is the manufacture of acetaldehyde from ethylene. This well-known reaction, which has been successfully developed on an industrial scale (Wacker process), combines the stoichiometric oxidation of ethylene by palladium(II) in aqueous solution with the *in situ* reoxidation of palladium(0) by molecular oxygen in the presence of a copper salt (Eqs. 1–4) [2].

$$C_2H_4 + H_2O + PdCl_2 \longrightarrow H_3C{-}CHO + Pd^0 + 2\,HCl \qquad (1)$$

$$Pd^0 + 2\,CuCl_2 \longrightarrow PdCl_2 + Cu_2Cl_2 \qquad (2)$$

$$Cu_2Cl_2 + 2\,HCl + \tfrac{1}{2}O_2 \longrightarrow 2\,CuCl_2 + H_2O \qquad (3)$$



$$C_2H_4 + \tfrac{1}{2}O_2 \longrightarrow H_3C{-}CHO \qquad (4)$$

In an industrial context, this oxidation proceeds either in one stage or in two stages [3]. The single-stage Hoechst process involves feeding an oxygen/ethylene mixture into an aqueous solution of palladium and copper. The two-stage Wacker process requires the oxygen-free stoichiometric oxidation of ethylene by a mixture of palladium and copper salts in a first stage and the reoxidation of the catalytic mixture with air in a separate reactor in a second stage. Both processes give small amounts of by-products such as 2-chloroethanol, acetic acid, oxalic acid, and chloroacetaldehyde. However, the formation of chlorinated products can be avoided by using chlorine-free oxidants such as ferric sulfate [4], heteropolyacid [5], ben-

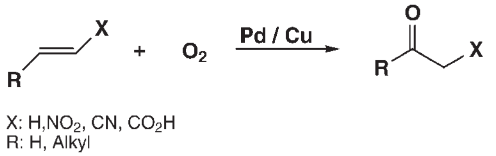
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

zoquinone [6] or two-component systems, consisting of benzoquinone and iron(II) phthalocyanine [7]. The nature of the products in the palladium-catalyzed oxidation of ethylene is also strongly dependent on the reaction conditions. For instance, 2-chloroethanol becomes the major product of ethylene oxidation at high pressure and high cupric chloride concentration [8].

When media other than water are used, different but related processes operate. Thus, the oxidation of ethylene in acetic acid can be directed to give vinyl acetate, ethylene glycol acetate, or 2-chloroethyl acetate [9]. Similarly, the synthesis of acetals or ketals can be achieved in an alcoholic medium [10]. Although the oxidation of alkenes in such a medium is closely parallel to the Wacker process, the chemistry of these reactions is far beyond the scope of this section, which is limited to Wacker-type reactions in aqueous media, and will not be discussed here.

The Wacker reaction has also been applied to numerous simple alkenes such α-alkenes or cycloalkenes, or to functionalized alkenes such nitroethylene, acrylonitrile, styrene, allyl alcohol, or maleic acid [3]. The carbonyl group is formed at the carbon atom of the double bond where the nucleophile would add in a Markovnikov addition (Eq. 5). Among these different alkenes, the oxidation of propene to acetone is the only oxidation which has been developed to an industrial scale.

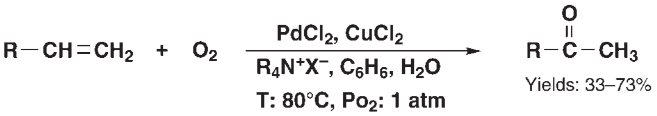


(5)

Conversion and selectivity for the oxidation of these alkenes were found to be very dependent on the water-solubility of the alkene. Indeed, high-molecular-mass alkenes do not react under the standard biphasic Wacker conditions due to their low solubility in water. Furthermore, the products obtained are often highly contaminated by chlorinated products and isomerized alkenes [11, 12]. In order to overcome these problems, numerous studies have been undertaken. Only the most significant approaches for the oxidation of higher α-alkenee (1-hexene and larger) will be developed here.

- Co-solvent or solvent is generally used to oxidize these water insoluble alkenes efficiently [12]. Among the different solvents described in the literature (dimethyl sulfoxide, acetone, tetrahydrofuran, dioxane, acetonitrile), dimethylformamide appears to be the most suitable one for the oxidation. Indeed, by employing a water/dimethylformamide mixture, oxidation of 1-dodecene to 2-dodecanone can be achieved with yields greater than 80%. However, hydrolysis of dimethylformamide is also possible during the reaction, yielding dimethylamine which can lead to the formation of inactive complexes.

- Phase-transfer catalysis constitutes an alternative technique to avoid poisoning of the catalyst and for its easily recovery. Moreover, under suitable phase-transfer catalysis conditions (benzene/water system; cf. Section 4.6.1), terminal alkenes can be converted in high yields to the corresponding 2-alkanones (Eq. 6) [13]. The reaction is very sensitive to the nature of the phase-transfer agent. Although some results are contradictory in the literature [14], it seems that only quaternary ammonium salts containing at least one long-chain alkyl group, such as tetradecyltrimethylammonium bromide or dodecyltrimethyl ammonium chloride, are suitable as phase-transfer catalysts.



$$R-CH=CH_2 + O_2 \xrightarrow[R_4N^+X^-,\ C_6H_6,\ H_2O \quad T:\ 80°C,\ Po_2:\ 1\ atm]{PdCl_2,\ CuCl_2} R-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 \quad (6)$$

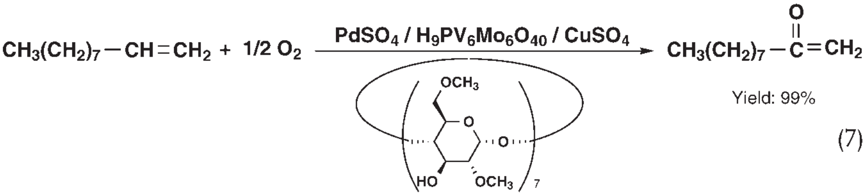
Yields: 33–73%

Although isomerization of alkenes occurs simultaneously with the oxidation, rhodium and ruthenium complexes can also be used instead of palladium for the oxidation of terminal alkene [15]. With these catalysts, symmetrical quaternary ammonium salts such as tetrabutylammonium hydrogensulfate are effective. Interestingly, the rate of palladium-catalyzed oxidation of terminal alkenes can be improved by using poly(ethylene glycol) (PEG) instead of quaternary ammonium salts [16]. Thus, the rates of PEG-400-induced oxidation of 1-decene are up three times faster than those observed with cetyltrimethylammonium bromide under the same conditions. Interestingly, internal alkenes can be efficiently oxidized in this polyethylene glycol/water mixture.

- Microemulsion systems have also been proposed to perform the oxidation of sparingly water-soluble alkenes [17]. The microemulsion system consisted of formamide/1-hexene/2-propanol as co-surfactant and $C_9H_{19}C_6H_4(OCH_2CH_2)_8OH$ as surfactant. In such a medium, the oxidation rates of 1-hexene to 2-hexanone were three times faster than those observed in the water/dimethylformamide mixture under similar conditions.

- Immobilized catalysts have also been described for the oxidation of water-insoluble alkenes. Most studies have been done with polymer-anchored palladium catalysts [18]. For instance, palladium supported on a highly rigid cyanomethylated polybenzimidazole produces a highly effective catalyst for the Wacker oxidation of 1-decene, with activity higher than homogeneous systems in some cases [19]. This water-soluble polymer-anchored palladium catalyst can be recycled and used at high temperature without metallic palladium precipitation. The reoxidation agent can also be incorporated into the polymer support in the form of *p*-quinone groups [20]. In this case, reoxidation of the resulting hydroquinone groups seems to be the rate-limiting step. Recently, supported aqueous-phase catalysts have also been proposed to perform the alkene oxidation [21]. In this approach, palladium and copper salts are dissolved in an aqueous film supported on a high-surface-area silica gel (see Section 4.7). With this supported catalyst, the ketone yields are rather low ($< 25\%$) and significant isomerization of the alkene occurs. The activity and the selectivity of the catalyst are sensitive to the water content of the catalyst and to the oxygen pressure. The high yields in isomeric alkenes have been attributed to the slow reoxidation of palladium(0) to palladium(II) due to low oxygen diffusion in this heterogeneous material.

- Inverse-phase Transfer Catalysis (cf. Section 4.6.2) has been successfully applied to perform the quantitative and selective oxidation of 1-decene in an aqueous two-phase system [22]. The success of this oxidation is mainly due to the use of β-cyclodextrin – a cyclic oligosaccharide composed of seven glucopyranose units – functionalized with hydrophilic or lipophilic groups. The best results have been obtained with a multicomponent catalytic system composed of $PdSO_4$, $H_9PV_6Mo_6O_{40}$, $CuSO_4$, and per(2,6-di-*O*-methyl)-β-cyclodextrin (Eq. 7) [23].



$$CH_3(CH_2)_7-CH=CH_2 + 1/2\ O_2 \xrightarrow{PdSO_4\ /\ H_9PV_6Mo_6O_{40}\ /\ CuSO_4} CH_3(CH_2)_7-\overset{\overset{\displaystyle O}{\|}}{C}=CH_2 \qquad (7)$$

In this reaction, the chemically modified β-cyclodextrins behave mainly as inverse-phase transfer catalysts. Actually, owing to the formation of inclusion complexes, the chemically modified cyclodextrins transfer the higher alkenes into the aqueous phase, and thus improve the mass transfer between aqueous and organic layers. It has been found that the mass-transfer efficiency is strongly dependent on the nature of the substituent group and on the degree of substitution the cyclodextrin (Figure 1). These results have been mainly correlated with the solubility of cyclodextrins in water and with the weak stability of the host–guest complexes which would facilitate the dissociation–association reactions between the organic compounds and cyclodextrin.

This multicomponent catalytic system also made it possible to oxidize in high yields a wide range of straight-chain higher α-alkenes [24]. However, the oxidation rate and the ketone selectivity were strikingly dependent on the nature of the cyclodextrin and on the chain length of the alkene (Figure 2). The alkene optimal size and shape was reached with 1-decene. Attempts to oxidize internal alkenes in biphasic medium with cyclodextrins modified in this way failed due to the lack of accessibility of the double bond in the inclusion complex.

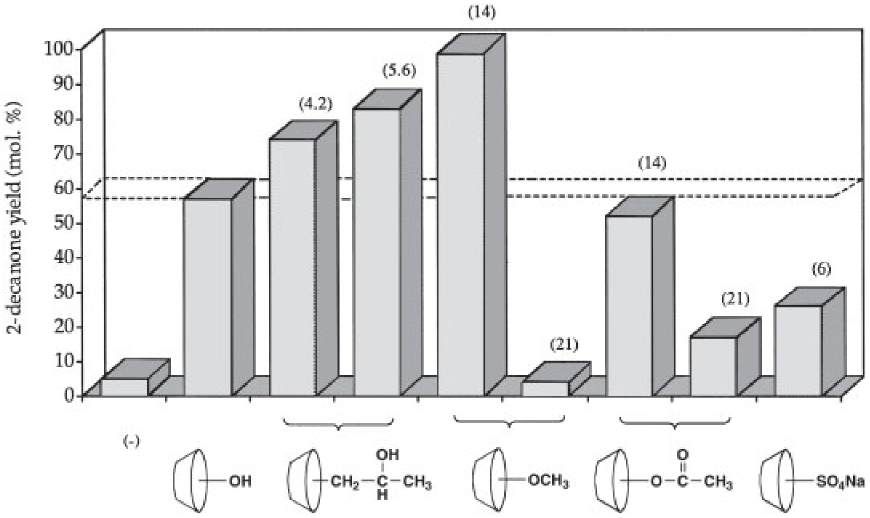


Fig. 1 Effect of the nature of the substituent group and of the substitution degree of the cyclodextrin on 2-ketone yields. The value in bracket indicates the number of functionalized hydroxy group. $PdSO_4$ (0.86 mmol), $CuSO_4$ (10 mmol), $H_9PV_6Mo_6O_{40}$ (10 mmol), DMCD (1 mmol), water (30 mL), 1-alkene (40 mmol), 6 hours, T: 80 °C, PO_2: 1 bar.

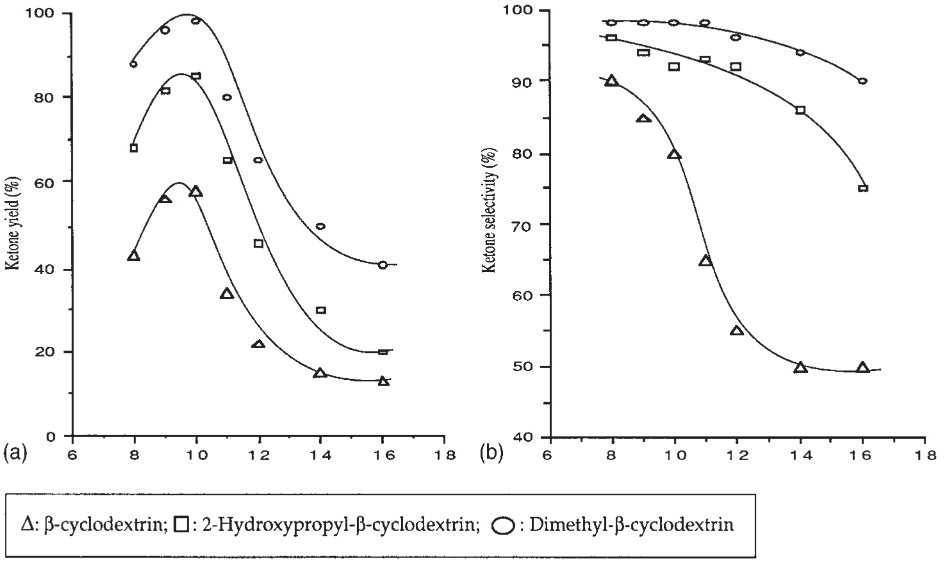


Fig. 2 Effect of chain length of alkene on 2-ketone yield and selectivity after 6 hours of reaction in the presence of various cyclodextrins. $PdSO_4$ (0.86 mmol), $CuSO_4$ (10 mmol), $H_9PV_6Mo_6O_{40}$ (10 mmol), DMCD (1 mmol), water (30 mL), 1-alkene (40 mmol), 6 hours, T: 80 °C, PO_2: 1 bar.

6.4.2.2
Conclusions

Although the Wacker-type oxidation of alkenes has been applied for more than four decades using ethylene as substrate, processes involving higher alkenes are still the subject of investigations because of their poor solubility in water. This problem can be overcome using different approaches. Particularly interesting in this context is the inverse-phase transfer system using host molecules such as cyclodextrins which, upon careful choice of the substituent, avoid the isomerization into internal alkenes. This recent concept proves so far that new ideas may lead to major improvements in a well-known and intensively studied system. For industrial applications, it is probable that the activities obtained so far with higher alkenes should be increased by at least one order of magnitude while keeping the same selectivity: this may be the challenge of this reaction in the near future.

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6.4.3
Methyltrioxorhenium(VII) as an Oxidation Catalyst

Fritz E. Kühn, Wolfgang A. Herrmann

6.4.3.1
Introduction

Even by 1989, the importance of rhenium compounds in oxidation catalysis was still minimal [1]. This picture has changed dramatically since organorhenium(VII) oxides, especially the water-soluble methyltrioxorhenium (MTO, **1**), have proven to be excellent catalyst precursors for a surprisingly broad variety of processes, most notably for a variety of oxidation reactions [2, 3]. This article summarizes the behavior of MTO and its peroxo derivatives in the presence of water and under catalytic condition in aqueous systems, particular attention being given to the most recent findings.

6.4.3.2
Synthesis of Methyltrioxorhenium(VII)

MTO was first synthesized in 1979 in a quite time-consuming (weeks) and low-scale (milligrams) synthesis [4]. The breakthrough towards possible applications came only about 10 years later, when the first efficient synthetic route, starting from dirhenium heptoxide and tetramethyltin, was reported [5]. The major drawback of this otherwise quite good approach is the loss of half of the Re due to the formation of the unreactive trimethylstannyl perrhenate or zinc perrhenate, respectively. An improvement was the use of mixed esters of perrhenic and trifluoroacetic acid, avoiding the loss of rhenium [6]. This route reached the laboratory pilot-plant stage for MTO in 1999 [7]. A further modification of the synthesis allows avoidance of the moisture-sensitive dirhenium heptaoxide as a starting material, using instead Re powder or perrhenates [8, 9]. This method is of particular interest since it allows recyclization of the catalyst decomposition products from reaction solutions. Scheme 1 gives an overview of this latter method.

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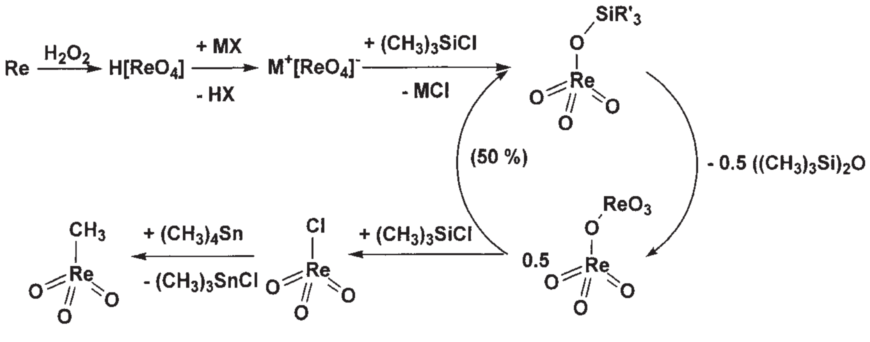

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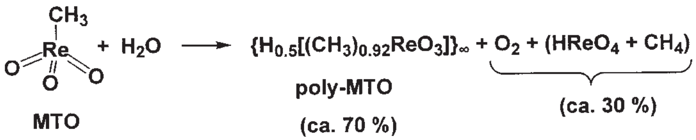
Scheme 1

6.4.3.3
Behavior of Methyltrioxorhenium in Water

MTO hydrolyzes rapidly in basic aqueous solutions and much more slowly in acidic media. At low concentrations ($\sigma_{\mathrm{MTO}} < 0.008$ M) the formation of methane gas and perrhenate is detected. The decomposition of MTO seems to be irreversible. At higher concentrations a second reaction, a faster reversible polymerization–precipitation, takes place to yield a golden-colored solid of the empirical composition $\{H_{0.5}[(CH_3)_{0.92}ReO_3]\}$ (poly-MTO) in about 70% yield (Eq. 1) [10–15].



$$CH_3ReO_3 + H_2O \longrightarrow \underset{\substack{\text{poly-MTO} \\ \text{(ca. 70 \%)}}}{\{H_{0.5}[(CH_3)_{0.92}ReO_3]\}_\infty} + \underbrace{O_2 + (HReO_4 + CH_4)}_{\text{(ca. 30 \%)}} \qquad (1)$$

The reaction follows first-order reversible kinetics. The rate of polymerization–precipitation is independent of the concentration of H^+, and the reaction does not occur in the presence of oxidants [10]. The structure of the crystalline domains of poly-MTO can be described as double layers of corner-sharing CH_3ReO_5 octahedra (AA′) with intercalated water molecules (B) in a ...AA′BAA′... layer sequence. It adopts the three-dimensional extended ReO_3 motif in two dimensions as a $\{ReO_2\}_n$ network. The oxo groups of two adjacent layers are opposite each other, with an intercalated water layer. Hydrogen bridges are formed between the oxo groups and the water molecules, enhancing the structure of the polymer. The double layers are interconnected by van der Waals attractions generated by the nonpolar methyl groups, which are orientated inside the double layer (Figure 1). These structural features explained the observed lubricity of poly-MTO. Substoichiometry with respect to the CH_3/Re ratio of 4.6 : 5 and partial reduction by extra hydrogen equiva-

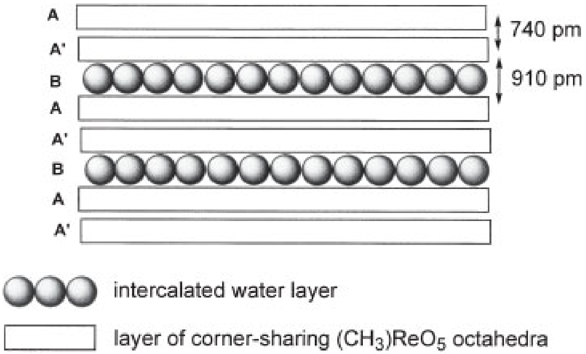


Fig. 1 Structure of crystalline domains of poly-MTO.

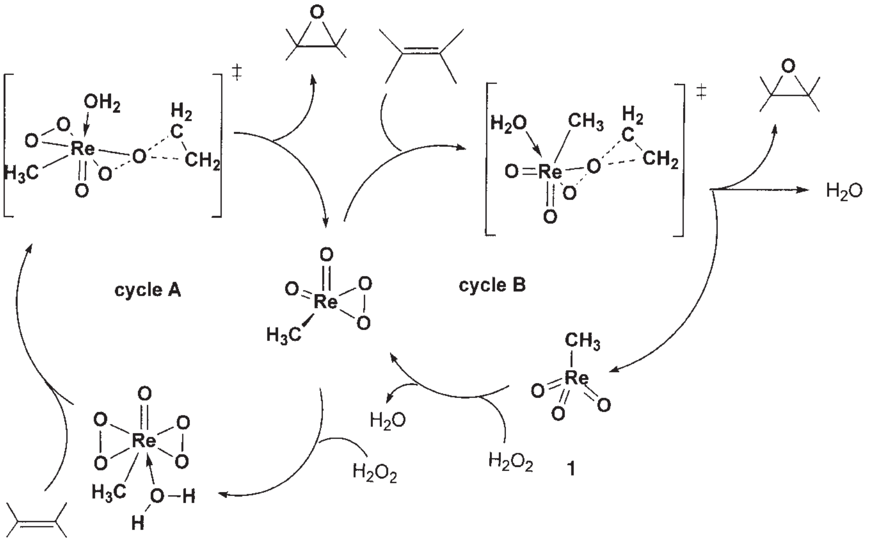
lents are responsible for a high electric conductivity of poly-MTO [13, 14]. Poly-MTO also contains amorphous areas with a defect stacking of double layers and with a smaller content of water. The conductivity of poly-MTO is attributed to occasional demethylation and to the inclusion of extra hydrogen in the lattice. A theoretical study of MTO dimers, trimers, and tetramers has been performed. The tetramer already provides a good model for the interpretation of the IR and Raman spectra of poly-MTO and assigns the bridging oxygen atoms as the best candidates to bind the excess protons present in poly-MTO [16]. Terminal oxygens of monomeric MTO seem to be easily available for the formation of bridging oxygens [17].

Poly-MTO undergoes similar reactions and catalytic processes as MTO in the presence of proper reaction partners (e.g., H_2O_2) [11]. The polymeric structure of the polymer is destroyed during the reaction and the reactions lead to monomeric reaction products, in analogy to the products obtained by reaction with monomeric MTO. Poly-MTO has even been suggested as a convenient storage form of MTO.

6.4.3.4
Catalyst Formation and Applications in Alkene Epoxidation

The catalytic activity of MTO in the epoxidation of alkenes was noticed soon after it became accessible in greater amounts and attracted significant interest in the following years [18]. An important breakthrough in the understanding of the role of MTO in oxidation catalysis was the isolation and characterization of the reaction product of MTO with excess H_2O_2, i.e., a bisperoxo complex of stoichiometry $(CH_3)Re(O_2)_2O \cdot H_2O$ [19]. This reaction takes place in any organic solvent or water. The structures of $(CH_3)Re(O_2)_2O \cdot H_2O$ and $(CH_3)Re(O_2)_2O \cdot (O{=}P\text{-}[N(CH_3)_2]_3)$ (X-ray diffraction) were determined; the structure of ligand-free complex $(CH_3)Re(O_2)_2O$ is known from the gas phase [19, 20].

Experiments with the isolated bis(peroxo) complex $(CH_3)Re(O_2)_2O \cdot H_2O$ have shown that it is an active species in alkene epoxidation catalysis and several other



Scheme 2

catalytic reactions [19, 20]. In-situ experiments show that the reaction of MTO with one equivalent of H_2O_2 leads to a monoperoxo complex of the likely composition $(CH_3)Re(O_2)O_2$ [21, 22]. $(CH_3)Re(O_2)O_2$ has never been isolated and exists only in equilibrium with MTO and $(CH_3)Re(O_2)_2O \cdot H_2O$. The monoperoxo complex is also catalytically active in oxidation processes. Kinetic experiments indicate that the rate constants for the transformation of most substrates into their oxidation products by catalysis with the mono- and bisperoxo complexes are of a comparable order of magnitude [21–23]. These results are supported by density functional calculations [24–26]. The transition states in the alkene epoxidation process starting from $(CH_3)Re(O_2)O_2$ and $(CH_3)Re(O_2)_2O \cdot H_2O$ are not different enough in energy to exclude one of these two catalysts totally from the catalytic process. The activation parameters for the coordination of H_2O_2 to MTO have also been determined. They indicate a mechanism involving nucleophilic attack. The protons lost in converting H_2O_2 to a coordinated O_2^{2-} ligand are transferred to one of the terminal oxygen atoms which remains on the Re as the aqua ligand L. The rate of this reaction is not pH-dependent [27].

Two catalytic pathways for the alkene epoxidation may be described, depending on the concentration of the hydrogen peroxide used. If a solution containing 89% H_2O_2 is used, only $(CH_3)Re(O_2)_2O \cdot H_2O$ appears to be responsible for the epoxidation activity (Scheme 2, cycle A). When a solution of 30 wt.% H_2O_2 or less is used, the monoperoxo complex, $(CH_3)Re(O_2)O_2$, also takes part in the epoxidation process and a second catalytic cycle is involved as shown in Scheme 2, cycle B. For both cycles, a concerted mechanism is suggested in which the electron-rich double bond of the alkene attacks a peroxidic oxygen of $(CH_3)Re(O_2)_2O \cdot H_2O$. It has been inferred from experimental data that the system may involve a spiro arrangement [24–29].

The most important drawback of the MTO-catalyzed process is the concomitant formation of diols instead of the desired epoxides, especially in the case of more sensitive substrates [30]. It was quickly detected that the use of Lewis base adducts of MTO significantly decreases the formation of diols, due to the reduced Lewis acidity of the catalyst system. However while the selectivity increases, the conversion decreases [30–32]. It was found that biphasic systems (water phase/organic phase) and addition of a significant excess of pyridine as a Lewis base not only hamper the formation of diols but also increase the reaction velocity in comparison to MTO as catalyst precursor [33, 34]. Additionally it was shown that 3-cyanopyridine and especially pyrazole as Lewis bases are even more effective and less problematic than pyridine itself, whereas pyridine *N*-oxides are less efficient [35–37]. From *in situ* measurements under one-phase conditions it was concluded that both electronic and steric factors of the aromatic Lewis base involved play a prominent role during the formation of the catalytically active species. The Brønsted basicity of pyridines lowers the activity of hydronium ions, thus reducing the rate of opening the epoxide ring [38]. MTO forms trigonal-bipyramidal adducts with monodentate *N*-bases and (distorted) octahedral adducts with bidentate Lewis bases [39, 40]. The monodentate Lewis-base adducts of MTO react with H_2O_2 to form mono- and bisperoxo complexes analogous to those of MTO, but coordinated by one Lewis base molecule instead of H_2O. From the Lewis base–MTO complexes to the bisperoxo complexes a clear increase in electron deficiency at the Re center can be observed by spectroscopic methods. The activity of the bisperoxo complexes in alkene epoxidation depends on the Lewis bases, the redox stability of the ligands, and the excess of Lewis base used. The peroxo complexes of the MTO Lewis bases are, in general, more sensitive to water than MTO itself [40]. Furthermore, in the presence of alkenes which are not readily transformed to their epoxides, 2,2′-bipyridine can be oxidized to its *N*-oxide by the MTO/H_2O_2 system [41]. Low to moderate stereoinduction values (up to about 40% *ee* with conversions of around 10% at $-5\,^{\circ}C$ reaction temperature) can be achieved when prochiral alkenes, e.g., *cis*-β-methylstyrene or α-pinene, are epoxidized with chiral amine adducts of MTO [42].

MTO has also been successfully applied as an alkene epoxidation catalyst in ionic liquids [43, 44]. The values of the rate constants for the formation of the peroxo complexes of MTO have been found to be highly dependent on the concentration of water in the solvent. Ionic liquids can behave like organic solvents and aqueous solutions of high salt concentrations.

Alternative strategies to improve MTO-catalyzed oxidations have made use of host–guest inclusion chemistry [45–47]. It was found that a urea/hydrogen peroxide (UHP) complex is a very effective oxidant in heterogeneous alkene epoxidations and silane oxidations catalyzed by MTO [45]. Even steroidal dienes, uracil, and purine have been successfully oxidized by the MTO/H_2O_2–urea system [46, 47]. The oxidation of the plasmid pBG1 has also been reported as the first example of double-strand DNA cleavage mediated by the catalytic system MTO/H_2O_2 [47].

A particularly important role of water and pH values becomes evident when one looks at the catalyst deactivation processes. Whereas MTO and its peroxo complexes are quite stable in acidic media, basic conditions lead to significantly reduced catalyst stabilities. In spite of the extraordinarily strong Re–C bond [48], characteristic of MTO, the cleavage of this bond plays a prominent role in the decomposition processes of these complexes [10, 49–51]. Concerning MTO, the full kinetic pH profile for the base-promoted decomposition to CH_4 and ReO_4^- was examined. Spectroscopic and kinetic data give evidence for mono- and dihydroxo complexes of formulae $CH_3ReO_3(OH^-)$ and $CH_3ReO_3(OH^-)_2$ prior to and responsible for the decomposition process. In the presence of hydrogen peroxide, $(CH_3)Re(O_2)O_2$ and $(CH_3)Re(O_2)_2O \cdot H_2O$ decompose to methanol and perrhenate with a rate that is dependent on $[H_2O_2]$ and $[H_3O]^+$. The complex peroxide and pH dependencies are explained by two possible pathways: attack of either hydroxide on $(CH_3)Re(O_2)O_2$ or HO_2^- on MTO. The bisperoxo complex decomposes much more slowly to yield O_2 and MTO [51]. Thus critical concentrations of strong nucleophiles have to be avoided; a large excess of hydrogen peroxide stabilizes the catalyst. It turned out to be advantageous to keep the steady-state concentration of water during the oxidation reaction as low as possible to depress catalyst deactivation.

In summary, epoxidations with the MTO/H_2O_2 display several advantages. MTO is easily available, it is active in low concentrations of both MTO (0.05 mol%) and H_2O_2 (< 5 wt%), and it works with a broad temperature range (-40 to $+90\,^\circ$C) and is stable in water in acidic conditions as well as in basic media in special cases. Furthermore, the MTO/H_2O_2 system works in a broad variety of solvents, ranging from highly polar solvents (e.g., nitromethane, water) to solvents with low polarity (e.g., toluene). However, the reactions between MTO/H_2O_2 and alkenes are approximately one order of magnitude faster in semi-aqueous solvents (e.g., 85% H_2O_2) than in methanol. The rate constants for the reaction of MTO/H_2O_2 with aliphatic alkenes correlate closely with the number of alkyl groups on the alkene carbons. The reactions become significantly slower when electron-withdrawing groups such as –OH, –CO, –Cl, and –CN are present in the substrates.

A major advantage of MTO is that it does not decompose hydrogen peroxide. This is in striking contrast to many other oxidation catalysts. Turnover numbers of up to 2500 mol product/mol catalyst (reaction conditions: 0.1 mol% MTO, 5 mol% pyrazole) and TOFs of up to 14 000 mol product/mol catalyst per hour have been reported, with typical MTO concentrations of 0.1–1.0 mol%. However, these impressive results have only been reached in perfluorinated alcohols as solvents with cyclohexene as substrate [52].

High selectivity (epoxide vs. diol) can be adjusted by temperature control, trapping of water, or the use of certain additives, such as aromatic Lewis-base ligands, which additionally accelerate the epoxidation reactions. Selectivities of $> 95\%$ can be reached.

In comparison to the standard system for epoxidation which uses *m*-chloroperoxybenzoic acid as oxidizing agent, the MTO/H_2O_2/aromatic Lewis-base system displays several advantages: (1) it is safer but equal in price; (2) due to the suppression of epoxide ring opening, it is much broader in scope of applications; (3) its selectivity is higher; (4) it is more reactive, requires less solvent, the product work-up is easier, and the only byproduct formed is water.

6.4.3.5
Other Oxidation Reactions

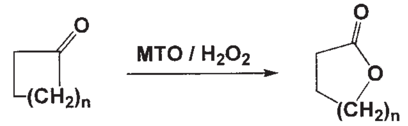
6.4.3.5.1
Oxidation of Conjugated Dienes, Allylic Alcohols, and Alkynes

Special cases closely related to the topic discussed above are the oxidation of conjugated dienes and the epoxidation of allylic alcohols. Conjugated dienes are oxidized to epoxides or diols, respectively, in the presence of water with the MTO/H_2O_2 system. The biphasic system MTO/H_2O_2/CH_2Cl_2 oxidizes 1,4-polybutadiene efficiently [53, 54]. The extension of epoxidation (10–50%) can be modulated by the amount of oxidant added, without significant change in the molecular weight of the polymer [54]. Allylic alcohols are epoxidized to the epoxy alcohols by hydrogen peroxide in the presence of MTO [32, 55, 56]. Provided that no acid is added, the product is mostly epoxide, accompanied by minor amounts of triol resulting from acid-catalyzed ring opening. With added acid the triol is obtained. The 1,3-transposition of allylic alcohols, also catalyzed by MTO, is strongly inhibited, however, by the presence of traces of water [57] and therefore not discussed in this review. The oxidation of aromatic compounds [58–60] by the MTO/H_2O_2 system is also inhibited by water and therefore not described here.

The MTO/H_2O_2 system also catalyzes the oxidation of both internal and terminal alkynes. It provides a significantly cleaner and safer method of alkyne epoxidation than the oxidation by organic peracids [61]. Internal alkynes yield carboxylic acids and α-diketones. Rearrangement products were observed only for aliphatic alkynes. Terminal alkynes give carboxylic acids, derivatives thereof, and acids as the major products.

6.4.3.5.2
Baeyer–Villiger Reaction and Related Conversions

γ-Butyrolactones are obtained in good yields and high regioselectivity from the corresponding cyclobutanones on oxidation with H_2O_2 catalyzed by MTO. Lactonization was found to be chemoselective in the presence of double bonds, aromatic rings, or chlorine substituents [62]. It has been shown that the MTO/H_2O_2 system is also catalytically active in the Baeyer–Villiger oxidation (Eq. 2) of ketones [63] and the Baeyer–Villiger rearrangement of flavone derivatives to produce 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-ones and quinone derivatives [64].



(2)

It is somewhat surprising that the MTO/H_2O_2 system presents this activity since these oxidations involve nucleophilic attack at the carbonyl group, which is in contrast to all the preceding examples where the substrates attacked the electrophilic Reperoxo complexes, e.g., in alkene epoxidation. Nevertheless, the bisperoxo complex of MTO reacts stoichiometrically with cyclobutanone in the absence of H_2O_2. This reversed behavior may be due to substrate binding to rhenium. The unsymmetrical geometry of the bisperoxo complex, displaying a polarity within the peroxo ligands, may also be responsible for the observed behavior.

Low H_2O_2 concentrations are sufficient and no H_2O_2 decomposition is observed at temperatures up to 70 °C. This is an advantage of the catalytic MTO/H_2O_2 system over the known transition metal Baeyer–Villiger catalysts containing V, Mo, Mn, or Os. TOFs of 18 000 [mol/mol cat. per hour] are obtained for cyclobutanone with the MTO/H_2O_2 system, but in other cases TONs up to 100 are usual. Cycloketones can be converted into lactones even below room temperature (15 °C) by diluted hydrogen peroxide (10 wt.%).

MTO has been shown to catalyze the H_2O_2-mediated oxidation of cyclic β-diketones to carboxylic acids. Most of the diketones studied were oxidized efficiently at conversions of $> 80\%$, and the acid products reached quantitative yields in most cases. A significant excess of nearly 6 equivalents of H_2O_2 was employed for these reactions in a 1:1 acetonitrile/water solution at room temperature [65].

6.4.3.5.3
Oxidation of Sulfur Compounds

Organic sulfides can be oxidized to the corresponding sulfoxides by hydrogen peroxide in the presence of MTO [66–71]. Using ethanol as solvent, the MTO/H_2O_2 system can be used to oxidize dialkyl, diaryl, and alkyl aryl sulfides to sulfoxides ($R_2S/H_2O_2 = 1:1.1$) or sulfones ($R_2S/H_2O_2 = 1:2.2$) with excellent yields and selectivities even in the presence of oxidatively sensitive functions on the sulfide side chain. A high selectivity of sulfoxide over sulfone was achieved, except in the presence of water, which enhanced sulfone formation [66, 67]. The rate constants for the oxidation of sulfoxides to sulfones are significantly smaller than for the oxidation of sulfides to sulfoxides, and the reaction rate is negligible without a catalyst

[68, 69]. MTO can also be used in the oxidation of sulfides with the water-free system urea–hydrogen peroxide as oxidant in acetonitrile. Partial enantioselective oxidation of methyl phenyl sulfide was observed with MTO in the presence of a (+)-camphor-derived pyrazine carboxylic acid [70]. Thiophenes are oxidized to sulfones by way of sulfoxide intermediates. The rate constants for the oxidation of thiophenes are two to four orders of magnitude smaller than those for the oxidation of aliphatic sulfides [71]. MTO in conjunction with hydrogen peroxide also provides a convenient method for the oxidation of thioether Fischer carbene complexes to their respective phenylsulfinyl derivatives [72]. Furthermore, the oxidation of a (thiolato)cobalt(III) complex by MTO and H_2O_2 in aqueous solutions of dilute perchloric acid has been reported [73]. Thiobenzophenones and thiocamphor are oxidized with the MTO/H_2O_2 system to sulfines ($Ar_2C{=}S{=}O$) and in a second step via transient sultine (from epoxidation of the C=S bond) to sulfur monoxide. The latter compound is oxidized to SO_2 [74].

6.4.3.5.4
Oxidation of Anilines, Amines, Phosphines, Arsines, and Stibines

A broad range of aromatic and aliphatic amines are readily oxidized to their corresponding *N*-oxides using the MTO/H_2O_2 catalytic system [75–80]. The oxidation of arylamines proceeds ca. 50 times faster than without catalyst. Nitrosobenzene is obtained by the oxidation of aniline, while the oxidation of 4-substituted *N*,*N*-dimethylanilines yields the *N*-oxide as the only product. It has been found that electron withdrawing substituents present on the substrate inhibit the reaction. Kinetic results suggest that both the mono- and the bisperoxo complexes of MTO are involved in the oxidation process. In general, the reactions are facile and high yielding at or below room temperature. Furthermore, a broad variety of aromatic and aliphatic secondary amines are oxidized to the corresponding *N*-oxides. The amines are converted to the corresponding hydroxylamines prior to transformation to the nitrones in very good yields. The hydroxylamine formation is rate determining. Both H_2O_2 and the urea–hydrogen peroxide complex can be used together with MTO. Benzylamines are selectively oxidized to oximes. Primary amines are oxidized to nitro compounds by MTO catalysis. Recently the application of the MTO/H_2O_2 system in the synthesis of verongamine and purealidin N, tyrosine-derived marine sponge metabolites, has been reported [81].

Tertiary phosphines, triarylarsines and triarylstibines are converted to their oxides R_3EO ($E = P$, As, Sb) by MTO/H_2O_2. The kinetic data support a mechanism involving nucleophilic attack of the substrate at the rhenium peroxides [82]. In the absence of peroxides, MTO also catalyzes the oxidation of tertiary phosphines to phosphine oxides [83–85]. The oxygen source in this case in sulfoxides which are, in turn, deoxygenated. It is assumed that MTO forms a sulfoxide adduct first which is then deoxygenated by triphenylphosphine, resulting in the formation of MTO and the sulfide. Espenson et al. demonstrated that Tol_3P is oxidized to

Tol_3PO in the presence of 1% MTO. In the absence of oxygen, the concentration of Tol_3PO seems to level off at ca. 50% conversion, suggesting that the rhenium catalyst is deactivated over time. In the presence of oxygen, much more Tol_3PO is formed, suggesting that most of the oxygen found in Tol_3PO derives from molecular oxygen. With an excess of MTO the reaction goes to completion in an aerobic environment, the reaction being stoichiometric and MTO not recovered. Instead the MTO has been reduced to methyl dioxorhenium(V).

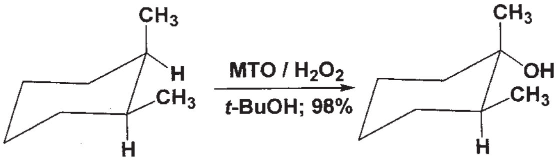
The activation of oxygen in systems containing MTO has been assumed to arise from its reaction with a dioxorhenium(V) complex, giving the peroxo complex that rapidly converts phosphine to phosphine oxide [84].

6.4.3.5.5
Oxidation of Halides

The reactions between hydrogen peroxide and chlorine and bromine ions in aqueous acidic solutions, ordinarily very slow, are strongly catalyzed by both the mono- and bisperoxo complexes of MTO. The chloride oxidation steps are three to four orders of magnitude slower than the corresponding bromine oxidation steps. The catalyzed reactions are about 10^5 times faster than the uncatalyzed reactions under similar conditions. In a first step HOX is formed, then HOX reacts with X^- to form X_2. When H_2O_2 is used in excess the reaction yields O_2 [86–88]. The strong catalytic effect of chloride anions together with MTO on Green S dye oxidation by hydrogen peroxide has been observed recently [89]. The catalytic effect is estimated to be at least 2000-fold, compared to the uncatalyzed reaction, for an MTO concentration of $3 \cdot 10^{-6}$ mol/L and a Cl^- concentration of 0.1 mol/L at pH 13.

6.4.3.5.6
Oxidation of C–H Bonds

MTO/H_2O_2 also catalyzes the insertion of oxygen into a variety of activated and unactivated C–H bonds. Alcohols or ketones are formed (Eq. 3). In the case of tertiary substrates alcohols are obtained as products. Suitable substrates proved that the reaction is stereospecific with retention of configuration. The reaction temperatures range from 40 to 80 °C and nearly quantitative yields have been obtained in several cases. However, the reaction times are generally longer than those used for most epoxidations, requiring between 10 and 72 h [90–92]. The reaction can be accelerated by the addition of pyrazine-2-carboxylic acid, which also increases the total yield.



(3)

6.4.3.6
Perspectives

Methyltrioxorhenium(VII) (MTO), a water-soluble and water-stable metal alkyl, has become the most versatile oxidation catalyst in organic chemistry, with new or improved applications still being published quite frequently [93–99]. The secret of its outstanding reactivity is the thermally and chemically extremely stable rhenium–methyl bond. In addition, the CH_3 group requires only little space, so that the heptavalent rhenium can exploit its pronounced Lewis acidity with regard to incoming substrates. It is striking that destruction of the methyl-to-rhenium bond effects a complete breakdown of most of the reported reactions, e.g., catalytic epoxidation. It is thus clearly the organometallic moiety that guarantees the unique reactivity of MTO. During the last decade MTO has proved to be an extremely useful catalyst in organic transformations for lab chemistry and it now stands on the verge of industrial application.

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6.5
Carbonylation Reactions

Matthias Beller, Jürgen G. E. Krauter

6.5.1
Introduction

Apart from hydroformylation, the potential advantages of two-phase catalysis for other carbonylation reactions has not been thoroughly evaluated. Despite considerable industrial interest in synthesis using carbon monoxide as low-cost feedstock, so far only a few examples of carbonylation reaction under biphasic conditions have been described. Examples include reactive carbonylations; carbonlyation of aryl-, benzyl- and allyl-X ($X = Br$, Cl), and hydrocarboxylations. The main part of this section focuses on synthetic developments of new two-phase processes using water-soluble catalyst systems. Other biphasic reactions using a hydrophilic solvent, e.g., water, only as reactand or using phase-transfer conditions [1] are not recognized as biphase catalysis, and therefore are only treated in special cases.

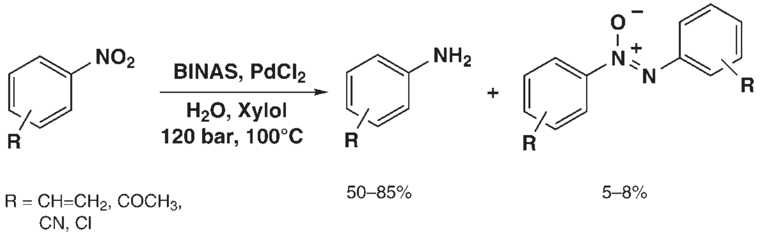
6.5.2
Reductive Carbonylations

Metal-catalyzed reductive carbonylation of nitro aromatics using carbon monoxide has been the subject of intensive investigation in recent years because of the commerical importance of amines, urethanes, and isocyanates [2]. However, catalyst efficiency is still an unsolved problem for industrial applications. In this respect a biphasic reaction medium could offer interesting possibilities regarding the ease of catalyst recycling. Thus, palladium catalysts have been applied in the presence of water-soluble ligands such as TPPTS (sodium *m*-trisulfonated triphenylphosphine) and BINAS (**1**) for the carbonylation of substituted nitro aromatics (Eq. 1). Interestingly, the nitro group can be selectively reduced to an amino group, even in the presence of halide substituents or a vinyl group [3]. Thus, *m*-nitrostyrene yielded 3-aminostyrene in 50% isolated yield.

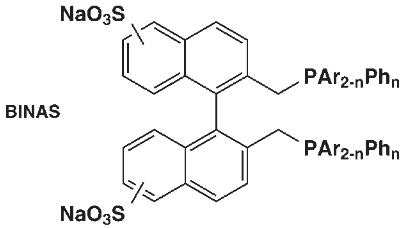
The reduction of nitrobenzene to aniline using water as solvent without the addition of any base or ligand is also reported with $[Rh(CO)_4]^-$ as catalyst [4] (Eq. 2).

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

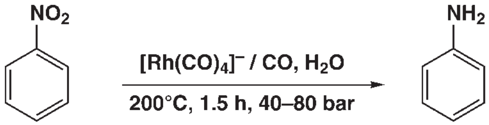
ISBN: 3-527-30712-5



(1)



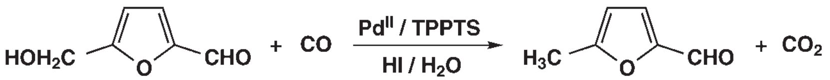
(1) Ar = m–C_6H_4–SO_3Na



(2)

Best turnover numbers (TON up to 1000) were achieved using $PPN^+[Rh(CO)_4]^-$ ($PPN^+ = (Ph_3P)_3N^+$). In general, the conversion is increased by the addition of tetraalkylammonium salts, such as $[Et_3NCH_2Ph]^+Cl^-$, which act as phase-transfer agent, whereas no addition of ammonium salt is necessary if the PPN^+ catalyst is used. From this observation it is deduced that the catalysis takes place in the organic phase. Recycling of the catalyst by simple phase separation is *not* possible because the catalyst is dissolved after the reaction partly in the water and partly in the organic phase.

Another reductive carbonylation in biphasic media was developed by Sheldon and co-workers [5]. While investigating the carbonylation of 5-hydroxymethylfurfural it was found that the benzylic hydroxy group can be reduced to give the corresponding methyl group (Eq. 3). The homogeneously catalyzed deoxygenation reaction takes place in acidic aqueous medium in the presence of a water-soluble palladium/TPPTS catalyst and strong coordinating anions.

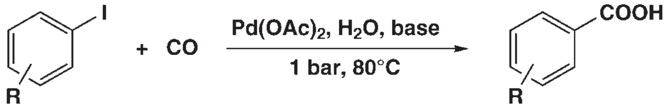


(3)

6.5.3
Carboxylation of C–X Derivatives

The hydroxycarbonylations (carboxylations) of alkyl, aryl, benzyl and allyl halides are from a retrosynthetic and mechanistic standpoint closely related. This type of reaction is widely used in organic synthesis [6], although a stoichiometric amount of salt by-product makes these methods less attractive on a large scale. The use of water-soluble catalysts for carbonylation of organic halides was scarcely studied in the past. Up to now palladium, cobalt, and nickel compounds in combination with water-soluble ligands have been used as catalysts for various carboxylations.

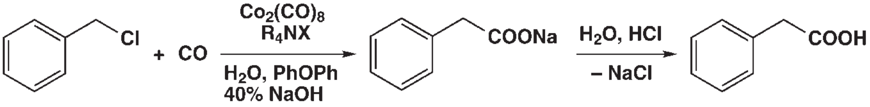
Beletskaya and co-workers have shown that the reaction is possible in neat water as solvent. Thus, aryl iodides have been carbonylated with various palladium salts lacking phosphine ligands as depicted in Eq. (4) [7]. Although this reaction is not a truely biphasic process the results are remarkable regarding catalyst efficiency. Thus, a maximum turnover number (TON) of 100 000 was described (R = *p*-COOH, quantitative yield after 6 days). Quite different is the performance of a water-soluble palladium phosphine catalyst described by Kalck et al. [8]. The hydrocarboxylation of the less activated bromobenzene with either Pd(TPPTS)$_3$ or a mixture of Pd(OAc)$_2$ and TPPTS proceeds only sluggishly (turnover frequency TOF $< 10\ h^{-1}$). In order to prevent decomposition of palladium an excess of phosphine has to be used. At least 15 equiv. of ligand is necessary to prevent formation of metallic palladium. Because of rapid oxidation of the ligand the re-use of the water phase is not possible.



(4)

R e.g.: H, *p*-NO$_2$, *p*-MeO, *p*-NH$_2$, *p*-OH

The carbonylation of chloroarenes has been described by Alper and Grushin [27] and Jenner and Bentaleb [28]. While the former showed that square-planar complexes of divalent palladium, [L$_2$PdCl$_2$], where L = tertiary phosphine, are active catalysts for the biphasic carbonylation of aromatic halides, including chloroarenes (when L = tricyclohexylphosphine), to the corresponding carboxylic acids, the latter demonstrated that chloroarenes can be converted into aromatic acids via catalytic reaction with aqueous methyl formate under biphasic conditions. [PdCl$_2$(PCy$_3$)$_2$] was the most efficient catalyst. The addition of [Ru$_3$(CO)$_{12}$] and ammonium formate improved yield and selectivity of the carbonylation reaction. The mechanism should involve oxidative addition of the C–Cl bond to a zero-valent Pd species followed by CO insertion. However, the palladium catalyst may also directly activate methyl formate. Compared to other carbonylations of aryl-Hal compounds the procedure is quite convenient (no solvent, no initial pressurization) [27].

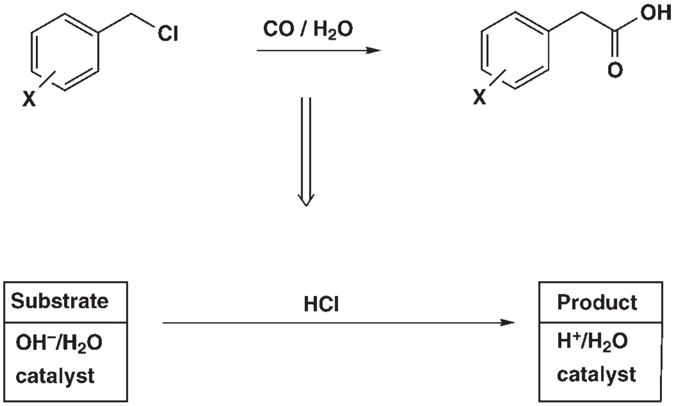


Scheme 1 Carboxylation of benzyl chloride.

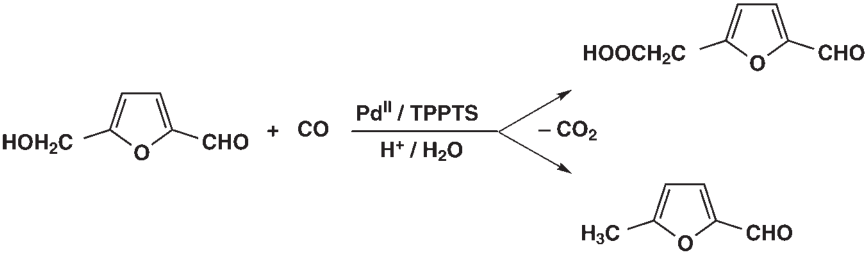
Apart from aryl–X derivatives, and more interestingly from an industrial point of view, metal-catalyzed carbonylations of substituted benzyl halides to give the corresponding phenylacetic acids were investigated [9]. Two-phase systems are applied with the catalyst and substrate being dissolved in the organic phase and the product formed is dissolved in an excess of alkaline aqueous solution. Despite significant disadvantages such as indispensable addition of phase-transfer agents and additional salt as by-product, the carbonylation of benzyl chloride to give phenylacetic acid for use in perfume constituents and pesticides has been reported to be practiced on a commercial scale by Montedison [10]. The conversion takes place in the presence of 5–10 mol% of $Co_2(CO)_8$ and a benzyltrialkylammonium surfactant in a biphasic medium employing diphenyl ether and aqueous 40% NaOH as solvents (Scheme 1).

Other metal catalysts which have been utilized for biphasic carbonylation of benzylic halides to carboxylic acids under phase-transfer conditions, besides cobalt carbonyl [11], include palladium(0) complexes [12] and water-soluble nickel cyanide complexes [13]. Although not investigated in detail, it must be assumed that catalysis takes place in all these reactions in the organic phase.

However, by the use of the water-soluble ligand $Ph_2P(m\text{-}C_6H_4SO_3Na)$ (TPPMS), a palladium catalyst which is active in the water phase is formed [14]. Nevertheless, the addition of surfactants such as $n\text{-}C_7H_{15}SO_3Na$ is effective in accelerating this reaction (TON = 95; TOF ca. 10 h^{-1} at 30 °C) [15]. This effect is attributed not to a simple surface activation by the sulfonate but to counterphase transfer catalysis [16]. Unfortunately, under the reaction conditions described the product is also soluble to a large extent in the water phase. Thus, the reaction/catalyst separation is difficult again. The same applies to a catalyst system using a ruthenium(III)–EDTA complex [17]. Some years ago, we described a new carbonylation process for substituted benzyl chlorides on the basis of water-soluble palladium catalysts which are preferable to other known systems with respect to catalytic efficiency [18]. Here, the palladium-catalyzed, atmospheric-pressure carboxylation of substituted benzylic chlorides occurs readily in an aqueous sodium hydroxide/organic solvent two-phase system, giving phenylacetic acids (Scheme 2). The catalyst, consisting of a palladium salt and a water-soluble sulfonated phosphine, is dissolved in an alkaline aqueous solution. During the reaction the corresponding phenylacetic acid is formed directly by carboxylation and *in situ* neutralization in 80–94% yield. TONs up to 1500 and TOFs up to 135 h^{-1} are reached. The catalyst system could be re-used three times without significant loss of activity.



Scheme 2 Carboxylation of substituted benzyl chlorides.



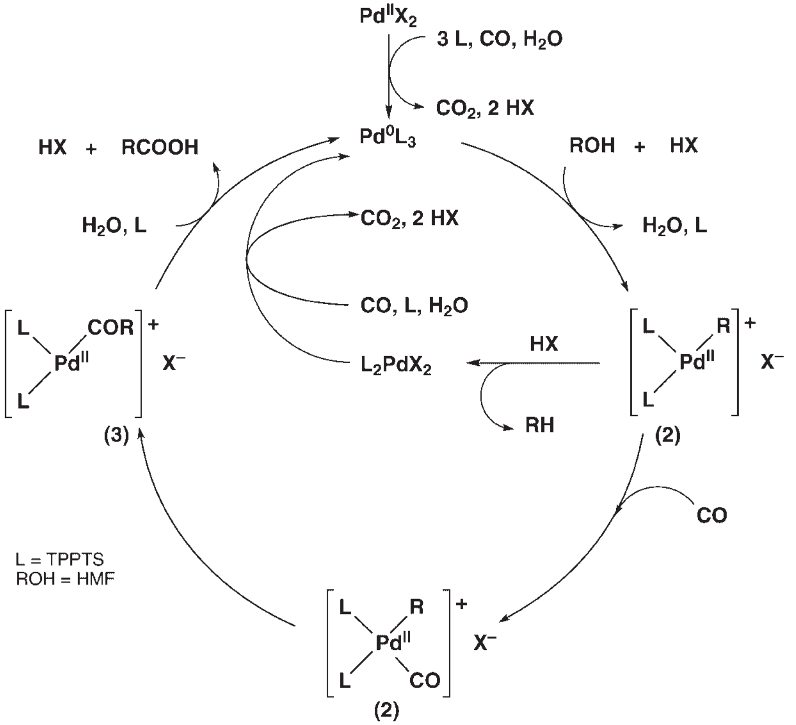
Scheme 3 Carboxylation of 5-hydroxymethylfurfural.

Based on the palladium-catalyzed carbonylation of benzylic halides Sheldon and co-workers investigated the functionalization of 5-hydroxymethylfurfural (HMF) to 5-formylfuran-2-acetic acid (FFA) in aqueous medium in the presence of a water-soluble palladium/TPPTS catalyst (Scheme 3) [5]. Here, the hydroxy group displays similar reactivity under acidic conditions compared with benzylic halides.

Both selectivity and activity of HMF carbonylation are influenced by the TPPTS/Pd molar ratio, maximum efficiency being observed for a TPPTS/Pd ratio of 6 : 1. Interestingly, acids with weakly or noncoordinating anions afford mainly carbonylation, those with strongly coordinating anions reduction.

The key intermediate in the catalytic cycle proposed by Sheldon (Scheme 4) is an $[L_2PdR]^+X^-$ (**2**) complex, which controls the chemoselectivity of the reaction. Either coordination of CO, insertion into the Pd–C σ-bond and hydrolysis forms FFA or – if X^- is a strongly coordinating anion and the coordination of CO is less favorable – protonation gives MF and L_2PdX_2, which is reduced subsequently to PdL_3 by CO.

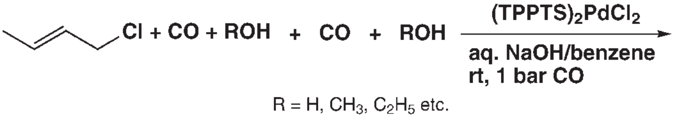
The transition metal-catalyzed carbonylation of allylic compounds has been developed as a simple extension of carbonylations of benzylic derivatives. In this respect nickel cyanide has been used as a catalyst precursor for carbonylation of allyl



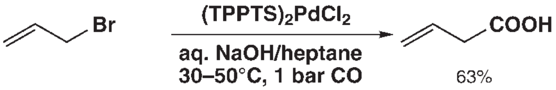
Scheme 4 Proposed catalytic cycle for the carboxylation of 5-hydroxymethylfurfural.

halides [19]. The key catalytic species is believed to be a water-soluble cyanotricarbonylnickel anion. Without additional phase-transfer catalyst the carbonylation of allyl bromide leads in a biphasic process to (*E*)-2-butenoic acid in 82% yield (TON = 10).

In general for carbonylations, palladium as catalyst metal is preferable to nickel with respect of catalyst efficiency. Thus, Okano, Kiji, and co-workers described some other efficient palladium-catalyzed carbonylations of allyl chloride and substituted allyl halides (Eqs. 5–10). In greater detail, the water-soluble palladium complex $PdCl_2[Ph_2P(m\text{-}C_6H_4SO_3Na)]_2$ has been used in a two-phase system (e.g., aqueous NaOH/benzene medium) at atmospheric carbon monoxide pressure, giving 3-butenoic acids [20]. In the carbonylation of allyl chloride a mixture of 2-butenoic acid, which was formed by base-catalyzed isomerization, and 3-butenoic acid was obtained in up to 90% yield (TON = 135), albeit at moderate selectivity (24 : 76). Clearly, the isomerization depends on the concentration of the base and was therefore suppressed by a method of continuous addition to the aqueous medium.



(5)



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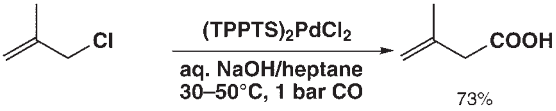

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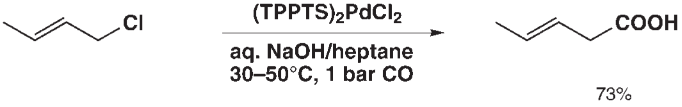

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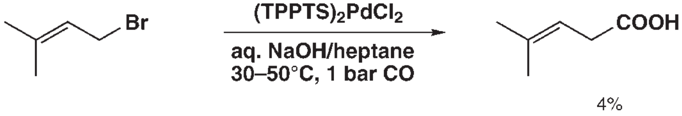

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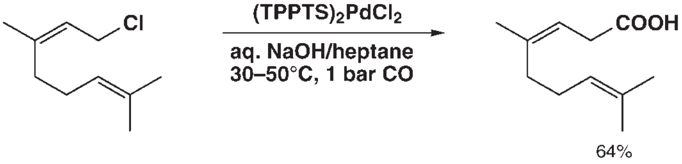
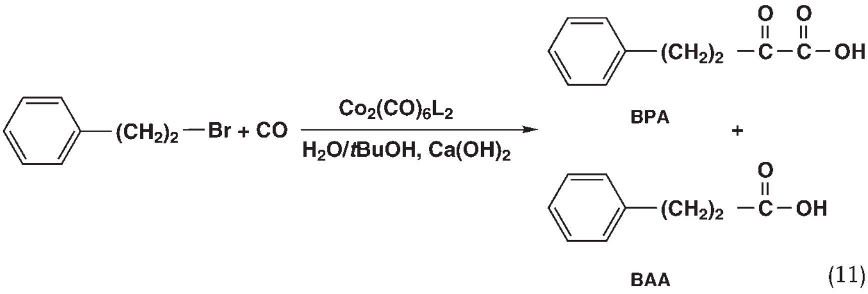


(10)

So far, easily available alkyl halides have not been applied to biphasic carbonylations. However, the carbonylation of phenethyl bromide with hydrophilic cobalt catalysts to give benzylpyruvic acid (BPA) and benzylacetic acid (BAA) was investigated (Eq. 11) [21].

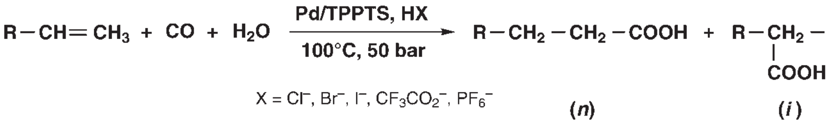


(11)

Using two-phase catalysis it is found that weakly basic phosphines, such as TPPTS and TPPMS, show rather good results compared with those obtained with the water-insoluble phosphines as ligands. Interestingly, the double/monocarbonylation selectivity strongly depends on the nature of the phosphine.

6.5.4
Hydrocarboxylation of Alkenes

Biphasic hydrocarboxylations have attracted recent interest. One of the first examples was reported by Monflier and co-workers [22]. As shown in Eq. (12), the reaction of olefins, such as styrene, ethylene, propene, 1-hexene, and 1-decene, proceeds in the presence of a palladium/TPPTS catalyst and a Brønsted acid as a co-catalyst. Best results are given by styrene and ethylene, with more than 90% yield of acid. Detailed studies revealed that the catalytic activity is increased by lowering the pH value, with an optimum at pH 1.8. The nature of anion only slightly affects the rate of the hydroxycarboxylation reaction. In case of the halogenides as coordinating anions, no precipitation of metallic palladium is observed after the reaction, so catalyst recycling is possible in principle. So far, *n*/iso-selectivities are at least moderate, thus precluding specific synthetic use of the method. Typical values for branched to linear (*n*/iso) ratios range from 1.0 to 1.4.



$$\mathrm{R{-}CH{=}CH_3 + CO + H_2O \xrightarrow[100^\circ C,\ 50\ bar]{Pd/TPPTS,\ HX} \underset{(\mathit{n})}{R{-}CH_2{-}CH_2{-}COOH} + \underset{(\mathit{i})}{R{-}\underset{\displaystyle COOH}{\underset{|}{CH_2}}{-}CH_3}} \tag{12}$$

$X = Cl^-, Br^-, I^-, CF_3CO_2^-, PF_6^-$

Long-chain aliphatic olefins give only insufficient conversion to the acids due to low solubility and isomerization side reactions. In order to overcome these problems the effect of co-solvents and chemically modified β-cyclodextrins as additives was investigated for the hydrocarboxylation of 1-decene [23]. Without such a promoter, conversion and acid selectivity are low, 10% and 20% respectively. Addition of co-solvents significantly increases conversion, but does not reduce the isomerization. In contrast, the addition of dimethyl-β-cyclodextrin increased conversion and induced 90% selectivity toward the acids. This effect is rationalized by a host/guest complex of the cyclic carbohydrate and the olefin which prevents isomerization of the double bond. This pronounced chemoselectivity effect of cyclodextrins is also observed in the hydroformylation and the Wacker oxidation of water-insoluble olefins [24, 25]. More recent studies of the biphasic hydrocarboxylation include the reaction of vinyl aromatic compounds to the isomeric arylpropanoic acids [29, 30], and of small, sparingly water-soluble alkenes such as propene [31].

6.5.5
Conclusions

Apart from hydroformylations, other biphasic carbonylation reactions of organic substrates are still a relatively unexplored research area. So far, nearly all reported reactions in a two-phase system suffer similarly to their homogeneous counterparts from low catalyst efficiency. Thus, the principle advantages of biphasic catalysis have not been realized due to insufficient product/catalyst separation as well as to metal losses with product stream and rapid catalyst deactivation. However, it may be predicted for the future that careful design of water-soluble catalyst systems will make it possible to overcome this problems.

In view of the vast number of homogeneous carbonylation reactions known it is easy to say that biphasic carbonylations have not yet reached their culmination point. Moreover, the actual importance of other two-phase media, e.g., fluorous biphasic systems [26] (cf. Section 7.2), will lead to further exploitation for carbonylations.

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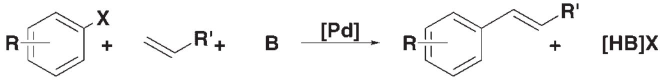
6.6
C–C Coupling Reactions (Heck, Stille, Suzuki, etc.)

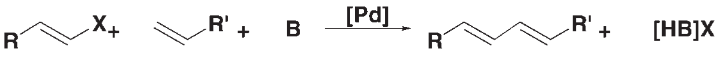
Wolfgang A. Herrmann, Claus-Peter Reisinger, Peter Härter

6.6.1
Introduction

Here, the term “Heck-type reaction” summarizes palladium-catalyzed C–C coupling processes where vinyl or aryl derivatives are functionalized with alkenes, alkynes, or organometallic reagents (see Eqs. 1 and 2) [1]. Aryl and vinyl chlorides are most reluctant to undergo Pd-catalyzed activation, as expected from C–X bond dissociation energies [2].



(1)



(2)

X = I, Br, N_2, BF_4 B = base: NR_3, K_2CO_3, NaOAc

Although most applications of Heck-type reactions are carried out in polar aprotic media, there are several successful approaches using partially or completely aqueous solution and aqueous–organic biphasic systems. Furthermore, the methodology was expanded to N–C and P–C bond forming reactions; in addition, cross-coupling reactions will also be discussed here. In most cases, the recovery and re-use of the water-soluble catalyst is of minor importance, because the procedures are developed for the laboratory scale with respect to fine chemical synthesis. The main advantage of this approach may be the significant change in thermodynamics, resulting in milder reaction conditions and improvements in chemo- and regioselectivity. Recently, a novel type of biphasic system has been introduced using fluorous hydrocarbons/organic phases as solution media [43]. The main impetus for the employment of the fluorous biphase concept (FBS; see Section 7.2) is the easy recovery of the catalyst, a subject which is of crucial importance in industrial applications [44]. This methodology also provides a possibility

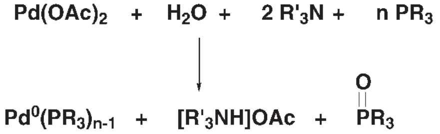
Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

of performing reactions under biphasic conditions with substrates which are labile towards water.

6.6.2
Catalysts and Reaction Conditions

Palladium is one of the most versatile and efficient catalyst metals in organic synthesis. Solubility in water is achieved by utilization of simple palladium(II) salts or water-soluble ligands, such as TPPTS and TPPMS. The active catalysts for Heck-type reactions are zerovalent palladium(0) species [3], which are often generated *in situ* by thermal decomposition of a Pd(II) precursor or by the application of a reducing agent, e.g., 1–6 equiv. of a phosphine in the presence of base generates Pd(0) and the phosphine oxide (Eq. 3) [4].



$$\mathrm{Pd(OAc)_2} + \mathrm{H_2O} + 2\,\mathrm{R'_3N} + n\,\mathrm{PR_3} \longrightarrow \mathrm{Pd^0(PR_3)_{n-1}} + [\mathrm{R'_3NH}]\mathrm{OAc} + \overset{\mathrm{O}}{\overset{\|}{\mathrm{PR_3}}} \tag{3}$$

The isolation of water-soluble palladium(0) complexes was achieved by Herrmann and co-workers by gel-permeation chromatography for Pd(TPPTS)$_3$ [5]. An X-ray determination was reported by Casalnuovo and Calabrese for Pd(TPPMS)$_3$ [6]; this is the first published structure of a transition metal complex containing a sulfonated phosphine.

Furthermore, the combination of palladium(II) salts with tetrabutylammonium halide additives, called "Jeffery conditions", is an efficient system for Heck-type reactions [7a], but the mechanistic implications are unknown. Also, nonionic phosphine ligands, such as triphenylphosphine which yields $Pd(PPh_3)_4$, are applied in water-miscible organic solvents, like DMF and acetonitrile. In these cases, the application of water is of crucial importance, but the role is often not well investigated. The fluorous biphase concept can be performed in several ways. In the most straightforward approach the catalyst is modified such that it gains high solubility in the fluorous phase. Ligands used in palladium catalyzed reactions are fluoro-tagged phosphines of type $P(C_6H_5{-}R^f)_3$ (with $R = OCH_2C_7F_{15}$, C_6F_{13}, $O(CH_2)_2$-$OCH_2CF_2[OCF(CF_3)CF_2]_P(OCF_2)_MOCF_3$; cf. Section 7.2).

Since the strongly electron withdrawing fluorinated compounds considerably change the chemical character of the complexes care has to be taken as to install spacer groups in order to isolate these electronic effects from the palladium centre. Generally, the reaction temperature is kept at 80 °C. This is low enough to prevent formation of palladium black and allows installation of single phase conditions. After cooling the mixture to room temperature the phases separate again and allow the isolation of the product simply by decanting the organic solvent.

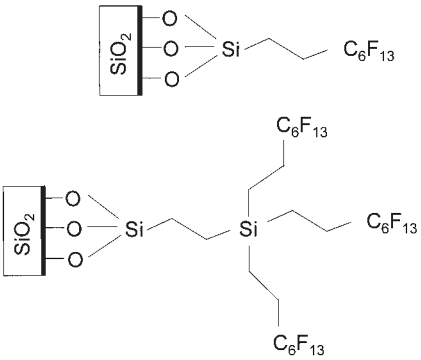
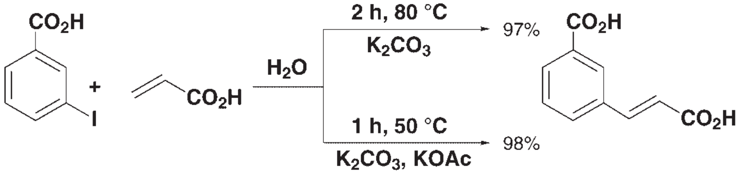


Figure 1

This methodology has been further developed by using fluorous reversed-phase silical gel (FRPSG) (Figure 1) as "a substitute solvent" for the perfluoro-tagged catalysts [45]. The catalysts dissolve in the fluorous surface of the silica particles and remain there throughout the reaction as has been demonstrated in Suzuki reactions which were conducted up to six times using the same support/catalyst particles without loss of activity (vide infra). This protocol avoids expensive fluorinated solvents, at the same time making catalyst recovery more easy and effective.

6.6.3
Olefination

Since the pioneering work by Beletskaya and co-workers [8] the intra- and (more commonly) intermolecular arylation of alkenes has been shown to proceed very smoothly in aqueous medium in the presence of palladium acetate. At the beginning, the methodology seemed to be limited to aryl iodides under a strong influence of the base: it was shown that the presence of potassium acetate instead of carbonate yielded lower reaction temperatures and higher rates (Eq. 4).

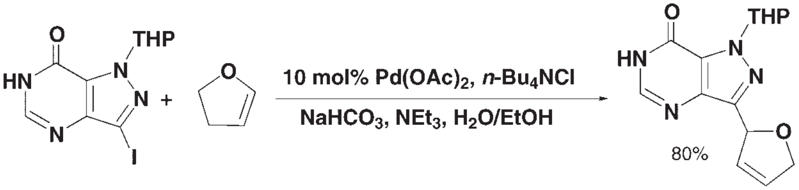


(4)

Several years later, a similar approach succeeded even in the application of deactivated bromoanisole (because it was donor-substituted) with acrylic acid in water at 100 °C, using 1 mol% palladium chloride with 3 equiv. of sodium carbonate, which demonstrates the efficient application of water as the reaction medium [9].

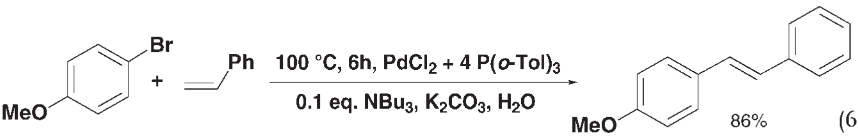
Further investigations by Jeffery indicated the rate- and selectivity-enhancing ability of tetraalkylammonium salts in Heck-type reactions [7]. In particular, tetrabutylammonium chloride, bromide and hydrogensulfate are extensively applied in aqueous DMF and acetonitrile, resulting in the fast and clean conversion of phenyl iodide with acrylic acid in 96% yield.

This approach was adopted by Daves for the coupling of iodo derivatives of nitrogen heterocycles with cyclic enol ethers and furanoid glycals in a water/ethanol mixture, using tetrabutylammonium chloride as a promoter (Eq. 5) [10]. Surprisingly, the use of absolute ethanol as reaction solvent was ineffective.



(5)

Furthermore, comparative studies with arylphosphine ligands in aqueous organic media demonstrated the superior activity of palladium tri(*o*-tolyl)-phosphine complexes [11] with an unusual combination of 10 mol% tributylamine with 1.5 equiv. of potassium carbonate in water [9]. The catalyst system was successfully applied to bromobenzene and even bromoanisole with water-insoluble styrene, yielding 86% product in 6 h with 1 mol% Pd (Eq. 6).

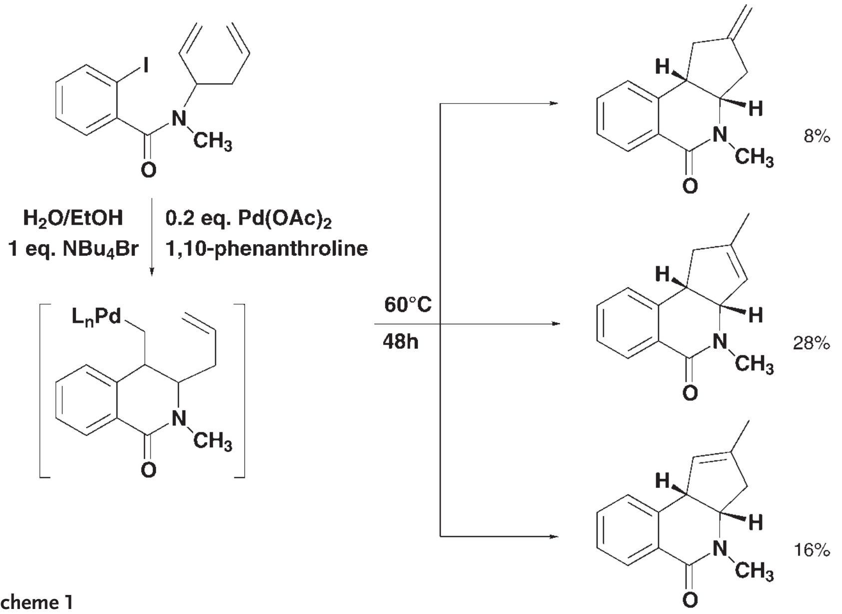


(6)

If water-soluble phosphine ligands are applied, extremely mild reaction conditions can be achieved. Especially, Pd(TPPMS)$_3$, which converts 4-iodotoluene in 2 h at 30 °C (10 mol% Pd), is tolerant of a broad range of functional groups, including those present in unprotected nucleotides and amino acids [6].

Interestingly, even the coupling of donor-substituted iodoarenes and cyclic alkenes can be conducted by palladium acetate with TPPTS at only 25 °C in aqueous acetonitrile. However, the low rates observed require a reaction time of up to 48 h for high conversions [12].

The application of ethylene in Heck reactions often shows different activities from other alkenes, because of Wacker-type side reactions. It was found, however, that iodo- and acceptor-substituted bromoarenes are cleanly converted in aqueous media to the corresponding styrenes utilizing a palladium-TPPMS complex [13]. Furthermore, high purity *o*- and *p*-vinyltoluenes were prepared on a large scale (in



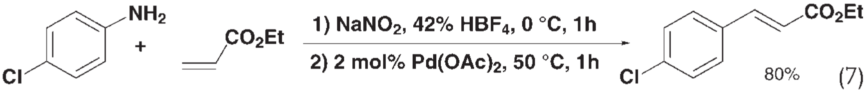
Scheme 1

up to a 10-gallon (38-L) reactor) in a dimethylformamide/water mixture with palladium tri(*o*-tolyl)phosphine complexes [14]. Here, the role of water may be the dissolution of the inorganic base (potassium carbonate) in the organic media.

Even superheated (to 260 °C) or supercritical (to 400 °C) water was employed in the Heck reaction with several catalyst precursors and aryl halides with styrene. However, all conversions show large amounts of side products and the yields were in the 5–30% range, indicating radical intermediates and by-products from decomposition of the arene starting material [15].

The progress of tandem Heck reactions in organic synthesis [16] led to their first application in the aqueous phase. Hence, a double Heck reaction on a substrate for which β-hydride elimination is possible results in three tricyclic products (Scheme 1) [17].

Surprisingly, the application of 1,10-phenanthroline as a ligand suppresses β-hydride elimination completely and raises the total yield of double cyclization products to 52%. This may arise from the hydrophobic effect of the heterocycle and the alkene in water/ethanol, forming an aggregate in the transition state favored in water [18]. In addition, an efficient one-pot procedure for Heck reactions starting with aniline derivatives, forming arenediazonium salts with sodium nitrite in 42% aqueous HBF_4, was reported (Eq. 7) [19]. The process has several advantages: short reaction times, high catalytic turnover frequency, superior reactivity of the diazonium nucleofuge, and, most significantly, the use of aqueous reaction conditions. Therefore, this route toward ring-modified phenylalanine and tyrosine was used via a ring nitration and reduction sequence, expanding the field of artificial amino acids [20].

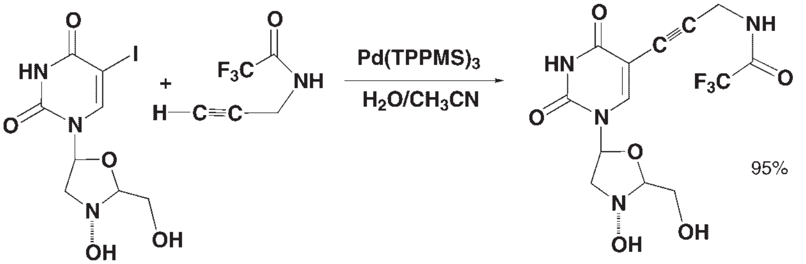


(7)

There is one example of olefination of iodoaromatics with acrylates under biphasic fluoro conditions [46]. Pd acetate or $Pd_2(dba)_3$ are used as catalyst precursors together with fluoro-tagged phosphines of type $P(C_6H_{5-x}R^f_x)_3$ with a mixture of acetonitril and D-100 being the fluorous phase. After formation of the catalyst by stirring the Pd salts with phosphine in the fluorous phase the reaction is carried at 80 °C resulting in complete conversion. The product is isolated by decanting the acetonitrile phase at 0 °C. The catalyst performance strongly depends on the Pd/phosphine ratio. With an excess of phosphine (Pd/P = 1:4) no reaction takes place under biphasic conditions although with acetonitril as solvent a 45% conversion was observed. The conversions in the first runs are not dependent on the nature of the fluorous side groups R^f of the phosphines. But in the second and third runs considerable decrease of catalytic activity was found. This is partly due to increased solubility of the catalyst in the organic phase, when R^f-groups contain ether groups.

6.6.4
Alkyne Coupling

The palladium-catalyzed coupling of terminal acetylenes with aryl and vinyl halides is a widely used reaction in organic synthesis [21]. Hence, the application of water-soluble palladium complexes was first reported in aqueous acetonitrile with $Pd(TPPMS)_3$ and CuI as promoter, but limited to aryl iodides [6]. The advantages of this catalyst already mentioned are low reaction temperatures and short reaction times with high yields (Eq. 8). Further ligand variations with TPPTS [12] and guanidino-functionalized phosphines [22] revealed that this methodology works also without any Cu(I) promoter, when higher amounts of palladium (10 mol%) are used.



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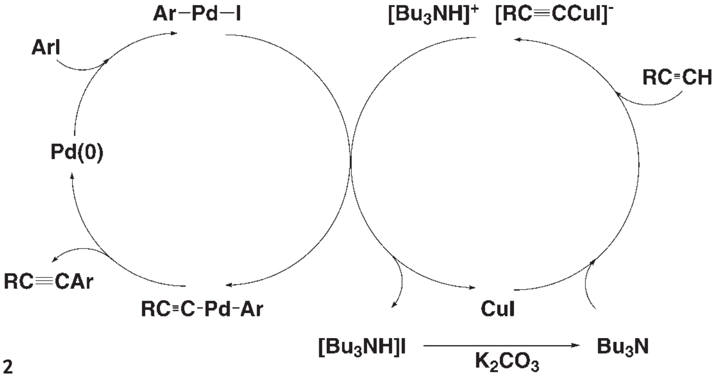
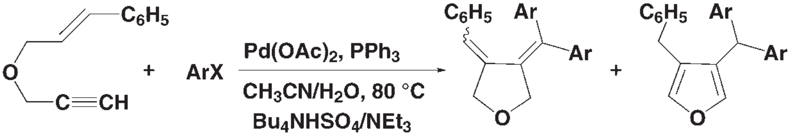


Scheme 2

Furthermore, Bumagin and Beletskaya reported the first coupling in neat water in the presence of a small amount tributylamine (10 mol%) and potassium carbonate as base [23]. Surprisingly, the catalyst system consists of water-insoluble triphenylphosphine with PdCl$_2$ and CuI at room temperature, resulting in high yields with aryl iodides and phenylacetylene. The role of cuprous iodide was noted to be important to facilitate the reaction, which may be rationalized by two connected catalytic cycles (Scheme 2).

In addition, the application of “Jeffery’s conditions” by Sinou and co-workers, with extra triphenylphosphine and tetrabutylammonium hydrogensulfate, confirmed that CuI is not essential to success in alkyne coupling reactions [24]. Moreover, they reported the most efficient coupling of bromoanisole with propargyl alcohol in 81% yield. These results prompted the authors to apply these conditions in a cascade reaction, consisting of an intermolecular Heck reaction followed by cyclization of the intermediate σ-complex (Eq. 9). The product, which is a mixture of (E) and (Z) stereomers (approximately 1 : 1), was sometimes contaminated with a by-product resulting from aromatization, especially for longer reaction times.

 (9)

The fluorous biphase concept was successfully used for Pd catalyzed Sonogashira couplings of arylbromides and alkynes by Bannwarth and his co-workers [47]. The reactions are carried out at 100 °C in a mixture of DMF and 1,2,2,3,4,4,5,5,6,6-decafluoro-1,3-bis(trifluoromethyl)cyclohexane with CuI (5%) as promotor and a catalyst concentration of 2%. Electron-deficient and electron-rich bromoarenes as well as three different types of alkynes bearing a silyl, an aromatic or an aliphatic substituent were investigated. The catalysts were prepared from

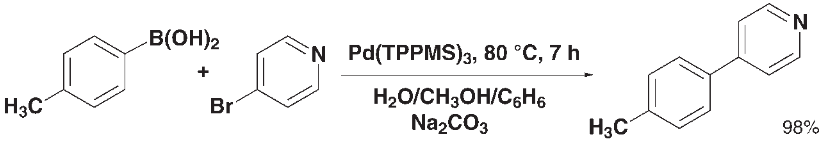
$PdCl_2$ and fluoro-tagged arylphosphines of the type $P(p\text{-}C_6H_4R^f)_3$, $R^f = C_2H_4C_8F_{17}$, $OCH_2C_7F_{15}$. Using this protocol, the reactions show similar trends as were found with typical Sonogashira conditions. In all cases a decrease in activity was found in the third run of the same fluorous catalyst solution. Recently, the same group published a fluorous biphasic protocol without using perfluorinated solvents (*vide supra*) but fluorous reversed phase silica particles [45]. The same type of catalysts were tested with various loadings. As a result, the catalysts show high reactivity even at a concentration of 0.2 mol%. But again, under these conditions the activity decreases considerably after the first run.

6.6.5
Cross-coupling Reactions

The field of Heck-type reactions has been extended by a variety of cross-coupling reactions, each of which has its own name because of its uniqueness and importance in organic synthesis.

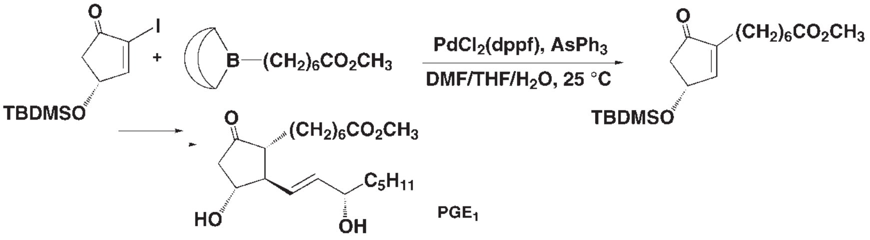
6.6.5.1
Suzuki Coupling

The Suzuki coupling is defined by the presence of boron-containing coupling reactants. Thus, the palladium-catalyzed cross-coupling reaction of aryl or alkenyl halides with alkenylboronates or arylboronic acids is a regio- and stereoselective bond formation affording, in particular, unsymmetric substituted biaryls [25]. Once again, the first application of this approach in aqueous phase was reported by Casalnuovo and Calabrese demonstrating the high efficiency of their $Pd(TPPTS)_3$-based catalyst system. Thus, 4-bromopyridine was coupled with *p*-tolylboronic acid in a water/methanol/benzene solvent mixture in 98% yield (Eq. 10) [6].



(10)

Later, the same methodology was applied by Wallow and Novak for the synthesis of water-soluble poly(*p*-phenylene) derivatives via the “poly-Suzuki” reaction of 4,4′-biphenylylene bis(boronic acid) with 4,4′-dibromodiphenic acid in aqueous dimethylformamide [26]. These aromatic, rigid-chain polymers exhibit outstanding thermal stability (decomposition above 500 °C) and play an important role in high-performance engineering materials [27] conducting polymers [28] and nonlinear optical materials [29].



Scheme 3 TBDMSO = t-butyldimethylsilyl
dppf = 1.1-bis(diphenylphosphinoferrocene)

Furthermore, this regio- and stereoselective bond formation between unsaturated carbon atoms was applied to the synthesis of functionalized dienes under extremely mild conditions. Thus, even vinylic boronic esters containing an allylic acetal moiety and alkenylboronate having a chiral protected allylic alcohol were successfully accomplished with vinylic iodides under aqueous conditions in 60–90% yield [30]. In addition, an exceptionally simple and efficient synthesis of a prostaglandin (PGE$_1$) precursor was reported by Johnson, applying a DMF/THF/water solvent mixture with a bis(diphenylphosphino)ferrocene palladium catalyst [31]. It is curious that the presence of water is an absolute necessity in order to succeed in this approach (Scheme 3).

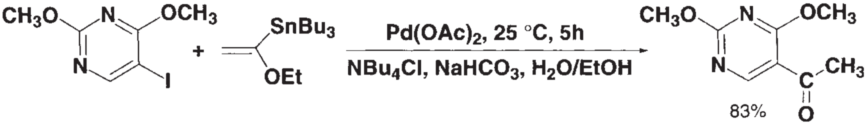
It is noteworthy that 9-alkyl-9-BBN (9-BBN = 9-boracyclo[3.3.1]nonyl) reagents are easily prepared by hydroboration of the corresponding alkene, demonstrating the high variability of this approach in organic synthesis.

The FBS concept was also used for the Suzuki coupling of arylboronic acids with bromoarenes [48]. In contrast to the activity problems found in Sonogashira couplings, Suzuki coupling reactions can be carried out with only little decrease of catalyst activity even after six runs with the same solution. The catalysts used in these investigations are of the same type as described above. Applying the reversed phase methodology (FRPSG), the catalyst concentrations can be as low as 0.01 mol% for a quantitative conversion of *p*-$NO_2C_6H_4Br$ with phenylboronic acid. The scope of the FBS concept ranges from electron-deficient and electron-rich arylbromides on the one side and phenylboronic acid and electron-rich boronic acids like 3-thienylboronic acid on the other side [44].

6.6.5.2
Stille Coupling

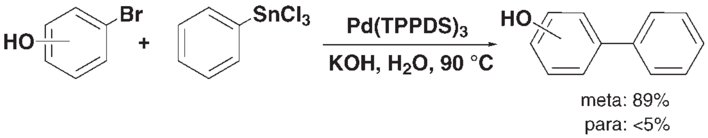
The Stille coupling depends on tin-containing reagents. Although the cross coupling of organotin reagents with organic halides proceeds under extremely mild conditions, it seems to be the most unexplored field of palladium-catalyzed reactions [32], because of the high toxicity of the volatile tetraorganotin compounds.

Thus, the first application in aqueous medium was reported by Daves in 1993, describing the synthesis of a pyrimidine derivative formed by *in situ* hydrolysis of the intermediate enol ether (Eq. 11) [33].



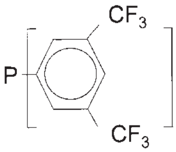
(11)

In 1995, Beletskaya [34] and Collum [35] reported independently the application of alkyltrichlorostannanes instead of tetraorganotin compounds, overcoming the disadvantage of three inert anchoring groups ("atom economy") and technologically more important, because of their lower toxicity and availability via economic direct synthesis from tin(II) compounds [36]. Furthermore, the hydrolysis of the tin–halide bond in water results in higher water-solubility, activation of the C–Sn bond toward electrophiles (e.g., in transmetallation) and less toxic by-products. The reaction may be accomplished via intermediate anionic hydroxo complexes [37], produced *in situ* in aqueous alkaline solution, and proceeds in most cases in 3 h at 90–100 °C (Eq. 12).



(12)

For insoluble halides to react smoothly, water-soluble phosphine ligands such as TPPMS and TPPDS have to be employed, otherwise the catalyst decomposes rapidly and palladium black is formed. The most reactive organotin reagent studied has proved to be phenyltrichlorostannane, although methyl transfer was also successful with soluble substrates. Stille reactions using the FBS concept have also be reported [49]. In this study, several types of fluorous-tagged phosphine ligands of the structures **1** and **2** coordinated to $PdCl_2$ were investigated.



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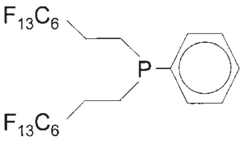
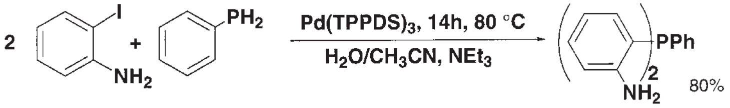


2

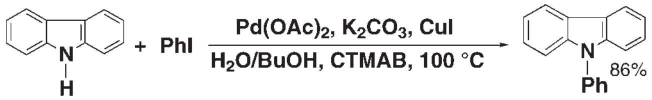
6.6.5.3
Miscellaneous

A newer development in Heck-type reactions is P–C and N–C bond formation, which results by coupling of aryl halides with phosphorous compounds [38] and amines [39]. The first application in aqueous medium was achieved by coupling of a dialkyl phosphite with an aromatic iodide to give an arylphosphonate in 99% yield. In 1996, Stelzer and co-workers presented a P–C cross-coupling reaction between primary and secondary phosphines and functional aryl iodides to water-soluble phosphines (Eq. 13), which are potentially applicable as ligands in aqueous-phase catalysis [40]. Surprisingly, the large excess of phosphine ligands (starting material, product, and added triphenylphosphine) present in the reaction mixture obviously does not inhibit the palladium catalyst.



(13)

A rather unusual procedure has been published for the palladium- and copper-catalyzed synthesis of triarylamines, using an alkaline water–ethanol emulsion stabilized by cetyltrimethylammonium bromide [41]. Anyway, this method overcomes the problem in the synthesis of *N*-aryl carbazoles (Eq. 14), which are not accessible by the method developed by Hartwig and Buchwald [42].



(14)

6.6.6
Conclusions

The advantages of Heck-type reactions in aqueous phase are demonstrated by the large number of successful approaches presented here. The change in the thermodynamics caused by using water as reaction medium results in milder reaction conditions, higher yields, and improvements in chemo- and regioselectivity. The trend in the last few years has changed towards systems which are designed to improve the catalyst recovery. The results reported in this field give great promise for more efficient catalyst systems in the near future.

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6.7
Hydrocyanation

Henry E. Bryndza, John A. Harrelson, Jr.

6.7.1
Introduction

Hydrogen cyanide, HCN or hydrocyanic acid, is a remarkably versatile C_1 building block for the modern synthetic chemist today. Its use, however, has been limited by its relatively difficult synthesis/purification as well as by its high flammability, its tendency toward base-catalyzed explosive polymerization, and its toxicity. Most of the recent hydrocyanation literature comes from industry rather than academic laboratories.

If toxicity and handling difficulties are the drawbacks of HCN as a feedstock, the versatility of the nitrile functional group as a synthon is a significant advantage. Moreover, the full miscibility of HCN with water at 25 °C offers a potential advantage to pursuing hydrocyanation catalysis in aqueous media. Therefore, hydrocyanation reactions offer the potential for generating new nitrogenous products which are useful intermediates. These reactions include the addition of HCN to C=C, C=O, and C=N double bonds to generate new alkyl nitriles, cyanohydrins, and aminonitriles, respectively. All of these reactions have commercial impact today [1], although aqueous hydrocyanation catalysis remains an emerging area of technology.

6.7.2
HCN as a Synthon

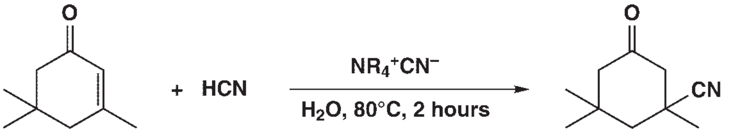
6.7.2.1
Michael Additions of HCN to Activated Alkenes

The addition of HCN to activated alkenes, as in Michael additions (Eq. 1), has been known and commercially practiced for many years. However, due to the potential for competitive addition of water to Michael substrates under conditions of general base catalysis, few examples of these additions are known in aqueous me-

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

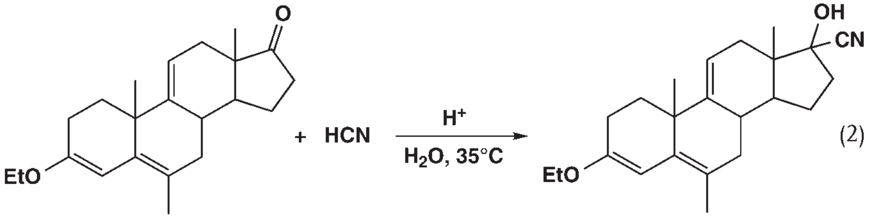
dia. However, the use of aqueous media for the tetraalkylammonium cyanide-catalyzed addition of HCN to isophorone (Eq. 1) was recently reported to give the corresponding nitrile in 98% yield under mild conditions [2]. Main Group organometallic cyanides as well as organic cyanide salts have been reported as catalysts for these reactions.



(1)

6.7.2.2
Synthesis of Cyanohydrins from Ketones and Aldehydes

More common is the general acid- or base-catalyzed addition of HCN to ketones and aldehydes to give cyanohydrins (Eq. 2) [1]. Because of the propensity of HCN to spontaneously and exothermically polymerize under basic conditions, general acid catalysis is sometimes favored over basic media, as was the case in the recent Sumitomo [3] and Upjohn work [4, 5]. Several recent applications of aqueous media have recently been reported to lead to asymmetric hydrocyanation catalysis. In one example, Arena at Allied Signal has reported the addition of HCN to monosaccharides in which the L-sugar products are preferentially complexed by aluminates and driven out of solution to generate new sweetener intermediates [6]. Loos and co-workers have recently reported the use of hydroxynitrile lyase as a catalyst for the general asymmetric hydrocyanation of aldehydes in aqueous media (Eq. 3) [7]. These reactions proceed under mild conditions in water or water-containing solvents to produce single-enantiomer products with a wide variety of substrates.



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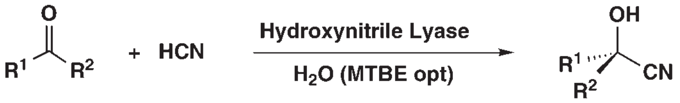
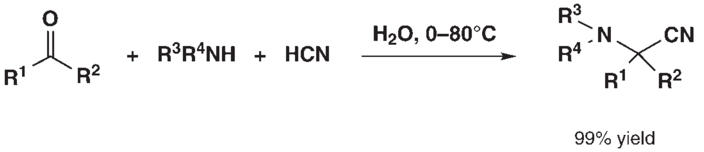


(3)

86–99% yield
93–99% ee

6.7.2.3
Strecker Synthesis of Aminonitriles

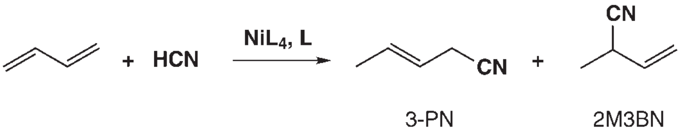
Another variant of this HCN addition to polar C=X bonds is the Strecker synthesis of aminonitriles from ketones or aldehydes, HCN, and ammonia (Eq. 4) [8]. Given the basic environment inherent in this synthesis, these processes are normally run under conditions of general base catalysis and both organometallic (e.g., NaCN) and organic cyanide salts have been reported as catalysts. Because water is a product in Strecker syntheses and can slow the overall rate of reaction, these commercially important processes are not generally run in aqueous media. However, a number of recent patents to Distler and co-workers at BASF do teach the use of aqueous media to facilitate isolation of pure products [9], and researchers at Grace [10], Stauffer [11], Mitsui [12], and Hoechst [13] have reportedly used aqueous media to control the rates of formaldehyde aminohydrocyanation to isolate intermediate addition products in good yields. Moreover, the use of aqueous media has also proven advantageous when amides, rather than nitriles, are the desired products.



(4)

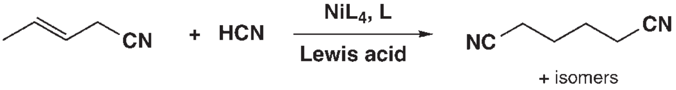
6.7.2.4
HCN Addition to Unactivated C=C Double Bonds

The addition of HCN to C=C double bonds can be effected in low yields to produce Markovnikov addition products. However, through the use of transition metal catalysts, the selective anti-Markovnikov addition of HCN to alkenes can take place. The most prominent example of the use of aqueous media for transition metal-catalyzed alkene hydrocyanation chemistry is the three-step synthesis of adiponitrile from butadiene and HCN (Eqs. 5–7). First discovered by Drinkard at DuPont [14], this nickel-catalyzed chemistry can use a wide variety of phosphorus ligands [15] and is practiced commercially in nonaqueous media by both DuPont and Butachimie, A DuPont/Rhône-Poulenc joint venture. Since the initial reports of Drinkard, first Kuntz [16] and, more recently, Huser and Perron [17, 18] from Rhône-Poulenc have explored the use of water-soluble ligands for this process to facilitate catalyst recovery and recycle from these high-boiling organic products.



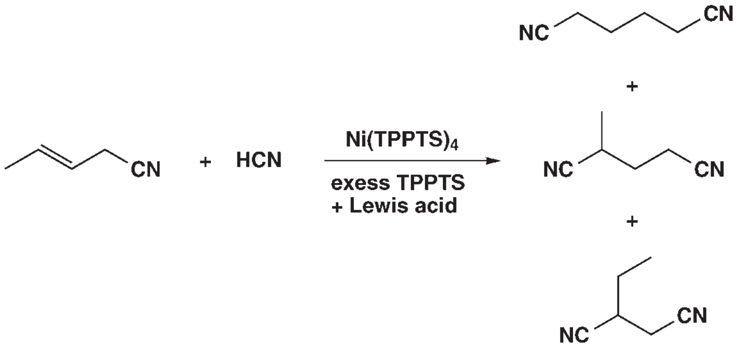
(5)

(6)



(7)

The initial report by Kuntz [16] teaches the use of sulfonated triphenylphosphine (usually the trisodium salt of tri(*m*-sulfonatophenyl)phosphine (TPPTS), cf. Section 3.2.1) with a source of nickel(0) as the catalyst for adding HCN to butadiene in 81% yield to give 3-pentenenitrile (3-PN), and HCN to 3-PN to produce adiponitrile, each in yields of about 60%. The balance of the products comprises branched dinitriles such as methylglutaronitrile and ethylsuccinonitrile (Eq. 8). Kuntz has recovered and recycled these catalysts multiple times, indicating the simplicity of separations induced by the aqueous media. He also reports modest yields of hydrocyanation products when these catalysts were applied to the nonoptimized hydrocyanation of styrene and 1-hexene, indicating some likelihood of the generality of this aqueous chemistry. Finally, Kuntz provides examples in which other salts (e.g., barium) and other cyanide sources (e.g., acetone cyanohydrin) are used for these reactions with good success. The use of other metal systems (and other sulfonated ligands) is mentioned but not exemplified in this patent.

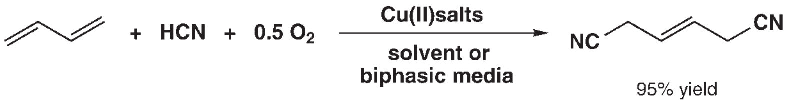


(8)

Huser and Perron have extended this work to the isomerization of 2-methyl-3-butenenitrile (2M3 BN) to 3-PN (isomerization step; Eq. (6) 92% yield) [17]. This patent mentions the use of iron and palladium catalysts but does not provide examples beyond nickel. In other work these same inventors discuss the use of other water-soluble ligands such as those containing carboxylate, phosphate, and alkylsulfonate substituents [18], while also exploring a wide range of Lewis acid co-catalysts for the addition of HCN to 3-pentenenitrile (Eq. 7) [19]. In general, the addition of strong Lewis acids facilitates this hydrocyanation and the promoted catalysts reported by Huser and Perron are much more active than those originally reported by Kuntz in which adventitious boron Lewis acids (generated during the reduction of Ni(II) with borohydride) were probably facilitating the HCN addition. In this light, it appears that zinc Lewis acids are more effective co-catalysts but less selective for adiponitrile than weaker species such as tin or europium halides. In general these water-soluble catalysts can be prepared by treatment of nickel(0) precursors with phosphines followed by extraction into water, by dissolution of nickel(II) salts such as chlorides or cyanides into an aqueous solution of ligand followed by chemical reduction with zinc or borohydride, or by electrochemical reduction of aqueous nickel(II) salts [20]. There is no mention in these reports about the potentially advantageous use of phase-transfer reagents to facilitate dissolution of very nonpolar alkenes in the aqueous media.

Asymmetric water-soluble ligands are known for the metal-catalyzed hydrocyanation of achiral alkenes. However, neither Jenck [21] or Davis [22] actually provides any examples of hydrocyanation catalysis in these patents so the performance of these mono- and bisphosphines in aqueous and supported aqueous media cannot be assessed although this may be a promising route for the synthesis of biologically active nitrile intermediates and products.

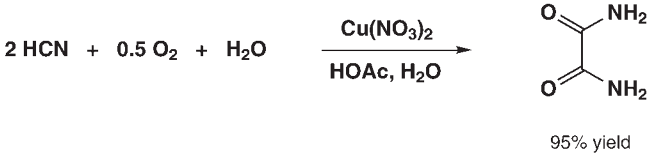
A final example of aqueous media used in the hydrocyanation of butadiene is provided by Waddan at ICI [23]. In this chemistry, copper nitrate salts in aqueous media (among many others) are used for the oxidative dihydrocyanation of butadiene to dicyanobutenes (Eq. 9). Good conversions of butadiene are reported in nonaqueous media but no examples are actually provided in which water is added as a solvent. Moreover, because of problems with alkene and HCN dimerization and the risk of explosion hazards, these reactions appear to work best when conducted stepwise (i.e., HCN addition to catalyst followed by oxidation followed, in turn, by butadiene addition), leading one to wonder about the productivity of these systems.



(9)

6.7.2.5
Cyanide Coupling Reactions

A final type of aqueous cyanide chemistry is the oxidative coupling of cyanide to produce oxamide (Eq. 10). Both batch and continuous reactions have been demonstrated at Hoechst by Riemenschneider and Wegener [24], who report advantages of aqueous media not only in concurrently hydrolyzing the coupled products but also in facilitating product isolation from the reaction medium. This clever combination of reactive solvent is reportedly the basis for the commercial production of oxamide [2].



(10)

6.7.3
Summary

Even from the admittedly limited examples of hydrocyanation reactions, it is clear that HCN is a versatile reagent and that its chemistry is generally compatible with aqueous media. Some traditional advantages which recommend the use of aqueous or biphasic media include the high solubility of HCN in water, the facility in removing products from catalysts, the ability to control rates of reactions more finely and the concomitant hydrolysis of nitrile functional groups to amides along with C–C bond formation. Commercial applications of aqueous hydrocyanations are only starting to emerge, but they could well develop quickly and improved catalysts and separation technologies come into play in the chemical industry.

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6.8
Allylic Substitution

Denis Sinou

6.8.1
Introduction

Since the discovery of the reaction of π-allylpalladium complexes with carbonucleophiles by Tsuji et al. [1], the organic chemistry of such complexes has attracted considerable attention and is now a usual tool in synthetic organic chemistry leading to the formation of carbon–carbon bonds as well as carbon–heteroatom bonds [2–4]. Important characteristics of this reaction are its very high chemo-, regio- and stereoselectivity and the very mild experimental conditions. In the late 1980s palladium(0)-catalyzed reaction of sodium azide with various allyl esters [5] or 1,3-diene monoepoxides [6] was reported to occur in aqueous tetrahydrofuran, leading to allylic azides in quite good yields, but it was only in 1991 that it was shown that palladium(0)-catalyzed alkylation could be performed in a two-phase system with water/organic solvent using water-soluble complexes [7].

6.8.2
Scope of the Reaction

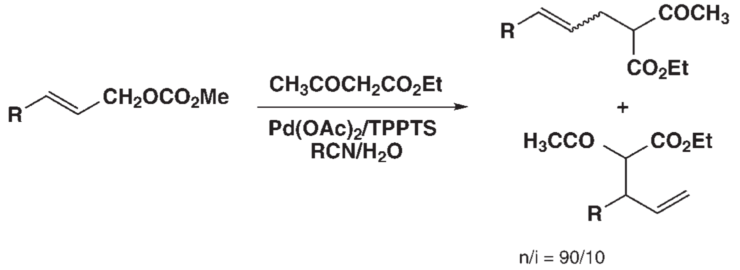
The water-soluble palladium(0) complex was generated *in situ* from $Pd(OAc)_2$ or $Pd_2(dba)_3$ (dba = dibenzylideneacetone) in association with TPPTS in water/nitrile mixture [7]. The use of a nitrile as the co-solvent being beneficial very important for the recycling of the catalyst, probably because of stabilization of the palladium(0) catalyst. The formation of a $Pd(TPPTS)_3$ species was demonstrated through a series of ^{31}P-NMR experiments and by cyclic voltametry [8, 9].

A detailed investigation using (E)-2-hexenyl methyl carbonate as the π-allyl precursor and ethyl acetoacetate as the nucleophile (Eq. 1) showed that the regioselectivity of the reaction was not affected by the $Pd(OAc)_2$/TPPTS ratio, the temperature of the reaction, the water/nitrile ratio, or the nature of the nitrile [12]; the linear and branched products were always obtained in a 90 : 10 ratio, quite similar to those observed in a usual organic medium. However, the catalytic activity was

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

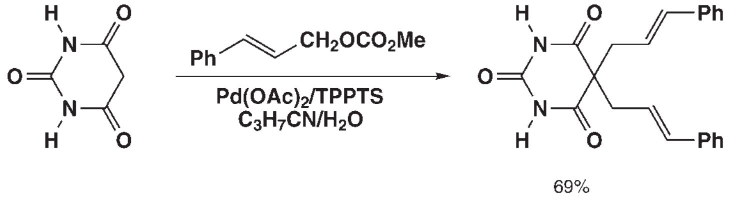
deeply affected by these parameters. The highest activity was obtained for a $[Pd(OAc)_2]$/TPPTS ratio of 9 : 1 and in acetonitrile as the solvent; this could be related to the solubility of the nitrile in water, the transfer of the reactants from the organic phase to the aqueous phase probably being the limiting step.



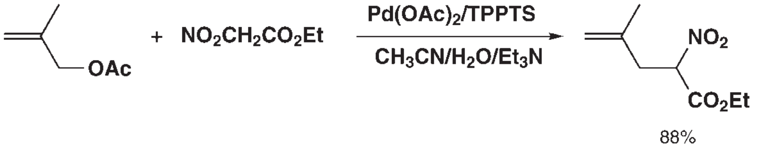
(1)

The allylation reaction was extended to various carbonucleophiles [7, 10–12]. It was observed that the selectivity in the formation of mono- and diallylated compounds was very sensitive to the nature of carbonucleophile and its pK_a. The acyclic carbonucleophiles such as ethyl acetoacetate, acetylacetone, dimethyl malonate, dicyanomethane, and bis(phenylsulfone)methane, gave predominantly the monoallylated product (Eq. 2), although the cyclic carbonucleophiles such as tetronic acid, dimedone, and barbituric acid gave predominantly the diallylated product (Eq. 3).

Alkylation of allylic acetates also occurred under these conditions, NEt_3 – or better 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu) – being used as the base, as well as that of vinyl epoxides.



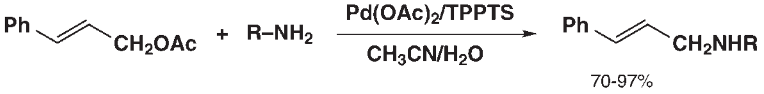
(2)



(3)

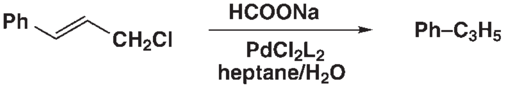
The alkylation reaction in a two-phase system was extended to various heteronucleophiles [12]. Secondary amines (morpholine, benzylmethylamine, etc.) as well as primary amines (*n*-butylamine, 2,2-diethylpropargylamine, cyclohexylamine, α-methylbenzylamine, etc.) reacted for example with (*E*)-cinnamyl acetate to give only the monoalkylation product in quite good yields (Eq. 4). Even the bis(*N*,*O*-boc)-

protected hydroxylamine HN(boc)(Oboc) (boc = *t*-butoxycarbonyl) or hydroxylamine hydrochloride gave the *N*-allyl-protected hydroxylamine or the bis(cinnamyl)-hydroxylamine, respectively. Sodium azide and sodium *p*-toluene sulfinate, which are soluble in water reacted also under these conditions giving the expected allyl azide and allyl *p*-toluene sulfone in 92 and 95% yield, respectively.



(4)

Allyl chlorides and acetates were reduced to the corresponding alkenes in a two-phase system heptane/water in the presence of water-soluble palladium complexes containing ligands such as polyether phosphines, TPPMS, or carboxylic phosphines using HCO_2Na as the hydrogen donor (Eq. 5) [13]. The most active catalyst was $PdCl_2L_2$ with L being a polyether phosphine in a heptane/water solution at reflux, giving a mixture of nonenes in 82% yield, although $PdCl_2$ (P-*n*-$Bu_3)_2$ gave lower yields under these conditions. From the mechanistic point of view, the palladium catalyst transferred the organic substrate into the aqueous phase as a π-allyl-palladium species, which then reacted with sodium formate to give the corresponding alkenes.



(5)

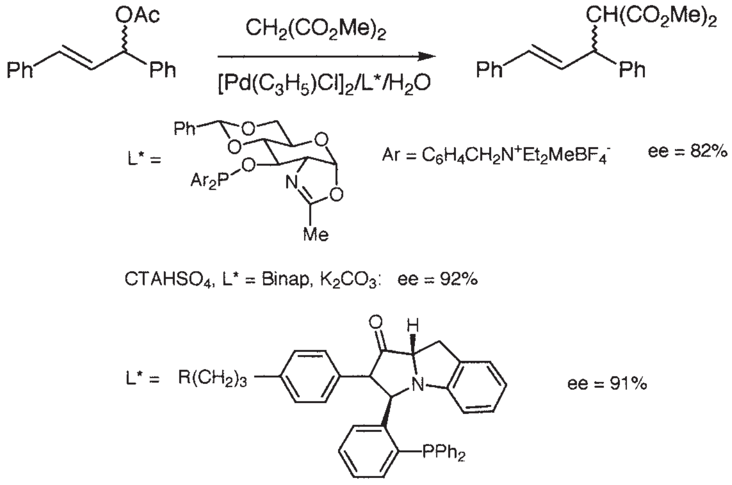
Yield (%) = P(*n*-Bu)$_3$/22; P[($C_2H_4O)_3CH_3]_3$/95;
PPh_2*m*NaO_3SPh/84

All types of nucleophiles, including carbo- as well as heteronucleophiles, allowed an easy recycling of the catalyst using benzonitrile or butyronitrile as the organic solvent, without any decrease in the yields [12].

Asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate in water or in an aqueous/organic biphasic medium was performed in the presence of the complex obtained from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a chiral amphiphilic phosphinite-oxazoline derived from natural **D**-glucosamine. The enantioselectivity obtained was up to 85% *ee* [14]; recycling of the catalyst was possible (Eq. 6).

It was observed that the rate of palladium-catalyzed allylic alkylation in water was drastically enhanced when the reaction was performed in the presence of surfactants [15]. Enantioselectivity up to 92% was obtained in the reaction of dimethyl malonate with 1,3-diphenyl-2-propenyl acetate when a chiral ligand such as Binap was used in the presence of cetyltrimethylammonium hydrogen sulfate (Eq. 6) [16].

A water-soluble polymer-bound Pd(0)-phosphine catalyst was also efficiently used in aqueous or mixed aqueous/organic media, the catalyst being recycled by



(6)

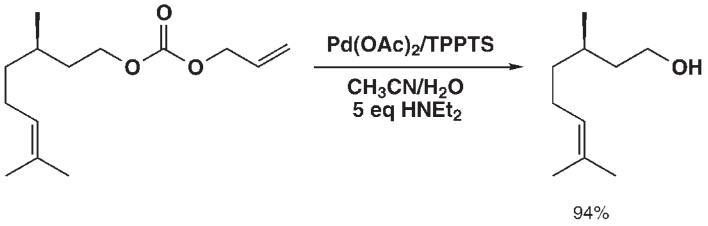
solvent or thermal preparation methods [17]. Amphiphilic resin-supported palladium-phosphine complexes showed high catalytic activity in allylic substitution reactions of various allylic acetates with different nucleophiles in aqueous media [18, 19]. Enantiomeric excess up to 98% was obtained using amphiphilic resin-supported MOP ligand or resin-supported *P,N*-chelating palladium complexes, the catalyst being recydable (Eq. 6) [20, 21]. The catalyst could be recovered by simple filtration and reused without any loss of activity and enantioselectivity.

Another approach in order to recycle the palladium-catalyst was the use of supported aqueous-phase catalysis (SAPC). Alkylation of (*E*)-cinnamyl ethyl carbonate by ethyl acetoacetate or morpholine occurred in acetonitrile or benzonitrile using $Pd(OAc)_2$–TPPTS supported on silica. No leaching of the catalyst was observed, allowing proper recycling of the catalyst [22–26]. Polyhydroxylated supports such as cellulose and chitosan were also successfully used in this approach [27–29].

6.8.3
Applications

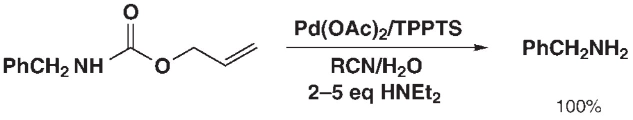
A very interesting application of this palladium-catalyzed alkylation in a biphase system is the removal of the allyloxycarbonyl group from allylic esters, carbamates, and carbonates. In a homogeneous organic medium, a variety of nucleophilic species have been used for intercepting the intermediate π-allyl complexes, including carbonucleophiles, amines, thiols, carboxylates and hydride donors. Genêt et al. used the aqueous palladium catalyst obtained from $Pd(OAc)_2$ and TPPTS for the catalytic allyl transfer, diethylamine being the allyl scavenger [30–33]. Either nitrile/water or diethyl ether/water were equally suitable for removal of the aloc moiety from nitrogen or oxygen.

Deprotection of aloc-protected primary alcohols such as (*R*)-citronellol, occurred in a few minutes upon exposure to $Pd(OAc)_2$–TPPTS in CH_3CN/H_2O, diethylamine being used in a 2–2.5-fold excess (Eq. 7) [30, 31]. Under these conditions, *t*-butyldiphenyl ether or ester functions are stable. The deprotection of secondary alcohols such as menthol proceeded smoothly.



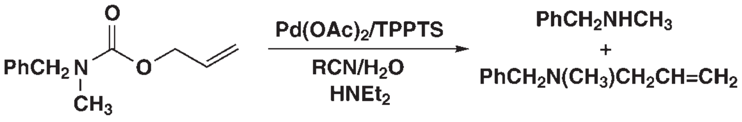
(7)

The *N*-aloc protecting group of primary amines such as benzylamine was cleaved rapidly under these standard conditions in quantitative yields (Eq. 8) [30, 32]. It is to be noticed that the *N*-protected amino acid derived from phenylalanine was deprotected without racemization.



(8)

The deprotection of aloc derivatives of secondary amines such as *N*,*N*-benzylmethylamine under the above conditions gave a substantial amount of the undesired allylamine [32]. However, the use of a 40-fold excess of diethylamine as the π-allyl scavenger led to the desired benzylmethylamine in quite good yield (Eq. 9). The formation of the undesired allylamine was also suppressed using a fivefold excess of diethylamine in a butyronitrile/water system. *N*-Allyloxycarbamates derived from secondary amines, such as morpholine, piperidine, proline, and ephedrine, reacted under the above-mentioned conditions at room temperature within 15 min to give the parent amines in quantitative yields without formation of the undesired allylamine.

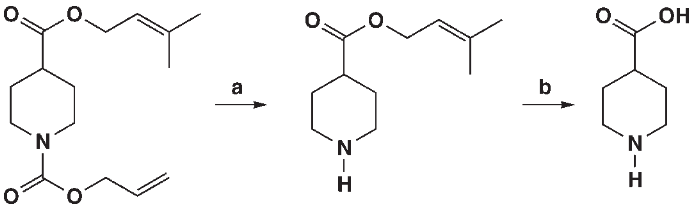


(9)

eq. of Et_2NH/solvent/ratio = $2/CH_3CN/30{:}70$; $40/CH_3CN/97{:}3$; $5/C_3H_7CN/100{:}0$

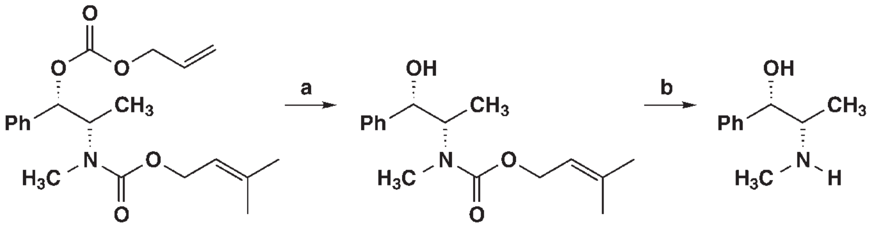
Deprotection of allyl groups from carboxylic allyl esters is also possible using these conditions [31, 33]. In a homogeneous CH_3CN/H_2O medium, the facility of cleavage of the allyl group follows the order allyl > cinnamyl > dimethylallyl.

However, under biphasic conditions (C_3H_7CN/H_2O) the allyl group of phenylacetic acid allyl ester was still cleaved at room temperature giving phenylacetic acid in quite good yields, whereas the cinnamyl and the dimethylallyl esters remained intact even after three days at 25 °C. This procedure was used for the selective cleavage of allyloxycarbamate in the presence of substituted allyl carboxylate. For example, the allyloxycarbamate of isonipecotic acid (Eq. 10) was selectively and quantitatively cleaved under homogeneous conditions, in the presence of 1% of palladium complex, without affecting the dimethylallyl carboxylate; the resulting monodeprotected product was then treated with a higher amount of catalyst (5 mol%) to give the free amino acid. In reverse, selective cleavage of an allyloxycarbonate could be performed in the presence of an allylcarbamate, using successively C_3H_7CN and CH_3CN as the nitrile. Selective removal of the allyloxycarbonyl group of doubly protected (1*R*,2*S*)-ephedrine (Eq. 11) occurred in a biphasic butyronitrile/water medium with 5% of palladium complex, the amine being deprotected using a homogeneous acetonitrile/water medium in the presence of 5% palladium catalyst.



(10)

a) 1% mol $Pd(OAc)_2$/TPPTS, CH_3CN/H_2O, 5 eq Et_2NH, 20 min, 96% yield
b) 5% mol $Pd(OAc)_2$/TPPTS, CH_3CN/H_2O, 5 eq Et_2NH, 10 min, 100% yield



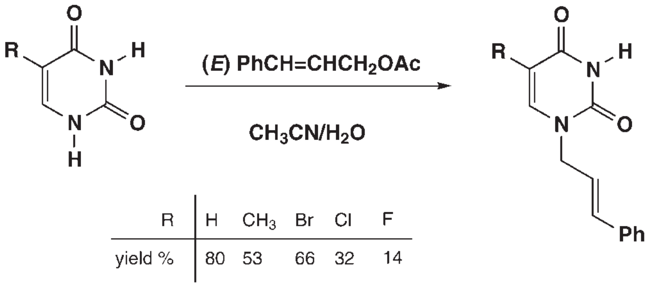
a) 5% mol $Pd(OAc)_2$/TPPTS, C_3H_7CN/H_2O, 5 eq Et_2NH, 20 min, 100% yield
b) 5% mol $Pd(OAc)_2$/TPPTS, CH_3CN/H_2O, 5 eq Et_2NH, 15 min, 100% yield

(11)

This methodology was applied for the preparation of tetrapeptides using the selective removal of an allyl carbamate in the presence of a substituted allylic ester [33].

The use of the water-soluble sodium azide as the allyl scavenger allowed the cleavage of allyloxycarbonyl-protected alcohols to occur under essentially neutral conditions [35]. It has also been shown that the phosphines (*tert*-Bu-*p*-$C_6H_4)_nP(C_6H_4$-*m*-$SO_3Na)_{3-n}$ ($n = 1, 2$) were more efficient than TPPTS in the deprotection of long alkyl chain alcohols [36].

The use of water or a two-phase water/organic solvent system as the reaction medium could also change the selectivity of a given reaction. This was effectively observed in the allylation of uracils and thiouracils [37, 38]. Although the reaction of uracil with (*E*)-cinnamyl acetate in the presence of $Pd(PPh_3)_4$ in tetrahydrofuran gave a complex mixture of mono- and diallylated products, performing the reaction in CH_3CN/H_2O with $Pd(OAc)_2$–TPPTS as the catalyst led to allylation only at N1 in quite good yield (Eq. 12). The reaction was extended to various 5-substituted uracils.



R	H	CH_3	Br	Cl	F
yield %	80	53	66	32	14

(12)

The same behavior was observed in the allylation of thiouracils. Performing the reaction in CH_3CN/H_2O with $Pd(OAc)_2$–TPPTS as the catalyst gave a unique product of monoallylation at sulfur, whereas the use of dioxane as the solvent in the presence of $Pd(PPh_3)_4$ again gave a complex mixture of products of allylation at N1, N3, and sulfur.

6.8.4
Conclusions

Although the first aim of the use of a water-soluble palladium catalyst in allylic alkylation in a two-phase system was the recycling of the catalyst, this methodology finds quite interesting applications in the deprotection of peptides as well as in the selective alkylation of uracils and thiouracils. More recently, the effective use of supported aqueous-phase catalysis as well as asymmetric alkylation in water in the presence of surfactants or amphiphilic resin-supported phosphines open new applications and developments for the future.

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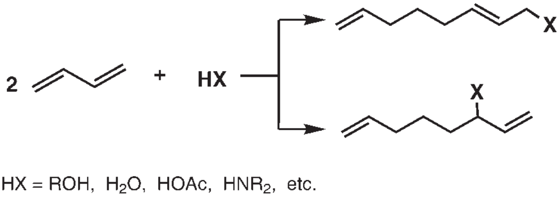
6.9
Hydrodimerization

Noriaki Yoshimura

6.9.1
Introduction

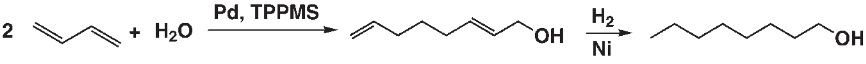
The linear telomerization reaction [1] of dienes (the taxogen) with nucleophiles (the telogen) such as alcohols, amines, carboxylic acids, active methylene compounds, phenols, or water provides an elegant method for the synthesis of various useful compounds (Eq. 1).



(1)

This reaction is catalyzed by nickel or palladium complexes. However, the selectivity and activity of nickel catalysts are lower than those of palladium catalysts. Palladium-catalyzed reactions give linear dimers selectively and no cyclization takes place. Not only the zerovalent palladium complexes but also certain bivalent ones can be used as active catalysts in combination with excess PPh_3. However, the zerovalent palladium complexes are somewhat tedious to prepare and unstable in oxygen, so easily available and stable bivalent palladium compounds such as $Pd(OAc)_2$ are generally used with PPh_3. A proposed mechanism is given in Figure 1 [1 f].

If water serves as telogen together with 2 mol of taxogen, the telomerization becomes a special hydrodimerization (Eq. 2). The consequent product in the case of butadiene as taxogen can be hydrogenated to produce 1-octanol, which has a considerable market as a raw material for plasticizers for poly(vinyl chloride).



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Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

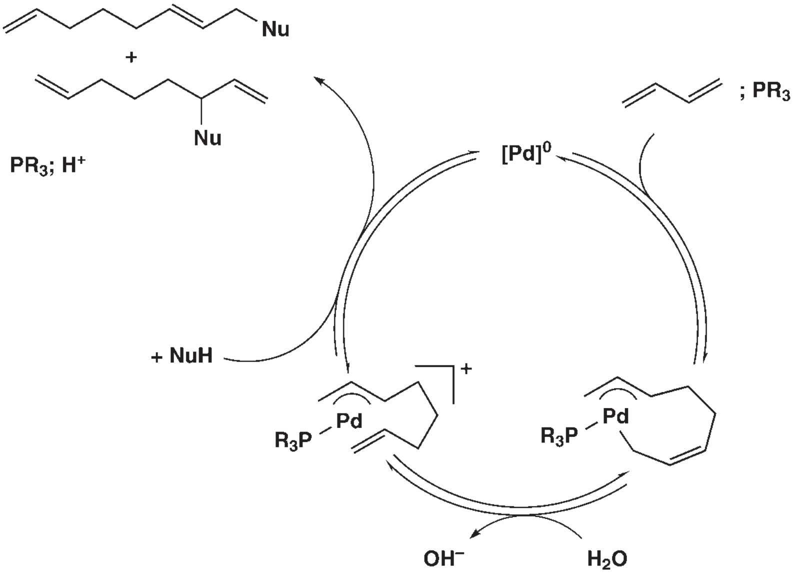


Fig. 1 Proposal for a mechanism [22, 23].

The hydrodimerization has so far been carried out in polar organic solvents such as *t*-BuOH, THF, acetone, and acetonitrile by using triphenylphosphine-modified palladium complexes. Conventional attempts to commercialize the palladium-complex-catalyzed telomerization have failed, in spite of great efforts, for the following reasons: (1) palladium complex catalysts are thermally unstable and the catalytic activity decreases markedly when, as a means of increasing the thermal stability, the ligand concentration is increased; (2) a sufficiently high reaction rate to satisfy industrial needs cannot be obtained; (3) low selectivity; and (4) distillative separation of reaction product and unreacted butadiene from the reaction mixture causes polymeric products to form and the palladium complex to metallize. The palladium complex is so expensive that its separation from the reaction medium and re-use become important. This point is especially crucial for continuous processes.

Concerning the catalyst separation from the telomerization reaction mixture, apart from direct distillation the following methods have been reported:

1. The telomerization reaction is carried out using the catalyst modified with amine-containing phosphines, then hydrochloric acid is introduced into the above reaction mixture. As a result phosphine is changed to the hydrochloric acid salt of the amine, so the modified catalyst is dissolved in water. The catalyst can be re-used after treatment with an alkaline solution [2].
2. The two-phase reaction method using an aqueous homogeneous catalyst enables products to separate by decantation or solvent extraction [3a].

In 1991, Kuraray succeeded in commercializing the production of 1-octanol by developing an aqueous homogeneous catalyst [3b].

6.9.2
Development of Technologies

Conventional dimerization of butadiene uses a trivalent phosphine as a ligand. It has been reported [4] that the catalytic activity in the telomerization is highest when the molar ratio P/Pd is kept at 1–2 : 1 and rapidly decreases when the ratio becomes about 6 : 1. Also, on telomerization with water (hydrodimerization), the catalytic activity decreases markedly with increasing P/Pd molar ratio (Figure 2).

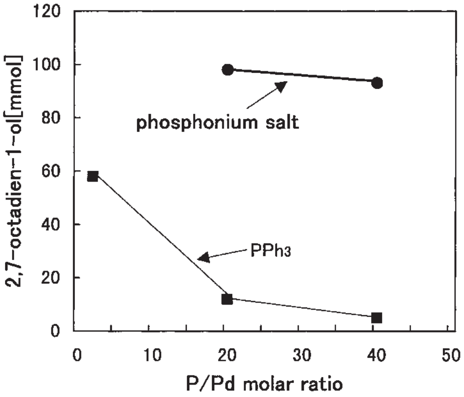
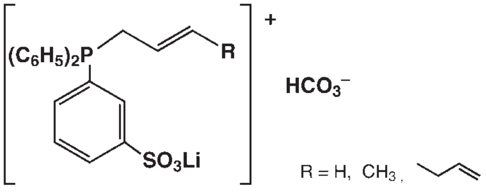


Fig. 2 Effect of the ligand concentration on the telomerization of butadiene with water in sulfolane/water (50 : 50, wt./wt.) solution containing 2 mM $Pd(OAc)_2$ and 8 wt.% triethylamine, at 75 °C for 1 h under 5 bar CO_2.

On the other hand, in order to increase the thermal stability of a palladium complex catalyst, it is necessary for a large excess of the phosphine ligand to be present together with the catalyst. This contradiction was solved by using a tetravalent phosphonium salt (**1**) as a ligand [5]. With the use of the new phosphonium salt ligand (a salt of triphenylphosphine monosulfonate, TPPMS; cf. Section 3.2.1), increasing the P/Pd molar ratio not only maintains the reaction rate at a high level



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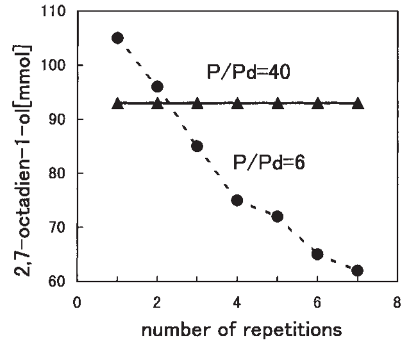


Fig. 3 The catalytic activity of repeated hydrodimerization in sulfolane/water (50 : 50) solution containing 2 mM $Pd(OAc)_2$ and 8 wt.% triethylamine, at 75 °C for 1 h under 5 bar CO_2. Products are extracted with hexane.

(Figure 3) but shows no appreciable time-dependent deterioration of the catalytic activity upon repeated reactions, as shown in Figure 3.

Another problem associated with the use of a phosphine on a commercial scale is its conversion, due to the presence of a small amount of oxygen in the reaction zone, to the corresponding phosphine oxide, which will not act effectively as a ligand. The use of a phosphonium salt can minimize this type of conversion. Although the mechanism of the action of the phosphonium salt has not been made clear, it is considered, from the fact that aryl groups should be present, that a very rapid equilibrium with the corresponding phosphine may partially occur. Upon analysis of the actual reaction mixture, however, no trivalent phosphine is detected either in the reaction solution or in the palladium complex.

For the hydrodimerization of butadiene with water, attempts have been made to increase the reactivity by adding acidic solids [6], salts such as sodium phosphate [7], emulsifiers [8], carbon dioxide [9], or the like, with no satisfactory result. In particular, the reaction rate increases under carbon dioxide pressure, but carbonate ions, not carbon dioxide itself, are considered to play an important role in this effect. It is known that the carbonate ion concentration in water is very low even under carbon dioxide pressure. If the carbonate ion is the true reactant, the reaction rate should increase in proportion to the carbonate ion concentration. But inorganic carbonates showed little effect on the reaction rate. Therefore various tertiary amines without active hydrogen were added to the reaction mixture under carbon dioxide pressure [10]. Diamines and bifunctional amines inhibited the reaction. The reaction rate increased only in the presence of a monoamine having a pK_a of at least 7, almost linearly with its concentration (Figure 4).

Telomerization requires a solvent that can dissolve in both water and butadiene. To select a suitable solvent for this purpose the separability of the reaction products from the catalyst used should be considered. According to past reports, the se-

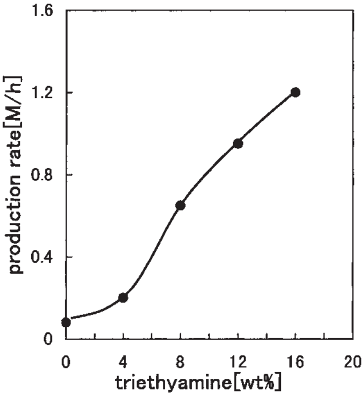


Fig. 4 The effect of concentration of triethylamine on the rate of telomerization of butadiene with water in sulfolane/water (80 : 20) solution containing 2.7 mM $Pd(OAc)_2$ and 54 mM ligand, at 75 °C for 3 h under 15 bar CO_2.

Tab. 1 Effect of solvent on the telomerization of butadiene with water as telogen.[a)]

Solvent	*Octadienol*		
	Yield [mmol]	*Selectivity [%]*	*Ratio*[b)]
Sulfolane	91	92	92 : 8
CH_3CN	30	60	81 : 19
t-BuOH	18	67	71 : 29
Acetone	12	49	53 : 47
Dimethylsulfoxide	8	65	72 : 28
Dimethylformamide	9	67	82 : 18
Water only	1	71	81 : 19

[a)] In solvent/water (55 : 45) solution (60 mL) containing 230 mmol butadiene, 0.1 mmol $Pd(OAc)_2$, 12 wt.% triethylamine, 2 mmol ligand, at 75 °C for 3 h under CO_2.

[b)] 2,7-octadien-1-ol/1,7-octadien-3-ol.

lectivity to 2,7-octadien-1-ol, which is of high industrial value, has been 70% at most. Use of sulfolane, which had not been studied as a reaction solvent, realized a high 2,7-octadien-1-ol selectivity of at least 83%, and a high reaction rate (Table 1) [10]. Sulfolane, having both high stability in its aqueous solution and high solubility for butadiene, is considered to be the most suitable solvent for industrial long-term use. Recently, it has been reported [11] that hydrodimerization into 2,7-octadiem-1-ol can be performed in the absence of co-solvent with moderately high yields when trialkylamine with a long alkyl chain is used in a two-phase aqueous catalyst system (Pd/TPPTS). The effect of amines having long alkyl chains is explained by an increase of mass transfer between the organic and aqueous phases, due to the formation of micelles.

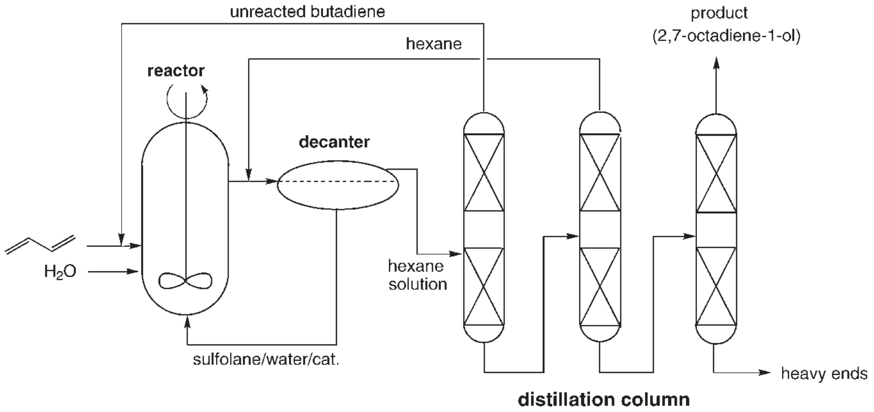


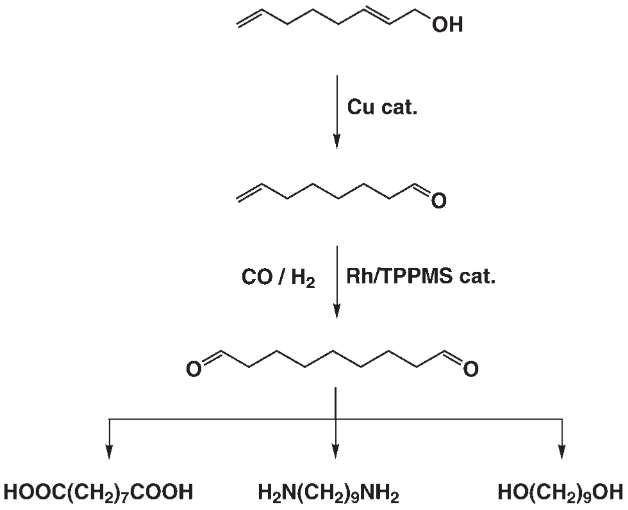
Fig. 5 Extraction method for separating butadiene hydrodimerization products from catalyst-containing reaction mixture.

For the telomerization of butadiene, distillative separation methods cannot be employed to separate the product from the reaction mixture containing catalyst, because the palladium complex catalyst has a lower thermal stability and high-boiling compounds would accumulate in the catalyst-containing solution that has been recycled. Therefore an extraction separation method has been chosen (Figure 5). In the present reaction, water acts as a nucleophile and the product hardly dissolves in water. Therefore the process is capable of retaining the catalyst component in the aqueous solution being used, and of extracting the product selectively. Thus, in order to solubilize the catalyst component in the aqueous sulfolane solution used, a hydrophilic group (e.g., sulfonic acid salt) was introduced into the phosphonium salt ligand and the product was extracted with an aliphatic saturated hydrocarbon such as hexane [5, 10, 12, 13]. This extraction separation method has the advantages that: (1) the catalyst and product can be separated without heating them, so that thermal deactivation is avoided; (2) extraction equilibrium is achieved for all compounds, so that the accumulation of catalyst poisons and high-boiling by-products is minimal. This method is commercially applicable only when the resultant catalytic lifetimes and the elution losses of catalytic components into the extractant layer containing the product are within commercially acceptable ranges.

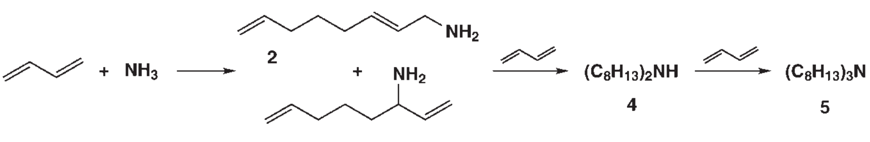
6.9.3
Process of the Manufacture of 1-Octanol and Other Derivatives

This process consists of four steps: hydrodimerization, extraction, hydrogenation, and distillation [12–14]. The telomerization step comprises feeding butadiene and water continuously to the reaction zone in the presence of a separately prepared palladium catalyst (1–5 mmol L^{-1}), a phosphonium salt ligand (40–50 mol/mol of palladium), and a solution of triethylammonium hydrogencarbonate in aqueous sulfolane, and reacting them at a temperature of 60–80 °C under a total pressure of carbon dioxide of 10–20 bar, to achieve a 2,7-octadien-1-ol selectivity of 90–93% and a 2,7-octadien-3-ol selectivity of 4–5%. In the following extraction step, 50–70% of the reaction products are extracted with hexane, and the aqueous sulfolane containing the catalyst, part of the products, and the triethylammonium hydrogencarbonate is again circulated to the reaction step. The eolution loss of the catalyst is only several parts per million. The sulfolane concentration is set at about 40 wt.% in view of the extraction ratio of the products, the solubility of butadiene, and the elution loss of the catalyst. After unreacted butadiene and hexane have been recovered from the extraction mixture, 2,7-octadien-1-ol is purified by distillation. The 2,7-octadien-1-ol obtained is hydrogenated on a fixed bed in the presence of a nickel catalyst and at 30–80 bar H_2 and 130–180 °C to yield 1-octanol nearly quantitatively. A plant with a capacity of approx. 5000 t/y is on stream.

2,7-Octadien-1-ol is a highly reactive compound having double bonds and a hydroxyl group. Reacting this compound in the presence of a copper chromite catalyst at a temperature of 220 °C causes intramolecular dehydrogenation/hydrogenation, to yield isomerized 7-octenal in a yield of at least 80% [15]. This aldehyde is hydroformylated to the dialdehyde, which is then hydrogenated to give 1,9-nonanediol [16]. The extraction separation method is also applicable to this hydroformylation. The dialdehyde can also give, on air oxidation in an acetic solvent with a copper catalyst, azelaic acid and, on reductive amination in ammonia in the presence of a nickel catalyst, 1,9-nonanediamine (Scheme 1).



Scheme 1



Scheme 2

Tab. 2 Comparison of single-phase versus two-phase catalytic reaction process in the telomerization of butadiene and ammonia.[a)]

Process	*Selectivity [%]*			*Ratio*	*Total yield [%]*[b)]
	2 + 3	*4*	*5*	*(2 + 3):4:5*	
Single-phase	2	4	61	1:2:31	21
Two-phase	31.5	25.5	1.5	21:17:1	24

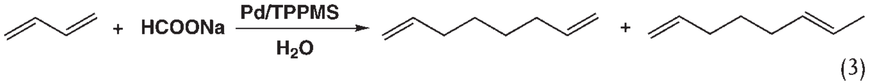
[a)] Reaction conditions: single-phase: $T = 100\,^\circ\mathrm{C}$, $t = 1$ h, butadiene/ammonia = 10:1, Pd/butadiene = 1:1000, 20 mL *t*-butyl alcohol, Pd/PPh_3 = 1:3.4; two-phase: $T = 100\,^\circ\mathrm{C}$, $t = 1$ h, butadiene/ammonia = 10:1, Pd/butadiene = 1:1000, H_2O/CH_2Cl_2 = 2:1, Pd/TPPTS = 1:4.

[b)] Based on ammonia.

6.9.4
Applications

Homogeneous telomerization reaction of butadiene with ammonia produces trioctadienylamines (5) as a major product. It is different from the primary and secondary amines obtained (4) because the nucleophilicity of the alkylamine is stronger than that of ammonia (Scheme 2). When this reaction is carried out in two phases using an aqueous homogeneous palladium catalyst modified by TPPTS, primary and secondary octadienylamines are obtained as major products, as shown in Table 2. The primary amine is immediately extracted into the organic phase from the aqueous catalyst phase by using solvents such as toluene. In this way, the consecutive reactions of primary products that are slightly soluble in water are avoided. The primary octadienylamines are formed with a selectivity of 88% [18].

Telomerization of butadiene with formic acid or its salts can produce 1,7-octadiene (Eq. 3), which is useful as a modifier for polyolefins. This reaction proceeds with the same system that is used for the production of octadienol, at a temperature of 50–70 °C, to yield 1,7-octadiene/1,6-octadiene in a ratio of 88:12. Since these compounds phase-separate together, the product layer can be readily separated and the sulfolane layer containing the catalyst can be circulated for re-use [19].



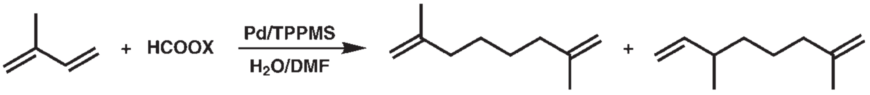
(3)

Tab. 3 Hydrodimerization of isoprene with formic acid alkali-metal salt.[a)]

Alkali metal	*Temperature [°C]*	*Conversion [%]*	*Selectivity [%]*	
			6	***7***
Na	60	65	14	73
K	85	91	88	11

[a)] 0.027 mmol Pd(acac)$_2$, 0.054 mmol TPPMS, 18.5 mmol formic acid alkali-metal salt, 5 mL DMF, 5 mL H_2O and 2.5 g isoprene for 2 h.

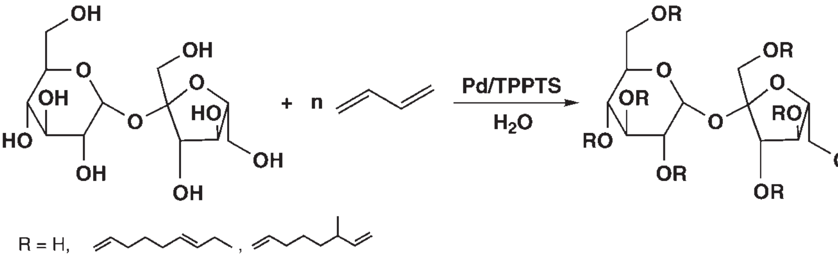
When reductive dimerization of isoprene in the presence of an alkali-metal salt of formic acid is carried out, the regioselectivity to dimethyloctadiene (Eq. 4) varies with the species of alkali metal, as shown in Table 3 [20].



X = Na, K, H

6 **7** (4)

Etherification of carbohydrate is an important reaction. The two-phase reaction of butadiene with saccharose by an aqueous palladium complex catalyst increases the reaction yield of the desired ether products (Eq. 5) [21].



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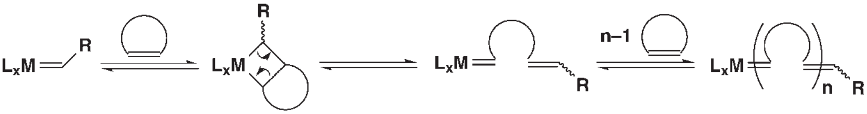
6.10
Alkene Metathesis

Robert H. Grubbs, David M. Lynn

6.10.1
Introduction

Alkene metathesis is a transition-metal-catalyzed reaction in which alkene bonds are cleaved and redistributed to form new alkenes [1–3]. The reaction proceeds through the formal [2 + 2] cycloaddition of an alkene and a metal alkylidene to yield a metallocyclobutane intermediate (Scheme 1). The productive retrocycloaddition of this intermediate generates a new metal alkylidene and a new alkene product. These processes are generally reversible, and the reaction is under thermodynamic control.



Scheme 1

The versatility of the metathesis reaction has attracted the attention of chemists with interests ranging from polymer chemistry to organic synthesis. For example, cyclic alkenes will undergo ring-opening metathesis polymerization (ROMP) to yield polymers having backbone unsaturation (Scheme 1) [1, 4, 5]. ROMP is particularly well suited to the polymerization of highly strained monomers as the reaction is driven by relief of monomer ring strain. Recently, the polymerization of acyclic α,ω-dienes *via* acyclic diene metathesis has been demonstrated [6], and applications to the synthesis of small molecules and natural products *via* ring-closing metathesis and cross-metathesis have received much attention [7, 8].

Over the last 20 years, metathesis catalysts have evolved from poorly defined, heterogeneous mixtures to well-defined, single-component metallocycles and alkylidenes [9–18]. These complexes react in controlled, consistent ways, and their activities can be attenuated through simple ligand substitution. In contrast to hetero-

Aqueous-Phase Organometallic Catalysis, Second Edition
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ISBN: 3-527-30712-5

Tab. 1 Relationship between metal center and alkene selectivity.

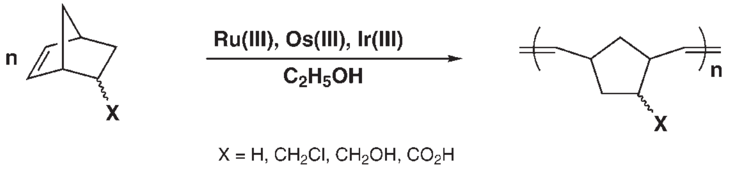
Metal center:			
Titanium	***Tungsten***	***Molybdenum***	
Acids	Acids	Acids	↑ Increasing reactivity
Alcohols, water	Alcohols, water	Alcohols, water	
Aldehydes	Aldehydes	Aldehydes	
Ketones	Ketones	*Alkenes*	
Esters, amides	*Alkenes*	Ketones	
Alkenes	Esters, amides	Esters, amides	

geneous systems, for example, several of these well-defined alkylidenes initiate living ROMP [4]. An important result of having catalysts based on a variety of transition metals was the observation of trends in functional-group tolerance [19, 20]. In particular, it was found that as the metal centers in these complexes were chosen from further right in the Periodic Table, the resulting alkylidenes reacted more selectively with alkenes in the presence of other harder, Lewis-basic functional groups (Table 1) [3].

Historically, alkene metathesis has been limited to the polymerization of cyclic hydrocarbons in highly purified organic solvents, due to the extreme sensitivities of early transition metal catalyst systems to oxygen, water, and polar functional groups [21]. It was quickly realized that the development of metathesis catalysts that were particularly tolerant of polar and protic functional groups would offer several advantages, the most obvious being the use of substrates and solvents without rigorous purification and drying. More tolerant catalysts would also broaden the scope of the reaction, enabling the ROMP of highly functionalized monomers and obviating the need for functional group protection/deprotection schemes. Additionally, the possibility of water-tolerant and, ultimately, water-soluble catalysts could enable the metathesis of alkeneic substrates in aqueous solution. These potential benefits prompted a search for active catalysts based on late transition metals that would be stable toward functional groups and which might function homogeneously in water.

6.10.2
"Classical" Group VIII Catalysts

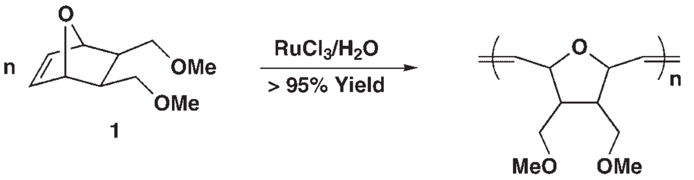
Soon after the discovery of the alkene metathesis reaction, reports indicated that complexes of ruthenium, osmium, and iridium could initiate ROMP. Michelotti et al. initially reported the polymerization of norbornene and its derivatives catalyzed by the hydrates of $RuCl_3$, $OsCl_3$, and $IrCl_3$ in refluxing ethanol (Eq. 1) [22, 23].



(1)

These complexes also functioned well in benzene, although small amounts of ethanol were necessary to initiate polymerization. The order of activity for these catalysts was Ir(III) > Os(III) > Ru(III), and they were found to polymerize monomers with *exo* substituents more readily than *endo* isomers. Rinehart and Smith later demonstrated that these complexes initiated the aqueous polymerization of a substituted norbornene derivative in the presence of anionic emulsifiers and suitable reducing agents [24]. This reaction gave particularly low yields of polymer (typically less than 9%), but the overall tolerance of these complexes to polar and protic functionalities made them ideal candidates for further study.

For the ROMP of functionalized 7-oxanorbornenes, possible only *via* these late transition metal catalysts, it was found that the best catalyst was $RuCl_3$ in a mixture of ethanol and benzene [20, 25]. However, the lack of a preformed alkylidene in this "precatalyst" limited its practical usefulness, as polymerizations were preceded by lengthy initiation periods ranging from several hours to several days [25, 26]. Rigorous exclusion of water and oxygen from these systems was found to lengthen initiation periods, while the addition of small amounts of water substantially increased initiation rates. The conclusion that water functioned as a cocatalyst in these systems eventually led to the discovery that $RuCl_3$ functioned as an excellent ROMP initiator in entirely aqueous environments [27, 28]. For example, the emulsion polymerization of *exo*-5,6-bis-methoxymethyl-7-oxanorbornene **1** (Eq. 2) proceeded quantitatively with initiation periods as short as 30 min [27].

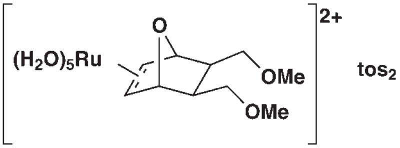


(2)

The molecular masses of poly(**1**) synthesized in aqueous media were typically high ($M_n \approx 10^6$), and polydispersity indices (PDIs) were often lower (< 2.0) than the polydispersities of polymers produced by classical systems in organic solvents [27, 29, 30]. These low polydispersities have been attributed to the low occurrence of termination reactions during the polymerization and the relative inactivity of the propagating species toward the acyclic alkenes in the polymer, which suppresses chain-transfer reactions [25]. Although initiation occurred more quickly in aqueous systems, the extent of initiation was still low. In fact, it has been estimated that fewer than 1% of the metal centers are converted to active alkylidenes. As a result, polymer properties were inconsistent from run to run and depended heavily on the purity of the notoriously impure $RuCl_3$ complex [25, 29, 30]. Molecular masses were generally independent of monomer/catalyst ratios, indicating that these aqueous polymerizations were not living.

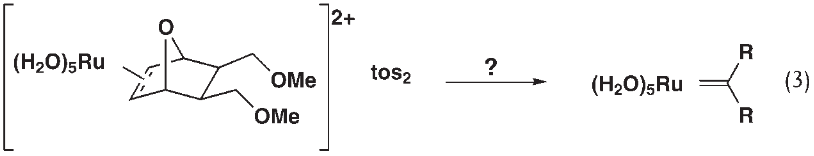
The problems outlined above prompted an investigation of the mechanism through which initiation occurred in these ill-defined systems. During the examination of used aqueous ruthenium solutions, it became evident that these solutions could be used to initiate additional polymerizations, and that the catalytic species in these solutions became more active upon successive use [25, 27]. Initiation periods for these recycled solutions were as low as 10 s after two or three polymerizations, and catalyst solutions could be re-used up to 14 times without a decrease in activity. This effect was observed for aqueous polymerizations initiated by other Ru(III) complexes, including K_2RuCl_5 and $[Ru(NH_3)_5Cl]Cl_2$, which reached the same limiting initiation time of 10 s upon re-use [25].

Studies employing Ru(II) complexes, such as $[(C_6H_6)Ru(H_2O)_3]tos_2$ (tos = *p*-toluenesulfonate), revealed similar effects on recycling, although they were initially more active than their Ru(III) counterparts. For example, in aqueous polymerizations of **1** catalyzed by $Ru(H_2O)_6tos_2$, induction periods were initially as short as 50 s. An important step in the identification of the active species in this polymerization was made when a ruthenium–alkene complex (Structure **2**) was observed after polymerization of **1** initiated by $Ru(H_2O)_6tos_2$ [25–27].



2

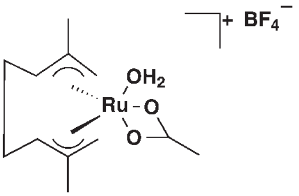
Recycled solutions of **2** initiated ROMP as quickly as the recycled Ru(III) solutions, closer examination of which revealed NMR resonances identical to those of the alkene protons in **2** [25]. It was therefore suggested that a key step in the initiation process using Ru(III) was the *in situ* formation of a Ru(II)–alkene complex [27]. Current evidence supports the disproportionation of the Ru(III) species to form Ru(II) and Ru(IV) species, followed by formation of a Ru(II)–alkene complex [25]. The equilibrium constant for disproportionation is small, accounting for the poor initiation efficiency of the Ru(III) systems [30]. An alternative, the disproportionation of an equilibrium amount of Ru(III)–alkene complex to a Ru(II)–alkene complex and a Ru(IV) species, is unlikely since Ru(III)–alkene complexes are generally unstable. Formation of a ruthenium alkylidene, the requisite active species in these polymerizations, *via* rearrangement of **2** has been proposed (Eq. 3), although the mechanism for this reaction is not known [20].



(3)

2

Water-soluble bisallyl Ru(IV) complexes **3** and **4** also initiate the emulsion polymerization of norbornene [31]. The lack of preformed alkylidenes in these complexes limits initiation efficiency, although the onset of initiation is not subject to lengthy initiation periods. Speculation on the active species in polymerizations initiated by these bisallyl complexes has not been reported.



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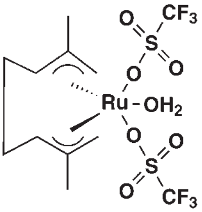
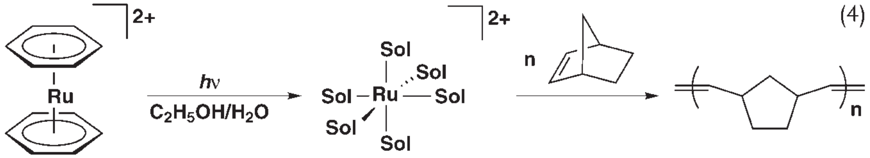


4

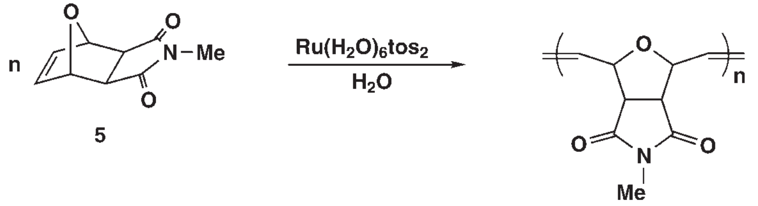
Karlen and co-workers have described a photoinitiated ROMP (PROMP) system in water/ethanol mixtures using a variety of cationic ruthenium complexes with photolabile ligands [32, 33]. For example, the irradiation of $[Ru(CH_3CN)_6](tos)_2$ or $[(C_6H_6)_2Ru9](tos)_2$ leads to partially and fully solvated Ru(II) species which initiate the ROMP of highly strained alkenes, presumably in the manner outlined below (Eq. 4).

(4)



6.10.3
Polymers Prepared via Aqueous ROMP

The Group VIII complexes discussed above are generally limited to the ROMP of functionalized norbornenes and 7-oxanorbornenes (cf. also Section 6.12.6). These complexes have been used to initiate the polymerization and copolymerization of monomers containing alkyl [22, 23, 34], aryl [30], ether [27, 29, 35], alcohol [25], ester [30, 34], anhydride [25, 34, 36, 37], carboximide [38, 39], and fluoromethyl [30] functionalities in aqueous environments. Aqueous polymerization of dicarboxyimide functionalized monomer **5** initiated by $Ru(H_2O)_6tos_2$ gave quantitative yields of a polymer having excellent thermal properties (Eq. 5) [38]. Additionally, polyacid materials were synthesized *via* the ROMP of anhydride-functionalized monomer **6**, which spontaneously opened to the diacid upon polymerization in aqueous environments (Eq. 6) [25, 26, 37]. Kiessling et al. have recently used $RuCl_3$ to initiate the polymerization of **7** and other saccharide-containing monomers to produce a variety of new glycopolymers having biological activities (Eq. 7) [40–42]. Many polymers based on the ROMP of functionalized 7-oxanorbornenes have been investigated for their potentials as ionophoric materials [26].



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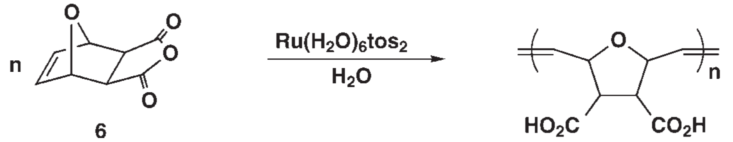

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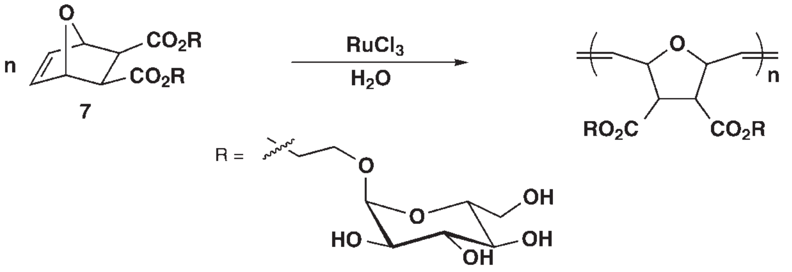


(7)

As previously mentioned, the molecular masses of the polymers obtained from these aqueous reactions are generally higher than desired due to the small number of active species. Although the propagating species in these polymerizations do not typically react with acyclic alkenes, modest control over molecular mass is possible when certain acyclic chain-transfer agents are employed [35, 44]. For example, Feast and Harrison have used very high concentrations of *cis*-2-butene-1,4-diol or its dimethyl ether as chain-transfer agents [35]. The chain-transfer constants in these reactions were small, and inclusion of these alkenes in the reaction mixture was shown to affect initiation periods and catalyst activities in complex ways.

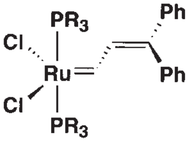
The microstructures of polymers synthesized in aqueous media have been well studied by ^1H and ^{13}C NMR. Although most polymers prepared using these catalysts contain a high degree of *trans* alkene bonds, the ratio of *trans* to *cis* alkenes has been found to vary considerably from catalyst to catalyst [35]. For example, poly-**1** prepared in water using $RuCl_3$ generally contains 60% *trans* alkenes, while polymer samples prepared from $OsCl_3$ and $IrCl_3$ contain 75% and 90% *trans* alkenes, respectively. In all cases, poly-**1** prepared by these catalysts was atactic. For the polymerization of *exo*-5,6-bis(methoxycarbonyl)-7-oxanorbornene, $RuCl_3$ gave a polymer having 88% *trans* alkene bonds, while $[Ru(\eta^6\text{-}C_6H_6)(H_2O)_3]tos_2$ and $Ru(H_2O)_6tos_2$ gave polymers containing equal amounts of *cis* and *trans* alkenes [30]. In the $RuCl_3$-initiated polymerizations, the ratio of *trans* to *cis* alkenes remained constant over prolonged reaction times, again demonstrating the relative absence of chain-transfer reactions that would eventually result in thermodynamic equilibration. A notable reversal in the *trans/cis* selectivities in these reactions is observed in the emulsion polymerization of norbornene initiated by bisallylruthenium complexes **3** and **4**, which yield polynorbornene having 85–90% *cis* alkene bonds [31].

6.10.4
Alkylidenes as Catalysts

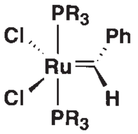
6.10.4.1
Well-defined Ruthenium Alkylidenes

The insight derived from the investigation of ill-defined ruthenium ROMP initiators was successfully applied to the development of Ru(II) alkylidenes **8** and **9** [15–18]. In contrast to the classical complexes, these well-defined alkylidenes initiated ROMP quickley and quantitatively, reacted readily with acyclic alkenes, and could be used to initiate living polymerizations in organic solvents.

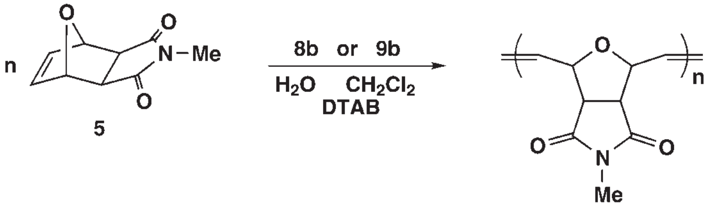
Although these well-defined complexes were insoluble in water, they were highly water-tolerant, and complexes **8b** and **9b** were used to catalyze living ROMP in aqueous emulsions (Eq. 8) [45, 46]. Introduction of a small amount of organic solvent was necessary to achieve controlled initiation, and these reactions worked best in the presence of cationic emulsifiers. Initiation was fast and complete, and polymer molecular masses were found to vary linearly with the ratios of monomer to initiator, indicating that these aqueous ROMP systems were indeed living [45]. Polymers having narrow polydispersities ($PDI \leq 1.10$) were prepared from hydrophilic and hydrophobic monomers, and well-defined block copolymers were synthesized via sequential monomer addition. Kiessling and co-workers have recently applied this methodology to the synthesis of water-soluble, biologically active glycopolymers [47].



8a R = Ph
8b R = Cy



9a R = Ph
9b R = Cy

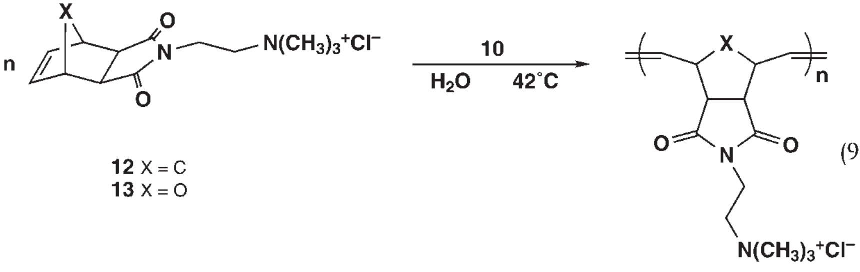


(8)

6.10.4.2
Water-soluble Alkylidenes

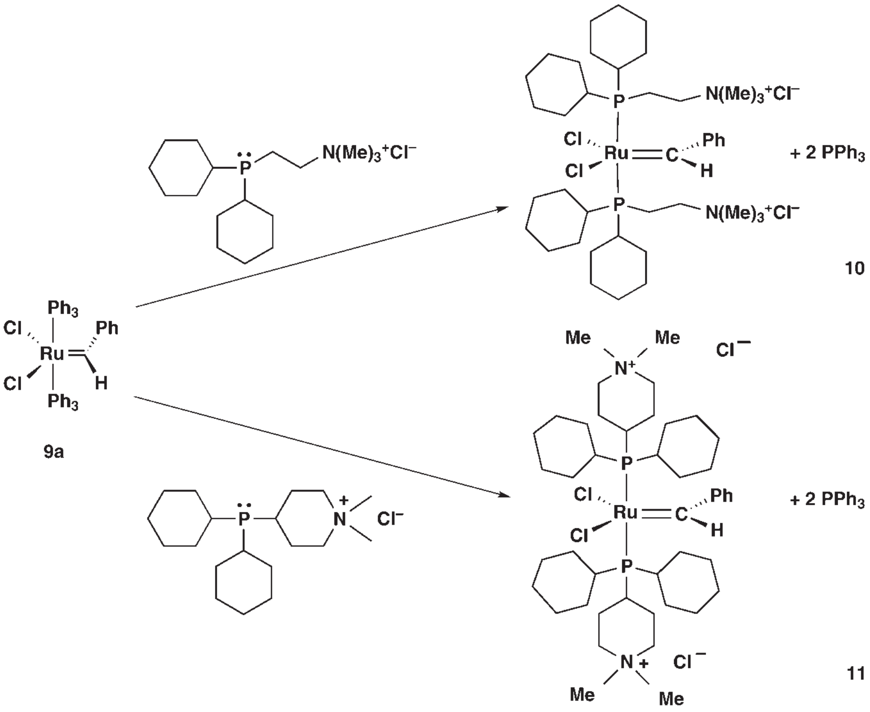
Water-soluble derivatives of alkylidenes **8** and **9** were prepared *via* phosphine ligand substitution reactions. Exchange of the phosphines in **8a** for $PhP(p\text{-}C_6H_4SO_3Na)_2$ afforded a water-soluble vinyl alkylidene [20]. This alkylidene was soluble in water, but the triarylphosphine ligands were too small and insufficiently electron-donating to produce an active catalyst [48]. Analogous substitution of the phosphines in **9a** for more sterically demanding, electron-rich, water-soluble phosphines yielded ruthenium alkylidenes **10** and **11** (Scheme 2), which were soluble in both water and methanol [49].

In contrast to the "classical" catalysts, alkylidenes **10** and **11** initiated ROMP quickly and quantitatively [49, 50]. A propagating alkylidene species was directly observed by ^1H NMR during the polymerization of most monomers, although the catalyst often decomposed before polymerization was complete. In the ROMP of water-soluble monomers **12** and **13** initiated by **10**, for example, conversions ranging from 45 to 80% were usually observed (Eq. 9) [50].



12 X = C
13 X = O

(9)

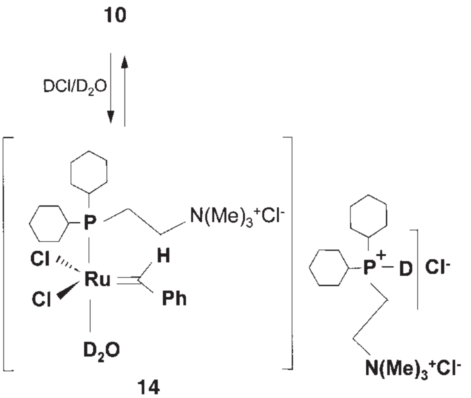


Scheme 2

It was found, however, that monomers could be *quantitatively* polymerized by **10** and **11** in the presence of stoichiometric amounts of a strong Brønsted acid [50]. The effect of the acid in these systems was determined to be twofold, eliminating small concentrations of detrimental hydroxide ions, and accelerating the rate of metathesis with respect to termination reactions. Remarkably, the acids did not react to decompose the ruthenium alkylidene, and a propagating alkylidene species was clearly observed following complete consumption of monomer. Addition of more monomer to the reaction mixture resulted in further quantitative polymerization, enabling the synthesis of block copolymers.

Considerable progress has been made in the characterization and applications of the ruthenium catalysts that will function in aqueous and protic media. A number of approaches have been made to produce conditions and ligand systems that will allow ruthenium based alkene metathesis in aqueous and protic media to reach the same generality as metathesis in organic solvents.

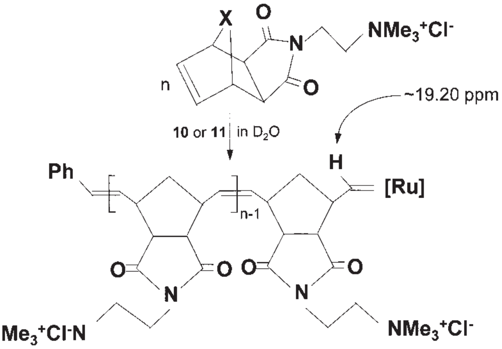
The complexes **10** and **11** have been studied in more detail. These compounds can be used to polymerize water soluble monomers if the reaction is carried out in the presence of one equivalent of acid. The acid neutralizes the base formed by the loss of the basic ligand and also helps to trap the phosphine to produce a high concentration of the active coordinate complex **14** (Eq. 10).



14

(10)

Reaction with a water-soluble monomer results in a polymer of narrow polydispersity index (PDI = 1.2) and the living polymer (Structure **15**) can be observed in solution (Eq. 11); [51]).



15

(11)

The down field shift of the alkylidene proton to 19.20 ppm is characteristic of such structures. This living polymer alkylidene is stable for extended periods of time. Solutions contain significant amounts of the living alkylidene after 3 months.

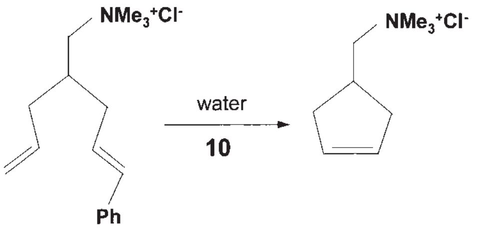
In a similar way, the complexes **10** and **11** react with simple alkenes to produce new alkylidenes. For example, the reaction with 2-butene results in the formation of the stable ethylidene complex **16**.

When a similar reaction is carried out using ethylene, the expected methylene complex is not observed. It appears as though the methylene complex is not stable in water and decomposes rapidly to a mixture of ruthenium hydride species.

As indicated by the instability of the methylene complex, the reactive of the alkylidenes in water are significantly different than in organic media. One of the first indicators was the observed exchange of the benzylidene proton in **10** and **11**. When these complexes are dissolved in D_2O, the characteristic signal for the benzylidene proton vanishes. If protons are added to the solution the signal reappears.

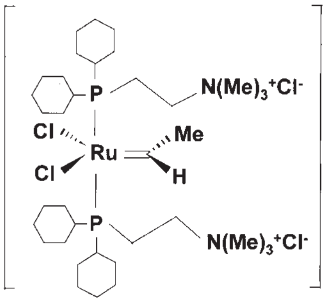
This exchange reaction is clean and only occurs at a significant rate in aqueous solutions. Although the mechanism was not well established, the solvolysis of one of the halides followed by deprotonation to form the corresponding carbine complex is most consistent with the results. This mechanism may provide an insight into the mechanisms of decomposition that are facilitated by high dielectric solvents [52].

Applications of the water-soluble catalysts to initiate methathesis of less strained alkenes are limited by the instability of some of the alkylidenes in water. For example, diethyldiallylmalonate, a standard metathesis substrate in organic solvents, does not ring close in either methanol or water/methanol mixtures. In this case the chain carrying species is the ruthenium methylene complex. As seen above, this complex is unstable in water. However, when the reaction is redesigned to use substrate **17** so that the methylene is not the chain carrying intermediate, ring closing can be carried out under aqueous conditions (Eq. 12).



(12)

17

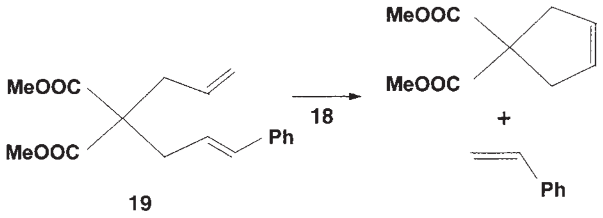


18

With this substrate, the benzylidene is both the initiator and chain carrying alkylidene and it's stability allows the reaction to be carried out in good yields [53].

In a related complex, the sulfone analog of cyclohexyl phosphine was prepared and tested as an active ligand for metathesis. This ligand was sufficiently polar to produce a catalytically active complex **18** that was soluble in dichloromethane, benzene, methanol and methanol : water (3 : 1).

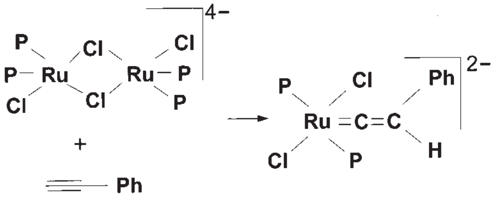
In the ring closure of substrate **19**, the activity of the catalyst in the mixture methanol/water was significantly lower than for the corresponding reaction in methylene chloride (Eq. 13) [54]. The complex **18** is not soluble in pure water.



MeOH at 40°/12h: 98%
$MeOH/H_2O$ at 40°/12h: 78%
CH_2Cl_2 at 25°/4h: 100%

(13)

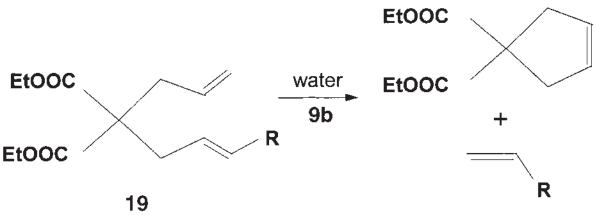
Another class of catalysts was produced using water-soluble ligands. In this case, ionic complexes were prepared containing ionic phosphine ligands. Saoud reported the synthesis of vinylidene and allenylidene complexes that contained the TPPMS ligand (TPPMS $= Ph_2P[3\text{-sulfonato}C_6H_4]^-Na^+$). These complexes are easily prepared from acetylene precursors and show good activity in methanol or under biphasic (organic/water) conditions (Eq. 14; P = TPPMS) [55].



(14)

In homogeneous methanol solution and in a mixture of acidic water and diethyl ether, the catalyst induced the cross metathesis of methylacrylate with cyclopentene to give either the $C_7H_{11}CO_2CH_3$ (56% in homogeneous solution) or $C_{12}H_{19}CO_2CH_3$ (42% under biphasic conditions). In these cases, the water appears to activate the catalyst since it has been observed in the past that aryl phosphines are poor ligands for such metathesis reactions. It is also interesting that the corresponding *para*-substituted analogs were not active for the metathesis of unstrained alkene. Since different initiators containing different alkylidenes all produce the same chain carrying alkylidenes, the role of the different phosphines is very interesting.

Sinou has reported [56] that in some cases the ring closing metathesis of acyclic dienes can be carried out using the biscyclohexylphosphine catalyst **9b** in water without the need for surfactants. These are heterogeneous reactions since neither the substrate nor catalyst is soluble in water. For example, the ring closure of diethyl diallylmalonate in water alone using 5 mol% **9b** gave only a 51% conversion after an hour without the use of a surfactant. However, the addition of some surfactant SDS increased the yield to 100% after one hour. In contrast, when the phenyl substituted substrate **19d** was used the yield was independent of whether or not a surfactant was used (Eq. 15).



19

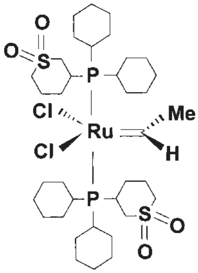
(15)

Compd.	R	Surfactant	Time	Conversion
19a	H	none	1hr	51%
19b	H	SDS	1hr	100%
19c	Ph	none	1hr	95%
19d	Ph	SDS	1hr	94%

In contrast to the reactions above with the water-soluble ligands, it is assumed that these reactions take place in the organic phase of the reaction mixture. Under these circumstances, the concentration of the substrate and catalysts are very high and the intermediates are not exposed to an aqueous environment. With the lower molecular weight substrates, the surfactant helps to form a stable reaction media. With higher molecular weight substrates, the surfactant are not required to form stable organic phases.

Blechert has used a water compatible support for a metathesis catalyst [57]. The support swells with water and allows ring-closing metathesis to be carried out in aqueous media. The commercially available PEGA-NH_2 (Structure **20**) resin was functionalized and connected to a phosphine free metathesis catalyst to prepare heterogeneous complex **21**.

Since **21** will swell in water it can be used in aqueous, as well as, methanol solvents. These catalysts were particularly effective in methanol and produced good yields for the first time for the ring closing of the hydrochloride salt of diallylamine. It was proposed that since the analogous non-supported catalyst was not active in water for simple ring closings (in contrast to the work discussed above), the reactions are taking place in the resin pores. This is particularly interesting since with this support design, the complex is released from the support on the first catalytic turnover. As a consequence, the active species in these systems



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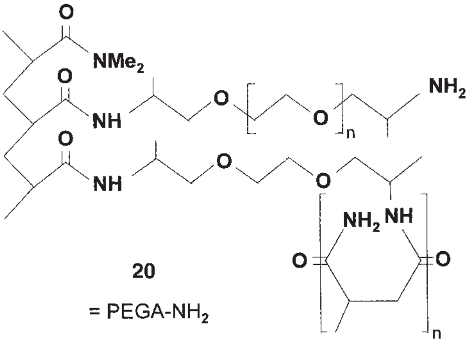
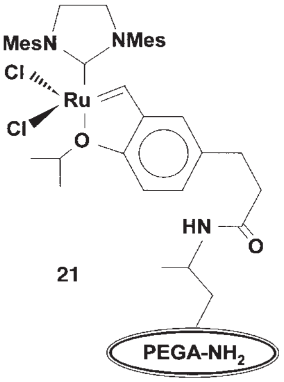


20

= PEGA-NH$_2$

would be the same as with the unsupported catalyst. In this case, the support is delivering the catalyst to the aqueous environment.

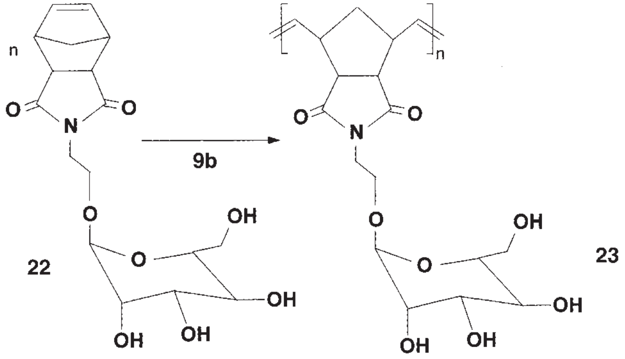


21

The remaining two examples of metathesis chemistry in water are related to the synthesis of polymers. In the first case, the solubility and stability of the ruthenium catalysts in water is exploited in the emulsion polymerization of norbornenes and cyclooctadiene. In emulsion polymerization, a water-soluble initiator is required. Claverie [58] used complex **11** or the related complex RuCl$_2$-(TPPTS)$_2$(=CHCO$_2$Et) (where TPPTS = tris(3-sulfonatophenyl)phosphine, sodium salt). These two complexes were used with standard surfactants to product well controlled polynorbornene latexes. The typical particle size ranged from 50–100 nm. Less strained monomers such as cyclooctadiene were not polymerized under emulsion conditions. In this case, the hydrophobic catalysts **9b** was used in a microemulsion technique to produce a latex of polybutadiene.

Kiessling has pioneered the use of ROMP polymers to explore a variety of protein-saccharide interactions that are critical components of diverse biological processes [59].

ROMP techniques have been used to prepare a family of monomers displaying a single saccharide residue. These hydrophilic monomers **22** have been polymerized under a variety of conditions. Early polymers were prepared by the use of ill-defined $RuCl_3$ catalysts. Recently, catalyst **9b** was used under a variety of conditions to produce polymers for the required biological studies. Suspension conditions using DTAB as surfactant is required to obtain high molecular weight polymers **23** (Eq. 16).



(16)

Although a number of systems are now available that will allow some metathesis reactions to take place in aqueous solution, the generality and activity of these systems is not yet sufficient to carry out many RCM and cross metathesis reactions with the desired catalyst efficiency. The instability in water of the ruthenium alkylidenes known to date has not allowed alkene metathesis processes in aqueous media to reach the level of utility that is possible in organic solvents.

6.10.5
Summary

The synthesis of alkylidenes incorporating late transition metals has resulted in alkene metathesis catalysts having unprecedented functional group tolerance. In particular, the discovery that complexes of Group VIII transition metals were efficient ROMP catalysts introduced several advantages. Relative to their early transition metal counterparts, these “classical” catalysts functioned well in the presence of a variety of polar and protic functional groups (Table 2), and they functioned homogeneously in water.

Tab. 2 Early vs. late transition metal selectivity.

Metal center:				
Titanium	***Tungsten***	***Molybdenum***	***Ruthenium***	
Acids	Acids	Acids	*Alkenes*	↑
Alcohols, water	Alcohols, water	Alcohols, water	Acids	
Aldehydes	Aldehydes	Aldehydes	Alcohols, water	Increasing reactivity
Ketones	Ketones	*Alkenes*	Aldehydes	
Esters, amides	*Alkenes*	Ketones	Ketones	
Alkenes	Esters, amides	Esters, amides	Esters, amides	

The lessons learned from these complexes were eventually applied to the synthesis of well-defined ruthenium alkylidenes **8** and **9**. Although they were insoluble in water, these alkylidenes could be used to initiate the living ROMP of functionalized norbornenes and 7-oxanorbornenes in aqueous emulsions. Substitution of the phosphine ligands in **9** for bulky, electron-rich, water-soluble phosphines produced water-soluble alkylidenes **10** and **11**, which served as excellent initiators for the ROMP of water-soluble monomers in aqueous solution. These new ruthenium alkylidene complexes are powerful tools in the synthesis of highly functionalized polymers and organic molecules in both organic and aqueous environments.

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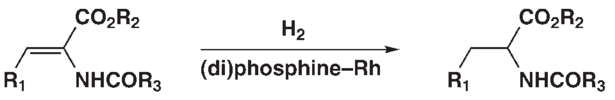
6.11
Asymmetric Synthesis

Denis Sinou

During the last 20 years there have been very important advances in asymmetric synthesis via the use of a soluble chiral organometallic catalyst [1]. Now enantioselectivities higher than 95% have been obtained currently in reactions such as hydrogenation, isomerization, epoxidation, hydroxylation, and allylic substitution. Although water-soluble ligands were known since the 1960s and were used as catalysts in asociation with rhodium or ruthenium complexes in a two-phase system, it is only recently that this methodology was extended to the reduction of prochiral substrates using chiral water-soluble phosphines.

The water-solubilization of the typical chiral phosphines used (Structures **1**–**16**) are mainly due to the presence of a sodium sulfonate or a quaternary ammonium function in the molecule. The enantioselective hydrogenation of some α-amino acid precursors **17** (Eq. 1) to the α-amino acids **18** has been thoroughly investigated using rhodium complexes associated with these chiral ligands, in water or in an aqueous/organic two-phase system (Table 1). Under these conditions the reaction rates are generally lower than in a homogeneous organic phase.



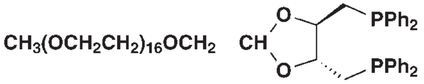
17 **18** (1)

for example
a: $R_1 = R_2 = H$, $R_3 = CH_3$; **b**: $R_1 = H$, $R_2 = R_3 = CH_3$; **c**: $R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$,
d: $R_1 = C_6H_5$, $R_2 = R_3 = CH_3$; **e**: $R_1 = R_3 = C_6H_5$, $R_2 = H$; **f**: $R_1 = R_3 = C_6H_5$, $R_2 = CH_3$,
g: R_1 = 3-MeO-4-AcO-C_6H_3, $R_2 = H$, $R_3 = CH_3$

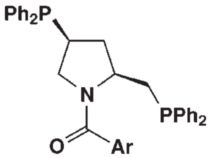
Among the first chiral water-soluble ligands used in hydrogenation were PGE-17-DIOP (**1**) and ligands **2** and **3** [2–4]; however, the rhodium catalysts containing these ligands gave low enantioselectivities and could not be recycled. The most investigated chiral ligands were the sulfonated phosphines **5**–**8** [5, 6] and those possessing a quaternary ammonium function (**4** and **10**–**12**) [7–11]. It is to be noticed that rhodium complexes of water-soluble 1,2-diphosphines such as **4**,

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

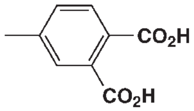
ISBN: 3-527-30712-5

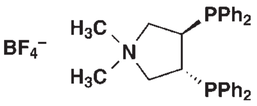


(*R*,*R*)-PGE-17-DIOP **1**



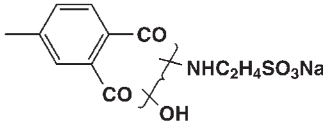
(*S*,*S*)-**2** Ar =

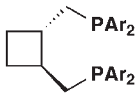




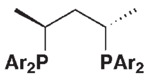
(*R*,*R*)-**4**

(*S*,*S*)-**3** Ar =



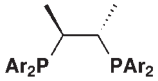


(*S*,*S*)-CBD **5**



(*S*,*S*)-BDPP **6**

Ar = 3-$NaO_3SC_6H_4$

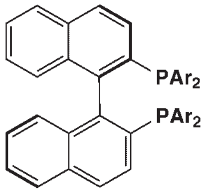


(*S*,*S*)-CHIRAPHOS **7**

Ar = 3-NaO_3S-C_6H_4-

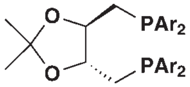
(*R*)-PROHPOS **8**

Ar = 3-NaO_3S-C_6H_4-

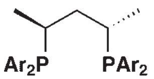


(*R*)-BINAP **9**

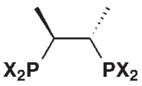
Ar = 3-NaO_3S-C_6H_4-



(*R*,*R*)-**10**

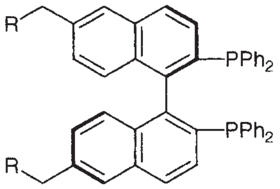


(*S*,*S*)-**11**



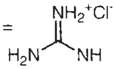
(*S*,*S*)-**12**

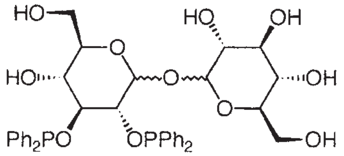
a X = *p*-Me_3N-$C_6H_4{}^+BF^-$; **b** X = *p*-Me_2HN-$C_6H_4{}^+BF^-$



(R)- diamo-BINAP **13** R = $NH_3{}^+Br^-$

(R)- digm-BINAP **14** R =





15 α,α
16 β,β

CHIRAPHOS (**7**), and **12** generally retained their high enantioselectivity in water or in a two-phase system (*ee* = 65–96%). On the other hand, rhodium complexes of 1,4-diphosphines such as CBD (**5**) or DIOP (**10**) and 1,3-diphosphines such as BDPP (**6**) and **11** gave lower enantioselectivities in aqueous phase than the insolu-

Tab. 1 Asymmetric hydrogenation of α-amino acid precursors **17** at 25 °C using a rhodium catalyst.

Precursor 17	***Ligand***	***Solvent***	***p_{H_2} [bar]***	***Product***		
				ee [%]	***Config.***	***Refs.***
17a	(*R*,*R*)-**1**	H_2O	1	11	*R*	[3]
17a	(*S*,*S*)-**2**	H_2O/Na_2HPO_4	1	31	*R*	[4]
17a	(*S*,*S*)-**3**	H_2O	1	34	*R*	[4]
17a	(*R*)-**9**	H_2O	1	70	*S*	[15]
17a	**15**	H_2O/AcOEt (1:1)	5	65	*S*	[13]
17b	(*R*)-**9**	H_2O	1	69	*S*	[15]
17b	**15**	H_2O	5	55	*S*	[13]
17b	**16**	H_2O	5	80	*S*	[14]
17c	(*R*,*R*)-**1**	H_2O	1	30	*R*	[3]
17c	(*S*,*S*)-**2**	H_2O	5	60	*R*	[4]
17c	(*S*,*S*)-**5**	H_2O/AcOEt (1:1)	1	34	*S*	[6]
17c	(*S*,*S*)-**6**	H_2O/AcOEt (1:1)	15	65	*R*	[6]
17c	(*S*,*S*)-**7**	H_2O/AcOEt (1:2)	10	87	*R*	[6]
17ca)	(*R*,*R*)-**4**	H_2O	1	90	*S*	[7]
17c	(*R*,*R*)-**10a**	H_2O	14	25	*S*	[9]
17c	(*R*,*R*)-**10b**	H_2O	14	34	*S*	[9]
17c	(*S*,*S*)-**11a**	H_2O	14	67	*R*	[9]
17c	(*S*,*S*)-**11b**	H_2O	14	71	*R*	[9]
17c	(*S*,*S*)-**11b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	73	*R*	[9]
17c	(*S*,*S*)-**12a**	H_2O	14	94	*R*	[9]
17c	(*S*,*S*)-**12b**	H_2O	14	90	*R*	[9]
17d	(*S*,*S*)-**5**	H_2O/AcOEt (1:1)	1	20	*S*	[6]
17d	(*S*,*S*)-**6**	H_2O/AcOEt (1:1)	15	45	*R*	[6]
17d	(*S*,*S*)-**7**	H_2O/AcOEt (1:1)	10	81	*S*	[6]
17d	(*R*,*R*)-**10a**	H_2O	14	8	*S*	[6]
17d	(*R*,*R*)-**10b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	25	*S*	[9]
17d	(*S*,*S*)-**11a**	H_2O	14	40	*R*	[9]
17d	(*S*,*S*)-**11a**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	45	*R*	[9]
17d	(*S*,*S*)-**11b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	50	*R*	[9]
17d	(*S*,*S*)-**12a**	H_2O	14	68	*R*	[9]
17d	(*S*,*S*)-**12a**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	77	*R*	[9]
17d	(*S*,*S*)-**12b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	74	*R*	[9]
17d	**15**	H_2O	5	55	*S*	[14]
17d	**15**	H_2O/AcOEt (1:1)	5	68	*S*	[14]
17d	**16**	H_2O	5	88	*S*	[14]
17d	**16**	H_2O/AcOEt (1:1)	5	87	*S*	[14]
17e	(*S*,*S*)-**5**	H_2O/EtOAc (1:2)	1	13	*S*	[6]
17e	(*S*,*S*)-**6**	H_2O/EtOAc (1:1)	15	44	*R*	[6]
17e	(*S*,*S*)-**7**	H_2O/EtOAc (1:2)	10	86	*R*	[6]
17e	(*R*)-**8**b)	H_2O/EtOAc (1:2)	10	70	*S*	[6]
17f	(*R*,*R*)-**10a**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	9	*S*	[9]
17f	(*R*,*R*)-**10b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	11	*S*	[9]
17f	(*S*,*S*)-**11a**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	54	*R*	[9]
17f	(*S*,*S*)-**11b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	67	*R*	[9]
17f	(*S*,*S*)-**12a**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	65	*R*	[9]

Tab. 1 (cont.)

Precursor 17	***Ligand***	***Solvent***	p_{H_2} ***[bar]***	***Product***		
				ee [%]	***Config.***	***Refs.***
17f	(*S,S*)-**12b**	$H_2O/EtOAc/C_6H_6$ (2:1:1)	14	58	*R*	[9]
17g	(*S,S*)-**5**	H_2O/EtOAc (1:2)	1	37	*S*	[6]
17g	(*S,S*)-**6**	H_2O/EtOAc (1:1)	10	58	*R*	[6]
17g	(*S,S*)-**7**[c]	H_2O/EtOAc (1:2)	10	88	*R*	[6]
17g	(*R*)-**8**[b]	H_2O/EtOAc (1:2)	10	80	*S*	[6]
17g	(*R,R*)-**10a**	H_2O	14	42	*S*	[9]
17g	(*R,R*)-**10b**	H_2O	14	67	*S*	[9]
17g	(*S,S*)-**11a**	H_2O	14	76	*R*	[9]
17g	(*S,S*)-**11b**	H_2O	14	79	*R*	[9]
17g	(*S,S*)-**12a**	H_2O	14	93	*R*	[9]
17g	(*S,S*)-**12b**	H_2O	14	88	*R*	[9]

[a] Reduced as the sodium salt.

[b] As a mixture of 55% tetrasulfonated **8** and 35% trisulfonated **8**, together with 10% phosphine oxide.

[c] As a mixture of 60% tetrasulfonated **7** and 40% trisulfonated **7**.

ble analogs (8–34% for **5** and **10**, and 40–71% for **6** and **11**, respectively). Hanson and co-workers [12] prepared a surface-active tetrasulfonated chiral diphosphine derived from BDPP which in the reduction of **17d** in a two-phase system showed improved reactivity and similar selectivity to the unmodified BDPP (with *ee* up to 69%). Carbohydrate-based phosphinites **15** and **16** derived from α,α- and β,β-trehalose associated with rhodium complexes gave enantioselectivities up to 88% in the reduction of **17** [13, 14].

Increasing pressure or – more importantly – a gradual change of the solvent from alcohol to water decreases the enantioselectivity, although increasing the water content gives a system more independent to increasing pressure. However, this was not true for the catalyst obtained by association of a rhodium complex with the tetrasulfonated BINAP **9** [15]; the enantioselectivities obtained (up to 70%) are quite similar in pure water and in methanol.

The drop in enantioselectivity going from the organic system to the aqueous phase was attributed to solvent effects and the difference in enantioselectivity is due to the reaction kinetics in the two solvents [16]. When the reaction was carried out in alcohol/water solvent mixtures, an increase in water content induced a decrease in enantioselectivity. In a systematic study of the influence of various solvents on the enantioselectivity in the reduction of dehydroamino acids, a linear relationship was found between log (% *S*/% *R*) and the solvophobicity parameter S_p of various solvents, log (% *S*/% *R*) decreasing with increasing S_p.

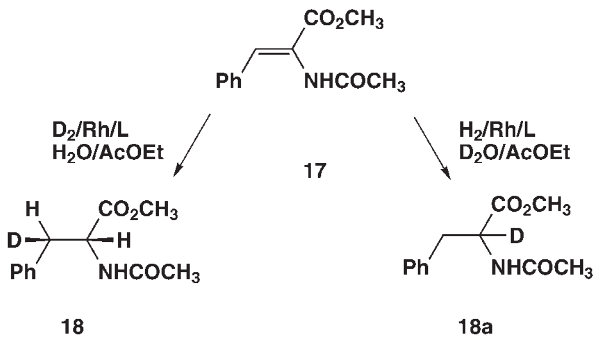
One of the important points is that these catalytic solutions can be readily recycled, without loss of enantioselectivity, as shown in Table 2. This recycling was performed with little rhodium loss in a two-phase system ($< 0.1\%$).

Tab. 2 Catalyst recycling in the asymmetric hydrogenation of α-amino acid precursors **17** at 25 °C using a rhodium catalyst.

Precursor 17	*Ligand*	*Solvent*	p_{H_2} *[bar]*	*Cycle*	*Product*		
					ee [%]	*Config.*	*Refs.*
17c	(*S*,*S*)-**5**	H_2O/AcOEt (1:1)	1	1	34	*S*	[6]
				2	37	*S*	
17d	(*S*,*S*)-**5**	H_2O/AcOEt (1:1)	1	1	20	*S*	[6]
				2	23	*S*	
17d	(*S*,*S*)-**7**[a]	H_2O/AcOEt (1:1)	10	1	82	*R*	[6]
				2	88	*R*	
				3	87	*R*	
17d	(*S*,*S*)-**12a**	H_2O/AcOEt/C_6H_6 (2:1:1)	14	1	75	*R*	[9]
				2	77	*R*	
				3	77	*R*	
17d	**15**	H_2O/AcOEt (1:1)	5	1	68	*S*	[14]
				2	66	*S*	
17d	**16**	H_2O/AcOEt (1:1)	5	1	87	*S*	[14]
				2	85	*S*	
17e	(*S*,*S*)-**12a**	H_2O	14	1	93	*R*	[9]

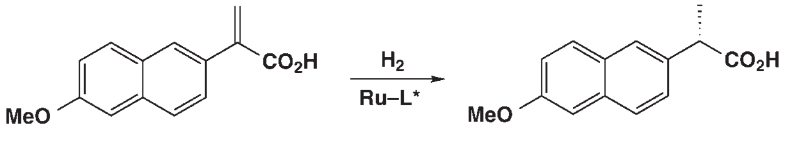
[a] As a mixture of 60% tetrasulfonated **7** and 40% trisulfonated **7**.

The biphasic hydrogenation of α-amino acid precursors was shown to be a truly homogeneous process, the reduction occurring in the aqueous phase [15]. However, water was not only a solvent, but also had a chemical effect on the reduction [18–20]. Hydrogenation of α-acetamidocinnamic acid methyl ester in AcOEt/D_2O in the presence of a rhodium complex associated with a sulfonated ligand such as TPPTS occurred with a 75% regiospecific monodeuteration at the position α to the acetamido and the ester functions, the amount of deuterium incorporation depending on the ligand used (Eq. 2). When the reduction was performed under a deuterium atmosphere in the presence of water, hydrogen incorporation occurred at the same position, the overall reaction being a *cis* addition of HD (**18** and **18a**).



(2)

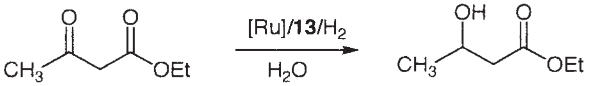
The ruthenium catalyst obtained from $[Ru(C_6H_6)Cl_2]_2$ and 2 equiv. of tetrasulfonated (*R*)-BINAP (**9**) was used in the reduction of some dehydroamino acids in water at room temperature and under 1 bar of hydrogen [21]. Enantiomeric excesses as high as 85–88% have been achieved, the direction of enantioselection being the opposite of that obtained from the water-soluble catalyst rhodium-BINAP in the same solvent. The enantioselectivity in this case is lower in water than in methanol, and declines with increasing hydrogen pressure. Reduction of unsaturated acid **19** in a two-phase AcOEt/H_2O system using this Ru–BINAP (**9**) catalyst (Eq. 3) allowed the preparation of naproxen (**20**) in 78.4% *ee*, *ee* values over the range 78.0–82.7% being obtained over several recycles of the catalytic solution [23]. The supported aqueous phase catalysis (SAPC) was extended to this chiral system. If enantioselectivity up to 70% was obtained in the synthesis of naproxen (**19**) in ethyl acetate as the solvent saturated with water, the use of ethylene glycol in place of water as the hydrophilic phase gave *ee* values up to 96%. In all cases the catalyst could be recycled with the same *ee* without any leaching of ruthenium.



19 **20**

(3)

Among the other reduced prochiral substrates, methylene succinic acid was hydrogenated with *ee* values up to 59 and 50% using respectively the catalysts Rh–**3** [3] and Ru–BINAP (**9**) [21]. The hydrogenation of the *β*-keto ester **21** was also performed in water in the presence of ruthenium complexes associated with ligands **13** and **14** (Eq. 4) [24, 25]; the hydroxy ester **22** was obtained with enantioselectivities up to 94%.



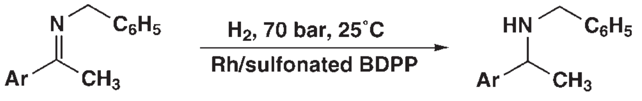
21 **22**

(4)

1st cycle: 94% ee
2nd cycle: 91% ee
3rd cycle: 94% ee

Sinou and co-workers have reported the influence of the degree of sulfonation of chiral BDPP on the enantioselectivity in the reduction of some dehydroamino acids [6]. This drastic effect was more pronounced in the reduction of prochiral imines [26, 27]. The rhodium complex of monosulfonated BDPP gives *ee* up to 96% in the reduction of imines **23** (Eq. 5), although the tetrasulfonated or disulfonated BDPP gave only 34% and 2% *ee* respectively for the reduction of the benzylimine of acetophenone. An explanation for this surprising effect was proposed [28].

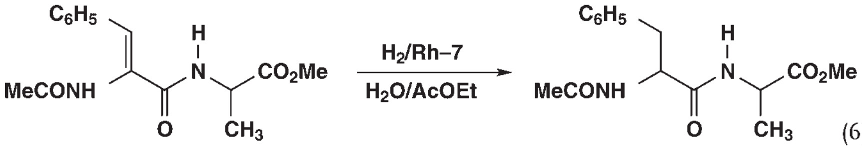
Dehydropeptides **25** (Eq. 6) were reduced in a two-phase system using $[Rh(cod)Cl]_2$ associated with ligands **5** and **6** [22]; the diastereomeric excess (*de*) of the dipeptide **26** obtained was strongly dependent on the absolute configuration of the substrate. For example, reduction of Ac-Δ-Ph-(*S*)-Ala-OCH_3 using Rh-**6** gave a *de* as high as 72% in favor of the (*R*,*S*) diastereomer, although a *de* of only 6% was obtained for Ac-Δ-Ph-(*R*)-*Ala*-OCH_3 in favor of the (*R*,*R*) diastereomer.



23 **24**

(5)

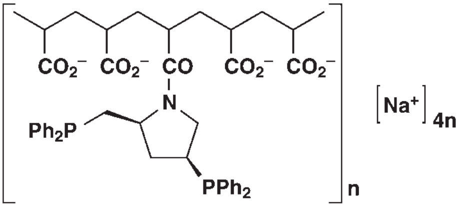
Ar/%ee: C_6H_5/96; 4–$MeOC_6H_4$/95; 4–ClC_6H_4/92



25 **26**

(6)

The binding of the chiral ligand PPM to a water-soluble polymer such as polyacrylic acid gave a macroligand **27** [29], which was used in the reduction of α-acetamidocinnamic acid (**13c**); enantioselectivities up to 56% and 74% were obtained using water and EtOAc/H_2O (1:1) as the solvents, respectively.



(*S*,*S*)–**27**

Formates of sodium, potassium, and ammonium can also be used as the reducing agent in the reduction of compounds **17c** and **17d** in the presence of the catalyst Rh-**5** [30] with enantioselectivity up to 43% at 50 °C.

Enantioselectivities up to 43% were also obtained in the hydroxycarboxylation of vinylarenes in the presence of $Pd(OAc)_2$ and tetrasulfonated BDPP **6** or CBD **5** [31].

Some preliminary results were obtained concerning the asymmetric Pd-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate in water or in an aqueous/organic biphasic medium, using as the chemical ligands phosphines derived from carbohydrates (*ee* up to 85%) [32], amphiphilic resin-supported MOP and *P*,*N*-chelating ligands (*ee* up to 98%) [33, 34], or BINAP in the presence of surfactants (*ee* up to 92%) [35].

In conclusion, it can be shown that asymmetric catalysis, and particularly asymmetric hydrogenation, occurs in a two-phase system, allowing the very easy recycling of the catalyst without loss of enantioselectivity. Different techniques have been used in order to solubilize the catalyst and the products in the aqueous phase. It is obvious that in the future other asymmetric organometallic-catalyzed reactions in water or in a two-phase system will appear in the literature.

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6.12
Catalytic Polymerization

Stefan Mecking

6.12.1
Introduction

By comparison with the intensively investigated syntheses of low molecular weight compounds by biphasic catalysis, catalytic polymerization in aqueous systems has received less attention. This is somewhat surprising, as polymerization in aqueous systems offers unique advantages, as illustrated by the large-scale applications of free-radical emulsion and suspension polymerization.

In *emulsion polymerization*, polymer latexes are obtained as a product [1, 2]. A polymer latex is a stable dispersion of polymer particles in the size range of ca. 50 to 1000 nm in a liquid medium, usually water. Latexes are also referred to as polymer dispersions or polymer colloids. Coagulation and precipitation of the polymer particles are usually prevented by surfactants adsorbed to the particle surface. In a typical aqueous emulsion polymerization, a water-immiscible monomer is polymerized in the presence of a surfactant employing a water-soluble initiator, such as potassium peroxodisulfate. Water-soluble radicals formed by thermal decomposition of the initiator add monomer to form initially water-soluble oligoradicals, which can nucleate particles by different mechanisms. During emulsion polymerization the emulsified monomer droplets serve as a reservoir for monomer; however, polymerization does not usually occur in these droplets but in the polymer particles formed to which the monomer diffuses through the aqueous phase. Particular features of emulsion polymerization and polymer latexes are: (1) the high heat capacity of water enables effective removal of the heat of polymerization; (2) a low viscosity of latexes by comparison to solutions of polymers in organic solvents is advantageous for the polymerization process, and also for subsequent processing and applications of the latexes; (3) film formation upon evaporation of the dispersing medium (water) is a key step in many applications.

In *suspension polymerization* also, a water-immiscible alkeneic monomer is polymerized. However, by contrast to emulsion polymerization a monomer-soluble initiator is employed, and usually no surfactant is added. Polymerization occurs in

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

the monomer droplets, with kinetics similar to bulk polymerization. The particles obtained are much larger ($> 15\ \mu m$) than in emulsion polymerization, and they do not form stable latexes but precipitate during polymerization.

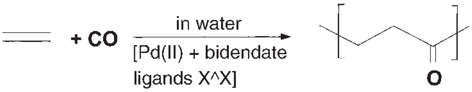
In *dispersion polymerization*, in contrast to emulsion or suspension polymerization, a monomer which is soluble in the reaction medium is polymerized. In analogy to the aforementioned types of polymerization, an insoluble polymer is obtained. The reaction is carried out in the presence of non-ionic surfactants or soluble polymers, which can stabilize the polymer particles generated to form a stable latex. With particle sizes of ca. 1 to 15 μm, dispersion polymerization can cover the particle size range between emulsion and suspension polymerization.

Catalytic polymerization in aqueous systems is of interest, as polymer-microstructures and corresponding properties of materials which are inaccessible by free-radical polymerization can be obtained [3].

6.12.2
Copolymerization of Carbon Monoxide with Alkenes

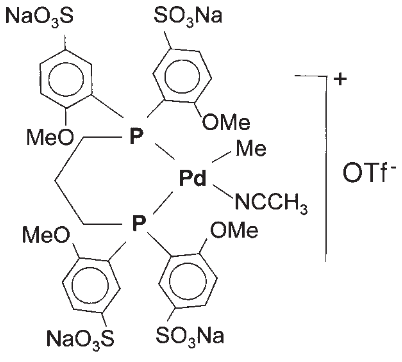
In a patent filed as early as 1948, Reppe and Magin described the reaction of ethylene with carbon monoxide in the presence of an aqueous solution of potassium nickel(II) cyanide at 150 °C and 150 bar [4]. Along with propionic acid and diethyl ketone, higher molecular weight solid “polyketones” were obtained. The alternating copolymerization of alkenes with carbon monoxide has received continued industrial and academic interest, one reason being the low cost of carbon monoxide as a monomer [5].

More recently several groups have reported on alternating copolymerization of CO with ethylene and/or 1-alkenes in aqueous systems, catalyzed by cationic palladium complexes with water-soluble bidentate nitrogen- or phosphine-based ligands (Eq. 1) [6–10]. In addition to such *in situ* systems, Structure **1** has been used as a well-defined water-soluble precursor. High activities of 6.1×10^4 TOF have been reported (90 °C, 60 bar ethylene/CO) for the formation of alternating ethylene–CO copolymer with M_w $1.2 \times 10^5\ \mathrm{g\,mol^{-1}}$ (M_w/M_n ca. 2) [11].



(1)

Whereas the polyketones were usually reported to precipitate from the aqueous phase, under emulsion conditions latexes of ethylene–undecenoic acid–CO terpolymers and of 1-alkene–CO copolymers can be obtained, which are film-forming at room temperature [12]. Using a miniemulsion technique (cf. Section 6.12.3), water-insoluble diphosphine ligands can be employed without the necessity for hydrophilic modification.



1

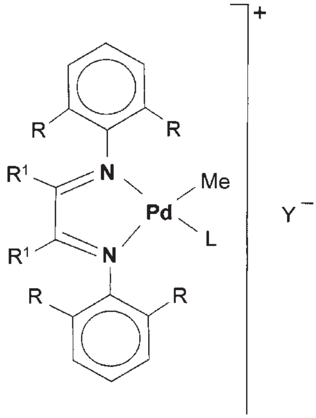
6.12.3
Polymerization of Ethylene and 1-Alkenes

In commercial polyalkene production, Ziegler or Phillips catalysts based on early transition metals (Ti, Zr, Cr, V) are employed. However, due to their high oxophilicity, such catalysts require strictly anhydrous conditions. In recent years, discovery of several new types of catalysts for ethylene and 1-alkene polymerization based on late transition metals have inspired a strong interest in this area. Due to their lower oxophilicity, such catalysts can be much more stable towards polar media.

Ethylene polymerization in water by a well-defined rhodium complex, $[(\mathrm{N}\frown\mathrm{N}\frown\mathrm{N})\mathrm{RhMe(OH_2)(OH)}]^+$, was reported by Flood and co-workers in 1993 ($\mathrm{N}\frown\mathrm{N}\frown\mathrm{N}$ = 1,4,7-trimethyl-1,4,7-triazacyclononane) [13].

In 1995 Brookhart and co-workers reported that cationic diimine-substituted palladium complexes (Structure **2**) can polymerize ethylene to high molecular weight, highly branched material in organic solvents like methylene chloride [14, 15]. Such polymerizations can also be carried out in water [16]. Detailed investigations revealed that in this suspension-type aqueous polymerization the catalyst is stable over 16 h or longer [17]. Activities of 900 TOF are similar to nonaqueous polymerizations in methylene chloride. However, this high stability is only due to an “encapsulation” of the water-insoluble catalyst in the growing hydrophobic polymer, which protects the catalyst from the access of water. Polymerization of 1-alkenes by catalysts of type **2** in aqueous emulsion has been claimed to afford stable latexes [18].

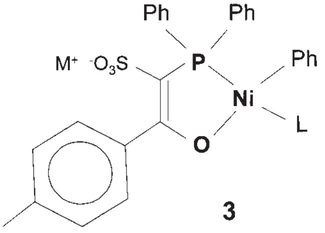
In view of the many potential applications, synthesis of a largely linear polyethylene with some degree of crystallinity in aqueous emulsion would be of interest. Very recently, Mecking et al. and Spitz et al. independently reported nickel(II)-catalyzed polymerization of ethylene to linear material in aqueous emulsion [19, 20].



2

2a: $R{=}R^1{=}Me$; L=NCMe; $Y{=}SbF_6^-$

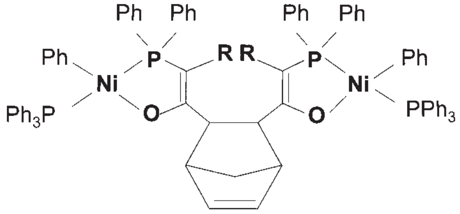
Neutral nickel(II) complexes **3** and **4** based on known bidentate $\overset{\frown}{\mathrm{P}\;\mathrm{O}}$ ligands [21] were found to be suited as catalyst precursors. Using a water-soluble catalyst precursors (**3a**), stable latexes of low molecular weight polyethylene could be obtained at rates of TOF = 10^3 TO [19, 22]. By introducing electron-withdrawing perfluorinated substituents into bidentate $\overset{\frown}{\mathrm{P}\;\mathrm{O}}$-ligands, Claverie et al. have obtained highly active catalysts (Structure **5**) [23]. At rates of up to 1.7×10^5 TOF low molecular weight linear material (M_w 3×10^3 g mol^{-1}) can be obtained in aqueous emulsion at ethylene pressures of 25 bar.



3

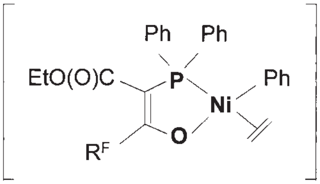
3a: $M^+{=}Na$ (hydrophilic)

3b: $M^+{=}\ H_{33}C_{16}NMe_3$ (lipophilic)



4

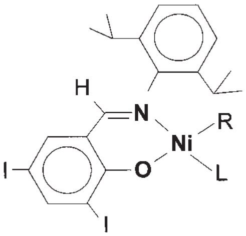
(R=C(O)OMe; Ph)



5

(R^F = CF_3; C_6F_5; presumed intermediate species)

High molecular weight polyethylene has been prepared in aqueous polymerizations with salicylaldiminatonickel(II) catalysts **6** [22]. Semicrystalline polyethylenes of M_n up to 10^5 g mol^{-1} with narrow polydispersities (M_w/M_n 2 to 4) are accessible in a suspension-type polymerization. Although these catalysts display a limited stability to water, activities of 3×10^3 TOF at room temperature are observed. Polymer crystallinity can be influenced by employing norbornene as a comonomer. High molecular weight, amorphous ethylene–norbornene copolymers which form films at room temperature can be obtained in aqueous polymerizations [22].



6

6a: R=Ph; L=PPh_3; **6b**: R=Me; L=pyridine

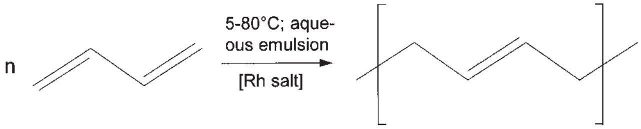
Synthesis of stable latexes requires suitable nucleation of primary particles and subsequent stabilization. In analogy to classical free-radical emulsion polymerization, water-soluble complexes can be employed for catalytic synthesis of polymer dispersions. As a different strategy, a very fine initial dispersion of a *hydrophobic* catalyst precursor can be achieved as a solution in a large number of toluene/hexadecane miniemulsion [24] droplets (∅ ca. 100 nm), dispersed in the continuous aqueous phase [23, 25]. Employing miniemulsions of the aforementioned perfluorinated catalysts **5**, Claverie et al. have prepared stable latexes of low molecular weight linear polyethylene at high polymerization rates [23]. Latexes of ethylene copolymers with 1-alkenes have also been prepared [26]. In addition to the various attractive aspects of polymerization in emulsion, in such copolymerizations another significant advantage is relevant: in conventional ethylene copolymerizations using late transition metal catalysts in organic media, incorporation of 1-alkenes is usually low and requires addition of large amounts of the comonomer. In emulsion, the high local concentration of the liquid comonomer in droplets can enable higher comonomer incorporations. Copolymerization of ethylene with undec-10-en-1-ol is also possible [26].

With miniemulsions of salicylaldiminato complexes (Structure **6b**) stable latexes of high molecular weight, semicrystalline polyethylene (M_n 10^5 g mol^{-1}, M_w/M_n 2 to 4) could be obtained [25].

Alkene polymerization in an aqueous system using an early transition metal catalyst has also been reported [27]. A toluene solution of styrene is prepolymerized briefly by a catalyst prepared by combination of $[(C_5Me_5)Ti(OMe)_3]$ with a borate and an aluminum alkyl as activators. The reaction mixture is then emulsified in water, where further polymerization occurs to form syndiotactic polystyrene stereoselectively. It is assumed that the catalyst is contained in emulsified droplets and is thereby protected from the access of water, with the formation of crystalline polymer enhancing this effect. The crystalline polystyrene formed is reported to precipitate from the reaction mixture as relatively large particles of 500 μm.

6.12.4
Polymerization of Conjugated Dienes

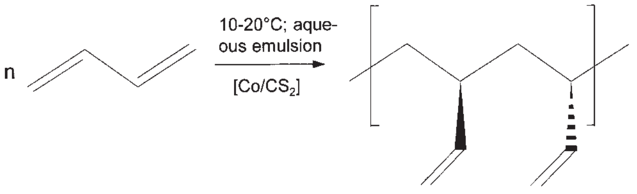
Butadiene polymerization in water as a reaction medium catalyzed by rhodium salts was already reported in the 1960s by Rinehart et al. and by Canale and coworkers. Utilizing $RhCl_3 \cdot 3\,H_2O$ as a catalyst precursor, butadiene is polymerized stereoselectively in aqueous emulsion to semicrystalline *trans*-1,4-polybutadiene exclusively (Eq. 2; $> 99\%$ *trans*) [28, 29].



(2)

By comparison, free-radical butadiene polymerization in aqueous emulsion typically yields polymers with 60% *trans*-incorporated units under similar conditions [30]. Polymer molecular weights of $2.6 \times 10^4\ \text{g mol}^{-1}$ were determined by light scattering. At 50 °C catalyst activity was virtually constant over 30 h, evidencing a remarkably high stability in the aqueous polymerization [31]. On the basis of polymer microstructure and comparative experiments with radical inhibitors, a coordination polymerization mechanism was suggested and free-radical polymerization can be excluded. Rhodium(I) species, formed by reduction by butadiene monomer of Rh^{III} salts used as catalyst precursors, have been suggested as the active species. In agreement herewith, Rh^I complexes such as $[Rh_2Cl_2(C_4H_6)_3]$ are also active catalysts with moderate activities of up to ca. 2×10^3 TOF (with formic acid as a co-catalyst) [32]). Polymerization of *cis*- or *trans*-pentadiene in aqueous emulsion has also been reported [33]. Precipitation of considerable portions of the polymer has been mentioned at high conversions in butadiene polymerization [31, 34].

Polymerization of butadiene by modified cobalt catalysts, such as the *in situ* system $[Co^{III}(acac)_3]/AlEt_3/H_2O/CS_2$, can yield highly crystalline syndiotactic 1,2-polybutadiene (T_m 205 °C) [35, 36]. Such stereospecific polymerizations can be carried out in aqueous emulsion [37–39], and polymer latexes can be obtained (Eq. 3) [38]. A "prepolymerization" with a small portion of butadiene monomer in the presence of only trace amounts of water is required. A hydrocarbon solution of this "prepolymerized" catalyst mixture is subsequently dispersed in water together with further butadiene, and polymerization proceeds. It has been speculated that



(3)

the catalytically active species is shielded from the access of water by the polymer formed during the "prepolymerization" [37].

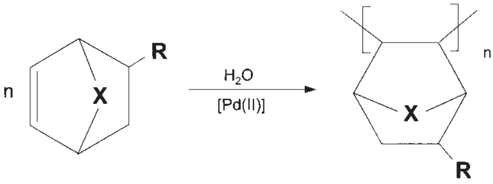
The aforementioned catalytic polymerizations offer access to special polymer microstructures in aqueous emulsion. However, it must be noted that particularly the expensive rhodium complexes used in pioneering work display only moderate activities.

6.12.5
Vinyl-type Polymerization of Cyclic Alkenes

By comparison with ring opening metathesis polymerization (ROMP) of cyclic alkenes (Section 6.12.6), their vinyl-type polymerization, leaving the ring structure intact, has been less thoroughly investigated. An early example of an aqueous polymerization is provided by rhodium-catalyzed cyclobutene polymerization in emulsion. Under similar conditions to those described by Rinehart for butadiene polymerization (Section 6.12.4), Natta et al. obtained a crystalline, highly stereoregular polymer with low conversions (Eq. 4) [40]. In contrast to ruthenium-catalyzed aqueous ROMP of cyclobutene ring opening is only a minor side reaction.

(4)

Tolerance of vinyl-type norbornene polymerization using $[Pd(NCCH_3)_4](BF_4)_2$ as an initiator towards added amounts of water (1000 equivalents with respect to Pd) had been described by Risse [41]. A polymerization of norbornene affording an aqueous latex was reported in 1993 by Perez et al. Norbornene was reacted in aqueous emulsion at 70 °C with SDS as an emulsifier and $PdCl_2$ as a catalyst precursor [42, 43]. With low catalyst activities of 70 TOF, a stable latex consisting of low molecular weight, oligomeric material (DP_n ca. 10) was obtained. Interestingly, very small latex particles of 10 to 20 nm diameter were reported. In the well-known free-radical polymerization of olefinic monomers, such small particles are only obtained by microemulsion polymerization. $PdCl_2$ is slightly water-soluble, and the authors have reasoned that polymerization occurs preferentially at the interface between water and monomer droplets (albeit the catalytically active species has not been identified unambiguously). At the same time, Novak et al. briefly reported polymerization of polar substituted norbornadienes in aqueous emulsion with $PdCl_2$ (Eq. 5) [44].



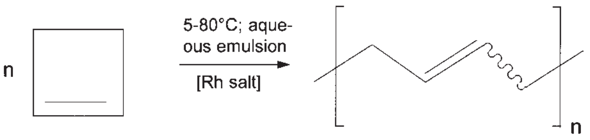
(5)

Rico-Lattes and co-workers have polymerized a water-soluble norborn-5-en-2-yl substituted gluconamide and a lactbionamide with water-soluble $[PdCl_2(NaTPPTS)_2]$ in aqueous solution [45]. With moderate efficiency (86 TON during an entire polymerization run) oligomers with a degree of polymerization DP = 17 respectively 12 were obtained in a vinyl-type polymerization. The water-soluble oligomers form aggregates in solution. Like their ROMP analogs, such glycopolymers have been suggested as therapeutic agents. By polymerization of 2-(methyleneammonium)norborn-5-ene chloride with $PdCl_2$ in aqueous solution, a cationic polyelectrolyte with a degree of polymerization DP = 94 was obtained. Cell transfection by DNA complexes of this polyelectrolyte has been investigated [46].

Polymerization of butylnorbornene by a catalyst system containing one equivalent of tricyclohexylphosphine or the water-soluble phosphine ligand NaTPPTS, $[\{(allyl)Pd(\mu\text{-}Cl)\}_2]/phosphine/Li[B(C_6F_5)_4]$, has also been described. For such aqueous suspension-type polymerizations, high activities of $> 10^4$ TOF have been reported [47]. Poly(butylnorbornene) of M_n up to 4×10^5 g mol^{-1} was obtained in the form of micron-sized beads.

6.12.6
Ring Opening Metathesis Polymerization

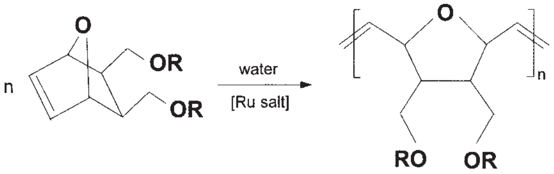
Ring opening metathesis polymerization (ROMP) of cyclic alkenes can be carried out with a variety of catalysts based on different metals [48–53]. Most often molybdenum, tungsten, and ruthenium catalysts have been employed. In aqueous systems, ruthenium catalysts are used preferentially due to their functional group tolerance (cf. Section 6.10.3). An early example of aqueous ROMP was provided by Natta et al. with polymerization of cyclobutene and 3-methylcyclobutene using $RuCl_3$ as a catalyst precursor [54]. Polymerization occurs exclusively via ring opening (Eq. 6).



(6)

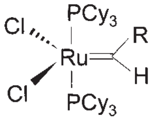
Rinehart et al. have reported ROMP of norbornene and of 2-functionalized norborn-5-enes with polar ester moieties in aqueous emulsion with moderate activities. Iridium(III) or iridium(IV) salts in combination with a reducing agent, or Ir^I alkene complexes, were employed as catalyst precursors [32, 55].

In 1988, Novak and Grubbs reported ROMP of aqueous solutions of functionalized 7-oxanorbornenes using $RuCl_3$ or $[Ru^{II}(OH_2)_6](OTs)_2$as catalyst precursors (Eq. 7) [56]. In comparison to polymerization in organic solutions, polymer molecular weights were found to be higher at narrower molecular weight distributions ($M_w = 1.3 \times 10^6$ g mol^{-1}; M_w/M_n 1.2). The high catalyst stability towards water is underlined by the possibility of multiple recycling of the catalyst solutions. An analysis by Feast and Harrison of the polymers resulting from aqueous ROMP with $RuCl_3$ or $OsCl_3$ revealed these materials to be atactic with a varying ratio of *cis* to *trans* double bonds in the backbone [57, 58]. As a general feature, in ROMP of norbornene using $RuCl_3$ as a catalyst precursor, *trans* linkages are usually obtained preferentially. A number of other functionalized norbornenes have been polymerized to high molecular weight polymers in aqueous media [59–62]. Albeit this issue was only mentioned as an aside, it is probable in all these cases and in the aforementioned polymerization that the catalyst precursor and the monomer initially formed a homogeneous solution, and the water-insoluble polymer precipitated during the polymerization reaction when a largely aqueous reaction medium was employed. Acyclic alkenes can function as chain-transfer agents to regulate molecular weights [57, 59, 63] and analysis of the resulting oligomeric products supported the presence of ruthenium alkylidene species [63]. Also, in accordance with the intermediacy of a ruthenium alkylidene species in the aqueous polymerization, addition of ethyl diazoacetate as a carbene source to $[Ru^{II}(OH_2)_6](OTs)_2$ enabled ROMP of less reactive low-strain cyclic alkenes like cyclooctene [64].



(7)

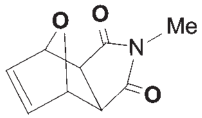
In the 1980s, well-defined metal alkylidenes were introduced as catalyst precursors for alkene metathesis [48, 51–53]. For aqueous ROMP especially, ruthenium alkylidenes represent readily activated, well-defined, easy to handle catalyst precursors or initiators. Whereas in initial work vinyl-substituted carbenes (cf. Structure **7a**) were employed [65], soon afterwards more straightforward routes to aryl-substitued carbenes (**7b**) were also developed [66]. Today, vinyl-substituted carbenes are also accessible in one-pot procedures [67], and are commercially available.



7

7a: R=-CH=CPh$_2$; **7b**: R=Ph

Due to the water insolubility of these metal carbenes, aqueous polymerizations represent heterogeneous multiphase mixtures. Investigation of ROMP of the hydrophilic monomer **8** or of a hydrophobic norbornene in aqueous emulsion (catalyst precursor **7b** added as methylene chloride solution) or suspension demonstrated that the polymerization can occur in a living fashion. For example, at a monomer to catalyst ratio **8**/**7b** = 100 with 78% yield, poly-**8** of M_w/M_n 1.07 vs. polystyrene standards was obtained [68]. Using water-soluble carbene complexes of type **9** and water-soluble monomers **10**, living polymerization can be carried out in aqueous solution, without the addition of surfactants or organic co-solvents [69].



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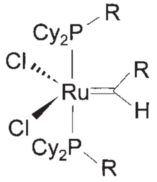
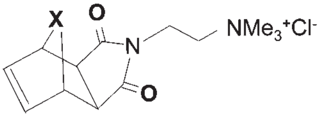


9

9a: R = – (CH$_2$)$_2$NMe$_3$$^+Cl^-$; **9b**: R = C$_7H_{15}N^+Cl^-$

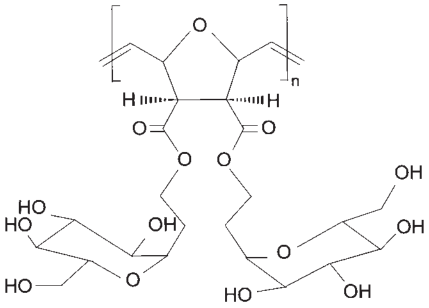


10

10a: X=O; **10b**: X=CH$_2$

ROMP of norbornene in aqueous emulsion employing ruthenium(IV) complexes [70] with bis(allyl) ligands such as the water-soluble $[(\eta^3:\eta^3\text{-}C_{10}H_{16})Ru(OH_2)(OAc)]BF_4$ as catalyst precursors has been reported by Wache [71]. High molecular weight polymer with an unusually high *cis* content was obtained with rates of 100 TOF.

The synthesis of neoglycopolymers via ROMP has been investigated extensively (the term neoglycopolymer refers to a synthetic, non-natural polymer bearing carbohydrate moieties) [72]. In comparison to other synthetic methods, ROMP can offer the potential of a good functional group tolerance and the possibility of molecular weight control at the same time. As the monomers and also the desired polymers are highly hydrophilic and water-soluble, aqueous ROMP can offer the advantage of a homogeneous reaction, beneficial for molecular weight control and catalyst efficiency. ROMP of 7-oxanorbornenes substituted with glucose or mannose moieties bound via *C*- or *O*-glycosidic linkages afforded neoglycopolymers, exemplified by Structure **11** [73–77].



11

Formation of a polymer latex in ROMPs in emulsion has been mentioned very briefly in some of the above cases without further discussion of the latex properties. ROMP of the functionalized monomer in Eq. (7) by $RuCl_3$ to stable dispersions of high molecular weight polymer (10^5 g mol^{-1} vs. polystyrene standards) stabilized by an (ethylene oxide)–(propylene oxide)–(ethylene oxide) triblock copolymer has been reported by Booth et al. [78]. Whereas the monomer is water-soluble, the polymeric product is not, and in this respect the reaction resembles a dispersion polymerization. The stable latexes obtained consist of remarkably small particles, for example, 60 nm diameter. Emulsion polymerization of norbornene by various ruthenium catalysts has recently been investigated in detail by Claverie et al. [79]. Using the water-soluble carbene complex **9b** or an *in situ* system $[RuCl_2(NaTPPTS)_2]$/ethyl diazoacetate as water-soluble catalysts, average activities of up to 10^4 TOF were observed at 80 °C (in a 15 min experiment). Polynorbornene latexes consisting of relatively small particles of generally less than 150 nm diameter were obtained, with solids contents of up to 46%. The observed dependence of particle numbers on reaction conditions indicates that homogeneous nucleation occurs, even in the presence of surfactant micelles. To enable utilization of the commercially available hydrophobic carbene complex **7b** as a catalyst precursor for latex synthesis, the latter was employed as a solution in toluene/hexadecane miniemulsion droplets (cf. Section 6.12.3). Hereby, in addition to norbornene, cyclooctene and cyclooctadiene, which are unreactive towards the water-soluble catalysts, can be polymerized to latexes of high molecular weight polymers. Copolymerization of cyclopentene and cyclooctene by **7b** in miniemulsion has also been reported independently by researchers from BASF [80].

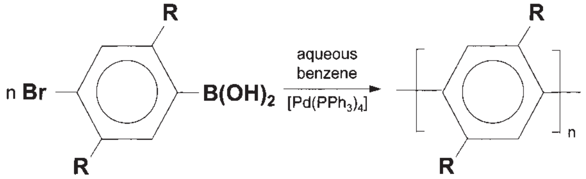
6.12.7
Polymerization of Alkynes

Polymerization of alkynes is of particular interest for the synthesis of conducting polymers [81]. Studies on alkyne polymerization in aqueous systems have mostly been restricted to phenylacetylene and (4-methylphenyl)acetylene as monomers. Polymerization with various water-soluble (e.g., $[RhCl(tppms)_3] \cdot 4\,H_2O$ (tppms = $3\text{-}Ph_2PC_6H_4SO_3Na$) or liphophilic rhodium complexes as catalyst precursors was investigated [82–84]. Polymers with a high *cis* content and molecular weights up to ca. $10^4\ g\,mol^{-1}$ are obtained with total catalyst productivities of up to a maximum of 10^3 TON. The iridium complex $[IrCl(CO)(TPPTS)_2]$ is also active for aqueous phenylacetylene polymerization. In addition to these biphasic polymerizations of water-insoluble monomers, polymerization of the acid-functionalized alkynes (4-carboxyphenyl)acetylene [85] and propynoic acid [86] in aqueous solution has been reported with various rhodium catalysts. High molecular weight polymers with a stereoregular *cis–transoidal* structure were obtained in good yields.

6.12.8
Polymerization by Suzuki Coupling

Transition metal-catalyzed coupling reactions of aromatic halides, such as Heck or Suzuki coupling, are used extensively for the synthesis of low molecular weight organic compounds (see Section 6.6). With bifunctional substrates, polymers can be obtained. In contrast to all other polymerization reactions considered in this Section, such reactions represent step-growth type polymerizations. In step-growth polymerization, high molecular weights are only obtained at very high conversion, for example, in the polycondensation of bifunctional substrates A–A and B–B, present in equal molar amounts, 99% conversion corresponds to a degree of polymerization of only $DP_n = 100$. C–C coupling of aromatic halides usually requires the addition of a base in stoichiometric amounts, and the most common Brønstedt bases are water-soluble and can be employed conveniently in biphasic aqueous/organic systems.

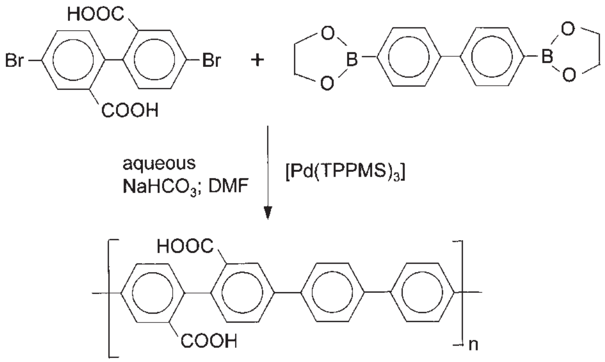
The use of Suzuki coupling for the synthesis of polyphenylene polymers was introduced by Rehahn, Schlüter, and Wegner (Eq. 8) [87]. Poly(*p*-2,5-di-*n*-hexylphenylene) was prepared in a biphasic mixture of benzene and water as a reaction medium, using sodium carbonate as a water-soluble base. This AB-type polymerization afforded polymers containing an average of about 28 phenylene units.



(8)

This method is applicable to a variety of alkyl-substituted phenylene AB-type monomers [88]. The procedure was also extended to the condensation of AA and BB monomers [89]. Hereby, poly-*p*-phenylene polymers containing ether and carbonyl linkages in the polymer backbone are accessible. By polymerization of the AB_2 monomer 3,5-dibromobenzene boronic acid in a biphasic aqueous/organic medium, Kim and Webster obtained hyperbranched polyphenylenes [90]. Suzuki polycondensation in aqueous systems has proven to be a versatile method, which has been applied to the synthesis of a variety of different polymer types [91].

Polymerization via Suzuki coupling in aqueous solution was reported by Novak et al. for the first time (Eq. 9) [92]. A water-soluble catalyst precursor, $[Pd(tppms)_3]$ (tppms = $3\text{-}Ph_2PC_6H_4SO_3Na$) was employed. The resulting polymer is water-soluble, and has a weight-average molecular weight on the order of 5×10^4 g mol^{-1}. Alike traditional Suzuki coupling for the synthesis of low molecular weight compounds, polymerization can be accompanied by side reactions which can strongly affect the structure of the resulting polymer. Aryl–aryl′ interchange in the intermediate complexes $[(aryl)Pd\{P(aryl')_3\}L_2]$ can result in chain transfer or incorporation of phosphorus in the polymer backbone, whereby the backbone rigidity is lost or branches can even be formed [93, 94].



(9)

6.12.9
Summary and Outlook

The principal possibility of aqueous catalytic polymerization of olefinic monomers was demonstrated early on, with pioneering work originating from the 1960s. However, since then significant advantages have been achieved only in very recent years: (1) the scope of polymers prepared in aqueous catalytic polymerizations has grown substantially; (2) the preparation of stable aqueous polymer latexes has been investigated; (3) strong improvements in catalytic activity have been achieved. High molecular weight polymers ranging from amorphous or semicrystalline hydrocarbons to highly polar water-soluble materials are now accessible.

What issues can be of interest in the future? With respect to latexes prepared by catalytic polymerization, latex stability under different conditions, film formation, and film properties are certainly an issue. Co- and terpolymerization of readily available monomers, including polar-functionalized alkenes, are of interest as they can enable control of these properties. Particle morphology, e.g., generating domains of different polarity such as in core–shell particles, represents another interesting aspect. Concerning mechanisms, a comprehensive picture remains to be established with regard to particle formation, polymerization kinetics, and for instance the location of the catalytically centers during the different stages of the reaction (aqueous phase, inside monomer droplets or polymer particles, or on the interface). Further improvements in catalyst performance based on a systematic understanding are certainly also an issue. In a polymerization aimed at preparing a latex, it is desirable to leave the catalyst in the product in order to maintain the intriguing simplicity of this direct route to a polymer dispersion. Thus, catalyst performance must be higher than the levels acceptable in many catalytic syntheses of small molecules, where the catalyst is recovered.

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6.13
Oleochemistry

Arno Behr

6.13.1
Introduction

In fat chemistry ("oleochemistry") no considerable application of homogeneous catalysis and of industrial importance is known so far [1]. One reason for this is the modest reactivity of the starting chemicals. Oleochemicals are molecules with a long carbon chain. The double bonds of unsaturated fatty compounds are always in internal positions. Hence, the steric hindrance of oleochemicals is often very high, and the coordination to metal complexes is made difficult. In addition all fatty compounds contain a substituent with a heteroatom such as carboxyl, ester, aldehyde, alcohol, or amine groups. These substituents often react with organometallic compounds and can inactivate the catalyst.

In spite of these relatively unfavourable characteristics of unsaturated oleochemicals, organometallic catalysis has – nevertheless – gained some access to fatty chemistry [2, 3], and aqueous-phase organometallic catalysis also is well known. Because the fatty compounds are organic nonpolar molecules, the addition of water always generated a liquid–liquid two-phase system (LLTP). If the organometallic catalyst is soluble in water, these LLTP systems are ideal for achieving a nearly complete recycle of the homogeneous metal catalyst (see Section 4.2).

The most typical examples in oleochemistry are the hydrogenation, the carbon monoxide reactions hydroformylation and hydrocarboxylation, and the oxidation reaction.

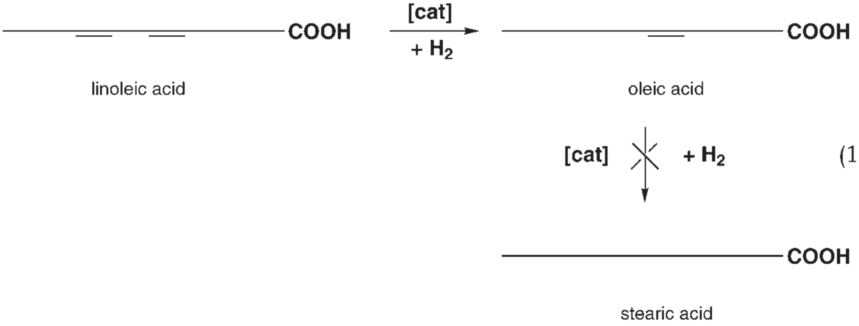
6.13.2
Hydrogenation

One important aim in oleochemistry hydrogenations is the selective hydrogenation of multiply unsaturated fatty compounds to singly unsaturated products. A typical example is the selective hydrogenation of linoleic acid ($C_{18:2}$) to oleic acid ($C_{18:1}$) without significant formation of stearic acid ($D_{18:0}$) as shown in Eq. (1). This

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

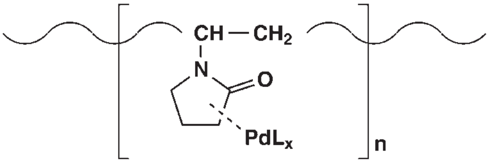
ISBN: 3-527-30712-5

reaction was studied intensively under homogeneous conditions in organic solvents. As organometallic catalysts carbonyl complexes of cobalt [4–6], iron [7, 8] and chromium [9–20] were used, and also catalyst systems based on platinum/tin [21–27], palladium/aluminum [28], iridium [29], rhodium [30–32], and ruthenium [33]. However, in all these investigations recycling of the homogeneous catalyst was not possible.



(1)

Selective hydrogenation of oleochemicals in combination with catalyst recycle was first studied by Bayer and Schumann [34, 35]. They used the LLTP system with water-soluble polymers as catalyst ligands. Polymers such as polyvinylpyrrolidone (PVP), poly(vinyl alcohol), polyoxyethylene or polyethyleneimine are the ligands of water-soluble palladium hydrogenation catalysts (see for example Structure **1**). After the oleochemical substrate is added to this aqueous catalyst solution, the mixture is stirred vigorously at room temperature. After the hydrogenation reaction, the two phases are allowed to separate, and the aqueous catalyst solution can be re-used directly without any further activation. Bayer compared the activity (reacted substrate molecules per metal atom/min) of the catalysts with slow enzymes. The same author described the selective hydrogenation of triglycerides in water using a Ni/PVP catalyst formed by the reduction of nickel sulfate with sodium boranate in the presence of PVP [36, 37].



1

A water-soluble rhodium hydrogenation catalyst has been found by Patin and co-workers [38]. Hydrogenations are carried out in very mild conditions, with Rh/TPPTS in H_2O/EtOH (1:1) and the catalyst is not air-sensitive and is easily prepared. However, the hydrogenation of linoleic acid is not selective, but yields only stearic acid.

Tab. 1 Selective hydrogenation with palladium SSCs in different carbonate solvents.

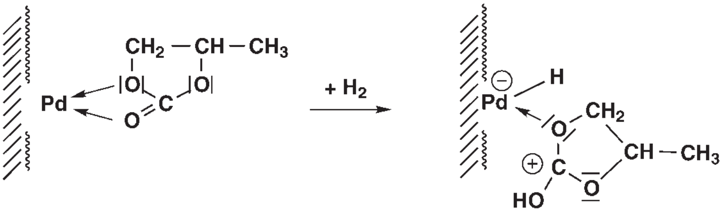
	$C_{18:0}$ [%]	$C_{18:1}$ [%]	$C_{18:2}$ [%]	T [°C]	t [min]
Starting mixture:					
– Sunflower-oil fatty acid methyl esters	2	22	70	–	–
Hydrogenation products in:					
– Propene carbonate	2	92	0	25	23
– Ethylene carbonate	4	91	0	60	110
– Glyceryl carbonate	5	88	0	25	180

A new development is biphasic hydrogenation using solvent-stabilized colloid (SSCs) catalysts [39–41]. Palladium colloid systems, especially, were proven to give high reactivity and selectivity. Best solvents are dimethylformamide and particularly the two cyclic carbonic acid esters, ethylene carbonate and 1,2-propene carbonate. In these solvents sodium tetrachloropalladate – stabilized by a sodium carbonate buffer – is reduced with hydrogen to yield the solvent-stabilized palladium colloid. Transmission electron microscopy of the palladium colloid demonstrates that the colloid particles are spherical with an average diameter of 4 nm.

The hydrogenation of the oleochemicals can proceed in the same apparatus in which the catalyst is formed. The fatty compound is added to the catalyst solution, thus yielding a biphasic system of two immiscible liquids. After the necessary quantity of hydrogen has been introduced, an intensive stirrer mixes the two liquid phases and the gas phase. On the laboratory scale, typical hydrogenations were carried out at room temperature and at ambient pressure allowing a reaction time of about 30 min. After the reaction the two phases are separated and the solvent/water phase is recycled with the colloid catalyst to the reactor.

Broad screening of the possible donor solvents proved that only a few solvents are suitable for use in phase separation and colloid stabilization. By far the best results are obtained with propene carbonate (Table 1), which is favored by the high selectivity to $C_{18:1}$ and the short reaction time.

It can be assumed that the solvent propene carbonate acts simultaneously as a solvent and as a complex ligand to the palladium. A structural proposal is given in Eq. (2): propene carbonate may coordinate to the metal via two oxygen atoms. If the hydrogen molecule adds to this complex, the carbonate chelate ligand gives



(2)

Tab. 2 Selective hydrogenation of different oleochemicals with palladium SSCs ($T = 25\,°\mathrm{C}$, $p = 1$ bar H_2; solvent propene carbonate).

Oleochemical	$C_{18:0}$ [%]	$C_{18:1}$ [%]	$C_{18:2}$ [%]	$C_{18:3}$ [%]
Sunflower oil				
– Untreated	2	22	70	0
– Hydrogenated	4	86	4	0
– Fatty acids, hydrogenated	2	93	0	0
– Fatty esters, hydrogenated	2	86	1	0
Palm-kernel fatty acids				
– Untreated	1	81	11	0
– Hydrogenated	2	90	0	0
Rape-seed oil (new)				
– Untreated	2	60	20	8
– Hydrogenated	5	87	1	0

rise to a heterolytic splitting of the hydrogen into a palladium hydride species and a proton, which is picked up by the ligand. The palladium hydride than acts as the starting complex for the catalytic hydrogenation cycle.

The propene carbonate-stabilized palladium colloid is an excellent catalyst for the hydrogenation of a great number of different fatty acids, fatty esters, and triglycerides. Table 2 gives a survey of results with sunflower, palm-kernel and rapeseed oils, acids, and esters. The yield of $C_{18:1}$ products after hydrogenation is in the range of 86–93%. In all examples the reaction time is very short.

The kinetics of the selective hydrogenation with palladium SSCs is shown in Figure 1. At room temperature the linoleic acid ($C_{18:2}$) is completely hydrogenated after 45 min. During this time no additional stearic ester is formed. This result is characteristic of the high selectivity of the palladium SSC. Obviously, the double unsaturated fatty compound coordinates essentially better than the monounsaturated compounds to the palladium.

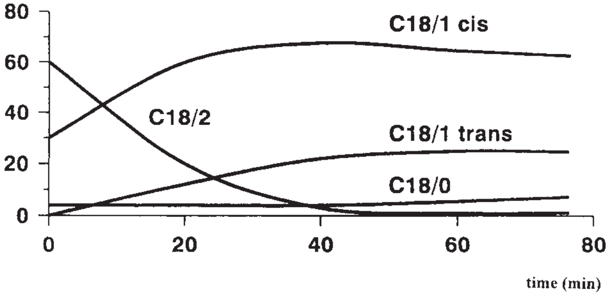
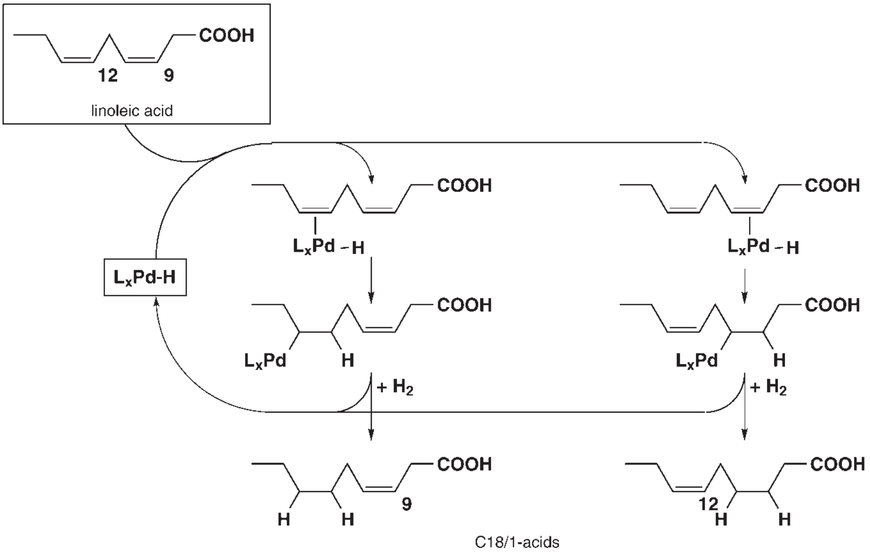


Fig. 1 Kinetics of the selective hydrogenation of sunflower oil fatty acid methyl esters ($T = 25\,°\mathrm{C}$, solvent propene carbonate; Pd/ester ratio 1 : 5000).



Scheme 1 Mechanistic proposal for the selective hydrogenation of linoleic acid with Pd SSCs ($L_xPd{-}H$ = stabilized palladium hydrido species).

These observations are summarized in a mechanistic proposal shown in Scheme 1. The palladium hydrido species (compare Eq. 2) is able to add equally to the double bonds in positions 9 and 12. The alkene inserts into the Pd–H bond, yielding the corresponding alkyl complexes. After reaction with hydrogen the monounsaturated fatty acids ($C_{18:1}$) are set free, and the palladium hydride species is formed again, thus starting a new catalytic cycle.

The reaction time can be influenced by different paramters. By an enhanced hydrogen exposure at 5 bar the reaction time can be reduced substantially. For technical realization, it is of high economic importance that the SSC be active even in low concentrations. If the weight ratio of fatty acids to palladium is changed from 10 000 : 1 to 100 000 : 1, the reaction time increases steadily. However, at very low catalyst concentrations the reaction time is still very short. Another point of great importance is the number of possible catalyst recycles. An eight-fold recycle of the palladium SSC had no essential influence on activity and selectivity. The reaction could easily be scaled-up to the pilot scale.

6.13.3
Hydroformylation

Instead of alkenes, unsaturated fat chemicals also can be hydroformylated. First studies were done in the 1960s by Lai and Ucciani [42, 43], who investigated cobalt bislaurate and dicobaltoctacarbonyl as catalyst precursors. Frankel et al. [44] also used $Co_2(CO)_8$ and obtained fatty aldehydes at reaction temperatures of about

100 °C and fatty alcohols when working at 180 °C. Starting from oleic acid methyl ester, yields of up to 84% were obtained. Conversions of oleochemical feedstocks with Rh catalysts were possible, too [45].

To solve the problem of metal recycle, one idea was to fix the rhodium on an inactive support. This rhodium was then extracted from the support by a triphenylphosphine-containing solution, thus producing *in situ* the homogeneous homophase catalyst solution. Friedrich et al. [46] described such a process of rhodium-catalyzed hydroformylation including filtration of the supported catalyst, cooking of the support in a rotary furnace, and thermal stressing distillation of the filtrate, thus separating Rh from the products.

As early as 1978 Andreetta et al. [47] applied this technique to the hydroformylation of alkenes and oleochemicals. They used the alternative of working in two phases, however, not during the reaction but after hydroformylation. The catalyst was composed of a rhodium component, e.g., $Rh_4(CO)_{12}$, and an aminophosphine ligand, e.g., $P(CH_2CH_2CH_2NEt_2)_3$. After the reaction the catalyst was recovered by one of the following methods. One possibility was the extraction of the catalyst and of the excess phosphines by means of dilute sulfuric acid solutions at ambient pressure. Addition of alkali to the aqueous solution causes the separation of an oily catalyst which is recovered preferentially by extraction with the starting alkene or oleochemical. The second method was the extraction of the catalyst with water under a carbon dioxide atmosphere of 3–5 bar. Carbon dioxide is then removed from the aqueous solution (which contains the catalyst and the free phosphine as phosphinoammonium bicarbonates) by boiling at atmospheric pressure in a stirred vessel, once again in presence of the starting alkene. Andreetta et al. described the recycle of rhodium catalysts by these methods and without substantial losses.

A very similar procedure has been described by Bahrmann and Cornils [48] for the hydroformylation of oleylalcohol. They carried out the reaction in a homogeneous organic phase at 130 °C and a syngas pressure of 270 bar. The catalyst was formed by rhodiumtris(2-ethylhexanoate) and aromatic phosphines and was soluble in an organic medium. The special feature was the choice of the ligand: the used the TPPTS ligand, modified as an ammonium salt with high-molecular-weight hydrocarbon chains. This ligand $TPPTS^{-}NHR_3^{+}$ with butyl to dodecyl substituents dissolved the rhodium in the starting oleyl alcohol. After the reaction (Figure 2) an excess of aqueous sodium hydroxide solution was added to the product mixture, thus forming the water-soluble sodium sulfonates. Hence, the organic rhodium-free phase could be separated and was hydrogenated in a second reaction step to the target nonadecadiol product. The aqueous phase contained the ligand and more than 99% of the starting rhodium metal. By changing the pH value from 8.5 to 1.0 by addition of aqueous hydrochloride solution and by addition of new tertiary amine, the initial catalyst is re-formed and can be recycled to the reactor (cf. Section 6.1.4).

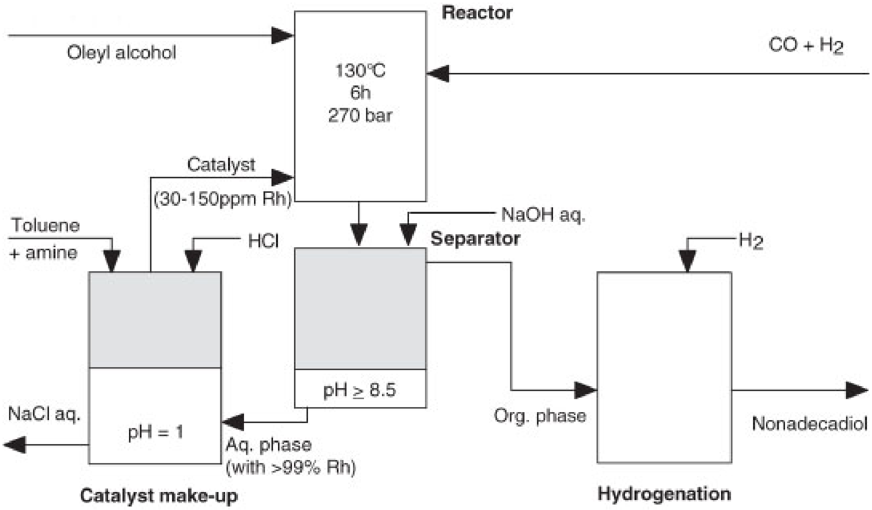


Fig. 2 Hydroformylation of oleyl alcohol: catalyst recycle by LLTP technique.

In the meantime, many other catalytic systems have been described for the hydroformylation of fatty compounds, especially by Fell's group [49–51]. They used water-soluble catalysts, for instance consisting of $Rh_4(CO)_{12}$ and surface-active sulfobetaine derivatives of tris(2-pyridyl)phosphine [49]. Other ligand systems are the sodium salt of TPPTS in combination with detergents [50] and the lithium salt of triphenylphosphinemonosulfonic acid TPPMS [51].

Another possible way to separate they catalyst from the fatty products was found by Davis [52–54] and further investigated by Fell [55]. This new method is supported aqueous-phase catalysis (SAPC; cf. Section 4.7). On a hydrophilic support, e.g., silicon oxide with a high surface area, a thin aqueous film is applied which contains the water-soluble rhodium catalyst, for instance $HRh(CO)L_3$ with sodium TPPTS ligands. Oleyl alcohol and syngas react at the organic/aqueous interface and form the formylstearyl alcohol in a yield of 97%. The catalyst can be separated from the product by simple filtration without loss of activity.

Hydroformylation of oleochemicals, carried out thus by means of aqueous-phase catalysis, can provide a great number of different fatty derivatives which may be useful in many industrial applications [56–66].

6.13.4
Hydrocarboxylation

An interesting reaction of oleochemicals with carbon monoxide is hydrocarboxylation, the reaction of unsaturated compounds with CO and water yielding carboxylic acids. If oleic acid is used as the starting compound, the product is a branched

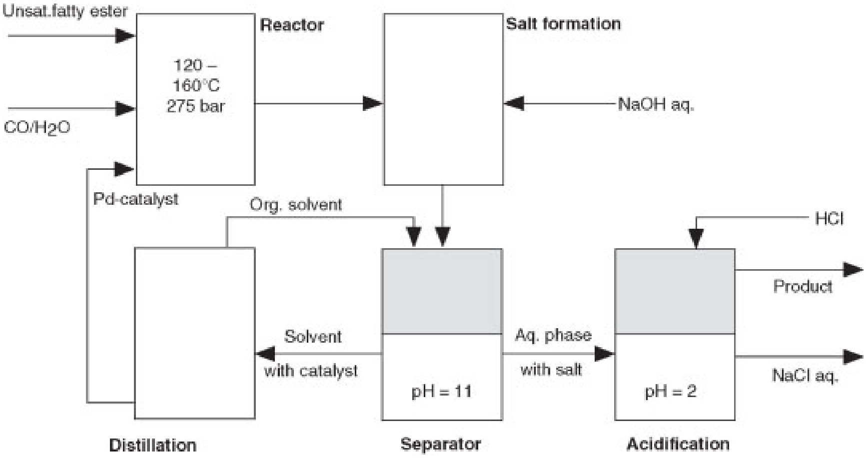


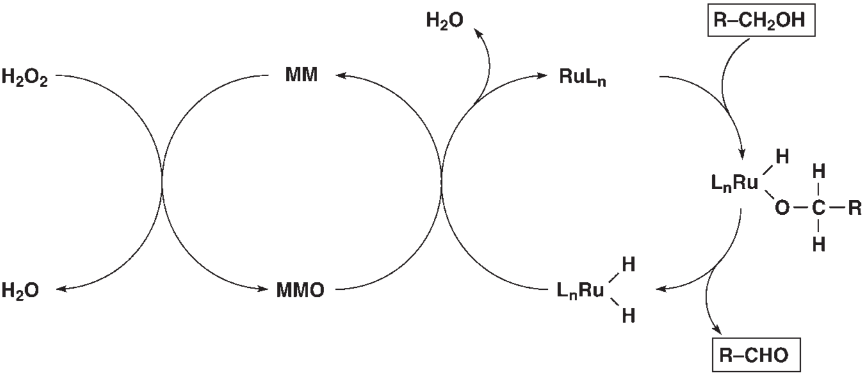
Fig. 3 Hydrocarboxylation of unsaturated fatty esters: catalyst recycle by LLTP technique.

C_{19}-dicarboxylic acid. Reppe and Kröper [67, 68] have studied this reaction using the catalysts nickel tetracarbonyl and nickel iodide and obtained products in about 70% yield. Levering [69] used dicobaltoctacarbonyl and Frankel and Thomas [70, 71] palladium phosphine catalysts. The recycle of this palladium catalyst via the LLTP technique is shown in Figure 3.

The hydrocarboxylation of an unsaturated fatty acid ester is carried out in a single organic phase. As product, the monoester of a dicarboxylic acid is formed. When this product is treated with aqueous sodium hydroxide solution this acid is converted into a water-soluble sodium salt. In the following separator the water-insoluble palladium catalyst is extracted from the aqueous phase by addition of an organic solvent. When the aqueous product phase is acidified with aqueous hydrochloride solution the released carboxylic acid forms a second organic phase and can easily be separated. The catalyst-containing solvent phase passes a distillation step, thus recycling the solvent to the separator and the palladium catalyst to the reactor.

6.13.5
Oxidation

Oxidation of unsaturated oleochemicals can proceed in different ways, and yields numerous products. Typical oxidations of fatty acids are, for instance, ketonizations yielding keto acids [72, 73], hydroxylations to bishydroxy acids [74], epoxidations to epoxy acids [75–78] and oxidative splitting reactions [72, 74] yielding mixtures of mono- and dicarboxylic acids. However, not only the double bond but also the functional group of the fatty compound, can be oxidized. One example is the ruthenium-catalyzed oxidation of fatty alcohols to fatty aldehydes or fatty acids



Scheme 2 Mechanism of the ruthenium-catalyzed oxidation of fatty alcohols to aldehydes (MM = *N*-methylmorpholine; MMO = *N*-methylmorpholine oxide).

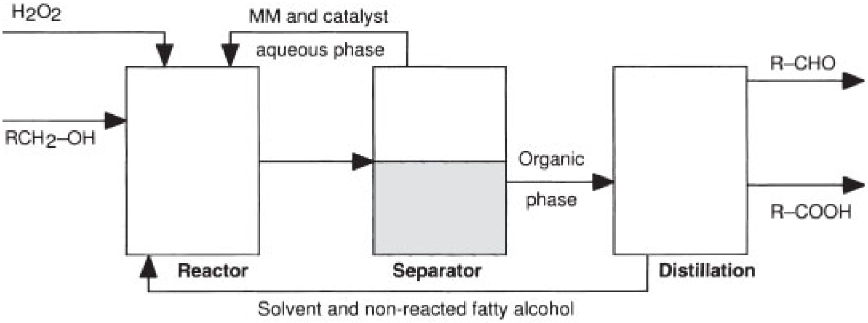


Fig. 4 Oxidation of fatty alcohols: catalyst recycle by LLTP technique.

[79]. As catalyst a ruthenium precursor is used, for instance $RuCl_2(PPh_3)_2$. A very smooth oxidation agent is *N*-methylmorpholine oxide (MMO), which can be prepared *in situ* starting from *N*-methylmorpholine (MM) and aqueous hydrogen peroxide solution. The mechanistic steps are shown in Scheme 2: the left-hand of the two integrated cycles demonstrates the repeated formation of MMO from MM and H_2O_2; the right-hand cycle is the catalytic cycle with the ruthenium complex catalyst. First the fatty alcohol adds to the RuL_n species yielding a ruthenium dihydride complex and the fatty aldehyde, which reacts further to the carboxylic acid. The dihydride species reacts with MMO yielding back the MM, the by-product water and the catalytic complex RuL_m, thus closing the catalytic cycle.

The technical realization of this process can once again proceed via the LLTP technique (Figure 4): the reactor contains the aqueous MM/catalyst phase; then the reaction unit is charged with fatty alcohol and an aqueous hydrogen peroxide solution. After the oxidation is finished the whole mixture is passed into a separator, where the aqueous MM/catalyst phase is detached and recycled to the reactor.

The organic phase enters a multistage distillation unit, where both products, fatty aldehydes and acids, are isolated. Solvent as well as unchanged fatty alcohol is recycled to the reactor. In this way a very effcient overall oxidation with MM/H_2O_2 can be achieved.

6.13.6
Oligomerization

In recent years some work has been done to link oleochemicals with petrochemicals via oligomerization. One possibility is the *Diels-Alder reaction* of linoleic acid esters with dienophiles, for instance with quinones or α,β-unsaturated aldehydes and ketones [80]. Using scandium or copper triflates as catalysts the reaction can be carried out at very mild temperature conditions (25–40 °C) with good yields ($<$94%). For the first time in oleochemistry it was possible to carry out Diels-Alder cycloadditions with low catalyst concentrations instead of stoichiometric amounts of Lewis acids. The most successful way to recycle the catalyst was the successive extraction of the triflates with water. After removing the water and drying in vacuum the catalyst was used three times without any loss of yield.

Another interesting goal is the linkage of unsaturated oleochemicals with non-activated unsaturated petrochemicals, for instance alkenes like ethene or propene. This *cooligomerization* has already been investigated in the 90s, however, no good method to recycle the expensive rhodium catalysts could be found so far [81]. In a recent work this problem could be solved [82]: this new recycling concept uses "temperature-dependent solvent systems" [83]. These solvent systems allow a single-phase reaction process on one hand and an easy separation of catalyst and products via the two-phase technique on the other hand. The cooligomerization of conjugated sunflower fatty acid methyl ester with ethene was carried out with rhodiumtrichloride-trihydrate in a biphasic mixture of the solvents propylene carbonate and 1,4-dioxane. Such mixtures of unpolar fatty compounds, polar cyclic carbonates, and medium-polar dioxane result in a homogeneous system at reaction temperature (70 °C) so that the reaction can be proceeded without any mass transfer limitations. However, after cooling down to room temperature (20 °C), these solvent systems form two separate fluid phases, one more polar one with the polar catalyst inside and the more unpolar one with the unpolar product inside. Recycling experiments with the propylene carbonate phase showed that the rhodium catalyst can be used several times without greater loss of metal.

6.13.7
Hydrosilylation

The hydrosilylation of unsaturated fatty compounds yields interesting chemicals with a new C–Si bond. As a model reaction the conversion of *10-undecenoic acid* *methyl ester* and triethoxysilane was chosen, catalyzed by the Speier catalyst ($H_2PtCl_2 \cdot 6\,H_2O$). In a very smooth reaction yields of about 80% could be reached after a very short reaction time of 4 min [84, 85]. Once again, the problem of the catalyst recycle could be solved by using the temperature-dependent phase behavior of solvent mixtures of toluene, cyclohexane, and propylene carbonate. The reaction proceeded at a temperature over 40 °C as a homogeneous single phase reaction; the separation of the hydrosilylation product and the platinum catalyst occurred at a temperature under 40 °C yielding two separate fluid phases.

Further investigations showed that other platinum catalysts can also be used with high yields, for instance, platinumdichloride and the Karstedt catalyst, a platinum(0)-divinyltetramethyldisiloxane complex [86]. Oleochemicals with internal double bonds were also found to be reactive in platinum-catalyzed hydrosilylations [87]: *methyl linolenate* (with two internal double bonds) reacted with chlorohydrosilanes giving yields up to 83%. The hydrosilylation of *methyl linolenate* (with three internal double bonds) gave a mixture of regioisomeric 1 : 1- and 2 : 1-hydrosilylation adducts, however, only in total yields of 40%.

6.13.8
Isomerization

Joó and Darensbourg [88] describe the synthesis of a water-soluble analogue of the Vaska's complex, *trans*-$[IrCl(CO)(TPPTS)_2]$. The behavior of this complex in water is markedly different from that of Vaska's complex in organic solvents. The new complex proved to be active in the hydrogenation of the double bonds of short-chain unsaturated acids, for instance, of crotonic and maleic acid. In addition, this complex was demonstrated to be an effective catalyst for both hydrogenation and isomerization of unsaturated fatty acids in soybean lecithin. More significantly was the observation that *cis/trans*-isomerization was selective over hydrogenation in these liposomes. For example, oleic acid was isomerized to elaidic acid with little hydrogenation to stearic acid only.

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6.14
Halogen Chemistry

Mario Bressan, Antonino Morvillo

6.14.1
Introduction

A large number of halogenated organics have been produced commercially in the past few decades, which have been used for a variety of purposes. The quest for environmentally friendly technology in general has risen to a substantial thrust to get away from chlorocarbons and halogenated materials altogether, due to the generic deleteriousness associated to them: all of the 12 persistent organic pollutants (POP), recently recommended by U.N. Environment Program to be phased out of production and use, are indeed chlorinated organics. Halogenated compounds continue to be produced and utilized, however, as they are still both the best solvents for some high-tech processes and flexible starting materials for a variety of organic syntheses.

6.14.2
Reductive and Oxidative Dehalogenation

Dehalogenation of halo-organics before their release from current processes, and the retrospective treatment of the mess created as a result of past expediency, are important issues because of the environmental persistence of these species in groundwater [36]: compounds involved vary from volatile aliphatics to heavy aromatics such as polychlorophenols, polychlorinated biphenyls (PCBs), and dioxins. Indeed, serious problems are associated with the combustion of chlorinated organics, since these classes of compounds, although thermodynamically unstable, are characterized by a high degree of chemical inertness and thermal stability: total conversion of chlorinated organics to innocuous materials (HCl, CO_2, and H_2O) cannot be achieved without considerable expense.

The ubiquitous presence of methane monooxygenase (MMO) and cytochrome *P*-450 (CyP450) enzymic systems indicates that they may be of principal importance on a global scale for the oxidative degradation of halo-organics in biological

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

systems. In many instances, however, current techniques of bioremediation of contaminated groundwaters involving entire microorganisms are inadequate because of toxic pollutant concentrations, nutrient limitations, and the lack of membrane permeability for halo-organics (which, coupled with absence of suitable extracellular enzymes, is the accepted basis for a molecule being recalcitrant) [1]. MMO is capable of oxidizing a wide variety of haloalkenes at rates comparable with those of other substrates for the enzyme, by being the competitive inhibitor tetrachloroethylene the only chlorinated ethylene not turned over [2]. The rates observed are at least two orders of magnitude faster than the rates reported for whole-cell oxidation reactions by nonmethanotrophs and 2–10 times faster than comparable oxidations catalyzed by CyP450 containing mixed-function oxidase systems [3].

CyP450 and other reduced iron porphyrins are also reported to mediate reductive dehalogenation of a variety of haloalkanes and -alkenes [4], and of the aliphatic portion of DDT [5]. Reductive dehalogenation refers specifically to the reaction in which two electrons and a proton act as substrates along with the halogenated compound to yield a reduced product and the corresponding halide (Eq. 1).

$$\mathrm{RX} + 2\mathrm{e}^- + \mathrm{H}^+ \rightarrow \mathrm{RH} + \mathrm{X}^- \tag{1}$$

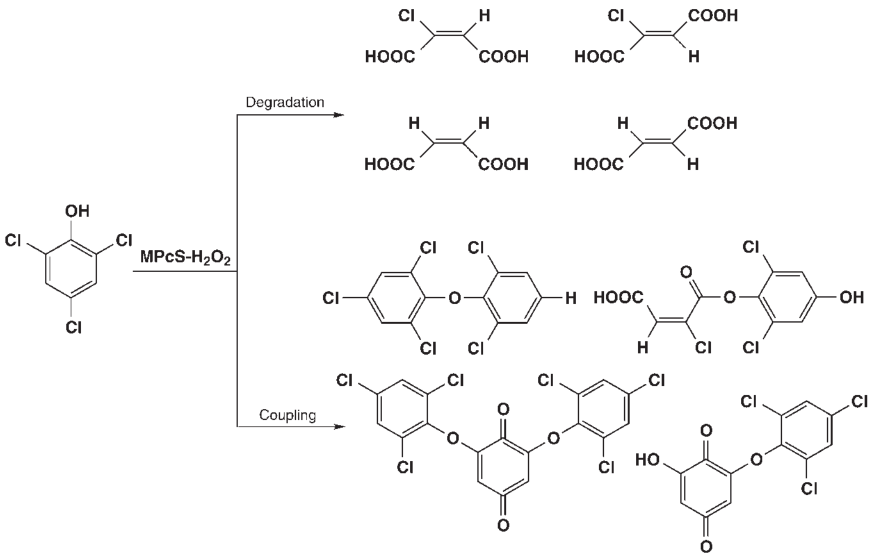
Compounds with high halogen substitution and therefore with carbon atoms in high formal oxidation states are expected to be resistant to the degradation under aerobic conditions and more susceptible to a reductive degradation. Products similar to those resulting from treatment with anaerobic bacteria or CyP450 were obtained by depositing a stable ordered film of myoglobin (Mb) and a surfactant on electrodes: a highly reduced form of Mb was produced in the films, which were used to catalyze reduction of organohalide pollutants such as trichloroacetic acid and polyhaloethylenes [6]. Lindane dechlorination is effected by iron-containing hemin and hematin, and by cobalt-containing protoporphyrin and various cobalamins [7]. Vitamin B_{12}, but not hematin, was also shown to reductively dechlorinate pentachlorophenol and trichlorophenoxyacetic acid [8]; cobalamins have also been used in the reductive dechlorination of CCl_4, polychlorinated ethanes, polychlorobenzenes and PCBs [9]. Reductive dehalogenation of chlorinated aliphatic hydrocarbons and freons occurs with participation of coenzyme F430, a nickel porphyrinoid present in anaerobic bacteria [10].

Liquid-phase catalysts are close models to enzymes and can be a gentle alternative method of destruction of halogenated hydrocarbons. Transition metal complexes, in particular metal porphyrins, corrins and phthalocyanines, have been studied in homogeneous abiotic aqueous systems as potential remediation catalysts, but further identification of degradative products is necessary, since innocuous products must result if synthetic catalysts are to be used effectively. Moreover, the implementation of homogeneous catalysts is still impractical because of problems with separating the catalyst; in principle these can be overcome by immobilizing the complexes on a solid support. There are numerous examples of supported catalysts, but their application in aqueous systems has rarely been investigated [11].

Cationic water-soluble iron, cobalt and nickel porphyrins with various functional groups in *meso* positions suitable for immobilization have been tested as catalysts for reductive dehalogenation of CCl_4 with dithiothreitol: $CHCl_3$, CH_2Cl_2, and CO were found to be breakdown products [12]. Nickel(I) octaethyl isobacteriochlorin has been used as model for F430 factor for the reduction and coupling of alkyl halogenide [13]. Photoreductive dehalogenation of aqueous $CHBr_3$ is mediated by the anionic cobalt macrocycle CoPcS (PcS = tetrasulfophthalocyanine anion) adsorbed on the positively charged titania surface [14]. Nonspecific biomimetic macrocycles, CoTMPyP (TMPyP = tetrakis-(*N*-methyl-4-pyridiniumyl) porphyrin cation) and CoPcS, were used as homogeneous and mineral-supported catalysts: they are able to reductively dechlorinate CCl_4 in water, even at high concentrations that would inhibit microbial activity [15]. A C–X bond in aliphatic or benzylic halides can be transformed into a C–H bond in a transfer hydrodehalogenation reaction with formate as hydrogen donor and water-soluble ruthenium catalysts, $RuCl_2(TPPMS)$ (TPPMS = *m*-sulfophenyldiphenylphosphine anion) or $Ru(H_2O)_3(PTA)_3(tos)_2$ (PTA = 1,3,5-triaza-7-phosphaadamantane; tos = tosyl) [16].

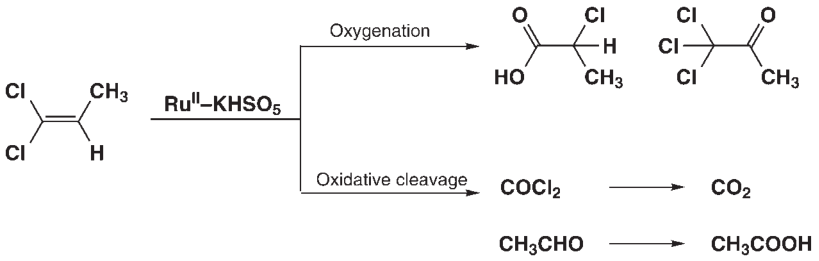
The oldest catalytic oxidative system for dehalogenation is Fenton's reagent; essentially the hydroxyl radical is one of the few chemical species capable of attacking refractory halo-organic compounds; the scope of the reaction in terms of effective substrate-oxidation vs. H_2O_2-dismutation is often limited by sensitivity to pH and a narrow H_2O_2/Fe^{2+} ratio [17]. Various water-soluble iron or manganese sulfophenylporphyrins catalyze with exceedingly high activity (turnover frequency, TOF, up to $20\ s^{-1}$) the oxidative dechlorination of trichlorophenol (TCP) with $KHSO_5$ in aqueous acetonitrile [18]. The more easily accessible MnPcS or FePcS catalysts equally behave in water also in the presence of the environmentally safe oxidant H_2O_2 with TOFs in excess of $0.1\ s^{-1}$. Products of dechlorination (up to two chloride ions were released per TCP molecule), of aromatic ring cleavage, and of oxidative coupling have been detected (Scheme 1). The catalysts which have also been successfully tested for the dechlorination of chloroanilines [37], maintain their activities with H_2O_2 when immobilized on cationic resins [19].

Ruthenium tetroxide was shown to oxidize PCBs in water [20]. Water-soluble ruthenium complexes, such as $[Ru(H_2O)_2(DMSO)_4]^{2+}$, are effective catalysts for the $KHSO_5$ deep oxidation of a number of chloroaliphatics, of α-chlorinated alkenes, polychlorobenzenes, and polychlorophenols. When the reactions are carried out in water in the presence of surfactant agents, degradation of the substrates is definitely faster. Aromatic substrates are mainly converted into HCl and CO_2, polychlorophenols being more sensitive to oxidation than substituted benzenes [21]. Replacement of the DMSO-"solvated" ruthenium by RuPcS results in a definite improvement of the reaction course with hydrogen peroxide, since dismutation of



Scheme 1 Oxidation of TCP by MPcS catalysts (M = Mn, Fe) and hydrogen peroxide.

the oxidant is significantly lowered: oxidation of chlorophenols in water leads to the complete disappearance of the substrates within minutes, with almost quantitative (80%) evolution of inorganic chlorine and massive (50%) formation of carbon dioxide [38]. The above ruthenium-based catalytic systems are also able to degrade α-chlorinated alkenes to HCl and the appropriate carboxylic acid and/or CO_2 with TOFs in excess of 1 s^{-1} (Scheme 2) [22, 39].



Scheme 2 Oxidation of 1,1′-dichloropropene by Ru(II) catalysts and monopersulfate.

6.14.3
Coupling and Carbonylation Reactions

Halo-organics could be simple and inexpensive starting materials for many organic syntheses, such as the important carbon–carbon bond formation, and have been considered significant as intermediates for the prebiotic synthesis of organic compounds in the primitive aqueous environment [23].

A number of important palladium-catalyzed coupling reactions starting from aryl and vinyl halides have been successfully imported into aqueous media [24]. Suzuki coupling between 1-iodocycloalkenes and vinylboronic esters to give the corresponding 1-vinylcycloalkenes derivatives has been carried out in the presence of palladium salts and water-soluble tri(*m*-sulfophenyl)phosphine anion (TPPTS) and sulfonated diphosphines [25]. The synthesis of a terphenyl derivative complexed by the cationic moiety $[Cp^*Ru]^+$ by Suzuki coupling of $[Cp^*Ru(BrC_6H_4Br)]^+$ with phenylboronic acid under catalysis by $[Pd(PPh_3)_4]$ in a DME/water mixture is reported to occur in quantitative yield [26].

The palladium-catalyzed reaction of haloarenes with alkenes or alkynes (Heck reaction) is a useful synthetic method and several variations have been devised in recent years to perform the reaction in aqueous media: coupling of iodobenzene and methylacrylate to methyl cinnamate proceeds in exceedingly good yields when carried out in a mixture of the organic phase of the reactants and water [27]. Iodo- and bromobenzenes react cleanly with ethylene to yield substituted styrenes in good yields, when $[PdCl_2(TPPMS)_2]$ catalyst is used in water or in a water/acetonitrile mixture; these reactions provide a synthetic route to poly(phenylenevinylenes) [28]. Palladium-catalyzed coupling of terminal alkynes with aryl halides occurs in quite good yields in the presence of a quaternary ammonium salt and a base in an acetonitrile/water solution, without any added cuprous iodide [29]. Reactions of 4-carboxyphenylacetylenes with 4-iodobenzoic acid are carried out in water or water/acetonitrile in the presence of palladium acetate and water-soluble aryl alkyl guanidinium phosphines, yielding various amounts of cross- or homocoupling products. A comparative study of TPPTS and the aryl alkyl guanidinium phosphines in the aqueous-phase palladium-catalyzed C–C coupling between 4-iodobenzoate and trifluoroacetylpropargylamine shows the latter to be of superior activity [30].

Aqueous palladium-catalyzed Stille coupling shows much of the versatility found for the original version using the lipophilic n-Bu_3SnR in organic solvents, with some notable advantages. Unlike the organic conditions, where the n-Bu_3SnR reagent transfers vinyl and aryl groups preferentially over the *n*-Bu groups, the aqueous variant does not require group-selective transfer; furthermore, whereas halogen substituents on the tin dramatically retard the Stille coupling in organic media, hydrolysis of the $RSnCl_3$ reagent apparently facilitates both solubilization and C–Sn bond activation. Two relevant and closely related studies were reported recently, dealing with Stille coupling of water-soluble aryl and vinyl halides with allyl-, aryl-, and vinyltrichlorostannanes to give a variety of coupling products, among them alkyl-, aryl- and vinyl-substituted benzoic acids: the reaction is carried out in alkaline media and catalyzed by palladium salts in the presence of the water-soluble phosphines TPPMS and di(*m*-sulfophenyl)phenylphosphine anion (TPPDS) [31].

Palladium-catalyzed hydrocarbonylation of aryl halides can be conducted in biphasic conditions, even if the palladium complex is a normal PPh_3 derivative, probably insoluble in the aqueous phase [32]. The selective hydroxycarbonylation of bromobenzene to benzoic acid has also been successfully explored with the water-soluble $[Pd(TPPTS)_3]$ complex, which leads to better yields, probably by improving the contact between the catalytic species and the nucleophilic agent and preventing the precipitation of metallic palladium under the reaction conditions [33]. The zwitterionic $[Rh(cod)]BPh_4$ complex is reported to catalyze the carbonylation of benzylic and allylic bromides to carboxylic esters in a biphasic system (aqueous $NaOH/CH_2Cl_2$, with phase-transfer agents) [34]. Another class of useful – even if complex – reactions is represented by the $Co_2(CO)_8$-catalyzed carbonylation of phenethyl bromide to benzylpyruvic and benzylacetic acids: this reaction has been investigated in the aqueous phase and in the presence of water-soluble phosphines TPPTS and TPPMS, and exhibits variable reactivity and selectivity [35].

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6.15
Biological Conversions

Peter J. Quinn

6.15.1
Introduction

Water is the universal solvent in biology. In the order of 80% of the gross weight of living organisms consists of water. The catalysts responsible for mediating the biochemical reactions that create and sustain life depend on an aqueous environment to preserve their stability and catalytic functions. Moreover, their activity is limited to reaction conditions of temperature, pressure, pH, etc., which are compatible with survival of the living organism.

Many biological catalysts, “enzymes,” often acquire their catalytic functions under these stringent reaction conditions by incorporating transition metals into their catalytic site. The metals are coordinated to ligands, which are constituents of the polypeptide chain and participate in the formation of transition-state complexes with substrates in the performance of biochemical reactions. Whereas Nature can provide a rich diversity of organometallic catalysts that require an aqueous solvent, it is a challenge – as seen below – to the chemist to duplicate these enzymic reactions so that they can be exploited and adapted to industrial-scale processes.

This chapter will be concerned with a description of biological substrates for organometallic catalysts. Examples will be given as to how these catalysts have helped to understand important questions, such as why and how these substrates are produced by living organisms. Finally, the chapter will conclude with a discussion of the use of organometallic catalysts in aqueous systems to perform highly specific reactions.

6.15.2
Biological Substrates

All living cells are bounded by a membrane that divides living from nonliving matter. Higher organisms are further compartmentalized by a complex system of subcellular membranes. An important group of constituents of these membranes are

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

lipids. The particular feature of these lipids is that the are amphipathic and are arranged in a bimolecular layer which serves to orient and support the various functional proteins. The hydrocarbon components of these lipids are usually unsaturated, straight-chain fatty acids in which *cis* double bonds are located at specific positions along the hydrocarbon chain. Such fatty acids also dominate the lipid metabolid storage depots and represent the major source of fat in our diet.

Chemical modifications of these unsaturated fatty acids in living organisms have greatly increased our knowledge of the role of these constituents in biological membranes. Their presence in food, however, presents problems with storage and catalytic hydrogenation in processing of fats and oils to prevent spoilage, and development of off-flavors in a common practice. Such processing, nevertheless, results in the creation of *trans* isomers of fatty acids which are known to present a health risk. Improved practices are actively being sought to meet regulations framed to reduce or eliminate *trans*-fatty acids in processed oils.

6.15.3
Hydrogenation of Unsaturated Lipids in Aqueous Dispersions

The idea that chemical modification of the lipids of biological membranes could be achieved *in situ* was first demonstrated in 1976 [1]. The rationale underlying the work was that if the unsaturated double bonds were largely responsible for the fluid character of the membrane lipid matrix, their saturation would result in a reduction in fluidity. Although simple in concept, the practice required application of an entirely novel approach to the catalytic hydrogenation of lipids.

It was found that conventional hydrogenation catalysts, such as Adam's catalyst, were unable to bring about hydrogenation of unsaturated lipids dispersed in aqueous systems. The reason was apparent; the catalyst was located in the aqueous phase and the substrate double bonds were sequestered in a hydrophobic domain created within dispersed aggregates of the lipid. The solution to this problem was to employ homogeneous catalysts in which complexes of transition metal atoms with suitable ligands were able to gain access to the lipid substrate arranged in a bilayer configuration. The initial work was performed using rhodium complexes with triphenylphosphines (TPP) designed for hydrogenation and hydroformylation reactions in organic solvents [2] but subsequently water-soluble homogeneous catalysts [3] were found to be active against lipid substrates in aqueous dispersions.

One of the objectives in performing hydrogenation reactions *in situ* was to modulate the fluidity of biomembranes and to examine the role of membrane lipid fluidity in biochemical and physiological functions. Secondly, because membrane lipids with six or more unsaturated double bonds were found to be significant components of some membranes, such as the retinal rod membranes of the eye, the hydrogenation of these lipids was thought to be a useful tool to identify their role in these membranes.

Many transition metal complexes capable of activating molecular hydrogen are known [4]. Most of these comlexes have been shown to catalyze the efficient reduction of unsaturated bonds, e.g., alkeneic ones. When such catalysts are used in biological systems, however, there are a number of factors that need to be taken into account. In the case of living organisms, for example, it is essential that the catalyst is nontoxic or at least the level of toxicity is low at concentrations required to sustain a reasonable level of hydrogenation. Toxicity can arise by breakdown of the catalyst complex and liberation of the transition metal element and/or ligands of the complex, either of which may be toxic. Furthermore, side reactions may lead to the formation of unwanted, although not necessarily toxic, by-products. Such reactions include ligand exchange with biomolecules resulting in complexes with altered catalytic properties. Side reactions are potentially damaging in the case of sulfonated derivatives of Wilkinson's catalyst, for example, where the catalytically active species, $RhH(SP\phi_2)_3$ and $[Rh(SP\phi_2)_3]^+$ are known to hydrogenate $=C=O$ functions in addition to *cis* unsaturated bonds of alkenes. Reaction of biochemical compounds of a susceptible chemical configuration could have repercussions on cell viability.

Chemical catalysis is often performed under conditions of temperature, etc., that are well outside the physiological range. In biological applications, the catalyst complex must be stable under the conditions required to preserve stability of biomembranes or viability of living organisms. At the same time reasonable reaction rates must be sustained under these physiological conditions. Ideally the presence of the catalyst in the system should not affect the properties of the membrane other than in the response of the membrane to the altered level of saturation of the constituent lipids. This can be achieved by removal of the catalyst complex at the completion of the hydrogenation reaction.

Because of these relatively requirements there are comparatively few complexes that are suitable for biological applications. The group of complexes such as $[Co(CN)_5]_3^-$, for example, although very active under conditions appropriate for hydrogenation of biological membranes, are stable only in the presence of excess cyanide [5]. Another common ligand, 2-aminopyridine, although producing highly active catalysts under relatively mild conditions, is highly toxic to living cells. Another group of the type $RuCl_n(H_2O)_{6-n}$ require high temperatures and concentrated chloride solutions to produce even modest rates of hydrogenation of unsaturated fatty acids [6]. Finally, the classic group of organometallic compounds containing low-valent transition metal ions are largely unsuitable because of their unstable character in aqueous media.

6.15.3.1
Water-insoluble Homogeneous Catalysts

The first catalyst used in homogeneous catalytic hydrogenation of membrane lipids was Wilkinson's catalyst [2, 7, 8]. One of the features of Wilkinson's catalyst that limits its use in biomembrane systems is its low solubility in water. Nevertheless, the catalyst is active against unsaturated lipid substrates, but at a somewhat reduced rate. This can be seen in Figure 1, which shows the relationship between the initial rate of hydrogenation of soya phosphatidylcholine in aqueous mixtures of tetrahydrofuran in the presence of Wilkinson's catalyst. It can be seen that the initial rate of hydrogen uptake decreases as the proportion of water in the system increases, and reaches a limiting rate when the phospholipid assumes a bilayer form. Despite differences in initial reaction rate, virtually complete hydrogenation occurs in all combinations of solvent.

In adapting water-insoluble catalysts for use in biological systems it is necessary to introduce the catalyst into the membrane using a solvent vector. Solvents such as tetrahydrofuran and dimethyl sulfoxide have been found to be useful. The introduction of catalyst in a minimum amount of solvent, which is miscible with water, causes the insoluble complex to partition into the hydrophobic domain created by the lipid substrate. The catalyst obviously cannot be removed subsequently from the substrate without destroying the integrity of the membrane. It is also important to verify that the solvent used to introduce the catalyst does not perturb the stability of the membrane.

The original studies of hydrogenation of phospholipids dispersed in aqueous systems were performed using Wilkinson's catalyst introduced in a solvent vector of tetrahydrofuran [1, 9, 10]. It was shown that complete hydrogenation of the dispersed lipid could be achieved under relatively mild conditions of temperature, hy-

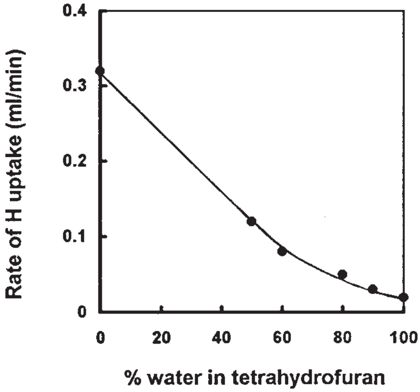

Fig. 1 Initial rate of uptake of hydrogen by a dispersion of soya phosphatidylcholine in aqueous tetrahydrofuran in the presence of Wilkinson's catalyst [1].

drogen pressure, and catalyst concentration. Biophysical studies employing differential scanning calorimetry and X-ray diffraction confirmed that the solvent used to deliver the catalyst and the presence of catalyst in the lipid bilayer did not drastically alter the structural properties of the membrane. Wilkinson's catalyst has also been used to hydrogenate model membranes prepared from lipid extracts of rat liver mitochondria and microsomes and human erythrocytes [11].

It was found that the presence of cholesterol markedly influences the hydrogenation of mixed phospholipid dispersions [12] because it restricts partition of the catalyst into the lipid bilayer structure. It was also found that no dihydrocholesterol forms during hydrogenation of the phospholipid, showing that cholesterol is not a substrate for reaction under the conditions employed.

6.15.3.2
Water-soluble Homogeneous Catalysts

A major advance in the application of homogeneous catalytic hydrogenation methods to modulate lipid phase behavior was the use of water-soluble catalysts. The need to employ solvent vectors to introduce the catalyst into the membrane can be avoided and there is more scope for removal of the catalyst at the end of the reaction. Water-soluble complexes can be removed simply by washing, gel filtration, density gradient centrifugation, and, in the case of charged complexes, by adsorption to ion-exchange resins.

Synthesis of the first water-soluble catalyst complexes was reported in 1973 [3] and was based on the use of sulfonated triphenylphosphine to replace TPP. The sulfonated derivative was found to stabilize the lower oxidation states of a number of transition metals such as Rh, Ru, Ir, Pt, Ni, and Cu in aqueous systems and these water-soluble catalysts facilitated hydrogenation of soluble substrates like pyruvic acid.

The water-soluble complexes appear to have very similar chemical properties to their nonsulfonated TPP counterparts. The presence of the charged sulfonyl group renders the catalyst complex very soluble in neutral aqueous solutions [13] and solubility can be modulated by salt concentration or pH. The sulfonate group is not generally coordinated to the metal and infrared spectra indicate only minor differences in the electronic state of the central metal ion compared with the TPP complexes. The synthesis and reactivity of a range of monosulfonated triphenylphosphine (TPPMS) complexes have been reported [14, 15]. The solubility of metal complexes of phosphines in water can be increased by using multisulfonated TPP [6, 17]. These types of catalysts do not penetrate readily into lipid substrates but partition can be influenced by the use of complexes with phosphine-like ligands [18] or attachment of amphiphilic, long-chain aliphatic ternary phosphines to the metal [19].

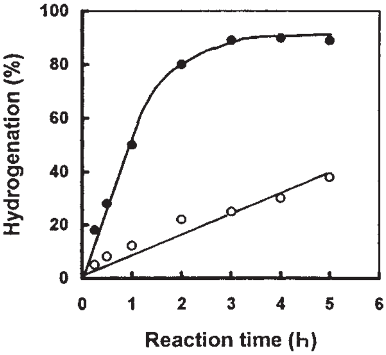

Fig. 2 Hydrogenation of multilamellar dispersions (○) and single bilayer vesicles (●) of soya lecithin in the presence of the sulfonated derivative of Wilkinson's catalyst [22].

Homogeneous catalytic complexes composed of triphenylphosphine ligands are generally unstable in the presence of oxygen and this places a major limitation on their use with living organisms under aerobic conditions. This problem has been largely overcome by synthesis of catalytic complexes based on sulfonated alizarin derivatives of Ru and Pd [20]. The Pd(II)–alizarin complex is not only resistant to inactivation by oxygen, which renders it more stable over relatively long reaction times, but it is also readily soluble in water [21]. Since it retains high activity under physiological conditions, it need only be added to biological systems in trace amounts, thereby avoiding toxicity problems. Toxicity not only arises from the metal ions and ligands but also from the detergent action of these surface-active complexes.

Hydrogenation of unsaturated phospholipids dispersed in aqueous systems using a water-soluble homogeneous catalyst was first reported in 1978 [22]. The catalyst was a sulfonated derivative of Wilkinson's catalyst which did not appear to affect the structure of bilayers with respect to their permeability barrier properties [23]. The catalyst was found to hydrogenate oil-in-water emulsions and two-phase oil/water systems without the need for organic co-solvents [24].

The reaction rate could be increased significantly by screening the electrostatic charge on the sulfonate groups with inorganic cations added to the aqueous phase. This allowed the catalyst to penetrate into the substrate at the interface; partition of the catalyst from the aqueous into the lipid phase could not be detected. Further evidence for exclusion of catalyst from the lipid phase can be seen in comparison of hydrogenation rates of multibilayer dispersions of unsaturated phospholipids and highly dispersed vesicular suspensions, illustrated in Figure 2. The reaction rate in multilamellar dispersions could be accelerated by dispersing the phospholipid in the presence of the catalyst rather than as shown in Figure 2, where catalyst was added to dispersed substrate.

The reactivity of water-soluble palladium catalyst, $Pd(QS)_2$ (palladium di(sodium) alizarin monosulfonate), has been examined in multilamellar dispersions of unsaturated phospholipids [25]. With substrates of dioleoylphosphatidylcholine there was a transient appearance of *trans* $\omega 9$ but no *cis* double bonds were observed when the *trans* $\omega 9$ derivative of phosphatidylcholine was used as substrate. It was suggested that hydrogenation may proceed by a *cis–trans* isomerization followed by reduction of the *trans* double bond. Hydrogenation of di-18 : 2 and di-18 : 3 derivatives of phosphatidylcholines show highly complex patterns of partially saturated molecular species including combinations of *cis* and *trans* positional isomers with little evidence of bond migration. Comparisons of the rate of hydrogenation of unsaturated molecular species of phosphatidylcholines with dioleoylphosphatidylethanolamine showed a slight preference of the reduced $Pd(QS)_2$ catalyst for phosphatidylcholines. There was a preference for polyunsaturated molecular species compared with the monounsaturated molecular species of phosphatidylcholine. Differences in accessibility of catalyst to substrates presented in bilayer form compared with those in hexagonal-II configuration may explain the different susceptibility of phosphatidylcholines and phosphatidylethanolamines. These differences persisted in mixed dispersions hydrogenated at temperatures at which phase separations of bilayer and hexagonal-II structure would be expected to occur in the substrate.

6.15.3.3
Sources of Hydrogen

Hydrogenation in the presence of homogeneous catalysts is conventionally performed in the presence of hydrogen gas. The rate of homogeneous hydrogenation can be increased at physiological temperatures by increasing the pressure of the hydrogen. Although many biological systems can be preserved under these conditions, hydrogen gas is not the most convenient form of hydrogen and alternative strategies have been explored. Several classes of compounds, including amines, alcohols, sugars, and silicon or tin hydrides, can serve as H-donors in catalyzed hydrogen transfer but, in general, conditions required for a meaningful conversion are not biocompatible.

Photochemical reaction of the ruthenium bipyridyl complex $[RuCl_2(bipy)_3]$ together with ascorbic acid as a sacrificial electron donor [25, 26] has been shown to catalyze the reduction of water and generate molecular hydrogen in the presence of water-soluble Wilkinson's catalyst [27]. This system has been exploited to catalyze the light-dependent hydrogenation of phospholipid multilayer dispersions, emulsified triglycerides, and membranes of the living protozoan, *Tetrahymena pyriformis* [28, 29].

6.15.4
Hydrogenation of Biological Membranes

The level of unsaturation of lipids in living cells is controlled within relatively precise limits. The molecular mechanisms that are responsible for this control are not understood. Unsaturated lipids are believed to be required for preserving the fluidity of the lipid bilayer matrix and to maintain the activity of intrinsic membrane proteins with certain limits. When organisms are subjected to environmental stress or shifted to different growth conditions they often adapt by altering the level of unsaturation of their constituent lipids. All these factors have been experimentally tested by use of homogeneous catalytic hydrogenation methods.

6.15.4.1
Topology of Unsaturated Lipids in Membranes

The topology of lipids in the membrane of complex organisms or in subcellular membrane preparations can be probed by determining access to hydrogenation catalysts. Water-soluble catalyst complexes, for example, are not readily permeable to membranes and when added to suspensions of cells or closed vesicular structures their action has been shown to be largely restricted to the outer monolayer, at least at short time intervals after commencement of the reaction [30] (see also Figure 2). Selective hydrogenation of lipid classes has also been observed. This is exemplified by the pattern of hydrogenation observed during incubation of suspensions of pea chloroplasts in the presence of $Pd(QS)_2$ catalyst [31]. Figure 3 shows the extent of hydrogenation of the three major galactolipid classes at intervals during the hydrogenation reaction and there is a marked difference in sus-

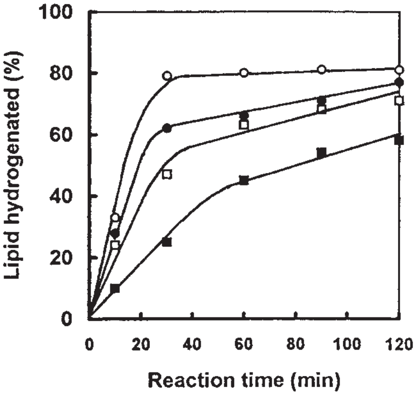

Fig. 3 Time course of hydrogenation of membrane lipids of pea chloroplasts *in situ* in the presence of palladium–alazarin catalyst: ○ monogalactosyldiacylglycerol; ● digalactosyl diacylglycerol; □ sulfoquinovosyldiacylglycerol; ■ phosphatidylglycerol [31].

ceptibility of membrane lipids to hydrogenation. Galactolipids are more readily hydrogenated than the acidic lipids of the membrane. This effect could be due to a charge repulsion between the negatively charged functional groups of sulfoquinovosyldiacylglycerols and phosphatidylglycerols and the sulfonated alizarin groups on the palladium catalyst complex.

6.15.4.2
Function of Unsaturated Lipids in Membranes

Extensive hydrogenation of chloroplast suspensions has shown that inhibition of whole-chain electron transport occurs before inhibition of either photosystem-II or photosystem-I activity is observed, suggesting that removal of unsaturated double bonds may cause a decrease in fluidity of the membrane which is required to facilitate communication between the photosystems situated in different lateral domains in the membrane [32, 33]. To test the notion that plastoquinol diffusion between photosystem-II and cytochrome b_6/f complex was a rate-limiting step in photosynthetic electron transport when the fluidity of the thylakoid membrane was reduced, measurements were performed on the reduction rate of flash-oxidized cytochrome f in pea chloroplasts subjected to lipid hydrogenation [34]. The results of reduction of *cis*-unsaturated fatty acyl residues achieved in the presence of palladium–alizarin catalyst is shown in Table 1 together with the effect of rotational correlation time of the spin probe, 16-doxyl stearate. It can be seen that a 30% reduction in unsaturated bonds results from the treatment with catalyst and there is a significant reduction in membrane fluidity as judged by the motion of the spin probe. Nevertheless, despite a reduction in the full-chain electron transport, no change in the rate of reduction of flash-oxidized cytochrome b_6/f was observed, leading to the conclusion that the rate of diffusion of plastoquinol is unaffected by the reduced fluidity of the thylakoid membrane due to the saturation of membrane lipids. The function of the unusual fatty acid, *trans*-Δ^3-hexadecenoic acid, of phosphatidylglycerol in chloroplast membranes has also been investigated by homogeneous catalytic methods [35].

Tab. 1 Changes in fatty acyl composition [mol%] of pea thylakoid membranes and motion of 16-doxyl stearate resulting from hydrogenation in the presence of palladium–alizarin catalyst.

Fatty acid	*Control*	*Hydrogenated*
16:0	11	12
16:1	2	2
16:3	1	Trace
18:0	2	15
18:1	5	19
18:2	6	13
18:3	73	39
Rotational correlation time [s] of 16-deoxy stearate at 20 °C	1.65	2.07

The effect of hydrogenation on membrane protein function has been examined using the Ca^{2+} pump of sarcoplasmic reticulum of rabbit hind-leg muscle [36, 37]. Up to 35% of the unsaturated bonds of the membrane lipids could be saturated in the presence of Wilkinson's catalyst. ATPase activity was completely inhibited on adding catalyst but this could be prevented by preserving the catalyst in its hydride form. When the effect of hydrogenation of sarcoplasmic reticulum on calcium pump activity was assayed in buffers saturated with H_2, it was found that removal of 25% of *cis* double bonds did not affect the activity of Ca^{2+}-ATPase.

6.15.4.3
Acclimation of Membranes to Low Temperature

Catalytic hydrogenation has been used to examine the mechanism of retailoring membrane lipids in the process of cold adaptation in *Tetrahymena pyriformis* [35]. Isolated cilial membranes, when hydrogenated in the presence of Pd(II)–sulfonated alizarin complex, showed a marked increase in order parameter and rotational correlation time of electron spin resonance probes as the constituent lipids became saturated. This was associated with a dramatic decrease in endogeneous phospholipase A activity of the membrane, even when only a small proportion of the unsaturated bonds had been hydrogenated. The way that endogenous phospholipases respond to the change in physical state of the substrate is believed to be the mechanism whereby the biochemical changes responsible for thermal adaptation are bought about.

Some organisms or differing strains of the same organism suffer loss in viability resulting from a sudden exposure to cold. These effects appear to be related to the extent of unsaturation in lipids of constituent membranes. Catalytic hydrogenation has proven to be a useful method to investigate the molecular basis of chilling sensitivity. The phase behavior of membrane lipids of the blue–green alga *Anacystis nidulans* is believed to underlie the chilling sensitivity of this organism [37] and catalytic hydrogenation studies have been undertaken to examine this hypothesis [38, 39].

Recently, catalytic hydrogenation methods have been used to establish a connection between membrane physical properties and expression of desaturase genes in blue–green algae [40].

6.15.4.4
Membrane Unsaturation and Stability at High Temperatures

Adaptation of organisms to elevated temperature is often associated with a shift in the molecular species of membrane lipids to more saturated fatty acyl substituents. It is often argued that this change renders the membrane more stable at elevated temperatures. This hypothesis has been examined in considerable detail in chloroplast photosynthetic membranes, which are ideal for hydrogenation studies because of the highly unsaturated lipids present and the dependence on these lipids to maintain structural stability and organization. The original studies were performed using Wilkinson's catalyst [41]; it was found that loss of up to 40% of unsaturated bonds did not alter the ultrastructural features of the membrane or photosynthetic electron transport processes. Later studies using water-soluble catalysts [42, 43] showed that saturation of the lipids results in a decrease in electron transfer between the "primary" electron acceptor QA and "secondary" acceptor QB. Fluorescence induction kinetics indicated that there is an optimal level of lipid unsaturation to maintain an efficient electron transfer from QA^- to the plastoquinone pool. Furthermore, the proportion of photosystem-IIb, which has a reduced complement of ligh-harvesting chlorophyll-II [44–46], compared with photosystem-IIa, the form of photosystem-II with complete peripheral chlorophyll *a*/*b* light-harvesting chlorophyll-II, increases with increased hydrogenation of the membrane lipid.

Hydrogenation of the lipids of the photosynthetic membrane of higher plant chloroplasts prevents disruption of the membrane exposed to elevated temperatures. Freeze-fracture electron microscopic studies of hydrogenated chloroplasts has revealed the presence of particle-free domains within lipids [47]. When exposed to elevated temperatures (40–45 °C), a treatment that results in a loss in photosynthetic electron transport [48], a membrane destacking and dissociation of supramolecular protein complexes [49], hydrogenated membranes show a reduced tendency to destack and vesiculate. Chlorophyll *a* fluorescence measurements and differential scanning calorimetry suggest that the hydrogenation of thylakoid membrane lipids causes an increased thermal stability of pigment protein complexes of the photosystem-II light harvesting apparatus. Similar stabilization of photosystem-I complex subjected to heat stress has also been observed [50].

6.15.4.5
Biochemical Homeostasis of Unsaturated Lipids

The process of regulation of the level of unsaturated lipids in biomembranes has been examined in potato tubers [51]. When membrane lipids of microsomal suspensions were hydrogenated in the presence of $Pd(QS)_2$ catalyst there was a marked rigidification of the hydrocarbon domain of the membrane as judged by electron spin resonance probe measurements and a stimulation of NADH reductase using ferricyanide as the electron acceptor. This suggests that hydrogenation results in stimulation of the electron transport pathway responsible for desaturating fatty acids. Similar findings have been reported in yeast microsomes hydrogenated with Pd complex [52]. Nevertheless, there is a risk of creating unusual molecular species of lipid which may block metabolic reactions such as desaturation by processes of competitive inhibition [53].

The hydrogenation of polyunsaturated phosopholipids of trout liver microsomes in the presence of a $Pd(QS)_2$ catalyst has also been reported [54]. Long-chain

(C20 : 5ω3; C22 : 6ω3) fatty acyl residues were preferentially hydrogenated compared with oleic and linoleic acids. The physical state of the membrane lipid matrix, as judged by the motion of fluorescent probes, became more viscous as a consequence of catalytic hydrogenation.

Hydrogenation of the constituent lipids of suspensions of isolated rat liver mitochondria in the presence of homogeneous catalyst has been demonstrated [55]. One effect of hydrogenation was a loss of ability of phospholipase A_2 to hydrolyse endogeneous phospholipids of the organelle but not the extracted lipids dispersed in aqueous media irrespective of whether they were hydrogenated or not. It was suggested that the extent of unsaturation of mitochondrial lipids may regulate their enzymic turnover in the membrane.

Information on the pathways of unsaturated membrane lipid biosynthesis and processes of redistribution from the site of synthesis to the different subcellular membranes has been obtained from studies of the unicellular green alga, *Daniella salina* [56]. Membrane lipids of the alga can be extensively hydrogenated in the presence of water-soluble palladium–alizarin catalyst under conditions that permit full recovery of the cells within 24 h. When cells are incubated with the catalyst under 1 bar of hydrogen for less than 2 min, only the unsaturated lipids of the surface (plasma) membrane are reduced. Cells treated in this way cease growth for about 12 h, during which time the hydrogenated acyl chains are partially reconverted to their original level of unsaturation. Restoration of lipid unsaturation permits a resumption of growth as membrane functions are presumably restored. Subfractionation of hydrogenated cells showed that the plasma membrane component of the microsomal fraction was hydrogenated to the greatest extent and endoplasmic reticulum to a considerably lesser extent.

6.15.4.6
Hydrogenation of Living Cells

In addition to work on *Tetrahymena* [29] and *Daniella* [56], described above, hydrogenation studies have been performed using a variety of other cell types. Such studies have shown that different cells have been found to vary considerably in their ability to survive hydrogenation of the plasma membrane. The protozoan *Tetrahymena nimbres,* for example, appears to be particularly sensitive [30]. Hydrogenation of lymphocytes with Wilkinson's catalyst has been reported [57] but this catalyst was found to be highly toxic to the cells. More success has been obtained with the use of the water-soluble palladium–alizarin catalyst, which has been used to hydrogenate plasma membranes of a living murine leukemia cell line [58]. Survival of more than 80% of the cells was achieved under optimum treatment conditions which resulted in 40% reduction of total cell fatty acid *cis* double bonds, mainly in polyunsaturated 18 : 2, 20 : 4, and 22 : 6 compounds.

A novel catalyst consisting of colloidal palladium adsorbed onto the surface of a water-insoluble polymer, polyvinylpyrrolidone, has been shown to hydrogenate only the outer leaflet of rat platelets [59]. The effect of hydrogenation was to influence the asymmetric distribution of the phospholipids of the membrane. Catalytic hydrogenation of a phytopathogenic fungus [60] has also been reported.

6.15.5
Conclusions

The chemical modification of membranes containing unsaturated hydrocarbon substituents is a useful tool in the study of the role of these lipids in membrane structure and stability. Homogeneous catalytic hydrogenation of biological membranes in isolated organelles or living cells has developed rapidly over the past few years with the introduction of more active catalytic complexes, especially under conditions of hydrogenation more compatible with living organisms. Advances in targeting catalysts to specific membranes and localizing action to specific membrane sites are likely to be important in future developments.

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6.16
Other Recent Examples

Wolfgang A. Herrmann, Ana M. Santos, Fritz E. Kühn

6.16.1
Introduction

As exemplified in the previous sections, organometallic catalysis in water and biphasic water-containing systems has not only been intensively examined during recent years but its scope has also considerably broadened. Between 1945 and 1997, the publishing date of the first edition of this book, about 1650 articles dealing with catalysis in aqueous media appeared in scientific journals. Approximately the same number of articles has been published between 1998 and the end of 2002. In the first half of 2003 nearly 200 new articles appeared [1]. Most of the research dedicated to reactions in aqueous-phase and aqueous biphasic or multiphase systems refer to the reactions described in the previous sections. In this chapter some other new results, not described above in more detail, on reactions in aqueous media will be presented.

6.16.2
Isomerizations

Recently, the nickel-catalyzed isomerization of geraniol and prenol has been investigated in homogeneous and two-phase systems. The best results with respect to activity and selectivity have been obtained in homogeneous systems with a bis(cycloocta-1,5-diene)nickel(0)/1,4-bis(diphenylphosphanyl)butane/trifluoroacetic acid combination. Catalyst deactivation occurs in the course of the reaction owing to coordination of the aldehyde group that is formed to the nickel species or as a result of protonolysis of hydrido or (π-allyl)nickel complexes [2].

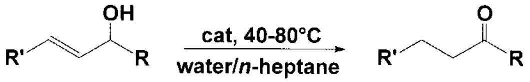
Isomerization of allylic and homoallylic alcohols is also catalyzed by the zwitterionic Rh(I) complex (sulphos)Rh(COD), with sulphos = $[O_3S(C_6H_4)CH_2C(CH_2PPh_2)_3]^-$, in water/*n*-octane to give the corresponding aldehyde or ketone in high yields and chemoselectivity. A π-allyl metal hydride mechanism was proposed on the basis of various independent experiments in both homogeneous and biphasic systems [3 a].

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Additionally, a water-soluble rhodium bisphosphine complex was used for the aqueous-phase isomerization of selected allylic alcohols. For the isomerization of cinnamyl alcohol, the catalyst was recycled with slight loss of activity, and the optimum phosphine/rhodium ratio was found to be 6 : 1 [3 b].

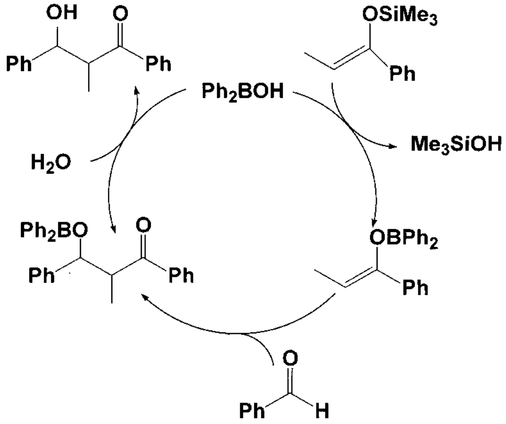
The isomerization of allylic alcohols, being a process of current industrial interest in geraniol chemistry [4], was furthermore used as a liquid/liquid test reaction for high-throughput screening (HTS) of polyphasic fluid reactions. Nowadays high-throughput synthesis methodologies, such as combinatorial techniques, are applied to the discovery of pharmaceuticals, catalysts, and a multitude of other new materials [5]. The effectiveness of this approach has been demonstrated for restricted libraries in the case of catalysis in a single liquid phase. High-throughput screening in one phase is assumed to be unproblematic as long as the reactions are not too fast compared with the micromixing rates. However, numerous reactions of interest, e.g., hydrogenation, carbonylation, and hydroformylation, operate in gas/liquid or gas/liquid/liquid systems [6]. Inadequate control of phase and catalyst presentation, a result of non-optimized agitation, may dramatically affect the estimation of selectivity and reactivity. Therefore, a major challenge is to develop special reactors for rapid catalyst screening that would ensure good mass and heat transport in a small volume. The liquid/liquid test reaction, based on the isomerization of allylic alcohols (see Eq. 1) was performed with various Rh-, Ru-, Pd-, and Ni-based catalyst systems in aqueous/*n*-heptane reaction mixtures with a residence time of 100 s at 80 °C. The best results with respect to conversion have been achieved with $RhCl_3$ and $RuCl_3$/TPPTS catalyst systems [7].



(1)

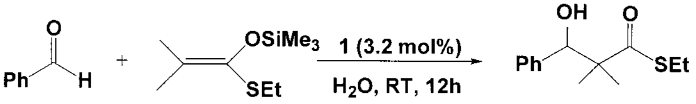
6.16.3
Aldolizations

As already exemplified in many other cases throughout this book, the main driving force for performing aldolizations in water is the reduction or even exclusion of any harmful organic solvents [8]. Nevertheless, many of these reactions proceed sluggishly in pure water, probably because most of the organic reagents are not completely dissolved. Several useful synthetic reactions in an aqueous medium need the presence of an organic co-solvent [9]. To overcome this problem Lewis acid-surfactant combined catalysts (LASCs, **1**) have been developed. In the presence of a catalytic amount of an LASC, organic materials rapidly form a dispersed colloidal system in water and several organic reactions proceed smoothly without the use of organic solvents. In order to solve the problems associated with catalyst recovery, polymer-supported Lewis acid catalysts have been developed, which show



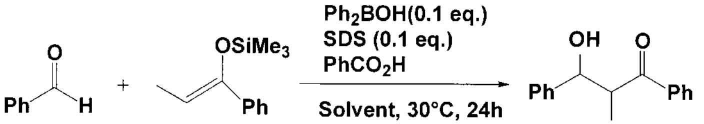
Scheme 1

high activity in water and can be easily recovered and reused. Among the reactions performed with these polymer-supported catalysts is the aldolization reaction given in Eq. (2), promoted by a scandium based catalyst (see also Section 3.1.2). Yields of 98% have been reached by the reaction of benzaldehyde with 1-ethylthio-1-trimethylsiloxy-2-methylpropene at room temperature in water in the presence of 3.2 mol% of catalyst [10a].



(2)

Diphenylboronic acid (Ph_2BOH), which is soluble in water, is an effective catalyst for the Mukaiyama aldol reaction in the presence of dodecyl sulfate (SDS) as surfactant. Yields of 93% with *syn*/*anti* ratios of 94 : 6 have been reached according to Eq. (3). The proposed mechanism of this reaction is shown in Scheme 1 [10b].



(3)

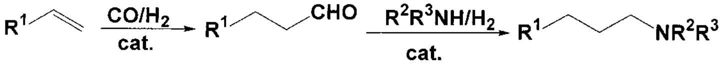
Furthermore, lead(II) and lanthanide(III) complexes were synthesized, which work well as chiral Lewis acids in aqueous media. Until then chiral crown ether-based Lewis acids had not been successfully used in catalytic asymmetric reactions. The asymmetric aldol reactions, however, proceed smoothly at − 10 to 0 °C in water–alcohol solutions, while high levels of diastereo- and enantioselectivity are retained. In most previously established catalytic asymmetric aldol reactions the use of aprotic anhydrous solvents and reaction temperatures of − 78 °C were necessary. In the asymmetric aldol reaction using rare earth metal triflates $M(OTf)_3$ and chiral bispyridino-18-crown-6, slight changes in the ionic diameter of the metal cations greatly affect the diastereo- and enantioselectivities of the products. The substituents at the 4-position of the pyridine rings of the crown ether influence the binding ability of the crown ether with the M cations. The binding ability of the crown ether with the M cation, however, is important for achieving high selectivities in the asymmetric aldol reactions. Water plays an essential role in obtaining good yields and selectivities. Several aldehyde and silyl enol ethers derived from ketones and thioesters can be applied [11].

Additionally, organocatalytic cross-aldol reactions catalyzed by cyclic secondary amines in aqueous media provide a direct route to a variety of aldols, including carbohydrate derivatives, and may warrant consideration as a prebiotic route to sugars [12a].

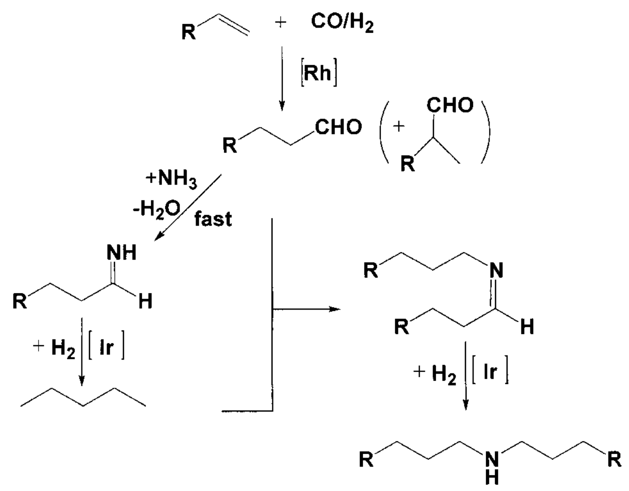
Dichloroindium hydride, generated by transmetallation between tributyltin hydride and indium trichloride, predominantly reduces unsaturated ketones (enones) with 1,4 selectivity in the presence of aldehydes. Under anhydrous conditions, the successive aldol reaction between the resulting enolates and the remaining aldehydes proceeds with high *anti*-selectivity. The stereochemistry, however, is reversed to be *syn*-selective by the use of water and methanol as an additive and solvent, respectively [12b].

6.16.4
Hydroaminomethylation

Aliphatic amines are amongst the most important bulk and fine chemicals in the chemical and pharmaceutical industry [13]. Hydroaminomethylation of alkenes to amines presents an atom-economic, efficient and elegant synthetic pathway towards this class of compounds. In hydroaminomethylation a reaction sequence of hydroformylation of an alkene to an aldehyde with subsequent reductive amination proceeds in a domino reaction (see Eq. 4) [14]. Recently, the highly selective hydroamination of alkenes with ammonia to form linear primary and secondary aliphatic amines with a new Rh/Ir catalytic system ([{Rh(cod)Cl}$_2$], [{Ir(cod)Cl}$_2$], aqueous TPPTS solution) has been described (see Scheme 2) [15]. The method is of particular importance for the production of industrially relevant, low molecular weight amines.



(4)



Scheme 2

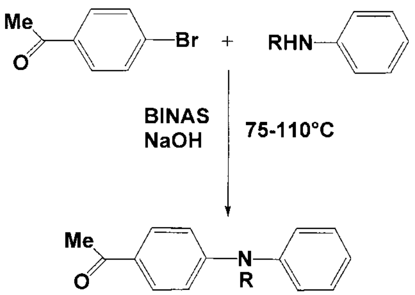
6.15.5 Aminations

New methodologies have been reported in recent years for the amination of aromatic halides and triflates with amines according to Eq. (5) to yield aromatic amines of the type ArNRR′ [16]. In contrast to the homogeneous reaction conditions (1–5 mol% Pd(0) catalyst and 1.4 equiv. *tert*-butoxide in PhMe at 80–100 °C), by using a two-phase protocol, the separation of products (and unreacted starting material) from the catalyst and subsequent reapplication of the catalyst in further reactions is made facile [17]. The use of the six-fold sulfonated ligand BINAS-6 permits the Pd(0) catalyzed amination of aromatic halides in water containing single- or two-phase systems [18]. NaOH is used instead of the expensive NaO^{t}Bu as the base. Further advantages are the facile catalyst/product separation and the recycling of the water-soluble Pd(0)/BINAS-6 catalyst. Yields higher than 90% have been reached according to Eq. (6).

$$\mathrm{ArX} + \mathrm{HNRR^1} \xrightarrow[\text{toluene, 80-100°C}]{\mathrm{Pd^0L,\ NaOBu^t}} \mathrm{ArNRR^1} \qquad (5)$$

6.16.6 Hydrosilylations

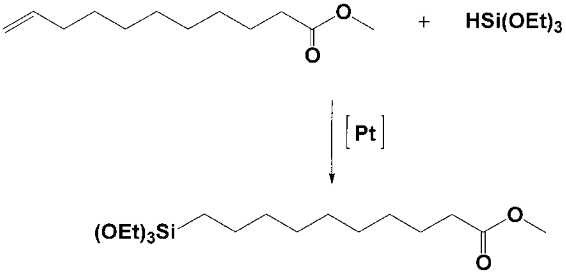
The hydrosilylation of 1-alkenes can be carried out with catalysts of subgroup VIII. Platinum compounds (especially, e.g., the Speier catalyst ($H_2PtCl_6 \cdot H_2O$) and the



(6)

Karstedt solution, a complex compound of $H_2PtCl_6 \cdot (H_2O)_6$) and vinyl-substituted disiloxanes are well known and very active catalysts [19]. Several other catalytic systems, e.g., $Pt(cod)_2$, leading to the formation of platinum colloids have been examined [20]. More recently, hydrosilylation with the Speier catalyst has been tested both under single- and two-phase conditions. The hydrosilylation reaction was thereby optimized for technical realization [21].

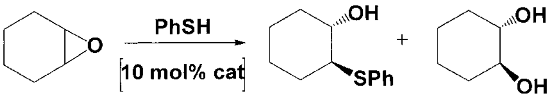
Various Pt(IV), Pt(II), and Pt(0) catalysts were screened for the hydrosilylation of fatty acid esters (Eq. 7) containing terminal as well as internal double bonds. The reaction of terminally unsaturated fatty acid esters proceeds smoothly with short reaction times for nearly all catalysts examined, whereas the Pt(IV) and Pt(II) or Pt(0) species with labile ligands are sufficiently active in the reaction of internally unsaturated compounds. For methyl linoleate, a conjugation of the two internal double bonds before the hydrosilylation was observed. The reaction can be carried out in solid as well as in solvent systems, permitting catalyst recycling and reuse. In these systems, however, hydrogenation and double-bond isomerization are found as side reactions [22].



(7)

6.16.7
Thiolysis

Ring opening of 1,2-epoxides with thiol-derived nucleophiles is a well established route to β-hydroxy sulfides that has been applied for the preparation of allylic alcohols, cyclic sulfides, thioketones, and important intermediates for the synthesis of natural products and compounds of biological and pharmacological interest [23]. The thiolysis of 1,2-epoxides is usually performed fundamentally in two ways: by using thiolates under basic conditions or thiols in the presence of a variety of activating agents [24]. Recently, the Lewis acid catalyzed thiolysis of epoxides in an aqueous medium has been investigated [25]. The pH dependence of thiolysis of 1,2-epoxides with thiophenol in water and the influence of a Lewis acid catalyst was under examination. $InCl_3$ showed a very high efficiency in catalyzing this process at pH 4. The regioselectivity of the nucleophilic attack is markedly influenced on going from pH 9 to pH 4. A one-pot procedure running solely in water to prepare *trans*-2-(phenylsulfinyl)cyclohexan-1-ol was reported starting from epoxycyclohexane, via thiolysis reaction and oxidation with TBHP (TBHP = *tert*-butyl hydroperoxide). The thiolysis of epoxycyclohexane by thiophenol in water is shown in Eq. (8).



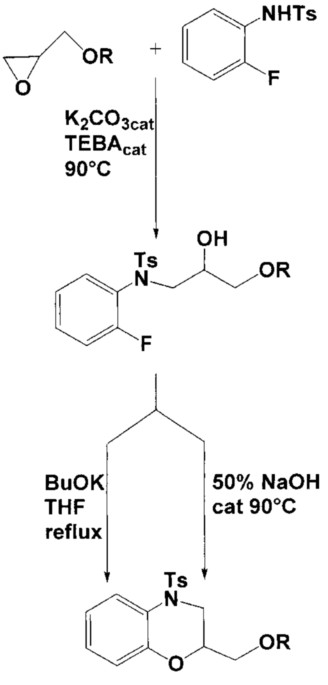
(8)

6.16.8
Synthesis of Various Heterocycles

Easy and efficient access routes to heterocyclic complexes are of significant interest in organic chemistry and its application in synthesis in both laboratory and industry. During recent years, several novel routes towards such compounds in aqueous media have been described. 2-Substituted 3,4-dihydro-2*H*-1,4-benzoxazines have been prepared in excellent yields and short reaction times through the cyclization of hydroxysulfonamides in water under phase-transfer catalysis conditions (Scheme 3) [26].

Reactions of 6-amino-1,3-dimethyluracil with substituted α-ketoalkynes using homogeneous nickel catalysts in an aqueous alkaline medium afford substituted 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives in quantitative yields under very mild conditions. A mechanism has been proposed for the reaction involving the nucleophilic attack by a Ni(0) anion, formed in situ, on the triple bond of the substrate [27].

Additionally, the efficient synthesis of substituted phenylalanine-type amino acids using a rhodium catalyzed, conjugate addition of arylboronic acids has been described. The reactions are run in water using a low loading (0.5 mol%) of the rhodium catalyst [28].



Scheme 3

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7
Other Biphasic Concepts

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

7.1
Nonaqueous Organic/Organic Separation (SHOP Process)

Dieter Vogt

7.1.1
Introduction

The Shell higher-alkene process was undoubtedly the first commercial catalytic process taking benefit from two-phase (but nonaqueous) liquid/liquid technology. In this special case two immiscible organic phases are used to separate the catalyst from the products formed, with the more or less pure products forming the upper phase.

The basis for this nickel-catalyzed oligomerization of ethylene goes back to Ziegler and his school at the Max Planck Institute of Mülheim. There the so-called "nickel effect" [1, 2] was found, and Wilke and co-workers learned how to control the selectivity of nickel-catalyzed reactions by use of ligands. Keim introduced $\widehat{P\;O}$ chelate ligands and on this basic carried out the basic research for the oligomerization process at the Shell research company at Emeryville [3–12]. The whole process was developed in a collaboration between Shell Development, USA, and the Royal Shell Laboratories at Amsterdam in the Netherlands [13–22]. The SHOP is not only a process for ethylene oligomerization, but a very efficient and flexible combination of three reactions: oligomerization, isomerization, and metathesis. It was designed to meet the market needs for linear α-alkenes for detergents [23].

The first commercial plant was built at Geismar, LA, USA, in 1977. The development of this plant and that at Stanlow (UK) is summarized in Table 1, together with other oligomerization capacities based on other technology [24]. The two operational SHOP sites today have a total capacity of nearly 1 million tons of α-alkenes per year. This is about one-half of the total amount made by oligomerization. Today linear α-alkenes are produced mainly by ethylene oligomerization because of the high product quality and the good availability of ethylene. The wide application and increasing need for short-chain α-alkenes as co-monomers for polymers cause the linear alkene market to continue growing.

Aqueous-Phase Organometallic Catalysis, Second Edition
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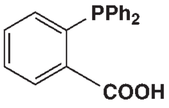
Tab. 1 Linear α-alkene capacities via ethylene oligomerization.

Technology	***Company***	***Location***	***Capacity [10^3 t/y]***		
			Initial (year)	***Expansion (year)***	***Present total***[a]
Ziegler-type	Chevron	Cedar Bayou, TX	125 (1966)	125 (1990)	249
	Ethyl	Pasadena, TX	400 (1971)	55 (1989)	472
	Ethyl	Feluy, Belgium	200 (1992)		200
	Chemopetrol	Czech Republic	120 (1992)		120
	Mitsubishi Kasei Corp.	Kurashiki, Okayama Pref., Japan	50		50
SHOP	Shell	Geismar, LA	200 (1977)	390 (1989)	590
				320 (2002)	910
	Shell	Stanlow, UK	170 (1982)	100 (1989)	278
Zr	Idemitsu Petrochemicals	Ichihara, Chiba Pref., Japan	50 (1989)		50

[a] In 1992.

7.1.2
Process Description

The oligomerization is carried out in a polar solvent in which the nickel catalyst is dissolved but the nonpolar products, the α-alkenes, are almost insoluble. Preferred solvents are alkanediols, especially 1,4-butanediol (1,4-BD). This use of a biphasic organic liquid/liquid system is one of the key features of the process. The nickel catalyst is prepared *in situ* from a nickel salt, e.g., $NiCl_2 \cdot 6\,H_2O$, by reduction with sodium borohydride in 1,4-BD in the presence of an alkali hydroxide, ethylene, and a chelating $\overset{\frown}{\mathrm{P\ O}}$ ligand such as *o*-diphenylphosphinobenzoic acid (Structure **1**) [11, 20]. Suitable ligands are the general type of diorganophosphino acid derivatives (**2**).



1

2

The nickel concentration in the catalyst system is in the range 0.001–0.005 mol% (approx. 10–50 ppm). The oligomerization is carried out in a series of reactors at temperatures of 80–140 °C and pressures of 7–14 MPa. The rate of the reaction is controlled by the rate of catalyst addition [19]. A high partial pressure of ethylene is required to obtain good reaction rates and high product linearity [11]. The linear α-alkenes produced are obtained in a Schulz–Flory-type distribution with up to 99% linearity and 96–98% terminal alkenes over the whole range from C_4 to C_{30}^{+} (cf. Table 2) [23].

Tab. 2 Comparison of product qualities of technical C_6–C_{18} α-alkenes [25].

Product	***Wax-cracking***	***Quality [wt.% α-alkene]***		
		Chevron	***Ethyl***	***Shell SHOP***
α-Alkenes	83–89	91–97	63–98	96–98
Branched alkenes	3–12	2–8	2–29	1–3
Paraffins	1–2	1.4	0.1–0.8	0.1
Dienes	3–6	–	–	–
Monoalkenes	92–95	99	>99	99.9

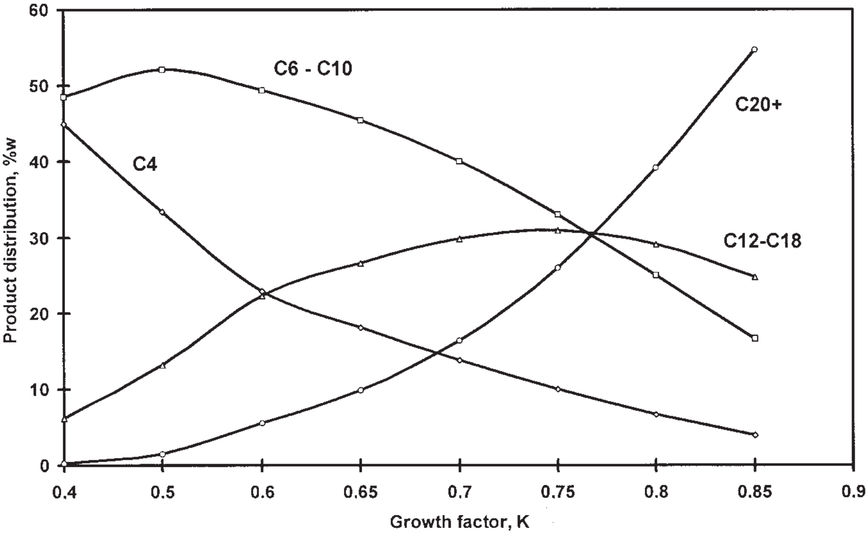


Fig. 1 Schulz–Flory product distribution dependence on the chain-growth factor *K*.

The shape of the Schulz–Flory distribution and the chain length of the α-alkenes are controlled by the geometric chain-growth factor K, defined as $K = n(C_{n+2})/n(C_n)$ (Figure 1).

For the economy of the whole process it is very important that the K-factor can easily be adjusted by varying the catalyst composition. Usually the value is between 0.75 and 0.80. The heat of the reaction is removed by water-cooled heat exchangers between the reactors (Figure 2). In a high-pressure separator the insoluble products and the catalyst solution as well as unreacted ethylene are separated.

The catalyst solution is fed back into the oligomerization reactor. Washing of the oligomers by fresh solvent in a second separator removes traces of the catalyst. This improves product quality and the catalyst utilization [26]. Traces of remaining catalyst in the product can lead to the formation of insoluble polyethylene during upstream processing, resulting in fouling of process equipment [27].

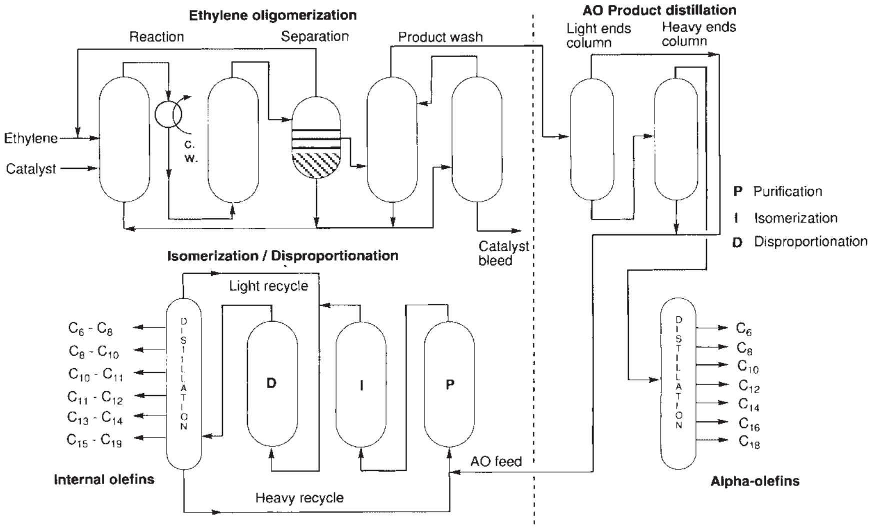
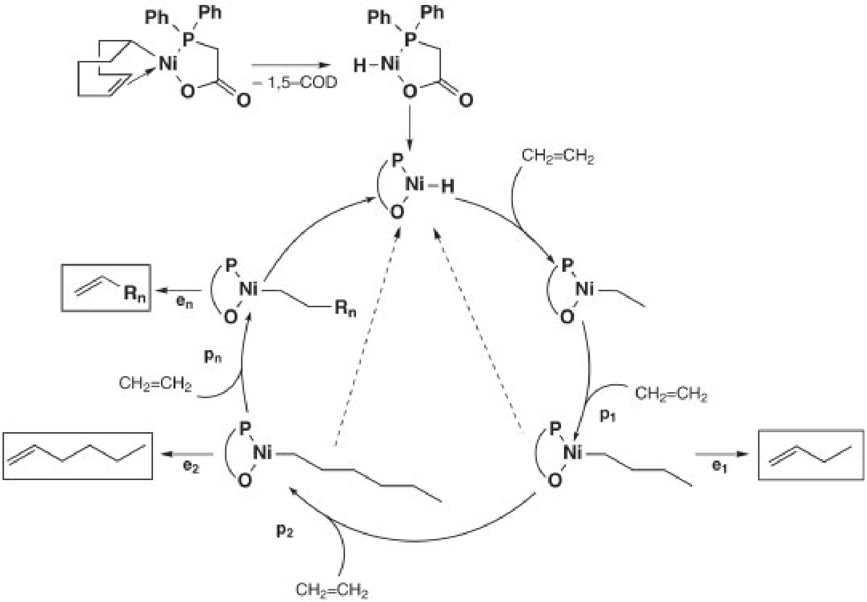


Fig. 2 Flow scheme of the Shell higher-alkene process (SHOP). AO = α-alkene; C.w. = cooling water.

The formation of insoluble polyethylene cause problems also in other parts of the process. During catalyst preparation this can be avoided by adding the preformed, stable nickel complex and the chelate ligand separately to the oligomerization reactor. By this simple change, the catalyst utilization is enhanced markedly, resulting in a significant reduction of nickelt salt and borohydride consumption [28–30]. So one major problem is the complete separation of the catalyst. Many attempts have been made to improve this [19]. One approach was using methanol/water solvent mixtures together with sulfonated ligands [31–37]. In the course of this it was shown that the catalyst is not deteriorated by water [38], which might lead to new approaches in the future.

Completely different liquid/liquid two-phase applications for oligomerization of ethylene were reported recently. Chauvin used ionic liquids as solvents for oligomerization catalysts [39] (cf. Section 7.6). Another approach is the use of perfluorinated solvents together with catalysts bearing perfluorinated ligands [40, 41] (cf. Section 7.2).

Further processing of the product α-alkenes involves separation into the desired product fractions in a series of distillation columns. First the lower C_4–C_{10} α-alkenes are stripped off. In a heavy-ends column the C_{20+} α-alkenes are removed from the desired C_{12}–C_{20} α-alkenes. Finally the middle-range products meeting the market needs are separated into the desired cuts and blends. The very high flexibility of the "SHOP" results from the following steps. The C_4–C_{10} and the C_{20+} fractions are combined to be isomerized to internal linear alkenes and then subjected to a metathesis reaction. Both steps require about 80–140 °C and 0.3–



Scheme 1 Postulated mechanism for ethylene oligomerization via a P͡O-stabilized nickel hydride species: **p_1**, **p_2** · · · **p_n** = propagation steps; **e_1**, **e_2** · · · **e_n** = elimination steps.

2 MPa. Isomerization is accomplished by a typical isomerization catalyst such as Na/K on Al_2O_3 or a MgO catalyst in the liquid phase [42], where about 90% of the α-alkenes are converted to internal alkenes. Metathesis of the lower and higher internal alkenes gives a mixture of alkenes with odd and even carbon chain lengths. The mixture comprises about 11–15% of the desired C_{11}–C_{14} linear internal alkenes, which are separated by distillation. The undesired fractions can be recycled, feeding the light alkenes directly back to metathesis while the higher-boiling fractions are again subjected to isomerization. Because of the high proportion of short-chain alkenes in the metathesis feed, the double bonds in the end product are shifted toward the chain ends. Altogether the different possibilities of shifting products to the desired chain length and double-bond position makes the "SHOP" an elegant and flexible process operating today. It is furthermore one of the larger applications of homogeneous catalysis.

The mechanism of the nickel-chelate complex-catalyzed oligomerization has been investigated in detail by Keim and co-workers [43–52]. Based on these results, the mechanism shown in Scheme 1 was postulated.

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7.2
Catalysis in Fluorous Phases

István T. Horváth

7.2.1
Introduction

The increasing demand for environmentally benign processes with high product selectivities at economically favorable reaction rates has renewed interest in homogeneous organometallic catalysis [1]. The development of simple and efficient separation of the generally thermally sensitive organometallic catalysts from the products under mild conditions is crucial for their industrial applications. The use of biphasic systems, in which one of the phases contains the dissolved catalyst and the other products, could allow easy separation of the products. Since the formation of a liquid–liquid biphase system is due to the sufficiently different intermolecular forces of two liquids [2], the selection of a catalyst phase depends primarily on the solvent properties of the product phase at high conversion levels. For example, if the product is apolar the catalyst phase should be polar, and vice versa: if the product is polar the catalyst phase should be apolar. The success of any biphasic system depends on whether the catalyst could be designed to dissolve preferentially in the catalyst phase. Perhaps the most important rule for such design is that the catalyst has to be like the catalyst phase, since it has been known for centuries that "similia similibus solvuntur," or "like dissolves like" [3].

7.2.2
The Fluorous Concept

Perfluorinated alkanes, dialkyl ethers, and trialkylamines are unusual because of their nonpolar nature and low intermolecular forces. Their miscibility, even with common organic solvents such as toluene, THF, acetone, and alcohols, is low at room temperature, so these materials could form fluorous biphase systems [2]. The term "fluorous" was introduced [4, 5], as the analog to the term "aqueous," to emphasize the fact that one of the phases of a biphase system is richer in fluorocarbons than the other. Fluorous biphase systems can be used in stoichiometric

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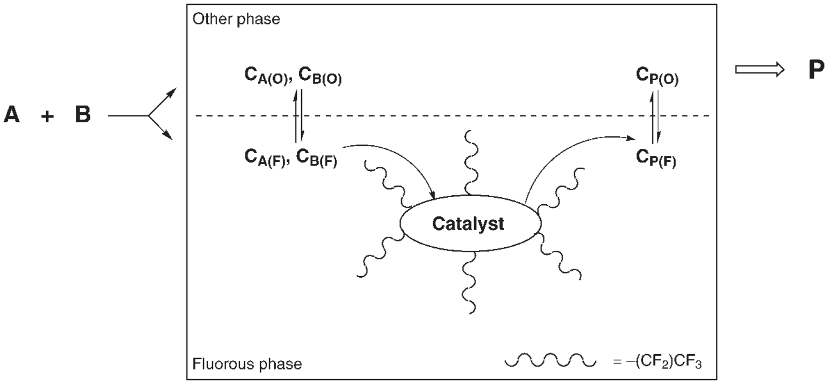

Fig. 1 The fluorous biphase concept for the catalytic conversion of substrates **A** and **B** to product **P**. The attachment of appropriate fluorous ponytails to the ligands of the homogeneous catalyst ensures that the fluorous catalyst remains in the fluorous phase.

and catalytic chemical transformations by immobilizing reagents and catalysts in the fluorous phase. A fluorous organometallic catalyst system consists of a fluorous phase containing a preferentially fluorous soluble organometallic compound and a second product phase, which may be any organic or nonorganic solvent with limited solubility in the fluorous phase (Figure 1).

The fluorous biphase concept for the catalytic conversion of substrates **A** and **B** to product **P**. The attachment of appropriate fluorous ponytails to the ligands of the homogeneous catalyst ensures that the fluorous catalyst remains in the fluorous phase.

Organometallic complexes can be made fluorous soluble by attaching fluorocarbon moieties to ligands with appropriate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain other heteroatoms (the "fluorous ponytails"). It should be emphasized that *perfluoroaryl* groups do offer dipole–dipole interactions [6], making perfluoroaryl containing ligands soluble in common organic solvents and therefore less compatible with fluorous biphase systems.

The most effective fluorous solvents are perfluorinated alkanes, perfluorinated dialkyl ethers, and perfluorinated trialkyl amines. Their remarkable chemical inertness, thermal stability, and nonflammability coupled with their unusual physical properties make them particularly attractive for catalyst immobilization. Furthermore, these materials are practically *nontoxic* by oral ingestion, inhalation, or intraperitoneal injection [7]. Although their thermal degradation can produce toxic decomposition products, such decomposition generally begins only at very high temperatures well above the thermal stability limits of most organometallic compounds.

A fluorous biphase reaction could proceed either in the fluorous phase or at the interface of the two phases, depending on the solubilities of the substrates in the fluorous phase. When the solubilities of the substrates are very low in the fluorous

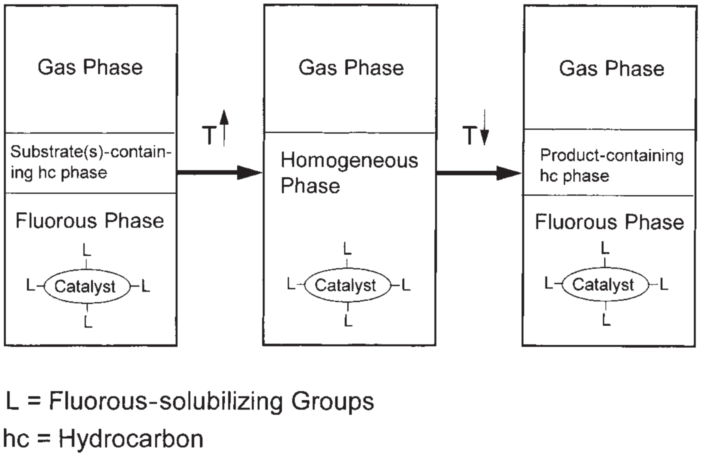

Fig. 2 The temperature-dependent fluorous-liquid/liquid biphase concept.

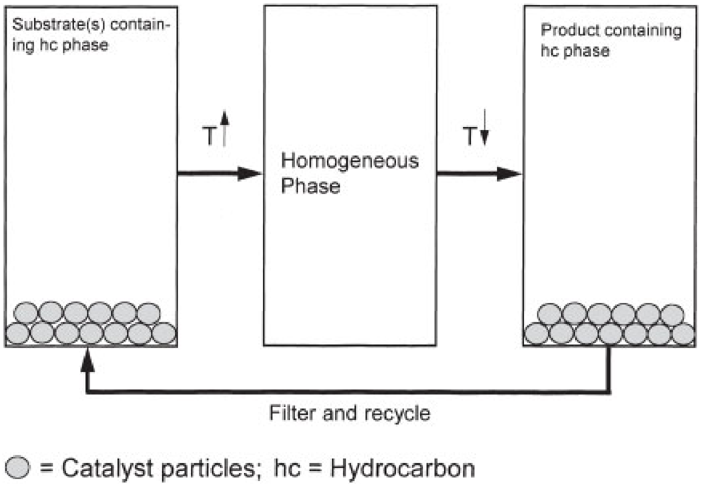

Fig. 3 The temperature-dependent fluorous-solid/liquid biphase concept.

phase, the chemical reaction may still occur at the interface or appropriate phase transfer agents may be added to facilitate the reaction. It should be emphasized that a fluorous biphase system might become a one-phase system by increasing the temperature. Thus, a fluorous catalyst could combine the advantages of one phase catalysis with biphase product separation by running the reaction at higher temperatures and separating the products at lower temperatures (Figure 2). Alternatively, the temperature-dependent solubilities of *solid* fluorous catalysts in liquid substrates or in conventional solvents containing the substrates (Figure 3) [8] could eliminate the need of fluorous solvents.

Tab. 1 Calculations for electronic properties of various phosphines.[a)]

Phosphine	***P Mulliken population [q]***	***P lone pair level [eV]***	***Protonation energy [eV]***	***P–H [Å]***	***H-P-L angle [deg]***
$P[CF_2CF_3]_3$	0.83	− 11.7	− 6.5	1.189	85.9
$P[CF_2CF_2CF_2CF_3]_3$	0.83	− 11.7	− 6.4	1.192	85.4
$P[CH_2CF_2CF_3]_3$	0.62	− 10.6	− 7.7	1.205	86.3
$P[(CH_2)_2CF_2CF_3]_3$	0.48	− 9.9	− 8.3	1.218	92.3
$P[(CH_2)_3CF_2CF_3]_3$	0.40	− 9.5	− 8.6	1.225	91.8
$P[(CH_2)_4CF_2CF_3]_3$	0.38	− 9.3	− 8.8	1.226	92.0
$P[(CH_2)_5CF_2CF_3]_3$	0.36	− 9.2	− 8.9	1.228	91.8
$P[(CH_2CH_2CH_2CH_3]_3$	0.33	− 8.7	− 9.3	1.230	91.7

a) The calculations were performed using the UniChem version of MNDO93 and employed the PM3 parameter set. Full geometry optimizations were performed.

Because of the well-known electron-withdrawing properties of the fluorine atom, the attachment of fluorous ponytails to ligands could change significantly the electronic properties and consequently the coordinating power of the ligands. Insertion of insulating groups before the fluorous ponytail may be necessary to decrease the strong electron-withdrawing effects, an important consideration if catalyst reactivity is desired to approximate that observed for the unmodified species in hydrocarbon solvents. For example, theoretical calculations show that the electronic properties of $P[(CH_2)_x(CF_2)_yCF_3]_3$ ($x = 0$, $y = 2$ or 4 and $x = 0-5$, $y = 2$) can be tuned by varying the number of methylene groups $[-(CH_2)_x-]$ between the phosphorus atom and the perfluoroalkyl moiety [9] (Table 1). It was later shown that the electron-withdrawing effect of even five methylene units was observable according to the variation in υ_{CO} values of *trans*-$[IrCl(CO)L_2]$ complexes [10]. It appears that between eight and ten methylene groups would be needed to insulate effectively the lone pair of the phosphorus atom from the perfluoroalkyl moiety [11].

A large variety of fluorous ligands have been prepared by attaching fluorocarbon moieties to ligands appropriate in size and number. Fluorous soluble phosphines [12], phosphites [12c, 13], polyamins [14], pyridines [15], bipyridines [16], peralkylated 1,4,7-triazacyclononane [17], tris(pyrazolyl)borates [18], 1,4,8,11-tetraazacyclotetradecane [19], porphyrins [20], phthalocyanines [21], diketonates [22], salens [23], and cyclopentadienes [24] have been prepared. In addition, several fluorous chiral ligands have been synthesized including analogs of chiral phosphines [25], diimines [26], diamines [27], diols [28], amino-thiol [29], and salens [30].

The organometallic complexes of the fluorous ligands have similar structures and spectroscopic properties to the parent compounds. The major difference arises from the presence of the fluorous ponytails on the ligands, which provide a fluorous blanket around the hydrocarbon domain of the catalyst. If the electron withdrawing effect of the fluorous ponytails on the ligands is not mitigated by insulating groups, the reactivity of the organometallic catalysts could be altered.

7.2.3
Process and Applications

A fluorous biphase reaction could proceed either in the fluorous phase or at the interface of the two phases, depending on the solubilities of the reactants in the fluorous phase and the relationship of mass transport to the chemical reaction velocity. When the solubilities of the reactants are very low in the fluorous phase, the chemical reaction may still occur at the interface or appropriate phase-transfer agents may be added to facilitate the reaction. It should be emphasized that a fluorous biphase system might become a one-phase system on increasing the temperature. Thus, a fluorous catalyst could combine the advantages of one-phase catalysis with biphase product separation by running the reaction at higher temperatures and separating the products at lower temperatures.

Fluorous organometallic catalysts are best suited for converting apolar reactants to products of higher polarity, as the partition coefficients of the reactants and products will be higher and lower, respectively, in the fluorous phase. The net results are no or little solubility limitation on the reactants and easy separation of the products. Furthermore, as the conversion level increases, the proportion of polar products increases, further enhancing separation. One of the most important advantages of the fluorous biphase catalyst concept is that many well-established hydrocarbon-soluble catalysts can be converted to fluorous-soluble ones. Accordingly, several fluorous analogs of hydrocarbon-soluble catalysts have been prepared and shown to have comparable catalytic performance with the additional benefit of facile catalyst recycling. Thus, fluorous organometallic catalysts have been successfully used for the Negishi reaction [31], Heck reaction [32], Stille coupling [33], Suzuki coupling [34], Sonogashira coupling [35], allylic substitution [36], cyclodimerization of conjugated enynes [37], cyclopropanation [38], Kharash addition [39], Friedel-Crafts acylation [40], hydrogenation [41], hydroformylation [42], hydroboration [43], hydrosililation [44], and oxidation reactions [19–23]. Chiral fluorous organometallic catalysts were used for asymmetric hydrogenation [45], carbon–carbon bond formation reactions [46], and epoxidation [30 a–d, 47].

The great potential of the fluorous-liquid/liquid concept for catalyst recovery was first demonstrated for the hydroformylation of alkenes [9]. It was well known that the application of hydrocarbon soluble phosphine modified rhodium catalysts for the hydroformylation of higher alkenes such as decene-1 is limited by catalyst degradation during distillation of the aldehyde from the catalysts [48]. While the use of water soluble catalysts could provide easy separation for heavy aldehydes, the low solubility of the higher alkenes in water could limit the application of aqueous catalysts [49]. In contrast, the fluorous soluble $P[CH_2CH_2(CF_2)_5CF_3]_3$ modified rhodium catalyst system is an excellent catalyst for the hydroformylation of decene-1 at 100 °C under 11 bar CO/H_2 (1 : 1) in perfluoromethylcyclohexane and the aldehydes can be easily separated from the fluorous catalyst phase [4, 5]. High pressure NMR and IR have revealed that $HRh(CO)[P\{CH_2CH_2(CF_2)_5CF_3\}_3]_3$ and $HRh(CO)_2[P\{CH_2CH_2(CF_2)_5CF_3\}_3]_2$ are the two species in solution under CO/H_2 (1:1) pressure [9]. Comparative kinetics studies have shown that the fluorous catalyst is about ten times slower than the triphenylphosphine modified rhodium catalyst. The *normal/iso* selectivity is about the same for these two systems. Rhodium analysis of the product phases obtained by simply removing the product phase from the reactor through a deep-leg at 15 °C during nine subsequent (semi-continuous) hydroformylation of decene-1 showed the loss of about 1 ppm rhodium/mol aldehyde product [9]. While the use of heavier fluorous solvents and longer fluorous ponytails on the phosphine will further decrease the rhdoium loss, the recovery of such low level of rhodium can be achieved during the final purification of the aldehydes from the unreacted and isomerized alkenes and other heavier side products.

Fluorous biphase organometallic catalysis is now a well-established area and provides a complementary approach to aqueous and ionic biphase organometallic catalysis [50]. Since each catalytic chemical reaction could have its own *perfectly* designed catalyst (the chemzyme), the possibility to select from biphase systems ranging from fluorous to aqueous systems provides a powerful portfolio for catalyst designers.

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7.3
Nonaqueous Ionic Liquids (ILs, NAILs)

Hélène Olivier-Bourbigou

7.3.1
Introduction

The role of the solvent in organic and catalyzed homogeneous reactions is of the utmost importance. Interactions of solutes with the solvent are often specific. The energy associated with solvation is often large, especially for ions, and is a major factor influencing the rate and selectivity of reactions [1] (cf. Section 2.3).

Many coordination chemists are concerned with enhancing the chemical reactivity and/or selectivity of metal complexes, particularly for applications in catalysis. For example, a coordinatively unsaturated cationic metal complex, which is often the intermediate implicated in activation of organic molecules, is considered. Wanted is a solvent

– able to solubilize the metal ion while maintaining its ionic character, and
– which involves a weak, labile metal–solvent bond.

If traditional organic solvents are used, a compromise has often to be made between their solvation and their coordination properties. The development of catalysis should parallel that of highly polar novel solvent media [2].

7.3.2
NAILs as a New Class of Solvents

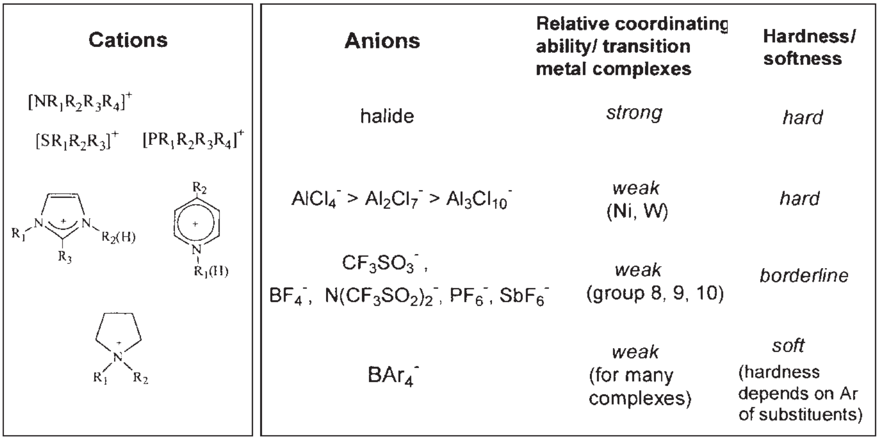
NAILs were developed many years ago by electrochemists looking for “ideal” electrolytes for technical use in batteries or in metal electrodeposition [3]. Nowadays, NAILs may be viewed as a new class of remarkable solvents. They are attracting growing interest in a broad range of area such as organic synthesis and catalysis, extraction and gas separation processes, analytical applications, and also liquids for “engineering” purposes [4]. Generally they are composed of large organic cations with low symmetry, associated with organic or inorganic anions. *N*,*N*′-dialkylimidazolium cations, e.g., 1-butyl-3-methyl imidazolium [BMIM], are very often

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

preferred because they yield low melting salts with high termal stability (Figure 1). Probably the most striking property, universal for all NAILs, is their nonvolatile character. For this reason, they have often been described as potential "greener" alternatives to traditional volatile organic solvents. However, the most attractive feature of these solvents is the possibility to adjust their physicochemical properties (e.g. viscosity, density, melting point, thermal stability, solubility...) by changing the structure of the anion and/or the cation. The spectrum of their properties may be larger than that of organic or inorganic classical solvents. An illustration of this high versatility is given by their exceptional solubility characteristics with organic or inorganic substrates. With regards to organic and catalytic reactions, the differential solubilities between reagents and products in ionic liquids may enable both an effective reaction and separation/isolation of the products. NAILs offer new opportunities as solvents for multiphasic (biphasic) catalysis or extraction processes and may bring an optimization of reaction activity and selectivity [4d, g]. However, the right combination of catalyst, solvent, and product is crucial for the success of this technology.

In transition metal-catalyzed reactions, the coordinating ability (nucleophilicity) and/or reactivity of anions towards the metal active center is often determinant. The coordination properties of anions have been the object of many studies [5]. These properties depend in large part on the nature of the anions themselves (size, charge), but also on the hardness of the metal center, its oxidation state, and its surrounding ligands. Here the qualitative Hard and Soft Acids and Bases (HSAB) concept developed by Pearson can be applied to classify some typical anions in respect of their softness or hardness to transition metal complexes (Figure 1). Ionic transition metal complexes of the type $[L_{n-1}M]^+X^-$, are particularly suitable for use



Cations

$[NR_1R_2R_3R_4]^+$

$[SR_1R_2R_3]^+$ $[PR_1R_2R_3R_4]^+$

Anions	Relative coordinating ability/ transition metal complexes	Hardness/ softness
halide	*strong*	*hard*
$AlCl_4^- > Al_2Cl_7^- > Al_3Cl_{10}^-$	*weak* (Ni, W)	*hard*
$CF_3SO_3^-$, BF_4^-, $N(CF_3SO_2)_2^-$, PF_6^-, SbF_6^-	*weak* (group 8, 9, 10)	*borderline*
BAr_4^-	*weak* (for many complexes)	*soft* (hardness depends on Ar of substituents)

Fig. 1 Examples of cations and anions commonly used for the formation of NAILs and relative anion coordination ability towards transition metal complexes.

in NAILs because of their excellent ability to dissolve and stabilize ionic metal salts. Even if quantification of the "polarity" of NAILs has proven to be extremely difficult [6], these solvents are polar enough to dissolve ionic catalysts, yet weakly coordinating (nucleophilic) enough to avoid competition with the substrate for the free coordination site on the active center. This combination of properties cannot be easily attained with traditional organic solvents or water. Catalytic reactions using non ionic transition metal complexes can also be performed in NAILs. However, in that case, ligands have to be specially designed to render the complex soluble in the polar phase and nonextractable in the product second phase. Finally, biocatalytic [7] and noncatalyzed organic reactions can also be successfully performed in these media [4d].

7.3.3
Applications in Organic Synthesis and Catalysis

7.3.3.1
Salts Containing Strongly Coordinating Anions to Stabilize Anionic Complexes

The first report of catalytic reactions carried out in ionic liquids was published by Parshall [8], using $PtCl_2$ as a hydrogenation catalyst precursor dissolved in tetrabutylammonium tin trichloride. In this way, the catalyst could be re-used several times. Remarkably, Parshall was able to characterize *in situ* the active species, i.e., $[HPt(SnCl_3)_4]^{3-}$. Subsequently, Knifton described various carbonylation reactions catalyzed by ruthenium and palladium complexes such as hydroformylation, carboxylation of alkenes and glycol synthesis, using phosphonium halides as the polar phase [9]. In the same way, Perron and Jenck [10] have carried out the carboxylation reaction of diacetoxybutene into dialkyl adipate catalyzed by palladium in tetrabutylammonium bromide. Palladium-catalyzed Heck reactions of bromobenzene with butyl acrylate was firstly described in tetraalkylammonium or phosphonium halides as reaction medium [11]. Now, extensive studies of C–C coupling reactions in lower-melting ionic liquids are described and indicate that the use of NAILs makes possible the conversion of commercially interesting chloroarenes and the possibility of using inexpensive inorganic bases [12].

The main advantage of these coordinating anions is that they stabilize the active species. This is particularly obvious in the case of palladium complexes, whose tendency to decompose into black metal is well documented. Imidazolium-based ionic liquids can generate *in situ* formation of metal-imidazolylidene carbene complexes by a deprotonation of the imidazolium cation. The ease of deprotonation depends on the nucleophilicity of the anions. In this case, NAILs may act as both solvents and catalyst ligand precursors [13].

7.3.3.2
Salts Containing Weakly Coordinating Anions for Cationic and Molecular Complexes

7.3.3.2.1
Hard Anions (Chloroaluminates)

Aluminum halides can form with ammonium halides stoichiometric and nonstoichiometric mixtures containing the X^-, AlX_4^-, $Al_2X_7^-$ and/or $Al_3X_{10}^-$ hard anions [14]. Dramatic changes in the solvation characteristics and electrochemical windows of these ionic liquids can be achieved by simply varying the ratio of aluminum halide to organic salt in the mixture. Haloaluminate salts containing polynuclear anions are potentially strong Lewis acids due to the ability of polynuclear anions to dissociate into aluminum halide and mononuclear anion. Gutmann acceptor numbers have been used as a qualitative non-thermodynamic measure of their Lewis acidity. Acidic chloroaluminates are extremely poor donor and strong acceptor media (value around 100, between water and trifluoroacetic acid, depending on the melt composition) compared to other classical organic solvents [15]. These ionic liquids have been used in the synthesis of organometallic compounds and in few organic reactions [16]. In a similar way, trialkylaluminum and alkylaluminum chloride derivatives form with dialkylimidazolium chloride low melting liquids over a wide range of composition. The presence of an aluminum–carbon bond proves useful in catalysis [17]. Liquid salts containing fluorinated anions such as $Al_2Et_2F_2^-$ and $Al_2Et_5F_2^-$ have also been obtained [18]. Inorganic cations such as Li^+ can also be used. For example, mixtures of LiCl with $AlEtCl_2$ form liquids, liquid at room temperature, for appropriate molar ratio [19]. Obviously, aluminum halide based salts are water-sensitive.

Acidic chloroaluminates (*hard anions*) have been utilized in catalytic reactions which need the presence of Lewis acidity (Ziegler-Natta type catalysts) and for which there is no Lewis acid-base interaction between the reaction products and aluminum chloride. Polymerization of ethylene catalyzed by $(C_5H_5)_2TiCl_2/Al_2Me_3Cl_3$ complexes has been carried out in acidic chloroaluminates [20].

The cationic nickel complex $[\eta^3\text{-allylNi}(PR_3)]^+$, already described by Wilke et al. [21], as an efficient catalyst precursor for alkene dimerization when dissolved in chlorinated organic solvents. It proved to be very active in acidic chloroaluminate ionic liquids. In spite of the strong potential Lewis acidity of the medium, a similar phosphine effect is observed. Biphasic regioselective dimerization of propylene into 2,3-dimethylbutenes can then be achieved in chloroaluminates. However, there is a competition for the phosphine between the soft nickel complex and the hard aluminum chloride coming from the dissociation of polynuclear chloroaluminate anions. Aromatic hydrocarbons, when added to the system, can act as competitive bases thus preventing the de-coordination of phosphine ligand from the nickel complex [22b]. Performed in a continuous way, in IFP pilot plant facilities, dimerization of propene and/or butenes with this biphasic system (Difasol® process) compares favorably to the industrial Dimersol® homogeneous process in terms of yields and selectivity into dimers. The cationic Ni active species can be generated in the reactor from neutral commercially available Ni salt precursors. Chloroaluminates act as both the solvent and co-catalyst (activator). The active Ni species is immobilized in the ionic liquid phase without the need of specially designed ligands. Owing to the good solubility and retention of the cationic Ni catalyst in the ionic liquids and to the poor solubility of the alkeneic products, the process scheme is essentially reduced to a small continuous well-stirred carbon–steel reactor followed by a decanter. This new biphasic technology enables lower cost for the dimer (e.g., octenes) production and is now being commercialized [23].

The same acidic chloroaluminate ionic liquids have been used as solvent for tungsten aryloxide complexes for the metathesis of alkenes [24]. Slightly acidic chloroaluminates also dissolve the $[Cl_2W{=}NPh(PMe_3)_3]$ complex which catalyze ethene oligomerization without the addition of co-catalysts [25]. In a similar way, Ni-catalyzed 1-butene dimerization into linear octenes was carried out in acidic chloroaluminates buffered with small amount of weak bases [26]. Neutral chloroaluminates (1-ethyl-3-methylimidazolium chloride/$AlCl_3 = 1$) were employed to immobilize ruthenium carbene complexes for biphasic ADMET (acyclic diene metathesis) polymerization of an acyclic diene ester [27].

7.3.3.2.2
Borderline Anions

The cationic rhodium complex $[Rh(nbd)(PPh_3)_2]^+$ (nbd = norbornadiene), previously described by Osborn as a catalyst precursor for the hydrogenation of alkenes and dialkenes when dissolved, e.g., in acetone [28], has proved to be active in dialkylimidazolium PF_6^-, $CuCl_2^-$ or SbF_6^- salts [29]. Due to the very low solubility of alkanes in ionic liquids, the reaction is truly biphasic. The rhodium loss in the organic phase is under the limit of detection. The catalyst can be used repeatedly. In this case, the presence of coordinating anions, such as traces of chloride, inhibits the catalyst activity. Halide contaminants may arise from unreacted starting material used in the preparation of NAILs or from the possible decomposition of the halogenated anion (e.g., PF_6^-). Purification and quality control of ionic liquids are then crucial [30].

Highly soluble cationic ruthenium-clusters complexes have also been used for hydrogenation of aromatic substrates [31]. Compared with water these ionic liquids dissolve higher concentration of hydrogen gas which leads to increased reaction rate in biphasic conditions.

Asymmetric hydrogenation has been successfully achieved in this same type of media using $[Rh(nbd)(DIOP)_2]^+$ or $[RuCl_2(BINAP)]_2 \cdot NEt_3$ complexes as catalyst precursors (DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis[diphenylphosphino]butane) [29, 32]. In this case, NAILs open up a new and facile way to recycle the expensive chiral metal complex.

The catalytic transformation of diallyltosylamide with cationic [(*p*-cymene)RuCl(PCy_3)=C=C=CPh_2][X] complexes (X = PF_6^-, BF_4^- or $CF_3SO_3^-$) as catalyst precursor can also be performed in different 1-butyl-3-methylimidazolium salts [33]. In one single phase, using toluene as the solvent, the ring closing metathesis (RCM) selectivity depends on the nature of the counter-anion of the catalyst. In ionic liquids, an anion exchange rapidly takes place and the catalytic system involves the anion of the ionic salt rather than that of the initial ruthenium precursor. New possibilities for the access to macrocycles from selected dienes are open in NAILs.

Cationic copper(I) catalyst has also been immobilized in these ionic liquids to perform the living-radical polymerization of methyl methacrylate. The polymer can be separated by an extraction procedure using toluene [34].

The same weakly coordinating anion-based salts can be used to perform reactions catalyzed by molecular transition metal complexes. For example, the hydroformylation of alkenes using Rh(acac)$(CO)_2$ and PPh_3 as catalyst precursors has a high reaction rate when run in the biphasic system [29a]. However, contrary to the Rh-catalyzed hydrogenation reaction, the active catalytic species is extracted in the organic phase. The modification of the neutral phosphine (or phosphite) ligand by the introduction of appropriated polar or ionic groups, proved to be an effective and powerful tool to immobilize the rhodium in the ionic phase [35]. Rh-hydroformylation using the biphasic technology with water as the catalyst phase is already industrially demonstrated. However, this process is limited to C2–C5 alkenes, due to the low solubility of higher alkenes. Thanks to the higher solubility of alkenes in NAILs compared to water, these media open up new opportunities for biphasic reactions. An interesting attractive approach is the combination of NAILs with supercritical CO_2 · $ScCO_2$ is quite soluble in ionic liquids and decreases their viscosity, thereby enhancing the mass transfer. On the other hand, ionic liquids are not soluble in $scCO_2$. Hence, $scCO_2$ can be used as a mobile phase to remove the non-volatile products from the ionic phase without any contamination. Continuous flow process using [BMIM][PF_6]/$scCO_2$ system was investigated for the Rh-hydroformylation of 1-octene [36].

Many other examples of transition metal catalyzed reactions such as oxidation, dimerization or telomerization of conjugated diene have been performed in these borderline anions-based ionic liquids and are described in recent reviews [4].

7.3.3.3
Salts Containing Chloroaluminate Anions as Solvents and Acidic Catalysts

Pure chloroaluminate based ionic liquids have no proton donating ability. However, these liquids can demonstrate Brønsted acidity as a result of intentional or unintentional protonic species. These protons behave as superacids with Hammett acidity functions ranging from -12.6 to -18. The proton speciation in acidic salts has been the subject of numerous papers [37]. With increasing $AlCl_3$ molar fraction in the ionic liquid, the solvent interaction is weaker and the Brønsted superacidity of the proton is increased. Protonation of aromatic hydrocarbons to generate several arenium ions and carbocations have been achieved in these solvents [38]. Thus, it is expected that cationic-catalyzed reactions could be achieved in these media. Chloroaluminates are in fact good solvents and acidic catalysts for paraffin-alkene alkylation, e.g., isobutane/ethene or isobutane/butene [39]. Other acid-catalyzed reactions such as isobutene or light alkene oligomerization and polymerization and alkylation of aromatic hydrocarbons have been achieved in these media [40]. Oxidative electropolymerization of benzene into poly(*para*-phenylene) has been described using haloaluminates [41].

These media have also proved to be suitable stoichiometric solvents for Friedel-Craft acylation reactions of aromatic hydrocarbons and ferrocene [42].

7.3.3.4
Supported Ionic Liquid Catalysis

Acidic chloroaluminates have been anchored on solid supports, either by simple impregnation or by chemical grafting on the support surface through the cation (or the anion). These systems have been investigated to catalyze the alkylation of aromatic compounds or of alkenes with isobutane [43]. This technique offers some advantages such as the ease of separation of the products and the better dispersion of the catalyst. However, the deactivation of the catalyst, mainly due to the adsorption of heavy by-products on the solid surface, and the difficulty to regenerate it are main limitations. This concept has also been applied for Rh-catalyzed hydroformylation. The surface of a mineral support is modified with a monolayer of covalently attached PF_6^- or BF_4^- based ionic liquids fragment. The surface is then treated with additional layer of free ionic liquid which serves as Rh-catalyst solvent. Compared to biphasic liquid–liquid systems, improved activity is described probably due to larger interface area and a higher concentration of Rh active site at the interface [44].

The use of ionic liquids as novel phase in organic synthesis, compatible with high-throughput synthesis and process automation technology, may also be promising [45, 46].

7.3.3.5
Solvents for Organic Reactions

Most discussion of solvent effects rely on the concept of solvent polarity (cf. Introduction of this book). The investigation of ionic liquid effect on chemical reactions is at the present time probably the most productive way to characterize these solvent "polarity". A nice example is given by the Diels-Alder reaction of cyclopentadiene with methyl acrylate. Polar solvents, particularly water, dramatically enhance both the reaction rate and the *endo* to *exo* stereoselectivity [47]. A similar effect has been observed in NAILs. As for water and other polar solvents, solvophobic interactions or, more probably, hydrogen bonding could be used to explain this rate acceleration and the control of the *endo/exo* selectivity. In this case, the chemical nature of the ions clearly determines the outcome of the reaction [48].

7.3.4
Concluding Remarks

NAILs contitute a unique class of versatile solvents for organic and catalyzed reactions. They are probably the only solvents able to combine "polarity" (dissociating character) with weak nucleophilicity (solvating character).

The use of these solvents already covers a wide range of area and interests. It could probably be extended to other horizons. From a practical point of view, their low vapor pressure prevents atmospheric pollution thereby complying with the criteria required for industrial development. From a fundamental point of view, we still have to clarify the type of interactions between active species or transition states and the anions and cations present in these salts, in order to draw up a rationalization of the selection of the solvent.

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7.4
Immobilization of Organometallic Catalysts Using Supercritical Fluids

Walter Leitner, Aaron M. Scurto

7.4.1
Introduction

Supercritical fluids (SCFs) are substances heated above their critical temperature T_c and compressed above their critical pressurre p_c [1]. At temperatures greater than T_c, isothermic compression results in a continuous increase of the fluid density without condensing it into a liquid. Just like gases, supercritical fluids fill the entire space available, have negligible surface tension, and are miscible with other gases. At the same time, they can act as solvents for liquid and even solid materials, whereby the solvent properties can be "tuned" over a wide range by adjusting the fluid density through comparably small changes of temperature and/or pressure. This unique set of properties opens new approaches for the immobilization of organometallic catalysts, and a systematic discussion of these methods is the subject of the present review. General aspects of the use of these fascinating reaction media for organometallic catalysis have been reviewed in detail [1–3] and a short review comparing some of the immobilization techniques for hydroformylation as a common benchmark reaction has appeared very recently [4].

Carbon dioxide is by far the most widely used supercritical fluid ($scCO_2$). Its mild critical properties are evident from the schematic phase diagram in Figure 1. It is nontoxic and nonflammable, and can be handled safely on laboratory and industrial scales. Unlike classical organic solvents, CO_2 is not classified as a "volatile organic chemical" (VOC) and applications of CO_2 have a GRAS ("generally regarded as safe") status. The economic viability of $scCO_2$ technology on various scales is demonstrated by commercial applications (e.g., natural product extraction [5, 6], wood impregnation [7], and dry cleaning [8]). A commercial-scale multipurpose plant for heterogeneous catalysis involving $scCO_2$ has started operation recently [9, 10]. Examples of organometallic catalysis in supercritical fluids are by no means restricted to this particular medium [1–3] but applications focusing on catalyst immobilization have utilized CO_2 exclusively so far. As many of the potential benefits of CO_2 for multiphase catalysis are also retained in the

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

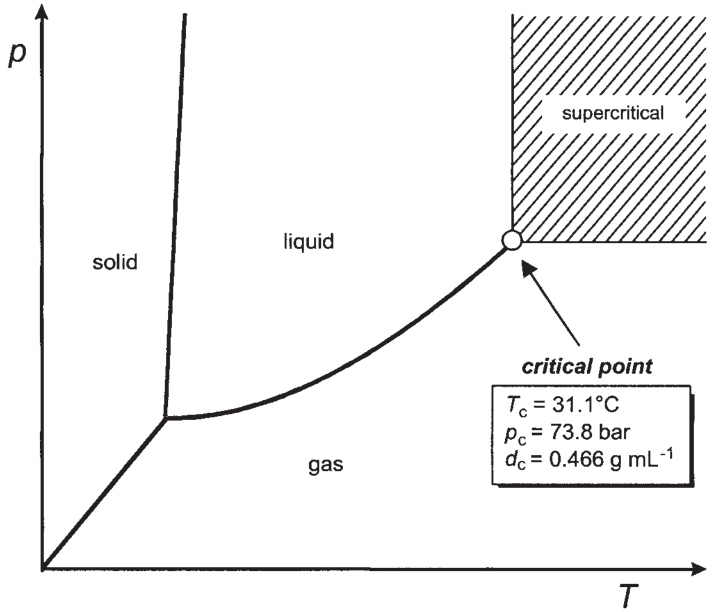


Fig. 1 Schematic phase diagram and critical data of carbon dioxide.

near-critical liquid region, operation at or even below room temperature can also be envisaged.

Any method for the immobilization of organometallic catalysts faces the paradoxical condition to combine the need for intimate contact of reagents and catalyst during the reaction stage with a maximum of discrimination at the separation stage. Introducing phase boundaries and confined spaces will greatly facilitate separation, but often create additional mass-transfer barriers reducing turnover rates and/or selectivities. A well-known example for this problem is the aqueous biphasic system for hydroformylation (see Section 6.1), which cannot be applied to long-chain alkenes because of their insufficient aqueous solubility. Furthermore, catalyst leaching and cross-contamination between the substrate and catalyst phases are crucial factors for practical implementation. As will be discussed in more detail in the individual sections, the properties of $scCO_2$ can be beneficial in this context in various ways. The gas-like mass-transfer properties, for example, can facilitate exchange between catalyst and substrate phase (cf. Section 4.1). Cross-contamination of CO_2 into the catalyst phase is not an issue and the relatively poor solvent power of $scCO_2$ for organometallic compounds may reduce leaching as compared to classical organic solvents. Most importantly, the design of SCF-based continuous flow systems that resemble gas-phase heterogeneous catalytic processes is a very attractive new approach to reaction engineering of organometallic catalysis.

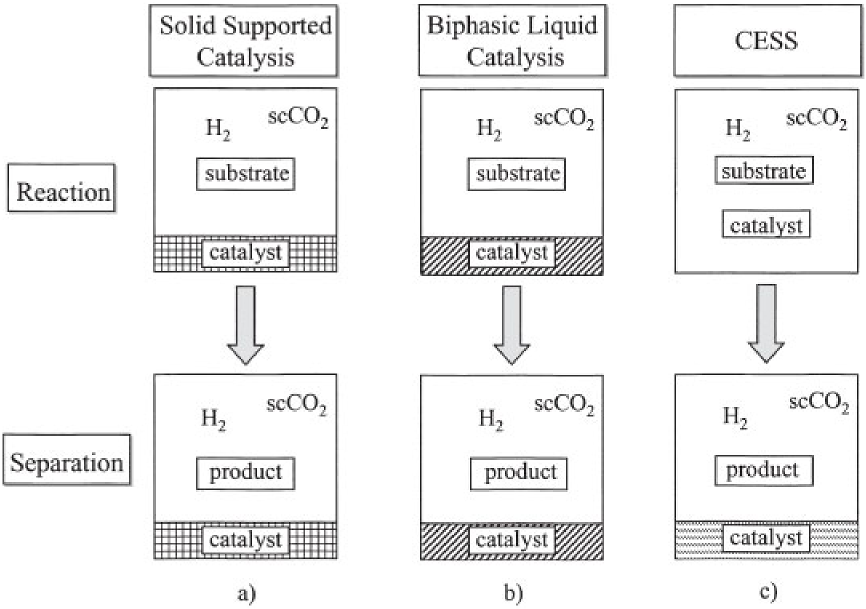


Fig. 2 Different reaction/separation sequences using $scCO_2$ as the mobile phase.

Three fundamentally different approaches to catalyst immobilization involving SCFs can be distinguished. Firstly, the organometallic catalyst can be anchored to a solid organic or inorganic support which is then contacted with the supercritical reaction medium. As seen from Figure 2a, such a reaction is truly biphasic (solid–supercritical fluid) in nature, regardless of the presence of additional gaseous reagents. This is in sharp contrast to the situation with supported catalysts in organic solvents, where triphasic (solid/liquid/gas) reaction systems often lead to severe mass transport limitations. A similar situation is encountered for liquid/supercritical multiphase catalysis (Figure 2b), where the traditional counterpart is also triphaisc (Liquid 1/Liquid 2/Gas) if gaseous regants are involved. Finally, a third option can be envisaged, where the tunable solvent properties of the SCF are utilized to control the solubility of the organometallic catalyst in the reaction medium without any additional support or solvent. In certain cases, these systems can be operating under truly monophasic supercritical conditions during the reaction stage (Figure 2c: CESS = **c**atalysis and **e**xtraction using **s**upercritical **s**olutions). This approach is reminiscent of the temperature-controlled catalysts in conventional solvents sometimes referred to as “smart catalysts.”

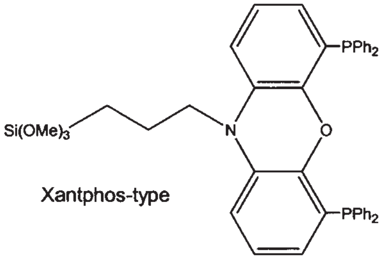
In the process schemes depicted in Figure 2, carbon dioxide is used as the product-containing phase and hence would correspond to the mobile phase under continuous operation. Naturally, this requires that products and substrates are sufficiently CO_2-soluble to ensure acceptable space–time velocities. Polymeric substrates or most very polar substances such as carboxylic acids, carbohydrates, etc., cannot be processed under these conditions. It is, however, possible to design so-called "inverted" systems, where a highly CO_2-philic catalyst is immobilized in the $scCO_2$ phase while the substrates and/or products reside in a second phase, for example in a liquid polar phase such as water. In the following sections, we will highlight the different techniques and discuss prototypical examples in detail.

7.4.2
Practical Approaches to Multiphase Catalysis Involving Supercritical Fluids

7.4.2.1
Supercritical Fluids and Supported Catalysts

One of the very first examples of organometallic catalysis in $scCO_2$ was the hydrogenation of CO_2 itself to yield formic acid or its derivatives [11, 12]. Early on, ruthenium complexes bearing silyl-ether phosphine ligands (Structure **3**) were anchored on silica supports via sol–gel techniques to yield highly efficient catalysts for hydrogenation of CO_2 under supercritical conditions [13, 14]. In the presence of dimethylamine, turnover numbers up to 110 800 were observed for the formation of dimethylformamide with these materials. The nature of the support has a pronounced effect on the performance of the materials; even higher efficiencies were reported with a mesoporous ruthenium–silica hybrid aerogel (cf. **4**, [15]).

A similar technique was used to immobilize rhodium with silyl-ether phosphine ligands (**2**) on silica for the hydroformylation of 1-hexene [16–18]. This method



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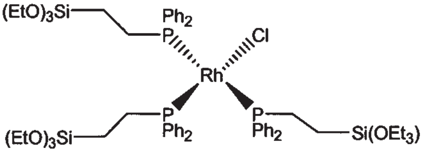

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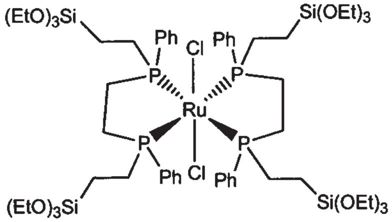

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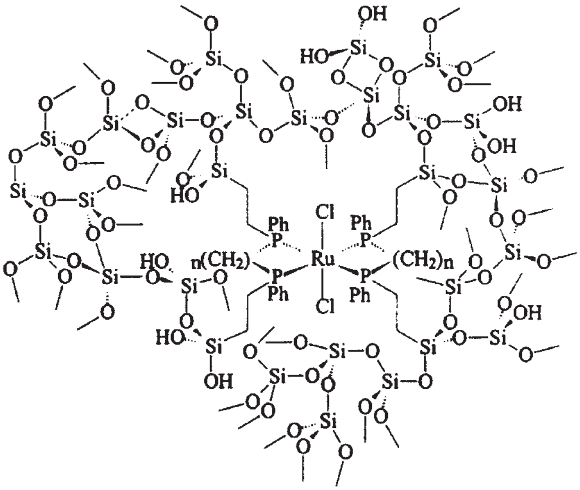
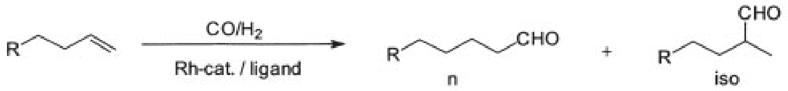


4

achieved a normal to iso ratio (*n*/*iso*) of the aldehyde of 4.5 compared to approximately 3 using toluene as a solvent for the corresponding free homogeneous catalyst. Platinum–phosphine complexes immobilized in the zeolite MCM-41, in conjunction with $SnCl_2$, were also effective for the hydroformylation of 1-hexene with high selectivity for *n*-heptanal and no hydrogenated byproducts [19]. More recently, silica-supported ligands of the XANTPHOS-type (**1**) (see Section 3.2.2) were shown to form highly selective rhodium catalysts for continuous-flow hydroformylation of long-chain alkenes in $scCO_2$ [20]; see Equation (1). The structure of the chelating ligand ensures a very high *n*/*iso* ratio, amounting to $>30:1$ in the conversion of long chain alkenes. The silica-bound catalyst showed reasonable turnover frequencies under supercritical conditions, comparable to those of its homogeneous counterpart in conventional solvents. Reactions were operated in a fixed-bed arrangement largely identical to that applied with traditional heterogeneous catalysts in $scCO_2$. No apparent rhodium leaching was reported and the catalyst exhibited a stable performance under continuous-flow conditions for 6.7 h during the experiments (see Table 1 in connection with Eq. 1).



(1)

Supported aqueous-phase catalyst (SAPC; cf. Section 4.7) were combined with supercritical CO_2 as a replacement for the organic liquid phase [21]. Ruthenium was supported on silica and combined with the ligand TPPTS in water with a $scCO_2/H_2$ phase. The $scCO_2$ method yielded better conversions for the hydrogena-

Tab. 1 Hydroformylation of long chain alkenes and representative results from multiphase catalysis involving $scCO_2$.

Ligand	*Approach*	*Operation*	*R*	*TOF*[a)]	*Conv.*[b)]	*n/iso*	*Refs.*
Xantphos-type	$scCO_2$/silica	continuous	C_4H_9	160 h^{-1}	14%	33	[20]
TPPDS	$scCO_2$/IL	continuous	C_4H_9	13 h^{-1}	5%	3	[43]
TPPOP	CESS, biphasic	semi-batch	C_2H_5	95 h^{-1}	54%	6.5	[63]
3-H^2F^6-TPP[c)]	CESS, monophasic	semi-batch	C_2H_5	430 h^{-1}	$>$ 99%	5.5	[76]

[a)] Turnover frequency.

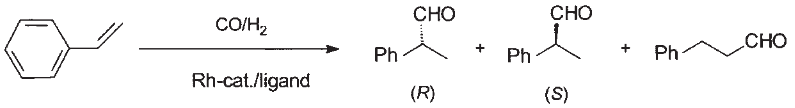
[b)] Conversion per single pass.

[c)] 3-H^2F^6-TPP = Structure **5** on p. 680.

tion of cinnamaldehyde than using toluene in the same method. In addition to silica, organic polymers were also used as catalyst supports with $scCO_2$ as the substrate phase. Heck and Suzuki cross-coupling reactions (see Section 6.6) were performed with palladium complexed to commercially available amino and phosphino polystyrene resins [22]. Use of the amine resin for the coupling of butyl acrylate and aryl iodides gave yields greater than 80% with no phosphine ligand ("ligandless") and with the addition of external tri-*tert*-butylphosphine. The results of the same coupling, but using the phosphino resin, were very dependent on the base used; CO_2-soluble bases rendered better yields. Using a quaternary phosphonium salt such as tetrabutylphosphonium acetate as a base also resulted in good yields, possibly due to the melting of the salts forming an ionic liquid solvent. A polymer-supported chromium–porphyrin complex has been prepared for the ring-opening polymerization of 1,2-cyclohexene oxide and CO_2 itself [23]. It was found that the complex supported on ArgoGel Cl performs better than a CO_2-soluble version and with easier recycling.

Amphiphilic resin-supported ruthenium(II) complexes similar to those shown in Structure **3** (cf. also Section 7.5) were employed as recyclable catalysts for dimethylformamide production from supercritical CO_2 itself [24]. Tertiary phosphines were attached to crosslinked polystyrene–poly(ethylene glycol) graft copolymers (PS–PEG resin) with an amino groups to form an immobilized chelating phosphine. Catalytic activity declined with each subsequent recycling step, probably due to oxidation of the phosphines and to metal leaching.

The chiral BINAPHOS ligand was anchored on an organic resin using a copolymerization strategy. After loading with rhodium, the material was packed as a fixed-bed in a column of commercial equipment for supercritical fluid chromatography. The potential for continuous operation was demonstrated for the asymmetric hydroformylation of styrene (Eq. 2) to yield the chiral branched aldehydes with *ee* values up to 86% (cf. Table 2) [25]). Under the optimized reaction conditions, a small library of structurally diverse alkenes could be hydroformylated in $scCO_2$ sequentially over the same catalyst bed with excellent regio- and enantioselectivity using this straightforward technology.

 (2)

Tab. 2 Enantioselective hydroformylation of styrene using rhodium catalysts of BINAPHOS-type ligands immobilized in scCO$_2$.

Ligand	*Approach*	*Operation*	*conv.*	*iso*	*ee*	*Refs.*
polymer-BINAPHOS	scCO$_2$/solid	continuous	93%	81%	86%	[25]
3-H^{2}F^6-BINAPHOS	CESS, monophasic	semi-batch	98%	93%	92%	[91]

An anionic rhodium iodide–carbonyl complex was supported on polyvinylpyrrolidone for the carbonylation of methanol [26]. Depending on the reaction conditions and method of extraction, less than 0.08% rhodium leaching was observed. Saturation of the support with methyl iodide was found to be vital to the longevity and recyclability of the catalyst. In an example spanning nano- and colloidal science, bimetallic Pd–Au nanoparticles were bound within polystyrene-*block*-poly(4-vinylpyridine), forming colloidal particles for hydrogenations [27]. The resulting colloidal particles had turnover frequencies in scCO$_2$ roughly one order of magnitude higher than in conventional solvents for the hydrogenation of alkynes.

An “inverted” system based on the CO$_2$-soluble catalyst Pd(OAc)$_2$/P^{t}Bu$_3$ has been utilized for Suzuki coupling of solid-phase-bound substrates [28]. The use of scCO$_2$ with polymer-supported substrates seems highly attractive owing to the known plasticizing and swelling effects of compressed CO$_2$ on polymeric compounds. Excess reagents and catalysts can readily be stripped off with scCO$_2$, yielding the solid-phase-bound product without the need for subsequent drying or purification steps. Interesting applications of this technique to parallel and/or high-throughput synthesis of biologically active compounds can be envisaged.

7.4.2.2
Liquid/Supercritical Biphasic Systems

7.4.2.2.1
Biphasic Systems Consisting of Ionic Liquids and scCO$_2$

In liquid/supercritical systems, the liquid phase acts as a support to retain the catalyst just like the solid materials described above. There are, however, no covalent bonds and no restrictions on the mobility of the catalyst; the environment resembles much more the typical situation of homogeneous catalysis. In order to immobilize the catalyst efficiently, the solubility of the organometallic intermediates in the liquid phase must be largely preferred over their solubility in the supercritical phase. As scCO$_2$ is a rather feeble solvent for many organometallic catalysts [29], the risk of catalyst leaching can be expected to be reduced as compared to similar liquid/liquid multiphase systems. The liquid phase is required only in the amount necessary to solubilize the catalyst, with enough substrate to ensure a reasonably fast conversion and to exchange the product back into the supercritical phase. Although it acts as a "solvent", the economic constraints are therefore clearly different from a conventional reaction medium, and more elaborate and costly systems may be tolerated if they remain in the reactor as the stationary phase.

In order to act as the stationary phase efficiently, the liquid phase must not lead to any significant cross-contamination into the $scCO_2$ to prevent its depletion during continuous-flow operation. Most organic solvents have mixture critical points in the vicinity of the pure solvent's critical point. Thus they would be miscible with the SCF and would not form a separate phase for catalyst immobilization. It is important to note that the solubility of a compound in $scCO_2$ is determined not only by its polarity, but very strongly also by its vapor pressure. To account for the contribution of volatility and solvation to the solubility process, Zosel has coined the term "Destraktion" (from latin *desitallare* and *extrahere*) in his pioneering work on natural product extraction with SCFs [5]. Therefore, highly polar and/or very non-volatile liquids, which do not become miscible with CO_2 until hyperbaric conditions are reached, are potentially useful as liquid catalyst phases together with $scCO_2$.

Ionic liquids (ILs; see Section 7.3) are low-melting ($< 100\,^\circ C$) salts of organic cations that are attracting wide interest as solvents for organometallic catalysis [30–33]. Consisting of discrete cations and anions, ILs exhibit no measurable vapor pressure and consequently they show generally no detectable solubility in pure $scCO_2$. Carbon dioxide, however, has a remarkable affinity for ILs, leading to high concentrations of CO_2 in the liquid phase and rapid mass transfer between the two media [34]. Without a large expansion in volume, an IL phase in contact with $scCO_2$ may contain up to a > 0.6 mol fraction of CO_2 and the supercritical fluid can be used to extract even high-boiling organic substances from the IL phase very efficiently [35]. These properties make IL/$scCO_2$ biphasic systems highly attractive for application in catalyst immobilization, especially under continuous-flow conditions schematically represented in Figure 3 (for related examples in biocatalysis, see refs. [36, 37]). At present, a lack of toxicological data and high material costs of the ionic liquid need to be considered when contemplating practical applications of a system using ILs and $scCO_2$, but rapid progress on these points can be expected [38, 39].

Chiral ruthenium catalysts bearing BINAP-type ligands were effectively dissolved in ILs and used for enantioselective hydrogenation of prochiral α,β-unsaturated acids, followed by subsequent CO_2 extraction [40]. A pronounced effect of protic co-solvents such as water or ^{i}PrOH was noted for the reaction stage with certain substrates. The catalyst solution could be recycled four times without any noticeable decrease in conversion or enantioselectivity.

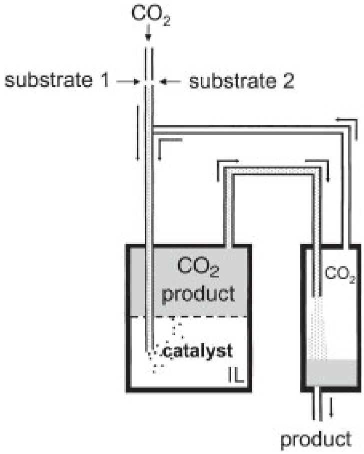


Fig. 3 Simplified flow scheme for continuous organometallic catalysis using IL/scCO_2 biphasic systems.

The above-mentioned hydrogenation of CO_2 in the presence of amines to give dialkylformamides has been carried out directly in an IL/scCO_2 system, whereby the ionic liquid was shown to play a dual role [41]. It dissolves the ruthenium–phosphine catalyst efficiently and leads at the same time to a distinct phase distribution of the polar carbamate intermediates and the less polar products formed during the conversion of CO_2. As a result, the selectivity of the reaction can be increased above that attained in conditions where scCO_2 is used as the sole reaction medium.

The palladium-catalyzed dimerization of methyl acrylate was found to proceed smoothly in a [BMIM][BF_4]/scCO_2 biphasic system [42] (BMIM = 1-butyl-3-methylimidazolium). The catalytic system comprises phosphonium salts and HBF_4 as co-catalysts, making the IL environment particularly attractive. The partitioning of substrates and products between the IL and scCO_2 was investigated and the data were used for planning of the reaction conditions. Turnover numbers up to 560 and turnover frequencies up to 195 h^{-1} were obtained under optimized conditions.

Hydroformylation of long-chain alkenes also occurs under biphasic IL/scCO_2 conditions (Table 1), whereby the chemical properties of IL and catalyst have to be matched properly [43]. Phosphite ligands proved to be incompatible with $[PF_6]^-$- or $[BF_4]^-$-based ILs, because small amounts of F^- liberated from the anion by hydrolysis reacted with the ligands, leading to catalyst deactivation. Sulfonated derivatives of triphenylphosphine are chemically more robust, but their well-established sodium salts showed only limited solubility in the ILs envisaged in this study. The optimum solution was finally elaborated by using imidazolium salts of monosulfonated triphenylphosphine, e.g., [PMIM][$Ph_2P(m\text{-}C_6H_4SO_3)$], which combined chemical stability with high solubility in ILs such as [BMIM][PF_6]. Most significantly, this system was operated under continuous-flow conditions with the IL/catalyst phase remaining stationary in the reactor while $scCO_2$ was transporting the substrates and products through the apparatus. The system showed a stable performance over 30 h whereby less than 0.06% of the originally loaded rhodium was leached into the product stream.

The nickel complex shown in Eq. (3) has been developed by Wilke and co-workers as a precursor for a highly active and enantioselective catalyst for the hydrovinylation reaction, a synthetically interesting and truly atom-economic C–C bond-forming reaction [44–46]. In conventional solvents, the neutral precatalyst needs to be transformed into the cationic active species by chloride abstraction, which is typically achieved with strong Lewis acids such as Et_2AlCl. Alternatively, sodium or lithium salts of noncoordinating anions such as $[B(3,5\text{-}CF_3)_2C_6H_3]^-$ (BARF) can be used to activate hydrovinylation catalysts [47] and the Wilke catalyst/NaBARF system was successfully employed in pure $scCO_2$ [48]. Using the precatalyst in an IL/$scCO_2$ biphasic system revealed that the ILs can act simultaneously as stationary phase and chloride-abstracting agents to activate the complex for catalytic hydrovinylation [49]. The choice of the anion has a decisive influence on the performance of the active species, providing an additional parameter by which to optimize the catalytic system (Figure 4).

The chiral hydrovinylation catalyst could be effectively immobilized for continuous operation in active and selective form by simply dissolving the Wilke catalyst in [EMIM][BTA] (BTA = $(CF_3SO_3)_2N$) and using compressed CO_2 as the mobile phase (Eq. 3). High conversion and good enantioselectivity were obtained over

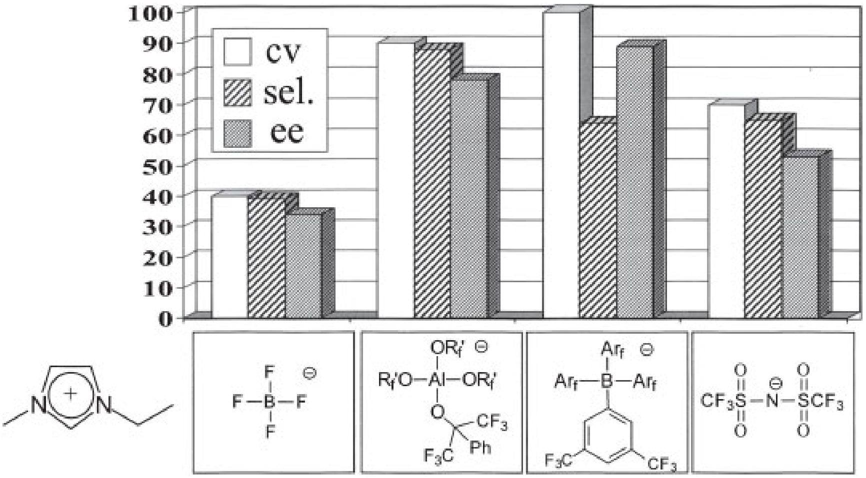
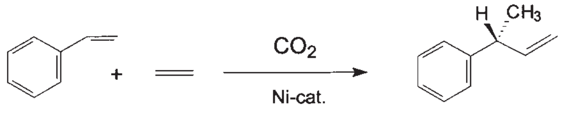


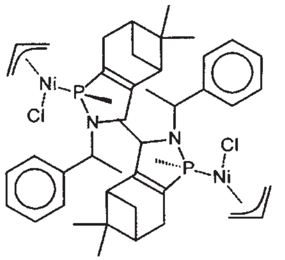
Fig. 4 Activation and tuning of the nickel catalyst shown in Eq. (3) for hydrovinylation by combination of different imidazolium-based ILs and compressed CO_2 [49]; cv = conversion, sel. = selectivity.



(3)

Method A [48]
activation with NaBARF,
batchwise recycling:
rapid deactivation after 4 cycles

Method B [49]
activation with [EMIM][BTA],
continuous-flow:
stable performance of 60 h



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more than 60 h which is quite remarkable in light of the highly sensitive nature of this particular nickel catalyst system.

7.4.2.2.2

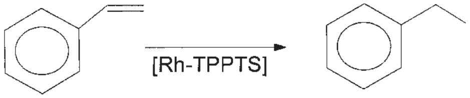
Biphasic Systems Consisting of Poly(ethylene glycol) and $scCO_2$

Most recently, poly(ethylene glycol) (PEG) has been suggested as a nonvolatile catalyst phase together with $scCO_2$ [50]. Liquid PEG of low to moderate molecular weight serves as a reasonably good solvent for many typical organometallic catalysts, but these systems are still soluble in $scCO_2$ or form emulsion-type mixtures, which may be interesting media for catalysis in their own right [51]. For multiphase catalysis the use of high molecular weight PEG is preferred, however, owing to its low solubility in $scCO_2$. PEGs with average molecular weights above 1000 are waxy solids under ambient conditions, but they melt under CO_2 pressure to become liquids under typical conditions of $scCO_2$ catalysis. The approach was demonstrated for the rhodium-catalyzed hydrogenation of styrene as a test reaction using Wilkinson's complex [$(PPh_3)_3RhCl$] as the catalyst. During batchwise recycling by extraction of the ethylbenzene product with the $scCO_2$ phase, the catalyst remained stable in the PEG environment and could be recycled four times without noticeable loss of activity. Rhodium contamination in the product was below the detection limit (less than one part per million). Using PEG_{900} as the liquid catalyst phase, measurable amounts of PEG were detected among the extracted products; but for PEG_{1500}, the contamination was found to be as low as 0.1% by weight.

7.4.2.2.3
Biphasic Systems Consisting of Water and $scCO_2$

The chemical and physicochemical behavior of the binary mixture H_2O/CO_2 [52] suggests that water is yet another attractive liquid to be combined with supercritical carbon dioxide in multiphase catalysis. The solubility of water in $scCO_2$ is low, but not insignificant. However, the extraction of environmentally benign and non-toxic H_2O would be less of a problem than with other stationary phases. CO_2, as one of the most soluble gases in water, aids in the mass transfer properties. This is particularly true if emulsions or microemulsions can be formed ([53] and refs. therein). The low pH of aqueous phases in the presence of compressed CO_2 (ca. pH 3–3.5) must be considered and the use of buffered solutions can be beneficial in the design of suitable catalytic systems, as demonstrated for colloid-catalyzed arene hydrogenation in water/$scCO_2$ [54].

Higher reaction rates and selectivities were observed in water/$scCO_2$ than in classical organic/water systems in the ruthenium-catalyzed hydrogenation of cinnamaldehyde to give the corresponding unsaturated alcohols [21]. The catalysts were kept in the aqueous phase using the trisulfonated triphenylphosphine ligand TPPTS. Use of rhodium catalysts leads to preferential hydrogenation of the C=C double bond, again with higher rates and selectivities under supercritical biphasic conditions. The beneficial effects of the supercritical phase were qualitatively attributed to the absence of the gas/liquid phase boundary and enhanced mass transport properties as compared to classical organic solvents. Indeed, a further increase in reaction rates has been established upon formation of a microemulsion for rhodium-catalyzed hydrogenation of styrene using especially designed hydrophilic/CO_2-philic surfactants (Eq. 4) [55]. These microemulsions can be broken down at the reaction temperature of 40 °C by reducing the pressure from ca. 250 bar to ca. 70 bar. The product can be extracted with CO_2 under these conditions and the aqueous phase containing catalyst and surfactant was recycled effectively three times.



(4)

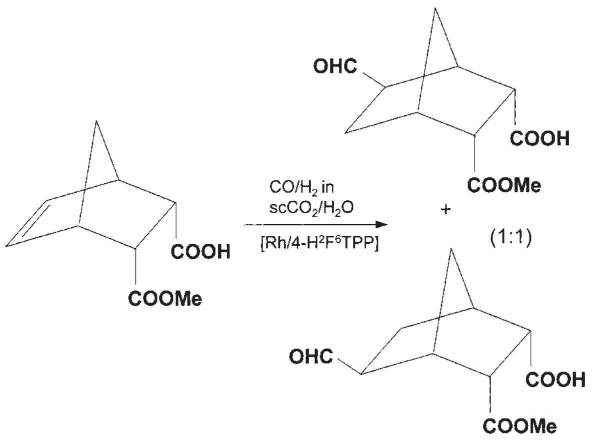
H_2O/toluene: TOF = 4 h^{-1}
$H_2O/scCO_2$: TOF = 26 h^{-1}
$H_2O/scCO_2$/surfactant: TOF = 150 h^{-1}

The Mizoroki–Heck reaction was carried out in water/$scCO_2$ and ethylene glycol/$scCO_2$ using the typical sulfonated triphenylphosphine ligand TPPTS [56]. The reaction is claimed to occur under monophasic conditions although this seems unlikely under the CO_2 pressures and temperatures with the amounts of catalyst and co-solvent employed. Catalyst recycling was achieved by phase separation after complete decompression rather than by using CO_2 extraction. Nevertheless, this example demonstrates the scope of the multiphase approach with polar solvents and $scCO_2$.

All aqueous/$scCO_2$ systems discussed up to now use CO_2 as the phase for substrates and products. Naturally, this restricts the applications to relatively nonpolar and/or volatile components with sufficient solubility in the supercritical medium. Intriguing alternatives for processing highly polar substrates are "inverted" aqueous systems. In this approach, a CO_2-philic catalyst resides in the nonpolar CO_2 phase and the water-soluble substrates and products are contained in the aqueous layer. The product stream of these systems is obtained without the need for depressurization of the CO_2 phase, which is an important cost factor in SCF processing. Furthermore, the aqueous solution is not contaminated with any organic solvent or catalyst residues, which is particularly important if the product is a fine chemical for direct further use in aqueous solution.

A highly fluorous "CO_2-philic" rhodium catalyst was effectively immobilized in an inverted H_2O/$scCO_2$ system for the prototypical hydroformylation reaction shown in Eq. (5) [57]. Emulsion-type mixtures are formed under the reaction conditions upon stirring, which separate rapidly when stirring is stopped. After removal of the aqueous phase from the bottom of the reactor, a clear supercritical catalyst phase remains in the reactor that can be re-used for subsequent reactions. Recycling is very efficient at moderate catalyst loadings, but noticeable deactivation occurs at very low rhodium concentrations, probably caused by the low pH of the aqueous solution in the presence of CO_2.

An intriguing inverted H_2O/$scCO_2$ system has been reported for the generation of H_2O_2 from CO_2 and O_2 in the presence of "CO_2-philic" palladium catalysts [58]. The system exploits well many of the advantages of the $scCO_2$ reaction medium, leading, for example, to increased safety with the highly delicate reactant gas mixture. As H_2O_2 is used in aqueous phase directly, no further workup of the water



(5)

phase would be needed. An interesting extension of this concept is the use of H_2O_2 for direct oxidation reactions such as the formation of epoxides from alkenes [59].

7.4.2.3
Catalysis and Extraction Using sc Solutions (CESS)

The schematic phase behavior of CO_2 depicted in Figure 1 is only valid for the pure compound and the phase behavior of mixtures is much more complex [6]. The phase behavior of mixtures is a function of composition and the actual phase diagram can vary considerably even for seemingly similar components. Reaction systems are mixtures of at least three substances (substrate, product, and solvent), but in most cases more components of variable composition are present and a full description of the phase behavior is not a trivial matter [60]. Suffice is to say here that one can adjust operating points for such mixtures where a liquid phase is in equilibrium with a compressed gas phase at pressures and temperatures beyond the supercritical data of pure CO_2. Although this mixture as a whole is then not "supercritical", the compressed CO_2 phase will behave like a supercritical fluid exhibiting also certain solvent properties. Therefore, any component in such a mixture will partition between the liquid and the supercritical phase similarly to the manner described in Section 7.4.2.2. Exploiting this rich phase behavior and controlling the partitioning of substrates and catalysts allows the design of integrated reaction/separation schemes that rely on CO_2 as the only mass separating agent. For applications to organometallic catalysis, we propose to refer to such processes as "catalysis and extraction using supercritical solutions" (CESS).

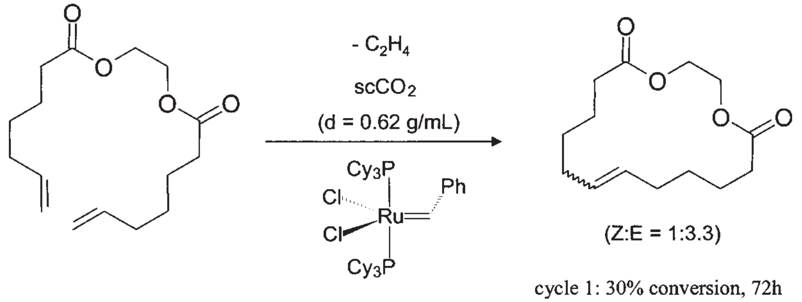
The "solvent power" of a fluid phase is of course related to its polarity, and compressed CO_2 has a fairly low dielectric constant under all conditions ($\varepsilon = 1.2-1.6$). There is a widespread myth that $scCO_2$ therefore behaves "just like hexane"; however, this is a misunderstanding. Most importantly, the solvent properties of the supercritical fluid depend very strongly on its bulk density. As a result the solvent properties of $scCO_2$ can be varied considerably with pressure and temperature, whereby higher density corresponds generally to higher solubility. Appreciable solubilities in pure $scCO_2$ usually require densities in the range of or above d_c, but the solvent power shows a gradual onset rather than a sharp discontinuity in the vicinity of the critical point.

The molecular structure of the solute plays an important role in its solubility in $scCO_2$ with three factors being most important. Certainly, compounds with low polarity are more soluble than very polar compounds or salts. However, the solubility increases strongly with increasing vapor pressure of the substrate, resulting in high solubilities for many compounds that would be immiscible with conventional nonpolar liquid solvents. Finally, some specific groups like perfluoroalkyl groups, polysiloxane substituents, or polyether/polycarbonate copolymers are known to result in a high affinity to compressed CO_2 beyond simple polarity or volatility arguments (ref. [61] and refs. therein). These "CO_2-philic" substituents can lead to quite dramatic solubility enhancements allowing control of the phase preference of certain components at several stages of a reaction/separation process.

If the main impetus to use $scCO_2$ lies in the recycling of the catalyst, it is not mandatory to work under fully homogeneous conditions at the reaction stage. It may even be planned to carry out the reaction in the absence of CO_2, which is then used only in the separation step and for downstream processing. An early example for this approach is provided by a BASF patent proposing to regenerate phosphine-modified rhodium hydroformylation catalysts via extraction of the so-called "heavy ends" after the more volatile short-chain aldehyde products have been removed by standard distillation [62]. More recently, the hydroformylation of long chain alkenes was carried out with CO_2-insoluble catalysts in a liquid/$scCO_2$ biphasic system followed by supercritical fluid extraction of the products and repeated re-use of the catalyst (Eq. 1) [63, 64]. In both cases, the catalysts would not have been recyclable by standard distillation procedures as the high boiling points of the components would result in thermal composition of the organometallic catalyst.

The importance of the partitioning of substrates, catalysts, and intermediates between the liquid (mainly organic) and compressed gas (mainly CO_2) phase for selectivity and conversion in catalytic processes has been noted in several studies [65–67]. Even substrates with melting points higher than the actual reaction temperature can be converted if the melting point depression under CO_2 pressure is large enough to render them liquid under the biphasic conditions [68].

In order to exploit fully the potential benefits of the supercritical state for both reaction and separation, it may be preferred to carry out the reaction in a fully homogeneous single-phase reaction mixture. For example, the selectivity between desired intramolecular ring-closing metathesis and competitive intermolecular oligomerization can be controlled by density variation under homogeneous supercritical conditions [69, 70]. Following the reaction step, supercritical extraction of the macrocyclic product leaves the poorly soluble Grubbs catalyst in the reactor in active form (Eq. 6) [71]. A variety of trialkylphosphine complexes have similar solubility properties to the Grubbs catalyst and similar recycling techniques may be envisaged. Examples reporting certain benefits during the reaction step, as compared to reactions in conventional solvents, include the hydrogenation of CO_2 formic acid and its derivatives with ruthenium trimethylphosphine catalysts [2], the hydroformylation of long-chain alkenes catalyzed by rhodium triethylphosphine complexes [72], and the hydroboration of alkenes with rhodium tricyclohexylphosphine catalysts [73].

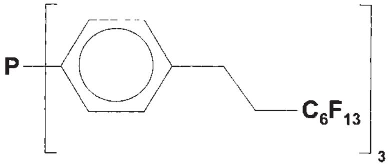


(Z:E = 1:3.3)

cycle 1: 30% conversion, 72h
cycle 2: 67% conversion, 170 h

(6)

Many, if not most, organometallic complexes exhibit solubilities in $scCO_2$ that are, however, too low even for catalytic applications. In particular, this applies to the large class of catalysts bearing arylphosphine ligands, a structural motif also found frequently in chiral ligands for enantioselective catalysts. The introduction of perfluoroalkyl groups into the ligand periphery is a convenient strategy for solubilizing metal catalysts bearing this type of ligand (cf. Structure **5**) [29]. These catalysts are soluble in $scCO_2$ at high density, but become insoluble at lower density [74]. Therefore, they separate from the reaction mixture or partition into a liquid phase upon density reduction [75] and can be recycled if product extraction is carried out under these conditions. The efficiency of this type of regulated system for catalyst immobilization has been demonstrated for the hydroformylation of long-chain alkenes as shown in Table 1 [76].



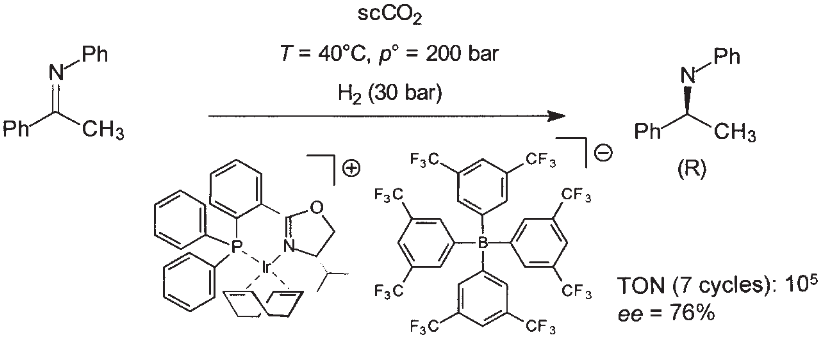
5 (= 4 – H^2F^6–TPP)

Perfluoroalkyl groups can be introduced into ligand frameworks by a variety of methods, and successful applications in $scCO_2$ have been reported for rhodium-catalyzed alkene hydroformylation [77, 78], hydroboration [73], and hydroaminomethylation [79], as well as palladium-catalyzed C–C bond-forming reactions [28, 80–83] and various metal-catalyzed polymerization processes [84–86]. Chiral arylphosphine ligands bearing perfluoroalkyl groups have been investigated for enantioselective catalytic hydrogenation [87–89] and hydroformylation [88, 90, 91] in $scCO_2$. A perfluoroalkyl derivative of BINAPHOS showed identical enantioselectivity at enhanced regioselectivity in $scCO_2$ as compared to the parent compound in benzene solution [88]. The catalyst could be recycled very efficiently using the

CESS procedure whereby the number of recyclings was limited by the stability of the ligand framework rather than by the method (Eq. 2 and Table 2) [91].

The introduction of perfluoroalkyl groups into the ligand periphery of an organometallic complex can lead to a considerable increase in molecular weight and size of the catalytically active species. This has been utilized to separate "CO_2-philic" catalysts from the products in a continuous-flow membrane reactor [92]. This intriguing methodology may be particularly useful where highly fluorinated polymers or copolymers are used to stabilize and solubilize organometallic [93, 94] or colloidal [95] catalysts in $scCO_2$ as the reaction medium.

Many organometallic catalysts, and especially many chiral catalysts, are cationic and modification of the anion has been found to be very effective for enhancing their solubility in $scCO_2$. Tris(3,5-dimethylphenyl)borate (BARF) has proven extremely useful for this purpose early on [96], and very pronounced anion effects on the activity and selectivity of the catalysts are observed in many cases [48, 87, 97]. Using BARF-modified "CO_2-philic" chiral iridium catalysts (Eq. 7), greatly enhanced reaction rates at almost identical *ee* values were observed for the enantioselective hydrogenation of imines upon changing from CH_2Cl_2 to $scCO_2$ as the solvent.



TON (7 cycles): 10^5
ee = 76%

(7)

The iridium catalyst was found to be sufficiently soluble in $scCO_2$ for catalysis in the form of the substrate complex, but precipitated quantitatively once all the substrate had been consumed. Supercritical fluid extraction at that stage yielded the solvent- and metal-free product in crystalline form, leaving the active and selective catalyst behind for further use. Under batch operation, noticeable deactivation occurred after the fourth cycle; this might be avoided by working in a closed system, as demonstrated for the hydrovinylation reaction shown in Eq. (3) [48, 49].

7.4.3
Conclusions and Outlook

Supercritical fluids can open entirely new and distinct approaches to the immobilization of organometallic catalysts. Traditionally, research in homogeneous catalysis is largely oriented towards exploiting the molecular diversity of organometallic compounds through rational or high-throughput catalyst development. There is no doubt that this will remain a major source of innovation as many catalytic processes are yet to be discovered and many of the known transformations are not yet useful for practical synthesis. At the same time, however, it becomes clear that reaction engineering needs to become an equally important focus for research in homogeneous catalysis. Catalyst immobilization is one very important aspect of this research, but developing methods for selectivity and reactivity control by variation of parameters such as residence times, flow rates, etc., seem equally intriguing. Owing to the gas/liquid-like properties of supercritical fluids, multiphase catalysis using $scCO_2$ is ideally suited on this borderline between molecular design and reaction engineering.

At present, there is growing evidence for the reliability and the widespread applicability of the techniques. Some patterns of possible benefits and difficulties associated with the use of $scCO_2$ in multiphase catalysis are also emerging, even though our understanding of the chemical and physicochemical principles is far from being complete. Furthermore, in contrast to heterogeneous catalysis, no data on pilot plant operation are currently available and no ecological analysis of a potential process utilizing organometallic catalysts with $scCO_2$ has been published. In fact, it seems quite difficult to evaluate this balance on a generic basis as the overall costs are dominated largely by investment and the design of the equipment will depend strongly on the scale and the exact mode of operation. However, the expanding and successful application of $scCO_2$ technology in a wide range of industries on a very different scale may serve as convincing evidence for the potential of economic viability.

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7.5
The Amphiphilic Approach

Paul C. J. Kamer, Joost N. H. Reek, Piet W. N. M. van Leeuwen

7.5.1
Separation Methods

Especially when a catalyst is expensive and produces low-value bulk chemicals or when it is toxic, its separation from the reaction medium is pivotal [1 a]. In some cases, the high costs of sophisticated ligands, e.g., for asymmetric catalysis, render recycling of the ligand equally important. A challenging separation principle is based on the difference in solubility of the reagents and the catalyst in two immiscible solvents. There are basically two ways of applying this principle. Most extensively investigated is two-phase catalysis (Figure 1; cf. Section 4.2). The catalyst is located in a solvent, usually water, which is immiscible with the solvent containing the reagents. The catalytic reaction occurs in the catalytic phase or at the phase boundary. In some instances the product forms the second, immiscible solvent, making the use of a second solvent redundant [1 b, c].

In the other approach, the catalytic reaction is initially performed in a homogeneous reaction medium and in a second step, i.e., not in the reactor, the catalyst is extracted (Figure 1 b). Several variations on this extraction concept can be envisaged; only the most common ones will be discussed.

7.5.1.1
Two-phase Catalysis

This concept was first realized industrially in the Shell higher-alkene process (SHOP) designed by Keim et al. [2, 3] (cf. Section 7.1). Ethylene is oligomerized in a polar phase of 1,4-butanediol that also contains the nickel complex of a phosphino carboxylate. The product α-alkenes (C_{4-20}) are not soluble in the polar solvent and can be separated easily. In general, the distribution factor of catalysts and reagents between two organic phases is not very high and the use of water, which is immiscible with most organic products, as the phase containing the catalyst is an apparent remedy. Catalysis in water required the development of water-soluble ligands (cf. Section 3.2).

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

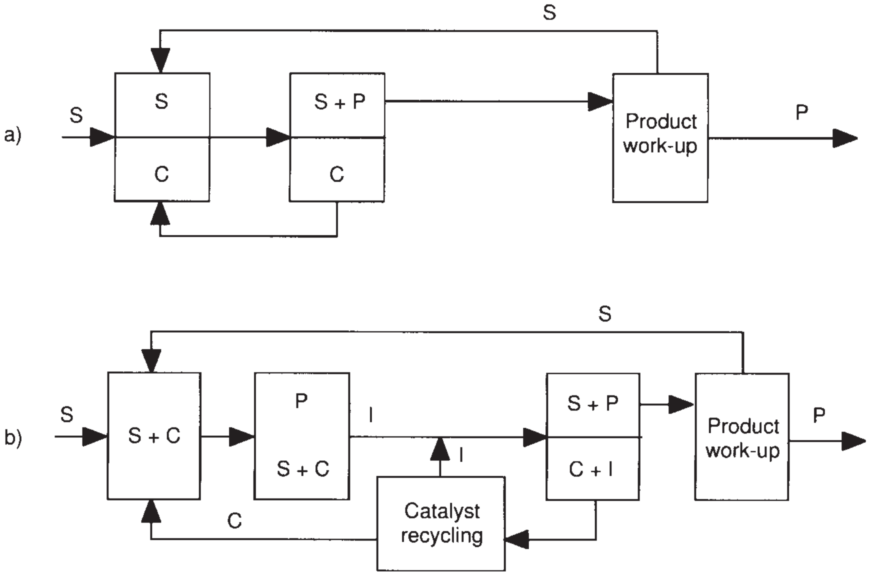


Fig. 1 Simplified flow diagrams for (a) two-phase catalysis and (b) the extraction concept [1 b, c] (C = catalyst, S = substrate, P = product, I = immiscible solvent).

Aqueous biphasic catalysis allows easy separation of product and catalyst. Conducting the catalysis in water can have both detrimental and beneficial effects on the selectivity. The application of this system, however, is limited by the (in)solubility of the substrate in water. The use of co-solvents or surface-active agents may enhance phase mixing, but is likely to induce catalyst loss by increasing the catalyst concentration in the product phase or giving rise to stable emulsions. Interestingly, Horváth [4] recently introduced a novel concept for biphasic catalysis which may be especially suitable for the hydroformylation of hydrophobic higher alkenes. This system consists of a fluorocarbon-rich phase containing rhodium complexed to a fluorinated ligand $P[CH_2CH_2(CF_2)_5CF_3]_3$, adn a common organic solvent. The advantage of this fluorous biphasic system (FBS) is that the product aldehydes are less soluble in the fluorous phase than the alkenes because of their higher polarity (cf. Section 7.2).

Other important biphasic concepts are based on the use of room-temperature ionic liquids (cf. Section 7.3) and, more recently, supercritical CO_2 (cf. Section 7.4) [31]. In addition, the second phase needs not necessarily to be another solvent. An amphiphilic approach can also be based on the use of micellar systems or vesicles formed by surfactants (cf. Section 4.5). A properly functionalized ligand itself can also function as the surfactant (cf. Section 3.2.4), which can even result in the formation of very stable aggregates [32].

7.5.1.2
The Extraction Concept

The amount of work done in this field is rather modest compared with that in two-phase catalysis, although it offers some major advantages. Catalysis is conducted in a homogeneous medium, which may be the pure substrate, with concomitantly high reaction rates, since substrate solubility is not limited. Naturally, the advantages have to offset the extra costs arising from the continuous catalyst recycle. For many years, the extraction concept has been applied industrially in the DuPont adiponitrile process [5 a]. The nickel arylphosphite catalyst that is exploited in the hydrocyanation of butadiene is separated from the polar high-boiling adiponitrile by extraction with cyclohexane (cf. Section 6.7).

The extraction concept mostly utilizes an amphiphilic ligand system that allows transfer of the catalyst back and forth from an organic to an aqueous layer by varying the pH of the system. After the reaction the organic phase is washed with water of an appropriate pH. At this pH the catalyst and excess ligand become water-soluble, either by protonation or deprotonation, and are extracted in the aqueous phase. The organic products can thus be separated from the catalyst. For some catalytic reactions it can be advantageous that water is not present during the reaction. The cycle can be completed by neutralization of the aqueous phase and extracting the catalyst and excess ligand into a new batch of substrate. A disadvantage of this system is that it also produces salts, albeit in catalytic quantities only.

For cobalt, this method has been commercialized in the Kuhlmann process, using amphiphilic $HCo(CO)_4$ [5 b]. The Kuhlmann process (now the Exxon process) involves cobalt-catalyzed hydroformylation of higher alkenes, for which the flowsheet – a liquid/liquid separation – is shown in Figure 2. In this process the hydroformylation is done in the organic phase consisting of alkene and aldehyde. A loop reactor, or a reactor with an external loop to facilitate heat transfer, is often used.

A liquid/liquid separation of product and catalyst is performed in separate vessels after the reaction has taken place. The reaction mixture is sent to a gas separator and from there to a countercurrent washing tower in which the effluent is treated with aqueous Na_2CO_3. The acidic $HCo(CO)_4$ is transformed into the water-soluble conjugate base $NaCo(CO)_4$. The product is scrubbed with water to remove the traces of base. The oxo crude goes to the distillation unit.

The basic solution in water containing $NaCo(CO)_4$ is treated with sulfuric acid in the presence of syngas, and $HCo(CO)_4$ is regenerated. This can be extracted from water into the substrate, alkene, and is returned to the reactor. Compared with other schemes (former processes of BASF, Ruhrchemie) the elegant detail of the Kuhlmann process is that the cobalt catalyst is not decomposed via (partial) oxidation but is left in the system as the tetracarbonylcobaltate.

There are several ways of applying the extraction concept *without* utilization of an amphiphilic ligand system. Three interesting alternatives will be discussed.

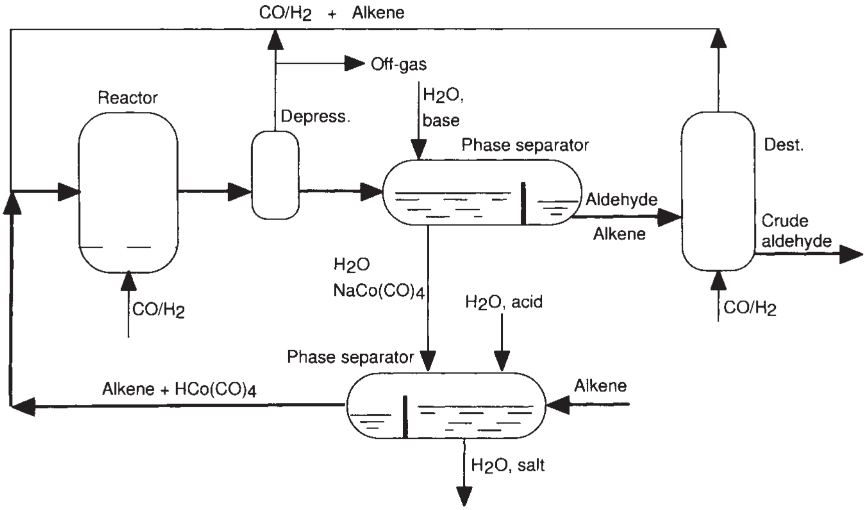


Fig. 2 Simplified scheme for the Kuhlmann hydroformylation process (Dest. = distillation unit).

The first concerns the hydroformylation of higher alkenes ($> C_7$) using a hydrido rhodium carbonyl catalyst [6]. Rhodium can be removed from the organic reaction medium by extraction with an aqueous solution containing sulfonated or carboxylated nitrogen ligands, such as bipyridines or phenanthrolines, at a reduced syngas pressure. Contacting the separated aqueous phase with a new organic layer under high CO/H_2 pressure leads to reversible decomplexation of the nitrogen ligand and regenerates the desired rhodium carbonyl catalyst. Evidently this method is limited to metal carbonyl catalysts. A similar recycling procedure has been patented for hydrido cobalt carbonyl catalysts [7], in which case TPPTS serves as complexing agent.

A second alternative for the separation of hydroformylation products from a rhodium [8] or cobalt [9] catalyst is to perform the catalytic reaction in a polar solvent using complexes of monosulfonated trialkyl- or triarylphosphines (e.g., TPPMS). Addition of both water and an apolar solvent such as cyclohexane gives a biphasic system. After separation of the apolar layer, the added apolar solvent must be stripped from the products. In order to form a homogeneous system with new substrate alkene, the polar catalytic phase must be freed from water, e.g., by azeotropic or extractive distillation. Clearly, these extra co-distillation steps are energy-consuming.

Thirdly, separation of catalyst and products can be conveniently achieved by extraction with water if the products are water-soluble, e.g., in the hydroformylation of allyl alcohol [10, 11]. In the ARCO process the hydroformylation products are extracted (more than 99%) from the organic reaction medium containing the conventional $HRh(CO)(PPh_3)_3$ catalyst, excess PPh_3, and diphosphines. The losses of rhodium and phosphines due to solubility in water are negligible.

7.5.2
Use of Amphiphilic Phosphines

7.5.2.1
Catalysis Using Amphiphilic Ligands

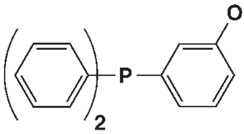
A relatively new approach involves the functionalization of phosphines or other ligands with weakly basic or acidic functionalities. An early study reports on a modified cobalt catalyst [12]. This cobalt carbonyl complex containing the $P(CH_2CH_2NEt_2)_3$ ligand was claimed to be extractable into dilute carbonic acid and could be re-extracted into an organic phase by simply reducing the CO_2 pressure.

For rhodium, several studies concerning the use of amphiphilic ligands have been reported. Rhodium catalysts derived from tris(2-pyridyl)phosphine achieve selective hydroformylation of 1-hexene both in a homogeneous acetophenone system and, at a much lower rate, in a two-phase water/1-hexene system [13]. Attempts to extract the rhodium complex from the homogeneous system with water were not successful; the use of HCl or HBF_4 resulted in rapid evolution of H_2 and about half the rhodium could not be extracted from the orange, organic phase.

By using thiolate ligands containing an amino group, recoverable dirhodium μ-thiolato complexes have been obtained [14] (cf. Section 3.2.3). Addition of dilute aqueous sulfuric acid to the hydroformylation reaction mixture causes the immediate and complete precipitation of the yellow ammonium sulphate salt. This solid is insoluble in water and common organic solvents, but can be easily regenerated – by addition of an aqueous base and extraction with an organic solvent – and re-used without loss of activity.

Amino-derived BDPP (2,4-bis[diphenylphosphino]pentane) has been used in asymmetric hydrogenation catalysis [15–17] (cf. Sections 6.2 and 6.9). NMR analysis showed that a ten-fold excess of HBF_4 is sufficient to protonate reversibly all four amino groups in the $[Rh(diene)(BDPP)]BF_4$ complex. Recycling of the catalyst after enantioselective hydrogenation of dehydroamino acid derivatives in methanol is achieved by acidification with aqueous HBF_4 followed by extraction of the product with Et_2O. Immobilization of the protonated BDPP rhodium complex on a Nafion support has been studied as well [18].

An extensive study on rhodium-catalyzed hydroformylation using amphiphilic phosphines has been performed by Van Leeuwen and co-workers [19–22] (cf. Section 3.2.2). The amphiphilic ligands based on triphenylphosphine form complexes having an amphiphilic character when coordinated to rhodium (Structures **1**–**9**). In the hydroformylation of 1-octene the selectivity is unaffected by these additional functionalities, as compared with the parent PPh_3 [19]. Also, most ligands showed



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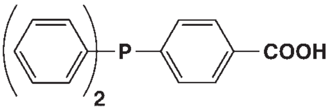

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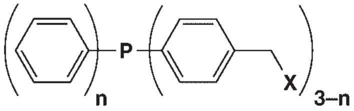
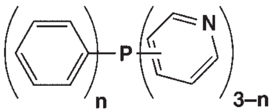
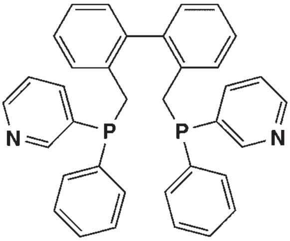


3 n = 2, X = NEt_2
4 n = 1, X = NEt_2
5 n = 2, X = NPh_2
6 n = 1, X = NMePh



7 n = 2, *4*-pyridyl
8 n = 2, *3*-pyridyl
9 n = 1, *3*- pyridyl



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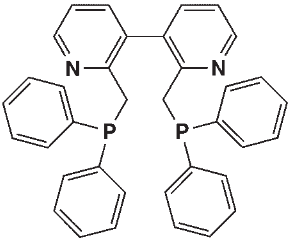

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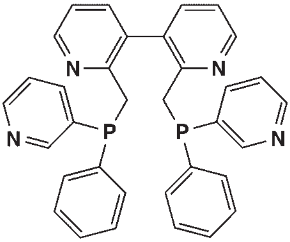

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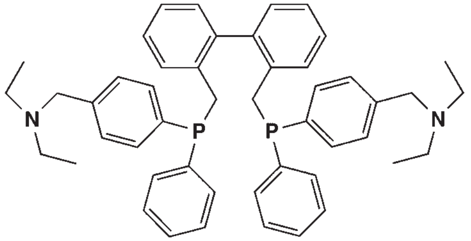

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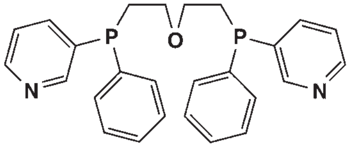
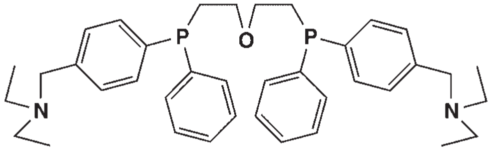
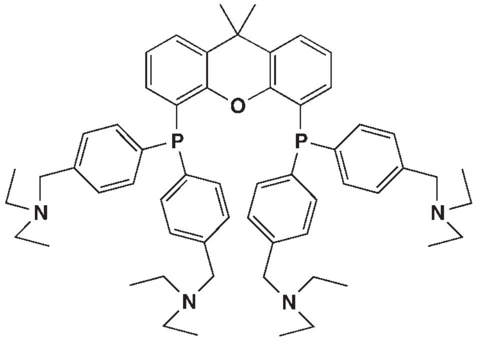


14 POPpy



15 POPam

reaction rates comparable with that of PPh_3. Similar results were obtained by Andersson and co-workers using 4-bis[(2-diethylaminoethyl)diphenyl]phosphine N3P as ligand [33]. The use of pyridylphosphines as ligands resulted in faster hy-



16 XANTHAM

droformylation catalysis; this was ascribed to the higher χ-value [23], which is known to increase the reaction rate as a result of a less strong bonding of the CO molecules to the rhodium centre facilitating alkene coordination [24].

For the rhodium-catalyzed hydroformylation of higher alkenes, novel amphiphilic diphosphines have been reported (Structure **10–16**), based on BISBI (2,2′-bis[diphenylphosphino]methyl-1,1′-biphenyl), XANTHAM, POPpy and POPam, which can be used in the rhodium recycling system [21, 22].

The series of new diphosphines have been tested in the rhodium-catalyzed hydroformylation (Table 1) of 1-octene. The reaction rates for the catalysts derived from the pyridyl-modified ligands **10–12** and POPpy are higher than those of BISBI and **13**, which is consistent with earlier observations made for the pyridyl-modified triphenylphosphines [19].

All BISBI-type diphosphine-modified catalysts give selectivities around 90% to linear aldehydes. As can be seen in Table 1, POP (2,2′-bis(diphenylphosphino)-diethyl ether) and its amphiphilic derivatives give rise to mainly linear aldehyde (88–89%). Although the selectivity for linear aldehydes is moderate compared with XANTHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene), virtually no isomerization is observed.

It can be seen that the rhodium catalyst derived from XANTPHOS and XANTHAM gives rise to an even higher yield of linear aldehyde owing to both a high linear/branched (n/i) ratio and a relatively low activity for isomerization. This is ascribed to the well-defined template structure of both rigid ligands, which preferentially occupy two equatorial sites in the catalytically active rhodium hydride owing to their relatively large natural bite angle. This geometry leads to a higher proportion of linear (n-)aldehyde formation as compared with geometries with axial–equatorial chelates [25, 26]. XANTPHOS and XANTHAM give similar results in the hydroformylation of 1-octene. The reaction rate of the XANTHAM-derived catalyst, however, is somewhat higher despite the electron-donating effect of the four aminomethyl groups, which has a negative effect on the reaction rate [27, 28].

Tab. 1 Hydroformylation of 1-octene under standard conditions.[a)]

Ligand	*Time [h]*	*Conversion [%]*[b)]	*Selectivity [%]*			*n/i*	*TOF*[d)]
			Isomers[c)]	*n-Ald.*	*i-Ald.*		
PPh_3[e)]	2	81.2	1.5	72.6	25.6	2.8	2000
1[e)]	2	76.6	0.8	73.1	26.1	2.8	1900
3[e)]	2	76.2	0.3	73.3	26.0	2.8	1900
4[e)]	2	72.6	0.8	73.0	26.1	2.8	1800
8[e)]	2	86.3	2.7	71.7	25.6	2.8	2100
9[e)]	1	80.2	2.7	71.7	25.6	2.8	3900
BISBI	21	82.8	7.6	90.2	2.2	41	182
10	20	91.4	7.9	90.3	1.8	51	210
11	21	91.5	7.2	89.0	3.8	24	204
12	21	93.6	7.8	89.2	3.0	30	206
13	21	76.9	6.5	90.6	2.9	32	172
POP	20	67.0	0.0	88.2	11.8	7.5	168
POPpy	20	88.0	0.7	89.3	10.0	8.9	207
POPam	21	71.5	0.0	88.0	12.0	7.3	178
XANTPHOS	24	61.6	3.9	94.1	2.0	46	123
XANTHAM	24	67.9	4.0	94.1	1.9	49	137

[a)] Conditions: 20 bar H_2/CO (1:1), 80 °C, toluene (20 mL), $[L] = 17 \times 10^{-4}$ M, $[Rh] = 1.7 \times 10^{-4}$ M, [1-octene] = 0.84 M.

[b)] Percentage of 1-octene converted.

[c)] Percentage of 2-, 3- and 4-octene formed.

[d)] Turnover frequency in mol aldehydes/mol Rh per hour, averaged over the time given.

[e)] $[L] = 34 \times 10^{-4}$ M.

7.5.2.2
Distribution Characteristics of the Free Ligands

The distribution characteristics of the free ligands have been reported as a function of the pH. These data are of interest for the following reasons. First, they can serve to decide which ligands are most suitable for the present goal. Secondly, the distribution characteristics of the free ligand can give an indication of the behavior of the corresponding rhodium complex. The complex is expected to be extracted at a milder pH than the ligand since it contains several ligands with accordingly more functional groups.

The distribution characteristics of the free ligands were determined by measuring the UV-absorption spectra. In Figure 3 the D–pH plots are depicted for the phosphines functionalized with the benzylic amines **3**–**6**. A clear correlation between the ease of extraction and the basicity of the amino group was observed. The N_3P ligand of Andersson and co-workers containing three basic amino groups was extracted efficiently to the aqueous phase at slightly higher pH compared with ligand **4**. At pH values higher than 5.5 the ligands **10** and **11** are mostly located in

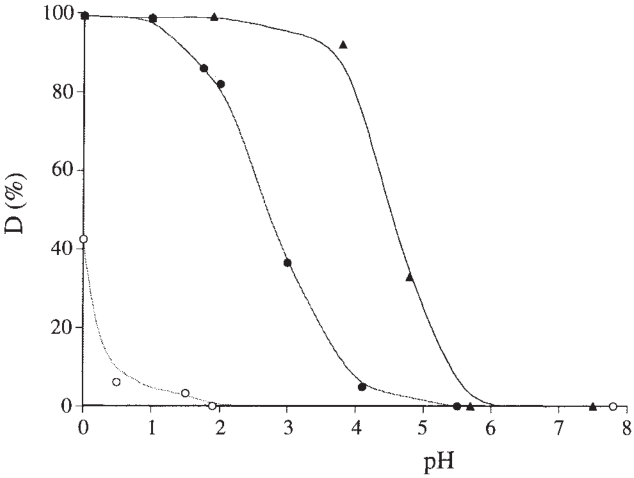


Fig. 3 Extraction curves of ligands **3** (●), **4** (▲) and **6** (○). D = distribution coefficient = $C_{H_2O}/(C_{H_2O} + C_{org}) \cdot 100\%$.

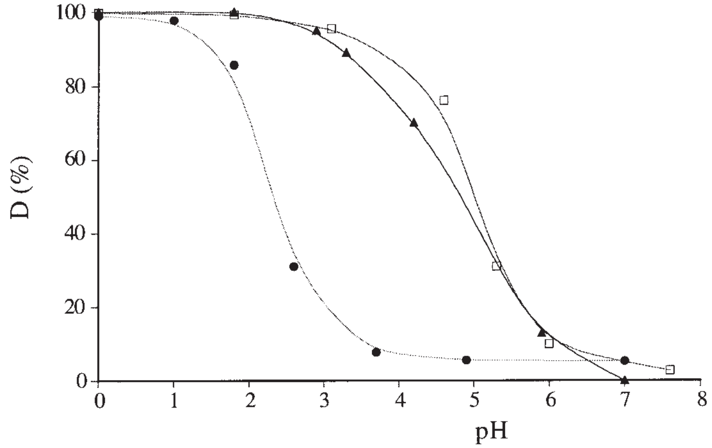


Fig. 4 Extraction curves of POPpy (●), POPam (□) and XANTHAM (▲).

the Et_2O layer, and only at pH values below 1 are both ligands extracted into the aqueous phase. Ligand **10** was extracted at a slightly higher pH than **11**. Ligands **12** and **13** were more readily extracted: they were extracted quantitatively at the relatively high pH of 2.

In Figure 4 the *D*–pH plots for POPpy, POPam and XANTHAM are depicted. POPpy is located mostly in the Et_2O layer at pH values of 4 to 7. Extraction of the ligand into the aqueous phase occurs at a pH of 3 and is complete at pH 1. The curve closely resembles that of PhP(3-pyridyl)$_2$ [20]. The recorded extraction curves for POPam and XANTHAM are almost the same and closely resemble that of

Tab. 2 Results of the recycling experiments: rhodium measurements by ICP–AES and retention of activity.[a]

Ligand	*Acidic extraction*	*Rhodium content [μg]*			*Rh recovery*[b]	*Rh balance*[c]	*RA*[d]
		First organic layer	*Aqueous layer*	*New organic layer*	*[%]*	*[%]*	*[%]*
4[e]	Titrations: 6 × extraction at pH 2.2	46	17	2258	97	96	87
9[e]	Titrations: 5 × extraction at pH 1.8	862	18	1356	57	98	60
10	Titrations: 5 × extraction at pH 1	252	719	219	18	96	14.1
11	Titrations: 5 × extraction at pH 1	51	1027	144	12	99	10.9
12	Titrations: 7 × extraction at pH 4–4.5	34	1150	47	41	100	2.5
13	Titrations: 7 × extraction at pH 5	11	8[f]	1108	91	99	72.1
POPpy	8 acidic extractions at pH 3	30	996	216	17	100	16
POPam	8 acidic extractions at pH 5–5.5	< 0.7	432	791	65	99	58
XANTHAM	9 acidic extractions at pH 5–5.5	< 0.7	26	1193	98	99	86

[a] The 95% confidence interval of the mean measured values is ± 4.5% for contents > 10 μg, otherwise ± 10%.

[b] Rhodium recovered in the new organic layer as percentage of the total amount measured.

[c] Rhodium mass balance, defined as the total amount of rhodium measured as a percentage of the starting amount (1235 μg).

[d] Retention of activity, defined as the turnover frequency of the recovered rhodium as a percentage of the original turnover frequency as measured in the first run (see text).

[e] Total amount of rhodium 2414 μg.

[f] Persistent emulsion contained 97 μg.

$PhP(C_6H_4CH_2NEt_2)_2$ [20]. Both ligands are completely located in the organic layer at pH 7, but are extracted more than 60% at pH 4.5. Extraction is complete at pH 2.5.

7.5.2.3
Rhodium Recycling

The efficiency of the rhodium recycling system using the new amphiphilic ligands was determined by re-use of the catalyst solution in a second hydroformylation run and by determination of the absolute amount of rhodium (metal) recovered using ICP–AES.

The results of the optimization of the recycling procedure are summarized in Table 2. The turnover frequency of the first run (TOF1) is taken as the number of moles of aldehyde formed per mole of rhodium averaged over the reaction time. Since the TOF of the second run (TOF2) was determined after a similar conversion of 1-octene, the quotient of both TOF values is a measure for the recovery of catalytically active rhodium and is referred to as the retention of activity (RA).

It can be seen that rhodium and excess ligand can be recycled and 1-octene can indeed by hydroformylated in a second run. The selectivity is generally exactly the same as in the first run. The recovery of rhodium as measured by rhodium analyses by ICP–AES can be nearly complete. Apparently, the rhodium and excess ligand are mostly recycled, but the rhodium in the eventual toluene phase is only partly active due to a certain amount of irreversible catalyst decomposition. Andersson and co-workers showed that the retention of activity could be improved by employing an extraction procedure using hydrochloric acid followed by anion metathesis between the stable rhodium chloride and $NaBPH_4$ [34]. Several hydroformylation runs could be performed without significant loss of activity. Using amphiphilic bidentate ligands the originally highly selective and active rhodium hydrides can be regenerated up to 72% (ligand **13**). In contrast with ligand **13**, ligands **10**–**12** are unsuitable for application in rhodium recovery. Treatment with basic solutions leads to extensive, irreversible decomposition. The decomposition reactions of the rhodium complexes have not been elucidated but NMR analysis established that the excess ligand did not decompose and was recycled. Presumably, the presence of a pyridyl nitrogen atom, whether positioned in a bipyridine backbone or a pyridyl ring, facilitates irreversible decomposition of the rhodium hydride species to trivalent rhodium species which cannot be extracted from the aqueous layer. The small amount of rhodium which was re-extracted in toluene could be largely regenerated to the active hydride, since the same selectivity was observed as in the first hydroformylation.

The catalytic mixture of POPpy was not recovered from the aqueous phase. The recovered toluene phase accordingly showed a low retention of activity (13%). Evidently, POPpy is also unsuitable for rhodium re-use, as observed earlier for pyridyl-modified PPh_3 and BISBI ligands [20, 21]. Also the recovery of POPam proved to be troublesome; only 59% of the total amount of rhodium charged was found in the new organic layer.

Successive extraction of the catalytic mixture of XANTHAM affected the recovery of rhodium. Although the overall rhodium recovery was almost quantitative (97%), a retention of activity of 86% was observed when the acidic titration procedure was performed at pH 5–5.5. This result equals the success of $PhP(C_6H_4CH_2NEt_2)_2$ [20].

The extraction concept is also applicable to sophisticated syntheses of fine-chemicals as recently shown by Ohe, Uemura and co-workers [35]. They prepared a novel amphiphilic phosphinite-oxazoline chiral ligand based on D-glucosamine. The corresponding palladium complex was an efficient catalyst for asymmetric allylic substitution reactions and could be recycled by simple acid/base extraction and reused in the second reaction without loss of enantioselectivity.

7.5.3
Conclusions

Efficient separation of catalyst from the reaction medium can be achieved by extraction of polar rhodium complexes of TPPMS with water [8]. However, many catalytic processes for the production of fine chemicals require the use of modified tailor-made catalysts. The introduction of amphiphilic substituents on phosphines opens the way to easy separation of ligands that induce high selectivity and/or activity in catalytic reactions simply by extraction with acidic or basic water.

The novel amphiphilic diphosphines give rise to hydroformylation catalysts which are highly active and selective. Functionalization of the ligands with the diethylamino groups allows the separation of the product aldehydes from the rhodium catalyst, and the recovery of rhodium to the extent of 99.95% from the organic reagents by simple acidic extraction. XANTHAM is very promising for use as a ligand in the rhodium-catalyzed hydroformylation of higher alkenes as it is even somewhat more active than the catalyst derived from the hydrophobic XANTPHOS ligand. For commercial application in a process producing commodity aldehyde, a rhodium recovery of 99.98% [29] or even more [30] is mentioned in the literature. The 86% retention of activity is high, but far form satisfactory from an industrial point of view. The improved procedure developed by Andersson offers a possible solution to this problem. Even less of irreversible decomposition could be envisaged by performing all recycling steps under syngas pressure. It would be interesting to apply the improved extraction procedure in a system employing the high-performance bidentate ligands (cf. Section 3.2.2). Finally, the present recovery procedure in combination with the XANTHAM ligand may already be applied to the batchwise hydroformylation of fine chemicals.

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7.6
Catalysis with Water-soluble Polymer-bound Ligands in Aqueous Solution

Stefan Mecking, Ernst Schwab

7.6.1
Introduction

A facile separation of the catalyst from the reaction products and unreacted substrates remains one of the key challenges in homogeneous catalysis. Since the advent of homogeneous catalysts based on well-defined catalyst precursors, their immobilization by binding to microporous insoluble organic resins or inorganic supports has been investigated [1]. However, such heterogenized catalysts often display lower activities in comparison to their non-immobilized analogs, which may be due to diffusion limitations. Also, the cross-linked copolymers used most often possess a heterogeneous structure consisting of domains of strongly differing composition, such that the local concentration of, for example, resin-bound phosphine ligand moieties can vary strongly [2]. Leaching of precious metals remains a serious problem. Also, limited mechanical and temperature stability of resins can be disadvantageous.

Binding of catalytically active complexes to *soluble* polymers is an attractive alternative. First reports originate from the 1970s [3, 4], but since then the concept has received increased attention only recently [5]. Most often, typical ligands such as phosphines are attached covalently to a linear polymer. For separation after a catalytic reaction, membrane techniques are an elegant approach. On suitable membranes with nanometer-sized pores the polymer-bound catalyst is retained, while the low molecular weight products and residual substrates pass the membrane. Although the concept was introduced by Bayer and Schurig in the 1970s [4], it has since then received attention only recently [6]. Industrial interest has arisen over the past few years, but to date there are no confirmed applications [7]. As an alternative approach, the catalyst can be recovered by phase separation of the polymer, brought about by changes in solvent composition, pH, or – particularly elegantly – by simple temperature changes as demonstrated by Bergbreiter and others [8, 9]. The aforementioned work has focused predominantly on catalysis with soluble polymer-bound catalysts in a (single, homogene-

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

ous) organic phase, in which the substrates are soluble and thus mass transfer should not be an issue.

Water-soluble polymers, such as poly(ethylene oxide), can be attached covalently to, e.g., phosphine ligands, to render them water-soluble. Most often this concept has been applied to biphasic catalysis as an alternative to the introduction of ionic water-soluble moieties, such as the sulfonate groups of the archetypical trisulfonated triphenylphosphine (TPPTS; cf. Section 3.2.1).

Catalysis with water-soluble polymer-bound catalysts in a single homogeneous aqueous phase, the subject to this section, can be of interest for the conversion of water-soluble organic substrates. With a view to applications, the use of water as a nonhazardous, environmentally benign solvent can be advantageous.

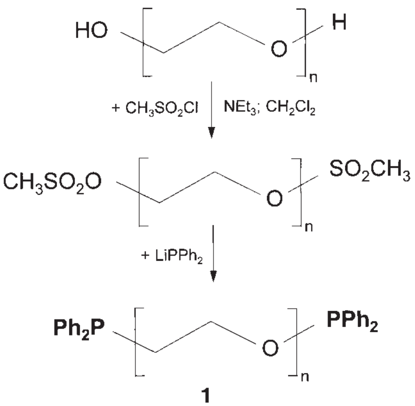
7.6.2
Catalysis with Water-soluble Polymer-bound Ligands in Aqueous Solution

Poly(ethylene oxide) (PEO) has been employed frequently as a water-soluble catalyst support [9]. Further water-soluble polymers investigated include other linear polymers such as poly(acrylic acid) [10], poly(*N*-alkylacrylamide)s [11], and copolymers of maleic anhydride and methylvinylether [12], as well as dendritic materials such as poly(ethyleneimin) [10a, c] or PEO derivatives of polyaryl ethers [13]. The term “dendritic” refers to a highly branched, tree-like structure and includes perfectly branched dendrimers as well as statistically branched, hyperbranched macromolecules.

Poly(ethylene oxide) and poly(*N*-alkylacrylamide)s are known to undergo a temperature-dependent phase change whereupon they separate from an aqueous phase at increased temperatures [14]. This inverse temperature dependence, i.e., the occurrence of a lower critical solution temperature, can be related to an entropically favorable decrease in hydrogen bonding between water and the polymer with increasing temperature. In order to exploit this physical property for catalyst recovery, Bergbreiter et al. attached phosphines covalently to commercially available PEO or PEO-*b*-PPO-*b*-PEO block copolymers [Schemes 1 and 2; PPO = poly(propylene oxide)] [9a].

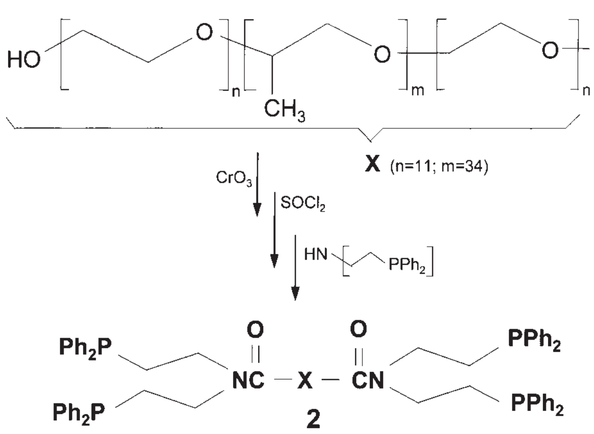
The poly(alkylene oxide)-bound phosphine ligands **1** and **2**, as well as a cationic rhodium(I) complex of **1**, were demonstrated to possess inverse temperature-dependent solubility. The effects of these solubility properties on catalysis have been demonstrated in the hydrogenation of allyl alcohol in water. An approximately 20-fold decrease in rate is observed when the temperature is raised from 0 °C to 40–50 °C [9a]. This unusual temperature dependence has been termed “smart behavior”.

In the former catalyst system, the phosphine moieties are attached only as the two end groups of a linear polymer. Generally, higher loading can be achieved by multiple functionalization of the backbone of a linear polymer, or also by reaction



1

Scheme 1 Synthesis of **1**.

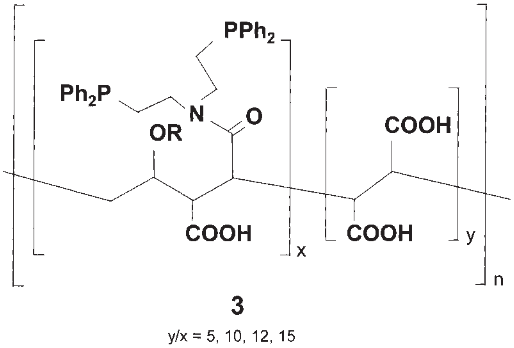


2

Scheme 2 Synthesis of **2**.

of the multiple end groups of a highly branched, dendritic polymer, as illustrated by the following approaches.

Another interesting concept for recycling of catalysts is binding to polymers with a pH-dependent solubility in water as described by Bergbreiter [12]. Commercially available poly(maleic anhydride-*co*-methyl vinyl ether) ($M_n = 5 \cdot 10^4\,\mathrm{g\,mol^{-1}}$, $M_w/M_n = 3.5$) was used by Bergbreiter as a starting material in the synthesis of phosphine-modified polymers of Structure **3**. An *in situ* catalyst **3**/[Rh(cod)$_2$]OTf was employed for the rhodium-catalyzed hydrogenation of various alkenes in aqueous solution, which proceeds with moderate activities (Table 1). In water, the rhodium catalyst can be recovered by acidifying the solution to pH < 5. After filtration the recycled catalyst can be redissolved in water at pH > 7.5. As shown in Table 1, the catalyst has been re-used for up to three cycles according to this princi-



3

Tab. 1 Activity of base-soluble, acid-insoluble Rh(I) hydrogenation catalyst **3**/[Rh(cod)]OTf in water.[a]

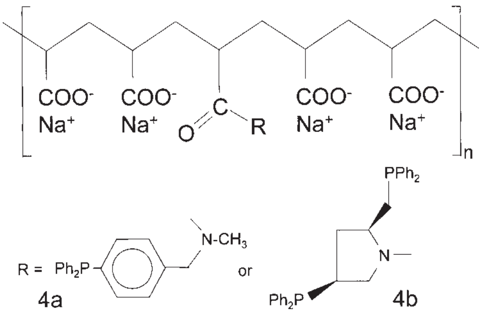
Substrate	*TOF* *[h^{-1}]*	*Yield* *[%]*
Allyl alcohol		
1st cycle	8	> 95[b]
2nd cycle	7.4	> 95[b]
3rd cycle	6.9	> 95[b]
Acrylic acid	19	> 95[b]
N-Isopropylacrylamide	84	94[c]
α-Acetamidoacrylic acid	42	90[c]
Sodium *p*-styrenesulfonate	8	> 90[b]

[a] Hydrogenation reactions were run at 25 °C using 0.2 mol% catalyst ($[\mathrm{Rh}]_{\mathrm{aqueous}} = 8 \cdot 10^{-4}$ M).
[b] Estimated by H_2 uptake.
[c] Isolated yield.

ple. Some loss of activity occurred which was assumed to be a result of partial phosphine oxidation.

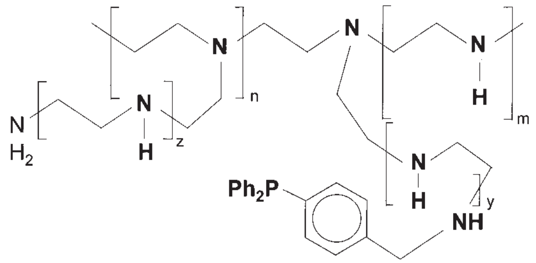
Andersson [10a, c] has used both acidic and basic polymeric supports based on phosphine-substituted poly(acrylic acid) (PAA) and poly(ethyleneimine) (PEI) respectively (polymer-bound ligands **4a**, **4b** and **5**). In the latter case, presumably a branched dendritic PEI was employed, and the phosphine ligand was bound selectively to the multiple end groups.

The catalyst formed by reaction of these polymer-bound ligands **4a** and **5** with $[Rh(nbd)_2]SO_3CH_3$ (nbd = norbornadiene) was used for hydrogenation of water-soluble (and also water-insoluble) alkenes in aqueous solution. The hydrogenation of acrylic acid proceeded smoothly (TOF ca. 100 h^{-1} at 25 °C, 1 atm) in water with the PEI-bound catalyst, whereas with the PAA-bound catalyst precipitation of the catalyst occurred due to the change in pH caused by the added acrylic acid [10c]. A possible effect of salt formation of acrylic acid with the basic PEI on the reactivity of the unsaturated acid was not investigated. With 1-buten-4-ol as the substrate



4

COO⁻/P = approx. 5



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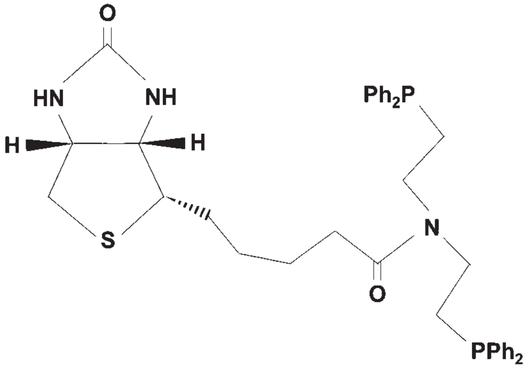
both catalysts were active for hydrogenation. The recovery and recycling of the supported catalysts were not described. Andersson also studied asymmetric rhodium-catalyzed hydrogenations of α-acetamidocinnamic acid in aqueous solution (and of the acid and its methyl ester in a biphasic system) with a chiral PAA-bound phosphine **4b** [10d]. The enantioselectivity of the reaction (at room temperature, 1 bar H_2) of ca. 70% *ee* in homogeneous solution (slightly alkaline, $pH > 8$) was somewhat lower than in biphasic experiments (89% *ee*). Also, the reaction rates were lower in the aqueous system despite its homogeneous nature. This finding and the lower enantioselectivity was ascribed to a possible coordination of the substrate carboxylate group to the catalyst; a conceivable effect of hydrogen solubility was not investigated. The polymer-bound catalyst was recycled by extraction of the product from the catalyst-containing aqueous phase with ethyl acetate. No reduction in selectivity was found in a repeated run, but some rhodium was lost in considerable amounts (ca. 7%).

Very recently, Fan et al. [13] reported on the use of a water-soluble PEO-substituted first- and second-generation Fréchet-type dendrimer with a chiral BINOL (1,1′-bi-2-naphthol) unit in catalysis. The enantiomeric excess in asymmetric hydrogenation of 2-[*p*-(2-methylpropyl)phenyl]acrylic acid with [RuCl(BINAP)(cymene)]Cl in an aqueous system was reported to increase upon addition of the dendritic



BINOL ligand. Hydrogenation at room temperature and 50 atm H_2 pressure occurs at a TON of 5 h^{-1} with a maximum *ee* of 67%.

In the aforementioned work, ligands are attached covalently to a polymer. An interesting non-covalent attachment was reported early on by Wilson and Whitesides [15]. An achiral phosphine ligand linked to a biotin unit (Structure **6**) interacted specifically with the protein avidin in aqueous solution to impose stereoselectivity in catalytic hydrogenation. In the rhodium-catalyzed hydrogenation of α-acetamidoacrylic acid in buffered aqueous solution, *ee* values of up to 40% were observed at TONs of 500 in a 48 h run. Catalyst recovery was not a motivation for this work, but during workup the catalyst was separated from the low molecular weight products by ultrafiltration.

7.6.3
Conclusions

Polymer-bound catalysts soluble in organic solvents or in water have seen considerable advances in the past 10 years. They can be utilized in biphasic techniques, or in a single homogeneous organic or aqueous phase. In the latter two cases, recovery from the low molecular weight reaction products and unreacted substrates can be achieved by means of membrane techniques, or by temperature- or pH-induced separation. Most investigations of soluble polymer-bound catalysts have focused on homogeneous organic systems. By comparison, reactions in single-phase homogeneous aqueous solutions are somewhat restricted as the range of organic substrates which are water-soluble is limited.

Soluble polymer-bound catalysts can be expected to receive continued attention as they offer specific advantages. By comparison to aqueous two-phase catalysis, a range of substrates much broader with respect to their solubility can be employed. By comparison to heterogenization on solid supports, the selectivity and activity of homogeneous complexes can be retained better. However, it must also be noted that to date no system has been unambiguously proven to meet the stability and recovery efficiency required for industrial applications.

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8
Aqueous-phase Catalysis: The Way Ahead

Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

8.1
State of the Art

Boy Cornils, Wolfgang A. Herrmann

This book is focused on the technique of aqueous, homogeneous two-phase catalysis, with the active catalyst for the reaction being (and – if not otherwise stated – remaining) dissolved in water. Thus, the reactants can be separated from the reaction products, which are typically organic in nature and relatively nonpolar, after the reaction is completed by simply separating the second phase from the catalyst solution. The catalyst can be recirculated without any problems (cf. Chapter 1 and Sections, 4.1 and 4.2).

As described, aqueous biphase catalysis makes it possible to utilize fully the inherent advantages of homogeneous catalysis. A major aspect of this new technology is the tailoring of organometallic complexes as catalysts, as is nowadays becoming increasingly important both for industrial applications and for new reactions, and for new products [1] (cf. Chapters 2, 3 and 5). The fact that selectivity- and yield-reducing operations (such as thermal stress caused by chemical catalyst removal or distillations) for separating product and catalyst are avoided makes it possible to use sensitive reactants and/or to obtain sensitive reaction products from homogeneous catalysis. Figure 1 of Section 5.2 demonstrates the advantages of the aqueous technique over the conventional one, taking the hydroformylation reaction as an example (cf. also Section 6.1): The aqueous variant gets rid of all technical equipment except for the column, 9 – a tremendous cost-saving [2].

Furthermore, this spontaneous separation of catalyst and product is the most effective and the only successful method of immobilizing a homogeneous catalyst and thus making it “heterogeneous” – just by anchoring it on the “liquid support,” water [3].

The concept and development of aqueous, homogeneous two-phase catalysis followed unconventional routes for chemical processes. After the idea was first expressed by Manassen [4] (not Bailar [5], as erroneously stated by Papadogianakis and Sheldon [6]), it was very quickly taken over by the university-based researcher Joó [7] (Debrecen, Hungary, whose inventive importance for the biphasic techniques has been partly underestimated [7b]) and in the industrial field by Kuntz [8]. However, these studies remained curiosities and the far-sighted visions of

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Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5

Kuntz, particularly, found no echo in the academic community. The reason may have been that the idea of organometallic complex catalysts in the presence of water seemed unnatural or even perverse, although even air-stable aquocarbonyl complexes of transition metals such as rhenium [9] were known in the meantime. In addition, metal–carbon bonds are thermodynamically unstable relative to their hydrolysis products (cf. Section 2.2), although it was well known that reaction rates could be increased by a factor of up to 10^{11} by aqueous media [10]. In simple terms, organometallic chemistry was not ready for aqueous operation before the early 1980s.

It was not until the work at Ruhrchemie AG (and thus the occupation of a skilled and experienced team in industry) that development led to the first large-scale utilization of the aqueous, homogeneous catalysis technique at the beginning of the 1980s, viz. in hydroformylation (the oxo process) [11]. The generally used embodiment of two-phase catalysis, for example as practised in Shell's SHOP method [12], was thus extended to *aqueous* two-phase catalysis. These (and the other industrial applications; see Chapter 6) have led to the literature concerning these particularly attractive aqueous variants being dominated by publications from industry, particularly patent literature, rather than from academia, for virtually a decade.

It was only in 1996 that the sleepy-headed academic literature provocatively asked "Why water?" [13]. This development sequence was quite unusual: the idea from academia, initial experimental work in the 1970s by an industrial chemist (Kuntz, then at Rhône-Poulenc), first industrial use in the 1980s (i.e., 20 years ago) by another industrial company – Ruhrchemie – and only then (for about the last eight years) more detailed scientific study. The fact that some "re-invention of the wheel" is occurring in these intensified academic studies is due not least to the widespread unwillingness of the academic community to read and take note of patents, especially non-English ones. Joó and Kathó [14] politely referred to this time delay between academic and industrial research as an "induction period", although it was more like a serious case of mass transfer inhibition.

The difference between biphasic catalysis in general (cf. processes mentioned in Chapter 7) and the aqueous biphasic technique in particular is enormous. The aqueous variant is not just a special version, because the utilization of water as a solvent and a liquid support offers different advantages quite apart from the fact of simply going "biphasic" (cf. Table 1).

The various properties of water in different aspects (being important for the reactivity, reaction kinetics or mechanisms, reaction engineering, or other concerns) are discussed elsewhere. The procedures for tailoring the water-solubility of the catalysts are many-sided and may be generalized much more easily than the corresponding methods for SHOP (cf. Section 7.1), fluorous phase (Section 7.2), supercritical solvents (Section 7.4), water-soluble polymer-bound catalysts (Section 7.6), or NAIL utilization (Section 7.3): no wonder that all other biphasic applications remain singular or are still just proposals. Both the scientific and industrial com-

Tab. 1 Properties of water as a liquid support of aqueous two-phase catalysis.

Property	
1	Polar and easy to separate from apolar solvents or products; polarity may influence (improve) reactivity
2	Nonflammable, incombustible
3	Widely available in suitable quality
4	Odorless and colourless, making contamination easy to recognize
5	Formation of a hexagonal two-dimensional surface structure and a tetrahedral three-dimensional molecular network, which influence the mutual (in)solubility significantly, chaotropic compounds lower the order by H-bond breaking
6	High Hildebrand parameter as unit of solubility of nonelectrolytes in organic solvents
7	A density of 1 g/cm^3 provides a sufficient difference from most organic substances
8	Very high dielectric constant
9	High thermal conductivity, high specific heat capacity, and high evaporation enthalpy
10	Low refractive index
11	High solubility of many gases, especially CO_2
12	Formation of hydrates and solvates
13	Highly dispersible and high tendency toward micelle formation, stabilization by additives
14	Amphoteric behaviour in the Brønsted sense
15	Advantageously influencing chemical reactivity

munities expect realistic applications (other than the ones effected so far) due to the versatility of possible catalyst tailoring.

Many of the different possibilities of adjusting to the proper degree of water-solubility by balancing polar and apolar properties between the aqueous and the organic phase through suitable chemical modification of the ligand or the catalyst have been proven (cf. Chapters 2, 3, 5 and 6). The status of hydroformylation (oxo synthesis) as the first, most advanced and quantitatively important application (annual output some 800 000 tons; in total since the start of the Oberhausen plant: 5 MM tons) has been described in some detail (Section 6.3.1 and [2, 14, 15]). The new process configuration, completely different from the status beforehand, confirmed the following focal points:

- the catalyst – for the first time to be supplied in water-soluble form, in satisfactory quality, and inexpensively;
- the process procedure – two-phase with phase separation during continuous operation;
- the completely new, simple circulation of the aqueous catalyst solution;

- the reactor with special mixing of two phases;
- the possibility of a particular energy balance, as a result of which the process (in the case of the hydroformylation) becomes a net steam supplier by utilizing the exothermic heat of reaction.

The reaction engineering (see Section 8.2.1) is advanced insofar that many alternative process concepts [11e, 15d] were tested during the development phase; however, only a few were pursued further in the concept stage up to the pilot plant reactor. There remained the principle of the biphasic Ruhrchemie/Rhône-Poulenc oxo process which was developed in long-term tests and protected by a matched patent strategy, as described in Section 6.1.3.

Aqueous, two-phase catalysis is also utilized industrially in a number of other processes apart from hydroformylation. The hydrodimerization of butadiene and water, a telomerization variant yielding 1-octanol or 1,9-nonanediol (cf. Section 6.9), is carried out at a capacity of 5000 tonnes per annum by the Kuraray Corporation in Japan. Rhône-Poulenc is operating two-phase, aqueous, catalytic C–C coupling processes (using TPPTS obtained from Ruhrchemie) for small-scale production of various vitamin precursors such as geranylacetones. Moreover, TPPTS-modified Ru catalysts have been proposed for the homogeneously catalyzed hydrogenation to convert unsaturated ketones into saturated ones.

Homogeneous, aqueous two-phase catalysis has also gained industrial significance in the production of the important intermediate, phenylacetic acid (PAA). The previous process (benzyl chloride to benzyl cyanide with hydrolysis of the latter) suffered from the formation of large amounts of salt (1400 kg/kg of PAA). The new carbonylation method reduces the amount of salt by 60% and makes use of the great cost difference between –CN (approx. US $ 1.4/kg) and –CO (less than US $ 0.2/kg) [16]. Finally, the Suzuki coupling of aryl halides and arylboronic acids substituting Pd/TPPMS by Pd/TPPTS catalysts deserves to be mentioned (Sections 6.6 and 6.16).

The field is in flux. As a consequence of the increased scientific study of aqueous biphasic homogeneous catalysis an increasing number of commercial applications may be expected in the future [14, 17]. Several processes are the subject of detailed surveys and reviews [17].

8.2
Improvements to Come

Further methodological progress in aqueous-phase homogeneous catalysis will comprise both the improvement of the technology and extension of the respective reactions to other applications.

8.2.1
Reaction Engineering

In Chapter 1 (Introduction) and in Section 6.1.2, the question where the aqueous-biphasic reaction takes place – and thus the basis of reactor construction, reaction engineering, and modeling – has been discussed. Today, the scientific community broadly accepts that the reaction takes place at the phase boundary or in an interfacial layer with a relatively small thickness which has been proven via process modeling on the basis of appropriate kinetic models making possible a more optimal reactor and mixing design (cf. Section 4.1). Additionally, there is much (industrially initiated) work underway to investigate the addition of counter-ions or surface-active ligands (Section 4.3) or to test measures which increase the widths of the interfacial layers or to check consequences of micelle/vesicle-forming devices (Section 4.5) (cf. [31]).

The basics of the RCH/RP oxo process as the most important process using aqueous-biphasic catalysis have been described in detail in Section 6.1.3.1. Supportive publications give additional annotations from different views [32] such as reaction control to avoid consecutive reactions [32c], alternative concepts of catalyst recycling (e.g., by extraction, absorptive/desorptive or other means, etc.) [32d–h, j, o]), micellar heterogenization (!) [32i–k], reactor or catalyst designs [32n, p, q], or with the help of investigations in micro reactors [32m]. Even for the so far not solved problem of the hydroformylation of higher alkenes such as tripropylene or 1-dodecene, hydroformylation rates, or macro-kinetic equations have been measured, and proposals for the apparative configuration have been made [33a, b].

At the present state it seems that other practised aqueous-biphasic processes such as hydrodimerization (Section 6.9) or carbonylation (Section 6.5) require different embodiments of the technology. There are numerous proposals but it is clear that any additional process step compared to the Ruhrchemi/Rhône-Poulenc version costs additional money for investment, energy, and other running costs. This is also true for thermoregulated (cf. Section 4.6.3) or micellar or microemulsion variants (see Section 4.5 and [32h, 34]), even when combined with membrane reactors (Section 4.4) [34d] or hollow nanospheres [34g]. From (experimental) studies of the RCH/RP process using various ligands (even those which are more active or more selective compared to TPPTS and which may require lower P surplusses) it is also known that “exotic” (although highly advantageous) ligands do not pay the costs for additional process steps. Next to realization may be processes using mixture gaps without additional thermal or investment expenses.

The work for alternative concepts of aqueous-phase conversions will continue.

8.2.2
Other Technologies

Theoretically, aqueous, two-phase homogeneous catalyses with their underlying principle of phase separation during continuous operation can be achieved by combining various basic and auxiliary unit operations such as extraction, extraction using solvent mixtures, reactive extraction, distillation, osmosis, reverse osmosis, phase transfer, absorption or adsorption, immobilization or partial immobilization, etc. (cf. Section 4.2). Depending on the properties – or more precisely: the property differences – of the reactants and the reaction products (e.g., solubility, polarity, boiling point), complex processes have been proposed [18]. However, every additional process step and every additional ingredient introduced into the process results in growing material losses at increased costs. For this reason, phase separation will remain the only viable low-cost option for industrial-scale applications.

Combination of aqueous homogeneous catalysis with some characteristics of heterogeneous catalysis ("supported aqueous-phase catalysis," SAPC; cf. Section 4.7) also lead to a fundamentally different technology. This variant, which is particularly seductive for scientists (because it seems logical), has indeed produced good initial results in hydrogenation and hydroformylation. However, in industrial use the problems inherent in the system need to be overcome, especially stability questions regarding the support similar to those, in its time, in the SLPC variant of the oxo process. The future has to show how far the gap between homogeneous and heterogeneous catalysis (Figure 1) may be bridged by aqueous variants of SOMC ("surface organometallic chemistry" [20]), combinations of catalytic active sites of zeolites and water-soluble precursors, colloids, clusters, or mesoporous organometals [19, 35].

A serious drawback of this special variant originates from the notorious "leaching" of the catalyst, concerning the (usually expensive) transition metal, the ligand (which, as a tailor-made compound to meet special demands, may be even more expensive), or both. Leaching normally results from the dissociation of the metal from one of the "anchoring" ligands, thus liberating the (active) molecular catalyst. But leaching may also originate from structural changes with concomitant weakening of certain bonds during the catalytic cycle, during which the coordination

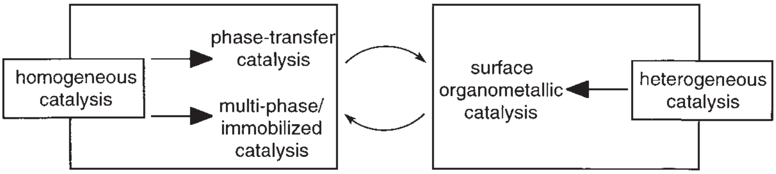


Fig. 1 Technologies at the borderline between heterogeneous and homogeneous catalysis [19].

sphere of a metal undergoes continuous changes in composition and structure (e.g., the change between tetragonal *tetra*carbonylhydridocobalt and trigonal-bipyramidal *tri*carbonylhydridocobalt during the catalytic cycle of the classical oxo process). This is immanent for hydroformylation and has so far prevented (despite some hundreds of different approaches) this immobilization by anchoring. It is – at the least – in doubt whether an aqueous technique can solve this problem.

8.2.3
Other Feedstocks and Reactions

In the case of hydroformylation, there is great interest in the use of alkenes higher than hexene. The previous technology is restricted to the use of propene and butenes (cf. Section 6.1). A reason which has been postulated for this (and other conversions) is the decreasing solubility in water with increasing number of carbon atoms in the starting alkenes and the products (Figure 2) and the associated mass-transfer problems in the two-phase reaction.

Quite obviously, the problem is solved if the reaction is carried out in a homogeneous phase using thermoreversible catalysts, and only the catalyst/product separation is carried out in the heterogeneous phase. This is the great advantage of the use of FBSs or ionic liquids and a tremendous stimulus for various *non*aqueous, “biphasic” alternatives (cf. Chapter 7). However, for various reasons, neither of the methods mentioned will be used for the hydroformylation of higher alkenes (which is under great cost pressure) or for other large-tonnage chemicals.

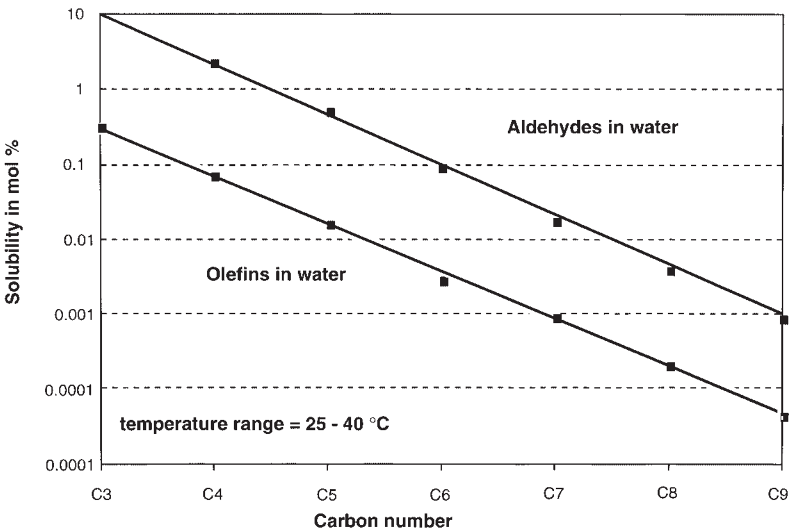


Fig. 2 Solubility of alkenes and aldehydes in water.

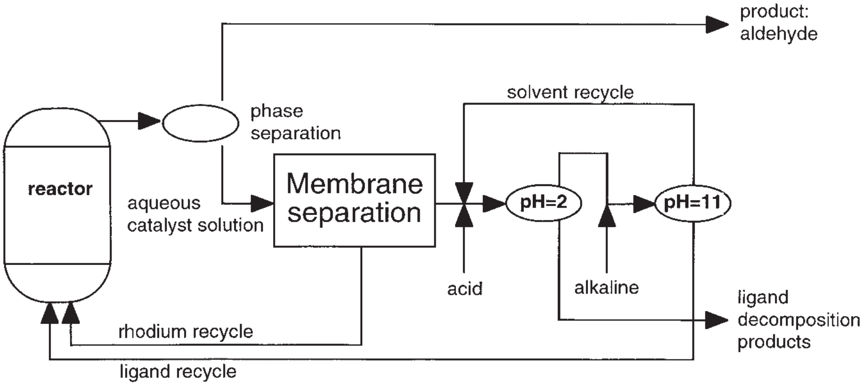


Fig. 3 The inclusion of membrane techniques in aqueous-phase processes.

On the other hand, the possibility of achieving thermoreversibility, i.e., reaction in a homogeneous phase at higher temperature and in two phases at lower temperature, by means of appropriately tailored catalysts (specifically by means of tailored ligands), appears to have better prospects. Corresponding developments by Jin and Fell (cf. Section 4.6.3) based on ethoxylated phosphines underline this elegant procedure. The advantage of this method is that the desired property, i.e., the thermoreversibility of the phase behavior, is introduced by the ligand itself and not by costly auxiliaries and additives. The ability to recycle the catalyst is therefore ensured in principle and the above warnings regarding additives and additional process steps do not apply. The above-mentioned limitations are, however, valid for solubilizing/thermoregulating additives such as poly(ethylene glycol), for polymer-bound, soluble catalysts, and for other proposals [21, 38 e, 45 f].

Combinations of thermoregulating reaction mixtures with the use of membrane processes are discussed in Sections 4.4 and 6.1.4 and [22]. Although the membrane process constitutes an additional process step, its use allows regeneration of the catalyst simultaneously and continuously and could thus be acceptable in terms of cost. The integration of membrane techniques in an aqueous-phase process is demonstrated in Figure 3 [22].

The academic world is working intensively on extending the aqueous, two-phase, homogeneously catalyzed method to reactions of other substrates. These include hydrogenations (these important reactions will have a hard time because of the dominance of *heterogeneous* hydrogenation processes; cf. Section 6.2), selective hydrogenations (in which tailor-made ligands are most likely to be able to show their full potential, which is also true for the interesting area of enantiomeric reactions; cf. Section 3.2.5 and 6.11), other carbonylations and C–C couplings (which can make direct use of the know-how developed for hydroformylation; cf. Sections 6.3 and 6.4), hydrocyanations (Section 6.7), the production of polymers (especially by ROMP reactions, cf. Sections 6.10 and 6.12), oxidations (cf. Section 6.4), hydrations and aminations, allylations (Section 6.8), etc. [17]. Some other conversions and name reactions are compiled in Table 3 in Chapter 1 (Introduction): the trend to transform other homogeneously catalyzed reactions to the aqueous-biphasic technique is unbroken. In the case of hydroformylation, work is being carried out on variants of the earlier Aldox process (simultaneous hydroformylation, aldolization, and hydrogenation, e.g. propene → 2-ethylhexanol). This work leads into the field of the less-studied multifunctional (also multicomponent) homogeneous catalysis for which there are no models, especially not in the aqueous variant. Increasing work has been done in the area of asymmetric syntheses, aiming mainly of fine chemicals as intermediates for pharmaceuticals or for agricultural purposes (cf. Section 6.11) [34 d, f, 36 a, i, 37 c, 38].

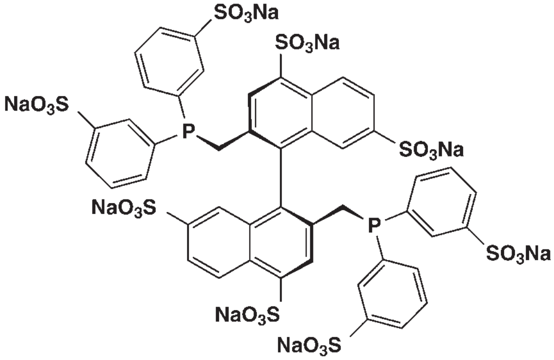
Although of great scientific attractivity and of importance for fine chemicals, the industrial implementation of these developments will depend much on the additional expense of the tailored, water-soluble catalysts being compensated for by greater activity and selectivity (including enantiomeric selectivity) and by the simple process configuration of the aqueous variants which can be achieved by their use. Particularly in the case of catalyst and/or ligand mixtures, this is often questionable. New approaches to special modifications of water-soluble ligands may be helpful, as well as chemical engineering knowledge of the mechanism in the presence of water, as the key to catalyst design, activity, performance, recycle, and lifetime/reactivation.

8.3
Focal Future Developments

Within only 20 years of commercial application of aqueous, two-phase homogeneous catalysis, over four million tonnes of building blocks have been produced. Nevertheless, the state of development and the degree of maturity are such that the following further developments may be expected in due course.

The technique of aqueous catalytic reactions has had such an impact on the field of more general two-phase reactions that scientists have now also proposed and tested other solutions. “Fluorous” systems (FBS, perfluorinated solvents; cf. Section 7.2) and “nonaqueous ionic liquids” (NAILs, molten salts; cf. Section 7.3) meet the demand for rapid separation of catalyst and product phases and, owing to the thermoreversibility of their phase behavior, have advantages in the “homogeneous” reaction and the “heterogeneous” separation. However, it is safe to predict that the specially tailored ligands necessary for these technologies will be too expensive for normal applications. Compared to the cheap and ubiquitous solvent water, with its unique combination of properties (cf. Table 1), other solvents may well remain of little importance, at least for industrial applications. Other ideas are mentioned in Section 7.6.

Until now, TPPTS has proven itself the standard ligand for aqueous two-phase systems. High water-solubility (approx. 1.1 kg/L) and ready availability (sulfonation of TPP) are advantages which favor industrial use. The high level of scientific interest has led to the development of a series of other ligands which are able to increase the activity of the Rh catalysts that they are used to modify while retaining sufficient solubility in water. However, the fact that they enable the amount used to be decreased and the *n*/*i* ratio of the aldehyde mixtures produced to be increased [23] has not been sufficient to compensate for their high costs in everyday operation. The situation may be different for enantiomeric reactions (cf. Section 3.2.5). A particularly promising candidate for aqueous Ph-catalyzed hydroformylation, BINAS-8 (**1**) [24], has four sulfo groups per phosphorus atom despite being a diphosphine (compared with three in the case of TPPTS).



Exotic ligands, e.g., dextrins, supramolecular compounds, and templates are attractive for academic applications in aqueous homogeneous reactions and can be expected to gain much publicity. However, so far there is no experience of their practical use so that questions of long-term stability, recycling, and dependence on parameter changes and also of toxicity, environmental behavior, costs, etc., remain to be solved. The cost of such ligands need not be prohibitive (as when the "expensive" rhodium is used as the central atom in oxo catalysts) if virtually loss-free recycling of the ligands as well as the central atoms can be guaranteed. Interest is concentrated especially on the dextrins as potential inexpensive candidates. The search for new ligands is one of the focal points for the occupation with aqueous-phase organometallic catalysis, and a lot of exiting results emerged from that work, especially as far as ligands for asymmetric reactions are concerned (see Section 3.2). Especially diphosphines are the backbone for respective experimental work, partly in combination with special reaction conditions such as micellar circumstances, thermoregulated prerequesites, etc., but newly developed ligands have also been described [36]. Because of their relation to TPPTS as the most used ligand (specially the different solubility properties or their tensioactive behavior) a certain focal point is still the testing of TPPMS and TPPDS [37]. For example, the addition of TPPDS to TPPTS acts as a modifyer and dramatically increases the regioselectivity of alkene hydroformylation [37b].

Ligand *mixtures* with tailored activities (for example TPP as a "promoter ligand" and additive to TPPTS [25]) are attractive for scientific work and also enable particular effects to be achieved. Mixtures might be controlled in academic work. However, for industrial use it must be ascertained that *all* catalyst components can be recirculated simultaneously and in the same way with little expense, which can virtually never be ensured in the case of complicated mixtures. The same applies to the use of soluble polymers (both as phase separation agents and as ligands; cf. Section 7.6 and [26]).

Apart from rhodium, interest so far concentrates on palladium and ruthenium (cf. Section 3.1), and in special cases on rhenium (cf. Section 6.4.3) or the lanthanides (Section 3.1.2). Besides these recently mentioned central atoms [39], other elements of interest have been described, i.e., osmium [37d, 40], tungsten [41], or – interestingly – indium [42]. Bimetallic catalysts may be of interest for special reactions such as hydroaminomethylations (Rh/Ir; [43a]) or the hydrogenation of aromatic nitro compounds (Pd/Pt; [43b]). For hydroformylations no other central atom (cobalt or central atom mixtures such as Pt/Sn) has so far been able to qualify for use in the industrial aqueous, biphasic oxo process. Should good results be obtained using central-atom mixtures in experiments on multifunctional, aqueous homogeneous catalysis, again the problem of simultaneous recycling of both components must be overcome. However, the prospects for industrial use of such mixtures are poor for the reasons stated.

The addition of additives has frequently been tested in scientific laboratories sometimes not without success. The patent literature also lists a whole series of additives (cf. Sections 4.3 and 6.1.1; recent publications [34i, 36a, 38a, 44]). Although these additives are interesting in basic research, in industrial practice detailed engineering and cost sutdies have resulted in none of them being accepted for economic use. The same applies to special technical solutions, e.g., the use of ultrasonic reactors to solubilize the reactants [27]. There is still some research work for the aqueous-phase conversion of higher substrates (e.g., higher alkenes by hydroformylation; cf. Figure 2) but economic solutions are not in sight [32a, n, 34i, 45].

The level of scientific work on supercritical CO_2 ($scCO_2$) has increased and overlaps with the properties of media for FBSs [28]. However, new and specific process variants with disadvantageous properties arising from perfluorinated compounds are no longer introduced by the solvents (e.g., $scCO_2$), but only by the ligands present in catalytic amounts. In these developments too, simultaneous catalyst regeneration with the aid of membrane separation is conceivable.

The environmental aspects of the aqueous biphasic processes have been intensively studied and discussed taking Ruhrchemie/Rhône-Poulenc's oxo process as an example of economic relevance. Homogeneously catalyzed aqueous processes are particularly environmentally friendly [15 b]. According to Sheldon [29] the "*E*-factor" of the aqueous oxo process is between 0.04 and 0.1, depending on the way in which the by-products are considered. It thus falls into the product category of "oil chemicals", i.e., this is one of the production operations which, owing to their size and importance, are both economic and very environmentally sensitive. Other oxo processes with *E*-factors $\gg 0.1$ correspond to the category of "bulk chemicals." The environmental friendliness expressed by a favorable *E*-factor of the new biphasic process shows up in many places: the high selectivity of the chemical reaction (and thus low by-product formation), the low capital costs, the great reduction in amounts of waste gas and waste water (in the case of water, by a factor of 70) and the energy consumption (the oxo process is changed from a steam consumer to a net steam supplier, and the power consumption is more than halved), etc. [2 a].

Further progress is expected from new developments and combinations of processes. Thus, it would be possible to make the disposal of the gaseous (and highly pure) waste gas streams (residual propane content of the propylene feed) cost-effective and a source of electric power by connection to novel, compact, membrane fuel cells. Potential synergisms would also occur in the operating temperature of the cells (medium-temperature cells at 120 °C using the residual exothermic heat of reaction from the oxo reaction), the membrane costs by means of combined developments (e.g., for membrane separations of the catalysts [22]), and also in the development of the "zero-emission" automobile by the automotive industry. The combination of hydroformylation with fuel cells would further reduce the *E*-factor – thus approaching a "zero-emission chemistry."

Moreover, examination of the Sheldon *E*-factors convincingly demonstrates the practicability of this concept as compared with Trost's [30] enigmatic "atom economy" which is concerned with esoteric examples of little relevance. Some people believe that the newer version of the "atom economy", justifiably emphasizing homogeneous catalysis with exotic examples of "the myriad of substances that are required to serve the needs of society" (!) [30 b], are better founded.

Homogeneous catalysis has never been the prototype of a "heat-and-beat" technology in chemistry. Given the opportunity of quickly and easily separating the homogeneous catalyst from the reaction products in an aqueous process, it will be even more interesting (and more feasible) to make use of all the intrinsic features of homogeneous catalysis. This applies particularly to the possibility of tailoring the catalyst by varying the central atom, the ligand, or the phase in which it is used.

In this sense, homogeneously catalyzed aqueous syntheses will lead to an even more sophisticated field of chemistry under the most environmentally friendly conditions.

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Aqueous-Phase Organometallic Catalysis, Second Edition
Edited by Boy Cornils and Wolfgang A. Herrmann

ISBN: 3-527-30712-5