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ISBN: 3-527-30796-6

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WILEY-VCH Verlag GmbH & Co. KGaA

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Cover Picture
The front cover is showing a Kabuki actor dressed like a devil, drawn by Sharaku. Nickel was first isolated in 1751 from an ore referred to as ''devil Nick copper''. Miners named the ore in that way because it resembled copper ore, but did not yield their objective copper. (Old Nick, informal the devil; Satan, from Webster's Unabridged Dictionary). Nickel was named after its accursed nickname. Reproduced with permission of the Tokyo National Museum.

Library of Congress Card No.: Applied for
British Library Cataloging-in-Publication Data: 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 Asco Typesetters, Hong Kong
Printing Strauss GmbH, Mörlenbach
Bookbinding J. Schäffer GmbH, Grünstadt

ISBN-13 978-3-527-30796-8
ISBN-10 3-527-30796-6

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Preface

The monographs, *The Organic Chemistry of Nickel*, *Volume 1* (1974) and *Volume 2* (1975), which were written by P. W. Jolly and G. Wilke, have long been the "Bible" for organonickel chemists. Unfortunately, however, during the past three decades no books have been published specializing in organonickel [1], whilst in sharp contrast there has been a flood of monographs focusing on organopalladium [2]. As a measure of academic activity, Figure 1 compares the number of publications in journals and letters relating to Ni, Pd, and Pt during the past four decades (SciFinder, searched on 5th March, 2004). Within the last decades, although academic interest in organonickel has clearly fallen, it is still comparable to that in organopalladium. By contrast, during the last three years in industry, all of the group 10 transition metals have vied one with another, as demonstrated by the number of patents relating to Ni, Pd, and Pt (1139, 1173, and 1251, respectively in 2001; 1319, 1320, and 1469, respectively in 2002; and 1268, 1208, and 1481, respectively in 2003).

Nickel and palladium were born under diametrically opposite stars – nickel was

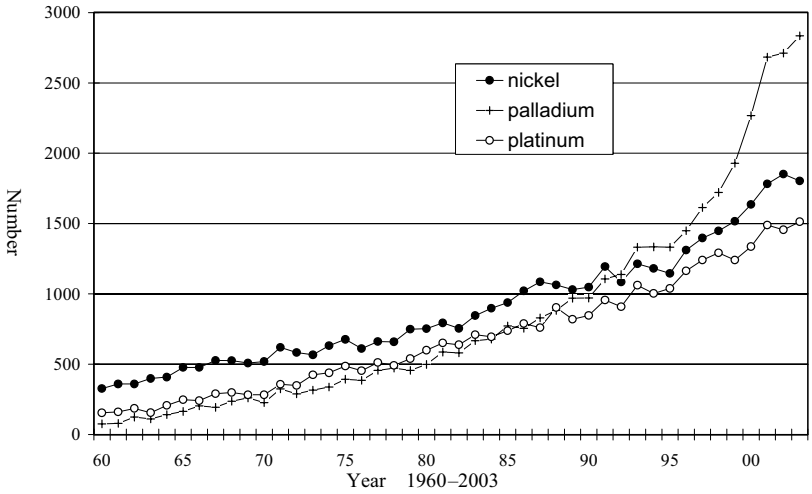

Fig. 1. The number of publications in journals and letters (SciFinder, 5, March, 2004).

Fig. 2. (a) A Kabuki actor dressed like a devil, drawn by Sharaku (front cover). Reproduced with permission of Tokyo National Museum. (b) One of wooden images of Buddhist saints (a *Bosatsu* who is a Buddhistic goddess of wisdom) decollating the wall of Byodo-in, Uji, Japan. Reproduced with permission of ©平等院, 1999.

born poor, and palladium to wealth. Nickel was first isolated in 1751 by a Swedish mineralogist, A. F. Cronstedt (1722–1765), from an ore referred to as ''devil Nick copper''. Miners named the ore in that way because it resembled copper ore, but did not yield their objective copper. (Old Nick, *informal* the devil; Satan, from *Webster's Unabridged Dictionary*). Nickel was named after its accursed nickname (Fig. 2(a)), whereas palladium was discovered in 1803 in South African crude platinum ore. Palladium was named after *Pallas*, a name associated with Greek mythology, the goddess of wisdom (Fig. 2(b)). Nickel has transmigrated repeatedly, and today – as a result of many studies and discoveries – has been re-incarnated in the shape of the goddess of wisdom.

The advantage of using Ni as a catalyst is its low cost, which is about one-tenth to one-fiftieth that of Pd and Pt (see Table 1). However, certain disadvantages of Ni and its derivatives (e.g., $Ni(CO)_4$[3], Ni_3S_2) are associated with toxicity, human carcinogenesis, and skin allergies.

I feel that a book dealing with recent developments in organonickel chemistry would be beneficial to both organometallic chemists and synthetic organic chemists, alike. This book covers many discoveries which have been made during the past three decades, and I am very pleased to have received authoritative reviews of all chapters from experts working at the forefront of organonickel chemistry. These colleagues are also active researchers in the field of organopalladium chemistry, and recognize that these two transition metals show many similarities – and indeed many dissimilarities; for example, Ni forms $Ni(CO)_4$, while Pd never forms

Tab. 1. Price comparison of Ni, Pd, and Pt and their dichlorides (Aldrich Catalog, 2004).

	Ni slug (99.995) [a, b]	***Pd slug (99.95)*** [a, b]	***Pt slug (99.99)*** [a, b]
EU g^{-1}	5.4	62.9 [11.6]	83.1 [15.4]
EU mol^{-1}	317	6693 [21.1]	16 212 [51.1]
	$NiCl_2$ (99.99)	***$PdCl_2$ (99.999)***	***$PtCl_2$ (99.99)***
EU g^{-1}	26.0	120.0 [4.6]	250.8 [9.6]
EU mol^{-1}	3370	21 277 [6.3]	66 713 [19.8]

1 euro (EU) = 130 Yen.
[a] Figures in parenthesis refer to the purity in %.
[b] Figures in square brackets refer to price rates relative to nickel compounds.

$Pd(CO)_4$; and η^3-allylnickel is nucleophilic, while η^3-allylpalladium is electrophilic, and so on. Consequently, comparisons made sporadically in this book between Ni and Pd may help the reader to understand more deeply the characteristics of these metals.

Finally, I would like to acknowledge the assistance of those reviewers who checked the content of each chapter to minimize errors and enhance the book's academic value. The project of publishing this book in its present form began with an invitation from Wiley-VCH, and I would like also to acknowledge the initiative of Dr. Elke Maase and the cooperation of Carola Schmidt in bringing the book to fruition. My acknowledgments are also extended to my wife, Keiko, to my secretary, Kiyomi Nishina, and also to my colleagues, Dr. Shuji Tanaka and Dr. Masanari Kimura for their help.

Yoshinao Tamaru
December 2004

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Abbreviations

⇢	Multi-step reactions
□	Vacant site on transition metal
1°, 2°, 3°	Primary, secondary, tertiary
AcO^-	Acetate ion
acac	Acetylacetonate
AO	Atomic orbital
aq	Aqueous
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
bpy	2,2′-Bipyridyl
Bu	*n*-Butyl
Bz	Benzoyl; PhCO
Bzl	Benzyl; $PhCH_2$
CAN	Ceric ammonium nitrate
cat	Catalyst
cat M	Catalytic reaction with respect to the Metal (over reaction arrows)
CN	Coordination number
CHD	Cyclohexadiene
COD (cod)	1,5-Cyclooctadiene (when used as a ligand)
COT (cot)	1,3,5,7-Cyclooctatetraene (when used as a ligand)
CDT (cdt)	1,5,9-Cyclododecatriene (when used as a ligand)
Cp*	Pentamethylcyclopentadienyl; C_5Me_5
Cp	Cyclopentadienyl; C_5H_5
Cy (*c*-Hex)	Cyclohexyl
Δ	Crystal field splitting
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	Diisobutylaluminum hydride
δ^+, δ^-	Partial positive, negative charge
diglyme	Diethylene glycol dimethyl ether ($MeOCH_2CH_2OCH_2CH_2OMe$)
DMA	*N*,*N*-Dimethylacetamide
DMAD	Dimethyl acetylenedicarboxylate
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide

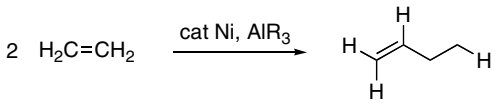
DMG	Dimethyl glyoxime
DMI	1,3-Dimethylimidazolidinone
DMPE (dmpe)	1,2-Bis(dimethylphosphino)ethane (when used as a ligand)
DMSO	Dimethyl sulfoxide
d^n	Electron number in *d* orbital
DPPB (dppb)	1,4-Bis(diphenylphosphino)butane (when used as a ligand)
DPPE (dppe)	1,2-Bis(diphenylphosphino)ethane (when used as a ligand)
DPPEN	cis-1,2-Bis(diphenylphosphino)ethylene
DPPF (dppf)	1,1′-Bis(diphenylphosphino)ferrocene (when used as a ligand)
DPPP (dppp)	1,3-Bis(diphenylphosphino)propane (when used as a ligand)
d_σ, d_π	*d* Orbital with σ, π symmetry
e	Electron (as in 18e rule)
ee	Enantiomeric excess
en	Ethylenediamine; $H_2NCH_2CH_2NH_2$
Eq.	Equation
equiv.	Equivalent
Et	Ethyl
η	Hapticity in π-bonding ligands
$HBpz_3$	Tris (pyrazolyl)borate
HOMO	Highest occupied molecular orbital
HMPA	Hexamethylphosphoric triamide
c-Hex	Cyclohexyl
Hex	*n*-Hexyl
i-Bu	*iso*-Butyl
i-Pr	*iso*-Propyl
IR	Infrared
κ	Hapticity in σ-bonding ligands
KHDMS	Hexamethyldisilazane potassium salt ($KN(SiMe_3)_2$)
L	Generalized ligand a 2e neutral ligand (e.g., PPh_3, pyridine)
LUMO	Lowest unoccupied molecular orbital
μ	Descriptor for bridging
m-	Meta
Me	Methyl
MAO	Methylaluminoxane: -$[Al(Me)O]_n$-
ML_n	Generalized metal fragment with n ligands (L)
MO	Molecular orbital
MS	Molecular sieves
Ms	Methanesulfonyl: $CH_3SO_2^-$
NBD (nbd)	Norbornadiene (when used as a ligand)
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Np	Neopentyl
Nu	Nucleophiles
OAc^-	Acetate anion

o-Tol	*o*-Tolyl: 2-methylphenyl
Ph	Phenyl
phen	1,10-Phenanthroline
pin	Pinacolate: $OCMe_2CMe_2O$
PFS	*p*-Fluorostyrene
PMB	*p*-Methoxybenzyl: 4-$CH_3OC_6H_4CH_2$-
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
i-Pr	*iso*-Propyl
pro-R, or -*S*	Stereochemical descriptor
Py (py)	Pyridine (when used as a ligand)
R	Alkyl group
RCM	Ring-closing metathesis
ROMP	Ring-opening metathesis polymerization
Sia	Siamyl: 1,2-dimethylpropyl
sec-Bu	secondary Butyl
TASF	Tris(diethylamino)sulfonium fluoride
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyl(dimethyl)silyl
TBDPS	*tert*-Butyldiphenylsilyl
t-Bu	tertiary Butyl
TDMPP	Tri(2,6-dimethoxyphenyl)phosphine
Tf	Trifluoromethanesulfonyl
TFP (tfp)	Tri(2-furyl)phosphine (when used as a ligand)
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Tri(isopropyl)silyl
TMEDA (tmeda)	*N*,*N*,*N*,*N*-Tetramethyl-1,2-diaminoethane (when used as a ligand)
TMM	Trimethylenemethane
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
Ts	Tosyl; *p*-toluenesulfonyl; *p*-$CH_3C_6H_4SO_2$
TsOH	*p*-Toluenesulfonic acid; *p*-$CH_3C_6H_4SO_3H$
X	Generalized a 2e anionic ligand (e.g., Cl^-)

1
Introductory Guide to Organonickel Chemistry

Yoshinao Tamaru

Most organic chemists may be embarrassed and intrigued when they encounter the type of reaction described in Eq. (1.1). In organic chemistry, most C–C bonds are formed or cleaved by making use of, more or less, polarized functional groups, for example, C=O, C–O, and C–halogens. Ethylene is lacking in these ordinary functionalities and has only the double bond as a reactive group. Consequently, these chemists may ask themselves: "What is happening here? Does the process proceed via a radical reaction or a [2+2]cycloaddition followed by ring opening?"



(1.1)

This reaction, which marks the cornerstone for the flourishing development of transition metal-catalyzed reactions and their use in industry, was discovered by chance – as with many other great discoveries – by Ziegler (who was awarded the Nobel Prize for chemistry in 1963), Wilke, and their coworkers while investigating the production of polyethylene and ethylene oligomers (C_6–C_8) promoted by organolithiums and organoaluminums [1]. These investigators found that 1-butene was obtained exclusively instead of the expected ethylene oligomers, but also noted that contaminants such as nickel and acetylene changed the course of the reaction (today these are referred to as "nickel effects"; see Section 1.6.3 and Schemes 1.26 and 1.27). At the same time, these researchers realized the uncovered potential of transition metal catalysis in organic transformations and, after conducting many tests with a wide range of transition metals, they established the protocol of low-pressure polyethylene production based on the titanium-alkylaluminum catalytic system.

The aim of this chapter is to outline the basic concepts in the coordination chemistry as well as the elementary processes and basic reaction patterns in nickel-catalyzed synthetic reactions. Together, these may help the reader to understand the content of the following chapters, which describe much more sophisticated reactions than that shown in Eq. (1.1).

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ISBN: 3-527-30796-6

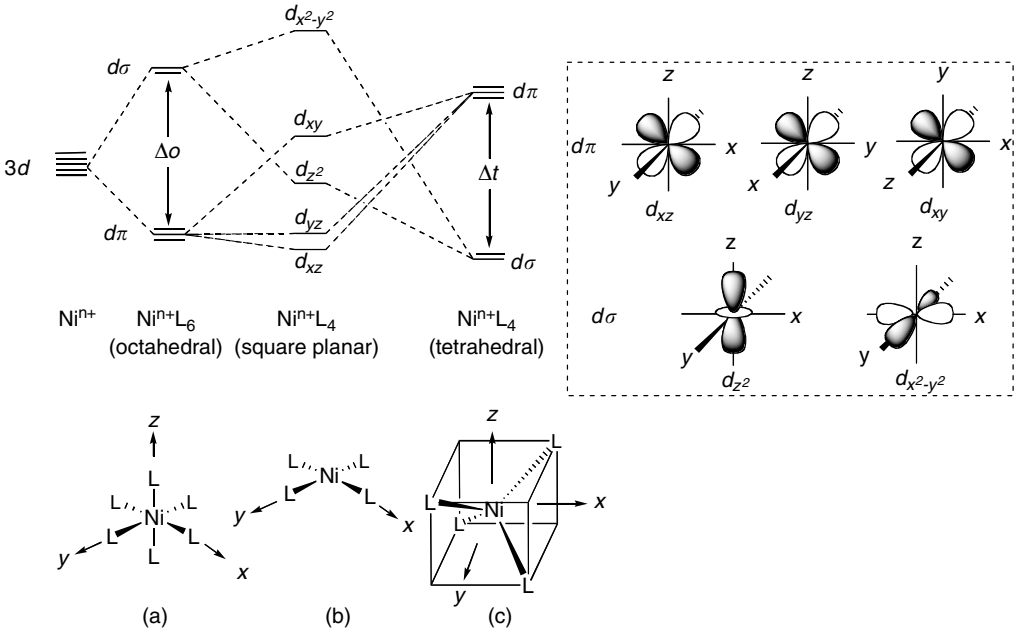


Fig. 1.1. Schematic presentation of the *d* orbital splitting in the crystal fields of an octahedral (a), a square planar (b), or a tetrahedral (c) environment.

1.1 The Crystal Field

If one imagines a nickel atom or its ions isolated in space, it has the five degenerated *d* orbitals ($dxy, dyz, dxz, dx^2\text{-}y^2$, and dz^2), all lying at the same energy level. As six ligands (represented here with L, such as Cl^-, NH_3, and H_2O) approach the nickel from the $\pm x, \pm y$, and $\pm z$ directions to form an octahedron, the *d* orbitals split into two groups, $d\sigma$ and $d\pi$ (Fig. 1.1(a)). The orbitals of $d\sigma$ group ($dx^2\text{-}y^2, dz^2$, the orbitals with the σ bonding character) that point toward the L groups are greatly destabilized by electrostatic repulsion and move to a higher energy position. The $d\pi$ group orbitals (dxy, dyz, dxz, the orbitals with the π bonding character), on the other hand, are less destabilized because these orbitals point away from L. The magnitude of the energy difference (designated by Δ and called the "crystal field splitting" or the "ligand field splitting") between the $d\sigma$ and $d\pi$ groups depend on the charges on Ni and L and the distance between them.

If the two Ls move away along the z axis, the other four Ls on the $\pm x, \pm y$ axes will move closer to the central Ni, and this results in a square planar complex. The expected energy change of the *d* orbitals is shown in Figure 1.1(b), where the orbitals that possess the x and y components ($dxy, dx^2\text{-}y^2$) rise, while those possessing the z component (dz^2, dxz) fall. The energy diagram of a tetrahedral complex is

shown in Figure 1.1(c), where those orbitals $d\sigma(dz^2, dx^2\text{-}y^2)$ that spread along x, y, and z axes are apparently away from L and stabilize, whereas $d\pi$ are all in touch with L and destabilize. The relative energy levels of $d\sigma$ and $d\pi$ orbitals are reversed between the octahedral and tetrahedral complexes.

The energy levels in Figure 1.1 are drawn deliberately for all the octahedral, square planar and tetrahedral complexes to have the identical energy to that of the isolated Ni(0), the orbitals of which are fully occupied with 10e. For d^8 Ni(II), a square planar complex is likely most favored, as the 8e occupy from the most stable d_{xz} up to the d_{xy} orbitals, leaving the most unstable $dx^2\text{-}y^2$ orbital unoccupied. This is in accord with the structures that many Ni(II) complexes display (e.g., $Me_2Ni(PR_3)_2$, $[Ni(CN)_4]^{2-}$).

1.2
Nickel has Wings: The Mond Method

In the industrial process of Na_2CO_3 production (the Solvay soda process, 1865), erosion of the nickel bulb of CO_2 lines in an unduly short time period was a serious problem. Mond, in 1890, discovered that metallic nickel, although being a very hard solid with a high melting point (1455 °C), reacted with CO (a small contaminant of CO_2 in the above process) to form gaseous $Ni(CO)_4$ (b.p. 43 °C, extremely poisonous) at ambient temperature. He also found that $Ni(CO)_4$ decomposed at over 180 °C, depositing Ni metal. This unique reaction of Ni and CO has been utilized even today as the industrial refining method of metallic nickel (the Mond method). In fact, nickel is the only metal that reacts with CO at room temperature and at atmospheric pressure of gaseous CO [2]. Having been greatly impressed by the demonstration of the above transformations, one of Mond's contemporaries noted, philosophically, that "Mond gave wings to a metal" [3].

1.3
The Ligand Field

Why does nickel react with CO so easily? Why is $Ni(CO)_4$ formed selectively, and not $Ni(CO)_3$ or $Ni(CO)_5$? To address this question, the idea of the ligand field is useful. The model makes up matching pairs between the nine atomic orbitals of Ni (the five 3*d*, the one 4*s*, and the three 4*p* atomic orbitals) and the molecular orbitals of CO. The most straightforward – but somewhat approximate – explanation is as follows. The C and O atoms of CO hybridize to make two *sp*-orbitals. One electron each of C and O atoms is then used to make a *sp*-σ bond, and the two sets of lone pair electrons of C and O reside on their *sp*-hybridized orbitals. The one electron on each of the 2*p* orbitals of C and O forms a π bond, and the two 2*p* electrons on O interact with the empty 2*p* orbital of C to form a charged π bond (Fig. 1.2(a)). On the other hand, the one 4*s* and the three 4*p* orbitals of an Ni mix to make up the four empty sp^3-hybridized orbitals. The combination of the four empty sp^3 orbitals

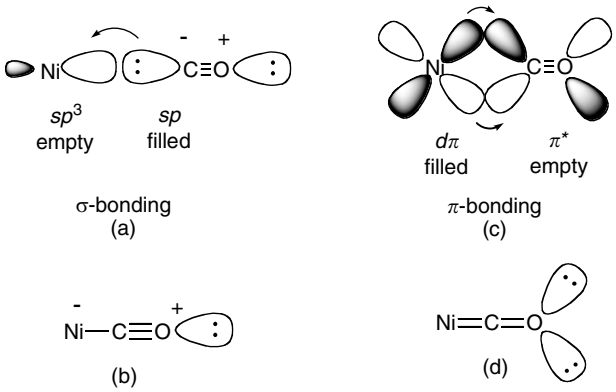


Fig. 1.2. The σ (a and b) and π-bonding interaction (c and d) between an Ni and CO.

of the Ni and the four sets of the *sp* lone pair electrons on the C of four CO provides the four bonding and the four anti-bonding molecular orbitals of the Ni–CO bond (σ and σ^* orbitals; Fig. 1.3). This process is similar to producing tetrahedral methane (CH_4) from the sp^3-hybridized C and the 1*s* orbitals of four hydrogen atoms. The difference between these reactions is that in the case of methane, the carbon bears four valence electrons and each hydrogen one valence electron, and these form the four *covalent* bonds. In contrast, in the case of $Ni(CO)_4$ the nickel bears no valence electrons in the sp^3 orbitals: the two electrons of the Ni–CO σ-bond are donated from the C; hence the σ-bond should be ionic in nature (Ni^-–C) as depicted in Figure 1.2(b).

In addition to the σ-bonding, there operates another bonding mechanism, so-called ''back bonding'' or ''back donation''. As is illustrated in Figure 1.2(c), the π^* orbital of the CO has a proper symmetry with the $d\pi$ atomic orbital of the Ni, and these two interact to each other to make up a new π-bonding orbital, lower in energy than the $d\pi$ atomic orbital (and at the same time, a π^* anti-bonding orbitals higher in energy). In the case of $Ni(CO)_4$, the three π-bonding and the three π^*-anti-bonding molecular orbitals form (Fig. 1.3). Owing to mismatch of symmetry, the $d\sigma$ orbitals cannot interact with the $p\pi^*$ orbital of CO and so remain at the same energy level. The π^* orbital of the CO is empty and the $d\pi$ orbital of an Ni is filled, so the *d* electrons of the Ni flow into the π^* orbital of CO (*back donation*). This mechanism operates so effectively that CO is sometimes called a ''π-acid ligand''. In all, the donation of 2e from the C atom (σ-bonding) and the back donation of 2e from the Ni (π-bonding) result in the formation of a formal Ni=C double bond (Fig. 1.2(d)). The reader should note that each CO possesses two π^* orbitals, which makes CO as a strong π-acid ligand. For clarity, only one of the two π^* orbitals is depicted in Figure 1.2(c).

The back donation significantly perturbs the electronic structure of CO, filling electrons in the anti-bonding π^* orbital and rendering the bond long and weak. In

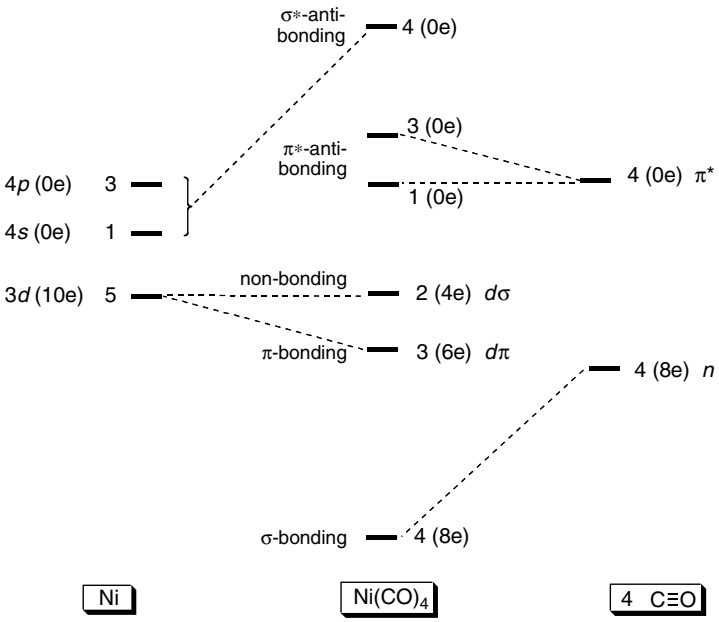


Fig. 1.3. Orbital interaction between an Ni(0) and four CO that forms 4σ bonding (8e), 3π bonding (6e) and two non-bonding (4e) molecular orbitals. All anti-bonding orbitals are empty. Values indicated beside the energy levels refer to the number of the orbitals.

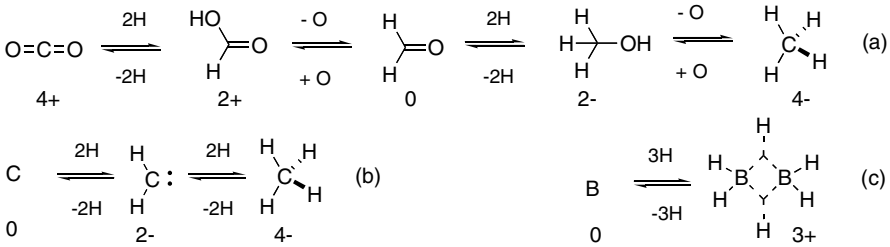
this way, in general, the ligands coordinating to metals can be polarized and elongated, and therefore activated toward chemical reactions, the σ and π bonds in the ligands can be weakened or broken, and chemical bonds can be made or broken within and between different ligands. This rich pattern of the activation of ligands is a characteristic feature of organometallic chemistry.

Figure 1.3 illustrates how the whole system, composed of an Ni (left) and four CO (right), is energetically stabilized by forming tetrahedral $Ni(CO)_4$. That is, all the four sets of lone pair electrons on the C of CO are accommodated in the low-lying sp^3 σ-bonding orbitals, and the 6e of 10*d* electrons of an Ni are in the low-lying π-bonding orbitals.

The other sets of hybridization of the one 4*s* and the three 4*p* of an Ni, for example, $(sp^2 + p)$ forming 3 sp^2 and 1*p* atomic orbitals, are apparently more unfavorable than the sp^3 hybridization, because a σ-bond makes a stronger bond and is more stable in energy than a π-bond – that is, the more the number of σ-bonds the more stable the complexes. This is the reason why $Ni(CO)_4$ is formed selectively, and not $Ni(\sigma\text{-}CO)_3$ or $Ni(\sigma\text{-}CO)_3(\pi\text{-}CO)$. Then why is $Ni(CO)_5$ not formed? This is simply because an Ni is already saturated and no atomic orbitals are available to interact with the fifth CO.

1.4
The Formal Oxidation Number

It is sometimes very useful to assign a formal oxidation number to carbon and some heteroatoms that are frequently outside the octet rule, such as N, P, and S in organic molecules. For this, we impose an ionic model on the compound by artificially disconnecting it into an ion pair. In doing this, each electron pair in any bond is assigned to the most electronegative of the two atoms that constitute the bond. Some examples are shown in Scheme 1.1. The oxidation number of carbon ranges from 4− (e.g., methane) to 4+ (e.g., carbon dioxide). All the reactions in which the oxidation number is increased (making bond with oxygen or electronegative elements or losing hydrogen) are oxidations. The reverse processes are reductions. So, as shown in the Eq. (a) of Scheme 1.1, each of all the steps from carbon dioxide to methane is 2e reduction, and each of the reverse processes from methane to carbon dioxide is 2e oxidation.



Scheme 1.1. The count of the formal oxidation number. Figures indicate the formal oxidation number of carbon (Eqs. (a) and (b)) and boron (Eq. (c)).

In organometallic chemistry, a confusing matter arises because most metal elements are less electronegative (or more electropositive) than H (Table 1.1). Hence, as shown in Eqs. (b) and (c) of Scheme 1.1, in contrast to the formation of methylcarbene and methane from atomic C and 2H and 4H are 2e and 4e reduction, respectively, the formation of BH_3 from an atomic B and 3H is 3e oxidation, as we disconnect BH_3 as one B^{3+} and three H^-, that is, bond formation with H is reduction for an C, but it is oxidation for an B. The dotted trigonal line of B_2H_6 in Eq. (c) of Scheme 1.1 indicates that the three atoms, B, H, and B, form a three-center–two electron bond.

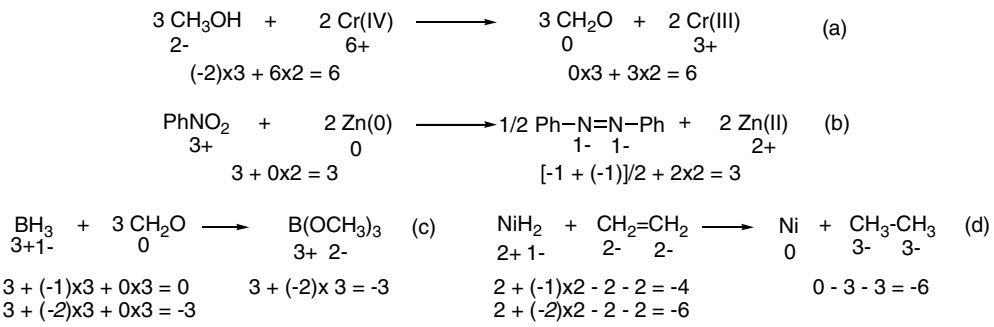
The idea of oxidation number provides a convenient way to determine the stoichiometric amounts of the reagents required in a variety of oxidation and reduction reactions. For example, as is shown in Eq. (a) of Scheme 1.2, for the oxidation of an alcohol with chromium(VI) reagents, balancing the formal oxidation number of the starting materials and the products shows that 2/3 mol of Cr(VI) are necessary to oxidize 1 mol of an alcohol to an aldehyde or a ketone. For the reduction of nitrobenzene to azobenzene with zinc dust under alkaline conditions, the amount of

Tab. 1.1. Physical properties of Group 8, 9, and 10 transition metal elements.

55.845 6, 3, 2, 0, −2 1.8 **26** **Fe** $[Ar]3d^64s^2$	**58.933** 3, 2, 0, −1 1.9 **27** **Co** $[Ar]3d^74s^2$	**58.693** 4, 3, 2, 1, 0, −1 1.8 **28** **Ni** $[Ar]3d^84s^2$
101.07 8, 6, 4, 3, 2, 0, −2 – **44** **Ru** $[Kr]4d^75s^1$	**102.906** 5, 4, 3, 2, 1, 0 2.3 **45** **Rh** $[Kr]4d^85s^1$	**106.42** 4, 2, 1, 0 2.2 **46** **Pd** $[Kr]4d^{10}$
190.23 8, 6, 4, 3, 2, 0, −1 – **76** **Os** $[Xe]5d^66s^2$	**192.217** 6, 4, 3, 2, 1, 0, −1 2.2 **77** **Ir** $[Xe]5d^76s^2$	**195.078** 4, 2, 0 2.3 **78** **Pt** $[Xe]5d^96s^1$
relative atomic mass oxidation state electronegativity **atomic number** electron configuration	Electronegativity: H (2.2), Li (1.0), B (2.0), C (2.6), N (3.0), O (3.4), F (4.0), Na (0.9), Mg (1.3), Al (1.6), Si (1.9), P (2.2), S (2.6).	

Zn dust is very crucial (Eq. (b) in Scheme 1.2). Loading of the excess amount of Zn can cause over-reduction of azobenzene to *N*,*N*′-diphenylhydrozine. One mole of nitrobenzene produces 0.5 mol azobenzene; hence the total formal oxidation number of azobenzene should be divided by 2. Balancing the oxidation numbers of the starting material side and the product side indicates that 2 mol of Zn dust is the exact amount required to perform the reaction successfully.

For the hydride reduction, however, special care is needed, since – as is apparent



Scheme 1.2. Balancing of the formal oxidation number in oxidation and reduction reactions. Special care is needed when balancing formal oxidation numbers for hydride reduction reactions.

from Eqs. (c) and (d) – the formal oxidation number of the hydrogen on C and metals is counted in a different way: H^- to metals (e.g., BH_3) and H^+ to C. Accordingly, simple summation of the oxidation numbers results in a higher oxidation number being given to the reactant side by the number of hydrogens (Scheme 1.2(b)). For the hydride reduction, we should regard a hydride as a 2e donor, since H^- changes to H^+ in the reaction. The borohydride reduction (Eq. (c)) is not accompanied by the change of the oxidation number of the metal. On the other hand, the reduction with nickel hydride is accompanied by the change of the oxidation number of the metal (Eq. (d)). Even for such cases, the same idea applied to Eq. (c) holds.

1.5 The 16- and 18-Electron Rule

As the octet rule is a useful guide in organic chemistry (filling all the atomic orbitals of carbon with electrons: $2s^2 2p^6$), the 16- or 18-electron rule is useful in organonickel chemistry (filling all the atomic orbitals of an Ni with electrons: $3d^{10} 4s^2 4p^6$). The tendency of transition metals to form complexes in which the metal has an effective atomic number corresponding to the next higher inert gas has long been recognized. The number of valence electrons (VE) consists of the valence electrons of the metal itself and the electrons donated or shared by the ligands, and would be 18 for an inert-gas configuration. If one restricts attention to Ni complexes, essentially all of the well-characterized compounds have 16 or 18 VE.

With regard to Ni complexes and Ni intermediates, Tolman's proposal may be expressed as follows [4]:

1. Ni complexes may exist in a significant concentration at moderate temperatures only if the valence shell of an Ni contains 16 or 18 electrons. A significant concentration is one that may be detected spectroscopically or *kinetically* and may be in the gaseous, liquid, or solid state.
2. Organonickel reactions, including catalytic ones, proceed through elementary steps involving only intermediates with 16 or 18 VE.

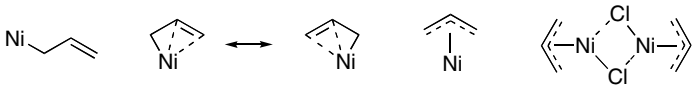
For example, $Ni(CO)_4$ (VE 18) is dissociated into $Ni(CO)_3$ (VE 16) and CO in solution. $Ni(CO)_4$ is coordinatively saturated and no longer has any ability to interact with other molecules. By contrast, $Ni(CO)_3$ is coordinatively unsaturated and can accept 2e ligands. Usually, the equilibrium lies heavily to the $Ni(CO)_4$ side. The same holds for the saturated $Ni(cod)_2$ (VE 18) and the unsaturated Ni(cod) (VE 14) + COD.

Some of the common ligands and their ligand types and electron counts are summarized in Table 1.2. The symbol L signifies a neutral 2e ligand, which can be a lone pair donor, such as PPh_3, CO, a π-bond donor, such as ethylene, acetylene, and a σ-bond donor such as H_2 and C–C. The symbol X refers to 2e ligands

Tab. 1.2. Common ligands and their electron counts.

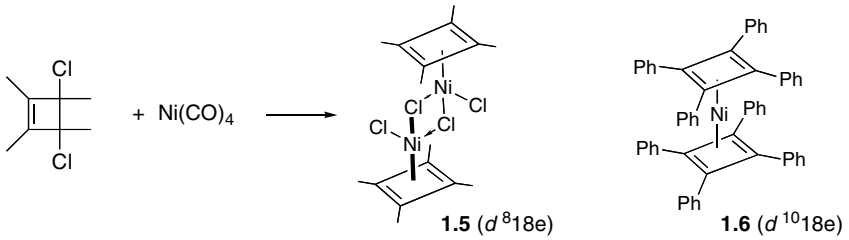
Ligand	*Type*	*Electron count*
H, Me, Ph, Cl, η^1-allyl	X	2
PPh_3, CO, NH_3 (lone pair donors), $CH_2{=}CH_2$ (π-donor), H_2 (σ-donor)	L	2
η^3-Allyl, κ^2-acetate, κ^2-acetylacetonate	LX	4
η^4-Butadiene, η^4-cyclobutadiene	L_2	4
η^5-Cyclopentadienyl (Cp)	L_2X	6
η^6-Benzene	L_3	6

bearing an anionic charge, such as Cl^-, H^-, and Me^-. The symbol η (eta) (a Greek letter h, hapticity, *haptic* from Gr. *hapticos*, able to grasp or perceive) indicates the number of ligand atoms bound to the metal. So, benzene, when coordinated to a metal in type L_3, is indicated as η^6-benzene, and the cyclopentadienyl group in type L_2X as η^5-Cp. Sometimes η is used without a superscript, such as η-benzene and η-Cp, when the number of ligand atoms is obvious. Allyl groups can exist in two forms, η^1-allyl (type X) and η^3-allyl (type LX). The double bond of η^1-allylnickel **1.1** does not interact with any nickel atomic orbitals, but conjugates with the C-M orbital, are bestowed a certain characteristic reactivity which is different from other η^1-alkyl complexes. The allyl group of η^3-allylnickel can be considered as a combination of an alkyl and a C=C group. The two resonance structures **1.2a** and **1.2b** show how all the three carbons are bound to an Ni as LX. This is also expressed as **1.3**. η^3-Allylnickel chloride **1.4** is an air-stable, square planar 16-electron complex (8e from Ni, 4e from allyl and 4e from Cl_2), with chloride ions bridging in a dimeric structure. The bridging group is represented in formulas by using the Greek letter μ (mu) as $[(\mu\text{-Cl})_2(\eta^3\text{-}CH_2{=}CHCH_2Ni)_2]$ ((η^3-allyl)nickel chloride dimer). The Greek letter κ (kappa) is used instead of η in those cases that ligands bind to metals via heteroatoms, such as κ^2-acetylacetonate (κ^2-acac).



1.1 **1.2a** **1.2b** **1.3** **1.4**

Cyclobutadiene is a compound that is extremely unstable not only because of its strain but an anti-aromatic electronic character (cyclic 4π electron anti-Hückel compound) and was a target from synthetic and physical organic points of view. Only under special conditions (e.g., a solid argon matrix), it has a life-time long enough to be spectroscopically detectable [5]. The two double bonds, however, locate nicely to server as an L_2 4e donor to transition metals and the stabilization of cyclobutadiene by the coordination to transition metals was suggested theoretically [6]. In fact, cyclobutadiene forms some stable complexes with nickel, e.g., **1.5** and **1.6**, and some other transition metals [7].



1.5 ($d^8$18e) **1.6** (d^{10}18e)

Scheme 1.3. Formation of stable cyclobutadiene Ni complexes: $[(\mu\text{-Cl})_2(\eta^4\text{-cyclobutadiene})\text{Ni(II)}]_2\text{Cl}_2$ (**1.5**) and bis(η^4-cyclobutadiene)Ni(0) (**1.6**).

The molecular orbital diagram of a square planar cyclobutadiene (in fact, it has a rectangular structure), as illustrated in Figure 1.4(a), tells us that the 2e of the totally 4π electrons occupy bonding Ψ_1 orbital and the other 2e occupy two degenerated non-bonding Ψ_2 and Ψ_3 orbitals one each (the Hund rule). Figure 1.4(b) shows how $\Psi_1 \sim \Psi_4$ molecular orbitals interact with the atomic orbitals of an Ni. These interactions of four molecular orbitals of cyclobutadiene and nine atomic

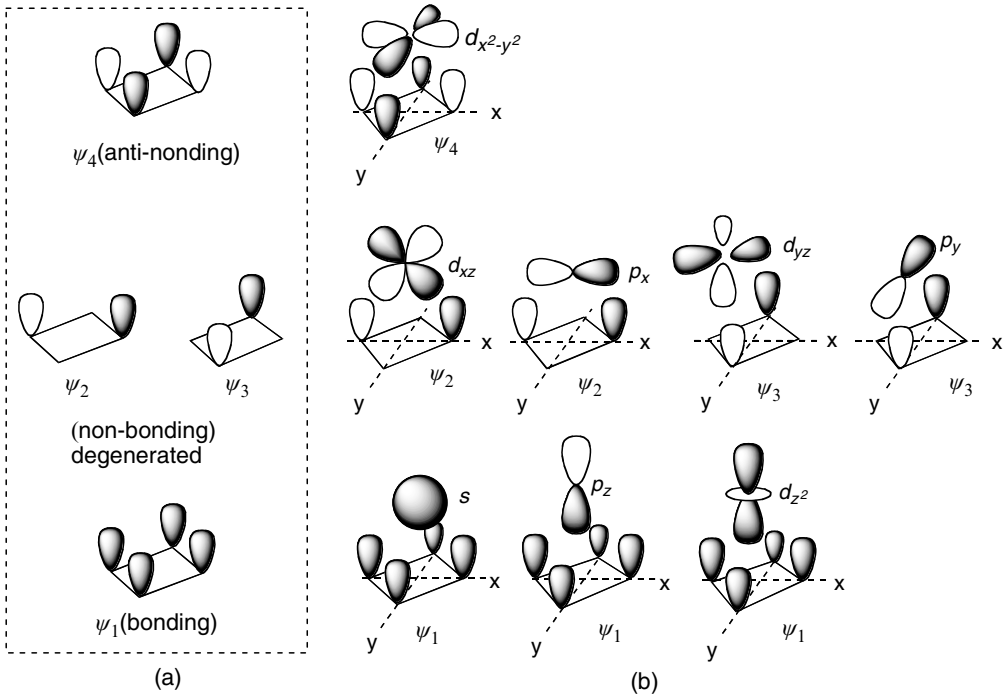


Fig. 1.4. Molecular orbitals of cyclobutadiene (a) and the molecular orbitals–atomic orbitals interaction between cyclobutadiene and Ni (b). For clarity, the orbitals of cyclobutadiene are shown only on one face.

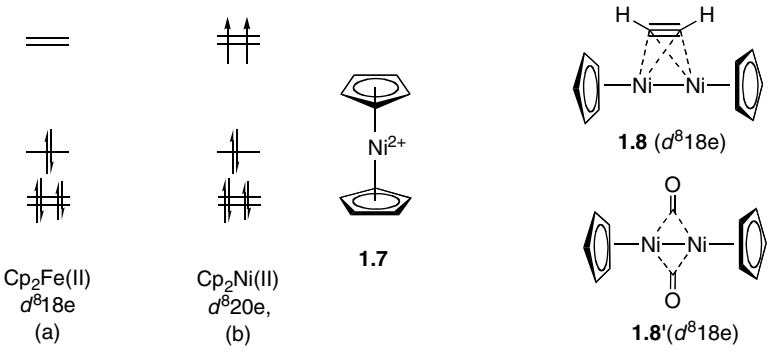


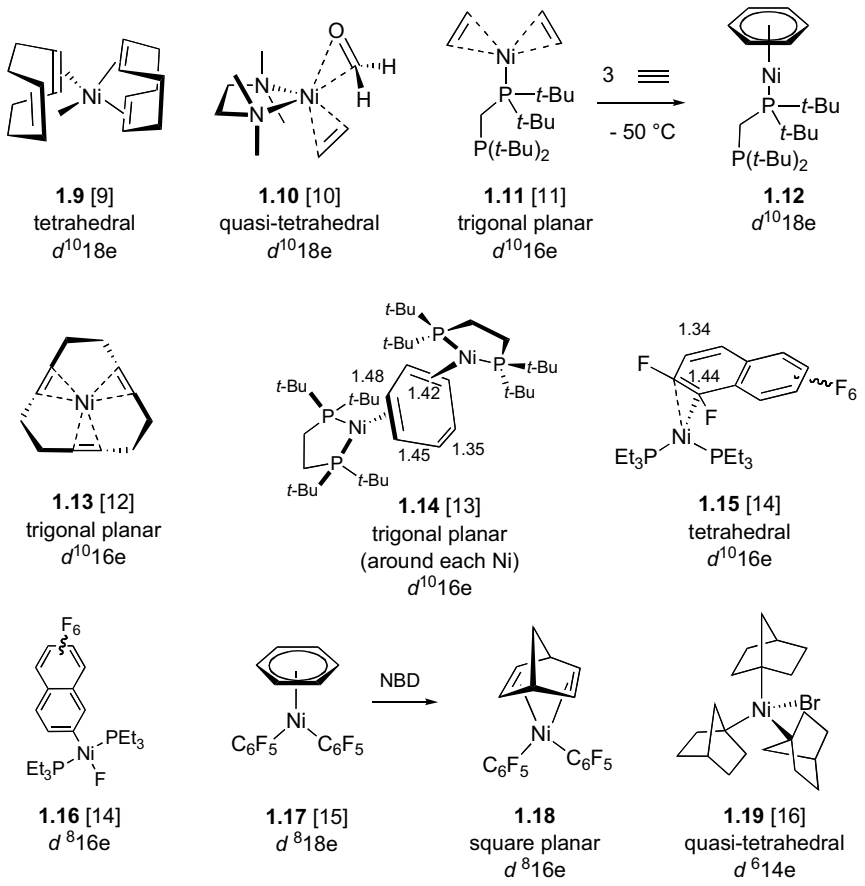
Fig. 1.5. The *d* orbital energy diagram of ferrocene ($Cp_2Fe(II)$) (a) and nickellocene **1.7** (b).

orbitals of an Ni make up 13 molecular orbitals; six bonding, one non-bonding, and six anti-bonding orbitals. The six bonding molecular orbitals are filled with 12e. The reader should note that the three Ni–Cl bonding orbitals accommodate 6e, hence the complex **1.5** has a stable d^8 18e electronic configuration. The complex **1.6** is another example which demonstrates that cyclobutadiene owes its stability to the coordination interaction with an Ni.

1.6
The Structure, Reactivity, and Electronic Configuration of Nickel-Complexes

Ferrocene, $Cp_2Fe(II)$, is the monumental organometallic compound that serves as a milestone for the explosive developments in organometallic chemistry [8]. Ferrocene is a stable orange crystalline material, and has an ideally stable electronic configuration, $d^6$18e, 6e from an Fe and 12e from 2Cp; as is shown in Figure 1.5(a), all the 6*d* electrons are accommodated in the three low-lying orbitals. The nickel analog, nickellocene (**1.7**) has 20 VE (8e from an Ni and 12e from 2Cp) and is outside of the 18e rule. The extra 2e are indulged to occupy the high-lying degenerate orbitals, one each (Hund's rule; Fig. 1.5(b)). Hence the complex is paramagnetic and extremely sensitive to oxidation, causing instantaneous decomposition in air. In contrast, the CpNi complexes with 18 VE, e.g., **1.8** [acetylenebis(η^5-cyclopentadienyl)nickel(II)] and **1.8′** [dicarbonylbis(η^5-cyclopentadienyl)nickel(II)], are rather stable [17]. The electron count of **1.8** and **1.8′** is as follows: **1.8**, 6e (Cp) + 2e (acetylene) + 8e (Ni) + 2e (adjacent Ni); and **1.8′**, 6e (Cp) + 2e (CO) + 8e (Ni) + 2e (adjacent Ni).

Figure 1.6 shows some organonickel complexes of chemical and structural interest, all the structures of which are determined using X-ray crystallographic analysis [9–16]. As is observed in the complexes **1.9**–**1.15**, for the d^{10} Ni complexes, the five *d* orbitals are fully occupied, so, in general, there is no preference for specific geometries (c.f., Fig. 1.1). Probably owing to avoiding steric repulsion between ligands, nickel(0) generally forms tetrahedral (with four ligands) or trigonal planar com-



1.9 [9]
tetrahedral
d^{10}18e

1.10 [10]
quasi-tetrahedral
d^{10}18e

1.11 [11]
trigonal planar
d^{10}16e

1.12
d^{10}18e

1.13 [12]
trigonal planar
d^{10}16e

1.14 [13]
trigonal planar
(around each Ni)
d^{10}16e

1.15 [14]
tetrahedral
d^{10}16e

1.16 [14]
d^{8}16e

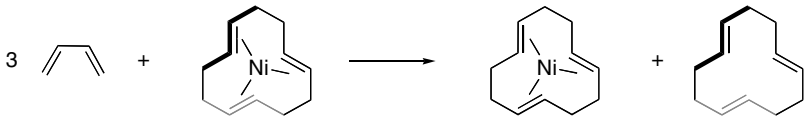
1.17 [15]
d^{8}18e

1.18
square planar
d^{8}16e

1.19 [16]
quasi-tetrahedral
d^{6}14e

Fig. 1.6. Some organonickel complexes of chemical and structural interests. All the structures have been determined by X-ray analyses. Figures indicate bond distances (Å).

plexes (with three ligands). Complex **1.13** is the famous Wilke's complex, isolated as a reactive intermediate for the trimerization of butadiene. Thus, CDT, the ligand of **1.13** offers the seats for CDT of the next generation. In other words, as is shown in Eq. (1.2), CDT on an Ni is handed down from generation to generation.



(1.2)

All the three *trans*-double bonds of **1.13** adopt a propeller-like arrangement around the Ni atom, hence **1.13** is chiral. In fact, the enantiomer shown in **1.13**

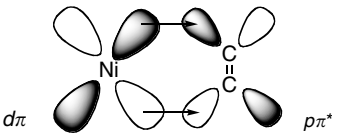


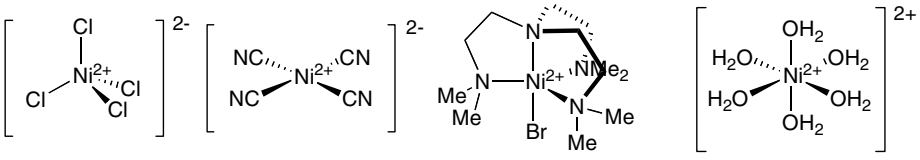
Fig. 1.7. The $d\pi$-$p\pi$ interaction pushing the electron density from the nickel $d\pi$ to the alkene $p\pi^*$.

has been resolved (by use of a chiral phosphine ligand) and its specific rotation is determined to be $[\alpha]_D^{-30^\circ} = +104^\circ$ [12].

The complex **1.10** is an interesting example which shows that the π-coordinated double bonds of ethylene and formaldehyde intersect perpendicularly to each other [10]. This unique spatial arrangement of ethylene and formaldehyde impels us to imagine a through-space orbital interaction between the ligands – a LUMO (C=O)-HOMO (C=C) interaction. The butterfly-like complex **1.11**, despite the presence of a good chelating phosphine ligand, is coordinatively unsaturated and forms a trigonal planar d^{10}16e complex [11]. Note the difference of the spatial arrangements of the two π-ligands between **1.10** and **1.11**. In **1.11**, a P, Ni, and all the Cs of two ethylene molecules lie in a plane. The complex **1.11** is highly reactive towards acetylene, and forms the η^6-arene complex **1.12** even at a temperature as low as -50 °C. In the dinuclear complex **1.14**, the originally aromatic and hexagonal benzene ring is distorted and forms the structure of cyclohexatriene with alternating single and double bonds [13]. The bond distances of the double bonds coordinating to an Ni are significantly longer than that of a standard double bond (1.34 Å). The bond length of the uncoordinated double bond of **1.14** is within a standard value. The lengthening of the coordinated double bond is due to $d\pi$-$p\pi^*$ back donation, filling the anti-bonding $p\pi^*$ orbital with the $d\pi$ electrons, hence rendering the double bond long and weak. The $d\pi$-$p\pi^*$ back donation is illustrated in Figure 1.7. Similar bond lengthening is reported for the complex **1.15**, which is considered to be an intermediate leading to the oxidative addition product **1.16**.

As is expected from the crystal field splitting (Fig. 1.1), the d^8 nickel complexes **1.16–1.18** show a strong tendency to form a square planar structure, leaving the most unstable dx^2-y^2 orbital empty. Ni(II) complexes also have a strong tendency to adopt the $d^8$16e configuration. The complex **1.17** is one of rare examples adopting $d^8$18e electronic configuration. The benzene ring of the complex **1.17** is labile and is readily replaced by other aromatic molecules (e.g., toluene, anisole) or by alkenes. Replacement with norbornadiene (NBD) forms a rather stable complex **1.18**.

For nickel complexes, 0 and 2+ are the oxidation states observed most frequently. The oxidation states of 1+ and 3+ are supposed to be the active forms in the redox system of some enzymes (e.g., nickel hydrogenase) [18]. The oxidation state of 4+ is very rare. The complex **1.19** is one such example, and is stable in crystalline form for several days in air, but readily decomposes in solution [16]. The stability of the complex can be attributed to the strong σ-bond electron-donor capabilities of the 1-norbonyl group and bromide anion, which provide the neces-



(a) tetrahedral $d^8$16e

(b) square planar $d^8$16e

(c) trigonal bipyramidal $d^8$18e

(d) octahedral $d^8$20e

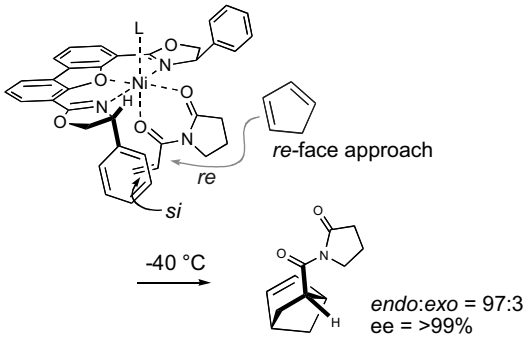
Fig. 1.8. Some inorganic Ni(II) d^8 complexes of structural and chemical interests.

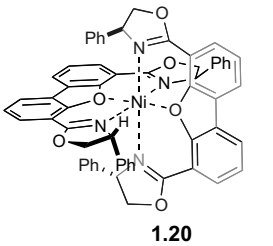
sary electron density for stabilizing the formal 4+ oxidation state. Both the crystal field and the ligand field require the complex **1.19** to be paramagnetic, with unpaired 2e in the $d\pi$ orbitals. In fact, **1.19** is diamagnetic; this is due to distortion, lowering the symmetry from T_d to C_{3v} (e.g., T_d for methane, C_{3v} for bromomethane), which splits the energy levels of the $d\pi$ orbitals and produces one orbital of lower energy that accommodates the 2e in pairs. The formal oxidation state of Ni(4+) has been claimed (speculated) sporadically to rationalize reaction schemes [19].

Figure 1.8 shows some inorganic Ni(II) complexes of structural and chemical interests. In contrast to organic Ni(II) complexes, which show a tendency towards having a square planar configuration, inorganic Ni(II) complexes can have a variety of configurations. For example, $[NiCl_4]^{2-}$ can not have a square planar configuration owing to the strong electrostatic repulsion between the neighboring chloride ions, and hence the complex adopts a tetrahedral arrangement, where the electrostatic repulsion becomes minimal. In contrast, $[Ni(CN)_4]^{2-}$ is square planar because of the lack in such a strong electronic and steric repulsion between the ligands. The tetradentate ligand, $N(CH_2CH_2NMe_2)_3$, topologically forces the Ni complex to accept the trigonal bipyramidal structure (Fig. 1.8(c)).

The hexahydrate complex of Ni(II) (e.g., $Ni(SO_4)\cdot 6H_2O$) is a green solid and is stable in solution (Fig. 1.8(d)). However, this aqua complex is outside of the 18e rule, d^8 20e. This phenomenon is observed for many other transition metals. Pale red $Co^{2+}(H_2O)_6$ is, for example, a 19-electron complex, and blue $Cu^{2+}(H_2O)_6$ is a 21-electron complex. This is due to a small Δo splitting (Fig. 1.1). The six H_2Os make the relatively weak σ-bonds and hence render the $d\sigma$ orbitals weakly antibonding. Accordingly, the $d\sigma$ orbitals can accommodate extra electrons. In a sense, the water molecules may be regarded as a solvent to stabilize the positive charge of metals. In other words, the solvation stabilization overrides the electronic configurational destabilization.

The propensity of Ni^{2+} to form octahedral complexes with weak-field ligands is utilized for the asymmetric Diels–Alder reaction (Scheme 1.4) [20]. The *si*-face of the acrylamide C=C bond forms a π-π stack with the 4-phenyl group of the chiral oxazolidine ligand, and only the *re*-face is open to the cycloaddition toward cyclopentadiene. The central Ni(II) serves as a Lewis acid and activates the acrylic double bond toward the Diels–Alder reaction by lowering its LUMO. In fact, the





1.20
meso (*RR*,*SS*-complex)

Scheme 1.4. The asymmetric Diels–Alder reaction promoted in the octahedral coordination sphere of Ni^{2+}.

cycloaddition reaction even proceeds at −40 °C and provides the cycloaddition product with a high enantiomeric excess (ee).

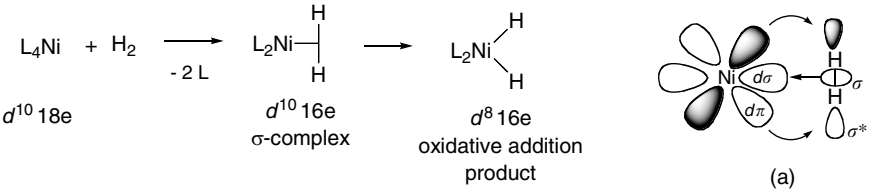
The reaction shows an interesting chiral amplification – that is, a slight ee of the *RR* ligand is good enough to assure a high ee in the product. The *RR*-*SS* combination forms a strain-free *meso* complex **1.20**, while the homo-chiral pair *RR*-*RR* does not form because of the steric repulsion between the 4-phenyl groups of the oxazolidine rings. The steric repulsion that the *RR*-*RR* complex experiences is readily understood by imagining an inversion the stereocenters bearing the phenyl groups of the ligand of **1.20** (shown in gray). This means that almost all of the *SS* ligand portion is engaged in forming the *RR*-*SS* complex. The remaining portion of the *RR* ligand forms the Ni^{2+} complex, which is coordinatively unsaturated and is able to activate the acrylamide through coordination.

1.7
The Elementary Reactions

Nickel-catalyzed or -promoted reactions usually proceed via the following six elementary processes: 1) oxidative addition; 2) insertion (or addition); 3) transmetallation; 4) reductive elimination; 5) β-hydrogen elimination (or dehydrometallation); and 6) β-carbon elimination, of which the ''insertion'' and the ''transmetallation'' have, more or less, the common ground in organic chemistry [21].

1.7.1
Oxidative Addition

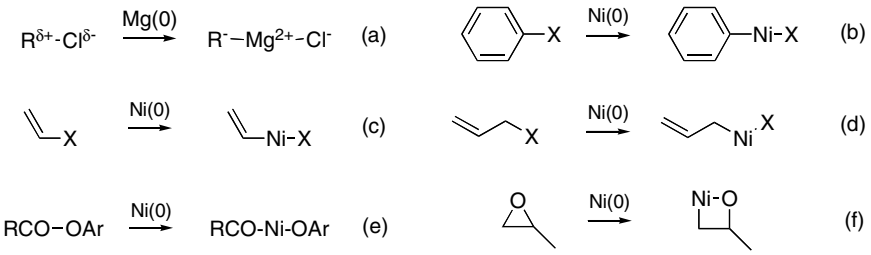
As discussed previously in Section 1.3, the addition of H_2 to an C is regarded as reduction of the carbon atom – that is, the addition of one and two molecules of H_2 forms carbene (C^{2-}) and methane (C^{4-}) from C^0, respectively. On the other hand, addition of H_2 to an Ni is regarded as oxidation of the Ni; Ni^0 to Ni^{2+}. This



Scheme 1.5. Oxidative addition of an Ni(0) upon the H–H σ-bond. The schematic presentation of the σ-$d\sigma$ (donation) and the σ^*-$d\pi$ interaction (back donation).

is simply a matter of formalism. In organic chemistry, the oxidation number of H is assigned 1^+ (a proton), while in organometallic chemistry, the oxidation number of H is 1^- (a hydride). In organic chemistry, the events transforming an C to CH_2: and CH_4 are rather imaginative, but in organometallic chemistry, this type of reaction is in all likelihood. As depicted in Scheme 1.5, an Ni(0) interacts with H_2 through the σ-$d\sigma$ bonding and the σ^*-$d\pi$ back bonding, both of which cooperate to cleave the H–H bond and make the two Ni–H bonds. In this process, an Ni(0) offers 2e to create two Ni–H bonds and the oxidation number changes from 0 to 2^+. In organometallic chemistry, the formal oxidation number of a metal is equal to the number of the σ-type ligands (X) attached to the metal.

The process of generating Grignard reagents is a type of oxidative addition, where Mg(0) is changed to Mg(II) via *oxidative* addition of the Mg(0) upon the R–Cl bond. As shown in Eq. (a) of Scheme 1.6, this example is appealing because as Mg loses 2e, the previously positively charged R group changes to the negatively charged R group (''umpolung'' = changing the polarity).

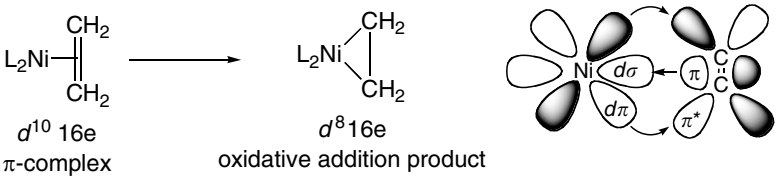


Scheme 1.6. Formation of organometallics via oxidative addition of metals upon a variety of C-heteroatom σ-bonds.

In contrast to Mg(0), Ni(0) is capable of undergoing oxidative addition towards a wide variety of compounds with C–heteroatom bonds. Aryl, alkenyl, and allyl halides (and triflate, $CF_3SO_3^-$) are good substrates, where coordination of these unsaturated compounds through the double bonds helps to facilitate this process (cf., **1.15**). The rate of addition decreases in the order: C–I > C–Br > C–Cl > C–F. The

C–F bond is so strong that it is very difficult to cleave. Some of the Ni(0) species – and especially those coordinated by electron-donating σ-ligands, such as $(alkyl)_3P$ and H^-, are capable of undergoing oxidative addition to the Csp^2–F and even the Csp^3–F bonds (cf., **1.16**). Raney nickel is a typical example capable of undergoing oxidative addition to the C–S bond, and reductively cleaves the C–S bond. The acyl C–O bonds of aryl esters (Eq. (e)) [22], as well as the C–O bonds of epoxides (Eq. (f)) [23], are also subject to the oxidative addition of an Ni(0).

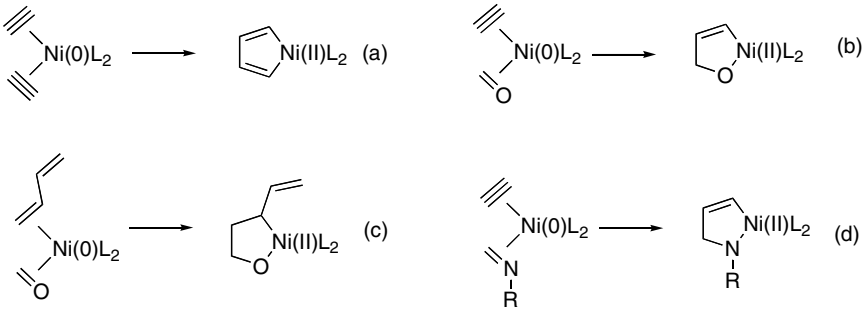
As with the oxidative addition of an Ni(0) to σ-bonds, the oxidative addition of an Ni(0) to π-bonds also takes place, breaking the π-bond and making new two σ-bonds. Scheme 1.7 illustrates how the π-$d\sigma$ (donation) and π^*-$d\pi$ (back donation) orbital interactions function to form nickellacyclopropane.



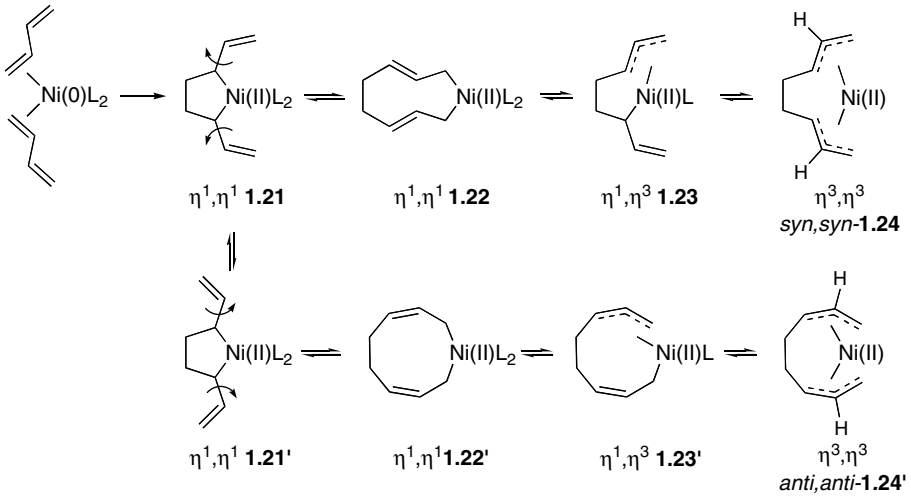
Scheme 1.7. Schematic presentation of oxidative addition of an Ni(0) upon a double bond. The π-$d\sigma$ (donation) and π^*-$d\pi$ (back donation) interaction.

As shown in Scheme 1.8, a similar oxidative addition takes place across two or more π-ligands of a wide variety of combinations of the ligands. The first example is an intermediate supposed for the production of cyclooctatetraene by tetramerization of acetylene (the Reppe reaction; Eq. (a)) [24]. Alkynes and dienes react with carbon monoxide, carbon dioxide, and even with aldehydes and ketones in ways shown in Eqs. (b)–(d) (Scheme 1.8) [25–27]. All of these transformations are accompanied by the oxidation of an Ni(0) and cyclization, and hence are commonly referred to as oxidative cyclization.

Among nickellacycles, the Wilke complexes **1.21**–**1.24**, formed by the oxidative addition of an Ni(0) to two molecules of butadiene, and are the most famous and



Scheme 1.8. Oxidative cyclization of an Ni(0) across a variety of combinations of alkynes, dienes, and carbonyl compounds.

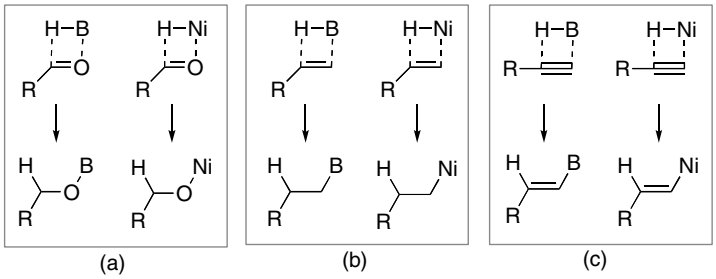


Scheme 1.9. Oxidative cyclization of an Ni(0) and two molecules of butadiene forming a variety of η^1,η^1-, η^1,η^3- and η^3,η^3-complexes.

cost-effective in chemistry (Scheme 1.9). All of the intermediates equilibrate one to another, and can exist in a variety of forms. Some of these are shown in Scheme 1.9 (see also **1.9** and **1.13** in Fig. 1.6). In the absence of ligands, the η^3,η^3-complexes **1.24** and **1.24′** may be most abundant, because these have a *self-saturated* L_2X_2 $d^8$16e electronic configuration. All the others are unsaturated, being either X_2 ($d^8$12e, e.g., **1.21**, **1.22**) or LX_2 ($d^8$14e, e.g., **1.23**). The population of the X_2 complexes may increase in the presence of bidentate ligands, such as DPPE [1,2-bis(diphenylphosphino)ethane] and that of the LX_2 by monodentate ligands, such as PPh_3. The all *syn,syn*-isomer **1.24** is correlated to the all *anti,anti*-isomer **1.24′** through many steps, as shown. The most crucial process of this *syn-anti* isomerization involves the isomerization between **1.21** and **1.21′** through rotation about the single bonds indicated with arrows. The complex **1.21** is all *cisoid* with respect to the allylnickel moieties, while the complex **1.21′** is all *transoid*. The *syn* and *anti* geometries of η^3-nickel complexes (or η-allylnickel complexes) are defined as follows. In the η^3-three carbon skeleton, those having substituents on the terminal carbon C_1 and/or C_3 *cis* to the substituents on the central carbon C_2 (an H atom !, in this particular case) are *syn*, and those of opposite are *anti*. That is, the *cisoid* η^1-complex **1.21** is transformed to the *syn*-η^3-**1.24** without changing the olefinic geometries and the *transoid* η^1-**1.21′** to the *anti*-η^3-**1.24′**.

1.7.2 Insertion

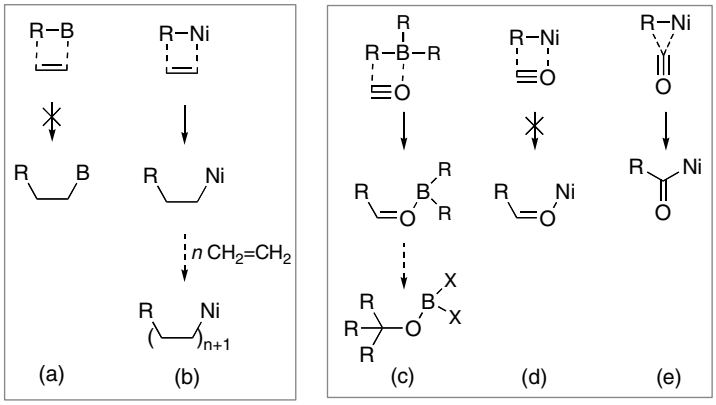
The nickel hydride Ni–H and the hydrides of main group elements – for example, B–H of diborane B_2H_6 – show similar reaction patterns, with respect to regio- and



Scheme 1.10. The insertion reaction of C=O, C=C, and C≡C into metal hydrides.

stereoselectivity, towards polar double bonds as well as to non-polar double and triple bonds (Scheme 1.10) [28]. In organic chemistry, these reactions are referred to as either the hydride *reduction* of carbonyls, *hydrogenation* of alkenes and alkynes, or *addition* of B–H to alkenes and alkynes (or *hydroboration*), as in organic chemistry the change of functional groups of organic molecules is the main concern. On the other hand, in organometallic chemistry, where the change of the metallic species is the main concern, these reactions are simply regarded as the *insertion* of C=O, C=C and C≡C into the B–H or Ni–H bond. These reactions proceed, more or less, via a four-membered cyclic transition state (syn addition).

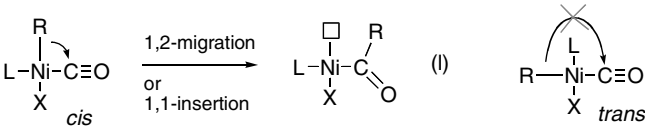
As is apparent from Scheme 1.11, the situation changes dramatically when it comes to the reactivities of the Ni–R and B–R species. The B–R species never react with ethylene (Eq. (a)), while the Ni–R species engages in the reaction with ethylene (Eq. (b)). In fact, even under room temperature, the insertion of ethylene into the Ni–R bond is repeated almost infinitely, and polyethylene forms (Eq. (b)). The B–R species reacts with carbon monoxide in a similar way with aldehydes and ketones. The BR_3 species repeats the same process two more times finally to provide a tertiary alcohol (Eq. (c)). The Ni–R species, on the other hand, reacts with



Scheme 1.11. The insertion reaction of C=C and CO into metal alkyls.

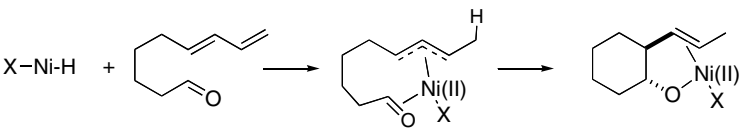
CO in a quite different way, and never reacts in the way shown in Eq. (d). Formally, CO inserts into the Ni–R bond at the C atom and forms an acylnickel species, as shown in Eq. (e) in Scheme 1.11.

Mechanistically, the CO insertion proceeds by the migration of the alkyl group from an Ni (accompanying the Ni–R σ-bond breaking) to the carbon of CO (accompanying the Ni–CO σ-bond strengthening) (Scheme 1.12). This process is referred to as either *1,2-migration* of the R (from the Ni to the C of CO), *1,1-insertion* of the Ni–R (to the same C of CO) or, by putting together these two, *migratory insertion* of CO upon the Ni–R bond. For the migratory insertion to proceed, the R and the C≡O groups must be *cis* to each other. The *trans*-isomer is topologically unable to undergo the 1,2-migration (Scheme 1.12. The symbol □ denotes a vacant site on Ni).



Scheme 1.12. The insertion of CO into the Ni–R bond.

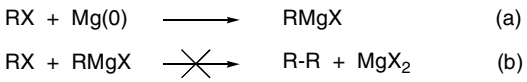
Sequential insertion of different molecules (or functionalities) diversifies the insertion reactions. Scheme 1.13 shows that the diene inserts to the Ni–H bond regioselectively, providing an internal η^3-allylnickel species. Then, the formyl group undergoes insertion into the thus-formed η^3-allylnickel bond [29]. The latter process is regarded as the nucleophilic addition of η^3-allylnickel to an aldehyde, and is a unique reactivity which is associated specifically with the η^3-allylnickel species among the Group 10 η^3-allylmetal species; neither η^3-allylpalladiums nor η^3-allylplatinums undergo nucleophilic addition to carbonyl compounds. It should be noted that in all the insertion processes discussed above, the formal oxidation number of the nickel does not change but remains at 2+.



Scheme 1.13. The sequential insertion of a diene and an aldehyde upon the Ni–H and Ni–η^3-allyl bonds, respectively.

1.7.3 Transmetallation

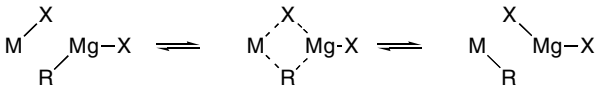
Grignard reagents (RMgX), which were first prepared in 1900, have been among the most popular and useful organometallic reagents, as they react with a wide variety of carbonyl compounds to produce C–C bonds: these include CO_2, aldehydes,



Scheme 1.14. Formation of Grignard reagent (a) and its reaction with an alkyl halide (b). Generally, the reaction (b) takes place easily only when R = allyl.

ketones, esters, and carbonates. The reagent, however, is usually not reactive toward alkyl halides (Scheme 1.14(b)). This is fortunate for the Grignard reagents, because if that reaction could proceed, their preparation would become a very difficult task!

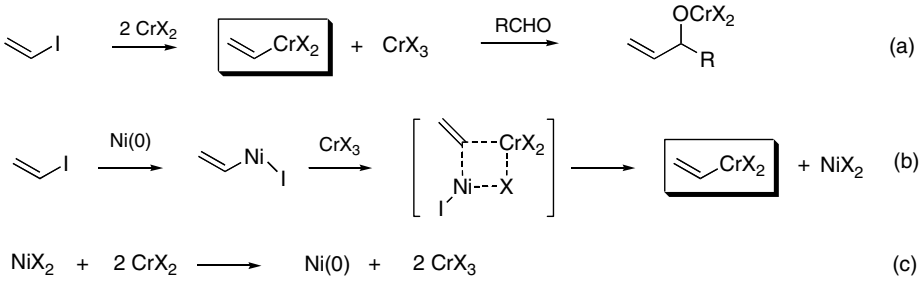
The change in reactivity of Grignard reagents in the presence of a catalytic amount of transition metal salts has long been recognized. A cobalt salt helps the Grignard reagents to undergo a coupling reaction with alkyl halides (the Kharash reaction), while a cuprous salt guides the Grignard reagents selectively to undergo 1,4-addition to conjugated enones, instead of 1,2-addition to the C=O. The newly gained reactivity is apparently ascribed to a new metallic species RM, generated by exchanging X and R between MX and the R of RMgX (Scheme 1.15). This equilibrium process is termed ''transmetallation''. In order for the equilibrium to go to the right, M must be less electropositive than Mg. Fortunately, almost all transition metals are less electropositive than Mg (see Table 1.1), and transmetallation works in favor of the formation of RM. However, this condition is not always necessary; an all-important point is that the species RM formed by transmetallation is, irrespective of the population in the equilibrium, more reactive than RMgX toward the given target reaction.



Scheme 1.15. The transmetallation between Grignard reagent and a metal salt.

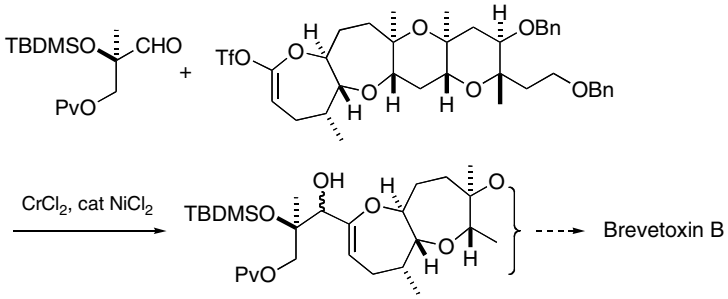
In addition to the ''Wilke nickel effect'' (see Section 1.1), there is another ''nickel effect'' that is closely associated with transmetallation. The Grignard-type vinylation of aldehydes with vinylchromium(III) is now known as the NHK reaction (Nozaki–Hiyama–Kishi reaction; Eq. (a) in Scheme 1.16) [30]. The reaction proved indispensable for the total synthesis of palitoxin (a marine natural product), but the original authors (Nozaki and Hiyama) and Kishi soon realized independently that the reaction was not reproducible and that its success depended on the source and batch of the Cr(II) and Cr(III) salts. After prolonged investigation and careful scrutiny, both groups concluded that a trace amount of nickel in the Cr(II) or Cr(III) species was essential in order to promote the reaction. Initially, palladium salts were thought to be an effective catalyst, but again it transpired that a trace amount of nickel in the palladium salt was the true active species. The reaction is mediated

by a facile oxidative addition of an Ni(0) upon vinyl iodide (Scheme 1.16(b)). Transmetallation between vinylnickel(II) iodide and CrX_3 produces vinylchromium(III), which undergoes nucleophilic addition to aldehydes. The Ni(0) species is produced by the reduction of 1 mol of Ni(II) with 2 mol of Cr(II), and enters a catalytic cycle (Eq. (c) in Scheme 1.16).



Scheme 1.16. The NHK reaction catalyzed by an Ni(0) species: the second 'Nickel Effect'. a) Chromium(II)-mediated vinylation of aldehydes with vinyl iodide under the Barbier conditions; b) Ni(0)-catalyzed generation of nucleophilic vinylchromium(III) species that involves transmetallation between vinylnickel(II) and $Cr(III)X_3$; c) Reduction process of Ni(II) to Ni(0) with 2 equiv. Cr(II).

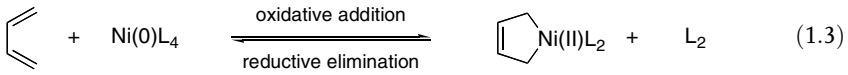
The NHK reaction shows a wide compatibility with functional groups, chemoselectivity (aldehydes ≫ ketones), and a low basicity; hence the reaction has been widely used for the total synthesis of many natural products of structural complexity. Examples include a brefeldin series by Schreiber [31], allopumiliotoxin 339A by Kibayashi [32], and brevetoxin B by Nicolaou [33]. One of these examples is shown in Scheme 1.17, and illustrates how well the reaction works [33]. In this particular case, the aldehyde possesses no enolizable α-proton with respect to aldehyde. The low basicity of the NHK reagent allows one to perform the vinylation of chiral aldehydes bearing enolizable protons, without racemization.



Scheme 1.17. Application of the NHK reaction for total synthesis of Brevetoxin B (dotted arrow denotes many steps of the reaction).

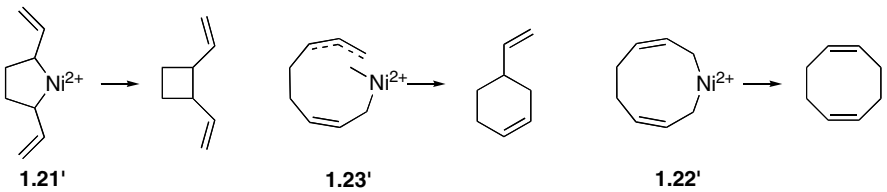
1.7.4
Reductive Elimination

Reductive elimination is the reverse of oxidative addition. As shown in Eq. (1.3), the formation of nickella-3-cyclopentene from butadiene and Ni(0) is oxidative addition, whilst the reverse to produce a mixture of butadiene and an Ni(0) is reductive elimination. As mentioned in Section 1.7.1, oxidative addition is accompanied by an increase in the formal oxidation number of Ni by 2 units; conversely, in reductive elimination the formal oxidation number is decreased by 2 units. This is why the process is termed reductive elimination. This type of microscopic reverse is seen very clearly in organic transition metal chemistry. The reaction of Eq. (1.3)



(1.3)

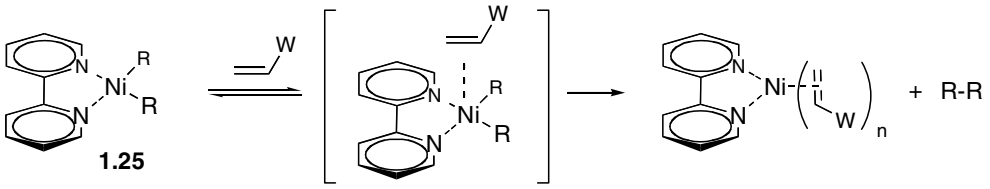
is by itself not productive, but the insertion of another molecule (e.g., of butadiene) renders the chemistry productive (Scheme 1.18). Reductive elimination of an Ni(0) from **1.21′**, **1.23′**, and **1.22′** provides *cis*-1,2-divinylcyclobutane, 4-vinylcyclohexene, and 1,5-cyclooctadiene, respectively. In the most cases this reductive elimination is rate-determining, though the selective formation of one of these is clearly dependent upon the reaction conditions.



Scheme 1.18. Various types of reductive eliminations of (butadiene)$_2$Ni^{2+} complexes.

It is now well recognized that, in most cases, reductive elimination is accelerated by the coordination of the fifth electron-deficient ligand (associative activation). In this regard, it is fortunate for organonickel chemistry that most Ni(II) complexes have unsaturated $d^8$16e configuration and still have one vacant coordination site for coordination of the fifth ligand. A. Yamamoto remains among the outstanding pioneers in this field, and showed that dialkyl(bpy)Ni(II) complexes **1.25** are thermally stable and activated in the presence of some electron-deficient alkenes (e.g., acrylonitrile, maleic anhydride) to undergo reductive elimination to provide the coupling product R–R and (alkene)$_n$(bpy)Ni(0) (n = 1 or 2) in quantitative yields (Scheme 1.19). Yamamoto also succeeded in detecting the five-coordinated complexes using both infra-red and ultra-violet spectroscopy [34].

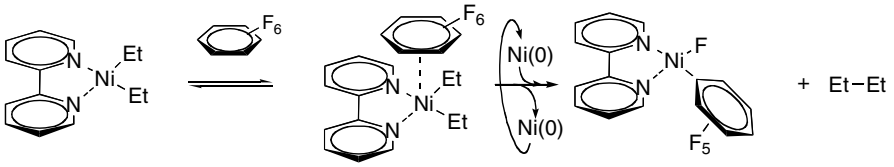
T. Yamamoto (a former coworker of A. Yamamoto) has shown that the rate of reductive elimination of diethyl(bpy)Ni(II) (**1.25**, R = Et) is expressed as k[Et$_2$Ni(bpy)][aromatic compound], and a plot of a log k value against a $\Sigma\sigma$ value



Scheme 1.19. Acceleration of reductive elimination by the fifth coordination with an electron-deficient alkene (W = electron-withdrawing group).

(σ = the Hammett σ value of the substituents on aromatic compound) affords a linear correlation with ρ-value of +1.4. Furthermore, as is illustrated in Scheme 1.20, when hexafluorobenzene is used as an aromatic compound, reductive elimination is coupled with oxidative addition of an Ni(0) upon the C–F bond [35].

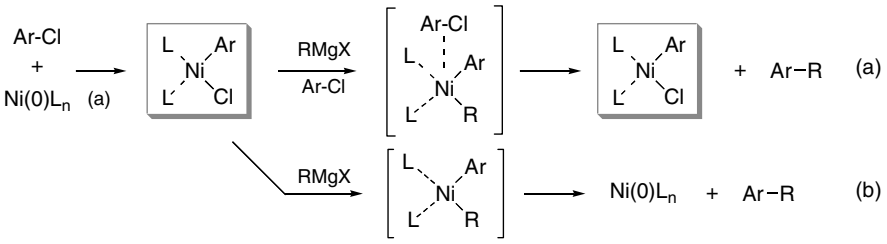
These observations are suggestive of why the Kumada–Tamao coupling reaction proceeds so smoothly when using unreactive (in terms of organotransition-metal chemistry) aryl *chlorides* as substrates [36]. In palladium chemistry, the oxidative addition of Pd(0) on the aryl–Cl bond has long been regarded as almost impractical, but a recent breakthrough led to the palladium-catalyzed transformation of chloroarenes to aromatic derivatives, and this remains among the most topical subjects currently under investigation [37].



Scheme 1.20. Acceleration of reductive elimination and concomitant oxidative addition of hexafluorobenzene.

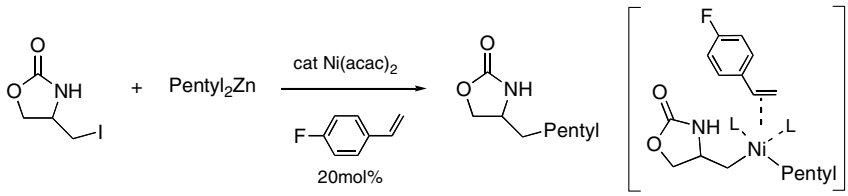
The Kumada–Tamao (or the Corriu–Kumada–Tamao) reaction proceeds according to Eq. (b) in Scheme 1.21 – that is, oxidative addition of an Ni(0) upon an aryl chloride, transmetallation between the thus-formed arylnickel(II) chloride and a Grignard reagent, followed by reductive elimination [38]. The idea of an associative elimination (Scheme 1.21(a)) that achieves both reductive elimination to give a cross-coupling product and oxidative addition to feed arylnickel(II) chloride simultaneously, may be worth further examination.

In general, the higher the electronegativity of the ligand R, the easier and more rapid the reductive elimination. Accordingly, aryl(Csp^2)-aryl(Csp^2) coupling proceeds quantitatively in most cases, and the success of the aryl(Csp^2)-alkyl(Csp^3) coupling subtly depends on the reaction conditions, especially the type of organometallic. All types of organometallics (e.g., RMgX, R_nZnX_{2-n}, R_nAlX_{3-n}, R_nBX_{3-n},



Scheme 1.21. Corriu–Kumada–Tamao cross-coupling reaction (b). Possible concerted or concomitant reductive elimination-oxidative addition by the fifth coordination of aryl chloride (a).

etc.) display characteristic reactivities, with alkyl-alkyl coupling being most difficult and having been developed only recently. For example, Knochel has succeeded in the coupling reaction shown in Eq. (1.4) [39], but this is successful only in the presence of 20 mol% *p*-fluorostyrene, which may serve as the fifth ligand to facilitate reductive elimination. Remarkably, the reaction is tolerant to the acidic amide NH bond and the carbamate CO, the characteristic behavior associated with organozinc reagents.



(1.4)

In order for reductive elimination to proceed, the organic ligands to be coupled must be cis to each other. The *trans*-isomers never undergo reductive coupling, and must isomerize to the *cis*-isomers prior to undergoing reductive elimination. To help the reductive elimination, bidentate ligands – especially those having a large bite angle (θ) – have been shown to be effective, as they topologically force the organic ligands cis and closer to each other [40].

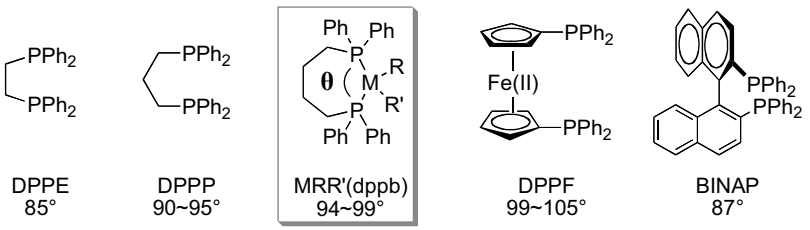
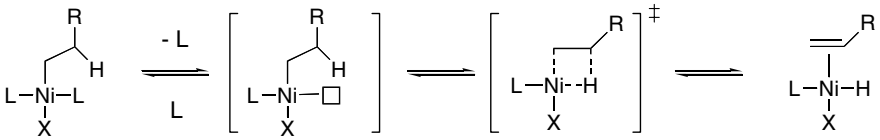


Fig. 1.9. The bite angles (θ) of typical bidentate ligands.

1.7.5
β-Hydrogen Elimination

The instability of nickel alkyl complexes, or in general, of transition metal-alkyl complexes, had long prohibited their isolation until the mid-1950s. The main reason for this instability was attributed to the weakness of the metal-alkyl bonds (thermodynamic instability). However, this was not the case; rather, the transition metal-alkyl bond strengths are comparable to those of typical elemental metal-alkyl bonds. There are two kinetic pathways that facilitate the decomposition of transition metal-alkyl complexes: one is *β*-hydrogen elimination, which was first proposed by Wilkinson; and the other is reductive elimination (see Section 1.7.4). The thermal instability of some dimethyl- and di(neopentyl)metal complexes that do not have *β*-hydrogen and are unable to undergo *β*-hydrogen elimination is mostly attributed to the ease of reductive elimination.

β-hydrogen elimination is the reverse of migratory insertion of an alkene into an Ni–H bond (Scheme 1.10(b)). As shown in Scheme 1.22, *β*-hydrogen elimination is thought to proceed via a concerted mechanism – that is, via a single transition state, where both the alkyl and *β*-hydrogen remain on the Ni, and hence the coordination number increases by one unit. Accordingly, for this process to proceed smoothly, a preceding dissociation of one L is necessary.



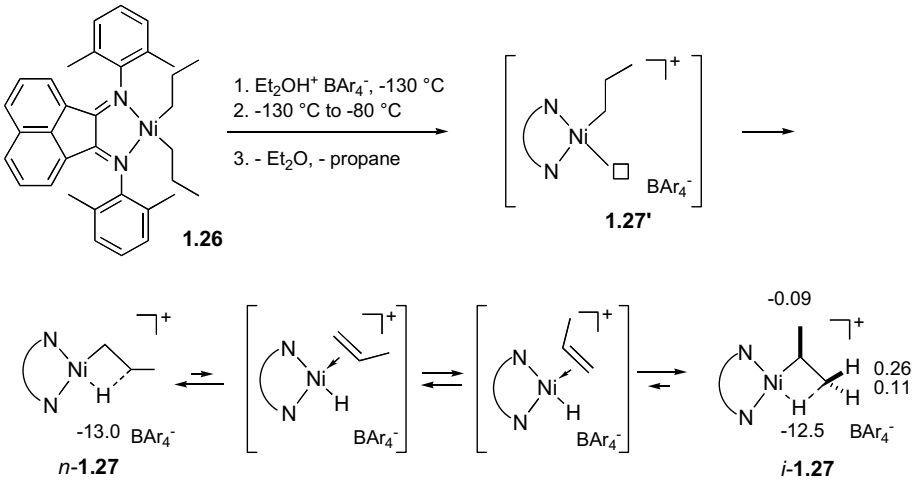
Scheme 1.22. *β*-Hydrogen elimination (towards the right) and insertion of an alkene into an Ni–H bond (towards the left).

The unusual stability of dialkyl(bpy)Ni(II) complexes (**1.25**, Scheme 1.19) may be attributed to the bidentate bipyridyl ligand, which is not only a good *σ*-donor, but also a good *π*-acceptor. Moreover, it binds tightly to an Ni and always keeps the Ni(II) saturated.

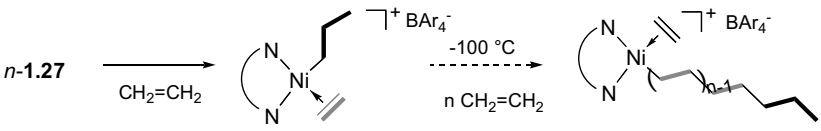
In contrast, the diimine complex **1.26**, which is of close structural similarity to **1.25** but of different electronic nature and steric requirement for the ligand, is rather unstable. Although **1.26** is stable in the solid state for an indefinite period at temperatures below −15 °C and under inert atmosphere, it is thermally sensitive when in solution, and liberates the reductive elimination product, hexane, in CD_2Cl_2 above −20 °C [41]. The cationic diimine complex **1.27′**, generated by protonation with 1 equiv. of $Et_2O^+H\ BAr_4^-$ and liberation of 1 mol of propane at low temperature, is formulated as the $d^8$14e $[L_2XNi(II)]^+$ cationic complex. These types of coordinatively unsaturated cationic metallic species tend to show a *β*-hydrogen agostic structure, a structural equivalent to the transition state supposed for *β*-hydrogen elimination (Scheme 1.22) [42]. The structure of *i*-**1.27** has been well

characterized using low-temperature ^{1}H NMR. For example, at −130 °C in $CDCl_2F$, the agostic hydrogen is observed at −12.5 ppm (t, J = 19 Hz). The other two geminal hydrogens on the agostic methyl group are chemically inequivalent and appear at 0.26 and 0.11 ppm (multiplet). The methyne proton appears as a complex multiplet, which becomes a septet above −80 °C. Dynamic NMR analysis has revealed that the exchange of agostic and nonagostic protons occurs with a $\Delta G^{\neq}$ of 8.0 Kcal mol^{-1} at −99 °C, and the barrier for the exchange of agostic and nonagostic methyl groups is slightly higher, 9.0 Kcal mol^{-1} at −77 °C.

It should be realized that there is a crucial difference between the agostic structures in Schemes 1.22 and 1.23. In the equilibrium in Scheme 1.22, the agostic complex is a transition state structure for β-hydrogen elimination (towards the right) or for migratory insertion of an alkene into the Ni–H (towards the left). On the other hand, in the equilibrium initiated from cationic unsaturated complexes **1.27′** ($d^8$14e) (Scheme 1.23), the agostic complexes *i*-**1.27** and *n*-**1.27** are intermediates and lower in energy than the alkene–NiH complexes shown in square brackets in Scheme 1.23. *n*-**1.27** serves as a very efficient catalyst for the polymerization of ethylene. As shown in Scheme 1.24, the polymerization of ethylene even proceeds at −100 °C.



Scheme 1.23. Generation of a coordinatively unsaturated alkylnickel(II) cationic complex **1.27′** and its isomerization to β-hydrogen agostic complexes *n*-**1.27** and *i*-**1.27**. The figures indicate chemical shifts (in ppm) in ^{1}H NMR.

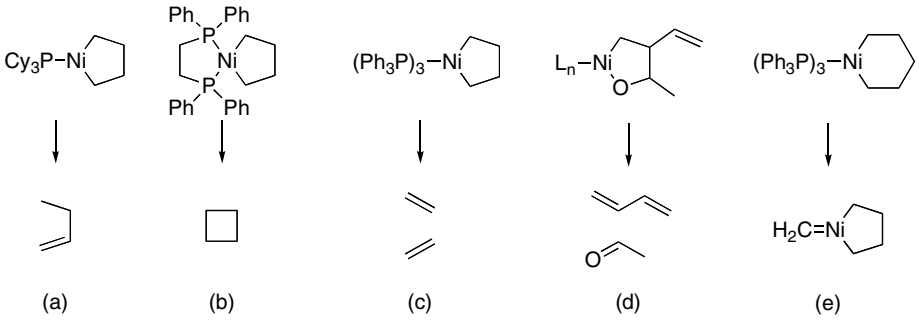


Scheme 1.24. Polymerization of ethylene catalyzed by an α-(diimine)alkylnickel(II) cationic complex.

The Ni(II)- and Pd(II)-α-diimine complexes, such as **1.26**, which were developed recently by Brookhart and others, exhibit high reactivity for the polymerization of ethylene (Scheme 1.24), the copolymerization of ethylene and functionalized alkenes, the oligomerization of ethylene and α-olefins, and the homo-polymerization of cyclic and internal acyclic olefins [43].

1.7.6
α- and β-Carbon Elimination (C–C Bond Cleavage)

By using nickellacycles as the probes, Grubbs has demonstrated that all of the competitive reactions, namely β-hydrogen elimination (Scheme 1.25(a)), reductive elimination (Eq. (b)), and reductive ring opening (Eq. (c)) (the reverse of oxidative cyclization), are subject to the number of phosphine ligands in the complexes [44]. The β-hydrogen elimination proceeds cleanly when Cp_3P is used as the ligand. The ligand has a large cone angle, and hence blocks the coordination of another ligand to the Ni(II) center, keeping the fourth coordination site vacant. With DPPE, reductive elimination giving rise to cyclobutane takes place selectively. The reductive ring opening (Eq. (c)) accompanies cleavage of the C_β–C_γ bond and is closely related to the β-hydrogen elimination, the cleavage of the C_β–H_β bond. However, examples of this type of C–C bond cleavage reaction are very scare, most likely because, for this reaction to proceed the Ni–C_α and C_β–C_γ bonds must be *syn* to each other, and this conformation is only possible for nickellacycloalkanes. For most alkylnickel(II) species, the alkyl chains take on an extended zigzag conformation and only the C_β–H_β bonds take a conformation *syn* to the Ni–C_α bonds. In fact, $(PPh_3)_2Pt^{2+}(n\text{-Bu})_2$ undergoes β-hydrogen elimination approximately 10^4 times faster than $(PPh_3)_2Pt^{2+}(CH_2)_4$ (cf. Scheme 1.25(a), Pt^{2+} in place of Ni^{2+}) [45]. The catalytic version of C–C bond cleavage has been developed recently (Scheme 1.25(d)) [46]. Again in this case, a five-membered ring is a common structural motif. Equation (e) in Scheme 1.25 demonstrates a novel C_α-elimination, providing a carbene complex which serves as the catalyst for the olefin metathesis [47]. This

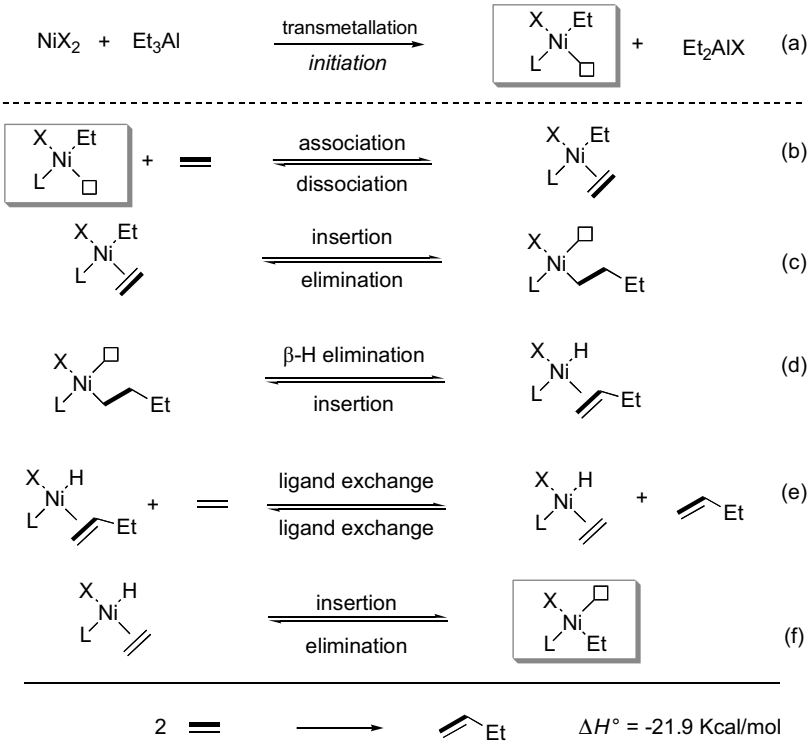


Scheme 1.25. Effects of the number of the coordinated phosphine ligands on the modes of decomposition of nickellacyclopentane and -cyclohexane. a) β-Hydrogen elimination (L_1); b) reductive elimination (L_2); c) β-carbon elimination (L_3); and e) α-carbon elimination (L_3).

reaction was reported by Grubbs as early as 1978, at which time the catalyst performance was modest, though this is in fact a protocol of the ruthenium-based Grubbs olefin metathesis catalysts which is currently undergoing investigation [48].

1.8 Catalytic Reactions

Catalytic reactions usually start with oxidative addition and end up with either reductive elimination or β-hydrogen elimination with regeneration of a catalytically active nickel species. During these two events, the insertion of a variety of unsaturated molecules, transmetallation with organometallics, and skeletal rearrangement take place. First, we should consider the Wilke 1-butene formation, the dimerization of ethylene (Eq. (1.1)), elementary steps of which are shown in Scheme 1.26. The reaction starts with transmetallation between a catalytic amount of a

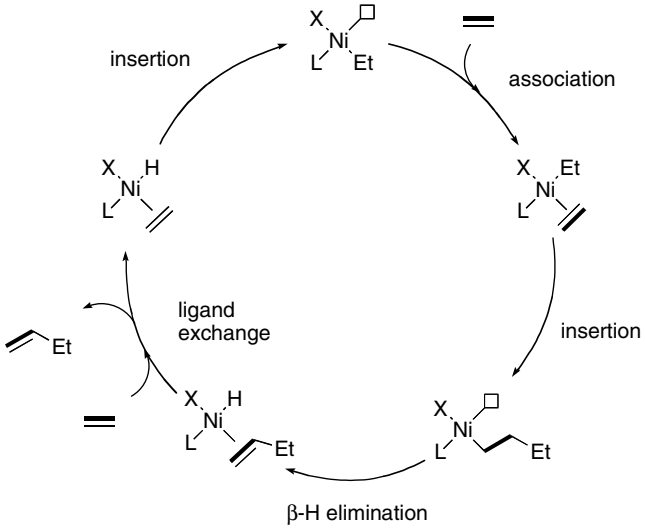


Scheme 1.26. Elementary processes for the Ni-catalyzed dimerization of ethylene. Summation of Eqs. (b) to (f) leaves 2 mol ethylene as the starting material and 1 mol 1-butene as the product. (The symbol □ denotes a vacant site on Ni.)

Ni(II) salt and Et_3Al, which produces the key reactive intermediate, EtNi(II) species with one vacant coordination site (Eq. (a)). The EtNi(II) species then reacts with ethylene to form (η^2-ethylene)ethylnickel(II) (Eq. (b)). The insertion of ethylene into the Ni-ethyl bond yields the BuNi(II) species (Eq. (c)), which is coordinatively unsaturated and undergoes β-hydrogen elimination to give (η^2-1-butene)nickel(II)-hydride (Eq. (d)). Ligand exchange between 1-butene and ethylene (Eq. (e)), followed by insertion of ethylene into the Ni–H bond regenerates the coordinatively unsaturated EtNi(II) species (Eq. (f)).

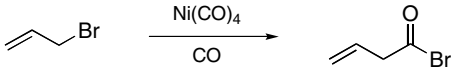
The summation of Eqs. (b) to (f) in Scheme 1.26 leaves 2 mol ethylene as the starting material and 1 mol 1-butene as the product. All of the processes (b) to (f) are microscopic reverse, and hence the driving force of this reaction is partly ascribed to its large exothermic property ($\Delta H^\circ = -21.9$ Kcal mol^{-1}). Provided that the β-hydrogen elimination step (Eq. (d)) was very slow, then the reactions (b) and (c) would be repeated infinitely and provide polyethylene. The number of times that the cycle of Eqs. (b) and (c) repeat depends on the reaction conditions (temperature, pressure, etc.) and the types of ligands. Under Wilke's original conditions, 1-butene was produced almost exclusively [1, 49]. The Shell higher olefin process (SHOP), which was started in 1977, typically produces a mixture of 1-butene, 1-hexene, and 1-octene in varying ratios, these being controlled by market demands [3, 50].

The means of expression in Scheme 1.26 is both intricate and time-consuming in drawing. Hence, catalytic reactions are frequently presented as shown in Scheme 1.27, where the catalytic species are placed on a circle and the reactants and products are placed outside the circle, with the curved arrows directing inwards and outwards, respectively. As is apparent from Scheme 1.27, the ligand L and an anionic species do not change all through the reaction, and in this sense



Scheme 1.27. Catalytic cycle presentation of the Ni-catalyzed dimerization of ethylene.

these are regarded as a *spectator ligand* and a *spectator anion*, respectively; indeed, for clarity they are sometimes omitted from the schemes.

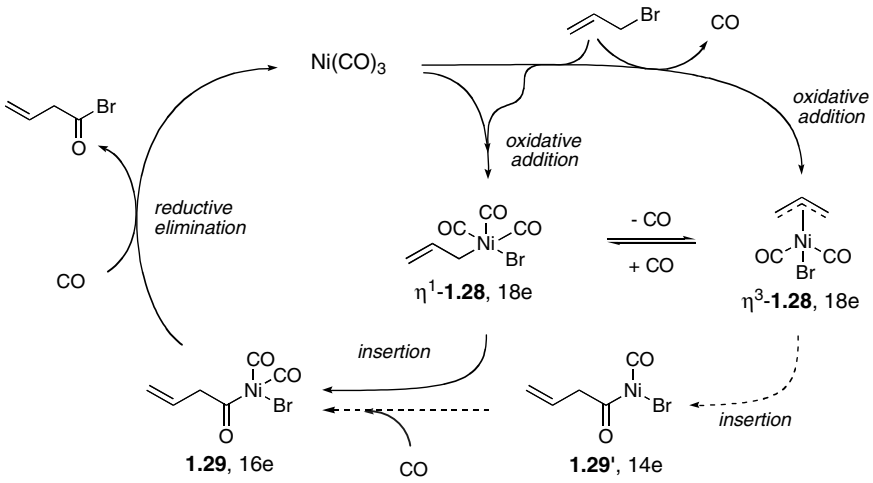


(1.5)

Equation (1.5) illustrates the carbonylation of allyl bromide catalyzed by $Ni(CO)_4$ under an atmosphere of CO. The reaction provides 3-butenoyl bromide and, as illustrated in Scheme 1.28, proceeds in order of: 1) oxidative addition of $Ni(CO)_3$ into the C–Br bond of allyl bromide, giving **1.28**; 2) migratory insertion of CO into the Ni–allyl bond, forming an acylnickel species **1.29**; and 3) reductive elimination to yield 3-butenoyl bromide with regeneration of $Ni(CO)_3$. For most organic chemists, this reaction may be easier to access than that of Eq. (1.1), because it possesses many familiar functionalities and has a reaction pattern similar to that of the Grignard reaction. However, when looked at in detail, this reaction is more complicated than it appears. For example, in Scheme 1.28 $Ni(CO)_3$ is proposed as an intermediate, but the question remains as to whether this is reasonable. The dissociation of $Ni(CO)_4$ to $Ni(CO)_3$ and CO is highly endothermic, and $Ni(CO)_3$ must be present in a minute concentrations, especially under the carbonylation conditions (an atmosphere of CO).

$$Ni(CO)_4 \rightarrow Ni(CO)_3 + CO \qquad \Delta H^\circ = +22\sim23 \text{ Kcal mol}^{-1}$$

The initial oxidative addition can proceed either through coordination of the C=C double bond of allyl bromide to $Ni(CO)_3$ or through the coordination of bromide to $Ni(CO)_3$, which provide the η^3-allyl complex (η^3-**1.28**) or the η^1-allyl

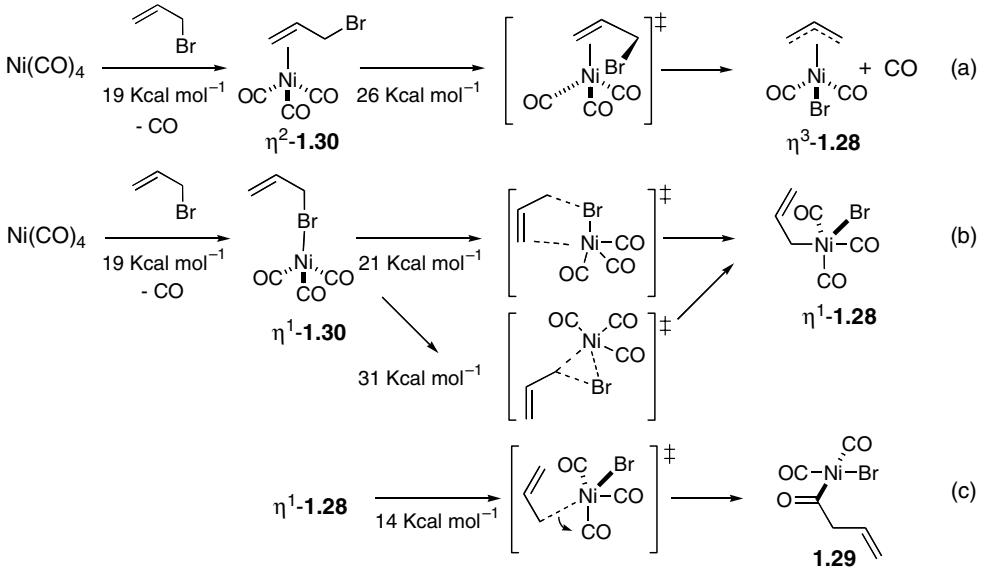


Scheme 1.28. Catalytic cycle for the nickel-catalyzed carbonylation of allyl bromide under an atmosphere of CO.

complex (η^1-**1.28**), respectively. The migratory insertion of CO of η^1-**1.28** provides the $d^8$16e acyl complex (**1.29**), whereas the reaction of η^3-**1.28** leads to the coordinatively unsaturated $d^8$14e acyl complex (**1.29′**). Two additional questions here are: 1) Is the latter process realistic? and 2) How does the allyl group migrate – does CO move toward the allyl C–Ni bond, or does the allyl group move and ride on the C of CO?

Calculation methods at high levels are very helpful in addressing these questions, especially with regard to the transition state structures and the activation energies for each of the elementary steps. The results obtained at the DFT (B3LYP) level are sketched out in Schemes 1.28 and 1.29 [51].

With regard to the problem of which of $Ni(CO)_4$ or $Ni(CO)_3$ is a real species, the calculations conclude that both are equally probable; the reaction of $Ni(CO)_3$ with allyl bromide – irrespective of the formation of the η^2-bound complex η^2-**1.30** or the η^1-bound complexes η^1-**1.30** – is exothermic and barrier free. On the other hand, the formation of η^2-**1.30** and η^1-**1.30** by displacement of CO from $Ni(CO)_4$ is endothermic, and the activation energy is the same (19 Kcal mol^{-1}) for both pathways (Eqs. (a) and (b) in Scheme 1.29). The following oxidative addition process is rate-determining, and the reaction giving rise to η^3-**1.28** proceeds as shown in Eq. (a) in Scheme 1.29, where formation of the Ni–C and Ni–Br bonds and loosening of the Ni–CO bond anti to the C–Br bond proceed in concert. For the formation of η^1-**1.28**, two routes are conceivable (Eq. (b)); one route involves migration of

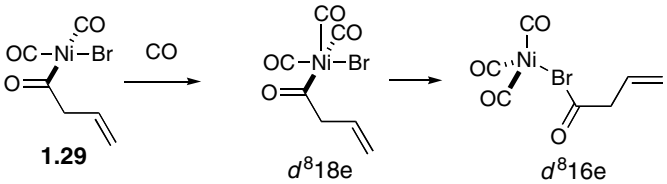


Scheme 1.29. Microscopic views of oxidative addition of $Ni(CO)_4$ into the allyl C–Br bond (Eqs. (a) and (b)) and migrative insertion (Eq. (c)). Values in Kcal mol^{-1} refer to the activation energy.

the allyl fragment from the halogen to the metal, and is less probable owing to its large activation energy (31 Kcal mol^{-1}). The other route involves a slide of the allyl fragment along a direction parallel to the Ni–Br bond, where the carbon originally bound to bromine becomes the terminal methylene carbon in the final product. η^1- and η^3-**1.28** isomerize to each other either by losing ($\eta^1 \rightarrow \eta^3$) or gaining CO ($\eta^3 \rightarrow \eta^1$) and by overcoming a barrier of less than 10 Kcal mol^{-1}.

As for the migratory insertion of CO, η^1-**1.28** is more reactive than η^3-**1.28** and forms the square-planar acylnickel complex **1.29** (Eq. (c), Scheme 1.29), during which the allyl group migrates to the carbon of one of the two *cis*-coordinated CO and, simultaneously, the Ni–CO bond becomes shorter. The same acylnickel complex **1.29** can be derived from η^3-**1.28**, although this route is apparently unfavorable owing to the inherent instability of the coordinatively unsaturated $d^8$14e complex, **1.29′** ($\Delta H^\circ_{1.29'} - \Delta H^\circ_{1.29} = 11$ Kcal mol^{-1}).

Once the acylnickel complex **1.29** is formed, the following few steps are all barrier-free, exothermic, and proceed spontaneously (Scheme 1.30). The coordination of CO facilitates reductive elimination (associative mechanism, see Section 1.7.4) to yield first the Ni(0)-η^1-acyl bromide complex and then the acyl bromide, the final product.



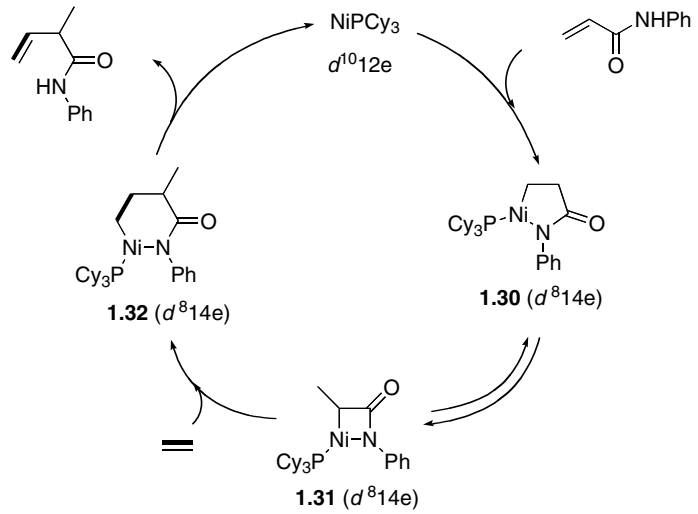
Scheme 1.30. Microscopic views of reductive elimination of **1.29** giving rise to the final product. All the steps are exothermic and barrier free, and the reactions proceed spontaneously.

The example shown in Scheme 1.31 emphasizes the importance of the *electronic* and *steric* effects of the ligands. Because of the stability (to air) and the ease of handling (solid and odorless), PPh_3 has been used most widely as the ligand of catalytic reactions. PPh_3 is not only an appropriate electron donor to an Ni, but also an electron acceptor from the Ni (back donation or back bonding, *vide infra*). The molecular size allows it to coordinate to an Ni by four molecules, forming $Ni(PPh_3)_4$, which is a flammable solid and usually prepared in situ, for example:

NiX_2 + DIBAL (or Zn-dust, Et_2Zn, a reducing agent) + 4 PPh_3 or

$Ni(cod)_2$ + 4 PPh_3.

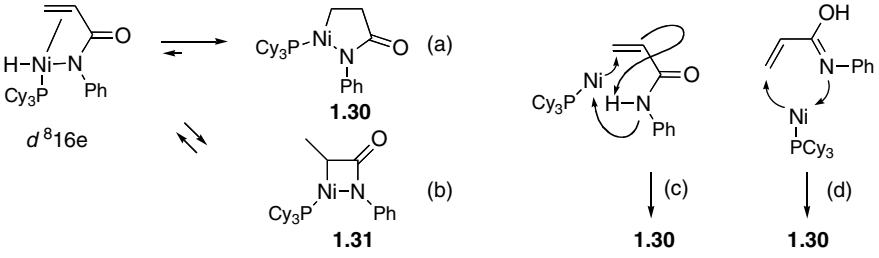
However, as shown in Scheme 1.31 (and also in the subsequent chapters), the success (course) of reactions depends markedly on the *electronic* and *steric* effects



Scheme 1.31. Catalytic cycle for the Ni-catalyzed hydrovinylation of acrylamide with ethylene.

of the ligands. In order to promote the particular reaction shown in Scheme 1.31, the use of sterically bulky and highly basic ligand, PCy_3 (Cy = cyclohexyl), is essential. This ligand is so bulky that the maximum number which can coordinate to an Ni is limited to two. In solution, $Ni(PCy_3)_2$ equilibrates with $Ni(PCy_3) + PCy_3$. The thus-generated $NiPCy_3$ complex is coordinatively unsaturated and shows a strong propensity to fill the vacant sites with ligands of a small size. In this particular case, $NiPCy_3$ reacts with acrylamide, a bidentate ligand, to provide 2-azanickellacyclopentane **1.30** [52]. Acrylic acid forms the 2-oxa-analogue of **1.30** [53].

The intermediate **1.30** may be formed either via initial oxidative addition of an Ni(0) upon the N–H bond followed by *endo*-hydrometallation (Scheme 1.32(a)), or via oxidative addition across acrylamide, either stepwise (Eq. (c)) or in concert (Eq. (d)). Owing to its unsaturated 14e configuration, the intermediate **1.30** is still labile and is subject to β-hydrogen elimination. *Exo*-hydrometallation – a process which



Scheme 1.32. Formation of nickellalactam **1.30** via *endo*-hydrometallation (Eq. (a)) or oxidative cyclization (stepwise Eq. (c) or concertedly Eq. (d)) and its isomerization to **1.31** via β-hydrogen elimination and *exo*-hydrometallation (Eq. (b)).

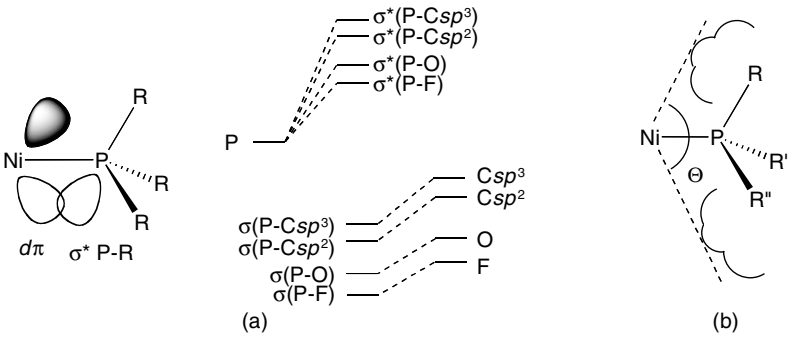
is preferred to *endo*-hydrometallation – leads however to a strained 2-azacyclobutane intermediate **1.31** (Scheme 1.32(b)). Compound **1.31** acquires a higher reactivity towards the insertion of ethylene to give a six-membered 2-aza-metallalactam **1.32**; this occurs not only because of its strain, but also because of the stability of the product **1.32**. β-Hydrogen elimination of **1.32** and reductive elimination of the thus-formed N–Ni–H intermediate provides the final product with regeneration of $NiPCy_3$. Clearly, the reductive elimination is competitive to *endo*-hydrometallation (regenerating **1.32**) or to *exo*-hydrometallation (giving the 4,5-dimethyl derivative of **1.30**).

One might propose a more straightforward mechanism, namely the direct formation of **1.31** (Scheme 1.32(b)), but this is not the case. The formation of **1.30** has been demonstrated spectroscopically; in fact, X-ray structure analysis has shown that the PEt_3 derivative of **1.30** forms a cyclic tetramer, where the Ni(II) centers have a square planar structure ($d^8$16e) with the coordination of the amide oxygen of the adjacent **1.30** unit [54].

It is worth noting that all of the intermediates **1.30–1.32** have the same electronic configuration; they differ only in the ring size, and this difference bestows each of them with unique roles in the catalytic cycle. For example, **1.32** is thermodynamically the most stable and plays a decisive role in liberating the final product, whilst **1.30** and **1.31** are configurational isomers and equilibrate to each other in favor of **1.30** (Eqs. (a) and (b) in Scheme 1.32). The major component **1.30** is not productive; rather, only the minor isomer **1.31** is productive and undergoes insertion of ethylene. An interesting point here is that in organometallic chemistry the Curtin–Hammett principle applies to *configurational* isomers, because organometallic configurational isomers can change one to another with activation energies within a few Kcal mol^{-1}, in the same way that *conformational* isomers do in organic molecules [55]. Here, the principle tells us that the ratio of products formed from conformational isomers is not determined by the *conformation population ratio*.

Although the two reactions shown in Eq. (1.1) and in Scheme 1.31 appear to be somewhat different in appearance, they are closely related to each other in terms of reaction type; the former is hydrovinylation of ethylene and the latter hydrovinylation of an alkene.

Tolman has quantified the electronic effect of various phosphine ligands on the basis of the ν(CO) (the A_1 carbonyl stretching frequencies) of a series of complexes of $Ni(CO)_3L$ (L = P ligand), based on the assumption that the more electron-donating the ligand L, the lower the frequency of ν(CO) of the complexes, and vice versa [56]. One extreme is that of the trialkylphosphine complexes, which show ν(CO) values as low as 2055 cm^{-1}. The other extreme is the PF_3 complex, which shows ν(CO) values as high as 2110 cm^{-1}. The latter type of ligands are sometimes referred to as π-acid ligands, because the σ^* orbital of, for example the P–F bond, is low in energy and able to serve as an electron pool from the Ni $d\pi$ orbitals (Scheme 1.33(a)). This back donation compensates for the weak donative Ni–P σ-bonding that stems from the weak basicity associated with PF_3. Ph_3P is inferior to R_3P as a donative ligand but is superior as a π-acid ligand, because Ph_3P has the σ^*(P-Csp^2) lying lower than the σ^*(P-Csp^3) of R_3P.



Scheme 1.33. The $d\pi$-σ^* back donation interaction (a) and the cone angle (b).

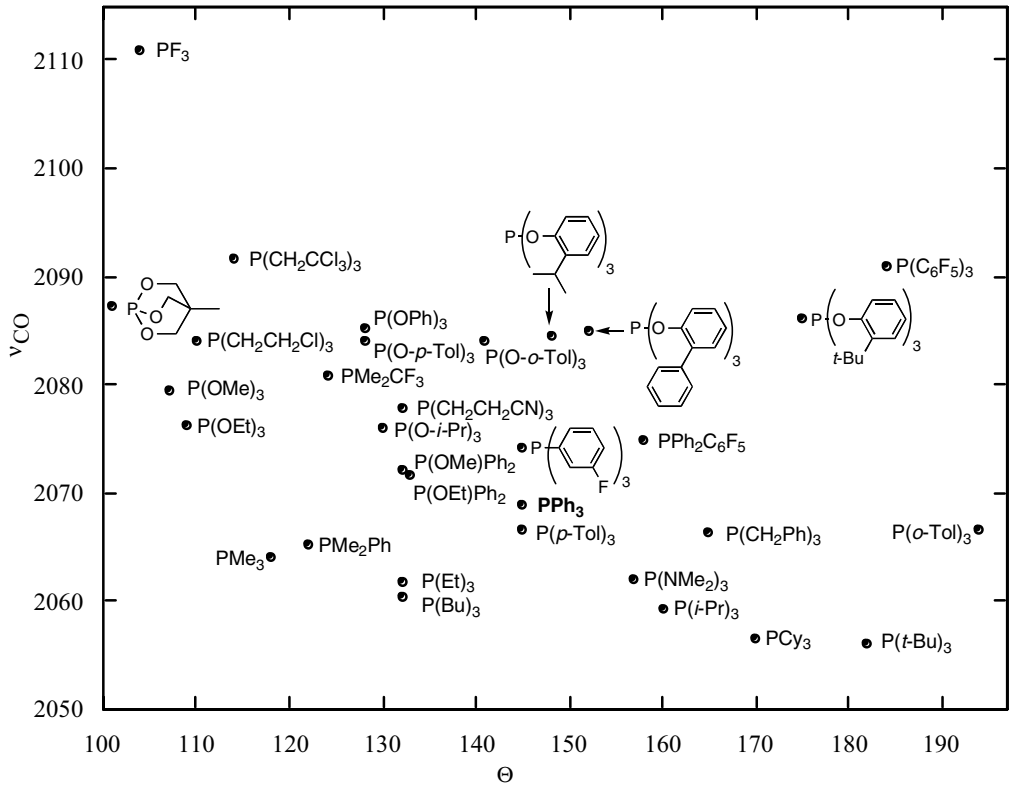


Fig. 1.10. Plots of the Tolman scales of electronic (νCO, in cm^{-1}) and the steric effects (θ, in degrees) of phosphine ligands. Reproduced from Ref. [56] with permission of the American Chemical Society.

Tolman has also evaluated the steric effects of phosphine ligands with a cone angle θ (Scheme 1.33(b)) [56]. This is determined by measuring the angle of the cone that will just contain all of the ligand molecule (space-filling model), setting the apex of the cone at an Ni.

In practice, Figure 1.10 can be used to identify the electronic and steric natures of phosphine ligands. By examining Figure 1.10 vertically, it is possible to find many phosphine ligands with different electronic natures, without changing the steric requirement of the ligand. Then, by examining the figure horizontally, alternative ligands can be found with different sizes, but without changing their electronic nature.

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2
Nickel-catalyzed Cross-coupling Reactions

Tamotsu Takahashi and Ken-ichiro Kanno

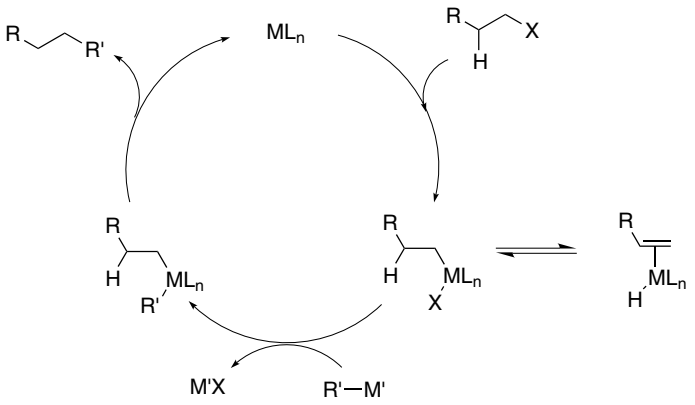
Nickel phosphine complex-catalyzed cross-coupling reaction first began with alkyl or aryl Grignard reagents, as reported by Kumada and colleagues [1] and Corriu et al. [2], and with alkenylaluminum by Baba and Negishi [3]. Since then, such cross-coupling has been recognized as one of the most useful methods for carbon–carbon bond formation in organic synthesis. Not only Grignard and organoaluminum reagents but also various organometallic compounds such as organozinc [4], organozirconium [5], organoboron [6], organotin [7], and organosilicon [8] have been found to be useful for these cross-coupling reactions. In the case of catalysts, Ni, Pd, Fe, Mn, and other transition metals can be used. In this chapter, attention is focused on the latest developments in nickel-catalyzed cross-coupling reactions investigated since 1995. Several excellent reviews on this subject have been published [9], and the reader is advised to consult these for details of nickel-catalyzed cross-coupling reactions carried out before 1995. The sections of this chapter are categorized in terms of the organic electrophiles utilized in the cross-coupling reactions.

2.1
Cross-coupling of Alkyl Electrophiles with Organometallic Compounds

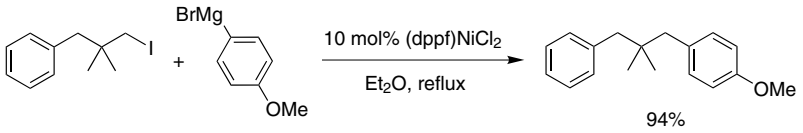
A generally widely accepted mechanism for the cross-coupling reaction is shown in Scheme 2.1. In the case of an alkyl-alkyl coupling reaction, this involves oxidative addition of alkyl electrophiles to nickel, producing alkylnickel complexes, transmetallation of alkylmetals (which affords bis(alkyl)nickel complexes), and the reductive coupling of two alkyl groups on nickel. However, alkyl electrophiles have shown unsatisfactory results in cross-coupling reactions, as the oxidative addition of alkyl electrophiles to transition metal catalysts is a slow process, whereas β-hydrogen elimination of the resulting alkyl groups on metal proceeds very easily [10, 11]. Consequently, until now the organo-electrophiles have been limited to aryl or alkenyl moieties. In order to circumvent this difficulty, alkyl iodide without β-hydrogen was used, as shown in Eq. (2.1) [12].

Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6



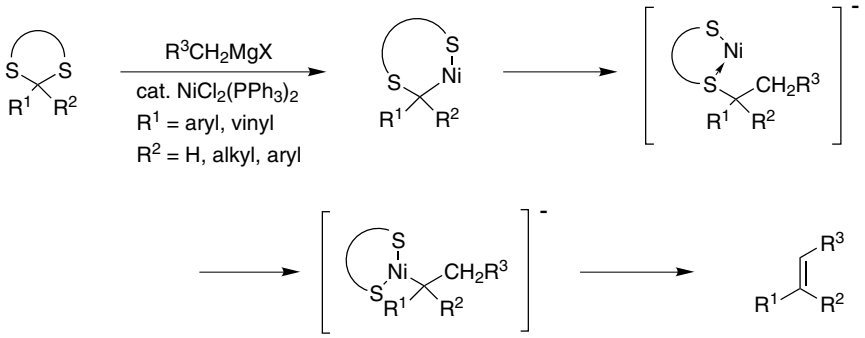
Scheme 2.1. A general mechanism of the metal-catalyzed cross-coupling reaction.



(2.1)

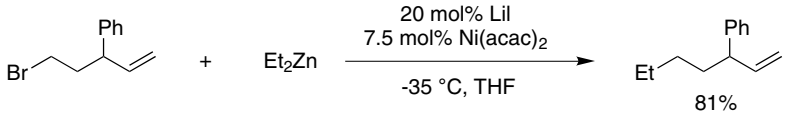
Dithioacetals can be used for the coupling reaction with Grignard reagents, with chelation of the S atom assisting activation of the alkyl-S bond for the cross-coupling reaction, as shown in Scheme 2.2 [13].

It is interesting to note that a functional group in the alkyl electrophiles has a remarkable effect on the cross coupling reaction. As shown in Eq. (2.2), when the carbon–carbon double bond, carbonyl group, and nitrile are in the alkyl electrophiles, the cross-coupling proceeds smoothly. The alkyl bromide without such functionalities affords only a bromine–zinc exchange product in high yields

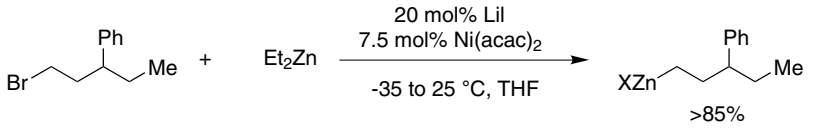


Scheme 2.2. Nickel-catalyzed alkene formation from dithioacetals and Grignard reagents.

(Eq. (2.3)). However, when one double bond is present in the molecule, the corresponding ethylated product is obtained in >80% yield [14].

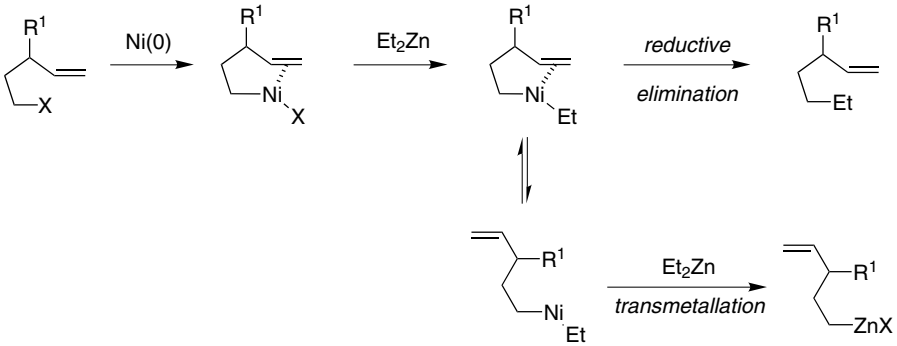


(2.2)



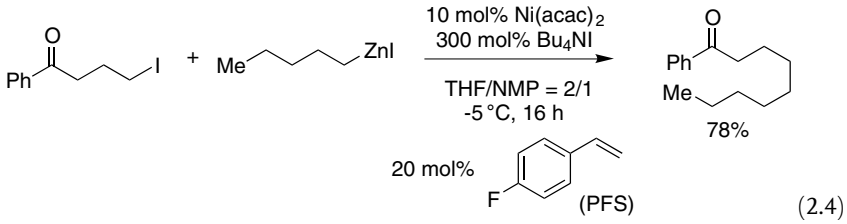
(2.3)

This indicates that the reductive elimination step from the dialkylnickel intermediate is accelerated by coordination of the carbon–carbon double bond (see Section 1.7.4; Eq. (1.4)). In the absence of the carbon–carbon double bond, transmetallation of alkylnickel to zinc occurs more rapidly than reductive elimination, and therefore a bromine–zinc exchange product is obtained, as shown in Scheme 2.3 [14].

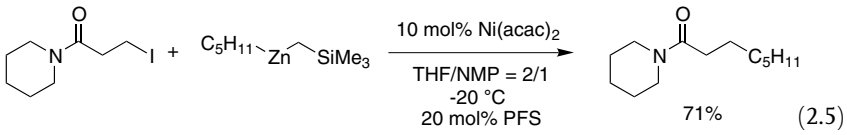


Scheme 2.3. Effects of π-coordination on the nickel-catalyzed alkyl-alkyl coupling reaction.

The important point here is the acceleration of the reductive elimination of the dialkylnickel species, this being achieved by coordination of unsaturated bonds. In the above case, the double bond is in the alkyl electrophiles. The addition of *p*-fluorostyrene has a similar effect, as the diorganozinc reacts with primary alkyl iodides in the presence of a $Ni(acac)_2$ catalyst and *p*-fluorostyrene. Under these conditions, alkylzinc halides do not provide the product. The use of Bu_4NI improves the reaction in the case of alkylzinc halides; for example, primary and secondary alkylzinc iodides can react with functionalized primary alkyl iodides in the presence of $Ni(acac)_2$ catalyst (Eqs. (2.4) and (2.5)) [15].

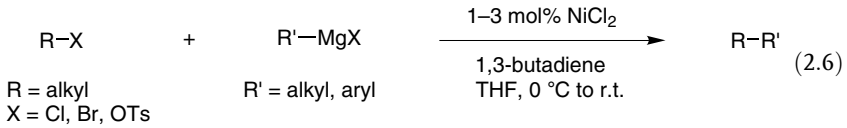


(2.4)



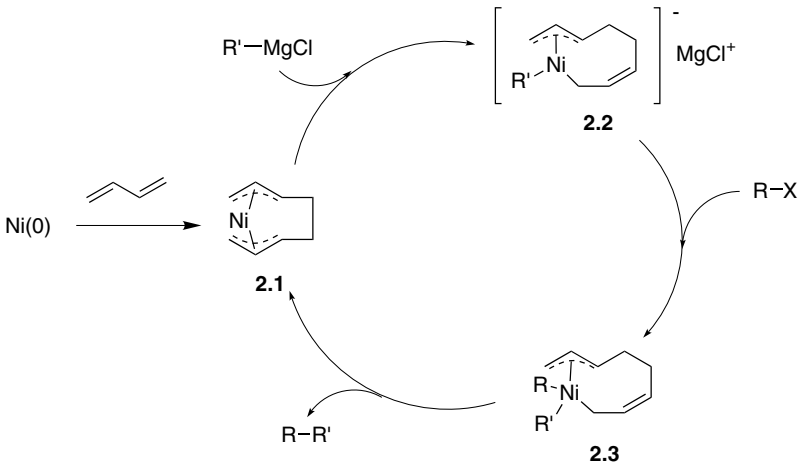
(2.5)

The following example outlines the use of butadiene to control the nickel metal center, whereby alkyl chlorides, bromides or tosylates react with alkyl or aryl Grignard reagents in the presence of nickel chloride and butadiene (Eq. (2.6)) [16].



(2.6)

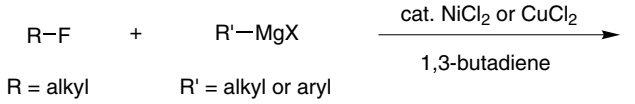
According to the proposed mechanism, the key point of this reaction is the use of butadiene (Scheme 2.4). First, butadiene dimerizes on nickel to give a bis(π-allyl)nickel species **2.1**. Alkyl Grignard reagent then reacts with the nickel species such that alkyl nickel **2.2** is formed as an ate complex. This ate complex, in turn,



Scheme 2.4. A proposed mechanism for the butadiene-assisted coupling reaction catalyzed by nickel.

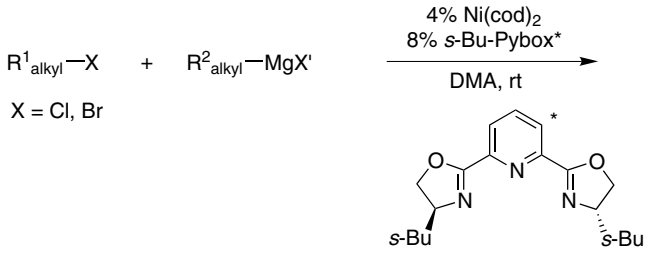
reacts with alkyl electrophiles to form bis(alkyl)nickel intermediate **2.3**. The formal oxidation state of this nickel complex **2.3** is 4. Nucleophilic attack of the nickel metal center of the ate complex to alkyl halides appears to proceed rapidly. β-Hydrogen elimination from alkyl nickel intermediates is disturbed as the coordination sites of the nickel center were occupied by bis(alkyl)butadiene moiety (see Section 1.7.5). A radical mechanism is excluded in this reaction [16].

This system could be applied to the cross-coupling reaction of alkyl fluoride compounds (Eq. (2.7)). Although $CuCl_2$ produced the best results as a catalyst, nickel chlorides gave yields of between 44% and 67% of the cross-coupling products [17].



(2.7)

Cross-coupling of secondary alkyl bromides was successfully achieved with *s*-BuPybox in the presence of $Ni(cod)_2$ in DMA (Eq. (2.8)). The $Ni(cod)_2$/*s*-BuPybox can also be employed for the coupling reaction of primary alkyl iodide or bromide at room temperature [18].

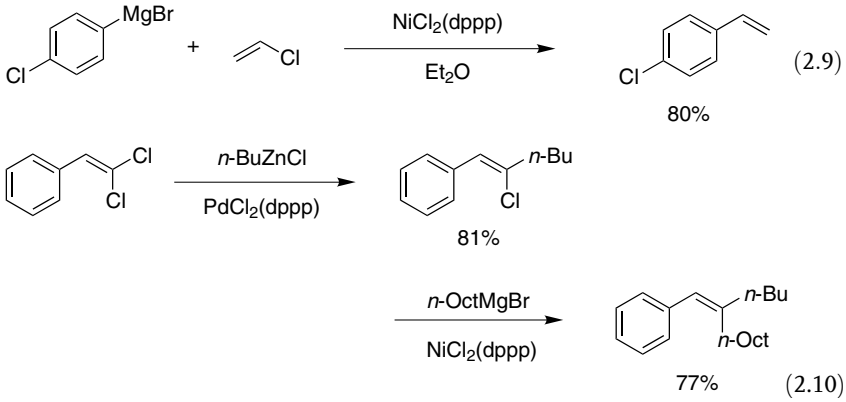


(2.8)

2.2
Cross-coupling of Alkenyl Electrophiles with Organometallic Compounds

The cross-coupling reaction of alkenyl halides with Grignard reagents catalyzed by nickel-phosphine complexes was first developed in 1972 [1, 2], and with alkenylaluminum reagents in 1976 [3], as referred to above.

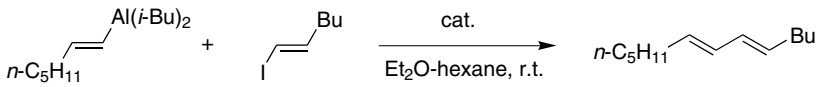
The reactivity of alkenyl halide is high, and differs from that of alkyl halides (see Section 2.1). As shown in Eq. (2.9), vinyl chloride is more reactive than aryl chloride [19]. It is also of interest to note that a nickel-catalyzed cross-coupling reaction is more powerful than the palladium-catalyzed reaction, and this feature can be used for the stepwise cross-coupling reaction of β,β-dichlorostyrene, as shown in Eq. (2.10) [20]. In the first step of the reaction, one C–Cl bond trans to the phenyl group in β,β-dichlorostyrene reacted with the organozinc reagent in the presence of the palladium catalyst. The remaining C–Cl bond could react with the Grignard reagent, catalyzed by the nickel complex, to afford the corresponding β,β-dialkylated styrene in high yield.



(2.9)

(2.10)

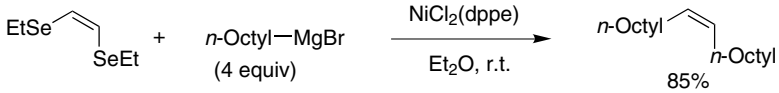
As for alkenyl-alkenyl coupling reaction, stereoselectivity of the Ni-phosphine-catalyzed reaction is lower than that of the Pd-catalyzed reaction, as shown in Eq. (2.11) [3]. When alkenyl electrophiles have certain functional groups (e.g., a nitro group) which is reactive towards low-valency nickel metal complexes, then Pd should be used as the catalyst. Alkenylzinc reagents are very efficient for alkenyl-alkenyl cross-coupling reactions, and alkenylzirconium can also be used [22].



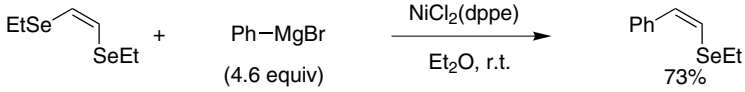
cat $Ni(acac)_2$ / DIBAL / PPh_3 70%; 95% *E,E*
cat $PdCl_2(PPh_3)_2$ / DIBAL 74%; 99% *E,E*

(2.11)

During recent years, nickel-catalyzed cross-coupling has been applied to the stereoselective reaction of alkenyl sulfides [21], selenides [23–25], tellurides [26], triflates [27], and phosphates [28–30]. As shown in Eq. (2.12), cross-coupling of (*Z*)-1,2-bis(ethylseleno)ethene with the alkyl magnesium bromides proceeds at both of the C–Se bonds to afford symmetrical alkenes in high yield with complete retention of configuration. In the case of phenylmagnesium bromide, the monoarylation occurs at one of the C–Se bonds to afford (*Z*)-2-ethylselenostyrene (Eq. (2.13)) [24].

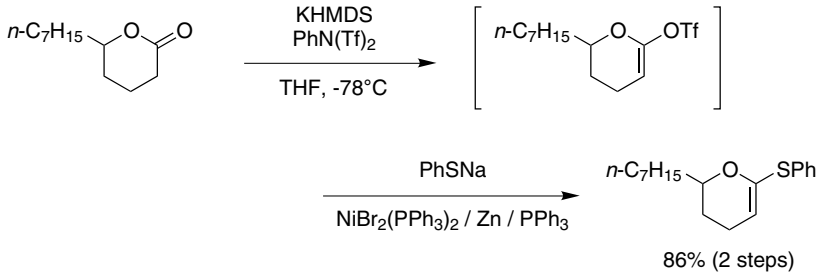


(2.12)



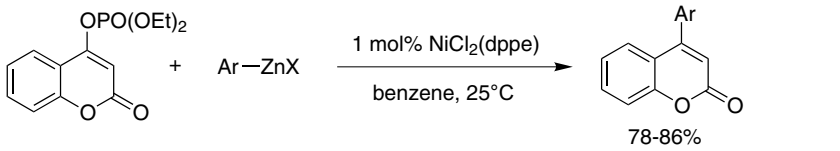
(2.13)

α-Arenesulfanyl enol ether is prepared by the cross-coupling of enol triflates, which is converted from a lactone, as shown in Eq. (2.14) [27].



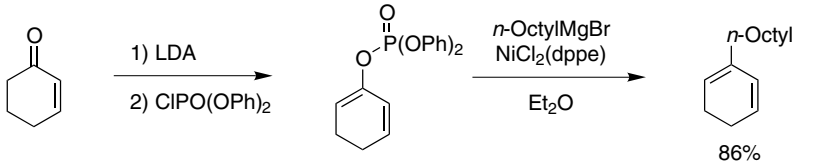
(2.14)

In order to synthesize 4-substituted coumarin, a nickel-catalyzed Negishi cross-coupling was used using arylzinc reagent (Eq. (2.15)) [29].



(2.15)

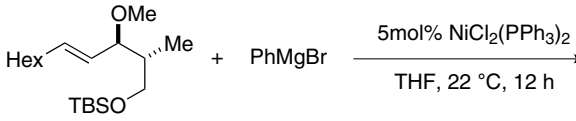
Not only alkenyl electrophiles but also dienyl compounds can be used for the coupling reaction. The reaction shown in Eq. (2.16) is the nickel-catalyzed cross-coupling of dienyl phosphate with alkyl Grignard reagent [30].



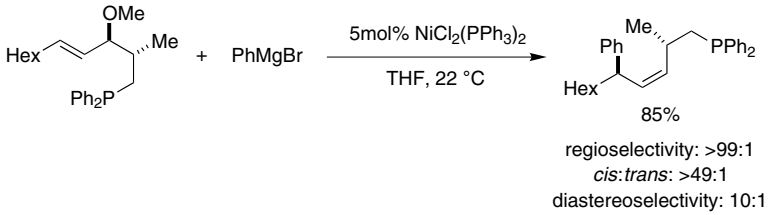
(2.16)

2.3 Cross-coupling of Allyl Electrophiles with Organometallic Compounds

The reactions of allylic ethers with alkyl or phenyl Grignard reagents do not proceed, even in the presence of a nickel catalyst. When a phosphine moiety is in the allylic ethers, selective carbon–carbon bond formation proceeds, as shown in Eqs. (2.17) and (2.18). The key point of this reaction is the coordination of the phosphine moiety to the nickel metal center [31, 32].



(2.17)



(2.18)

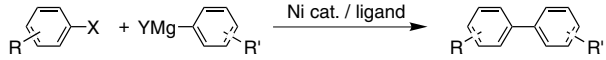
2.4 Cross-coupling of Aryl Electrophiles with Organometallic Compounds

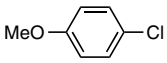
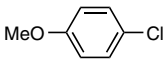
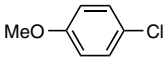
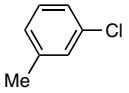
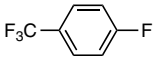
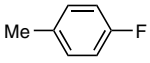
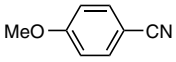
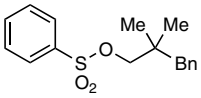
The aryl-aryl coupling reaction is a high-activity area of cross-coupling reactions which has attracted much attention among industrial applications [33]. Halides, nitriles, and sulfonates have been used as aryl electrophiles. As with arylmetal compounds, aryl Grignard reagents and arylboron compounds are mainly used. Recent results for aryl-aryl coupling are summarized in Table 2.1 for Grignard reagents, and in Table 2.2 for arylboron compounds. Recent research investigations have focused on the use of relatively unreactive electrophiles such as aryl chlorides and fluorides, and mild conditions such as room temperature.

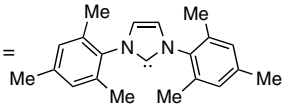
Nickel-catalyzed cross-coupling reactions between aryl Grignard reagents and aryl chlorides can proceed effectively, even at ambient temperature. In these cases, appropriate selection of the ligand for the nickel catalysts is essential. Sterically demanding *N*-heterocyclic carbenes [34], hindered alkylphosphines [34], and dialkylphosphine sulfides [35] were chosen to be used as effective ligands (entries 1–3 in Table 2.1). In contrast, the corresponding palladium-catalyzed reactions with a *N*-heterocyclic carbene ligand require a higher temperature (80 °C) [36], but this may lead to problems of selectivity. Under refluxing THF, a heterogeneous Ni/C catalyst with PPh_3 also works for the cross-coupling reaction (entry 4) [37–39].

Nickel catalysts can activate unreactive C–F and C–CN bonds of aryl electrophiles. In the cross-coupling reactions with aryl fluorides, nickel catalysts with *N*-heterocyclic carbene ligands show excellent reactivity (entry 5) [40], and catalysts with relatively simpler ligands (e.g., DPPE, DPPP, or DPPF) also have sufficient activity (entry 6) [41]. These reactions can proceed at ambient temperature. In cross-couplings with nitriles as electrophiles, pre-treatment of the Grignard reagents with stoichiometric quantities of alkoxides or sulfides is necessary in order to prevent direct reaction of the nucleophiles with the nitrile groups (entry 7) [42–44]. Among the ligands examined, the nickel-trimethylphosphine complex provided the best results.

Tab. 2.1. Nickel-catalyzed cross-couplings of aryl electrophiles with Grignard reagents.



Entry	*Electrophile*	*Grignard*	*Catalyst*	*Ligand*	*Conditions*	*Yield [%]*	*Reference (s)*
1		PhMgCl	$Ni(acac)_2$	IMes[a]	THF, r.t.	71	34
2		PhMgCl	$Ni(acac)_2$	*t*-Bu_3P	THF, r.t.	71	34
3		PhMgCl	$Ni(cod)_2$	*t*-$Bu_2P(S)H$	THF, r.t.	96	35
4		PhMgCl	Ni/C	PPh_3	THF, reflux	83	37–39
5		PhMgBr	$Ni(acac)_2$	IMes[a]	THF, r.t.	98	40
6		PhMgCl	$Ni(acac)_2$	DPPF	THF, r.t.	59	41
7		PhMgO*t*-Bu	$NiCl_2(PMe_3)_2$	–	THF, 25–60 °C	91	42–44
8		*p*-*t*-BuC_6H_4MgBr	$NiCl_2(dppf)$	–	THF, reflux	84	45

[a] IMes = 

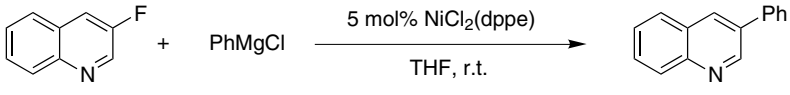
Usually, four mechanisms are considered for cross-coupling reactions of aryl halides. These include: 1) nucleophilic aromatic substitution; 2) elimination–addition via an aryne intermediate; 3) a radical reaction; and 4) a polar pathway, probably via oxidative addition. Two mechanisms have been suggested for the cross-coupling reactions mentioned above. One is a polar reaction via oxidative additions based on ρ-values of the substituent effects on the aryl fluorides [40], while another possibility is an elimination–addition mechanism similar to a substitution reaction of 2-fluoropyridine with organolithium reagents. An ate complex of aryl-substituted nickel intermediate has also been proposed as a possible intermediate [41].

A unique reactivity of Grignard reagents toward arenesulfonate esters in the presence of nickel catalysts has been reported [45]. When a neophyl ester of arenesulfonate is treated with an aryl Grignard reagent in the presence of a catalytic amount of $NiCl_2$(dppf), C–S bond activation of the sulfonate occurs selectively instead of C–O bond cleavage to afford the corresponding biaryls (entry 8).

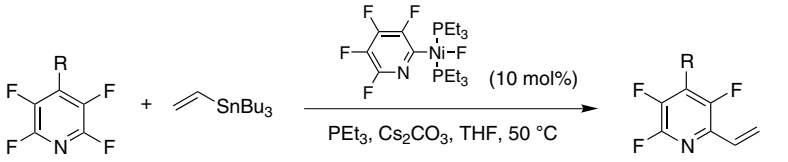
The coupling reaction conditions of arylboron compounds are summarized in Table 2.2 [46]. Recently, cross-coupling with organoboranes has been optimized as being applicable for aryl chlorides (entries 1–5) [47–52] and aryl sulfonates (entries 6–10) [53–57], without any loss of efficiency. Compared with an aryl Grignard reagent, the reactivity of arylborane towards aryl chloride is different. In the case of Pd-catalyzed coupling, the reaction proceeds at room temperature with electron-rich and sterically hindered phosphine or *N*-containing carbene ligands. In the case of Ni-catalyzed reactions, a higher temperature is required, but functional groups such as CN, CHO, CO_2Me, COMe, NHAc, OMe, and NH_2 are tolerated in the reaction of aryl chloride.

The use of arenesulfonates improved the reaction temperature, such that the reaction would proceed even at room temperature (entry 10) [57]. Somewhat simple phosphines such as DPPF, PCy_3, and PPh_3 are sufficiently effective. It is of interest to note that palladium catalysts with the same ligands did not lead to the product, and a nickel catalyst has an advantage over palladium in this respect.

Aryltrimethylammonium salt has been used for the coupling of Grignard reagent [60]. In the case of arylboranes, aryltrimethylammonium triflate chosen as an electrophile gives very good results in the presence of a nickel catalyst with an *N*-heterocyclic carbene ligand (entry 11) [58]. It is also of interest to note that, under the same conditions, a palladium catalyst did not give any product. For aryl bromides, nickel(II) chloride can catalyze the cross-couplings without any ligands (entry 12) [59]. C–F bond activation of heterocyclic compounds has been also demonstrated, as shown in Eqs. (2.19) and (2.20). Fluoroazines, fluorodiazines [41], and fluoropyridine [61] react with aryl Grignard reagents or alkenyl tin compounds, respectively, to give the coupling product.



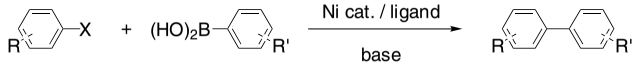
97% (2.19)

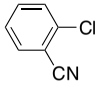
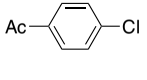
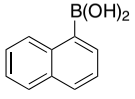
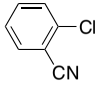
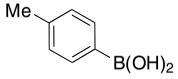
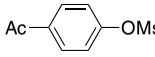
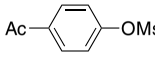
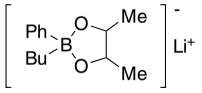


(R = H or F) (2.20)

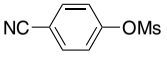
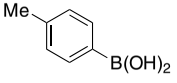
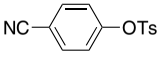
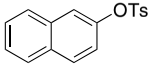
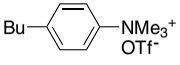
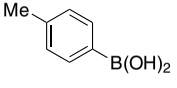
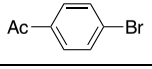
The reaction of titanium-alkyne complexes with aryl iodides was catalyzed by $Ni(cod)_2$ to afford alkenylation product of aryl halides (Eq. (2.21)) [62].

Tab. 2.2. Nickel-catalyzed cross-couplings of aryl halides with arylboronic acids.

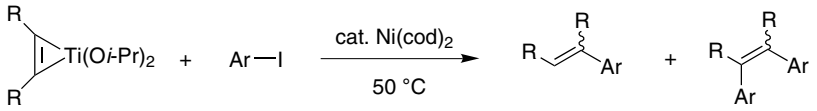


Entry	Electrophile	Arylborane	Catalyst	Ligand	Base	Conditions	Yield [%]	Reference(s)
1		$PhB(OH)_2$	$NiCl_2(dppf)$+BuLi	–	K_3PO_4	dioxane, 80 °C	96	47, 48
2		$PhB(OH)_2$	$NiCl_2(dppf)$	–	K_3PO_4	dioxane, 95 °C	95	49
3			$NiCl_2(dppe)$	TPPTS	K_3PO_4, Zn	dioxane/H_2O, 50 °C	99	50
4			$NiCl_2(PPh_3)_2$	PPh_3	K_3PO_4	toluene, 80–100 °C	97	51
5		$PhB(OH)_2$	Ni/C	PAr_3	K_3PO_4, LiBr	dioxane, Δ	92	52
6		$PhB(OH)_2$	$NiCl_2(dppf)$+Zn	–	K_3PO_4	dioxane, 100 °C	51	53
7			$NiCl_2(PPh_3)_2$	–	–	THF, 60 °C	95	54

Tab. 2.2 *(continued)*

Entry	*Electrophile*	*Arylborane*	*Catalyst*	*Ligand*	*Base*	*Conditions*	*Yield [%]*	*Reference(s)*
8			$NiCl_2$(dppf)+BuLi	–	K_3PO_4	toluene, 100 °C	97	55
9		$PhB(OH)_2$	$NiCl_2(PCy_3)_2$	PCy_3	K_3PO_4	dioxane, 130 °C	96	56
10		$PhB(OH)_2$	$Ni(cod)_2$	PCy_3	K_3PO_4	THF, r.t.	99	57
11			$Ni(cod)_2$	IMes[a]	CsF	dioxane, 80 °C	95	58
12		$PhB(OH)_2$	$NiCl_2 \cdot 6H_2O$	–	K_3PO_4	dioxane, 130 °C	87	59

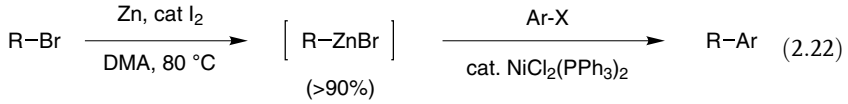
[a] IMes, see Table 2.1.



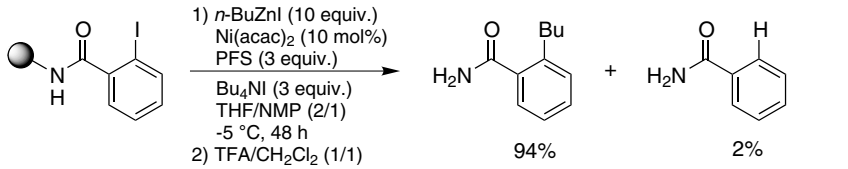
(2.21)

Various alkyl bromides can be converted into alkylzinc reagent in situ in the presence of 1–5 mol% iodine. The in-situ prepared alkylzinc reagents are useful for the alkylation of arenes (Eq. (2.22)) [63]. The coupling reaction of resin-bound ortho-substituted aryl iodide with alkylzinc reagents does not give satisfactory results with palladium catalysts. The combination of Ni(acac)$_2$ and *p*-fluorostyrene (PFS) as a promoter leads to excellent yields, as shown in Eq. (2.23) [64].

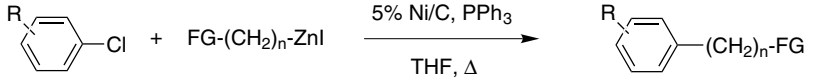
Heterogeneous nickel catalysts, Ni/C, can efficiently promote the coupling reaction with organozinc reagents. First, Ni(0)/C should be prepared by treatment with 2 equiv. *n*-BuLi or MeMgBr with 3–4 equiv. PPh_3. This reaction tolerates various functional groups such as ketones, esters, nitriles, aldehydes and even sulfur(II)-containing compounds (Eq. (2.24)) [65].



(2.22)



(2.23)



(2.24)

2.5 Asymmetric Cross-coupling Reactions

This subject is detailed in Chapter 9, Section 9.1.

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3
Reaction of Alkenes and Allyl Alcohol Derivatives

Yuichi Kobayashi

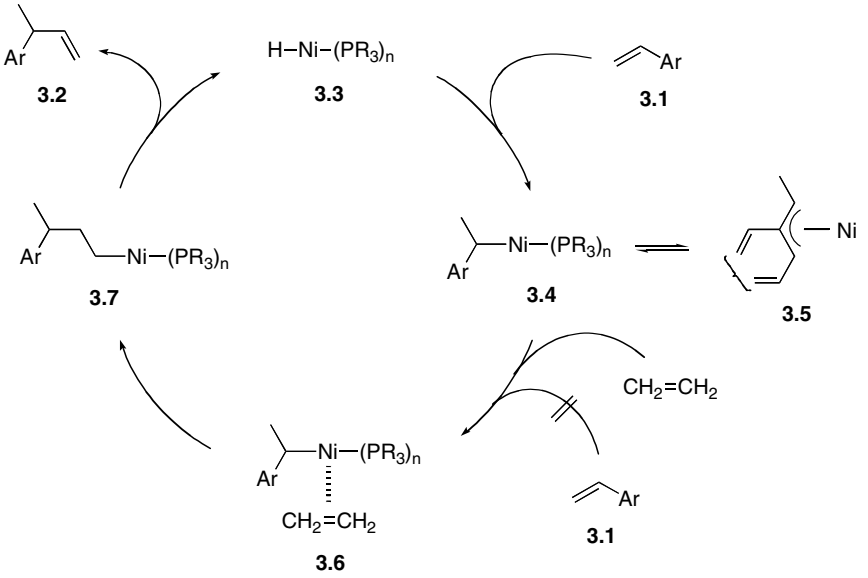
Nickel complexes as catalysts or stoichiometric reagents show high reactivity towards olefins, and this results in the formation of a carbon–carbon bond. Several types of reaction have been developed and are controlled by nickel complexes, where the contribution of functional groups at proximal positions forwards the further steps, causing the reactions to become specific to the molecules in question. The olefins, when conjugated with the other olefins and acetylenes, show specific and characteristic reactions, and these are described separately in the following chapters. This chapter presents the reactions of nonconjugated simple alkenes, enones, vinyl arenes, and allylic alcohol derivatives. In the last case, the reaction proceeds through the so-called π-allylnickel (η^3-allylnickel) intermediates. When possible and relevant, comparisons with other metals such as palladium are presented.

3.1
Hydrovinylation of Olefins

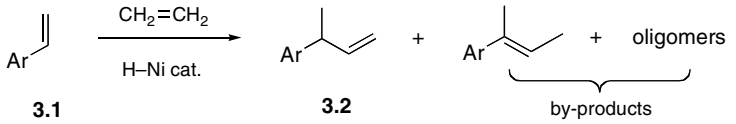
Reaction of vinyl arenes **3.1** and ethylene in the presence of a nickel catalyst produces 3-aryl-1-butenes **3.2** (Eq. 3.1). The catalytic cycle for the reaction shown in Scheme 3.1 starts with an Ni–H complex **3.3** produced in situ from a nickel precursor and a Lewis acid. The hydride adds preferentially to vinyl arene **3.1** over the vinyl group in a Markovnikov fashion to produce a σ-nickel complex **3.4**, since the complex **3.4** is stabilized by forming an η^3-benzylic-nickel complex **3.5**. The ligand bound to the nickel atom in the complex prevents access of vinyl arene **3.1** by a steric reason, and instead allows the selective coordination of ethylene. The ethylene π-complex **3.6** thus produced changes into a σ-complex **3.7**, which undergoes β-hydrogen elimination and produces **3.2** with regeneration of an Ni–H species. The use of a low temperature and a short reaction time prevents the formation of by-product(s).

Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6

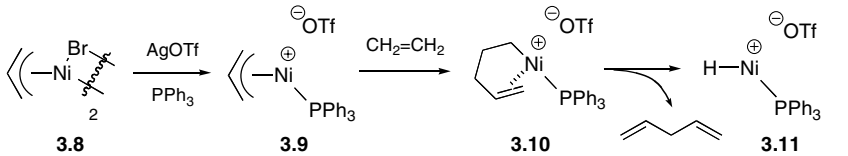


Scheme 3.1. The catalytic cycle for the hydrovinylation of vinyl arenes (e.g., styrene).



(3.1)

The combination of a nickel complex and a Lewis acid such as $BF_3{\cdot}OEt_2$ or $AlEt_2Cl$, when used to generate an active Ni–H species [1, 2], is incompatible with vinyl arenes possessing Lewis basic centers on the aromatic ring, since unwanted coordination of the basic center to the Lewis acid takes place prior to the generation of an Ni–H. This incompatibility with substrates is overcome with a cationic Ni–H complex such as **3.11** synthesized in situ from (allyl-NiBr)$_2$ (**3.8**), AgOTf, and PPh_3 in the presence of ethylene (Eq. 3.2) [3]. Figure 3.1 presents substrates studied with the **3.8**/AgOTf/PPh_3 catalyst system in CH_2Cl_2 at <-50 °C for 2 h and the yields of the products **3.2**.



(3.2)

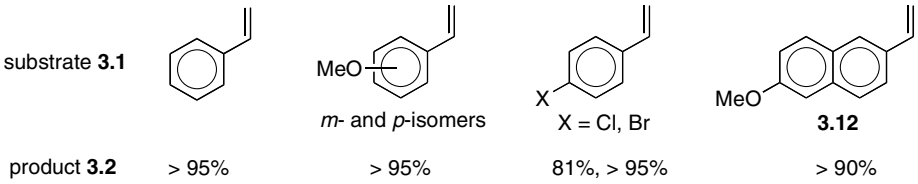
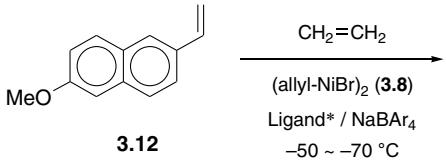
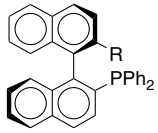


Fig. 3.1. The substrates and the product yields for the hydrovinylation catalyzed by a cationic Ni–H species.

An asymmetric version of the reaction is also studied with substrate **3.12** because the products of a general structure **3.2** in Eq. (3.1) are potential precursors for important anti-inflammatory agents (see Section 8.3). As is shown in Eq. (3.3) and in the table attached below the equation, 62% ee and 80% ee are recorded with an MOP (**3.14**) and a benzyl ether derivative **3.15**, respectively, in combination with $Na^+BAr_4^-$ at <-50 °C. With **3.16**, the reaction shows a low yield and a low ee. These results clearly indicate an important role of weak coordination of the *O*-alkyl ether group to the nickel atom.

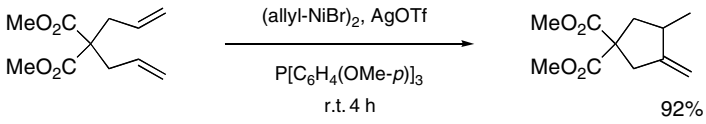




Ligand*	R	% ee
(*R*)-MOP (**3.14**)	OMe	62
(*R*)-**3.15**	OBn	80
(*R*)-**3.16**	Et	3

(3.3)

The catalytic system of **3.8**/AgOTf/PR_3 ($R = C_6H_4(OMe\text{-}p)$) developed above is also effective for an intramolecular hydrovinylation of 1,ω-dienes (Eq. (3.4)) [4]. There is a requirement for a higher temperature (room temperature), though the intramolecular formation of a five-membered ring is likely due to an absence of the benzylic stabilization effect found in the case of vinyl arenes (cf. **3.4** and **3.5** in Scheme 3.1).

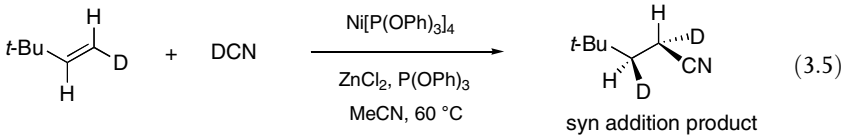


(3.4)

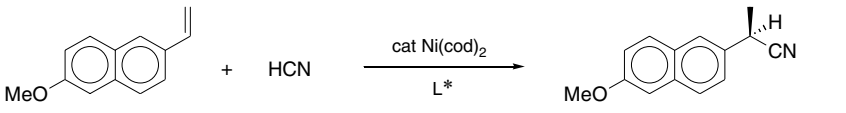
3.2
Hydrocyanation of Olefins

Simple olefins as well as dienes (see Section 5.3.2) undergo addition of HCN to the double bond [5]. The reaction is promoted by a Ni-phosphite complex in the presence of a Lewis acid such as $ZnCl_2$, and proceeds in a manner of syn addition (Eq. (3.5)) [6]. Due to their importance in the manufacture of nonsteroidal anti-inflammatory agents, phosphinite ligands derived from sugars have been developed which attain a high level of asymmetric induction (Eq. (3.6); see Section 9.3). The results obtained with **3.12** are summarized in the tables below Eq. (3.6) [7]. Electron-withdrawing substituents on a phosphorus-linked aryl group (Ar) and a nonpolar reaction medium contribute substantially to the gaining of a better ee.

Asymmetric hydrocyanation of norbornene is also reported with moderate ee [8].

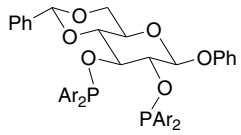


(3.5)



3.12 (*S*)-**3.17**

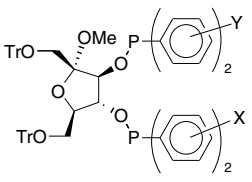
L* =



3.18

Ligands **3.18** giving (*S*)-**3.17**

Ar	solvent	% ee
Ph	benzene	40
Ph	THF	29
3,5-Me_2–C_6H_3	benzene	16
3,5-$(CF_3)_2$–C_6H_3	benzene	78
3,5-$(CF_3)_2$–C_6H_3	C_6F_6	85



3.19

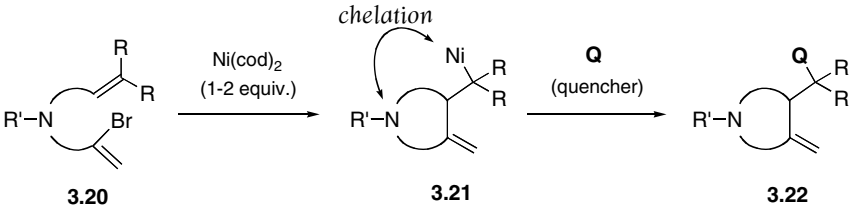
Ligands **3.19** giving (*R*)-**3.17**

X	Y	% ee
H	H	46
3,5-$(CF_3)_2$–C_6H_3	3,5-$(CF_3)_2$–C_6H_3	56
H	3,5-$(CF_3)_2$–C_6H_3	58
3,5-$(CF_3)_2$–C_6H_3	H	89

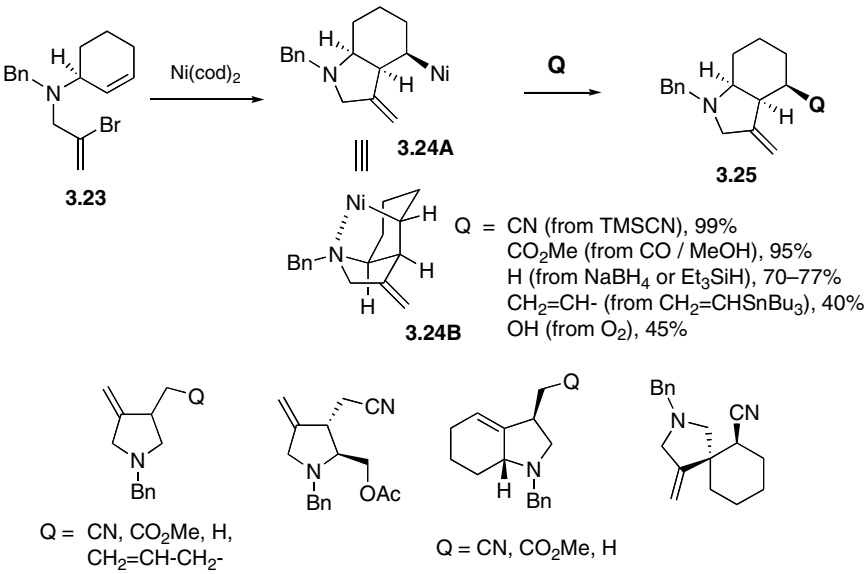
(3.6)

3.3
Heck-type Cyclization

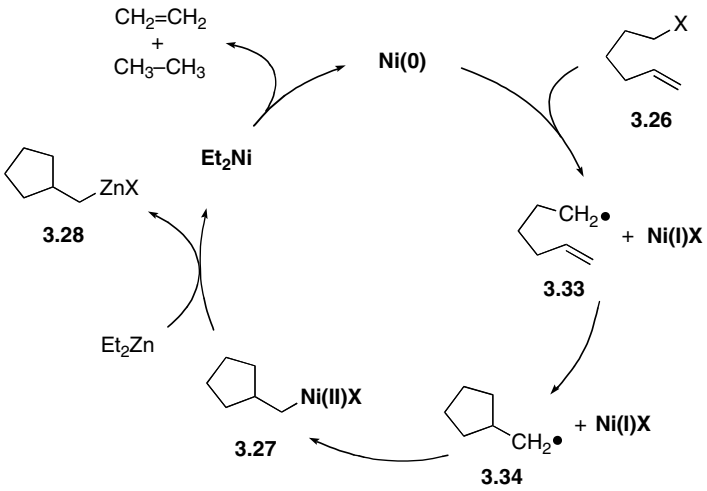
Nitrogen-containing 2-halo-1,ω-vinylalkenes **3.20** undergoes oxidative addition to Ni(cod)$_2$ followed by alkene insertion to afford an intermediates **3.21** (Scheme 3.2) [9]. The nitrogen chelating to the nickel atom stabilizes the intermediates **3.21** and prevents an otherwise usual reaction such as β-hydrogen elimination, thus allowing reaction with different reagents (quencher Q) to furnish a product **3.22**. The chelation provides an additional benefit of controlling stereochemistry, as presented in Scheme 3.3. Oxidative addition of Ni(cod)$_2$ and cyclization of **3.23** take place, thereby keeping the chelation (see **3.24B**), and quenching with reagents (Q) provides a product **3.25** with high stereoselectivity. Additional examples are also presented in Scheme 3.3.



Scheme 3.2. The Ni(cod)$_2$-promoted cyclization-functionalization (Q) of 2-halo-1,ω-vinylalkenes containing a nitrogen atom.



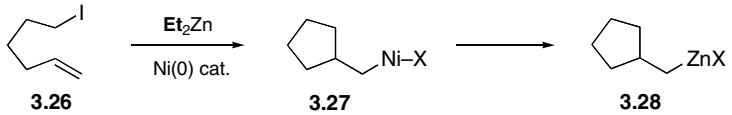
Scheme 3.3. The examples of the Ni(cod)$_2$-promoted intramolecular cyclization-functionalization.



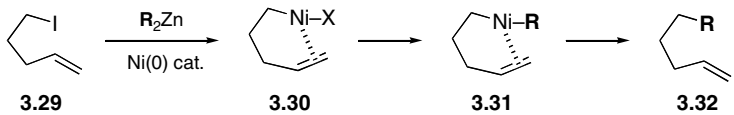
Scheme 3.4. The catalytic cycle for the cyclozincation of Eq. (3.7).

3.4 Olefin Insertion

Compounds such as **3.26** in which a halogen atom and an olefinic part are located in an appropriate position are good substrates for the Et_2Zn-mediated cyclization to afford (cycloalkyl)methylzinc species **3.28** (Eq. (3.7)) [10, 11]. Nickel, as well as palladium, complexes are essential catalysts for the cyclization. In cases when the cyclization is retarded by some factors (vide infra), the olefin moiety coordinates with the nickel atom and assists the coupling reaction (Eq. (3.8)) [12]. A proposed reaction course for Eq. (3.7) is illustrated in Scheme 3.4. The first step involves a single electron transfer from an Ni(0) to the carbon–halogen bond of **3.26** and generates a species **3.33** of radical nature-nickel(I) complex. This species undergoes olefin insertion producing **3.34**, and eventually a nickel(II) complex **3.27**. Finally, transmetallation with Et_2Zn produces an organozinc **3.28** and Et_2Ni. The latter regenerates an Ni(0) catalyst for the next catalytic cycle.



(3.7)

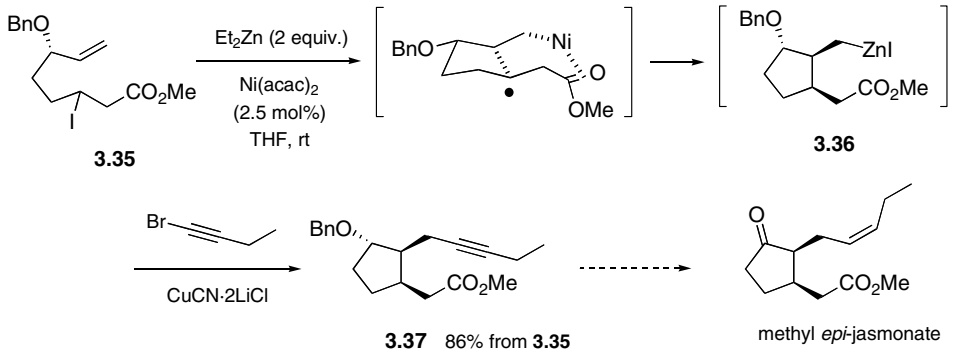


(3.8)

The synthetic advantages of this radical cyclization are: 1) production of the zinc reagents **3.28** which react with a wide range of electrophiles; and 2) tolerance of

functional groups such as ester and amide groups. Examples of this cyclization and further elaboration of the organozincs thus formed are presented in Schemes 3.5 to 3.7.

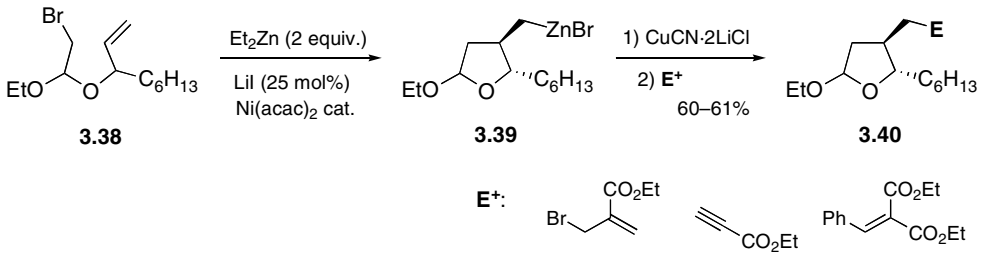
The reaction of **3.35** proceeds through a conformation in which all of the substituents occupy the most stable pseudo-equatorial positions to furnish a zinc reagent **3.36** which, after transmetallation with CuCN·2LiCl, undergoes coupling with bromoacetylene to produce **3.37** in 86% yield (Scheme 3.5) [11b]. Methyl *epi*-jasmonate, a natural product, is synthesized from **3.37** through several steps.



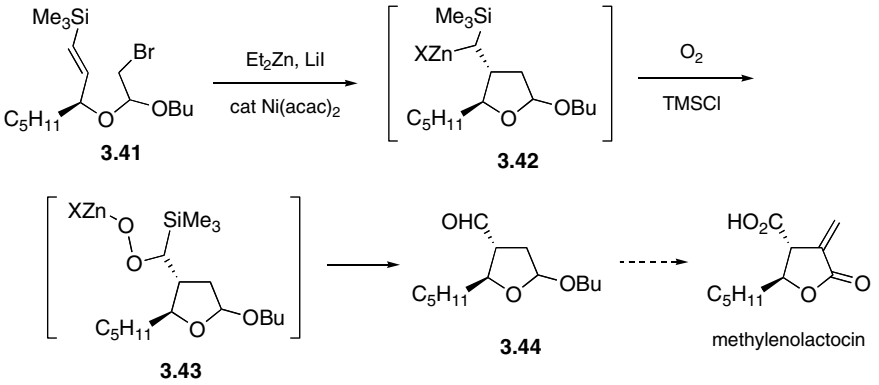
Scheme 3.5. The synthesis of methyl *epi*-jasmonate based on the Ni-catalyzed cyclozincation.

It should be noted that the methods developed previously for prostaglandin synthesis would meet difficulty in installing two side chains in a cis fashion on the cyclopentanone ring because such methods rely mostly on the enolate chemistry, and hence result in affording a thermodynamically more stable trans isomer.

Scheme 3.6 demonstrates other types of reaction of zinc reagent **3.39** produced by the Ni-catalyzed cyclization of **3.38** [13]. Allylic coupling with an allylic bromide, 1,4-addition to propiolate, and 1,4-addition to an electron-deficient olefin are efficiently conducted after transmetallation with CuCN·2LiCl. It is interesting to note that a different potency between nickel and palladium catalysts is observed in this tetrahydrofuran cyclization; palladium catalysts afford a mixture of cyclized and un-cyclized products.



Scheme 3.6. The synthesis of tetrahydrofuran derivatives via the Ni-catalyzed cyclozincation.

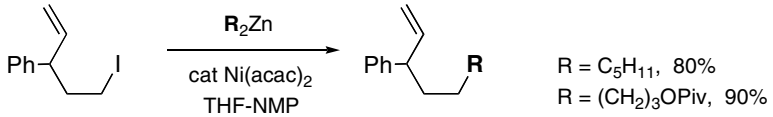


Scheme 3.7. The total synthesis of methylenolactocin.

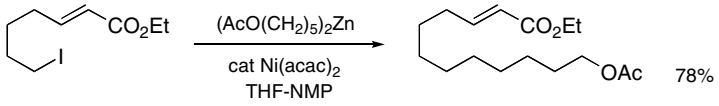
Direct oxidation of a zinc reagent **3.42** with oxygen produces aldehyde **3.44**, probably through an intermediate **3.43** (Scheme 3.7) [13]. Further oxidation and introduction of methylene unit upon **3.44** complete a total synthesis of methylenolactocin (a natural product). Further advantage of this method is the ready availability of the starting materials. For example, **3.38** and **3.41** are prepared by the NBS (*N*-bromosuccinimide) treatment of an appropriate combination of an allyl alcohol and an alkyl vinyl ether.

In cases where the olefin moiety is not available for the ring closure owing to ring strain (e.g., forming a four-membered ring), a large loss of entropy (e.g., forming a seven-membered ring), or conjugation with an ester group, another reaction such as that shown in Eq. (3.8) (vide supra) takes place [12, 14]. After oxidative addition of an Ni(0) upon an iodide **3.29** (via one-electron transfer; see Scheme 3.4), the resulting nickel species **3.30** undergoes transmetallation with R_2Zn to afford **3.31**. Subsequent reductive elimination gives a coupling product **3.32**, and thereby the coordinated olefin reduces the electron density on the nickel(II), thus facilitating reductive elimination (see Section 1.7.4). Examples of the reaction are shown in Eqs. (3.9) and (3.10).

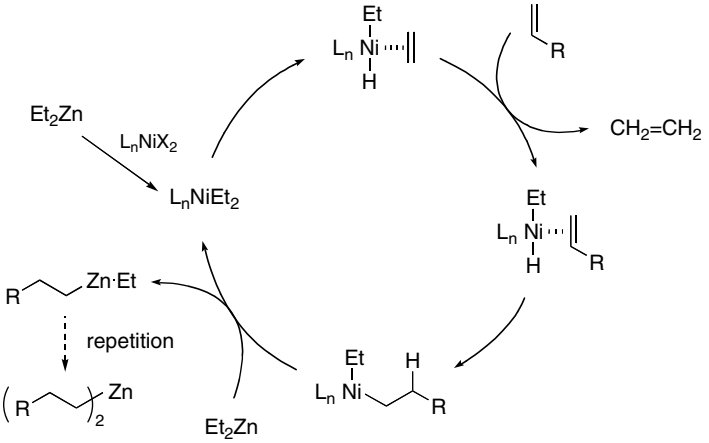
Simple alkyl halides (mostly iodides) with no olefin moiety undergo iodo-zinc exchange via an alkylnickel species to give the corresponding zinc reagents. Readers should be aware of the difference of reaction features that similar intermediates, **3.10** and **3.31** display; the former is cationic and the latter neutral.



(3.9)



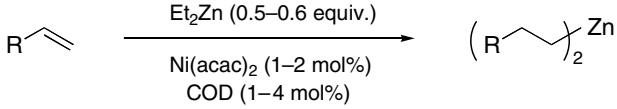
(3.10)



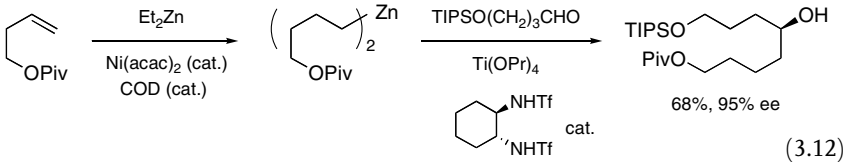
Scheme 3.8. The catalytic cycle for the nickel-catalyzed olefin metathesis.

3.5
Nickel-catalyzed Hydrozincation of Olefins

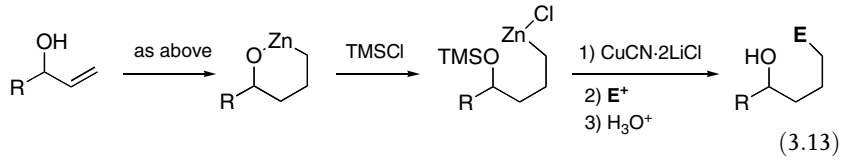
Simple olefins undergo nickel-catalyzed olefin metathesis with Et_2Zn (Eq. (3.11)) [15], and a catalytic cycle proposed for this is shown in Scheme 3.8. The reaction proceeds with olefin possessing not only an ester group, but also a free hydroxy group, and the zinc reagents thus produced can be used for further reactions (Eqs. (3.12) and (3.13)). In the latter reaction, the alkoxy moiety in the cyclic zinc intermediate must be converted into the TMS ether in order to increase its reactivity.



(3.11)

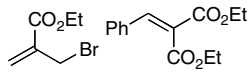


(3.12)



(3.13)

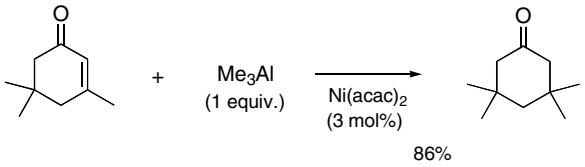
R = *i*-Pr, C_6H_{13}, Ph, $(CH_2)_2OTIPS$.

E^+ = I_2, PhCOCl, Et—≡—Br, 

3.6
Ni-catalyzed Addition of Organometallics to Electron-deficient Olefins

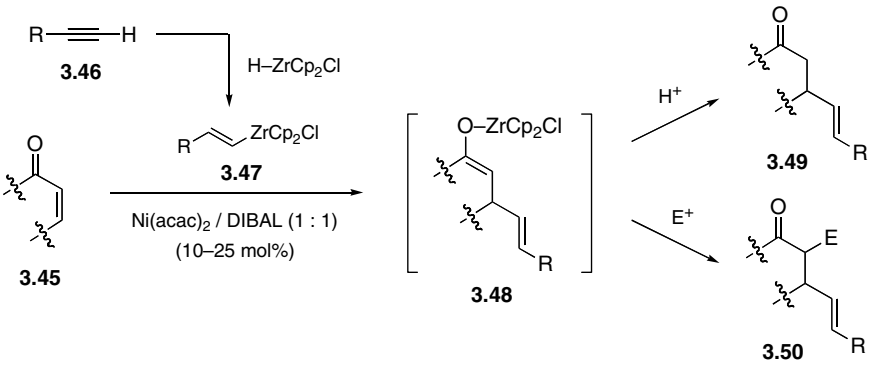
3.6.1
The Reaction with Organometallics

Similar to copper reagents which catalyze the conjugate addition of Grignard reagents to electron-deficient olefins, nickel complexes also catalyze the conjugate addition of organometallics such as those based on aluminum, zirconium, and zinc. The reactivity, as well as synthetic advantages, of the latter reaction is described below.



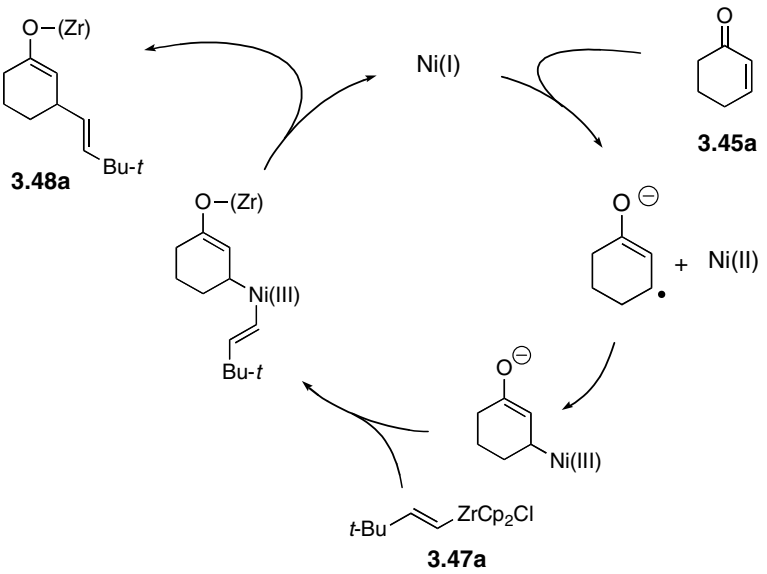
(3.14)

The reaction of Me_3Al and 2-cyclohexenones in the presence of $Ni(acac)_2$ (ca. 3 mol%) was reported independently by Ashby [16] and Mole [17] (Eq. (3.14)). A few years later, Schwartz applied the reaction to alkenyl zirconium reagents **3.47** to produce zirconium enolates **3.48** (Scheme 3.9; see Section 4.6.2) [18]. Hydrolysis of the enolate affords **3.49**, while trapping with an electrophile (E^+) produces **3.50**. A synthetic advantage of the method is the direct use of acetylenes as a source of alkenyl reagents.



Scheme 3.9. The Ni-catalyzed 1,4-addition of in situ-generated alkenyl zirconium reagents.

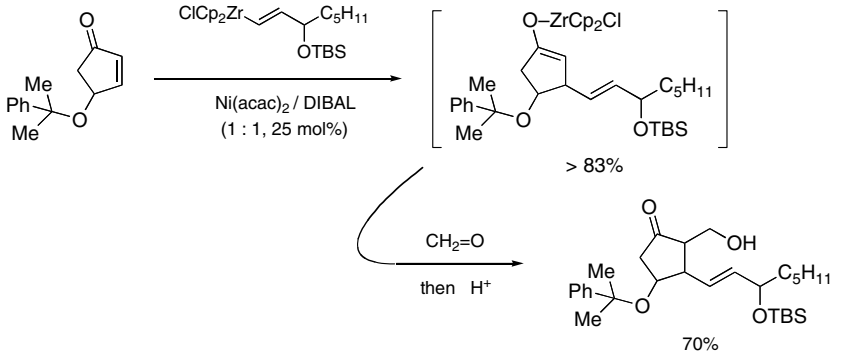
A proposed catalytic cycle based on the mechanistic study is presented in Scheme 3.10 with cyclohexenone (**3.45a**) as a typical enone [19]. Reaction between $Ni(acac)_2$ and DIBAL produces Ni(I) species (note: the authors state negative comments for the production of Ni(0) species), which transfers one electron to enone **3.45a** to produce Ni(III)-bound species after recombination of the resulting



Scheme 3.10. The reaction mechanism of Ni-catalyzed 1,4-addition involving a novel Ni(I)–Ni(III) catalytic cycle.

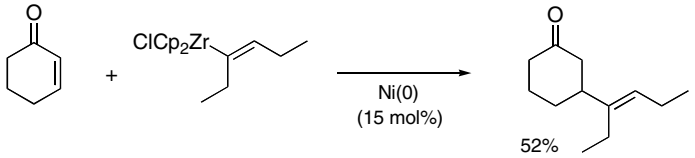
ketyl and Ni(II) species. Subsequently, transmetallation of the Ni(III) species with alkenyl zirconium **3.47a** and reductive elimination thereof follow to produce the zirconium enolate **3.48a** and the pivotal Ni(I).

The nickel-catalyzed conjugate addition is applied to prostaglandin synthesis, as summarized in Eq. (3.15), in which the resulting zirconium enolate is trapped with formaldehyde to furnish the known intermediate.



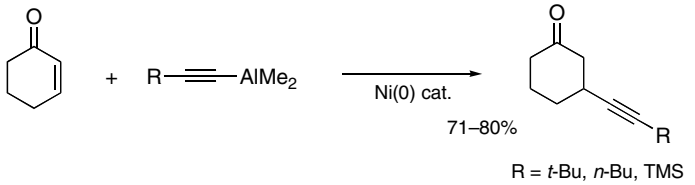
(3.15)

An internal acetylene also furnishes the conjugate addition product (Eq. (3.16)).



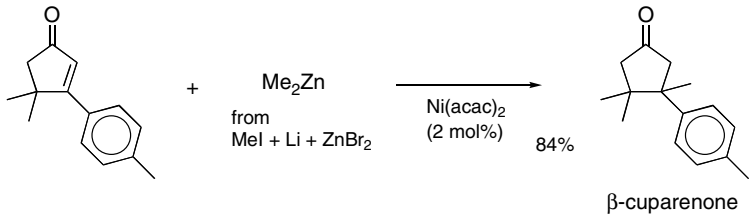
(3.16)

The $Ni(acac)_2$/DIBAL catalyst system allows the conjugate addition of aluminum acetylides (Eq. (3.17)) [20]. This is another synthetic advantage of the reaction, as copper acetylides are inactive toward the conjugate addition.

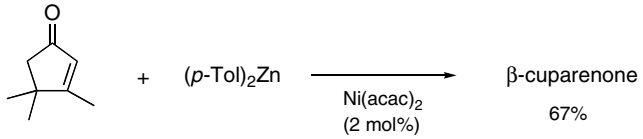


(3.17)

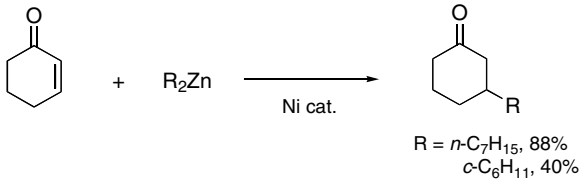
Organozinc reagents formulated as R_2Zn are prepared from RX, Li, and $ZnBr_2$ under ultrasonic irradiation, and are used in the nickel-catalyzed conjugate addition. Equations 3.18–3.20 are examples of this reaction [21–23]. Alkyl, alkenyl, aryl groups can be delivered to the β position of enones. Success with $(alkyl)_2Zn$ is noteworthy, since an alkyl zirconium reagent of the above type is marginally reactive. The high performance of the R_2Zn/Ni catalyst system is seen in Eqs. (3.18) and (3.19), while no reaction takes place with Me_2CuLi and MeMgX/Cu catalyst due to steric hindrance.



(3.18)

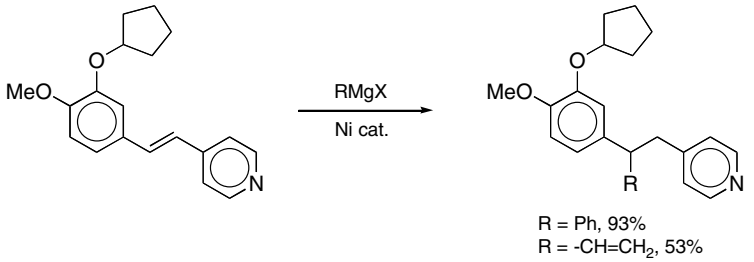


(3.19)



(3.20)

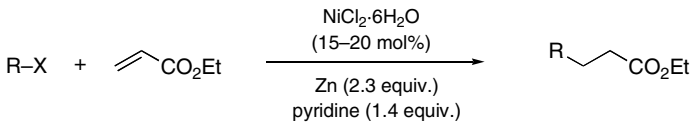
A nickel complex also catalyzes the addition of RMgX to an electron-deficient alkenyl pyridine (Eq. (3.21)) [24].



(3.21)

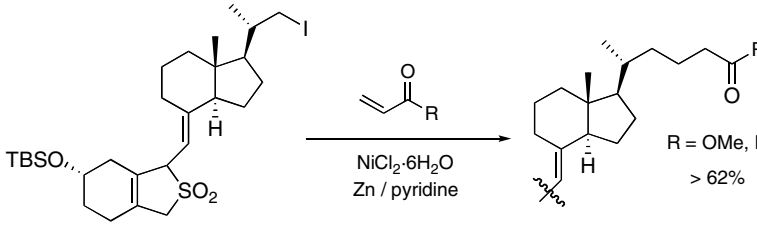
3.6.2
The Reaction with Organic Halides as Nucleophiles

Alkyl halides and alkenyl halides react with electron-deficient olefins in the presence of $NiCl_2 \cdot 6H_2O$ as a catalyst, Zn (2.3 equiv.), and pyridine (1.4 equiv.) (Eq. (3.22)) [25]. The geometry of the alkenyl halides is maintained during the reaction, without isomerization. More than 1 equiv. of H_2O is required for the reaction to be completed, implying the formation of zinc enolate [26]. A catalyst quantity of 15–20 mol% of $NiCl_2 \cdot 6H_2O$ provides sufficient H_2O for the enolate quench. Alternatively, the combination of a lower loading catalyst and the addition of H_2O from outside is also effective for the reaction.



R–X	yield, %	R–X	yield, %
n-$C_7H_{15}Br$	75	Ph–I	92
c-$C_6H_{11}Br$	73	Ph, Br	80
Br	77	Ph, Br	80

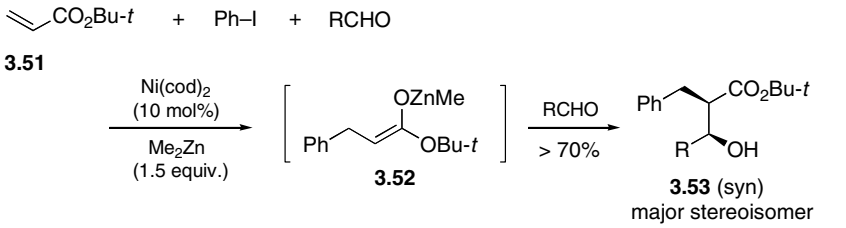
(3.22)



(3.23)

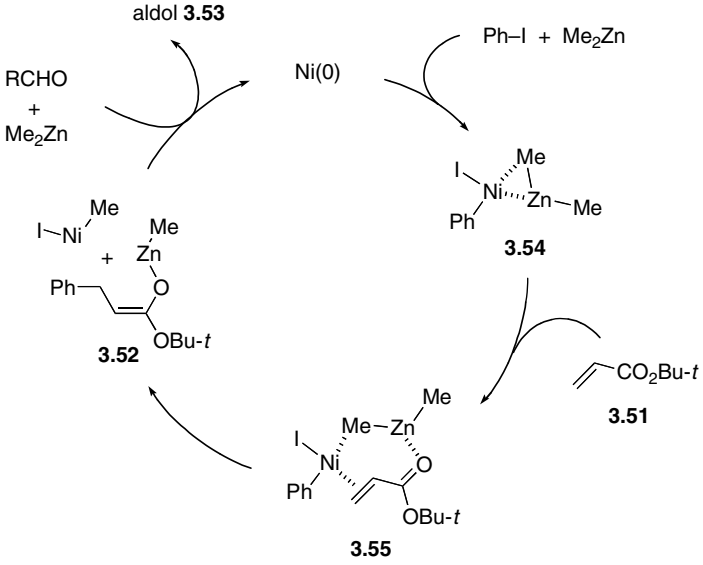
This reaction is applied to synthesis of the vitamin D_3 side chain (Eq. (3.23)) [27].

The postulated zinc enolate in the above reaction is available for aldol reaction with an aldehyde under anhydrous conditions. Thus, reaction between acrylate **3.51**, Ph-I, and PhCHO takes place with $NiCl_2$ (100 mol%), Zn, and pyridine in refluxing THF for 24 h to furnish the aldol adduct **3.53** (R = Ph) in 79% yield with a 2:1 diastereomeric ratio (dr), or more efficiently with $Ni(cod)_2$ (10 mol%) and Me_2Zn (1.5 equiv.) at 0 °C for 1 h to afford the same adduct in 88% yield with a better dr of 86:14 (Eq. (3.24)) [28]. It is noteworthy that Et_2Zn not only reduces the quantity of $Ni(cod)_2$ to 10 mol%, but also accelerates the reaction to be completed within 1 h. Generality of the reaction under the latter conditions is demonstrated with aliphatic (R = Et, *i*-Pr, *t*-Bu) and aromatic (R = *p*-(MeO)C_6H_4, 2-furyl) aldehydes.



(3.24)

In a catalytic cycle illustrated in Scheme 3.11, complex **3.54** derived from Ph-Ni-I and Me_2Zn is proposed to explain the role of Me_2Zn. Thus, the zinc atom, by che-

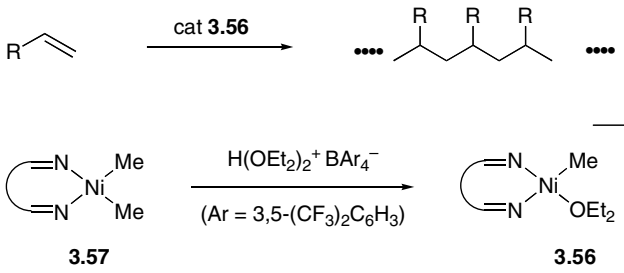


Scheme 3.11. The mechanism for the Ni-catalyzed Me_2Zn-mediated conjugate addition/aldol reaction of halides.

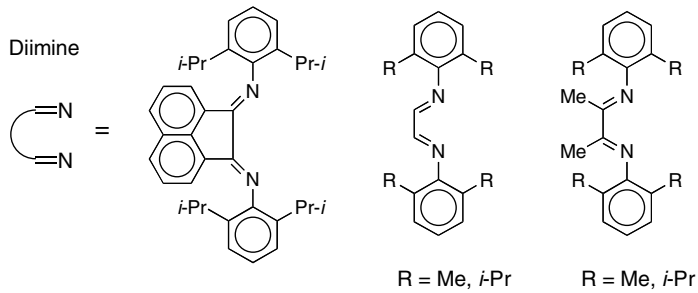
lation to the carbonyl oxygen, accelerates transfer of the Ph group from nickel to the enone olefin to produce zinc enolate **3.52**, which undergoes the aldol reaction.

3.7
Polymerization of Ethylene and α-Olefins using Ni(II)-based Catalysts

The cationic nickel complexes in which a bulky diimine is incorporated as a ligand are extremely efficient catalysts for the polymerization of ethylene and α-olefins (Eq. (3.25)) [29, 30]. Due to the importance of this reaction in polymer science and technology, extensive investigations have been reported in this area. The principle of the polymerization is described in the following section, but it should be noted that similar palladium complexes also function well as polymerization catalysts.

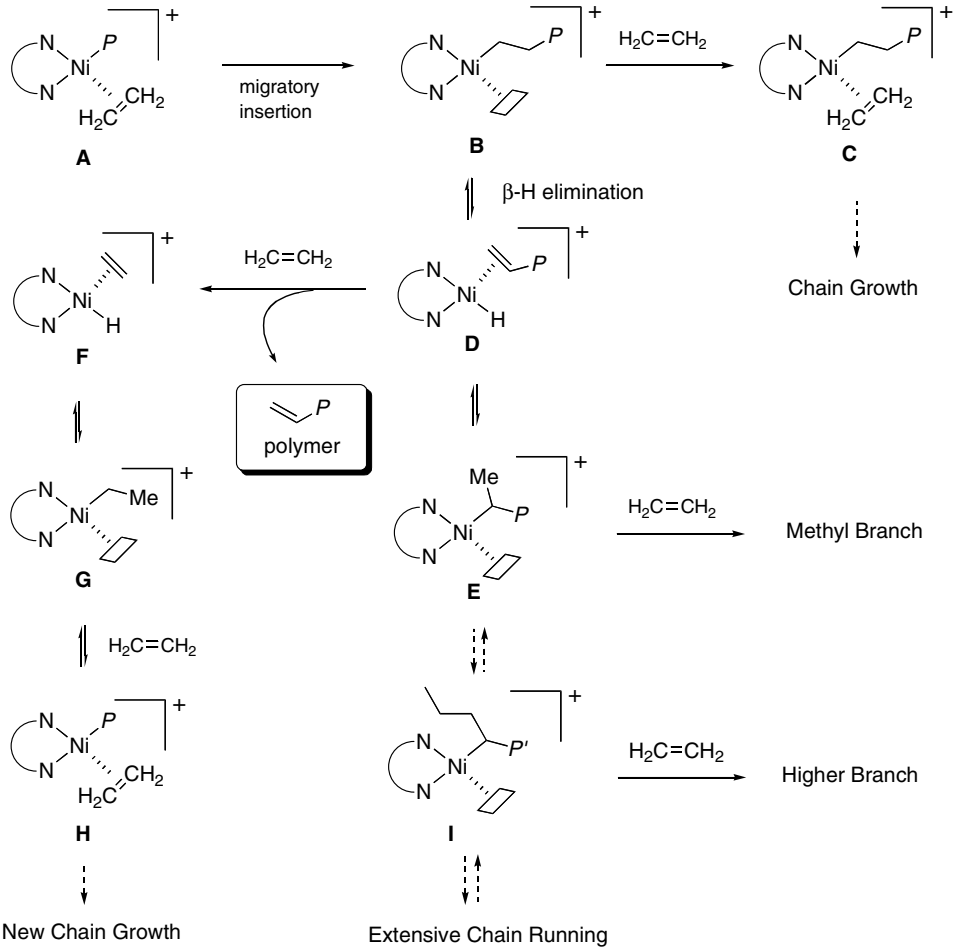


(3.25)



(3.26)

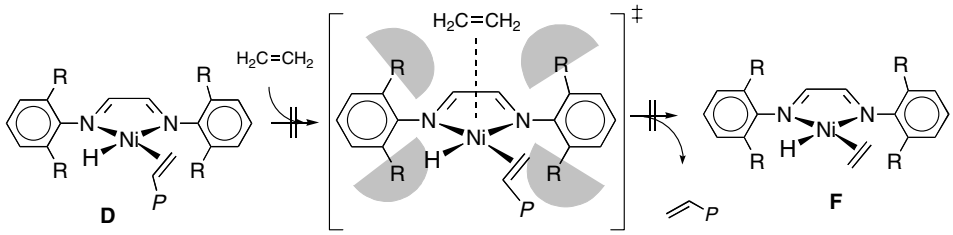
The cationic nickel complexes **3.56** are prepared by protonation of dimethyl complexes **3.57** with $H(OEt_2)_2^+ \cdot BAr_4^-$ (Ar = 3,5-$(CF_3)_2C_6H_3$), as shown in Eq. (3.26). The exposure of nickel complexes **3.56** to ethylene, propylene, or 1-hexene resulted in the formation of high molecular-weight polymers. Conveniently, the complex **3.57** is prepared in situ by treatment of the diimine-$NiBr_2$ complex with methylaluminoxane [a polymer expressed as $-(Al(Me)O)_n-$] in the presence of an alkene. The ratio of linear over branches (the methyl branch is predominant) is controlled mainly by the steric bulk of the diimine ligand, temperature, and ethylene pressure. A higher ethylene pressure (3 atm versus 1 atm) and use of the sterically less congested diimine ligand (R = Me in place of *i*-Pr) produce a higher linear ratio. At higher temperatures, the branching tends to increase.



Scheme 3.12. The polymerization mechanism of ethylene with the diimine-Ni catalyst **3.56**.

These results are well understood according to a reaction mechanism proposed on the basis of kinetic studies (Scheme 3.12) [31, 32]. A high ethylene pressure accelerates the coordination of ethylene to a vacant site of **B** to produce **C**. Repetition of **A** → **B** yielding **C** is responsible for linear polymerization. The *β*-hydrogen elimination of **B** to **D** is retarded by the use of a bulky ligand and low temperature. Reinsertion of the hydride within complex **D** in an opposite direction results in the production of a complex **E** with a branched alkyl group, which upon further reaction produces the methyl branch. Chain running, **E** → **I** and further, provides higher-branch polymers (see Schemes 1.22 to 1.24).

Scheme 3.12 illustrates the principle for the polymerization. In order to terminate the polymerization and re-start a new polymerization (chain transfer), the olefin ligand in a complex **D** should be exchanged with ethylene through an associa-

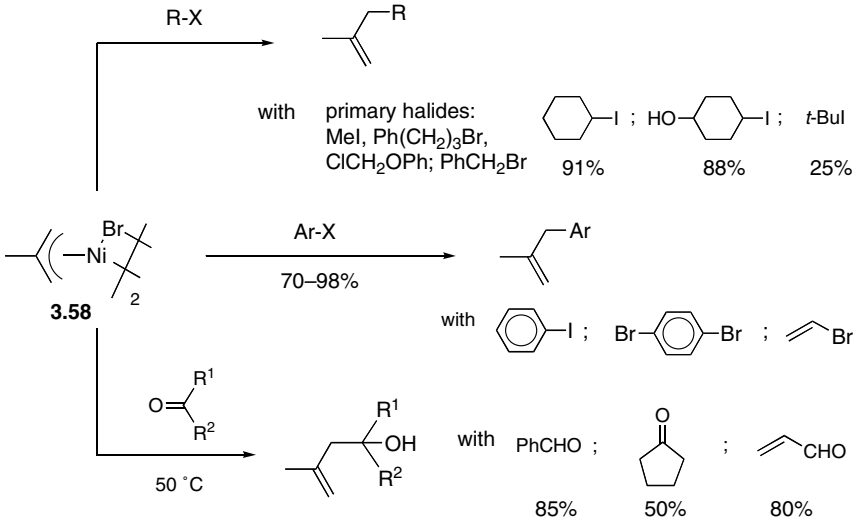


Scheme 3.13. The inhibition of the transformation of **D** into **F** by a sterically bulky *o*-substituent R.

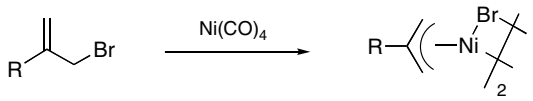
tive process. The steric bulk of the diimine ligand prevents the access of ethylene from the axial direction (Scheme 3.13), thus allowing the polymerization to proceed selectively.

3.8 The Nucleophilic Reactions of π-Allylnickel Complexes

The reaction of allylic bromides and an excess Ni(0) species such as $Ni(CO)_4$ and $Ni(cod)_2$ produces π-allylnickel complexes **3.58** (Eq. (3.27)) which, in a polar solvent, undergo nucleophilic substitution with different types of electrophiles as seen in Scheme 3.14 [33]. Here one can clearly identify the difference in reactivity between π-allylnickel halides and π-allylpalladium halides, as the latter never display nucleophilic reactivity.



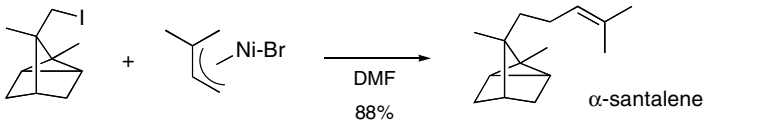
Scheme 3.14. The typical reactions displayed by the π-allyl nickel complex **3.58**.



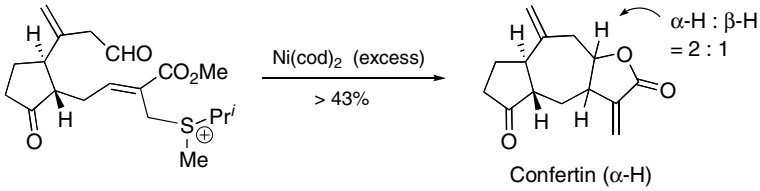
(3.27)

3.58 R = H, Me, OMe, CO_2Et

A wide range of alkyl halides (R–X) undergoes substitution reactions. In differing from the classical S_N2 reaction, secondary and tertiary alkyl halides are also good substrates. Single electron transfer from the nickel complex to halides is suggested [34], and one successful application of this alkylation is the synthesis of natural products such as α-santalene (Eq. (3.28)) and *β-epi*-santalene [33a, 35]. The reactions with aryl and alkenyl halides (Ar–X) are similar to the so-called metal-catalyzed cross-coupling reaction (see Chapter 2). Complexes **3.58** show somewhat low reactivity towards carbonyl compounds, which in turn allows chemoselective transformations and compatibility with most carbonyl groups. The construction of α-methylene-γ-lactone in Eq. (3.29) is a representative example of the synthetic advantage of the reaction [36, 37]. Reviews by Semmelhack [38] and by Baker [39] are recommended to the reader to help grasp the chemistry of π-allylnickel complexes which are described in detail in this section.

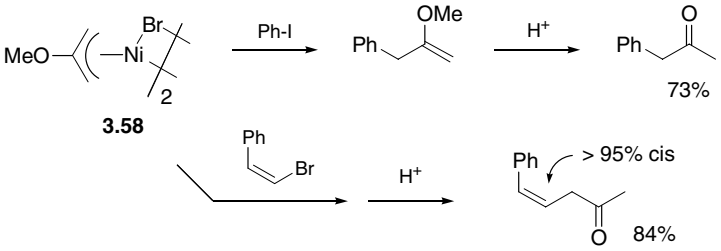


(3.28)



(3.29)

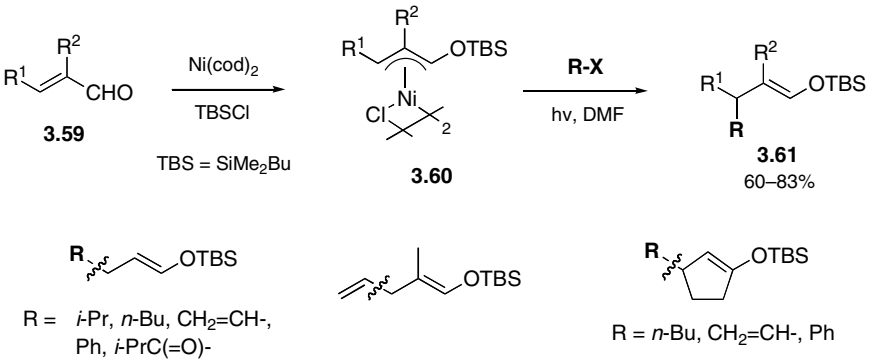
Scheme 3.15 demonstrates the reactions of the methoxy complex **3.58** (R = OMe) with electrophiles to afford, after hydrolysis, methyl ketones, some of which are difficult to obtain by other methods [40].



Scheme 3.15. The reaction of the methoxy complex **3.58** with phenyl iodide and alkenyl bromide (with retention of configuration).

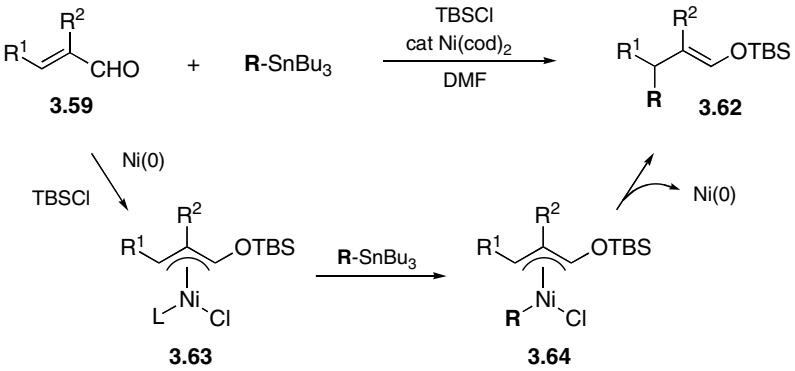
3.9
π-Allylnickel Complexes from Enones

The reaction of enones **3.59** and a stoichiometric quantity of $Ni(cod)_2$ in the presence of a silyl chloride such as TMSCl and TBSCl produces π-allylnickel complexes **3.60** (the Mackenzie complex; Scheme 3.16), which have unique reactivity. Under irradiation with a sunlamp, the complexes **3.60** undergo reaction with various electrophiles such as alkenyl halides, aryl halides, alkyl halides, and acyl chlorides, some of which are listed in Scheme 3.16 [41]. Recent advancements associated with this complex are described in Section 4.6.2.

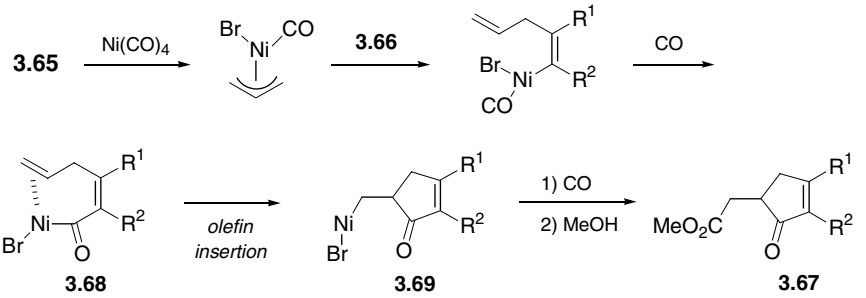


Scheme 3.16. The preparation of the Mackenzie complex **3.60** and its reaction with various halides.

When alkenyl and acyl stannanes are employed as reaction partners, enones **3.59** in the presence of TBSCl and a catalytic amount of $Ni(cod)_2$ furnish enol ethers **3.62** (Scheme 3.17), which probably proceeds as indicated through π-allylnickel intermediates **3.63** and **3.64** [42].



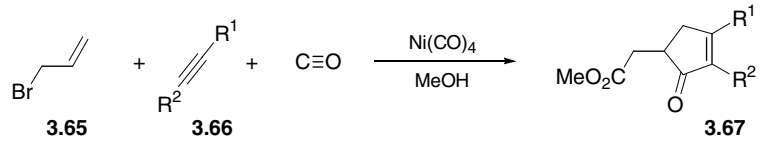
Scheme 3.17. The Ni-catalyzed conjugative 1,4-addition of organostannanes and TBSCl across enals **3.59**.



Scheme 3.18. The plausible reaction pathway for the transformation shown in Eq. (3.30).

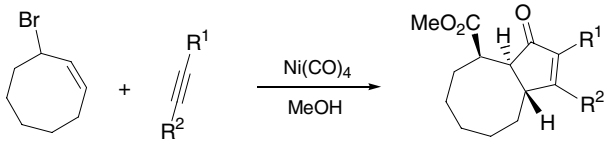
3.10
Carbonylative Cycloaddition of Allylic Halides and Acetylenes

The reaction between allylic halides **3.65**, acetylenes **3.66**, and $Ni(CO)_4$ that forms cyclopentenone ring (Eq. (3.30)) has a long history which extends over 30 years [43, 44]. Although attractive, the reaction has been little utilized in organic synthesis because of the stoichiometric use of $Ni(CO)_4$, a highly toxic and volatile reagent (see Section 1.2), and the formation of by-products; several steps involved in Scheme 3.18 are competitive with other reactions that produce a mixture of products. Recently, a conventional method has been reported that uses $Ni(cod)_2$ under a CO atmosphere, in place of $Ni(CO)_4$ [45].



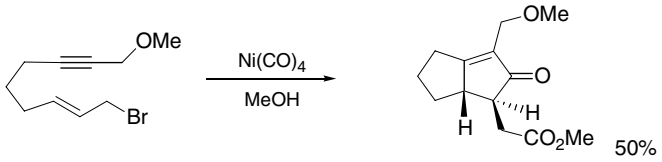
(3.30)

The reactions shown in Eqs. (3.31) and (3.32) are useful extensions of the carbonylative cycloaddition [46, 47], and the synthesis of methylenomycin B (a natural product) may be accomplished [48]. The use of chiral acetylenic sulfoxides provides a modest enantiomeric excess [49].



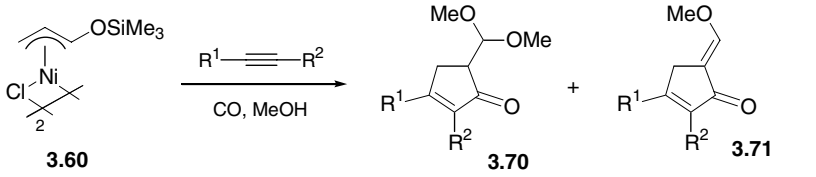
R^1	Me	Me	CH_2OMe	TMS	TMS
R^2	CH_2OH	CO_2Me	H	CH_2OMe	H
% yield	51	81%	77	17	57

(3.31)



(3.32)

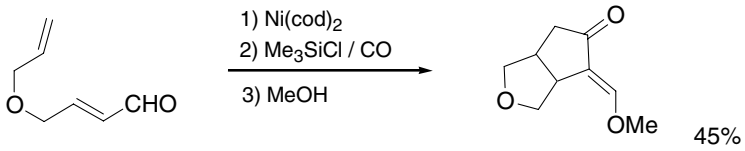
A similar reaction takes place with the π-allylnickel complex **3.60**, prepared from acrolein, $Ni(cod)_2$, and Me_3SiCl according to the method of Mackenzie (Scheme 3.16) [41, 42], under a CO atmosphere giving acetal **3.70** and enol **3.71**, as major and minor products, respectively (Eq. (3.33)) [50]. It is interesting that in this particular case the reaction ends up at the stage of an Ni complex similar to **3.69** in Scheme 3.18, without further carbonylation. Instead, the Ni intermediate probably undergoes β-hydrogen elimination to furnish **3.71** as a primary product, which further reacts with methanol to provide **3.70**. An intramolecular version is also successful (Eq. (3.34)).



The yields of **3.70**

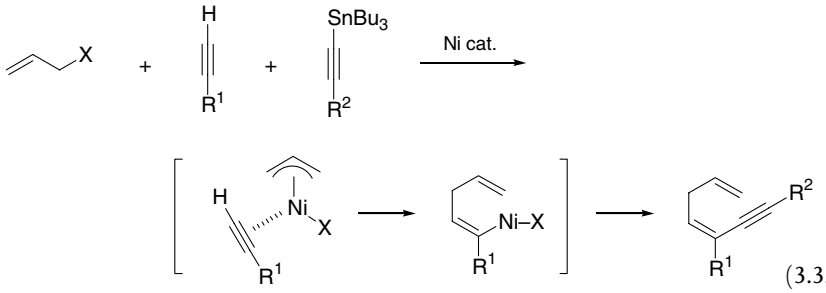
R^1	H	H	CO_2Me	CH_2OMe
R^2	TMS	Ph	Me	Me
% yield	80	40	95	26

(3.33)



(3.34)

In relation to the above carbonylation, the following reaction has been extensively studied, as described in Chapter 4 (Eq. (3.35)).

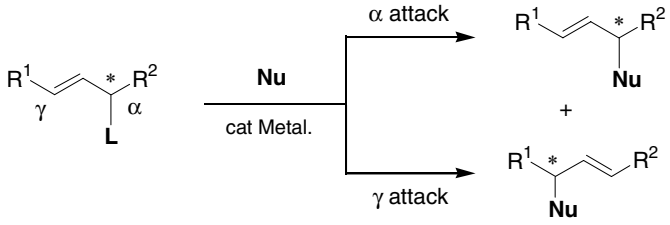


(3.35)

3.11
Nucleophilic Allylation Toward π-Allylnickel Complexes

3.11.1
Allylation with Grignard Reagents

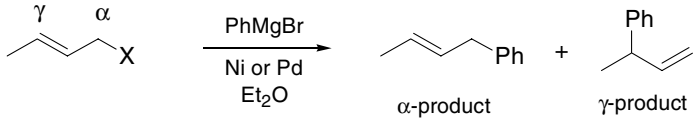
Although nickel-catalyzed nucleophilic allylation has been studied over the past three decades, nickel catalysis has attracted much less attention than Pd catalysis as a tool in organic synthesis. This is most likely because of the moderate regio- and/or stereoselectivities, the use of Grignard reagents which are too reactive to be compatible with many carbonyl groups, the low reactivity with soft nucleophiles, and in particular the fact that Pd catalysis provides similar or better results. However, recent studies have disclosed new aspects of high efficiency and selectivity for nickel-catalyzed allylation.



(3.36)

L: OC(=O)R, OR, OPh, OH, SH, SR
Nu: hard nucleophiles, soft nucleophiles

Early studies conducted during the 1970s revealed that allylic alcohols, ethers, and esters are substrates in the nickel- and palladium-catalyzed reaction with organometallic nucleophiles (Eq. (3.36)). The regiochemistry is highly susceptible to the nature of the organometallic nucleophile, catalyst, and ligand, as well as to the stereoelectronic bias around the allylic moiety of substrates. Typical examples are shown in Table 3.1 for Eq. (3.37) [51], and these suggest that there is a general trend that Ni- and Pd-catalysts show opposite regioselectivities, providing the γ- and α-products, respectively. More detailed examples of Ni- and Pd-catalyzed allylation with allylic compounds have been compiled in review articles [52].



(3.37)

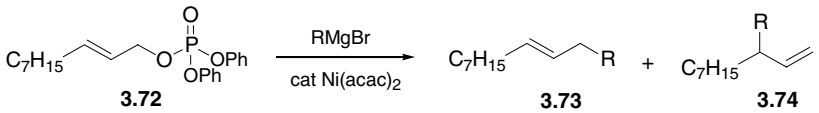
A high level of regioselectivity is attained with allylic phosphonate **3.72** and $Ni(acac)_2$ as a catalyst (Eq. (3.38)) [53]. In contrast, an aryl group attached to the γ

Tab. 3.1. Allylation with phenylmagnesium bromide.

X	*Cat. [10 mol%]*	*Yield [%]*	*α:γ*
$OSiEt_3$	$NiCl_2(dppf)$	100	12:88
$OSiEt_3$	$NiCl_2(dppp)$	44	59:41
$OSiEt_3$	$NiCl_2(PPh_3)_2$	100	67:33
$OSiEt_3$	$PdCl_2(dppf)$	100	96:4
$OSiEt_3$	$PdCl_2(PPh_3)_2$	52	90:10
OPh	$NiCl_2(dppf)$	>80	14:86
OPh	$PdCl_2(dppf)$	>80	90:10
OTHP	$NiCl_2(dppf)$	>80	19:81
OTHP	$PdCl_2(dppf)$	>80	89:11
Cl	$NiCl_2(dppf)$	>80	25:75
Cl	$PdCl_2(dppf)$	>80	82:18
Cl	no catalyst	–	2:1
OH	$NiCl_2(dppf)$	30–50	20:80
OH	$PdCl_2(dppf)$	30–50	91:9

carbon substantially dictates the regioselectivity so as to maintain the π-conjugation between the aryl group and the olefinic double bond (Eq. (3.39)) [54].

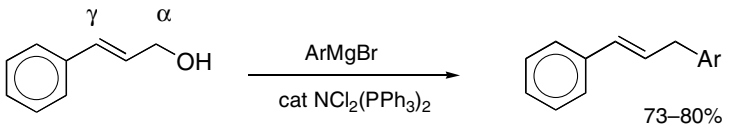
Preservation of conjugation is also reported in the geminal dimethylation of allylic dithioacetals (Eq. (3.40)) [55] and dimethyl acetals [56].



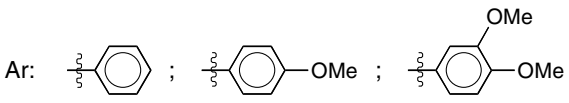
3.72 **3.73** **3.74**

RMgBr	% yield	**3.73** : **3.74**
PhMgBr	66	92 : 8
 MgBr	78	> 99 : 1

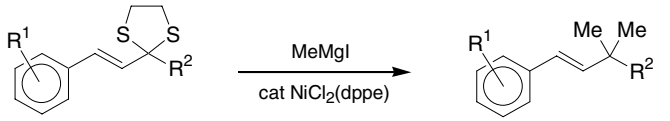
(3.38)



(3.39)

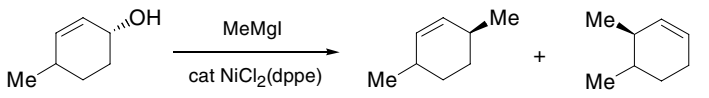


Nickel-catalyzed allylation proceeds with overall inversion of configuration (Eqs. (3.41) and (3.42)) [57, 58], indicating that the reaction proceeds with a widely



(3.40)

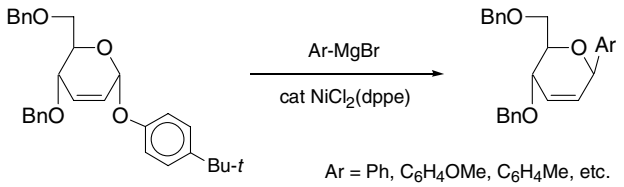
R^1 = H, Me, OMe; R^2 = H, Me



(3.41)

3.75a, α-Me — 53 : 47 from **3.75a**

3.75b, β-Me — 89 : 11 from **3.75b**

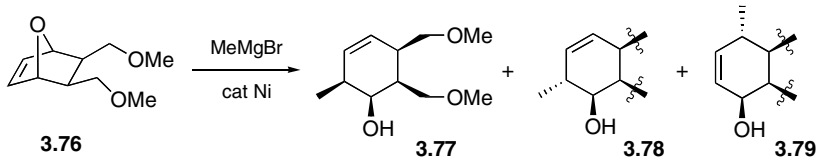


(3.42)

Ar = Ph, C_6H_4OMe, C_6H_4Me, etc.

accepted catalytic cycle consisting of: 1) oxidative addition of an Ni(0) species upon the C–O bond with inversion; 2) transmetallation of the resulting π-allylnickel complex with a Grignard reagent; and 3) reductive elimination with retention.

Lautens et al. have recently reported that a reaction course can be tuned by an appropriate combination of the nickel catalyst and solvent (Eq. (3.43)) [59]. A prod-



3.76 **3.77** **3.78** **3.79**

retention product — inversion products

cat.	solvent	retention	inversion
$Ni(cod)_2$	THF	70%	–
	Et_2O	48%	–
	Et_2O-HMPA	30%	–
$NiCl_2(dppp)$	THF	64%	–
	Et_2O-HMPA	–	95%
	toluene-HMPA	–	80%

(3.43)

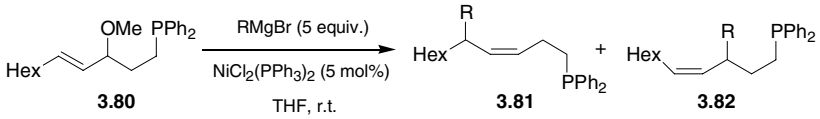
uct **3.77** is a compound of complete *retention* of configuration, which is realized with $Ni(cod)_2$ as a catalyst under the conditions specified in the table shown below Eq. (3.43). Interestingly, high regioselectivity delivering the methyl group at the allylic termini proximal to the hydroxyl group is attained. On the other hand, when the reaction proceeds with the "normal" inversion mode, low regioselectivity is observed giving a mixture of regioisomers **3.78** and **3.79**. Unusual syn oxidative addition with retention of configuration or carbometallation from the less-hindered olefin face is likely involved for the overall retention giving **3.77**. The fact that the reaction of cyclic allyl halides and palladium complexes proceeds with syn oxidative addition may support the former mechanism [60].

3.11.2
Allylation with Soft Nucleophiles

In contrast to the palladium-catalyzed reaction, the nickel-catalyzed reaction with soft nucleophiles is less efficient [61], and consequently the nickel catalysts have been studied to a much lesser degree.

3.11.3
Regiochemical Control Based on Internal Chelation

As mentioned above, the reaction of allylic alcohol derivatives with Grignard reagents in the presence of an Ni or Pd catalyst usually produces a mixture of regioisomers. Recently, a new approach to high regioselectivity was reported by Hoveyda, who installed a Lewis basic PPh_2 group onto allylic ethers at an appropriate position (Eq. (3.44)) [62]. The reaction of **3.80** with RMgBr (R = Ph, Me) proceeds with high regio- and cis olefin-selectivities, and is found to be faster than that without such a phosphine auxiliary. Homologues which are one carbon longer also display high regioselectively.

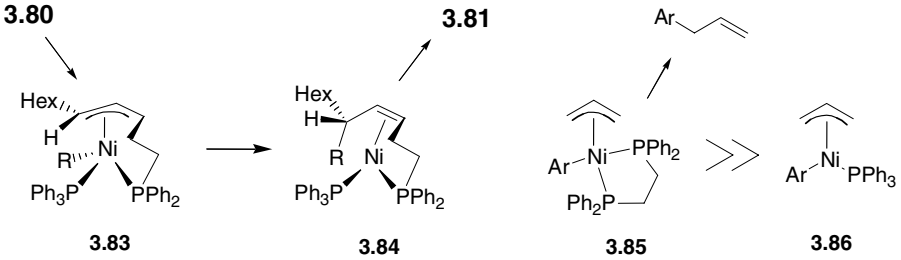


3.80 **3.81** **3.82**

R	time	**3.81** : **3.82**	yield
Ph	3 h	8 : 1	70%
Me	18 h	> 99 : 1	73%

(3.44)

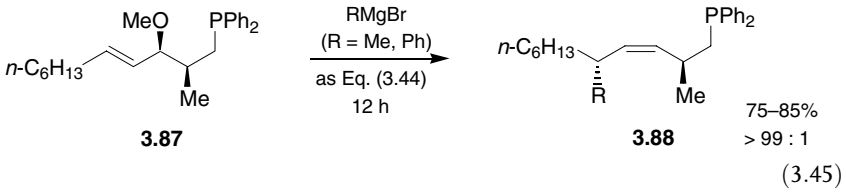
Such regioselectivity is well understood when supposing chelation of the internal phosphine atom to the π-allyl nickel atom to form an 18-electron π-allylnickel **3.83**.



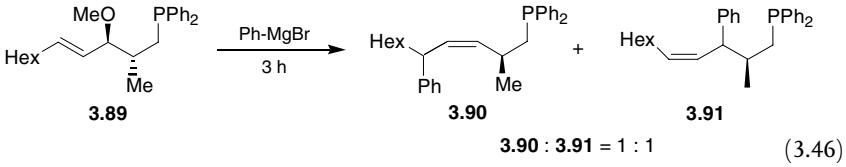
Scheme 3.19. The 18-electron π-allylnickels **3.83** and **3.85** undergo facile reductive elimination.

This subsequently undergoes reductive elimination to produce a cis olefin **3.81** both regio- and stereoselectively (Scheme 3.19). The reductive elimination of an 18-electron π-allylnickel complex **3.85**, according to Kurosawa, proceeds more rapidly than that of a 16-electron complex **3.86** [63]. The results of a series of reactions represented by Eq. (3.44) are in accord with this generalization. In contrast to $NiCl_2(PPh_3)_2$, bidentate $NiCl_2$(dppe) and $NiCl_2$(dppb) complexes are ineffective (yield: <10%). Since bidentate phosphine ligands dissociate less readily than PPh_3, this observation supports the notion that exchange of the PPh_2 of **3.80** with one of the phosphine moieties of the metal complex is critical to the efficiency and selectivity of the C–C bond formation.

A π-allylnickel intermediate **3.83** suggests that substituents on the methylene tether connecting the allylic moiety and the PPh_2 group may interfere with the chelation, and thus change the selectivity and reactivity. Indeed, high selectivities are recorded with **3.87** (Eq. (3.45)), while its diastereomer **3.89** affords a mixture of the regio- and olefin-isomers (Eq. (3.46)). In the latter case, the chelation-form similar to **3.83** is unfavored by the methyl group projecting inside the π-allyl system, and hence the reaction probably proceeds without chelation assistance.



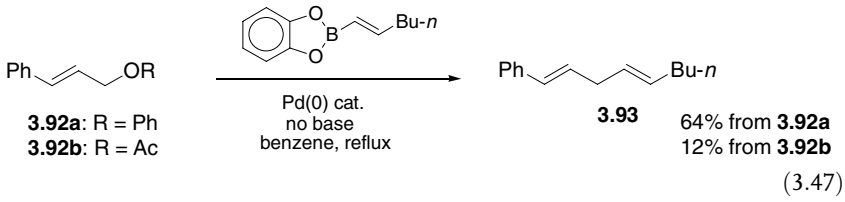
(3.45)



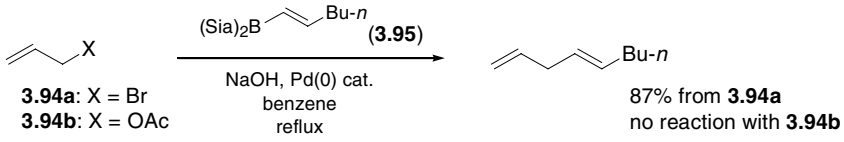
(3.46)

3.11.4
Organometallics other than Grignard Reagents for Allylation

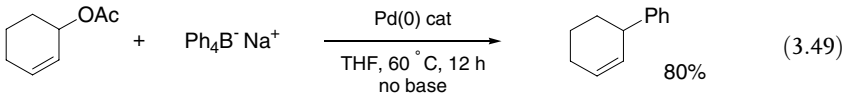
The main synthetic advantage of allylation is the possibility of furnishing a chiral carbon–carbon bond at a secondary allylic carbon with a given nucleophile. As mentioned above, Grignard reagents are convenient reagents for the efficient achievement of allylation. The highly nucleophilic nature – and hence the incompatibility with many functional groups – have, however, restricted its use in the organic synthesis of complex molecules. To improve this situation, organometallics originally developed as reagents for palladium-catalyzed coupling reactions with alkenyl and aryl halides, were applied to the allylation. Unfortunately, organometallics based on aluminum, boron, silicon, tin, zinc, and zirconium are successful only with a limited class of allylic substrates, in which the allylic moiety is located in the terminal position of molecules and/or a reactive halogen atom is used as the leaving group. For example, the palladium-catalyzed reaction shown in Eq. (3.47) proceeds well with phenyl ether **3.92a**, but a low yield of **3.93** is recorded with acetate **3.92b** [64a,b]. Dialkyl boranes such as **3.95** are unreactive with allyl acetate (**3.94b**) (Eq. (3.48)) [64c,d]. In contrast, one of the Ph groups from Ph_4B^- Na^+ is transferred onto the cyclohexenyl ring (Eq. (3.49)) [65].



(3.47)



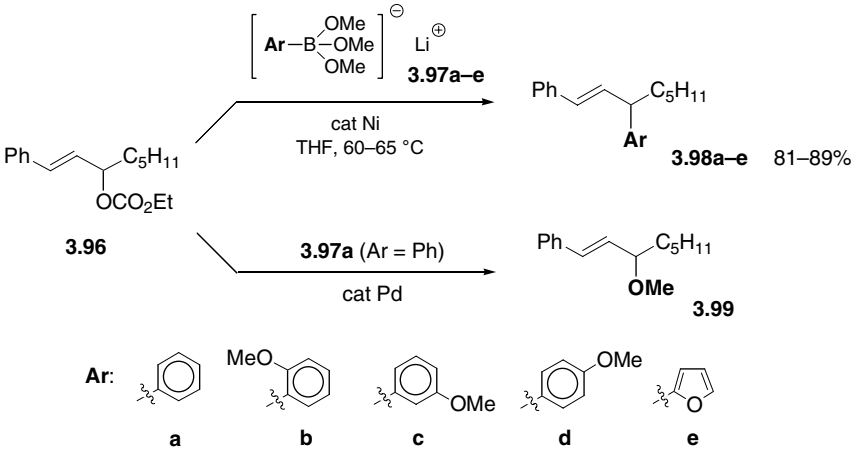
(3.48)



(3.49)

3.11.4.1 Ni-catalyzed Allylation with Lithium Borates Derived from Trimethyl Borate

Recently, lithium borates **3.97** prepared in situ from ArLi and $B(OMe)_3$ were introduced as new reagents for allylation (Scheme 3.20) [66]. These are highly reactive in the presence of a nickel catalyst (entries 1 and 2, Table 3.2), while typical palladium catalysts affords a methyl ether **3.99** (entries 3 and 4).



Scheme 3.20. The Ni- and Pd-catalyzed allylation of carbonate **3.96** with lithium borates **3.97**.

Tab. 3.2. Results of the reaction shown in Scheme 3.20.

Entry	*Catalyst*	*Yield [%]*	
		3.98a	*3.99*
1	$\mathbf{Ni}Cl_2(PPh_3)_2$	97	0
2	$\mathbf{Ni}Cl_2(dppf)$	98	0
3	$\mathbf{Pd}(PPh_3)_2$	<10	66
4	$\mathbf{Pd}(dppf)$	0	54

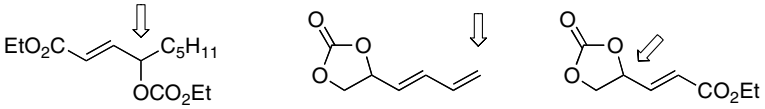
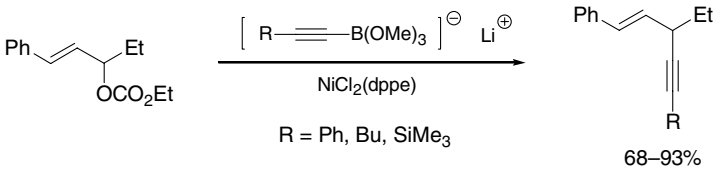


Fig. 3.2. The allylic substrates for the coupling reaction with borates **3.97**. The arrows indicate the reaction sites.

α,β-Unsaturated ester as well as cyclic carbonates listed in Figure 3.2 are also good substrates of the Ni-catalyzed allylation [67]. These results indicate that an ester and a carbonate groups withstand the reaction conditions.

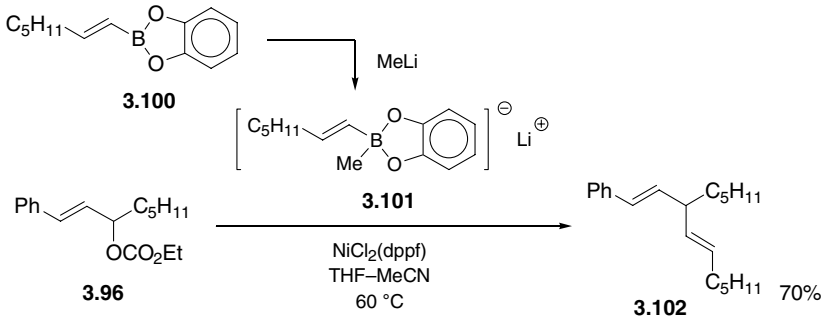
Acetylene borates afford ene-ynes (Eq. (3.50)), in which DPPE and DPPEN provide good results, whereas neither PPh_3, DPPF, nor DPPP do not [68].



(3.50)

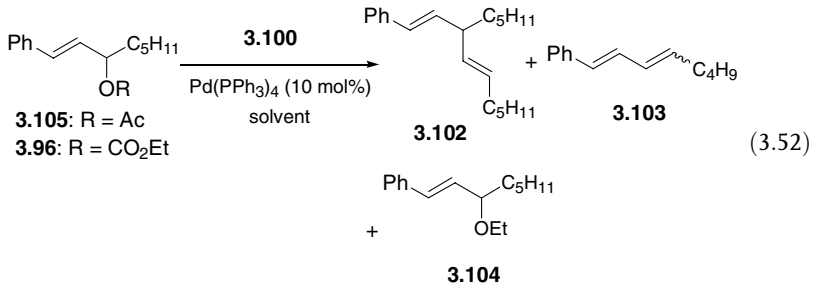
3.11.4.2 Allylation with Lithium Borates Derived from Acetylene

In contrast to the coupling reaction with alkenyl and aryl halides, trivalent alkenyl boranes such as **3.95** are poor reagents for allylation, and hence transmetallation to copper reagents is recommended. By contrast, heptenyl boronate ester **3.100** derived from 1-heptyne and catecholborane is transformed into the corresponding lithium borate **3.101**, which undergoes the nickel-catalyzed reaction with a carbonate **3.96** to provide an allylation product **3.102** in good yield (Eq. (3.51)) [69].



(3.51)

In relation to this reaction, the reactivity of the alkenyl boronate ester **3.100** under palladium catalysis has been studied (Eq. (3.52); Table 3.3). Under the conditions used in Eq. (3.47) (acetate **3.105** and cat. $Pd(PPh_3)_4$ in benzene), a diene **3.103** is produced in 70% yield (entry 1), while an 18:82 mixture of **3.102** (a desired product) and **3.103** is obtained under the conditions optimized for the nickel-catalyzed coupling (cf. entry 2 and Eq. (3.51)). On the other hand, a carbonate **3.96** gives

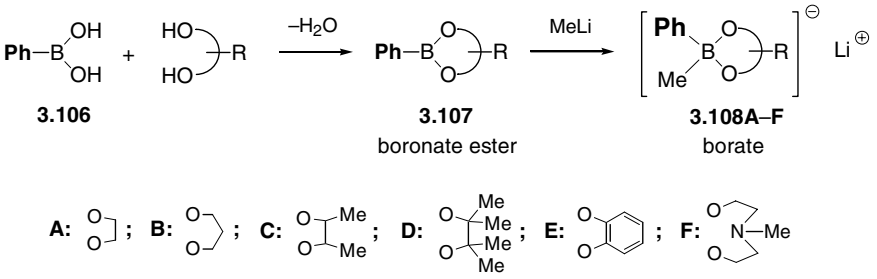


(3.52)

Tab. 3.3. The $Pd(PPh_3)_4$-catalyzed allylation with a boronate ester **3.100** (Eq. 3.52).

Entry	*Ester*	*Conditions*	*Combined yield [%]*	*Ratio*
				3.102:3.103:3.104
1	**3.105**	benzene, reflux	70	0:100:0
2	**3.105**	THF-MeCN, 60 °C	nd	18:82:0
3	**3.96**	THF, 60 °C	95	18:9:73
4	**3.96**	THF-MeCN, 60 °C	87	27:56:17

nd = not determined.



Scheme 3.21. The preparation procedure of phenylborates **3.108A–F**.

a mixture of the three products (entries 3 and 4). Thus, it is concluded that a combination of the borates **3.101** and $NiCl_2$(dppf) is the best choice for the allylation.

3.11.4.3 Allylation with Borates Derived from Cyclic Boronate Esters

Although the methoxy borates **3.97** (Scheme 3.20) and catechol-bound borate **3.101** (Eq. (3.51)) possess sufficient reactivity in allylation with simple sec allylic esters at 45–65 °C, a new borate of higher reactivity is required for reaction with more complicated esters in synthetic application. Among MeLi-derived phenylborates **3.108A–F**, each of which possesses a cyclic diol ligand (Scheme 3.21), **3.108A–C** show higher reactivity with carbonate **3.96** (Table 3.4). In particular, **3.108C** allows the reaction to proceed at room temperature or below, irrespective of the nickel catalyst (entries 3 and 4) [70].

Lithium borates of a general structure **3.110** possessing the best diol ligand (**C**) display high performance for the arylation of a wide structural and electronic variety of allylic carbonates. Some examples are shown in Scheme 3.22 (reactions (1) to (3)). The reaction with cyclohexenyl carbonate proceeds with complete inversion of configuration (Scheme 3.22 (reaction 3)).

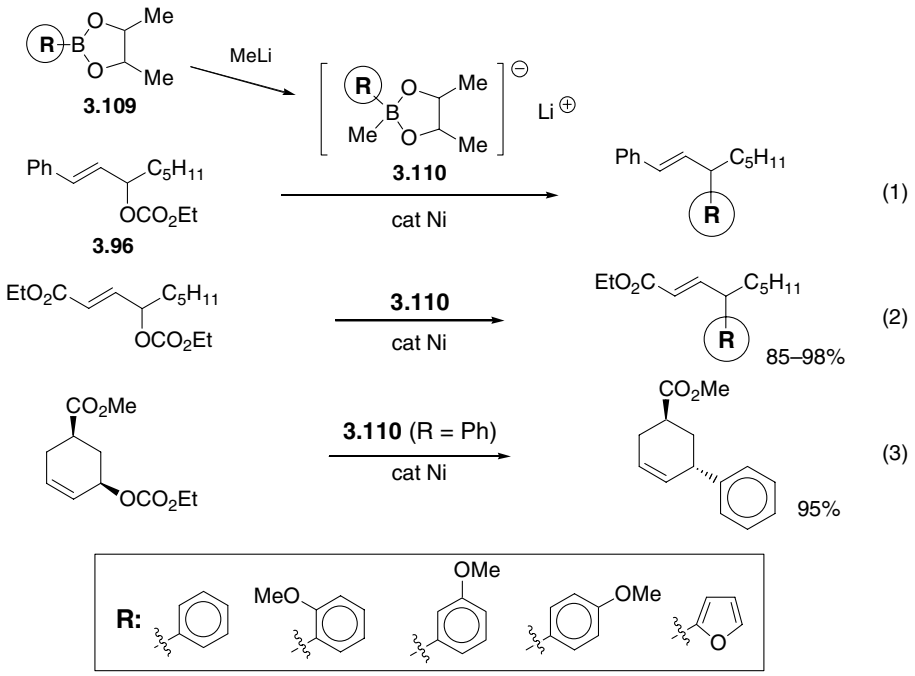
3.11.5 The Design of Functionalized Reagents for Allylation

Recently, much attention has been focused on the preparation of functionalized organozincs. To date, the reactivity of these organozincs for coupling with alkenyl and aryl substrates has been shown to be quite similar to those prepared using

Tab. 3.4. The $NiCl_2$(dppf)-catalyzed allylation of a carbonate **3.96** with phenylborates **3.108A–C** in THF to yield **3.98a** (cf. Scheme 3.20).

Entry	*Borate*	*Temp. [°C]*	*Time [h]*	*Yield of 3.98a [%]*
1	**3.108A**	40	12	95
2	**3.108B**	35	12	84
3	**3.108C**	r.t.	4	88
4	**3.108C**	5	12	97

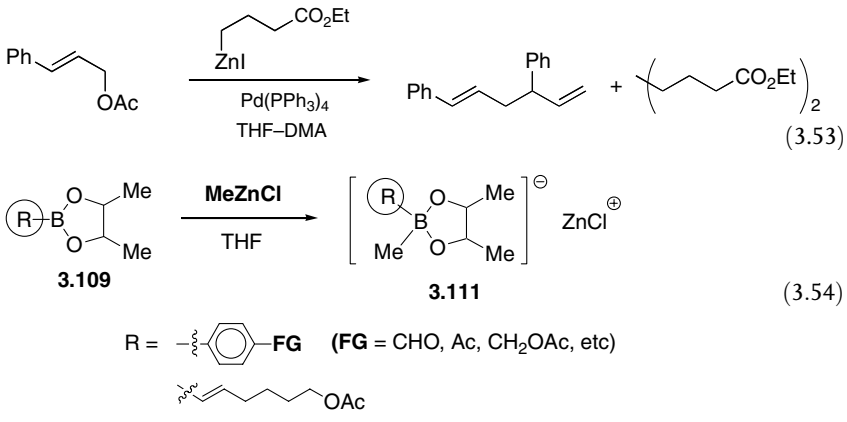
r.t. = room temperature.



Scheme 3.22. The allylation of a wide electronic and structural variety of allylic substrates with lithium borates **3.110**.

classical methods [71]. Allylation with these reagents appears to be awkward however, and an attempt to react with an allylic acetate resulted in the homocoupling, as shown in Eq. (3.53) [72]. Thus, transmetallation to a more reactive copper reagent is one way to achieve successful allyl coupling [73, 74].

The reaction of the boronate ester **3.109** with MeZnCl in place of MeLi produces a new zinc borate **3.111** (Eq. (3.54)) without nucleophilic methylation at a carbonyl



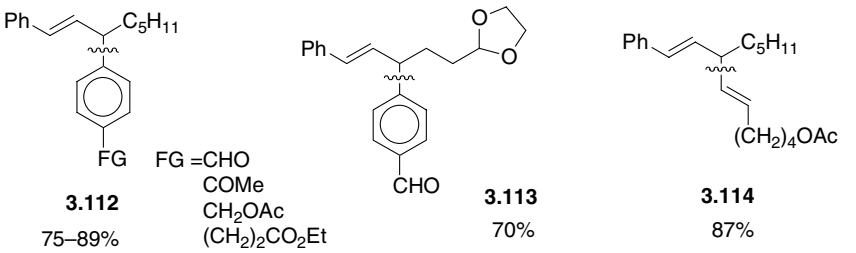


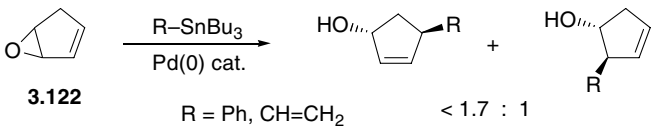
Fig. 3.3. The yields of the allylation products with functionalized zinc borates **3.111** (Eq. (3.54)).

carbon on R [75]. The zinc borates undergo allylation to furnish the products shown in Figure 3.3. Among these, the result obtained with the aldehyde-borate **3.113** is noteworthy in that: 1) the borate is indeed generated from the corresponding boronate ester **3.109** ($R = C_6H_4CHO$-*p*) and MeZnCl cleanly and without attack at the aldehyde-carbon; and 2) the electron-withdrawing nature of the aldehyde group does not affect the reactivity. In addition, the synthesis of **3.113** demonstrates the efficiency of the present methodology as two aldehyde groups in the molecule are differentiated.

3.11.6
Nickel-catalyzed Reactions of Cyclopentenyl Acetate and Borates

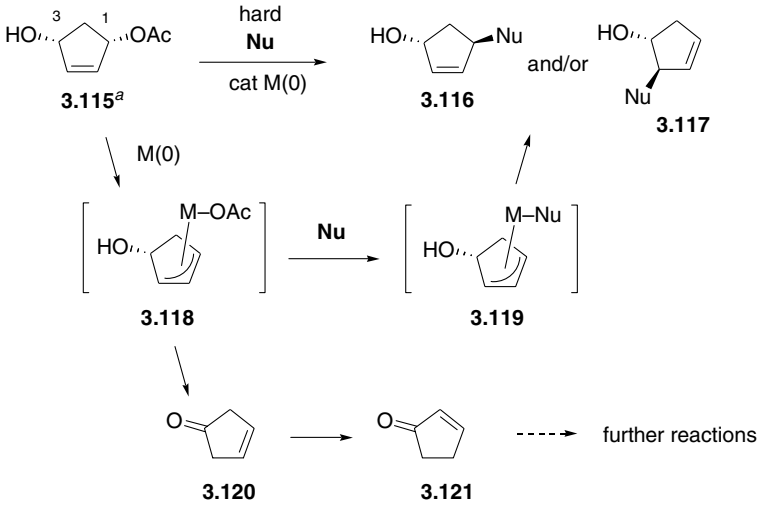
Although efficient methods have been established for the preparation of both enantiomers of 4-cyclopentene-1,3-diol mono-acetate (**3.115**) [76, 77], the lack of a method to install hard nucleophiles on the cyclopentene ring prevented its use in organic synthesis (Scheme 3.23). An intermediate **3.119**, as would be expected for metal-catalyzed transformations, shows a lack of steric or electronic bias, and this leads selectively to either **3.116** or **3.117** because the hydroxyl group and the M–Nu portions in the π-allyl metal intermediates (**3.118** and **3.119**) are placed at opposite sides to each other.

The reaction of the palladium-catalyzed allylation of mono-epoxide **3.122** and organostannanes (Eq. (3.55)) [78] is an example showing the low regioselectivity. The reaction proceeds through a π-allylpalladium intermediate similar to **3.119**.



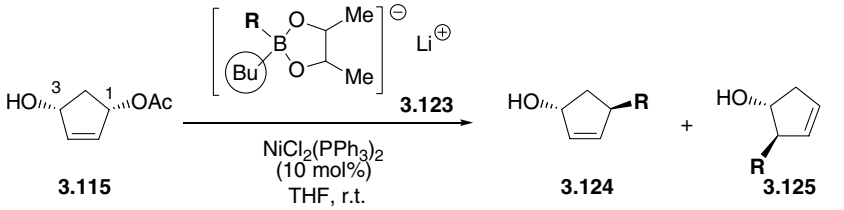
(3.55)

Attempted phenylation of **3.115** using the phenylborate **3.110** (Me ligand, R = Ph) and $NiCl_2(PPh_3)_2$ (10 mol%) under the best conditions developed for *acyclic* esters produces, unfortunately, an undesired enone **3.121**. This indicates that *β*-



Scheme 3.23. The expected reaction(s) of **3.115** with hard nucleophiles. [a] (1*S*,3*R*)-Isomer is depicted in this scheme.

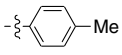
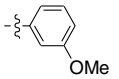
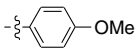
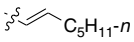
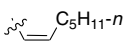
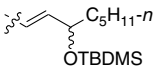
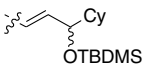
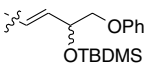
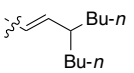
hydrogen elimination of the π-allyl intermediate **3.118** (M = Ni) to ketone **3.120** is a more rapid process than transmetallation with phenylborate **3.110** (Scheme 3.23). A similar elimination that is catalyzed by palladium is reported for epoxide **3.122** [79]. In sharp contrast, advanced phenylborate **3.123a** with the Bu ligand furnishes the coupling products (Eq. (3.56) and Table 3.5, entry 1), whilst the low regioselectivity producing **3.124a** and **3.125a** in 0.9:1 dr is improved greatly to 13:1 dr by the addition of *t*-BuCN (2–5 equiv.) and NaI (0.5–1 equiv.) [80, 81].



R for **3.123**–**13.125**, see Table 3.5 (3.56)

The generality of the reaction and the effect of additives (*t*-BuCN and NaI) on high regioselectivity are shown in Table 3.5. In addition, the borates **3.123** do not undergo hydrolysis and are compatible with the hydroxyl group in the substrate **3.115**. In other words, a slight excess of **3.123** (1.2–1.8 equiv.) is sufficient to complete the reaction. This advantage is significant, especially in the situation where the preparation of **3.123** comprises multiple steps.

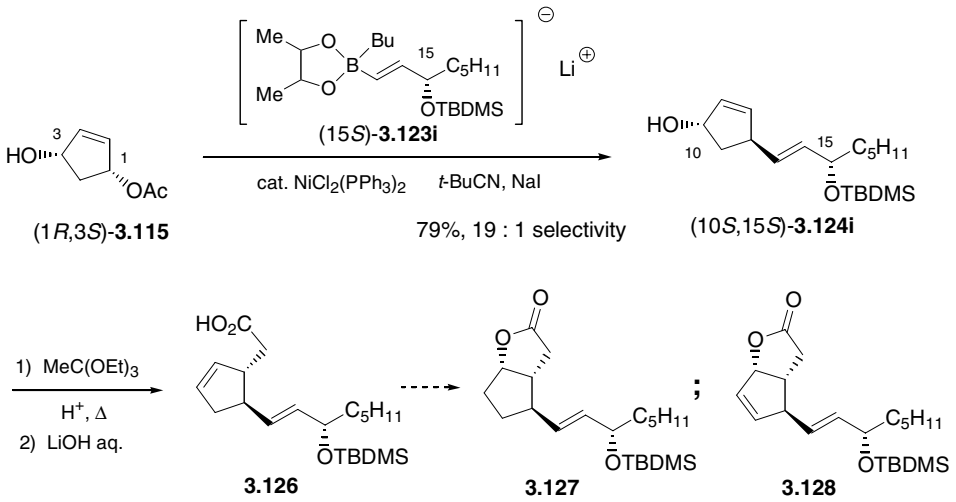
Tab. 3.5. The nickel-catalyzed regio- and stereoselective installation of aryl and alkenyl groups to mono-acetate **3.115** (Eq. 3.56).

Entry	*a–l*	*R*	*Yield [%]*[a]	*3.124:3.125*	
				With additive[b]	*No additive*
1	**a**		84	13:1	0.9:1
2	**b**		80	7:1	1.2:1
3	**c**		81	12:1	1.5:1
4	**d**		84	6:1	0.7:1
5	**e**		81	9:1	–
6	**f**		63	8:1	–
7	**g**		89	6:1	3:1
8	**h**		85	5:1	1.3:1
9	**i**		67	15:1	5.4:1
10	**j**		85	15:1	5.5:1
11	**k**		80	17:1	8:1
12	**l**		85	6:1	2.5:1

[a] Yields for the reaction in the presence of additives.
[b] *t*-BuCN (2–5 equiv.) and NaI (0.5–1 equiv.).

3.11.7
Synthetic Application of Nickel-catalyzed Reactions of Cyclopentenyl Acetate and Borates

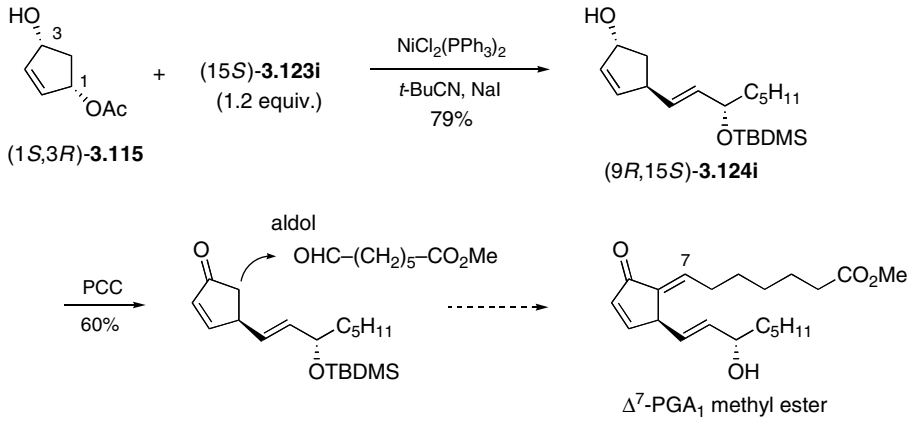
The asymmetric synthesis of 11-deoxy PGE_2 and PGA_2 intermediates **3.127** and **3.128** is a successful application of the method described in Section 3.11.6. As shown in Scheme 3.24, the reaction with (1*R*,3*S*)-**3.115** and 1.2 equiv. (15*S*)-**3.123i**



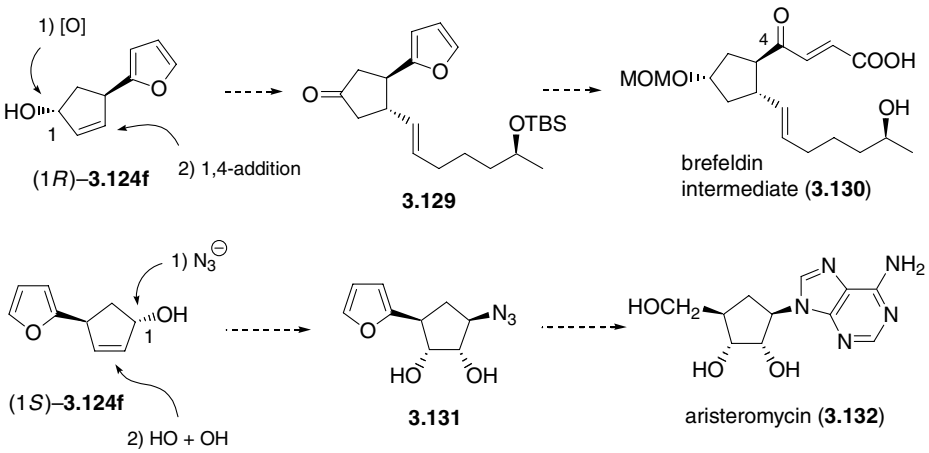
Scheme 3.24. The application of an borate (15*S*)-**3.124i** to the synthesis of the classical prostaglandin (PG) intermediates.

(PG numbering) produces the product **3.124i** with 19:1 regioselectivity (cf. Table 3.5, entry 9), indicating no interference of the chiral centers on the mono-acetate and any chiral borates.

The short-step synthesis of Δ^7-PGA$_1$ methyl ester [80c], an artificial anti-tumor agent, is another application of the nickel-catalyzed reaction (Scheme 3.25). The requisite mono-acetate (1*S*,3*R*)-**3.115** is the enantiomer used for the classical PG (Scheme 3.24), and its reaction with (15*S*)-**3.123i** also furnishes (9*R*,15*S*)-**3.124i** with excellent regioselectivity (21:1). Oxidation with PCC followed by aldol reaction with the α-chain aldehyde produces Δ^7-PG A$_1$ methyl ester.



Scheme 3.25. The short-cut synthesis of Δ^7-PGA$_1$ methyl ester.

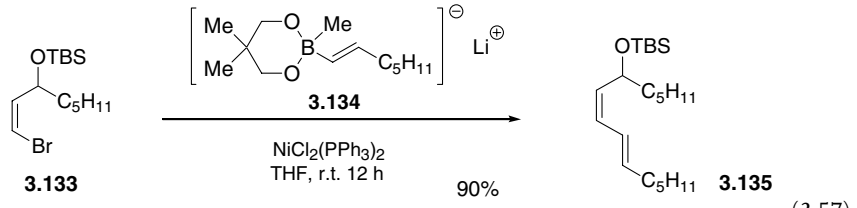


Scheme 3.26. The synthesis of intermediates of brefeldin and aristeromycin.

The syntheses of the brefeldin A intermediate **3.130** [82] and aristeromycin (**3.132**) [83] have been accomplished from (1*R*)- and (1*S*)-enantiomers of the furan product **3.124f**, respectively (Scheme 3.26).

3.11.8
Extension of the Lithium Borate/Nickel Catalyst for Coupling with Alkenyl and Aryl Substrates

The above borates **3.123** originally developed for allylation may be applied to the coupling reaction with alkenyl and aryl substrates, which are quite poor substrates toward conventional coupling reagents due to the steric reason. Indeed, the alkenyl coupling reaction of cis bromide **3.133** proceeds with the modified borate **3.134** and a nickel catalyst at room temperature to afford a diene **3.135** efficiently (Eq. (3.57)) [84]. This reaction was later applied to the synthesis of the anti-bacterial kormicin (active against a marine Gram-negative organism), the human leukocyte activator 10,11-dihydro-LTB_4, and the HMG-CoA reductase inhibitor decarestrictine D (Fig. 3.4) [85, 86].



(3.57)

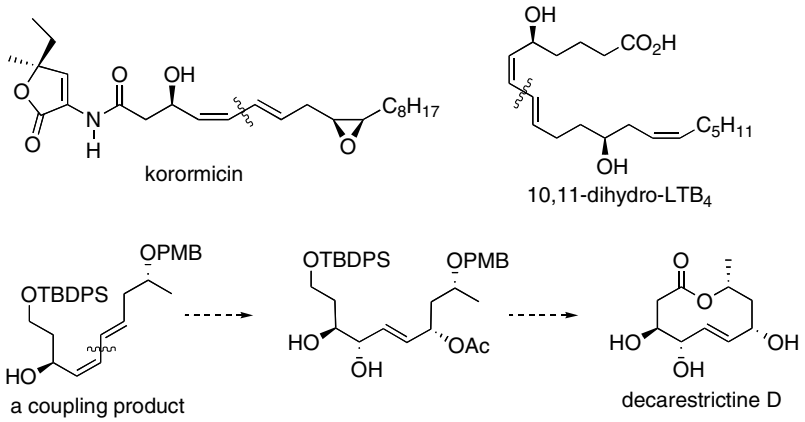
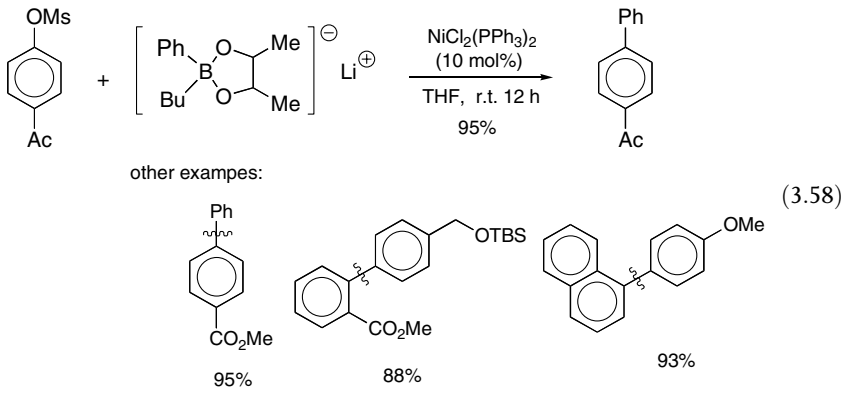


Fig. 3.4. Biologically active compounds synthesized through the coupling reaction of Eq. (3.57).

In contrast to the high reactivity of aryl triflates, aryl mesylates and tosylates are poor substrates in the previously described coupling reaction. The borate/nickel catalyst is an efficient reagent system for coupling with such sulfonates (Eq. (3.58)) [87].



(3.58)

3.12 Nickel Enolates

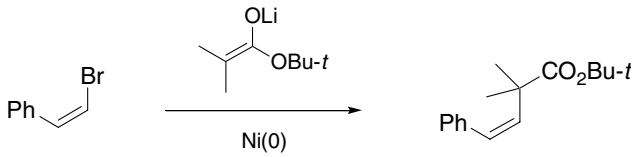
Nickel enolates have been proposed as intermediates in several organic reactions. Oxygen-bound and carbon-bound nickel species have been isolated and characterized using both spectroscopy and X-ray analysis (Fig. 3.5). The nickel enolates

Fig. 3.5. Two structural forms of nickel enolates.

promote several types of reaction, with the overall conversion from the enolate precursor being barely accessible with the classical enolates. The preparation and reactions of the nickel enolates are detailed in the following sections.

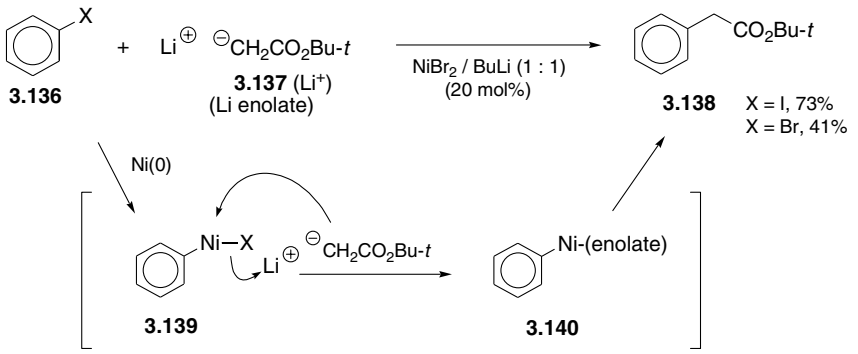
3.12.1 Reactions of Ni(II) Complexes with Lithium or Potassium Enolates

The reaction of aryl halide **3.136** and lithium enolate **3.137** in the presence of a nickel catalyst ($NiBr_2 + n$-BuLi) takes place at −70 °C to produce **3.138** through a postulated "nickel enolate **3.140**" (Scheme 3.27) [88]. In the case of a crotonate anion, reaction with PhI takes place at the γ position. Alkenyl halides also produce coupling products without isomerization of the olefin geometry (Eq. (3.59)). Palladium complexes have recently been reported to catalyze the same arylation [89].

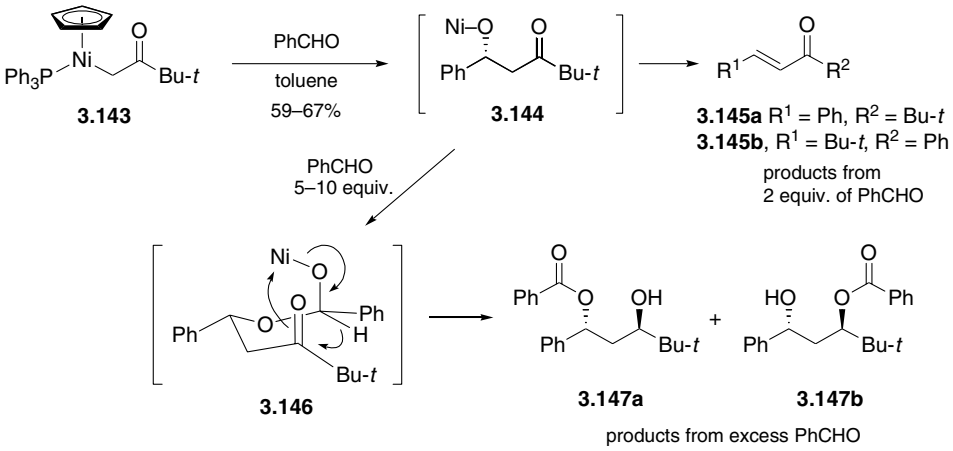


(3.59)

The reaction between Cp*(PPh_3)NiCl (**3.141**) and potassium enolate **3.137** produces a nickel enolate [90]. The carbon-bound structure **3.142** was initially disclosed using X-ray diffraction, and further supported using spectroscopy (^{1}H and ^{13}C NMR, infra-red) (Eq. (3.60)). This was the first structural confirmation of nickel enolate chemistry. Similarly, the reaction between Cp(PPh_3)NiCl and the potassium enolate derived from MeC(=O)Bu-*t* affords an enolate, for which the carbon-bound structure **3.143** has been determined using spectroscopy (Scheme 3.28). The reaction of **3.143** with MeI in C_6D_6 at 45 °C for 2 days affords the methylation product, EtC(=O)Bu-*t*, in 33% yield and Cp(PPh_3)NiI in 74% yield, while TMSCl furnishes the corresponding TMS enol ether and Cp(PPh_3)NiCl in

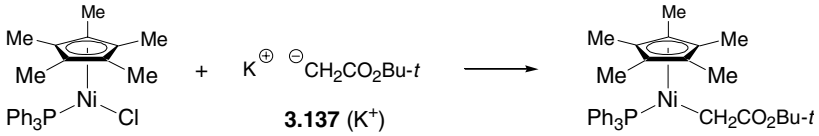


Scheme 3.27. The Ni-catalyzed coupling reaction of aryl halides and lithium enolate.



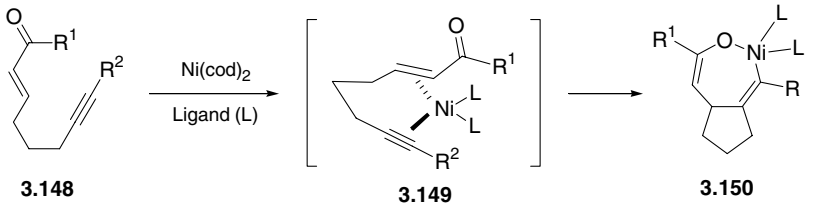
Scheme 3.28. The reaction of Ni-enolate **3.143** with PhCHO.

73% and 84% yields, respectively. Reaction with PhCHO produces different groups of products, depending on the stoichiometry of PhCHO and the reaction temperatures (Scheme 3.28). With 2 equiv. PhCHO at room temperature for 8 h, enones **3.145a** and **3.145b** are produced, whilst the use of 5–10 equiv. PhCHO at 0 °C affords a mixture of **3.147a** and **3.147b** in 59–67% yields. The reaction in the latter case proceeds through **3.146** giving **3.147a** directly, while isomerization produces **3.147b**.



(3.60)

The oxidative cyclization of alkynyl enones and enals, **3.148**, with $Ni(cod)_2$ produces nickel enolates **3.150** (Eq. (3.61)) [91]. The reactions of these complexes are described in Chapter 4 (see Section 4.6.2).

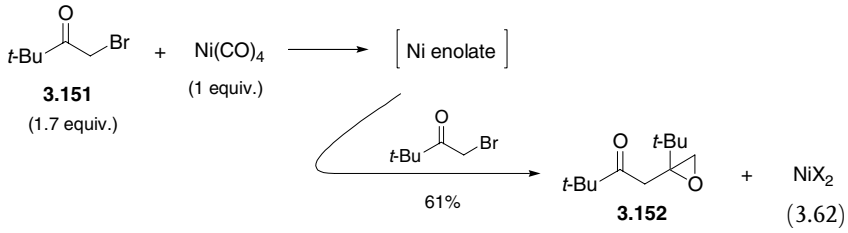


(3.61)

Enol acetate, upon reaction with Ni(0), produces nickel enolate, which subsequently undergoes the aldol reaction [92].

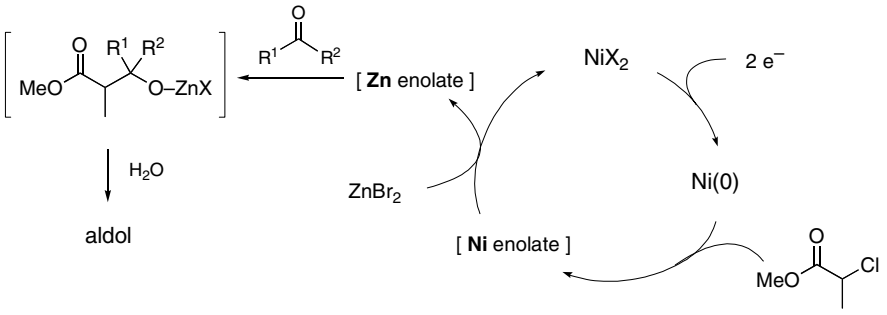
3.12.2 The Reformatsky-type Reaction

α-Halo carbonyl compound **3.151** reacts with electron-rich $Ni(CO)_4$ to produce a nickel enolate, which is highly nucleophilic towards the remaining α-halo carbonyl carbon, furnishing β,γ-epoxy ketone **3.152** in good yield (Eq. (3.62)) [93]. As might be expected, a stoichiometric quantity of $Ni(CO)_4$ is required to complete the reaction.

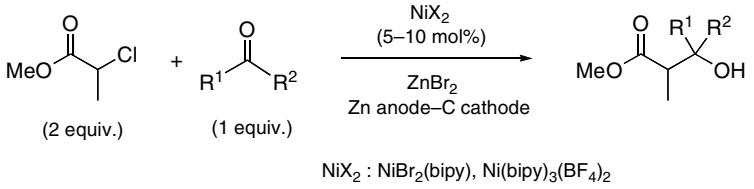


(3.62)

The above reaction suggests the possibility of a catalytic variant in combination with a process for recycling Ni(II) to an active Ni(0) species. Such a catalytic process is realized with an electrochemical system (Eq. (3.63)) consisting of a DMF solution of an α-chloro-ester, a carbonyl compound, $ZnBr_2$ (5 equiv.), and 5–10% of an Ni complex such as $NiBr_2$(bipy) or $Ni(bipy)_3(BF_4)_2$ with a zinc anode and a carbon cathode [94]. Under these conditions, NiX_2 is reduced to an Ni(0) species, which attacks α-chloro-propionate to form a nickel enolate of unidentified structure (Scheme 3.29). Subsequent transmetallation with $ZnBr_2$ produces a zinc enolate and NiX_2, thus closing the catalytic cycle. Although the zinc anode produces the requisite Zn(II) during electrolysis, the addition of $ZnBr_2$ provides better results. Such an electrochemical system is applied to chloro(difluoro)acetate [95].

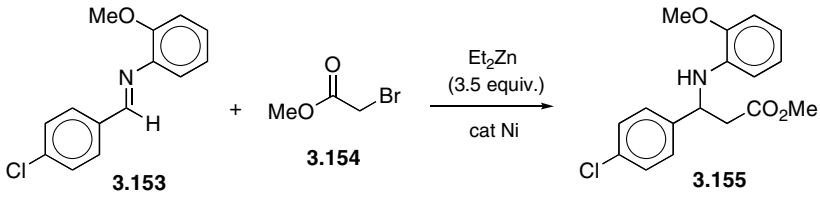


Scheme 3.29. The nickel-catalyzed Reformatsky reaction under electrochemical conditions.

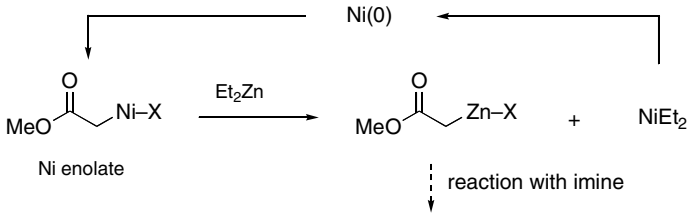


(3.63)

It has been reported that Et_2Zn promotes the Rh-catalyzed Reformatsky-type reaction of α-bromo esters with carbonyl compounds, in which Et_2Zn contributes not only to transmetallation of the initially formed Rh(III) enolate to Zn enolate, but also to reduction of the R(III) to active Rh(I), probably through Rh(III)Et_2 [96]. A similar reaction between α-bromo ester **3.154** and imines **3.153** proceeds with a nickel catalyst such as $Ni(acac)_2$, $NiCl_2(PPh_3)_2$, which exhibits as high a catalytic activity as $RhCl(PPh_3)_3$ (Eq. (3.64)) [97]. Equation (3.65) illustrates the crucial role of Et_2Zn and the nickel enolate involved in the reaction.



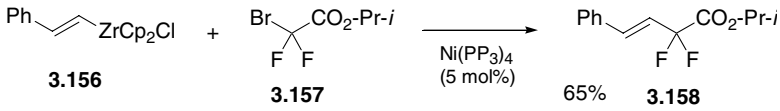
(3.64)



(3.65)

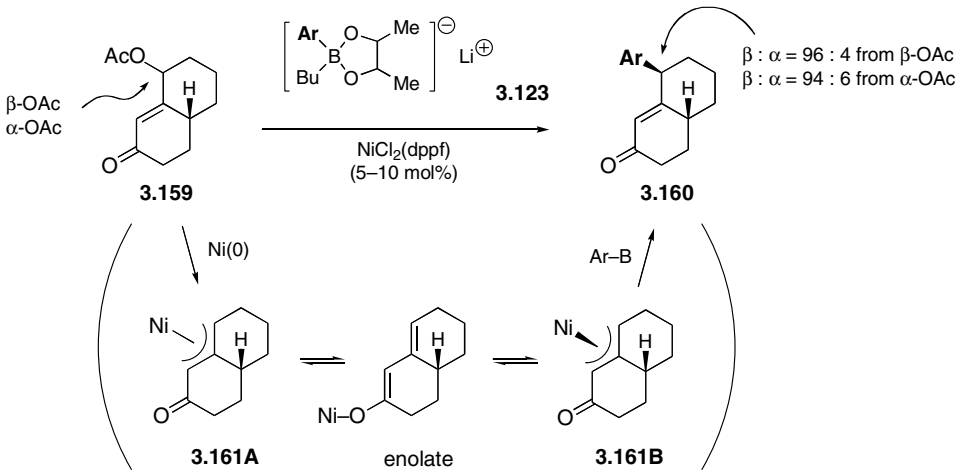
3.12.3
Other Reactions through Nickel Enolates

The reaction of bromo(difluoro)acetate **3.157** with alkenyl zirconium reagent **3.156** proceeds with a nickel catalyst to produce **3.158** in 65% yield (Eq. (3.66)), in which transmetallation between zirconium reagent **3.156** and the nickel enolate generated from ester **3.157** and Ni(0) is probably involved [98].



(3.66)

Although the reaction of allyl acetate with hard nucleophiles such as lithium borates proceeds with overall inversion (see Section 3.11.4), the stereochemistry



Scheme 3.30. Ni-catalyzed coupling reaction of octalenone, producing the β-aryl stereoisomer.

observed in the nickel-catalyzed reaction of γ-acetoxy-octalenone **3.159** and the lithium borate **3.123** is unusually independent of the substrate stereochemistry (Scheme 3.30) [99]. Rapid interconversion between the π-allyl nickel stereoisomers **3.161A** and **3.1761B** exists through the nickel enolate, and less congested π-allyl nickel **3.161B** undergoes coupling with the aryl borate preferentially to produce **3.160** in a stereoselective manner.

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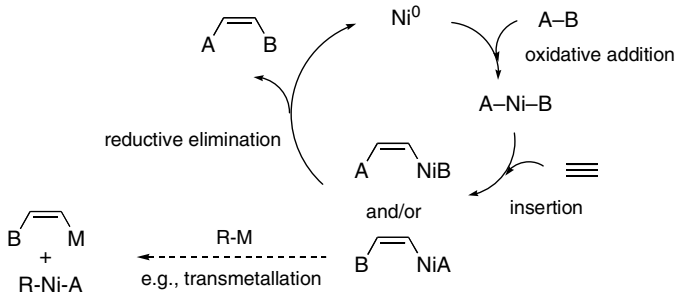
4
Reaction of Alkynes

Shin-ichi Ikeda

Since the earliest investigations represented by cycloaddition [1] and carboxylation [2], the nickel-catalyzed reactions of alkynes have been extensively studied by many research groups. This chapter highlights recent developments in the nickel-catalyzed reactions of alkynes. Recent advancements in cycloaddition and the carboxylation of alkynes are described in Chapters 6 and 7, respectively.

The most extensively studied reaction is the addition reaction of an A–B species (e.g., H–H, H–metals, metals–metals, C–H, and C–metals, where metals = Si, Sn, B, etc.) to alkynes (Scheme 4.1). Generally, the addition of an A–B species to alkynes starts with oxidative addition of the A–B species to a nickel(0) complex to generate an A–Ni–B species (see Section 1.7.1). The insertion of an alkyne into either the A–Ni or the B–Ni bond gives the alkenylnickel intermediate(s), which undergo reductive elimination to produce the alkenes functionalized with an A and B functionalities at the 1,2-positions (see Section 1.7.4). The A and B groups are usually introduced on the same face of alkynes, and *cis*-alkenes with respect to A and B are produced. When an A–B is C–X (X = halogens, O, N), the alkenylnickel X intermediates are capable of undergoing, instead of reductive elimination,

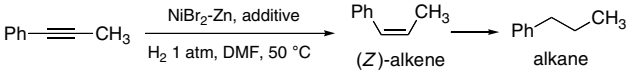


Scheme 4.1. The catalytic cycle for the addition of an A–B species upon alkynes catalyzed by a nickel(0) species: cis addition of an A–B to an alkyne.

Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6

Tab. 4.1. Nickel-catalyzed hydrogenation of alkynes with 1 atm H_2.



Additive	*Time [h]*	*Yield [%]*	
		(Z)-alkene	*alkane*
None	3	93	1
	6	0	98
DIPHOS	4	92	1
	15	90	2
$H_2N(CH_2)_2NH_2$	8	92	trace
	24	93	2

further reactions with organometallics (transmetallation; see Section 1.7.3, dotted arrow), the other alkynes, alkenes, CO and others (insertion; see Section 1.6.2), thus furnishing a variety of multi-component connection products.

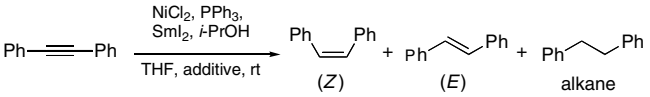
The oxidative cyclization of an Ni(0) complex upon alkynes across other unsaturated molecules, such as dienes, enones, and carbonyls, is another type of reaction which currently is attracting much interest (see Scheme 1.8).

4.1 Hydrogenation

Alkynes are hydrogenated to alkenes and alkanes successively by various transition metals. The nickel catalysts for hydrogenation are usually prepared by the reduction of nickel salts with H_2 [3], metals [4], alkali metal hydride [5], and $NaBH_4$ [6]. The catalyst activities depend on the type of nickel salts, reducing agents, and solvents. Alkynes are hydrogenated successively to (*Z*)-alkenes and alkanes by a catalytic amount of $NiBr_2$ and Zn under 1 atm of H_2 (Table 4.1) [7]. Interestingly, ethylenediamine and DIPHOS effect the partial hydrogenation of alkynes. That is, in the absence of these additives, mono-hydrogenation and di-hydrogenation proceed in a sequence, and the mono-hydrogenation can be achieved by controlling the reaction time or the amount of H_2, charged. In the presence of the additives, only mono-hydrogenation takes place, irrespective of the reaction time and the amount of H_2.

The partial and stereoselective reduction of alkynes to either (*E*)- or (*Z*)-alkenes has been reported (Table 4.2) [8]. Again here, the selectivity shows marked dependence on the kind of additives. SmI_2 in isopropanol, in the presence of a catalytic amount of $NiCl_2$, selectively reduces alkynes to (*Z*)-alkenes. HMPA changes the reaction features: it accelerates the reaction and guides the reaction to provide (*E*)-alkenes selectively.

Tab. 4.2. Stereoselective reduction of alkynes with SmI_2 catalyzed by $NiCl_2$.



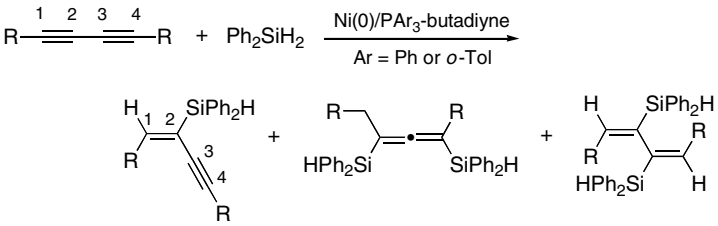
Additive	*Time [h]*	*Yield [%]*	*Ratio*		
			(Z)	*(E)*	*alkane*
None	2	68	91	9	0
HMPA	0.5	89	1	90	9

4.2
Hydrometallation and Related Reactions

The addition of an H–M species to alkynes is well known and is effectively promoted by various transition-metal catalysts [9–11]. Nickel complexes catalyze the addition of $H–SiR_3$ (hydrosilylation), $H–SnR_3$ (hydrostannylation), $H–BR_2$ (hydroboration), $H–AlR_2$ (hydroalumination), etc.

4.2.1
Hydrosilylation and Hydrostannylation

The hydrosilylation of alkynes with alkyl- and arylsilanes, such as Ph_2SiH_2, $PhMe_2SiH$, and Et_3SiH [9], has been studied under catalytic systems composed of an Ni(0), triarylphosphine, and butadiyne [12]. In all cases examined, the reaction is characterized by *cis*-addition of hydrogen and silicon. Disubstituted alkynes provide a mixture of silicon-substituted ethenes, butadienes (insertion of another alkyne), and hexatrienes (double insertion of alkynes) along with benzenes (cyclic trimers of alkynes). The reaction of disubstituted buta-1,3-diynes proceeds stepwise and provides the 1,2-addition products as the primary product, delivering the silicon at C2 (Scheme 4.2). The subsequent addition, depending on the kind of substituents at C1 and C4 of buta-1,3-diynes, proceeds selectively either in a 1,4 fash-

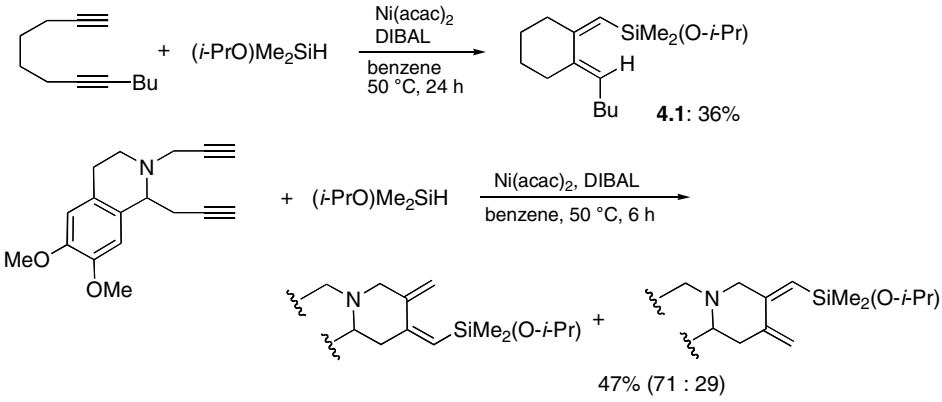


R = TMS	~2%	90~92%	0%
R = Ph	~2%	0%	37%

Scheme 4.2. The Ni(0)-catalyzed double hydrosilylation of 1,4-disubstituted 1,3-butadiynes.

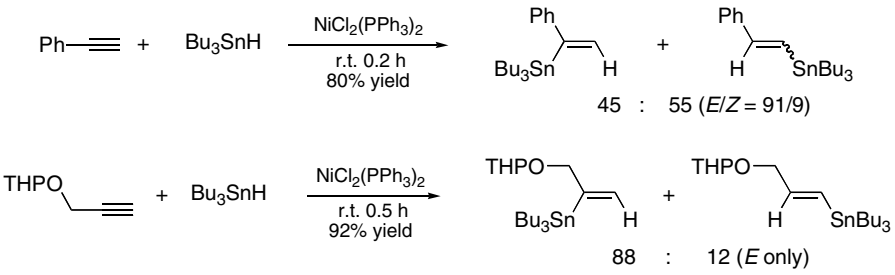
ion leading to allenes (R = TMS) or in a 1,2 fashion leading to 1,3-butadienes (R = Ph). The latter reaction, giving rise to a symmetrically substituted diene, demonstrates that the hydrosilylation takes place twice with the same regioselectivity.

Hydrosilylation across two molecules of alkynes has been reported [13]. An internal version is shown in Scheme 4.3, where 1,7-octadiynes react with a variety of hydrosilanes to provide 1,2-dialkylidenecyclohexanes [14]. As is apparent from the structure of a product **4.1**, one of the exocyclic double bonds is assembled with (*Z*)-silylmethylene and the other with (*E*)-pentylidene groups. Moreover, the selective formation of **4.1** indicates that the hydrosilylation is regioselective and delivers the hydrogen on the most-substituted and the silicone on the least-substituted alkyne termini. The reaction of a nitrogen-containing 1,7-octadiyne shows modest regioselectivity and produces a mixture of regioisomers, which suggests that the nitrogen atom and an Ni(II) center do not interact in controlling the regioselectivity. All the results suggest the following reaction sequence: 1) oxidative addition of an Ni(0) upon an Si–H bond; 2) insertion of alkyne into the H–Ni–Si species forming a vinylnickel bond; 3) insertion of the other alkyne into the vinylnickel bond (cyclization); and 4) reductive elimination. It is not clear, however, that on the first occasion which of the two triple bonds inserts into which of the H–Ni and Ni–Si bonds.



Scheme 4.3. The nickel-catalyzed hydrosilylation of 1,7-octadiynes furnishing 1,2-dialkylidenecyclohexanes. Both the H and Si of Me_2(O-*i*-Pr)SiH are stereoselectively delivered inside of the exocyclic diene.

Hydrostannylation also seems to occur with *cis*-addition [10] in the presence of transition metals [10], including a nickel catalyst [15]. However, the regioselectivity is not very high (Scheme 4.4). Contamination with a small amount of the (*Z*)-isomer may be attributed to thermal isomerization of the primary (*E*)-product (via a radical mechanism). A nickel(0) catalyst may be generated in situ by reduction of $NiCl_2$ with Bu_3SnH.



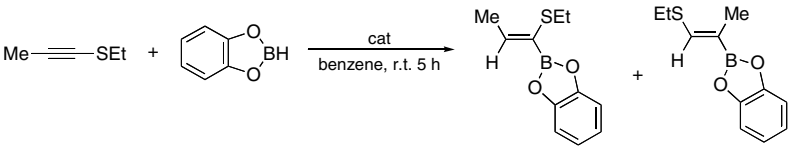
Scheme 4.4. The nickel-catalyzed hydrostannylation of alkynes.

4.2.2 Hydroboration

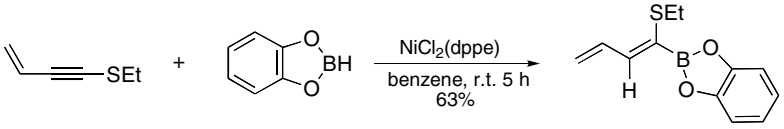
Hydroboration with catecholborane, an unreactive hydroboration agent, smoothly occurs under mild conditions in the presence of a variety of transition-metal catalysts [11, 16, 17]. The hydroboration of 1-(alkylthio)-1-alkynes with catecholborane in the presence of $NiCl_2$(dppe) or $NiCl_2$(dppp) takes place both regio- and stereoselectively and provides (*Z*)-alkenylboronates with the boryl group in the α-position with respect to the sulfur atom (Table 4.3) [18]. Interestingly, rhodium catalysts, which have been most commonly applied to the catalytic hydroboration of alkenes and alkynes, show poor regioselectivity for the hydroboration of alkylthioalkynes, yielding the addition products, albeit in low yield (Table 4.3).

Conjugated 1-(alkylthio)-enyne undergoes hydroboration in the same fashion to 1-(alkylthio)-1-alkynes and provides a geminally heterosubstituted diene as a sole product (Scheme 4.5). The palladium-catalyzed hydroboration under similar conditions takes place in a 1,4-addition fashion, yielding a geminally heterosubstituted allene [19].

Tab. 4.3. Transition metal-catalyzed hydroboration of 1-(alkylthio)alkyne with catecholborane. Nickel shows a higher catalytic performance than rhodium, the putative transition metal for hydroboration.



Catalyst	*Yield [%]*	*Ratio*
$[RhCl(C_2H_2)_2]_2$	23	90:10
$[Rh(cod)(PPh_3)_2]_2PF_6$	45	74:26
$NiCl_2$(dppe)	100	>99:<1
$NiCl_2$(dppp)	97	98:2



Scheme 4.5. The nickel-catalyzed hydroboration of (1-alkylthio)-3-buten-1-yne with catecholborane.

4.2.3
Hydroalumination

In the presence of a $Ni(acac)_2$ catalyst, hydroalumination of internal alkynes with DIBAL principally proceeds via *cis*-addition. However, the reaction is somewhat less stereoselective [20].

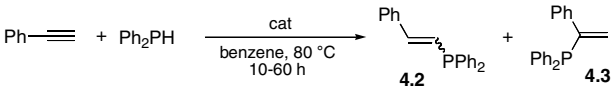
4.2.4
Miscellaneous: the Addition of H–P and H–S Groups

The addition of diphenylphosphine to alkynes occurs with various palladium and nickel catalysts to yield the alkenylphosphines, both regio- and stereoselectively [21]. In a particular reaction shown in Table 4.4, nickel catalysts appear to be much more efficient than palladium catalysts. The regioselectivity depends on the type of Ni species used. $Ni[P(OEt_3)]_4$ and $Ni(acac)_2$ catalysts mainly provide **4.2**, whereas the $NiBr_2$ and $Ni(acac)_2/(EtO)_2P(O)H$ systems provide the other isomer **4.3** as the major product. Similar nickel catalysts promote the addition of the H and P of $R_2P(=O)H$ [22] and of the H and S of thiophenol to alkynes [22, 23].

4.3
bis-Metallation

Catalytic activation of the bonds composed of metallic (or metalloid) elements opens the way to new synthetic methods of organometallic (or organometalloid)

Tab. 4.4. Nickel-catalyzed hydrophosphorylation with diphenylphosphine.

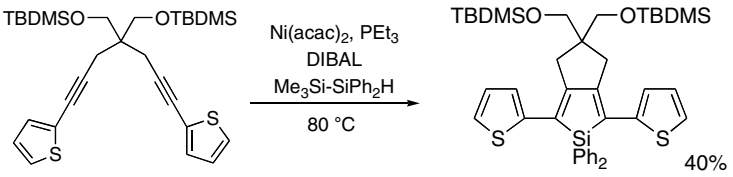


Catalyst	*Yield [%]*	*4.2:4.3*	*E/Z of 4.2*
$Ni[P(OEt_3)]_4$	93	90:10	50/50
$Ni(acac)_2$	82	73:27	67/33
$NiBr_2$	90	14:86	100/0
$Ni(acac)_2 + (EtO)_2P(O)H$	90	5:95	100/0

compounds [24]. Nickel complexes catalyze bond cleavage of the homogeneous ($R_3Si–SiR'_3$, $R_3Ge–GeR_3$) and the heterogeneous metal–metal bonds ($R_3Si–BR'_2$, $R_3Ge–BR'_2$) and deliver these metallic fragments upon alkynes in a 1,2 fashion in most cases, and in a 1,1 fashion in limited number of cases.

4.3.1
bis-Silylation and bis-Germylation

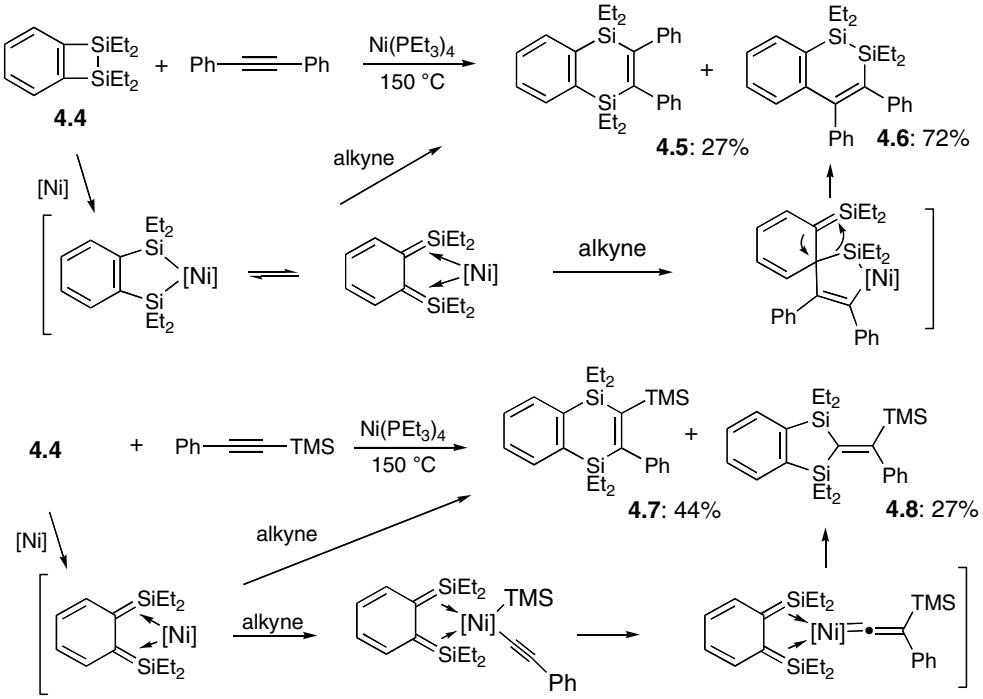
Almost three decades ago, Kumada et al. reported that *sym*-tetramethyldisilane ($Me_2HSiSiMe_2H$) and internal alkynes react to provide tetrasubstituted dimethylsilacyclopentadienes in good yields at 90 °C in the presence of $NiCl_2(PEt_3)_2$ [25]. This unique reaction is rationalized by supposing an active intermediate, either dimethylsilylene on a nickel(0) [Me_2Si: Ni(0)] or bis(dimethylsilyl)nickel(II) [$Ni(SiHMe_2)_2$], generated via a few steps initiated by oxidative addition of a nickel(0) complex upon the Si–H bond. The nickel(0) complex is generated by the reduction of $NiCl_2$ with Si–H. As illustrated in Scheme 4.6, modification and application of the reaction to 1,6-diynes has opened a new and effective access to functionalized silacyclopentadienes and silole-thiophene co-polymers, which are new functional materials [26].



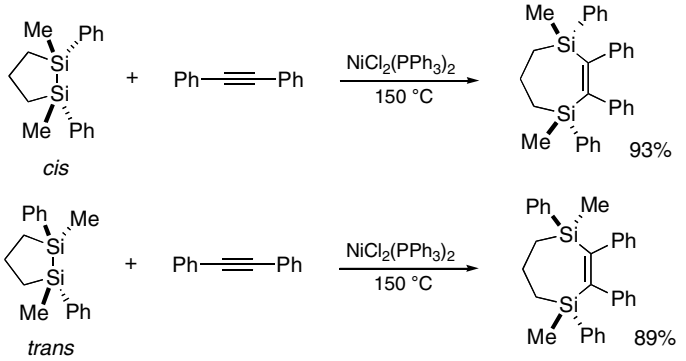
Scheme 4.6. The nickel-catalyzed synthesis of silacyclopentadienes (silols).

The direct oxidative addition of a Ni(0) complex to Si–Si bonds has been evidenced by the reactions shown in Schemes 4.7 and 4.8. At a high temperature, 3,4-benzo-1,1,2,2-tetraethyl-1,2-disilacyclobutane (**4.4**) reacts with internal alkynes to give a mixture of **4.5** and **4.6** in the presence of $Ni(PEt_3)_4$ [27]. On the other hand, the reaction of **4.4** with phenyl(trimethylsilyl)acetylene provides a mixture of **4.7** and **4.8**. The same class of products **4.5** and **4.7** forms, probably via the Diels–Alder-type cycloaddition of an *o*-quinodimethane-nickel(0) complex and alkynes.

Although the mechanism shown in Scheme 4.7 is speculative, the formation of **4.6** and **4.8** strongly supports the intermediacy of an *o*-quinodimethane–nickel(0) complex as a common intermediate. It is worth noting that *o*-quinodimethane (composed of all carbons) is itself a reactive intermediate. In view of the intrinsic instability of the C=Si double bond, the *o*-quinodimethane that appears in Scheme 4.7 is very unstable, and its intermediacy in the reaction course may owe to the coordination stabilization with an Ni(0). The routes leading to **4.6** and **4.8** are rather complicated and worth a few comments. The insertion of an alkyne into the Ni–C



Scheme 4.7. The nickel-catalyzed cycloisomerization of disilane **4.4** and alkynes involving oxidative addition of an Ni(0) upon the Si–Si bond.

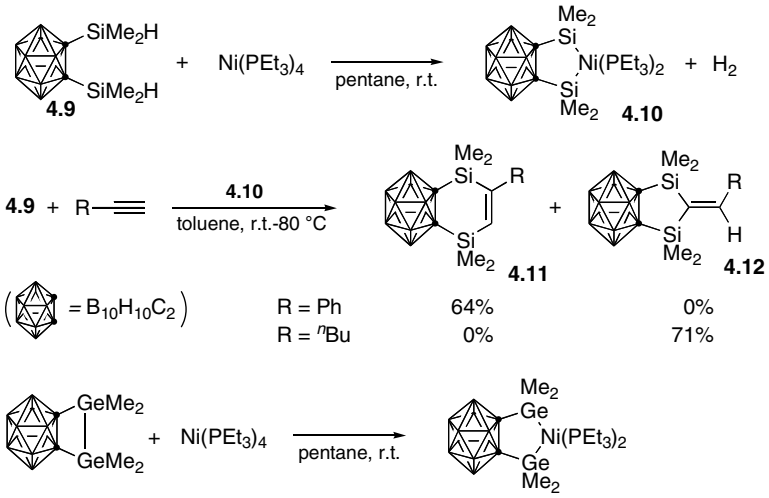


Scheme 4.8. The nickel-catalyzed stereospecific disilylation of diphenylacetylene.

bond of a nickella-2-silacyclopropane, followed by 1,3-migration of the $SiEt_2$ group of the thus-formed spiro intermediate provides **4.6**. Oxidative addition of the Ni(0) of the *o*-quinodimethane–nickel(0) complex upon the alkyne C–Si bond, followed by 1,3-migration of the TMS group from the Ni to the C-bearing phenyl group pro-

vides a vinylidene carbene complex, which undergoes reductive elimination to give **4.8**. 1,2-Disilacyclopentanes stereospecifically add to diphenylacetylene in the presence of $NiCl_2(PPh_3)_2$ to give 1,4-disilacyclohept-2-ens (Scheme 4.8). The stereospecificity indicates that the insertion of the alkyne upon the Ni–Si bonds of a 1-nickella-2,6-disilacyclohexane intermediate proceeds with complete retention (or inversion) of the configurations of the both silicone stereocenters [28].

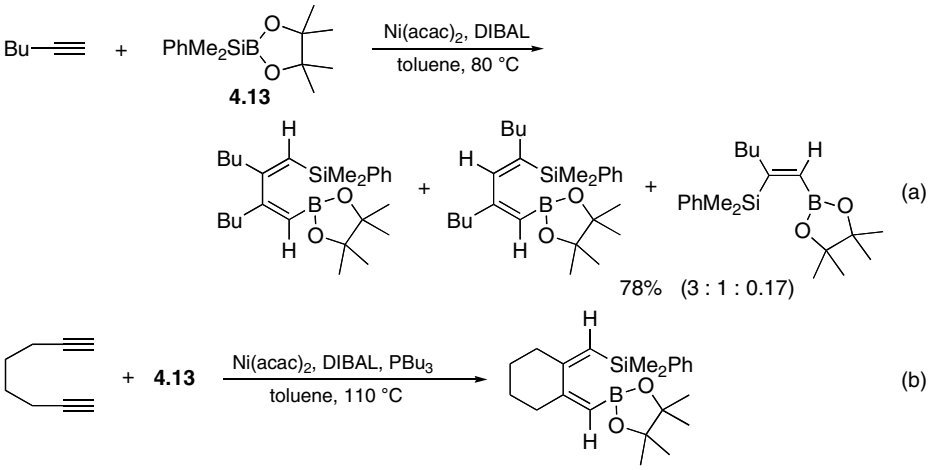
A nickel(II)–carborane complex **4.10**, prepared by the reaction of *o*-bis(dimethylsilyl)carborane (**4.9**) and $Ni(PEt_3)_4$ catalyzes the disilylation of alkynes with **4.9** (Scheme 4.9) [29]. The reaction is accompanied by evolution of 1 equiv. of H_2. The course of the reaction depends heavily on the type of alkyne substituent; phenylacetylene undergoes 1,2-disilylation giving rise to **4.11**, while 1-hexyne undergoes 1,1-disilylation to form **4.12**. The latter is formed via 1,2-migration of the Ni (see Section 1.7.5) of the primary insertion product. Almost parallel chemistry has been developed for the digermylcarborane derivatives [30].



Scheme 4.9. The nickel-catalyzed disilylation and digermylation of alkynes.

4.3.2
Silaboration and Geraboration

Palladium and platinum complexes catalyze the addition of the Si and B groups of silylboranes to alkynes [24]. Nickel complexes also work similarly well (Scheme 4.10) [31]. The reaction starts with oxidative addition of an Ni(0) complex upon the Si–B bond of **4.13**, followed by the successive insertion of two molecules of alkynes, and terminates with reductive elimination. While internal *sym*-alkynes can be transformed to 1-boryl-4-silyl-(*Z*,*Z*)-1,3-dienes in high yields with high stereoselectivity, terminal alkynes suffer from low regioselectivity and provide mixtures of the head-to-head and head-to-tail coupling products. The structural motif com-



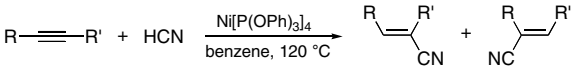
Scheme 4.10. The nickel-catalyzed silaboration across two alkyne units.

mon to all products is trans with respect to the B and butyl groups. This suggests that insertion of an alkyne upon the Ni–B bond with regioselective Ni–C bond formation at the most substituted alkyne terminal initiates the sequential reactions. Some germylboranes show a similar reaction pattern [31].

4.4 Hydrocyanation, Hydroacylation, and Related Reactions

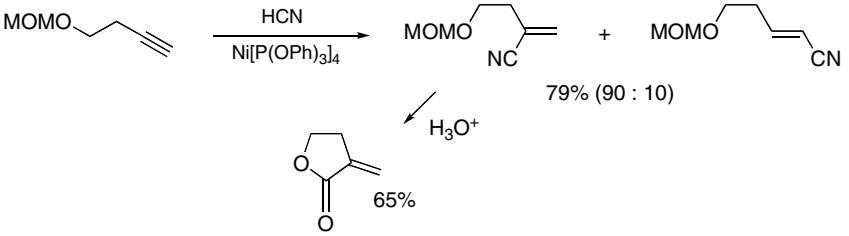
By the catalysis with $Ni[P(OPh)_3]_4$, addition of HCN upon alkynes takes place at elevated temperatures. The reaction, as usual, proceeds in a cis fashion and provides α,β-unsaturated nitriles with *E* geometry (Table 4.5) [32]. A wide variety of alkynes, encompassing alkyl-, aryl-, and silyl-substituted terminal and internal alkynes, are examined.

Tab. 4.5. Nickel-catalyzed hydrocyanation of alkynes.



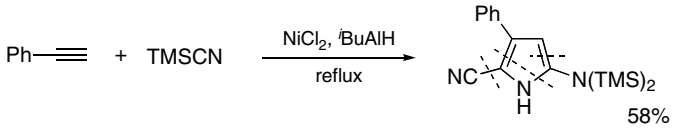
Run	*R*	*R′*	*Yield [%]*	*Ratio*
1	Ph	Ph	93	–
2	Bu	H	73	14:86
3	Ph	H	45	98:2
4	TMS	H	74	25:75
5	TMS	Bu	94	72:28
6	TMS	Ph	80	20:80

Unsymmetrical alkynes form two regioisomers. The regioselectivity is under the subtle balance of both electronic and steric effects of the substituents, and the alkyl and TMS groups tend to guide the cyano group on the same carbon (runs 2, 4, 6 in Table 4.5) and phenyl group on the distal carbon (runs 3 and 6). This tendency for regioselectivity is used in the short synthesis of α-methylene-γ-butyrolactone (Scheme 4.11) [33].

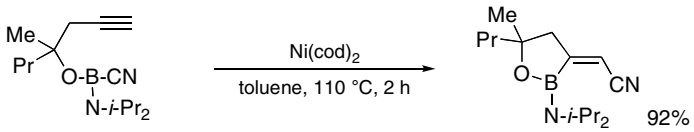


Scheme 4.11. The nickel-catalyzed regioselective hydrocyanation of alkynes: a short synthesis of α-methylene-γ-butyrolactone.

Me_3SiCN reacts with phenylacetylene in the presence of an Ni(0) complex to provide pyrrole in modest yield (Eq. (4.1)) [34]. The pyrrole may be disconnected into three C≡N units as shown. The mechanism and the role of the nickel catalyst in this reaction are not clear, but $Ni(cod)_2$ efficiently catalyzes the cyanoboration of alkynes by an intramolecular process (Eq. (4.2)) [35].



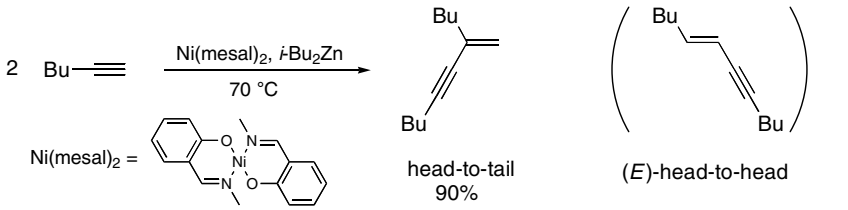
(4.1)



(4.2)

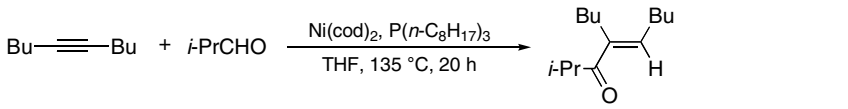
Many transition metals – especially palladium [36] – are able to activate the C–H bond of alkynes through oxidative addition. A unique catalytic system, $Ni(mesal)_2$ and $i\text{-}Bu_2Zn$, efficiently promotes the selective "head-to-tail" dimeriztion of 1-alkynes (Eq. (4.3)) [37]. On the other hand, a Ni(0) complex modified with bulky phosphine ligands catalyzes the selective dimerization, giving rise to the (*E*)-"head-to-head" isomer [38].

The hydroacylation of alkynes provides a useful and straightforward method for preparing α,β-unsaturated enones. Some Ni(0) complexes modified with electron-donating phosphine ligands show an efficient catalytic performance for the hydroacylation of alkynes with aldehydes (Eq. (4.4)) [39]. The reaction may proceed in



(4.3)

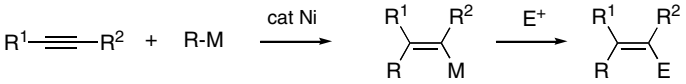
order of: 1) oxidative addition of an Ni(0) complex upon the C–H bond of an aldehyde; 2) insertion of an alkyne into the Ni–H bond; and 3) reductive elimination of the vinylacylnickel(II) thus formed. The high yield formation of the enone is remarkable, since the vinylacylnickel(II) is subject of decarbonylation giving rise to a vinylalkylnickel(II)–CO complex, which might end up with reductive elimination forming a mixture of vinyl-H (β-hydrogen elimination followed by reductive elimination) and vinyl-R (reductive elimination).



(4.4)

4.5
Carbometallation and Related Reactions

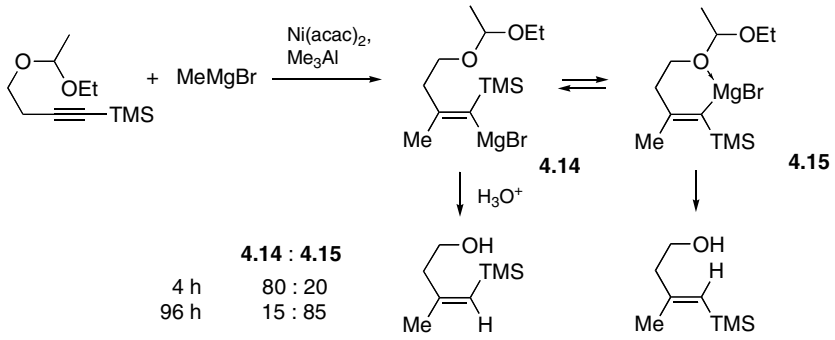
The addition of organometallic reagents to alkynes is a useful synthetic method for the preparation of alkenyl metal species, which can be used for further functionalizations by the reaction with various electrophiles (Scheme 4.12) [40]. Nickel complexes catalyze the regio- and stereoselective addition of C–Mg (carbomagnesiation), C–Zn (carbozincation), and C–Sn (carbostannylation) species upon alkynes.



Scheme 4.12. The nickel-catalyzed carbometallation of alkynes.

4.5.1
Carbomagnesiation

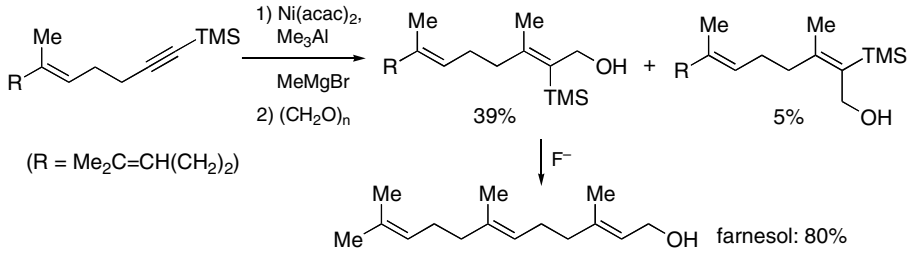
The Ni(0) complex generated by the reduction of $Ni(acac)_2$ with Me_3Al catalyzes the regio- and stereoselective addition of MeMgBr to silyl-substituted alkynes, delivering the metal on the carbon bearing the Si group (Scheme 4.13) [41]. The



Scheme 4.13. The nickel-catalyzed methylmagnesiation and isomerization of vinylmagnesium species.

vinylmagnesium is stereochemically labile under the conditions and undergoes isomerization in favor of **4.15**, stabilized by the coordination of the ethereal oxygen to magnesium(II).

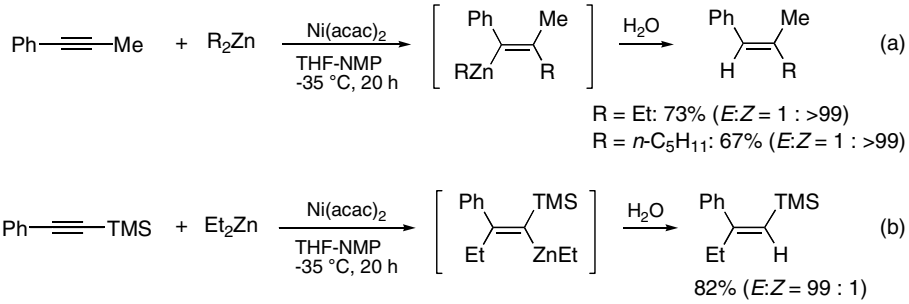
This methodology is applied to the synthesis of terpene derivatives such as farnesol (a natural product) (Scheme 4.14).



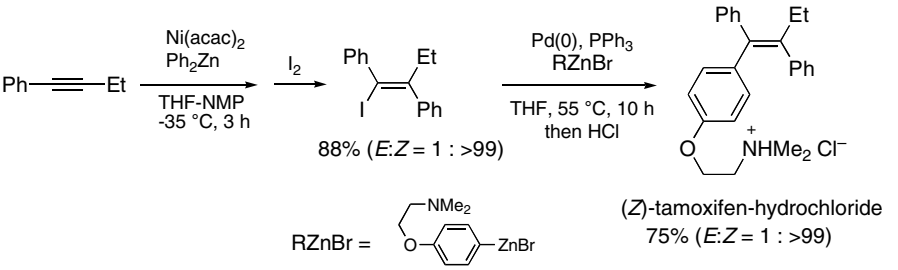
Scheme 4.14. The nickel-catalyzed methylmagnesiation and its application to the synthesis of farnesol.

4.5.2 Carbozincation

Both regio- and stereoselectivity of the carbometallation of alkynes is greatly improved by using organozinc reagents in place of Grignard reagents (Scheme 4.15) [42]. The regioselectivity of the reaction is almost perfect and controlled by the type of substituents on the alkynes; thus, the phenyl and silyl groups direct the organo groups of organozincs away from the carbons that they attach. The silyl group is a more powerful directing group (c.f., Eqs. (a) and (b) in Scheme 4.15). The resulting alkenyl zinc reagents can be used for further elaboration with various electrophiles, and hence are applicable to the synthesis of stereochemically defined tri- and tetrasubstituted alkenes [43]. An application of the present methodology to the synthesis of (*Z*)-tamoxifen-hydrochloride is shown in Scheme 4.16.



Scheme 4.15. The nickel-catalyzed regio- and stereoselective organozincation.



Scheme 4.16. The nickel-catalyzed regio- and stereoselective organozincation and its application to the synthesis of tamoxifen.

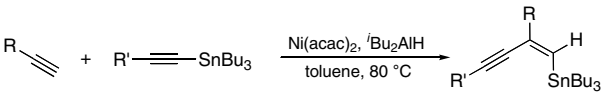
4.5.3
Carbostannylation

Cross-coupling of organostannanes with organic electrophiles – the so-called Kosugi–Migita–Stille reaction – is a highly versatile method for carbon–carbon bond formation, and has been widely used as a reliable strategy for the synthesis of complex natural and unnatural products [44]. Among organostannanes used in the cross-coupling, alkenylstannanes are a very important class of compounds. Recently, Shirakawa and Hiyama have reported the palladium- and nickel-catalyzed carbostannylation of alkynes, which provides an easy access to alkenylstannanes [45]. Nickel complexes catalytically promote the *syn*-selective addition of alkynyl- (Table 4.6), allyl- (Table 4.7), and acylstannanes (Table 4.8) to alkynes.

The alkynylstannylation of terminal arylacetylenes in the presence of a Ni(0) complex, generated in situ from $Ni(acac)_2$ and DIBAL, selectively furnishes (*Z*)-2-(1-alkynyl)ethenylstannanes (Table 4.6) [46]. In contrast, the corresponding reaction catalyzed by palladium tends to produce mixtures of regioisomers [47].

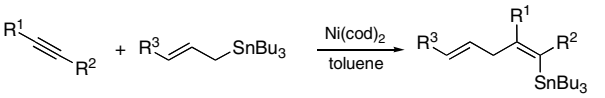
Allylstannylation of alkynes is also catalyzed by a nickel(0) and a palladium(0) complex. The nickel catalyst shows a better catalytic performance and allows most types of alkynes to participate in the reaction, whereas a stannyl group regioselectively attacks the alkyne carbon having a more electron-withdrawing substituent

Tab. 4.6. Nickel-catalyzed alkynylstannylation of alkynes.



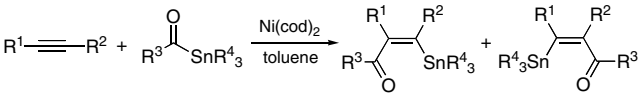
R	*R′*	*Time [h]*	*Yield [%]*
Ph	n-C_6H_{13}	24	72
p-$CF_3C_6H_4$	n-C_6H_{13}	10	70
p-$MeOC_6H_4$	n-C_6H_{13}	36	56
p-$CF_3C_6H_4$	1-cyclohexenyl	5	79

Tab. 4.7. Nickel-catalyzed allylstannylation of a wide variety of alkynes.



R^1	R^2	R^3	*Conditions*	*Yield [%]*
H	H	H	80 °C, 14 h	80
Me	Ph	H	100 °C, 12 h	77
TMS	Ph	H	100 °C, 14 h	76
TMS	CO_2Et	H	100 °C, 40 h	78
Me	Ph	Me	100 °C, 14 h	64

Tab. 4.8. Nickel-catalyzed acylstannylation of unsymmetrical alkynes.



R^1	R^2	R^3	R^4	*Conditions*	*Yield [%]*	*Ratio*
Me	Ph	Ph	Me	100 °C, 1.5 h	61	83:17
Bu	CO_2Me	Ph	Me	30 °C, 2.5 h	66	88:12
Bu	CO_2Me	Et	Bu	30 °C, 24 h	47	79:20
Me	Ph	Et_2N	Bu	100 °C, 2 h	81	64:36

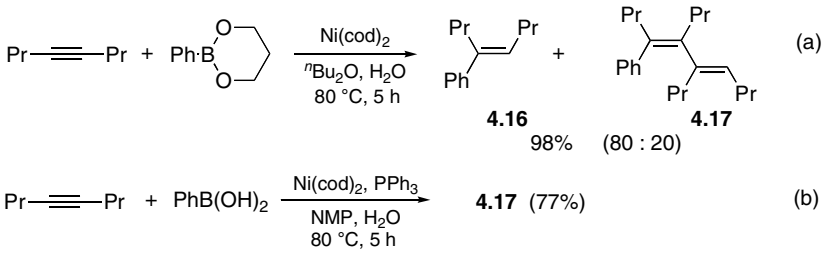
(Table 4.7) [46]. On the other hand, the palladium catalyst is effective only for some alkynes bearing highly electron-withdrawing substituents [48].

The acylstannylation of alkynes provides a very efficient way to introduce the two useful functional groups, acyl and stannyl, at the same time in a cis fashion upon the vicinal carbons of alkynes. $Ni(cod)_2$ serves as an excellent catalyst (Table 4.8), though the regioselectivity is not very high [49]. Importantly, the reaction is successful even with a carbamoyl group (the last row in Table 4.8).

4.5.4 Miscellaneous

Nickel(0) complexes also activate the carbon–boron bond of arylboronic acids or esters. $Ni(cod)_2$ effectively catalyzes the addition of the aryl group of the arylborons to alkynes in the presence of water (Scheme 4.17) [50]. Thus, 2-pheny-1,3-dioxa-2-borinane reacts with 4-octyne in 1:1 and 1:2 molar ratios in the presence of $Ni(cod)_2$ to give a mixture of hydroarylation products **4.16** and **4.17**. Modifications of the reaction conditions (reagents, solvents, ligands) change the reaction features dramatically and, under the conditions shown in Eq. (b), the dimer **4.17** is produced as a sole product. The products may be formed by hydrolysis, instead of reductive elimination, of a vinyl–Ni–B intermediates (c.f., Table 4.3 and Scheme 4.10).

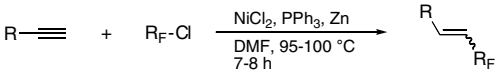
The C–H proton of terminal alkynes is so acidic that acetylides are generated readily in the presence of an appropriate base and undergo cross-coupling reaction with organonickel species, for example, arylnickel(II) [51] and allylnickel(II) [52]. The reaction involving metal acetylides is treated in detail in Chapter 2.



Scheme 4.17. The nickel-catalyzed cis addition of an H and an Ph upon alkynes.

The perfluoroalkylation of unsaturated substrates with perfluoroalkyl halides is a versatile method for introducing perfluoroalkyl group to organic compounds [53]. Some nickel(0) complexes, generated by the reduction of $NiCl_2$ with Zn, catalytically promote the addition of perfluoroalkyl groups to the terminal carbon of alkynes (Table 4.9) [54]. The mechanism utilized is not clear, although the involvement of a single electron transfer has been suggested.

Tab. 4.9. Nickel-catalyzed perfluoroalkylation of alkynes.



R	R_F	*Yield [%]*	*E/Z*
n-C_5H_{11}	n-C_6F_{13}	73	66:34
n-C_5H_{11}	$H(CF_2)_4$	72	66:34
Ph	n-C_6F_{13}	65	60:40
MOM	n-C_6F_{13}	56	100:0

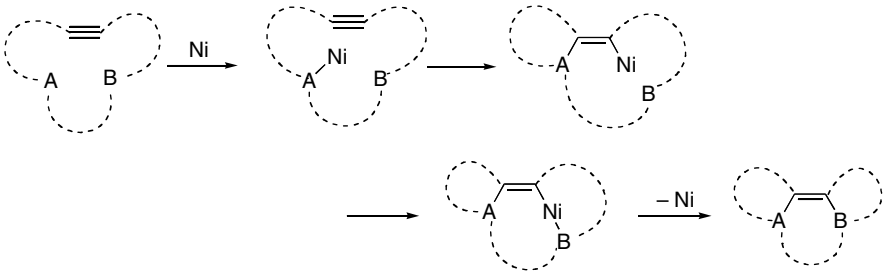


Fig. 4.1. The nickel-catalyzed sequential reaction that furnishes the open-chain and mono-, bi-, tricyclic alkenes in one pot.

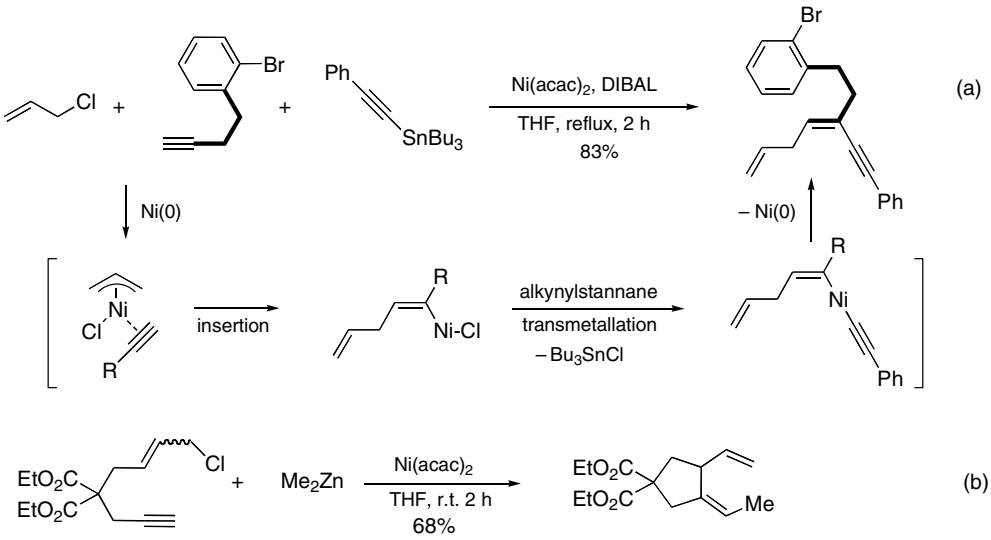
4.6
The Sequential Reaction

A sequential reaction – the so-called ''domino'', ''tandem'', or ''cascade'' reaction – by multi-component coupling, which permits complex molecules to be relatively well constructed in a single operation, is a fascinating process in synthetic chemistry [55]. The nickel-catalyzed sequential reaction has recently gained increasing interest [56]. As illustrated in Figure 4.1, the catalytic sequential reaction with alkynes proceeds via the activation of a unit A by a nickel catalyst – for example, oxidative addition, to generate an A–Ni species, followed by insertion of a carbon–carbon triple bond of alkynes leading to an alkenylnickel intermediate. This is then transformed into products upon capturing another unit B, in most cases via reductive elimination. The intramolecular and fully intermolecular reactions have been developed for routine use.

4.6.1
Sequential Reaction Starting with Activation of Organic Halides

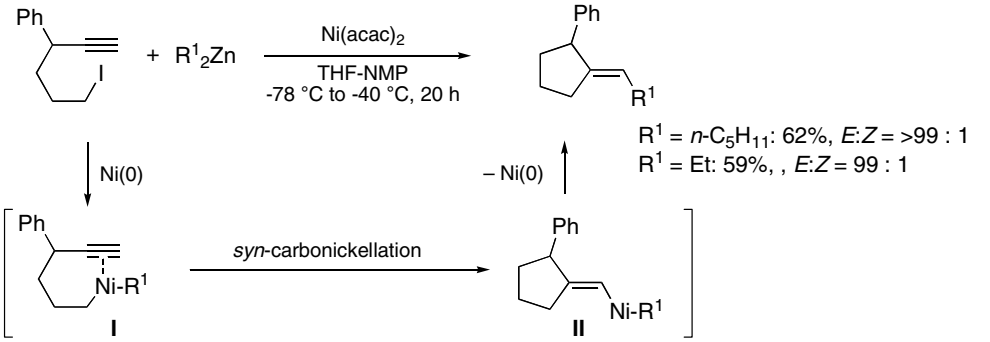
The example shown in Scheme 4.18(a) is unique in many respects. The most interesting is the difference in reactivity between the two alkynes. The terminal alkyne plays the leading part, while the alkynylstannane plays a supporting role to stop the catalytic cycle. The catalytic reaction proceeds as follows: 1) oxidative addition of an Ni(0) complex upon allyl chloride; 2) insertion of an terminal alkyne delivering the Ni on the most substituted carbon and generating a vinylnickel(II) species [57]; 3) which undergoes transmetallation with alkynylstannane; and 4) reductive elimination of the vinylalkynylnickel(II) thus formed to furnish the three-component connection product. The reaction overall, both regio- and stereoselectively, introduces an allyl group at the terminal carbon and an alkynyl group of alkynylstannane at the internal carbon of the terminal alkyne [58].

Me_2Zn and Me_3Al also play effective supporting roles in stopping the catalytic cycle for the multi-component connection reaction. One example is shown in Eq. (b) in Scheme 4.18 [59].



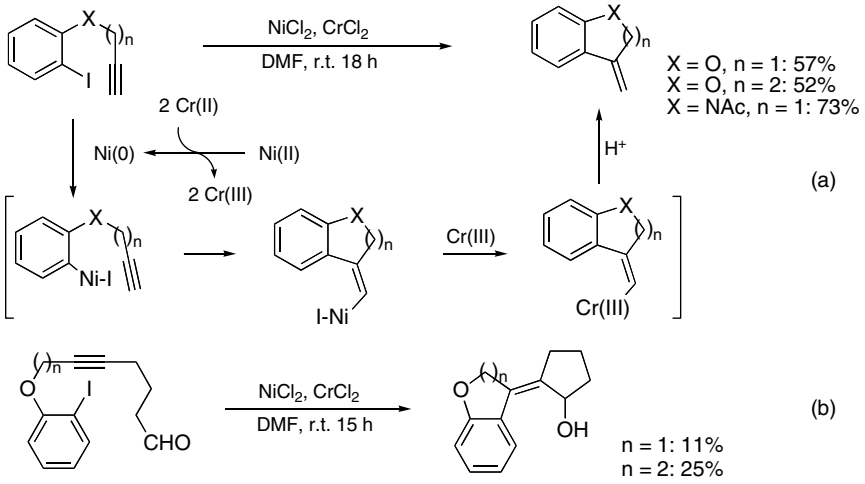
Scheme 4.18. The nickel-catalyzed intermolecular sequential reactions of allyl chlorides, alkynes, and organostannanes (a) or organozincs (b).

Scheme 4.19 indicates that not only an allylnickel(II), but also an alkylnickel(II) intermediate **I**, engages in the insertion of an alkyne to provide an intermediate **II**. Furthermore, **II** selectively undergoes reductive elimination [42]. The behaviors of **I** and **II** are remarkable, as these alkylnickel species are, in general, reluctant toward insertion and reductive elimination, and instead, are prone to undergo *β*-hydrogen elimination (see Sections 1.7.4 and 1.7.5). The authors have suggested that coordination stabilization to the alkyne is crucial for the formation of **I** and subsequent reactions. Otherwise, organozinc – rather than organonickel – may be formed.



Scheme 4.19. The nickel-catalyzed *cis*-dialkylation of alkynes.

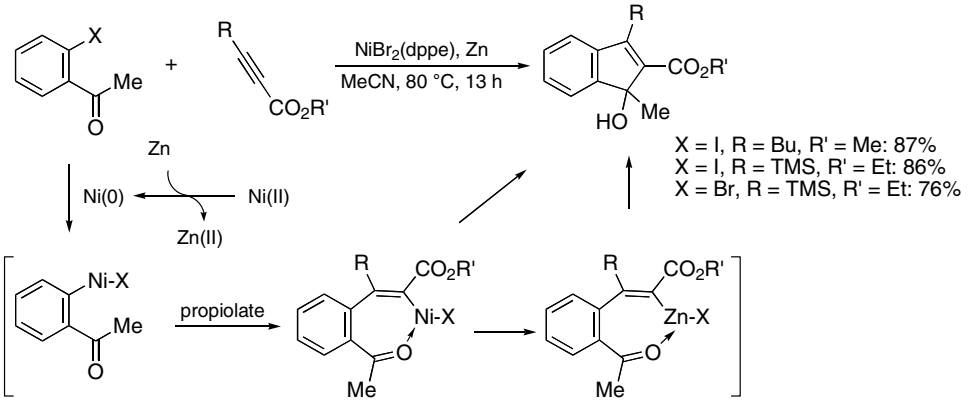
Chromium(II) chloride-mediated and nickel-catalyzed reactions of alkenyl and aryl halides with aldehydes are indispensable synthetic methods for carbon–carbon bond formation in compounds of structural complexity (the so-called NHK reaction; see Section 1.7.3) [60]. Some extensions to iodoaryl-tethered alkynes and alkynals are shown in Scheme 4.20 [61]. The reaction proceeds via oxidative addition of an Ni(0) complex to aryl iodide, intramolecular *syn*-insertion of alkyne, followed by transmetallation and hydrolysis (Eq. (a)) or nucleophilic attack toward the tethered aldehyde (Eq. (b)). The low yields in Eq. (b) may be due to premature transmetallation between Ni(II) and Cr(III) species at the arylnickel(II) stage, the arylchromium(III) thus formed being reactive towards an aldehyde (both inter- and intramolecularly) rather than to an alkyne. In the NHK reaction, alkenylchromium(III) species have been prepared from alkenyl iodides or triflates by the catalysis of an Ni(0) complex.



Scheme 4.20. The application of the NHK reaction to sequential mono- (a) and di-cyclization (b)

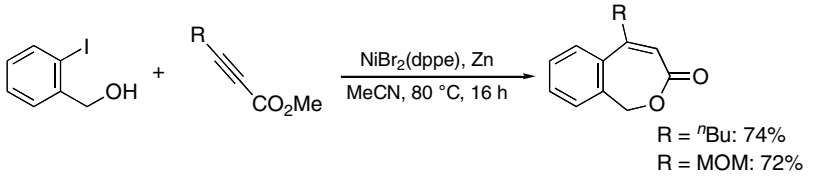
Recently, an alternative method for generating 2-alkenylchromiun(III) species has been reported which utilizes nonactivated terminal alkynes as the starting materials. The reaction of the reagents with aldehydes provides a variety of 1,2-disubstituted allyl alcohols in good yields [62].

A catalytic amount of $NiBr_2$(dppe) with a stoichiometric zinc dust promotes the reaction of *o*-haloacetophenones and propiolates to afford indenol derivatives in good yields (Scheme 4.21) [63]. The reaction, like the NHK reaction, may proceed as follows: 1) oxidative addition of aryl halide to an Ni(0) complex generated by reduction of the Ni(II) complex by zinc powder in situ; 2) regioselective insertion of a propiolate to the arylnickel(II) intermediate; and 3) intramolecular nucleophilic addition to the tethered ketone. Generally, vinylnickel is not sufficiently reactive to undergo nucleophilic addition to a ketone. Accordingly, vinylzinc may participate in the final step.



Scheme 4.21. The modification of the NHK reaction (Zn in place of Cr(II) as a reducing agent of Ni(II)) and its application to a sequential reaction. In the NHK reaction, a nucleophile is vinylchromium(III), while in this case may be vinylzinc.

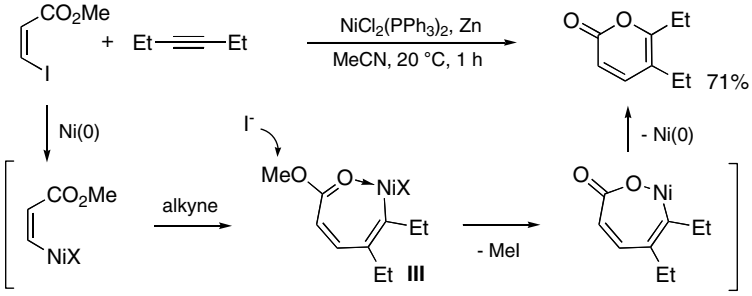
The reaction of *o*-iodobenzyl alcohols with propiolates under the same catalytic conditions provides seven-membered lactones (Eq. (4.5)) [64]. The lactones may be produced after isomerization of the primary (*E*)-hydroxy esters to the (Z)-isomers.



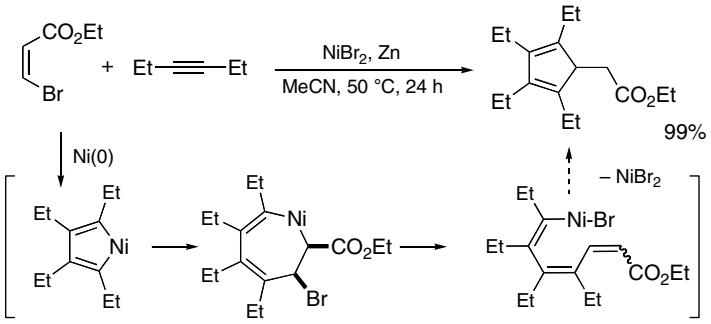
(4.5)

The Ni(0) complex, generated under conditions similar to those in Scheme 4.21 and Eq. (4.5), guides the reaction of an alkyne and (*Z*)-3-iodopropenoate in a different course (Scheme 4.22) [65]. The intermediate generated via usual insertion reaction of an alkyne may be formulated as **III**, which shows close structural similarity to the intermediate shown in Scheme 4.21. However, in this case, the carbonyl is an ester and less electrophilic than a ketone. Accordingly, no nucleophilic attack on the carbonyl by neither vinylnickel nor vinylzinc takes place; rather, nucleophilic attack on the methyl carbon by an iodide anion may occur to give rise to nickella-2-oxacyclohepta-4,6-dien-3-one, which undergoes reductive elimination to produce the final product.

The reaction also depends on type of halide involved. As shown in Scheme 4.23, (*Z*)-3-bromopropenoate reacts in a quite different manner from the iodo isomer. The oxidative addition of an Ni(0) complex upon the C–Br bond is so difficult that



Scheme 4.22. The effects of carbonyl electrophiles on the reaction course (c.f., Scheme 4.21)



Scheme 4.23. The effects of halides on the reaction course (c.f., Scheme 4.22). In a strict sense, the reaction is not catalytic, but stoichiometric with respect to Ni(0). Reduction of $NiBr_2$ to Ni(0) with Zn supports the catalytic cycle.

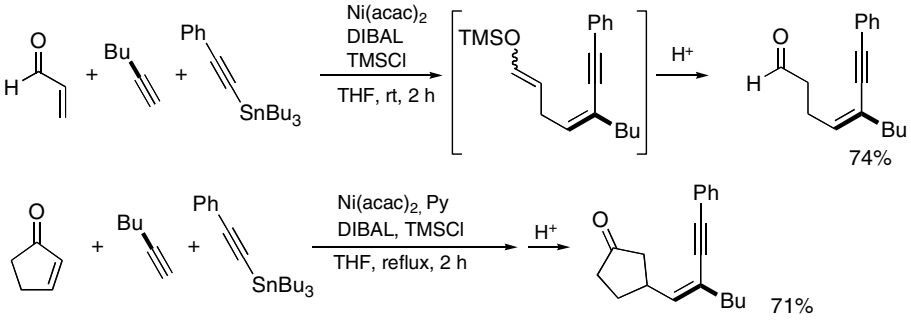
an Ni(0) complex first undergoes oxidative cyclization across two molecules of alkyne. The nickellacyclopentadiene thus formed is reactive toward insertion of (*Z*)-3-bromopropenoate and forms a nickellacycloheptadiene intermediate. Ring opening via *β*-Br elimination, followed by Michael addition, provides the ester enolate of the final product, having an $Ni(II)Br^+$ species as a counterion. In the normal situation at this stage *β*-hydrogen elimination proceeds with great ease, but in this particular case the process is not favorable because *β*-hydrogen elimination provides an unstable anti-aromatic compound, fulvene, which is destabilized further by an electron-withdrawing ester group. Therefore, $Ni(II)Br^+$ may be replaced with $Zn(II)Br^+$, liberating $Ni(II)Br_2$.

The roles that an Ni(0) complex plays in Schemes 4.22 and 4.23 are essentially different. In the former reaction, an Ni(0) complex, once generated, functions as a real catalyst to bring the reaction to completion. In contrast, in the latter reaction, an Ni(0) complex is oxidized and recovered as $NiBr_2$ in each reaction cycle. Accordingly, in order to bring the reaction to completion, reduction of $NiBr_2$ to Ni(0) by a stoichiometric amount of Zn is required.

4.6.2
Sequential Reaction with Enones

The nickel-catalyzed sequential coupling of the three components, alkynes, enones, and organometallics, provides an excellent method for the synthesis of regiochemically and stereochemically defined tri- and tetrasubstituted alkenes.

The three components – α,β-enones, alkynes, and alkynylstannanes – combine with each other both regio- and stereoselectively in the presence of an Ni(0) catalyst and chlorotrimethylsilane (Me_3SiCl) (Scheme 4.24) [66, 67]. Enones are introduced at the terminal position of 1-hexyne, and the alkynyl groups of the tin reagents at the internal carbon, cis to each other. The reaction pattern is very similar to that illustrated in Scheme 4.18, where a terminal alkyne serves as a hinge to connect an allyl halide and an alkynyltin.

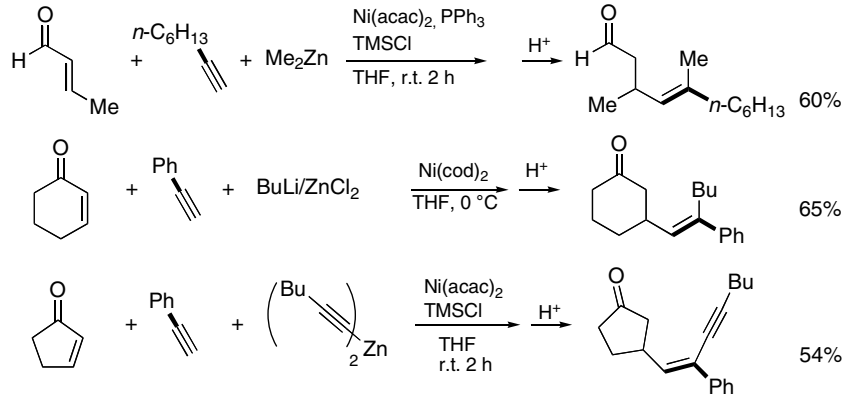


Scheme 4.24. The nickel-catalyzed three-component connection reaction of enones, terminal alkynes, and alkynylstannanes.

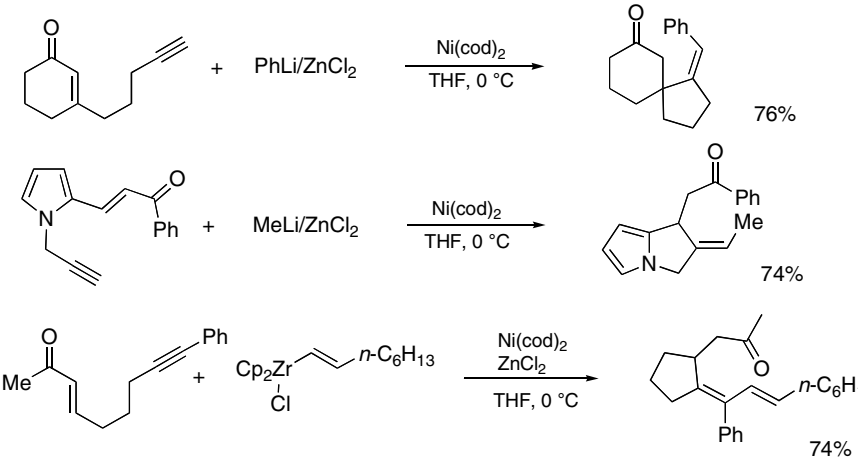
The reaction with organozincs, in place of organostannanes, also proceeds smoothly and delivers the organozinc at the internal carbon of the terminal alkynes (Scheme 4.25) [68, 69]. With organozincs, not only alkynes but also alkyl groups can be introduced. Chiral induction for this reaction is achieved by using nickel catalysts modified with chiral monodentate oxazoline ligands [70].

Some interesting examples of the above reaction applied to ω-alkynylenones are illustrated in Scheme 4.26. The reaction is quite general and useful for the construction of spiro compounds, bicyclic compounds and monocyclic compounds with stereochemically defined double bonds [71, 72]. The last example demonstrates that alkenylzirconiums, being readily prepared by hydrozirconation of terminal alkynes, can be utilized to the reaction in the presence of $ZnCl_2$.

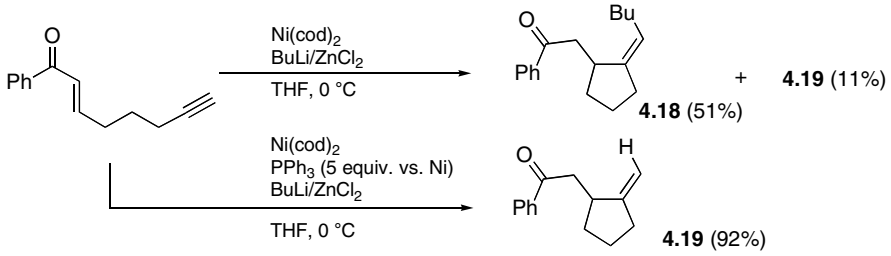
The reaction with alkylzincs shows significant ligand effects (Scheme 4.27). The reaction, when carried out in the absence of phosphine ligands, selectively undergoes reductive elimination to provide **4.18**. In contrast, the use of a nickel catalyst modified with PPh_3 promotes β-hydrogen elimination to give **4.19** exclusively in a quantitative yield.



Scheme 4.25. The nickel-catalyzed three-component connection reaction of enones, terminal alkynes, and organozincs.

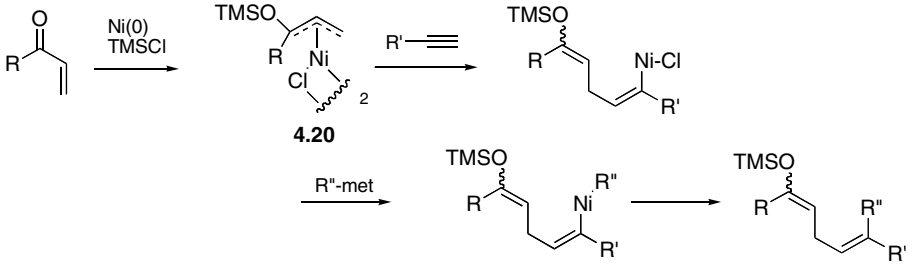


Scheme 4.26. The nickel-catalyzed three-component reaction of enones, alkynes, and organozincs, of which the enones and the alkynes are connected by a three-carbon unit.



Scheme 4.27. The effects of phosphine ligand on the reaction courses: reductive elimination in the absence and β-hydrogen elimination in the presence of PPh_3.

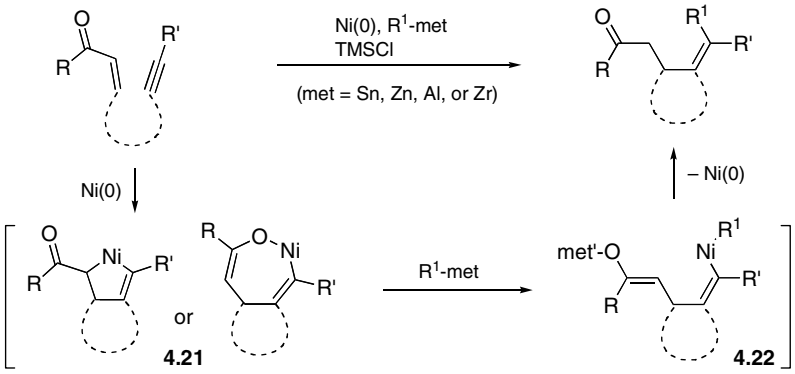
It is unclear how the electron-deficient alkene reacts with the terminal alkyne. One mechanism of sequential coupling via insertion of the alkyne to a π-allyl intermediate **4.20** (the Mackenzie complex), generated from a nickel(0) species, an enone, TMSCl, and a Lewis acid, has been discussed (Scheme 4.28) [73]. However, the coupling reaction using the complex **4.20** does not work [74].



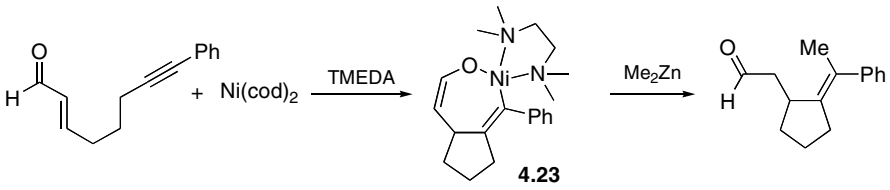
Scheme 4.28. The nickel-catalyzed three-component connection reaction of enones, alkynes, and organozincs. A possible route involving the Mackenzie complex **4.20**.

A more reasonable mechanism involves the first formation of a nickel metallacycle **4.21** via oxidative cyclization of an Ni(0) across an alkyne and an enone. Transmetallation with an organometallic (R^1-met) leads to an alkenyl(R^1)Ni(II) intermediate **4.22**, which undergoes reductive elimination to provide the final product (Scheme 4.29).

Recently, a metallacycle **4.23** has been isolated and the structure has been fully characterized both spectroscopically and by X-ray structure analysis (Scheme 4.30) [75]. This has a η^1-nickel-*O*-enolate form, and treatment of **4.23** with dimethylzinc yields the same product as that obtained from a catalytic reaction (see Scheme 4.26).

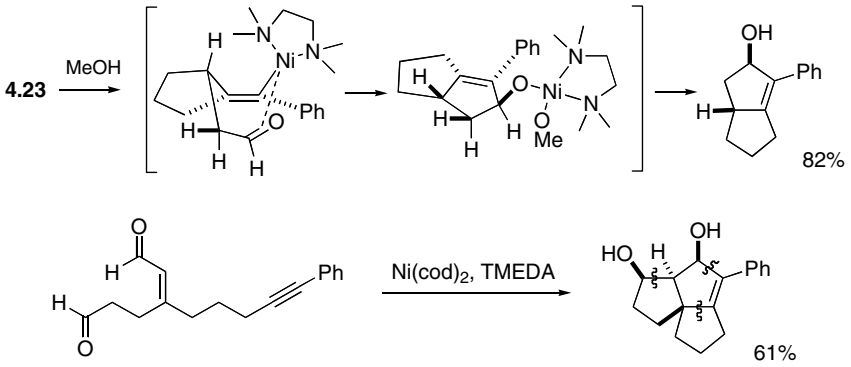


Scheme 4.29. The most plausible reaction pathway for the nickel-catalyzed three-component connection reaction of enones, alkynes, and organometallics.



Scheme 4.30. The isolation of an oxidative cyclization intermediate **4.23**. A proof for the reaction mechanism is shown in Scheme 4.26.

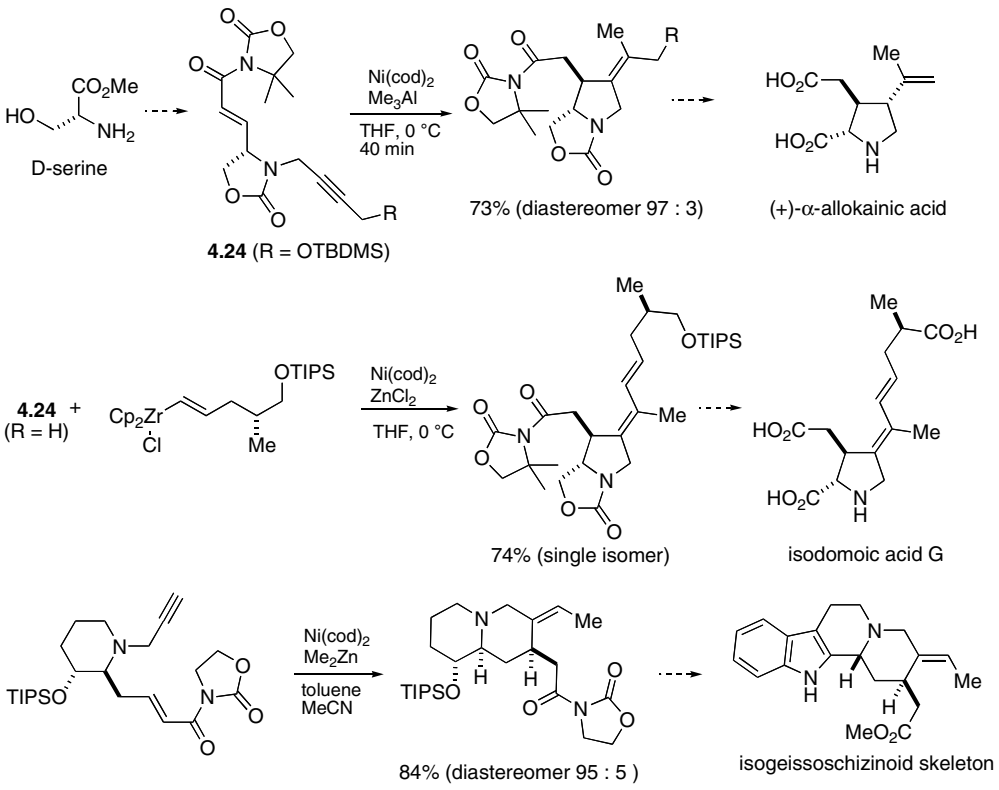
The vinylnickel moiety of **4.23** undergoes nucleophilic addition to the aldehyde generated by protonation with 1 equiv. of methanol (Scheme 4.31) [76]. The reaction is stoichiometric with respect to $Ni(cod)_2$. The nucleophilic addition of a vinylnickel species to aldehydes is not common (c.f., Scheme 4.21), and the unusually high reactivity observed in Scheme 4.31 may be attributed to the electron-donating ability of TMEDA, as well as to a special arrangement that enables both reaction partners to move close together. The synthetic efficiency of the present reaction may be apparent from the example shown in the lower part of Scheme 4.31; a one-pot operation provides a tricyclic compound in a good yield and with a high diastereoselectivity.



Scheme 4.31. The nickel-promoted multi-bond formation that involves nucleophilic addition of vinylnickel(II) species upon an aldehyde. The reaction is stoichiometric with respect to $Ni(cod)_2$.

The nickel-mediated reaction was used as a strategy for the total synthesis of natural products, α-alokainic acid [77, 78] and isodomoic acid G [79], and the synthesis of isogeissoschizine skeleton (Scheme 4.32) [80].

A sequential reaction of an enone and an ω-enyne in the presence of a Ni(0) catalyst and $ZnCl_2$ provides a cyclization product **4.25** [81] (Scheme 4.33), where the

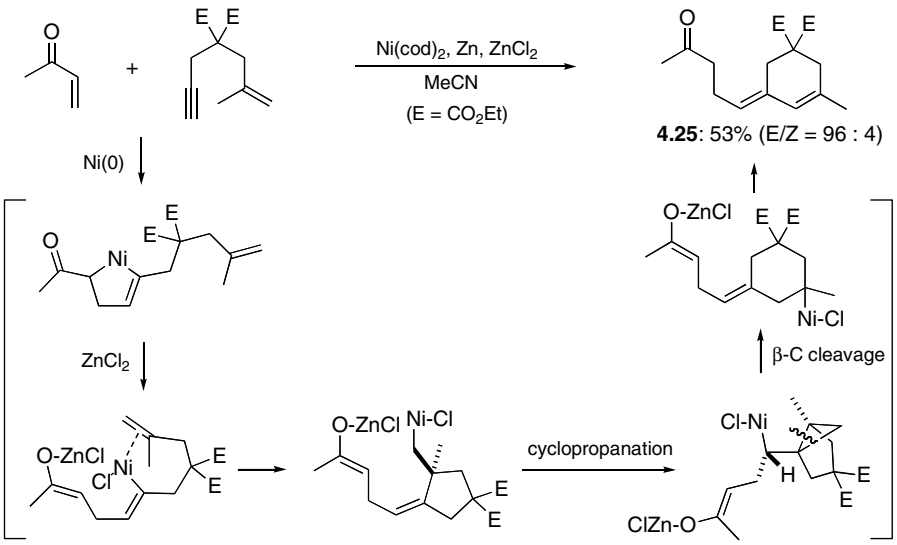


Scheme 4.32. The natural product syntheses utilizing a strategy of the nickel-catalyzed multi-component connection reaction.

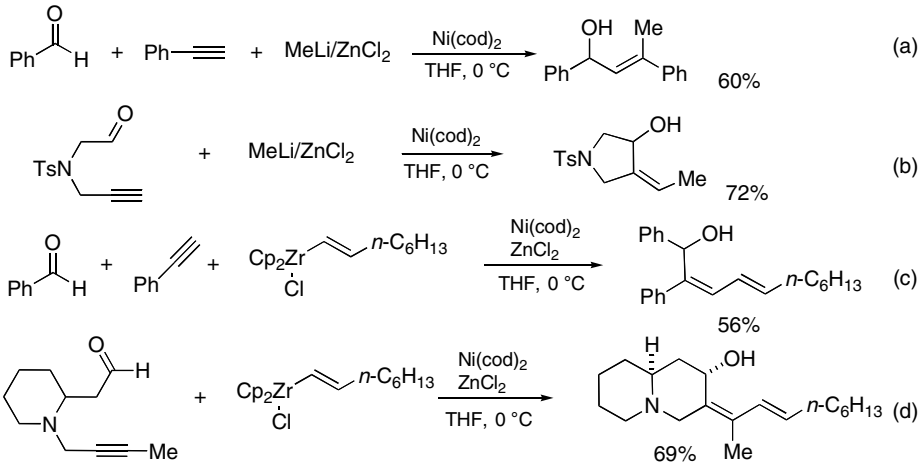
double bond of the enyne participates in the reaction in a unique way. Based on the product structure, the processes of cyclopropanation and β-C elimination (see Section 1.7.6) have been proposed.

4.6.3
Sequential Reaction with Aldehydes and Imines

The reaction conditions for the oxidative cyclization of alkynes and enones described in Section 4.6.2 are directly applicable to the combination of alkynes and aldehydes (Scheme 4.34; c.f. Scheme 1.8(b)) [82]. The reaction is useful for preparing stereochemically defined allyl alcohols, and is successful both for inter- and intramolecular reactions. Alkenylzirconiums, which are readily available by hydrozirconation of terminal alkynes, are good reaction partners and widen the scope of the reaction. The reaction requires 1 equiv. $ZnCl_2$, though the role of this additive is not clear. Remarkably, for intermolecular coupling, the regiochemistry of alkyne



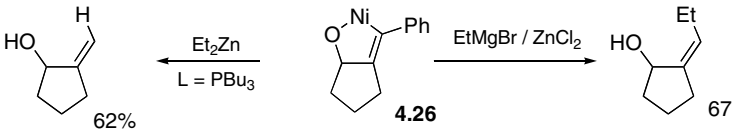
Scheme 4.33. The nickel-promoted sequential reaction involving cyclopropanation and β-C elimination.



Scheme 4.34. The Ni(0)-catalyzed three-component connection reaction of alkynes, aldehydes, and organozincs (or -zirconiums).

insertion observed for alkenylzirconiums (Eq. (c)) is opposite to that of $MeLi/ZnCl_2$ (Eq. (a)).

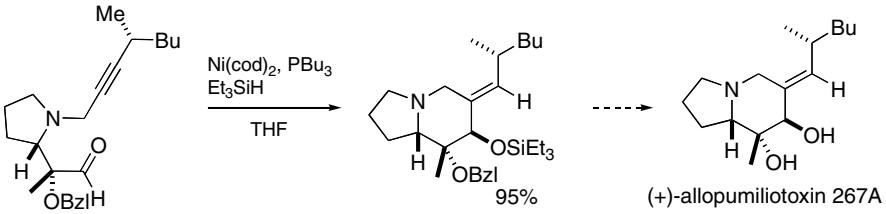
As shown in Scheme 4.27, phosphine ligands exert similar effects in these reactions; $Ni(cod)_2$ alone selectively promotes reductive elimination, while a Ni(0) com-



Scheme 4.35. The selective reductive elimination and β-hydrogen elimination in the presence and absence of PBu_3.

plex modified by PBu_3 promotes β-hydrogen elimination (Scheme 4.35; see Section 4.7).

For the synthesis of bicyclic nitrogen heterocycles, Et_3SiH, in place of a combination of Et_2Zn and phosphine, is used to deliver an H atom on a distal acetylenic carbon. The strategy is successfully applied to the total synthesis of a natural alkaloid, allopumiliotoxin 267A in an optically active form (Scheme 4.36) [83].

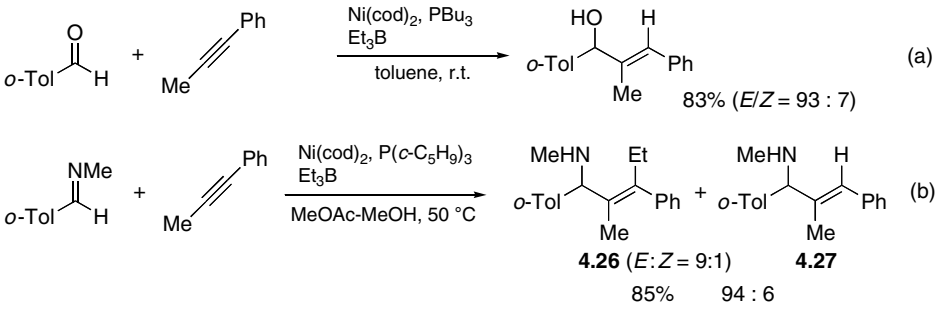


Scheme 4.36. The total synthesis of optically active (+)-allopumiliotoxin 267A based on the nickel-catalyzed reductive cyclization of an alkyne and an aldehyde.

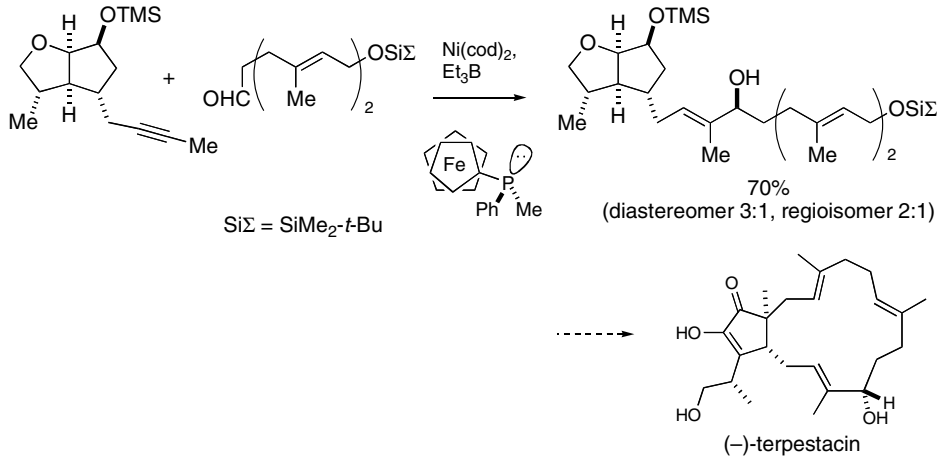
In 1998, it was revealed for the first time that Et_3B serves as a unique reducing agent in the nickel-catalyzed reductive coupling reaction of aldehydes and 1,3-dienes (see Section 5.2.3). Generally, Et_3B displays lower reactivities (e.g., transmetallation, nucleophilicity) than Et_2Zn. Despite the diminished reactivities, Et_3B shows a good performance for the reductive coupling of aldehydes and alkynes (Scheme 4.37(a)) [84]. In contrast to the reaction with aldehydes, Et_3B delivers the ethyl group at the distal carbon of alkynes for the reaction with imines (Scheme 4.37(b)) [85]. In this way asymmetric induction is achieved [86], and the technique has been applied to the total synthesis of (−)-terpestacin (a natural product) (Scheme 4.38) [87].

4.6.4
Sequential Reaction with Epoxides

The Ni(0) species generated from a combination of $Ni(cod)_2$, Et_3B, and Bu_3P is able to undergo oxidative addition upon epoxides at the least-substituted C–O

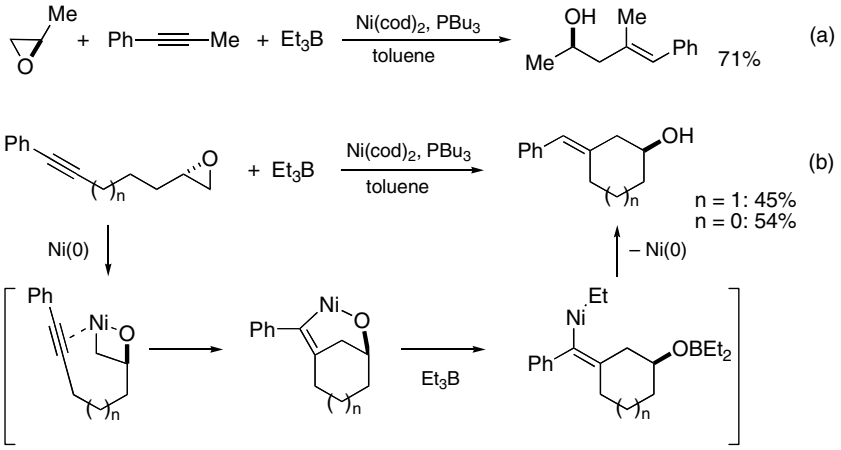


Scheme 4.37. The nickel-catalyzed reductive coupling of alkynes and aldehydes (a) and alkylative coupling of alkynes and imines (b).



Scheme 4.38. The asymmetric induction for the nickel-catalyzed reductive coupling and alkynes and aldehydes and its application to the total synthesis of (−)-terpestacin.

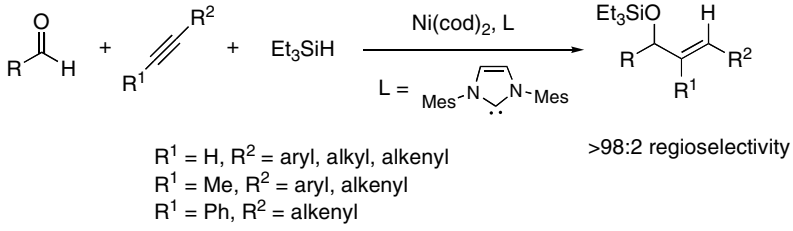
bond (Scheme 4.39) [88]. Since a wide variety of optically active epoxides are available and the stereochemistry of the chiral center remains intact, the reaction can be a very powerful tool in the synthesis of optically active homoallyl alcohols. The reaction mechanism is outlined in Eq. (b) of Scheme 4.39. Oxidative addition at the terminal C–O bond, followed by insertion of an alkyne in an *exo-dig* fashion, produces a bicyclic oxametallacycle which possesses a double bond at the bridge-head position (an anti-Bredt intermediate). Transmetallation with Et_3B, followed by *β*-hydrogen elimination yields the final product (see Section 4.7).



Scheme 4.39. The nickel-catalyzed ring opening of epoxides and subsequent insertion of alkynes: Preparation of optically active homoallyl alcohols.

4.7 Addenda

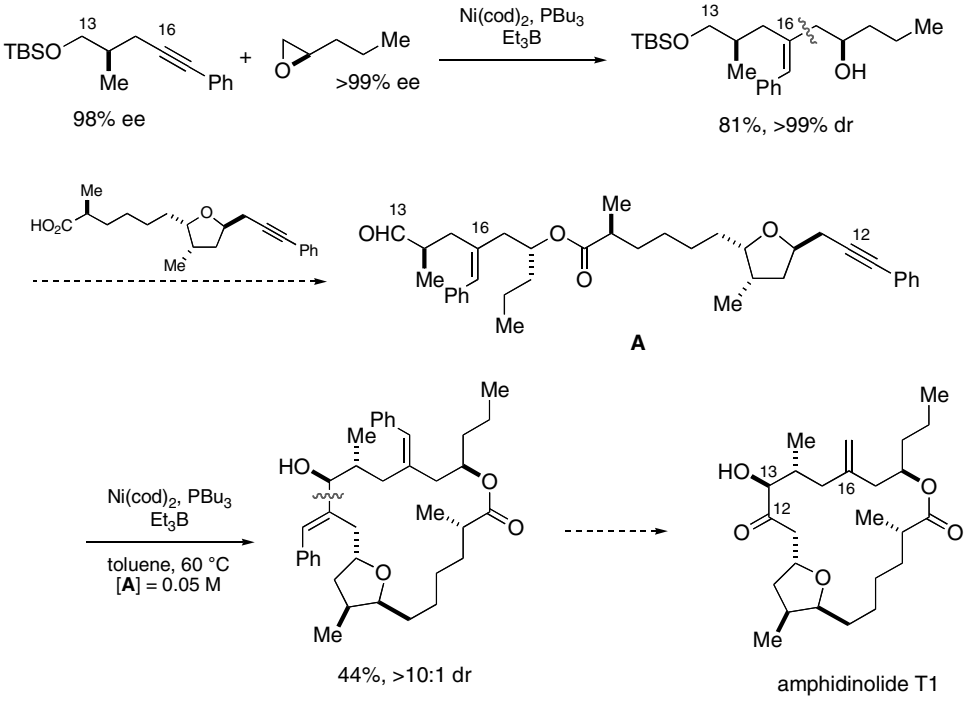
A nickel–carbene catalyst introduced recently shows remarkably different reactivity and regioselectivity for the reductive coupling of alkynes and aldehydes (Eq. (4.6)) from those of the original Ni(0)/PBu_3 catalytic system (Schemes 4.34(a) and 4.36) [89].



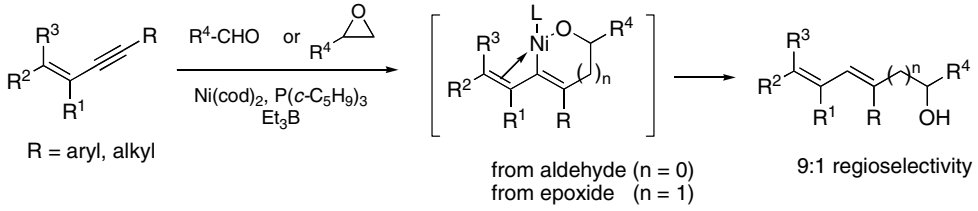
(4.6)

The two nickel-catalyzed reductive coupling reactions, alkyne-epoxide (Scheme 4.39) and alkyne-aldehyde (Scheme 4.37(a)), developed by Jamison, have been successfully applied to an enantioselective total synthesis of amphidinolide T1 (Scheme 4.40) [90].

The vinyl groups of conjugated enynes not only nicely navigate a nickel to an adjacent, allylic position, thus forming a conjugated diene intermediate bearing the nickel at C2 position for the nickel-catalyzed reductive coupling reactions of alkyne-aldehyde (Scheme 4.37(a)) and alkyne-epoxide (Scheme 4.39), but also dramatically enhance the reaction rates (Scheme 4.41) [91].



Scheme 4.40. The total synthesis of amphidinolide T1 utilizing the nickel-catalyzed reductive coupling reactions of alkyne-epoxide (Section 4.6.4) and alkyne-aldehyde coupling reactions (Section 4.6.3).



Scheme 4.41. The nickel-catalyzed regioselective reductive coupling reactions of vinylalkynes and epoxides (and aldehydes).

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5
Reaction of Dienes and Allenes

Masanari Kimura and Yoshinao Tamaru

1,3-Butadiene and isoprene (2-methyl-1,3-butadiene) are among the most important building blocks both in the laboratory and in the chemical industry. 1,3-Butadiene ($\Delta H_f = +26.1$) and 1,2-butadiene (methylallene $\Delta H_f = +38.8$) are highly unsaturated and labile even toward relatively unreactive reagents, such as O_2 in air, and undergo polymerization during storage.

Although the [4+2]cycloaddition – the so-called Diels–Alder reaction – of butadiene to afford 4-vinylcyclohexene is a thermally permitted process, it only proceeds under harsh conditions (e.g., at 250 °C under high pressure). In contrast, nickel complexes promote the [4+2]cycloaddition under milder conditions (e.g., at 0 °C under ambient pressure) [1]. Furthermore, the complexes even promote thermally forbidden [4+4]cycloaddition and other reactions. Many other 1,3-dienes and allenes are also subject to dimerization, oligomerization, and polymerization under nickel catalysis, and hence serve as useful C4 and C3 carbon resources for a variety of organic syntheses.

This chapter deals with recent developments in the nickel-catalyzed functionalizations of conjugated dienes and allenes, and incorporates the following topics: 1) dimerization and polymerization; 2) allylic and homoallylic alkylation of carbonyl compounds (dienes and allenes as nucleophiles); and 3) 1,2- and 1,4-addition reactions of reagents X–Y toward dienes and allenes.

5.1
Dimerization and Polymerization of 1,3-Dienes

Nickel complexes are extremely effective catalysts for the dimerization and polymerization of dienes. The catalytic reactions are described in Chapter 6, Section 6.4. The major subject of this section relates to the structures and reactivities of Ni(II)·(butadiene)$_2$ complexes (the stoichiometric reactions) and recent developments in the field of polymerization.

Modern Organonickel Chemistry. Edited by Y. Tamaru

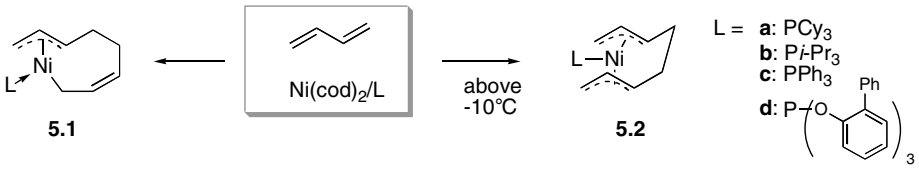
ISBN: 3-527-30796-6

5.1.1

Structure of Ni-(butadiene)$_2$ Complexes Stabilized by Phosphine Ligands

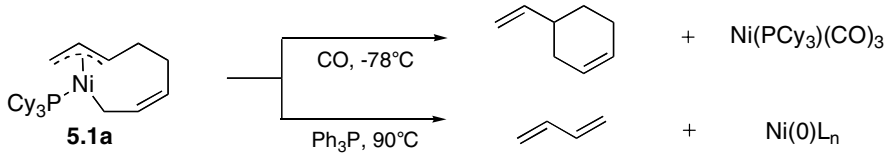
Ni(cod)$_2$ reacts with 2 mol butadiene (oxidative cyclization), and generally forms two types of complexes **5.1** and **5.2**, depending upon the nature of the ligands [2].

With basic phosphines of a large cone angle (e.g., PCy_3 or $P(i\text{-}Pr)_3$), η^1,η^3-octadienylnickel(II) complexes **5.1** are the products (Scheme 5.1). With a less bulky PMe_3, a mixture of **5.1** and η^3,η^3-octadienylnickel(II) species **5.2** is formed, and these do not isomerize with each other on warming from −30 °C to 60 °C. The less basic ligands (e.g., triphenylphosphine and tris-(*o*-phenylpheny)phosphite) also provide the η^1,η^3-octadienylnickel complexes **5.1**, which undergo rearrangement irreversibly at temperatures above −10 °C to give **5.2**. At room temperature, reductive elimination takes place to leave the starting Ni(cod)$_2$ and the phosphine ligands.



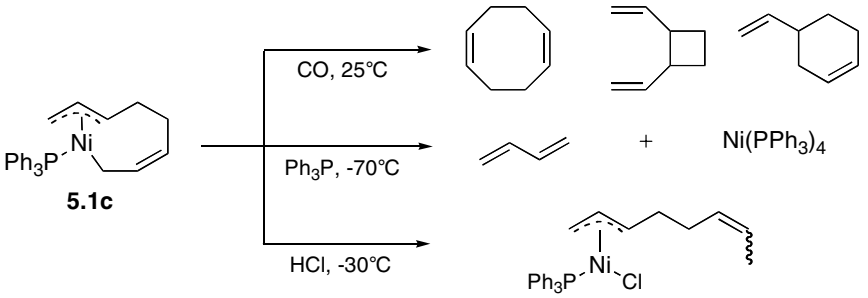
Scheme 5.1. The two structural forms of ligand-stabilized Ni(II)·(butadiene)$_2$ complex.

At −78 °C in toluene, **5.1a** absorbs 3 equiv. CO and provides Ni(PCy$_3$)(CO)$_3$ and vinylcyclohexene in quantitative yield (Scheme 5.2). In contrast, treatment with an excess amount of PPh_3 at 90 °C results in the liberation of 2 mol butadiene.



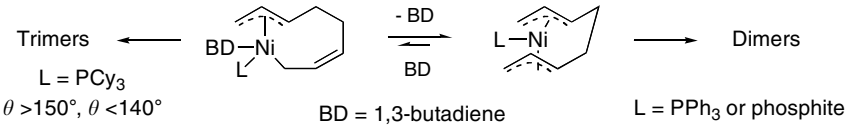
Scheme 5.2. Reaction of Ni(PCy$_3$)(η^1,η^3-octadiene) with CO and PPh_3.

The reaction of **5.1c** with CO at −78 °C leads to vinylcyclohexene, whereas at 25 °C, a mixture of 1,5-cyclooctadiene, 1,2-divinylcyclobutane, and 4-vinylcyclohexene is formed (Scheme 5.3). Butadiene is liberated on treatment of an ethereal solution of **5.1c** at −70 °C with an excess amount of PPh_3 with concomitant formation of Ni(PPh$_3$)$_4$. Protonation with HCl at −30 °C takes place at one of the two terminal carbons and gives a triphenylphosphine-stabilized *syn*-η^3-allylnickel(II) chloride complex. The double bond of the substituent is partially isomerized to trans.



Scheme 5.3. Reaction of Ni(PPh$_3$)(η^1,η^3-octadiene) (**5.1c**) with some ligands or HCl.

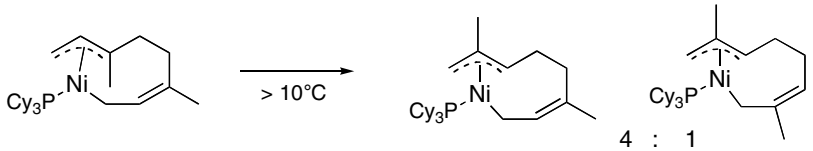
The formation of butadiene trimer (see Section 6.4.1) was quantitatively analyzed by means of multi-linear regression method (Scheme 5.4) [3], where the ligand properties are characterized by the steric (cone angle: θ) and the electronic parameters (Tolman's value: χ; see Section 1.8, Figure 1.10). The analysis concludes that phosphine ligands with a higher donor character (with a smaller χ value) and a cone angle $< 140°$ or $> 150°$ favor the formation of η^1,η^3-octadienylnickel(II)·butadiene complex and tend to lead to trimers.



Scheme 5.4. Ligand-property control of Ni/butadiene/P–ligand complexes.

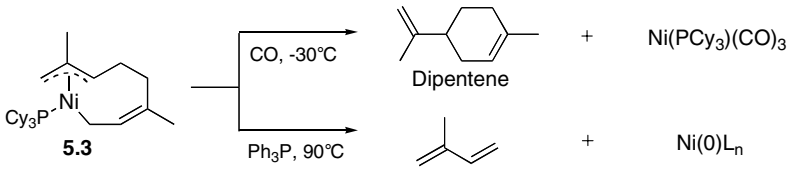
5.1.2
Dimerization of Substituted 1,3-Dienes

The complexes formed by the reaction of an Ni(0) and 2 equiv. isoprene have a common structural motif of η^1,η^3-dimethyloctadienylnickel(II), irrespective of the type of ligands. The reaction in the presence of PCy$_3$ has been investigated in the greatest detail. Nuclear magnetic resonance (NMR) measurements indicate that the initially formed complex bears the two methyl groups in the 3- and 6-positions (head-to-head), which rearranges at temperatures above 10 °C to give a 4:1 mixture of 2,6- (head-to-tail) and 2,7-dimethyl-substituted allylnickels (tail-to-tail) (Eq. (5.1)) [2].



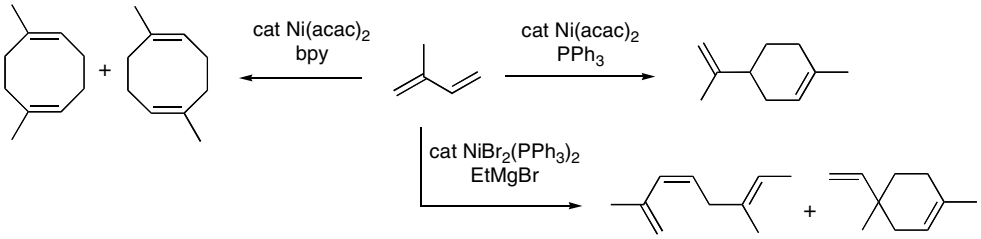
(5.1)

Treatment of 2,6-dimethylsubstituted allylnickel **5.3** with CO at −30 °C causes reductive elimination (ring closure) to give a terpene, dipentene, and $Ni(PCy_3)(CO)_3$. On the other hand, the reaction with an excess amount of PPh_3 at 90 °C results in degradation to produce 2 mol isoprene (Scheme 5.5) [4].



Scheme 5.5. Reaction of **5.3** with CO and PPh_3.

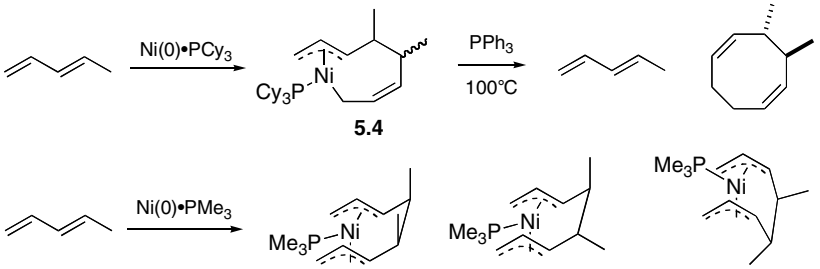
Isoprene undergoes dimerization in the presence of nickel catalysts to give a wide variety of cyclic and linear dimers, depending on the type of ligands. An Ni(0) species prepared from $NiBr_2(PPh_3)_2$ and ethylmagnesium bromide provides a mixture of a linear and a cyclic dimer (Scheme 5.6) [5]. Combinations of PPh_3-$Ni(acac)_2$ and bipyridine-$Ni(acac)_2$ promote the selective cyclodimerization to provide dipentene and cyclooctadiene, respectively.



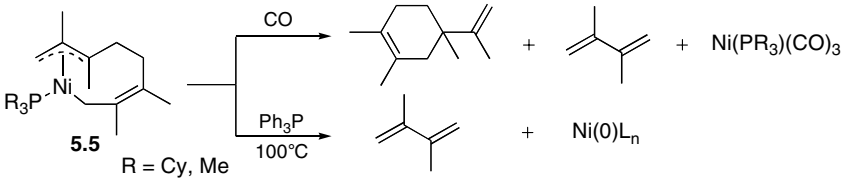
Scheme 5.6. Selective dimerization of isoprene catalyzed by various Ni–ligand complexes.

The reactions of piperylene (1,3-pentadiene) with Ni(0) complexes modified by phosphine ligands are rather complicated. *trans*-Piperylene reacts with Ni(0)-PCy_3 to provide an η^1,η^3-dimethyloctadienylnickel(II) species **5.4**, which upon exposure to an excess amount of PPh_3 at 100 °C liberates *trans*-piperylene (and *cis*-, in a small quantity) and *trans*-3,4-dimethyl-1,5-cyclooctadiene (Scheme 5.7) [2]. PMe_3 affords an isomeric mixture of η^3,η^3-dimethyloctadienylnickel(II) complexes, all of which are head-to-head isomers.

Reactions of 2,3-dimethylbutadiene with Ni(0)·PCy_3 or PMe_3 lead to η^1,η^3-2,3,6,7-tetramethyloctadienyl complexes **5.5** (Scheme 5.8) [6]. The complexes **5.5** react with CO to give mixtures of 2,4-dimethyldipentene and the starting diene, while they undergo degradation to give the starting diene when treated with PPh_3 at 100 °C.



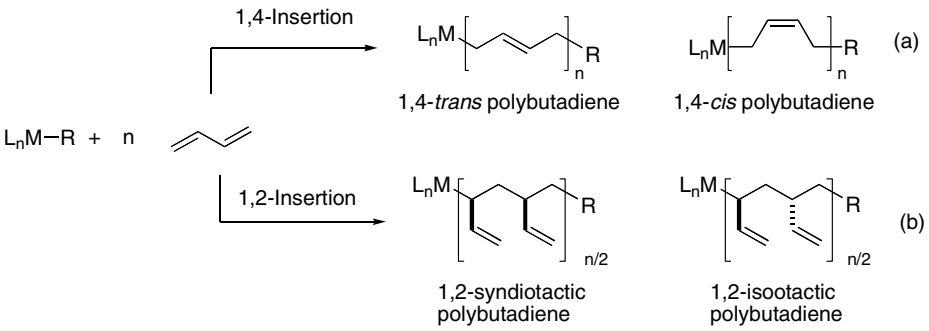
Scheme 5.7. Stoichiometric reaction of an Ni(0) complex with piperylene in the presence of trialkylphosphines.



Scheme 5.8. Reaction of η^1,η^3-nickel(II) complexes **5.5** with CO and PPh_3.

5.1.3
Ni-catalyzed Polymerization of Butadiene

Butadiene and isoprene are important feedstocks for the manufacture of synthetic rubbers. Since the discovery of the Ziegler–Natta catalyst for the polymerization of ethylene and propylene, the polymerization of conjugated diene has been studied mostly in this line [7]. The regio- and stereoregularity in the polymerization is dependent on the transition-metal catalysts. For example, the catalytic systems, VCl_3/$AlEt_2Cl$, $CoCl_2$/$AlEt_2Cl$, $Cr(acac)_3$/$AlEt_3$, and $MoO_2(OR)_2$/$AlEt_3$ have proven to be particularly effective for the *cis*-1,4, *trans*-1,4, *1,2*-isotactic, and *1,2*-syndiotactic polymerization of butadiene, respectively (Scheme 5.9). Of these reactions, *cis*-1,4-

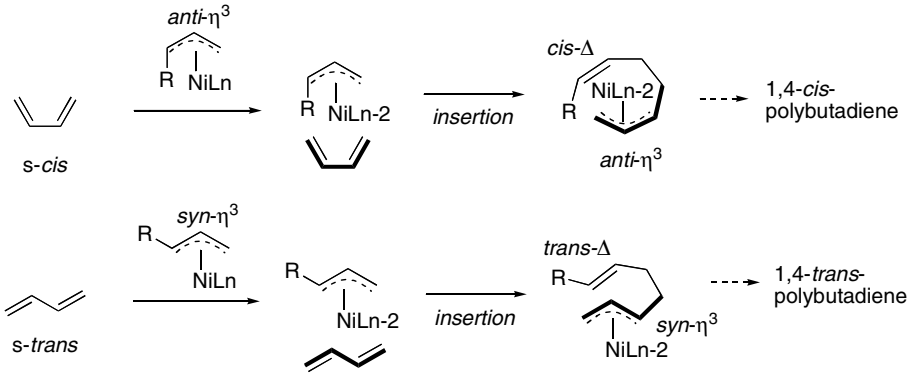


Scheme 5.9. The four modes of 1,3-butadiene insertion into R-MLn.

polymerization is particularly important for the production of synthetic rubber tires.

The polymerization of isoprene is rather complex because the methyl group renders the molecule unsymmetric, and hence the regiochemistry (head-to-head or head-to-tail) and the stereochemistry (*E* or *Z* of the trisubstituted double bonds) becomes other important issues to be addressed. The head-to-tail poly-(*Z*)-1,4-isoprene shows similar physical properties to those of natural rubber, while the very hard and water-proof properties of head-to-tail poly-(*E*)-1,4-isoprene is well suited for golf-balls.

Although the Ziegler–Natta-type catalysts are the major catalysts that have been put to practical use, detailed experimental [8] and theoretical studies [9] on the Ni-based polymerization of butadiene have been conducted. Allylnickel(II) complexes are active catalysts for the 1,4-polymerization of butadiene, with chain propagation generally considered to proceed via an allyl insertion mechanism (Scheme 5.10) [10, 11].



Scheme 5.10. Anti-cis and syn-trans correlation of the 1,4-polymerization of butadiene.

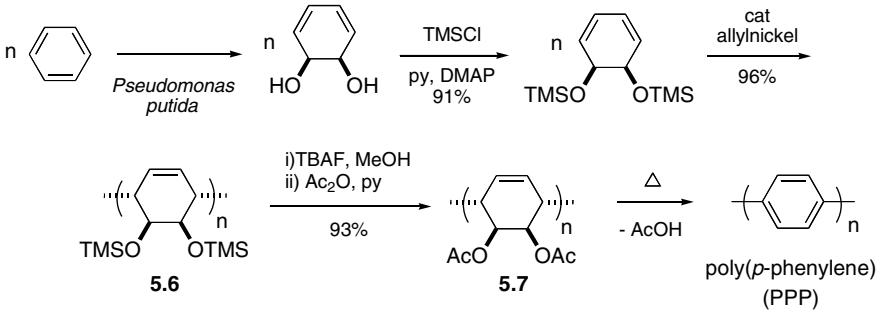
Free monomer butadiene coordinates to an empty site of the nickel metal in two different modes: either a *s*-cis or a *s*-trans conformation. An anti- or syn-η^3-butenyl complex is formed under kinetic control by diene insertion from the *s*-cis (anti insertion) or *s*-trans (syn insertion) conformation, respectively. The stereochemistry of the polymer is determined by the geometry (syn or anti) of the active η^3-allyl complexes on the butadiene insertion process.

The X-type ligands of the allylnickel(II) complexes play an important role in stereoregular polymerization. Neutral allylnickel(II) species, such as $[Ni(CH_2CH{=}CCH_3)I]_2$, provide *trans*-1,4-regulating polymers, whereas cationic allylnickel species, such as $[Ni(C_3H_5)Cl]_2$ and $[Ni(C_3H_5)O_2CCF_3]_2$, furnish *cis*-1,4-regulating polymers [12]. Both of the *trans*- and *cis*-regulating processes have been traced by means of ^1H and ^{13}C NMR spectroscopy [13–15]. The DFT methods define the detailed mechanistic aspects for the *trans*- and *cis*-1,4-polymerizations of butadiene using butenylnickel(II)L(butadiene) complexes as the models [16, 17].

5.1.4

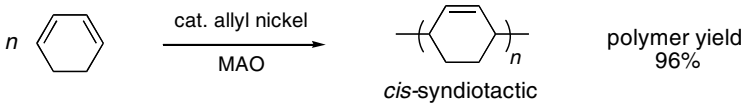
Stereo- and Regioselective Polymerization of Conjugated Cyclic Dienes

1,4-Linked, stereoregular precursors to poly(*p*-phenylene) (PPP) are prepared via Ni-catalyzed polymerization of microbially prepared *cis*-5,6-dihydroxy-1,3-cyclohexadiene. Masking the hydroxy groups of the monomer as a trimethylsilyl ether and the use of bis[(π-allyl)(trifluoroaceto)nickel(II)] catalyst promote the polymerization of 1,3-cyclohexadiene exclusively in a *cis*-1,4-fashion in 96% yield. This polymerization system not only affords a stereoregular polymer but also permits a degree of molecular weight control (Scheme 5.11) [18]. The polymer **5.6** thus obtained is transformed to acetic acid ester **5.7** and then to a PPP via pyrolytic elimination of acetic acid.



Scheme 5.11. Allylnickel-catalyzed polymerization of cyclohexadiene and subsequent transformation to poly(*p*-phenylene) (PPP).

Bis(η^3-allylnickel bromide)/methylaluminoxane (MAO) is also effective for the 1,3-cyclohexadiene polymerization. The crystalline polymer obtained is *cis-syndiotactic* with 1,4-linkage (Eq. (5.2)). The catalyst is also useful for the copolymerization of cyclohexadiene and butadiene [19, 20].



(5.2)

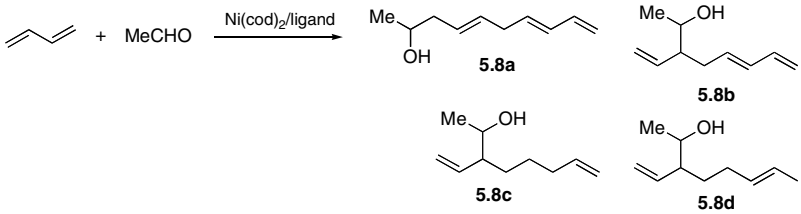
5.2
Allylation and Homoallylation of Aldehydes with Dienes and Allenes

5.2.1

Allylation of Aldehydes via Dimerization of 1,3-Dienes

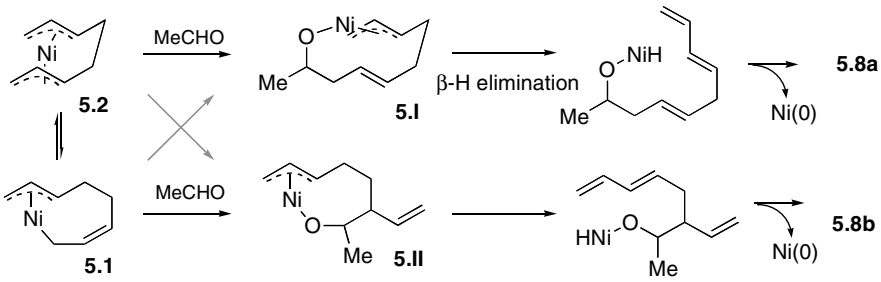
1,3-Butadiene and an Ni(0) complex readily undergo oxidative cyclization and form an η^3,η^3-bisallylnickel complex (e.g., **6.1**) and an η^1,η^3-bisallylnickel complex (e.g.,

Tab. 5.1. Nickel-catalyzed allylation of acetaldehyde with butadiene.



Ligand	*Yield [%]*			
	5.8a	*5.8b*	*5.8c*	*5.8d*
PPh_3	71	12	5	4
$P(n\text{-}Bu)_3$	40	19	26	8
$P(c\text{-}Hex)_3$	3	29	40	18

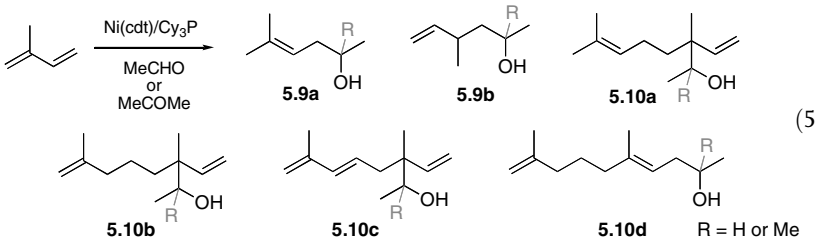
6.2). One of the outstanding features of the allylnickel(II) species is their nucleophilic reactivity toward carbonyl compounds, these not being observed for either allylpalladium(II) or allylplatinum(II) species (See Section 1.7.2, Scheme 1.13). These two characteristics combine to bestow Ni(0) complexes with catalytic activities that promote the dimerization-allylation of aldehydes with dienes. The results of the reaction between acetaldehyde and 1,3-butadiene in the presence of phosphine ligands are shown in Table 5.1 [21, 22]. In general, four types of isomers, composed of two trienyl alcohols **5.8a**,**b** and two dienyl alcohols **5.8c**,**d**, are formed. The effects of the phosphine ligands on product distribution are remarkable; PPh_3 shows high selectivity in favor of **5.8a**. The straight-chain isomer **5.8a** may be formed via an intermediate **5.I**, which undergoes *β*-hydrogen elimination and reductive elimination with regeneration of an Ni(0) complex (Scheme 5.12). In similar way, an intermediate **5.II**, formed by allylation at the internal allylic termini of **5.1** or **5.2**, leads to a branched isomer **5.8b**. It is difficult to explain the formation of the dienyl alcohols **5.8c**,**d**, since a stoichiometric amount of reducing agent is necessary to produce these alcohols (e.g., a hydride reduction of **5.II**).



Scheme 5.12. Mechanistic explanation for the catalytic formation of trienyl alcohols, **5.8a** and **5.8b**, by the reaction of acetaldehyde and 2 mol butadiene.

Isoprene does not react with acetaldehyde under the above-optimized conditions, $Ni(cod)_2{\cdot}PPh_3$. The combination of Ni(cdt) and PCy_3 promotes the reaction to afford a complex mixture of allylation and homoallylation products (Eq. (5.3)). The 2:1 adducts **5.10a–d** are the major components, whilst the 1:1 adducts **5.9a**,**b** are also obtained as minor products.

Acetone reacts with isoprene in the presence of $Ni(0){\cdot}P(O\text{-}o\text{-}Tol)_3$, and selectively provides a mixture of products in a good combined isolated yield involving a dienol **5.10d** (R = Me) as the main constituent [23]. Again, in this reaction the origin of reducing agents necessary for the formation of dienols **5.10a**,**b**,**d** and enols **5.9** is not known, and it is difficult to provide a mechanistic rationale for the results.

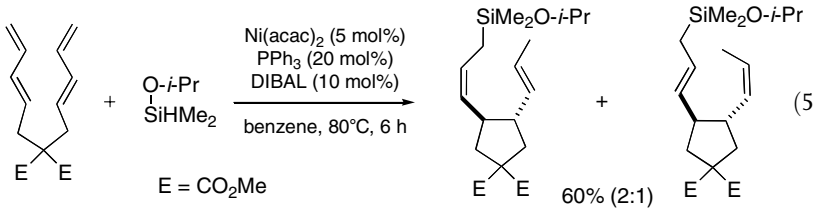


(5.3)

5.2.2

Allylation of Aldehydes with Dienes Promoted by Silane ($R_{4-n}SiH_n$)

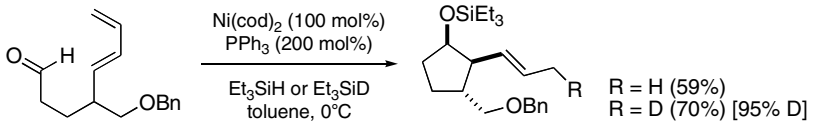
An η^3-allylnickel species is formed by Markovnikov insertion of a 1,3-diene into an Ni–H complex, generated by oxidative addition of an Ni(0) complex upon the Si–H bond of trialkylsilanes [24]. A Ni(0)-catalyzed 1,ω-hydrosilylation across the two diene units of 1,3,8,10-undecadiene provides *trans*-substituted cyclopentanes (Eq. (5.4)) [25]. The reaction shows an interesting stereoselectivity with respect to the geometry of the substituents, as in both isomers one of the two double bonds is cis and the other trans.



(5.4)

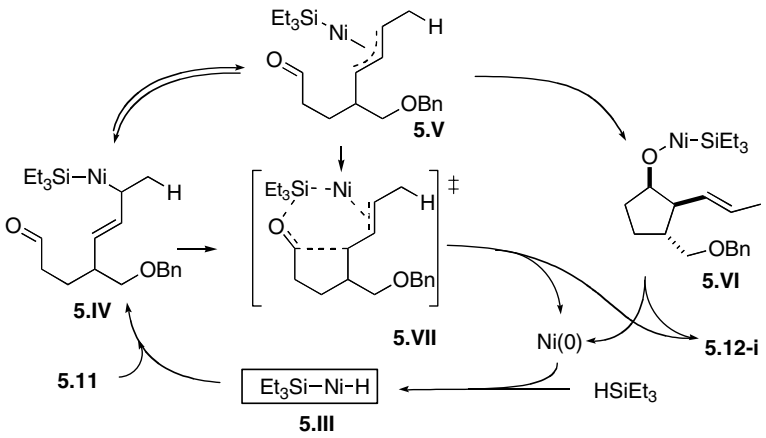
The η^3-allylnickel species thus formed, which bears a silyl group (R_3Si–Ni(II)-η^3-allyl), is expected to be highly nucleophilic toward an aldehyde, as the R_3Si group might serve as an efficient Lewis acid to activate the aldehyde. Indeed, Mori et al. realized this idea in the cyclization reaction of ω-dienyl aldehyde **5.11** (Eq. (5.5)) [26]. That is, when a toluene solution of **5.11**, $Ni(cod)_2$ (100 mol%), PPh_3 (200 mol%), and Et_3SiH (150 mol%) was stirred at 0 °C, an intramolecular allylation of

aldehyde and trapping of the aldehyde oxygen with silicon took place to give **5.12-i** with excellent stereoselectivity.



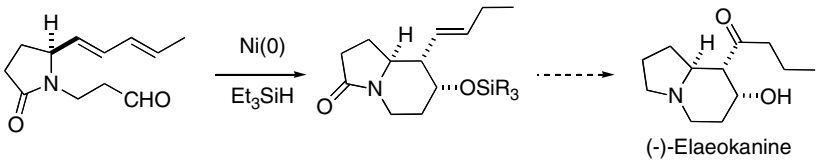
5.11 **5.12-i** (5.5)

By using an excess amount of Et_3SiH (5 equiv.), the reaction can be performed catalytically with respect to $Ni(cod)_2$. Triethylsilyl deuteride (Et_3SiD) delivers the D to the correct position (95% D content), and a proposed reaction mechanism for this is outlined in Scheme 5.13. A nickel hydride complex **5.III**, generated by oxidative addition of Et_3SiH to an Ni(0) complex, adds to the diene moiety of ω-dienyl aldehyde **5.11** according to the Markovnikov rule to provide **5.IV** and its η^3-allyl derivative **5.V**. The intermediate **5.V** attacks the aldehyde to afford **5.VI**, which further undergoes reductive elimination giving rise to a final product **5.12-i** and an Ni(0) species. Another route involves a concerted silyl group transfer to the aldehyde oxygen, nucleophilic allylation, and regeneration of an Ni(0) species via a transition state **5.VII**.



Scheme 5.13. Ni(0)-mediated intramolecular allylic cyclization of ω-dienyl aldehydes using hydrosilane as a reducing (and promoting) agent.

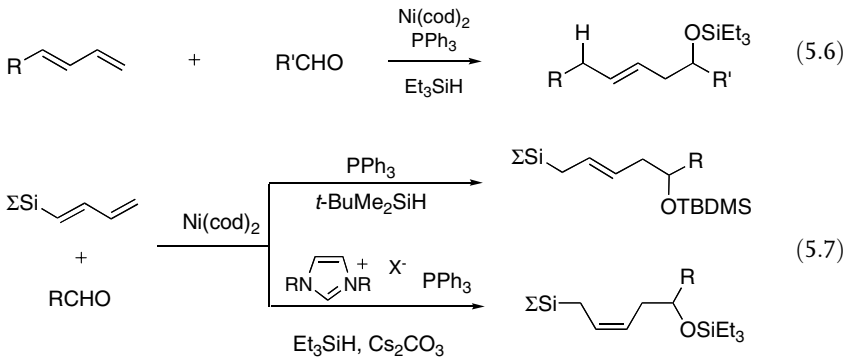
The reaction tolerates the cyclization of cyclohexa-1,3-dienes, cyclohepta-1,3-dienes and cyclohepta-1,3,5-trienes having aldehyde groups as the side chains to form a variety of fused, bridged, and spiro bicyclic skeletons [27]. This strategy is successfully applied to the synthesis of the indolizidine framework of (−)-Elaeokanine C (a natural product) (Scheme 5.14) [28, 29].



Scheme 5.14. Formal total synthesis of (−)-elaeokanine C by Ni-catalyzed allylic cyclization.

This chemistry is extended to an asymmetric version. By using a chiral cyclic phosphine, ω-formyl-1,3-dienes undergo similar cyclization to provide five- and six-membered carbocyclic compounds and pyrrolidines in up to 86% enantiomeric excess (ee) [30].

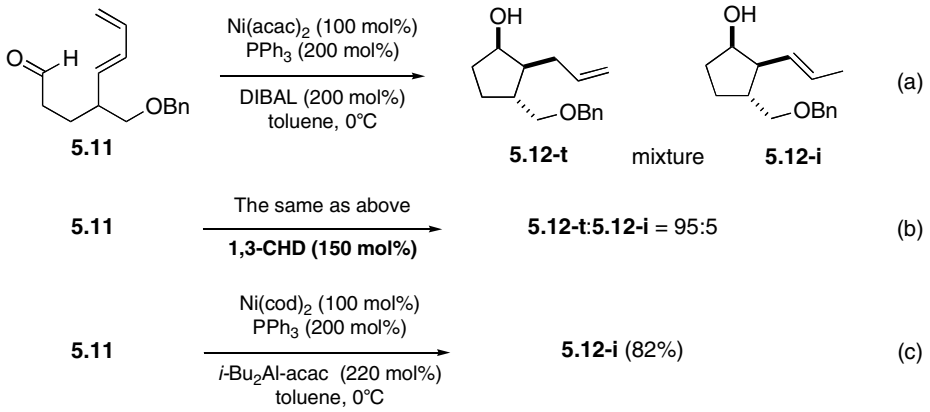
Intermolecular allylation of aldehyde with 1,3-dienes and triethylsilane in the presence of a catalytic amount of $Ni(cod)_2$ and PPh_3 proceeds with excellent regio- and stereoselectivity to provide homoallylic alcohols (Eq. (5.6)) [31a]. 1-Silyl-1,3-butadienes react with aldehydes providing either *trans*- or *cis*-homoallyl alcohols selectively under the conditions shown in Eq. (5.7) [31b]. Aromatic aldehydes possessing electron-donating groups enhance the yields of the *cis*-allylsilanes, whereas *trans*-allylsilanes are obtained in better yields for those with electron-withdrawing groups.



5.2.3

Allylation of Aldehydes with Dienes Promoted by Diisobutylaluminum Hydride (DIBAL) or Diisobutylaluminum(III)(acac)

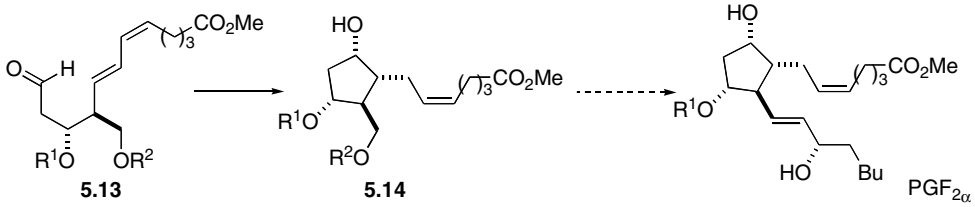
ω-Dienyl aldehyde **5.11** also undergoes allylation-cyclization smoothly by treatment with a stoichiometric amount of a nickel hydride complex, prepared from $Ni(acac)_2$ and 2 equiv. DIBAL in the presence of PPh_3, to provide cycloalkanols as a mixture of **5.12-t** (a homoallylation product) and **5.12-i** (an allylation product; Scheme 5.15(a)) [32]. This is in sharp contrast to the results shown in Eq. (5.5). The reaction using 10 mol% of a nickel hydride complex (relative to **5.11**) selectively affords



Scheme 5.15. Allylation versus homoallylation cyclization of ω-dienyl aldehyde **5.11** promoted by Ni-DIBAL and Ni-*i*-Bu_2Al(acac).

5.12-t in 10% yield (100% based on the nickel hydride complex). When 150 mol% of 1,3-cyclohexadiene, as a dummy ligand, is added to the mixture of ω-dienyl aldehyde **5.11**, $Ni(acac)_2$ (100 mol%), PPh_3 (200 mol%), and DIBAL (200 mol%), **5.12-t** is produced selectively along with a small amount of **5.12-i** in a ratio of 95:5. These results indicate that an excess proportion of the diene affects the course of the reaction, with allylation giving **5.12-i** and homoallylation giving **5.12-t**.

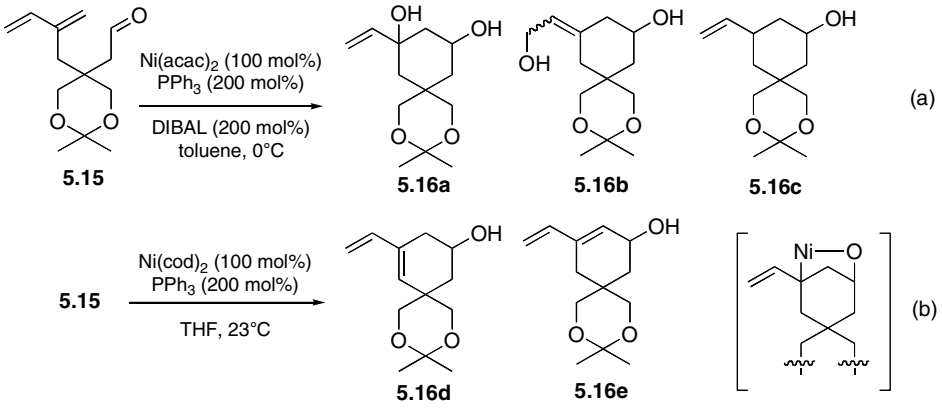
The cyclization of an optically active ω-dienyl aldehyde **5.13** gives a key intermediate **5.14,** which has the correct α-chain and the four contiguous chiral carbon stereocenters as an intermediate for the synthesis of $PGF_{2\alpha}$ (a natural product) (Scheme 5.16) [33].



Scheme 5.16. Formal total synthesis of $PGF_{2\alpha}$ via homoallylation–cyclization of ω-dienyl aldehyde.

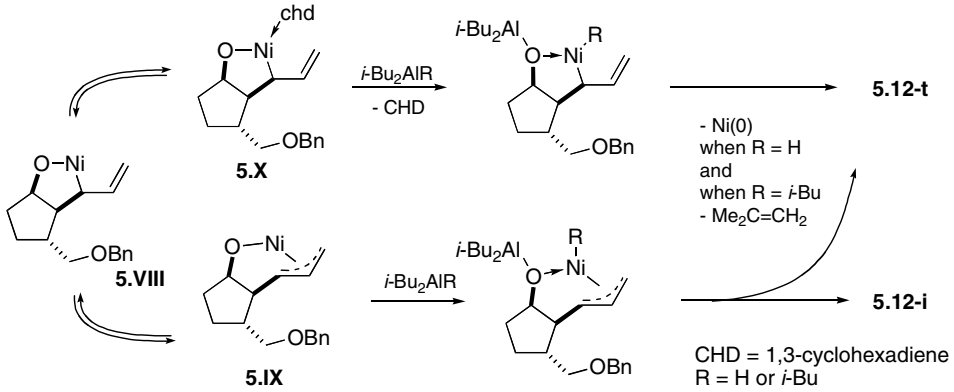
The reaction of **5.11** with $Ni(cod)_2$ (100 mol%) and PPh_3 (200 mol%) in the presence of diisobutylaluminum(III) acetylacetonate [34] (220 mol%) in toluene selectively provides **5.12-i** in 82% yield (Scheme 5.15(c)) [35]. As in the case of Ni(II)-DIBAL (Scheme 5.15(b)), the reaction in the presence of 1,3-cyclohexadiene produces **5.12-t** exclusively in high yield.

Dienyl aldehyde **5.15**, in having an aldehyde tether at the C2 position of 1,3-butadiene moiety, displays a quite different reaction behavior compared to the same molecule with an aldehyde tether at the C1 position (e.g., **5.11**). On exposure to a stoichiometric amount of $Ni(acac)_2$ in the presence of 2 equiv each of DIBAL and PPh_3, **5.15** provides a mixture of **5.16a**, **5.16b**, and **5.16c** in a ratio of 1.5:1:1.3 (Scheme 5.17(a)) [36]. One of the two hydroxy groups of **5.16a**,**b** stems from aldehyde, and the other allylic OH from O_2 in air, this being introduced by oxidation during work-up. On the other hand, the reaction with $Ni(cod)_2$ in the absence of DIBAL provides a mixture of other types of products **5.16d** and **5.16e** in a ratio of 1:3 containing trace amounts of **5.16a** and **5.16b** (Scheme 5.17(b)). Moreover, the combination of cat $Ni(cod)_2$ and a stoichiometric amount of Et_3SiH does not promote cyclization of **5.15** (see Section 5.2.2).

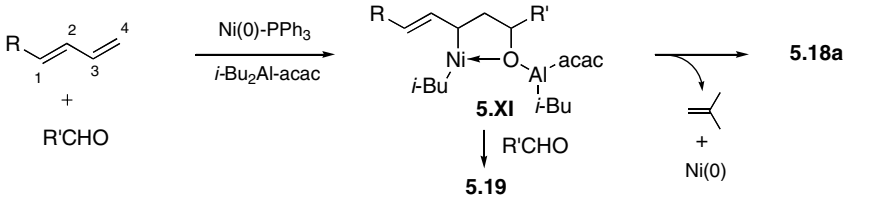


Scheme 5.17. Nickel(0)/DIBAL-promoted cyclization of dienyl aldehyde **5.15**.

These results indicate that cyclization promoted by an Ni(0) complex with DIBAL (and probably also *i*-$Bu_2Al(acac)$) and that promoted by an Ni(0) complex with Et_3SiH are mechanistically different. While the reaction with Et_3SiH proceeds as shown in Scheme 5.13, the reaction with an aluminum species starts with oxidative cyclization of an Ni(0) across a diene and aldehyde, and provides either η^1-allyl- (**5.VIII**) or η^3-allylnickel(II) intermediate (**5.IX**) (Scheme 5.18; see also Section 1.7.1). These intermediates equilibrate to each other and, in the presence of a bidentate ligand, cyclohexadiene, **5.X** might be favored. Transmetallation through **5.X** (R = H) followed by reductive elimination provides **5.12-t**. When R = *i*-Bu, β-hydrogen elimination, giving rise to an Ni–H and isobutylene, precedes the reductive elimination. In the absence of a bidentate diene ligand, both **5.VIII** and **5.IX** might undergo transmetallation and reductive elimination to provide a mixture of **5.12-t** and **5.12-i**. The reaction in Scheme 5.17 may be accounted for in a similar way – that is, **5.16a**,**b** are formed via oxidation with air, **5.16c** via hydrolysis, and **5.16c**,**d** via β-hydrogen elimination of a bicyclic oxa-nickel(II) intermediate.

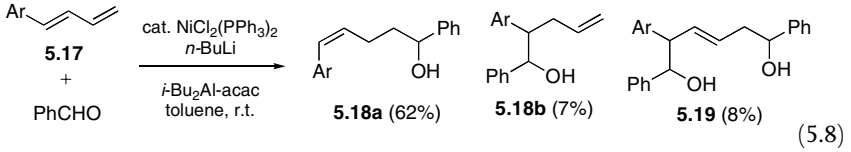


Scheme 5.18. Effect of cyclohexadiene (CHD) on regioselective hydrogen delivery to the internal allylic terminus.



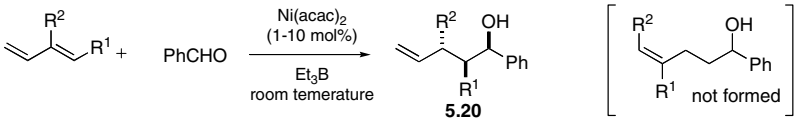
Scheme 5.19. Reaction scheme accounting for the formation of **5.18a** and **5.19**.

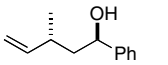
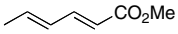
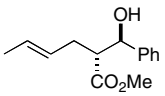
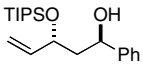
Treatment of a diene **5.17** and benzaldehyde in a 1:1 ratio with 20 mol% of a Ni(0)-PPh_3 complex in the presence of *i*-Bu_2Al(acac) gives a mixture of a linear adduct **5.18a**, a branched adduct **5.18b**, and a linear 1:2 adduct **5.19** (Eq. (5.8)) [37]. The Ni(0) species is generated beforehand in situ by the reduction with *n*-BuLi (e.g., $NiBu_2 \rightarrow Ni(0) + \text{octane}$). An account of the formation of **5.18a** and **5.19** is shown in Scheme 5.19. An intermediate **5.XI**, formed by oxidative cyclization of an Ni(0) species across the C3=C4 double bond and benzaldehyde followed by transmetallation, reacts in two different ways; one is β-hydrogen elimination and reductive elimination giving rise to **5.18a**, and the other is nucleophilic attack of **5.XI** to benzaldehyde to give **5.19**. Apparently, **5.18b** is formed by oxidative cyclization of an Ni(0) species across the C1=C2 double bond and benzaldehyde. Owing to steric (and partly electronic; loss of benzylic conjugation) reasons, this pathway is not favorable and **5.18b** forms as a minor product.



(5.8)

Tab. 5.2. Ni(0)-catalyzed and Et_3B-promoted homoallylation of benzaldehyde with 1,3-dienes, providing 1,3-*anti*-**5.20** selectively.



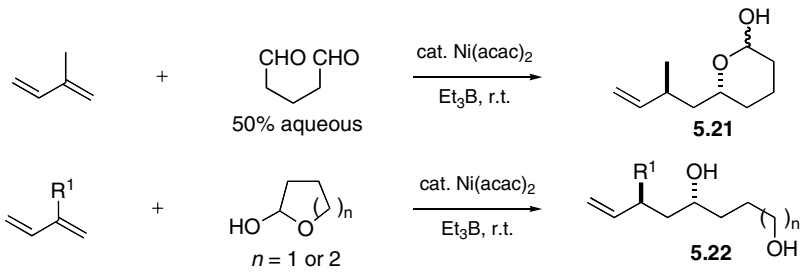
Diene	*Time [h]*	*Yield [%]*	*[isomer ratio]*
	35		90 [1,3-*syn*:*anti* = 1:15]
	66		91 [1,2-*syn*:*anti* = 1:>25]
	65		65 [1,3-*syn*:*anti* = 1:>25]

5.2.4
Homoallylation of Aldehydes Promoted by Triethylborane or Diethylzinc

Both allylic electrophiles (e.g., allyl halides) and allylic nucleophiles (e.g., allylzinc(II), allylsilane(IV), allyltin(IV)) are highly reactive, and both nucleophilic and electrophilic allylations are among the most useful and viable processes in organic syntheses. Accordingly, to date, a vast number of efficient methodologies has been developed. On the other hand, homoallylation (longer by one carbon than allylation) has received little attention owing to the *normal* reactivity of homoallylic nucleophiles and electrophiles as well as the difficult availability of the homoallylic reagents.

Recently, 1,3-dienes were shown to serve as homoallyl anion equivalents and to react with aromatic aldehydes in the presence of a catalytic amount of $Ni(acac)_2$ and a stoichiometric amount of Et_3B at room temperature to provide 1-aryl-4-pentenols **5.20** (Table 5.2) [38]. The reaction proceeds with high regio- and stereoselectivities, selectively yielding a 1:1 adduct of diene and aldehyde. 2-Substituted 1,3-dienes react with aldehyde at the C1 position to provide 1,3-*anti*-**5.20**, and 1-substituted 1,3-dienes furnish either 1,2-*syn*-**5.20** (from *Z* diene) or 1,2-*anti*-**5.20** (from *E* diene) selectivity. This is the first example to demonstrate that trialkylborane is able to serve as a reducing agent and promote reductive coupling of 1,3-diene and aldehydes (*homoallylation*, cf. Eq. (5.8)).

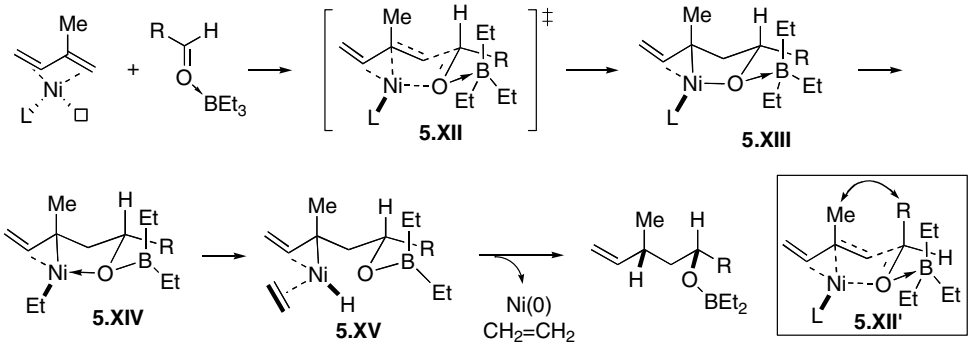
The reaction tolerates water and a hydroxy functional group (Scheme 5.20) [39]. For example, isoprene reacts with a 50% aqueous solution of glutaraldehyde regioselectively at the C1 position, and stereoselectively to provide 1,3-*anti*-**5.21** as a single isomer, being 1,3-*anti* with respect to a THP oxygen and a methyl group. Glutaraldehyde is only stable in water and is available commercially as an aqueous



Scheme 5.20. Ni(0)-catalyzed and Et_3B-promoted homoallylation of aldehydes with 1,3-dienes. The reaction is compatible with water and hydroxy groups.

solution. Cyclic hemiacetals ($n = 1$ or 2) undergo (probably through their hydroxy aldehyde form) homoallylation with 1,3-dienes under similar conditions and form bishomoallylic diols **5.22** with excellent 1,3-asymmetric induction.

A plausible mechanism for nickel-catalyzed homoallylation of aldehydes with isoprene and Et_3B is outlined in Scheme 5.21. An *s-trans*-diene-Ni(0) complex reacts with an aldehyde activated by coordination to Et_3B. An oxa-nickellacyclopentane intermediate **5.XIII** is formed through a cyclic transition state **5.XII**, where aldehyde is arranged in such a way to place the oxygen to the vacant site of the *s-trans*-diene-Ni(0) complex and the R aldehyde substituent in a quasi-equatorial position so as to avoid a quasi-1,3-diaxial repulsion that a transition state **5.XII′** with alternative orientation of aldehyde experiences. One of the ethyl groups of **5.XIII** migrates from B to Ni(II) to form **5.XIV**, which then undergoes β-hydrogen elimination to give an intermediate **5.XV** with *cis*-configuration with respect to the η^1-allyl carbon and H. Reductive elimination through **5.XV** with retention of configuration delivers the hydrogen at the allylic position, providing the final product with the correct stereochemistry. In this mechanism, Et_3B not only plays as an activation agent of an aldehyde, but also serves as a reducing agent.

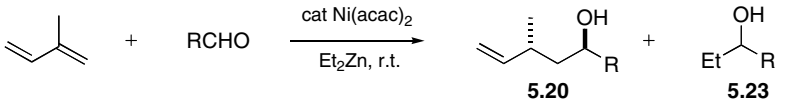


Scheme 5.21. Plausible reaction mechanism for the nickel-catalyzed homoallylation of aldehydes promoted by Et_3B.

Tab. 5.3. Ni(0)-catalyzed homoallylation of aldehydes and ketones with isoprene promoted by Et_2Zn or Et_3B, showing complementary reactivity.

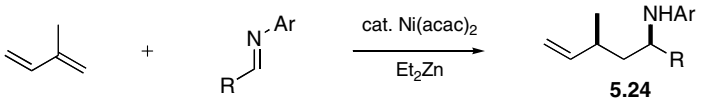
Carbonyl	*Product*	*Et_2Zn*	*Et_3B*
		Time Yield [syn:anti]	*Time Yield [syn:anti]*
Ph, CHO	OH, Ph	0.5 h 28% (3-phenylpentanal)	70 h 81% [1:20]
Cy–CHO	OH, Cy	0.5 h 83% [1:>20]	10 h 28%
O	OH, 4, 5 Me	1 h 69% [4-Me:5-Me = 5:1]	46 h 0%

Diethylzinc also promotes nickel-catalyzed homoallylation of aldehydes with a variety of 1,3-dienes (Eq. (5.9)) [40]. In this reaction, however, reactive aldehydes (e.g., aromatic aldehydes) are plagued with the ethylation of aldehydes furnishing **5.23**, and hence with diminished yields of the expected homoallylation products. However, the combination of Et_2Zn and $Ni(acac)_2$ is particularly effective for the homoallylation of less-reactive aliphatic aldehydes and ketones, which are either reluctant or entirely unreactive under the $Et_3B/Ni(acac)_2$ conditions. Thus, these two methods complement each other (Table 5.3).



5.20 **5.23** (5.9)

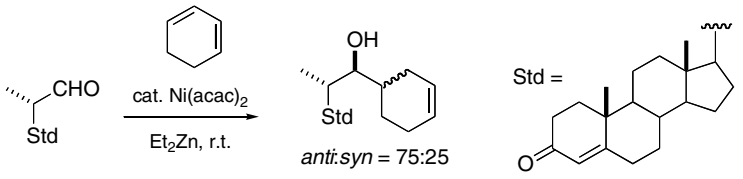
Imines undergo homoallylation with conjugated dienes in the presence of Et_2Zn and an Ni(0) catalyst to provide 1,3-*syn*-**5.24** in good yield (Eq. (5.10)) [41]. The stereoselectivity is opposite to that observed for aldehydes (Tables 5.2 and 5.3).



5.24 (5.10)

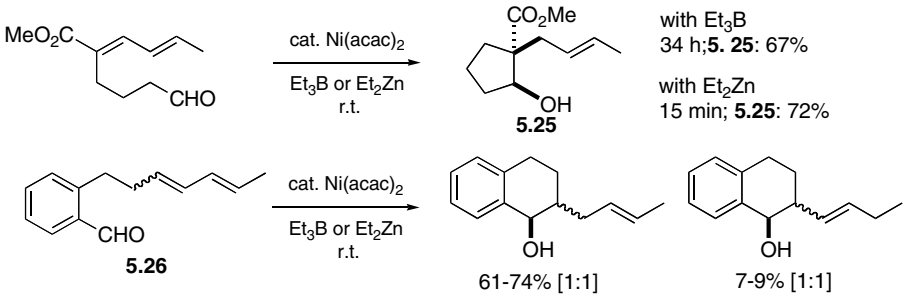
1,3-*syn* selective

Although cyclic dienes are reluctant to react with aldehydes under the $Et_3B/Ni(acac)_2$ conditions, they react smoothly with aldehydes under $Et_2Zn/Ni(acac)_2$ conditions. For example, cyclohexadiene reacts with steroidal aldehyde to provide a corresponding homoallylation product in good yield (Eq. (5.11)) [42].



(5.11)

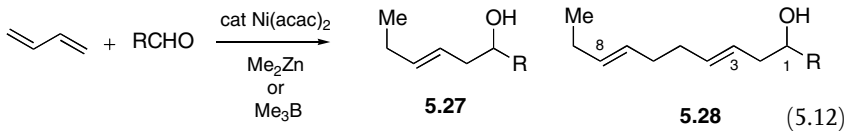
The protocol for intermolecular homoallylation of aldehyde with 1,3-dienes is applied successfully to an intramolecular version of ω-dienyl aldehyde forming five- and six-membered rings (Scheme 5.22) [43]. Generally, aliphatic ω-dienyl aldehydes show remarkably high stereoselectivity. For example, 5-methoxycarbonyl-(5*E*,7*E*)-nonadienal provides **5.25** as a single stereoisomer. On the other hand, benzaldehyde derivatives show almost no stereoselectivities, and both (*E*)- and (*Z*)-**5.26** provide cyclization products as a mixture of cis and trans isomers in a ratio of 1:1. Furthermore, homoallylation accompanies allylation.



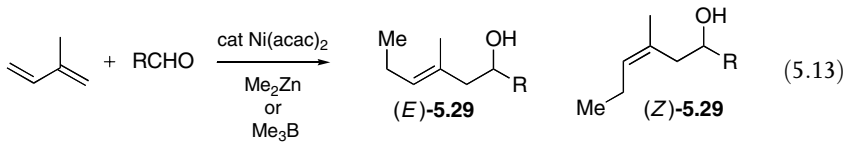
Scheme 5.22. Nickel-catalyzed intramolecular homoallylation of ω-dienyl aldehydes promoted by Et_3B or Et_2Zn.

5.2.5
Allylation of Aldehydes Promoted by Dimethylzinc, Trimethyborane, and Related Compounds: the Three-component Connection Reactions

When Me_2Zn is employed in place of Et_2Zn, the Ni(0)-catalyzed reaction of 1,3-butadienes and aldehydes takes a completely different course. The methyl group of Me_2Zn and an aldehyde add to a diene in 1,4-fashion and provide a homoallyl alcohol **5.27** in good yield (Eq. (5.12)) [44]. For example, benzaldehyde, 1,3-butadiene, and Me_2Zn combine one with another linearly in this sequence in a 1:1:1 ratio to provide (*E*)-3-phenyl-3-hexen-1-ol **5.27** in quantitative yield. Dihydrocinnamaldehyde furnishes a 1:1:1 coupling product **5.27** ($R = CH_2CH_2Ph$) as a major product, together with a 1:2:1 combination product **5.28** ($R = CH_2CH_2Ph$) as a minor product. An increase in steric bulk around the carbonyl moiety increases the relative proportions of **5.28** to **5.27**, and acetone produces a 1:2:1 adduct **5.28** ($R = Me_2$) as sole product.



(5.12)

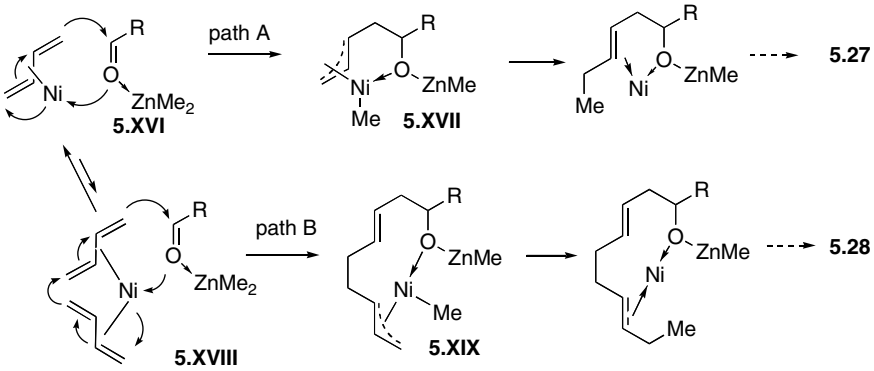


(5.13)

Isoprene undergoes a similar three-component coupling reaction, combining regioselectively with benzaldehyde at the C1 position and with the methyl group of Me_2Zn at the C4 position (Eq. (5.13)). The yield is good, but the stereoselectivity is rather poor, and a mixture of (*E*)- and (*Z*)-**5.29** is produced in a ratio of ca. 2:1.

Me_3B, generated from 3 MeLi and BCl_3, takes the place of Me_2Zn for the (*E*)-stereoselective coupling reaction of isoprene [45]. With Me_3B, aromatic and aliphatic aldehydes undergo a three-component connection reaction to provide (*E*)-**5.29** almost exclusively.

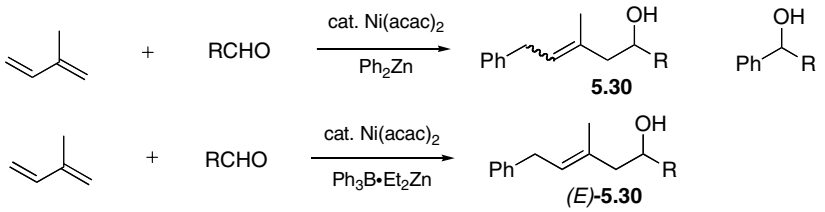
A plausible reaction mechanism is outlined in Scheme 5.23. A 1:1 complex of 1,3-butadiene and an Ni(0) species reacts with an aldehyde activated by coordination to Me_2Zn via a transition state **5.XVI** to give a 1:1:1 coupling product **5.27** (path A), where an intermediate **5.XVII** with a *syn*-η^3-allylnickel(II) structure undergoes reductive elimination to deliver the methyl group to the distal position, so that coordination of the Ni(0) species both to the oxygen of OZn and the *trans*-C=C bonds is better maintained. For less-reactive carbonyl compounds, such as bulky aliphatic aldehydes and ketones, a transition state **5.XVI** is too high in energy to surmount. For such cases, a transition state **5.XVIII** is assumed to be responsible (path B). Despite a smaller equilibrium concentration of a 2:1 complex of



Scheme 5.23. Possible mechanism for the 1:1:1 and 1:2:1 coupling reaction of 1,3-butadiene, Me_2Zn, and carbonyls.

butadiene and an Ni(0) species, the 2:1 complex might have higher nucleophilic reactivity than the 1:1 complex, owing to its higher polarizability.

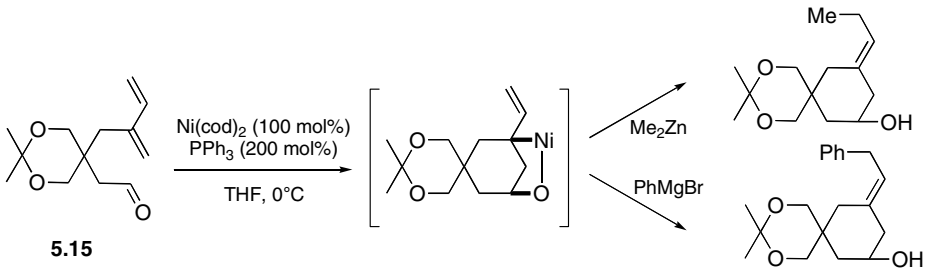
Organozinc compounds with no β-hydrogen atoms accessible can similarly undergo a three-component connection reaction. Ph_2Zn serves as a phenylating agent for the reaction of 1,3-butadiene and aldehydes to provide 5-phenyl-3-pentenols **5.30** (Scheme 5.24). However, Ph_2Zn is more reactive than dialkylzinc, and a side reaction – the phenylation of aldehyde – becomes a serious problem for the reaction with reactive aldehydes. The combination of Ph_3B and Et_2Zn easily circumvents this problem [46]. Moreover, the $Ph_3B{\cdot}Et_2Zn$ reagent shows excellent *E*-selectivity, and (*E*)-3-methyl-5-phenyl-3-pentenols (*E*)-**5.30** are obtained in good yields.



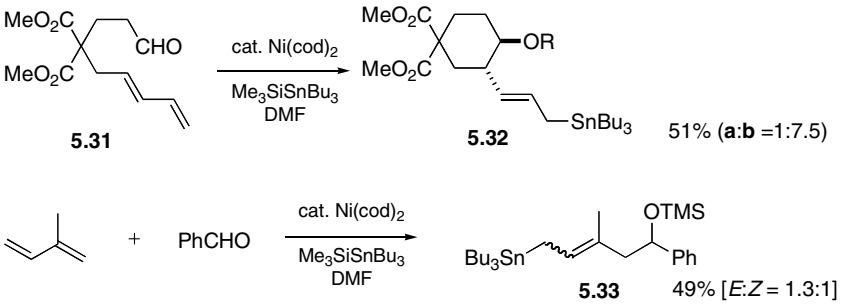
Scheme 5.24. Nickel-catalyzed three-component coupling reaction of isoprene, aldehydes, and a phenyl group of phenylating agents.

Transmetallation of an oxanickellacycle, generated from **5.15** via oxidative cyclization of a stoichiometric $Ni(cod)_2$, with Grignard reagents, followed by reductive elimination, provides three-component coupling products (Scheme 5.25, cf. Scheme 5.17) [47]. Methyl, phenyl, and allyl Grignard reagents are selectively introduced to the distal allylic terminus, while alkynyl Grignard reagents are introduced nonregioselectively at both the distal and proximal allylic termini.

Ni(0)-catalyzed bis-metallic cyclization of an ω-dienyl aldehyde **5.31** with $Me_3SiSnBu_3$ provides a mixture of cyclohexanols *trans*-**5.32a** (R = TMS) and *trans*-**5.32b** (R = H) with high stereoselectivity, having a *trans*-allylstannyl group as the side chain (Scheme 5.26) [48]. A similar reaction proceeds intermolecularly be-



Scheme 5.25. Reaction of Grignard reagents with oxanickellacycle generated from **5.15**.

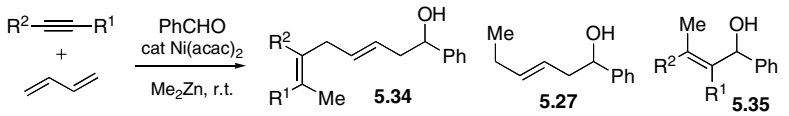


Scheme 5.26. Nickel(0)-catalyzed intra- and intermolecular bis-metallation across dienes and an aldehydes with $Me_3SiSnBu_3$.

tween isoprene and the SiSn reagent, placing the Sn group on the C4 position of isoprene and the Si group on the oxygen of aldehyde. No stereoselectivity with respect to the tri-substituted double bond is observed.

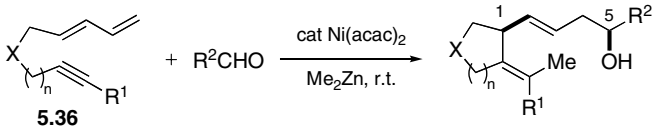
5.2.6
The Multi-component Connection Reaction

In the presence of $Ni(acac)_2$ catalyst, the four components of Me_2Zn, internal alkynes, 1,3-butadiene, and carbonyl compounds combine in this order in a 1:1:1:1 ratio at room temperature to furnish (3*E*,6*Z*)-octadien-1-ols **5.34** with high stereoselectivity and excellent yields (Eq. (5.14)) [49]. The three-component coupling product **5.27** (Eq. (5.12)) and the Montgomery reaction product **5.35** ($R^1 = R^2 =$ Et; see Section 4.6.3) are obtained as minor products. Under similar conditions, conjugated alkynes or electron-deficient alkynes also function well. Unsymmetrically disubstituted alkynes show almost no regioselectivity, despite a large steric and electronic bias between the substituents. As mentioned previously (Eq. (5.12)), the Ni(0)-catalyzed three-component connection reaction of Me_2Zn, 1,3-butadiene, and sterically demanding aldehydes provides 1:2:1 adducts consisting of Me, 1,3-butadiene, and aldehydes, respectively (Scheme 5.23). In contrast, in the present four-component connection reaction, no such 1:2:1 adducts are formed at all. In this context, the selective formation of the 1:1:1:1 adducts – regardless of the kinds of carbonyl compounds – suggests that an alkyne has a strong tendency to prohibit 1:2:1 adduct formation, probably through occupation of one of the two butadiene coordination sites of an intermediate **5.XVIII** (Scheme 5.23) [49].



(5.14)

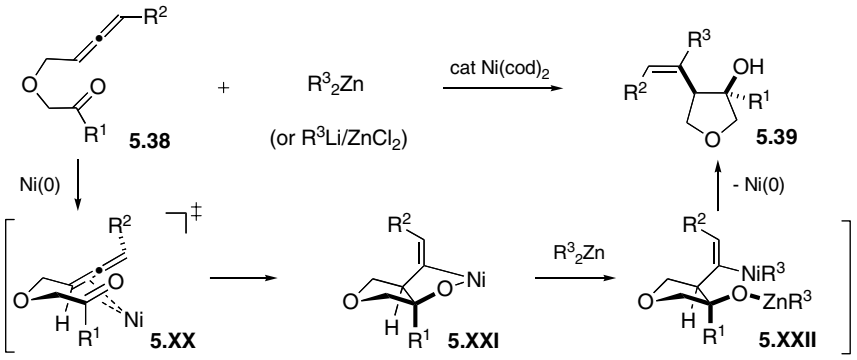
The same reaction conditions are applicable to an intramolecular four-component coupling reaction. In the presence of a catalytic amount of $Ni(acac)_2$, the conjugate addition of Me_2Zn and carbonyl compounds across 1,ω-dienynes **5.36** occurs at the terminal positions of the alkyne and the diene moieties, respectively, with through-space interaction of the alkyne and the diene groups ensuring C–C coupling at the internal positions (Eq. (5.15)) [50]. It is worth mentioning that, under these conditions the Ni(0)-mediated intramolecular Diels–Alder reaction of 1,ω-dienynes does not proceed at all (see Section 6.4.4). Terminal alkynes provide the cyclization products **5.37** ($R^1 = H$) in moderate yields, whereas internal alkynes give the products **5.37** in good to excellent yields. The most interesting aspect of the present reaction is the high remote 1,5-diastereoselectivity, giving rise to the 1,5-*syn*-isomers, either exclusively or selectively (> 10:1). The reaction is also stereoselective with respect to the exocyclic double bonds as shown in **5.37** (100% selectivity in all cases).



(5.15)

5.2.7
Cyclization of Allenyl Aldehydes

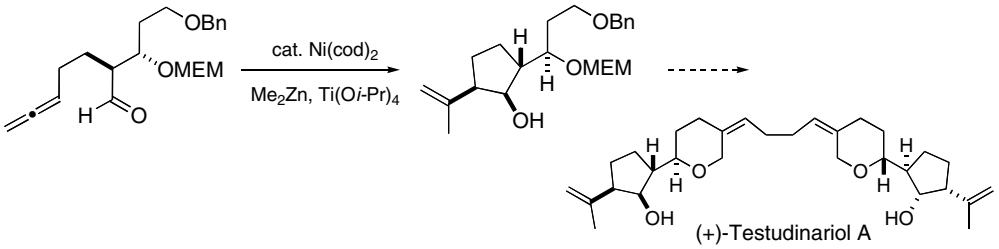
At almost the same time, Montgomery and Kang reported that ω-allenyl aldehydes and ketones **5.38** undergo cyclization to provide *cis*-2-vinylcyclopentanols **5.39** with excellent stereoselectivity when exposed to a catalytic amount of $Ni(cod)_2$ and organozincs (Scheme 5.27) [52, 53]. Both terminal **5.38** ($R^2 = H$) and internal allenes



Scheme 5.27. Nickel(0)-catalyzed stereoselective cyclization of ω-allenyl aldehydes and ketones.

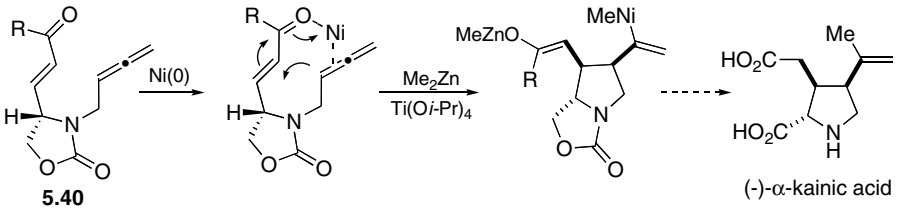
($R^2 \neq H$) enjoy this process, with the latter allowing preparation of the stereochemically defined tri-substituted vinyl substituents.

A plausible reaction mechanism is outlined in Scheme 5.27. Oxidative cyclization of an Ni(0) species across the internal allene double bond and the carbonyl group first takes place to give **5.XXI** via a transition state **5.XX**, where the R^2 points away from the Ni(0)-alkene η^2-bond for steric reasons. Transmetallation with an organozinc reagent forms an intermediate **5.XXII** which, upon reductive elimination affords a zinc alkoxide, an alcoholate of the final product **5.39**. The reductive elimination process is extremely susceptible to ligands. *n*-Bu_3P induces β-hydrogen elimination (when $R^3 = Et$) and **5.39** ($R^3 = H$) forms predominantly along with small amount of **5.39** ($R^3 = Et$). In contrast, ethyl group transfer takes place selectively in the absence of a phosphine ligand. Analogous Ni-catalyzed cyclization of allenyl aldehyde with Me_2Zn is utilized in preparing the core structure of (+)-testudinariol A, a natural product (Scheme 5.28) [54].



Scheme 5.28. Synthesis of (+)-Testudinariol A via the Ni(0)-catalyzed cyclization of an ω-allenyl aldehyde.

Conjugated enones, such as 2,7,8-trienylnonanal **5.40** (R = H) and -nonanone **5.40** ($R \neq H$), undergo Michael-type oxidative cyclization upon an Ni(0) species across the electron-deficient double bond and the allene double bond. Thus, treatment of *N*-allenyl oxazolidinone **5.40** with $2MeLi/ZnCl_2$ in the presence of $Ni(cod)_2$ and Ti(O-*i*-Pr)$_4$ directly and selectively affords the product with the identical stereochemistry to that of the natural product α-kainic acid (97:3) (Scheme 5.29) [51].

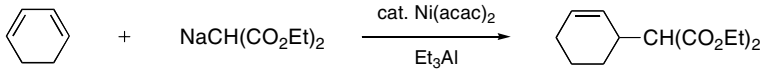


Scheme 5.29. Synthesis of α-kainic acid by the Ni(0)-promoted cyclization of allenyl enones.

5.3
Addition Reaction of HX on Dienes and Allenes

5.3.1
Addition of Active Methylene Compounds to 1,3-Dienes

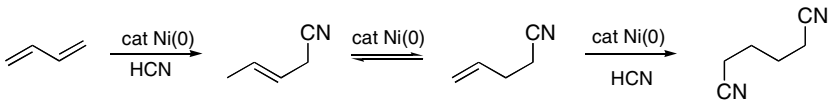
1,3-Cyclohexadiene reacts with diethyl malonate in ethanol containing 50 mol% sodium ethoxide at room temperature using an Ni(0) complex prepared from Ni(II)$(acac)_2$ and Et_3Al (Eq. (5.16)) [55]. The reaction is clean, and a formal 1,4-addition product of active methylene compounds (e.g., diethyl malonate and ethyl acetoacetate) is obtained in quantitative yield. Hydrogen cyanide reacts in a similar way (see Section 5.3.2), but benzenesulfinic acid ($PhSO_2H$) fails to form 2-cyclohexenyl phenyl sulfone. Cyclopentadiene undergoes the addition reaction similarly, albeit with modest or low yields. A proposed reaction mechanism involves: 1) the formation of an H–Ni(II)–X complex; 2) addition of the H–Ni to cyclohexadiene, forming an η^3-cyclohexenylnickel(II) intermediate; and 3) reductive elimination of Ni(II) X with generation of a cyclohexene product with a substituent at the C3 position and an Ni(0) complex.



(5.16)

5.3.2
Hydrocyanation of 1,3-Dienes

The sequence of reactions shown in Scheme 5.30 is the DuPont adiponitrile process that utilizes cheap feed stocks, 1,3-butadiene and hydrogen cyanide. This method was commercialized in 1971 and currently supplies ca. 75% of the world's demand for adiponitrile. The hydrolysis and hydrogenation of adiponitrile provide adipic acid and hexamethylenediamine, respectively, both being the starting monomer for the production of Nylon-6,6. In fact, adipic acid is almost exclusively produced by the more economical cyclohexane oxidation method. Few data have been published with regard to the details of these reactions. The process consists of three discrete steps: 1) Markovnikov addition of hydridonickel(II) cyanide to 1,3-diene yielding 1-cyano-2-butene; 2) isomerization to terminal nitrile, 1-cyano-3-



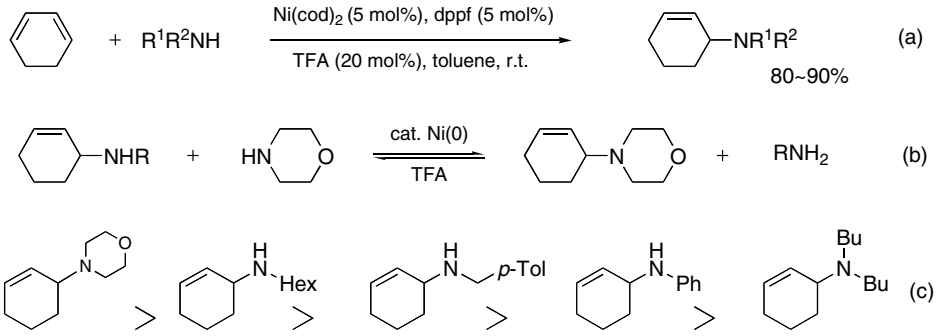
Scheme 5.30. DuPont process for the production of adiponitrile from 1,3-butadiene and HCN catalyzed by an Ni(0) species.

butene; and 3) anti-Markovnikov addition of HCN to the terminal double bond. All of these three steps are promoted in one pot with $Ni[P(OAr)_3]_4$ as catalyst [56]. An Ni–H species may play a central role in these transformations. Markovnikov addition of an Ni–H to 1,3-diene affords η^3-allylnickel(II) cyanide, which undergoes reductive elimination to selectively produce 1-cyano-2-butene. Repeated addition (insertion) and elimination (β-hydrogen elimination) of an Ni–H species isomerizes the internal double bond to the terminal position. The addition of an Ni–H species in anti-Markovnikov fashion forms an intermediate $(N{\equiv}C)Ni^{2+}(CH_2CH_2CH_2CH_2C{\equiv}N)$, which is only reactive enough to undergo reductive elimination to produce adiponitrile with the regeneration of an Ni(0) species (see Sections 3.2 and 9.3).

5.3.3
Hydroamination of 1,3-Dienes and Allenes

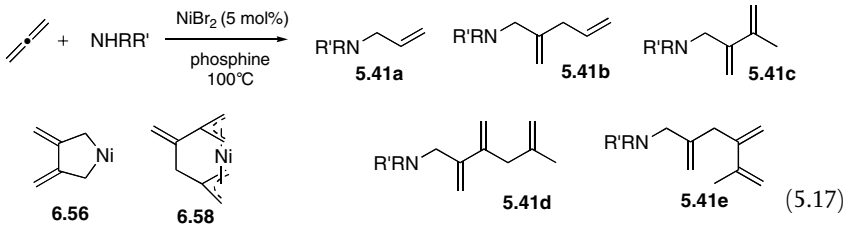
The hydroamination of 1,3-dienes is an efficient route by which to prepare allylic amines, and many transition-metal catalysts have been studied, but with little success. A combination of $Ni(cod)_2$, dppf, and trifluoroacetic acid serves as a highly active catalyst for addition reaction of amines to dienes to form allylic amines (Scheme 5.31(a)) [57].

Primary and secondary aliphatic amines with modest steric bulk all give the 1:1 addition products in good isolated yields. Aromatic amines are reluctant to react at room temperature or even at elevated temperatures (60 °C). The addition reaction of aromatic amines is promoted nicely by a Pd(0) species [58]. The Ni(0) catalyst also promotes the substitution of aliphatic primary or secondary amines for the amines of allyl amines (Scheme 5.31(b)). The substitution proceeds so effectively that the relative thermodynamic stability among 3-aminocyclohexenes can be determined based on the composition at equilibrium (Scheme 5.31(c)). 3-Morpholinocyclohexene is approximately 10-fold more stable than 3-(*N*,*N*-dibutylamino)cyclo-



Scheme 5.31. (a) Nickel-catalyzed hydroamination of cyclic dienes; (b) the substitution reaction of allylamines with the other primary or secondary amines; and (c) the relative thermodynamic stability of 3-aminocyclohexenes.

hexene; the relative stability depends mainly on steric factors, with only minimal effect due to electronic factors.

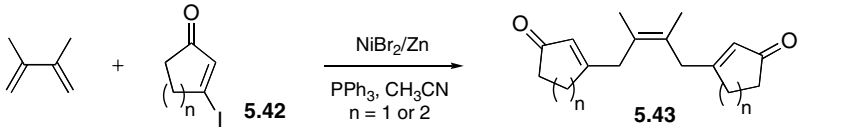


(5.17)

In the presence of $NiBr_2$ (5 mol%) and a phosphine ligand, allene reacts with amines to provide **5.41d** as a major product which consists of three molecules of allene and one molecule of amine (Eq. (5.17)) [59]. Thus, when a mixture of allene (150 mmol), morpholine (50 mmol), and $NiBr_2$ (1 mmol), and phenyl(di-isopropoxy)phosphine in ethanol is heated in a sealed tube at 100 °C for 1 h, a mixture of **5.41a** (trace), **5.41b** (1%), **5.41c** (22%), **5.41d** (72%), and **5.41e** (5%) is obtained. Apparently, the major isomer **5.41d** is derived from an intermediate **6.58** by nucleophilic attack of an amine at the η^3-allylnickel(II) moiety, cross-conjugated with methylene (see Section 6.5.1). **5.41e** is the product formed by nucleophilic attack of an amine at the other η^3-allylnickel(II) center of **6.58**. The second major product, **5.41c**, is derived from an intermediate **6.56** in a similar manner.

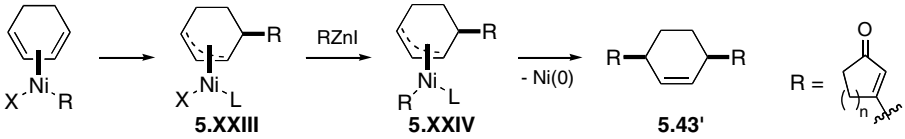
5.3.4
1,4-Dialkenylation of 1,3-Dienes

Treatment of 2,3-dimethyl-1,3-butadiene with β-iodocyclopentenone or β-iodocyclohexenone **5.42** ($n = 1$ or 2) in the presence of zinc powder and a catalytic amount of nickel bromide and triphenylphosphine at 80 °C provides diketones **5.43** (Eq. (5.18)) [60]. Cyclohexadiene displays similar reactivity and provides 1,4-*cis*-disubstituted 2-cyclohexene exclusively.



(5.18)

The reaction may proceed as follows (Scheme 5.32). An Ni(0) species, generated by reduction with Zn(0), undergoes oxidative addition upon the C–I bond of **5.42**.



Scheme 5.32. Reaction mechanism for the Ni-catalyzed dialkylation of conjugated dienes.

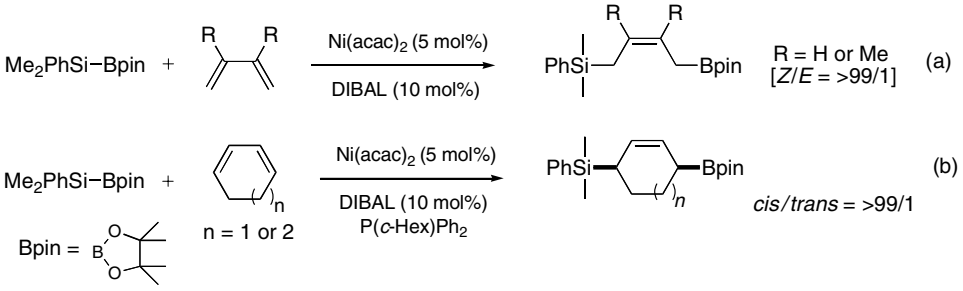
1,3-Cyclohexadiene undergoes insertion into the cycloalkenylnickel(II) iodide thus formed to provide an η^3-allylnickel(II) iodide complex **5.XXIII** bearing the Ni(II) atom and the cycloalkenyl group on the same face of the cyclohexane ring (cis insertion). Cycloalkenylzinc iodide, generated in situ by zincation of **5.42**, undergoes transmetallation with **5.XXIII** to yield an intermediate **5.XXIV**, which undergoes reductive elimination with retention of configuration to provide 1,4-*cis*-disubstituted 3-cyclohexene.

In order for this reaction to proceed successfully, the oxidative addition of an Ni(0) upon **5.42** must proceed much faster than the oxidative addition of a Zn(0) on **5.42**. The latter process must also be much slower than the generation of **5.XXIII**, otherwise the Kumada–Tamao cross coupling (homo-coupling in this case) would result. In fact, very slow zincation of **5.42** is independently confirmed under the identical conditions shown in Eq. (5.18).

The reaction pattern of the present symmetric 1,4-dialkenylation is reminiscent of the symmetrical 1,4-acetoxylation of cyclic dienes catalyzed by Pd(II) salt [61]. The present reaction does not involve redox, but the latter is accompanied by the oxidation of cyclohexadiene.

5.3.5
Addition of Si–B and Csp^2–B compounds on 1,3-Dienes

The silicon–boron bond of (dimethylphenylsilyl)pinacolborane is cleaved into the Si and B fragments which add stereoselectively to acyclic 1,3-dienes in 1,4-fashion to produce (*Z*)-4-boryl-1-silyl-2-alkene as a single isomer in the presence of an Ni(0) species generated by reduction of $Ni(acac)_2$ with DIBAL (Scheme 5.33(a)) [62, 63].

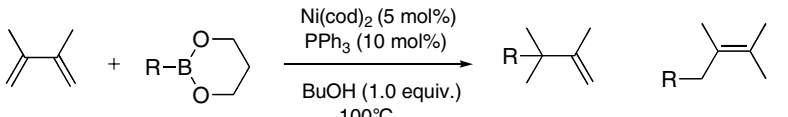


Scheme 5.33. Nickel(0)-catalyzed silaboration of conjugated dienes.

Silaboration of cyclic 1,3-dienes does not proceed under the above conditions; rather, a sterically congested ligand, cyclohexyl(diphenyl)phosphine, effects the 1,4-addition. With this ligand *cis*-4-boryl-1-silyl-2-cycloalkenes are obtained in high yield with excellent stereoselectivity (Scheme 5.33(b)). Although the silaboration of 1,3-dienes is also catalyzed by a Pt complex, the adducts are usually obtained as

a 1:1 mixture of *Z*- and *E*-isomers [64]. The products possess both allylsilane and allylborane moieties, which could be utilized for the diastereoselective allylation of aldehydes.

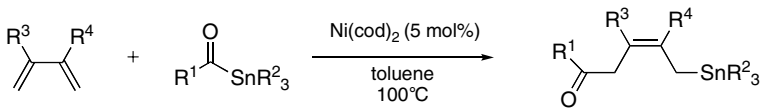
The aryl and alkenyl groups of aryl- and alkenylboronates are transferred to 1,3-dienes in the presence of a catalytic amount of $Ni(cod)_2$ and a stoichiometric amount of a proton source (Eq. (5.19)) [65]. Thus, hydroarylation of 1,3-dienes takes place to give a mixture of 1,2- and 1,4-addition products when 5 mol% of $Ni(cod)_2$, 10 mol% triphenylphosphine, 1 equiv. of 2-(*p*-tolyl)-1,3-dioxa-2-borinane, and 1 equiv. butanol are heated at 100 °C in 1,4-dioxane. A proton source such as an alcohol, aniline, or water, in one equivalent, is essential; otherwise no reaction proceeds at all. The use of more acidic proton sources (e.g., acetic acid, phenol) or less acidic proton donors (e.g., aliphatic amines) suppress the yields.



(5.19)

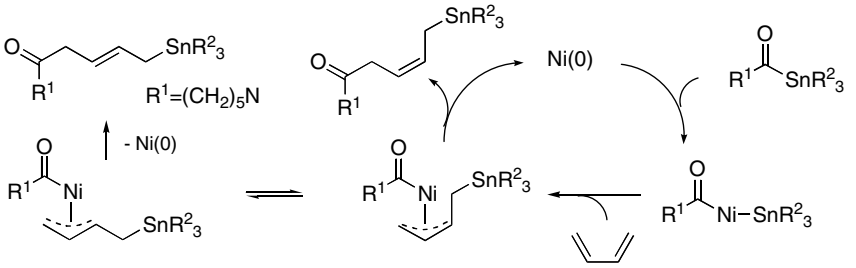
5.3.6
Carbostannylation of 1,3-Dienes and Allenes

With Ni(0) complexes the C–Sn bonds of aromatic and aliphatic acylstannanes are cleaved into the acyl and stannyl fragments, which add to 1,3-dienes in a 1,4-manner to provide (*Z*)-5-trialkylstannyl-3-penten-1-one with excellent stereoselectivity (Eq. (5.20)) [66]. Carbamoylstannanes ($R_3SnCONR_2$) are exceptional, and provide (*E*)-isomers as the major product. The reaction is applicable to a variety of 2-substituted and 2,3-disubstituted 1,3-dienes, but not to 1-substituted ones. The regioselectivity for the reaction of unsymmetrical 1,3-dienes is low and at best 1:2. Toluene is the solvent of choice; polar solvents (e.g., DMF, THF) cause decarbonylation of an acylnickel(II) intermediate. The products are assembled with a latent nucleophile (allylstannane) and an electrophile (carbonyl), and may be useful as synthetic intermediates.



(5.20)

A plausible catalytic cycle, which starts with oxidative addition of an Ni(0) complex upon the Sn–CO bond is outlined in Scheme 5.34. An *s-cis*-1,3-diene inserts into the Sn–Ni bond of the acylstannylnickel(II) intermediate and provides a *syn*-η^3-allyl(acyl)nickel(II) intermediate, which via reductive elimination leads to the final product with regeneration of a catalytically active Ni(0) species. The stereo-

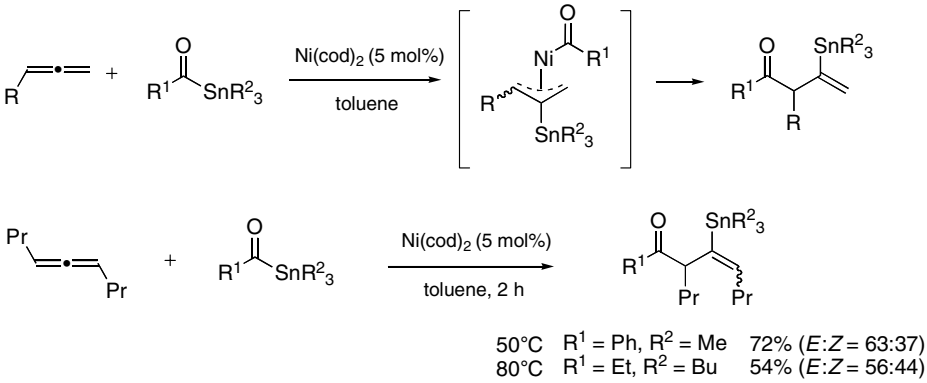


Scheme 5.34. The catalytic cycle for the Ni(0)-catalyzed acylstannylation of conjugated 1,3-dienes.

chemical outcome depends on the type of the R^1 of acylstannane. While benzoylstannanes ($R^1 = Ph$) afford the *Z* isomers exclusively, carbamoylstannanes ($R^1 = NR_2$) give the *E* isomers as the major products. The carbamoyl group appears to be sluggish when undergoing reductive elimination, and an equilibrium between the *syn* and *anti*-η^3-allyl(acyl)nickel(II) intermediates in favor of the former may precede the reductive elimination.

Under conditions similar to those used for the acylstannylation of 1,3-dienes, a variety of alkyl, aryl, and methoxyallenes undergoes 1,2-acylstannylation with aromatic and aliphatic acylstannanes, selectively placing the acyl group on the most substituted allylic terminus (Scheme 5.35) [67]. The reason for this is not clear, but this is in contrast to the regioselectivity observed for reductive elimination in Scheme 5.34, where reductive elimination selectively proceeds at the least-substituted allylic terminus.

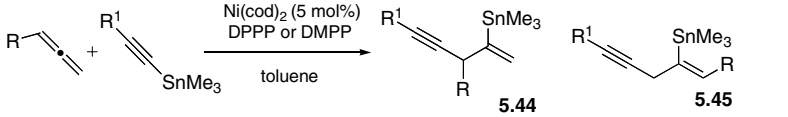
This method is useful for the preparation of terminal alkenes geminally substituted by stannyl and alkyl groups, as this class of alkenylstannane compounds is difficult to prepare using other methods (e.g., carbostannylation of alkynes; see Section 4.5.3). 1,1-Disubstituted allenes show the same regioselectivity as mono-



Scheme 5.35. Nickel(0)-catalyzed acylstannylation of terminal and internal allenes.

substituted allenes. Symmetric internal allenes show no stereoselectivity and provide mixtures of *E* and *Z* isomers in a ratio of ca. 1:1.

The C*sp*–Sn bond of alkynylstannanes, encompassing arylethynyl- and silylethynylstannanes, is also subject to oxidative addition upon an Ni(0) complex. An ethynyl(stannyl)nickel(II) intermediate undergoes 1,2-addition to allenes (parent, mono-, 1,1-disubstituted allenes) in a way similar to that shown in Scheme 5.35 (Eq. (5.21)) [68, 69]. A bidentate phosphine ligand is not only essential to bring the reaction to completion, but also plays an important role in determining the regioselectivity of the reductive elimination step. DPPP (1,3-bis(diphenylphosphino)-propane) promotes reductive elimination at the most substituted allylic terminus (giving **5.44**), while DMPP (1,3-bis(dimethylphosphino)propane) at the least-substituted allylic terminus (giving **5.45**).

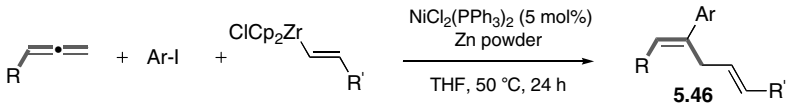


DPPP 50°C R = H, R^1 = TMS 91%
DMPP 30°C R = *n*-Bu, R^1 = Ph 82% (1:2)

(5.21)

5.3.7
Carbozirconation of Allenes

The highly regio- and stereoselective assembly of allenes, aryl iodides (and vinyl iodides), and alkenylzirconiums is carried out by nickel catalysts. The treatment of a substituted allene with an aryl iodide and an alkenylzirconium reagent in the presence of $NiCl_2(PPh_3)_2$ and zinc powder in THF at 50 °C leads to a three-component connection product **5.46** in moderate to good yields with high *E* selectivity [70]. In Eq. (5.22), thick bonds are used to simplify following the allene carbons. The reaction is highly regioselective, and delivers the aryl group to the allene central carbon and the alkenyl group of zirconium reagent to the unsubstituted terminal carbon. The reaction tolerates a variety of functional groups such as acetyl, methoxy, and ethoxycarbonyl groups on the aromatic ring of aryl iodides, and is successfully extended to some vinyl iodides. Selection of the Ni catalyst is crucial, as the halides on the nickel complex show a profound effect on the yield. $Ni(cod)_2$ is totally inactive.



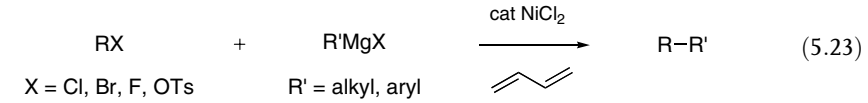
R = Cy, Ar = 4-$PhCO_2Et$, R' = *n*-Pr 81% (*E*/*Z* = 99/1)
R = Ph, Ar = 4-PhOMe, R' = Ph 65% (*E*/*Z* = 98/2)

(5.22)

5.3.8

Wurtz-type Coupling Reaction of Organic Halides and Grignard Reagents Mediated by the Butadiene–Nickel complex (5.1)

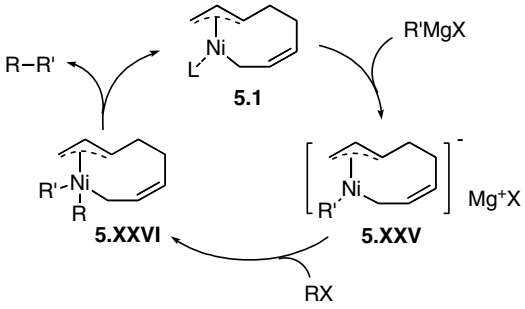
The Ni-catalyzed cross-coupling reactions of Grignard reagents with aryl and alkenyl halides (the Kumada–Tamao Coupling; see Section 1.7.4, Scheme 1.21) is among the most useful methods for C–C bond formation. This method, however, is not applicable to alkyl halides because an alkylnickel(II) halide intermediate readily undergoes facile β-hydrogen elimination. The alkyl-alkyl cross-coupling reaction is one of the most simple but challenging subjects to be addressed, even in modern organic chemistry. $NiCl_2$ promotes the cross-coupling reaction of primary alkyl chlorides, bromides, tosylates [71], and even fluorides [72] with alkyl Grignard reagents in the presence of butadiene as an additive (Eq. (5.23)). The reaction is limited to primary alkyl halides, and is not applicable to either secondary or tertiary alkyl halides.



(5.23)

The reaction of *n*-decyl bromide with 1.3 equiv. *n*-butylmagnesium chloride in the presence of 1 mol% of $NiCl_2$ and 10 mol% 1,3-butadiene (0.07 *M* in THF) at 0 °C affords the coupling product tetradecane, quantitatively. This is the first successful example of a cross-coupling reaction for primary alkyl chlorides. In the absence of butadiene, a trace amount of tetradecane is obtained, and mostly decane and decene are formed. *n*-Decyl bromide does not undergo oxidative addition upon an Ni(0) species in THF containing 1,3-butadiene without a Grignard reagent, and remains intact.

A proposed reaction pathway is depicted in Scheme 5.36. A nickel(II) complex **5.1** reacts with the Grignard reagent to form an ate complex of nickel **5.XXV**, which is nucleophilically active enough to undergo an S_N2 reaction with an alkyl halide to



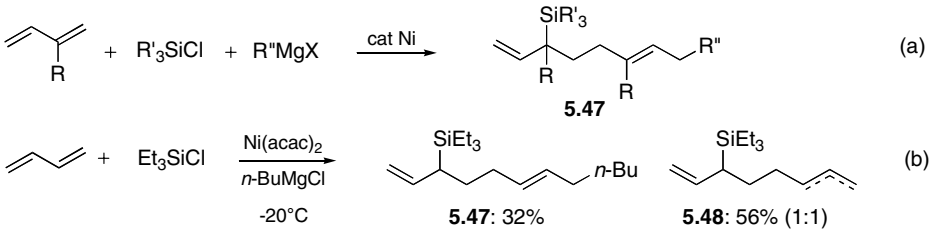
Scheme 5.36. Proposed reaction pathway for the cross-coupling reaction of Grignard reagents with primary alkyl halides promoted by **5.1**.

provide an intermediate **5.XXVI**. The intermediate **5.XXVI** must be very high in energy and unstable, because the formal oxidation number of the nickel is 4+ (see Section 1.5, compound **1.19**), and hence readily undergoes reductive elimination to provide the cross-coupling product R–R′, with regeneration of **5.1**.

The relative reactivity of C9–C11 alkyl halides (RX; X = F, Cl, Br) is in the order of chloride < fluoride < bromide, which is determined by competitive experiments using *n*-$C_5H_{11}MgBr$. The higher reactivity of fluoride than chloride is inconsistent with the above-mentioned simple S_N2 reaction mechanism, but some as yet unresolved factors might be responsible for this variation.

5.3.9
Carbosilylation of Diene Dimers

An Ni(0) complex catalyzes the dimerization–carbosilylation of 1,3-dienes in the presence of trialkylsilyl chlorides and Grignard reagents to give rise to 1,6-dienes **5.47** with high regio- and stereoselectivity (Scheme 5.37(a)) [73]. When a catalytic amount of $Ni(acac)_2$ is mixed with a solution of isoprene, a trialkylsilyl chloride, and cyclohexylmagnesium in THF at −20 °C, the trialkylsilane and cyclohexyl groups are introduced at the C3 and C8 positions of (*E*)-3,6-dimethyl-1,5-octadiene (Scheme 5.37(a), R = Me, R″ = Cy). The reaction of the primary alkyl Grignard reagent and 1,3-butadiene produces a mixture of **5.47** and **5.48** (a mixture of terminal and internal olefins) (Scheme 5.37(b)).



Scheme 5.37. Nickel(0)-catalyzed dimerization–carbosilylation of 1,3-dienes with trialkylsilyl chlorides and Grignard reagents.

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6
Cyclooligomerization and Cycloisomerization of Alkenes and Alkynes

Shinichi Saito

Nickel-catalyzed cyclooligomerization and cycloisomerization reactions of alkenes and alkynes form the cornerstones of organic transition metal chemistry (Reppe, in the 1940s; see Section 6.3.1), and so far these have been among the main subjects studied extensively. In this chapter, nickel-catalyzed cyclooligomerization and cycloisomerization reactions will be described, as will certain nickel-mediated (stoichiometric) reactions, which are closely related to the catalytic reactions. Emphasis is placed on recent developments in nickel chemistry, as earlier studies have been repeatedly reviewed from several viewpoints [1–10]. Cyclization and cycloaddition reactions which involve the addition of other substrates (e.g., hydrosilanes, hydrostannanes and disilanes) will be described in other appropriate chapters in this monograph.

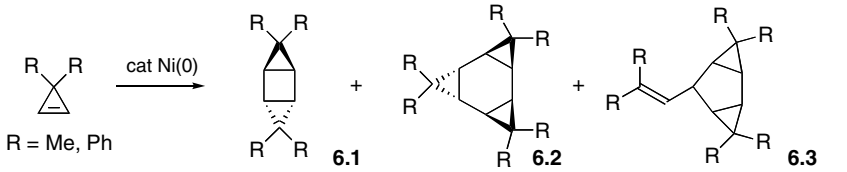
6.1
Cyclooligomerization of Alkenes

In nickel-catalyzed cyclooligomerization reactions of alkenes, strained compounds such as cyclopropenes, methylenecyclopropanes, and norbornadiene are normally used as the reactive substrates. The reactions may involve either the cleavage of the weakened carbon–carbon π bond – as is the case for many cyclooligomerization and cycloisomerization reactions – or the cleavage of the strained carbon–carbon σ bond, which is followed by the formation of new carbon–carbon σ bonds. Unstrained alkenes usually produce linear oligomers in the presence of nickel catalysts (see Chapter 3).

Cyclopropenes are highly strained carbocyclic compounds. For example, the calculated strain energy of cyclopropene is 228 KJ mol^{-1} (54.5 Kcal mol^{-1}) [10]. Accordingly, cyclopropenes are prone to undergo cyclooligomerization in the presence of a Ni catalyst. As an example, 3,3-dimethylcyclopropene provides cyclodimerization and cyclotrimerization products (Eq. (6.1)) [11a, b]. A generally accepted mechanism for this reaction is shown in Scheme 6.1, where the Ni(0) complex interacts with the π bond of the cyclopropene molecule and forms a Ni(0)-η^2-olefin

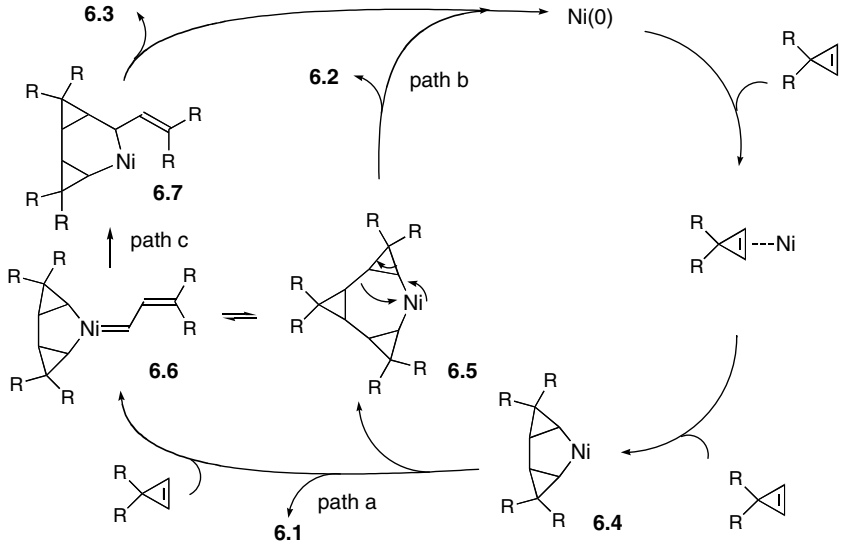
Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6



(6.1)

complex. This complex reacts with another cyclopropene and gives a nickellacyclopentane **6.4**. The cyclobutane derivative **6.1** is formed by the reductive elimination of **6.4** with the regeneration of a Ni(0) species (path a). The seven-membered nickellacycle **6.5** is formed by the insertion of another cyclopropene and undergoes reductive elimination to give rise to **6.2** (path b). The carbene complex **6.6**, which may be formed either directly by the reaction of **6.4** with cyclopropene or stepwise by the isomerization of **6.5**, as indicated by curved arrows (the α- and β-C elimination; see Section 1.7.6), further undergoes insertion of the carbene carbon into the Ni–C(α) bond to give a six-membered metallacycle **6.7**. Reductive elimination of **6.7** finally furnishes a vinylcyclopentane **6.3** (path c).



Scheme 6.1. The catalytic cycle for the nickel-catalyzed cyclooligomerization of cyclopropenes.

Bipyridyl complexes **6.8** [12] and **6.9** [13] (Fig. 6.1) of close structural similarity to the intermediates proposed in Scheme 6.1 are isolated, and their structures are determined spectroscopically and by X-ray structural analyses. Palladium complexes also catalyze the cyclooligomerization of cyclopropenes [1a, 11d–f].

Cyclopropenones are more strained compounds than cyclopropenes, but gain stability owing to the aromatic nature (a 2π electron Hückel compound) and form

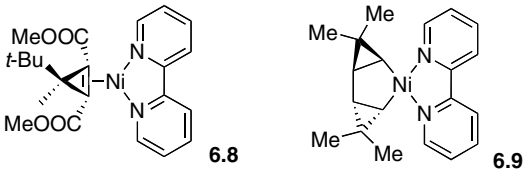
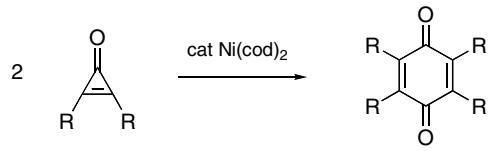


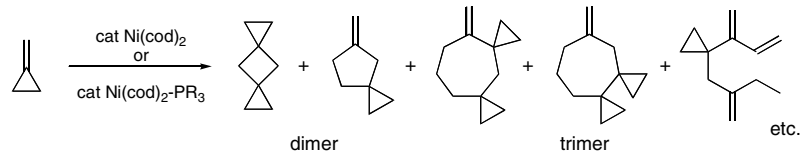
Fig. 6.1. The analogues of reactive intermediates proposed in Scheme 6.1. The structures are determined using X-ray analyses.

an electron-deficient double bond. They display completely different reactivity from cyclopropenes, and selectively undergo cleavage of the σ-bond to give the cyclodimerization products, benzoquinones, in modest yields (Eq. (6.2)) [14].

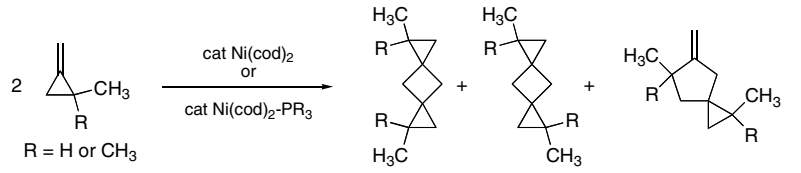


(6.2)

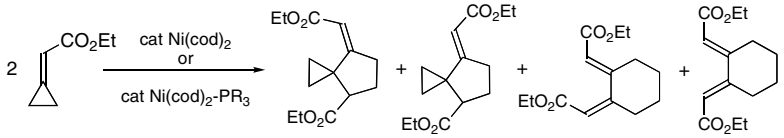
While a large number of cycloaddition reactions of methylenecyclopropanes has been reported [15], the number of the cyclooligomerization reactions is relatively small. The parent methylenecyclopropane (strain energy = 175 KJ mol^{-1} (41.7 Kcal mol^{-1}) [10]) undergoes dimerization, trimerization (cyclic and acyclic), and higher oligomerization (Eq. (6.3)) [16]. The ratio of the dimers, trimers, and oligomers depends on the ligands bound to the Ni(0) [16a]. The reactions of substituted methylenecyclopropanes are rather selective, and cyclic dimers are obtained (Eq. (6.4)) [15]. Methylenecyclopropanes bearing an ethoxy carbonyl group on the exocyclic double bond are characteristic for an electron-deficient double bond, and the cyclodimerization products are produced selectively (Eq. (6.5)) [17], where cleavage of the strained σ bond and a facile cyclopropenyl-butenyl rearrangement [16d] are observed.



(6.3)

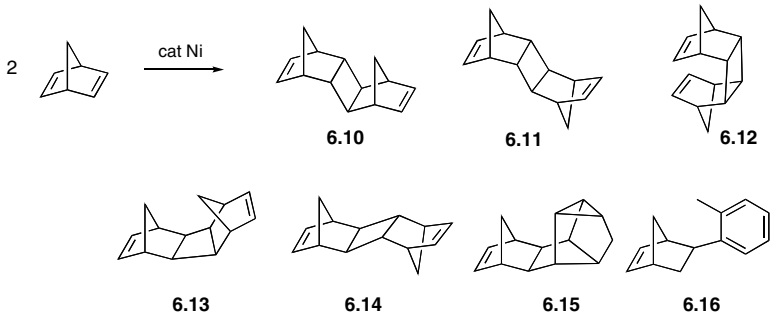


(6.4)



(6.5)

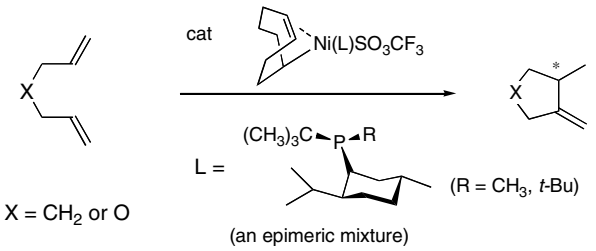
The cyclodimerization of norbornadiene is catalyzed by many transition metals, including nickel. While only a couple of examples have appeared for the linear dimerization of norbornene [18], the nickel-catalyzed cyclooligomerization of norbornadiene and related compounds has been studied extensively. As shown in Eq. (6.6), there are several possible structures for the dimers. While the *exo-trans-endo* dimer **6.10**, *endo-trans-endo* dimer **6.11**, and *exo-trans-exo* dimer **6.14** are the major products in many reactions, the ratio of the products depends heavily on the type of catalysts used [19–21]. The dimer **6.10** is formed as the major isomer together with **6.11** in a ratio of 3:1 in a 41% combined isolated yield when the reaction is carried out in the presence of $Ni(CO)_4$ [19d], whilst selective formation of **6.14** is observed when the reaction is carried out in the presence of $NiBr_2$–Zn [18b] or metallic Ni [21a]. Occasionally, an unusual dimerization–aromatization product **6.16** is formed [20]. The trimerization of norbornadiene has also been reported [21].



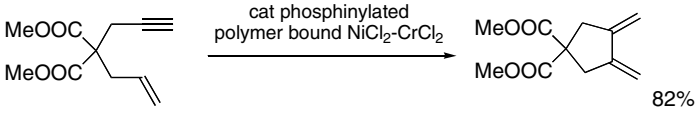
(6.6)

6.2 Cycloisomerization of Alkenes

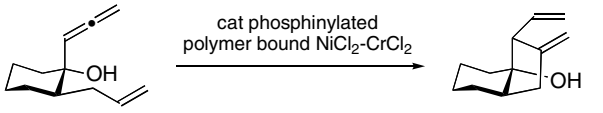
A few examples have been reported of the nickel-catalyzed cycloisomerization of nonconjugated dienes and related compounds [22]. Some 1,5- and 1,6-dienes undergo cycloisomerization in the presence of cationic nickel catalysts (Eq. (6.7)) [22a]. The cycloisomerization of 6-hepten-1-yne [22b] and 1,2,7-octatriene [22c] also proceeds smoothly in the presence of a catalytic amount of $NiCl_2$ (Eqs. (6.8) and (6.9)). In these reactions, sequential reactions take place: 1) addition of a nickel hydride to the most unsaturated carbon–carbon multiple bond; 2) insertion of the terminal alkene into the nickel-C bond thus formed; and 3) β-hydrogen elimination with regeneration of the nickel hydride. Chromium(II) chloride serves as a one-electron reducing agent.



(6.7)



(6.8)



(6.9)

6.3 Cyclooligomerization of Alkynes

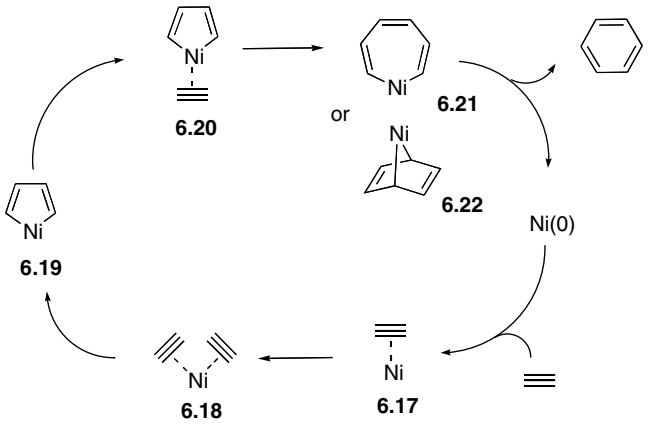
The cyclooligomerization of alkynes is catalyzed by a variety of transition metals such as Ni, Co, Pd, and Rh. The first nickel-catalyzed trimerization and tetramerization of acetylene yielding benzene and cyclooctatetraene, respectively – which marks also the first example of a transition metal-catalyzed cyclooligomerization of alkynes – was reported in 1948 by Reppe and co-workers [23]. Since then, a vast number of examples has appeared related to this subject [1, 3, 5, 24–28].

6.3.1 Cyclotrimerization of Alkynes

The cyclotrimerization of alkynes which leads to the formation of benzene rings is generally catalyzed by the Ni(0) coordinated with electron-donating ligands such as organophosphorous compounds [1, 23c, 30–32]. Cyclooctatetraenes tend to form when the Ni(0) complexes with weakly coordinating ligands are used (see Section 6.3.4). A generally accepted mechanism for cyclotrimerization is shown in Scheme 6.2.

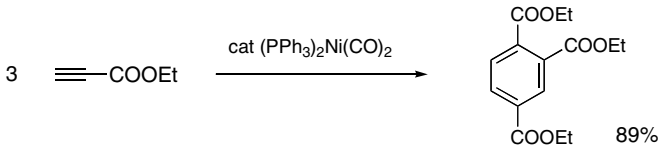
Nickellacyclopentadiene **6.19**, which is formed by the coordination of two alkyne molecules with a Ni(0) species and oxidative cyclization, is a key intermediate in this reaction. Some complexes with structural similarity to **6.19** have been isolated and characterized chemically and spectroscopically [29].

In many reactions, of the possible two regioisomers (1,3,5- and 1,2,4-trisubstituted benzenes), the unsymmetrically substituted benzenes are formed as the major products when terminal alkynes are employed [30–32]. The reaction of

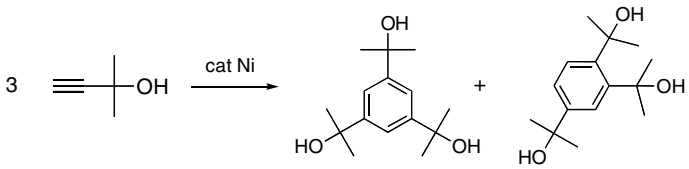


Scheme 6.2. The catalytic cycle for the nickel-catalyzed cyclotrimerization of acetylene, yielding benzene.

ethyl propiolate in the presence of $(PPh_3)_2Ni(CO)_2$ selectively provides 1,2,4-tris-(ethoxycarbonyl)benzene (Eq. (6.10)) [32a]. The reaction of sterically hindered propargyl alcohols and their derivatives are exceptional, and they selectively provide both the symmetric and unsymmetric benzenes depending on the type of nickel catalysts used (Eq. (6.11)). For example, 1,3,5-tris(1-hydroxy-1-methylethyl)benzene is formed selectively in excellent yield when 2-methylbut-3-yn-2-ol is reacted in the presence of $(n\text{-}Bu_3P)_2NiBr_2$ [31b]. The selectivity is high, but the yield is not acceptable with $(PPh_3)_2Ni(CO)_2$ as the catalyst [31d]. The reaction becomes less selective when $(n\text{-}Bu_3P)_2Ni[C{\equiv}CC(CH_3)_2OH]_2$ is used as the catalyst [31a]. On the other hand, when $(PPh_3)_2NiI_2$ is used as the catalyst, unsymmetric 1,2,4-tris(1-hydroxy-1-methylethyl)benzene is isolated in high yield [31c].



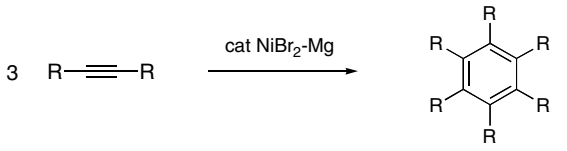
(6.10)



(6.11)

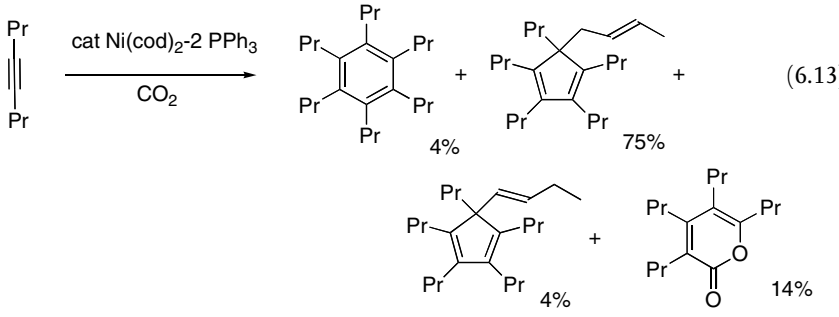
$(n\text{-}Bu_3P)_2NiBr_2$	100	:	0	84%
$(PPh_3)_2Ni(CO)_2$	100	:	0	20%
$(n\text{-}Bu_3P)_2Ni[C{\equiv}CC(CH_3)_2OH]_2$	82	:	18	100%
$(PPh_3)_2NiI_2$	0	:	100	85%

Unsymmetrical internal alkynes provide benzenes as a mixture of all possible regioisomers. When symmetric internal alkynes are employed, it is not necessary to worry about the regioselectivity, and many examples have been reported [32g–i]. For example, hexaethylbenzene forms by the reaction of 3-hexyne in the presence of $NiBr_2$–Mg (Eq. (6.12)) [32h]. The two reactions shown in Eqs. (6.12) and (6.13) are in marked contrast. The latter reaction is accelerated under a CO_2 atmosphere and forms cyclopentadiene as the major product of the cyclotrimerization of 4-octyne [33].



(6.12)

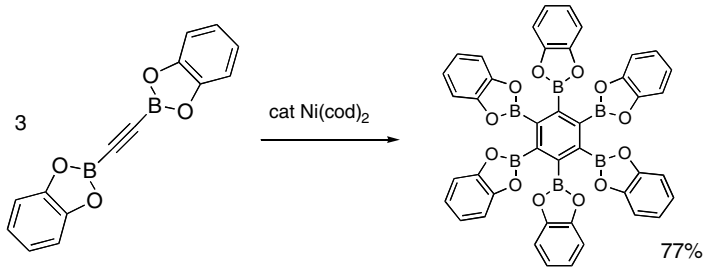
R = Et (97%), R = Me (35%), R = Me_3SiOCH_2(95%)



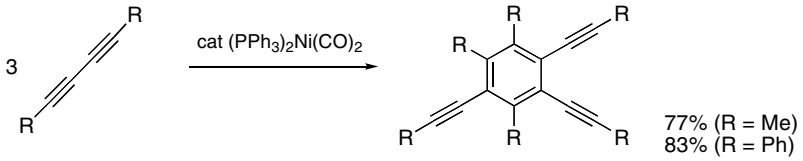
(6.13)

Recent interest in this area has been related to the development of a new and recyclable catalyst such as the silica-immobilized catalyst [30h,i], and an application of the reaction to the synthesis of functionalized polysubstituted benzenes. As an example, the synthesis of hexaborylbenzene is shown in Eq. (6.14) [32i].

Some conjugated alkynes such as 1,3-diynes (Eq. (6.15)) [32c] and 1,3-enynes [30g] react similarly, and the corresponding 1,2,4-trisubstituted benzenes are isolated in good yields in the presence of a nickel catalyst.



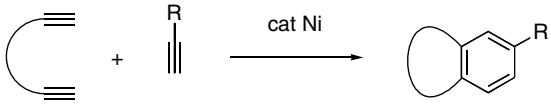
(6.14)



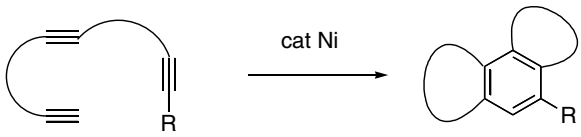
(6.15)

6.3.2
Co-cyclotrimerization and Cycloisomerization of Alkynes

Active studies have been carried out in the field of co-cyclotrimerization – the synthesis of benzene rings from different alkyne components – because this type of reaction is synthetically more useful and can be more selective compared to the (homo)cyclotrimerization discussed in Section 6.3.1. Various approaches have been examined in order to achieve the regio- and chemoselective synthesis of substituted benzenes. For example, tethering the two or three alkyne units is a viable approach (Eqs. (6.16) and (6.17)). This approach has been proved to be very effective for Co- [26–28] and Rh catalyzed reactions [27, 28].

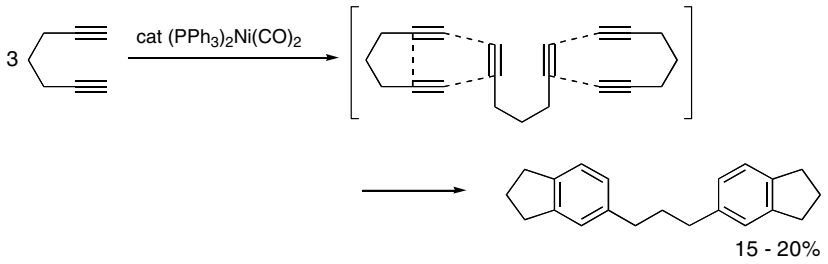


(6.16)

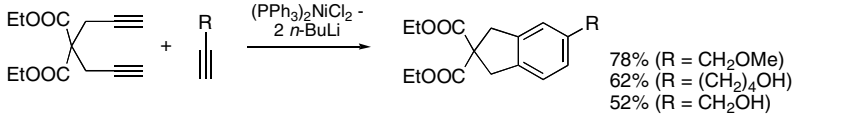


(6.17)

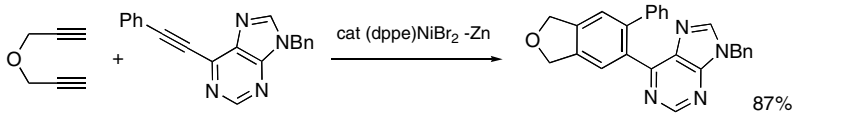
The nickel-catalyzed co-cyclotrimerization reaction was first reported by Colthup and co-workers. Their aim was the polymerization of a 1,6-heptadiyne by nickel catalysis, but the product obtained was a low molecular-weight material, 1,3-bis(7-indanyl)propane (albeit in low yield), the product of so-called "co-cyclotrimerization" (Eq. (6.18)) [34a]. Subsequently, the wide applicability of co-cyclotrimerization methodology was exemplified by the synthesis of indanes (Eq. (6.19)) [34f,g], biaryls [34j], arylalkynes [34l], 6-arylpurines (Eq. (6.20)) [34m], various heterocyclic compounds [34c,d,h,i], and benzoquinones from *o*-di(alkynylacyl)benzene and alkynes (Eq. (6.21)) [34b]. Equation (6.22) demonstrates a useful application of the asymmetric synthesis of isoindoline and isoquinoline derivatives [34h].



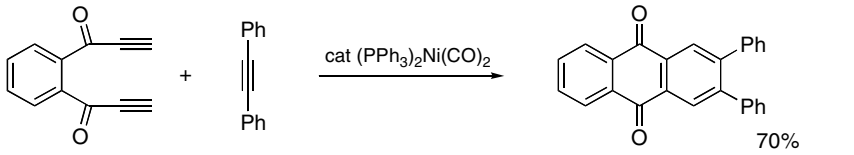
(6.18)



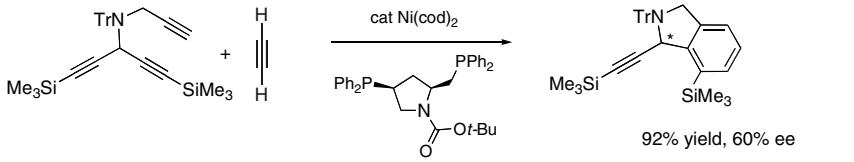
(6.19)



(6.20)

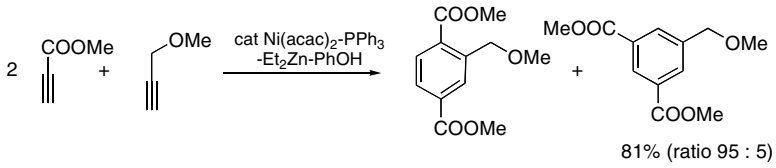


(6.21)



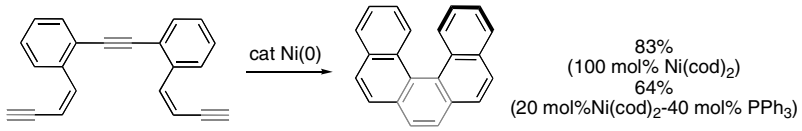
(6.22)

As expected, the intermolecular co-cyclotrimerization of more than two different types of alkynes produces a mixture of many isomeric benzenes [34e]. Provided that the two or three alkynes had different steric and/or electronic natures from each other, the selective co-cyclotrimerization could be realized under carefully controlled conditions. Indeed, the co-cyclotrimerization of methyl propiolate and methyl propargyl ether provides a single isomer in a remarkable yield (Eq. (6.23)) [34k].



(6.23)

While the cycloisomerization of triyne has been most successfully achieved using Co catalysts [26], Ni(0) can also be a good catalyst [35]. For example, helicenes are prepared by the nickel-catalyzed (or nickel-mediated) reaction (Eq. (6.24)) [35b]. In Eq. (6.24), the benzene ring formed is shown in gray. An enantioselective synthesis of a helicene has also been reported [35a].

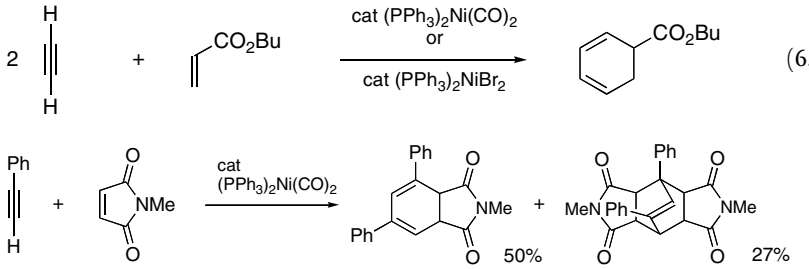


(6.24)

6.3.3
Co-cyclotrimerization of Alkynes with other Unsaturated Compounds

The incorporation of an alkene as the third component widens the scope of co-cyclotrimerization. The co-cyclotrimerization of alkynes and other unsaturated hydrocarbons was first reported by Reppe and co-workers [23c], wherein the nickel-catalyzed reaction of acetylene with acrylates provided co-cyclotrimerization products in the ratio of 2:1 (e.g., Eq. (6.25)). These authors also reported formation of the 1:2 and 1:1:1 co-cycloadducts of acetylene, butyl acrylate, and butyl vinyl ether. Similarly, the reaction of phenylacetylene and *N*-methylmaleimide provides dihydrophthalimide and its Diels–Alder adduct in a good combined isolated yield (Eq. (6.26)) [36a].

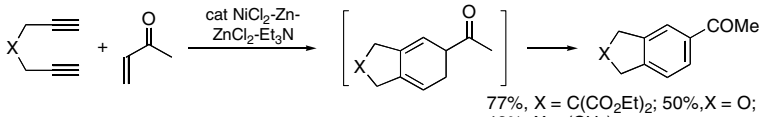
The bimetallic system, Ni–Zn [36e,j] or Ni–Al [36d,h,k], opens a new approach, which relies on a mechanism which is different from that outlined in Scheme 6.2.



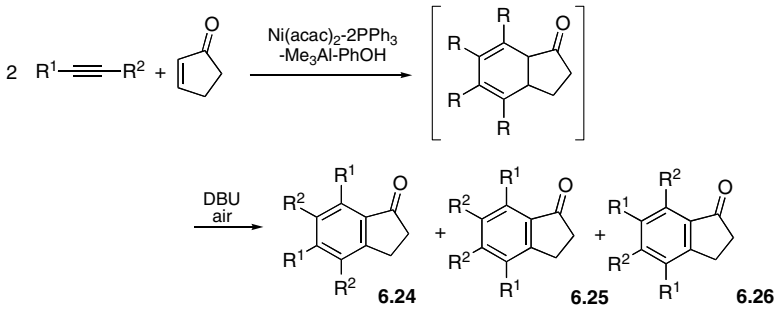
(6.25)

(6.26)

In these bimetallic systems, a $Zn(II)X_2$ salt (or an $Al(III)X_3$ salt) produced by reduction of a nickel(II) species may serve as a Lewis acid, which interacts with enones to promote first the oxidative cyclization of a Ni(0) species across an alkyne and an enone (Eqs. (6.27)–(6.29)). The primary product is cyclohexadiene, which undergoes dehydrogenation spontaneously under air or in the presence of a base (DBU = 1,8-diazabicyclo[5.4.0]-7-undecene) [36e]. The reaction of cyclopentenone and terminal alkynes shows marked regioselectivity, depending on the steric size of the alkyne substituents; when it is small, the isomer **6.24** is dominant, but isomer **6.25** forms exclusively when the substituent is large [36d,h].



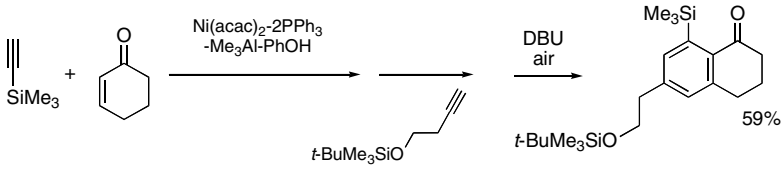
(6.27)



R^1	R^2	Total yield [%]	Ratio [**6.24 : 6.25 : 6.26**]
Et	Et	60	- : - : -
n-Bu	H	71	82 : 14 : 4
t-$BuMe_2SiOCH_2$	H	42	>99 : 0 : 0
t-$BuMe_2SiO(CH_2)_2$	H	81	93 : 7 : 0
t-Bu	H	45	11 : 89 : 0
Me_3Si	H	33	0 : >99 : 0

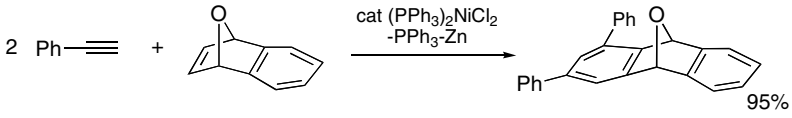
(6.28)

The success of the 1:1:1 co-cycloaddition of three different components (two different alkynes and enones) by sequential addition of different alkynes is not only a great advancement in this field but also supports the intervention of nickellacyclopentene as an intermediate (Eq. (6.29)) [36h].

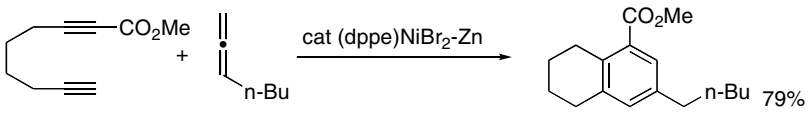


(6.29)

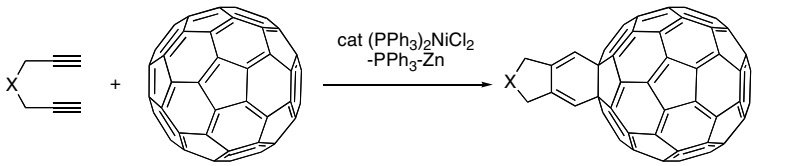
Under similar bimetallic conditions, the co-cyclotrimerization of oxa-benzonorbornadiene (Eq. (6.30)) [36f,l], an allene (Eq. (6.31)) [36m,n], and a fullerene (Eq. (6.32)) [36g] proceeds successfully.



(6.30)

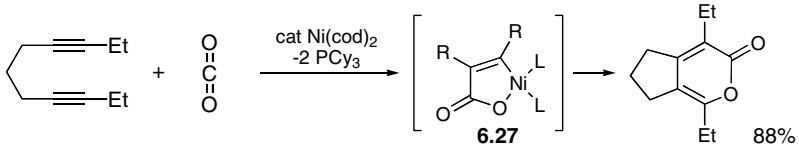


(6.31)

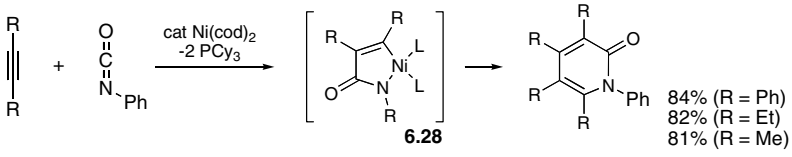


(6.32)

Heterocumulenes such as carbon dioxide [33, 37] and isocyanates [36b,c, 38] are good substrates for the co-cyclotrimerization reactions. For example, the reaction of 1.6-diynes with carbon dioxide proceeds smoothly in the presence of $Ni(cod)_2$ and PCy_3 (Eq. (6.33)) [33f]. Under the same catalytic system, a variety of alkynes reacts with phenyl isocyanate to give pyridones (Eq. (6.34)) [38a]. Metallic heterocycles such as **6.27** [33d,g] and **6.28** [36b] are assumed to be the intermediates of these reactions. The reaction is applicable to the synthesis of a variety of polymers [36c, 37, 38b].



(6.33)

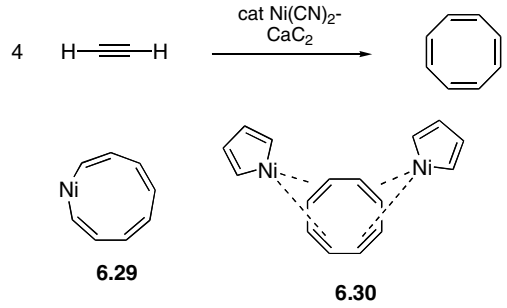


(6.34)

6.3.4
Cyclotetramerization of Alkynes

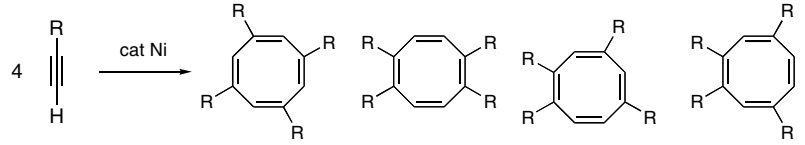
The cyclotetramerization of alkynes yielding cyclooctatetraene is one of the most remarkable reactions which can be efficiently achieved by transition-metal catalysts. The nickel-catalyzed reaction was first reported as early as in 1948 (Eq. (6.35)) [23a]. A mixture of $Ni(CN)_2$ and CaC_2 catalyzes the reaction, though the precise mechanism of the reaction is not clear. It is reasonable to postulate a nickellacyclononatetraene **6.29** [23a] as an intermediate (c.f., Scheme 6.2). The bimetallic complex **6.30** is also a possible candidate as an intermediate, and this has been isolated and its structure determined using X-ray analysis [8, 39d]. Experiments with labeled acetylene exclude the formation of a nickel-η^4-cyclobutadiene complex or a nickel-η^6-benzene complex as the intermediate [39e,k].

In contrast to the cyclotrimerization reaction (see Section 6.3.1), the cyclotetramerization proceeds relatively smoothly in the presence of a Ni(0) and weakly coordinating ligands or nitrogen ligands.



6.29 **6.30** (6.35)

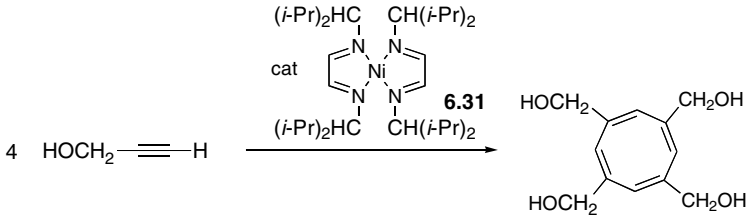
Apparently, the regiochemistry of the cyclotetramerization of (unsymmetrical) terminal alkynes is more complicated than that of the cyclotrimerization; as shown in Eq. (6.36), four isomers rather than two (1,3,5- and 1,2,4-trisubstituted benzenes) are possible [39].



(6.36)

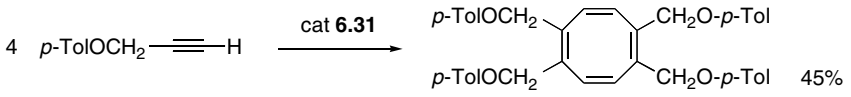
Remarkably, symmetric 1,3,5,7-tetrakis(hydroxymethyl)cyclooctatetraene forms selectively by the reaction of propargyl alcohol in the presence of the nickel catalyst bound with a 1,4-diaza-1,3-diene ligand **6.31** (Eq. (6.37)) [39j]. The same catalyst shows contrasting regioselectivity toward a hydroxy-protected propargyl alcohol, and in this case 1,2,5,6-tetrasubstituted cyclooctatetraene is formed selectively (Eq. (6.38)) [39g].

The 1,4-diazabutadiene ligands shown in Eqs. (6.37)–(6.39) [39h] characteristically possess sterically bulky substituents on the nitrogen atoms, which exert salient steric and electronic effects on the reactivity and regioselectivity.

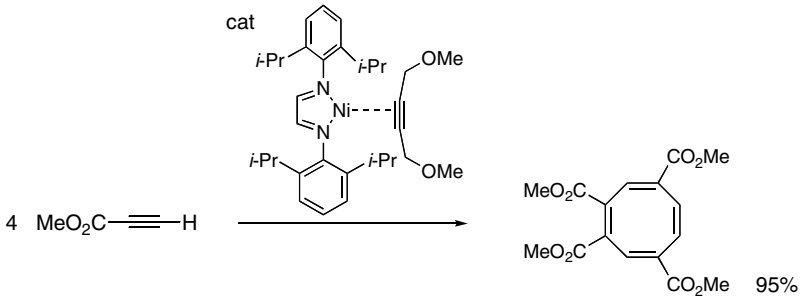


100% (tetramer : trimer = 99 : 1)

(6.37)

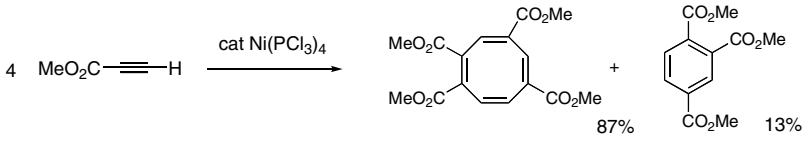


(6.38)



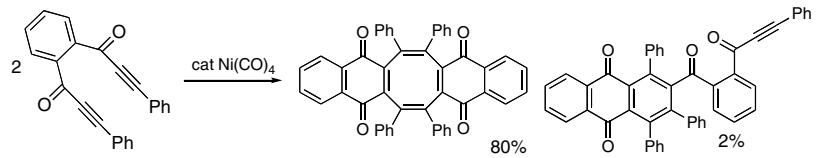
(6.39)

A 1,2,4,6-tetrasubstituted cyclooctatetraene, an unsymmetrically substituted tetraene [39a,l], forms when $Ni(PCl_3)_4$ is used (Eq. (6.40)) [39a]. The yields are based on 66% conversion. Cyclooctatetraenes are also prepared by the dimerization of 1,ω-diynes (e.g., Eq. (6.41)) [39c].



(yields based on 66% conversion)

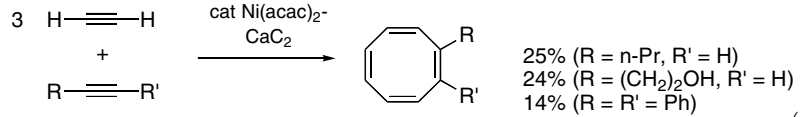
(6.40)



(6.41)

6.3.5
Co-cyclotetramerization of Alkynes

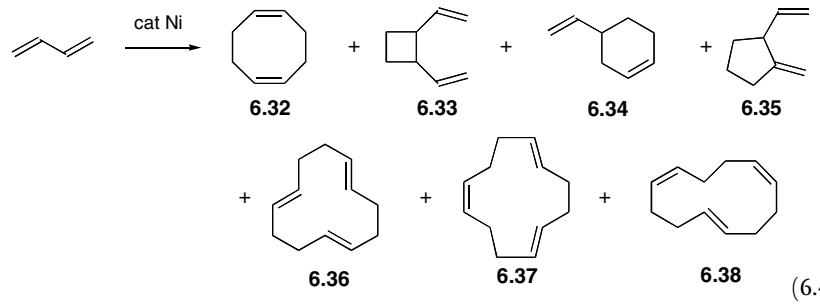
As in the case of the co-cyclotrimerization of alkynes (see Sections 6.3.2 and 6.3.3), the co-cyclotetramerization of two different alkynes also takes place (Eq. (6.42)) [40]. The reaction is usually carried out in the presence of a large excess of acetylene, so that only one molecule of the substituted alkyne is incorporated into the product. Several mono- and disubstituted cyclooctatetraenes may be prepared using this method [40].



(6.42)

6.4
Cyclooligomerization of Dienes

The nickel-catalyzed cyclodimerization and cyclotrimerization of 1,3-butadiene were first reported by Reed in 1954 [41a]. Extensive studies subsequently carried out by Wilke, Heimbach, and co-workers have led to an understanding of the reaction mechanism involved [1–4a, 5, 6, 8, 9, 42, 43]. The formation of cyclic dimers, trimers, and higher oligomers is usually observed (Eq. (6.43)).

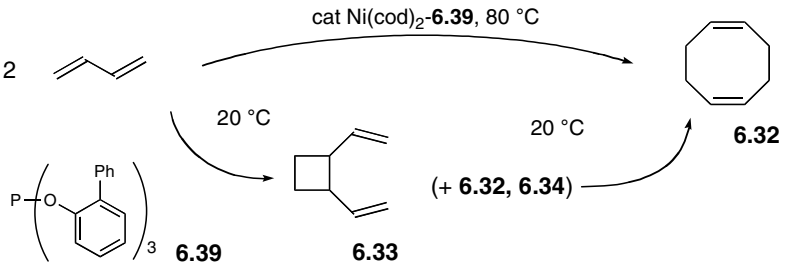


(6.43)

6.4.1 Cyclodimerization and Cyclotrimerization of 1,3-Butadiene

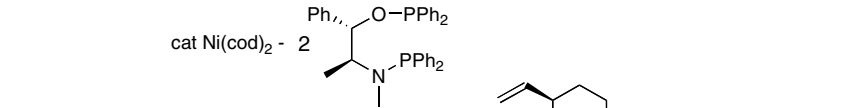
Nickel(0)-phosphine or -phosphite ligands are good catalysts for the cyclodimerization of 1,3-butadiene, and the distribution of the isomers can be controlled by choosing appropriate ligands [41, 44–46]. For example, 1,5-cyclooctadiene (**6.32**, COD) is produced in high yield when the reaction is carried out in the presence of $Ni(cod)_2$ and bulky phosphite ligands such as tris(biphenyl-2-yl)phosphite (**6.39**) at 70–80 °C [41n–p].

1,2-Divinylcyclobutane (**6.33**) is isolated in 30–40% yield when the reaction is carried out at a lower temperature (20 °C) or for a shorter period [41c]. These results suggest that the formation of **6.33** and its rearrangement to **6.32**, proceeds (more or less) under these reaction conditions, and this has been confirmed by an independent experiment using the isolated sample of **6.33** in the presence of a nickel catalyst (Scheme 6.3) [41d,g]. The isomer **6.34** forms selectively in the presence of some chiral aminoalcohol-based phosphine ligands [45a]. Modest chiral induction (up to 21% ee) is observed (Eq. (6.44)) [45].

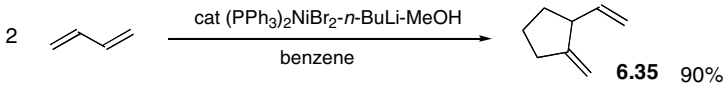


Scheme 6.3. Nickel-catalyzed cyclodimerization of 1,3-butadiene.

Although 2-vinylmethylenecyclopentane (**6.35**) is occasionally formed as a minor product, the selective formation of **6.35** takes place when the reaction is carried out in the presence of methanol (Eq. (6.45)) [46].

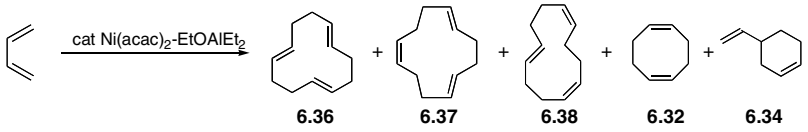


(6.44)



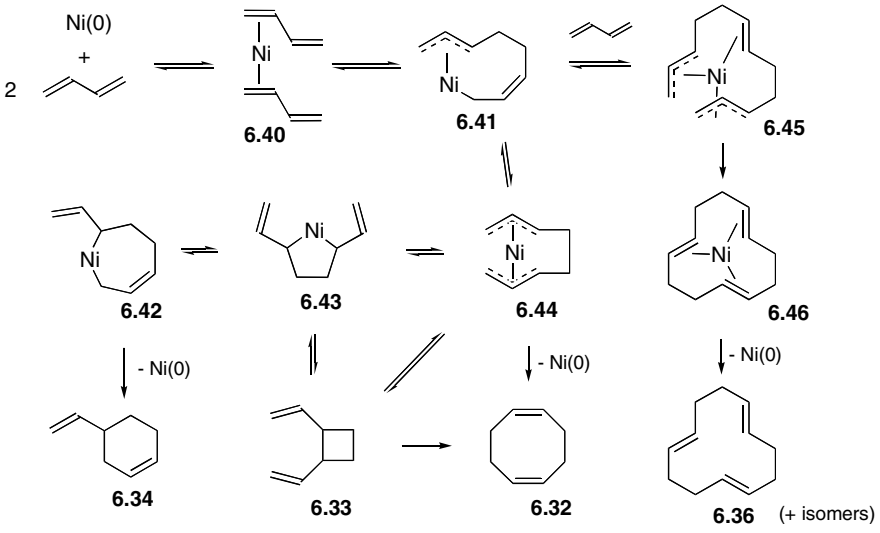
(6.45)

The cyclotrimerization of 1,3-butadiene has also been studied in depth. The selective formation of *trans*, *trans*, *trans*-cyclododecatriene (**6.36**) takes place in the presence of a Ni(0) species generated by reduction of $Ni(acac)_2$ with $Al(OEt)Et_2$ (Eq. (6.46)) [41b,e,h,j]. The effects of the cone angle, the electronic nature of phosphorous compounds, and the ligand:nickel ratio on the selectivities of dimers (**6.32–6.35** and others) and trimers (**6.36–6.38** and others) have been studied extensively [41l,m]. Whilst the cyclodimerization proceeds predominantly in the presence of a Ni(0) species and a phosphine ligand, the cyclotrimerized products are isolated as the major products when the phosphine:nickel ratio is low.



(6.46)

A generally accepted mechanism for the cyclic dimerization and trimerization of 1,3-butadiene is outlined in Scheme 6.4 [1]. Thus, the Ni(0) species interacts with two molecules of butadiene and forms a nickellacycle **6.41** via oxidative cyclization. This complex isomerizes to various nickellacycles such as **6.42–6.44**, and the cyclodimerization products **6.32–6.34** are formed by reductive elimination of the Ni(0) species. Clearly, distribution of the dimers is subject to the ratio of **6.42–6.44**, and the reaction rate of the individual step of the reductive elimination. The insertion

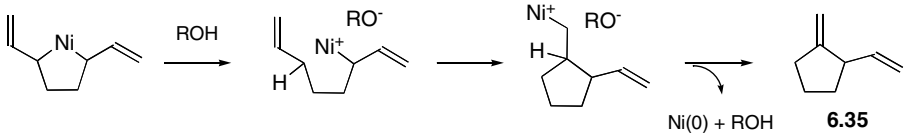


Scheme 6.4. Reaction pathway of the nickel-catalyzed dimerization and trimerization of 1,3-butadiene.

of another butadiene molecule to **6.41** provides **6.45**, which undergoes reductive elimination to give, for example, an all-*trans*-cyclododecatriene-Ni(0) complex **6.46**. Coordination of butadienes to the Ni(0) of **6.46** liberates all-*trans*-cyclododecatriene (**6.36**) and **6.40**. As is the case for the cyclooligomerization of alkynes (see Section 6.3.4), the higher cyclic oligomers (including cyclic trimers) are formed preferentially when weakly coordinating ligands are present in the reaction system.

The proposed mechanism is supported experimentally by the isolation and reaction of various nickel–butadiene intermediates [41g,h,j, 44]. For example, nickellacycles similar to **6.41** are isolated and fully characterized [41g, 44f]. Detailed computational mechanistic study have also been carried out [47].

The formation of **6.35** is rationalized according to Scheme 6.5, which involves protonolysis and exo-mode insertion, followed by β-hydrogen elimination [46].

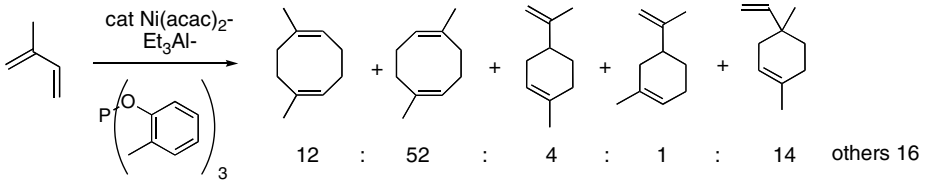


Scheme 6.5. Nickel-catalyzed dimerization of 1,3-butadiene in the presence of a proton source.

6.4.2
Cyclodimerization and Cyclotrimerization of Substituted 1,3-Dienes

Owing mainly to steric reasons, substituted dienes display lower reactivities than the parent 1,3-butadiene. Moreover, the regioselectivity (e.g., head-to-head, head-to-tail, etc.) is another condition that makes the reaction difficult to analyze, and accordingly far fewer studies have been carried out using substituted dienes [1, 48].

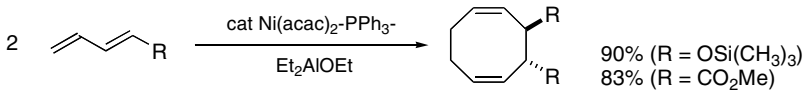
Isoprene reacts in the presence of various nickel catalysts, and usually provides a complex mixture of dimers and trimers [42, 49]. The selectivity can be managed to some extent by choosing an appropriate catalyst (Eq. (6.47)) [49c,e].



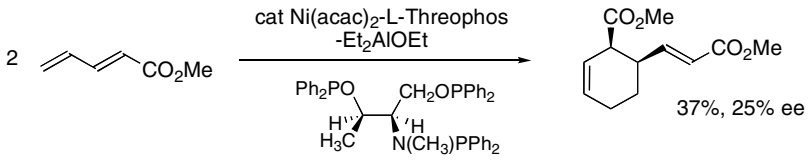
(6.47)

Some sterically or electronically biased 1,3-dienes show unique selectivity [56b,c]. For example, 1-methoxycarbonyl- and 1-siloxy-1,3-dienes provide *trans*-3,4-disubstituted 1,5-cyclooctadienes with high selectivity and in excellent yields when the reactions are carried out under the $Ni(acac)_2$-PPh_3-Et_2AlOEt catalyst (Eq. (6.48)) [50a,d]. By contrast, the same reaction by the catalysis of $Ni(cod)_2$-phosphines

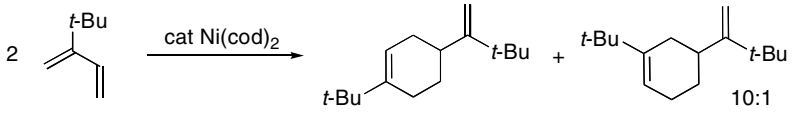
furnishes a mixture of vinylcyclohexenes [50b,c]. Based on these observations, the intermediacy of a Ni-diene-Al(III) complex is proposed [50c]. The enantioselective formation (up to 25% ee) of a vinylcyclohexene derivative is observed for the cyclodimerization of methyl sorbate (Eq. (6.49)) [50f]. The nickel-catalyzed cyclodimerization of 2-*tert*-butyl- and 2-trimethylsilyl-1,3-butadiene provides a mixture of positional isomers of vinylcyclohexene, with 1,4-isomers predominating over the 1,3-isomers (Eq. (6.50)) [50e].



(6.48)



(6.49)

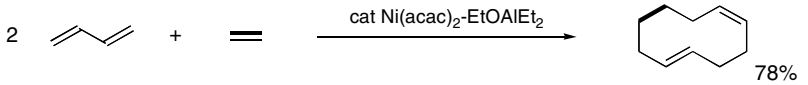


(6.50)

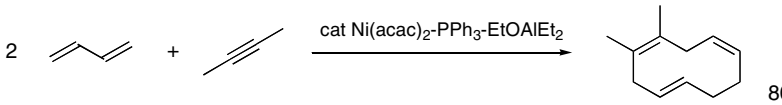
6.4.3
Co-cyclooligomerization of 1,3-Dienes

1,3-Butadiene undergoes co-cyclooligomerization with alkenes [51], alkynes [52], and other conjugated dienes [53] in the presence of nickel catalysts. For the reaction of butadiene with ethylene, 1,5-*cis,trans*-cyclodecadiene is formed (Eq. (6.51)) [51a]. Usually, the cyclooligomerization products of butadiene itself are isolated as the by-products.

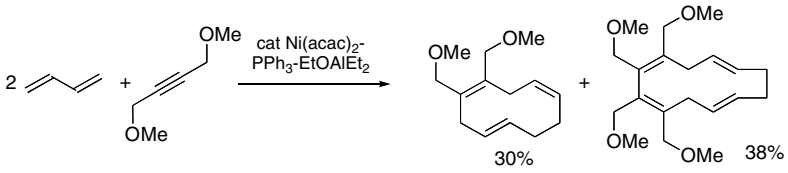
The co-cyclooligomerization of butadiene with alkynes has been studied extensively, and the 2:1 co-cyclization products of butadiene and alkynes form as the major products. For example, as is shown in Eq. (6.52), 2-butyne reacts with butadiene in a 1:2 ratio to provide *trans,cis,cis*-1,4,7-cyclodecatriene in high yield under appro-



(6.51)



(6.52)

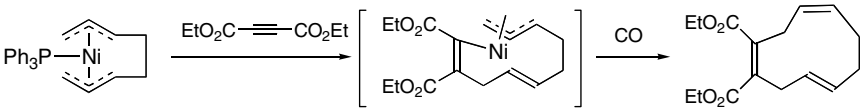


(6.53)

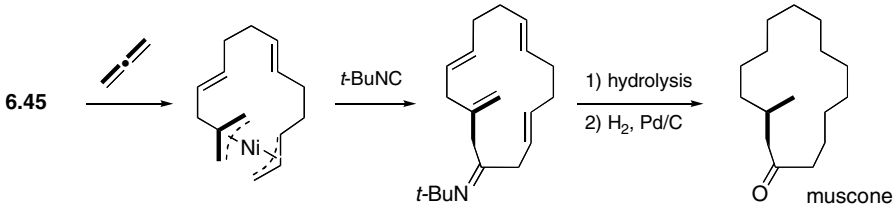
priate reaction conditions [52]. This reaction has been applied to the synthesis of macrocyclic compounds [52b,f]. The 2:2 co-cyclization product is produced occasionally in addition to the 1:2 adduct (Eq. (6.53)) [52c,g].

1,3-Cyclohexadiene skeleton is formed from 1 mol butadiene and 2 mol phenylacetylene [52c]. Substituted cyclooctadiene and cyclohexene derivatives are the major products for the co-cyclooligomerization of 1,3-butadiene with substituted dienes [53]. The co-oligomerization of azadienes has also been investigated [54].

Some stoichiometric reactions with respect to the Ni(0) species have been reported. Thus, the isolated sample of bis-η^3-allyl nickel complex is subjected to the reaction with allene (1,2-propadiene) [55a] and substituted alkynes (Scheme 6.6) [55b]. In Scheme 6.6, the vinyl(allyl)nickel(II) intermediate formed by the insertion of diethyl acetylenedicarboxylate is reluctant to undergo reductive elimination, and carbon monoxide is used to accelerate this process (see Section 1.7.4). The complex **6.45** also reacts with alkynes [55c–e] and allene [55e–g]. The reaction of **6.45** with 1,2-propadiene is shown in Scheme 6.7. One of the two η^3-allylnickel moieties



Scheme 6.6. The stoichiometric reaction of the bis-η^3-allyl nickel complex and an alkyne. CO induces the reductive elimination (cyclization).

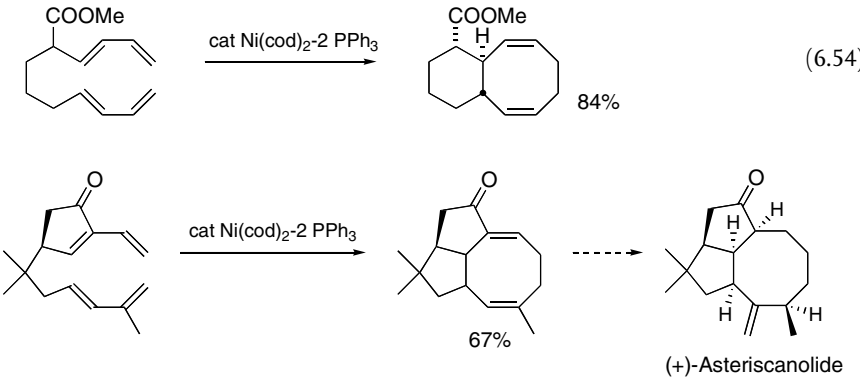


Scheme 6.7. Nickel-promoted (stoichiometric) synthesis of muscone (a thick line indicates the carbons originated from allene).

reacts with allene and forms a stable bis(η^3-allyl)nickel species, which undergoes migratory insertion into an isonitrile and reductive elimination to give rise to a 15-membered cyclic imine. Hydrolysis and hydrogenation provide muscone, the odorous principle of musk [55f,g].

6.4.4 Co-cycloisomerization of 1,3-Dienes

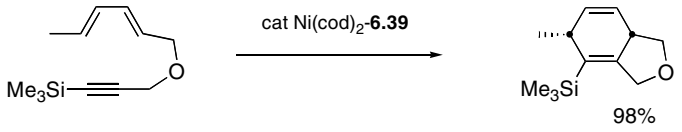
As is the case for other cyclooligomerization and co-cyclooligomerization reactions, the selective formation of carbocyclic compounds is accomplished by means of a nickel-catalyzed intramolecular co-cycloisomerization of dienes [56, 57]. For example, the thermally forbidden nickel-catalyzed intramolecular [4+4] cycloaddition of dienes is effected by the Ni(0) complex (Eq. (6.54)) [56a]. This reaction is applied to the synthesis of a polycyclic natural product, asteriscanolide (Scheme 6.8) [56d], with the origin of stereoselectivity being addressed by computational calculation [56g].



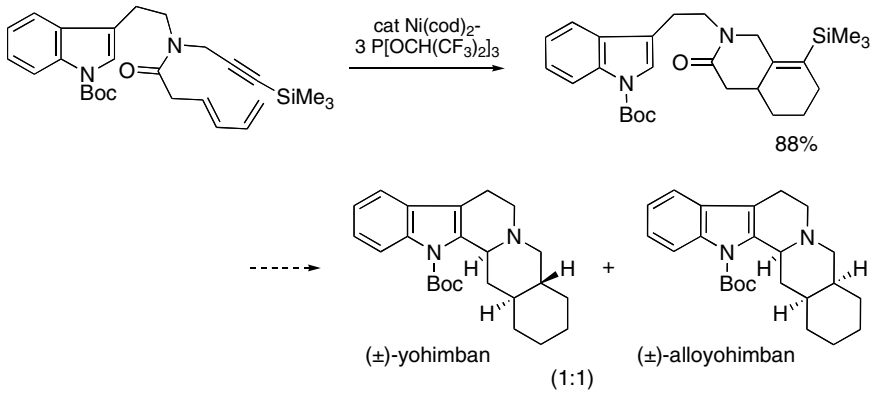
(6.54)

Scheme 6.8. Nickel-catalyzed co-cycloisomerization of 1,3-dienes and its application to the total synthesis of (+)-asteriscanolide.

The intramolecular [4+2] cycloaddition of ω-dienynes [57] is a thermally permitted process and proceeds at elevated temperatures (e.g., 180–200 °C). The reaction is accelerated by a Ni(0) complex and proceeds smoothly at room temperature to provide a cyclohexadiene skeleton in good yield (Eq. (6.55)) [57]. The reaction has been widely applied to the synthesis of natural products, such as steroids and vitamin D analogues [57b,d] as well as alkaloids including (±)-yohimban and (±)-alloyohimban (Scheme 6.9) [57c].



(6.55)



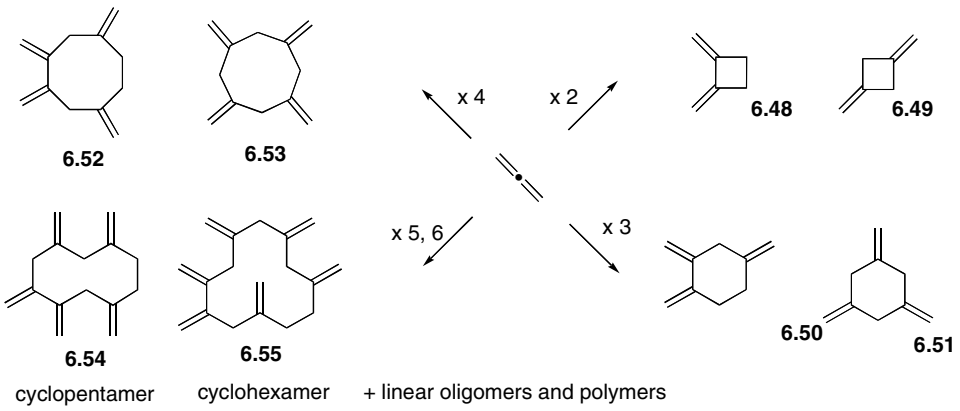
Scheme 6.9. Synthesis of yohimban alkaloids by the nickel-catalyzed intramolecular [4+2]cycloaddition of 1,ω-dieneyne.

6.5
Cyclooligomerization of Allenes and Cumulenes

6.5.1
Cyclooligomerization of Allene (1,2-Propadiene)

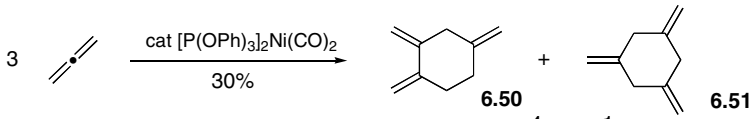
The nickel-catalyzed cyclooligomerization of allene is rather complicated, and a mixture of cyclization products is formed composed of dimers, trimers, and tetramers, etc. (Scheme 6.10) [58].

Whilst the dimers **6.48** and **6.49** have been formed only minimally [58c], the trimers **6.50** and **6.51** are formed as major products by the catalysis of a nickel(0) complex (Eq. (6.56)) [58a,c,f,h]. The tetramers **6.52** and **6.53** are prepared in moderate yields when a nickel–phosphine complex is used as the catalyst [58d,f,h]. A high selectivity is achieved at a higher nickel:phosphine ratio. $Ni(cod)_2$ (Eq. (6.57))

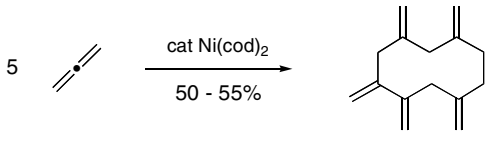


Scheme 6.10. Nickel-catalyzed cyclooligomerization of 1,2-propadiene (allene).

[58b,h], $[P(OPh)_3]_2Ni(CO)_2$ [58c], and $Ni(PPh_3)_2$ [58d] catalyze the formation of the pentamer **6.54**.



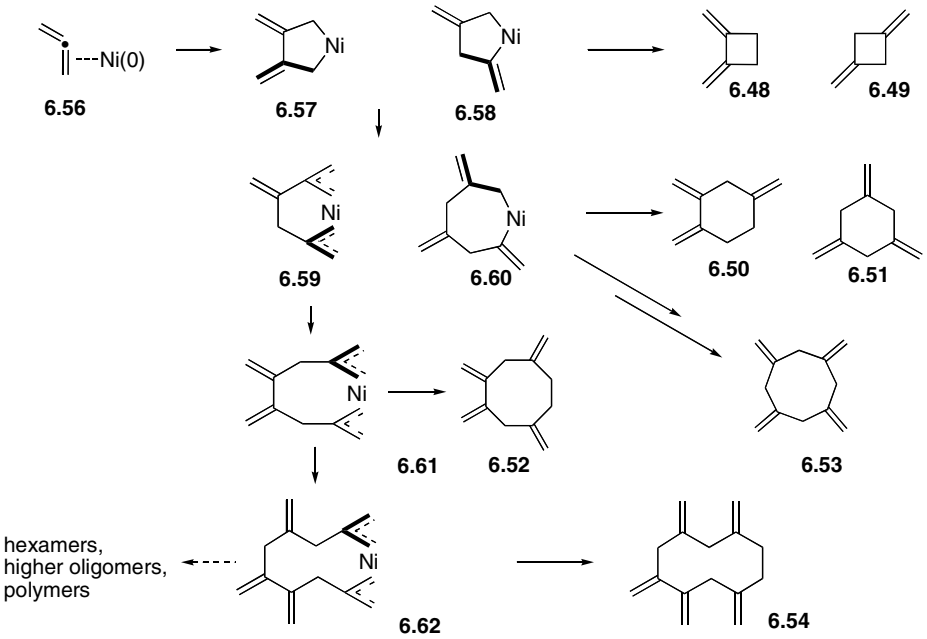
(6.56)



(6.57)

The generally accepted reaction pathway is shown in Scheme 6.11, which is supported by the isolation of some intermediates. In this scheme, for the reader's convenience, the newly introduced allene molecule at any stage is indicated as a thick line. The ligands are omitted for clarity, but as usual the course of the reaction is controlled by the steric and electronic nature of the ligands bound to the nickel.

Allene coordinates with a Ni(0) species and forms complexes such as **6.56** [58d,i], **6.57**, and **6.58**. The structure of **6.57** has been determined using X-ray analysis [58j]. The third molecule of allene inserts into the allyl-nickel bond of **6.57** and

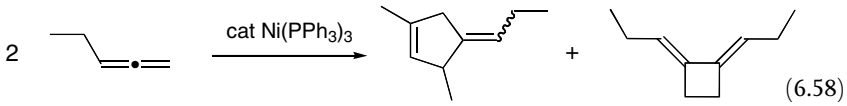


Scheme 6.11. Reaction mechanism for the nickel-catalyzed cyclooligomerization of allene.

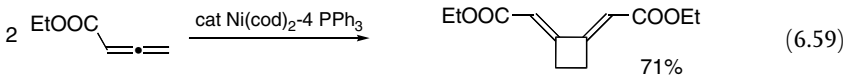
6.58, and forms **6.59** and **6.60**, respectively. The bis-η^3-allyl complex **6.59** is isolated and characterized spectroscopically [58g, i] and the structure is determined by an X-ray analysis [58h]. Reductive elimination at this stage provides **6.50** and **6.51** with the regeneration of a Ni(0) species. A further insertion of allene into the η^3-allylnickel terminal of **6.59** cross-conjugated with an exo-methylene leads to a symmetric bis(η^3-allyl)nickel complex **6.61** [58f]. Reductive elimination of **6.61** forms a cyclic tetramer **6.52** [58f]. Similar transformation leads **6.60** to **6.53**. The cyclic pentamer is also formed by reductive elimination through **6.62**, formed by the further reaction of **6.61** with allene. It is generally observed that the trialkyl-, triarylphosphine and mixed alkyl(aryl)phosphine ligands accelerate the insertion of the fourth allene molecule to provide **6.61** and hence help the preferential formation of the tetramers. On the other hand, the phosphite ligands, owing to electronic effects, retard the insertion of the fourth allene to **6.59** and assist the selective formation of the cyclic trimer [58i]. Facile insertion of allene to **6.61** takes place when $Ni(cod)_2$ is used as the catalyst; as in the case of cyclooligomerization of other alkenes and alkynes, the absence of the strongly coordinating ligands facilitates the insertion reaction.

6.5.2
Cyclooligomerization of Substituted Allenes

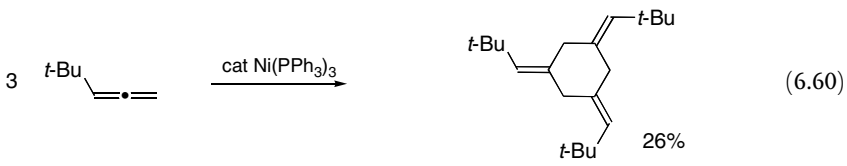
Much fewer studies have been carried out on the reaction of substituted allenes. The formation of polymers [59a] a linear dimer [59c,h], and a mixture of cyclic and acyclic oligomers (Eq. (6.58)) [59d] has been reported for the nickel-catalyzed reaction of alkylallenes. The regioselective formation of a cyclic dimer takes place for the nickel-catalyzed reaction of 1,3-diphenylallene [59b]. Some electronically or sterically biased allenes undergo cycloisomerization selectively. For example, allenyl cyanide is transformed into cyclic dimers and trimers [59d], and ethyl allenecarboxylate forms cyclic dimers selectively and in good yield (Eq. (6.59)) [59e]. *t*-Butylallene undergoes cyclotrimerization selectively in the presence of $Ni(PPh_3)_3$ (Eq. (6.60)) [59d].



(6.58)



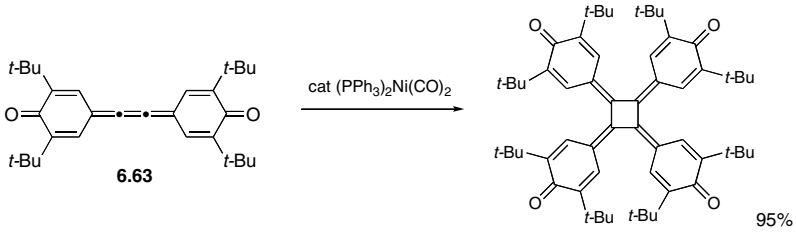
(6.59)



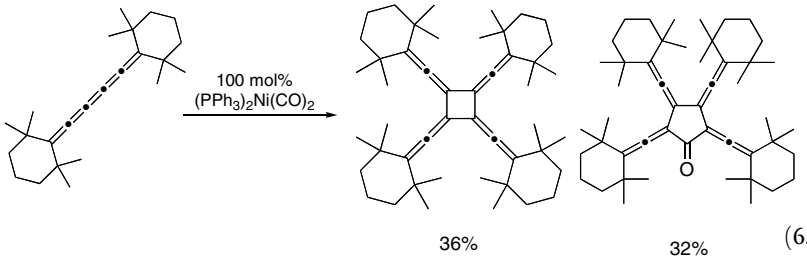
(6.60)

6.5.3 Cyclooligomerization of Cumulenes

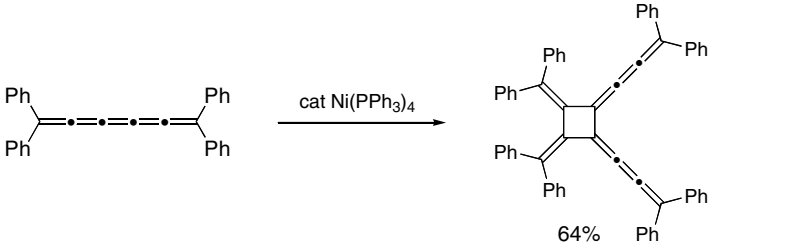
The cyclooligomerization of cumulenes provides an efficient entry for the preparation of radialenes [5, 60, 62]. Usually, cyclodimerization or cyclotrimerization takes place at the internal double bonds. For example, butatrienes such as **6.63** provide the cyclic dimers in excellent yields (Eq. (6.61)) [60a]. Hexapentaenes ([5]cumulenes) also undergo cyclodimerization and furnish various cyclobutanes. In this case, the mode of cyclodimerization depends on the steric size of the substituents bound to the cumulene termini. For example, when a bulky group is attached, dimerization takes place selectively at the central double bond and forms a [4]radialene with higher symmetry (Eq. (6.62)). In this reaction, dimerization accompanied by the insertion of CO also takes place. On the other hand, less sterically bulky hexapentaenes react at the next double bond to the central double bond and form either a parallel "head-to-head" dimer (Eq. (6.63)) or an anti-parallel "head-to-



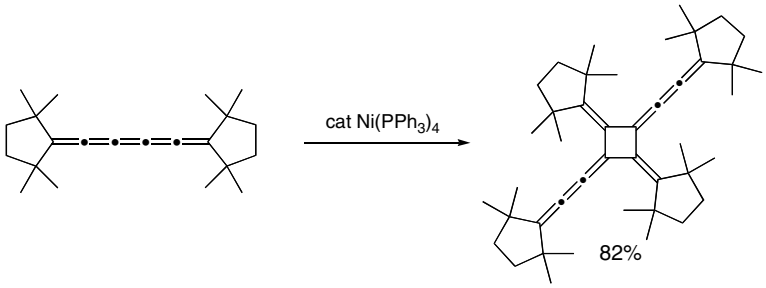
(6.61)



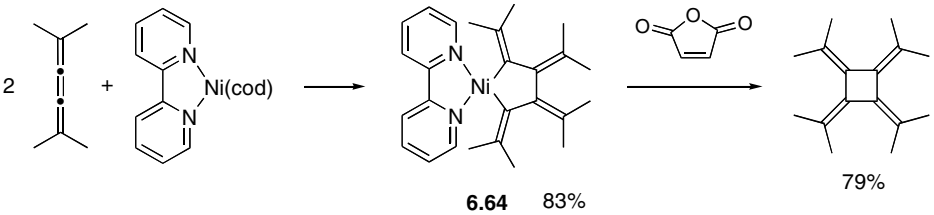
(6.62)



(6.63)



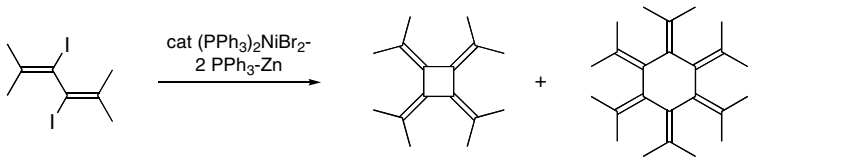
(6.64)



Scheme 6.12. Isolation of the bipyridyl complex of oxidative addition product **6.64** and its reductive elimination promoted by an electron-deficient alkene.

tail'' dimer (Eq. (6.64)) with lower symmetry [60g,h]. The difference in cyclization modes in Eqs. (6.62)–(6.64) may be rationalized taking the higher coordinating ability (reactivity) of the cumulenic C_2=C_3 (C_4=C_5) double bond compared to the central C_3=C_4 double bond and the relative steric size of the substituents (tetramethylcyclopentylidene > tetramethylcyclohexylidene > diphenylmethylene) into consideration: the reaction at the C_3=C_4 double bond is favored when a very bulky substituent is bound. In the presence of bipyridine ligand, the nickellacycle **6.64** is isolated, which undergoes reductive elimination by the coordination of another electron-deficient ligand, maleic anhydride (Scheme 6.12; see Section 1.7.4) [60k].

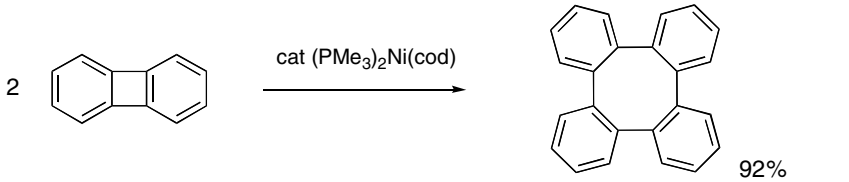
Cumulenes generated in situ from 2,3-dihalo-1,3-butadienes undergo cyclooligomerization in the presence of a Ni(0) complex. A large solvent effect on the reaction modes is observed [60c–f,l]. 2,5-Dimethyl-2,3,4-hexatriene generated in situ by the reduction of 2,5-dimethyl-3,4-diiodo-2,4-hexadiene selectively undergoes cyclodimerization in the presence of a nickel complex in benzene solution. The same reaction in DMF furnishes the cyclic trimer almost exclusively (Eq. (6.65)) [60c,f]. A small number of examples for co-cyclooligomerization of allenes with acetylene [60j] and alkenes [58d] has appeared. The cycloisomerization of 1,ω-enallenes is discussed in Section 6.2 (Eq. (6.9)).



(6.65)

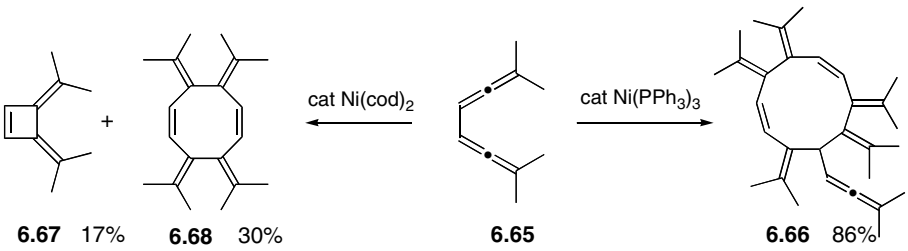
6.6
Cyclooligomerization and Cycloisomerization of Miscellaneous Compounds

Biphenylene, a compound with a strained σ bond, undergoes cyclodimerization in the presence of $(PMe_3)_2Ni(cod)$ (Eq. (6.66)) [61]. The oxidative addition of a Ni(0) species to the strained σ bond triggers the reaction [63].

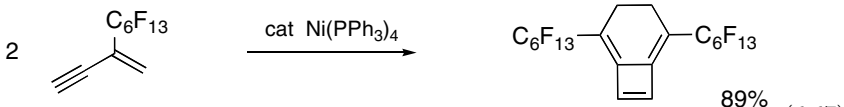


(6.66)

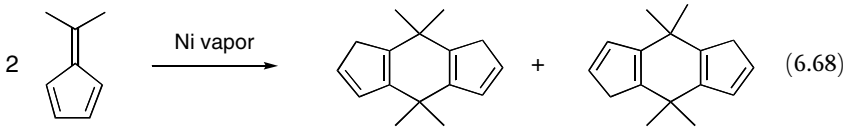
Although conjugated enynes usually undergo cyclotrimerization at the alkyne part [30g, 32a], an unusual nickel-catalyzed cyclodimerization involving the double and triple bond is observed for the cyclodimerization of 1-buten-3-ynes bearing the perfluoroalkyl groups at the 2-position (Eq. (6.67)) [64]. The cyclooligomerization of a conjugated bis-allene compound **6.65** proceeds in the presence of a Ni(0) catalyst [65]. The structure of the products depends on the structure of the nickel catalyst employed (Scheme 6.13). Thus, **6.65** undergoes cyclotrimerization in the pres-



Scheme 6.13. Nickel-catalyzed cyclodimerization and cyclotrimerization of a conjugated bis-allene **6.65**.



(6.67)



(6.68)

ence of $Ni(PPh_3)_3$, while **6.65** provides a mixture of a [2+2] cycloaddition product **6.67** and a cyclodimerization product **6.68** when $Ni(cod)_2$ is used as the catalyst. A [6+6]cycloaddition of dimethylfulvene proceeds when it is exposed to the Ni vapor (Eq. (6.68)) [66].

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7
Nickel-mediated and -catalyzed Carboxylation

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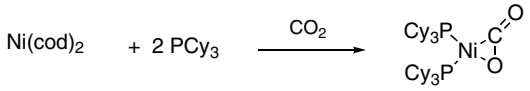
Transition metal-mediated or -catalyzed carboxylation is a useful tool for one-carbon elongation reactions in synthetic organic chemistry. In addition, carbon dioxide fixation is a very fascinating process because there is abundant CO_2 in the air. Although CO_2 is a useful resource in synthetic organic chemistry, it has been used very infrequently, except for Grignard reactions. It is well known that CO_2 coordinates to transition metals, and particularly strongly to a nickel complex. In this respect there are two major coordination modes, namely η^2-side-on coordination and η^1-C-on coordination, though η^1-end-on coordination has also been proposed as a result of calculations (Fig. 7.1) [1].

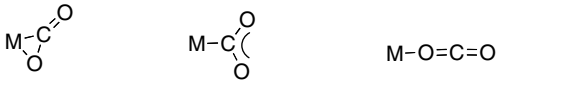
The first structurally characterized carbon dioxide complex was synthesized by treating $Ni(PCy_3)_2$ with CO_2 (Eq. (7.1)), since which several reports have been made on the synthesis of nickel–carbon dioxide complexes and the use of CO_2 in synthetic organic chemistry.



(7.1)

7.1
Nickel-mediated or -catalyzed Carboxylation of 1,3-Diene

Oxidative coupling of diene and CO_2 using a nickel complex provides a π-allylnickel complex, the structure of which has been confirmed using X-ray crystal-

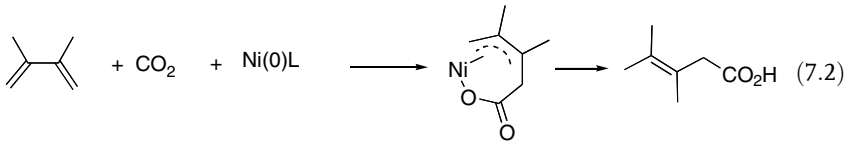


η^2-side-on coordination η^1-C coordination η^1-end-on coordination

Fig. 7.1. Modes of coordination of carbon dioxide to nickel metal.

Modern Organonickel Chemistry. Edited by Y. Tamaru

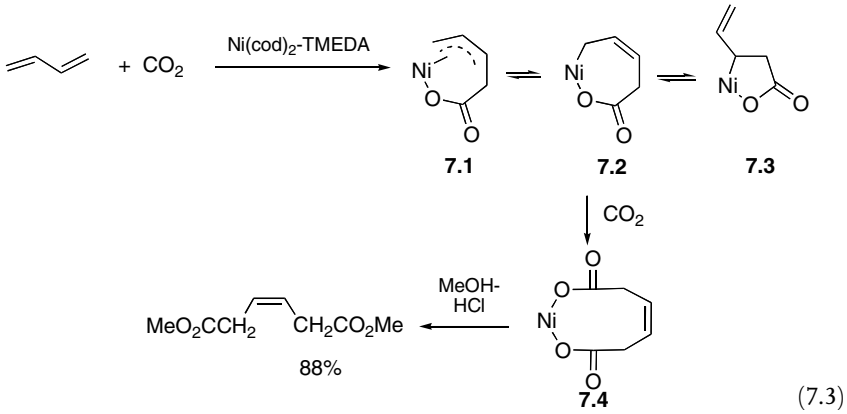
ISBN: 3-527-30796-6



(7.2)

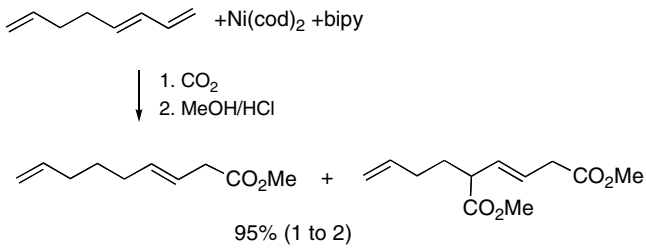
lography [3]. Acidic treatment of this complex affords 3,4-dimethyl-3-pentenoic acid (Eq. (7.2)) [3].

The reaction of butadiene and CO_2 in the presence of $Ni(cod)_2$ and tetramethylethylenediamine (TMEDA) produces the π-allylnickel complex **7.1**, which is in a state of equilibrium with σ-oxanickelaheptene **7.2** and σ-oxanickelacyclopentane **7.3** (Eq. (7.3)). Further reaction with CO_2 gives a nickeladicarboxylate complex **7.4**, which is treated with MeOH-HCl to produce *cis*-dicarboxylic acid ester in high yield [3].



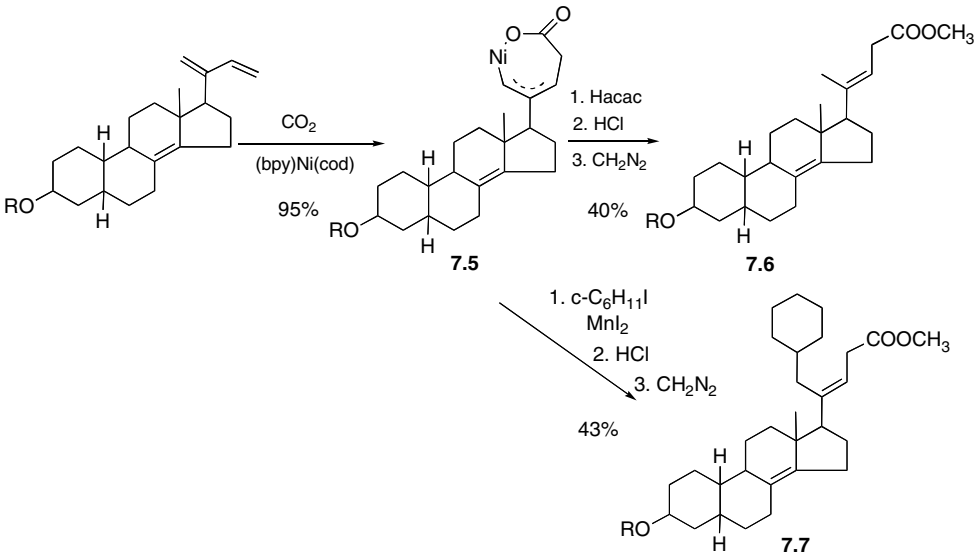
(7.3)

1,3,7-Octatriene is treated in a similar manner to give a mixture of mono- and dicarboxylic acid esters in a ratio of 1 to 2 (Eq. (7.4)). In this reaction, no products resulting from an attack of CO_2 at the alkene part of the molecule can be isolated [4].



(7.4)

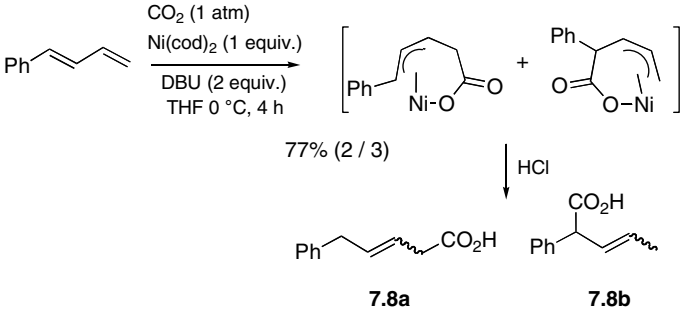
As an application of this reaction, 2-substituted butadiene reacts with (bpy)-Ni(cod) and CO_2 to give nickelalactone **7.5** in high yield. Protonation followed by esterification of **7.5** gives ester **7.6** (Scheme 7.1).



Scheme 7.1. Reaction of diene and CO_2.

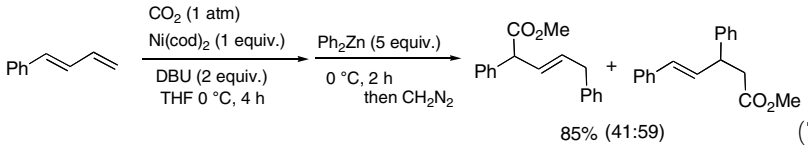
Ultrasound-activated cross-coupling of **7.5** with cyclohexyl iodide in the presence of MnI_2 affords 4-substituted-5-cyclohexyl-3-pentenoic acid **7.7**, although the role of MnI_2 is not clear [5].

Recently, a nickel-mediated carboxylation reaction of diene was reported [6]. When diene is reacted with CO_2 (1 atm) using $Ni(cod)_2$ and DBU as a ligand, β,γ-unsaturated carboxylic acids **7.8a** and **7.8b** are obtained in good yields (Scheme 7.2).



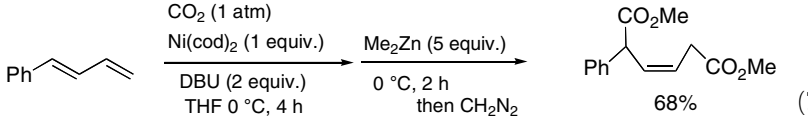
Scheme 7.2. Nickel-mediated carboxylation of 1,3-diene.

This reaction can be further extended to the arylative carboxylation by combination with transmetallation. When diene is treated with $Ni(cod)_2$ and DBU under CO_2, Ph_2Zn is then added to give arylative carboxylic ester in high yield (Eq. (7.5)).



(7.5)

However, when Me_2Zn is added to the solution of oxanickelacycle, dicarboxylic acid esters is obtained in good yield after treatment with CH_2N_2, though the reason for this is not clear at this stage (Eq. (7.6)).

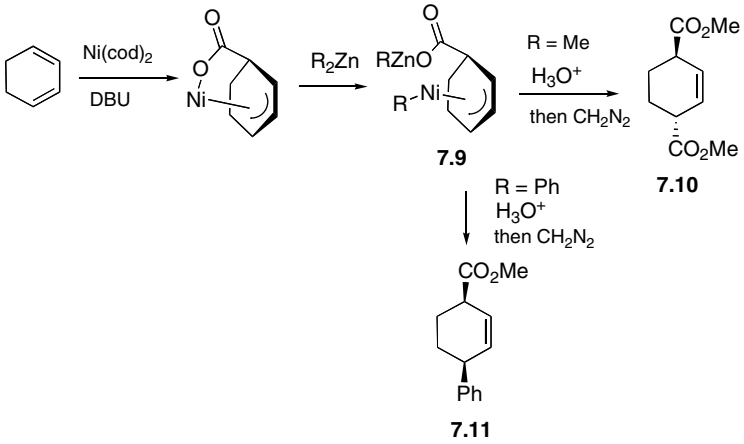


(7.6)

When cyclohexadiene is treated with $Ni(cod)_2$ under CO_2 and Ph_2Zn is then added to the solution, phenylative carboxylation of cyclohexadiene proceeds smoothly to give methyl 4-phenylcyclohexenecarboxylate **7.11** after treatment with CH_2N_2. The stereochemistry of phenylation product **7.11** is determined as being *cis*. Presumably, π-allylnickel complex **7.9** (R = Ph) should be formed as an intermediate via transmetallation, and a phenyl group attacks from the same side of the nickel metal to give a *cis*-product.

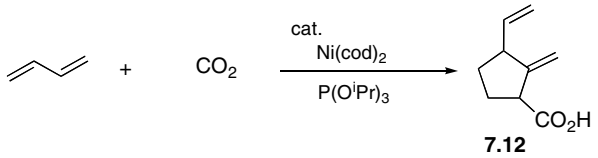
The use of Me_2Zn for this reaction affords methyl *trans*-2-cyclohexene-1,4-dicarboxylate **7.10**. In this case, π-allylnickel complex **7.9** (R = Me) should be formed, but it is fairly stable under these reaction conditions. Thus, before reductive elimination, it is attacked by the second CO_2 from the rear of the nickel complex to give a *trans*-product (Scheme 7.3).

Nickel-mediated cocyclization of 1,3-diene and CO_2, which proceeds via a bis-π-allylnickel complex, is one of the most extensively studied transition metal-



Scheme 7.3. Arylative carboxylation of cyclohexadiene.

catalyzed CO_2 fixation processes. A functionalized cyclopentanecarboxylic acid has been synthesized from 1,3-butadiene and CO_2 using $Ni(cod)_2$ and the phosphine ligand [7]. When a mixture of 1,3-butadiene (166 mmol), $Ni(cod)_2$ (0.20 mmol) and $P(O\text{-}i\text{-}Pr)_3$ (0.6 mmol) in DMF is allowed to stand at 60 °C for 23 h in a steel autoclave, 2-methylene-3-vinylpentanecarboxylic acid **7.12** (5.86 mmol) is obtained (Eq. (7.7)).



7.12 (7.7)

This reaction would proceed as shown in Figure 7.2. The reaction of 1,3-diene with Ni(0) gives π-allylnickel complex **7.13**. Insertion of the carbon–oxygen bond of CO_2 into the carbon–nickel bond gives complex **7.14**, and further insertion of the double bond into the nickel–carbon bond gives complex **7.15**. β-Hydrogen elimination from **7.15** affords complex **7.16**, and reductive elimination gives cyclopentene derivative **7.12** with the regeneration of Ni(0).

A highly regio- and stereoselective ring-closing carboxylation of bis-1,3-dienes **7.17** has been reported (Scheme 7.4) [8]. This reaction proceeds in the presence of a zinc reagent to give cyclized carboxylic acid **7.19**. A THF solution of bis-diene **7.17a**, a catalytic quantity of $Ni(cod)_2$ (20 mol%), PPh_3 (40 mol%), and Et_2Zn (4.5 equiv.) is stirred under an atmosphere of CO_2 at 0 °C for 3.5 h to give cyclized compound **7.19a** in 75% yield. The reaction proceeds in a highly regio- and stereo-

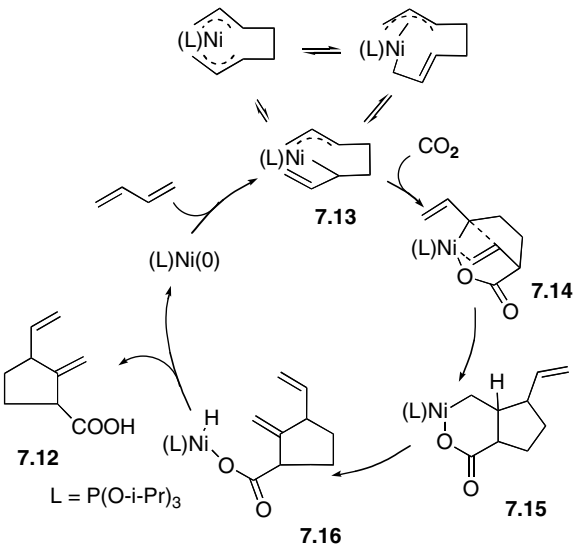
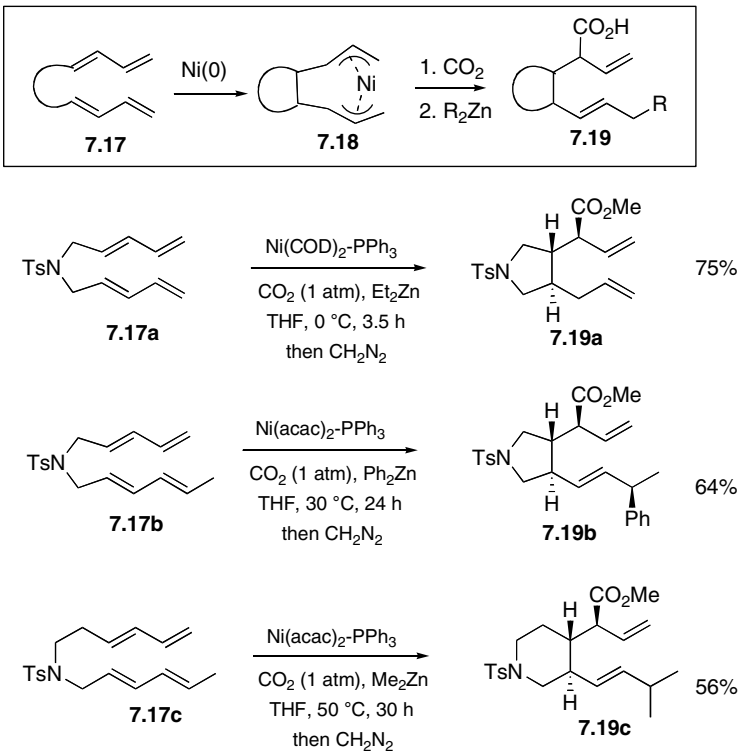


Fig. 7.2. Possible reaction course.



Scheme 7.4. Nickel-catalyzed ring-closing carboxylation.

selective manner, and only a single product is obtained. In this reaction, a catalytic amount of $Ni(acac)_2$ (5 mol%) can be used instead of air-sensitive $Ni(cod)_2$, and the desired compound **7.19a** is obtained in 72% yield. Various zinc reagents can be used for this reaction, and even in six-membered ring formation, the reaction proceeds in a highly regio- and stereoselective manner to give **7.19c**.

The reaction appears to start with oxidative cycloaddition of bis-diene **7.17** by an Ni(0) complex to produce bis-π-allylnickel complex **7.18**, and insertion of CO_2 into the nickel–carbon bond of **7.18** affords carboxylate **7.20**. Transmetallation of complex **7.20** with Et_2Zn then provides ethylnickel complex **7.21**, which can undergo β-hydride elimination to afford complex **7.22**, from which an Ni(0) complex is reproduced and provides carboxylic acid **7.19** after hydrolysis (Fig. 7.3).

The remarkable features of this reaction are that it proceeds via a catalytic quantity of nickel complex, the stereochemistry is highly controlled, the yield is high, and 1 atm pressure of CO_2 can be used.

Very recently, the same authors achieved a successful nickel-mediated asymmetric carboxylative cyclization. Treatment of bis-diene **7.17** with $Ni(acac)_2$ and (*S*)-MOP as a chiral ligand under an atmosphere of CO_2 gives cyclized compounds **7.19** with high enantiomeric excess (Scheme 7.5) [9].

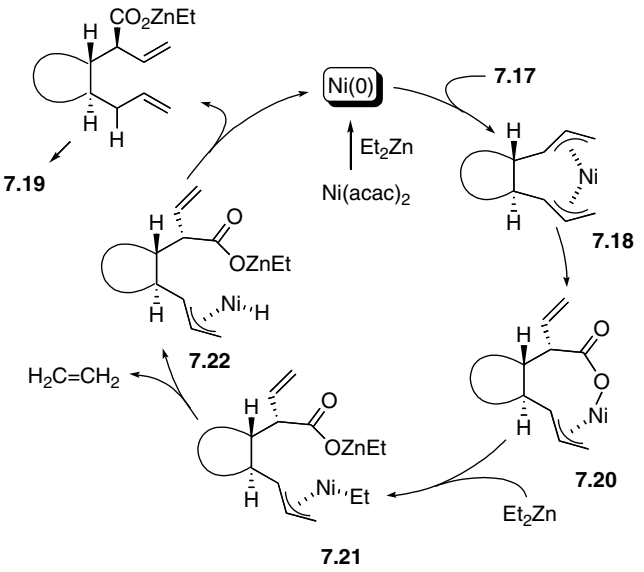
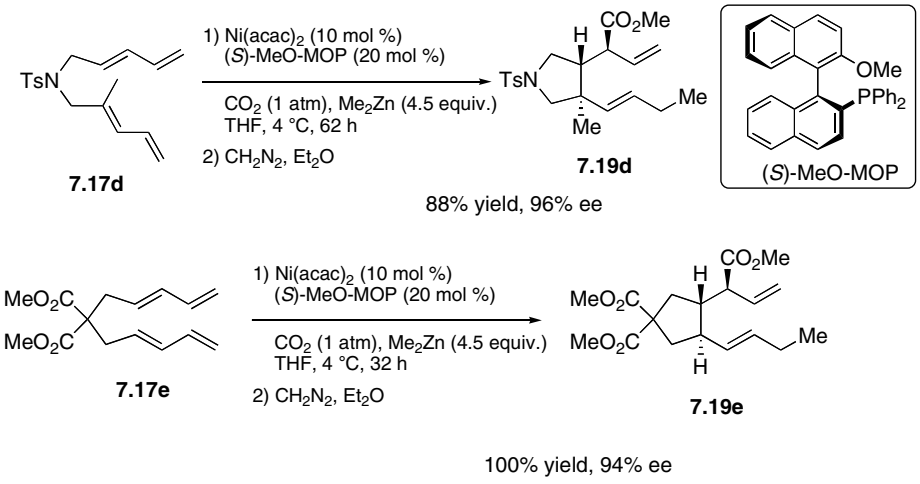


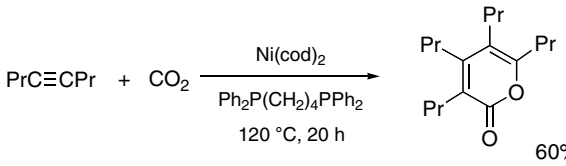
Fig. 7.3. Possible reaction course for nickel-catalyzed ring-closing carboxylation.



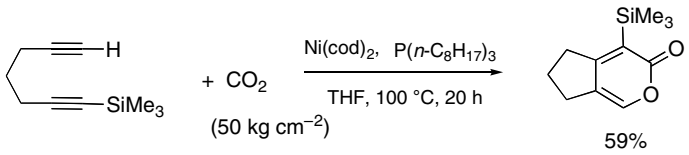
Scheme 7.5. Nickel-catalyzed asymmetric carboxylative cyclization.

7.2
Nickel-mediated or -catalyzed Carboxylation of Alkyne

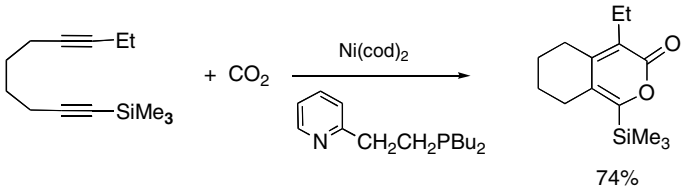
In 1977, the synthesis of α-pyrone from CO_2 and terminal alkyne using $Ni(cod)_2$ and bidentate phosphine ligand was reported [10]. Although the yield was not good due to a simultaneous [2+2+2]cocyclization reaction of alkyne, this was the first example of nickel-catalyzed carboxylation into alkyne. The same authors later reported that disubstituted alkyne improved the yields (Eq. (7.8)).



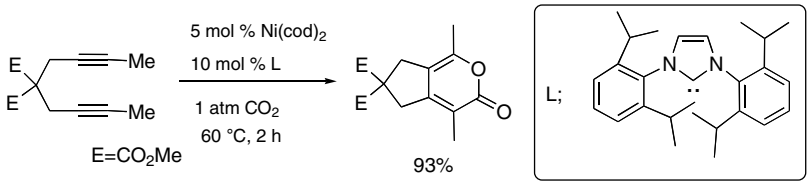
(7.8)



(7.9)



(7.10)



(7.11)

Using this procedure for an intramolecular reaction, bicyclic α-pyrone is synthesized from diyne and CO_2 (50 kg cm^{-2}) (Eq. (7.9)) [11]. In this reaction, disubstituted diyne also affords good results (Eq. (7.10)). The same reaction has been carried out using $Ni(cod)_2$ and *N*-heterocyclic carbene as a ligand under an atmosphere of carbon dioxide at 60 °C (Eq. (7.11)) [12]. The reaction proceeds smoothly under mild conditions within a short time period, and the desired product is obtained in high yield. In this reaction, the authors claim that oxanickelacycle **7.23** should be formed as an intermediate (Fig. 7.4).

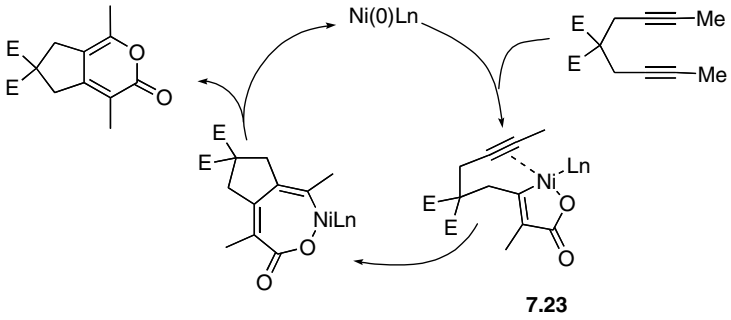
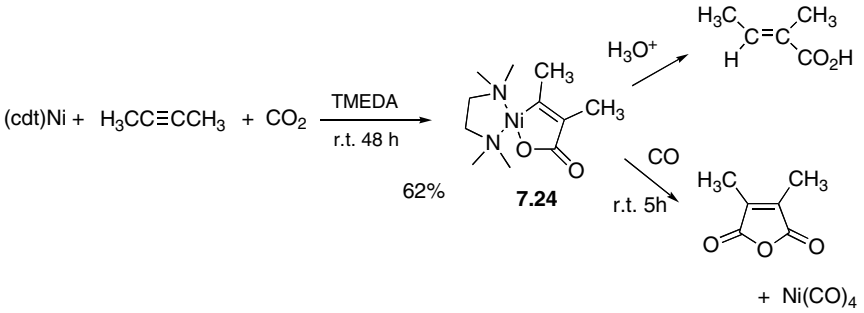


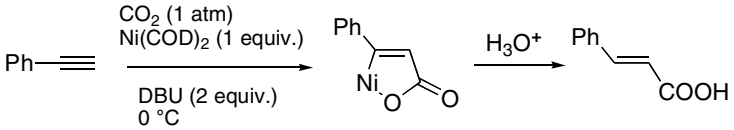
Fig. 7.4. Reaction course for formation of α-pyrone.

On the other hand, the reaction of CO_2 (1 atm) and alkyne using a stoichiometric quantity of $Ni(cod)_2$ and TMEDA as a ligand provides oxanickelacycle **7.24** under mild conditions. Hydrolysis of **7.24** affords carboxylic acid, while the insertion of carbon monoxide affords cyclic anhydride [13].



Scheme 7.6. Reaction of alkyne and CO_2 under mild conditions.

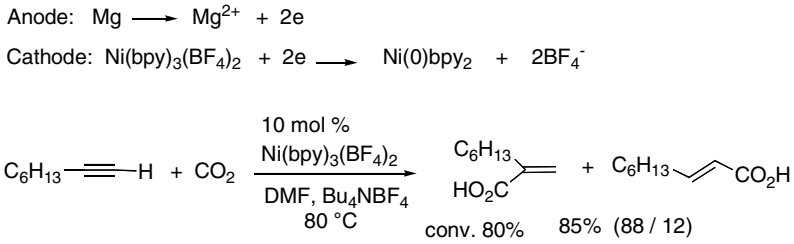
Using this reaction, a procedure for the regio- and chemo-selective synthesis of α,β-unsaturated carboxylic acids from terminal alkyne has been developed. In this reaction, a stoichiometric quantity of $Ni(cod)_2$ and 2 equiv. of DBU are used (Eq. (7.12)) [14].



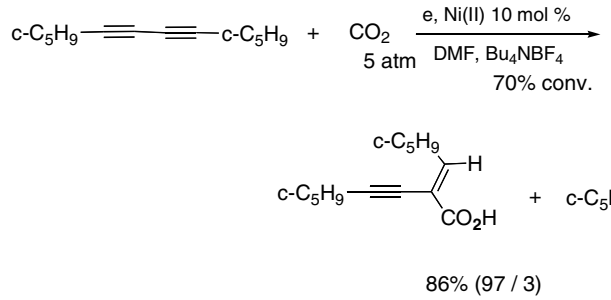
(7.12)

The electrochemical reduction of $Ni(bpy)_3(BF_4)_2$ yields an active catalyst for the reaction of terminal alkyne and CO_2. A novel electrochemical carboxylation allowed transformation of terminal alkynes into α-substituted acrylic acids with selectivity of 65–90% and in relatively good overall yields [15].

The same authors report electrosynthesis of 2-vinylidene-3-yne carboxylic acids from CO_2 and disubstituted 1,3-diyne. The reaction is catalyzed by a nickel–triamine complex and proceeds in a regio- and stereoselective addition to one triple bond (Eq. (7.13)).

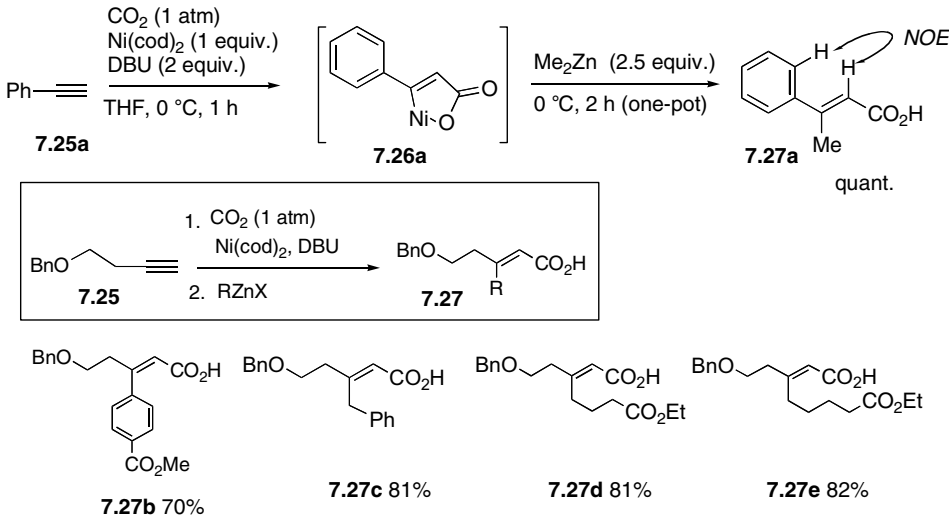


Scheme 7.7. Electrochemical carboxylation.



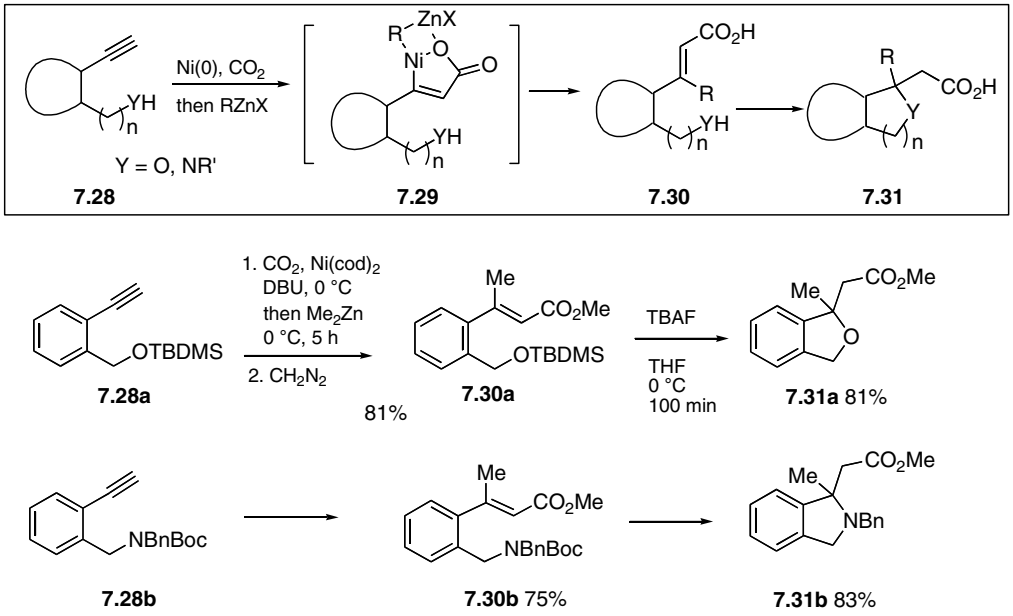
(7.13)

As nickelacycle has active nickel–Csp^2 and nickel–oxygen bonds, which can be used for further transformation, a highly regio- and stereoselective synthesis of β,β'-disubstituted unsaturated carboxylic acid has been developed utilizing a nickel-mediated CO_2 coupling process and a transmetallation process (Scheme 7.8) [16]. When phenylacetylene **7.25a** (1.1 equiv.) is reacted with CO_2 (1 atm) in the presence of a stoichiometric quantity of $Ni(cod)_2$ (1.0 equiv.) and DBU (2 equiv.), nickelacycle **7.26a** would be formed. Dimethylzinc (2.5 equiv.) is added to this solution at 0 °C, and the mixture is stirred at 0 °C for 2 h. Hydrolysis of the reaction mixture with 10% aqueous HCl solution affords β-methylcinnamic acid **7.27a** in quantitative yield. In this reaction, various zinc reagents can be used and functionalized trisubstituted α,β-unsaturated carboxylic acids **7.27** are obtained in high yields.



Scheme 7.8. Alkylative carboxylation to alkyne.

The same group extends this reaction to the synthesis of heterocycles (Scheme 7.9) [17]. That is, if alkyne **7.28** having the heteroatom in a tether is converted into α,β-unsaturated carboxylic acid **7.30** using nickel-mediated alkylative carboxylation, then Michael addition of the heteroatom to resultant α,β-unsaturated carbo-



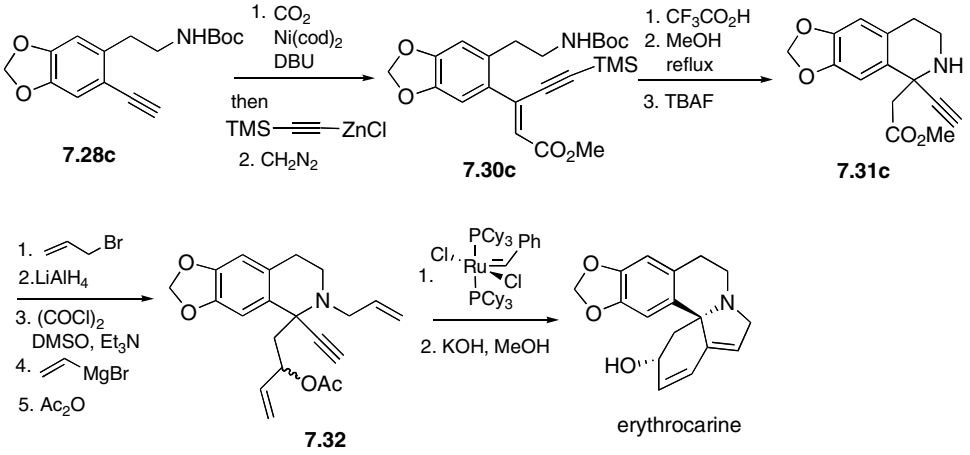
Scheme 7.9. Synthesis of heterocycles using alkylative carboxylation.

xylic acid **7.30** gives nitrogen or oxygen heterocycles **7.31** having a tetrasubstituted carbon center. When alkyne **7.28a** is treated with CO_2 in the presence of $Ni(cod)_2$ and DBU under an atmosphere of CO_2, the desired α,β-unsaturated carboxylic ester **7.30a** is obtained after treatment with CH_2N_2. Deprotection of the *tert*-butyl-(dimethyl)silyl (TBDMS) group affords isobenzofurane **7.31a** in 81% yield. In the case of nitrogen as a heteroatom, isoindoline **7.31b** is obtained in high yield.

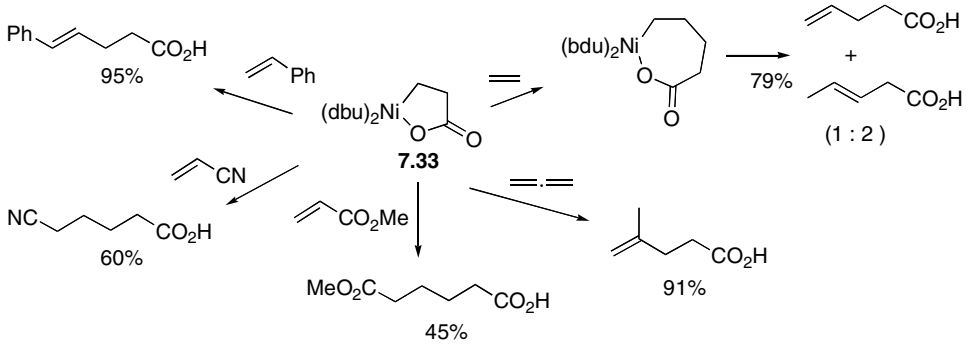
The total synthesis of erythrocarine has been achieved using this procedure (Scheme 7.10). The reaction of alkyne **7.28c** with CO_2 in the presence of $Ni(cod)_2$ and DBU produces oxanickelacycle, after which alkynylzinc reagent is added to the solution to produce trisubstituted alkyne **7.30c** in 69% yield after treatment with CH_2N_2. Deprotection of the *t*-butoxycarbonyl group, followed by Michael addition of the resultant amine and then deprotection of the silyl group, gives isoquinoline derivative **7.31c**, which is then converted into dienyne **7.32**. Ruthenium-catalyzed dienyne metathesis followed by deprotection of the acetyl group affords erythrocarine.

7.3 Nickel-mediated Carboxylation of Alkene

Mono-olefins are known to react stoichiometrically with Ni(0) and CO_2 to yield nickelaoxacyclopentanes. One of the first olefins studied was norbornene [18], but less-activated acyclic mono-olefins such as ethene and hexenes also couple with CO_2 [19]. The first isolation of oxanickelacycle produced from olefin is a 1:1 cou-

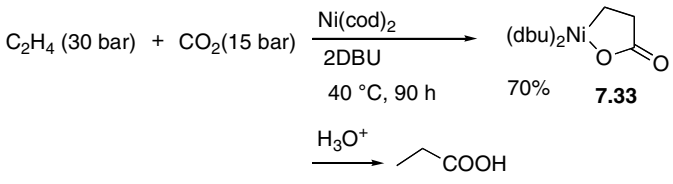


Scheme 7.10. Total synthesis of erythrocarine.

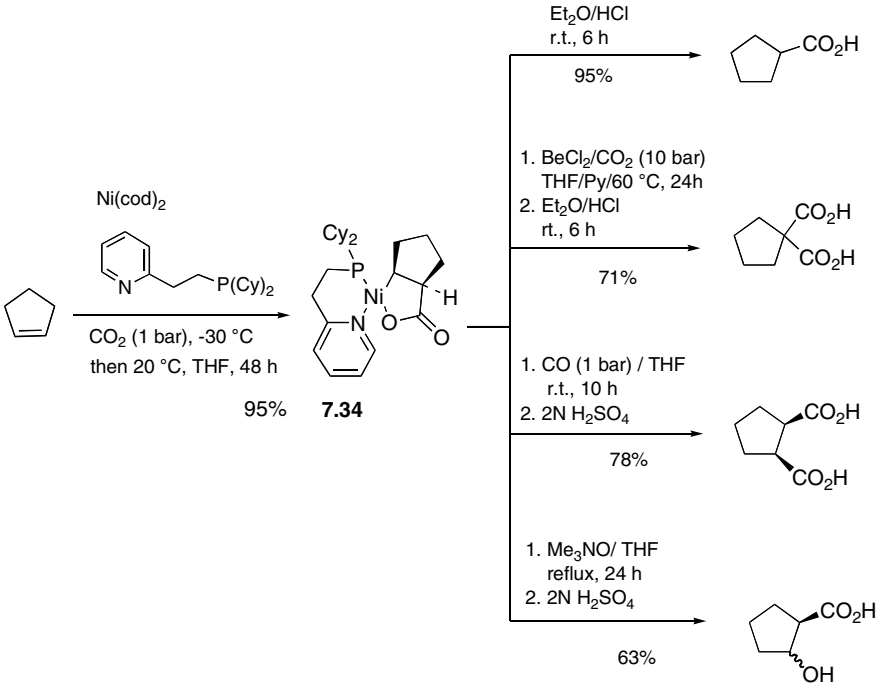


Scheme 7.11. Reaction with oxanickelacycle.

pling product **7.33** of ethene and CO_2, and the structure is confirmed using X-ray crystallography [20]. This is a 16-electron complex with square-planar coordination of the nickel atom, in which two nitrogen atoms of the DBU ligands occupy neighboring coordination positions and the carboxylate moiety is bound to the metal through both Ni–O and Ni–Csp^3 bonds. Hydrolysis of oxanickelacycle **7.33** affords propionic acid (Eq. (7.14)). Subsequent reactions with unsaturated compounds, such as styrene, ethylene, allene, and α,β-unsaturated compounds, as shown in Scheme 7.11, are also investigated.



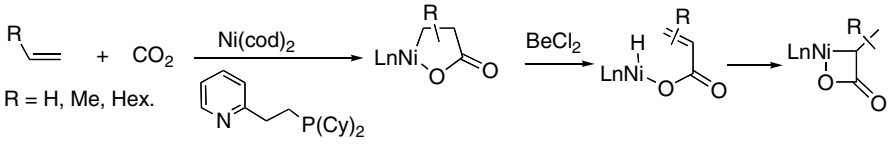
(7.14)



Scheme 7.12. Reaction of cyclopentene, CO_2 and $Ni(COD)_2$.

Furthermore, cyclopentene is treated with $Ni(cod)_2$ and 2-[2-(dicyclohexylphosphino)ethyl]pyridine as a ligand to give bicyclic nickel complex **7.34**, which is treated with Et_2O-HCl to afford cyclopentanecarboxylic acid (Scheme 7.12) [21]. Treatment of this complex with CO_2 in the presence of $BeCl_2$ affords dicarboxylic acid. On the other hand, the complex **7.34** is treated with carbon monoxide to give cyclopentane-1,2-dicarboxylic acid. Refluxing of complex **7.34** with trimethylamine *N*-oxide in THF solution gives 2-hydroxy cyclopentanecarboxylic acid.

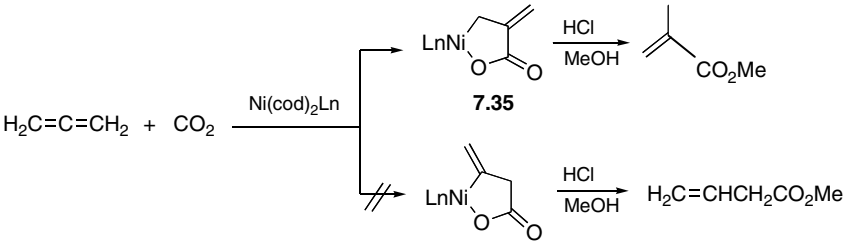
Five-membered nickelacycle is prepared from alkene, CO_2 and $Ni(cod)_2$ in the presence of a heterobifunctional ligand (Scheme 7.13). A ring contraction of five-membered nickelacycle to four-membered metallacycles occurred on addition of $BeCl_2$, or on heating. The four-membered nickelacycle with higher reactivity is capable of undergoing reaction with CO_2, CO and ethylene (see Schemes 1.31 and 1.32) [22].



Scheme 7.13. Ring contraction of nickelacycle.

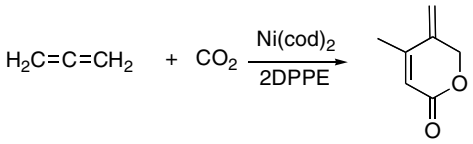
7.4
Nickel-mediated Carboxylation of Allene

1,2-Diene reacts with CO_2 in the presence of $Ni(cod)_2$ and 1,2-bis(dicyclohexylphosphino)ethane or 2,2′-bipyridyl to form oxanickelacycle. The structure of the hydrolysis product indicates that the reaction proceeds via oxanickelacyle **7.35** (Scheme 7.14), and infers that CO_2 is inserted at the central carbon of 1,2-diene [23].

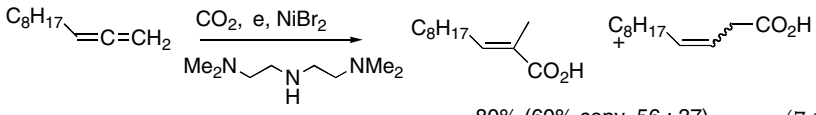


Scheme 7.14. Reaction of allene with CO_2.

By contrast, when a CH_3CN solution of $Ni(cod)_2$, DPPE, and allene is stirred in an autoclave at 80 °C for 45 h under 15 atm of CO_2, lactone is obtained in 20% yield (Eq. (7.15)) [24].



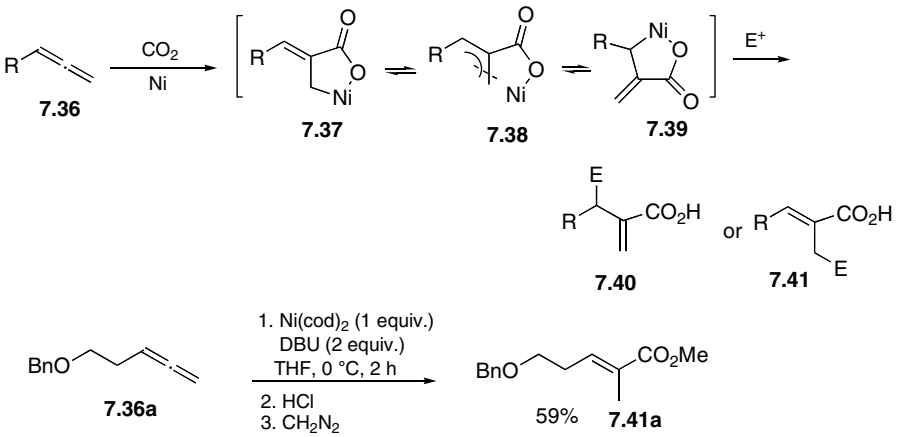
(7.15)



(7.16)

Reductive electrocarboxylation of allene with a nickel complex in the presence of a magnesium anode affords carboxylic acid (Eq. (7.16)). A 10:1 substrate-to-nickel ratio and a 2:1 ligand-to-metal ratio are used, and electrolysis is carried out in a single-compartment cell fitted with a central magnesium anode surrounded with a carbon fiber cathode. The carboxylation reaction is performed at a constant current intensity under CO_2 pressure (5 atm) [25].

In the case of substituted allene **7.36**, CO_2 reacts at the central carbon of allene in the presence of Ni(0), and oxanickelacycle **7.37**, **7.39** and/or π-allylnickel complex **7.38** should be obtained (Scheme 7.15) [26]. When **7.36a** is reacted with CO_2 in the presence of $Ni(cod)_2$ (1 equiv.) and DBU (2 equiv.) at 0 °C for 2 h, carboxylic acid methyl ester **7.41a** is obtained in 59% yield after treatment with CH_2N_2.



Scheme 7.15. Reaction of substituted allene and CO_2.

This indicates that terminal alkene coordinates to Ni(0) at the opposite site of the substituent (Fig. 7.5) to form oxanickelacycle **7.37** and/or **7.38**.

Since it is thought that an intermediary oxanickelacycle **7.37** is in a state of equilibrium with π-allylnickel complex **7.38**, an electrophile attacks at the allylic position. When the reaction with benzaldehyde is examined, α-methylene-γ-lactone is isolated in 60% yield after acid-catalyzed dehydration (Scheme 7.16). In a similar

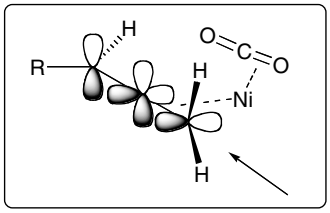
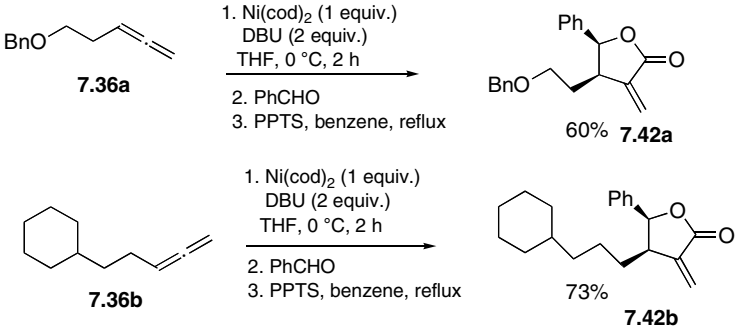
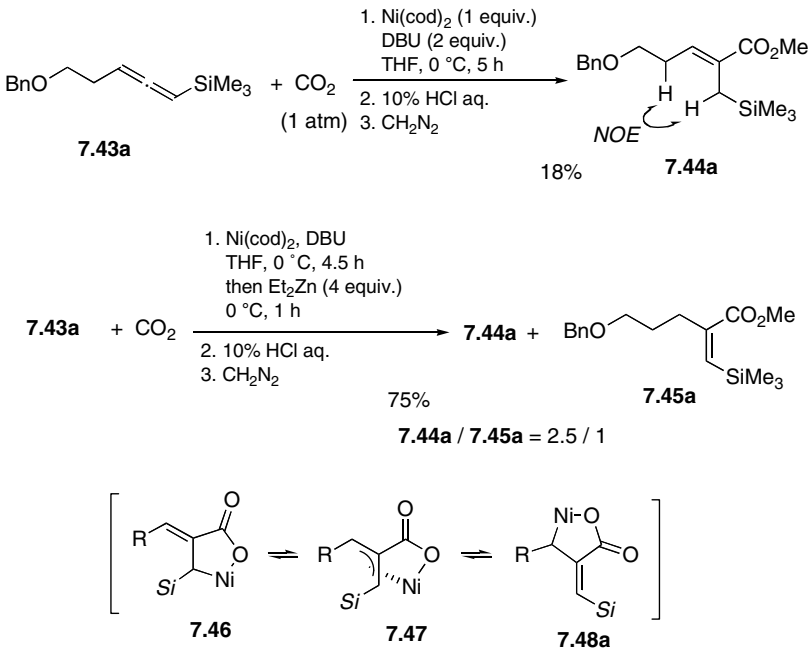


Fig. 7.5. Coordination of allene into Ni(0).



Scheme 7.16. Synthesis of α-methylene-γ-lactone.



Scheme 7.17. Reaction of allene bearing a silyl group with CO_2.

manner, various terminal allenes **7.36** afford α-methylene-γ-lactone **7.42** in high yields [26].

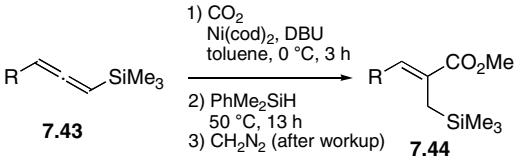
Nickel-mediated carboxylation of trimethylsilylallene **7.43a** gives allylsilanes **7.44a** having a carboxyl group at the 2-position, but the yield is low. In order to improve the yield of **7.44a**, Et_2Zn is added to the intermediary oxazirconacycle solution to give the desired product in high yield, but a relatively large amount of vinylsilane **7.45a** is formed (Scheme 7.17). The intermediary oxanickelacycles should be **7.46**, which is in a state of equilibrium with π-allylnickel complex **7.47**, and σ-oxanickelacycle **7.48** and vinyl silane **7.45a** would be formed from **7.48** and Et_2Zn.

The use of $PhMe_2SiH$ instead of Et_2Zn for this reaction gives a good selectivity for formation of allylsilane **7.44**. Various allylsilanes are synthesized using this method (Table 7.1) [27].

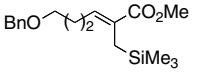
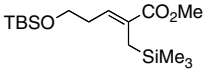
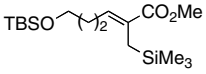
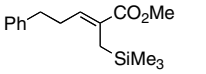
7.5 Various Nickel-mediated Carboxylations

Recently, the generation of (2,3-η)-naphthalyne-nickel(0) complex and reaction with CO_2 has been reported. Sodium-amalgam reduction of a (3-bromonaphthyl)-nickel(II) complex gives the first monomeric nickel(0) complex of 2,3-naphthalyne,

Tab. 7.1. Regio- and stereoselective carboxylation of trimethylsilylallene.

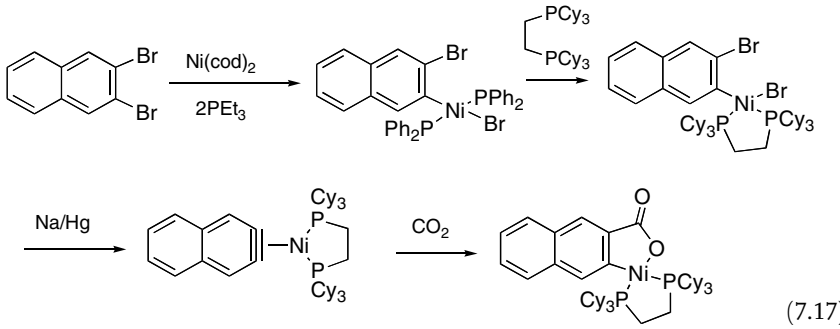


7.43 **7.44**

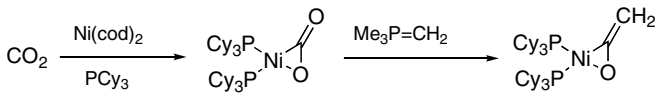
		Product		*Yield [%]*
R = –$(CH_2)_3$OBn	**7.43a**		**7.44a**	59
R = –$(CH_2)_2$OTBS	**7.43b**		**7.44b**	59
R = –$(CH_2)_3$OTBS	**7.43c**		**7.44c**	78
R = –$(CH_2)_2$Ph	**7.43d**		**7.44d**	66

which reacts with CO_2 to produce isolable oxanickelacycle, the structure of which is confirmed using X-ray crystallography (Eq. (7.17)) [28].

The η^2-coordination of CO_2 to the nickel complex $(Cy_3P)_2NiCO_2$ is favored for a reaction with ylide due to the electrophilic carbon of the coordination of CO_2 [29]. When $(Cy_3P)_2NiCO_2$ is treated with an excess of trimethyl phosphorus ylide, a nickel ketene complex is formed (Eq. (7.18)). The nickel ketene complex shows characteristic infra-red (IR) stretches of a η^2-(C,O) coordinated nickel ketene complex. The band at 1570 cm^{-1} may be assigned to the C=O stretch of the ketene coordinating to the nickel with η^2-(C,O). The IR stretch at 1611 cm^{-1} can be assigned to the C=C double bond in the ketene ligand.

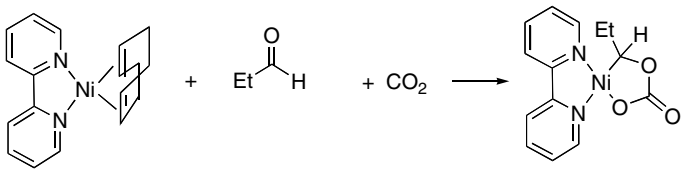


(7.17)



(7.18)

Reaction of the nickel(bpy)(cod) complex with benzaldehyde or propionaldehyde and CO_2 results in the formation of oxanickelacycle (Eq. (7.19)). A detailed kinetic analysis of this reaction has been carried out [30].



(7.19)

7.6 Perspectives

Carbon dioxide is abundant in the air, and is considered to be a very important resource in synthetic organic chemistry. However, few studies have been conducted on the utilization of CO_2, except for its use in the Grignard reaction because of its stability. Recently, organometallic complexes have been shown to play an important role in synthetic organic chemistry. As CO_2 can coordinate to the transition metals to form organometallic complexes, novel utilization of CO_2 is expected. It is known that CO_2 coordinates to Ni(0) to form a nickel complex under very mild conditions. Oxidative coupling of CO_2 and an unsaturated double or triple bond using Ni(0) yields oxanickelacycle, which is a very useful intermediate in synthetic organic chemistry. In general, a stoichiometric quantity of nickel complex is required for the utilization of CO_2, mainly because the five-membered oxanickelacycle formed is stable. In order to realize nickel-catalyzed CO_2 fixation, the transmetallation of oxanickelacycle with another metal should be an important tool. In the past, CO_2 has been used in the synthesis of carboxylic acids. However, if it were possible to use CO_2 for the synthesis of other carbonyl compounds (e.g., ketone and aldehyde), then CO_2 should serve as a valuable one-carbon unit source, instead of carbon monoxide. Indeed, in the near future, CO_2 is expected to become an important resource in synthetic organic chemistry.

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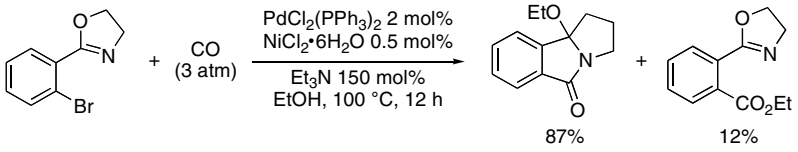
8
Carbonylation and Decarbonylation

Yoshinao Tamaru

Transition metal-catalyzed carbonylation is a useful tool, via which carbonyl functionalities such as aldehyde, ketone, and carboxylic acid can be introduced into a molecule. As with the carbonylation of organic halides, however, nickel appears not to stand comparison with palladium [1]. This is because CO coordinates very strongly with nickel and tends to saturate the coordination sites of the metal (see Section 1.2) so that both oxidative addition of nickel on C–X bonds and migratory insertion of CO into a nickel-C bond are rate-limiting (see Schemes 1.28 and 1.29) [2]. In fact, nickel complexes can be utilized very well for decarbonylation reactions (see Section 8.1). However, as shown in Eq. (8.1), nickel can assist palladium in improving the reactivity. Under similar conditions in the absence of $NiCl_2$, these amide and ester products are created in 44% and 8% yields, respectively (100 °C, 24 h) [3].



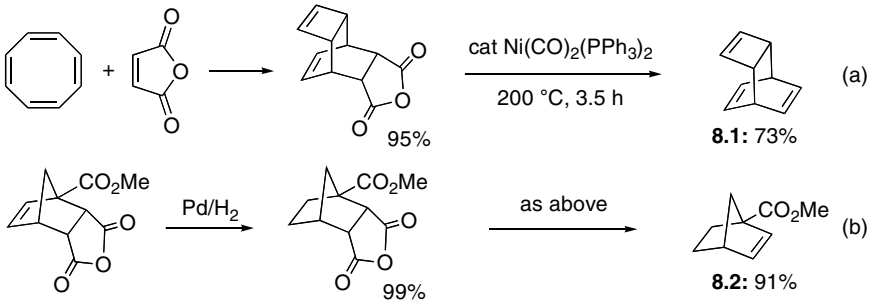
(8.1)

8.1
Decarbonylation

The Nenitzescu's hydrocarbon (tricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene, **8.1**) is a compound of interest from a theoretical point of view. Earlier preparations of the compound suffered from a low yield of the final oxidative bis-decarboxylation step (e.g., with $Pb(OAc)_4$ [4]) or in the ability to scale up other oxidative decarboxylation steps [5]. The decarbonylation-decarboxylation catalyzed by $Ni(CO)_2(PPh_3)_2$ in refluxing diglyme provides highly efficient access to this compound. Under the conditions shown in Eq. (a) in Scheme 8.1, **8.1** is obtained in 78% isolated yield on a 20-g scale [6]. The same procedure was applied to the synthesis of some

Modern Organonickel Chemistry. Edited by Y. Tamaru

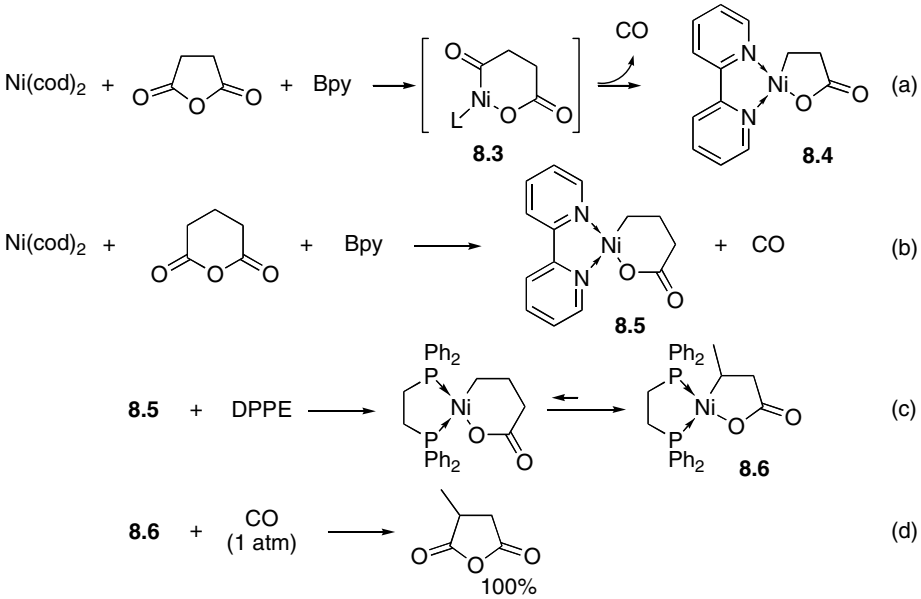
ISBN: 3-527-30796-6



Scheme 8.1. The nickel(0)-catalyzed decarbonylation-decarboxylation method utilized to prepare molecules with strained double bond.

bridgehead substituted norbornenes, for example, **8.2** [7]. This nickel-catalyzed decarbonylation-decarboxylation method enables maleic anhydride to serve as a synthetic equivalent of acetylene in the Diels–Alder reaction. Acetylene itself is a very poor dienophile, and the mechanism for the decarbonylation is described in Scheme 8.2, while the decarboxylation is a reverse process discussed in Section 7.3 (a microscopic reverse).

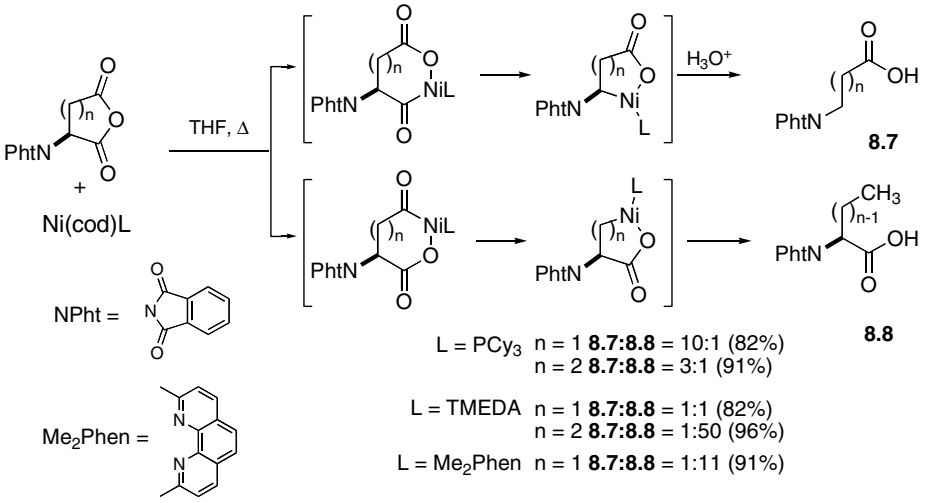
The nickel-catalyzed decarbonylation process has been clarified by the isolation of its intermediates (Scheme 8.2) [8]. $Ni(cod)_2$ undergoes oxidative addition upon



Scheme 8.2. The nickel(0)-promoted decarbonylation of cyclic anhydrides forming nickella-lactones.

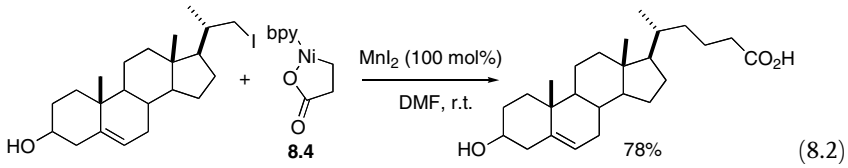
the CO–O bonds of succinic anhydride, and an intermediate **8.3** thus formed extrudes CO to provide a nickel-lactone **8.4** (Eq. (a)). Glutaric anhydride reacts in a similar manner to provide **8.5** (Eq. (b)). By exposure to DPPE, the six-membered nickel-lactone isomerizes to a five-membered nickel-lactone **8.6** through β-hydrogen elimination and re-insertion of the alkene thus liberated upon Ni–H in Markovnikov fashion (see Schemes 1.13 and 1.32) [9]. The metallacycle **8.6** undergoes carbonylation to provide α-methylsuccinic anhydride; thus, the reaction sequence (b)~(d) is, overall, an isomerization of glutaric anhydride to α-methylsuccinic anhydride [9].

The position of oxidative addition of an Ni(0) species for unsymmetric cyclic anhydride depends markedly on the type of ligand. Both for aspartic anhydride (n = 1) and glutamic anhydride (n = 2), PCy_3 promotes the Ni(0) insertion at the distal CO–O bond of the amino substituent. From a synthetic viewpoint, Ni(0) insertion at the proximal CO–O bond may be desirable, since it could be utilized as a synthetic block of the α-amino acid fragment. For this purpose, TMEDA and 2,9-dimethyl-1,10-phenanthroline are the ligands of choice for aspartic anhydride and glutamic anhydride, respectively [10].



Scheme 8.3. The nickel(0)-promoted decarbonylation of unsymmetric cyclic anhydrides.

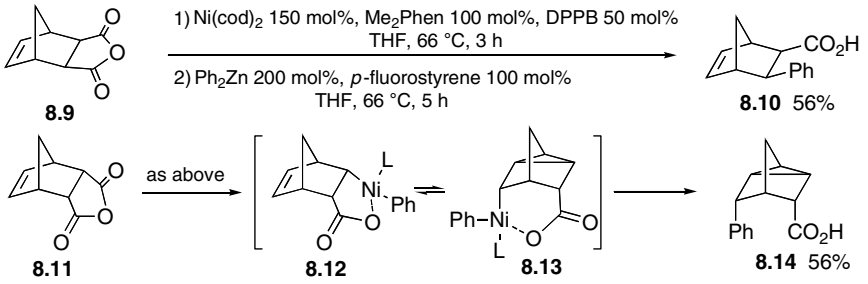
In the presence of MnI_2 (slightly more than 100 mol%), **8.4** undergoes a cross-coupling reaction with sterically hindered primary and secondary alkyl iodides in good to modest yields (Eq. (8.2)). Without MnI_2, the yield of coupling products reduces by approximately one-third [11]. The nickel complexes **8.4** and **8.5** can also be prepared by the reaction of $Ni(acac)_2$, Bpy, and a corresponding anhydride with the use of Et_3Al as a reducing agent [12]. The cross-coupling reaction of **8.4** and **8.5** with aliphatic iodides bearing functional groups (e.g., CHO, CN) is effected by



(8.2)

MnI_2 under ultrasound irradiation. MnI_2 is thought to accelerate the reaction by forming a bimetallic complex [12].

The *exo*-isomer **8.9** of the Diels–Alder products of cyclopentadiene and maleic anhydride undergoes decarbonylation as expected, and forms a nickella-tricyclic intermediate, which reacts with Ph_2Zn (*a nucleophile*) to provide a cross-coupling product **8.10** with complete retention of configuration (Scheme 8.4). Both DPPB and *p*-fluorostyrene are essential, the former acting to remove CO on a nickellacycle intermediate, and the latter accelerating reductive elimination as a fifth ligand (see Section 1.6.4 and Eq. (1.4)) [13]. The *endo*-isomer also undergoes decarbonylation in a similar manner, except that an intermediate **8.12** equilibrates with **8.13** and undergoes reductive elimination through **8.13** to provide **8.14** as a single isomer. The selective formation of **8.14** may be due either to the thermodynamic stability or the kinetic ease of reductive elimination of an intermediate **8.13** [13].



Scheme 8.4. The nickel(0)-promoted decarbonylation and reductive coupling with Ph_2Zn.

8.2
Electrochemical Carbonylation

The nickel complex Ni^0bpy generated from Ni^{2+}bpy serves as an efficient catalyst for the electrochemical conversion of organic halides into symmetrical ketones. Carbonylation is achieved with the use of either CO (method A), CO_2 (method B), or $Fe(CO)_5$ as the CO source of ketones (method C) [14]. The standard reaction conditions for these methods are as follows.

8.2.1
Method A: Utilization of CO [15]

Stainless (Fe_{64}/Ni_{36}) rod sacrificial anode, nickel cathode, DMF (50 mL), Bu_4NBF_4 (1.5 mmol), $FeCl_2$ (1.2 mmol), Bpy (1 mmol), RX (20 mmol), CO supply at ambient pressure, constant current 1∼2 A cm^{-2}, −1.2 V versus SCE.

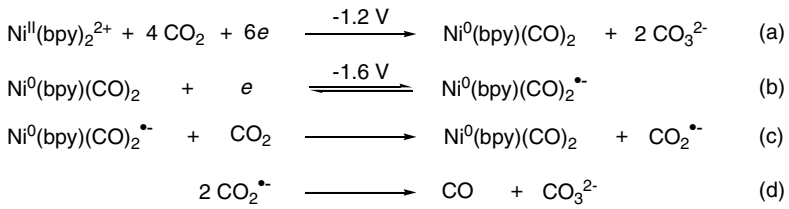
8.2.2
Method B: Utilization of CO_2 as a CO Source [16]

$Ni(bpy)Br_2$ (0.6 mmol), Bpy (0.9 mmol), NMP (30 mL), CO_2 saturation, Bu_4NBF_4 (3 mmol), 10 × (−1.6 V versus SCE), RX (10 × 0.6 mmol).

8.2.3
Method C: Utilization of $Fe(CO)_5$ as a CO Source [17]

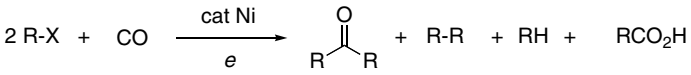
Stainless (Fe_{64}/Ni_{36}) rod sacrificial anode I = 0.5 A (25 mA · cm^{-2}), nickel cathode, DMF (50 mL), Bu_4NBF_4 (1.5 mmol), RX (20 mmol), $Fe(CO)_5$ (3 mmol), $Ni(bpy)Br_2$ (3 mmol).

In method B, the formation of $Ni^0(bpy)(CO)_2$ and the reduction of CO_2 into CO are thought to proceed as shown in Scheme 8.5. The $Ni^0(bpy)_2$ complex initially formed at −1.2 V/SCE reacts stoichiometrically with CO_2 to yield a stable $Ni^0(bpy)(CO)_2$ complex (Eq. (a)). This complex is in turn reduced at −1.6 V/SCE to give an intermediate $Ni^0(bpy)(CO)_2^{\cdot -}$ (Eq. (b)), which further reacts with CO_2 via a catalytic process to give CO and CO_3^{2-} (Eqs. (b)∼(d)).



Scheme 8.5. The electrochemical generation of $Ni^0(bpy)(CO)_2$ from $Ni^{2+}(bpy)_2$ and CO_2.

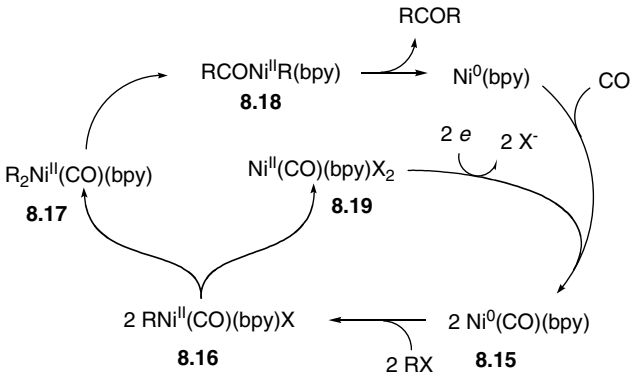
Primary benzylic, allylic, and aliphatic ketones can be prepared in good yields (Scheme 8.6). However, secondary alkyl halides, and even α-phenylethyl bromide, provide the corresponding ketones in ca. 5% yield (monitored by GLC). The major product is a reductive coupling product R–R (method C). Aromatic ketones are difficult to prepare using any of these methods as the reduction products (Ar–H), along with biphenyl or benzoic acid, are the major byproducts created when using methods A and B, respectively.



	Method A	Method B	Method C
$PhCH_2Cl$	80	75	90
$PhCH_2Br$	70	85	70
$MeCH{=}CHCH_2Cl$	65	85	–
Hex-I	50	60	80
Hex-Br	60	80	40
PhI	25	–	15
$4\text{-}CF_3C_6H_4Br$	50	0	–

Scheme 8.6. The comparison of the % isolated yields of symmetrical ketones by three different electrochemical reductive coupling methods A∼C.

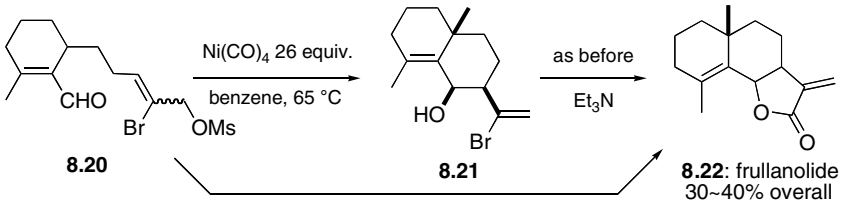
The electrochemical reductive carbonylation of organic halides may proceed according to Scheme 8.7. An active species **8.15** undergoes oxidative addition upon RX and forms **8.16**, which disproportionates to give **8.17** and **8.19**. Migratory insertion of CO into the R–Ni bond of **8.17**, followed by reductive elimination of the **8.18** thus formed, produces a symmetrical ketone with generation of Ni^0(bpy). The two-electron reduction of **8.19** regenerates an active species **8.15**.



Scheme 8.7. The plausible catalytic cycle for the electrochemical ketone synthesis from organic halides.

8.3
Termination of Cascade Reactions by Carbonylation

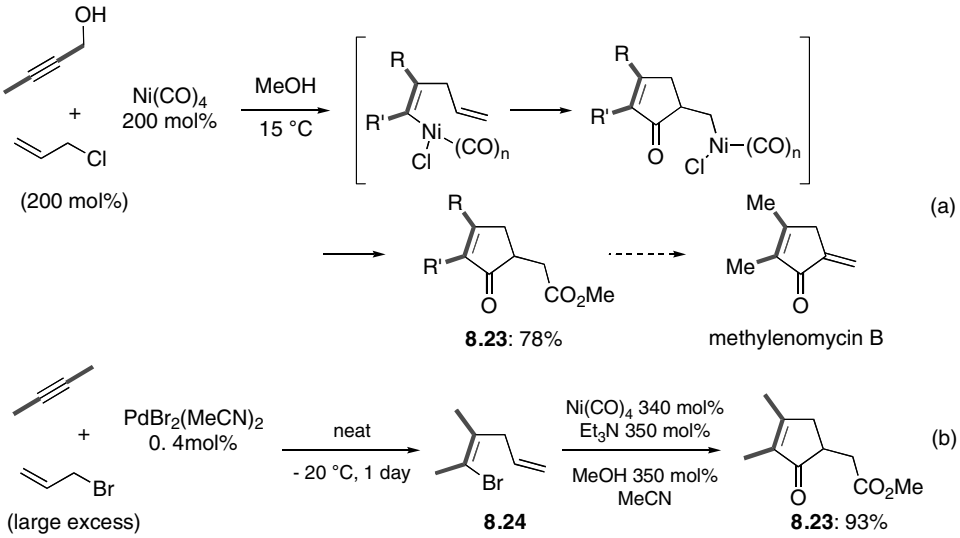
Scheme 8.8 illustrates both the strong and weak points of nickel chemistry [18]. The reaction is carried out in the presence of a large excess of $Ni(CO)_4$, and both (*E*)- and (*Z*)-**8.20** provide a mixture of an allylation product **8.21** and an allylation-carbonylation product **8.22**, an expected product frullanolide, under the various



Scheme 8.8. The $Ni(CO)_4$-promoted single-step synthesis of frullanolide. In fact, **8.20** provides a mixture of **8.21** and **8.22**, and the intermediate **8.21** is subjected to further carbonylation.

reaction conditions examined. This indicates that a π-allylnickel, generated from allyl mesylate **8.20** and $Ni(CO)_4$, is an excellent nucleophilic allylating agent, whilst a vinylnickel, formed by oxidative addition of $Ni(CO)_4$ upon **8.21**, is reluctant to undergo carbonylation. In order to convert **8.21** to **8.22**, further treatment with an excess quantity of $Ni(CO)_4$ in the presence of Et_3N is inevitable.

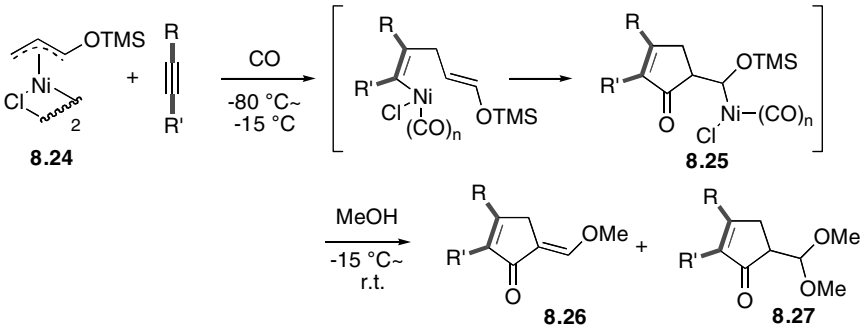
A mixture of allyl chloride, propargyl alcohol, and $Ni(CO)_4$ in methanol provides a dicarbonylation product **8.23** in remarkably good yield (Scheme 8.9). This reaction may involve the following sequence: *cis* addition across an alkyne of an η^3-allylnickel, generated in situ from allyl chloride and $Ni(CO)_4$, migrative CO insertion, intramolecular *exo-trig* alkene insertion, insertion of another CO, and methanolysis. The product **8.23** is useful as a precursor of methylenomycin B, a member of the cyclopentenoid antibiotics [19]. The same transformation can be performed in stepwise fashion: first, palladium-catalyzed *cis*-allylbromination of



Scheme 8.9. The $Ni(CO)_4$-promoted sequential cross-coupling of allyl halides and alkynes accompanied by double carbonylation.

alkyne with an excess of allyl bromide; and second, $Ni(CO)_4$-promoted double carbonylation in the presence of a limited quantity of MeOH [20].

The Mackenzie complex **8.24** reacts with unsymmetric alkynes, delivering the allyl group on the alkyne carbon which is most negatively charged (e.g., R = CO_2Me, R′ = TMS, Ph; Scheme 8.10). An intermediate **8.25** is reluctant to undergo further carbonylation, and so undergoes β-hydrogen elimination. The product **8.27** may be a Michael addition product of methanol upon **8.26** [21].

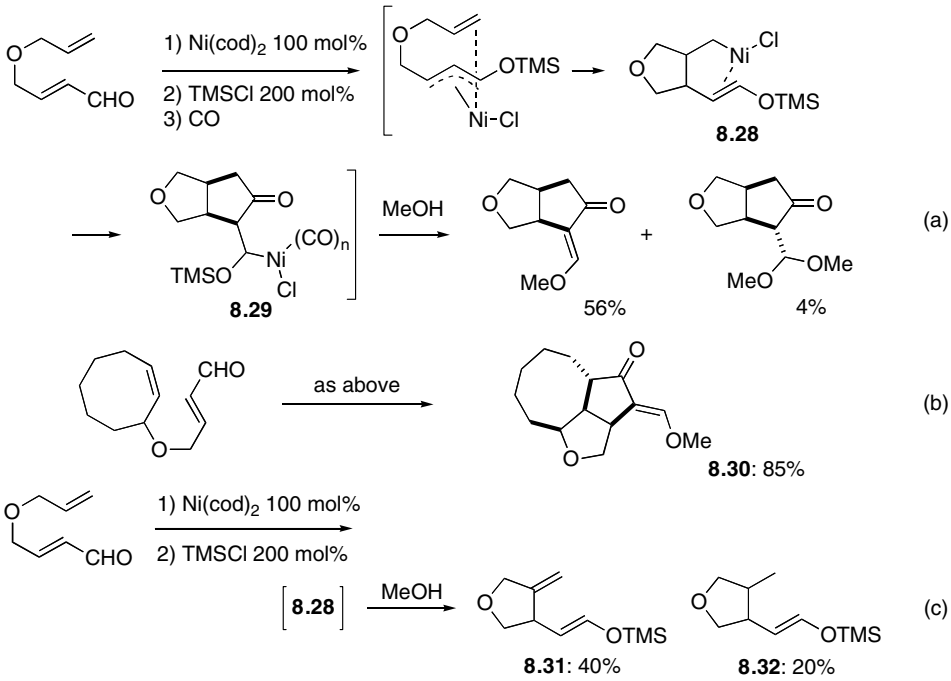


Scheme 8.10. The reaction of the Mackenzie complex **8.24** with alkynes under a CO atmosphere.

Scheme 8.11 shows that an η^3-allylnickel is also capable of undergoing addition reaction upon *alkenes* intramolecularly, thereby forming a five-membered ring intermediate **8.28**, which then undergoes migratory CO insertion and cyclization to provide a bicyclic intermediate **8.29** (Eq. (a)). As was observed above, the nickel species would not undergo carbonylation; rather, it undergoes β-hydrogen elimination [21, 22]. Equation (b) demonstrates the versatility of the present reaction, despite its not being catalytic and requiring a stoichiometric quantity of an Ni(0) species. Even in the absence of CO, an η^3-allylnickel reacts with alkene to furnish a tetrahydrofuran ring intermediate **8.28**. This in turn indicates that in Eq. (a), even in the absence of CO, $Ni(cod)_2$ and TMSCl are able to lead the reaction to an intermediate **8.28**, and CO drives **8.28** to **8.29**. In Eq. (c), β-hydrogen elimination predominates over hydrolysis [22].

8.4
Carbonylation Forming Carboxylic Acid under Phase-Transfer Conditions

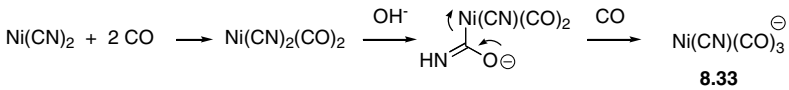
Carbon monoxide is utilized for the hydrocarboxylation of alkynes and allenes, as well as for the carboxylation of organic halides and allylic alcohols under basic phase-transfer conditions. $Ni(CN)_2 \cdot 4H_2O$ as a catalyst, cetyl(trimethyl)ammonium bromide (CTAB) or tetrabutylammonium bromide (TBAB), or sometimes PEG-400 as a phase-transfer reagent, 5 M~7 M NaOH as a base, toluene (Tol) or isobutyl



Scheme 8.11. The intramolecular addition reaction of the in-situ generated Mackenzie complexes upon alkenes.

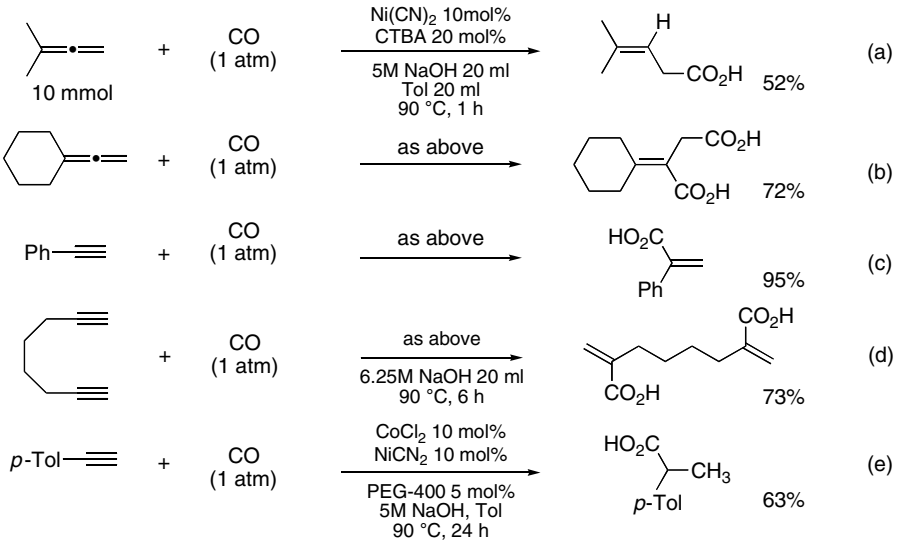
methyl ketone (IBMK) as an organic phase are commonly used. Without a phase-transfer reagent, in general, reactions either do not proceed at all, or show poorer yields (one-fifth).

Cyano(tricarbonyl)nickel(0) anion **8.33** is an active species which is formed in an aqueous phase under alkaline conditions (Eq. (8.4)) and is characterized as an ammonium salt, $(Ph_3P)_2N^+Ni(CO)_3CN^-$ [23].



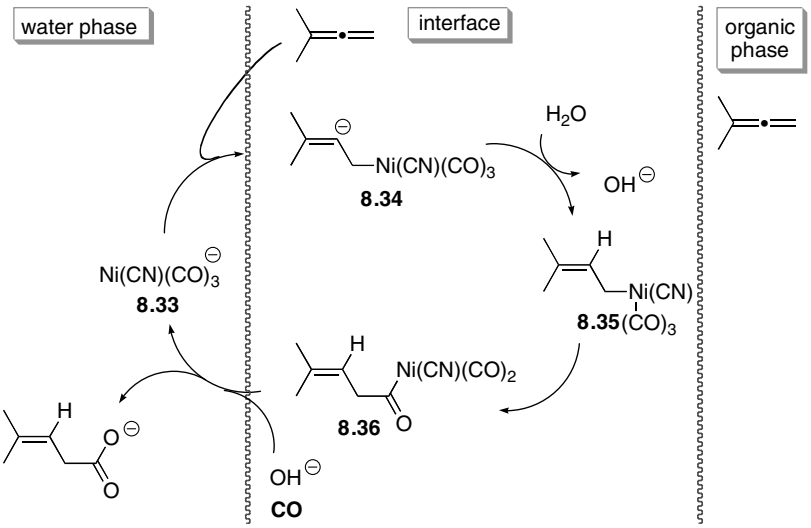
(8.4)

Reactions take place within a specialized environment, at an interface between an organic and inorganic water phase, and are expected to enhance reactivities of both nucleophiles and electrophiles. For example, 1,2-dienes (allenes) and alkynes are reluctant to undergo nucleophilic addition, whilst alkoxides, for example, only add nucleophiles under very harsh conditions (high temperatures and pressures). In contrast, under the phase-transfer conditions, cyano(tricarbonyl)nickel(0) anion **8.33** undergoes addition reaction at 90 °C upon allenes (Eqs. (a) and (b)) [24] and alkynes (Eqs. (c) and (d)) [25] to form carboxylic acids (Scheme 8.12).



Scheme 8.12. The Ni-catalyzed hydrocarboxylation reaction of allenes and alkynes under phase-transfer conditions.

Scheme 8.13 shows a catalytic cycle for the hydrocarboxylation of 1,1-dimethylallene. At an interface, **8.33** attacks allene at the terminal carbon and forms the η^1-allylnickel(II) intermediate **8.35**, which in turn undergoes CO insertion and forms an acylnickel species **8.36**. Coordination of CO with the nickel and nucleophilic

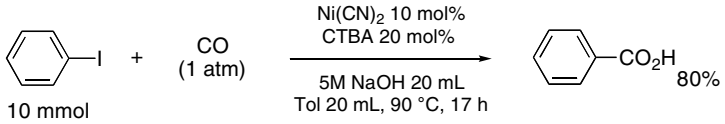


Scheme 8.13. The catalytic cycle for the nickel-catalyzed hydrocarboxylation of allenes with CO under phase-transfer conditions.

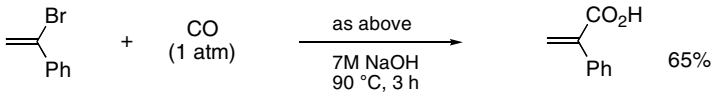
cleavage of the acyl–Ni bond yields carboxylate, with regeneration of **8.33**. Allenes usually react with nucleophiles at the central carbon because of the higher *s* character of the central carbon (sp versus sp^2), as well as allylic anion stabilization of the resulting intermediate. By contrast, in the present reaction, allenes react selectively at the terminal carbon. The stabilization gained by forming allylnickel species **8.34** and **8.35** may be a major factor for this unusual regioselectivity. The mechanism through which the dicarboxylic acid is formed (Eq. (b) in Scheme 8.12) is not clear. Nonetheless, this reaction is useful for the preparation of succinic acid derivatives from readily available (pentamethylene)allene. The reaction is also applicable to mono-substituted allenes (e.g., 1,2-pentadiene to 3-hexenoic acid in 48% isolated yield) [24].

The hydrocarboxylation of alkynes may proceed in similar way as depicted in Scheme 8.13, where alkynes are attacked by **8.33** at the internal carbon. The reaction is applicable to aromatic and aliphatic alkynes, but not to internal alkynes, which remain intact under the conditions (Eqs. (c) and (d) in Scheme 8.12). $CoCl_2$ and $Ni(CN)_2$ cooperate to convert aromatic alkynes to aliphatic carboxylic acids (Eq. (e) in Scheme 8.12) [26]. Under the phase-transfer conditions, $CoCl_2$ itself is capable of performing this transformation, albeit in low yield.

Aryl iodides (not bromides; see Eq. (8.5)) [27] and vinyl bromides (Eq. (8.6)) [28] are subject to carboxylation with CO catalyzed by $Ni(CN)_2$ under phase-transfer catalyst conditions. In these reactions, the same cyano(tricarbonyl)nickel anion **8.33** is thought to be an active species, although the mechanism involved has not been discussed explicitly.

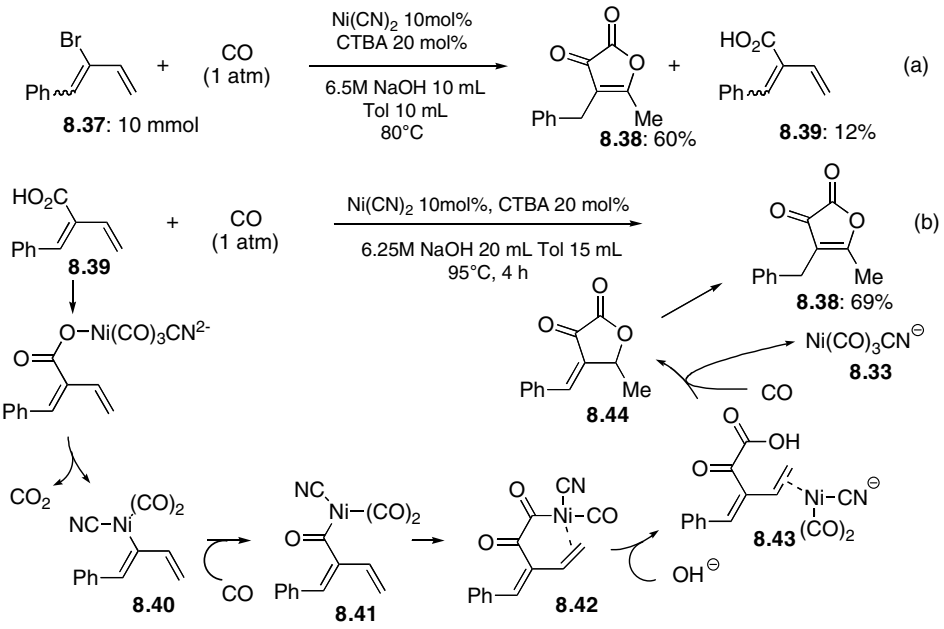


(8.5)



(8.6)

Under normal phase-transfer carboxylation conditions, bromobutadiene **8.37** is converted to an expected carboxylic acid **8.39**, albeit in low yield. In this reaction, an unexpected dicarbonylation product **8.38** is created as a major product (Eq. (a) in Scheme 8.14) [29]. Interestingly, it was later clarified that **8.39** could be converted into **8.38** under similar conditions (Eq. (b) in Scheme 8.14), and this was rationalized according to the mechanism shown below the equation [30]. Carboxylnickel(0) dianion extrudes CO_2 and forms a vinylnickel(II) intermediate **8.40**; this undergoes carbonyl insertion twice and provides a square-planar acylnickel intermediate **8.42** which is stabilized by coordination with a terminal double bond. Hydrolytic cleavage of the acyl–nickel bond, followed by CO coordination to an Ni, liberates an unsaturated carboxylic acid as a lactone **8.44** and a catalytically active species **8.33**.

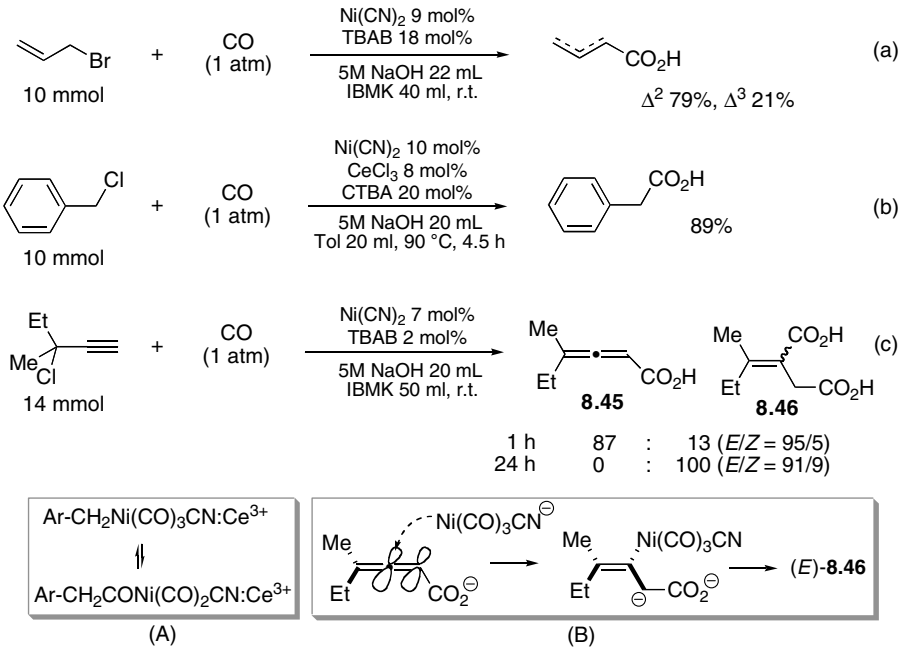


Scheme 8.14. The Ni-catalyzed double carbonylation under phase-transfer conditions and a proposed reaction mechanism.

As expected, **8.33** serves as a good nucleophile towards allyl [31], benzyl [32], and propargyl halides (Scheme 8.15) [33]. In these reactions, halides are added dropwise into a well stirred phase-transfer catalytic medium saturated with CO. In Eq. (a), a Δ^3-carboxylic acid (a primary product) isomerizes to a Δ^2-isomer under the conditions and provides a mixture of Δ^2- and Δ^3-acids, reflecting their relative thermodynamic stabilities [31].

In the absence of $CeCl_3$, the conversion of benzyl chloride to phenylacetic acid is very low, for example, 35% (Eq. (b)) [32]. A catalytic quantity of $CeCl_3$ as well as $LaCl_3$ greatly accelerates the reaction, and provides a variety of substituted phenylacetic acids and 1- and 2-naphthylacetic acids in 42∼90% isolated yields. The role of the lanthanide salts may be to promote migratory insertion of CO by coordination with CN or CO (Scheme 8.15(A)).

As is apparent from the reaction time and product distribution, propargyl chlorides are transformed first to allene carboxylic acids **8.45** (via a SN_2' mechanism) and then to methylene-succinic acids **8.46** (via Michael addition) with high (*E*)-stereoselectivity (Eq. (c)) [33]. The origin of stereoselectivity is illustrated in Scheme 8.15(B), where cyano(tricarbonyl)nickel anion attacks the allene central carbon from the least hindered side of the plane defined as the acrylic acid moiety (in this case, from the opposite side of Et group). The reader should note that, due to the electron-withdrawing carboxylate, the regiochemistry observed here is opposite to that in Eqs. (a) and (b) in Scheme 8.12.

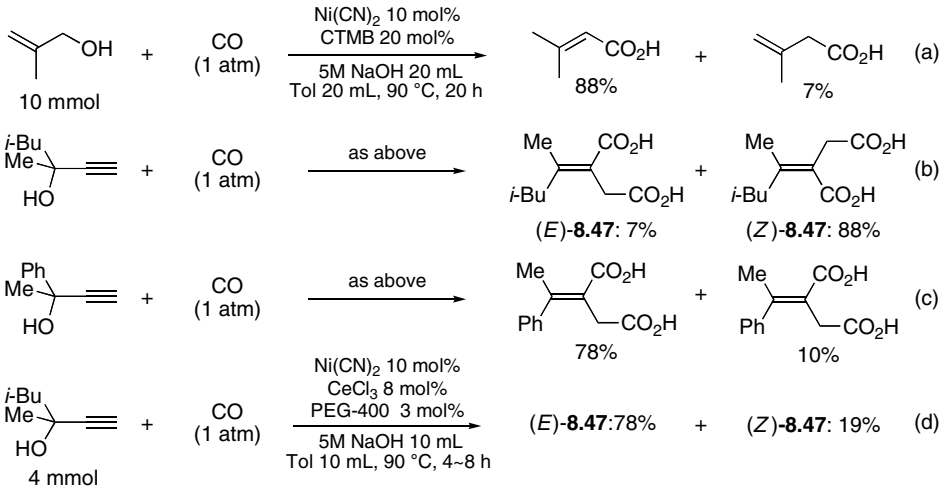


Scheme 8.15. The Ni-catalyzed carboxylation of allylic, benzyl, and propargyl halides with CO under phase-transfer conditions.

Interestingly, even allyl alcohols [34] and propargyl alcohols [35] also undergo carboxylation with CO under phase-transfer catalytic conditions. The carboxylation of allyl alcohols is believed to proceed as shown in Scheme 8.17, where the hydroxy group of **8.48** serves as a leaving group in conjunction with nucleophilic attack by $Ni(CO)_3CN^-$.

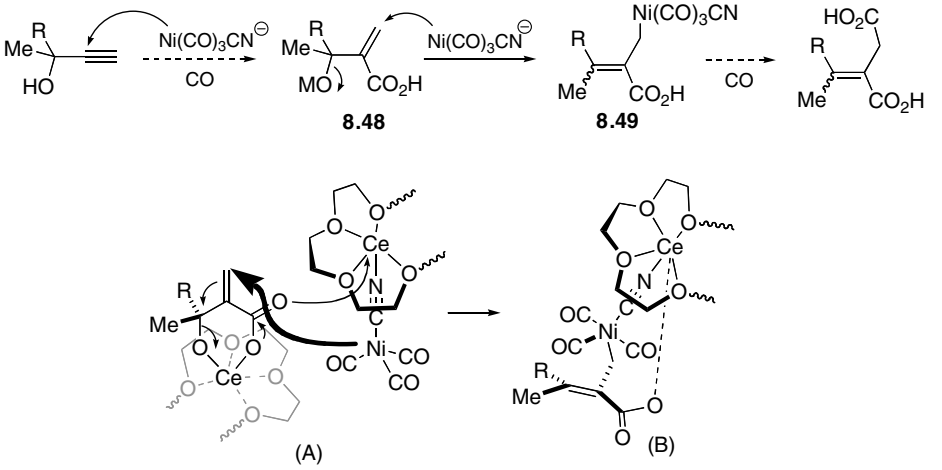
Tertiary propargyl alcohols first produce an α-carboxylation product (cf. Eqs. (c) and (d) in Scheme 8.12), and then follow the process utilized by allyl alcohols (Scheme 8.17) [35]. The latter process may be more facile than carboxylation of allyl alcohols themselves (Eq. (a) in Scheme 8.16), as nucleophilic addition of $Ni(CO)_3CN^-$ is facilitated by the electronegative CO_2^- substituent. It is important to note that the present carboxylation differs mechanistically from that of propargyl chloride (Eq. (c) in Scheme 8.15). The reaction displays contrasting stereoselectivity: the α-phenyl group guides the reaction to provide (*E*)-isomers selectively (Eq. (c)), while alkyl substituents, larger than methyl group, furnish (*Z*)-isomers selectively (Eq. (b) in Scheme 8.16).

The stereoselectivity is inverted when α-alkyl-α-methylpropargyl alcohols are subjected to the reaction conditions characterized by the use of $CeCl_3$ as a co-catalyst and PEG-400 as a phase-transfer reagent (cf. Eqs. (b) and (d) in Scheme 8.16) [35b]. A rationale is as follows: a bulky cerium–$Ni(CO)_3CN^-$ complex approaches to the six-membered cerium β-hydroxy-α-methylenecarboxylate from the less-



Scheme 8.16. The Ni-catalyzed carboxylation of allylic and propargylic alcohols with CO under phase-transfer conditions.

hindered side of the ring – that is, the side on which the methyl group resides (Scheme 8.17). Meanwhile, the static interaction between CO_2^- and the Ce^{3+} of the nucleophile forces the CO_2^- unit to move towards the Ce^{3+} ion center to form a complex B and hence to provide (*E*)-isomers selectively. The (*E*)-selectivity under these conditions is within 80~90% for many tertiary (α-methyl-α-alkyl-, α-methyl-α-phenyl-) and secondary (α-alkyl-, α-phenyl)propargyl alcohols.



Scheme 8.17. The reaction mechanism for the Ni-catalyzed carboxylation of allylic, benzyl, and propargyl alcohols with CO under phase-transfer conditions and the origin of selective formation of (*E*)-**8.47**.

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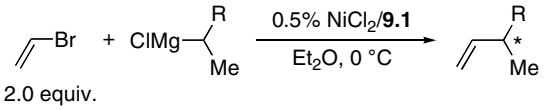
9
Asymmetric Synthesis

Ryo Shintani and Tamio Hayashi

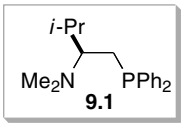
9.1
The Cross-coupling Reaction

Transition metal-catalyzed cross-coupling reactions represent a powerful approach for the construction of carbon–carbon bonds. As a result, these processes have been widely studied during the past few decades. Among the transition metals employed, the majority of the investigations have focused on nickel- and palladium-catalyzed cross-couplings of aryl and alkenyl halides with various organometallic reagents [1]. In addition to the simple, nonasymmetric cross-coupling reactions, the enantioselective variants of these have also been the topics of interest in organic and organometallic chemistry [2].

During the late 1970s and early 1980s, nickel-catalyzed asymmetric cross-coupling reactions of 1-arylethylmagnesium chlorides with vinyl bromide were described in the presence of chiral phosphine ligands [3]. It was first demonstrated that $NiCl_2$/**9.1** catalyzed the coupling reactions efficiently, affording the products in good enantiomeric excess (ee) (Scheme 9.1). The prerequisite of these reactions



Entry	R	Yield [%]	ee [%][a]
1	Ph	>95[b]	81
2	4-MeC_6H_4	94	83
3	2-naphthyl	88	72
4	*n*-hex	45[b]	6



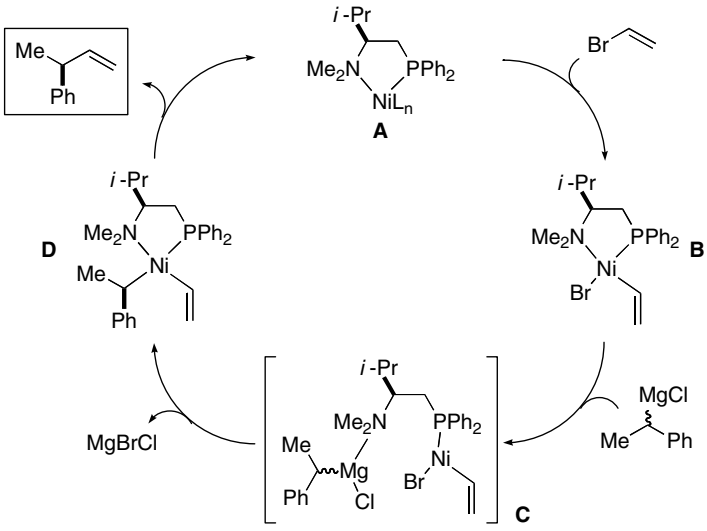
[a] Calculated from optical rotations.
[b] Determined by GLC.

Scheme 9.1. Enantioselective cross-couplings between vinyl bromide and secondary alkyl Grignard reagents in the presence of Ni/**9.1**.

Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6

using racemic secondary alkyl Grignard reagents as a coupling partner is that the equilibration of two enantiomeric forms of the Grignard reagents has to be faster than the actual coupling reaction with vinyl bromide. The proposed catalytic cycle depicted in Scheme 9.2 invokes that the dimethylamino group of the ligand **9.1** directs the approach of the Grignard reagents to the nickel-center in a diastereoselective fashion (formation of **D** via **C**), following the preceding oxidative addition of vinyl bromide (formation of **B** from **A**). The reductive elimination of diorganonickel species provides the coupling product and regenerates the nickel catalyst (formation of **A** from **D**).

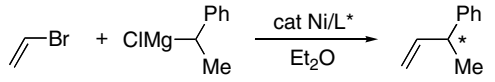


Scheme 9.2. Proposed catalytic cycle for the enantioselective Grignard cross-coupling reaction in Scheme 9.1.

Following these pioneering studies, there appeared other successful ligands, such as **9.2**–**9.4**, in the asymmetric Grignard cross-coupling reaction to afford the product in relatively good enantioselection (Scheme 9.3) [4–6].

The same reaction can also be catalyzed with similar efficiency by chiral palladium complexes. For example, Pd/**9.5** affords 79% ee of the product [7]. Secondary organozinc reagents provide better results than corresponding Grignard reagents when palladium catalysts are used (Scheme 9.4) [8].

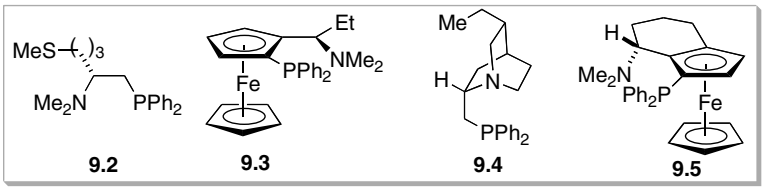
Asymmetric Grignard cross-coupling reactions can also be used to construct axially chiral binaphthyl derivatives, and there have been some reports in the literature on nickel catalysis to induce such axial chirality. For example, enantioselective couplings between 2-substituted-1-bromonaphthalenes and 2-substituted-1-naphthylmagnesium bromides in the presence of Ni/**9.8** have been developed, which furnishes enantio-enriched substituted binaphthyls (Scheme 9.5) [9]. It is worth



2.0 equiv.

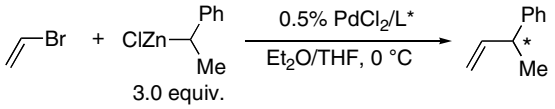
Entry	Catalyst	Temp [°C]	Yield [%]	ee [%]
1	0.8% $NiCl_2$/**9.2**	–5	N/A	88[a]
2	0.5% $NiBr_2$/1.0% **9.3**	–20	76	82
3	0.5% $NiCl_2$/**9.4**	0	50	85

[a] Calculated from optical rotation.

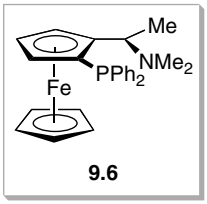


9.2 **9.3** **9.4** **9.5**

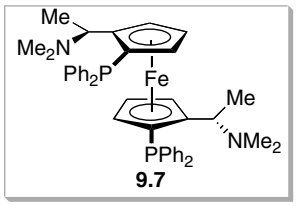
Scheme 9.3. Enantioselective cross-couplings between vinyl bromide and *sec*-phenethylmagnesium chloride in the presence of various chiral nickel complexes.



3.0 equiv.



9.6



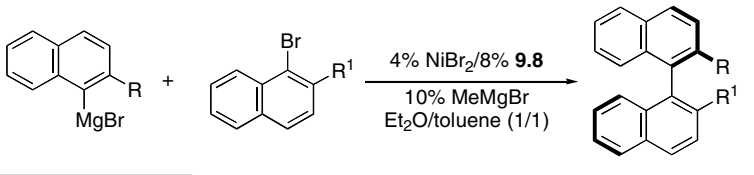
9.7

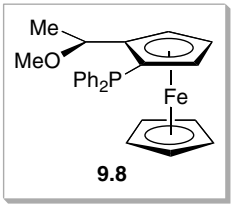
9.6: >95% GLC yield
85% ee (by optical rotation)

9.7: 100% yield
93% ee (by optical rotation)

Scheme 9.4. Enantioselective cross-couplings between vinyl bromide and *sec*-phenethylzinc chloride in the presence of chiral palladium complexes.

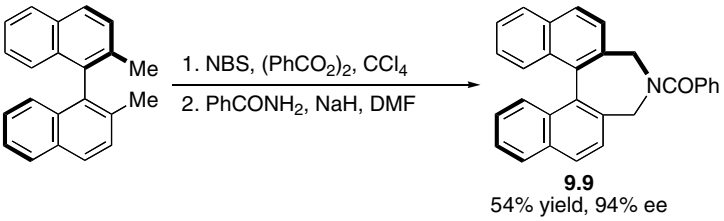
noting that the coupling between 2-methyl-1-naphthylmagnesium bromide and 1-bromonaphthalene provides significantly higher ee than the reverse combination (1-naphthylmagnesium bromide and 2-methyl-1-bromonaphthalene) for the synthesis of 2-methyl-1,1′-binaphthyl (entry 2 versus entry 3). This observation strongly suggests that the bis(naphthyl)-nickel species, which is generated after oxidative addition and transmetallation, undergoes reductive elimination without epimerization.





Entry	R	R^1	Temp [°C]	Yield [%]	ee [%]
1	Me	Me	–15	69	95
2	Me	H	–30	92	83
3	H	Me	–10	25	16
4	Et	H	–20	85	77

Scheme 9.5. Enantioselective cross-couplings between 1-naphthyl bromides and 1-naphthylmagnesium bromides in the presence of Ni/**9.8**.



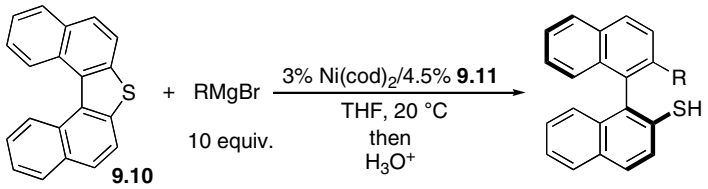
Scheme 9.6. Functionalization of enantio-enriched 2,2′-dimethyl-1,1′-binaphthyl.

The highly enantio-enriched 2,2′-dimethyl-1,1′-binaphthyl obtained by this method can be further functionalized as shown in Scheme 9.6, furnishing cyclic amide **9.9** with no loss of enantiomeric excess.

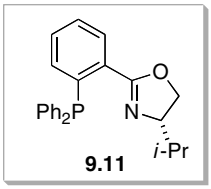
Another way to construct axially chiral binaphthyls by nickel catalysis was achieved by using a novel strategy [10]. Thus, dinaphthothiophene **9.10** was enantioselectively ring-opened and alkylated by Grignard reagents in the presence of Ni/**9.11** (Scheme 9.7). Based on the catalytic cycle described in Scheme 9.8, it was proposed that the stereochemical outcome of this coupling reaction was determined at or after the transmetallation step, since the ee values of the products depend on the nature of the Grignard reagents (e.g., entry 1 versus entry 4).

The products, such as **9.12**, obtained in this cross-coupling reaction can be further converted to various functionalized binaphthyl compounds (**9.14**–**9.17**) through the sulfoxide intermediate **9.13** as shown in Scheme 9.9 without any loss of ee.

It is worth noting that a palladium-catalyzed enantioselective desymmetrization of prochiral biaryl ditriflates has also been developed for the asymmetric synthesis of axially chiral biaryls (Scheme 9.10) [11].



9.10

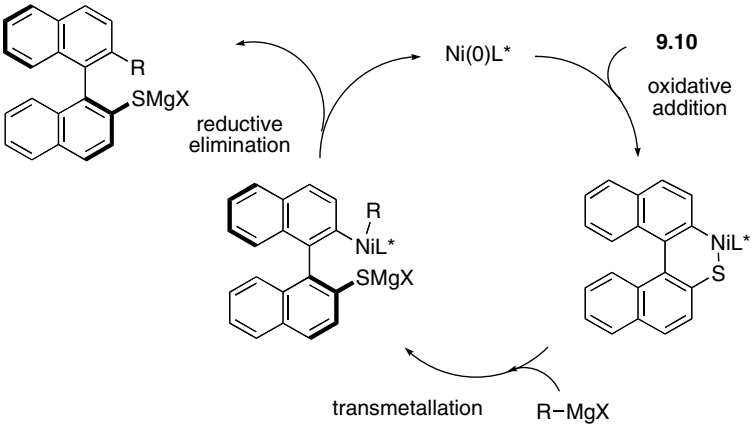


9.11

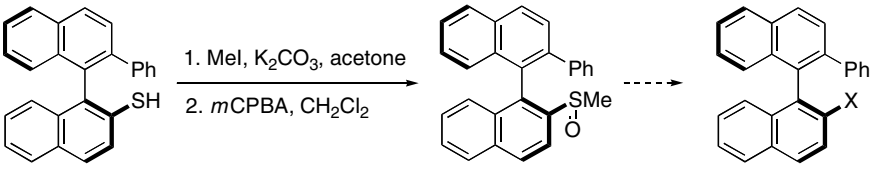
Entry	R	Yield [%]	ee [%]
1	Ph	92	95
2	4-MeC_6H_4	97	95
3	4-$MeOC_6H_4$	96	93
4	Me[a]	54	54

[a] MeMgI was used at 0 °C.

Scheme 9.7. Enantioselective ring-opening and alkylation of dinaphthothiophene **9.10** by Grignard reagents in the presence of Ni/**9.11**.



Scheme 9.8. Proposed catalytic cycle for the enantioselective Grignard cross-coupling reaction in Scheme 9.7, taking place the event of enantio-enrichment not at the stage of oxidative addition, but somewhere after the oxidative addition.

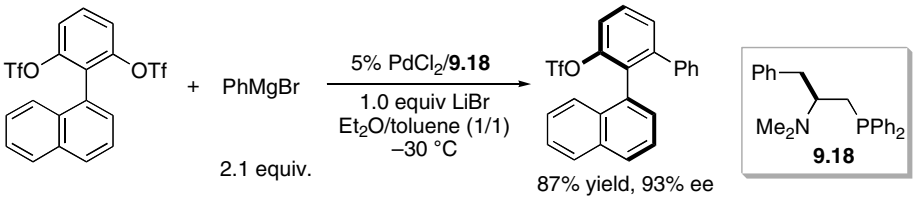


9.12

9.13
91% yield

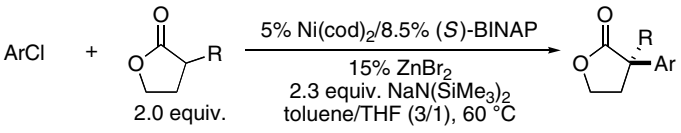
9.14: X = Me
9.15: X = I
9.16: X = B(pin)
9.17: X = PPh_2

Scheme 9.9. Preparation of several derivatives of enantio-enriched 2′-phenyl-1,1′-binaphthyl-2-thiol **9.12**.

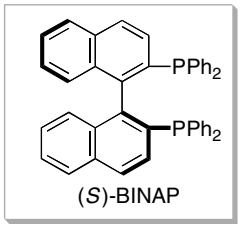


Scheme 9.10. Palladium-catalyzed enantioselective desymmetrization of prochiral biaryl ditriflates.

Not only Grignard reagents but also other nucleophiles have been used in the nickel-catalyzed asymmetric cross-coupling reactions. For example, a Ni/(*S*)-binap catalyzed asymmetric α-arylation of α-substituted γ-butyrolactones has been recently described, constructing quaternary stereocenters in high enantioselection (Scheme 9.11) [12]. The presence of $ZnBr_2$ (5–30 mol%) is essential for the acceleration of the reaction, leading to the high isolated yield. The $ZnBr_2$ presumably acts as a Lewis acid, facilitating halide abstraction from an oxidative addition intermediate Ni(Ar)(Cl)((*S*)-binap). It is also important to mention that the use of a Pd(0)/(*S*)-binap catalyst under similar conditions provides much lower yield and ee, with the opposite enantiomer of the product enriched (e.g., 58% yield, 54% ee for entry 2), although palladium catalysis was shown to be highly enantioselective for the α-arylation or α-vinylation of cyclopentanones [13].



Entry	Ar	R	Yield [%]	ee [%]
1	Ph	Me	86	>97
2	3-$MeOC_6H_4$	Me	86	96
3	3-$Me_2NC_6H_4$	Me	81	>97
4	2-naphthyl	Me	95	94
5	4-$TBSOC_6H_4$	Me	67	95
6	4-$EtO_2CC_6H_4$	Me	73	90
7	Ph	*n*-Pr	84	98
8	3-$MeOC_6H_4$	allyl	56	95
9	2-naphthyl	Bn	91	96

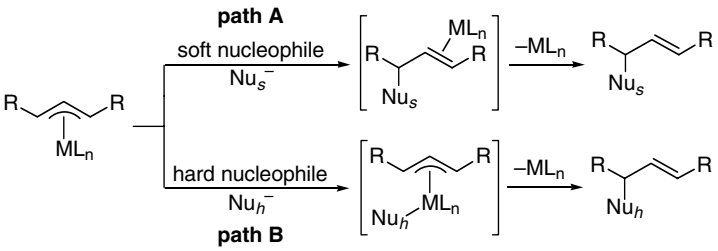


Scheme 9.11. Asymmetric α-arylation of α-substituted γ-butyrolactones in the presence of Ni/(*S*)-binap.

9.2
Allylic Substitution

9.2.1
Allylic Substitution by Carbon Nucleophiles

Since the first finding of a palladium-catalyzed asymmetric allylic alkylation in 1977 [14], the asymmetric allylation of soft nucleophiles (e.g., dimethyl malonate) by palladium catalysis has been developed considerably during the past few decades [15]. In contrast, asymmetric allylation of hard nucleophiles (e.g., Grignard reagents) has seen much less success. From a mechanistic viewpoint, an allylation of hard nucleophiles is considered to undergo a different pathway from that of soft nucleophiles (Scheme 9.12). Thus, a hard nucleophile is believed to attack the transition metal portion of a metal/η^3-allyl complex (path B) and, aside from few exceptions [16], most of the reports on allylation of hard nucleophiles utilize nickel complexes as the catalysts.

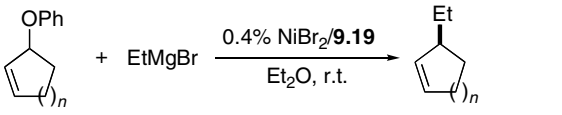


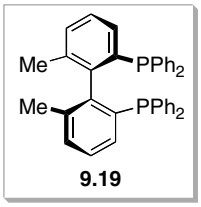
Scheme 9.12. Reaction pathways of metal-catalyzed allylic substitution reactions depending on the types of nucleophiles (soft and hard).

The first successful results in asymmetric allylation by Grignard reagents were described in 1991, which achieved good enantioselectivity in the couplings between allyl phenyl ethers and Grignard reagents in the presence of Ni/**9.19** as the catalyst (Scheme 9.13) [17]. Good yield and ee are obtained for the reactions with EtMgBr; however, a significant decrease in the yield and/or ee is observed when sterically smaller or larger Grignard reagents (e.g., MeMgBr, *n*-PrMgBr) are used.

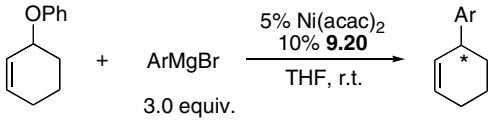
More recently, a ferrocene-based P,N-bidentate ligand **9.20** was utilized for the allylation reaction, achieving high ee with several aromatic Grignard reagents (Scheme 9.14) [18]. However, the expansion into five-membered or acyclic substrates leads to a decrease in enantiomeric excess (~40% ee).

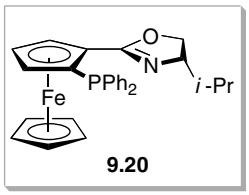
Arylboronic acids, instead of Grignard reagents, can also be used as the nucleophiles in the nickel-catalyzed asymmetric allylation reactions, although the level of enantioselectivity is only moderate (Scheme 9.15) [19]. The use of acyclic substrates leads to even lower enantioselectivity (18–28% ee) in modest yield under these conditions.





Scheme 9.13. Enantioselective allylic substitution reactions by ethylmagnesium bromide in the presence of Ni/**9.19**.

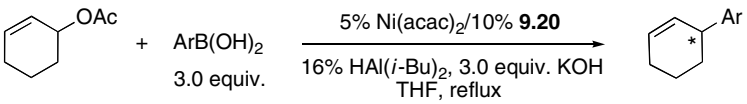




Entry	Ar	Yield [%]	ee [%]
1	Ph	98	87
2	4-$MeOC_6H_4$	69	91
3	1-naphthyl[a]	39	80
4	2-naphthyl[a]	72	88

[a] In the presence of 16% HAl(*i*-Bu)$_2$.

Scheme 9.14. Enantioselective allylic substitution reactions by arylmagnesium bromides in the presence of Ni/**9.20**.

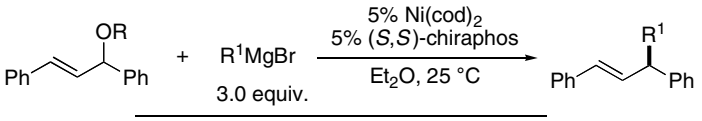


Entry	Ar	Yield [%]	ee [%]
1	Ph	81	50[a]
2	4-$MeOC_6H_4$	41	43
3	1-naphthyl	13	25
4	2-naphthyl	31	45

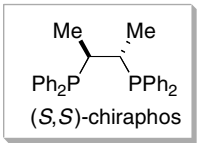
[a] Determined by optical rotation.

Scheme 9.15. Enantioselective allylic substitution reactions by arylboronic acids in the presence of Ni/**9.20**.

Compared with the cyclic allylic substrates described above, corresponding acyclic substrates have met even less success in the reaction with hard nucleophiles catalyzed by chiral nickel complexes. It was demonstrated that a Ni/(*S*,*S*)-chiraphos complex catalyzes coupling reactions between acyclic allylic ethers and alkyl



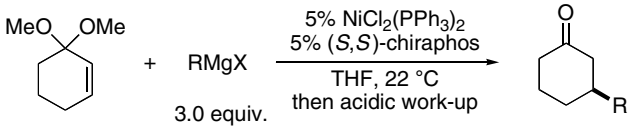
Entry	R	R^1	Yield [%]	ee [%]
1	Me	Me	81	74
2	Me	Et	91	73
3	Ph	Et	56	64
4	H	Me	10	73



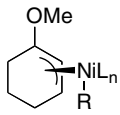
Scheme 9.16. Enantioselective allylic substitution reactions of acyclic substrates by alkyl Grignard reagents in the presence of Ni/(*S*,*S*)-chiraphos.

Grignard reagents with relatively high enantioselection (Scheme 9.16) [20]. It is worth noting that an unprotected allylic alcohol can also be employed in this reaction, albeit in low yield (entry 4).

The dimethyl acetal of 2-cyclohexen-1-one can be incorporated as an allylic substrate in the reaction with Grignard reagents by nickel catalysis [21]. The reaction presumably goes through an intermediate **9.21**. In the presence of (*S*,*S*)-chiraphos, various 3-substituted cyclohexanones can be obtained in good ee after hydrolysis (Scheme 9.17). The overall transformation is, therefore, a surrogate of the asymmetric conjugate addition to α,β-enones (see Section 9.4.2 for more details on conjugate addition reactions). It should be noted that the presence of PPh_3 in the catalyst system is essential for the high enantioselectivity. Thus, when 5 mol% of $NiCl_2$((*S*,*S*)-chiraphos) is used without any additional PPh_3, the product is obtained in very low ee (80% yield, 10% ee for entry 1).



Entry	RMgX	Yield [%]	ee [%]
1	EtMgBr	90	85
2	*n*-BuMgCl	85	85
3	*i*-BuMgCl[a]	63	70
4	PhMgBr	67	83
5	$PhCH_2CH_2MgCl$	81	84



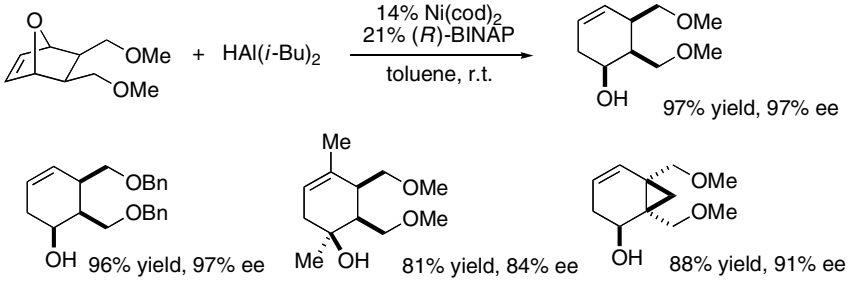
9.21

[a] Reaction was run at 50 °C.

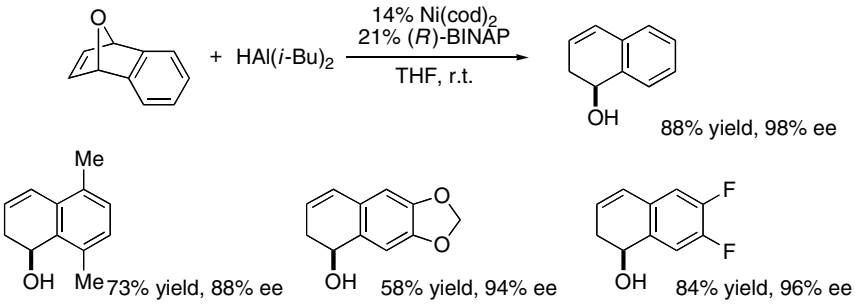
Scheme 9.17. Regio- and enantioselective allylic substitution reactions of dimethyl acetal of 2-cyclohexen-1-one by Grignard reagents in the presence of Ni/(*S*,*S*)-chiraphos.

9.2.2
Allylic Substitution by Hydride Nucleophiles

A nickel-catalyzed reductive ring-opening of oxa-bicyclic alkenes has been developed [22]. By using (*R*)-BINAP as a chiral ligand, high enantioselectivity is achieved in a number of substrates (Schemes 9.18–9.20). It is important to note that a slow addition of $HAl(i\text{-}Bu)_2$ [DIBAL-H] (over 1–4 h) is necessary for obtaining ring-opened products in high ee. In some cases, the catalyst loading can be lowered to 4 mol% with the same level of ee, although the addition rate of DIBAL-H must be even slower (over 8–12 h).



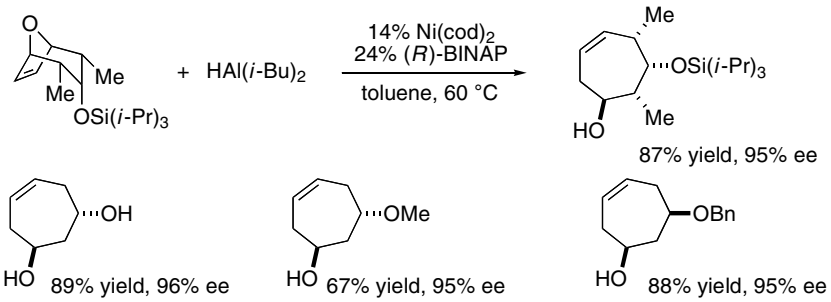
Scheme 9.18. Enantioselective reductive ring-opening of 7-oxabicyclo[2.2.1]hept-2-enes in the presence of Ni/(*R*)-binap.



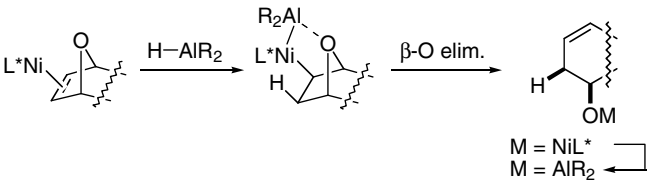
Scheme 9.19. Enantioselective reductive ring-opening of 7-oxabenzonorbornadiene in the presence of Ni/(*R*)-binap.

It was proposed that a coordination of Ni/(*R*)-binap to the alkene facilitates the subsequent diastereoselective hydro-nickellation, followed by the β-oxygen elimination (Scheme 9.21). The enantioselective ring-opening desymmetrizations of the same class of substrates by carbon-, nitrogen-, and oxygen-based nucleophiles by palladium or rhodium catalysis have also been reported [22d].

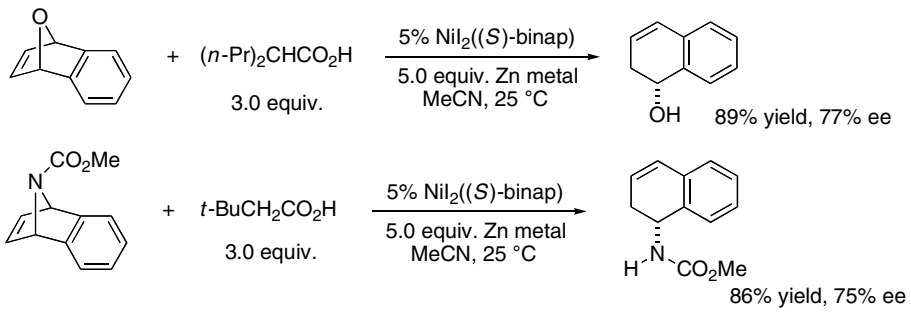
The nickel- or palladium-catalyzed asymmetric reductive ring-opening of oxa- and aza-bicyclic alkenes has been also achieved, using a combination of zinc metal/carboxylic acid, instead of DIBAL-H, as a reducing agent (Scheme 9.22)



Scheme 9.20. Enantioselective reductive ring-opening of bicyclic allylic ethers in the presence of Ni/(*R*)-binap.



Scheme 9.21. Proposed reaction pathway for the enantioselective reductive ring-opening reactions of bicyclic allylic ethers in Schemes 9.18–9.20.



Scheme 9.22. Asymmetric reductive ring-opening of oxa- and aza-bicyclic allylic alkenes, using a combination of zinc metal/carboxylic acid as a reducing agent in the presence of Ni/(*S*)-binap.

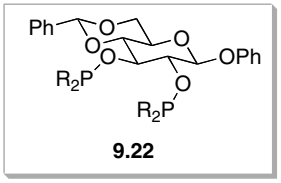
[23]. In this system, the nickel catalyst generally affords higher yield of the products in somewhat lower enantioselectivity than the palladium catalyst ($PdCl_2$((*R*)-binap)).

9.3
Hydrocyanation and Hydrovinylation Reactions

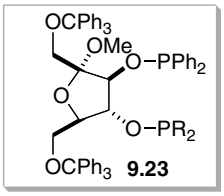
A regioselective, Markovnikov addition of HCN or ethylene to 1-alkenes provides an efficient way of creating stereogenic centers in the carbon–carbon bond-forming

process, considering that a wide variety of 1-alkenes are readily available. Therefore, the development of its enantio-controlling variant is of high value in organic chemistry.

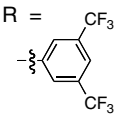
Glucose- and fructose-derived bidentate chiral phosphinite ligands **9.22** and **9.23** have been used in the nickel-catalyzed asymmetric hydrocyanation reactions [24]. Electron-deficient 3,5-bis(trifluoromethyl)phenyl groups are essential on phosphorus atoms of the ligands for achieving high enantioselectivity in these reactions (Scheme 9.23). The products thus obtained can easily be converted to profen drugs by hydrolysis of the nitrile group (e.g., ibuprofen from the product in entry 2, and naproxen from the product in entry 6 or 7).

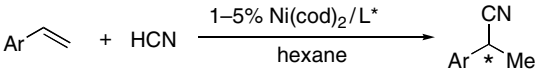


9.22



9.23





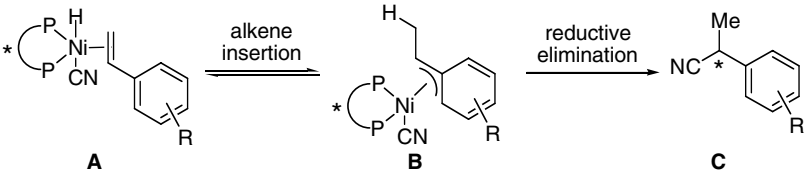
Entry	Ar	Ligand	ee [%]
1	4-MeC_6H_4	**9.22**	70
2	4-(*i*-Bu)C_6H_4	**9.22**	56
3	4-$PhOC_6H_4$	**9.22**	60
4	1-naphthyl	**9.22**	68
5	2-naphthyl	**9.22**	77
6	6-MeO-2-naphthyl	**9.22**	85-91 (*S*)
7	6-MeO-2-naphthyl	**9.23**	89-95 (*R*)

Yields are not provided.

Scheme 9.23. Regio- and enantioselective hydrocyanation of styrene and its derivatives in the presence of chiral nickel complexes.

Scheme 9.24 describes a part of the catalytic cycle of this hydrocyanation reaction, and it is proposed that the stereochemical outcome of this process is determined at the reductive elimination step (**B** → **C**), based on the mechanistic studies that showed the reversibility between intermediates **A** and **B** (see Section 3.1).

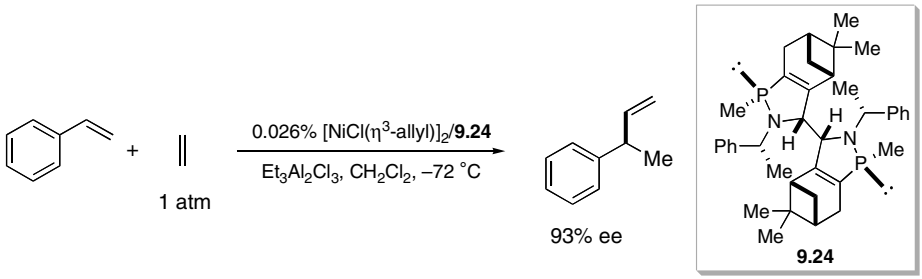
The hydrovinylation of alkenes is even more challenging in the sense that it must overcome undesired oligomerizations and/or polymerizations, which can



A **B** **C**

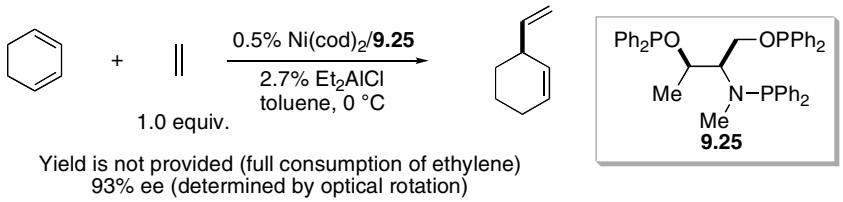
Scheme 9.24. Proposed reaction pathway of the hydrocyanation involving an equilibrium between intermediates **A** and **B** (Scheme 9.23).

compete with the desired hydrovinylation process [25]. The hydrovinylation reaction has a long history, and various transition metals (e.g., Ru, Rh, Ni, and Pd) are known to catalyze the reaction. In terms of its asymmetric variant, the first highly enantioselective example appeared in 1988. Thus, Ni/**9.24** was used as an effective catalyst to achieve 93% ee in the reaction with styrene, although the precise yield is unknown (Scheme 9.25) [26].



Scheme 9.25. Enantioselective hydrovinylation of styrene catalyzed by Ni/**9.24**.

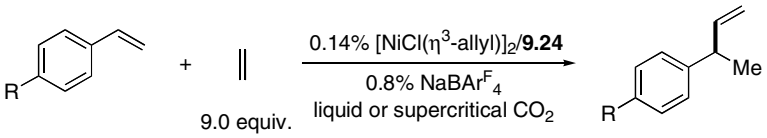
Since then, the development of asymmetric hydrovinylation has been mostly focused on the use of nickel complexes as the catalysts. For example, a nickel-catalyzed asymmetric hydrovinylation reaction of 1,3-cyclohexadiene was reported in the presence of ligand **9.25** [27]. A high ee of 93% was obtained under these reaction conditions (Scheme 9.26).



Scheme 9.26. Enantioselective hydrovinylation of 1,3-cyclohexadiene in the presence of Ni/**9.25**.

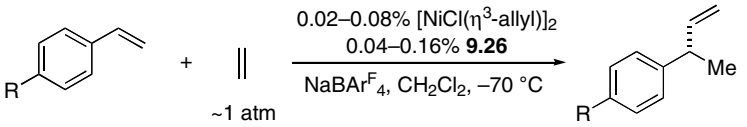
A nickel-catalyzed asymmetric hydrovinylation of styrenes in liquid or supercritical CO_2 has also been developed [28]. The use of Ni/**9.24** in combination with $NaBAr^F{}_4$ (Ar^F = 3,5-bis(trifluoromethyl)phenyl) efficiently provides hydrovinylation products in good enantiomeric excess (Scheme 9.27). An asymmetric hydrovinylation reaction of styrene can be conducted in ionic liquid/compressed CO_2 as well using the same ligand to provide the product in up to 89% ee [29].

A phosphoramidite ligand **9.26** [30] is also effective in these nickel-catalyzed asymmetric hydrovinylation reactions, achieving high catalytic activity and enantioselectivity (Scheme 9.28) [31].



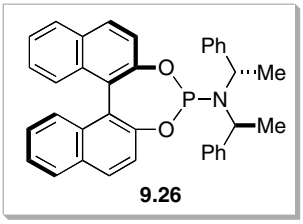
Enrty	R	Temp [°C]	Conv. [%]	Selectivity [%]	ee [%]
1	H	1	>99	89	86
2	Cl	24	>99	87	81
3	*t*-Bu	35	>99	44	89

Scheme 9.27. Enantioselective hydrovinylation of styrene and its derivatives in liquid or supercritical CO_2 catalyzed by Ni/**9.24**.



Enrty	R	Conv. [%]	Selectivity [%]	ee [%]
1	H	100	85	95
2	*i*-Bu	28	100	68
3	Br	83	99	92
4	Cl[a]	100	81	91

[a] Reaction at –30 °C.



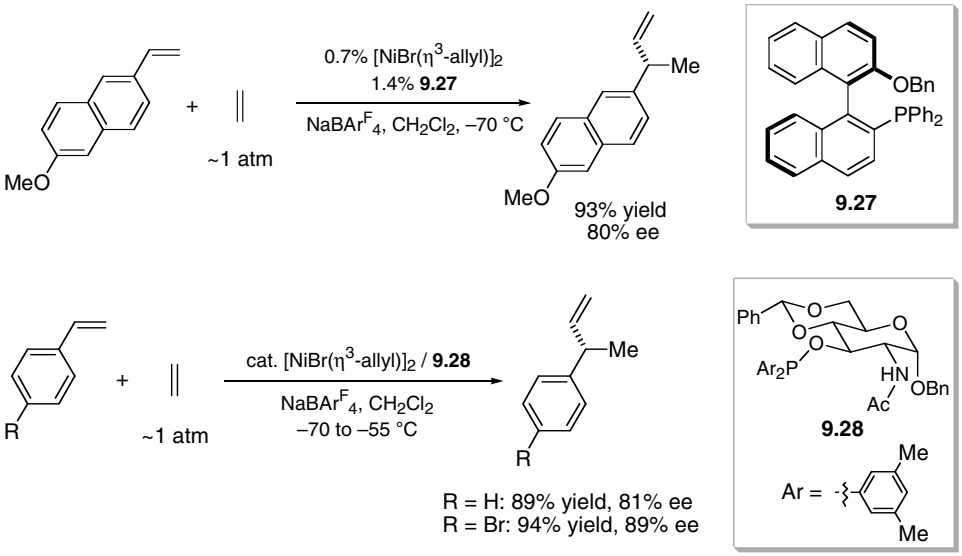
9.26

Scheme 9.28. Enantioselective hydrovinylation of styrene and its derivatives in the presence of Ni/**9.26**.

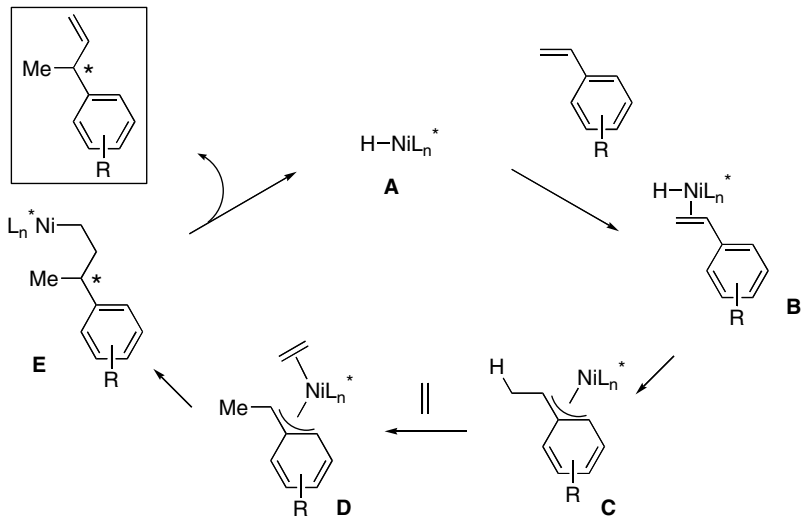
Furthermore, a range of phosphorus-based chiral ligands has been employed in the nickel-catalyzed asymmetric hydrovinylation of styrene and its derivatives [32]. Chiral monodentate ligands such as **9.27** and **9.28** are found to be particularly useful to achieve the high yield, yet with good enantioselectivity (Scheme 9.29).

A general catalytic cycle of the hydrovinylation of styrenes is proposed in Scheme 9.30. A nickel-hydride species **A** generated in situ coordinates to a styrene derivative, which inserts into the nickel-hydride in a Markovnikov fashion to afford a Ni/(η^3-benzyl) species **C**. Coordination of ethylene, followed by insertion and β-hydride elimination (**D** → **E** → **A**), furnishes the hydrovinylation product, regenerating the nickel-hydride species.

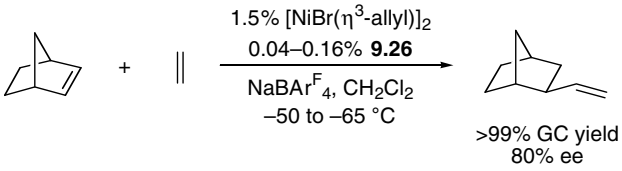
Recently, the reaction scope has been expanded to norbornene. The reaction provides *exo*-(vinyl)norbornane in good enantiomeric excess when the phosphoramidite ligand **9.26** is used as a chiral ligand (Scheme 9.31) [33].



Scheme 9.29. The highly productive and enantioselective hydrovinylation of styrenes in the presence of Ni/**9.27** and Ni/**9.28**.



Scheme 9.30. The generally accepted catalytic cycle for the enantioselective hydrovinylation of styrenes.

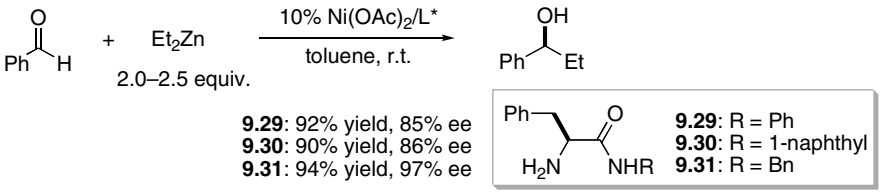


Scheme 9.31. Ni-catalyzed hydrovinylation of norbornene yielding *exo*-(vinyl)norbornane in good ee.

9.4
Reactions of Organometallic Reagents with Aldehydes and Enones

9.4.1
Reaction with Aldehydes

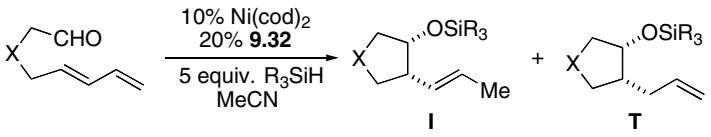
Enantioselective addition of organometallic reagents to aldehydes in the presence of a chiral catalyst is one of the most established carbon–carbon bond-forming asymmetric processes, providing enantio-enriched secondary alcohols [34]. Among the nucleophiles used in the literature, diethylzinc has been by far the most extensively studied [35]. A series of chiral α-amino acid amides, such as **9.29**–**9.31**, have been applied to a nickel-catalyzed enantioselective addition of diethylzinc to benzaldehyde (Scheme 9.32) [36]. Control experiments revealed that the reaction did not proceed in the absence of a metal salt such as $Ni(OAc)_2$ under otherwise identical reaction conditions.

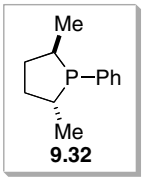


Scheme 9.32. Enantioselective addition of diethylzinc to benzaldehyde in the presence of a catalytic amount of chiral nickel complexes.

A nickel catalyst promotes the reductive cyclization of ω-formyl-1,3-dienes in the presence of hydrosilanes (Scheme 9.33; see also Section 5.2.2) [37]. The ligand of choice for this asymmetric catalysis is a monodentate phosphine **9.32**, which achieves moderate to good enantioselectivity. Other ligands, such as (*S*)-BINAP and ligand **9.11**, failed to achieve this.

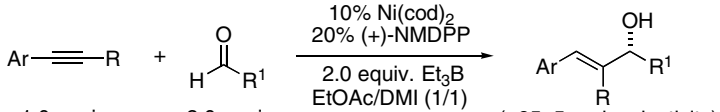
As another example of nickel-catalyzed reductive couplings with aldehydes, an asymmetric coupling of internal alkynes and aldehydes has been recently developed [38]. The reaction generally proceeds with high regio- and enantioselectivity

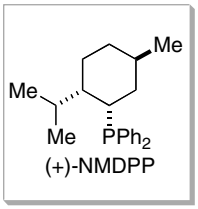




Entry	X	R_3SiH	Temp [°C]	Yield [%] I+T	Ratio I/T	ee [%] I/T
1	$C(CO_2Me)_2$	$(EtO)_3SiH$	–30	83	>50/1	73/—
2		Ph_2MeSiH	–20	83	1/1	40/85
3		$(EtO)_3SiH$	–30	80	>50/1	64/—
4	NTs	$(EtO)_3SiH$	0	60	4.6/1	48/41

Scheme 9.33. Reductive cyclization of ω-formyl-1,3-dienes catalyzed by Ni/**9.32** in the presence of hydrosilanes.





Entry	Ar	R	R^1	Yield [%]	ee [%]
1	Ph	Me	*i*-Pr	95	90
2	Ph	Me	*n*-Pr	82	65
3	4-$MeOC_6H_4$	Me	*i*-Pr	80	88
4	1-naphthyl	Me	*i*-Pr	93	90
5	Ph	*i*-Pr	*i*-Pr	58	92
6	Ph	CH_2NHBoc	*i*-Pr	60	96
7	Ph	$SiMe_3$	*n*-Pr	43	92

Scheme 9.34. Asymmetric reductive coupling of internal alkynes and aldehydes in the presence of Ni/(+)-nmdpp (DMI = 1,3-dimethylimidazolidinone).

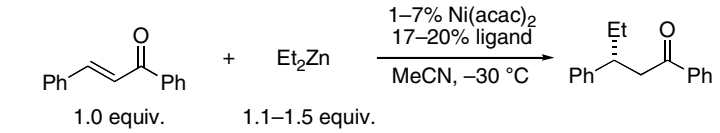
in the presence of a Ni/(+)-nmdpp catalyst, affording synthetically useful chiral allylic alcohols (Scheme 9.34).

9.4.2
Reaction with Enones

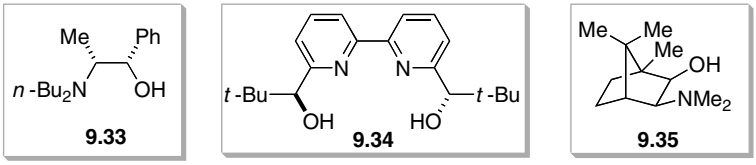
The conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is a useful approach for the construction of carbon–carbon bonds [39]. As a result, the catalytic enantioselective variants of this process have been extensively investigated [40].

Among examples described in the literature for asymmetric conjugate addition reactions, the copper and rhodium catalyses may be particularly worth mentioning. In the copper catalysis, alkylzinc reagents (e.g., diethylzinc) are generally used as the nucleophile, and early successes were restricted almost entirely to cyclic enone substrates (e.g., 2-cyclohexen-1-one) [40a]; however, a few catalysts have been recently reported that provide very good enantioselectivity for a number of acyclic enones [41]. By contrast, rhodium catalysis requires the use of aryl or alkenyl metal species (e.g., phenylboronic acid) as the nucleophilic component, and a variety of cyclic and acyclic enones have been successfully employed in this way [42].

In addition to copper and rhodium, some chiral nickel complexes have also recorded successes in this arena. The early studies in the nickel-catalyzed asymmetric conjugate addition reactions were mostly devoted to the addition of organozinc reagents to chalcones. Pioneering investigations established that certain chiral amino alcohols functioned as effective ligands for the enantioselective addition of diethylzinc to chalcone, furnishing β-chiral ketones in good ee (Scheme 9.35) [43–45].



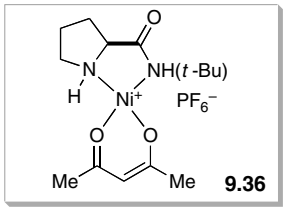
Entry	$Ni(acac)_2$ [%]	Ligand [%]	Additive	Yield [%]	ee [%]
1	7.0	**9.33** (17)	2,2'-bipyridyl (7.0%)	47	90
2	1.0	**9.34** (20)	none	75	72
3	7.0	**9.35** (17)	2,2'-bipyridyl (7.0%)	75	85

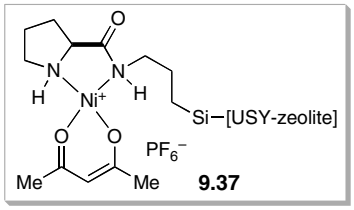


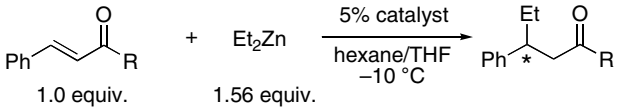
Scheme 9.35. Enantioselective conjugate addition of diethylzinc to chalcone in the presence of chiral nickel complexes.

Based on these successes in homogeneous catalysis, a highly enantioselective conjugate addition reaction catalyzed by a chiral nickel complex on a solid support has been developed (Scheme 9.36) [46]. Interestingly, an N,N-bidentate ligand **9.37** supported by USY-zeolite provides better enantioselectivity than a structurally similar, unsupported ligand **9.36** (entry 1 versus entry 2; entry 3 versus entry 4). This enhanced selectivity is attributed to the additional steric constrains at the surface of the support.

A further report has been made on homogeneous catalysis, by the use of chiral



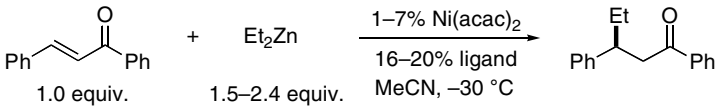




Entry	R	Catalyst	Yield [%]	ee [%]
1	Ph	**9.36**	75	77
2		**9.37**	80	91
3	Me	**9.36**	85	75
4		**9.37**	74	95

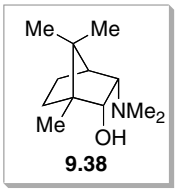
Scheme 9.36. Enantioselective conjugate addition of diethylzinc to chalcone in the presence of a chiral nickel complex on a solid support.

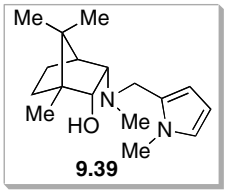
amino alcohol ligands **9.38** and **9.39** in combination with $Ni(acac)_2$ for the conjugate addition of diethylzinc to chalcone (Scheme 9.37) [47]. The same catalyst system in entry 2, however, failed to induce any significant enantioselectivity on cyclic enones such as 2-cyclohexen-1-one (12% ee). Similar systems have also been described for chalcone, using ligands **9.40** and **9.41** [48, 49].

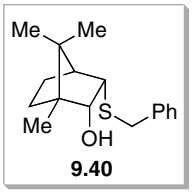


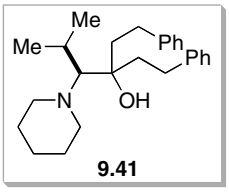
Entry	$Ni(acac)_2$ [%]	Ligand [%]	Yield [%]	ee [%]
1	1.0	**9.38** (16)	74	84
2[a]	7.0	**9.39** (16)	83	83
3	2.0	**9.40** (20)	69	80
4[b]	1.5	**9.41** (20)	71	91

[a] Reaction was run at –25 °C. [b] Reaction was run in EtCN.

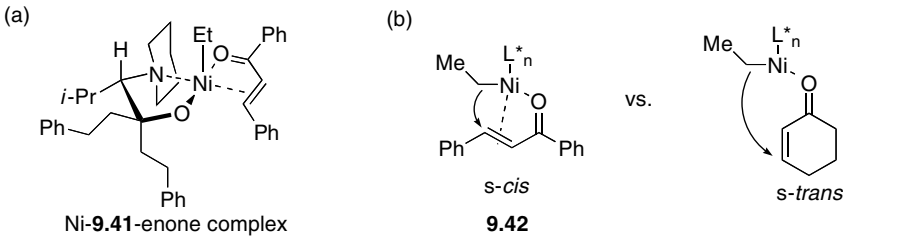








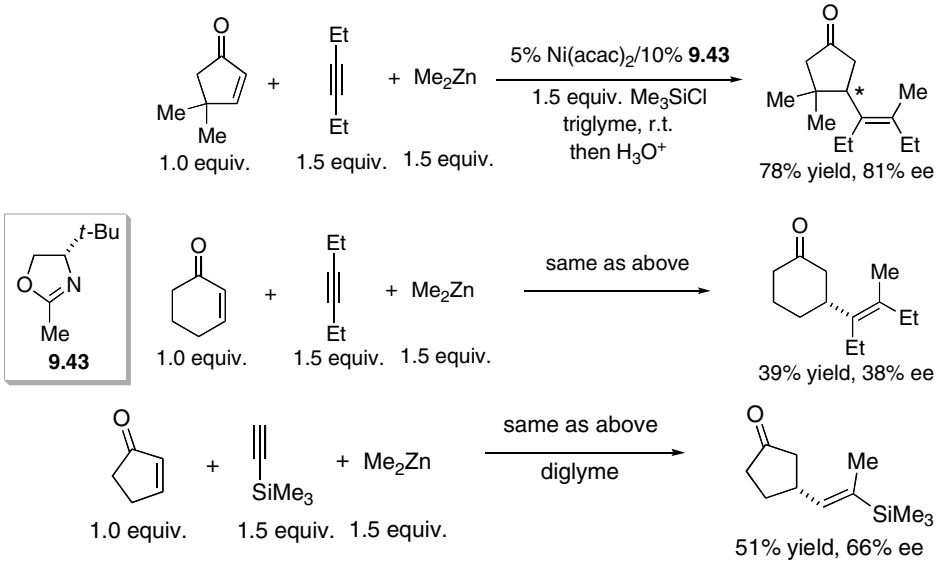
Scheme 9.37. Enantioselective conjugate addition of diethylzinc to chalcone in the presence of chiral nickel complexes.



Scheme 9.38. Model for the enantioselective conjugate addition catalyzed by a chiral nickel(II) complex (a) and transition states for acyclic and cyclic enones (b).

The origin of enantioselectivity in entry 4, for example, is depicted in Scheme 9.38(a). Likewise, in these nickel-catalyzed conjugate addition reactions of diethylzinc to enones, it is generally believed that the ethyl group is transferred intramolecularly from the nickel to the enone via a transition state **9.42**. Due to this conformational requirement, cyclic enones, which cannot take an s-*cis* conformation, are not suitable substrates to induce high enantioselectivity (Scheme 9.38(b)).

As a variant of the nickel-catalyzed conjugate addition to enones, a Ni/oxazoline **9.43** catalyst has been used to effect asymmetric three-component coupling reactions of cyclic enones, alkynes, and dimethylzinc (Scheme 9.39) [50]. Although the yield and enantioselectivity are not always high, this method can introduce highly substituted (sterically defined) alkenes at the β-position of carbonyl compounds from simple precursors.

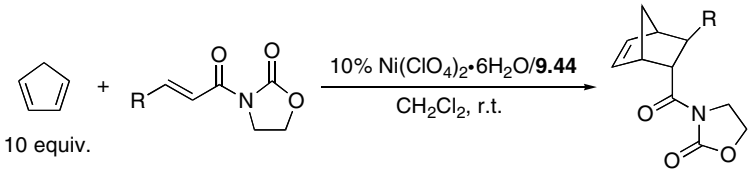


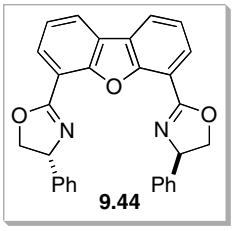
Scheme 9.39. Asymmetric three-component coupling reaction of cyclic enones, alkynes, and dimethylzinc in the presence of Ni/**9.43**.

9.5
Activation of Carbonyl Compounds for Cycloaddition and Other Related Reactions

9.5.1
The Diels–Alder Reaction

Catalytic enantioselective Diels–Alder reactions can be achieved by various Lewis acidic transition metals [51]. Among these, nickel(II) complexes have also been used as efficient catalysts in combination with nitrogen-based chiral chelating ligands. For example, a Ni(II)/**9.44** complex is an effective catalyst for the reactions between cyclopentadiene and 3-alkenoyl-2-oxazolidinones, showing high *endo*- and enantioselectivity (Scheme 9.40) [52].





9.44

Entry	R	Yield [%]	*endo*:*exo*	*endo* ee [%]
1	H	95	92:8	89
2	H[a]	96	97:3	>99
3	Me	90	92:8	93
4	*n*-Pr	quant	93:7	94

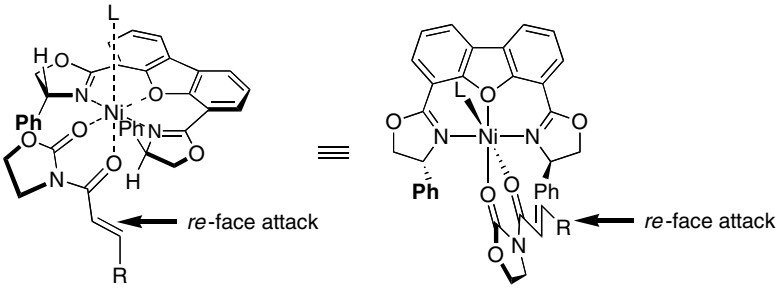
[a] Reaction at –40 °C.

Scheme 9.40. Enantioselective Diels–Alder reaction between cyclopentadiene and 3-alkenoyl-2-oxazolidinones in the presence of Ni/**9.44**.

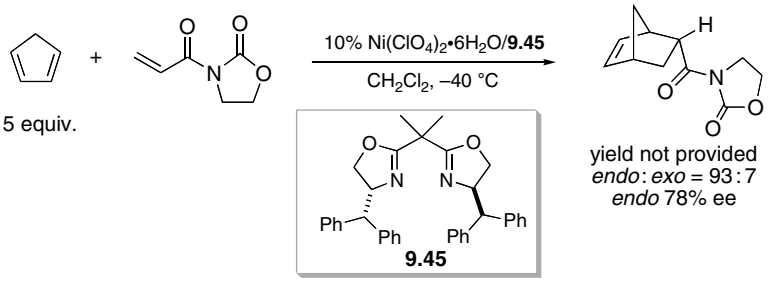
The origin of enantioselectivity can be rationalized by the *re*-face attack of cyclopentadiene to the dienophile chelated to a Ni/**9.44** complex in a square bipyramidal structure as drawn in Scheme 9.41 (Scheme 1.4; see Section 1.6). In this transition state structure, the *si*-face of the dienophile is effectively blocked by the phenyl group (boldface) of the ligand **9.44**.

In this system, a high positive nonlinear effect [53] is observed, presumably due to the formation of a *meso*-Ni(**9.44**)$_2$ complex as well as a hetero-chiral Ni(**9.44**) dimer, both of which are catalytically inactive [52b]. It was also shown that other metal perchlorate/**9.44** complexes (e.g., Mg(II), Fe(II), Co(II), Cu(II), and Zn(II)) can also induce high enantioselectivity in the Diels–Alder reaction of cyclopentadiene with 3-acryloyl-2-oxazolidinone under similar conditions.

The use of a Ni(II)/bis(oxazoline) **9.45** catalyst provides moderately good enan-



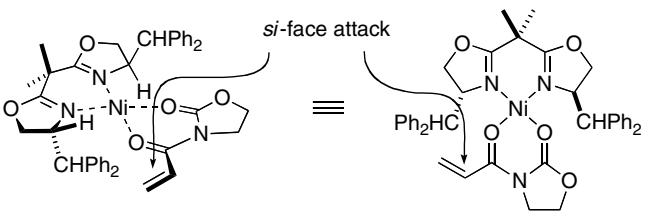
Scheme 9.41. Octahedral transition state model for the enantioselective Diels–Alder reaction in Scheme 9.40.



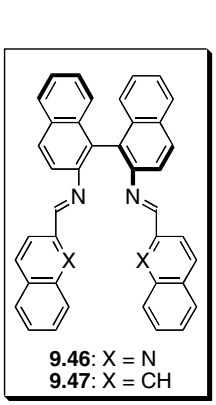
Scheme 9.42. Enantioselective Diels–Alder reaction between cyclopentadiene and 3-acryloyl-2-oxazolidinone in the presence of Ni/**9.45**.

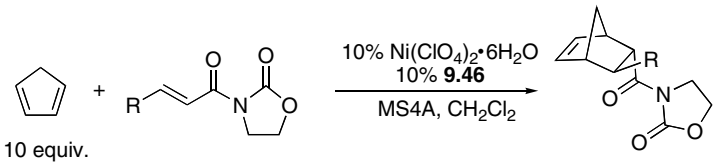
tiomeric excess (78% ee) in the reaction between cyclopentadiene and 3-acryloyl-2-oxazolidinone (Scheme 9.42) [54]. Unlike the catalyst system with the ligand **9.44** described above, a square planar transition state structure of the nickel/**9.45**/dienophile complex is proposed, which leads to a preferential *si*-face attack to the dienophile, providing the opposite enantiomer of the product enriched (Scheme 9.43).

A binaphthyl-based chiral diimine ligand **9.46** has also been utilized in the nickel(II)-catalyzed enantioselective Diels–Alder reactions of cyclopentadiene with



Scheme 9.43. Square-planar transition state model for the enantioselective Diels–Alder reaction in Scheme 9.42.





Entry	R	Temp [°C]	Yield [%]	*endo*:*exo*	*endo* ee [%]
1	H	–40	94	>99:1	94
2[a]	H	–40	quant.	88:12	50
3	Me	r.t.	85	80:20	92
4[b]	Ph	r.t.	96	73:27	90

[a] Ligand **9.47** was used. [b] 20 mol% catalyst was used.

Scheme 9.44. Enantioselective Diels–Alder reactions between cyclopentadiene and 3-alkenoyl-2-oxazolidinones in the presence of Ni/**9.46**.

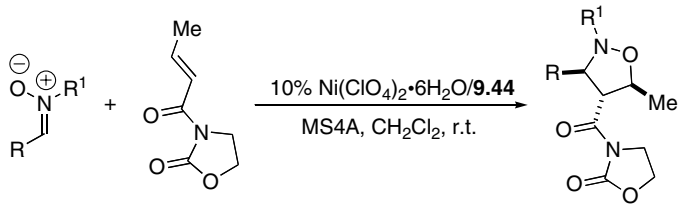
3-alkenoyl-2-oxazolidinones (Scheme 9.44) [55]. It is worth noting that the quinoline moiety in the ligand **9.46** (X = N) is essential for the high enantio-control, and the use of analogous ligand **9.47** (X = C) provides a significantly lower ee (entry 2; 50% ee).

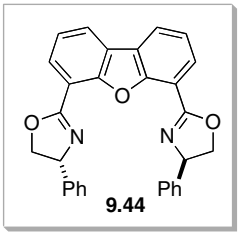
9.5.2
The 1,3-Dipolar Cycloaddition Reaction

1,3-Dipolar cycloadditions are powerful methods for constructing a variety of five-membered heterocycles in a convergent manner from relatively simple precursors [56]. In addition to the Diels–Alder reaction – as described in the previous section – chiral nickel(II) complexes can also function as excellent Lewis acid catalysts for the enantioselective 1,3-dipolar cycloaddition of nitrones. The oxazoline-based ligand **9.44** has been used in this context to achieve high enantioselectivity with 3-crotonoyl-2-oxazolidinone and various nitrones (Scheme 9.45; cf. Scheme 9.40) [57].

The presence of MS4A (100–500 mg/1-mmol scale) is essential to achieve high enantioselectivity, and the catalyst loading can be lowered to 2 mol% without decreasing the yield and ee in some cases. MS4A is considered to facilitate the abstraction of water, by which the Ni/**9.44**/dienophile complex forms a trigonal bipyramidal structure, rather than a square bipyramidal structure (octahedron), leading to a better stereoselectivity (Scheme 9.46; cf. Scheme 5.41).

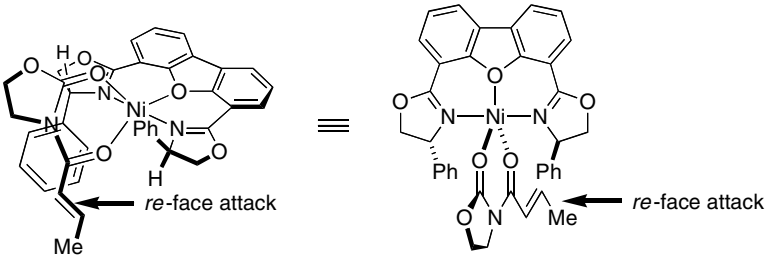
A similar system using pybox ligand **9.48** has also been reported, achieving excellent *endo*-selectivity and enantioselectivity in high yield (Scheme 9.47) [58]. The Ni(II)/pybox catalyst used in these reactions is typically prepared in the presence of MS4A at 40 °C prior to the catalytic reactions.





Entry	R	R^1	Yield [%]	*endo*:*exo*	*endo* ee [%]
1	Ph	Me	72	98:2	>99
2	Ph	Ph	96	98:2	89
3	4-$MeOC_6H_4$	Ph	100	>99:1	87
4	4-MeC_6H_4	Ph	100	99:1	>99
5	1-naphthyl	Ph	25	74:26	9
6	2-naphthyl	Ph	100	99:1	45
7	Et	Bn	92	94:6	97

Scheme 9.45. Enantioselective 1,3-dipolar cycloaddition between nitrones and 3-crotonoyl-2-oxazolidinone in the presence of Ni/**9.44**.

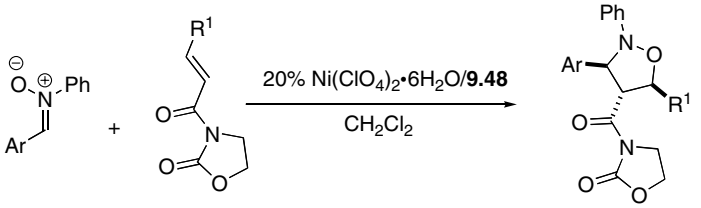


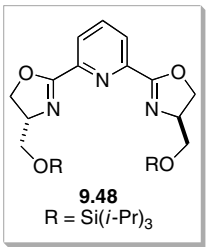
Scheme 9.46. Trigonal-bipyramidal transition state model for the enantioselective 1,3-dipolar cycloadditions in Scheme 9.45.

Subsequently, a modified system of these cycloaddition reactions has been developed to conduct the reaction in an alcoholic medium (*t*-BuOH), obtaining similar results as in dichloromethane [59].

9.5.3
The Ene Reaction and Conjugate Addition Reaction

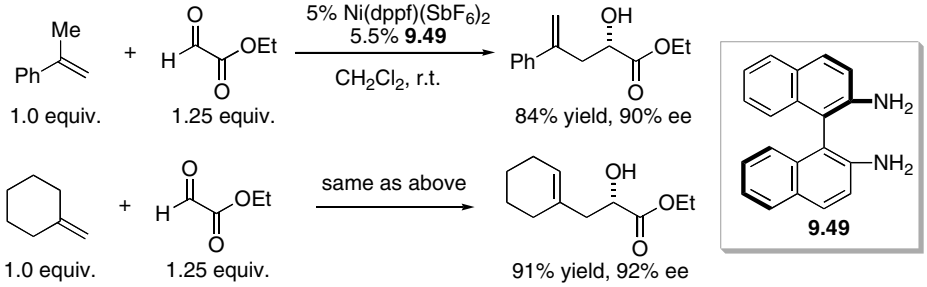
An enantioselective ene reaction catalyzed by a Ni(II)/dppf has been achieved in the presence of chiral diamine **9.49** [60]. A combination of dppf/**9.49** is essential for achieving high catalytic activity and enantioselectivity (Scheme 9.48).





Entry	Ar	R^1	Temp [°C]	Yield [%]	*endo*:*exo*	*endo* ee [%]
1	Ph	H	0	99	>99:1	>99
2	Ph	Me	25	95	98:2	96
3	4-MeC_6H_4	H	0	95	>99:1	>99
4	4-MeC_6H_4	Me	25	90	>99:1	96
5	4-$MeOC_6H_4$	H	0	98	>99:1	>99
6	4-$MeOC_6H_4$	Me	25	80	>99:1	97
7	4-BrC_6H_4	Me	25	72	>99:1	98

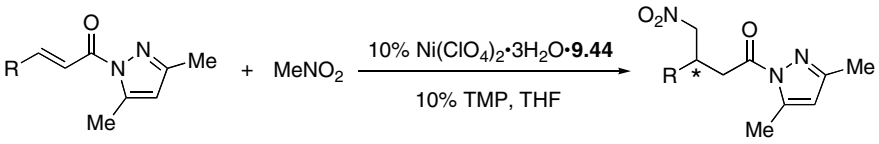
Scheme 9.47. Enantioselective 1,3-dipolar cycloaddition between nitrones and 3-alkenoyl-2-oxazolidinones in the presence of Ni/**9.48**.

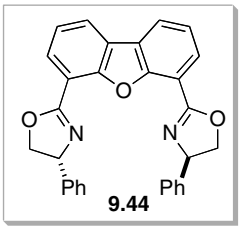


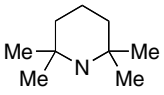
Scheme 9.48. Enantioselective ene reactions catalyzed by Ni/dppf/**9.49**.

Conjugate addition of various nucleophiles to α,β-unsaturated chelating carbonyl compounds can also be effected by a Ni(II)-based Lewis acid catalysts [61]. For example, a nickel-catalyzed highly enantioselective conjugate addition of nitromethane to α,β-unsaturated carbonyl compounds has been realized by the use of ligand **9.44** and 2,2,6,6-tetramethylpiperidine (TMP) (Scheme 9.49) [62]. A catalytic TMP is crucial for nitromethane to undergo the Michael addition reaction. The scope of this reaction is rather broad, although the reaction time is typically around 4–7 days.

Subsequently, malononitrile was also shown to be a suitable nucleophile for the Ni/**9.44**/TMP-catalyzed conjugate addition reactions, furnishing the 1,4-addition products in good enantioselectivity (Schemes 9.50 and 9.51) [63].

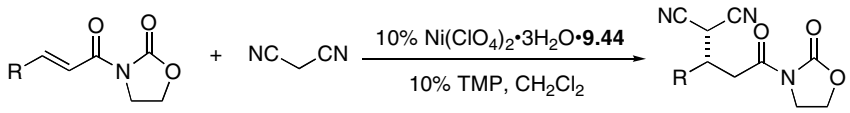






Entry	R	Temp [°C]	Yield [%]	ee [%]
1	Me	–20	85	94
2	Et	0	93	94
3	*i*-Pr	–20	74	97
4	*t*-Bu	0	39	95
5	(*E*)-MeCH=CH-	–20	49	77
6	MeO_2C	r.t.	91	83
7	Ph	–20	90	93
8	2-furyl	–20	75	97
9	2-thienyl	–20	83	97

Scheme 9.49. Enantioselective conjugate addition of nitromethane catalyzed by Ni/**9.44** and 2,2,6,6-tetramethylpiperidine (TMP).

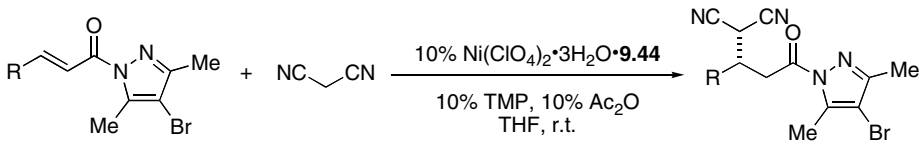


Entry	R	Temp [°C]	Yield [%]	ee [%]
1	Me	–20	90	85
2	*i*-Pr	–20	90	87
3	*t*-Bu	0	58	90
4	Ph	r.t.	95	75

Scheme 9.50. Enantioselective conjugate addition of malononitrile in the presence of Ni/**9.44**/TMP.

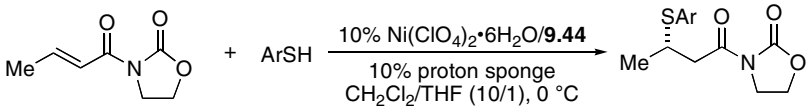
A highly enantioselective conjugate addition of thiophenols catalyzed by the Ni(II)/**9.44** has also been reported [64]. Under the optimized conditions, several aromatic thiols undergo 1,4-addition to 3-crotonoyl-2-oxazolidinone, achieving high yield and ee, although the typical reaction time is as long as 96 h (Scheme 9.52).

The same ligand **9.44** can also be applied to a nickel-catalyzed enantioselective addition of *N*-methyl aromatic amines to 3-alkenoyl-2-oxazolidinones (Scheme

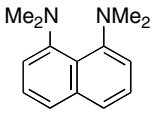


Entry	R	Yield [%]	ee [%]
1	Me	92	88
2	*i*-Pr	94	93
3	*t*-Bu	82	91
4	Ph	87	88
5	2-furyl	78	55

Scheme 9.51. Enantioselective conjugate addition of malononitrile in the presence of Ni/**9.44**/TMP/Ac_2O.

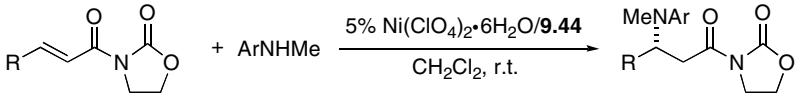


Entry	Ar	Yield [%]	ee [%]
1	Ph	84	94
2	2-MeC_6H_4	99	95
3	mesityl	36	98
4	2-(*t*-Bu)C_6H_4	96	94
5	1-naphthyl	92	55
6	2-naphthyl	88	91



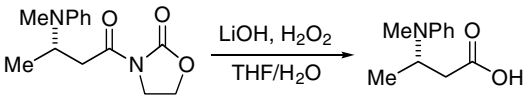
proton sponge

Scheme 9.52. Enantioselective conjugate addition of thiols in the presence of Ni/**9.44**.



Entry	R	Ar	Yield [%]	ee [%]
1	Me	Ph	62	90
2	Me	4-$MeOC_6H_4$	75	76
3	Me	4-MeC_6H_4	87	48
4	Me	4-ClC_6H_4	23	96
5	*n*-Pr	Ph	25	95

Scheme 9.53. Enantioselective conjugate addition of *N*-methyl aromatic amines in the presence of Ni/**9.44**.

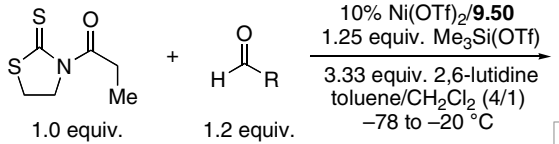


Scheme 9.54. Hydrolysis of the product in Scheme 9.53 to a β-amino acid.

9.53) [65]. The products thus obtained can easily be converted to enantio-enriched β-amino acids by treatment with LiOH and H_2O_2 in aqueous THF (Scheme 9.54).

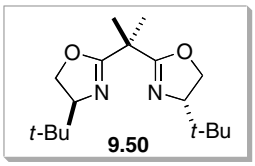
9.5.4
Addition of Nickel-Enolate Intermediates

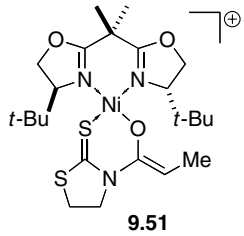
A Ni(II)/bis(oxazoline) **9.50** complex is an effective catalyst to achieve highly enantioselective aldol reactions between an *N*-(propionyl)thiazolidinethione and various aldehydes (Scheme 9.55) [66]. Unlike magnesium-catalyzed *anti*-aldol processes [67], these nickel-catalyzed conditions provide *syn*-aldol adducts predominantly (*syn*:*anti* = 88:12–98:2), presumably through an intermediate **9.51**, a chelation form of a (*Z*)-enolate.



Entry	R	*syn*:*anti*	Yield [%]	ee [%]
1	Ph	94:6	81[a]	97
2	4-MeC_6H_4	93:7	80	95
3	1-naphthyl	93:7	73	92
4	2-naphthyl	92:8	82[a]	93
5	(*E*)-PhCH=CH	88:12	63	93
6	Me	97:3	86	93
7	*i*-Pr	98:2	70	90

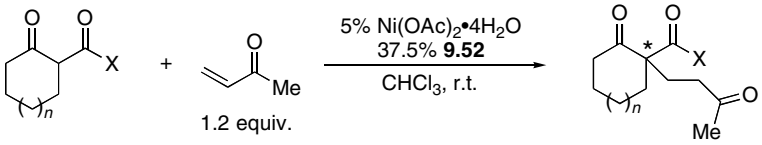
[a] 5 mol% catalyst was used.

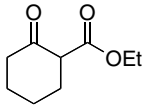
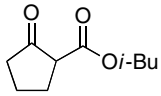
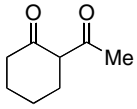


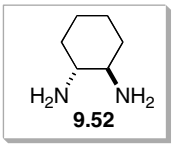


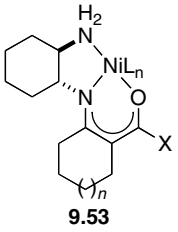
Scheme 9.55. Enantioselective aldol reactions between *N*-(propionyl)thiazolidinethione and aromatic and aliphatic aldehydes in the presence of Ni/**9.50**.

Nickel-catalyzed enantioselective conjugate addition of β-keto esters and 1,3-diketones to methyl vinyl ketone has also been reported. Thus, a Ni(II)/diamine **9.52** catalyst is able to create quaternary stereocenters in moderate to good enantioselectivity (Scheme 9.56) [68]. The reaction presumably goes via nucleophilic addition of an intermediate **9.53** composed of a chiral enamine coordinated to nickel(II).

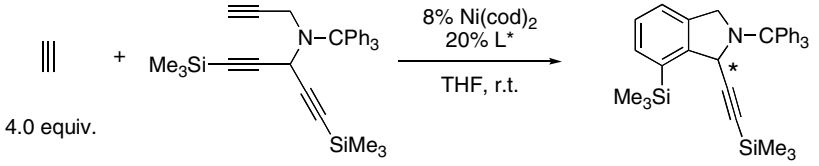


Entry	Substrate	Yield [%]	ee [%]
1		37	91
2		31	74
3		57	41

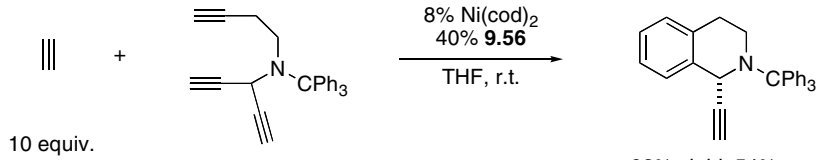




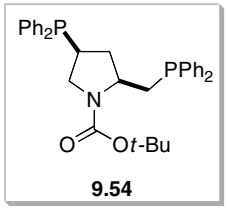
Scheme 9.56. Enantioselective conjugate addition of β-keto esters and 1,3-diketones to methyl vinyl ketone in the presence of Ni/**9.52**.

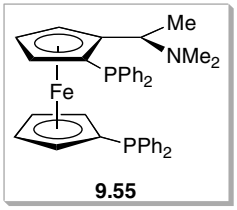


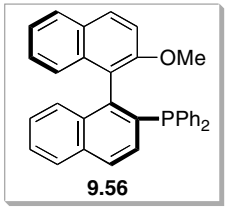
9.54: 92% yield, 60% ee
9.55: 52% yield, 73% ee



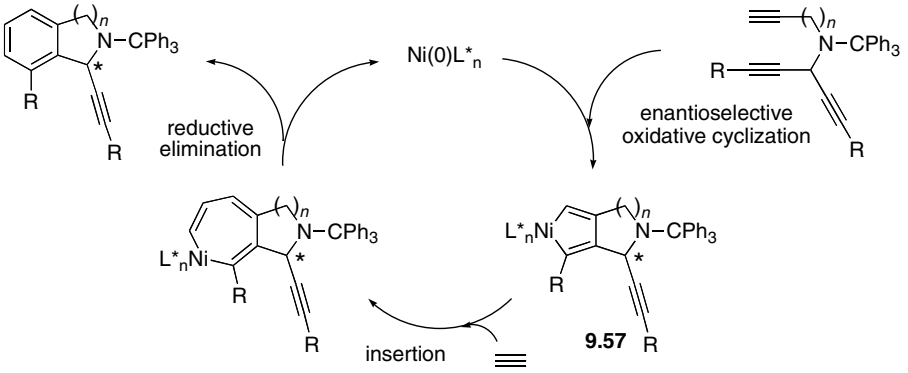
62% yield, 54% ee







Scheme 9.57. Enantioselective synthesis of isoindolines and isoquinolines by [2+2+2] cycloadditions in the presence of chiral nickel(0) complexes.



Scheme 9.58. Proposed catalytic cycle for the reactions in Scheme 9.57.

9.6 Other Reactions

Transition metal-catalyzed [2+2+2] cycloaddition of alkynes is a convergent method for the synthesis of highly substituted aromatic compounds. Asymmetric synthesis of isoindolines and isoquinolines has been developed by the use of a nickel(0)-catalyst.

The reaction proceeds presumably through a nickellacyclopentadiene intermediate (Scheme 9.57) [69]. The origin of enantioselectivity in this reaction is a differentiation of the two enantiotopic alkynes using a chiral Ni(0)/phosphine catalyst (Scheme 9.58; enantioselective desymmetrization), selectively forming one of the two diastereomeric intermediates **9.57** during an oxidative cyclization step.

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10
Heterogeneous Catalysis

Tsutomu Osawa

The heterogeneous nickel (Ni) catalyst was first reported by Sabatier et al.* as early as 1897 [1] for gas-phase hydrogenation, since which time it has been used for a wide variety of reactions, including hydrogenation, hydrogenolysis, reductive amination, desulfurization, methanation, and steam reforming, either in the laboratory or on an industrial scale. In this chapter, heterogeneous Ni catalysts and reactions catalyzed by them are described from a synthetic organic chemistry viewpoint. The general characteristics of the heterogeneous catalyst and catalysis (reaction on a solid surface) are introduced, after which methods of Ni catalyst preparation and their reactions are described. Most of this chapter relates to the heterogeneous Ni catalyst for asymmetric synthesis, and it is hoped that the information provided will help synthetic organic chemists to become familiar with – and to use – heterogeneous Ni catalysts as a routine.

10.1
Heterogeneous Catalysts and Catalytic Reactions

Compared with their homogeneous counterparts, heterogeneous catalytic reactions possess certain characteristic features because they proceed on a solid surface. The general characteristics of a heterogeneous catalyst and catalysis are briefly outlined in this section, though detailed discussions of the differences between homogeneous and heterogeneous catalyses are described elsewhere [2].

*) Two French chemists, P. Sabatier (1854–1941) and F. A. V. Grignard (1871–1935) were awarded the Nobel Prize in 1912, the former for the contribution to the catalytic hardening of natural unsaturated fatty acids and the industrial methanol synthesis, and the latter for the synthesis of organomagnesium reagents (Grignard reagents).

Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6

Tab. 10.1. General characteristics of heterogeneous catalysts and catalytic reactions.

Property	*Characteristics*
Catalyst availability	Commercially available for general reactions
Catalyst preparation	Easy, but sometimes requires special know-how
Catalyst reproducibility	Good, but requires special caution with raw materials
Catalyst separation	Easy (only filtration) and low costs
Catalyst re-use	Easy recovery and re-use
Reaction apparatus	Special apparatus needed for a high-pressure reaction
Large-scale production	Easy to scale up
Catalyst storage	Generally sensitive to air
Catalyst characterization	Difficult to understand the phenomena on the solid
Active sites (species)	Difficult to create single types of active sites

10.1.1 Comparison of Heterogeneous and Homogeneous Catalysts and Catalytic Reactions

The general characteristics of heterogeneous catalysts and catalytic reactions are summarized in Table 10.1.

Although the preparation of heterogeneous catalysts is generally more straightforward than that their homogeneous counterparts, a degree of specialized knowledge is required to prepare solid catalysts. Heterogeneous catalysts possess various properties, including the specific surface area of the metal and its support, the metal crystallite size (distribution), the pore size of the support, the particle size of the catalyst, the promoter, and also impurities. As each of these factors affects the catalytic activity and selectivity, special care must be taken in catalyst preparation. For example, different raw materials and preparation methods produce different catalysts, even if designated by the same name (e.g., 20% Ni/Al_2O_3 = 20% nickel loaded on alumina). Therefore, correct raw materials and catalyst preparation methods must be chosen for any intended reaction. The ease with which the catalyst is separated, re-used, and scaled-up for the reaction are usually claimed to be advantages of heterogeneous catalysts, which can be used in flow reactors that successively generate the products or, in the case of the gas-phase reaction or fast reaction, in the liquid phase. These are important factors from a practical viewpoint.

There are, however, some disadvantages associated with heterogeneous catalysts. Reactions conducted over heterogeneous catalysts occasionally require specialized equipment (not normally for laboratory-based organic syntheses) – perhaps a stainless steel autoclave for high-pressure reactions and/or a specialized apparatus for the gas feed. Also, analyses of the reaction mechanism and the creation of single type active sites on the solid are more difficult to perform for heterogeneous reactions than for homogeneous.

10.1.2
Reactions over Heterogeneous Catalysts in Liquids

The syntheses of fine chemicals using heterogeneous catalysts are usually carried out in a liquid phase. Special care must be taken with liquid phase reactions catalyzed by heterogeneous catalysts, as these differ from homogeneous reactions. An example is hydrogenation over a heterogeneous catalyst, which is a three-phase system: 1) the gas phase of hydrogen; 2) the liquid phase of the reactant and solvent; and 3) the solid phase of the catalyst (Fig. 10.1).

In order for the reaction to proceed at a reasonable rate, hydrogen in the gas phase must pass through the gas–liquid interfacial barrier, diffuse into the liquid, and reach the active site on the catalyst surface. The substrates should diffuse in the liquid, reach the active site on the surface, be converted to the product, and then diffuse again into the liquid. If the catalyst is porous, diffusion in the pores should also be taken into account. Every step can be a rate-determining step, and the position of that step can alter the selectivity of the product. The parameters affecting the mass diffusion include the agitation speed, the pressure of the gas phase, the amount of catalyst, the particle size (distribution) of the catalyst, the pore size (distribution), and the concentration of the substrate [3]. In order to draw upon the maximum power of the catalyst, attention must be paid to whether the reaction is under surface reaction control or mass diffusion control. For example, in the enantio-differentiating hydrogenation of α-ketoesters over cinchona-modified Pt/Al_2O_3, a low enantioselectivity is obtained under the gas–liquid and/or liquid–solid transport resistance [4].

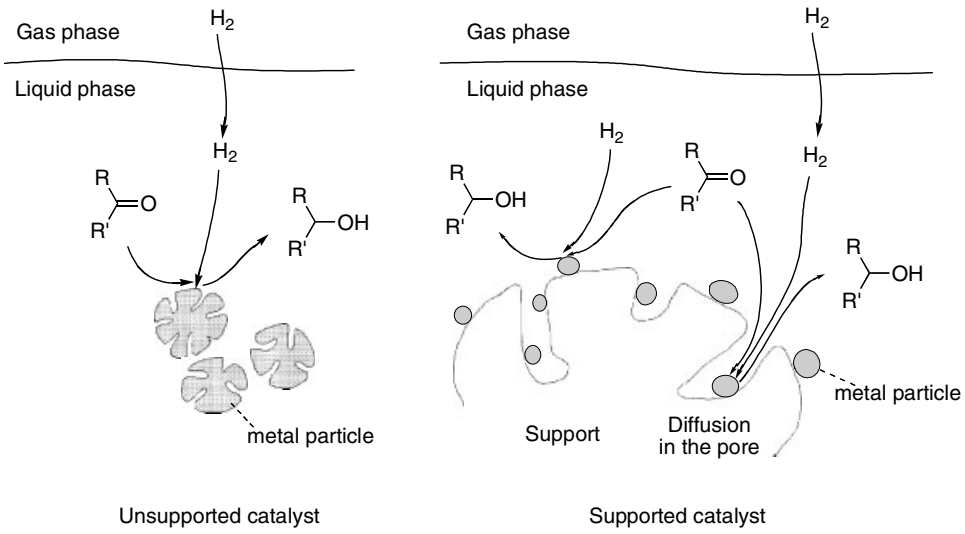


Fig. 10.1. The three-phase system for hydrogenation over a heterogeneous catalyst.

10.2
Heterogeneous Ni Catalysts

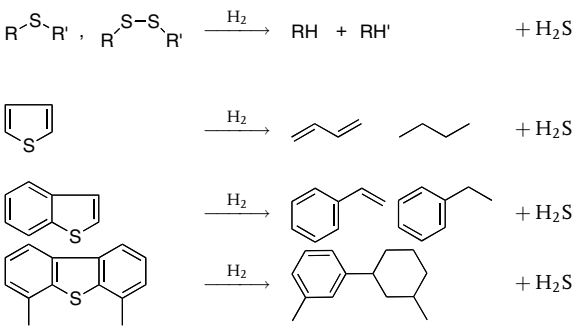
Heterogeneous Ni catalysts are widely used for reactions related to the petroleum refining industry and for organic functional group transformations in the fine chemical industry.

10.2.1
Reactions in the Petroleum Industry

In the fuel or petroleum industries, steam reforming, hydrodesulfurization, and methanation reactions are catalyzed over heterogeneous Ni catalysts. A summary of the reactions and the representative catalysts are shown in Table 10.2.

Steam reforming of methane or natural gas (light to moderate hydrocarbons) is a process for the production of hydrogen and synthesis gas (a mixture of CO and hydrogen) [5], both of which are among the most important raw materials in the chemical industry. They are mainly consumed in ammonia synthesis (49% of the total hydrogen consumed worldwide), methanol synthesis (10%), and petroleum refining [6]. The demand for hydrogen is steadily increasing, because ultradeep hydrodesulfurization is required due to strict regulations relating to the sulfur con-

Tab. 10.2. Ni-catalyzed reactions used in the petroleum industry.

Process Name	*Reaction*	*Catalyst*
Steam reforming	$C_nH_m + nH_2O \rightarrow nCO + (n + m/2)H_2$ $CO + H_2O \rightleftharpoons CO_2 + H_2$ (Water gas shift reaction) $CO + 3H_2 \rightleftharpoons CH_4 + H_2O$ (Methanation)	Ni/Al_2O_3
Hydrodesulfurization		$Ni–Mo/Al_2O_3$ $Co–Mo/Al_2O_3$
Methanation	$CO + 3H_2 \rightarrow CH_4 + H_2O$ $CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O$ $C_nH_{2n+2} + (n-1)H_2 \rightarrow nCH_4$	Ni/Al_2O_3 Ni/Kieselguhr

tent in diesel oil and the increase in demand for fuel cell systems. From an economical viewpoint, Ni/Al_2O_3 with alkaline or Ni/MgO is a conventional catalyst for steam reforming in large-scale plants. The reaction is highly endothermic and in an industrial environment is operated at a high temperature (1000–1150 K). A high partial pressure (2–4 MPa) of excess steam is required to prevent carbon deposition on the catalyst surface. The water gas shift reaction constitutes steam reforming. Part of the CO is consumed by the methanation reaction and, as the water gas shift reaction and methanation reach thermodynamic equilibrium, the composition of the gas product is determined by the reaction temperature, pressure, and ratio of hydrocarbon to steam, irrespective of the type of hydrocarbon present. The reaction conditions for steam reforming are severe for the catalyst and reactor tube materials, and consequently a catalyst with sufficient activity at lower temperatures is currently under investigation. A Ni catalyst with a bimodal pore structure (comprising mesopore and macropore together) increases the catalytic activity three- to four-fold compared with commercial catalysts, and lowers the reaction temperature by 25 K [6].

Hydrodesulfurization is the hydrogenolysis of sulfur-containing compounds and is aimed at reducing the sulfur content of petroleum fractions. Accordingly, this process is vastly important in the petroleum refining field [7]. Crude oil usually contains 0.1–3% sulfur, and this must be reduced to 500 ppm, since the sulfur-containing fuel causes SO_x air pollution. The reactions of representative sulfur-containing compounds are shown in Table 10.2. The type and size of the sulfur-containing molecules depend on the distillate fuel fractions. Fractions with higher boiling points (e.g., gas oil or vacuum gas oil) are usually rich in sterically hindered and less-reactive (difficult to remove) sulfur-containing molecules. The $CoO(3.5–6\%)\text{-}MoO_3(9–16\%)/Al_2O_3$ or $NiO(3–5\%)\text{-}MoO_3(13–26.5\%)/Al_2O_3$ are widely used in this process, these catalysts being sulfided in the reactor before using CS_2, H_2S, or suffering compounds in the feedstock. The active species of the hydrodesulfurization catalyst would be the Co(Ni)-Mo-S phase. The hydrodesulfurization reaction is usually performed at 573–623 K and at 5–10 MPa. When producing affordable ultra-low-sulfur fuels, an improvement in the catalyst and the process is required, as many countries have imposed more stringent environmental regulations for the sulfur content of diesel oil. For example, in Japan and the European Union the intended permitted S content of gas oil is <50 ppm in 2005, and in the US is 15 ppm in 2006. Further information relating to ultradeep hydrodesulfurization processes is available in Refs. [8] and [9], and references cited therein.

Methanation is the reaction in which methane is produced from CO, CO_2, or alkanes using hydrogen. The process is used conventionally to remove trace amounts of CO from the feedstock of an ammonia synthesis, or for increasing the calorific value of the synthesis gas through the reaction between CO and H_2 to methane. The reaction over a Ni catalyst is carried out below 623 K. The Ru catalyst is more active than the Ni catalyst, and is used at 473–523 K to remove CO in the H_2 feed and hence to avoid deactivation of the Pd or Pt catalyst for the production of hydrogen peroxide or hydroxylamine. Ni/ZrO_2 and Ru/TiO_2 are effective for the

removal of CO in a hydrogen-rich gas stream for supplying pure hydrogen to the polymer electrolyte cells [10].

Ni catalysts are used in the production of atmospheric gas for heat treatment when producing metal products from ingots. $NiO(5–10\%)/SiO_2{\cdot}Al_2O_3$ produces a mixture of CO, H_2, and N_2 from propane and air at 1173–1273 K, and this gas is used to create an atmosphere of cementation and radiant quenching or annealing of steel. A $NiO(20–30\%)/Al_2O_3$ is also applied for the decomposition of ammonia (773–1173 K), with the decomposed gas (a mixture of N_2 and H_2) being used for the radiant heat-treatment of stainless steel, copper, and copper alloy to avoid cementation.

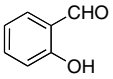
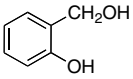
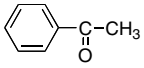
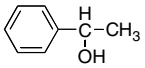
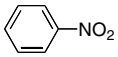
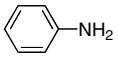
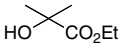
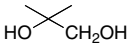
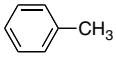
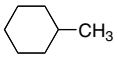
10.2.2 Transformation of Organic Functional Groups

The representative reductive transformations of organic functional groups catalyzed by heterogeneous catalysts are listed in Table 10.3 [2, 3, 11]. The main reactions catalyzed by heterogeneous nickel catalysts are hydrogenation, reductive amination, and hydrogenolysis. Most of these reactions are also catalyzed by many other transition metals, but these are more expensive than nickel (see Preface).

Tab. 10.3. Representative reductive transformations of organic functional groups catalyzed by heterogeneous catalysts.

Reaction			*Catalyst*
	$\xrightarrow{H_2}$		Ni, Pd, Pt, Rh
—C≡C—	$\xrightarrow{H_2}$		Ni, Pd
	$\xrightarrow{H_2}$		Ni, Ru, Pt, Rh
	$\xrightarrow{H_2}$		Ni, Pd, Pt
—C≡N	$\xrightarrow{H_2}$	$—CH_2NH_2$	Ni, Co, Pd, Rh, Pt
$—NO_2$	$\xrightarrow{H_2}$	$—NH_2$	Ni, Pd, Pt
—COOH(R)	$\xrightarrow{H_2}$	$—CH_2OH$	Ni, Cu–Cr oxide, Re
—COOH	$\xrightarrow{H_2}$	—CHO	$Cr–ZrO_2$, Cr_2O_3
Aromatics	$\xrightarrow{H_2}$		Ni, Rh, Pt, Ru
	$\xrightarrow{H_2,\ NH_3}$		Ni, Pd, Pt
R–X	$\xrightarrow{H_2}$	RH + XH	Ni, Pd
R–S–R'	$\xrightarrow{H_2}$	RH + R'H + H_2S	Ni, Mo

Tab. 10.4. Representative reactions and their conditions catalyzed by Raney Ni catalyst.

$H_2C{=}CHCH_2OH$	Raney Ni, H_2; r.t., 0.1 MPa	$CH_3CH_2CH_2OH$
$CH_3CH_2CH_2CHO$	Raney Ni, H_2; r.t., 0.1 MPa	$CH_3(CH_2)_3OH$
	Raney Ni, H_2; r.t., 0.1 MPa	
$CH_3OCH_2CH_2{-}\overset{\overset{O}{\|}}{C}{-}CH_3$	Raney Ni, H_2; 373–383 K, 10 MPa	$CH_3OCH_2CH_2{-}\overset{\overset{H}{\|}}{\underset{\underset{OH}{\|}}{C}}{-}CH_3$
	Raney Ni, H_2; 303 K, 0.1–0.3 MPa	
	Raney Ni, H_2; r.t., 0.1 MPa	
$NC(CH_2)_5COOH$	Raney Ni, H_2, NH_4OH; 403 K, 10 MPa	$H_2N(CH_2)_6COOH$
	Raney Ni, H_2; 383 K, 34 MPa	
	Raney Ni, H_2; 423 K, 10 MPa	
CH_3CH_2CHO	Raney Ni, H_2, NH_3; 408 K, 7 MPa	$CH_3CH_2CH_2NH_2$

The choice of the appropriate catalyst depends on the catalytic activity, catalyst selectivity, the scale of the reaction, purity of the reactant, reaction equipment, and economical efficiency. For reference, readers are directed towards a series of useful guidebooks that list the reaction types with appropriate catalysts and reaction conditions [11]. The choice of catalyst from a practical viewpoint has been described elsewhere [2]. Examples of the representative reactions and conditions catalyzed by nickel catalysts [11c] are listed in Table 10.4. The hydrogenation of ketones usually requires more severe conditions compared to that of carbon–carbon double bonds or aldehydes. The hydrogenation of aromatic ketones proceeds more easily than those of aliphatic ketones, although accompanying side reactions may occur, such as hydrogenolysis and/or hydrogenation of the aromatic rings.

The hydrogenation of aromatic nitro compounds to anilines is among the most useful transformations, and proceeds readily at ambient temperature. As the reaction is highly exothermic (560 kJ mol^{-1}), removal of the reaction heat is important. Care should be taken to control the catalyst:substrate ratio, the scale of the reaction, and the reaction temperature and pressure. The detailed safety and handling considerations are discussed elsewhere [12]. Carboxylic acids and esters are the most difficult functional groups to be hydrogenated, and these reactions are gener-

ally carried out over Cu–Cr oxide or Re (for hydrogenation to alcohol) and Cr–ZrO_2 or Cr_2O_3 (for hydrogenation to aldehyde). The Raney nickel catalyst is exceptionally reactive for the hydrogenation of α-amino acid esters and α-hydroxy acid esters to the corresponding alcohols. Hydrogenation of the aromatic ring usually requires high pressure and high temperature.

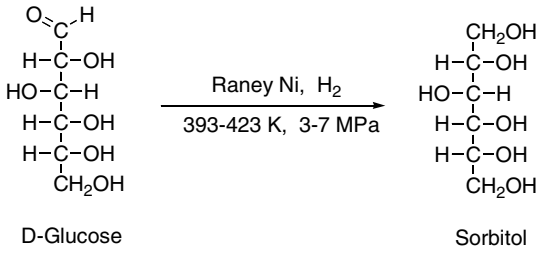
Excellent detailed monographs and reviews relating to the transformation of organic functional groups over heterogeneous catalysts [2, 3, 13–15] – and especially over nickel catalysts [16–18] – are available. A brief description of preparation methods for nickel catalysts and their reactions are outlined in the following section.

Heterogeneous nickel catalysts are generally classified into two groups: unsupported and supported. Unsupported nickel catalysts are further classified according to the catalyst structure and its preparation method – that is, Raney (skeletal type) nickel, amorphous alloy catalyst such as nickel boride, reduced nickel (obtained by the reduction of nickel oxide under a hydrogen stream), nickel catalyst obtained by the decomposition of nickel formate or nickel oxalate, Urushibara nickel, and fine nickel powder. Supported catalysts are prepared from different types of supports and preparation methods. Raney nickel (both alloy and stabilized activated catalyst) and supported nickel catalysts are available commercially, and can be used for research studies on the transformations of common organic functional groups. Catalyst manufacturers supply various types of Raney nickel and supported nickel catalysts customized for specified reactions. The detailed composition and preparation methods of commercial catalysts are rarely known; hence, if a reaction does not proceed satisfactorily with a commercial catalyst, or if a special catalyst (e.g., asymmetric) is needed, it should be prepared in-house.

In the following section, the general features and recent advances in Raney Ni, Ni boride, and supported Ni catalysts for organic syntheses are described, based on their wide range of applications. Preparation methods for Ni catalysts used in asymmetric syntheses are described in Section 10.4.1.

10.2.2.1 **Raney Nickel**

Raney Ni was discovered by Murray Raney in 1927, and is the most widely used unsupported Ni catalyst for liquid-phase reactions. It serves as a versatile hydrogenation catalyst in the production of fine chemicals, and also in the hydrogenation of D-glucose to sorbitol (Eq. (10.1)), which is used in the cosmetic, food, and drink industries, and as a starting material in the manufacture of ascorbic acid [19].



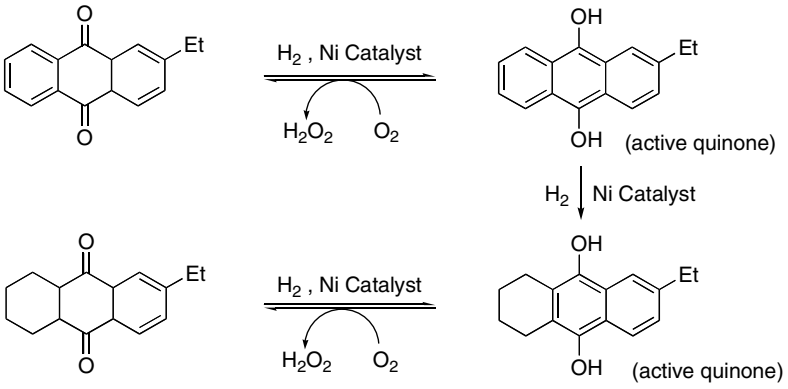
(10.1)

Raney nickel is prepared by treating a Ni–Al alloy with an alkaline solution to leach out (digest) the aluminum component, thus leaving the active nickel species in the form of a porous material. The different types of classical preparation methods provide the Raney Ni catalysts with varying activities. These are designated as W1, W2, W3, W4, W5, W6, W7, and W8 [20]. The preparation procedures for these catalysts differ in terms of the temperatures at which the alloy is added to the NaOH solution, the concentrations of the NaOH solution, digesting temperatures and times, and washing processes. The preparation methods and characteristics of each type have been reviewed [3]. The high activity of Raney Ni is attributed to the high surface area (50–120 $m^2\ g^{-1}$), and the large amount of hydrogen adsorbed on and in the metal particles (25–100 $cm^3\ g^{-1}$). The Raney Ni catalyst is supplied as a Ni–Al alloy or as a stabilized activated Ni.

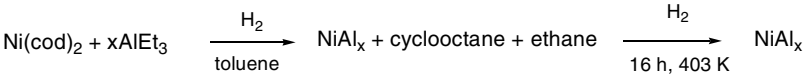
The morphology and microstructure of the alloy and the activated catalysts have been widely studied [21, 22]. Raney Ni contains the phases of NiAl, Ni_2Al_3, $NiAl_3$, and eutectic. The digestion of aluminum from $NiAl_3$ and eutectic is relatively straightforward, while it is more difficult to digest Ni_2Al_3, and almost impossible to remove aluminum from the NiAl phase. The commercially available alloy is usually a 50 wt% nickel alloy. This is a compromise between the readily digestible $NiAl_3$ and the more mechanically strong Ni_2Al_3. The distribution of the two main phases consists of a core of Ni_2Al_3 with a shell of $NiAl_3$ [23].

A new technique for Raney Ni preparation, termed "melt-quenching", has been developed. A cooling rate of $10^6\ K \cdot s^{-1}$ is used to prepare the alloy, with H_2-pretreatment at 773 K; this results in an increased content of the Ni_2Al_3 phase, which benefits the formation of an ultra-uniform Ni with a high surface area [24]. By using Raney Ni prepared in this manner, a higher selectivity of "active quinones" is attained in the hydrogenation of 2-ethylanthraquinone than when using commercially available Raney Ni [25]. The quinones are used in the production of H_2O_2 (Scheme 10.1).

A wet chemical method has been reported for production of the Ni–Al system [22]. This consists of the reaction between $Ni(cod)_2$ and $AlEt_3$ in toluene (Scheme



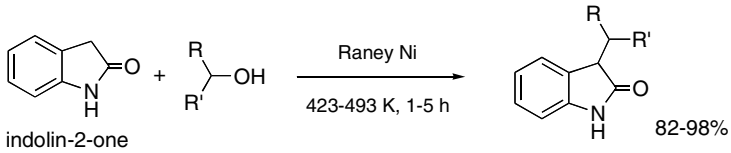
Scheme 10.1. Hydrogenation of 2-ethylanthraquinone over the Ni catalyst and its use for the production of hydrogen peroxide.



Scheme 10.2. Preparation of nickel-aluminide by a wet chemical method.

10.2). A black-brown dispersion is dried and heated under hydrogen to yield a black powder of nickel aluminide (particle size 2–5 nm). This method offers an opportunity to prepare nanoscale $NiAl_x$ in which the composition can be controlled by the stoichiometry of the starting nickel and aluminum components. For butyronitrile hydrogenation, the catalyst $NiAl_x$ ($x > 1.5$) shows a two- to five-fold greater activity than commercial Raney Ni.

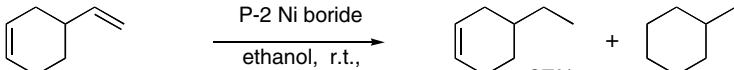
In addition to hydrogenation, C–C bond formation catalyzed by Raney Ni has also been reported, where alkylation of indolin-2-one with alcohols attains an 82–98% yield of 3-alkyloxindoles (Eq. (10.2)) [26].



(10.2)

10.2.2.2 Nickel Boride

A nickel boride catalyst is prepared by the reduction of nickel salts (generally nickel acetate or nickel chloride) with sodium or potassium borohydride [27, 28]. Conventionally, the catalyst prepared by reduction in an aqueous solution is called *P-1 Ni boride*, while reduction in 95% ethanol produces a colloidal catalyst referred to as *P-2 Ni boride*. The Ni boride is neither ferromagnetic nor pyrophoric. The notorious isomerization of the double bond during the hydrogenation is minimal over the P-1 and P-2 Ni borides. For example, the P-2 Ni boride has a low isomerization capability and is effective in selective alkene hydrogenation (Eqs. (10.3) and (10.4)) [29]. Whilst selective hydrogenation of an alkyne to an alkene is generally carried out using Pd catalysts (e.g., Lindler catalyst), the P-2 Ni boride also shows high selectivity (Eq. (10.5)) [28].



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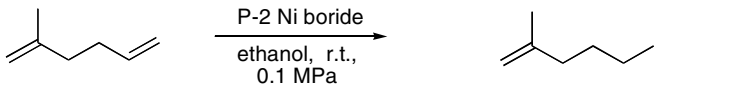

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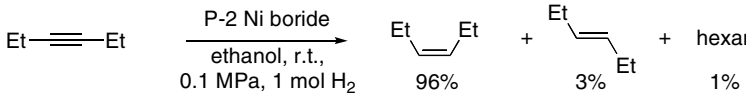


(10.5)

Amorphous alloy catalysts such as Ni boride have been intensively studied during the past two decades [30, 31]. The hydrogenation of various substrates (e.g., benzaldehyde, glucose, cyclopentadiene, adiponitrile, benzene, acrylonitrile, cinnamaldehyde, furfural, nitrobenzene, 2-ethylanthraquinone) over Ni boride is generally successful [32]. The composition of Ni boride catalysts prepared by the reduction with potassium borohydride are $Ni_{69}B_{31}$–$Ni_{77}B_{23}$ for the bulk composition measured by inductively coupled plasma (ICP) analysis, and $Ni_{71}B_{29}$–$Ni_{75}B_{25}$ for the surface composition measured by X-ray photoelectron spectroscopy (XPS) analysis.

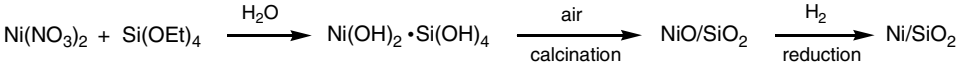
XPS analysis further revealed that boron, when bound to Ni, donated electrons to the nickel. Based on these concepts, it was proposed that variations in *3d* orbital electron density on the Ni modified the activity and selectivity of the catalyst [33, 34]. Reviews have been published on the catalytic features of Ni borides supported on various materials (SiO_2, Al_2O_3, MCM-41, SBA-15, or bentonite) [35, 36]. Applications of Ni boride to asymmetric synthesis are discussed in Section 10.3.2.

10.2.2.3 **Supported Nickel Catalysts**

The main objectives of preparing a supported Ni catalyst are to gain a high Ni surface area on a porous material, and to minimize the sintering of Ni metals at high temperatures. Thus, supported Ni catalysts can be used for gas-phase reactions at high temperatures, as well as for liquid-phase reactions. The type of support used, and the preparation method used, both affect the activity and selectivity of the catalyst.

Supported Ni catalysts are prepared by conventional impregnation, precipitation, co-precipitation, or ion-exchange methods. The general features of the conventional preparation methods have been described elsewhere [3, 37, 38], and preparation methods using a sol-gel process and citric acid are outlined in the following section.

The metal particle size of the supported catalyst is important because it correlates not only with the surface area of the metal (i.e., catalytic activity) but also with the selectivity of the catalyst in some cases. Reaction in which selectivity is dependent upon the metal particle size are termed "structure-sensitive reactions" (in the reverse case, structure-insensitive reactions). The distribution of metal particle size in catalysts prepared by conventional methods (e.g., impregnation) is quite broad. Hence, because reaction selectivity might depend on the metal particle size, a preparation method in which metal particle size could be controlled would be desirable. Preparation using sol-gel chemistry enables a homogeneous metal particle size to be provided, the size being controlled by the metal ion concentration of the starting material. A typical preparation procedure is shown in Scheme 10.3.

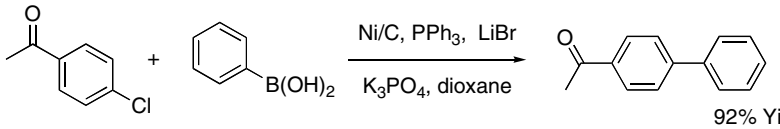


Scheme 10.3. Preparation procedure of the supported Ni catalyst by a sol-gel method.

Nickel(II) nitrate is dissolved in ethylene glycol, and an appropriate quantity of Ni solution (depending on the desired loading on the catalyst) is poured into the tetraethoxysilane and stirred in a N_2 atmosphere. Water is then added to the mixed solution and the solution is stored without being stirred. The fine precipitates are filtered, calcined in air, and reduced in a hydrogen stream [39]. The key to controlling the Ni particle size is to disperse NiO homogeneously among the support material before the reduction; the homogeneous NiO distribution is due to the Ni–O–Si chemical bonding [39].

Hydrogenation of propionaldehyde accompanies decomposition of the aldehyde to produce ethane, CO, and H_2. The selectivity of this reaction over Ni/SiO_2 prepared by the sol-gel process depends on the mean Ni particle size; 1-propanol/CO $\approx$ 3 for Ni of $\sim$2 nm; 1-propanol/CO $\approx$ 0.5 for Ni of 7–10 nm [40].

Catalyst preparation using citric acid was first reported for mixed oxide catalysts [41], while citric acid use to prepare supported Ni catalysts with the sol-gel process was developed more recently [42]. Tetraethoxysilane is added to an aqueous alcoholic solution of nickel(II) nitrate and citric acid. After storing for 3 days, the obtained gel is dried, calcined, and reduced in a hydrogen stream. The advantages of using the Ni citrate complex are: i) a high Ni surface area is achieved due to aggregation of the Ni species being inhibited by the formation of nickel citrate; and ii) a catalyst is produced with mesopores. The space occupied by citric acid becomes pores that do not shrink when the citric acid is eliminated. A catalyst with mesopores (>5 nm) is favorable for the hydrogenation of 3-pentanone or 4-heptanone because of the lesser restriction of diffusion in the pores [43].



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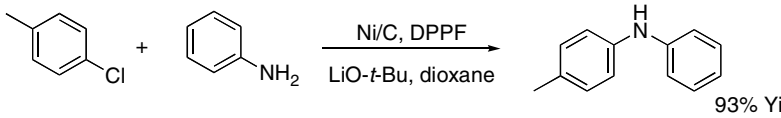
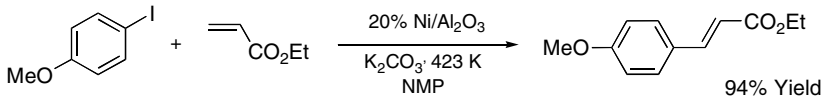


(10.7)

C–C bond formation catalyzed by supported Ni catalysts was first reported in 1999. Lipshutz et al. suggested that Ni on charcoal (Ni/C) catalyzed a variety of cross-coupling reactions, such as the Negishi–, Suzuki– (Eq. (10.6)), and Kumada–Tamao couplings, and amination of aromatic halides, especially the less-reactive chlorides (Eq. (10.7)) [44]. They prepared Ni(II)/C from nickel(II) nitrate and activated charcoal by an impregnation method. In-situ reduction of the Ni(II)/C with *n*-BuLi or *n*-BuMgCl (see Sections 1.7.3–1.7.5) assured the higher conversion and better yields than reduction in a hydrogen atmosphere. Removal of the catalyst by simple filtration left a reaction mixture containing only traces of Ni, which is an

important feature from a practical viewpoint. Later, however, it was revealed that catalysis using Ni/C was most likely of a homogeneous rather than a heterogeneous nature [44]. An equilibrium exists between the homogeneous Ni species located inside and outside the pores of charcoal and the homogeneous Ni species favors inside the pores. The trace amount of Ni outside the pores is beneficial for the recovery of Ni by simple filtration.



(10.8)

An example of the Heck reaction catalyzed by supported Ni (Ni/Al_2O_3 and Ni/HY-Zeolite) is shown in Eq. (10.8) [45]. The vinylation of 4-iodoanisole with ethyl acrylate proceeds in high yield, producing *trans*-ethyl cinnamate, although a considerable amount of the Ni catalyst is leached out under these conditions.

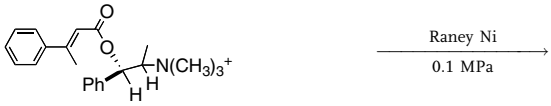
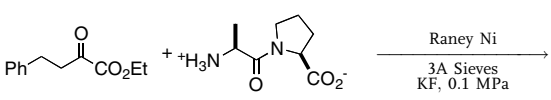
10.3
Asymmetric Syntheses over Heterogeneous Nickel Catalysts

For asymmetric syntheses, two approaches are available: i) a diastereo-differentiating reaction; and ii) an enantio-differentiating reaction. A diastereo-differentiating reaction is defined as one in which a chiral moiety is incorporated into the substrate itself, whereas in an enantio-differentiating reaction a chiral moiety is incorporated into a reagent, a catalyst, or a solvent, but *not* into the substrate. The difference between these two reaction types is less clear-cut in heterogeneous catalysis than in homogeneous catalysis, however. For example, asymmetric hydrogenation over a cinchona-modified Pt or Pd catalyst [46] is generally recognized as an enantio-differentiating reaction. However, the cinchona alkaloid may either reside on the metal surface or dissolve in the reaction mixture. In the former case, it acts as a modifier on the surface, but in the latter case it serves as a chiral auxiliary of the substrate [47].

10.3.1
Diastereo-differentiating Reactions

The most common diastereo-differentiating reactions over heterogeneous Ni catalysts are hydrogenations. As this reaction is also well catalyzed by Pd catalysts, a greater number of studies over heterogeneous Pd catalysts have been reported. Diastereo-differentiating hydrogenations over heterogeneous catalysts have been reviewed in the literature [48–50], and some typical examples over Raney nickel are shown in Table 10.5.

Tab. 10.5. Diastereo-differentiating reactions over the heterogeneous Ni catalysts.

Reaction		*de [%]*	*Reference*
	Raney Ni, 6.9 MPa	92	51
	Raney Ni 0.1 MPa	68	52
	Raney Ni, 0.5 MPa	95	53
	Raney Ni, 0.5 MPa i-PrOH	69	54
	Raney Ni 3A Sieves KF, 0.1 MPa	89	55
	i) Raney Ni, 0.1 MPa ii) TBAF in THF	88	56

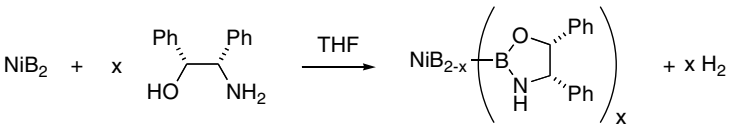
10.3.2
Enantio-differentiating Reactions

A heterogeneous enantio-differentiating catalyst is defined here as one that originally has catalytic activity, with enantio-differentiating ability being bestowed by the adsorption of optically active substances on the catalyst surface. In the case of homogeneous enantio-differentiating catalysts, chiral environment around the organometal atom is important. However, for heterogeneous enantio-differentiating catalysts the active site is generally the metal surface, and so the structure of the metal surface and mode of adsorption of chiral compounds are key issues. Organometal complexes that intrinsically have both catalytic activity and an enantio-differentiating ability and are linked to the solid surface are categorized as heterogenized catalysts, and their reactions are described in Chapter 9 (see Scheme 9.36).

A heterogeneous enantio-differentiating Ni catalyst was first reported in 1932, when Schwab et al. demonstrated that Ni on quartz dehydrogenates racemic 2-butanol in 10% ee at a low conversion [57]. In this reaction, the chiral arrangement of the quartz crystal is responsible for the kinetic resolution. A Ni catalyst modified with an optically active organic compound was first reported in 1939,

when glucose-modified Raney Ni was shown to hydrogenate 2-methylcinnamic acid in ~10% ee [58]. In 1963, Izumi et al. developed a tartaric acid-modified Ni catalyst [59], and to the present day this is the only enantioselective heterogeneous Ni catalyst to be used for a practical application. This topic is dealt with in Section 10.4.

Oxaza-borolidine Ni boride (Scheme 10.4) catalytically reduces acetophenone in 94% ee by using BH_3-THF as a reducing agent [60]. Based on the facts that: i) this catalyst can be recycled with little or no loss of catalyst performance; ii) no traces of the amino alcohol can be detected in the liquid phase after reduction; and iii) inelastic neutron spectroscopy shows the disappearance of O–H absorption of the amino alcohol after reaction with NiB_2 [61], it is claimed that the amino alcohol is anchored on the surface of NiB_2. The use of hydrogen, instead of BH_3-THF, as the reducing agent provides a poorer enantioselectivity (ee <2%).

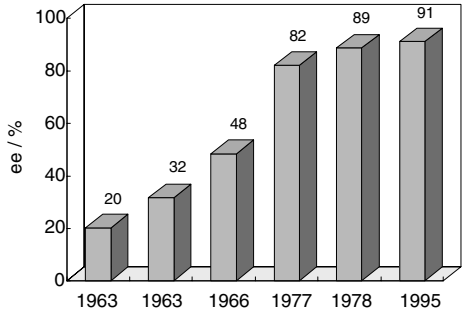


Scheme 10.4. Preparation of the oxaza-borolidine Ni-boride catalyst.

10.4
Tartaric Acid-modified Nickel Catalyst

As many detailed reviews on tartaric acid-modified Ni catalysts have been published [62–71], only a summary of important points relating to this catalyst, together with some recent developments, are described in this section.

Historically, catalyst performance has been improved gradually by conducting detailed studies of the hydrogenation of methyl acetoacetate (Eq. (10.9)). Historical changes in ee values for the hydrogenation of methyl acetoacetate are shown in Figure 10.2, with an ee of 91% being attained in 1995.



1963: Discovery of glutamic acid-modified Raney Ni [72]
1963: Discovery of tartaric acid-modified Raney Ni [59]
1966: Discovery of 2,3-dimethyl tartaric acid-modified Raney Ni [73]
1977: Discovery of tartaric acid-modified reduced Ni [74]
1978: Discovery of tartaric acid-NaBr-modified Raney Ni [75]
1995: Discovery of deep modification of tartaric acid-NaBr-modified Raney Ni [76]

Fig. 10.2. Historical changes in ee-values for the enantiodifferentiating hydrogenation of methyl acetoacetate.

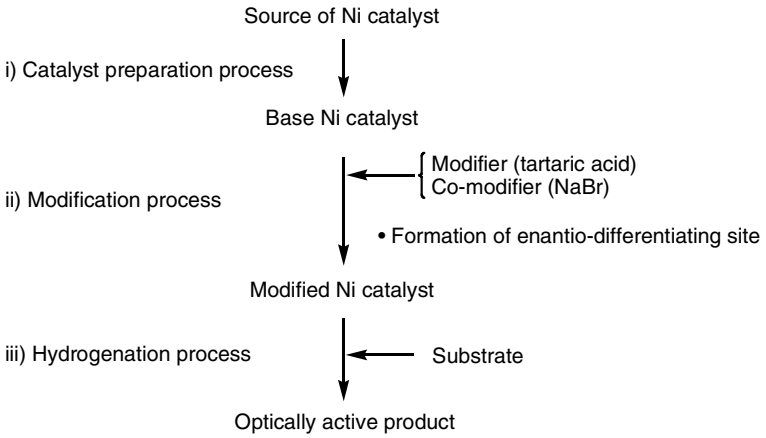
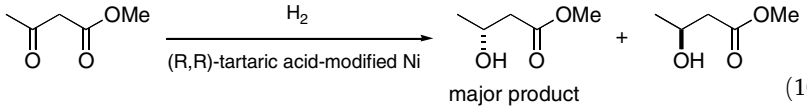


Fig. 10.3. Outlines of the overall process of enantio-differentiating hydrogenation over the tartaric acid-modified Ni catalyst.



(10.9)

The overall process of enantio-differentiating hydrogenation over a tartaric acid-modified Ni catalyst is outlined in Figure 10.3. This process consists of the following three stages: i) catalyst preparation; ii) modification; and iii) hydrogenation. In catalyst preparation, the activated *base Ni catalyst* is created, where the base Ni catalyst is defined as that with hydrogenation activity, and is converted to an enantio-differentiating catalyst via modification. Modification is the formation of an enantio-differentiating site on a Ni surface by the adsorption of tartaric acid and a co-modifier. These two stages include many variables that affect enantioselectivity and hydrogenation activity, and these are described in Sections 10.4.1 and 10.4.2.

10.4.1
Preparation of the Base Ni Catalyst

Basically, all Ni catalysts mentioned in Section 10.2 can be used to prepare tartaric acid-modified Ni catalysts (see Section 10.4.2). However, only a limited type of base Ni catalysts can produce modified Ni catalysts with high enantioselectivity; these include Raney Ni, reduced Ni, fine Ni powder, and supported Ni catalysts (Ni/Al_2O_3 or Ni/SiO_2). The type of appropriate base Ni catalyst depends on the substrate(s) to be reduced [77]. Moreover, the preparation method used for base Ni

catalysts significantly affects their enantioselectivity. Representative methods of preparing base Ni catalysts are described below, together with practical comments.

10.4.1.1 Raney Ni Catalyst

Preparation [78] A commercially available Ni–Al alloy (Ni:Al = 41:59 wt%) (2 g) is digested with a 20% NaOH solution at 373 K for 1 h. The catalyst is then washed with 500 mL (20 × 25 mL) de-ionized water.

Comment Raney Ni has been the most intensively investigated base Ni catalyst, as it produces a modified catalyst with high hydrogenation activity and high enantioselectivity. Although various preparation methods (including W1–W8 [22]) are known, the above-described simple method is sufficient to achieve satisfactory results for a base Ni catalyst to prepare tartaric acid-modified Ni. A commercially available activated Raney Ni catalyst may also be used, but it is strongly recommended that the activation process (digestion of the alloy) be carried out in the laboratory, as variables in the digestion process significantly affect the resultant enantioselectivity. As any remaining aluminum is detrimental to enantioselectivity, a high-temperature digestion (373 K) is recommended [78]. For extensive removal of the remaining surface aluminum, the Raney Ni catalyst should be pre-modified with tartaric acid solution at pH 3.2, 373 K (Fig. 10.4). During pre-modification, the Raney Ni surface is conditioned by the weak acidic solution (tartaric acid solution), as well tartaric acid being adsorbed onto the surface. Raney Ni alloy with a Ni:Al ratio of 41:59 (corresponding stoichiometrically to $NiAl_3$) gives a higher enantioselectivity than the 50:50 alloy [70]. This may be due to differences in the Ni_2Al_3:$NiAl_3$ ratio in the alloy. The $NiAl_3$ phase is favorable for attaining an Ni surface for high enantioselectivity. An influence of the pure phase of Ni_2Al_3, $NiAl_3$, and the Al/$NiAl_3$ eutectic on the enantio-differentiating ability of the corresponding modified catalysts has been reported. Among these catalysts, a tartaric acid-NaBr-modified Ni prepared from the Al/$NiAl_3$ eutectic recorded the highest enantioselectivity [79].

10.4.1.2 Reduced Ni Catalyst

Preparation [74] Commercially available Ni oxide is reduced in a hydrogen stream (8 dm^3 h^{-1}) at 623 K for 1 h before use.

Comment Whilst the hydrogenation activity of the reduced Ni catalyst prepared by this method is much lower than that of Raney Ni, the enantioselectivity of the modified reduced Ni is higher. It is reported that different manufacturers or lot numbers of Ni oxide affect the enantioselectivity of the modified reduced Ni catalyst [80–82]; thus, the choice of Ni oxide is important. Whatever the nature of the factors affecting enantioselectivity, a high calcination temperature (1373 K) of the

precursor of Ni oxide (resulted in olive green Ni oxide) is important in order to attain high enantioselectivity [83].

10.4.1.3 Supported Ni Catalyst

Precipitation method of preparation [84] $Ni(NO_3)_2 \cdot 6H_2O$ (10 g) and a support (the theoretical amount is changed according to the percentage of the loading) are mixed in 50 mL distilled water. The mixture is degassed and then gently stirred for 15 min at ambient temperature, and again for 15 min at 348 K. Na_2CO_3 (3.7 g) in 25 mL distilled water, preheated to 348 K, is added to the mixture during 1 min with vigorous stirring. The precipitate is then aged for 15 min at 348 K with gentle stirring. The precipitate is washed with warm distilled water (3×50 mL). The sample is dried at 383 K for 24 h, and then reduced in a hydrogen stream at 523–773 K.

Impregnation method of preparation [78] $Ni(NO_3)_2 \cdot 6H_2O$ (1 g) and a support are mixed in 25 mL distilled water. Water is slowly evaporated on a steam-bath with stirring. The residue is dried for 3 h at 383 K, and then reduced in a hydrogen stream at 673 K.

Comment There are many variables affecting resultant enantioselectivity in the preparation of a supported Ni catalyst [84], including the percentage of Ni loading, type of support, precipitation temperature, aging temperature and time, agitation speed of the solution, and reduction temperature in the hydrogen stream. Thus, it is not easy to attain maximum performance. Generally, the investigation of a supported metal catalyst is to obtain stable, highly dispersed metal particles (small metal particles with high surface area) on the support in order to obtain a high activity. However, in the case of tartaric acid-modified supported Ni catalysts, it is generally accepted that a large Ni crystallite size produces a high enantioselectivity [70, 86, 87]. A nickel surface with fewer defects would be needed for regular arrangement of the tartaric acid to attain a high enantioselectivity [86]. A large Ni crystallite size is generally incompatible with high hydrogenation activity. In the development of a supported Ni catalyst, a high hydrogenation activity and a high enantioselectivity are important subjects to be addressed.

10.4.1.4 Fine Nickel Powder

Preparation [88] Commercially available fine Ni powder (Vacuum Metallurgical Co., Ltd., Chiba; Japan; mean particle diameter 20 nm) is treated in a hydrogen stream at 553–573 K for 30 min before use.

Comment This catalyst is prepared by sublimation of an Ni metal in an inert gas [89]. The temperature of the catalyst activation in the hydrogen stream is critical for hydrogenation activity and enantioselectivity, as sintering of the fine Ni powder occurs easily at a temperature of 573 K. The hydrogenation activity of this catalyst

is similar to that of Raney Ni. The hydrogen treatment is carried out to reduce the nickel oxide on the surface, while thermal treatment of the catalyst enlarges the mean crystallite size of Ni [88]. The merits of using this catalyst are the higher durability of enantioselectivity compared to modified Raney Ni (see Section 10.4.3.1), and the higher enantioselectivity for the hydrogenation of 3-octanone [88].

10.4.2
Modification of the Base Nickel Catalyst

The adsorption of tartaric acid (modifier) and an inorganic salt (co-modifier) onto a Ni surface is termed a ''modification process''. The tartaric acid-NaBr-modified Ni catalyst recognizes an enantio-face of a substrate through an interaction between the tartaric acid adsorbed on the Ni surface and the substrate. A co-modifier, such as an inorganic salt, is known to improve the enantioselectivity of the catalysts [75, 87, 90–92]. Among various inorganic salts examined, NaBr is the best co-modifier. There are two types of modification process (Fig. 10.4): A) pre-modification; and B) in-situ modification [92, 93]. Pre-modification means that a modification is carried out before hydrogenation of the substrate, whereas in-situ modification means that the modification occurs during or just before hydrogenation.

Pre-modification Many variables affect enantioselectivity, including temperature, pH, time, concentration of tartaric acid, and concentration of the co-modifier [65, 68, 94]. The most satisfactory and representative modification conditions are illustrated schematically in Figure 10.4[A].

In-situ modification A reduced Ni or fine Ni powder should be used as the base catalyst to attain a high enantioselectivity for the in-situ modification (Fig. 10.4[B]) [93]. Pre-modification of the Raney Ni catalyst brings about a high hydrogenation activity and a high enantioselectivity, though the in-situ-modified Raney Ni shows a low enantioselectivity [95]. This is caused by aluminum remaining on the Raney Ni surface, but this is removed during pre-modification at pH 3.2 and 373 K.

The in-situ modification has the advantage of using tartaric acid and NaBr in smaller amounts as compared to pre-modification. Tartaric acid (100 mg) and NaBr (2 mg) are adequate for the reduced Ni catalyst (1.2 g). Furthermore, while in-situ modification produces no waste containing Ni ions, pre-modification leads to large amounts of waste solution containing Ni ions.

10.4.3
Enantio-differentiating Hydrogenation over Tartaric Acid-NaBr-modified Nickel Catalysts

Enantio-differentiating hydrogenation over a tartaric acid-modified Ni catalyst has been examined from atmospheric pressure to 9–10 MPa, the high pressure being necessary to attain high enantioselectivity. Reciprocal shaking or a stirred autoclave constructed from stainless steel is used for high-pressure hydrogenation (Fig. 10.4).

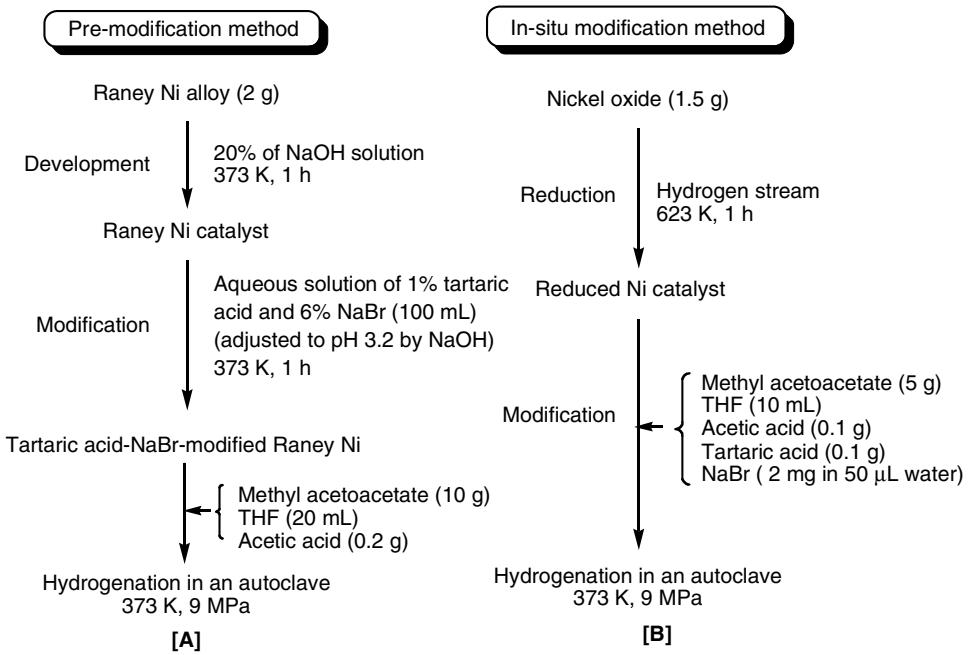


Fig. 10.4. Enantio-differentiating hydrogenation using pre-modification [A] and in-situ modification methods [B].

10.4.3.1 **Hydrogenation of Functionalized Ketone**

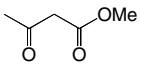
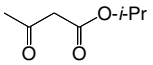
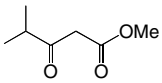
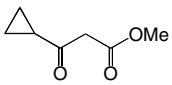
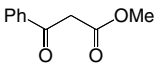
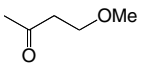
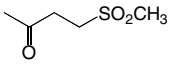
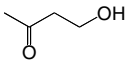
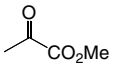
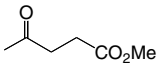
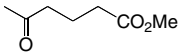
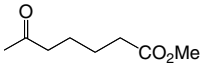
At present, various β-functionalized ketones can be hydrogenated in >90% ee over a tartaric acid-NaBr-pre-modified Raney Ni catalyst (Table 10.6). The highest enantioselectivity of 98% is achieved for hydrogenation of methyl 3-cyclopropyl-3-oxopropanoate [97]. The enantioselectivity of hydrogenation of β-keto alcohols, β-keto ethers, and β-keto sulfones – all of which were recorded during the 1980s – is ~70%, and no better ee-values have since been reported.

By contrast, the hydrogenation of α-, γ-, δ-, and ε-ketoesters are in the region of 15 to 60% ee. The use of a carboxylic acid as an additive affects enantioselectivity. In the case of hydrogenation of β- and γ-ketoesters, a small amount of acetic acid increases the enantioselectivity [75, 81, 82, 102]. The use of a large amount of pivalic acid is indispensable for attaining high enantioselectivity in the hydrogenation of δ- and ε-ketoesters, which is the same characteristic of the hydrogenation of alkyl ketones (see Section 10.4.3.2). The hydrogenation of β-keto esters carrying a bulky alkyl group and δ- and ε-keto esters at lower temperatures increases enantioselectivity [96].

The durability of catalysts for repeated process runs is important, and the durability of enantioselectivity in the hydrogenation of methyl acetoacetate is shown graphically in Figure 10.5.

Although the pre-modified Raney Ni catalyst is successful in attaining high enantioselectivity and high hydrogenation activity, it is of poor durability with

Tab. 10.6. Enantio-differentiating hydrogenation of functionalized ketones over the pre-modified Ni catalyst.

Substrate	*Catalyst*[a]	*Additive*	*Temp [K]*	*% ee*	*Configuration*	*Reference*
	MRNi	Acetic acid	373	91	R	76
	MRNi	Acetic acid	333	87	R	96
	MRNi	Acetic acid	333	96	R	96
	MRNi	Acetic acid	373	98	R	97
	MRNi	Acetic acid	333	88	R	98
	MRNi	Acetic acid	358	68	R	99
	MRNi	Acetic acid	373	68	R	100
	MRNi	Acetic acid	373	70	R	101
	MRNi	Acetic acid	373	15	R	96
	MHNi	Acetic acid	373	51	R	82
	MRNi	Pivalic acid	333	61	S	96
	MRNi	Pivalic acid	333	61	S	71

[a] MRNi: (*R*,*R*)-tartaric acid-NaBr-pre-modified Raney Ni.
MHNi: (*R*,*R*)-tartaric acid-NaBr-pre-modified reduced Ni.

repeated use, and the enantioselectivity is lost after the third run (△ in Fig. 10.5) [103]. Tai et al. showed that the durability of enantioselectivity of pre-modified Raney Ni was enhanced by treatment with an amine solution (▲) [104]. The use of reduced Ni instead of Raney Ni as the base catalyst also enhances the durability of enantioselectivity of pre-modified catalysts (□) [95]. The gradual decrease in

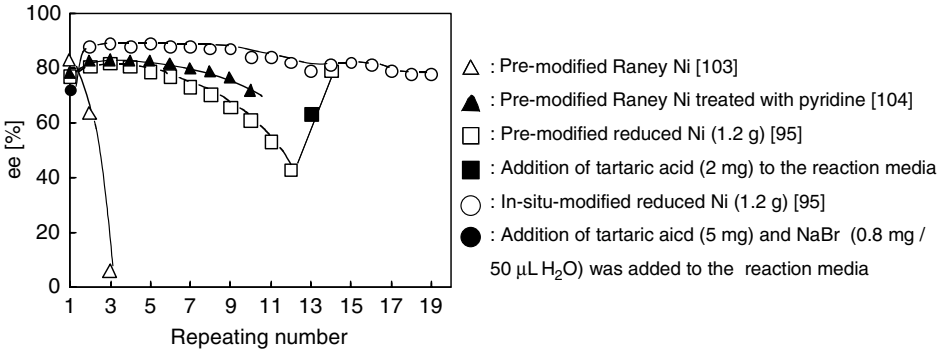


Fig. 10.5. Repeated use of pre-modified and in-situ-modified Ni catalysts for the hydrogenation of methyl acetoacetate.

enantioselectivity during repeated runs may be caused by desorption of tartaric acid from the catalyst surface, as the addition of tartaric acid to the reaction medium (■) recovers the original enantioselectivity (runs 13 and 14 in Fig. 10.5). By contrast, an in-situ-modified reduced Ni (○) shows high enantioselectivity and high hydrogenation activity after the 20 runs [95]. The representative conditions for hydrogenation using an in-situ-modified reduced Ni are shown in Figure 10.4[B]. (*R*,*R*)-Tartaric acid and NaBr are added to the reaction mixture only during the first run. The use of reduced Ni or fine Ni powder and the use of in-situ modification realizes the high durability of enantioselectivity.

10.4.3.2 **Hydrogenation of Alkyl Ketones**

For the enantio-differentiating hydrogenation of 2-alkanones, only a few percent ee is obtained under optimum conditions for the hydrogenation of methyl acetoacetate. The type and amount of carboxylic acid added to the reaction mixture significantly affects enantioselectivity in the liquid-phase hydrogenation of 2-alkanones (Fig. 10.6) [105]. The addition of double the molar quantity of a bulky carboxylic acid (e.g., pivalic acid) to the substrate is important to attain high enantioselectivity.

Representative results for the hydrogenation of alkyl ketones are listed in Table 10.7. The highest ee-value of 85% is attained for the hydrogenation of 3,3-dimethyl-2-butanone, whilst hydrogenation of 2-butanone produces 72% ee; hence, this catalyst recognizes the difference between methyl and ethyl groups. For the hydrogenation of 3-alkanones, the addition of 1-methyl-1-cyclohexanecarboxylic acid produces a higher ee than that for pivalic acid [77].

The effect of hydrogenation temperature on enantioselectivity is dependent upon the structure of the alkanones (Fig. 10.7), though the mechanism of this temperature effect has not yet been elucidated.

In-situ modification may also be applied to the hydrogenation of 2-octanone [109]. The durability of enantioselectivity of in-situ-modified reduced Ni is higher than that of pre-modified Raney Ni (Fig. 10.8) [110]. However, in contrast to the hydrogenation of methyl acetoacetate (see Fig. 10.5), the enantioselectivity of

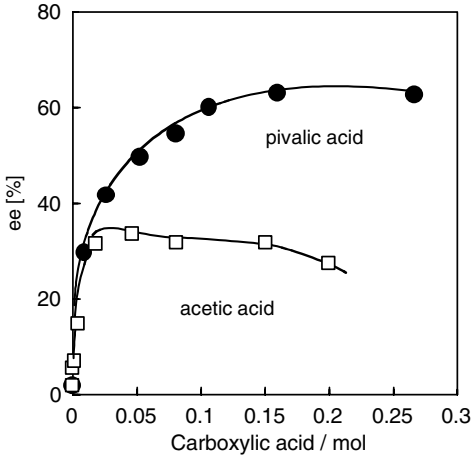
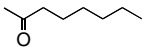
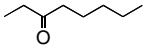
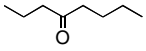


Fig. 10.6. Effect of amount of carboxylic acid on ee-value in the hydrogenation of 2-octanone (0.064 mol) over pre-modified Raney nickel.

in-situ-modified reduced Ni falls in the fifth run. The addition of tartaric acid and sodium 2-ethylhexanoate to alternate runs improves enantioselectivity, which remained at ~60% ee during 16 runs at 373 K. Sodium 2-ethylhexanoate is added to supply sodium ion. The presence of a large amount of pivalic acid in the reaction medium causes tartaric acid and Na^+ to desorb from the Ni surface, and this requires the addition of tartaric acid and sodium 2-ethylhexanoate on alternate runs [110].

Tab. 10.7. Enantio-differentiating hydrogenation of alkyl ketone.

Substrate	*Catalyst*[a]	*Additive*	*Temp [K]*	*% ee*	*Configuration*	*Reference*
	MRNi	Pivalic acid	333	80	S	106
	MRNi	Pivalic acid	333	85	S	107
	MRNi	Pivalic acid	333	72	S	108
	MHNi	MCA[b]	373	43	S	77
	MRNi	Pivalic acid	373	6	S	70

[a] MRNi: (*R*,*R*)-tartaric acid-NaBr-pre-modified Raney Ni.
MHNi: (*R*,*R*)-tartaric acid-NaBr-pre-modified reduced Ni.
[b] MCA: 1-methyl-1-cyclohexanecarboxylic acid.

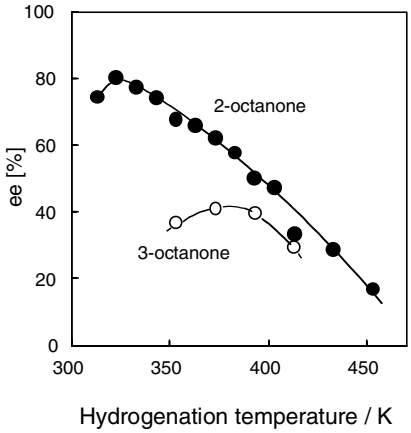


Fig. 10.7. The dependence of ee-value on reaction temperature.

For the gas-phase hydrogenation of 2-butanone, the highest enantioselectivity of 31% is recorded when using a tartaric acid pre-modified Ni/SiO_2 catalyst [111]. It is noteworthy that moderate enantioselectivity is attained without any addition of a carboxylic acid to the feed; the addition of a carboxylic acid to the reaction medium is mandatory to attain enantioselectivity for the liquid-phase hydrogenation.

10.4.4 What Happens on the Nickel Surface?

10.4.4.1 Adsorption of a Modifier and a Co-modifier

The adsorbed species of modification reagents have been investigated using both chemical and physico-chemical techniques. In the case of pre-modification, the effects of pH changes on the ee have been mainly investigated while determining the adsorbed species of tartaric acid [65, 78, 94].

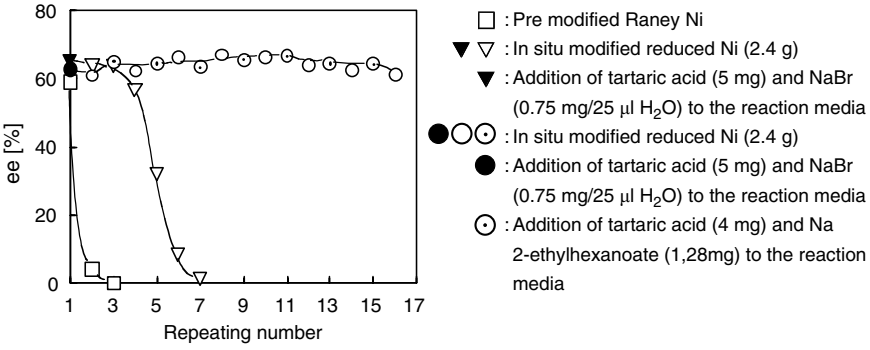


Fig. 10.8. Repeated use of pre-modified Raney Ni and in-situ-modified reduced Ni in the hydrogenation of 2-octanone at 373 K.

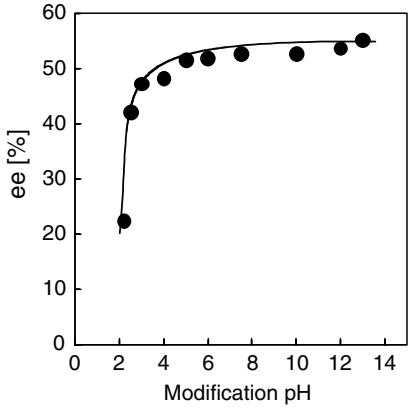


Fig. 10.9. Relationship between modification pH and ee-value over modified reduced Ni (modification temperature 373 K).

The relationship between modification pH and ee for the hydrogenation of methyl acetoacetate using a reduced Ni catalyst as the base catalyst is shown in Figure 10.9 [78]. When the pH of the modification solution is not adjusted with an NaOH solution (corresponding to pH 2.2), the ee is very low. The adsorption species at this pH may be nickel(II) tartrate, taking the corrosion of Ni surface at 373 K into account. With the increase in pH, the ee increases and then reaches a plateau at pH values over 6. These results indicate that the species for effective enantio-differentiation may be monosodium tartrate or di-sodium tartrate. LiOH, KOH, or RbOH, in place of NaOH, shows a lower ee [112]. Although the reason for this phenomenon is not clear, the sodium ion is one of the most important factors for attaining high enantioselectivity.

The role of NaBr remains a matter of controversy; however, one suggested mechanisms by which NaBr improves enantioselectivity is that the Br^- ion blocks non-enantio-differentiating sites where racemic compounds are produced [113]. Another explanation is that NaBr changes the intrinsic enantioselectivity of the product-determining surface complex [114].

In the case of in-situ modification, the conditions are significantly different from those of pre-modification, as in-situ modification is carried out in an organic solvent and the source of Na^+ is NaBr (and sodium 2-ethylhexanoate). The adsorbed species of tartaric acid may be either a free acid or its sodium salt, which is produced by the sodium ion supplied by NaBr (and sodium 2-ethylhexanoate). The addition of a small amount of NaBr to the reaction medium increases both enantioselectivity and hydrogenation rate; for the pre-modification method, the addition of NaBr causes the hydrogenation rate to decrease [93]. NaBr added to the reaction medium for in-situ modification plays the following roles: i) the Na^+ ion increases enantioselectivity and hydrogenation rate; and ii) the Br^- ion increases enantioselectivity but decreases hydrogenation rate.

With regard to the characterization of adsorbed species using physico-chemical techniques, few investigations were made until the 1980s. Subsequently, XPS

studies indicated that the hydroxy groups of tartaric acid had minimal interaction with the surface Ni atoms; whether the adsorption species is nickel tartrate or sodium tartrate has not been determined [115]. Studies using reflection absorption infrared spectroscopy (RAIRS) have suggested that sodium tartrate is the major fraction on the surface of the tartaric acid-NaBr-modified Ni [116].

Recent developments in analytical instrumentation, including XPS, RAIRS, FT-IR, scanning electron microscopy with an X-ray micro-analyzer, temperature programmed desorption (TPD), or scanning tunneling microscopy (STM), have produced a wealth of valuable information. A tartaric acid-modified Ni-Ce oxide has been studied using XPS and FT-IR [92], and nickel tartrate was seen to be adsorbed onto the catalyst surface. XPS analysis showed that the ratio of Ni^{2+}:Ni^0 on the surface of the tartaric acid-NaBr-modified Raney Ni catalyst is approximately 1:1, whilst the surface of Raney Ni contains only an Ni^0 [117]. Analyses using STM, RAIRS and ab initio calculations (DTF) showed that (*R*,*R*)-tartaric acid is adsorbed onto Ni(110) from the gas phase in its bi-tartrate form, which locally reconstructs the Ni atoms and leaves a chiral footprint on the Ni surface [118]. The adsorption of (*R*,*R*)-tartaric acid on a Ni(111) surface has been also studied using RAIRS, STM, and TPD [119]. The adsorption of (*R*,*R*)-tartaric acid onto the Ni(111) produces ordered adlayer structures. At 300 K, back-to-back mono-tartrate species with dimer formation between the free carboxylic acid groups are proposed. The hydroxy groups interact via hydrogen bonding to the hydroxy groups on neighboring molecules. At 350 K, bi-tartrate molecules are surrounded by four other bi-tartrate molecules.

The adsorbed species on the surface of tartaric acid-NaBr-modified Ni change depending on the variability of the method used to prepare the base Ni catalysts, as well as their modification method, and especially whether tartaric acid is adsorbed from the liquid or gas phase and whether Na^+ exists in the modification solution, or not. Hence, further systematic studies must be conducted to determine which surface species are necessary for effective enantio-differentiation, and how a surface with a high enantio-differentiating ability may be constructed.

10.4.4.2 Mechanism of Enantio-differentiating Hydrogenation

The kinetic study Kinetic studies of unmodified and pre-modified Ni catalysts have been examined in order to understand the features of a catalyst which has both hydrogenation activity and enantio-differentiating ability. The results of these investigations are summarized in Table 10.8.

Ozaki et al. showed that the reaction rate and activation energy of tartaric acid-modified Ni and malic acid-modified Ni were the same, and concluded that the surface reaction between methyl acetoacetate and hydrogen – regardless of modifier type – is rate-determining. This means that the enantio-differentiating step is independent of the rate-determining step, and this is consistent with the results of Yasumori et al. and Woerde et al. – that the activation energy is the same between the unmodified and modified catalysts. In contrast, Sachtler and Kean showed that the activation energy of the modified Ni is lower than that of unmodified Ni. The

Tab. 10.8. Kinetic studies of unmodified Ni and tartaric acid-modified Ni catalysts.

Author(s) [Ref.]	*Catalyst, reaction*	*Activation energy [kJ mol^{-1}]*		*Reaction rate*	*ee of modified catalyst [%]*	*Temp. range tested [K]*
		Unmodified	*Modified*			
Ozaki et al. (1978) [120]	Raney Ni liquid phase 0.1 MPa	–	44	–	26	303–353
Yasumori et al. (1982) [121]	Decomposed Ni, gas phase 0.1 MPa	44	44	Decrease after modification	37–48	323–353
Woerde et al. (1982) [122]	0.5% Ni/SiO_2 gas phase 0.1 MPa	61	61	Decrease after modification	<15	333–363
Nitta et al. (1983) [123]	50% Ni/SiO_2 liquid phase 0.1–13 MPa	Proposal of Langmuir–Hinshelwood type rate equation			30–60	–
Sachtler (1985) [124]	14% Ni/SiO_2 gas phase 0.1 MPa	57	46	Increase after modification	37	300–321
Keane (1997) [125]	11.6% Ni/SiO_2 liquid phase 0.1 MPa	52	47	Increase 2-fold after modification	~22	318–383

decrease in activation energy after modification is attributed to stabilization of the adsorption state of methyl acetoacetate through interaction with tartaric acid [125].

The mode of enantio-differentiation Although enantio-differentiation models for hydrogenation over tartaric acid-modified Ni have been proposed by many groups since 1978, the subject remains a matter of controversy. These models are divided roughly into three categories: i) enantio-differentiation is carried out through a 1 to 1 interaction between tartaric acid adsorbed onto the Ni surface and the substrate; ii) enantio-differentiation is carried out by interaction between the Ni tartrate complex and the substrate; and iii) other models. Half of the models proposed belong to category i).

Yasumori has proposed that the half-hydrogenated methyl acetoacetate interacts with tartaric acid through hydrogen bonding, as shown in Figure 10.10(a) [121]. Klabunovskii et al. introduced a model of intermediate complex between acetylacetone and tartaric acid on a Ni–Cu/aerosil catalyst, where hydrogenation proceeds at the step of metal surface, as shown in Figure 10.10(b) [66]. In 1983, Tai et al. suggested hydrogen bond interaction between the two hydroxy groups of tartaric acid and the two carbonyl groups of methyl acetoacetate [99], and this model has contributed significantly to the optimization of catalyst preparation conditions and

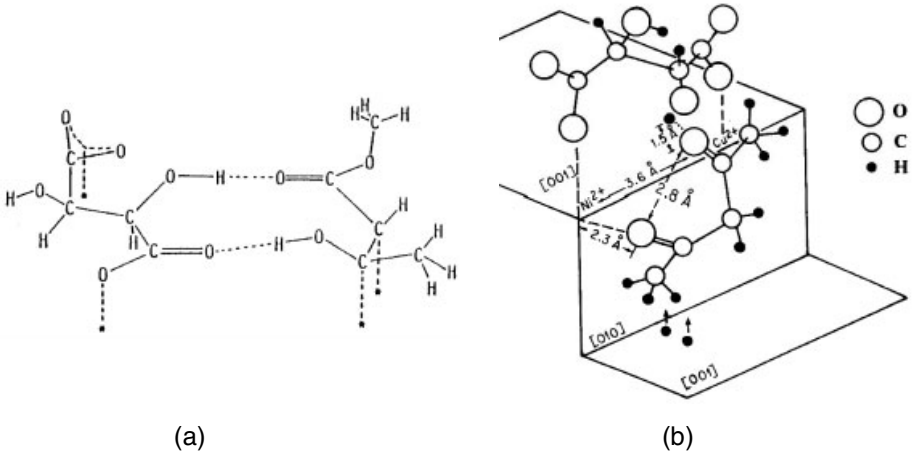


Fig. 10.10. Models for asymmetric induction proposed by Yasumori et al. (a) and Klabunovskii (b). Fig. 10.10 (a) is reproduced from Ref. [121] with permission from the Royal Society of Chemistry and (b) from Ref. [64] with permission from Elsevier.

reaction conditions. Recently, these authors updated this model to an "extended stereochemical model" in order to explain the features of hydrogenation of α-, β-, γ-,δ-ketoesters, and 2-alkanones (Fig. 10.11) [71].

Leclercq et al. have suggested an interaction between tartaric acid and methyl acetoacetate on the Ni–Ce oxide catalyst through a stable six-membered ring, in which one of the enantiotopic C–H bonds of the active methylene group of methyl acetoacetate is involved (Fig. 10.12(a)) [92]. Osawa et al. have proposed a model which explains the importance of Na^+ for attaining high enantioselectivity. Tartaric acid is adsorbed onto the Ni surface as the di-sodium salt. Methyl acetoacetate then

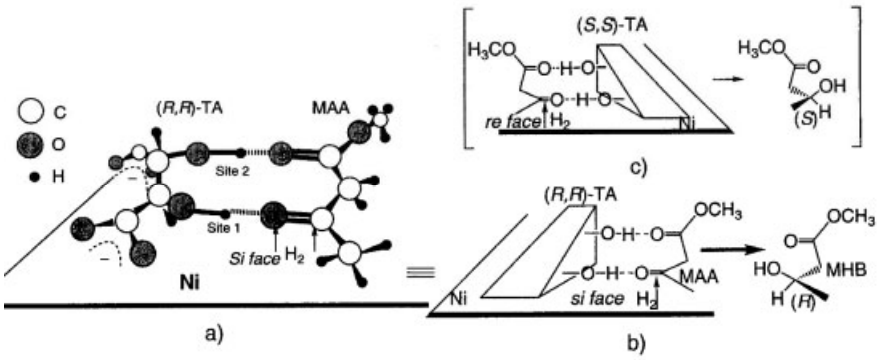


Fig. 10.11. The extended stereochemical model introduced by Tai et al., reproduced from Ref. [71] with permission from Wiley-VCH.

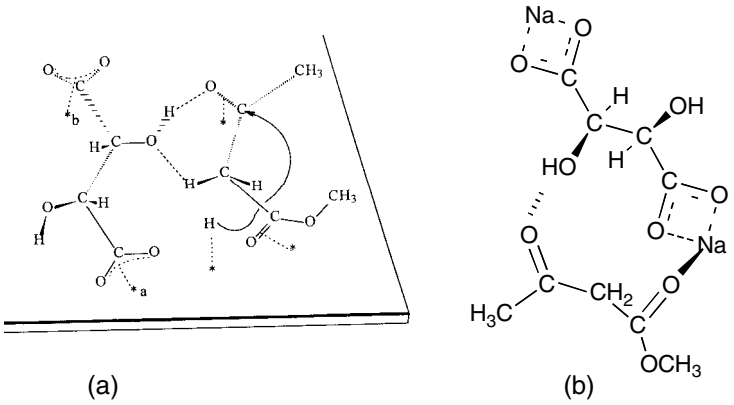


Fig. 10.12. The transition state models proposed by Leclercq et al. [92] (a) and Osawa et al. [70] (b). Fig. 10.12 (a) is reproduced from Ref. [92] with permission from Elsevier.

interacts with sodium tartrate through a hydrogen bond and a dipole-Na^+ interaction, as illustrated in Figure 10.12(b) [70].

As with the model of category ii), three models have been introduced. Hoek et al. assumed that the Na–Ni-tartrate complex shown in Figure 10.13(a) (Na not shown in the figure) acted as the template, and that one of the Ni atoms in the adsorption complex was the site on which the enantio-differentiating hydrogenation takes place [85]. Keane et al. have shown that Ni(II) tartrate has both an enantio-differentiating ability and hydrogenation activity [126]. The proposal by Kukula et al., based on XPS analysis, is that the modified Ni surface consists of two active centers; a metallic nickel and a nickel complexed with tartaric acid, which are arranged in an approximate 1:1 ratio on the surface [117]. The enantio-differentiating reaction is carried out over the latter center.

Recently, based on the physico-chemical analyses of a single crystal surface in a high vacuum, Humblot et al. offered a new type of enantio-differentiating model

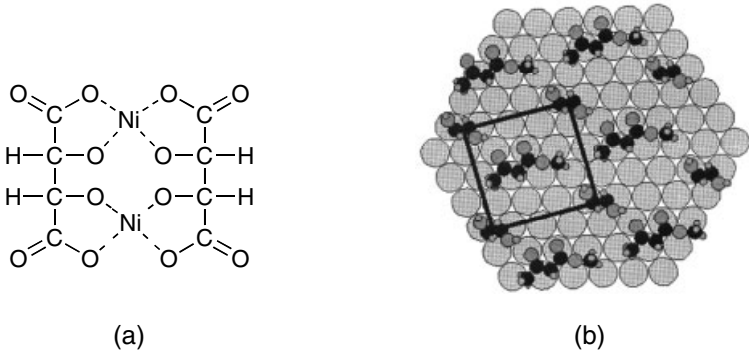


Fig. 10.13. The schematic projection of Ni tartrate (a) and adlayer of (*R*,*R*)-tartaric acid and methyl acetoacetate on Ni(111) (b), reproduced from Ref. [127] with permission from Elsevier.

(a category iii) in that the adsorption of tartaric acid induces the chiral footprint on the Ni surface, and this contributes to the enantio-differentiating ability of the catalyst [118]. Jones et al. have proposed that, at a low tartaric acid coverage, the low coverage of methyl acetoacetate rearranges the tartrate modifiers to produce a two-dimensional co-crystal. In this adlayer, methyl acetoacetate molecules have the same orientation and hence it is adsorbed with the equivalent enantio-face on Ni surface (Fig. 10.13(b)) [127].

10.4.5 Concluding Remarks on Tartaric Acid-NaBr-modified Ni Catalysts

The tartaric acid-NaBr-modified Ni catalyst attains an 80–98% ee for the hydrogenation of various types of β-functionalized ketones and 2-alkanones. For the hydrogenation of methyl acetoacetate, the use of reduced Ni and an in-situ modification permits repeated use of the catalyst, without loss of hydrogenation activity and enantioselectivity. These facts indicate that although the tartaric acid-NaBr-modified Ni catalyst is at the stage of practical application, the results of kinetic studies and the mode of enantio-differentiation remain too diverse to comprehend. The more efficient enantio-differentiating catalysts will be developed by a combination of chemical and physico-chemical studies, and especially of aspects of surface chemistry.

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Modern Organonickel Chemistry. Edited by Y. Tamaru

ISBN: 3-527-30796-6

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