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Asymmetric Hydrogenation

Tsuneo Imamoto

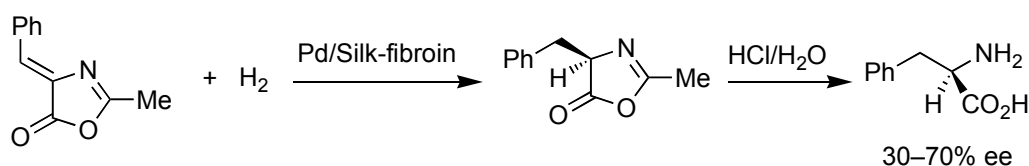
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1. Introduction

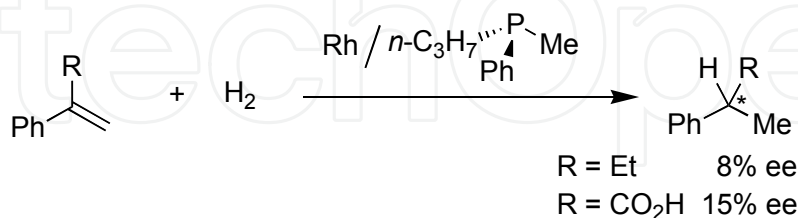
The asymmetric hydrogenation of prochiral unsaturated compounds, such as alkenes, ketones, and imines, is one of the most efficient and straightforward methods for the preparation of optically active compounds. This method uses dihydrogen and small amounts of chiral transition metal complexes and is now recognized as economical, operationally simple, and environmentally friendly. It is frequently used in both academia and industry for the synthesis of chiral amino acids, amines, alcohols, and alkanes in an enantiopure or enantiomerically enriched form.

Asymmetric hydrogenation can basically be classified into two categories, homogeneous and heterogeneous hydrogenation. Heterogeneous hydrogenation is technically simple and has a longer history than homogeneous hydrogenation. In 1956, Akahori et al. reported the asymmetric hydrogenation of azalactones in the presence of silk-fibroin-supported palladium (Scheme 1) [1]. This pioneering work was later extended to the hydrogenation of prochiral ketones using a Raney nickel or platinum catalyst that was modified by chiral auxiliaries, such as tartaric acid or cinchona alkaloids. However, prepared heterogeneous catalysts have as yet provided moderate to good enantioselectivities but not very high selectivities, so the method is not useful in practice except in some limited cases. In sharp contrast, homogeneous hydrogenation has developed enormously in the past four decades, and has become the useful methodology in modern science and technology. Therefore, this chapter focuses on homogeneous asymmetric hydrogenation.



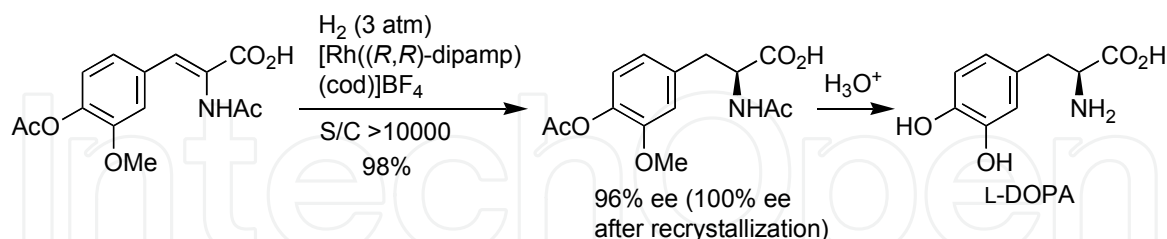
Scheme 1. Asymmetric hydrogenation of an azalactone catalyzed by silk-fibroin-supported palladium

Homogeneous asymmetric hydrogenation was first reported independently by Knowles and Horner in 1968 [2,3]. They replaced the triphenylphosphine of the Wilkinson catalyst ($\text{RhCl}(\text{PPh}_3)_3$) with optically active methylphenyl(*n*-propyl)phosphine and examined its catalytic performance in the hydrogenation of prochiral alkenes. The optical yields were low, but catalytic asymmetric hydrogenation was shown experimentally to have occurred unequivocally in the homogeneous system (Scheme 2).



Scheme 2. First example of homogeneous asymmetric hydrogenation

In 1971, Kagan et al. synthesized a chelating diphosphine ligand with two phenyl groups on each of the two phosphorus atoms [4]. The ligand, 4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane (DIOP), is the first example of a C_2 -symmetric phosphine ligand. Its high capacity for asymmetric induction, up to 88%, was demonstrated in the hydrogenation of α -dehydroamino acids and enamides [5], and these excellent results stimulated the design and synthesis of many other C_2 -symmetric phosphine ligands. The most notable ligand reported in the period up to 1979 was 1,2-bis(*o*-anisylphenylphosphino)ethane (DIPAMP) developed by Knowles (Nobel laureate in 2001) et al. at Monsanto in 1975, which provided very high enantioselectivity values up to 96% in the hydrogenation of α -dehydroamino acids [6]. The methodology was used to produce (*S*)-3-(3,4-dihydroxyphenyl)alanine (L-DOPA), which is useful in the treatment of Parkinson's disease. This was the first example of asymmetric catalysis on an industrial scale (Scheme 3) [7].



Scheme 3. The Monsanto process for the production of L-DOPA

Another landmark ligand was 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), developed by Noyori (Nobel laureate in 2001) et al. in 1980 [8]. The appearance of BINAP heralded marked advances in asymmetric hydrogenation and other transition-metal-catalyzed asymmetric catalyses. The methodology developed by Noyori et al. using BINAP resolved longstanding problems, such as the limited applicability of the method, which was attributed to substrate specificity and unsatisfactory catalytic activity. Thus, a wide range of prochiral alkenes and carbonyl substrates, including simple ketones, were subjected to hydrogenation with much lower catalyst loadings, to generate the corresponding saturated

compounds with exceedingly high enantioselectivity. The method based on the Ru-BINAP catalyst system has allowed the use of asymmetric hydrogenation in the industrial production of many useful optically active compounds such as pharmaceutical ingredients, agrochemicals, and flavors [9].

In 1993, the research groups of Pfaltz, Helmchen, and Williams independently reported a P,N-ligand phosphinooxazoline (PHOX) [10–12]. The utility of this ligand in asymmetric hydrogenation was demonstrated by Pfaltz et al. using its iridium complex. They showed that largely unfunctionalized alkenes were enantioselectively hydrogenated by Ir-PHOX and related catalysts [13,14]. Their studies significantly expanded the scope of asymmetric hydrogenation and offered a new tool for the efficient production of chiral building blocks.

In contrast, homogeneous asymmetric hydrogenation using chiral complexes of early transition metals or less-expensive late transition metals has also been investigated. Some success has been achieved in the hydrogenation of alkenes and imines with chiral catalysts containing titanium, zirconium, lanthanides, or iron. However, because of the length limitation on this chapter, rhodium-, ruthenium-, and iridium-catalyzed asymmetric hydrogenation will be described here.

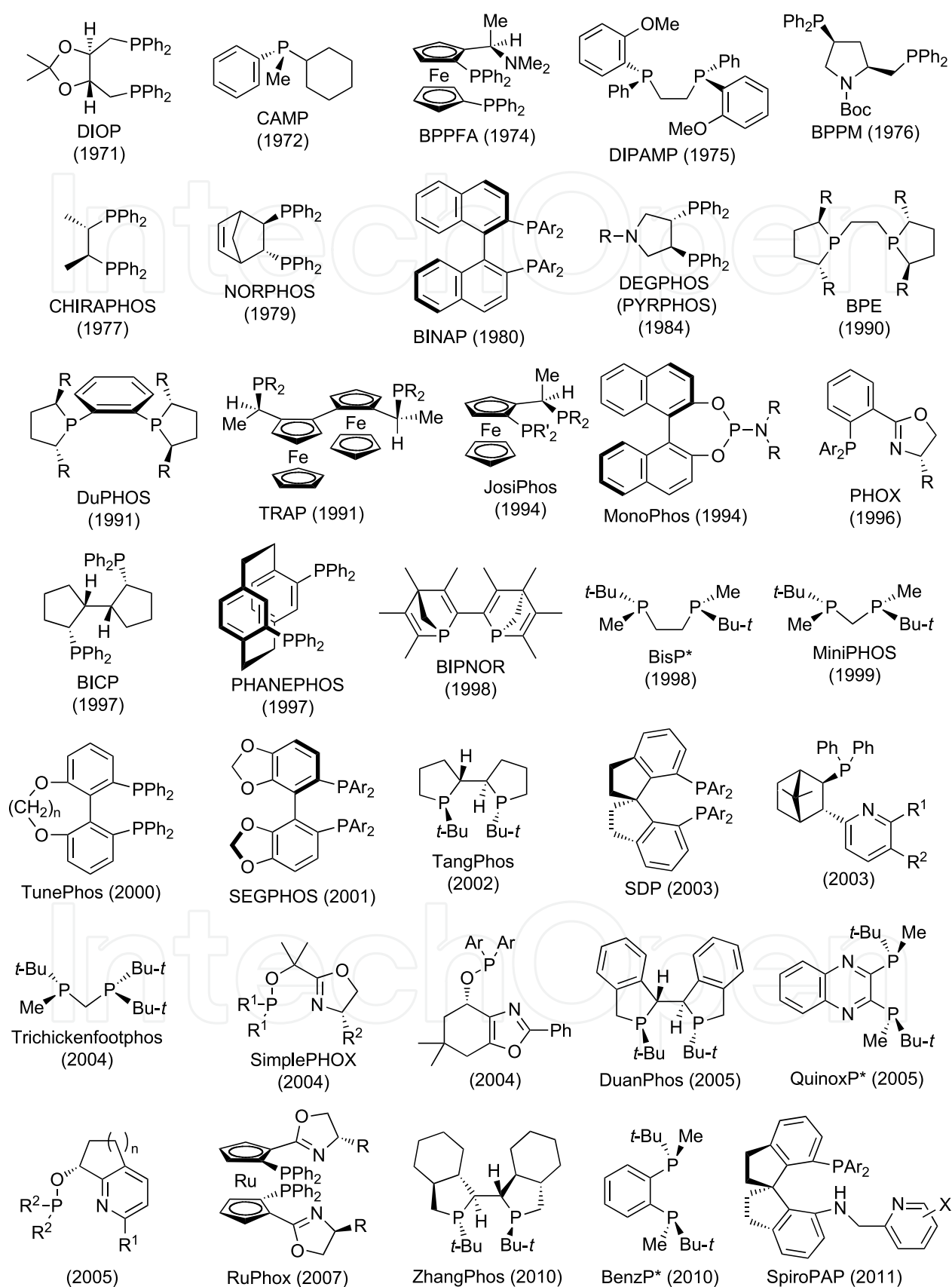
Based on extensive experiments, computations, and theoretical considerations, asymmetric hydrogenation is now highly advanced, so any broad overview of this area is difficult. Fortunately, many exhaustive reviews have been published, together with excellent accounts of asymmetric hydrogenation. The author hopes that this chapter, together with the review articles [15–18], will provide good references for the process.

2. Chiral Phosphine Ligands for Asymmetric Hydrogenation

The design and synthesis of new chiral phosphine ligands are crucial for the development of transition-metal-catalyzed asymmetric catalysis. Over the past four decades, thousands of chiral phosphine ligands have been synthesized and their catalytic efficiencies evaluated [19–21]. Figure 1 illustrates representative phosphine ligands, including P,N-hybrid ligands, that have attracted much attention because of their novelty, conceptual importance, and/or practical utility.

Most of them are C_2 -symmetric bidentate diphosphine ligands. In the hydrogenation process based on C_2 -ligands, the number of structures that the catalyst–substrate complexes can adopt is reduced to half compared with those formed from C_1 -symmetric catalysts, and consequently, C_2 -symmetric ligands achieve higher enantioselectivity than C_1 -symmetric ligands. Conversely, many C_1 -symmetric ligands, including JosiPhos, Trichickenfootphos, and PHOX, display superior enantioselectivity, depending on the reaction.

DIPAMP is a typical C_2 -symmetric and P-chiral (P-stereogenic) diphosphine ligand. This ligand played an outstanding role in the early stages of the history of asymmetric hydrogenation. Nevertheless, little attention had been paid to this class of P-chiral phosphine ligands for more than 15 years, mainly because of the difficulties inherent in their synthesis and apprehension about possible stereomutation at P-stereogenic centers. The author's

**Figure 1.** Representative chiral phosphine ligands

research group has developed efficient methods for the preparation of P-chiral phosphine ligands using phosphine–boranes as the key intermediates and prepared (*R,R*)-1,2-bis(*tert*-butylphenylphosphino)ethane in 1990, (*S,S*)-1,2-bis(*tert*-butylmethylphosphino)ethane (BisP*) in 1998, and (*R,R*)-bis(*tert*-butylmethylphosphino)methane (MiniPHOS) in 1999 [22–24]. Of these ligands, BisP* and MiniPHOS display enantioselectivities higher than those of DIPAMP in Rh-catalyzed asymmetric hydrogenation. These findings triggered the synthesis of structurally analogous but more rigid P-chiral phosphine ligands, and many highly efficient and practically useful ligands have since been reported (TangPhos, Trichickenfootphos, DuanPhos, QuinoxP*, ZhangPhos, BenzP*, etc.).

As mentioned above, many chiral phosphine ligands have been shown to exhibit excellent enantioselectivity and some outstanding ligands have been used in the industrial production of useful optically active compounds. However, there are no “omnipotent” ligands, and so the development of more efficient, operationally convenient, and widely applicable chiral phosphine ligands is still a vital research topic in the field of asymmetric catalysis.

3. Rhodium-catalyzed Asymmetric Hydrogenation

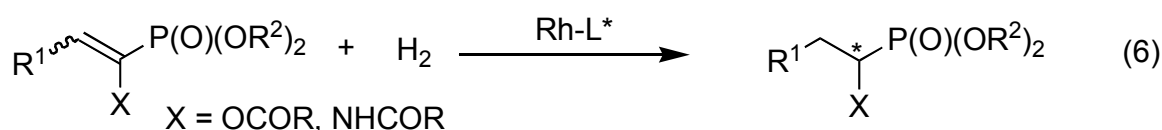
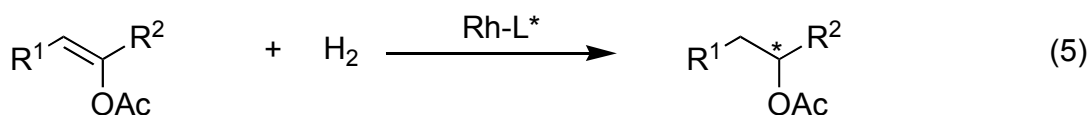
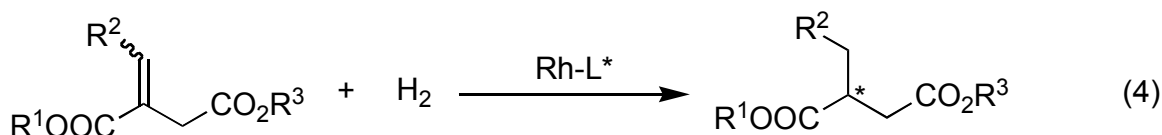
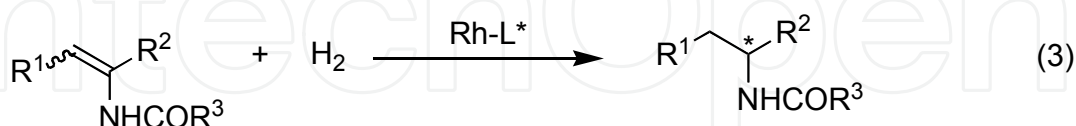
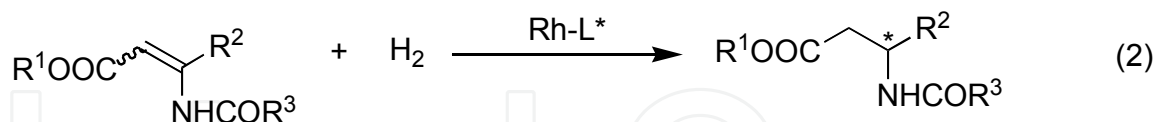
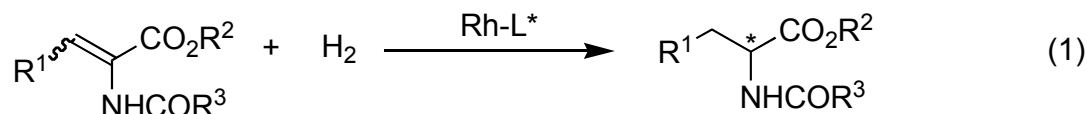
3.1. General scope

Rhodium-catalyzed hydrogenation is well suited to the enantioselective reduction of α - and β -dehydroamino acid derivatives and enamides. Thus, chiral α - and β -amino acids and secondary amine derivatives can be obtained in an enantiomerically pure or enriched form by the hydrogenation of amino-functionalized alkenes (Equations 1–3). The catalytic efficiency and enantioselectivity are largely dependent on the chiral ligands and substrates used. In general, electron-rich and structurally rigid ligands, such as DuPhos, DuanPhos, ZhangPhos, QuinoxP*, and BenzP*, provide the corresponding products in high to almost-perfect enantioselectivity. Di- or tri-substituted alkenes are readily hydrogenated, but tetrasubstituted alkenes require higher hydrogen pressure, higher catalyst loading, and/or a higher reaction temperature to facilitate the hydrogenation reaction.

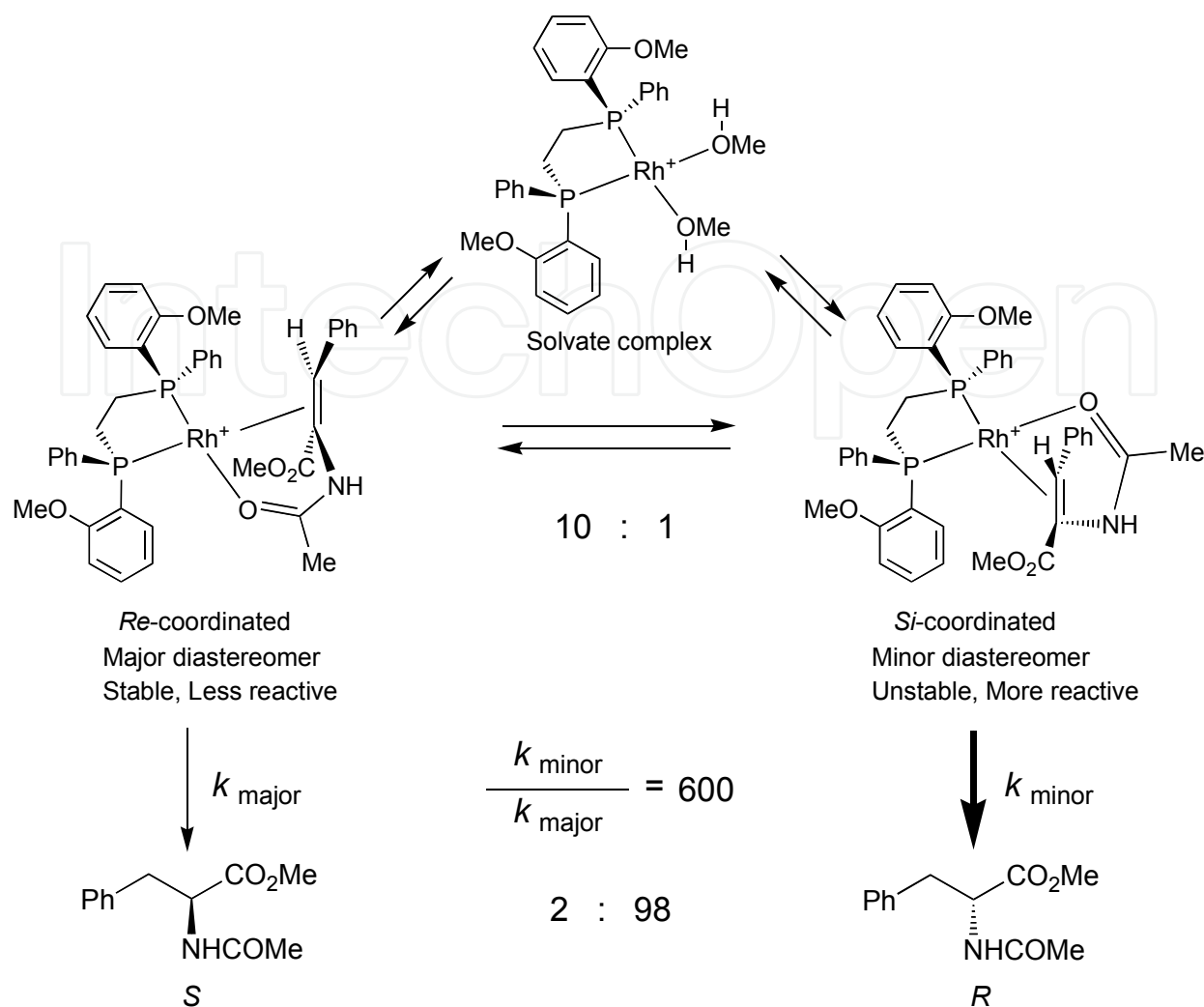
Rhodium catalysts are also used for the hydrogenation of itaconic acid derivatives, enol esters, and ethenephosphonates (Equations 4–6). As in the hydrogenation of dehydroamino acids and enamides, the oxygen functional groups capable of coordination to the rhodium atom play an important role in accelerating the reaction, as well as in the enantioselection.

3.2. Reaction mechanism

Since the discovery of rhodium-catalyzed asymmetric hydrogenation, the reaction mechanism, including the catalytic cycle and the origin of the enantioselection process, has been studied extensively. Early studies using cationic rhodium complexes with C₂-symmetric diphosphine ligands with two diaryl substituents at each phosphorus atom led to the so-called “unsaturated mechanism”. This mechanism, proposed by Halpern and Brown, is based on the following experimental facts and considerations [25–28].



1. The solvate complex generated by the hydrogenation of a precatalyst reacts with a prochiral substrate, such as methyl (Z)- α -acetamidocinnamate (MAC), providing two diastereomeric catalyst-substrate complexes in a considerably high ratio. For example, the Rh-(S,S)-DIPAMP solvate complex binds to MAC to generate *Re*- and *Si*-coordinated adducts in a ratio of about 10:1.
2. The configuration of the major isomer does not correspond to the configuration of the product if it is assumed that the oxidative addition of H₂ occurs in an *endo*-manner and that the stereochemical integrity is maintained through to the final reductive elimination step.
3. At ambient temperatures, major and minor catalyst-substrate complexes are interconverted rapidly. The minor isomer is much more reactive with H₂ than the major isomer, and the reaction proceeds according to the Curtin-Hammett principle.
4. The oxidative addition of dihydrogen to the catalyst-substrate complex is rate-determining and irreversible, and enantioselection is determined at this step.
5. The kinetic and equilibration data are consistent with the stereochemical outcome (*R*:*S* = 98:2; 96% ee).
6. At low temperatures, enantioselectivity is significantly reduced. This fact is interpreted as reflecting that the interconversion between the major and minor isomers is very slow or almost in a frozen state at low temperatures. As a consequence, the major isomer competitively reacts with dihydrogen to generate the opposite enantiomeric product, resulting in lower enantioselectivity.

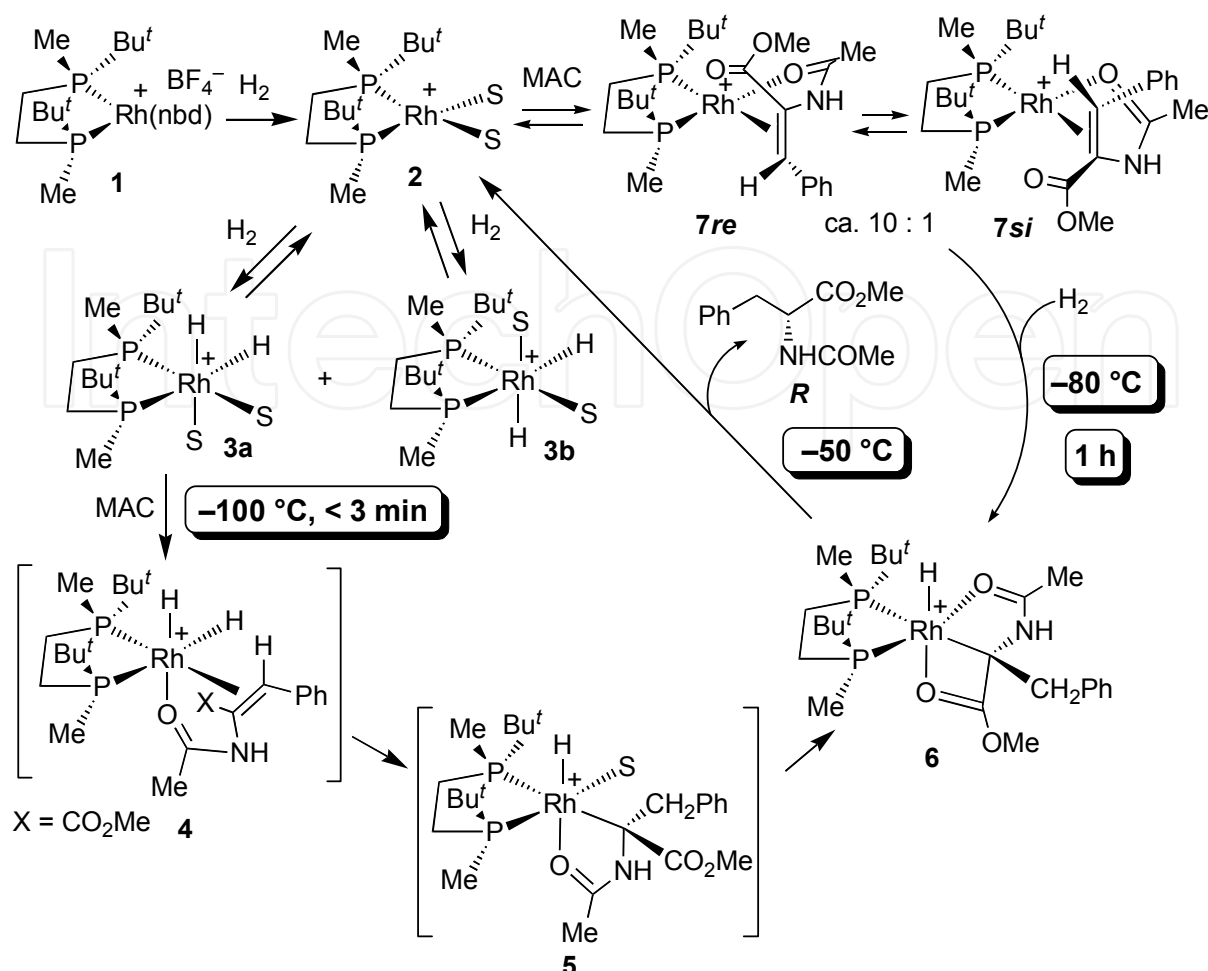


Scheme 4. Unsaturated mechanism: hydrogenation of MAC with Rh-(*S,S*)-DIPAMP leading to (*R*)-phenylalanine methyl ester with 96% ee

7. A significant reduction in enantioselectivity is also observed when the reaction is performed under higher H₂ pressure. This fact is interpreted by considering that the reaction of the less-reactive major isomer with dihydrogen is facilitated under high H₂ pressure.

The key points in this mechanism are illustrated in Scheme 4. This enantioselection mechanism is quite unique, differing from those of other asymmetric catalyses. It should be noted that this mechanism does not correspond to the “lock and key” principle, which is widely invoked in stereoselective reactions catalyzed by enzymes.

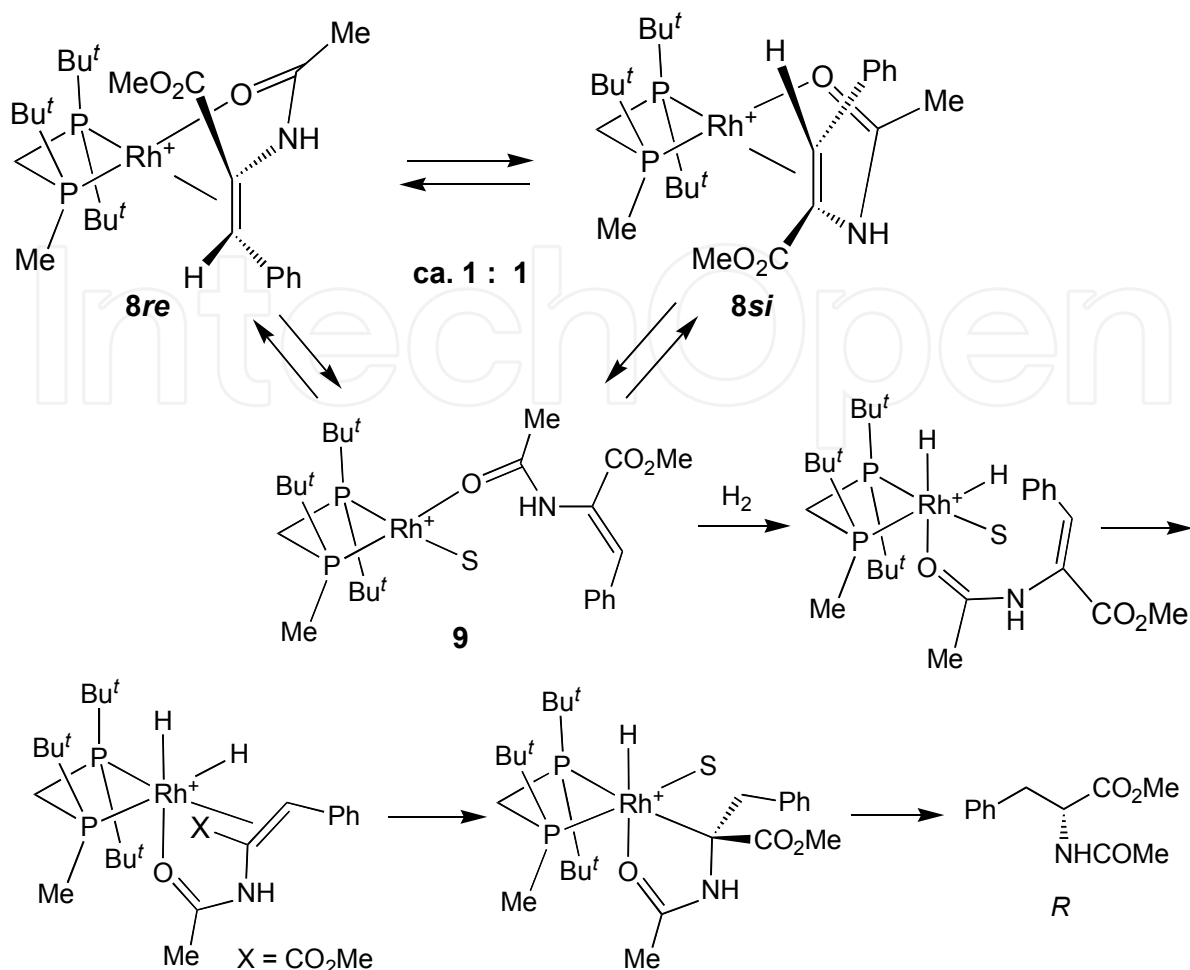
In contrast, the development of electron-rich diphosphine ligands has revealed a new mechanistic aspect of rhodium-catalyzed asymmetric hydrogenation. It has been reported that rhodium catalysts with electron-rich phosphine ligands (DuPhos, BPE, BisP*, MiniPHOS, Trichickenfootphos, TangPhos, DuanPhos, ZhangPhos, QuinoxP*, BenzP*, etc.) display very high to almost-perfect enantioselectivity in the hydrogenation of many dehydroamino acids and enamides. The origin of this exceedingly high enantioselectivity



Scheme 5. Mechanism of the asymmetric hydrogenation of MAC with Rh-(*S,S*)-*t*-Bu-BisP*

cannot be explained well in terms of the “unsaturated mechanism” mentioned above. Gridnev and Imamoto et al. studied the hydrogenation mechanism using $[\text{Rh}(\text{t-Bu-BisP}^*)(\text{nbd})]\text{BF}_4$ (**1**) [29,30]. One of their notable findings was that the solvate complex $[\text{Rh}(\text{t-Bu-BisP}^*)(\text{CD}_3\text{OD})_2]\text{BF}_4$ (**2**) reacted with H_2 at -90°C to produce equilibrium amounts (ca. 20%) of rhodium dihydride complexes $[\text{RhH}_2(\text{t-Bu-BisP}^*)]\text{BF}_4$ (**3a** and **3b**; dihydride diastereomers). The dihydride complexes reacted with MAC, even at very low temperatures (-100°C), and were rapidly (within 3 min) converted to the monohydride intermediate **6** (Scheme 5). The reaction is considered to proceed through the associated intermediate **4** and monohydride **5**.

On the contrary, the hydrogenation of the catalysts–substrate complexes (**7re** and **7si** = ca. 10:1) was relatively slow. It required about 1 h at -80°C to generate the same concentration of monohydride **6**. The reaction is considered to proceed through the solvate complex **2**, which is generated by the reversible dissociation of **7re** and **7si**, and to proceed via dihydrides **3a** and **3b**, **4**, and **5**. It is reasonable to infer that the enantioselection is determined at the migratory insertion step from **4** to **5**. There are eight possible diastereomers of **4**. Among them, complex **4** is energetically most stable, is preferentially formed, and undergoes migratory insertion via the lowest transition state, resulting in the formation of the (*R*)-hydrogenation product.



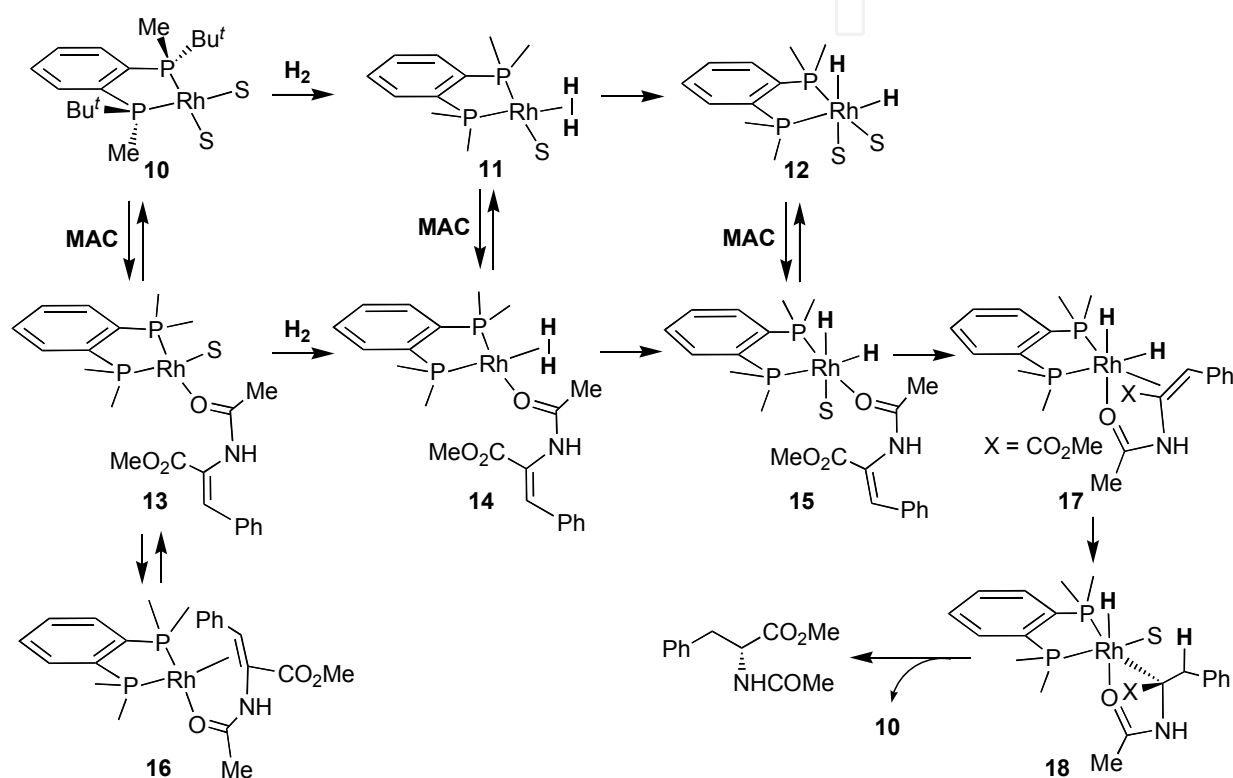
Scheme 6. Reaction pathway from catalyst–substrate complexes to (*R*)-*N*-acetylphenylalanine methyl ester

The origin of the enantioselection process has also been studied using MAC and Trichickenfootphos, a C_1 -symmetric three-hindered phosphine ligand [31,32]. In this case, two of the four possible diastereomeric catalyst–substrate complexes are thermodynamically stable and exist in a ratio of about 1:1. Remarkably, the respective complexes reacted with dihydrogen to yield the same (*R*)-product. NMR and computational studies have demonstrated that the complexes (**8re** and **8si**) dissociate the C=C double bond to generate nonchelating complex **9**, which in turn reacts with dihydrogen, with subsequent association and migratory insertion, to yield the (*R*)-product (Scheme 6).

Recently, the hydrogenation mechanism has also been studied using $[Rh((R,R)\text{-BenzP}^*)(\text{nbd})]\text{BF}_4$ [33]. Low-temperature NMR and density functional theory (DFT) calculations have revealed more detailed aspects of the mechanism. DFT calculations showed the relative stability of each intermediate and the transition state energies. Consequently, the most reasonable reaction pathway from the solvate complex **10** to the product is proposed to be as shown in Scheme 7. The solvate complex **10** is readily hydrogenated to dihydride **12** via **11**, followed by the reaction of **12** with MAC to produce the nonchelating dihydride intermediate **15**. The nonchelating catalyst–substrate complex **13**

is also readily subjected to hydrogenation because dihydrogen is readily coordinated at the vacant site of the complex, leading to **15** via **14**. On the contrary, the hydrogenation of the chelating catalyst–substrate complex **16** requires a much higher activation energy, so the unsaturated pathway does not operate in this reaction system.

Enantioselection occurs at a later stage. The recoordination of the double bond of complex **15** to the rhodium atom occurs readily in the non-hindered quadrant to form the chelated dihydride intermediate **17**. This undergoes migratory insertion to produce monohydride **18**, followed by reductive elimination to generate a product with the correct absolute configuration.

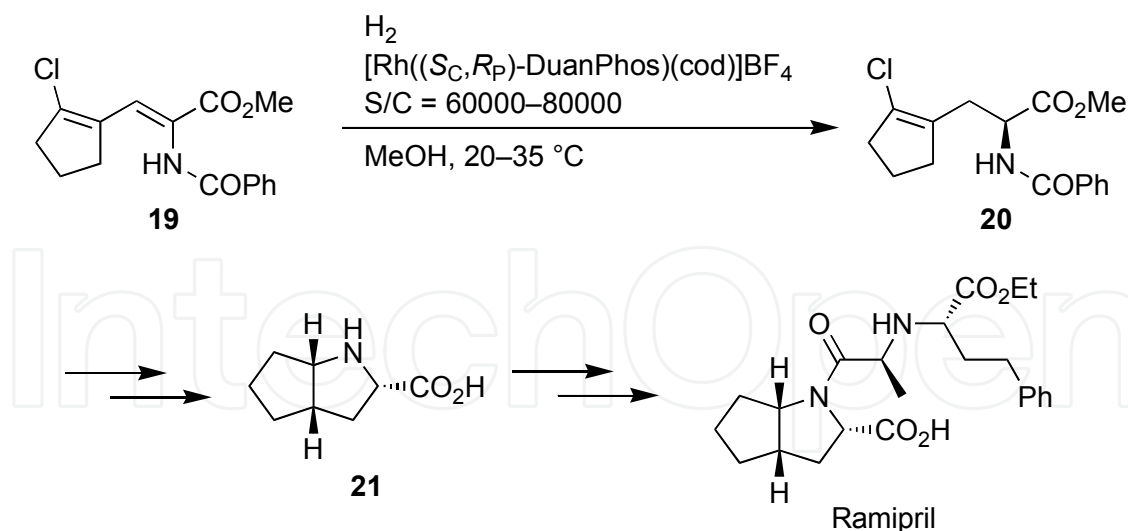


Scheme 7. The reaction pathway of the asymmetric hydrogenation of MAC catalyzed by the Rh-(*R,R*)-BenzP* complex

3.3. Application to the synthesis of useful optically active compounds

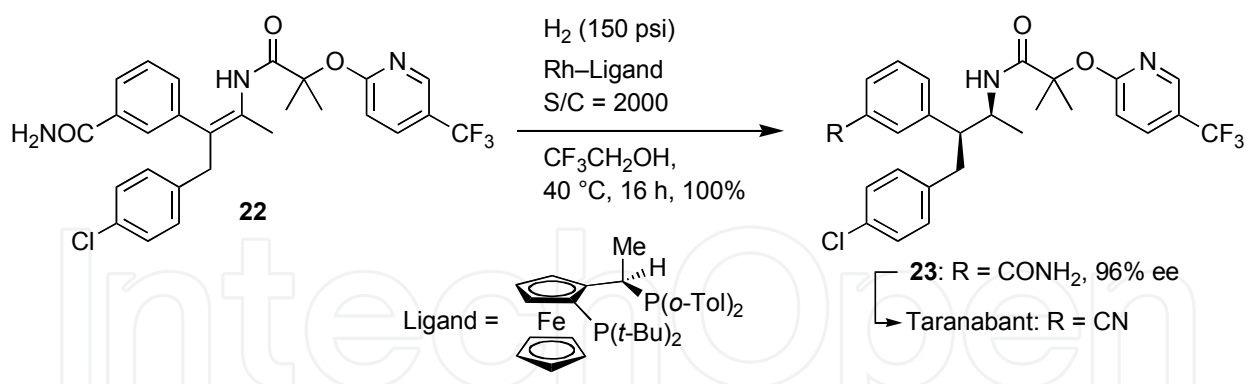
Rhodium complexes with chiral phosphine ligands have been widely used in academia and industry for the synthesis of the chiral building blocks of natural products, pharmaceuticals, and agrochemicals. Schemes 8–11 show representative examples.

Zhang et al. developed a new process for the production of ramipril, an angiotensin-converting enzyme inhibitor, used to treat high blood pressure and congestive heart failure (Scheme 8) [34]. The α -dehydroamino acid methyl ester **19** was efficiently hydrogenated under mild conditions with a rhodium–DuanPhos complex to yield compound **20** with 99% ee. The hydrolysis of the vinyl chloride moiety of compound **20**, followed by its cyclization, generated bicyclic amino acid **21**, which was converted to ramipril.



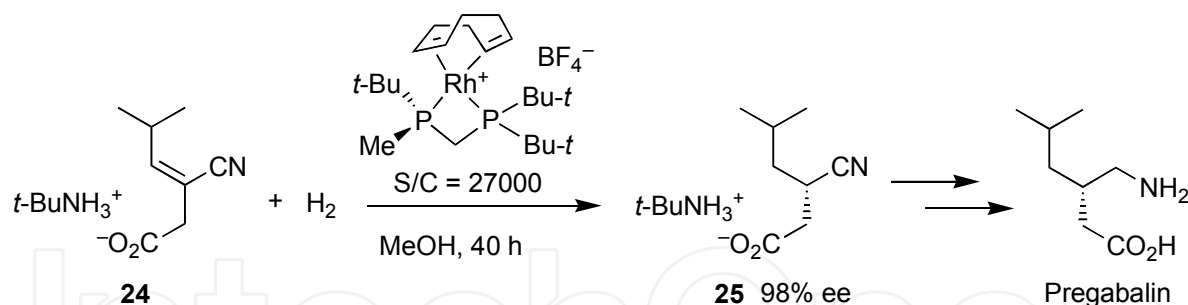
Scheme 8. Synthesis of ramipril via Rh-catalyzed asymmetric hydrogenation

Merck Research Laboratories identified taranabant, as a potential selective cannabinoid-1 receptor inverse agonist, for the treatment of obesity. One of the synthetic routes to taranabant is shown in Scheme 9, and involves the rhodium-catalyzed asymmetric hydrogenation of a tetrasubstituted enamide **22**. The hydrogenation reaction to introduce two stereogenic centers is achieved with a JosiPhos-type ligand and trifluoroethanol as the solvent, to produce compound **23** with 96% ee, and one recrystallization of the product increases the ee value to > 99.5%. The final dehydration of the primary amide with cyanuric chloride generates taranabant [35,36].



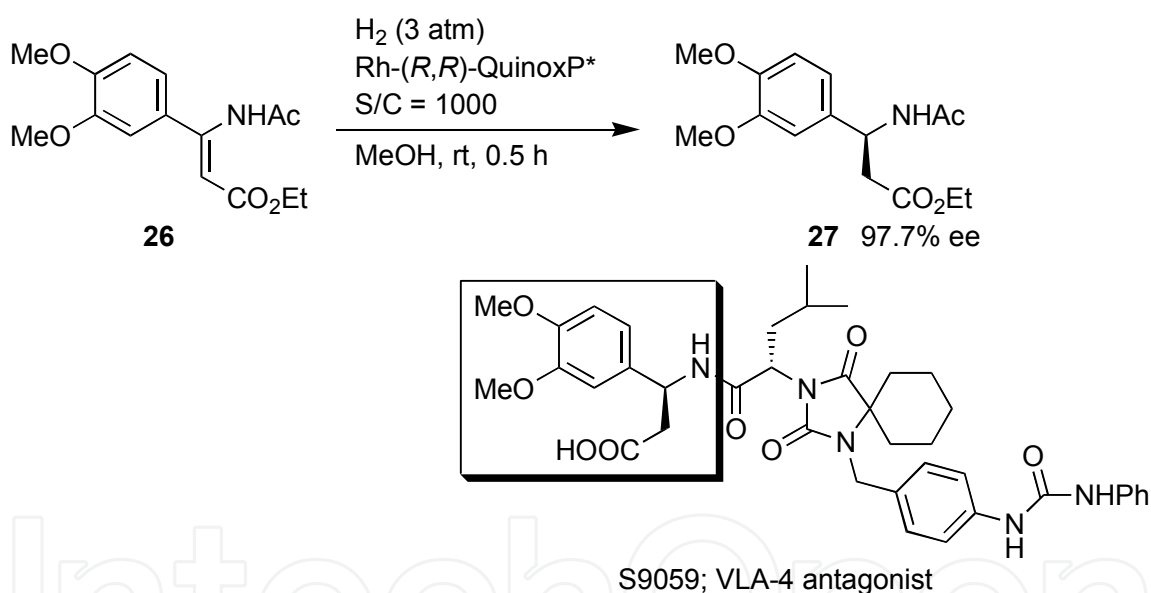
Scheme 9. Synthesis of taranabant via Rh-catalyzed asymmetric hydrogenation

Pregabalin, a kind of optically active γ -amino acid, is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures. This drug is marketed by Pfizer under the trade name Lyrica. A chemical synthesis of pregabalin is shown in Scheme 10, where the key intermediate **25** is obtained by the asymmetric hydrogenation of *tert*-butylammonium (Z)-3-cyano-5-methyl-3-hexenoate (**24**) using a Rh-Trichickenfootphos catalyst. The very low catalyst loading (S/C = 27,000), mild conditions (50 psi H₂ pressure, room temperature), and high enantioselectivity (98% ee) indicate the potential utility of this process in the large-scale production of pregabalin [37].



Scheme 10. Synthesis of a key intermediate in the production of pregabalin

Chiral β -amino acid derivatives are useful building blocks for the synthesis of β -peptides and β -lactam antibiotics. Asymmetric hydrogenation of β -dehydroamino acids with chiral rhodium catalysts is a useful method for the production of key chiral intermediates. An example of the preparation of a building block of the very late antigen-4 (VLA-4) antagonist S9059 is shown in Scheme 11. The hydrogenation of compound **26** in the presence of 0.1 mol % catalyst under 3 atm H_2 pressure proceeded rapidly, to produce the corresponding product **27** with 97.7% ee [33].



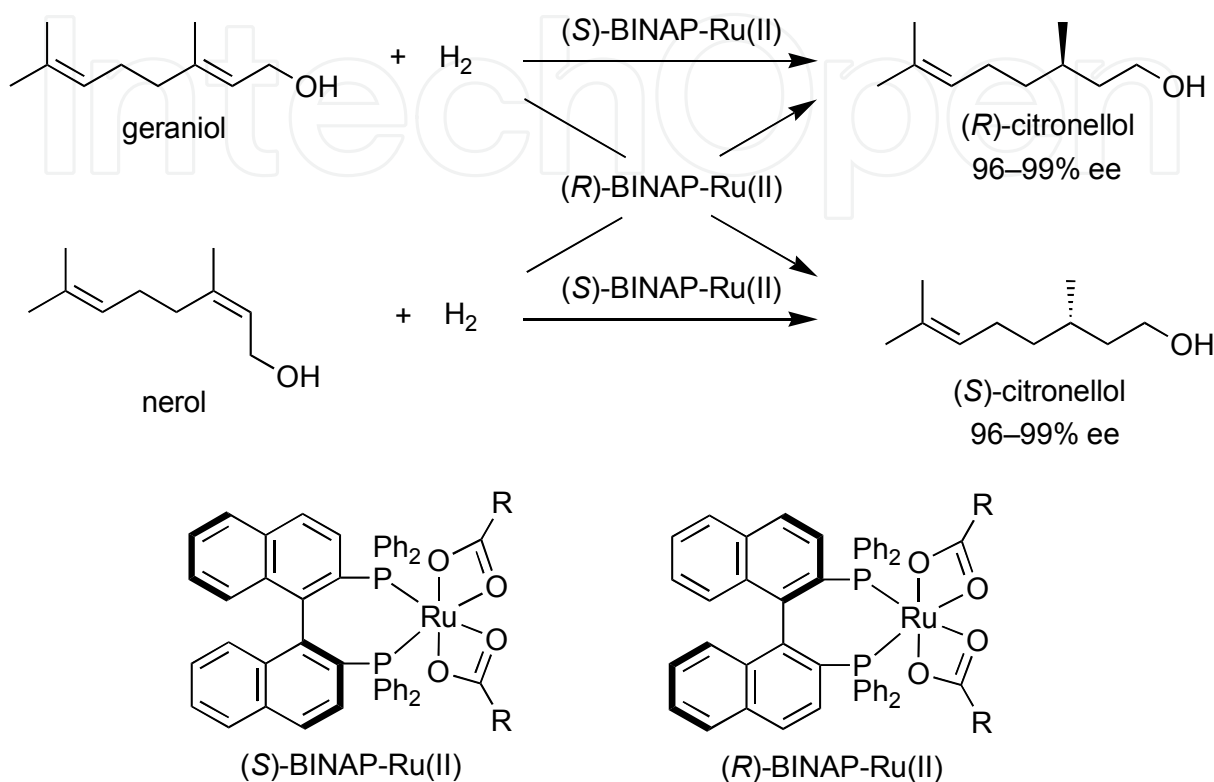
Scheme 11. Asymmetric hydrogenation of a *N*-acetyl- β -dehydroamino acid ester

4. Ruthenium-catalyzed Asymmetric Hydrogenation

4.1. Hydrogenation of functionalized alkenes

The discovery of chiral ruthenium catalysts significantly expanded the scope of asymmetric hydrogenation. Noyori et al. made the first breakthrough in this area using BINAP-Ru(II) dicarboxylate complexes. These complexes catalyze the highly enantioselective hydrogenation of the carbon-carbon double bonds of the substrates, the asymmetric hydrogenation of which had been difficult to achieve with the rhodium catalysts reported until then. For example, geraniol and its geometric isomer nerol, a kind of allyl alcohol, are

subjected to hydrogenation with (*S*)-BINAP-Ru to produce (*R*)-citronellol and (*S*)-citronellol, respectively, and conversely, the use of (*R*)-BINAP-Ru produces the (*S*)- and (*R*)-products, respectively. Notably, the hydrogenation proceeds with a quite low catalyst loading (*S/C* = 50,000) to generate the products with a quantitative yield, with excellent enantioselectivities (96–99% ee) (Scheme 12) [38].

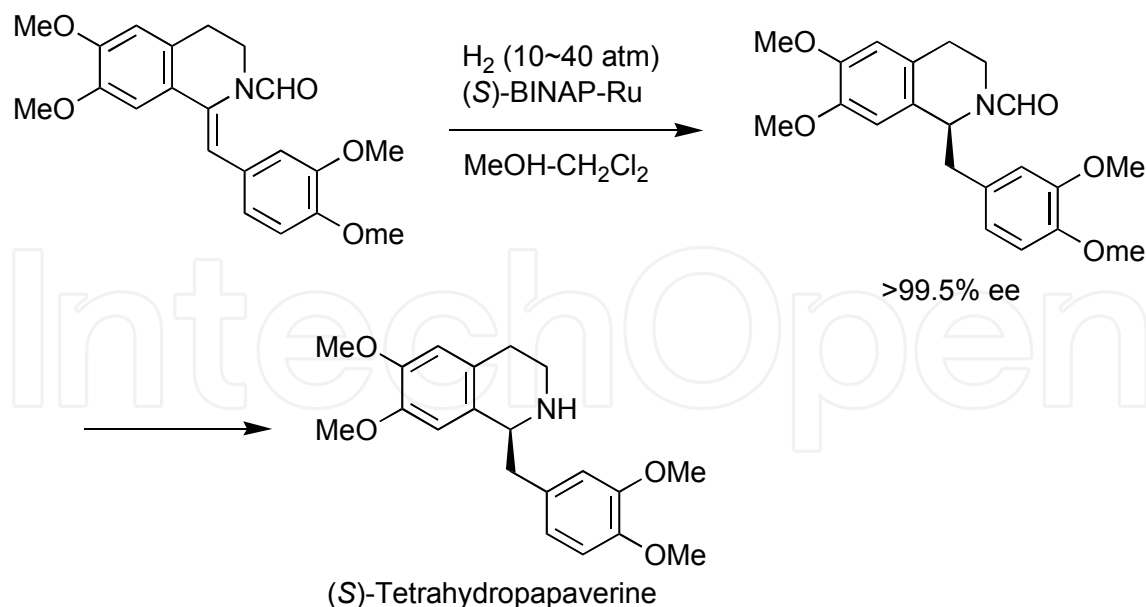


Scheme 12. Asymmetric hydrogenation of geraniol and nerol with BINAP-Ru(II) catalysts

The Ru(II) catalyst systems have been successfully applied to the enantioselective hydrogenation of α,β -unsaturated carboxylic acid esters, lactones, and ketones. Enamides are also efficiently hydrogenated with these catalysts. Using this catalyst system, isoquinoline alkaloids, morphine, and its artificial analogues can be prepared in an enantiopure form. A representative example, the synthesis of (*S*)-tetrahydropapaverine, is shown in Scheme 13 [39].

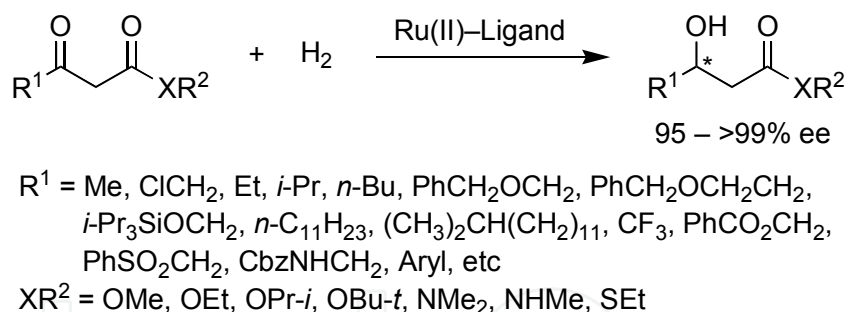
4.2. Hydrogenation of β -Keto esters and related substrates

Optically active β -hydroxy carboxylic esters are an important class of compounds in the synthesis of naturally occurring and biologically active compounds. Noyori et al. demonstrated a useful method for the catalytic asymmetric synthesis of this class of compounds using BINAP-Ru(II) complexes as the catalysts. The BINAP-Ru dicarboxylate complexes, which proved to be highly efficient for the enantioselective hydrogenation of various olefins, were not effective in this transformation. Instead, halogen-containing complexes RuX₂(binap) (X = Cl, Br, or I) were excellent catalyst precursors. The reactions with *S/C* > 1000 proceeded smoothly under 50–100 atm H₂ pressure, with excellent enantioselectivities, up to > 99% [40].



Scheme 13. Synthesis of (S)-tetrahydropapaverine via Ru-catalyzed asymmetric hydrogenation

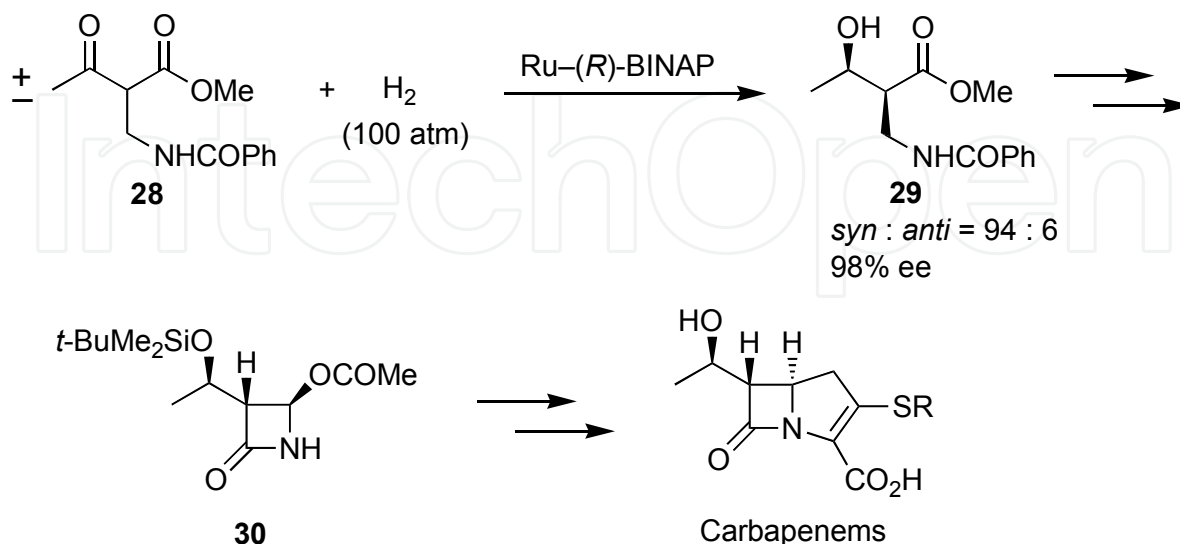
The scope of this reaction was extensively expanded using various chiral phosphine ligands. As a result, a variety of β -keto esters, amides, and thiol esters with a functional group ($R^1 = \text{ClCH}_2$, alkoxymethyl, aryl, etc.) were hydrogenated in excellent enantioselectivities (Scheme 14). This method is currently used in academia and industry for the preparation of numerous chiral building blocks for the synthesis of biologically active compounds.



Scheme 14. Ruthenium-catalyzed asymmetric hydrogenation of β -keto esters and related substrates

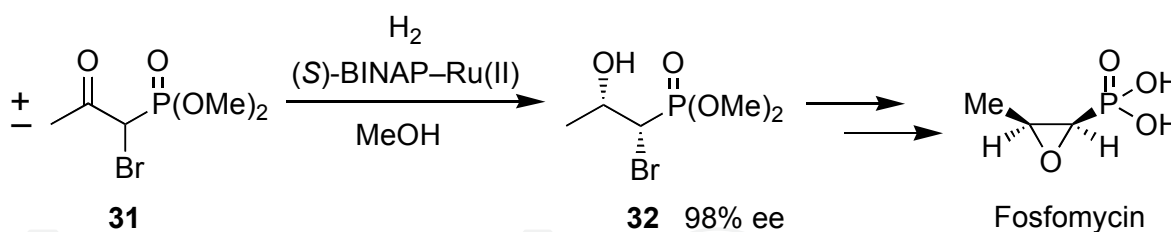
The hydrogenation of a β -keto ester bearing one substituent at the α -position provides four possible stereoisomeric β -hydroxy esters. Because stereomutation at the α -position of the β -keto ester occurs readily, it should be possible to selectively hydrogenate one of the β -keto ester enantiomers to yield only one stereoisomer, if the reaction conditions and the chiral ligand are selected appropriately. Noyori et al. established this dynamic kinetic resolution process using BINAP-Ru complexes [41,42]. The great utility of this method has been demonstrated in the production of many enantiopure building blocks. A representative example of the production of carbapenems by Takasago International Corporation is shown in Scheme 15 [43,44]. The hydrogenation of racemic **28** occurs with full conversion to yield the (2*S*,3*R*) product **29** with high diastereo- and enantioselectivity, and the product is further converted to the key intermediate, azetidinone **30**. The use of the DTBM-SEGPHOS-Ru(II)

(DTBM-SEGPHOS = 5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole) complex for this reaction yields **29** almost exclusively (98.6% diastereomeric excess, 99.4% ee) [45].



Scheme 15. Industrial synthesis of a carbapenem intermediate with Ru-BINAP-catalyzed hydrogenation

Another example is shown in Scheme 16. Racemic dimethyl 1-bromo-2-oxopropylphosphonate (**31**) is hydrogenated in the presence of the (S)-BINAP-Ru complex to yield (1*R*,2*S*)-1-bromo-2-hydroxypropylphosphonate (**32**) with 98% ee. The product is converted into fosfomycin, a clinically used antibiotic [46].



Scheme 16. Synthesis of fosfomycin via dynamic kinetic resolution

4.3. Hydrogenation of simple ketones

The development of ruthenium catalysts containing enantiopure diphosphines and diamines has allowed the asymmetric hydrogenation of simple ketones to optically active secondary alcohols. After examining numerous chiral diamines, Noyori, Ohkuma, and their co-workers found that the most effective catalyst systems were BINAP-DPEN (DPEN = 1,2-diphenylethylenediamine) (**33**) and BINAP-DAIPEN (DAIPEN = 1,1-di-4-anisyl-2-isopropyl-1,2-ethylenediamine) (**34**) (Fig. 2) [16,17,47]. In particular, the latter catalytic system (**34**), which has sterically more demanding 3,5-xylyl moieties on the phosphorus atoms exhibited exceedingly high catalytic activities and enantioselectivities in the hydrogenation of a wide range of ketone substrates.

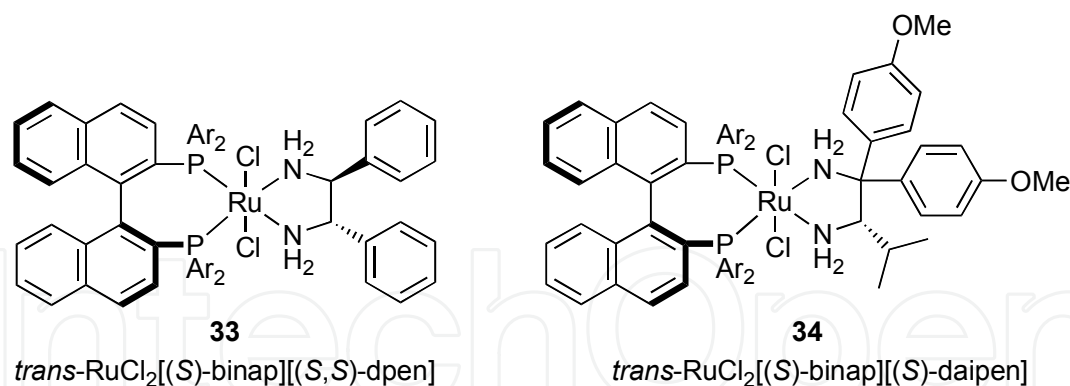


Figure 2. Ru(II) complexes with BINAP and chiral diamine

Representative examples of compounds obtained with these catalysts are shown in Figure 3. Alkyl aryl ketones, unsymmetric diaryl ketones, heteroaromatic ketones, unsymmetric dialkyl ketones, fluoro ketones, amino ketones, and α,β -unsaturated ketones are hydrogenated with very high to almost-perfect enantioselectivities. High chemoselectivity is one of the characteristic features of this hydrogenation method. Therefore, only the carbonyl group is hydrogenated and the other functional groups, such as the carbon–carbon double bond and the nitro group, remain intact.

Recently, chiral ruthenabicyclic complexes have been prepared and their exceedingly high catalytic performance has been demonstrated in the asymmetric hydrogenation of ketones [48]. Scheme 17 shows a typical example of the hydrogenation of acetophenone. The reaction under 50 atm H₂ pressure in the presence of 0.001 mol% catalyst proceeds very rapidly and is completed within 6 min, producing 1-phenylethanol with an essentially quantitative yield and more than 99% ee. The exceedingly high turnover frequency (> 600/s) and almost-perfect enantioselectivity are the best so far reported for ketone hydrogenation. The catalyst has been successfully applied to the asymmetric hydrogenation of several ketones, which are difficult substrates to reduce with high efficiency using existing catalysts. These facts, together with the easy preparation of these catalysts, strongly predict the promising results in the hydrogenation of a wide range of ketone substrates.

4.4. Mechanism of ketone hydrogenation catalyzed by ruthenium complexes of diphosphine and diamine

The mechanism of the Ru(II)-diphosphine/diamine-catalyzed asymmetric hydrogenation of ketones has been extensively studied by Noyori et al. [49]. The catalytic cycle demonstrated by them is shown in Scheme 18 [17,47,49].

The precatalyst **35** is converted via an induction process to the ruthenium hydride species **36**, which is equilibrated with other active species **37**, **38**, and **39**. The 18-electron Ru(II) hydride species **38** reacts with a ketone to produce a secondary alcohol and **39**. Complex **39** returns to **38** by the direct addition of H₂ or via **36** and **37**, and again reacts with the ketone. The marked catalytic activity and enantioselectivity originate from a nonclassical metal–ligand bifunctional mechanism. Therefore, the active species **38** involves the H^{δ-}–Ru^{δ+}–N^{δ-}–H^{δ+} quadrupole, in

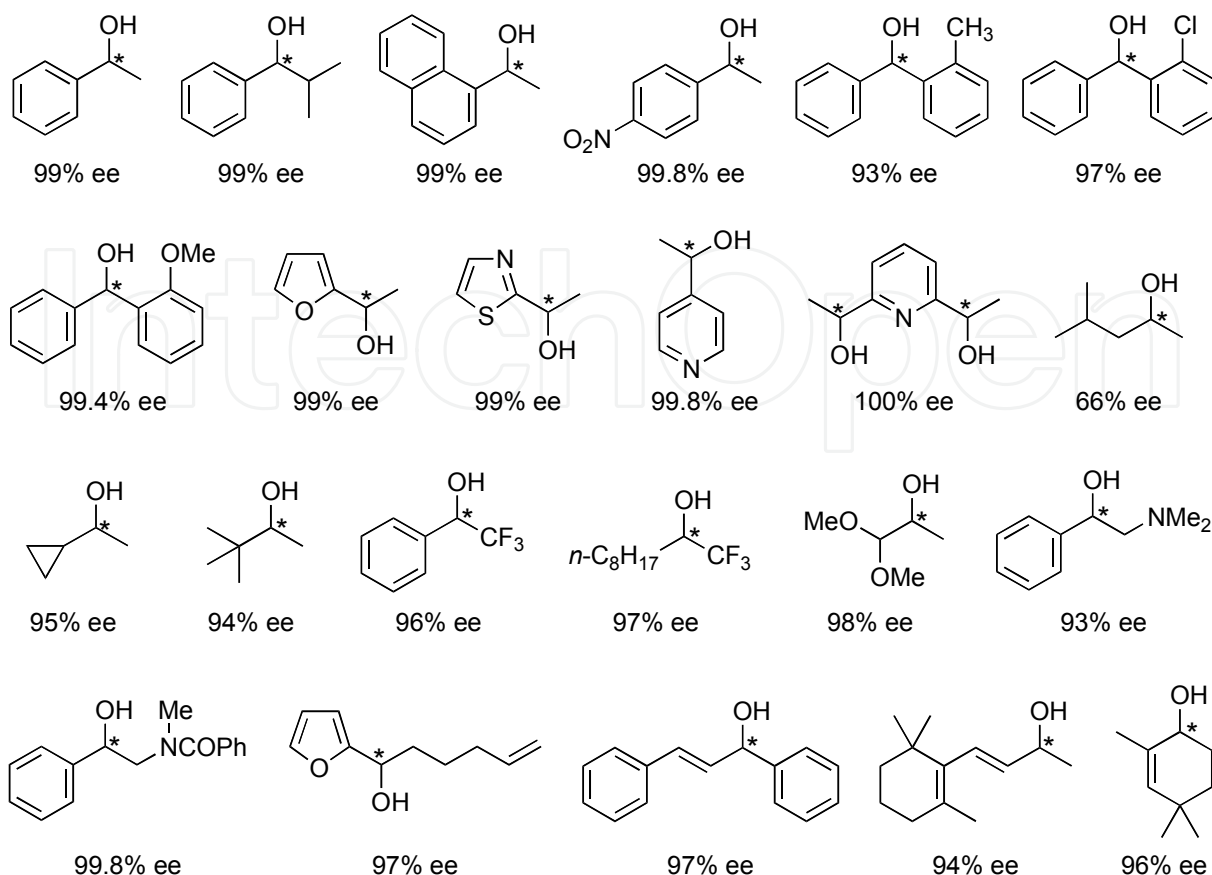
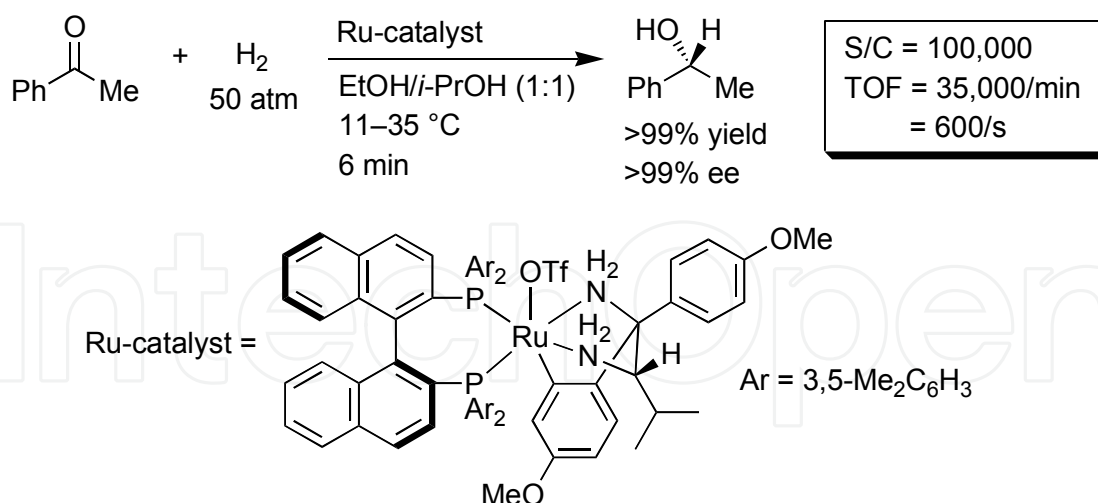
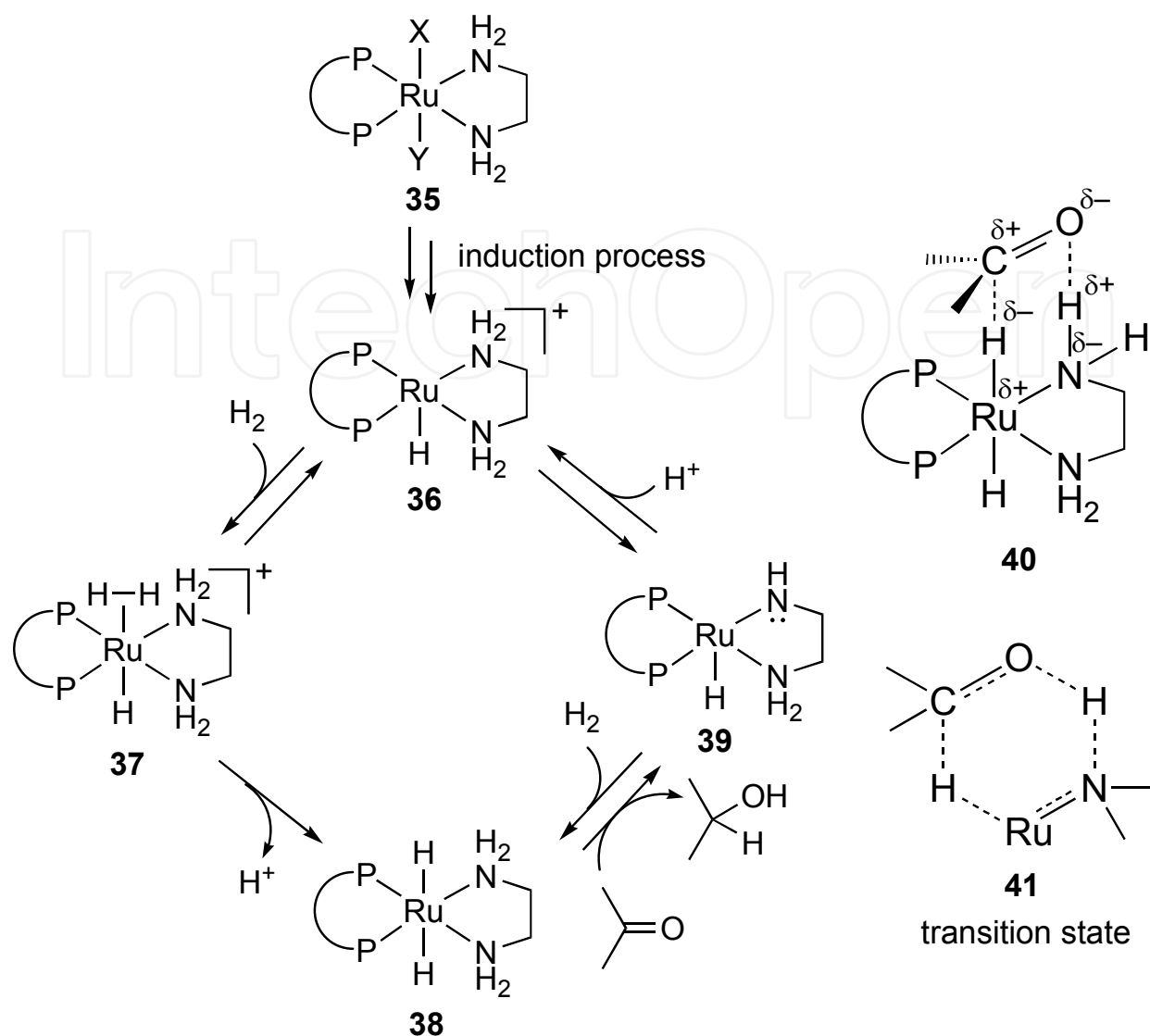


Figure 3. Representative examples of the ruthenium-catalyzed asymmetric hydrogenation of simple ketones



Scheme 17. Asymmetric hydrogenation of acetophenone catalyzed by a ruthenabicyclic complex

which two hydrogen atoms effectively interact with the $\text{C}^{\delta+}=\text{O}^{\delta-}$ dipole of the ketone, as shown in structure 40. The reaction of the carbonyl group proceeds through a pericyclic six-membered transition state (41). It should be noted that the reduction of the carbonyl group occurs in an outer coordination sphere of 18-electron $\text{Ru}(\text{H}_2)(\text{diphosphine})(\text{diamine})$, without any direct interaction with the metal center.



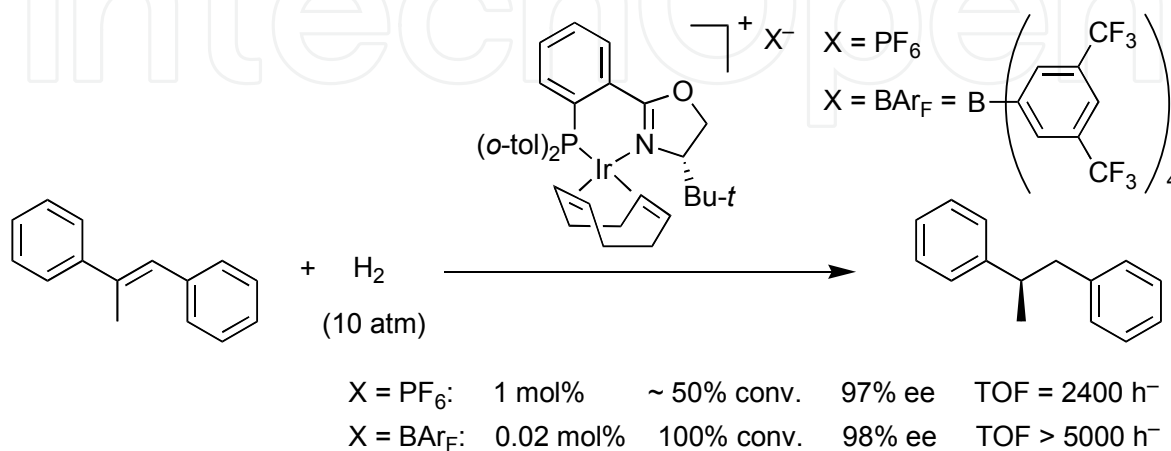
Scheme 18. Mechanism of ketone hydrogenation catalyzed by Ru(II)-diphosphine/diamine catalysts

5. Iridium-catalyzed Asymmetric Hydrogenation

5.1. Hydrogenation of unfunctionalized alkenes

Chiral rhodium and ruthenium catalysts are frequently used as the most versatile catalysts for the asymmetric hydrogenation of alkenes. However, the range of the substrates used is limited to alkenes with a coordinating functional group adjacent to the C=C double bond, except for several examples. The high enantioselectivities obtained by using rhodium or ruthenium catalysts are responsible for the coordination of the functional group to the metal center and the alkene π -bonding. In contrast, alkenes lacking coordinating groups have long been notoriously difficult to hydrogenate with high enantioselectivity. This difficulty was overcome by Pfaltz et al. in 1998 by using iridium complexes bearing chiral P,N-ligands [50]. Thus, they used Ir-PHOX complexes, which seemed to be the chiral analogues of Crabtree's catalyst $[\text{Ir}(\text{cod})(\text{PCy}_3)(\text{pyridine})]^+[\text{PF}_6]^-$ (Cy = cyclohexyl) [51,52]. Their initial study using

$[\text{Ir}(\text{phox})(\text{cod})][\text{PF}_6]^-$ yielded high enantioselectivities of up to 98% ee in the hydrogenation of model substrates, but the turnover numbers were not large. The low activity of the catalysts was attributed to their deactivation during the hydrogenation reaction, and further experiments led them to the discovery of dramatic counterion effects. The replacement of the PF_6^- anion with a bulky, apolar, and weakly coordinating anion BARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) (BARF^-) markedly improved the catalytic activity, allowing the use of catalyst loadings as low as 0.02 mol% (Scheme 19) [50,53].



Scheme 19. Anion effect on the hydrogenation of (*E*)- α -methylstilbene

These successful results have significantly advanced this area of research with the development of numerous chiral P,N-ligands [13,54–58]. Representatives of the chiral iridium complexes so far reported are shown in Fig. 4. It should be noted that iridium complex **54**, with an *N*-heterocyclic carbene oxazoline ligand, is also effective in this kind of asymmetric hydrogenation [59].

Figure 5 shows some representative results for the asymmetric hydrogenation of unfunctionalized alkenes. Many rationally designed ligands display very high enantioselectivity (usually 99% ee) in the hydrogenation of a standard model substrate, (*E*)- α -methylstilbene. Purely alkyl-substituted alkenes are also reduced with high enantioselectivity. In the hydrogenation of 1,1-diarylethenes, two different aryl groups are effectively distinguished to produce the corresponding alkanes with good to excellent enantioselectivity. Notably, even tetrasubstituted alkenes are subject to hydrogenation, although the enantioselectivity depends largely on the substrate and the ligand structure.

Pfaltz et al. have demonstrated the practical utility of this methodology in the hydrogenation of γ -tocotrienyl acetate **55** to produce γ -tocopheryl acetate **56**, a precursor of γ -tocopherol, which is a component of vitamin E. The two prochiral (*E*)-configured C=C bonds of **55** are enantioselectively reduced under the conditions shown in Scheme 20 to generate the (*R,R,R*)-configuration product **56** with 98% purity [60]. This method provides a highly effective stereoselective route to this class of compounds and has great advantages over previous strategies, which used a stepwise approach to introduce the stereogenic centers into the side chain.

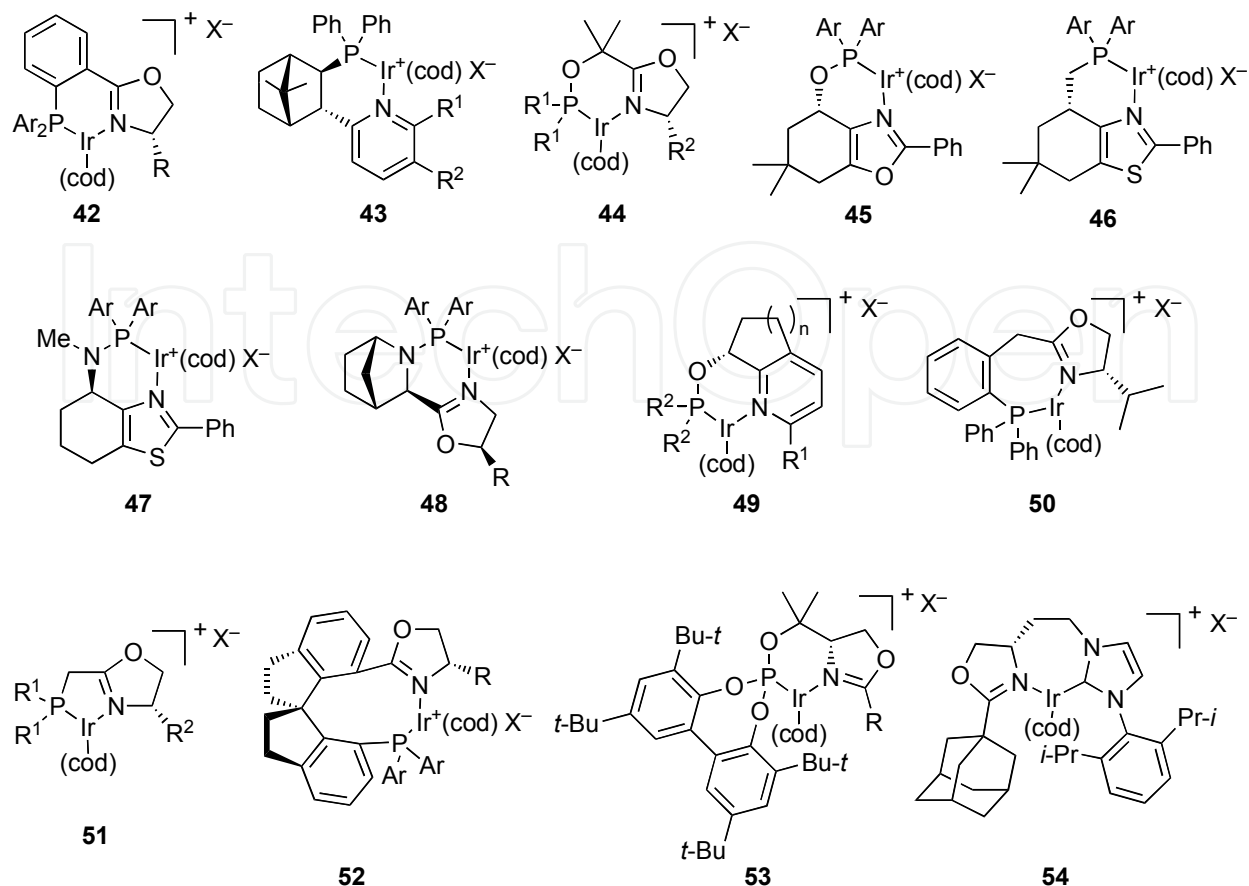


Figure 4. Representative chiral iridium complexes for asymmetric hydrogenation, $X = \text{BARf}$

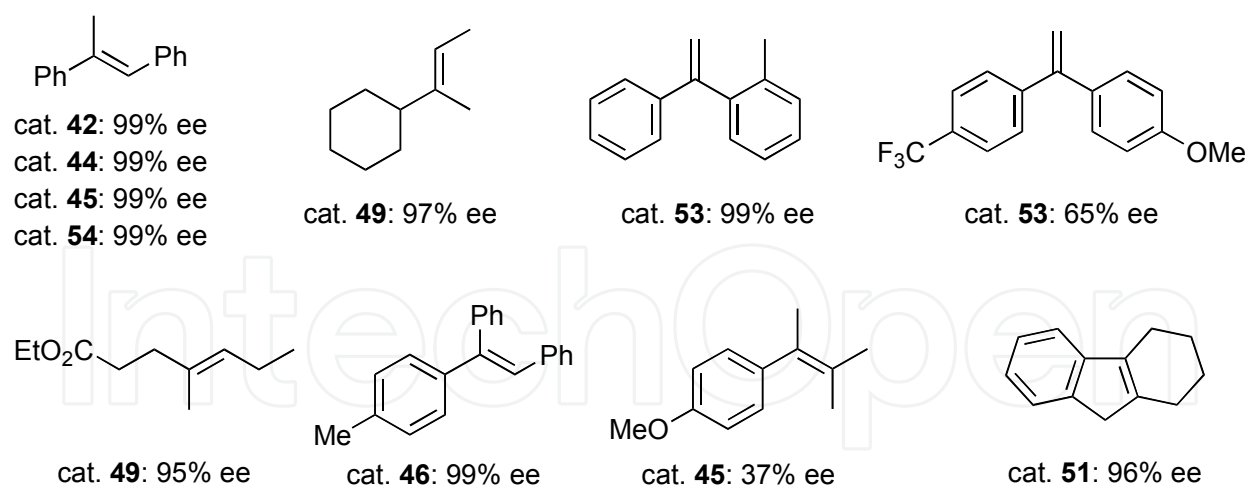
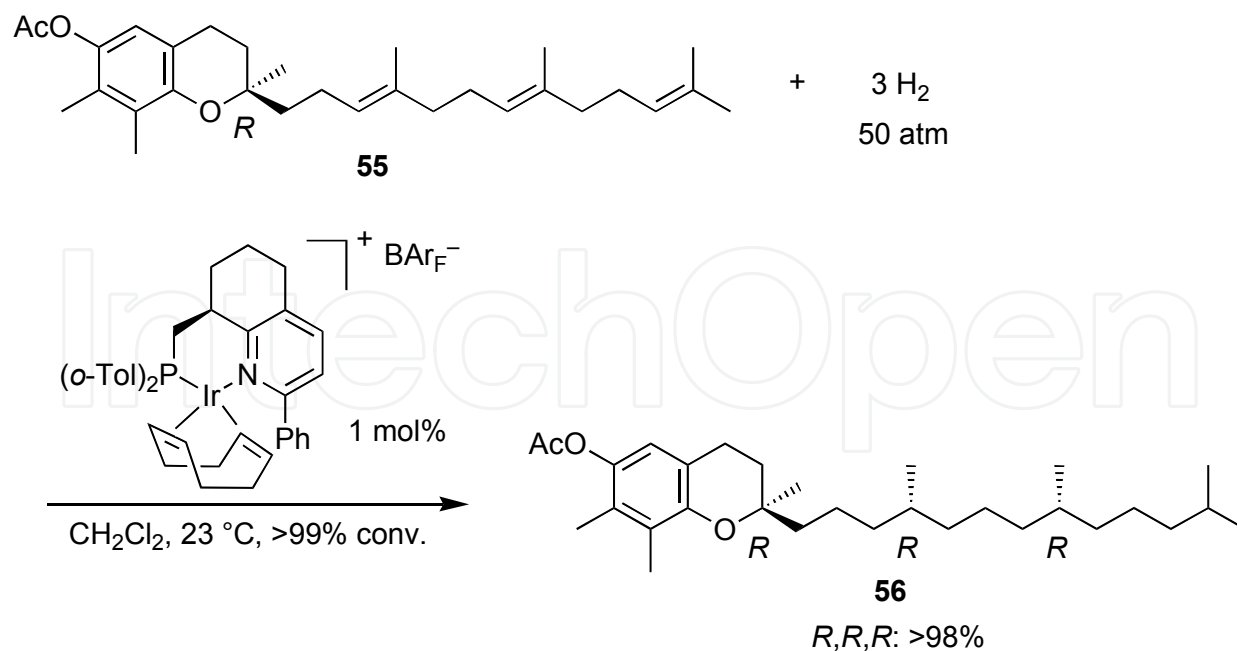


Figure 5. Representative examples of Ir-catalyzed largely unfunctionalized alkenes

5.2. Hydrogenation of functionalized alkenes

Recent studies of iridium-catalyzed asymmetric hydrogenation have significantly broadened its substrate spectrum. Therefore, not only unfunctionalized alkenes but also alkenes with functional groups connected to their $\text{C}=\text{C}$ double bonds have been hydrogenated with high to excellent enantioselectivity. Figure 6 shows examples of the



Scheme 20. Asymmetric hydrogenation of γ -tocotrienyl acetate

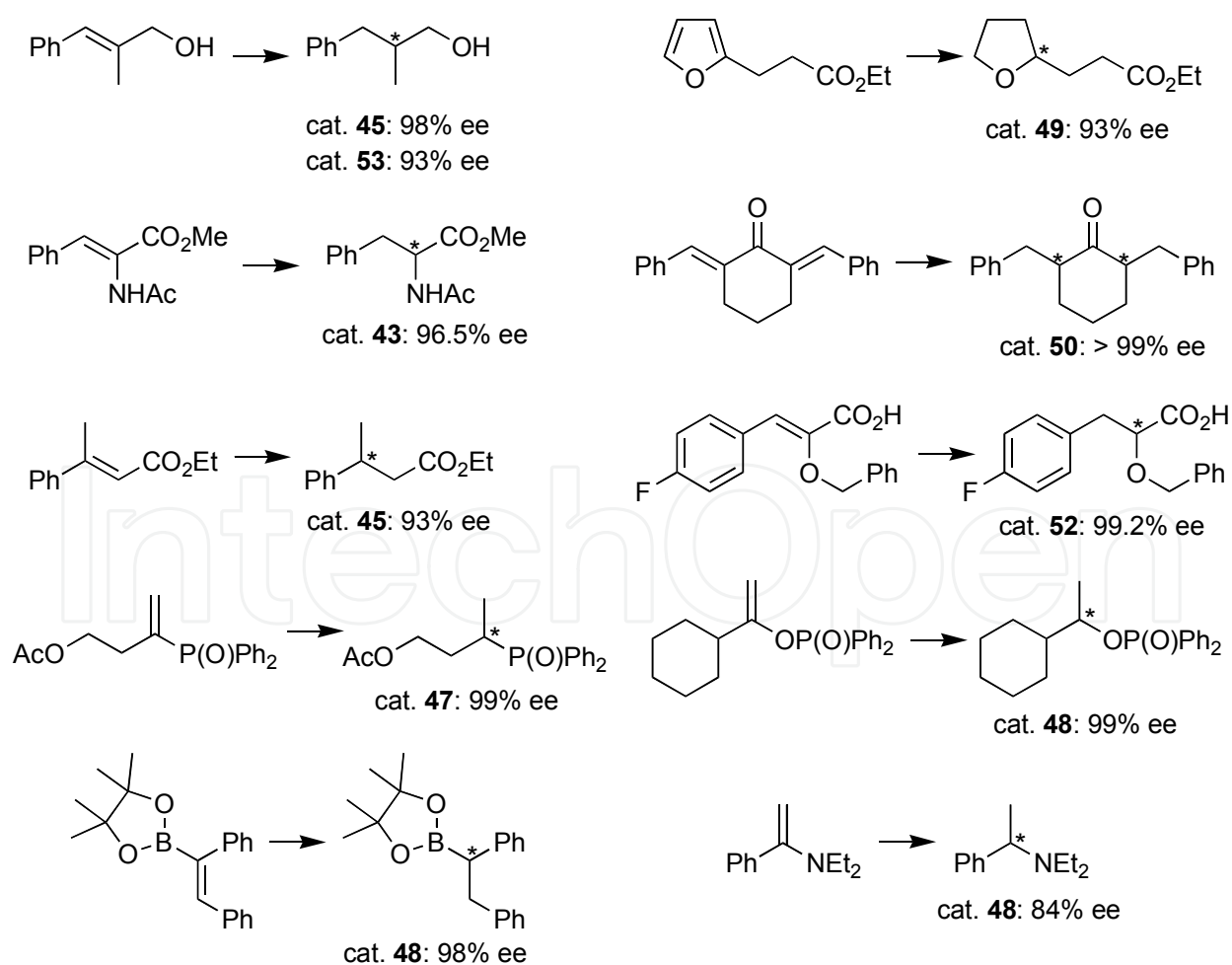
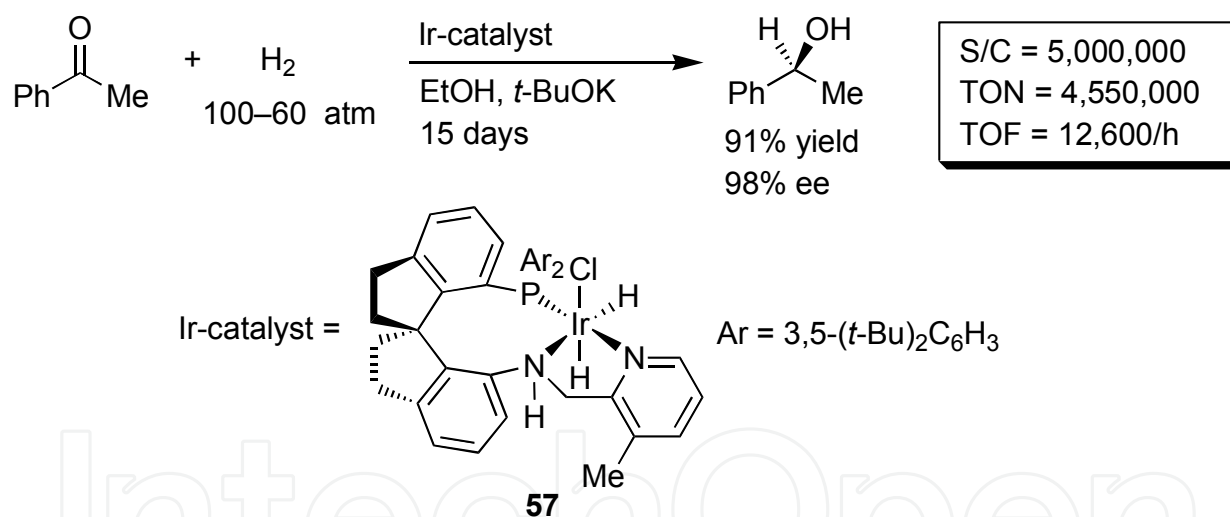


Figure 6. Representative examples of Ir-catalyzed asymmetric hydrogenation of functionalized alkenes

hydrogenation of allyl alcohols [61], furan rings [62], α -dehydroamino acid derivatives [63], α,β -unsaturated ketones [64], α,β -unsaturated carboxylic acid esters [61], α -alkoxy α,β -unsaturated acids [65], vinylphosphine oxides [66], enol phosphinates [67], vinyl boronates [68], and enamines [69,70]. Notably, substituted furans, vinyl boronates, and even enamines are hydrogenated with full conversion in high to excellent enantioselectivity.

5.3. Hydrogenation of simple ketones

It is well known that chiral iridium catalysts are applicable to the enantioselective hydrogenation of imines [71]. Recently, it has been shown that ketones, including α,β -unsaturated ketones, are also efficiently hydrogenated when iridium catalysts are used with P,N-ligands [72,73]. In contrast to the iridium complexes used with bidentate P,N-ligands, which tend to lose their activity under hydrogenation conditions, the complexes used with tridentate complexes resist deactivation and eventually exhibit high catalytic activity [73]. A typical example obtained by the use of catalyst **57** is shown in Scheme 20. The exceedingly high turnover number (TON), turnover frequency (TOF), and excellent enantioselectivity are comparable to those of chiral ruthenium complexes and indicate their great potential utility in the production of chiral secondary alcohols from ketones.



Scheme 21. Ir-catalyzed asymmetric hydrogenation of acetophenone

6. Conclusion

Since the discovery of homogeneous asymmetric hydrogenation, this area has progressed significantly over the past four decades. A variety of alkenes, including unfunctionalized alkenes, are hydrogenated enantioselectively using transition metal complexes with chiral ligands. Rhodium, ruthenium, and iridium are most frequently used as the center metals of these complexes, and the methods involving these complexes have become common processes in the efficient preparation of the chiral building blocks of natural products, pharmaceuticals, agrochemicals, and flavors.

Chiral complexes of titanium, zirconium, and lanthanides exhibit unique asymmetric hydrogenation properties, although at present, their practical use is limited to some special cases. Some late transition metals, such as palladium, cobalt, iron, and copper, are known to have potential utility in homogeneous asymmetric hydrogenation. The use of inexpensive metal complexes is clearly attractive for the manufacture of useful optically active compounds by asymmetric hydrogenation.

Asymmetric hydrogenation is a perfect atom-economic reaction, is usually carried out under mild conditions, and proceeds with an essentially quantitative yield. Undoubtedly, it is one of the most environmentally benign reactions and hence further investigations, using a variety of chiral metal catalysts, should allow the development of much more efficient and convenient methodologies for the preparation of optically active compounds.

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