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Rhodium(I)-Catalyzed Asymmetric Hydrogenation

Tsuneo Imamoto

Chiba University, Faculty of Science, Department of Chemistry, Yayoi-cho, Inage-ku, 263-8522 Chiba, Japan

1.1 Introduction

The asymmetric hydrogenation of prochiral unsaturated compounds, such as alkenes, ketones, and imines, is one of the most straightforward methods for the synthesis of optically active compounds. This method using molecular hydrogen and small amounts of chiral transition-metal complexes is operationally simple, environmentally friendly, and frequently employed in both academia and industry.

During the last five decades, the homogeneous asymmetric hydrogenation by the use of rhodium, ruthenium, iridium, and other transition-metal complexes has remarkably progressed with the developments of thousands of chiral ligands. The catalytic performance of asymmetric hydrogenation is largely affected by the used transition metal, and rhodium-catalyzed hydrogenation has constituted a unique and large research area to provide useful technologies for the production of optically active pharmaceuticals, agrochemicals, and fine chemicals.

Previously, Chi, Tang, and Zhang described an excellent review of Rh-catalyzed asymmetric hydrogenation covering the literatures published until 2003 [1]. This review describes the subsequent advancement of this area, citing the literatures published since 2004.

1.2 Chiral Phosphorus Ligands

Chiral phosphorus ligands play pivotal roles in Rh-catalyzed asymmetric hydrogenation as well as in many other transition-metal-catalyzed asymmetric transformations [2]. Although numerous chiral phosphorus ligands have been designed and synthesized over the past half a century and many of them have been used in both academia and industry, the work to develop more efficient ligands is still actively underway. This section summarizes the chiral phosphorus ligands used for Rh-catalyzed asymmetric hydrogenation that have been reported since 2004. They are largely classified into several types according to their structural variations, electronic properties, and characteristic activities toward prochiral unsaturated substrates.

Rhodium Catalysis in Organic Synthesis: Methods and Reactions, First Edition. Edited by Ken Tanaka.

1.2.1 P-Chirogenic Bisphosphine Ligands

1.2.1.1 Electron-Rich C_2 Symmetric Ligands

BisP*- and MiniPHOS-Based Ligands BisP* and MiniPHOS are typical P-chirogenic phosphine ligands, possessing a bulky alkyl group and a methyl group at the phosphorus atoms (Figure 1.1). These ligands exhibit excellent enantioselectivities in some representative catalytic asymmetric reactions, but because of their high air sensitivity, they are not widely used, except in the mechanistic study of Rh-catalyzed asymmetric hydrogenation [3]. Further studies to overcome the drawbacks of these ligands, QuinoxP* [4, 5], Ad-QuinoxP* [6], **L1** [7], AlkynylP* [8], BenzP* [5, 9], DioxyBenzP* [5], TMB-QuinoxP* [10], and BipheP* [11] have been designed and synthesized (Figure 1.1). Among these ligands, QuinoxP* and BenzP* are air-stable crystalline solids and are frequently used not only in Rh-catalyzed asymmetric hydrogenation but also in many other catalytic asymmetric transformations [12].

Bisphosphacycle Ligands In 2002, Tang, Zhang, and coworkers reported the synthesis of a P-chirogenic bisphospholane ligand, TangPhos, and its excellent enantioinduction ability and high catalytic activity in Rh-catalyzed asymmetric hydrogenation [13, 14]. The superior catalytic performance of the TangPhos-Rh complex is responsible for its very rigid molecular structure consisting of three fused five-membered rings and the asymmetric environment arising from the *tert*-butyl groups that effectively shield the two diagonal quadrants. The great success of TangPhos ligand has prompted the synthesis of analogous bisphosphacycle ligands, all of which possess *tert*-butyl groups at the P-chirogenic phosphorus atoms (Figure 1.2). A seven-membered bisphosphacycle ligand, Binapine, exhibits high enantioinduction ability in the hydrogenation of β-dehydroamino acids and 2-pyridyl-substituted ketones [15, 16]. DiSquareP* and **L2**, which contain highly strained four-membered phosphacycles, have their potential utility in Rh-catalyzed asymmetric hydrogenation [17, 18]. In 2005, Liu and Zhang reported DuanPhos ligand composed of two connected benzophospholanes [19]. Both enantiomers of this ligand are commercially available and widely used

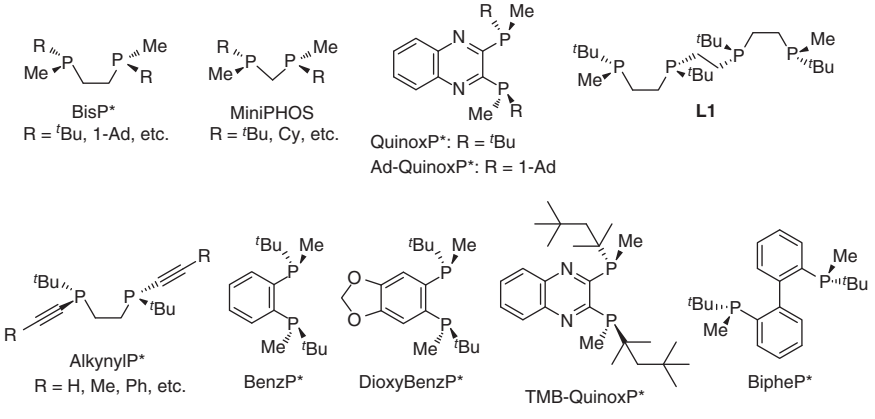


Figure 1.1 Electron-rich P-chirogenic phosphine ligands.

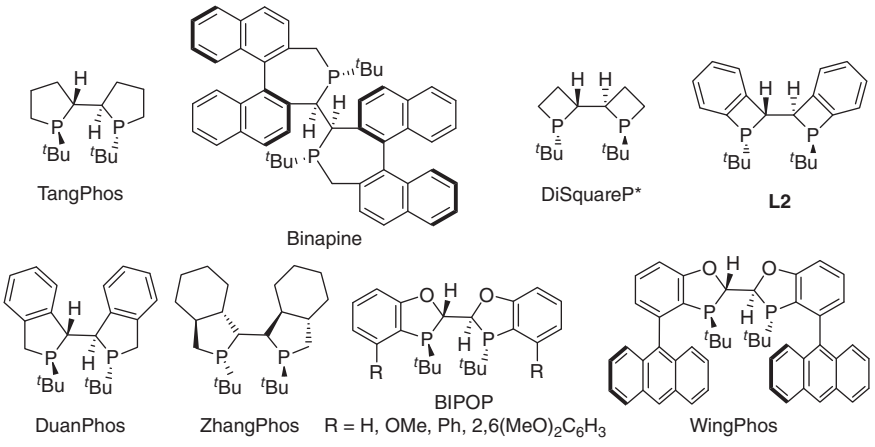


Figure 1.2 C_2 symmetric bisphosphacycle ligands possessing *tert*-butyl groups at the P-chirogenic centers.

in Rh-catalyzed asymmetric hydrogenation of various prochiral substrates and often employed in the industrial production of chiral ingredients [20]. Zhang-Phos ligand is more rigid and electron-rich than TangPhos and DuanPhos, and it shows exceedingly high enantioselectivities in the hydrogenation of not only standard probing substrates but also *N*-aryl *β*-enamino esters and *α*-aryl imino esters [21]. Tang and coworkers have developed P-chirogenic bisoxaphospholane ligands BIPOP and WingPhos [22, 23]. These ligands provide unique catalytic performance and have been successfully employed in the hydrogenation that difficultly proceeds with the use of other predecessor ligands [24].

1.2.1.2 Three-Hindered Quadrant Ligands

In 2004, Hoge and coworkers reported a novel C_1 symmetric bisphosphine ligand, di-*tert*-butylphosphino-*tert*-butyl(methyl)phosphinomethane named Trichickenfootphos (TCFP) [25]. This ligand forms a four-membered Rh complex, in which the three *tert*-butyl groups effectively hinder three quadrants, and its superior catalytic performance was demonstrated by the highly efficient synthesis of a pregabalin precursor [25a]. The three-hindered quadrant motif, apart from the traditional C_2 symmetric design concept, has prompted the synthesis of analogous ligands (**L3** [26], MaxPHOS [27], **L4** [28], MeO-POP [29], 3H-BenzP* [30a], 3H-QuinoxP* [30]) (Figure 1.3). All of these ligands have proved their high catalytic activities in Rh-catalyzed asymmetric hydrogenations of various substrates.

1.2.1.3 Ligands Bearing Two or Three Aryl Groups at the Phosphorus Atom

DIPAMP synthesized by Knowles and coworkers is a landmark chiral phosphine ligand in the history of Rh-catalyzed asymmetric hydrogenation. Nevertheless, the ligand has not been widely used because of its high but somewhat insufficient enantioselectivities (up to 96% in the hydrogenation of α-dehydroamino acid derivatives) and the inconvenient synthesis with traditional methods. New

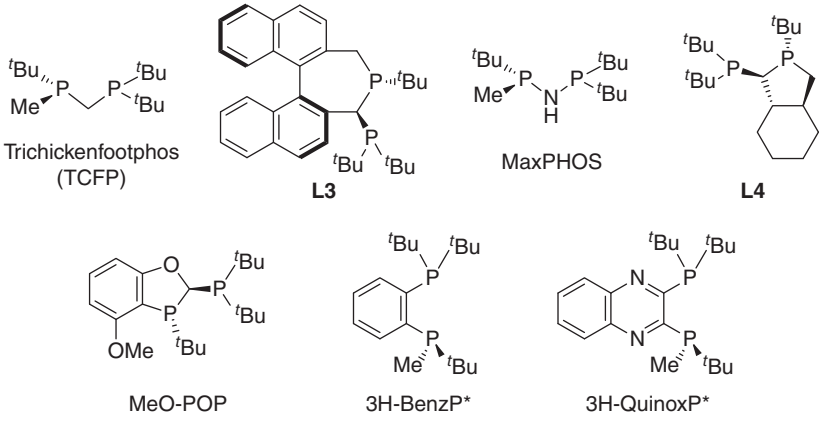


Figure 1.3 P-Chirogenic three-hindered quadrant ligands.

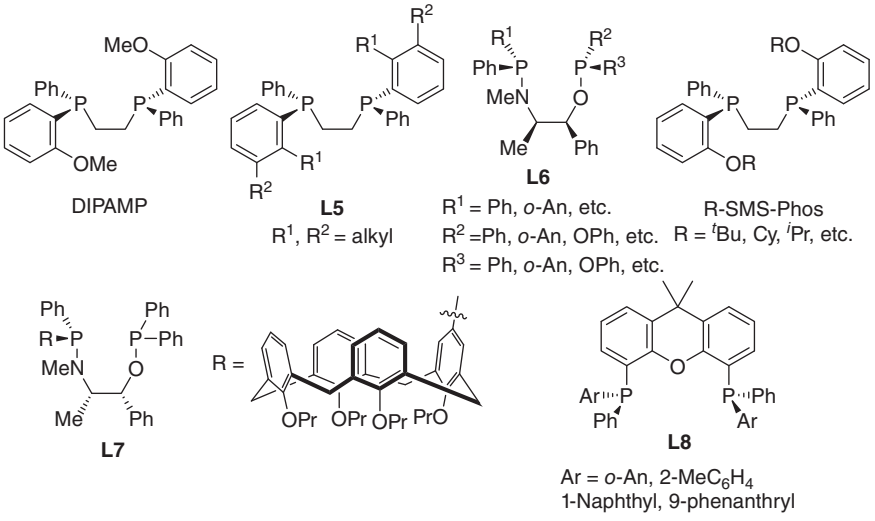


Figure 1.4 P-Chirogenic ligands bearing two or three aryl groups at the phosphorus atom.

synthetic methodology using phosphine-boranes as the intermediates has enabled the synthesis of analogous ligands (**L5** [31], **L6** [32], R-SMS-Phos [33], **L7** [34], **L8** [35]) (Figure 1.4). Among these ligands, **L5** and R-SMS-Phos provide superior enantioselectivities up to >99% in comparison with DIPAMP. Ligands **L7** and **L8** exhibit unique catalytic performance, arising from the supramolecular component and the large bite angle of the Rh complex.

1.2.2 DuPhos, BPE, and Analogous Ligands

DuPhos and BPE possessing chiral phospholanyl cycles are versatile ligands not only for Rh-catalyzed asymmetric hydrogenation but also for many other transition-metal-catalyzed reactions. The great success of DuPhos and BPE

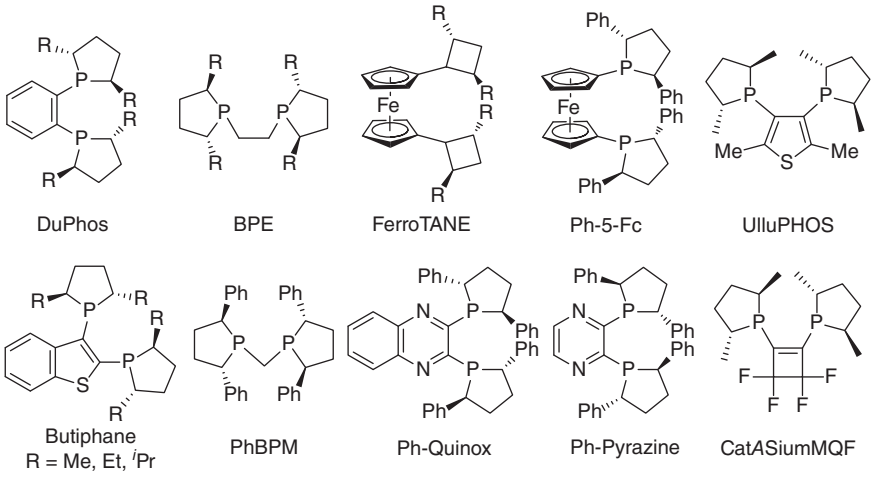


Figure 1.5 DuPhos, BPE, and analogous ligands.

provided the opportunity to synthesize ferrocene-based ligands, FerroTANE and Ph-5-Fc, with the chiral phosphacycle motif. Furthermore, several analogous ligands (UlluPHOS [36], Butiphane [37], PhBPM [38], Ph-Quinox [39], Ph-Pyrazine [39], and Cat*A*SiumMQF [40]) have been reported since 2004 (Figure 1.5). Among all of these bisphosphacycle ligands, DuPhos is still the most frequently used in Rh-catalyzed asymmetric hydrogenation.

1.2.3 Ferrocene-Based Bisphosphine Ligands

In 1974, Hayashi and coworkers synthesized a chiral ferrocene-based bisphosphine ligand, BPPFA, and demonstrated its high catalytic performance in Rh-catalyzed asymmetric hydrogenation. Since Hayashi's pioneering work, numerous ferrocene-based chiral phosphorus ligands have been synthesized and applied in catalytic asymmetric reactions. Figure 1.6 shows ferrocene-based phosphorus ligands, most of which have been reported since 2004.

A landmark discovery in this area is Josiphos ligand, developed by Togni and coworkers in 1994. The ligand has been widely used not only in Rh-catalyzed asymmetric hydrogenation but also in many other catalytic asymmetric reactions [41]. Another notable ligand is a trans-chelating ligand, TRAP, synthesized by Kuwano et al. in 1991. This ligand with its unique coordination style provides characteristic enantioselectivity and activity in various asymmetric transformations and is particularly useful for Rh-catalyzed hydrogenation of indole derivatives [42]. BoPhoz ligand developed by Boaz is a phosphine–aminophosphine ligand. By selecting the substituents on the phosphorus atoms, the BoPhoz-Rh catalyst provides excellent enantioselectivity and reactivity in the hydrogenation of various prochiral substrates [43]. TaniaPhos [44], Walphos [45], MandyPhos [44b, 45a] are commercially available as the ligand kits with the substituent variations on the phosphorus atoms. It is possible to control the enantioselectivity and activity by ligand of choice according to prochiral substrates. PingFer [46], TriFer [47], and BoPhoz* [48] possess P-chirogenic

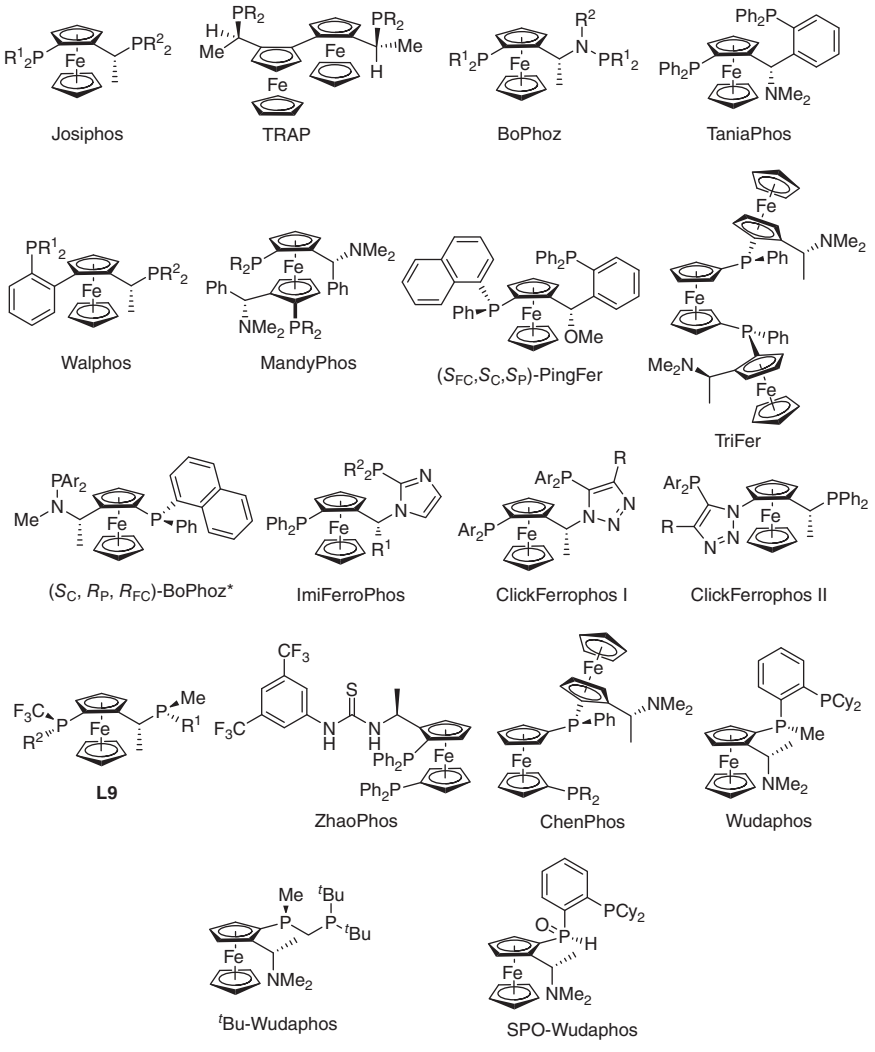


Figure 1.6 Ferrocene-based chiral phosphine ligands.

center in addition to the planar chiral ferrocene backbone. ImiFerroPhos [49], ClickFerrophos I [50], ClickFerrophos II [51], **L9** [52], ZhaoPhos [53], ChenPhos [54], Wudaphos [55], ^{t}Bu-Wudaphos [56], and SPO-Wudaphos [57] have been synthesized recently and proved their characteristic enantioinduction abilities and employed in the asymmetric hydrogenations that had long been difficultly achieved. For example, ZhaoPhos exhibits high enantioselectivities in the hydrogenation of nitroalkenes, substituted quinolines and isoquinolines, and imines, by means of the hydrogen bonding interaction of the thiourea component with the substrate functional groups. ChenPhos, Wudaphos, ^{t}Bu-Wudaphos, and SPO-Wudaphos, all of which contain a dimethylamino group in the ligand molecules, promote the hydrogenation of the substrates bearing acidic functionalities via non-covalent ion pair interaction.

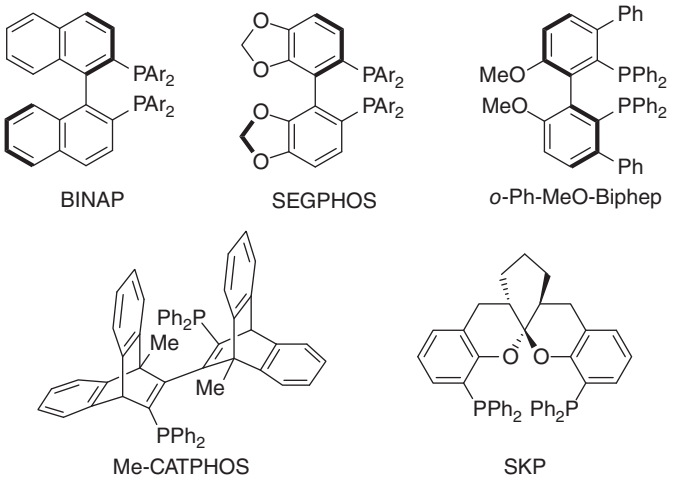


Figure 1.7 C_2 symmetric bisphosphine ligands with axial chirality.

1.2.4 C_2 Symmetric Triaryl- or Diarylphosphine Ligands with Axial Chirality

The ligands of this class, particularly BINAP and SEGPHOS, are frequently used as benchmark ligands in Ru-catalyzed asymmetric hydrogenation and many other catalytic asymmetric reactions [58]. New ligands, such as *o*-Ph-MeO-BIPHEP [59], Me-CATAPHOS [60], and SKP [61], have been added in this class since 2004 (Figure 1.7), and each ligand has shown characteristic activity in Rh-catalyzed asymmetric hydrogenation. For example, SKP-Rh complex bearing a large bite angle is effective for the hydrogenation of β-branched enol esters and can be used for the synthesis of optically active primary alcohols with excellent enantiomeric excesses (ee's) [61b].

1.2.5 Phosphine–Phosphite and Phosphine–Phosphoramide Ligands

Phosphine–phosphite and phosphine–phosphoramide ligands are often used in Rh-catalyzed asymmetric hydrogenation [62]. As shown in Figure 1.8, new ligands, such as *o*-BINAPHOS [63], **L10** [64], Me-AnilaPhos [65], PEAPhos [66], **L11** [67], THNAPhos [68], **L12** [69], **L13** [70], **L14** [71], HY-Phos [68b], **L15** [72], **L16** [72], Quinaphos [73], **L17** [74], and **L18** [75], have been added in this class. Most of these ligands possess rigid chiral backbones such as binaphthyl, biphenyl, and TADDOL moieties and provide high to excellent enantioselectivities in the Rh-catalyzed hydrogenation of α- and β-dehydroamino acid derivatives, enamides, and enol esters.

1.2.6 Other Bidentate Ligands

Figure 1.9 shows other bidentate phosphorus ligands bearing two aryl substituents on the phosphorus atoms. Bisaminophosphine ligands, **L19** [76]

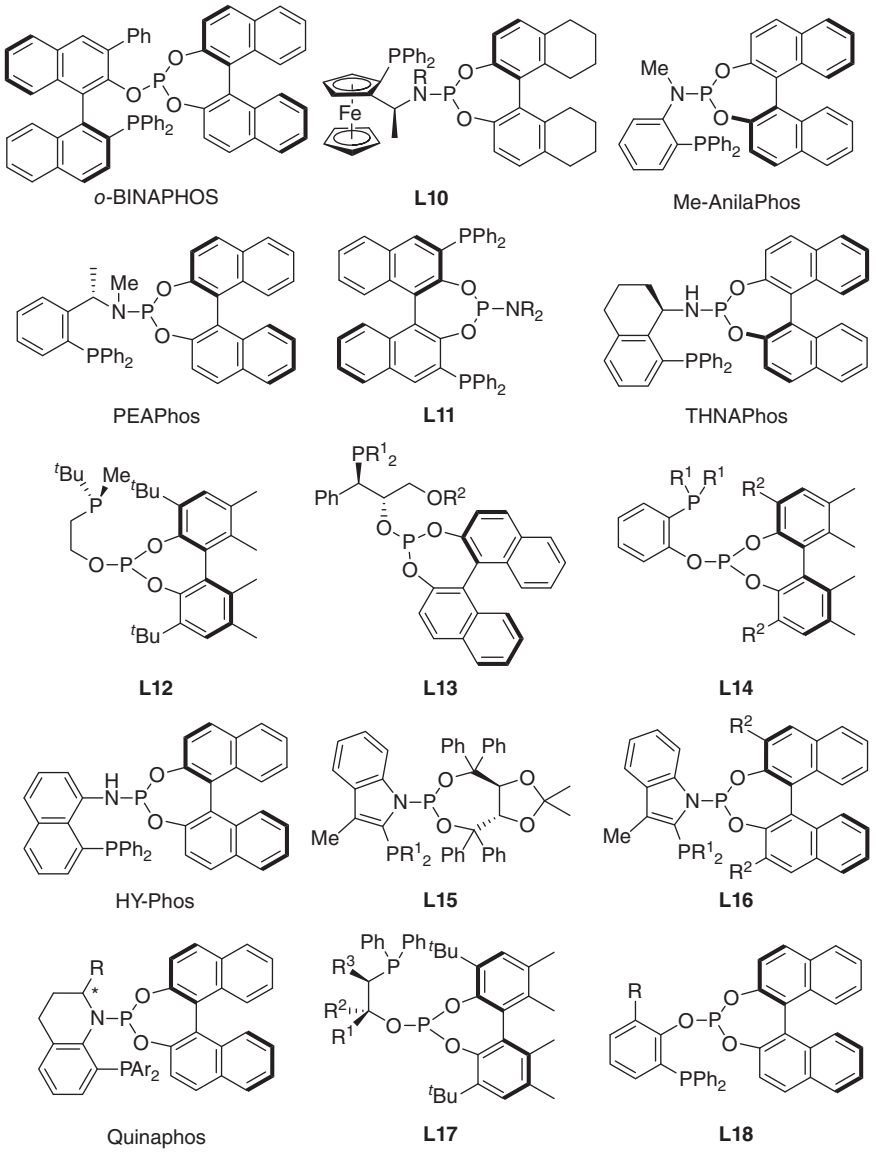


Figure 1.8 Chiral phosphine–phosphite and phosphine–phosphoramide ligands.

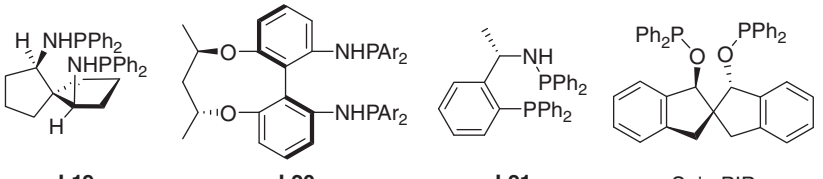


Figure 1.9 Chiral bidentate aminophosphine and phosphinite ligands.

and **L20** [77], exhibit high enantioselectivities of up to 99.9% in the hydrogenation of α-dehydroamino acid derivatives and dimethyl itaconate. A phosphine–aminophosphine ligand, **L21** [43e], has been successfully utilized for the hydrogenation of α,β-unsaturated phosphonates with benzoyloxy or acylamino group at the α-position. A bisphosphinite ligand, SpiroBIP [78], is less reactive and of somewhat lower enantioinduction ability in the hydrogenation of standard α-dehydroamino acid derivatives in comparison with the bisaminophosphine ligands **L19** and **L20**.

1.2.7 Monodentate Phosphorus Ligands

Monodentate phosphorus ligands are also useful for Rh-catalyzed asymmetric hydrogenation. Typically, the MonoPhos family with wide substituent diversity is often used for the ligand optimization in Rh-catalyzed asymmetric hydrogenation by utilizing high-throughput screening methods [79]. In addition to MonoPhos, SIPHOS [80], **L22** [81], DpenPhos [82], FAPhos [83], PhthalaPhos [84], **L23** [82b], and **L24** [85] have been reported since 2004 (Figure 1.10). Each new ligand has shown unique catalytic performance in Rh-catalyzed asymmetric hydrogenation, and in particular, DpenPhos and secondary phosphine oxide-type ligands **L23** and **L24** demonstrate prominent enantioselectivity and activity toward α,β-unsaturated phosphonates and β,β-diarylacrylic acids.

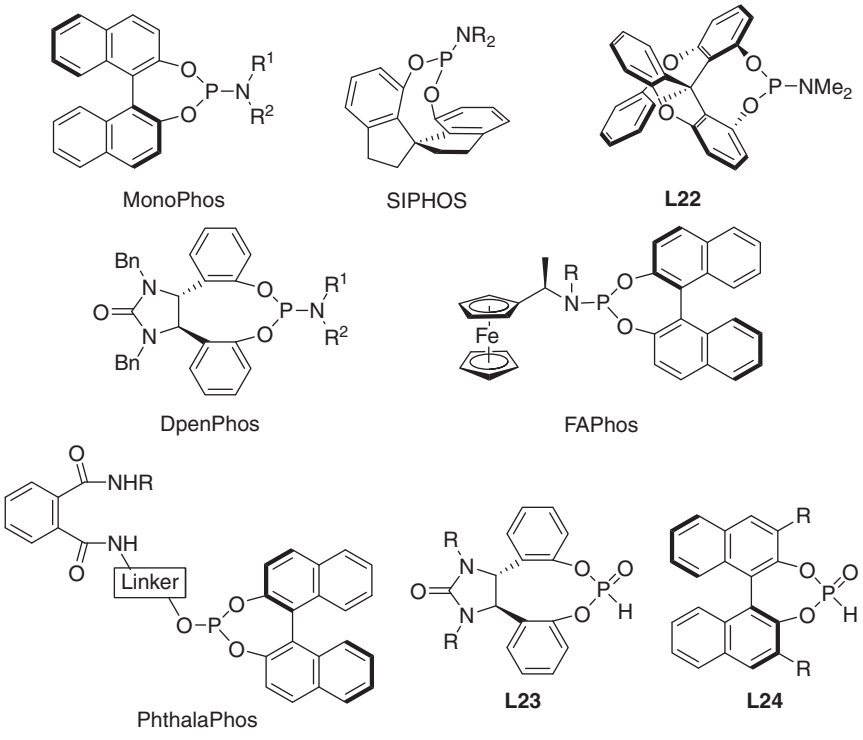


Figure 1.10 Chiral monodentate phosphorus ligands.

1.3 Application of Chiral Phosphorus Ligands in Rhodium-Catalyzed Asymmetric Hydrogenation

1.3.1 Hydrogenation of Alkenes

1.3.1.1 Hydrogenation of Enamides

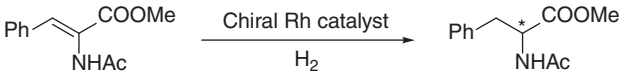
Hydrogenation of α-Dehydroamino Acid Derivatives α-Dehydroamino acid derivatives are most frequently used prochiral substrates in Rh-catalyzed asymmetric hydrogenation. Among many of this class of compounds, methyl (*Z*)-α-acetamidocinnamate (MAC) has been employed as a typical probing substrate for the evaluation of the enantioselectivity and catalytic efficiency of newly synthesized chiral phosphorus ligands. Table 1.1 shows the asymmetric hydrogenation results obtained by the use of the ligands that have been reported since 2004. Most of the ligands exhibit exceedingly high enantioselectivities, and some ligands such as DiSquareP*, **L4**, BenzP*, and TMB-QuinoxP* have proved high efficiency (S/C ≥ 10 000), while some of other ligands, especially electron-rich ligands such as TCFP, DuanPhos, and ZhangPhos, may also show similarly high TON.

During the past 14 years, many chiral phosphorus ligands including previously reported ligands such as DuPhos, Josiphos, and FerroTANE have been employed in the asymmetric hydrogenation of various α-dehydroamino acid derivatives. Great efforts have been made to achieve efficient hydrogenation of tetrasubstituted or sterically congested trisubstituted alkene substrates. Some examples are shown in Scheme 1.1 [86], Scheme 1.2 [5, 33f, 87], Scheme 1.3 [88], Scheme 1.4 [89], and Scheme 1.5 [14h]. In addition to these examples, numerous natural and unnatural α-amino acid derivatives including the pharmaceutically important chiral ingredients have been prepared by using DuPhos [90–96], MandyPhos [97], TCFP [98], DuanPhos [99], TangPhos [100], BoPhoz [43j], FerroTANE [96], **L13** [70c], QuinoxP* [5], and BenzP* [5]. Furthermore, many chiral drugs containing α-amino acid components have been produced in industry via Rh-catalyzed asymmetric hydrogenation [101–104].

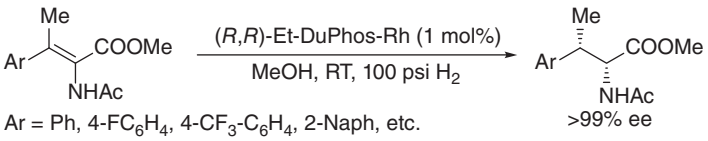
Hydrogenation of β-Dehydroamino Acid Derivatives Chiral β-amino acids and their derivatives are found in natural products as important components, and some of them are used as chiral drugs. Rhodium-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives is a convenient and straightforward method for the synthesis of this class of compounds [105]. The enantioselectivity and catalytic efficiency depend largely on the used chiral ligands and substrate structures. Table 1.2 lists the hydrogenation results of some representative β-dehydroamino acid esters.

In general, the use of electron-rich bisphosphines enables the hydrogenation of both *E*- and *Z*-isomers under mild conditions to provide the same absolute configuration products with high to excellent ee's, while *Z*-isomers give rise to somewhat lower ee's of the products than *E*-isomers. Interestingly, the use of phosphine–phosphoramide ligand **L10** (R = H) for *E*- and *Z*-isomers affords the corresponding products with opposite configuration. In this case, the N—H hydrogen atom on the ligand plays a crucial role in the stereoselection of the hydrogenation.

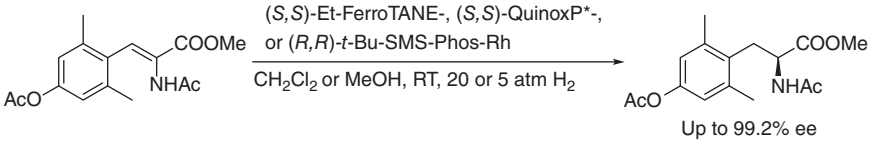
Table 1.1 Asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate (MAC).



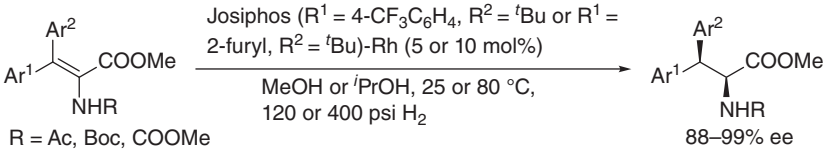
Ligand	S/C	Reaction conditions	% ee (configuration)	References
(*R*)-TCFP	100	MeOH, RT, 50 psi	>99 (*R*)	[5]
(*R*)-**L22**	100	CH_2Cl_2, RT, 25 psi	98.4 (*S*)	[81]
(*S,R*)-*o*-BINAPHOS	100	THF, RT, 15 psi	>99 (*S*)	[63]
(*S*)-*o*-Ph-MeO-BIPHEP	100	CH_2Cl_2, RT, 25 psi	98 (*S*)	[59a]
(R_P,R_P,S_C,S_C)-DiSquareP*	50 000	MeOH, RT, 6 atm	>99 (*R*)	[17]
(*S,S*)-**L5** (R^1 = ^{i}Pr, R^2 = H)	1 000	^{i}PrOH, 50 °C, 2 atm	>99 (*R*)	[31]
(R_C,S_P)-DuanPhos	100	MeOH, RT, 20 psi	>99 (*R*)	[19]
(S_C,R_P,S_a)-**L10** (R = Me)	100	CH_2Cl_2, RT, 10 bar	99.9 (*R*)	[64d]
(S_{FC},S_C,S_P)-PingFer	200	MeOH, RT,100 psi	99.6 (*S*)	[46]
(S_C,S_a)-PEAPhos	100	CH_2Cl_2, RT, 10 bar	99.1 (*R*)	[66a]
(*R*)-Me-AnilaPhos	100	CH_2Cl_2, RT, 1 bar	97.9 (*S*)	[65]
(R_C,R_C,R_a)-SpiroBIP	100	MeOH, RT, 5 atm	94 (*R*)	[78]
L1	100	MeOH, RT, 3 atm	99 (*R*)	[7]
(*R,R*)-PhBPM	3 000	MeOH, 30 °C, 10 bar	99 (*S*)	[38]
(*R*)-**L11**	100	MEK, RT, 1 bar	98.2 (*R*)	[67a]
(*S,S*)-AlkynylP*	100	MeOH, RT, 3 atm	99.6 (*R*)	[8]
(*S*)-HY-Phos	100	CH_2Cl_2, RT, 10 atm	99 (*S*)	[68b]
(1*R*,2*S*,R_a)-**L13**	100	THF, RT, 20 bar	99 (*R*)	[70a]
(*S*)-MaxPHOS	330	MeOH, RT, 3 bar	99 (*S*)	[27a]
(R_a,S_C)-Quinaphos (Ar = Ph, R = 1-Naph)	1 000	CH_2Cl_2, RT, 30 bar	>99 (*S*)	[73]
(*R,R*,R_a)-**L20** (Ar = xylyl)	100	MeOH, RT, 5 atm	98 (*S*)	[77]
L4	10 000	MeOH, RT, 50 psi	98 (*S*)	[28]
ZhangPhos	100	MeOH, RT, 20 psi	>99 (*S*)	[21]
(R_C,R_P)-BIPOP	100	MeOH, RT, 100 psi	97 (*R*)	[22]
(*R,R*)-*t*-Bu-SMS-Phos	30 000	MeOH, RT, 1 bar	99.8 (*S*)	[33c]
(*R,R*)-QuinoxP*	1 000	MeOH, RT, 2 atm	99.9 (*R*)	[5]
(*R,R*)-Ad-QuinoxP*	100	MeOH, RT, 3 atm	99.9 (*R*)	[6]
(*R,R*)-BenzP*	10 000	MeOH, RT, 5 atm	99.8 (*R*)	[5]
(*R*)-3H-BenzP*	1 000	MeOH, RT, 3 atm	99.2 (*R*)	[30]
(*R*)-3H-QuinoxP*	1 000	MeOH, RT, 3 atm	98.4 (*R*)	[30]
(*R,R*)-TMB-QuinoxP*	10 000	CH_2Cl_2, RT, 5 atm	99.8 (*R*)	[10]



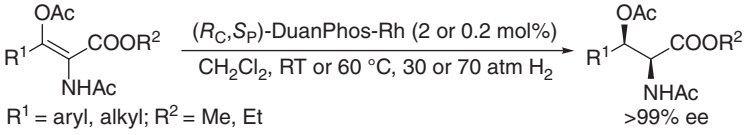
Scheme 1.1



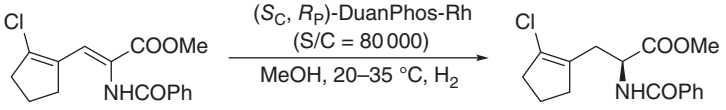
Scheme 1.2



Scheme 1.3



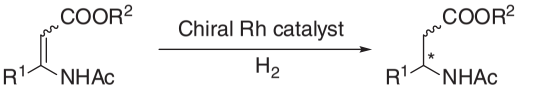
Scheme 1.4



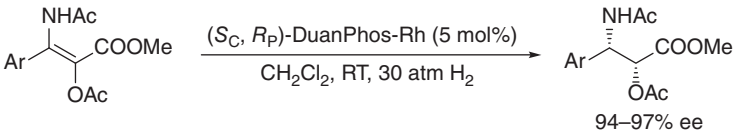
Scheme 1.5

In addition to the hydrogenation examples shown in Table 1.2, various β-dehydroamino acid esters have been subjected to asymmetric hydrogenation by the use of TCFP [106, 107], DuPhos [108, 109], SIPHOS [110], DuanPhos [111], and Walphos [112] with the significant expansion of the substrate scope. It is particularly noted that α-alkoxy tetrasubstituted dehydroamino acid derivatives are hydrogenated by the use of DuanPhos-Rh complex to give the corresponding products with two chirogenic centers in excellent enantioselectivities (Scheme 1.6) [111].

Table 1.2 Asymmetric hydrogenation of representative β-dehydroamino acid esters.

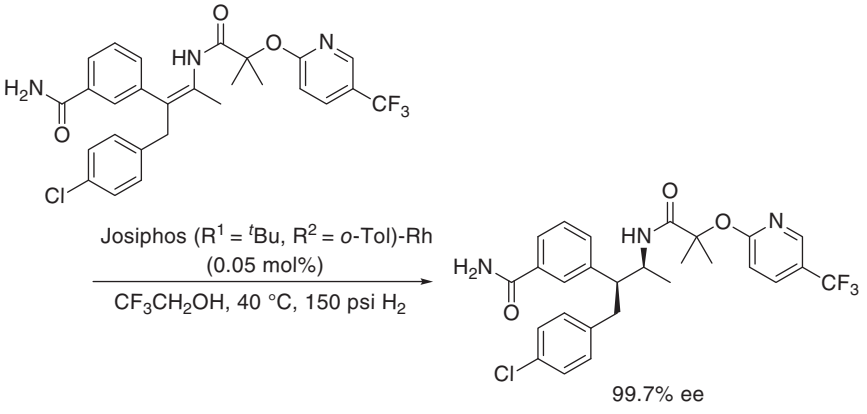


Ligand	R^1	R^2	Geometry	S/C	Reaction conditions	% ee (configuration)	References
(*R*)-TCFP	Me	Me	*E*	100	THF, RT, 20 psi	99 (*R*)	[25b]
(*R*)-TCFP	Me	Me	Z	100	THF, RT, 20 psi	99 (*R*)	[25b]
(*R*)-TCFP	Ph	Et	Z	100	THF, RT, 20 psi	96 (*S*)	[25b]
(R_C,S_p)-DuanPhos	Me	Et	*E*	100	MeOH, RT, 20 psi	>99 (*R*)	[19]
(R_C,S_p)-DuanPhos	Me	Et	*Z*	100	MeOH, RT, 20 psi	97 (*R*)	[19]
(R_p)-ZhangPhos	Me	Me	*E*	100	THF, RT, 20 psi	>99 (*S*)	[21]
(R_p)-ZhangPhos	Me	Me	*Z*	100	THF, RT, 20 psi	97 (*S*)	[21]
(R_p)-ZhangPhos	Ph	Me	*Z*	100	THF, RT, 20 psi	95 (*S*)	[21]
(R_C,R_p)-BIPOP	Me	Me	*E*	100	CH_2Cl_2, RT, 100 psi	99 (*R*)	[22]
(R_C,R_p)-BIPOP	Me	Me	*Z*	100	CH_2Cl_2, RT, 100 psi	99 (*R*)	[22]
(*R*,*R*)-*t*-Bu-SMS-Phos	Me	Me	*E*	100	MeOH, RT, 1 bar	97.3 (*S*)	[33c]
(*R*,*R*)-*t*-Bu-SMS-Phos	Me	Me	*Z*	100	MeOH, RT, 1 bar	80.1 (*S*)	[33c]
(S_C,S_a)-PEAPhos-Ph	Me	Me	*E*	100	MeOH, RT, 10 bar	88 (*R*)	[66b]
(S_C,S_a)-PEAPhos-Ph	Me	Me	*Z*	100	MeOH, RT, 10 bar	96 (*R*)	[66b]
(S_C,S_a)-PEAPhos-Ph	Ph	Et	*Z*	100	MeOH, RT, 10 bar	>99 (*S*)	[66b]
(*R*,*R*)-QuinoxP*	Me	Me	*E*	1000	MeOH, RT, 3 atm	99.9 (*R*)	[5]
(*R*,*R*)-QuinoxP*	Me	Me	*Z*	1000	MeOH, RT, 3 atm	99.0 (*R*)	[5]
(*R*,*R*)-QuinoxP*	Ph	Me	*Z*	1000	MeOH, RT, 3 atm	98.1 (*S*)	[5]
L10 (R = H)	Me	Me	*E*	100	CH_2Cl_2, 5 °C, 10 bar	98 (*R*)	[64c]
L10 (R = H)	Me	Me	*Z*	100	CH_2Cl_2, 5 °C, 10 bar	92 (*S*)	[64c]



Scheme 1.6

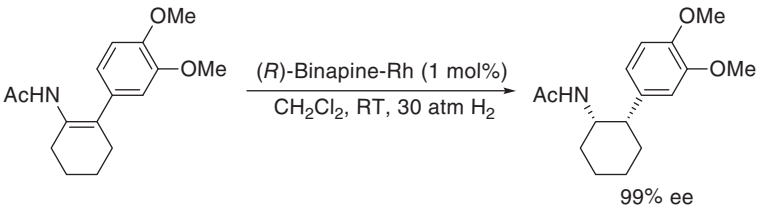
Hydrogenation of Other Enamides Enantioselective hydrogenation of *N*-acylenamides is a useful method of the synthesis of chiral amines, and Rh catalysts are most frequently used for this purpose [113, 114]. Simple enamides such as 1-acetamido-1-arylethene are often used for the standard probing substrates for the evaluation of new chiral phosphorus ligands [5, 7, 19, 21, 22, 23a, 26, 33c, 38, 64a, b, d, 66a, 67b, 70b, 73, 84a, 110, 115]. In addition to these fundamental studies, great efforts have been devoted to achieving efficient hydrogenation of functionalized enamides for the synthesis of biologically active chiral amines. For example, Wallace et al. achieved an efficient hydrogenation of a tetrasubstituted enamide by using Josiphos ligand (Scheme 1.7) [116]. The hydrogenation takes place even with low catalyst loading to give the product with 99.7% ee, which is converted into taranabant, a cannabinoid-1 receptor (CB1R) inverse agonist.



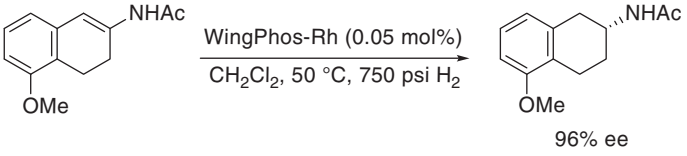
Scheme 1.7

The hydrogenation of cyclic enamides is generally notoriously difficult. Zhang and coworkers have proved the applicability of Binapine ligand in this kind of hydrogenation while it requires considerably high H_2 pressure (Scheme 1.8) [117]. Tang and coworkers have demonstrated the high catalytic performance of WingPhos-Rh complexes toward cyclic enamides, as exemplified in Scheme 1.9 [23a].

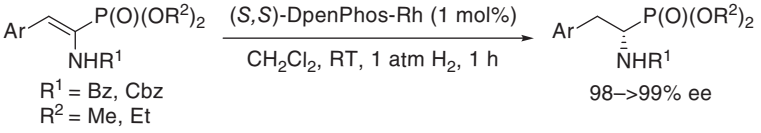
Chiral aminophosphonates are an important class of compounds for pharmaceutical use. Asymmetric hydrogenation of enamides bearing a phosphonate functional group at α- or β-position is a straightforward method for the synthesis of such compounds. α-Phosphonate-substituted enamides are smoothly hydrogenated even under 1 atm H_2 pressure [30, 33c, 43e, 82a, 118], as exemplified in Scheme 1.10 [82a]. In contrast, the hydrogenation of β-enamidophosphonates



Scheme 1.8

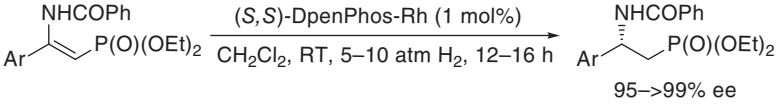


Scheme 1.9



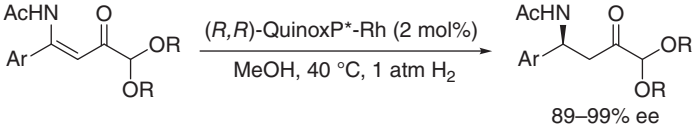
Scheme 1.10

requires higher H_2 pressure and longer reaction times [60b, 71, 82a, 119], as shown in Scheme 1.11 [82a].

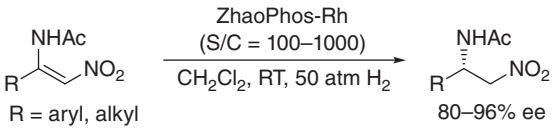


Scheme 1.11

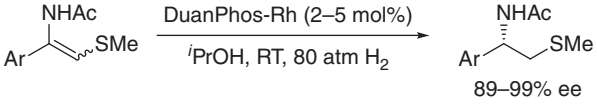
The significance of chiral amines possessing functional groups for pharmaceutical use has prompted the investigations on the Rh-catalyzed asymmetric hydrogenation of functionalized enamides. The functional groups attached at α- or β-position of enamides are alkoxy [117, 120, 121], keto [20b, e–g, j, 30b, 117, 122–124], cyano [14f, 125, 126], alkenyl [20h, i, 127], perfluoroalkyl [20j, 128], nitro [14g, 53c], sulfonyl [14i], and alkylthio [129]. Three hydrogenation examples are shown in Schemes 1.12–1.14 [53c, 124, 129].



Scheme 1.12



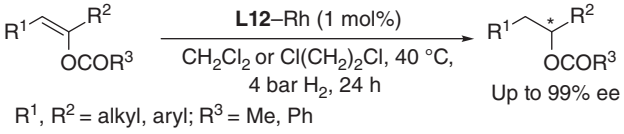
Scheme 1.13



Scheme 1.14

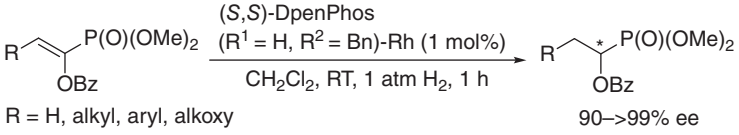
1.3.1.2 Hydrogenation of Enol Esters

In contrast to the numerous examples of the asymmetric hydrogenation of enamides, relatively less attention has been paid to the hydrogenation of structurally similar enol esters, because the coordination ability of the enol esters to Rh atom is weaker than that of enamides and the hydrogenation requires more forcing reaction conditions. Recent studies have demonstrated that phosphine–phosphite ligands (**L12** [69b], **L13** [70c–e]), phosphine–phosphoramide ligand ((*Sa*)-Quinaphos [73]), P-chirogenic ligand *t*-Bu-SMS-Phos [33c], and spiroketal-based diphosphine ligand (SKP [61b]) are effective for the enantioselective hydrogenation of simple enol esters. Especially, **L12**-Rh catalyst is applicable to a wide range of substituted enol esters to afford the corresponding products with high ee's (Scheme 1.15) [69b].



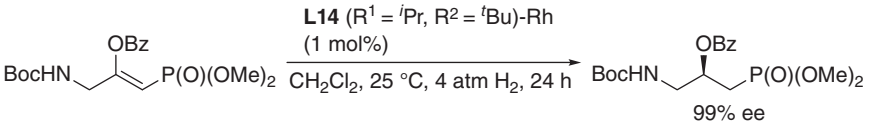
Scheme 1.15

On the other hand, enol esters with a phosphonate functional group at the α-position have attracted considerable attention for their asymmetric hydrogenation, because the products are useful chiral building block for the synthesis of enzyme inhibitors, antibacterial agents, antibiotics, anticancer agents, and pesticides. High to excellent enantioselectivities have been observed by the use of BisP* and MiniPHOS [118], Me-DuPhos [130], THNAPhos [68a], HY-Phos [68b], **L21** [43e], *t*-Bu-SMS-Phos [33c], **L13** (R^1 = Cy; R^2 = Me or CPh_3) [70d], DpenPhos [131], **L13** (R^1 = Ph, R^2 = Me or CPh_3) [70e], ClickFerrophos II (Ar = 3,5-Xylyl, R = Ph) [51], 3H-QuinoxP* [30], and 3H-BenzP* [30]. One example with the use of DpenPhos is shown in Scheme 1.16 [131].



Scheme 1.16

In contrast to the abovementioned reactions, very few reports dealing with the hydrogenation of β-substituted derivatives have appeared, while considerably high enantioselectivities have been observed by the use of **L14** ($R^1 = {}^i$Pr, $R^2 = {}^t$Bu) [69a, 71] and DpenPhos [131], as exemplified by Scheme 1.17 [71].



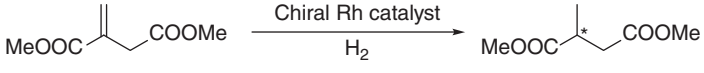
Scheme 1.17

1.3.1.3 Hydrogenation of α,β-Unsaturated Acids, Esters, and Related Substrates

Itaconic acid and its derivatives are typical α,β-unsaturated acid derivatives bearing a carboxylic functional group that acts as a coordinating directing group. This class of compound is often used for the evaluation of the enantioinduction ability of newly synthesized chiral phosphorus ligands. Table 1.3 summarizes the hydrogenation results of dimethyl itaconate that have been reported since 2004. Very high to almost perfect enantioselectivities are observed in most cases.

During the past 14 years, significant advances have been made in the hydrogenation of α,β-unsaturated carboxylic acids and their derivatives with no directing groups or with weak directing groups. Thus, extensive investigations using new chiral phosphorus ligands in addition to the traditionally used ones have revealed high enantioselectivities and TON in the hydrogenation

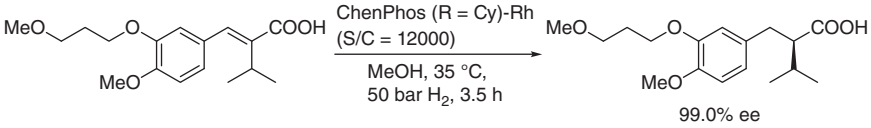
Table 1.3 Asymmetric hydrogenation of dimethyl itaconate.



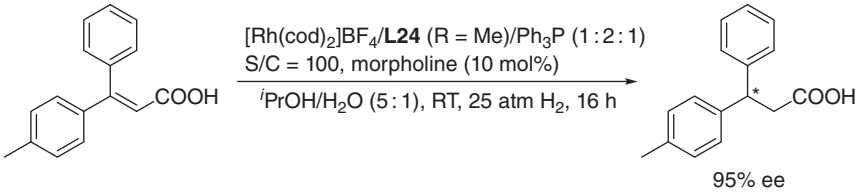
Ligand	S/C	Reaction conditions	% ee (configuration)	References
(S_C,R_P,S_a)-**L10** (R = Me)	10 000	CH_2Cl_2, RT, 10 bar	99.1 (*S*)	[64a]
(1*R*,5*R*,6*R*)-**L19**	250	THF, RT, 1 atm	96 (*R*)	[76]
(*R*,*R*)-UlluPHOS	1 000	MeOH, 27 °C, 30 psi	>99.5 (*S*)	[36]
(S_C,S_a)-PEAPhos	100	CH_2Cl_2, RT, 10 bar	99.9	[66a]
(R_C,S_P)-DuanPhos	100	THF, RT, 20 psi	>99 (*S*)	[19]
(*R*,*R*)-PhBPM	100	CF_3CH_2OH, RT, 1 bar	99.2 (*R*)	[67a]
(*S*,*S*)-Ph-Quinox	1 000	MeOH, 25 °C, 10 bar	99.8 (*S*)	[39]
(R_a,S_C)-Quinaphos (Ar = Ph, R = 1-Naph)	1 000	CH_2Cl_2, RT, 30 bar	>99 (*R*)	[73]
ZhangPhos	100	THF, RT, 20 psi	>99 (*R*)	[21]
(*R*,*R*)-*t*-Bu-SMS-Phos	30 000	MeOH, RT, 1 bar	99.4 (*R*)	[33c]
(*R*,*S*a)-**L13** (R = Me)	10 000	THF, RT, 20 bar	99 (*S*)	[70e]

of a wide range of substrates. In particular, many ferrocene-based ligands (Josiphos [132, 133], BoPhoz [43d, i, 48], TaniaPhos [49b], Walphos [45a, e, 134], MandyPhos [135–137], TriFer [47], ChenPhos [54, 138], ZhaoPhos [53d–f, h, 139], Wudaphos [55a], and ^{t}Bu-Wudaphos [56b]) have served for this kind of transformation. Other ligands including a phosphine–phosphoramide ligand (THNAPhos) [140], a P-chirogenic ligand (*t*-Bu-SMS-Phos) [33c], and a phosphine oxide ligand (**L24**) [85] also facilitate the hydrogenation.

Two examples are shown in Schemes 1.18 and 1.19. ChenPhos bearing dimethylamino group in the ligand serves as an effective ligand for the synthesis of a key intermediate of the renin inhibitor aliskiren (Scheme 1.18) [54a]. Scheme 1.19 shows the hydrogenation of β-phenyl-β-*p*-tolyl-substituted acrylic acid with the use of a mixed ligand system consisting of a chiral ligand (**L24**) and an achiral ligand (Ph_3P) [85]. It is noted that analogous propionic acids with sterically similar substituents at β,β-positions can be accessed in high enantiopurity using the same catalyst by simply switching the *E*- and *Z*-substrates for the hydrogenation.

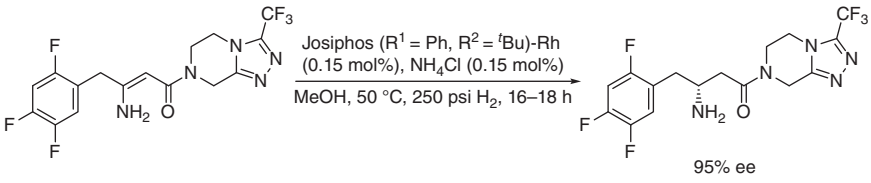


Scheme 1.18



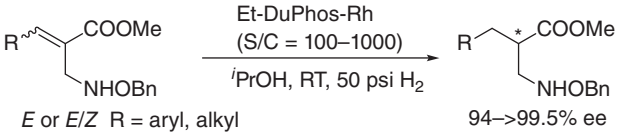
Scheme 1.19

The asymmetric hydrogenation of unprotected β-enamine esters or amides has been accomplished by the use of Josiphos or TangPhos [14a, 141–146]. Scheme 1.20 shows an example used for the production of sitagliptin [145]. It has been also reported that this kind of reaction proceeds smoothly in the presence of $(Boc)_2O$ by trapping the product primary amines that are apt to coordinate to Rh atom to deactivate the catalyst [142].



Scheme 1.20

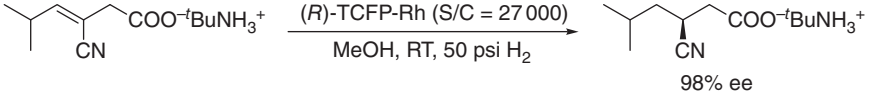
Asymmetric hydrogenation of α-aminomethyl-α,β-unsaturated carboxylic esters is a useful method for the synthesis of enantioenriched β^2-amino acid derivatives. Some successful results of up to >99.5% enantioselectivity and 10 000 TON have been obtained by using TangPhos [147], MonoPhos [148], BoPhoz [43g], the phosphine–phosphoramide ligand **L16** [72], Et-DuPhos [149], *t*-Bu-SMS-Phos [33c], PhthalaPhos [84b], and the DuPhos-type ligand Cat*A*SiumMQF [40], as exemplified in Scheme 1.21 [149].



Scheme 1.21

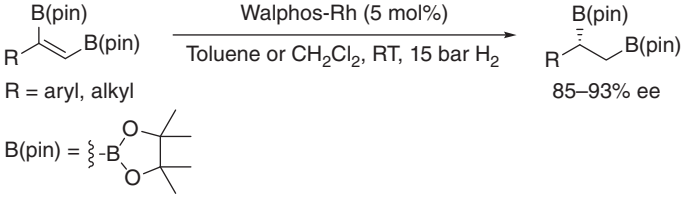
1.3.1.4 Hydrogenation of Other Functionalized Alkenes

During the past 14 years, various functionalized alkenes have been tested for Rh-catalyzed asymmetric hydrogenation, and the substrate scope has been greatly expanded. A striking example is shown in Scheme 1.22 [25a]. In this hydrogenation, TCFP is used with excellent enantioselectivity and high TON of up to 27 000 to afford the pregabalin intermediate. The very high catalytic efficiency is ascribed to the chiral environment constructed by the three-hindered quadrant ligand and to the carboxylate group that acts as a directing group.



Scheme 1.22

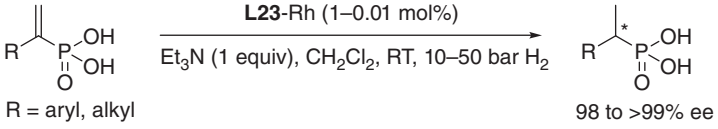
Morken and coworker reported that pinacolatoboryl alkenes were subjected to asymmetric hydrogenation in high enantioselectivities with Walphos-Rh catalyst [45b, 150], as shown in Scheme 1.23 [150]. This hydrogenation coupled with subsequent oxidation procedure provides a useful protocol for the synthesis of enantioenriched secondary alcohols.



Scheme 1.23

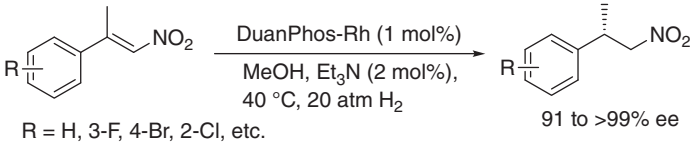
Efficient asymmetric hydrogenation of α,β-unsaturated phosphonic acids and esters without a directing group such as acylamino or enol ester group has remained a difficult problem. This difficulty has been overcome by the use

of ferrocene-based phosphorus ligands, such as FAPhos [83a], BoPhoz [43h], ImiFerroPhos [49c], ClickFerrophos II [51], and Walphos [151]. In particular, Walphos is effective for β,β-disubstituted α,β-unsaturated phosphonic esters to furnish the products with up to 98% ee [151]. Ding and coworkers have revealed that monodentate secondary phosphine oxide ligand **L23** is effective for α-substituted α,β-unsaturated phosphonic acids [82b]. As shown in Scheme 1.24, the reaction proceeds in excellent enantioselectivity even with 0.01 mol% catalyst loading. Dong, Zhang, and coworkers have achieved a similar transformation using SPO-Wudaphos containing a chiral secondary phosphine oxide and a dimethylamino group [57]. The reaction proceeds smoothly under mild conditions without base. Their control experiments demonstrate that non-covalent ion pair interaction plays a critical role for the hydrogenation.

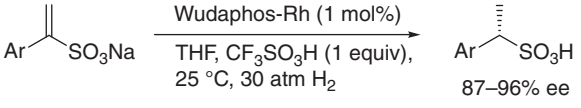


Scheme 1.24

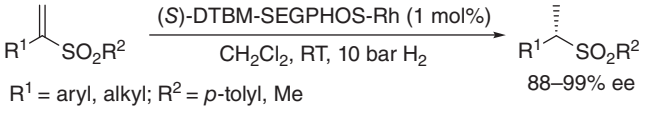
Zhang and coworkers have reported the efficient asymmetric hydrogenation of α,β- or β,β-disubstituted nitroalkenes with Rh complexes of Josiphos, DuanPhos, and ZhaoPhos [53a, 152–154], as exemplified in Scheme 1.25 [153]. They have observed also that sodium α-arylethenylsulfonates [55b] and α-substituted vinyl sulfones [155] are hydrogenated in high to excellent enantioselectivities (Schemes 1.26 and Scheme 1.27).



Scheme 1.25



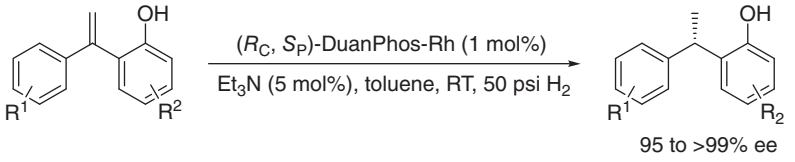
Scheme 1.26



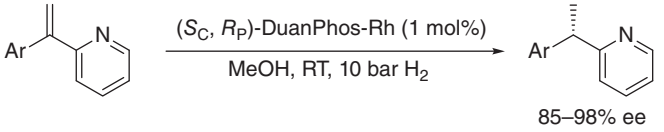
Scheme 1.27

It has been reported that terminal alkenes bearing a phenol moiety [156, 157], a pyridyl group [43k, 158], or a carboxyl group [20d, 56a] are subjected to facile

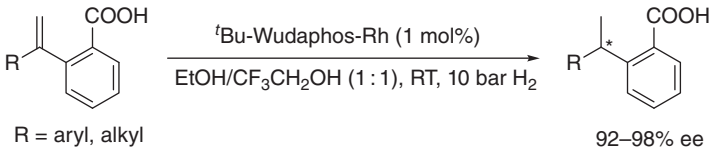
asymmetric hydrogenation. In these reactions, the functional groups interact with the Rh atom to facilitate the hydrogenation (Schemes 1.28–1.30) [56a, 156, 158].



Scheme 1.28

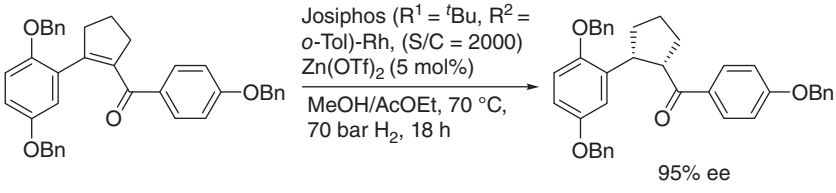


Scheme 1.29



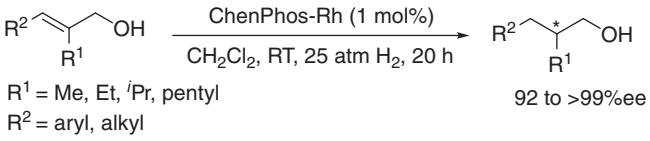
Scheme 1.30

Rhodium-catalyzed asymmetric hydrogenation of α,β-unsaturated ketones is also noteworthy. May and coworkers found that tetrasubstituted α,β-enones were hydrogenated with Josiphos-Rh catalyst in the presence of zinc triflate, as exemplified in Scheme 1.31 [159]. The addition of catalytic zinc triflate enhances the hydrogenation and suppresses the epimerization of the product. The product ee can be increased to >99.8% by recrystallization, and this hydrogenation process has been conducted on a large scale [160].



Scheme 1.31

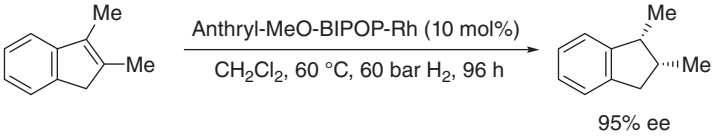
Zhang, Chen, and coworkers reported that 2-substituted-2-alkenols (allylic alcohols) were effectively hydrogenated with ChenPhos-Rh catalyst to give ≥99% ee for most substrates (Scheme 1.32) [54b]. The excellent catalytic performance is responsible for the hydrogen bonding interaction between the dimethylamino group of the ligand and the substrate OH group.



Scheme 1.32

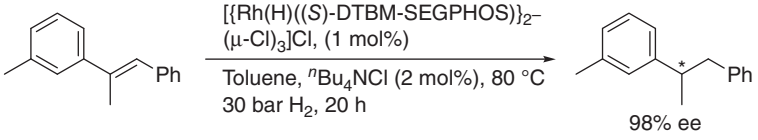
1.3.1.5 Hydrogenation of Unfunctionalized Alkenes

In contrast to many successful results of Ir-catalyzed asymmetric hydrogenation of unfunctionalized or minimally functionalized alkenes, its rhodium version has remained notoriously difficult to achieve. Indeed, there are only fewer examples concerning this kind of asymmetric hydrogenation. Recently, it has been reported that indene-type tetrasubstituted alkenes can be hydrogenated in high enantioselectivities of up to 95% with anthryl-MeO-BIPOP-Rh catalyst, though the reaction requires high catalyst loading and forcing reaction conditions (Scheme 1.33) [161].



Scheme 1.33

Mashima and coworkers have disclosed that chloride-bridged dinuclear Rh(III) complexes with chiral bisphosphines are effective for the asymmetric hydrogenation of simple alkenes (Scheme 1.34) [162]. This novel protocol is applicable to many other simple alkenes including the substrates bearing a functional group with weak coordination ability, such as allylic alcohols, alkenyl boranes, and cyclic unsaturated sulfones. It is considered that this hydrogenation would proceed via the direct attack of the Rh(III)-monohydride species to the alkene double bond.

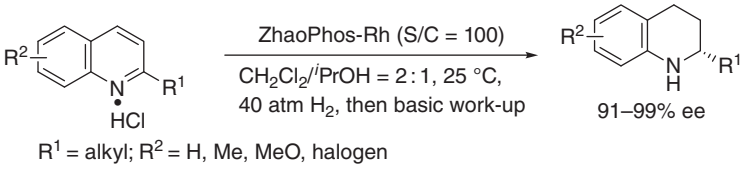


Scheme 1.34

1.3.1.6 Hydrogenation of Heteroarenes

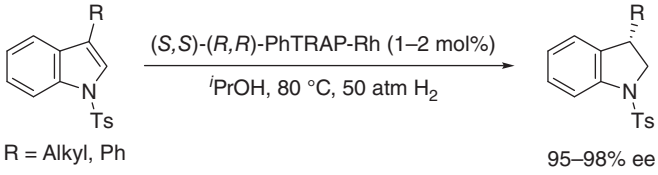
Asymmetric hydrogenation of heteroarenes provides chiral saturated or partially saturated heterocyclic molecules that are useful as the building blocks for the synthesis of biologically active compounds. This asymmetric transformation has been mostly conducted with the use of chiral complexes of Ir, Ru, and Pd, and relatively less attention has been paid to the use of Rh catalysts [163]. Three examples published since 2004 are shown below [37, 42a, b, 53g]. Zhang, Zhao, and coworkers have found that ZhaoPhos ligand is suited for the hydrogenation

of hydrochloride salts of quinoline and isoquinoline derivatives (Scheme 1.35) [53g]. The hydrogenation of *N*-tosyl derivatives of indoles can be hydrogenated with PhTRAP-Rh complex (Scheme 1.36) [42a, b]. Scheme 1.37 shows that a substituted furan is subjected to asymmetric hydrogenation, though the reaction is conducted under harsh conditions [37].

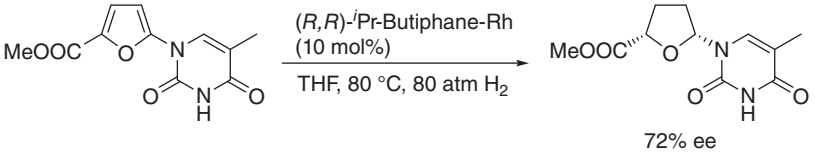


R^1 = alkyl; R^2 = H, Me, MeO, halogen

Scheme 1.35



Scheme 1.36



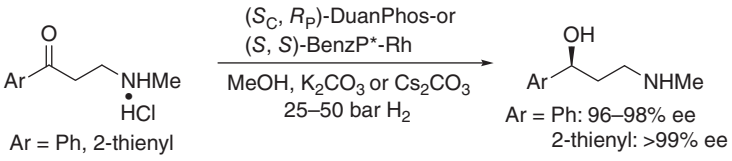
Scheme 1.37

1.3.2 Hydrogenation of Ketones

The enantioselective hydrogenation of various ketones with chiral Ru complexes has been frequently employed in both academia and industry for the production of enantioenriched secondary alcohols [164]. In contrast, the use of Rh complexes for ketone hydrogenation results in lower TON compared with Ru catalysts in most cases, while the enantioselectivities approach to more than 99% in some cases.

X. Zhang, W. Zhang, and coworkers have achieved highly enantioselective hydrogenation of β-secondary amino ketones by the use of electron-rich bisphosphine ligands, DuanPhos and BenzP* [20a, 165]. The practical utility of the process has been demonstrated in the synthesis of the chiral intermediates of pharmaceutically important compounds, such as fluoxetine, atomoxetine, and duloxetine (Scheme 1.38).

Zhang, Wu, and coworkers found that β-ketoenamides were hydrogenated with DuanPhos-Rh catalyst in highly enantioselective (up to 99%) and diastereoselective (up to dr 99 : 1) manner to give *anti*-1,3-amino alcohol



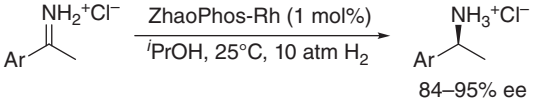
Scheme 1.38

derivatives [20e]. W. Zhang, Z. Zhang, and coworkers reported that cyclic α-ketoenamides were subjected to hydrogenation with 3H-QuinoxP*-Rh catalyst to furnish *trans*-1,2-amino alcohol derivatives with excellent enantioselectivities [30b]. It has been also reported that BoPhoz-Rh and Binapine-Rh catalysts are effective for the hydrogenation of α-ketoesters and 2-pyridyl ketones, respectively [16, 43b].

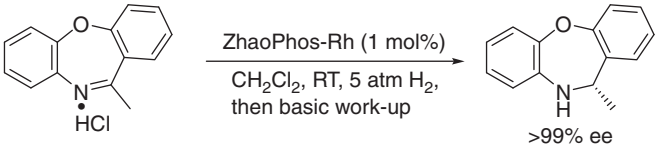
1.3.3 Hydrogenation of Imines, Oximes, and Hydrazones

The asymmetric hydrogenation of C=N bond by Rh catalyst is a valuable protocol for the synthesis of chiral amine derivatives, and several approaches have provided some promising results. For example, the hydrogenation of N-protected imines or oxime acetates with the Rh complexes of TangPhos [20k], ZhangPhos [21], Josiphos [166], and TCFP [167] proceeds in good to excellent enantioselectivity, while the reactions are carried under harsh conditions and/or with high catalyst loading. Similar approach is directed to the hydrogenation of hydrazones using Taniaphos [44a, 168], Josiphos [168], and BenzP* [169] to give enantioselectivities of up to 99%.

Zhang and coworkers have succeeded the hydrogenation of unprotected imines using ZhaoPhos ligand, as shown in Scheme 1.39 [53b]. In this case, the use of HCl salts of imines is crucial for the success of the reaction. Thus, the anion binding interaction between the thiourea of the ligand and chloride counterion plays an important role in this catalytic system. This procedure is applicable to the hydrogenation of cyclic imines, as exemplified in Scheme 1.40 [53i].



Scheme 1.39



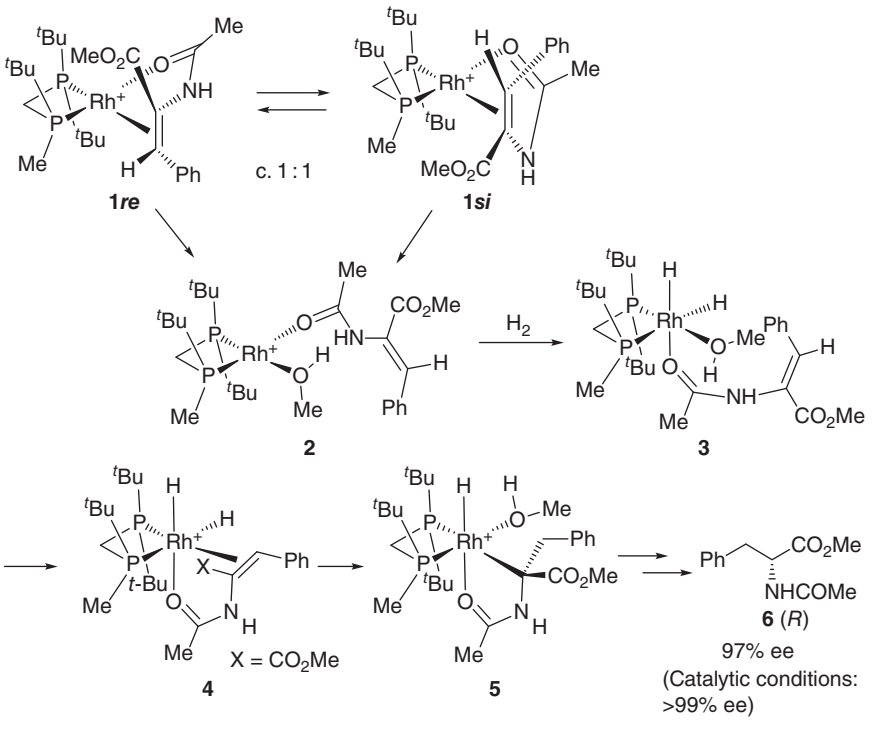
Scheme 1.40

1.4 Enantioselection Mechanism of Rhodium-Catalyzed Asymmetric Hydrogenation

The reaction mechanism of rhodium-catalyzed asymmetric hydrogenation of enamides and related substrates has long been extensively studied. A well-known mechanism is the Halpern–Brown mechanism (so-called unsaturated mechanism (alkene first mechanism) and major/minor concept) [170, 171]. The mechanism was proposed on the basis of the observation that the minor diastereomer catalyst–substrate complex (Rh(I)-chelating complex coordinated with the alkene moiety and the amide oxygen atom of α-dehydroamino acid esters such as MAC) was more reactive than the major diastereomer complex and the chirality of the hydrogenation product corresponded to the stereochemistry of the minor diastereomer rather than the major diastereomer. While this classic mechanism is often used for the explanation of the chirality of the products by assuming the existence of major/minor diastereomer catalyst–substrate complexes and their relative stability, it can be difficultly applied for the explanation of numerous results with very high enantioselectivity (≥99%) and the resulting chirality of the products, especially obtained by the use of electron-rich phosphine ligands. Indeed, there have been some experimental facts, in which the chirality of the products does not correspond to the stereochemistry of the minor diastereomers but that of the major ones, different from the prediction by the Halpern–Brown mechanism. Furthermore, it has been revealed that there are no distinct relationships between the concentration ratio (major/minor ratio) of the diastereomer complexes and the chirality of the products. Thus, exceedingly high enantioselectivities have been observed in many cases when the ratios range from very large to almost 1 : 1 or even no tetracoordinate Rh(I)-chelating complexes are formed.

Gridnev, Imamoto, and coworkers have studied the catalytic cycle and the origin of the enantioselectivity of Rh-catalyzed asymmetric hydrogenation of α- and β-dehydroaminio acid derivatives, enamides, and related substrates using ^{t}Bu-BisP*, ^{t}Bu-MiniPHOS, TCFP, BenzP*, and other electron-rich phosphine ligands [3, 5, 7, 118, 172]. Their NMR and DFT computation studies have demonstrated that these Rh-catalyzed hydrogenations proceed via dihydride pathways [3, 5, 172].

Scheme 1.41 shows one example of their studies based on low temperature NMR and DFT computations [172c]. In this case, TCFP-Rh solvated complex reacts with MAC to form tetracoordinate Rh(I)-chelating complexes (**1*re***, **1*si***) in about 1 : 1 ratio; no distinct major/minor ratio is observed. Each diastereomer does not react directly with H_2 but undergoes dissociation of the alkene moiety to give the same intermediate **2**, non-chelating Rh(I)-substrate complex coordinated with the amide oxygen atom, which in turn is subjected to oxidative addition with H_2 to give Rh(III)-dihydride complex **3**. The coordinated methanol molecule is dissociated, and instead the C=C double bond is intramolecularly coordinated to the Rh atom to form hexacoordinate Rh(III)-dihydride complex **4**. This complex is very unstable and rapidly undergoes migratory insertion to give **5**, which is converted into product **6** (*R*) via reductive elimination. It should be noted



Scheme 1.41 Reaction of [Rh((*R*)-TCFP)] – MAC diastereomer complexes with H_2.

that the enantioselectivity is determined at the stage of formation of **4**, which is in the lowest energy state compared with other possible diastereomers.

The abovementioned dihydride pathway can be applicable for the explanation of the stereochemical outcomes of the hydrogenation of many other substrates bearing a coordinative functional group. The main factors to control the enantioselectivity are as follows:

1) The hexacoordinate Rh(III)-chelating ring is formed, avoiding steric repulsion with the bulky alkyl group on the phosphorus atom.
2) The C=C double bond undergoes migratory insertion to the Rh—H bond trans to the Rh—P bond.
3) The rhodium atom binds to the more electron-deficient carbon atom.

Thus, the origin of the very high enantioselectivity can be explained by considering the cooperative interaction of abovementioned steric and electronic factors for lowering the transition state energy.

1.5 Conclusion

Rhodium-catalyzed asymmetric hydrogenation is an almost perfect atom-economical reaction, usually carried out under mild conditions, and proceeds

with essentially quantitative yield. Although rhodium metal is expensive, the very high TON as well as excellent enantioselectivities renders its methodology practically useful for the production of enantiomerically pure or enriched high-value added compounds.

During the past 14 years, extensive investigations have been devoted into this area, and many chiral phosphorus ligands have been developed with the significant expansion of the substrate scope together with enhanced catalytic activities and enantioselectivities. This trend of investigation will further continue to overcome so far unsolved difficult problems, and the Rh-catalyzed asymmetric hydrogenation will become one of the sophisticated and truly useful methods for the synthesis of a variety of optically active compounds.

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