

Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamines and Imines

Jian-Hua Xie, Shou-Fei Zhu, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

CONTENTS

1. Introduction	1713
2. Enantioselective Hydrogenation of Enamines	1714
2.1. Enantioselective Hydrogenation of N-Acyl Enamines	1715
2.1.1. Chiral Rhodium Catalysts	1715
2.1.2. Chiral Ruthenium Catalysts	1736
2.1.3. Chiral Iridium Catalysts	1736
2.2. Enantioselective Hydrogenation of Unfunctionalized Enamines	1737
2.2.1. Chiral Titanium Catalysts	1737
2.2.2. Chiral Rhodium Catalysts	1738
2.2.3. Chiral Iridium Catalysts	1739
3. Enantioselective Hydrogenation of Imines	1741
3.1. Enantioselective Hydrogenation of N-Aryl/Alkylimines	1741
3.1.1. Chiral Iridium Catalysts	1741
3.1.2. Chiral Rhodium Catalysts	1749
3.1.3. Chiral Ruthenium Catalysts	1751
3.1.4. Other Chiral Catalysts	1752
3.2. Enantioselective Hydrogenation of Activated Imines	1752
3.2.1. Chiral Rhodium Catalysts	1752
3.2.2. Chiral Ruthenium Catalysts	1753
3.2.3. Chiral Palladium Catalysts	1754
3.2.4. Chiral Iridium Catalysts	1755
3.3. Enantioselective Hydrogenation of N-H Imines	1755
4. Summary and Outlook	1756
Author Information	1756
Biographies	1756
Acknowledgment	1757
References	1757

1. INTRODUCTION

Chiral amines are an important class of organic compounds that can be used as resolving reagents, chiral auxiliaries, and intermediates for the synthesis of a variety of biologically active molecules including natural and unnatural products. Catalytic enantioselective hydrogenation of enamines and imines with chiral transition metal complexes bearing chiral ligands was found to be one of the most efficient and convenient methods

for the preparation of chiral amines and their derivatives (Scheme 1).

As outlined in Scheme 1, chiral primary amines can be obtained by enantioselective hydrogenation of *N*-acetyl enamines, *N*-tosyl/phosphinylimines (activated imines), and *N*-H imines; chiral secondary amines can be achieved by enantioselective hydrogenation of either *N*-acetyl enamines or *N*-alkyl/aryl imines; and chiral tertiary amines can only be produced from the enantioselective hydrogenation of *N,N*-dialkyl/arylenamines. These hydrogenation reactions provide a direct and atom-economic pathway for the synthesis of a wide range of chiral amines. It is noteworthy that the enamines in the context of this review are limited to *N*-acetyl enamines and *N,N*-dialkyl/arylenamines; both are electron-rich enamines. The dehydroamino acid derivatives, which produced chiral amino acids or esters in the hydrogenation reaction, are not included.

The chiral catalysts used for the hydrogenation of enamines and imines are the main determinant to the reactivity and enantioselectivity. To date, a broad range of chiral catalysts have been developed for the hydrogenation of enamines and imines, providing the desired chiral amines or their derivatives with good to excellent enantioselectivities. Some of them have been successfully applied to the industrial production of chiral drugs and agrochemicals.¹ The most notable example is the chiral iridium-Xyliphos catalyst, which has been used in the enantioselective synthesis of the herbicide (S)-Metolachlor (Scheme 2).² Although the enantioselectivity of iridium complex of Xyliphos (1a) was only moderate (79% ee) for the key step, the hydrogenation of imine intermediate, exceptionally high turnover numbers (up to 10⁶), and initial turnover frequencies (1.8 × 10⁶ h⁻¹) allowed industrial production at the largest scale ever demonstrated.

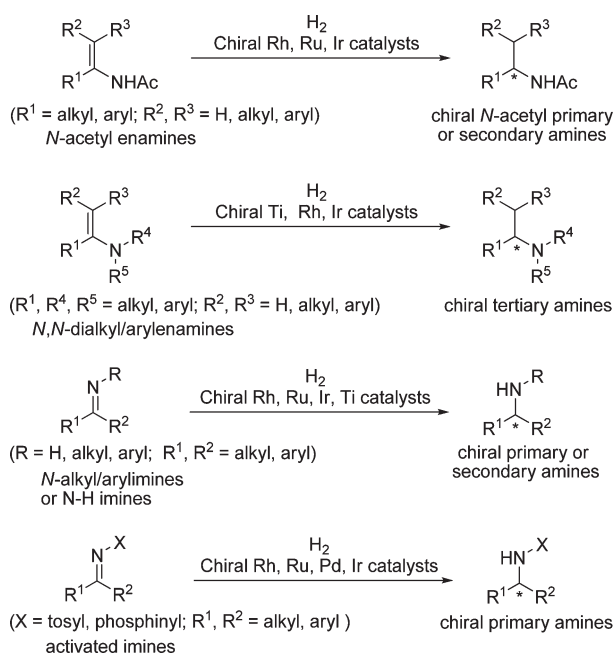
Despite significant progress in the past decades, catalytic highly enantioselective hydrogenation of enamines and imines is still a challenging endeavor. The reasons for this are as follows. (1) Electron-rich enamines and imines are poor substrates for enantioselective hydrogenation, and the turnover number and turnover frequency are normally not high. (2) Electron-rich enamines, especially *N,N*-dialkyl/arylenamines, and imines are sensitive to moisture, resulting in hydrolysis of substrates. (3) Except for the *N*-acetyl enamines and the "activated" imines, e.g., *N*-tosylimines and *N*-phosphinylimines, which chelate to the metal center of the catalyst, a prerequisite for obtaining high enantioselectivity in hydrogenation reactions,³

Special Issue: 2011 Frontiers in Transition Metal Catalyzed Reactions

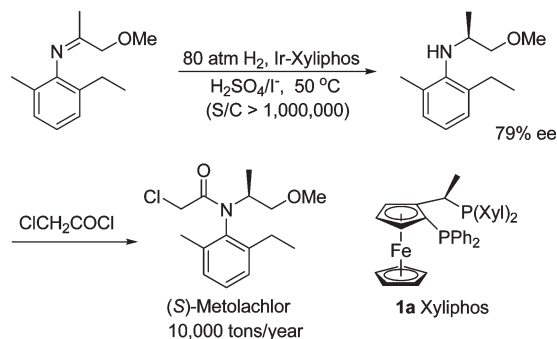
Received: July 13, 2010

Published: December 17, 2010

Scheme 1. Catalytic Enantioselective Hydrogenation of Enamines and Imines



Scheme 2. Enantioselective Synthesis of (S)-Metolachlor



N,N -dialkyl/arylenamines and simple imines coordinate to the metal center of catalyst only in a configurationally unstable η^1 - or η^2 -fashion (Figure 1).⁴ Thus, enantiocontrol during the hydrogenation of N,N -dialkyl/arylenamines and simple imines is very difficult. (4) In the case of β -substituted N -acetyl enamines and acyclic imines, they are often isolated as a mixture of Z/E -isomers,⁵ which makes it difficult for the catalyst to convert all stereoisomers in a selective manner. Furthermore, imine–enamine tautomerization of the substrates, which allows the possibility for Z/E -isomers inter-conversion, evokes ambiguous interactions between the catalyst and substrate, lowering the enantioselectivity for these hydrogenations.

This review is intended to provide an overview of the transition metal-catalyzed enantioselective hydrogenation of enamines and imines for the synthesis of chiral amines, not including chiral amino acid derivatives, and is focused on the development of chiral metal catalysts for such transformations. However, to have a complete overview of the developments in

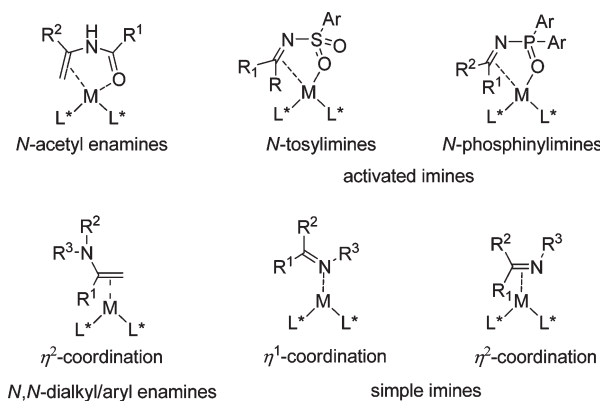
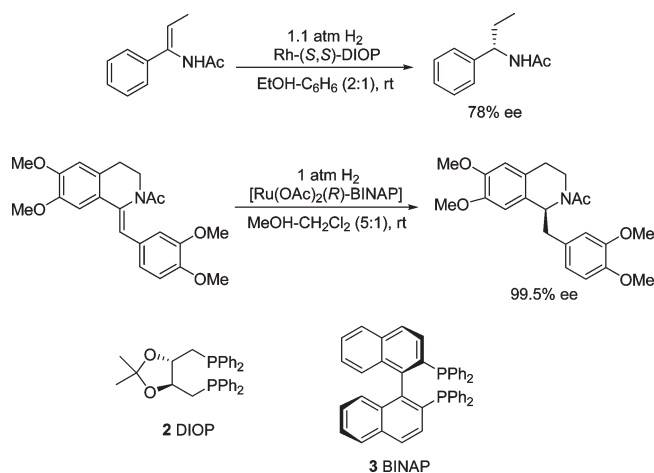


Figure 1. Coordination models of enamines and imines to the metal center of catalysts.

Scheme 3. Early Examples of Enantioselective Hydrogenation of N -Acyl Enamines



chiral metal catalysts for the hydrogenations of enamines and imines, it is inevitable for this review to have some overlap with the contents in previous reviews⁶ or chapters of books.⁷ Recently, two comprehensive reviews concerning chiral amine synthesis and the mechanisms of transition metal-catalyzed enantioselective hydrogenation of functionalized enamines and imines have been published by Nugent and El-Shazly⁸ and Kalck and co-workers.⁹ This review covers the literature up to early 2010.

2. ENANTIOSELECTIVE HYDROGENATION OF ENAMINES

The first example of enantioselective hydrogenation of N -acyl enamines was reported by Kagan and Dang¹⁰ by using the ligand DIOP (**2**) in 1972. Although the ee value of the product was not more than 78%, this study opened a new approach to protected chiral amines (Scheme 3). After Noyori et al.¹¹ introduced a chiral ruthenium catalyst bearing ligand BINAP (**3**) in the hydrogenation of N -acyl-1-alkylidenetetrahydroisoquinolines, the level of enantioselectivity in the hydrogenation of N -acyl enamines was increased significantly to 99.5% ee. However, only

the (*Z*)-isomer of *N*-acyl tetrahydroisoquinoline derivatives was hydrogenated, whereas the (*E*)-isomer was recovered intact.

Ten years later, the rhodium catalysts based on diphosphine ligands, Me-DuPhos and Me-BPE, were used by Burk et al.¹² in the hydrogenation of *Z/E*-mixtures of β -substituted *N*-acyl α -arylenamines, and high enantioselectivities were obtained. This was an important finding because it demonstrated that both *Z*- and *E*-isomer of the enamide substrate are reduced with high enantioselectivity. Thereafter, many highly efficient rhodium catalysts based on chiral diphosphine ligands were developed, and the enantioselective hydrogenation of *N*-acyl enamines was dominated by chiral catalysts containing diphosphine ligands for a long time.

In 2002, Zhou and co-workers¹³ reported the first example of rhodium-catalyzed highly enantioselective hydrogenation of *N*-acyl α -arylenamines with monodentated phosphorus ligands, achieving a comparable or even better enantioselectivity than those obtained by using chiral catalysts with diphosphine ligands. Since then, many efficient chiral monodentated phosphorus ligands with various backbones have been developed and successfully applied in the rhodium or iridium-catalyzed enantioselective hydrogenation of *N*-acyl α -arylenamines.

The catalytic enantioselective hydrogenation of unprotected enamines, for example, *N,N*-dialkyl/arylenamines, is far less documented compared to *N*-acyl enamines. The first highly enantioselective hydrogenation of unprotected enamines was reported by Lee and Buchwald¹⁴ in 1994. By using a chiral *ansa*-titanium catalyst, they achieved high enantioselectivities in the hydrogenation of *N,N*-dialkyl α -arylethenamines. Recently, highly efficient rhodium- and iridium-catalyzed enantioselective hydrogenations of *N,N*-dialkylethenamines were developed by Zhou and co-workers.¹⁵ These catalytic enantioselective hydrogenations of unprotected enamines provide a direct method for the synthesis of chiral tertiary amines.

2.1. Enantioselective Hydrogenation of *N*-Acyl Enamines

Since the pioneering work of Kagan and Dang¹⁰ on rhodium-catalyzed enantioselective hydrogenation, which began with the (*E*)-*N*-(1-phenylprop-1-enyl)acetamide substrate using the diphosphine ligand DIOP (**2**), an enormous amount of rhodium catalysts bearing chiral phosphorus ligands have been developed for the enantioselective hydrogenation of *N*-acyl enamines. With these chiral rhodium catalysts and also chiral ruthenium and iridium catalysts, a wide range of acyclic and cyclic *N*-acyl enamines have been hydrogenated to enantiomerically enriched amines with good to excellent ee values (Scheme 4).

2.1.1. Chiral Rhodium Catalysts. Chiral rhodium catalysts based on either diphosphine ligands or monophosphorus ligands have received intensive studies in the past decades. A number of diphosphorus ligands, especially DuPhos, BPE, and DIOP type diphosphines, and atropisomeric biaryl and ferrocene-based diphosphorus ligands, as well as a wide range of monodentate phosphorus ligands including phosphoramidites, phosphites, phosphonites, and phosphines, have been proven to be effective for the rhodium-catalyzed enantioselective hydrogenation of *N*-acyl enamines.

2.1.1.1. Chiral Diphosphorus Ligands. In 1996, Burk et al.¹² made a breakthrough in enantioselective hydrogenation of enamides with rhodium catalysts containing diphosphine ligands DuPhos (**12**) and BPE (**13**) (Scheme 5). With these rhodium catalysts, a wide range of enamides **4** were hydrogenated to *N*-acetyl amines **5** with high enantioselectivities (up to 97.8% ee).

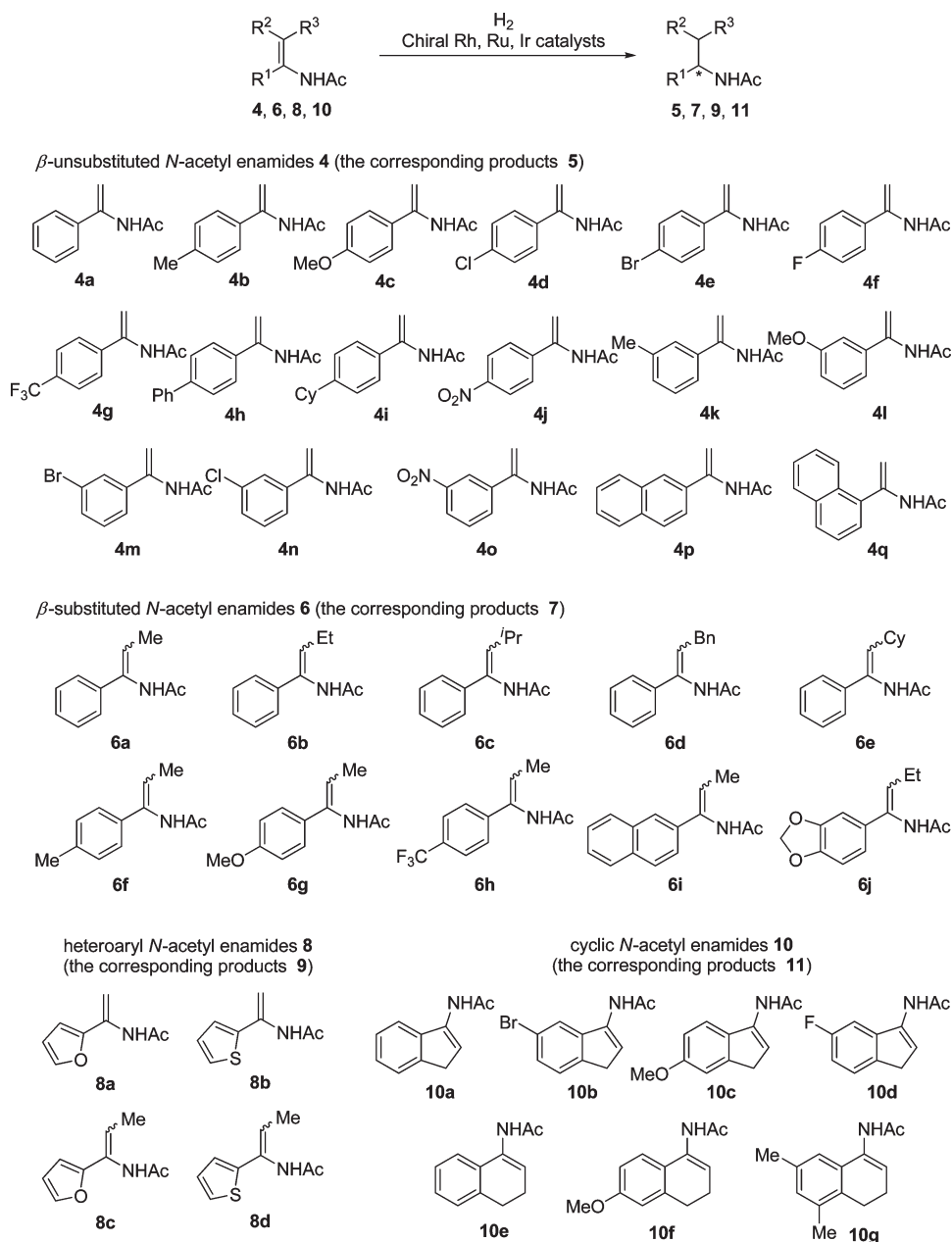
More importantly, these catalysts can hydrogenate the *Z/E*-mixtures of β -substituted α -arylenamines **6**, thus allowing the production of a diverse array of chiral amines **7** (95.4–98.5% ee). Subsequently, these rhodium catalysts were successfully applied in the hydrogenation of α -alkylenamines and cyclic enamides, affording chiral amines **15** (>99% ee) and a cyclic amine **11e** (92% ee) with high enantioselectivities and activities (for hydrogenation of α -alkylenamines **14a**, turnover number (TON) up to 5000 and turnover frequency (TOF) > 500 h⁻¹).¹⁶ It is furthermore to be noted that the bulky α -alkylenamines **14** were hydrogenated with opposite sense of chiral induction to that of α -arylenamines **4**. A computational modeling study reported by Feldgus and Landes suggested that the hydrogenation of α -alkyl- and α -arylenamines involves different coordination pathways.¹⁷

Encouraged by this pioneering work, many research groups have devoted their efforts to discovering new efficient chiral diphosphorus ligands for the rhodium- or other metal-catalyzed enantioselective hydrogenation of enamides, and a large number of chiral bidentate phosphorus ligands have been synthesized for these transformations. The prominent examples include DuPhos and BPE-type 1,2-diphosphines, DIOP-type 1,4-diphosphines, atropisomeric biaryl diphosphorus ligands, and the ferrocene-based diphosphorus ligands.

Chiral DuPhos and BPE-type Diphosphine Ligands. Since Burk et al.¹² reported excellent results of DuPhos and BPE ligands in the rhodium-catalyzed enantioselective hydrogenation of enamides, many 1,2-diphosphines sharing some features with DuPhos and BPE ligands have been developed and applied successfully to such a transformation for the synthesis of chiral amines (Figure 2).

In 1999, after the successful application of diphosphine Me-PennPhos (**16**) in the rhodium-catalyzed enantioselective hydrogenation of simple ketones,¹⁸ Zhang et al.¹⁹ used this conformationally rigid diphosphine ligand **16** in the enantioselective hydrogenation of enamides. Under the optimal reaction conditions (S/C = 100, 2.7 atm H₂, MeOH, room temperature (rt), 20 h), several cyclic enamides **10** derived from α -indanones and α -tetralones were hydrogenated to chiral cyclic amine derivatives **11** with high enantioselectivities (>97% ee) regardless of the substituents on the aromatic ring of the substrates. The tetrasubstituted cyclic enamides **24** derived from β -methyl α -indanone and α -tetralone can also be reduced to the corresponding cyclic amines with good to high enantioselectivities (**25a**, 98% ee; **25b**, 73% ee; Scheme 6). The hydrogenation of the cyclic enamide **10e** with this catalyst can be performed at S/C = 2000 to yield the chiral amine **11e** in 98% ee. However, lower enantioselectivities were obtained in the hydrogenation of the enamides derived from β -tetralone (**26a**, 71% ee) and acyclic α -arylenamines (**4a**, 75% ee; **6a**, 90% ee; **6h**, 88% ee). The ligand Binaphane **17**, also developed by Zhang and co-workers,²⁰ has a binaphthyl moiety and a rigid 1,2-bis(phosphino)benzene backbone, and the rhodium complex of this ligand showed high enantioselectivities (96–98% ee, Table 1) in the hydrogenation of α -arylenamines **4** under the optimized conditions. Notably, in the hydrogenation of the *Z/E*-mixtures of β -substituted α -arylenamines **6**, the rhodium catalyst with ligand **17** gives higher enantioselectivities (95–99.6% ee, Table 1) than the catalysts derived from DuPhos (**12**) and BPE (**13**).

Encouraged by the success of Me-PennPhos and Binaphane ligands, Zhang and co-workers subsequently developed DuPhos-type ligands **18**²¹ from the easily obtained D-mannitol, BPE-type ligands **19**²² and **20**.²³ The ligand **18b** showed high

Scheme 4. *N*-Acetyl Enamines and the Corresponding Amine Products

enantioselectivities in the rhodium-catalyzed enantioselective hydrogenation of α -arylenamides **4** (91–99% ee, Table 1) and cyclic enamide **10d** (96% ee) derived from 5-fluoroindanone in MeOH at room temperature for 24 h (S/C = 100). The ligand **19a** was effective for the hydrogenation of β -substituted α -arylenamides (93.1–99.5% ee, Table 1). The ligand **20** was found to be highly efficient for the hydrogenations of both α -arylenamides **4** and β -substituted α -arylenamides **6**. The enantioselectivities (97 to >99% ee, Table 1) achieved by the ligand **20** in the hydrogenation of β -substituted α -arylenamides **6** are comparable to or better than those obtained with ligands Me-DuPhos and BPE.

In 2003, Saito and co-workers²⁴ reported a series of C_1 -symmetric phosphine ligands UACPs (**21**) by replacing one of the chiral phospholane rings in Me-DuPhos ligands by an achiral

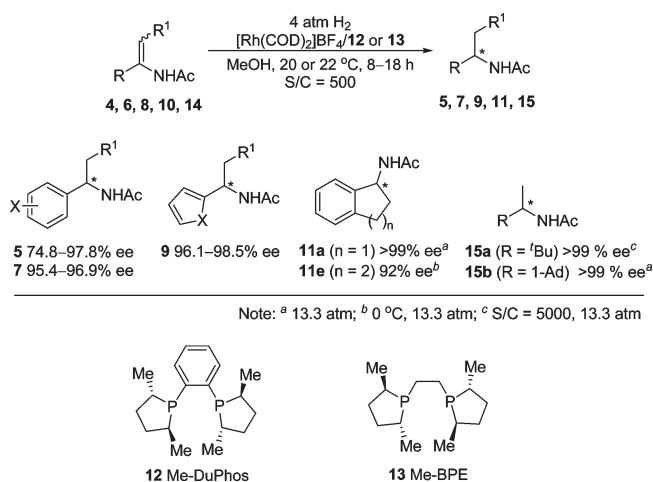
diphosphino group. Ligands **21** showed a remarkable enantioselectivity in the rhodium-catalyzed hydrogenation of the (*Z*)-*N*-benzoyl-1-phenylpropenamine ((*Z*)-**28**), giving 99% ee with 100% conversion within 15 h at 30 °C under 4 atm H₂ pressure in MeOH, which was better than that obtained by the ligand Me-DuPhos (**12**) (78% ee with 25% conversion) (Scheme 7). This result indicated that adjusting the phospholane ring of ligand Me-DuPhos can improve the enantioselectivity of catalysts for the hydrogenation of enamides.

In the study of enantioselective hydrogenation of dihydro- β -carboline derivatives for the synthesis of indole alkaloids with a tetrahydro- β -carboline framework, Beller and co-workers²⁵ found that the diphosphine ligand catASium MNXyF (**22a**)²⁶ is highly enantioselective (96% ee) for the rhodium-catalyzed

hydrogenation of exocyclic enamide **30**, a type of cyclic enamide with an exocyclic carbon double bond (Scheme 8). By further screening this type of diphospholane ligand, they found that the ligand MalPhos (**23**)²⁷ with a maleic anhydride backbone gave even higher enantioselectivity (97% ee).

Although some research groups are dedicated to finding highly efficient chiral DuPhos/BPE-type of diphosphine ligands for enamide hydrogenations, other groups engage themselves in the discovery of new enamide hydrogenations with the existing diphosphine ligands or applying them to the synthesis of pharmaceuticals. For the synthesis of optically active 3-substituted-3,4-dihydro-2*H*-1,4-benzoxazines **35** (Scheme 9), which represent the structure motifs of many naturally occurring substances and chiral drugs, Zhou et al.²⁸ studied the rhodium-catalyzed enantioselective hydrogenation of

Scheme 5. Enantioselective Hydrogenation of *N*-Acetyl Enamides with DuPhos and BPE



exocyclic enamides **34** and found that Me-DuPhos (**12**) is an effective ligand for such a transformation. Under the optimal conditions, a series of (*Z*)-3-arylidene-4-acetyl-3,4-dihydro-2*H*-benzoxazines **34** were reduced to optically active 3,4-dihydro-2*H*-1,4-benzoxazines **35** with high enantioselectivities (90.6–98.6% ee) regardless of the substituents on the aromatic ring of the substrates.

In 2002, Storace et al.²⁹ used Me-DuPhos (**12**) as a chiral ligand in the rhodium-catalyzed enantioselective hydrogenation of a *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)but-1-enyl)acetamide (**6j**) to prepare (*R*)-*N*-(1-(benzo[*d*][1,3]dioxol-5-yl)butyl)acetamide (**7j**), a key intermediate for the synthesis of an inhibitor of leukocyte elastase, DMP 777 (Scheme 10). Wang et al.³⁰ employed this hydrogenation to synthesize a potent, orally bioavailable Trk A/B inhibitor AZ 23 (Scheme 10).

Chiral DIOP-type Diphosphine Ligands. Owing to the fact that the seven-membered chelate ring of DIOP (**2**) metal complex is conformationally flexible, DIOP itself only provides moderate to good enantioselectivity for the rhodium-catalyzed hydrogenation of enamides. To overcome the drawback of DIOP ligand, Zhang and co-workers³¹ developed a 1,4-diphosphine BICP (**38**) ligand with two five-membered carbon rings on its

Scheme 6. Enantioselective Hydrogenation of Cyclic Enamides 24 and 26 with Rh-16

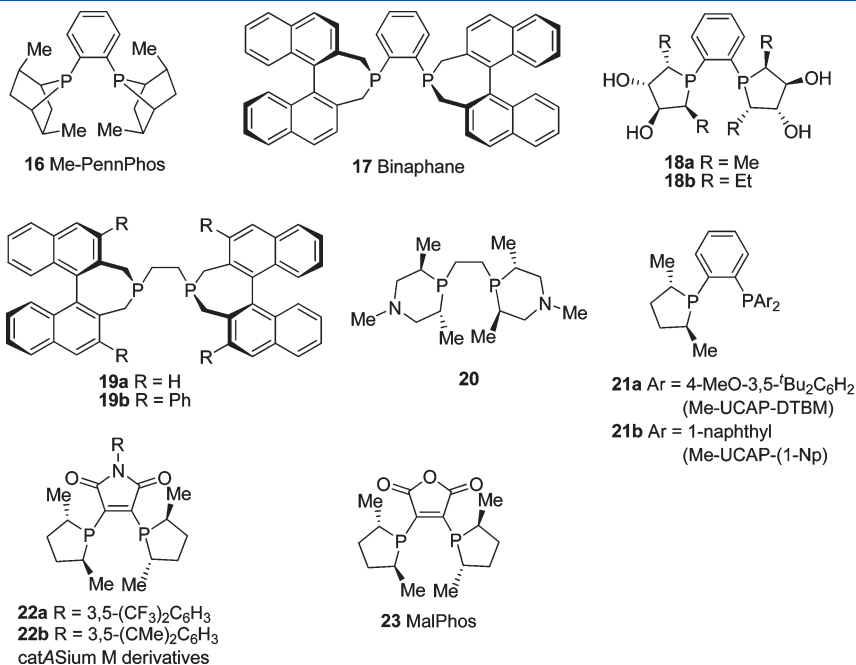
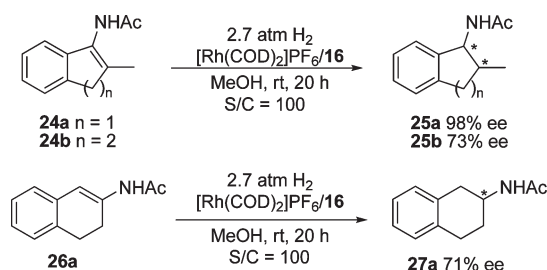


Figure 2. DuPhos and BPE-type diphosphine ligands.

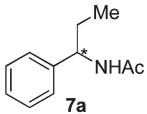
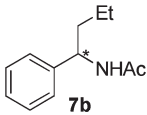
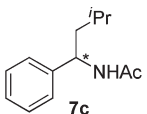
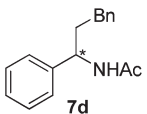
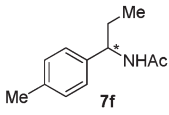
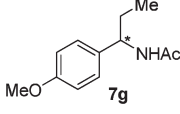
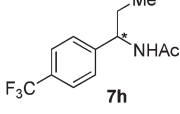
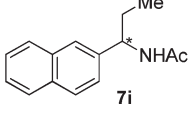
Table 1. Enantioselective Hydrogenation of Enamides **4** and **6** with Diphosphine Ligands **17**–**53b**

$\text{X-C}_6\text{H}_4\text{-CH=CH-R-NHAc} \xrightarrow[\text{solvent}]{\text{H}_2, [\text{Rh}(\text{COD})_2]\text{BF}_4/\text{L}^*} \text{X-C}_6\text{H}_4\text{-CH}_2\text{-CH(R)-NHAc}$

4 (R = H) **5** (R = H)
6 (R = Me, Et, etc.) **7** (R = Me, Et, etc.)

Product	Ligand (% ee)											
	17^a	18b^b	19a^c	20^d	38^e	40a^f	41a^g	42^g	43a^h	48ⁱ	49ⁱ	53b^j
 5a	90.0	96		96	86.3	98.3	93	93	98.5	92.9	96.8	99.5
 5b					86.1				98.6	95.1	97.0	99.7
 5c		95			91.6				99.0			99.5
 5d									97.8	94.9	97.0	98.2
 5e												99.9
 5f									97.9	90.1	96.0	99.2
 5g	82.0	98		98	86.4	97.7				95.1	99.0	
 5h	75.7			98	93.0	>99						
 5i	90.0			>99								
 5j	89.0			95	85.7	98.8				94.8	97.7	99.4
 5k												99.6
 5m												99.2
 5p	89.5	99		>99	85.2	>99			>99.0			99.3

Table 1. Continued

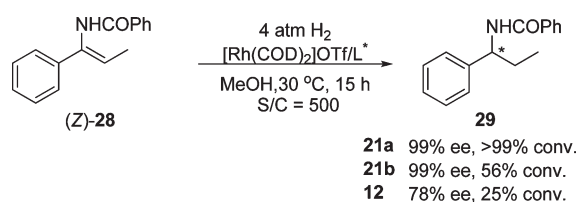
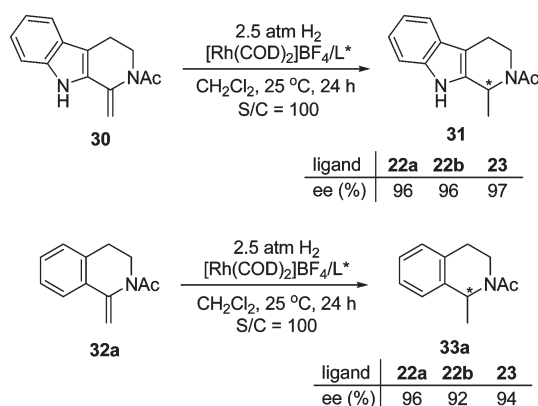
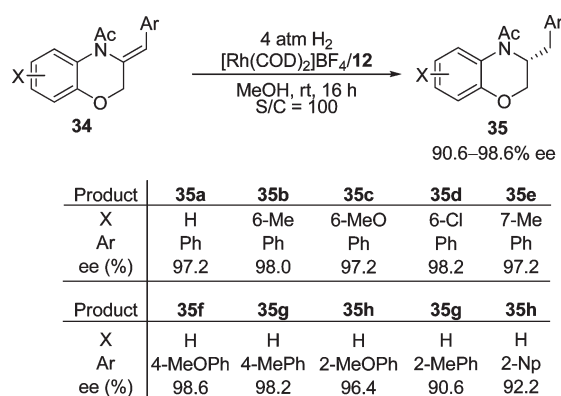
Product	Ligand (% ee)											
	17 ^a	18b ^b	19a ^c	20 ^d	38 ^e	40a ^f	41a ^g	42 ^g	43a ^h	48 ⁱ	49 ⁱ	53b ^j
 7a	99.1		97.5	99	95.0	97.3	98	97	>99.0			
 7b	97.0								>99.0			
 7c	97.6		97.7	98	93.5	99.0	98	98				
 7d	95.0			97	90.5	98.6	98	97				
 7f									99.0			
 7g	99.6	92	99.5	97	95.2	98.0	98	98	>99.0			
 7h	97.0	91	93.1	98	95.1	98.3	95	94				
 7i	98.3		99.5	>99	93.6	>99	97	97				

^a Reaction conditions: S/C = 100, 1.3 atm, CH₂Cl₂, rt, 24 h. ^b Reaction conditions: S/C = 100, 10 atm, MeOH, rt, 24 h. ^c Reaction conditions: S/C = 100, 2.7 atm, MeOH, rt, 24 h. ^d Reaction conditions: S/C = 100, 1 atm, CH₂Cl₂, rt, 24 h. ^e Reaction conditions: S/C = 100, 2.7 atm, toluene, rt, 24 h. ^f Reaction conditions: S/C = 100, 10 atm, MeOH, rt, 48–60 h. ^g Reaction conditions: S/C = 100, 3 atm, MeOH, rt, 24 h. ^h Reaction conditions: S/C = 100, 1 atm, CH₂Cl₂, rt, 12 h. ⁱ Reaction conditions: S/C = 200, 1 atm, tetrahydrofuran (THF), 5 °C, 0.5 h. ^j Reaction conditions: S/C = 200, 10 atm, toluene, 5 °C, 0.5–1 h.

backbone to increase the rigidity of the ligand (Figure 3). The BICP ligand was found to be efficient for the rhodium-catalyzed enantioselective hydrogenations of α -arylenamides³² and methoxymethyl (MOM)-protected β -hydroxy enamides.³³ Although the enantioselectivities of hydrogenations of α -arylenamides **4** and the *Z/E*-mixtures of β -substituted α -arylenamides **6** to the corresponding chiral amines **5** (85.2–93.0% ee) and **7** (90.5–95.2% ee) are a little lower than those obtained by the Rh-Me-DuPhos catalyst,¹² the Rh-BICP catalyst gives comparable or better results than the Rh-Me-DuPhos catalyst in the

hydrogenation of the *Z/E*-mixtures of MOM-protected β -hydroxy enamides (90–99% ee, Scheme 11). However, the Rh-BICP catalyst only provided moderate enantioselectivity in the hydrogenation of cyclic enamides **8a** (63.5% ee), **8b** (64.5% ee), and **32b** (Scheme 12, 77.8% ee).

Introduction of two alkyl substituents at the α -position of the diphenylphosphino groups to rigidify the ligand DIOP (**2**) was first reported by Kagan et al.³⁴ However, lower enantioselectivity than that of ligand DIOP (**2**) was obtained, presumably due to the two methyl groups in the ligand **39** (Figure 3) located in the

Scheme 7. Enantioselective Hydrogenation of (Z)-28 with UACPs Ligands 21**Scheme 8. Enantioselective Hydrogenation of Exocyclic Enamides 30 and 32a with Ligands 22 and 23****Scheme 9. Enantioselective Hydrogenation of Exocyclic Enamides 34 with Ligand Me-DuPhos**

axial positions of the chelated rhodium complex, resulting in a conformationally unfavorable catalyst for the hydrogenation. In 2000, Li and Zhang³⁵ and Yan and RajanBabu³⁶ independently developed the ligand DIOP* (40), which provided an excellent enantioselectivity in the rhodium-catalyzed hydrogenation of α -arylenamides. For the hydrogenations of a wide range of α -arylenamides including the *Z/E*-mixtures of β -substituted α -arylenamides, up to >99% ee's were achieved with the catalyst Rh-40a (R = Me) (Table 1).³⁵ This result is obviously better than those obtained with the Rh-BICP catalyst. Further study showed that increasing the size of the α -alkyl groups of the DIOP* ligand has little impact on the enantioselectivity or reactivity of reaction.³⁶

Further modifications of DIOP ligand were reported by Zhang and co-workers³⁷ and Lee et al.³⁸ It is enlightening that the equatorial orientation of all substituents in the metal–ligand seven-membered chelate ring of the Rh-DIOP* catalyst is the key for obtaining high enantioselectivity of hydrogenation. Zhang and co-workers³⁷ synthesized a series of conformationally rigid DIOP-type ligands 41 and 42 (SK-Phos) with a 1,4-dioxane ring (Figure 3). These ligands are highly efficient for the rhodium-catalyzed enantioselective hydrogenation of β -substituted α -arylenamides 6 (94–98% ee, Table 1) and MOM-protected β -hydroxy enamides 46 (96–99% ee, Scheme 11). Furthermore, the hydrogenation of a cyclic enamide 32b with the rhodium catalyst of ligand 41a yielded *N*-acetylsalsolidine (33b) in 94% ee (Scheme 12).

On the basis of the hypothesis that the consecutive *gauche* steric interactions between the *N*-substituents and phosphinomethyl groups of the ligands may restrict the conformational flexibility of the seven-membered metal chelate ring, Lee et al.³⁸ developed BDPMI ligands 43 containing an imidazolidin-2-one backbone (Figure 3). The *N*-alkyl groups of BDPMI ligands play an important role on the enantiocontrol of rhodium-catalyzed hydrogenation of α -arylenamides. With the rhodium complex of the ligand 43a as the catalyst, excellent enantioselectivities were achieved in the hydrogenation of α -arylenamides 4 (97.8 to >99.0% ee, Table 1) and the *Z/E*-mixtures of β -substituted α -arylenamides 6 ($\geq 99.0\%$ ee, Table 1).

Lee and co-workers³⁹ also introduced two methyls at the α -positions of the diphenylphosphino groups of the BDPMI ligand and developed BDPMI* ligand 44 (Figure 3). The BDPMI* ligand 44 showed nearly the same enantioselectivity as that obtained with BDPMI ligand 43a in the hydrogenation of enamide 4a (98.6% ee vs 98.5% ee). Moreover, to facilitate the separation and subsequent reuse of Rh-BDPMI catalyst, Lee et al.⁴⁰ introduced two imidazole moieties into the *N*-alkyl groups of BDPMI to make ligand 45. After treatment with trimethyloxonium tetrafluoroborate, the rhodium catalyst of the ligand 45 was immobilized in an ionic liquid. The resulting immobilized catalyst maintained high enantioselectivity (97% ee) and was reused three times for the hydrogenation of enamide 4a without any loss of catalytic efficiency. However, in the fourth run, the catalytic activity was decreased.

Chiral Atropisomeric Biaryl Diphosphine Ligands. BINAP is the first chiral atropisomeric biaryl diphosphine ligand applied in the catalytic enantioselective hydrogenation of enamides. In 1986, Noyori et al.¹¹ reported that the ruthenium complex of BINAP is a highly efficient catalyst for the hydrogenation of (*Z*)-*N*-acyl tetrahydroisoquinoline derivatives, offering a series of tetrahydroisoquinolines with up to 99.5% ee. However, the rhodium complex of BINAP gives lower enantioselectivities (<76% ee) for this transformation.⁴¹ In 1998, Chan and co-workers⁴² developed a new type of binaphthyl or H₈-binaphthyl-based bisaminophosphine ligands BDPAP (48) and H₈-BDPAP (49, Figure 4) and demonstrated that these atropisomeric diphosphorus ligands are highly effective in the rhodium-catalyzed enantioselective hydrogenation of α -arylenamides with excellent enantioselectivities. Under the optimal conditions, a variety of α -arylenamides 4 were hydrogenated to chiral amides with 90.1–99.0% ee (Table 1) by using H₈-BDPAP ligand.

In 2002, Zhang and co-workers⁴³ used a 3,3'-diphenyl-substituted BIPHEP ligand *o*-Ph-hexaMeO-BIPHEP (50)

Scheme 10. Enantioselective Synthesis of DMP 777 and AZ 23

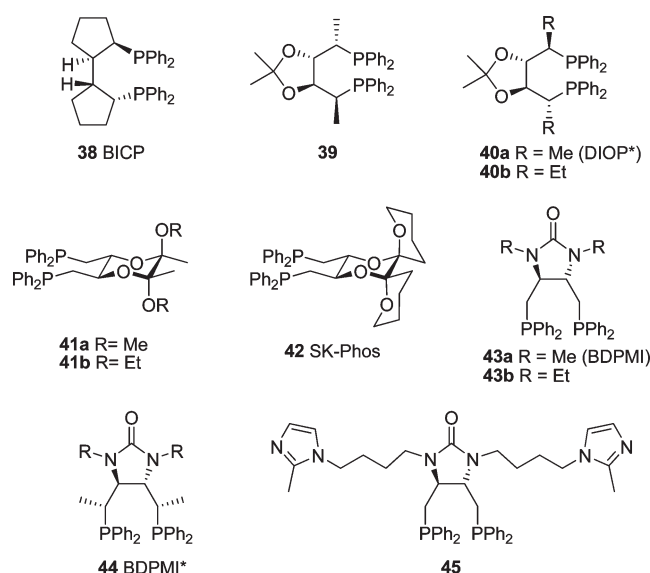
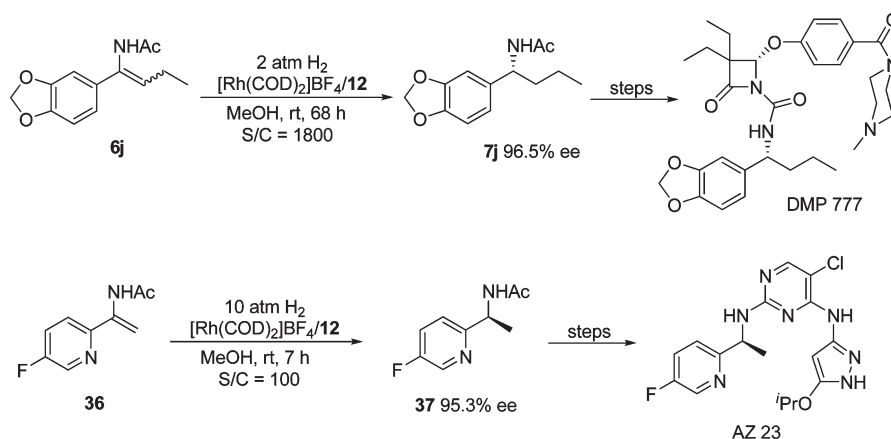
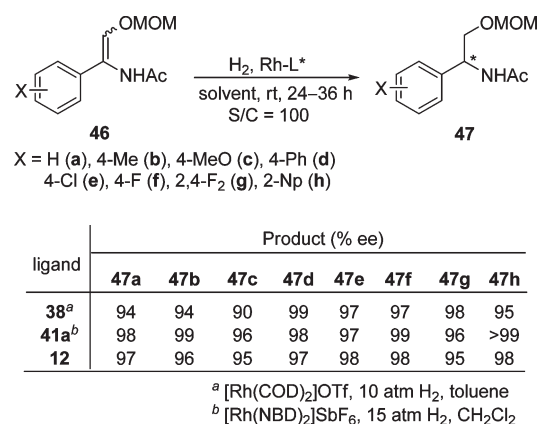


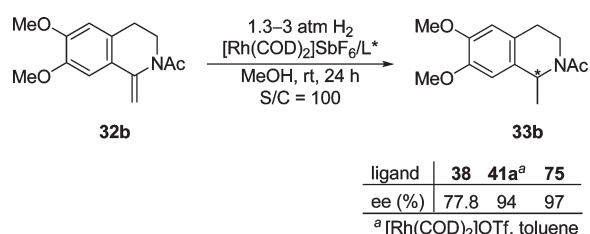
Figure 3. DIOP-type of 1,4-diphosphine ligands.

developed by themselves in the rhodium-catalyzed hydrogenation of enamides and found that the ligand **50** was very efficient for the hydrogenation of cyclic enamides. The hydrogenation of enamide **10e** derived from α -tetralone with the catalyst Rh/**50** gave cyclic amine **11e** with 98% ee under the conditions of 1.7 atm of H_2 pressure and $-20^\circ C$ in CH_2Cl_2 for 24 h ($S/C = 200$). This was comparable with the best results obtained with Penn-Phos ligand (**16**) and significantly better than those observed with other chiral biaryl phosphine ligands, such as hexaMeO-BIPHEP, MeO-BIHEP, and BINAP, showing a strong influence of *o*-phenyl groups of the ligand **50** on enantioselectivity of reaction. In the hydrogenation of a tetrasubstituted cyclic enamide **24a** (Scheme 6), derived from a β -methyl- α -indanone, the ligand **50** also gave as high as 99% ee with full conversion. However, very low enantioselectivity (37% ee) was observed for the hydrogenation of a tetrasubstituted cyclic enamide **24b**. The rhodium catalyst with ligand **50** has been successfully applied in the enantioselective hydrogenation of a racemic cyclic carbamate **56** for the synthesis of a chiral precursor of sertraline ((1*S*,4*S*)-**57**) (Scheme 13).

Scheme 11. Enantioselective Hydrogenation of MOM-Protected β -Hydroxy Enamides **46**

The *ortho*-substituted BINAPo ligand **51** (*o*-BINAPo), developed by Zhou and Zhang,⁴⁴ gave high enantioselectivities for the hydrogenation of enamides **4**. Up to 96.3% ee was obtained with the rhodium catalyst containing ligand **51b**, which has phenoxy groups at the 3,3'-positions of the binaphthyl backbone. However, the BINAP ligand **52**, which has alkoxy substituents at the 3,3'-positions, only provided moderate to good enantioselectivities for the rhodium-catalyzed enantioselective hydrogenation of the substrate **4a**.⁴⁵ Wang et al.⁴⁶ recently developed a new type of bisaminophosphine ligands **53** based on a 4,4',6,6'-tetrakis-trifluoromethylbiphenyl structure. These bisaminophosphine ligands **53** exhibited extremely high enantioselectivities (97.6–99.9% ee, Table 1) in the rhodium-catalyzed enantioselective hydrogenation of enamides **4** even at a catalyst loading of 0.1 mol %. Binaphthyl-based triphosphorus bidentate phosphine–phosphoramidite ligands **54** were reported by Zhang⁴⁷ in 2006. These ligands showed excellent enantioselectivities in the rhodium-catalyzed enantioselective hydrogenation of α -arylenamides, especially the *ortho*-substituted α -arylenamides (Scheme 14). The hydrogenation of an α -(1-naphthyl)enamide (**4q**) lead to chiral (*R*)-1-(1-naphthyl)ethylamine (**5q**), a key precursor to Cinacalcet hydrochloride for treatment of hyperparathyroidism and hypercalcemia⁴⁸ (Scheme 15).

Scheme 12. Enantioselective Hydrogenation of Cyclic Enamide 32b



Scheme 13. Enantioselective Synthesis of the Chiral Precursor of Sertraline

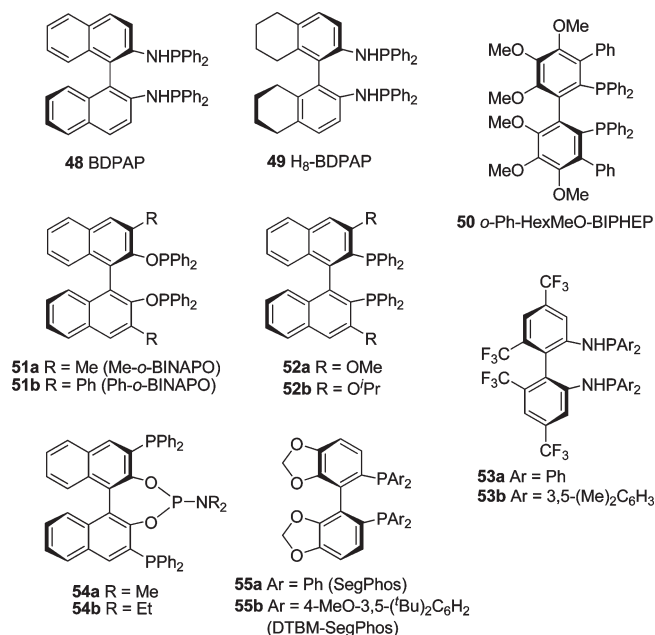
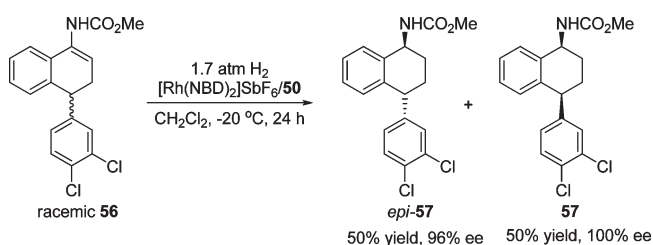
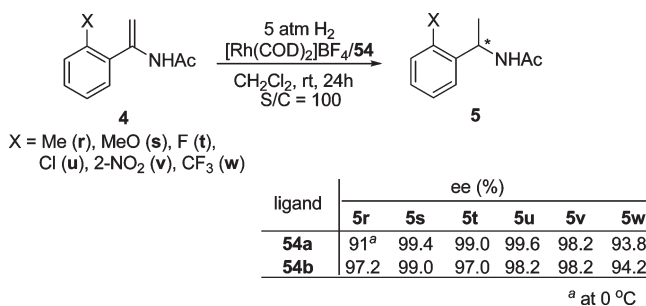


Figure 4. Atropisomeric biaryl diphenylphosphorus ligands.

With DTBM-SegPhos (**55b**) as the ligand, Lu and co-workers⁴⁹ achieved highly enantioselective hydrogenation of the trisubstituted or disubstituted exocyclic double bond of *N*-tosyl-4-alkyl-1,3-oxazolin-2-ones **58**, which are enamides in nature. Under the conditions of 30 °C and 60 atm H₂ pressure in toluene for 4 days (S/C = 100), a series of *N*-tosyl-4-alkyl-1,3-oxazolin-2-ones **58** were reduced to the corresponding enantiomerically enriched *N*-tosyl-4-alkyl-1,3-oxazolidin-2-ones **59** in quantitative yields with high enantioselectivities (up to 99% ee, Scheme 16). This provides a novel access to chiral *N*-tosyloxazolidinones, which can be converted into optically active amino acids, amino alcohols, and piperidine derivatives.

Chiral Ferrocene-Based Diphosphine Ligands. Diphosphorus ligands with ferrocene backbone also showed high enantioselectivity in the rhodium-catalyzed enantioselective hydrogenation of enamides. In 2000, Kagan and co-workers⁵⁰ developed chiral diphosphine ligands **60** and **61** with only the planar chirality of ferrocene (Figure 5). They found that the ligand **60b** with a PCy₂ group and a PPh₂ group gave 94% ee in the hydrogenation of the β -substituted enamide (*Z*)-**6a** under 1 atm H₂ at room temperature, whereas the ligand **60a** with two PPh₂ groups provided a poor enantioselectivity (65% ee). The ligand **61a** with a PCy₂ group direct linked to the ferrocene ring

Scheme 14. Enantioselective Hydrogenation of *ortho*-Substituted α -Arylenamides **4** with Ligand **54**

gave a moderate ee value (82% ee). These results demonstrated that the chiral 1,3-diphosphinylferrocene ligand **60b** is better than the corresponding chiral 1,2-diphosphinoferrocene ligand **61a**.

The ferrocene-based 1,5-diphosphines **62** (TanaiPhos, Figure 5) were developed by Knochel and co-workers⁵¹ in 1999. Although these ligands gave excellent results in the ruthenium-catalyzed enantioselective hydrogenation of 1,3-dicarbonyl compounds, only moderate enantioselectivities were obtained in the rhodium-catalyzed hydrogenation of enamides. For the hydrogenation of the *Z/E*-mixtures of β -substituted enamide **6b**, ligands **62a** and **62b** gave 68 and 76% ee, respectively.⁵² Subsequently, they developed a new type of ligands **63** bearing an α -*S*-configurational methoxy group.⁵³ These new ligands gave high enantioselectivities (92–97% ee) in the rhodium-catalyzed hydrogenation of α -arylethenamides **4** under mild reaction conditions (S/C = 100, 1 atm H₂, 25 °C, MeOH/toluene, 1.5–15 h). These results showed that the ligand **63**, containing a methoxy group with an α -*S*-configuration, gives better enantioselectivity than the ligand **62**, containing a dialkylamino group with an α -*R*-configuration, in the rhodium-catalyzed hydrogenation of enamides. Chen et al.⁵⁴ recently reported that the *P*-chiral 1,5-diphosphinoferrocene ligands **64** (PingFer), sharing the same skeleton with the ligand **63**, showed even better enantioselectivity in the rhodium-catalyzed hydrogenation of α -arylethenamides **4**. Under the conditions of 6.7 atm H₂ pressure and room temperature in MeOH at S/C = 200, the ligand **64b** gave 96.3% ee for the reduction of the substrate **4a**, whereas the ligand **63a** provided 86.4% ee, demonstrating that the introduction of *P*-chirality into the ferrocene-based phosphine ligands enhances the enantioselective discrimination of catalysts.

Scheme 15. Enantioselective Synthesis of Cinacalcet Hydrochloride via Enamides Hydrogenation

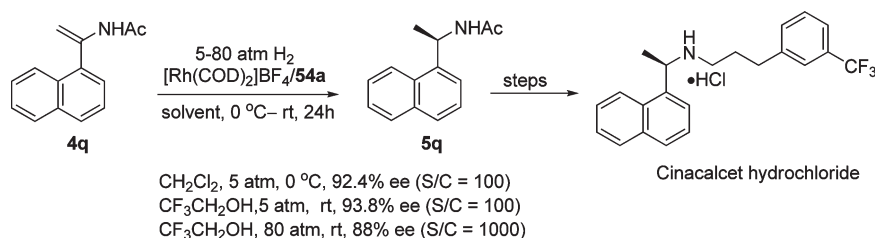
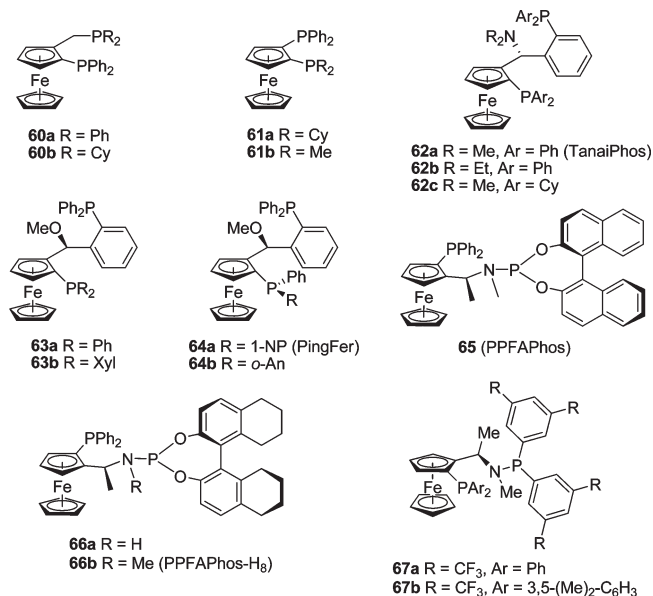
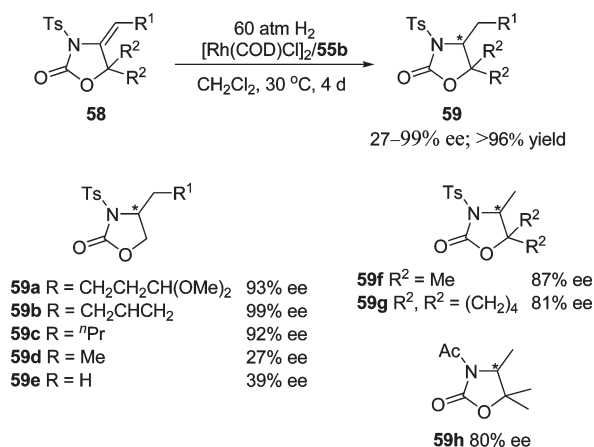
Scheme 16. Enantioselective Hydrogenation of *N*-Tosyl-4-alkyl-1,3-oxazolin-2-ones 58

Figure 5. Ferrocene-based diphosphorus ligands.

In 2004, Hu and Zheng⁵⁵ introduced a new family of highly efficient unsymmetrical phosphine–phosphoramidite ligands **65** (PPFAPhos, Figure 5) containing a ferrocenyl backbone and an axially chiral binaphthyl moiety for the rhodium-catalyzed enantioselective hydrogenation of enamides. Under the optimal conditions, several enamides **4** were hydrogenated to the corresponding hydrogenated products **5** with excellent enantioselectivities (98.7–99.6% ee, Table 2) by using the chiral ligand **65**. When the catalyst loading was decreased to as low as 0.02 mol % (S/C = 5000), a high enantioselectivity was still obtained. The similar phosphine–phosphoramidite ligands **66** with a more rigid H₈–binaphthyl moiety were also introduced by Zheng and co-workers⁵⁶ in 2005. In contrast, however, these H₈–binaphthyl-derived ligands **66** exhibited somewhat lower enantioselectivity than the analogue binaphthyl ligand **65** in the rhodium-catalyzed hydrogenation of enamides (Table 2).

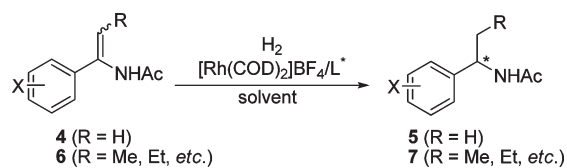
The fluorinated phosphinoferrocenylaminophosphine ligands **67** were introduced into the rhodium-catalyzed enantioselective hydrogenation of enamides by Chan and co-workers⁵⁷ in 2005. Among these ligands, the ligand **67a** gave good to high enantioselectivities (98.3–99.7% ee, Table 2) in the hydrogenation of enamides **4** (S/C = 500, 20 atm H₂, 5 °C, 30 h). It is worthy of note that the rhodium complex of ligands **67** was very stable to air and moisture either in solid or in solution, and the reactions can be performed in air or in water-containing solvent.

In 2006, Allwein et al.⁵⁸ employed the Josiphos type ligands **1** in the rhodium-catalyzed enantioselective hydrogenation of

N-trifluoroacetyl α -arylethenamines **68** and found that both ligands **1b** and **1c** performed very well, providing the corresponding chiral *N*-trifluoroacetyl amines **69** in good ee values (92–97% ee, Scheme 17).

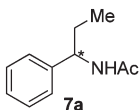
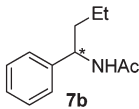
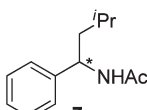
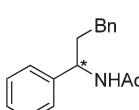
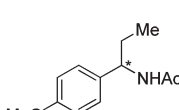
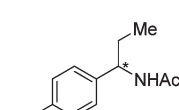
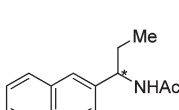
In 2008, Wallace et al.⁵⁹ successfully applied Josiphos-type ligand **1d** in the rhodium-catalyzed enantioselective hydrogenation of the tetrasubstituted enamide **70**, leading to the synthesis of a cannabinoid-1 receptor (CB1R) inverse agonist taranabant (**72**, Scheme 18). Under the optimal conditions of 10 atm H₂ pressure and only 0.05 mol % of catalyst derived from [Rh(NBD)₂]BF₄ and ligand **1d** in trifluoroethanol (TFE), the enamide **70** was hydrogenated to the corresponding chiral amide **71** in 96% ee with quantitative conversion.

***P*-Chiral Diphosphine Ligands.** Diphosphine ligands with chirality on the *P*-atoms represents another type of very important chiral phosphorus ligands for the rhodium-catalyzed enantioselective hydrogenation of enamides. Because the early *P*-chiral diphosphine ligands such as DIPAMP reported by Knowles in 1970s⁶⁰ are unstable and difficult to synthesize, the development of this type of chiral diphosphine ligands has been slow. It was not until ligands BisP* (**73**, Figure 6) reported by Imamoto et al.⁶¹ in 1998 that the *P*-chiral diphosphine ligands regained significant attention. To date, many efficient *P*-chiral diphosphine ligands have been developed, and some of them showed high enantioselectivity in the enantioselective hydrogenation of enamides. In 2001, Gridnev, Imamoto, and

Table 2. Enantioselective Hydrogenation of Enamides **4** and **6** with Diphosphorus Ligands

Product	Ligand (% ee)											
	65 ^a	66b ^b	67a ^c	73a ^d	74a ^d	75 ^e	79 ^f	92b ^g	93 ^h	94 ^g	95b ^h	97 ⁱ
	99.6	96.9	98.3	99	66	>99	99	99.5	99.7	96	93.4	97
		96.4	99.4					99.1	99.8	96	96.4	85
		97.1	99.3	96	86		99	99.8				77
	98.8	95.5		99	88			98.5	99.9	99	95.8	
	99.0	96.0	99.7				99	98.8	99.8	98	97.0	91
	98.7											
	99.2	98.3	98.6			>99	>99	99.0	99.4	98	96.3	
			98.5			99	>99					94
						>99						
		99.0	99.0	97	87			99.9	99.9	96	96.4	
						>99						
				93	71							
						>99	98					94

Table 2. Continued

Product	Ligand (% ee)											
	65 ^a	66b ^b	67a ^c	73a ^d	74a ^d	75 ^e	79 ^f	92b ^g	93 ^h	94 ^g	95b ^h	97 ⁱ
						98				96		
									99.1			
						98						
						99						
						98				94		
						98						
						99						

^a Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 1 h. ^b Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 24 h. ^c Reaction conditions: S/C = 500, 20 atm, THF, 5 °C or rt, 16 or 30 h. ^d Reaction conditions: S/C = 100, 3 atm, MeOH, rt, 24–30 h. ^e Reaction conditions: S/C = 100, 1.3 atm, MeOH, rt, 12 h. ^f Reaction conditions: S/C = 100, 6.7 atm, CH₂Cl₂, 0 °C, 12 h. ^g Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 12 h. ^h Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 24 h. ⁱ Reaction conditions: S/C = 100, 6 atm, toluene, 25 °C, 20 h.

co-workers⁶² used ligands BisP* (73) and MiniPhos (74)⁶³ in the rhodium-catalyzed enantioselective hydrogenation of α -aryl- and alkylenamides. They found that the rhodium catalyst with ligand ^tBu-BisP* (73a) is highly efficient for the hydrogenation of the α -arylenamides **4** with *meta*- or/and *para*-substituents on the phenyl ring, providing the corresponding chiral amine derivatives **5** with ee values of 93–99% (Table 2). However, lower enantioselectivities (~50% ee) were obtained for the hydrogenation of enamides **4** with *ortho*-substituents. The ligand ^tBu-MiniPhos (74a) showed lower enantioselectivities for the α -arylenamide substrates **4** (Table 2). For the hydrogenation of α -alkylenamides such as *tert*-butyl- (14a) and 1-admantylamide (14b), both ^tBu-BisP* (73a) and MiniPhos (74a) ligands gave as high as 99% ee of enantioselectivity. The Rh-^tBu-BisP* catalyst has been applied in the enantioselective synthesis of acetylcholinesterase inhibitor SDZ-ENA-713 (Scheme 19).

In 2001, Tang and Zhang⁶⁴ reported a new type of *P*-chiral diphosphine ligand TangPhos (75) with two five-membered rings in the backbone (Figure 6). They found that the ligand TangPhos is highly efficient for the rhodium-catalyzed enantioselective hydrogenation of α -arylenamides. A variety of α -arylenamides **4** and the *Z/E*-mixtures of β -substituted enamides **6** were reduced under mild reaction conditions by the Rh-TangPhos catalyst to enantiomerically enriched amines with excellent enantioselectivities (>98% ee, Table 2). The hydrogenation of cyclic enamide **32b** also proceeded smoothly with this Rh-TangPhos catalyst, yielding the (R)-(-)-*N*-acetyl salso-lidine (**33b**) in quantitative yield with 97% ee (Scheme 12). It is worthy to mention that the rhodium complex of TangPhos (75) is an extremely efficient chiral catalyst (up to 10 000 TON and 99.3% ee) for the hydrogenation of the model substrate **4a**. The Rh-TangPhos catalyst was also used in the enantioselective

hydrogenation of *N*-phthaloyl enamines. Under the conditions of 30 atm H₂ pressure and 25 °C in ethyl acetate for 18 h (S/C = 100), *N*-phthaloyl α -arylenamines **84** with *meta*- and *para*-substituents were reduced to the corresponding chiral amines **85** in >97% ee (Scheme 20).⁶⁵

Very recently, Zhang and co-workers⁶⁶ reported that the Rh-TangPhos catalyst is highly enantioselective for the hydrogenation of (*Z*)-isomers of β -arylenamides (Scheme 21). Under the optimal conditions (S/C = 100, 30 atm H₂, EtOAc, rt, 20 h), the substrate (*Z*)-*N*-(1-phenylprop-1-en-2-yl)-acetamide (**86a**) (R = Me, Ar = Ph) was reduced to the chiral 2-phenylisopropylamine (**87a**) in 99.3% ee; however, the corresponding (*E*)-isomer gave very low enantioselectivity (32% ee). A variety of (*Z*)- β -arylenamides **86** have been hydrogenated by Rh-TangPhos catalyst, and as high as up to >99.9% ee was achieved. It is worth mentioning that this hydrogenation provides a practical method for the preparation of β -arylisopropylamines, an important class of chiral compounds with valuable pharmaceutical applications. For example, (*S*)-amphetamine, a useful stimulant with strong biological and physiological effects, selegiline for treatment of Alzheimer's disease, and important chiral drugs such as (*R,R*)-formoterol and (*R*)-tamsulosin can be prepared by this hydrogenation method (Scheme 21).

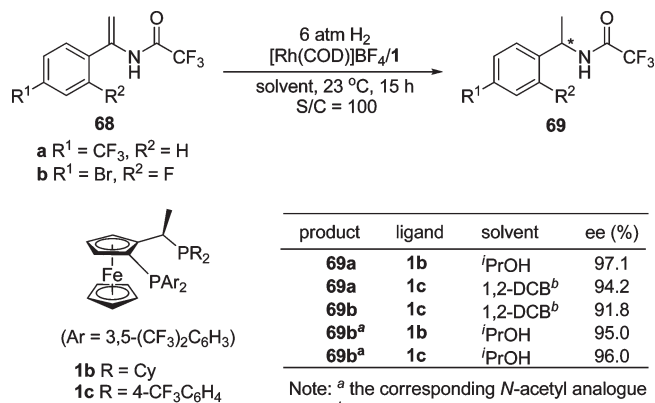
A *P*-chiral diphosphine ligand DisquareP* (**76**) with two four-membered rings in the backbone was developed by Imamoto

et al. in 2004.⁶⁷ This ligand also gave high enantioselectivities (up to >99% ee) for the rhodium-catalyzed hydrogenation of α -arylenamides **4a** (>99% ee) and **4c** (99% ee). However, for the hydrogenation of β -substituted α -arylenamides **6**, only the (*Z*)-isomer gave high enantioselectivity. For example, the (*Z*)-isomer of β -methyl- α -phenylamide ((*Z*)-**6a**) was reduced by catalyst Rh-DisquareP* to the amide **7a** in perfect enantioselectivity (>99% ee). In sharp contrast, the hydrogenation of the (*E*)-isomer yielded the chiral amide **7a** with only 37% ee.

Another highly electron-donating and conformationally rigid *P*-chiral diphosphine DuanPhos (**77**), a benzo derivative of TangPhos ligand, was developed by Liu and Zhang⁶⁸ in 2005. The rhodium complex of DuanPhos ligand exhibited remarkably high enantioselectivities for the hydrogenations of α -arylenamide **4a** (>99% ee), the *Z/E*-mixtures of β -substituted α -arylenamides **6g** and **6h** (99% ee), and the cyclic enamide **10a** (98% ee).⁶⁹

Considering that the trialkyl *P*-chiral diphosphine ligands are extremely sensitive to air owing to the high electron density at the *P*-atoms, as well as that this drawback has prevented their widespread application in asymmetric catalysis, Imamoto et al.⁷⁰ developed a new air-stable *P*-chiral diphosphine ligand QuinoxP* (**78**) in 2005. The ligand ^{*t*}Bu-QuinoxP* (**78a**) exhibited excellent enantioselectivities in the rhodium-catalyzed hydrogenation of the α -arylenamide **4a** (99.9% ee) and α -alkylenamide **14b** (96.3% ee). In addition to ^{*t*}Bu-QuinoxP*, the ligand Ad-QuinoxP*

Scheme 17. Enantioselective Hydrogenation of *N*-Trifluoroacetyl α -Arylethenamides **68**



Scheme 18. Enantioselective Synthesis of Taranabant (72**)**

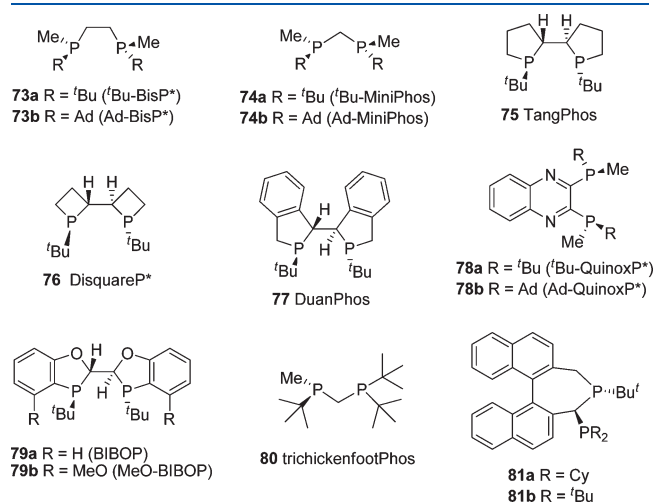
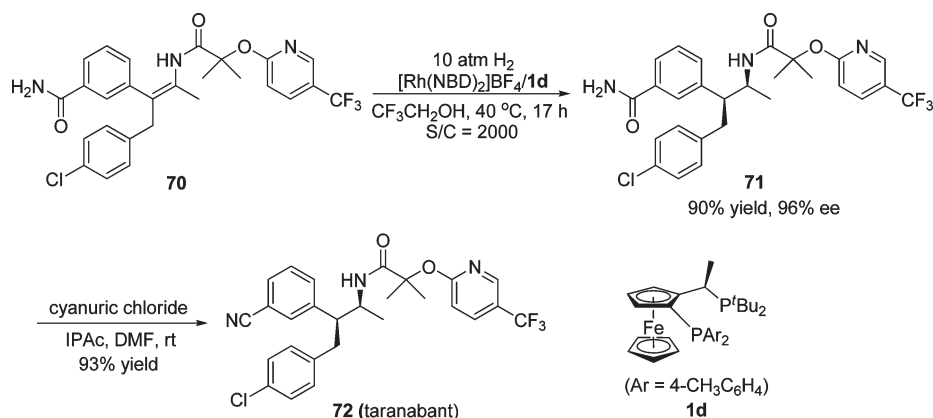
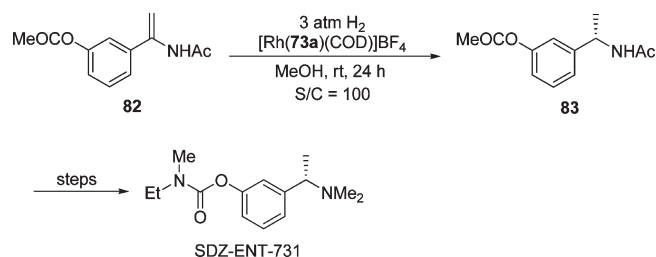
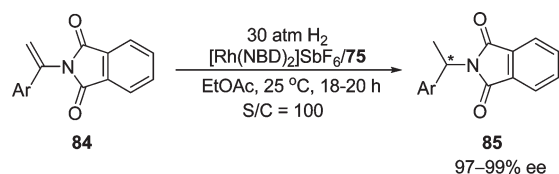
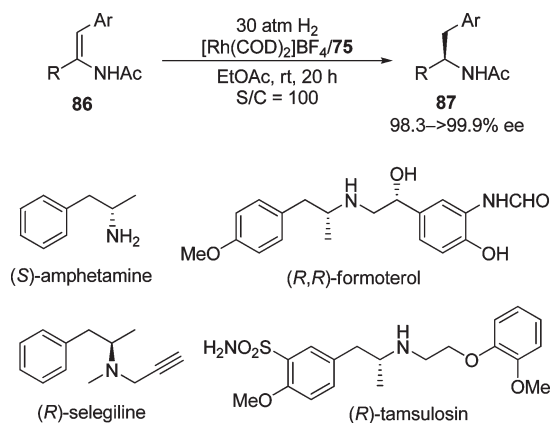


Figure 6. *P*-Chiral diphosphine ligands.

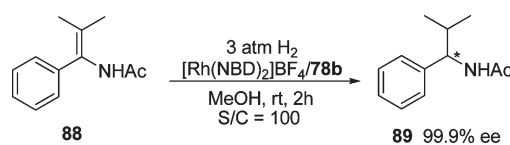
Scheme 19. Enantioselective Synthesis of SDZ-ENA-713

Scheme 20. Enantioselective Hydrogenation of *N*-Phthaloyl α -Arylenamides **84**Scheme 21. Enantioselective Hydrogenation of (*Z*)- β -Arylenamides **86**

(**78b**) with more bulky 1-adamantyl (Ad) groups also has excellent enantioselectivity in the rhodium-catalyzed enamide hydrogenation.⁷¹ In the hydrogenation of the tetrasubstituted enamide **88** catalyzed by Rh-**78b**, the chiral amide **89** was obtained with 99.9% ee (Scheme 22).

In 2010, Tang et al.⁷² developed another type of air-stable *P*-chiral diphosphine ligands BIBOPs (**79**) with a rigid bisdihydrobenzo[*d*][1,3]oxaphosphole structure. The comparison of ligands **79** in the rhodium-catalyzed hydrogenation of α -arylenamides showed that the ligand **79a** with no substituent at the 4,4'-position of backbone has the highest enantioselectivity. Under the conditions of 0 °C and 6.7 atm H₂ in dichloromethane (DCM) for 12 h (S/C = 100), a series of α -arylenamides **4** were reduced to chiral amines **5** in $\geq 99\%$ ee (Table 2). The turnover numbers of hydrogenation of the enamide **4g** were up to 2000 (S/C = 2000, $>99\%$ ee).

Recently, C₁-symmetric *P*-chiral diphosphines were also reported to have high enantioselectivity in the rhodium-catalyzed hydrogenation of enamides. Typical examples are the ligand

Scheme 22. Enantioselective Hydrogenation of Tetrasubstituted Enamide **88**

trichickenfootPhos (**80**)⁷³ and ligands **81**,⁷⁴ which showed high enantioselectivities in the rhodium-catalyzed hydrogenation of the α -arylenamide **4a** (98% ee) and the α -alkylenamide **14a** (99% ee). However, only moderate to good enantioselectivities were obtained for the hydrogenation of the α -arylenamide **4h** (80% ee) with ligand **81b** and the cyclic tetraenamide **24a** (85% ee) with ligand **81a**.

Other Chiral Diphosphine Ligands. Recently, many diphosphine ligands based on various backbones have been developed, and some of them have showed high enantioselectivity in the hydrogenation of enamides. In 2005, Kadyrov et al.⁷⁵ reported that the diphosphine **90** (Figure 7) containing a bornene backbone is a highly efficient chiral ligand for the rhodium-catalyzed enantioselective hydrogenation of α -*tert*-butyl/arylenamides (**14a** and **4**), especially the α -arylenamides **4** with electron-withdrawing substituents. The reaction proceeded smoothly with a substrate-to-catalyst ratio of S/C = 100 at ambient temperature to give the hydrogenation products in almost quantitative yield with 84–99% ee by using ligands **90a** and **90b**, whereas the catalyst derived from the ligand **90c** gave low asymmetric induction.

AaPhos (**91**) ligand with a cyrhetrene backbone developed by Bolm and co-workers⁷⁶ showed a good enantioselectivity in the hydrogenation of α -arylenamide **4a**. With the catalyst generated from [Rh(COD)₂]BF₄ and the ligand **91b**, the hydrogenation of the α -arylenamide **4a** gave the chiral 1-phenylethylamine (**5a**) in 93% ee.

The easily synthesized phosphine–phosphoramidite ligands **92** (PEAphos) with phenylethylamine and binaphthyl moieties was developed by Zheng and co-workers⁷⁷ in 2006. The PEA-Phos ligands showed high enantioselectivity in the rhodium-catalyzed hydrogenation of *N*-acetyl α -arylenamine **4a**, with the ligand **92b** being the most enantioselective (99.5% ee, Table 2).

THNAPhos ligands **93**, an analogue of PEAphos ligands, with a rigid 1,2,3,4-tetrahydronaphthylamine backbone, were also developed by Zheng and co-workers⁷⁸ in 2007. With the matched configurations, the THNAPhos ligands gave higher enantioselectivities (99.3–99.7% ee, Table 2) than those obtained with the PEAphos ligand **92b** in the hydrogenation of *N*-acetyl α -arylenamines **4** under the same reaction conditions (Table 4).⁷⁹ Moreover, the rhodium catalyst of the ligand **93** was also effective for the hydrogenation of the *Z/E*-mixtures of *N*-acetyl β -ethyl substituted 1-phenylmethanamine (**6b**), affording the chiral amine **7b** in up to 99.1% ee. By replacing the 1,2,3,4-tetrahydro-1-naphthylamine moiety of the ligand **93** with a 1-naphthylamine to form the phosphine–phosphoramidite, ligand **94** (HY-Phos), which has only an axial chirality, was prepared.⁸⁰ Compared with the ligand THNAPhos (**93**), the ligand HY-Phos (**94**) displayed somewhat lower enantioselectivity (96–99% ee vs 99.3–99.7% ee, Table 2) in the hydrogenation of the disubstituted α -arylenamides **4** but significantly higher enantioselectivities (91–96% ee vs 78–91% ee) in the

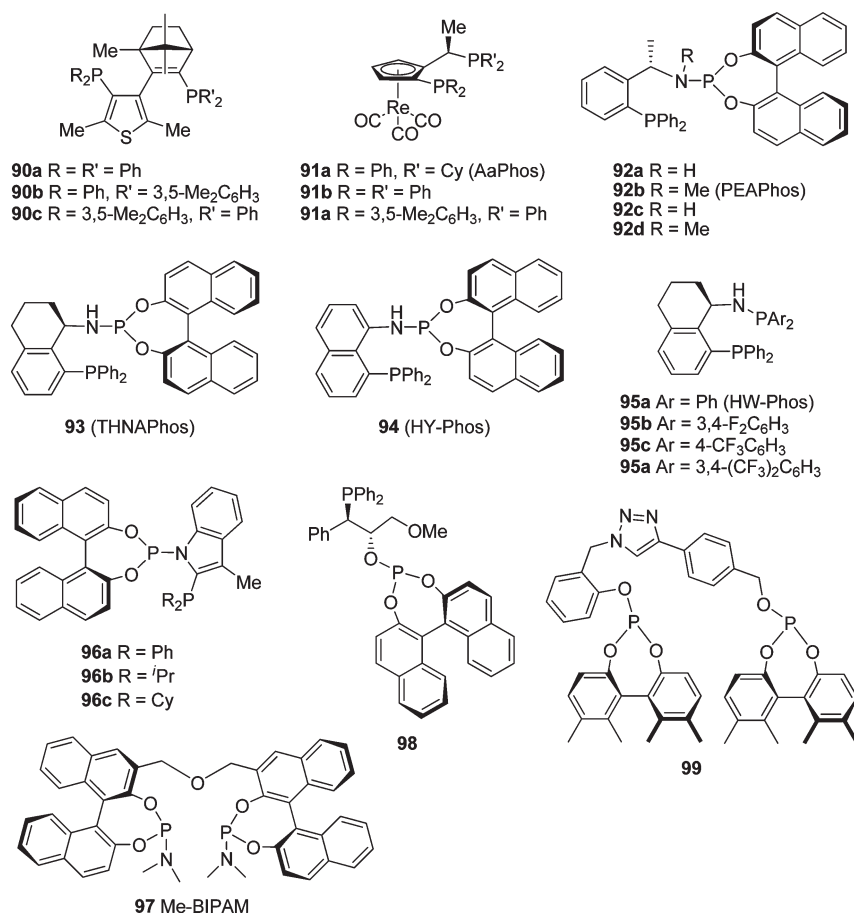


Figure 7. Other diphosphorus ligands.

hydrogenation of β -methyl- α -arylenamides **6**. The ligand HW-Phos (**95**), with only chiral 1,2,3,4-tetrahydro-1-naphthylamine backbone, showed lower enantioselectivity in the hydrogenation of *N*-acetyl α -arylenamides **4**, with the ligand **95b**, having two F-atoms on the 3,5-positions of the phenyl ring of the aminophosphino moiety, being the most enantioselective (93–97% ee) (Table 2).⁸¹

IndolPhos (**96**), another readily available hybrid phosphine–phosphoramidite ligand based on a rigid 3-methylindole backbone, was developed by Wassenaar and Reek.⁸² Among the IndoPhos ligands, the ligand **96b** has been demonstrated to be the most effective in the rhodium-catalyzed hydrogenation of the α -arylenamide **4a**, and 94% ee was obtained under the conditions of 10 atm H₂ pressure and room temperature in CH₂Cl₂ for 16 h (S/C = 100).⁸³ Bidentate diphosphoramidite ligand **97** derived from the ether-linked BINOL (1,1'-binaphthyl-2,2'-diol) was developed by Miyaura and co-workers.⁸⁴ This ligand showed good enantioselectivity in the rhodium-catalyzed hydrogenation of enamides. Under the optimal conditions, the α -arylenamides **4** with substituents on the *para*- or *meta*-positions of the phenyl ring were hydrogenated to the corresponding chiral amides **5** with 77–97% ee (Table 2), whereas no reaction took place for the substrates with an *ortho*-substituent.⁸⁵

Compared with wide application of phosphoramidite ligands, there are few successful examples of phosphite ligands in the rhodium-catalyzed enantioselective hydrogenation of enamides. In 2008, Vidal-Ferran and co-workers⁸⁶ reported that the

phosphine–phosphite ligand **98** with matched chiralities gave high enantioselectivity (98% ee) in the hydrogenation of the α -arylenamide **4a** (S/C = 100, 20 atm H₂, THF, rt, 12 h). In the same year, Zhang and Takacs⁸⁷ developed a diphosphite ligand **99** with a click-connected scaffold and obtained 96% ee of enantioselectivity in the rhodium-catalyzed hydrogenation of *N*-(1-(4-chlorophenyl)vinyl)acetamide (**4d**).

2.1.1.2. Monophosphorus Ligands

Chiral Monodentate Phosphoramidites. Chiral monophosphoramidites are the first type of highly efficient monodentate ligands reported in the rhodium-catalyzed asymmetric hydrogenation of *N*-acyl enamines. In 2002, Zhou and co-workers⁸⁸ designed and synthesized a new type of spiro phosphoramidite ligands SiPhos (**100**) based on a spirobiindane backbone (Figure 8). These spiro monophosphoramidite ligands showed high enantioselectivities in the rhodium-catalyzed hydrogenation of *N*-acetyl aryl enamines **4**. The reactions were performed under the conditions of 50 atm H₂, 5 °C in toluene in the presence of a rhodium catalyst generated in situ from 1.0 mol % of [Rh(COD)₂]BF₄ and 2.2 mol % of SiPhos ligand **100a**, providing a series of *N*-acetyl amines **5** in high yields with excellent enantioselectivities (91–99.3% ee, Table 3).¹³ The dialkylamino group on the phosphorus atom of SiPhos ligands **100** has an obvious effect on the enantioselectivity of the reaction, with a small dialkylamino group necessary for obtaining high enantioselectivity (for the substrate **4a**: 96% ee (**100a**), 57% ee (**100b**), 38% ee (**100c**)). Introducing either electron-donating or electron-withdrawing substituents on the 4- and 4'-position of SiPhos

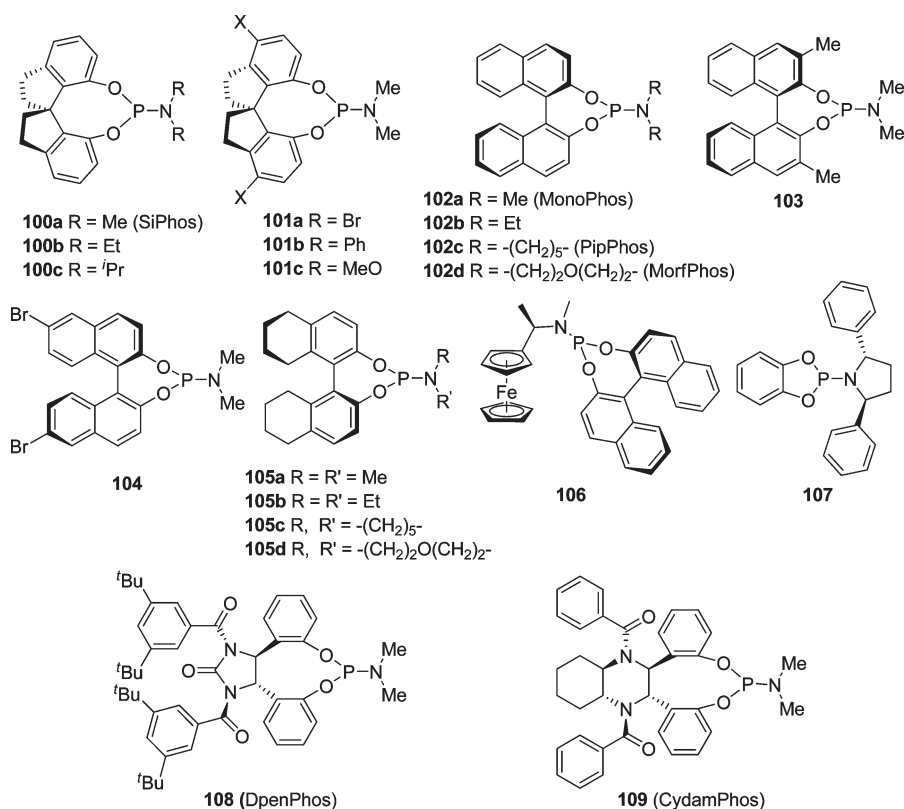


Figure 8. Chiral monophosphoramidite ligands.

(ligands **101**) has no significant improvement in the enantioselectivity of the reaction.⁸⁹ Under similar reaction conditions, the rhodium catalysts with ligands **101** gave comparable enantioselectivities (95–99% ee) for the hydrogenation of several *N*-acetyl enamines **4**. Chiral 1-aminoindanes **11** ($n = 1$) are key intermediates for the synthesis of chiral drugs such as rasagiline for Parkinson's disease.⁹⁰ The rhodium complex containing a SiPhos ligand **100a** is also an efficient catalyst for the enantioselective hydrogenation of cyclic enamides **10a–c** derived from indanone derivatives. Under the conditions of 100 atm H₂ pressure at 0 °C in toluene, cyclic enamides **10a–c** were hydrogenated to the corresponding cyclic amines **11a–11c** with 94, 88, and 95% ee, respectively.⁹¹

The monophosphoramidite ligands with a binaphthyl structure also showed excellent enantioselectivity in the rhodium-catalyzed enantioselective hydrogenation of enamides. Chan and co-workers⁹² and de Vries, Feringa, and co-workers⁹³ independently reported that the rhodium complexes of MonoPhos ligands **102** (Figure 8) were efficient catalysts for the enantioselective hydrogenation of enamides **4**. Under the conditions of 1 mol % catalyst generated in situ from [Rh(COD)₂]₂BF₄ with 2 equiv of **102a** in CH₂Cl₂ and 20 atm H₂ pressure at low reaction temperature (–20 °C), substrates **4** were reduced to *N*-acetyl amines **5** with 70–96% ee (Table 3).⁹² Introduction of two methyl groups onto the 3- and 3'-positions of MonoPhos (ligand **103**), increasing the steric hindrance of ligand, led to a dramatic drop of enantioselectivity. In the hydrogenation of **4d** with ligand **103**, the amine product **5d** was obtained with only 44% ee with an opposite configuration compared to that obtained with MonoPhos ligand. In contrast, the introduction of substituents such as Br at the 6- and 6'-positions of MonoPhos (ligand **104**) has little effect on enantioselectivity.⁹⁴

In 2003, Chan and co-workers⁹⁵ found that the enantioselectivity of the hydrogenation of **4a** was significantly improved to 99% ee by replacing the dimethylamino group in MonoPhos with a diethylamino group (ligand **102b**) (Figure 8). A systematic study of the dialkylamino moiety on the MonoPhos ligand by de Vries, Feringa, and co-workers⁹⁶ showed that the ligands with piperidyl (PipPhos, **102c**) and morpholine (MorfPhos, **102d**) moieties were the choice of dialkylamino group for the binaphthyl-type monophosphoramidite ligands **102**, enhancing enantioselectivity of reaction to 99% ee at room temperature. With PipPhos or MorfPhos ligand, cyclic enamides **9** derived from indanone and tetralone can also be easily hydrogenated to chiral cyclic amines **11** with 97–99% ee under 55 atm H₂ with 2 mol % rhodium catalyst.

Furthermore, the rhodium complexes with a PipPhos and/or a MorfPhos are efficient catalysts for the enantioselective hydrogenation of the (*Z*)-isomer of β -ethyl-substituted enamides, (*Z*)-**6b**, giving amine product **7b** with 96 and 98% ee, respectively. However, these catalysts are inefficient for the hydrogenation of the (*E*)-isomer of **6b** (ee < 30%). In the enantioselective hydrogenation of α -alkylenamide **14a** (R = *t*Bu, Scheme 5), PipPhos ligand gave the desired product **15a** with 82% ee.

A rigid backbone in the monophosphoramidite ligands is beneficial to the enantioselectivity of hydrogenation of enamides. This was further verified by the ligand with an octahydrobinaphthyl backbone, H₈-MonoPhos, **105a**. In the enantioselective hydrogenation of enamide **4a**, Chan and co-workers achieved 96.2% ee by using ligand **105a**,⁹⁷ which was better than that obtained with MonoPhos ligand **102a**. de Vries, Feringa, and co-workers⁹⁶ also examined monophosphoramidite ligands with an octahydrobinaphthyl backbone and found that the ligands with piperidyl (**105c**, 98% ee) or morpholyl (**105d**, 97% ee) moiety

Table 3. Enantioselective Hydrogenation of Enamides **4** with Monophosphoramidite Ligands

product	ligands (% ee)									
	100a^a	102a^b	102b^c	102c^d	102d^d	105a^e	106^f	107^g	108^h	109ⁱ
	98.7	95	99	99	>99	96	99		97.6	98.1
	99.7	92	98			95	>99	97	99.3	98.4
		90	98	99	99	92	98	97	97.4	95.7
	99.3	92		99	99		99	94	99.8	95
	99.5	96	99			98	99		99.7	95.3
	98.9	96	99.6			99	99			92.2
	91.6	93	98			95				
		96	98			98	99.5			
		70							98.4	96.8

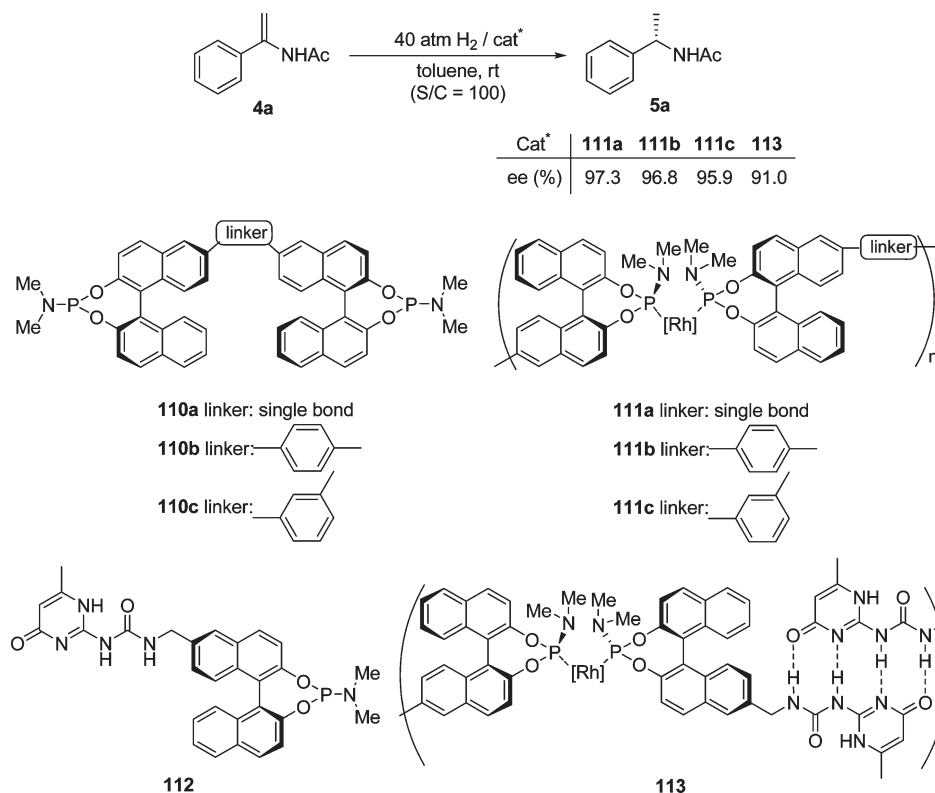
^a Reaction conditions: S/C = 100, 50 atm, 5 °C, 12 h. ^b Reaction conditions: S/C = 100, 20 atm, CH₂Cl₂, −20 °C, 8 h. ^c Reaction conditions: S/C = 100, 20 atm, THF, 5 °C, 4–16 h. ^d Reaction conditions: S/C = 100, 25 atm, CH₂Cl₂, rt, 8 h. ^e Reaction conditions: S/C = 100, 20 atm, THF, −10 °C, 6–18 h. ^f Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 20 h. ^g Reaction conditions: S/C = 100, 25 atm, CH₂Cl₂, rt, 16 h. ^h Reaction conditions: S/C = 100, 40 atm, CH₂Cl₂, rt, 2 h. ⁱ Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 2 h.

on the phosphorus atom were optimal for the hydrogenation of enamide **4a**. Rhodium catalysts bearing octahydrobinaphthyl phosphoramidite ligands **105c** and **105d** were also efficient for the enantioselective hydrogenation of cyclic enamides and β -substituted enamides, providing the corresponding chiral amines with up to 99% ee.

In 2006, Zheng and co-workers⁹⁸ introduced chiral ferrocenyl amines into the binaphthyl-type monophosphoramidite ligands to improve the enantioselectivity for the synthesis of chiral

amines. They demonstrated that the monophosphoramidite ligand **106** (Figure 8) with a (*R*)-*N*-methyl α -ferrocenyl-ethylamine moiety provided excellent enantioselectivity for the rhodium-catalyzed hydrogenation of enamides. Under the conditions of 10 atm H₂ pressure and room temperature in CH₂Cl₂ for 20 h, the rhodium complex of ligand **106** gave excellent enantioselectivities (98–99.5% ee) for the hydrogenation of *N*-acetyl enamides **4** (Table 3). The rhodium complex of ligand **106** was also an efficient catalyst for the hydrogenation of

Scheme 23. Enantioselective Hydrogenation of 4a with Self-Assembled Chiral Catalysts



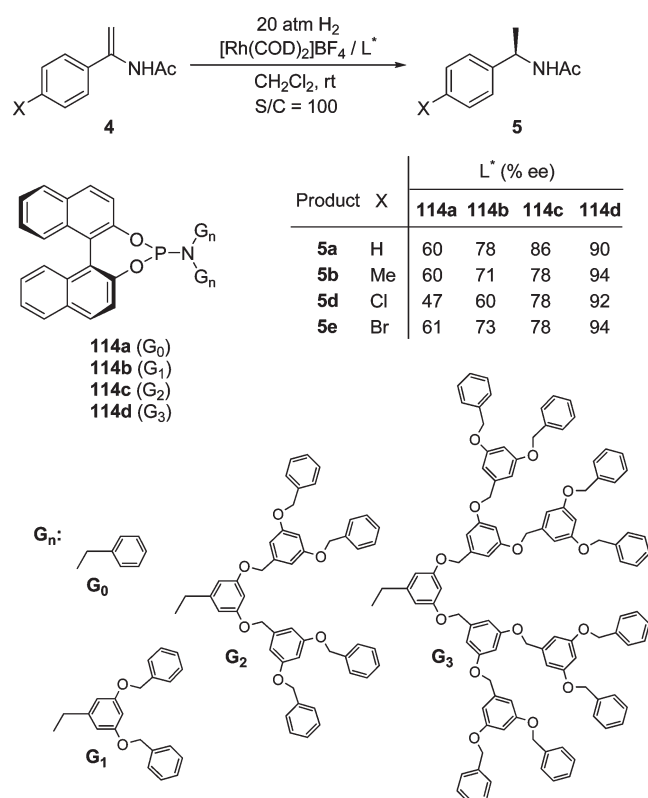
the *Z/E*-mixtures of β -substituted enamide **6a** ($R = \text{Me}$) and **6b** ($R = \text{Et}$), offering the corresponding *N*-acetyl amines **7a** and **7b** with 94 and 96% ee, respectively.

The monophosphoramidite ligand **107**⁹⁹ (Figure 8) was synthesized from an achiral catechol and a chiral amine. The rhodium catalyst containing ligand **107** afforded comparable enantioselectivities with other monophosphoramidites (96.5–97% ee) in the hydrogenation of enamides **4** (Table 3). High enantioselectivity (99% ee) was obtained with ligand **107** in the hydrogenation of (*Z*)- β -substituted enamide (*Z*)-**6b**. For the hydrogenation of (*E*)-**6b**, the ligand **107** also gave the product **7b** in 90% ee with the same configuration. This result showed that the rhodium complex of ligand **107** could be an efficient catalyst for the enantioselective hydrogenation of the *Z/E*-mixtures of β -substituted enamides. The hydrogenation of the *Z/E*-mixtures of **6b** (2:3) yielded *N*-acetyl amine **7b** with 93% ee, which was the calculated average of the enantioselectivities for the *Z*- and *E*-isomers of substrate.

Liu and Ding¹⁰⁰ reported a new class of phosphoramidite, DpenPhos (**108**, Figure 8). The ligand **108** was synthesized by the reaction of the corresponding chiral diol, derived from enantiomerically pure 1,2-di(2-dimethoxyphenyl)-1,2-ethylenediamine, with hexamethylphosphorus triamide (HMPT) or hexaethylphosphorus triamide in good yield. The ligand **108** having 3,5-di-*tert*-butylbenzoyl groups on the amide nitrogens and a dimethylamino group on the phosphorus atom has a high enantioselectivity in rhodium-catalyzed enantioselective hydrogenation of enamides **4** (96.1–99.8% ee) (Table 3). However, the synthetic process of ligand DpenPhos was rather tedious. To surmount this drawback and keep the advantages of excellent enantioselectivity and fine-tuning capability of ligand

DpenPhos, Ding and co-workers¹⁰¹ developed another type of monophosphoramidite ligands, CydamPhos (**109**) (Figure 8). The CydamPhos ligand was synthesized from the readily accessible enantiomerically pure *trans*-1,2-diaminocyclohexane and salicylaldehyde derivatives in 3 steps with good yields. Ligand **109** proved to be efficient in rhodium-catalyzed enantioselective hydrogenation of α -arylenamides **4** with enantioselectivities of 91.8–98.4% ee (Table 3). This result is inferior to that obtained with ligand DpenPhos (**108**) and showed that the five-membered heterocyclic backbone in the ligand DpenPhos (**108**) is better than the six-membered heterocyclic backbone in the ligand CydamPhos (**109**) in terms of enantioinduction.

The excellent performance of monodentate phosphoramidite ligands in the rhodium-catalyzed hydrogenations encouraged chemists to immobilize them or design self-assembly strategies to examine the reuse of them. Of course, once the monophosphoramidite ligands are polymerized or assembled, they are no longer monodentate. However, the nature of coordination of the immobilized or assembled ligands to the central metal of catalysts bears more of a resemblance to the monodentated phosphoramidites. Using this concept, Wang and Ding¹⁰² used linkers such as a single methylene unite to make bis-MonoPhos (Scheme 6), which were capable of self-assembly to polymer catalysts **111** by reacting with the catalyst precursor $[\text{Rh}(\text{COD})_2]\text{BF}_4$. The self-supporting catalysts **111** showed high enantioselectivities (**111a**, 97.3% ee; **111b**, 96.8% ee; **111c**, 95.9% ee) in the enantioselective hydrogenation of arylenamide **4a** under 40 atm H_2 at 25 °C in toluene, which were comparable with those obtained by using the analogous monomeric ligands. A self-supporting catalyst **113**, obtained by reaction of rhodium precursor $[\text{Rh}(\text{COD})_2]\text{BF}_4$ with monophosphoramidite ligand

Scheme 24. Enantioselective Hydrogenation of 4 with Dendrimer-Supported Monophosphoramidites

112 through a noncovalent self-assembly method (hydrogen bonding and metal coordination), was also developed.¹⁰³ When the catalyst **113** was applied to the enantioselective hydrogenation of arylenamide **4a** under 40 atm H₂ pressure in toluene at room temperature, *N*-acetyl amine **5a** was obtained with 91.0% ee (see Scheme 23). However, no data regarding the ability to use this approach in a reiterative catalyst manner was commented on for catalyst **113**.

Dendrimer-supported monophosphoramidites are also a choice for making monodentate ligands recyclable. Fan and co-workers¹⁰⁴ designed a series of dendrimer-supported monophosphoramidite ligands **114a–d** based on binaphthyl backbone, affording high enantioselectivities in the rhodium-catalyzed hydrogenation of arylenamides **4** (Scheme 24). A unique positive dendritic effect on enantioselectivity was observed in the reaction. When the dendrimer generation of the ligand **114** was increased from the first generation (**114a**, G₀) to the third generation (**114d**, G₃), the enantioselectivity of the product **5** was remarkably enhanced from 47–61 to 90–94% ee in the rhodium-catalyzed asymmetric hydrogenation of enamides **4**.

Chiral Monodentate Phosphites. The application of chiral monophosphites for the rhodium-catalyzed enantioselective hydrogenation of enamides was first reported by Reetz et al.¹⁰⁵ in 2002. Under the conditions of 0.2 mol % catalysts generated in situ from [Rh(COD)₂]₂BF₄ and ligands **115** (Figure 9) and 60 atm H₂ pressure at 30 °C in CH₂Cl₂, the model substrate **4a** was hydrogenated with up to 95.3% ee. The alkoxy group on the phosphorus atom of the ligand was demonstrated to be important for obtaining high enantioselectivity. The ligands derived

from achiral alcohols such as benzyl alcohol (**116c**, 94.2% ee) gave good results. The chirality on the alcohol moiety of the ligand provided only a small contribution to the enantioselectivity of the reaction, and the ligand **115d** with a (*R*)-1-phenylethoxy gave the best enantioselectivity (95.3% ee). With monophosphite ligand **115d**, α -arylenamines **4** were hydrogenated to the corresponding amines **5** with 94.9–97.0% ee (Table 4). Rhodium complex of monophosphite ligand **115d** was also an efficient catalyst for the enantioselective hydrogenation of β -substituted α -arylenamide **6a**. Up to 97% ee was obtained for the (*Z*)-**6a** (95% *Z*), and up to 76.2% ee was obtained for the (*E*)-**6a** (84% *E*).

Compared with simple monophosphites, the monodentate phosphites derived from the easily available carbohydrates afforded considerably higher enantioselectivities in the hydrogenation of enamides. Zheng and co-workers¹⁰⁶ developed a series of binaphthyl–carbohydrate monodentate phosphites derived from D-fructose and D-glucose. The phosphite **116** (Figure 9) exhibited a better enantioselectivity in the rhodium-catalyzed enantioselective hydrogenation of arylenamides **4**. Fructose- and glucose-derived phosphites have several chiral centers, and the phosphite **116** with a (*R*)-binaphthyl and a “D-fructose” moiety was demonstrated to be a chirality-matched ligand. Under the optimized conditions (S/C = 100, CH₂Cl₂, 10 atm H₂, rt), a variety of chiral *N*-acetyl arylamines **5** were obtained with high enantioselectivities (95.0–98.5% ee) with a rhodium complex of phosphite ligand **116** (Table 4). Generally, the α -arylenamide substrates with electron-withdrawing substituents on the phenyl ring gave higher enantioselectivities than those with electron-donating substituents. The rhodium catalyst containing phosphite **116** was also efficient for the enantioselective hydrogenation of the *Z/E*-mixtures of β -substituted α -arylenamide **6a**, providing *N*-acetyl arylamine **7a** with 96.7% ee.

The D-mannitol-based monophosphite **117** (ManniPhos, Figure 9) was also found to be an excellent ligand for the enantioselective hydrogenation of enamides.¹⁰⁷ The rhodium-catalyzed enantioselective hydrogenation of enamides **4** by using monophosphite ligand **117** provided chiral *N*-acetyl amines **5** with 79.1–99.9% ee (Table 4). Most prominently, the ligand **117** provided an extremely high enantioselectivity (99.2% ee) in the hydrogenation of the *Z/E*-mixtures of β -substituted α -arylenamide **6a**. This is the best result obtained to date for the enantioselective hydrogenation of β -substituted α -arylenamides. Furthermore, the monophosphite **117** (ManniPhos) was also an efficient ligand for the enantioselective hydrogenation of cyclic enamides. With the rhodium complex of ligand **117** as the catalyst, the enantioselective hydrogenation of cyclic enamide **10a** yielded chiral cyclic amine **11a** with 96.0% ee. It should be noted that the rhodium catalyst bearing ligand **117** has a high activity; it can hydrogenate the enamide **4a** with 99.5% ee at 0.1% mol catalyst loading (S/C = 1000, 100% conversion) and 95.9% ee at 0.02 mol % catalyst loading (S/C = 5000, 88% conversion). The chiral binaphthyl moiety in the ligand **117** is required for obtaining high enantioselectivity. Replacement of the chiral binaphthyl structure in the monophosphite **117** with an achiral biphenyl structure led to an extremely low enantioselectivity (49.7% ee) in rhodium-catalyzed enantioselective hydrogenation of enamide **4a**. In another example, the chiral monophosphite with a chiral biphenyl backbone developed by Rampf and co-workers¹⁰⁸ also gave a low enantioselectivity in the hydrogenation of enamides.

Table 4. Enantioselective Hydrogenation of Enamides **4** with Chiral Monophosphites

product	ligand (% ee)					
	115j ^a	116 ^b	117 ^c	118 ^b	119a ^d	122a ^e
	94.9	95.0	99.8	99.0	99.0	89
					98	90
		95.9	99.5	98.9	99	88
	95.8	98.5	99.7	99.5	98	87
		98.5	99.9	99.6	98	
		96.5	99.7	99.3	97	
		98.5	99.9	99.3		
		96.9	99.5	99.5		

^a Reaction conditions: S/C = 500, 60 atm, CH₂Cl₂, 30 °C, 20 h. ^b Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 12 h. ^c Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, 20 °C, 12 h. ^d Reaction conditions: S/C = 100, 10 atm, CH₂Cl₂, rt, 20 h. ^e Reaction conditions: S/C = 50, 60 atm, CH₂Cl₂, 20 °C, 20 h.

A series of octahydrobinaphthyl-based carbohydrate monodentate phosphites have been synthesized.¹⁰⁹ Among them, the monophosphite **118** (Figure 9) derived from D-fructose showed the highest level of asymmetric induction for the rhodium-catalyzed hydrogenation of α -arylenamides **4** (97.3–99.6% ee, Table 4). In the enantioselective hydrogenation of β -substituted Z/E-mixtures α -arylenamides **6a** and **6b**, the ligand **118** gave N-acetyl arylamines **7a** and **7b** with 97.3 and 99.0% ee, respectively. The ee values obtained with the octahydrobinaphthyl-based monophosphite **118** are a little lower than those obtained with the binaphthyl-based ManniPhos (monophosphite **116**, Table 4).

Zheng and co-workers¹¹⁰ reported a type of recoverable and soluble PEGpoly (ethyleneglycol) monomethyl ether-derived polymer monophosphites (MeOPEG-monophosphites) **119a–c** (Figure 9), which are highly efficient for the rhodium-catalyzed enantioselective hydrogenation of α -arylenamides. MeOPEG-monophosphite **119a** gave 96–99% ee in the hydrogenation of α -arylenamides **4** (Table 4) and 97% ee in the hydrogenation of the Z/E-mixtures of β -substituted enamide **6b**. The rhodium catalyst containing MeOPEG-monophosphite ligand **119a** can be recycled four times without seriously diminishing enantioselectivity in the enantioselective hydrogenation of the model substrate **4a**. Polymer-supported monophosphite

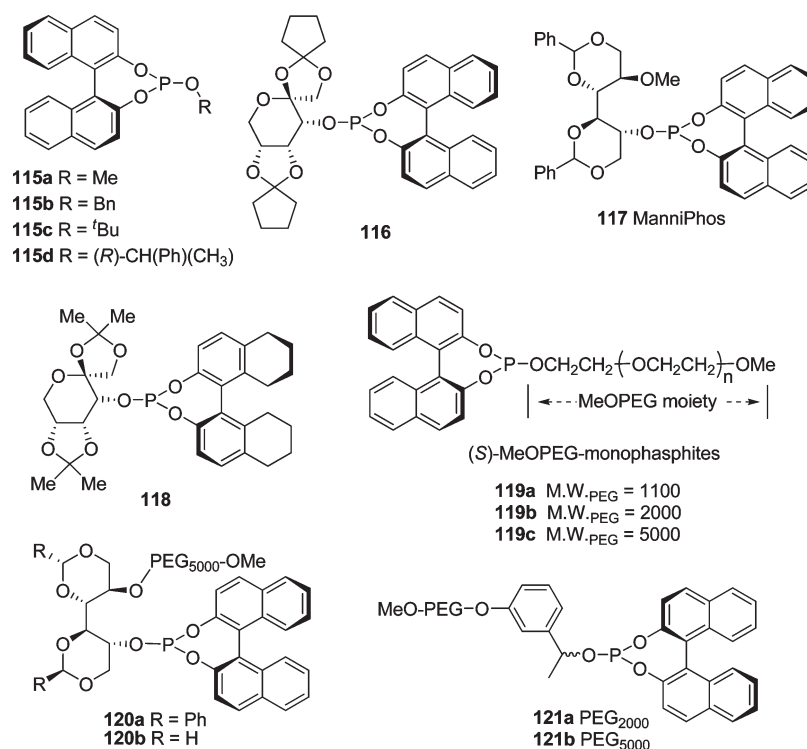


Figure 9. Chiral monophosphite ligands.

ligands **120** and **121**, developed by Chen et al.,¹¹¹ also showed very high enantioselectivity (95.7–96.4% ee) for the hydrogenation of the α -arylenamide **4a**.

Recently, Fan and co-workers¹¹² developed supramolecular chiral dendritic monophosphite ligands **122** assembled by hydrogen bonding (Scheme 25). The rhodium catalysts of these supramolecular chiral dendritic monophosphites showed good enantioselectivity for the hydrogenation of α -arylenamides **4**. Under atmospheric hydrogen pressure at 20 °C in CH₂Cl₂ and in the presence of the rhodium catalyst generated in situ from 2 mol % of [Rh(COD)₂]BF₄ and 2.2 mol % of ligand, the ligand **122a** gave 82% ee for the hydrogenation of substrate **4a**. Higher enantioselectivity (89% ee) was observed when the reaction was performed at higher hydrogen pressure (ca. 60 atm). The enantioselectivity increased with increasing dendrimer generation, and the third-generation dendritic monophosphite ligand **122a** afforded comparable enantioselectivity to that obtained with the free ligand **123a** (86 vs 85% ee). With the third-generation dendritic monophosphite ligand **122a**, several enamides **4** were hydrogenated to chiral amines **5** with 87–90% ee (Table 4).

Other Chiral Monodentate Phosphorus Ligands. In addition to chiral monophosphoramidites and monophosphites, chiral monophosphonites and monophosphines have also been used as ligands for rhodium-catalyzed enantioselective hydrogenation of enamides. Reetz et al.¹¹³ applied monophosphonite ligand **124a** (Scheme 26) in the rhodium-catalyzed enantioselective hydrogenation of α -arylenamides. In the presence of 0.2 mol % catalyst generated in situ from [Rh(COD)₂]BF₄ and the ligand **124a** under 1.5 atm of H₂ pressure at room temperature, the α -arylenamide **4a** was hydrogenated to the amine **5a** in 75.6% ee.^{113,114} Beller and co-workers¹¹⁵ achieved up to 93% ee for the hydrogenation of arylenamides **4** by using a rhodium complex of the monophosphine ligand **125a** as the catalyst. The

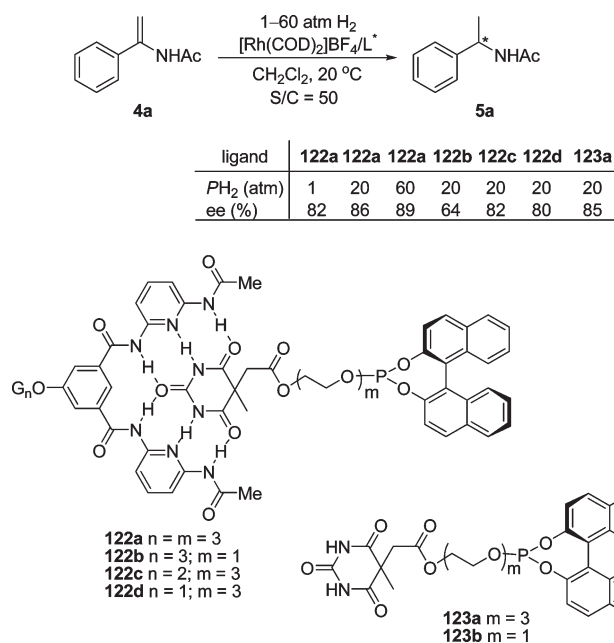
enantioselectivity of the reaction depends on the nature of the substituent at the phosphorus atom of ligands **125** and the nature of enamide substrates **4**. The aryl-substituted phosphines are better chiral ligands than the alkyl-substituted ones in terms of enantioselectivity.

A secondary monophosphine ligand, (2*S*,5*S*)-2,5-diphenylphospholine, was also applied for the rhodium-catalyzed enantioselective hydrogenation of β -substituted enamides **6** for the synthesis of chiral *N*-acetyl amines **7**, albeit with low enantioselectivity (<28% ee).¹¹⁶

Mixed Chiral Monodentate Phosphorus Ligands. A mechanistic study on the rhodium-catalyzed olefin hydrogenation using monodentate ligands (phosphoramidites, phosphites, or phosphonites) has shown that two monophosphorus ligands are bound to the metal in the transition state of reaction.¹¹⁷ Thus, the use of a mixture of two different chiral monodentate ligands L_a and L_b in rhodium-catalyzed hydrogenation would lead to the formation of two homocoordination catalysts [RhL_aL_a] and [RhL_bL_b] and one heterocoordination catalyst [RhL_aL_b]. These three species can be formed in various ratios and are in equilibrium in solution (Scheme 27). If the heterocoordination catalyst [RhL_aL_b] dominates and/or shows higher activity and enantioselectivity, a superior catalytic profile can be expected from the mixed ligands.

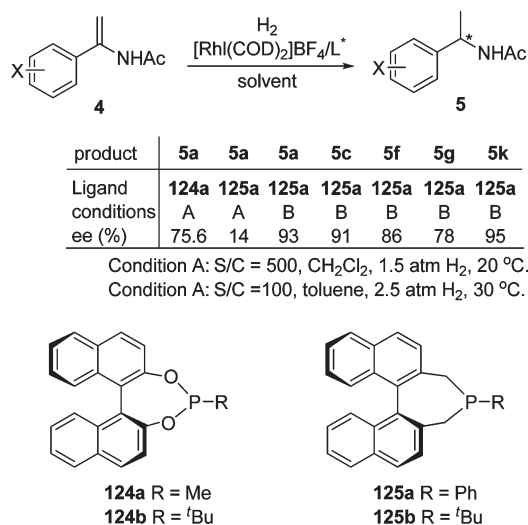
The use of mixed monophosphorus ligands to control enantioselectivity of hydrogenation was first attempted by Chen and Xiao.¹¹⁸ They used a mixture of monodentate phosphite ligands derived from bisphenol and chiral alcohol in the enantioselective hydrogenation of dimethyl itaconate; however, no enhancement of enantioselectivity was observed in their experiments. Reetz et al.¹¹³ and Feringa and co-workers¹¹⁹ independently introduced mixtures of chiral monodentate phosphorus ligands such as phosphites, phosphonites, and phosphoramidites with a binaphthyl backbone into the rhodium-catalyzed

Scheme 25. Enantioselective Hydrogenation of 4a with Dendritic Monophosphites



Note: G_n dendritic receptors, see Scheme 24.

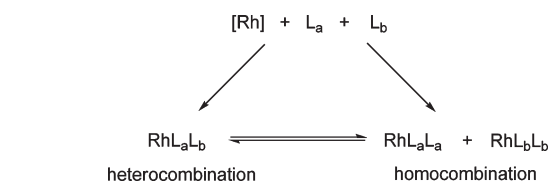
Scheme 26. Enantioselective Hydrogenation of Enamides 4 with Ligands 124a and 125a



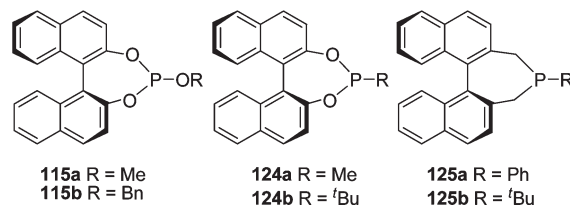
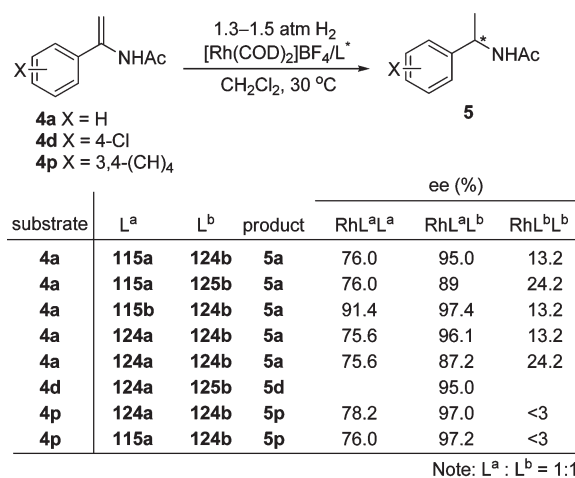
hydrogenation of olefins such as α -dehydroamino esters, dimethyl itaconate, and enamides. Higher enantioselectivities have been achieved by using mixed chiral phosphorus ligands. For example, in the rhodium-catalyzed enantioselective hydrogenation of enamide 4a, 96.1% ee was obtained by a combination of 124a (R = Me) and 124b (R = ^tBu), whereas the homocatalysts Rh-124a and Rh-124b yielded the corresponding hydrogenation product 4a with 75.6 and 13.2% ee, respectively (Scheme 28).^{113,114}

The application of a mixture of a chiral and an achiral monophosphorus ligand in the rhodium-catalyzed enantioselective

Scheme 27. Catalytic Complexes Obtained by Using Mixed Monophosphorus Ligands



Scheme 28. Enantioselective Hydrogenation of Enamides 4 with Mixed Monophosphorus Ligands



hydrogenation of enamides was tested by Beller and co-workers.¹¹⁵ By using a mixture of a chiral monophosphine 125a and an achiral ligand tris(4-methoxyphenyl)phosphine [P(4-MeOC₆H₄)₃] (1:1), the enamide 4a was hydrogenated to the chiral amine 5a with 88% ee, but this enantioselectivity is inferior to that obtained with the single monophosphine 125a (93% ee).

2.1.1.3. Other Chiral Ligands. In 2003, Evans et al.¹²⁰ reported a type of unsymmetrical hybrid bidentate phosphonite-thioether ligand 126 (Figure 10), which was efficient for the rhodium-catalyzed enantioselective hydrogenation of *N*-acetyl enamides. Under mild reaction conditions, the ligand 126 gave high enantioselectivity for the hydrogenation of enamide 4a (95% ee) and cyclic enamide 10a (92% ee).

Recently, Reek and co-workers¹²¹ reported a chiral dinuclear rhodium catalyst 128 bridged by two anionic sulfonamido-phosphoramidite ligands 127 and found it is a good catalyst for enantioselective hydrogenation of enamides (Scheme 29). Under the conditions of 50 atm H₂ pressure and room temperature in CH₂Cl₂ for 18 h, the cyclic enamides 26a and 26b derived from β -tetralone were converted to the cyclic amides 27a and

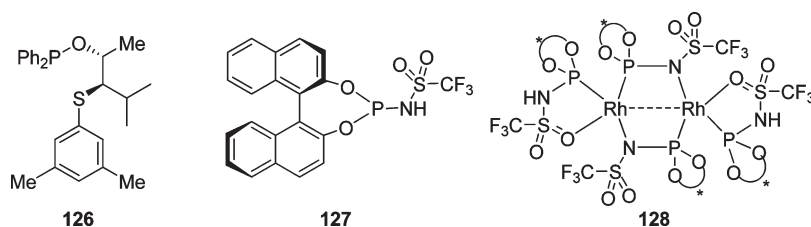
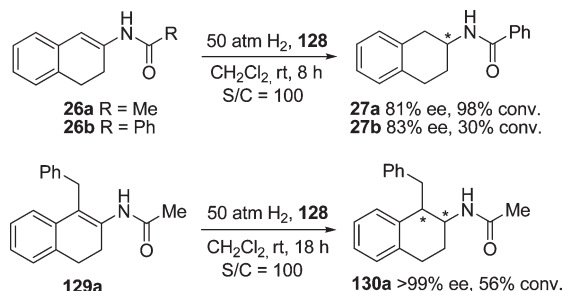


Figure 10. Phosphonite–thioether ligand **126** and sulfonamido–phosphoramidite ligand **127**.

Scheme 29. Enantioselective Hydrogenation of Enamides **26** and **129a** with Catalyst **128**

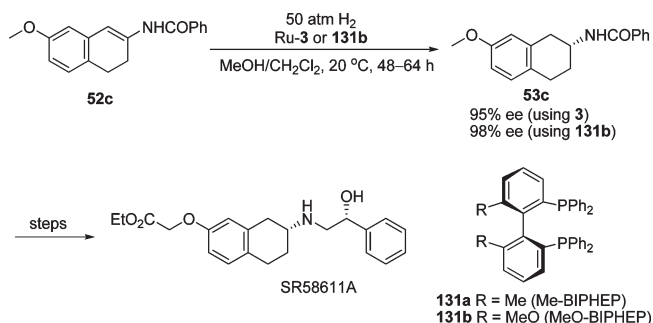


27b in good enantioselectivities (81% and 83% ee, respectively), whereas the mononuclear cationic catalyst $[\text{Rh}(\mathbf{127})_2(\text{COD})]\text{BF}_4$ gave very low conversion and moderate ee value (1% conversion, 69% ee). A sterically hindered tetrasubstituted enamide **129a**, *N*-(1-benzyl-3,4-dihydronaphthalen-2-yl)acetamide, was also selectively hydrogenated by the catalyst **128** in high enantioselectivity (>99% ee), albeit with slightly slow reaction rate (56% conversion after 18 h). The enantioselectivity provided by the dinuclear catalyst **128** is obviously better than that afforded by a ruthenium catalyst Ru-DuPhos (52% ee, see Scheme 31), which was the previously highest enantioselective catalyst for the hydrogenation of this tetrasubstituted enamide substrate.

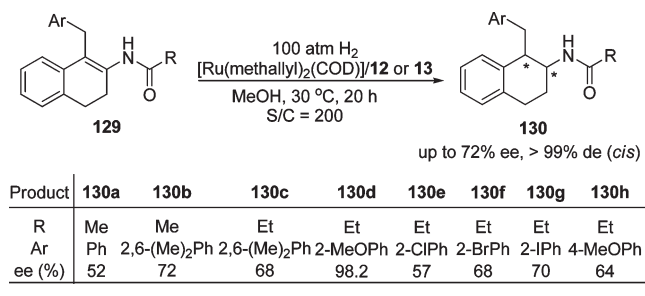
2.1.2. Chiral Ruthenium Catalysts. After Noyori et al.¹¹ reported the asymmetric hydrogenation of (*Z*)-*N*-acyl-1-alkyldenetetrahydroisoquinolines by using the ruthenium complexes of BINAP (**3**) as the catalysts (Scheme 3), a few examples of ruthenium-catalyzed asymmetric hydrogenation of enamides for the synthesis of chiral amides have been reported. In 1999, Agbossou and co-workers¹²² demonstrated that the ruthenium complexes of BINAP and MeO-BIPHEP (**131b**) ligands were highly effective for the hydrogenation of cyclic *N*-benzoyl enamine **26c** derived from 7-methoxy-3,4-dihydronaphthalen-2(1*H*)-one. This reaction provides an efficient method for the synthesis of chiral atypical β -adrenergic phenylethaminotetraline agonist SRS8611A (Scheme 30). Subsequently, Bruneau and co-workers¹²³ extended the substrates of this reaction to *N*-acetyl/benzoyl cyclic enamines derived from β -tetralones and chroman-3-one derivatives, affording the corresponding cyclic amines with up to 96% ee.

By using Me-DuPhos (**12**) and BPE (**13**) as ligands, Bruneau and co-workers¹²⁴ realized the ruthenium-catalyzed enantioselective hydrogenation of the tetrasubstituted enamides **129** derived from 1-substituted-2-tetralones, obtaining the corresponding chiral amides **130** as single *cis*-diastereoisomers in good yields (>95%) with ee values up to 72% (Scheme 31). In

Scheme 30. Enantioselective Synthesis of SRS8611A



Scheme 31. Enantioselective Hydrogenation of Tetrasubstituted Enamides **129**



contrast, the Rh-Me-DuPhos catalyst, which was efficient for the hydrogenation of α -arylenamides,¹² showed no activity in this reaction.

The ruthenium complex of ferrocene-based chiral ligands also showed good enantioselectivity and activity in the hydrogenation of enamides. Ramsden and co-workers¹²⁵ reported that the ligand **132** (*P*-FerroTANE) with a ferrocene backbone is highly efficient for the ruthenium-catalyzed enantioselective hydrogenation of cyclic enamide **133**. When the hydrogenation was performed at S/C of 1000 under 8 atm H_2 pressure at 65 °C, the chiral amide **134** (*N*-acetylcolchinel), a key intermediate for the synthesis of the drug substance ZD6126, was obtained in 91.6% ee with 100% conversion (Scheme 32). In a comparison study, the ruthenium or rhodium catalysts containing other chiral ligands such as DuPhos (**12**) and BPE (**13**) yielded the chiral amide **134** with only moderate enantioselectivity (<76% ee).

2.1.3. Chiral Iridium Catalysts. Chiral iridium catalysts are rarely applied in the enantioselective hydrogenation of *N*-acyl enamine. In 2004, Grützmaier and co-workers¹²⁶ reported the asymmetric hydrogenation of *N*-acetyl enamine **4a** with an

Scheme 32. Enantioselective Synthesis of ZD6126

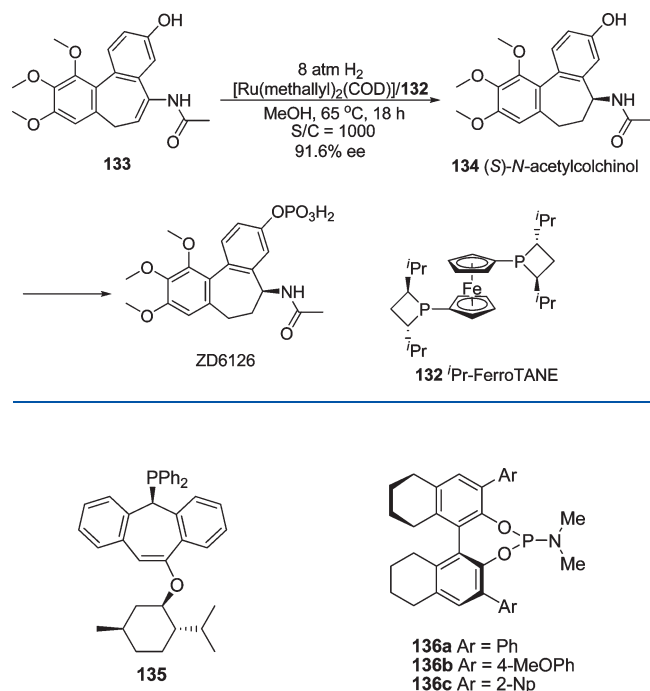


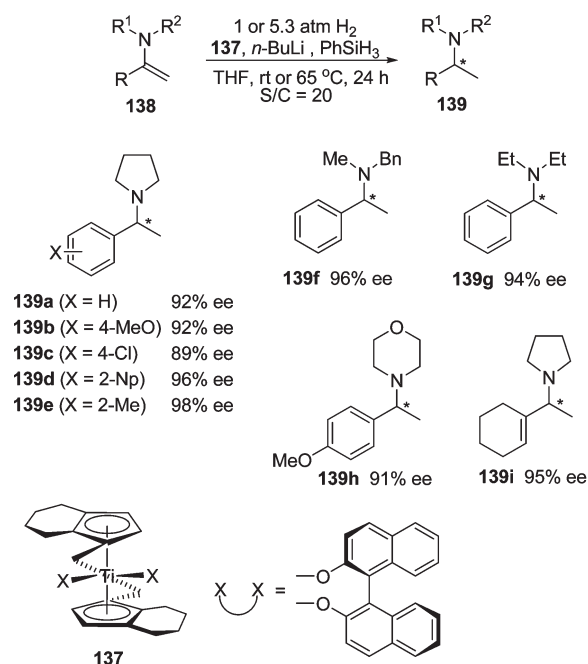
Figure 11. Phosphine–olefin ligand **135** and monophosphoramidite ligands **136**.

iridium complex of the phosphine–olefin ligand **135** (Figure 11) as the chiral catalyst and obtained the corresponding chiral amine **5a** with moderate enantioselectivity (60% ee). Although the enantioselectivity is not high, this result shows that the chiral olefin can be used as a steering ligand in the iridium-catalyzed enantioselective hydrogenations.

Recently, Beller and co-workers¹²⁷ demonstrated that the iridium complexes of monophosphoramidite ligands **136** (Figure 11) with the aryl groups on the 3,3'-positions of the octahydrobinaphthyl backbone can act as effective chiral catalysts for the hydrogenation of enamides **4**. For example, in the presence of an iridium catalyst generated in situ from 2 mol % of [Ir(COD)Cl]₂ and 4 mol % of the ligand **136b**, which has two *para*-methoxyphenyl groups on the 3,3'-positions, the substrate **4a** was hydrogenated to the chiral amine **5a** in 88% ee with >99% conversion. The enantioselectivity of the reaction can be improved to 93% ee after the addition of non-coordinating salt NaClO₄ as an additive. Other substrates such as the β -substituted enamide **6a** (*Z/E*-ratio 9/1; 29% ee, 58% conversion) and *N*-acetyl cyclic enamides **10e** (60% ee, 17% conversion) were also evaluated, but the enantioselectivities and conversions were not satisfied.

2.2. Enantioselective Hydrogenation of Unfunctionalized Enamines

In contrast with the hydrogenation of *N*-acyl enamines, there are very few examples of successful enantioselective hydrogenation of *N,N*-dialkyl enamines, which provides a direct approach to the synthesis of chiral tertiary amines. The reason is that an *N*-acyl group in the enamides is considered a prerequisite for the substrates to have good enantioselectivity by forming a chelate complex with the metal of the catalyst in transition state (see Figure 1). Actually, the *N,N*-dialkyl

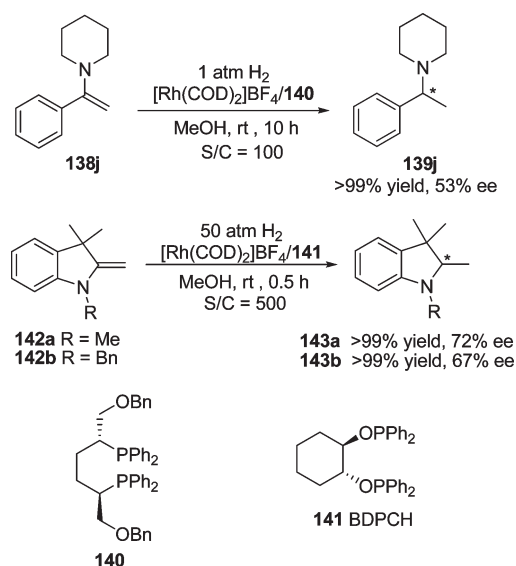
Scheme 33. Enantioselective Hydrogenation of Enamines **138** with Titanium Catalyst **137**

enamines belong to the most difficult substrates for the catalytic enantioselective hydrogenation in term of enantioselectivity.

In 1994, Lee and Buchwald¹²⁸ reported the enantioselective hydrogenation of *N,N*-dialkyl enamines to chiral tertiary amines catalyzed by chiral *ansa*-titanocene complex. Recently, several groups investigated more efficient chiral catalysts for the hydrogenation of unfunctionalized enamines. To date, in addition to Buchwald's titanium catalyst, the rhodium and iridium complexes containing chiral phosphorus ligands or/and phosphine oxazoline ligands have been demonstrated to be highly efficient catalysts for the hydrogenation of *N,N*-dialkyl enamines and other unprotected enamines.

2.2.1. Chiral Titanium Catalysts. Lee and Buchwald¹²⁸ used an *ansa*-titanium complex **137** as the chiral catalyst for enantioselective hydrogenation of *N,N*-dialkyl α -arylethenamines **138**. After activation with 2.0 equiv of *n*-BuLi and 2.5 equiv of phenylsilane (PhSiH₃), the catalyst **137** (5 mol %) can efficiently hydrogenate *N,N*-dialkyl α -arylethenamines **138** to the corresponding chiral tertiary amines **139** in good yields (72–89%) with high enantioselectivities (89–98% ee) under the conditions of either under 1 atm H₂ pressure at room temperature or under 5.3 atm H₂ pressure at 65 °C in THF (Scheme 33).

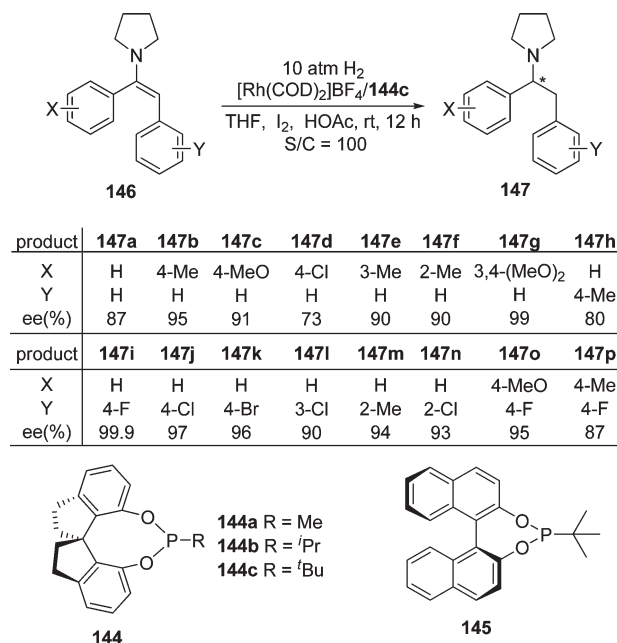
Changing the substituents on the nitrogen or on the phenyl ring of the substrate had little effect on the enantioselectivity. However, the reaction rate was influenced by the steric hindrance of the substrate. As the substituents on the double bond and N-atom became bulkier, higher hydrogen pressure (5.3 atm) and higher temperature (65 °C) were required for obtaining a reasonable reaction rate. For the same reason, the more sterically hindered substrate such as the pyrrolidine enamine derived from pinacolone was difficult to be hydrogenated. An additional limitation of this reaction is that the catalyst, in its present form,

Scheme 34. Enantioselective Hydrogenation of *N,N*-Dialkyl-enamines with Ligands **140** and **141**

does not tolerate aromatic bromides. When 1-pyrrolidinyl-1-(4-bromophenyl)ethane was subjected to the reaction, mostly unreacted starting material was recovered along with a small amount of debrominated enamine.

2.2.2. Chiral Rhodium Catalysts. In 2000, Börner and co-workers¹²⁹ investigated several chiral diphosphine ligands including DIOP (**2**) in the rhodium-catalyzed enantioselective hydrogenation of unfunctionalized enamines and found that the rhodium complex containing a conformationally flexible 1,4-diphosphine **140** (Scheme 34) gave the best enantioselectivity for the hydrogenation of an acyclic enamine, 2-*N*-piperidinyl styrene (**138j**). Under the conditions of 1 atm H₂ pressure at room temperature in methanol for 10 h, the acyclic enamine **138j** was reduced to the 2-*N*-piperidinylethylbenzene (**139j**) in quantitative yield with 53% ee. However, for the hydrogenation of cyclic enamines **142**, the more rigid diphosphine ligand **141** (BDPCH) proved to be the best choice. With the rhodium catalyst of the ligand **141**, cyclic enamines **142a** (R = Me) and **142b** (R = Bn) were hydrogenated to chiral amines **143a** and **143b** in 72 and 67% ee, respectively. It is noteworthy that the rhodium catalyst of DIOP ligand afforded only racemic product, although its activity was quite good.

In 2006, Zhou and co-workers^{15a} reported a highly enantioselective rhodium-catalyzed hydrogenation of 1-(1,2-diarylviny)pyrrolidines **146** for the synthesis of chiral tertiary amines **147** (Scheme 35). In the presence of 2 mol % I₂ and 20 mol % HOAc as the additives and the rhodium catalyst generated in situ from 1 mol % of [Rh(COD)₂]₂BF₄ and 2.2 mol % of chiral spiro monophosphonite **144c**, the enamine 1-(1,2-diphenylvinyl)pyrrolidine (**146a**) was hydrogenated in THF under 10 atm of hydrogen pressure at room temperature to the chiral amine **147a** in 100% conversion with 87% ee within 12 h. Of all the chiral ligands tested, the spiro monophosphonite **144c**, with a sterically bulky *tert*-butyl on the phosphorus atom, was the best ligand, and the corresponding binaphthyl-based monophosphonite **145** gave a moderate ee value (56% ee). However, the bidentate phosphorus ligands such as BINAP (**2**) and Josiphos

Scheme 35. Enantioselective Hydrogenation of 1-(1,2-Diarylviny)pyrrolidines with Ligand **144c**

(**1e**) were inefficient in this reaction. The enantioselectivity of the reaction was also sensitive to the nature of the substituents of the enamine substrates. Generally, the substrates with electron-donating substituents (X group) on the α -phenyl ring and/or electron-withdrawing substituents (Y group) on the β -phenyl ring gave higher enantioselectivity. The highest enantioselectivity (99.9% ee) was achieved in the hydrogenation of the enamine **146i** having a 4-F on the β -phenyl ring of the substrate (Scheme 35). In addition, this catalyst is sensitive to the steric hindrances of the *N*-alkyl groups. When the pyrrolidine moiety was changed to a piperidine or morphine, the ee values of the hydrogenation products were lowered to 75% and 77%, respectively.

With the chiral rhodium complexes of Josiphos-type ligands as the catalysts, Hsiao et al.¹³⁰ of Merck realized the enantioselective hydrogenation of primary enamines for the synthesis of β -amino acid derivatives. After screening a wide range of chiral ligands, they found that the rhodium complex of the ligand **1f** was efficient for the hydrogenation of the primary enamine esters **148**, providing the corresponding β -amino acid esters **149** with up to 96.1% ee (Scheme 36), whereas the rhodium complex of the ligand **1e** acted as a highly effective catalyst for the hydrogenation of the primary enamine amides **150** (97.1% ee). Interestingly, the deuteration experiments indicate that the reaction is the hydrogenation of the carbon–nitrogen double bond of the imine tautomer, rather than the direct hydrogenation of the carbon–carbon double bond of the enamines.

Subsequently, this highly efficient asymmetric hydrogenation was successfully applied in the preparation of sitagliptin (**153**), a potent selective DPP-4 inhibitor for the treatment of type II diabetes (T2DM) (Scheme 37).¹³¹ The hydrogenation was carried out at S/C = 330 at 50 °C and 16.7 atm H₂ pressure in MeOH for 16–18 h, providing the corresponding product **153** in 98% yield with 95% ee.

In 2005, Zhang and co-workers¹³² reported the rhodium-catalyzed asymmetric hydrogenation of *N*-aryl enamines **154** using TangPhos ligand (**75**) (Scheme 38). In the presence of 1 mol % of the chiral rhodium catalyst, under 6 atm H₂ pressure at 50 °C in TFE (2,2,2-trifluoroethanol) for 18 h, a wide range of *N*-aryl enamines **154** were hydrogenated to chiral *N*-aryl β-amino acid esters **155** in good to high enantioselectivities (78.9–96.3% ee).

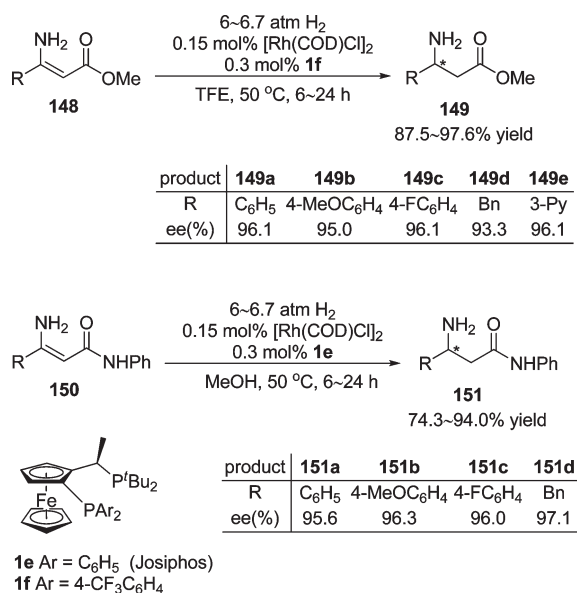
2.2.3. Chiral Iridium Catalysts. Recently, three groups independently investigated catalytic enantioselective hydrogenation of unfunctionalized enamines with chiral iridium catalysts. Andersson and co-workers¹³³ used the chiral iridium catalysts based on phosphine oxazoline ligands **156** as the catalyst to hydrogenate *N,N*-dialkyl α-arylethenamines to produce the corresponding chiral tertiary amines **138** with 64–87% ee (Scheme 39). However, in the hydrogenation of the substrate **138a** with a cyclic dialkylamino group, only very low enantiomeric excess (33% ee) was obtained.

Baeza and Pfaltz¹³⁴ introduced their developed phosphine oxazoline ligands **157** to this transformation. They found that the iridium complex of the ligand **157a** has high enantioselectivities (90–91% ee) for the hydrogenation of *N*-methyl-*N*-phenyl α-arylethenamines (**138n–p**) (Scheme 40). The iridium complex of the ligand **158a** was also efficient for the hydrogenation of *N*-methyl-*N*-benzyl α-arylethenamines (**138f** and **138q–s**). However, both catalysts Ir-**157a** and Ir-**158a** showed low enantioselectivities (<54% ee) for the hydrogenation of the *N*-pyrrolidinyl (**138a**) and *N,N*-diethyl α-phenylethenamine

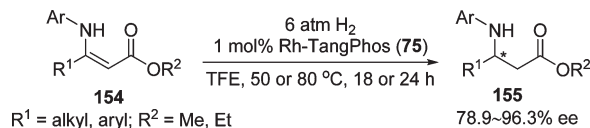
(**138h**). Furthermore, the iridium complex of the ligand **158a** was also efficient for the hydrogenation of a cyclic *N*-pyrrolidinyl enamine **161a** derived from 6-methoxytetralone, giving the corresponding amine product **162a** with 87% ee. With an iridium complex of the pyridine–phosphinite ligand **159** as the catalyst, the *N*-methyl-*N*-benzyl cyclic enamine **161c** was reduced to the chiral amine **162c** in moderate ee value (71% ee). It is noteworthy that, in the hydrogenation of the pyrrolidine enamine **146a**, the catalyst Ir-**160a** gave lower enantioselectivity (69% ee) than the catalyst Rh-**144c** (87% ee, Scheme 35). This result indicated that the rhodium catalyst of the chiral spiro phosphinite ligand **144c** is suitable for the hydrogenation of 1-(1,2-diarylvinyl)pyrrolidines.

An efficient chiral iridium catalyst was developed by Zhou and co-workers^{15b} for the enantioselective hydrogenation of unfunctionalized *N,N*-dialkyl enamines. In the search for a highly efficient methodology for the synthesis of cyclic chiral tertiary amines, they found that the iridium complex of the spiro monophosphoramidite SiPhos-pe ligand (**100d**) was a highly enantioselective catalyst for the hydrogenation of cyclic *N,N*-dialkyl enamine. The addition of I₂ is significant for obtaining full conversion and high enantioselectivity for this reaction. Compared with other monodentate phosphorus ligands such as phosphoramidites **102e** and **102f** with a binaphthyl backbone and the bidentate phosphorus ligands such as BINAP(**2**), SynPhos (**260**), and Josiphos (**1e**), the spiro phosphoramidite ligand **100d** with a bis[(*S*)-1-phenylethyl]amine moiety was

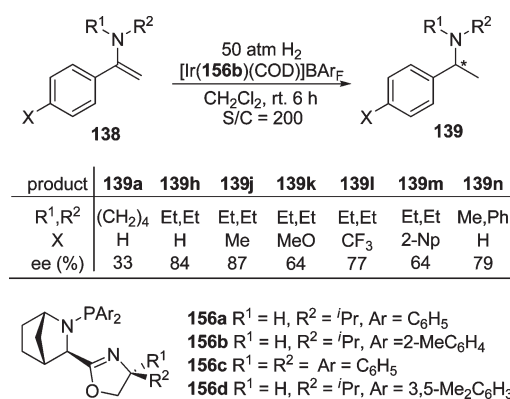
Scheme 36. Enantioselective Hydrogenation of Unprotected Enamines 148 and 150



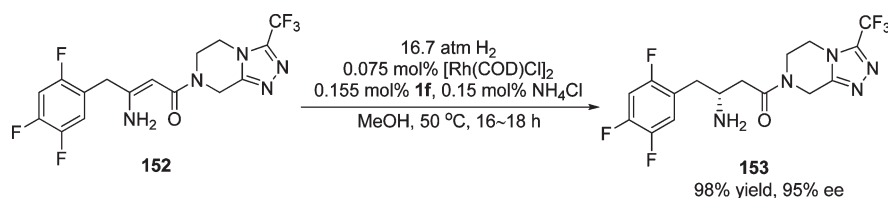
Scheme 38. Enantioselective Hydrogenation of *N*-Aryl Enamines 154



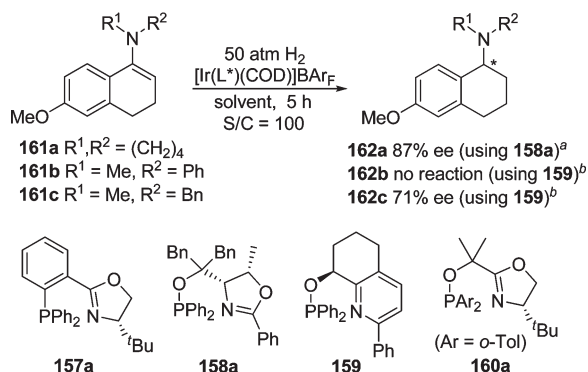
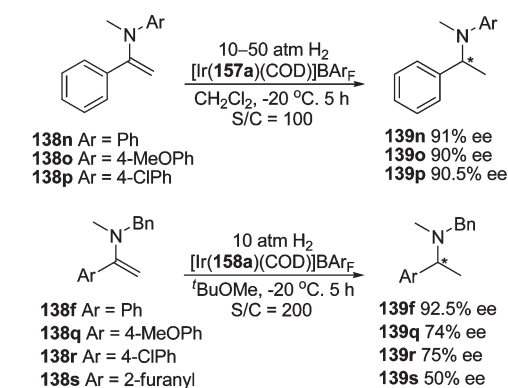
Scheme 39. Enantioselective Hydrogenation of Unfunctionalized Enamines with Ir-156 Catalyst



Scheme 37. Preparation of Sitagliitin (153)



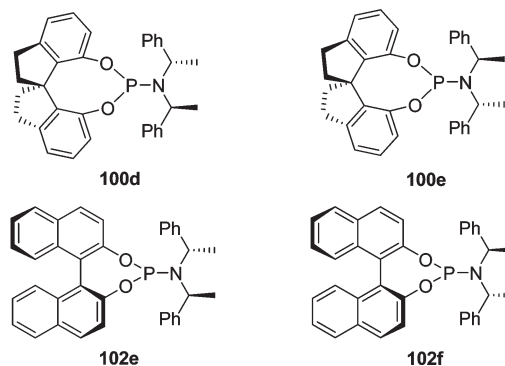
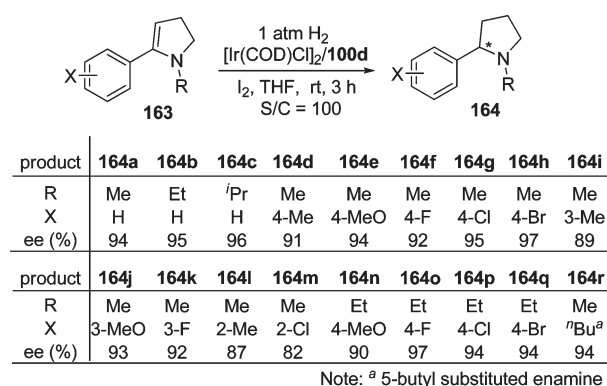
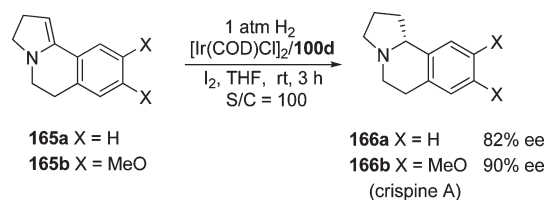
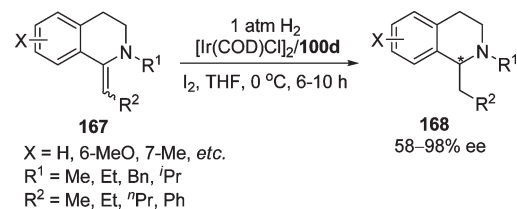
Scheme 40. Enantioselective Hydrogenation of Unfunctionalized Enamines with Ir Catalysts



shown to be the most efficient ligand for the hydrogenation of α -aryl dihydropyrrole derivatives **163**. A variety of cyclic enamines **163** with a five-membered ring could be hydrogenated to the chiral cyclic tertiary amines **164** with 72–97% ee by the iridium catalyst Ir-**100d** (Scheme 41). However, this catalyst is less efficient for the hydrogenation of the cyclic enamine with a six-membered ring.

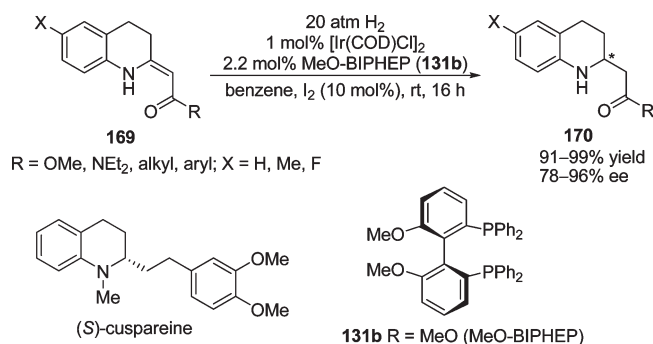
The Ir-**100d** catalyst has been successfully applied to the synthesis of chiral tricyclic amines (Scheme 42). The hydrogenation of tricyclic enamine such as 2,3,5,6-tetrahydropyrrolo-[2.1-*a*]isoquinolines **165a** (X = H) and **165b** (X = MeO) catalyzed by the Ir-**100d** catalyst afforded the corresponding tricyclic amines **166a** and **166b** with 88 and 90% ee, respectively. This reaction provided a convenient approach to isoquinoline alkaloid crispine A (**166b**),¹³⁵ which was isolated from *Carduus crispus*, Linn. (welded thistle) and has a significant cytotoxic activities.¹³⁶

This highly efficient iridium catalyst has also been applied to enantioselective hydrogenation of unfunctionalized enamines with an exocyclic double bond.¹³⁷ In combination with iodine or potassium iodide, the Ir-**100d** catalyst hydrogenated the *N*-alkyl tetrahydroisoquinolines **167** with an exocyclic double bond at the α -position under ambient hydrogen pressure (1 atm H₂), providing chiral *N*-alkyl tetrahydroisoquinolines **168** in high yields with up to 98% ee (Scheme 43). The substituent on the phenyl ring of the substrate has little effect on the enantioselectivity of the reaction. However, the hydrogenation reaction is sensitive to the steric hindrance of the alkyl groups on the *N*-atom and on the double bond of the enamine, and a small R¹ and/or R² was necessary for achieving high ee values of the

Scheme 41. Enantioselective Hydrogenation of Cyclic *N,N*-Dialkyl Enamine **163**Scheme 42. Enantioselective Hydrogenation of 2,3,5,6-Tetrahydropyrrolo[2.1-*a*]isoquinolines **165**Scheme 43. Enantioselective Hydrogenation of Exocyclic Enamines **167**

products. When the R¹ group was changed from a methyl group to a benzyl and an isopropyl, the ee values of the product decreased from 98 to 90 and 71% ee, respectively. When the R² group was an ethyl or a propyl instead of an H atom or a Me group, the corresponding products were obtained in low enantioselectivities (58 and 60% ee, respectively). It is worthy of mentioning that, if the R² group on the terminal carbon of the

Scheme 44. Enantioselective Hydrogenation of *N*-Aryl Exocyclic Enamines 170



double bond was not hydrogen, the substrates were usually prepared as a *Z/E*-mixture, and the Ir-100d catalyst was efficient for the hydrogenations of both the (*Z*)- and (*E*)-isomers.

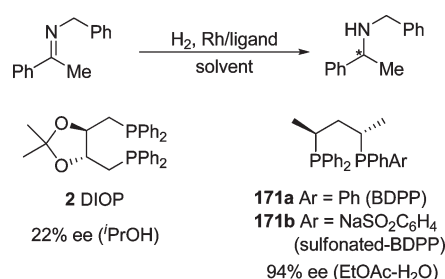
The iridium-catalyzed enantioselective hydrogenation of exocyclic *N*-arylenamines 169 was reported by Zhou and co-workers¹³⁸ in 2009. By using an iridium complex in situ generated from 1 mol % of [Ir(COD)Cl]₂ and 2.2 mol % of MeO-BIPHEP (131b) as the catalyst in the presence of 10 mol % of iodine as the additive, the exocyclic *N*-arylenamines 169 were hydrogenated to the corresponding chiral tetrahydroquinoline derivatives 170 in high yields with up to 96% ee (Scheme 44). The naturally occurring tetrahydroquinoline alkaloid (*S*)-cuspareine can be conveniently synthesized starting from the hydrogenation product 170 (X = H, R = 3,4-(MeO)₂C₆H₄) in two steps.

3. ENANTIOSELECTIVE HYDROGENATION OF IMINES

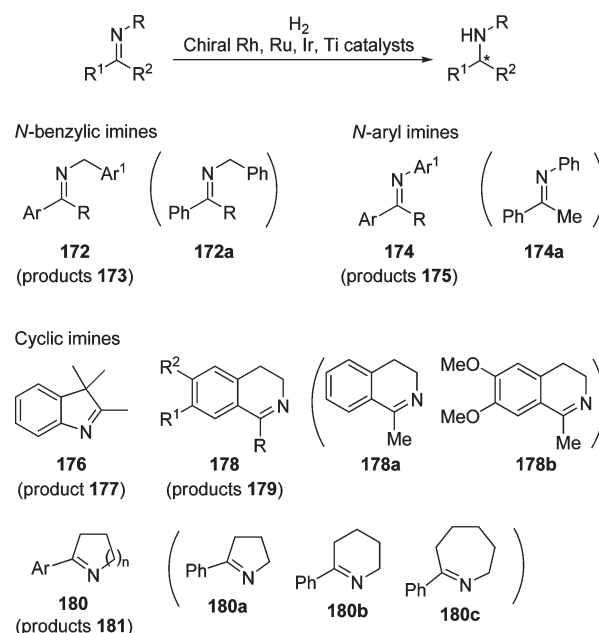
In 1975, Scorrano and co-workers¹³⁹ reported the first example of catalytic enantioselective hydrogenation of imine. They obtained 22% ee of enantioselectivity for the hydrogenation of the *N*-(α -methylbenzylidene)benzylamine by using a rhodium complex of DIOP ligand (2). Although this catalytic enantioselective imine hydrogenation provides new access to optically enriched chiral amines, no significant progress was made in the following decade. The chiral catalysts developed in the early stage were dominated by the rhodium complexes of chiral diphosphines, and only moderate enantioselectivities (60–70% ee) were obtained.¹⁴⁰ Until 1989, by using the rhodium complex of monosulfonated bidentate BDPP ligand 171b as the catalyst (Scheme 45), Bakos et al.¹⁴¹ significantly improved the enantioselectivity for the hydrogenation of *N*-benzyl imines to up to 94% ee. Since then, various highly enantioselective chiral catalysts have been developed, and promising results were achieved in catalytic imine hydrogenation.

In addition to the aforementioned well-known iridium-Xylophos catalyst, which led to the large-scale production of the amine herbicide (*S*)-Metolachlor (Scheme 2),² Buchwald's titanocene catalyst,¹⁴² Pfaltz's iridium-PHOX catalyst,¹⁴³ and Zhang's iridium-f-Binaphane catalyst¹⁴⁴ also exhibited excellent results for catalytic enantioselective hydrogenation of imines. To date, a variety of highly efficient catalysts such as rhodium, iridium, ruthenium, and titanium complexes based on a wide range of chiral ligands have been developed for the enantioselective hydrogenation of imines, with the chiral iridium catalysts being the most outstanding.

Scheme 45. Early Examples of Enantioselective Hydrogenation of Imines



Scheme 46. Common *N*-Aryl/Alkyl Imines and the Corresponding Hydrogenation Products

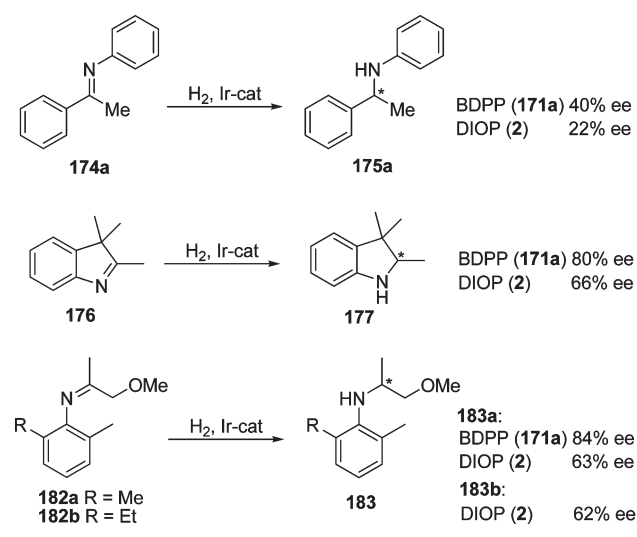
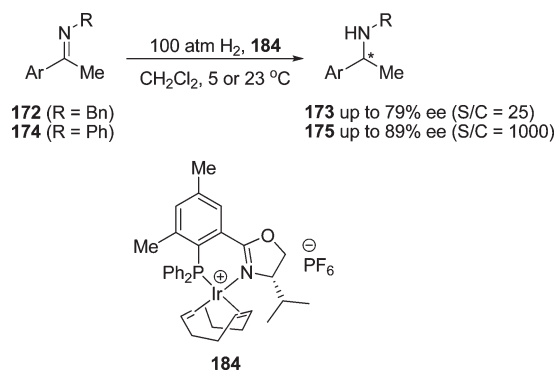


Furthermore, the scope of imine substrate has also been expanded. Various types of *N*-aryl/alkylimines, the activated imines such as *N*-tosylimines and *N*-diphenylphosphinylimines, and the unprotected imines now can be hydrogenated to the corresponding chiral amines or amine derivatives in high enantioselectivities, although for most of the highly enantioselective catalysts, the substrate affinity is still within a narrow range.

3.1. Enantioselective Hydrogenation of *N*-Aryl/Alkylimines

The *N*-aryl/alkyl imines have received increasing attention as substrates for enantioselective imine hydrogenation. The catalytic enantioselective hydrogenation of acyclic and cyclic *N*-aryl/alkyl imines provides a direct approach to a wide range of chiral secondary amines (Scheme 46).

3.1.1. Chiral Iridium Catalysts. Chiral iridium catalysts for imine hydrogenation began to appear in the literature in 1990. In this year, Osborn and co-workers¹⁴⁵ and Spindler et al.¹⁴⁶ reported independently the iridium-catalyzed enantioselective hydrogenation of *N*-arylimines 174 by using diphosphine DIOP (2) and BDPP (171a) ligands, and obtained moderate enantioselectivities (Scheme 47). Subsequently, Spindler and

Scheme 47. Enantioselective Hydrogenation of Imines with Ir-DIOP/BDPP Catalysts**Scheme 48. Enantioselective Hydrogenation of Imines with Catalyst 184**

co-workers² introduced chiral ferrocenyl-based diphosphine Xyliphos (**1a**) ligand in this hydrogenation, which finally led to an industrial process for the synthesis of the chiral herbicide (*S*)-Metolachlor (Scheme 2). In 1997, Pfaltz and co-workers¹⁴³ used the iridium catalyst **184** based on phosphino oxazoline ligands for imine hydrogenation, providing high enantioselectivities (89% ee) for the reduction of *N*-aryl/alkyl imines (Scheme 48).

Encouraged by these significant examples, a number of research groups devoted their efforts to the development of highly efficient chiral iridium catalysts for imine hydrogenation, and many chiral diphosphorus ligands, phosphino oxazoline ligands, were found to be highly enantioselective for iridium-catalyzed enantioselective hydrogenation of *N*-aryl/alkylimines.

3.1.1.1. Diphosphine Ligands. Ligand DIOP (**2**) is one of the first diphosphine ligands to be explored for the iridium-catalyzed enantioselective hydrogenation of imines. Although only moderate enantioselectivities were obtained for the hydrogenation of imines such as a cyclic imine **176** (66% ee),¹³⁹ this encouraged the investigations of modified DIOP ligands and other diphosphine ligands for such transformations. In 1994, Achiwa and co-workers¹⁴⁷ tested their developed MOD-DIOP

(**185**) ligand (Figure 12)¹⁴⁸ in the imine hydrogenation and achieved 81.4% ee for an cyclic imine **176** and 45.5% ee for an *N*-aryl imine **174a** (under the conditions of 0.5 mol % of $[\text{Ir}(\text{COD})\text{Cl}]_2$ as the catalyst precursor and Bu_4NI as the additive, under 100 atm H_2 at 20 °C in the mixture solvent of methanol and benzene for 48 h). A slightly higher enantioselectivity of 85% ee was obtained when Zhang and co-workers¹⁴⁹ introduced the DIOP-type ligand **186b** in the hydrogenation of the cyclic imine **176** in the presence of I_2 as an additive under 67 atm H_2 pressure at 0 °C in CH_2Cl_2 (S/C = 100). Furthermore, with the MOD-DIOP (**185**) ligand and in the presence of bismuth(III) iodide (BiI_3) as an additive, Kanai and co-workers¹⁵⁰ obtained high enantioselectivity (90% ee) for the hydrogenation of a cyclic imine **192**, 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine (Scheme 49). This reaction provided an enantioselective method for the preparation of Levofloxacin, a potent antibacterial agent.¹⁵¹

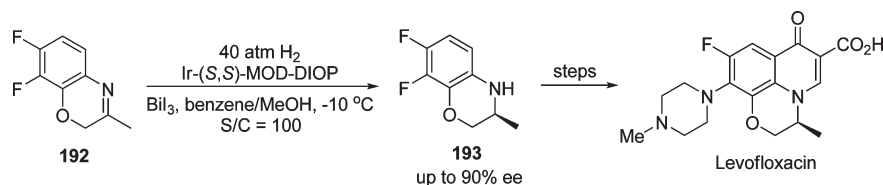
The modified pyrrolidine diphosphines, such as the ligand **187a** (BCPM) and its analogue **187b** (MCCPM), were found to be more efficient than the DIOP-type ligands and the original BPPM ligand in the hydrogenation of a cyclic imine **176**.¹⁵² In the presence of BiI_3 as an additive and under 100 atm H_2 in methanol and benzene at −30 or −10 °C (S/C = 100), BCPM and MCCPM ligands offered the corresponding chiral amine **177** with 91 and 90% ee, respectively. However, these ligands were ineffective for the hydrogenation of acyclic imine such as *N*-aryl imine **174a** and cyclic imines with a six-membered ring such as 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**178b**, 14% ee, Scheme 50). By careful investigation of the additives, Achiwa and co-workers¹⁵³ found that the addition of phthalimide is highly helpful for improving the enantioselectivity of the hydrogenation of cyclic imines **178**. With this additive, and BCPM (**187a**) or BINAP (**3**) as the ligand, a number of optically active 1,2,3,4-tetrahydroisoquinoline alkaloids were produced with up to 93% ee (Scheme 50).

In 1998, Zhu and Zhang¹⁵⁴ used another type of 1,4-diphosphine ligand BICP (**38**) in the iridium-catalyzed imine hydrogenation. They found that the BICP ligand was also effective for the hydrogenation of the cyclic imine **176**, and as high as 95% ee was achieved in the presence of phthalimide as an additive under 67 atm H_2 pressure and 0 °C in CH_2Cl_2 for 100 h (S/C = 100). Currently, the most efficient 1,4-diphosphine ligand capable of hydrogenation of acyclic imines is the ligand DDPPM (**188**) derived from *D*-isomannide.¹⁵⁵ Under the mild conditions of atmospheric hydrogen pressure (1 atm H_2) and room temperature in CH_2Cl_2 for 24 h (S/C = 100), the iridium complex of the ligand **188** offered good to high enantioselectivities (80–94% ee) for the hydrogenation of *N*-aryl imines **174**.¹⁵⁶ The formations of dimeric/trimeric iridium(III) polyhydride complexes **195** and **196** from the reaction of $[\text{Ir}(\text{188})(\text{COD})]\text{PF}_6$ with molecular hydrogen inhibited the activity of the catalyst (Figure 13).

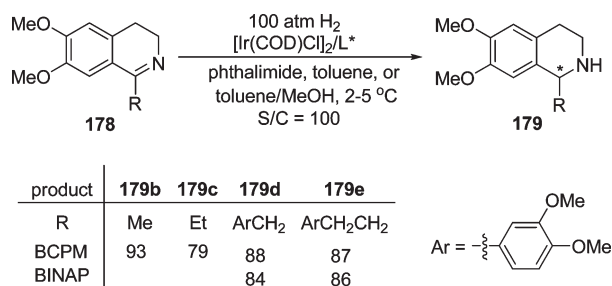
Ligand BINAP (**3**) also showed good to high enantioselectivity in the iridium-catalyzed hydrogenation of imines. In 1995, Tani et al.¹⁵⁷ used an iridium complex of Tol-BINAP as the catalyst for the hydrogenations of a cyclic imine, 2-phenylpiperidine (**180b**), and *N*-aryl imine **174a** in methanol under 60 atm H_2 pressure at 20 °C, and obtained 90% ee and 70% ee, respectively.

For the synthesis of 1-hydroxymethyl-substituted tetrahydroisoquinoline alkaloids, such as a (*S*)-calycotomine, Morimoto et al.¹⁵⁸ investigated the Ir-BINAP catalyst for the enantioselective

Scheme 49. Enantioselective Hydrogenation of Cyclic Imine 192



Scheme 50. Enantioselective Hydrogenation of Cyclic Imines 178



hydrogenation of the isoquinoline-type imines **178**. The catalyst Ir-(R)-BINAP can reduce 1-benzoyloxymethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**178f**) to 1-benzoyloxymethyl-substituted tetrahydroisoquinoline derivative **179f** in good yield (85%) and enantioselectivity (86% ee) in the presence of F₄-phthalimide as an additive (Scheme 51). Meanwhile, the addition of a parabanic acid was crucial for obtaining high enantioselectivity (89% ee) in the hydrogenation of the 1-(3-benzoyloxy)propyl-substituted cyclic imine **178g**.

The carboxylato(diphosphine)iridium(III) complexes **196** and **197** were developed by Sablong and Osborn¹⁵⁹ in 1996 (Figure 14). The complex **196a** containing a BINAP (**2**) ligand showed moderate enantioselectivities (up to 67% ee) for the hydrogenation of acyclic imines such as **174a** and **182a**. However, the complex **198** containing a BDPP (**171a**) ligand gave better enantioselectivity (up to 90% ee) for the hydrogenation of the *N*-arylimine **182a**. Recently, Genet, Mashima, and co-workers¹⁶⁰ found that the mononuclear halo-carboxylatoiridium(III) complexes **196c–e** and the cationic dinuclear triply halogen-bridged iridium(III) complexes **198** can effectively hydrogenate cyclic imines **180a–c** to the corresponding products **181a–c** with up to 91% ee at S/C = 1000 (60 atm H₂, 20 °C, toluene, 40 h).

The ferrocene-based diphosphines are the most promising ligands in the enantioselective hydrogenation of imines. In addition to the aforementioned highly efficient Josiphos ligands,¹⁶¹ several other diphosphines based on the ferrocene backbone have been reported to be efficient ligands in the iridium-catalyzed hydrogenation of imines. After the successful application of Josiphos ligand in industrial synthesis of (S)-Metolachlor, Blaser, Spindler, and co-workers¹⁶² developed a series of Josiphos-type ligands **1** (Figure 12) for systematic investigation of the electronic and steric effects of the ligands on imine hydrogenations. They found that the activity of the iridium catalysts containing ferrocenyl diphosphine ligands varied dramatically in the hydrogenation of *N*-arylimines, and the optimal combination of the R and R' groups on the ferrocenyl

backbone was different for each substrate. Extremely high catalytic activity and moderate to good enantioselectivities (up to 80% ee) were observed for the hydrogenation of the imine **182b** with the iridium complex of **1a** (Xyliphos) as the catalyst. With the same type of catalysts, the *N*-arylimines **174** can also be hydrogenated with enantioselectivities up to 96% ee, albeit with higher catalyst loading. The immobilized Xyliphos ligands bonded to silica and polystyrene as well as the soluble dimeric Xyliphos ligands **190** were developed by Pugin et al.¹⁶³ in 2002. These immobilized iridium catalysts gave similar enantioselectivities (up to 80% ee) but lower activities (TONs < 200 000) than the homogeneous analogues. These negative effects were tentatively explained by the higher catalyst concentration on the surface of support, leading to deactivation of the catalysts by irreversible dimer formation.

The chiral ferrocene diphosphine ligand **190** having only a planar chirality, developed by Reetz et al.¹⁶⁴ in 1999, gave only moderate enantioselectivity (79% ee) for the hydrogenation of the cyclic imine **176**. Very high enantioselectivity was achieved in the catalytic enantioselective hydrogenation of imines by using an iridium complex of the chiral ferrocene binaphane ligand **191** (f-Binaphane).¹⁴⁴ In searching for efficient chiral ligands for catalytic enantioselective hydrogenation of imines, Xiao and Zhang found that the Binaphane ligand **191** with a strong electron back-donating ferrocene backbone has excellent enantioselectivity in the iridium-catalyzed hydrogenation of imines. Up to 94% ee of enantioselectivity was obtained for the hydrogenation of *N*-arylimines **174** (−5 °C, with iodine as an additive), and over 99% ees were achieved for the hydrogenation of the *N*-arylimines **174** with *N*-2,6-dimethylphenyl group, albeit with a lower conversion (77–80%). The hydrogenation of *N*-arylimines **174** with *N*-2-methyl-6-methoxyphenyl group also gave ee values of up to 98% ee, and the corresponding hydrogenation products, upon treatment with cerium ammonium nitrate (CAN), can provide chiral 1-arylethylamines (Scheme 52).

The *P*-chiral diphosphine ligands also showed promising enantioselectivity in the iridium-catalyzed hydrogenation of the acyclic aromatic *N*-aryl imines. In 2006, Imamoto et al.¹⁶⁵ reported that the iridium complex of the ligand ^tBu-BisP* (**73a**) with a BAr_F (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) counterion exhibited exceedingly high catalytic activity for the hydrogenation of imines. A series of *N*-arylimines **174** were hydrogenated to the corresponding chiral amines **175** in high yields (91–99%) with good to excellent enantioselectivities (83–99% ee) under the mild conditions of 1 atm of hydrogen pressure in CH₂Cl₂ at room temperature for 1.5–12 h (S/C = 200). Recently, Zhang and co-workers¹⁶⁶ screened a range of diphosphophine ligands including TangPhos (**75**), DuanPhos (**77**), and DuPhos (**12**) in the iridium-catalyzed hydrogenation of *N*-arylimines **174**, and found that the highly rigid and electron-donating *P*-chiral diphosphine DuanPhos was the most efficient

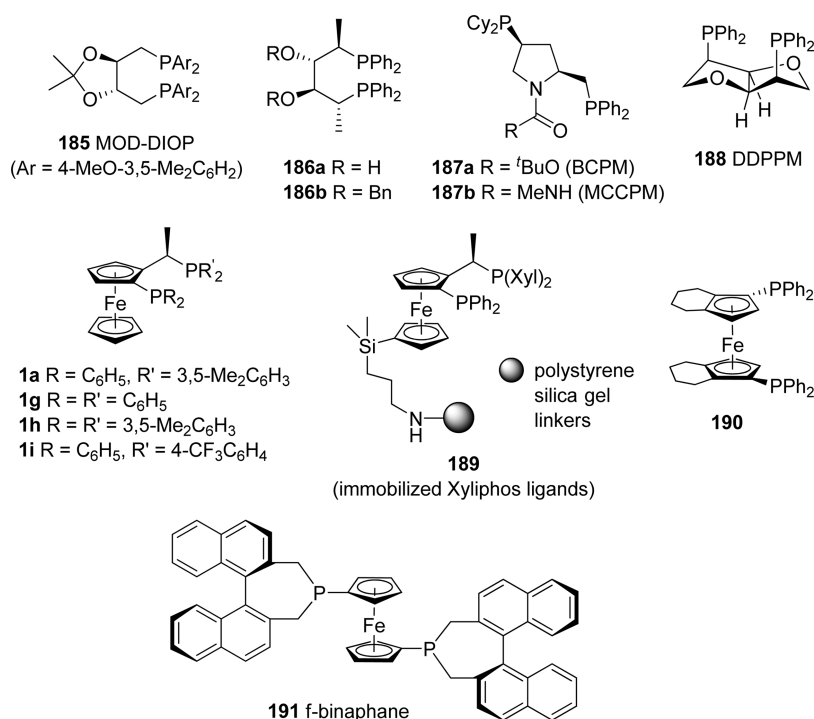


Figure 12. Diprophosphine ligands for imine hydrogenation.

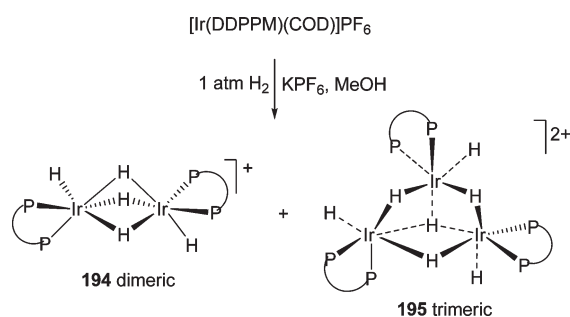
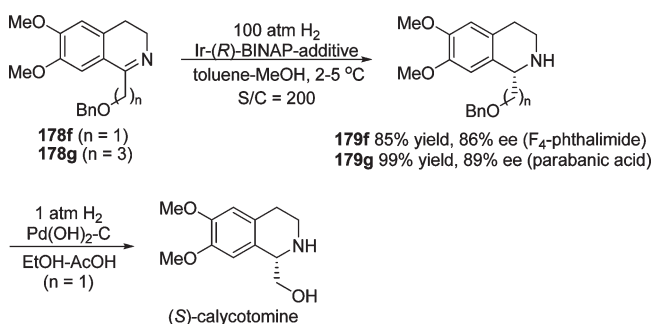


Figure 13. Dimeric and trimeric iridium DDPPM complexes.

ligand among them in terms of reactivity and enantioselectivity. Under the optimal conditions (S/C = 1000, 5 atm H₂, rt, CH₂Cl₂, 12 h), the iridium complex [Ir(77)(COD)]BAR_F showed 89–99% ee enantioselectivities for the hydrogenation of a series of acyclic aromatic *N*-aryl imines **174**. At extremely low catalyst loading (down to 0.01 mol %, S/C = 10 000), the hydrogenation of the standard substrate **174a** was also performed smoothly with a comparable enantioselectivity (92% ee). Furthermore, this highly efficient imine hydrogenation can also be performed under ambient hydrogen pressure (1 atm) with no obvious erosion of the ee value of product.

Chiral diphosphinite, diphosphite, and phosphine–phosphite ligands also showed good enantioselectivity in the iridium-catalyzed hydrogenation of imines. In 2003, Castillón, Claver, and co-workers¹⁶⁷ used the diphosphinite ligand **199** and the diphosphite ligand **200** (Figure 15) with a xylofuranoside backbone in the iridium-catalyzed enantioselective hydrogenation of imines. The diphosphinite ligand **199** gave moderate ee values (up to 57% ee) for the hydrogenation of the substrate **174a**, while almost no ee value was observed in the reactions with

Scheme 51. Enantioselective Hydrogenations of Cyclic Imines **178f** and **178g**



diphosphite ligands **200a** and **200b**. However, after adding Bu₄NI as an additive, the diphosphite ligand **200b** with *tert*-butyl groups on the biphenyl moiety offered the hydrogenation product with 46% ee. Subsequently, they developed several C₂-symmetric diphosphinite ligands **201** with different electron-donating or electron-withdrawing groups on the *P*-phenyl rings, as well as C₁-symmetric phosphinite–phosphite ligands **202** based on glucosamine backbone.¹⁶⁸ These glucosamine-based chiral ligands showed better enantioselectivity than those with xylofuranoside backbone in the iridium-catalyzed hydrogenation of imines. In the hydrogenation of the *N*-aryl imine **174a**, the diphosphinite ligand **201b** with electron-donating 4-methoxy groups on the *P*-phenyl rings gave the best result (70% ee), but in the hydrogenation of the *N*-benzylimine **172a**, the phosphinite–phosphite ligand **202a** was the choice (76% ee).

Chiral phosphine–phosphite ligand was introduced into the iridium-catalyzed enantioselective hydrogenation of *N*-arylimines by Pizzano and co-workers in 2005.¹⁶⁹ After comparing several ethylene- or benzene-bridged phosphine–phosphite

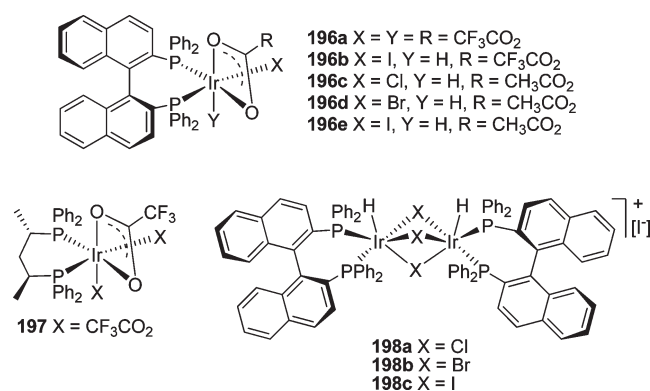
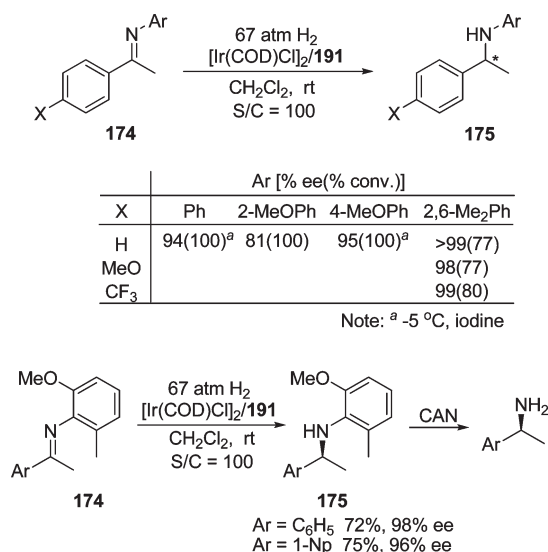


Figure 14. Carboxylato(diphosphine)iridium(III) complexes and cationic dinuclear triply halogen-bridged iridium(III) complexes.

Scheme 52. Enantioselective Hydrogenation of *N*-Aryl Imines **174 with Catalyst Ir-191**



ligands **203** and **204a–d** bearing a chiral 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethylbiphenyl moiety in the iridium-catalyzed hydrogenation of the *N*-arylimine **174a**, they found that the ethylene-bridged ligand **204d** with 3,5-methyl groups on the *P*-phenyl rings was the best ligand, affording the hydrogenation product with up to 84% ee under 30 atm H₂ pressure and room temperature in CH₂Cl₂ for 24 h (S/C = 100). Changing the achiral PAr₂ group of this ligand to a *P*-chiral PAr¹Ar² group such as a P(C₆H₅)(2-MeOC₆H₄) resulted in the *P*-chiral phosphine–phosphite ligand (*S_p*,*S_a*)-**204e**, which gave a similar enantioselectivity (72–85% ee) as that of ligand **204d** in the hydrogenation of *N*-arylimines **174**.¹⁷⁰

3.1.1.2. Phosphorus–Nitrogen Ligands. Chiral phosphine–nitrogen ligands, especially phosphine oxazolines, have been proven to be one of the most efficient chiral ligands for the iridium-catalyzed enantioselective hydrogenation of imines. Since Pfaltz and co-workers¹⁴³ reported the highly efficient iridium-catalyzed enantioselective hydrogenation of imines with phosphine oxazoline ligands in 1997, many phosphine oxazoline ligands and related phosphorus–nitrogen ligands have been investigated by the groups of Pfaltz and others in

the iridium-catalyzed hydrogenation of imines, and some of them exhibited promising enantioselectivity.

Leitner, Pfaltz, and co-workers¹⁷¹ used supercritical carbon dioxide (scCO₂) as a solvent for the Ir-PhOX/PF₆-catalyzed imine hydrogenation. To improve the catalyst solubility in scCO₂, they modified the phosphine oxazoline PhOX ligand **157b** (Figure 16) by introducing perfluoroalkyl groups into the *P*-phenyl groups and verified the counterions of the cationic iridium complexes. Finally, they found that the cationic iridium complex with the modified PhOX ligand was an efficient catalyst for the hydrogenation of the *N*-arylimine **174a** in supercritical carbon dioxide (scCO₂). Under the optimal conditions (scCO₂ [*d*(CO₂) = 0.75 g/mL] at 40 °C and 30 atm H₂ pressure), the cationic iridium complex (0.078 mol %) of perfluoroalkyl groups modified PhOX ligand provided the hydrogenation product with up to 81% ee. The catalyst loading could be further reduced to as little as 0.014 mol % without any deleterious effect on the reaction rate. Thus, >90% conversion of the imine, corresponding to >6 800 turnovers, could be achieved within 6 h, albeit with some loss in enantioselectivity. Moreover, the catalyst could be recycled three times with very little loss of the reactivity or enantioselectivity of the reaction. Leitner, Pfaltz, and co-workers¹⁷² subsequently addressed the problem of diminishing rates in imine hydrogenation in scCO₂ by combining the solvent with ionic liquid.

In 2002, Pfaltz and co-workers¹⁷³ developed a series of chiral phosphinite oxazoline ThrePhOX ligands **158** derived from threonine. These new oxazoline-based phosphorus–nitrogen ligands showed good enantioselectivity in the iridium-catalyzed hydrogenation of the *N*-arylimine **174a**. With BAr_F[−] as a counteranion, the cationic iridium complexes Ir-**158b** and Ir-**158c** provided chiral amine **175a** with up to 80% ee in CH₂Cl₂ under 50 atm H₂ pressure and room temperature for 4 h (S/C = 100). Under the same conditions, the iridium complexes of the phosphine oxazoline *Neo*PhOX ligands **160** gave a little better enantioselectivity.¹⁷⁴

Recently, promoted by the success in the catalytic enantioselective hydrogenation of olefins¹⁷⁵ with modified PhOX and related oxazoline-based phosphorus–nitrogen ligands, Baeza and Pfaltz¹⁷⁶ reinvestigated iridium-catalyzed imine hydrogenation with a wide range of chiral phosphorus–nitrogen ligands that have been developed in their group during the last 10 years. Screening the ligands showed that the phosphine oxazoline ligands **157b** (85% ee), **160b** (85% ee), **206a** (88% ee), and **207b** (89% ee) have better enantioselectivities in the hydrogenation of the *N*-arylimine **174a**. By using the cationic iridium complexes of the ligands **157b**, **160b**, and **206a** as the catalysts and under the optimal reaction conditions (S/C = 200, 5 atm H₂, 0 or −20 °C, CH₂Cl₂, 6–8 h), a variety of *N*-arylimines **174** were hydrogenated to the corresponding chiral amines **175** with 74–90, 77–95, and 81–96% ee, respectively (Scheme 53). The *N*-arylimine **208a** derived from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one was also hydrogenated to the chiral amine **209a** with up to 82% ee.

Apart from Pfaltz's chiral oxazoline-based phosphorus–nitrogen ligands, many other phosphorus–nitrogen ligands, mainly phosphine oxazolines (Figure 17), have been developed by different groups and have shown good to excellent results in the iridium-catalyzed enantioselective hydrogenation of imines. In 2003, Cozzi et al.¹⁷⁷ reported a series of heterocyclic phosphine oxazoline ligands **210** and **211** (HetPhOX) derived from thiophene and benzo[*b*]thiophene. These ligands gave moderate

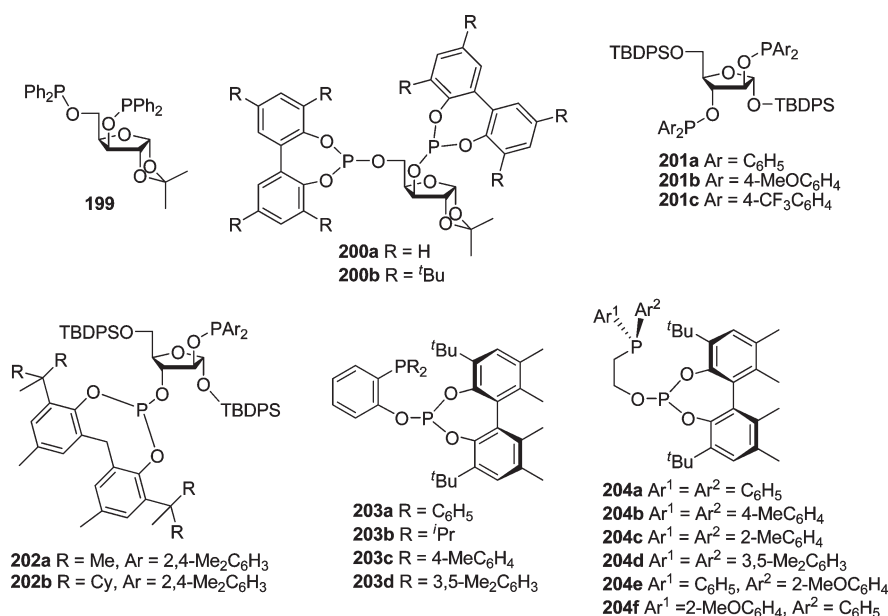


Figure 15. Chiral diphosphinite, diphosphite, and phosphine–phosphite ligands.

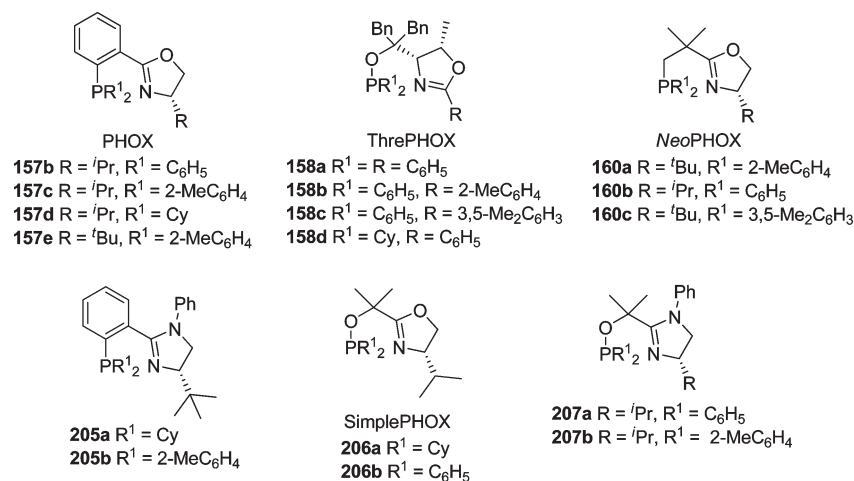


Figure 16. Pfaltz's phosphine oxazolines.

to good enantioselectivity in the iridium-catalyzed hydrogenation of the *N*-arylimine **174a**, and the benzo[*b*]thiophene derived phosphine oxazoline ligands **211** proved to be superior in terms of enantioselectivity. By using the catalyst Ir-**211a**, the chiral amine **175a** was obtained with 86% ee under the conditions of 50 atm H₂ and room temperature in CH₂Cl₂ for 4 h (S/C = 1000). However, the tetrathiafulvalene-based heterocyclic phosphino oxazoline ligand **212** (TTF-PHOX), developed by Avarvari and co-workers,¹⁷⁸ gave only moderate enantioselectivity (up to 68% ee) for the same hydrogenation reaction.¹⁷⁹

The phosphine oxazoline ligands **213** (Figure 17) with a diphenylphosphinomethyl group being tethered to the oxazoline ring at C-4 were developed by James and co-workers¹⁸⁰ in 2004. These ligands readily form the [Ir(COD)(**213**)]PF₆ complexes with a five-membered chelating ring, which showed moderate enantioselectivity for the hydrogenation of *N*-benzylimine **172a**. For example, by using the Ir-**213b** catalyst, the amine product **173a** was obtained with 63% ee at room temperature in CH₂Cl₂ under 3 atm H₂ pressure (S/C = 25). On the contrast, Hou and

co-workers¹⁸¹ synthesized a series of benzylic phosphine oxazoline ligands **214**, which coordinated to iridium to form iridium complexes with a flexible seven-membered chelating ring. Among these benzylic phosphine oxazoline ligands, the ligand **214a** gave higher enantioselectivity in the hydrogenation of *N*-arylimines **174** (up to 88% ee) under 50 atm H₂ pressure and room temperature in CH₂Cl₂ for 24 h (S/C = 333). The *N*-arylimines, derived from 1-indanone and 1-tetralone, were also hydrogenated with 61 and 62% ee, respectively, under the same reaction conditions.

Chiral spiro phosphine oxazoline ligands showed prominent results in the enantioselective hydrogenation of imines. In 2006, Zhou and co-workers¹⁸² developed a new type of phosphine oxazoline ligand SIPHOX (**215**) with a rigid spirobiindane scaffold. The iridium complexes of these spiro *P,N*-ligands were prepared by reacting the ligand **215** with [Ir(COD)Cl]₂ in the presence of sodium tetrakis-3,5-bis(trifluoromethyl)phenylborate (NaBAR_F). The Ir-SIPHOX complexes were extraordinarily stable under hydrogen pressure and could hydrogenate

N-arylimines **174** under ambient H₂ pressure with excellent enantioselectivity and full conversion. With the catalyst Ir-**215e**/BARF, a wide range of *N*-arylimines **174** can be hydrogenated to the corresponding chiral amines **175** in high yields with 90–97% ee under mild conditions (S/C = 100, 1 atm, H₂, 10 °C, *tert*-butyl methyl ether, 20 h).

The crystal structure analysis of the Ir-**215a** complex showed that the SIPHOX ligand **215a** constructed a crowded and

efficient chiral environment around the iridium metal center (Figure 18). In the crystal, the ligand acted as a rigid pincer, and the iridium atom was clamped in a nine-membered heterometal ring. The spirobiindane backbone, *P*-phenyl groups, and isopropyl group on the oxazoline ring created a crowded and rigid environment around the central metal. Such crowded structure efficiently prevents the autoaggregation of the catalyst. The ESI-MS measurement also supports the stability of the catalyst. After treatment of the Ir-**215a** complex with 50 atm of H₂ at room temperature for 3 h, no dimeric or trimeric species was detected in the ESI-MS analysis. The excellent stability of the Ir complexes of SIPHOX ligands **215** under hydrogen atmosphere interprets why they have extremely high activity in the hydrogenation.

In 2009, Ding and co-workers¹⁸³ developed a new class of chiral spiro phosphine oxazoline ligands SpinPHOX (**216**) based on the spiro[4.4]-1,6-nonadiene backbone. The cationic iridium complexes of the ligands **216** were also found to be highly

Scheme 53. Enantioselective Hydrogenation of *N*-Arylimines with Pfaltz's Iridium Catalysts

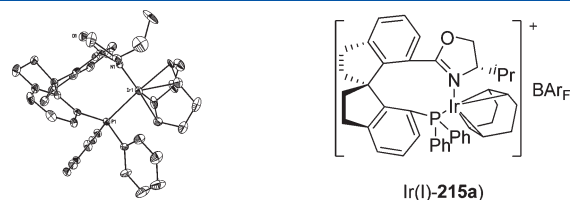
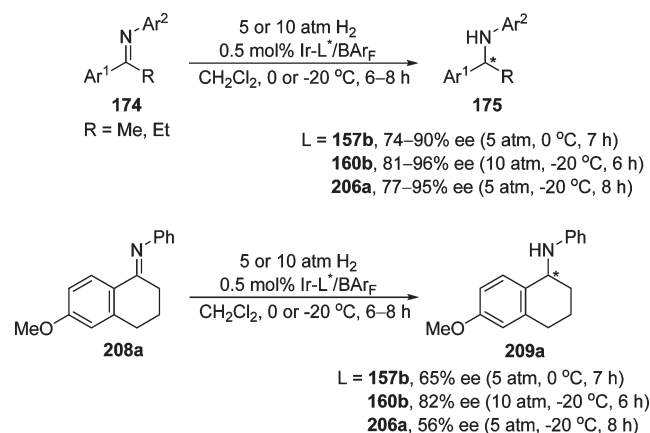


Figure 18. Crystal structure of Ir(I)-**215a** (omitted BARF).

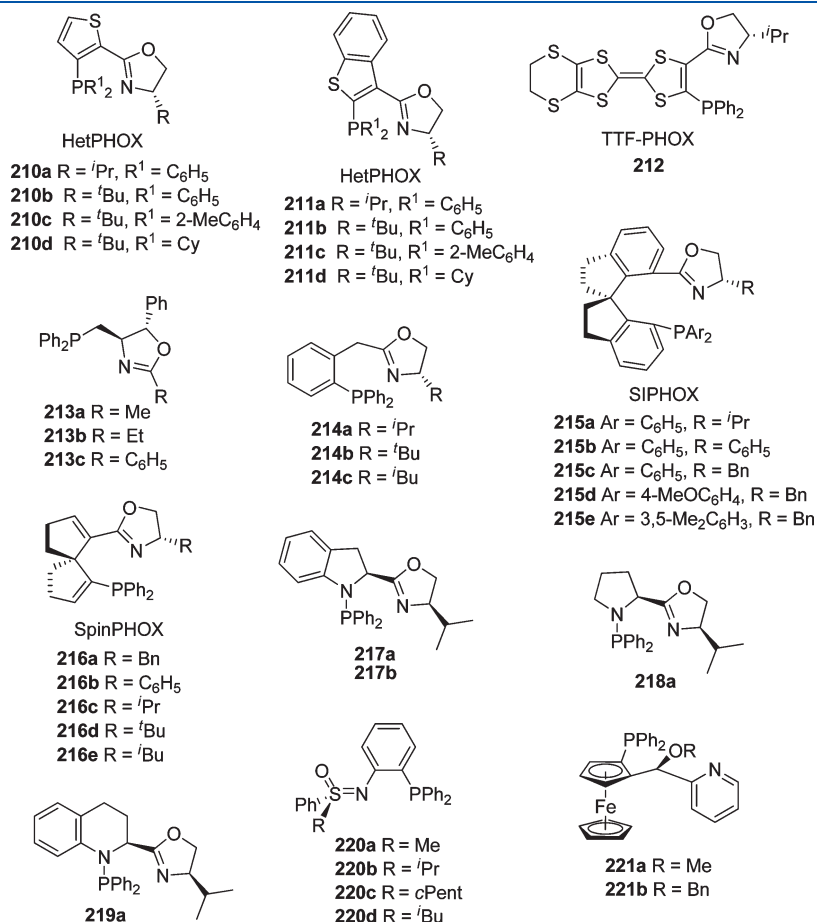
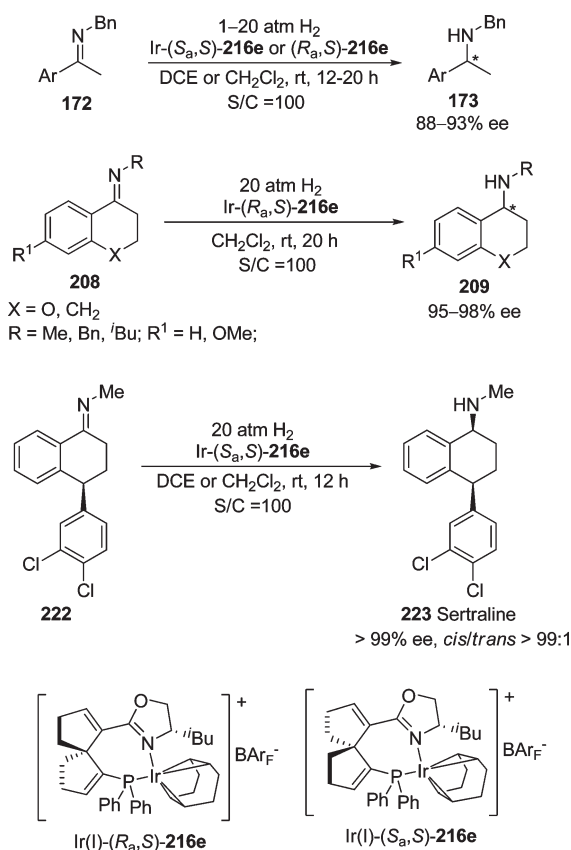


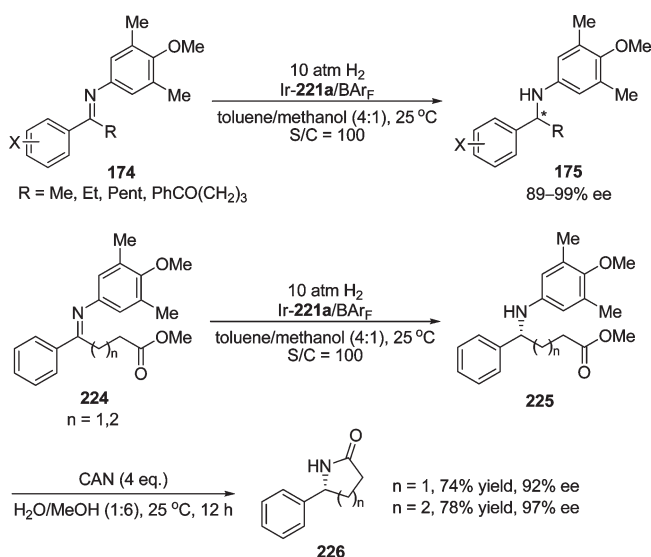
Figure 17. Chiral phosphine–nitrogen ligands.

Scheme 54. Enantioselective Hydrogenation of Imines with Catalysts Ir-216



efficient in the hydrogenation of imines. With the iridium complex of the ligand **216c**, having an isopropyl group on the oxazoline ring, as the catalyst, a variety of *N*-arylimines **174** with different substituents were hydrogenated under 1 atm H₂ pressure and 10 °C in 1,2-dichloroethane (S/C = 100) to afford the corresponding chiral amines with good to excellent enantioselectivities (88–95% ee). The most prominent feature of these chiral spiro iridium complexes is that they can also efficiently catalyze the hydrogenation of *N*-alkylimines, more challenging substrates. A series of *N*-alkylimines **172** and **208** derived from acyclic and cyclic ketones were hydrogenated with the Ir-**216e** catalyst to provide the corresponding chiral amines **173** and **209**, respectively, with 88–98% ee under similar reaction conditions (Scheme 54). This methodology has been successfully applied in the enantioselective synthesis of sertraline (**223**), an antidepressant chiral drug.¹⁸⁴

Chiral aminophosphine oxazoline ligands **217–219**,¹⁸⁵ derived from (*S*)-indoline carboxylic acid, (*S*)-proline, and (*S*)-tetrahydroisoquinoline carboxylic acid, respectively, also exhibited good enantioselectivity in the iridium-catalyzed hydrogenation of *N*-aryl- and *N*-alkylimines.¹⁸⁶ With catalysts Ir-**217**, *N*-benzylimine **172a** and *N*-arylimine **174a** were hydrogenated to the corresponding chiral amines **173a** and **175a** with 82 and 90% ee, respectively (S/C = 50, 20, or 50 atm H₂ pressure and 25 °C in CH₂Cl₂). The chiral aminophosphine oxazoline ligands **156** derived from (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (Scheme 39) were reported by Andersson and co-workers¹⁸⁷ were also efficient for the iridium-catalyzed

Scheme 55. Enantioselective Hydrogenation of *N*-Aryl Imines with Catalyst Ir-221

enantioselective hydrogenation of *N*-arylimines **174**. For example, the iridium complex of ligand **156d**, which has an isopropyl on the oxazoline ring and 3,5-dimethylphenyl on the *P*-atom, hydrogenated the imine **174**, producing the corresponding chiral amines **175** with up to 92% ee in CH₂Cl₂ at 20 atm H₂ and room temperature with a catalyst loading of 0.5 mol %.

Moessner and Bolm¹⁸⁸ reported the phosphinosulfoximine ligands **220**, a new class of phosphine–nitrogen ligands for the iridium-catalyzed enantioselective hydrogenation of *N*-arylimines **174**. With the iridium complex of the ligand **220d**, having an isobutyl group on the sulfur atom, as the catalyst and in the presence of iodine as the promoter, a variety of *N*-arylimines **174** were hydrogenated to the chiral amines **175** in full conversions with 69–98% ee (S/C = 200, toluene, 20 atm H₂, rt, 4–6 h). When 0.1 mol % of the catalyst was used for the hydrogenation of the substrate **174a**, the amine product **175a** was obtained in full conversion with 95% ee, albeit 50 atm H₂ pressure was required.

The ferrocene-based pyridine–phosphine ligands **221**, developed by Cheemala and Knochel¹⁸⁹ in 2007, also showed good to excellent enantioselectivity in the iridium-catalyzed hydrogenation of *N*-arylimines **174**. With the Ir-**221** catalyst, as high as 89–99% ee were obtained for the hydrogenation of the imines **174** with *N*-(4-methoxy-3,5-dimethyl)phenyl under the conditions of 10 atm H₂ pressure and 25 °C in a mixture solvent of toluene and methanol (4:1) for 2–6 h (Scheme 55). This protocol has been extended to the enantioselective synthesis of the chiral γ - and δ -lactams **226**.

3.1.1.3. Other Chiral Ligands. In addition to chiral diphosphines and phosphorus–nitrogen ligands, other chiral ligands such as monodentate phosphoramidites and *N*-donor ligands have also been used for the iridium-catalyzed enantioselective hydrogenation of imines. In 2003, Feringa et al.¹⁹⁰ developed a type of monodentate secondary phosphine oxides and showed that the ligand **227a** (Figure 19) with a *tert*-butyl group and a phenyl group on the phosphorus atom gave moderate enantioselectivity in the iridium-catalyzed hydrogenation of *N*-benzylimines **172**. Up to 76% ee was obtained by the Ir-**227a** catalyst under the conditions of 25 atm H₂ pressure and room temperature

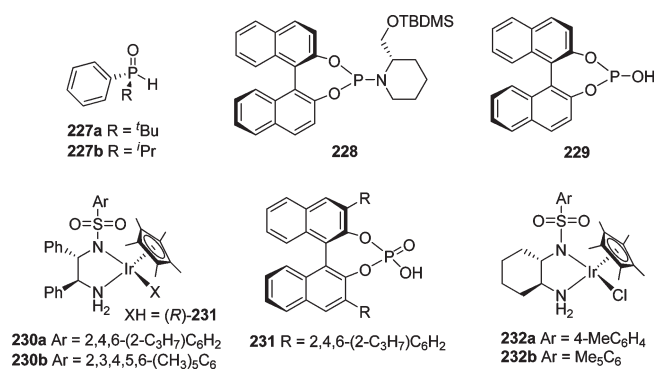


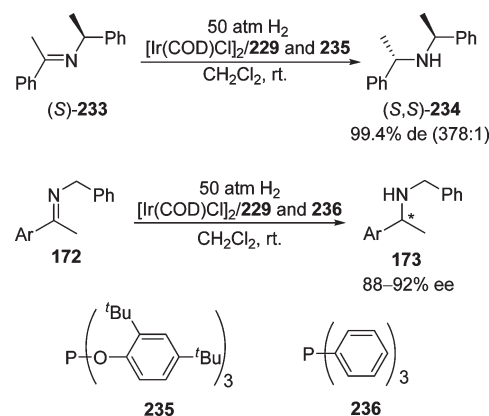
Figure 19. Other chiral ligands and chiral iridium catalysts.

in toluene (*S*/*C* = 20). In the presence of pyridine as an additive, the enantioselectivity of the reaction was increased to 83% ee, and the ligand amount could be reduced to the L/Ir 1:1 without loss of enantioselectivity. Subsequently, Faller et al.¹⁹¹ and Murai et al.¹⁹² independently introduced monodentate phosphoramidite ligands in the iridium-catalyzed imine hydrogenation. Faller et al. used MonoPhos (**102a**, Figure 8) as the ligand and acridine as the additive for the hydrogenation of a cyclic imine **178**, obtaining the corresponding chiral amine **179** in 96% conversion with 45% ee. Up to 73% ee was achieved by Murai et al.¹⁹² for the hydrogenation of the *N*-arylimine **174a** with the phosphoramidite ligand **228** (Figure 19) containing a (*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)piperidiny group on the phosphorus atom. In 2009, Mršić¹⁹³ reported that the monophosphoramidite ligand **102c** (PipPhos, Figure 8) with a simple piperidiny group on the phosphorus atom afforded excellent enantioselectivity in the iridium-catalyzed hydrogenation of *N*-arylimines **174**. With the catalyst Ir-**102c**, the *N*-aryl imines **174** with an *N*-(2-methoxy)phenyl group or related groups were hydrogenated under 1 or 5 atm H₂ pressure at room temperature in CH₂Cl₂ (*S*/*C* = 100) to the corresponding chiral amines **175** with up to 99% ee. Under the same conditions, the cyclic imine **178b** was hydrogenated to the 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisquinoline (**179b**) with 62% ee.

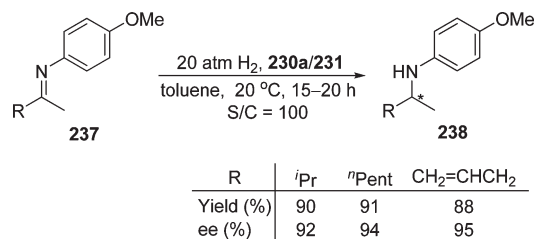
In 2007, Reetz and Bondarev¹⁹⁴ reported that the mixture of chiral phosphorus acid diesters and achiral phosphine ligands was also effective for the iridium-catalyzed enantio- and diastereoselective hydrogenation of *N*-alkylimines. In the diastereoselective hydrogenation of the (*S*)-1-phenyl-*N*-(1-phenylethylidene)ethanamine (**233**), the combination of a chiral binaphthyl phosphoric acid **229** and an achiral tris(2,4-di-*tert*-butylphenyl) phosphite (**235**) gave the best diastereoselectivity (>99% de, Scheme 56). Meanwhile, the combination of a chiral binaphthyl phosphoric acid **229** and an achiral trisphenylphosphine (**236**) yielded the chiral amines **173** with 88–92% ee in the reduction of the *N*-benzylimines **172**. The phosphine–olefin ligand **135** also showed good enantioselectivity (86% ee) in the iridium-catalyzed hydrogenation of *N*-aryl imine **174a**.¹²⁶

Chiral *N*-tosylethylenediamine ligands, which are widely used in enantioselective transfer hydrogenations,¹⁹⁵ have also been applied in the iridium-catalyzed enantioselective hydrogenation of imines. In 2008, Xiao and co-workers¹⁹⁶ reported that the iridium complexes **230**, derived from a chiral monosulfonated (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine and a chiral binaphthyl-based phosphoric acid **231**, were very efficient catalysts for the hydrogenation of *N*-arylimines. Under the conditions of 20 atm H₂ pressure at 20 °C in toluene (*S*/*C* = 100) and addition of

Scheme 56. Diastereoselective and Enantioselective Hydrogenation of Imines with Ligands **229**



Scheme 57. Enantioselective Hydrogenation of *N*-Aryl Imines with Iridium Catalyst **230a**

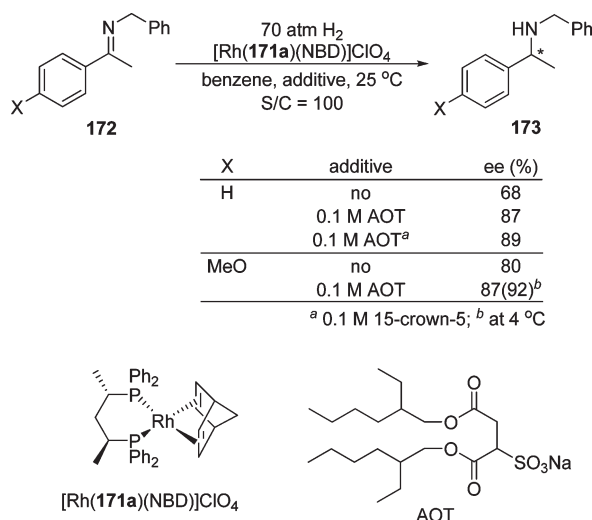


1 mol % of additional phosphoric acid **231**, a wide range of *N*-arylimines **174** derived from aryl alkyl ketones have been hydrogenated to the chiral amines **175** with 84–98% ee by using the catalyst Ir-**230a**. Furthermore, the hydrogenation of *N*-arylimines **237** derived from dialkylketones also gave high enantioselectivities (92–95% ee, Scheme 57).

Chiral iridium complexes **232** derived from chiral monosulfonated (1*S*,2*S*)-cyclohexane-1,2-diamines were introduced in imine hydrogenation by Ikariya and co-workers¹⁹⁷ in 2009. These iridium catalysts showed moderate enantioselectivities (39–78% ee) for the hydrogenation of *N*-benzylimines **172**. However, the iridium catalysts **232** have no enantioselectivity for the hydrogenation of *N*-arylimine **174a**.

3.1.2. Chiral Rhodium Catalysts. Compared with the great success of the chiral iridium catalysts in enantioselective hydrogenations of imines in the past two decades, the chiral rhodium catalysts based on diphosphines and other chiral ligands have received less attention. Although Bakos et al.¹⁴¹ reported a high enantioselectivity (up to 94% ee) in the hydrogenation of imines by using the chiral rhodium catalyst bearing a monosulfonated bidentate ligand BDPP (**171b**) in 1989, only a few examples of imine hydrogenation with chiral rhodium catalyst have been documented in the literature.

In 1996, Buriak and Osborn¹⁹⁸ reported that the enantioselectivity of the hydrogenation of *N*-benzylimines **172** catalyzed by the [Rh(**171a**)(NBD)]ClO₄ was enhanced by adding reverse sodium bis(2-ethylhexyl) sulfosuccinate (AOT) micelles (Scheme 58). The enantioselectivity was increased from 68% ee in neat benzene to 87% ee in the presence of 0.1 M AOT in

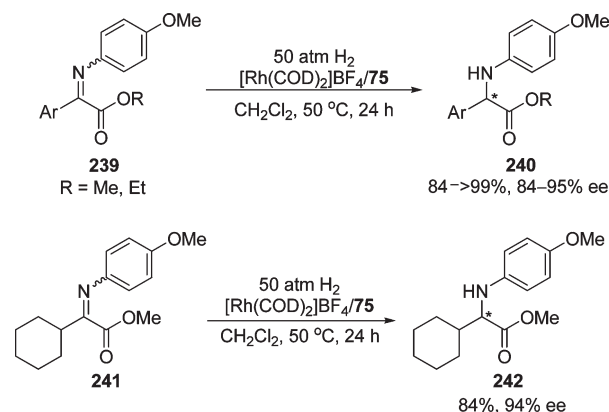
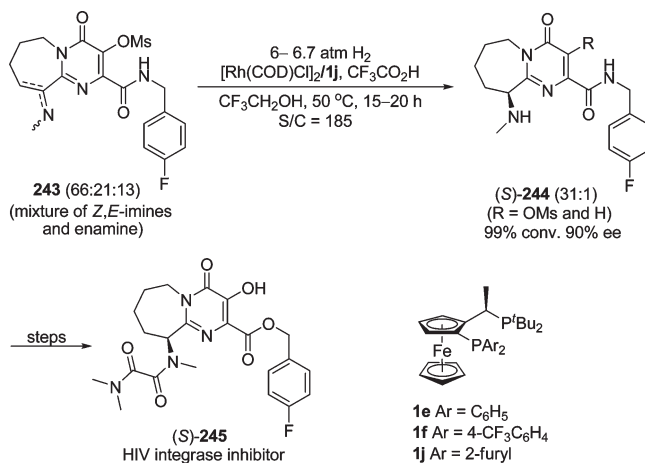
Scheme 58. Enantioselective Hydrogenation of *N*-Benzymines **172 with [Rh(**171a**)(NBD)]ClO₄**

benzene. If the reaction was carried out at 4 °C, the ee value could be further increased to 92% for the hydrogenation of the *N*-benzylimine with a *para*-methoxy group on the 1-phenyl ring.

Börner and co-workers¹⁹⁹ screened a range of diphosphine and diphosphinite ligands including DIOP (**2**) and BDPC (141, Scheme 34) in the rhodium-catalyzed enantioselective hydrogenation of *N*-benzymines **172** and found that the diphosphines forming seven-membered chelating rings had higher activities than the diphosphines forming smaller chelate rings. Dialkylphosphine ligands are less active than diarylphosphine ligands. The reactivity of the Rh-diphosphine catalyst was increased by the addition of *p*-toluenesulfonic acids. Interestingly, the rhodium complexes of chiral diphosphinite and diphosphite ligands showed an excellent reactivity. With a cationic rhodium complex of the chiral diphosphinite ligand **141** as the catalyst, up to 71% ee was obtained under the conditions of 50 atm H₂ pressure at room temperature (S/C = 100).

Chiral rhodium complexes of diphosphine ligands have shown good to excellent enantioselectivity for the hydrogenation of α -aryliminoesters. After screening a series of diphosphine ligands including DuPhos (**12**) and Binaphane (**17**), Zhang and co-workers²⁰⁰ found that the rhodium complex containing the TangPhos (**75**) ligand gave the best enantioselectivity and reactivity. A variety of *N*-4-methoxyphenyl α -aryliminoesters **239** were hydrogenated in CH₂Cl₂ under 50 atm H₂ pressure at 50 °C for 24 h (S/C = 100) to the corresponding chiral α -aryl amino acid derivatives **240** in 84 to >99% conversion and 84–95% ee (Scheme 59). When the catalyst loading was reduced to ca. 0.1 mol % (S/C = 1000), a comparable result was obtained for the hydrogenation of the standard imino ester (Ar = Ph, R = Me). In the hydrogenation of α -alkyliminoester such as methyl 2-cyclohexyl-2-(4-methoxyphenylimino)acetate (**241**), high enantioselectivity (94% ee) and conversion (84%) were also obtained.

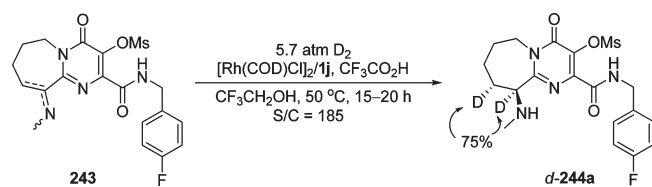
In the search for highly efficient methods for the synthesis of HIV integrase inhibitor (*S*)-**245**, Zhong et al.²⁰¹ developed a unique enantioselective hydrogenation of the highly functionalized mixture of imines (*Z*- and *E*-**243a**) and enamine **243b** (*Z*-**243a**/*E*-**243a**/**243b** = 66:21:13, Scheme 60). With the rhodium

Scheme 59. Enantioselective Hydrogenation of Iminoesters **239 and **241** with Rh-**75******Scheme 60. Synthesis of HIV Integrase Inhibitor (*S*)-**245****

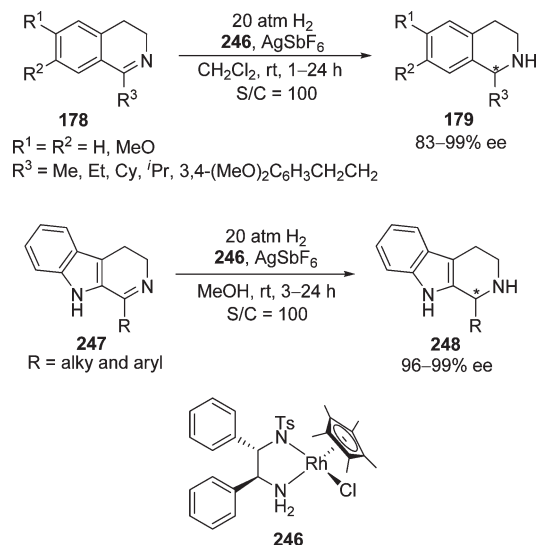
complex of the Josiphos-type ligand **1j** as the catalyst, the chiral amine (*S*)-**244a** (R = OMs) was obtained in 99% conversion with 90% ee under the conditions of 6–6.7 atm H₂ pressure at 50 °C in trifluoroethanol and in the presence of 0.5 mol % of trifluoroacetic acid (S/C = 185), albeit with small amount of byproduct (*S*)-**244b** (R = H), formed from the hydrogenolytic cleavage of the mesylate group from (*S*)-**243a**. This protocol could be performed on a 500 g scale.

Interestingly, the hydrogenation proceeded predominantly through the enamine tautomer, although the substrate **243** was dominated with imine form. The hydrogenation of the substrate **243** with D₂ gave the product with deuterium at both the *ipso*- and *alpha*-positions of the secondary amine product *d*-**244a** in roughly equal proportion (Scheme 61). More telling was the fact that the two deuterium atoms were exclusively *cis* based on NMR spectroscopy.

Li and Xiao²⁰² realized highly enantioselective hydrogenation of the cyclic imines to the chiral tetrahydroisoquinolines and tetrahydro- β -carboline (Scheme 62) by using the rhodium catalyst **246** (Rh-TsDPEN). Under the conditions of 20 atm H₂ pressure at room temperature in CH₂Cl₂ and in the presence of 4 mol % AgSbF₆ and a small amount of water (S/C = 100), a

Scheme 61. Hydrogenation of Imines/Enamine 243 with D₂

Scheme 62. Enantioselective Hydrogenation of Cyclic Imines 178 and 247 with Catalyst 246



range of cyclic imines **178** were hydrogenated to tetrahydroisoquinolines **179** in high yields with 83–99% ee. For the hydrogenation of imines **247** to tetrahydro- β -carboline **248**, high yields and up to 99% ee of enantioselectivities were obtained.

3.1.3. Chiral Ruthenium Catalysts. Chiral ruthenium catalysts, which have been widely applied in the hydrogenation of ketone, also showed good enantioselectivity in the hydrogenation of imines. The most prominent chiral ruthenium catalysts for the enantioselective hydrogenation of imines were Noyori type of ruthenium diphosphine/diamine complexes (Figure 20). In 2001, Morris and co-workers²⁰³ introduced Ru-(diphosphine)(diamine) catalysts based on BINAP ligand in the hydrogenation of *N*-aryl/alkylimines, producing the corresponding chiral amines with moderate enantioselectivities (up to 71% ee). For example, the hydrogenation of the *N*-benzyl and *N*-phenylimines **172a** and **174a** with the catalyst $\text{RuHCl}((R,R)\text{-BINAP})((R,R)\text{-DACH})$ (**249a**) (0.2 mol %) under the conditions of 3 atm H_2 pressure at 20 °C in the presence of KO^iPr as the base for 36 h afforded chiral amines **173a** and **175a** in 100% conversion with 71 and 60% ee, respectively.

By screening a wide range of chiral ruthenium diphosphine/diamine complexes, Cobley and Henschke²⁰⁴ found that the ruthenium dichloro complex $\text{RuCl}_2((R,R)\text{-Et-Duphos})((R,R)\text{-DACH})$ (**249b**) was an efficient catalyst for the hydrogenation of *N*-arylimine **174a**. When the hydrogenation was conducted under 20 atm H_2 pressure and 65 °C in isopropanol (4.1 M)

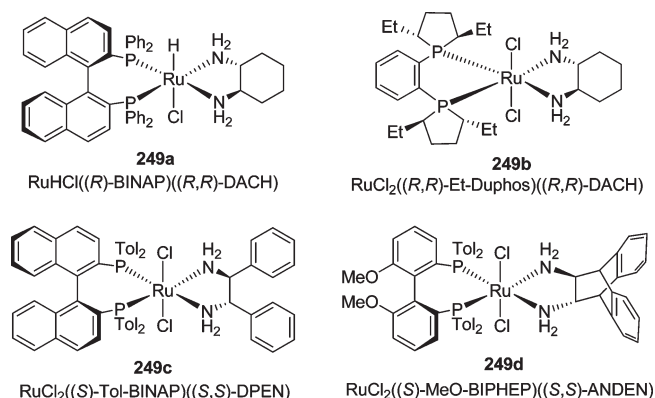


Figure 20. Ruthenium diphosphine/diamine catalysts.

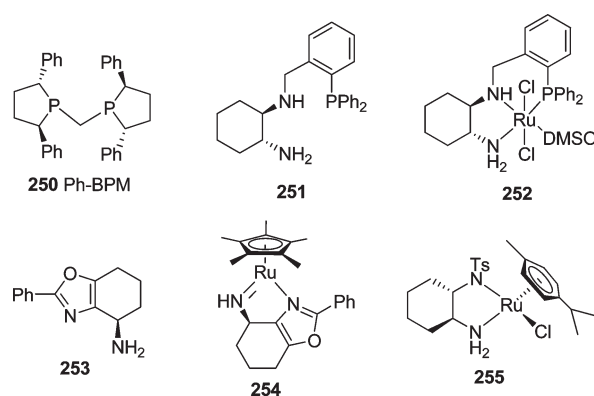


Figure 21. Chiral ligands and chiral ruthenium catalysts.

with 5 mol % $^t\text{BuOK}$ for 69 h, 97% conversion and 94% ee were obtained. For the hydrogenation of the *N*-benzylimine **172a**, the catalyst $\text{RuCl}_2((S,S)\text{-Tol-BINAP})((S,S)\text{-DPEN})$ (**249c**) gave the best results. In this hydrogenation, the amount of base was a key factor for obtaining high enantioselectivity. When the reaction was performed in the presence of 100 mol % $^t\text{BuOK}$, racemic product was obtained. However, when the amount of the base was reduced to 5 mol %, the enantioselectivity was enhanced to 63% ee (97% conversion). Cyclic imines could also be hydrogenated to the corresponding chiral amines by chiral ruthenium diphosphine/diamine complexes. Under similar hydrogenation conditions, the catalyst $\text{RuCl}_2((S,S)\text{-MeO-BIPHEP})((S,S)\text{-ANDEN})$ (**249d**) provided 88% ee for the hydrogenation of the cyclic imine **176**. Meanwhile, for the hydrogenation of the dihydroisoquinoline **178a**, the catalyst $\text{RuCl}_2((R,R)\text{-Et-Duphos})((R,R)\text{-DACH})$ (**249b**) gave a better result (79% ee in 80% conversion).

In 2007, Jackson and Lennon²⁰⁵ reported that the chiral 1,2-diphosphine **250** (Ph-BPM, Figure 21) was also an efficient ligand for the ruthenium diphosphine/diamine-catalyzed imine hydrogenation. When the reactions were performed at 60 °C under 10 atm H_2 in isopropanol and in the presence of 5–10 mol % of $^t\text{BuOK}$ (S/C = 200), the $\text{RuCl}_2(\textbf{250})((S,S)\text{-DPEN})$ catalyst gave 71, 82, and 89% ee for the hydrogenations of *N*-benzylimine **172a**, *N*-arylimine **174a**, and cyclic imine **178a**, respectively. In the same year, Clarke et al.²⁰⁶ prepared chiral ruthenium complex **252** by heating a chiral tridentate phosphine–nitrogen ligand **251** with $[\text{Ru}(\text{DMSO})_4\text{Cl}_2]$ in THF at 120 °C in a microwave oven. The ruthenium complex **252** was

used to catalyze the hydrogenation of cyclic imine **176** to the corresponding amine **177** in high yield (98%), but with low enantioselectivity (37% ee).

Chiral ruthenium diamine/imine complexes have also been applied for the hydrogenation of imines. Andersson and co-workers²⁰⁷ reported the chiral ruthenium catalyst **254** derived from the chiral ligand **253** containing an sp^2 nitrogen atom and a primary amine group. This chiral ruthenium catalyst exhibited a moderate enantioselectivity (52% ee in 80% conversion) in the hydrogenation of *N*-arylimine **174a**. In the study of ruthenium complex of the chiral *N*-sulfonylated diamine ligand for the hydrogenation of acyclic imines, Ikariya and co-workers¹⁹⁷ achieved 74% ee enantioselectivity in the hydrogenation of the *N*-benzylimine **172a** by using the ruthenium complex **255** as the catalyst.

3.1.4. Other Chiral Catalysts. In 1992, Willoughby and Buchwald¹⁴² introduced a chiral titanocene catalyst **137** (Scheme 33) derived from Brintzinger's *ansa*-titanocene complex²⁰⁸ in the enantioselective hydrogenation of imines (Scheme 63). This chiral titanocene catalyst **137** was highly enantioselective for the hydrogenation of imines, in particular cyclic imines.^{5,209} After being activated by *n*-BuLi and phenylsilane (PhSiH₃), the catalyst **137** hydrogenated various cyclic imines **180** (R = alkyl or aryl; n = 1–3) to chiral cyclic amines **181** in good yields (72–86%) with excellent enantioselectivities (95–99% ee). However, for the acyclic *N*-alkylimines **256**, relatively lower enantioselectivities (53–93% ee) were observed. The reason for this is likely due to the fact that the acyclic imines are mixtures of *anti*- and *syn*-isomers, which interconvert during the reaction. Furthermore, this chiral titanocene catalyst **137** can tolerate many functional groups found in organic synthesis.

In 1999, Brintzinger and co-workers²¹⁰ developed a chiral biphenyl-bridged titanocene catalyst **258** (Figure 22), which showed a comparable enantioselectivity for the hydrogenation of imines. In the presence of 2 equiv of *n*-BuLi, the catalyst **258** hydrogenated the *N*-benzylamine imine **172a** to the chiral amine **173a** in 95% yield with 76% ee. For the hydrogenation of the cyclic imine 5-phenyl-3,4-dihydro-2H-pyrrole (**180a**), up to 98% ee and 95% yield were achieved by the catalyst **258** (S/C = 1000, 150 atm H₂, toluene, 80 °C, 12 h).

Chiral palladium complex of the ligand BINAP (**2**) was found to be an efficient catalyst for the hydrogenation of α -fluorinated iminoesters **261** in fluorinated alcohol.²¹¹ The solvent 2,2,2-trifluoroethanol (TFE) is important for achieving high reactivity and enantioselectivity. Catalyzed by the palladium complex generated from Pd(OCOFCF₃)₂ and BINAP (**2**), the α -fluorinated iminoesters **261** were hydrogenated to the corresponding fluoro α -amino acid derivatives **262** in 75 to >99% conversion and 30–91% ee under 100 atm H₂ pressure at room temperature in 2,2,2-trifluoroethanol for 24 h (S/C = 25) (Scheme 64). This hydrogenation reaction has been applied in the synthesis of chiral β,β -difluoroglutamic acid and β,β -difluoroproline derivatives **263** and **264**.²¹²

Recently, chiral gold complex has emerged as an efficient catalyst for enantioselective hydrogenation of imines. Corma and co-workers²¹³ reported a new neutral dimeric gold complex **259** (Figure 22) containing the Me-Duphos (**12**) ligand for the hydrogenation of imines. In the presence of 0.1 mol % of complex **259** as the catalyst, the *N*-arylimine **174a** was hydrogenated to the corresponding amines in 75% ee under 4 atm H₂ pressure at 45 °C in ethanol. By using a palladium complex of the SynPhos ligand **260** (Figure 22), 95% ee of enantioselectivity was achieved

Scheme 63. Enantioselective Hydrogenation of Imines with Chiral Titanocene Catalyst **137**

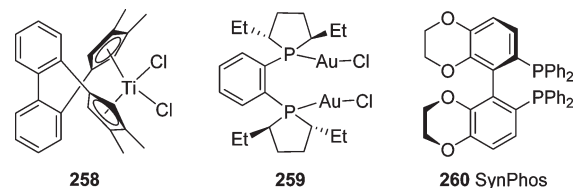
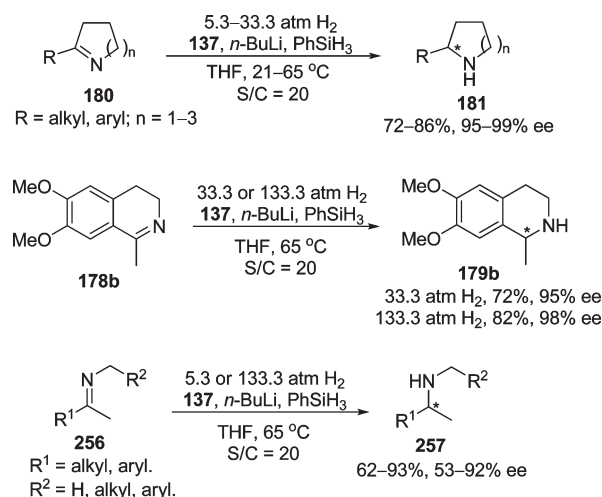


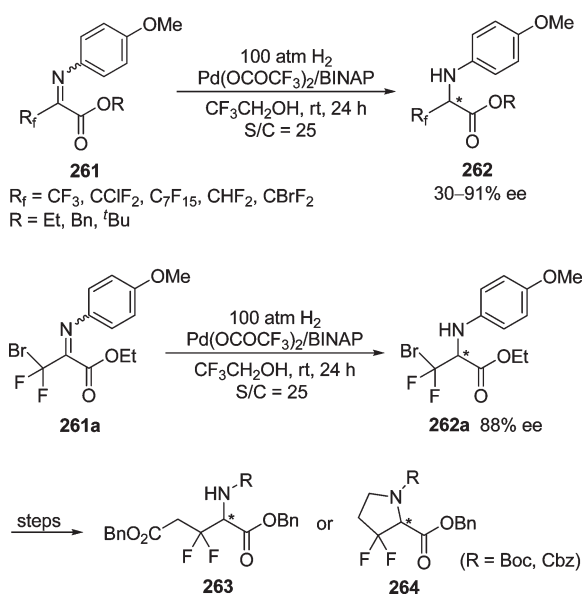
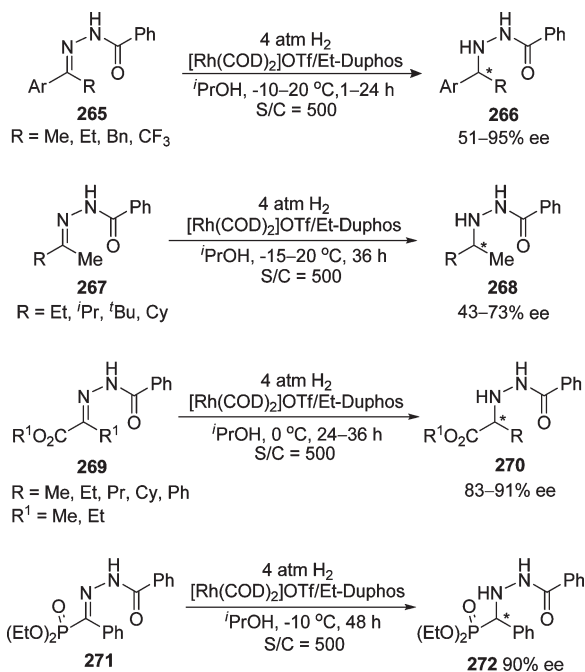
Figure 22. Other chiral ligands and catalysts for imine hydrogenation.

in the hydrogenation of 4-methoxy-*N*-(1-phenylethylidene)aniline, but with low conversion (25%).²¹⁴

3.2. Enantioselective Hydrogenation of Activated Imines

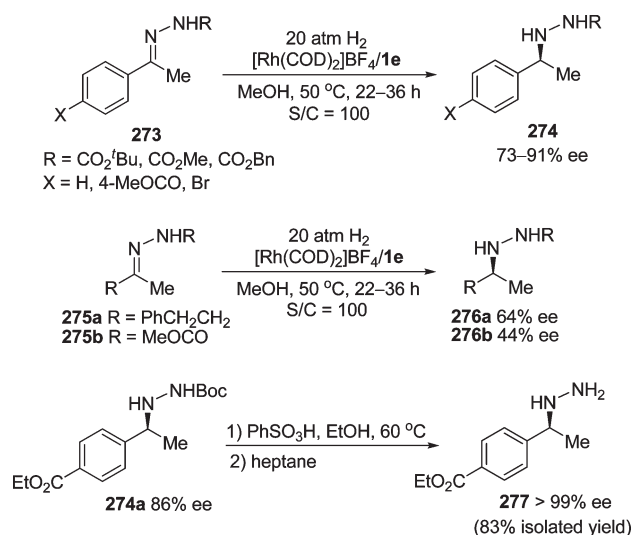
Enantioselective hydrogenation of activated imines, such as *N*-acylhydrazones, *N*-tosylimines, and *N*-diphenylphosphinylimines with electronic-withdrawing substituents at the nitrogen atom, have received increasing attention in the past few decades. The chiral rhodium, palladium, and ruthenium complexes bearing diphosphine ligands have been proven to be efficient catalysts for the hydrogenation of *N*-acylhydrazones, *N*-tosylimines, and *N*-diphenylphosphinylimines, as well as related analogues.

3.2.1. Chiral Rhodium Catalysts. In 1992, Burk and Feaster²¹⁵ developed highly enantioselective hydrogenation of *N*-acylhydrazone derivatives by using the cationic rhodium complex of DuPhos (**12**) ligand as the catalyst (Scheme 65). With the Rh-Et-DuPhos catalyst (0.2 mol %), generated in situ from [Rh(COD)₂]OTf and Et-DuPhos ligand, a series of *N*-benzoylhydrazones **265** containing aryl and methyl substituents were consistently hydrogenated, under the optimal conditions of 4 atm H₂ pressure at −10 to 20 °C in *i*PrOH, to the corresponding chiral amine derivatives **266** with high enantioselectivities (88–97% ee). Substitution on the methyl group of the *N*-benzoylhydrazones **265** tended to afford somewhat lower enantioselectivities (Et, 85% ee; Bn, 84% ee, CF₃, 55% ee). For the hydrogenations of the *N*-benzoylhydrazones **269** and **271** derived from α -keto esters and diethyl benzoylphosphonate, high enantioselectivities (83–91 and 90% ee, respectively) also have been achieved. However, only low to moderate ee values (43–73% ee) were obtained for the hydrogenation of the

Scheme 64. Enantioselective Hydrogenation of α -Fluorinated Iminoesters 261 with Pd-BINAP**Scheme 65. Enantioselective Hydrogenation of *N*-Acylhydrazone Derivatives with Rh-Et-DuPhos**

N-benzoylhydrazones **267** containing two alkyl substituents. It is worthwhile mentioning that the *N*-benzoylhydrazine products can be easily converted into chiral amines by treatment with samarium diiodide.

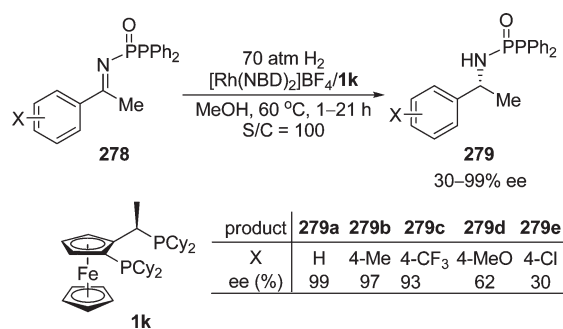
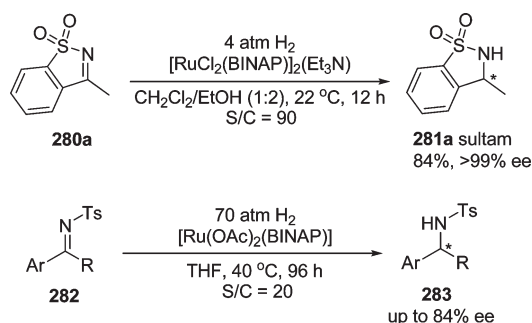
Recently, Yoshikawa and Tan et al.²¹⁶ demonstrated that the chiral rhodium complexes of ferrocene-based ligands Josiphos (**1e** and **1f**, Scheme 36) and TanaiPhos (**62**, Figure 5) were highly enantioselective for the hydrogenation of *N*-alkoxycarbonyl hydrazones (Scheme 66). The hydrogenation reactions of

Scheme 66. Enantioselective Hydrogenation of *N*-Alkoxycarbonyl Hydrazones with Rh-1e

N-alkoxycarbonyl hydrazones **273** were performed in MeOH under 20 atm H_2 pressure at 50 °C for 22–30 h ($\text{S/C} = 100$), yielding the corresponding chiral amines **274** with 73–91% ee with nearly full conversions by using rhodium catalysts generated in situ from 1.0 mol % of $[\text{Rh}(\text{COD})_2]\text{BF}_4$ and 1.1 mol % of the ligand **1e** or **62c**. The Boc-protected hydrazones **275** derived from 4-phenylbutan-2-one (**275a**) and methyl 2-oxopropanoate (**275b**) could also be hydrogenated with high conversions but with lower enantioselectivities (64 and 44% ee, respectively). By treatment with benzenesulfonic acid in EtOH at 60 °C, the obtained optically active Boc hydrazine **274a** was easily deprotected to the chiral hydrazine **277**. The ester group of the hydroazine, if present, can tolerate such deprotected conditions.

In 2001, Spindler and Blaser²¹⁷ realized the catalytic enantioselective hydrogenation of *N*-diphenylphosphinyl imines by using the rhodium complexes of diphosphines as the catalysts. Under the conditions of 60 °C and 70 atm of H_2 pressure in methanol ($\text{S/C} = 100\text{--}500$), the *N*-diphenylphosphinyl imine **278a** derived from acetophenone was hydrogenated by the rhodium complex of the Josiphos-type diphosphine ligand **1k**, providing the chiral *N*-diphenylphosphinyl amine **279a** in full conversion with 99% ee. However, the *N*-diphenylphosphinyl acetophenone imines with *para*-MeO (**291d**) and *para*-Cl (**291e**) gave significantly lower enantioselectivities (Scheme 67).

3.2.2. Chiral Ruthenium Catalysts. In 1986, Okamoto and co-workers²¹⁸ reported the enantioselective hydrogenation of *N*-tosylimines. By using cobalt complex bearing a quinine moiety as the catalyst, methyl *N*-(*p*-toluenesulfonyl)-1-imino-1-phenylacetate was hydrogenated to the corresponding chiral amine with 20% ee. A highly enantioselective hydrogenation of the cyclic *N*-sulfonylimine **280a** was achieved by Oppolzer et al.²¹⁹ in 1990 with the ruthenium catalyst $[\text{RuCl}_2(\text{BINAP})]_2(\text{Et}_3\text{N})$, and the hydrogenation product sultam **281a** was obtained in 84% yield with >99% ee (Scheme 68). However, this ruthenium catalyst was less active and less enantioselective for the hydrogenation of a similar, but acyclic substrate. Charette and Ciroux²²⁰ attempted the hydrogenation of the *N*-tosylimines **282** derived from aryl

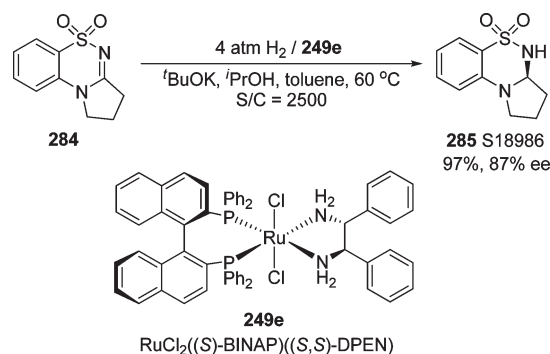
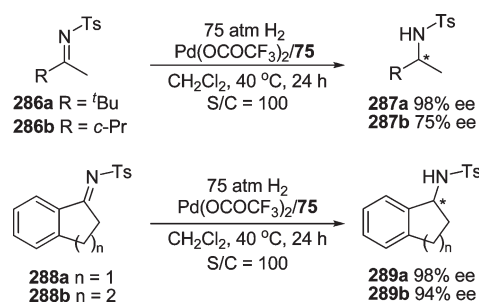
Scheme 67. Enantioselective Hydrogenation of *N*-Diphenylphosphinyl Imines with Rh-1kScheme 68. Enantioselective Hydrogenation of *N*-Tosylimines with Ru-BINAP

alkyl ketones with this ruthenium catalyst and achieved low enantioselectivities (<26% ee). By using the [Ru(OAc)₂BINAP] catalyst, they improved the enantioselectivity of this reaction to 84% ee.

In 2003, Lennon and co-workers²²¹ used the chiral ruthenium diphosphine/diamine complexes as the catalysts for the hydrogenation of the dihydropyrrolo benzothiadiazine dioxide **284** (Scheme 69). The complex RuCl₂((*R*)-BINAP)((*R,R*)-DPEN) (**249e**) was found to be a suitable catalyst, providing the corresponding chiral sulfonamide product **285** (S 18986), a selective AMPA receptor positive modulator, in 97% yield with 87% ee (S/C = 2 500).

3.2.3. Chiral Palladium Catalysts. In contrast, chiral palladium catalysts of diphosphine ligands exhibited higher enantioselective inductivity than chiral ruthenium catalysts in the hydrogenation of *N*-tosylimines. In 2006, Zhang and co-workers²²² introduced the chiral palladium complexes bearing diphosphine ligands into enantioselective *N*-tosylimine hydrogenations and significantly improved the enantioselectivity of the reaction. By screening the chiral diphosphine ligands, they found that the TangPhos (**75**, Figure 6) was an excellent ligand in terms of conversion and enantioselectivity. Under the optimal conditions (S/C = 100, 75 atm H₂, 40 °C, CH₂Cl₂, 24 h), a variety of *N*-tosylimines **282** (Scheme 68) were hydrogenated by the catalyst generated in situ from Pd(OCOCF₃)₂ and the ligand **75** to the chiral *N*-tosylamines **283** in 93–99% ee with full conversions. The hydrogenation of *N*-tosylimines derived from dialkylketones such as 3,3-dimethylbutan-2-one (**286a**) and 1-cyclopropylethanone (**286b**) also gave good to high enantioselectivities (98 and 75% ee, respectively) with the Pd-TangPhos

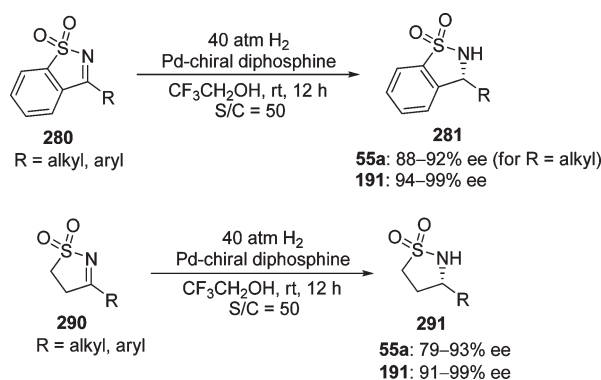
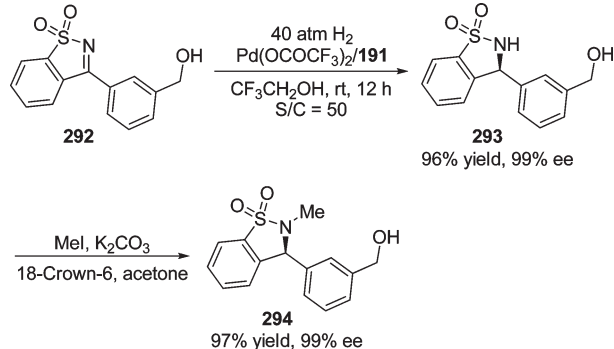
Scheme 69. Enantioselective Synthesis of S 18986

Scheme 70. Enantioselective Hydrogenation of *N*-Tosylimines with Pd-75

catalyst (Scheme 70). Furthermore, excellent enantioselectivities were achieved for the hydrogenation of the cyclic *N*-sulfonylimines derived from indenone (**288a**, 98% ee), tetralone (**288b**, 94% ee), and saccharin (**280a**, 94% ee) under similar reaction conditions.

Later, Zhou and co-workers²¹⁴ found that, in the solvent of 2,2,2-trifluoroethanol (TFE), the chiral palladium complexes of diphosphines such as SynPhos (**260**), BINAP (**2**), MeO-BI-PHEP (**131b**), and SegPhos (**55a**) were also efficient catalysts for the hydrogenation of *N*-tosylimines. With the Pd-SynPhos complex generated in situ from Pd(OCOCF₃)₂ and SynPhos as the catalyst, several *N*-tosylimines **282** were hydrogenated with high yields (84–98%) and high enantioselectivities (88–97% ee) (S/C = 50, 40 atm H₂, TFE, rt, 12 h). For the hydrogenation of the cyclic *N*-sulfonylimines **290**, the chiral palladium complex of SegPhos (**55a**) gave the best enantioselectivities among the palladium catalysts screened. With this chiral palladium catalyst and under similar conditions, chiral sultams **291** were obtained in 79–93% ee (Scheme 71). Further study demonstrated that the chiral palladium complex of ferrocene-based ligand f-Binaphane (**191**) exhibited higher enantioselectivities (up to 99% ee) than the chiral palladium complex of ligand SegPhos (**55a**) in the hydrogenation of cyclic *N*-sulfonylimines **290** (Scheme 71).²²³

This highly efficient hydrogenation of cyclic *N*-sulfonylimine provides a convenient route to the synthesis of chiral sultams with biological activity. Compound **294**, a chiral sultam with anti-HIV activity,²²⁴ has been easily synthesized by using the palladium-catalyzed enantioselective hydrogenation of the cyclic

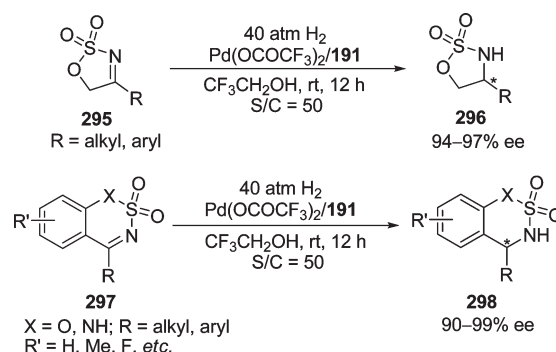
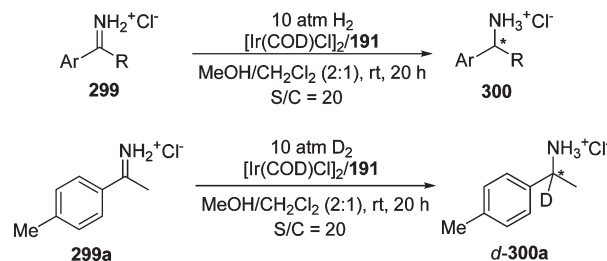
Scheme 71. Enantioselective Hydrogenation of Cyclic N-Tosylimines with Chiral Pd Catalysts**Scheme 72. Enantioselective Hydrogenation of N-Sulfonylimine 292 for the Synthesis of an Anti-HIV Active Compound 294**

N-sulfonylimine **292** as the key step. The *N*-methylation of the hydrogenation product **293** (99% ee) with methyl iodide gave the final product **294** in high yield (Scheme 72).

Enantioselective hydrogenation of cyclic imines to chiral sulfamidates was also reported by Zhou and co-workers²²⁵ in 2008. Under the conditions of 40 atm H₂ pressure at room temperature in 2,2,2-trifluoroethanol in the presence of 2.0 mol % chiral palladium catalyst generated in situ from Pd(OCOCF₃)₂ and *f*-Binaphane (**191**), a series of cyclic imines **295** and **297** were hydrogenated to chiral sulfamidates in high yields with 90–99% ee (Scheme 73). At lower catalyst loading (ca. 0.5 mol %), the reaction still proceeded smoothly without loss of enantioselectivity. The obtained chiral sulfamidates could be converted to chiral β -amino alcohols and amines via ring-opening reactions with LiAlH₄.

Furthermore, the chiral palladium catalysts of diphosphines were demonstrated to be effective for the hydrogenation of *N*-diphenylphosphinyl imines. Under the optimal reaction conditions (TFE, 4 Å MS, 66.7 atm H₂, rt, 8 h), the Pd-SegPhos catalyst, generated in situ from 2 mol % of Pd(OCOCF₃)₂ and 2.4 mol % of ligand SegPhos (**55a**), converted a series of *N*-diphenylphosphinyl imines **278** to the chiral amines derivatives **279** in high yields with 87–99% ee.^{214,226}

3.2.4. Chiral Iridium Catalysts. The iridium complex of monodentate phosphorus ligands was demonstrated to be an effective catalyst for the hydrogenation of *N*-diphenylphosphinyl

Scheme 73. Enantioselective Hydrogenation of Cyclic Imines to Chiral Sulfamidates**Scheme 74. Enantioselective Hydrogenation of Aryl Alkyl N–H Imines**

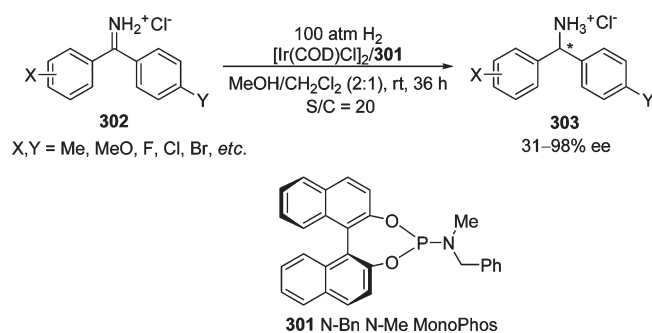
acetophenone imine.¹⁹⁰ Catalyzed by the iridium complex of the chiral monodentate phosphine oxide ligand **227a** (Figure 19), *N*-diphenylphosphinyl acetophenone imine **278a** was hydrogenated to *N*-diphenylphosphinyl amine **279a** in 100% conversion with 70% ee.

3.3. Enantioselective Hydrogenation of N–H Imines

Recently, a new breakthrough has been made in the catalytic enantioselective hydrogenation of imine with N–H bond, providing chiral primary amines directly. By using the chiral iridium complex based on chiral diphosphine ligand *f*-Binaphane (**191**) as the catalyst, Gosselin, Zhang, and co-workers²²⁷ realized the highly efficient hydrogenation of N–H imines, providing chiral primary amines with excellent enantioselectivities. The hydrogenation reaction was performed in the mixture solvent of methanol and dichloromethane (2:1) under 10 atm H₂ pressure at room temperature, and a variety of aryl alkyl N–H imines **299** have been hydrogenated to the corresponding chiral primary amines **300** in high yields with 80–95% ee (Scheme 74). Under similar reaction conditions, dialkyl and diaryl N–H imines also could be hydrogenated in high yields, albeit with lower enantioselectivities (<73% ee). The result of isotopic labeling of 1-phenylethanamine (**299a**) with D₂ in MeOH/CH₂Cl₂ showed exclusive formation of the α -deuterio-amine hydrochloride **d-300a**, suggesting a pathway consistent with reduction of the imine tautomer.

Considering that the chiral iridium complex of *f*-Binaphane (**191**) gave low enantioselectivity for the hydrogenation of diaryl N–H imine, Zhang, Gosselin, and co-workers²²⁸ subsequently screened a wide range of chiral phosphorus ligands including bidentate phosphines, such as BINAP (**2**), SegPhos (**55a**), and Josiphos (**1e**), and monodentate phosphorus ligands, such as

Scheme 75. Enantioselective Hydrogenation of Diaryl N–H Imines



MonoPhos (**102a**) and MonoPhos-pe (**102e** and **102f**), and finally found that the iridium complex containing a *N*-benzyl-*N*-methyl-MonoPhos ligand **301** gave the best results (Scheme 75). Under similar reaction conditions ($S/C = 20$, 100 atm H_2 , rt, MeOH/ CH_2Cl_2 (2:1)), the diaryl *N*–H imines **302** were hydrogenated by the Ir-*N*-Bn-*N*-Me-MonoPhos catalyst to chiral diarylmethylamines **303** in high yields (80–96%) with 31–98% ee. This hydrogenation appears to be sensitive to the steric and electronic nature of the substituents at the *ortho*-position of the aromatic ring. Chloro, bromo, and methyl substituents at the 2-position gave high enantioselectivities (82–91% ee). Diminishing enantioselectivities were observed in the reaction of the substrates with coordinating 2-methoxy and 2-fluoro substituents (76% and 36% ee, respectively).

4. SUMMARY AND OUTLOOK

As can be seen from the contents of this review, a number of chiral metal catalysts have been developed in the past few decades for the enantioselective hydrogenation of enamines and imines. They provide highly efficient methods for the synthesis of a wide range of chiral amines with or without protecting groups. For the hydrogenation of *N*-acetyl enamines, the chiral rhodium complexes bearing diphosphine ligands such as Duphos, Me-PennPhos, H_8 -BDPAP, t Bu-BisP*, TangPhos, and monodentate phosphorus ligands such as SiPhos, PipPhos, DpenPhos, and ManniPhos were efficient chiral catalysts. However, in the hydrogenation of *N*-alkyl/aryl imines, the chiral iridium catalysts containing phosphine oxazoline ligands, such as PHOX, SI-PHOX, and SpinPHOX, and diphosphine ligands, such as Xyliphos, *f*-Binaphane, and *N*-sulfonyl diamine iridium complex, exhibit outstanding performance. Furthermore, the highly efficient catalysts for activated imines hydrogenation were dominated by palladium complexes of chiral diphosphine ligands such as TangPhos and *f*-Binaphane.

Undoubtedly, the highly enantioselective hydrogenation of unfunctionalized enamines and *N*–H imines are the most prominent events in this area. The iridium catalysts bearing monodentate phosphoramidite ligands SiPhos-pe and MonoPhos and diphosphine ligand *f*-Binaphane proved to be highly efficient for the hydrogenation of *N,N*-dialkyl/arylenamines and/or *N*–H imines, offering the corresponding chiral tertiary amines and/or unprotected primary amines with excellent enantioselectivities. However, these successful cases are very uncommon.

In short, despite the impressive progress that has been achieved regarding the catalytic enantioselective hydrogenation

of enamines and imines, this research area remains challenging. New and highly efficient chiral catalysts for such transformations are expected in the coming years.

AUTHOR INFORMATION

Corresponding Author

*E-mail: qlzhou@nankai.edu.cn.

BIOGRAPHIES



Jian-Hua Xie was born in 1968. He received his B.S. degree from Sichuan Normal College in 1992 and his M.S. degree from Nankai University in 1997 under the mentorship of Professor Tian-Lin Liu. After working at Di'ao Pharmacy for 3 years, he returned to Nankai University, where he earned his Ph.D. in 2003 under the guidance of Professor Qi-Lin Zhou. He then worked in Prof. Zhou's group as a Lecturer and was promoted as an associate professor in 2005. In 2007, he spent one year as a postdoctoral fellow in Prof. Michael P. Doyle's Group at Maryland University. He is now associate professor in the Institute of Elemento-Organic Chemistry, Nankai University. His research interests focus on asymmetric catalysis and organic synthesis.



Shou-Fei Zhu was born in Anhui Province, China, in 1977. He received his B.S. degree in chemistry from Nankai University in 2000. In 2005, he received his Ph.D. degree in chemistry under the supervision of Prof. Qi-Lin Zhou at Institute of Elemento-Organic Chemistry, Nankai University. He then worked in Prof. Qi-Lin Zhou's research group. In 2008, he was promoted to an associate professor of chemistry. His research interests focus on

asymmetric synthesis, particularly on development of chiral ligands and catalysts as well as new asymmetric reactions.



Qi-Lin Zhou was born in Nanjing, China, in 1957. He received his B.S. degree from Lanzhou University in 1982 and his Ph.D. degree from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Prof. Yao-Zeng Huang in 1987. He did postdoctoral research with Prof. Klaus Müllen at Max-Planck Institute of Polymer Science, Prof. Andreas Pfaltz at the University of Basel, and Prof. Michael P. Doyle at Trinity University. In 1996 he was appointed associate professor at the East China University of Science and Technology, Shanghai, and promoted to full professor in 1997. In 1999 he moved to Nankai University as a Cheung Kong Scholar. He received the Prize for Creation in Organic Synthesis in 2005 (Chinese Chemical Society) and Yao-Zeng Huang Prize of Organometallic Chemistry in 2006 (Chinese Chemical Society). He was elected as a member of Chinese Academy of Sciences in 2009. His current research interests include transition metal-catalyzed reactions, asymmetric catalysis, and synthesis of biologically active compounds.

ACKNOWLEDGMENT

We thank National Natural Science Foundation of China, the National Basic Research Program of China (973 Program, No. 2006CB806106, 2010CB833300), the Ministry of Health (Grant No. 2009ZX09501-017), and "111" Project of the Ministry of Education of China (Grant No. B06005) for financial support.

REFERENCES

- (1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 2004. (b) Caprio, V.; Williams, J. M. J. Eds. *Catalysis in Asymmetric Synthesis*; Wiley VCH: Chichester, U.K., 2009.
- (2) Blaser, H. U.; Buser, H. P.; Loers, K.; Hanreich, R.; Jalett, H. P.; Jelsch, E.; Pugin, B.; Schneider, H. D.; Spindler, F.; Wagmann, A. *Chimia* **1999**, *53*, 275.
- (3) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169.
- (4) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Retting, S. J. *Inorg. Chem.* **1991**, *30*, 5002.
- (5) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.
- (6) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
- (7) (a) Nugent, T. C. Ed. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, Germany, 2010. (b) Andersson, P.; Munslow, I. M. Eds. *Modern Reduction Methods*; Wiley-VCH: Weinheim, Germany, 2008. (c) de Vries, J. G.; Elsevier, C. J. Eds. *Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, Germany, 2007. (d) Beller, M.; Bolm, C. Eds. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.
- (8) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.
- (9) Fabrello, A.; Bachelier, A.; Urrutigoity, M.; Kalck, P. *Coord. Chem. Rev.* **2010**, *254*, 273.
- (10) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
- (11) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.
- (12) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.
- (13) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348.
- (14) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985.
- (15) (a) Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 11774. (b) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366.
- (16) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.
- (17) Feldgus, S.; Landes, C. R. *Organometallics* **2001**, *20*, 2374.
- (18) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100.
- (19) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 1774.
- (20) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679.
- (21) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.
- (22) Chi, Y.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 4849.
- (23) Yan, Y.; Zhang, X. *Tetrahedron Lett.* **2006**, *47*, 1567.
- (24) Matsumura, K.; Shimizu, H.; Saito, T.; Kumobayashi, Adv. *Synth. Catal.* **2003**, *345*, 180.
- (25) Enthaler, S.; Erre, G.; Junge, K.; Addis, D.; Kadyrov, R.; Beller, M. *Chem. Asian. J.* **2008**, *3*, 1104.
- (26) Holz, J.; Zayas, O.; Jiao, H.; Baumaqnn, W.; Spannenberg, A.; Monsees, A.; Riermeier, T. H.; Almena, J.; Kadyrov, R.; Börner, A. *Chem.—Eur. J.* **2006**, *12*, 5001.
- (27) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701.
- (28) Zhou, Y.-G.; Yang, P.-Y.; Han, X.-W. *J. Org. Chem.* **2005**, *70*, 1679.
- (29) Storace, L.; Anzalone, L.; Confalone, P. N.; Davis, W. P.; Fortunak, J. M.; Giangordano, M.; Haley, J. J., Jr.; Kamholz, K.; Li, H.-Y.; Ma, P.; Nugent, W. A.; Parsons, R. L., Jr.; Sheeran, P. J.; Silverman, C. E.; Waltermire, R. E.; Wood, C. C. *Org. Process Res. Dev.* **2002**, *6*, 54.
- (30) Wang, T.; Lamb, M. L.; Scott, D. A.; Wang, H.; Block, M. H.; Lyne, P. D.; Lee, J. W.; Davies, A. M.; Zhang, H.-J.; Zhu, Y.; Gu, F.; Han, Y.; Wang, B.; Mohr, P. J.; Kaus, R. J.; Josey, J. A.; Hoffmann, E.; Thress, K.; MacIntyre, T.; Wang, H.; Omer, C. A.; Yu, D. *J. Med. Chem.* **2008**, *51*, 4672.
- (31) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.
- (32) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590.
- (33) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100.
- (34) Kagan, H. B.; Fiaud, J. C.; Hoornaert, C.; Meyer, D.; Poulin, J. C. *Bull. Soc. Chim. Belg.* **1979**, *88*, 923.
- (35) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871.
- (36) (a) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199. (b) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 4137.
- (37) Li, W.; Waldkirch, J. P.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 7618.
- (38) Lee, S.-G.; Zhang, Y. J.; Song, C. E.; Lee, J. K.; Choi, J. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 847.
- (39) Zhang, Y. J.; Kim, K. Y.; Park, J. H.; Song, C. E.; Lee, S.-g. *Adv. Synth. Catal.* **2005**, *347*, 563.

- (40) Lee, S.-G.; Zhang, Y. J.; Piao, J. Y.; Yoon, H.; Song, C. E.; Choi, J. H.; Hong, J. *Chem. Commun.* **2003**, 2624.
- (41) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, 59, 297.
- (42) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, 120, 5808.
- (43) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, 4, 1695.
- (44) Zhou, Y.-G.; Zhang, X. *Chem. Commun.* **2002**, 1124.
- (45) Hopkins, J. M.; Dalrymple, S. A.; Parvez, M.; Keay, B. A. *Org. Lett.* **2005**, 7, 3765.
- (46) Wang, C.-J.; Gao, F.; Liang, G. *Org. Lett.* **2008**, 10, 4711.
- (47) Zhang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, 45, 5515.
- (48) Franceschini, N.; Joy, M. S.; Kshirsagar, A. *Expert Opin. Invest. Drugs* **2003**, 12, 1413.
- (49) Shen, Z.; Lu, X.; Lei, A. *Tetrahedron* **2006**, 62, 9237.
- (50) (a) Argouarch, G.; Samuel, O.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2885. (b) Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2893.
- (51) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, 38, 3212.
- (52) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem.—Eur. J.* **2002**, 8, 843.
- (53) Lotz, M.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, 41, 4708.
- (54) Chen, W.; Roberts, S. M.; Whittall, J.; Sterner, A. *Chem. Commun.* **2006**, 2916.
- (55) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, 6, 3585.
- (56) Zeng, Q.-H.; Hu, X.-P.; Duan, Z.-C.; Liang, X.-M.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, 16, 1233.
- (57) Li, X.; Jia, X.; Xu, L.; Kok, S. H. L.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, 347, 1904.
- (58) Allwein, S. P.; McWilliams, J. C.; Secord, E. A.; Mowrey, D. R.; Nelson, T. D.; Kress, M. H. *Tetrahedron Lett.* **2006**, 47, 6409.
- (59) Wallace, D. J.; Campos, K. R.; Shultz, C. S.; Klapars, A.; Zewge, D.; Crump, B. R.; Phenix, B. D.; McWilliams, J. C.; Kraska, S.; Sun, Y.; Chen, C.-Y.; Spindler, F. *Org. Process Res. Dev.* **2009**, 13, 84.
- (60) Knowles, W. S. *Acc. Chem. Res.* **1983**, 16, 106.
- (61) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, 120, 1635.
- (62) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, 123, 5268.
- (63) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, 64, 2988.
- (64) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, 41, 1612.
- (65) Yang, Q.; Gao, W.; Deng, J.; Zhang, X. *Tetrahedron Lett.* **2006**, 47, 821.
- (66) Chen, J.; Zhang, W.; Geng, H.; Li, W.; Hou, G.; Lei, A.; Zhang, X. *Angew. Chem., Int. Ed.* **2009**, 48, 800.
- (67) Imamoto, T.; Oohara, N.; Takahashi, H. *Synthesis* **2004**, 1353.
- (68) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646.
- (69) Guan, Z.-H.; Huang, K.; Yu, S.; Zhang, X. *Org. Lett.* **2009**, 11, 481.
- (70) Imamoto, T.; Sugita, K.; Yashida, K. *J. Am. Chem. Soc.* **2005**, 127, 11934.
- (71) Imamoto, T.; Kumada, A.; Yashida, K. *Chem. Lett.* **2007**, 36, 500.
- (72) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, 12, 176.
- (73) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, 126, 5966.
- (74) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, 130, 2560.
- (75) Kadyrov, R.; Ilaldinov, I. Z.; Almehna, J.; Monsees, A.; Riermerier, T. H. *Tetrahedron Lett.* **2005**, 46, 7397.
- (76) (a) Bolm, C.; Xiao, L.; Hintermann, L.; Focken, T.; Raabe, G. *Organometallics* **2004**, 23, 2362. (b) Stemmler, R. T.; Bolm, C. *J. Org. Chem.* **2005**, 70, 9925.
- (77) Huang, J.-D.; Hu, X.-P.; Duan, Z.-C.; Zeng, Q.-H.; Yu, S.-B.; Deng, J.; Wang, D.-Y.; Zheng, Z. *Org. Lett.* **2006**, 8, 4367.
- (78) Wang, D.-Y.; Hu, X.-P.; Huang, J.-D.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Xu, X.-F.; Zheng, Z. *Angew. Chem., Int. Ed.* **2007**, 46, 7810.
- (79) Qiu, M.; Hu, X.-P.; Wang, D.-Y.; Deng, J.; Huang, J.-D.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *Adv. Synth. Catal.* **2008**, 350, 1413.
- (80) Yu, S.-B.; Huang, J.-D.; Wang, D.-Y.; Hu, X.-P.; Deng, J.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2008**, 19, 1862.
- (81) Qiu, M.; Hu, X.-P.; Huang, J.-D.; Wang, D.-Y.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *Adv. Synth. Catal.* **2008**, 350, 2683.
- (82) Wassenaar, J.; Reek, J. N. H. *Dalton Trans.* **2007**, 3750.
- (83) Wassenaar, J.; Reek, J. N. H. *J. Org. Chem.* **2009**, 74, 8403.
- (84) Yamamoto, Y.; Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Miyaura, N. *Chem. Lett.* **2005**, 1224.
- (85) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Tetrahedron Lett.* **2009**, 50, 3158.
- (86) Fernández-Pérez, H.; Pericàs, M. P.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2008**, 350, 1984.
- (87) Zhang, Q.; Takacs, J. M. *Org. Lett.* **2008**, 10, 545.
- (88) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480.
- (89) Zhu, S.-F.; Fu, Y.; Xie, J.-H.; Liu, B.; Xing, L.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2003**, 14, 3219.
- (90) Oldfield, V.; Keating, G. M.; Perry, C. M. *Drugs* **2007**, 67, 1725.
- (91) Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* **2004**, 69, 4648.
- (92) Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, 43, 5541.
- (93) van den Berg, M. R.; Haak, M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, 344, 1003.
- (94) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, 345, 308.
- (95) Jia, X.; Li, X.; Xu, L.; Shi, Q.; Yao, X.; Chan, A. S. C. *J. Org. Chem.* **2003**, 68, 4539.
- (96) Bernsman, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, 70, 943.
- (97) Li, X.; Jia, X.; Lu, G.; Au-Yeung, T. T.-L.; Lam, K.-H. T.; Lo, W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, 14, 2687.
- (98) Zeng, Q.-H.; Hu, X.-P.; Duan, Z.-C.; Liang, X.-M.; Zheng, Z. *J. Org. Chem.* **2006**, 71, 393.
- (99) Hoen, R.; van den Berg, M.; Bernsman, H.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2004**, 6, 1433.
- (100) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, 127, 10488.
- (101) Zhao, B.; Wang, Z.; Ding, K. *Adv. Synth. Catal.* **2006**, 348, 1049.
- (102) Wang, X.; Ding, K. *J. Am. Chem. Soc.* **2004**, 126, 10524.
- (103) Shi, L.; Wang, X.; Sandoval, C. A.; Li, M.; Qi, Q.; Li, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2006**, 45, 4108.
- (104) Zhang, F.; Li, Y.; Li, Z.-W.; He, Y.-M.; Zhu, S.-F.; Fan, Q.-H.; Zhou, Q.-L. *Chem. Commun.* **2008**, 6048.
- (105) Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* **2002**, 43, 7941.
- (106) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett.* **2003**, 5, 4137.
- (107) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* **2004**, 69, 2355.
- (108) Hannen, P.; Militzer, H.-C.; Vogl, E. M.; Rampf, F. A. *Chem. Commun.* **2003**, 2210.
- (109) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, 16, 693.
- (110) Hu, X.-P.; Huang, J.-D.; Zeng, Q.-H.; Zheng, Z. *Chem. Commun.* **2006**, 293.
- (111) Chen, W.; Roberts, S. N.; Whittall, J. *Tetrahedron Lett.* **2006**, 47, 4263.

- (112) Li, Y.; He, Y.-M.; Li, Z.-W.; Zhang, F.; Fan, Q.-H. *Org. Biomol. Chem.* **2009**, 1890.
- (113) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, 42, 790.
- (114) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, 15, 2165.
- (115) Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2912.
- (116) Galland, A.; Dobrota, C.; Toffano, M.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **2006**, 17, 2354.
- (117) Reetz, M. T.; Meiswinkel, A.; Mehler, G.; Angermund, K.; Graf, M.; Thiel, W.; Mynott, R.; Blackmond, D. J. *Am. Chem. Soc.* **2005**, 127, 10305.
- (118) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, 42, 8737.
- (119) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, 1, 1087.
- (120) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, 125, 3534.
- (121) Patureau, F. W.; de Boer, S.; Kuil, M.; Meeuwissen, J.; Breuil, P.-A. R.; Siegler, M. A.; Spek, A. L.; Sandee, A. J.; de Bruin, B.; Reek, J. N. H. *J. Am. Chem. Soc.* **2009**, 131, 6683.
- (122) Devocelle, M.; Mortreux, A.; Agbossou, F.; Dormony, J.-R. *Tetrahedron Lett.* **1999**, 40, 4551.
- (123) Renaud, J. L.; Dupau, P.; Hay, A.-E.; Guingouain, M.; Dixneuf, P. H.; Bruneau, C. *Adv. Synth. Catal.* **2003**, 345, 230.
- (124) Dupau, P.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, 343, 331.
- (125) Lennon, I. C.; Ramsden, J. A.; Brear, C. J.; Broady, S. D.; Muir, J. C. *Tetrahedron Lett.* **2007**, 48, 4623.
- (126) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhrer, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Eur. Chem. J.* **2004**, 10, 4198.
- (127) Erre, G. E.; Enthaler, S.; Junge, K.; Addis, D.; Beller, M. *Adv. Synth. Catal.* **2009**, 351, 1437.
- (128) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 5985.
- (129) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2000**, 41, 2351.
- (130) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, 126, 9918.
- (131) (a) Clausen, A. M.; Dziadul, B.; Cappuccio, K. L.; Kaba, M.; Starbuck, C.; Hsiao, Y.; Dowling, T. M. *Org. Process Res. Dev.* **2006**, 10, 723. (b) Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, J. D., III *J. Am. Chem. Soc.* **2009**, 131, 8798.
- (132) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, 7, 5343.
- (133) Cheruku, P.; Church, T. L.; Trifonova, A.; Wartmann, T.; Andersson, P. G. *Tetrahedron Lett.* **2008**, 49, 7290.
- (134) Baeza, A.; Pfaltz, A. *Chem.—Eur. J.* **2009**, 15, 2266.
- (135) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, 128, 9646.
- (136) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, 58, 6795.
- (137) Yan, P.-C.; Xie, J.-H.; Hou, G.-H.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.* **2009**, 351, 3243.
- (138) Wang, X.-B.; Wang, D.-W.; Lu, S.-M.; Yu, C.-B.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2009**, 20, 1040.
- (139) Levi, A.; Modena, G.; Scorrano, G. *J. Chem. Soc., Chem. Commun.* **1975**, 6.
- (140) James, B. R. *Catal. Today* **1997**, 37, 209.
- (141) Bakos, J.; Orosz, Á.; Heil, B.; Laghmari, M.; Lhoste, P.; Sino, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684.
- (142) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, 114, 7562.
- (143) Schbider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem.—Eur. J.* **1997**, 3, 887.
- (144) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, 40, 3425.
- (145) (a) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, 112, 9400. (b) Chan, Y. N. C.; Meyer, D.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 869.
- (146) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 869.
- (147) Morimoto, T.; Nakajima, N.; Achiwa, K. *Chem. Pharm. Bull.* **1994**, 42, 1951.
- (148) Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, 41, 1149.
- (149) Liu, D.; Li, W.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, 15, 2181.
- (150) Satoh, K.; Inenaga, M.; Kanai, K. *Tetrahedron: Asymmetry* **1998**, 9, 2657.
- (151) Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull. Jpn.* **1987**, 35, 1896.
- (152) Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett* **1995**, 748.
- (153) (a) Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, 6, 2661. (b) Morimoto, T.; Suzuki, N.; Achiwa, K. *Heterocycles* **1996**, 43, 2557.
- (154) Zhu, G.; Zhang, X. *Tetrahedron: Asymmetry* **1998**, 9, 2415.
- (155) Carcedo, C.; Dervisi, A.; Fallis, I. A.; Ooi, L.; Malik, K. M. A. *Chem. Commun.* **2004**, 1236.
- (156) Dervisi, A.; Carcedo, C.; Ooi, L.-L. *Adv. Synth. Catal.* **2006**, 348, 175.
- (157) Tani, K.; Onouchi, J.-I.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955.
- (158) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, 9, 183.
- (159) Sablong, R.; Osborn, J. A. *Tetrahedron: Asymmetry* **1996**, 7, 3059.
- (160) Yamagata, T.; Tadaoka, H.; Nagata, M.; Hirao, T.; Kataoka, Y.; Ratovelomanana-Vidal, V.; Genet, J. P.; Mashima, K. *Organometallics* **2006**, 25, 2505.
- (161) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, 116, 4062.
- (162) Blaser, H.-U.; Buser, H.-P.; Häusel, R.; Jalett, H.-P.; Spindler, F. *J. Organomet. Chem.* **2001**, 621, 34.
- (163) Pugin, B.; Landert, H.; Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2002**, 344, 974.
- (164) Reetz, M. T.; Beuttenmüller, Goddard, R.; Pastó, M. *Tetrahedron Lett.* **1999**, 40, 4977.
- (165) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, 8, 2289.
- (166) Li, W.; Hou, G.; Chang, M.; Zhang, X. *Adv. Synth. Catal.* **2009**, 351, 3123.
- (167) Guiu, E.; Muñoz, B.; Castillón, S.; Claver, C. *Adv. Synth. Catal.* **2003**, 345, 169.
- (168) Guiu, E.; Aghmiz, M.; Díaz, Y.; Muñoz, B.; Claver, C.; Meseguer, B.; Militzer, C.; Castillón, S. *Eur. J. Org. Chem.* **2006**, 627.
- (169) Vargas, S.; Rubio, M.; Suárez, A.; Pizzano, A. *Tetrahedron Lett.* **2005**, 46, 2049.
- (170) Vargas, S.; Rubio, M.; Suárez, A.; del Rio, D.; Alvarez, E.; Pizzano, A. *Organometallics* **2006**, 25, 961.
- (171) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, 121, 6421.
- (172) Solinas, M.; Pfaltz, A.; Cozzi, P. G.; Leitner, W. *J. Am. Chem. Soc.* **2004**, 126, 16124.
- (173) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, 344, 40.
- (174) Schrems, M. G.; Pfaltz, A. *Chem. Commun.* **2009**, 6210.
- (175) Roseblade, S.; Pfaltz, A. *Acc. Chem. Res.* **2007**, 40, 1402.
- (176) Baeza, A.; Pfaltz, A. *Chem.—Eur. J.* **2010**, 16, 4003.
- (177) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833.
- (178) Réthoré, C.; Fourmigué, M.; Avarvari, N. *Chem. Commun.* **2004**, 1384.
- (179) Réthoré, C.; Riobé, F.; Fourmigué, M.; Avarvari, N.; Suisse, I.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2007**, 18, 1877.
- (180) Ezhova, M. B.; Patrick, B. O.; James, B. R.; Waller, F. J.; Ford, M. E. *J. Mol. Catal. A: Chem.* **2004**, 224, 71.

- (181) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Adv. Synth. Catal.* **2010**, 352, 103.
- (182) Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, 128, 12886.
- (183) Han, Z.; Wang, Z.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2009**, 48, 5345.
- (184) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, 27, 1508.
- (185) (a) Blanc, C.; Hannedouche, J.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2003**, 44, 6469. (b) Blanc, C.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2004**, 15, 757.
- (186) Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, 15, 2159.
- (187) (a) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, 6, 3825. (b) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem.—Eur. J.* **2006**, 12, 2318.
- (188) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, 44, 7564.
- (189) Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, 9, 3089.
- (190) Jiang, X.-B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, 5, 1503.
- (191) Faller, J. W.; Milheiro, S. C.; Parr, J. J. *Organomet. Chem.* **2006**, 691, 4945.
- (192) Murai, T.; Inaji, S.; Morishita, K.; Shibahara, F.; Tokunaga, M.; Obora, Y.; Tsuji, Y. *Chem. Lett.* **2006**, 1424.
- (193) Mršić, N.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Am. Chem. Soc.* **2009**, 131, 8358.
- (194) Reetz, M. T.; Bondarev, O. *Angew. Chem., Int. Ed.* **2007**, 46, 4523.
- (195) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H. Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 6.1.
- (196) Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, 130, 14450.
- (197) Shirai, S.-Y.; Nara, H.; Kayaki, Y.; Ikariya, T. *Organometallics* **2009**, 28, 802.
- (198) Buriak, J. M.; Osborn, J. A. *Organometallics* **1996**, 15, 3161.
- (199) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron: Asymmetry* **1999**, 10, 4009.
- (200) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, 45, 6360.
- (201) Zhong, Y.-L.; Krska, S. W.; Zhou, H.; Reamer, R. A.; Lee, J.; Sun, Y.; Askin, D. *Org. Lett.* **2009**, 11, 369.
- (202) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, 130, 13208.
- (203) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2001**, 20, 1047.
- (204) Copley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, 345, 195.
- (205) Jackson, M.; Lennon, I. C. *Tetrahedron Lett.* **2007**, 48, 1831.
- (206) Clarke, M. L.; Diaz-Valenzuela, B.; Slawin, A. M. *Organometallics* **2007**, 26, 16.
- (207) Cheruku, P.; Church, T. L.; Andersson, P. G. *Chem. Asian. J.* **2008**, 3, 1390.
- (208) Wild, F. R. W. P.; Zsolnai, J.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1988**, 342, 21.
- (209) (a) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, 58, 7627. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 11703.
- (210) Ringwald, M.; Stürmer, Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, 121, 1524.
- (211) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, 3, 313.
- (212) Suzuki, A.; Mae, Masayuki, Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, 69, 5132.
- (213) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *Chem. Commun.* **2005**, 3451.
- (214) Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *J. Org. Chem.* **2007**, 72, 3729.
- (215) (a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, 114, 6266. (b) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, 50, 4399.
- (216) Yoshikawa, N.; Tan, L.; McWilliams, J. C.; Ramasamy, D.; Sheppard, R. *Org. Lett.* **2010**, 12, 276.
- (217) Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2001**, 343, 68.
- (218) Kobayashi, K.; Okamoto, T.; Oida, T.; Tanimoto, S. *Chem. Lett.* **1986**, 2031.
- (219) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, 29, 4117.
- (220) Charette, A.; Ciroux, A. *Tetrahedron Lett.* **1996**, 37, 6669.
- (221) Copley, C. J.; Foucher, E.; Lecouvé, J.-P.; Lennon, I. C.; Ramsden, J. A.; Thominot, G. *Tetrahedron: Asymmetry* **2003**, 14, 3431.
- (222) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, 45, 3832.
- (223) Yu, C.-B.; Wang, D.-W.; Zhou, Y.-G. *J. Org. Chem.* **2009**, 74, 5633.
- (224) Rolfe, A.; Young, K.; Hanson, P. R. *Eur. J. Org. Chem.* **2008**, 5254.
- (225) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, 10, 2071.
- (226) Wang, Y.-Q.; Zhou, Y.-G. *Synlett* **2006**, 1189.
- (227) Hou, G.; Gosselin, F.; Li, W.; McWilliams, C.; Sun, Y.; Weisel, M.; O'Shea, P. D.; Chen, C.-Y.; Davies, I. W.; Zhang, X. *J. Am. Chem. Soc.* **2009**, 131, 9882.
- (228) Hou, G.; Tao, R.; Sun, Y.; Zhang, X.; Gosselin, F. *J. Am. Chem. Soc.* **2010**, 132, 2124.