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Chiral Diphosphine and Monodentate Phosphorus Ligands on a Spiro Scaffold for Transition-Metal-Catalyzed Asymmetric Reactions

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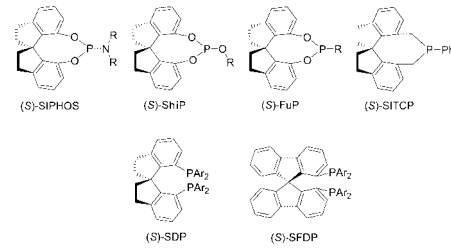
RECEIVED ON JUNE 5, 2007

CONSPECTUS

The preparation of chiral compounds in enantiomerically pure form is a challenging goal in modern organic synthesis. The use of chiral metal complex catalysis is a powerful, economically feasible tool for the preparation of optically active organic compounds on both laboratory and industrial scales. In particular, the metals coordinated by one or more chiral phosphorus ligands exhibit amazing enantioselectivity and reactivity. Many chiral phosphorus ligands have been synthesized and used in transition-metal-catalyzed asymmetric reactions in past decades. However, a large number of reactions still lack effective chiral ligands, and the enantioselectivities in many reactions are substrate-dependent. The development of effective chiral phosphorus ligands, especially ligands having novel chiral backbones, is still an important task in the area of asymmetric catalysis.



Chiral phosphorus ligands with spiro backbones

Molecules containing a spirocyclic framework are ubiquitous in nature. The synthesis of molecules with this spiro structure can be traced back to 100 years ago. However, the use of this spirocyclic framework to construct chiral phosphorus ligands is a recent event. This Account outlines the design and synthesis of a new family of chiral spiro phosphorus ligands including spiro diphosphines and spiro monodentate phosphorus ligands with 1,1′-spirobiindane and 9,9′-spirobifluorene backbone and their applications in transition-metal-catalyzed asymmetric hydrogenation and carbon−carbon bond formation reactions.

The chiral spiro diphosphine lgands SDP with a 1,1′-spirobiindane backbone and SFDP with a 9,9′-spirobifluorene backbone, and the spiro monophosphorus ligands including phosphoramidites, phosphites, phosphonites, and phospholane with a 1,1′-spirobiindane backbone were synthesized in good yields from enantiomerically pure 1,1′-spirobiindane-7,7′-diol and 9,9′-spirobifluoren-1,1′-diol.

The ruthenium complexes of chiral spiro diphosphine ligands proved to be very effective catalysts for asymmetric hydrogenations of ketones, α-arylaldehydes and α,β-unsaturated acids. The rhodium complexes of chiral spiro monophosphorus ligands are highly enantioselective for the asymmetric hydrogenations of α- and β-dehydroamino acid derivatives, α-arylethenyl acetamides and non-*N*-acyl enamines. The spiro monophosphorus ligands were demonstrated to be highly efficient for the Rh-catalyzed asymmetric addition of arylboronic acids to aldehydes and *N*-tosylarylimines, Pd-catalyzed asymmetric allylation of aldehydes with allylic alcohols, Cu-catalyzed asymmetric ring opening reactions with Grignard reagents, and Ni-catalyzed asymmetric hydrovinylation of styrene derivatives with ethylene.

The chiral spiro phosphorus ligands show high enantioselectivities for a wide range of transition-metal-catalyzed asymmetric reactions. In most of these transformations, the enantioselectivities of spiro phosphorus ligands are superior to those obtained by using the corresponding phosphorus ligands with other backbones. These results arise from the intriguing chiral inducement of spiro structures of the ligands.

Introduction

Many biologically active compounds, such as pharmaceuticals, agrochemicals, flavorings, and functional materials, exhibit "handedness." The preparation of these "handed" (chiral) compounds in enantiomerically pure form is a challenging goal in modern organic synthesis. Undoubtedly,

Published on the Web 03/01/2008 www.pubs.acs.org/acr
10.1021/ar700137z CCC: $40.75

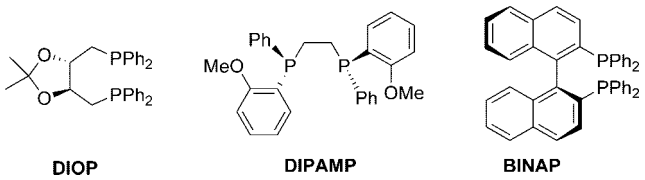


FIGURE 1. Examples of chiral phosphorus ligands.

the use of chiral metal complex catalysis is a powerful, economically feasible tool for the preparation of optically active organic compounds on both laboratory and industrial scales.[1] In particular, the metals coordinated by one or more chiral phosphorus ligands exhibit amazing enantioselectivity and reactivity[2] (Figure 1).

Initially, the design and synthesis of chiral phosphorus ligands focused on monodentate *P*-chiral phosphines, but the level of asymmetric inducement was rather low.[3] The situation changed drastically in 1971 when Dang and Kagan introduced the tartrate-derived C_2-symmetric diphosphine DIOP in asymmetric hydrogenation, achieving high enantioselectivites.[4] The interest in ligand design shifted from *P*-chiral monophosphines to chelating diphosphines with chirality at their backbones, especially those with C_2-symmetry. This trend was further bolstered by the success of the diphosphine DIPAMP in the production of the chiral drug L-DOPA by the Monsanto Company, providing the first example of an industrial application of asymmetric catalysis.[5] However, diphosphine ligands were mainly applied in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acids until Noyori and Takaya reported in 1980 the outstanding diphosphine ligand BINAP, which was successfully applied in the ruthenium-catalyzed asymmetric hydrogenation of various functionalized olefins and ketones.[6] Inspired by BINAP, a large number of diphosphine ligands with biaryl backbones have been developed in the past two decades.[7]

Although many chiral phosphorus ligands have been synthesized and used in transition-metal-catalyzed asymmetric reactions, a large number of reactions still lack effective chiral ligands, and the enantioselectivities in many reactions are substrate-dependent. Therefore, the development of effective chiral phosphorus ligands, especially ligands having novel chiral backbones, is still an important and challenging task for chemists. In this Account, we highlight our efforts to develop chiral spiro phosphorus ligands with 1,1′-spirobiindane and 9,9′-spirobifluorene backbones and to apply them in transition-metal-catalyzed asymmetric hydrogenation and carbon−carbon bond formation reactions.

Design and Synthesis of Chiral Spiro Phosphorus Ligands with 1,1′-Spirobiindane and 9,9′-Spirobifluorene Backbones

Molecules containing a spirocyclic framework are ubiquitous in nature. The synthesis of molecules with this spiro structure can be traced back to the late 1890s.[8] However, the use of this spirocyclic framework to construct chiral phosphorus ligands is a recent event. In 1900, von Baeyer introduced the name "spirocyclane" for bicyclic hydrocarbons having two rings with a common carbon atom (spiro carbon), construing them to be shaped like pretzels.[9] Actually, due to the tetrahedron structure of the spiro carbon, bicyclic spiro compounds are not true "pretzels" because the two rings of the spiro compounds lie in perpendicular planes. This structural feature not only restricts the rotation of the two rings and gives rise to an axial chirality in spiro compounds having substituents on the rings but also increases molecular rigidity. In spiro molecules, two rings connect at a quaternary center through σ-bonds, which makes racemization of chiral spiro compounds virtually impossible. With these characteristics, spiro compounds, especially C_2-symmetric spiranes, are ideal backbones for chiral phosphorus ligands. However, the chiral spiro phosphorus ligand was not studied until the past decade, probably due to the difficulty of synthesizing optically pure spiro compounds.

In 1992, Kumar used chiral spiro diols *cis*,*cis*-(+)- and (−)-spiro[4,4]nonane-1,6-diol as chiral auxiliaries in the reduction of ketones with lithium aluminum hydride, giving the corresponding alcohols with good enantioselectivities.[10] Chan and Jiang used the chiral spiro diol as a backbone to synthesize the chiral phosphinite ligands SpirOP and demonstrated that they were highly enantioselective in rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives.[11] Very recently, additional research groups have participated in the development of chiral ligands with spiro backbones.[12]

Seeking chiral ligands with novel backbones, we became interested in the chiral spirobiindane and spirobifluorene phosphorus compounds. Spiro[4,4]nonane is not itself a chiral molecule. Substitutions on the spiro cycles introduce more than one chiral center into the molecule and increase the difficulty of synthesizing optically pure ligands. However, spirobiindane and spirobifluorene, which can be regarded as benzo derivatives of spiro[4,4]nonane, only have axial chirality, and their highly rigid spiro structures make them good potential backbones of chiral ligands (Figure 2).

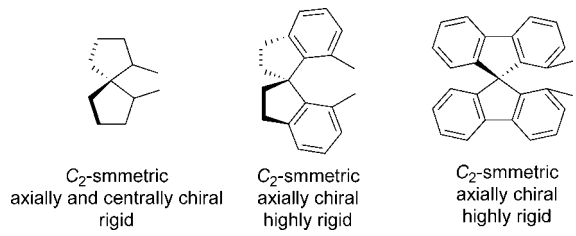


FIGURE 2. Spiro backbones for phosphorus ligands.

The chiral spiro phosphorus ligands (*R*)- or (*S*)-SDP (**6**) with a 1,1′-spirobiindane backbone were synthesized from optically pure (*R*)- or (*S*)-1,1′-spirobiindane-7,7′-diol (**1**)[13] in high yields by the methods illustrated in Scheme 1.[14]

The chiral ligands with a 9,9′-spirobifluorene backbone (SFDP, **8**)[15] (Scheme 2) are easily prepared from enantiomerically pure 9,9′-spirobifluoren-1,1′-diol (**7**)[16] by the same procedure used for the SDP ligands.

The structural characteristics of SDP and SFDP ligands were revealed by X-ray analysis of single crystals of complexes [$PdCl_2$((*S*)-**6a**)][14b] and [$PdCl_2$((*R*)-**8a**)].[15a] Both complexes have a square-planar configuration, and the eight-membered heterometallocyclic rings formed by chelation of the ligands **6a** and **8a** to palladium are highly rigid (Figure 3). The P−Pd−P bite angles in [$PdCl_2$((*S*)-**6a**)] and [$PdCl_2$((*R*)-**8a**)] are 96.0° and 96.7°, respectively, which are greater than that of [$PdCl_2$((*R*)-BINAP)] (92.7°).[17] In addition, one *P*-phenyl group on each phosphorus atom in these two palladium complexes lies parallel to the indane or fluorene ring. The central distances between the *P*-phenyls and the indane or fluorene ring are 3.5 and 4.2 Å in [$PdCl_2$((*S*)-**6a**)] and 3.5 and 3.6 Å in [$PdCl_2$((*R*)-**8a**)], thereby indicating the existence of $\pi-\pi$ stacking interactions between the *P*-phenyl rings and the indane or fluorene ring. This $\pi-\pi$ stacking interaction was also observed in complex [$PdCl_2$((*R*)-BINAP)].[17]

Very recently, the enantioselectivity-inducing potential of chiral monodentate phosphorus ligands was rediscovered,[18] and several efficient chiral monophosphorus ligands based on the 1,1′-binaphthalene backbone such as monophosphine MOP,[19] monophosphoamidite MonoPhos,[20] and monophosphite[21] were reported and applied in the asymmetric hydrogenation of functionalized olefins and other asymmetric transformations with good to excellent enantioselectivities. These results showed that the chiral inducement by monophosphorus ligands could be equal or even superior to that obtained by bidentate phosphorus ligands. Current development of phosphorus ligands has witnessed a strong competition between monodentate and bidentate phosphorus ligands. We have synthesized a series of chiral spiro monodentate phosphorus ligands including phosphoramidites **9**,[22] phosphites **10**,[23] phosphonites **11**, [24] and phospholane **12**[25] ligands with a 1,1′-spirobiindane scaffold from spiro diol **1** in good yields by using simple procedures (Figure 4).

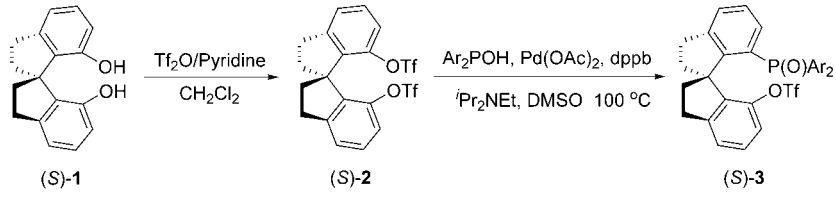
Asymmetric Catalytic Hydrogenation

Asymmetric hydrogenation utilizing molecular hydrogen to reduce prochiral olefins, ketones, and imines is currently one of the most efficient methods for the production of chiral amino acid derivatives, chiral alcohols, and chiral amines, which are important building blocks for constructing enantiomerically pure pharmaceuticals and functional materials. The transition metal complexes of SDP and SFDP families of ligands, as well as chiral spiro monophosphorus ligands, proved to be very effective catalysts with high enantioselectivities for the hydrogenation of a broad scope of unsaturated substrates.

Hydrogenation of Ketones. The enantioselective reduction of carbonyl compounds catalyzed by well-defined transition metal complexes is an efficient synthetic tool for producing optically active alcohols. One of the best catalysts for ketone hydrogenation is the $RuCl_2$[(diphosphine)(1,2-diamine)] complex, which was initially reported by Noyori.[26] The ruthenium complexes of chiral spirobiindane diphosphines, $RuCl_2$[(SDPs)(1,2-diamine)], were also found to be highly effective catalysts in the asymmetric hydrogenation of prochiral ketones.[14a] The steric hindrance of the ligand has a strong influence on the enantioselectivity of the catalyst. A bulkier ligand provides higher enantioselectivity; the ligand **6d** (Xyl-SDP) containing 3,5-dimethyl groups on the *P*-phenyl rings is the best, giving 99% enantiomeric excess (ee) in the asymmetric hydrogenation of acetophenone. The reactivities of the $RuCl_2$[(SDPs)(1,2-diamine)] catalysts are extremely high. For example, using the catalyst $RuCl_2$[((*S*)-**6d**)((*R,R*)-DPEN)], the hydrogenation of acetophenone can be carried out at a catalyst loading of 0.001 mol %. A variety of simple ketones including aromatic, heteroaromatic, and α,β-unsaturated ketones can be hydrogenated by the catalyst $RuCl_2$[((*S*)-**6d**)((*R,R*)-DPEN)], producing the corresponding chiral secondary alcohols in excellent enantioselectivities (Figure 5).

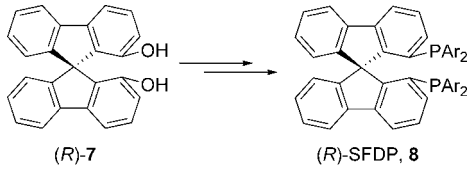
The $RuCl_2$[(diphosphine)(1,2-diamine)] complex catalyzed asymmetric hydrogenation of ketones was performed under basic reaction conditions. The two enantiomers of α-arylcycloketone compounds can racemize rapidly under these conditions, allowing dynamic kinetic resolution (DKR) of the racemate by asymmetric hydrogenation. Thus, we applied $RuCl_2$[(SDPs)(1,2-diamine)] catalysts in the asymmetric hydrogenation of racemic α-arylcycloketones.[27] Through DKR, use of the catalyst $RuCl_2$[((*S*)-**6d**)((*R,R*)-DPEN)] converted both enan-

SCHEME 1. The Synthetic Route for SDP Ligands



6	Ar	
6a	C_6H_5	(SDP)
6b	*p*-$CH_3C_6H_4$	(Tol-SDP)
6c	*p*-$CH_3OC_6H_4$	(An-SDP)
6d	3,5-$(CH_3)_2C_6H_3$	(Xyl-SDP)
6e	4-CH_3O-3,5-$(CH_3)_2C_6H_2$	(DM-SDP)

SCHEME 2. The Synthesis of SFDP Ligands



8	Ar	
8a	C_6H_5	(SFDP)
8b	*p*-$CH_3C_6H_4$	(Tol-SFDP)
8c	*p*-$CH_3OC_6H_4$	(An-SFDP)
8d	3,5-$(CH_3)_2C_6H_3$	(Xyl-SFDP)
8e	3,4,5-$(CH_3)_3$-C_6H_2	(TM-SFDP)

tiomers of racemic α-aryl cyclohexanones to the α-aryl cyclohexanols. The *cis*/*trans* stereoselectivities (>99/1) and enantioselectivities (up to 99.9% ee) are excellent (Scheme 3).

Hydrogenation of Aldehydes. Although exciting progress had been achieved in asymmetric hydrogenation of ketones, no successful example of asymmetric hydrogenation of aldehydes, providing enantiomer-enriched primary alcohols, had been reported prior to our work.[28] In the hydrogenation of prochiral ketones, at least one new stereogenic center is generated. However, no new stereogenic center is generated in the hydrogenation of α-branched aldehydes, which makes enantiocontrol of the reaction extremely difficult. Our attempts to achieve the asymmetric hydrogenation of racemic α-arylaldehyde via DKR using $RuCl_2$[(SDPs)(1,2-diamine)] complexes as catalysts led to remarkable results (Figure 6).[29] The complex $RuCl_2$[((*S*)-**6e**)((*R*,*R*)-DACH)] was the optimum choice of catalyst, and a bulky alkyl group at the α-position of the racemic α-arylaldehydes was crucial for obtaining high enantioselectivity. This result represents the first example of asymmetric hydrogenation of aldehydes via DKR.

The chiral primary alcohols prepared by the process in Figure 6 have wide potential applications in the synthesis of chiral pharmaceuticals, pesticides, and natural products. For example, the product (*S*)-2-(4-methoxyphenyl)-3-methylbutan-

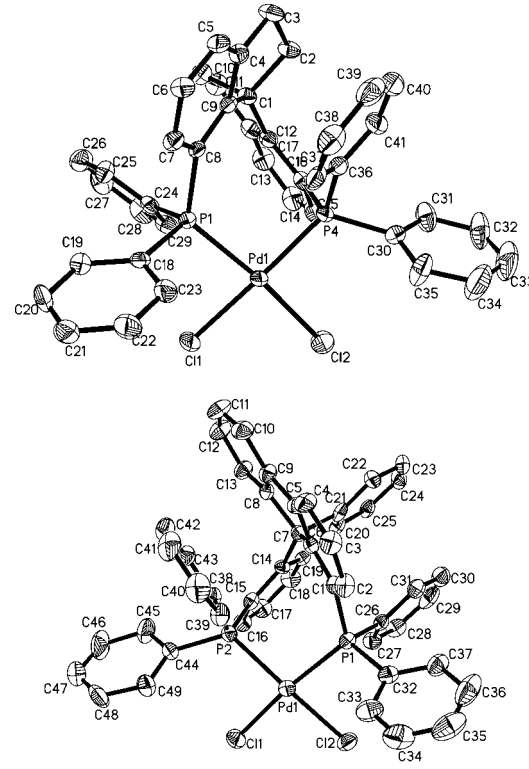


FIGURE 3. OPTER diagrams of [$PdCl_2$((*S*)-**6a**)] (top) and [$PdCl_2$((*R*)-**8a**)] (bottom).

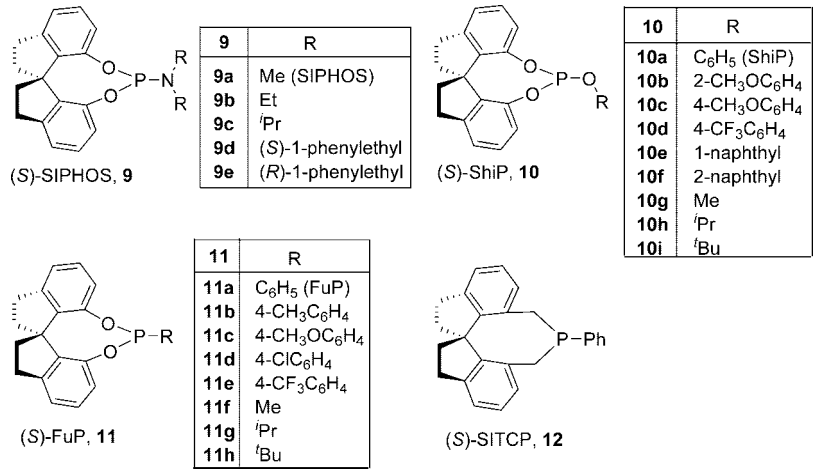


FIGURE 4. Chiral spiro monophosphorus ligands with a 1,1′-spirobiindane backbone.

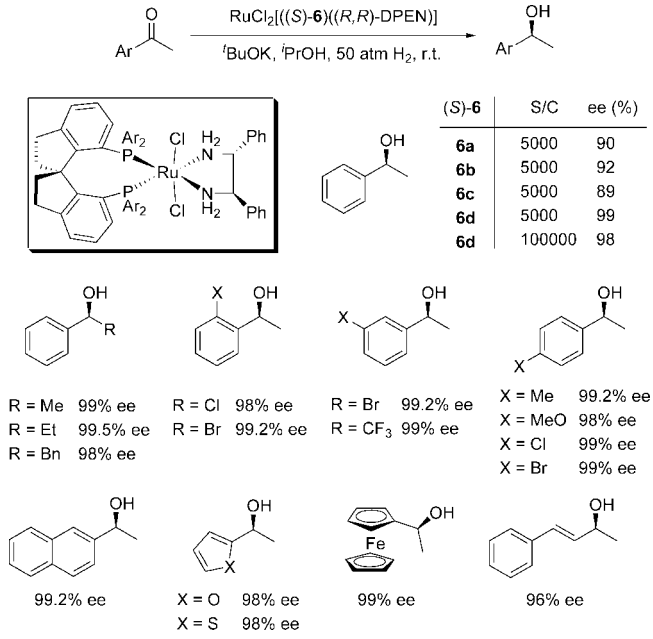
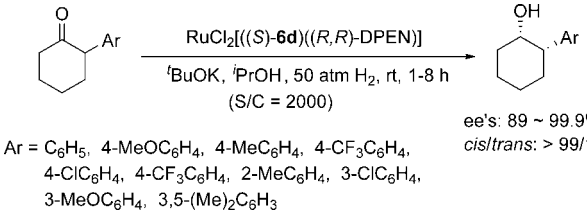


FIGURE 5. Ru-catalyzed asymmetric hydrogenation of ketones using SDP ligands.

SCHEME 3. Hydrogenation of α-Arylcyclohexanones Using $RuCl_2$[((*S*)-**6d**)((*R*,*R*)-DPEN)]



1-ol (94% ee) is the key intermediate for the synthesis of natural product (1*S*,4*S*)-*cis*-7-methoxy-calamenene.[30] Quinolylmethoxyphenyl acetic acid derivatives are important leukotriene receptor antagonists and lipoxygenase inhibitors (e.g., BAY × 1005 [31]) and can be synthesized easily by our method (Scheme 4).

Hydrogenation of α,β-Unsaturated Carboxylic Acids. Enantioselective hydrogenation of α,β-unsaturated carboxylic acids catalyzed by transition metal complexes is a straightforward method for the synthesis of optically active carboxylic acids, which are widely used as chiral drugs or important intermediates in the synthesis of pharmaceutically interesting compounds.[32] A number of chiral diphosphine ligands have been used successfully in the ruthenium-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[33] The Ru-diacetate complexes ligated by SDP and SFDP ligands (**6a** and **8a**) were applied in the asymmetric hydrogenation of tiglic acid. The results illustrated in Scheme 5 clearly show that the SFDP ligand, which has a larger bite angle, is superior to the ligands BINAP and SDP in terms of enantioselectivity.[15] Introducing 3,5-dimethyl (ligand **8d**) and 3,4,5-trimethyl (ligand **8e**) groups on the *P*-phenyls of the SFDP ligand enhanced the enantiomeric excess of hydrogenation products. Interestingly, the enantioselectivity of the reaction was further increased as the catalyst loading was reduced from 1 mol % to 0.1 and 0.01 mol %. Thus, this catalytic hydrogenation might preferentially occur at higher concentrations, which is very important for a catalyst used on a production scale.

A variety of tiglic acid derivatives have been hydrogenated by using the catalyst Ru/**8d** (Figure 7). High enantioselectivities (>94% ee) and good yields (~90%) were obtained for all tested substrates regardless of the bulkiness of the R^1 and R^2 groups. However, the reaction rate was obviously retarded when a large group was introduced at either the α- or β-position in the tiglic acid type substrates.

In contrast to the excellent results obtained in the asymmetric hydrogenation of tiglic acids, α-arylacrylic acids, and other α,β-unsaturated carboxylic acids, initial attempts at asymmetric hydrogenation of cinnamic acid derivatives were

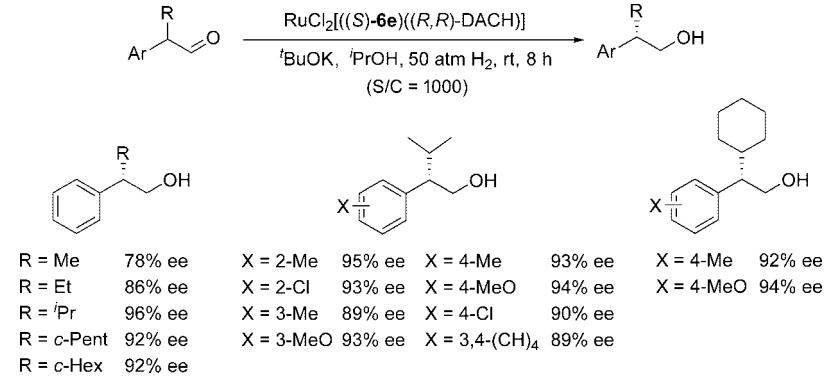
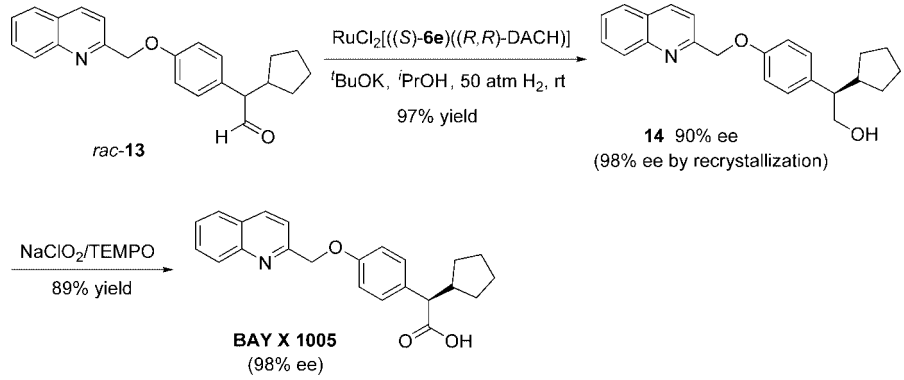
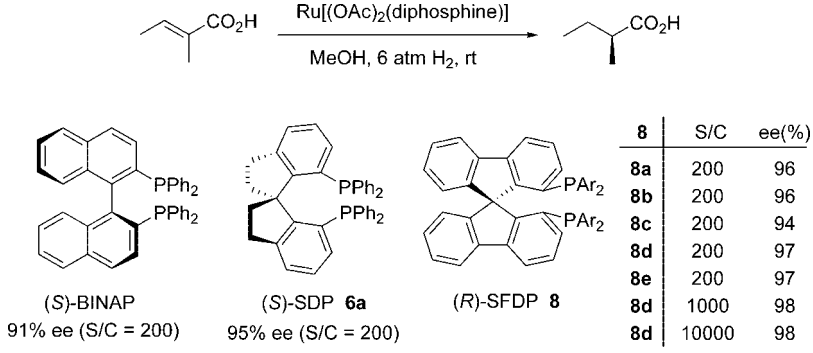


FIGURE 6. Hydrogenation of α-arylaldehydes using $RuCl_2$[((*S*)-**6e**)((*R,R*)-DACH)].

SCHEME 4. Preparation of BAY × 1005



SCHEME 5. Asymmetric Hydrogenation of Tiglic Acid with Ru-Diacetate Catalysts



8	S/C	ee(%)
8a	200	96
8b	200	96
8c	200	94
8d	200	97
8e	200	97
8d	1000	98
8d	10000	98

far from successful. The Ru-diacetate complex ligated with BINAP had been applied in the hydrogenation of α-methylcinnamic acid, but the enantioselectivity was very low (<40% ee). By using the H_8-BINAP ligand, Takaya significantly improved the enantioselectivity to 89% ee.[33c] However, when the catalyst Ru[$(OAc)_2$((*R*)-**8e**)] was employed, an unprecedented enantioselectivity (94% ee) in the hydrogenation of α-methylcinnamic acid was achieved. In this reaction, the steric hindrance of the substituents on the *P*-phenyl rings of the SFDP ligand has a notably positive influence on the reactivity and enantioselectivity of the catalysts (Scheme 6).[15]

A variety of α-methylcinnamic acid derivatives were hydrogenated by ruthenium catalyst ligated with TM-SFDP (**8e**) to yield the corresponding saturated acids in excellent enantiomeric excesses (Figure 8). This result represents the highest

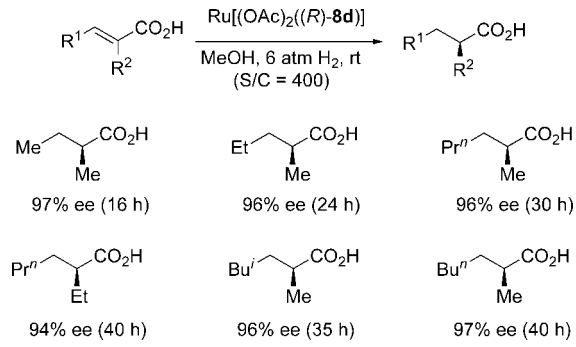
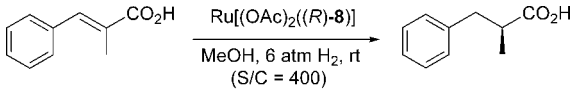


FIGURE 7. Hydrogenation of tigilic acid derivatives with Ru[$(OAc)_2$((*R*)-**8d**)].

SCHEME 6. Asymmetric Hydrogenation of α-Methylcinnamic Acid Using Ru-Diacetate Catalysts



(*R*)-**8**	time (h)	yield (%)	ee (%)
(*R*)-**8a** (SFDP)	48	93	60
(*R*)-**8b** (Tol-SFDP)	48	91	70
(*R*)-**8c** (An-SFDP)	30	89	45
(*R*)-**8d** (Xyl-SFDP)	24	93	87
(*R*)-**8e** (TM-SFDP)	18	91	94

level of enantiocontrol reported to date in the asymmetric hydrogenation of cinnamic acid derivatives.

Asymmetric hydrogenation of α-aryloxyl or alkoxyl unsaturated carboxylic acids has not received much attention despite the fact that its products, α-aryloxyl or alkoxyl carboxylic acids, are important in organic syntheses and industrial production. When the catalyst [Ru(OAc)$_2$((*R*)-**8e**)], which provided the highest enantioselectivity in the asymmetric hydrogenation of cinnamic acid derivatives, was employed for the asymmetric hydrogenation of α-phenoxycrotonic acid, only a moderate level of enantioselectivity was obtained. However, when the catalyst [Ru(OAc)$_2$((*R*)-**8b**)] having a 4-methyl group on each *P*-phenyl ring of the ligand was used, the enantioselectivity of this reaction was improved significantly to 94% ee. With the catalyst [Ru(OAc)$_2$((*R*)-**8b**)], a number of crotonic acids substituted with different α-aryloxyl groups can be hydrogenated to the corresponding chiral saturated acids in high yields with good to high enantioselectivities (Figure 9).[15b]

Asymmetric Hydrogenation of Enamines. The Rh(I)-catalyzed asymmetric hydrogenation of functionalized enamines, such as α- and β-dehydroamino acid derivatives, and enamides is one of the most efficient methods for the synthesis of chiral amines. In the past three decades, Rh(I)-complexes bearing chelating diphosphine ligands dominated this field.[2] Recently, several Rh(I)-complexes bearing monodentate phosphorus ligands were developed, and high enantioselectivities were obtained in the asymmetric hydrogenation of functionalized enamines.[18] However, the successful monodentate phosphorus ligands that have been reported are limited to phosphoramidites and phosphites containing a 1,1′-binaphthylene backbone. We have developed a series of chiral monophosphoramidite and monophosphonite ligands bearing a spirobiindane backbone and demonstrated that they are highly enantioselective in Rh(I)-catalyzed hydrogenation of *N*-acyl and non-*N*-acyl enamines.

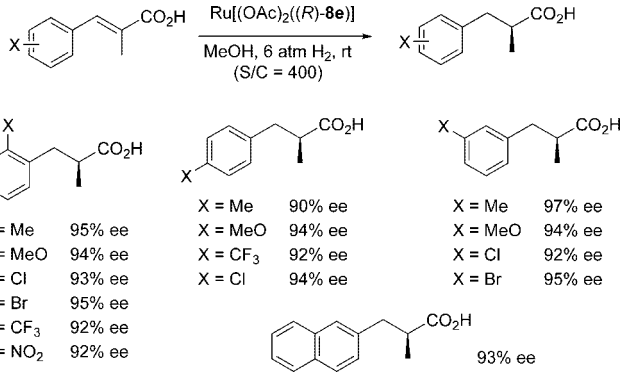


FIGURE 8. Asymmetric hydrogenation of α-methylcinnamic acid derivatives with Ru[(OAc)$_2$((*R*)-**8e**)].

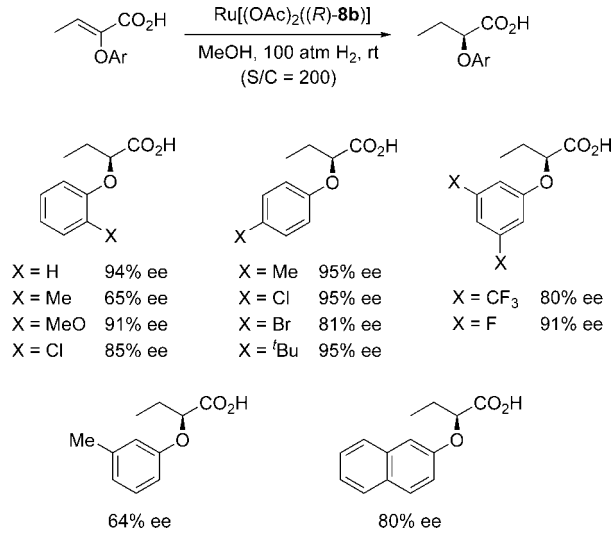


FIGURE 9. Hydrogenation of α-aryloxy crotonic acids catalyzed by [Ru(OAc)$_2$((*R*)-**8b**)].

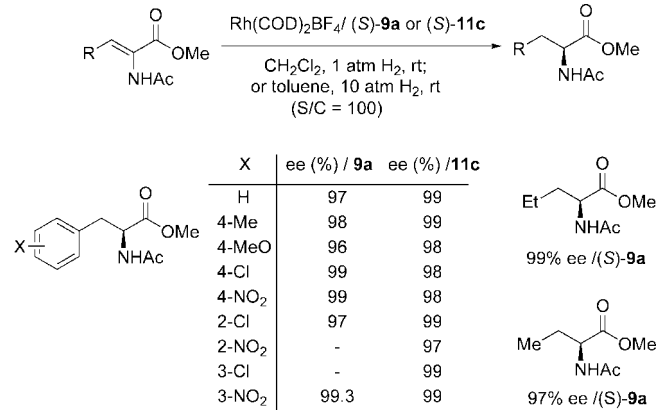
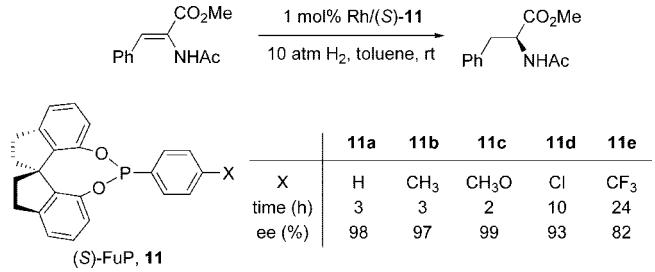


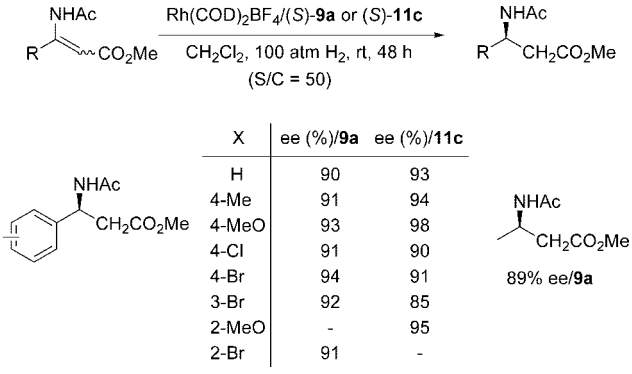
FIGURE 10. Asymmetric hydrogenation of α-dehydroamino acid derivatives catalyzed by Rh(I)/(*S*)-**9a** or (*S*)-**11c**.

Spiro monophosphoramidite ligands **9** were very effective in the hydrogenation of α-dehydroamino acid derivatives. The ligand SIPHOS (**9a**), which has two dimethyl groups on the nitrogen, gave the best results.[22b,d] For a variety of α-dehydroamino acid derivatives, excellent enantioselectivities (96−99.3% ee) were obtained under ambient H_2 pressure (Figure 10). These results are better than or comparable to



	11a	11b	11c	11d	11e
X	H	CH_3	CH_3O	Cl	CF_3
time (h)	3	3	2	10	24
ee (%)	98	97	99	93	82

FIGURE 11. Electronic effect of ligands in Rh(I)-catalyzed asymmetric hydrogenation of (*Z*)-methyl-2-acetamido-3-phenylacrylate.



X	ee (%)/**9a**	ee (%)/**11c**
H	90	93
4-Me	91	94
4-MeO	93	98
4-Cl	91	90
4-Br	94	91
3-Br	92	85
2-MeO	-	95
2-Br	91	-

FIGURE 12. Asymmetric hydrogenation of β-dehydroamino acid derivatives using Rh(I)/(*S*)-**9a** or (*S*)-**11c**.

those achieved with diphosphine ligands[34] and other monophosphorus ligands.[18]

To study the electronic effects of ligands, spiro phosphonite ligands **11**, which have different substituents at the *para* position of the *P*-phenyl ring, were prepared and applied in the hydrogenation of (*Z*)-methyl-2-acetamido-3-phenylacrylate.[24a] It was found that an electron-withdrawing substituent on the *P*-phenyl ring of the ligand dramatically diminished both the reactivity and enantioselectivity of the catalyst in the reaction. In contrast, the ligand **11c** having an electron-donating *p*-MeO group gave the best enantioselectivity and the fastest reaction rate. The data in Figure 11 clearly indicate that electron-rich monophosphorus ligands are beneficial to both enantioselectivity and reactivity of the rhodium catalysts in this reaction.

The Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives is another model reaction. Although a higher hydrogen pressure (100 atm) was needed for the hydrogenation of β-dehydroamino acid derivatives, both the phosphoramidite ligand SIPHOS (**9a**) and the phosphonite ligand **11c** gave high enantioselectivities in this transformation (Figure 12).[22d,24a] It is noteworthy that the Rh(I) complexes of ligands **9a** and **11c** can hydrogenate *Z*/*E* mixtures of β-aryl-β-(acylamino)acrylates to produce β-amino acid derivatives. This is of practical importance because the β-(acylamino)acrylate substrates are normally prepared as a mixture of *Z*- and *E*-isomers.

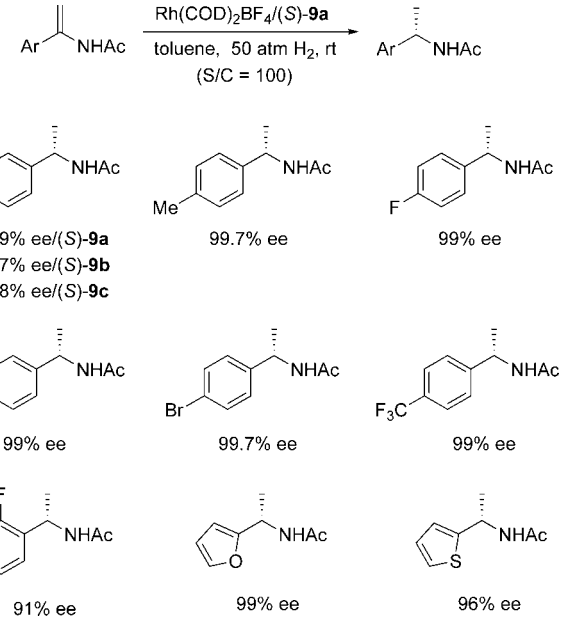


FIGURE 13. Hydrogenation of α-arylethenyl acetamides using Rh(I)/(*S*)**-9**.

The spiro phosphoramidite ligands **9** were highly enantioselective in the asymmetric hydrogenation of α-arylethenyl acetamides. In this reaction, a smaller dialkylamino group in the ligand was found to be crucial for obtaining high enantioselectivity. Using the ligand SIPHOS (**9a**), a series of α-arylethenyl acetamides can be hydrogenated with 91−99.7% ee.[22a] This result was superior to that obtained by using the ligand MonoPhos (90−94% ee),[35] showing that the 1,1′-spirobiindane backbone confers better enantioselective inducement than the 1,1′-binaphthalene backbone in the hydrogenation of α-arylethenyl acetamides (Figure 13).

Optically active cyclic amines are an important class of compounds that are used widely in pharmaceutical synthesis. For example, chiral 1-aminoindanes are the key intermediates for drugs such as rasagiline for Parkinson's disease.[36] The asymmetric hydrogenation of *N*-(1,2-dehydro-1-indanyl)acetamide is a potential method to produce enantiomer-enriched 1-aminoindane. With the Rh/**9a** catalyst, *N*-(1,2-dehydro-1-indanyl)acetamides were successfully hydrogenated to 1-aminoindanes in high enantioselectivities (Figure 14).[22d]

In the current approaches to asymmetric hydrogenation of enamides, a substantial drawback is the requirement for an *N*-acyl group in the substrate. This *N*-acyl group is considered indispensable for the substrate to form a chelated complex with the metal of the catalyst in the transition state, giving good reactivity and enantioselectivity.[37] Until our study, only

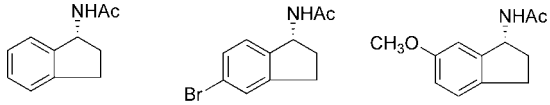
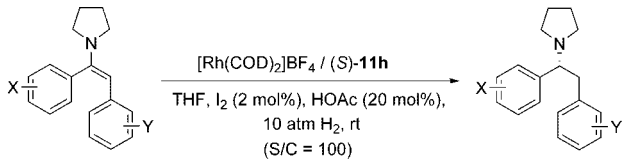


FIGURE 14. Asymmetric hydrogenation of cyclic enamides using Rh(I)/(*S*)-**9a**.

SCHEME 7. Hydrogenation of (*E*)-1-(1-Pyrrolidinyl)-1,2-diarylethenes Using Rh(I)/(*S*)-**11h**



X	H	4-Me	4-MeO	4-Cl	3-Me	2-Me	3,4-$(MeO)_2$	4-MeO
Y	H	H	H	H	H	H	H	4-F
ee (%)	87	91	95	73	90	90	99	95
X	H	H	H	H	H	H	H	3-Me
Y	4-Me	4-F	4-Cl	4-Br	3-Cl	2-Me	2-Cl	4-F
ee (%)	80	99.9	97	96	90	94	93	90

two reports have tackled the challenging class of enamine substrates without an *N*-acyl group, and moderate to excellent enantioselectivities have been achieved.[38] During our study on the asymmetric hydrogenation of non-*N*-acyl enamines, we found that the phosphonite **11h**, which has a ^{t}Bu group on the P-atom, was an admirable ligand for the asymmetric hydrogenation of (*E*)-1-(1-pyrrolidinyl)-1,2-diarylethenes. In the presence of 2 mol % I_2 and 20 mol % acetic acid as additives, a variety of (*E*)-1-(1-pyrrolidinyl)-1,2-diarylethenes can be hydrogenated by the Rh(I)/(*S*)-**11h** catalyst, yielding the corresponding tertiary amines with excellent enantioselectivities (up to 99.9% ee) (Scheme 7).[24b] Other ligands such as the diphosphine ligands BINAP, Josiphos, and SDP (**6a**) and the monodentate phosphorus ligands MonoPhos, H-MOP, SIPHOS (**9a**), and ShiP (**10a**) provided the hydrogenation product with very low enantioselectivities under the same reaction conditions.

Asymmetric Catalytic Carbon−Carbon Bond Formation

Asymmetric catalytic carbon−carbon bond formation is one of the most essential and effective tools for the construction of chiral organic molecules. The metal complexes of monodentate spiro phosphorus ligands were demonstrated to be very effective for different types of asymmetric carbon−carbon bond formation reactions.

Addition of Arylboronic Acids to Aldehydes and *N*-Tosylarylimines. The enantioselective addition of aryl organometallic reagents to aromatic aldehydes is a very useful method for the synthesis of enantiomer-enriched chiral diarylmethanols, which are important intermediates for the synthesis of biologically and pharmaceutically active compounds. However, reports of successful transition-metal-catalyzed asymmetric addition of aryl organometallic reagents to aromatic aldehydes are scarce. In 1998, Miyaura and co-workers first reported the enantioselective Rh-catalyzed addition of phenylboronic acid to naphthaldehyde by using the (*S*)-MeO-MOP ligand, giving naphthylphenylmethanol in low enantioselectivity (41% ee).[39] However, by employing the ligand (*S*)-**10f**, which has a 2-naphthoxy substituent on the P-atom, the enantioselectivity of this reaction was remarkably improved to 87% ee. Either electron-rich or electron-deficient benzaldehydes and various arylboronic acids can be applied as substrates and reagents in the reaction, producing diarylmethanols in high yields (88−98%) with good enantioselectivities (62−87% ee) (Figure 15).[23b]

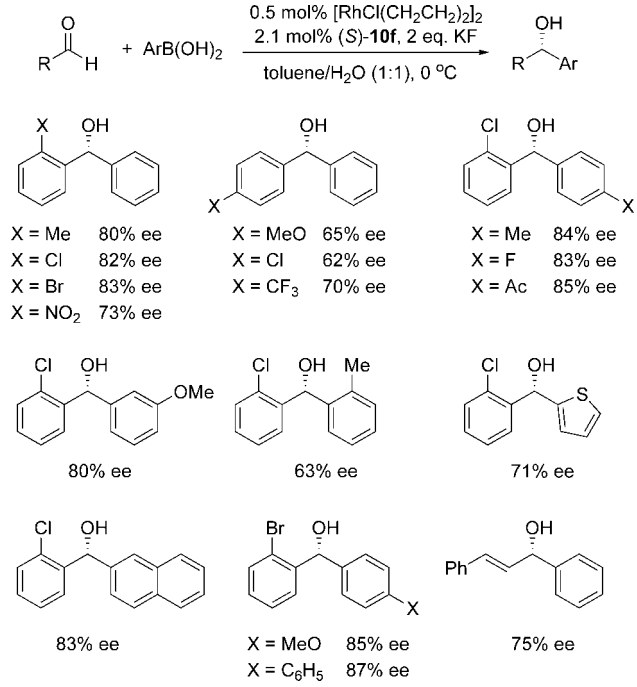


FIGURE 15. Asymmetric addition of arylboronic acids to aldehydes using Rh(I)/(*S*)-**10f**.

By extension of this Rh(I)/ShiP catalyst system to the addition of arylboronic acids to *N*-tosylarylimines, high enantioselectivities were achieved. With the catalyst generated *in situ* from $Rh(acac)(C_2H_2)_2$ and (*S*)-ShiP (**10a**), which has a phenoxy group on the *P*-atom, the arylation of a variety of aromatic imines with different arylboronic acids gave *N*-tosylmethylamine products in good yields (65−85%) with excellent enantioselectivities (85−95% ee) (Figure 16).[40]

To understand the prominent enantioselective inducement of spiro phosphite ligands **10** in the Rh-catalyzed addition of arylboronic acids to imines, we grew a single crystal of

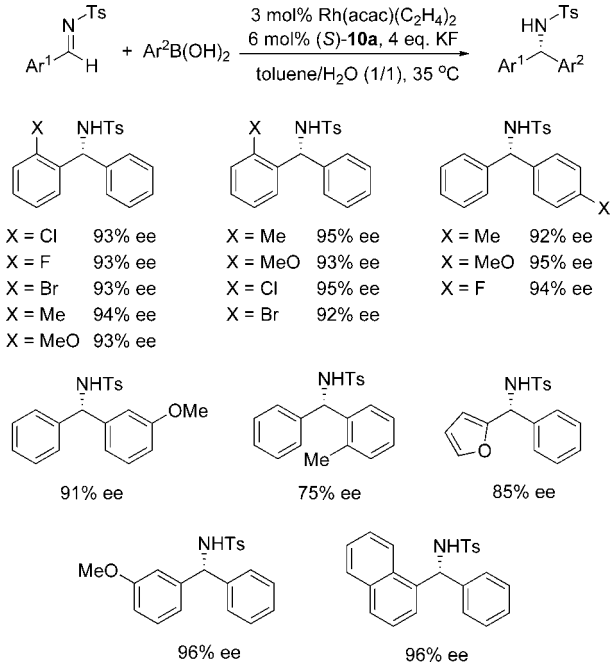


FIGURE 16. Addition of arylboronic acids to *N*-tosylarylimines using Rh(I)/(*S*)-**10a**.

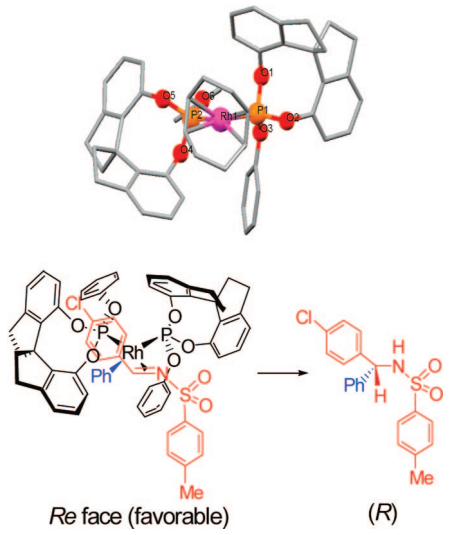
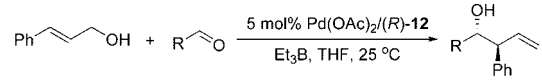


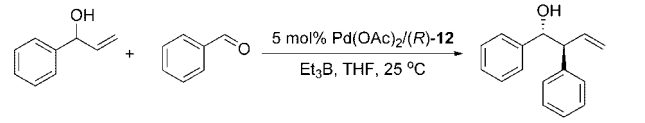
FIGURE 17. Crystal structure of [Rh(COD)((*S*)-**10a**)$_2$]BF_4 and the stereorecognition model.

[Rh(COD((*S*)-**10a**)$_2$)]BF_4 that was suitable for X-ray diffraction. The structure analysis showed that two coordinating spiro phosphite ligands created an effective asymmetric environment around the rhodium. Two phenyl groups of the phosphite ligand **10a** blocked the back side of the complex. From the proposed stereorecognition model (Figure 17), it can be seen that the phenyl group transferred favorably to the *Re* face of the imine, providing the corresponding product with the *R* configuration, which is consistent with the X-ray analysis of a single crystal of the addition product.[40]

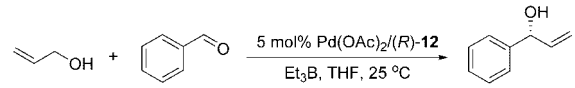
SCHEME 8. Asymmetric Allylation of Aldehydes with Allylic Alcohols Using Pd(II)/(*R*)-**12**



R	yield (%)	*anti*/*syn*	ee (%)
C_6H_5	80	98/2	82
4-$MeOC_6H_4$	97	99/1	74
2-$MeOC_6H_4$	91	95/5	69
4-$CF_3C_6H_4$	71	97/3	58
1-naphthyl	99	99/1	79
2-naphthyl	95	99/1	73
2-furyl	73	99/1	78
c-C_6H_{11}	50	99/1	83



60% yield, *anti*/*syn* = 98:2, 79% ee



80% yield, 80% ee

Allylation of Aldehydes with Allylic Alcohols. Catalytic enantioselective allylation of aldehydes represents one of the most efficient strategies for the synthesis of chiral homoallylic alcohols. In 2004, Zanoni and co-workers reported Pd-catalyzed asymmetric allylation of benzaldehyde with allyl esters by umpolung of π-allylpalladium complexes.[41] In consideration of synthetic efficiency and green chemistry, we attempted the direct use of allylic alcohols as allylation reagents in this transformation and found that chiral monodentate spiro phenylphospholane SITCP (**12**) was a competent ligand for this task. In the presence of the Pd(II)/(*R*)-**12** catalyst and Et_3B as the reducing reagent, a series of aromatic, heteroaromatic, and aliphatic aldehydes can be allylated by cinnamyl alcohol to provide the corresponding homoallylic alcohols in good enantioselectivities and excellent diastereoselectivities. The simple allylic alcohol prop-2-en-1-ol also can serve as an allylation reagent (Scheme 8).[25]

Cu-Catalyzed Ring-Opening Reactions. Enantioselective desymmetrization of meso oxabicyclic alkenes with a nucleophile, that is, asymmetric ring opening (ARO), is an efficient strategy by which cyclic compounds with multiple stereocenters can be constructed in one operation. Many organometallic reagents such as dialkylzinc have been applied successfully in this reaction, and excellent stereoselectivities and enantioselectivities were achieved.[42] However, the Grignard reagent, the most readily available organometallic reagent, has been scarcely utilized in the ARO reactions.[42b] The reason for the rare application of the Grignard reagent in this important reaction might be attributed to the complex

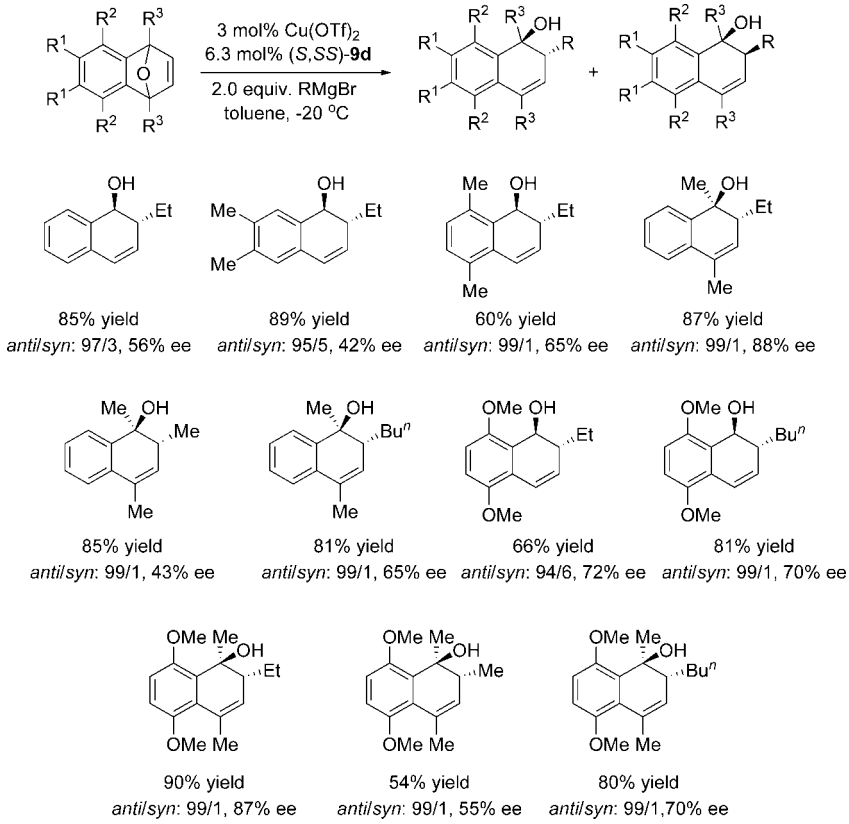


FIGURE 18. Cu(II)-catalyzed asymmetric ring-opening reaction by using (*S,SS*)-**9d**.

mechanism of the ARO reaction with this hard nucleophile. In a study of Cu-catalyzed ARO reactions with Grignard reagents, we demonstrated that the phosphoramidite (*S,SS*)-**9d**, which has a di-((*S*)-1-phenylethyl)amino group on the P-atom, was the best choice of ligands for this reaction. Using Cu(II)/(*S,SS*)-**9d**, the ARO of various oxabenzonorbornadiene substrates with different Grignard reagents yielded ring-opening products with excellent *anti*/*syn* selections and good enantioselectivities (Figure 18).[43]

Hydrovinylation of α-Alkyl Vinylarenes. Ni-catalyzed asymmetric hydrovinylation of vinylarenes is an important carbon−carbon bond-forming reaction, and impressive progress has been achieved.[44] During the study of Ni-catalyzed asymmetric hydrovinylation, we were aware that this transformation could be a new approach for the construction of all-carbon quaternary stereocenters if an α-alkyl vinylarene is used as the substrate. By using spiro phosphoramidite ligand (*S,RR*)-**9e**, different α-alkyl vinylarenes reacted with ethylene under ambient pressure to afford the hydrovinylation products bearing a chiral all-carbon quaternary center in excellent enantioselectivities. These vinylation products are potentially useful intermediates for the synthesis of versatile optically active molecules, such as chiral carboxylic acids and aldehydes (Figure 19).[45]

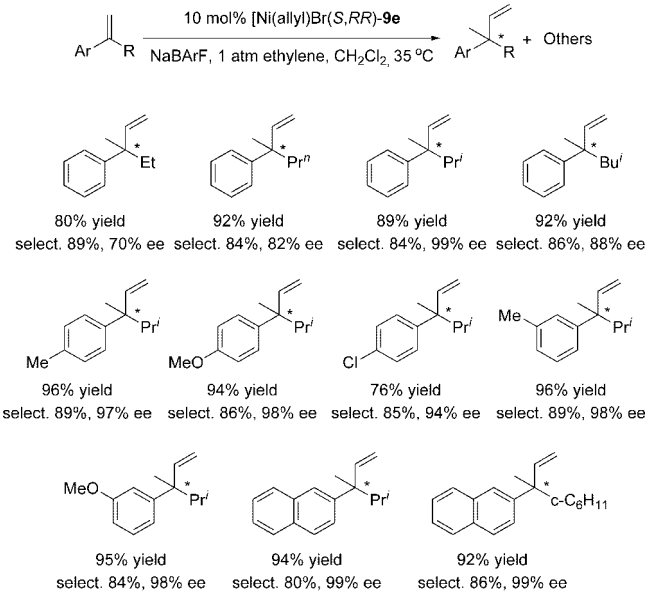


FIGURE 19. Asymmetric hydrovinylation of vinylarenes with Ni(I)/(*S,RR*)-**9e**.

Conclusions

A series of C_2-symmetric chiral spiro phosphorus ligands including diphosphines, monodentate phosphoramidites, phosphites, phosphonites, and phospholanes that are based on spirobiindane and spirobifluorene backbones have been synthesized and applied to various transition-metal-catalyzed

processes. Gratifyingly, these chiral spiro phosphorus ligands furnish excellent enantioselectivities for a wide range of reactions such as the Ru-catalyzed asymmetric hydrogenations of racemic α-arylaldehydes and α,β-unsaturated acids, the Rh-catalyzed asymmetric hydrogenations of α-arylethenyl acetamides and non-*N*-acyl enamines, and the Ni-catalyzed asymmetric hydrovinylation of α-alkyl vinylarenes to construct chiral all-carbon quaternary centers. These results arise from the intriguing chiral inducement of spiro phosphorus ligands. In the coming years, further investigations will disclose the merits of this family of chiral spiro phosphorus ligands for more transition-metal-catalyzed asymmetric reactions.

We are deeply indebted to a highly talented group of co-workers whose names are listed in the relevant references. We also thank the National Natural Science Foundation of China, the Major Basic Research Development Program (Grant No. 2006CB806106), and the "111" project (B06005) of the Ministry of Education of China for financial support.

BIOGRAPHICAL INFORMATION

Jian-Hua Xie was born in 1968. He received his B.S. degree from Sichuan Normal College in 1992 and 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 is now associate professor in the Institute of Elemento-organic Chemistry in the same university. His research interests focus on asymmetric catalysis and organic synthesis.

Qi-Lin Zhou was born in 1957. He graduated from Chemistry Department, Lanzhou University, in 1982 and received his Ph.D. from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, in 1987. He spent several years as postdoctoral fellow in Germany (with Professor Klaus Müllen), Switzerland (with Professor Andreas Pfaltz), and the United States (with Professor Michael Doyle). In 1996, he was appointed associate professor in the Institute of Fine Chemicals, East China University of Science and Technology, and one year later, he became full professor. In 1999, he was promoted to Cheung Kong Scholar in the Institute of Elemento-oragnic Chemistry, Nankai University.

FOOTNOTES

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REFERENCES

1 (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalyses*; Springer: Berlin, 1999. (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley & Sons: New York, 2000. (c) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley & Sons: New York, 2001.

2 Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029–3070.

3 For a review, see: (a) Lagasse, F.; Kagan, H. B. Chiral Monophosphines as Ligands for Asymmetric Organometallic Catalysis. *Chem. Pharm. Bull.* **2000**, *48*, 315–324. For early articles, see: (b) Knowles, W. S.; Sabacky, M. J. Catalytic Asymmetric Hydrogenation Employing a Soluble, Optically Active, Rhodium Complex. *Chem. Commun.* **1968**, 1445–1446. (c) Horner, L.; Siegel, H.; Büthe, H. Asymmetric Catalytic Hydrogenation with an Optically Active Phosphine Rhodium Complex in Homogeneous Solution. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942.

4 Dang, T. P.; Kagan, H. B. The Asymmetric Synthesis of Hydratropic Acid and Amino-acids by Homogeneous Catalytic Hydrogenation. *J. Chem. Soc. D, Chem. Commun.* **1971**, 481.

5 (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. Asymmetric Hydrogenation with a Complex of Rhodium and a Chiral Bisphosphine. *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. Asymmetric Hydrogenation. Rhodium Chiral Bisphosphine Catalyst. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952.

6 Noyori, R.; Takaya, H. BINAP: An Efficient Chiral Element for Asymmetric Catalysis. *Acc. Chem. Res.* **1990**, *23*, 345–350.

7 For recent review, see: Shimizu, H.; Nagasaki, I.; Saito, T. Recent Advances in Biaryl-Type Bisphosphine Ligands. *Tetrahedron* **2005**, *61*, 5405–5432.

8 Krapcho, A. P. Synthesis of Carbocyclic Spiro Compounds via Intramolecular Alkylation Routes. *Synthesis* **1974**, 383–419.

9 von Baeyer, A. Systematik und Nomenclatur Bicyclischer Kohlenwasserstoffe. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3771–3775.

10 Srivastava, N.; Mital, A.; Kumar, A. A Novel Chiral Auxiliary from Chiral Spiranes, cis,cis-(+)- and (-)-Spiro[4,4]nonane-1,6-diol as Chiral Modifier in Aluminium Hydride Reduction of Phenyl Alkyl Ketones. *Chem. Commun.* **1992**, 493–494.

11 Chan, A. S. C.; Hu, W.-H.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.-Z.; Mi, A.-Q.; Yan, M.; Sun, J.; Lou, R.-L.; Deng, J.-G. Novel Spiro Phosphinite Ligands and Their Application in Homogeneous Catalytic Hydrogenation Reactions. *J. Am. Chem. Soc.* **1997**, *119*, 9570–9571.

12 (a) Lait, S. M.; Parvez, M.; Keay, B. A. Synthesis of a Novel Spiro-phosphino-oxazine Ligand and Its Application to Pd-Catalyzed Asymmetric Allylic Alkylation. *Tetrahedron: Asymmetry* **2004**, *15*, 155–158. (b) Wu, S.; Zhang, W.; Zhang, Z.; Zhang, X. Synthesis of New Monodentate Spiro Phosphoramidite Ligand and Its Application in Rh-Catalyzed Asymmetric Hydrogenation Reactions. *Org. Lett.* **2004**, *6*, 3565–3567. (c) Frexa, Z.; Beentjes, M. S.; Batema, G. D.; Dieleman, C. B.; van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; Fraanje, J.; Goubitz, K.; van Leeuwen, P. W. N. M. SPANphos: A C_2-Symmetric trans-Coordinating Diphosphane Ligand. *Angew. Chem., Int. Ed.* **2003**, *42*, 1284–1287.

13 (a) Birman, V. B.; Rheingold, A. L.; Lam, K.-C. 1,1′-Spirobiindane-7,7′-diol: A Novel, C_2-Symmetric Chiral Ligand. *Tetrahedron: Asymmetry* **1999**, *10*, 125–131. (b) Zhang, J.-H.; Liao, J.; Cui, X.; Yu, K.-B.; Deng, J.-G.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L.; Chung, L.-W.; Ye, T. Highly Efficient and Practical Resolution of 1,1′-Spirobiindane-7,7′-diol by Inclusion Crystallization with N-Benzylcinchonidinium Chloride. *Tetrahedron: Asymmetry* **2002**, *13*, 1363–1366.

14 (a) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. Synthesis of Spiro Diphosphines and Their Application in Asymmetric Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2003**, *125*, 4404–4405. (b) Xie, J.-H.; Duan, H.-F.; Fan, B.-M.; Cheng, X.; Wang, L.-X.; Zhou, Q.-L. Application of SDP Ligands for Pd-Catalyzed Allylic Alkylation. *Adv. Synth. Catal.* **2006**, *346*, 625–632.

15 (a) Cheng, X.; Zhang, Q.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. Highly Rigid Diphosphane Ligands with a Large Dihedral Angle Based on a Chiral Spirobifluorene Backbone. *Angew. Chem., Int. Ed.* **2005**, *44*, 1118–1121. (b) Cheng, X.; Xie, J.-H.; Li, S.; Zhou, Q.-L. Asymmetric Hydrogenation of α,β,-Unsaturated Carboxylic Acids Catalyzed by Ruthenium(II) Complexes of Spirobifluorene Diphosphine (SFDP) Ligands. *Adv. Synth. Catal.* **2006**, *348*, 1271–1276.

16 Cheng, X.; Hou, G.-H.; Xie, J.-H.; Zhou, Q.-L. Synthesis and Optical Resolution of 9,9′-Spirobifluorene-1,1′-diol. *Org. Lett.* **2004**, *6*, 2381–2383.

17 Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. Palladium-Catalyzed Asymmetric Arylation of 2,3-Dihydrofuran with Phenyl Triflate. A Novel Asymmetric Catalysis Involving a Kinetic Resolution Process. *Organometallics* **1993**, *12*, 4188–4196.

18 For reviews, see: (a) Komarov, I. V.; Börner, A. Highly Enantioselective or Not? - Chiral Monodentate Monophophosphorus Ligands in the Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197–1200. (b) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. Chiral Monodentate Phosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation. *Tetrahedron: Asymmetry* **2004**, *15*, 2101–2111.

19 Hayashi, T. Chiral Monodentate Phosphine Ligand MOP for Transition-Metal-Catalyzed Asymmetric Reactions. *Acc. Chem. Res.* **2000**, *33*, 354–362.

20 van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands. *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540.

21 Reetz, M. T.; Mehler, G. Highly Enantioselective Rh-Catalyzed Hydrogenation Reactions Based on Chiral Monophosphite Ligands. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890.

22 (a) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. Monodentate Chiral Spiro Phosphoramidites: Efficient Ligands for Rhodium-Catalyzed Enantioselective Hydrogenation of Enamides. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348–2350. (b) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. Novel Monodentate Spiro Phosphorus Ligands for Rhodium-Catalyzed Hydrogenation Reactions. *Chem. Commun.* **2002**, 480–481. (c) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. Highly Enantioselective Copper-Catalyzed Conjugate Addition of Diethylzinc to Enones Using Chiral Spiro Phosphoramidites as Ligands. *J. Org. Chem.* **2003**, *68*, 1582–1584. (d) Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Olefins Using Monodentate Spiro Phosphoramidite Ligands. *J. Org. Chem.* **2004**, *69*, 4648–4655.

23 (a) Shi, W.-J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. Highly Regioselective Asymmetric Copper-Catalyzed Allylic Alkylation with Dialkylzincs Using Monodentate Chiral Spiro Phosphoramidite and Phosphite Ligands. *Tetrahedron: Asymmetry* **2003**, *14*, 3867–3872. (b) Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Aldehydes Using Chiral Spiro Monophosphite Ligands. *Org. Lett.* **2006**, *8*, 1479–1481.

24 (a) Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. Synthesis of Monodentate Chiral Spiro Phosphonites and the Electronic Effect of Ligand in Asymmetric Hydrogenation. *J. Org. Chem.* **2004**, *69*, 8157–8160. (b) Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. Highly Efficient Rh(I)-Catalyzed Asymmetric Hydrogenation of Enamines Using Monodente Spiro Phosphonite Ligands. *J. Am. Chem. Soc.* **2006**, *128*, 11774–11775.

25 Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. Synthesis and Application of Chiral Spiro Phospholane Ligand in Pd-Catalyzed Asymmetric Allylation of Aldehydes with Allylic Alcohols. *Org. Lett.* **2005**, *7*, 2333–2335.

26 Noyori, R.; Ohkuma, T. Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

27 Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. Ru^{II}-SDP-Complex-Catalyzed Asymmetric Hydrogenation of Ketones. Effect of the Alkali Metal Cation in the Reaction. *J. Org. Chem.* **2005**, *70*, 2967–2973.

28 Hydrogen transfer reduction of α-branched aldehydes has been reported, but an asymmetric version of this reaction has not been documented. (a) Miecznikowski, J. R.; Crabtree, R. H. Hydrogen Transfer Reduction of Aldehydes with Alkali-Metal Carbonates and Iridium NHC Complexes. *Organometallics* **2004**, *23*, 629–631. (b) Wu, X.; Liu, J.; Li, X.; Zanotti-Gerosa, A.; Hancock, F.; Vinci, D.; Ruan, J.; Xiao, J. On Water and in Air: Fast and Highly Chemoselective Transfer Hydrogenation of Aldehydes with Iridium Catalysts. *Angew. Chem., Int. Ed.* **2006**, *45*, 6718–6722.

29 Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. Ru-Catalyzed Asymmetric Hydrogenation of Racemic Aldehydes via Dynamic Kinetic Resolution: Efficient Synthesis of Optically Active Primary Alcohols. *J. Am. Chem. Soc.* **2007**, *129*, 1868–1869.

30 Brenna, E.; Negri, C. D.; Fuganti, C.; Gatti, F. G.; Serra, S. Enantioselective Synthesis of cis-7-Methoxy-calamenene via Claisen Rearrangement of an Enzymatically Resolved Allyl alcohol. *Tetrahedron: Asymmetry* **2004**, *15*, 335–340.

31 Hatzemann, A.; Fruchtmann, R.; Mohrs, K. H.; Raddatz, S.; Müller-Peddinghuas, R. Model of Action of The New Selective Leukotriene Synthesis Inhibitor BAY ×1005 {(*R*)-2-[4-(quinolin-2-yl)phenyl]-2-cyclopentyl acetic acid} and Structurally Related Compounds. *Biochem. Pharmacol.* **1993**, *45*, 101–111.

32 Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley, New York, 1977 and 1980; Vols. *1* and *2*.

33 (a) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP-Ruthenium(II) Complexes. *J. Org. Chem.* **1987**, *52*, 3174–3176. (b) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; de Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. Enantioselective Hydrogenation Reactions with a Full Set of Preformed and Prepared in situ Chiral Diphosphine-Ruthenium(II) Catalysts. *Tetrahedron: Asymmetry* **1994**, *5*, 675–690. (c) Uemura, T.; Zhang, X.-Y.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. Highly Efficient Enantioselective Synthesis of Optically Active Carboxylic Acids by $Ru(OCOCH_3)_2$[(*S*)-H_8-BINAP]. *J. Org. Chem.* **1996**, *61*, 5510–5516. (d) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C. Highly Effective Chiral Dipyridylphosphine Ligands: Synthesis, Structural Determination, and Applications in the Ru-Catalyzed Asymmetric Hydrogenation Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 11513–11514.

34 (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. Synthesis of 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), an Atropisomeric Chiral Bis(triaryl)phosphine, and Its Use in the Rhodium(I)-Catalyzed Aasymmetric Hydrogenation of α-(Acylamino)acrylic Acids. *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934. (b) Burk, M. J. C_2-Symmetric Bis(phospholanes) and Their Use in Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519.

35 Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. Rhodium/MonoPhos-Catalysed Asymmetric Hydrogenation of Enamides. *Adv. Synth. Catal.* **2002**, *344*, 1003–1007.

36 (a) Youdim, M. B. H.; Finberg, J. P. M.; Levy, R.; Sterling, J.; Lerner, D.; Berger-Paskin, T.; Yellin, H.; Veinberg, A. U.S. Patent 5,786,390, 1995. (b) Cohen, S.; Herzig, Y.; Levy, R.; Speiser, T.; Sterling, J.; Veinberg, A.; Youdim, M. B. H.; Finberg, J. P. M. U.S. Patent 5,994,408, 1997.

37 Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, New York, 1985.

38 (a) Lee, N. E.; Buchwald, S. L. Asymmetric Hydrogenation of Enamines with a Chiral Titanocene Catalyst. *J. Am. Chem. Soc.* **1994**, *116*, 5985–5986. (b) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. Rhodium(I) Catalyzed Asymmetric Hydrogenation of Enamines. *Tetrahedron Lett.* **2000**, *41*, 2351–2355.

39 Sakai, M.; Ueda, M.; Miyaura, N. Rhodium-Catalyzed Addition of Organoboronic Acids to Aldehydes. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279–3281.

40 Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. Enantioselective Rh-Catalyzed Arylation of *N*-Tosylarylimines with Arylboronic Acids. *Org. Lett.* **2006**, *8*, 2567–2569.

41 Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.; Tredici, I.; Vidari, G. Enantioselective Catalytic Allylation of Carbonyl Groups by Umpolung of π-Allyl Palladium Complexes. *Angew. Chem., Int. Ed.* **2004**, *43*, 846–849.

42 (a) Lautens, M.; Fagnou, K.; Hiebert, S. Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes. *Acc. Chem. Res.* **2003**, *36*, 48–58. (b) Millward, D. B.; Sammis, G.; Waymouth, R. M. Ring-Opening Reactions of Oxabicyclic Alkene Compounds: Enantioselective Hydride and Ethyl Additions Catalyzed by Group 4 Metals. *J. Org. Chem.* **2000**, *65*, 3902–3909.

43 Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. Copper-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Grignard Reagents. *J. Org. Chem.* **2005**, *70*, 3734–3736.

44 (a) Goossen, L. J. Asymmetric Hydrovinylation: New Perspectives through Use of Modular Ligand Systems. *Angew. Chem., Int. Ed.* **2002**, *41*, 3775–3778. (b) RajanBabu, T. V. Asymmetric Hydrovinylation Reaction. *Chem. Rev.* **2003**, *103*, 2845–2860.

45 Shi, W.-J.; Zhang, Q.; Xie, J.-H.; Zhu, S.-F.; Hou, G.-H.; Zhou, Q.-L. Highly Enantioselective Hydrovinylation of α-Alkyl Vinylarenes. An Approach to the Construction of All-Carbon Quaternary Stereocenters. *J. Am. Chem. Soc.* **2006**, *128*, 2780–2781.