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New chiral phosphorus ligands with spirobiindane backbone for asymmetric hydrogenations*

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Abstract: Chiral spiro phosphorus ligands including monophosphoramidites and diphosphines, which contained 1,1'-spirobiindane as a backbone, were designed and synthesized. These spiro ligands were proven to be highly efficient for rhodium- and ruthenium-catalyzed asymmetric hydrogenations of prochiral olefins and ketones with excellent enantioselectivities.

Keywords: Monophosphoramidites; prochiral olefins; asymmetric hydrogenation; chiral spiro phosphorus ligands; 1,1'-spirobiindane.

INTRODUCTION

Chiral phosphorus ligands play an important role in various transition metal-catalyzed aymmetric reactions, and many effective chiral phosphorus ligands have been synthesized over the past two decades. Among the chiral phosphorus ligands that have been reported, the phosphorus ligands supported by axially atropisomeric scaffolds have proved to be the most active, selective, and versatile ligands in the asymmetric catalysis [1]. In recent years, many research groups have devoted their efforts to the discovery of new efficient atropisomeric ligands with unusual electronic and steric profiles [2]. We became interested in the design and synthesis of new chiral phosphorus ligands with a highly rigid spirobiindane scaffold. As Noyori and coworkers suggested that the highly skewed position of the naphthyl rings in BINAP was the determining factor for the ligand to be effective in asymmetric catalytic reactions [3], the phosphorus ligands containing a rigid spirobiindane scaffold would reduce the conformational obscurity of catalyst and create an effective asymmetric environment around the central metal, and subsequently leads to high enantioselectivities in asymmetric reactions. We report herein the results of our study on the synthesis of a new type of axially chiral phosphorus ligands containing a chiral 1,1'-spirobiindane scaffold and their applications in the transition metal-catalyzed asymmetric hydrogenations.

RESULTS AND DISCUSSION

Design and synthesis of chiral spiro phosphorus ligands

In asymmetric catalysis, chiral C_2-symmetric biaryls, such as 1,1'-binaphthalene, were widely used as backbones of ligands. By contrast, chiral spiranes, another class of C_2-symmetric molecules, which also possess an axial chirality, have not been paid much attention [4]. The high rigidity of the spiro cyclic

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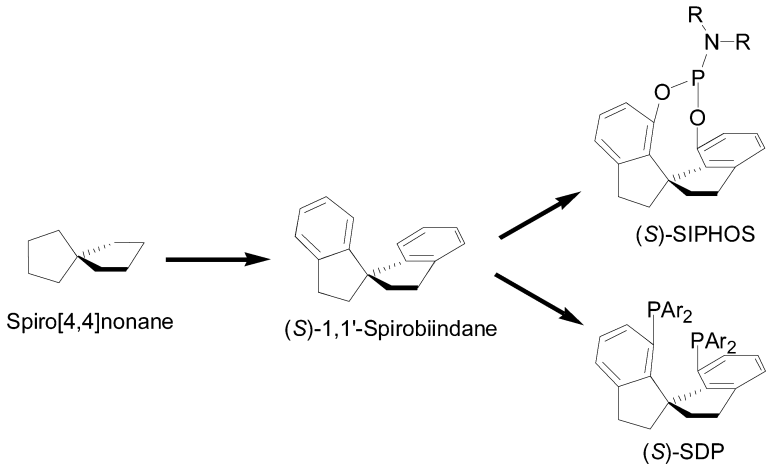
framework should decrease the flexibility of the ligands and their related complexes, and consequently benefit asymmetric induction in the catalysis. Spiro[4,4]nonane itself is not a chiral molecule. Substitutions on the spiro cycles introduced more than one chiral center into the molecule and increased the difficulty in the synthesis of optically pure ligands. However, spirobiindane, which can be regarded as a benzo derivative of spiro[4,4]nonane, has only axial chirality and its rigid spiro structure makes it a potential backbone of chiral ligands (Scheme 1).



Scheme 1

Chiral spiro phosphoramidite ligands were conveniently synthesized in moderate to good yields from enantiomerically pure (*S*)-1,1'-spirobiindane-7,7'-diol [(*S*)-1] (**1**) (Fig. 1) [5]. Heating the mixture of diol **1** and $P(NMe_2)_3$ or $P(NEt_2)_3$ in toluene afforded SIPHOS [SIPHOS = O,O'-(7,7'-spirobiindiane-1,1'-diyl)-*N,N*-dialkylphosphoramidite] ligands **2a** and **2b** in high yields. Ligands **2c**, **2d**, and **3**, which brought bulk amino groups, were produced with a different procedure. Condensation of diol **1** with PCl_3, followed by a treatment with the corresponding lithium dialkylamide, provided ligands **2c**, **2d**, or **3** in moderate yields [6]. In order to study the electronic effect of ligands in the asymmetric hydrogenation, spiro phosphoramidite ligands **2e–g**, which have 4,4'-substituents on the spirobiindane backbone, were also prepared under the same conditions [7].

Considering the facts that the rings of spirobiindane in SIPHOS ligands are not directly connected to the *P*-atom and the electronic property of the substituents could not be efficiently transferred to the *P*-atom, we further synthesized the chiral spiro phosphonite ligands **4** (Fig. 2). In the ligands **4**, a substituent with different electronic nature was introduced at the *para* position of the *P*-phenyl group, so that we can study the real electronic effect of the monodentate phosphorus ligand in the asymmetric hydrogenation. These chiral phosphonite ligands **4** were easily prepared by the reaction of optically pure 1,1'-spirobiindane-7,7'-diol (**1**) and the corresponding dichloroarylphosphine ($ArPCl_2$) in the presence of Et_3N at room temperature in 56–81 % yields [8].

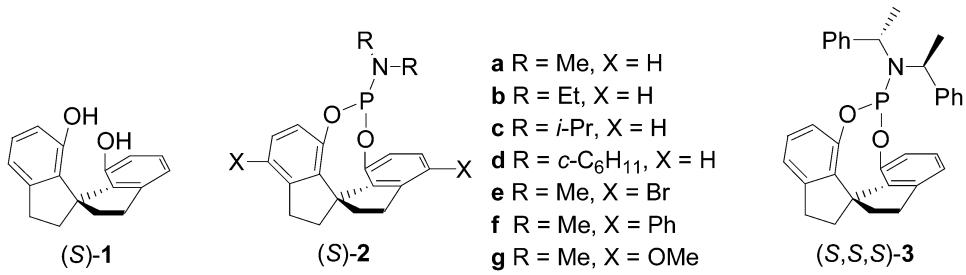


Fig. 1

Chiral diphosphine ligands SDP **5a–e** were also synthesized from enantiomerically pure 1,1'-spirobiindane-7,7'-diol (**1**) (Fig. 2) [9]. The diol (*S*)-**1** was converted into ditriflate in quantitative yield. Monophosphinylation of ditriflate was achieved by the reaction with diaryphospine oxide in the presence of Pd-catalyst, followed by the reduction with trichlorosilane. The second Ar_2P group was introduced by repeating the phosphinylation and the reduction steps. All the desired diphosphine compounds were produced in high yields.

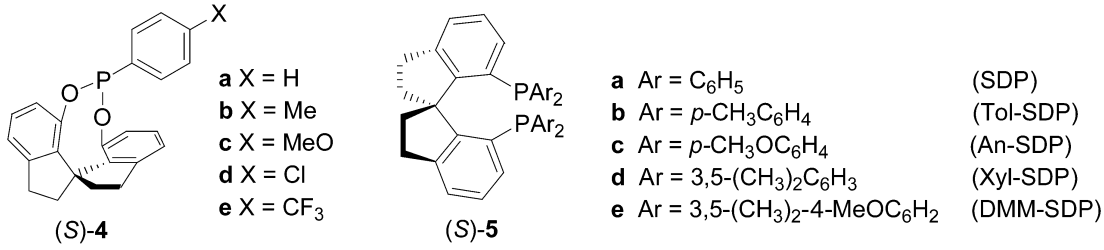
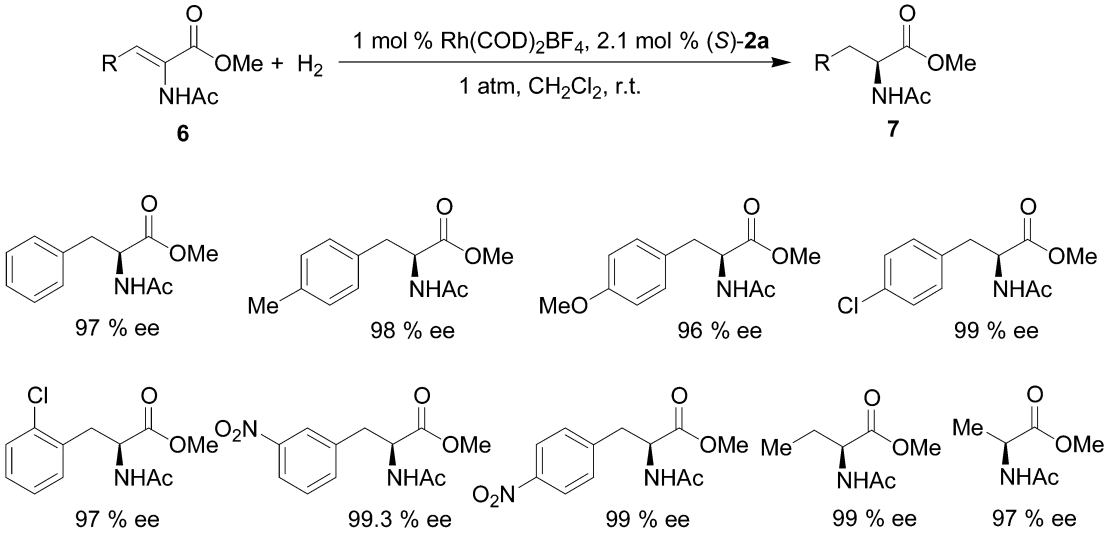


Fig. 2

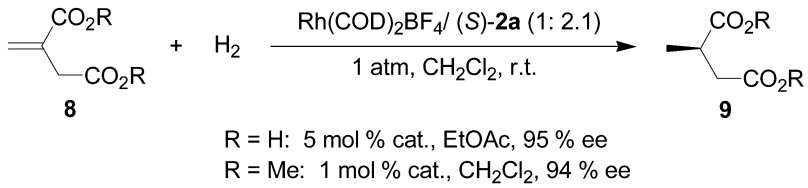
Asymmetric hydrogenation using spiro monophosphoramidite ligands

Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives has been extensively studied and afforded a model reaction to test the effectiveness of new chiral ligands. The Rh complexes of SIPHOS ligands can catalyze the hydrogenation of α-dehydroamino esters under mild conditions, providing α-amino acid derivatives in up to 99 % ee [10]. The hydrogenation of methyl 2-acetamido cinnamate (**6**) was performed at room temperature under ambient H_2 pressure in the presence of 1 mol % catalyst formed in situ from [$Rh(COD)_2BF_4$] and SIPHOS ligand (*S*)-**2a** (1:2.1). Excellent enantioselectivities (96–99.3 % ee) were achieved in nonprotic solvents such as CH_2Cl_2. The enantioselectivities are higher than or comparable to those achieved with other monodentate phosporous ligands and bidentate phosphorous ligands (Scheme 2).



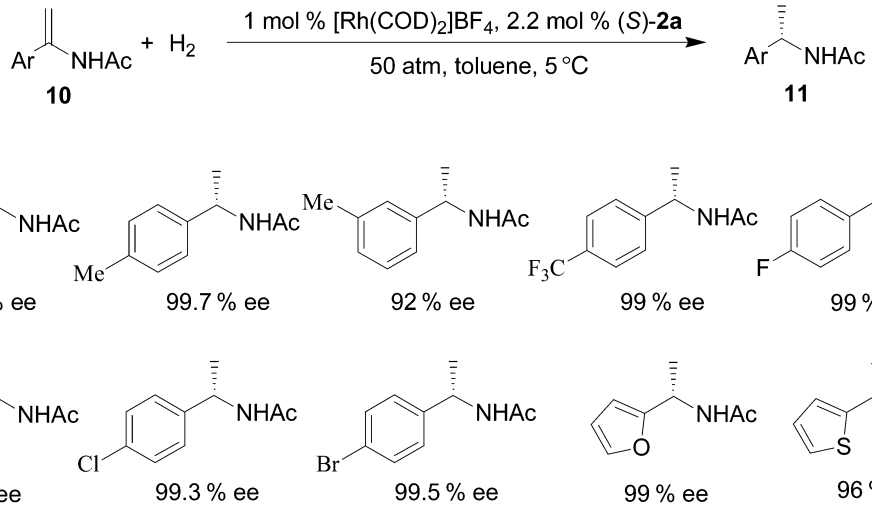
Scheme 2

Under similar conditions, the asymmetric hydrogenation reactions of itaconic acid derivatives **8** were also performed, and high enantioselectivities were obtained. The hydrogenation with acid needed more catalyst to go to completion (Scheme 3).



Scheme 3

We further applied Rh/SIPHOS catalysts in the asymmetric hydrogenation of α-arylethenyl acetamides (**10**). In this reaction, all the reported ligands that gave high level of enantiocontrol were bidentate phosphorus ligands until SIPHOS ligands were found to have extremly high enantioselectivities [11]. Using 1 mol % of catalyst Rh/**2a**, 1-phenyethenyl acetamide was hydrogenated under 50 atm of H_2 pressure at 5 °C providing 1-phenylethyl acetamide in quantitative yield with 99 % ee. A variety of α-arylethenyl acetamides (**10**) can be hydrogenated under the same conditions to produce corresponding α-arylethylamine derivatives with excellent enantiomeric excess (Scheme 4).



Scheme 4

In the Rh-catalyzed asymmetric hydrogenation of α-arylethenyl acetamides, the catalysts prepared in situ from cationic Rh complexes were active and provided a similar level of enantiocontrol, although the catalyst with a bulkier counter anion, such as $[Rh(COD)_2PF_6]$/(*S*)-**2a** and $[Rh(COD)_2SbF_6]$/(*S*)-**2a**, needed a longer time to complete the reaction. In sharp contrast, the catalyst prepared from a neutral Rh complex $[Rh(COD)Cl]_2$ was completely inert under the same condition. This might imply that the difficult dissociation of chloride hindered the coordination of substrate to Rh atom. The systematic investigation on the structure of phosphoramidite ligands **2** led to a finding that smaller alkyl groups on the nitrogen atom of the ligand are critical for obtaining high enantioselectivity. For instance, in the hydrogenation of 1-phenylethenyl acetamide, as the alkyl groups on the nitrogen atom of ligands **2** changed from methyl (**2a**), to ethyl (**2b**) and isopropyl (**2c**), the enantioselectivity of reaction decreased quickly from 99 to 57 and 38 % ee.

Optically active cyclic amines are an important class of compounds that are widely used in pharmaceutical synthesis. For example, chiral 1-aminoindanes are the key intermediates for drugs such as rasagiline for Parkinson's disease. Asymmetric hydrogenation of *N*-(1,2-dehydro-1-indanyl)acetamide is a potential method to produce enantioenriched 1-aminoindane. Using the Rh/**2a** catalyst, *N*-(1,2-dehydro-1-indanyl)acetamide was successfully hydrogenated to 1-aminoindane in 100 % yield with 94 % ee. Under the same reaction conditions, 5-Br and 6-MeO substituted 1-aminoindanes were also prepared in 88 and 95 % ee, respectively (Fig. 3) [12].

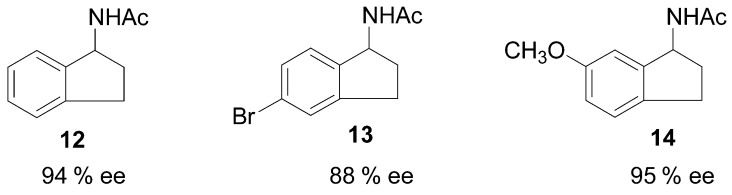
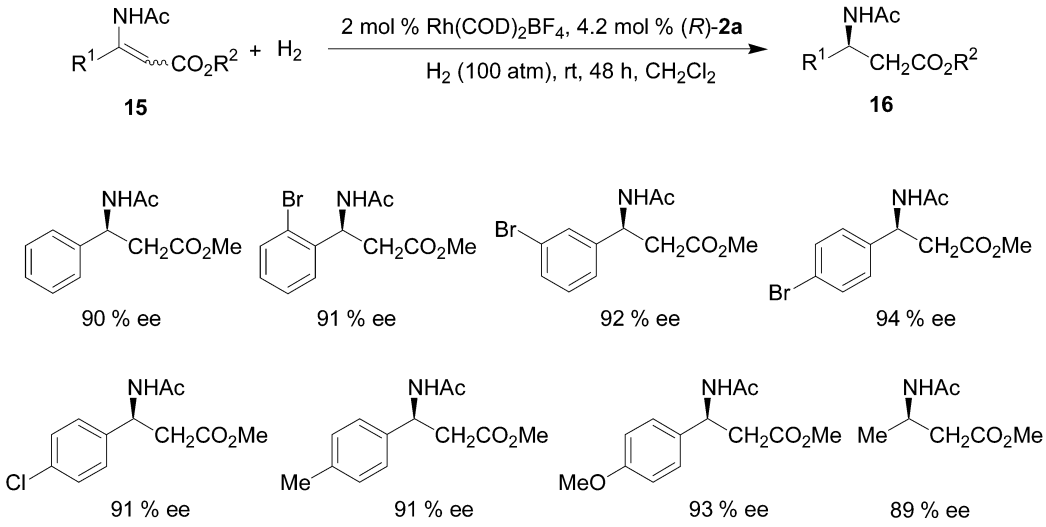


Fig. 3

Enantiomerically pure β-amino acid derivatives are important building blocks in the synthesis of many chiral drugs. Recently, asymmetric hydrogenation of β-(acylamino)acrylate derivatives has attracted much attention because it provides a convenient method for the synthesis of β-amino acid derivatives. Since the β-(acylamino)acrylates are normally formed as a mixture of *Z*- and *E*-isomers, the

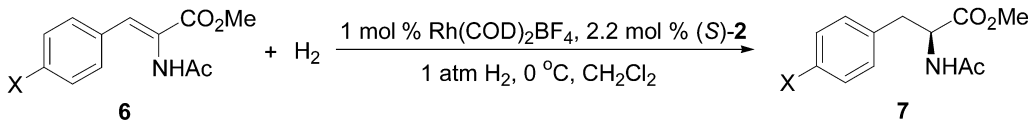
development of efficient catalyst that can hydrogenate the mixture of the two isomers is significantly important. We are delighted that the Rh/**2a** complex can catalyze asymmetric hydrogenations of *Z*/*E* mixtures of β-aryl β-(acylamino)acrylate derivatives, which cannot be separated by silica gel column chromatography, providing β-amino acid derivatives in high enantioselectivities (up to 94 % ee) (Scheme 5) [11].



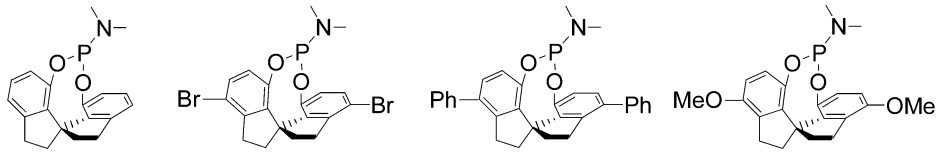
Scheme 5

Electronic effect of the ligands in asymmetric hydrogenation

Electronic properties of chiral ligands play an important role in the transition metal-catalyzed asymmetric reactions. However, in the design of chiral ligand, most considerations are based on the steric effect [2], and the electronic effect of ligands has been less explored [13]. This prompted us to study the electronic effect of the monophosphorus ligand in the Rh-catalyzed asymmetric hydrogenation. A study of the electronic effect of the spiro monophosphoramidite SIPHOS ligands in the asymmetric hydrogenation of α-dehydroamino esters and enamides showed that the substituents on the rings of spirobiindane in SIPHOS ligands only have a weak electronic effect in the Rh-catalyzed asymmetric hydrogenation (Schemes 6 and 7) [7]. By contrast, spiro phosphonite ligands **4** exhibited a manifest electronic effect in the Rh-catalyzed asymmetric hydrogenation of α- and β-dehydroamino esters (Scheme 8) [8].



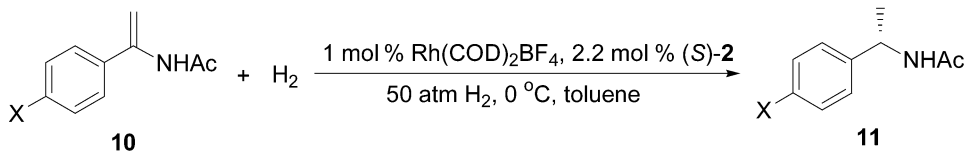
6 **7**



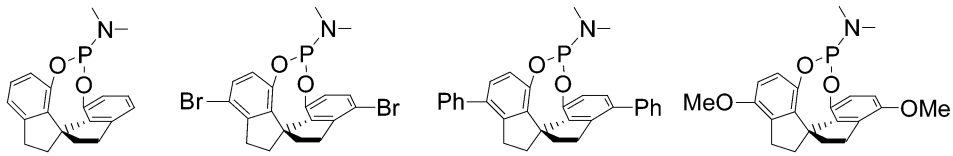
(*S*)-**2a** (*S*)-**2e** (*S*)-**2f** (*S*)-**2g**

X = H	97.8 % ee (10 h)	98.2 % ee (6 h)	97.5 % ee (10 h)	96.5 % ee (8 h)
X = Cl	98.8 % ee (8 h)	98.5 % ee (6 h)	98.0 % ee (10 h)	97.5 % ee (8 h)
X = OMe	95.6 % ee (12 h)	95.3 % ee (20 h)	94.5 % ee (14 h)	93.7 % ee (12 h)
X = NO_2	99.1 % ee (4 h)	98.7 % ee (4 h)	99.1 % ee (8 h)	97.1 % ee (4 h)

Scheme 6



10 **11**



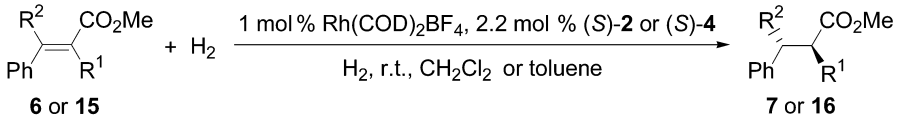
(*S*)-**2a** (*S*)-**2e** (*S*)-**2f** (*S*)-**2g**

X = H	98.0 % ee (24 h)	97.1 % ee (30 h)	97.7 % ee (30 h)	95.0 % ee (24 h)
X = Cl	98.1 % ee (24 h)	98.6 % ee (30 h)	98.0 % ee (30 h)	93.7 % ee (24 h)
X = Me	99.0 % ee (24 h)	97.8 % ee (30 h)	97.8 % ee (30 h)	95.4 % ee (24 h)

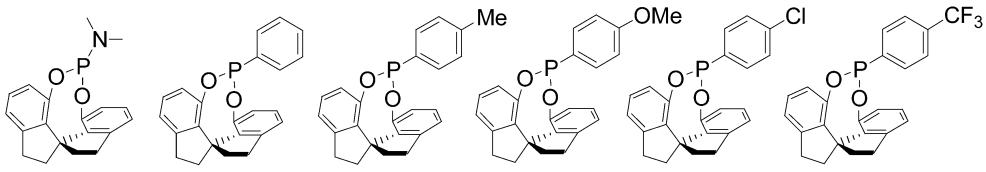
Scheme 7

In the hydrogenation of 2-acetamidocinnamic esters, all 4,4'-substituted SIPHOS ligands [(*S*)-**2e–g**] gave the rates that are similar to that with SIPHOS ligand (*S*)-**2a**. Ligands 4,4'-dibromo-SIPHOS [(*S*)-**2e**] and 4,4'-diphenyl-SIPHOS [(*S*)-**2f**] produced the corresponding hydrogenation product with the nearly same enantioselectivity as that produced by SIPHOS ligand (*S*)-**2a**. However, 4,4'-dimethoxy-SIPHOS [(*S*)-**2g**] ligand provided somewhat lower enantioselectivities in the hydrogenation of all four 2-acetamidocinnamic esters, showing that the substitutions with an electron-donating group at 4,4'-positions decreased the level of asymmetric reduction of SIPHOS ligands.

In the hydrogenation of enamides, the situation was the same as in the hydrogenation of 2-acetamidocinnamic esters. The phosphoramidites (*S*)-**2e** and (*S*)-**2f** behaved very similarly to their parental SIPHOS ligand (*S*)-**2a**, achieving high enantioselectivities in the hydrogenation of *N*-acetyl-α-aryl-enamides, albeit the reaction rates were slower. In the hydrogenations of all three studied enamides, the



6 or **15** **7** or **16**



	(*S*)-**2**	(*S*)-**4a**	(*S*)-**4b**	(*S*)-**4c**	(*S*)-**4d**	(*S*)-**4e**
R^1 = NHAc R^2 = H	97 % ee (4 h)	98 % ee (3 h)	97 % ee (3 h)	99 % ee (2 h)	93 % ee (10 h)	82 % ee (24 h)
R^1 = H R^2 = NHAc	90 % ee (40 h)	92 % ee (40 h)	92 % ee (40 h)	93 % ee (40 h)	87 % ee (48 h, 70 % conv.)	40 % ee (48 h, 30 % conv.)

Conditions: 1 mol % $Rh(COD)_2BF_4$, 2.2 mol % (*S*)-**2** or **4**, toluene, 10 atm H_2 for α-acetamidocinnamic esters, 1 mol % $Rh(COD)_2BF_4$, 2.2 mol % (*S*)-**2** or **4**, CH_2Cl_2, 100 atm H_2 for β-acetamidocinnamic esters.

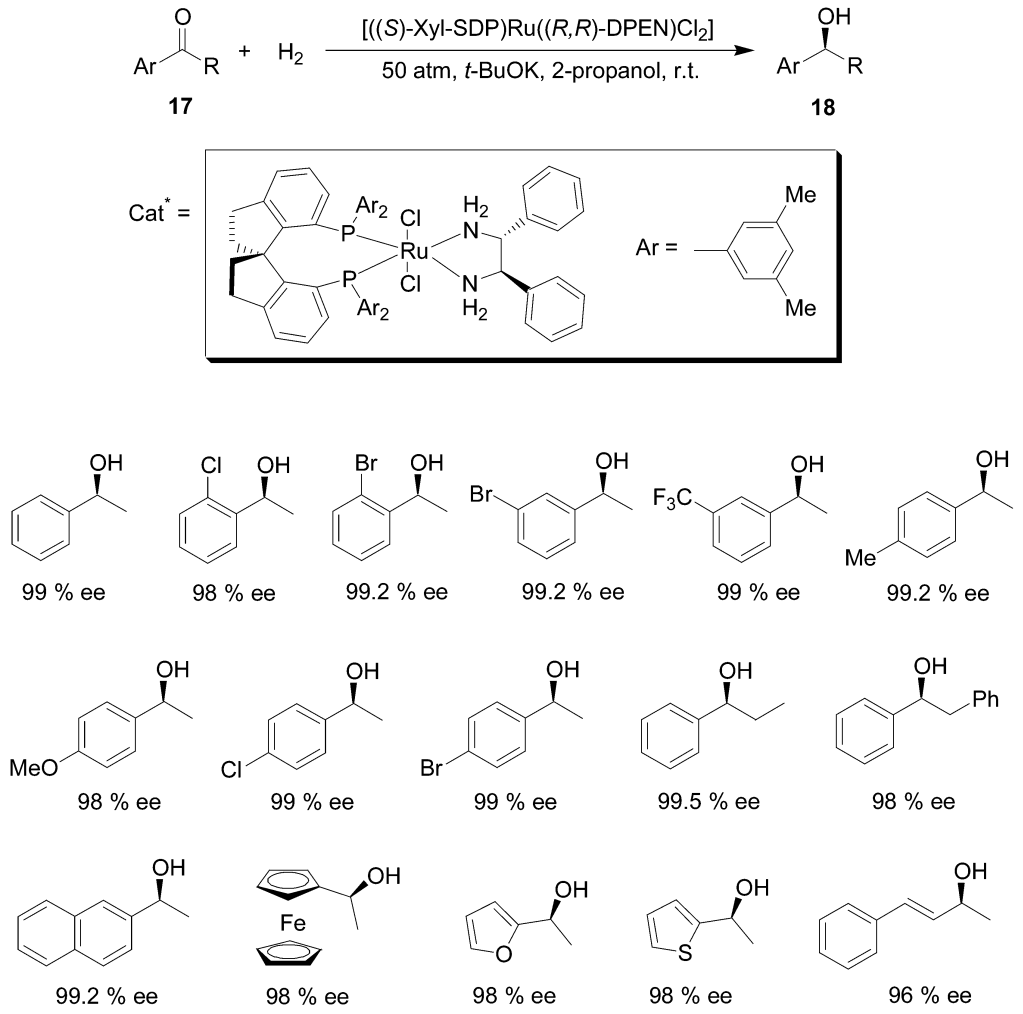
Scheme 8

ligand (*S*)-**2g** once again afforded slightly lower enantioselectivities (by 3–4 % ee) compared to SIPHOS ligand (*S*)-**2a**.

In the study on the electronic effect in hydrogenation reaction using the spiro phosphonite ligands **4**, we found that the electron-withdrawing substitutent on the *P*-phenyl ring dramatically decreased both the reactivity and enantioselectivity of the ligand. The results are shown in Scheme 8. In the Rh-catalyzed hydrogenation of (*Z*)-2-acetaminocinnamate, the ligand (*S*)-**4c** bearing an electron-donating *para* methoxy group was found to be the most active and selective. The reaction completed in 2 h and enantiomeric excess of the hydrogenation product reached 99 % ee. However, the ligands (*S*)-**4d** and (*S*)-**4e** containing *para* chlorine and trifluoromethyl groups were much less effective in both activity and enantioselectivity. In the hydrogenation of methyl (*Z*/*E*)-β-(acetamino)cinnamate (*Z*/*E* = 88:12), ligands (*S*)-**4a** and (*S*)-**4b** had an activity which was similar to that of SIPHOS ligand (*S*)-**2a**, while their enantioselectivities (92 % ee) were higher than that of SIPHOS ligand (*S*)-**2a** (90 % ee). Ligand (*S*)-**4c** provided the highest enantioselctivity (93 % ee). But ligands (*S*)-**4d** and (*S*)-**4e**, with electron-withdrawing groups, gave incomplete reactions and much lower enantioselectivities [8].

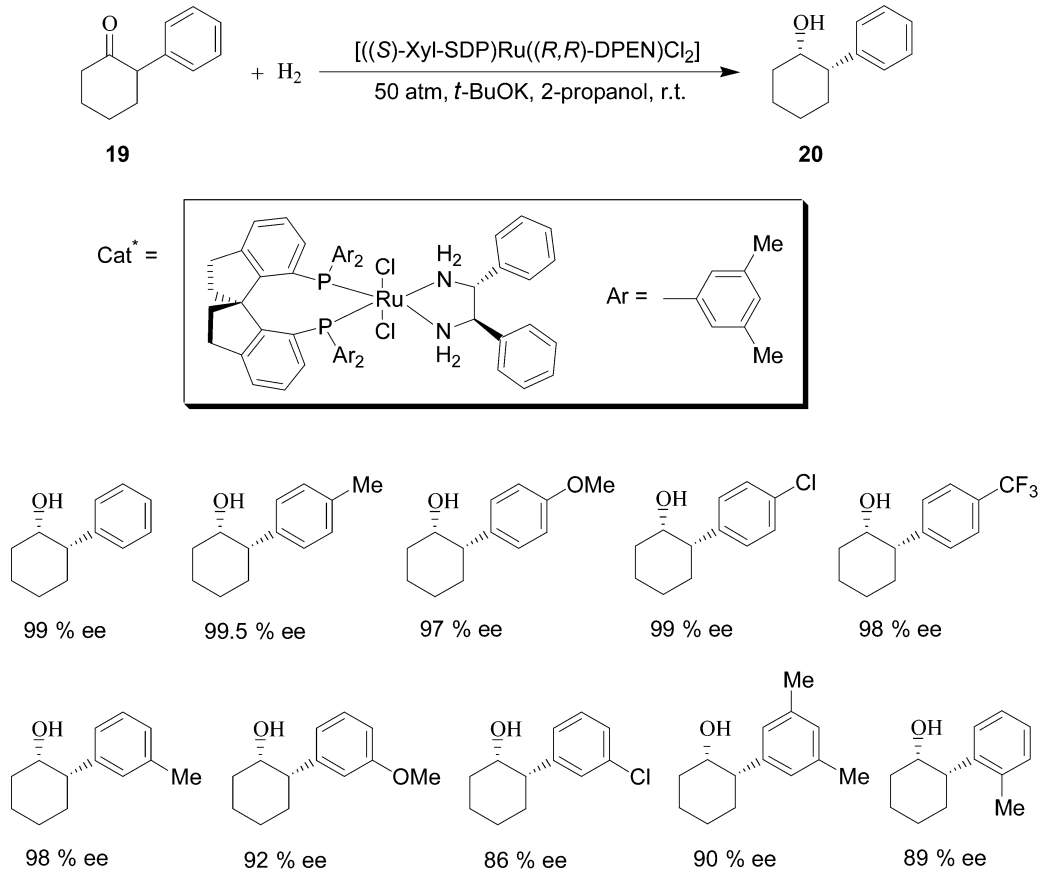
Asymmetric hydrogenation using spiro diphospine ligands

The catalytic asymmetric hydrogenation of prochiral ketones to optically secondary alcohols is among the most fundamental subjects in modern synthetic chemistry. The most effective catalysts available for the asymmetric hydrogenation of ketones to date are those derived from diphosphine ruthenium dichloride diamine complexes, which was initiated by Noyori and coworkers [14]. The Ru-complexes of spiro diphospine (SDP) ligands were very effective catalysts in the asymmetric hydrogenation of simple ketones. Among the SDP ligands, (*S*)-Xyl-SDP (**5d**) having 3,5-dimethyl groups on the *P*-phenyl rings was found to be the most enantioselective. For instance, the catalyst {[(*S*)-Xyl-SDP]Ru[(*R,R*)-DPEN]Cl_2} provided 1-phenylethanol in 98 % ee and 100 000 turnover number in the hydrogenation of acetophenone. A variety of ketones, including aromatic, heteroaromatic, and α,β-unsaturated ketones, can be hydrogenated by {[(*S*)-Xyl-SDP]Ru[(*R,R*)-DPEN]Cl_2} catalyst in excellent enantioselectivities and high turnover numbers (Scheme 9) [9a].



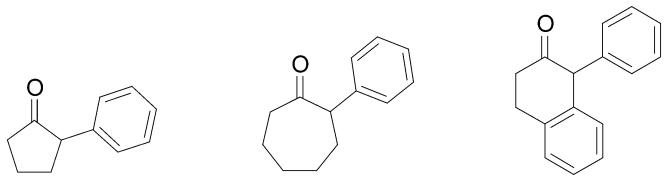
Scheme 9

Asymmetric hydrogenation of α-arylcycloketones is of importance in organic synthesis, which produced the *cis*-α-arylcycloalcohols, a very useful class of building blocks for the synthesis of biologically active compounds and chiral drugs. Noyori and coworkers reported that the $RuCl_2$[(*S*)-Tol-BINAP][(*S*)-DPEN] catalyst was very efficient in the asymmetric hydrogenation of racemic α-arylcycloalkanones by a kinetic resolution method, providing the corresponding chiral cyclic alcohols with excellent *cis*/*trans* selectivity and enantioselectivity [15]. The $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] complex was also a highly efficient catalyst for the hydrogenation of 2-arylcyclohexanones [16]. The results summarized in Scheme 10 showed that (1) the hydrogenations of all substrates gave almost quantitative *cis* isomer; (2) the introduction of either electron-donating or -withdrawing group at the *para* or *meta* position of the phenyl ring in 2-phenylcyclohexanone had a little influence on the enantioselectivity; and (3) the substitutions at the *ortho* or 3,5-position of the phenyl ring in 2-arylcyclohexanone caused a notable decrease of the enantioselectivity. The highest enantioselectivity (99.9 % ee) was achieved in the hydrogenation of 2-(3-methoxyphenyl)cyclohexanone.



Scheme 10

Extending the scope of the substrate to other α-arylcycloketones, such as 2-phenylcyclopentanone (**21**), 2-phenylcycloheptanone (**22**), and 1-phenyl-2-tetralone (**23**), the corresponding products have high *cis*/*trans* ratio (>99:1), but the enantioselectivities of the products varied from moderate to good (60–87 % ee) (Fig. 4).



21 60 % ee **22** 87 % ee **23** 72 % ee

Fig. 4

CONCLUSION

New types of chiral phosphorus ligands with a spirobiindane backbone were designed and synthesized from enantiomerically pure 1,1'-spirobiindane-7,7'-diol. Among them, monophosphoramidite ligands SIPHOS and diphosphine ligands SDP are extremely efficient in asymmetric hydrogenations, such as Rh-catalyzed hydrogenations of α-dehydroamino acid derivatives, β-(acylamino)acrylate derivatives, α-arylethenyl acetamides, and Ru-catalyzed hydrogenation of a series of aromatic, heteroaromatic, α,β-unsaturated ketones and α-arylcycloketones. Ongoing efforts in this laboratory are directed to expand the range of application of this interesting family of chiral spiro phosphorus ligands.

ACKNOWLEDGMENTS

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