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Synthesis of novel chiral binaphthyl phosphorus ligands and their applications in Rh-catalyzed asymmetric hydrogenation

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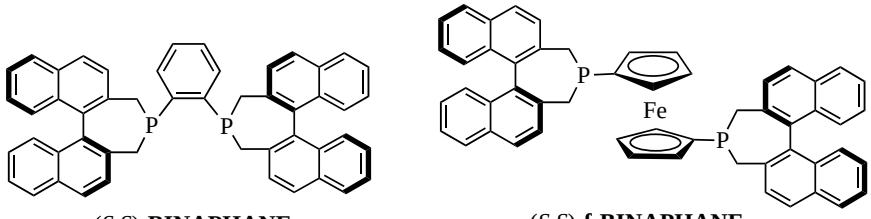
Abstract—A series of new chiral mono- or bidentate phosphorus ligands were efficiently prepared through a key intermediate (*S*)-4-chloro-4,5-dihydro-3*H*-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene and its derivatives. These ligands were applied in the Rh-catalyzed asymmetric hydrogenation of α-dehydro amino acids, enol acetates, itaconates, and enamides. Good to excellent enantioselectivities were obtained (up to 99.5% ee). © 2002 Elsevier Science Ltd. All rights reserved.

Discovery of new chiral phosphorus ligands plays a critical role in asymmetric catalysis.[1] Atropisomeric 1,1′-binaphthalene core is the parent framework of steadily increasing families of chiral ligands for asymmetric reactions.[2] Reetz[3] and Pringle[4] prepared chelating chiral phosphites using readily accessible Binaphthol (BINOL) as the starting material and demonstrated that they are excellent ligands for Rh-catalyzed asymmetric hydrogenation of dehydroamino acids. Feringa[5] has developed a variety of chiral phosphoramidites from BINOL and high enantioselectivities (up to 98% ee) were achieved in Michale addition of cyclic enones. Gladiali[6] and Stelzer[7] made several mono- or bidentate chiral phosphanes as well as the corresponding racemic chelating derivatives bearing the 1,1′-binaphthyl core. However, only limited applications of these ligands for asymmetric catalysis were reported.[6a]

Recently, we prepared two chiral chelating phosphane ligands, BINAPHANE[8] and f-BINAPHANE[9] (Fig. 1), which gave excellent enantioselectivities for Rh-catalyzed asymmetric hydrogenation of β-substituted-α-aryl-enamides and Ir-catalyzed asymmetric hydrogenation of acyclic imines. By using NaH as the base, condensation of (*R*)-2,2′-dichloromethyl-1,1′-binaphthyl with 1,2-bis-(phosphino)benzene or 1,1′-bis(phosphino)ferrocene yielded BINAPHANE or f-BINAPHANE in good yields. The (*R*)-2,2′-dichloromethyl-1,1′-binaphthyl was synthesized from (*R*)-BINOL through four-step reactions in 63% overall yield. However, this synthetic route is not flexible for generating a variety of structurally diverse of ligands and is too long for making these chiral ligands.

Herein, we report a simple and efficient new pathway for making chiral phosphorus ligands. Using (*S*)-2,2′-dimethyl-1,1′-binaphthyl and it's 3,3′-diphenyl derivative, an array of new chiral mono- or bidentate phosphorus ligands (*S*)-**1**–(*S*,*S*)-**5** (Fig. 2) were efficiently synthesized through a dilithiated species (*S*)-**7** and (*S*)-4-chloro-4,5-dihydro-3*H*-4-phosphacyclohepta[2,1-*a*;3,4-*a*] binaphthalene (*S*)-**8**.



(*S*,*S*)-**BINAPHANE** (*S*,*S*)-**f-BINAPHANE**

Figure 1.

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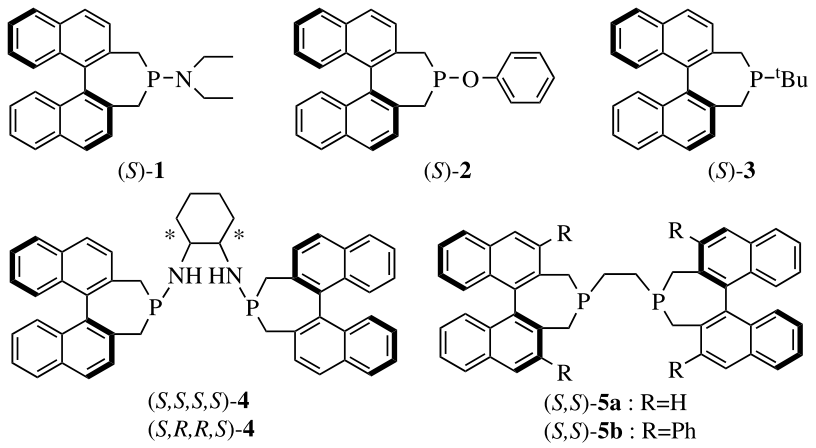
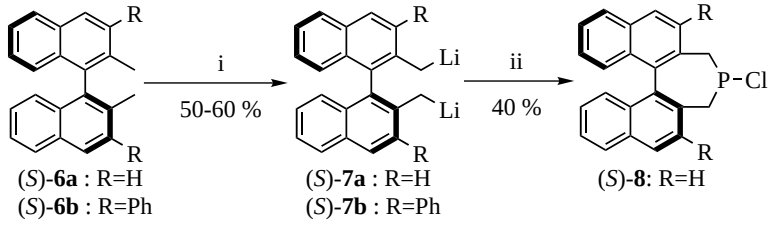
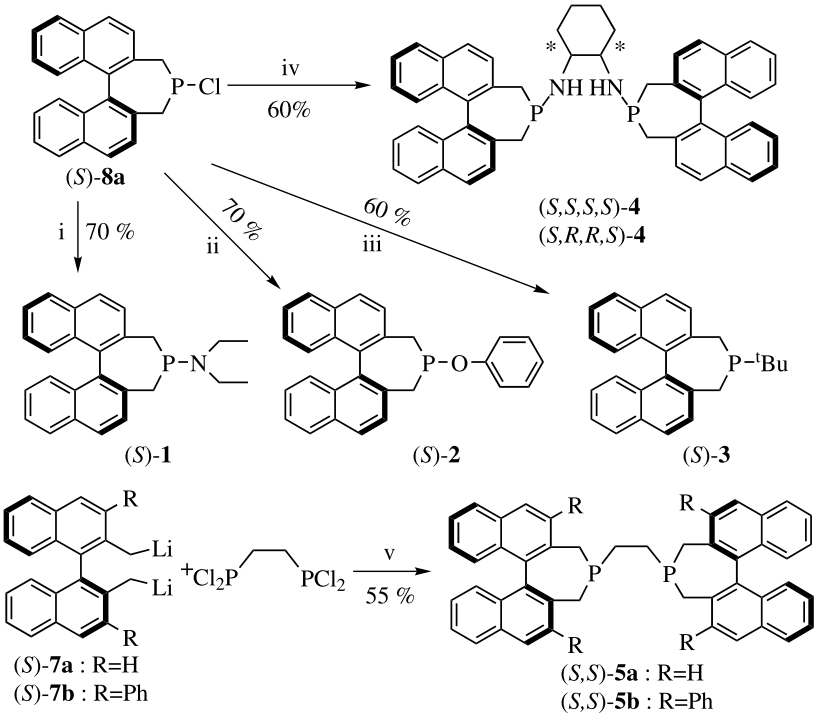


Figure 2.



Scheme 1. Synthesis of synthon (*S*)-**8**. *Reagents and conditions*: (i) *n*-BuLi, Et_2O, −78°C to rt, 30 min; rt, 24 h; −78°C, 3 h; (ii) PCl_3, hexane, rt, 12 h.



Scheme 2. Synthesis of phosphorus ligands **1**–**5**. *Reagents and conditions*: (i) diethylamine, Et_3N, toluene, –40°C, 12 h; (ii) phenol, Et_3N, toluene, –40°C, 12 h; (iii) *t*-BuMgBr, THF, rt, 12 h; (iv) (*S*,*S*)- or (*R*,*R*)-1,2-diaminocyclohexane, Et_3N, toluene, –40°C, 12 h; (v) hexane, rt, 12 h.

The key synthon, (*S*)-4-chloro-4,5-dihydro-3*H*-4-phosphacyclohepta[2,1-*a*;3,4-*a*′] binaphthalene (*S*)-**8** for the synthesis of many phosphorus ligands **1**–**4**, can be prepared as shown in Scheme 1. The starting material, (*S*)-2,2′-dimethyl-1,1′-binaphthyl (*S*)-**6a**, was easily prepared through two-step operations from (*S*)-BINOL according to recent literatures methods.[8,10] (*S*)-3,3′-Diphenyl-2,2′-dimethyl-1,1′-binaphthyl (*S*)-**6b** was made by the method of Maruoka.[11] 2,2′-Dimethyl-1,1′-binaphthyl (*S*)-**6a** was lithiated with 2.5 equiv. of *n*-butyllithium in ether and the dilithium salt (*S*)-**7a** was separated under N_2 as red powder in 60% yield.[12] Another dilithium species (*S*)-**7b** was prepared in the same way from (*S*)-**6b** in 50% yield. Reaction of (*S*)-**7a** with phosphine trichloride in hexane at rt overnight, followed by recrystallization from CH_2Cl_2/hexane, yielded the pure synthon **8** as yellow powder.

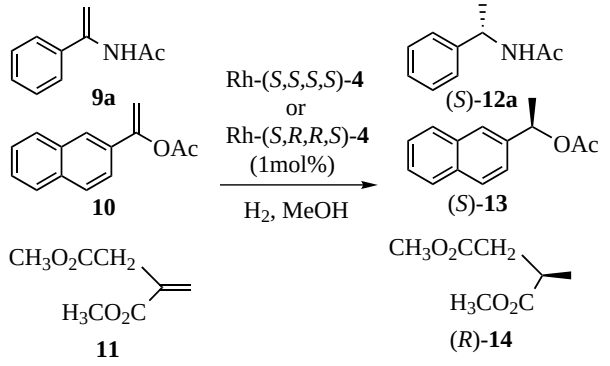
As shown in Scheme 2, chiral phosphoramidite ligands (*S*)-**1**, (*S*,*S*,*S*,*S*)-**4** or (*S*,*R*,*R*,*S*)-**4**, and phosphite ligand (*S*)-**2** were synthesized by nucleophilic substitution of (*S*)-**8**. Recrystallization from CH_2Cl_2/hexane gave desired ligands as white powder in satisfactory yields. The reaction of the synthon (*S*)-**8** with *t*-butyl Grignard reagent in THF afforded the monodentate phosphane ligand (*S*)-**3** in 60% yield. However, owing to the difficulty of preparation of $XMgCH_2CH_2MgX$, this route is not applicable for the synthesis of ligand **5**. Nucleophilic attack of 1,2-bis(dichlorophosphine)ethane with (*S*)-**7** provided an efficient way to prepare bidentate phosphane ligands (*S*,*S*)-**5**.

We have used monodentate phosphorus ligands (*S*)-**1**–**3** for the Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamido acrylates. The hydrogenation reaction was performed at ambient temperature under 60 psi of H_2 in MeOH for 24 h. Using $Rh(COD)_2SbF_6$–(*S*)-**1**–**3** (1:2) as an in-situ catalyst with a substrate to metal ratio of 100:1, quantitative conversions were obtained for hydrogenation reactions. Low and moderate ee's were achieved (59.3% ee for (*S*)-**1**, 55.8% ee for (*S*)-**2**), 6.3% ee for (*S*)-**3**). The *R*-enantiomer is the preferred product in all cases.

In order to investigate the cooperative effect of the 1,1′-binaphthyl motif and *trans*-1,2-diaminocyclohexane. Two phosphoramidite ligands (*S*,*S*,*S*,*S*)-**4** and (*S*,*R*,*R*,*S*)-**4** were employed for Rh-catalyzed hydrogenation of several substrates (Table 1). In comparison with ligand (*S*,*S*,*S*,*S*)-**4**, (*S*,*R*,*R*,*S*)-**4** was found to be more effective for asymmetric hydrogenation (Table 1, entry 5 versus entry 2, entry 6 versus entry 4).

Bidentate chiral phosphane ligands (*S*,*S*)-**5a** and **5b** were used for the Rh-catalyzed asymmetric hydrogenation of enamides **9a**–**g**, Table 2 shows the experimental results. Although Rh-(*S*,*S*)-**5a** only offers good enantioselectivity for hydrogenation of α-arylenamides without a substitution in the β-position (entry 1, 77.2% ee; entry 2, 93.5% ee), it is effective for reducing β-substituted-α-arylenamides (entries 3–7, 93.1–99.5% ee). This

Table 1. Asymmetric hydrogenation of enamide **9a**, enol acetate **10**, itaconate **11** with Rh-(*S*,*S*,*S*,*S*)-**4** or Rh-(*S*,*R*,*R*,*S*)-**4** catalyst[a]



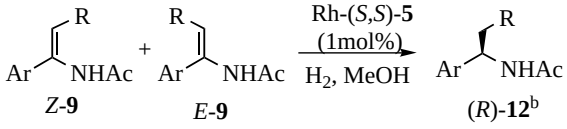
Entry	Substrate	Ligand	Ee (%)[b]	Configuration[c]
1	**9a**	(*S*,*S*,*S*,*S*)-**4**	44.3	*S*
2	**10**	(*S*,*S*,*S*,*S*)-**4**	77.0	*S*
3	**11**	(*S*,*S*,*S*,*S*)-**4**	65.9	*R*
4	**9a**	(*S*,*R*,*R*,*S*)-**4**	70.9	*S*
5	**10**	(*S*,*R*,*R*,*S*)-**4**	90.4	*S*
6	**11**	(*S*,*R*,*R*,*S*)-**4**	85.5	*R*

[a] The reaction was carried out at room temperature under an initial hydrogen pressure of 40 psi for 24 h. The catalyst was made in situ by stirring a solution of $Rh(COD)_2SbF_6$ and chiral ligand **4** in MeOH. The reaction proceeded in quantitative yield.

[b] Enantiomeric excesses were determined by chiral GC with a Supelco chiral select 1000 column (for **12a** and **13**), or a gamma dex 225 column (for **14**).

[c] The configurations were determined by comparison of optical rotations with reported data.

Table 2. Asymmetric hydrogenation of enamide **9** by Rh-(*S*,*S*)-**5**[a]



Entry	Substrate	Ar, R	Ligand	Ee (%)[c]
1	**9a**	C_6H_5, H	(*S*,*S*)-**5a**	77.2
2	**9b**	2-Np, H	(*S*,*S*)-**5a**	93.5
3	**9c**	C_6H_5, CH_3	(*S*,*S*)-**5a**	97.5
4	**9d**	C_6H_5, $CH(CH_3)_2$	(*S*,*S*)-**5a**	97.7
5	**9e**	4-MeO-C_6H_5, CH_3	(*S*,*S*)-**5a**	99.5
6	**9f**	4-CF_3-C_6H_5, CH_3	(*S*,*S*)-**5a**	93.1
7	**9g**	2-Np, CH_3	(*S*,*S*)-**5a**	99.5
8	**9a**	C_6H_5, H	(*S*,*S*)-**5b**	49.3

[a] The reaction was carried out at room temperature under an initial hydrogen pressure of 40 psi for 24 h. The catalyst was made in situ by stirring a solution of $Rh(NBD)_2SbF_6$ and chiral ligand (*S*,*S*)-**5** in MeOH [substrate (0.5 mmol)]:[Rh]:(*S*,*S*)-**5** = 100:1:1.1. The reaction proceeded in quantitative yield.

[b] The configurations were determined by comparison of optical rotations with reported data.

[c] Enantiomeric excesses were determined by chiral GC with a Supelco chiral select 1000 column, or Chiral HPLC with a Regis (*S*,*S*)-Whelk-01 column.[13]

catalytic system can tolerate the *E*- and *Z*-mixture substrates of enamides. A small electronic effect was observed. For example, hydrogenation of **9e** bearing an electron-donating 4-methoxy substituent in the aryl group proceeded with the higher enantioselectivity (entry 8, 99.5% ee) than the result obtained with **9c** (entry 3, 97.5% ee). Hydrogenation of **9f** bearing an electron-withdrawing 4-CF_3 substituent in the aryl group proceeded with the lower enantioselectivity (entry 6, 93.1% ee). Compared with Rh-(*S*,*S*)-**5a**, Rh-(*S*,*S*)-**5b** gave a poor enantioselectivity for hydrogenation of α-arylenamide (entry 8, 49.3% ee). The effect of 3,3′-diphenyl substituent in binaphthyl backbone for the Rh-catalyzed hydrogenation currently is under investigation.

In conclusion, a simple and effective route for preparing phosphorus ligands bearing an 1,1′-binaphthyl motif was established. An array of new chiral mono- or bidentate phosphorus ligands (*S*)-**1**–(*S*,*S*)-**5** were efficiently obtained through a dilithiated species (*S*)-**7** and (*S*)-4-chloro-4,5-dihydro-3*H*-4-phosphacyclohepta-[2,1-*a*;3,4-*a*′]binaphthalene (*S*)-**8**. The applications of ligands **1**–**5** in Rh-catalyzed asymmetric hydrogenation were tested. Excellent enantioselectivities (93–99% ee) have been observed in hydrogenation of an isomeric mixture of *E*- and *Z*-β-substituted-α-arylenamides by using Rh-(*S*,*S*)-**5a** as the catalyst. Other applications of ligands **1**–**5** for asymmetric catalysis will be disclosed in due course.

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