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Rhodium-catalyzed asymmetric hydrogenation with aminophosphine ligands derived from 1,1′-binaphthyl-2,2′-diamine

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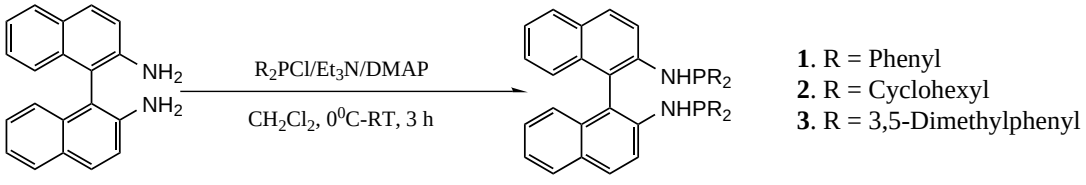
Abstract—Chiral ligands 2,2′-bis(dicyclohexylphosphinoamino)-1,1′-binaphthyl and 2,2′-bis[bis(3,5-dimethylphenyl)phosphinoamino]-1,1′-binaphthyl were synthesized by reacting 1,1′-binaphthyl-2,2′-diamine with dicyclohexylchlorophosphine and bis(3,5-dimethylphenyl)chlorophosphine, respectively. Application of these ligands to the Rh-catalyzed asymmetric hydrogenation of a variety of amidoacrylic acids and esters provided chiral amino acid derivatives with excellent enantioselectivities (up to 99% e.e. and quantitative yields).

Asymmetric hydrogenation reactions are important in practical organic synthesis ranging from laboratory scale research to large scale production.[1] Chiral phosphine ligands play a significant role in various metal-catalyzed asymmetric reactions.[2–7] Over the past three decades, most effort on asymmetric hydrogenation has been focused on the use of rhodium and ruthenium catalysts containing chiral phosphine ligands. Recently, it has been shown that some of the results obtained with phosphinite,[8] phosphite,[9] phosphonite,[10] or phosphoroamidite[11] ligands can match those obtained by using phosphines. Rhodium catalysts bearing aminophosphine ligands also have shown good to excellent enantioselectivity and high reactivity in asymmetric hydrogenation.[12,13] Since many effective phosphine ligands are quite difficult to prepare, the search for easily prepared and highly effective new chiral ligands is still of high interest.

Schmid,[14] Pregosin[15] and RanjanBabu[8b,16] reported that in asymmetric hydrogenation, the enantioselectivities of transition metal phosphine/phosphinite catalysts were significantly influenced by the substituents on the phosphorous atoms. In our initial study, we found the rhodium catalyst containing bidentate aminophosphine **1** (BDPAB)[17a,b] to be effective in the hydrogenation of enamides[13] and dehydroamino acid derivatives.[17c] Expanding the scope of this study, we developed a series of substituted bisaminophosphine ligands and tested their effectiveness in the rhodium-catalyzed hydrogenation of amidoacrylic acids and esters. The ligands 2,2′-bis(diphenylphosphinoamino)-1,1′-binaphthyl **1** (BDPAB), 2,2′-bis[bis(3,5-dimethylphenyl)-phosphinoamino]-1,1′-binaphthyl **3** (Xyl-BDPAB)[18] and 2,2′-bis(dicyclohexylphosphinoamino)-1,1′-binaphthyl **2** (Cy-BDPAB)[19] were derived from 1,1′-binaphthyl-2,2′-diamine (BINAM) as shown in Scheme 1.



Scheme 1. Synthesis of bisaminophosphines.

Keywords: aminophosphine ligand; asymmetric hydrogenation; rhodium; amino acid derivatives.

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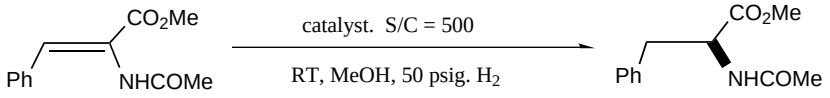
The experimental results revealed that rhodium catalysts bearing these bisaminophosphine ligands gave very different enantioselectivities in the hydrogenation of methyl acetamidocinnamate (Table 1). When the phenyl groups on the phosphorus of the aminophosphine ligand were replaced with cyclohexyl groups (i.e. ligand **2**), the reactivity of the rhodium catalyst remained high, however, the enantioselectivity dropped sharply. In contrast, the enantioselectivity was enhanced greatly when the phenyl groups on the phosphorous were replaced with sterically hindered 3,5-dimethylphenyl groups (i.e. ligand **3**). The choice of anions, such as BF_4^- or SbF_6^-, had little influence on the enantioselectivity.

Further study revealed that the {Rh[(*S*)-**3**]}BF_4 catalyst remained highly active and enantioselective in the hydrogenation of methyl acetamidocinnamate under different conditions. The choice of solvent had little influence on the enantioselectivity of the reaction (Table 2, entries 1–5) and lowering the reaction temperature gave only slightly higher ee (Table 2, entries 5, 8 and 9). The ee remained unchanged when the molar ratio of substrate to catalyst was increased from 500 to 5000 (Table 2, entries 5, 6 and 7).

Expanding on the successful lead in the asymmetric hydrogenation of acetamidocinnamate, we examined the hydrogenation of other amidoacrylic acids and esters[20] and the results are summarized in Table 3. The high enantioselectivities of the {Rh[(*S*)-**3**]}BF_4 catalyst in the hydrogenation of these substrates were relatively independent of the substituents on the phenyl ring of the substrate. This high efficiency offered an opportunity for the preparation of a variety of chiral amino acids with high enantiomeric purity. Under identical conditions, the differences in enantioselectivites between the {Rh[(*S*)-**1**]}$^+$ and {Rh[(*S*)-**3**]}$^+$ were quite significant.

In conclusion, a highly effective bisaminophosphine ligand has been synthesized and used in the rhodium-catalyzed asymmetric hydrogenation of amidoacrylic acids and esters. Excellent enantiomeric excesses (96–99%) have been achieved with the {Rh[(*S*)-**3**]}BF_4 catalyst for a variety of substrates. The application of the

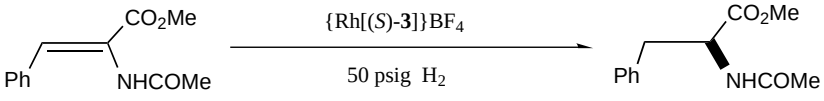
Table 1. The asymmetric hydrogenation of methyl acetamidocinnamate catalyzed by rhodium complexes containing ligands **1**, **2**, and **3**[a]



Ligand	[Rh(COD)$_2$]X	Ee[b] (%)
(*S*)-**1**	[Rh(COD)$_2$]BF_4	90
(*S*)-**1**	[Rh(COD)$_2$]SbF_6	91
(*S*)-**2**	[Rh(COD)$_2$]BF_4	11
(*S*)-**2**	[Rh(COD)$_2$]SbF_6	13
(*S*)-**3**	[Rh(COD)$_2$]BF_4	98.5
(*S*)-**3**	[Rh(COD)$_2$]SbF_6	98.6

[a] All reactions were completed within 10 min. The substrate concentrations were 0.25 M. The rhodium catalysts were prepared by reacting ligands **1**–**3** with [Rh(COD)$_2$]X in dichloromethane at room temperature.
[b] *S* Configuration was obtained in all experiments.

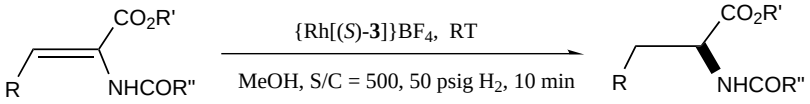
Table 2. Effects of solvent, temperature and substrate-to-catalyst ratio on the asymmetric hydrogenation of methyl acetamidocinnamate with {Rh[(*S*)-**3**]}BF_4[a]



Entry	Solvent	Sub./cat.	Temp. (°C)	Ee (%)
1	THF	500	rt	98
2	Acetone	500	rt	97
3	CH_2Cl_2	500	rt	97
4	EtOH	500	rt	98
5	MeOH	500	rt	98
6	MeOH	2000	rt	98
7[b]	MeOH	5000	rt	98
8	MeOH	500	0	99
9	MeOH	500	−25	99

[a] Reactions were carried out under an initial hydrogen pressure of 50 psig. Quantitative conversions were obtained within 10 min.
[b] The initial hydrogen pressure was 50 psig and quantitative conversion was obtained within 30 min.

Table 3. Asymmetric hydrogenation of amidoacrylic acids and esters with {Rh[(*S*)-**3**]}BF_4[a]



Entry	R	R′	R″	Ee[b] (%)[c]
1	Ph	Me	Me	98(91)
2	4-Me-Ph	Me	Me	98(89)
3	4-MeO-Ph	Me	Me	98(87)
4	4-O_2N-Ph	Me	Me	96(82)
5	4-AcO-Ph	Me	Me	98(87)
6	2-Furanyl	Me	Me	98(84)
7	3,4-Methylenedioxyl-Ph	Me	Me	98(81)
8	2-Cl-Ph	Me	Me	97
9	3-Cl-Ph	Me	Me	97
10	4-F-Ph	Me	Me	98
11	4-Cl-Ph	Me	Me	98
12	4-Br-Ph	Me	Me	98
13	4-Cl-Ph	Me	Ph	99
14	4-F-Ph	Me	Ph	99
15	Ph	H	Me	98
16	H	Me	Me	97
17	H	H	Me	98

[a] The reactions were carried out at room temperature under 50 psig H_2. Quantitative conversions were obtained within 10 min. The conversion and enantiomeric excess were determined by GC analysis. Concentration of the substrates = 0.25 M. The rhodium catalyst was prepared by reacting (*S*)-**3** with $[Rh(COD)_2]BF_4$ in CH_2Cl_2 at room temperature.
[b] All products had the *S* configuration.
[c] The data in parentheses were results obtained using {Rh[(*S*)-**1**]}BF_4 as the catalyst.

catalyst to the asymmetric hydrogenation of other classes of substrates is under investigation.

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18. **(*S*)-2,2′-Bis[bis(3,5-dimethylphenyl)phosphinoamino]-1,1′-binaphthyl[(*S*)-Xyl-BDPAB], (*S*)-3**. To a 50 ml round-bottom Schlenk flask containing (*S*)-1,1′-binaphthyl-2,2′-diamine (200 mg, 0.7 mmol) and DMAP (10 mg) were added 10 ml dried CH_2Cl_2 and 0.7 ml dried Et_3N. The solution was cooled with an ice-bath to 0°C. Bis(3,5-dimethylphenyl)phosphine chloride (450 mg, 1.6 mmol) was added in a dropwise manner within 15 min. The reaction mixture was stirred at room temperature for 3 h, and the solvent was evaporated in vacuo. The residue was purified using a flash silica gel column (toluene as the eluent) under N_2. Concentration of the filtrate and removal of solvent under vacuum overnight gave (*S*)-**3** (465 mg, 87% yield). Colorless crystals were obtained by recrystallization from methanol/CH_2Cl_2 (v/v = 4). ^{31}P NMR ($CHCl_3$): δ 26.1 (s). ^1H NMR ($CHCl_3$): δ 2.35 (s, 12H), 2.8 (s, 12H), 5.00 (d, J = 8.5 Hz, 2H), 6.96 (s, 2H), 6.98 (s, 2H), 7.00 (s, 2H), 7.01 (s, 2H), 7.04 (s, 2H), 7.10 (s, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 8.10 (d, J = 8.0 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H), 8.24–8.27 (dd, J = 4.5, 9.0 Hz, 2H). ^{13}C NMR ($CHCl_3$): methyl carbons 21.09, 21.11.
19. **(*S*)-2,2′-Bis(dicyclohexylphosphinoamino)-1,1′-binaphthyl [(*S*)-Cy-BDPAB], (*S*)-2**. (*S*)-**2** was synthesized in 78% yield using a method similar to the preparation of (*S*)-**3**. Colorless crystals were obtained by recrystallization from ether. ^{31}P NMR (CH_2Cl_2): δ 42.77; ^1H NMR (CH_2Cl_2): δ 0.21–0.27 (m, 2H), 0.56–0.61 (m, 2H), 0.73–1.60 (m, 40H), 3.77 (d, J = 10.5 Hz, 2H), 6.84 (d, J = 7.5 Hz, 2H), 7.03–7.10 (m, 4H), 7.67 (d, J = 7.5 Hz, 2H), 7.73 (d, J = 9.5 Hz, 2H), 7.78–7.81 (dd, J = 4.5, 9.0 Hz, 2H).
20. **A typical procedure for the rhodium-catalyzed asymmetric hydrogenation of amidoacrylic acids and esters**. In a glove-box 0.01 mmol $[Rh(COD)_2]BF_4$, 0.01 mmol of the bisaminophosphine ligand and 1 ml dried CH_2Cl_2 were placed in a 4 ml glass bottle and the mixture was stirred at room temperature for 1 h to prepare a stock solution of the catalyst. In a typical experiment, 10 μl (0.0001 mmol) of the catalyst solution was added in a 50 ml autoclave which was charged with 0.05 mmol substrate and 190 μl solvent. The autoclave was closed and the atmosphere was displaced by hydrogen several times and finally 50 psig H_2 was charged. The mixture was stirred at rt for 10 min before releasing the H_2. The enantiomeric excess and conversion were determined by GC. The hydrogenation product of acetamidoacrylic acid was converted to its methyl ester before the GC analysis with a capillary chiral column (CHROMPACK, CP Chirasil-DEX CB, 25 m×0.25 mm). Other hydrogenation products were analyzed using a (CHROMPACK, Chirasil-L-Val, 25 m×0.25 m) column.