Asymmetric Synthesis of Chiral Amine Derivatives through Enantioselective Hydrogenation with a Highly Effective Rhodium Catalyst Containing a Chiral Bisaminophosphine Ligand

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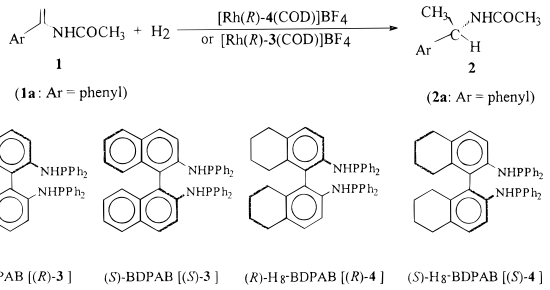
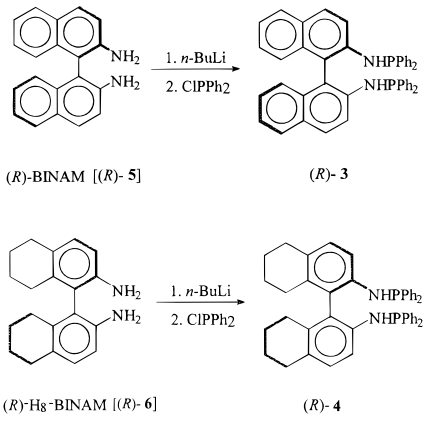
Homogeneous asymmetric hydrogenation by transition-metal complexes is one of the most powerful methods for the synthesis of optically active organic compounds.[1] High enantioselectivities were obtained in the synthesis of chiral amino acids and their derivatives through the asymmetric hydrogenation catalyzed by rhodium complexes containing chiral diphosphine ligands such as DIPAMP,[2] DIOP,[3] Chiraphos,[4] Norphos,[5] BPPM,[6] BDPP,[7] BINAP,[8] Duphos,[9] BICP,[10] and others.[11] The easily prepared bisaminophosphines[12] were also found to be effective ligands for the catalytic hydrogenation reactions leading to chiral amino acids. Recently, a diphosphinite ligand bearing a spirocyclic backbone has been found to be very efficient and highly enantioselective in the hydrogenation of dehydroamino acid derivatives and other substrates in our laboratory.[13] Phosphinite ligands derived from D-glucose were also found to be highly effective.[14] In striking contrast to the broad success in the synthesis of optically active amino acids and other chiral compounds, only limited success has been achieved on the asymmetric synthesis of chiral amines and their derivatives through enantioselective hydrogenation of enamides. The well-known chiral diphosphine ligands such as DIOP, Phellanphos, and Nopaphos were used as chiral ligands in the asymmetric catalytic hydrogenation of α-phenylenamide (**1a**).[15] However, the enantiomeric excess (ee) values of the product **2a** were quite low (25−68%). Recently, Burk et al. reported an important breakthrough on the enantioselective hydrogenation of arylenamides with Rh catalysts containing Duphos and BPE ligands (ee = 74.8−98.5%).[16] From a practical point of view, it is important to develop effective chiral ligands which are easy to prepare so that the related chemistry can be widely used. Herein we wish to report a highly effective Rh catalyst containing an easily prepared chiral bisaminophosphine ligand for the synthesis of a variety of valuable α-arylethylamine derivatives with excellent enantioselectivities (up to 99.0% ee) and high reactivities.



In our initial study we focused our attention on the development of chiral catalysts containing 2,2′-bis(diphenylphosphinoamino)-1,1′-binaphthyl (BDPAB)[12e] and 2,2′-bis(diphenylphosphinoamino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (H_8-BDPAB).[17] An important advantage of the use of this class of catalysts is that the ligands can be easily prepared from the corresponding diamines.



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(16) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.

(17) The procedure for the preparation of (*R*)-**4**: (*R*)-5,5′6 6′,7,7′,8,8′-Octahydro-1,1′-binaphthyl-2,2′-diamine (200 mg, 0.7 mmol) in THF (20 mL) was charged to a 50 mL flask under a nitrogen atmosphere. This flask was cooled to −30 °C, and into the solution was added a solution of *n*-butyllithium in hexane (0.88 mL of a 1.6 M solution, 1.4 mmol) in a dropwise manner. The mixture was stirred for 2 h at −30 °C with a magnetic stirrer. Then a solution of chlorodiphenylphosphine (0.32 mL, 1.8 mmol) in THF (5 mL) was added dropwise. The system was allowed to stir for 5 h, and the temperature was raised to about 25 °C. The mixture was filtered to remove the solid. The THF solvent was removed in *vacuo* to give 420 mg of (*R*)-**4**. The crude product was purified by recrystallization in diethyl ether solvent at −30 °C for 24 h to afford 390 mg of white, needlelike crystals of (*R*)-**4** (84.0% of theoretical yield). The analytical data of (*R*)-**4** were as follows: mp: 137−139 °C. $[\alpha]_D = -47°$ ($c = 1.0$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (m, 22H); 6.98 (d, $J_{H-H} = 8.34$ Hz, 2H); 4.27 (d, $J_{P-H} = 7.0$ Hz, 2H); 2.67 (m, 4H); 2.10 (m, 4H); 1.58 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.9, 141.7, 141.2, 141.0, 140.6, 140.5, 136.1, 131.0, 130.8, 130.4, 130.2, 129.6, 128.9, 128.7, 128.4, 128.3, 128.2, 123.2, 112.7, 112.5, 29.3, 27.3, 23.1, 23.0. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 27.25 ppm. Anal. Calcd for $C_{44}H_{42}N_2P_2$: C 79.97, H 6.41, N 4.24. Found: C 79.78, H 6.40, N 4.24.

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Table 1. Asymmetric Hydrogenation of **1a** Using Rh-(*R*)-4 Catalyst[a]

entry	solvent	ee value (%)	config
1	THF	92.1	*R*
2	methanol	91.0	*R*
3	benzene	80.5	*R*
4	diethyl ether	73.2	*R*
5[b]	THF	91.0	*R*
6[c]	THF	89.5	*R*
7[d]	THF	96.8	*R*

[a] Unless otherwise noted, the reaction conditions were S/C = 100, P_{H_2} = 14.5 psi, reaction time = 10 min, room temperature. [b] S/C = 1000. [c] P_{H_2} = 1000 psi. [d] Hydrogenation was performed at 5 °C for 30 min.

H_8-BINAM[18] (H_8-BINAM = 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine) was easily obtained via the partial hydrogenation of BINAM (BINAM = 1,1′-binaphthyl-2,2′-diamine) using a similar method as in the preparation of H_8-BINOL.[19]

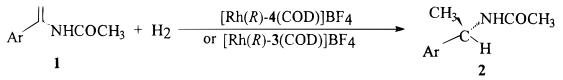
The hydrogenation of **1a** with a Rh catalyst containing (*R*)-**4** gave excellent ee value (96.8% ee) for the product **2a**, and the rate of reaction was very fast. (Reaction conditions: S/C = 200, 1 atm H_2 , 5 °C, THF as solvent. Complete conversion was achieved within 30 min.) In comparison, the same reaction under otherwise identical conditions except with a Rh catalyst containing (*R*)-**3** gave only 92.9% ee for the product. The results of the asymmetric hydrogenation of **1a** catalyzed by Rh-(*R*)-**4** complex under a variety of conditions are summarized in Table 1. It was noted that the enantioselectivity of the catalyst was sensitive to the solvent used. Higher ee values of **2a** were achieved in protic and/or polar solvents. In contrast, the hydrogen pressure had very little effect on the enantioselectivity. For example, in the hydrogenation of **1a** using Rh-(*R*)-**4** catalyst in THF, the following results were obtained: P_{H_2} = 14.5 psi, ee = 92.1%; P_{H_2} = 100 psi, ee = 90.7%; P_{H_2} = 1000 psi, ee = 89.5%. The substrate/catalyst ratio had a small influence on the enantioselectivity in the Rh-(*R*)-**4** catalyzed hydrogenation of **1a** (entry 5 vs 1). Lower reaction temperature led to higher ee values of **2a** (entry 7 vs 1).

The rates of the hydrogenation of **1a** catalyzed by Rh-(*R*)-**4** or Rh-(*R*)-**3** complex were substantially higher than those using other catalyst systems. Complete conversion for the hydrogenation of **1a** using Rh-(*R*)-**4** or Rh-(*R*)-**3** catalyst was achieved within 10 min at ambient temperature and within half an hour at 5 °C.

A variety of valuable chiral amine derivatives with high ee values can be synthesized through the asymmetric hydrogenation of enamides **1** with Rh-(*R*)-**4** or Rh-(*R*)-**3** catalyst, as shown in Table 2.

It was clearly observed that the enantioselectivities of the hydrogenation of **1** catalyzed by Rh-(*R*)-**4** were consistently higher than those from the same reaction with Rh-(*R*)-**3** catalyst. These results are consistent with our previous studies on the alkylation of aldehydes with trialkylaluminum and with diethylzinc using Ti-H_8-BINOL (H_8-BINOL = 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) and Ti-BINOL (BINOL =1,1′-bi-2-naphthol) catalysts.[20] It is quite possible that the improved enantioselectivity of the catalysts is due to the increased steric effect caused by the partial hydrogenation of the binaphthyl backbone. A similar effect was also observed by Takaya et al. in the asymmetric hydrogenation of some unsaturated carboxylic acids and other substrates catalyzed by Ru catalysts containing H_8-BINAP [H_8-BINAP = 2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl] and BINAP [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl].[21]

Table 2. Asymmetric Hydrogenation of **1** Catalyzed by Rh-(*R*)-**4** or Rh-(*R*)-**3** Complexes[a]



1 **2**

entry	Ar	product	cat.	conv[b] (%)	ee[b] (%)	config
1	C_6H_5	**2a**	[Rh(*R*)-**4**(COD)]BF_4	100	96.8 (13.7)	*R*
2	C_6H_5	**2a**	[Rh(*R*)-**3**(COD)]BF_4	100	92.9	*R*
3	*p*-$CF_3C_6H_4$	**2b**	[Rh(*R*)-**4**(COD)]BF_4	100	99.0 (4.6)	*R*
4[c]	*p*-$CF_3C_6H_4$	**2b**	[Rh(*R*)-**4**(COD)]BF_4	100	98.7	*R*
5	*p*-$CF_3C_6H_4$	**2b**	[Rh(*R*)-**3**(COD)]BF_4	100	95.1	*R*
6	*p*-$CH_3C_6H_4$	**2c**	[Rh(*R*)-**4**(COD)]BF_4	100	97.0 (4.6)	*R*
7	*p*-$CH_3C_6H_4$	**2c**	[Rh(*R*)-**3**(COD)]BF_4	97.6	95.1	*R*
8	*p*-ClC_6H_4	**2d**	[Rh(*R*)-**4**(COD)]BF_4	100	97.0 (1.9)	*R*
9	*p*-ClC_6H_4	**2d**	[Rh(*R*)-**3**(COD)]BF_4	100	94.9	*R*
10	*p*-FC_6H_4	**2e**	[Rh(*R*)-**4**(COD)]BF_4	100	96.0	*R*
11	*p*-FC_6H_4	**2e**	[Rh(*R*)-**3**(COD)]BF_4	85.5	90.1	*R*
12	*m*-$CH_3C_6H_4$	**2f**	[Rh(*R*)-**4**(COD)]BF_4	100	97.7	*R*
13	*m*-$CH_3C_6H_4$	**2f**	[Rh(*R*)-**3**(COD)]BF_4	93.4	94.8	*R*
14	2-furanyl	**2g**	[Rh(*R*)-**4**(COD)]BF_4	100	98.4	*R*
15	2-furanyl	**2g**	[Rh(*R*)-**3**(COD)]BF_4	100	96.1	*R*

[a] sub/cat. = 200; P_{H_2} = 1 atm; reaction temperature = 5 °C; reaction time = 30 min, THF as solvent. The conversion and ee values were determined by GLC with a CHIRASIL-L-VAL column. The configurations were determined by comparing optical rotations with the reported values.[16] [b] Data in brackets were obtained using [Rh(*S*-BINAP)(COD)]BF_4 as catalyst (sub/cat. = 20; P_{H_2} = 100 psi; 25 °C; 83 h; THF as solvent). [c] sub/cat. = 1000, reaction time = 1.0 h.

The high catalytic activity and enantioselectivity of Rh-(*R*)-**4** are relatively independent of the electronic features of the substrates. Substitution at *meta*- or *para*-position of the phenyl ring of the parent enamide **1a** did not give much influence on the enantioselectivity for the products. However, no reaction was observed in the hydrogenation of the *ortho*-substituted **1a** under the standard conditions. This might have been due to the strong steric hindrance effect of the *ortho*-substituent which significantly weakened the coordination of the substrate to the catalyst.

In conclusion, we have developed an easily prepared chiral bisaminophosphine ligand which has been found to be extremely effective in the Rh-catalyzed asymmetric hydrogenation of enamides leading to chiral arylamine derivatives with excellent ee. The simplicity and high efficiency clearly make it an excellent choice of catalyst for the practical preparation of highly valued chiral amine derivatives via the catalytic asymmetric hydrogenation of enamides.

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(18) The procedure for the preparation of (*R*)-**6**: A 50 mL autoclave equipped with a magnetic stirring bar was charged with 200 mg (*R*)-**1**, 1′-binaphthyl-2,2′-diamine (purchased from Aldrich Chemical Co.), 20 mg of PtO_2, 20 mL of glacial acetic acid, and 2 mL of water. The autoclave was closed, and 3 atm of H_2 was charged. The solution was stirred for 24 h at 50 °C. After releasing the hydrogen gas and removing the solid catalyst by filtration, the mixture was neutralized with aqueous $NaHCO_3$ solution followed by extraction with 20 mL of ethyl acetate three times. The combined extracts were dried with sodium sulfate, and the solvent was removed with a rotary evaporator to give 200 mg of crude product. The crude product was purified by crystallization with 5 mL of ethyl acetate and 15 mL of hexane to give 180 mg of crystals of (*R*)-**6** (88% of theoretical yield). The analytical data for (*R*)-**6** were as follows: mp: 210 °C dec; $[\alpha]_D$ = 133° (*c* = 1.0, pyridine); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (d, J_{H-H} = 8.0 Hz, 2H); 6.60 (d, J_{H-H} = 8.2 Hz, 2H); 3.07 (s, 4H); 2.70 (m, 4H); 2.22 (m, 4H); 1.67 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.9, 136.6, 129.6, 128.0, 122.4, 113.5, 29.7, 27.4, 23.6 ppm. Anal. Calcd for $C_{20}H_{24}N_2$: C 82.15, H 8.27, N 9.58. Found: C 82.34, H 8.06, N 9.61.

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