Chiral monophosphorous ligands derived from BINOL and chiral additional groups for asymmetric hydrogenation of α-dehydroamino acid derivatives

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Abstract

New chiral monodentate phosphorus ligands including a chiral additional group have been prepared. Their Rh complexes show highly catalytic activity and enantioselectivity for asymmetric hydrogenation of α-dehydroamino acid derivatives.

Keywords: Asymmetric hydrogenation, monophosphorus ligand, binol

Introduction

The homogeneous catalytic asymmetric hydrogenation is one of the most efficient and convenient methods for preparing optically active amino acids, amines, and itaconic acids, which were widely applied in pharmacy and fine chemicals industries.[1,2] Chiral phosphorus, especially diphosphorus, have been widely used as the most efficient chiral ligands for asymmetric hydrogenation.[3] While monodentate P-ligands have the advantage of being readily accessible, in recent years, monophosphines,[4] monophosphonites,[5] monophosphoramidites,[6] and monophosphites[7] have been developed and successfully applied in asymmetric hydrogenations.

Most of the successful monodentate ligands are phosphorus derivatives of binaphthol, which including a binaphthyl (*R*)- or (*S*)-moiety as the diol backbone and an additional group (Figure 1). It is believed that binol skeleton play a crucial role in achieving high enantioselectivity in the asymmetric hydrogenation of olefin. The absolute configuration of the hydrogenated compound is usually imposed by the absolute configuration of the binol moiety. [7c-7f]

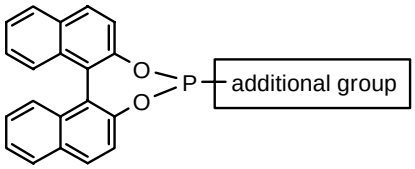
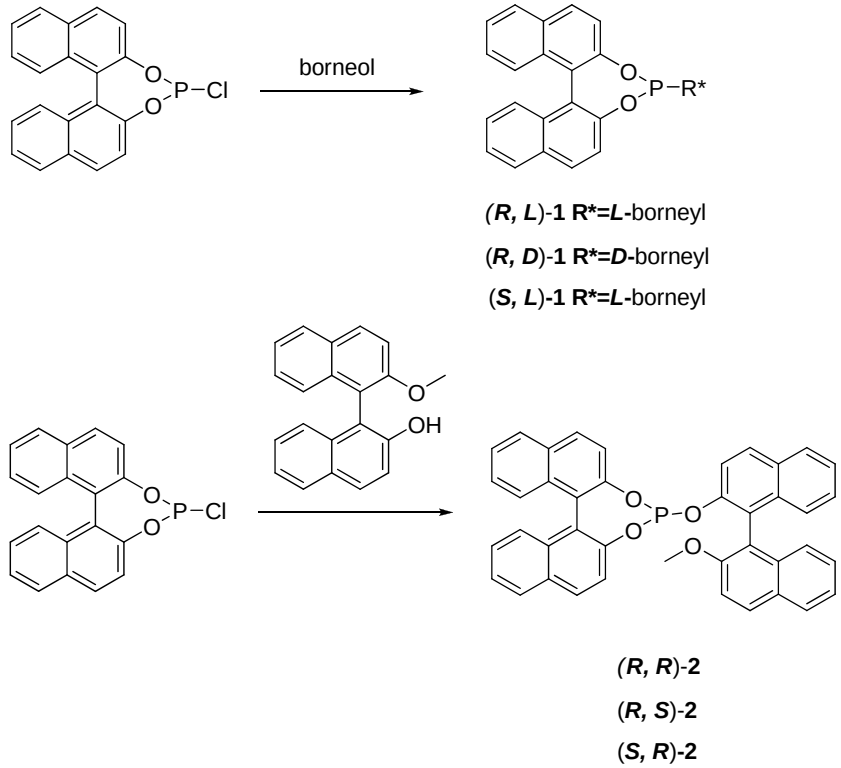


Figure 1

To ascertain the the influence of the additional group on the enantioselectivity and yield of the asymmetric hydrogenation process, to make further known of catalytic processes, we now report that monophosphorus compounds derived from BINOL and a chiral additional group were used as chiral ligand for asymmetric hydrogenation of α-dehydroamino acid derivatives.

Results and Discussion

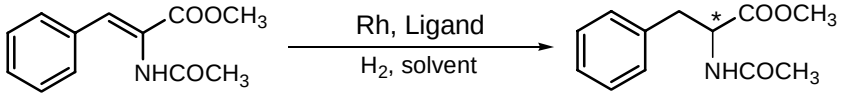
Preparation of the monophosphorus ligands **1** and **2** derived from BINOL and a series of chiral additional groups is illustrated in Scheme 1. Treatment of BINOL with PCl_3, subsequent reaction with chiral compounds in the present of Et_3N afforded the desired products.[8]



Scheme 1

Ligands **1 and 2** were examined for asymmetric hydrogenation of methyl (Z)-2-acetamidocinnamate, and the results were listed in Table 1 (entries 1-3). Interestingly, we found that Rh complex of (***R, L***)**-1** could give the desired product in the highest enantioselectivity. The reaction catalyzed by Rh/(***R, L***)**-1** in CH_2Cl_2 could give higher ee than that in other solvents such as THF and toluene (entries 4, 5).The hydrogen pressure had little effect on the enantioselectivity and conversion. $Rh(COD)_2BF_4$ provided the same enantioselectivity as $Rh(COD)_2SbF_6$, however, neutral catalyst $[Rh(COD)Cl]_2$ displayed poor catalytic activity (entries 5, 6). The matched (***R, L***)**-1** provided better enantioselectivity than (***S, L***)**-1** (compare entry 3 with entry 8). For the ligands (***R, D***)**-1,**

Table 1. Asymmetric hydrogenation of methyl (Z)-2-acetamidocinnamate[a]



Entry	ligand	solvent	H_2(atm)	conv,(%)[b]	ee,(%)[c]	config
1	(***R, L***)**-1**	toluene	1.2	70	84.1	*R*
2	(***R, L***)**-1**	THF	1.2	100	86.2	*R*
3	(***R, L***)**-1**	CH_2Cl_2	1.2	100	88.7	*R*
4	(***R, L***)**-1**	CH_2Cl_2	20	100	88.3	*R*
5[d]	(***R, L***)**-1**	CH_2Cl_2	1.2	100	88.4	*R*
6[e]	(***R, L***)**-1**	CH_2Cl_2	1.2	0		
7	(***R, D***)**-1**	CH_2Cl_2	1.2	100	21.6	*R*
8	(***S, L***)**-1**	CH_2Cl_2	1.2	100	74.5	*R*
9	(***R, R***)**-2**	CH_2Cl_2	1.2	65	56.9	*R*
10	(***R, S***)**-2**	CH_2Cl_2	1.2	89	33.8	*S*
11	(***S, R***)**-2**	CH_2Cl_2	1.2	0		

[a] All of the reactions were carried out at room temperature for 4 h, substrate/catalyst= 100:1.

[b] The conversion of the substrates were determined by GC-MS Agilent 6890-5973N HP-5 column.

[c] Ees were determined by chiral GC using Varian Chiralsil-L-Val column. [9] The configuration was assigned by comparing the experimental results with published data.[9]

[d] $Rh(COD)_2BF_4$ was used instead of $Rh(COD)_2SbF_6$.

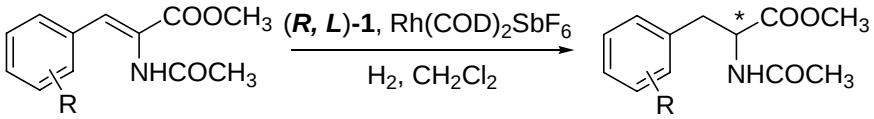
[e] $[Rh(COD)Cl]_2$ was used instead of $Rh(COD)_2SbF_6$.

the dramatic decrease in enantioselectivity may be due to a mismatched combination between the (*R*)-BINOL and *D*-borneyl (entry 7). (***R, R***)**-2** and (***R, S***)**-2** including a bulky

additional group only displayed low reaction rates and poor enantioselectivities in hydrogenation reactions (entry 9, 10). (***S, R*)-2** showed no activity in asymmetric hydrogenation (entry 11). The configuration of product of liand **1** and **2** showed no apparent trend. Monophorus ligands bearing *R*-binol moiety consistently afforded (*S*)-α-amino acid derivatives.

The asymmetric hydrogenation of other α-dehydroamino acid esters catalyzed by Rh/(***R, L*)-1** was also investigated under the optimized conditions, and the results were listed in Table 2. All of the tested substrates could be completely converted to the desired products with high enantioselectivity. The results also revealed that an electron-withdrawing group on the phenyl ring of the substrates can enhance the enantioselectivity (Table 2, entry 5 and 6), while an electron-donor group gave negative effects (Table 2, entry 7). Noticeably, we found that ligand (***R, L*)-1** gave high enantioselectivity even after being stored under N_2 in a refrigerator for more than half a year (Table 2, entry 8).

Table 2. Asymmetric hydrogenation of α-dehydroamino acid derivatives[a]



Entry	substrate	conv,(%)[b]	ee,(%)[c]	config
1	R= H	100	88.7	*R*
2	R= *o*-CH_3	100	85.5	*R*
3	R= *m*-CH_3	100	85.3	*R*
4	R= *p*-CH_3	100	84.0	*R*
5	R= *p*-F	100	90.1	*R*
6	R= *p*-Cl	100	89.3	*R*
7	R= *p*-CH_3O	100	82.2	*R*
8[d]	R= H	100	88.4	*R*

[a] All of the reactions were carried out at room temperature for 4 h, p(H_2) = 1.2 atm, substrate/catalyst = 100:1.

[b] The conversion of the substrates were determined by GC-MS Agilent 6890-5973N HP-5 column.

[c] Ees were determined by chiral GC using Varian Chiralsil-L-Val column.[9] The configuration was assigned by comparing the experimental results with published data.[9]

[d] (***R, L*)-1** was stored under N_2 in refrigerator for more than half a year.

Conclusions

In conclusion, several new monophosphorus ligands derivied from BINOL and chiral additional groups have been synthesized and used as chiral ligand for asymmetric hydrogenation of α-dehydroamino acid derivatives. Ligand (***R, L***)**-1** exhibited the best catalytic activity. We have observed that the steric effects of bulky additional group is unfavorable to the asymmetric hydrogenation reaction. We also found that the additional group of the monophorous ligands may have influence on the absolute configuration of the products. More detailed studies of these ligands and their applications in asymmetric catalysis are in progress.

Experimental Section

General Procedures. The ^{1}H NMR spectra were measured on a Varian INOVA-400 spectrometer and the chemical shifts were referenced to tetramethylsilane (^{1}H) as internal standard or H_3PO_4 (^{31}P) as external standard. All reactions were performed in a dry argon atmosphere using standard techniques. THF and Toluene were distilled over Na. NEt_3 and CH_2Cl_2 were distilled over CaH_2. $[Rh(COD)_2]BF_4$ and $[Rh(COD)_2]SbF_6$ were synthesized according to literature procedure[10]. 2'-methoxy-1,1'-binaphthalenyl-2-ol was prepared following literature procedures.[11] Chemicals and reagents were purchased from commercial suppliers and used as received.

General procedure for the preparation of ligands 1 and 2

BINOL (0.286 g, 1 mmol) in 5 mL of PCl_3 was heated under reflux for 6 h. Excess of PCl_3 was removed by distillation in vacuo. The residue was dissolved in THF (2mL). A solution of chiral alcohol (1 mmol) and triethylamine (0.1 mL) in THF (3 mL) was added to the flask.The mixture was stirred overnight. The resulting mixture was purified through an silica gel column. After removal of the solvent in vacuum, the product was isolated as colorless solids.

(***R, L***)**-1.** Yield: 0.385 g, 82 %. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ= 7.88-7.96 (m, 4H), 7.22-7.51 (m, 8H), 4.53 (m, 1H), 1.92-2.10 (m, 2H) 1.380-1.56 (m, 2H), 1.14-1.22 (m, 3H), 0.93 (s, 3H), 0.82 (s, 3H), 0.72 (s, 3H). ^{31}P-NMR: δ =147.92. HRMS (ESI) calcd for $C_{30}H_{29}Na_1O_3P_1[M+Na]^+$: m/z = 491.1747. Found: 491.1739.

(***R, D***)**-1.** Yield: 0.393 g, 84 %. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ= 7.93-8.01 (m, 4H), 7.54-7.56 (m, 1H), 7.40-7.47 (m, 5H), 7.27-7.30 (m, 2H), 4.53 (m, 1H), 1.98-2.27 (m, 2H), 1.47-1.73 (m, 2H), 1.22-1.29 (m, 3H),1.00 (s, 3H), 0.89 (s, 3H), 0.78 (s, 3H). ^{31}P-NMR: δ

=148.02. HRMS (ESI) calcd for $C_{30}H_{29}Na_1O_3P_1[M+Na]^+$: m/z = 491.1747. Found: 491.1736.

(***S, L***)**-1.** Yield: 0.368 g, 78 %. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ= 7.88-7.96 (m, 4H), 7.22-7.51 (m, 8H), 4.53 (m, 1H), 1.96-2.19 (m, 2H) 1.43-1.68 (m, 2H), 1.17-1.20 (m, 3H), 0.95 (s, 3H), 0.85 (s, 3H), 0.73 (s, 3H). ^{31}P-NMR: δ =147.87. HRMS (ESI) calcd for $C_{30}H_{29}Na_1O_3P_1[M+Na]^+$: m/z = 491.1747. Found: 491.1734.

(***R, R***)**-2.** Yield: 0.481 g, 78 %. ^{1}H-NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.88-8.19 (m, 8H), 7.10-7.60 (m, 16H), 3.75 (s, 3H). ^{31}P-NMR: δ =144.87. HRMS (ESI) calcd for $C_{41}H_{27}Na_1O_4P_1[M+Na]^+$: m/z = 637.1539. Found:637.1519.

(***R, S***)**-2.** Yield: 0.452 g, 73 %.^{1}H-NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.71-8.17 (m, 8H), 7.13-7.51 (m, 16H), 3.78 (s, 3H). ^{31}P-NMR: δ =146.06. HRMS (ESI) calcd for $C_{41}H_{27}Na_1O_4P_1[M+Na]^+$: m/z = 637.1539. Found:637.1523.

(***S, R***)**-2.** Yield: 0.467 g, 76 %.^{1}H-NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.14-8.12 (m, 24H), 3.76 (s, 3H). ^{31}P-NMR: δ =145.43. HRMS (ESI) calcd for $C_{41}H_{27}Na_1O_4P_1[M+Na]^+$: m/z = 637.1539. Found:637.1514.

General procedure for the Rh(I)-catalyzed asymmetric hydrogenation

The catalyst was made in situ by mixing $[Rh(COD)_2]BF_4$ or $[Rh(COD)_2]SbF_6$ (0.005mmol) and monodentate phosphorus ligands (0.01mmol) in CH_2Cl_2 (3 mL) for 10 min. The catalyst solution was transferred into a 100 mL stainless steel autoclave equipped with a glass liner, which contained α-dehydroamino acid derivatives (0.5 mmol) and a magnetic stirring bar. After purging with hydrogen for 6 times, the system was pressurized with hydrogen (1.2 atm). The reaction mixture was stirred at r.t for 4h. The reaction mixture were filtered over a short pad of gel and analyzed by GC.

Enantiomeric excess determination

The racemic mixtures of all products were prepared by hydrogenation of the substrates using Pd/C or Wilkinson's catalyst.

Methyl 2-acetamido-3-phenylpropionate. GC (FULI 9790 Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=11.93 min, t_S=13.20 min.

Methyl 2-acetamido-3-(2-methylphenyl)propionate. GC (FULI 9790 Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=11.75 min, t_S=13.10 min.

Methyl 2-acetamido-3-(3-methylphenyl)propionate. GC (FULI 9790 Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=12.98 min, t_S=13.55 min.

Methyl 2-acetamido-3-(4-methylphenyl)propionate. GC (FULI 9790 Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=13.73 min, t_S=15.22 min.

Methyl 2-acetamido-3-(4-methoxyphenyl)propionate. GC (FULI 9790n Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=24.07 min, t_S=26.17 min.

Methyl 2-acetamido-3-(4-Fluorophenyl)propionate. GC (FULI 9790 Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=10.39 min, t_S=10.88 min.

Methyl 2-acetamido-3-(4-chlorophenyl)propionate. GC (FULI 9790 Chirasil-L-Val column 25 m X 0.25 mm X 0.25 μm; 140 °C) t_R=21.24 min, t_S=23.12 min.

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