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Asymmetric hydrogenation of dehydroamino acid derivatives catalyzed by a new aminophosphine phosphinite ligand derived from ketopinic acid

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Abstract

A new chiral aminophosphine phosphinite *N*,*O*-bis(diphenylphosphino)-(1*S*,2*R*)-1-(*N*-methylamino) methyl-2-hydroxyl-7,7-dimethylbicyclo[2.2.1]heptane was synthesized from ketopinic acid and its application to the asymmetric hydrogenation of dehydroamino acid derivatives examined.

1. Introduction

The asymmetric hydrogenation of dehydroamino acid derivatives is a very useful method for the preparation of chiral amino acids.[1] A host of chiral ligands have been synthesized and used for this type of reaction. Among them, the chiral aminophosphine phosphinite (AMPP) ligands have attracted much attention due to their easy preparation.[2] The preparation of these ligands from inexpensive starting materials is of potential industrial value. In a previous paper we reported the synthesis of new 1,3-aminoalcohols (1*S*,2*S*)- and (1*S*,2*R*)-1-hydroxylmethyl-2-amino-7,7-dimethylbicyclo[2.2.1]heptane from a readily available starting material, ketopinic acid, and its application in catalytic enantioselective reduction of prochiral ketones.[3] Since the readily available ketopinic acid represents a different class of chiral source from the 2-amino-1,2-diphenyl-ethanol which we have used successfully, the preparation and application of aminophosphine phosphinites from ketopinic acid will significantly expand the scope of this chemistry. In this paper, we report the synthesis of a chiral aminophosphine phosphinite from ketopinic acid and

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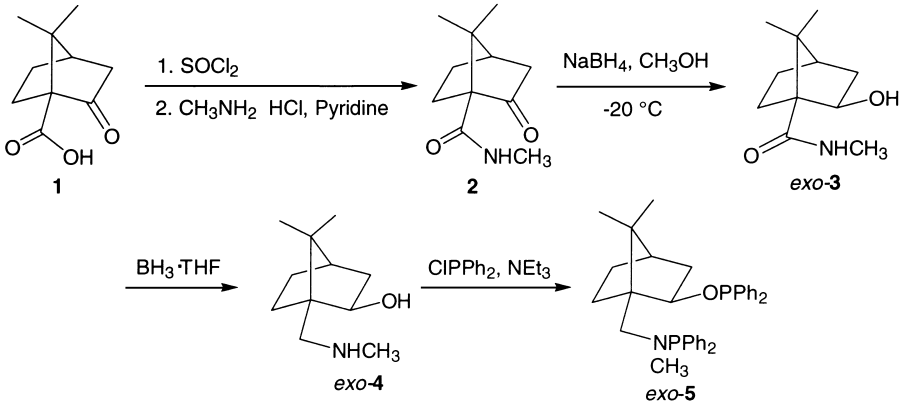
the application of this new ligand in the rhodium catalyzed enantioselective hydrogenation of dehydroamino acid derivatives.

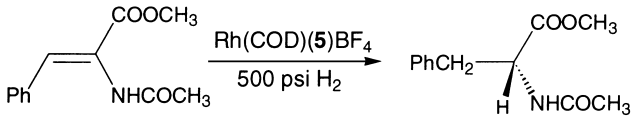
2. Results and discussion

The reaction of ketopinic acid with thionyl chloride followed by the addition of methylamine hydrogen chloride in the presence of pyridine produced compound **2**, which was then reduced with $NaBH_4$ in –20°C to produce *exo*-**3** in almost quantitative yield (Scheme 1). Compound **3** reacted with BH_3·THF to give aminoalcohol **4** (90% yield). Finally the chiral phosphine phosphinite **5** was obtained by the reaction of **4** with two equivalents of chlorodiphenylphosphine in anhydrous benzene in the presence of triethylamine (58% yield).



Scheme 1.

The catalytic activity and enantioselectivity of Rh-**5** catalyzed hydrogenation were studied by using methyl (*Z*)-2-acetamidocinnamate as the model substrate (Scheme 2) and the results are listed in Table 1.



Scheme 2.

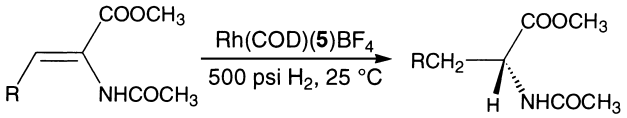
The effects of reaction temperature and pressure of H_2 on the enantioselectivity of the reaction were quite small (entries 1 and 2: the e.e. value changed from 79 to 77% when the temperature increased from 0 to 25°C; entries 2 and 3: the e.e. values were 77 and 78% under the pressure of 500 psig and 250 psig, respectively). However, the effect of solvents on the enantioselectivity of the reaction was quite significant. Acetone was found to be the best solvent for this reaction.

The results of hydrogenation of other dehydroamino acid derivatives (Scheme 3) catalyzed by Rh(COD)(*exo*-**5**)BF_4 are listed in Table 2. The substituents have significant influence on the e.e. of the products. Electron-withdrawing groups increased the enantioselectivity of products.

Table 1
The effect of solvent and reaction condition on the hydrogenation of (*Z*)-2-acetamidocinnamate catalyzed by Rh(COD)(**5**)BF_4[a]

Entry	Solvent	Temperature (°C)	Pressure (psi)	E.e.[b]	Config.[c]
1	Acetone	0	500	79	*R*
2	Acetone	25	500	77	*R*
3	Acetone	25	250	78	*R*
4	Methanol	25	500	74	*R*
5	THF	25	500	62	*R*
6	Dichloromethane	25	500	72	*R*

[a]The substrate-to-catalyst ratio was 100:1 and 100% conversion was observed in all cases. [b]The e.e. values were determined by GLC using a Chrompack-L-Val column. [c]The configuration was determined by comparison with authentic samples.



Scheme 3.

Table 2
The hydrogenation of acetamidocinnamic acid methyl ester and substituted analogues by Rh(COD)(**5**)BF_4[a]

Entry	Substrate (R=)	E.e.%[b]	Config.[b]
1	2-Cl-Ph	42	*R*
2	3-Cl-Ph	85	*R*
3	4-Cl-Ph	84	*R*
4	4-F-Ph	80	*R*
5	4-AcO-Ph	80	*R*
6	3-CH_3-4-AcO-Ph	75	*R*
7	4-CH_3O-Ph	82	*R*
8	4-NO_2-Ph	90	*R*
9	4-CH_3-Ph	62	*R*
10	Ph	77	*R*
11	2-furyl	83	*R*
12	3,4-(Methylenedioxy)phenyl	76	*R*

[a]In all cases the substrate-to-catalyst ratio was 100:1 and 95-100% conversions were observed at 25 °C under 500 psig of H_2; [b]The e.e. values were determined by GLC with a Chrompack Chirasil-L-Val column and the configuration was determined by comparison with authentic samples.

In conclusion, we have synthesized a new chiral aminophosphine phosphinite ligand from readily available ketopinic acid and the new ligand was found to be effective in Rh-catalyzed hydrogenation reactions leading to amino acid derivatives. Further study of other applications of this new ligand is in progress.

3. Experimental

Unless otherwise indicated, all reactions were carried out under N_2 atmosphere. Melting points were measured using an Electrothermal 9100 apparatus in capillaries and the data were uncorrected. Optical rotations were measured on a Perkin–Elmer Model 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer. Mass analyses were performed on a Finnigan Model Mat 95 ST mass spectrometer. GLC analyses were performed using a Hewlett–Packard HP 4890A apparatus. The ketopinic acid was prepared from camphorsulfonic chloride according to a literature procedure[4] and the other chemicals were purchased from Acros or Aldrich and were used as received.

3.1. Preparation of (1S)-7,7-dimethylbicyclo[2.2.1]heptane-1-N-methylcarboxylamide-2-one **2**

To a flask containing 1.85 g (10 mmol) of (+)-ketopinic acid, 2 ml thionyl chloride was added. The mixture was stirred at room temperature for 2 h and then at reflux temperature for 1 h. The excess thionyl chloride was removed under reduced pressure and the crude acid chloride was obtained.

Pyridine (2 ml) was added to a solution of methylamine hydrogen chloride 1.34 g (20 mmol) in 25 ml of THF at –10°C, the mixture was stirred for 30 min and the solution of acid chloride obtained above in 10 ml of dry THF was added slowly. After the stirring was continued at the same temperature for 1 h and then 0°C for 6 h, 10 ml water and 20 ml ether were added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography (silica gel, hexane:ethyl acetate, 1:1, v/v) to afford colorless solid **2** 1.77g (91%). Mp = 59–60°C, $[\alpha]_D = 93.9$ ($c = 0.57$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 0.967 (s, 3H), 1.27 (s, 3H), 1.38–1.61 (m, 2H), 1.92–2.20 (m, 3H), 2.45–2.57 (m, 2H), 2.83–2.84 (d, J = 4.8 Hz, 3H), 7.60 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): 20.314, 20.928, 25.624, 27.665, 28.363, 43.096, 43.711, 50.038, 64.513, 169.684 ppm; MS (ESI): 196 (M^+ +1, 100%); calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.47; H, 8.81; N, 7.13.

3.2. (1S,2R)-2-Hydroxyl-7,7-dimethylbicyclo[2.2.1]heptane-1-N-methylcarboxylamide **3**

To a flask containing 1.95 g of compound **2** (10 mmol) and 0.76 g of sodium borohydride (20 mmol), 30 ml of absolute methanol was added at –20°C and the reaction mixture was stirred for 8 h and then warmed to 0°C. After the solvent was removed in vacuo, 10 ml of water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by flash chromatography gave compound **3** 1.93 g (98%). Mp = 133–134°C, $[\alpha]_D = -22.65$ ($c = 0.49$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.03 (s, 3H), 1.06–1.24 (m, 1H), 1.28 (s, 3H), 1.30–1.35 (m, 1H), 1.77–1.83 (m, 2H), 1.87–1.91 (m, 1H), 1.92–1.96 (m, 1H), 1.97–2.12 (m, 1H), 2.85–2.87 (d, J = 4.0 Hz, 3H), 4.03–4.09 (d,d, $J_1 = 3.6$ Hz, $J_2 = 3.4$ Hz, 1H), 4.28 (br, 1H), 6.53 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$): 20.792, 21.581, 25.973, 27.210, 30.116, 41.328, 45.486, 49.651, 57.161, 175.032 ppm; calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.13; H, 9.75; N, 6.98.

3.3. (1S,2R)-1-(N-Methyl aminomethyl)-2-hydroxyl-7,7-dimethylbicyclo[2.2.1]heptane **4**

A solution of borane·THF complex (15 ml, 1 M in THF) was added to a solution of 1.56 g compound **3** (8 mmol in 10 ml of dry THF). The mixture was stirred at room temperature for 12 h and then was quenched with 2N hydrogen chloride. The solution was diluted with dichloromethane and then sodium carbonate was added to make the pH of the solution about 9–10. The organic layer was separated and the water layer was extracted with $CHCl_3$ (3×15 ml). Concentration and chromatography of the crude product (methanol:ethyl acetate, 2:1) afforded compound **4** 1.32 g (90% yield). Mp = 74–76°C; $[\alpha]_D = -24.2$ ($c = 0.66$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 0.84 (s, 3H), 1.09–1.13 (m, 2H), 1.16 (s, 3H), 1.45–1.46 (m, 1H), 1.66–1.70 (m, 3H), 1.71–1.82 (m, 1H), 2.47 (s, 3H), 2.51–2.58 (d, J = 2.612 Hz, 1H), 3.06–3.09 (d, J = 2.412 Hz, 2H), 3.90–4.07 (dd, J = 3.748, 3.756 Hz, 1H); MS (ESI): 184 (M+1,100); exact mass calculated for $C_{11}H_{21}NO$: 183.1623. Found: 183.1621.

3.4. Preparation of N,O-bis(diphenylphosphino)-(1S,2R)-1-(N-methylamino)methyl-2-hydroxyl-7,7-dimethylbicyclo[2.2.1]heptane **5**

92 mg of *exo*-**4** (0.50 mmol) was placed in a Schlenk flask and an inert atmosphere was introduced by three cycles of vacuum/argon. Triethylamine (0.13 ml, 0.90 mmol) in 3 ml of anhydrous benzene was added. The reaction mixture was stirred well and cooled to 0°C with an ice bath. A solution of 0.16 ml of chlorodiphenylphosphine (0.90 mmol) in 1 ml of anhydrous benzene was added dropwise to the mixture. After all of the chlorodiphenylphosphine was added, the ice bath was removed and the stirring was continued at ambient temperature for 24 h. Filtration of the triethylammonium chloride followed by flash column chromatography on silica gel (benzene as eluent) gave 160 mg of **5** (58%). ^{31}P NMR ($CDCl_3$): 74.29 (s, P (N)), 115.21 (s, P(O)) ppm; ^1H NMR ($CDCl_3$): 0.86–0.92 (m, 1H), 0.93 (s, 3H), 1.06–1.09 (m, 1H), 1.24 (s, 3H), 1.45–1.52 (m, 1H), 1.85–1.86 (m, 1H), 2.46–2.47 (d, J = 4.12 Hz, 3H), 3.37–3.45 (dd, J = 14.61, 15.54 Hz, 1H), 3.67–3.74 (dd, J = 12.65, 12.59 Hz), 4.26–4.28 (m, 1H), 7.08–7.66 (m, 20H) ppm. $C_{35}H_{39}NOP_2$ (551.6483), calcd: C, 76.21; H, 7.13; N, 2.54; P, 11.23. Found: C, 75.94; H, 7.18; N, 2.52; P, 11.16.

3.5. Typical procedures for the prepation of catalyst and for asymmetric catalytic hydrogenation

In an inert atmosphere glove box, $[Rh(COD)_2]BF_4$ (4.1 mg, 0.01 mmol) and *exo*-**5** (5.9 mg, 0.0105 mmol) were dissolved in 1 ml of anhydrous acetone. After 10 min of stirring, the solution of [Rh(COD)(*exo*-**5**)]BF_4 obtained was ready for use in asymmetric hydrogenation. In a 50 ml stainless steel autoclave were added the substrate methyl (*Z*)-2-acetaminocinnamate (0.1 mmol), 0.1 ml (0.001 mmol) of catalyst solution prepared above and 1 ml of the degassed acetone under nitrogen atmosphere. The vessel was pressurized with 500 psi of H_2 and the reaction was carried out at room temperature for 7 h. The e.e. value and the conversion level were determined by chiral GLC analysis with a Chirasil-L-Val column or HPLC analysis with a Chiralcel OD column.

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