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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 2455–2458

Asymmetric hydrogenation of enamides with a new chiral phosphine–phosphinite ligand

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Received 23 May 2005; accepted 7 June 2005

Abstract—A new mixed chiral phosphine–phosphinite **4** obtained from enantiomerically pure (*S*)-(+)-3-boronatodiphenyl-phosphanyl butanoic acid **1** was synthesized in four steps. This new chiral ligand was used in the asymmetric hydrogenation of dehydroamino acids with enantioselectivities being obtained of up to 90.8%.

1. Introduction

Chiral amino acids are important intermediates in pharmaceutical industry both as nutritional supplements and as synthetic intermediates. A convenient synthesis of these compounds is through the homogeneous catalytic asymmetric hydrogenation of prochiral amidoacrylic acids or esters. Rhodium catalysts containing chiral phosphine ligands have proven to be highly effective for this type of reaction.[1] While the majority of the developments in this area involve bidendate phosphine, phosphite, and phosphinite ligands, or mixed phosphine–phosphite[2] ligands, the corresponding phosphine–phosphinite ligands have only rarely been exploited.[3]

One of the targets in our study of catalytic asymmetry is the development of effective chiral ligands that can be easily prepared and successfully applied in asymmetric synthesis. We have recently reported the synthesis of chiral α-substituted β-amidophosphine boranes either by diastereoselective alkylation[4] of β-amidophosphine boranes using classical *O*-benzylated phenylglycinol as the chiral inducer, or by the 1,4-addition of nucleophilic phosphine boranes species to α,β-unsaturated amides.[5] Hydrolysis of these compounds led to chiral intermediate **1**.[6] Herein, we report the synthesis of a new mixed chiral phosphine–phosphinite **4** obtained from enantiomerically pure (*S*)-(+)-3-boronatodiphenyl-phosphanyl butanoic acid **1**. The results of using this ligand in the asymmetric hydrogenation of dehydroamino acids and enantioselectivities are also discussed.

2. Results and discussion

The synthesis of ligand **4** is outlined in Scheme 1. The reduction of enantiomerically pure (*S*)-(+)-3-boronatodiphenyl-phosphanyl butanoic acid **1** with borane solution in THF gave the corresponding hydroxyl phosphine borane **2** in 70% yield. Removal of the borane protection[7] (DABCO, toluene, 40 °C, 8 h) led in quantitative yields to the phosphine alcohol intermediate **3**. The deprotonation of hydroxy phosphine **3** with triethylamine followed by treatment with diphenylchlorophosphine in the presence of DMAP gave the expected phosphine–phosphinite ligand **4** in 66% yield. Next, the cationic Rh(I) complex was prepared by mixing 1 equiv of the ligand with 0.5 equiv of $[RhCl(COD)]_2$ in methanol followed by the addition of 2 equiv of sodium tetrafluoroborate solution in methanol leading to the expected complex **5** in nearly quantitative yield. In the ^{31}P NMR spectrum of **5**, resonance peaks of the two phosphorus nuclei appeared as a doublet of doublet δ 19.3 (dd, J_{P-P} = 38.6, J_{P-Rh} = 149.1 Hz) and 136.1 (dd,

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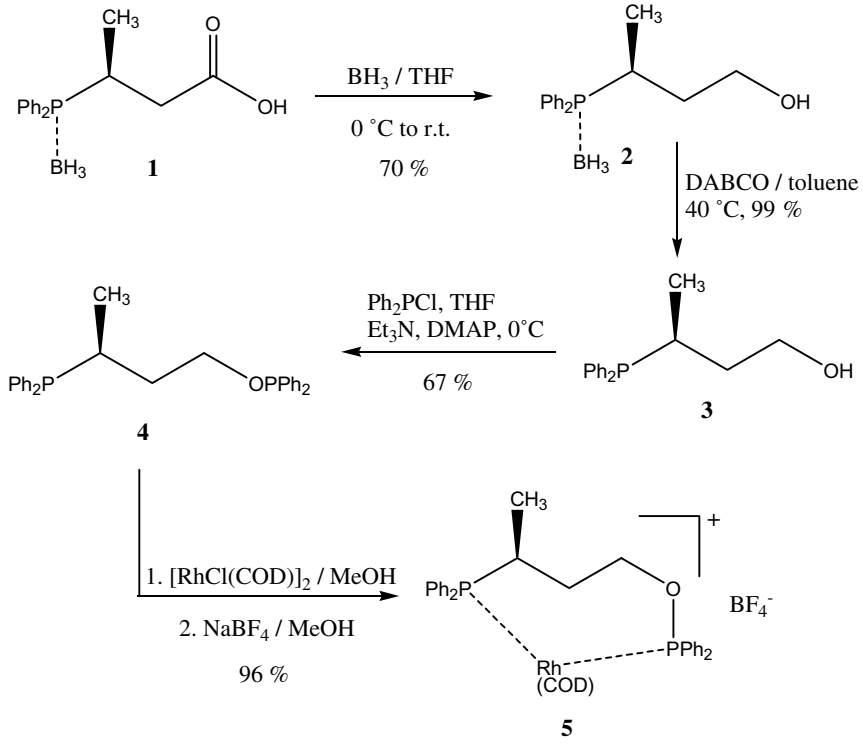
doi:10.1016/j.tetasy.2005.06.004

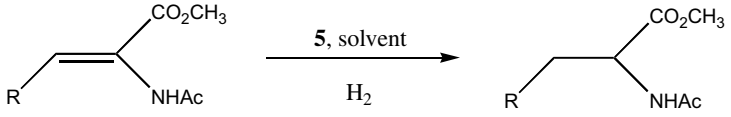


Scheme 1.

J_{P-P} = 38.6, J_{P-Rh} = 169.8 Hz) show that the phosphine–phosphinite **4** coordinates to the rhodium in a bidendate fashion.

Asymmetric hydrogenations of methyl (*Z*)-α-acetamidocinnamate **6a** and α-(*N*-acetamido)acrylate **6b** were carried out (Scheme 2). The effects of various reaction parameters, such as solvent, substrate concentration, hydrogen pressure, and substrate/catalyst ratio were investigated. The results are summarized in Table 1.

Hydrogenation of **6a** proceeded under an atmospheric pressure of hydrogen in methanol and dichloromethane (entries 1 and 5) to give the expected product with good enantioselectivities (83.4–90.8% ee). When the substrate concentration was lowered, we had to perform the



6a: R = Ph
6b: R = H

Scheme 2.

Table 1. Asymmetric hydrogenation of α-dehydroaminoacids **6a** and **6b** catalyzed by **7**[a]

Entry	Substrate	S/C ratio	Solvent	Substrate (mol L^{-1})	H_2 (bars)	Time (h)	Conv (%)	ee[b] (%)
1	**6a**	200	MeOH	0.25	1	1	100	83.4
2	**6a**	200	MeOH	0.13	1	1	76.5	88.8
3	**6a**	1000	MeOH	0.13	10	21	100	84.4
4	**6a**	200	Acetone	0.25	1	1	37.2	89.6
5	**6a**	200	CH_2Cl_2	0.25	1	1	100	90.8
6	**6a**	200	AcOEt	0.25	1	1	2	—
7	**6b**	200	MeOH	0.25	1	1	100	83.4
8	**6b**	200	MeOH	0.10	1	1	100	88.1
9	**6b**	200	CH_2Cl_2	0.25	1	1	43.6	90.7
10	**6b**	200	AcOEt	0.25	1	1	14.4	83.6

[a] All reactions were carried out at room temperature.
[b] The ee values were determined by HPLC analysis as described in the literature. All products were in an (*S*)-configuration, based on the comparison with published data.[8]

asymmetric hydrogenation under 10 bars of pressure of hydrogen for 21 h to obtain quantitative conversion (entry 3). Conversely, asymmetric hydrogenation led to low conversion in acetone (37% conversion, 89.6% ee, entry 4) and in ethyl acetate (2% conversion, entry 6).

Hydrogenation of **6b** in methanol led to quantitative conversion and good enantioselectivity. Changing the solvent (entries 9 and 10) provided good levels of enantioselectivity but much lower conversions.

Finally, we carried out the asymmetric hydrogenation, under an atmospheric pressure of hydrogen, in methanol, of dimethyl itaconate. Under these conditions we obtained the expected hydrogenated product in quantitative conversion within an hour in 41.2% ee with an (*S*)-configuration.

3. Conclusion

In conclusion, a new, simple, chiral phosphine–phosphinite ligand has been synthesized and tested for the enantioselective hydrogenation of dehydroamino acids. The results demonstrate that complex **5** is a highly efficient catalyst in asymmetric hydrogenation reactions. Further investigations, especially by modifying the nature of the group next to the phosphine moiety and the nature of the phosphinite part, are currently under investigation within our laboratory and will be reported in due course.

4. Experimental

4.1. General

Optical rotations were measured using a sodium lamp at ambient temperature and specific rotations are reported as follows: $[\alpha]_\lambda$ (*c* g/100 mL) with the units of degree g cm^{-3}. IR spectra were recorded using KBr pellets or NaCl plates, with only partial data reported. NMR spectra were recorded on a Bruker DX 300 spectrometer operating at 300 MHz for proton, 75.4 MHz for carbon and 121.5 MHz for phosphorus. This probe is equipped with pulsed-field (*z*) gradients. Chemical shifts (δ) are expressed in ppm relative to TMS for ^{1}H and ^{13}C nuclei and to H_3PO_4 for ^{31}P nuclei. Data are reported as follows: chemical shift, mulitiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet), coupling constants (Hz), integration.

Solvents were purified by conventional methods prior to use. TLC was performed on Merck 60F-250 silica gel plates and column chromatography over silica gel SI 60 (230–240 mesh). Melting points were taken on a Kofler apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba EA 1100 analyzer.

4.2. 3-(*S*)-Boronatodiphenylphosphanyl-butanol 2

To a cooled (0 °C) solution of **1** (295 mg, 1.03 mmol) in THF (18 mL) was slowly added 1 M borane solution in THF (4.1 mL, 4.1 mmol). The solution was stirred for an hour at room temperature. The mixture was cooled to 0 °C, then water (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were dried over $MgSO_4$. The solvent was removed under vacuum and the residue subjected to column chromatography over SiO_2 with cyclohexane–EtOAc (v/v = 7:3) as an eluent to give the title compound **2** as a white oil: $[\alpha]_D^{20} = +5.0$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz): δ 0.5–0.8 (m, 3H), 1.05 (dd, *J* = 6.9, 16.6 Hz, 3H), 1.4–1.6 (m, 1H), 1.7–1.8 (m, 1H), 1.85 (s, 1H), 2.7–2.9 (m, 1H), 3.5–3.7 (m, 2H), 7.3–7.5 (m, 6H), 7.6–7.8 (m, 4H). ^{13}C NMR (75.5 MHz): δ 12.2 (d, *J* = 1.7 Hz), 25.3 (d, *J* = 37.7 Hz), 32 (d, *J* = 2.85 Hz), 58.7 (d, *J* = 12.6 Hz), 127, 127.4, 127.7, 127.8, 130.1, 130.2, 131.6, 131.7. ^{31}P NMR (121.5 MHz): δ 25.3. Anal. Calcd for $C_{16}H_{22}BOP$: C, 70.59; H, 8.08. Found: C, 70.32; H, 8.21.

4.3. 3-(*S*)-Diphenylphosphanyl-butanol 3

A solution of **2** (665 mg, 3.35 mmol) and DABCO (1.51 g, 13.5 mmol) in freshly distilled toluene (17 mL) was heated at 40 °C for 4 h. The solution was then cooled to room temperature and charged on silica pad (2 cm) and eluted with 20 mL of toluene. Toluene was removed under vacuum and the residue dissolved in dichloromethane (25 mL). The organic phase was washed with 1 M HCl (25 mL). The aqueous phase was then washed with dichloromethane (10 mL). The organic layers were dried over $MgSO_4$. The solvent was removed under vacuum to give the title compound **3** as a yellow oil. $[\alpha]_D^{20} = -2.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz): δ 1.5 (br, 1H), 1.6–1.8 (m, 2H), 2–2.1 (m, 2H), 3.7 (t, *J* = 6.4 Hz, 2H), 7.1–7.5 (m, 10H). ^{13}C NMR (75.5 MHz): δ 21.8 (d, *J* = 13.7 Hz), 31.6 (d, *J* = 13.7 Hz), 32.2 (d, *J* = 11.4 Hz), 59.7 (d, *J* = 10.8 Hz), 127.2–127.6, 132.4–132.7, 136 (d, *J* = 13.7). ^{31}P NMR (121.5 MHz): δ 0.5. Anal. Calcd for $C_{16}H_{19}OP$: C, 74.33; H, 7.35. Found: C, 74.08; H, 7.45.

4.4. 3-(*S*)-Diphenylphosphanyl-1-diphenylphosphinite butane 4

To a cooled (0 °C) solution of **3** (80 mg, 0.31 mmol) and DMAP (6.1 mg, 0.05 mmol) in freshly distilled and degassed THF (6 mL) were added triethylamine (45 μL, 0.32 mmol) and chlorodiphenylphosphine (110 μL, 0.6 mmol). The reaction mixture was stirred for 5 h and the solvent removed under vacuum. Under argon, the residue was diluted with freshly distilled and degassed diethyl ether (5 mL). The solution was charged on an alumina pad [previously dried under vacuum (200 °C)] and eluted with 20 mL of diethyl ether. The ether solvent was removed under vacuum to give the title compound **4** as a colorless oil: $[\alpha]_D^{20} = +4.5$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz): δ 1 (dd, *J* = 6.9, 15 Hz, 3H), 1.4–1.6 (m, 1H), 1.9–2.1 (m, 1H), 2.5–2.7 (m, 1H), 3.9–4.1 (m, 2H), 7.2–7.7 (m, 20H). ^{13}C NMR (75.5 MHz): δ 16.3 (d, *J* = 16.4 Hz), 26.5 (d, *J* = 9.6 Hz), 35.3 (dd, *J* = 7.3, 16.9 Hz), 68.2 (dd, *J* = 12.8, 19.2 Hz), 128–131, 134, 137, 142. ^{31}P NMR (121.5 MHz): δ 0.3, 114.0. HRMS (EI) calcd for $C_{28}H_{28}O_2P$ 442.1615. Found 442.1619.

4.5. Rhodium complex 5

Under an argon atmosphere, an oven-dried Schlenk tube containing a magnetic stirrer bar was charged with phosphine–phosphinite **4** (119.3 mg, 0.27 mmol) in freshly degassed methanol (6 mL). $[Rh(COD)Cl]_2$ (64.4 mg, 0.13 mmol) was then added and the solution stirred for an hour at room temperature. A solution of $NaBF_4$ (60 mg, 0.54 mmol) in freshly degassed methanol (4 mL) was then added via a syringe pump over a 2 h period. At the end of the addition, the solution was stirred for a further hour. The solvents were removed under vacuum. Freshly distilled diethyl ether (15 mL) was then added to the residue and the mixture filtered off. The residue was then washed with chloroform and filtered to remove salts. Chloroform was then removed under vacuum to give the title rhodium complex as dark red crystals. Yield: 96%. ^{13}C NMR (75.5 MHz): δ 12.3, 17.8, 26.6, 29.2, 29.5, 64.3, 126–131. ^{31}P NMR (121.5 MHz): δ 19.3 (dd, $J = 38.6$, 149.1 Hz), 136.1 (dd, $J = 38.6$, 169.8 Hz).

Acknowledgements

We warmly thank Solvias laboratories for their interest in this research.

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