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Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by Phosphinamides Prepared From L-Serine

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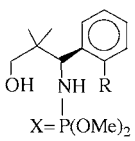
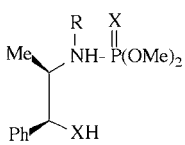
ABSTRACT: *Synthesis of several new chiral phosphinamide catalysts with a proximal hydroxyl group from L-serine was described. These compounds have been successfully used in the asymmetric catalytic borane reduction of prochiral ketones. The optically active secondary alcohols were obtained with an enantiomeric excess (ee) up to 81% and excellent yields.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:288–291, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10145

INTRODUCTION

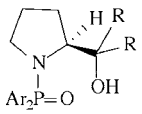
The enantioselective reduction of prochiral ketones is an important reaction for the synthesis of optically active secondary alcohols [1]. A catalytic enantioselective borane reduction using oxazaborolidine prepared from chiral amino alcohols is one of the most efficient methods [2] which give excellent enantiomeric excess (ee) values and often have wide substrate scope. Other catalysts such as chiral sulfur reagents [3,4] and chiral phosphorus reagents [5] were also used in this reaction. In recent years, many excellent results were achieved using chiral phosphorus reagents as catalysts. According to their structure, they can be devided in two types. One is chiral oxazaphospholidine borane complexes [6] and the other is chiral phosphinamides containing an N—P=O unit [7]. Several research groups' work proved that introduction of a proximal hydroxyl group in the phosphinamides was beneficial to enantioselectivity. For instance, the asymmetric catalytic reduction of prochiral ketones in presence of chiral phosphinamide catalysts **1–3** reported by Kellogg [4] and Wills [8,9], provided the optically active alcohols with good yields and moderate to excellent ee.



1 X=O, S
R=H, Cl



2 X=O, S
R=H, Me



3 R=H, Ph
Ar=Ph, p-MeOC$_6$H$_4$

In this paper, we report the preparation of several new chiral phosphinamide catalysts with a proximal hydroxyl group and their application to the asymmetric borane reduction of prochiral ketones.

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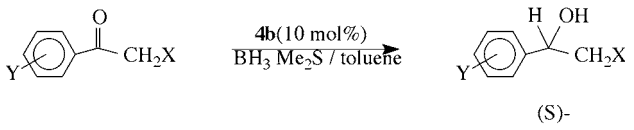
The chiral phosphinamides **4** could be prepared by the process described in Scheme 1. The hydroxyl group in L-serine methyl ester hydrochloride **5** was protected with triphenylmethyl chloride in CH_2Cl_2 after the N-phosphinylation by diphenylphosphinic chloride in presence of Et_3N in a one-pot reaction. Compound **6** was obtained with 64% yield over two steps. Then compound **6** reacted with Grignard reagent in dry THF which gave the target products **4** with 78–90% yield. These compounds were fully stable to the reaction conditions and could be recovered and reused after the reduction reaction.

Firstly, the application of **4b** for the synthesis of a range of optically active alcohols through the reduction of ketones was examined. The reaction was carried out in dry toluene using $BH_3{\cdot}Me_2S$ as reducing agent in presence of 10 mol% of catalyst **4b** (see Scheme 2). The major configuration of the obtained secondary alcohols was S determined by comparison with the specific rotation. The results were summarized in Table 1.

As shown in Table 1, we found that temperature had no signiciant effect on the reduction reaction. Carrying out the reaction at 30–40°C seemed to give a little higher enantioselectivity in the reduction of acetophenone. However, low temperature was beneficial to ee when α-chloroacetophenone was used as the substrate. This finding was contrary to Wills' observation, which revealed that reduction of ketones in toluene with catalyst **3** at 110°C gave the best asymmetric inductions [8,9].

In Table 2, the structure effect of the catalyst **4** on the asymmetric borane reduction of prochiral ketones was shown. It revealed that the electron density of the quarternary carbon binding the hydroxyl group has a dramatic influence on the enantioselectivity. When R in catalyst **4** was an alkyl group (R = Et, **4d**), poor enantioselectivity was obtained. It was much higher when R was an aromatic group (**4a–c**). In this case, the mature of the substituent attached on the benzene ring also had a marked effect on the enantioselectivity. The electron-withdrawing substituted catalyst **4a** (R = *p*-F-C_6H_4) had a better



SCHEME 2

catalytic activity than the electron-donating substituted catalyst **4c** (R = *p*-Me-C_6H_4). The catalytic ability of unsubstituted catalyst **4b** (R = C_6H_5) was in between. These observations implied that increasing the electron-withdrawing ability of R improved the enantioselectivity. These findings provided useful informations not only for the design of the chiral phosphinamide catalysts with a proximal hydroxyl group but also interpreting the catalytic mechanism.

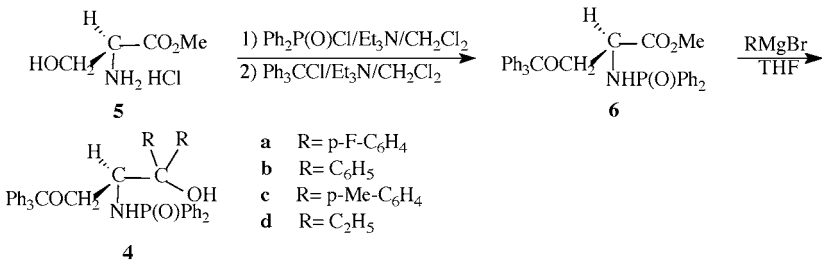
In conclusion, we have demonstrated that phosphinamides prepared from L-serine were capable of the asymmetric reduction of ketones by borane in high yields and selectivity (ee 81%). The effect of the electron characteristic of the substituent R on the catalytic activity was also discussed. Further investigation of the catalytic activity and the optimal conditions are still in progress and our findings will be reported in due course.

EXPERIMENTAL

^1H and ^{31}P NMR were recorded in $CDCl_3$ as solvent on FX-900Q and AC-P200 instruments using TMS as an internal standard for ^1H NMR, 85% H_3PO_4 as external standard for ^{31}P NMR. Elemental analyses were conducted on MF-3 automatic analyzer. Specific rotations were measured by a Perkin Elmer 241MC polarimeter.

Preparation of Compound **6**

To a premixed solution of 40-ml CH_2Cl_2, 3.03 g (30 mmol) Et_3N, and 1.09 g (7 mmol) L-Serine methyl ester hydrochloride, 1.66 g (7 mmol) diphenylphosphinic chloride in 10-ml CH_2Cl_2 was added dropwise at 0–5°C. After the addition, the reaction mixture was



SCHEME 1

TABLE 1 Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by Chiral Phosphinamide Catalyst **4b**

X	*Y*	*Temperature (°C)*	*Yield[a] (%)*	*ee[b] (%)*
H	H	−20–rt	92	41
H	H	30–40	83	51
H	H	60–70	92	42
H	H	Reflux	92	39
Cl	H	0–rt	83	78
Cl	H	−20–rt	92	78
Cl	H	30–40	97	63

[a]Isolated yield.
[b]Determined by HPLC using a Chiracel OD column using hexane/*i*-PrOH as eluent.

warmed to room temperature and stirred overnight. Then 1.95 g (7 mmol) triphenylmethyl chloride in 10-ml CH_2Cl_2 was added. After refluxing for 8 h, the content was cooled to room temperature, washed with water and saturated brine. The organic phase was dried over with anhydrous Na_2SO_4. Removing the solvent gave the crude product which was purified by column chromatography (200–300 mesh, petroleum ether/EtOAc (1:2) as eluent). The product **6** was obtained as a white solid. Yield 64%; m.p. 125–127°C; $[\alpha]_D^{25} = -11.7$ (*c* 1, CH_2Cl_2); ^{31}P NMR 25.20 ppm (s), ^{1}H NMR 3.35 (d, H, CH_2, $^2J_{HH} = 2.21$ Hz, $^3J_{HH} = 8.10$ Hz), 3.50 (d, H, CH_2, $^2J_{HH} = 2.20$ Hz, $^3J_{HH} = 8.10$ Hz), 3.74 (s, 3H, CH_3), 3.82 (t, 1H, CH, $^3J_{HH} = 8.20$), 4.10 (s, 1H, NH), 7.24–7.95 (m, 25H, Ar H). $C_{35}H_{32}NO_4P$ Required: C 74.85, H 5.74, N 2.49. Found: C 74.60, H 5.72, N 2.50.

Preparation of Catalyst **4**

4a: To a 30-ml *p*-FC_6H_4MgBr solution prepared from 0.29 g (12 mmol) Mg and 0.92 g (6 mmol) *p*-FC_6H_4Br in situ by the routine procedure, a mixture of 0.30 g (0.53 mmol) **6** and 10-ml THF was added dropwise at room temperature. After the reaction was complete (monitored by TLC), 2-ml saturated NH_4Cl solution was added slowly to destroy the excess *p*-FC_6H_4MgBr. The insoluble material was filtered and the solution was dried with anhydrous $MgSO_4$. Removing the solvent in vacuum gave the crude product which was purified by column chromatography (200–300 mesh, petroleum ether/EtOAc (1:2) as eluent). A total of 0.3 g **4a** was obtained as a white solid. Yield 78.9%; m.p. 176–178°C; $[\alpha]_D^{25} = +35.0$ (*c* 3.0, $CHCl_3$); ^{31}P NMR 23.99 ppm, ^{1}H NMR 3.39 (d, H, CH_2, $^2J_{HH} = 2.28$ Hz, $^3J_{HH} = 9.20$ Hz), 3.41 (d, H, CH_2, $^2J_{HH} = 2.30$ Hz, $^3J_{HH} = 9.20$ Hz), 3.85 (t, 1H, CH, $^3J_{HH} = 8.90$ Hz), 4.10 (s, H, NH), 5.20 (s, 1H, OH), 6.90–7.67 (m, 33, Ar H). $C_{46}H_{38}F_2NO_3P$ Required: C 76.55, H 5.31, N 1.94. Found: C 76.63, H 5.39, N 1.93.

4b was prepared according to the above method for **4a**, using 0.56 g (1 mmol) **6** and C_6H_5MgBr. A total of 0.59 g **4b** was isolated as a white solid. Yield 86.0%; m.p. 183–185°C; $[\alpha]_D^{25} = +31.1$ (*c* 0.9, CH_2Cl_2); ^{31}P NMR 23.22 ppm, ^{1}H NMR 3.47 (d, H, CH_2, $^2J_{HH} = 2.29$ Hz, $^3J_{HH} = 9.20$ Hz), 3.52 (d, H, CH_2, $^2J_{HH} = 2.30$ Hz, $^2J_{HH} = 9.20$ Hz), 4.07 (t, 1H, CH, $^3J_{HH} = 8.90$ Hz), 4.27 (s, 1H, NH), 5.44 (s, 1H, OH), 7.24–7.76 (m, 35, Ar H). $C_{46}H_{40}NO_3P$ Required: C 80.56, H 5.88, N 2.04. Found: C 80.62, H 5.89, N 1.97.

4c was prepared according to the above method for **4a**, using 0.30 g (0.53 mmol) **6** and *p*-Me-C_6H_4MgBr. The product **4c** (0.29 g) was isolated as a white solid. Yield 78.4%. m.p. 109–111°C; $[\alpha]_D^{25} = +39.5$ (*c* 1.9, $CHCl_3$); ^{31}P NMR 23.35 ppm, ^{1}H NMR 2.25–2.36 (m, 6H, $2CH_3$), 3.39 (d, 1H, CH_2, $^2J_{HH} = 2.30$ Hz, $^3J_{HH} = 9.38$ Hz), 3.43 (d, 1H, CH_2, $^2J_{HH} = 2.31$ Hz, $^3J_{HH} = 9.38$ Hz), 4.07 (t, 1H, CH, $^3J_{HH} = 8.90$ Hz), 4.10 (s, H, NH), 4.14 (s, 1H, OH), 6.90–7.67 (m, 33, Ar H). $C_{48}H_{44}NO_3P$ Required: C 80.19, H 6.21, N 1.96. Found: C 79.99, H 6.24, N 1.69.

4d was prepared according to the above method for **4a**, using 0.40 g (0.7 mmol) **6** and EtMgBr. The product **4d** (0.37 g) was isolated as a viscous. Yield 90.0%; $[\alpha]_D^{25} = +6.0$ (*c* 3.0, $CHCl_3$); ^{31}P NMR 23.72 ppm, ^{1}H NMR 0.55–0.70 (m, 6H, $2CH_3$), 1.24–1.39 (m, 4H, $2CH_2$), 3.14 (d, 2H, CH_2, $^2J_{HH} = 2.25$ Hz, $^3J_{HH} = 8.24$ Hz), 3.18 (d, 2H, CH_2, $^2J_{HH} = 2.24$ Hz, $^3J_{HH} = 8.24$ Hz), 3.72 (t, 1H, CH, $^3J_{HH} = 8.31$ Hz), 4.10 (s, H, NH), 5.20 (s, 1H, OH), 7.23–7.95 (m, 25, Ar H). $C_{38}H_{40}NO_3P$ Required: C 77.40, H 6.84, N 2.38. Found: C 77.23, H 7.05, N 2.18.

TABLE 2 Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by Chiral Phosphinamide Catalysts **4a–d**

4	*X*	*Y*	*Temperature (°C)*	*Yield[a] (%)*	*ee[b] (%)*
a	H	H	−20–rt	92	55
b	H	H	−20–rt	92	41
c	H	H	−20–rt	97	31
d	H	H	−20–rt	75	0
a	Cl	H	−20–rt	83	81
b	Cl	H	−20–rt	91	78
c	Cl	H	−20–rt	97	63
d	Cl	H	−20–rt	77	7
a	H	2-Cl	30–40	93	45
b	H	2-Cl	30–40	92	36
c	H	2-Cl	30–40	92	22

[a]Isolated yield.
[b]Determined by HPLC using a Chiracel OD column using hexane/*i*-PrOH as eluent.

General Procedure for the Reduction of Prochiral Ketones

The catalyst **4** (10% mmol) was dissolved in 2-ml dry toluene, and then borane-methyl sulfide (2 M

in THF, 1.2 mmol) was added under nitrogen atmosphere. After stirred for 30 min, the prochiral ketone (1 mmol) in 4-ml toluene was added dropwise for 30 min. The reaction mixture was stirred at required temperature until the ketone disappeared (monitored by TLC). Ten milliliter saturated NH_4Cl solution was added and the water phase was extracted twice with CH_2Cl_2. The combined organic layer was washed with water and saturated NaCl solution, dried over with anhydrous $MgSO_4$. The resulting chiral secondary alcohol and chiral catalyst were separated by column chromatography (200–300 mesh, petroleum ether/EtOAc (5:1) as eluent). The ee values of the purified chiral secondary alcohols were determined by HPLC or GC with chiral column. The recovered catalysts could be reused with no loss of catalytic activity.

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