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Asymmetric carbonyl reduction with borane catalyzed by chiral phosphinamides derived from L-amino acid

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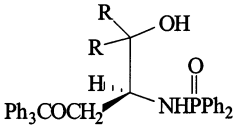
Abstract—Two types of chiral phosphinamide catalysts **3a–d** and **4a–c** were prepared from L-phenylalanine and L-proline, respectively. Their applications in the asymmetric borane reduction of prochiral ketones were investigated. The chiral secondary alcohols were obtained with excellent chemical yields and moderate to high enantiomeric excesses.

1. Introduction

The reduction of ketones to enantiomerically enriched alcohols is a pivotal transformation in synthetic organic chemistry.[1] Many asymmetric catalysts have been developed for borane reductions of prochiral ketones, most significantly the oxazaborolidines[2] prepared from chiral amino alcohols, which give excellent ee values and often have wide substrate scope. Chiral sulfur reagents[3,4i] and chiral phosphorous reagents[4] have also been used in this reaction. In recent years, great progress has been achieved using chiral phosphorous reagents as catalysts for the reduction of prochiral ketones. In general, according to the structure, they can be divided into two types—chiral oxazaphospholidine borane complexes[4j] and chiral phosphinamides containing an N–P=O unit.[4a] The structure of chiral phosphinamides (reported earlier) is very simple and their catalytic activities are not good.[4c,d] Several research groups[4i,k,l] have since proved that the introduction of a proximal hydroxyl group in the phosphinamides leads to higher enantioselectivity. Recently, we have prepared chiral phosphinamides **1** and **2** from L-serine and studied their application in the asymmetric borane reduction of prochiral ketones.[5] It was also found that the R group had a dramatic influence on the enantioselectivity of the reduction.



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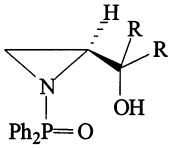

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In the study reported herein, we synthesized two types of chiral phosphinamide catalysts **3a–d** and **4a–c** from L-phenylalanine and L-proline, respectively, and examined their catalytic activities in the asymmetric borane reduction of ketones.

2. Results and discussion

Compounds **3a–d** were relatively easy to prepare through the reaction of L-phenylalanine methyl ester hydrochloride with diphenylphosphinyl chloride in the presence of triethylamine, followed by nucleophilic addition of Grignard reagent. The products **3a–d** were conveniently separated with yields of 66–79% (Scheme 1).

Firstly, the application of catalyst **3a–d** to the reduction of acetophenone was investigated. The *S*-isomer of 1-phenylethanol formed preferentially. The results are summarized in Table 1.

As shown in Table 1, we found that on increasing the amount of the catalyst from 1 to 10 mol%, the

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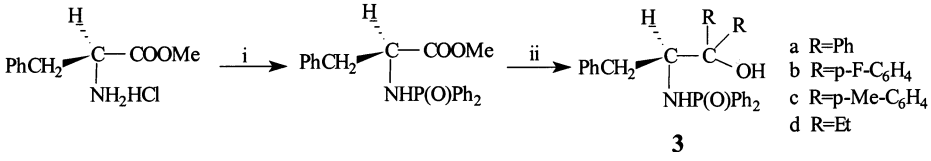
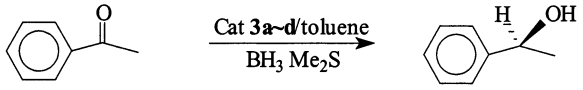


Scheme 1. *Reagents and conditions*: (i) Et_3N, CH_2Cl_2, $Ph_2P(O)Cl$, rt; (ii) RMgBr, THF, rt.

Table 1. Asymmetric borane reduction of acetophenone catalyzed by **3a–d**



3 (mol%)	Temp. (°C)	Yield (%)[a]	$[\alpha]_D$	ee%[b] (ee%[c])
3a (1)	30–40	92	−13.6	30
3a (5)	30–40	83	−25.3	54 (52)
3a (10)	30–40	98	−33.0	73 (71)
3a (15)	30–40	83	−33.6	73 (71)
3a (10)	0–rt	78	−8.6	19
3a (10)	Reflux	93	−11.3	25
3b (10)	30–40	92	–	(83)
3c (10)	30–40	83	−22.5	48
3d (10)	30–40	100	0	0

[a] Isolated yield.
[b] Determined by specific rotation, for (*S*)-1-phenylethanol $[\alpha]_D^{20} = -45.5$ (*c* 2.0, MeOH).[4d]
[c] Determined by chiral HPLC.

enantioselectivity of the reactions improved. However, no obvious change in enantioselectivity was observed when the loading of **3a** was increased to 15 mol%. On the other hand, temperature also had a significant effect on the reaction. The best result (73% ee) was obtained at 30–40°C. Neither higher (reflux) nor lower temperature (0°C), however, was beneficial to the catalytic activities. These results revealed that the best enantioselectivity was obtained at 30–40°C in the presence of 10 mol% **3a**. Moreover, the results suggest that the nature of catalyst **3** has a dramatic influence on the catalytic activity. For example, the use of catalyst **3a** which had no substituent on the benzene ring led to moderate enantioselectivity (73% ee). The enantioselectivity was increased greatly (83% ee) with catalyst **3b**, which bears a strongly electron-withdrawing substituent at the *para*-position of the benzene ring. However, the ee value decreased markedly (48% ee) when an electron-donor substituent was present (catalyst **3c**). It should be noted that nearly no asymmetric induction was observed with **3d**. These results demonstrated that increasing the electron-withdrawing ability of the R group in the catalyst **3** was beneficial for the improvement of the enantioselectivity.

The reduction of a series of ketones was then examined using 10 mol% **3a–d** at 30–40°C. The results are summarized in Table 2.

Under the above optimized conditions, reduction of 2-chloroacetophenone with **3a** gave 83% ee (entry 2). Lower temperature had no obvious effect on the selectivity (82% ee, entry 1). But at higher temperature the level of asymmetric induction decreased. For instance, 70% (entry 3) and 33% (entry 4) enantiomeric excess was obtained at 60–70°C and reflux temperature, respectively. No obvious change was detected when **3b** was used under the same conditions (entry 5), while the enantioselectivity decreased greatly in the presence of **3c** and **3d** (entries 6 and 7). This trend is similar to that seen in the reduction of acetophenone.

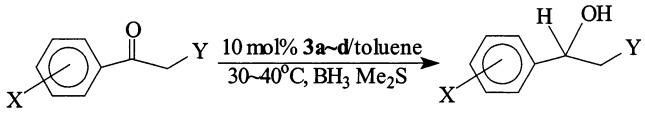
The data listed in Table 2 also shows that when the substituted acetophenone was employed, the secondary alcohols were produced in high yields but with decreased enantiomeric excesses (entries 8–17).

In summary, as far as the acyclic chiral phosphonamide catalyst **3** was concerned, only moderate to high enantiomeric excesses were obtained in the asymmetric borane reduction of prochiral ketones.

Our study was then extended to the preparation of the cyclic chiral phosphonamides **4a–c**, which could be easily obtained from L-proline as shown in Scheme 2. The application of **4a–c** in the asymmetric borane reduction of a range of prochiral ketones was also investigated. The reaction was carried out in refluxing toluene with 10 mol% **4**. In all cases, the reaction was complete in several minutes. The optically active secondary alcohols were isolated in excellent chemical yields and moderate to high enantiomeric excess. Moreover, the catalysts could be recycled and reused without loss of catalytic activity. The experimental results are summarized in Table 3.

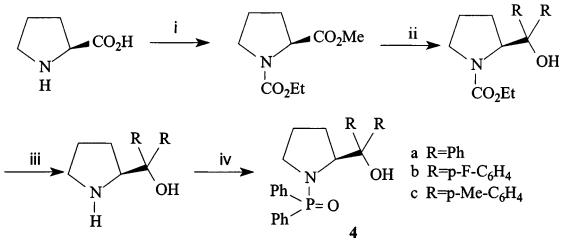
As the results show, the nature of the substrates and the catalysts were found to influence the level of asymmetric induction greatly. Among the five substrates listed in Table 3, only moderate ee values have been encountered in the reduction of acetophenone (entries 1–3), 2-chloroacetophenone (entries 4–6) and 4-methylacetophenone (entries 7–9) except for α-chloroacetophenone and 4-methoxyacetophenone. Wills[4l] reported that reduction of α-chloroacetophenone catalyzed by **4a** gave 2-chloro-1-phenylethanol with 84% ee. The same result was obtained in our research (entry 10). However, to our surprise, the introduction of a methyl group (**4c**) or fluorine (**4b**) at the *para*-position of the benzene ring in catalyst **4a** led to a marked increase in the stereoselectivity. Under the same conditions, α-chlorophenylethanol was obtained in 92% ee (entry 11) and 93% ee (entry 14) when **4b** and **4c** were used,

Table 2. Asymmetric borane reduction of prochiral ketones catalyzed by **3a–d**



Entry	X	Y	Cat.	Yield (%)[a]	$[\alpha]_D$	ee%[e] (ee%[f])
1[b]	H	Cl	**3a**	92	−40.9	82 (82)
2	H	Cl	**3a**	95	−38.6	80 (83)
3[c]	H	Cl	**3a**	100	−32.7	70 (67)
4[d]	H	Cl	**3a**	92	−15.7	33
5	H	Cl	**3b**	100	–	(82)
6	H	Cl	**3c**	97	−21.7	46
7	H	Cl	**3d**	89	−6.2	7
8	*o*-Cl	H	**3a**	93	−27.3	42 (41)
9	*o*-Cl	H	**3b**	100	−15.8	24 (27)
10	*o*-Cl	H	**3c**	89	−22.0	34
11	*o*-Br	H	**3a**	94	−15.7	24 (23)
12	*o*-Br	H	**3b**	88	−25.0	43
13	*p*-MeO	H	**3a**	100	−12.8	40
14	*p*-MeO	H	**3b**	93	/	37 (37)
15	*p*-MeO	H	**3c**	100	−15.0	46
16	*p*-NO_2	H	**3a**	91	−13.9	38
17	2,3,4-Cl_3	H	**3a**	91	−18.2	35

[a] Isolated yield.
[b] 0°C–rt.
[c] 60–70°C.
[d] Reflux.
[e] Determined by specific rotation, for (*R*)-2-chloro-1-phenylethanol $[\alpha]_D^{20}=+47$ (*c* 1.84, cyclohexane),[6] for (*R*)-1-(2-chlorophenyl)ethanol $[\alpha]_D^{20}=+65.7$ (*c* 0.625, $CHCl_3$),[7] for (*R*)-1-(2-bromophenyl)ethanol $[\alpha]_D^{20}=+58.8$ (*c* 0.57, CH_2Cl_2),[8] for (*R*)-1-(4-methoxyphenyl)ethanol $[\alpha]_D^{20}=+32.3$ (*c* 2.0, $CHCl_3$).[9]
[f] Determined by chiral HPLC.



Scheme 2. *Reagents and conditions*: (i) $ClCO_2Et/K_2CO_3$, MeOH, rt; (ii) RMgBr, THF, rt; (iii) KOH, MeOH, reflux; (iv) $Ph_2P(O)Cl$, Et_3N, CH_2Cl_2.

respectively. Moreover, an ee of 94% was obtained when the amount of **4b** was reduced to 5 mol% (entry 12). It is interesting that an ee of 81% was obtained even when only 1 mol% **4b** was used (entry 13). When 4-methoxyacetophenone was employed as the substrate, a similar *para*-substitution effect was observed. For instance, compared with **4a**, the use of **4b** and **4c** afforded 1-(4-methoxyphenyl)ethanol with high enantiomeric excess of up to 90% (entry 17). Nevertheless, reduction of the other substrates catalyzed by **4a–c** did not follow the rule.

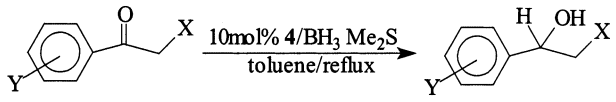
In conclusion, acyclic chiral phosphinamide **3** and cyclic phosphinimide **4** were prepared from L-phenylalanine and L-proline, respectively. Moderate to high enantiomeric excesses and excellent yields were obtained in the asymmetric borane reduction of prochiral ketones catalyzed by **3** or **4**. In general, the cyclic phosphinamide **4** demonstrated better enantioselectivity than the acyclic phosphinamide **3**. The catalytic ability was improved especially when the *para*-position of the R group in catalyst **4** was substituted. These findings will provide very useful information for the design of new types of catalysts and further interpretation of the catalytic mechanism.

3. Experimental

3.1. General

^1H and ^{31}P NMR were recorded in $CDCl_3$ as a solvent on an AC-P200 instrument using TMS as an internal standard for ^1H NMR or 85% H_3PO_4 as an external standard for ^{31}P NMR. Elemental analyses were conducted on a MF-3 automatic analyzer. Melting points were determined on a MP-500 melting point apparatus. Specific rotations were measured by a Perkin Elmer 241MC polarimeter. All temperatures were uncorrected.

Table 3. Asymmetric borane reduction of prochiral ketones catalyzed by **4a–c**



Entry	Y	X	Cat.	Yield (%)[a]	e.e%[b]
1	H	H	**4a**	92	65
2	H	H	**4b**	92	65
3	H	H	**4c**	92	63
4	*o*-Cl	H	**4a**	96	71
5	*o*-Cl	H	**4b**	92	71
6	*o*-Cl	H	**4c**	90	69
7	*p*-Me	H	**4a**	92	63
8	*p*-Me	H	**4b**	93	58
9	*p*-Me	H	**4c**	89	71
10	H	Cl	**4a**	97	84
11	H	Cl	**4b**	96	92
12[c]	H	Cl	**4b**	93	94
13[d]	H	Cl	**4b**	90	81
14	H	Cl	**4c**	91	93
15	*p*-MeO	H	**4a**	96	83
16	*p*-MeO	H	**4b**	97	88
17	*p*-MeO	H	**4c**	95	90

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] 5 mol% **4b** was used.
[d] 1 mol% **4b** was used. In all cases the major configuration of the product is *R*.

3.2. (*S*)-*N*-Diphenylphosphinyl-phenylalanine methyl ester

Triethylamine (2.02 g, 20 mmol) was added to a solution of L-phenylalanine methyl ester hydrochloride (1.94 g, 9 mmol) in CH_2Cl_2 (40 ml) at room temperature. The resulting mixture was stirred for 30 min and a solution of diphenylphosphinyl chloride (2.13 g, 9 mmol) in CH_2Cl_2 (10 ml) was added dropwise. After being stirred overnight the reaction mixture was washed successively with water and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent the crude product was purified by recrystallization from petroleum ether and ethyl acetate (1/8) to afford 2.43 g of product as a white solid. Yield 71%, mp 155–157°C, $[\alpha]_D^{20}$ +16.0 (*c* 1.0, CH_2Cl_2). ^{31}P NMR 23.7 ppm (s), ^{1}H NMR 3.09 (d, 2H, CH_2, $J=5.84$ Hz), 3.65 (s, 3H, CH_3), 4.05 (m, 2H, CH), 7.15–7.81 (m, 15H, Ph-H). Anal. calcd for $C_{22}H_{22}NO_3P$: C, 69.65; H, 5.84; N, 3.69. Found: C, 69.60; H, 5.89; N, 3.64%.

3.3. Typical procedure for the preparation of 3

To a solution of 4-methylphenylmagnesium bromide in THF (20 ml), prepared from 4-bromotoluene (3.42 g, 20 mmol) and magnesium (0.96 g, 40 mmol) was added (*S*)-*N*-diphenylphosphinyl-phenylalanine methyl ester (0.75 g, 2 mmol) in 10 ml THF at 30°C. After the addition the reaction mixture was stirred at room temperature for several hours (monitored by TLC). The solution was filtered and the excess 4-methylphenylmagnesium bromide was destroyed by adding a saturated NH_4Cl solution (10 ml) under ice bath cooling. After stirred for 30 min the suspension was filtered and the filtrate was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (3×15 ml). The organic phase was dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude product. Recrystallization from petroleum ether and ethyl acetate (1/5) gave the pure product **3c**.

3.3.1. (2*S*)-1,1-Di(4-methylphenyl)-2-(*N*-diphenylphosphinyl)amino-3-phenyl-1-propanol, 3c. White solid, yield 76%, mp 218–220°C, $[\alpha]_D^{20}$ −22.5 (*c* 0.4, $CHCl_3$). ^{31}P NMR 27.2 ppm (s), ^{1}H NMR 2.30 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.53, 3.10 (ABX, 2H, CH_2, $J=14.60$, 9.38 Hz), 3.63 (bs, 2H, NH, OH), 4.09–4.15 (m, 1H, CH), 6.99–7.51 (m, 23H, Ph-H). Anal. calcd for $C_{35}H_{34}NO_2P$: C, 79.07; H, 6.45; N, 2.63. Found: C, 78.92; H, 6.41; N, 2.52%.

3.3.2. (2*S*)-1,1,3-Triphenyl-2-(*N*-diphenylphosphinyl)-amino-1-propanol, 3a. White solid, yield 69%, mp 223–225°C, $[\alpha]_D^{20}$ −31.1 (*c* 1.0, $CHCl_3$). ^{31}P NMR 27.4 ppm (s), ^{1}H NMR 2.54, 3.10 (ABX, 2H, CH_2, $J=14.62$, 10.20 Hz), 3.80 (bs, 2H, NH, OH), 4.09–4.16 (m, 1H, CH), 7.12–7.66 (m, 25H, Ph-H). Anal. calcd for $C_{35}H_{34}NO_2P$: C, 79.07; H, 6.45; N, 2.63. Found: C, 78.92; H, 6.41; N, 2.52%.

3.3.3. (2*S*)-1,1-Di(4-fluorophenyl)-2-(*N*-diphenylphosphinyl)amino-3-phenyl-1-propanol, 3b. White solid, yield 79%, mp 233–236°C, $[\alpha]_D^{20}$ −28.7 (*c* 1.0, $CHCl_3$). ^{31}P NMR 27.3 ppm (s), ^{1}H NMR 2.89, 3.98 (ABX, 2H, CH_2, $J=14.58$, 10.31 Hz), 3.70 (bs, 2H, NH, OH), 4.09–4.16 (m, 1H, CH), 7.12–7.66 (m, 25H, Ph-H). EI/MS 521 (M^+-H_2O), HRMS (FAB) for (M^+-H_2O): 521.17201. Found: 521.17236.

3.3.4. (2*S*)-3-Ethyl-2-(*N*-diphenylphosphinylamino)-1-phenyl-3-pentanol 3d. White solid, yield 66%, mp 147–149°C, $[\alpha]_D^{20}$ −69.5 (*c* 1.0, CH_2Cl_2). ^{31}P NMR 25.02 ppm (s), ^{1}H NMR 0.84 (t, 3H, CH_3, $J=7.34$ Hz), 0.97 (t, 3H, CH_3, $J_{H-H}=7.34$ Hz), 1.22–1.85 (m, 4H, 2 CH_2), 2.31 (t, 1H, CH, $J=12.52$ Hz), 2.72 (bs, 1H, OH), 2.94, 4.10 (ABX, 2H, CH_2, $J=11.48$, 12.52 Hz), 3.16 (bs, 1H, NH), 7.01–7.67 (m, 15H, Ph-H). Anal. calcd for $C_{25}H_{30}NO_2P$: C, 73.69; H, 7.42; N, 3.44. Found: C, 73.66; H, 7.51; N, 3.55%.

3.4. *N*-Ethoxycarbonyl-L-proline methyl ester

To a 250 ml 3-neck flask were added L-proline (11.5 g, 0.1 mol), anhydrous K_2CO_3 (17.2 g, 0.13 mol) and anhydrous MeOH (200 ml). And then ethyl chloroformate (23.9 g, 0.22 mol) was added dropwise at room temperature. The mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was treated with 100 ml water and extracted with 4×60 ml $CHCl_3$. The combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product as a light yellow oil which was not further purified and directly used in the following procedure. Yield 94.5%, $[\alpha]_D^{25}=-60.3$ (*c* 1.26, $CHCl_3$).

3.5. Typical procedure for the preparation of *N*-ethoxycarbonyl-(*S*)-2-(diarylhydroxymethyl)pyrrolidines

To a solution of PhMgBr prepared from bromobenzene (23.55 g, 0.15 mol), Mg (0.8 g, 0.45 mol) and THF (200 ml) was added a mixture of *N*-ethoxycarbonyl-L-proline methyl ester (5.0 g, 0.025 mol) in THF (30 mL) under ice bath cooling. After the addition, the ice bath was removed and the reaction mixture was stirred overnight at room temperature. The insoluble solid was filtered and a saturated NH_4Cl solution (20 ml) was added slowly to the filtrate under ice cold to destroy the excess PhMgBr. After stirring for 30 min, the mixture was filtrated and the filtrate was evaporated under reduced pressure. The residue was treated with water (20 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent gave the crude product as a light yellow oil, yield 93%, which was not purified further but used directly in the following procedure.

3.6. Typical procedure for the preparation of (*S*)-2-(diarylhydroxymethyl) pyrrolidines

To a mixture of *N*-ethoxycarbonyl-(*S*)-2-(diphenylhydroxymethyl)pyrrolidine (7.50 g) and MeOH (100 ml) was added solid KOH (15.0 g). After heating under reflux for 4 h, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was treated with water (100 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/EtOAc as eluent).

3.6.1. (2*S*)-2-(Diphenylhydroxymethyl)pyrrolidine (R = C_6H_5). White solid, yield 68.1%, mp 73–75°C, $[\alpha]_D^{20}$ −57.2 (*c* 2.0, MeOH). Ref. 10, mp 76.5–77.5°C.

3.6.2. (2*S*)-2-[Di-(4-fluorophenyl)hydroxymethyl]pyrrolidine (R = p-F-C_6H_4). White solid, yield 67.7%, mp 68–70°C, $[\alpha]_D^{20}$ −57.0 (*c* 0.73, CH_2Cl_2), 1.42–1.91 (m, 4H, β-CH_2, γ-CH_2), 2.80–3.05 (m, 2H, δ-CH_2), 3.20 (bs, 2H, NH, OH), 4.45–4.50 (m, 1H, α-CH), 6.89–7.61 (m, 8H, Ph-H). Anal. calcd for $C_{17}H_{17}F_2NO$: C, 70.57; H, 5.92; N, 4.84. Found: C, 70.46; H, 6.11; N, 4.77%.

3.6.3. (2*S*)-2-[Di-(4-methylphenyl)hydroxymethyl]pyrrolidine (R = 4-Me-C_6H_4). White solid, yield 65.4%, mp 93–94°C, $[\alpha]_D^{20}$ −58.0 (*c* 1.0, $CHCl_3$). ^1H NMR 1.30–1.55 (m, 4H, β-CH_2, γ-CH_2), 2.14 (s, 6H, $2CH_3$), 2.80–2.90 (m, 2H, δ-CH_2), 3.20 (bs, 2H, NH, OH), 4.08–4.10 (m, 1H, α-CH), 6.92–7.34 (m, 8H, Ph-H). Anal. calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.89; H, 8.50; N, 4.77%.

3.7. Typical procedure for the preparation of 4a–c

To a mixture of (2*S*)-2-(diarylhydroxymethyl)-pyrrolidine (3 mmol), Et_3N (4 mmol, 0.40 g) and CH_2Cl_2 (15 mL) was added a solution of $Ph_2P(O)Cl$ (3.2 mmol, 0.76 g) in CH_2Cl_2 (5 ml) under ice-salt cooling. After the addition, the reaction mixture was stirred overnight. The solution was washed with water, saturated NaCl solution and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product which was further purified by column chromatography on silica gel (200–300 mesh, petroleum ether/EtOAc as eluent).

3.7.1. *N*-Diphenylphosphinyl-(2*S*)-2-(diphenylhydroxymethyl)pyrrolidine, 4a. White solid, yield 49.2%, mp 167–169°C, $[\alpha]_D^{20}$ −57.0 (*c* 0.73, CH_2Cl_2), Ref. 4l, mp 164–166°C.

3.7.2. *N*-Diphenylphosphinyl-(2*S*)-2-[di-(4-fluorophenyl)-hydroxymethyl]pyrrolidine, 4b. White solid, yield 41.7%, mp 158–160°C, $[\alpha]_D^{20}$ −44.4 (*c* 1.1, CH_2Cl_2), ^{31}P NMR 34.67 ppm (s), ^1H NMR 1.17–1.45 (m, 2H, CH_2), 1.90–2.13 (m, 2H, CH_2), 2.39–3.00 (m, 2H, CH_2), 4.73–4.80 (m, 1H, CH), 5.60 (bs, 1H, OH), 6.92–7.53 (m, 18H, Ph-H). Anal. calcd for $C_{29}H_{26}NO_2F_2P$: C, 71.16; H, 5.35; N, 2.86. Found: C, 71.15; H, 5.42; N, 2.62%.

3.7.3. *N*-Diphenylphosphinyl-(2*S*)-2-[di-(4-methylphenyl)hydroxymethyl]pyrrolidine, 4c. White solid, yield 63.5%, mp 158–160°C, $[\alpha]_D^{20}$ −38.2 (*c* 1.1, $CHCl_3$), ^{31}P NMR 34.65 ppm (s), ^1H NMR 1.81–1.47 (m, 2H, CH_2), 1.89–2.15 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.41–3.04 (m, 2H, CH_2), 4.68–4.80 (m, 1H, CH), 5.60 (bs, 1H, OH), 7.03–7.70 (m, 18H, Ph-H). Anal. calcd for $C_{31}H_{32}NO_2P$: C, 77.32; H, 6.70; N, 2.91. Found: C, 77.27; H, 6.73; N, 2.77%.

3.8. Typical procedure for the borane reduction of prochiral ketones catalyzed by 3a–d and 4a–c

To a solution of toluene (2 ml) and **3** or **4** (10 mol%), $BH_3{\cdot}Me_2S$ (1.2 equiv.) was added under N_2. The mixture was stirred for 20 min and then heated to reflux temperature. A solution of prochiral ketone (1 mmol) in dry toluene (4 ml) was added in 30 min. After the addition, the reaction was complete (monitored by TLC). A saturated NH_4Cl solution (10 ml) was added and stirred for another 10 min. The organic phase was separated and the water layer was extracted with EtOAc (2×10 ml). The combined organic layer was washed with a saturated NaCl solution and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was further purified by column chromatography on silica gel. Meanwhile the catalyst **3** or **4** could be recycled and reused. Chiral HPLC analysis gave the enantiomeric excess of the chiral secondary alcohols.

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