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Synthesis of Chiral Phosphorus Reagents and Their Catalytic Activity in Asymmetric Borane Reduction of *N*-Phenyl Imine of Acetophenone

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ABSTRACT: *Eleven chiral trivalent or quatrivalent phosphorus reagents were synthesized starting from* L*-proline,* D*-camphor, (+)- or (−)-1,1′-binaphthalene-2,2′-diol, (−)-α-phenylethylamine, etc. and their application as catalysts in asymmetric borane reduction of N-phenyl imine of acetophenone was preliminarily investigated. N-Phenyl α-phenylethylamine was obtained in good yield with low to moderate enantioselectivity.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:546–550, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10190

INTRODUCTION

Optically active secondary amines are important versatile intermediates in the preparation of many biologically active compounds. They have also been widely used as chiral auxiliary in the asymmetric catalysis. During the past two decades much attention of the organic chemists has been drawn to their synthesis. The most challenging method is the enantioselective reduction of the corresponding ketimines. Although some good results were obtained via the asymmetric hydrogenation [1] and hydrosilylation [2] in enantioselective reduction of acyclic imines, there is still a challenge for other reduction methods in this important research area [3]. During the past decade significant progress has been achieved in the preparation of chiral secondary alcohols through asymmetric borane reduction of the corresponding prochiral ketones [4]. However, little attention has been focused on the preparation of chiral secondary amines via asymmetric borane reduction of imines, especially, asymmetric borane reduction of imines catalyzed by chiral phosphorus reagents. To the best of our knowledge, the only report was in 1996 by Brunel and Buono [5]. In their investigation, moderate enantioselectivity was obtained in asymmetric borane reduction of imines catalyzed by chiral reagent **1**.

Herein, we report the synthesis of a series of chiral trivalent and quadrivalent phosphorus compounds starting from L-proline, D-camphor, (−)-1, 1′-binaphthalene-2,2′-diol, (−)-α-phenylethylamine, etc. and the preliminary investigation of their catalytic activity in asymmetric borane reduction of ketimine.

RESULTS AND DISCUSSION

Synthesis of Chiral Phosphorus Reagents

L-prolinol is conveniently available through the reduction of L-prolinol. According to our previous

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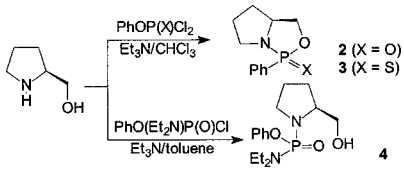
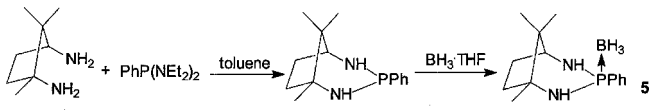
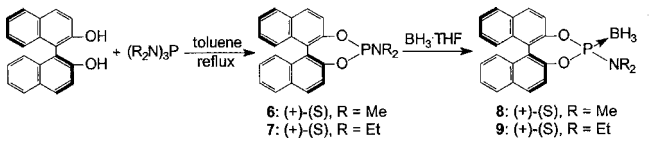
work [6], chiral phosphoramidates **2** and **3** were obtained by the cyclization of L-prolinol with *O*-phenyl phosphorodichloridate or *O*-phenyl phosphorodichloridothioate in the presence of triethylamine. Two orientations existed in the reaction of L-prolinol with *O*-phenyl *N*,*N*-diethyl phosphoramidochloridate, namely, N-phosphorylation and O-phosphorylation. N-phosphorylation product **4** was obtained as the major one with low isolated yield at room temperature [7].



Borane complex **5** was prepared via the cyclization of *N*,*N*,*N*′,*N*′-tetrathyl phenylphosphonous diamide with (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine, which was derived from D-camphor through oxidation and amination [5].



The reaction of (−)-(*S*)-binaphthol with hexaalkyl phosphorous triamide afforded cyclic phosphoramidates **6** and **7**. Further reaction of **6** and **7** with BH_3·THF gave the corresponding borane complexes **8** and **9**, respectively.



To understand the structure of this type of borane complex, crystallographic study of **9** was conducted via X-ray refraction. The molecular structure of compound **9** is shown in Fig. 1.

As shown in Table 1, the bonds between the central phosphorus atom and the four groups connected to it are of single bond length. The six bond angles at the central phosphorus atom deviated little from the normal tetrahedral angle. The bond angles O(1)—P—N, O(1)—P—O(2), and O(2)—P—B are slightly smaller, N—P—O(2), N—P—B, and O(1)—P—B are slightly larger.

According to our reported method [7], the reaction of (−)-(*S*)-binaphthol with diethyl phosphorochloridate led to product **10**, with one phenolic hydroxyl phosphorylated.

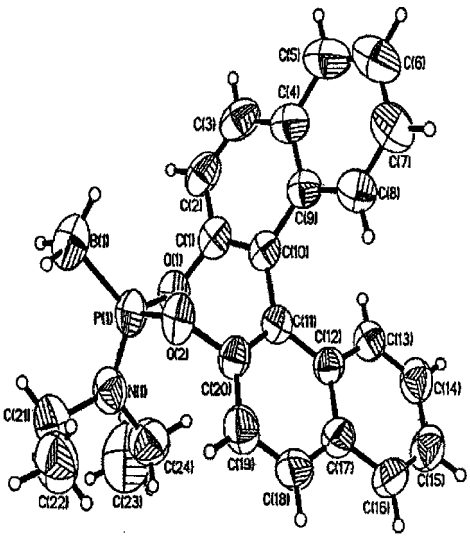
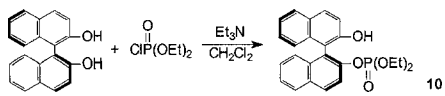
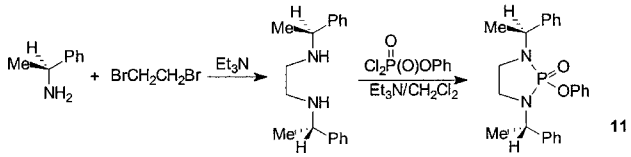


FIGURE 1 Molecular structure of compound **9**.



The reaction of (−)-α-phenylethylamine with 1, 2-dibromoethane provided (−)-*N*,*N*′-bis(α-phenylethyl)ethane-1,2-diamine [9]. Further cyclization with phenyl phosphorodichloridate gave cyclophosphorodiamide **11**.



Compound **12** was prepared by the reaction of L-(−)-diisopropyl tartrate with hexaethyl phosphorous triamide according to the literature [10].

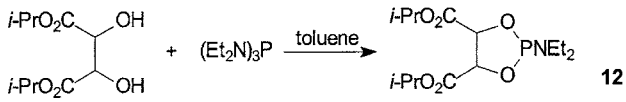
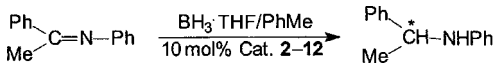


TABLE 1 Selected Bond Lengths (Å) and Bond Angles (°) of **9**

P(1)–O(1)	1.608	O(1)–P(1)–N(1)	100.2
P(1)–O(2)	1.616	N(1)–P(1)–O(2)	112.4
P(1)–N(1)	1.608	N(1)–P(1)–B(1)	117.0
P(1)–B(1)	1.884	O(1)–P(1)–O(2)	101.6
O(1)–C(1)	1.412	O(1)–P(1)–B(1)	117.9
O(2)–O(20)	1.410	O(2)–P(1)–B(1)	106.8

Catalytic Asymmetric Borane Reduction of Imine

Preliminary investigation of the catalytic effect of chiral phosphorus reagents **2–12** in asymmetric borane reduction of imine was carried out using *N*-phenyl imine of acetophenone as substrate and BH_3·THF as reductant. The experimental results are listed in Table 2.



Preliminary tests showed that solvents, such as toluene, THF, chloroform, and methylene chloride, had no significant influence on enantioselectivity. Hence, toluene was chosen as the solvent. It was found that the reaction temperature (20–50°C) was not an essential factor to the catalytic activity to most of the catalysts. However, the reaction ran very slowly, even no reaction occurred below 20°C. The optimal reaction temperature was 20–30°C. Furthermore, no obvious difference on chemical yield and enantioselectivity was observed when the amount of the catalyst ranged from 6 to 30 mol%. Thus, 10 mol% of catalyst was used.

As shown in Table 2, the structure of the chiral phosphorus reagent had a marked influence on the catalytic effect. Enantioselectivity was obviously enhanced with a slight drop in yield when P=O bond (**2**) was changed into P=S bond (**3**) in the cyclophosphoramidates derived from L-prolinol. Furthermore, acyclic phosphoramidate **4** with a proximal hydroxyl group derived from L-prolinol had better catalytic activity than those of cyclic phosphoramidates **2, 3**, and **11**, derived from (−)-α-phenylethylamine. For example, better enantioselectivity and higher yield were obtained when **4** was used as catalyst, which was also much higher than that of phosphate **10**, which contained a proximal phenolic hydroxyl group. Better result was obtained with borane complex **9** rather than trivalent phosphorus reagent **7**. Additionally, it was found that the carbon backbone has an important role on their catalytic effect. For example, moderate enantioselectivity was observed for borane complex **8** derived from (−)-(*S*)-binaphthol, while quite lower enantioselectivity was obtained for the borane complexes **5** and **12**, which were derived from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine and L-(−)-tartrate, respectively.

TABLE 2 10 mol% Chiral Phosphorus Reagents Catalyzed Asymmetric Borane Reduction of *N*-phenyl imine of Acetophenone in Toluene at 20–30°C

Catalyst	*Yield*[a] *(%)*	$[\alpha]^{25}_D$ *(c, EtOH)*	*ee*[b] *(%)*	*Configuration*
2	51	+2.0 (1.9)	8	S
3	35	+5.8 (0.4)	32	S
4	73	+15.3 (0.8)	59	S
5	53	+2.1 (2.1)	9	S
7	58	+1.0 (1.2)	4	S
8	48	+12.6 (0.8)	48	S
9	48	+6.5 (1.6)	25	S
10	45	+2.6 (1.1)	10	S
11	89	−7.2 (2.5)	28	R
12	63	+4.0 (3.2)	15	S

[a]Isolated yield.
[b]Determined by comparison of maximum sepecific rotation value of (+)-(*S*)-*N*-phenyl-α-phenylethylamine, $[\alpha]_D^{25}$ + 26.1 (*c* 2.15, EtOH) [9].

In conclusion, acyclic phosphoramidates containing a proximal hydroxyl group (for example, catalyst **4**) and the cyclic phosphoranidite–borane complexes containing sterically hindered and rigid backbone (for example, catalyst **8**) had good catalytic activity in asymmetric borane reduction of imines. These findings will play an important role on the further design and synthesis of these types of new catalysts.

EXPERIMENTAL

^1H and ^{31}P NMR were recorded in $CDCl_3$ on a Bruker AC-P200 instrument using TMS as an internal standard for ^1H and 85% H_3PO_4 as an external standard for ^{31}P. Specific rotations were measured on a Perkin-Elmer 241MC polarimeter. Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined on a Yanaco MP-500 melting point apparatus. All temperatures are uncorrected. All of the solvent was used after drying and redistillation.

Synthesis of **2**

To a stirred mixture of L-(+)-prolinol (1.01 g, 10 mmol), triethylamine (2.02 g, 22 mmol), and 20 ml of chloroform was added dropwise a solution of *O*-phenyl phosphorodichloridate (2.11 g, 10 mmol) in 10 ml of chloroform at 60°C. The resulting mixture was refluxed for 3 h, then cooled to room temperature. The reaction mixture was washed with water (30 ml) and dried over anhydrous magnesium sulfate. After removal of solvent the crude product (3.20 g) was purified by column chromatography on silica gel (300–400 mesh, gradient eluted with petroleum ether/ethyl acetate) to give 2.00 g of **2**. Yield, 83%, n^{25}_D 1.5338. ^{31}P NMR (δ, ppm): 21.67, 16.42; ^1H NMR (δ, ppm): 1.48–2.20 (m, 4H), 2.78–3.26 (m, 1H), 3.32–4.62 (m, 4H), 7.16 (m, 5H).

Anal. Calcd for $C_{11}H_{14}NO_3P$: C, 55.23%; H, 5.90%; N, 5.86%; Found: C, 54.94%; H, 5.85%; N, 5.69%.

Synthesis of **3**

Similarly, 2.02 g of **3** was obtained through the reaction of L-(+)-prolinol (1.01 g, 10 mmol) with *O*-phenyl phosphorodichloridothioate (2.27 g, 10 mmol). Yield, 79%, m.p. 78–79°C, $[\alpha]^{25}_D$–26.7 (*c* 1, $CHCl_3$). ^{31}P NMR (δ, ppm): 74.85, 83.33; ^{1}H NMR (δ, ppm): 1.48–2.24 (m, 4H), 2.84–3.28 (m, 1H), 3.34–4.68 (m, 4H), 7.14 (m, 5H). Anal. Calcd for $C_{11}H_{14}NO_2PS$: C, 51.95%; H, 5.46%; N, 5.50%; Found: C, 51.82%; H, 5.46%; N, 5.30%.

Synthesis of **4**

To a stirred mixture of L-(+)-prolinol (1.01 g, 10 mmol), triethylamine (1.01 g, 10 mmol), and 15 ml of toluene was added a solution of *O*-phenyl diethylphosphoramidochloridate (2.48 g, 10 mmol) in 15 ml of toluene at room temperature. The resulting mixture was stirred for 48 h and then filtered. After removal of solvent the residue was purified by column chromatography on silica gel (200–300 mesh, eluted with petroleum ether/ethyl acetate) to afford 1.29 g of **4**. Yield, 41%, n^{25}_D 1.4536, $[\alpha]^{25}_D$ +31.0 (*c* 0.4, $CHCl_3$). ^{31}P NMR (δ, ppm): 13.82; ^{1}H NMR (δ, ppm): 0.99 (t, 6H), 1.82 (m, 4H), 3.24 (m, 9H), 3.54 (s, 1H), 7.17 (m, 5H). Anal. Calcd for $C_{15}H_{25}N_2O_3P$: C, 57.69%; H, 8.01%; N, 8.97%; Found: C, 57.76%; H, 8.07%; N, 8.79%.

Synthesis of **5**

A mixture of (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine (0.83 g, 5.8 mmol), *N*,*N*,*N*′,*N*′-tetraethyl phenylphosphonous diamide (1.47 g, 5.8 mmol), and 50 ml of anhydrous toluene was refluxed under nitrogen atmosphere until the reactant was completely consumed (monitored by TLC). After colling to room temperature, 2 M solution of BH_3TFH in THF (2.9 ml) was added and the resulting mixture was stirred overnight at room temperature. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to give 0.55 g of **5**. Yield, 36%, m.p. 145–147°C, $[\alpha]^{25}_D$ +22.0 (*c* 0.1, $CHCl_3$). ^{31}P NMR (δ, ppm): 64.63; ^{1}H NMR(δ, ppm): 0.81 (s, 3H), 1.17 (s, 6H), 1.23–1.69 (m, 7H), 2.60 (s, 2H), 3.30 (dd, 1H), 7.38–7.86 (m, 5H). Anal. Calcd for $C_{14}H_{24}BN_2P$: C, 64.14%; H, 9.13%; N, 10.69%; Found: C, 64.20%; H, 9.18%; N, 10.27%.

Synthesis of **6**

A mixture of (−)-(*S*)-binaphthol (1.14 g, 4 mmol), hexamethyl phosphorous triamide (0.90 g, 5.5 mmol), and 25 ml of dry toluene was refluxed under nitrogen atmosphere until (−)-(*S*)-binaphthol disappeared (monitored by TLC, about 8–9 h). After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford 1.39 g of **6**. Yield, 96%, m.p. 190–192°C, $[\alpha]^{25}_D$ +580.8 (*c* 0.3, $CHCl_3$). ^{31}P NMR (δ, ppm): 149.09; ^{1}H NMR (δ, ppm): 2.53 (d, 6H), 7.39–7.92 (m, 12H). Anal. Calcd for $C_{14}H_{24}BN_2P$: C, 64.14%; H, 9.13%; N, 10.69%; Found: C, 64.20%; H, 9.18%; N, 10.27%.

Synthesis of **7**

Similarly, the reaction of (−)-(*S*)-binaphthol (1.14 g, 4 mmol) with hexacthyl phosphorous triamide (1.21 g, 5.5 mmol) gave 1.36 g of **7**. Yield, 8.8%, m.p. 204–207°C, $[\alpha]^{25}_D$ +473.8 (*c* 0.3, $CHCl_3$). ^{31}P NMR (δ, ppm): 150.10; ^{1}H NMR (δ, ppm): 1.04 (t, 6H), 2.80–3.12 (m, 4H), 7.32–7.96 (m, 12H). Anal. Calcd for $C_{24}H_{22}NO_2P$: C, 74.41%; H, 5.69%; N, 3.62%; Found: C, 74.24%; H, 5.87%; N, 3.62%.

Synthesis of **8**

To a solution of **6** (0.43 g, 1.2 mmol) in 10 ml of THF was added 2 M solution of BH_3·THF in THF (2 ml) under nitrogen atmosphere at room temperature. The resulting mixture was stirred for 2 h at the same temperature. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to give 0.40 g of **8**. Yield, 90%, m.p. 201–204°C, $[\alpha]^{25}_D$ +597.7 (*c* 0.6, $CHCl_3$). ^{31}P NMR (δ, ppm): 131.99; ^{1}H NMR (δ, ppm): 1.20–1.60 (m, 3H), 2.61 (d, 6H), 7.27–7.95 (m, 12H). Anal. Calcd for $C_{22}H_{21}BNO_2P$: C, 70.81%; H, 5.63%; N, 3.76%; Found: C, 70.58%; H, 5.69%; N, 4.02%.

Synthesis of **9**

Similarly, the reaction of **7** (0.46 g, 1.2 mmol) and 2 M solution of BH_3·THF in THF (2 ml) afforded 0.47 g of **9**. Yield, 98%, m.p. 144–146°C, $[\alpha]^{25}_D$ +470.0 (*c* 0.4, $CHCl_3$). ^{31}P NMR (δ, ppm): 131.88; ^{1}H NMR(δ, ppm): 1.21–1.60 (m, 3H), 1.67 (t, 6H), 2.80–3.12 (m, 4H), 7.26–7.98 (m, 12H). Anal. Calcd for $C_{24}H_{25}BNO_2P$: C, 72.39%; H, 6.28%; N, 3.52%; Found: C, 71.97%; H, 6.37%; N, 3.48%. The crystal of **9** suitable for

X-ray analysis was obtained by slow evaporation of the solvent (methylene chloride) for a couple of days.

Synthesis of **10**

To a stirred mixture of (−)-(*S*)-binaphthol (0.72 g, 2.5 mmol), *O*,*O*-diethyl phosphorochloridate (0.43 g, 2.5 mmol), and 20 ml of methylene chloride was added dropwise a solution of triethylamine (0.25 g, 2.5 mmol) in 5 ml of methylene chloride at 0°C. The reaction mixture was stirred for 24 h at room temperature and washed successively with distilled water and saturated aqueous NaCl. The organic layer was dried over anhydrous magnesium sulfate. After removal of solvent the crude product was recrystallized from ethyl acetate to give 0.86 g of **10**. Yield, 82%, m.p. 178–180°C, $[\alpha]^{25}_{D}$ −5.1 (*c* 1, $CHCl_3$). ^{31}P NMR (δ, ppm): −4.91; ^{1}H NMR (δ, ppm): 0.83 (t, 3H), 1.16 (t, 3H), 3.43 (dq, 2H), 3.80 (dg, 2H), 4.90 (br, 1H). Anal. Calcd for $C_{24}H_{23}O_5P$: C, 68.24%; H, 5.45%; Found: C, 68.05%; H, 5.35%.

Synthesis of **11**

To a stirred mixture of (−)-*N*,*N*′-di-(α-phenylethyl) ethane-1,2-diamine (2.68 g, 10 mmol), triethylamine (2.42 g, 24 mmol), and 40 ml of methylene chloride was added dropwise *O*-phenyl phosphorodichloridate (2.11 g, 10 mmol) at 0°C. The resulting mixture was stirred for 24 h at room temperature, then adjusted to pH = 7 with 2 N aqueous NaOH, and washed with distilled water and saturated aqueous NaCl. The organic layer was dried over anhydrous magnesium sulfate. After removal of solvent the residue was purified by column chromatography on silica gel (200–300 mesh, eluted with petroleum ether/ethyl acetate) to afford 3.25 g of **11** as a thick liquid. Yield, 80%, $[\alpha]^{25}_{D}$ −3.5 (*c* 1, $CHCl_3$). ^{31}P NMR (δ, ppm): 17.86; ^{1}H NMR (δ, ppm): 1.54 (d, 3H), 2.86 (m, 4H), 4.40 (q, 4H), 7.30 (m, 15H). Anal. Calcd for $C_{24}H_{27}N_2O_2P$: C, 70.94%; H, 6.65%; N, 6.90%; Found: C, 70.85%; H, 6.45%; N, 6.70%.

Synthesis of **12**

A mixture of L-(−)-diisopropyl tartrate (0.43 g, 10 mmol), hexaethyl phosphorous triamide (3.71 g, 15 mmol), and 30 ml of dry toluene was refluxed for 10 h under a nitrogen atmosphere. After removal of solvent the crude product was purified by distillation under reduced pressure to give 1.34 g of **12**. b.p. 120–122°C/66 Pa. yield 33%, n^{25}_{D} 1.4538 (Lit. [10]: b.p. 138–139°C/1 mmHg, n^{20}_{D} 1.4572).

General Procedure for Asymmetric Borane Reduction of Imine

To a solution of *N*-phenyl imine of acetophenone (prepared according to Ref. [11]) (0.78 g, 4 mmol), catalyst (0.4 mmol), and 10 ml of dry toluene was added 2 M solution of BH_3·THF in THF (2 ml) at room temperature. The reaction mixture was stirred at 20–30°C until TLC showed complete consumption of the starting material. Ten milliliters of 1 M H Cl was introduced and stirred for several minutes. The organic layer was separated and washed with water (2 × 10 ml). The combined aqueous phase was made basic with saturated aqueous NaOH and extracted with ether (3 × 10 ml). The combined organic layers were dried over anhydrous magnesium sulfate. After removal of solvent the crude product was purified by distillation under reduced pressure, b.p. 178–180°C/1.3 k Pa (Ref. [12]: b.p. 142°C/1.5 mmHg).

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