A Convenient Synthetic Route to (S_P)-Methylphosphine Borane Derivatives via an Asymmetric Lithiation/ Trapping-Reductive Elimination Strategy

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Enantioenriched *P*-chiral secondary phosphine boranes are extremely useful precursors for the synthesis of *P*-chirogenic ligands for asymmetric catalysis.[1] The most common route used for the preparation of these compounds involves the synthesis and resolution of diastereomeric derivatives followed by reductive cleavage and protonation.[2] During the course of our studies on new methods for the synthesis of enantiopure *P*-chiral phosphines,[3] we required an alternative procedure for preparing the corresponding secondary phosphine boranes. In this paper, we describe an efficient route to these compounds in enantiopure form by asymmetric lithiation/ trapping-reductive elimination (Scheme 1).

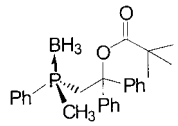
The achiral dimethylphosphine borane precursors **1a**−**d** used in this study were typically prepared by the method of Muci and Evans[4] from chlorodimethylphosphine borane and the corresponding Grignard reagent. Asymmetric lithiation of dimethylphosphine boranes **1a**−**d** in the presence of *s*-BuLi (−)-sparteine complex (Et_2O, −78 °C)[4] followed by sequential trapping of the resultant organolithium derivatives with benzophenone and final alkoxide acylation with trimethylacetyl chloride furnished the enantioenriched adducts **2** in very good yields on a preparative scale. *Significantly, these highly crystalline compounds could usually be brought to >99% optical purity by recrystallization from the appropriate solvent system*.[5] In addition, simple reduction of these adducts in the presence of lithium naphthalenide in THF or Li/ NH_3−THF at −78 °C followed by protonation (MeOH) gave the corresponding secondary phosphine boranes **3a**−**d** with enantiopurities exceeding 99%. The optical purities of **3a**−**d** were determined by prior conversion to appropriate tertiary phosphine boranes by alkylation of the corresponding lithium derivatives with 2-(chloromethyl)benzothiophene to give the chiral P/S ligand precursors **4a**−**d** or benzyl bromide (for **3b**)[6] (Scheme 2). In all cases, stereochemical comparisons were made to authentic racemates by chiral HPLC using a CHIRALPAK AD column. A collection of representitive results obtained via this sequence appears in Table 1.

In conclusion, we have shown that representitive secondary phosphine boranes of high enantiopurity can be readily prepared by an efficient asymmetric lithiation/ trapping-reductive elimination procedure. The subsequent utilization of new *P*-chirogenic ligands available from these precursors, including those derived from **5a**−**d**, will be described in future accounts from these laboratories.

Experimental Section

General Methods. All experiments were carried out under an argon atmosphere in oven-dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. Column flash chromatography was performed on Merck silica gel 60 (230−400 mesh) and Aldrich neutral alumina (~150 mesh). Chiral HPLC was performed using a CHIRALPAK AD [250 × 4.6 mm (*L* × i.d.)] HPLC column (Daicel Chemical Industries).

(S_P)-2-(Methylphenylphosphinoborane)-1,1-diphenylethyl 2,2-Dimethylpropionate (2a).



To a cooled (−78 °C) solution of (−)-sparteine (2.6 mL, 11 mmol, 1.1 equiv) in ether (40 mL) was added *s*-butyllithium (9.2 mL, 11 mmol, 1.2 M in cyclohexane, 1.1 equiv) slowly via syringe. The reaction mixture was allowed to stir for 10 min, and a solution of dimethylphenylphosphinoborane (1.5 g, 10 mmol) in ether (40 mL) was added dropwise via cannula. The reaction mixture was allowed to stir at −78 °C for 3 h, and a solution of benzophenone (2.0 g, 11 mmol, 1.1 equiv) in THF (10 mL) was then added dropwise via cannula. The solution was stirred for an additional 2 h at −78 °C and then warmed to 0 °C for 8 h. At 0 °C, trimethylacetyl chloride (1.8 mL, 15 mmol, 1.5 equiv) was added, and the solution was allowed to stir as the ice bath warmed to room temperature over 10 h. The solvent was then removed in vacuo, and the thick heterogeneous oil was taken up in dichloromethane (50 mL). To the mixture was added 5% aqueous sulfuric acid (20 mL) in one portion, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered (silica gel), and concentrated in vacuo. The resulting crude colorless solid was purified by slow vapor recrystallization from dichloromethane with pentane yielding (2.9 g, 6.9 mmol, 69%) of (S_P)-2-(methylphenylphosphinoborane)-1,1-diphenylethyl 2,2-dimethylpropionate (**2a**) as a colorless solid: mp 160.5−161.3 °C (dichloromethane/pentane); $[\alpha]^{28}_D$ +18° (c = 4.96, solvent THF); IR (KBr) 3062, 2974, 2396 (BH), 1731 (C=O), 1151 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54−7.47 (m, 2H, Ar-*H*), 7.40−7.06 (m, 13H, Ar-*H*), 3.74 (dd, J = 14.7 Hz, J_{P-H} = 9.9 Hz, 1H, PC(H)*H*C), 3.57 (dd, J = 14.7 Hz, J_{P-H} = 11.7 Hz, 1H, PC*H*(H)C), 1.21 (s, 9H, C(CH_3)$_3$), 1.08 (d, J_{P-H} = 9.9 Hz, PCH_3), 0.76 (very broad s, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.7 (s, −CO_2−) 144.4 (d, J_{P-C} = 5.1 Hz, Ar*C*), 144.1 (d, J_{P-C} = 6.0 Hz, Ar*C*), 131.1 (d, J_{P-C} = 9.1 Hz, Ar*C*), 130.7 (d, J_{P-C} = 1.3 Hz, Ar*C*), 130.5 (d, J_{P-C} = 27.2 Hz, Ar*C*), 128.5 (d, J_{P-C} = 9.9 Hz, Ar*C*), 128.2 (s, Ar*C*), 128.0 (s, Ar*C*), 127.5 (s, Ar*C*), 127.4 (s, Ar*C*), 126.2 (s, Ar*C*), 126.1 (s, Ar*C*), 83.4 (s, RPh_2*C*O−), 39.1 (s, *C*C(CH_3)$_3$), 36.5 (d, J_{P-C} = 32.3 Hz, P*C*H_2C), 127.1 (s, C(*C*H_3)$_3$), 11.4 (d, J_{P-C}

(1) Yamanoi, T.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988−2989 and references therein.

(2) Miura, T.; Yamada, H.; Kikuchi, S.-i,; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 1877−1880 and references therein.

(3) (a) Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org Chem.* **2000**, *65*, 4776−4778. (b) Al-Masum, M.; Livinghouse, T. *Tetrahedron Lett.* **1999**, *40*, 7731−7734. (c) Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116−5117.

(4) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076.

(5) In general, recrystallization to near optical purity could most readily be achieved by solvent diffusion in a closed system.

(6) In the case of **3b**, separation of the isomers **4b** in an authentic racemic mixture by chiral HPLC was not achieved. For this reason, optical purity was established for the corresponding *P*-benzyl derivative (**6**, see the Supporting Information).

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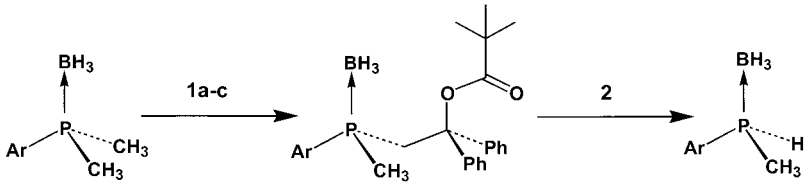
Scheme 1

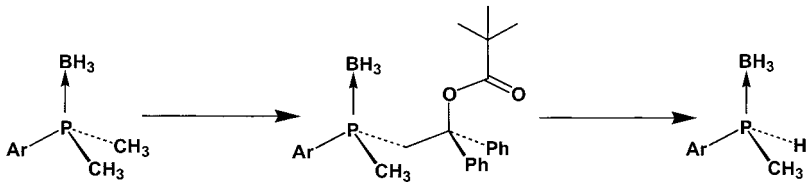


1a-d 2a-d 3a-d

a: Ar = C_6H_5
b: Ar = 2-(*i*-Pr)C_6H_4
c: Ar = 2-(Me)C_6H_4
d: Ar = 2-(MeO)C_6H_4

1a) *s*-BuLi/(-)-sparteine, b) Ph_2CO, c) *t*-BuCOCl; 2) Li-naphthalenide

Table 1. Preparation of Enantioenriched Secondary Phosphine Boranes[a]

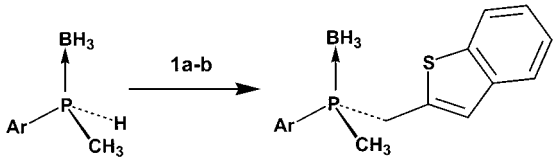


1a-d 2a-d 3a-d

Ar	% ee before recrystallization	% yield (>99% ee)	% yield (>99% ee)
C_6H_5	75	69[b]	93
2-(*i*-Pr)C_6H_4	>99	70[c]	94
2-(Me)C_6H_4	87	76[b]	93
2-(MeO)C_6H_4	83	46[b]	99

[a] Absolute stereochemistry of **3a**−**d** was assigned (*S*) by analogy.[4] [b] Percent ee determined by chiral HPLC using a CHIRALPAK AD column. [c] Percent ee determined by anology to the corresponding alcohol **5b** (see the Supporting Information).

Scheme 2



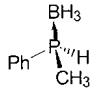
3a-d 4a-d

4a: Ar = C_6H_5 (94%, >99% ee)
4b: Ar = 2-(*i*-Pr)C_6H_4 (81%, >98% ee)
4c: Ar = 2-(Me)C_6H_4 (71%, >99% ee)
4d: Ar = 2-(MeO)C_6H_4 (88%, >99% ee)

1a) *n*-BuLi-THF, -78 °C, b) 2-(chloromethyl)benzothiophene, -78 °C - rt

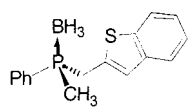
= 39.2 Hz, P*C*H$_3$); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 5.4 (apparent broad d, J_{B-P} = 59.9 Hz); TLC R_f 0.14 (10% ethyl acetate/ hexanes); LRMS *m*/*z* (EI) 404 ($M^+ - BH_3$, 5.7%) 57, 77, 89, 109, 124, 140, 165, 180 (100%), 200, 301; exact mass calcd for $C_{26}H_{29}O_2P$ ($M^+ - BH_3$) requires *m*/*z* 404.1917 found *m*/*z* 404.1905. Separation of the enantiomers of the recrystallized product with chiral HPLC (CHIRALPAK AD, 10% *i*-PrOH/ hexanes, 1.0 mL/ min, t_R = 4.78 (major), 6.42 min) indicated an ee of >99%.

(S_P)-Methylphenylphosphinoborane (3a).



A solution of (S_P)-2-(methylphenylphosphinoborane)-1,1-diphenylethyl 2,2-dimethylpropionate (**2a**) (230 mg, 0.50 mmol, 1.0 equiv) in THF (5.0 mL) was added dropwise via cannula to a cooled (−78 °C) solution of lithium naphthalenide (5.0 mL, 2.5 mmol, 0.5 M, 5.0 equiv). The solution was allowed to stir for 10 min, and a mixture of THF, MeOH, and AcOH (8:1:1) (0.5 mL) was added very slowly. To the resulting solution were added saturated ammonium chloride (2 mL), water (2 mL), and ether (5 mL). The aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were washed with brine and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The amorphous crude solid was purified by flash column chromatography on silica gel (5% ethyl acetate/ hexanes for elution) yielding (S_P)-methylphenylphosphine-borane (**3a**) (85 mg, 0.46 mmol, 93%) as a colorless oil: $[\alpha]^{24}_D$ −8.3° (*c* = 1.20, sol. THF); IR (film, NaCl) 3057, 2394 (BH), 1064 (broad), 995 (sharp), 930 (broad), 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73−7.65 (m, 2H, Ar-*H*), 7.54−7.42 (m, 3H, Ar-*H*), 5.59 (d sep, J_{P-H} = 370.8 Hz, J = 6.3 Hz, 1H, P*H*), 1.61 (dd, J_{P-H} = 11.1 Hz, J_{P-H} = 6.3 Hz, 3H, PC*H*$_3$), 0.80 (q, J_{B-H} = 99.0 Hz, 3H, PB*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 132.0 (d, J_{P-C} = 9.2 Hz, Ph*C*), 131.4 (d, J_{P-C} = 2.3 Hz, Ph*C*), 128.8 (d, J_{P-C} = 10.3 Hz, Ph*C*), 126.1 (d, J_{P-C} = 56.5 Hz, Ph*C*), 8.1 (d, J_{P-C} = 38.4 Hz, P*C*H$_3$); ^{31}P NMR ($CDCl_3$, 121 MHz) δ −16.0 (apparent q, J_{B-P} = 52.3 Hz); TLC R_f 0.22 (10% ethyl acetate/hexanes).

(S_P)-Benzo[*b*]thiophene-2-ylmethylphenylmethylphosphinoborane (4a).



n-Butyllithium (280 μL, 0.47 mmol, 1.7 M in hexanes, 1.1 equiv) was added dropwise to a cooled (−78 °C) solution of (S_P)-methylphenylphosphinoborane (**3a**) (59 mg, 0.43 mmol), HMPA (146 μL, 0.84 mmol, 2.0 equiv), and THF (1.0 mL). The solution

was stirred for 10 min, and a solution of 2-chloromethylbenzo[*b*]thiophene (86 mg, 0.47 mmol, 1.1 equiv) in THF (1.0 mL) was added dropwise slowly. The solution was allowed to stir for 10 h at −78 °C, and water (3.0 mL) was added. The aqueous phase was extracted with ether (3 × 2 mL), and the combined organic phases were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude light yellow solid was purified by flash column chromatography (gradient elution with 20−50% dichloromethane/ hexanes) yielding (S_P)-benzo[*b*]-thiophene-2-ylmethylphenylmethylphosphinoborane (**4a**) (110 mg, 0.39 mmol, 94%) as a colorless solid: mp 136.4−138.3 °C (dichloromethane/hexanes); $[\alpha]^{28}_D$ −63° (*c* = 1.00, solvent THF); IR (KBr) 3054, 2402 (BH), 2377 (BH), 2347 (BH), 1432 (sharp),-1066 (sharp), 738 (broad) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73−7.59 (m, 4H, Ar-*H*), 7.51 (m, 1H, Ar-*H*), 7.45−7.39 (m, 2H, Ar-*H*), 7.32−7.23 (m, 2H, Ar-*H*), 6.86 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 3.49 (dd, *J* = 25.2, 15.6 Hz, 2H, PCH_2Ar), 1.61 (d, J_{P-H} = 9.9 Hz, 3H, PCH_3), 0.85 (very broad q, J_{B-H} = 109.8 Hz, 3H, BH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5 (d, J_{P-C} = 2.6 Hz, Ar*C*), 139.4 (s, Ar*C*), 134.4 (d, J_{P-C} = 8.6 Hz, Ar*C*), 131.6 (d, J_{P-C} = 9.3 Hz, Ar*C*), 131.5 (s, Ar*C*), 128.6 (d, J_{P-C} = 9.8 Hz, Ar*C*), 128.3 (d, J_{P-C} = 52.8 Hz, Ar*C*), 124.2 (s, Ar*C*), 124.0 (s, Ar*C*), 123.9 (s, Ar*C*), 123.0 (s, Ar*C*), 121.8 (s, Ar*C*), 30.9 (d, J_{P-C} = 31.7 Hz, P*C*H_2Ar), 9.0 (d, J_{P-C} = 38.2 Hz, P*C*H_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 11.5 (apparent broad d, J_{B-P} = 68.0 Hz); TLC R_f 0.15 (10% ethyl acetate/hexanes); LRMS *m*/*z* (EI) 270 ($M^+ - BH_3$, 42%) 77, 103, 121, 136, 147 (100%), 240, 270; exact mass calcd for $C_{16}H_{15}PS$ ($M^+ - BH_3$) requires *m*/*z* 270.0632, found *m*/*z* 270.0637. Separation of the enantiomers by chiral HPLC (CHIRALPAK AD, 10% *i*-PrOH/hexanes, 1.0 mL/ min, t_R= 8.79 (major), 10.14 (min) demonstrated the ee to be >99%.

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Supporting Information Available: Experimental procedures and listings of ^1H, ^{13}C, and ^{31}P NMR, IR, and HRMS or elemental composition data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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