Enantioselective Deprotonation as a Vehicle for the Asymmetric Synthesis of C_2-Symmetric *P*-Chiral Diphosphines

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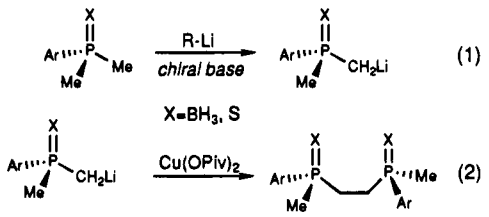
Chiral diphosphines[1] are the ligands of choice for a wide range of enantioselective transition-metal-catalyzed processes.[2] While chirality may be independently incorporated on either the linking carbon chain or the phosphorus centers of these ligands, only a limited number of *P*-chiral diphosphines have been reported due to the difficulties associated with the synthesis of enantiomerically enriched phosphorus stereocenters.[3] The purpose of this Communication is to disclose a convenient approach to the synthesis of C_2-symmetric *P*-chiral diphosphines[4] that relies upon successive enantioselective deprotonation of aryldimethylphosphine−boranes or aryldimethylphosphine sulfides (eq 1) and subsequent oxidative coupling to the diphosphine precursors (eq 2) with high overall enantioselectivity (≥96%) for the two-step process.

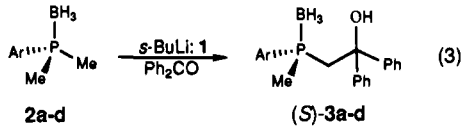


(1)

(2)

Enantioselective Deprotonation. A survey of reaction solvents and alkyllithium reagents led to the selection of the *s*-BuLi−(−)-sparteine (**1**)[5] complex as the preferred chiral base and ether as the optimal solvent for the enantioselective metalation of the phosphine−borane substrates. Deprotonation of dimethylphenylphosphine−borane (**2a**)[6,7] with the *s*-BuLi−(−)-sparteine (**1**) complex (Et_2O, −78 °C), followed by trapping with benzophenone (1.1 equiv, THF, −20 °C), affords adduct **3a** in 79% ee and 88% yield[8] (eq 3, Table 1).[9] Similar results were obtained for the *o*-anisyl derivative **2b**[7a,10] (83% ee) and the 1-naphthyl-substituted phosphine **2d** (82% ee), while the highest enantioselectivity was observed with *o*-tolyl substrate **2c**, which provided **3c** in 87% ee (86% yield). Preliminary studies on the optimal ratio of sparteine to alkyllithium base in the deprotonation of **2a** indicate that reaction enantioselection can be maintained with as little as 0.7 equiv of (−)-sparteine/equiv of alkyllithium base. The sense of asymmetric induction in the deprotonation of **2a** (Ar = Ph) was determined by correlation of the metalation product derived from **2a** with (*R*)-methylphenylpropylphosphine oxide.[11] The absolute configurations of the other phosphine−boranes **3b−d** were assigned by analogy.

Table 1. Enantioselective Deprotonation of Phosphine−Boranes (Eq 3)[a]



(3)

2a-d (*S*)-**3a-d**

substrate	Ar	yield, %	ee,[b,c] %	**3a−d** $[\alpha]_D$ (*c*)
2a	phenyl	88	79	+15.6° (0.81)[d]
2b	*o*-anisyl	81	83	+61.8° (1.58)[d]
2c	*o*-tolyl	84	87	+5.5° (1.90)[d]
2d	1-naphthyl	86	82	+39.3° (5.50)[e]

[a] See ref 9 for deprotonation conditions. [b] See ref 8 for conditions for enantiomer analysis. [c] Absolute configurations of **3b−d** assigned by analogy. [d] Measured in $CHCl_3$. [e] Measured in CH_2Cl_2.

The analogous enantioselective metalation[9] of phosphine sulfides **4a−e**[10,12] was carried out with the sparteine complex of *n*-BuLi (Et_2O, −78 °C, 79% ee) rather than the *s*-BuLi complex (55% ee) employed in the preceding experiments (eq 4, Table 2). This latter alkyllithium base consistently afforded lower levels of asymmetric induction in the metalation of this family of substrates. Again, diethyl ether appears to be the solvent of choice for optimal enantiotopic group discrimination. As in the previous case (eq 3), the sense of asymmetric induction in the deprotonation of **4a** (Ar = Ph) was determined by correlation of the metalated intermediate with (*R*)-methylphenylpropylphosphine sulfide.[13] It is noteworthy that the sense of asymmetric induction for the metalation of **2a** and **4a** is the same. As before, the absolute configurations of phosphine sulfides **5b−e** have been tentatively assigned by analogy. These

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(2) For recent reviews on asymmetric catalysis, see: (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: Weinheim, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994.

(3) For a recent review, see: Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375−1411.

(4) For an independent approach to the synthesis of this family of ligands see: Corey, E. J.; Chen, Z.; Tanoury, G. *J. Am. Chem. Soc.* **1993**, *115*, 11000−11001.

(5) (a) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479−1486 and references therein. (b) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239 and references therein. (c) Papasergio, R. I.; Skelton, B. W.; Twiss, P.; White, A. H.; Raston, C. L. *J. Chem. Soc., Dalton Trans.* **1990**, 1161−1172 and references therein. (d) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427−1430.

(6) Prepared from dimethylphenylphosphine and BH_3·THF. See the supporting information for details.

(7) (a) Schmidbaur, H.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 781−782. (b) Schmidbaur, H. *J. Organomet. Chem.* **1980**, *200*, 287−306.

(8) All enantiomeric and diastereomeric ratios were determined by HPLC using a Daicel Chiracel OD or OD-H column.

(9) Procedure for the enantioselective deprotonation/oxidative coupling of **2a**: To a cooled (−78 °C) solution of sparteine (253 μL, 1.1 mmol) in 4 mL of Et_2O was added 835 μL of *s*-BuLi (1.32 M in cyclohexane, 1.1 mmol). After stirring for 10 min, dimethylphenylphosphine−borane (152 mg, 1.0 mmol) was added via cannula as a solution in 4 mL of Et_2O. After 3 h at −78 °C, $Cu(OPiv)_2$ (797 mg, 3.0 mmol) was added to the reaction *via* cannula as a solution in 4.0 mL of THF, and the reaction was warmed to −20 °C. The adducts **6a** and **6b** were isolated after a conventional extractive workup which included an NH_4OH extraction to remove the copper salts. Chiral HPLC analysis (Daicel Chiracel OD-H column; flow rate 1.0 mL/min; 96% hexane, 2% *i*-PrOH, 2% ethyl acetate; T_r((*S,R*)-**7a**) = 11.20 min, T_r((*R,R*)-**6a**) = 13.10 min, T_r((*S,S*)-**6a**) = 15.72 min) determined the C_2:*meso* ratio to be 79:21 and the enantiomeric excess of the C_2 product to be 98%. Flash chromatography (11 × 36 cm silica; 30% pentane, 70% chloroform; R_f (*meso*) = 0.28, R_f (C_2) = 0.23) afforded 82 mg (54%) of (*S,S*)-**6a** as a white crystalline solid. The procedure for the deprotonation of phosphine sulfides **4a−e** is analogous to that described above except that *n*-BuLi is employed as the base.

(10) Substrates **2b−d** were prepared from the reduction of the corresponding phosphine sulfides **4b−d** (LAH, THF, 66 °C) and subsequent protection with BH_3·THF. Sulfide **4a** was prepared from dimethylphenylphosphine and elemental sulfur (ref 12). Phosphine sulfides **4b−4d** were prepared by reaction of dimethylthiophosphinous chloride (Parshall, G. W. *Inorg. Syntheses* **1974**, *15*, 191−193) with the indicated Grignard reagent. See the supporting information for details.

(11) The deprotonation of **2a** with *n*-BuLi−(−)-sparteine complex, reaction with ethyl triflate, borane removal with excess diethylamine, and oxidation with hydrogen peroxide afforded (*R*)-methylphenylpropylphosphine oxide, $[\alpha]^{23}_D$ +11.9° (*c* = 1.13, MeOH), lit. $[\alpha]^{23}_D$ +17.3° (*c* = 1−3, MeOH). Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4784−4786.

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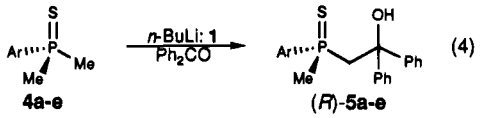
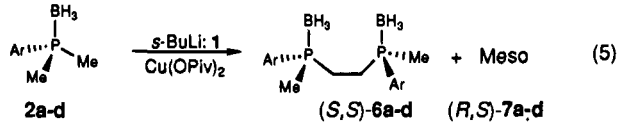
Table 2. Enantioselective Deprotonation of Phosphine Sulfides (Eq 4)[a]



substrate	Ar	yield, %	ee,[b,c] %	5a–e $[\alpha]_D$ (c)
4a	phenyl	94	78	+24.4° (0.88)[d]
4b	*o*-anisyl	83	76	+39.5° (1.03)[d]
4c	*o*-tolyl	79	79	+28.9° (0.82)[d]
4d	1-naphthyl	80	60	+42.6° (1.00)[e]
4e	*t*-BuO	80	81	+10.8° (0.50)[e]

[a] See ref 9 for deprotonation conditions. [b] See ref 8 for conditions for enantiomer analysis. [c] Absolute configurations of **5b–e** assigned by analogy. [d] Measured in $CHCl_3$. [e] Measured in CH_2Cl_2.

Table 3. Synthesis of Chiral Bis(phosphine–Boranes) (Eq 5)[a]



a, Ar = phenyl; **b**, Ar = *o*-anisyl; **c**, Ar = *o*-tolyl; **d**, Ar = 1-naphthyl

substrate	yield, %	6:7[b]	ee,[b] %, of 6	mp of 6,[d] °C	$[\alpha]_D$ (c)
2a	72	79:21	98	145–147	+33.6° (0.98)[e]
2b	69	85:15	99	144–145	+162° (0.60)[f]
2c	67	88:12	99	127–129	+29.6° (0.61)[f]
2d	68	85:15	96	190–191	+111° (0.52)[e]

[a] For a typical procedure, see ref 9. [b] See ref 8 for conditions for enantiomer and diastereomer analysis. [c] Absolute configurations of **6b–d** were assigned by analogy. [d] Enantiomeric purity >99%. [e] Measured in CH_2Cl_2. [f] Measured in $CHCl_3$.

two sets of experiments represent the first successful application of enantiotopic group discrimination to the generation of enantiomerically enriched phosphorus centers.[14]

Oxidative Coupling. Practical considerations such as deprotonation enantioselectivity, product crystallinity, and ease of chromatographic diastereomer separation led to the selection of the phosphine–boranes **2a–d** for the diphosphine synthesis. Enantioselective deprotonation of these substrates under standard conditions,[9] followed by oxidative coupling with the THF-soluble copper(II) pivalate $[Cu(OPiv)_2]$[15] resulted in the formation of the desired C_2-symmetric products **6a–d** accompanied by minor amounts of the analogous *meso* diastereomers **7a–d** in good yield (eq 5, Table 3). The C_2-symmetric diphosphines **6a–c** (96–99% ee)[16] were separated from the *meso* diastereomeric contaminants **7a–c** by flash chromatography while the purification of **6d** was effected by selective crystallization. All of the bis(phosphine–boranes) produced by this method are white crystalline solids that can be enriched to high enantiomeric purity (>99% ee) by a single recrystallization (ethyl acetate/hexane).

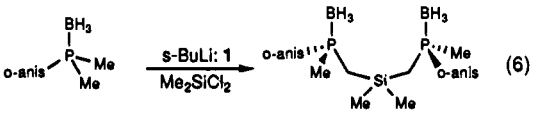
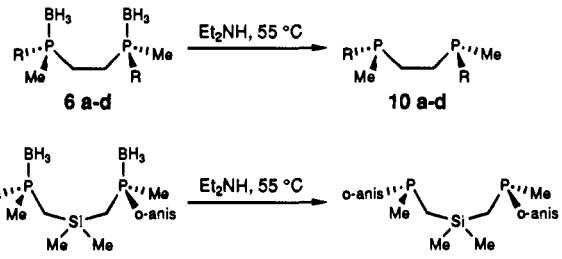


Table 4. Deprotection of Bis(phosphine–Boranes) (Eqs 7 and 8)



substrate	yield, %	$[\alpha]_D$ (c)[a]
6a (R = Ph)	100	**10a**, +69.5° (1.16)
6b (R = *o*-anisyl)	91	**10b**, −212° (1.27)
6c (R = *o*-tolyl)	96	**10c**, −28.9° (1.62)
6d (R = 1-naphthyl)	91	**10d**, −267° (1.40)
8 (R = *o*-anisyl)	81	**11**, −1.14° (1.38)

[a] Rotation measured in CH_2Cl_2.

We have also investigated other coupling methods that take advantage of the enantioselective deprotonation/asymmetric amplification strategy. For example, enantioselective deprotonation of **2b** followed by treatment with 0.45 equiv of Me_2SiCl_2[17] (Et_2O, −20 °C) afforded the C_2-symmetric bis(phosphine–borane) **8** (>99% ee) along with the *meso* diastereomer **9** in a 89:11 ratio, respectively (eq 6). Direct crystallization of the reaction mixture afforded enantiomerically pure C_2 diastereomer **8** in 73% isolated yield (1:1 EtOH/hexane, −25 °C, mp 84–87 °C). Other related diphosphines synthesized by this procedure will be reported in due course.

Phosphine Deprotection. Removal of the borane protecting group may be readily effected by treatment of bis(phosphine–boranes) **6a–d** and **8** with excess diethylamine (neat, 55 °C, 12–18 h)[18] to afford the corresponding (*S,S*)-diphosphines **10a–d** and **11** in excellent yields after flash chromatography (eqs 7 and 8, Table 4).[19,20] Further investigation into the scope of this strategy for ligand synthesis as well as the use of these ligands in asymmetric catalysis will be reported shortly.

Acknowledgment. We gratefully acknowledge the NIH, the NSF, Merck, and Pfizer for research support. The NIH BRS Shared Instrumentation Grant Program (Grant 1-S10-RR04870) and the NSF (Grant CHE88-14019) are acknowledged for providing NMR facilities.

Supporting Information Available: Text describing the experimental procedures, spectral data, and enantiomeric purity assays for all compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) In direct analogy to the stereochemical proof of **2a** (ref 11), phosphine sulfide **4a** was transfomed into (*R*)-methylphenylpropylphosphine sulfide $[\alpha]^{23}_D$ +17.3° (*c* = 1.27, MeOH), lit. $[\alpha]^{23}_D$ +22° (*c* = 1–3, MeOH)). Zon, G.; Debruin, K. E.; Naumann, K.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7023–7027.

(14) The metalation of dimethylphenylphosphine oxide with the *n*-BuLi–(−)-sparteine complex (hexane) has been reported to proceed with low enantioselectivity (~12% ee): Byrne, L. T.; Engelhardt, L. M.; Jacobsen, G. E.; Leung, W.-P.; Papasergio, R. I.; Raston, C. L.; Skelton, B. W.; Twiss, P.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1989**, 105–113.

(15) Maryanoff, C. A.; Maryanoff, B. E.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 5839–5840. For a recent application of the use of $Cu(OPiv)_2$ for related oxidative coupling reactions see ref 4.

(16) In the absence of a double stereodifferentiating bias for the oxidative coupling step, the anticipated product enantiomer ratio (ER) should be the square of the ER of the metalated precursor. For a similar approach to the enantiomeric enrichment of chiral alcohols, see: Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 99–100.

(17) Juge, S.; Merdes, R.; Stephan, M.; Genet, J. P. *Phosphorus, Sulfu, and Silicon Relat. Elem.* **1993**, *77*, 199.

(18) (a) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252. For other methods of BH_3 group removal from phosphine–boranes, see: (b) Yamago, S.; Yanagawa, M.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1994**, 2093–2094. (c) McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319–9322.

(19) Reprotection of diphosphines **10a–d** and **11** with BH_3·THF and analysis by chiral HPLC established that no epimerization occurs during the deprotection reaction.

(20) Aryl-substituted diphosphines such as **10a–d** and **11** are sufficiently stable to air, although the mobile phase was purged with argon prior to chromatography as a precaution. Diphosphines **10a–d** and **11** have been found to be configurationally unstable in chloroform-*d*.