A Direct Synthesis of *P*-Chiral Phosphine−Boranes via Dynamic Resolution of Lithiated Racemic *tert*-Butylphenylphosphine−Borane with (−)-Sparteine

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The preeminence of chiral phosphines as controller ligands for a wide range of asymmetric processes has become firmly established. Although myriad examples of phosphines possessing carbon-centered chirality have been synthesized and subsequently evaluated in the above context, comparatively few *P*-chiral ligands have received scrutiny due to their relative inaccessibility.[2] In this paper, we show that a variety of *P*-chiral phosphine−boranes can be directly prepared from a *racemic* 2°-phosphine−borane precursor with excellent enantiocontrol via dynamic resolution/alkylation of the corresponding lithium derivative in the presence of (−)-sparteine.[3−5]

Studies on Dynamic Resolution. The racemic substrate selected for initial study, (±)-*tert*-butyl phenylphosphine−borane (**1**),[6] was readily prepared in 52% overall yield by treatment of $PhPCl_2$ in Et_2O with *t*-BuMgCl (1 equiv, −78 → 0 °C) followed by direct reduction of the intermediate chlorophosphine ($LiAlH_4$, Et_2O) and complexation with BH_3·SMe_2 (BMS) (Scheme 1). Lithiation of **1** with *n*-BuLi (1.0 equiv) in Et_2O at −78 °C in the presence of (−)-sparteine (1.3 equiv) furnished a nearly homogeneous solution which, upon warming to ca. 0 °C, deposited a voluminous precipitate. Further warming of this suspension to ca. 25 °C for 30 min followed by cooling to −78 °C and alkylative trapping with 2-(chloromethyl)anisole[7] provided the corresponding scalemic phosphine−borane **2** in 74% yield. Analysis of **2** prepared in this manner by chiral HPLC using a CHIRALPAK AD column revealed its enantiomeric excess (ee) to be 88%.[8] Significantly, the extent of enantiomeric enrichment was found to be time and temperature dependent. Accordingly, reduction of the temperature in a typical dynamic resolution experiment to 30 min at 0 °C resulted in a decrease in ee to 35%. By way of contrast, simple stirring of the suspended (−)-sparteine·lithium complex of **1** for 1 h at 25 °C prior to alkylation resulted in an increase in ee to 95%.[8] The absolute sense of optical induction was readily determined to be (*R*) by methylation (CH_3I) of the (−)-sparteine·lithium complex of **1** to secure *tert*-butylmethylphenylphosphine−borane (**3**), in 93% ee ($[\alpha]^{21}_D$ −10 (*c* = 1, CH_3OH) [lit. for the (*R*)-enantiomer, $[\alpha]^{23}_D$ −8.2 (*c* = 1, CH_3OH)[6a]]).

Scheme 1

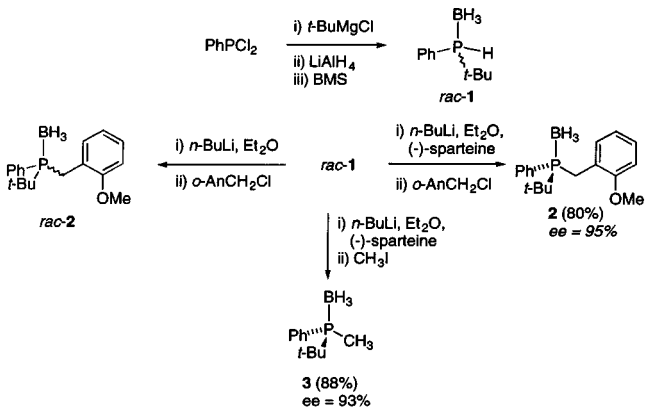
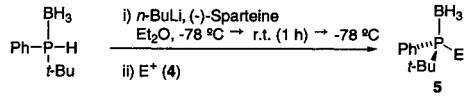
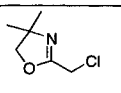
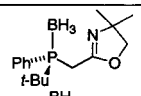
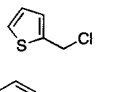
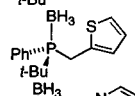
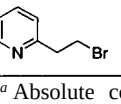
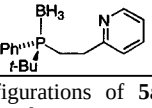


Table 1. Monoalkylations of Dynamically Resolved *tert*-Butylphenylphosphine−Borane



Electrophile (**4**)	Product (**5**)	Yield (%)	ee (%)[a]	$[\alpha]_D$ (*c*)
a 		90	>82[b]	+62° (0.99, CH_2Cl_2)
b 		85	95	+135° (1.04, CH_2Cl_2)
c 		90	92	-50° (1.03, CH_2Cl_2)

[a] Absolute configurations of **5a**−**c** assigned by analogy to **3**. [b] Uncertainty in ee due to poor resolution on HPLC fitted with CHIRALPAK AD column.

Having determined what appeared to be optimum conditions for the dynamic resolution of lithiated **1**, a representative series of halides possessing a secondary ligating moiety were examined as alkylating agents. In all cases, scalemic phosphine−borane precursors to prospective bidentate ligands were produced with excellent enantiomeric differentiation and in good isolated yields (Table 1).[9] It is of interest in a preparative context that

(1) Recipient of a Japan Society for the Promotion of Science Fellowship, 1997.

(2) (a) For a recent review, see: Petrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375−1411. (b) For the use of (−)-sparteine-mediated enantioselective deprotonation in the asymmetric synthesis of *P*-chiral diphosphines, see: Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076. (c) For a route to stereogenic P-trisubstituted phosphorus by crystallization-induced asymmetric transformation, see: Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293−9294.

(3) (a) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158−2160. (b) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209−8216 and references therein.

(4) For a recent review, see: Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447−456.

(5) The stereochemical behavior (racemization) of chiral phosphine−borane anions has been described. Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroatom. Chem.* **1992**, *3*, 563−575. Imamoto, T.; Matsuo, M.; Nonomura, T.; Kishikawa, K.; Yanagawa, M. *Heteroatom. Chem.* **1993**, *4*, 475−486.

(6) (a) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244−5252. (b) Optically pure (*R*)-*tert*-butylphenylphosphine−borane: Imamoto, T.; Matsuo, M.; Nonomura, T.; Kishikawa, K.; Yanagawa, M. *Heteroatom. Chem.* **1993**, *4*, 475−486.

(7) The use of this substrate gave exceptionally well-resolved HPLC traces so that optimization of the conditions for dynamic resolution could be readily achieved.

(8) In all instances involving monohalide trapping agents, an authentic sample of *racemic* phosphine−borane was prepared for comparison by chiral HPLC.

(9) Procedure for a representative dynamic resolution/alkylation of **1**: (*R*)-*P*-(2-Methoxyphenylmethyl)-*P*-*tert*-butylphenylphosphineborane (**2**). A test tube (16 × 100 mm) equipped with a magnetic stirring bar was flame dried under a flow of argon. Ether (2.8 mL), (−)-sparteine (0.15 mL, 0.65 mmol, 1.3 equiv), and *tert*-butylphenylphosphine−borane (90 mg, 0.50 mmol, 1.0 equiv) were added to the tube. The solution was cooled to −78 °C, and *n*-butyllithium (0.21 mL, 0.50 mmol, 2.4 M in hexane, 1.0 equiv) was added. The solution was allowed to warm to room temperature whereupon a thick suspension of white precipitate formed. After the reaction mixture had stirred for 1 h at room temperature (23 °C), it was again cooled to −78 °C and 2-methoxybenzyl chloride (99 mg, 0.63 mmol, 1.3 equiv) was added as a neat liquid. The solution was allowed to warm to −20 °C very slowly (over 2−3 h) and stirred at −20 °C for a total of 24 h. The reaction mixture was washed with 5% aqueous sulfuric acid (2 mL), and the aqueous phase was extracted with ether (3 × 1 mL). The combined organic phases were washed with water (1 mL) and brine (1 mL), dried ($MgSO_4$), and filtered through a short plug of silica gel. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexane for elution), furnishing **2** as a colorless solid (120 mg, 0.40 mmol, 80%): mp 62.6−63.0 °C (1% ethyl acetate/hexane).

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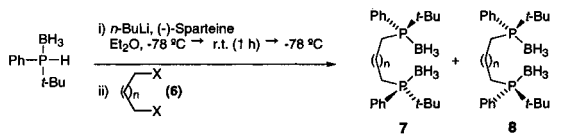
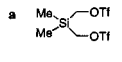
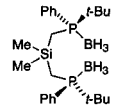
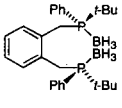
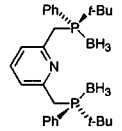
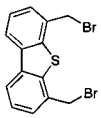
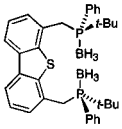
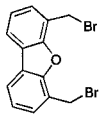
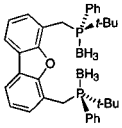
Table 2. Bisalkylations Involving Dynamically Resolved *tert*-Butylphenylphosphine−Borane



	Electrophile (**6**)	Product (**7**)	**7**:**8**[a]	m.p. of **7** (°C)[b]	$[\alpha]_D$ (*c*) of **7**	yield (%)[b]	% ee[c]
a			15.0:1	141-145	-22° (0.99, CH_2Cl_2)	67	d
b			21.7:1	183-190 (decomp.)	+438° (1.03, CH_2Cl_2)	68	>99
c			11.3:1	191-198 (decomp.)	-35° (1.01, CH_2Cl_2)	71	>99
d			18.4:1	210-220 (decomp.)	+39° (1.03, CH_2Cl_2)	76	>99
e			11.8:1	218-229 (decomp.)	+101° (1.01, $CDCl_3$)	75	>99

[a] Diastereomeric ratios were determined by NMR. [b] Melting points and yields determined after recrystallization or chromatography. [c] Percent ee determined before recrystallization by HPLC fitted with a CHIRALPAK AD column. [d] No resolution could be obtained by HPLC fitted with a CHIRALPAK AD column.

nonactivated primary bromides are useful substrates in the dynamic resolution/alkylation procedure (entry c, Table 1).

The use of dihalides as well as related coupling agents was then examined in a study directed toward the synthesis of optically pure *P*-chiral bis(phosphine−boranes). In principle, optical amplification[6a] should be operative in these instances leading to the formation of the desired C_2-symmetric diphosphine derivatives contaminated with minor amounts of the corresponding meso diastereomers.[10,11] In the majority of cases, enantiomerically pure (>99%) bis(phosphine−boranes) could be obtained from the crude bisalkylation products by chromatography or a single recrystallization. The results of a number of representative bisalkylations are illustrated in Table 2.

Removal of the borane protecting group could be achieved by treatment of the bis(phosphine−boranes) with excess diethylamine (neat, 55 °C, 12 h)[6a] or, more conveniently, using pyrrolidine (neat, rt to 35 °C, 24 h). Evaporation of the pyrrolidine followed by low-temperature sublimation of the residual pyrrolidine−borane in vacuo furnished the corresponding diphosphines in excellent yield.[12] In conclusion, we have shown that dynamic resolution/alkylation is a useful procedure for the synthesis of a wide range of scalemic *P*-chiral phosphine−boranes. Additional details on the scope of this process for ligand construction as well as the use of these new ligand types in asymmetric catalysis will be the topics of future accounts from these laboratories.

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Supporting Information Available: Text describing the experimental procedures, spectral data, and enantiomeric purity assays for all compounds (21 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(10) In all instances involving coupling with biselectrophiles, an authentic sample of meso bis(phosphine−borane) was prepared for comparative purposes.

(11) An additional strategy that employs asymmetric amplification has appeared.[2b]

(12) Reprotection of the diphosphines derived from **5b**, **7c**, **7d**, and **7e** with BH_3·SMe_2 and analysis by HPLC fitted with a CHIRALPAK AD column established that no epimerization occurs during the pyrrolidine-mediated deprotection reaction.