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One-ligand Catalytic Asymmetric Deprotonation of a Phosphine Borane: Synthesis of *P*-Stereogenic Bisphosphine Ligands

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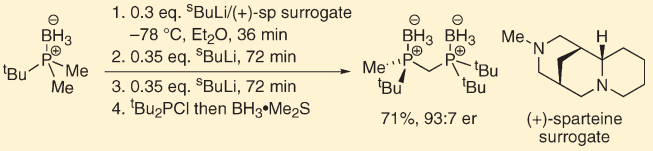
Supporting Information

ABSTRACT: A new protocol for the catalytic asymmetric deprotonation of a phosphine borane using *s*-BuLi and substoichiometric quantities of chiral diamines is reported. The method involves three sequential additions of *s*-BuLi, and use of (−)-sparteine or the (+)-sparteine surrogate facilitates access to *P*-stereogenic phosphines with opposite configuration. The method is exemplified by the catalytic asymmetric synthesis of each enantiomer of precursors to QuinoxP*, trichickenfootphos, and Mini-PHOS.



P-Stereogenic bisphosphine ligands are widely used in transition metal-catalyzed asymmetric hydrogenation[1] and representative examples of ligands developed in academia and industry include Mini-PHOS,[2] trichickenfootphos (TCFP)[3] and Quinox P*[4] (Figure 1). Despite the utility of such *P*-stereogenic chiral ligands, synthesis of enantiopure ligand precursors has involved asymmetric deprotonation in the presence of a stoichiometric amount of (−)-sparteine[2a] or resolution either using chiral stationary phase HPLC[3a] or via the preparation of diastereomeric phosphine adducts.[2c] As a result, our recent efforts[5−8] have focused on the development of a *catalytic* asymmetric deprotonation variant of the lithiation-trapping of dimethylphosphine boranes, first reported by Evans et al.[9] and subsequently exploited in the synthesis of *P*-stereogenic bisphosphine ligands by Imamoto and co-workers.[10]

In particular, we have investigated the lithiation-trapping of *t*-butyldimethylphosphine borane **1** using *s*-BuLi in the presence of a substoichiometric amount of (−)-sparteine or the (+)-sparteine surrogate[11,12] to enable the catalytic asymmetric synthesis of both antipodes of *P*-stereogenic compounds. This approach is termed one-ligand catalysis to distinguish it from the two-ligand catalytic protocol that is required for high yield and enantioselectivity in the lithiation-trapping of *N*-Boc pyrrolidine and *O*-alkyl carbamates.[5,8] An example of the one-ligand catalytic deprotonation-trapping of phosphine borane **1** (→ (*R*)- or (*S*)-**2**) is shown in Scheme 1.[5] Deprotonation of **1** was accomplished using *s*-BuLi and 0.2 equiv of (−)-sparteine in Et_2O at −78 °C and trapping with oxygen produced hydroxy phosphine borane (*R*)-**2** in 57% yield and 77:23 er. Slightly better enantioselectivity was obtained using the (+)-sparteine surrogate: a 54% yield of (*S*)-**2** of 86:14 er was obtained. The moderate enantioselectivity is the key limitation of this one-ligand catalytic approach. Hence, we now report a modified protocol involving sequential addition of *s*-BuLi, which solves this limitation.

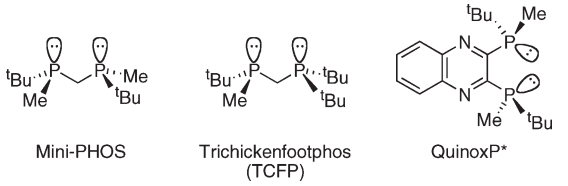
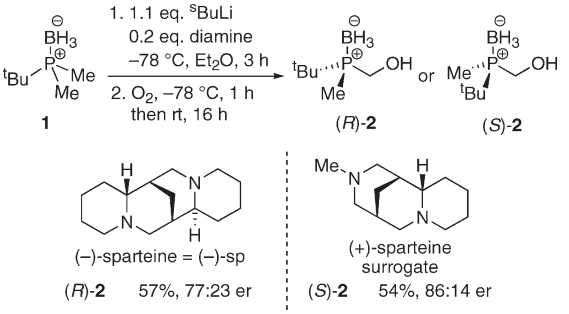


Figure 1. Examples of *P*-stereogenic bisphosphine ligands.

Scheme 1



Furthermore, our method is applied to the catalytic asymmetric synthesis of precursors to the important *P*-stereogenic bisphosphine ligands QuinoxP*, trichickenfootphos and Mini-PHOS.

For evaluation of catalytic efficiency, we selected the lithiation and benzophenone trapping of phosphine borane **1** to give hydroxy phosphine borane (*S*)-**3** (using (−)-sparteine) or (*R*)-**3** (using the (+)-sparteine surrogate) and the results are shown

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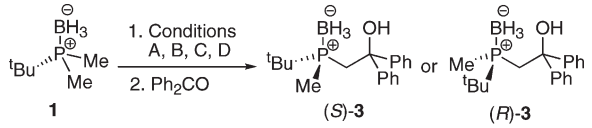
Table 1. Asymmetric Lithiation-Trapping of Phosphine Borane 1



Conditions:

A: 1.1 eq. ^{s}BuLi, 1.0 eq. diamine, Et_2O, –78 °C, 3 h

B: 1.1 eq. ^{s}BuLi, 0.2 eq. diamine, Et_2O, –78 °C, 3 h

C: (i) 0.2 eq. ^{s}BuLi, 0.2 eq. diamine, Et_2O, –78 °C, 36 min
(ii) 0.4 eq. ^{s}BuLi, –78 °C, 72 min
(iii) 0.4 eq. ^{s}BuLi, –78 °C, 72 min

D: (i) 0.3 eq. ^{s}BuLi, 0.3 eq. diamine, Et_2O, –78 °C, 36 min
(ii) 0.35 eq. ^{s}BuLi, –78 °C, 72 min
(iii) 0.35 eq. ^{s}BuLi, –78 °C, 72 min

entry	diamine	equiv of diamine	conditions	yield (%)[a]	er (*S*:*R*)[b]
1	(−)-sp	1.0	A	72	95:5
2	(−)-sp	0.2	B	64	80:20
3	(−)-sp	0.2	C	94	86:14
4	(−)-sp	0.3	D	89	86:14
5	(+)-sp surrogate	1.0	A	75	8:92
6	(+)-sp surrogate	0.2	B	63	14:86
7	(+)-sp surrogate	0.2	C	84	12:88
8	(+)-sp surrogate	0.3	D	83	9:91

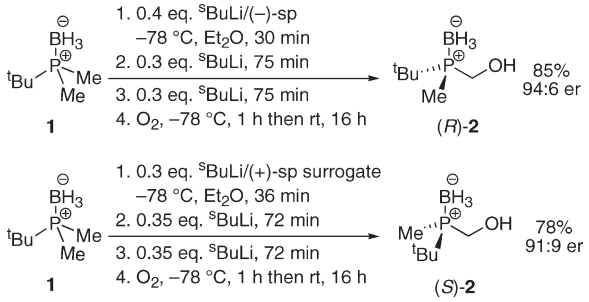
[a] Yield after purification by column chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC.

in Table 1. For comparison, a stoichiometric reaction using (−)-sparteine was carried out. Thus, *s*-BuLi (1.1 equiv) and (−)-sparteine (1.0 equiv) were premixed in Et_2O at −78 °C. Then, phosphine borane **1** (in Et_2O) was added and the reaction was left for 3 h. After trapping with benzophenone, workup, and purification by chromatography, adduct (*S*)-**3** was obtained in 72% yield and 95:5 er (Entry 1). A similar procedure but using 0.2 equiv of (−)-sparteine (our originally reported one-ligand catalytic procedure[5]) delivered (*S*)-**3** in 64% yield and lower enantioselectivity (80:20 er, entry 2). The reduced enantioselectivity is due to background racemic lithiation from uncomplexed *s*-BuLi. To minimize this pathway, we decided to investigate the addition of *s*-BuLi in batches during the 3 h lithiation period.

Thus, a revised catalytic protocol using 0.2 equiv of (−)-sparteine was devised. To start with, phosphine borane **1** (in Et_2O) was added to a premixed solution of 0.2 equiv of *s*-BuLi/(−)-sparteine (in Et_2O at −78 °C). After 36 min, 0.4 equiv of *s*-BuLi was added and the solution was stirred for 72 min before addition of another 0.4 equiv of *s*-BuLi. A further 72 min of reaction time was allowed (giving a total of 3 h) before trapping with benzophenone. To our delight, this sequential addition approach gave higher enantioselectivity: adduct (*S*)-**3** of 86:14 er was isolated in 94% yield (entry 3). A related protocol but with 0.3 equiv of (−)-sparteine gave the same enantioselectivity (86:14 er, entry 4).

A similar set of results was obtained using the (+)-sparteine surrogate (entries 5−8). Using stoichiometric (+)-sparteine surrogate, adduct (*R*)-**3** was formed in 75% yield and 92:8 er (entry 5). This is slightly lower enantioselectivity than that obtained with (−)-sparteine (95:5 er entry 1) and such a trend appears to be general for asymmetric lithiation-trapping of

Scheme 2



phosphine boranes and sulfides.[12,13] As we have noted previously, better enantioselectivity (86:14 er, 63% yield, entry 6) was obtained using the original catalytic procedure with the (+)-sparteine surrogate than that obtained with (−)-sparteine (80:20 er, entry 2). Our conjecture is that *s*-BuLi/(+)-sparteine surrogate deprotonates **1** faster than *s*-BuLi/(−)-sparteine (as established from a competition experiment[8]) and this facilitates more efficient catalytic turnover of the (+)-sparteine surrogate. Crucially, use of the new sequential addition method with the (+)-sparteine surrogate led to further improvements (entries 7−8) such that at 0.3 equiv of loading, adduct (*R*)-**3** was obtained in 83% yield and 91:9 er (entry 8), a result which essentially matches that obtained with a stoichiometric amount of the (+)-sparteine surrogate (92:8 er, entry 5). This 0.3 equivalent sequential addition method was carried out as follows. Phosphine borane **1** (in Et_2O) was added to 0.3 equiv of *s*-BuLi/(+)-sparteine surrogate (in Et_2O at −78 °C). After 36 min, 0.35 equiv of *s*-BuLi was added and the solution was stirred for 72 min before addition of 0.35 equiv of *s*-BuLi. The reaction was stirred for 72 min (total reaction time = 3 h) and then trapped with benzophenone.

The use of a syringe pump for the slow addition of *s*-BuLi over 3 h was also explored. However, the syringe would often become blocked presumably due to crystallization of *s*-BuLi at the tip of the syringe. As a result, the sequential addition protocol was preferred. From the catalytic lithiation-trapping of phosphine borane **1** we conclude that the sequential approach with 0.3 equiv of (+)-sparteine surrogate is optimal as it facilitates yield and enantioselectivity which are comparable to those obtained from the stoichiometric reaction. Hence, this protocol was adopted for the catalytic asymmetric synthesis of precursors to some *P*-stereogenic bisphosphine ligands. In contrast, it appeared that a higher loading of (−)-sparteine would be required to match the stoichiometric reaction and a sequential protocol using 0.4 equiv of (−)-sparteine was therefore deployed.

Next, the sequential catalytic lithiation-trapping approach was used in the formal synthesis of some *P*-stereogenic ligands. First, we explored the synthesis of hydroxy phosphine borane (*R*)- and (*S*)-**2** which Imamoto has used to synthesize QuinoxP*.[4,14] Thus, phosphine borane **1** was added to 0.4 equiv of *s*-BuLi/(−)-sparteine (in Et_2O at −78 °C) and stirred for 30 min. Then, 0.3 equiv of *s*-BuLi was added and the solution was stirred for 75 min. A further 0.3 equiv of *s*-BuLi was added and, after 75 min reaction time, oxygen was used to trap the lithiated intermediate. After workup and chromatography, hydroxy phosphine borane (*R*)-**2** was isolated in 85% yield and 94:6 er (Scheme 2). The enantioselectivity was essentially the same as that obtained using stoichiometric (−)-sparteine (see Table 1, entry 1) and

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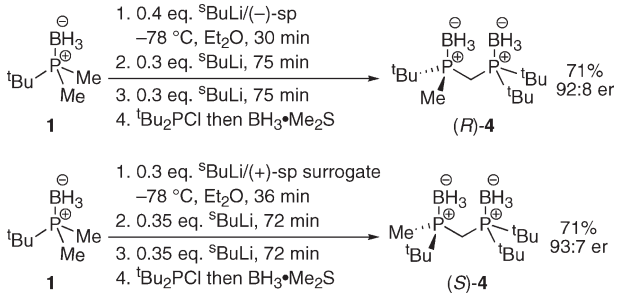
Scheme 3

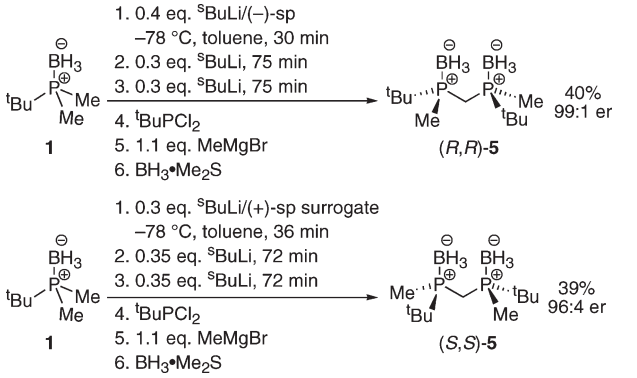


justifies the use of 0.4 equiv of (−)-sparteine and a sequential *s*-BuLi addition protocol. A similarly good result was obtained using 0.3 equiv of (+)-sparteine surrogate: adduct (*S*)-**2** was obtained in 78% yield and 91:9 er (Scheme 2). In addition, it was also possible to recover the (+)-sparteine surrogate (75% recovery) from the acidic aqueous layer during the workup (see Experimental Section). Thus, this approach facilitates the catalytic asymmetric synthesis of either enantiomer of Imamoto's bisphosphine ligand, QuinoxP*.

We then explored the direct synthesis of bisphosphine boranes (*R*)- and (*S*)-**4** (precursor to trichickenfootphos[3]) and (*R,R*)- and (*S,S*)-**5** (precursor to MiniPHOS[2]) by trapping the lithiated intermediate with appropriate chlorophosphines. The syntheses are summarized in Schemes 3 and 4. Our approach to trichickenfootphos involves asymmetric deprotonation of phosphine borane **1** (using *s*-BuLi and a chiral diamine), reaction with *t*-Bu_2PCl and then final *P*-protection with BH_3•Me_2S. Before investigating the catalytic asymmetric synthesis, the stoichiometric approach was evaluated and the key observation was that the *t*-Bu_2PCl electrophile should be added as a THF solution to enable high yields of (*R*)-**4**. Apparently, the (−)-sparteine-complexed lithiated intermediate is not that reactive (presumably due to steric hindrance) and does not trap efficiently in Et_2O. We speculate that addition of a THF solution of the *t*-Bu_2PCl probably leads to a more reactive THF-complexed lithiated phosphine borane.[15] With this information in hand, we performed the catalytic variants. Thus, bisphosphine borane (*R*)-**4** was formed in 71% yield and 92:8 er from a one-pot process using 0.4 equiv of (−)-sparteine and sequential addition of *s*-BuLi. In a similar fashion, the antipode (*S*)-**4** (71% yield, 93:7 er) was obtained via the protocol with 0.3 equiv of (+)-sparteine surrogate (Scheme 3).

Finally, we also carried out the catalytic asymmetric synthesis of Mini-PHOS precursors (*R,R*)- and (*S,S*)-**5** (Scheme 4). The lithiated phosphine borane was trapped with *t*-$BuPCl_2$ (in THF) and then reacted with methyl magnesium bromide to displace the intermediate chlorophosphine before protecting the phosphine with BH_3•Me_2S. In these reactions, the best yields were obtained with toluene as the solvent (rather than Et_2O) and the products were purified by recrystallization of the crude reaction mixture. This direct recrystallization method removes the *meso*-bisphosphine borane diastereomer that is produced in ∼50% yield due to the nonselective addition of the methyl magnesium bromide. Use of 0.4 equiv of (−)-sparteine and sequential addition of *s*-BuLi gave bisphosphine borane (*R,R*)-**5** in 40% yield and 99:1 er. Similarly, use of 0.3 equiv of (+)-sparteine surrogate delivered (*S,S*)-**5** in 39% yield and 96:4 er (Scheme 4). These direct, catalytic, one-pot syntheses of (*R,R*)- and (*S,S*)-**5** represent the most efficient route to either enantiomer of Mini-PHOS.

Scheme 4



In summary, a simple sequential addition protocol for the efficient catalytic asymmetric deprotonation of phosphine borane **1** using *s*-BuLi and 0.4 equiv of (−)-sparteine or 0.3 equiv of (+)-sparteine surrogate has been optimized. Our approach means that it is no longer necessary to use stoichiometric amounts of chiral diamines in such lithiation-trapping reactions. Furthermore, we showcase our new catalytic deprotonation protocol in the asymmetric synthesis of (*R*)- or (*S*)-**4** and (*R,R*)- or (*S,S*)-**5** which are protected forms of the *P*-stereogenic bisphosphine ligands trichickenfootphos and Mini-PHOS respectively.

EXPERIMENTAL SECTION

General Experimental Details. Water is distilled water. Brine refers to a saturated aqueous solution. Et_2O, THF and toluene were freshly distilled from benzophenone ketyl or dispensed from a solvent purification system under a N_2 atmosphere. (−)-Sparteine and the (+)-sparteine surrogate were distilled over CaH_2 before use. Petrol refers to the fraction of petroleum ether boiling in the range 40−60 °C. All reactions were carried out under O_2-free Ar using oven-dried and/or flame-dried glassware. *s*-BuLi was titrated against *N*-benzylbenzamide before use.[16] Flash column chromatography was carried out using silica gel 60 (0.035−0.070 mm particle size). Thin layer chromatography was carried out using F_{254} aluminum-backed silica plates. ^1H (400 MHz), ^{13}C (100.6 MHz) and ^{31}P (162 MHz) NMR spectra were recorded on 400 MHz instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H 7.27) and or $CDCl_3$ (δ_C 77.0, central line of triplet). ^{13}C and ^{31}P NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Optical rotations were recorded at rt (20 °C) (using the sodium D line; 259 nm) and $[\alpha]_D$ measurements are given in units of 10^{-1} deg cm^2 g^{-1}. Chiral stationary phase HPLC was performed using a multiple wavelength, UV/vis diode array detector; integration was performed at 210 or 230 nm. Phosphine borane **1**[17] and the (+)-sparteine surrogate[3] were prepared using the published procedures.

General Procedure A: Catalytic Deprotonation using 0.2 Equivalent Ligand. *s*-BuLi (0.23 mL of a 1.3 M solution in cyclohexane, 0.3 mmol, 0.2 equiv) was added dropwise to a stirred solution of (−)-sparteine or the (+)-sparteine surrogate (0.30 mmol, 0.2 equiv) in Et_2O (3 mL) at −78 °C under Ar. After stirring for 15 min, a solution of phosphine borane **1** (200 mg, 1.52 mmol, 1.0 equiv) in Et_2O (4 mL) was added dropwise over 30 min using a syringe pump. The resulting solution was stirred for 36 min. Then, *s*-BuLi (0.47 mL of a 1.3 M solution in cyclohexane, 0.61 mmol, 0.4 equiv) was added dropwise and the resulting solution was stirred for 72 min. Then, *s*-BuLi (0.47 mL of a

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1.3 M solution in cyclohexane, 0.61 mmol, 0.4 equiv) was added dropwise. The resulting solution was stirred for 72 min to give a solution of the lithiated intermediate in Et_2O.

General Procedure B: Catalytic Deprotonation using 0.3 Equivalent Ligand. *s*-BuLi (0.3 mL of a 1.3 M solution in cyclohexane, 0.4 mmol, 0.3 equiv) was added dropwise to a stirred solution of (−)-sparteine or the (+)-sparteine surrogate (0.4 mmol, 0.3 equiv) in Et_2O or toluene (5 mL) at −78 °C under Ar. After stirring for 15 min, a solution of phosphine borane **1** (180 mg, 1.36 mmol, 1.0 equiv) in Et_2O or toluene (2 mL) was added dropwise over 30 min using a syringe pump. The resulting solution was stirred for 36 min. Then, *s*-BuLi (0.36 mL of a 1.3 M solution in cyclohexane, 0.45 mmol, 0.35 equiv) was added dropwise and the resulting solution was stirred for 72 min. Then, *s*-BuLi (0.36 mL of a 1.3 M solution in cyclohexane, 0.45 mmol, 0.35 equiv) was added dropwise. The resulting solution was stirred for 72 min to give a solution of the lithiated intermediate in Et_2O.

General Procedure C: Catalytic Deprotonation using 0.4 Equivalent Ligand. *s*-BuLi (2.33 mL of a 1.3 M solution in cyclohexane, 3.0 mmol, 0.4 equiv) was added dropwise to a stirred solution of (−)-sparteine (3.0 mmol, 0.4 equiv) in Et_2O or toluene (15 mL) at −78 °C under Ar. After stirring for 15 min, a solution of phosphine borane **1** (1.0 g, 7.58 mmol, 1.0 equiv) in Et_2O or toluene (10 mL) was added dropwise over 30 min using a syringe pump. The resulting solution was stirred for 30 min. Then, *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.28 mmol, 0.3 equiv) was added dropwise and the resulting solution was stirred for 75 min. Then, *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.28 mmol, 0.3 equiv) was added dropwise. The resulting solution was stirred for 75 min to give a solution of the lithiated intermediate in Et_2O.

(*S*)-*P*-(2,2-Diphenyl-2-hydroxyethyl)-*P*-methyl-*tert*-butylphosphine (*S*)-3 (Table 1, entry 3). Using general procedure A, phosphine borane **1** (200 mg, 1.52 mmol, 1.0 equiv) in Et_2O (4 mL), *s*-BuLi (0.23 mL of a 1.3 M solution in cyclohexane, 0.3 mmol, 0.2 equiv) and (−)-sparteine (71 mg, 0.30 mmol, 0.2 equiv) in Et_2O (3 mL), *s*-BuLi (0.47 mL of a 1.3 M solution in cyclohexane, 0.61 mmol, 0.4 equiv) and then *s*-BuLi (0.47 mL of a 1.3 M solution in cyclohexane, 0.61 mmol, 0.4 equiv) gave the lithiated intermediate. Then, a solution of benzophenone (304 mg, 1.7 mmol, 1.1 equiv) in Et_2O (2 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. 5% $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 19:1 petrol-EtOAc and then 9:1 petrol-EtOAc as eluent gave adduct (*S*)-**3** (446 mg, 94%, 86:14 er by CSP-HPLC) as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.50 (m, 4H), 7.38−7.31 (m, 4H), 7.28−7.21 (m, 2H), 4.58 (s, 1H), 2.88 (t, J = 14.5 Hz, 1H), 2.67 (dd, J = 14.5, 6.5 Hz, 1H), 1.17 (d, J = 13.5 Hz, 9H), 0.74 (d, J = 10.0 Hz, 3H), 1.10−0.15 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.7 (d, J = 8.5 Hz), 145.2 (d, J = 2.0 Hz), 128.3, 128.1, 127.1, 126.1, 125.3, 77.0 (d, J = 1.0 Hz), 34.2 (d, J = 28.0 Hz), 28.0 (d, J = 36.5 Hz), 24.7 (d, J = 2.0 Hz), 6.4 (d, J = 35.0 Hz); ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$) δ 20.6 (br m); HPLC: Daicel Chiralcel OD, 19:1 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 254 nm, 11.0 min [(*R*)-**3**], 13.1 min [(*S*)-**3**]. Spectroscopic data consistent with those reported in the literature.[12b]

(*R*)-*P*-(2,2-Diphenyl-2-hydroxyethyl)-*P*-methyl-*tert*-butylphosphine (*R*)-3 (Table 1, entry 8). Using general procedure B, phosphine borane **1** (231 mg, 1.75 mmol, 1.0 equiv) in Et_2O (3 mL), *s*-BuLi (0.4 mL of a 1.3 M solution in cyclohexane, 0.5 mmol, 0.3 equiv) and (+)-sparteine surrogate (102 mg, 0.5 mmol, 0.3 equiv) in Et_2O (5 mL), *s*-BuLi (0.47 mL of a 1.3 M solution in cyclohexane, 0.6 mmol, 0.35 equiv) and then *s*-BuLi (0.47 mL of a 1.3 M solution in cyclohexane, 0.6 mmol, 0.35 equiv) gave the lithiated intermediate. Then, a solution of benzophenone (383 mg, 2.0 mmol, 1.2 equiv) in Et_2O (3 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. 5% $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 19:1 petrol-EtOAc and then 9:1 petrol-EtOAc as eluent gave adduct (*R*)-**3** (457 mg, 83%, 91:9 er by CSP-HPLC) as a white solid, HPLC: Daicel Chiralcel OD, 19:1 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 254 nm, 11.5 min [(*R*)-**3**], 13.6 min [(*S*)-**3**].

(*R*)-*tert*-Butyl(hydroxymethyl)methylphosphine borane (*R*)-2 (Scheme 2). Using general procedure C, phosphine borane **1** (1.0 g, 7.58 mmol, 1.0 equiv) in Et_2O (10 mL), *s*-BuLi (2.33 mL of a 1.3 M solution in cyclohexane, 3.0 mmol, 0.4 equiv) and (−)-sparteine (710 mg, 3.0 mmol, 0.4 equiv) in Et_2O (15 mL), *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.28 mmol, 0.3 equiv) and then *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.28 mmol, 0.3 equiv) gave the lithiated intermediate. Then, the mixture was allowed to warm to rt over 16 h under an atmosphere of O_2 (balloon of O_2). 20% $Na_2SO_{3(aq)}$ (25 mL) and 5% $HCl_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (25 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 3:1 petrol-EtOAc and then EtOAc as eluent gave adduct (*R*)-**2** (958 mg, 85%, 94:6 er by CSP-HPLC of the phosphine sulfide) as a white solid, $[\alpha]_D$ −10.3 (*c* 0.9 in $CHCl_3$) (lit.,[14] −9.8 (*c* 0.47 in $CHCl_3$) for (*R*)-**2** of 95:5 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (d, J = 13.5 Hz, 1H), 3.94 (dd, J = 13.5, 2.5 Hz, 1H), 2.17 (s, 1H), 1.24 (d, J = 10.0 Hz, 3H), 1.18 (d, J = 13.5 Hz, 9H), 0.36 (qd, J = 95.0, 12.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 57.1 (d, J = 38.0 Hz), 27.3 (d, J = 32.0 Hz), 25.5 (d, J = 2.0 Hz), 2.8 (d, J = 34.5 Hz); ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$) δ 28.0 (br m). Spectroscopic data consistent with those reported in the literature.[6]

(*S*)-*t*-Butyl(hydroxymethyl)methylphosphine Sulfide. A mixture of phosphine borane (*R*)-**2** (50 mg, 0.34 mmol, 1.0 equiv), DABCO (45 mg, 0.40 mmol, 1.2 equiv) and sulfur (27 mg, 0.89 mmol, 2.5 equiv) in dry, degassed toluene (5 mL) was stirred and heated at 80 °C under Ar for 16 h. The mixture was allowed to cool to rt and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 2:1 petrol-EtOAc gave (*S*)-phosphine sulfide (29 mg, 52%, 94:6 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −7.0 (*c* 1.1 in $CHCl_3$)(lit.,[18] +3.3 (*c* 1.1 in $CHCl_3$) for (*R*)-phosphine sulfide of 97:3 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (d, J = 12.5 Hz, 1H), 3.74 (d, J = 12.5 Hz, 1H), 2.92 (br s, 1H), 1.62 (d, J = 12.0 Hz, 3H), 1.23 (d, J = 16.0 Hz, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 57.5 (d, J = 50.0 Hz), 32.6 (d, J = 47.5 Hz), 24.5 (d, J = 1.0 Hz), 12.3 (d, J = 48.5 Hz); ^{31}P{^{1}H} (161.9 MHz, $CDCl_3$) δ 63.1; HPLC: Daicel Chiralcel OD, 97:3 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 230 nm, 26.2 min [(*R*)], 28.0 min [(*S*)]. Spectroscopic data consistent with those reported in the literature.[18]

(*S*)-*tert*-Butyl(hydroxymethyl)methylphosphine Borane (*S*)-2 (Scheme 2). Using general procedure B, phosphine borane **1** (2.0 g, 15.2 mmol, 1.0 equiv) in Et_2O (20 mL), *s*-BuLi (3.5 mL of a 1.3 M solution in cyclohexane, 4.5 mmol, 0.3 equiv) and (+)-sparteine surrogate (883 mg, 4.5 mmol, 0.3 equiv) in Et_2O (30 mL), *s*-BuLi (4.1 mL of a 1.3 M solution in cyclohexane, 5.3 mmol, 0.35 equiv) and then *s*-BuLi (4.1 mL of a 1.3 M solution in cyclohexane, 5.3 mmol, 0.35 equiv) gave the lithiated intermediate. Then, the mixture was allowed to warm to rt over 16 h under an atmosphere of O_2 (balloon of O_2). 20% $Na_2SO_{3(aq)}$ (25 mL) and 5% $HCl_{(aq)}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (25 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography

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using 3:1 petrol-EtOAc and then EtOAc as eluent gave adduct (*S*)-**2** (1.76 g, 78%, 91:9 er by CSP-HPLC of the phosphine sulfide) as a white solid, $[\alpha]_D$ +6.0 (*c* 1.0 in $CHCl_3$).

Recovery of the (+)-Sparteine Surrogate. The acidic aqueous layer was basified by the dropwise addition of 5 M $NaOH_{(aq)}$ (25 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give crude (+)-sparteine surrogate (665 mg, 75% recovery) as a pale yellow oil.

(*R*)-*t*-Butylmethylphosphino-di-*t*-butylphosphinomethane Diborane (*R*)-4 (Scheme 3). Using general procedure C, phosphine borane **1** (500 mg, 3.79 mmol, 1.0 equiv) in Et_2O (5 mL), *s*-BuLi (1.17 mL of a 1.3 M solution in cyclohexane, 1.5 mmol, 0.4 equiv) and (−)-sparteine (355 mg, 1.5 mmol, 0.4 equiv) in Et_2O (7.5 mL), *s*-BuLi (0.87 mL of a 1.3 M solution in cyclohexane, 1.14 mmol, 0.3 equiv) and then *s*-BuLi (0.87 mL of a 1.3 M solution in cyclohexane, 1.14 mmol, 0.3 equiv) gave the lithiated intermediate. Then, a solution of *t*-Bu_2PCl (753 mg, 4.2 mmol, 1.1 equiv) in THF (5 mL) was added dropwise over 10 min. The mixture was stirred at −78 °C for 1 h and then at rt for 14 h. Then, $BH_3 \cdot SMe_2$ (2.84 mL of 2.0 M solution in THF, 5.68 mmol, 1.5 equiv) was added dropwise and the resulting mixture was stirred at rt for 4 h. 5% $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 19:1 petrol-Et_2O as eluent gave adduct (*R*)-**4** (783 mg, 71%, 92:8 er by CSP-HPLC of the phosphine sulfide) as a white solid, R_F (19:1 petrol-Et_2O) 0.05; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (d, *J* = 13.0 Hz, 1H), 1.90 (dd, *J* = 13.0, 1.5 Hz, 1H), 1.59 (d, *J* = 10.0 Hz, 3H), 1.36 (d, *J* = 13.5 Hz, 9H), 1.29 (d, *J* = 12.5 Hz, 9H), 1.21 (d, *J* = 13.5 Hz, 9H), 1.10−0.20 (br m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 34.0 (dd, *J* = 25.0, 2.5 Hz), 33.2 (dd, *J* = 25.0, 1.0 Hz), 29.7 (dd, *J* = 33.0, 3.5 Hz), 28.1 (d, *J* = 2.0 Hz), 27.6 (d, *J* = 1.5 Hz), 25.0 (d, *J* = 2.0 Hz), 8.9 (dd, *J* = 20.5, 14.5 Hz), 6.3 (d, *J* = 32.5 Hz); ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$) δ 48.5 (br d, *J* = 68.5 Hz), 31.9 (br d, *J* = 68.5 Hz). Spectroscopic data consistent with those reported in the literature.[3a]

(*S*)-*t*-Butylmethylphosphino-di-*t*-butylphosphinomethane Disulfide. A mixture of phosphine borane (*R*)-**4** (100 mg, 0.34 mmol, 1.0 equiv), DABCO (85 mg, 0.76 mmol, 2.2 equiv) and sulfur (55 mg, 1.7 mmol, 5.0 equiv) in dry, degassed toluene (10 mL) was stirred and heated at 80 °C under Ar for 16 h. The mixture was allowed to cool to rt and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 7:1 petrol-EtOAc gave (*S*)-phosphine sulfide (109 mg, 97%, 92:8 er by CSP-HPLC) as a white solid, mp 122−123 °C; R_F(7:1 petrol-EtOAc) 0.2; $[\alpha]_D$ +47.4 (*c* 1.0 in $CHCl_3$); IR (NaCl) 2962, 2869, 1472, 1393, 1367, 1217, 1167, 891, 759, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (dt, *J* = 15.0, 12.5 Hz, 1H), 2.44 (td, *J* = 15.0, 10.0 Hz, 1H), 2.12 (d, *J* = 12.5 Hz, 3H), 1.49 (d, *J* = 16.0 Hz, 9H), 1.35 (d, *J* = 15.0 Hz, 9H), 1.25 (d, *J* = 16.5 Hz, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 40.0 (dd, *J* = 41.5, 3.0 Hz), 39.1 (d, *J* = 42.0 Hz), 35.7 (dd, *J* = 52.0, 3.5 Hz), 28.0 (d, *J* = 2.0 Hz), 27.4 (d, *J* = 1.5 Hz), 24.4 (d, *J* = 2.0 Hz), 21.5 (dd, *J* = 38.5, 28.0 Hz), 15.2 (d, *J* = 52.0 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 59.3 (d, *J* = 23.0 Hz), 76.6 (d, *J* = 23.0 Hz); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{32}P_2S_2$ $(M + Na)^+$ 349.1313, found 349.314; HPLC: Daicel Chiralpak AD, 97:3 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 210 nm, 12.1 min [(*S*)], 14.0 min [(*R*)].

(*S*)-*t*-Butylmethylphosphino-di-*t*-butylphosphinomethane Diborane (*S*)-4 (Scheme 3). Using general procedure B, phosphine borane **1** (1.0 g, 7.58 mmol, 1.0 equiv) in Et_2O (10 mL), *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.27 mmol, 0.3 equiv) and (+)-sparteine surrogate (441 mg, 2.27 mmol, 0.3 equiv) in Et_2O (15 mL), *s*-BuLi (2.0 mL of a 1.3 M solution in cyclohexane, 2.6 mmol, 0.35 equiv) and then *s*-BuLi (2.0 mL of a 1.3 M solution in cyclohexane, 2.6 mmol, 0.35 equiv) gave the lithiated intermediate. Then, a solution of *t*-Bu_2PCl (1.51 g, 8.33 mmol, 1.1 equiv) in THF (10 mL) was added dropwise over 20 min. The mixture was stirred at −78 °C for 1 h and then at rt for 15 h. Then, $BH_3 \cdot SMe_2$ (5.68 mL of 2.0 M solution in THF, 11.4 mmol, 1.5 equiv) was added dropwise and the resulting mixture was stirred at rt for 4 h. 5% $HCl_{(aq)}$ (25 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 19:1 petrol-Et_2O as eluent gave adduct (*S*)-**4** (1.57 g, 71%, 93:7 er by CSP-HPLC of the phosphine sulfide) as a white solid, $[\alpha]_D$ −4.4 (*c* 1.2 in $CHCl_3$).

(*R*,*R*)-bis(*t*-Butylmethylphosphino)methane (*R*,*R*)-5 (Scheme 4). Using general procedure C, phosphine borane **1** (1.00 g, 7.6 mmol, 1.0 equiv) in toluene (20 mL), *s*-BuLi (2.32 mL of a 1.3 M solution in cyclohexane, 3.0 mmol, 0.4 equiv) and (−)-sparteine (710 mg, 3.0 mmol, 0.4 equiv) in toluene (15 mL), *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.3 mmol, 0.3 equiv) and then *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.3 mmol, 0.3 equiv) gave the lithiated intermediate. Then, a solution of *t*-$BuPCl_2$ (1.31 g, 8.3 mmol, 1.1 equiv) in toluene (10 mL) was added dropwise over 20 min. The mixture was stirred at −78 °C for 1 h and then at rt for 14 h. The mixture was cooled to −78 °C and MeMgBr (2.8 mL of a 3 M solution in Et_2O, 8.4 mmol, 1.1 equiv) was added dropwise over 35 min. The mixture was stirred at −78 °C for 6 h and then at rt for 6 h. Then, $BH_3 \cdot SMe_2$ (4.2 mL of 2.0 M solution in THF, 8.4 mmol, 1.1 equiv) was added dropwise and the resulting mixture was stirred at rt for 8 h. 5% $HCl_{(aq)}$ (25 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid. Purification by recrystallization from MeOH gave adduct (*R*,*R*)-**5** (784 mg, 40%, 99:1 er by CSP-HPLC of the phosphine sulfide) as a white fluffy powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (t, *J* = 12.0 Hz, 2H), 1.55 (d, *J* = 10.0 Hz, 6H), 1.19 (d, *J* = 14.0 Hz, 18H), 1.04−0.20 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.0 (dd, *J* = 33.5, 5.5 Hz), 24.6 (d, *J* = 2.5 Hz), 12.8 (t, *J* = 20.0 Hz), 6.6 (d, *J* = 34.0 Hz); ^{31}P{^{1}H} (161.9 MHz, $CDCl_3$) δ 27.3 (q, *J* = 49.5 Hz). Spectroscopic data consistent with those reported in the literature.[2a]

(*S*,*S*)-bis[(*t*-Butyl)methylphosphinothioyl]methane. A mixture of phosphine borane (*R*,*R*)-**5** (100 mg, 0.40 mmol, 1.0 equiv), DABCO (100 mg, 0.89 mmol, 2.2 equiv) and sulfur (65 mg, 2.0 mmol, 5.0 equiv) in dry, degassed toluene (10 mL) was stirred and heated at 80 °C under Ar for 16 h. The mixture was allowed to cool to rt and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 7:1 petrol-EtOAc gave (*S*,*S*)-phosphine sulfide (111 mg, 97%, 99:1 er by CSP-HPLC) as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (t, *J* = 13.0 Hz, 2H), 2.12 (d, *J* = 12.5 Hz, 6H), 1.25 (d, *J* = 17.0 Hz, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 35.5−34.9 (m), 25.5 (t, *J* = 38.0 Hz), 24.1 (t, *J* = 1.0 Hz), 16.1−15.5 (m); ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$) δ 56.4; HPLC: Daicel Chiracel AD, 3:97 v/v *i*-PrOH-hexane, 0.5 mL min^{-1}, 11.9 min (*S*,*S*). Spectroscopic data consistent with those reported in the literature.[18]

(*S*,*S*)-bis(*t*-Butylmethylphosphino)methane (*S*,*S*)-5 (Scheme 4). Using general procedure B, phosphine borane **1** (1.00 g, 7.6 mmol, 1.0 equiv) in toluene (20 mL), *s*-BuLi (1.75 mL of a 1.3 M solution in cyclohexane, 2.3 mmol, 0.3 equiv) and (+)-sparteine surrogate (440 mg, 2.3 mmol, 0.3 equiv) in toluene (15 mL), *s*-BuLi (2.04 mL of a 1.3 M solution in cyclohexane, 2.65 mmol, 0.35 equiv) and then *s*-BuLi (2.04 mL of a 1.3 M solution in cyclohexane, 2.65 mmol, 0.35 equiv) gave the lithiated intermediate. Then, a solution of *t*-$BuPCl_2$ (1.31 g, 8.3 mmol, 1.1 equiv) in toluene (10 mL) was added dropwise over 20 min. The mixture was stirred at −78 °C for 1 h and then at rt for 14 h. The mixture was cooled to −78 °C and MeMgBr (2.8 mL of a 3 M solution in Et_2O,

8.4 mmol, 1.1 equiv) was added dropwise over 35 min. The mixture was stirred at −78 °C for 6 h and then at rt for 6 h. Then, $BH_3 \cdot SMe_2$ (5.7 mL of 2.0 M solution in THF, 11.4 mmol, 1.5 equiv) was added dropwise and the resulting mixture was stirred at rt for 8 h. Five percent $HCl_{(aq)}$ (25 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid. Purification by recrystallization from MeOH gave adduct (*S*,*S*)-**5** (764 mg, 39%, 96:4 er by CSP-HPLC of the phosphine sulfide) as a white fluffy powder.

■ ASSOCIATED CONTENT

Supporting Information. Copies of $^1H/^{13}C$ NMR spectra of all compounds and CSP-HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Tang, W.; X. Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
(2) (a) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (b) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118. (c) Imamoto, T.; Tamura, K.; Ogura, T.; Ikematsu, Y.; Mayama, D. *Tetrahedron: Asymmetry* **2010**, *21*, 1522.
(3) (a) Hoge, G; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966. (b) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560.
(4) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.
(5) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378.
(6) Genet, C.; Canipa, S. J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc.* **2006**, *128*, 9336.
(7) Gammon, J. J.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750.
(8) Canipa, S. J.; O'Brien, P.; Taylor, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2407.
(9) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.
(10) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.
(11) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (b) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Synth.* **2006**, *83*, 141. (c) O'Brien, P. *Chem. Commun.* **2008**, 655.
(12) Kann was the first to report the use of the (+)-sparteine surrogate in the asymmetric deprotonation of phosphine boranes: (a) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894. (b) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531.
(13) Gammon, J. J.; Gessner, V. H.; Barker, G. R.; Granander, J.; Whitwood, A. C.; Strohmann, C.; O'Brien, P.; Kelly, B. *J. Am. Chem. Soc.* **2010**, *132*, 13992.
(14) Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 4185.
(15) It is well-known that asymmetric deprotonation using *s*-BuLi/(−)-sparteine in THF leads to poor enantioselectivity as THF preferentially coordinates to *s*-BuLi. However, we have recently shown that highly enantioselective lithiation of phosphine borane **1** in THF is possible using *s*-BuLi and the (+)-sparteine surrogate. See: Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(16) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, 281.
(17) Crepy, K.; Imamoto, T. *Org. Synth.* **2005**, *82*, 22.
(18) Gammon, J. J.; O'Brien, P.; Kelly, B. *Org. Lett.* **2009**, *11*, 5022.