Catalytic asymmetric deprotonation of phosphine boranes and sulfides as a route to *P*-stereogenic compounds†

Jonathan J. Gammon,[a] Steven J. Canipa,[a] Peter O'Brien,*[a] Brian Kelly[b] and Sven Taylor[c]

Received (in Cambridge, UK) 23rd April 2008, Accepted 26th June 2008
First published as an Advance Article on the web 17th July 2008
DOI: 10.1039/b806864j

A comparison between phosphine boranes and sulfides in their catalytic asymmetric deprotonation using organolithiums and sub-stoichiometric amounts of (−)-sparteine has revealed superior catalytic efficiency in the phosphine sulfide deprotonation.

The last five years have seen a significant increase in the use of *P*-stereogenic phosphines as ligands in metal-catalysed asymmetric processes.[1] One class of *P*-stereogenic ligand that has been widely utilised is based on a diphosphine with at least one *t*-Bu substituent at each phosphorus atom. The original ligand in this class is BisP*,[2] developed by Imamoto, and other representative members include Zhang's Tangphos[3] and Hoge's affectionately named tri-chickenfootphos[4] (Fig. 1). Other closely related ligands developed by Imamoto include MiniPHOS[5] and QuinoxP*.[6] The popularity of such *P*-stereogenic ligands in asymmetric catalysis stems not only from the high enantioselectivity that they impart but also from the development of efficient methodology for their synthesis. The synthetic route of choice to this class of ligands is the asymmetric deprotonation of phosphine boranes and sulfides using *s*-BuLi or *n*-BuLi and (−)-sparteine, originally reported by Evans in 1995.[7]

Recently, our group[8] disclosed a catalytic variant of the Evans protocol in which the *s*-BuLi-mediated deprotonation of phosphine borane **1** can be carried out with good enantioselectivity using sub-stoichiometric amounts of (−)-sparteine or our (+)-sparteine surrogate.[9,10] Thus, deprotonation of phosphine borane **1** using 1.1 equiv. *s*-BuLi and 0.2 equiv. of the chiral diamine was followed by $CuCl_2$-promoted dimerisation to give either (*S*,*S*)-**2** or (*R*,*R*)-**2** (protected forms of BisP*) in satisfactory yield and ≥ 99 : 1 er (Scheme 1).

In this paper, we report the first examples of the catalytic asymmetric deprotonation of phosphine sulfides. In addition, by comparing phosphine boranes and sulfides under the same catalytic conditions, we have identified some fundamental and unexpected differences. Finally, use of a phosphine sulfide allowed us to complete the catalytic asymmetric synthesis of either enantiomer of an analogue of Hoge's tri-chickenfootphos.

To start with, we directly compared *t*-Bu-substituted phosphine borane **1** with phosphine sulfide **4** using lithiation–silylation under three sets of conditions: (i) 1.1 equiv. RLi and 1.2 equiv. (−)-sparteine (*stoichiometric*); (ii) 1.1 equiv. RLi and 0.2 equiv. (−)-sparteine (*catalytic*) and (iii) 1.1 equiv. RLi only (*background*). Three different organolithium bases (RLi) were investigated and the results are shown in Table 1.

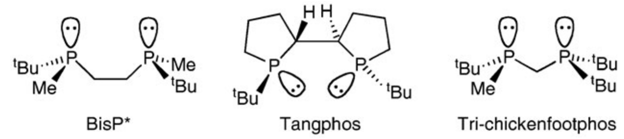
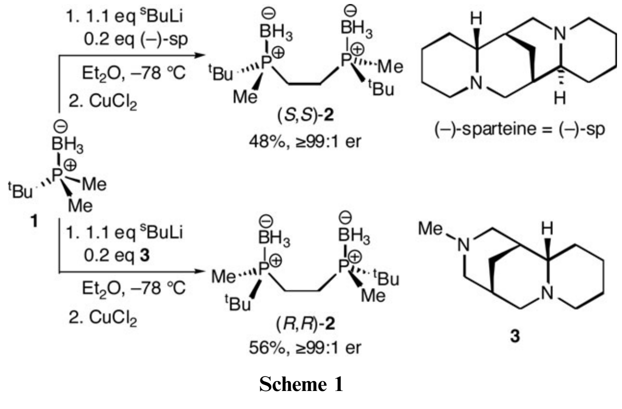


Fig. 1

Using *s*-BuLi under stoichiometric conditions (1.2 equiv. (−)-sparteine), lithiation of phosphine borane **1** proceeded with higher enantioselectivity (92 : 8 er, entry 1) than that of phosphine sulfide **4** (84 : 16 er, entry 2). Both reactions gave the same sense of induction.[11] Under catalytic conditions (0.2 equiv. (−)-sparteine) using *s*-BuLi, there was a dramatic reduction in enantioselectivity with phosphine sulfide **4** (60 : 40 er, entry 4) which is a result of a significant background lithiation by uncomplexed *s*-BuLi (as demonstrated by the generation of an 83% yield of *rac*-**6** using *s*-BuLi alone, entry 6). In contrast, the relative reduction in er was less using phosphine borane **1** (74 : 26 er, entry 3).

With the less reactive *n*-BuLi as base, some unexpected results were obtained. Under stoichiometric conditions, both phosphine borane **1** and sulfide **4** were deprotonated with good yield and enantioselectivity to give (*R*)-**5** (76%, 89 : 11 er, entry 7) and (*S*)-**6** (88%, 88 : 12 er, entry 8), respectively. Despite several attempts, we have been unable to lithiate phosphine borane **1** using *n*-BuLi alone at −78 °C[12] (entry 11) and this suggested that the catalytic conditions should work well. Unfortunately, however, there was no turnover of the ligand using *n*-BuLi and 0.2 equiv. (−)-sparteine: (*R*)-**5** of 84 : 16 er was obtained in



Scheme 1

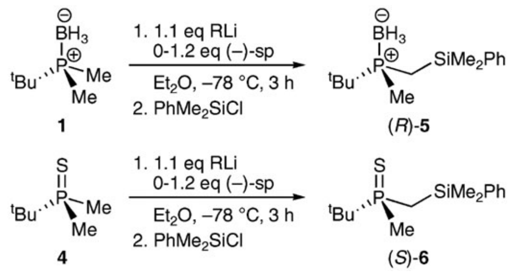
---

[a] Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: paob1@york.ac.uk; Fax: +44-1904-432516; Tel: +44-1904-432535
[b] Celtic Catalysts Ltd, Nova Centre, Belfield Innovation Park, Dublin 4, Ireland
[c] F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data. See DOI: 10.1039/b806864j

This journal is © The Royal Society of Chemistry 2008

Table 1 Lithiation–silylation of phosphine borane **1** and phosphine sulfide **4** using RLi–(−)-sparteine

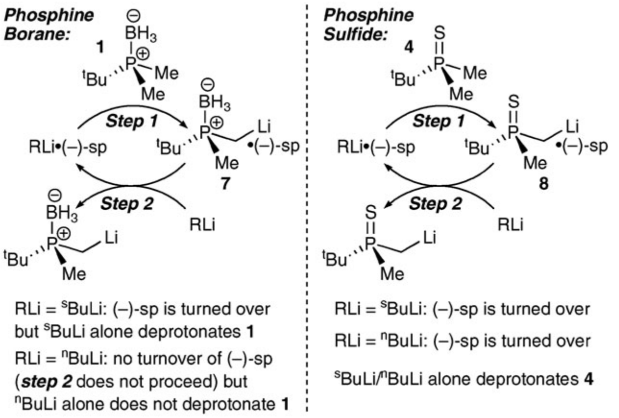


Entry	RLi[a]	Equiv. (−)-sp	Product	Yield (%)[b]	Er[c]
1	*s*-BuLi	1.2	(*R*)-**5**	74	92 : 8
2	*s*-BuLi	1.2	(*S*)-**6**	74	84 : 16
3	*s*-BuLi	0.2	(*R*)-**5**	76	74 : 26
4	*s*-BuLi	0.2	(*S*)-**6**	75	60 : 40
5	*s*-BuLi	0	*rac*-**5**	70	—
6	*s*-BuLi	0	*rac*-**6**	83	—
7	*n*-BuLi	1.2	(*R*)-**5**	76	89 : 11
8	*n*-BuLi	1.2	(*S*)-**6**	88	88 : 12
9	*n*-BuLi	0.2	(*R*)-**5**	21	84 : 16
10	*n*-BuLi	0.2	(*S*)-**6**	82	83 : 17
11	*n*-BuLi	0	*rac*-**5**	0	—
12	*n*-BuLi	0	*rac*-**6**	45	—
13	Me_3SiCH_2Li	1.2	(*R*)-**5**	0	—
14	Me_3SiCH_2Li	1.2	(*S*)-**6**	88	88 : 12
15	Me_3SiCH_2Li	0.2	(*S*)-**6**	79	82 : 18
16	Me_3SiCH_2Li	0	*rac*-**6**	18	—

[a] A solution of **1** or **4** in Et_2O was added to a pre-mixed solution of the RLi and (−)-sparteine (where used) in Et_2O at −78 °C. [b] Isolated yield after chromatography. [c] Er determined by chiral HPLC (the sense of induction is the same in each case[11] but, due to a Cahn–Ingold–Prelog priority change, (*R*)-**5** is equivalent to (*S*)-**6**).

21% yield. Since we have already demonstrated turnover of (−)-sparteine using *s*-BuLi at −78 °C, it can be concluded that the organolithium base is not an innocent bystander in the catalytic process.[13] The turnover of (−)-sparteine with *n*-BuLi could be improved by carrying out the reaction at −50 °C but the enantioselectivity was lower (80 : 20 er).[14] In contrast, with phosphine sulfide **4**, (−)-sparteine was efficiently recycled and there was only a slight reduction in enantioselectivity using *n*-BuLi–0.2 equiv. (−)-sparteine: (*S*)-**6** of 83 : 17 er was generated in 82% yield (entry 10). This is especially impressive given that there is a significant background lithiation of **4** using *n*-BuLi (45% yield, entry 12). Finally, we also compared the *s*-BuLi and *n*-BuLi results with those obtained using Me_3SiCH_2Li. There was no lithiation of phosphine borane **1** using stoichiometric amounts of Me_3SiCH_2Li and (−)-sparteine at −78 °C[15] (entry 13). However, the results with phosphine sulfide **4** (entries 14–16) mirrored those obtained using *n*-BuLi and there were no obvious advantages in using Me_3SiCH_2Li.

From the results presented in Table 1, some important conclusions can be drawn. For the lithiation of phosphine borane **1**, *s*-BuLi–(−)-sparteine gives the highest enantioselectivity (92 : 8 er) and acceptable enantioselectivity can be obtained under catalytic conditions (74 : 26 er). There is no turnover of (−)-sparteine in the *n*-BuLi-mediated deprotonation of phosphine borane **1** using 0.2 equiv. (−)-sparteine at −78 °C (21% yield, 84 : 16 er) as (−)-sparteine cannot be displaced from the lithiated intermediate **7** by *n*-BuLi (Step 2, Scheme 2). In contrast, lithiation of phosphine sulfide **4** proceeds with the highest enantioselectivity (89 : 11 er) using *n*-BuLi–(−)-sparteine. Significantly, high yield *and* good enantioselectivity can be obtained in the lithiation of phosphine sulfide **4** using *n*-BuLi and 0.2 equiv. (−)-sparteine (82% yield, 83 : 17 er) ((−)-sparteine is efficiently displaced in lithiated intermediate **8**, Scheme 2); *s*-BuLi gives inferior results to *n*-BuLi due to a fast background deprotonation of **4** by uncomplexed *s*-BuLi. These comparisons are summarised schematically in Scheme 2.[16]

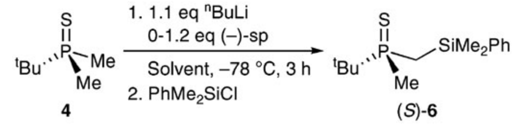


Scheme 2

Given the high catalytic efficiency observed with phosphine sulfide **4**, we briefly explored lower loadings and the use of toluene (Table 2). In Et_2O, it was possible to lower the amount of (−)-sparteine to 0.1 equiv. whilst maintaining good enantioselectivity (84 : 16 er, entry 3). Use of 0.05 equiv. (−)-sparteine with phosphine sulfide **4** gave 74 : 26 er (entry 4). In toluene, the catalytic asymmetric deprotonation of phosphine sulfide **4** was even more efficient: use of 1.1 equiv. *n*-BuLi in conjunction with just 0.05 equiv. (−)-sparteine generated adduct (*S*)-**6** of 85 : 15 er in 88% yield (entry 8), almost the same as the stoichiometric result (90% yield, 89 : 11 er, entry 6) and despite an appreciable background deprotonation reaction using *n*-BuLi alone (54% yield, entry 9).

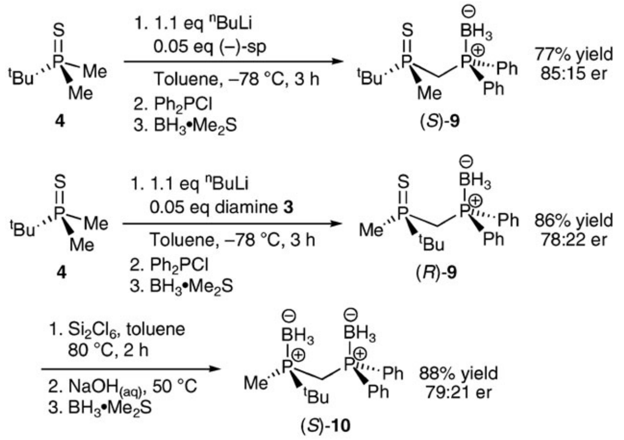
The use of 1.1 equiv. *n*-BuLi and 0.05 equiv. (−)-sparteine in toluene represents our optimised conditions for the deprotonation of phosphine sulfide **4**. To illustrate the usefulness of the catalytic phosphine sulfide methodology in ligand synthesis, we prepared each enantiomer of diphosphine **9**, an analogue of Hoge's tri-chickenfootphos.[4] Thus, catalytic asymmetric deprotonation of **4** using *n*-BuLi and (−)-sparteine, trapping with Ph_2PCl and then borane protection gave a 77% yield of (*S*)-**9** of 85 : 15 er (Scheme 3). Alternatively, use of the (+)-sparteine surrogate **3** under otherwise identical conditions gave (*R*)-**9** of 78 : 22 er in 86% yield. To show that our methodology is useful for the synthesis of *P*-stereogenic ligands, we converted phosphine sulfide (*R*)-**9** into bisphosphine borane (*S*)-**10** using a modified version of a protocol used in Zhang's Tangphos synthesis.[3] Thus, with the rigorous exclusion of oxygen throughout the procedure, reaction of (*R*)-**9** of 78 : 22 er with Si_2Cl_6 in toluene at 80 °C[3,17] followed by treatment with aqueous NaOH and then $BH_3 \cdot Me_2S$ gave (*S*)-**10**[18] in 88% yield. Crucially, there was no loss

Table 2 Lithiation–silylation of phosphine sulfide **4** using *n*-BuLi–(−)-sparteine



Entry	Solvent	Equiv. (−)-sp	Yield (%)[a]	Er[b]
1	Et$_2$O	1.2	88	88 : 12
2	Et$_2$O	0.2	82	83 : 17
3	Et$_2$O	0.1	74	84 : 16
4	Et$_2$O	0.05	88	74 : 26
5	Et$_2$O	0	45	—
6	Toluene	1.2	90	89 : 11
7	Toluene	0.2	89	83 : 17
8	Toluene	0.05	88	85 : 15
9	Toluene	0	54	—

[a] Isolated yield after chromatography. [b] Er determined by chiral HPLC.



Scheme 3

of er during the process: (*S*)-**10** was generated with 79 : 21 er. Furthermore, unmasking of the free diphosphine from diphosphine boranes like (*S*)-**10** is well documented in similar compounds.[4,5] It was also important to demonstrate that enantiomerically pure *P*-stereogenic ligands could be obtained using our route. Thus, a sample of (*R*)-**9** of 78 : 22 er was recrystallised to give racemic crystals (52% recovery) and a mother liquor that contained (*R*)-**9** of 99 : 1 er (48% recovery).

In conclusion, we report the first examples of the catalytic asymmetric deprotonation of phosphine sulfides and demonstrate the potential in *P*-stereogenic ligand synthesis with the preparation of bisphosphines (*S*)- and (*R*)-**9**. The optimised deprotonation conditions involved using *n*-BuLi and 0.05 equiv. chiral diamine in toluene at −78 °C. Significant differences between the results obtained with phosphine boranes and sulfides were identified as part of our study. It seems likely that the efficiency of the catalytic asymmetric deprotonation of phosphine sulfides could prove useful in the synthesis of *P*-stereogenic chiral ligands.

We thank Celtic Catalysts and F. Hoffmann-La Roche Ltd for funding.

Notes and references

1 (*a*) W. Zhang, Y. Chi and X. Zhang, *Acc. Chem. Res.*, 2007, **40**, 1278; (*b*) A. Grabulosa, J. Granell and G. Muller, *Coord. Chem. Rev.*, 2007, **251**, 25; (*c*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (*d*) K. V. L. Crepy and T. Imamoto, *Top. Curr. Chem.*, 2003, **229**, 10; (*e*) K. V. L. Crepy and T. Imamoto, *Adv. Synth. Catal.*, 2003, **103**, 3029.

2 T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa and K. Yamaguchi, *J. Am. Chem. Soc.*, 1998, **120**, 1635.

3 W. Tang and X. Zhang, *Angew. Chem., Int. Ed.*, 2002, **41**, 1612.

4 (*a*) G. Hoge, H.-P. Wu, W. S. Kessel, D. A. Pflum, D. J. Greene and J. Bao, *J. Am. Chem. Soc.*, 2004, **126**, 5966; (*b*) I. D. Gridnev, T. Imamoto, G. Hoge, M. Kouchi and H. Takahashi, *J. Am. Chem. Soc.*, 2008, **130**, 2560.

5 Y. Yamonoi and T. Imamoto, *J. Org. Chem.*, 1999, **64**, 2988.

6 T. Imamoto, K. Sugita and K. Yoshida, *J. Am. Chem. Soc.*, 2005, **127**, 11934.

7 A. R. Muci, K. R. Campos and D. A. Evans, *J. Am. Chem. Soc.*, 1995, **117**, 9075.

8 C. Genet, S. J. Canipa, P. O'Brien and S. Taylor, *J. Am. Chem. Soc.*, 2006, **128**, 9336.

9 M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870.

10 (*a*) P. O'Brien, *Chem. Commun.*, 2008, 655; (*b*) A. J. Dixon, M. J. McGrath and P. O'Brien, *Org. Synth.*, 2006, **83**, 141.

11 The sense of induction in the asymmetric deprotonation of phosphine borane **1** and sulfide **4** using RLi–(−)-sparteine is the same in each case. This was shown by converting borane (*R*)-**5** of 75 : 25 er into sulfide (*S*)-**6** of 75 : 25 er (*via* reaction with DABCO and S_8 in refluxing toluene for 12 h, quantitative yield). Note that, due to a Cahn–Ingold–Prelog priority change, (*R*)-**5** is equivalent to (*S*)-**6**. The sense of induction is consistent with that obtained by Evans (ref. 7) and Imamoto (ref. 2).

12 Phosphine borane **1** can be lithiated using *n*-BuLi alone at temperatures higher than −78 °C. The following results were obtained by lithiating **1** using *n*-BuLi at the stated temperature for 3 h and then trapping with benzophenone: −50 °C (11% yield); −42 °C (29% yield); 0 °C (51% yield).

13 A. Ramirez, X. Sun and D. B. Collum, *J. Am. Chem. Soc.*, 2006, **128**, 10326.

14 Lithiation of **1** with *n*-BuLi–0.2 equiv. (−)-sparteine in Et$_2$O at −50 °C for 3 h and trapping with PhMe$_2$SiCl gave a 49% yield of (*R*)-**5** of 80 : 20 er.

15 Lithiation of **1** with Me$_3$SiCH$_2$Li–(−)-sparteine in Et$_2$O at −20 °C for 3 h and trapping with PhMe$_2$SiCl gave a 75% yield of (*R*)-**5** of 75 : 25 er.

16 The structures of the organolithium reagents (*e.g.* RLi and RLi·(−)-sp) and the lithiated phosphine boranes and sulfides (*e.g.* **7** and **8**) in Scheme 2 are schematic representations only and nothing is implied about their true solution structure (*e.g.* C–Li contact, aggregation state). For reports on the solution and solid-state structures of lithiated phosphine boranes and sulfides, see: (*a*) K. Izod, C. Wills, W. Clegg and R. W. Harrington, *Organometallics*, 2007, **26**, 2861; (*b*) K. Izod, C. Wills, W. Clegg and R. W. Harrington, *Organometallics*, 2006, **25**, 338; (*c*) X.-M. Syn, K. Manabe, W. W.-L. Lam, N. Shiraishi, J. Kobayashi, H. Utsumi and S. Kobayashi, *Chem.–Eur. J.*, 2005, **11**, 361; (*d*) K. Izod, W. McFarlane, B. V. Tyson, W. Clegg and R. W. Harrington, *Chem. Commun.*, 2004, 570; (*e*) K. Izod, *Coord. Chem. Rev.*, 2002, **227**, 153; (*f*) H. Schmidbauer, E. Weiss and B. Zimmer-Gasse, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 782.

17 (*a*) G. Zon, K. E. DeBruin, K. Naumann and K. Mislow, *J. Am. Chem. Soc.*, 1969, **81**, 7012; (*b*) K. Naumann, G. Zon and K. Mislow, *J. Am. Chem. Soc.*, 1969, **81**, 7023.

18 A sample of *rac*-**10** was independently prepared from phosphine borane **1** for conclusive proof that desulfurisation of (*R*)-**9** had occurred.

This journal is © The Royal Society of Chemistry 2008