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Kinetic resolution of *P*-stereogenic phosphine boranes via deprotonation using *s*-butyllithium/(−)-sparteine

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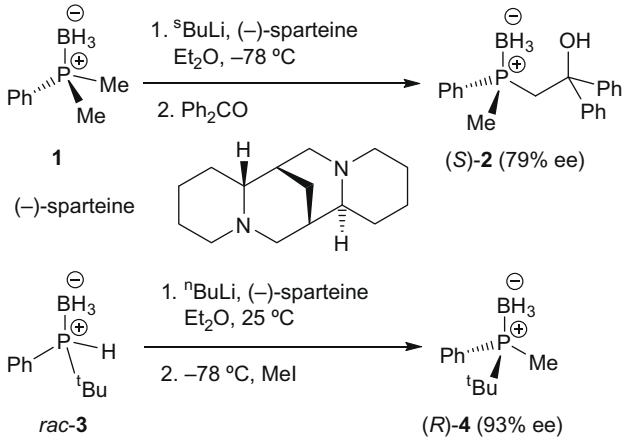
ABSTRACT

The attempted kinetic resolution of racemic secondary phosphine boranes [*t*-BuPhP(BH_3)H and *t*-BuMeP(BH_3)H] by P–H deprotonation using 0.5 equiv of *s*-BuLi and (−)-sparteine was unsuccessful and generated racemic benzyl bromide-trapped adducts in 42–49% yield. In contrast, an efficient kinetic resolution was observed with racemic tertiary phosphine boranes [*t*-BuPhP(BH_3)Me and *t*-BuEtP(BH_3)Me] by C–H deprotonation on the P–Me group using 0.5 or 0.6 equiv of *s*-BuLi and (−)-sparteine. For example, the use of 0.6 equiv of *s*-BuLi/(−)-sparteine with *t*-BuEtP(BH_3)Me and trapping with DMF gave the (*R*)-aldehyde adduct in 37% yield and 83:17 er together with recovered (*R*)-*t*-BuEtP(BH_3)Me in 44% yield and 74:26 er. These are the first examples of kinetic resolution of *P*-stereogenic phosphine boranes via deprotonation using *s*-BuLi/(−)-sparteine.

1. Introduction

An increasing number of useful *P*-stereogenic bisphosphine ligands[1] are being synthesised using *n*-BuLi or *s*-BuLi and (−)-sparteine chiral base methodology (e.g., Imamoto's BisP*,[2] MiniPHOS[2b,3] and QuinoxP[4], and Zhang's Tangphos[5]). Most of the chiral base routes utilise Evans' asymmetric desymmetrisation of dimethylphosphine boranes as the key step.[6] For example, lithiation of phosphine borane **1** using *s*-BuLi/(−)-sparteine and trapping with benzophenone gave *P*-stereogenic phosphine borane (*S*)-**2** in 79% ee (Scheme 1). A limitation of this approach is that a methyl group will inevitably be one of the substituents in the product.

Subsequently, Livinghouse reported a different (−)-sparteine approach to *P*-stereogenic phosphines in which a dynamic thermodynamic resolution of a lithiated secondary phosphine borane was utilised.[7] Thus, racemic lithiated **3** was formed and equilibrated in the presence of (−)-sparteine at 25 °C (a temperature at which lithiated **3** is configurationally unstable) and then trapped at −78 °C with methyl iodide to give (*R*)-**4** in 93% ee (Scheme 1). Since the equilibration is driven by precipitation, attempts to extend the Livinghouse method to other substituents have met with limited success.[8,9] In order to address the limitations of these two methods, we reasoned that it should be possible to carry out each of these two processes in a kinetic resolution manifold. Thus, we planned to use 0.5 equiv of *n*-BuLi or *s*-BuLi and (−)-sparteine followed by electrophilic trapping (with E^+) to carry out the kinetic resolution



Scheme 1. Asymmetric synthesis of *P*-stereogenic phosphines via organolithium reagents and (−)-sparteine.

of secondary phosphine boranes *rac*-**5** (non-racemic **6** and **5**) by deprotonation of the PH proton and of tertiary phosphine boranes *rac*-**7** (non-racemic **8** and **7**) by deprotonation of a proton on the PMe group (Scheme 2). To the best of our knowledge, this strategy has not previously been reported but, if successful, it could constitute a general route to *P*-stereogenic phosphines such as **5–8** equipped with any R^1 and R^2 groups. Herein, we report our preliminary investigations.

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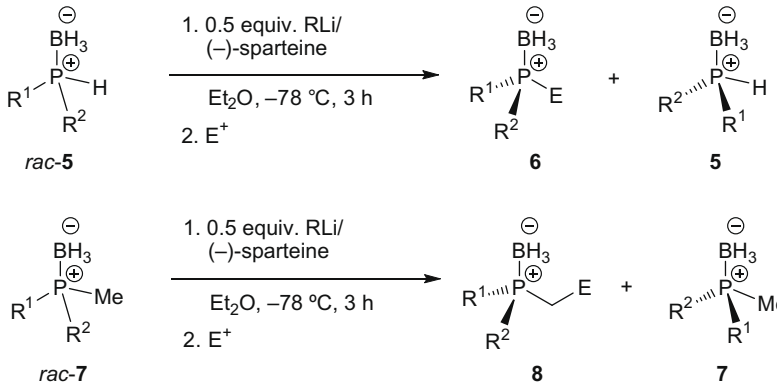
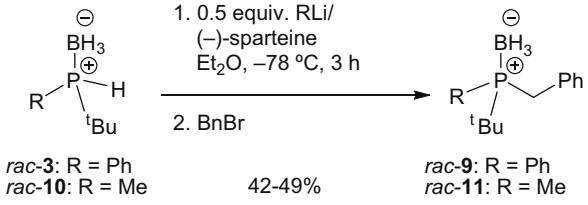


Scheme 2. Proposed kinetic resolution strategy for the synthesis of secondary and tertiary *P*-stereogenic phosphine boranes.

2. Results and discussion

To start with, we prepared secondary phosphine boranes *rac*-**3** (from the one-pot reaction of $PhPCl_2$ with *t*-BuMgBr, $LiAlH_4$ and $BH_3{\cdot}Me_2S$) and the volatile *rac*-**10** (from the one-pot reaction of *t*-$BuPCl_2$ with MeMgBr, $LiAlH_4$ and $BH_3{\cdot}Me_2S$). Next, we attempted to carry out the kinetic resolution of phosphine boranes *rac*-**3** and *rac*-**10** via deprotonation using 0.5 equiv of organolithium reagents and (−)-sparteine in Et_2O at −78 °C and subsequently trapping with benzyl bromide. The use of *s*-BuLi and *n*-BuLi was investigated under three different procedures: (i) addition of a pre-mixed organolithium reagent/(−)-sparteine to the phosphine borane; (ii) addition of the phosphine borane to pre-mixed organolithium reagent/(−)-sparteine and (iii) addition of organolithium reagents to phosphine borane and (−)-sparteine. Under all these conditions, we isolated 42–49% yields of benzylated adducts *rac*-**9** and *rac*-**11** as shown by chiral HPLC (Scheme 3). No kinetic resolution was observed.

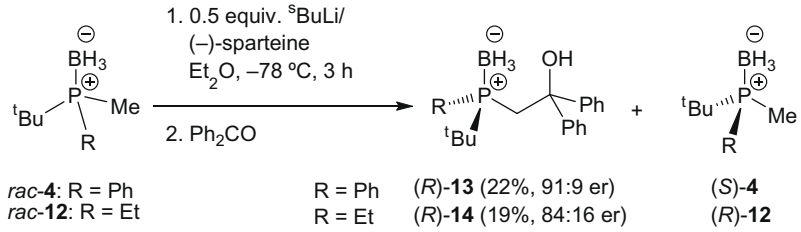


Scheme 3. Attempted kinetic resolution of secondary phosphine boranes.

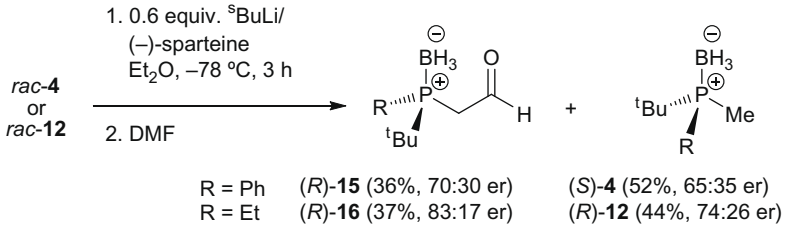
Next, we turned our attention to tertiary phosphine boranes *rac*-**4** and *rac*-**12** which contained a *P*-methyl group suitable for deprotonation. Phosphine borane *rac*-**4** was prepared by a sequential one-pot reaction of $PhPCl_2$ with *t*-BuMgCl, MeMgBr and $BH_3{\cdot}Me_2S$ whereas *rac*-**12** was prepared from PCl_3 by reaction with *t*-BuMgCl, EtMgCl, MeMgBr and $BH_3{\cdot}Me_2S$. With *rac*-**4** and *rac*-**12** in hand, the kinetic resolution was attempted by adding a pre-cooled (−78 °C) solution of 0.5 equiv of *s*-BuLi/(−)-sparteine in Et_2O to a solution of the phosphine borane *rac*-**4** or *rac*-**12** in Et_2O at −78 °C. After 3 h, benzophenone was added and, after chromatography, adducts (*R*)-**13** (22%, 91:9 er by chiral HPLC)[10] and (*R*)-**14** (19%, 84:16 er by chiral HPLC) were isolated (Scheme 4). Much lower enantioselectivity was observed using *n*-BuLi in place of *s*-BuLi. The stereochemistry of (*R*)-**13** has been secured (vide infra) and that of (*R*)-**14** is tentatively assigned by analogy. Unfortunately, it was not possible to recover the resolved starting materials (*S*)-**4** and (*R*)-**12** in pure form and hence they could not be analysed further (for % yield and er). However, these results clearly show that a kinetic resolution had occurred and that this strategy is a viable route to *P*-stereogenic phosphines.

In order to improve the conversion to product, we increased the amount of reagent to 0.6 equiv of *s*-BuLi/(−)-sparteine and trapping with a different electrophile (DMF) to allow recovery of the enantioenriched starting phosphine boranes. Thus, kinetic resolution of phosphine borane *rac*-**4** using 0.6 equiv of *s*-BuLi/(−)-sparteine followed by DMF trapping gave aldehyde (*R*)-**15** (36%, 70:30 er) and recovered phosphine borane (*S*)-**4** (52%, 65:35 er). In this example, it was possible to isolate both the product and recovered starting material after chromatography. Even better results were obtained with phosphine borane *rac*-**12**, which gave (*R*)-**16** in 37% yield and 83:17 er together with recovered phosphine borane (*R*)-**12** in 44% yield and 74:26 er (Scheme 5).[11] In order to determine the ers of (*R*)-**15**, (*S*)-**4**, (*R*)-**16** and (*R*)-**12**, a range of subsequent transformations was required. The er of (*R*)-**15** was determined by chiral HPLC of the corresponding alcohol (obtained by $NaBH_4$ reduction). To obtain the er of (*R*)-**16**, it was reduced to the primary alcohol using $NaBH_4$ and converted into a hydroxy phosphine sulfide (by reaction with DABCO and sulfur in toluene at 80 °C[12]) which was suitable for chiral HPLC analysis. The ers of (*S*)-**4** and (*R*)-**12** were obtained by chiral HPLC analysis of (*S*)-**13** and (*S*)-**14,** respectively (which were formed from (*S*)-**4** and (*R*)-**12** by racemic lithiation/benzophenone trapping).

The absolute configuration of the recovered phosphine borane **4** was assigned as (*S*) based on a comparison of its specific rotation {$[\alpha]_D$ = –6.3 (*c* 1.1, $CHCl_3$); $[\alpha]_D$ = +3.0 (*c* 1.0, MeOH)} with that reported for (*R*)-**4** of 93% ee {$[\alpha]_D$ = −10 (*c* 1, MeOH)}.[7] This allows the stereochemistry of (*R*)-**15** and, by analogy, (*R*)-**13** to be as-



Scheme 4. Kinetic resolution of tertiary phosphine boranes.



Scheme 5. Kinetic resolution of tertiary phosphine boranes.

signed. We have also extended our assignment of stereochemistry to the ethyl-substituted series (*R*)-**14**, (*R*)-**16** and (*R*)-**12** (although these assignments have not been proven unequivocally and are only tentative at this stage).

3. Conclusion

In conclusion, we have reported the first examples of the kinetic resolution of racemic *P*-stereogenic tertiary phosphine boranes via deprotonation using *s*-BuLi/(−)-sparteine. This strategy may prove useful for the preparation of *P*-stereogenic compounds that cannot be accessed by chiral base-mediated desymmetrisation of dimethyl-substituted phosphine boranes.

Acknowledgement

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10. A pre-cooled solution of *s*-BuLi (0.38 mL of a 1.3 M solution in hexanes, 0.50 mmol, 0.5 equiv) and (−)-sparteine (117 mg, 0.50 mmol, 0.5 equiv) in Et_2O (3 mL) at −78 °C was added dropwise to a stirred solution of phosphine borane *rac*-**4** (194 mg, 1.00 mmol, 1.0 equiv) in Et_2O (6 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 3 h and then a solution of benzophenone (91 mg, 0.50 mmol, 0.5 equiv) in Et_2O (2 mL) was added dropwise. The resulting mixture was allowed to warm to rt over 4 h and stirred at rt for 16 h. Next, 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 ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 19:1 petrol–EtOAc as eluent gave phosphine borane (*R*)-**13** (83 mg, 22%, 91:9 er) as a white solid, mp 125–126 °C; R_f (19:1 petrol–EtOAc) 0.2; IR (NaCl) 3466, 3016, 2399, 1493, 1448, 1368, 1215, 1057, 753, 700, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.57 (m, 2H, Ph), 7.51–7.46 (m, 2H, Ph), 7.46–7.40 (m, 1H, Ph), 7.34–7.28 (m, 4H, Ph), 7.26–7.21 (m, 1H, Ph), 7.17–7.12 (m, 2H, Ph), 6.93–6.86 (m, 3H, Ph), 4.71 (s, 1H, OH), 3.46 (t, $J_{PH} = J_{HH} = 14.5$ Hz, 1H, PCH_AH_B), 2.87 (dd, $J_{HH} = 14.5$, $J_{PH} = 6.5$ Hz, 1H, PCH_AH_B), 1.14 (d, $J_{PH} = 14.0$ Hz, 9H, CMe_3), 1.30–0.30 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.9 (d, $J_{PC} = 9.0$ Hz, *ipso*-Ph), 144.3 (d, $J_{PC} = 2.0$ Hz, *ipso*-Ph), 133.2 (d, $J_{PC} = 8.0$ Hz, Ph), 131.0 (d, $J_{PC} = 2.5$ Hz, Ph), 128.2 (Ph), 128.0 (d, $J_{PC} = 9.5$ Hz, Ph), 127.3 (Ph), 127.1 (Ph), 126.6 (Ph), 126.4 (d, $J_{PC} = 51.0$ Hz, *ipso*-Ph), 126.3 (Ph), 125.4 (Ph), 77.6 (COH), 33.3 (d, $J_{PC} = 28.5$ Hz, PCH_2), 30.2 (d, $J_{PC} = 34.5$ Hz, $PCMe_3$), 25.4 (d, $J_{PC} = 2.0$ Hz, CMe_3); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 22.2 (br m); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{30}BOP$ $(M+Na)^+$ 399.2020, found 399.2010; HPLC: Daicel Chiralcel OD, 19:1 v/v hexane–*i*-PrOH, 0.5 mL min^{-1}, 254.4 nm, 10.4 min [(*S*)-**13**], 12.2 min [(*R*)-**13**]. A sample of (*S*)-**13** of 65:35 er (formed by lithiation-benzophenone trapping of (*S*)-**4**) had $[\alpha]_D = +14.6$ (*c* 1.0, $CHCl_3$).
11. A pre-cooled solution of *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes, 1.20 mmol, 0.6 equiv) and (−)-sparteine (281 mg, 1.20 mmol, 0.5 equiv) in Et_2O (5 mL) at −78 °C was added dropwise to a stirred solution of phosphine borane *rac*-**12** (292 mg, 2.00 mmol, 1.0 equiv) in Et_2O (10 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 3 h and then DMF (292.4 mg, 4.00 mmol, 2.0 equiv) was added dropwise. The resulting mixture was allowed to warm to rt over 4 h and then stirred at rt for 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 (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using 9:1 petrol–EtOAc and then 4:1 petrol–EtOAc as eluent gave phosphine borane aldehyde (*R*)-**16** (129 mg, 37%, 83:17 er by chiral HPLC of the corresponding hydroxy phosphine sulfide obtained by reduction with $NaBH_4$ and treatment with DABCO/sulfur) as a colourless oil, R_f (9:1 petrol–EtOAc) 0.1; IR (NaCl) 2975, 2872, 2742, 2379, 2258, 1719, 1465, 1369, 1194, 1071, 1033, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (dd, $J = 3.5$, 2.0 Hz, 1H, CHO), 2.82 (td, $J = 13.0$, 3.5 Hz, 1H, PCH_AH_B), 2.70 (td, $J = 13.0$, 3.5 Hz, 1H, PCH_AH_B), 1.76–1.65 (m, 2H, PCH_2Me), 1.21–1.12 (m, 12H, CMe_3 + PCH_2Me), 0.90–0.05 (m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.9 (d, $J_{PC} = 1.0$ Hz, CHO), 36.2 (d, $J_{PC} = 20.0$ Hz, PCH_2CHO), 28.7 (d, $J_{PC} = 31.0$ Hz, CMe_3), 25.2 (d, $J_{PC} = 2.0$ Hz, CMe_3), 13.9 (d, $J_{PC} = 31.5$ Hz, PCH_2Me), 7.5 (d, $J_{PC} = 2.0$ Hz, PCH_2Me); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 35.0 (br m); HRMS (ESI) *m*/*z* calcd for $C_8H_{20}BOP$ $(M+H)^+$ 175.1418, found 175.1418 and phosphine borane (*R*)-**12** (129 mg, 44%, 74:26 er by chiral HPLC of the corresponding hydroxy phosphine borane (*S*)-**14** obtained by lithiation-benzophenone trapping) as a white solid, mp 41–42 °C; $[\alpha]_D = -8.9$ (*c* 1.05, $CHCl_3$); R_f (29:1 petrol–EtOAc) 0.25; IR (NaCl) 3006, 2975, 2365, 1216, 1071, 1016, 901, 884, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70–1.50 (m, 2H, PCH_2), 1.18 (t, $J_{PH} = 7.5$ Hz, 3H, PCH_2Me), 1.15 (d, $J_{PH} = 9.5$ Hz, 3H, PMe), 1.14 (d, $J_{PH} = 13.5$ Hz, 9H, CMe_3), 0.80 to −0.05 (br m, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.2 (d, $J_{PC} = 34.5$ Hz, CMe_3), 25.1 (d, $J_{PC} = 2.5$ Hz, CMe_3), 14.2 (d, $J_{PC} = 34.0$ Hz, PCH_2), 7.4 (d, $J_{PC} = 2.0$ Hz, PCH_2Me), 4.4 (d, $J_{PC} = 34.5$ Hz, PMe); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 28.2 (br m); HRMS (ESI) *m*/*z* calcd for $C_7H_{20}BP$ $(M+Na)^+$ 169.1288, found 169.1295.
12. We have a number of examples in our group where the conversion of phosphine boranes into phosphine sulfides using DABCO and sulfur in toluene at 80 °C proceeds with no loss of er.