A simple route to chiral phosphinous acid–boranes†

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We report a simple one-pot synthesis of enantiomerically enriched alkyl- and arylphenylphosphinous acid–borane starting from readily available (R_P)-(−)-menthylhydrogenophenylphosphinate and organolithium reagents.

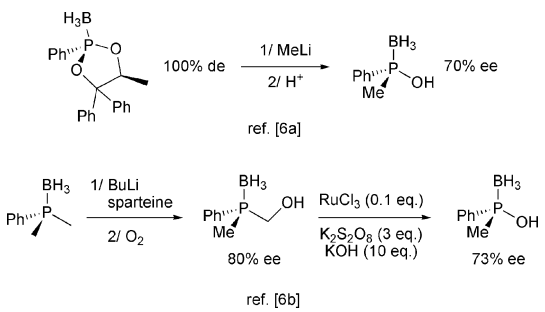
The availability of chiral organophosphorous compounds has allowed tremendous achievements in chemistry, in particular in the field of asymmetric metal catalysis.[1] However most of the popular chiral P-ligands, such as the ubiquitous BINAP, are based on chiral C-backbones. In comparison, the occurrence of P-stereogenic ligands in literature is lower because their synthesis often presents a challenge. As P-chiral compounds could not be found in the natural pool of chirality, they were initially obtained by the resolution of racemic mixtures by means of a chiral auxiliary. Nowadays, stereoselective syntheses are supplanting this methodology.[2] For instance, one of the most convenient and versatile approach to chlorophosphine–boranes or phosphinite–boranes, which are precursors of P-chiral tertiary phosphine–boranes,[3] is the nucleophilic substitution of chiral 1,3,2-oxazaphospholidine–boranes with organolithium reagents. However, this method, which was initially described by Jugé *et al.*,[4] suffers from limitations. For instance, the subsequent acidolysis (or methanolysis) step is limited to not sterically hindered substituents. As recently stated,[2d] an overall methodology is still lacking.

Recently, Pietrusiewicz and Stankevic demonstrated the potentiality of chiral phosphinous acid–boranes as key intermediates for the preparation of various P-stereogenic compounds, such as bulky tertiary and secondary phosphine–boranes, phosphinite–boranes or boranatophosphinous–sulfonic anhydrides.[5] Some enantiopure phosphinous acid–boranes are available, but only from racemic resolution.[5e,f] Despite promising results, this methodology is at a very early stage of development. In particular, an efficient and versatile stereoselective route to chiral phosphinous acid–boranes remains to be designed. To our knowledge there are only two reports of stereoselective syntheses (Scheme 1), and none exceeds 73% of enantiomeric excess (ee).[6] Herein we report a simple one-pot and stereoselective synthesis of phosphinous acid–boranes, with up to 99% ee.

The phosphinous acid-secondary phosphine oxide (SPO) tautomerism is well known.[7] Usually, only the latter, which is the more stable, is observed.[8] Curiously, despite the tautomeric equilibrium, SPOs do not react with boranes, under mild conditions. We knew from the report of Pietrusiewicz and coworkers[5b] that the reaction could occur at room temperature when deprotonating the SPO. Recently, our interest in SPOs[9] prompted us to design an enantioselective synthesis of such compounds from (R_P)-(−)-menthyl hydrogenophenylphosphinate **1**.[9c] We felt that this approach could be adapted to the synthesis of phosphinous acid–boranes.

Initially, we examined the model reaction of enantiopure (R_P)-(−)-**1**[10] with MeLi (2.5–3 equiv.) at −78 °C in THF. The first equivalent of organometallic reagents was required to abstract the proton carried by (R_P)-(−)-**1**, whereas the second equivalent was used for the substitution of menthyloxy group. At this stage, lithium phosphinate species (*S*)-**2a** was quenched with $BH_3{\cdot}SMe_2$. The desired methylphenyl phosphinous acid–borane (*S*)-(−)-**3a** was obtained in 78% overall yield and 95% ee (Table 1, entry 1). Of note, when the reaction was carried out with MeMgBr instead of MeLi, (*S*)-(−)-**3a** was obtained with poorer yield (64%) and ee (86%).

Then, we briefly explored the scope of this first approach (method A) using various organolithium reagents in similar conditions. The phosphinous acid–boranes **3a–g** were obtained in good yields (Table 1). Good enantioselectivities (91–98% ee) were observed with aryllithium reagents (entries 4–6) and *n*-butyllithium (89% ee, entry 2). Conversely, **3g** and **3c** were obtained with modest 72 and 60% ee, respectively (entries 7 and 3). The latter case was particularly enlightening. Indeed, we knew that the first step of the procedure afforded **2c** with at least 84% ee.[9c] In addition, ee's remained unchanged when stirring **2c** at room temperature for 3 days, suggesting that this compound did not racemize under our conditions. Thus, a significant loss of enantiopurity occurred upon the addition of $BH_3{\cdot}SMe_2$. This statement is in agreement with the recent report of Stankevic *et al.*, who noticed that the deprotonation of resolved enantiopure *tert*-butylphenylphosphine oxide, followed by the addition of BH_3, afforded **3c** with only 74% ee.[5a]



Scheme 1 Previously reported stereoselective routes to chiral phosphinous acid–boranes.

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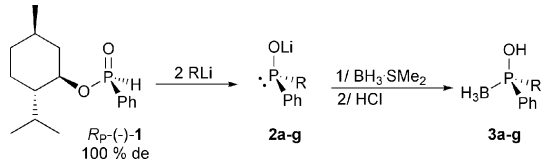
Table 1 One-pot synthesis of phosphinous acid–boranes **3a–g** (method A)



Entry	R	Product	Yield[a] (%)	ee[b] (%)
1	Me	*S*-(−)-**3a**	78	95
2	*n*-Bu	(−)-**3b**	84	89
3	*t*-Bu	*S*-(−)-**3c**	82	60
4	2-MeC_6H_4	(+)-**3d**	93	98
5	2-PhC_6H_4	(−)-**3e**	84	93
6	1-Naphthyl	*R*-(−)-**3f**	88	91[c]
7	1-Furyl	(+)-**3g**	92	72

[a] Yields after purification. [b] Enantiomeric excesses were determined by HPLC analysis on Chiralpak AS-H (λ = 254 nm; 1 mL min^{-1}; eluent: hexane–*i*-PrOH mixtures). [c] Enantiomeric excess was determined by HPLC analysis on Chiralpak OD-H (λ = 254 nm; 1 mL min^{-1}; eluent: hexane–EtOH) (8 : 2).

Unsatisfied with these results we decided to explore a new approach (method B). After the addition of (R_P)-(−)-**1** to organolithium reagents,[11] lithium phosphinate species **2a–g** were trapped by addition of Me_3SiCl. The resulting O-silylated product **4** was then protected using $BH_3{\cdot}SMe_2$ and desilylated by treatment with aqueous HCl. All steps were conveniently monitored by ^{31}P NMR. This one-pot procedure afforded the desired phosphinous acid–borane **3a–g** in 70–85% yields after purification. All results are summarised in Table 2.

Using this method almost all enantioselectivities have been improved (Table 2, entries 3, 5, 6 and 7). Of note, when the reaction was performed with *t*-BuLi, *S*-(−)-**3c** was obtained with 84% ee. This value, which corresponds to the enantioselectivity of the first step, seemed to indicate that the three last steps occurred without significant racemization. To verify this point, we synthesized *tert*-butylphenylphosphine oxide **5** by adding (R_P)-(−)-**1** to *tert*-butyllithium.[9c] A single crystallisation afforded (*S*)-(−)-**5** with 99.6% ee.[9b] Addition of Me_3SiCl and the subsequent addition of $BH_3{\cdot}SMe_2$ afforded (*S*)-(−)-**3c** with >99% ee, as indicated by HPLC analysis (Scheme 2).

In conclusion, we reported simple diastereoselective one-pot syntheses of enantioenriched chiral phosphinous acid–boranes starting from cheap and readily available (R_P)-(−)-menthylhydrogenophenylphosphinate and organolithium reagents. Although direct trapping of the resulting lithium phosphinate species with $BH_3{\cdot}SMe_2$ afforded the desired products with up to 98% ee, it generally resulted in partial racemization. Such loss could be avoided by using Me_3SiCl as trapping agent. This general approach affords an unprecedented versatile diastereoselective entry to chiral phosphinous acid–boranes, and therefore, to a broad range of P-chiral compounds.

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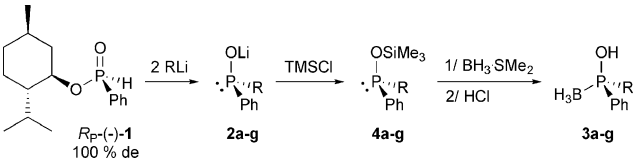
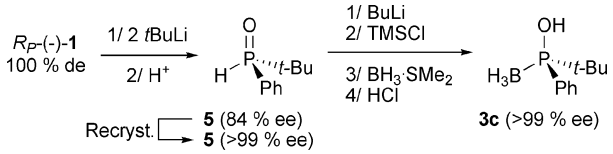
Table 2 One-pot synthesis of phosphinous acid–boranes **3a–g** (method B)



Entry	R	**4a–g** (δ^{31}P/ ppm)	Product	Yield[a] (%)	ee[b] (%)
1	Me	100	*S*-(−)-**3a**	78	95
2	*n*-Bu	106	(−)-**3b**	70	89
3	*t*-Bu	115	*S*-(−)-**3c**	70	84
4	2-Me(C_6H_4)	97	(+)-**3d**	75	97
5	2-Ph(C_6H_4)	99	(−)-**3e**	85	95
6	1-Naphthyl	92	*R*-(−)-**3f**	75	99[c]
7	1-Furyl	75	(+)-**3g**	72	80

[a] Yields after purification. [b] Enantiomeric excesses were determined by HPLC analysis on Chiralpak AS-H (λ = 254 nm; 1 mL min^{-1}; eluent: hexane–*i*-PrOH mixtures). [c] Enantiomeric excess was determined by HPLC analysis on Chiralpak OD-H (λ = 254 nm; 1 mL min^{-1}; eluent: hexane–EtOH) (8 : 2).



Scheme 2 Two-step stereoselective synthesis of enantiopure **3c**.

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