Efficient Preparation of (*S*)- and (*R*)-*tert*-Butylmethylphosphine Borane. A novel entry to important P-stereogenic Ligands.

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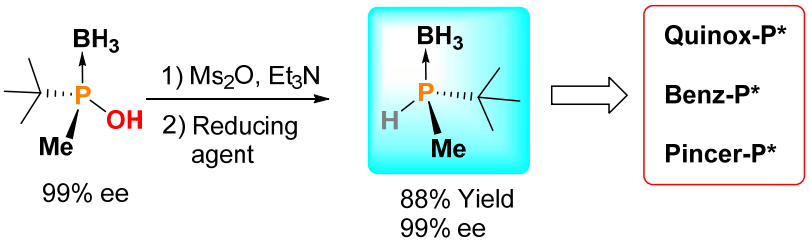

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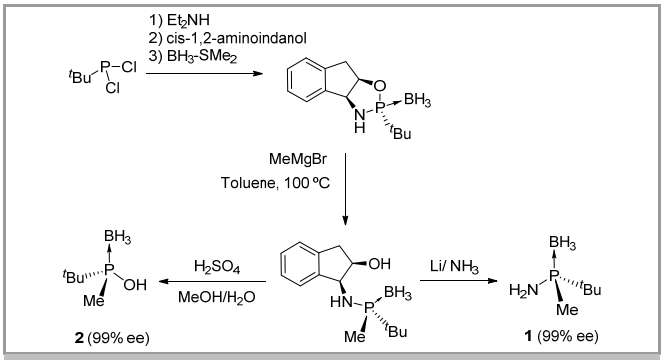
Abstract A novel one-pot reductive methodology for the synthesis of optically pure *tert*-butylmethylphosphine borane is reported. The preparation uses as starting material *tert*-butylmethylphosphinous acid borane which is available in both enantiomeric forms from cis-1,2-aminoindanol and dichloro-*tert*-butylphosphine. The process is based in the reduction of a mixed anhydride, the configurational stability of which has been studied in several solvents and temperatures. Tetrabutylammonium borohydride was the best reducing agent allowing for the development of a practical process. To demonstrate the utility of the new methodology the product obtained in this manner was used in the preparation of Quinox-P*.

Key words phosphorus, P-ligands, P-stereogenic phosphines, stereospecific reductions, ligand synthesis.

P-Stereogenic phosphines are a subclass of phosphine ligands that has recently grown into one of the most efficient type of ligands for asymmetric hydrogenation and other relevant industrial processes.[1] In this respect, the development of synthetic methodology allowing for the efficient synthesis of such compounds is of crucial importance. In our group, we have developed a novel strategy for the synthesis of valuable P-stereogenic synthons like *tert*-butylmethylaminophosphine borane **1** and *tert*-butylmethylphosphinous acid borane **2** (Scheme 1).[2] Compounds **1** and **2** have been employed in the synthesis of MaxPHOS, SIP and phosphinooxazoline ligands that have proven very efficient in asymmetric hydrogenation and [2+2+2] cycloaddition reactions.[2a,e,f] Compounds **1** and **2** are valuable because they bear in common the *tert*-butylmethylphosphine moiety which provides a high steric bias when the phosphorus is coordinated to the metal center.

Another important P-stereogenic building-block of the same family is the *tert*-butylmethylphosphine borane **3**, that has been used by Imamoto for the synthesis of C_2 symmetric Quinox-P*, Benz-P* and Pincer-P* ligands (Figure 1).[3] These ligands have demonstrated to be very efficient in numerous catalytic processes.[4] The synthesis reported for **3** relies on the stereoselective deprotonation of *tert*-butyldimethylphosphine borane with the sparteine/s-BuLi couple, followed by oxidation of the corresponding phosphide with O_2 to yield the corresponding hydroxymethylphosphine **4** (Scheme 2). Further oxidation of **4** with $RuCl_3$/ $K_2S_2O_8$ leads to the phosphinecarboxylic acid which spontaneously decarboxylates to yield **3**. The synthesis reported for **3** bears several shortcomings like the use of sparteine, a natural diamine for which the unnatural enantiomer is difficult to obtain, and the need for optical enrichment of intermediate **4** by crystallization.[5]



Scheme 1 Synthesis of optically pure P-stereogenic synthons.

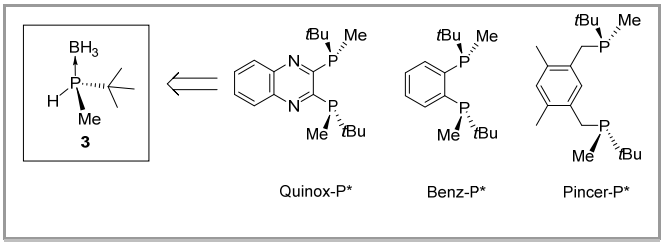
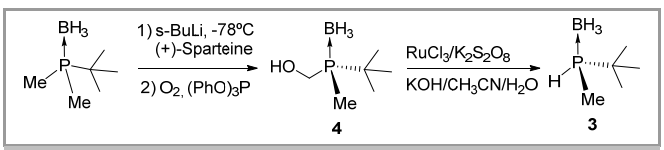


Figure 1 *tert*-Butylmethylphosphine borane **3** serves as a precursor for important P-stereogenic C_2-bisphosphines.

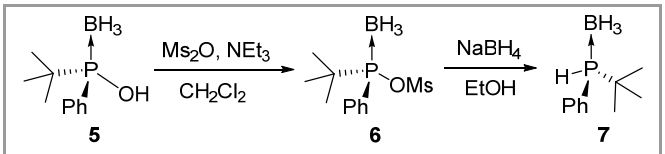


Scheme 2 Reported synthesis for optically enriched *tert*-butylmethylphosphine borane **3**.

With this picture in mind, we thought that alternative preparations of optically pure **3** would be valuable for either the preparation of new or already existing P-stereogenic ligands.

Here we report on the reduction of phosphinous acid **2** leading to optically pure *tert*-butylmethylphosphine **3** in a stereospecific fashion. To demonstrate the utility of the novel preparation, the secondary phosphine borane thus obtained was further transformed into Quinox-P*.

Optically enriched phosphinous acid boranes are attractive synthetic intermediates; despite of this, they have been scarcely used in ligand synthesis. Pietrusiewicz and Buono independently reported the preparation of optically pure *tert*-butylphenylphosphinous acid borane **5** and its reduction to the corresponding secondary phosphine **7** (Scheme 3).[6] In the case of **5**, a two-step procedure was necessary to accomplish the transformation. The mixed anhydride **6** was isolated, according to the authors, without loss of optical purity. Overall the reduction takes place with inversion of configuration at the P-center.

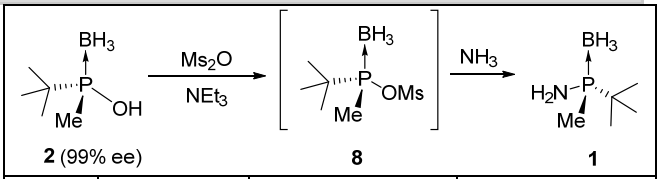


Scheme 3 Reduction of *tert*-butylphenylphosphinous acid according to Pietrusiewicz and Buono.

We have recently reported that methanesulfonyl (mesyl) anhydrides derived from **2** and **5** can undergo nucleophilic substitution reaction at phosphorus (S_N2@P) with amine nucleophiles.[2a] In this work, we noticed that the mesyl anhydride derived from **2** was not configurationally stable and could not be isolated as the phenyl analog **6**.

In order to determine the optimal solvent and temperature conditions in which intermediate **8** would preserve the initial optical purity we studied the transformation of **2** into the amine derivative **1** (Table 1). Optically pure phosphinous acid **2**, was treated with mesyl anhydride and NEt_3 to yield the mixed anhydride **8** which was left some time in solution before bubbling an excess of $NH_{3\,(g)}$ into the reaction mixture. This was a convenient method since the optical purity of **1** could be readily determined by chiral GC. Initially, using different solvents, the formation of **8** was carried out at 0 °C and the solution was left 1h at the same temperature before bubbling ammonia (Table 1, entries 1-6). The use of toluene, THF, Et_2O and DME afforded the final substitution product **1** with a high degree of racemization (22-46% ee). On the other hand, acetonitrile and dichloromethane produced less racemization affording the final product in 80 and 91% ee respectively. At this stage we studied the effect of the temperature. Using the best solvent in the series and lowering the temperature to –10 °C the enantiomeric excess increased to 97% ee (Table 1, entry 7). Running the reaction at –20 °C in CH_2Cl_2 the racemization was completely supressed and the product was isolated in 99% ee (Table 1, entry 8). To show the importance of temperature, an almost complete racemization took place when a CH_2Cl_2 solution of **8** was stirred 3h at room temperature (Table 1, entry 9).

Table 1 Solvent and temperature effect on the stereochemical integrity of the phosphinyl-mesyl anhydride.

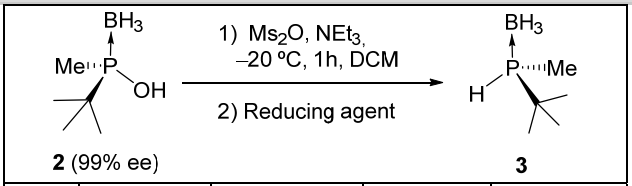


Entry	Solvent[a]	Temp (ºC)[a]/time [b]	ee of 1 (%)[c,d]
1	Toluene	0 / 1h	29
2	THF	0 / 1h	22
3	Et2O	0 / 1h	42
4	DME	0 / 1h	46
5	ACN	0 / 1h	80
6	DCM	0 / 1h	91
7	DCM	-10 / 1h	98
8	DCM	-20 / 1h	99
9	DCM	rt / 3h	29

[a] Solvent and temperature employed in the formation of the mixed anhydride. [b] Time left before bubbling ammonia gas into the reaction mixture. [c] Enantiomeric excess of the amino phosphine product was directly determined by chiral GC. [d] Amino phosphine **1** was isolated in 80-90% yield

From the previous study, we concluded that intermediate **8** was stable to racemization at –20 °C in CH_2Cl_2. Thus, the reduction of phosphinous acid **2** had to be ideally performed at the same conditions of solvent and temperature. With this constraints in mind we began to search for the reagent that could fulfil such requirements (Table 2). The use of $NaBH_4$, which was used successfully in the reduction of **6**, did not produce any reduction product (Table 2, entry 1). We attributed this lack of reactivity to the poor solubility of $NaBH_4$ in CH_2Cl_2. Reduction with $BH_3{\cdot}SMe_2$ or $NaBH(OAc)_3$ was also unproductive (Table 2, entries 2-3). Diisobutylaluminium hydride (DIBAl-H) at –20 °C produced a low yield (13%) of the desired secondary phosphine (Table 2, entry 2). Increasing the reaction temperature to 0 °C and shortening the reaction time to 2h improved the yield to 34% but with a concomitant loss of optical purity (Table 2, entry 3). We reasoned that the sluggish reactivity observed for the DIBAL-H reagent was due to the steric hindrance created by the isobutyl groups of the reagent. Hence, we next tried the use of the smaller alane (AlH_3) generated from $LiAlH_4$ and $AlCl_3$. Addition of alane over the mixed anhydride **8** in CH_2Cl_2 at –20 °C afforded this time the secondary phosphine **3** with 80% yield and 97% enantiomeric excess (Table 2, entry 6). Finally, in search for a commercial reducing agent that could be easily handled and stored, we turned our attention to tetrabutylammonium borohydride ($[NBu_4][BH_4]$). The high solubility of this reagent in CH_2Cl_2 permits reductions to be carried out in the absence of protic solvents.[7] The use of $[NBu_4][BH_4]$ provided an efficient reduction of the intermediate **8** producing the secondary phosphine **3** with inversion of configuration in 86% yield and 99% enantiomeric excess (Table 2, entry 7). Using the opposite enantiomer of the phosphinous acid, the enantiomer of **3** was obtained in 99% ee (Table 2, entry 8), thus demonstrating that the reduction process is completely stereospecific.

Table 1 Reduction trials to *tert*-butylmethylphosphine Borane

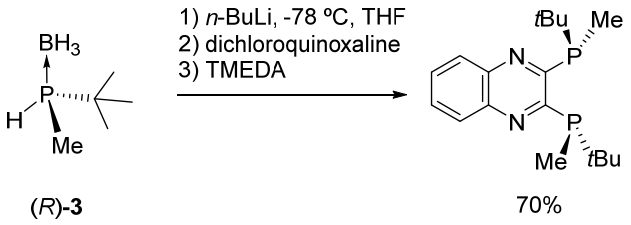


2 (99% ee) **3**

Entry	Reagent	Red. Cond.[a]	Yield (%)	ee (%)[b]
1	$NaBH_4$	-20 °C, 16h	0	-
2	$BH_3{\cdot}SMe_2$	-20 °C, 16h	0	-
3	$NaBH(OAc)_3$	-20 °C, 16h	0	-
4	DIBAL-H[c]	-20 °C, 16h	13	-
5	DIBAL-H[c]	0 °C, 2h	34	82 (*S*)
6	AlH_3[d]	-20 °C, 4h	80	97 (*S*)
7	$[NBu_4][BH_4]$[e]	-20 °C, 4h	86	99 (*S*)
8	$[NBu_4][BH_4]$[e]	-20 °C, 4h	88	99 (*R*)

[a] Reduction conditions. [b] Enantiomeric excess was determined by chiral HPLC of the corresponding benzyl derivative of *tert*-butylmethylphosphine borane. [c] The commercial 1M solution in hexanes was used. [d] A 1.5M suspension of alane in Et_2O was used. The reagent suspension was prepared from $LiAlH_4$ and $AlCl_3$. [e] For work-up and isolation reasons, *N*-methylmorpholine was used as a base instead of triethylamine.

To demonstrate the utility of this novel reduction methodology, optically pure *tert*-butylmethylphosphine borane prepared by us was employed in the preparation of Quinox-P* ligand following Imamoto's procedure (Scheme 4).[3b] Deprotonation of **3** with n-BuLi at –78 °C provided the corresponding lithium phosphide which was reacted in situ at low temperature with dichloroquinoxaline. Removal of the borane protecting groups provided, in a single-pot process, Quinox-P* in 70% yield and 99% optical purity as determined by optical rotation.[8]



(*R*)-**3** 70%

Scheme 4 Preparation of Quinox-P* starting from *tert*-Butylmethylphosphine Borane prepared by the new reduction methodology.

In summary, we have devised a novel reductive methodology for the synthesis of optically pure *tert*-butylmethylphosphine borane which is a strategic P-stereogenic intermediate for the synthesis of important chiral phosphine ligands. The novel preparation uses as starting material *tert*-butylmethylphosphinous acid borane which is available in both enantiomeric forms. The process is based in the reduction of the mixed mesyl anhydride derivative **8** which was found to be configurationally stable in CH_2Cl_2 at –20 °C. Tetrabutylammonium borohydride was the reducing agent of choice, allowing for the development of a practical one-pot process. The usefulness of the new reductive methodology was demonstrated with the preparation of Quinox-P* following the original Imamoto's procedure. We think that the novel preparation will improve the availability of **3** and thus foster its incorporation into novel ligand structures.

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General Experimental Procedures. All reactions were carried out under nitrogen atmosphere with dried solvents. THF, Et_2O and CH_2Cl_2 were dried in a PureSolv purification system from Innovative Technology, Inc. *N*-methylmorpholine was dried with molecular sieves and kept under N_2. Other commercially available reagents and solvents were used with no further purification. Thin layer chromatography was carried out using TLC-aluminum sheets with silica gel (Merk 60 F_{254}). Silica gel chromatography was performed by using 35–70 mm silica or an automated chromatography system (Combiflash®, Teledyne Isco). NMR spectra were recorded at 23°C on a Varian Mercury 400 or Varian 500. ^1H NMR and ^{13}C NMR spectra were referenced either to relative internal TMS or to residual solvent peaks. ^{31}P NMR spectra were referenced to phosphoric acid. Optical rotations were measured at room temperature (25°C) using a Jasco P-2000 iRM-800 polarimeter. Concentration is expressed in g/100 mL. The cell sized 10 cm long and had 1 mL of capacity, measuring λ was 589 nm, which corresponds to a sodium lamp. Synthesis of **2**-(*S*) and **2**-(*R*) was performed as previously described.[2a]

Procedures

(+)-(*S*)-*tert*-butylmethylphosphine borane, (+)-3.

Reduction with alane: A solution (*S*)-*tert*-butyl(methyl)phosphinous acid borane (+)-**2** (100mg, 0.75 mmol) and methansulfonic anhydride (195 mg, 1.12 mmol) in CH_2Cl_2 (4 mL) was cooled to –20 °C. To this solution, anhydrous NEt_3 (0.26 mL, 1.87 mmol) was slowly added and the mixture was stirred for 1.5 h at –20 °C. A solution of AlH_3 (1.5 M in Et_2O, made *in situ* by mixing $LiAlH_4$ (4 eq) and $AlCl_3$ (1 eq) in Et_2O) (2 mL, 3.0 mmol) was added dropwise and the mixture was stirred 4 h at –20 °C. Consumption of the starting material was observed by TLC. The solution was warmed to 0 °C and HCl (1 M in H_2O) was slowly added. The resulting suspension was filtered through a plug of Celite®. The organic layer was separated and the aqueous phase was extracted thrice with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated on a rotary evaporator under reduced pressure. Purification by column chromatography (SiO_2, isocratic CH_2Cl_2) yielded 90 mg (80%, 97% ee) of (+)–**3** as a colorless semisolid. Spectroscopic data was in agreement with the literature.[3a]

(–)-(*R*)-*tert*-butylmethylphosphine borane, (–)-3.

Reduction with $[Bu_4N][BH_4]$: A solution of (*R*)-*tert*-butyl(methyl)-phosphinous acid borane (–)-**2** (200mg, 1.50 mmol) and methansulfonic anhydride (313 mg, 1.80 mmol) in CH_2Cl_2 (6 mL) was cooled to –20 °C. To this solution, anhydrous *N*-methylmorpholine (205 µL, 1.87 mmol) was slowly added, and the mixture was stirred 1.5 h at –20 °C. A solution of $[Bu_4N][BH_4]$ (1.15 g, 4.5 mmol) in 2 mL of CH_2Cl_2 was slowly added and the mixture was further stirred 2 h at –20 °C. After this time, consumption of the starting material was observed by TLC. The reaction was quenched by slow addition of HCl (1 M in H_2O). The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator under reduced pressure. Purification by short column chromatography (SiO_2, isocratic hexanes/CH_2Cl_2, 6:4) yielded 154 mg (88%, 99% ee) of pure (–)-**3** as a colorless semisolid. Spectroscopic data was in agreement with the literature.[3a]

$[\alpha]_D$: – 4.5 (c 0.60, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$) δ; 4.40 (dm, J_P = 355 Hz, 1H, HP), 1.31 (dd, J = 11 and 6 Hz, 3H, CH_3), 1.21 (d, J_P = 15 Hz, 9H, tBu), 0.48 (br q, J_B = 96 Hz, 3H, BH_3) ppm.

^{31}P NMR (202 MHz, $CDCl_3$) δ; 11.7 (q, J_B = 48 Hz) ppm.

Enantiomeric excess determination for 3: Optical purity for **3** was determined by derivatization to the corresponding benzyl phosphine which was analyzed by chiral HPLC.

(–)-(*R*)-Benzyl-*tert*-butylmethylphosphine borane. A sample of (–)-**3** (34 mg, 0.31 mmol) was dissolved in anhydrous THF (3 mL) and cooled to –78 °C. Then *n*-BuLi (0.250 mL, 0.39 mmol, 1.6 M in hexanes) was slowly added at –78 °C. The mixture was left stirring for 50 min. At low temperature, benzyl bromide (37 µL, 0.31 mmol) was then added. The reaction was left to warm to room temperature and left to stir overnight.

The mixture was then quenched by addition of NH_4Cl at 0 °C. The mixture was extracted twice with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated on a rotary evaporator under reduced pressure. The benzyl-*tert*-butylmethylphosphine borane was obtained pure as a white solid (99%). Spectroscopic data was in agreement with the literature.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.15 – 7.35 (m, 5H, Ph), 2.90 – 3.11 (m, 2H, CH_2), 1.21 (d, *J* = 14 Hz, 9H, *t*Bu), 1.04 (d, *J* = 10 Hz, 3H, CH_3), 0.09 – 0.85 (m, 3H, BH_3) ppm.

Chiral HPLC analysis: Daicel Chiralcel OD-H; heptane/i-PrOH = 9:1, 0.5 mL/min, 210 nm, t_S= 18.6 min, t_R = 20.6 min.

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Supporting Information

NO (this text will be deleted prior to publication)

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† These authors contributed equally to the present work.

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