Efficient Preparation of (S)- and (R)-tert-Butylmethylphosphine–Borane: A Novel Entry to Important P-Stereogenic Ligands

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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 the starting material tert-butylmethylphosphinous acid–borane, which is available in both enantiomeric forms from cis-1,2-aminoindanol and tert-butyldichlorophosphine. The process is based on 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 phosphone ligands that have 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 synths like amino(tert-butyl)methylphosphine–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 C2 symmetric Quinox-P*, Benz-P*, and Pincer-P* ligands (Figure 1).3 These ligands have been 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 O2 to yield the corresponding (hy-
droxymethyl-phosphine 4 (Scheme 2). Further oxidation of 4 with RuCl₃/K₂S₂O₈ 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.²

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 phosphineborane thus obtained was further transformed into quinoxaline-P⁻.

Optically enriched phosphinous acid–boranes are attractive synthetic intermediates; despite this, they have been scarcely used in ligand synthesis. Pietrusiewicz and Buono independently reported the preparation of optically enriched tert-butylmethylphosphinous acid–borane 3 in a stereospecific fashion. To demonstrate the utility of the novel preparation, the secondary phosphineborane thus obtained was further transformed into quinoxaline-P⁻.

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We have recently reported that methanesulfonyl (mesyl) anhydrides derived from 2 and 5 can undergo nucleophilic substitution reaction at phosphorus (SP₂OP) with amine nucleophiles. In this work, we noticed that the mesyl anhydride derived from 2 was not configurationally stable and could not be isolated as the phenyl analogue 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 Et₃N to yield the mixed anhydride 8 which was left some time in solution before bubbling an excess of NH₃gas 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 for 1 h at the same temperature before bubbling ammonia (Table 1, entries 1–6). The use of toluene, THF, Et₂O, 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 98% ee (Table 1, entry 7). Running the reaction at −20 °C in CH₂Cl₂ the racemization was completely suppressed 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 CH₂Cl₂ solution of 8 was stirred for 3 h at room temperature (Table 1, entry 9).

| Entry | Solvent ¹ | Temp°, time² | ee (%) ³ of 1 |
|-------|-----------|-------------|--------------|
| 1     | toluene   | 0 °C, 1 h   | 29           |
| 2     | THF       | 0 °C, 1 h   | 22           |
| 3     | Et₂O      | 0 °C, 1 h   | 42           |
| 4     | DME       | 0 °C, 1 h   | 46           |
| 5     | MeCN      | 0 °C, 1 h   | 80           |
| 6     | CH₂Cl₂    | 0 °C, 1 h   | 91           |
| 7     | CH₂Cl₂    | −10 °C, 1 h | 98           |
| 8     | CH₂Cl₂    | −20 °C, 1 h | 99           |
| 9     | CH₂Cl₂    | r.t., 3 h   | 29           |

¹ Solvent and temperature employed in the formation of the mixed anhydride.
² Time before bubbling ammonia gas into the reaction mixture.
³ Enantiomeric excess of the aminophosphine product was directly determined by chiral GC.
⁴ 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 CH₂Cl₂. Thus, the reduction of phosphinous acid 2 had to be ideally performed under the same conditions of solvent and temperature. With this constraint in mind we began to search for the reagent that could fulfill such requirements (Table 2). The use of NaN₃, which was used successfully in the reduc-
of 6, did not produce any reduction product (Table 2, entry 1). We attributed this lack of reactivity to the poor solubility of NaBH₄ in CH₂Cl₂. Reduction with BH₃·SMe₂ or NaBH(OAc)₃ was also unproductive (Table 2, entries 2 and 3). Diisobutylaluminum hydride at −20 °C produced a low yield (13%) of the desired secondary phosphine (Table 2, entry 4). Increasing the reaction temperature to 0 °C and shortening the reaction time to 2 h improved the yield to 34% but with a concomitant loss of optical purity (Table 2, entry 5). We reasoned that the sluggish reactivity observed for the DIBAL-H reagent was due to the steric hindrance entry 5). 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 (AlH₃) generated from LiAlH₄ and AlCl₃. Addition of alane over the mixed anhydride 8 in CH₂Cl₂ at −20 °C afforded this time the secondary phosphine 3 in 80% yield and 97% ee (Table 2, entry 6). Finally, in the search for a commercial reducing agent that could be easily handled and stored, we turned our attention to tetrabutylammonium borohydride ([Bu₄N][BH₄]). The high solubility of this reagent in CH₂Cl₂ permits reductions to be carried out in the absence of protic solvents.7 The use of [Bu₄N][BH₄] provided an efficient reduction of the intermediate 8 producing the secondary phosphine 3 with inversion of configuration in 86% yield and 99% ee (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.

| Entry | Reagent | Reduction Conditions* | Yield (%) | ee (%) |
|-------|---------|-----------------------|----------|-------|
| 1     | NaBH₄   | −20 °C, 16 h          | 0        | −     |
| 2     | BH₃·SMe₂ | −20 °C, 16 h          | 0        | −     |
| 3     | NaBH(OAc)₃ | −20 °C, 16 h       | 0        | −     |
| 4     | DIBAL-H⁺  | −20 °C, 16 h          | 13       | −     |
| 5     | DIBAL-H⁺  | 0 °C, 2 h             | 34       | 82 (S) |
| 6     | AlH₃⁺     | −20 °C, 4 h           | 80       | 97 (S) |
| 7     | [Bu₄N][BH₄]⁺ | −20 °C, 2 h       | 86       | 99 (S) |
| 8     | [Bu₄N][BH₄]⁺ | −20 °C, 2 h        | 88       | 99 (R) |

*Reduction conditions.

Table 2 Reduction Trials to tert-Butylmethylphosphine–Borane

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

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Special Topic

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 the starting material tert-butylmethylphosphinous acid–borane which is available in both enantiomeric forms. The process is based on the reduction of the mixed mesyl anhydride derivative 8 which was found to be configurationally stable in CH₂Cl₂ 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 by 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.

All reactions were carried out under a N₂ atmosphere with dried solvents; THF, Et₂O, and CH₂Cl₂ were dried in a PureSolv purification system from Innovative Technology, Inc. NMM was dried with molecular sieves and kept under N₂. Other commercially available reagents and solvents were used with no further purification. TLC was carried out using TLC-aluminum sheets with silica gel (Merck 60 F₂₅₄). 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 and ¹³C NMR spectra were referenced either to relative internal TMS or to residual solvent peaks. ¹³P NMR spectra were referenced to H₃PO₄. Optical rotations were measured at rt. (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 A was 589 nm, which corresponds to a sodium lamp. Synthesis of (S)-2 and (R)-2 was performed as previously described.24
(+)-(S)-tert-Butylmethylphosphine-Borane [(+)-3]

Reduction with Alane

A solution of (S)-tert-butylmethyolphosphinous acid–borane [(+)-2, 100 mg, 0.75 mmol] and MsO (195 mg, 1.12 mmol) in CH2Cl2 (4 mL) was cooled to −20 °C. To this solution, anhyd Et3N (0.26 mL, 1.87 mmol) was slowly added and the mixture was stirred for 1 h at −20 °C. A solution of AlH3 [1.5 M in Et2O, made in situ by mixing LiAlH4 (4 equiv) and AlCl3 (1 equiv) in Et2O] (2 mL, 3.0 mmol) was slowly added and the mixture was stirred for 1 h at −20 °C. Consumption of the starting material was observed by TLC. The solution was warmed to 0 °C and 1 M aq HCl was slowly added. The resulting suspension was filtered through a plug of Celite. The organic layer was separated and the aqueous phase was extracted with CH2Cl2 (3 ×). The combined extracts were washed with brine, dried (MgSO4), and concentrated on a rotary evaporator under reduced pressure. Purification by column chromatography (silica gel, isocratic CH2Cl2) gave (+)-3 as a colorless semisol; yield: 90 mg (80%); 97% ee. Spectroscopic data was in agreement with the literature.3

Reduction with [Bu4N][BH4]−

A solution of (R)-tert-butylmethylphosphinous acid–borane [(−)-2, 200 mg, 1.50 mmol] and MsO (313 mg, 1.80 mmol) in CH2Cl2 (6 mL) was cooled to −20 °C. To this solution, anhyd N-methylmorpholine (205 μL, 1.87 mmol) was slowly added, and the mixture was stirred for 1 h at −20 °C. A solution of [Bu4N][BH4]−(1.15 g, 4.55 mmol) in CH2Cl2 (2 mL) was slowly added and the mixture was stirred for a further 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 1 M aq HCl. The organic layer was separated and the aqueous phase was extracted with CH2Cl2 (2 ×). The combined extracts were washed with brine (5 mL), dried (MgSO4), and concentrated on a rotary evaporator under reduced pressure. Purification by short column chromatography (silica gel, isocratic CH2Cl2 6:4) gave pure (−)-3 as a colorless semisolid; yield: 154 mg (88%); 99% ee. Spectroscopic data was in agreement with the literature.3a

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Optical rotation recorded by us matched exactly the $\alpha_0$ described by Imamoto and co-workers for a pure sample of Quinox-P*.

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