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Enantioselective synthesis of both enantiomers of *tert*-butylphenylphosphine oxide from (*S*)-prolinol

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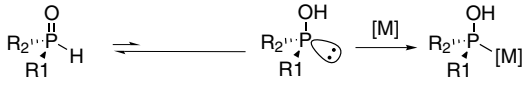
Abstract—Both enantiomers of *tert*-butylphenylphosphine oxide can be easily synthesised starting from (*S*)-prolinol-based oxazaphospholidine.

Secondary phosphine oxides (SPOs) are effective intermediates for the preparation of tertiary phosphines and phosphine oxides,[1] and enantiopure SPOs have been used to obtain chiral tertiary mono- and diphosphine oxides.[2,3]

In the last decade, achiral SPOs have proved to be efficient ligands in a number of transition metal reactions. For instance, platinum complexes coordinated by SPOs are able to catalyse hydration of nitriles to amides[4] while palladium/SPOs complexes are effective in cross-coupling reactions of aryl chlorides.[5] We have recently reported that these ligands are suitable for an unusual palladium catalysed [2+1] cycloaddition of terminal alkynes with norbornene derivatives.[6] However, the use of chiral SPOs in enantioselective catalysis is much less developed and it is expected that new asymmetric applications will emerge.[7] Indeed, in very recent letters, their activity has been tested successfully in iridium- or rhodium-catalysed asymmetric hydrogenation of imines[8] or of functionalised olefins[9] and in palladium-catalysed asymmetric allylic alkylation.[10]

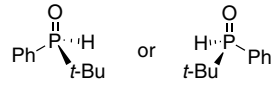
In these reactions, the coordination of chiral SPOs to the metal through the tautomer displaying a trivalent phosphorus atom proceeds without racemisation (Scheme 1).[6,10a,11]



Scheme 1. Coordination behaviours of SPOs.

Among the chiral SPOs ligands tested in metal catalysed transformations, *tert*-butylphenylphosphine oxide **1** appears to be the most promising. In contrast to the racemic SPOs which are readily available, enantiomerically pure SPOs requires chemical resolution[2a] or separation by chiral chromatography.[8] To the best of our knowledge, only one report describes the enantioselective synthesis of **1** in a four step sequence including a crystallisation to obtain an highly pure diastereomer.[12] Hence, the development of an efficient strategy to prepare *tert*-butylphenylphosphine oxide **1** in an optically pure form is in high demand. In this letter, we report the first direct (one-pot, two-steps) enantioselective synthesis of *tert*-butylphenylphosphine oxide **1** (Scheme 2).

When enantiomerically pure oxazaphospholidine (R_P)-**2**, easily prepared from $PhP(NMe_2)_2$ and *S*-(+)-prolinol,[13] was treated with *tert*-butyllithium in THF at low temperature, alcoholate **3**, resulting from the cleavage



(*S*)-(-)-**1** (*R*)-(+)-**1**

Scheme 2. Structure of *tert*-butylphenylphosphine oxide **1**.

Keywords: Secondary phosphine oxides; Oxazaphospholidine; Enantioselective synthesis; *S*-(+)-Prolinol; Tricoordinated organophosphorus compound.
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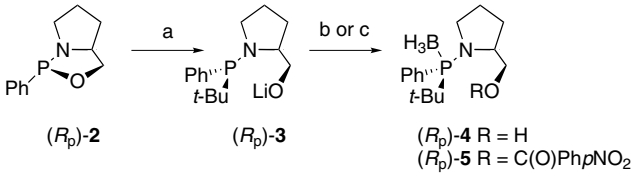


Scheme 3. Synthesis of compounds **4** and **5**. Reagents and conditions: (a) *t*-BuLi, THF, −78 °C, 15 min; (b) Me_3SiCl, THF,−78 °C, 15 min then, BH_3–Me_2S, rt, 12 h and KF, MeOH, rt, 24 h, 64% of **4**; (c) *p*-$NO_2PhC(O)Cl$, THF, −78 °C, 15 min and BH_3–Me_2S, rt, 12 h, 51% of **5**.

of the P–O bond, was obtained (see Scheme 3). At this stage, the reaction mixture was quenched by addition of Me_3SiCl followed by BH_3–Me_2S. The resulting BH_3 protected silylether was converted into the alcool **4** in the presence of KF in methanol. The diastereomeric excess detected on the crude derivative **4** was found to be $\geqslant$91% by ^1H and ^{31}P NMR. This NMR analysis shows clearly that the ring opening of the oxazaphospholidine **2** proceeds with high diastereoselectivity.

To date, this powerful synthetic methodology developed by Jugé and co-workers was based exclusively on the regio- and stereoselective nucleophilic substitution of either 1,3,2-oxazaphospholidine–boranes and from the analogous phosphine oxides (both derived from the enantiomers of ephedrine as template) but not on unprotected tricoordinated ($\sigma^3\lambda^3$) compounds.[14]

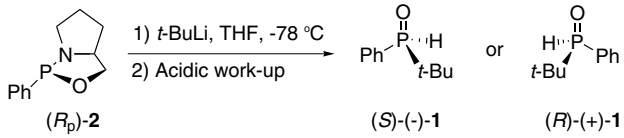
Subsequent treatment of **3** by sulfuric acid on silica (4 equiv) followed by hydrolysis gave compound **1** with 23% yield and 18% ee (Table 1, entry 1).

This encouraging result prompted us to optimise this reaction. We tried various acids of different strengths (Table 1). We were delighted to find that the acid not only plays an important role in the yield and enantioselectivity of the reaction but also allows control of the enantiomer obtained. By using acids of high acidity ($pK_a \leqslant 1$) or Amberlyst 15 resin, (+)-(*R*)-**1** was obtained with fairly good yields and enantioselectivities (Table 1, entries 2–4). When acids of low acidity ($pK_a \approx 3$–5) were used, (−)-(*S*)-**1** was the preferred enantiomer obtained with acceptable ee's (Table 1, entries 5–8). Using *p*-toluenesulfonic acid afforded (*R*)-**1** in 88% yield[15] and up to 91% ee (Table 1, entry 4). After a single recrystallisation from petroleum ether/diethyl ether (2/1), compound **1** was determined to be essentially optically pure (>99%) in 75% yield.[16]

In order to get some information on the stereochemical course of the reaction, it was necessary to determine whether the ring opening step occurred with inversion or retention of configuration at the phosphorus atom. Therefore compound **5** a derivative of intermediate **3** protected with BH_3, resulting from the reaction of **3** with *p*-nitrobenzoyl chloride, was isolated and crystallised from petroleum ether/diethyl ether (Scheme 3). The structure of **5** determined by X-ray diffraction (Fig. 1) highlights a π stacking interaction between aromatic groups with an interplane distance of 378.7 pm and reveals that the ring opening of **2** proceeded with a retention of configuration to afford (R_P)-**5**.[17] This is in agreement with results observed by Jugé and co-workers on the ring opening of an ephedrine based oxazaphospholidine.[14] This implies that in the case of strong acids the hydrolysis proceeds with retention of configuration whereas in the case of weak organic acids inversion of configuration occurs.

Jugé and co-workers[14] showed that the ring opening of the protected ephedrine based oxazaphospholidine by *tert*-butyllithium proceeded diastereoselectively with retention of configuration on the phosphorus atom to

Table 1. Effects of the acid on the hydrolysis



Entry[a]	Acid	Yield[b] (%)	ee[c] (%)	Enantiomer
1	H_2SO_4/silica	23	18	(***R***)-(+)
2	Amberlyst 15	70	74	(***R***)-(+)
3	Triflic acid	20	87	(***R***)-(+)
4	PTSA	88	91	(***R***)-(+)
5	Formic acid	77	77	(***S***)-(−)
6	Acetic acid	84	71	(***S***)-(−)
7[d]	Acetic acid	76	81	(***S***)-(−)
8[d]	*p*-Nitrobenzoic acid	72	85	(***S***)-(−)

[a] All reactions were carried out with 1.2 mmol of **2** in THF at −78 °C. **2**/*t*-BuLi/acid/H_2O = 1/1.05/4/4.6. A 15 min delay between the addition of *t*-BuLi and hydrolysis was necessary.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by HPLC analysis on a Daicel Chiralcel AD-H column at $\lambda = 254$ nm; flow rate 1 mL/min; eluent: hexane/*i*-PrOH 90/10, $t(S) = 9.56$ min, $t(R) = 13.12$ min.
[d] For the hydrolysis dry organic acid is added, 15 min prior to water. PTSA = *p*-toluenesulfonic acid.

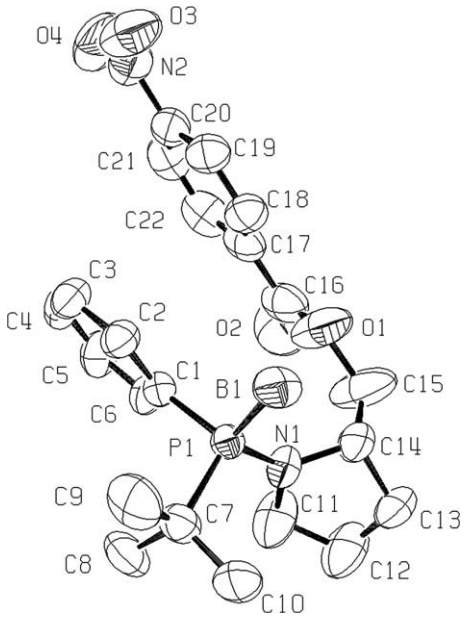
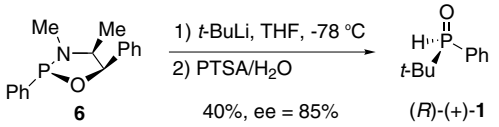


Figure 1. X-ray structure of **5**. H's omitted for clarity. Selected bond lengths: P1–N1 1.662(2), P1–C1 1.817(2), P1–C7 1.862(3), P1–B1 1.932(3). Selected bond angles: N1–P1–C1 108.59(10), N1–P1–C7 108.74(13), C1–P1–C7 105.35(11), N1–P1–B1 110.78(15), C1–P1–B1 111.58(13), C7–P1–B1 111.60(14).



Scheme 4. Ring opening of the unprotected ephedrine **6** based oxazaphospholidine by *tert*-butyllithium.

give aminophosphine borane. Nevertheless, no reaction was observed with the latter under acidolysis conditions. We thus decided to extend our conditions to the unprotected (1*R*,2*S*)-(−)-ephedrine derivative **6**. Preliminary results indicate that the ring opening and acidolysis occurred with poorer global yield (40%) but the stereoselectivity of the reaction remains the same as with the prolinol based phosphine (Scheme 4).

The enantiomeric excesses observed are similar when using *p*-toluenesulfonic acid (+)-(*R*)-**1**, (85% ee) but much lower when using formic acid (−)-(*S*)-**1** (25% ee).

In conclusion, we have developed a convenient, enantioselective synthesis of *tert*-butylphenylphosphine oxide. Most of all, this method allows the stereochemistry control of the final product. Efforts are underway to elucidate the mechanism details of the hydrolysis reaction, particularly the influence of the strength of the acid and to define the scope and limitations of this reaction.

Acknowledgements

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15. A brief study of the reaction with *p*-toluene sulfonic acid showed that a 5 min delay between the addition of *t*-BuLi and the hydrolysis (acid and water) decreased the yield to 67% but did not alter the ee's.
16. *Preparation of tert-butylphenylphosphine oxide* **1**: *t*-BuLi (0.75 mL of 1.7 M solution in pentane, 1.27 mmol) was added slowly to a stirred and cooled (−78 °C) solution of (R_P)-oxazaphospholidine **2** (248 mg, 1.2 mmol) in dry THF (5 mL). After 15 min, dry acid (4.8 mmol) and water (0.1 mL, 5.5 mmol) were added successively and the reaction mixture was stirred at room temperature for 12 h. After evaporation of THF, the crude mixture was diluted with Et_2O (10 mL), water (2 mL) and potassium carbonate (248 mg, 1.8 mmol) was added. The organic phase was separated off, and the aqueous phase was extracted with Et_2O (3×5 mL) and CH_2Cl_2 (3×5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuum. Purification by chromatography (silica gel, Et_2O/light petroleum 4/1), afforded 23–88 % of (*S*)-(−)-**1** or (*R*)-(+)-**1** as a white solid. After recrystallisation from Et_2O/light petroleum (1/2), (*S*)-(−)-**1** or (*R*)-(+)-**1** were obtained as single enantiomer with ee >99%. White crystals, mp: 75–77 °C. For NMR data, see: Haynes, R. K. et al. *Eur. J. Org. Chem.* **2000**, 3205–3216, in Ref. 3. The reaction was carried out on a gram scale: treatment with *p*-toluenesulfonic acid under the same conditions confirmed a similar result (Table 1, entry 4).
17. Crystal data for compound **5**: $M_w = 428.26$, orthorhombic, colourless crystal ($0.4 \times 0.25 \times 0.25$ mm^3), $a = 8.0310(1)$ Å, $b = 11.1670(2)$ Å, $c = 25.9190(5)$ Å, $V = 2324.47(7)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $\rho = 1.22$ g cm^{-3}, $\mu(MoK_\alpha) = 1.48$ cm^{-1}, 15,230 reflections measured at 293 K (Nonius Kappa CCD diffractometer) in the 0.79–28.27° θ range, 5390 unique ($R_{int} = 0.029$), 271 parameters refined on F^2 using 4865 reflections (Shelxl [Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. Univ. of Göttingen, Germany; 1997]) to final indices $R[F^2 > 4\sigma F_2] = 0.052$, $wR = 0.1460$ $[w = 1/[\sigma^2(Fo^2) + (0.0947P)^2 + 0.3371P]$ where $P = (Fo^2 + 2Fc^2)/3]$. The last residual Fourier positive and negative peaks were equal 0.311 and −0.389, respectively.CCDC 277820 (compound **5**) contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.