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Preparation of Bi- and Tridentate Doubly *P*-Chiral Diphosphine Dioxide Ligands for Asymmetric Catalysis

William W.-L. Lam , Richard K. Haynes,* Lam.-Lung Yeung,* and Eric W.-K. Chan

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay Road, Kowloon,Hong Kong.

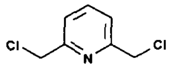
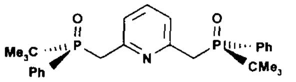
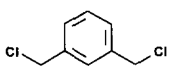
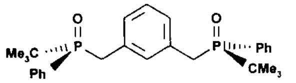
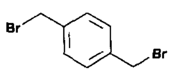
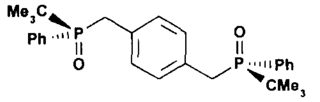
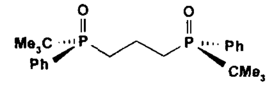
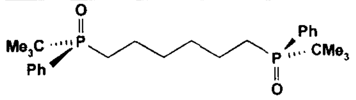
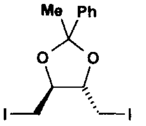
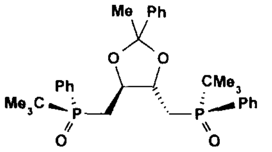
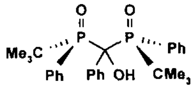
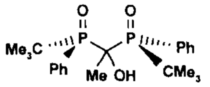
Abstract: Syntheses of bi- and tridentate doubly *P*-chiral diphosphine dioxides through reaction of the individual enantiomers of optically pure lithiated *tert*-butylphenylphosphine oxide with different bifunctional electrophiles are described. Copyright © 1996 Elsevier Science Ltd

The importance of chiral, enantiomerically-pure phosphines as chiral auxilliaries in stereo-differentiating organic reactions is underscored by their use as ligands in asymmetric homogenous catalysis.[1] The most successful class of phosphine ligand are cis-chelating diphosphines,[2] a prime example of which is provided by the Monsanto catalyst DIPAMP.[3] Most recent efforts focus on the preparation of doubly *P*-chiral diphosphines.[4] We now describe our contribution to this activity through exploitation of the observation that the individual enantiomers of *tert*-butylphenylphosphine oxide upon lithiation react with alkyl halides to give tertiary phosphine oxides without loss of configuration at phosphorus.[5] Through reaction with bifunctional electrophiles, we obtain enantiomerically-pure diphosphine dioxides, potential precursors of doubly *P*-chiral diphosphines from the lithiated secondary phosphine oxides.

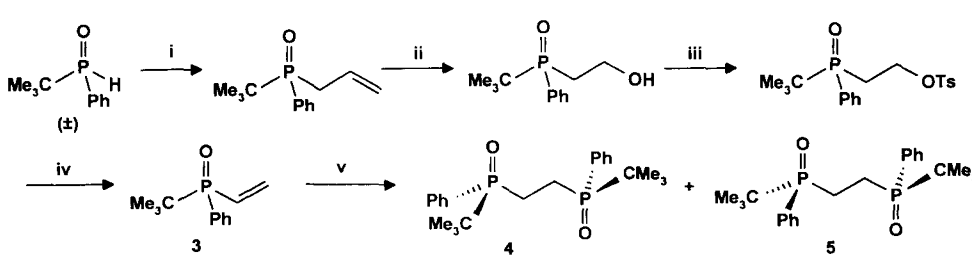
A solution of either (R_P)- (**1**) or (S_P) *tert*-butylphenylphosphine oxide (**2**) (1.0 mmol) in THF (5 ml) at -78 °C under nitrogen was treated dropwise with LDA or *n*-BuLi (1.1 mmol). After stirring for 15 min, the solution was treated with the electrophiles at -78 °C, and then stirred for 1-2 hr. Standard work-up and flash chromatography on silica gel afforded the corresponding adducts. The results involving the (R_P)-phosphine oxide **1** are summarized in Table 1 overleaf.[6,7] For entries 1-6, dihalides (0.5 eq.), and for entries 7 and 8, benzoyl chloride and acetyl chloride (each 0.5 equiv), were used as electrophiles. In the latter cases, it was not possible to isolate the intermediate acyl phosphine oxides, even for excess electrophile. Some limitations were apparent. Thus, no reaction took place with secondary alkyl iodides such as 2,4-diiodopentane and (±)-*trans*-1,2-diiodocyclohexane.[8,9] Remarkably, whereas the lithiated phosphine oxide from (R_P)-*tert*-butylphenylphosphine oxide **1** reacted smoothly with the diiodide derived from (*R*,*R*)-tartrate (entry 5), the lithiated (S_P)-reagent did not.[10]

An alternative route to the diphosphine dioxides is through conjugate addition of the lithiated secondary phosphine oxides or of lithiated methyl dialkyl or alkylaryl tertiary phosphine oxides to vinyl phosphine oxides. Whilst a neutral variant of the first reaction is known in providing diastereoisomeric material,[11] examples of conjugate addition of lithiated secondary or lithiated methyl tertiary phosphine oxides

Table 1: Doubly *P*-Chiral Diphosphine Dioxides from Lithiated (R_P)-*tert*-Butylphenylphosphine Oxide

Entry	Electrophile	Product	Yield %[a]	$[\alpha]_D^{20}$	δ_p ppm[b], m.p. °C
1			73	+68.0 c 1.03/$CHCl_3$	46.5, prisms, 75-78 °C
2			88	+78.2 c 1.33/$CHCl_3$	44.8, prisms, 67-69 °C
3			19	+78.0 c 1.00/$CHCl_3$	45.6, oil
4	$I(CH_2)_3I$		70	+60.0 c 1.01/$CHCl_3$	49.1, needles, 114-117 °C,
5	$I(CH_2)_6I$		83	+65.0 c 1.30/$CHCl_3$	49.0, needles, 118-119 °C
6			71	-9.2 c 2.38/EtOH	46.7,46.2, needles, 153-154 °C
7	PhCOCl		80	+62.5 c 1.02/$CHCl_3$	47.5,47.9, glass
8	MeCOCl		73	+63.6 c 1.21/$CHCl_3$	47.1, 47.4, glass

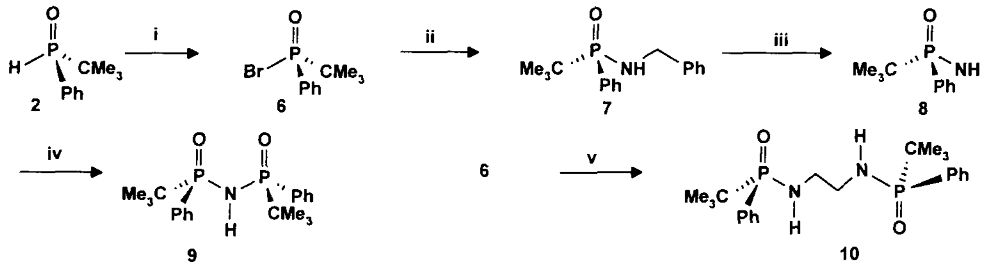
[a]Yields were not optimized; [b]determined by ^{31}P NMR at 161 MHz in $CDCl_3$ relative to trimethyl phosphite.



Scheme 1 *Reagents and conditions* : i. THF, *n*-BuLi, -78 °C, allyl bromide, (78 %); ii. a. O_3, CH_2Cl_2-MeOH, -78 °C; b. $NaBH_4$ (89%); iii. TsCl, Et_3N, CH_2Cl_2 (92%); iv. DBU, CH_2Cl_2 (90%); v. *n*-BuLi added to (*S*)-*tert*-butylphenylphosphine oxide **2**, THF, -78 °C, followed by **3** to give **4** and **5** (1:1; 78%), **4** separated from **5** by flash-column chromatography.

to vinyl phosphine oxides are unknown. The requisite racemic *tert*-butylphenylvinylphosphine oxide **3** was prepared in large scale (60% overall yield from 50 mmol of racemic *tert*-butylphenylphosphine oxide) (Scheme 1). The conjugate addition of lithiated (S_P)-*tert*-butylphenylphosphine oxide in THF at 78 °C to the racemic vinylphosphine oxide smoothly gave a 1:1 mixture of diastereomeric diphosphine dioxides (78%), which were readily separated by column chromatography to provide the (S_P,S_P) -diphosphine dioxide **4**, needles, m.p. 142-3°C, $[\alpha]_D^{20}$ -62.3° (c 1.19, $CHCl_3$), and the *meso* compound **5**, needles, m.p. 144-6°C.

To obtain potentially valuable aza-diphosphine dioxides, it was necessary to convert the secondary phosphine oxides into reagents containing a leaving group suitable for displacement by amine. Thus, treatment of lithiated (S_P)-*tert*-butylphenylphosphine oxide **2** in THF with either bromine or 1,2-dibromoethane at -78 °C gave stable crystalline (R_P)-*tert*-butylphenylphosphinobromidate **6** (54-68%), needles, m.p. 81-83 °C, $[\alpha]_D^{21}$ +31.3° (c 0.26, $CHCl_3$).[12] This was then converted into the highly crystalline *N*-benzylphosphoramidate **7**,[6] which with formic acid in ethanol underwent smooth debenzylation to give phosphoramidate **8**. This was treated with (R_P)-*tert*-butylphenylphosphinobromidate **6** to give the (R_P,R_P)-bisphosphoramidate **9**[6] (63%), needles, m.p. 138-140 °C, $[\alpha]_D^{21}$ +43.6° (c 1.0, $CHCl_3$) (Scheme 2). The diamidate **10**,[6,13] (74%), prisms, m.p. 218-219 °C $[\alpha]_D^{21}$ -59.8° (c 0.62, $CHCl_3$) was obtained from the bromidate **6** and ethylenediamine in diethyl ether.



Scheme 2 *Reagents and conditions* : i. a. THF, *n*-BuLi, -78 °C; b. $BrCH_2CH_2Br$ (68%); ii. benzylamine, Et_2O, Et_3N, rt. (82%); iii. H_2, HCO_2H, EtOH, 10% Pd/C catalyst, rt.; iv. (R_P)-*tert*-butylphenylphosphinobromidate **6**, Et_3N, Et_2O, rt (63 %); v. $H_2NCH_2CH_2NH_2$, Et_2O, rt (74%)

In summary, highly convenient routes for the synthesis of enantiomerically pure *P*-chiral bi- and tridentate phosphine ligands have been developed. Whilst we have here focussed on the one set of ligands - *tert*-butyl and phenyl - with respect to the phosphine oxide, we are now preparing secondary phosphine oxides bearing different aryl and alkyl groups in our laboratory. The uses of all types for the preparation of phosphines and the application of both the phosphine oxides and the derived phosphines for asymmetric catalysis will be reported elsewhere.

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5. Haynes, R. K.; Freeman, R. N.; Mitchell, C. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 2919.
6. All new compounds were characterized by spectroscopic methods and elemental analysis and/or accurate mass spectra.
7. Reduction of the diphosphine dioxides to phosphines, formation of phosphine Rh-complexes and uses in asymmetric hydrogenation will be reported elsewhere.
8. In contrast, enantiomericaly pure *tert*-butyl(*o*-anisyl)phosphine-borane and related compounds react both with primary and secondary alkyl halides, also without loss of stereochemical integrity: Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, T.; Hikosaka, M.; Yanagawa, M. *Heteroatom Chem.* **1992**, *3*, 563; Imamoto, T.; Matsuo, M.; Nonomura, T.; Kisjikawa, K.; Yanagawa, M. *Heteroatom Chem.* **1993**, *4*, 475.
9. Livinghouse and co-workers have shown that dialkyl- or diarylphosphine-borane anion reacts with α,ω-dihaloalkanes to give the corresponding diphosphine adducts: McKinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *35*, 9319; McKinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655. In an alternative approach to *trans*-cyclohexyl-1,2-diphosphine dioxide from the open chain hexyl-1,6-diphosphine dioxide (entry 5, Table), the diphosphine dioxide was treated with 2.2 equiv. *n*-BuLi at -78 °C in THF to convert it into the dilithiated reagent. This latter was then treated with anhydrous $CuCl_2$ according to a procedure used for oxidative coupling of anions: Minami, T.; Okada, Y.; Nomura, S.; Hirota, S.; Nagahara, Y. and Fukuyama, K. *Chem. Lett.* **1986**, *4*, 613. Whilst formation of the desired product did take place, it was not possible to bring the reaction to completion, or to separate the *trans*-cyclohexyl-1,2-diphosphine dioxide from the unreacted open-chain diphosphine dioxide.
10. The diiodide from (*R*,*R*)-tartrate with lithiated racemic secondary phosphine oxide provided significant kinetic resolution. Thus, lithiated racemic secondary phosphine oxide (1.0 eq) with diiodide (0.5 eq) in THF at -78 °C gave recovered secondary phosphine oxide with 54% ee enrichment in the (S_P)-isomer, while with 0.4 equiv. of diiodide, secondary phosphine oxide with 66% ee was recovered.
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12. (R_P)-*tert*-Butylphenylphosphinobromidate **6** is enantiomerically pure, as established by NMR assay at 400 MHz with *tert*-butylphenylphosphinothioic acid according to the method described in ref. 5. The bromidate been reported previously, but with substantially lower optical rotation: see Omelanczuk, J.; Mikołajczyk, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2223.
13. The absolute configuration of compound **10** is secured by X-ray crystallography; details may be obtained from the authors. Thus, displacement of bromide from bromidate **6** by amine proceeds with clean inversion, in contrast to an apparently stereoretentive outcome with thiolate as described in the paper quoted in ref. 12.

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