Preparation of Enantiomerically Pure Tertiary Phosphine Oxides from, and Assay of Enantiomeric Purity with, (R_p)- and (S_p)-*tert*-Butylphenylphosphinothioic Acids

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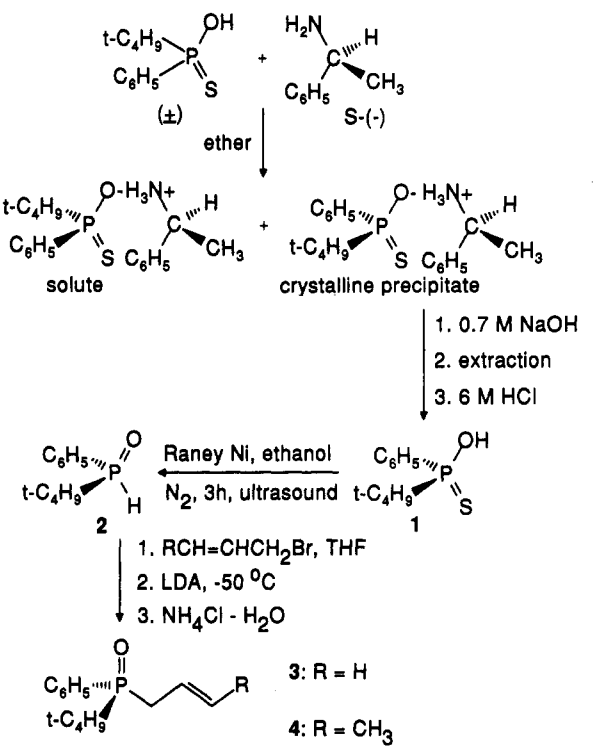
Summary: A convenient multigram scale method has been developed for preparation of enantiomerically-pure (R_p)- and (S_p)-tertiary phosphine oxides including allyl- and but-2-enyl-*tert*-butylphenylphosphine oxides wherein (R_p)- and (S_p)-*tert*-butyl-phenylphosphinothioic acids are converted into (R_p)- and (S_p)-*tert*-butylphenylphosphine oxides by ultrasound irradiation in the presence of Raney-Ni at room temperature and the secondary phosphine oxides then metalated and treated with alkyl halides.

Our interest in conjugate addition reactions of lithiated 3-alkylallylic sulfoxides, phosphine oxides, and phosphonates with cyclic enones[1] has turned toward development of enantiomerically pure reagents which provide adducts suitable for elaboration into synthetically useful targets.[2,3] We and others have succeeded in preparing[4] and carrying out conjugate addition reactions[5] with lithiated optically active allylic sulfoxides, but because of difficulty of access or of configurational instability, these are not optimum substrates. While Hua and co-workers have elegantly utilized lithiated allylic oxazaphospholidine oxides,[6] the method of synthesis is not applicable to 3-alkylallylic systems.[7] In contrast, 3-alkylallylic acyclic and cyclic phosphonates, nonstereogenic at phosphorus but bearing chiral ligands, are easily prepared from nucleophilic phosphorus by alkylation with the allylic halide, but the lithiated reagents are either unstable or provide conjugate adducts with poor diastereoselectivity.[8] Phosphorus acid diamides bearing homochiral ligands are also easily prepared,[9] and the derived allyl-[9] and butenylphosphonamides provide lithiated reagents which in contrast to the phosphonates undergo stereoselective conjugate addition.[10] Because of their greater synthetic utility with regard to Wittig–Horner and related methodologies, we have focused on tertiary phosphine oxides and have prepared the highly crystalline (R_p)- and (S_p)-*tert*-butylphenylphosphine oxides from the corresponding *tert*-butylmethylphenylphosphine oxides.[3] The lithiated reagents undergo essentially complete diastereoselective conjugate addition to enantiofacial cyclic enones in high yields.[3] Nevertheless, the preparations are bedevilled by a tedious resolution step and are not amenable to large-scale operations. We now describe here a method which allows us to prepare not only multigram quantities of the enantiomerically-pure butenyl-*tert*-butylphenylphosphine oxides but also other enantiomerically-pure tertiary phosphine oxides.

Scheme 1



(±)-*tert*-Butylphenylphosphinothioic acid was prepared[11] and resolved by an adaptation[12] of literature methods (Scheme 1).[13–15] Desulfurization of the thioic acid with Raney nickel proceeds with retention of con-

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(7) The $AlCl_3$-catalyzed procedure for preparing the dichlorallylphosphine precursor is ineffective for preparation of homologues: Haynes, R. K.; Stokes, J. P. Unpublished work.

(8) Phosphonates of the type $(RO)_2P(O)CH_2CH{=}CHCH_3$ where RO– is (+)- or (–)-menthoxide or $(RO)_2$ is derived from a homochiral diol ((*R,R*)-2,4-pentanediol, 1,1′-bi-2-naphthol) were prepared from $(RO)_2PH$ and butenyl bromide in the presence of NaH in THF: Haynes, R. K.; Stokes, J. P. Unpublished work.

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(10) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032.

(11) Dichlorophenylphosphine was converted on a 0.75 mol scale by *tert*-butylmagnesium chloride into *tert*-butylphenylphosphine oxide which was then sulfurated in toluene; *cf.* Hoffmann, H.; Schellenbeck, P. *Chem. Ber.* **1966**, *99*, 1134. More details are given in the supplementary material.

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Table 1. Phosphine Oxides from Lithiated (R_P)- and (S_P)-*tert*-Butylphenylphosphine Oxides

		(R_P)-enantiomer[a]		(S_P)-enantiomer[a]	
phosphine oxide	mp (°C)	yield (%)	$[\alpha]^{20}_D$	yield (%)	$[\alpha]^{20}_D$
allyl	71–73	56	−31.8° (*c* 1.53, MeOH)	91	+30.0° (*c* 1.85, MeOH)
2-butenyl	101.5–102.5	80	−39.6° (*c* 1.15, $CHCl_3$)[b]	75	+39.7° (*c* 1.08, $CHCl_3$)[c]
benzyl	180–184[d]	68	−111.7° (*c* 1.17, MeOH)		–
methyl	99–100	54	+23.5° (*c* 1.61, MeOH)[e]		–

[a] All phosphine oxides were assayed by ^{1}H NMR spectroscopy at 600 MHz for enantiomeric purity. In each case the other enantiomer was not able to be detected.[23] Unless indicated the optically pure phosphine oxides are new compounds. [b] Lit.[3] $[\alpha]^{20}_D$ −16.1° (*c* 1.05, $CHCl_3$). [c] Lit.[3] $[\alpha]^{20}_D$ +16.0° (*c* 0.79, $CHCl_3$). [d] Lit.[11] mp 187–189 °C, racemic form only. [e] Lit.[20] $[\alpha]^{20}_D$ 22.7 ° (MeOH).

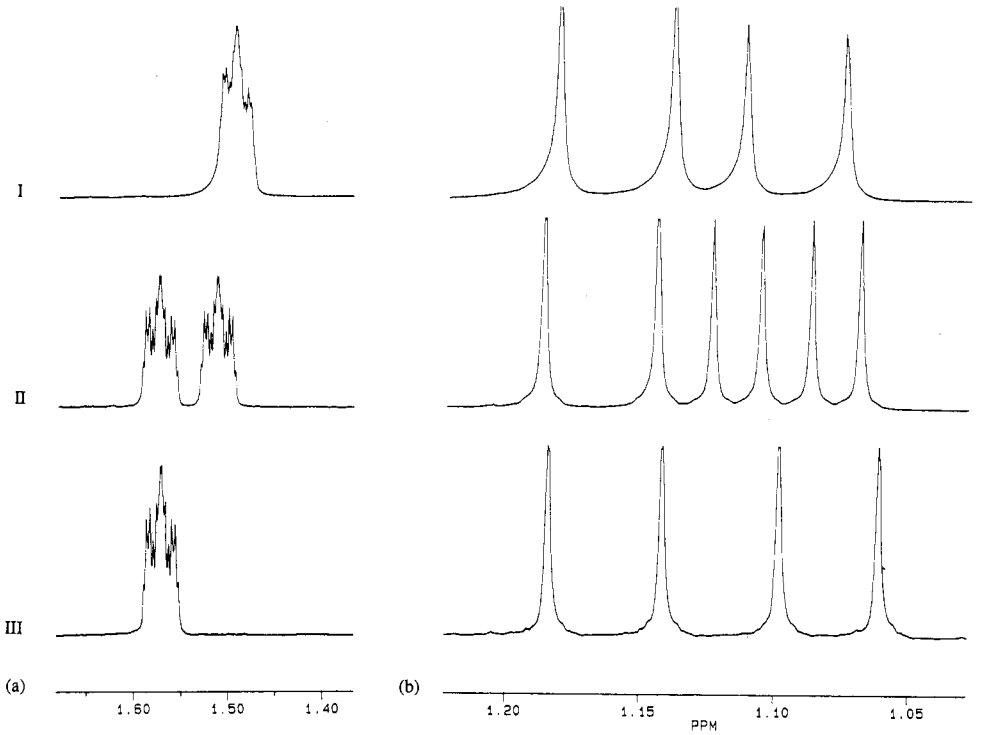

Figure 1. Expanded sections of 600-MHz ^{1}H NMR spectrum of I (R_p)-, II (R_p,S_p), and III (S_p)-(*E*)-but-2-enyl-*tert*-butylphenylphosphine oxides in the presence of 1 equiv of (R_p)-*tert*-butylphenylphosphinothioic acid in $CDCl_3$: (a) allylic methyl region; (b) *tert*-butyl region. Note that chemical shifts of NMR signals in racemic mixture do not necessarily coincide with respective signals from each of the enantiomers (*cf.* ref 20).

figuration to give the corresponding *tert*-butylphenylphosphine oxide, although in our hands use of the literature method[16,17] invariably gave partially or completely racemized products. However, *ultrasonic irradiation*[18] of a degassed mixture of (R_p)-(+)-*tert*-butylphenylphosphinothioic acid (1) (10 g) and Raney nickel[19] in ethanol during 3 h at 15–20 °C with mechanical stirring provided (S_p)-(−)-*tert*-butylphenylphosphine oxide (2) in 87% yield. ^{1}H NMR assay at 600 MHz (see below) indicated that the product had an enantiomeric purity of >99.6%. Similarly, the (S_p)-enantiomer gave the (R_p)-(+)-phosphine oxide (enantiomeric purity >99.6%, 79% yield). Due to susceptibility to oxidation, the secondary phosphine oxides were used directly in the next step without further purification.

The configurational stability of lithiated P-chiral secondary phosphine oxides has not previously been documented (*cf.* refs 16 and 17). However, we find that direct lithiation with butyllithium or LDA at low temperature gives a stable anion which undergoes alkylation with retention of configuration. Optimum conditions for the preparation of tertiary phosphine oxides (Table 1) involve addition of a mixture of the secondary phosphine oxide and 3 equiv of an alkyl or allylic halide in THF to a solution of LDA at −50 °C in THF and then warming to room temperature. Allyl bromide and (R_p)-(−)-*tert*-butylphenylphosphine oxide gave (R_p)-(−)-allyl-*tert*-butylphenylphos-

(12) The procedure involved treatment of the acid (40–50 g) in ether with (*S*)-(−)-α-methylbenzylamine in ether followed by collection of the crystalline, ether-insoluble (R_p)-(+)-acid–(*S*)-(−)-amine salt for 12 h. The pure salt had $[\alpha]^{20}_D$ = +30.3° (*c* 2.6, $CHCl_3$) [lit.[14] +24.3° (*c* 2.4, MeOH)]. If the NMR assay showed contamination from the diastereomeric salt, the salt was dissolved in chloroform and induced to recrystallize by addition of ether. The (+)-acid (20–25 g) and starting amine were recovered in the standard way. The crude (−)-acid was recovered from the ether-soluble (*S*)-(−)-acid–(*S*)-(−)-amine salt. If the NMR assay showed contamination, the salt was dissolved in ether and treated with (*R*)-(+)-α-methylbenzylamine to provide the ether-insoluble (*S*)-(−)-acid–(*R*)-(+)-amine salt [$[\alpha]^{20}_D$ = −30.35° (*c* 2.6, $CHCl_3$)] from which the pure (−)-acid was recovered; *cf.* refs 13 and 14. The resolution is very easily and quickly carried out.

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(18) We are most grateful to Professor A. Alexakis, Laboratoire de Chimie des Organo-Eléments, Université P. et M. Curie, Paris, for bringing to our attention the use of ultrasound to facilitate a Raney nickel hydrogenolysis reaction: Alexakis, A.; Lensen, N.; Mangeney, D. *Synlett* **1991**, 625.

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phine oxide (3) in an unoptimized yield of 56%. Similarly, the (*S*)-(+)-enantiomer was prepared. From (*E*)-1-bromobut-2-ene (3 equiv) and the *tert*-butylphenylphosphine oxides were obtained the corresponding (*E*)-butenylphosphine oxides together with small amounts (*ca.* 5%) of the (*Z*)-isomers. Recrystallization from pentane enabled the pure (*E*)-isomers to be obtained in 75–80% yields. ^{1}H NMR spectroscopic assay indicated >99.6% enantiomeric purity; that is, the other enantiomer was not able to be detected (Figure 1). The entire operation leading to **4** and its enantiomer can be performed routinely *without the use of chromatography* to purify the products. The facile preparation of the (R_p)-enantiomer **4** is especially useful in the context of the total synthesis of vitamin D and steroid derivatives.[2,3] Also prepared were the (R_p)-benzyl and methyl compounds; this represents a more convenient preparation of the latter compound than that previously described.[3,20]

Finally, we emphasize the convenience of the NMR assay method as originally developed by Harger which involves the use of each of the intermediate, resolved phosphinothioic acids forming diastereomeric complexes with the phosphine oxide products.[21,22] Sections of 600-MHz NMR spectra of the (R_p)-, (R_p,S_p)-, and (S_p)-butenylphosphine oxides admixed with equivalent amounts of the (R_p)-phosphinothioic acid are reproduced in Figure 1.[23]

In summary, a new and efficient method for the preparation of multigram quantities of chiral phosphine oxides of high optical purity has been developed. This approach to preparing chiral phosphine oxides will not only have important applications in the synthesis of vitamin D compounds and other natural products, but is equally well applicable to the preparation of chiral phosphines which are currently in great demand for the design of new catalysts.[24]

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Supplementary Material Available: Experimental procedures for preparation of phosphine oxides in Table 1, in addition to racemic compounds, and spectroscopic data (6 pages). This material is contained in libraries in microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(23) An assay of the sensitivity of the method at 400 MHz through addition of racemic phosphine oxide to the NMR solution of the (R_p)-butenylphosphine oxide indicated addition of a maximum of 0.4% of the other enantiomer was required for its detection.

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