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Stereoselective Preparation of Functionalized Tertiary *P*-Chiral Phosphine Oxides by Nucleophilic Addition of Lithiated *tert*-Butylphenylphosphine Oxide to Carbonyl Compounds.

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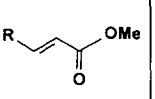
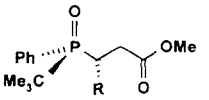
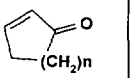
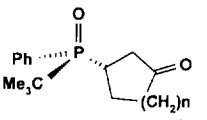
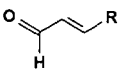
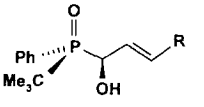
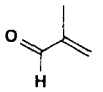
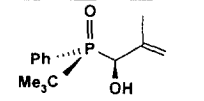
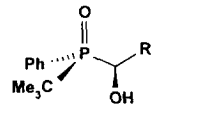
Abstract: Nucleophilic carbonyl and conjugate addition reactions of configurationally stable lithiated *P*-chiral *tert*-butylphenylphosphine oxide with aldehydes and α,β-unsaturated carbonyl compounds occur in good yields with diastereoselectivities ranging from 33 to ≥98 %.

Enantiomerically-pure phosphorus compounds are in great demand as chiral auxilliaries for asymmetric synthesis.[1] For many of these compounds, chirality resides not in phosphorus but rather in the ligands, which are bound to phosphorus by a heteroatom. In general, separation of the diastereomers produced by displacement reactions with chiral hetereoatom nucleophiles, corresponding to the ligands, at electrophilic phosphorus is required during preparation of the pure compounds.[2] The most common route to the most robust, and therefore the most desirable phosphorus-based chiral auxilliaries, namely *P*-chiral phosphine oxides and phosphines, involves single, twofold or threefold displacement of the ligands by organometallic nucleophiles.[2] For example, displacement of *O*-menthyl from phosphinates with organometallic nucleophiles with inversion of configuration at phosphorus is well known.[3] The method suffers from the exacting procedure required to obtain the diasteremerically pure menthylphosphinate precursor, and is not generally applicable. Stereochemically and electronically differentiated *O*-, *S*- or *N*-alkyl leaving groups underpin methods involving twofold displacement.[4] Whilst these methods offer more flexibility than that involving single displacement, the ligand precursors generally are not readily accessible,[5] and equilibration of the diastereomeric intermediates produced in the displacement steps is required in order to improve diastereoselectivity.

We have developed a route to *both* enantiomers of tertiary phosphine oxides wherein the enantiomers of a *secondary* phosphine oxide, *tert*-butylphenylphosphine oxide, are lithiated, and treated with alkyl halides to give the (R_P)- and (S_P)-phosphine oxides without loss of configuration.[6] The secondary phosphine oxides are readily obtained by resolution, and subsequent stereoselective desulfurisation of the enantiomers of, *tert*-butylphenylphosphinothioic acid. The method is significant in that it represents a potential *general* route to enantiomerically pure tertiary phosphine oxides. As noted above, displacement reactions on electrophilic tetracoordinate phosphorus is generally used to prepare optically active phosphine oxides,[1,2] and the alternative of using nucleophilic phosphinyl anions, as in the present case, for this purpose is rare.[7,8] Thus, we have initiated a programme whose aim is to provide enantiomerically-pure tertiary phosphine oxides via the enantiomerically-pure secondary phosphine oxides.

As entry into this area, we now report on results of an exploratory study of reactions of lithiated *tert*-butylphenylphosphine oxide with aldehydes, and acyclic and cyclic α,β-unsaturated carbonyl compounds as a route to functionalized tertiary phosphine oxides. Because of the exploratory nature of the work, we initially used racemic phosphine oxide. With benzaldehyde, and 1- and 2-naphthaldehydes, the (S_P)-enantiomer was used. The reactions proceed rapidly and cleanly, and are technically easy to perform. The *tert*-butylphenylphosphine oxide[6] (1.0 mmol) in THF (5 ml) at -78 °C under nitrogen was treated with LDA or BuLi (1.1 mmol). After 15 min., the solution was treated with a solution of the carbonyl compound (1.1

Table 1: Preparation of *P*-Chiral Phosphine Oxides from Carbonyl Compounds

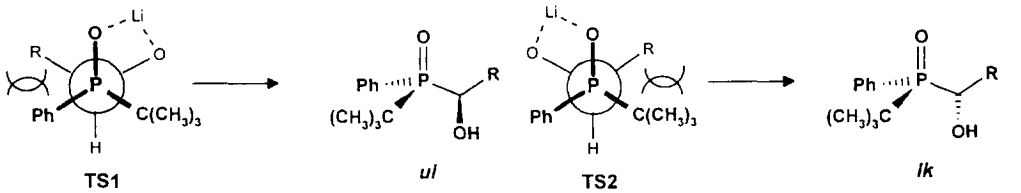
Entry	Electrophile	Products[a]	R	Yield[b] (%)	diastereomer ratio[c]	δ_P (ppm)[d]
1			H	63	-----	48.9
2			Ph	78	91:9[e]	47.6/48.9
3			Me	67	77:23[e]	50.4
4			n = 1	78	98:2[f]	47.7
5			n = 2	81	98:2[f]	47.5
6			Ph	77	80:20	45.0/45.2
7			Me	63	80:20	45.0/45.2
8			H	65	78:22	44.1/44.2
9				77.2	82:18	44.2/44.3
10			cyclohexyl	80	85:15	41.8/42.0
11			CMe_3	44	g	41.5
12			Ph[h]	77	98:2	44.8
13			Me	80	70:30	46.1/46.4
14			2-Pyridyl	76	80:20	42.1/42.4
15			Me_2CHCH_2	78	67:33	41.6/41.9
16			1-Naphthyl[i]	71	92:8	45.5/46.3
17			2-Naphthyl[j]	71	85:15	44.8/46.2
18			2-Thienyl	68	82:18	45.6/46.3
19			2-Furyl	76	90:10	45.4/46.4

[a]Relative configuration of major diastereoisomer is depicted in each case, except for entries 12, 16 and 17, where absolute configurations of the individual enantiomers are depicted; [b]yields were not optimized - total yield for two diastereoisomers is given; [c]determined by ^{1}H NMR (400 MHz) and ^{31}P NMR (161 MHz) spectroscopy, except where indicated otherwise; [d]in $CDCl_3$ relative to trimethyl phosphite; [e]determined by ^{1}H NMR (400 MHz); [f]determined by ^{1}H NMR (400 MHz) in admixture with 1.0 equiv. of (*R*)-*tert*-butylphenylphosphinothioic acid; [g]only one diastereomer was detectable; [h]$[\alpha]_D^{20}$ for major, purified isomer from lithiated (*S*)-*tert*-butylphenylphosphine oxide: +41.6° (c 1.14, $CHCl_3$); [i]$[\alpha]_D^{20}$ for major, purified isomer from lithiated (*S*)-*tert*-butylphenylphosphine oxide: +44.1° (c 1.05, $CHCl_3$); [j] $[\alpha]_D^{20}$ for major, purified isomer from from lithiated (*S*)-*tert*-butylphenylphosphine oxide: + 43.8° (c 1.11, $CHCl_3$).

mmol) in THF (2 ml), and the resulting mixture was stirred at -78 °C for 1-3 h. Standard work-up and flash chromatography afforded the corresponding adducts (Table).[9] If diastereomer ratios were not apparent from the ^1H or ^{31}P NMR spectra, then spectra were measured after admixture with (*R*)-*tert*-butylphenylphosphinothioic acid.[6,10] The reagent adds well in a conjugate sense with acrylate derivatives and cyclic enones (entries 1-5); stereoselectivity is essentially complete for the cyclic enones. Carbonyl addition reactions (entries 6-19) also proceed well. Stereoselectivities are good, and for pivalaldehyde, essentially complete. Notably, with the exception of acetaldehyde (entry 13, R = Me), *the mixtures of diastereomers are easily separated into the pure components by flash column chromatography.*

The relative configurations of the products from methyl cinnamate (entry 2, R = Ph) and cyclopentenone (entry 4, n = 1) are secured by X-ray crystallographic determination.[11] Whilst we have to probe the conjugate additions with enantiomerically pure secondary phosphine oxide, we note that for other conjugate addition reactions of the lithiated enantiomers, retention of configuration at phosphorus is observed, as described in the following communication. Whilst the relative configuration of the major diastereomer from racemic lithiated phosphine oxide and benzaldehyde was secured by X-ray crystallography,[11] this of course does not indicate the absolute configuration of the major product from the lithiated (S_P)-enantiomer (entry 12, R = Ph). However, that this is as depicted was established as follows. The product was converted by CS_2 and methyl iodide with NaH in THF into the *S*-methylthionocarbonate. Treatment of the latter with Bu_3SnH according to Barton deoxygenation provided (S_P)-benzyl-*tert*-butylphenylphosphine oxide (56% overall) $[\alpha]_D^{20}$ +108.2° (c 1.01, $CHCl_3$), identical with the product, $[\alpha]_D^{20}$ +110.5° (c 1.08, $CHCl_3$) from lithiated (S_P)-*tert*-butylphenylphosphine oxide and benzyl bromide.[6] We have unambiguously established that alkylation of the lithiated phosphine oxides proceeds with retention of configuration at phosphorus.[6] Thus, the carbonyl addition reactions also proceed with retention. Assignment of relative configuration to the major (*ul*) products from the other reactions was straightforward. The α-proton of the *ul* adduct in the ^1H NMR spectra was deshielded through the proximity of the phenyl ring relative to that of the *lk* adduct.[9]

The lithiated phosphine oxide is likely to react as a P(III) dialkyl phosphinite with an O-Li contact,[8] although definitive data on the structure of such reagents is not at hand. For the carbonyl addition reactions with aldehydes, it is noted that the reactions proceed under kinetic control; treatment of the minor *lk*-product from 2-pyridylaldehyde (entry 14) with *n*-BuLi at -78 °C under nitrogen during 2 h results in no detectable change. Thus, the ratios of the diastereomers can be rationalized through consideration of the relative energies of diastereomeric five-membered transition states TS1 and TS2 involving O-Li contacts, and which provide *ul* and *lk* products respectively, as depicted for the lithiated (*S*)-*tert*-butylphenylphosphine oxide. In TS1 and TS2, gauche interactions involving the R-group and phenyl, and the R-group and *tert*-butyl respectively, are apparent. TS1 is favoured overall based on the substantially smaller gauche interaction between R



and phenyl as compared to *tert*-butyl.[12] It is noteworthy that even for bulky R groups, as in 1- and 2-naphthyl, the predominance of the *ul* product is maintained, and thus we have a reaction whose stereoselectivity is tolerant of a wide range of substituents. Diastereoisomeric transition states involving reaction through the *re*- face of the lithiated (*S*)-phosphine oxide with the *Re*- and *Si*-faces respectively of the aldehyde experience gauche interactions between R on the aldehyde and both the phenyl and *tert*-butyl substituents, and are likely to be inaccessible.

For the conjugate addition reactions, operation of a closed transition state involving the carbonyl group of the cyclic enones is not feasible, and thus an open transition state involving the *Re*-face of the (*S*)-phosphine oxide and the *Si*-face of the enone may be assumed, with the P-OLi ensemble projecting over the ring and the *tert*-butyl projecting away.

To summarize, these reactions involving addition nucleophilic phosphorus to carbonyl electrophiles offer a simple route to a variety of functionalized tertiary phosphine oxides, and hence the corresponding phosphines. A number of the products will provide use as new ligands for asymmetric catalysis. The reactions of lithiated *tert*-butylphenylphosphine oxide with other electrophiles and the applications to preparation of doubly *P*-chiral diphosphine oxides as potential precursors to doubly P-chiral diphosphines is reported in the following communication.

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