Synthetic, Stereochemical and Mechanistic Studies on the Asymmetric Phosphonylation of Aldehydes *via* 2-Triorganosiloxy-1,3,2-oxazaphospholidines

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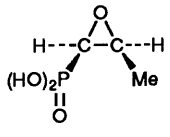
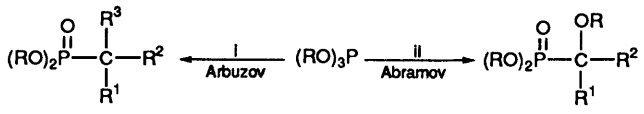
The chiral 2-triorganosiloxy-1,3,2-oxazaphospholidines {(1*R*,2*S*)-ephedrine}POSiR$_3$ (R$_3$ = Ph$_3$ **4**, Bu^{t}Me$_2$ **5**, Et$_3$ **6**) have been prepared *via* the reactions of {(1*R*,2*S*)-ephedrine}PCl **1** with R$_3$SiOH in the presence of NEt$_3$. Each of these organophosphorus(III) esters exists as an equilibrium mixture of two epimers with a diastereoselectivity (d.s.) that is dependent upon the nature of the silicon substituents; R$_3$ = Et$_3$ [86.0(2)%], Bu^{t}Me$_2$ [87.9(2)%], Ph$_3$ [94.1(2)%]. The epimers do not interconvert readily on the NMR time-scale but do so slowly on the chemical reactivity time-scale, attesting to the relatively high configurational stability at phosphorus. All three 2-triorganosiloxy-1,3,2-oxazaphospholidines undergo the Abramov reaction with benzaldehyde and pivalaldehyde at room temperature to afford the α-triorganosiloxy phosphonate esters {(1*R*,2*S*)-ephedrine}P(=O)CHR′(OSiR$_3$) (R′ = Ph **10–12**, Bu^t **13–15**) in high yields and with good stereoselectivities. In the best cases, with R′ = Ph, a single isomer accounts for 76% (R$_3$ = Ph$_3$), 67% (R$_3$ = Bu^{t}Me$_2$) and 73% (R$_3$ = Et$_3$) respectively of the product mixtures, whereas with R′ = Bu^t, the corresponding values are 61, 86 and 84% respectively. Evidence is presented to support the conclusion that the major product isomers of structures **10–15** result from reaction of the aldehydes with the major epimers of compounds **4–6** with *retention* of configuration at phosphorus. The absolute configurations at the phosphorus and α-carbon atoms for the major isomer of {(1*R*,2*S*)-ephedrine}P(=O)CHBu^t(OSiPh$_3$) have been assigned as (S_P,S_C) by solution NOE experiments, which support a mechanism involving retention of configuration. The relative rates and stereoselectivities of the reactions of compounds **4–6** with carbonyls are sensitive to the nature of the substituents on both the silicon atom and the aldehyde. Reactions of compounds **4–6** with ketones are much slower than those with the aldehydes above, as expected on both electronic and steric grounds.

Compounds containing the phosphono group [(RO)$_2$P(=O)] have widespread applications in biochemistry and medicine.[1] In particular, phsophonate esters [(RO)$_2$P(=O)R′] which contain functionality in the R′ residue are becoming increasingly important as mimetics for biologically important molecules such as readily hydrolysable phosphate esters and amino acids[2] and as therapeutic chemicals[1] with potent antiviral, antibacterial and antiparasitic properties: for example, naturally occurring phosphonomycin is a wide-spectrum antibiotic.[3]



Furthermore, in common with many biologically important compounds, phosphonomycin contains stereogenic centres and the physiologically desirable properties that it displays are influenced strongly by the absolute configuration of the molecule. Indeed, naturally occurring phosphonomycin exists exclusively as the (1*R*,2*S*) isomer.[4] Consequently, it is desirable to have synthetic routes to functionalised phosphonate esters which permit a high level of stereochemical control. Of the available methods for the synthesis of phosphonate esters, the Arbuzov[5] and Abramov[6] reactions are among the most versatile (Scheme 1), the latter particularly so since a range of unsaturated organic substrates (such as aldehydes, ketones, imines, azides, *etc.*) may be phosphonylated by tertiary and/or secondary phosphites[7] and the functionality can be generated along with the carbon–phosphorus bond, thus avoiding the need to protect and deprotect moieties which may interfere with the reaction.

Moreover, since asymmetric centres can be created at the

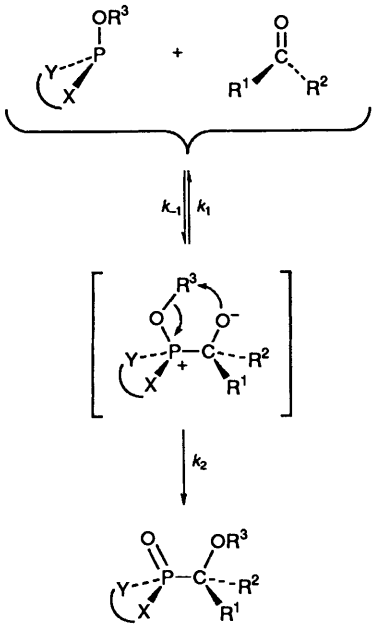


Scheme 1 Synthetic routes to phosphonate esters. *Reagents:* i, R^{1}R^{2}R^{3}CX (−RX); ii, R^{1}COR^2.

α-carbon atoms of phosphonate esters during the Abramov reaction shown in Scheme 1, it should prove possible to control the stereochemistry at this site by the use of chiral tertiary phosphites. Here we wish to describe some of our studies on the development of an asymmetric variant of Abramov phosphonylation using new chiral organophosphorus(III) reagents: part of this work has been communicated briefly.[8]

Trialkyl phosphites undergo the Abramov reaction only under forcing conditions, but the replacement of one alkoxy residue on phosphorus with a trialkylsiloxy group increases greatly the reactivity of the resulting silyl phosphite ester [(RO)$_2$POSiR′$_3$] towards unsaturated organic substrates.[9] Two factors are believed to be important in this increase in reactivity; (a) the siloxy group is more electron releasing than analogous alkoxy groups, thus resulting in a higher energy phosphorus(III) lone-pair occupying an orbital of increased p-character and consequently a more nucleophilic phosphorus centre,[9] (b) the trialkylsilyl group is transferred more readily in the transition state of the Abramov reaction, the mechanism of which has been proposed to be as shown in Scheme 2.[6]

We have recently initiated a programme of research to develop new, novel main-group and transition metal (1,*n*)-bifunctional reagents (*n* > 1) for use in both stoichiometric and catalytic organic/organometallic synthesis. With regard to asymmetric phosphonylation, we recognise that the silylated phosphites (RO)$_2$POSiR′$_3$ may be regarded as (1^N,3^E)-bifunc-



Scheme 2 Proposed mechanism for the Abramov reaction. R^1,R^2 = H, alkyl; R^3 = alkyl, SiR_3.

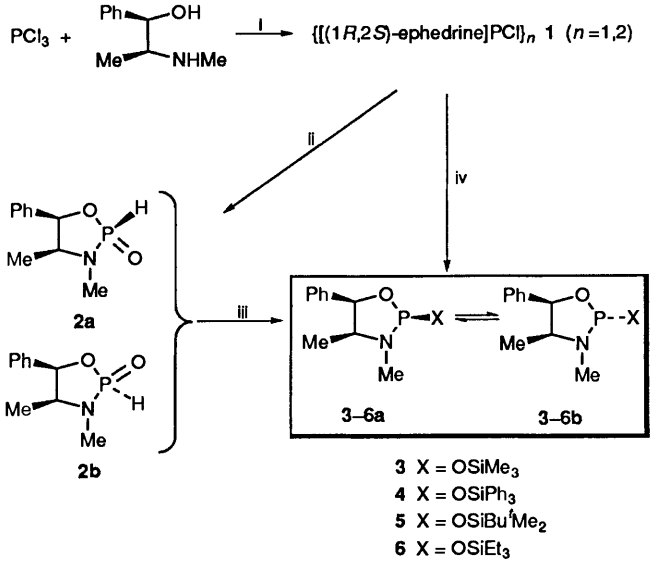
tional reagents containing the [P–O–Si] unit in which the nucleophilic *N* (phosphorus) and electrophilic *E* (silicon) termini are separated by a single, electronically conducting spacer atom (oxygen). Our strategy has therefore been to synthesize silyl phosphite esters which contain homochiral auxiliaries coordinated to either the phosphorus or silicon terminus. It was considered that chiral-recognition properties may be increased if the auxiliaries were to be coordinated to the nucleophilic terminus rather than to the electrophilic atom since the developing stereogenic centres in the Abramov reaction are more intimately connected with phosphorus than with silicon (Scheme 2). Moreover, we envisaged that chelating, dianionic ligands based on oxygen and/or nitrogen donor atoms (XY in Scheme 2) would form the most suitable molecular frameworks for the auxiliaries. Here we describe our studies with one such auxiliary, (1*R*,2*S*)-ephedrine.

Results and Discussion

Synthesis of the Chiral 2-*Chloro*-1,3,2-*oxazaphospholidine,* {(1R,2S)-*Ephedrine*}*PCl.*—The auxiliary (1*R*,2*S*)-ephedrine is readily introduced into the phosphorus atom coordination sphere to afford {(1*R*,2*S*)-ephedrine}PCl **1** in 80% isolated yield (Scheme 3).

Inch and co-workers have reported the isolation of compound **1** in an isomerically pure form, as a distillable liquid, from a reaction similar to that used here and they assigned the structure as being monomeric and having the geometry **b** (Fig. 1) in which the chlorine atom is on the opposite side of the phospholidine ring to the C–Ph and C–Me substituents (*trans* geometry).[10] This same configuration is favoured also by Brown and co-workers, who isolated compound **1** as a low melting solid after distillation, again as a single isomer.[11]

In our hands, compound **1** was also isolated as a low melting, white crystalline solid which we also observed to be a single isomer; both the room-temperature and low (213 K)-temperature ^1H NMR spectra ($CDCl_3$) revealed resonances due only to a single species. In our initial communication, we reported compound **1** as being monomeric; however, we found that although the mass spectrum of compound **1** (in both electron-impact and chemical-ionisation modes) did not reveal any peaks above that of the monomeric molecular ion at *m*/*z*



Scheme 3 *Reagents and conditions:* i, *N*-methylmorpholine (3 mol equiv.), toluene, 16 h, room temp. 80% yield; ii, water (1 mol equiv.), NEt_3 (2 mol equiv.), toluene, 1 h, room temp., 74% yield, d.s. 56%; iii, Me_3SiCl (1 mol equiv.), NEt_3 (2 mol equiv.), toluene, 5 h, room temp.; iv, R_3SiOH (1 mol equiv.), NEt_3 (2 mol equiv.), toluene, 16 h, room temp. **4** (R_3 = Ph_3, 91% yield); **5** (R_3 = Bu^tMe_2, 78% yield); **6** (R_3 = Et_3, 82% yield). No specific conformation of the oxazaphospholidine ring is implied in the structures of compounds **1**–**6**.

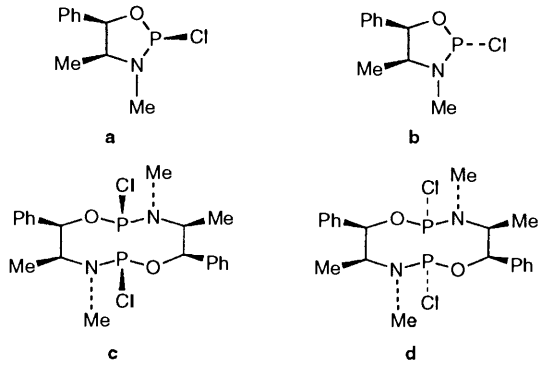


Fig. 1 Epimeric forms of monomeric (**a**, **b**) and dimeric (**c**, **d**) compound **1**

229, solution relative molecular mass measurements suggested a *dimeric* formulation for our isolated product (found: 454 and 467; calc. for dimeric **1**: 458). Furthermore, a dimeric structure is consistent with the observation that reaction of compound **1** with sulfur in toluene solvent proceeds readily only at 80 °C to afford [{(1*R*,2*S*)-ephedrine}P(=S)Cl]$_n$ (*n* unknown) as a mixture of two isomers in the ratio 1.5:1 (by ^{31}P NMR spectroscopy): the analogous dimeric compound 3-methyl-2-phenyl-1,3,2-oxazaphospholidine[12] also reacts with sulfur only in refluxing benzene, whereas the monomeric isomer of the same phospholidine reacts instantaneously at room temperature.[12] In the absence of X-ray crystallographic evidence we are not able unambiguously to assign a structure to compound **1**, but two plausible alternatives are shown in Fig. 1 (**c** and **d**), based on a similar proposed geometry for 3-methyl-2-phenyl-1,3,2-oxazaphospholidine (see Experimental section).

In contrast to other chlorophospholidine species such as (*rac*-*O*,*O*-binaphtholato)PCl[13] and (*O*,*O*-dimethyl-L-tartrato)-PCl,[14] compound **1** remains unchanged after exposure to moist air in $CDCl_3$ solution for over 48 h at room temperature.

Although when *N*-methylmorpholine is used in the synthesis of compound **1** only a single product is obtained, we have observed that, with triethylamine as base, compound **1** is isolated as a pale yellow oil which appears to be a mixture of

two interconverting compounds in the ratio of 91:9, each of which can be observed clearly by ^{1}H NMR spectroscopy only at low temperature (below 221 K in C_7D_8). The major species (91%) appears to be identical (by NMR spectroscopy) with that obtained using *N*-methylmorpholine (dimeric **1**) whereas the minor species may be either a monomeric form of compound **1** (either **a** or **b** in Fig. 1) or the epimer of dimeric **1**.*

Synthesis and Configuration of 2-*Triorganosiloxy*-1,3,2-*oxazaphospholidines* {(1R,2S)-*Ephedrine*}*POSiR*$_3$ (*R*$_3$ = *Me*$_3$, *Ph*$_3$, *Bu*^{t}*Me*$_2$, *Et*$_3$).—*Synthesis.* Two synthetic routes from chloride **1** to the 2-triorganosiloxy-1,3,2-oxazaphospholidines {(1*R*,2*S*)-ephedrine}POSiR$_3$ have been investigated (Scheme 3). Hydrolysis of chloride **1** afforded {(1*R*,2*S*)-ephedrine}-P(=O)H **2** as a mixture of epimers in the percentage ratio 56:44 in favour of **2a** based on the same NMR criteria as those used to assign the configurations in [(1*R*,2*S*)-ephedrine}P(=O)Cl.[11,15] The use of an excess of water results in displacement of the ephedrine auxiliary and formation of $(HO)_2P(=O)H$ (observed by ^{31}P NMR spectroscopy). Compound **2** is stable to epimerisation at phosphorus up to at least 100 °C (by ^{1}H NMR spectroscopy in C_7D_8). Subsequent silylation of compound **2** with Me_3SiCl afforded {(1*R*,2*S*)-ephedrine}$POSiMe_3$ **3** but the reaction is not clean, unlike silylation reactions of other secondary phosphites.[16] In addition to ^{31}P NMR resonances assignable to the two possible epimers at δ 128.2 and δ 130.1 (*vide infra*), several resonances are observed in the region δ 25 to −14, suggestive of four-coordinate phosphorus species, possibly resulting from electrophilic attack on the ephedrine ring.[17] However, we did not observe the formation of {(1*R*,2*S*)-ephedrine}PCl **1**, unlike the analogous reaction of (*rac*-*O*,*O*-binaphtholato)P(=O)H with Me_3SiCl where (*rac*-*O*,*O*-binaphtholato)PCl was a major product.[13]

However, species {(1*R*,2*S*)-ephedrine}POSiR$_3$ (R$_3$ = Ph_3 **4**, Bu^tMe_2 **5**, Et_3 **6**) were isolated readily and in high yields upon reaction of chloride **1** with an equimolar quantity of R_3SiOH in the presence of a base such as NEt_3 (Scheme 3). Mass spectral and relative molecular mass studies on products **4**–**6** indicated these compounds to be *monomeric*: specifically, the highest mass peaks are the monomeric molecular ions, at *m*/*z* 469, 325 and 325 respectively, and solution relative molecular mass measurements on products **4** and **5** gave M = 477 (calc. for monomer, 469) and 317 (calc. for monomer, 325) respectively.

All three silyl phosphites were isolated consistently as mixtures of two compounds which, on the basis of the similarities of their NMR parameters, may be assigned to the two possible epimers, *syn* (**a**)-form and *anti*-(**b**)-form (Scheme 3). The observed diastereoselectivities (d.s.), 94.1(2)% (**4**), 87.9(2)% (**5**) and 86.0(2)% (**6**), indicate that the composition of the mixture is influenced by the nature of the substituents on silicon. Our observations further suggest that these diastereoselectivities are the result of *thermodynamic* control since the epimers of compound **4** have been shown to interconvert at room temperature. Thus, repeated flash chromatography of compound **4** on an alumina column (Brockman Grade I) afforded an isomerically pure sample (albeit in low yield) which, upon subsequent storage at room temperature under nitrogen, reverted back to the initial epimeric mixture within 2 days. Similar chromatographic treatment of compounds **5** and **6** did not result in significant improvements to their diastereoselectivities but we suspect that both will engage in similar, slow epimerisations. Furthermore, as found for other three-coordinate organophosphorus compounds, inversion at phosphorus is slow on the NMR time-scale, there being no evidence for interconversion of the epimers for **4**–**6** up to at least 373 K (by ^{1}H and ^{31}P NMR spectroscopy in C_7D_8). Since neither coalescence nor line-broadening was observed up to 373 K, a lower limit of ~20 kcal mol^{-1}† for the activation barrier to epimerisation may be gauged from the NMR spectra of compounds **4**–**6**. The actual barriers are presumably significantly higher.

Consequently, the observed room temperature d.s.-values for compounds **4**–**6** can be translated to equilibrium constants of 15.9, 7.3 and 6.1, which correspond to ΔG-values of 1.7, 1.2 and 1.1 kcal mol^{-1} respectively. The trends in these parameters may reflect the relative steric requirements of the R_3SiO groups. The selectivities decrease upon heating, thus effectively precluding the isolation of either isomer **a** or **b** in pure form by manipulation of the equilibrium constant. For example, heating of compound **4** at 80 °C for over 18 h reduces the d.s. to 83%.

In an effort to determine whether a bimolecular epimerisation process is feasible for compounds **4**–**6**, we have performed a cross-over experiment by mixing equimolar quantities of {(1*R*,2*S*)-ephedrine}$POSiPh_3$ and {diamine}$POSiEt_3$[18] (diamine is *N*,*N*′-dimethylethylenediamine) in $CDCl_3$ at room temperature. After 48 h, ^{31}P NMR spectroscopy did not reveal the expected cross-over products, {(1*R*,2*S*)-ephedrine}$POSiEt_3$ and {diamine}$POSiPh_3$, suggesting that an intramolecular epimerisation mechanism may be more likely.

Compounds **4**–**6** are sensitive to hydrolysis, each decomposing to give several species which display ^{31}P NMR resonances in the range δ +4 to −14. In each case, a peak at δ ~3.6 is observed and may be assigned to $(HO)_2P(=O)H$ [*cf.* δ_P 4 for $(HO)_2P(=O)H$ in tetrahydrofuran (THF)]. The qualitative order of hydrolytic sensitivity is **4** > **6** > **5**, the same order as found in the (*O*,*O*-dimethyltartrato)POSiR$_3$ system,[14] where increased stability appears to reflect (i) a lowering of Lewis acidity in the silicon atom as a result of the substituents becoming more electron releasing and (ii) steric congestion around the silicon atom, thereby hindering approach of water molecules. These observations are consistent with hydrolysis *via* an S_N2-Si mechanism.[16]

We reasoned that since replacement of an alkoxy group on phosphorus with a siloxy group increases the reactivity of organophosphorus(III) esters in the Abramov reaction,[9] so further enhancement of reactivity should result from replacement of the silicon atom with a more Lewis acidic atom such as tin. Specifically, we investigated the reaction of chloride **1** with Ph_3SnOH in the hope of preparing {(1*R*,2*S*)-ephedrine}-$POSnPh_3$. However, the major product was observed to be {(1*R*,2*S*)-ephedrine}P(=O)H **2** (a mixture of diastereoisomers by ^{31}P NMR spectroscopy), presumably formed according to the reaction in eqn. (1). Indeed, examination of the crude product mixture by mass spectrometry showed Ph_3SnCl to be present.

* We have not investigated this dynamic process in great detail but pathways for interconverting isomers of the chloride **1** may include: (a) the presence of small quantities of $NHEt_3Cl$ produced as a side-product in the synthesis of chloride **1** (Scheme 3), (b) a bimolecular exchange of chloride between two molecules of compound **1** or (c) trace acidic impurities. Option (a) is possible since although treatment of pure chloride **1** with NEt_4Br in chloroform does not result in {(*O*,*N*-ephedrine)PBr} (^{31}P NMR spectroscopy), the reaction between {(*O*,*N*-ephedrine)PBr} (δ_P 190.7) and $NHEt_3Cl$ under the same conditions results in complete conversion into chloride **1** after 2 h at room temperature, suggesting that halide ion exchange under these conditions is possible. Option (b) is also a possibility since the cross-over experiment involving an equimolar mixture of {(*O*,*N*-ephedrine)PCl} and {(*O*,*O*-dimethyltartrate)PBr}[14] results in the observation of signals due to {(*O*,*N*-ephedrine)PBr} and {(*O*,*O*-dimethyltartrate)PCl} (by ^{31}P NMR spectroscopy), thus providing a precedent for bimolecular exchange. Option (c) is also a possibility but we have not investigated this effect in detail.

† 1 cal = 4.184 J.

{ephedrine}PCl + Ph_3SnOH ⟶
{ephedrine}P(=O)H + Ph_3SnCl (1)

The presence of NEt_3 in the reaction mixture did not affect the product composition significantly. Careful examination of the crude reaction mixture by ^{31}P NMR spectroscopy did, however, reveal a low-intensity resonance at δ 129.3 which may be assignable to the desired compound {(1*R*,2*S*)-ephedrine}$POSnPh_3$ (*cf.* {(1*R*,2*S*)-ephedrine}$PCSiPh_3$, δ 130.1).

Configurations. Although it is clear that two stereoisomers are present in solution for compounds **4–6**, *syn*-S_P (**a**) and *anti*-R_P (**b**) as shown in Scheme 3, the spectroscopic data alone do not permit unambiguous assignments of the configuration at phosphorus. Several groups have reported NMR data on oxazaphospholidine systems of the forms shown in Fig. 2.[12,17,19,20]

Robert and Weichmann have suggested that the isomer which has the X group on the same side of the oxazaphospholidine ring to the 4-H and 5-H groups (*anti* form **b**) will have a larger $^3J_{PH}$ coupling between phosphorus and 5-H than will the alternative *syn* epimer (**a**). Juge[19] and Richter[20] report that the favoured isomers of compounds analogous to those in Fig. 2, where X = Ph, are the *anti* epimers and possess $^3J_{PH}$-values in the range 2–4 Hz. We found that the *minor* isomers of compounds **4–6** have $^3J_{PH}$-values between 2.6–3.0 Hz whereas the *major* isomers have couplings too small to measure with our facilities. On the basis of this criterion alone we might assign the minor isomers of compounds **4–6** as being *anti* and the major isomers as being *syn*.

However, the results of semi-empirical calculations on compounds **4–6** at the AM1 level suggest that the more thermodynamically favoured epimer is consistently the *anti* form (**b**) by 0.6–1.7 kcal mol^{-1}, in good agreement with the experimentally determined values (*vide supra*). Whilst it may not be prudent to put much weight on the absolute energies, the qualitative trend is the same for each phosphite ester. Molecular models of *syn* (**a**) and *anti* (**b**) forms of compound **4** are shown in Fig. 3.

In an effort to shed further light on this assignment problem we have performed derivatisation experiments on epimeric mixtures of compounds **4** and **5**. Compound **4** can be oxidised cleanly with (i) sulfur and (ii) Bu^{t}OOH to afford {(1*R*,2*S*)-ephedrine}P(=S)$OSiPh_3$ **7** and {(1*R*,2*S*)-ephedrine}P(=O)-$OSiPh_3$ **8** respectively. Each of these crude products was obtained as a mixture of the two possible epimers with d.s.-values of 90 and 66% respectively (Scheme 4). We envisage that both reactions will proceed under *kinetic control* since they appear to be significantly more rapid than the epimerisation of substrates **4** or **5** and also with *retention* of configuration at phosphorus.[21] The identification of the major epimers of products **7** and **8** should then shed some light on the configurations of the silyl phosphite precursors.

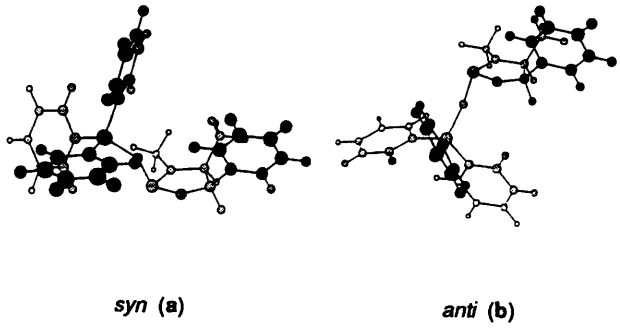


Fig. 3 Molecular models of the *syn* (**a**) and *anti* (**b**) forms of compound **4**. All structures were fully optimised using the BFGS gradient-minimisation routine with energies computed using the AM1 Hamiltonian. Calculations were performed using MOPAC version 6.0 which has been optimised to run in parallel mode on a Silicon Graphics PowerSeries four-processor computer.

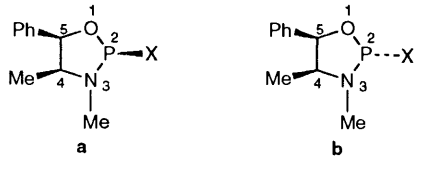
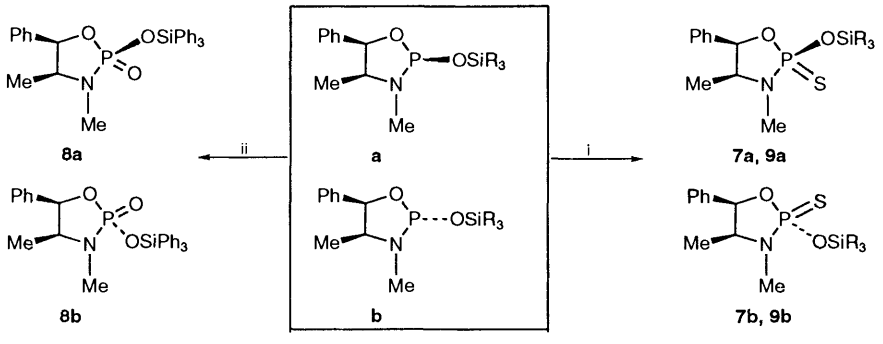


Fig. 2 Possible epimers of monomeric {(1*R*,2*S*)-ephedrine}PX. X = Me, Ph, Bu^t.

In the absence of direct X-ray crystallographic evidence, two NMR-based criteria have been used frequently to differentiate R_P and S_P epimers in related oxazaphospholidine systems.[15,21] One is based on the relative chemical-shift positions of the 5-H hydrogens, which are found consistently to be of higher frequency in that isomer where the [P=X] (X = O, S) moiety is on the same side of the phospholidine ring as is the 5-H hydrogen.[15] The second criterion is based on relative values of the $^3J_{PH}$ coupling to the 5-H hydrogen, which is reported to be larger and in the approximate range 3–7 Hz for the epimer in which the [P=X] (X = O, S) moiety is on the opposite side of the phospholidine ring to the 5-H hydrogen, whereas the same coupling constant for the alternative isomer is often too small to be observed.[21] In the case of compound **7**, the chemical-shift criterion suggests that the major epimer has the configuration S_P (**7b**). However, the observed $^3J_{PH}$-values for the major (4.0 Hz) and minor (3.8 Hz) isomers are both in the region expected (~3–6.5 Hz)[21] for *syn* configurations **b**. Normally, configurations of type **a** have $^3J_{PH}$ < 1 Hz.[21] In the case of compound **8**, the two epimers are produced with a d.s. of only 66%, but again the major isomer has the lower frequency 5-H resonance and a larger $^3J_{PH}$ coupling to 5-H (5.6 Hz *vs.* 2.0 Hz in the minor isomer); both pieces of evidence are more consistent with the



Scheme 4 Reactions of phospholidines **4** and **5** with (i) sulfur to afford compounds **7** (R_3 = Ph_3) and **9** (R_3 = Bu^tMe_2) and (ii) Bu^{t}OOH to afford compound **8** (R_3 = Ph_3)

major isomer being assigned configuration **8b**. Compound **5** also reacts readily with sulfur at room temperature to afford a mixture of two products formulated as the epimers of [(1*R*,2*S*)-ephedrine}P(=S)OSiBu^{t}Me$_2$ **9** (d.s. 86%). On the basis of both chemical-shift and coupling-constant criteria the major isomer appears to be the same as that for compound **7**, with a lower frequency 5-H resonance and a slightly larger $^3J_{PH}$ coupling to 5-H than the minor isomer (δ 5.47 *vs.* 5.59; *J* 5.1 *vs.* 3.3 Hz respectively). The $^3J_{PH}$ coupling in related systems has been correlated with the P–O–C(5)–H dihedral angle (θ) where it has been found that the small $^3J_{PH}$-values in compounds having configuration **a** correlate to θ-values between 87–96° (from single-crystal X-ray work) whereas the larger couplings in the **b** configurations correlate to θ-values between 136–139°, in agreement with a Karplus-type relationship.[21] However, AM1 calculations on both the **a** and **b** forms of compounds **7** and **9** suggest that the dihedral angles θ differ by less than 1°, which is not inconsistent with the very similar $^3J_{PH}$ values observed for the two epimers.

Consequently, the derivatisation experiments suggest that the major isomers of compounds **7–9** are of the **b** form (Scheme 4) which presumably implies that the major epimers of compounds **4** and **5** have the *anti-*R_P forms (**b** in Scheme 4). The observation of somewhat lower d.s.-values in the products **7–9** compared with those of the starting materials **4** and **5** may suggest that the minor epimers of substrates **4** and **5** are slightly more reactive towards both sulfur and Bu^{t}OOH than are the major epimers although we have not investigated this effect further.

Whilst we are aware that the evidence presented above is not conclusive we feel that support for the *anti-*R_P (**b**) form is somewhat stronger than for the epimeric *syn-*S_P (**a**) form and in the absence of more direct experimental evidence such as X-ray diffraction we prefer to assign the configurations of the major isomers of compounds **4–6** as R_P. We note that this assignment is the reverse of that given in our preliminary communication[8] which was based solely on the relative magnitudes of $^3J_{PH}$-values.

Reactions of {(1R,2S)-*Ephedrine*}*POSiR*$_3$ (*R*$_3$ = *Ph*$_3$ **4**, *Bu*^{t}*Me*$_2$ **5**, *Et*$_3$ **6**) *with Aldehydes and Ketones.*—(a) *Reactions with aldehydes and ketones.* The silylated organophosphorus(III) esters **4–6** undergo the Abramov reaction with benzaldehyde and pivalaldehyde (Bu^{t}CHO), as illustrated in Scheme 2, smoothly over the course of several hours at room temperature to afford the α-siloxy phosphonate esters {(1*R*,2*S*)-ephedrine}-P(=O)CHR′(OSiR$_3$) (R′ = Ph, R$_3$ = Ph$_3$ **10**, Bu^{t}Me$_2$ **11**, Et$_3$ **12**; R′ = Bu^t, R$_3$ = Ph$_3$ **13**, Bu^{t}Me$_2$ **14**, Et$_3$ **15**). However, when the reactions of compounds **4–6** with benzaldehyde were followed by $^{31}P\{^1H\}$ NMR spectroscopy it was observed that several species were produced in the crude product mixture, each of which gave rise to a single ^{31}P resonance in the δ 40–30 region of the spectra, consistent with four-coordinate phosphorus species as required for products **10–12**.[22] Although multiple products are expected since each of the products **10–15** has four possible diastereoisomers (Fig. 4), we find that in each case one isomer of {(1*R*,2*S*)-ephedrine}P(=O)CHR′(OSiR$_3$) predominates in the crude mixture (Table 1). A single recrystallisation of these crude mixtures afforded compounds **10** and **11** as white, crystalline solids in high yield (88 and 84% respectively), which have been characterised by standard techniques (see Experimental section). Compounds **12**, **14** and **15** could be obtained only as oily solids. Compound **11** could be obtained in up to 95% isomeric purity but in a lower overall yield. The major isomer of compound **13** could be isolated in essentially 100% isomeric purity by selective crystallisation from toluene, but in only low (26%) yield.

Mass spectrometry located the molecular ions for products

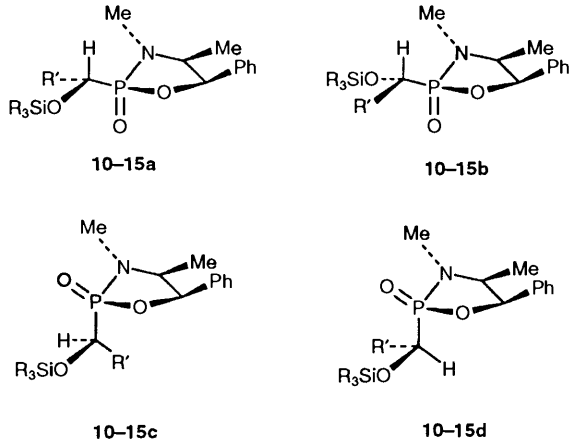
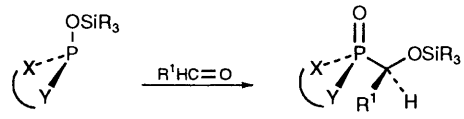


Fig. 4 Configurational isomers for α-siloxyphosphonate esters **10–15** (R′ = Ph, **10–12**; Bu^t, **13–15**; R$_3$ = Ph$_3$, **10** and **13**; Bu^{t}Me$_2$, **11** and **14**; Et$_3$, **12** and **15**)

Table 1 Percentage contribution of the major isomers to the crude product mixtures and recrystallised yields for α-siloxyphosphonate esters **10–15**



R^1 = Ph,Bu^t; X-Y = (1*R*,2*S*)-ephedrine

Compound	Crude contribution (%)	Recrystallised yield (%)
10	76	88
11	67	84
12	73	77
13	61	26[a]
14	86	81
15	84	

[a] This compound was isolated in essentially 100% isomeric purity (see text).

10–15 as the highest mass peaks, and relative molecular mass measurements on compounds **10** (found: M, 576; required: 506) and **13** (found: M, 556; required: 544) confirmed that these compounds, and presumably the other phosphonate esters, are monomeric in solution.

The α-siloxyphosphonate esters **10–15** are more stable to air and moisture in solution than are the phospholidines **4–6**. Thus, $CDCl_3$ solutions of compounds **10**, **13** and **14** exposed to the air are stable for up to 4 days at room temperature, as evidenced by ^{31}P NMR spectroscopy.

Treatment of compound **6** with either benzophenone or acetophenone (1 mol equiv.) at room temperature for 24 h did not result in any reaction, indicating the ketones to be less susceptible to Abramov phosphonylation than were the aldehydes, a result noted previously for achiral silyl phosphites.[6] Heating of the same mixtures to 80 °C for 24 h did result in reaction but only to the extent of ~ 10% conversion of substrate **6**, and several products were observed by ^{31}P NMR spectroscopy in the region expected of phosphonate esters, none of which was isolated.

(b) *Assignment of configuration.* Since compounds **10–15** contain asymmetric centres at both the phosphorus and α-carbon atoms in addition to the chiral auxiliary, there are four possible diastereoisomers for each phosphonate ester as shown in Fig. 4. The oxazaphospholidine rings are depicted with a C_4-envelope conformation in which the C-4 atom is out of the plane

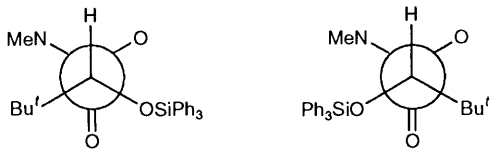


Fig. 5 Newman projections down the C_α–P bond of the probable conformations of compound **13**

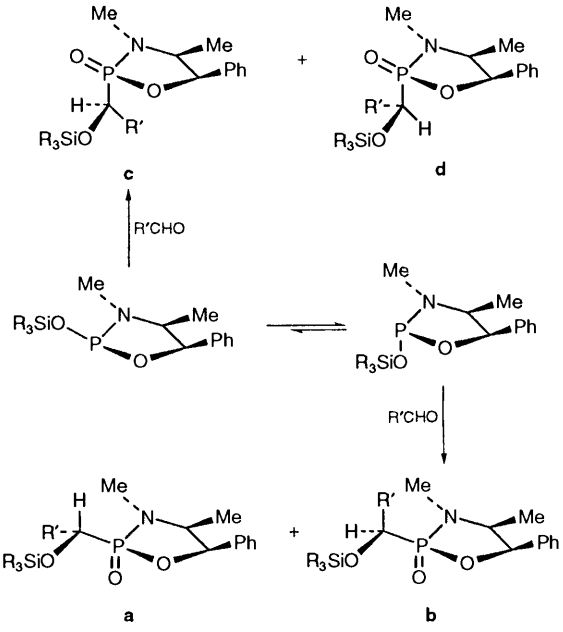
of the other oxazaphospholidine ring atoms, similar to the conformations found in several phosphonate and thiophosphonate esters by X-ray diffraction:[21] however, we do not wish to imply that these specific conformations are necessarily the most stable ones in our solution systems.

The failure to resolve $^3J_{PH}$ coupling to the 5-H hydrogens in the major isomers of compounds **10–15** suggests that the P=O function is *anti* with respect to the ephedrine phenyl and methyl substituents, which implies either of the structures **a** or **b** in Fig. 4 and sets the phosphorus atom configuration as S_P.[21]

Since the major isomer of compound **13** crystallises from solution in pure form, we have been able to perform nuclear Overhauser effect (NOE) studies on this compound. The important observation of a 2.3% positive NOE from the [*Me*CHNMe] methyl to the [PC*H*Bu^t(OSiPh$_3$)] hydrogen suggests strongly that this isomer is of either form **a** or form **b** since forms **c** and **d** would not be expected to show any NOE effects between these sets of hydrogen atoms. Moreover, the failure to observe any NOE between the [*Me*CHNMe] and [PCHBu^t(OSiPh$_3$)] resonances suggests that the P–C_α bond is configurationally locked about phosphorus; the two most reasonable possibilities are illustrated in the Newman projection down the C_α–P bond (Fig. 5). The observation of small, positive NOE effects between [N*Me*] and [PC*H*Bu^t(OSiPh$_3$)] (0.3%) and between [PCH*Bu*^{t}(OSiPh$_3$)] and [N*Me*] (1.3%) are more consistent with configuration **a** than with **b** in Figs. 4 and 5. Consequently, on the basis of the available data, we believe that the major isomer of compound **13** has configuration **a** (S_P, S_C). The similar, small $^3J_{PH}$ couplings for all of the products **10–15** suggest that they all possess the *anti* configuration,[21] but we have not performed NOE studies or X-ray analyses to delineate the absolute configuration at C_α of any product other than compound **13**.

(c) *Mechanism of reaction.* The mechanism of the Abramov reaction has been investigated previously[6] and the main features are summarised in Scheme 2. Particularly important is the demonstration that transfer of the triorganosilyl group (R^3) to the carbonyl oxygen is *intramolecular*, which results in retention of relative configuration at phosphorus.[6] Moreover, it appears that the Abramov reaction is *kinetically* controlled under the conditions used in this study since the major isomer of phosphonate ester **13** is stable to epimerisation in $CDCl_3$ solution over at least 3 weeks at room temperature and the stability of phosphonate esters is well documented.[21,*] Consequently, since the major isomers of the α-siloxyphosphonates possess the *anti*-S_P geometry (**a** or **b** in Fig. 4), then they must presumably result from preferential reaction of the aldehyde with the *anti*-R_P {(1*R*,2*S*)-ephedrine}POSiR$_3$ which are consistently the *major* diastereoisomers of compounds **4–6** (Scheme 5).

We have been able to differentiate between the stereoisomers



Scheme 5 Reactions of oxazaphospholidines with aldehydes (R = Ph, Bu^t), showing retention of configuration at phosphorus.

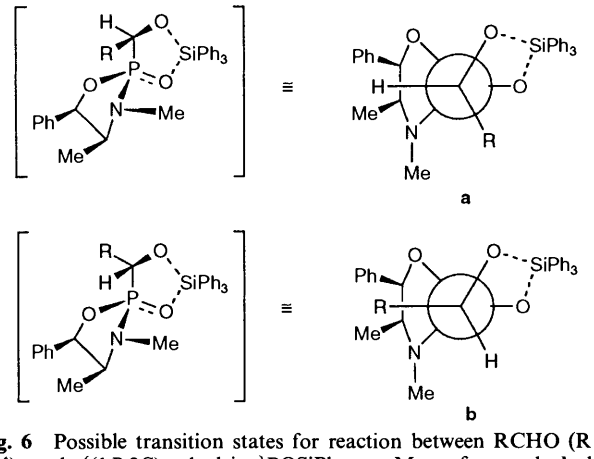


Fig. 6 Possible transition states for reaction between RCHO (R = Bu^t) and {(1*R*,2*S*)-ephedrine}POSiPh$_3$. **a** More favoured, **b** less favoured. The figure represents possible relative configurations and no specific conformations are implied.

a and **b** only for the major isomer of phosphonate ester **13**: by NOE studies the configuration is suggested to be (S_P, S_C). Consequently, we may speculate on the nature of the transition state for the formation of compound **13**. The lack of free rotation about the P–C_α bond in the product may imply a similar rigidity in the transition state. Furthermore, for intramolecular silyl-group transfer, the [P–O–SiR$_3$] and carbonyl oxygen functions must approach either a *syn* or *gauche* arrangement (see Scheme 2). A comparison between the two most plausible transition states that lead to (S_P, S_C) and (S_P, R_C) isomers respectively, using ball-and-stick models, suggests that in the case of compound **13** the transition state leading to (S_P, S_C) is the more readily attainable possibly because it engenders less severe steric interactions between the carbonyl *tert*-butyl group, the N-Me, 4-Me and 5-Ph groups of ephedrine and the phenyl groups on silicon (Fig. 6).

Although this rationale has not been subjected to more rigorous analysis, we find qualitative support for these conclusions in that the reactions of phospholidines **4–6** with Bu^{t}CHO are slower than those with PhCHO, presumably reflecting (i) the less electrophilic nature of the carbonyl carbon in the former due to the presence of the more electron-releasing

* Although compound **13** is stable at room temperature for several weeks, upon being heated to 80 °C for *ca.* 18 h it does react to afford the same product mixture as that obtained in its own formation. However, we have also found that heating of the related phosphonate esters {diamine}P(=O)CHPh(OSiR$_3$) to 80 °C for several hours under vacuum does not result in the reformation of {diamine}POSiR$_3$.[18]

tert-butyl group and (ii) the greater steric requirements of the *tert*-butyl group over the phenyl group. Furthermore, for each aldehyde it is observed that the qualitative order of reactivity is **6** > **4** > **5**; presumably, the smaller substituents on silicon will entail less severe steric interactions[6] whilst the more electron-withdrawing phenyl groups in compound **4** will act to reduce charge accumulation on silicon in the transition state of the rate-determining step (taken to be k_2 in Scheme 2). Consequently, it appears that both steric and electronic factors associated with the aldehyde and the substituents on silicon are important in controlling the rates and stereochemistry (see Table 1) of the Abramov reaction.

Conclusions.—The diastereoisomeric 2-triorganosiloxy-1,3,2-oxazaphospholidines, {(1*R*,2*S*)-ephedrine}$POSiR_3$ (R_3 = Ph_3 **4**, Bu^tMe_2 **5**, Et_3 **6**) can be prepared readily as a mixture of the two possible epimers with diastereoselectivities of 94.1(2), 87.9(2) and 86.0(2)%, respectively. Although configurationally stable on the NMR time-scale, epimerisation does occur on the chemical reactivity time-scale. The assignment of configuration in these compounds using NMR criteria is not without ambiguity and, in the absence of direct crystallographic studies, derivatisation experiments can be useful in this regard. Thus, oxidation reactions with either sulfur or *tert*-butyl hydroperoxide suggest that the major epimers of compounds **4–6** have the *anti*-R_P configuration. Compounds **4–6** undergo the Abramov reaction (Scheme 2) with aldehydes smoothly at room temperature to afford the α-siloxyphosphonate esters {(1*R*,2*S*)-ephedrine}P(=O)*C*HR′(OSiR_3) (R′ = Ph, Bu^t) in good yields where the presence of the chiral ephedrine auxiliary permits control over the stereochemistry at the α-carbon atom (in italics). NMR studies have permitted assignment of the absolute configurations at phosphorus and the α-carbon atom of the derivative {(1*R*,2*S*)-ephedrine}P(=O)CHBu^t($OSiPh_3$) as (S_P, S_C). As a result of these stereochemical assignments, it appears that the major epimers of the phospholidines **4–6** react with aldehydes R′CHO with retention of configuration at phosphorus to afford the major observed isomers of {(1*R*,2*S*)-ephedrine}P(=O)CHR′(OSiR_3).

We are currently looking to develop systems that are both more reactive and more selective than {(1*R*,2*S*)-ephedrine}-$POSiR_3$, by controlled modification of the triorganosiloxy group and/or the auxiliary. We have recently shown that chelating diolato auxiliaries result in *less* reactive silyl phosphite esters[13,14] but that chelating diamine auxiliaries lead to *more* reactive esters than do amino alcohols such as ephedrine.[18] Others have noted previously a similar increase in nucleophilicity of phosphorus upon replacing OMe groups with NMe_2 groups in PX_3 systems.[6] Moreover, we believe that the problem of selectivity can be simplified by switching to an axially symmetric chiral diamine auxiliary[23] where only two possible stereoisomers exist for the products of Abramov phosphonylation. Detailed kinetic investigations are also in progress to examine further the mechanism of the Abramov reaction.

The strategy described in this paper in which the chiral auxiliary is coordinated to the nucleophilic terminus (phosphorus) seems well suited to stoichiometric asymmetric phosphonylation. However, two factors may limit the development of the strategy reported here: (i) constraining a phosphorus(III) atom in an ester chelate ring has been shown to lower its basicity[24] compared with an acyclic analogue, which may explain the limited reactivity towards Abramov phosphonylation of systems containing chelating tartrate and binaphthol,[13,14] (ii) moreover, one of our main objectives is to develop a catalytic asymmetric phosphonylation process and this may be more likely to result from having the chiral auxiliary at the electrophilic terminus rather than at phosphorus. Indeed, we are actively pursuing this hypothesis by incorporating metal-based chiral electrophiles into metallophosphite esters. The results of these studies will form the basis of future reports.

Experimental

All manipulations were performed under an atmosphere of dry dinitrogen, using Schlenk and cannula techniques or in a dinitrogen-filled dry box. Solvents were pre-dried over sodium wire or 4 Å molecular sieves before reflux and subsequent distillation, under dinitrogen, from a suitable drying agent (given in parentheses); pentane, THF (sodium benzophenone ketyl) and toluene (sodium metal). All solvents were deoxygenated before use. Elemental analyses and relative molecular mass measurements were performed by the Microanalytical Laboratory of this department, the latter using an Hitachi Perkin-Elmer 115 Molecular Weight Apparatus. Mass spectra were collected on a VG Autospec instrument in either the electron-impact or chemical ionisation modes. IR spectra were recorded as either thin films or Nujol mulls between KBr windows on a Perkin-Elmer 257 grating spectrophotometer. NMR spectra were obtained on JEOL FX90Q, JEOL FX100 and Bruker AM 400 instruments operating at 100 MHz or 400 MHz for ^1H, 100 MHz for ^{13}C, and 36 MHz for ^{31}P. Deuteriated solvents were dried by flash chromatography on a column of basic alumina (Brockmann Grade I) and were deoxygenated before use. Spectra were referenced internally using either the residual solvent resonance for ^1H and ^{13}C, or $SiMe_4$ as δ_H, δ_C = 0, and externally for ^{31}P using 85% H_3PO_4 as zero ppm. All spectra are reported at 298 K in $CDCl_3$ unless stated otherwise, the ^{13}C and ^{31}P spectra being run under conditions of broad-band ^1H decoupling, unless noted otherwise. *J* Values are given in Hz. The compounds (1*R*,2*S*)-ephedrine, PCl_3, NEt_3, *N*-methylmorpholine, R_3SiOH, Bu^t-OOH (as a 3 mol dm^{-3} solution in 2,2,4-trimethylpentane), monoclinic sulfur and all carbonyl compounds were purchased from commercial sources and were either recrystallised [in the case of (1*R*,2*S*)-ephedrine and Ph_3SiOH], chromatographed on a short column of Brockmann Grade I basic alumina (*N*-methylmorpholine, NEt_3, Bu^tMe_2SiOH, Et_3SiOH and liquid carbonyls) or used as received (PCl_3, Bu^tOOH, sulfur and solid carbonyls). Diastereoselectivity values for compounds **4–6** were average values of at least eight separate determinations with esds calculated according to the equation $\{\Sigma_n(x_i - x)^2/n-(n-1)\}^{\frac{1}{2}}$ where x is the mean value of n determinations.[25] Diastereoselectivity (d.s.) refers to the direct percentage contribution of the major component A to a mixture of epimers A and B, $\{[A]/([A]+[B])\} \times 100$.[26]

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*PCl* **1**.—A solution of (1*R*,2*S*)-ephedrine (1.36 g, 8.26 mmol) in toluene (15 cm^3) was added dropwise over the course of *ca.* 20 min to a stirred solution of PCl_3 (0.72 cm^3, 8.26 mmol) and *N*-methylmorpholine (2.72 cm^3, 24.78 mmol) in toluene (20 cm^3) at −78 °C. The resulting pale yellow mixture became cloudy within seconds. The mixture was allowed to warm to room temp. slowly, was stirred thus for 16 h, and darkened after 30 min at room temp. Subsequently, the mixture was filtered and the volatiles were removed under reduced pressure to afford a pale yellow mobile oil. Upon cooling to −35 °C, the oil crystallised and when washed with pentane afforded the *title product* as a white solid, which was recrystallised from pentane (1.5 g, 80%), m.p. (uncorrected) 82–85 °C (Found: C, 51.9; H, 6.15; N, 6.1; Cl, 14.9. $C_{10}H_{13}ClNOP$ requires C, 52.30; H, 5.71; N, 6.10; Cl, 15.43%); $\delta_H(CDCl_3)$ 7.5–7.3 (m, 5 H, Ph), 5.90 (1 H, dd, $^3J_{HH}$ 8, $^3J_{PH}$ 2, PhC*H*O), 3.71 (1 H, qdd, $^3J_{HH}$ 8 and 7, MeC*H*O), 2.76 (3 H, d, $^3J_{PH}$ 16, NMe) and 0.79 (3 H, d, $^3J_{HH}$ 7, *Me*CHN); $\delta_C(CDCl_3)$ 136.19 (d, $^3J_{PC}$ 2.4, PhC_{ipso}), 127.89 (s, PhC), 126.56 (s, PhC),

87.38 (d, $^2J_{PC}$ 9.2, PhCHO), 57.68 (br s, MeCHN), 28.73 (d, $^2J_{PC}$ 13.3, NMe) and 14.18 (d, $^3J_{PC}$ 4.7, *Me*CHN); $\delta_P(CDCl_3)$ 171.5 (s); *m/z* 229 $(M)^+$, 211 $(M - Cl + OH)^+$, 194 $(M - Cl)^+$ and 123 $(M - Ph - 2Me - H)^+$. Brown and co-workers[11] found that **1** crystallised following distillation. We have not found it necessary to distill our product but find that the crude mobile oil comprises only a single isomer and purification by recrystallisation affords a sample suitable for elemental analysis. Significantly, the oil always contains a small quantity of toluene which may be the cause of an oil forming prior to crystallisation from pentane. However, we find that both the oil and solid forms of the chloride **1** show no differences in either their NMR properties or their reactions with R_3SiOH reagents.

The procedure for the synthesis of chloride **1** reported here differs in the order of addition of reagents to that reported by Brown[11] and could result in a local excess of PCl_3, a condition which might be more conducive to formation of dimer. Consequently, we performed the synthesis of compound **1** under conditions in which (i) the PCl_3 is in local excess and (ii) the ephedrine is in local excess and found that the products obtained were identical by ^1H and ^{31}P NMR.

In another experiment[27] designed to probe the monomer/dimer problem, the synthesis of compound **1** was performed using *racemic* ephedrine [obtained by mixing (1*R*,2*S*)-(−) and (1*S*,2*R*)-(+) forms in a 1:1 ratio]. The single product obtained was identical by NMR spectroscopy with that obtained using (1*R*,2*S*)-ephedrine. We suggest two possible explanations: (i) compound **1** is in fact monomeric, or (ii) the enantiomeric dimers of chloride **1** comprising two (+) or two (−) molecules of ephedrine are formed to the exclusion of the diastereoisomeric dimers which comprise one (+) and one (−) molecule of ephedrine per dimer.

Triethylamine may be used in place of *N*-methylmorpholine but with the former it is harder to remove completely traces of the ammonium by-product, and it occasionally produces a minor species in equilibrium with the required product **1**.

Minor species: $\delta_H(C_7D_8$; 221 K) 7.0 (5 H, m, Ph), 5.06 (1 H, dd, $^3J_{HH}$ 7, $^3J_{PH}$ 4, PhC*H*O), 3.09 (1 H, m, MeC*H*N), 2.24 (3 H, d, $^3J_{PH}$ 19, NMe) and 0.66 (3 H, d, $^3J_{HH}$ 7, *Me*CHN).

Reaction of Chloride **1** *with Sulfur.*—A solution of elemental sulfur dissolved in toluene (78 mg, 2.44 mmol in ~15 cm^3) was added to a mixture of chloride **1** (0.56 g, 2.44 mmol) in toluene (10 cm^3) and the mixture was analysed by ^{31}P NMR spectroscopy. No reaction was observed after 24 h at room temperature. The mixture was then heated to 80 °C for 3 days after which time ^{31}P NMR analysis in C_6D_6 solvent revealed resonances assignable to the two possible epimers of thiophospholidine {(1*R*,2*S*)-ephedrine}P(=S)Cl: δ_P 80.1 (s) and 74.6 (s)[11] in the ratio 1.5:1.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*H* **2**.—A solution of deoxygenated water in THF (2.65 cm^3, 2.65 mmol; 1.0 mol dm^{-3}) was added dropwise to a stirred solution of {(1*R*,2*S*)-*O*,*N*-ephedrine}PCl **1** (0.61 g, 2.65 mmol) and NEt_3 (0.74 cm^3, 5.30 mmol) in toluene (30 cm^3) at room temperature. The resulting pale yellow solution became cloudy within seconds and darkened after 10 min. After being stirred for 1 h, the mixture was worked up as described for chloride **1** to afford the title product as an oily solid (0.38 g, 74%), ν_{max}(thin film)/cm^{-1} 2390s *ν*(P–H) and 1260s, br *ν*(P=O); $\delta_H(CDCl_3)$ 7.2–7.0 (10 H, m, Ph, **2a**/**2b**), 7.31 (1 H, d, $^1J_{PH}$ 664, PH, **2a**), 7.27 (1 H, d, $^1J_{PH}$ 655, PH, **2b**), 5.59 (1 H, dd, $^3J_{HH}$ 6, $^3J_{PH}$ 2, PhC*H*O, **2a**), 5.34 (1 H, dd, $^3J_{HH}$ 6, $^3J_{PH}$ 6, PhC*H*O, **2b**), 3.49 (2 H, m, $^3J_{HH}$ 6, MeC*H*N, **2a**/**2b**), 2.65 (3 H, d, $^3J_{PH}$ 10, NMe, **2a**/**2b**), 2.56 (3 H, d, $^3J_{PH}$ 10, NMe, **2a**/**2b**), 0.65 (3 H, d, $^3J_{HH}$ 6, *Me*CHN, **2a**/**2b**) and 0.56 (3 H, d, $^3J_{HH}$ 7, *Me*CHN, **2a**/**2b**); $\delta_P(CDCl_3)$ 21.0 (dm, $^1J_{PH}$ 651, **2b**), 17.8 (dpent, $^1J_{PH}$ 660, J_{PH} 10, **2a**); *m/z* 211 $(M)^+$, 196 $(M - Me)^+$, 182 $(M - N - Me)^+$ and 166 $(M - N - 2Me - H)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*POSiMe*$_3$ **3**.—A solution of Me_3SiCl in toluene (0.53 cm^3, 4.32 mmol in ~30 cm^3) was added dropwise at room temperature to a stirred solution of compound **2** (0.91 g, 4.32 mmol) and NEt_3 (1.21 cm^3, 8.64 mmol) in toluene (30 cm^3). After 5 h at room temperature, the mixture was filtered, the residue was washed with toluene (2 × 5 cm^3), and all extracts were combined and reduced under reduced pressure to afford title compound **3** as a pale, mobile oil which was studied by ^{31}P NMR spectroscopy: $\delta_P(CDCl_3)$ 130.1 (s, **3b**) and 128.2 (s, **3a**).

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*POSiPh*$_3$ **4**.—A solution of Ph_3SiOH (0.85 g, 3.09 mmol) in toluene (15 cm^3) was added over the course of *ca.* 10 min to a stirred solution of {(1*R*,2*S*)-*O*,*N*-ephedrine}PCl **1** (0.71 g, 3.09 mmol) and NEt_3 (0.86 cm^3, 6.18 mmol) in toluene (20 cm^3). The resulting pale yellow solution became cloudy within seconds. After being stirred for 16 h, the mixture was filtered and the residue was washed with toluene (2 × 5 cm^3). All washings and mother liquor were then combined and the toluene was removed under reduced pressure to afford the product as a mobile oil (1.32 g, 91%) [flash chromatography of a toluene solution of product **4** down a short (~2 cm) column of Brockman Grade I alumina afforded an isomerically pure sample although in low yield]; ν_{max}(thin film)/cm^{-1} 1000–910s, br, *ν*(POSi); $\delta_H(CDCl_3)$ 7.7–7.0 (20 H, m, Ph, **4a**/**4b**), 5.44 (1 H, dd, $^3J_{HH}$ 6.6, $^3J_{PH}$ 2.8, PhC*H*O, **4a**), 5.41 (1 H, d, $^3J_{HH}$ 7.3, PhC*H*O, **4b**), 3.54 (1 H, m, MeC*H*N, **4a**), 3.42 (1 H, m, $^3J_{HH}$ 7.3 and 6.5, $^3J_{PH}$ 2.6, MeC*H*N, **4b**), 2.63 (3 H, d, $^3J_{PH}$ 12.0, NMe, **4a**), 2.47 (3 H, d, $^3J_{PH}$ 13.4, NMe, **4b**), 0.79 (3 H, d, $^3J_{HH}$ 7.0, *Me*CHN, **4a**) and 0.58 (3 H, d, $^3J_{HH}$ 6.5, *Me*CHN, **4b**); $\delta_C(CDCl_3)$ 138.31 (d, $^3J_{PC}$ 3.1, PhC_{ipso}), 136–126 (several resonances, PhC, **4a**/**4b**), 86.29 (d, $^2J_{PC}$ 13.1, PhCHO, **4a**), 85.54 (d, $^2J_{PC}$ 9.3, PhCHO, **4b**), 58.73 (d, $^2J_{PC}$ 6.2, MeCHN, **4a**), 56.45 (d, $^2J_{PC}$ 6.2, MeCHN, **4b**), 29.01 (d, $^2J_{PC}$ 20.7, NMe, **4a**), 28.66 (d, $^2J_{PC}$ 16.5, NMe, **4b**), 14.88 (d, $^3J_{PC}$ 3.6, *Me*CHN, **4a**) and 14.50 (d, $^3J_{PC}$ 5.0, *Me*CHN, **4b**); $\delta_P(CDCl_3)$ 131.1 (s, **4a**) and 127.6 (s, **4b**); *m/z* 469 $(M)^+$, 411 $(M - N - 2Me - CH_2)^+$ and 363 $(M - Si - Ph - H)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*POSiBu*^{t}*Me*$_2$ **5**.—The procedure followed was analogous to that of compound **4** above using the following quantities: chloride **1** (1.16 g, 5.05 mmol), Bu^tMe_2SiOH (0.67 g, 5.05 mmol) and NEt_3 (1.41 cm^3, 10.10 mmol). The product was normally isolated as a liquid but upon subsequent treatment with pentane at room temperature *compound* **5** was isolable as a crystalline solid (1.3 g, 78%) (Found: C, 58.75; H, 8.75; N, 4.25. $C_{16}H_{28}NO_2PSi$ requires C, 59.0; H, 8.67; N, 4.30%); ν_{max}(thin film)/cm^{-1} 1080–960s br, *ν*(POSi); $\delta_H(CDCl_3)$ 7.3–7.0 (5 H, m, Ph), 5.47 (1 H, d, $^3J_{HH}$ 7.3, PhC*H*O, **5b**), 5.32 (1 H, dd, $^3J_{HH}$ 6.7, $^3J_{PH}$ 2.6, PhC*H*O, **5a**), 3.38 (1 H, m, $^3J_{HH}$ 6.5, $^3J_{PH}$ 2.4, MeC*H*N, **5b**), 3.29 (1 H, m, $^3J_{HH}$ 6.6, MeC*H*N, **5a**), 2.61 (3 H, d, $^3J_{PH}$ 12.4, NMe, **5a**), 2.43 (3 H, d, $^3J_{PH}$ 13.6, NMe, **5b**), 0.85 (9 H, s, Bu^t, **5a**), 0.84 (9 H, s, Bu^t, **5b**), 0.63 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN, **5a**), 0.52 (3 H, d, $^3J_{HH}$ 6.5, *Me*CHN, **5b**) and 0.11–0.06 (several, Me_2Si); $\delta_C(CDCl_3)$ 138.56 (d, $^3J_{PC}$ 3.0, PhC_{ipso}, **5b**) 128–126 (several resonances, PhC), 86.07 (d, $^2J_{PC}$ 12.9, PhCHO, **5a**), 85.45 (d, $^2J_{PC}$ 9.2, PhCHO, **5b**), 58.63 (d, $^2J_{PC}$ 6.2, MeCHN, **5a**), 56.14 (d, $^2J_{PC}$ 6.3, MeCHN, **5b**), 28.86 (d, $^2J_{PC}$ 19.9, NMe, **5a**), 28.78 (d, $^2J_{PC}$ 15.1, NMe, **5b**), 25.54 (s, Me_3C, **5b**), 25.49 (s, Me_3C, **5a**), 18.08 (s, Me_3C, **5b**), 17.89 (s, Me_3C, **5a**), 14.50 (d, $^3J_{PC}$ 5.3, *Me*CHN, **5b**), −3.31 (d, $^3J_{PC}$ 4.1, $SiMe_2$, **5a**), −3.45 (d, $^3J_{PC}$ 4.3, $SiMe_2$, **5a**), −3.53 (d, $^3J_{PC}$ 2.6, $SiMe_2$, **5b**) and −3.56 (d, $^3J_{PC}$ 3.0, $SiMe_2$, **5b**);

$\delta_P(CDCl_3)$ 130.3 (s, **5a**) and 128.3 (s, **5b**); *m/z* 325 $(M)^+$, 295 $(M - 2Me)^+$ and 284 $(M - 2Me - C + H)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*POSiEt*$_3$ **6**.—The procedure followed was analogous to that of compound **4** above using the following quantities: chloride **1** (0.80 g, 3.50 mmol), Et_3SiOH (0.46 g, 3.50 mmol) and NEt_3 (0.98 cm^3, 7.0 mmol) (0.93 g, 82%); ν_{max}(thin film)/cm^{-1} 900–1020s br, ν(POSi)}; $\delta_H(CDCl_3)$ 7.4–7.1 (5 H, m, Ph), 5.50 (1 H, d, $^3J_{HH}$ 7.0, PhC*H*O, **6b**), 5.34 (1 H, dd, $^3J_{HH}$ 7.0, $^3J_{PH}$ 3.0, PhC*H*O, **6a**), 3.42 (2 H, m, MeC*H*N, **6a**/**6b**), 2.63 (3 H, d, $^3J_{PH}$ 12.0, NMe, **6a**), 2.46 (3 H, d, $^3J_{PH}$ 14.0, NMe, **6b**) and 1.0–0 (m, $SiEt_3$ and *Me*CHN, **6a**/**6b**): $\delta_C(CDCl_3)$ 138.69 (d, $^3J_{PC}$ 2.0, PhC_{ipso}, **6b**) 129–125 (several resonances, PhC), 86.15 (d, $^3J_{PC}$ 13.3, PhCHO, **6a**), 85.41 (d, $^2J_{PC}$ 9.3, PhCHO, **6b**), 58.83 (d, $^2J_{PC}$ 5.2, MeCHN, **6a**), 56.28 (d, $^2J_{PC}$ 5.6, MeCHN, **6b**), 33.67 (d, $^2J_{PC}$ 16.0, NMe, **6a**), 28.80 (d, $^2J_{PC}$ 16.0, NMe, **6b**), 14.62 (d, $^3J_{PC}$ 5.3, *Me*CHN, **6b**), 6.58 [d, $^3J_{PC}$ 4.6, $Si(CH_2Me)_3$, **6b**] and 5.81 [s, $Si(CH_2Me)_3$, **6b**]; $\delta_P(CDCl_3)$ 130.5 (s, **6a**) and 128.4 (s, **6b**); *m/z* 325 $(M)^+$, 296 $(M - Et)^+$, 281 $(M - Et - Me)^+$ and 219 $(M - Et - Ph)^+$.

Reaction of Chloride **1** *with* Ph_3SnOH.—A solution of Ph_3SnOH in toluene (0.16 g, 0.44 mmol in 35 cm^3) was added dropwise at room temperature to a stirred solution of {(1*R*,2*S*)-ephedrine}PCl **1** (0.10 g, 0.44 mmol) and NEt_3 (0.12 cm^3, 0.89 mmol) in toluene (10 cm^3). The mixture was stirred for 4 h during which time it went only slightly cloudy, suggesting that not much $NHEt_3Cl$ had been formed. The volatiles were removed under reduced pressure and the oily residue was examined by ^{31}P NMR spectroscopy and mass spectrometry (see text).

Reaction of Compound **4** *with Sulfur: Synthesis of* {(1R,2S)-*Ephedrine*}*P*(=*S*)*OSiPh*$_3$ **7**.—A toluene solution of elemental sulfur (70 mg, 2.19 mmol, in ~10 cm^3) was added at room temperature to a stirred solution of compound **4** (in the form of an epimeric mixture with d.s. 94%; 1.02 g, 2.19 mmol) in toluene (20 cm^3). After being stirred for 1 h the solution was filtered and the volatile materials were removed under reduced pressure to afford the *title compound* **7** as a crystalline solid. Reaction was essentially quantitative by ^{31}P NMR spectroscopy. No recrystallisation or chromatography was performed on compound **7** prior to analysis (Found: C, 66.7; H, 5.5; N, 2.8%; M^+, 508. $C_{28}H_{28}NO_2PSSi$ requires M, 501; C, 67.0; H, 5.6; N, 2.8%); ν_{max}(Nujol)/cm^{-1} 715 ν(P=S); $\delta_H(C_6D_6)$ 7.9–7.0 (20 H, m, Ph), 5.21 (1 H, dd, $^3J_{PH}$ 3.8, $^3J_{HH}$ 6.2, PhC*H*O, minor), 4.96 (1 H, dd, $^3J_{PH}$ 4.1, $^3J_{HH}$ 5.8, PhC*H*O, major), 3.04 (m, $^3J_{HH}$ 6.5, MeC*H*N), 2.33 (3 H, d, $^3J_{PH}$ 12.5, NMe, minor), 2.29 (3 H, d, $^3J_{PH}$ 13.8, NMe, major), 0.47 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN, minor) and 0.44 (3 H, d, $^3J_{HH}$ 6.5, *Me*CHN, major); $\delta_C(C_6D_6)$ 136–125 (several resonances, PhC), 81.78 (s, PhCHO, minor), 81.69 (d, $^2J_{PC}$ 2.6, PhCHO, major), 60.16 (d, $^2J_{PC}$ 10.6, MeCHN, minor), 59.61 (d, $^2J_{PC}$ 8.4, MeCHN, major), 30.13 (d, $^2J_{PC}$ 7.9, NMe, minor), 28.96 (d, $^2J_{PC}$ 6.7, NMe, major), 14.41 (d, $^3J_{PC}$ 1.2, *Me*CHN, minor) and 13.08 (d, $^3J_{PC}$ 5.0, *Me*CHN, major); $\delta_P(C_6D_6)$ 70.9 (s, minor) and 70.3 (s, major); *m/z* 501 $(M)^+$ and 424 $(M - Ph)^+$.

Reaction of Compound **4** *with Bu*^{t}*OOH: Synthesis of* {(1R,2S)-*Ephedrine*}*P*(=*O*)*OSiPh*$_3$ **8**.—A chilled (~4 °C) solution of Bu^{t}OOH in 2,2,4-trimethylpentane (3 mol dm^{-3}; 0.14 cm^3, 0.43 mmol) was added to a solution of compound **4** (in the form of an epimeric mixture with d.s. 90%; 0.2 g, 0.43 mmol) in toluene (~2 cm^3) cooled to 0 °C in ice. The mixture was allowed to warm to room temperature and was stirred for 1 h. After this time the volatiles were removed under reduced pressure and the residual oil was analysed by ^1H and ^{31}P NMR spectroscopy and shown to comprise only two isomeric products in the ratio 34:66% assigned as epimers of title compound **8** on the basis of the NMR data below. When the reaction was performed as above but was stirred at room temperature for *ca.* 16 h, the resultant product profile and composition was not significantly altered; $\delta_H(CDCl_3$, phenyl resonances omitted) 5.53 (1 H, dd, $^3J_{HH}$ 6.1, $^3J_{PH}$ 2.0, PhC*H*O, minor), 4.89 (1 H, dd, $^3J_{HH}$ 5.6, $^3J_{PH}$ 5.6, PhC*H*O, major), 3.53 (1 H, dqd, $^3J_{HH}$ 6.4, $^3J_{PH}$ 17.8, MeC*H*N, minor), 3.27 (1 H, dqd, $^3J_{HH}$ 6.4, $^3J_{PH}$ 11.2, major), 2.44 (3 H, d, $^3J_{PH}$ 10.4, NMe, minor), 2.39 (3 H, d, $^3J_{PH}$ 10.9, NMe, major), 0.66 (3 H, d, $^3J_{HH}$ 5.9, *Me*CHN, minor) and 0.64 (3 H, d, $^3J_{HH}$ 6.4, *Me*CHN, major); $\delta_P(CDCl_3)$ 10.8 (s, major) and 10.5 (s, minor).

Reaction of Compound **5** *with Sulfur: Synthesis of* {(1R,2S)-*Ephedrine*}*P*(=*S*)*OSiBu*^{t}*Me*$_2$ **9**.—A solution of elemental sulfur in toluene (23 mg, 0.71 mmol, in ~15 cm^3) was added at room temperature to a stirred solution of compound **5** (as an epimeric mixture with d.s. 91%; 0.23 g, 0.71 mmol) in toluene (20 cm^3). After being stirred for 1 h, the solution was filtered and the volatile materials were removed under reduced pressure to afford title compound **9** as a pasty solid. Reaction was essentially quantitative by ^{31}P NMR spectroscopy. No recrystallisation or chromatography was performed on the product **9** prior to analysis; $\delta_H(CDCl_3)$ 7.4–7.1 (5 H, m, Ph), 5.59 (1 H, dd, $^3J_{HH}$ 6.1, $^3J_{PH}$ 3.3, PhC*H*O, minor), 5.47 (1 H, dd, $^3J_{HH}$ 6.0, $^3J_{PH}$ 5.1, PhC*H*O, major), 3.7–3.5 (m, MeC*H*N, both epimers), 2.74 (3 H, d, $^3J_{PH}$ 12.4, NMe, minor), 2.65 (3 H, d, $^3J_{PH}$ 12.2, NMe, major), 0.96 (9 H, s, Bu^t, minor), 0.94 (9 H, s, Bu^t, major) and 0.8–0.0 (several, $SiMe_2$, both isomers); $\delta_P(CDCl_3)$ 71.0 (s, major) and 70.7 (s, minor).

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*CHPh*(*OSiPh*$_3$) **10**.—Benzaldehyde (0.23 cm^3, 2.34 mmol) was added dropwise at room temperature to a stirred solution of {(1*R*,2*S*)-ephedrine}$POSiPh_3$ **4** (1.10 g, 2.34 mmol) in toluene (15 cm^3). After 16 h, the pale yellow solution was filtered, and the filtrate was concentrated to ~4 cm^3 and layered with pentane (~10 cm^3). Subsequent cooling to −35 °C afforded the *title product* as a crystalline solid (1.19 g, 88%) (Found: C, 72.3; H, 6.25; N, 2.35. $C_{35}H_{34}NO_3PSi$ requires C, 73.00; H, 5.95; N, 2.43%); ν_{max}(Nujol)/cm^{-1} 1262s ν_{max}(P=O); NMR data for major isomer only: $\delta_H(CDCl_3)$ 7.9–7.0 (25 H, m, Ph), 5.60 (1 H, d, $^3J_{HH}$ 6.3, PhC*H*O), 5.16 (1 H, d, $^2J_{PH}$ 11.1, PhC*H*P), 3.44 (1 H, dqd, $^3J_{HH}$ 6.5, $^3J_{PH}$ 11.1, MeC*H*N), 2.39 (3 H, d, $^3J_{PH}$ 8.6, NMe) 0.29 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN); $\delta_C(CDCl_3)$ 137–135 (several resonances, PhC), 79.98 (s, PhCHO), 74.45 (d, $^1J_{PC}$ 156.6, PCHPh), 61.22 (d, $^2J_{PC}$ 7.0, MeCHN), 30.53 (d, $^2J_{PC}$ 5.4, NMe) and 14.57 (br s, *Me*CHN); $\delta_P(CDCl_3)$ 34.7 (s); *m/z* 575 $(M)^+$ and 469 $(M - PhCHO)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*CHPh*(*OSiBu*^{t}*Me*$_2$) **11**.—The same procedure as for compound **10** was followed by using benzaldehyde (0.19 cm^3, 1.92 mmol), {(1*R*,2*S*)-ephedrine}$POSiBu^tMe_2$ **5** (0.62 g, 1.92 mmol) and afforded the *title product* as a crystalline solid (0.69 g, 84%) (Found: C, 63.95; H, 7.80; N, 3.25. $C_{23}H_{34}NO_3PSi$ requires C, 64.00; H, 7.94; N, 3.25%); ν_{max}(Nujol)/cm^{-1} 1255s, ν(P=O); NMR of major isomer only: $\delta_H(CDCl_3)$ 7.4–7.0 (10 H, m, Ph), 5.57 (1 H, d, $^3J_{HH}$ 6.4, PhC*H*O), 5.12 (1 H, d, $^2J_{PH}$ 12.0, PhC*H*P), 3.47 (1 H, dqd, $^3J_{HH}$ 6.6, $^3J_{PH}$ 11.0, MeC*H*N), 2.66 (3 H, d, $^3J_{HH}$ 8.5, NMe), 0.82 (9 H, s, Bu^t), 0.30 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN), 0.03 (3 H, s, $SiMe_2$) and −0.11 (3 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 138.28 (s, C_{ipso}, *Ph*CHO), 135.90 (d, $^2J_{PC}$ 9.6, C_{ipso}, PCH*Ph*), 128–125 (several resonances, PhC), 79.96 (s, PhCHO), 73.25 (d, $^1J_{PC}$ 155.2, PCHPh), 61.13 (d, $^2J_{PC}$ 6.7, MeCHN), 30.59 (d, $^2J_{PC}$ 5.3, NMe), 25.72 (s, Me_3C), 18.21 (s, Me_3C), 14.50 (br s, *Me*CHN), −4.85 (br s, $SiMe_2$) and −5.06

(br s, $SiMe_2$); $\delta_P(CDCl_3)$ 35.1 (s); *m/z* 431 $(M)^+$, 416 $(M - Me)^+$ and 374 $(M - Bu^t)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*CHPh*(*OSiEt*$_3$) **12**.—The same procedure as for compound **10** was followed by using benzaldehyde (0.27 cm^3, 2.68 mmol), {(1*R*,2*S*)-ephedrine}-$POSiEt_3$ **6** (0.87 g, 2.68 mmol) and afforded the title product as an oily solid (0.88 g, 77%); ν_{max}(thin film)/cm^{-1} 1260s, br, ν(P=O); NMR for major isomer only: $\delta_H(CDCl_3)$ 7.7–7.0 (10 H, m, Ph), 5.54 (1 H, d, $^3J_{HH}$ 6.4, PhC*H*O), 5.09 (1 H, d, $^2J_{PH}$ 11.7, PC*H*Ph), 3.46 (1 H, dqd, $^3J_{HH}$ 6.6, $^3J_{PH}$ 11.5, MeC*H*N), 2.63 (3 H, d, $^3J_{HH}$ 8.6, NMe), 0.81 [6 H, m, $Si(CH_2Me)_3$], 0.48 [9 H, t, $^3J_{HH}$ 7.2, $Si(CH_2Me)_3$] and 0.42 (3 H, d, $^3J_{HH}$ 6.9, *Me*CHN); $\delta_C(CDCl_3)$ 135.81 (d, $^2J_{PC}$ 9.3, C_{ipso}, PCH*Ph*), 138.16 (d, $^3J_{PC}$ 2.6, C_{ipso}, *Ph*CHO), 138–126 (several resonances, PhC), 79.81 (d, $^2J_{PC}$ 5.2, PhCHO), 72.22 (d, $^1J_{PC}$ 169.0, PCHPh), 60.80 (d, $^2J_{PC}$ 7.6, MeCHN), 30.06 (d, $^2J_{PC}$ 5.4, NMe), 14.23 (s, *Me*CHN), 6.30 [s, $Si(CH_2Me)_3$] and 4.35 [s, $Si(CH_2Me)_3$]; $\delta_P(CDCl_3)$ 35.9 (s); *m/z* 431 $(M)^+$, 402 $(M - Et)^+$ and 325 $(M - Et - Ph)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*CHBu*^{t}(*OSiPh*$_3$) **13**.—Pivalaldehyde (0.47 cm^3, 4.38 mmol) was added dropwise at room temperature to a stirred solution of {(1*R*,2*S*)-ephedrine}$POSiPh_3$ **4** (0.68 g, 1.46 mmol) in toluene (15 cm^3). After 48 h, a fine powder was observed to have precipitated from solution. This was isolated by filtration, washed with pentane (2 × 5 cm^3) and dried *in vacuo*. Recrystallisation from toluene afforded crystals of isomerically pure *title compound* **13** (0.21 g, 26%). To determine the composition of the crude mixture, the initially formed toluene suspension was evaporated to dryness and the residue was dissolved in $CDCl_3$ to afford a clear solution, which was then examined by $^{31}P\{^1H\}$ NMR spectroscopy (Found: C, 71.2; H, 6.7; N, 2.7. $C_{33}H_{38}NO_3PSi$ requires C, 71.30; H, 6.89; N, 2.52%); ν_{max}(Nujol)/cm^{-1} 1255s br, ν(P=O); NMR of major isomer only: $\delta_H(CDCl_3)$ 7.8–6.9 (20 H, m, Ph), 5.60 (1 H, d, $^3J_{HH}$ 5.7, PhC*H*O), 3.88 (1 H, d, $^2J_{PH}$ 5.6, PC*H*Bu^t), 3.55 (1 H, dqd, $^3J_{HH}$ 6.0, $^3J_{PH}$ 10.3, MeC*H*N), 2.66 (3 H, d, $^3J_{PH}$ 9.7, NMe), 1.07 (9 H, s, Bu^t) and 0.53 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN); $\delta_C(CDCl_3)$ 136–127 (several resonances, PhC), 82.24 [d, $^1J_{PC}$ 152.6, P(O)*C*HBu^t], 79.60 (s, Ph*C*HO), 62.12 (d, $^2J_{PC}$ 5.7, Me*C*HN), 35.85 (d, $^2J_{PC}$ 3.9, Me_3C), 32.83 (d, $^2J_{PC}$ 4.0, NMe), 27.65 (d, $^3J_{PC}$ 6.4, Me_3C) and 15.15 (d, $^3J_{PC}$ 1.8, *Me*CHN); $\delta_P(CDCl_3)$ 40.2 (s); *m/z* 556 $(M)^+$, 540 $(M - Me)^+$ and 498 $(M - Bu^t)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*CHBu*^{t}(*OSiBu*^{t}*Me*$_2$) **14**.—Pivalaldehyde (0.4 cm^3, 3.96 mmol) was added at room temperature to a stirred solution of {(1*R*,2*S*)-ephedrine}-$POSiBu^tMe_2$ **5** (0.32 g, 0.99 mmol) in pentane (15 cm^3). After being stirred for 4 days at room temperature the volatiles were removed under reduced pressure, and the residue was dissolved in $CDCl_3$ and analysed by ^{31}P NMR spectroscopy (see text). Recrystallisation of the crude product from pentane afforded title compound **14** as an oily solid (0.33 g, 81%); ν_{max}(thin film)/cm^{-1} 1245s br, ν(P=O); NMR of major isomer only: $\delta_H(CDCl_3$ 7.3–7.1 (5 H, m, Ph), 5.60 (1 H, d, $^3J_{HH}$ 6.5, PhC*H*O), 3.77 (1 H, d, $^2J_{HH}$ 4.8, PC*H*Bu^t), 3.46 (1 H, dqd, $^3J_{HH}$ 6.7, $^3J_{PH}$ 9.0, MeC*H*N), 2.69 (3 H, d, $^3J_{PH}$ 9.6, NMe), 1.05 (9 H, s, PhCH*Bu*^{t}), 0.85 (9 H, s, Si*Bu*^{t}Me_2), 0.64 (3 H, d, $^3J_{HH}$ 6.8, *Me*CHN), 0.06 (3 H, s, $SiMe_2$) and −0.03 (3 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 138–125 (several resonances due to phenyl carbons), 79.84 (s, Ph*C*HO), 79.04 [d, $^1J_{PC}$ 149.0, P(O)*C*HBu^t], 62.06 (d, $^2J_{PC}$ 5.6, Me*C*HN), 35.87 (d, ^2J 4.0, Me_3C) 35.82 (s, Me_3C), 32.89 (d, $^2J_{PC}$ 4.3, NMe), 27.79 (d, $^3J_{PC}$ 6.5, Me_3C), 26.37 (s, Me_3C), 18.09 (s, Me_3C), 16.15 (d, $^3J_{PC}$ 2.0, *Me*CHN), 0.92 (br s, $SiMe_2$) and −2.98 (br s, $SiMe_2$); $\delta_P(CDCl_3)$ 42.7 (s); *m/z* 411 $(M)^+$, 353 $(M - Bu^t - H)^+$ and 325 $(M - Bu^tCHO)^+$.

Synthesis of {(1R,2S)-O,N-*Ephedrine*}*P*(=*O*)*CHBu*^{t}(*OSiEt*$_3$) **15**.—Pivalaldehyde (0.164 cm^3, 1.51 mmol) was added dropwise at room temperature to a stirred solution of {(1*R*,2*S*)-ephedrine}$POSiEt_3$ **6** (0.49 g, 1.51 mmol) in toluene (15 cm^3). After 16 h, the pale yellow solution was filtered, the volatiles were removed under reduced pressure, and the residue was examined by NMR spectroscopy (see text). Recrystallisation from pentane produced title compound **15** as an oily solid, ν_{max}(thin film)/cm^{-1} 1260s br, ν(P=O); NMR of major isomer only: $\delta_H(CDCl_3)$ 7.3–6.9 (5 H, m, Ph), 5.62 (1 H, d, $^3J_{HH}$ 6.6, PhC*H*O), 3.82 (1 H, d, $^2J_{PH}$ 5.1, PC*H*Bu^t), 3.52 (1 H, m, J_{HH} 7.0, MeC*H*N), 2.71 (3 H, d, $^3J_{PH}$ 9.7, NMe), 1.08 (9 H, s, Bu^t) and 1.00–0.40 (18 H, m, *Me*CHN + $SiEt_3$); $\delta_C(CDCl_3)$ 136.23 (d, $^3J_{PC}$ 9.2, PhC_{ipso}), 137–125 (several resonances due to phenyl carbons), 80.17 (s, Ph*C*HO), 79.54 [d, $^1J_{PC}$ 150.0, P(O)*C*HBu^t], 61.68 (d, $^2J_{PC}$ 5.5, Me*C*HN), 35.61 (s, Me_3C), 32.50 (d, $^2J_{PC}$ 5.1, NMe), 27.58 (d, $^3J_{PC}$ 6.5, Me_3C), 15.84 (d, $^3J_{PC}$ 2.6, *Me*CHN), 6.98 [br s, $Si(CH_2Me)_3$] and 5.30 [br s, $Si(CH_2Me)_3$]; $\delta_P(CDCl_3)$ 42.9 (s); *m/z* 411 $(M)^+$, 382 $(M - Et)^+$ and 325 $(M - 3Et + H)^+$.

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Note Added in Proof

Since submission of this paper, a number of groups in both the USA and Japan have published strategies for asymmetric phosphonylation which are complementary to ours [(*a*) N. J. Gordon and S. A. Evans, Jr., *J. Org. Chem.*, 1993, **58**, 5293; 5295; (*b*) T. Yokomatsu, T. Yamagishi and S. Shibuya, *Tetrahedron: Asymmetry*, 1993, **4**, 1779; 1783; (*c*) V. Blazis, A. De La Cruz, K. Koeller and C. D. Spilling, *Phosphorus, Sulfur and Silicon*, 1993, **75**, 159 and references therein] involving chelating chiral amino alcohol auxiliaries (*a*), diamine auxiliaries (*b*) and metal-based catalytic systems (*c*) mirroring the ideas outlined in this paper. However, recent results in our laboratory have led us to design improved phosphonylating reagents for (i) stoichiometric phosphonylation, [*O*,*N*-(1*R*,2*S*)-ephedrine]P–N($SiMe_3$)$_2$ and (ii) for catalytic phosphonylation, [*O*,*N*-(1*R*,2*S*)-ephedrine]B–O–P-(OMe)$_2$ based on criteria discussed in this paper and elsewhere.[18] The former reagent is especially effective affording stereoselectivities in the Abramov reaction with aldehydes of up to *ca.* 98% which is far superior to those reported by both the American and Japanese groups. Details of these asymmetric phosphonylation systems will be published shortly.

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