# [$1^N,3^E$]-Bifunctional Phosphorodiamidites and the Diastereoselective Phosphonylation of Aldehydes. Controlling, Elucidating and Rationalising the Stereochemical Course of the Asymmetric Abramov Reaction

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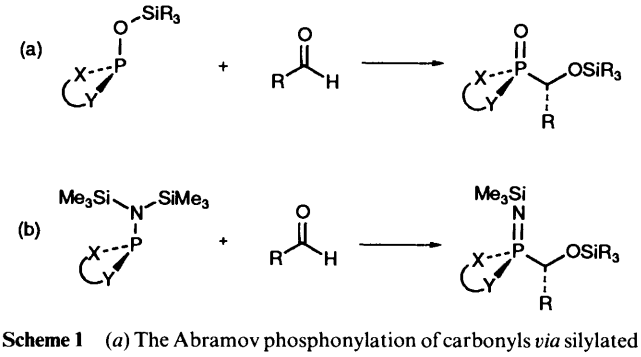
The novel, chiral phosphorodiamidite [(1*R*,2*S*)-*O*,*N*-ephedrine]$PN(SiMe_3)_2$ **2** has been prepared cleanly in both high chemical (83%) and epimeric (>98%) yields from the reaction of $LiN(SiMe_3)_2$ with [(1*R*,2*S*)-*O*,*N*-ephedrine]PCl **1**. The configuration at phosphorus has been shown to be $S_P$ by a combination of NMR and derivatisation studies. Phosphorodiamidite **2** phosphonylates aldehydes (RCHO) readily *via* the Abramov reaction to afford α-siloxyimidophosphonate esters of the form [(1*R*,2*S*)-*O*,*N*-ephedrine]$P(NSiMe_3)CHR(OSiMe_3)$ (R = alkyl and substituted phenyl) with diastereoselectivities up to 96% (for R = Bu$^t$). In each case, NMR spectroscopy reveals that both major and minor product esters have the $S_P$ configuration supportive of the Abramov reaction proceeding with *retention* of configuration at phosphorus and this is supported by X-ray diffraction studies on α-siloxyimidophosphonate esters with R = 2-naphthyl **9** and 2-$Ph_2PC_6H_4$ **11**. Subsequently, an empirical method of assigning configurations to *both* the phosphorus and α-carbon atoms is proposed on the basis of $^1H$ and $^{31}P$ NMR measurements. Experiments also suggest that the Abramov reaction (i) is subject to *kinetic* control under the conditions reported here but can be reversed under more forcing thermal conditions or in the presence of trace acid, (ii) involves *intramolecular* transfer of the triorganosilyl group, (iii) involves significant [P–C] bond formation in the rate-determining step, (iv) probably does not proceed *via* pre-coordination of the carbonyl oxygen atom to silicon (by $^{29}Si\{^1H\}$ NMR) in contrast to metallophosphite systems and (v) the configuration at the α-carbon stereocentre is controlled primarily by *steric* rather than distal electronic factors in systems where R = $XC_6H_4$. Consequently, steric interactions in the rate-determining transition state may account for the reversal in face-selectivity in the reactions between compound **2** and 2-$C_{10}H_7CHO$, for which the major product isomer **9** has the ($S_P$,$S_C$) configuration, and **2** and 2-$Ph_2PC_6H_4CHO$, for which the major product isomer **11** has the ($S_P$,$R_C$) configuration.

The phosphoro group [$(RO)_2P(=O)O$] is of fundamental significance in many of the most important molecules that control molecular replication, cell biochemistry and metabolic processes in all living species.[1] Consequently, the mechanisms by which the phosphoro group is transferred to and from substrates have been studied intensively.[2] However, the study of systems containing the phosphoro function under physiologically relevant conditions is often complicated by competing pathways involving P–O bond fission such as enzyme-catalysed hydrolysis and alcoholysis.[3] Not only do such reactions affect the constitution of the system under study but may also alter drastically any stereochemistry at the phosphorus atom itself.[4] Since many important biochemical interactions, especially those involving enzymes, are dependent upon the molecular topology and detailed stereochemistry of the substrates it is obviously highly desirable to be able to control, rationalise and predict the stereochemical course of phospho-transfer processes of both a chemical and biochemical nature.[5]

One of the most widely employed and flexible methods of investigating organophosphate biomolecules is to study model systems based on the phosphonate scaffold which contain the phosphono functionality [$(RO)_2P(X)R$] (X = O, S), where R is a carbon-donor organic residue.[6] These molecules benefit from the presence of the P–C bond, which is generally more resistant towards chemical and enzymic hydrolysis or alcoholysis than is the P–O bond and form useful, stable modified phosphate mimetics. Indeed, phosphonate mimics of organophosphate biomolecules are widely studied for their physiological applications as enzyme inhibitors, antiviral agents and antibiotics,[7] and in drug design through antisense oligonucleotide technology.[8] Consequently, the development of new stereoselective methods of phosphonylation is highly desirable.

As part of a research programme which seeks to exploit enzymic design criteria in the development of new main-group and transition element reagents for stereoselective syntheses we are investigating stoichiometric and catalytic asymmetric phosphonylation processes, an area in which there has been increasing activity over the last 2 years with several excellent studies being published.[9] We have focused upon the development of an asymmetric variant of the Abramov reaction (Scheme 1a) in which chiral [$1^N,3^E$]-bifunctional organophosphorus(III) esters[10] containing the P–X–M functionality (X = O, N; M = Si, B, Al, transition element) are used as the




**Scheme 1** (*a*) The Abramov phosphonylation of carbonyls *via* silylated organophosphorus(III) esters; (*b*) the Abramov phosphonylation of carbonyls *via* chiral phosphoroamidite esters. R = alkyl, aryl; X-Y = chiral, chelating dianionic auxiliary (diols or amino alcohols)

phosphono-transfer agents. As shown in Scheme 1, the Abramov reaction has a strong resemblance to both the Ene and Mukaiyama-Aldol reactions[11] and indeed, may be viewed as a phospho-Mukaiyama process.

Two strategies are being investigated concurrently in our laboratory for the development of (i) stoichiometric and (ii) catalytic asymmetric phosphonylation systems. In the first of these, a chiral auxiliary is covalently bonded to the nucleophilic (*N*) phosphorus atom where it is envisaged to have a strong stereoelectronic effect upon the configuration of the developing stereogenic centre at the α-carbon atom (Scheme 1a). A number of different auxiliaries have been studied, all based upon chelating, dianionic oxygen and/or nitrogen coordinating ligands such as (+)-dimethyl-L-tartrate,[12] binaphthol[12] and (1*R*,2*S*)-ephedrine.[13] It has been observed that nitrogen-based auxiliaries promote the Abramov reaction better than do oxygen-based auxiliaries,[14] consequently we have focussed more on chiral amino alcohol functions than on diol groups, whilst Spilling and co-workers are investigating related systems with chiral $C_2$-symmetric diamino auxiliaries.[15] We envisaged that further reactivity enhancement could be achieved by moving to an even more nitrogen-rich phosphorus coordination sphere by replacing the siloxy group with an isoelectronic and isolobal bis(trimethylsilyl)amido function.[16] The products of the Abramov reaction *via* bis(trimethylsilyl)amido reagents lead to phosphorus esters containing the P=NR moiety (Scheme 1b).

Recently, we have extended our initial studies by combining efficient, readily available, relatively inexpensive auxiliaries with the bis(trimethylsilyl)amido function to produce organophosphorus reagents which phosphonylate aldehydes with diastereoselectivities up to ~96%.[17] This system has also allowed us to probe mechanistic features of the Abramov reaction using a combination of spectroscopic, X-ray crystallographic[17] and isotopic labelling[14] techniques which suggest that reaction proceeds with overall retention of configuration at phosphorus and with preferential X–Si rather than P–X bond cleavage (*vide infra*).

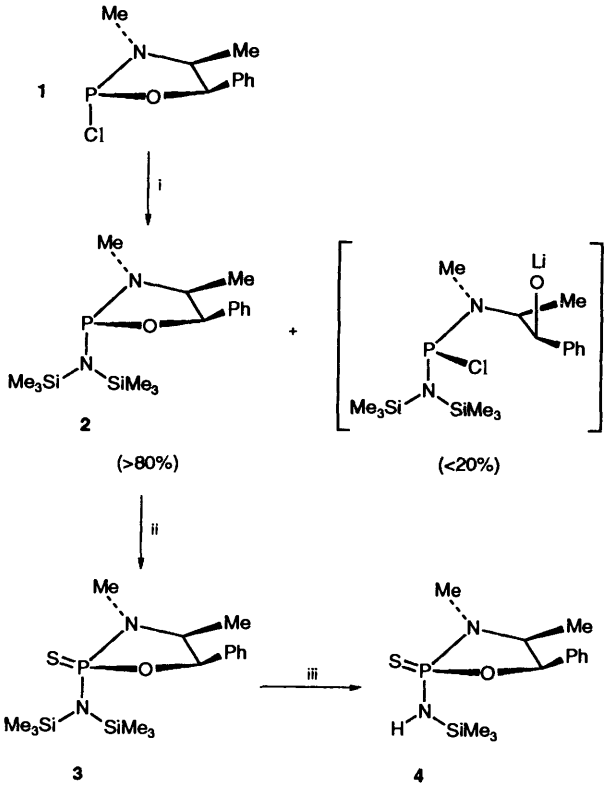
The above system in which the chiral auxiliary is coordinated to phosphorus is adequate for stoichiometric phosphonylations but the development of an efficient catalytic system may be facilitated better by having the chiral auxiliary bound to the electrophilic (*E*) terminus of the [$1^N$,$3^E$]-bifunctional organophosphorus(III) esters.[9,18] The electrophilic group may then function as an endogeneous chiral Lewis acid to pre-coordinate and activate the substrate in a stereocontrolled fashion prior to phosphono-group transfer. The [$1^N$,$3^E$] reagent may then be envisaged to operate like the active site of an enzyme where the enthalpy gain of preliminary substrate coordination outweighs the loss of entropy upon binding and hence provides a significant rate enhancement to the reaction. Steps to achieve these goals are currently underway in our laboratory.

In this paper, we provide details of our investigations into stoichiometric asymmetric phosphonylation and attempt to rationalise the stereochemical course of the asymmetric Abramov reaction.

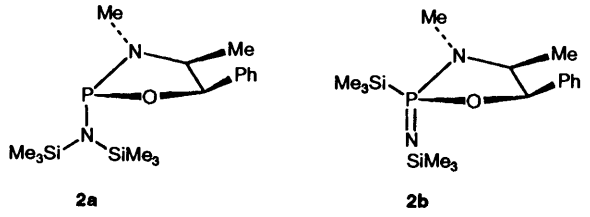
## Results and Discussion

*Synthesis and Configuration of* [(1R,2S)-O,N-*Ephedrine*]*PN*-(*SiMe*$_3$)$_2$.—The chlorophosphoramidite [(1*R*,2*S*)-*O*,*N*-ephedrine]PCl **1** has been synthesized[13,19,20] in high yield as a single epimer which, on the basis of spectroscopic and derivatisation studies, has been assigned the $R_P$ configuration. It has been shown that the chlorine atom in compound **1** may be displaced readily by carbon-based nucleophiles with predominantly overall retention of configuration at phosphorus.[20,21] In an analogous manner, chloride **1** reacts smoothly with LiN(SiMe$_3$)$_2$ in tetrahydrofuran (THF) solvent at reduced temperature to afford the product of halide-atom metathesis, [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2**, as a pale yellow liquid (Scheme 2). Consistently, the crude product **2** is contaminated with up to ~20% of a second compound which appears to contain ephedrine bound to phosphorus and a single high-frequency $^{31}$P NMR resonance at δ 164.3 ppm which is consistent with retention of the P–Cl bond (*cf* $\delta_P$ 148.2 for **2**). We envisage that this compound may be {Li}{[(1*R*,2*S*)-*N*-ephedrine]PCl[N(SiMe$_3$)$_2$]} resulting from the cleavage of the ephedrine chelate ring at the [P–O] bond, a reaction for which there is precedent.[20] The formation of both compound **2** and the δ 164.3 species is rapid. Thus, when LiN(SiMe$_3$)$_2$ was added to a solution of chloride **1** maintained at −78 °C in THF solvent and the mixture allowed to warm to −50 °C and analysed after *ca.* 2 min by $^{31}$P{$^1$H} NMR spectroscopy at this temperature, it was observed that chloride **1** had been completely consumed and two products were observed, at δ 163.4 and δ 146.8 in the approximate ratio 1:3 respectively, which correspond to {Li}{[(1*R*,2*S*)-*N*-ephedrine]PCl[N(SiMe$_3$)$_2$]} and compound **2**, respectively. Warming to ambient temperature and stirring for 1 h, as in the synthesis of compound **2**, resulted in no significant observable changes other than slight shifts of the δ values to 165.4 and 148.3 respectively, suggesting that the compound at δ 163.4 is indeed a by-product rather than an intermediate. Removal of the THF solvent and treatment of the crude mixture with pentane resulted in selective extraction of compound **2**. Thus, formation of compound **2** is extremely rapid and appears to afford only the single epimer of compound **2** at low temperature which also appears to be the only epimer at room temperature.

Spectroscopic analysis is consistent with the formulation of compound **2** as shown in Scheme 2; in particular, high-resolution mass spectrometry locates the parent ion at *m*/*z* 354.171 722 (Calc. 354.171 259) and the $^{31}$P{$^1$H} NMR




**Scheme 2** *Reagents and conditions:* i, LiN(SiMe$_3$)$_2$ (1 mol equiv.), THF, −78 °C; followed by 1 h at room temp. (83%); ii, sulfur (1 mol equiv.), toluene, 30 min at room temp. (87%); iii, exposure to moist air, 14 days at room temp.



**2a** **2b**

**Fig. 1** Constitutional isomers of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN-$(SiMe_3)_2$ **2**

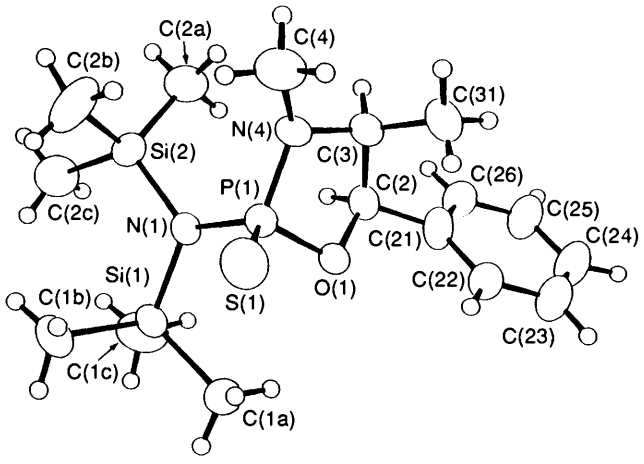


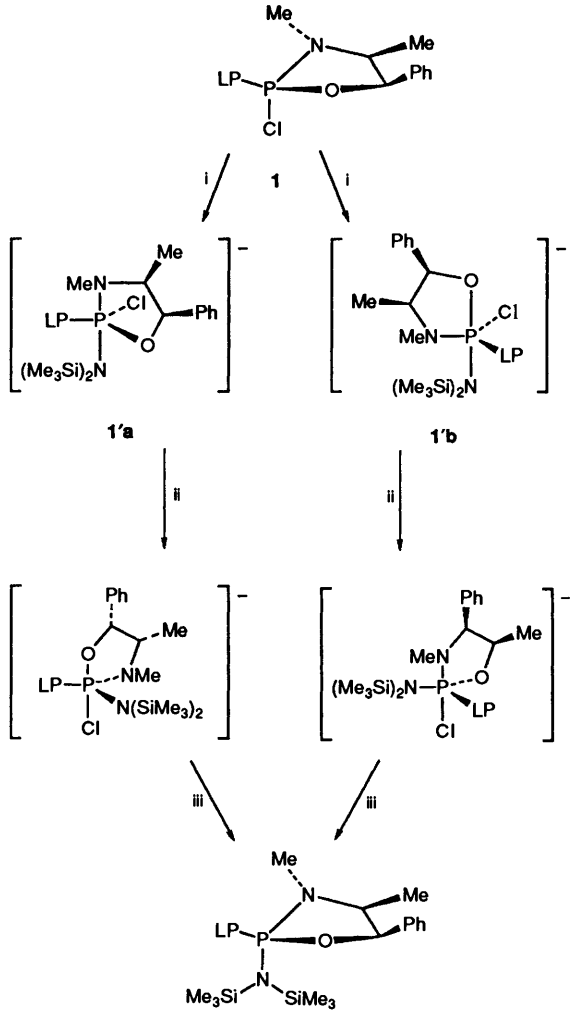
**Fig. 2** Molecular structure of $R_P$-[(1*R*,2*S*)-*O*,*N*-ephedrine]P(S)N-$(SiMe_3)_2$ **3**. Selected distances (Å) and angles (°). S(1)–P(1) 1.931(2), N(1)–P(1) 1.654(3), N(4)–P(1) 1.661(3), O(1)–P(1) 1.604(2); P(1)–N(1)–Si(1) 116.86(14), P(1)–N(1)–Si(2) 119.91(14), Si(1)–N(1)–Si(2) 120.80(14), C(4)–N(4)–P(1) 122.5(3), C(3)–N(4)–P(1) 111.4(2), C(4)–N(4)–C(3) 117.8(3).

resonance at $\delta$ 148.2 is in a frequency range more consistent with phosphorus(III) rather than phosphorus(V) and hence supportive of phosphorodiamidite structure **2a** rather than the imidophosphoroamidate isomer **2b** (Fig. 1).

NMR spectroscopic analysis of compound **2** reveals that a single epimer accounts for at least 98% of the product. Subsequent treatment with basic alumina results in a product of isomeric purity > 98%, which has been used for all subsequent synthetic studies. Based on the above mentioned observation of overall retention of configuration at phosphorus[20,21] in nucleophilic substitutions involving chloride **1**, we envisaged that the observed epimer of compound **2** had the $S_P$ configuration. $^1$H NMR spectroscopic data were consistent with this assignment but in the absence of direct crystallographic studies on chloride **1** itself we preferred to support our assignments with an X-ray study on a derivative formed by addition of sulfur to compound **2**, a reaction which has been shown to proceed with retention of configuration at phosphorus.[22]

The sulfur adduct [(1*R*,2*S*)-*O*,*N*-ephedrine]P(S)[$N(SiMe_3)_2$] **3** was isolated as crystals and characterised by spectroscopic and single-crystal X-ray techniques. NMR spectroscopy revealed a single epimer to be present, and analysis of coupling constants[21] in the $^1$H NMR spectrum is more supportive of an $R_P$ configuration than the alternative $S_P$ (*vide infra*). Subsequently, the absolute configuration at phosphorus was confirmed as $R_P$ (Fig. 2) by single-crystal X-ray diffraction which, in turn, suggests that the configuration of substrate **2** is $S_P$. The same configuration has been proposed for related compounds [(1*R*,2*S*)-*O*,*N*-*N*-Me-ephedrine]$PNMe_2$ and [(1*R*,2*S*)-*O*,*N*-*N*-Pr$^i$-ephedrine]$PNMe_2$.[23]

Overall retention of configuration at phosphorus in the conversion of chloride **1** into compound **2** may be rationalised by a reaction sequence which involves (i) attack of $[N(SiMe_3)_2]^-$ on the electrophilic phosphorus atom of



**Scheme 3** Possible mechanisms for the conversion of chloride **1** into silylamine **2**. *Reagents/reactions:* i, $LiN(SiMe_3)_2$; ii, pseudorotation about the phosphorus lone-pair (LP); iii, extrusion of chloride.

chloride **1** to afford a five-coordinate intermediate **1′** in which $[N(SiMe_3)_2]^-$ occupies an axial position (the more favoured site for an incoming reagent) followed by (ii) pseudorotation of **1′** to place chlorine in an axial site (the more favoured site for a leaving group) and termination by (iii) chloride elimination from intermediate **1′** to afford product **2** (Scheme 3). Since (a) the five-membered ephedrine chelate ring is more likely to span axial-equatorial rather than di-equatorial positions and (b) consideration of electronic repulsions between bond pairs and lone pairs on the basis of simple valence shell electron pair repulsion (VSEPR) theory would likely place the phosphorus lone pair in an equatorial position, we envisage that the most favourable and accessible five-coordinate intermediates may be **1′a** and **1′b** respectively, which are formed by direct approach of $[N(SiMe_3)_2]^-$ along a vector *anti* to either the ephedrine nitrogen or oxygen atoms (Scheme 3). In order to place the chlorine atom in an axial position prior to displacement, intermediates **1′a** and **1′b** must presumably undergo pseudorotations, possibly of the Berry type, about either the lone pair or chelate oxygen atom in the case of **1′a**, or the lone pair or the chelate nitrogen atom in the case of **1′b**. Although it is not possible for us to distinguish, *a priori*, between these pseudorotation pathways, the fact that pseudorotation about the lone pair leads to an axial-equatorial chelate ring whereas pseudorotation about either the chelate oxygen or nitrogen atom results in di-equatorial chelate rings may suggest that the

lone-pair pseudorotation pathway has the lower energy barrier. In any case, pseudorotation about either lone pair, oxygen atom or nitrogen atom, followed by elimination of chloride ion, leads to overall *retention* of configuration at phosphorus as observed experimentally. A similar sequence of events was postulated to explain retention of configuration in the metathetical reactions of [(1*R*,2*S*)-*O*,*N*-ephedrine]P(O)Cl.[24] An alternative scenario involves displacement of either the oxygen or the nitrogen arm of the ephedrine ring directly from intermediate **1'a** and **1'b** followed by re-complexation in a position *trans* to chlorine. Indeed, there is precedent for such ring cleavage in oxazaphospholidine systems[25,26] and we have noted above how a by-product in the synthesis of compound **2** may have resulted from a similar ring fission.

The room-temperature $^1$H NMR spectrum of compound **2** reveals a single resonance for the $SiMe_3$ hydrogens, consistent with both (i) the $N(SiMe_3)_2$ nitrogen atom having a trigonal planar geometry and (ii) rapid rotation (on the NMR timescale) about the P–$N(SiMe_3)_2$ bond. Indeed, planarity of the $N(SiMe_3)_2$ nitrogen atom is evident from the crystal structure of compound **3**; the sum of the angles around N-1 is ~358°. Cooling of a $C_7D_8$ solution of compound **2** to −90 °C results in broadening but not de-coalescence of the $SiMe_3$ resonances in the $^1H\{^{31}P\}$ spectrum, suggesting that although P–N bond rotation may be slowing it remains significantly rapid on the NMR timescale. Low-temperature $^1H\{^{31}P\}$ NMR studies on compound **3** reveal a similar scenario in which broadening ($\Delta_{1/2}$ ~7 Hz at −100 °C) but not de-coalescence of the $SiMe_3$ resonances is observed at −100 °C.

In common with other silylated esters [(1*R*,2*S*)-*O*,*N*-ephedrine]$POSiR_3$, compound **2** hydrolyses upon exposure to moist air over *ca.* 16 h at room temperature, necessitating the use of dry, deoxygenated solvents for all subsequent chemistry.[13]

*Chemical Stability of* [(1R,2S)-O,N-*Ephedrine*]*P*(*S*)[*N*-(*SiMe*$_3$)$_2$] **3**.—When a solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]P(S)[$N(SiMe_3)_2$] **3** in $C_6D_6$ solution is exposed to moist air for several days, a clean conversion into another compound, **4**, is observed to take place by $^{31}P\{^1H\}$ NMR spectroscopy. The resonance at $\delta$ 86.6 due to substrate **3** diminishes gradually to be replaced by a single resonance at $\delta$ 79.2 due to the new product **4**, the conversion proceeding to completion over the course of 14 days at room temperature.

Comparison of the NMR spectral data for compounds **3** and **4** suggests that the two species are very similar; in particular, the $^{31}$P NMR resonance of compound **4** suggests that the sulfur atom is retained, and this is supported by both mass spectrometry and elemental analysis. The combined data are consistent with compound **4** being [(1*R*,2*S*)-*O*,*N*-ephedrine]P(S)NH($SiMe_3$), resulting from replacement of one of the amido-bound trimethylsilyl groups with a hydrogen, presumably by hydrolysis of substrate **3** (Scheme 2). In particular, elemental analysis is consistent with this composition for compound **4**, and $^1$H NMR spectroscopy locates the NH hydrogen at $\delta_H$ 2.66 as a slightly broadened doublet coupling to phosphorus (7.3 Hz).

Removal of a trialkylsilyl group by hydrolysis is commonly proposed to proceed by nucleophilic attack of water on the silicon atom, the $S_N2$-Si mechanism,[27] and we envisage that a similar process may be occurring here. This process would not be expected to affect the configuration at phosphorus: however, the $^1$H NMR spectrum of compound **4** suggested that the configuration at phosphorus was *opposite* to that in substrate **3**. Specifically, the observation that the $^3J_{PH}$ coupling between phosphorus and the PhC*H*O ephedrine hydrogen, which is 5.8 Hz in compound **3**, is much smaller in compound **4** (0.9 Hz), is consistent with a geometry in which the P=X (X = O, S) function is *anti* to the ephedrine ring C-phenyl and C-methyl substituents,[21] the opposite of that found in compound **3**. Consequently we considered it desirable to perform an X-ray diffraction study on monosilane **4** to probe this apparent anomaly. The result, as illustrated in Fig. 3, reveals that *the configuration at phosphorus is the same as that in compound* **3**. Consequently, it appears that the NMR criterion of $^3J_{PH}$ coupling used above as a method of determining the configuration at phosphorus in 1,3,2-oxazaphospholidine systems is not infallible[13] and wherever possible should be combined with other, more direct, probes of molecular structure such as X-ray diffraction. This feature of oxazaphospholidine systems is discussed in more detail in a later section.

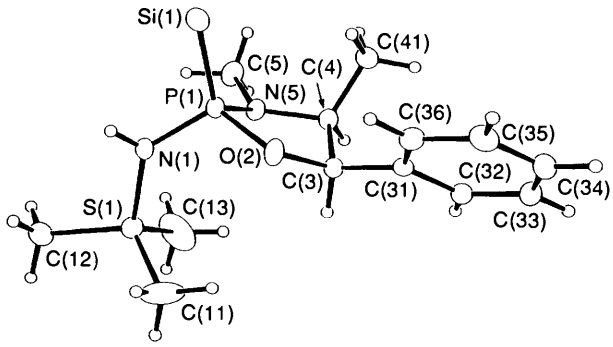
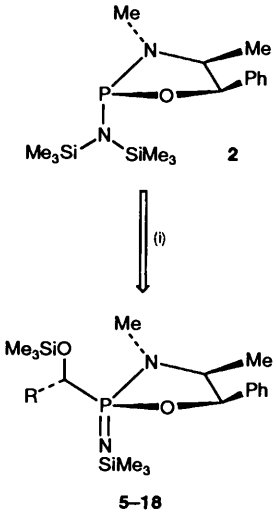



**Fig. 3** Molecular structure of $S_P$-[(1*R*,2*S*)-*O*,*N*-ephedrine]P(S)NH-($SiMe_3$) **4**. Selected distances (Å) and angles (°). S(1)–P(1) 1.9485(6), N(1)–P(1) 1.627(2), N(5)–P(1) 1.6598(14), O(2)–P(1) 1.6085(13); P(1)–N(1)–Si(1) 131.14(10), C(4)–N(5)–P(1) 110.52(11), C(5)–N(5)–P(1) 120.86(12), C(4)–N(5)–C(5) 119.51(14).

*Reactions of the* [$1^N$,$3^E$]-*Bifunctional Phosphorodiamidite* **2** *with Aldehydes*.—The phosphorodiamidite **2** reacts with various aldehydes in an Abramov reaction according to Scheme 1b, to afford diastereoisomeric α-siloxyimidophosphonate esters (R = Ph **5**, Bu$^t$ **6**, Pr **7**, Bu **8**, 2-$C_{10}H_7$ **9**, 1-$C_{10}H_7$ **10**, *o*-$Ph_2PC_6H_4$ **11**, *p*-$NCC_6H_4$ **12**, *p*-$O_2NC_6H_4$ **13**, *p*-$ClC_6H_4$ **14**, *p*-$MeC_6H_4$ **15**, *p*-$MeOC_6H_4$ **16**, *o*-$O_2NC_6H_4$ **17**, *o*-$BrC_6H_4$ **18**) in which both




| R | d.s. (%)[a] | Yield (%) |
|---|---|---|
| Ph **5** | 92 | 83 |
| Bu$^t$ **6** | 96 | 84 |
| Pr **7** | 80 | *b* |
| Bu **8** | 81 | *b* |
| 2-$C_{10}H_7$ **9** | 91 | 86 |
| 1-$C_{10}H_7$ **10** | 66 | 62[c] |
| *o*-$Ph_2PC_6H_4$ **11** | 80 | 76 |
| *p*-$NCC_6H_4$ **12** | 91 | 93 |
| *p*-$O_2NC_6H_4$ **13** | 90 | 97 |
| *p*-$ClC_6H_4$ **14** | 90 | 97 |
| *p*-$MeC_6H_4$ **15** | 91 | 96 |
| *p*-$MeOC_6H_4$ **16** | 91 | 97 |
| *o*-$O_2NC_6H_4$ **17** | 53 | 94 |
| *o*-$BrC_6H_4$ **18** | 54 | 95 |

**Scheme 4** The Abramov phosphonylation of aldehydes *via* chiral phosphorodiamidite **2**. *Reagent:* i, RCHO (R = alkyl, aryl), toluene or pentane, 3–96 h (the conformations of the oxazaphospholidine rings shown are not necessarily the lowest energy forms but are shown as non-planar in accord with the X-ray structures of compounds **9** and **11**). [a] Diastereoselectivities (d.s.) determined by integration of appropriate resonances in the $^1$H (400 MHz) and $^{31}P\{^1H\}$ (36.4 MHz) NMR spectra of pre-purified reaction mixtures. [b] Not isolated. [c] Determined by NMR spectroscopy.

the phosphorus atoms and the carbon atoms alpha (Cα) to phosphorus are stereogenic centres (Scheme 4). The presence of the chiral auxiliary ephedrine leads to stereoselective phosphonylation of the aldehyde substrates as revealed by NMR spectroscopy. In each of the above cases, one of the four possible diastereoisomers dominates the crude mixture (Scheme 4).

The reactions proceed smoothly in either pentane or toluene solvent at ambient temperature over the course of minutes (for aryl aldehydes) to several days (alkyl aldehydes and *p*-$MeOC_6H_4CHO$). The composition of the products is confirmed by elemental analysis and/or high-resolution mass spectrometry whilst their constitution as α-siloxyimidophosphonate esters is supported by NMR spectroscopy. In particular, the presence of a direct phosphorus–carbon bond is supported by the observation of large couplings, in the range 175–155 Hz, between the phosphorus and alpha carbon atoms in the $^{13}C$ NMR spectra characteristic of single-bond couplings to phosphorus(v). In addition, two separate resonances are observed in both the $^{1}H$ and $^{13}C$ NMR spectra for the two different trimethylsilyl functions. Moreover, the carbon atoms of one of these functions consistently shows a small coupling of 3.6–3.9 Hz to phosphorus; we assign these as the P=$NSiMe_3$ groups.[28] For each of the siloxy products **5**–**18**, the low-frequency phosphorus resonance ($\delta_C$ 17–28 ppm) is consistent with a four-co-ordinate phosphorus(v) environment.[29] In the case of compound **11**, it is possible to resolve $^{4}J_{PP}$ coupling of 3 Hz between the two chemically distinct phosphorus atoms.

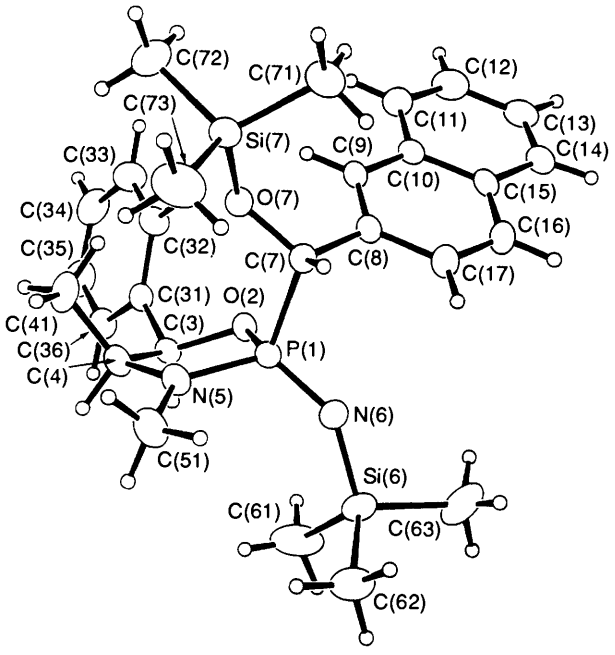



**Fig. 4** Structure of ($S_P$, $S_C$)-{(1*R*,2*S*)-*O*,*N*-ephedrine}P($NSiMe_3$)CH-2-$C_{10}H_7(OSiMe_3)$ **9**. Selected distances (Å) and angles (°): P(1)–N(6) 1.525(3), P(1)–C(7) 1.841(3), P(1)–N(5) 1.637(3), P(1)–O(2) 1.606(2); P(1)–N(6)–Si(6) 140.8(2), C(7)–O(7)–Si(7) 122.2(2), C(51)–N(5)–P(1) 125.4(2), C(4)–N(5)–P(1) 114.9(2), C(51)–N(5)–C(4) 119.4(3).

However, it is possible that the situation could be more complex since there is the possibility of (i) isomerism about the

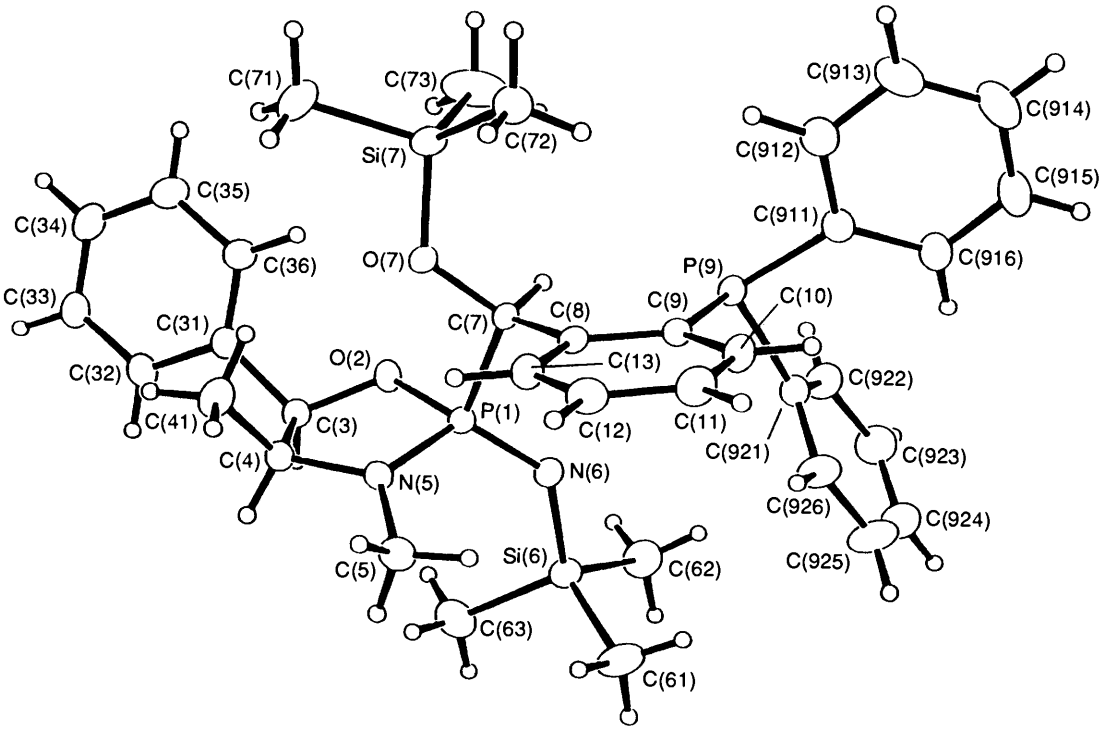



**Fig. 5** Structure of ($S_P$, $R_C$)-{(1*R*,2*S*)-*O*,*N*-ephedrine}P($NSiMe_3$)$CHC_6H_4$-2-$PPh_2(OSiMe_3)$ **11**. Selected distances (Å) and angles (°): P(1)–N(6) 1.526(2), P(1)–C(7) 1.835(2), P(1)–N(5) 1.653(2), P(1)–O(2) 1.609(2); P(1)–N(6)–Si(6) 134.9(2), C(7)–O(7)–Si(7) 123.4(2), C(5)–N(5)–P(1) 124.9(2), C(4)–N(5)–P(1) 114.3(2), C(5)–N(5)–C(4) 119.7(2).

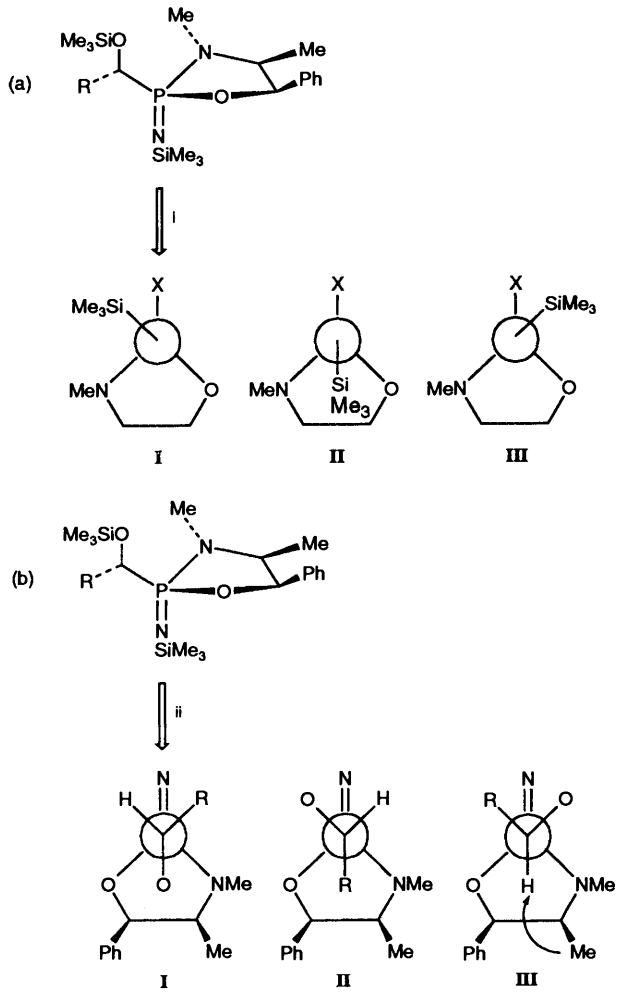



**Fig. 6** (i) Projection down the N=P bond vector. (ii) Projection down the $C^{\alpha}$–P bond; the trimethylsilyl groups on nitrogen and oxygen have been omitted for clarity. The configuration shown is that for compound **11**. In conformation **III**, two sites displaying mutual NOE effects are indicated.

$P{=}NSiMe_3$ function and (ii) isomerism caused by hindered rotation about the P–$C^{\alpha}$ bond. These could lead to several different diastereoisomers being formed, such as those illustrated in Fig. 6.

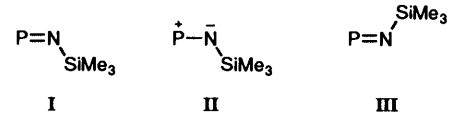
Isomerisation about the $P{=}NSiMe_3$ function is a possibility when the P–N–Si angle deviates significantly from 180°. Since this angle is 140.8(2) and 134.9(2)° in compounds **9** and **11**, respectively, isomerism may be possible. However, it is difficult to provide detailed comparisons since, although silylimidophosphoranes are well known,[30] few structural data are available.[31a] However, both the above angles are significantly less acute than the 119° reported for $Ph_2FP{=}NMe$,[31b] which may suggest that the nitrogen hybridisation tends more towards sp in compounds **9** and **11** than in $Ph_2FP{=}NMe$ which more closely approximates $sp^2$. To address these possibilities of isomerism we have examined an achiral analogue of esters **5**–**18**, racemic $\{N,N'\text{-}(CH_2NMe)_2\}P(NSiMe_3)CHPh(OSiMe_3)$, prepared readily by reaction of $\{N,N'\text{-}(CH_2NMe)_2\}PN(SiMe_3)_2$ with PhCHO.[16] This ester is synthesized as a *single* species (by NMR spectroscopy), suggesting that either the configurations about the $P{=}NSiMe_3$ and P–$C^{\alpha}$ functions are locked or they are fluxional on the NMR timescale. Variable-temperature studies reveal that the $^1H$ NMR spectrum is invariant between +90 and −50 °C. Consequently, there is *no evidence in this system for observable stereoisomers in solution between these temperature limits*. Subsequently, variable-temperature studies on ($S_P$, $S_C$)-**9** in $C_7D_8$ reveal no change in the $^1H$ NMR spectrum between −90 and +50 °C. Moreover, the observation of a nuclear Overhauser enhancement (NOE) of ~1% between the $Me_3C$ and $P{=}NSiMe_3$, hydrogens in compound **6** is more consistent with a $P{=}NSiMe_3$ conformation which is not fixed as in the molecular structures of compounds **9** and **11** (Fig. 4 and 5), but may imply some degree of rotation about the P=N bond possibly between forms **I** and **III** in Fig. 6 or fluxionality between bent and linear forms of the $P{=}NSiMe_3$ group, a process which has been shown to operate in related M=NR systems.[32] Presumably, the degree of resistance to rotation about the phosphorus–nitrogen bond will also be determined, in part, by the nature of the substituents on the alpha carbon atom.†

In addressing the question of rotation about the P–$C^{\alpha}$ bond we note that the solid-state geometries of both ($S_P$, $S_C$)-**9** and ($S_P$, $R_C$)-**11** contain *anti-periplanar* $Me_3SiO$ and $Me_3SiN$ functions. Heating of solutions of either ($S_P$, $S_C$)-**9** or ($S_P$, $R_C$)-**11** to 80 °C results in extrusion of aldehyde and epimerisation at $C^{\alpha}$ over the course of several hours, a process that would seem to warrant a transition state with a *syn-periplanar* arrangement of $Me_3SiO$ and $Me_3SiN$ groups (*vide infra*). Consequently, we believe that a certain degree of rotation about the P–$C^{\alpha}$ bond is possible under these conditions. However, as noted above, the $^1H$ NMR spectrum of ($S_P$, $S_C$)-**9** in $C_7D_8$ is invarient between −90 and +50 °C which may be consistent with either (i) rapid rotation on the NMR timescale at all temperatures studied, (ii) a fixed conformation at all temperatures studied or (iii) a conformationally mobile system in which one of the three conformations (**I**, **II**, **III** in Fig. 6) is favoured exclusively at low temperatures (presumably **III**). Since variable-temperature studies were uninformative, a different approach was required.

Examination of the $^1H$ NMR spectrum of a $C_7D_8$ solution of ($S_P$, $S_C$)-**11** at room temperature reveals an NOE of ~2% between the *Me*CHN and the PC*H*Ar resonances (in both directions) which is *inconsistent* with the fixed conformation about the P–$C^{\alpha}$ bond as observed in the solid state and illustrated in projection form in Fig. 6b(**I**). Therefore, since significant NOE effects between these two sets of resonances would be anticipated only in conformation 6b(**III**), this result suggests that, at room temperature, conformation 6b(**III**) is partially populated. Further support for this room-temperature fluxionality of the P–$C^{\alpha}$ bond comes from the observation that the above NOE effect between *Me*CHN and PC*H*Ar disappears at 223 K (−50 °C) presumably as the population of conformer 6b(**III**) diminishes in favour of the preferred conformer 6b(**I**), as observed in the solid state. Consequently, we presume that at least some degree of rotation about the P–$C^{\alpha}$ bond is feasible at room temperature, resulting in partial population of conformer **III** in Fig. 6b.

*Stereochemical Assignments in Oxazaphospholidine Systems Based on NMR Measurements*.—It has been noted on several

† Rotation about the P=NR bond may be facilitated by increasing the contribution of canonical form II as shown below. This will be most likely if the nitrogen can off-load electron density to the R function. Indeed, when R = $SiMe_3$, this should be possible since silicon is well known to stabilise α-carbanions by interaction of the carbon lone-pair orbital with (i) an Si–C σ* orbital and/or silicon d-orbitals.[33] A similar type of interaction in the $P{=}NSiMe_3$ system could lead to simple rotation about the P=N bond.



occasions[13,21] that the geometry at the phosphorus atom in oxazaphospholidine systems of the form [*N*,*O*-ephedrine]-P(=X)R (X = O, S; R = alkyl, aryl, alkoxy) may be determined by examination of the $^3J_{PH}$ coupling between phosphorus and the C-5 hydrogen (Fig. 7a). For systems in which the X function is *cis* to 5-H, $^3J_{PH}$ is normally very small (< ~1 Hz), whereas for systems with the X function *trans* to 5-H, $^3J_{PH}$ is normally within the range 3–6.5 Hz.[21] This result seems to correlate with a Karplus-type relationship involving the P–O–C(5)–H torsion angle ($\theta$) such that those compounds for which $\theta$ approaches 90°

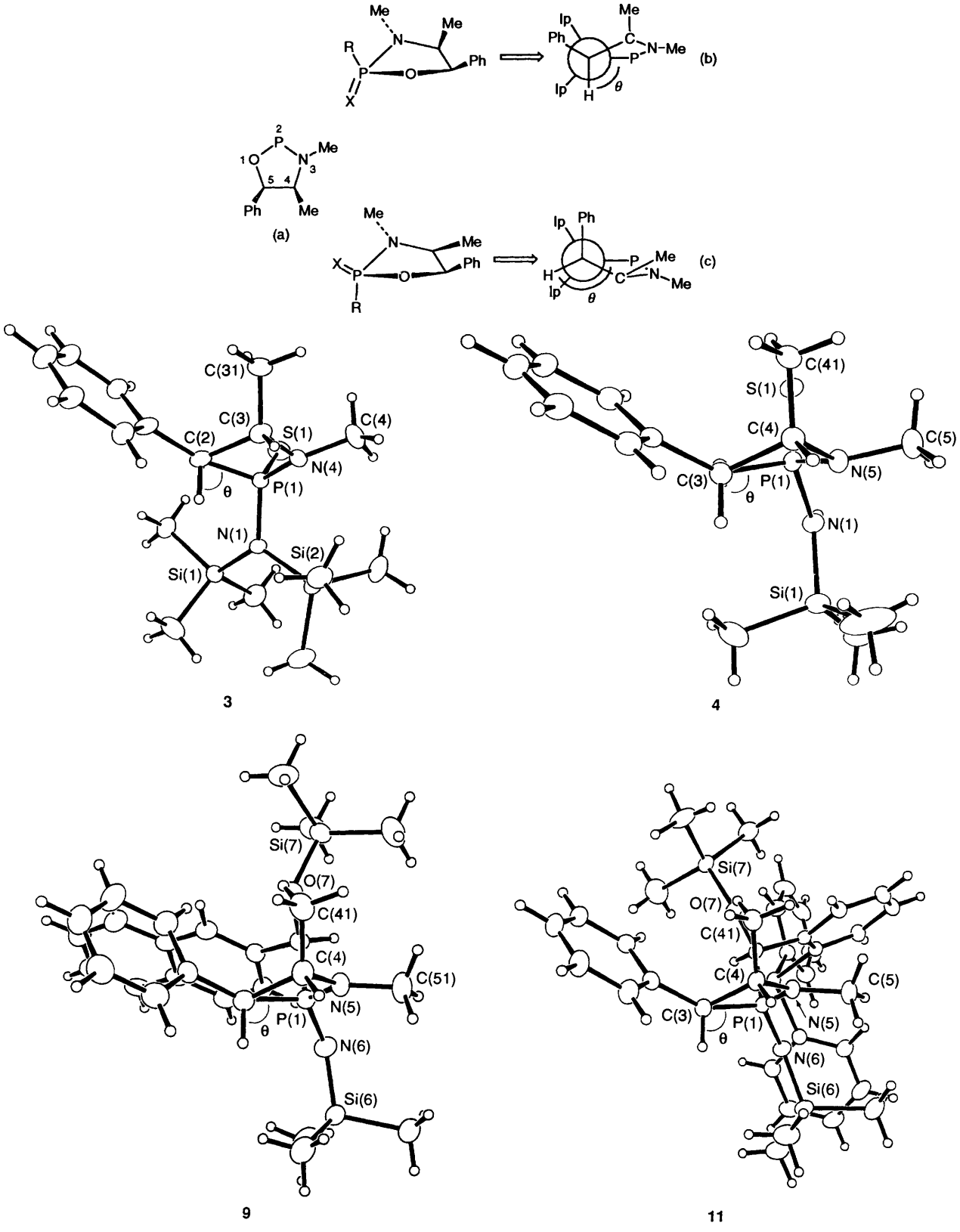
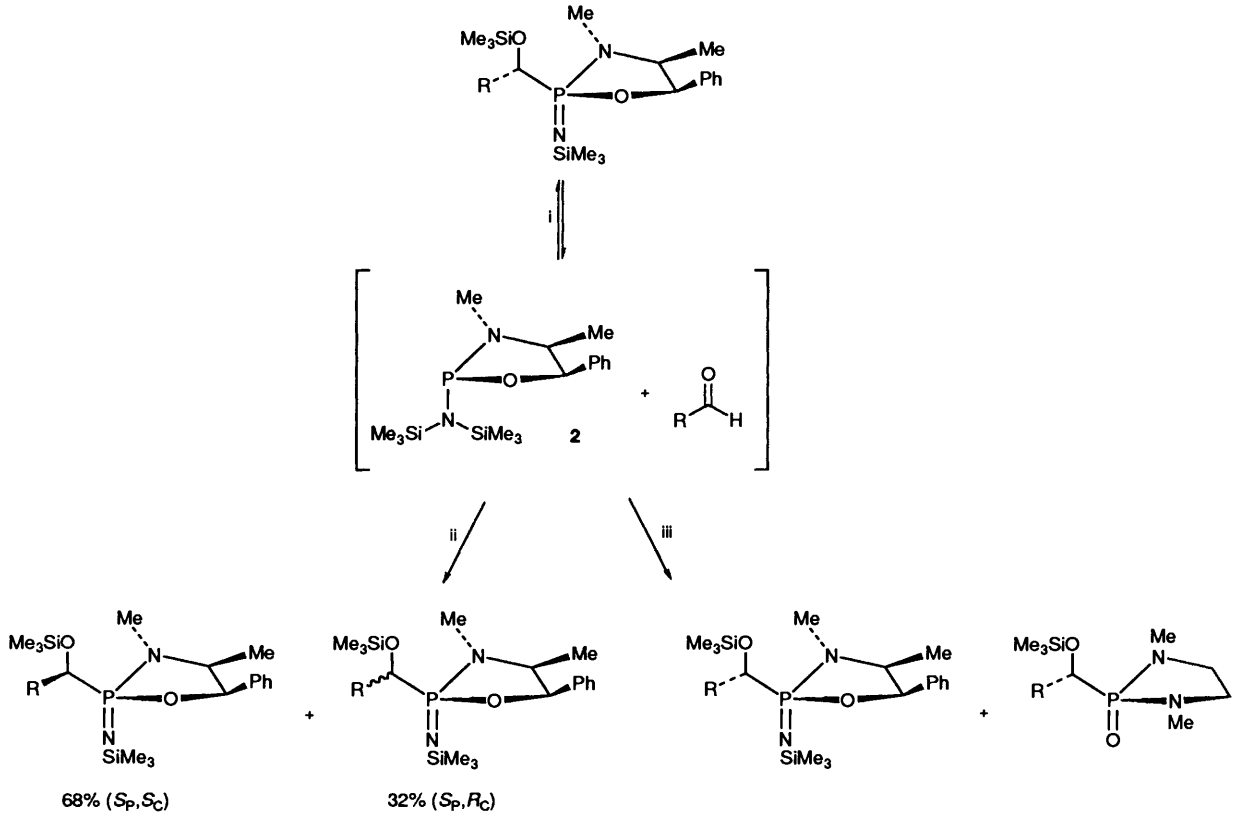



**Fig. 7** Structures of compounds **3**, **4**, **9** and **11** showing P–O–C(5)–H dihedral angle $\theta$. (a) Numbering scheme in oxazaphospholidines. Perspective views of oxazaphospholidines showing proposed conformations with (b) the X and 5-H functions *cis* and (b) the X and 5-H functions *trans*. lp Represents a lone pair.

have $^3J_{PH}$ < ~1 Hz. It has further been shown, from extensive X-ray diffraction studies,[21] that the implicated torsional angle is influenced by whether the C(5)-Ph substituent occupies a pseudo-equatorial or a pseudo-axial position within a C-4 or C-5 envelope conformation which, in turn, is determined by the severity of steric interactions between the C-5 substituents and the groups on phosphorus X and R. The implication is, when R is more sterically demanding than X, that (i) when the X function is *cis* to 5-H, then 5-Ph is pseudo-equatorial in order to reduce steric interactions with R, the P–O–C(5)–H torsion angle approaches 90°, and $^3J_{PH}$ is small whereas (ii) when X is *trans* to 5-H, then 5-Ph is pseudo-axial, the P–O–C(5)–H torsion angle deviates significantly from 90°, and $^3J_{PH}$ increases (Fig. 7). On the basis of this NMR criterion, we propose that the α-siloxyimidophosphonate esters **5**–**18** possess the $S_P$ configuration owing to their small $^3J_{PH}$ coupling, and indeed this geometry has been confirmed for compounds **9** and **11** by X-ray diffraction which reveals P–O–C(5)–H torsion angles of −89.46(14)° and −92.6(1)°, respectively. Similarly, the configuration of the phosphorus atom in compound **3** is known to be *R* by X-ray [P–O–C(5)–H torsion angle of −74.25(14)°] and this is consistent with the observed larger $^3J_{PH}$ value of 5.8 Hz as the dihedral θ deviates significantly from 90°. However, using the above $^3J_{PH}$ criterion, the configuration of the phosphorus atom in compound **4** is more consistent with *S* rather than *R* ($^3J_{PH}$ 0.9 Hz) yet X-ray diffraction reveals compound **4** to possess the $R_P$ configuration. The small coupling may be connected with the P–O–C(5)–H torsion angle of −99.26(9)° which is significantly closer to 90° than that in compound **3** and which would seem to suggest that reducing the steric demand of the amido function by replacing one trimethylsilyl group by hydrogen allows the oxazaphospholidine ring conformation to relax slightly. However, in each of the compounds **3**, **4**, **9** and **11** the phenyl ring on C-5 appears to adopt an equatorial position wherein the resultant P–O–C(5)–H torsion angles for compounds **9** and **11** are close to 90° and consequently we equate the small $^3J_{PH}$-value with an $S_P$ configuration consistent with assignments in related systems.[21]

Consequently, configuration assignments based on comparisons of $^3J_{PH}$ coupling constants in oxazaphospholidines should be treated with caution until supported by X-ray diffraction studies. We envisage that the most reliable results will be obtained within closely related families of compounds in which there is a significant and obvious steric differential between the X and R functions.[21]

*Mechanism and Stereocontrol in the Asymmetric Abramov Reaction.—Configurational stability of α-siloxyimidophosphonate esters.* Our investigations suggest that, under the ambient conditions reported here, the Abramov reaction is subject to *kinetic* control. Thus, a pure sample of ($S_P$, $S_C$)-[(1*R*,2*S*)-*O*,*N*-ephedrine]P(NSiMe$_3$)CH-2-C$_{10}$H$_7$(OSiMe$_3$) **9** is stable to epimerisation at both carbon and phosphorus in $C_6D_6$ solution at room temperature under nitrogen. However, upon heating a toluene solution of pure ($S_P$, $S_C$)-**9** to 80 °C for *ca.* 18 h the initially isomerically pure substrate **9** is converted into a mixture of ($S_P$, $S_C$)-**9** and a second isomer ($\delta_P$ 20.7), in the ratio 68:32 respectively; this second species is the minor isomer observed in the original synthesis of compound **9** and we assign its structure as ($S_P$, $R_C$)-**9**. The failure to observe coupling between the ephedrine hydrogen PhC*H*O and phosphorus atom in this minor component further suggests that the configuration at phosphorus remains *S*. The formation of product ($S_P$, $R_C$)-**9** can best be explained by extrusion of 2-C$_{10}$H$_7$CHO followed by reaction with compound **2** to afford, ultimately, an equilibrium distribution of isomers of **9** (Scheme 5). Continued heating over 4 days results in this second isomer growing in intensity in the mixture which now shows evidence of other products (by $^{31}$P NMR spectroscopy) with phosphorus resonances in the range δ 34–17, presumably due to further




**Scheme 5** 100%-($S_P$, $S_C$) R = 2-naphthyl. *Reagents and conditions:* i, 80 °C, $C_6D_6$; ii, 80 °C, 18 h, 68%-($S_P$, $S_C$), 32%-($S_P$, $R_C$); iii, 80 °C, 2h, [*N*,*N*′-(CH$_2$NMe)$_2$]POSiPh$_3$ (1 mol equiv.).

decomposition and/or rearrangement. Consequently, we have not been able to obtain a value for the equilibrium constant in this system. However, heating of two samples of compound **11** [one comprising 81% ($S_P$, $R_C$) and the other 57% ($S_P$, $R_C$)] at ~75 °C (in $C_6D_6$) for *ca.* 16 h results in conversion of both samples into a mixture with the same composition of 43% ($S_P$, $R_C$) and 57% ($S_P$, $S_C$). Further heating leads to some decomposition but this epimeric ratio is affected only slightly. Consequently, we may approximate an equilibrium constant between ($S_P$, $S_C$) and ($S_P$, $R_C$) epimers for ester **11** of 1.3 at 348 K, which requires the ($S_P$, $S_C$) epimer to be the more stable by ~0.8 kJ mol$^{-1}$.

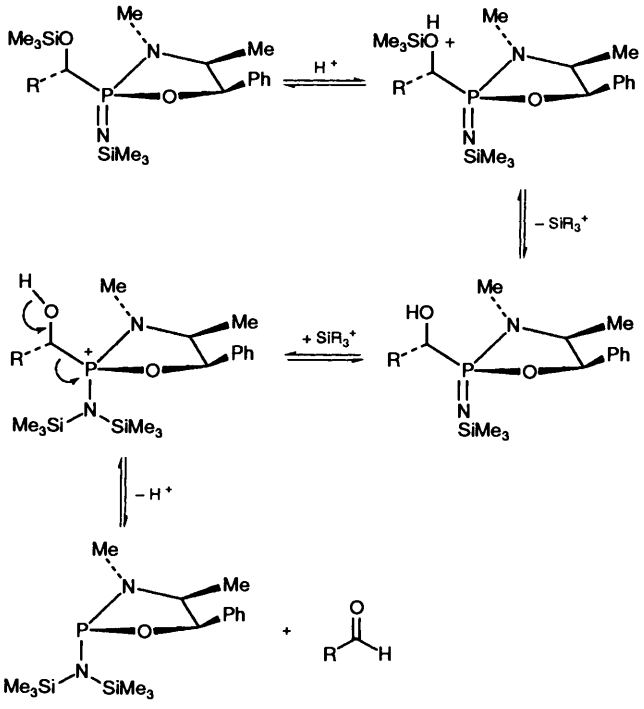
A racemisation mechanism involving reversible aldehyde extrusion is supported further by trapping experiments. At room temperature we were not able to observe the product of crossover in a mixture of ($S_P$, $S_C$)-**9** and {*N*,*N*′-$(CH_2NMe)_2$}-$POSiPh_3$ (2.8:1 molar ratio) in $C_6D_6$ solution over the course of 16 h at room temperature. However, when this mixture was warmed at 80 °C for 2 h, the crossover product {*N*,*N*′-$(CH_2NMe)_2$}P(O)CH-2-$C_{10}H_7$($OSiPh_3$), was observed to form by $^{31}$P NMR spectroscopy with a resonance at $\delta$ 30.0 [identified by comparison with an authentic sample; *cf* {*N*,*N*′-$(CH_2NMe)_2$}P(O)CHPh($OSiPh_3$) has $\delta$ 33.0[14]] which suggests that at elevated temperatures the Abramov reaction may be reversed and that the aldehyde is extruded from the α-siloxyphosphonate esters to be trapped subsequently by a competing phosphonylating agent such as {*N*,*N*′-$(CH_2NMe)_2$}$POSiPh_3$ (Scheme 5).

As a result of our previous demonstration that organophosphorus(III) esters of the form [*N*,*N*′-$(CH_2NMe)_2$]$POSiR_3$ undergo acid-catalysed silyl-group exchange in $CH_2Cl_2$ solvent,[14] all NMR spectra and solution studies on the Abramov reaction reported here have been performed in non-chlorinated solvents to reduce the likelihood of similar trace-acid-catalysed processes. Indeed, control experiments suggested this to be a wise precaution: a $CDCl_3$ solution of compound **11** [comprising 75% ($S_P$, $R_C$)] slowly epimerises over the course of 16 h at room temperature to a mixture comprising 49% ($S_P$, $R_C$). We envisage that the racemisation is catalysed by trace acid, since when the $CDCl_3$ is pre-treated with excess of $NEt_3$ the process is retarded but not stopped completely [mixture contains 69% ($S_P$, $R_C$) after 16 h]. A plausible mechanism for this acid-catalysed conversion is presented in Scheme 6.

It has been reported that the addition of tertiary phosphines to aldehydes, in the presence of hydrohalic acids, affords α-hydroxyphosphonium salts.[34] To test whether trace acid could be influencing our reactions in *non-chlorinated* solvents we performed the Abramov reaction between compound **2** and 2-naphthaldehyde in toluene solvent in the presence of 1 mole equivalent of $NEt_3$. Under these conditions, the diastereoselectivity remains unaltered and the reaction still proceeds to completion within 16 h at room temperature. Thus we believe that trace-acid catalysis is not a significant competing pathway when toluene is used as solvent. A similar result was obtained in related diamine systems.[14]

The above results demonstrate that elimination of aldehyde from the products formed in the Abramov reaction does *not* occur readily under the experimental conditions reported here, but can occur under either (i) more forcing thermal conditions or (ii) trace-acid catalysis. Therefore, the Abramov reaction is subject to *kinetic* control under the ambient, acid-free conditions employed here and in at least one case (compound **11**) it can be demonstrated that the kinetically observed product is different to the thermodynamically favoured isomer.

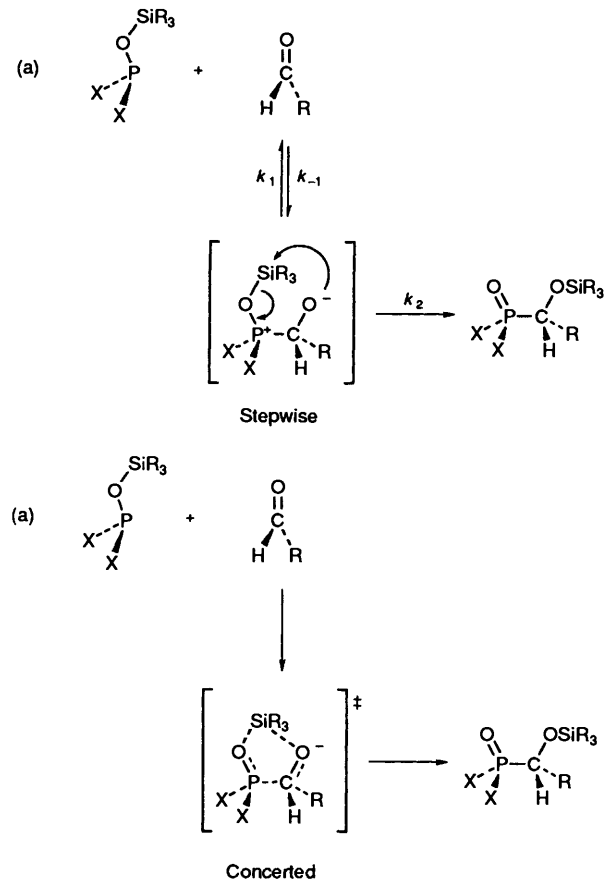
*Intra-* versus *Inter-molecular Silyl-group Transfer in the Abramov Reaction.*—We,[14] and others,[35] have shown through crossover experiments that silyl-group transfer in the Abramov reaction with P–O–$SiR_3$ reagents is an *intramolecular* process. Consistently, silyl-group transfer is also intramolecular when P–N–$SiMe_3$ reagents are used. Thus, an equimolar mixture of compound **2** and {*N*,*N*′-$(CH_2NMe)_2$}$POSiPh_3$ reacts with 2 mole equivalents of PhCHO to afford compound **5** and {*N*,*N*′-$(CH_2NMe)_2$}P(O)CHPh($OSiPh_3$) (between them constituting >95% of the product mixture), the crossover products expected from intramolecular silyl-group transfer. Consequently, the expected products of intermolecular silyl-group transfer, *i.e.* {*N*,*N*′-$(CH_2NMe)_2$}P(O)CHPh($OSiMe_3$) and [(1*R*,2*S*)-*O*,*N*-ephedrine]P($NSiMe_3$)CHPh($OSiPh_3$), can constitute up to ~5% of the product at most.




**Scheme 6** Possible mechanism for acid-catalysed racemisation of α-siloxyimidophosphonate esters

*Mechanistic Investigations of the Abramov Reaction.*—Current opinion suggests that the Abramov reaction may proceed by either (i) a stepwise process (Scheme 7a) *via* an intermediate 1:1 carbonyl adduct or (ii) a concerted process (Scheme 7b).[35] Indeed, although we were unable to observe any intermediates in the Abramov reaction by $^{31}$P NMR spectroscopy at room temperature, there is precedent for highly reactive intermediates related to those expected in the stepwise Abramov reaction. Thus, 1:1 carbonyl adducts formed in the reactions of aldehydes with organophosphorus(III) esters can be trapped with suitable reagents such as HX or $Me_3SiCl$.[33,34]

If an intermediate is produced in the Abramov reaction there are several possibilities as to its structure; some of the more reasonable ones are sketched in Fig. 8 where the sites of carbonyl attachment involve interactions of the carbonyl substrate with phosphorus (a and b), silicon (c) or both (d). In cases where the triorganosilyl group is replaced by a metal such as the systems reported by Shibuya[18] and Spilling[15] it is suggested that initial coordination of the carbonyl oxygen terminus to the metal is required to activate the carbonyl carbon terminus to nucleophilic attack. Indeed, this pre-coordination and activation step is supported by Hammett analyses which reveal rate enhancements as the substituents attached to the carbonyl group become increasingly electron-donating.[18] In an attempt to probe the possibility of carbonyl pre-coordination to silicon we investigated the effects of adding $Ph_2C{=}O$ to a




**Scheme 7** Proposed mechanisms of the Abramov reaction[32]

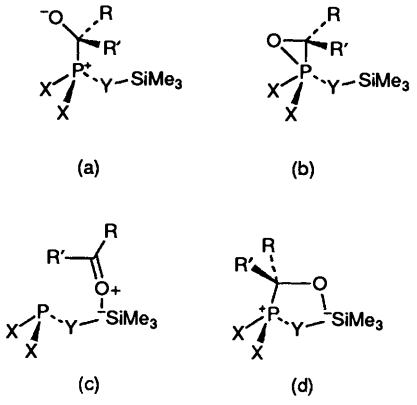



**Fig. 8** Plausible intermediates in the stepwise Abramov reaction

toluene solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]P[N(SiMe$_3$)$_2$] **2** *via* $^{29}$Si{$^1$H} NMR spectroscopy. Benzophenone was chosen because it was shown by $^{31}$P NMR that this substrate was not phosphonylated at room temperature by compound **2** (at least over 48 h) presumably suggesting that any interaction between phosphorus and carbonyl carbon is negligible. However, interaction between the oxygen atom of benzophenone and the silicon atoms should not be precluded and would, we envisaged, be revealed by changes in the $\delta_{Si}$ and $^2J_{PSi}$ parameters for compound **2**. The $^{29}$Si{$^1$H} NMR spectrum of pure compound **2** (1 mol dm$^{-3}$ in toluene, referenced to $\delta$ SiMe$_4$ = 0) revealed a single doublet resonance at $\delta$ 2.8 with $^2J_{PSi}$ 10 Hz [*cf.* $\delta$ 2.37 for N(SiMe)$_3$ and typical $^2J_{PSi}$ values are in the range 1–27 Hz[36]), as expected on the basis of rapid rotation about the [P–N(SiMe$_3$)$_2$] bond. Upon treatment with Ph$_2$C=O at room temperature (1 mole equivalent), both the $\delta_{Si}$ and $^2J_{PSi}$ parameters were *unaffected* after at least 5 days, suggesting that intermediates of the type (c) and (d) involving pre-coordination of the carbonyl to silicon are not formed to any appreciable extent in this system. Subsequently, qualitative Hammett analysis supports this conclusion (*vide infra*). At this stage we cannot differentiate between (a) and (b) but the commonly favoured intermediate is of the type (a).[9,35]

A qualitative analysis of the relative reactivities of several *para*-substituted benzaldehydes with compound **2** reveals that the most reactive aldehydes are those with *electron-withdrawing* substituents, the opposite trend to that reported for metallophosphite compounds for which pre-coordination of the carbonyl to the metal occurs prior to P–C bond formation.[18] In our system the qualitative order of reactivity is *p*-O$_2$NC$_6$H$_4$CHO (< 30 min, $\sigma_X$ +0.78) = *p*-NCC$_6$H$_4$CHO (< 30 min, $\sigma_X$ +0.66) > *p*-ClC$_6$H$_4$CHO (< 4 h, $\sigma_X$, +0.23) = C$_6$H$_5$CHO (< 4 h, $\sigma_X$ 0) > *p*-MeC$_6$H$_4$CHO (*ca.* 18 h, $\sigma_X$ −0.17) > *p*-MeOC$_6$H$_4$CHO (*ca.* 48 h, $\sigma_X$ −0.27), where approximate times required for completion of a 1 : 1 reaction employing a 0.25 mol dm$^{-3}$ solution of compound **2** at room temperature and the Hammett $\sigma_X$ substituent parameters are given in parentheses.[37] This is the same relative order as that found in reactions with [*N*,*N*′-(CH$_2$NMe)]POSiPh$_3$[14] and are supportive of a phosphonylation mechanism in which significant negative charge is developing at the carbonyl carbon atom in the rate-determining transition state, presumably indicating a substantial degree of P–C bond formation. Thus, if the reaction is stepwise (Scheme 7a) the rate-determining step is most likely to be formation of the intermediate adduct $k_1$ whereas, if reaction is concerted, the above results suggest that significant removal of electron density from the reaction centre *via* Si–O bond formation has a lower kinetic influence than does P–C bond formation (Scheme 7b).

If we proceed on the assumption that a stepwise process *via* a short-lived intermediate species provides a reasonable model of the mechanism for the Abramov phosphonylation, we may apply steady-state kinetics[38] to the Abramov reaction to relate the rate of formation of products (P) to the concentrations of the starting organophosphorus(III) ester (E) and aldehyde RCHO (Scheme 8). Such an analysis affords the second-order rate

$$E + RCHO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_2} P$$

E = phosphorodiamidite **2**
I = intermediate
P = α-siloxyimidophosphonate ester product

$$d[P]/dt = k_2 \cdot [I] \quad (1)$$

applying the steady-state approximation to I affords

$$k_2 \cdot [I] + k_{-1} \cdot [I] = k_1 \cdot [E] \cdot [RCHO]$$

*i.e.*,
$$[I] = \{k_1 \cdot [E] \cdot [RCHO]\}/(k_2 + k_{-1}) \quad (2)$$

substituting equation (2) in equation (1) affords

$$d[P]/dt = \{k_2 \cdot k_1/(k_2 + k_{-1})\} \cdot [E] \cdot [RCHO] \quad (3)$$

when $k_{obs} = \{k_2 \cdot k_1/(k_2 + k_{-1})\}$ equation (3) becomes

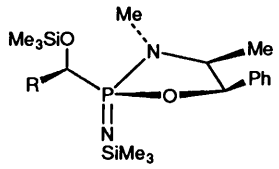
$$d[P]/dt = k_{obs} \cdot [E] \cdot [RCHO] \quad (4)$$

**Scheme 8**

expression shown in equation (4) where $k_{obs}$ is the observed rate constant.

A more detailed kinetic analysis of the Abramov reaction will be reported elsewhere but examination of equation (4) allows us

**Table 1** $^{31}P$ NMR ($C_6D_6$; 298 K; 36.2 MHz operating with a digital resolution of between 0.25 and 0.5 Hz) data for both diastereoisomers of compounds **5–18** along with diastereoselectivities (d.s.)




| R | Compound | $\delta_P$-Major[a] | $\delta_P$-Minor[a] | d.s. (%) | $\Delta P$[c] |
|---|---|---|---|---|---|
| Ph | **5** | 21.3 | 21.1 | 92 | +0.2 |
| 2-$C_{10}H_7$ | **9** | 21.0 | 20.7 | 91 | +0.3 |
| 1-$C_{10}H_7$ | **10** | 20.2 | 19.7 | 66 | +0.5 |
| *p*-$C_6H_4CN$ | **12** | 20.8 | 19.8 | 91 | +1.0 |
| *p*-$C_6H_4NO_2$ | **13** | 20.8 | 19.6 | 90 | +1.2 |
| *p*-$C_6H_4Cl$ | **14** | 21.0 | 20.9 | 90 | +0.1 |
| *p*-$C_6H_4Me$ | **15** | 21.5 | 21.1 | 91 | +0.4 |
| *p*-$C_6H_4OMe$ | **16** | 21.7 | 21.3 | 91 | +0.4 |
| *o*-$C_6H_4Br$ | **18** | 18.4 | 17.9 | 54 | +0.5 |
| *o*-$C_6H_4NO_2$ | **17** | 21.0[b] | 21.0[b] | 53 | −0.05 |
| *o*-$C_6H_4PPh_2$ | **11** | 22.0 | 23.0 | 80 | −1.0 |
| $Bu^t$ | **6** | 24.8 | *d* | 96 | |
| Pr | **7** | 28.0 | 24.5 | 80 | +3.5 |
| Bu | **8** | 27.9 | 24.3 | 81 | +3.6 |

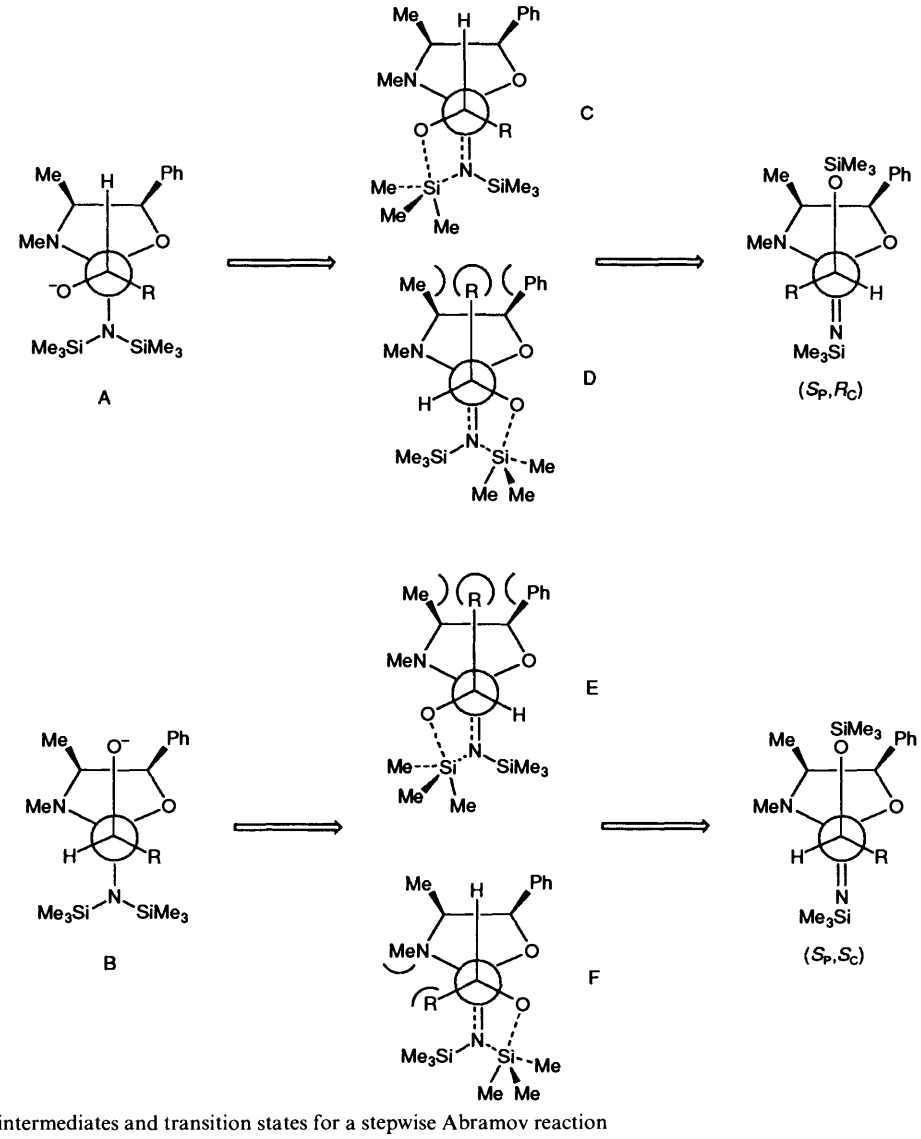
[a] In ppm. [b] Quoted to one decimal place; signals separated by 0.04 ppm. [c] Defined as [$\delta_P$(major) − $\delta_P$(minor)] in ppm. Values are not quoted at constant concentration but some indication of concentration errors may be obtained by noting that $\Delta P$ for compound **9** differs by 0.04 ppm over a five-fold concentration range from 1 mol $dm^{-3}$ to 0.2 mol $dm^{-3}$. [d] Not observed.

to identify two limiting kinetic scenarios: (a) $k_2 \gg k_{-1}$ and (b) $k_{-1} \gg k_2$. In the former situation, $k_{obs}$ reduces to $k_1$ and the rate of product formation is dominated by the *formation* of the 1:1 adduct, whereas in the latter situation $k_{obs}$ becomes $\{k_2 \cdot k_1\}/k_{-1}$ and the rate of product formation is then dependent upon the *formation and decomposition* of the 1:1 adduct. We have seen above how a qualitative Hammett analysis of the Abramov reaction[14] suggests P–C bond formation to be strongly implicated as the rate-determining step. Furthermore, given the almost identical stereoelectronic and hybridisation profiles about the phosphorus atom in the two compounds [*N*,*N*′-$(CH_2NMe)_2$]$POSiR_3$ ($R_3$ = $Bu^tMe_2$, $Et_3$) as reflected in $^{31}P$ NMR resonances ($\delta$ 119.3 and 119.9, respectively), the fact that the latter is a significantly faster phosphonylating agent than the former seems to suggest that *silyl-group transfer is also involved in the overall rate expression.*[13,14] This, in turn, is consistent with either a stepwise mechanism with scenario (b) $k_{-1} \gg k_2$ or a concerted mechanism. By analogy to closely related systems,[33,34] we favour the stepwise process. Consequently, if the proposals $k_1 \ll k_{-1}, k_2$ and $k_{-1} \gg k_2$ are a true reflection of the Abramov reaction then the rate of formation of the product esters is determined by both the rate of formation and the relative rates of decomposition of the intermediate 1:1 adducts. Subsequently, these factors are likely to be important in determining the stereochemistry of reaction (*vide infra*).

*Assigning* $C^\alpha$ *Configurations in* α*-Siloxyimidophosphonate Esters.*—The stereochemical results described earlier suggest immediately that the Abramov reaction proceeds with *retention of configuration at phosphorus* as illustrated in Scheme 4. Indeed, this conclusion is supported by both the X-ray studies on compounds **9** and **11** and by $^{18}O(*)$ isotopic labelling studies of the reaction between $\{N,N'\text{-}(CH_2NMe)_2\}PO^*SiPh_3$ and RCHO (R = Ph, $Bu^t$), which confirms that the Abramov reaction proceeds with complete O–Si rather than P–O bond cleavage, a necessary condition for retention of configuration.[14,18] What we need to address next is the stereochemistry at the alpha carbon atom ($C^\alpha$).

The first point to make is that even though the rate of phosphonylation shows a strong dependence, there appears to be essentially very little variation in diastereoselectivity (d.s.) as a function of the electronic properties of the *para*-substituents X when *p*-$XC_6H_4CHO$ are used as substrates (d.s.-values are all within the range 90–92%, Scheme 4 and Table 1). Consequently, it appears that distal electronic factors influence the kinetics strongly yet have little effect upon the face-selectivity of reaction. This, in turn, suggests that *steric* factors are perhaps more important in the selectivity-controlling step (presumably the P–C bond-forming step $k_1$ in Scheme 7a). Indeed, this seems reasonable given that the highest selectivities obtained are with pivalaldehyde (96%) where there is the greatest steric differential between carbonyl substituents (H and $Bu^t$).

Only for the major isomers of compounds **9** (91% d.s.) and **11** (80% d.s.) can we make unambiguous configuration assignments through X-ray diffraction. The configurations are ($S_P$, $S_C$) and ($S_P$, $R_C$) respectively. What we require is a simpler, more direct and general method of determining the configurations at phosphorus and $C^\alpha$, preferably based on empirical NMR measurements. We have seen above how this is possible for phosphorus from measurements of the $^3J_{PH}$ coupling between phosphorus and the C-5 hydrogen atom. Furthermore, it may be possible to assign configurations to the $C^\alpha$ atoms by examination of $^{31}P\{^1H\}$ NMR spectra. Thus, examination of the $^{31}P$ NMR resonances for the major and minor diastereoisomers of compounds **5**, **9** and **12–16** reveals that the major epimer consistently has the higher frequency resonance by up to 1.2 ppm (Table 1). A parameter $\Delta P$ can be defined as $\Delta P$ = $\delta_P$(major) − $\delta_P$(minor) and a selection of these values are listed in Table 1. Given that the configuration of the dominant epimer of **9** is $S_C$ by X-ray diffraction and that these compounds (**5**, **9**, **12–16**) are all derived from substituted benzaldehydes and are produced with similar diastereoselectivities (between 90–92%), we envisage that the major epimers of compounds **5**, **9** and **12–16** all possess the $S_C$ configuration. Consequently, *the* $S_C$ *epimers have higher frequency* $^{31}P$ *resonances than do the* $R_C$ *epimers.* This rationale is supported by the observation that for compound **11** the major epimer has the lower



**Scheme 9** Proposed intermediates and transition states for a stepwise Abramov reaction

frequency resonance by 1.0 ppm which, on the basis of the NMR criterion above, implies the $R_C$ configuration which is indeed confirmed by X-ray diffraction. Therefore, we propose that it may be possible to assign configurations at $C^{\alpha}$ in this closely related series of oxazaphospholidine complexes by examination of their $^{31}P$ NMR spectra; *when* ($S_P$, $S_C$) *dominates*, $\Delta P$ *is positive and where* ($S_P$, $R_C$) *dominates* $\Delta P$ *is negative.*

Assuming this rationale to be correct, we can see immediately that face-selectivity in the Abramov reaction is influenced strongly by the position of the substituents on the aryl ring of the benzaldehyde substrate. Substitution in either the *para* or the *meta* positions (compounds **5**, **9**, **12**–**16**) leads consistently to the ($S_P$, $S_C$) epimers being strongly favoured ($\Delta P$ positive) whilst substitution in the *ortho* position leads to a reduced preference for the $S_P$ isomer; indeed, for compounds **17** and **18** both epimers are produced in almost equal amounts; for compound **17** it appears that $\Delta P$ is negative, suggesting that the ($S_P$, $R_C$) epimer is slightly favoured. Indeed, we have subsequently isolated the major isomer of compound **17** isomerically pure and are currently attempting to obtain crystals suitable for X-ray diffraction. In cases where the *ortho* substituent is sufficiently sterically demanding, the ($S_P$, $R_C$) epimer becomes the major product (*e.g.*, **11**, for which $\Delta P$ is also negative, has d.s. 80%). Esters derived from the alkyl aldehydes are included in the Table for completeness; it is not yet clear whether the same NMR criterion may be used in these cases.

We recognise that the empirical NMR correlations outlined above are based on a rather limited basis set and we are currently examining correlations within a far wider range of derivatives.*

*Rationalising Stereocontrol in the Asymmetric Abramov Reaction.*—From the kinetic analysis above we envisage that

* Phosphorus chemical shifts in phosphate esters $(RO)_3P{=}O$ have been found to depend strongly upon (i) the O–P–O bond angles such that a ~ 3° change in these angles can cause a shift in the $^{31}P$ resonance of ~ 4 ppm and (ii) the R–O–P–O–R dihedral angles.[39] Since the $\Delta P$-values vary by up to 3.5 ppm for this closely related family of α-siloxyimidophosphonate esters (Table 1) and the difference in bond angles around phosphorus in the X-ray structures of compounds **9** and **11** differ by at most 2°, the shift differences observed between $S_C$ and $R_C$ epimers is not inconsistent with such small bond-angle changes. Moreover, it is possible that these bond-angle changes may influence conformational preferences of the N,O rings in compounds **5**–**18** and hence the $^{31}P$ resonances. Indeed, diastereoisomeric phosphoramidates containing six-membered chelating N,O ring systems have been shown to have $^{31}P$ resonances which depend upon the conformation of the chelate ring and on whether the P=O function occupies an axial or equatorial position (in these systems $\Delta P$ ~ 3 ppm).[40]

**Table 2**

| Run[a] | Aldehyde[b] | 2[b] | Solvent | Conditions | d.s. (%)[c] |
|---|---|---|---|---|---|
| 1 | 1 | 1 | toluene | A | 82 |
| 2 | 1 | 1 | THF | A | 78 |
| 3 | 1 | 1 | $CH_2Cl_2$ | A | 55 |
| 4 | 10 | 1 | toluene | A | 84 |
| 5 | 1 | 1 | toluene | B | 86 |
| 6 | 1 | 1 | toluene | C | 85 |

[a] The general reaction protocol involves mixing of both reagents in a given solvent at ambient temperature and stirring the mixture for 16 h prior to removal of the volatiles and examination of the product mixture by $^1H$ and $^{31}P$ NMR spectroscopy in $C_6D_6$ solvent. The rate of addition of reagents was either instantaneous mixing (protocol A), slow addition of aldehyde (during 2 h, protocol B) or slow addition of **2** (during 2 h, protocol C). [b] Number of molar equivalents. [c] All diastereoselectivities were determined by integration of appropriate resonances in the 100 MHz $^1H$ NMR spectra.

product stereochemistry will be determined by a combination of three rate constants $k_{obs} = k_2 \cdot k_1/k_{-1}$ which can be written as $k_{obs} = k_2 \cdot K$, where $K$ is the equilibrium constant for formation of the intermediate adduct. The stereochemistry will thus be determined by (i) the relative stability of the intermediates and (ii) their relative rates of silyl-group transfer. We presume that the most stable adducts will be those which minimise steric interactions between substituents on the ephedrine auxiliary and the aldehyde. Thus, **A** and **B** (Scheme 9) are presumably the least unfavourable with the more bulky aldehyde substituent (R) furthest from the substituents on the auxiliary. These two adducts represent two different diastereoisomeric intermediates formed by attack of phosphorus on the *re* and *si* faces of the prochiral aldehyde respectively. Subsequently, plausible transition states for silyl-group transfer may be represented by species **C**–**F** (Scheme 9) in which the silicon atom adopts a five-coordinate trigonal bipyramidal geometry† as expected,[41] where **C** and **D** lead to products with the ($S_P$, $R_C$) configuration and **E** and **F** lead to the ($S_P$, $S_C$) stereoisomers. Now, when the R substituent is extremely sterically demanding such as with *o*-$Ph_2PC_6H_4$, unfavourable steric interactions between R and the ephedrine substituents are likely in species **D**, **E** and **F** (as illustrated) such that silyl-group transfer *via* **C** is presumably most favoured. Thus, if silyl-group transfer is dominant the major observed stereoisomer should be ($S_P$, $R_C$) as is indeed found for compound **11**. Alternatively, in situations of lesser steric demand such as the 2-naphthyl and presumably *para*-substituted benzaldehydes, we suggest that the major product stereoisomer is determined predominantly by the stability of the intermediate adduct. Since for 2-naphthaldehyde (and presumably *para*-substituted benzaldehydes) the major products are ($S_P$, $S_C$), this may imply that adducts with the **B** structure are more stable than those with the **A** structure. We are currently probing the origin of stereoselectivity further *via* chemical[42] and molecular modelling studies.

*Other Variables in the Asymmetric Abramov Reaction.*—We have monitored how the diastereoselectivity of the phosphonylation reaction of *o*-(diphenylphosphanyl)benzaldehyde with compound **2** varies as a function of (a) solvent, (b) rate of addition and (c) concentration of reagents (Table 2).

Solvent appears to have a pronounced effect (runs 1–3), toluene having the highest selectivity (82% d.s.) whilst chlorinated solvents have the lowest selectivity (55% d.s.) presumably due to the higher likelihood of catalytic racemisation by trace acid (*vide supra*). However, in toluene solvent, the order of addition and the rate of addition (over a period of either seconds or hours) and the use of a large excess of aldehyde (10 mol equiv.) seems to have only a small effect upon the d.s.

*Conclusions.*—A significant body of data now exists on the stoichiometric asymmetric phosphonylation of aldehydes *via* {[AUX]P–X–M} organophosphorus(III) reagents (AUX = auxiliary, X = O, N; M = an electropositive main group or transition element): the Abramov reaction. In order to exploit this reaction better and to develop catalytic variants, a firm foundation is required. Thus, combining results reported here and elsewhere[13,34] we may begin to construct a mosaic of the asymmetric Abramov reaction.

(i) Reaction proceeds under *kinetic* control at room temperature. Raising the temperature (to 80 °C) or introducing trace acid causes epimerisation at the $C^\alpha$ atom of the product phosphonate esters *via* a process which involves extrusion of aldehyde. Ultimately, this leads to equilibration of the α-siloxyimidophosphonate esters. In at least one case, compound **11**, the kinetic product differs from the thermodynamic product.

(ii) The Abramov reaction proceeds with complete Si–X bond rather than P–X bond cleavage when M = $SiR_3$.[14]

(iii) Where M = $SiR_3$, silyl-group transfer is exclusively *intramolecular*.

(iv) Distal electronic perturbations due to variations in the *para* substituent of substituted benzaldehydes have a strong effect upon the rate but negligible effect upon the diastereoselectivity of the reaction, suggesting that the face-selective step is determined more strongly by *steric* interactions. The face-selectivity of reaction may be *reversed* if suitably sterically demanding substituents are introduced into the *ortho* positions of benzaldehyde (*cf.* **9** and **11** above).

(v) As a consequence of point (iv), increasing the steric congestion in the vicinity of the phosphorus atom may result in increased stereoselectivity and decreased rates of reaction. Towards this end we have recently synthesized the new phosphorodiamidite {(1*R*,2*S*)-*O*,*N*-*N*-Pr$^i$-ephedrine}$PN(SiMe_3)_2$ and are currently screening its phosphonylating abilities.[42]

(vi) It may prove possible to *predict*, in an empirical fashion, the configurations at both the phosphorus and $C^\alpha$ atoms in this closely related family of α-siloxyimidophosphonate esters by examination of $^1H$ and $^{31}P$ NMR parameters.

(vii) Qualitative analysis of relative reactivities as a function of the Hammett substituent constants $\sigma_X$ in *para*-substituted benzaldehydes suggests that the rate-determining transition state involves considerable P–C bond formation.

There are still a great many questions to be answered concerning stereoselectivity in the asymmetric Abramov reaction but information now exists which should prove extremely valuable in tackling the next major challenge in this area, developing efficient catalytic asymmetric phosphonylation systems. Work in this direction is already underway in several laboratories[9,18] including our own.

## Experimental

All reactions and manipulations were performed as described previously.[13] Elemental analyses were performed by the Microanalytical Laboratory of this department. Mass spectra were collected on a VG Autospec instrument operating in the

† The five-coordinate silicon has been drawn with the carbonyl oxygen atom in the axial position and the amide nitrogen atom in the equatorial position. This represents an earlier transition state since nucleophilic substitution at silicon such as that portrayed here is normally considered to involve bond-making and -breaking at the axial sites. Consequently, pseudorotation to place the nitrogen atom in the axial and the oxygen atom in the equatorial position would produce a later transition state.

electron-impact mode. The isotopic mass error on high-resolution mass peaks is within 10 ppm. IR spectra were recorded as either thin films (for liquids) or Nujol mulls (for solids) between KBr windows using 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 $^{31}P$. $^{29}Si\{^1H\}$ NMR spectra were recorded in 10 mm tubes at 17.8 MHz in toluene solvent, equipped with an external $C_6D_6$ lock, using a gated $^1H$ decoupling sequence to suppress NOE effects with a digital resolution of 0.25 ppm and delay time of 40 s between pulses. Deuteriated solvents were dried by flash chromatography on a column of basic alumina (Brockmann Grade I) and were deoxygenated before use. Spectra are referenced internally using either the residual solvent resonance for $^1H$ and $^{13}C$, $SiMe_4$ as $\delta_H$ and $\delta_C = 0$ or the methyl hydrogen resonance of toluene as $\delta_H$ 2.11 [in $C_6D_6$ with reference to $\delta(SiMe_4) = 0$]. Indeed, toluene has proved to be a convenient internal reference for many of the compounds reported here, since the presence of $Me_3Si$ groups makes $SiMe_4$ referencing inconvenient. 85% $H_3PO_4$ was used as external reference for $^{31}P$ at zero ppm. All spectra are reported at 298 K in $C_6D_6$ unless stated otherwise; the $^{13}C$ and $^{31}P$ spectra being run under conditions of broad-band $^1H$ decoupling. All NMR data reported for phosphonate esters **5**–**19** are for the major isomers only unless stated otherwise. *J* Values are given in Hz. The compounds (1*R*,2*S*)-ephedrine, $PCl_3$, $NEt_3$, *N*-methylmorpholine, monoclinic sulfur and all carbonyl compounds were purchased from commercial sources and were either recrystallised [(1*R*,2*S*)-ephedrine, solid carbonyls], chromatographed on a short column of Brockmann Grade I basic alumina (*N*-methylmorpholine, $NEt_3$, and liquid carbonyls), used as received [$PCl_3$, $LiN(SiMe_3)_2$ as a 1 mol $dm^{-3}$ solution in THF and sulfur] or prepared using literature procedures as in the case of *o*-(diphenylphosphanyl)benzaldehyde.[43] Diastereoselectivity (d.s.) refers to the direct percentage contribution of the major component **A** to a mixture of epimers **A** and **B**, $\{[\mathbf{A}]/([\mathbf{A}] + [\mathbf{B}])\} \times 100$ and have been determined by integration of appropriate resonances in both $^{31}P$ and $^1H$ NMR spectra.

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*PN*(*SiMe*$_3$)$_2$ **2**.—A solution of $LiN(SiMe_3)_2$ in THF solvent (1.07 $cm^3$ of a 1.0 mol $dm^{-3}$ solution, 1.07 mmol) was added dropwise at −78 °C to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PCl **1** (0.24 g, 1.07 mmol) in THF (20 $cm^3$) maintained also at −78 °C. The mixture was then allowed to warm to room temperature and was stirred thus for 1 h prior to work-up by removal of the volatile materials under reduced pressure and extraction of the crude mixture into pentane (~30 $cm^3$). Subsequent removal of the pentane under reduced pressure afforded the title compound as a pale yellow liquid (0.29 g, 83%). This material is consistently of ~96–98% epimeric purity but can be improved to >98% $S_P$ isomer by flash filtration of a pentane solution on basic alumina; $\delta_H(C_6D_6)$ 7.3–7.0 (5 H, m, Ph), 5.62 (1 H, d, $^3J_{HH}$ 5.6, PhC*H*O), 3.24 (1 H, dqd, $^3J_{PH}$ 5.8, $^3J_{HH}$ 6.4, MeC*H*N), 2.39 (3 H, d, $^3J_{PH}$ 10.8, NMe), 0.51 (3 H, d, $^3J_{HH}$ 6.5, *Me*CHN) and 0.36 (18 H, d, $^4J_{PH}$ 1.7, $SiMe_3$); $\delta_C(C_6D_6)$ 139.80 (d, $^3J_{PC}$ 5.5, Ph-C$^{ipso}$), 128.31 (s, Ph-C$^o$), 127.39 (s, Ph-C$^m$), 126.72 (s, Ph-C$^p$), 82.36 (d, $^2J_{PC}$ 11.9, Ph*C*HO), 59.58 (s, Me*C*HN), 29.39 (d, $^2J_{PC}$ 27.9, NMe), 13.21 (s, *Me*CHN) and 4.73 (d, $^3J_{PC}$ 9.1, $SiMe_3$); $\delta_P(C_6D_6)$ 148.2 (s) (Found: $M^+$, 354.171 722. Calc. for $C_{16}H_{31}N_2OPSi_2$: *M*, 354.171 259).

*Synthesis of* $R_P$-[(1R,2S)-O,N-*Ephedrine*]*P*(*S*)[*N*(*SiMe*$_3$)$_2$] **3**.—A solution of elemental sulfur in toluene solvent (0.019 g, 0.59 mmol in 5 $cm^3$ solution) was added at room temperature to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN($SiMe_3$)$_2$ **2** (0.21 g, 0.59 mmol) in toluene solvent (10 $cm^3$). After the mixture had been stirred for 30 min the volatile materials were removed under reduced pressure to afford an oil, which was recrystallised from pentane to afford the *title compound* $R_P$-[1*R*,2*S*)-*O*,*N*-*ephedrine*]P(S)[$N(SiMe_3)_2$] **3** as crystals (0.19 g, 87%) (Found: $M^+$, 386.142 882; C, 49.7; H, 8.2; N, 7.4. $C_{16}H_{31}N_2OPSSi_2$ requires *M*, 386.143 331; C, 49.7; H, 8.08; N, 7.24%); $\delta_H(C_6D_6)$ 7.3–7.0 (5 H, m, Ph), 5.29 (1 H, dd, $^3J_{PH}$ 5.8, $^3J_{HH}$ 5.8, PhC*H*O), 3.35 (1 H, dqd, $^3J_{PH}$ 6.6, $^3J_{HH}$ 6.7, MeC*H*N), 2.47 (3 H, d, $^3J_{PH}$ 13.2, NMe), 0.61 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN) and 0.41 (18 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 137.45 ($^3J_{PC}$ d, 6.6, Ph-C$^{ipso}$), 128.51 (s, Ph-C$^o$), 128.17 (s, Ph-C$^m$), 126.75 (s, Ph-C$^p$), 80.73 (s, Ph*C*HO), 59.06 ($^2J_{PC}$ d, 9.3, Me*C*HN), 31.33 (d, $^2J_{PC}$ 6.7, NMe), 12.81 ($^3J_{PC}$ d, 2.2, *Me*CHN) and 4.50 ($^3J_{PC}$ d, 2.1, $SiMe_3$); $\delta_P(C_6D_6)$ 86.6 (s).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*S*)*NH*(*SiMe*$_3$) **4**.—When a solution of disilylamine **3** in $CDCl_3$ or $C_6D_6$ solvent was left exposed to moist air, a clean quantitative conversion into $S_P$-[(1*R*,2*S*)-*O*,*N*-ephedrine]P(S)NH($SiMe_3$) **4** was observed to occur over the course of 14 days at room temperature. *Compound* **4** was purified by recrystallisation from pentane in a manner similar to compound **3** (Found: $M^+$, 314.103 782; C, 49.65; H, 7.4; N, 8.85. $C_{13}H_{23}N_2OPSSi$ requires *M*, 314.103 802; C, 49.70; H, 7.37; N, 8.90%); $\delta_H(C_6D_6)$ 7.3–7.0 (5 H, m, Ph), 5.21 (1 H, dd, $^3J_{PH}$ 0.9, $^3J_{HH}$ 5.7, PhC*H*O), 3.00 (1 H, dqd, $^3J_{PH}$ 6.5, $^3J_{HH}$ 6.4, MeC*H*N), 2.66 (1 H, d, $^2J_{PH}$ 7.3, NH), 2.39 (3 H, d, $^3J_{PH}$ 12.8, NMe), 0.72 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN) and 0.18 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 137.28 (d, $^3J_{PC}$ 7.9, Ph-C$^{ipso}$), 128.54 (s, Ph-C$^o$), 128.07 (s, Ph-C$^m$), 126.40 (s, Ph-C$^p$), 81.28 (d, $^2J_{PC}$ 2.0, Ph*C*HO), 60.52 (d, $^2J_{PC}$ 9.3, Me*C*HN), 29.22 (d, $^2J_{PC}$ 6.3, NMe), 12.10 (s, *Me*CHN) and 1.10 (s, $SiMe_3$); $\delta_P(C_6D_6)$ 79.2 (s).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CHPh*-(*OSiMe*$_3$) **5**.—Benzaldehyde (0.12 $cm^3$, 1.15 mmol) was added at room temperature to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN($SiMe_3$)$_2$ **2** (0.41 g, 1.15 mmol) in pentane solvent (15 $cm^3$). After being stirred for 3 h, the solution was filtered and the volatile materials were removed under reduced pressure to afford the title compound [(1*R*,2*S*)-*O*,*N*-ephedrine]P-($NSiMe_3$)CHPh($OSiMe_3$) as a liquid (0.44 g, 83%). This was found to be essentially pure compound **5** by $^1H$ and $^{31}P$ NMR spectroscopy with a diastereoselectivity of 92%; $\delta_H(C_6D_6)$ 7.7–7.0 (10 H, m, Ph), 5.42 (1 H, d, $^3J_{HH}$ 6.4, PhC*H*O), 5.05 (1 H, d, $^2J_{PH}$ 11.7, PC*H*Ph), 3.07 (1 H, dqd, $^3J_{PH}$ 11.8, $^3J_{HH}$ 6.6, MeC*H*N), 2.48 (3 H, d, $^3J_{PH}$ 8.9, NMe), 0.48 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.32 (9 H, s, $SiMe_3$) and 0.04 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 140.19 (s, Ph-C$^{ipso}$), 137.91 (d, $^3J_{PC}$ 9.2, Ph-C$^{ipso}$), 128–126 (several resonances, Ph-C), 79.12 (s, Ph*C*HO), 74.52 (d, $^1J_{PC}$ 162.3, P*C*HPh), 61.18 (d, $^2J_{PC}$ 7.9, Me*C*HN), 31.08 (d, $^2J_{PC}$ 5.6, NMe), 15.34 (s, *Me*CHN), 4.00 (d, $^3J_{PC}$ 3.8, $NSiMe_3$) and 0.12 (s, $OSiMe_3$); $\delta_P(C_6D_6)$ 21.3 (s) (Found: $M^+$, 460.213 308. Calc. for $C_{23}H_{37}N_2O_2PSi_2$: *M*, 460.213 124).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CHBu*$^t$-(*OSiMe*$_3$) **6**.—Pivaldehyde (1.10 $cm^3$, 10.15 mmol) was added dropwise at room temperature to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN($SiMe_3$)$_2$ **2** (0.60 g, 1.69 mmol) in toluene solvent (20 $cm^3$). After being stirred thus for 3 days, the volatile materials were removed under reduced pressure to afford [(1*R*,2*S*)-*O*,*N*-ephedrine]P($NSiMe_3$)CHBu$^t$($OSiMe_3$) **6** as a liquid (0.62 g, 84%). This was found to be essentially pure compound **6** by $^1H$ and $^{31}P$ NMR spectroscopy with a diastereoselectivity of 96%; $\delta_H(C_6D_6)$ 7.3–6.9 (5 H, m, Ph), 5.35 (1 H, dd, $^3J_{PH}$ 1.7, $^3J_{HH}$ 6.2, PhC*H*O), 3.73 (1 H, d, $^2J_{PH}$ 5.5, PC*H*Bu$^t$), 3.06 (1 H, dqd, $^3J_{PH}$ 10.6, $^3J_{HH}$ 6.7, MeC*H*N), 2.48 (3 H, d, $^3J_{PH}$ 10.4, NMe), 1.23 (9 H, s, $CMe_3$), 0.56 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.39 (9 H, s, $SiMe_3$) and 0.20 (9 H, s, $SiMe_3$);

$\delta_C(C_6D_6)$ 137.78 (d, $^3J_{PC}$ 9.5, Ph-$C^{ipso}$), 129–125 (several resonances, Ph-C), 81.36 (d, $^1J_{PC}$ 172.5, P*C*HBu$^t$), 78.97 (s, Ph*C*HO), 61.96 (d, $^2J_{PC}$ 6.2, Me*C*HN), 36.12 (d, $^2J_{PC}$ 4.1, *C*Me$_3$), 33.48 (d, $^2J_{PC}$ 3.7, NMe), 28.38 (d, $^3J_{PC}$ 5.6, C*Me*$_3$), 16.31 (d, $^3J_{PC}$ 2.6, *Me*CHN), 4.05 (d, $^3J_{PC}$ 3.6, NSiMe$_3$) and 1.02 (s, OSiMe$_3$); $\delta_P(C_6D_6)$ 24.8 (s) (Found: $M^+$, 440.243 608. Calc. for $C_{21}H_{41}N_2O_2PSi_2$: *M*, 440.244 424).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CHPr*(*OSiMe*$_3$) **7**.—A solution of butyraldehyde (0.24 cm$^3$, 2.70 mmol) in toluene solvent (5 cm$^3$) was added dropwise at −78 °C to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2** (4.5 cm$^3$ of a 0.3 mol dm$^{-3}$ solution in toluene, 1.35 mmol) in toluene (~10 cm$^3$) also maintained at −78 °C. The mixture was stirred at −78 °C for 2 h after which time it was allowed to warm to 0 °C and was stirred thus for 12 h. Finally, the mixture was stirred at room temperature for 4 days until reaction was complete (as determined by $^{31}P\{^1H\}$ NMR spectroscopy on aliquots). The final product mixture was then analysed by NMR and mass spectroscopy which revealed that reaction was less clean than with aryl aldehydes but the two major products were clearly identifiable by $^{31}P$ NMR spectroscopy; $\delta_P(C_6D_6)$ 28.0 (s, major isomer), 24.5 (s, minor isomer) (Found: $M^+$, 426.227 744. Calc. for $C_{20}H_{39}N_2O_2PSi_2$: *M*, 426.228 774).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CHBu*(*OSiMe*$_3$) **8**.—To a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2** (4.5 cm$^3$ of a 0.3 mol dm$^{-3}$ solution in toluene, 1.35 mmol) in toluene solvent (~10 cm$^3$) maintained at 78 °C was added a solution of pentanal (0.28 cm$^3$, 2.70 mmol) in toluene (5 cm$^3$) also at −78 °C. The mixture was stirred at −78 °C for 2 h then was allowed to warm to 0 °C and stirred thus for 12 h. Finally, the mixture was stirred at room temperature for 4 days until reaction was complete (as determined by $^{31}P\{^1H\}$ NMR spectroscopy on aliquots). The final product mixture was then analysed by NMR and mass spectroscopy in an analogous manner to that for compound **7** above, which again revealed two identifiable products; $\delta_P(C_6D_6)$ 27.9 (s, major isomer) and 24.3 (s, minor isomer) (Found: $M^+$, 440.242 733. Calc. for $C_{21}H_{41}N_2O_2PSi_2$: *M*, 440.244 424).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CH*-2-$C_{10}H_7$(*OSiMe*$_3$) **9**.—2-Naphthaldehyde (0.04 g, 0.28 mmol) was dissolved in toluene solvent (~5 cm$^3$) and this solution was added dropwise to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2** (0.10 g, 0.28 mmol) in toluene solvent (15 cm$^3$) maintained at room temperature. After being stirred thus for 16 h, the volatiles were removed under reduced pressure to afford the crude title product [(1*R*,2*S*)-*O*,*N*-ephedrine]P(NSiMe$_3$)CH-2-$C_{10}H_7$(OSiMe$_3$) as a pale yellow oil with a diastereoselectivity determined by $^{31}P$ NMR spectroscopy of 91%. Recrystallisation from a saturated solution in pentane at −35 °C affords a chemically and isomerically pure sample of the *major diastereoisomer* **9** as crystals (0.12 g, 86%) (Found: $M^+$, 510.228 654; C, 63.4; H, 7.75; N, 5.3. $C_{27}H_{39}N_2O_2PSi_2$ requires *M*, 510.228 774; C, 63.5; H, 7.70; N, 5.48%); $\delta_H(C_6D_6)$ 8.2–6.9 (12 H, m, ArH), 5.44 (1 H, d, $^3J_{HH}$ 6.4, PhC*H*O), 5.28 (1 H, d, $^2J_{PH}$ 12.0, PC*H*Ar), 3.06 (1 H, dqd, $^3J_{PH}$ 11.9, $^3J_{HH}$ 6.5, MeC*H*N), 2.48 (3 H, d, $^3J_{PH}$ 8.9, NMe), 0.48 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.35 (9 H, s, SiMe$_3$) and 0.08 (9 H, s, SiMe$_3$); $\delta_C$-($C_6D_6$) 137–122 (several resonances, Ph-C), 79.11 (s, Ph*C*HO), 74.89 (d, $^1J_{PC}$ 162.2, P*C*HAr), 61.16 (d, $^2J_{PC}$ 7.8, Me*C*HN), 31.14 (d, $^2J_{PC}$ 5.3, NMe), 15.36 (s, *Me*CHN), 4.03 (d, $^3J_{PC}$ 3.9, NSiMe$_3$) and 1.41 (s, OSiMe$_3$); $\delta_P(C_6D_6)$ 21.0 (s).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CH*-1-$C_{10}H_7$(*OSiMe*$_3$) **10**.—A solution of 1-naphthaldehyde in toluene solvent (0.39 g, 2.51 mmol in 10 cm$^3$ solvent) was added dropwise at −78 °C to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2** (0.89 g, 2.51 mmol) in toluene solvent (15 cm$^3$) maintained also at −78 °C. The mixture was stirred at −78 °C for 1 h then at 0 °C for 12 h. After this time the mixture was filtered and the volatiles were removed under reduced pressure to afford a yellow liquid, which was examined by NMR spectroscopy and shown to have a d.s. of 66% and a chemical yield of 62%; $\delta_H(C_6D_6)$ 8–7 (12 H, m, ArH), 6.17 (1 H, br d, $^3J_{PH}$ 13.0, PC*H*Ar), 5.40 (1 H, d, $^3J_{HH}$ 6.3, PhC*H*O), 2.98 (1 H, m, $^3J_{PH}$ 12.4, $^3J_{HH}$ 6.5, MeC*H*N), 2.61 (3 H, d, $^3J_{PH}$ 5.8, NMe), 0.19 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.30 (9 H, s, SiMe$_3$) and 0.10 (9 H, s, SiMe$_3$); $\delta_P(C_6D_6)$ 20.2 (s, major isomer) and 19.7 (s, minor isomer). The highest-mass peak in the mass spectrum of the crude product was observed to be the parent ion (Found: $M^+$, 510.229 431).

*Synthesis of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CHC*$_6$*H*$_4$-o-*PPh*$_2$(*OSiMe*$_3$) **11**.—A solution of *o*-(diphenylphosphanyl)-benzaldehyde (0.56 g, 1.3 mmol) in toluene solvent (8 cm$^3$) cooled in ice–water was added dropwise to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2** (0.69 g, 0.19 mmol) in toluene solvent (10 cm$^3$) maintained at −78 °C. The resulting yellow reaction mixture was maintained at this temperature for *ca.* 30 min, then was allowed to warm slowly to ambient temperature over the course of 16 h. The mixture was filtered and all volatile materials were removed under reduced pressure to afford a red-brown oil, which was examined by NMR spectroscopy and shown to consist only of two diastereoisomers of the title compound **11** (76%), with a diastereoselectivity of 80%. No other products were formed. The crude product was extracted into pentane and recrystallised to afford the *major diastereoisomer* of *compound* **11** as pure crystals (%) (Found: $M^+$, 644.256 114; C, 65.15; H, 7.15; N, 4.55. $C_{35}H_{46}N_2O_2P_2Si_2$ requires *M*, 644.257 313; C, 65.19; H, 7.19; N, 4.34%); $\delta_H(C_6D_6$; major epimer) 8.1–6.9 (19 H, m, ArH), 6.58 (1 H, dd, $^2J_{PH}$ 13.0, $^4J_{PH}$ 9.3, PC*H*Ar), 5.55 (d, 1 H, $J_{HH}$ 6.1, PhC*H*O), 3.11 (m, $^3J_{HH}$ = $^3J_{PH}$ = 6.4, MeC*H*N), 2.62 (3 H, d, $^3J_{PH}$ 8.7, NMe), 0.73 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.31 (9 H, s, SiMe$_3$) and −0.04 (9 H, s, SiMe$_3$); $\delta_C(C_6D_6$; major epimer) 146–126 (several resonances, Ph-C), 79.10 (s, Ph*C*HO), 72.60 (dd, $^1J_{PC}$ 166.3, $^3J_{PC}$ 29.3, P*C*HAr), 61.85 (d, $^2J_{PC}$ 7.2, Me*C*HN), 33.23 (d, $^2J_{PC}$ 5.0, MeN), 15.02 (s, *Me*CHN), 4.06 (d, $^3J_{PC}$ 4.2, SiMe$_3$) and 0.39 (s, SiMe$_3$); $\delta_H(C_6D_6$; minor epimer) 5.52 (1 H, d, $J_{HH}$ 6.9, PhC*H*O), 3.26 (1 H, m, $^3J_{HH}$ = $^3J_{PH}$ = 6.3, MeC*H*N), 2.49 (3 H, d, $^3J_{PH}$ 9.2, NMe), 0.47 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.34 (9 H, s, SiMe$_3$) and 0.05 (9 H, s, SiMe$_3$); $\delta_C(C_6D_6$, minor epimer) 79.55 (s, Ph*C*HO), 72.51 (dd, $^1J_{PC}$ 159.4, $^3J_{PC}$ 32.9, P*C*HAr), 60.92 (d, $^2J_{PC}$ 7.6, Me*C*HN), 31.72 (d, $^2J_{PC}$ 4.5, MeN), 15.94 (s, *Me*CHN); $\delta_P(C_6D_6$; major epimer) 22.0 (d, $^4J_{PP}$ 3, P=NSiMe$_3$) and −18.4 (d, $^4J_{PP}$ 3, PPh$_2$); $\delta_P(C_6D_6$; minor epimer) 23.0 (d, $^4J_{PP}$ 3, P=NSiMe$_3$) and −18.7 (d, $^4J_{PP}$ 3, PPh$_2$).

*Syntheses of* [(1R,2S)-O,N-*Ephedrine*]*P*(*NSiMe*$_3$)*CHC*$_6$*H*$_4$-*X*(*OSiMe*$_3$) (*X* = p-*CN* **12**, p-*NO*$_2$ **13**, p-*Cl* **14**, p-*Me* **15**, p-*MeO* **16**, o-*NO*$_2$ **17**, o-*Br* **18**).—In each case, the experimental procedure was the same apart from different reaction times used. Diastereoselectivities were determined on the crude reaction mixtures by both $^{31}P$ and $^1H$ NMR spectroscopy. A solution of the aldehyde in toluene solvent (5 cm$^3$) was added dropwise to a stirred solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN(SiMe$_3$)$_2$ **2** in toluene (20 cm$^3$) at room temperature under nitrogen. After being stirred at this temperature for the requisite amount of time, the mixture was filtered and the volatile material was removed under reduced pressure. The resulting product mixtures were shown to consist of two epimeric products. Purification was by either recrystallisation or chromatography on neutral alumina.

For compound **12**: 4-cyanobenzaldehyde (0.14 g, 1.11 mmol) and compound **2** (0.40 g, 1.11 mmol) were stirred for 35 min (0.5 g, 93%). Yellow oil (d.s. 91%); $\delta_H(C_6D_6)$ 7.5–6.9 (9 H, m, ArH), 5.43 (1 H, d, $^3J_{HH}$ 6.5, PhC*H*O), 4.95 (1 H, d, $^2J_{PH}$ 13.2, PhC*H*Ar), 3.15 (1 H, dqd, $^3J_{PH}$ 12.4, $^3J_{HH}$ 6.6, MeC*H*N), 2.49 (3 H, d, $^3J_{PH}$ 9.1, NMe), 0.56 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.29 (9 H, s, $SiMe_3$) and 0.00 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 137.46 (d, $^3J_{PC}$ 9.2, Ph-C$^{ipso}$), 159–125 (several resonances. Ar-C), 118.90 (d, $^6J_{PC}$ 1.7, CN), 79.17 (s, PhCHO), 73.09 (d, $^1J_{PC}$ 161.7, PCHAr), 61.04 (d, $^2J_{PC}$ 8.1, MeCHN), 30.83 (d, $^2J_{PC}$ 6.1, NMe), 15.35 (s, *Me*CHN), 3.80 (d, $^3J_{PC}$ 4.0, $NSiMe_3$) and −0.14 (s, $OSiMe_3$); $\delta_P(C_6D_6)$ 20.8 (s, major) and 19.8 (s, minor) (Found: $M^+$, 485.207 461. Calc. for $C_{24}H_{36}N_3O_2PSi_2$: *M*, 485.208 373).

For *compound* **13**: 4-nitrobenzaldehyde (0.22 g, 1.47 mmol) and compound **2** (0.52 g, 1.47 mmol) were stirred for 1 h (0.72 g, 97%). Yellow solid (d.s. 90%) (Found: C, 54.5; H, 7.05; N, 8.20. $C_{23}H_{36}N_3O_4PSi_2$ requires C, 54.6; H, 7.17; N, 8.31%); $\delta_H(C_6D_6)$ 8.0–6.9 (9 H, m, ArH), 5.38 (1 H, d, $^3J_{HH}$ 6.5, PhC*H*O), 4.94 (1 H, d, $^2J_{PH}$ 13.5, PhC*H*Ar), 3.14 (1 H, dqd, $^3J_{PH}$ 12.6, $^3J_{HH}$ 6.6, MeC*H*N), 2.47 (3 H, d, $^3J_{PH}$ 9.1, NMe), 0.53 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.21 (9 H, s, $SiMe_3$) and −0.05 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 147.43 (d, $^5J_{PC}$ 2.9, $C_6H_4NO_2$-C$^{ipso}$), 137.40 (d, $^3J_{PC}$ 9.2, Ph-C$^{ipso}$), 129–123 (several resonances, Ar-C), 79.20 (s, PhCHO), 72.97 (d, $^1J_{PC}$ 161.7, PCHAr), 61.06 (d, $^2J_{PC}$ 8.0, MeCHN), 30.72 (d, $^2J_{PC}$ 5.4, NMe), 15.34 (s, *Me*CHN), 3.79 (d, $^3J_{PC}$ 3.9, $NSiMe_3$) and −0.16 (s, $OSiMe_3$); $\delta_P$ ($C_6D_6$) 20.8 (s, major) and 19.6 (s, minor) (Found: $M^+$, 505.196 581. Calc. for $C_{23}H_{36}N_3O_4PSi_2$: *M*, 505.198 202).

For *compound* **14**: 4-chlorobenzaldehyde (0.21 g, 1.47 mmol) and compound **2** (0.52 g, 1.47 mmol) were stirred for 4 h (0.72 g, 97%). Yellow solid (d.s. 90%) (Found: $M^+$, 494.174 357; C, 56.1; H, 7.15; N, 5.45; Cl, 7.54. $C_{23}H_{36}ClN_2O_2PSi_2$ requires M, 494.174 152; C, 55.8; H, 7.33; N, 5.66; Cl, 7.16%); $\delta_H(C_6D_6)$ 7.5–6.9 (9 H, m, ArH), 5.39 (1 H, d, $^3J_{HH}$ 6.5, PhC*H*O), 4.92 (1 H, d, $^2J_{PH}$ 11.9, PhC*H*Ar), 3.08 (1 H, dqd, $^3J_{PH}$ 11.9, $^3J_{HH}$ 6.6, MeC*H*N), 2.44 (3 H, d, $^3J_{PH}$ 9.0, NMe), 0.49 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.27 (9 H, s, $SiMe_3$), −0.01 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 137.42 (d, $^3J_{PC}$ 9.2, Ph-C$^{ipso}$), 133.13 (d, $^5J_{PC}$ 4.1, $C_6H_4Cl$-C$^{ipso}$), 129–125 (several resonances, Ar-C), 78.88 (s, PhCHO), 73.17 (d, $^1J_{PC}$ 163.2, PCHAr), 60.88 (d, $^2J_{PC}$ 8.0, MeCHN), 30.75 (d, $^2J_{PC}$ 3.2, NMe), 15.15 (s, *Me*CHN), 3.69 (d, $^3J_{PC}$ 5.9, $NSiMe_3$) and −0.21 (s, $OSiMe_3$); $\delta_P(C_6D_6)$ 21.0 (s, major) and 20.9 (s, minor).

For *compound* **15**: 4-tolualdehyde (0.17 g, 1.47 mmol) and compound **2** (0.52 g, 1.47 mmol) were stirred for 16 h (0.68 g, 96%). Pale yellow oil (d.s. 91%); $\delta_H(C_6D_6)$ 7.6–6.9 (9 H, m, ArH), 5.43 (1 H, d, $^3J_{HH}$ 6.4, PhC*H*O), 5.04 (1 H, d, $^2J_{PH}$ 11.3, PhC*H*Ar), 3.11 (1 H, dqd, $^3J_{PH}$ 11.0, $^3J_{HH}$ 6.6, MeC*H*N), 2.49 (3 H, d, $^3J_{PH}$ 8.9, NMe), 2.08 (3 H, d, $^7J_{PH}$ 1.7, MeAr), 0.52 (d, 3 H, $^3J_{HH}$ 6.6, *Me*CHN), 0.32 (9 H, s, $SiMe_3$), 0.05 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 138–125 (several resonances, Ar-C), 78.94 (s, PhCHO), 74.32 (d, $^1J_{PC}$ 163.2, PCHAr), 61.17 (d, $^2J_{PC}$ 7.2, MeCHN), 31.08 (d, $^2J_{PC}$ 6.4, NMe), 21.18 (s, *Me*Ar), 15.36 (s, *Me*CHN), 4.04 (d, $^3J_{PC}$ 3.9, $NSiMe_3$), 0.17 (s, $OSiMe_3$); $\delta_P(C_6D_6)$ 21.5 (s, major) and 21.1 (s, minor) (Found: $M^+$, 474.230 006. Calc. for $C_{24}H_{39}N_2O_2PSi_2$: *M*, 474.228 774).

For compound **16**: 4-anisaldehyde (0.18 $cm^3$, 1.47 mmol) and compound **2** (0.52 g, 1.47 mmol) were stirred for 48 h (0.70 g, 97%). Pale yellow oil (d.s. 91%); $\delta_H(C_6D_6)$ 7.6–6.5 (9 H, m, ArH), 5.44 (1 H, d, $^3J_{HH}$ 6.4, PhC*H*O), 5.01 (1 H, d, $^2J_{PH}$ 10.8, PhC*H*Ar), 3.39 (3 H, s, *Me*OAr), 3.13 (1 H, dqd, $^3J_{PH}$ 11.7, $^3J_{HH}$ 6.5, MeC*H*N), 2.48 (3 H, d, $^3J_{PH}$ 9.0, NMe), 0.57 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN), 0.53 (9 H, s, $SiMe_3$) and 0.06 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6)$ 159.65 (d, $^5J_{PC}$ 2.7, $C_6H_4OMe$-C$^{ipso}$), 137.99 (d, $^3J_{PC}$ 9.4, Ph-C$^{ipso}$), 132–125 (several resonances, Ar-C), 79.12 (s, PhCHO), 74.00 (d, $^1J_{PC}$ 163.2, PCHAr), 61.15 (d, $^2J_{PC}$ 7.9, MeCHN), 54.73 (s, ArO*Me*), 31.05 (d, $^2J_{PC}$ 6.6, NMe), 15.40 (s, *Me*CHN), 4.07 (d, $^3J_{PC}$ 3.5, $NSiMe_3$) and 0.20 (s, $OSiMe_3$); $\delta_P(C_6D_6)$ 21.7 (s, major) and 21.3 (s, minor) (Found: $M^+$, 490.224 578. Calc. for $C_{24}H_{39}N_2O_3PSi_2$: *M*, 490.223 689).

For compound **17**: 2-nitrobenzaldehyde (0.16 g, 1.04 mmol) and compound **2** (0.37 g, 1.04 mmol) were stirred for 90 min (0.5 g, 94%). Yellow oil (d.s. 53%). Upon recrystallisation from a saturated pentane solution cooled to −35 °C, the major epimer crystallised selectively as crystals; $\delta_H(C_6D_6$; major epimer) 7.8–6.7 (9 H, m, ArH), 6.61 (1 H, d, $^2J_{PH}$ 15.6, PC*H*Ar), 5.44 (1 H, d, $^3J_{HH}$ 6.2, PhC*H*O), 2.99 (1 H, dqd, $^3J_{PH}$ 13.1, $^3J_{HH}$ 6.6, MeC*H*N), 2.19 (3 H, d, $^3J_{PH}$ 8.6, NMe), 0.68 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.30 (9 H, s, $SiMe_3$) and 0.11 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6$; major epimer) 137.34 (d, $^3J_{PC}$ 9.1, Ph-C$^{ipso}$, *Ph*CHO), 135–124 (several resonances, Ar-C), 78.98 (s, PhCHO), 67.91 (d, $^1J_{PC}$ 166.0, PCHAr), 61.54 (d, $^2J_{PC}$ 8.4, MeCHN), 32.38 (d, $^2J_{PC}$ 5.2, NMe), 14.97 (s, *Me*CHN), 3.61 (d, $^3J_{PC}$ 3.9, $NSiMe_3$) and −0.10 (s, $OSiMe_3$); $\delta_P(C_6D_6$; major epimer) 20.95; $\delta_H(C_6D_6$; minor epimer) 7.8–6.7 (9 H, m, ArH), 6.49 (1 H, d, $^2J_{PH}$ 13.4, PC*H*Ar), 5.39 (1 H, d, $^3J_{HH}$ 6.7, PhC*H*O), 3.04 (1 H, dqd, $^3J_{PH}$ 13.3, $^3J_{HH}$ 6.6, MeC*H*N), 2.39 (3 H, d, $^3J_{PH}$ 9.1, NMe), 0.60 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN), 0.27 (9 H, s, $SiMe_3$) and 0.10 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6$; minor epimer) 138–124 (several resonances, Ar-C), 79.25 (s, PhCHO), 66.67 (d, $^1J_{PC}$ 163.2, PCHAr), 60.80 (d, $^2J_{PC}$ 8.9, MeCHN), 30.42 (d, $^2J_{PC}$ 6.6, NMe), 15.50 (s, *Me*CHN), 3.57 (d, $^3J_{PC}$ 3.9, $NSiMe_3$) and −0.17 (s, $OSiMe_3$); $\delta_P(C_6D_6$; minor epimer) 21.00.

For compound **18**: 2-bromobenzaldehyde (0.12 $cm^3$, 1.05 mmol) compound **2** (0.37 g, 1.05 mmol) was stirred for 90 min (0.5 g, 95%). Yellow oil (d.s. 54%); $\delta_H(C_6D_6$; major epimer) 8.0–6.5 (9 H, m, ArH), 5.73 (1 H, d, $^2J_{PH}$ 12.2, PC*H*Ar), 5.47 (1 H, d, $^3J_{HH}$ 6.9, PhC*H*O), 3.06 (1 H, dqd, $^3J_{PH}$ 12.8, $^3J_{HH}$ 6.6, MeC*H*N), 2.48 (3 H, d, $^3J_{PH}$ 9.1, NMe), 0.51 (3 H, d, $^3J_{HH}$ 6.6, *Me*CHN), 0.31 (9 H, s, $SiMe_3$) and 0.09 (9 H, s, $SiMe_3$); $\delta_C(C_6D_6$; both epimers) 141–124 (several resonances, Ar-C), 79.21 (s, PhCHO), 78.78 (s, PhCHO), 73.09 (d, $^1J_{PC}$ 169.8, PCHAr, 72.51 (d, $^1J_{PC}$ 165.6, PCHAr), 61.79 (d, $^2J_{PC}$ 7.9, MeCHN), 61.03 (d, $^2J_{PC}$ 7.9, MeCHN), 32.94 (d, $^2J_{PC}$ 5.5, NMe), 30.96 (d, $^2J_{PC}$ 6.4, NMe), 15.74 (s, *Me*CHN), 14.90 (s, *Me*CHN), 3.99 (s, $NSiMe_3$), 3.98 (s, $NSiMe_3$), 0.16 (s, $OSiMe_3$) and 0.08 (s, $OSiMe_3$); $\delta_P(C_6D_6$; major epimer) 18.4 (s); $\delta_H(C_6D_6$; minor epimer) 8.0–6.5 (9 H, m, ArH), 5.75 (1 H, d, $^2J_{PH}$ 13.5, PC*H*Ar), 5.46 (1 H, d, $^3J_{HH}$ 6.5, PhC*H*O), 3.09 (1 H, dqd, $^3J_{PH}$ 11.0, $^3J_{HH}$ 6.6, MeC*H*N), 2.52 (3 H, d, $^3J_{PH}$ 8.9, NMe), 0.65 (3 H, d, $^3J_{HH}$ 6.7, *Me*CHN), 0.33 (9 H, s, $SiMe_3$) and 0.05 (9 H, s, $SiMe_3$); $\delta_P(C_6D_6$; minor epimer) 17.9 (s).

*Intramolecular* vs *Intermolecular Silyl-group Transfer. A Double Crossover Experiment.*—A solution of [(1*R*,2*S*)-*O*,*N*-ephedrine]PN($SiMe_3$)$_2$ **2** (0.21 g, 0.58 mmol) and (0.23 g, 0.58 mmol) in toluene solvent (20 $cm^3$) containing $NEt_3$ (80 $mm^3$, 0.58 mmol), which was added to prevent trace-acid-catalysed silyl-group exchange which may occur in systems of this nature,[14] was left for 16 h whereupon analysis by $^{31}P$ NMR spectroscopy revealed no silyl-group exchange to have occurred. Subsequently, PhCHO (117 $mm^3$, 1.16 mmol) was added and the mixture was stirred at ambient temperature for 3 h. The volatiles were then removed under reduced pressure and the resulting pale yellow viscous liquid was examined by $^{31}P$ NMR spectroscopy. [(1*R*,2*S*)-*O*,*N*-ephedrine]P($NSiMe_3$)-CHPh($OSiMe_3$) ($\delta$ 21.3) and {*N*,*N*′-($CH_2NMe)_2$}P(O)CHPh-($OSiPh_3$) ($\delta$ 30.3), the products of intramolecular silyl-group transfer, constitute >95% of the product mixture. Consequently, the intramolecular transfer of silyl groups appears to be the primary reaction mode operating in this system.

*Single-crystal X-ray Diffraction Analysis.*—All crystallographic measurements were carried out on a Stoe STADI4 diffractometer operating in the $\omega$–$\theta$ scan mode and (for compound **4**) using an on-line profile-fitting method.[44] In each

**Table 3** Crystallographic data for compounds **3**, **4**, **9** and **11**

| *Crystal Data* | | | | |
|---|---|---|---|---|
| Compound | **3** | **4** | **9** | **11** |
| Formula | $C_{16}H_{31}N_2OPSSi_2$ | $C_{13}H_{23}N_2OPSSi$ | $C_{27}H_{39}N_2O_2PSi_2$ | $C_{35}H_{46}N_2O_2P_2Si_2$ |
| M | 564.69 | 314.45 | 510.75 | 644.86 |
| Crystal dimensions/mm | 0.92 × 0.62 × 0.44 | 0.61 × 0.57 × 0.55 | 0.49 × 0.44 × 0.29 | 0.76 × 0.49 × 0.34 |
| Crystal system | Orthorhombic | Tetragonal | Orthorhombic | Orthorhombic |
| $a$/Å | 10.7911(6) | 9.7037(6) | 11.1893(6) | 9.0630(6) |
| $b$/Å | 12.1241(9) | | 12.8642(5) | 19.5294(9) |
| $c$/Å | 16.6992(10) | 30.217(5) | 20.8942(10) | 20.9326(9) |
| $V$/Å | 2186.1(2) | 3410.3(3) | 3007.5(2) | 3704.1(3) |
| Space group | $P2_12_12_1$ | $P4_12_22$ | $P2_12_12_1$ | $P2_12_12_1$ |
| $Z$ | 4 | 4 | 4 | 4 |
| $D_x$/g cm$^{-3}$ | 1.175 | 1.225 | 1.128 | 1.156 |
| $F$(000) | 832 | 1344 | 1096 | 1376 |
| $\mu$/mm$^{-1}$ | 3.092 | 0.349 | 1.759 | 1.926 |
| Radiation | Cu-K$\alpha$ | Mo-K$\alpha$ | Cu-K$\alpha$ | Cu-K$\alpha$ |
| $\lambda$/Å | 1.541 84 | 0.710 69 | 1.541 84 | 1.541 84 |
| max. transmission factor | 0.7312 | 0.9983 | 0.7712 | 0.8397 |
| min. transmission factor | 0.5301 | 0.8987 | 0.6440 | 0.6097 |
| Temperature/K | 200 | 200 | 200 | 200 |
| *Data Collection* | | | | |
| Scan mode | $\omega/\theta$ | $\omega/\theta$ | $\omega/\theta$ | $\omega/\theta$ |
| Scan width (° + $\alpha$-doublet splitting) | 1.05 | *a* | 1.05 | 1.05 |
| Scan speeds/° min$^{-1}$ | 1.5–8.0 | 1.5–8.0 | 1.5–8.0 | 1.5–8.0 |
| $2\theta_{min,max}$/° | 4.0, 130.0 | 4.0, 50.0 | 4.0, 130.0 | 4.0, 130.0 |
| No. of data collected | 3515 | 6016 | 5610 | 7125 |
| No. of unique data, $n$ | 3065 | 3010 | 4858 | 6015 |
| No. of observed data[b] | 2954 | 2929 | 4254 | 5730 |
| $R_{int}$[c] | 0.0403 | 0.0215 | 0.0264 | 0.0221 |
| $R_{sig}$[d] | 0.0210 | 0.0210 | 0.0280 | 0.0198 |
| *Refinement* | | | | |
| $\rho_{max}$, $\rho_{min}$/e Å$^{-3}$ | 0.21, −0.21 | 0.20, −0.17 | 0.25, −0.21 | 0.29, −0.37 |
| $\Delta/\sigma_{max}$ | 0.001 | 0.001 | 0.001 | 0.005 |
| $wR_2$[e] | 0.1069 | 0.0692 | 0.1105 | 0.1011 |
| $R_1$[f] | 0.0388 | 0.0251 | 0.0508 | 0.0370 |
| Weighting parameters $x$, $y$[g] | 0.0686, 0.8702 | 0.0381, 0.7915 | 0.0439, 2.0596 | 0.0704, 0.9113 |
| Extinction parameter, $x$[h] | 0.0086(6) | 0.0057(5) | 0.001 51(14) | 0.0021(2) |
| No. of parameters, $p$ | 217 | 409 | 316 | 397 |
| Goodness of fit[i] | 1.078 | 1.060 | 1.093 | 1.060 |
| 'Flack' parameter[j] | 0.00(3) | 0.00(8) | 0.00(3) | 0.01(2) |

[a] Scan divided into 30 steps, scan width and step sizes calculated from a learnt profile. [b] Criterion for observed reflection, $|F_o| > 4.0\sigma(|F_o|)$, used only in calculation of $R_1$. [c] $R_{int} = \Sigma|F_o^2 - F_o^2(mean)|/\Sigma[F_o^2]$. [d] $R_{sig} = \Sigma[\sigma(F_o^2)]/\Sigma[F_o^2]$. [e] $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2])^{\frac{1}{2}}$. [f] $R_1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. [g] Weighting scheme used: $w = [\sigma^2(F_o^2) + (xP)^2 + yP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. [h] Least-squares extinction expression used: $F_c^* = kF_c[1 + 0.001 * x * F_c^2 * \lambda^3]^{-\frac{1}{4}}$. [i] Goodness of fit $= \Sigma[w(F_o^2 - F_c^2)^2]/(n - p)]^{\frac{1}{2}}$. [j] See ref. 46.

case a unique set of data was collected together with its Freidel opposites. Crystal data are listed in Table 3 together with details of data collection and structure refinement. All four data sets were corrected for absorption semi-empirically using azimuthal $\psi$-scans.

Each structure was solved by direct methods using SHELXS-86[45] and refined by full-matrix least-squares (based on $F^2$) using SHELXL-93.[46] Refinement was essentially the same for all compounds such that all non-hydrogen atoms were refined with anisotropic displacement parameters. Geometrical restraints were applied to the phenyl groups such that each group remained flat with overall $C_{2v}$ symmetry. All hydrogen atoms were constrained in calculated positions (C–H = 0.93, 0.97 and 0.96 Å for phenyl, methine and methyl hydrogen atoms respectively) and were assigned a fixed isotropic thermal parameter of $n(U_{eq})$ of the parent carbon atom where $n$ was 1.5 for methyl hydrogens and 1.2 for all others. In all cases the absolute structure was confirmed by refinement of a 'Flack' parameter $x$.*[47]

* *Supplementary publication* (*see Instructions for Authors, January issue*): Tables of atomic coordinates, bond lengths and angles, and torsion angles for compounds **3**, **4**, **9** and **11** have been deposited at the Cambridge Crystallographic Data centre.

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