Stereoselective Phosphonylation of Aldehydes *via* Chiral Phosphordiamidites. A Potentially Versatile Asymmetric Route to Organophosphorus Biomolecules

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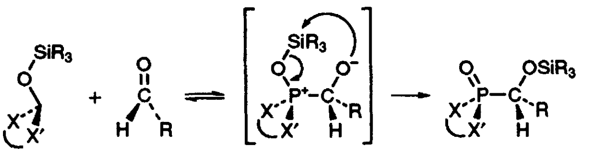
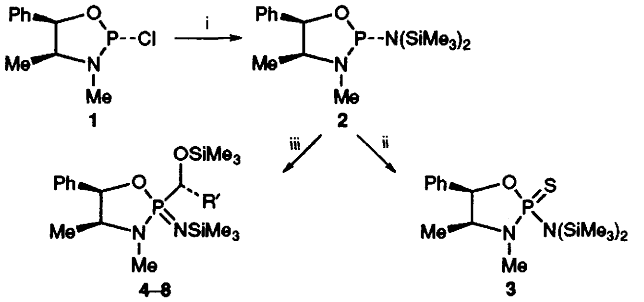
The novel, chiral phosphordiamidite, {*N,O*-(1*R*,2*S*)-MeNCHMeCHPhO}PN(SiMe$_3$)$_2$ containing deprotonated ephidrine has been shown to phosphonylate aldehydes readily to afford α-functionalised phosphonate esters with diasteroselectivities up to *ca.* 96%.

Compounds containing the phosphoro group [(RO)$_2$P(=O)O] are of fundamental significance in life, forming an intimate part of many of the most important molecules that control molecular replication, cell biochemistry and metabolic processes in all living species. Consequently, the mechanisms by which the phosphoro groups are transferred to and from substrates have been studied intensively. However, there are many physiologically active organophosphorus biomolecules that contain the related phosphono functionality [(RO)$_2$P(X)R] (X = O, S), where R is an carbon donor organic residue,[1] which are not accessible *via* the normal phosphoro transfer processes. Consequently, the development of new and controllable methodology for introducing the phosphono group into a substrate with both high chemo- and stereo-selectivity is highly desirable.



Scheme 1 Proposed mechanism of the Abramov reaction. R = alkyl, aryl; (X–X′) = chelating oxygen and/or nitrogen auxiliary.[11]



Scheme 2 (*i*) **1**, LiN(SiMe$_3$)$_2$ (1 equiv.) THF, −78 °C followed by 1 h room temp yield 83%; (*ii*) RCHO (R = Ph, Bu^t, 2-C$_{10}$H$_7$, Pr^n, Bu^n), toluene, 3–96 h, (*iii*) sulfur (1 equiv.), toluene, 30 min room temp., yield 87%; (No specific conformations of the oxazaphospholidine rings are implied in the scheme). Diastereoselectivities (92, 96, 91, 80, 81% for **4–8**) determined by integration of appropriate resonances in the ^{1}H (400 MHz) and ^{31}P{^{1}H} (36.4 MHz) NMR spectra of prepurified reaction mixtures. Isolated yields 83, 84, 86% for **4–6**, compounds **7** and **8** were not isolated.

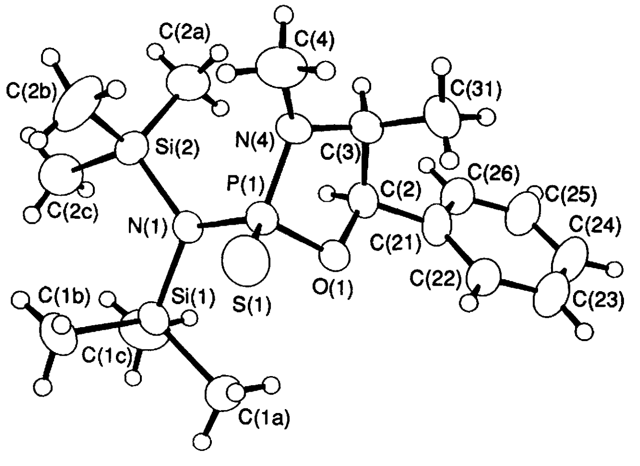


Fig. 1 Structure of {*O,N*-(1*R*,2*S*)-OCHPhCHMeNMe}P(=S)N(SiMe$_3$)$_2$ **3**. Selected distances (Å) and angles (°): S(1)–P(1) 1.931(2), N(1)–P(1) 1.654(3), N(4)–P(1) 1.661(3), O(1)–P(1) 1.604(2); P(1)–N(1)–Si(1) 116.86(14), P(1)–N(1)–Si(2) 119.91(14), Si(1)–N(1)–Si(2) 120.8((14), C(4)–N(4)–P(1) 122.5(3), C(3)–N(4)–P(1) 111.4(2), C(4)–N(4)–C(3) 117.8(3).

As part of a programme of research to design new main-group and transition-element reagents for stereoselective syntheses we are currently developing stoichiometric and catalytic asymmetric phosphonylation processes.[2] Interest in the area of asymmetric phosphonylation has increased markedly[3] over the last year with several excellent studies by both American and Japanese groups on asymmetric variants of the Abramov reaction[4] (Scheme 1), which provides versatile synthetic routes to α-functionalised phosphonic acids, a family of compounds which has desirable physiological properties, for example[5] as anti-bacterial, anti-parasitic and anti-viral agents.[6]

We are focusing on novel, chiral [1^N,3^E] bifunctional[7] organophosphorus(III) reagents of the forms (AUX)P–X–M and (RO)$_2$P–X–M(AUX) (X = O, N; M = main-group or

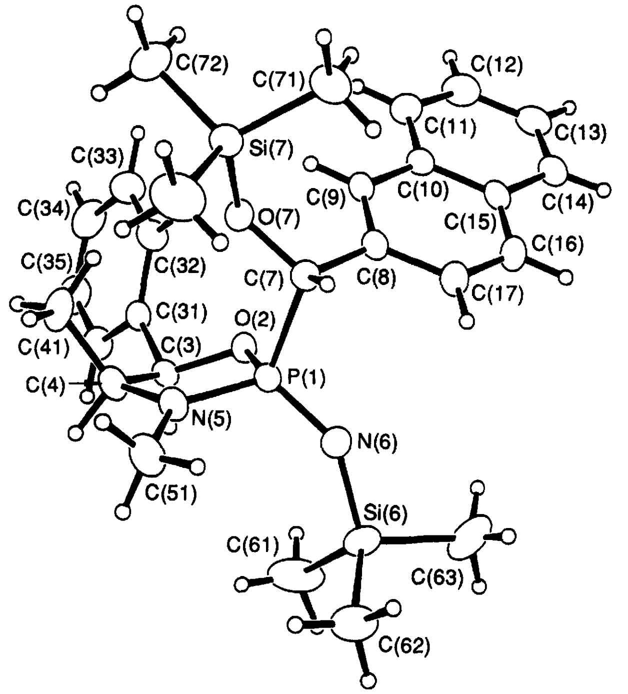


Fig. 2 Structure of {*O,N*-(1*R*,2*S*)-OCHPhCHMeNMe}P(=N-SiMe$_3$)C$_{11}$H$_8$(OSiMe$_3$) **6**. Selected distances (Å) and angles (°): P(1)–N(6) 1.525(3), P(1)–C(7) 1.841(3), P(1)–N(5) 1.637(3), P(1)–O(2) 1.606(2); P(1)–N(6)–Si(6) 140.8(2), C(7)–O(7)–Si(7) 122.2(2), C(51)–N(5)–P(1) 125.4(2), C(4)–N(5)–P(1) 114.9(2), C(51)–N(5)–C(4) 119.3(3).

transition-metal containing moiety; AUX is a chelating chiral auxiliary). Several features[8] influence the reactivity of reagents in the Abramov reaction, including: (*i*) increased reactivity results from having a more nitrogen-rich phosphorus coordination sphere and (*ii*) relative reactivity decreases in the order M = $SiMe_3 > SiEt_3 > SiPh_3 > SiBu^tMe_2$. These two design features have now been incorporated into a new compound, the phosphordiamidite [*N*,*O*-(1*R*,2*S*)-MeNCHMeCHPhO] $PN(SiMe_3)_2$ **2** [belonging to the (AUX)P–X–M family] containing deprotonated ephedrine, which we have found to be a very effective and highly stereoselective phosphonylating agent for aldehydes.

Compound **2** was isolated as a pale yellow liquid in high yield as shown in Scheme 2. NMR spectroscopy revealed it to consist of predominantly one epimer (> 98% by 400 MHz ^1H NMR spectroscopy) which we assign as having the S_P *anti*-configuration (Scheme 2). This seems the more reasonable assignment given that (*i*) the precursor **1**, is reported to possess an *anti* configuration and to react with Grignard reagents with overall retention of configuration at phosphorus,[9] (*ii*) the failure to resolve $^3J_{PH}$ coupling (<2Hz) to the [PhC*H*O] hydrogen is more consistent with the S_P configuration[2e] and (*iii*) oxidation of **2** with sulfur affords sulfide **3** in which the configuration of the phosphorus atom has been demonstrated to be R_P by single-crystal X-ray diffraction† (Fig. 1). Since the oxidation of **2** to **3** is expected to proceed with retention of configuration[10] this suggests that the phosphorus atom in **2** has the S_P configuration.

Compound **2** reacts readily with aldehydes (RCHO) *via* the Abramov reaction to afford {*N*,*O*-(1*R*,2*S*)-MeNCHMeCHPhO}$P(=NSiMe_3)CHR(OSiMe_3)$ (R = Ph **4**, Bu^t **5**, 2-naphthyl **6**, Pr^n **7**, Bu^n **8**).[2d] Particularly characteristic are the low-frequency ^{31}P resonances and the large $^1J_{PC}$ of 160–175 Hz. The stereoselectivities are high (Scheme 2) and comparable to the best previously reported selectivities.[3]

Both chemical[3,11] and isotopic labelling[8] studies suggest that the Abramov phosphonylation of aldehydes proceeds with overall *retention* of configuration at phosphorus in accord with Scheme 1.[11] Consequently, we envisaged the major products of **4**–**8** to have S_P configurations at phosphorus (Scheme 2). This assignment is supported by the small $^3J_{PH}$ coupling (<2 Hz) between phosphorus and the PhC*H*O methine hydrogens for each of **4**–**6** which is more consistent with the S_P configuration.[12] Conclusive evidence was subsequently obtained by a single-crystal X-ray study† on the major isomer of **6** (Fig. 2) which confirms the (S_P, S_C) configuration.[12] We envisage that the other esters will have similar configurations.

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Footnotes

† *Crystal data* for compound **3**: $C_{16}H_{31}N_2OPSSi_2$, M = 386.64, orthorhombic, space group $P2_12_12_1$, a = 10.7977(6), b = 12.1241(9), c = 16.6992(10) Å, U = 2099.6(4) nm^{-3}, Z = 4, D_c = 1.175 g cm^{-3}, μ = 3.092 mm^{-1}, $F(000)$ = 832, $wR_2 = [\Sigma w(F_o^2 - F_c^2)/\Sigma F_o^2]^{\frac{1}{2}}$ = 0.1069 on all 3065 reflections (one octant + Friedel opposites), $R_1 = \Sigma||F_o| - |F_c||/\Sigma F_o$ = 0.0388 [on 3065 F values with $F_o^2 > 2.0\sigma(F_o^2)$], goodness of fit on F^2 = 1.078 on 217 parameters.

6: $C_{27}H_{39}N_2O_2PSi_2$, M = 510.75, orthorhombic, space group $P2_12_12_1$, a = 11.1892(6), b = 12.8642(5), c = 20.8942(10) Å, U = 3007.5(2) nm^{-3}, Z = 4, D_c = 1.128 g cm^{-3}, μ = 1.759 mm^{-1}, $F(000)$ = 1096, wR_2 = 0.1105 on all 4858 reflections (one octant + Friedel opposites), R_1 = 0.0420 [on 4254 F values with $F_o^2 > 2.0\sigma(F_o^2)$], goodness of fit on F^2 = 1.093 on 316 parameters.

Crystallographic data for both compounds were collected in the range $4.0 < 2\theta < 130.0°$ at 200 K on a Stoe STADI4 diffractometer using ω/θ scans and graphite-monochromated copper $K\alpha$ radiation (λ = 1.54184 Å). Both data sets were corrected for absorption using azimuthal ψ-scans. Both structures were solved by direct methods using SHELXS-86[13] and both were refined on F^2 using SHELXL-93.[14] Refinement was similar for both structures with all non-hydrogen atoms refined with anisotropic thermal parameters and restraints applied to the phenyl groups so that they remained flat with overall C_{2v} symmetry. Hydrogen atoms were included in calculated positions and were assigned a fixed isotropic thermal parameter of $n(U_{eq})$ of the parent non-hydrogen atom where n was 1.5 for methyl atoms and 1.2 for all other hydrogen atoms. In each case, the absolute structure was based initially on the known configuration of the ephedrine chiral auxiliary (1*R*,2*S*) and confirmed later by the refinement of a 'Flack' parameter[15] to 0.00(3) for both structures. The weighting scheme $w = 1/[\sigma^2(F_o^2) + (xP)^2 + yP]$ was used where $P = (F_o^2 + 2F_c^2)/3$ and x,y were 0.0686, 0.8702 and 0.0439, 2.0596 for **3** and **6** respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 *The Role of Phosphonates in Living Systems*, ed. R. L. Hildebrand, CRC Press, Boca Raton, FL, 1983.

2 (*a*) V. Sum, A. J. Davies and T. P. Kee, *J. Chem. Soc., Chem. Commun.*, 1992, 1771; (*b*) I. F. Pickersgill, P. G. Devitt and T. P. Kee, *Synth. Commun.*, 1993, **23**, 1643; (*c*) N. Greene and T. P. Kee, *Synth. Commun.*, 1993, **23**, 1651; (*d*) V. Sum and T. P. Kee, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1369; (*e*) V. Sum and T. P. Kee, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2701.

3 (*a*) N. J. Gordon and S. A. Evans, Jr., *J. Org. Chem.*, 1993, **58**, 5293; 5295; (*b*) V. Blazis, A. De La Cruz, K. Koeller and C. D. Spilling, *Phosphorus, Sulfur, Silicon*, 1993, **73**, 159; (*c*) T. Yokomatsu, T. Yamagishi and S. Shibuya, *Tetrahedron Asymmetry*, 1993, **4**, 1779; 1783 and references cited therein.

4 V. S. Abramov, *Dokl. Acad. Nauk SSSR*, 1954, **95**, 991.

5 See for example; E. S. Krol, J. M. David and G. R. J. Thatcher, *J. Chem. Soc., Chem. Commun.*, 1991, 118; Z. Li, S. Racha and E. Abushanab, *Tetrahedron Lett.*, 1993, **34**, 3539; T. R. Burke Jr., M. S. Smyth, M. Nomizu, A. Otaka and P. P. Roller, *J. Org. Chem.*, 1993, **58**, 1336; R. Hamilton, B. J. Walker and B. Walker, *Tetrahedron Lett.*, 1993, **34**, 2847.

6 L. J. Jennings, M. Macchia and A. Parkin, *J. Chem. Soc., Perkin Trans 1*, 1992, 2197; D. M. Coe, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2695 and references cited therein.

7 T. P. Kee, *Educ. Chem.*, in the press.

8 P. G. Devitt and T. P. Kee, *J. Chem. Soc., Perkin Trans. 1* to be submitted for publication.

9 J. V. Carey, M. D. Barker, J. M. Brown and M. J. H. Russel, *J. Chem. Soc., Perkin Trans. 1*,, 1993, 831.

10 C. R. Hall and T. D. Inch, *Tetrahedron Lett.*, 1976, **40**, 3645.

11 D. A. Evans, K. M. Hurst and J. M. Takacs, *J. Am. Chem. Soc.*, 1978, **100**, 3467.

12 C. H. Schwalbe, G. Chopra, S. Freeman, J. M. Brown and J. V. Carey, *J. Chem. Soc., Perkin Trans. 2*, 1991, 2081.

13 G. M. Sheldrick, *Acta. Crystallogr., Sect. A.*, 1990, **46**, 467.

14 G. M. Sheldrick, *J. Appl. Crystallogr.*, 1993, in preparation.

15 H. D. Flack, *Acta. Crystallogr., Sect. A*, 1983, **39**, 876.