

## New, Chiral Silylated Organophosphorus(III) Reagents: Syntheses and Applications in the Asymmetric Phosphorylation of Aldehydes

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The new silylated organophosphorus(III) compounds, (1*R*,2*S*)-(O,*N*-ephedrine)POSiR<sub>3</sub> (R<sub>3</sub> = Ph<sub>3</sub>, ButMe<sub>2</sub>, Et<sub>3</sub>) have been synthesised and shown to react with benzaldehyde to afford the phosphonate esters (1*R*,2*S*)-(O,*N*-ephedrine)P(=O)CHPh(OSiR<sub>3</sub>) with good stereoselectivity.

Silylphosphite esters of the form (RO)<sub>2</sub>POSiR'<sub>3</sub>, have been shown to be remarkably versatile phosphorylating agents.<sup>1</sup> For example, they react with alkyl halides in the Arbuzov reaction,<sup>2</sup> with aldehydes, ketones and imines in the Abramov reaction<sup>3</sup> and with azides in the Staudinger reaction,<sup>4</sup> in each

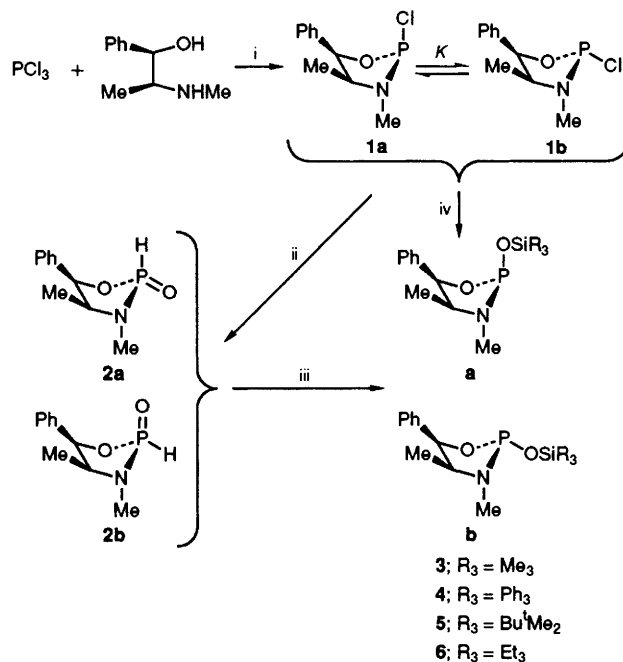
case affording products containing the phospho group, [(RO)<sub>2</sub>P(=O)]. There have been few reports of asymmetric phosphorylation reactions *via* chiral phosphite reagents. Previous work with chiral silyl phosphites has involved the generation of asymmetric centres at either the silicon or

phosphorus atoms but these compounds are difficult to synthesise and racemisation is problematic.<sup>5</sup> We report here the synthesis of a range of new, silylated organophosphorus(III) esters containing homochiral oxazaphospholane rings derived from (1*R*,2*S*)-(-)-ephedrine and the diastereoselective reactions of these reagents with benzaldehyde to afford phosphonate esters.

(1*R*,2*S*)-(O,*N*-Ephedrine)PCl<sub>2</sub> **1** was readily synthesised in 80% yield as shown in Scheme 1.† At room temperature, the <sup>1</sup>H NMR spectrum of **1** indicates it to be of sufficient purity for synthetic purposes and reveals resonances due only to a single species but upon cooling to -52 °C, separate signals are observed for two, isomeric compounds which we assign to the two possible diastereoisomers **1a** and **b** (Scheme 1). On the basis of the relative magnitudes of the coupling constants between phosphorus and the PhCHO hydrogen for **1a** and **b**, we assign the major isomer as **1a**.<sup>6</sup> Interestingly, Inch and Hall reported the preferential isolation of epimer **1b** from a similar reaction but using *N*-methylmorpholine as base.<sup>7</sup> The equilibrium constant (*K*) between **1a** and **b**, calculated from the <sup>1</sup>H NMR spectrum, is *ca.* 0.1 (at -52 °C), which translates into a diastereoisomeric excess (d.e.) of 82% of **1a**.

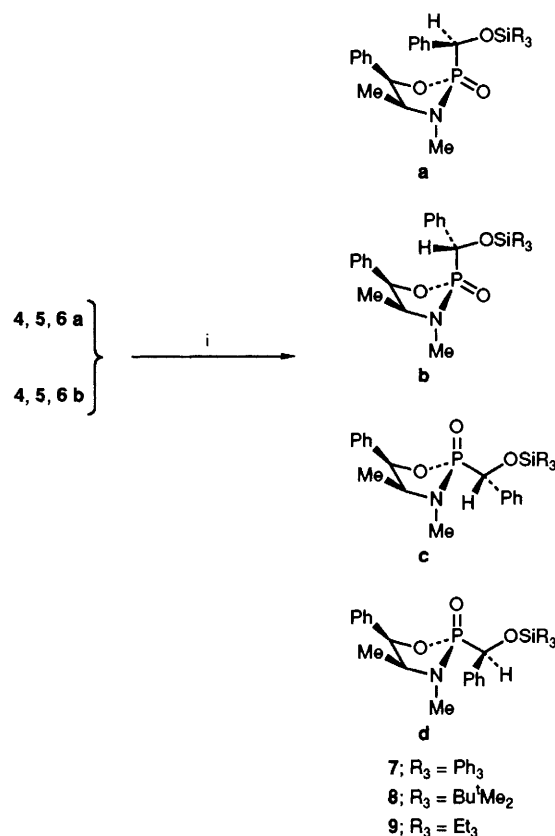
Treatment of the diastereoisomeric mixture **1** with H<sub>2</sub>O and NEt<sub>3</sub> afforded (1*R*,2*S*)-(O,*N*-ephedrine)P(=O)H **2** as a colourless solid (Scheme 1). Like **1**, compound **2** exists as a mixture of two epimers and by the same criteria a d.e. of 12% is found for **2a**. Silylation of **2** with a stoichiometric mixture of Me<sub>3</sub>SiCl and NEt<sub>3</sub> does not proceed very cleanly, unlike analogous silylation reactions of secondary phosphites;<sup>8</sup> <sup>31</sup>P

NMR spectroscopy revealed resonances at δ 130.1 and 128.2 in a ratio of 1.2:1, which may be assigned to the diastereoisomers **3b** and **a** respectively, but the presence of several additional resonances between δ 25 and -14 due to four-coordinate phosphorus species suggests that the ephedrine



**Scheme 1 Reagents and conditions:** i, NEt<sub>3</sub>, 3 equiv., toluene, 16 h room temp. (ephedrine added dropwise to a solution of PCl<sub>3</sub> and NEt<sub>3</sub> at -78 °C before warming to room temp.) yield: 80%, d.e. 82%; ii, H<sub>2</sub>O, 1 equiv., NEt<sub>3</sub>, 2 equiv., toluene, 1 h room temp., yield: 74%, d.e. 12%; iii, Me<sub>3</sub>SiCl, 1 equiv., NEt<sub>3</sub>, 2 equiv., toluene, 5 h, room temp; iv, R<sub>3</sub>SiOH, 1 equiv., NEt<sub>3</sub>, 2 equiv., toluene, 16 h, room temp., [yield (%), d.e. (%): **4** 91, 87; **5** 78, 77; **6** 82, 71]

† Selected NMR data for **1**–**9**. Reported in CDCl<sub>3</sub> at 298 K unless noted otherwise; coupling *J*H<sub>2</sub>, <sup>31</sup>P(<sup>1</sup>H)NMR ref. 85% H<sub>3</sub>PO<sub>4</sub>. The major isomer only is quoted for **7**–**9**. For **1a**: <sup>1</sup>H (C<sub>7</sub>D<sub>8</sub>, 221 K): δ 7.0 (m, 5H, Ph-*H*), 5.42 (d, 1H, <sup>3</sup>J<sub>HH</sub> 8, PhCHO), 3.09 (dq, 1H, <sup>3</sup>J<sub>HH</sub> 8, 7, MeCHN), 2.12 (d, 3H, <sup>3</sup>J<sub>PH</sub> 16, NMe), 0.21 (d, 3H, <sup>3</sup>J<sub>HH</sub> 7, MeCHN); <sup>31</sup>P(<sup>1</sup>H) (C<sub>7</sub>D<sub>8</sub>): δ 170.4 (average for isomers **1a** and **b**). For **1b**: <sup>1</sup>H (C<sub>7</sub>D<sub>8</sub>, 221 K): δ 7.0 (m, 5H, Ph-*H*), 5.06 (dd, 1H, <sup>3</sup>J<sub>HH</sub> 7, <sup>3</sup>J<sub>PH</sub> 4 run with <sup>31</sup>P coupling, PhCHO), 3.09 (m, obscured by resonance due to **1a**, MeCHN), 2.24 (d, 3H, <sup>3</sup>J<sub>PH</sub> 19, NMe), 0.66 (d, 3H, <sup>3</sup>J<sub>HH</sub> 7, MeCHN). For **2**: <sup>1</sup>H: δ 7.2–7.0 (m, 10H, Ph-*H*, **2a**, **b**), 7.31 (d, 1H, <sup>1</sup>J<sub>PH</sub> 664, P-*H*, **2a**), 7.27 (d, 1H, <sup>1</sup>J<sub>PH</sub> 655, P-*H*, **2b**), 5.59 (dd, 1H, <sup>3</sup>J<sub>HH</sub> 6, <sup>3</sup>J<sub>PH</sub> 2, PhCHO, **2a**), 5.34 (dd, 1H, <sup>3</sup>J<sub>HH</sub> 6, <sup>3</sup>J<sub>PH</sub> 6, PhCHO, **2b**), 3.49 (m, 2H, <sup>3</sup>J<sub>HH</sub> 6, MeCHN, **2a/b**), 2.65 (d, 3H, <sup>3</sup>J<sub>PH</sub> 10, NMe, **2a/b**), 2.56 (d, 3H, <sup>3</sup>J<sub>PH</sub> 10, NMe, **2a/b**), 0.65 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6, MeCHN, **2a/b**), 0.56 (d, 3H, <sup>3</sup>J<sub>HH</sub> 7, MeCHN, **2a/b**). <sup>31</sup>P: δ 21.0 (dm, <sup>1</sup>J<sub>PH</sub> 651, **2b**), 17.8 (dpnt, <sup>1</sup>J<sub>PH</sub> 660, <sup>1</sup>J<sub>PH</sub> 10, **2a**). For **3**: <sup>31</sup>P(<sup>1</sup>H): δ 130.1 (s, **3b**), 128.2 (s, **3a**). For **4**: <sup>1</sup>H: δ 7.7–7.0 (m, 20H, Ph-*H*, **4a/b**), 5.44 (dd, 1H, <sup>3</sup>J<sub>HH</sub> 6.6, <sup>3</sup>J<sub>PH</sub> 2.8, PhCHO, **4b**), 5.41 (d, 1H, <sup>3</sup>J<sub>HH</sub> 7.3, PhCHO, **4a**), 3.54 (m, 1H, MeCHN, **4b**), 3.42 (m, 1H, <sup>3</sup>J<sub>HH</sub> 7.3, 6.5, <sup>3</sup>J<sub>PH</sub> 2.6, MeCHN, **4a**), 2.47 (d, 3H, <sup>3</sup>J<sub>PH</sub> 13.4, NMe, **4a**), 2.63 (d, 3H, <sup>3</sup>J<sub>PH</sub> 12, NMe), 0.79 (d, 3H, <sup>3</sup>J<sub>HH</sub> 7, MeCHN, **4b**), 0.58 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6.5, MeCHN, **4a**). <sup>31</sup>P(<sup>1</sup>H): δ 130.1 (s, **4b**), 127.4 (s, **4a**). For **5**: <sup>1</sup>H: δ 7.3–7.0 (m, 5H, Ph-*H*), 5.47 (d, 1H, <sup>3</sup>J<sub>HH</sub> 7.3, PhCHO, **5a**), 5.32 (dd, 1H, <sup>3</sup>J<sub>HH</sub> 6.7, <sup>3</sup>J<sub>PH</sub> 2.6, PhCHO, **5b**), 3.38 (m, 1H, <sup>3</sup>J<sub>HH</sub> 6.5, <sup>3</sup>J<sub>PH</sub> 2.4, MeCHN, **5a**), 3.29 (m, 1H, <sup>3</sup>J<sub>HH</sub> 6.6, MeCHN, **5b**), 2.61 (d, 3H, <sup>3</sup>J<sub>PH</sub> 12.4, NMe, **5b**), 2.43 (d, 3H, <sup>3</sup>J<sub>PH</sub> 13.6, NMe, **5a**), 0.85 (s, 9H, Bu<sup>t</sup>, **5b**), 0.84 (s, 9H, Bu<sup>t</sup>, **5a**), 0.63 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6.7, MeCHN, **5b**), 0.52 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6.5, MeCHN, **5a**), 0.08 (s, Me<sub>2</sub>Si). <sup>31</sup>P(<sup>1</sup>H): δ 130.5 (s, **5b**), 128.2 (s, **5a**). For **6**: <sup>1</sup>H: δ 7.4–7.1 (m, 5H, Ph-*H*), 5.59 (d, 1H, <sup>3</sup>J<sub>HH</sub> 7.2, PhCHO, **6a**), 5.43 (dd, 1H, <sup>3</sup>J<sub>HH</sub> 7.0, <sup>3</sup>J<sub>PH</sub> 2.7, PhCHO, **6b**), 3.58 (m, 2H, MeCHN, **6a/b**), 2.63 (d, 3H, <sup>3</sup>J<sub>PH</sub> 12.5, NMe, **6b**), 2.46 (d, 3H, <sup>3</sup>J<sub>PH</sub> 13.8, NMe, **6a**), 1.0–0 (m, CH<sub>3</sub>CH<sub>2</sub>, MeCHN, **6a/b**). <sup>31</sup>P(<sup>1</sup>H): δ 130.5 (s, **6b**), 128.4 (s, **6a**). For **7**: <sup>1</sup>H: δ 7.9–7.0 (m, 25H, Ph-*H*), 5.60 (d, 1H, <sup>3</sup>J<sub>HH</sub> 6.3, PhCHO), 5.16 (d, 1H, <sup>2</sup>J<sub>PH</sub> 11.1, PhCHP), 3.44 (dq, 1H, <sup>3</sup>J<sub>HH</sub> 6.5, <sup>3</sup>J<sub>PH</sub> 11.1, MeCHN), 2.39 (d, 3H, <sup>3</sup>J<sub>PH</sub> 8.6, NMe), 0.29 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6.7, MeCHN). <sup>31</sup>P(<sup>1</sup>H): δ 34.7 (s). For **8**: <sup>1</sup>H: δ 7.4–7.0 (m, 10H, Ph-*H*), 5.57 (d, 1H, <sup>3</sup>J<sub>HH</sub> 6.4, PhCHO), 5.12 (d, 1H, <sup>2</sup>J<sub>PH</sub> 12.0, PhCHP), 3.47 (dq, 1H, <sup>3</sup>J<sub>HH</sub> 6.6, <sup>3</sup>J<sub>PH</sub> 11.0, MeCHN), 2.66 (d, 3H, <sup>3</sup>J<sub>HH</sub> 8.5, NMe), 0.82 (s, 9H, Bu<sup>t</sup>), 0.30 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6.7, MeCHN), 0.03 (s, 3H, Me<sub>2</sub>Si), -0.11 (s, 3H, Me<sub>2</sub>Si). <sup>31</sup>P(<sup>1</sup>H): δ 35.1 (s). For **9**: <sup>1</sup>H: δ 7.7–7.0 (m, 10H, Ph-*H*), 5.54 (d, 1H, <sup>3</sup>J<sub>HH</sub> 6.4, PhCHO), 5.09 (d, 1H, <sup>2</sup>J<sub>PH</sub> 11.7, PhCHP), 3.46 (dq, 1H, <sup>3</sup>J<sub>HH</sub> 6.6, <sup>3</sup>J<sub>PH</sub> 11.5, MeCHN), 2.63 (d, 3H, <sup>3</sup>J<sub>HH</sub> 8.6, NMe), 0.81 [m, 6H, Si(CH<sub>2</sub>Me)<sub>3</sub>], 0.48 [t, 9H, <sup>3</sup>J<sub>HH</sub> 7.2, Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>], 0.42 (d, 3H, <sup>3</sup>J<sub>HH</sub> 6.9, MeCHN). <sup>31</sup>P(<sup>1</sup>H): δ 35.9 (s).



**Scheme 2 Reagents and conditions:** i, PhCHO, 16 h, room temp., [recrystallised yields (%) **7** (88), **8** (84) and **9** (77)]

chelate ring has been partially ruptured: indeed, electrophilic attack on a chelated ephedrine ring has been reported previously.<sup>9</sup> However, **1** can be silylated directly using R<sub>3</sub>SiOH (R<sub>3</sub> = Ph<sub>3</sub>, Bu<sup>t</sup>Me<sub>2</sub>, Et<sub>3</sub>) to give the phosphorus(III) silyl esters, **4–6** respectively in high yields (Scheme 1). Once again, two diastereoisomers are observed for **4–6**† the major isomer in each case presumably being of the type **a** based on the coupling constant arguments used for **1** and **2**.<sup>6</sup> Inversion of configuration at phosphorus is slow on the NMR timescale and both isomers for each of **4–6** are resolved at ambient temperature allowing the d.e. values to be obtained directly from the <sup>1</sup>H NMR spectra (Scheme 1).

The esters **4–6** react with benzaldehyde at room temperature, in a similar fashion to other silylated phosphites,<sup>3</sup> to produce α-siloxy phosphonate esters **7–9** (Scheme 2).† Compounds **7–9** contain asymmetric centres at phosphorus and the α-carbon atoms in addition to the chiral auxiliary and so there are potentially four diastereoisomers for each ester (**a–d** in Scheme 2). Indeed, <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures for **7–9** reveals the presence of multiple products, but in each case one of the isomers **a–d** constitutes the major product; up to 77% **7**, 89% **8** and 67% **9** of the crude mixtures respectively. Recrystallisation of these mixtures from pentane affords **7–9** as white, crystalline solids in up to 88% isolated yield and 95% isomeric purity (highest purity obtained for **8**). On the basis of steric and NMR<sup>6</sup> considerations, we believe that the major isomer is of the type **c** in each

case, but this has yet to be confirmed. Thus, both the auxiliary and the nature of the silicon substituents appear to influence the stereoselectivity of reaction.

Studies are currently in progress to delineate fully the mechanism(s) and stereochemical selectivities observed and to further simplify and improve the latter by the use of chiral auxiliaries with better enantiofacial selectivity.

We thank the SERC for a studentship (to V. S.).

Received, 26th August 1992; Com. 2104587G

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