# Diphenylphosphinoyl chloride as a chlorinating agent – the selective double activation of 1,2-diols†

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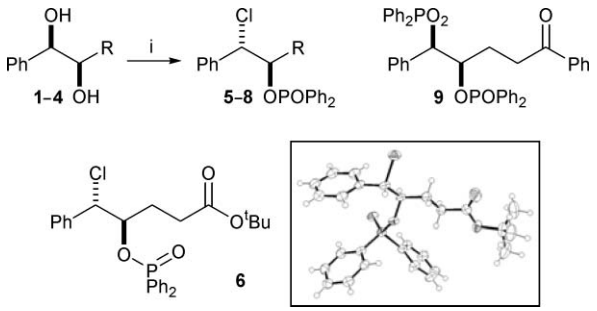
Treatment of 1,2-diols with diphenylphosphinoyl chloride in pyridine produces β-chloroethyl phosphinates which react with complete control of stereochemistry to give epoxides and azido-alcohols, useful intermediates in cyclopropane synthesis.

Stereochemically pure 1,2-diols, derived either from the catalytic asymmetric dihydroxylation of olefins[1] or from other sources, are important intermediates in asymmetric synthesis. The hydroxy groups can be activated and differentially displaced by a variety of nucleophiles, often with high levels of regiocontrol due to adjacent electronic conjugating groups. Cyclic acylium ions, most often generated by reaction of diols with orthoesters[2–4] or equivalents,[5] can be ring opened with fluoride,[5] chloride[2–4] and bromide to give vicinial halo-acylates.[3] Along with cyclic carbonates,[6] sulfites[7–9] and sulfates,[10–12] chloro- and bromo-ethyl esters are valuable intermediates in the stereoselective synthesis of epoxides,[6,13] β-amino-alcohols[8,9,14] diamines[11] and amino-acids.[7,10,15–17] In this paper we describe a new and simple method that provides not only the regioselective differentiation of 1,2-diols but also selective bis-activation.

During synthesis of cyclopropane-containing γ-amino ketones[18] and esters[19] the attempted bis-diphenylphosphinoylation of diols **1** and **2** with diphenylphosphinoyl chloride in pyridine resulted in inclusion of only one phosphinoyl group. Initially it was assumed that only one hydroxy group had reacted, but mass spectrometry and X-ray crystallography indicated that chlorine had replaced the hydroxy at the benzylic position with stereochemical inversion to give chloro-phosphinates **5** and **6** (Scheme 1). Methyl and diphenyl substituted diols[13] **3** and **4** also react selectively (Table 1). Only the reaction of diol **1** produced a small amount (3%) of bis-phosphinate product[18] **9**. The reactions of diols **1**, **2** and **3** produced only single stereo- and regioisomers of chloro-phosphinates.

The reaction of methyl cinnamate-derived diol[17] **10** produced a mixture of chloro-phosphinate regioisomers **11** and **12** along with bis-phosphinate **13** (Scheme 2). This result indicated that esters can also mediate the adjacent introduction of chlorine into 1,2-diols. This was confirmed when non-aryl diol[20] **14** produced only the 2-Cl isomer of chloro-phosphinate **15**.

X-Ray crystallography of chloro-phosphinate **6** (Scheme 1) showed that the introduction of chlorine occurred with inversion of stereochemistry,[21] probably by $S_N2$ reaction of chloride ion with the activated diol at the more activated position adjacent to either the aryl or ester groups. Hydrobenzoin **4** was chosen as a substrate to test the mechanism as it had substituted only once

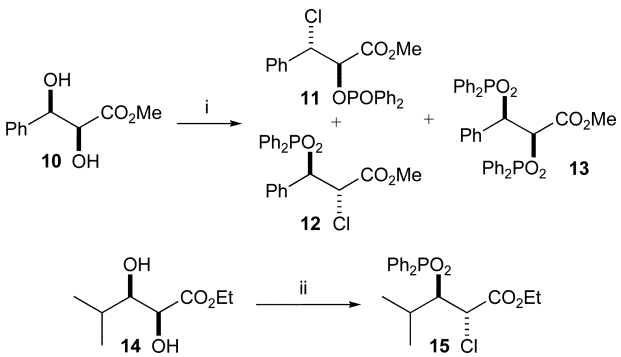



**Scheme 1** *Reagents and conditions*: i) $Ph_2POCl$, pyridine, see Table 1. Inset: X-ray crystal structure of chloro-phosphinate **6** with thermal ellipsoids at 50% probability.

**Table 1** Chloro-phosphinoylation of diols (see Scheme 1)

| R | Diol | Chloro-phosphinate | Yield (%)[a] |
|---|---|---|---|
| $(CH_2)_2COPh$ | **1** | **5** | 66[b] |
| $(CH_2)_2CO_2{}^tBu$ | **2** | **6** | 83 |
| Me | **3** | **7** | 60 |
| Ph | **4** | **8** | 71 |

[a] Isolated yield of chloro-phosphinate. [b] 3% biphosphinate **9** also isolated.




**Scheme 2** *Reagents and conditions*: i) $Ph_2POCl$, pyridine, **11** : **12** : **13** = 52 : 17 : 31 (by $^1H$ NMR); ii) $Ph_2POCl$, pyridine, 45%.

despite containing two benzylic alcohols. Two possible reaction pathways are either phosphinoylation of both alcohols followed by displacement of one phosphinate by chloride, or alternatively, reaction of the mono-phosphinate **16** with chloride, followed by a second phosphinoylation (Scheme 3).

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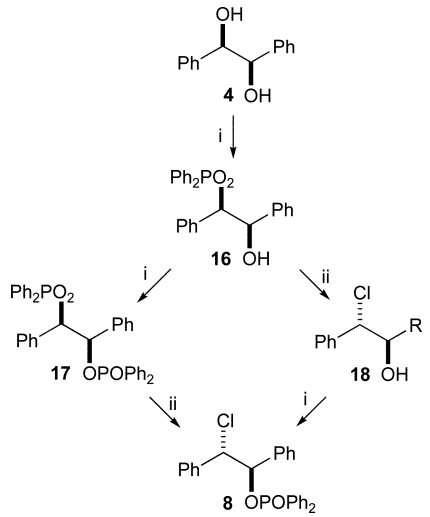
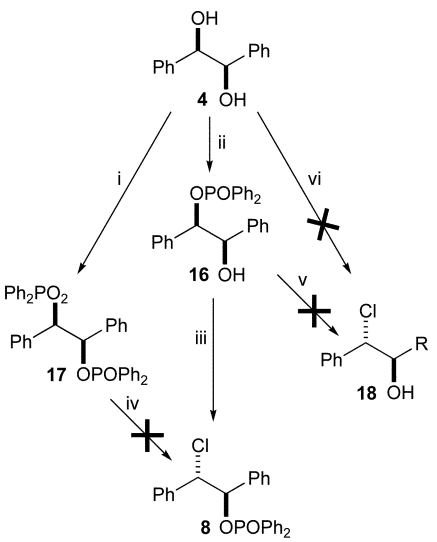


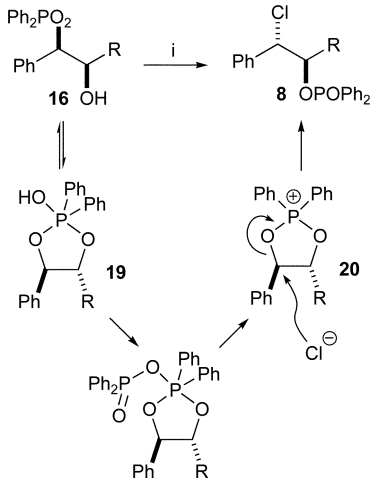
**Scheme 3** i) Phosphinoylation; ii) $S_N2$ diplacement by chloride.

The mono- and bis-phosphinates **16** and **17** were therefore synthesised from diol **4** to investigate their reactions with chloride ions in pyridine. Interestingly, neither the mono- nor bis-phosphinate reacts with pyridinium chloride, suggesting that these reactions do not take place in the chloro-phosphination reaction (Scheme 4). Unlike bis-phosphinate **17**, the mono-phosphinate **16** does react with diphenylphosphinoyl chloride to give chloro-phosphinate **8**. Finally, diol **4** does not react directly with pyridinium chloride.



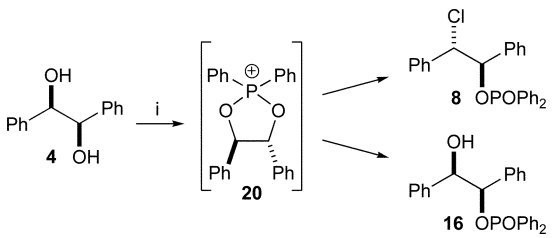
**Scheme 4** *Reagents and conditions*: i) $Ph_2POCl$, $Et_3N$, DMAP, THF, 36%; ii) $Ph_2POCl$, $Et_3N$, DMAP, $CH_2Cl_2$, 24%; iii) $Ph_2POCl$, pyridine, >95% (by $^1H$ NMR); iv) pyridine·HCl, pyridine, or $Ph_2POCl$, pyridine, 0%; v) pyridine·HCl, pyridine, 0%; vi) pyridine·HCl, pyridine, 0%.

Given that mono-phosphinate **16** reacts with diphenylphosphinoyl chloride to give chloro-phosphinate **8**, but that bis-phosphinate **17** is not an intermediate, an alternative pathway to those suggested above must be sought. In addition, as chloride seems not to be nucleophilic enough to displace diphenylphosphinate in these reaction conditions, a more electrophilic intermediate must be involved. Cyclic phosphonium ion **20**, formed *via* phosphinoylation of phosphorane **19**, is suitably reactive (Scheme 5).



**Scheme 5** *Reagents and conditions*: i) $Ph_2POCl$, pyridine.

Independent synthesis of phosphonium ion **20** and reaction with chloride ion was achieved *via* the reaction of diol **4** with $Ph_2PCl_3$ in pyridine (Scheme 6).[22] Along with unreacted diol, the major product of the reaction is chloro-phosphinate **8**. Peaks due to mono-phosphinate **16** can also be observed in the $^1H$ NMR spectrum of the crude reaction mixture. These products provide good evidence for the participation of phosphonium ion **20** in the chloro-phosphinoylation of diols with diphenylphosphinoyl chloride according to the mechanism proposed in Scheme 5.

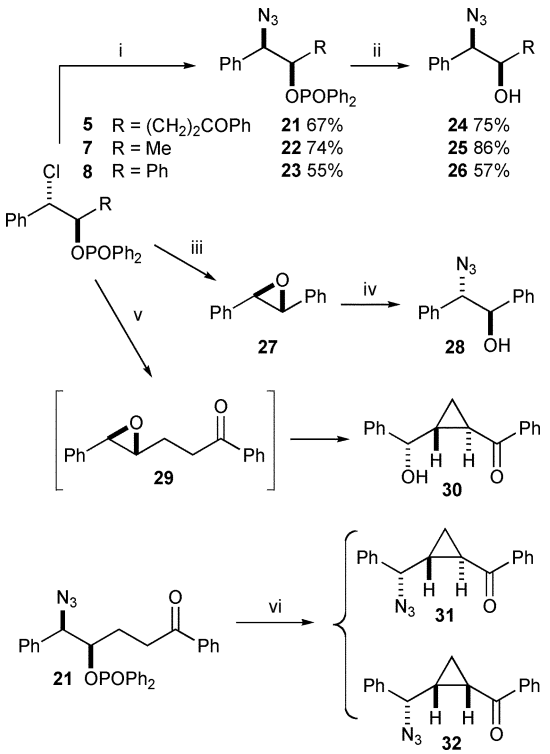


**Scheme 6** *Reagents and conditions*: i) $Ph_2PCl_3$, pyridine (**4** : **8** : **16** = 43 : 31 : 26, by $^1H$ NMR).

Finally, the reactions of the chloro-phosphinates were studied (Scheme 7). Displacement of the benzylic chlorides **5**, **7** and **8** with azide produced mono-azide phosphinates **21**–**23** as single diastereoisomers; the phosphinate neither acts as a leaving group nor participates in the displacement of chloride. As with the related *anti*-azido-phosphinate,[18] *syn*-azido-phosphinate **21** could be converted into mainly *trans*-cyclopropane **31**. *anti*-Chloro-phosphinates can also be converted into *anti*-epoxides **27** and **29**: treatment with potassium carbonate in methanol[13] results in removal of the diphenylphosphinate group[23] and ring closure. The synthesis of cyclopropane[24] **30** results from the *in situ* base-mediated reaction of epoxide **29**. Overall, change in the order of reagents in the conversion of chloro-phosphinate **8** into azido-alcohols **26** and **28** reverses the stereochemistry of the final product. Overall reaction occurs with maintenance of stereochemistry *via* epoxide **27**, but with inversion of stereochemistry at the benzylic position if the diphenylphosphinate is removed as the last step.

We hope to extend the simple chloro-phosphinoylation of 1,2-diols to the synthesis of more complex and widely functionalised




**Scheme 7** *Reagents and conditions*: i) $NaN_3$, DMF; ii) $K_2CO_3$, MeOH; iii) $K_2CO_3$, MeOH, 86%; iv) $NaN_3$, DMF, 75%; v) $K_2CO_3$, MeOH, 79%; vi) LDA, THF, 47% (**31** : **32** = 9 : 1).

molecules where the introduction of two different leaving groups with defined stereochemistry will have significant use.

## Acknowledgements

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21 Crystal data for **6**. $C_{27}H_{30}ClO_4P$, $M = 484.93$, orthorhombic, space group $P2_12_12_1$, $a = 5.8203(10)$, $b = 11.4038(2)$, $c = 37.8022(9)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $U = 2509.1(4)$ Å$^3$, $Z = 4$, $\mu$(Mo-K$\alpha$) = 0.247 mm$^{-1}$, 10165 reflections collected at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 4316 unique ($R_{int} = 0.056$); $R_1 = 0.053$, $wR_2 = 0.127$ [$I > 2\sigma(I)$], absolute structure parameter 0.02(10). CCDC reference number 600429. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606881b.
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