Phosphine oxide-catalysed chlorination reactions of alcohols under Appel conditions†

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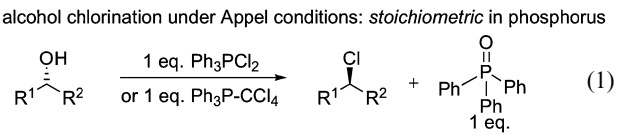
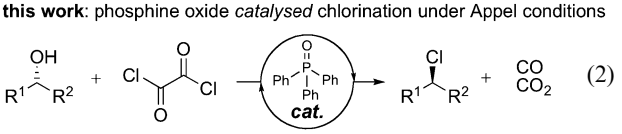
A phosphine oxide-catalysed chlorination reaction of primary and secondary alcohols has been developed. This process represents the first triphenylphosphine oxide-catalysed alcohol chlorination under Appel conditions.

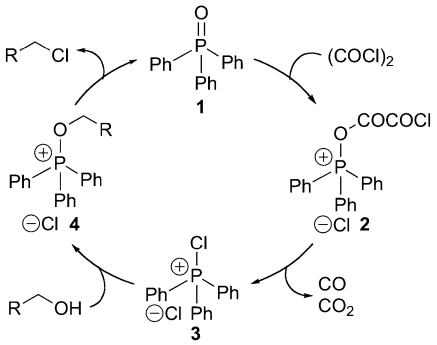
During the last five decades halophosphonium salts have emerged as versatile reagents for the conversion of aliphatic alcohols to alkyl halides.[1] Whilst chlorophosphonium salts and other phosphorus(v) halide reagents afford high yields of halides from alcohols under mild reaction conditions (*e.g.* eqn (1)) the concomitant generation of stoichiometric phosphine oxide by-products impacts severely on the atom efficiency and large-scale applicability of these reactions. Furthermore, purification of the product is not always straightforward.





Whilst many creative strategies have been developed to remove phosphine oxides from reaction mixtures[2] aiding purification the fundamental problem of phosphine oxide *generation* in these and other reactions has remained unsolved.[3] To address this problem we are developing new catalytic versions of the most important phosphorus-mediated transformations.[4] Herein we report the first triphenylphosphine oxide-catalysed chlorination of alcohols under Appel conditions (eqn (2) and Scheme 1).

The driving force for chlorination reactions under Appel conditions, in which chlorophosphonium salts such as **3** react with alcohols to afford chlorides, is the formation of the strong P=O bond in the phosphine oxide by-product **1**. However, it is the strength of this bond which makes catalysis very difficult. Harsh conditions are required for the reduction of phosphine oxides to phosphines from which the chlorophosphonium reagents are conventionally derived. To overcome these difficulties we sought a method to convert *phosphine oxides* into chlorophosphonium salts under mild conditions *e.g.* (**1** → **3**, Scheme 1),[5] thereby bypassing the difficult phosphine oxide reduction with a stoichiometric reductant.



Scheme 1 Proposed phosphine oxide-catalysed chlorination reaction.

We set out to establish whether oxalyl chloride could be used as indicated (**1** → **3**, Scheme 1)[5] to transform triphenylphosphine oxide into the required chlorophosphonium reagent and close the catalytic cycle. We first confirmed that stoichiometric chlorotriphenylphosphonium chloride **3** could be rapidly generated *in situ* from triphenylphosphine oxide and oxalyl chloride[5] and that this reagent was effective at chlorinating decanol (eqn (3), entry 1, Table 1).

Next we established the extent of the unwanted background reaction between oxalyl chloride and decanol (entry 2). The rapid (<10 min) consumption of starting material and formation of chloroglyoxalate **7** and bisester **8** indicated a significant side reaction which could compete with chlorination. However, an initial trial of the catalytic reaction using 30 mol% of triphenylphosphine oxide afforded a promising 46% of the desired chloride (entry 3) along with **7** and **8**.

Optimisation experiments were then carried out to suppress the formation of the esters. Addition of the alcohol to a solution of oxalylchloride and the catalyst over 2 hours afforded a 65% isolated yield of **6** (entry 4). A further modification involving simultaneous addition of both oxalyl chloride and decanol to a solution of 15 mol% catalyst and oxalyl chloride over 7 hours afforded an excellent yield of **6** (entry 5). Repetition of this reaction without catalyst (entry 6) resulted in exclusive formation of chloroglyoxalate **7**. Reducing catalyst loading to 10 mol% had a detrimental effect on yield (entry 7). Finally, the addition time could be

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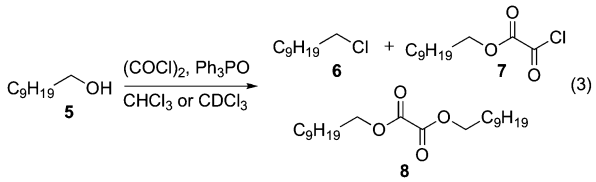
† Electronic supplementary information (ESI) available: General experimental information, spectroscopic data for new compounds and copies of relevant NMR spectra. See DOI: 10.1039/c002825h

Table 1 Development of a catalytic chlorination reaction



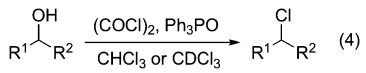
Entry	Ph_3PO mol%	Addition protocol[a]/addition time	Product (yield%)
1	100	**5** added to $(COCl)_2$ + Ph_3PO	**6** (80)[c]
2	0	**5** added to $(COCl)_2$	**7** (78) + **8** (22)[b]
3	30	**5** added to $(COCl)_2$ + Ph_3PO	**6** (46) + **7** (44) + **8** (10)[b]
4	25	**5** added to $(COCl)_2$ + Ph_3PO over 2 h	**6** (65)[c]
5	15	**5** and $(COCl)_2$ added to $(COCl)_2$ + Ph_3PO over 7 h[d]	**6** (83)[b]
6	0	**5** and $(COCl)_2$ added to $(COCl)_2$ over 7 h[d]	**7** (89)[b]
7	10	**5** and $(COCl)_2$ added to $(COCl)_2$ + Ph_3PO over 7 h[d]	**6** (75)[b]
8	18	**5** and $(COCl)_2$ added to $(COCl)_2$ + Ph_3PO over 5 h[d]	**6** (73)[b]

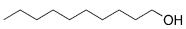
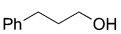
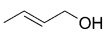
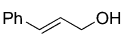
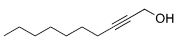
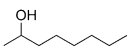
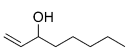
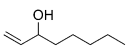
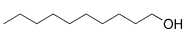
[a] Unless otherwise indicated the reactants were added in one portion. [b] Yield determined by ^1H NMR spectroscopy using $Cl_4C_2H_2$ as an internal standard. [c] Isolated yield. [d] Chloroform solutions of $(COCl)_2$ and **5** were added simultaneously to a solution of $(COCl)_2$ and Ph_3PO in chloroform over the time indicated; the initial amount of $(COCl)_2$ used was equimolar with the catalyst; 1 eq. of $(COCl)_2$ was used in total.

decreased to 5 hours and a good yield of product obtained with 18 mol% catalyst (entry 8).

With a protocol for catalytic chlorination in hand we examined a range of alcohol substrates under the optimal conditions (eqn (4), Table 2). The new method is effective for primary and secondary alcohols with yields ranging from 7–87%. The reaction is tolerant of aryl, alkene and alkyne substituents. The data in Table 2 also indicate the scope of the reaction at present; sterically more demanding substrates such as cyclohexanol were relatively unreactive with respect to chlorination (entry 9).‡

Table 2 Catalytic chlorination of alcohols



Entry	Alcohol substrate	Product	Yield[a] (%)
1		**5**	83 (68)
2		**9**	80 (42)
3		**9**	0[c]
4		**10**	73
5		**11**	70
6		**12**	88 (70)
7		**13**	67 (52)
8		**14**	69 (54)
9		**15**	64
10		**15**	0[c]
11	cyclohexanol	**16**	7
12		**17**[b]	48 (30)

[a] Yield determined by ^1H NMR spectroscopy using $Cl_4C_2H_2$ as an internal standard; isolated yields in brackets. [b] Oxalyl bromide was used in place of oxalyl chloride in this reaction which afforded bromodecane. Chloroform solutions of the substrate (1.00 eq.) and $(COCl)_2$ (0.85 eq.) were added simultaneously to a solution of Ph_3PO (0.15 eq.) and $(COCl)_2$ (0.15 eq.) in chloroform over 7 h at room temperature. [c] The above procedure was used without Ph_3PO catalyst.

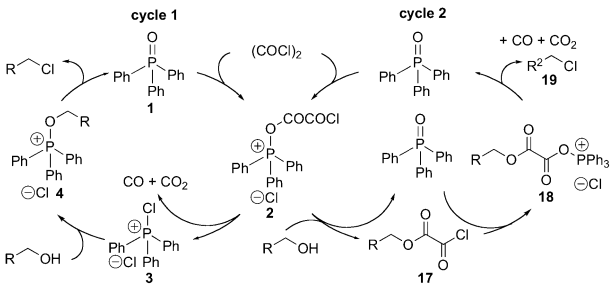
The corresponding bromination reaction using oxalyl bromide is feasible; however, this, and further catalytic halogenation reactions, awaits optimisation (entry 10).

A further two control experiments with no catalyst were conducted with more activated substrates (entries 3 and 10). No chloride products were formed in these reactions.

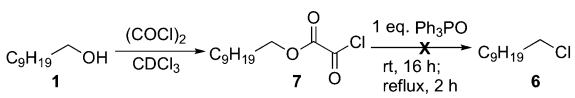
In a final study we examined the role of the phosphine oxide in more detail. In particular, we sought to establish whether glyoxalate esters such as **17** could decompose to chlorides *via* an uncatalysed or catalysed process (*e.g.* **17** or **18** → **19**, Scheme 2) as part of a potential second catalytic cycle (cycle 2, Scheme 2).

To this end we prepared chloroglyoxalate **7** from decanol, the key intermediate in cycle 2 (R = C_9H_{19}), by slow addition of the latter to oxalyl chloride (Scheme 3).

The stability of **7** was then investigated in the presence of triphenylphosphine oxide. Thus, exposure of **7** to one equivalent of triphenylphosphine oxide for 16 hours afforded no chlorinated product. The reaction mixture was then heated at



Scheme 2 Possible catalytic cycles for chlorination reaction.



Scheme 3 Investigation of the reactivity of chloroglyoxalate **7**.

reflux for a further two hours. Again no conversion of **7** to **6** took place.[6] That compound **7** is stable under these conditions suggests that the catalytic chlorination reactions are proceeding *via* the Appel-type pathway (cycle 1).

In conclusion the first triphenylphosphine oxide-catalysed Appel-type chlorination reaction has been developed. The reaction is effective for acyclic primary and secondary alcohols and generates only two gasses as byproducts. Given the diverse chemistry associated with halophosphonium salts[1c] this study provides a proof-of-concept for a range of redox neutral phosphine oxide-catalysed transformations driven by oxalyl halides and active oxalyl esters. The full details of these ongoing studies will be reported in due course.

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Notes and references

‡ General procedure for chlorination reactions in Table 2: to a solution of triphenylphosphine oxide (42 mg, 0.15 mmol) in $CHCl_3$ (1.5 mL) was added oxalyl chloride (0.012 mL, 0.142 mmol) and the reaction mixture stirred for 5 min. The appropriate alcohol (1.00 eq.) and oxalyl chloride (0.073 mL, 0.863 mmol) as solutions in $CHCl_3$ (1.0 mL) were then added simultaneously over 7 h *via* syringe pump. The solvent was removed *in vacuo* and the yield determined *via* ^{1}H NMR spectroscopy using tetrachloroethane as an internal standard (see ESI†).

1 (*a*) R. Bohlmann, in *Comprehensive Organic Transformations*, ed. R. C. Larock, Wiley-VCH, New York, 2nd edn, 1999, pp. 689–702; (*b*) R. Appel, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 801; (*c*) *Organophosphorus Reagents in Organic Synthesis*, ed. J. I. G. Cadogan, Academic Press, London, 1979, ch. 9; (*d*) G. W. Brown, in *The Chemistry of Functional Groups*, ed. S. Patai, Wiley-VCH, New York, 1971, p. 593; (*e*) W. Pluempanupat, O. Chantarasriwong, P. Taboonpong, D. O. Jang and W. Chavasiri, *Tetrahedron Lett.*, 2007, **48**, 223.

2 (*a*) For a recent review, see: S. Dandapani and D. Curran, *Chem.–Eur. J.*, 2004, **10**, 3130; for separation *via* impurity annihilation, see: (*b*) A. G. M. Barrett, R. S. Roberts and J. Schröder, *Org. Lett.*, 2000, **2**, 2999; for the use of tagged phosphines and phase-switching, see: (*c*) C. D. Smith, I. R. Baxendale, G. K. Tranmer, M. Baumann, S. C. Smith, R. A. Lewthwaite and S. V. Ley, *Org. Biomol. Chem.*, 2007, **5**, 1562; for the Appel reaction using polymeric triphenyl phosphine, see: (*d*) C. R. Harrison, P. Hodge, B. J. Hunt, E. Khoshdel and G. Richardson, *J. Org. Chem.*, 1983, **48**, 3721; (*e*) H. M. Relles and R. W. Schluenz, *J. Am. Chem. Soc.*, 1974, **96**, 6469.

3 For other recent chlorination reactions of alcohols not mediated by phosphorus(v) reagents, see: (*a*) B. D. Kelly and T. H. Lambert, *J. Am. Chem. Soc.*, 2009, **131**, 13930; (*b*) L. De Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, 2002, **4**, 553; (*c*) M. Yasuda, S. Yamasaki, Y. Onishi and A. Baba, *J. Am. Chem. Soc.*, 2004, **126**, 7186; (*d*) M. Yasuda, S. Yamasaki, Y. Onishi and A. Baba, *Org. Synth.*, 2006, **83**, 86; (*e*) L. Gomez, F. Gellibert, A. Wagner and C. Mioskowski, *Tetrahedron Lett.*, 2000, **41**, 6049.

4 Other research groups are also active in developing catalytic versions of phosphorus-mediated transformations. For the first phosphine-catalysed Wittig reaction, see: (*a*) C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski and C. G. Chass, *Angew. Chem., Int. Ed.*, 2009, **48**, 6836; for a creative phosphine oxide-catalysed aza-Wittig reaction, see: (*b*) S. P. Marsden, A. E. McGonagle and B. McKeever-Abbas, *Org. Lett.*, 2008, **10**, 2589; a phosphine oxide catalysed chlorination of alcohols using thionyl chloride has been reported, see: (*c*) T. Rhode, O. Huttenloch, F. Osswald and K. Wissel, *US Pat. Appl.* 0228016 A2, 2008. This process does not proceed *via* a chlorophosphonium species; (*d*) A. Dabee, P. Gauthier and J. P. Senet, *US Pat.* 5 672 770, 1994.

5 This reaction has been known for some time and proceeds in less than one minute at room temperature in $CHCl_3$, see: (*a*) M. Masaki and K. Fukui, *Chem. Lett.*, 1977, 151; for a very recent application of this reaction, see: (*b*) T. Yano, M. Hoshino, M. Kuroboshi and H. Tanaka, *Synlett*, 2010, 810.

6 These results are in agreement with a previous study on the decomposition of chloroglyoxalates in the presence of pyridine, see: S. J. Rhoads and R. E. Michel, *J. Am. Chem. Soc.*, 1963, **85**, 585.