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Catalysis of Phosphorus(V)-Mediated Transformations: Dichlorination Reactions of Epoxides Under Appel Conditions

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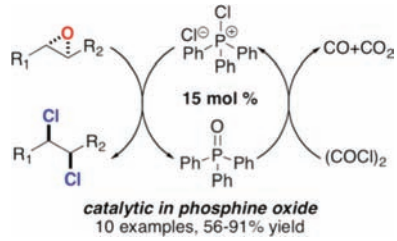
ABSTRACT



A stereospecific triphenylphosphine oxide-catalyzed 1,2-dichlorination reaction of epoxides has been developed. The reaction is effective for a range of terminal and internal epoxides. In contrast to the classical Appel-type dichlorination of epoxides, oxalyl chloride is used as a stoichiometric reagent to generate the chlorophosphonium salt responsible for dichlorination from *catalytic* triphenylphosphine oxide.

Alkyl chlorides are fundamentally important building blocks in synthetic organic chemistry.[1] They are also valuable end-products in their own right; for example, a range of bioactive naturally occurring polychlorinated hydrocarbons termed chlorosulfolipids have been isolated from fresh water microalgae and toxic Adriatic mussels.[2,3] These natural products, which contain numerous chlorine-bearing stereogenic centers, have driven the development of new methods for the stereocontrolled introduction of chlorine to functionalized organic substrates. For example, asymmetric transformations of carbonyl compounds,[4] diastereoselective dichlorination of alkenes[5] and stereospecific dichlorination of epoxides[6] have all recently been reported, and total syntheses of chlorosulfolipids have been disclosed exploiting these methods.[7] In contemplating the synthesis of polychlorinated target molecules, we were attracted to the chlorophosphonium salt-mediated dichlorination of epoxides (Scheme 1a),[6] a reaction that has most recently been investigated by Tanaka and Yoshimitsu,[6g] as a method to obtain vicinal dichloride building blocks for chlorosulfolipid synthesis.[7d]

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(2) (a) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957. (b) Haines, T. H.; Pousada, M.; Stern, B.; Mayers, G. L. *Biochem. J.* **1969**, *113*, 565. (c) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110. (d) Haines, T. H. In *Lipids and Biomembranes of Eukaryotic Microorganisms*; Erwin, J. A., Ed; Academic Press: New York, 1973; p 197. (e) Haines, T. H. *Annu. Rev. Microbiol.* **1973**, *27*, 403. (f) Ciminiello, P.; Fattorusso, E.; Forino, M.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Org. Chem.* **2001**, *66*, 578. (g) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; Di Rosa, M.; Iarno, A.; Poletti, R. *J. Am. Chem. Soc.* **2002**, *124*, 13114. (h) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; Di Meglio, P.; Ianaro, A.; Poletti, R. *Tetrahedron* **2004**, *60*, 7073.

(3) For reviews, see: (a) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S. *Pure Appl. Chem.* **2003**, *75*, 325. (b) Ciminiello, P.; Fattorusso, E. *Eur. J. Org. Chem.* **2004**, 2533. (c) Dembitsky, V. M.; Srebnik, M. *Prog. Lipid Res.* **2002**, *41*, 315.

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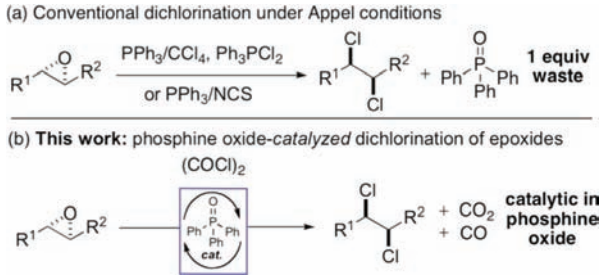
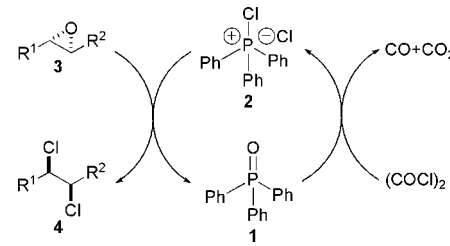
Scheme 1. (a) Stoichiometric and (b) Phosphine Oxide-Catalyzed Dichlorination of Epoxides



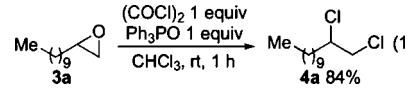
Our interest in this reaction stemmed both from the synthetic utility of the products[7d,8] and from the more fundamental challenge that it presented in terms of catalytic reaction development: the reaction is stoichiometric in phosphonium salt and therefore stoichiometric triphenylphosphine oxide is generated as waste. This impacts severely on the atom efficiency of this and many other widely used phosphorus(V)-mediated processes such as the Wittig, Mitsunobu and Appel reactions. Given the phosphorus waste generated by these processess and the drive toward the development of cleaner chemical reactions, the phosphine oxide problem is a pressing issue that needs to be addressed by catalysis.[9] Our work involves the development of new catalytic versions of important phosphorus(V)-mediated transformations. For example, we recently reported a new triphenylphosphine oxide-catalyzed chlorination reaction of alcohols.[10] Herein, we report the first examples of phosphorus-mediated dichlorination reactions that are catalytic with respect to triphenylphosphine oxide (Scheme 1b).

Scheme 2. Proposed Catalytic Dichlorination of Epoxides



Our plan for the design of catalytic reactions of this type is depicted in Scheme 2 and involves a catalytic cycle in which the transformation of triphenylphosphine oxide into chlorophosphonium salt **2**,[10,11] with concomitant loss of CO and CO_2, closes the catalytic cycle. This redox-neutral strategy[9a] avoids the difficult stoichiometric reduction of the strong phosphorus−oxygen double bond that would be necessary for catalytic turnover in an alternative phosphorus(III)/phosphorus(V) cycle. The increased atom efficiency[12] associated with replacement of stoichiometric triphenylphosphine oxide with CO and CO_2 as waste is also an appealing aspect of this strategy.

We began by establishing that the chlorophosphonium salt **2**, generated *in situ* from triphenylphosphine oxide and oxalyl chloride, was effective for the dichlorination of epoxide **3a** (eq 1).



We next reacted epoxide **3a** with oxalyl chloride (eq 2). The formation of two regioisomeric chlorooxalates **5a** and **5b** revealed a background reaction that could potentially compete with the desired dichorination process.

With this information in hand we began to investigate the feasibility of catalytic dichlorination reactions (Table 1) on substrate **3a**. In the first instance (entry 1) chloroform solutions of epoxide **3a** and oxalyl chloride were added to a solution of 20 mol % phosphonium salt **2** (formed from oxalyl chloride and triphenylphosphine oxide). By using this

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(7) For the total synthesis of (±)-hexachlorosulfolipid, see: (a) Nilewski, C.; Geisser, R. W.; Carreria, E. M. *Nature* **2009**, *457*, 573. For the total synthesis of danicalipin A, see: (b) Bedke, D. K.; Shibuya, G. M.; Pereira, A.; Gerwick, W. H.; Haines, T. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7570. For the total synthesis of malhamensilipin A, see: (c) Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 2542. For the total synthesis of (+)-hexachlorosulfolipid, see: . (d) Yoshimitsu, T.; Fukumoto, N.; Nakatani, R.; Kojima, N.; Tanaka, T. *J. Org. Chem.* **2010**, *75*, 5425.

(8) For the functional group interconversion of chlorides, see: (a) Larock, R. C. *Comprehensive Organic Transformations*; WILEY-VCH: Weinheim, 1999; p 667. (b) For elimination reactions of 1,2-dichlorides, see: (c) Larock, R. C. *Comprehensive Organic Transformations*; WILEY-VCH: Weinheim, 1999; p 259.

(9) Other research groups have been active in the development of catalytic versions of phosphorus-mediated reactions; for the first phosphine oxide-catalyzed aza-Wittig reaction, see: (a) McGonagle, A. E.; Marsden, S. P.; McKever-Abbas, B. *Org. Lett.* **2008**, *10*, 2589. For the first phosphine catalyzed Wittig reaction, see: (b) O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6836. For Wittig reactions coupled with phosphine oxide-promoted conjugate reduction and cyanosilylation, see: (c) Cao, J.-J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4976. For a phosphine-catalyzed reduction of alkyl silyl peroxides, see: (d) Harris, J. R.; Haynes, M. T., II; Thomas, A. M.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 5083.

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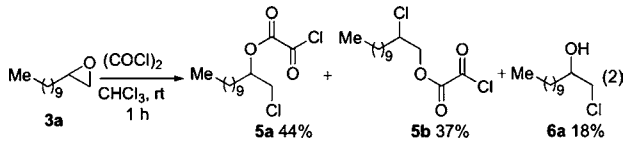
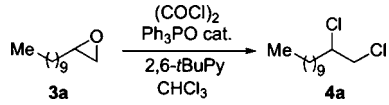


Table 1. Optimisation of Triphenylphosphine Oxide-Catalyzed Dichlorination Reaction[a]



entry	Ph_3PO, mol %	$(COCl)_2$, mol %	2,6-*t*BuPy, mol %	time, h	yield **4a**, %
1	20	100	0	6	58[b]
2	20	100	0	16	73[b]
3	20	100	150	6	78[c], 69[b]
4	15	100	150	16	56[c]
5	15	130	150	6	91[c]
6	0	130	150	6	0[b]

[a] Addition protocol: To solution of Ph_3PO (0.15 equiv) in chloroform (1.0 mL) was added $(COCl)_2$ (0.15 equiv). To this solution was simultaneously added a solution of epoxide (1 mmol, 1.0 equiv) and 2,6-ditertbutylpyridine (1.5 equiv) in chloroform (0.80 mL) and a solution of $(COCl)_2$ (0.75 or 1.15 equiv) in chloroform (0.80 mL) over the time indicated at room temperature. [b] Isolated yield after flash column chromatography. [c] Yield determined using ^1H NMR spectroscopy with tetrachloroethane as an internal standard.

addition protocol, we hoped to minimize the unwanted background reaction observed previously. An isolated yield of 58% was encouraging and was improved to 73% by extending the addition time to 16 h. The remainder of the mass balance in both cases consisted of oxalates **5a** and **5b**.

At this point, we were conscious that HCl present in the oxalyl chloride could react with the substrate to afford chlorohydrins *e.g.* **6a** that would then be converted into oxalate esters. Therefore, we sought a non-nucleophilic base to use as an additive. We found that 2,6-di-*tert*-butylpyridine did not react with oxalyl chloride and was effective as an additive in this regard (Entry 3). A decrease in catalyst loading in the presence of the additive resulted in a lower yield (Entry 4). However, this was improved to an excellent 91% when 1.3 equivalents of oxalyl chloride was used (Entry 5). A control experiment conducted under the optimal conditions, in the absence of triphenylphosphine oxide, afforded no dichloride product (Entry 6). Having identified conditions for the catalytic dichlorination of a terminal epoxide, we examined the scope of the reaction (Table 2). The reaction was effective for a range of epoxides with yields ranging from moderate to excellent. Terminal epoxides underwent efficient catalytic dichlorination at room temperature and alkenyl (Entry 3), aryl (Entries 4 and 5) as well as

(11) (a) Masaki, M.; Fukui, K. *Chem. Lett.* **1977**, 151. For recent applications of the reaction, see: (b) Yano, T.; Hoshino, M.; Kuroboshi, M.; Tanaka, H. *Synlett* **2010**, *5*, 801. (c) Yano, T.; Kuroboshi, M.; Tanaka, H. *Tetrahedron Lett.* **2010**, *51*, 698.

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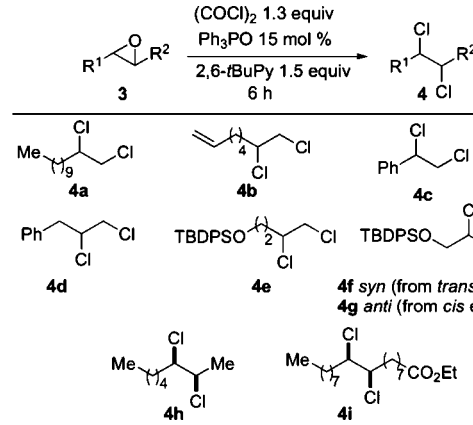
Table 2. Substrate Scope of the Dichlorination Reaction[a]



entry	product	solvent	temp. °C	yield %
1	**4a**	$CHCl_3$	23	91[c]
2	**4a**	EtOAc	23	94[c] 81[b]
3	**4b**	$CHCl_3$	23	84[c] 78[b]
4	**4c**	$CHCl_3$	23	66[c] 57[b]
5	**4d**	$CHCl_3$	23	75[c] 66[b]
6	**4e**	$CHCl_3$	23	72[c] 62[b]
7	**4f**	C_6H_6	80	56[c] 44[b]
8	**4g**	C_6H_6	80	0[b]
9	**4g**	C_6H_6	80	58[c] 46[b]
10	**4h**	C_6H_6	80	57[c]
11	**4i**	C_6H_6	80	66[c]

[a] Addition protocol for reagents: see Table 1 footnote a. [b] Isolated yield after flash column chromatography. [c] Yield determined using ^1H NMR spectroscopy with tetrachloroethane as an internal standard.

silyl-protected hydroxyl functionalities (Entry 6) were tolerated. Attempts to chlorinate epoxides derived from 1,2-disubstituted alkenes under analogous conditions failed. However, changing the solvent from chloroform to benzene and heating to 80 °C afforded reasonable results for these less reactive internal epoxides. In these cases alkenes were observed with dichlorides **4f** and **4g** as minor inseparable byproducts.[6g]

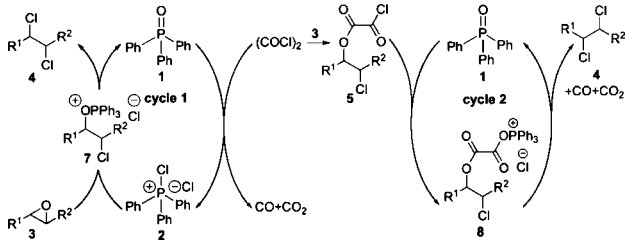
For example, *trans*-epoxide **3f** afforded *syn*-dichloride **4f** as the only diastereoisomer in reasonable yield. Likewise *cis*-epoxide **3g** gave rise to *anti*-dichoride **4g.** The stereochemistry of the products is consistent inversion with at both stereogenic centers. Products **4f** and **4g**, which contain a protected hydroxyl group are noteworthy since similar building blocks have been used by Tanaka and Yoshimitsu in their synthesis of chlorosulfolipids[6d,7d] and now they are available *via* a method that is catalytic in phosphorus.

We next applied the catalytic reaction to the synthesis of a biologically active naturally occurring dichlorinated fatty acid.[3c] To this end, 8,9-epoxyeliadic acid[13] was dichlorinated in 66% yield to afford **4i** (Entry 11). Subsequent saponification (LiOH, THF/CH_3OH, 6 h, 71%) afforded the natural product. Finally, subjecting *cis*-epoxide **3g** to the reaction conditions, in the absence of catalyst, afforded no chloride product (Entry 8).

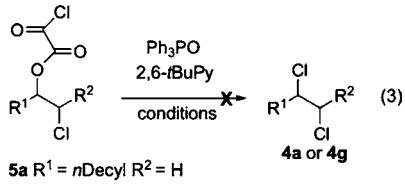
(13) See the Supporting Information for full details.

Having established that dichloride products of type **4** were not formed in the absence of phosphine oxide we further examined the role of the catalyst. Specifically, we sought to establish the feasibility of the intervention of a second catalytic cycle in which triphenylphosphine oxide functions as a nucleophilic catalyst (e.g., **5**→**8**→**4** Scheme 3, cycle 2).

Scheme 3. Potential Catalytic Cycles



The relevant chlorooxalates were prepared from epoxides **3a** and **3g** via the corresponding chlorohydrins[13] to investigate their reactivity with triphenylphosphine oxide (eq 3).[13]



5a R^1 = *n*Decyl R^2 = H
5b R^1 = H R^2 = *n*Decyl
5c R^1 = *n*Pr R^2 = $CH_2OTBDPS$
5d R^1 = $CH_2OTBDPS$ R^2 = *n*Pr

Chlorooxalates **5a** and **5b** were added to a solution of Ph_3PO under conditions identical to those used in the catalytic reactions; no dichloride products of type **4** were obtained. A similar experiment was conducted with **5c** and **5d** under the more vigorous conditions used for internal epoxides; again, no vicinal dichloride products were obtained. Finally, a reaction between **5a** and one equivalent of Ph_3PO also afforded no product. These results, which are in agreement with our earlier findings on the reactivity of chlorooxalates[10] and those of others,[14] are consistent with an Appel-type chlorination process (cycle 1, Scheme 3).

In summary, we have developed the first chlorophosphonium salt-mediated dichlorination reactions of epoxides that are catalytic in phosphorus. The new chemistry provides access to useful building blocks and naturally occurring biologically active chlorinated fatty acids. Significantly, *the usual stoichiometric triphenylphosphine oxide waste product has been replaced with CO and CO_2*. Specifically, this work further validates the concept of redox-neutral catalysis for phosphorus(V)-mediated transformations[9a,10] and the use of oxalyl chloride to induce phosphine oxide turnover in such processes. The application of this catalysis strategy to several other phosphorus(V)-mediated transformations is underway.

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Supporting Information Available: Full experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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