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Convenient *in situ* generation of various dichlorinating agents from oxone and chloride: diastereoselective dichlorination of allylic and homoallylic alcohol derivatives†

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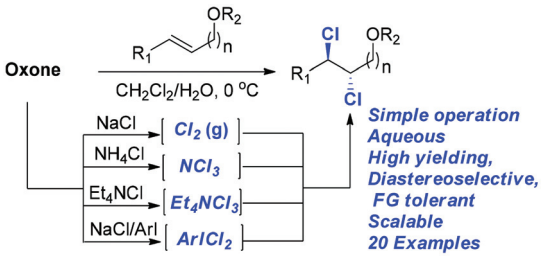
A safe and convenient protocol was developed for *in situ* generation of various dichlorinating agents (*cf.* Cl_2, NCl_3, Et_4NCl_3, $ArICl_2$) from oxone and chloride. The synthetic utility of this protocol was demonstrated by diastereoselective dichlorination of a series of allylic and homoallylic alcohol derivatives with excellent yields and diastereoselectivity.

Naturally-occurring organohalogen compounds are a unique family of natural products and over 2000 chlorine-containing natural products have been identified from various sources.[1] Many of these organohalogens display potent antibiotic or cytotoxic activities, which have attracted considerable attention from synthetic communities.[1,2] Particularly, polychlorosulfolipids characterized by the presence of vicinal dichloride (sp^3C–Cl) have posed formidable synthetic challenges for many decades since their discovery in the 1960s.[3] One of the most straightforward methods to access such functionality is chlorine (Cl_2) addition to alkenes.[4] Apparently, the use of molecular chlorine is less appealing due to the difficult measurement of stoichiometry, incompatibility of many functional groups and the hazardous laboratory operation. These problems could be alleviated by developing stable chlorine complexes or surrogates, which include (i) hypervalent iodine(III) dichloride ($ArICl_2$);[5] (ii) Mioskowski's reagent (Et_4NCl_3);[6] (iii) Markó–Maguire reagent ($KMnO_4$–TMSCl–$BnEt_3NCl$);[7] (iv) Yoshimitsu's method (NCS–PPh_3).[8] However, the preparation of Mioskowski's reagent or $ArICl_2$ still required excessive hazardous molecular chlorine,[5,6] while the Markó–Maguire method employed stoichiometric $KMnO_4$ and excess of Lewis acid trimethylsilyl chloride (TMSCl), which might not be tolerant of highly functionalized substrates and presented potential environmental impacts. Herein, we describe a practical protocol for convenient *in situ* generation of various dichlorinating agents (Cl_2, NCl_3, $ArICl_2$ and Et_4NCl_3) from low cost and environmentally friendly oxone and chloride sources (Scheme 1). The utility of this method was further demonstrated by diastereoselective dichlorination of allylic and homoallylic alcohol derivatives.



Scheme 1 *In situ* generation of various dichlorinating agents from oxone and chloride.

Due to the remarkable stability, simple handling and nontoxic nature, oxone has been widely used for oxidation in organic synthesis, especially for arene halogenation, epoxidation and oxidation of alcohols.[9] Particularly noteworthy is that the combination of oxone and chloride has been used for olefin functionalizations: 1,2-acetoxychlorination of simple alkenes,[10] α-chlorination of α,β-unsaturated ketones or esters[11] and hydroxychlorination of α,β-unsaturated esters[12] (Scheme 2, eqn (1)–(3)). Attracted by this oxidation ability of oxone towards chloride, we were interested in exploration of this environmentally benign oxone–chloride system for the more challenging vicinal dichlorination of allylic and homoallylic alcohol derivatives,[13] which served as the indispensable functional groups for the synthesis of vicinal dichlorides and trichlorides and have been elaborated into many chlorosulfolipid natural products.[3] To our delight, our initial studies indicated that vicinal dichlorination of cinnamyl alcohol using oxone–NaCl[14] was unexpectedly clean (Scheme 2) to give a *syn*, *anti* diastereomeric mixture of vicinal dichloride **2** favoring *anti*-diastereomer (~4 : 1), although the conversion was only 60%.

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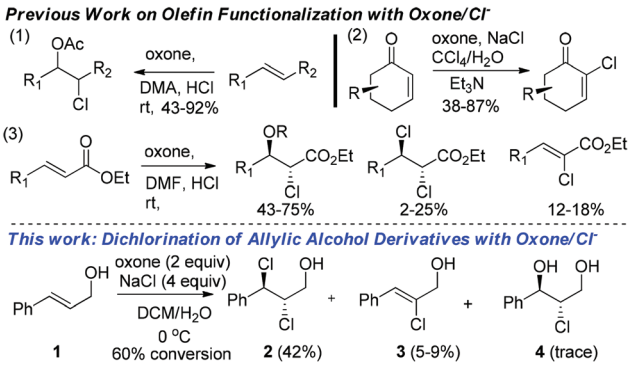
†Electronic supplementary information (ESI) available: Experimental procedure and copies of ^{1}H, ^{13}C-NMR spectra of all major dichlorinated compounds. See DOI: 10.1039/c3ob40670a



Scheme 2 Dichlorination of cinnamyl alcohol with oxone and NaCl.

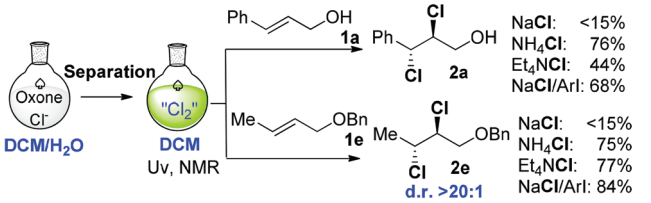
Table 1 Selected conditions for the dichlorination of cinnamyl alcohol with oxone and chloride[a]

Entry	Oxone (equiv.)	MCl (equiv.)	Temp (°C)	Time (min)	Conv. (%)	Yield (2, %)
1	2	NaCl (4)	0	30	60	42
2	2	NaCl (8)	0	30	65	47
3	**4**	**NaCl (4)**	**0**	**30**	**100**	**72 (89)**[b]
4	8	NaCl (4)	0	30	100	76
5	2	NH_4Cl (4)	0	30	54	36
6	**4**	**NH_4Cl (4)**	**0**	**30**	**100**	**74 (93)**[b]
7	4	Et_4NCl (4)	0→rt	8 h	100	69
8	4	NaCl (4)/ 4-MePhI (2)	0 (0→rt)	30 (24 h)	0 (100)	0 (75)

[a] Isolated yield for one-pot dichlorination, the diastereomeric ratio was about 4 : 1 based on ^{1}H NMR of crude materials. [b] Overall yield of 2 and 3.

The ^{1}H-NMR spectra of the *anti*-diastereomer **2** was identical to that reported in the literature.[5b] The major side product isolated in less than 10% yield was alkenyl chloride (**3**), which might be derived from dehydrohalogenation of the desired dichloride product (**2**). This encouraging result prompted us to further investigate the reaction conditions and chloride sources (Table 1).

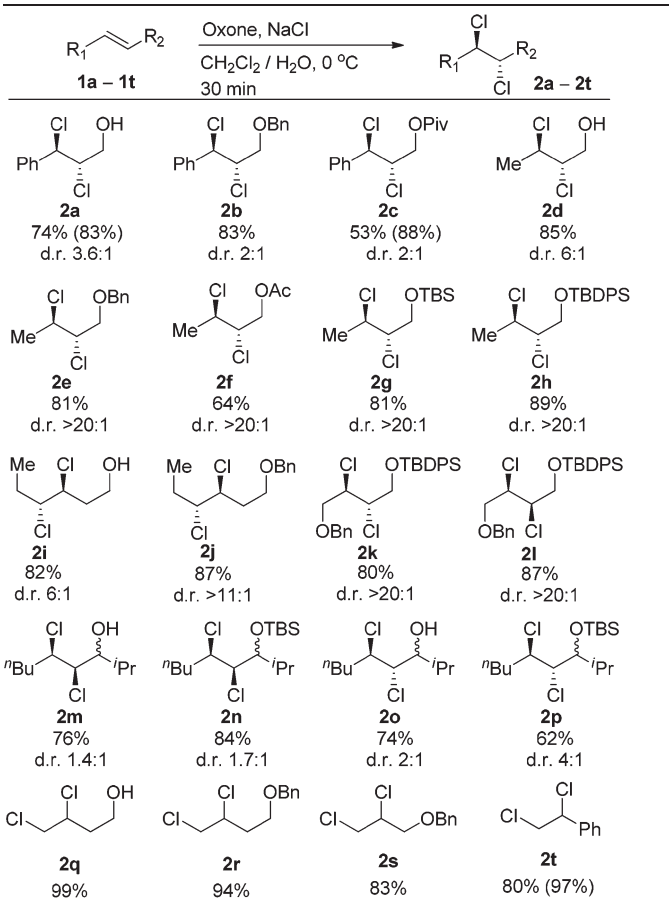
We found that the solvents (DCM–H_2O) were critical to the success of the dichlorination and the optimal stoichiometry of oxone and chloride was 4/4 with respect to the cinnamyl alcohol.[15] Under this condition, dichlorination was complete in 30 min at 0 °C to afford the dichloride (**2**) in 72% isolated yield (entry 3, Table 1). Noteworthy is that the water for dissolution of oxone did not compete with chloride for nucleophilic addition (substitution), since only trace amount of **4** was detected in the ^{1}H-NMR of the crude materials. Screening of other halide salts led us to identify NH_4Cl (entries 5 and 6) as another competent chloride source.[16] When Et_4NCl was used, dichlorination of cinnamyl alcohol also gave good yield (69%) after an extended reaction time at room temperature (entry 7). Interestingly, aryliodide completely suppressed the dichlorination of cinnamyl alcohol with oxone–NaCl at the initial stage (30 min), but reaction with a prolonged time (24 h) at ambient temperature afforded dichloride **2** in 75% yield (entry 8, in parentheses).



Scheme 3 Counter ion effects on the generation of dichlorinating agents.

Although it is well documented that oxone is able to oxidize the chloride ion to produce a mixture of hypochlorous acid (HOCl) and chlorine (Cl_2) in the presence of water,[9] we speculated that the counter ion (*cf.* Na^+, NH_4^+ and Et_4N^+) or additive (*p*-iodotoluene) may exert an influence on chlorinating species (Scheme 1). In order to verify this hypothetic influence and get some insights into the active dichlorinating species from various chloride sources, we designed and performed a series of experiments as shown in Scheme 3. First of all, we separated the DCM solution from the excess of oxone, salts and aqueous phase. The resulting DCM solution was dried over anhydrous Na_2SO_4 and then treated with cinnamyl alcohol and *trans*-crotyl benzylether (**1a** and **1e**). Not surprisingly, dichlorination with the DCM solution proceeded with very low conversion for both alkenes **1a** and **1e**. This result suggested that chlorine may be the active dichlorinating species[11] in the one-pot procedure. Additional evidence was that chlorine generated *in situ* from oxone–NaCl (8/16 equiv.) could be cannulated by nitrogen stream into another flask charged with **1e** solution in the anhydrous DCM, which led to the corresponding dichloride **2e** in 81% yield.[15] Surprisingly, the DCM solution separated from oxone–NH_4Cl effectively promoted the dichlorination to give **2a** in 76% yield (dr. = 4 : 1) and **2e** in 75% yield (dr. > 20 : 1). This unexpected result indicated that the oxone–NH_4Cl may not produce chlorine as the dichlorinating reagent. It was reported that the oxone–NH_4Cl could generate HOCl for oxidative chlorination of arenes and α-chlorination of ketones,[9,16] but olefin dichlorination could not occur with only HOCl. Therefore, we proposed that oxone–NH_4Cl may generate a different active dichlorinating agent: trichloramine,[17] which was supported by a comparison of a DCM solution of trichloramine prepared according to the literature procedure.[18] In addition, UV-vis spectra indicated the presence of NCl_3 from a DCM solution of oxone–NH_4Cl.[15] However, we cannot rule out the possibility of formation of a mixture of chloramine, dichloramine and trichloramine.[19] When Et_4NCl was used as the chloride source, the dry DCM solution obtained, surprisingly, only led to a lower conversion of **1a** with 44% yield of **2a** even with a longer reaction time, but it gave excellent yield of dichloride **2e** (77%) as a single diastereomer. We speculated that Mioskowski's reagent (Et_4NCl_3), not chlorine or hypochlorous acid, was generated as the active chlorinating agent, although more efforts are needed for its confirmation.[15] Lastly, when stoichiometric 4-iodotoluene was added to the solution of oxone–NaCl in DCM–H_2O, the resulting dry DCM solution could promote effective dichlorination with good

Table 2 Substrate scope of dichlorination of allylic and homoallylic alcohol derivatives using oxone and NaCl[a]



[a] Conditions: The reaction was run in 1.0 mmol of alkene, oxone (4.0 mmol), NaCl (4.0 mmol), DCM (10 mL), H_2O (2 mL); isolated yield (yield in parentheses including dehydrochlorination); the diastereomeric ratio was determined by ^{1}H NMR of the crude materials.

yields (**2a**: 68% and **2e**: 84%) and diastereoselectivity, presumably *via* hypervalent iodine(III) dichloride ($ArICl_2$),[5] which was confirmed by ^{1}H NMR[15] and is different from the well-known $ArI(OR)_2$(III).[20]

Finally, the optimized oxone–NaCl system was demonstrated by diastereoselective dichlorination of various allylic and homoallylic alcohol derivatives (Table 2). Electron-withdrawing pivalate (**1c**) gave lower dichlorination yield of **2c** than that of benzylether (**1b**). The low diastereoselectivity for **2a–2c** might be due to the competing S_N1/S_N2 chloride substitution at benzylic position (chloronium ion for S_N2).[5b,11] The dehydrochlorination was not observed for all aliphatic alkenes such as *trans*-crotyl alcohol (**1d**) and its derivatives (**1e–1h**), which gave higher dichlorination yields (64%–89%) with remarkably excellent *anti*-diastereoselectivity (**2d–2h**). In addition, a gram-scale dichlorination of *trans*-crotyl TBS ether **1g** (10 mmol, 1.86 g) was carried out to give dichlorides **2g** in 73% isolated yield as a single diastereomer (dr. > 20 : 1), which may serve as a building block for the total synthesis of hexachlorosulfolipid.[3] Homoallylic alcohol (**1i**) and its benzyl-ether (**1j**) were also suitable substrates for dicholorination, affording the corresponding dichlorides (**2i** and **2j**) in excellent yields (82% and 87%) and diastereoselectivity (>20 : 1), respectively. Remarkably, *trans*-butene-1,4-diol and *cis*-butene-1,4-diol derivatives, substrates used in total synthesis of some polychlorosulfolipids, underwent smooth and clean vicinal dichlorination to give the corresponding highly functionalized *anti*-dichloride (**2k**, 80% yield) and *syn*-dichloride (**2l**, 87% yield) with exclusive diastereoselectivity. For secondary allylic alcohols and their TBS ethers, high yields and exclusive diastereoselectivity of vicinal dichlorides (**2m–2p**, *anti* for *trans*-alkene, *syn* for *cis*-alkene) could be achieved, but with poor facial selectivity of the alkene controlled by $A^{1,3}$-strain.[13] Terminal alkenes, including styrene that is easily polymerized under some dichlorination conditions, underwent smooth dichlorination with oxone and NaCl or NH_4Cl (**2q–2t**).

In summary, a convenient method was developed for *in situ* generation of various active dichlorinating agents from an environmentally friendly oxone and various cheap chloride sources. The counter ion of the chloride has a tremendous effect on the generation of different dichlorinating species using oxone as the oxidant. The synthetic utility of this protocol was demonstrated by diastereoselective dichlorination of a series of allylic and homoallylic alcohol derivatives with excellent yields and diastereoselectivity. The active chlorinating species generated from oxone–chloride by this method may be exploited in the synthesis of other chlorinated organic compounds.

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Notes and references

1 (*a*) G. W. Gribble, *Acc. Chem. Res.*, 1998, **31**, 141; (*b*) M. Kladi, C. Vagias and V. Roussis, *Phytochem. Rev.*, 2004, **3**, 337; (*c*) *Naturally Occurring Organohalogen Compounds – A Comprehensive Update*, ed. G. W. Gribble, Springer-Verlag, Wien, 2010.

2 G. W. Gribble, *J. Chem. Educ.*, 2004, **81**, 1441.

3 For reviews, see: (*a*) D. K. Bedke and C. D. Vanderwal, *Nat. Prod. Rep.*, 2011, **28**, 15; (*b*) C. Nilewski and E. M. Carreira, *Eur. J. Org. Chem.*, 2012, 1685 and references therein. For a representative total synthesis, see: (*c*) C. Nilewski, R. W. Geisser and E. M. Carreira, *Nature*, 2009, **457**, 573.

4 For other reagents for vicinal dichlorination of alkenes, see: (*a*) L. Spiegler and J. M. Tinker, *J. Am. Chem. Soc.*, 1939, **61**, 940; (*b*) R. E. Buckles and D. F. Knaack, *J. Org. Chem.*, 1960, **25**, 20; (*c*) W. A. Nugent, *Tetrahedron Lett.*, 1978, **19**, 3427; (*d*) K. Sakai, K. Sugimoto, S. Shigeizumi and K. Kondo, *Tetrahedron Lett.*, 1994, **35**, 737; (*e*) N. B. Barhate, A. S. Gajare, R. D. Wakharkar and A. V. Bedekar, *Tetrahedron*, 1999, **55**, 11127; (*f*) J. A. Nobrega, S. M. C. Concalves and C. Peppe, *Synth. Commun.*, 2002, **32**, 3711.

5 (*a*) D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, 1968, **33**, 38; (*b*) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch and J. S. Chen, *J. Am. Chem. Soc.*, 2011, **133**, 8134.
6 T. Schlama, K. Gabriel, V. Gouverneur and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1997, **36**, 2342.
7 (*a*) I. E. Markó, P. R. Richardson, M. Bailey, A. R. Maguire and N. Coughlan, *Tetrahedron Lett.*, 1997, **38**, 2339.
8 Y. Kamada, Y. Kitamura, T. Tanaka and T. Yoshimitsu, *Org. Biomol. Chem.*, 2013, **11**, 1598.
9 For recent reviews, see: (*a*) H. Hussain, I. R. Green and I. Ahmed, *Chem. Rev.*, 2013, **113**, 3329; (*b*) V. V. K. M. Kandepi and N. Narender, *Synthesis*, 2012, 15.
10 H. R. Kim, H. S. Oh, H. J. Park, J. N. Kim, D. J. Jeon and E. K. Ryu, *Synth. Commun.*, 1998, **28**, 159.
11 It was also noted that simple alkenes could undergo efficient dichlorination: (*a*) R. K. Dieter, L. E. Nice and S. E. Velu, *Tetrahedron Lett.*, 1996, **37**, 2377; (*b*) K.-M. Kim and I.-H. Park, *Synthesis*, 2004, 2641.
12 J. S. Son, K. S. Jung, H. R. Kim and J. N. Kim, *Synth. Commun.*, 1998, **28**, 1847.
13 G. M. Shibuya, J. S. Kanady and C. D. Vanderwal, *J. Am. Chem. Soc.*, 2008, **130**, 12514.
14 For representative examples using oxone–NaCl, see: (*a*) M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati and A. Tsadjout, *Synlett*, 2000, 813; (*b*) H. W. You and K. J. Lee, *Synlett*, 2001, 105; (*c*) A. Schulze, G. Pagona and A. Giannis, *Synth. Commun.*, 2006, 1147; (*d*) P. T. Lang, A. M. Harned and J. E. Wissinger, *J. Chem. Educ.*, 2011, **88**, 652.
15 See the ESI.†
16 P. Swamy, M. A. Kumar, M. M. Reddy and N. Narender, *Chem. Lett.*, 2012, 432.
17 (*a*) K. W. Field and P. Kovacic, *Synthesis*, 1969, 135; (*b*) P. Kovacic and K. W. Field, *J. Org. Chem.*, 1971, **36**, 3566.
18 P. Kovacic and S. S. Chaudhary, *Org. Synth.*, 1968, **48**, 4.
19 (*a*) P. Kovacic, M. K. Lowery and K. W. Field, *Chem. Rev.*, 1970, **70**, 639; (*b*) V. C. Hand and D. W. Margerum, *Inorg. Chem.*, 1983, **22**, 1449.
20 (*a*) M. Frigerio, M. Santagostino and S. Sputore, *J. Org. Chem.*, 1999, **64**, 4537; (*b*) A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov and V. V. Zhdankin, *Org. Lett.*, 2010, **12**, 4644.