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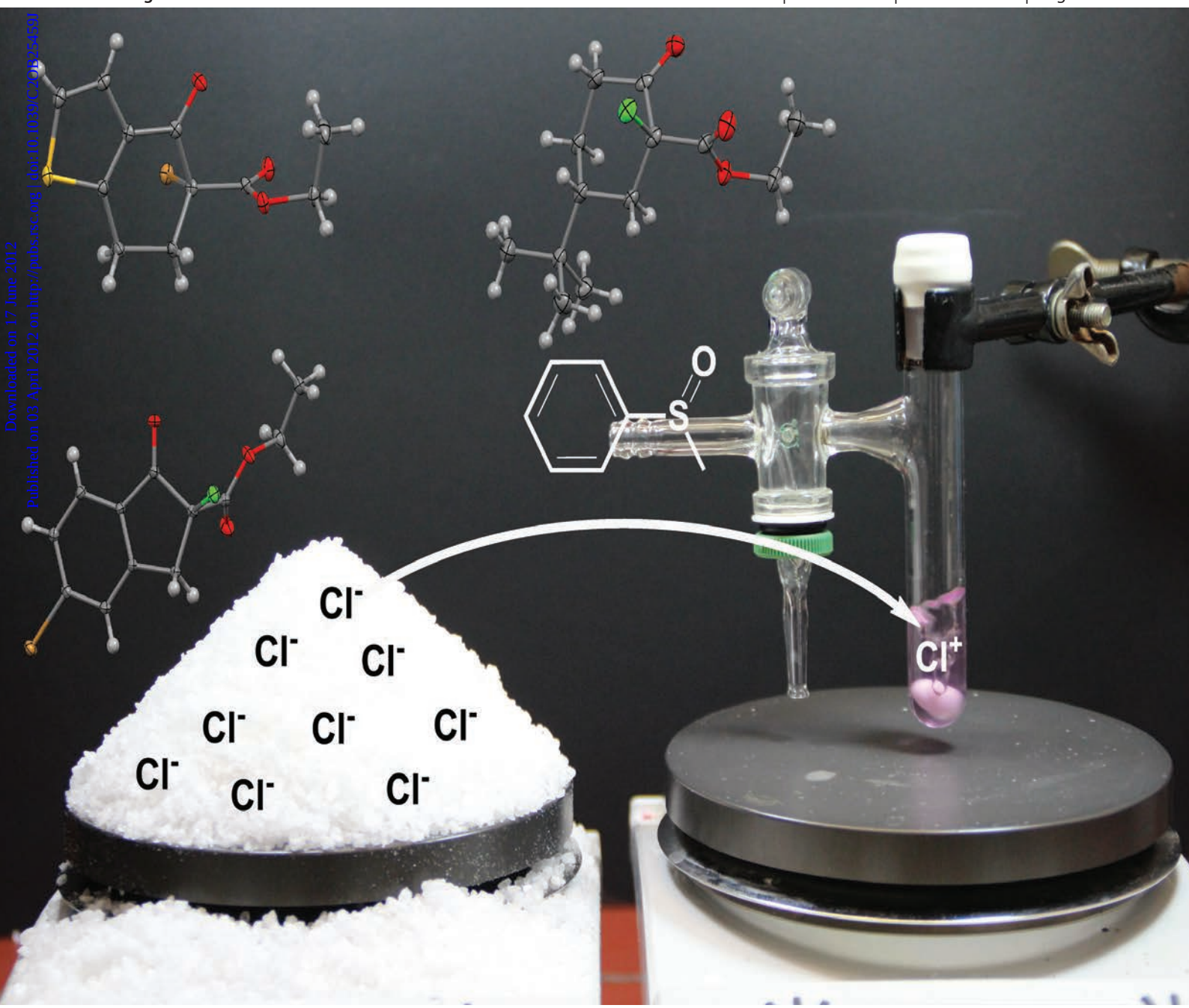

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COMMUNICATION

Sulfoxide-mediated Umpolung of alkali halide salts†

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A new protocol for the direct two-electron oxidative Umpolung of alkali halide salts is reported. This procedure, relying on the use of a commercially available sulfoxide as the oxidant, allows the electrophilic halogenation of carbonyl compounds as well as halolactonisation reactions to proceed from the corresponding sodium salts, at room temperature and under mild conditions.

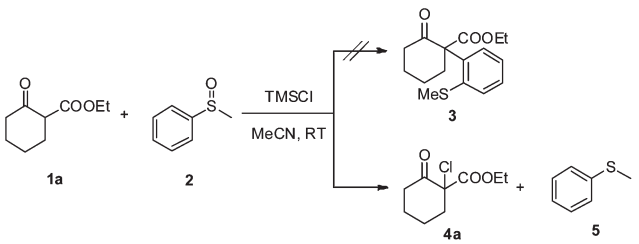
The substitution of a carbon–hydrogen with a carbon–halogen bond often has profound implications on the properties of the resulting organic compound. Interestingly, more than 4000 halogenated natural products, displaying a wide range of biological activities, have been isolated to date.[1] Given the broad availability of halide salts in Nature, a two-electron oxidative Umpolung of halide anions (X^- to X^+, where X = Cl, Br or I) is a likely strategy for enzymatic halogenation.[2]

In preparative chemistry, however, the direct Umpolung of halides is seldom employed. Typically, reagents like SO_2Cl_2,[3] NXS,[4] hypohalide salts[5] and others[6,7] are used for halogenation. Formal oxidation of X^- has been achieved by V_2O_5–H_2O_2–NH_4Br combinations,[8] CAN,[9] oxone,[10] or strong Lewis acids like $AlCl_3$–$Pb(OAc)_4$ and $ZnBr_2$–$Pb(OAc)_4$ couples.[11,12] The most efficient methods hinge on the use of hypervalent iodine compounds such as Koser's reagent,[13] (dichloroiodo)toluene[14] or (diacetoxyiodo)benzene.[15] Nevertheless, processes allowing a direct Umpolung of the ubiquitous sodium chloride or sodium bromide under simple conditions are scarce.[16] Herein, we report an Umpolung of simple alkali halides that takes place at room temperature using a commercially available sulfoxide as the oxidant.

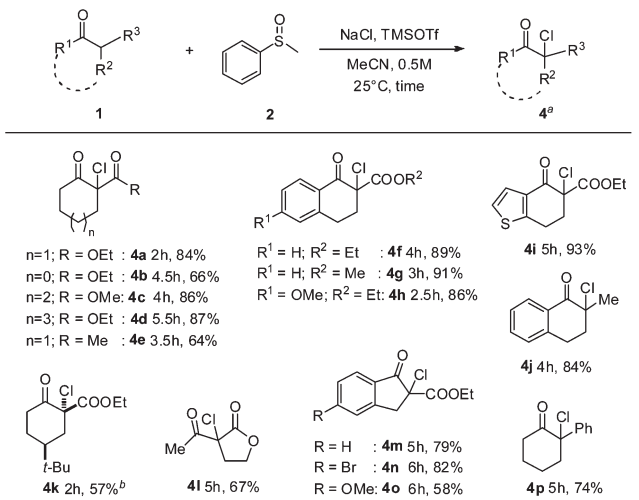
During our recent investigations on sulfoxide-mediated direct arylation reactions,[17] we found that the combination of β-ketoester **1a**, sulfoxide **2** and trimethylsilyl chloride (TMSCl), as activating agent did not yield the expected arylation compound **3**, but rather the α-chlorinated ketone **4a** and thioanisole (**5**) as byproducts (Scheme 1).[18]

In this interesting redox reaction, it appears that TMSCl functions simultaneously as both an activating agent and a chloride donor. This raised the question of whether such a transformation could be adapted for the direct oxidation of inorganic chloride salts. A thorough screening of activating agent–salt combinations[19] revealed that salts such as LiCl, NaCl, CsCl or $CaCl_2$ were all suitable chloride donors when used in conjunction with trimethylsilyl triflate (TMSOTf) as the activating agent. Of further interest was the observation that phenylmethyl sulfoxide **2** afforded up to 10-fold faster reaction times when compared with DMSO and other sulfoxide reagents.[19]

With these conditions in hand, the scope and limitations of the reaction were examined and the results are compiled in Scheme 2. In addition to six-membered cyclic β-ketoesters, five-,



Scheme 1 Initial experiment and sulfoxide-mediated redox chlorination.



Scheme 2 Scope of the direct Umpolung chlorination of carbonyl compounds **1** using sodium chloride. [a] All yields refer to pure, isolated compounds. [b] Compound **4k** was obtained as a 4 : 1 mixture of diastereoisomers. See the ESI† for details and X-ray structures of selected products.

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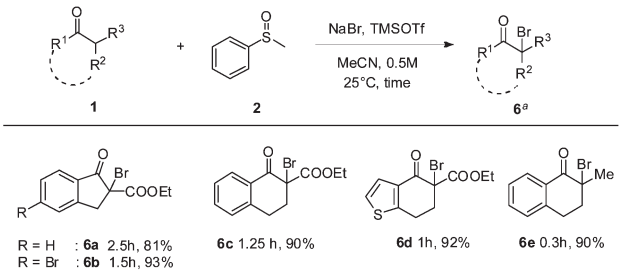
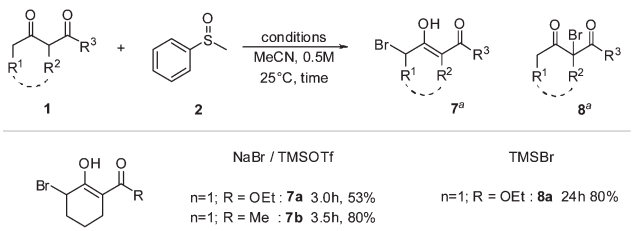
† Electronic supplementary information (ESI) available: Reaction optimisation, experimental procedures and characterisation of products. See DOI: 10.1039/c2ob25459j



Scheme 3 Scope of the direct Umpolung bromination of carbonyl compounds **1** using sodium bromide. [a] All yields refer to pure, isolated compounds. See the ESI† for details.



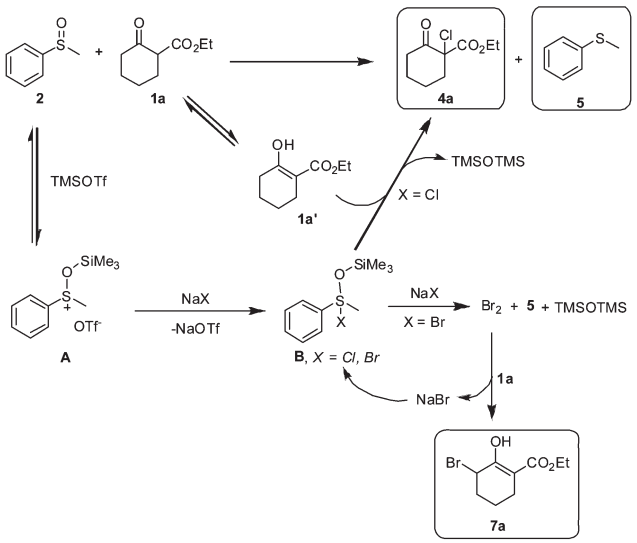
Scheme 4 Dual regioselectivity in the Umpolung bromination of carbonyl compounds **1** using sodium bromide or TMSBr. [a] All yields refer to pure, isolated compounds. See the ESI† for details.

seven- and eight-membered compounds underwent chlorination smoothly in good yields (Scheme 2, **4a–4d**). Various β-ketoesters derived from α-tetralone (**4f–h**) or 1-indanone (**4m–o**) provided the resulting chlorinated products in good to excellent yields. Furthermore a thiophene bearing compound could be chlorinated in excellent yield (**4i**). The reaction is not limited to β-ketoesters, and simple ketones displayed high reactivity as well.

The corresponding bromination reaction is possible under analogous reaction conditions, employing sodium bromide as the halogen donor. The brominated compounds **6a–e** were obtained in very good to excellent yields, up to 93% (Scheme 3).

Interestingly, if the substrate bears a methylene (–CH_2–) group in the α′-position, such as in **1a**, this bromination reaction takes a different course (Scheme 4). In these cases, the bromo enols **5** were formed as the exclusive reaction products. Such a drastic change in regioselectivity is characteristic of a direct reaction with elemental bromine (Br_2), as documented in the literature.[20] It is important to note that if TMSBr is employed instead of the TMSOTf–NaBr couple for the bromination of **1a**, the "standard" regioselectivity is again exclusively observed (Scheme 4). This key experimental fact suggests that different mechanisms (*vide infra*) operate under those two sets of conditions and highlight the uniqueness of the TMSOTf–sodium salt mixture.

Some mechanistic features for this reaction could be inferred by combined MS and NMR analysis. We believe that the reaction proceeds through an activated sulfoxide intermediate **A** (Scheme 5), which forms in a rapidly interconverting equilibrium with TMSOTf and sulfoxide **2**.[21] The presence of this dynamic species **A** was deduced through both NMR and ESI mass spectroscopy. On one hand, the observed NMR high-(low-) field shifts of the *ipso* (*para*) carbon in the aromatic ring suggest a positive charge at the sulfur position. On the other hand the



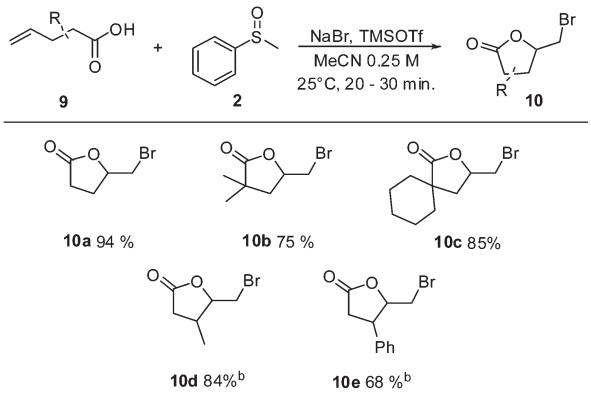
Scheme 5 Proposed mechanistic rationale for the sulfoxide-mediated Umpolung halogenation. See the ESI† for details.

Me_3Si-group exhibits NOE contacts and common diffusion constants in NOESY and DOSY spectra, respectively, with the aryl and methyl groups. Species **A** lends itself to nucleophilic attack by the halide anion to form the sulfurane **B**, an interesting species which conceptually bears a reasonably strong incipient base ($TMSO^-$) and a formally electropositive halide. Species **B** reacts with the enol substrate **1a′**, according to the much steeper decline of its NMR signals compared those of the keto counterpart **1a** in a kinetic study. This step ultimately leads to the observed products **4a** and sulfide **5**. NMR and GC analyses also identified hexamethyldisiloxane (TMSOTMS) as the ultimate fate of the TMS group, presumably through dehydro-condensation of TMSOH.

In the case of the bromination reaction, the presence of "free" bromide anion in solution (from NaBr) presumably allows the *in situ* formation of elemental bromine by direct nucleophilic attack onto the halide terminus of intermediate **B**. The much lower bromide concentrations when TMSBr is employed are likely to render this pathway ineffective. It is interesting to note that, although the stoichiometric brominations by elemental bromine depicted in Scheme 4 should theoretically require 2 equivalents of NaBr to reach completion, the fact that bromide anion (Br^-) is released upon halogenation means that this process is potentially self-sustainable. Accordingly, we observed full conversion of starting materials and yields superior to 50% employing a single equivalent of NaBr.

Finally, the conditions described herein were applied to the halolactonisation of ω-unsaturated carboxylic acids.[22] Employing the TMSOTf–NaBr couple, it was possible to obtain different bromo-butyrolactones (Scheme 6) in moderate to excellent yields. The results depicted in Scheme 6 are comparable to those reported in the recent literature.[23]

In summary, a new procedure for the direct Umpolung of halides under mild, metal-free conditions was developed. This reaction allows electrophilic halogenations (including halolactonisations) to proceed directly from the corresponding sodium salts and relies on the use of a sulfoxide as the net two-electron oxidant.



Scheme 6 Direct Umpolung halolactonisation of ω-alkenoic acids using sodium bromide. [a] All yields refer to pure, isolated compounds. [b] Compounds **10d/e** were obtained as 1 : 1 diastereoisomeric mixtures. See the ESI† for details.

Acknowledgements

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