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Copper-Catalyzed Remote sp^3 C−H Chlorination of Alkyl Hydroperoxides

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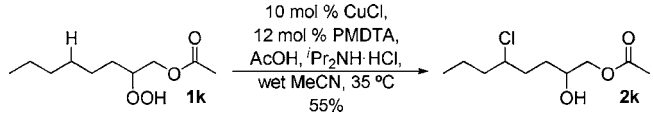
ABSTRACT

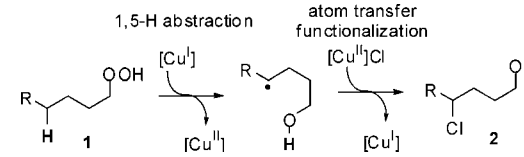


A copper-catalyzed methodology to functionalize remote sp^3 C−H bonds in alkyl hydroperoxides is presented. The atom-transfer chlorination utilizes simple ammonium chloride salts as the chlorine source, and the internal redox process requires no external redox reagents.

Metal-catalyzed C−H-activation radical reactions remain underdeveloped relative to two-electron C−H-activation processes.[1] However, the possibility of combining metal- and ligand-induced selectivity with the unique reactivity and functional-group tolerance of radical intermediates makes the development of metal-catalyzed radical processes attractive. In this paper, we describe catalytic remote C−H chlorination of alkyl hydroperoxides, an internal redox reaction requiring no external oxidant and utilizing simple amine hydrochloride salts as the chlorine source.

Metal-mediated atom transfer is an important elementary step that has been developed in catalytic methods for the synthesis of small molecules[2] and polymers.[3] Extending this concept to C−H functionalization[4] requires a catalytically competent means of abstracting an unactivated hydrogen atom to generate the radical intermediate necessary for metal-mediated atom-transfer functionalization. We envisioned that alkyl hydroperoxides could be suitable substrates for this process, since metal-mediated reduction of the hydroperoxide moiety would serve two purposes by enabling intramolecular C−H activation and serving as an internal reoxidant, permitting catalytic turnover after the reductive atom-transfer functionalization step (Scheme 1).

Scheme 1. Copper-Catalyzed Chlorination of Alkyl Hydroperoxides



Activation of O−X bonds for remote functionalization has a significant history.[5] Lead(IV) reagents react with alcohol O−H bonds to give ether products following distal hydrogen

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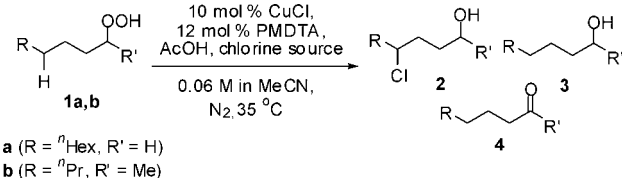
abstraction,[6] and alkyl nitrites are classical intermediates for photolytic processes, including the functionalization of steroidal methyl groups.[7] Metal-mediated halogenation of hydroperoxides has been demonstrated with both a stoichiometric metal oxidant and a stoichiometric metal reductant,[8] but to our knowledge, no metal-catalyzed versions of this reaction have been reported.[9]

In order to develop a simple catalytic system, we examined alkyl hydroperoxides as substrates that can generate a reactive intermediate in the presence of transition-metal catalysts that can potentially perform an intramolecular functionalization at a nonactivated δ carbon. The alkyl hydroperoxide substrates can be synthesized from the corresponding alcohols.[10] They can be purified by silica gel chromatography and are stable for several months in a freezer (for synthetic details, see the Supporting Information). In searching for a catalyst for a redox atom-transfer process, we took inspiration from atom-transfer radical polymerization. Among potential catalysts, we found that copper(I) complexes with chelating nitrogen ligands are capable catalysts for the formation of chloride **2a** from the hydroperoxide **1a**, together with the byproducts **3a** and **4a**. The combination of CuCl and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) in the presence of acetic acid and tetrabutylammonium chloride provided 16% of the alkyl chloride product. Variation of the solvent was not productive, though it was found that on dilution of the reaction mixture from 0.3 to 0.06 M the yield of chlorinated alcohol increased to 28% (Table 1, entry 4).

Table 1. Optimization of Remote C−H Functionalization of Alkyl Hydroperoxides



a (R = ^{n}Hex, R' = H)
b (R = ^{n}Pr, R' = Me)

					yield[a] (%)		
entry	substrate	ligand	chlorine source	comments	**2**	**3**	**4**
1	**1a**	bipyridine	Bu_4NCl	0.3 M	**0**		
2	**1a**		Bu_4NCl	0.3 M	**0**		
3	**1a**	PMDTA	Bu_4NCl	0.3 M	**16**	26	18
4	**1a**	PMDTA	Bu_4NCl		**28**	11	24
5	**1a**	TREN	Bu_4NCl		**28**	22	10
6	**1a**	Me_6TREN	Bu_4NCl		**16**	6	39
7	**1a**	CYCLAM	Bu_4NCl		**12**	5	5
8	**1a**	PMDTA	Bu_4NCl[b]	anhydrous[b]	**13**	6	20
9	**1a**	PMDTA	Bu_4NCl[b]	1 vol % H_2O	**24**	5	33
10	**1a**	PMDTA	$^iPr_2NH$·HCl	1 vol % H_2O	**28**	4	29
11	**1a**	PMDTA	NH_4Cl	24 h, addn[c] 1 vol % H_2O	**41**[d]	8	7
12	**1b**	PMDTA	Bu_4NCl	1 vol % H_2O	**58**	5	21
13	**1b**	PMDTA	$^iPr_2NH$·HCl	1 vol % H_2O	**61**	4	19
14	**1b**	PMDTA	NH_4Cl	1 vol % H_2O	**50**	8	21
15	**1b**	PMDTA	$^iPr_2NH$·HCl	2.5 × AcOH[e], 1 vol % H_2O	**65**[d]	3	17
16	**1b**	none	$^iPr_2NH$·HCl	2.5 × AcOH[e], 1 vol % H_2O	**25**	26	35

[a] Yields determined by HPLC. [b] Anhydrous Bu_4NCl was used in place of the hydrate. [c] The hydroperoxide was added over 24 h. [d] Isolated yield. [e] The amount of AcOH was increased from 4 equiv to 10 equiv.

A brief survey of other sp^3 nitrogen ligands did not improve the reaction efficiency (Table 1, entries 5−7).

Variable and irreproducable yields led us to examine the effect of water on reaction efficiency. Perhaps surprisingly, rigorous exclusion of water was detrimental to reaction yield (Table 1, entry 8). The controlled addition of water provided reproducibility, and optimal results were achieved by adding 1 vol % water to the solvent. Also, only a trace amount of product was detected when the reaction was carried out in air. Other chlorination sources were screened, and the use of NH_4Cl together with syringe pump addition of the hydroperoxide substrate over 24 h improved the yield to 41% (Table 1, entry 11), but we have been unable to improve this result with primary hydroperoxide substrates.

Moving to a secondary hydroperoxide **1b**, we found that the formation of alcohol (2-octanol) and carbonyl (2-octanone) byproducts was significantly decreased, and after a brief optimization, we obtained the chloride **2b** in 65% yield (Table 1, entry 15). The optimal method thus varies depending upon the type of chorination source used. For primary alkyl hydroperoxide substrates, which were highly reactive, NH_4Cl was found to give better yield (Table 1, entry 11), whereas for secondary alkyl hydroperoxide substrates, diisopropylamine hydrochloride gave the best yields (Table 1, entries 13 and 15). A control experiment with substrate **1b** in the absence of ligand (entry 16) exhibited similar rates of starting material conversion but inferior product formation,

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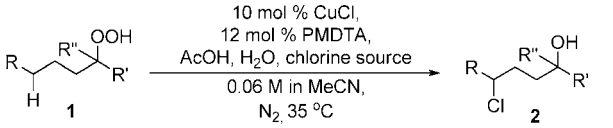
indicating that the ligand plays an important role in determining the chemoselectivity of the catalytic cycle.

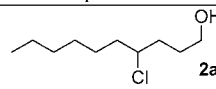
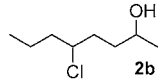
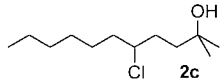
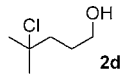
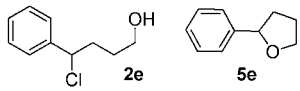
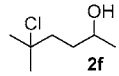
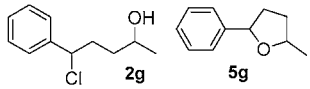
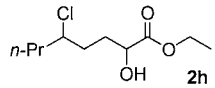
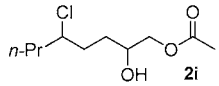
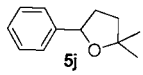
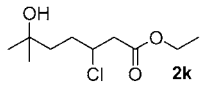
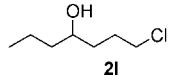
In the case of the tertiary alkyl hydroperoxide **1c** (Table 2, entry 3), the reaction was very sluggish, and even after 10 days, starting material remained unreacted. We hypothesized that copper(I) catalyst was being oxidized to an inactive copper(II) species over long reaction times and so examined reductants that might regenerate an active copper(I) species. Addition of a catalytic amount of sodium ascorbate as a reducing agent remarkably improves the rate of the reaction, giving 74% isolated yield of the product **2c** within 1 h.

We examined chlorination of a variety of alkyl hydroperoxide substrates using the standard methods developed above. Surprisingly, reaction efficiency is similar for the functionalization of secondary or tertiary C−H bonds, despite the significant difference in stability of the intermediate radical species (Table 2, entries 1 and 4 and entries 2 and 6). For substrates that target benzylic C−H bonds, similar yields are observed despite the increased reactivity of the C−H bond, and the product cyclizes into the corresponding furan under the reaction conditions (Table 2, entries 5, 7, and 10). Ester groups are also tolerated under the reaction conditions (Table 2, entries 8, 9, and 11).

Since a new stereocenter is created in the process of C−H activation, the investigation of the effect of a neighboring stereogenic center on diastereoselectivity of the reaction was of interest. To address this issue, a substrate with a methoxy group adjacent to the target C−H bond was designed (Scheme 2). In this case, no substantial diastereoselectivity was observed, and the product was isolated as a mixture of diasteromers (1.3:1). In addition to the expected 1,5 H-atom abstraction product **2m**, two other products, **6m** and **7m**, of

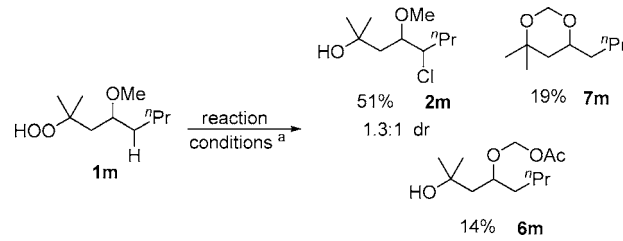
Table 2. CuCl-Catalyzed Remote C−H Functionalization of Alkyl Hydroperoxides



entry	substrate	product	yield (%)[a]
1[b]	**1a**	 **2a**	41
2[c]	**1b**	 **2b**	65
3[c]	**1c**[d]	 **2c**	74
4[b]	**1d**	 **2d**	32[e] (47)[f]
5[b]	**1e**	 **2e** **5e**	58 (1.8:1)[g]
6[c]	**1f**	 **2f**	46[e] (68)[f]
7[c]	**1g**	 **2g** **5g**	54 (1:1.8)[g]
8[b]	**1h**	 **2h**	40
9[c]	**1i**	 **2i**	55
10[c]	**1j**[d]	 **5j**	74
11[c]	**1k**	 **2k**	65
12[c]	**1l**	 **2l**	33

[a] Isolated yield unless otherwise noted. [b] NH_4Cl used as chorination source; slow addition of substrate over 24 h. [c] $iPr_2NH{\cdot}HCl$ used as chlorination source; slow addition of substrate over 1 h. [d] Sodium ascorbate (0.05 equiv) was added. [e] Lower isolated yields were observed in these cases due to product volatility. [f] Yields determined by HPLC. [g] Ratio chlorinated product/cyclized product.

Scheme 2. Chlorination of a Substrate Providing Mixtures of 1,5 and 1,6 Hydrogen Abstraction



[a] Reaction conditions: 0.1 equiv of CuCl, 0.12 equiv of PMDTA, 4 equiv of AcOH, 1.2 equiv of diisopropylamine hydrochloride, 0.06 M hydroperoxide in MeCN, 35 °C, slow addition of substrate.

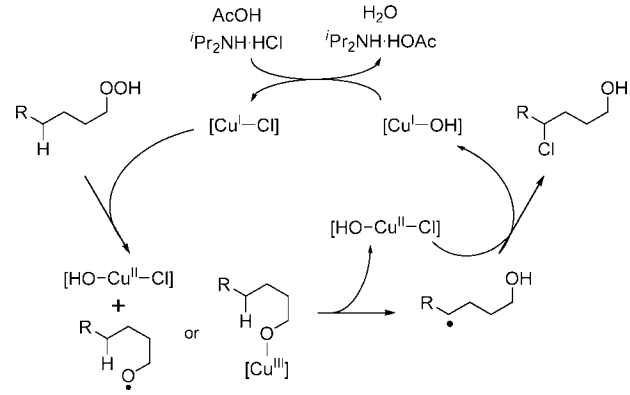


Figure 1. Plausible catalytic cycle.

1,6 abstraction of a C−H bond on the methoxy group were also formed.

A plausible mechanism for the reaction is shown in Figure 1. The copper catalyst reacts with the hydroperoxide to afford a reactive intermediate, likely an alkoxy radical or copper(III) alkoxide. The 1,5-hydrogen-atom abstraction[11] would then provide the intermediate radical necessary for atom transfer of a chlorine atom from a copper(II) species to the radical to form the observed product. The presence of an acid (AcOH) is necessary to facilitate regeneration of a copper(I) chloride from the initially formed copper(I) hydroxide.

The remote functionalization described here is characterized by operational simplicity. Because the alkyl hydroperoxide substrates are synthesized by substitution reactions with hydrogen peroxide, the inexpensive and environmentally benign hydrogen peroxide is the terminal oxidant for C−H functionalization. We believe this report will serve as a foundation for the development of catalytic stereoselective processes and the further development of metal-catalyzed radical processes triggered by C−H activation.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for all the compounds studied. This material is available free of charge via the Internet at http://pubs.acs.org.

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