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Copper-catalyzed radical ring-opening halogenation with HX†

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An efficient copper-catalyzed radical ring-opening halogenation with HX (aq) is described. This protocol features redox-neutral conditions, green halogen sources, and a broad substrate scope, providing practical access to distally chlorinated, brominated and iodinated alkyl ketones and alkyl nitriles with moderate to good yields.

Functionalized alkyl halides are valuable and versatile building blocks, which have found widespread applications in nucleophilic substitution (S_N),[1] cross couplings and other reactions.[2] Through diverse transformations, not only an alkyl chain but also functional groups could be incorporated into molecules simultaneously, thus enabling rapid assembly of molecular complexity. On the other hand, functionalized alkyl moieties widely exist in many natural products, pharmaceuticals (droperidol, fluanlsone, and cinolazepam) and biologically active compounds (Fig. 1).[3] Therefore, the construction of distally functionalized alkyl halides is important, but is relatively difficult and challenging. In recent years, radical C–C bond cleavage/halogenation has emerged as an efficient strategy to access the carbonyl-containing alkyl halides[4–6] and the cyano-containing alkyl halides.[7] Especially, thanks to the recent advances in the alkoxy radical chemistry,[8] ring-opening halogenation of cycloalkanols with diverse organic halogenating agents such as *N*-chlorosuccinimide (NCS), *tert*-butyl hypochlorite (*t*BuOCl), *N*-bromosuccinimide (NBS), tetrabutylammonium halide (TBAX) and CX_4 have been developed for the synthesis of distally halogenated alkyl ketones (Scheme 1a). However, these methods are restricted in the field of large-scale industrial applications, due to the requirement of expensive catalysts and stoichiometric amounts of oxidants ($K_2S_2O_8$ or PIDA), as well as the generation of large amounts of waste that need to be addressed. Therefore, it is still desirable and highly in demand to develop more atom-economical and environmentally benign protocols to obtain the functionalized alkyl halides.

Compared with the organic halogen source, inorganic halide salts are more attractive alternatives.[9] Recently, Morrill *et al.* reported a manganese-catalyzed electrochemical ring-opening chlorination of tensional cycloalkanols by using $MgCl_2$ as the chloride source.[10] However, too much $MgCl_2$ (5.0 equiv.) was required and the substrate scope was limited to the strained cycloalkanols. As we know, HCl (aq) is a bulk industrial chemical, which would be an ideal chloride source since it is much less expensive and it is a waste-free agent. Nevertheless, HCl is scarcely employed as the chloride source in radical organic chemistry.[9d] Recently, the Maruoka group and we revealed a series of C–C bond cleavages of cycloalkanol peroxides under cheap Cu, Fe, and Ni catalysis, which is complementary to the oxidative ring-opening of cycloalkanols.[11] As we know, the Cu(II)X species could undergo the halogen atom transfer to carbon-centered radicals, forming C–X bonds.[9a,12] In the 1980s, Cvetkovic's group disclosed the Fe(II)/Cu(II)-mediated remote sp^3 C–H halogenation of chain alkyl hydroperoxides through a 1,5-HAT process, wherein a stoichiometric amount of CuX_2 was required.[12b] Later on, Ball *et al.* reported a copper-catalyzed sp^3 C–H chlorination of alkyl hydroperoxides using ammonium chloride salts as the chlorine source.[9a] We expect that HX are probably applicable for this copper catalyzed

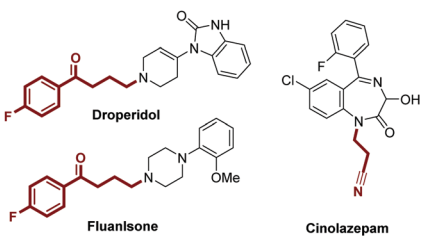

Fig. 1 Drugs containing functionalized alkyl fragments.

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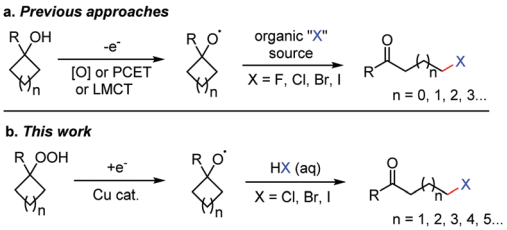
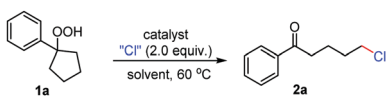


Scheme 1 Alkoxy radical-triggered ring-opening halogenation.

C–C bond cleavage/halogenation transformation. Herein, we disclose the copper-catalyzed ring-opening halogenation of cycloalkyl hydroperoxides with HX (aq), which provides facile access to a range of distally chlorinated, brominated and iodinated alkyl ketones (Scheme 1b). This process is typically redox neutral, highly atom economical and without generation of large amounts of waste materials, thus exhibiting great application potential in organic synthesis. Remarkably, this simple protocol is also applicable to the ring-opening halogenation of cycloketone oxime esters, offering distally halogenated alkyl nitriles with good yields.

Our initial study began with the chlorination of cyclopentyl hydroperoxide **1a** with 2.0 equiv. of HCl (36%, aq). After several trials, we found that the reaction of **1a** with HCl (36%, aq) proceeded efficiently in the presence of 10 mol% CuI in NMP at 60 °C under nitrogen, affording the desired δ-chlorinated alkyl ketone **2a** in 85% yield (Table 1, entry 1). Solvent screening showed that polar solvents are more suitable for this transformation and NMP is the optimal one (entries 2 and 3). Other copper catalysts such as CuCl, $Cu(OAc)_2$ and $Cu(CH_3CN)_4PF_6$ also displayed good to excellent catalytic efficiency, and the common $Cu(OAc)_2$ gave **2a** in 92% yield (entries 4–6). Besides copper catalysts, $Fe(OAc)_2$ resulted in a moderate yield of **2a**, while $CoCl_2$ and $NiCl_2$ proved to be ineffective (entries 7 and 8).

Table 1 Optimization of the reaction conditions[a]

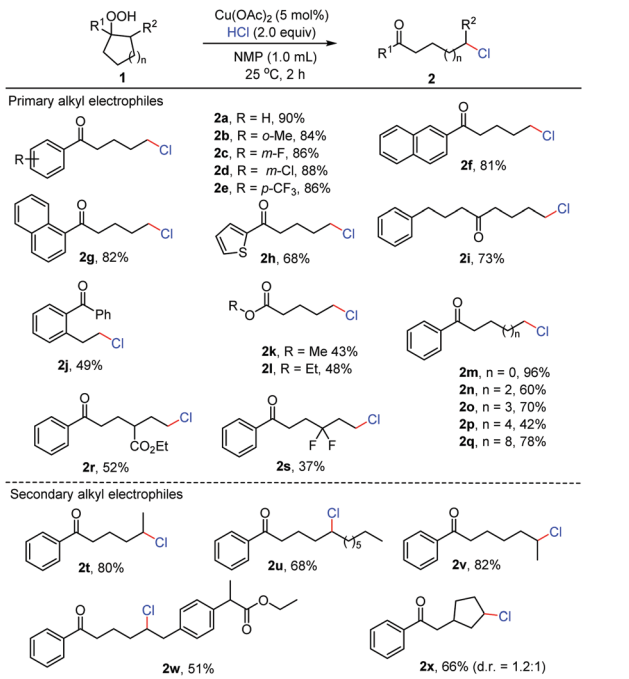


Entry	Catalyst (mol%)	Solvent	"Cl" Source	Yield[a] (%)
1	CuI (10)	NMP	HCl (aq)	85
2	CuI (10)	DMF	HCl (aq)	81
3	CuI (10)	DCM	HCl (aq)	17
4	CuCl (10)	NMP	HCl (aq)	85
5	$Cu(OAc)_2$ (10)	NMP	HCl (aq)	92
6	$Cu(CH_3CN)_4PF_6$ (10)	NMP	HCl (aq)	85
7	$Fe(OAc)_2$ (10)	NMP	HCl (aq)	66
8	$CoCl_2$, or $NiCl_2$	NMP	HCl (aq)	trace
9	$Cu(OAc)_2$ (10)	NMP	$MgCl_2$	88
10	$Cu(OAc)_2$ (10)	NMP	NaCl	trace
11	$Cu(OAc)_2$ (10)	NMP	NH_4Cl	15
12	$Cu(OAc)_2$ (5)	NMP	HCl (aq)	90[b] (95)[bc]
13	$Cu(OAc)_2$ (5)	NMP	HCl (aq)	10[bd] (trace)[e]

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), catalyst (*x* mol%), "Cl" Source (0.4 mmol, 2.0 equiv.), and solvent (1.0 mL) at 60 °C for 2 h under N_2. Isolated yields. [b] At 25 °C. [c] Cyclopentyl silyl peroxide was used. [d] In air. [e] No catalyst.

Chloride sources such as $MgCl_2$, NaCl and NH_4Cl were also examined instead of HCl (36%, aq). $MgCl_2$ afforded **2a** in 88% yield, while NaCl and NH_4Cl furnished poor yields (entries 9–11). To our delight, reducing the catalyst loading to 5 mol% and lowering the reaction temperature to 25 °C still led to **2a** in a comparable yield (entry 12). Notably, conducting the reaction in air only delivered **2a** in a 10% yield, and the control experiment revealed that the copper catalyst is essential to the reaction (entry 13).

With the optimal conditions in hand, we evaluated the substrate scope of this ring-opening chlorination reaction. A variety of cyclopentyl hydroperoxides were engaged in this C–C bond cleavage/chlorination reaction efficiently to afford the desired δ-chlorinated alkyl ketones **2a–2i** in moderate to good yields (Scheme 2). Substituents on the aromatic ring did not show an obvious effect on the yields (**2b–2e**). The 1-thienyl substituted substrate was also compatible, delivering the product **2h** in 68% yield. Besides 1-aryl substrates, 1-alkyl hydroperoxide **1i** also gave a 73% yield of the desired product **2i**. The hydroperoxide derived from indanone provided the expected product **2j** in 49% yield. Notably, 1-alkoxyl substrates **1k** and **1l** were also amenable, generating the δ-chlorinated esters **2k** and **2l** in moderate yields. Besides cyclopentyl hydroperoxides, more strained cyclobutyl substrates and less strained substrates with six-, seven-, eight-, and even twelve-membered rings all underwent this ring-opening halogenation process smoothly to deliver the corresponding products **2m–2s** in moderate to good yields. Ester and fluoride groups on the aliphatic ring were tolerated (**2r** and **2s**). Remarkably, the 1,



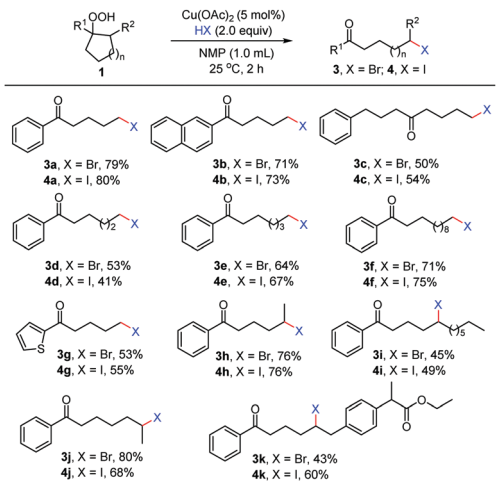
Scheme 2 Diversity of chlorinated alkyl ketones obtained. [a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), $Cu(OAc)_2$ (5 mol%), HCl (36%, aq) (0.4 mmol, 2.0 equiv.), in NMP (1.0 mL) at 25 °C for 2 h under N_2. Isolated yields.

2-disubstituted cycloalkyl hydroperoxides reacted regioselectively to afford the anticipated secondary chlorides **2t–2v** in 68–82% yields. The substrate derived from loxoprofen (a pharmaceutical molecule) also worked well to produce the secondary chloride **2w** in 51% yield. Norcamphor-derived hydroperoxide delivered the cyclic chloride **2x** in 66% yield.

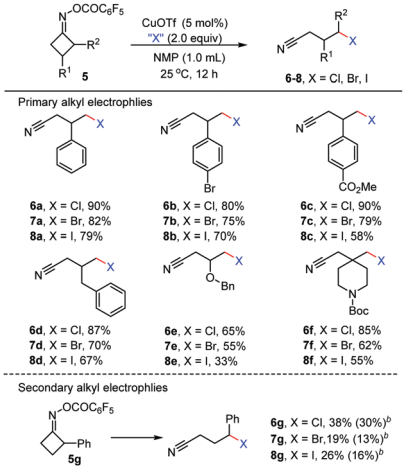
Encouraged by the above results, other HX (aq) including HBr, HI and HF were also assessed for this halogenation reaction (Scheme 3). Satisfactorily, both HBr (40%, aq) and HI (55–58%, aq) were efficient halogenating agents. When HBr was used as the bromine source, a variety of cycloalkyl hydroperoxides were converted into the corresponding brominated alkyl ketones **3a–3k** in moderate to good yields. Using HI as the iodine source also led to moderate to good yields of the iodinated alkyl ketones **4a–4k**. Unfortunately, HF (49%, aq) was incompetent for this transformation and 85% of the hydroperoxide could be recovered in this case. Other fluoride sources such as MgF_2 and CuF_2 also failed to give the expected fluorinated ketones.

To further explore the potential of this Cu/HX (aq) system, cycloketone oxime esters were examined, which would provide the valuable distally halogenated alkyl nitriles under cyanide-free conditions (Scheme 4).[7] To our delight, the ring-opening chlorination of 3-substituted cyclobutanone oxime esters with HCl (36%, aq) proceeded well to give the γ-chlorinated alkyl nitriles **6a–6f** in 65–90% yields. Functional groups such as CO_2Me, Br, OBn and *N*-Boc groups survived well in this transformation. However, the 2-phenyl oxime ester **5g** only offered the expected product **6g** in 38% yield, along with an inseparable β-hydrogen elimination by-product in 30% yield. It is noteworthy that when HBr (aq) and HI (aq) were employed as the halogen sources, the corresponding cyclobutanones instead of halogenated alkyl nitriles were obtained in moderate yields. We speculate that the strong acidity of HBr and HI probably led to the hydrolysis of the oxime esters. After screening of some inorganic salts, it was found that $MgBr_2{\cdot}6H_2O$ and ZnI_2 were efficient, delivering the desired γ-brominated and γ-iodinated alkyl nitriles (**7a–7f** and **8a–8f**) in 33–82% yields. Unfortunately, the less strained cycloketone oxime esters such as five- and six-membered substrates failed to give the desired products.

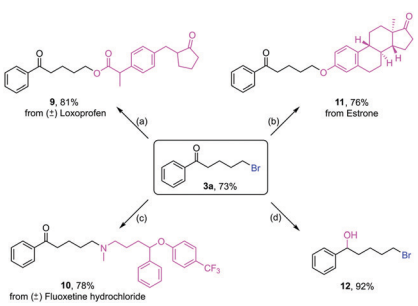
To demonstrate the synthetic utility of this protocol, larger scale reaction of **1a** was conducted (Scheme 5). Simple amplification of the reactions to 3.0 mmol scales still afforded 82% yield of **2a** and 73% yield of **3a**. In addition, **3a** was proved to be an efficient carbonyl-containing alkylation reagent. Through nucleophilic substitution, some drug molecules and natural products such as loxoprofen, fluoxetine hydrochloride and estrone could be keto-alkylated to afford **9**, **10** and **11** in 81%, 78% and 76% yields, respectively. The product **3a** can also be reduced with $NaBH_4$ to give the brominated alcohol **12** in 92% yield.



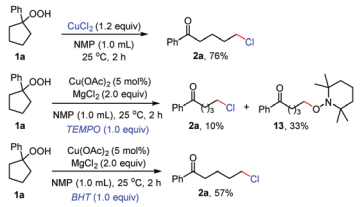
Scheme 3 Diversity of brominated and iodinated alkyl ketones obtained. [a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), $Cu(OAc)_2$ (5 mol%), HBr (40%, aq) or HI (55–58%, aq) (0.4 mmol, 2.0 equiv.), in NMP (1.0 mL) at 25 °C for 2 h under N_2. Isolated yields.



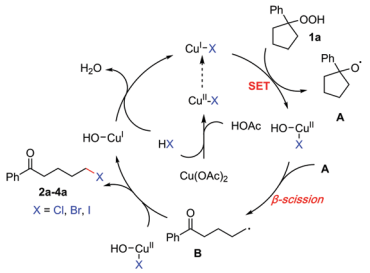
Scheme 4 Diversity of halogenated alkyl nitriles obtained. [a]Reaction conditions: **5** (0.2 mmol, 1.0 equiv.), CuOTf (5 mol%), HCl (36%, aq) or $MgBr_2{\cdot}6H_2O$, or ZnI_2 (0.4 mmol, 2.0 equiv.), in NMP (1.0 mL) at 25 °C for 12 h under N_2. Isolated yields. [b]Yields of β-hydrogen elimination by-products are given in parentheses.



Scheme 5 Synthesis of **3a** on a large scale and its derivatizations. [a]Reaction conditions: (a) **3a** (0.2 mmol, 1.0 equiv.), K_2CO_3 (0.6 mmol, 3.0 equiv.), loxoprofen (0.3 mmol, 1.5 equiv.), DMF (0.2 M), 90 °C, 12 h under N_2. (b) and (c) **3a** (0.2 mmol, 1.0 equiv.), K_2CO_3 (0.6 mmol, 3.0 equiv.), fluoxetine hydrochloride or estrone (0.3 mmol, 1.5 equiv.), acetone (0.2 M), 70 °C, 12 h under N_2. (d) **3a** (0.2 mmol, 1.0 equiv.), $NaBH_4$ (1.0 mmol, 5.0 equiv.), MeOH (0.05 M), 0 °C, under air.



Scheme 6 Mechanism studies.



Scheme 7 Proposed mechanism.

To clarify the reaction mechanism, some control experiments were performed (Scheme 6). Treatment of **1a** with 1.2 equiv. of $CuCl_2$ delivered the product **2a** in 76% yield. This indicates that the halogen source comes from the copper–halogen intermediate. The addition of 1.0 equiv. of TEMPO to the reaction of **1a** and $MgCl_2$ reduced the yield of **2a** to 10%, along with TEMPO-adduct **13** in a 33% yield. Moreover, the yield of **2a** was also decreased to 57% when radical inhibitor BHT (1.0 equiv.) was added. Both the results support a radical pathway for this reaction.

Based on the above observations, a proposed mechanism is depicted in Scheme 7.[9,12] First, anion exchange of $Cu(OAc)_2$ with HX (aq) forms the Cu(II)X species, which delivers the key Cu(I)X species through disproportionation.[13] Single-electron reduction of **1a** by Cu(I)X affords the cycloalkoxy radical **A**, which undergoes β-scission to give the keto-alkyl radical intermediate **B**. Radical **B** is trapped by Cu(II)X and undergoes subsequent halogen atom transfer (from copper(II)X species to **B**) to provide the target products **2a–4a** and regenerate the Cu(I)OH species. The HX is necessary to facilitate regeneration of the Cu(I)X from the Cu(I)OH species.

In summary, we have developed a simple and efficient copper-catalyzed radical ring-opening halogenation with HX (aq). It is shown that HX (aq) can also be used as an efficient source of radical halogenation. This protocol provided an economic, environmentally benign, and practical synthetic approach to the important distally halogenated alkyl ketones and halogenated alkyl nitriles.

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Conflicts of interest

The authors declare no competing financial interest.

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