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Visible-Light-Triggered Catalytic Halohydrin Synthesis from Epoxides and Trichloroacetonitrile by Copper and Iron Salts

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Preparation of vicinal halohydrins, in which copper or iron chlorides catalyze the ring-opening reaction of epoxides with visible light effectively, is described. The use of trichloroacetonitrile as a halogen source enables catalytic HCl generation under the mild conditions. This method can also be applied to the aziridine ring-opening reaction.

Keywords: Visible light, Halohydrin, Metal salts

Toward the sustainable design of chemical reactions, the application of earth-abundant and low-cost metals has been strongly desired in current organic synthesis.[1] This idea has been spreading throughout the field of photocatalysis, wherein the privileged Ru and Ir systems[2] would be supplanted by other metals such as first-row transition metals.[3-7] Thus, we sought to develop powerful visible-light-induced transformations by Cu or Fe catalysts.[8]

In 2011, Stephenson and co-workers reported a method for conversion of alcohols to the corresponding bromides using 1.0 mol % of Ru(bpy)$_3$Cl$_2$ as a visible-light-activated photocatalyst.[9,10] The reduction of CBr$_4$ in DMF was achieved to form a Vilsmeier–Haack reagent[11] through the oxidative quenching of excited-state Ru(II)* with CBr$_4$. It is expected that HBr generation via hydrolysis of the Vilsmeier intermediate might occur in the photoreaction in the presence of H$_2$O. Meanwhile, our group recently found that CCl$_3$CN could generate HCl under 365 nm UV irradiation, provoking ring-opening reactions of aziridines.[12] We hence envisaged that the combined use of CCl$_3$CN and photocatalysts might enable catalytic HCl generation under mild conditions. Herein, we describe Cu- and Fe-catalyzed halohydrin syntheses from epoxides using visible light (Figure 1).[13]

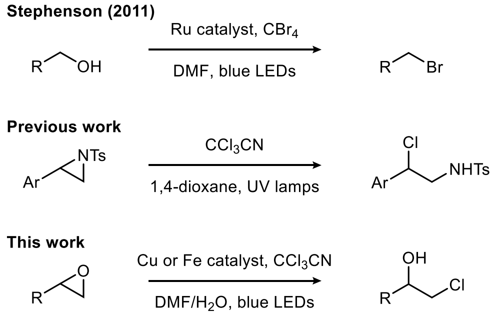
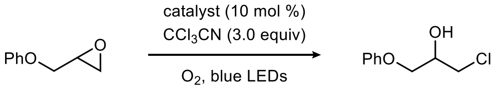


Figure 1. Application of halomethanes in photoreactions.

At the outset of our study, we attempted the reaction of glycidyl phenyl ether (**1a**) with the use of 10 mol % of catalyst and 3.0 equivalents of CCl$_3$CN under oxygen atmosphere with irradiation by blue LEDs in a 99:1 mixture of DMF and H$_2$O at 25 °C for 1 h (Table 1).[14] To our delight, CuCl afforded the desired chlorohydrin **2a** in 88% yield after purification by column chromatography (Entry 1). Almost no conversion of **1a** was observed without catalyst or without light (Entries 2 and 3). Other copper (I) salts such as CuI and CuPF$_6$•4CH$_3$CN were also effective to give **2a** in good yields (Entries 4 and 5). The highest yield was obtained by using CuCl$_2$ in DMF/H$_2$O, whereas switching the solvent to MeCN/H$_2$O or CH$_2$Cl$_2$/H$_2$O resulted in only trace amounts of **2a** (Entries 6–8). The use of 1,4-dioxane/H$_2$O also led to a good yield (Entry 9). Comparable yields were obtained by employment of FeCl$_2$•4H$_2$O and FeCl$_3$•6H$_2$O (Entries 10 and 11). CoCl$_2$, NiCl$_2$, and ZnCl$_2$

Table 1. Optimization of reaction conditions[a]

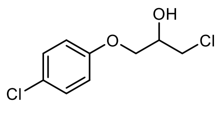


1a **2a**

Entry	Catalyst	**2a** (%)[b]
1	CuCl	88
2	None	<5[c]
3[d]	CuCl	<5[c]
4	CuI	85
5	CuPF$_6$•4CH$_3$CN	87
6	CuCl$_2$	90
7[e]	CuCl$_2$	<5[c]
8[f]	CuCl$_2$	<5[c]
9[g]	CuCl$_2$	87[c]
10	FeCl$_2$•4H$_2$O	88
11	FeCl$_3$•6H$_2$O	88
12	CoCl$_2$	<5[c]
13	NiCl$_2$	<5[c]
14	ZnCl$_2$	<5[c]
15	Ru(bpy)$_3$Cl$_2$•6H$_2$O	43[c]
16[h]	CuCl$_2$	<5[c]
17[i]	CuCl$_2$	<5[c]

[a]All reactions were carried out with 0.20 mmol of **1a**. [b]Isolated yield. [c]NMR yield. [d]In dark. [e]In MeCN:H$_2$O = 99:1. [f]In CH$_2$Cl$_2$:H$_2$O = 99:1. [g]In 1,4-dioxane:H$_2$O = 99:1. [h]CCl$_4$ was used. [i]CHCl$_3$ was used.

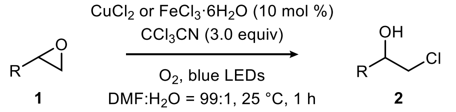
2a' :

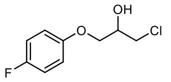
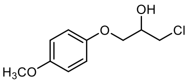
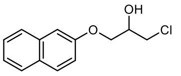
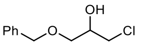
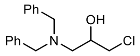
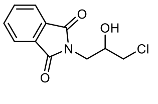
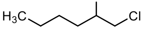
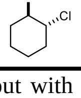


were also screened, but did not show any catalytic activity (Entries 12–14). Notably, when the reaction was performed using $Ru(bpy)_3Cl_2$•$6H_2O$, **2a’** was the major product in about 50% yield (Entry 15).[15] Control experiments with CCl_4 or $CHCl_3$ resulted in almost no consumption of starting material **1a** (Entries 16 and 17). This hierarchy of the reactivity matched our previous report.[12]

With the optimized reaction conditions in hand, we investigated the scope of epoxides in the Cu- and Fe-catalysis (Table 2). Several glycidyl phenyl ether derivatives bearing electron-deficient, electron-rich, or polycyclic aromatic rings provided chlorohydrins **2b**–**2d** in good to high yields (Entries 1–3). Glycidyl benzyl ether was applicable to furnish the corresponding product **2e** (Entry 4). Although a longer reaction time was needed for the consumption of *N*-glycidyldibenzylamine, amino and imido groups were also tolerated (Entries 5 and 6). The regioisomer was observed in the case of 1,2-epoxyhexane, where the product was isolated after esterification of **2h** with isobutyric anhydride (Entry 7). In addition, 1,2-epoxycyclohexane, as a representative candidate of 1,2-disubstituted epoxides, was converted to **2i** in moderate yield (Entry 8).

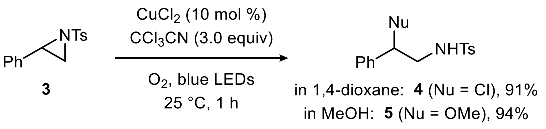
Table 2. Scope of epoxides[a]



Entry	Product	2 (%)[b]
1	 **2b**	[Cu] 94 [Fe] 77
2	 **2c**	[Cu] 92 [Fe] 75
3	 **2d**	[Cu] 90 [Fe] 82
4	 **2e**	[Cu] 80 [Fe] 79
5[c]	 **2f**	[Cu] 86 [Fe] 73
6	 **2g**	[Cu] 74 [Fe] 71
7	 **2h**	[Cu] 86[d,e] [Fe] 66[d,e]
8	 **2i**	[Cu] 61[d] [Fe] 57[d]

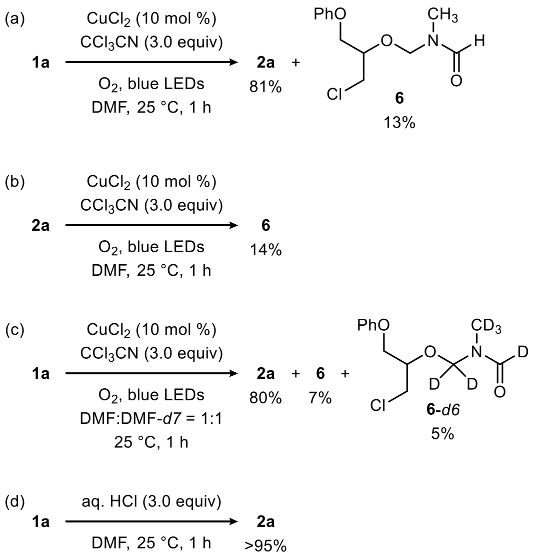
[a]Reactions were carried out with 0.20 mmol of **1**. [b]Isolated yield. [c]3 h. [d]NMR yield. Isolated after esterification, see Supporting Information for details. [e]Regioisomer (ca. 10%) was observed.

To expand the applicability of our methodology, *N*-tosylaziridine **3** was tested in the Cu catalysis. Delightfully, the reaction using dry 1,4-dioxane as the solvent yielded HCl adduct **4** in high yield, while the optimal reaction conditions for epoxides **1** led to less than 10% yield of the product due to undesired nucleophilic additions to **3** by DMF and H_2O. MeOH addition could be easily achieved to form **5** by changing the solvent (Scheme 1).[16]



Scheme 1. HCl or MeOH addition to aziridine **3**.

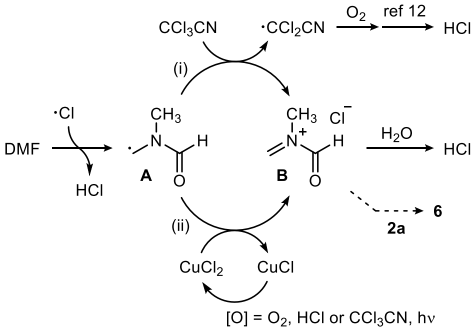
Lastly, we considered the mechanism of the present epoxide–HCl reaction. During the solvent screening, 13% of byproduct **6** was curiously obtained in dry DMF, where chlorohydrin **2a** could undergo nucleophilic addition to the DMF-derived iminium ion intermediate (Scheme 2a).[17] The reaction of **2a** under the same conditions afforded the chlorohydrin adduct **6** in 14% yield (Scheme 2b). Moreover, the reaction using a 1:1 mixed solvent of DMF and DMF-d_7 was investigated for the isotope competition (Scheme 2c). We did not observe a primary kinetic isotope effect (**6**:**6**-d_6 = 1.4:1),[18] implying that C–H bond cleavage of DMF was a fast process.[19] On the other hand, it was strongly indicated that HCl was generated by photodecomposition of CCl_3CN since HCl-adduct **2a** was produced by the treatment of **1a** with aqueous HCl solution (Scheme 2d).



Scheme 2. Mechanistic studies.

On the basis of these results, we proposed a mechanism of the Cu-catalyzed HCl generation in DMF (Scheme 3). First, homolysis of $CuCl_2$[20,21] and/or CCl_3CN would be initiated by photoirradiation to release a chlorine radical, which in turn would abstract a hydrogen atom from

DMF to provide HCl and radical **A**.[22] There are two possible pathways for the oxidation from **A** to **B**.[23] In pathway (i), CCl_3CN oxidizes **A**, leading to decomposition of the cyanodichloromethyl radical. The radical reacts with oxygen to generate HCl.[12] In pathway (ii), $CuCl_2$ oxidizes **A**. The resulting Cu(I) species reverts back to Cu(II) with the help of oxidants such as oxygen/HCl or CCl_3CN/light.[24] Hydrolysis of the iminium intermediate **B** could also generate HCl, whereas the reaction of **B** with halohydrin **2** leads to byproduct formation. Thus, the addition of H_2O to the solvent was important to suppress the side reaction that formed **6**.



Scheme 3. Proposed mechanism.

In summary, we have demonstrated catalytic ring-opening reactions of epoxides **1** using CCl_3CN as a visible-light responsive HCl generator for the synthesis of chlorohydrins **2**. It was found that copper and iron halide salts enabled the catalysis of the reaction under visible-light irradiation. The synthesis of β-chloroamine **4** and β-methoxyethylamine **5** was accomplished by the copper catalysis. Efforts are currently underway to broaden the applications of this methodology and to understand the precise reaction mechanism.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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15 The reaction using $Ru(bpy)_3Cl_2•6H_2O$ under argon atmosphere afforded **2a** in 75% NMR yield and **2a'** in 9% NMR yield.

16 The HCl addition to **3** using $FeCl_3•6H_2O$ in 1,4-dioxane led to low yield of **4** because of hydrolysis of **3**. In contrast, the MeOH addition using $FeCl_3•6H_2O$ proceeded without irradiation by blue LEDs to form **5** in 88% NMR yield.

17 In the proposed mechanism by Stephenson *et al.*, DMF attacks electrophilic tribromomethyl radical (see, ref 9a). However, DMF is not necessary for the present reaction.

18 The ratio was confirmed by HRMS analysis.

19 Zhao *et al.* observed a kinetic isotope effect value of 4.9 in the visible-light-driven coupling of DMF and alcohols, see: L. Li, G. Zhang, A. Savateev, B. Kurpil, M. Antonietti, Y. Zhao, *Asian J. Org. Chem.* **2018**, *7*, 2464.

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21 The reaction using stoichiometric amount of $CuCl_2$ (100 mol %) in the absence of CCl_3CN afforded **2a** in 11% NMR yield. $CuCl_2$ shows visible-light absorbance (λ_{max} = 436 nm).

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23 The HOMO level of radical **A** (-4.96 eV) is higher than that of DMF (-6.96 eV) on the basis of DFT calculations at the B3LYP/6-311+G** level (ΔE = 46.1 kcal/mol).

24 The additional results are shown in Supporting Information.