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# Copper-Mediated Oxidative Chloro- and Bromodifluoromethylation of Aliphatic Alcohols

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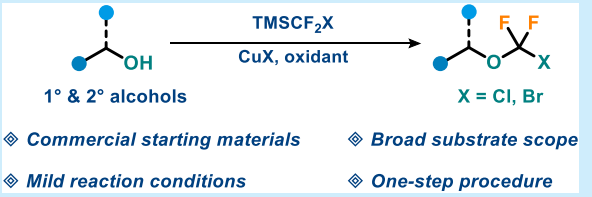
**ABSTRACT:** The synthesis of chloro- and bromodifluoromethyl alkyl ethers remained a fundamental challenge in synthetic chemistry. Herein we report the efficient and direct synthesis of chloro- and bromodifluoromethyl alkyl ethers through copper-mediated oxidative chrolo- and bromodifluoromethylation of aliphatic alcohols with difluorocarbene-reagents. This difluorocarbene-involved oxidative coupling protocol exhibited broad functional group compatibility and was applicable to a wide range of primary and secondary alcohols.

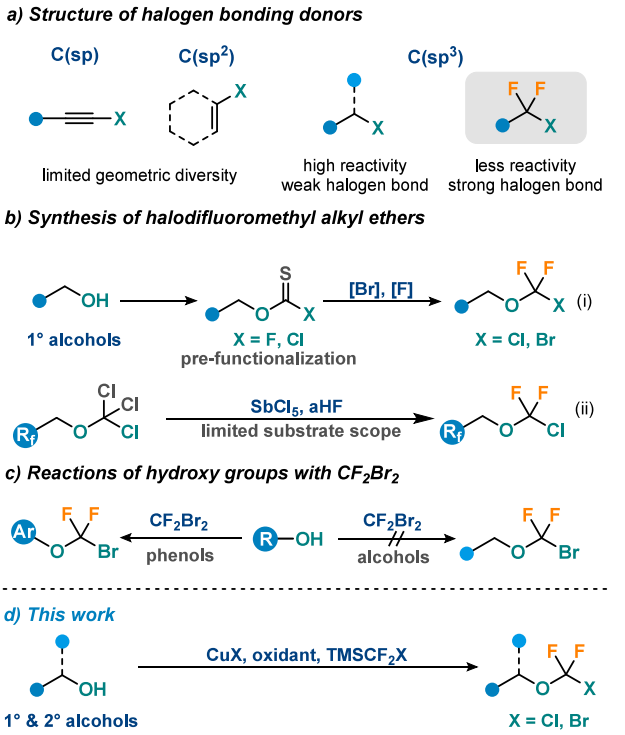





Halogen bonding (XB) is a well-established noncovalent interaction between the electropositive region on the halogen, the $\sigma$-hole, and a nucleophilic interaction partner.[1] This highly directional attraction has been exploited for a range of functional applications, such as crystal engineering,[2] catalysis,[3] drug design and protein−ligand complexation.[4] Traditional halogen bonding donors were typically confined to halogen atoms attached to $sp^2$- or sp-hybridized carbon atoms, exhibiting limited geometric diversity (Scheme 1a). In comparison, alkyl halides with $sp^3$ carbon−halogen bonds were generally less utilized due to their high reactivity and weak strength of halogen bonding.[5] Therefore, the strong electron-withdrawing groups (EWGs) were introduced as XB-tuning substituents to improve the XB strength. Fluorine was an ideal EWG, as it not only enhanced the halogen bonding strength but also reduced the reactivity by its shielding of the carbon atom. Consequently, halodifluoromethyl ($-CF_2X$) groups had emerged as promising halogen bonding donors (Scheme 1a).[6]

Recently, significant attention has been drawn to the synthesis and application of halodifluoromethyl-containing compounds, including halodifluoromethyl aryl ethers (Ar−O−$CF_2X$),[4d,7] halodifluoroacetamides (−NHCO−$CF_2X$),[8] and halodifluoroethyl ($-CH_2CF_2Cl$) groups.[9] In contrast, the application of chloro- and bromodifluoromethyl alkyl ethers was limited due to the scarcity of efficient and general synthetic methods.[10] Conventional approaches to chloro- and bromodifluoromethyl alkyl ethers relied on the desulfurization−halogenation of halothioformate derivatives (Scheme 1b, i).[8c,11] Nevertheless, this strategy suffered from the use of the highly toxic and strongly oxidizing agent $BrF_3$, or the expensive silver reagent $AgSCF_3$. Alternatively, chlorodifluoromethyl alkyl ethers could also be obtained from the Swarts reaction of trichloromethyl alkyl ethers (Scheme 1b, ii).[10a] However, this method was limited by harsh reaction conditions and narrow substrate scope, typically restricted to poly- or

**Scheme 1. Application and Synthesis of Chloro- and Bromodifluoromethyl Alkyl Ethers**

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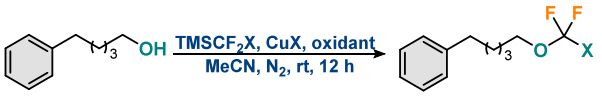
perfluorinated starting materials. Notably, all of the existing methods for the synthesis of halodifluoromethyl alkyl ethers depended on the prefunctionalized alcohol derivatives as starting materials. Therefore, the development of a direct and efficient method for the synthesis of chloro- and bromodifluoromethyl alkyl ethers from commercially available alcohols is highly desirable. Although the direct one-step preparation of bromodifluoromethyl aryl ethers from phenols was well established using $CF_2Br_2$ under basic reaction conditions, the analogous reaction between aliphatic alcohols and $CF_2Br_2$ was completely hindered, probably due to the intrinsic inertness of aliphatic alcohols (Scheme 1c, for details, see Supporting Information). Recently, our group has developed a direct and efficient synthesis of chloro- and bromodifluoromethyl aryl ethers through the copper-mediated difluorocarbene-involved oxidative chloro- and bromodifluoromethylation of phenols.[7d] Driven by our ongoing interest in oxidative fluoroalkylation[12] and extending this methodology to other nucleophiles,[13] we propose a difluorocarbene-based three-component oxidative coupling of aliphatic alcohols, difluorocarbene precursors and CuX (X = Cl, Br). If successful, this protocol would provide a one-step route to synthesize chloro- and bromodifluoromethyl alkyl ethers under mild reaction conditions using commercially available starting materials (Scheme 1d).

To assess the feasibility of our design, we commenced the investigation using 5-phenyl-1-pentanol (**1a**) as the model substrate for the reaction optimization. After the multidimensional evaluation of reaction parameters, we were pleased to observe the formation of bromodifluoromethyl alkyl ether **2a** in 53% yield using $TMSCF_2Br$ as a difluorocarbene precursor, CuBr as copper salt, Selectfluor as oxidant, and MeCN as the solvent (Table 1, entry 1). Alternative oxidants such as PIDA and $NaBrO_3$ all resulted in slightly diminished yields (entries 2−3). Notably, when oxidant and CuBr were first mixed and stirred for 5 min, followed by the addition of **1a** and then stirring another for 5 min, and finally the addition of $TMSCF_2Br$, these in-sequence additions of reagents resulted in a higher yield of **2a** (entry 4). Interestingly, the yield of **2a** was improved to 70% in the presence of the reduced amount of $TMSCF_2Br$ (1.5 equiv) (entry 5). Furthermore, when the amounts of both $TMSCF_2Br$ (1.5 equiv) and Selectfluor (1.75 equiv) were reduced, the yield of **2a** was still kept at 69% yield (entry 6). Encouraged by these results, we next explored the analogous oxidative chlorodifluoromethylation of **1a** using $TMSCF_2Cl$ as a difluorocarbene precursor, and CuCl as copper salt in MeCN. The chlorodifluoromethylated product **3a** was formed in 26% yield (entry 7). The oxidant proved to be crucial for the efficiency of this three-component coupling reaction (entries 8−10). Fortunately, **3a** was formed in 41% yield when $NaClO_2$ was used as the oxidant (entry 10). The reduction of the amounts of both $TMSCF_2Cl$ and $NaClO_2$ had a negligible impact on the yield of **3a** (entry 11). Further optimization of the reaction conditions showed that reducing the amount of CuCl and addition of $Et_4NCl$ resulted in the formation of **3a** in 44% yield (entry 12). Finally, the yield of **3a** was improved to 51% in the case of the addition of a catalytic amount of $SrCl_2$ (entry 13).

**Table 1. Optimization of Reaction Conditions**[a]




**1a** **2a** (X = Br); **3a** (X = Cl)

| entry | $TMSCF_2X$ (*x* equiv) | CuX | oxidant | yield (%)[b] **2a**/**3a** |
|---|---|---|---|---|
| 1 | $TMSCF_2Br$ (2.0) | CuBr | Selectfluor | 53/− |
| 2 | $TMSCF_2Br$ (2.0) | CuBr | PIDA | 42/− |
| 3 | $TMSCF_2Br$ (2.0) | CuBr | $NaBrO_3$ | 48/− |
| 4[c] | $TMSCF_2Br$ (2.0) | CuBr | Selectfluor | 59/− |
| 5[c] | $TMSCF_2Br$ (1.5) | CuBr | Selectfluor | 70/− |
| 6[c,d] | $TMSCF_2Br$ (1.5) | CuBr | Selectfluor | 69/− |
| 7 | $TMSCF_2Cl$ (3.0) | CuCl | Selectfluor | −/26 |
| 8 | $TMSCF_2Cl$ (3.0) | CuCl | PIDA | −/21 |
| 9 | $TMSCF_2Cl$ (3.0) | CuCl | $NaBrO_3$ | −/38 |
| 10 | $TMSCF_2Cl$ (3.0) | CuCl | $NaClO_2$ | −/41 |
| 11[d] | $TMSCF_2Cl$ (1.5) | CuCl | $NaClO_2$ | −/38 |
| 12[d,e] | $TMSCF_2Cl$ (1.5) | CuCl | $NaClO_2$ | −/44 |
| 13[d,e,f] | $TMSCF_2Cl$ (1.5) | CuCl | $NaClO_2$ | −/51 |

[a]Reaction conditions: **1a** (0.1 mmol), $TMSCF_2X$ (x equiv), CuX (5.0 equiv), oxidant (2.0 equiv), MeCN (0.1 M), under $N_2$, room temperature, 12 h. [b]Yields determined by $^{19}F$ NMR spectroscopy using $PhCF_3$ as an internal standard. [c]CuX (5.0 equiv), oxidant (2.0 equiv), MeCN (0.1 M), 5 min; then, **1a** (0.1 mmol), 5 min; then, $TMSCF_2X$ (x equiv), 12 h. [d]Oxidant (1.75 equiv). [e]CuCl (1.0 equiv), $Et_4NCl$ (1.0 equiv). [f]Addition of $SrCl_2$ (0.25 equiv).

Under the optimal reaction conditions (Table 1, entry 5), the substrate scope of the oxidative bromodifluoromethylation of aliphatic alcohol was extensively evaluated (Scheme 2). A wide range of aliphatic alcohols bearing ester, nitro, cyano, trifluoromethyl, chloride, and amide groups were well tolerated, as shown in the formation of **2b−q**. Alcohols derived from naphthalene and fluorene afforded the corresponding bromodifluoromethyl alkyl ethers (**2k−l**) in moderate yields. The formation of products **2p−q** demonstrated compatibility with the heterocyclic motifs. Secondary alcohol was also a viable substrate, delivering the desired product (**2r**) in moderate yield. Subsequent evaluation of benzyl alcohols revealed broad applicability. A variety of benzyl alcohols participated efficiently in this transformation, bearing functional groups such as ketone (**2s**), cyano (**2t**), nitro (**2u**), sulfone (**2v**), and pyridine (**2x**).

We next investigated the substrate scope of chlorodifluoromethylation (Scheme 3). A variety of primary alcohols were compatible with this oxidative protocol. Primary alcohols bearing electron-withdrawing and electron-donating groups, including ester, trifluoromethyl, ether, chloride, and alkyne, provided the desired products (**3b−f**) in moderate yields. Carbazole and naphthalene-derived alcohols performed well in the reaction (**3g−h**). Finally, the secondary alcohol also proved compatible, delivering the respective product (**3i**) in moderate yield.

To elucidate the mechanism of this novel oxidative coupling reaction, a series of experiments were carried out. $TMSCF_2Br$ underwent slow decomposition in MeCN, and the decomposition was accelerated in the presence of alcohol, CuBr, Selectfluor, or the $BF_4$ anion (Scheme 4a). Consequently, this halodifluoromethylation reaction might be initiated by the activation of $TMSCF_2Br$ with alcohol, CuBr, Selectfluor, or the $BF_4$ anion. Furthermore, when $FSO_2CF_2CO_2TMS$ or $BrCF_2PO(OEt)_2$ was employed as the difluorocarbene precursor under the oxidative chlorodifluoromethylation reaction conditions, target product **3a** was obtained in 11% or 5% yield, respectively (Scheme 4b, c). These results implied that the oxidative reaction proceeded through a difluorocarbene intermediate. Control experiments confirmed that both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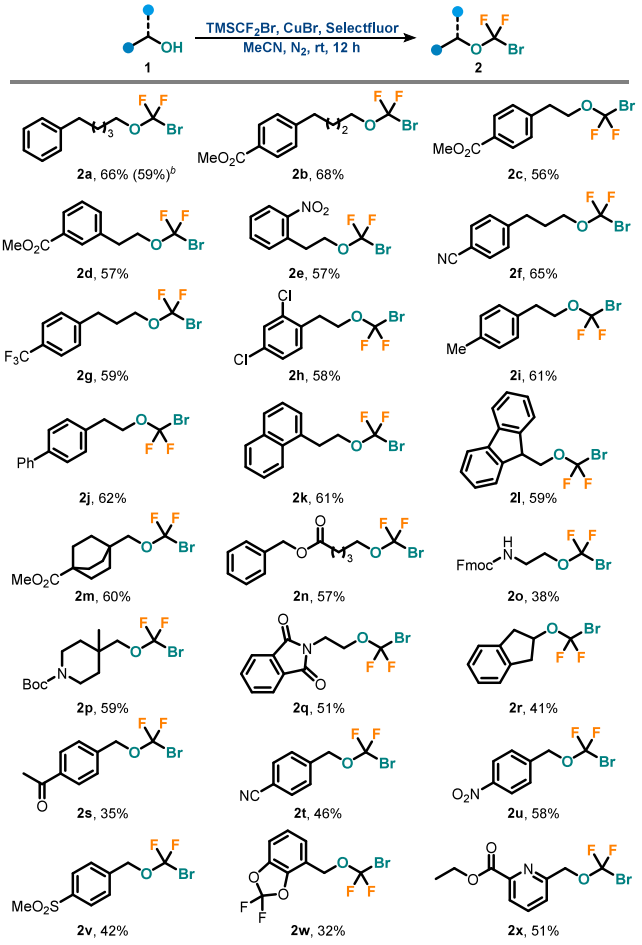
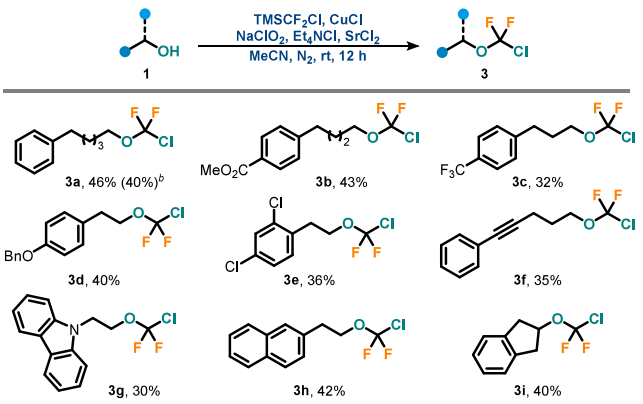
**Scheme 2. Substrate Scope of Bromodifluoromethylation**[a]




[a]Reaction conditions: **1** (0.6 mmol), $TMSCF_2Br$ (1.5 equiv), CuBr (5.0 equiv), Selectfluor (1.75 equiv), MeCN (0.1 M), under $N_2$, room temperature, 12 h. Isolated yields. [b]**1** (1 mmol).

**Scheme 3. Substrate Scope of Chlorodifluoromethylation**[a]

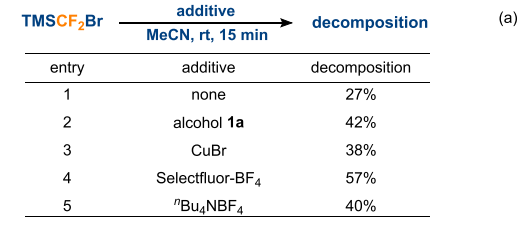



[a]Reaction conditions: **1** (0.6 mmol), $TMSCF_2Cl$ (1.5 equiv), CuCl (1.0 equiv), $NaClO_2$ (1.75 equiv), $Et_4NCl$ (1.0 equiv), $SrCl_2$ (0.25 equiv), MeCN (0.1 M), under $N_2$, room temperature, 12 h. Isolated yields. [b]**1** (1 mmol).

the copper salt and the oxidant were essential for the formation of bromodifluoromethyl alkyl ether **2a** (Scheme 4d, e). Reaction of difluoromethyl ether **4** with CuBr and Selectfluor failed to give the desired product **2a**, which excluded **4** as a possible intermediate for this oxidative bromodifluoormethylation process (Scheme 4f). In addition, the reaction of alcohol **1a** with $TMSCF_2Br$ and $CuBr_2$ did not yield the target product **2a** (Scheme 4g). In contrast, treatment of alcohol **1a** with $TMSCF_2Br$, Selectfluor and $CuBr_2$ delivered product **2a** in 3% yield (Scheme 4g). These results indicated that the high-valent copper(III) species was a mediator in the formation of the $ROCF_2$–X bond.[14]

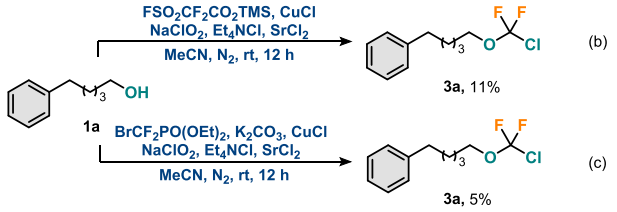
**Scheme 4. Mechanistic Investigation**

◈ *Initiation*

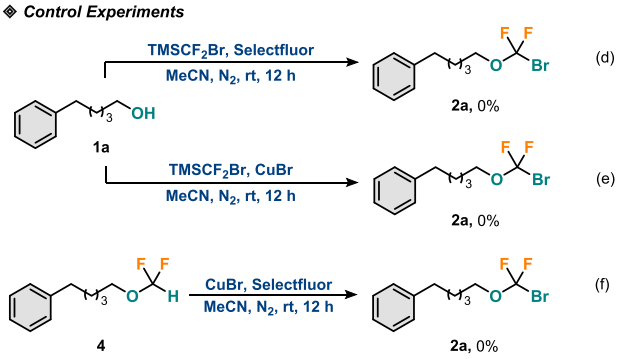



| entry | additive | decomposition |
|---|---|---|
| 1 | none | 27% |
| 2 | alcohol **1a** | 42% |
| 3 | CuBr | 38% |
| 4 | Selectfluor-$BF_4$ | 57% |
| 5 | $^nBu_4NBF_4$ | 40% |

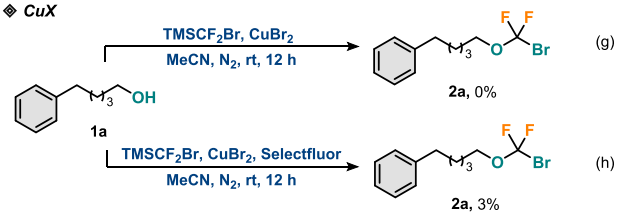
◈ *Difluorocarbene*



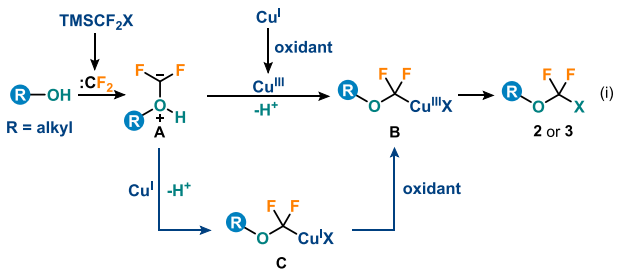

◈ *Control Experiments*




◈ *CuX*




◈ *Proposed Mechanism*




Based on the above results and related precedents,[7d,15] a plausible reaction mechanism was proposed in Scheme 4i. Initially, $TMSCF_2X$ (X = Cl, Br) underwent desilylation to



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generate difluorocarbene. Subsequently, the reaction of alcohol and difluorocarbene gave intermediate **A**, which then underwent oxidative coupling with CuX (X = Cl, Br) in the presence of the oxidant to form a high-valent $ArOCF_2Cu^{III}X$ complex **B** through two possible pathways. One pathway was the formation of the Cu(III) species from reaction of a Cu(I) complex with the oxidant followed by transmetalation of **A** to Cu(III). The second pathway proceeded through the formation of copper(I) species **C** from the transmetalation of **A** to Cu(I) and then the oxidation of **C** with the oxidant. Finally, the reductive elimination of complex **B** afforded the desired chloro- and bromodifluoromethyl alkyl ethers.

In summary, we have developed a copper-mediated oxidative chloro- and bromodifluoromethylation of aliphatic alcohols with difluorocarbene reagent $TMSCF_2X$ (X = Cl, Br). This strategy provided a novel and direct method for the synthesis of chloro- and bromodifluoromethyl alkyl ethers from commercially available alcohols in one-step, overcoming limitations of existing methods. Our laboratory is applying this strategy to other *C*-, *O*- and *N*-nucleophiles, as it provides a mild and efficient approach for the synthesis of halodifluoromethyl-containing compounds.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c04545.

Experimental procedures, characterization data, copies of $^1H$, $^{19}F$, and $^{13}C$ NMR spectra. (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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