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Difluorocarbene-Induced Ring-Opening Difluoromethylation-Halogenation of Cyclic (Thio)Ethers with $TMSCF_2X$ (X = Br, Cl)**

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Abstract: The ring-opening difluoromethylation-halogenation of cyclic (thio)ethers is reported through a simple strategy relying on carbon-chalcogen bond activation with difluorocarbene. The reaction proceeds through in situ protonation of the previously little-known difluoromethylene oxonium or sulfonium ylide intermediate followed by ring-opening with halide ion to afford halogenated acyclic difluoromethyl (thio)ethers that can then be employed for further elaboration. $TMSCF_2X$ (X = Br, Cl) are unique reagents to achieve this synthetic purpose, which serve as both the difluorocarbene source and the halide ion source.

Oxonium ylides, as highly reactive intermediates, are mainly formed through the interaction of free carbenes or metal carbenes with the unshared electron pairs of an oxygen atom, and have been well utilized in organic synthesis owing to the rapid development of the chemistry of diazo compounds in the past decades.[1] However, due to the relatively low Lewis basicity of the oxygen atom compared to phosphine and nitrogen atoms in electron neutral organic molecules, the generation of oxonium ylides requires a highly reactive carbene or metal carbene complex.[1c] On the other hand, in recent years, the chemistry of difluorocarbene has witnessed great progress and many new difluorocarbene regents have been developed to achieve versatile transformations.[2] However, difluorocarbene in its singlet ground state is only moderately electrophilic because of the combinational destabilization by the negative inductive effect of fluorine atom and stabilization by π-donation from the fluorine atom to the carbon atom.[2a,3] Therefore, in sharp contrast to difluoromethylene phosphonium and ammonium ylides, the formation of difluoromethylene oxonium ylides from difluorocarbene is more challenging, and the chemistry of fluorinated oxonium ylide has been noticeably scarce.[4–8]

Difluoromethyl ethers are of great synthetic interest[9] due to their wide application in developing enzyme inhibitors and activators, anti-HIV agents, antimicrobial agents, as well as anesthetic drugs.[9b,c,10] Among various methods for the synthesis of difluoromethyl ethers,[11–14] difluoromethylation of *O*-nucleophiles with difluorocarbene is the most convenient approach because of the abundance of *O*-nucleophiles such as phenols and alcohols and the easy availability of difluorocarbene sources.[2,3,15] Since our first introduction of $TMSCF_2Br$ as a mild difluorocarbene source in 2011,[16] it has been developed into a versatile difluorocarbene reagent by us and others.[2a–d,5,17,18] In 2017, by using $TMSCF_2Br$ as a unique and practical difluorocarbene reagent, we developed a general method for the efficient difluoromethylation of alcohols under weakly acidic conditions in a two-phase system of dichloromethane/water at room temperature.[5a] In that work, we first investigated the mechanistic difference between difluoromethylation of phenols and alcohols with difluorocarbene. Based on our experimental results[5a] and recent DFT calculation results from others,[6] we established that the reaction of phenols with difluorocarbene is an anionic pathway (Scheme 1A),[5a] while that of alcohols involves a difluoromethylene oxonium ylide intermediate (Scheme 1B).[5b] The facile interaction between difluorocarbene and the alcoholic oxygen atom to form oxonium ylide is attributed to the mildness of the difluorocarbene generation method.

Inspired by our understandings on the alcohol difluoromethylation mechanism,[5] we envisioned that dialkyl ethers, which contain a more Lewis basic oxygen atom than alcohols, should also react with difluorocarbene to generate a difluoromethylene oxonium ylide intermediate under our two-phase conditions (Scheme 1C). If feasible, the difluoromethylene oxonium ylide intermediate would be protonated to afford a difluoromethyl oxonium cation intermediate. Because oxonium salts are known to be powerful alkylating agents,[1d] we assumed that the difluoromethyl dialkyl oxonium cation would be attacked by a nucleophile on one alkyl substituent to give difluoromethyl ether. Considering that cyclic ethers are more Lewis basic than acyclic ethers due to the ring strain, we envisioned that cyclic ethers would undergo reaction with difluorocarbene to give ring-opening *O*-difluoromethylation products. To our knowledge, the ring opening *O*-fluoroalkyla-

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[**] TMS = trimethylsilyl

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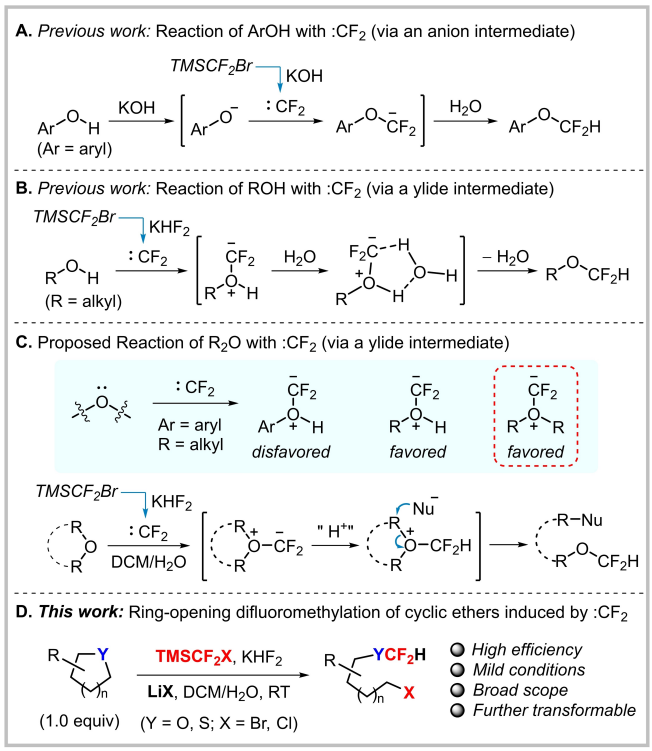


Scheme 1. Reaction of various *O*-nucleophiles with difluorocarbene. TMS = trimethylsilyl; DCM = dichloromethane; RT = room temperature.

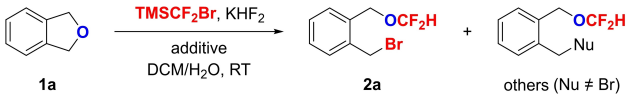
tion of cyclic ethers is still underdeveloped.[4,19] In 1995, Uneyama and coworkers demonstrated an *O*-difluoro(phenylseleno)methylation of cyclic ethers via difluoromethylene oxonium ylide intermediate generated in Pummerer type rearrangement of $PhSe(O)CF_2H$;[4] however, this process is far from efficient since large amounts of ethers were needed to trap difluorocarbene. Additionally, while difluorocarbene-induced ring-opening of cyclic amines has been well described[18,20] following our early report on the ring-opening of an N-heterocyclic compound with $TMSCF_2Br$,[21] the *N*-difluoromethyl groups could not be retained due to their ready hydrolysis.

As a continuation of our interest in the chemistry of fluorinated carbenes,[2a–d,5,17a,b,21,22] we aim to develop a method for efficient ring opening difluoromethylation of cyclic ethers with difluorocarbene reagents $TMSCF_2X$ (X = Br, Cl) (Scheme 1D), where the difluoromethyl group can be kept untouched due to the stability of difluoromethyl ethers. Undoubtedly, owing to much weaker nucleophilicity of oxygen atom than that of nitrogen atom, one of the major challenges in developing such a method is the identification of a proper nucleophile that can selectively open the heterocyclic ring but cannot react with difluorocarbene. Taking into account that $TMSCF_2X$ (X = Br, Cl) can also release halide ions, we eventually chose bromide and chloride ions as the ring-opening nucleophiles. Herein, we report a novel ring-opening difluoromethylation-halogenation of cyclic (thio)ethers with $TMSCF_2X$ (X = Br, Cl) as both the electrophilic difluorocarbene source and the nucleophilic halide ion source, which constitutes an efficient method for the synthesis of functionalized difluoromethyl (thio) ethers.

Our research started with probing the existence of difluoromethylene oxonium ylide intermediate using cyclic ether 1,3-dihydroisobenzofuran (**1 a**) instead of primary alcohols under otherwise the same conditions for difluoromethylation of primary alcohols[5a] (Table 1, entry 1). To our delight, a mixture of *O*-difluoromethylation products was detected in moderate yields. Control experiment in the absence of $TMSCF_2Br$ showed that no ring-opening reaction took place. Clearly, the difluoromethyl ethers were formed through the nucleophilic ring-opening of an *O*-difluoromethyl cyclic oxonium cation intermediate, which supports the involvement of a difluoromethylene oxonium ylide intermediate.

Next, we optimized the difluoromethylation of 1,3-dihydroisobenzofuran (**1 a**) with $TMSCF_2Br$. By employing the developed conditions for difluoromethylation of secondary and tertiary alcohols, as reported previously,[5a] the total yield of *O*-difluoromethylation products was increased as the amounts of $TMSCF_2Br$ and KHF_2 were simultaneously increased (Table 1, entries 2 and 3), which is similar to the reactivity profile of tertiary alcohols. When 4.0 equiv. of $TMSCF_2Br$ was used, cyclic ether **1 a** was ring-opened to difluoromethyl ethers quantitatively; however, the selectivity of the desired *C*-bromination over other *C*-functionalizations (mainly fluorination and formyloxylation[23]) was only moderate (Table 1, entry 3). Interestingly, a switch of the initiator to KF or CsF resulted in no difluoromethylation reaction, which is attributed to the competitive combination of the basic fluoride with difluorocarbene (Table 1, entries 4–5). Then we tried to add extra bromide salt

Table 1. Optimization of reaction conditions for the bromo-difluoromethylation of **1 a**.[a]



Entry	**1 a**/$TMSCF_2Br$/KHF_2	Additive [equiv.]	Total yield [%][b]	**2 a**/others[c]
1	1.0:2.0:4.0	none	62	ND
2	1.0:3.0:6.0	none	87	ND
3	1.0:4.0:8.0	none	99	79:21
4[d]	1.0:2.0:4.0	none	0	N/A
5[e]	1.0:2.0:4.0	none	0	N/A
6	1.0:4.0:4.0	LiBr (4.0)	99[f]	96:4
7	1.0:3.0:4.0	LiBr (4.0)	99	97:3
8	**1.0:2.0:4.0**	**LiBr (4.0)**	**99**	**97:3**
9	1.0:2.0:2.0	LiBr (4.0)	46[g]	ND
10	1.0:4.0:0.0	LiBr (8.0)	0	N/A
11	1.0:3.0:4.0	NaBr (4.0)	78	80:20
12	1.0:3.0:4.0	KBr (4.0)	75	68:32

[a] All reactions were performed using **1 a** (0.5 mmol, 1.0 equiv.) in DCM (0.3 mL)/H_2O (0.3 mL) at room temperature for 20 h. [b] Total yield of **2 a** and other *O*-difluoromethylation products. Determined by ^{19}F NMR spectroscopy analysis using $PhOCF_3$ as an internal standard. [c] Determined by GC-MS analysis using the relative areas of products. [d] KF was used instead of KHF_2. [e] CsF was used instead of KHF_2. [f] The conversion of $TMSCF_2Br$ was 72%. [g] The conversion of $TMSCF_2Br$ was 56%. DCM = dichloromethane; N/A = not applicable; ND = not determined.

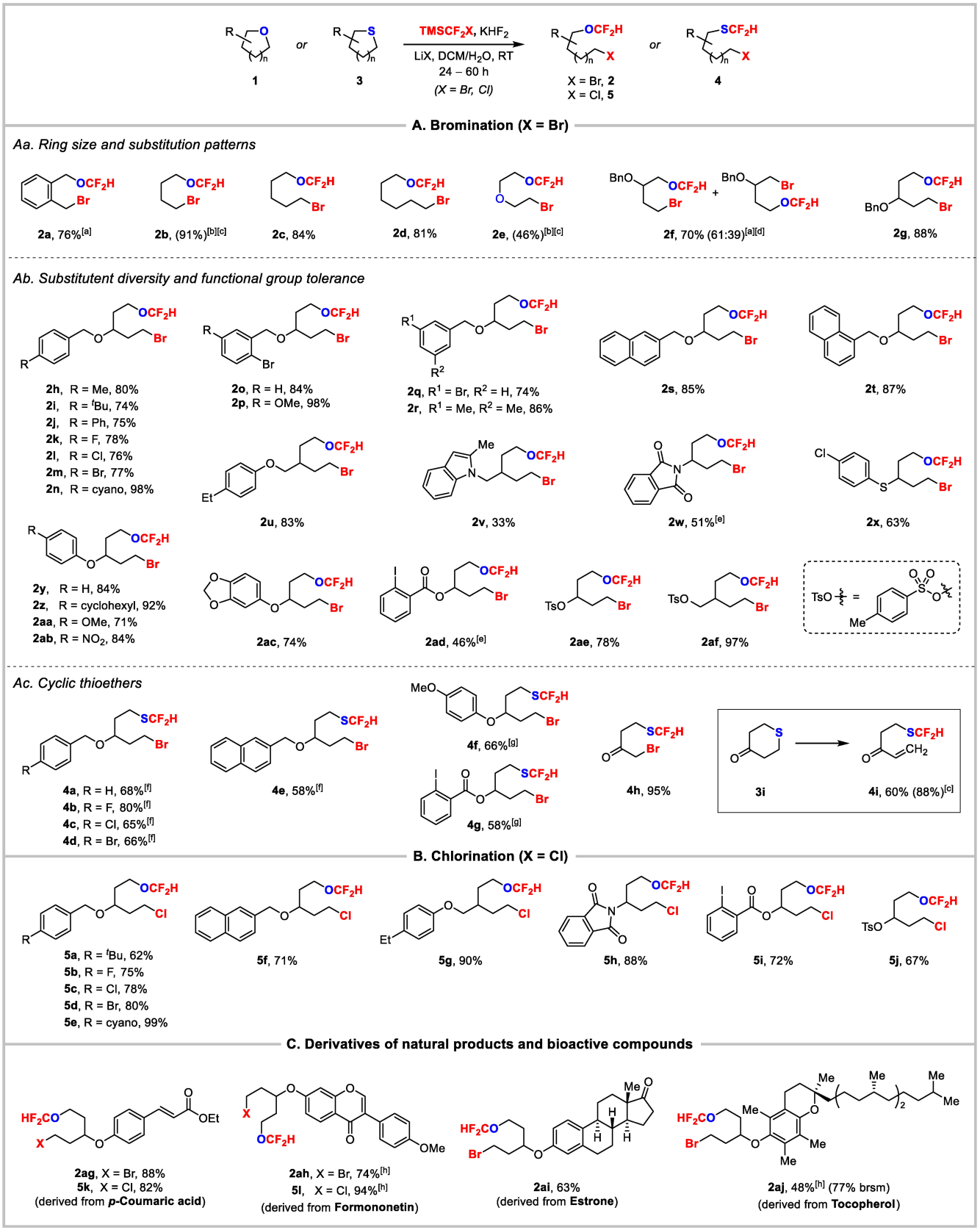
to the $TMSCF_2Br/KHF_2$ system to promote the C-bromination. Gratifyingly, the use of LiBr not only significantly enhanced the selectivity, but also largely improved the utilization efficiency of difluorocarbene (Table 1, entry 6). Further optimization of the reactant ratio showed that in the presence of 4.0 equiv. of LiBr, the use of only 2.0 equiv. of $TMSCF_2Br$ and 4.0 equiv. of KHF_2 is enough to realize the nearly full conversion of the cyclic ether (Table 1, entries 7 and 8). A comparison of the amount of KHF_2 used in the presence of LiBr showed that KHF_2 is necessary for the activation of $TMSCF_2Br$ and a 1:2 molar ratio of $TMSCF_2Br/KHF_2$ is optimal for the complete consumption of $TMSCF_2Br$ (Table 1, entries 8–10). However, NaBr and KBr failed to improve the reaction yields and selectivity (Table 1, entries 11 and 12). The remarkable promoting effects of LiBr probably arise from the relatively strong coordination interaction between lithium cation and the oxygen atom of the ether, which could facilitate the transfer of bromide ion and the anionic intermediates to difluorocarbene ($BrCF_2^-$ and pentacoordinate silicate anion $[Me_3Si(CF_2Br)F]^-$) from the organic/aqueous interface to the organic phase.[5b]

With the optimized conditions (Table 1, entry 8) in hand, we first tested the scope with respect to the ring size and substitution patterns of cyclic ethers (Scheme 2Aa). Among the commercially available three to seven-membered cyclic ethers, tetrahydrofuran (THF), tetrahydro-2*H*-pyran and oxepane underwent the ring-opening reaction smoothly to afford the difluoromethylation-bromination product in moderate to good yields (**2b**–**2d**). 1,4-Dioxane is also a viable substrate, albeit the yield is relatively low (**2e**). Although the three- and four-membered cyclic ethers were subjected to the ring-opening reaction, a complex mixture of *O*-difluoromethylation products was formed due to the competitive incorporation of nucleophiles other than bromide. 4-Benzoxy tetrahydro-2*H*-pyran, as a symmetrical substituted cyclic ether afforded the ring-opening product in good yield (**2h**). Substitution at the β-position of tetrahydrofuran provided good yield of a mixture of two regioisomers, with bromination at the relatively less sterically hindered carbon predominating (**2f**). Of note in these cases, the products were usually obtained in moderate to good yields though the cyclic ethers were used as the limiting reactant, showcasing the high efficiency of this difluoromethylation protocol.

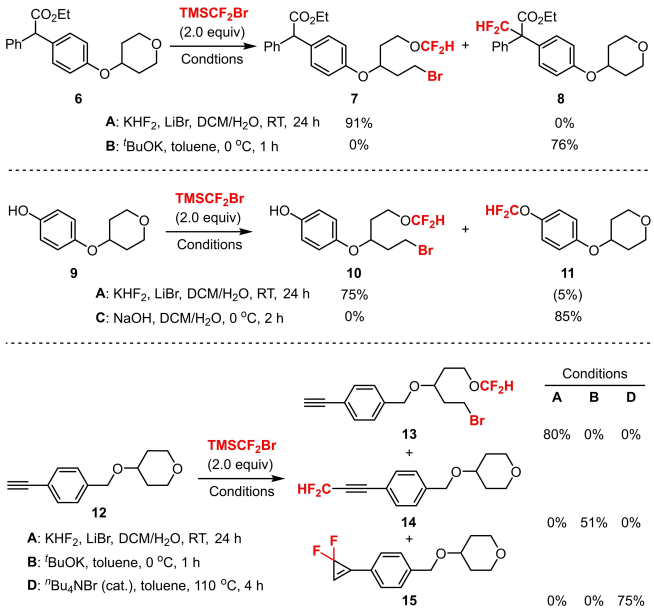
Given the potential implications of this developed protocol to derivation of complex cyclic ethers, we explored the versatility of substituents and the tolerance towards functional groups using 4-substituted tetrahydro-2*H*-pyrans as the substrates (Scheme 2Ab). A series of heteroatom- and functionalized methyl-substituted substrates participated in the reaction, providing the corresponding ring-opening products in moderate to excellent yields. To our delight, a range of diversely substituted acyclic ether functionalities including benzyl alkyl ethers (**2h**–**2t**) and aryl alkyl ethers (**2u** and **2y**–**2ab**) were amenable to the reaction and were not cleaved. The efficiency of the reaction was not impeded by the electronic nature of the aromatic rings. Benzo[*d*][1,3]dioxole, as a cyclic ether, was not activated for ring-opening (**2ac**), probably due to stabilization of the unshared electron pairs of the oxygen atoms by the aromatic ring. Carbonyl functionalities such as ester and imide can be kept intact; the moderate yields of **2y** and **2ad** are attributed to the low solubility of the corresponding substrates in dichloromethane. Tosylates, which are susceptible to undergo displacement reaction with nucleophiles, were inert towards halide ions under our conditions (**2ae** and **2af**). Moreover, some functionalities with heteroatoms that are more Lewis basic than the ethereal oxygen atoms can be tolerated to some extent, as exemplified by the ring-opening of two substrates containing indole and aryl alkyl thioether moieties, which produced the desired products in moderate yields (**2v** and **2x**).

This protocol is not limited to the transformation of cyclic ethers. Indeed, the use of cyclic thioethers instead of cyclic ethers could deliver the ring-opening *S*-difluoromethylation products in moderate to good yields (Scheme 2Ac). The relatively low yields of **4a**–**4g** compared to those of cyclic ethers probably result from the weaker electrophilicity of the difluoromethyl sulfonium cations than that of the difluoromethyl oxonium cations. In these cases, increasing the amount of $TMSCF_2Br$ was required (for details, see the Supporting Information). A five-membered cyclic thioether with a carbonyl group on the heterocycle ring readily underwent the reaction, exclusively at the carbon near the carbonyl group, providing the nucleophilic-substitution-ring-opening product in excellent yield (**4h**). However, the reaction of a symmetrical six-membered cyclic thioether with a carbonyl group afforded the elimination-ring-opening product (**4i**). The nucleophile used for trapping the difluoromethyl oxonium cation intermediate could be extended to chloride ion when changing $TMSCF_2Br$ to $TMSCF_2Cl$ and LiBr to LiCl (Scheme 2B). All the cyclic ethers examined produced the desired products in similar yields as those in the bromination; however, prolonged reaction time was essential due to the relative high stability of $TMSCF_2Cl$ (**5a**–**5j**). Importantly, our protocol is also suitable for the late stage modification of biologically relevant compounds including natural products and bioactive molecules. Cyclic ethers derived from *p*-coumaric acid (**2ag** and **5k**), formononetin (**2ah** and **5l**), estrone (**2ai**), and tocopherol (**2aj**) underwent the ring-opening reaction effectively to furnish the difluoromethylation-bromination and -chlorination products in good to excellent yields.

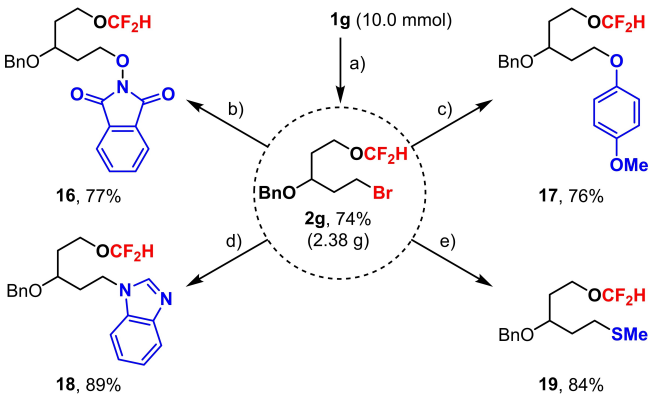
Remarkably, this ring-opening difluoromethylation reaction adds a new vector to the divergent synthesis of organofluorine compounds with difluorocarbene from ambident substrates and a given difluorocarbene reagent, which is often challenging with difluorocarbene sources other than $TMSCF_2X$ (X = Br, Cl).[2a–e,3] Taking advantage of the versatility of $TMSCF_2Br$ in the generation of difluorocarbene,[2a–d,5a,21,17a] we realized the selective transformation of several cyclic ethers with varying functional groups that are also reactive towards difluorocarbene (Scheme 3). Staring from the same substrate and the same reagent $TMSCF_2Br$, different functional groups were selectively fluoroalkylated, most of the time orthogonally, just by simply switching the reaction conditions. For diarylacetate-containing cyclic ether **6**, the use of weakly acidic aqueous KHF_2/LiBr conditions of this protocol provided the ring-opening difluoromethylation-bromination product **7** as the sole product in 91% yield, and the use of water-free basic conditions[17a] led



Scheme 2. Substrate scope. Conditions: for bromination, **1** or **3** (0.5 mmol), $TMSCF_2Br$ (1.0 mmol), KHF_2 (2.0 mmol), LiBr (2.0 mmol), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 24 h; for chlorination, **1** (0.5 mmol), $TMSCF_2Cl$ (1.0 mmol), KHF_2 (2.0 mmol), LiCl (2.0 mmol), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), RT, 60 h. Unless otherwise mentioned, the yields refer to isolated yields of analytically pure products. [a] Performed on 1-mmol scale. [b] Performed in CD_2Cl_2. [c] The yield was determined by ^{19}F NMR analysis using $PhOCF_3$ as an internal standard. [d] The isomer ratio was determined by ^{19}F NMR analysis of the isolated product. [e] The cyclic ether is of low solubility in CH_2Cl_2. [f] 2.5 mmol of $TMSCF_2Br$ was used. [g] 2.0 mmol of $TMSCF_2Br$ was used. [h] Performed on 0.25-mmol scale in CH_2Cl_2 (0.3 mL) and H_2O (0.3 mL). brsm = based on recovered starting material.



Scheme 3. Orthogonal transformations of ambident cyclic ether-containing substrates. The yields refer to isolated yields of analytically pure products. The yield in the parentheses refers to ^{19}F NMR yield of the side product that was confirmed by GC-MS analysis.

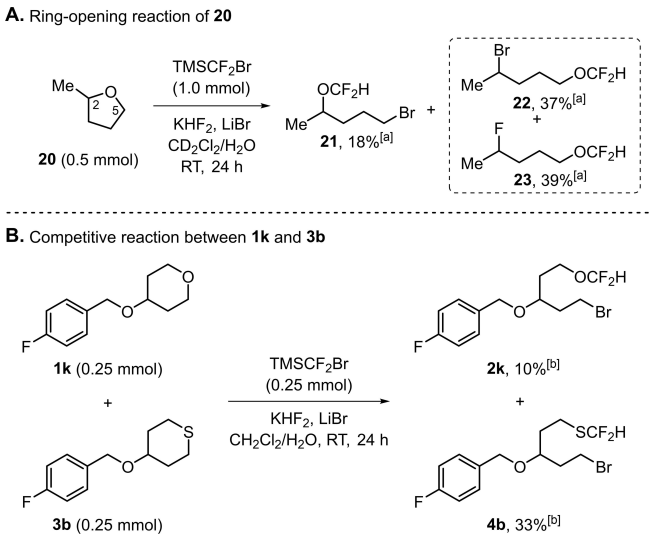


Scheme 4. Scale-up synthesis and synthetic application of bromination product **2g**. Conditions: a) $TMSCF_2Br$ (3.0 equiv.), KHF_2/LiBr, CH_2Cl_2/H_2O, RT; b) 1*H*-benzo[*d*]imidazole, NaH, THF, 60 °C; c) 4-$MeOC_6H_4OH$, NaH, DMF, RT; d) 2-hydroxyisoindoline-1,3-dione, DBU, 80 °C; e) MeSNa, THF, 60 °C.

to the exclusive formation of the C–H difluoromethylation product **8** in 76% yield. In the case of phenol-containing cyclic ether **9**, the ring-opening difluoromethylation-bromination is highly selective against the phenol-difluoromethylation under aqueous KHF_2/LiBr conditions, giving product **10** in 75% isolated yield after an easy separation, whereas the phenol-difluoromethylation occurred exclusively under aqueous basic conditions[21] to afford difluoromethyl aryl ether **11** in 85% yield. Furthermore, we showed that terminal alkyne-containing cyclic ether **12** could be fluoroalkylated orthogonally at three different functional groups. Thus, aqueous weakly acidic KHF_2/LiBr conditions, the water-free basic conditions[17a] and the high temperature neutral conditions[21] delivered the ring-opening difluoromethylation-bromination product **13**, the C–H difluoromethylation-bromination product **14** and the C–C triple bond difluoromethylenation product **15**, respectively, in moderate to good yields.

To evaluate the synthetic utility of this ring-opening difluoromethylation-halogenation reaction, we conducted the reaction on large scale and investigated further transformations of the products (Scheme 4). After a slight modification of the optimized conditions for the 0.5-mmol scale reaction, the synthesis of **2g** was easily scaled up to 10.0 mmol in 74% yield. Then, the brominated difluoromethyl ether **2g** was readily converted to various derivatives in good yields under classical nucleophilic substitution reaction conditions using *O*-, *S*- and *N*-nucleophiles (**16**-**19**). The so-obtained difluoromethyl ethers are difficult to synthesize through the direct ring-opening difluoromethylation-functionalization of cyclic ethers since these nucleophiles are incompatible with difluorocarbene. Considering the versatile synthetic utility of alkyl bromides,[24] our ring-opening difluoromethylation-bromination reaction provides a reliable approach towards the synthesis of structurally diverse functionalized difluoromethyl (thio)ethers from cyclic (thio)ethers.

Finally, to gain some insights into the reactivity features of difluorocarbene-induced ring-opening of cyclic ethers, we conducted preliminary mechanistic investigations (Scheme 5). First, we carried out the ring-opening reaction of 2-methyl tetrahydrofuran (**20**) by using CD_2Cl_2 instead of CH_2Cl_2 under otherwise the same as the optimized conditions (Scheme 5A). It is interesting that in addition to the expected C-5 bromination product **21**, the bromination and fluorination products arising from nucleophilic attack at the sterically hindered C-2 position were detected as the major products. Since fluorination at the less sterically hindered C-5 position was not detected, the C-5



Scheme 5. Mechanistic investigations. [a] The yields were determined by ^1H NMR analysis using $PhOCF_3$ as an internal standard (for details, see the Supporting Information). [b] The yields were determined by ^{19}F NMR analysis using $PhOCF_3$ as an internal standard.

bromination should be mainly an S_N2 pathway, while the C-2 halogenation should be mainly an S_N1 pathway, as a carbocation intermediate is less selective towards bromide and fluoride ions. Convincingly, the ring-opening manner of a difluoromethyl cyclic oxonium cation can proceed through S_N2, S_N1 or both depending on the substituent on the oxygen atom, with a preference for S_N2 at the CH_2 carbon and S_N1 at the substituted carbon, and S_N1 is much faster than S_N2. Second, with the finding that the ring-opening reaction of cyclic ether is more effective that of cyclic thioether, we studied the competitive reaction between **1k** and **3b** by using $TMSCF_2Br$ as the limiting reagent (Scheme 5B). In this case, the *S*-difluoromethylation product **4b** was formed predominantly, implying that cyclic ether is less effective than cyclic thioether in trapping difluorocarbene, albeit the difluoromethyl oxonium cation is more reactive towards nucleophiles than difluoromethyl sulfonium cation of similar structure.

In summary, we have developed a method for the synthesis of difluoromethyl (thio)ethers through ring-opening difluoromethylation-halogenation of cyclic (thio)ethers, which is achieved by using $TMSCF_2X$ (X = Br, Cl) both as unique difluorocarbene reagents and as nucleophilic halide sources under mild conditions. Different from the conventional *O*- and *S*- difluoromethylation approaches, our method features a C–O/S bond cleavage of (thio)ethers. This method is efficient for the transformation of a broad scope of cyclic (thio)ethers, and is applicable to the late-stage modification of biologically relevant small molecules. The bromination products can be converted to various functionalized difluoromethyl (thio)ethers. Meanwhile, we have presented a practical method for the activation of the C–O/C–S bond of (thio)ethers with difluorocarbene, that is, difluoromethyl oxonium or sulfonium cation formation, which proceeds via in situ protonation of difluoromethylene oxonium or sulfonium ylides that are generated from (thio)ethers and $TMSCF_2X$ (X = Br, Cl). Further applications of difluorocarbene-induced activation of inert bonds are under way in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: difluorocarbene · difluoromethyl ether · orthogonal synthesis · oxonium ylide · ring-opening

[1] a) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263; b) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50; c) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577; d) G. K. Murphy, C. Stewart, F. G. West, *Tetrahedron* **2013**, *69*, 2667; e) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427; f) G. K. Murphy, F. G. West, in *Molecular Rearrangements in Organic Synthesis* (Ed. C. M. Rojas), John Wiley & Sons, Hoboken, **2016**, p 497.

[2] a) C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842; b) W. Zhang, Y. Wang, *Tetrahedron Lett.* **2018**, *59*, 1301; c) X. Wang, X. Wang, J. Wang, *Tetrahedron* **2019**, *75*, 949; d) A. D. Dilman, V. V. Levin, *Acc. Chem. Res.* **2018**, *51*, 1272; e) X. Ma, Q. Song, *Chem. Soc. Rev.* **2020**, *49*, 9197; f) W. Zhou, W.-J. Pan, J. Chen, M. Zhang, J.-H. Lin, W. Cao, J.-C. Xiao, *Chem. Commun.* **2021**, *57*, 9316.

[3] a) D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585; b) W. R. Dolbier Jr., M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071; c) M. Fedoryński, *Chem. Rev.* **2003**, *103*, 1099.

[4] K. Uneyama, K. Maeda, Y. Tokunaga, N. Itano, *J. Org. Chem.* **1995**, *60*, 370.

[5] a) Q. Xie, C. Ni, R. Zhang, L. Li, J. Rong, J. Hu, *Angew. Chem. Int. Ed.* **2017**, *56*, 3206; *Angew. Chem.* **2017**, *129*, 3254; b) R. Zhang, C. Ni, Q. Xie, J. Hu, *Tetrahedron* **2020**, *76*, e131676.

[6] G.-K. Liu, X. Li, W.-B. Qin, X.-S. Peng, H. N. C. Wong, L. Zhang, X. Zhang, *Chem. Commun.* **2019**, *55*, 7446.

[7] For examples on metal stabilized oxonium (R_2O^+-CF_2M, but not free difluoromethylene oxonium ylide) generated from metal difluorocarbeneoid, see: a) D. Naumann, R Möckel, W. Tyrra, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 323; *Angew. Chem.* **1994**, *106*, 325; b) D. Naumann, W. Tyrra, *J. Prakt. Chem.* **1996**, *338*, 283.

[8] In two comprehensive reviews on fluorinated ylides, no example on difluoromethylene oxonium ylide was mentioned, a) D. J. Burton, Z.-Y. Yang, W. Qiu, *Chem. Rev.* **1996**, *96*, 1641; b) J.-H. Lin, J.-C. Xiao, *Acc. Chem. Res.* **2020**, *53*, 1498.

[9] a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; b) P. Jeschke, E. Baston, F. R. Leroux, *Mini-Rev. Med. Chem.* **2007**, *7*, 1027; c) B. Manteau, S. Pazenok, J.-P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140; d) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797; e) J. W. Lee, K. N. Lee, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2019**, *58*, 11171; *Angew. Chem.* **2019**, *131*, 11289.

[10] a) P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 2092; *Angew. Chem.* **2013**, *125*, 2146; b) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633; c) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 10146; d) Y. Zafrani, G. Parvari, D. Amir, L. Ghindes-Azaria, S. Elias, A. Pevzner, G. Fridkin, A. Berliner, E. Gershonov, Y. Eichen, S. Saphier, S. Katalan, *J. Med. Chem.* **2021**, *64*, 4516.

[11] Fluorination, for examples: a) Y. Hagooly, O. Cohen, S. Rozen, *Tetrahedron Lett.* **2009**, *50*, 392; b) W. R. Dolbier, F. Wang, X. Tang, C. S. Thomoson, L. Wang, *J. Fluorine Chem.* **2014**, *160*, 72; c) T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. L. Collier, V. Gouverneur, *Angew. Chem. Int. Ed.* **2015**, *54*, 9991; *Angew. Chem.* **2015**, *127*, 10129.

[12] Direct CF_2H transfer, for example: J. Zhu, Y. Liu, Q. Shen, *Angew. Chem. Int. Ed.* **2016**, *55*, 9050; *Angew. Chem.* **2016**, *128*, 9196.

[13] Direct OCF_2H transfer, see: J. W. Lee, W. Zheng, C. A. Morales-Rivera, P. Liu, M.-Y. Ngai, *Chem. Sci.* **2019**, *10*, 3217.

[14] *O*-difluoromethylation with difluorocarbene, examples: a) X.-Y. Deng, J.-H. Lin, J. Zheng, J.-C. Xiao, *Chem. Commun.* **2015**, *51*, 8805; b) K. Levchenko, O. P. Datsenko, O. Serhiichuk, A. Tolmachev, V. O. Iaroshenko, P. K. Mykhailiuk, *J. Org. Chem.* **2016**, *81*, 5803; c) X. Lin, C. Hou, H. Li, Z. Weng, *Chem. Eur. J.* **2016**, *22*, 2075; d) J. Yang, M. Jiang, Y. Jin, H. Yang, H. Fu, *Org. Lett.* **2017**, *19*, 2758; e) A. Polley, G. Bairy, P. Das, R. Jana, *Adv. Synth. Catal.* **2018**, *360*, 4161; f) G.-K. Liu, W.-B. Qin, X. Li, L.-T. Lin, H. N. C. Wong, *J. Org. Chem.* **2019**, *84*, 15948; g) Z. Zhu, V. Krishnamurti, X. Ispizua-Rodriguez, C. Barrett, G. K. S. Prakash, *Org. Lett.* **2021**, *23*, 6494.

[15] a) J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco, V. Gouverneur, *Chem. Soc. Rev.* **2021**, *50*, 8214; b) R. Britton, V. Gouverneur, J.-H. Lin, M. Meanwell, C. Ni, G. Pupo, J.-C. Xiao, J. Hu, *Nat. Rev. Methods Primers* **2021**, *1*, 47.

[16] F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, *Chem. Commun.* **2011**, *47*, 2411.

[17] Recent examples, a) Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6405; *Angew. Chem.* **2019**, *131*, 6471; b) Q. Xie, Z. Zhu, C. Ni, J. Hu, *Org. Lett.* **2019**, *21*, 9138; c) A. L. Trifonov, A. D. Dilman, *Org. Lett.* **2021**, *23*, 6977; d) Y. Jia, Y. Yuan, J. Huang, Z.-X. Jiang, Z. Yang, *Org.*

Lett. **2021**, *23*, 2670; e) R.-Y. Yang, H. Wang, B. Xu, *Chem. Commun.* **2021**, *57*, 4831; f) T. Mita, Y. Harabuchi, S. Maeda, *Chem. Sci.* **2020**, *11*, 7569; g) X. Liu, D. Du, S. Li, X. Wang, C. Xu, M. Wang, *Adv. Synth. Catal.* **2020**, *362*, 5135; h) R. Zhang, Z. Zhang, K. Wang, J. Wang, *J. Org. Chem.* **2020**, *85*, 9791; i) R. Zhang, Z. Zhang, Q. Zhou, L. Yu, J. Wang, *Angew. Chem. Int. Ed.* **2019**, *58*, 5744; *Angew. Chem.* **2019**, *131*, 5800; j) J. Wang, E. Tokunaga, N. Shibata, *Chem. Commun.* **2018**, *54*, 8881.

[18] Y. Kim, J. Heo, D. Kim, S. Chang, S. Seo, *Nat. Commun.* **2020**, *11*, 4761.

[19] An example on trifluoromethylation, S. Fantasia, J. M. Welch, A. Togni, *J. Org. Chem.* **2010**, *75*, 1779.

[20] J. Su, X. Ma, Z. Ou, Q. Song, *ACS Cent. Sci.* **2020**, *6*, 1819.

[21] L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12390; *Angew. Chem.* **2013**, *125*, 12616.

[22] a) L. Li, C. Ni, Q. Xie, M. Hu, F. Wang, J. Hu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9971; *Angew. Chem.* **2017**, *129*, 10103; b) Q. Xie, L. Li, Z. Zhu, R. Zhang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2018**, *57*, 13211; *Angew. Chem.* **2018**, *130*, 13395; c) Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, *Chem. Sci.* **2020**, *11*, 276; d) H. Liang, R. Liu, M. Zhou, Y. Fu, C. Ni, J. Hu, *Org. Lett.* **2020**, *22*, 7047; e) D. Chen, Z. Fan, L. Huang, K. Gao, P. Xiao, C. Ni, J. Hu, *Chem. Commun.* **2021**, *57*, 319.

[23] The formyloxylation side product (Nu = HCOO) probably arises from the reaction of difluorocarbene with water. A proposed mechanism is given in the Supporting Information.

[24] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reaction and Synthesis* (5th Ed), Springer, New York, **2007**, p. 217.

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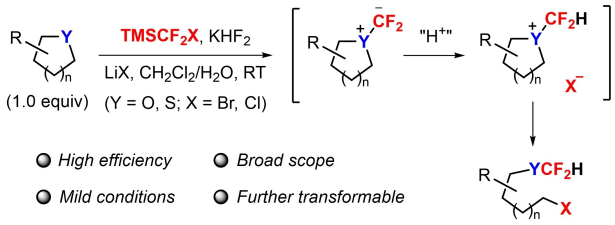

In-situ protonation of difluromethylene oxonium or sulfonium ylides (generated from difluorocarbene and cyclic (thio)ethers) constitutes the formal activation of C–O/S bond of (thio)ethers with difluormethyl cation, thus facilitating the ring-opening difluoromethylation-halogenation of cyclic (thio)ethers. (TMS = trimethylsilyl).

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