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Chemoselective desulfurization-fluorination/bromination of carbonofluoridothioates for the *O*-trifluoromethylation and *O*-bromodifluoromethylation of alcohols

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Herein, a method for synthesizing various alkyl trifluoromethyl and alkyl bromodifluoromethyl ethers using carbonofluoridothioates (R–OC(=S)F) as precursors has been described. Carbonofluoridothioates were obtained upon the reaction of an alcohol and $S{=}CF_2$ generated *via* the decomposition of an SCF_3 anion, and then selectively transformed into their corresponding trifluoromethyl and bromodifluoromethyl ethers upon changing the reaction conditions. This transformation has also been extended to the one-pot, two-step conversion of alcohols into alkyl trifluoromethyl ethers. A series of alkyl bromodifluoromethyl ethers has also been synthesized. These compounds open up a new avenue for the synthesis of a wide range of useful fluorinated products. In addition, this method is suitable for the late-stage introduction of trifluoromethyl ethers in complex small molecules.

carbonofluoridothioates, trifluoromethyl ethers, bromodifluoromethyl ethers, fluorination, alkyl

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1 Introduction

Substitution reactions that involve fluorine are crucial in drug discovery and development because fluorine can change the physicochemical properties of drug candidates [1–7]. Among the fluorine-containing functional groups reported to date, the trifluoromethoxy ($–OCF_3$) group is becoming an increasingly common structural motif in pharmaceutical agents because of its unique structural and electronic properties. Many CF_3O-containing compounds are vital because they exhibit high lipophilicity and often show enhanced *in vivo* uptake and transport in biological systems [8–14]. However, few methods are used to prepare trifluoromethyl ethers due to the limited number of trifluoromethoxylation reagents available and the reversible decomposition of trifluoromethoxide anions [15]. Therefore, the development of an efficient synthesis of CF_3O-containing compounds is highly desirable.

Over the past few decades, methods involving direct introduction of an $–OCF_3$ group have been developed. However, these approaches require stable CF_3O-donor reagents, which are challenging to be synthesized [16–25]. The traditional synthesis of trifluoromethyl ethers typically involves the nucleophilic substitution of their corresponding trichloromethyl ethers with fluoride [26–30]. Subsequently, the deoxyfluorination of fluoroformates (Scheme 1a) [31,32] and oxidative fluorodesulfurization of *S*-chlorine [33,34]/methyl carbonodithioates [9,35–38] are the most widely used procedures found in the literature (Scheme 1b, c). In addition, the preparation of fluoroformates (R–OC(=O)F) [31,32] and carbonochloridothioates (R–OC(=S)Cl) [33,34] requires harsh reaction conditions. The synthesis of xanthates (R–

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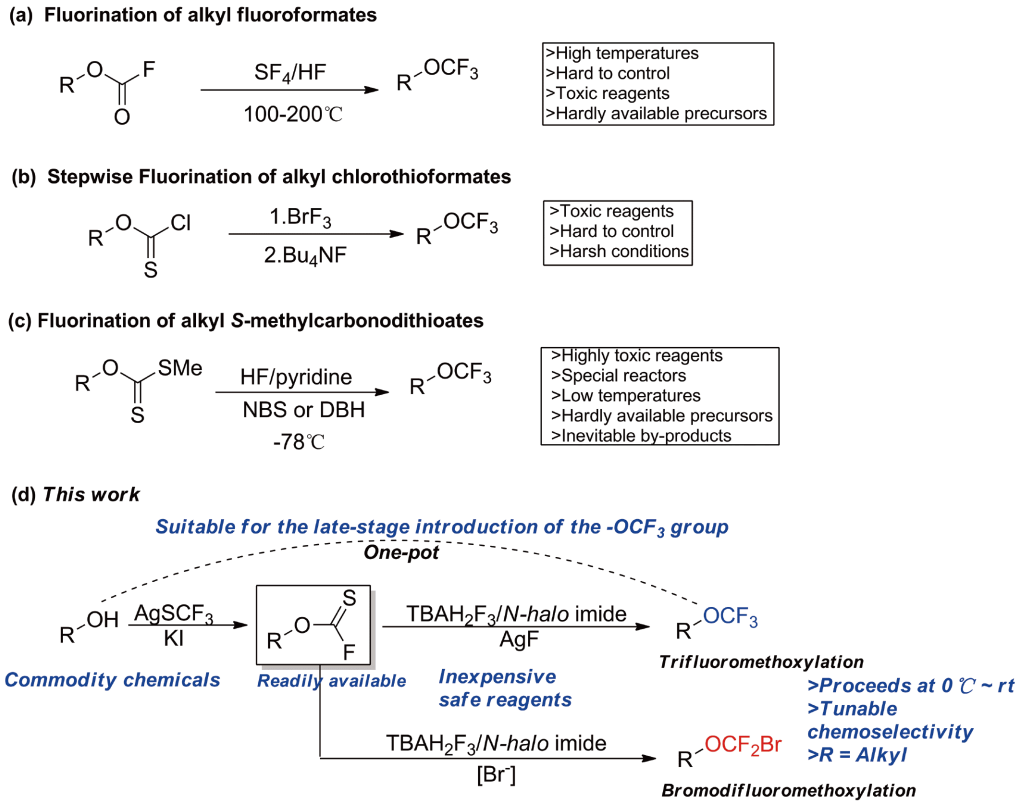


Scheme 1 Indirect methods used to introduce the CF_3O-group (color online).

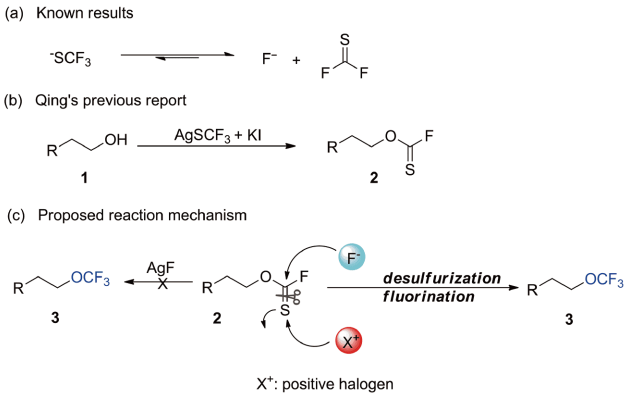
OC(=S)SMe) [9,35–38] typically uses a two-step protocol consisting of deprotonation, followed by alkylation with CS_2 and MeI. These reactions are highly sensitive to the steric and electronic properties of the substrates. Scheme 1 shows that each traditional method has at least one major limitation in terms of substrate scope, reaction conditions, precursor synthesis, and the use of toxic reagents. Notably, most of these synthetic methods have focused on the introduction of a trifluoromethoxy group onto an aromatic substrate. The introduction of a CF_3O-group in unactivated alkyl alcohols has rarely been reported and represents a significant challenge in this field.

Herein, we report a new method for synthesizing alkyl trifluoromethyl ethers using carbonofluoridothioates (R–OC(=S)F) as precursors, which can be simply obtained upon the reaction of an alcohol with $AgSCF_3$/KI [39]. This method was conducted under mild reaction conditions. In addition, the substrate scope was significantly increased compared with the traditional methods. Surprisingly, both alkyl trifluoromethyl and alkyl bromodifluoromethyl ethers can be prepared in a highly regioselective manner upon simply changing the reaction conditions. Moreover, we have also demonstrated a one-pot method to synthesize alkyl trifluoromethyl ethers, which can be applied to a variety of biologically active substrates.

Due to the reversible decomposition of trifluoromethylthio anions, which forms thiocarbonyl fluoride and fluoride anion (Scheme 2a) [40–44], Qing and co-workers [39] reported that treating an alcohol with $AgSCF_3$ and KI led to the formation of an R–OC(=S)F intermediate (**2**) (Scheme 2b). The –OC(=S)F group is a good leaving group, which is susceptible to nucleophilic attack. Qing *et al.* [39] and Xiao *et al.* [45] reported the dehydroxytrifluoromethylthiolation of alcohols *via* R–OC(=S)F. However, the direct synthesis of trifluoromethyl ethers from R–OC(=S)F *via* fluorination has not been reported. Inspired by these studies on desulfurization–fluorination [9,35–38], we propose that alkyl trifluoromethyl ethers can also be formed from carbonofluoridothioates. A positive halogen species (X^+) will initially attack the sulfur atom in R–OC(=S)F to activate the C=S double bond, followed by nucleophilic fluorination by the fluoride species to yield the corresponding trifluoromethyl ether (Scheme 2c).

2 Results and discussion

Initially, *O*-(5-phenylpentyl) carbonofluoridothioate (**2a**) was chosen as a model substrate to optimize the reaction conditions. According to our reaction design, various fluoride sources and positive halogen species were evaluated in the reaction (Table 1, entries 1–9). The $TBAH_2F_3$ and NBL8

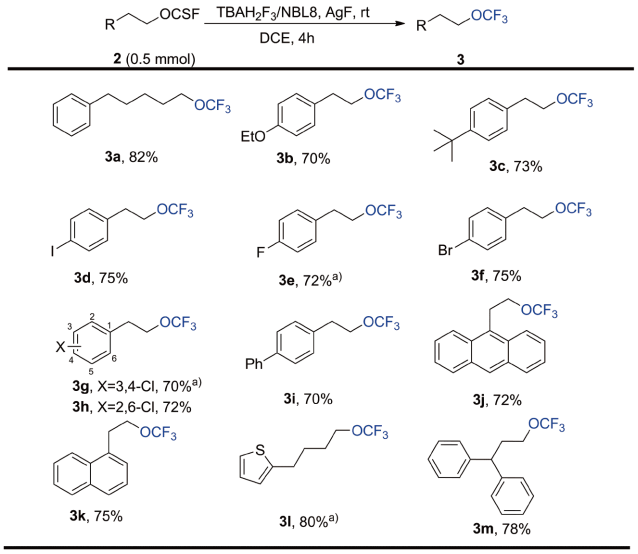


Scheme 2 Reaction design (color online).

system was found to be better than the other systems studied with **3a** obtained in 45% yield (Table 1, entry 9). However, the alkyl bromide was obtained as the major by-product and a small amount of bromodifluoromethyl ether **4a** was also observed. To increase the yield of **3a**, we investigated the use of some additives (Table 1, entries 10 and 11). To our delight, the yield of **3a** was improved to 72% when conducting the reaction in the presence of AgF, which may be beneficial for removing the Br^- as well as further increasing the concentration of F^- [46]. Different reaction solvents were then screened to improve the reaction efficiency and non-polar aprotic solvents proved to be better in the reaction (Table 1, entries 12–15). Among them, 1,2-dichloroethane (DCE) exhibited the best performance giving the desired product in 85% yield (entry 12).

We compared the reactivity observed during the fluorination of **2a** with $TBAH_2F_3$ and various oxidants with traditional precursors used to prepare trifluoromethyl ethers. Table 1 (entries 16–18) shows our results were comparable to their analogous reactions using traditional precursors, such as –OC(=O)F, –OC(=S)SMe, and –OC(=S)Cl, which generally afforded lower yields than –OC(=S)F.

With the optimized reaction conditions in hand, we then investigated the substrate scope in the reaction of primary carbonofluoridothioates using the $TBAH_2F_3$/NBL8 system (Scheme 3). Various alkyl carbonofluoridothioates were successfully converted into their corresponding trifluoromethyl ethers in moderate to good yield (**3a**–**3m**). Substrates bearing aryl groups with both electron-donating and electron-withdrawing substituents were successfully used in the reaction. A wide range of functional groups including ethoxy, aryl, *tert*-butyl, fluoro, chloro, bromo, and iodo was tolerated in the reaction. Among them, the –OC(=S)F group in long-chain alkyl carbonofluoridothioates (**2a**, **2l**, and **2m**) exhibited better stability, which led to better product yields. Multi-ring compounds including anthracene (**2j**) and naphthalene (**2k**) were also good substrates and exhibited good product yield.



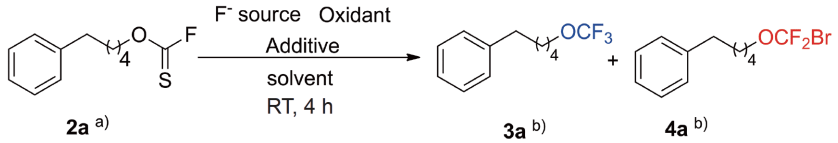
a) Yield determined using ^{19}F NMR spectroscopy of the crude reaction mixture with $PhCF_3$ as an internal standard.

Scheme 3 Synthesis of alkyl trifluoromethyl ethers using carbonofluoridothioates. Reaction conditions: **2**(0.5 mmol), $TBAH_2F_3$ (5.0 equiv.), NBL8 (4.0 equiv.), AgF (2.5 equiv.), dry DCE (3.0 mL), N_2 atmosphere, 4 h, room temperature. All yields are those of the isolated product (color online).

The small amount of R–OCF_2Br product observed during our optimization study (Table 1) aroused our interest. The known approaches used to prepare R–OCF_2Br compounds include the pioneering work by Wakselman *et al*. [47], which uses toxic difluorodibromomethane and a variety of phenol precursors. Later, Gouverneur and co-workers [48] reported the preparation of aryl-OCF_2Br precursors from phenols under harsh conditions using a multi-step synthesis. However, no method for the synthesis of alkyl bromodifluoromethyl ethers has been reported to date to the best of our knowledge. Considering the significance of the –OCF_2Br group in medicinal chemistry, we have successfully achieved the selective bromodifluoromethoxylation of an alkane under mild reaction conditions. Subsequently, we examined a range of solvents, additives, and the ratio of the fluorinating reagent and oxidant to improve the conversion efficiency (for details, see Supporting Information online). The reactions conducted in acetonitrile gave higher product yields compared with the other solvents studied, which may be due to the solvent effect increasing the nucleophilicity of Br^-. The amount of $TBAH_2F_3$ and NBL8 used in the reaction was crucial to achieving an efficient transformation. When an additional bromine source was added, the primary carbonofluoridothioate was transformed into its corresponding alkyl bromodifluoromethyl ether (**4a**) in 44% yield. The reaction was slightly temperature-sensitive with the highest yield (56%) obtained at 0 °C (entry 19).

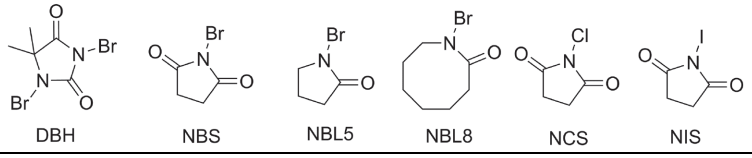
Subsequently, we turned our attention to extending the substrate scope in the reaction. Scheme 4 shows the substrates that participate in the *O*-trifluoromethylation reaction

Table 1 Optimization of the reaction conditions



Entry	F^- source [c] (equiv.)	Oxidant (equiv.)	Additive	Solvent	Yield [d] (%)	
					3a	**4a**
1	DAST(5)	none	none	DCM	n.d.	n.d.
2	HF/Py(40)	NBS(4)	none	DCM	10	n.d.
3	BAST(5)	none	none	DCM	n.d.	n.d.
4	$TBAH_2F_3$(5)	NBS(4)	none	DCM	25	5
5	$TBAH_2F_3$(5)	NCS(4)	none	DCM	20	n.d
6	$TBAH_2F_3$(5)	NIS(4)	none	DCM	15	n.d
7	$TBAH_2F_3$(5)	DBH(4)	none	DCM	15	7
8	$TBAH_2F_3$(5)	NBL5(4)	none	DCM	40	5
9	$TBAH_2F_3$(5)	NBL8(4)	none	DCM	45	5
10	$TBAH_2F_3$(5)	NBL8(4)	AgF	DCM	72	Trace
11	$TBAH_2F_3$(5)	NBL8(4)	KHF_2	DCM	50	5
12	$TBAH_2F_3$(5)	NBL8(4)	AgF	DCE	85	Trace
13	$TBAH_2F_3$(5)	NBL8(4)	AgF	MeCN	20	9
14	$TBAH_2F_3$(5)	NBL8(4)	AgF	THF	25	7
15	$TBAH_2F_3$(5)	NBL8(4)	AgF	Hexane	75	Trace
16 [e]	$TBAH_2F_3$(5)	NBL8(4)	AgF	DCE	n.d.	n.d.
17 [f]	$TBAH_2F_3$(5)	NBL8(4)	AgF	DCE	15	n.d.
18 [g]	$TBAH_2F_3$(5)	NBL8(4)	AgF	DCE	17	n.d.
19 [h]	$TBAH_2F_3$(2)	NBL8(4)	$TBABr_3$	MeCN	3	56

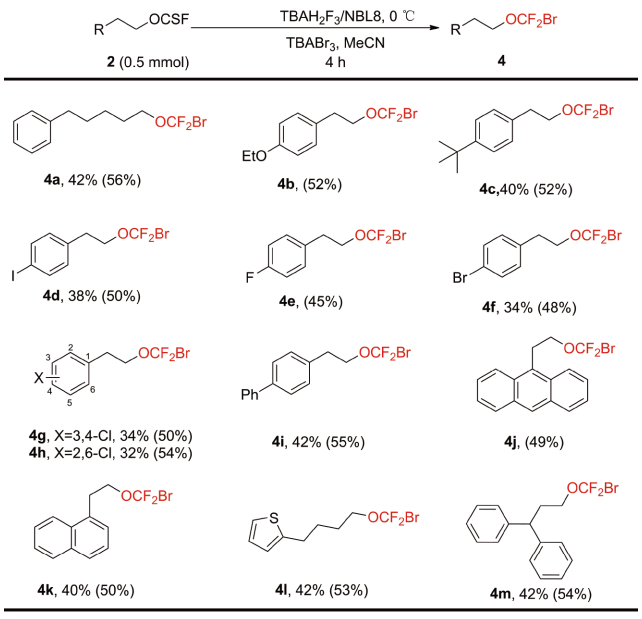
N-halo imides



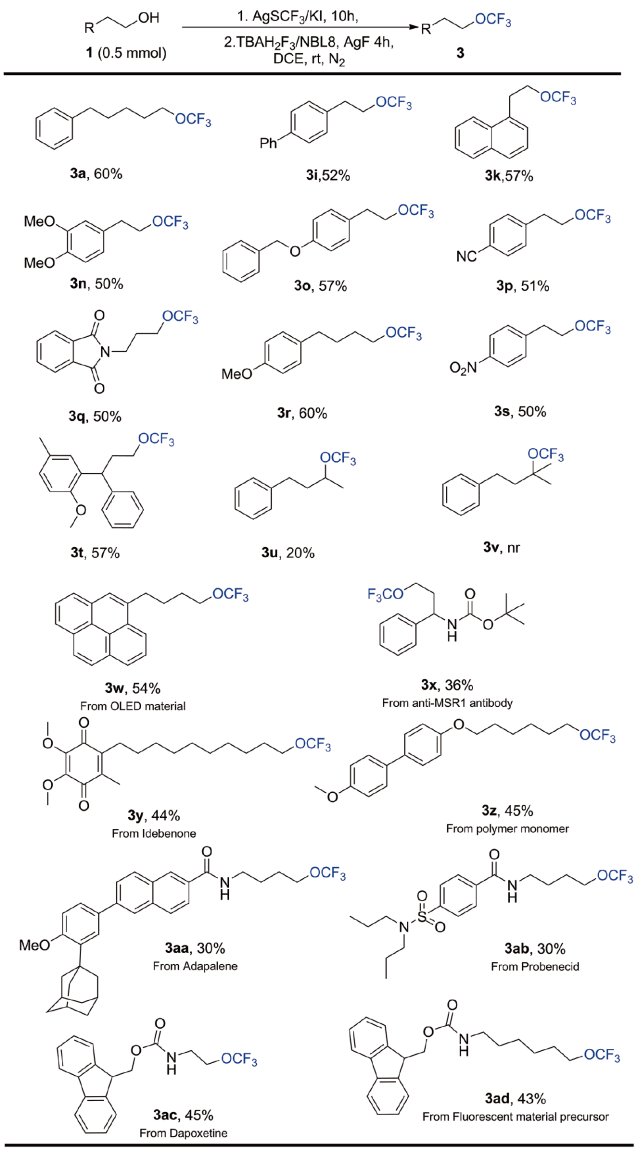
a) Preparation of **2a**: 1-naphthaleneethanol **1a** (0.5 mmol) was reacted with $AgSCF_3$ (1.5 equiv.) and KI (2.0 equiv.) in dry DCE (3.0 mL) at room temperature under N_2 atmosphere for 10 h. b) Reaction conditions: **2a** (0.2 mmol), F^- source (5.0 equiv.), oxidant (4.0 equiv.), additive (2.5 equiv.), solvent (2.0 mL), N_2 atmosphere, rt, 4 h. c) BAST=bis(2-methoxyethyl)aminosulfur trifluoride; $TBAH_2F_3$=tetra-*n*-butylammonium dihydrogen trifluoride. d) All yields were determined using ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard. e) Ph–C_5H_{10}–OC(=O)F was used as the substrate. f) Ph–C_5H_{10}–OC(=S)SMe was used as the substrate. g) Ph–C_5H_{10}–OC(=S)Cl was used as the substrate. h) Reaction conditions: $TBAH_2F_3$ (2.0 equiv.), NBL8 (4.0 equiv.), dry $TBABr_3$ (1.0 equiv.), distilled MeCN (2.0 mL), N_2 atmosphere, 0 °C, 4 h.

were also suitable for the *O*-bromodifluoromethylation reaction, predominately producing their corresponding alkyl bromodifluoromethyl ethers in moderate yield. In addition, the isolated yields were a little lower than those determined using ^{19}F nuclear magnetic resonance (^{19}F NMR) spectroscopy. This can be attributed to the water used in the separation process, which results in the decomposition of the R–OCF_2Br product at different degrees during high performance liquid chromatography (HPLC). The mild reaction conditions used for the synthesis of bromodifluoromethyl ethers are tolerated by a series of functional groups, such as *tert*-butyl (**2c**), iodo (**2d**), fluoro (**2e**), bromo (**2f**), chloro (**2g** and **2h**), and aryl (**2i**). Heterocycles, such as thiophene (**2l**), are also tolerated in the reaction. Compared with the *O*-trifluoromethylation reaction, the separation conditions were not tolerated by substrates containing an alkoxy group such as **4b**, which can only be detected using ^{19}F NMR spectroscopy.

Since some of the carbonofluoridothioate compounds were decomposed during the separation process, we next sought to directly convert alkyl alcohols into their corresponding alkyl trifluoromethyl ethers without isolating the R–OC(=S)F intermediate. This one-pot desulfurization-fluorination reaction applies to a variety of alcohol substrates (Scheme 5).



Scheme 4 Substrate scope during the synthesis of alkyl bromodifluoromethyl ethers using carbonofluoridothioates. Reaction conditions: **2** (0.5 mmol), $TBAH_2F_3$ (2.0 equiv.), NBL8 (4.0 equiv.), dry $TBABr_3$ (1.0 equiv.), distilled MeCN (2.0 mL), N_2 atmosphere, 4 h, 0 °C. All yields are those of the isolated product. The yields obtained using ^{19}F NMR spectroscopy with $PhCF_3$ as an internal reference are reported in the parentheses (color online).

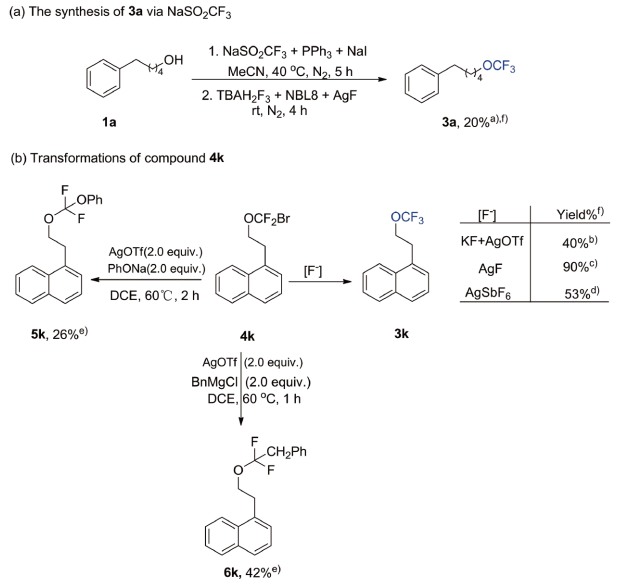


Scheme 5 Direct conversion of R–OH to R–OCF_3. Reaction conditions 1: alcohol **1** (0.5 mmol), $AgSCF_3$ (1.3 equiv.), KI (1.5 equiv.), DCE (2.0 mL), N_2 atmosphere, rt, 10 h. Reaction conditions 2: $TBAH_2F_3$ (5.0 equiv.), NBL8 (4.0 equiv.), AgF (2.5 equiv.), dry DCE (2.0 mL), N_2 atmosphere, rt, 4 h. All yields are those of the isolated product (color online).

The yields of **3a**, **3l**, and **3k** did not decrease significantly compared with those obtained during the fluorination of the isolated –OC(=S)F intermediate. Alcohols bearing alkoxy (**2n**, **2o**, **2r**, and **2t)**, cyano (**2p**), phthalimide (**2q**), and nitro (**2s**) groups were well tolerated in the reaction, providing their corresponding trifluoromethyl ethers (**3**) in 50%–60% yield. Under the same optimal conditions, secondary alcohol **2u** gave its corresponding product in a low 20% yield, which may be due to its significant steric effect. Furthermore, in the case of tertiary alcohols such as **2v**, no R–OCF_3 product was detected. A limitation of this method was that no desired product was observed by using benzyl alcohols and phenolic compounds due to their steric effects.

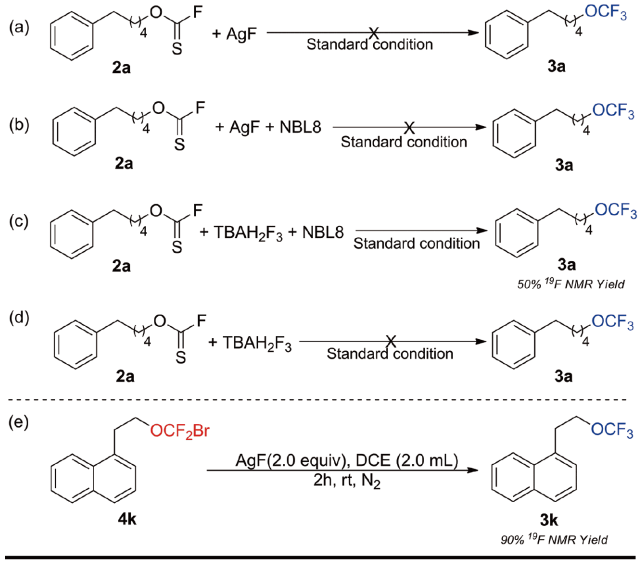
To further illustrate the value of this protocol, a series of molecules that have found applications in material sciences, such as pyrene **2w** in organic light-emitting diodes (OLEDs), monomer **2z**, and fluorescent material precursor **2ad**, were successfully used in the reaction and gave their corresponding trifluoromethyl ethers in moderate yield. The synthetic utility of this process was further highlighted by its amenability to the late-stage trifluoromethoxylation of biorelevant molecules. For example, Fmoc-glycinol, a precursor for anti-MSR1 antibodies, reacts to afford its CF_3O-analog (**3x**) in 36% yield. An intermediate of dapoxetine can also be converted into its trifluoromethoxylated derivative (**3ac**) in 45% yield. We then performed the late-stage functionalization of several drugs with different structures (**3y**, **3aa**, and **3ab**) that are commercially available and used for multiple purposes, including the treatment of Alzheimer's disease, acne, and gout.

The success of the one-pot *O*-trifluoromethylation of alcohols using $AgSCF_3$, $TBAH_2F_3$, and NBL8 prompted us to investigate the one-pot reaction of carbonofluoridothioates using $NaSO_2CF_3$. Compared with $AgSCF_3$, $NaSO_2CF_3$ is cheaper and more stable, and can also produce SCF_3 anions under reductive conditions [43,44]. Therefore, we chose **1a** as a model substrate in this reaction (Scheme 6a). However, trifluoromethyl ether **3a** was produced in low yield (20%). We speculated that the SCF_3 anion was not easily formed and decomposed in this system. Overall, this result demostrated the potential of $NaSO_2CF_3$ for preparing trifluoromethyl ethers from alcohols. However, the optimization of these



a) Reaction conditions 1: **1a** (0.2 mmol), $NaSO_2CF_3$ (2.0 equiv.), PPh_3 (4.0 equiv.), NaI (2.0 equiv.), distilled MeCN (2.0 mL), 40℃. N_2, 5 h. Reaction conditions 2: $TBAH_2F_3$ (5.0 equiv.), NBL_8 (4.0 equiv.), AgF (2.0 equiv.), rt, N_2, 4 h.
b) **4k** (0.2 mmol), KF (2.0 equiv.), AgOTf (2.0 equiv.), 60℃, dry DCE (2.0 mL), N_2, 2 h.
c) **4k** (0.2 mmol), AgF (2.0 equiv.), dry DCE (2.0 mL), rt, 2 h, N_2.
d) **4k** (0.2 mmol), $AgSbF_6$ (2.0 equiv.), dry DCE (2.0 mL), -78℃, 2 h, N_2.
e) All yields are those of the isolated products.
f) Yields determined using ^{19}F NMR spectroscopy of the crude reaction mixture using $PhCF_3$ as an internal standard.

Scheme 6 Synthesis of **3a** using $NaSO_2CF_3$ and the transformation of compound **4k** (color online).



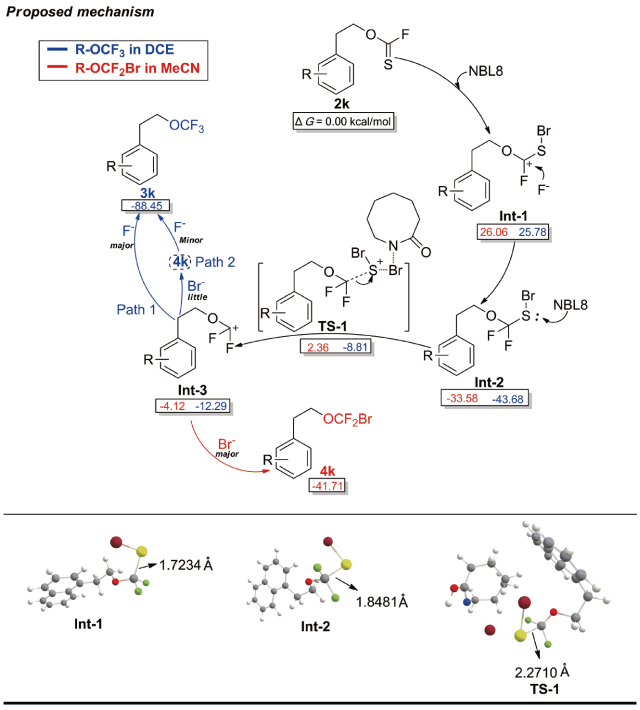
Scheme 7 Control experiments (color online).

reaction conditions is currently underway in our laboratory.

In view of the previous work reported in the literature, we believed that bromodifluoromethyl ethers (**4**) should have unique versatility because the facile substitution of the bromine atom can be exploited further. However, the direct transformation of the bromodifluoromethoxy group has not been reported to date. Herein, the utility of the bromodifluoromethoxy group has been showcased using the facile conversion of compound **4k** into a series of valuable fluorine-containing compounds, such as 1-(2-difluoro(phenoxy)-methoxy)ethyl)naphthalene (**5k**) and 1-(2-(1,1-difluoro-2-phenylethoxy)ethyl)naphthalene (**6k**). Furthermore, the bromodifluoromethoxy group can be easily converted into the trifluoromethoxy group *via* a Ag-mediated fluorination reaction. Fluorination of **4k** using KF/AgOTf, AgF, or $AgSbF_6$ gave trifluoromethyl ether **3k** in 40%, 90%, and 63% yield, respectively, which demonstrates the potential of this transformation to access medicinally important ^{18}F-labeled motifs that are currently not accessible *via* conventional methods.

We performed a series of control experiments in order to explore the fluorine source in the fluorination reaction (Scheme 7). It was found that neither the addition of AgF nor AgF/NBL8 led to the fluorination of *O*-(5-phenylpentyl) carbonofluoridothioate **2a** (Scheme 7a, b). However, **3a** was obtained in moderate yield (50%) when $TBAH_2F_3$ was added together with NBL8 (Scheme 7c). When only $TBAH_2F_3$ was added as the fluorinating reagent, the fluorinated product (**3a**) was not formed during the reaction (Scheme 7d). These results suggest that most of the F atoms in the product originate from $TBAH_2F_3$. However, $TBAH_2F_3$ alone does not undergo the fluorination reaction and may require the presence of NBL8 to generate a cationic species.

Density functional theory (DFT) calculations offered a preliminary insight into the mechanism of this transformation using **2k**, fluoride (F^-), and NBL8 (see Supporting Information online for details). A proposed mechanism is shown in Scheme 8. In the *O*-trifluoromethylation reaction carried out in DCE, the electron-rich C=S bond in **2k** can be attacked by NBL8 to form an S–Br bond. The formation of this bond weakens the C–S bond in **2k**. Subsequent nucleophilic attack by the fluoride ion at the electrophilic carbon atom forms a C–F bond to generate R–OCF_2(SBr). The increased C–S bond length observed from **Int-1** to **Int-2** results in **Int-2** undergoing further electrophilic attack by NBL8, which further weakens the C–S bond. Importantly, the transition state for this reaction (**TS-1**) was concerted and involved concomitant S–Br bond formation and C–S bond cleavage with the generation of a difluoromethoxy cationic intermediate (**Int-3**). Different from the previously proposed mechanism involving a similar process [37], our calculations show that the formation of **Int-3** was not due to the nucleophilic attack of F^-. The conversion of **Int-2** *via* transition state **TS-1** proceeds with an activation energy ($\Delta G^{\ddagger}$) of $35.94_{DCE}/34.87_{MeCN}$ kcal/mol, which is consistent with the rapid process. The bare –OCF_2 cation is highly electrophilic and is therefore trapped by F^- to generate the final trifluoromethoxylated product. Ag^+ can preferentially remove Br^- *via* the precipitation of AgBr, which can selectively form



Scheme 8 Proposed reaction mechanism (color online).

the R–OCF_3 product. It is worth noting that the R–OCF_2Br product can be further fluorinated by AgF to form R–OCF_3, as shown in Scheme 7e, indicating that bromodifluoromethyl ethers may also be an intermediate in the reaction. Although path 2 cannot be excluded, we regard it to be less likely based on our ^{19}F NMR analysis. No obvious bromodifluoromethyl ethers were detected during the formation of the R–OCF_3 products.

For the *O*-bromodifluoromethylation reaction, the reaction pathway is equivalent to the *O*-trifluoromethylation reaction. However, the ratio of NBL8 and $TBAH_2F_3$ affects the selectivity of the reaction in the MeCN system. In addition, the increased polarity of the solvent can increase the nucleophilicity of Br^-. The additional $TBABr_3$ further increases the nucleophilicity of Br^-, reducing the probability of nucleophilic attack by F^-, thereby increasing the selectivity of the reaction toward the bromodifluoromethyl ether product.

3 Conclusions

We have developed the first examples of the *O*-trifluoromethylation and *O*-bromodifluoromethylation of alkyl carbonofluoridothioates using oxidative desulfurization-fluorination/bromination. All reactions proceed with high efficiency and excellent functional-group compatibility. Mild reaction conditions and inexpensive reagents represent a major advancement relative to the existing fluorination processes. The pathway towards *O*-trifluoromethylation and *O*-bromodifluoromethylation can be controlled by simply changing the conditions using the same substrates. The *O*-trifluoromethylation reaction was also feasible in a one-pot process starting from alcohols. The late-stage *O*-trifluoromethylation of small complex molecules has also been proven to be efficient. Importantly, further derivatization of the bromodifluoromethoxy group provides access to compounds bearing difluoromethoxy and trifluoromethoxy groups. DFT calculations indicate a mechanism involving concerted S–Br bond formation and C–S bond cleavage in this transformation. We believe that the presented methodology will have wide application in pharmaceutical and agrochemical research, and will open new avenues toward innovation in organofluorine chemistry.

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Conflict of interest The authors declare no conflict of interest.

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