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Note

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Ag-mediated trifluoromethylthiolation of inert Csp^3-H bond

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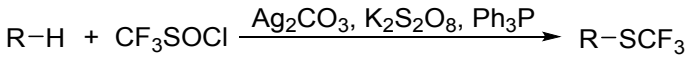
Abstract

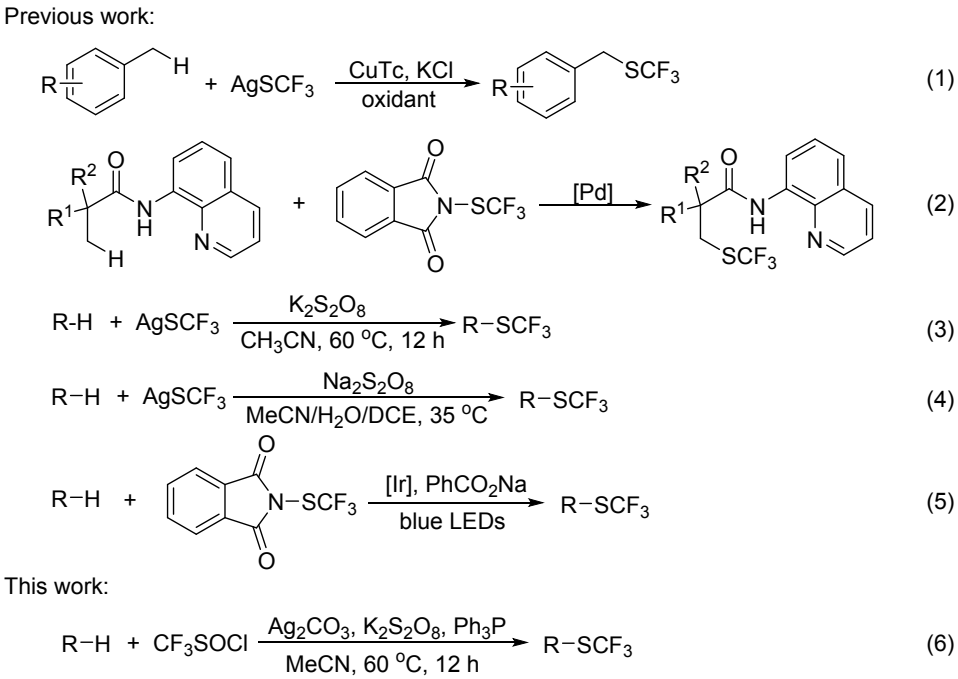


Ag-Mediated trifluoromethylthiolation of inert Csp^3-H bond with CF_3SOCl is described. Widely available reagents and operational simplicity make this protocol attractive.

Due to its strong electron-withdrawing nature (Hammett constants $\sigma_p = 0.50$, $\sigma_m = 0.40$) and high lipophilicity (Hansch parameter $\pi = 1.44$),[1] trifluoromethylthio group (CF_3S) has received increasing attention in medicinal chemistry, agrochemistry and material science.[2] Consequently, determined efforts have been devoted to the development of efficient methods for the installation of a CF_3S moiety to organic molecules.[2d,3] As C-H functionalization is an attractive concept because of its step economy, C-H trifluoromethylthiolation has become a straightforward strategy for CF_3S

installation. Compared with trifluoromethylthiolation of Csp^2-H bond[4] and Csp-H bond[5], trifluoromethylthiolation of insert Csp^3-H bond remains a challenging task.

In 2014, Qing reported a Cu-catalyzed Csp^3-H trifluoromethylthiolation, in which the Csp^3-H bond has to be an activated benzylic C-H bond (Scheme 1, eq 1).[6] Shortly afterwards, Besset disclosed a Pd-catalyzed trifluoromethylthiolation of inert Csp^3-H bond. The desired products could be obtained in moderate yields, but a bulky directing group is required to be incorporated into the substrates (eq 2).[7] Almost at the same time, Chen[8] and Tang[9] independently described a radical trifluoromethylthiolation of alkanes with $AgSCF_3$ under oxidative conditions (eqs 3-4). A wide substrate scope and good functional group compatibility were observed in both approaches. Recently, photocatalytic radical trifluoromethylthiolation was achieved by the group of Glorius (eq 5).[10] Although good site selectivity and high yields were obtained, an expensive photocatalyst is needed. Apparently, the trifluoromethylthiolation reagents used in the above methods are expensive or have to be prepared via tedious synthetic procedures. We have been interested in the development of effective protocols for the incorporation of fluorine-containing functionalities into organic molecules.[11] We found that trifluoromethanesulfinic chloride (CF_3SOCl) could act as a trifluoromethylthio source to realize Ag-mediated radical trifluoromethylthiolation of inert Csp^3-H bond (eq 6). All reagents in this protocol are widely available and easy to handle.

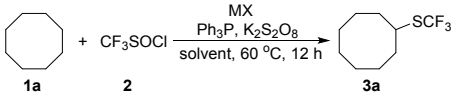


Scheme 1. Csp^3-H trifluoromethylthiolation

As it has been previously reported that phosphorus species could reduce CF_3SO_2Cl to provide active trifluoromethylthiolation intermediates,[12] Ph_3P was used as a reducing agent in our initial attempts at the trifluoromethylthiolation of octane with CF_3SOCl (Table 1). A brief survey of the metal complex (entries 1-5) revealed that Ag_2CO_3 was quite effective (entry 2). Interestingly, no desired product was observed in other solvents (entries 6-8) except CH_3CN. An oxidant is necessary in the reaction, and replacing $K_2S_2O_8$ with other oxidants dramatically decreased the yield (entries 9-10). A reaction temperature of 60 °C proved superior to a lower or higher temperature (entry 2 vs entries 11-12). Increasing the loading of oxidant from 1.0 equiv to 1.5 equiv increased the yield to 77% (entry 13). However, the results were not reproducible (yields varied between 47% and 77%) if substrate **1a** was used in the same equivalent with reagent **2** (entry 13).

To our delight, the reaction could be well reproduced by using slight excess of substrate **1a** (entry 14). A lower yield was obtained within a shorter reaction time (entry 15). 1 equiv of Ag_2CO_3 was necessary, and decreasing the loading of Ag_2CO_3 led to the dramatic decrease in the yield (entries 16-19). No desired product was observed by replacing Ag_2CO_3 with K_2CO_3 (entry 20), suggesting that Ag_2CO_3 played a crucial role in the reaction.

Table 1. Optimization of the reaction conditions

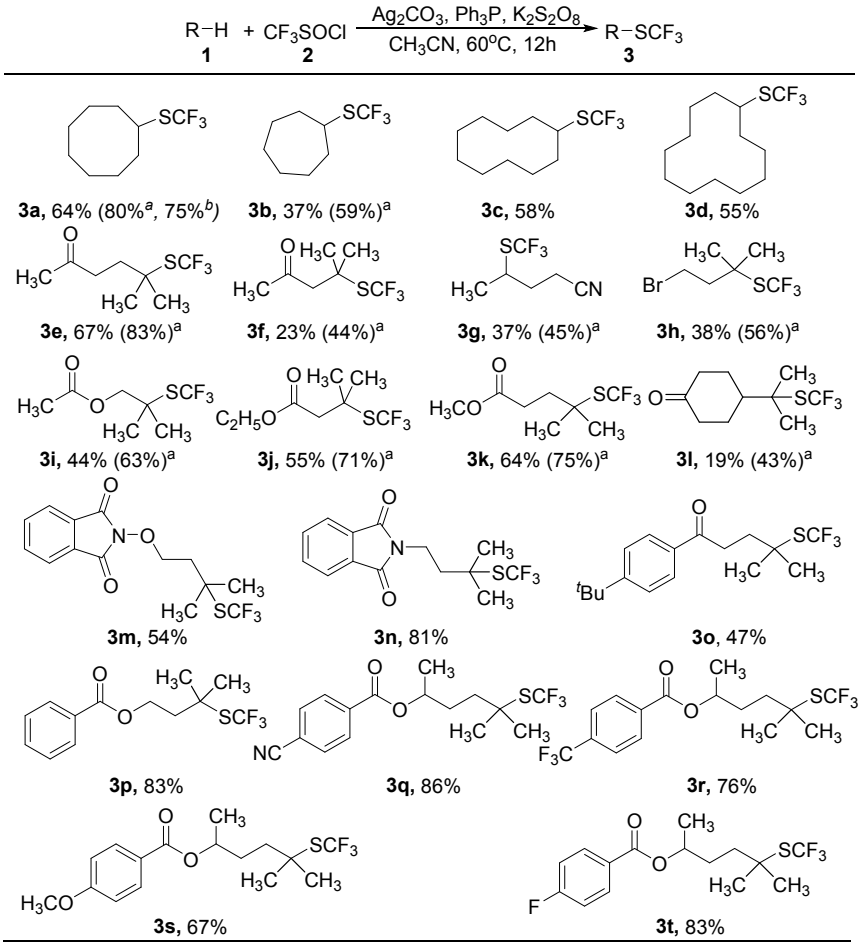


entry	MX	solvent	ratio[b]	yield (%)[c]
1	$AgNO_3$	CH_3CN	1:1:1:1.5:1	0
2	Ag_2CO_3	CH_3CN	1:1:1:1.5:1	55
3	AgF	CH_3CN	1:1:1:1.5:1	21
4	CuSCN	CH_3CN	1:1:1:1.5:1	0
5	CuCl	CH_3CN	1:1:1:1.5:1	0
6	Ag_2CO_3	DMF	1:1:1:1.5:1	0
7	Ag_2CO_3	DCM	1:1:1:1.5:1	0
8	Ag_2CO_3	$PhCH_3$	1:1:1:1.5:1	0
9[d]	Ag_2CO_3	CH_3CN	1:1:1:1.5:1	trace
10[e]	Ag_2CO_3	CH_3CN	1:1:1:1.5:1	trace
11[f]	Ag_2CO_3	CH_3CN	1:1:1:1.5:1	46
12[g]	Ag_2CO_3	CH_3CN	1:1:1:1.5:1	57
13	Ag_2CO_3	CH_3CN	1:1:1:1.5:1.5	77
14	Ag_2CO_3	CH_3CN	1.5:1:1:1.5:1.5	80
15[h]	Ag_2CO_3	CH_3CN	1.5:1:1:1.5:1.5	65
16	Ag_2CO_3	CH_3CN	1.5:1:0.8:1.5:1.5	57
17	Ag_2CO_3	CH_3CN	1.5:1:0.6:1.5:1.5	35
18	Ag_2CO_3	CH_3CN	1.5:1:0.5:1.5:1.5	0
19	-	CH_3CN	1.5:1:0:1.5:1.5	0
20	K_2CO_3	CH_3CN	1.5:1:1:1.5:1.5	0

[a]Reaction conditions:**1a**, **2** (0.4 mmol), MX (1 equiv), Ph_3P (1.5 equiv), and $K_2S_2O_8$ in CH_3CN (3 mL) at 60 °C for 12 h ; [b]Molar ratio of **1a**:**2**:MX:Ph_3P:$K_2S_2O_8$; [c]The yields were determined by ^{19}F NMR

spectroscopy; [d]$NaIO_4$ was used instead of $K_2S_2O_8$; [e]$PhI(OAc)_2$ was used instead of $K_2S_2O_8$; [f]The reaction temperature was 50 °C; [g]The reaction temperature was 70 °C; [h]The reaction time was 6 h.

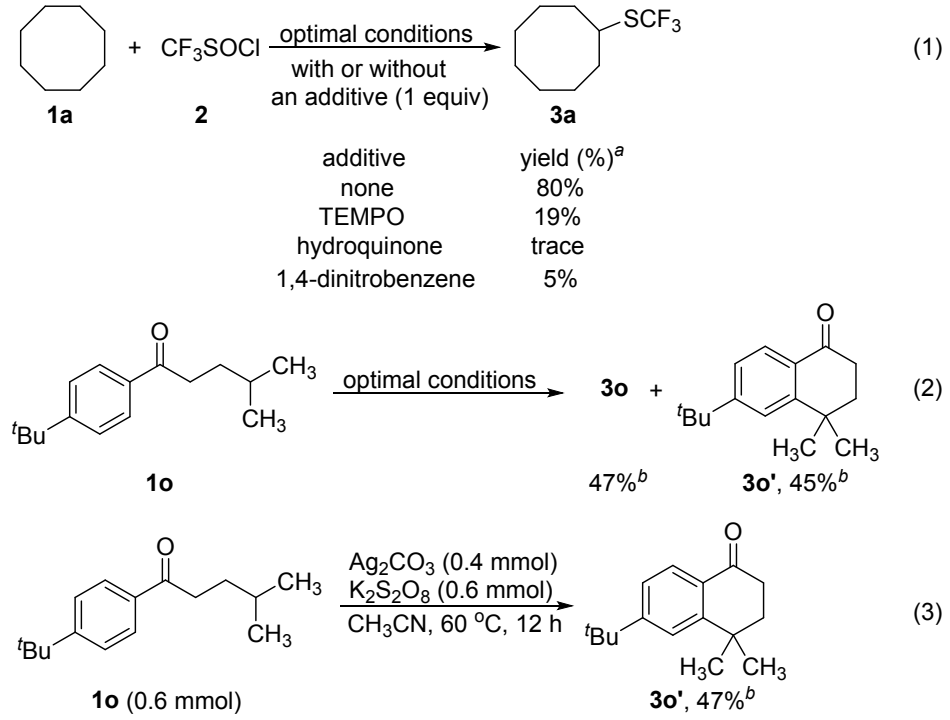
With the optimized reaction conditions in hand (Table 1, entry 14), we then investigated the substrate scope of the Ag-mediated trifluoromethylthiolation of inert Csp^3-H bond. As shown in Scheme 2, a variety of alkanes could be converted smoothly into the desired products in moderate to high yields. A large-scale reaction (10 mmol of CF_3SOCl) could also give the desired product in a good yield (**3a**, 75% ^{19}F NMR yield), demonstrating the potential application of this reaction. Some trifluoromethylthiolation products are volatile and therefore lower isolated yields compared to ^{19}F NMR yields were obtained. Although C-H bond dissociation energies decrease in the order of secondary > tertiary, both secondary and tertiary carbons were found to be quite reactive, and tertiary carbon showed a higher reactivity. If two tertiary carbons were present in the substrates, trifluoromethylthiolation would prefer to take place at the position which is remote from electron-withdrawing groups (**3q-3t**). A wide range of functional group could be tolerated, such as ketones, esters, amides, ethers, halides, and nitriles, demonstrating the synthetic utility of this protocol. To our surprise, the benzylic C-H bond is inert under these conditions. For instance, no desired product was observed for the conversion of toluene or 1-ethylnaphthalene.



Scheme 2. Ag-mediated trifluoromethylthiolation of inert Csp^3-H bond. Isolated yields; Reaction conditions: substrate **1** (1.5 equiv), CF_3SOCl (0.4 mmol, 1 equiv), Ag_2CO_3 (1 equiv), Ph_3P (1.5 equiv), and $K_2S_2O_8$ (1.5 equiv) in CH_3CN (3 mL) at 60 °C for 12 h. [a]The yields were determined by ^{19}F NMR spectroscopy; [b]A 75% ^{19}F NMR yield was obtained by increasing the reaction scale to 10 mmol (CF_3SOCl).

Some preliminary experimental results were collected to gain more mechanistic insights into the C-H trifluoromethylthiolation process. The reaction gave the desired product in low yields in the presence of a radical scavenger, such as TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), hydroquinone or 1,4-dinitrobenzene, suggesting that a radical pathway may be involved (Scheme 3, eq 1). For the conversion of substrate

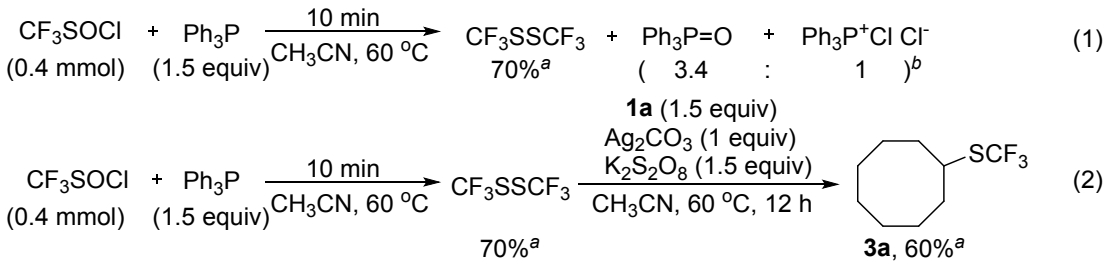
1o, a cyclization product (**3o'**) was produced in 45% yield (eq 2), further supporting the radical mechanism. Without the presence of the CF_3SOCl/Ph_3P system, substrate **1o** could also be converted into cyclization product **3o'**, indicating that the $Ag_2CO_3/K_2S_2O_8$ system would lead to the generation of a radical intermediate from the substrate (eq 3).



Scheme 3. Mechanistic evidence. [a]The yield was determined by ^{19}F NMR spectroscopy; [b]Isolated yield.

Although Ph_3P is a reducing agent and $K_2S_2O_8$ is an oxidizing agent, the reaction between them is quite slow, whereas the reaction of Ph_3P with CF_3SOCl occurred rapidly. Almost no Ph_3P was converted by heating the mixture of Ph_3P and $K_2S_2O_8$ at 60 °C for 10 min. But after stirring the mixture of Ph_3P and CF_3SOCl for 10 min, CF_3SOCl was completely consumed to produce a major product, CF_3SSCF_3, which was confirmed

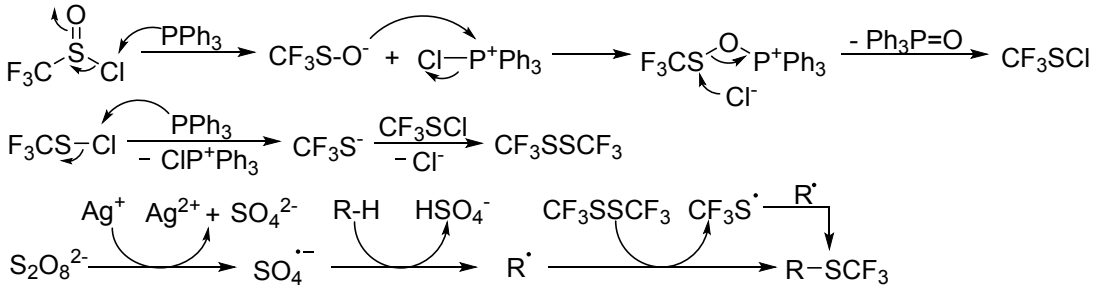
by ^{19}F NMR spectroscopy (δ: -46.2 ppm)[13] and GC-MS (M^+: 201.9) (Scheme 4, eq 1). ^{31}P NMR analysis of the reaction mixture revealed that Ph_3P was completely converted into two species, $Ph_3P{=}O$ and ($Ph_3P^+Cl\ Cl^-$) (δ : +65 ppm)[14] (eq 1). The molar ratio of these two species determined by ^{31}P NMR spectroscopy was 3.4:1 [$Ph_3P{=}O$: ($Ph_3P^+Cl\ Cl^-$)]. After the complete conversion of CF_3SOCl into CF_3SSCF_3, substrate **1a** and the $Ag_2CO_3/K_2S_2O_8$ reagent system were added and the resultant mixture was stirred at 60 °C for 12 h (eq 2). A 60% ^{19}F NMR yield of the desired product was obtained, suggesting that CF_3SSCF_3 is a key intermediate for this trifluoromethylthiolation process.



Scheme 4. Mechanistic investigations. [a]The yield was determined by ^{19}F NMR spectroscopy; [b]Molar ratio determined by ^{31}P NMR spectroscopy;

On the basis of the above results, the plausible mechanism is proposed as shown in Scheme 5. CF_3SOCl could be reduced by Ph_3P to form CF_3SCl (trifluoromethanesulfenyl chloride) via a halogen bonding process to form chlorophosphonium salt (ClP^+Ph_3) and an Arbuzov conversion to release $Ph_3P{=}O$.[12] A further halogen bonding process between Ph_3P and CF_3SCl generates chlorophosphonium salt (ClP^+Ph_3) and trifluoromethylthio

anion (CF_3S^-), which attacks CF_3SCl to produce CF_3SSCF_3 and a chloride anion. The disproportionation of peroxydisulfate anion in the presence of a Ag^+ salt gives sulfate radical anion.[15] The abstraction of a hydrogen atom from the substrates by the sulfate radical anion would readily occur to generate an alkyl radical. The reaction of the alkyl radical with CF_3SSCF_3 provides the final trifluoromethylthiolation product and a trifluoromethylthio radical ($CF_3S^{\cdot}$), the combination of which with the alkyl radical also furnishes the trifluoromethylthiolation product.



Scheme 5. The proposed reaction mechanism

In summary, we have described the Ag-mediate trifluoromethylthiolation of inert Csp^3-H bond with CF_3SOCl. All reagents used in this process were widely available, and the reactions occurred smoothly under mild conditions. A broad substrate scope and good functional group compatibility were observed, demonstrating the synthetic utility of this trifluoromethylthiolation protocol. Due to its operational convenience and step economy, the protocol may find application in the synthesis of CF_3S-containing pharmaceuticals and agrochemicals.

EXPERIMENTAL SECTION

General information. ^{1}H, ^{13}C and ^{19}F NMR spectra were detected on a 500 MHz, 400 MHz or 300 MHz NMR spectrometer. Data for ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity(s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, coupling constant (s) in Hz). Mass spectra were obtained on GC-MS or LC-MS (ESI). High resolution mass data were recorded on a high resolution mass spectrometer in the ESI mode. The mass analyzer type for HRMS-ESI is Fourier transform mass spectrometer. Unless otherwise noted, all reagents including CF_3SOCl (95% purity) were obtained commercially and used without further purification.

General procedure for trifluoromethylthiolation. Under a N_2 atmosphere, into a 15 mL sealed tube was added triphenylphosphine (0.6 mmol, 1.5 equiv), $K_2S_2O_8$ (0.6 mmol, 1.5 equiv), Ag_2CO_3 (0.4 mmol, 1.0 equiv), CH_3CN (3 mL), alkane substrate (0.6 mmol, 1.5 equiv), and trifluoromethanesulfinic chloride (0.4 mmol, 1.0 equiv). The tube was sealed and the mixture was stirred at 60 ^{o}C for 12 h. After being cooled to room temperature, the mixture was filtered to remove the solid. The solid was washed with dichloromethane, and the combined organic phase was concentrated to remove the

solvent. The residue was subjected to flash column chromatography to give the pure product.

cyclooctyl(trifluoromethyl)sulfane (**3a)**[8]**:** 64% yield; 54mg; ; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.53-3.46 (m, 1H), 2.11 – 2.04 (m, 2H), 1.83 – 1.69 (m, 4H), 1.63 – 1.49 (m, 8H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 131.7 (*q*, *J* = 306.1 Hz), 45.9, 32.9, 27.5, 25.9, 25.0.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -39.70 (s, 3F). **GC-MS (EI):** m/z = **212.2 (M^+).**

cycloheptyl(trifluoromethyl)sulfane **(3b)**[8]**:** 37% yield; 29mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.49-3.42 (m, 1H), 2.13-2.06 (m, 2H), 1.78-1.66 (m, 4H), 1.63 – 1.49 (m, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 131.6 (q, *J* = 306.2 Hz), 46.3, 35.8, 28.4, 25.7.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -39.68 (s, 3F). **GC-MS (EI):** m/z = **198.1 (M^+).**

cyclodecyl(trifluoromethyl)sulfane (**3c)**[8]: 58% yield; 56mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.59 – 3.53 (m, 1H), 1.97-1.79 (m, 4H), 1.71-1.61 (m, 4H), 1.57-1.52 (m, 10H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 131.7 (q, *J* = 306.1 Hz), 44.0, 32.2, 25.6, 25.1, 24.9, 23.7.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -39.61 (s, 3F). **GC-MS (EI):** m/z = **240.2 (M^+).**

cyclododecyl(trifluoromethyl)sulfane (**3d)**[8]: 55% yield; 59mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.35-3.29 (m, 1H), 1.86-1.77 (m, 2H), 1.69-1.61 (m, 2H), 1.57-1.50 (m, 2H), 1.42 – 1.31 (m, 16H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 131.8 (q, *J* = 306.1 Hz), 42.9, 31.3, 24.2, 24.0, 23.8, 23.7, 22.3.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -39.59 (s, 3F). **GC-MS (EI):** m/z = **268.1 (M^+).**

5-methyl-5-((trifluoromethyl)thio)hexan-2-one (**3e**)[8]: 67% yield; 57mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 2.60 (t, *J* = 8.1 Hz, 2H), 2.15 (s, 3H), 1.92 (t, *J* = 7.6 Hz, 2H), 1.41 (s, 6H) . ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 207.6, 131.1 (q, *J* = 308.1 Hz), 51.7, 39.4, 36.4, 30.2, 29.7.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.97(s, 3F). **GC-MS (EI):** m/z = **214.0 (M^+).**

4-methyl-4-((trifluoromethyl)thio)pentan-2-one (**3f**)[8]: 23% yield; 18mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 2.90 (s, 2H), 2.16 (s, 3H),1.58 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 205.5, 131.2 (q, *J* = 307.7 Hz), 54.8, 49.4, 32.1, 29.2.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.68 (s, 3F). **GC-MS (EI):** m/z = **200.0 (M^+).**

4-((trifluoromethyl)thio)pentanenitrile (**3g**)[8]: 37% yield; 27mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.42-3.34 (m, 1H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.07-1.91 (m, 2H), 1.49 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 130.9 (q, *J* = 308.1 Hz), 118.8, 40.2, 32.7, 22.4, 15.1.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -38.94 (s, 3F). **GC-MS (EI):** m/z = **183.0 (M^+).**

(4-bromo-2-methylbutan-2-yl)(trifluoromethyl)sulfane (**3h**)[8]: 38% yield; 38mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.48 (t, *J* = 8.3 Hz, 2H), 2.28 (t, *J* = 8.0 Hz, 2H),1.48 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 130.9 (q, *J* = 307.9 Hz), 52.0, 46.4, 29.7, 27.5.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.95 (s, 3F). **GC-MS (EI):** m/z = **251.9 (M^+).**

2-methyl-2-((trifluoromethyl)thio)propyl acetate (**3i**): 44% yield; 38mg; Colorless liquid; ^{1}H NMR(400 MHz, *CDCl$_3$*) δ 4.14 (s, 2H), 2.10 (s, 3H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ170.8, 130.9 (q, *J* = 309.1 Hz), 71.1, 50.1, 26.5, 21.0.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.45 (s, 3F). HRMS-ESI (m/z): Calcd for $C_7H_{15}F_3O_2SN$ $[M + NH_4]^+$, 234.0770. Found, 234.0770. IR(KBr): 2962, 1261, 1096, 1027, 799, 704 cm^{-1}.

ethyl 3-methyl-3-((trifluoromethyl)thio)butanoate (**3j)**: 55% yield; 51mg; Colorless liquid; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 4.15 (q, *J* = 7.1 Hz, 2H), 2.75 (s, 2H), 1.59 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 169.9, 131.1 (q, *J* = 307.9 Hz), 61.0, 49.2, 47.8, 29.4, 14.5.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.91 (s, 3F). HRMS-ESI (m/z): Calcd for $C_8H_{17}F_3O_2SN$ $[M + NH_4]^+$, 248.0927. Found, 248.0926. IR(KBr): 2962, 2929, 1734, 1466, 1371, 1119, 1035, 869, 805, 756, 721 cm^{-1}.

methyl 4-methyl-4-((trifluoromethyl)thio)pentanoate (**3k)**[9]: 64% yield; 59mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 3.66 (s, 3H), 2.47 (t, *J* = 8.3 Hz, 2H), 2.01 (t, *J* = 8.1 Hz, 2H), 1.43 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 173.7, 131.1 (q, *J* = 307.6 Hz), 52.1, 51.5, 37.9, 30.1, 29.5.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.97 (s, 3F). **GC-MS (EI):** m/z = **129.1 ($[M\text{-}SCF_3]^+$).**

4-(2-((trifluoromethyl)thio)propan-2-yl)cyclohexan-1-one (**3l)**[10]: 19% yield; 18mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 2.45 – 2.21 (m, 6H), 2.05-1.99 (m, 1H), 1.62-1.51 (m, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 210.9, 131.3 (q, *J* = 309.1 Hz), 55.5, 46.4, 40.9, 27.7, 27.2.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.01 (s, 3F). **GC-MS (EI):** m/z = **240.1 (M^+)**.

2-(3-methyl-3-((trifluoromethyl)thio)butoxy)isoindoline-1,3-dione (**3m)**[8]: 54% yield; 72 mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.83-7.79 (m, 2H), 7.76-7.73 (m, 2H), 4.38 (t, *J* = 6.4 Hz, 2H), 2.22 (t, *J* = 6.4 Hz, 2H), 1.56 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 163.7, 134.9, 131.0 (q, *J* = 307.6 Hz), 129.2, 123.9, 75.5, 50.8, 40.9, 30.0.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.89 (s, 3F). MS (EI): *m/z* =232.1 ($[M\text{-}SCF_3]^+$).

2-(3-methyl-3-((trifluoromethyl)thio)butyl)isoindoline-1,3-dione (**3n**)[8]: 81% yield; 103 mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.82-7.80 (m, 2H), 7.70-7.68 (m, 2H), 3.82 (t, *J* = 7.9 Hz, 2H), 2.04 (t, *J* = 7.9 Hz, 2H), 1.52 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 168.3, 134.3, 132.4, 131.0 (q, *J* = 307.9 Hz), 123.5, 50.4, 41.1, 34.5, 29.6.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.76 (s, 3F). **GC-MS (EI):** m/z = **317.1 (M^+).**

1-(4-(tert-butyl)phenyl)-4-methyl-4-((trifluoromethyl)thio)pentan-1-one (**3o**): 47% yield; 62 mg; Colorless liquid; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.14 (t, *J* = 7.7 Hz, 2H), 1.51 (s, 6H), 1.35 (s, 9H).^{13}C NMR (101 MHz, *CDCl$_3$*) δ 199.1 , 157.3 , 134.5 , 131.3 (q, *J* = 309.1 Hz), 128.4 , 125.9 , 52.1 , 37.1 , 35.5 , 34.4 , 31.4 , 30.0 . ^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.77(s, 3F) . HRMS-ESI (m/z): Calcd for $C_{17}H_{24}F_3OS$ $[M + H]^+$, 333.1494. Found, 333.1494. IR(KBr): 2967, 2907,2870, 1683, 1606, 1568, 1470, 1392, 1318, 1225, 1098, 999, 842, 755, 583 cm^{-1}.

3-methyl-3-((trifluoromethyl)thio)butyl benzoate (**3p**)[9]: 83% yield; 97 mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 4.52 (t, *J* = 6.7 Hz, 2H), 2.21 (t, *J* = 6.7 Hz, 2H), 1.56 (s, 6H). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 166.7, 133.4, 131.1 (q, *J* = 307.6 Hz), 130.4, 129.9, 128.7, 61.9, 50.6, 41.6, 30.1.^{19}F NMR (376 MHz, *CDCl$_3$*) δ -35.76 (s, 3F). **GC-MS (EI):** m/z = **292.1 (M^+)**.

5-methyl-5-((trifluoromethyl)thio)hexan-2-yl 4-cyanobenzoate (**3q**)[9]: 86% yield; 119 mg; ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 5.18-5.13 (m, 1H), 1.95 – 1.68 (m, 4H), 1.44 (s, 6H), 1.37 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR

(101 MHz, *CDCl₃*) δ 164.7 , 134.7 , 132.5 , 131.2 (q, *J* = 307.6 Hz), 130.3 , 118.3 , 116.6 , 72.8 , 51.8 , 38.9 , 31.4 , 29.7 , 20.2 .^{19}F NMR (376 MHz, *CDCl₃*) δ -35.80 (s, 3F). **GC-MS (EI):** m/z = **244.1** ([M-SCF_3]$^+$).

5-methyl-5-((trifluoromethyl)thio)hexan-2-yl 4-(trifluoromethyl)benzoate (**3r**)[9]: 76% yield; 118 mg; ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.14 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 5.30 – 4.93 (m, 1H), 1.98 – 1.66 (m, 4H), 1.46 (s, 6H), 1.39 (d, *J* = 6.3 Hz, 3H).^{13}C NMR (101 MHz, *CDCl₃*) δ 165.3, 134.7 (q, *J* = 32.7 Hz), 134.2, 131.3 (q, *J* =309.1), 130.3, 125.7 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.6 Hz),72.5, 51.9, 39.0, 31.5, 29.8, 20.4.^{19}F NMR (376 MHz, *CDCl₃*) δ -35.83 (s, 3F), -63.18 (s, 3F). ESI (m/z): $C_{16}H_{18}F_6O_2SNa$ $[M + Na]^+$, 411.1.

5-methyl-5-((trifluoromethyl)thio)hexan-2-yl 4-methoxybenzoate **(3s)**[9]: 67% yield; 93 mg; ^{1}H NMR (400 MHz, *CDCl₃*) δ 7.98 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.13-5.09 (m, 1H), 3.85 (s, 3H), 1.93 – 1.67 (m, 4H), 1.45 (s, 6H), 1.35 (d, *J* = 6.2 Hz, 3H).^{13}C NMR (101 MHz, *CDCl₃*) δ 166.2, 163.6, 131.8, 131.3 (q, *J* = 307.6 Hz), 123.3, 113.9, 71.2, 55.7, 52.0, 39.1, 31.6, 29.8, 20.4.^{19}F NMR (376 MHz, *CDCl₃*) δ -35.76 (s, 3F). **GC-MS (EI):** m/z = **350.2 (M^+).**

5-methyl-5-((trifluoromethyl)thio)hexan-2-yl 4-fluorobenzoate **(3t)**[9]: 83% yield; 112 mg; ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.06-8.02 (m, 2H), 7.10 (t, *J* = 8.5 Hz, 2H), 5.15-5.11 (m, 1H), 1.92– 1.68 (m, 4H), 1.45 (s, 6H), 1.36 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, *CDCl₃*) δ 166.1 (d, *J* = 253.5 Hz), 165.5, 132.4 (d, *J* = 9.8 Hz), 131.3 (q, *J* = 307.6 Hz),

127.2 (d, J = 3.4 Hz), 115.8 (d, J = 21.9 Hz), 71.9, 51.9, 39.0, 31.6, 29.8, 20.4.^{19}F NMR (376 MHz, $CDCl_3$) δ -35.80 (s, 3F) , -105.96 ~ -106.05 (m, 1F). **GC-MS (EI):** m/z = **237.1 (**$[M\text{-}SCF_3]^+$**).**

6-(tert-butyl)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**3o)'**: 45% yield; 41 mg; Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.33 (dd, J = 8.3, 19 Hz, 1H), 2.70 (t, J = 6.8 Hz, 2H), 2.01 (t, J = 6.8 Hz, 2H), 1.39 (s, 6H), 1.34 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 ,157.7, 152.3, 129.1, 127.5, 123.9, 122.6, 37.6, 35.6, 35.4, 34.4, 31.4, 30.1. HRMS-ESI (m/z): Calcd for $C_{16}H_{23}O$ $[M + H]^+$, 231.1743. Found, 231.1743. IR(KBr): 3351, 2961, 2868, 1685, 1604, 1465, 1387, 1285, 1198, 1092, 1021, 880, 837, 810, 696, 655, 569, 485 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information Available. Copies of ^{1}H/^{19}F/^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Leo, A.; Hansch, C.; Elkins, D. Partition coefficients and their uses. Chem. Rev. 1971, 71, 525-616; (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. Aromatic substituent constants for structure-activity correlations. J. Med. Chem. 1973, 16, 1207-1216; (c) Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. Chem. Rev. 1991, 91, 165-195.

(2) (a) Leroux, F.; Jeschke, P.; Schlosser, M. α-Fluorinated Ethers, Thioethers, and Amines: Anomerically Biased Species. Chem. Rev. 2005, 105, 827-856; (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Second ed.; Wiley-VCH: Weinheim, Germany, 2013; (c) Landelle, G.; Panossian, A.; Leroux, F. Trifluoromethyl ethers and -thioethers as tools for medicinal chemistry and drug discovery. Curr. Top. Med. Chem. 2014, 14, 941-951; (d) Xu, X.-H.; Matsuzaki, K.; Shibata, N. Synthetic Methods for Compounds Having CF_3-S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. Chem. Rev. 2015, 115, 731-764.

(3) (a) Tlili, A.; Billard, T. Formation of C-SCF_3 Bonds through Direct Trifluoromethylthiolation. Angew. Chem. Int. Ed. 2013, 52, 6818-6819; (b) Chu, L.; Qing, F.-L. Oxidative Trifluoromethylation and Trifluoromethylthiolation Reactions Using (Trifluoromethyl)trimethylsilane as a Nucleophilic CF_3 Source. Acc. Chem. Res. 2014, 47, 1513-1522; (c) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. Chem. Rev. 2015, 115, 826-870; (d) Shao, X.; Xu, C.; Lu, L.; Shen,

Q. Shelf-Stable Electrophilic Reagents for Trifluoromethylthiolation. Acc. Chem. Res. 2015, 48, 1227-1236; (e) Chachignon, H. l. n.; Cahard, D. State-of-the-Art in Electrophilic Trifluoromethylthiolation Reagents. Chin. J. Chem . 2016, 34, 445 - 454; (f) Zhang, P.; Lu, L.; Shen, Q. Recent Progress on Direct Trifluoromethylthiolating Reagents and Methods. Acta Chim. Sinica 2017, 75, 744 - 769.

(4) (a) Tran, L. D.; Popov, I.; Daugulis, O. Copper-promoted sulfenylation of sp^2 C-H bonds. J. Am. Chem. Soc. 2012, 134, 18237 - 18240,18234; (b) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. Trifluoromethanesulfonyl hypervalent iodonium ylide for copper-catalyzed trifluoromethylthiolation of enamines, indoles, and beta-keto esters. J. Am. Chem. Soc. 2013, 135, 8782 - 8785; (c) Xu, C.; Shen, Q. Palladium-Catalyzed Trifluoromethylthiolation of Aryl C-H Bonds. Org. Lett. 2014, 16, 2046-2049; (d) Yin, W.; Wang, Z.; Huang, Y. Highly ortho-selective trifluoromethylthiolation reactions using a ligand exchange strategy. Adv. Synth. Catal. 2014, 356, 2998-3006; (e) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. Copper-Catalyzed Regioselective Trifluoromethylthiolation of Pyrroles by Trifluoromethanesulfonyl Hypervalent Iodonium Ylide. Org. Lett. 2015, 17, 1094-1097; (f) Alazet, S.; Billard, T. Electrophilic aromatic trifluoromethylthiolation with the second generation of trifluoromethanesulfenamide. Synlett 2015, 25, 76–78; (g) Wang, Q.; Qi, Z.; Xie, F.; Li, X. Lewis Acid-Catalyzed Electrophilic Trifluoromethylthiolation of (Hetero)Arenes. Adv. Synth. Catal. 2015, 357, 355-360; (h) Yoshida, M.; Kawai, K.; Tanaka, R.; Yoshino, T.; Matsunaga, S. Cp*Co(III)-catalyzed directed C-H trifluoromethylthiolation of 2-phenylpyridines and 6-arylpurines. Chem. Commun. 2017, 53, 5974-5977.

(5) (a) Chen, C.; Chu, L.; Qing, F.-L. Metal-free oxidative trifluoromethylthiolation of terminal alkynes with CF3SiMe3 and elemental sulfur. J. Am. Chem. Soc. 2012, 134, 12454 - 12457; (b) Alazet, S.; Zimmer, L.; Billard, T. Base-catalyzed electrophilic trifluoromethylthiolation of terminal alkynes. Angew. Chem. Int. Ed. 2013, 52, 10814 - 10817; (c) Pluta, R.; Nikolaienko, P.; Rueping, M. Direct catalytic trifluoromethylthiolation of boronic acids and alkynes employing electrophilic shelf-stable N-(trifluoromethylthio)phthalimide. Angew. Chem. Int. Ed. 2014, 53, 1650 - 1653.

(6) Chen, C.; Xu, X.-H.; Yang, B.; Qing, F.-L. Copper-Catalyzed Direct Trifluoromethylthiolation of Benzylic C-H Bonds via Nondirected Oxidative C(sp^3)-H Activation. Org. Lett. 2014, 16, 3372-3375.

(7) Xiong, H.-Y.; Besset, T.; Cahard, D.; Pannecoucke, X. Palladium(II)-Catalyzed Directed Trifluoromethylthiolation of Unactivated C(sp^3)-H Bonds. J. Org. Chem. 2015, 80, 4204-4212.

(8) Wu, H.; Xiao, Z.; Wu, J.; Guo, Y.; Xiao, J.-C.; Liu, C.; Chen, Q.-Y. Direct trifluoromethylthiolation of unactivated C(sp^3)-H using silver(I) trifluoromethanethiolate and potassium persulfate. Angew. Chem. Int. Ed. 2015, 54, 4070 - 4074.

(9) Guo, S.; Zhang, X.; Tang, P. Silver-mediated oxidative aliphatic C-H trifluoromethylthiolation. Angew. Chem. Int. Ed. 2015, 54, 4065 - 4069.

(10) Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. Visible-Light-Promoted Activation of Unactivated C(sp(3))-H Bonds and Their Selective Trifluoromethylthiolation. J Am Chem Soc 2016, 138, 16200-16203.

(11) (a) Zheng, J.; Cai, J.; Lin, J.-H.; Guo, Y.; Xiao, J.-C. Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine. Chem. Commun. 2013, 49, 7513-7515; (b) Zheng, J.; Lin, J.-H.; Cai, J.; Xiao, J.-C. Conversion between Difluorocarbene and Difluoromethylene Ylide. Chem. - Eur. J. 2013,

19, 15261-15266; (c) Zheng, J.; Wang, L.; Lin, J.-H.; Xiao, J.-C.; Liang, S. H. Difluorocarbene-Derived Trifluoromethylthiolation and [18F]Trifluoromethylthiolation of Aliphatic Electrophiles. Angew. Chem. Int. Ed. 2015, 54, 13236-13240; (d) Deng, Z.; Lin, J.-H.; Cai, J.; Xiao, J.-C. Direct Nucleophilic Difluoromethylation of Carbonyl Compounds. Org. Lett. 2016, 18, 3206-3209; (e) Deng, X.-Y.; Lin, J.-H.; Xiao, J.-C. Pd-Catalyzed Transfer of Difluorocarbene. Org. Lett. 2016, 18, 4384-4387; (f) Zheng, J.; Cheng, R.; Lin, J.-H.; Yu, D. H.; Ma, L.; Jia, L.; Zhang, L.; Wang, L.; Xiao, J.-C.; Liang, S. H. An Unconventional Mechanistic Insight into SCF_3 Formation from Difluorocarbene: Preparation of ^{18}F-Labeled alpha-SCF_3 Carbonyl Compounds. Angew. Chem. Int. Ed. 2017, 56, 3196-3200; (g) Yu, J.; Lin, J.-H.; Xiao, J.-C. Reaction of Thiocarbonyl Fluoride Generated from Difluorocarbene with Amines. Angew. Chem. Int. Ed. 2017, 56, 16669 - 16673.

(12) (a) Chachignon, H.; Maeno, M.; Kondo, H.; Shibata, N.; Cahard, D. Novel Use of CF_3SO_2Cl for the Metal-Free Electrophilic Trifluoromethylthiolation. Org. Lett. 2016, 18, 2467-2470; (b) Lu, K.; Deng, Z.; Li, M.; Li, T.; Zhao, X. Transition metal-free direct trifluoromethylthiolation of indoles using trifluoromethanesulfonyl chloride in the presence of triphenylphosphine. Org. Biomol. Chem. 2017, 15, 1254 - 1260; (c) Jiang, L.; Yi, W.; Liu, Q. Direct Phosphorus-Induced Fluoroalkylthiolation with Fluoroalkylsulfonyl Chlorides. Adv. Synth. Catal. 2016, 358, 3700-3705.

(13) Jiang, L.; Qian, J.; Yi, W.; Lu, G.; Cai, C.; Zhang, W. Direct trifluoromethylthiolation and perfluoroalkylthiolation of C(sp^2)-H bonds with CF_3SO_2Na and $RfSO_2Na$. Angew. Chem. Int. Ed. 2015, 54, 14965 - 14969.

(14) Vetter, A. C.; Nikitin, K.; Gilheany, D. G. Long sought synthesis of quaternary phosphonium salts from phosphine oxides: inverse reactivity approach. Chem. Commun. 2018, 54, 5843-5846.

(15) House, D. A. Kinetics and Mechanism of Oxidations by Peroxydisulfate. Chem. Rev. 1962, 62, 185-203.