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A Metal-Free Diverse Synthesis of Difluoromethylthioethers and Difluorobis(arylthio)methanes from RSX (X = SR, Cl, SO_2Ph) and $TMSCF_2H$

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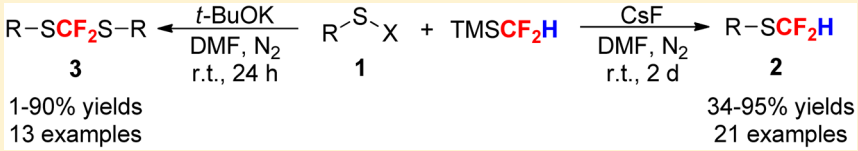
Supporting Information



ABSTRACT: Construction of difluoromethylthioethers (**2**) and difluorobis(arylthio)methanes (**3**) from RSX (X = SR, Cl, SO_2Ph) and $TMSCF_2H$ in the absence of transition metals has been explored. The reaction is dramatically influenced by the nature of the base and the molar ratio of the reactants. Reactions between RSX and $TMSCF_2H$ in the presence of CsF provided **2** in good yields, whereas the reaction of RSX with $TMSCF_2H$ in the presence of *t*-BuOK afforded **3** in good yields. These protocols allow for convenient and efficient access to both difluoromethylthioethers and difluorobis(arylthio)methanes.

INTRODUCTION

Organofluorine compounds play an integral role in the search for new drugs. At present, around 35% of agrochemicals and 20−30% of pharmaceuticals on the market contain fluorine.[1] It has been revealed that the fluorine and fluoroalkyl substituents in these molecules are critical functionalities to modulate their membrane permeability, metabolic stability, and bioavailability.[1,2] The introduction of fluorine atoms into biologically active organic frameworks has become a standard practice in drug discovery and development.[1a] Consequently, the development of new fluorination/fluoroalkylation reagents and the versatile methods to incorporate fluorine is extraordinarily important.[3,4]

The last several years has witnessed the explosive investigation of facile and direct difluoromethylations.[5] To date, only a small number of the methods can reach the efficiency of the corresponding trifluoromethylations.[6] Compared to the CF_3 moiety, the difluoromethyl group (CF_2H) has obvious advantages. It is isosteric and isopolar to the hydroxy (OH) and thiol (SH) units and acts as a more lipophilic hydrogen donor than OH and SH groups in hydrogen bonding.[7] Thus, it can construct membrane-permeability-enhanced analogues to those with OH or SH groups.[8] Among all the CF_2H-containing moieties, the SCF_2H functionality receives increasing attention.[6a] The difluoromethylthio group is generally considered as a more lipophilic hydrogen bonding donor than CF_2H itself, which has exhibited high availability in drug design.[9]

Traditional synthesis of SCF_2H moieties involves the nucleophilic attack of the in situ generated difluoromethyl carbene intermediates by thiolates.[10] This includes the difluoromethyl carbene reagents like HCF_2Cl, $FSO_2CF_2CO_2M$, $BrCF_2P(O)(OEt)_2$, XCF_2CO_2Na, $TMSCF_2Y$, HCF_2OTf, and $PhS(O)(NTs)CF_2H$.[1,5a,10,3e,11] The reactions of thiolates with electrophilic difluoromethylation reagents or a difluoromethyl radical precursor can also provide the desired difluoromethylthiolated products.[12] Recently, a copper-mediated nucleophilic difluoromethylation of organothiocyanates by $TMSCF_2H$ was reported, which allows for a late-stage difluoromethylthiolation of alkyl halides or arenediazonium salts in one pot.[6a] Later, a similar difluoromethylation combined with a $AlCl_3$-catalyzed C−H thiocyanation of arenes by *N*-thiocyanatosuccinimide (NTS) was explored, which gave aryl difluoromethyl thioethers as well.[13] These reactions, however, have disadvantages, such as suffering from the limited scope of substrates that have to form RSCN and the release of CN^- anion from RSCN, which is much less environmentally friendly. Shortly after, Shen et al. disclosed a copper-mediated direct difluoromethylthiolation of aryl and heteroaryl diazo compounds to difluoromethylthiolated arenes by a N-heterocyclic carbene (NHC) ligated difluoromethylthiolated silver complex [(SIPr)Ag(SCF_2H)].[14] Very recently, *N*-difluoromethylthiophthalimide, synthesized from [(SIPr)Ag(CF_2H)] and *N*-chlorosulfenylphthalimide, was used for the direct difluoromethylthiolation of various nucleophiles including aryl/vinyl boronic acids, alkynes, amines, thiols, β-ketoesters, oxindoles, and electron-rich heteroarenes under mild conditions.[15] Nevertheless, the preparation of a mass of the expensive and laborious [(SIPr)Ag(SCF_2H)] and *N*-difluoromethylthiophthalimide is unpractical, which inhibited their use in large scale.

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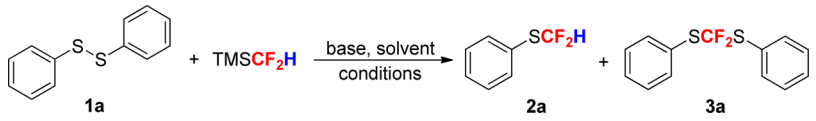
Table 1. Difluoromethylation of 1,2-Diphenyldisulfane (1a) by $TMSCF_2H$



entry	base	1a:$TMSCF_2H$:base	conditions[a]	yield (2a, %)[b]	yield (3a, %)[b]
1	$[Me_4N]F$	1:3:3	DMF, r.t., 2 d	18	0
2	$[n\text{-}Bu_4N][Ph_3SiF_2]$	1:3:3	DMF, r.t., 2 d	44	4
3[c]	KF	1:3:1.5	DMF, r.t., 2 d	58	7
4	CsF	1:3:2	DMF, r.t., 2 d	66	8
5	**CsF**	**1:3:3**	**DMF, r.t., 2 d**	**69** (53[d])	**11** (6[d])
6	**CsF**	**1:3:5**	**DMF, r.t., 2 d**	**86**	**11**
7	CsF	1:4:3	DMF, r.t., 2 d	63	3
8	CsF	1:1:2	DMF, r.t., 24 h	40	15
9	**CsF**	**1:5:4**	**DMF, r.t., 2 d**	**83**	**4**
10	CsF	1:3:3	DMSO, r.t., 2 d	29	0
11	CsF	1:3:3	THF, r.t., 2 d	5	1
12	CsF	1:3:3	NMP, r.t., 2 d	47	4
13	CsF	1:3:3	CH_3CN, r.t., 2 d	0	0
14	CsF	1:3:3	CH_2Cl_2, r.t., 2 d	0	0
15	CsF	1:2:2	DMF, 0 °C, 2 d	55	7
16	CsF	1:3:3	DMF, 40 °C, 2 d	68	14
17	CsF	1:3:3	DMF, 60 °C, 2 d	69	14
18	CsF	1:3:3	DMF, 70 °C, 2 d	66	17
19	CsF	1:3:3	CuSCN, DMF, r.t., 2 d	64	14
20	CsF	1:3:3	CuOAc, DMF, r.t., 2 d	41	9
21	CsF	1:3:3	CuOTf, DMF, r.t., 2 d	19	0
22	CsF	1:3:3	CuCl, DMF, r.t., 2 d	51	12
23[d]	*t*-BuOK	1:3:3	DMF, r.t., 2 d	20	81
24[d]	*t*-BuOK	2:1:2	DMF, r.t., 24 h	2	73
25[d]	*t*-BuOK	2:1:1	DMF, r.t., 24 h	21	23
26[d]	*t*-BuOK	1:1:1	DMF, r.t., 24 h	28	57
27[d]	***t*-BuOK**	**1:1:2**	**DMF, r.t., 24 h**	**1**	**81** (87)

[a]The reaction was conducted under a N_2 atmosphere (in a N_2-filled glovebox or using standard Schlenk and high vacuum techniques). All the solvents were dried before use. The solutions of $TMSCF_2H$ in solvents were added dropwise into the reaction. [b]Yields were determined by ^{19}F NMR analysis of the reaction mixture using $C_6H_5CF_3$ as an internal standard. Isolated yield is depicted in the parentheses. [c]1.5 equiv of 18-crown-6 was added. [d]$TMSCF_2H$ was added into the reaction in one portion via syringe.

On the other hand, it was known that $TMSCF_2H$ is substantially less reactive than the Ruppert–Prakash reagent ($TMSCF_3$).[16] The molecular orbital calculation of (difluoromethyl)- and (trifluoromethyl)fluorotrimethylsilicates has shown that the bond order of Si–CF_2H is much higher than that of Si–CF_3 (0.436 vs 0.220), leading to that the cleavage of Si–CF_2H is more difficult than that of Si–CF_3.[16] This may rationalize that methods for the direct nucleophilic difluoromethylation with $TMSCF_2H$ are scarce even though breakthroughs have been made in the conversion of aryl(vinyl) iodides, (hetero-)arenediazonium salts, organothiocyanates, and carbonyl compounds or imines into the corresponding CF_2H products.[6,13,14,16,17] Moreover, in contrast to $TMSCF_3$, $TMSCF_2H$ has a vulnerable C–H bond, and the $^-CF_2H$ anion derived from $TMSCF_2H$ is much more alkali than the $^-CF_3$ anion from $TMSCF_3$.[18] These made that $TMSCF_2H$ exhibits different reactivity, compared to $TMSCF_3$, under the similar reaction conditions.[6] Hence, the endeavor to establish useful difluoromethylation reactions and to deeply understand the property of $TMSCF_2H$ remains ongoing. In this article, we disclose a metal-free direct nucleophilic difluoromethylation of RSX (X = SR, Cl, SO_2Ph, CN) with $TMSCF_2H$ in the presence of different types of bases.

RESULTS AND DISCUSSION

At the beginning, the reaction of PhSSPh (**1a**) and $TMSCF_2H$ (3 equiv) in the presence of $[Me_4N]F$ (3 equiv) in DMF at room temperature for 2 days under a N_2 atmosphere was performed, which gave (difluoromethyl)(phenyl)sulfane (**2a**) in 18% yield (entry 1, Table 1). The same reaction using $[n\text{-}Bu_4N][Ph_3SiF_2]$ as base, which is more soluble in DMF than $[Me_4N]F$, provided **2a** in 44% yield, and, surprisingly, **3a**[10a,19] in 4% yield (entry 2, Table 1). Moreover, treatment of PhSSPh with $TMSCF_2H$ (3 equiv), KF (1.5 equiv), and 18-crown-6 (1.5 equiv) in DMF at room temperature under a N_2 atmosphere for 2 days furnished **2a** in 58% yield and **3a** in 7% yield (entry 3, Table 1), and the reaction with CsF (2 equiv) afforded **2a** in 66% yield and **3a** in 8% yield (entry 4, Table 1). Varying the molar ratio of **1a**/$TMSCF_2H$/CsF from 1:3:2 to 1:3:5 gradually increased the yields of **2a** from 66% to 86% (entries 4–6, Table 1). Either increasing the molar ratio of $TMSCF_2H$ or decreasing the amounts of $TMSCF_2H$ and CsF resulted in lower yields of **2a** (entries 7 and 8, Table 1). The utilization of 5 equiv of $TMSCF_2H$ and 4 equiv of CsF finally provided 83% of **2a** and 4% of **3a** (entry 9, Table 1). The solvent has great influence on the difluoromethylation. Taking DMSO, THF, and NMP instead of DMF, **2a** was obtained in much lower yields (entries 10–12, Table 1). The reaction run in CH_3CN or CH_2Cl_2 gave neither **2a**

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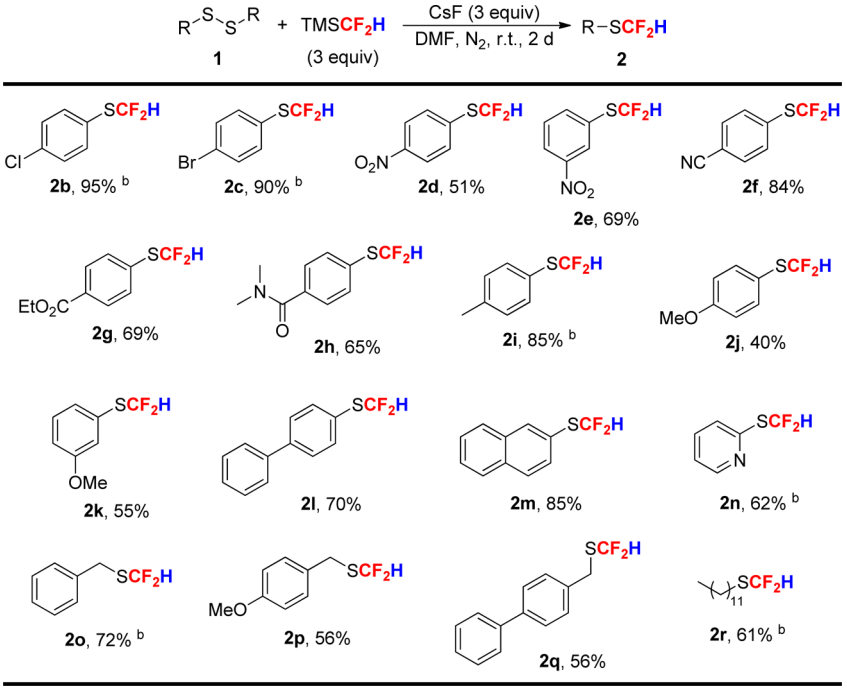
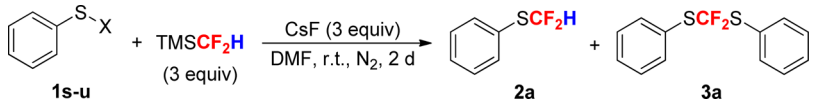
Table 2. Difluoromethylation of RSSR (1b−r) by $TMSCF_2H$ in the Presence of CsF[a]



[a]Reaction conditions: **1b−r** (0.2 mmol)/CsF (0.6 mmol)/$TMSCF_2H$ (0.6 mmol)/DMF (2.0 mL)/r.t./N_2/2 d, dropwise. Isolated yields. [b]The yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.[6a,14,20]

Table 3. Difluoromethylation of PhSX (1s−u) by $TMSCF_2H$ in the Presence of CsF and *t*-BuOK



entry	X	yield (**2a**/**3a**, %)[a,b]	yield (**2a**/**3a**, %)[b,c]
1	Cl (**1s**)	34/5	<1/55
2	SO_2Ph (**1t**)	47/8	1/87
3	CN (**1u**)	43/2	2/1

[a]Reaction conditions: **1s−u** (0.2 mmol)/CsF (0.6 mmol)/$TMSCF_2H$ (0.6 mmol)/DMF (2.0 mL)/r.t./N_2/2 d, dropwise. [b]The yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c]Reaction conditions: **1s−u** (0.4 mmol)/$TMSCF_2H$ (0.4 mmol)/*t*-BuOK (0.8 mmol)/DMF (2 mL)/r.t./N_2/24 h.

nor **3a** (entries 13−14, Table 1). The reaction temperature ranging from 0 to 70 °C barely affects the conversion, in which comparable yields were achieved (entries 15−18, Table 1). Copper catalysts that improved the difluoromethylation of RSCN by $TMSCF_2H$ did not facilitate the production of **2a** from PhSSPh and $TMSCF_2H$ (entries 19−22, Table 1).[6a,13,14]

Next, the combination of RSSR/$TMSCF_2H$ (3 equiv)/CsF (3 equiv)/DMF/r.t./N_2 was chosen as the standard reaction conditions to test the scope of the conversion. On the basis of this, numerous disulfanes (RSSR) were studied and the reactions occurred smoothly to give the corresponding $RSCF_2H$ in moderate to good yields (Table 2). Both the electron-rich and electron-poor 1,2-diaryldisulfanes are mildly transformed in the reaction. Functional groups such as chloro, bromo, nitro, cyano, ester, amide, methoxyl, and heteroaryl groups are all compatible with the reaction (**2b−n**). The sterically hindered 1,2-bis(2-nitrophenyl)disulfane and the active 4,4′-disulfanediyldiphenol and 4,4′-disulfanediyldianiline with reactive protons, however, failed to give the desired products. In addition, 1,2-dialkyldisulfanes underwent efficient difluoromethylation, which gave the alkyl difluoromethylthioethers in good yields (**2o−r**).

PhSX with different leaving groups (X) were also investigated in the reaction. PhSCl reacting with $TMSCF_2H$ in the presence of CsF under the standard reaction conditions provided **2a** in 34% yield and **3a** in 5% yield (entry 1, Table 3). Similarly, treatment of $PhSSO_2Ph$ with $TMSCF_2H$ produced **2a** in 47% yield and **3a** in 8% yield (entry 2, Table 3). The reaction of PhSCN with $TMSCF_2H$ and CsF gave **2a** in 43% yield and **3a** in 2% yield (entry 3, Table 3).[6a] These indicate that PhSX (X = Cl, SO_2Ph, CN) are suitable to this reaction, albeit affording lower yields of the products.

Furthermore, the use of *t*-BuOK instead of CsF as the base in the reaction of PhSSPh (**1a**) and $TMSCF_2H$ led to **3a** as the major product (entry 23, Table 1). The molar ratio of *t*-BuOK, **1a**, and $TMSCF_2H$ has a critical impact on the reaction (entries 23−27, Table 1). When PhSSPh reacted with an equal equivalent of $TMSCF_2H$ in the presence of 2 equiv of *t*-BuOK, difluorobis(phenylthio)methane (**3a**) was obtained in 87% isolated yield (entry 27, Table 1). The reaction is amenable to other aryl disulfides. ArSSAr bearing either electron-withdrawing

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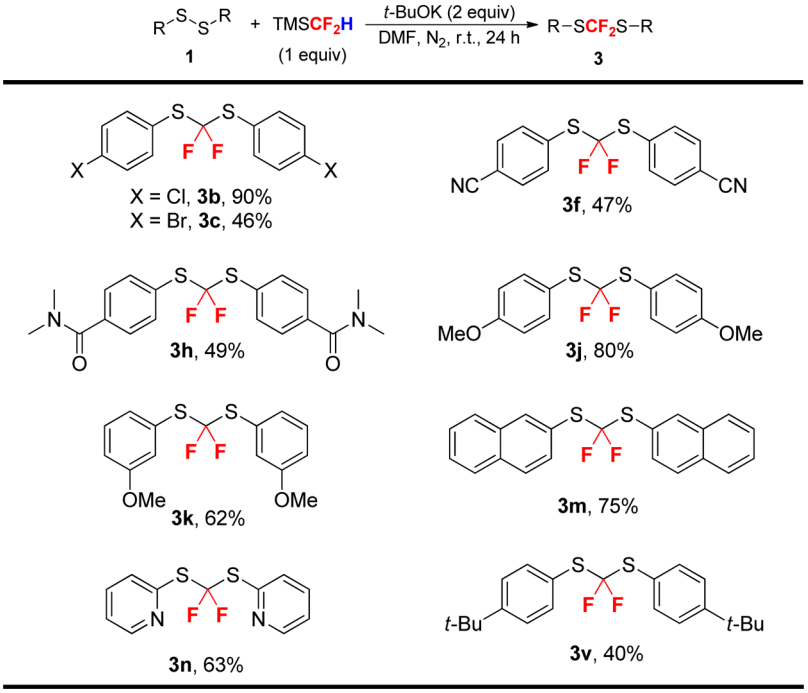
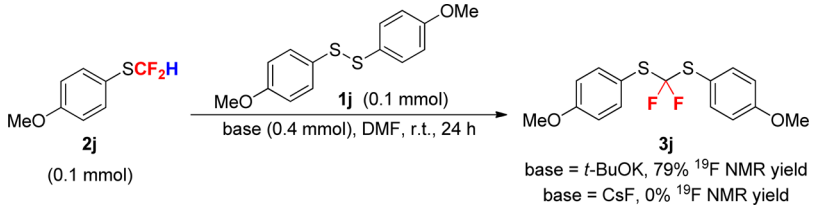
Table 4. Difluoromethylation of RSSR (1) by $TMSCF_2H$ in the Presence of *t*-BuOK[a]

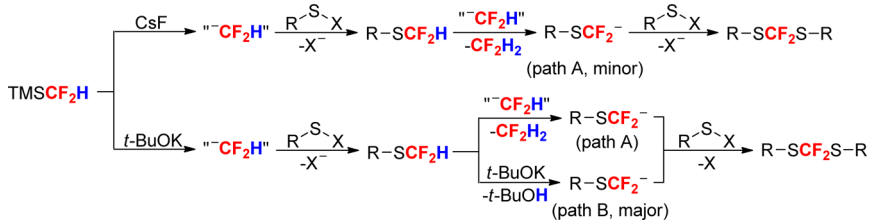


[a]Reaction conditions: **1** (0.4 mmol)/*t*-BuOK (0.8 mmol)/$TMSCF_2H$ (0.4 mmol)/DMF (2.0 mL)/r.t./N_2/24 h. Isolated yields.

Scheme 1. Generation of Difluorobis(arylthio)methane (3j) from Difluoromethylthioether (2j) in the Presence of *t*-BuOK



Scheme 2. A Proposed Mechanism for the Production of Difluoromethylthioethers and Difluorobis(arylthio)methanes from RSX (X = SR, Cl, SO_2Ph) and $TMSCF_2H$



or electron-donating groups (such as Cl, Br, CN, and $CONMe_2$, or OMe and *t*-Bu) on the phenyl rings gave the corresponding products ($ArSCF_2SAr$) in moderate to good yields (Table 4). 1,2-Di(naphthalen-2-yl)disulfane and 1,2-di(pyridin-2-yl)-disulfane reacted with $TMSCF_2H$ and *t*-BuOK under the standard reaction conditions, affording 75% of **3m** and 63% of **3n**, respectively. When 1,2-dibenzyldisulfane (**1o**) and 1,2-didodecyldisulfane (**1r**) were employed in the same reaction, no desired products were obtained. Interestingly, the reaction of C_6H_5SCl or $C_6H_5SSO_2Ph$ with $TMSCF_2H$ and *t*-BuOK could also provide **3a** as the major product (entries 1 and 2, Table 3). The mixture of C_6H_5SCN and $TMSCF_2H$ initiated by *t*-BuOK, however, surprisingly gave both **2a** and **3a** in very low yields (entry 3, Table 3).

In addition, the isolated difluoromethylthioether can be further transformed to difluorobis(phenylthio)methane. The reaction of **2j** and **1j** in the presence of excess *t*-BuOK gave **3j** in 79% yield (Scheme 1). Nevertheless, when the reaction was carried out in the presence of CsF, no **3j** was observed and only the starting **2j** was recovered.

On the basis of the results above, a plausible reaction mechanism was suggested for the generation of $RSCF_2SR$ from RSX and $TMSCF_2H$ (Scheme 2). Initially, $TMSCF_2H$ is activated by CsF or *t*-BuOK to form "$^-CF_2H$". The nucleophilic displacement of the X group of RSX by "$^-CF_2H$" gives difluoromethylthioether ($RSCF_2H$), which is further deprotonated by the excess "$^-CF_2H$" (path A) or *t*-BuOK (path B) to provide $RSCF_2^-$. The intermediate $RSCF_2^-$ then nucleophilically attacks a second RSX to eventually afford $RSCF_2SR$. CsF seems

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not to deprotonate $RSCF_2H$ because no reaction occurred between **1j** (1 equiv) and **2j** (1 equiv)/CsF (4 equiv) under the standard reaction conditions (Scheme 1). Hence, the deprotonation of $RSCF_2H$ by "$^-CF_2H$" (path A) looks reasonable when CsF was used as the base. In the cases of *t*-BuOK, path B might be predominant, which may be rationalized by the formation of **3j** from **2j** and **1j** in the presence of *t*-BuOK (Scheme 1). However, path A cannot be excluded yet. The good solubility and the strong basicity of *t*-BuOK in organic solvents might facilitate the fast deprotonation of $RSCF_2H$, leading to a dominant nucleophilic difluoromethylation of RSX by $RSCF_2^-$, thus generating $RSCF_2SR$ as the major products.

SUMMARY AND CONCLUSION

In summary, we have developed a convenient metal-free diverse synthesis of difluoromethylthioethers and difluorobis(arylthio)methanes from RSX (X = SR, Cl, SO_2Ph) and $TMSCF_2H$. The reactions between RSX and $TMSCF_2H$ in the presence of CsF provided difluoromethylthioethers in good yields, whereas treatment of RSX with $TMSCF_2H$ in the presence of *t*-BuOK afforded difluorobis(arylthio)methanes in good yields. The molar ratio of RSX, $TMSCF_2H$, and the base dramatically influenced the reaction. This is different from the observations in the previous literature using $TMSCF_3$ under the similar reaction conditions.[21] The reactions are compatible with various functional groups such as halo, nitro, cyano, amide, methoxyl, and heteroaryl groups. These transformations not only provide efficient access to difluoromethylthioethers and difluorobis(arylthio)methanes but also gain insights into the reactivity of $TMSCF_2H$, which are valuable for further development of the direct nucleophilic difluoromethylation reactions.

EXPERIMENTAL SECTION

General Information. All the reactions were performed under a nitrogen atmosphere. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a 500 or 400 MHz (for ^1H), 471 or 376 MHz (for ^{19}F), or 126 or 100 MHz (for ^{13}C) spectrometer, respectively. The ^1H and ^{13}C NMR chemical shifts were determined relative to TMS (δ = 0.0 ppm), and the ^{19}F NMR chemical shifts were determined relative to $PhCF_3$ (δ = 63.5 ppm) as the internal standards. The coupling constants were reported in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Melting points were measured and uncorrected. MS experiments were performed on a TOF-Q ESI or a CI/EI instrument. $TMSCF_2H$ was prepared according to the literaure.[22] **1a**, **1d**, **1e**, **1j**, and **1n** were purchased from a commercial source and used without further purification. **1b**,[23a] **1c**,[23a] **1f**,[23b] **1g**,[23c] **1h**,[23d] **1i**,[23a] **1k**,[23e] **1l**,[23e] **1m**,[23a] **1o**,[23a] **1p**,[23e] **1q**,[23e] **1r**,[23a] **1s**,[23f] **1t**,[23g] and **1u**[23h] were prepared according to the literatures. Solvents were dried and degassed before use according to the literature.[24] Products **2a**–**c**, **2i**, **2n**, **2o**, and **2r** were confirmed by GC–MS and ^{19}F NMR analysis of the reaction mixtures, and the yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.[6a,14,20]

General Procedure for the Synthesis of 2. In a nitrogen-filled glovebox, an oven-dried tube (10 mL) was charged with **1** (0.2 mmol), CsF (0.6 mmol), and DMF (1.5 mL) with stirring. A solution of $TMSCF_2H$ (0.6 mmol) in DMF (0.5 mL) was added dropwise in a period of 10 h. After 38 h, the reaction mixture was quenched by H_2O (20 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using petroleum ether/ethyl acetate or petroleum ether as eluent to give the title compounds.

(Difluoromethyl)(phenyl)sulfane (**2a**).[20a] 69% ^{19}F NMR yield. GC–MS (m/z): 160.0 (M^+). ^{19}F NMR (471 MHz): −94.3 (d, $J_{H\text{-}F}$ = 54.6 Hz, 2F).

(Difluoromethyl)(4-chlorophenyl)sulfane (**2b**).[14] 95% ^{19}F NMR yield. GC–MS (m/z): 193.9 (M^+). ^{19}F NMR (471 MHz): −94.5 (d, $J_{H\text{-}F}$ = 54.2 Hz, 2F).

(Difluoromethyl)(4-bromophenyl)sulfane (**2c**).[14] 90% ^{19}F NMR yield. GC–MS (m/z): 237.7 (M^+). ^{19}F NMR (471 MHz): −94.5 (d, $J_{H\text{-}F}$ = 54.6 Hz, 2F).

(Difluoromethyl)(4-nitrophenyl)sulfane (**2d**).[6a] Yellow oil (21 mg, 51%), petroleum ether/ethyl acetate = 20:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 6.95 (t, $J_{H\text{-}F}$ = 56.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5 (s), 135.0 (t, J = 2.8 Hz), 134.4 (s), 124.2 (s), 119.7 (t, $J_{C\text{-}F}$ = 276.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −91.2 (d, $J_{H\text{-}F}$ = 55.6 Hz, 2F).

(Difluoromethyl)(3-nitrophenyl)sulfane (**2e**).[6a] Yellow oil (28.4 mg, 69%), petroleum ether/ethyl acetate = 20:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (t, J = 2.0 Hz, 1H), 8.30 (m, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 6.91 (t, $J_{H\text{-}F}$ = 56.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0 (s), 130.2 (s), 129.9 (s), 124.7 (s), 119.6 (t, $J_{C\text{-}F}$ = 277.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ −91.5 (d, $J_{H\text{-}F}$ = 54.6 Hz, 2F).

4-[(Difluoromethyl)thio]benzonitrile (**2f**).[6a] Colorless oil (31 mg, 84%), petroleum ether/ethyl acetate = 20:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 4H), 6.91 (t, $J_{H\text{-}F}$ = 56.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5 (s), 132.8 (t, J = 2.6 Hz), 132.7 (s), 119.7 (t, $J_{C\text{-}F}$ = 277.6 Hz), 117.9 (s), 113.3 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.2 (d, $J_{H\text{-}F}$ = 57.2 Hz, 2F).

Ethyl 4-[(Difluoromethyl)thio]benzoate (**2g**).[14] Yellow oil (32 mg, 69%), petroleum ether/ethyl acetate = 20:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 6.89 (t, $J_{H\text{-}F}$ = 56.4 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8 (s), 134.0 (s), 132.0 (t, J = 2.6 Hz), 131.4 (s), 130.3 (s), 120.4 (t, $J_{C\text{-}F}$ = 276.7 Hz), 61.3 (s), 14.3 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.1 (d, $J_{H\text{-}F}$ = 57.2 Hz, 2F).

N,N-dimethyl 4-[(Difluoromethyl)thio]benzamide (**2h**). White solid (30 mg, 65%), petroleum ether/ethyl acetate = 1:1 as eluent for the column chromatography. m.p.: 55–56 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.86 (t, $J_{H\text{-}F}$ = 56.8 Hz, 1H), 3.12 (s, 3H), 2.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (s), 137.7 (s), 135.0 (s), 128.0 (s), 127.8 (t, J = 2.8 Hz), 120.6 (t, $J_{C\text{-}F}$ = 276.6 Hz), 39.5 (s), 35.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.3 (d, $J_{H\text{-}F}$ = 55.4 Hz, 2F). IR (KBr): 3236, 3080, 3026, 2989, 2927, 2854, 1626, 1596, 1558, 1508, 1479, 1444, 1403, 1325, 1268, 1215, 1095, 1076, 1051, 1012, 841, 771, 756, 749, 714, 669, 603, 564 cm^{-1}. HRMS-ESI (m/z) calcd. for [$C_{10}H_{11}F_2NOS$ + H]: 232.0608; Found: 232.0606.

(Difluoromethyl)(4-tolyl)sulfane (**2i**).[20b] 85% ^{19}F NMR yield. GC–MS (m/z): 174.0 (M^+). ^{19}F NMR (471 MHz): −94.4 (d, $J_{H\text{-}F}$ = 57.5 Hz, 2F).

(Difluoromethyl)(4-methoxyphenyl)sulfane (**2j**).[6a] Colorless oil (15.3 mg, 40%), petroleum ether as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.75 (t, $J_{H\text{-}F}$ = 57.2 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2 (s), 137.6 (s), 121.0 (t, $J_{C\text{-}F}$ = 274.8 Hz), 116.2 (t, J = 2.8 Hz), 114.9 (s), 55.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.3 (d, $J_{H\text{-}F}$ = 57.2 Hz, 2F).

(Difluoromethyl)(3-methoxyphenyl)sulfane (**2k**).[6a] Colorless oil (21 mg, 55%), petroleum ether as eluent for the column chromatography. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.15 (m, 1H), 7.01 (m, 1H), 6.89 (t, $J_{H\text{-}F}$ = 57.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0 (s), 130.1 (s), 127.3 (t, J = 3.2 Hz), 127.2 (s), 121.2 (t, $J_{C\text{-}F}$ = 275.8 Hz), 120.2 (s), 115.8 (s), 55.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.2 (d, $J_{H\text{-}F}$ = 57.1 Hz, 2F).

[1,1′-Biphenyl]-4-yl(difluoromethyl)sulfane (**2l**).[6a] White solid (33 mg, 70%), petroleum ether as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.62–7.58 (m, 4H), 7.46 (t, J = 7.6, 2H), 7.39 (t, J = 7.2 Hz, 1H), 6.86 (t, $J_{H\text{-}F}$ = 56.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8 (s), 139.9 (s), 135.7 (s), 128.9 (s),

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128.0 (s), 127.9 (s), 127.1 (s), 124.8 (t, J = 3.1 Hz), 120.9 (t, $J_{C\text{-}F}$ = 275.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.4 (d, $J_{H\text{-}F}$ = 57.2 Hz, 2F).

(Difluoromethyl)(naphthalen-2-yl)sulfane (**2m**).[14] White solid (35.5 mg, 85%), petroleum ether as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.87−7.83 (m, 3H), 7.60 (m, 1H), 7.57−7.52 (m, 2H), 6.90 (t, $J_{H\text{-}F}$ = 56.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4 (s), 133.5 (s), 133.5 (s), 131.4 (s), 129.1 (s), 127.9 (s), 127.8 (s), 127.4 (s), 126.9 (s), 123.4 (t, J = 2.8), 121.1 (t, $J_{C\text{-}F}$ = 275.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.2 (d, $J_{H\text{-}F}$ = 55.8 Hz, 2F).

2-((Difluoromethyl)thio)pyridine (**2n**).[6a] 62% ^{19}F NMR yield. GC−MS (m/z): 161.0 (M^+). ^{19}F NMR (471 MHz): −97.8 (d, $J_{H\text{-}F}$ = 57.5 Hz, 2F).

Benzyl(difluoromethyl)sulfane (**2o**).[6a] 72% ^{19}F NMR yield. GC−MS (m/z): 174.1 (M^+). ^{19}F NMR (471 MHz): −95.0 (d, $J_{H\text{-}F}$ = 57.0 Hz, 2F).

(Difluoromethyl)(4-methyoxylbenzyl)sulfane (**2p**).[25] Colorless oil (23 mg, 56%), petroleum ether as eluent for the column chromatography. ^{1}H NMR (400 MHz, acetone-d^6) δ 7.32 (d, J = 8.8 Hz, 2H), 7.13 (t, $J_{H\text{-}F}$ = 56.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 4.07 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, acetone-d^6) δ 160.1 (s), 130.9 (s), 129.4 (s), 122.3 (t, $J_{C\text{-}F}$ = 268.8 Hz), 114.9 (s), 55.5 (s), 31.8 (t, J = 3.4 Hz). ^{19}F NMR (376 MHz, acetone-d^6) δ −94.8 (d, $J_{H\text{-}F}$ = 55.3 Hz, 2F).

([1,1′-Biphenyl]-4-ylmethyl)(difluoromethyl)sulfane (**2q**). White solid (28 mg, 56%), petroleum ether/ethyl acetate = 20:1 as eluent for the column chromatography. m.p.: 69−71 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62−7.59 (m, 4H), 7.47 (m, 4H), 7.38 (t, J = 7.5 Hz, 1H), 6.80 (t, $J_{H\text{-}F}$ = 56.6 Hz, 1H), 4.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (s), 140.6 (s), 135.3 (s), 129.3 (s), 128.8 (s), 127.5 (s), 127.5 (s), 127.1 (s), 120.3 (t, $J_{C\text{-}F}$ = 273.0 Hz), 31.5 (t, J = 3.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.3 (d, $J_{H\text{-}F}$ = 57.3 Hz, 2F). IR (KBr): 3057, 3031, 2962, 2925, 2854, 1564, 1519, 1487, 1451, 1406, 1329, 1261, 1167, 1060, 1018, 846, 801, 760, 729, 692 cm^{-1}. HRMS-EI (m/z) calcd. for $C_{14}H_{12}F_2S$: 250.0628; Found: 250.0626.

(Difluoromethyl)(dodecyl)sulfane (**2r**).[6a] 61% ^{19}F NMR yield. GC−MS (m/z): 201.1 ($[M - CF_2H]^+$). ^{19}F NMR (471 MHz): −94.2 (d, $J_{H\text{-}F}$ = 54.2 Hz, 2F).

General Procedure for the Synthesis of 3. In a nitrogen-filled glovebox, an oven-dried tube (10 mL) was charged with **1** (0.4 mmol), *t*-BuOK (0.8 mmol), and DMF (1.5 mL) with stirring. A solution of $TMSCF_2H$ (0.4 mmol) in DMF (0.5 mL) was added in one portion by syringe. The reaction mixture was reacted at room temperature for 24 h, quenched by H_2O (20 mL), and extracted with ethyl acetate (50 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using hexane, petroleum ether/ethyl acetate, or ethyl acetate as eluent to give the title compounds.

Difluorobis(phenylthio)methane (**3a**).[26] Colorless oil (46.8 mg, 87%), hexane as eluent for the column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 4H), 7.45 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.4 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2 (s), 132.3 (t, $J_{C\text{-}F}$ = 314.9 Hz), 130.2 (s), 129.1 (s), 127.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.0 (s, 2F).

Bis((4-chlorophenyl)thio)difluoromethane (**3b**).[26] White solid (60.4 mg, 90%), hexane as eluent for the column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 4H), 7.37 (d, J = 8.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4 (s), 137.1 (s), 131.8 (t, $J_{C\text{-}F}$ = 315.1 Hz), 129.5 (s), 125.6 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.4 (s, 2F).

Bis((4-bromophenyl)thio)difluoromethane (**3c**).[26] White solid (42 mg, 49%), hexane as eluent for the column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.5 Hz, 4H), 7.46 (d, J = 8.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6 (s), 132.5 (s), 131.6 (t, $J_{C\text{-}F}$ = 316.1 Hz), 126.2 (s), 125.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.2 (s, 2F).

4,4′-((Difluoromethylene)bis(sulfanediyl))dibenzonitrile (**3f**). White solid (30 mg, 47%), petroleum ether/ethyl acetate = 10:1 as eluent for the column chromatography. m.p.: 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8 (s), 133.0 (s), 132.8 (t, $J_{C\text{-}F}$ = 312.1 Hz), 132.7 (s), 117.8 (s), 114.2 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.5 (s, 2F). IR (KBr): 3099, 3074, 3037, 2956, 2923, 2852, 2237, 1646, 1591, 1484, 1467, 1395, 1262, 1090, 1046, 1025, 875, 844, 833, 803, 659 cm^{-1}. HRMS-EI (m/z) calcd for $C_{15}H_8N_2F_2S_2$: 318.0097; Found: 318.0102.

4,4′-((Difluoromethylene)bis(sulfanediyl))bis(N,N-dimethylbenzamide) (**3h**). Yellow solid (40 mg, 49%), ethyl acetate as eluent for the column chromatography. m.p.: 122−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 4H), 7.43 (d, J = 8.0 Hz, 4H), 3.12 (s, 6H), 2.97 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (s), 138.2 (s), 135.9 (s), 132.0 (t, $J_{C\text{-}F}$ = 316.1 Hz), 128.8 (s), 127.8 (s), 39.5 (s), 35.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.4 (s, 2F). IR (KBr): 3060, 3045, 2955, 2925, 2854, 1632, 1506, 1483, 1459, 1402, 1262, 1223, 1098, 1078, 1040, 1026, 893, 847, 803, 760, 669, 575 cm^{-1}. HRMS-EI (m/z) calcd for $C_{19}H_{20}F_2N_2O_2S_2$: 410.0934; Found: 410.0939.

Difluorobis((4-methoxyphenyl)thio)methane (**3j**).[26] White solid (52.3 mg, 80%), petroleum ether/ethyl acetate = 50:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.8 Hz, 4H), 6.89 (d, J = 8.8 Hz, 4H), 3.83 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4 (s), 138.2 (s), 132.3 (t, $J_{C\text{-}F}$ = 314.9 Hz), 118.1 (s), 114.6 (s), 55.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −51.0 (s, 2F).

Difluorobis((3-methoxyphenyl)thio)methane (**3k**). Yellow oil (40.7 mg, 62%), petroleum ether/ethyl acetate = 20:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 8.0 Hz, 2H), 7.18 (d, J = 7.6 Hz, 2H), 7.13 (m, 2H), 6.98 (dd, J = 8.2 Hz, J = 1.9 Hz, 2H), 3.82 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7 (s), 132.3 (t, $J_{C\text{-}F}$ = 315.2 Hz), 129.8 (s), 128.3 (s), 121.0 (s), 116.4 (s), 55.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.6 (s, 2F). IR (KBr): 3087, 3058, 3017, 2960, 2925, 2854, 1593, 1577, 1473, 1421, 1288, 1261, 1235, 1170, 1096, 1077, 1042, 1016, 883, 873, 803, 774, 688 cm^{-1}. HRMS-EI (m/z) calcd. for $C_{15}H_{14}F_2O_2S_2$: 328.0403; Found: 328.0409.

Difluorobis(naphthalen-2-ylthio)methane (**3m**). White solid (55.3 mg, 75%), hexane as eluent for the column chromatography. m.p.: 86−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 2H), 7.87−7.84 (m, 6H), 7.64 (d, J = 9 Hz, 2H), 7.58−7.52 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5 (s), 133.7 (s), 133.4 (s), 132.7 (t, $J_{C\text{-}F}$ = 315.8 Hz), 132.1 (s), 128.7 (s), 128.2 (s), 127.8 (s), 127.6 (s), 126.8 (s), 124.7 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.4 (s, 2F). IR (KBr): 3051, 2962, 2924, 2853, 1499, 1438, 1261, 1096, 1043, 1006, 880, 864, 845, 823, 803, 750 cm^{-1}. HRMS-EI (m/z) calcd for $C_{21}H_{14}F_2S_2$: 368.0505; Found: 368.0508.

Difluorobis(pyridin-2-ylthio)methane (**3n**). Yellow oil (33.9 mg, 63%), petroleum ether/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.4 Hz, 2H), 7.73−7.66 (m, 4H), 7.30−7.27 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7 (s), 150.4 (s), 137.3 (s), 132.3 (t, $J_{C\text{-}F}$ = 316.6 Hz), 128.8 (s), 123.5 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.0 (s, 2F). IR (KBr): 3138, 3048, 2986, 2962, 2925, 2853, 1957, 1729, 1663, 1605, 1573, 1449, 1418, 1285, 1262, 1237, 1153, 1117, 1086, 1032, 989, 882, 764, 738,738, 721, 618, 510 cm^{-1}. HRMS-EI (m/z) calcd for $C_{11}H_8F_2N_2S_2$: 270.0097; Found: 270.0098.

Bis((4-(tert-butyl)phenyl)thio)difluoromethane (**3v**). Yellow solid (30.2 mg, 40%), hexane as eluent for the column chromatography. m.p.: 48−50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 4H), 7.41 (d, J = 8.0 Hz, 4H), 1.35 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6 (s), 135.9 (s), 132.2 (t, $J_{C\text{-}F}$ = 314.9 Hz), 126.2 (s), 123.9 (s), 34.8 (s), 31.2 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.3 (s, 2F). IR (KBr): 3082, 3030, 2962, 2925, 2869, 2855, 1596, 1490, 1462, 1400, 1379, 1364, 1261, 1089, 1021, 879, 800, 703, 557 cm^{-1}. HRMS-EI (m/z) calcd for $C_{21}H_{26}F_2S_2$: 380.1444; Found: 380.1449.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00089.

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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