

Fluorination of Sulfides Using IF_5–Et_3N–3HF

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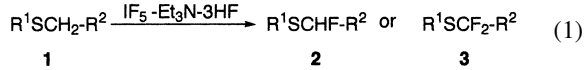
Mono- and difluorinations of sulfides were achieved using a novel fluorinating reagent, IF_5–Et_3N–3HF. The reagent is applicable for substrates having various electron-withdrawing groups, such as an ester, amide, ketone, nitrile, sulfone, or trifluoromethyl. Because more than one fluorine atom on IF_5 is used, a large excess amount of the reagent is not necessary, even for the difluorination reaction.

Recently, α-fluoroalkyl sulfides have been of great interest to synthetic and medicinal chemists because they can be converted to various organofluorine compounds,[1] and some of the derivatives were found to have interesting biological activities.[2] They can be directly prepared from the corresponding alkyl sulfides by a Pummerer-type rearrangement under mild conditions. Many reagents, such as (diethylamino)sulfur trifluoride (DAST),[3] *p*-TolIF_2,[4] XeF_2,[5] *N*-fluoropyridinium triflate,[6] $Bu_4NH_2F_3$–1,3-dibromo-5,5-dimethylhydantoin (DBH),[7] and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate),[8] and the electrochemical method[9] have been employed for the direct fluorination of sulfides. However, some of them are reported to cause side reactions during fluorination. For instance, DAST reduces a sulfoxide to a sulfide,[10] and *p*-TolIF_2 oxidizes the sulfide to the sulfoxide.[4] Furthermore, the difluorination reaction using $Bu_4NH_2F_3$–DBH has not been reported and the electrochemical method needs special equipment. Therefore, a new fluorination reagent applicable for a wide variety of α-fluoroalkyl sulfide syntheses has been desired.

Recently, IF_5–Et_3N–3HF was shown to be an effective fluorination reagent of various organic compounds.[11] The IF_5 itself is highly hygroscopic and decomposes in air with the generation of HF fumes. On the other hand, IF_5–Et_3N–3HF, a 1:1 mixture of IF_5 and Et_3N–3HF, is less hygroscopic and can be handled in air. We wish to now report on the selective mono- and difluorinations of sulfides by IF_5–Et_3N–3HF (Eq. 1).

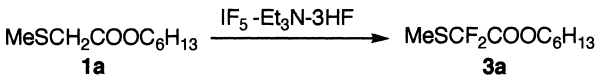


(1)

Results and Discussion

Reaction Conditions for Fluorination of (Methylthio)- and (Arylthio)acetates with IF_5–Et_3N–3HF. The fluorination reaction of (methylthio)acetate (**1a**) with IF_5–Et_3N–3HF was carried out under various reaction conditions until **1a** was completely consumed (Table 1). The reaction slowly proceeded in hexane at room temperature and a difluorinated product (**3a**) was obtained in 84% yield after 336 h. Because only a 1.2 molar amount of IF_5 was necessary to convert **1a** to **3a**, more than one fluorine atom of IF_5 was used for the fluorination.

Table 1. Fluorination of Hexyl (Methylthio)acetate **1a**[a]

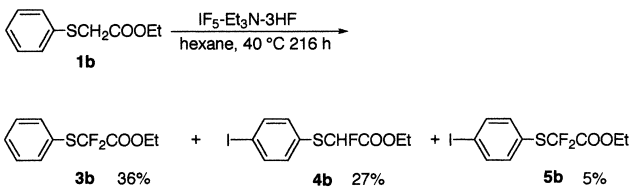


Solvent	React. Temp °C	React. Time h	Yield/%[b]
Hexane	rt	336	84
Hexane	40	48	97(90)
Heptane	60	7	97
$CHCl_3$	60	9	81
CH_3CN	60	12	81
Ethyl acetate	60	336	35

a) 1.2 molar amount of IF_5–Et_3N–3HF was used. b) GC yield based on **1a** used. In parenthesis, isolated yield.

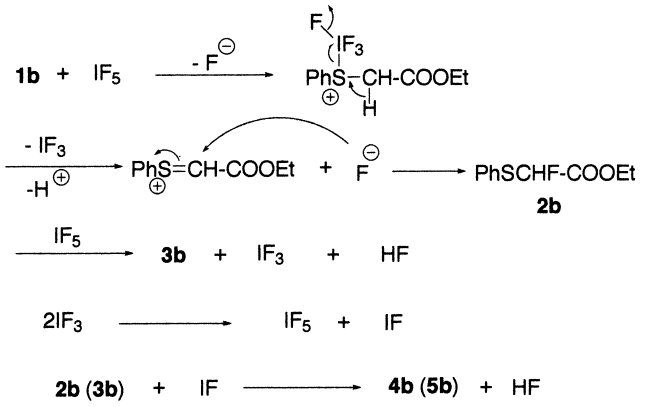
The reaction was accelerated at higher temperature and completed in 48 h at 40 °C and in 7 h at 60 °C. Hexane or heptane is a suitable solvent for this reaction, while polar solvents are less suitable.

The fluorination of (phenylthio)acetate (**1b**) proceeded more slowly, and it took 216 h even at 40 °C to complete the reaction. Furthermore, the expected difluoro product (**3b**) was obtained only in 36% yield, and a significant amount of (*p*-iodophenylthio) derivatives (**4b** and **5b**) was also formed (Eq. 2)

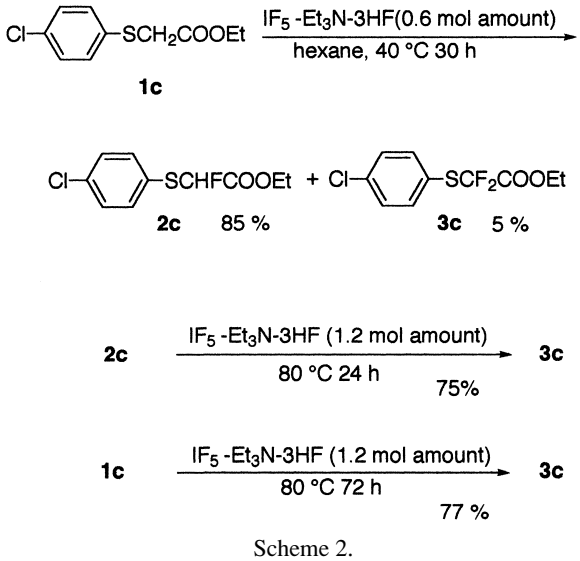


(2)

Mechanistic Aspects. The formations of **3b**, **4b**, and **5b** can be explained as shown in Scheme 1. A nucleophilic attack of the sulfur of **1b** on IF_5 produces a sulfonium ion and, subsequent elimination of HF and IF_3 provides a Pummerer intermediate. A fluoride ion attacks the carbon of the Pummerer intermediate to give the monofluorinated product **2b**. The second fluorination takes place in a similar manner to provide **3b** and the generated IF_3 disproportionates to IF_5 and IF.[12] Though IF_5



Scheme 1.



Scheme 2.

itself does not have the ability to cause iodination of the benzene ring, IF offers a stable iodonium cation species which can cause iodination of the benzene ring to provide **4b** and **5b**.[13] Because the regenerated IF_5 is used for fluorination of the substrate again, more than one fluorine atom on IF_5 is used, and a 2 molar amount of IF_5 is not necessary to obtain the difluorinated product in good yield, as shown in Table 1.

Fluorination of *p*-Chlorophenylthio Derivatives. When (*p*-chlorophenylthio)acetate (**1c**) was used instead of **1b**, the iodination reaction on the benzene ring was not observed, and the fluorination reaction selectively took place. The monofluorinated product (**2c**) could be selectively obtained by carrying out the reaction at 40 °C using a 0.6 molar amount of IF_5–Et_3N–3HF. On the other hand, the reaction of **2c** or **1c** with a 1.2 molar amount of IF_5–Et_3N–3HF at 80 °C selectively gave a difluorinated product (**3c**) (Scheme 2).

Fluorination of the Various Sulfides. Under similar reaction conditions, the fluorination of various sulfides was carried out and selective mono- or difluorination was achieved by choosing the reaction conditions, as shown in Table 2. Though the oxidative fluorination of (phenylthio)acetamides using *p*-TolIF_2 was recently reported, a side reaction, such as the oxidation of a sulfide to a sulfoxide or the electrophilic cyclization of a carbocation generated at the α-position of sulfur to the phenyl or benzyl group on nitrogen, was a serious problem, and the fluorinated products could not be obtained from the *N*-butyl- and *N*-phenyl(phenylthio)acetamides.[4b] When IF_5–Et_3N–3HF was used, the mono- and difluorinations of an *N*-unsubstituted acetamide derivative (**1g**), the *N*-monoalkylated ones (**1h**, **1j**), and an *N*,*N*-dialkylated one (**1i**) could be achieved without any serious side reactions (Entries 4–9), and the fluorinated products could be obtained in good yields even from an *N*-butylacetamide derivative (Entries 8 and 9). Compound **3p** is a key intermediate for an antifungally active compound, and was recently synthesized from **1p** using a 3 molar amount of an expensive electrophilic fluorination reagent at 105 °C.[6b] On the other hand, **1p** could be effectively converted to **3p** at 40 °C with a 1.2 molar amount of IF_5–Et_3N–3HF (Entry 16). From the sulfides having a cyano, a trifluoromethyl, or a sulfone group, the corresponding fluorinated products, were also obtained in good yields (Entries 17–19).

Conclusion

The selective introduction of fluorine atoms into the α-position of the sulfur of the various sulfides was achieved using IF_5–Et_3N–3HF. The reaction proceeded under mild conditions and an (alkylthio)- or (arylthio)ester, -amide, -ketone, -nitrile, -sulfone, or -trifluoromethane as well as alkyl aryl sulfide was effectively fluorinated.

Experimental

General. The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (^1H) and $CFCl_3$ (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FAB mate, or JMS-HX110. Elemental micro analyses were performed using a Yanagimoto CHN Corder MT-5. The Et_3N–3HF was prepared by the addition of freshly distilled Et_3N to anhydrous HF in a Teflon™ PFA vessel at 0 °C.[14] IF_5 in a stainless-steel cylinder was supplied by Daikin Industries, Ltd. (Methylthio)acetic acid ethyl ester and methylthiomethyl *p*-tolyl sulfone were purchased from Tokyo Kasei Kogyo. 1-(2,4-Difluorophenyl)-2-ethylthio-1-ethanone was supplied by Fukuzyu Pharmaceutical Co., Ltd. The other sulfur compounds were prepared from the corresponding thiols and halides.

IF_5–Et_3N–3HF. From a cylinder, IF_5 was transferred through a Teflon tube into a bottle made of Teflon™ PFA under an N_2 atmosphere. After measuring the amount of IF_5 in the bottle, a 1 molar amount of Et_3N–3HF was added to the bottle at room temperature. Though IF_5 itself is hygroscopic, the resulting IF_5–Et_3N–3HF is less hygroscopic. It can be used in the open air and kept in a Teflon™ PFA bottle for a few months without any change. However, it should be carefully handled with equipment made of Teflon™ in a bench hood. IF_5–Et_3N–3HF is insoluble in hexane and heptane, while being soluble in CH_2Cl_2, $CHCl_3$, acetonitrile, and ethyl acetate.

General Procedure for the Fluorination of Sulfides 1 with IF_5–Et_3N–3HF. IF_5–Et_3N–3HF (460 mg, 1.2 mmol), solvent (4 mL), and sulfide **1** (1 mmol) were introduced into a reaction vessel made of Teflon™ PFA and stirred at the temperature given in Table 1. After consumption of the starting material was confirmed

Table 2. Fluorination of Various Sulfides with IF_5–Et_3N–3HF[a)]

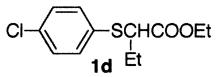
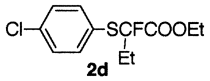
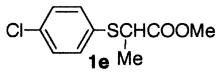
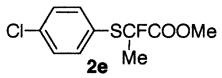
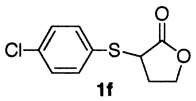
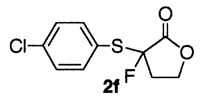
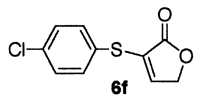
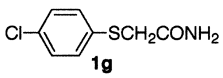
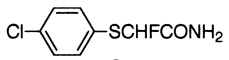
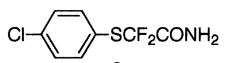
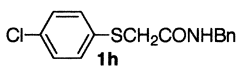
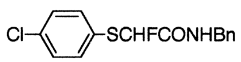
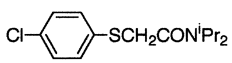
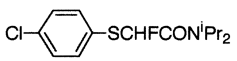
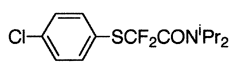
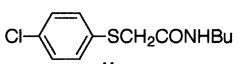
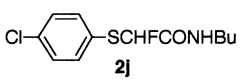
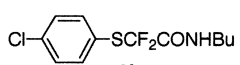
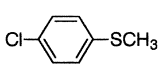
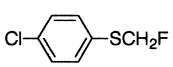
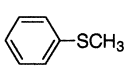
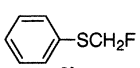
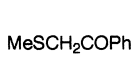
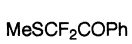
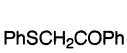
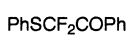
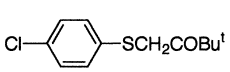
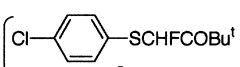
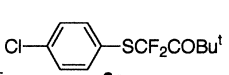
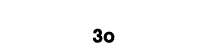
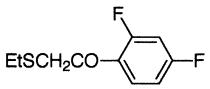
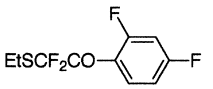
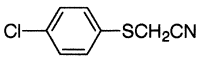
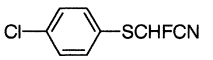
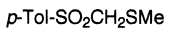
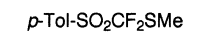
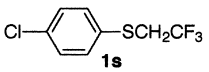
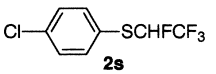
Entry	Substrate **1**	React. Cond.	Product	Yield, %[b)]
1	 **1d**	40 °C, 36 h	 **2d**	82
2	 **1e**	40 °C, 9 h	 **2e**	89
3	 **1f**	40 °C, 4 h	 **2f**  **6f**	65 20
4	 **1g**	40 °C, 4 h	 **2g**  **3g**	71 7
5	 **1h**	40 °C, 2 h	 **2h**	91
6	 **1i**	40 °C, 5 h	 **2i**	88
7	**1i**	80 °C ,96 h[c)]	 **3i**	83
8	 **1j**	40 °C, 3 h	 **2j**	88
9	**1j**	80 °C, 12 h[c)]	 **3j**	69
10	 **1k**	40 °C, 4 h	 **2k**	71
11	 **1l**	40 °C, 1 h	 **2l**	(88)
12	 **1m**	40 °C, 6 h[c)]	 **3m**	79
13	 **1n**	40 °C, 72 h[c),d)]	 **3n**	61
14	 **1o**	40 °C, 2 h	 **2o**  **3o**	91 4

Table 2. (continued)

15	 **1o**	80 °C, 24 h[c)]	 **3o**	84
16	 **1p**	40 °C, 4 h	 **3p**	80
17	 **1q**	70 °C, 5 h[c)]	 **2q**	82
18	 **1r**	60 °C, 24 h	 **3r**	88
19	 **1s**	80 °C, 24 h[c)]	 **2s**	74

a) If otherwise not mentioned, the reaction was carried out in hexane using 1.2 mol amount of IF_5–Et_3N–3HF. b) Isolated yield based on **1** used. In parenthsis, GC yield. c) Heptane was used as solvent. d) 2.4 mol amount of IF_5–Et_3N–3HF was used.

by GC, the reaction mixture was poured into ice-water and the product was extracted three times with ether. The combined ethereal phases were washed with aqueous $Na_2S_2O_3$, $NaHCO_3$, and brine and dried over $MgSO_4$. After concentration under reduced pressure, the product was isolated by column chlomatography (silica gel/hexane–ether).

Hexyl Difluoro(methylthio)acetate (3a). A clear liquid; ^{1}H NMR (400 MHz) δ 0.90 (3H, t, J = 6.8 Hz), 1.25–1.42 (6H, m), 1.69–1.76 (2H, m), 2.35 (3H, s), 4.30 (2H, t, J = 6.6 Hz); ^{19}F NMR (376 MHz) δ −86.32 (2F, s); IR (neat) 2961, 2935, 2861, 1769, 1468, 1293, 1123, 1001, 726 cm^{-1}; MS *m*/*z* (rel intensity) 226 (M^+, 5), 142 (10), 129 (16), 97 (24), 85 (23), 69 (7), 56 (19), 43 (100); HRMS (EI) Calcd for $C_9H_{16}F_2O_2S$: (M^+) 226.0839. Found: *m*/*z* 226.0846. Calcd for $C_9H_{16}F_2O_2S$: C, 47.77; H, 7.13; F, 16.79; S, 14.17%. Found: C, 47.61; H, 7.08; F, 16.69; S, 14.29%.

Ethyl Difluoro(phenylthio)acetate (3b).[4a,9a,9b] A clear liquid; ^{1}H NMR (400 MHz) δ 1.26 (3H, t, J =7.2 Hz), 4.25 (2H, q, J = 7.2 Hz), 7.38–7.49 (3H, m), 7.62 (2H, d, J = 7.1 Hz); ^{19}F NMR (376 MHz) δ −82.81 (2F, s); IR (neat) 2987, 1766, 1474, 1442, 1372, 1296, 1108, 1016, 978, 835, 753, 723, 690 cm^{-1}; MS *m*/*z* (rel intensity) 232 (M^+, 15), 159 (56), 139 (4), 109 (37), 96 (4), 91 (6), 82 (6), 77 (100), 69 (18), 65 (37), 51 (29), 45 (8); HRMS (EI) Calcd for $C_{10}H_{10}F_2O_2S$: (M^+) 232.0369. Found: *m*/*z* 232.0370.

Ethyl Fluoro(*p*-iodophenylthio)acetate (4b). A white solid; Mp 60 °C; ^{1}H NMR (400 MHz) δ 1.21 (3H, t, J = 7.2 Hz), 4.16 (2H, q, J = 7.2 Hz), 6.04 (1H, d, J = 51.7 Hz), 7.27 (2H, d, J = 9.0 Hz), 7.69 (2H, d, J = 8.3 Hz); ^{19}F NMR (376 MHz) δ −159.24 (1F, d, J = 51.7 Hz); IR (KBr) 2987, 1745, 1471, 1369, 1331, 1259, 1185, 1092, 1039, 1004, 944, 865, 802, 765, 621, 506 cm^{-1}; MS *m*/*z* (rel intensity) 470 (29), 340 (M^+, 91), 267 (57), 235 (51), 203 (10), 140 (100), 127 (14), 108 (93), 96 (18), 76 (45), 69 (39), 50 (37); HRMS (EI) Calcd for $C_{10}H_{10}FIO_2S$: (M^+) 339.9430. Found: *m*/*z* 339.9439.

Ethyl Difluoro(*p*-iodophenylthio)acetate (5b). A clear liquid; ^{1}H NMR (400 MHz) δ 1.29 (3H, t, J = 7.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 7.32 (2H, d, J = 8.5 Hz), 7.74 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −82.49 (2F, s); IR (neat) 2984, 2927, 1766, 1565, 1471, 1383, 1371, 1299, 1107, 1056, 1006, 977, 856, 815, 729, 698 cm^{-1}; MS *m*/*z* (rel intensity) 358 (M^+, 100), 285 (33), 264 (5), 235 (32), 203 (13), 158 (89), 108 (61), 76 (28), 50 (18); HRMS (EI) Calcd for $C_{10}H_9F_2IO_2S$: (M^+) 357.9336. Found: *m*/*z* 357.9349.

Ethyl (*p*-Chlorophenylthio)difluoroacetate (3c). A clear liquid; ^{1}H NMR (400 MHz) δ 1.30 (3H, t, J = 7.2 Hz), 4.29 (2H, q, J =7.2 Hz), 7.38 (2H, d, J = 8.3 Hz), 7.55 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −82.66 (2F, s); IR (neat) 2987, 1767, 1574, 1477, 1391, 1372, 1299, 1214, 1093, 1013, 978, 825, 748, 714, 702 cm^{-1}; MS *m*/*z* (rel intensity) 268 (M^+ + 2, 25), 266 (M^+, 68), 193 (100), 143 (69), 108 (82), 99 (20), 82 (17), 75 (23), 69 (18), 63 (15), 50 (14); HRMS (EI) Calcd for $C_{10}H_9ClF_2O_2S$: (M^+) 265.9980. Found: *m*/*z* 265.9992. Calcd for $C_{10}H_9ClF_2O_2S$: C, 45.04; H, 3.40; Cl, 13.29; F, 14.25; S, 12.02%. Found: C, 44.97; H, 3.45; Cl, 13.35; F, 14.43; S, 12.17%.

Ethyl (*p*-Chlorophenylthio)fluoroacetate (2c).[9i] A clear liquid; ^{1}H NMR (400 MHz) δ 1.21 (3H, t, J = 7.1 Hz), 4.16 (2H, q, J = 7.2 Hz), 6.03 (1H, d, J = 51.7 Hz), 7.34 (2H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −159.40 (1F, d, J = 51.7 Hz); IR (neat) 2984, 1758, 1574, 1477, 1390, 1370, 1325, 1272, 1187, 1095, 1013, 949, 859, 829, 744 cm^{-1}; MS *m*/*z* (rel intensity) 250 (M^+ + 2, 21), 248 (M^+, 55), 175 (100), 108 (18), 75 (12); HRMS (EI) Calcd for $C_{10}H_{10}ClFO_2S$: (M^+) 248.0074. Found: *m*/*z* 248.0093.

Ethyl 2-(*p*-Chlorophenylthio)-2-fluorobutanoate (2d). A clear liquid; ^{1}H NMR (400 MHz) δ 1.06 (3H, t, J = 7.3 Hz), 1.10 (3H, t, J = 7.1 Hz), 2.10–2.36 (2H, m), 3.97–4.08 (2H, m), 7.31 (2H, d, J = 8.5 Hz), 7.48 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −138.53 to −138.43 (1F, m); IR (neat) 2981, 1754, 1574, 1476, 1390, 1369, 1304, 1251, 1131, 1094, 1015, 972, 908, 826, 747, 718 cm^{-1}; MS *m*/*z* (rel intensity) 276 (M^+, 11), 256 (75), 210 (40), 203 (24), 183 (42), 175 (100), 147 (65), 139 (55), 108 (51), 103 (13), 75 (19), 71 (39), 57 (10), 45 (14), 39 (11); HRMS (EI)

Calcd for $C_{12}H_{14}ClFO_2S$: (M^+) 276.0387. Found: *m/z* 276.0405. Calcd for $C_{12}H_{14}ClFO_2S$: C, 52.08; H, 5.10; Cl, 12.81; F, 6.86; S, 11.59%. Found: C, 51.93; H, 5.11; Cl, 12.85; F, 6.86; S, 11.78%.

Methyl 2-(*p*-Chlorophenylthio)-2-fluoropropanoate (2e). A clear liquid; ^{1}H NMR (400 MHz) δ 1.91 (3H, d, J = 18.3 Hz), 3.60 (3H, s), 7.33 (2H, d, J = 8.5 Hz), 7.47 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −127.24 (1F, q, J = 18.3 Hz); IR (neat) 2953, 1759, 1573, 1476, 1442, 1390, 1283, 1128, 1091, 1014, 979, 911, 824, 747, 699 cm^{-1}; MS *m/z* (rel intensity) 250 (M^+ + 2, 19), 248 (M^+, 50), 189 (100), 108 (19), 40 (20); HRMS (EI) Calcd for $C_{10}H_{10}ClFO_2S$: (M^+) 248.0074. Found: *m/z* 248.0089. Calcd for $C_{10}H_{10}ClFO_2S$: C, 48.29; H, 4.05; Cl, 14.26; F, 7.64; S, 12.89%. Found: C, 48.29; H, 4.04; Cl, 14.28; F, 7.88; S, 13.10%.

2-(*p*-Chlorophenylthio)-2-fluoro-4-butanolide (2f). A white solid; Mp 71 °C; ^{1}H NMR (400 MHz) δ 2.55–2.60 (1H, m), 2.74–2.86 (1H, m), 4.32–4.45 (2H, m), 7.36 (2H, d, J = 8.5 Hz), 7.51 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −135.76 (1F, d, J = 15.9 Hz); IR (KBr) 1793, 1574, 1474, 1374, 1305, 1223, 1180, 1049, 1011, 947, 891, 822, 742, 675, 607, 495 cm^{-1}; MS *m/z* (rel intensity) 248 (M^+ + 2, 15), 246 (M^+, 40), 226 (100), 169 (74), 163 (55), 155 (20), 139 (47), 134 (65), 125 (60), 108 (49), 89 (14), 75 (41), 71 (32), 59 (22), 50 (20), 45 (18); HRMS (EI) Calcd for $C_{10}H_8ClFO_2S$: (M^+) 245.9917. Found: *m/z* 245.9914.

2-(*p*-Chlorophenylthio)-2-buten-4-olide (6f). A white solid, Mp 79–80 °C; ^{1}H NMR (400 MHz) δ 4.82–4.83 (2H, m), 6.72–6.73 (1H, m), 7.40 (2H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz); IR (KBr) 3087, 1758, 1477, 1438, 1390, 1343, 1280, 1156, 1093, 1050, 1008, 834, 821, 763, 727, 498 cm^{-1}; MS *m/z* (rel intensity) 228 (M^+ + 2, 37), 226 (M^+, 100), 169 (63), 139 (33), 134 (57), 125 (44), 108 (24), 75 (34), 71 (33); HRMS (EI) Calcd for $C_{10}H_7ClO_2S$: (M^+) 225. 9855. Found: *m/z* 225.9843.

2-(*p*-Chlorophenylthio)-2-fluoroacetamide (2g). A white solid, Mp 119 °C; ^{1}H NMR (400 MHz) δ 5.58 (1H, bs), 6.03 (1H, bs), 6.07 (1H, d, J = 52.7 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.53 (2H, d, J = 8.3 Hz); ^{19}F NMR (376 MHz) δ −155.46 (1F, d, J = 52.7 Hz); IR (KBr) 3415, 3177, 2946, 1671, 1474, 1408, 1241, 1092, 1001, 921, 824, 798, 657, 572, 511 cm^{-1}; MS *m/z* (rel intensity) 219 (M^+, 28), 175 (32), 143 (91), 108 (100), 75 (36), 63 (33), 44 (92); HRMS (EI) Calcd for $C_8H_7ClFNOS$: (M^+) 218.9921. Found: *m/z* 218.9913. Calcd for $C_8H_7ClFNOS$: C, 43.74; H, 3.21; Cl, 16.14; F, 8.65; N, 6.38; S, 14.60%. Found: C, 44.01; H, 3.38; Cl, 16.05; F, 8.56; N, 6.38; S, 14.81%.

2-(*p*-Chlorophenylthio)-2,2-difluoroacetamide (3g). A white solid, Mp 125–126 °C; ^{1}H NMR (400 MHz) δ 5.65 (1H, bs), 6.09 (1H, bs), 7.39 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −155.46 (2F, d, J = 52.7 Hz); IR (KBr) 3473, 3403, 3180, 1717, 1685, 1611, 1476, 1415, 1122, 1078, 1015, 983, 827, 795, 625, 505 cm^{-1}; MS *m/z* (rel intensity) 239 (M^+ + 2, 37), 237 (M^+, 100), 193 (76), 144 (80), 108 (56), 75 (22), 44 (55); HRMS (EI) Calcd for $C_8H_6ClF_2NOS$: (M^+) 236.9826. Found: *m/z* 236.9837.

***N*-Benzyl-2-(*p*-chlorophenylthio)-2-fluoroacetamide (2h).** A white solid, Mp 85 °C; ^{1}H NMR (400 MHz) δ 4.24 (1H, dd, J = 4.9, 14.6 Hz), 4.40 (1H, dd, J = 6.3, 14.6 Hz), 6.11 (1H, d, J = 52.0 Hz), 6.29 (1H, bs), 6.99–7.01 (2H, m), 7.26–7.33 (5H, m), 7.49 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −157.47 (1F, dd, J = 4.3, 52.0 Hz); IR (KBr) 3389, 1672, 1517, 1475, 1455, 1096, 1023, 984, 823, 799, 757, 720, 696, 614, 511, 472 cm^{-1}; MS *m/z* (rel intensity) 309 (M^+, 4), 166 (24), 143 (18), 108 (20), 91 (100), 65 (14); HRMS (EI) Calcd for $C_{15}H_{13}ClFNOS$: (M^+) 309.0390. Found: *m/z* 309.0393. Calcd for $C_{15}H_{13}ClFNOS$: C, 58.16; H, 4.23; Cl, 11.44; F, 6.13; N, 4.52; S, 10.30%. Found: C, 58.20; H, 4.37; Cl, 11.67; F, 6.31; N, 4.63; S, 10.50%.

***N*,*N*-Diisopropyl-2-(*p*-chlorophenylthio)-2,2-difluoroacetamide (3i).** A white solid, Mp 62–63 °C; ^{1}H NMR (400 MHz) δ 1.22 (6H, d, J = 6.59 Hz), 1.43 (6H, d, J = 6.83 Hz), 3.47–3.55 (1H, m), 4.40–4.46 (1H, m), 7.37 (2H, d, J = 8.5 Hz), 7.56 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −73.46 (2F, s); IR (KBr) 2974, 1653, 1573, 1444, 1376, 1347, 1146, 1093, 999, 897, 818, 787, 747, 608, 531, 504 cm^{-1}; MS *m/z* (rel intensity) 321 (M^+, 20), 193 (18), 128 (72), 108 (10), 86 (100), 43 (68); HRMS (EI) Calcd for $C_{14}H_{18}ClF_2NOS$: (M^+) 321.0765. Found: *m/z* 321.0774. Calcd for $C_{14}H_{18}ClF_2NOS$: C, 52.25; H, 5.64; Cl, 11.02; F, 11.81; N, 4.35; S, 9.96%. Found: C, 52.31; H, 5.60; Cl, 10.94; F, 11.78; N, 4.37; S, 9.99%.

***N*,*N*-Diisopropyl-2-(*p*-chlorophenylthio)-2-fluoroacetamide (2i).** A white solid, Mp 85 °C; ^{1}H NMR (400 MHz) δ 1.24 (3H, d, J = 6.3 Hz), 1.25 (3H, d, J = 6.3 Hz), 1.35 (3H, d, J = 6.8 Hz), 1.42 (3H, d, J = 6.8 Hz), 3.42–3.49 (1H, m), 4.16–4.22 (1H, m), 6.16 (1H, d, J = 55.9 Hz), 7.33 (2H, d, J = 8.3 Hz), 7.50 (2H, d, J = 8.3 Hz); ^{19}F NMR (376 MHz) δ −152.36 (1F, d, J = 55.9 Hz); IR (KBr) 2993, 1646, 1475, 1338, 1208, 1133, 1092, 1046, 1011, 933, 824, 788, 741, 635, 605 cm^{-1}; MS *m/z* (rel intensity) 303 (M^+, 3), 143 (37), 128 (45), 108 (41), 99 (10), 86 (59), 75 (12), 43 (100); HRMS (EI) Calcd for $C_{14}H_{19}ClFNOS$: (M^+) 303.0860. Found: *m/z* 303.0858. Calcd for $C_{14}H_{19}ClFNOS$: C, 55.34; H, 6.30; Cl, 11.67; F, 6.25; N, 4.61; S, 10.55%. Found: C, 55.47; H, 6.21; Cl, 11.63; F, 6.23; N, 4.71; S, 10.49%.

***N*-Butyl-2-(*p*-chlorophenylthio)-2-fluoroacetamide (2j).** A white solid, Mp 53 °C; ^{1}H NMR (400 MHz) δ 0.87 (3H, t, J = 7.3 Hz), 1.12–1.32 (4H, m), 3.05–3.24 (2H, m), 6.05 (1H, bs), 6.06 (1H, d, J = 52.2 Hz), 7.33 (2H, d, J = 8.5 Hz), 7.51 (2H, d, J = 8.3 Hz); ^{19}F NMR (376 MHz) δ −156.82 (1F, d, d J = 4.3, 52.2 Hz); IR (KBr) 3331, 2956, 2870, 1662, 1542, 1475, 1304, 1261, 1093, 1002, 977, 831, 805, 729, 701cm^{-1}; MS *m/z* (rel intensity) 275 (M^+, 22), 176 (20), 143 (56), 108 (53), 100 (55), 75 (15), 57 (100), 43 (49); HRMS (EI) Calcd for $C_{12}H_{15}ClFNOS$: (M^+) 275.0547. Found: *m/z* 275.0550. Calcd for $C_{12}H_{15}ClFNOS$: C, 52.26; H, 5.48; Cl, 12.86; F, 6.89; N, 5.08; S, 11.63%. Found: C, 52.18; H, 5.41; Cl, 12.83; F, 6.88; N, 5.18; S, 11.62%.

***N*-Butyl-2-(*p*-chlorophenylthio)-2,2-difluoroacetamide (3j).** A white solid, Mp 44 °C; ^{1}H NMR (400 MHz) δ 0.92 (3H, t, J = 7.3 Hz), 1.25–1.34 (2H, m), 1.43–1.50 (2H, m), 3.28 (2H, q, J = 6.8 Hz), 6.12 (1H, bs), 7.38 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −82.8 (2F, s); IR (KBr) 3311, 2957, 1678, 1544, 1475, 1308, 1092, 1035, 1014, 987, 930, 822 cm^{-1}; MS *m/z* (rel intensity) 293 (M^+, 49), 193 (18), 144 (30), 111 (13), 100 (55), 57 (100), 41 (19); HRMS (EI) Calcd for $C_{12}H_{14}ClF_2NOS$: (M^+) 293.0426. Found: *m/z* 293.0439. Calcd for $C_{12}H_{14}ClF_2NOS$: C, 49.06; H, 4.80; Cl, 12.07; F, 12.93; N, 4.77; S, 10.92%. Found: C, 48.94; H, 4.69; Cl, 12.21; F, 13.07; N, 4.87; S, 10.93%.

(*p*-Chlorophenylthio)fluoromethane (2k).[15] A clear liquid; ^{1}H NMR (400 MHz) δ 5.69 (2H, d, J = 52.7 Hz), 7.32 (2H, d, J = 8.5 Hz), 7.43 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −182.84 (1F, t, J = 52.7 Hz); IR (neat) 2943, 1895, 1637, 1574, 1478, 1429, 1390, 1322, 1232, 1096, 1013, 965, 818, 747, 731cm^{-1}; MS *m/z* (rel intensity) 176 (M^+, 100), 143 (65), 108 (76).

(Phenylthio)fluoromethane (2l).[9f] A clear liquid; ^{1}H NMR (400 MHz) δ 5.37 (2H, d, J = 52.9 Hz), 7.29–7.51 (5H, m); ^{19}F NMR (376 MHz) δ −182.25 (1F, t, J = 52.9 Hz); IR (neat) 3061,

2942, 1732, 1585, 1482, 1441, 1320, 1234, 1086, 1070, 1026, 960, 741, 691cm^{-1}; MS *m/z* (rel intensity) 142 (M^+, 100), 123 (37), 109 (51), 65 (35).

2,2-Difluoro-2-(methylthio)acetophenone (3m).[6b] A clear liquid; ^{1}H NMR (400 MHz) δ 2.37 (3H, s), 7.49–8.15 (5H, m); ^{19}F NMR (376 MHz) δ −82.31 (2F, s); IR (neat) 2936, 1704, 1598, 1449, 1270, 1133, 1063, 1004, 882, 831, 713, 686, 669, 637 cm^{-1}; MS *m/z* (rel intensity) 202 (M^+, 5), 105 (100), 77 (37); HRMS (EI) Calcd for $C_9H_8F_2OS$: (M^+) 202.0264. Found: *m/z* 202.0266.

2,2-Difluoro-2-(phenylthio)acetophenone (3n).[9a] A clear liquid; ^{1}H NMR (400 MHz) δ 7.37–8.14 (10H, m); ^{19}F NMR (376 MHz) δ −77.83 (2F, s); IR (neat) 1704, 1598, 1474, 1449, 1272, 1214, 1132, 1058, 1028, 986, 888, 825, 750, 712, 688, 642 cm^{-1}; MS *m/z* (rel intensity) 264 (M^+, 9), 105 (100), 77 (29); HRMS (EI) Calcd for $C_{14}H_{10}F_2OS$: (M^+) 264.0420. Found: *m/z* 264.0426.

1-(*p*-Chlorophenylthio)-1,1-difluoro-3,3-dimethyl-2-butanone (3o). A clear liquid; ^{1}H NMR (400 MHz) δ 1.29 (9H, s), 7.37 (2H, d, J = 8.5 Hz), 7.53 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −77.61 (2F, s); IR (neat) 2975, 1722, 1574, 1477, 1390, 1370, 1169, 1096, 1042, 1014, 863, 823, 786, 747 cm^{-1}; MS *m/z* (rel intensity) 280 (M^+ + 2, 17), 278 (M^+, 44), 193 (20), 143 (35), 108 (45), 85 (65), 57 (100), 41 (59); HRMS (EI) Calcd for $C_{12}H_{13}ClF_2OS$: (M^+) 278.0344. Found: *m/z* 278.0352. Calcd for $C_{12}H_{13}ClF_2OS$: C, 51.71; H, 4.70; Cl, 12.72; F, 13.63; S, 11.50%. Found: C, 51.47; H, 4.60; Cl, 12.76; F, 13.47; S, 11.71%.

1-(*p*-Chlorophenylthio)-1-fluoro-3,3-dimethyl-2-butanone (2o). A clear liquid; ^{1}H NMR (400 MHz) δ 1.24 (9H, s), 6.29 (1H, d, J = 54.2 Hz), 7.34 (2H, d, J = 8.5 Hz), 7.48 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −157.40 (1F, d, J = 54.2 Hz); IR (neat) 2974, 1718, 1574, 1476, 1390, 1367, 1331, 1224, 1095, 1011, 960, 865, 823, 793, 744 cm^{-1}; MS *m/z* (rel intensity) 260 (M^+, 23), 175 (11), 108 (14), 57 (100); HRMS (EI) Calcd for $C_{12}H_{14}ClFOS$: (M^+) 260.0438. Found: *m/z* 260.0421. Calcd for $C_{12}H_{14}ClFOS$: C, 55.27; H, 5.41; Cl, 13.60; F, 7.29; S, 12.30%. Found: C, 55.16; H, 5.41; Cl, 13.49; F, 7.36; S, 12.50%.

2-(Ethylthio)-2,2′,4′-tetrafluoroacetophenone (3p).[6b] A clear liquid; ^{1}H NMR (400 MHz) δ 1.37 (3H, t, J = 7.6 Hz), 2.92 (2H, q, J = 7.6 Hz), 6.91–7.02 (2H, m), 7.95–8.01 (1H, m); ^{19}F NMR (376 MHz) δ −82.7 (2F, d, J = 13.4 Hz), −99.4 to −99.5 (1F, m), −102.3 to −102.5 (1F, m); IR (neat) 2936, 1713, 1612, 1501, 1430, 1309, 1269, 1133, 1104, 1062, 1002, 975, 876, 857, 820, 743 cm^{-1}; MS *m/z* (rel intensity) 252 (M^+, 2), 192 (22), 141 (100), 113 (58), 63 (22); HRMS (EI) Calcd for $C_{10}H_8F_4OS$: (M^+) 252.0230. Found: *m/z* 252.0231.

(*p*-Chlorophenylthio)fluoroacetonitrile (2q). A clear liquid; ^{1}H NMR (400 MHz) δ 6.18 (1H, d, J = 48.8 Hz), 7.43 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −153.90 (1F, d, J = 48.8 Hz); IR (neat) 3088, 2955, 2252, 1906, 1644, 1574, 1477, 1390, 1264, 1238, 1095, 1014, 939, 824, 753, 732 cm^{-1}; MS *m/z* (rel intensity) 203 (M^+ + 2, 20), 201 (M^+, 53), 143 (100); HRMS (EI) Calcd for C_8H_5ClFNS: (M^+) 200.9815. Found: *m/z* 200.9798. Calcd for C_8H_5ClFNS: C, 47.65; H, 2.50; Cl, 17.58; F, 9.42; N, 6.95; S, 15.90%. Found: C, 47.43; H, 2.60; Cl, 17.60; F, 9.66; N, 6.95; S, 16.11%.

(Methylthio)difluoromethyl *p*-Tolyl Sulfone (3r). A white solid, Mp 49–50 °C; ^{1}H NMR (400 MHz) δ 2.49 (3H, s), 2.53 (3H, s), 7.42 (2H, d, J = 8.1 Hz), 7.88 (2H, d, J = 8.1 Hz); ^{19}F NMR (376 MHz) δ −83.83 (2F, s); IR (KBr) 3066, 1593, 1440, 1343, 1164, 1100, 993, 912, 810, 704, 653 cm^{-1}; MS *m/z* (rel intensity) 252 (M^+, 0.5), 139 (100), 97 (99), 91 (45), 65 (34), 51 (6), 45 (10); HRMS (Fab) Calcd for $C_9H_{10}F_2NaO_2S_2$: (M^+ + Na) 274.9988. Found: *m/z* 275.0010. Calcd for $C_9H_{10}F_2O_2S_2$: C, 42.84; H, 3.99; F, 15.06; S, 25.42%. Found: C, 43.06; H, 3.92; F, 15.05; S, 25.60%.

1-(*p*-Chlorophenylthio)-1,2,2,2-tetrafluoroethane (2s).[9f] A clear liquid; ^{1}H NMR (400 MHz) δ 5.78 (1H, dq, J = 50.0, 6.1 Hz), 7.37 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.5 Hz); ^{19}F NMR (376 MHz) δ −76.8 (3F, dd, J = 6.1, 15.9 Hz), −167.14 (1F, dq, J = 50.0, 15.9 Hz); IR (neat) 1904, 1576, 1477, 1392, 1351, 1276, 1194, 1134, 1096, 1014, 873, 828, 779, 746, 705, 692 cm^{-1}; MS *m/z* (rel intensity) 244 (M^+, 100), 175 (26), 143 (88), 108 (39), 75 (12), 69 (11), 43 (10); HRMS (EI) Calcd for $C_8H_5ClF_4S$: (M^+) 243.9737. Found: *m/z* 243.9732. Calcd for $C_8H_5ClF_4S$: C, 39.28; H, 2.06; Cl, 14.49; F, 31.06; S, 13.11%. Found: C, 39.07; H, 2.10; Cl, 14.37; F, 30.95; S, 13.39%.

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