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HCF_2Se/HCF_2S Installation by Tandem Substitutions from Alkyl Bromides

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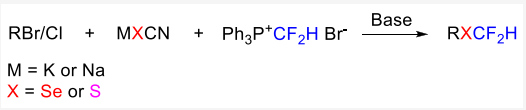
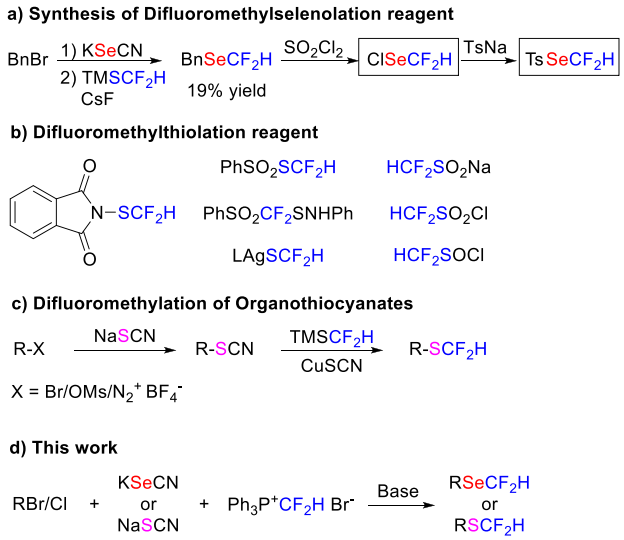
ABSTRACT: Herein we describe an efficient construction of HCF_2Se and HCF_2S groups by tandem substitutions between alkyl bromides and a reagent system consisting of MSeCN (or MSCN) and $Ph_3P^+CF_2H\ Br^-$. The tandem process occurs via the first nucleophilic substitution of alkyl bromides by −SeCN (or −SCN) and the subsequent nucleophilic difluoromethylation.



Fluorine-containing compounds play a significant role in pharmaceutical chemistry, agrochemical chemistry and material sciences, as the introduction of fluorinated groups into organic molecules can significantly improve their physical, chemical and biological properties. Among various fluorinated groups, difluoromethylchalcogen groups including difluoromethylseleno (HCF_2Se) and difluoromethylthio (HCF_2S) are of great interest because they can act as a mild hydrogen donor and show intermediate lipophilicity and a strong electron-withdrawing nature.[1] In recent years, numerous biologically active molecules containing difluoromethylthio units have appeared, such as Flomoxef, which is an oxacephem antibiotic.[2] Therefore, developing efficient methods for the incorporation of HCF_2Se or HCF_2S into organic molecules is of continuous interest.

Two strategies for HCF_2Se and HCF_2S installation have been well established, difluoromethylation of selenium[3] or sulfur-containing[4] compounds and direct difluoromethylselenolation[5] or difluoromethylthiolation.[6] Direct difluoromethylselenolation is highly efficient, but only two reagents have been developed, HCF_2SeCl and $TsSeCF_2H$ (Scheme 1, eq a). Billard reported that HCF_2SeCl could be generated in situ from $BnSeCF_2H$ by oxidative chlorination, and HCF_2SeCl was used to achieve electrophilic difluoromethylselenolation of various substrates, such as arenes,[5a] carbonyls,[5b] alkenes[5c] and alkynes.[5d,e] Additionally, Zhao developed a shelf-stable difluoromethylselenolation reagent, $TsSeCF_2H$, allowing for difluoromethylselenolation of aryl amines,[5f] aryl boronic acid[5g] and aldehydes.[5h] Apparently, the HCF_2Se installation methods are attractive, but the synthesis of the reagents requires tedious procedures and only a low yield was obtained for the preparation of a precursor, $BnSeCF_2H$ (19%). For HCF_2S installation, outstanding accomplishments have been achieved,[4,6] and many difluoromethylthiolation reagents[7] have been developed (Scheme 1, eq b). In 2015, Goossen developed an elegant two-step procedure for the installation of a HCF_2S group (Scheme 1, eq c).[4a] Organothiocyanates (RSCN) were prepared first, and the subsequent difluoromethylation of RSCN with $TMSCF_2H$ promoted by a stoichiometric copper complex led to the final construction of the HCF_2S group.

Scheme 1. Installation of HCF_2Se and HCF_2S Groups



We recently disclosed that electrophilic phosphonium salts can act as nucleophilic reagents in the presence of Cs_2CO_3.[8] Phosphonium salts have found widespread applications in organic synthesis,[9] and we found that difluoromethyl phosphonium salt $[Ph_3P^+CF_2H\ Br^-]$ could be considered as a $[HCF_2^-]$ equivalent, and thus this salt was used as a nucleophilic difluoromethylation reagent.[8a] Herein we describe the use of this reagent in the installation of HCF_2Se and

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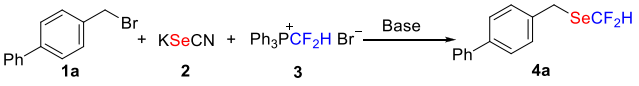
HCF_2S groups by tandem substitutions from alkyl bromides (Scheme 1, eq d). Stirring the mixture of alkyl bromides with $[Ph_3P^+CF_2H\ Br^-]$/KSeCN (or NaSCN) in the presence of Cs_2CO_3 smoothly provided the desired HCF_2Se-products (or HCF_2S-products). Moderate to good yields were obtained under mild conditions without the use of any transition metal for HCF_2Se installation, and the use of a catalytic amount of Ag_2CO_3 could give the HCF_2S-products in good yields.

Our initial attempt at the tandem reaction between substrate **1a** with KSeCN/$[Ph_3P^+CF_2H\ Br^-]$ did occur in the presence of Cs_2CO_3 in spite of a low yield (Table 1, entry 1). Other

Table 1. Optimization of Reaction Conditions[a]



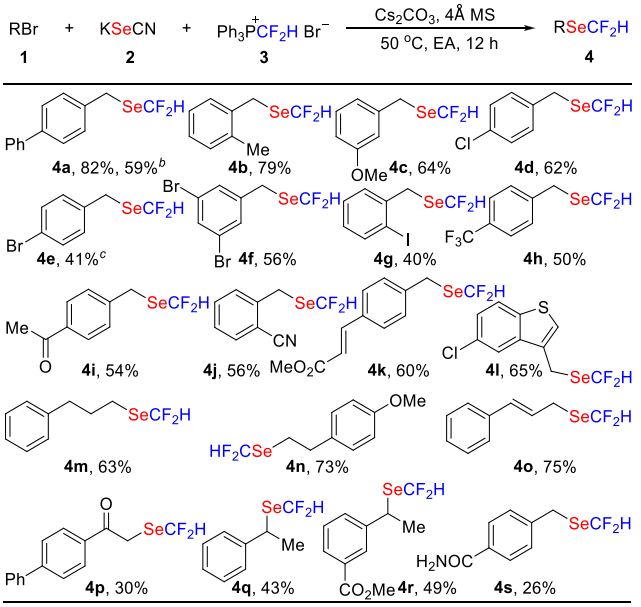
Entry	Base	Temp (°C)	Solvent (mL)	Yield (%)[b]
1	Cs_2CO_3	40	DMAc (2)	34
2	K_2CO_3	40	DMAc (2)	33
3	Na_2CO_3	40	DMAc (2)	29
4	$CsHCO_3$	40	DMAc (2)	27
5	CsF	40	DMAc (2)	10
6	Cs_2CO_3	40	EA (2)	52
7	Cs_2CO_3	40	DME (2)	50
8	Cs_2CO_3	40	MeCN (2)	29
9	Cs_2CO_3	40	DCM (2)	31
10	Cs_2CO_3	30	EA (2)	45
11	Cs_2CO_3	50	EA (2)	58
12	Cs_2CO_3	60	EA (2)	23
13	Cs_2CO_3	50	EA (3)	44
14	Cs_2CO_3	50	EA (1)	59
15[c]	Cs_2CO_3	50	EA (1)	83

[a]Reaction conditions: Substrate **1a** (0.2 mmol), **2** (0.24 mmol), **3** (0.6 mmol), and base (0.4 mmol) in solvent were heated for 12 h. [b]The yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c]50 mg 4 Å MS were added.

inorganic bases were also effective, but Cs_2CO_3 was found to be a superior choice (entries 1−5). Various reaction solvents were briefly surveyed (entries 6−9), and ethyl acetate (EA) seemed to be a suitable solvent (entry 6). The reaction temperature also played an important role (entries 10−12), and a moderate yield was obtained at 50 °C (entry 11). The yield was significantly increased by increasing the concentration and adding 4 Å MS (entry 15).

With the optimal reaction conditions in hand (Table 1, entry 15), we then investigated the substrate scope of the tandem reaction for the HCF_2Se installation. As shown in Scheme 2, the tandem process could be extended to a wide range of alkyl bromides, such as benzyl-, allyl-, and inert alkyl-bromides, α-carbonyl methyl-bromides, and secondary bromides. All reactions proceeded smoothly simply by stirring the mixture of RBr with $[Ph_3P^+CF_2H\ Br^-]$/KSeCN in the presence of Cs_2CO_3. The substitutions including halide, trifluoromethyl, carbonyl, cyano, and ester on the phenyl ring in benzyl bromides were all tolerated, and the reaction delivered the target products in moderate to excellent yields (**4a**−**4l**). Benzyl chlorides were less reactive (**4e**). Inert alkyl bromides showed high reactivity, and good yields were obtained (**4m**−**4n**). In the case of secondary bromides, the strong steric effects led to lower yields (**4q**−**4r**).

Scheme 2. Tandem Reactions for the Installation of HCF_2Se Group[a]



[a]Reaction conditions: substrate **1** (0.5 mmol), **2** (1.2 equiv), **3** (3.0 equiv), Cs_2CO_3 (2.0 equiv) and 4 Å molecular sieve (125 mg) in EA (2.5 mL) at 50 °C under a N_2 atmosphere for 12 h. [b]A 59% yield was obtained for a 1 mmol-scale reaction (1 mmol of **1a**). [c]Benzyl chloride was used instead of benzyl bromide.

The successful HCF_2Se incorporation prompted us to extend the tandem process to the installation of a HCF_2S group (Scheme 3). The use of NaSCN instead of KSeCN under similar conditions can only afford the desired HCF_2S-product (**6a**) in a 27% yield. To our delight, the yield was increased to 83% in DMAc by adding $[Ph_3P^+CF_2H\ Br^-]$ dropwise and using Ag_2CO_3 (0.2 equiv) as an additive. (For reaction conditions screened, please see the Supporting Information.) Under the optimal conditions, a variety of benzyl bromides could be well converted to give the expected products (**6a**−**6k**). Secondary bromides also exhibited low reactivity (**6l**). For the conversions of inert alkyl bromides, good yields still could be obtained by first stirring the RBr/NaSCN mixture and then adding $[Ph_3P^+CF_2H\ Br^-]$ dropwise (**6m**−**6q**). Various functional groups could be tolerated, such as ether, chloro, bromo, ester, carboxyl, keto, nitro and cyano groups, demonstrating good synthetic utility of this approach.

Based on the above results and our previous studies on nucleophilic reactions with phosphonium salts,[8] we propose that the reactions may proceed via a tandem process, including the first nucleophilic substitution of alkyl bromides RBr with KSeCN (or NaSCN) to give RXCN (X = Se or S) and the subsequent nucleophilic difluoromethylation of RXCN with phosphonium salt $[Ph_3P^+CF_2H\ Br^-]$ initiated by Cs_2CO_3 to afford the final products (Scheme 4). Indeed, the use of the deuterated salt, $[Ph_3P^+CF_2D\ Br^-]$, delivered the corresponding product (Scheme 5), suggesting that the CF_2H group is directly transferred without the cleavage of the CF_2−H bond.

In summary, we have developed an efficient protocol for the installation of HCF_2Se and HCF_2S groups by a tandem substitution process. The reactions between alkyl bromides RBr and $[Ph_3P^+CF_2H\ Br^-]$/KSeCN (or NaSCN) occurred smoothly to provide the expected products in moderate to

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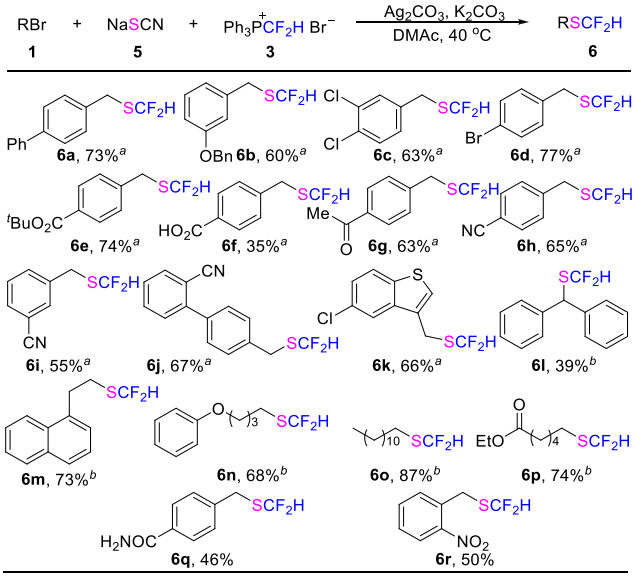
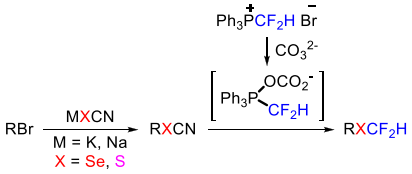
Scheme 3. Installation of HCF_2S Group[a]

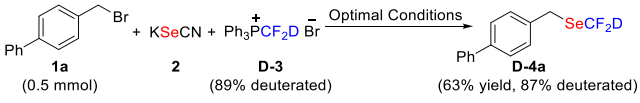


[a]Reaction conditions of Method a for benzyl bromides: The solution of **3** (1.5 mmol) in 5 mL DMAc was added dropwise via a syringe for 1.25 h at 40 °C into the mixture of substrate **1** (0.5 mmol), **5** (0.6 mmol), K_2CO_3 (1.0 mmol), and Ag_2CO_3 (0.1 mmol) in DMAc (0.2 mL). [b]Reaction conditions of Method b for secondary bromides and alkyl bromides: Substrate **1** (0.5 mmol), **5** (0.6 mmol), K_2CO_3 (1.0 mmol), and Ag_2CO_3 (0.1 mmol) in DMAc (0.2 mL) at 60 °C heat for 2 h. The solution of **3** (1.5 mmol) in 5 mL DMAc was added dropwise via a syringe for 1.25 h.

Scheme 4. Proposed Mechanism



Scheme 5. Evidence for Direct Difluoromethylation



good yields. Convenient operations and mild reaction conditions may make this installation protocol attractive.

EXPERIMENTAL SECTION

General Experimental Methods. ^1H, ^{13}C and ^{19}F NMR spectra were detected on a 500 MHz or 400 MHz NMR spectrometer. Data for ^1H 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-MSorLC-MS (ESI). High resolution mass data were recorded on a high resolution mass spectrometer in the EI, ESI or DART mode. The mass analyzer types for HRMS-EI, HRMS-ESI and HRMS-DART are time-of-flight, Fourier transform mass spectrometer and Fourier transform ion cyclotron resonance, respectively. Infrared spectroscopy was performed on a Thermo Scientific Nicolet iS5. Melting points were measured by DSC Q2000. The reactions are all carried out in dry solvents. Unless otherwise noted, the **1**, **2**, **5** series of compounds were obtained commercially and used without further purification. Compounds **1s** and **3** were synthesized according to literature methods.[10,8a]

*4-(Bromomethyl)benzamide (**1s**).* ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.58 (s, 2H). HRMS (ESI) m/z: $[M + H]^+$ calcd for C_8H_9BrNO 213.9862; found 213.9863.

*(Difluoromethyl)triphenylphosphonium Bromide (**3**).* ^1H NMR (400 MHz, CD_3OD) δ 8.25 (td, J = 47.2, 29.9 Hz, 1H), 8.13−8.05 (m, 3H), 8.00−7.87 (m, 12H). ^{19}F NMR (376 MHz, CD_3OD) δ −127.12 (dd, J = 77.7, 47.2 Hz, 2F). ^{31}P NMR (162 MHz, CD_3OD) δ 19.20 (t, J = 77.8 Hz, 1P).

*(Ddifluoromethyl)triphenylphosphonium Bromide (**D-3**).* ^1H NMR (400 MHz, CD_3CN) δ 8.04−7.96 (m, 3H), 7.96−7.87 (m, 6H), 7.80 (m, 6H). ^{19}F NMR (376 MHz, CD_3CN) δ −128.06 (dt, J = 78.2, 7.1 Hz, 2F). ^{31}P NMR (162 MHz, CD_3CN) δ 19.17 (tt, J = 78.0, 4.3 Hz, 1P).

General Procedures for the HCF_2Se Installation. Into a 15 mL Schlenk tube were added $Ph_3P^+CF_2H$ Br^- (589.8 mg, 1.5 mmol, 3.0 equiv), KSeCN (86.4 mg, 0.6 mmol, 1.2 equiv), Cs_2CO_3 (325.8 mg, 1.0 mmol, 2.0 equiv), 4 Å molecular sieve (125 mg) and EA (2.5 mL) under a N_2 atmosphere. Then alkyl bromides (0.5 mmol, 1.0 equiv) or alkyl chloride (**1e**) was added. The resulting mixture was stirred at 50 °C (oil bath) for 12 h under a N_2 atmosphere. When the reaction was completed, as monitored by ^{19}F NMR spectroscopy, the crude reaction mixture was diluted with EA (20 mL). The solution was washed with water (20 mL) and brine (20 mL), and then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to flash column chromatography to give the final product **4**.

*([1,1′-Biphenyl]-4-ylmethyl)(difluoromethyl)selane (**4a**).* Eluent: petroleum ether/ethyl acetate (100:1). For the 1-mmol-scale reaction, all loadings of each reagent and the reaction solvent were doubled. Stirring the mixture for 12 h gave a 59% yield (175.4 mg). Yellow oil, 121.4 mg, 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 13.9, 2H), 7.60 (d, J = 13.9, 2H), 7.52−7.36 (m, 5H), 7.14 (t, J = 55.1 Hz, 1H), 4.18 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.74 (d, J = 55.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.6 (s), 140.4 (s), 136.5 (s), 129.5 (s), 128.9 (s), 127.6 (s), 127.5 (s), 127.1 (s), 115.8 (t, J = 287.1 Hz), 26.1 (t, J = 2.7 Hz). IR (KBr): 3029, 2965, 1488, 1294, 1278, 1058, 845, 765, 696 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{12}F_2{}^{74}Se$ 292.0127; found 292.0130.

*(Difluoromethyl)(2-methylbenzyl)selane (**4b**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 93.1 mg, 79% yield. ^1H NMR(400 MHz, $CDCl_3$)) δ 7.26 (d, J = 6.7 Hz, 1H), 7.22−7.13 (m, 3H), 7.09 (t, J = 55.1 Hz, 1H), 4.13 (s, 2H), 2.41 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.81 (d, J = 55.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.7 (s), 134.9 (s), 130.9 (s), 129.8 (s), 127.9 (s), 126.4 (s), 115.8 (t, J = 286.8 Hz), 24.4 (t, J = 2.8 Hz), 19.2 (s). IR (KBr): 3019, 2971, 1294, 1277, 1057, 763 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_{10}F_2{}^{74}Se$ 229.9970; found 229.9978.

*(Difluoromethyl)(3-methoxybenzyl)selane (**4c**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 80.5 mg, 64% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 6.0 Hz, 1H), 7.14 (t, J = 55.1 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 4.06 (s, 2H), 3.80 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.97 (d, J = 55.2 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.9 (s), 138.9 (s), 129.9 (s), 121.3 (s), 115.7 (t, J = 286.8 Hz), 114.6 (s), 113.0 (s), 55.3 (s), 26.3 (t, J = 2.9 Hz). IR (KBr): 2960, 2836, 1600, 1488, 1265, 1042, 695 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_{10}F_2O^{74}Se$ 245.9919; found 245.9935.

*(4-Chlorobenzyl)(difluoromethyl)selane (**4d**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 79.2 mg, 62% yield. ^1H NMR(400 MHz, $CDCl_3$) δ 7.30−7.23 (m, 4H), 7.07 (t, J = 55.0 Hz, 1H), 4.05 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.72 (d, J = 55.0 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.1 (s), 133.3 (s), 130.4 (s), 129.1 (s), 115.5 (t, J = 287.4 Hz), 25.5 (t, J = 3.0 Hz). IR (KBr): 2966, 1596, 1491, 1094, 832 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_8H_7{}^{35}ClF_2{}^{74}Se$ 249.9424; found 249.9424.

*(4-Bromobenzyl)(difluoromethyl)selane (**4e**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 62.2 mg, 41% yield. ^1H NMR

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(400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.1 Hz, 2H), 7.08 (t, J = 55.0 Hz, 1H), 4.05 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$)) δ −92.70 (d, J = 55.0 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.6 (s), 132.0 (s), 130.7 (s), 121.3 (s), 115.5 (t, J = 287.6 Hz), 25.5 (t, J = 2.9 Hz). IR (KBr): 2966, 1590, 1487, 1294, 1277, 1068, 1011, 828 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_8H_7{}^{79}BrF_2{}^{74}Se$ 293.8919; found 293.8918.

*(3,5 Dibromobenzyl)(difluoromethyl)selane (**4f**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 106.6 mg, 56% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, J = 1.6 Hz, 1H), 7.45 (d, J = 1.7 Hz, 2H), 7.15 (t, J = 54.7 Hz, 1H), 4.02 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.30 (d, J = 54.8 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.6 (s), 133.1 (s), 130.8 (s), 123.1 (s), 115.1 (t, J = 288.4 Hz), 24.5 (t, J = 3.1 Hz). IR (KBr): 2863, 1583, 1554, 1058, 857, 742, 680 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_8H_6{}^{79}Br_2F_2{}^{74}Se$ 371.8029; found 371.8028.

*(Difluoromethyl)(2-iodobenzyl)selane (**4g**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 69.5 mg, 40% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 54.1 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 4.19 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.39 (d, J = 55.0 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.8 (s), 140.0 (s), 130.0 (s), 129.2 (s), 128.8 (s), 115.6 (t, J = 287.6 Hz), 100.7 (s), 32.0 (t, J = 2.9 Hz). IR (KBr): 2917, 2849, 1469, 1293, 1275, 1057, 755 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_8H_7F_2I^{74}Se$ 341.8780; found 341.8779.

*(Difluoromethyl)(4-(trifluoromethyl)benzyl)selane (**4h**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 72.9 mg, 50% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.11 (t, J = 54.9 Hz, 1H), 4.13 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$ δ −62.63 (s, 3F), −92.63 (d, J = 54.8 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.9 (s), 129.7 (q, J = 32.5 Hz), 129.4 (s), 125.9 (q, J = 3.8 Hz), 124.1 (q, J = 272.0 Hz), 115.3 (t, J = 287.8 Hz), 25.4 (t, J = 3.1 Hz). IR (KBr): 2966, 1618, 1417, 1326, 1066, 849 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_7F_5{}^{74}Se$ 283.9688; found 283.9695.

*1-(4-(((Difluoromethyl)selanyl)methyl)phenyl)ethanone (**4i**).* Eluent: petroleum ether/ethyl acetate (10:1). Yellow oil, 70.7 mg, 54% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.09 (t, J = 54.9 Hz, 1H), 4.11 (s, 2H), 2.57 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$)) δ −92.57 (d, J = 54.9 Hz, 2F). $^{13}C\{^1H\}$ NMR(101 MHz, $CDCl_3$) δ 197.5 (s), 143.2 (s), 136.2 (s), 129.2 (s), 128.9 (s), 115.4 (t, J = 287.7 Hz), 26.6 (s), 25.6 (t, J = 3.0 Hz). IR (KBr): 1682, 1605, 1268, 1058, 848 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_{10}F_2O^{74}Se$ 257.9919; found 257.9931.

*2-(((Difluoromethyl)selanyl)methyl)benzonitrile (**4j**).* Eluent: petroleum ether/ethyl acetate (10:1). Yellow oil, 68.8 mg, 56% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.7 Hz, 1H), 7.53 (td, J = 7.7, 1.2 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.35 (td, J = 7.6, 0.9 Hz, 1H), 7.18 (t, J = 54.8 Hz, 1H), 4.24 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.12 (d, J = 54.8 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.3 (s), 133.3 (s), 133.2 (s), 130.2 (s), 128.0 (s), 117.3 (s), 115.4 (t, J = 288.3 Hz), 112.4 (s), 23.7 (t, J = 3.2 Hz). IR (KBr): 2926, 2853, 2226, 1487, 1293, 1057, 766 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_7F_2N^{74}Se$ 240.9766; found 240.9775.

*(E)-Methyl 3-(4-(((difluoromethyl)selanyl)methyl)phenyl)acrylate (**4k**).* Eluent: petroleum ether/ethyl acetate (10:1). Yellow oil, 92.1 mg, 60% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 55.0 Hz, 1H), 6.41 (d, J = 16.0 Hz, 1H), 4.08 (s, 2H), 3.79 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.65 (d, J = 55.0 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.3 (s), 144.1 (s), 134.0 (s), 133.5 (s), 129.5 (s), 128.5 (s), 118.0 (s), 115.5 (t, J = 287.4 Hz), 51.7 (s), 25.8 (t, J = 3.0 Hz). IR (KBr): 2951, 2842, 1716, 1638, 1436, 1327, 1171, 1059, 982, 830 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{12}H_{12}F_2O_2{}^{74}Se$ 300.0025; found 300.0040.

*5-Chloro-3-(((difluoromethyl)selanyl)methyl)benzo[b]thiophene (**4l**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 101.9 mg, 65% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.40 (s, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 55.2 Hz, 1H), 4.27 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.17 (d, J = 54.7 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.81 (s), 138.80 (s), 130.9 (s), 130.7 (s), 126.8 (s), 125.3 (s), 124.1 (s), 121.7 (s), 115.6 (t, J = 287.5 Hz), 18.3 (t, J = 3.4 Hz). IR (KBr): 3094, 2926, 1421, 1292,1078, 1056, 834, 775 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_7{}^{35}ClF_2S^{74}Se$ 305.9145; found 305.9155.

*(Difluoromethyl)(3-phenylpropyl)selane (**4m**).*[3e] Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 78.9 mg, 63% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 2H), 7.25−7.18 (m, 3H), 7.17 (t, J = 55.0 Hz, 1H), 2.89 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.5 Hz, 2H), 2.17−2.06 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.21 (d, J = 55.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.9 (s), 128.6 (s), 126.2 (s), 115.5 (t, J = 286.6 Hz), 35.7 (s), 32.4 (s), 22.3 (t, J = 2.5 Hz). IR (KBr): 3027, 2937, 2855, 1603, 1496, 1279, 1060, 745, 699 cm^{-1}.HRMS (EI) m/z: $[M]^+$calcd for $C_{10}H_{12}F_2{}^{74}Se$ 244.0127; found 244.0127.

*(Difluoromethyl)(4-methoxyphenethyl)selane (**4n**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 96.4 mg, 73% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 2H), 7.09 (t, J = 55.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 3.81 (s, 3H), 3.07 (t, J = 6.2 Hz, 2H), 3.05 (t, J = 6.1 Hz, 2H). ^{19}F NMR(376 MHz, $CDCl_3$) δ −91.47 (d, J = 55.2 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5 (s), 132.5 (s), 129.5 (s), 115.4 (t, J = 286.7 Hz), 114.1 (s), 55.3 (s), 36.5 (s), 24.3 (t, J = 2.3 Hz). IR (KBr): 3000, 2937, 2836, 1611, 1512, 1058, 1034, 819 cm^{-1}.HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_{12}F_2O^{74}Se$ 260.0076; found 260.0088.

*Cinnamyl(difluoromethyl)selane (**4o**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 93.2 mg, 75% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.31 (m, 4H), 7.28 (d, J = 5.3 Hz, 1H), 7.14 (t, J = 55.2 Hz, 1H), 6.53 (d, J = 15.7 Hz, 1H), 6.36 (dt, J = 15.6, 7.7 Hz, 1H), 3.70 (d, J = 7.7 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.90 (d, J = 55.2 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.3 (s), 133.0 (s), 128.7 (s), 128.0 (s), 126.5 (s), 125.1 (s), 116.0 (t, J = 286.5 Hz), 25.4 (t, J = 2.7 Hz). IR (KBr): 3028, 2965, 1496, 1295, 1063, 963, 748, 692 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_{10}F_2{}^{74}Se$ 241.9970; found 241.9977.

*1-([1,1′-Biphenyl]-4-yl)-2-((difluoromethyl)selanyl)ethanone (**4p**).* Eluent: petroleum ether/ethyl acetate (10:1). White solid, mp 88.6 °C. 48.4 mg, 30% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 6.7 Hz, 2H), 7.48−7.36 (m, 3H), 7.30 (t, J = 55.6 Hz, 1H), 4.29 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.43 (d, J = 54.9 Hz). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 194.2 (s), 146.7 (s), 139.7 (s), 133.7 (s), 129.4 (s), 129.2 (s), 128.6 (s), 127.6 (s), 127.4 (s), 115.3 (t, J = 287.9 Hz), 27.8 (t, J = 2.2 Hz). HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{12}F_2O^{74}Se$ 320.0076; found 320.0085.

*(Difluoromethyl)(1-phenylethyl)selane (**4q**).* Eluent: petroleum ether/ethyl acetate (100:1). Yellow oil, 50.2 mg, 43% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 4H), 7.29−7.22 (m, 1H), 6.90 (t, J = 55.3 Hz, 1H), 4.63 (q, J = 7.0 Hz, 1H), 1.85 (d, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.92 (ddd, J = 306.8, 252.4, 55.3 Hz, 2F). ^{13}C $\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 142.6 (s), 128.9 (s), 127.7 (s), 127.3 (s), 116.8 (t, J = 286.2 Hz), 39.0 (s), 23.3 (s). IR (KBr): 2970, 2925, 2870, 1379, 1065, 764, 697 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_{10}F_2{}^{74}Se$ 229.9970; found 229.9972.

*Methyl 3-(1-((Difluoromethyl)selanyl)ethyl)benzoate (**4r**).* Eluent: petroleum ether/ethyl acetate (10:1). Yellow oil, 72.5 mg, 49% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.41 (dd, J = 7.7 Hz, 7.6 Hz,1H), 6.94 (t, J = 55.1 Hz, 1H), 4.67 (q, J = 7.1 Hz, 1H), 3.92 (s, 3H), 1.86 (d, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.66 (qd, J = 251.5, 55.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.7 (s), 143.3 (s), 131.8 (s), 130.8 (s), 129.0 (s), 128.8 (s), 128.2 (s), 116.4 (dd, J = 287.9, 285.7 Hz), 52.3 (s), 38.2 (t, J = 2.1 Hz), 23.1 (s). IR (KBr): 2954, 2926, 2871, 1724, 1289, 1056, 757, 697 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{11}H_{12}F_2O_2{}^{74}Se$ 288.0025; found 288.0021.

*4-(((Difluoromethyl)selanyl)methyl)benzamide (**4s**).* Eluent: dichloromethane/methanol (50:1). White solid, mp 127.6 °C. 34.7 mg, 26% yield. ^1H NMR (400 MHz, CD_3CN) δ 7.78 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.33 (t, J = 54.8 Hz, 1H), 6.76 (br, 1H), 6.05

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(br, 1H), 4.18 (s, 2H). ^{19}F NMR (376 MHz, CD_3CN) δ −93.33 (d, J = 54.7 Hz, 2F). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3CN) δ 168.2, 142.5, 132.8, 128.9, 127.9, 116.9 (t, J = 284.1 Hz), 25.2 (t, J = 3.0 Hz). IR (KBr): 3379, 3183, 1645, 1621, 1568, 1418, 1017, 619 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{10}F_2NO^{74}Se$ 259.9950; found 259.9948.

General Procedures for the HCF_2S Installation. Method A: Into a 15 mL Schlenk tube were added benzyl bromides (0.5 mmol, 1.0 equiv), NaSCN (48.6 mg, 0.6 mmol, 1.2 equiv), K_2CO_3 (138.2 mg, 1.0 mmol, 2.0 equiv), Ag_2CO_3 (27.6 mg, 0.1 mmol, 0.2 equiv) and DMAc (0.2 mL) under a N_2 atmosphere. Into this mixture under an argon atmosphere at 40 °C (oil bath), the solution of $Ph_3P^+CF_2H$ Br^- (589.8 mg, 1.5 mmol, 3.0 equiv) in DMAc (5 mL) was added dropwise via a syringe for 1.25 h. Upon the completion of addition, the resulting mixture was further stirred at the same temperature for 10 min. When the reaction was completed, as monitored by ^{19}F NMR spectroscopy, the crude reaction mixture was diluted with EA (20 mL). The solution was washed with water (3 × 20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to flash column chromatography to give the final product **6a**−**6k**. Method B: Into a 15 mL Schlenk tube were added alkyl bromides (0.5 mmol, 1.0 equiv), NaSCN (48.6 mg, 0.6 mmol, 1.2 equiv), K_2CO_3 (138.2 mg, 1.0 mmol, 2.0 equiv), Ag_2CO_3 (27.6 mg, 0.1 mmol, 0.2 equiv) and DMAc (0.2 mL) under a N_2 atmosphere at 60 °C for 2 h. Then the solution of $Ph_3P^+CF_2H$ Br^- (589.8 mg, 1.5 mmol, 3.0 equiv) in DMAc (5 mL) was added dropwise via a syringe pump for 1.25 h at 60 °C (oil bath). Upon the completion of addition, the resulting mixture was further stirred at the same temperature for 10 min. When the reaction was completed, as monitored by ^{19}F NMR spectroscopy, the crude reaction mixture was diluted with EA (20 mL). The solution was washed with water (3 × 20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to flash column chromatography to give the final product **6l**−**6p**.

*([1,1′-Biphenyl]-4-ylmethyl)(difluoromethyl)sulfane (**6a**).*[6d] Eluent: petroleum ether. White waxy solid, 91.3 mg, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.56 (m, 4H), 7.52−7.41 (m, 4H), 7.37 (tt, J = 7.5, 1.8 Hz, 1H), 6.79 (t, J = 56.5 Hz, 1H), 4.08 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.3 (d, J = 56.5 Hz, 2F).

*(3-(Benzyloxy)benzyl)(difluoromethyl)sulfane (**6b**).* Eluent: petroleum ether/ethyl acetate (40:1). Yellow oil, 84.0 mg, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 4H), 7.36 (d, J = 7.1 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 6.99 (m, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.91 (dd, J = 8.3, 2.1 Hz, 1H), 6.72 (t, J = 56.6 Hz, 1H), 5.07 (s, 2H), 3.99 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.5 (d, J = 56.7 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.2 (s), 137.9 (s), 136.9 (s), 130.0 (s), 128.7 (s), 128.2 (s), 127.6 (s), 121.6 (s), 120.3 (t, J = 274 Hz), 115.5 (s), 114.2 (s), 70.1 (s), 31.9 (t, J = 3.6 Hz). IR (KBr): 3065, 3034, 1598, 1584, 1489, 1447, 1381, 1323, 1298, 1265, 1237, 1157, 1027, 774, 739, 712, 697 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{14}F_2OS$ 280.0728; found 280.0732.

*(3,4-Dichlorobenzyl)(difluoromethyl)sulfane (**6c**).*[11] Eluent: petroleum ether. Yellow oil,76.5 mg, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.19 (dd, J = 8.3, 2.1 Hz, 1H), 6.76 (t, J = 56.0 Hz, 1H), 3.96 (s, 2H). ^{19}F NMR(376 MHz, $CDCl_3$) δ −94.01 (d, J = 56.0 Hz, 2F).

*(4-Bromobenzyl)(difluoromethyl)sulfane (**6d**).*[6d] Eluent: petroleum ether. Yellow oil, 97.8 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.7 Hz, 2H), 7.25 (d, J = 7.7 Hz, 2H), 6.77 (t, J = 56.3 Hz, 1H), 3.99 (d, J = 4.1 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.15 (d, J = 56.3 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.6 (s), 132.0 (s), 130.7 (s), 121.7 (s), 120.1 (t, J = 273.4 Hz), 31.1 (t, J = 3.7 Hz). IR (KBr): 2965, 1488, 1323, 1071, 1012, 830, 773 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_8H_7BrF_2S$ 251.9415; found 251.9425.

*tert-Butyl 4-(((difluoromethyl)thio)methyl)benzoate (**6e**).* Eluent: petroleum ether/ethyl acetate (40:1). Yellow oil, 101.4 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 6.73 (t, J = 56.3 Hz, 1H), 4.04 (s, 2H), 1.59 (s, 9H). ^{19}F NMR(376 MHz, $CDCl_3$) δ −94.2 (d, J = 56.3 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4 (s), 141.2 (s), 131.5 (s), 130.0 (s), 128.8 (s), 120.1 (t, J = 273.5 Hz), 81.2 (s), 31.5 (t, J = 3.7 Hz), 28.3 (s). IR (KBr): 2988, 2933, 1713, 1611, 1414, 1393, 1369, 1310, 1295, 1250, 1167, 1118, 1060, 1020, 850, 775, 763, 713 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{13}H_{16}F_2O_2S$ 274.0834; found 274.0837.

*4-(((Difluoromethyl)thio)methyl)benzoic Acid (**6f**).* Eluent: petroleum ether/ethyl acetate (5:1). White solid, 38.0 mg, 35% yield. Mp 141.8 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.97 (t, J = 56.3 Hz, 1H), 4.07 (s, 2H). ^{19}F NMR(376 MHz, CD_3OD) δ −95.51 (d, J = 56.3 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ 169.5 (s), 144.0 (s), 131.11 (s), 131.08 (s), 130.0 (s), 122.4 (t, J = 271.0 Hz), 32.1 (t, J = 3.7 Hz). IR (KBr): 2946, 2671, 2553, 1683, 1611, 1577, 1427, 1322, 1289, 1183, 1127, 1046, 1009, 933, 867, 773, 760, 711, 682, 669, 546, 496, 443 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_8F_2O_2S$ 218.0208; found 218.0217.

*1-(4-(((Difluoromethyl)thio)methyl)phenyl)ethenone (**6g**).* Eluent: petroleum ether/ethyl acetate (20:1). Yellow oil, 68.4 mg, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 6.75 (t, J = 56.2 Hz, 1H), 4.05 (s, 2H), 2.58 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.06 (d, J = 56.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.6 (s), 142.1 (s), 136.5 (s), 129.2 (s), 128.9 (s), 120.1 (t, J = 273.6 Hz), 31.3 (t, J = 3.8 Hz), 26.7 (s). IR (KBr): 1683, 1606, 1413, 1360, 1324, 1305, 1267, 1183, 1061, 1019, 959, 777, 668, 595, 573 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{10}H_{10}F_2OS$ 216.0415; found: 216.0423.

*4-(((Difluoromethyl)thio)methyl)benzonitrile (**6h**).*[4g] Eluent: petroleum ether/ethyl acetate (20:1). Yellow oil, 64.8 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 6.77 (t, J = 55.9 Hz, 1H), 4.05 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.79 (d, J = 55.9 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.4 (s), 132.6 (s), 129.7 (s), 119.8 (t, J = 274.2 Hz), 118.6 (s), 111.6 (s), 31.1 (t, J = 3.9 Hz). IR (KBr): 2956, 2923, 2852, 2229, 1922, 1809, 1607, 1506, 1416, 1318, 1249, 1021, 737, 551 cm^{-1}. HRMS (EI) m/z: $[M]^+$calcd for $C_9H_7F_2NS$ 199.0262; found 199.0268.

*3-(((Difluoromethyl)thio)methyl)benzonitrile (**6i**).* Eluent: petroleum ether/ethyl acetate (40:1). Yellow oil, 54.5 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 6.78 (t, J = 55.9 Hz, 1H), 4.03 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.80 (d, J = 55.8 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.5 (s), 133.4 (s), 132.4 (s), 131.4 (s), 129.7 (s), 119.9 (t, J = 274.1 Hz), 118.5 (s), 113.0 (s), 30.7 (t, J = 3.9 Hz). IR (KBr): 3064, 2972, 2232, 1601, 1583, 1483, 1432, 1325, 1256, 1231, 1061, 1026, 919, 903, 863, 798, 775, 760, 706, 684, 669, 607, 540, 454, 436 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_9H_7F_2NS$ 199.0262; found 199.0270.

*4′-(((Difluoromethyl)thio)methyl)-[1,1′-biphenyl]-2-carbonitrile (**6j**).* Eluent: petroleum ether/ethyl acetate (20:1). Yellow solid, 92.9 mg, 67% yield. mp 55.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.76 (d, J = 7.7 Hz, 1H), 7.65 (t, J = 8.3 Hz, 1H), 7.58−7.42(m, 6H), 6.80 (t, J = 56.5 Hz, 1H), 4.08 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.14 (d, J = 56.4 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.9 (s), 137.6 (s), 137.1 (s), 133.9 (s), 133.0 (s), 130.1 (s), 129.4 (s), 129.3 (s), 127.8 (s), 120.2 (t, J = 273.3 Hz), 118.8 (s), 111.3 (s), 31.4 (t, J = 3.7 Hz). IR (KBr): 3481, 2924, 2853, 2223, 1647, 1614, 1596, 1479, 1445, 1409, 1322, 1268, 1247, 1060, 1024, 888, 845, 764, 670 cm^{-1}. HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{11}F_2NS$ 275.0575; found 275.0586.

*5-Chloro-3-(((difluoromethyl)thio)methyl)benzo[b]thiophene (**6k**).* Eluent: petroleum ether. Yellow oil, 87.5 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 1.9 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.44 (s, 1H), 7.35 (dd, J = 8.6, 1.9 Hz, 1H), 6.81 (t, J = 56.2 Hz, 1H), 4.23 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.55 (d, J = 56.2 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.82 (s), 138.78 (s), 130.9 (s), 129.8 (s), 127.2 (s), 125.3 (s), 124.0 (s), 121.6 (s), 120.3 (t, J = 273.6 Hz), 24.7 (t, J = 4.2 Hz). IR (KBr): 3502, 3096, 1587, 1556, 1423, 1304, 1321, 1253, 1241, 1149, 1078, 1060, 1026,

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864, 835, 793, 772 cm^{-1}. HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{10}H_7ClF_2S_2$ 263.9641; found 263.9648.

*Benzhydryl(difluoromethyl)sulfane (**6l**).* Eluent: petroleum ether. Yellow oil, 49.0 mg, 39% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.3 Hz, 4H), 7.37 (dd, J = 7.7, 7.3 Hz, 4H), 7.30 (dd, J = 7.7, 7.3 Hz, 2H), 6.58 (t, J = 57.4 Hz, 1H), 5.61 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −95.38 (d, J = 57.4 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.9 (s), 129.0 (s), 128.3 (s), 127.9 (s), 120.8 (t, J = 272.8 Hz), 51.7 (t, J = 2.8 Hz). IR (KBr): 3063, 3029, 2065, 1600, 1494, 1450, 1320, 1302, 1070, 1031, 795, 749, 699, 669, 629, 586, 506 cm^{-1}. HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{14}H_{12}F_2S$ 250.0623, Found 250.0629.

*(Difluoromethyl)(2-(naphthalen-1-yl)ethyl)sulfane (**6m**).* Eluent: petroleum ether. Yellow oil, 87.7 mg, 73% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.65−7.52 (m, 2H), 7.50−7.44 (m, 1H), 7.41 (d, J = 6.8 Hz, 1H), 6.88 (t, J = 56.2 Hz, 1H), 3.50 (dd, J = 9.2, 6.8 Hz, 2H), 3.22 (dd, J = 9.2, 6.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.38 (d, J = 56.3 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.7 (s), 134.1(s), 131.6 (s), 129.1 (s), 127.7 (s), 126.8 (s), 126.4 (s), 125.8 (s), 125.6 (s), 123.3 (s), 120.8 (t, J = 273.1 Hz), 34.4 (s), 27.9 (t, J = 2.9 Hz). IR (KBr): 3527, 3064, 2941, 1597, 1510, 1457, 1436, 1395, 1320, 1285, 1228, 1061, 1020, 966, 780, 734, 423 cm^{-1}. HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{13}H_{12}F_2S$ 238.0623; found 238.0623.

*(Difluoromethyl)(4-phenoxybutyl)sulfane (**6n**).* Eluent: petroleum ether. Yellow oil,78.9 mg, 68% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 8.0, 7.4 Hz, 2H), 6.97 (dd, J = 8.0, 7.4 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 6.83 (t, J = 56.3 Hz, 1H), 4.00 (t, J = 5.5 Hz, 2H), 2.90 (t, J = 6.7 Hz, 2H), 1.99−1.85 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.68 (d, J = 56.3 Hz, 2F). $^{13}C\{^1H\}$ NMR(101 MHz, $CDCl_3$) δ 159.0 (s), 129.6 (s), 120.8 (s), 120.8 (t, J = 272.8 Hz), 114.6 (s), 67.1 (s), 28.3 (s), 27.0 (t, J = 3.2 Hz). IR (KBr): 3064, 3040, 2947, 2871, 1600, 1587, 1498, 1473, 1390, 1330, 1302, 1244, 1172, 1049, 948, 883, 803, 755, 692, 542 cm^{-1}. HRMS (EI) *m/z*: $[M]^+$calcd for $C_{11}H_{14}F_2OS$ 232.0728; found 232.0729.

*(Difluoromethyl)(dodecyl)sulfane (**6o**).*[4a] Eluent: petroleum ether. Colorless oil, 110.0 mg, 87% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, J = 56.5 Hz, 1H), 2.79 (t, J = 7.5 Hz, 2H), 1.71−1.61 (m, 2H), 1.44−1.34 (m, 2H), 1.34−1.22(m, 16H), 0.88 (t, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.83 (d, J = 56.5 Hz, 2F).

*Ethyl 6-((difluoromethyl)thio)hexanoate (**6p**).*[4a] Eluent: petroleum ether/ethyl acetate (20:1). Colorless oil, 83.7 mg, 74%. ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, J = 56.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.30 (t, J = 7.4 Hz, 2H), 1.67 (tt, J = 15.3, 7.5 Hz, 4H), 1.50−1.38 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −92.80 (d, J = 56.4 Hz, 2F).

*4-(((Difluoromethyl)thio)methyl)benzamide (**6q**).* Eluent: dichloromethane/methanol (100:1). White solid, mp 141.0 °C. 49.8 mg, 46% yield. ^1H NMR (400 MHz, CD_3CN) δ 7.80 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 6.99 (t, J = 56.2 Hz, 1H), 6.76 (br, 1H), 6.02 (br, 1H), 4.11 (s, 2H). ^{19}F NMR (376 MHz, CD_3CN) δ −94.72 (d, J = 56.4 Hz, 2F). $^{13}C\{H\}$ NMR (126 MHz, CD_3CN) δ 168.2, 141.2, 133.1, 128.9, 127.9, 121.3 (t, J = 270.2 Hz), 30.9 (t, J = 3.5 Hz). IR (KBr): 3374, 3182, 1645, 1621, 1418, 1066, 1004, 783 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_9H_{10}F_2NO_S$ 218.0446; Found 218.0447.

*(Difluoromethyl)(2-nitrobenzyl)sulfane (**6r**).* Eluent: petroleum ether/ethyl acetate (1:1). Yellow oil, 54.9 mg, 50% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 1H), 7.61 (td, J = 7.5, 1.4 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.51−7.43 (m, 1H), 6.81 (t, J = 55.8 Hz, 1H), 4.34 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.44 (d, J = 55.8 Hz, 2F). ^{13}C {H} NMR (126 MHz, $CDCl_3$) δ 148.0, 133.8, 133.6, 132.3, 128.9, 125.6, 120.2 (t, J = 273.9 Hz), 29.2 (t, J = 3.8 Hz). HRMS (DART) *m/z*: $[M-H]^-$ calcd for $C_8H_6F_2NO_2S$ 218.0093; found 218.0090.

Preliminary Mechanistic Studies. Into a 15 mL Schlenk tube were added **1a**, KSeCN, $Ph_3P^+CF_2D\ Br^-$ (589.8 mg, 1.5 mmol, 3.0 equiv) (89% deuterated), Cs_2CO_3 (325.8 mg, 1.0 mmol, 2.0 equiv), 4 Å molecular sieve (125 mg) and EA (2.5 mL) under a N_2 atmosphere. The resulting mixture was stirred at 50 °C (oil bath) for 12 h under a N_2 atmosphere. When the reaction was completed, as monitored by ^{19}F NMR spectroscopy, the crude reaction mixture was diluted with EA (20 mL). The solution was washed with water (20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to flash column chromatography (eluent: petroleum ether) to give the final product. The D/H ratio of the final product was determined by ^{19}F NMR spectroscopy. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 4.17 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.54 (t, J = 8.5 Hz, 2F). ^{13}C NMR$\{^1H\}$ (101 MHz, $CDCl_3$) δ 140.6, 140.4, 136.4, 129.4, 128.9, 127.6, 127.5, 127.1, 115.4 (tt, J = 285.8, 31.4 Hz), 26.0 (t, J = 3.0 Hz).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01718.

Copies of ^1H, ^{13}C, and ^{19}F NMR spectra for all compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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