Note

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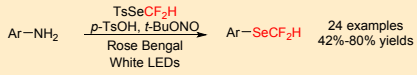
Metal-Free Difluoromethylselenolation of Arylamines Under Visible-light Photocatalysis

Kui Lu,[†,*] Quan Li,[†] Xiaolan Xi,[†] Ting Zhou,[†] and Xia Zhao[‡,*]

[†]*China International Science and Technology Cooperation Base of Food Nutrition/Safety and Medicinal Chemistry, College of Biotechnology, Tianjin University of Science & Technology, Tianjin, China, 300457*

[‡]*College of Chemistry, Tianjin Key Laboratory of Structure and Performance for Functional Molecules, Key laboratory of Inorganic-organic Hybrid Functional Material Chemistry, Ministry of Education, Tianjin Normal University, Tianjin, China, 300387*

*E-mail: lukui@tust.edu.cn; hxxyzhx@mail.tjnu.edu.cn;

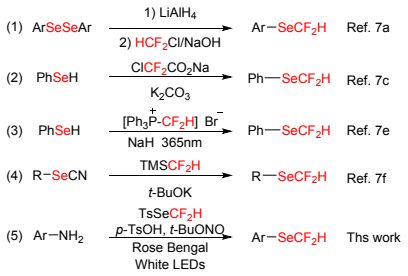


Abstract: A novel visible-light photocatalytic difluoromethylselenolation of aryl amines via *in situ* generation of aryldiazonium salts was achieved using Se-(difluoromethyl) 4-methylbenzenesulfonoselenoate, which was synthesized for the first time. The reagent is readily accessible and shelf-stable. The metal-free reaction conditions and the broad substrate scope provide a green protocol for the efficient and rapid introduction of the difluoromethylselenylether group.

Trifluoromethyl and difluoromethylchalcogen groups have attracted widespread attention in academia and industry over the past decade due to their unique

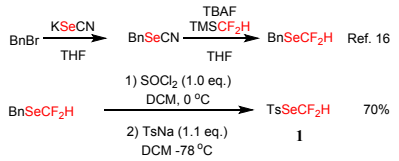
physicochemical properties including high lipophilicity and good cell membrane permeability.[1] Significant progress has been made towards the development of methods that allow the direct incorporation of OCF_3,[2] OCF_2H,[3] SCF_3[4] and SCF_2H[5] into organic molecules. The $SeCF_3$ group has a high Hansch lipophilicity parameter value (π_R = 1.29) which falls between that of the CF_3O and CF_3S groups and has recently gained significant interest in organofluorine chemistry and drug design.[6] More recently, strategies for incorporation of the related $SeCF_2H$ group have attracted attention in the synthetic community.[7] However, direct $SeCF_2H$ incorporation using a shelf-stable reagent has been rarely reported.[8]

Arylamines are inexpensive and widely available starting materials and are useful handles for the introduction of boryl,[9] phosphoryl,[10] sulfenyl,[11] stannyl,[12] and trifluoromethyl groups[13] via Sandmeyer-type chemistry. In 2018, we reported a visible-light mediated photocatalytic trifluoromethylthiolation of aryldiazonium salts and arylamines using S-trifluoromethyl 4-methoxylbenzenesulfonothioate ($TsSCF_3$)[14]. Recently, Billard and Tlili group developed a visible-light mediated trifluoromethylselenolation of aryldiazonium salts.[15] We report herein, the preparation of Se-(difluoromethyl) 4-methylbenzenesulfonoselenoate (**1**, $TsSeCF_2H$) for the first time (Scheme 1) and describe its use for the direct difluoromethylselenolation of arylamines under visible-light photocatalysis.



SCHEME 1. Methods for $SeCHF_2$ incorporation

We began with the synthesis of the difluoromethylselenolation reagent (**1**) using KSeCN, benzyl bromide (BnBr), CF_2HSiMe_3, and sodium 4-toluenesulfinate (TsNa) in three steps employing a protocol similar to the one used for the preparation of Se-(trifluoromethyl) 4-methylbenzenesulfonoselenoate (Scheme 2)[16].



SCHEME 2. Preparation of reagent 1

With the reagent **1** in hand, we attempted the difluromethylselenolation of ethyl 4-aminobenzoate (**2a**) with 4-methylbenzenesulfonic acid (TsOH), tert-butyl nitrite (TBN) and 1 in the presence of Rose Bengal (RB) under white light irradiation in dimethyl sulfoxide (DMSO) at room temperature, based on our previously reported conditions14. To our delight, the desired difluoromethylselenolation product **3a** was obtained in 54% yield (Table 1, entry 1). With the successful formation of **3a**, we turned to the optimisation of various reaction parameters to improve the reaction yield. While the use

of DMF or THF as reaction solvent afforded **3a** in a lower yield (Table 1, Entries 2 and 3), MeOH, water, or CH3CN furnished **3a** only in trace quantities. An increase in the reaction concentration of **2a** from 0.20 M to 0.25 M, afforded an increase in yield from 75% to 80%, respectively. However, a further increase in the concentration of **2a** to 0.30 M led to a diminished yield. Decreasing the photocatalyst loading to 5 mol% afforded the product in a reduced 41 % yield, while the absence of TsOH from the reaction condition furnished the product in 68% yield. The use of green light irradiation furnished **3a** in a much lowered 25% yield. Reactions carried out in the absence of the photocatalyst, or light irradiation did not afford any product. Further, the extension of reaction time to 30 h did not improve the yield.

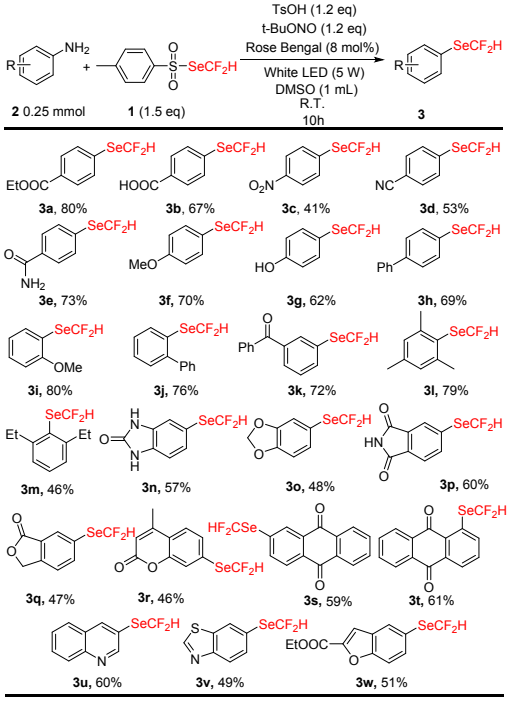
TABLE 1. Reaction Optimisation[a]

Entry	Deviation from standard conditions	Yield (%)
1	None	75
2	DMF instead of DMSO	62
3	THF instead of DMSO	52
4	MeOH instead of DMSO	Trace
5	H_2O instead of DMSO	Trace
6	MeCN instead of DMSO	Trace
7	**2a** (0.25 M)	80
8	**2a** (0.30 M)	72
9	Rose Bengal (5 mol%)	41
10	Without TsOH	68
11	Green LED instead of White LED	25
12	No Rose Bengal	0
13	No light	0
14	30h	72

[a] Reactions were performed with $TsSeCF_2H$ (0.3 mmol, 1.5 equiv.), **2a** (0.2 mmol, 1 equiv.), TsOH (0.24mmol, 1.2 equiv.), t-BuONO (0.24mmol, 1.2 equiv.) Rose Bengal (0.016 mmol, 8 mol%), and solvent (1 mL). The reaction mixture was stirred at rt for 10 hours.

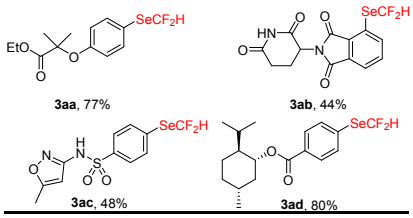
With the optimised reaction conditions in hand, the generality of this reaction was examined by employing a series of arylamines (**2b**–**2r**) as substrates, and the results are summarised in Scheme 3. Anilines bearing both electron-donating and electron-withdrawing substituents, as well as ortho-, meta- and para-substituted anilines were compatible with the reaction conditions and afforded the corresponding difluoromethylselenolation products (**3b**-**3k**) in moderate to good yields. Notably, sterically hindered anilines **2l** and **2m** were smoothly transformed to the desired products in 79 and 46% yields, respectively. Having evaluated sterics and electronics of aniline substitutions, we studied the compatibility of other complex functionalities on the aniline framework to the reaction conditions. The urea (**2n**), cyclic ketone (**2s** and **2t)**, acetal (**2o**), cyclic imide (**2p**), lactone (**2q**), and α, β-unsaturated lactone (**2r**) functionalities, as well

as aromatic heterocyclic amines (**2u**-**2w**) were compatible during this transformation and furnished the desired products (**3n**-**3w**) in moderate to good yields.



SCHEME 3. Substrate scope of the difluoromethylselenolation of arylamines

To further probe the relevance of the developed transformation to the preparation of medicinally relevant molecules, we carried out the functionalization of known biologically active scaffolds, and were pleased to find the successful incorporation of the difluoromethylselenyl group into a clofibrate derivative (**3aa**), pomalidomide (**3ab**), sulfamethoxazole (**3ac**), and L-menthol derivative (**3ad**) in moderate to good yields (Scheme 4)



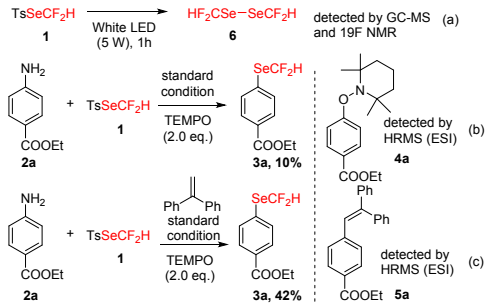
[a] Reaction conditions: amine (0.25 mmol), **1** (0.3 mmol), TsOH (0.24mmol), *t*-BuONO (0.24mmol) Rose Bengal (0.016 mmol, 8 mol%), and DMSO(1 mL) under the irratdation under white light irradiation at r.t. for 10 hours

SCHEME 4. Difluoromethylselenolation of bioactive molecules

To investigate the mechanism this reaction, we carried out a series of ^{19}F NMR experiments to examine the difluoromethylselenolation of **2a** by **1** under the optimised reaction condition with trifluoromethylbenzene as an internal standard (δ = -63.20 ppm). The NMR spectrum acquired after 15 min revealed the presence of three fluorine peaks, which were assigned to the desired product **3a** (δ = -90.47 ppm), **1** (δ = -91.06 ppm), and a unknown fluorine peak (δ = -88.59 ppm). The fluorine signal corresponding to **1** almost dispappeared in the NMR spectrum acquired after 30 min, and the intensities of the fluorine peaks of **3a** and the unknown compound increased. After 1 hour, the fluorine peak intensity of the unknown compound decreased and that of **3a** increased. To explore the structure of the unknown compound, we irradiate 1 under white light in the absence of **2a,** the photocatalyst, and other additives. We found only two fluorine peaks by ^{19}F NMR, **1** (δ = -91.06 ppm)and the unknown compound (δ = -88.59 ppm), and it was identified as 1,2-bis(difluoromethyl)diselane **6** ($HCF_2SeSeCF_2H$) by GC-MS (Scheme 5,

Eq. a). Further, TsOH was detected by ESI-HRMS even when the reaction was carried out in the absence of TsOH.

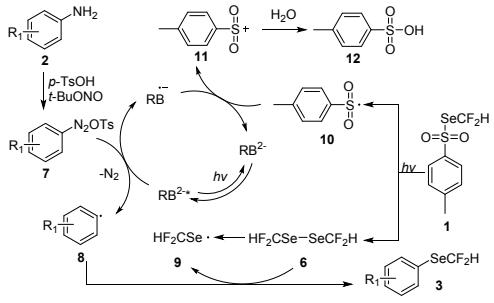
Based on related mechanisms in the literature,[14, 15] we suspected that aryl radicals might be key intermediates in this transformation, and to probe their presence, two radical trapping experiments were carried out (Scheme 5, Eq. b and Eq. c) under standard reaction conditions. When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 2 equiv) or 1,1-diphenylethylene (2 equiv) was added to the reaction under the standard reaction conditions, the yield of **3a** decreased to 10% or 42% respectively. Furthermore, the ESI-HRMS analysis of the reaction mixture indicated the formation of the TEMPO-arene adduct (**4a**) and triarylethylene (**5a**), which confirmed the intermediacy of free radical species in this reaction.



SCHEME 5. Investigations to elucidate the reaction mechanism

Based on the aforementioned results and related literature,[17] a plausible mechanism for the difluoromethylselenolation reaction is proposed (Scheme 6). The arylamine **2** reacts with TsOH and TBN to form an arenediazonium salt **7**. The photocatalyst Rose Bengal

(RB) undergoes excitation under visible light irradiation to RB*, which through a single electron transfer (SET) with arenediazonium salt **7** leads to the generation of RB·-and aryl radical **8**, which reacts with 1,2-bis(difluoromethyl)diselane **6** generated by the homolysis of the reagent **1** under visible light to deliver the corresponding aryl difluoromethylselenol ether **3** and difluoromethylselenol radical **9** which can self-combine to form **6**. Subsequently, the sulfone radical **10** undergoes a single electron transfer (SET) with the radical anion of the photocatalyst ($RB^{\cdot -}$) which leads to the formation of sulfite cation **11** along with the regeneration of the photocatalyst. The reaction of the sulphite cation **11** with water affords TsOH (**12**).



SCHEME 6. Plausible mechanism of Rose Bengal catalysed selenodifluoromethylation

Finally, the practical applications of this transformation were investigated. 6-mmol scale difluoromethylselenolation reaction of **2j** (Scheme 7) was carried out and the desired product **3j** was obtained in 64% yield.

SCHEME 7. Scale-up of the difluoromethylselenolation reaction

In summary, we report the synthesis of a novel shelf-stable reagent $TsSeCF_2H$, which allows direct difluoromethylselen-olations of aryl amines via in situ generated aryldiazonium salts under visible-light catalysis for the first time. Mechanistic investigations performed using ^{19}F NMR spectroscopy, and radical trapping experiments confirmed the intermediacy of free radicals in this reaction. The readily accessible reagents, metal-free reaction conditions, and the broad substrate scope provide a green and efficient protocol for preparation of aryl difluoromethylselenylether. Exploration of $TsSeCF_2H$-mediated difluoromethylselenolation applications of other relevant organic molecules is currently underway in our laboratory.

EXPERIMENTAL SECTION

1) General Experimental Methods.

All solvents were distilled prior to use. For chromatography, 200-300 mesh silica gel (Qingdao, China) was employed. The light-promoted reactions were done using standard LED lamp with five light emitting diodes (12-28 V, 5W, 465-470 nm). The distance from the light source to the irradiation vessel is 3 cm. ^1H, ^{13}C NMR and ^{19}F NMR spectra were recorded at 400 MHz and 100 MHz with Brucker ARX 400 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane(TMS) as internal standard. The

GC-MS spectra were recorded on Thermo Scientific Trace 1300. High resolution mass spectra were obtained on a Bruker SCION 436-GC SQ mass spectrometer or on a Bruker Apex IV FTMS spectrometer. Melting points are reported as uncorrected. Except $BnSeCF_2H$[8a], **1aa**[18] and **1ad**[19] were prepared according to the literature procedures, All reagents were obtained from commercial suppliers and used without further purification.

2) Preparation of 1

Under an argon atmosphere, to a flask equipped with a magnetic stir bar was added the benzyl (difluoromethyl)selane (10 mmol , 1.0 equiv.), sulfuryl chloride (10 mmol , 1.0 equiv.) and anhydrous DCM (4 mL). The mixture was stirred at 0 °C for 3 hours and then transferred to another flask with a solution of TsNa (11 mmol. 1.1 equiv.) in anhydrous DCM (16 mL) which had been cooled down to -78 °C. The mixture was stirred about 10-15 minutes at -78 °C and then filtered over a pad of silica. The filtrate was concentrated to dryness and purified directly by silica gel chromatography, eluting with petroleum ether/DCM (20:1), to give compound **1** (yellow liquid, 2.0 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.63 (t, J = 54.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -90.55 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.9, 145.3, 130.2, 126.7, 120.7 (t, J = 290.1 Hz), 21.9; IR (KBr): 2958, 2916, 2848, 1593, 1490, 1401, 1331, 1290, 1305, 1259, 1173, 1135, 1058, 1015, 809, 700, 682 cm^{-1}; HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_8H_9F_2O_2SSe$ 286.9451; Found 286.9524.

3) General procedure for the dimethylselenolation of aryl amines

To a sealed tube was added amine (0.25 mmol, 1.0 equiv.), *p*-TsOH (0.30 mmol, 1.2 equiv.) and Rose Bengale (0.02 mmol, 0.08 equiv.) and dry DMSO (1.0 mL). The reaction mixture was stirred for 5 minutes, then *t*-BuONO (0.30 mmol, 1.2 equiv.) and Se-(difluoromethyl) 4-methylbenzenesulfonoselenoate (**1**, 0.375 mmol 1.5 equiv.) was

added in turn, and the mixture was irradiated with white light LED (5 W) at room temperature for 10 h. After the irradiation, water (5 mL) was added to give an emusion which was extracted with ethyl acetate (3 × 5mL). The combined organic phase was washed with brine and dried over by anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue which was purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (from 60:1 to 2:1), to give compound **3**.

4) Characteristic data for 3a-3w and 3aa-3ad

ethyl 4-((difluoromethyl)selanyl)benzoate (3a): Yellow oil (56 mg, 80% yield from general procedure), petroleum ether/ethyl acetate 30:1(v/v) as eluents for column chromatography, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 54.8 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -89.93 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 135.4, 131.3, 130.4, 129.4, 116.7 (t, J = 290.0 Hz), 61.3, 14.3; IR (KBr):2982, 1712, 1592, 1465, 1395, 1367, 1267, 1178, 1105, 1073, 1043, 1013, 850, 748, 757, 693, 683, 664 cm^{-1}; HRMS (EI-quadrupole) m/z: Calcd for $[M]^+$ $C_{10}H_{10}O_2F_2Se$ 279.9814; Found 279.9807.

((difluoromethyl)selanyl)benzoic acid (3b): White solid (42 mg, 67% yield from general procedure), petroleum ether/ethyl acetate 5:1 (v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, DMSO - d6) δ 8.00 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 54.8 Hz, 1H); ^{19}F{^{1}H} NMR (376 MHz, DMSO-d6) δ -92.40 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d6) δ 167.6, 135.0, 131.2, 130.1, 129.7, 117.2 (t, J = 285.0 Hz). IR (KBr): 3472, 3090, 3047,2920, 2850, 2727, 2667, 2551, 1666, 1599, 1587, 1563, 1425, 1397, 1370, 1313, 1289, 1277,1245, 1181, 1128, 1075, 1060, 1036, 1015, 961, 866, 785,

695, 670, 543 cm^{-1}; m.p.190-191 ^oC; HRMS (ESI-quadrupole) m/z: Calcd for $[M-H]^-$ $C_8H_5O_2F_2Se$ 250.9429; Found 250.9425.

***(difluoromethyl)(4-nitrophenyl)selane (3c)*[7f]:** White solid (26 mg, 41% yield from general procedure), petroleum ether/ethyl acetate 20:1(v/v) as eluents for column chromatography, ^1H NMR (400MHz, $CDCl_3$）δ 8.19 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 54.4 Hz, 1H); $^{19}F\{^1H\}$ NMR (376MHz, $CDCl_3$) δ -89.9 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.5, 136.1, 132.4, 124.3, 116.2 (t, J = 288.0 Hz). The spectral data are in accordance with the literature report.

***((difluoromethyl)selanyl)benzonitrile (3d)*[7f]:** White solid (31 mg, 53% yield from general procedure), petroleum ether/ethyl acetate 20:1(v/v) as eluents for column chromatography, ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 55.6 Hz, 1H); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -89.87 (s, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 136.0, 132.7, 130.0, 118.0, 116.2 (t, J = 289.0 Hz), 113.2. The spectral data are in accordance with the literature report.

4-((difluoromethyl)selanyl)benzamide (3e): White solid (45.7 mg, 73% yield from general procedure), petroleum ether/ethyl acetate 20:1(v/v) as eluents for column chromatography, ^1H NMR (400 MHz, Methanol-d4) δ 7.86 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.49 (t, J = 54.8 Hz, 1H); $^{19}F\{^1H\}$ NMR (376 MHz, Methanol-d4) δ -92.58 (s, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, Methanol-d4) δ 170.0, 135.3, 134.4, 128.2, 127.2, 117.2 (t, J = 289.0 Hz); IR (KBr): 3435, 2957, 2927, 2870, 1716, 1592, 1456,

1395, 1370, 1287, 1178, 1116, 1077, 1062, 1015, 759, 685 cm^{-1}; m.p. 149-151°C; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_8H_7NOF_2SeNa$ 273.9553; Found 273.9540.

***(difluoromethyl)(4-methoxyphenyl)selane (3f)*[7f]:** Light yellow oil (42 mg, 70% yield from general procedure), petroleum ether/ethyl acetate 30:1(v/v) as eluents for column chromatography, ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 2H), 7.09 (t, J = 55.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -91.08 (s, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 138.6, 117.2 (t, J = 288.0 Hz), 115.3, 113.6, 55.5. The spectral data are in accordance with the literature report.

***((difluoromethyl)selanyl)phenol (3g)* [7f]:** Light yellow oil (41 mg, 61% yield from general procedure), petroleum ether/ethyl acetate 40:1 (v/v) as eluents for column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 2H), 7.09 (t, J =55.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 5.04 (s, 1H); $^{19}F\{^1H\}$ NMR (376MHz, $CDCl_3$) δ -91.06 (s, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 138.8, 117.1 (t, J = 288.0 Hz), 116.8, 113.9. The spectral data are in accordance with the literature report.

***[1,1'-biphenyl]-4-yl(difluoromethyl)selane (3h)* [7f]:** White solid (49 mg, 69.2% yield from general procedure), petroleum ether/ethyl acetate 60:1(v/v) as eluents for column chromatography, ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 4.8 Hz, 2H), 7.60-7.58 (m, 4H), 7.47 (t, J = 7.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 55.6 Hz, 1H);$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -90.21 (s, 2F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.6,

140.1, 136.9, 129.1, 128.3, 128.1, 127.3, 122.4, 117.2 (t, J = 287.0 Hz). The spectral data are in accordance with the literature report.

***(difluoromethyl)(2-methoxyphenyl)selane (3i)*:** Colorless oil (48 mg, 80% yield from general procedure), petroleum ether/ethyl acetate 20:1 (v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.2Hz, 1H), 7.37 (td, J = 7.8 Hz, 1.2 Hz, 1H), 7.30 (t, J = 56.0 Hz, 1H), 6.97-6.93 (m, 2H), 3.90 (s, 3H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -91.41 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 136.1, 130.8, 121.7, 116.7 (t, J = 286.0 Hz), 113.8, 111.2, 56.0; IR (KBr): 2939, 1581, 1477, 1434, 1273, 1247, 1181, 1164, 1125, 1055, 1032, 752, 693cm^{-1}; HRMS (EI-quadrupole) m/z: Calcd for $[M]^+$ $C_8H_8OF_2Se$ 237.9708; found 237.9702.

***[1,1'-biphenyl]-2-yl(difluoromethyl)selane (3j)*:** Light yellow oil (54 mg, 76% yield from general procedure), petroleum ether/ethyl acetate 30:1(v/v) as eluents for column chromatography. ^{1}H NMR (400MHz, $CDCl_3$）δ 7.76 (d, J = 7.6 Hz, 1H), 7.46-7.39 (m, 5H), 7.37-7.30 (m, 3H), 7.01 (t, J = 55.2 Hz, 1H); ^{19}F{^{1}H} NMR (376MHz, $CDCl_3$) δ -90.6 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.4, 141.7, 135.4, 130.8, 129.4, 129.1, 128.5, 128.2, 127.9, 124.9, 117.5 (t, J = 287.0 Hz); IR (KBr): 3054, 1582, 1496, 1462, 1446, 1424, 1291, 1270, 1026, 1006, 915, 871, 771, 746, 698cm^{-1}; HRMS (EI-quadrupole) m/z: Calcd for $[M]^+$ $C_{13}H_{10}F_2Se$ 283.9916; Found 283.9910.

(3-((difluoromethyl)selanyl)phenyl)(phenyl)methanone (3k): Colorless oil (56 mg, 72% yield from general procedure), petroleum ether/ethyl acetate 60:1(v/v) as eluents for

column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.89 (d, J = 8.0Hz, 1H), 7.86-7.84 (m, 1H), 7.81-7.79 (m, 2H), 7.64-7.60 (m, 1H), 7.53-7.48 (m, 3H), 7.22 (t, J = 55.2 Hz, 1H). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -90.28 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.6, 140.1, 138.9, 137.7, 137.1, 133.0, 131.0, 130.2, 129.5, 128.6, 123.8, 116.6 (t, J = 289.0 Hz); IR (KBr): 3059, 1656, 1597, 1580, 1565, 1447, 1400, 1309, 1267, 1180, 1152, 1040, 998, 945, 926, 849, 813, 782, 748, 713, 685, 664 cm^{-1}; HRMS (ESI-quadrupole) m/z: Calcd for $[M+H]^+$ $C_{14}H_{11}OF_2Se$ 312.9938; found 312.9950.

***(difluoromethyl)(mesityl)selane (3l)*:** Light yellow oil (49 mg, 79% yield from general procedure), petroleum ether/ethyl acetate 30:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.98 (t, J = 55.2 Hz, 1H), 2.54 (s, 6H), 2.29 (s, 3H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -89.34 (s, 2F). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.5, 140.3, 129.1, 122.4, 117.6 (t, J = 288.0 Hz), 25.0, 21.2; IR (KBr): 2924, 1598, 1457, 1377, 1280, 1269, 1059, 1005, 1020, 849, 730, 713, 713, 687, 660cm^{-1}; HRMS (EI-quadrupole) m/z: Calcd for $[M]^+$ $C_{10}H_{12}F_2Se$ 250.0072; Found 250.0068.

***(2,6-diethylphenyl)(difluoromethyl)selane (3m)*:** Light yellow oil (30 mg, 46% yield from general procedure), petroleum ether/ethyl acetate 30:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 7.6Hz, 2H), 6.98 (t, J = 55.2 Hz, 1H), 3.00 (q, J = 7.2 Hz, 4H), 1.23 (t, J = 7.6 Hz, 6H);

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -89.20 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 150.5, 130.7, 126.9, 124.7, 118.0 (t, J = 288.0 Hz), 30.9, 16.0; IR (KBr): 3440, 2954, 2918, 2849, 1630, 1462 cm^{-1}; HRMS (EI-quadrupole) m/z: Calcd for $[M]^+$ $C_{11}H_{14}F_2Se$ 264.0229; Found 264.0222.

***5-((difluoromethyl)selanyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (3n)*:** White solid (38 mg, 57% yield from general procedure), petroleum dichloromethane/methanol 20:1(v/v) as eluents for column chromatography, ^{1}H NMR (400 MHz, Methanol-d4) δ 7.37-7.35 (m, 2H), 7.32 (t, J = 55.2 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H); $^{19}F\{^{1}H\}$ NMR (376 MHz, Methanol-d4) δ -93.23 (s, 2F); $^{13}C\{^{1}H\}$ NMR(100 MHz, Methanol-d4) δ 156.4, 130.8, 130.3, 130.0, 117.5 (t, J = 286.0 Hz), 117.1, 114.2, 109.6; IR (KBr): 3176, 3107, 3087, 3013, 2883, 2829, 2787, 2727, 1716, 1626, 1483, 1366, 1291, 1271, 1197, 1064, 1047, 1025, 883, 804, 783, 749, 707, 695, 675, 598cm^{-1}; m.p. 279-281^{o}C; HRMS (ESI-quadrupole) m/z: Calcd for $[M+H]^+$ $C_8H_7F_2N_2OSe$ 264.9686; Found 264.9691.

***5-((difluoromethyl)selanyl)benzo[d][1,3]dioxole (3o)*[7f]:** Light yellow oil (30 mg, 48% yield from general procedure), petroleum ether/ethyl acetate 50:1 (v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.13 (s, 1H), 7.10 (t, J = 55.6 Hz, 1H), 6.79 (d, J = 8.0 Hz 1H), 6.0 (s, 2H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -91.04 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.4, 148.4, 131.4, 117.1 (t, J = 287.0 Hz), 116.9, 114.4 (t, J = 3.0 Hz), 114.3, 101.7. The spectral data are in accordance with the literature report.

***5-((difluoromethyl)selanyl)isoindoline-1,3-dione (3p)*:** White solid (41 mg, 59% yield from general procedure), petroleum ether/ethyl acetate 20:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.15 (s, 1H), 8.05 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.86 (d, J = 8.0Hz, 1H), 7.29 (t, J = 54.8 Hz, 1H); ^{19}F{^{1}H} NMR(376 MHz, $CDCl_3$) δ -89.83 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 167.2, 141.3, 133.5, 133.1, 131.7, 130.5, 124.5, 116.1 (t, J = 289.0 Hz); IR (KBr): 3854, 3736, 3676, 3650, 3629, 3467, 3191, 3078, 2714, 1770, 1746, 1717, 1604, 1421, 1370, 1353, 1293, 1190, 1111, 1054, 1040, 859, 752, 739, 692, 674, 650, 642, 587, 556, 500cm^{-1}; m.p. 141-142^{o}C; HRMS (ESI-quadrupole) m/z: Calcd for $[M]^+$ $C_9H_5NO_2F_2Se$ 276.9454; Found 276.9432.

***6-((difluoromethyl)selanyl)isobenzofuran-1(3H)-one (3q)*:** White solid (32 mg, 47% yield from general procedure), petroleum ether/ethyl acetate 20:1(v/v) as eluents for column chromatography, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 54.8 Hz, 1H), 5.35 (s, 2H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -90.3 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.9, 147.7, 141.8, 133.8, 127.3, 124.5, 123.4, 116.2 (t, J = 288.0 Hz), 69.7; IR (KBr): 3497, 3065, 3023, 2977, 2952, 2878, 1751, 1715, 1660, 1609, 1448, 1411, 1358, 1291, 1262, 1210, 1194, 1125, 1106, 1051, 1034, 1025, 1005, 912, 862, 831, 770, 692, 666, 627, 509 cm^{-1}; m.p. 109-110^{o}C; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_9H_6O_2F_2SeNa$ 286.9393; Found 286.9383.

***7-((difluoromethyl)selanyl)-4-methyl-2H-chromen-2-one (3r)*:** White solid (33 mg, 46% yield), petroleum ether/ethyl acetate 5:1(v/v) as eluents for column chromatography, ^{1}H

NMR (400 MHz, $CDCl_3$) δ .7.60 (d, J = 7.2 Hz, 1H), 7.56-7.35 (m, 2H), 7.24 (t, J = 54.8 Hz, 1H), 6.33 (s, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 153.4, 151.8, 131.2, 127.7 (t, J = 3.0 Hz), 125.3, 123.9, 120.7, 116.5 (t, J = 289.0 Hz), 116.2, 18.7; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -89.98 (s, 2F); IR (KBr): 3427, 3085, 3060, 2962, 2926, 1766, 1728, 1716, 1682, 1622, 1594, 1542, 1434, 1389, 1289, 1247, 1174, 1090, 1051, 1039, 1008, 946, 904, 868, 822, 708, 675, 563cm^{-1}; m.p. 150-152^oC; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_{11}H_8O_2F_2SeNa$ 312.9550; Found 312.9534.

***2-((difluoromethyl)selanyl)anthracene-9,10-dione (3s)*:** Light yellow solid (56 mg, 59% yield from general procedure), petroleum ether/ethyl acetate 50:1(v/v) as eluents for column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 1.2 Hz, 1H), 8.32-8.30 (m, 2H), 8.26 (d, J = 8.4 Hz, 1H), 8.04 (dd, J = 8 Hz, 1.6 Hz, 1H), 7.84-7.81 (m, 2H), 7.33 (t, J = 54.8 Hz, 1H); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -89.72 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.9, 182.7, 140.7, 134.9, 134.8, 134.2, 133.9, 133.8, 133.7, 133.6, 132.4, 128.6, 127.9, 127.8, 116.7 (t, J = 288.0 Hz); IR (KBr): 3455, 3070, 3031, 2963, 2923, 2852, 1676, 1580, 1322, 1283, 1259, 1170, 1054, 1043, 953, 927, 853, 797, 710, 675, 632cm^{-1}; m.p. 128-130^oC; HRMS (EI-quadrupole) m/z: Calcd for $[M]^+$ $C_{15}H_8O_2F_2Se$ 337.9658; Found 337.9651.

***1-((difluoromethyl)selanyl)anthracene-9,10-dione (3t)*:** Light yellow solid (51 mg, 61% yield from general procedure), petroleum ether/ethyl acetate 30:1(v/v) as eluents for column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31-8.24 (m, 3H), 7.94 (d, J =

8.0 Hz, 1H), 7.83-7.81 (m, 2H), 7.71 (t, J = 8 Hz, 1H), 7.42 (t, J = 53.6 Hz, 1H); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -97.99 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 184.1, 182.5, 136.1, 135.8, 134.6, 134.5, 134.0, 133.8, 133.2, 132.7, 130.5, 127.6, 127.3, 125.9, 117.1(t, J = 285.0 Hz); IR (KBr): 3439, 3076, 2973, 1978, 1854, 1665, 1642, 1593, 1568, 1447, 1419, 1338, 1313, 1277, 1242, 1179, 1164, 1125, 1097, 1064, 1032, 951, 926, 881, 805, 727, 706, 682, 642, 620cm^{-1}; m.p. 189-190^oC; HRMS (ESI-quadrupole) m/z: Calcd for $[M+H]^+$ $C_{15}H_9O_2F_2Se$ 338.9730; Found 338.9698.

***3-((difluoromethyl)selanyl)quinoline (3u)*:** Light yellow solid (40 mg, 60% yield from general procedure), petroleum ether/ethyl acetate 50:1(v/v) as eluents for column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 1.6 Hz, 1H), 8.53 (d, J = 0.8 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.83-7.82 (m, 2H), 7.61 (t, J = 7.2Hz, 1H), 7.23 (t, J = 54.8Hz, 1H); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -89.98 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.3, 147.9, 144.5, 131.0, 129.6, 128.5, 127.9, 127.6, 117.2, 116.1 (t, J = 289.0Hz); IR (KBr): 3448, 3048, 2964, 1853, 1615, 1581, 1563, 1491, 1368, 1353, 1318, 1291, 1254, 1058, 1041, 1017, 952, 910, 780, 750, 688, 629, 174cm^{-1}; m.p. 76-77^oC; HRMS (ESI-quadrupole) m/z: Calcd for $[M+H]^+$ $C_{10}H_8NF_2Se$ 259.9785; Found 259.9766.

6-((difluoromethyl)selanyl)benzo[d]thiazole (3v): Colorless oil (30 mg, 49% yield from general procedure), petroleum ether/ethyl acetate 60:1(v/v) as eluents for column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.31 (d, J = 1.2 Hz, 1H),

8.12 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.21 (t, J = 55.2 Hz, 1H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -90.34 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 155.7, 154.0, 135.0, 134.4, 130.3, 124.5, 120.3, 116.9 (t, J = 288.0 Hz); IR (KBr): 3059, 1582, 1538, 1456, 1429, 1389, 1290, 1268, 1200, 1157, 1135, 1035, 877, 839, 805, 742, 691, 670 cm^{-1}; HRMS (ESI-quadrupole) m/z: Calcd for $[M+H]^+$ $C_8H_6NF_2SSe$ 265.9349; Found 265.9335.

ethyl 5-((difluoromethyl)selanyl)benzofuran-2-carboxylate (3w): White solid (41 mg, 51% yield from general procedure), petroleum ether/ethyl acetate 20:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 1.2 Hz, 1H), 7.74 (dd, J = 8.8 Hz, 1.6 Hz 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.52 (s, 1H), 7.18 (t, J = 55.2 Hz, 1H). 4.46 (q, J = 7.2 Hz, 2H) 1.44 (t, J = 7.2Hz, 3H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -90.74 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 156.1, 146.9, 135.8, 131.8, 128.5, 117.9, 116.9 (t, J = 288.0 Hz), 113.6, 113.3, 61.9, 14.4; IR (KBr): 3059, 1582, 1538, 1456, 1429, 1389, 1290, 1268, 1200, 1157, 1135, 1035, 877, 839, 805, 742, 691, 670cm^{-1}; m.p. 105-106^{o}C; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_{12}H_{10}O_3F_2SeNa$ 342.9655; Found 342.9640.

***ethyl 2-(4-((difluoromethyl)selanyl)phenoxy)-2-methylpropanoate (3aa)*:** Colorless oil (65 mg, 77% yield from general procedure), petroleum ether/ethyl acetate 50:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.8 Hz, 2H), 7.09 (t, J = 55.6 Hz, 1H), 6.79 (dd, J = 11.6 Hz, 2.8 Hz, 2H), 4.23 (q, J = 7.2 Hz,

2H), 1.62 (s, 6H), 1.23 (t, J = 7.2Hz, 3H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -90.87 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 174.0, 157.1, 138.0, 129.3, 119.5, 117.0 (t, J = 288.0 Hz), 79.4, 61.7, 25.5, 14.2; IR (KBr): 2990, 1731, 1585, 1570, 1488, 1467, 1383, 1365, 1281, 1239, 1176, 1136, 1058, 968, 915, 827, 765, 712, 691, 670cm^{-1}; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_{13}H_{16}O_3F_2SeNa$ 361.0125; Found 361.0113 .

***4-((difluoromethyl)selanyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (3ab)*:** White solid (42 mg, 44% yield from general procedure), petroleum ether/ethyl acetate 1:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 54.4 Hz, 1H), 4.99 (dd, J = 12.0 Hz, 5.4 Hz, 2H), 2.95-2.71 (m, 3H), 2.20-2.14 (m, 1H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -91.82 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 167.7, 166.9, 166.4, 137.3, 135.1, 133.4, 130.4, 126.5, 123.1, 116.0 (t, J = 288.0 Hz), 49.7, 31.5, 22.7; IR (KBr): 3208, 3094, 1786, 1771, 1712, 1391, 1368, 1342, 1325, 1308, 1261, 1197, 1117, 1048, 1016, 993, 891, 813, 801, 736, 720, 663, 613, 572, 533, 470cm^{-1}; m.p. 236-238^{o}C; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_{14}H_{10}N_2O_4F_2SeNa$ 410.9666; Found 410.9667.

***4-((difluoromethyl)selanyl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (3ac)*:** White solid (44 mg, 48% yield from general procedure), petroleum ether/ethyl acetate 2:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.22 (t, J = 54.8 Hz, 1H), 6.25 (s, 1H), 2.39

(s, 3H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -89.69 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.5, 157.6, 140.0, 136.1, 130.1, 127.9, 116.5 (t, J = 289.0 Hz), 95.7, 12.9; IR (KBr): 3092, 2993, 2915, 2850, 2811, 1617, 1474, 1408, 1387, 1351, 1295, 1265, 1184, 1173, 1072, 1058, 1043, 1011, 938, 915, 826, 802, 750, 665, 601, 563cm^{-1}; m.p. 161-162^{o}C; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_{11}H_{10}N_2O_3F_2SSeNa$ 390.9438; Found 390.9423.

***(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-((difluoromethyl)selanyl)benzoate (3ad)*:** Colorless oil (78 mg, 80% yield from general procedure), petroleum ether/ethyl acetate 50:1(v/v) as eluents for column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 54.8 Hz, 1H), 6.79 (td, J = 11.2 Hz, 4.0 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H). 1.62 (s, 6H) 1.23 (t, J = 7.2Hz, 3H); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -89.91 (s, 2F); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.5, 135.6, 131.7, 130.5, 129.4 (t, J = 3.0 Hz), 116.8 (t, J = 287.0 Hz), 75.4, 47.4, 41.0, 35.4, 31.6, 26.6, 23.7, 22.2, 20.9, 16.6; IR (KBr): 3436, 2957, 2925, 2870, 1716, 1592, 1456, 1392, 1370, 1287, 1270, 1178, 1116, 1077, 1063, 1015, 961, 759, 685cm^{-1}; HRMS (ESI-quadrupole) m/z: Calcd for $[M+Na]^+$ $C_{18}H_{24}O_2F_2SeNa$ 413.0802; Found 413.0809 .

AUTHOR INFORMATION

Corresponding Author

*E-mail: lukui@tust.edu.cn; hxxyzhx@mail.tjnu.edu.cn;

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Mechanistic studies for reagent **1** under white LED, by 19F NMR monitoring, and by trapping experiments as well as Spectroscopic for compounds **1, 3a-3w and 3aa-3ad** is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

1 (a) Hansch, C.; Leo A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991,** *91,* 165−195. (b) Muller, K.; Faeh C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science.* **2007,** *317,* 1881 − 1886. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008,** *37,* 320−330. (d) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine‐Containing Functional Groups. *Angew. Chem. Int. Ed.* **2013,** *52,* 8214−8264. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J.; Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014,** *114,* 2432−2506. (f) Landelle, G.; Panossian, A.;

Leroux, F. R. Trifluoromethyl Ethers and –Thioethers as Tools for Medicinal Chemistry and Drug Discovery. *Curr. Top. Med. Chem.* **2014,** *14,* 941−951. (g) Liu, Q.-H.; Ni, C.-F.; Hu, J.-B. China's Flourishing Synthetic Organofluorine Chemistry: Innovations in the New Millennium. *Natl. Sci. Rev.* **2017,** *4,* 303−325.

2 (a) Leroux, F. R.; Manteau, B.; Vors, J. P.; Pazenok, S. Trifluoromethyl Ethers–Synthesis and Properties of an Unusual Substituent. *Beilstein. J. Org. Chem.* **2008,** *4,* 13. (b) Lin, J.-H.; Ji, Y.-L.; Xiao, J.-C. Recent Advances in C-H Trifluoromethylthiolation and Trifluoromethoxylation Reactions. *Curr. Org. Chem.* **2015,** *19,* 1541 − 1553. (c) Tlili, A.; Toulgoat, F.; Billard, T. Synthetic Approaches to Trifluoromethoxy-Substituted Compounds. *Angew. Chem. Int. Ed.* **2016,** *55,* 11726 − 11735. (d) Besset, T.; Jubault, P.; Pannecoucke, X.; Poisson, T. New Entries Toward the Synthesis of OCF_3-Containing Molecules. *Org. Chem. Front.* **2016,** *3,* 1004−1010. (e) Lee, K. N.; Lee, J. W.; Ngai, M. Y. Recent Development of Catalytic Trifluoromethoxylation Reactions. *Tetrahedron.* **2018,** *74,* 7127−7135. (f) Ghiazza, C.; Billard, T.; Tlili, A. Merging Visible-Light Catalysis for the Direct Late-Stage Group-16-Trifluoromethyl Bond Formation. *Chem. -Eur. J.* **2019,** *25,* 6482−6495. (g) Zhang, X.-F.; Tang, P.-P. Recent Advances in New Trifluoromethoxylation Reagents. *Sci. China. Chem.* **2019,** *62,* 525−532. (h) Lee, J. W.; Lee, K. N.; Nagi, M. Y. Synthesis of Tri- and Difluoromethoxylated Compounds by Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 11171−11181.

3 Lee, J. W.; Zheng, W.-J.; Morales, C. A.; Liu, P.; Nagi, M. Y. Catalytic Radical Difluoromethoxylation of Arenes and Heteroarenes. *Chem. Sci.* **2019,** *10,* 3217−3222.

4 (a) Tlili, A.; Billard, T. Formation of C-SCF_3 Bonds through Direct Trifluoromethylthiolation. *Angew. Chem. Int. Ed.* **2013,** *52,* 6818−6819. (b) Toulgoat, F.; Alazet, S.; Billard, T. Direct Trifluoromethylthiolation Reactions: The “Renaissance” of an Old Concept. *Eur. J. Org. Chem.* **2014,** *2014*, 2415−2428. (c) Shao, X.-X.; Xu, C.-F.;

Lu, L.; Shen, Q. Shelf-Stable Electrophilic Reagents for Trifluoromethylthiolation. *Acc. Chem. Res.* **2015,** *48,* 1227−1236. (d) Xu, X.-H.; Matsuzaki, K.; Shibata, N. Synthetic Methods for Compounds Having CF_3–S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. *Chem. Rev.* **2015,** *115,* 731−764. (e) Chachignon, H.; Cahard, D. State of the Art in Electrophilic Trifluoromethylthiolation Reagents. *Chin. J. Chem.* **2016,** *34,* 445 − 454. (f) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. Late Stage Trifluoromethylthiolation Strategies for Organic Compounds. *Org. Biomol. Chem.* **2016,** *14,* 7150−7182. (g) Zhang, P.-P.; Lu, L.; Shen, Q. Recent Progress on Direct Trifluoromethylthiolating Reagents and Methods. *Acta Chim. Sin.* **2017,** *75,* 744−769.

5 (a) Xiong, H.-Y.; Pannecoucke, X.; Besset, T. Recent Advances in the Synthesis of SCF_2H- and SCF_2FG-Containing Molecules. *Chem. - Eur. J.* **2016,** *22,* 16734−16749. (b) Zhao, X.; Wei, A.-Q.; Li, T.-J.; Su, Z.-Y.; Chen, J.; Lu, K. Transition-Metal Free Direct Difluoromethylthiolation of Electron-rich Aromatics with Difluoromethanesulfonyl Chloride. *Org. Chem. Front.* **2017,** *4,* 231−235. (c) Pannecoucke, X.; Besset, T. Use of $ArSO_2SR_f$ Reagents: an Efficient Tool for the Introduction of SR_f Moieties. *Org. Biomol. Chem.* **2019,** *17,* 1683−1693. (d) Hardy, M.-A.; Chachignon, H.; Cahard, D. Advances in Asymmetric Di- and Trifluoromethylthiolation, and Di- and Trifluoromethoxylation Reactions. *Asian J. Org. Chem.* **2019,** *8,* 591−609.

6 (a) Ghiazza, C.; Tlili, A.; Billard, T. Electrophilic Trifluoromethylselenolation of Terminal Alkynes with Se-(trifluoromethyl) 4-methylbenzenesulfonoselenoate. *Beilstein J. Org. Chem.* **2017,** *13,* 2626−2630. (b) Ghiazza, C.; Debrauwer, V.; Billard, T.; Tlili, A. Exploring the Reactivity of Trifluoromethyl Tolueneselenosulfonate with Alkynes under Copper Catalysis. *Chem. - Eur. J.* **2018,** *24,* 97−100. (c) Tlili, A.; Ismalaj, E.; Glenadel, Q.; Ghiazza, C.; Billard, T. Synthetic Approaches to Trifluoromethylselenolated Compounds. *Chem. - Eur. J.* **2018,** *24,* 3659 − 3670. (d) Ghiazza, C.; Khrouz, L.;

Monnereau, C.; Billard, T.; Tlili, A. Visible-Light Promoted Fluoroalkylselenolation: Toward the Reactivity of Unsaturated Compounds. *Chem. Commun.* **2018,** *54,* 9909 − 9912. (e) Glenadel, Q.; Ismalaj, E.; Billard, T. A Metal-Free Route to Heterocyclic Trifluoromethyl- and Fluoroalkylselenolated Molecules. *Org. Lett.* **2018,** *20,* 56−59. (f) Ghiazza, C.; Ndiaye, M.; Hamdi, A.; Tlili, A.; Billard, T. Regioselective Remote C H Fluoroalkylselenolation of 8-Aminoquinolines. *Tetrahedron.* **2018,** *74,* 6521−6526.

7 (a) Suzuki, H.; Yoshinaga, M.; Takaoka, K.; Hiroi, Y. A Simple Synthesis of Aryl Difluoromethyl Selenides and Tellurides. *Synthesis.* **1985,** *1985,* 497−499. (b) Uneyama, K.; Maeda, K.; Tokunaga, Y.; Itano, N. Reaction of Difluoromethyl Phenyl Selenoxide with Acetic Anhydride. A Route to Difluoro(phenylseleno)methylation of Ethers. *J. Org. Chem.* **1995,** *60,* 370−375. (c) Mehta, V. P.; Greaney, M. F. S-, N-, and Se-Difluoromethylation Using Sodium Chlorodifluoroacetate. *Org. Lett.* **2013,** *15,* 5036−5039. (d) Lin, Y.-M.; Yi, W.-B.; Shen, W.-Z.; Lu, G.-P. A Route to α-Fluoroalkyl Sulfides from α-Fluorodiaroylmethanes. *Org. Lett.* **2016,** *18,* 592−595. (e) Heine, N. B.; Studer, A. Radical Difluoromethylation of Thiols with (Difluoromethyl)triphenylphosphonium Bromide. *Org. Lett.* **2017,** *19,* 4150−4153. (f) T, D.; N, J.; Zhang, C.-P. A Convenient, Transition Metal-Free Synthesis of Difluoromethyl selenoethers from Organic Selenocyanates and $TMSCF_2H$. *Tetrahedron.* **2018,** *74,* 5642−5649.

8 (a) Glenadel, Q.; Ismalaj, E.; Billard, T. Benzyltrifluoromethyl (or Fluoroalkyl) Selenide: Reagent for Electrophilic Trifluoromethyl (or Fluoroalkyl) Selenolation. *J. Org. Chem.* **2016,** *81,* 8268−8275. (b) Ghiazza, C.; Billard, T.; Tlili, A. Trifluoromethyl- and Fluoroalkylselenolations of Alkynyl Copper (I) Compounds. *Chem. - Eur. J.* **2017,** *23,* 10013−10016. (c) Ghiazza, C.; Glenadel, Q.; Tlili, A.; Billard, T. Trifluoromethylselenolation and Fluoroalkylselenolation of Alkenes by Electrophilic Addition. *Eur. J. Org. Chem.* **2017,** *2017,* 3812−3814. (d) Ghiazza, C.; Tlili, A.; Billard,

T. Direct α‐C–H Trifluoromethylselenolation of Carbonyl Compounds. *Eur. J. Org. Chem.* **2018,** *2018,* 3680−3683.

9 For Selected examples see: (a) Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J. Direct Conversion of Arylamines to Pinacol Boronates: A Metal-Free Borylation Process. *Angew. Chem. Int. Ed.* **2010,** *49,* 1846−1849. (b) Yu, J.; Zhang, L.; Yan, G. Metal‐Free, Visible Light-Induced Borylation of Aryldiazonium Salts: A Simple and Green Synthetic Route to Arylboronates. *Adv. Synth. Catal.* **2012,** *354,* 2625−2628. (c) Qiu, D.; Jin, L.; Zheng, Z.; Meng, H.; Mo, F.; Wang, X.; Zhang, Y.; Wang, J. Synthesis of Pinacol Arylboronates from Aromatic Amines: A Metal-Free Transformation. *J. Org. Chem.* **2013,** *78,* 1923−1933. (d) Qiu, D.; Zhang, Y.; Wang, J. Direct Synthesis of Arylboronic Pinacol Esters from Arylamines. *Org. Chem. Front.* **2014,** *1*, 422−425. (e) Qiu, D.; Meng, H.; Jin, L.; Tang, S.; Wang, S.; Mo, F.; Zhang, Y.; Wang, J. Synthesis of Arylboronic Pinacol Esters from Corresponding Arylamines. *Org. Synth.* **2014,** *91,* 106−115. (f) Xu, Y.-L.; Yang, X.-Y.; Fang, H. Additive- and Photocatalyst-Free Borylation of Arylazo Sulfones under Visible Light. *J. Org. Chem.* **2018,** *83,* 12831−12837.

10 Wang, S.; Qiu, D.; F.; Mo, F.; Zhang, Y.; Wang, J. Metal-Free Aromatic Carbon–Phosphorus Bond Formation via a Sandmeyer-Type Reaction. *J. Org. Chem.* **2016,** *81,* 11603−11611.

11 For Selected examples see: (a) Adams, D. J.; Goddard, A.; Clark, J. H.; Macquarrie, D. J. Trifluoromethylthiodediazoniation: A Simple, Efficient Route to Trifluoromethyl Aryl Sulfides. *Chem. Commun.* **2000,** 987−988. (b) Majek, M.; Jacobivon Wangelin, A. Organocatalytic Visible Light Mediated Synthesis of Aryl Sulfides. *Chem. Commun.* **2013,** *48,* 5507−5509. (c) Koziakov, D.; Majek, M.; Jacobivon Wangelin, A. Metal-Free Radical Thiolations Mediated by Very Weak Bases. *Org. Biomol. Chem.* **2016,** *14,* 11347−11352. (d) Matheis, C.; Wagner, V.; Goossen, L. J. Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero) Aromatic Amines

Catalyzed by Copper. *Chem. - Eur. J.* **2016,** *22,* 79−82. (e) Koziakov, D.; Majek, M.; Jacobivon Wangelin, A. Radical Aromatic Trifluoromethylthiolation: Photoredox Catalysis vs. Base Mediation. *Eur. J. Org. Chem.* **2017,** *2017,* 6722−6725.

12 For Selected examples see: (a) Qiu, D.; Meng, H.; Jin, L.; Wang, S.; Tang, S.; Wang, X.; Mo, F.; Zhang, Y.; Wang, J. Synthesis of Aryl Trimethylstannanes from Aryl Amines: A Sandmeyer-Type Stannylation Reaction. *Angew. Chem. Int. Ed.* **2013,** *52,* 11581−11584. (b) Qiu, D.; Wang, S.; Tang, S.; Meng, H.; Jin, L.; Mo, F.; Zhang, Y.; Wang, J. Synthesis of Trimethylstannyl Arylboronate Compounds by Sandmeyer-Type Transformations and Their Applications in Chemoselective Cross-Coupling Reactions. *J. Org. Chem.* **2014,** *79,* 1979−1988.

13 For Selected examples see: (a) Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. Silver-Mediated Trifluoromethylation of Aryldiazonium Salts: Conversion of Amino Group into Trifluoromethyl Group. *J. Am. Chem. Soc.* **2013,** *135,* 10330−10333. (b) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. Copper-Promoted Sandmeyer Trifluoromethylation Reaction *J. Am. Chem. Soc.* **2013,** *135,* 8436−8439. (c) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Goossen, L. J. Sandmeyer Trifluoromethylation of Arenediazonium Tetrafluoroborates. *Angew. Chem. Int. Ed.* **2013,** *52,* 7972−7975. (d) Wang, X.; Xu, Y.; Zhou, Y.; Zhang, Y.; Wang, J. Conversion of Aromatic Amino into Trifluoromethyl Groups through a Sandmeyer-Type Transformation. *Synthesis.* **2014,** *46,* 2143−2148. (e) Bayarmagnai, B.; Matheis, C.; Risto, E.; Goossen, L. J. One-Pot Sandmeyer Trifluoromethylation and Trifluoromethylthiolation *Adv. Synth. Catal.* **2014,** *356,* 2343−2348.

14 Zhao, X.; Zheng, X.-C.; Tian, M.-M.; Tong, Y.-F.; Yang, B.; Wei, X.-F.; Qiu, D.; Lu, K. Visible-Light Photocatalytic Trifluoromethylthiolation of Aryldiazonium Salts:

Conversion of Amino Group into Trifluoromethylthiol Group. *Org. Chem. Front.* **2018,** *5,* 2636−2640.

15 Ghiazza, C.; Debrauwer, V.; Monnereau, C.; Khrouz, L.; Médebielle, M.; Billard, T.; Tlili, A. Visible-Light-Mediated Metal-Free Synthesis of Trifluoromethylselenolated Arenes. *Angew. Chem. Int. Ed.* **2018,** *57,* 11781−11785.

16 Glenadel, Q.; Ghiazza, C.; Tlili, A.; Billard, T. Copper-Catalyzed Direct Trifluoro- and Perfluoroalkylselenolations of Boronic Acids with a Shelf-Stable Family of Reagents. *Adv. Synth. Catal.* **2017,** *359,* 3414−3420.

17 Romero, N.; Nicewicz, D. Organic Photoredox Catalysis. *Chem. Rev.* **2016,** *116,* 10075−10166.

18 Li, Y.; Tian, K.; Qin, A.; Zhang, L.; Huo, L.; Lei, L.; Shen, Z.; Song, H.; Feng, Z. Discovery of Novel Urea Derivatives as Dual-Target Hypoglycemic Agents that Activate Glucokinase and PPARγ. *Eur. J. Med. Chem.* **2014**, *76*, 182−192.

19 Asaoka, S.; Joza, A.; Minagawa, S.; Song, L.; Suzuki, Y.; Iyoda, T. Fast Controlled Living Polymerization of Arylisocyanide Initiated by Aromatic Nucleophile Adduct of Nickel Isocyanide Complex. *ACS. Macro. Lett.* **2013**, *2*, 906−911.