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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02424 • Publication Date (Web): 24 Oct 2019

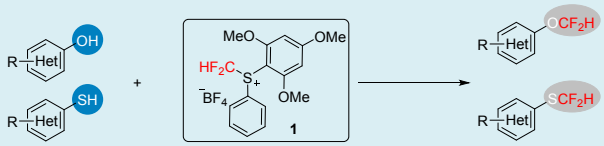
Difluoromethylation of Phenols and Thiophenols with *S*-(Difluoromethyl)sulfonium Salt: Reaction, Scope and Mechanistic Study

Guo-Kai Liu,*†[a] Wen-Bing Qin,†[a] Xin Li,[a] Li-Ting Lin [a] and Henry N. C. Wong[b]

[a] School of Pharmaceutical Sciences, Shenzhen University Health Science Centre, Shenzhen University, 3688 Nanhai Ave., Shenzhen 518060, China

[b] Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

Supporting Information



ABSTRACT: A facile and practical approach for the difluoromethylation of phenols and thiophenols was described. Making use of the recently developed bench-stable *S*-(difluoromethyl)sulfonium salt as the difluorocarbene precursor, a wide variety of diversely functionalized phenols and thiophenols were readily converted to their corresponding aryl difluoromethyl ethers in good to excellent yields in the presence of lithium hydroxide. Chemoselectivity of various *O, S*-nucleophiles toward difluorocarbene was systematically studied, suggesting the reactivity order ArS– > RS–, ArO– > ROH > RO– , ArSH, ArOH, RSH.

INTRODUCTION

Difluoromethoxy group (OCF_2H) is an importantly structural motif, and have found widespread utility in pharmaceuticals[1], agrochemicals[2] and materials.[3] Particularly, Aryl difluoromethyl ethers play important roles in medicinal chemistry and drug discovery because the difluoromethyl group is capable of serving as a bioisostere to CH_3OH and SH units,[4] as well as a lipophilic hydrogen-bond donor.[5] As illustrated in Figure 1, aryl difluoromethyl ether moiety is present in the selective phosphodiesterase type 4 (PDE 4) inhibitor Roflumilast, used for treatment of chronic obstructive pulmonary disease (COPD).[6] Pantoprazole is popular as an irreversible proton pumping inhibitor,[7] while Garenoxacin is a novel broad-spectrum quinolone antiseptic.[8] It is noteworthy that GRN-529, developed by Wyeth, is in clinical trials stage for the treatment of autism in children.[9] Therefore, the development of practical, efficient approaches to aryl difluoromethyl ethers remains attractive.

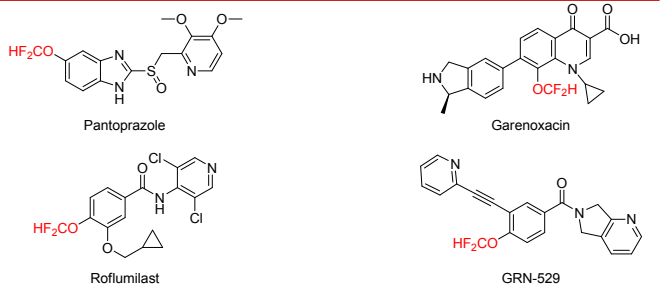
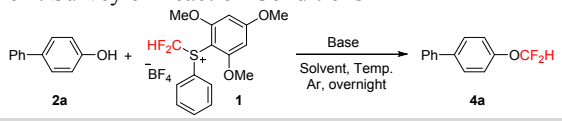


Figure 1. Drugs containing OCF_2H building block

Generally, $ArOCF_2H$ and $ArSCF_2H$ are synthesized via *O, S*-difluoromethylation of phenols and thiophenols, which represents a routine strategy for the preparation of aryl difluoromethyl (thio)ethers, although a few examples installed these compounds by metal-catalyzed or visible light-promoted difluoromethylthiolation and difluoromethoxylation using difluoromethoxylating reagent and difluoromethylthiolating reagents.[10] Phenols are sufficiently acidic to form phenoxide anions under strongly alkaline conditions, and phenoxide anions react readily with difluorocarbenes generated *in situ* from various reagents. In the past decades, many efforts have been circumvented to develop reagents and protocols for this purpose.[11] Initially, the ozone-depleting substrates (ODS), *i.e.*, HCF_2Cl,[11a] HCF_3[11b] and CF_2Br_2[11c] were used for the difluoromethylation of phenols. Afterwards, some non-ozone-depleting substrates (NODS) difluorocarbene precursors have been recorded for the synthesis of difluoromethyl ethers from phenols, including FSO_2CF_2COOH,[12a] $PhCOCF_2Cl$,[12b] $PhSO_2CF_2Cl$,[12c] $BrCF_2P(O)(OEt)_2$,[13a] ClF_2COONa,[13b] *n*-$Bu_3N(CF_2H)Cl$,[13c] HCF_2OTf,[14a] and $BrCF_2CO_2Et$.[14b] However, these approaches employing ODS and NODS reagents somewhat suffer from high reaction temperature, long reaction time, and a narrow substrate scope. These reagents usually do not tolerate a great deal of functional groups, thus limiting their widespread applicability. To remedy these problems, Hu revealed an efficient protocol using the commercially available $TMSCF_2Br$ as a difluorocarbene source.[15] Later, Xiao reported $Ph_3P^+CF_2COO^-$ (PDFA) as an efficient phosphonium ylide reagent that also leads to difluoromethylation reaction of phenols and thiophenols, though only a few simple examples

were demonstrated.[16] As another possibility, our group has develope

Table 1. Survey of Reaction Conditions[a]



entry	base (equiv)	solvent	temp (°C)	yield (%)
1	LiOH (2.2)	toluene	rt.	70
2	LiOH (2.2)	chlorobenzene	rt.	63
3	LiOH (2.2)	THF	rt.	20
4	LiOH (2.2)	DCM	rt.	78
5	LiOH (2.2)	CH_3CN	rt.	38
6	LiOH (2.2)	fluorobenzene	rt.	80
7	KOH (1.0 M, 2.2)	fluorobenzene	rt.	60
8	NaH (2.2)	fluorobenzene	rt.	73
9	K_3PO_4 (2.2)	fluorobenzene	rt.	30
10	NaOAc (2.2)	fluorobenzene	rt.	13
11	Cs_2CO_3 (2.2)	fluorobenzene	rt.	28
12	LiOH (1.6)	fluorobenzene	rt.	60
13	LiOH (3.0)	fluorobenzene	rt.	57
14	LiOH (2.2)	fluorobenzene	0	59
15	LiOH (2.2)	fluorobenzene	10	60
16	NaH (2.2)	fluorobenzene	10	81
17	NaH (2.2)	fluorobenzene	0	62

[a] Reaction conditions (unless otherwise specified): 2a (0.2 mmol), 1 (1.2 equiv, 0.24 mmol), fluorobenzene (2.0 mL), rt, overnight, isolated yields.

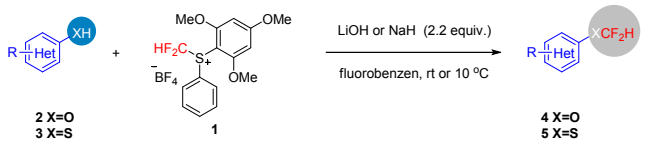
-d bench-stable sulfonium salts **1**, which we have employed as a highly effective difluoromethylating reagent for *C*-selective difluoromethylation of β-ketoesters and malonates,[17a] and also as a difluorocarbene precursor for *O*-difluoromethylation of aliphatic alcohols involving a five-membered transition state.[17b] Herein we examined whether sulfonium salt **1** can react with phenols and thiophenols under mild conditions to furnish diverse aryl difluoromethyl (thio)ethers.

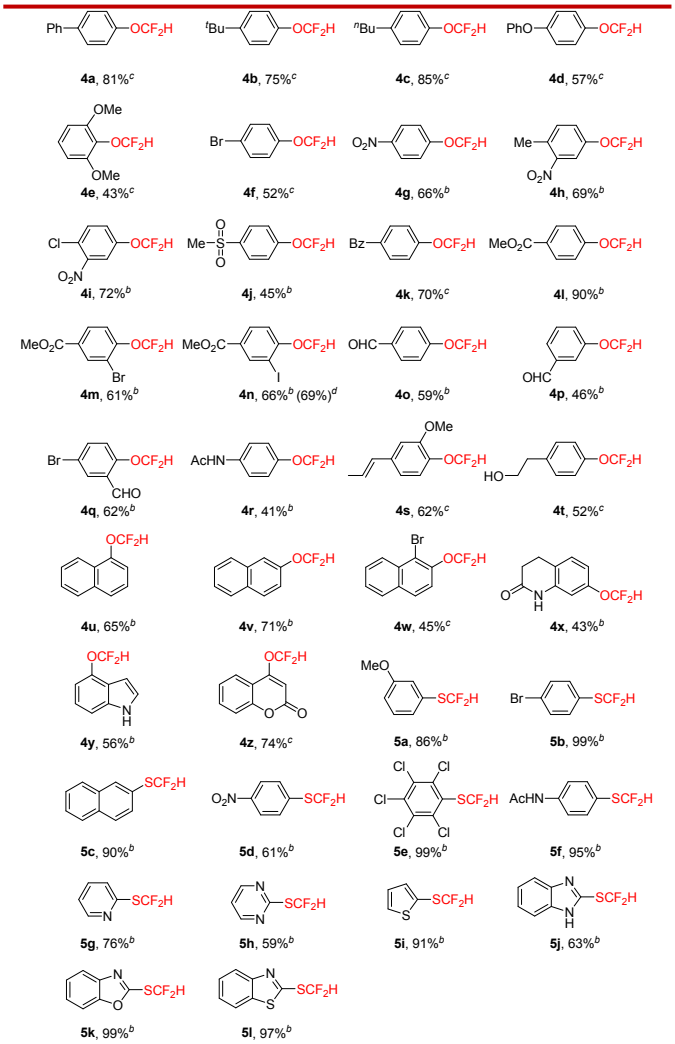
RESULTS AND DISCUSSION

Reaction conditions were optimized using 4-phenylphenol (**2a**) as a model substrate (Table 1). Thus, the reaction smoothly occurred with the use of 2.2 equivalents of LiOH at room temperature in toluene, affording difluoromethyl ether **4a** in an isolated yield of 70% (entry 1). Subsequently, the effect of various solvents was investigated (entries 2-6), dichloromethane and arene solvents such as toluene, chlorobenzene and fluorobenzene, were suitable solvents, with fluorobenzene being proved to be the best (80%, entry 6). Next, various bases were investigated and results clearly showed that strong bases (entries 6-8) are superior to weaker ones (entries 9-11). NaH gave a high yield (73%) as that of LiOH (entry 8). Yield fell when the quantity of LiOH was reduced to 1.6 or increased to 3.0 equivalents (entries 12-13). Reaction temperature also showed influence on yields. Reactions that were run at 0 °C and 10 °C led to lower yields of 59 % and 60%, respectively (entries 14-15), but higher yield of 81% was obtained at 10 °C in the presence of NaH (entry 16).

Using the optimized reaction conditions (entries 6 and 16, Table 1), we then examined the scope of phenols for the synthesis of various aryl difluoromethyl ethers. Both electron-deficient (**2f-q**) and electron-rich phenols (**2a-e, 2s-t**) were readily difluoromethylated to give good to high yields. A broad range of functional groups, including nitro (**4g-i**), sulfone (**4j**), ester (**4l-n**), aldehyde (**4o-q**), alkene (**4s**), alcohol (**4t**), amine (**4y**), amide (**4r, 4x**), benzoyl (**4k**), and methoxy

Scheme 1. Difluoromethylation of phenols and thiophenols[a]





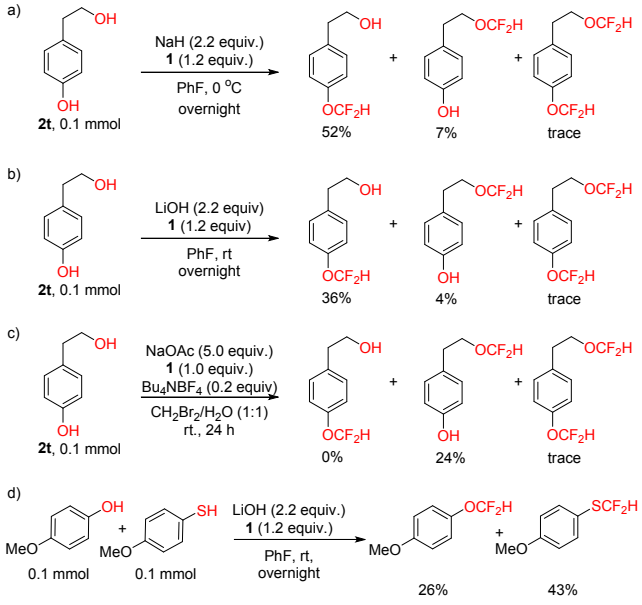
[a] Reaction conditions: **2** (0.2 mmol, 1.0 equiv), base (0.44 mmol, 2.2 equiv), **1** (0.24 mmol, 1.2 equiv), fluorobenzene (2.0 mL), rt, over night. Yields are for the isolated products **4**. [b] LiOH was used as a base. [c] NaH was used as a base, and the reaction proceed at 10 °C. [d] 5.0 mmol scale with LiOH as a base. Me = methyl, MeO = methoxy, ^{t}Bu = *tert*-butyl, Ac = Acetyl, Bz = benzoyl, Ph = phenyl.

(**4e**) were compatible with this reaction. The reaction also tolerated chloro, bromo and iodo substitutions at the *para*-positions (**4f, 4i**) or *ortho*-positions (**4m, 4n**), which allows further transformation through cross-coupling reactions. Importantly, this protocol exhibited chemoselectivity in a phenol bearing aliphatic alcohol (**4t**, 52%), alkene (**4s**, 62%), implying that phenoxides are more reactive than aliphatic alkoxides and alkenes in capturing difluorocarbene. Naphthols **2u-w** also took part in difluoromethylation reaction, leading to moderate to good yields. Remarkably, enol **2z** also proved to

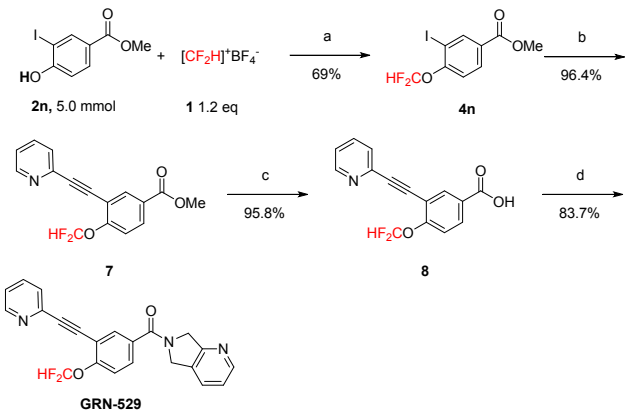
be a suitable substrate, offering the desired product **4z** in 74% yield. Heterocyclic compounds such as quinolinone, indole and coumarin were also well tolerated in this reaction, providing the desired products **4x**, **4y** and **4z** in 43%, 56% and 74% yields, respectively.

The potential usage of this protocol was further demonstrated in the difluoromethylation of thiophenols **3**. As shown in Scheme 1, under similar reaction conditions, *S*-(difluoromethyl)sulfonium salt **1** exhibited better reactivity with thiophenols than phenols, providing aryl difluoromethyl thioethers in high to excellent yields in all cases, regardless of whether the thiophenols containing electron-donating (**4a, 4f**) or electron-withdrawing groups (**4b, 4d, 4e**). Importantly, many heterocycles of pharmaceutical interest, including pyridine, pyrimidine, thiophene, imidazole, oxazole and thiazole were readily amenable under the mild reaction conditions, installing medicinally useful difluoromethythiolated heterocyclic compounds (**5g-l**).

Scheme 2. Study of chemoselectivity in difluoromethylation of (thio)phenols and alcohols[a]



Scheme 3. Synthesis of the drug candidate GRN-529



Reaction conditions: a) **2n** (1.39 g, 5 mmol), LiOH (11.0 mmol, 2.2 equiv.) and fluorobenzene (20.0 mL), **1** (6.0 mmol, 1.2 equiv.), rt, overnight. b) 2-Ethynylpyridine (1.01 equiv.), $Pd(PPh_3)_2Cl_2$ (1.0 mol%), CuI (2.0 mol%), NH_4OH (8 equiv.), NMP, 40 °C, 6 h. c) NaOH (1.2 equiv.), H_2O/CH_3OH, 40-45 °C, 3hr. d) AcOH, H_2O. d) CDI (1.1 equiv), DIPEA (3.1 equiv.), NMP, 6,7-Dihydro-5H-pyrrolo[3,4-b]pyridine dihydrochloride (1.05 equiv.).

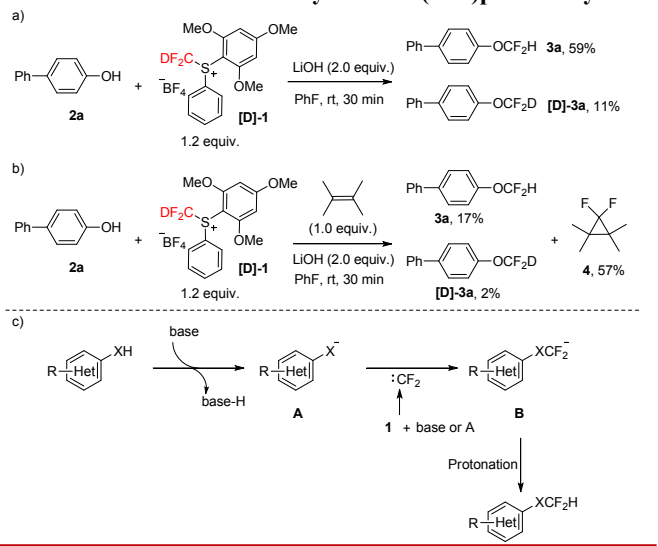
Subsequently, the chemoselectivity of this protocol as demonstrated in **4t** was studied further in order to give an insight into chemoselectivity. Thus, the difluoromethylation of **2t** was performed under the current condition, as well as under that reported previously by us,[17b] leading to different results. These results indicate that phenoxides (ArO –) are more reactive than aliphatic alkoxides (RO –) (Scheme 2a) and aliphatic alcohols (ROH) (Scheme 2b). Furthermore, aliphatic alcohols (ROH) are more reactive toward difluorocarbene than phenols (ArOH) (Scheme 2c). In addition, consistent with results shown in Scheme 1, thiophenoxide (ArS –) can more efficiently capture difluorocarbene than phenoxide (ArO –) (Scheme 2d) when they coexisted in a reaction mixture. We systematically investigated the reactivities of various *O, S*-nucleophiles toward difluorocarbene (see Supporting Information). Experimental results clearly suggest that the order of reactivities of *O, S*-nucleophiles is ArS– > RS–, ArO – > ROH > RO–, ArSH, ArOH, RSH.

To demonstrate the usefulness of this difluoromethylation protocol, the synthesis of the drug candidate GRN-529 was carried out (Scheme 3). As can be seen, difluoromethylation of the easily available phenol **2n** generated the key intermediate **4n** in an isolated yield of 69%, which underwent stepwise cross-coupling, hydrolysis (saponification) and amide formation to produce GRN-529 in an overall yield of 53.5%.

According to the mechanism proposed previously, difluoromethylation of phenols proceeds via reaction of phenoxides with *in situ* generated difluorocarbene. In order to gain more information and illustrate the plausible reaction pathway, some control experiments were carried out. Thus, the deuterated sulfonium salt **[D]-1** gave the deuterated product **[D]-3a** in a yield of only 11%, while **3a** was generated in 59% yield (Scheme 4a), suggesting that the reaction proceeds via a difluorocarbene process. Consistent with this phenomenon, addition of tetramethylethylene to the reaction expectedly generated 3,3- difluoro-1,1,2,2-tetramethylcyclopropane **4** in 57% yield (Scheme 4b), which provides a solid evidence that difluorocarbene was generated during this process. Therefore,

on the basis of the experimental data mentioned above and literatures reported previously by other groups, we propose the reaction mechanism in Scheme 4c. Thus, (thio)phenols are treated with base to deliver (thio)phenoxide **A**, which reacts with difluorocarbene generated *in situ* from reagent **1a** to give difluoromethylated anion **B**. Subsequent protonation yields the desired products.

Scheme 4. Control experiments and plausible reaction mechanism for difluoromethylation of (thio)phenols by 1a



CONCLUSIONS

In conclusion, we have developed a facile access to difluoromethyl aryl (thio)ethers from (thio)phenols with an *S*-(difluoromethyl)sulfonium salt **1** under mild reaction conditions. In this way, (thio)phenols bearing a variety of functional groups furnished desired products in good to excellent yields. The mechanistic study suggests that difluoromethylation occurs via a difluorocarbene process. A systematic study reveals that the reactivity and chemoselectivity of various *O*, *S*-nucleophiles toward difluorocarbene is ArS– > RS–, ArO– > ROH > RO–, ArSH, ArOH, RSH.

EXPERIMENT SECTION

General Experimental Information: ^{1}H NMR spectra were recorded on either a Bruker Ascend™ 400MHz (400 MHz) spectrometer, or a Bruker Ascend™ 500MHz (500 MHz) spectrometer at ambient temperature unless otherwise indicated. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet-doublet, m = multiplet, br = broad), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on either a Bruker Ascend™ 500MHz (126 MHz) spectrometer or a Bruker Ascend™ 400MHz (101 MHz) spectrometer at ambient temperature and were proton decoupled. Chemical shifts are reported in ppm from tetramethylsilane on the scale with the solvent resonance employed as the internal standard.

^{19}F NMR spectra were recorded on a Bruker AscendTM 400MHz (376 MHz) spectrometer at ambient temperature. Chemical shifts are reported in ppm from $CFCl_3$ as the internal standard. ESI-MS analyses were performed in positive ionization mode on an Agilent 1260-Infinity LC/MSD or a Q-Exactive high resolution mass spectrometer. All solvents and reagents were dried and purified by the usual techniques prior to use. Commercially available reagents were used as received. Reactions were monitored by TLC (detection with UV light). Flash chromatography: silica gel (300-400 mesh).

Difluoromethylation of Phenols 2 and Thiophenols 3 with Electrophilic Difluoromethylating Reagent 1

General Procedure A: phenols **2** or thiophenols **3** (0.2 mmol, 1.0 equiv), LiOH (0.44 mmol, 2.2 equiv) and fluorobenzene (2.0 mL) were added into a flame-dried Schlenk tube under argon atmosphere and stirred at room temperature for 30 min. Then **1** (0.24 mmol, 1.2 equiv) was added into the mixtures in one portion directly, and the reaction was stirred under argon atmosphere of argon at room temperature overnight. After filtering through celite and removing the solvent in vacuum, the residue was purified by flash column chromatography on silica gel to obtain the pure products.

General Procedure B: phenols **2** (0.2 mmol, 1.0 equiv), NaH (0.44 mmol, 2.2 equiv) and fluorobenzene (2.0 mL) were added into a flame-dried Schlenk tube under argon atmosphere and stirred at 10 oC for 30 min. Then **1** (0.24 mmol, 1.2 equiv) was added into the mixtures in one portion directly, and the reaction was stirred under an atmosphere of argon at 10 oC overnight. After filtering through celite and removing the solvent in vacuum, the residue was purified by flash column chromatography on silica gel to obtain the pure products.

4-(difluoromethoxy)-1,1'-biphenyl (4a)[18a]. Following general procedure **B**, **4a** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (35.8 mg, 81%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 11.5, 8.0 Hz, 4H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.58 (t, *J* = 73.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.6 (t, *J* = 2.8 Hz), 140.1, 138.6, 128.9, 128.5, 127.5, 127.0, 119.8, 116.0 (t, *J* = 259.8 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.2 (d, *J* = 74.2 Hz).

*1-(tert-butyl)-4-(difluoromethoxy)benzene (**4b**)*[18a]. Following general procedure **B**, **4b** was purified by silica gel chromatography (PE) as a colorless oil (30.2 mg, 75%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.38 (m, 2H), 7.11 – 7.05 (m, 2H), 6.51 (t, *J* = 74.3 Hz, 1H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.9 (t, *J* = 2.8 Hz), 148.4, 126.7, 119.1, 116.1 (t, *J* = 258.9 Hz), 34.4, 31.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -79.0 (d, *J* = 75.7 Hz).

*1-butyl-4-(difluoromethoxy)benzene (**4c**)*. Following general procedure **B**, **4c** was purified by silica gel chromatography (PE) as a colorless oil (34.3 mg, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.50 (t, *J* = 74.4 Hz, 1H), 2.63 (t, *J* = 7.7Hz, 2H), 1.61 (dd, *J* = 14.9, 7.3 Hz, 2H), 1.39 (dq, *J* = 14.3, 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.2, 140.2, 129.6, 119.4, 116.2 (t, *J* = 258.9 Hz), 34.9, 33.7, 22.3, 13.9. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.4 (d, *J* = 74.4 Hz). HRMS (ESI-TOF) m/z: $(M-H)^-$ Calcd for $C_{11}H_{13}F_2O$: 199.0940. Found: 199.0931.

*1-(difluoromethoxy)-4-phenoxybenzene (**4d**)*[18a]. Following general procedure **B**, **4d** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (27.0 mg, 57%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.17 – 7.11 (m, 3H), 7.08 – 7.00 (m, 4H), 6.50 (t, *J* =

74.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.2, 154.7, 146.5 (t, *J* = 2.9 Hz), 129.9, 123.5, 121.4, 117.0, 118.8, 116.03 (t, *J* = 260.2 Hz). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -80.7 (d, *J* = 74.0 Hz).

2-(difluoromethoxy)-1,3-dimethoxybenzene ***(4e)***. Following general procedure **B**, **4e** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (17.5 mg, 43%), m.p. 65.0-66.8 °C. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.15 (t, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 6.57 (t, *J* = 76.4 Hz, 1H), 3.89 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.2, 129.4 (t, *J* = 3.5 Hz), 126.4, 116.9 (t, *J* = 259.5 Hz), 105.2, 56.3. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -81.6 (d, *J* = 76.5 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_9H_{11}F_2O_3$: 205.0671. Found: 205.0673.

1-bromo-4-(difluoromethoxy)benzene ***(4f)***[18a]. Following general procedure **B**, **4f** was purified by silica gel chromatography (PE) as a colorless oil (23.2 mg, 52%). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.49 (m, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.51 (t, *J* = 73.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 150. 0 (t, *J* = 2.9 Hz), 132.8, 121.5, 118.5, 115.6 (t, *J* = 261.2 Hz). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -81.2 (d, *J* = 73.6 Hz).

1-(difluoromethoxy)-4-nitrobenzene ***(4g)*** [18a]. Following general procedure **A**, **4g** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (25.0 mg, 66%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 9.2 Hz, 2H), 7.28 (d, *J* = 9.2 Hz, 2H), 6.66 (t, *J* = 72.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.5 (t, *J* = 2.8 Hz), 144.8, 125.8, 119.3, 115.0 (t, *J* = 263.7 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -82.6 (d, *J* = 72.2 Hz).

4-(difluoromethoxy)-1-methyl-2-nitrobenzene ***(4h)***. Following general procedure **A**, **4h** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (28.1 mg, 69%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.57 (t, *J* = 72.6 Hz, 1H), 2.60 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.3, 148.9 (t, *J* = 3.1 Hz), 133.9, 130.8, 124.7, 116.2, 115.3 (t, *J* = 263.3 Hz), 19.9. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.9 (d, *J* = 72.4 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_8H_8F_2NO_3$: 204.0467. Found: 204.0468.

1-chloro-4-(difluoromethoxy)-2-nitrobenzene ***(4i)***[18b]. Following general procedure **A**, **4I** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (32.3 mg, 72%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 2.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.60 (t, *J* = 71.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1 (t, *J* = 3.0 Hz), 148.1, 133.0, 124.9, 123.8, 117.4, 115.0 (t, *J* = 265.3 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -82.4 (d, *J* = 72.2 Hz).

1-(difluoromethoxy)-4-(methylsulfonyl)benzene ***(4j)***. Following general procedure **A**, **4j** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (20.0 mg, 45%), m.p. 81.8-83.2 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.65 (t, *J* = 72.5 Hz, 1H), 3.07 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.9 (t, *J* = 2.8 Hz), 137.2, 129.7, 119.7, 115.1 (t, *J* = 263.0 Hz), 44.6. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -82.3 (d, *J* = 72.3 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_8H_9F_2O_3S$: 223.0235. Found: 223.0237.

(4-(difluoromethoxy)phenyl)(phenyl)methanone ***(4k)***[18c]. Following general procedure **B**, **4k** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (34.8 mg, 70%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.57 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.65 (t, *J* = 73.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 195.3, 154.3 (t, *J* = 2.7 Hz), 137.4, 134.4, 132.6, 132.2, 129.9, 128.4, 118.6, 115.4 (t, *J* = 261.2 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.7 (d, *J* = 73.3 Hz).

Ethyl 4-(difluoromethoxy)benzoate ***(4l)***. Following general procedure **A**, **4l** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (36.4 mg, 90%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.03 (m, 2H), 7.20 – 7.12 (m, 2H), 6.60 (t, *J* = 73.2 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.6, 154.6 (t, *J* = 2.8 Hz), 131.6, 127.4, 118.0 (t, *J* = 260.5 Hz), 112.8, 61.1, 14.3. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.7 (d, *J* = 72.9 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_{10}H_{11}F_2O_3$: 217.0671. Found: 217.0673.

Methyl 3-bromo-4-(difluoromethoxy)benzoate ***(4m)***. Following general procedure **A**, **4m** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (34.3 mg, 61%), m.p. 44.3-45.1 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 2.1 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 6.63 (t, *J* = 72.6 Hz, 1H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.0, 151.5 (t, *J* = 2.8 Hz), 135.4, 130.2, 128.5, 119.9, 115.4 (t, *J* = 263.9 Hz), 114.8, 52.6. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.9 (d, *J* = 72.5 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_9H_7F_2O_3Br$: 280.9619, 282.9599. Found: 280.9619, 282.9599.

Methyl 4-(difluoromethoxy)-3-iodobenzoate ***(4n)***. Following general procedure **A**, **4n** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (43.3 mg, 66%), m.p. 56.4-57.1 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.53 (d, *J* = 1.4 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.63 (t, *J* = 72.5 Hz, 1H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.8, 154.2 (t, *J* = 2.6 Hz), 141.5, 131.2, 128.6, 118.4, 115.5 (t, *J* = 263.8 Hz), 88.1, 52.5. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.8 (d, *J* = 72.4 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_9H_8F_2O_3I$: 328.9481. Found: 328.9482.

4-(difluoromethoxy)benzaldehyde ***(4o)***[15]. Following general procedure **A**, **4o** was purified by silica gel chromatography (PE) as a colorless crystal (20.3 mg, 59%). ^1H NMR (400 MHz, Chloroform-*d*) δ 10.00 (s, 1H), 7.98 – 7.89 (m, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.65 (t, *J* = 72.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 190.6, 155.7 (t, *J* = 2.7 Hz), 133.4, 131.7, 119.2, 115.2 (t, *J* = 262.0 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -82.0 (d, *J* = 72.5 Hz).

3-(difluoromethoxy)benzaldehyde ***(4p)***. Following general procedure **A**, **4p** was purified by silica gel chromatography (PE) as a colorless oil (15.9 mg, 46%). ^1H NMR (400 MHz, Chloroform-*d*) δ 10.03 (s, 1H), 7.76 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.65 (s, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.61 (t, *J* = 73.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 191.0, 151.6 (t, *J* = 2.8 Hz), 138.0, 130.6, 127.1, 125.8, 119.4, 115.5 (t, *J* = 261.8 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.6 (d, *J* = 73.0 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_8H_7F_2O_2$: 173.0409. Found: 173.0410.

5-bromo-2-(difluoromethoxy)benzaldehyde ***(4q)***. Following general procedure **A**, **4q** was purified by silica gel chromatography (PE) as a colorless oil (31.1 mg, 62%). ^1H NMR (400 MHz, Chloroform-*d*) δ 10.33 (s, 1H), 8.06 (d, *J* = 2.6 Hz, 1H), 7.74 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.68 (t, *J* = 72.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz,

$CDCl_3$) δ 187.0, 151.4 (t, *J* = 2.9 Hz), 138.2, 131.7, 129.1, 122.0, 119.4, 115.2 (t, *J* = 264.8 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.9 (d, *J* = 72.2 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_8H_6F_2O_2Br$: 250.9514, 252.9493. Found: 250.9516, 252.9495.

N-(4-(difluoromethoxy)phenyl)acetamide ***(4r)***[15]. Following general procedure **A**, **4r** was purified by silica gel chromatography (EtOAc/PE=4/1) as a white solid (16.5 mg, 41%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 6.47 (t, *J* = 74.0 Hz, 1H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.6, 147.3 (t, *J* = 2.9 Hz), 135.4, 121.4, 120.4, 116.0 (t, *J* = 260.1 Hz), 24.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.7 (d, *J* = 73.7 Hz).

(E)-1-(difluoromethoxy)-2-methoxy-4-(prop-1-en-1-yl)benzene ***(4s)***. Following general procedure **B**, **4s** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (26.6 mg, 62%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.10 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.54 (t, *J* = 75.4 Hz, 1H), 6.38 (dd, *J* = 15.7, 1.7 Hz, 1H), 6.22 (dq, *J* = 15.8, 6.6 Hz, 1H), 3.91 (s, 3H), 1.91 (dd, *J* = 6.6, 1.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.0, 138.8 (t, *J* = 3.1 Hz), 136.8, 130.1, 126.5, 122.3, 118.9, 116.3 (t, *J* = 259.4 Hz), 109.8, 55.9, 18.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.4 (d, *J* = 75.1 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_{11}H_{13}F_2O_2$: 215.0878. Found: 215.0880.

2-(4-(difluoromethoxy)phenyl)ethan-1-ol ***(4t)***. Following general procedure **B**, **4t** was purified by silica gel chromatography (EtOAc/PE=4/1) as a colorless oil (19.6 mg, 52%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.22 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.51 (t, *J* = 74.1 Hz, 1H), 3.87 (t, *J* = 6.5 Hz, 2H), 2.87 (t, *J* = 6.5 Hz, 2H), 1.66 (br, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.8 (t, *J* = 2.8 Hz), 135.9, 130.3, 119.8, 116.0 (t, *J* = 259.5 Hz), 63.5, 38.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.6 (d, *J* = 73.9 Hz). HRMS (ESI-TOF) m/z: $(M+Na)^+$ Calcd for $C_9H_{10}F_2O_2Na$: 211.0541. Found: 211.0542.

1-(difluoromethoxy)naphthalene ***(4u)***[18a]. Following general procedure **A**, **4u** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (25.3 mg, 65%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.27 – 8.18 (m, 1H), 7.95 – 7.86 (m, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 7.6, 0.5 Hz, 1H), 6.70 (t, *J* = 74.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.4 (t, *J* = 2.5 Hz), 134.7, 127.8, 127.0, 126.6, 126.5, 125.4, 125.3, 121.6, 116.6 (t, *J* = 258.9 Hz), 113.7. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -79.9 (d, *J* = 74.1 Hz).

2-(difluoromethoxy)naphthalene ***(4v)***[18a]. Following general procedure **A**, **4v** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (27.6 mg, 71%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.85 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.48 (m, 3H), 7.32 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.66 (t, *J* = 74.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.0 (t, *J* = 2.3 Hz), 133.8, 131.1, 130.1, 130.1, 127.8, 127.8, 127.5, 127.5, 127.0, 126.9, 125.7, 125.7, 119.7, 116.1 (t, *J* = 259.3 Hz), 115.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.6(d, *J* = 73.9 Hz).

1-bromo-2-(difluoromethoxy)naphthalene ***(4w)***[15]. Following general procedure **B**, **4w** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (24.6 mg, 45%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.59 – 7.54 (m, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 6.66 (t, *J* = 73.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.0 (t, *J* = 2.9 Hz), 132.8, 132.2, 129.2, 128.2, 128.2, 127.2, 126.6, 120.6, 116.2 (t, *J* = 262.6 Hz), 114.7. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.7 (d, *J* = 73.7 Hz).

7-(difluoromethoxy)-3,4-dihydroquinolin-2(1H)-one ***(4x)***. Following general procedure **A**, **4x** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (18.4 mg, 43%), m.p. 137.4-138.8 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.25 (br, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.76 (dd, *J* = 8.2, 2.3 Hz, 1H), 6. 66 (d, *J* = 2.3 Hz, 1H), 6.50 (t, *J* = 73.9 Hz, 1H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 150.5 (t, *J* = 2.9 Hz), 138.6, 129.0, 120.8, 115.9 (t, *J* = 260.1 Hz), 113.7, 107.3, 30.6, 24.7. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.8 (d, *J* = 73.7 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_{10}H_{10}F_2NO_2$: 214.0674 Found: 214.0675.

4-(difluoromethoxy)-1H-indole ***(4y)***. Following general procedure **A**, **4y** was purified by silica gel chromatography (EtOAc/PE=10/1) as a colorless oil (20.5 mg, 56%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 2.8 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.88 (dd, *J* = 6.9, 0.5 Hz, 1H), 6.70 (t, *J* = 2.3 Hz, 1H), 6.69 (t, *J* = 74.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.7 (t, *J* = 2.7 Hz), 137.7, 124.4, 122.4, 120.7, 116.7 (t, *J* = 258.2 Hz), 109.0, 108.8, 99.6. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -79.6 (d, *J* = 74.8 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_9H_8F_2NO$: 184.0568. Found: 184.0570.

4-(difluoromethoxy)-2H-chromen-2-one ***(4z)***[14b]. Following general procedure **B**, **4z** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (31.4 mg, 74%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.35 (t, *J* = 8.4 Hz, 2H), 6.86 (t, *J* = 71.2 Hz, 1H), 5.99 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.0, 159.0, 153.5, 133.4, 124.53, 123.0, 117.0, 114.5 (t, *J* = 264.6 Hz), 114.0, 96.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -85.0 (d, *J* = 71.1 Hz).

(difluoromethyl)(3-methoxyphenyl)sulfane ***(5a)***[14b]. Following general procedure **A**, **5a** was purified by silica gel chromatography (PE) as a colorless oil (32.7 mg, 86%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.33 (t, *J* = 8.0 Hz, 1H), 7.19 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.14 (t, *J* = 2.1 Hz, 1H), 6.99 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.87 (t, *J* = 57.0 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 130.2, 127.3, 127.2 (t, *J* = 3.1 Hz), 121.2 (t, *J* = 275.1 Hz), 120.2, 115.8, 55.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.2 (d, *J* = 57.2 Hz).

(4-bromophenyl)(difluoromethyl)sulfane ***(5b)***[18a]. Following general procedure **A**, **5b** was purified by silica gel chromatography (PE) as a colorless oil (47.5 mg, 99%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.53 (m, 2H), 7.49 – 7.45 (m, 2H), 6.83 (t, *J* = 56.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.9, 132.6, 124.9 (t, *J* = 3.1 Hz), 124.8, 120.2 (t, *J* = 275.9 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.6 (d, *J* = 56.6 Hz).

(difluoromethyl)(naphthalen-2-yl)sulfane ***(5c)***[19a]. Following general procedure **A**, **5c** was purified by silica gel chromatography (PE) as a colorless oil (37.8 mg, 90%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.89 (dt, *J* = 7.4, 3.7 Hz, 3H), 7.65 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.63 – 7.55 (m, 2H), 6.94 (t, *J* = 56.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.5, 133.5, 133.4, 131.4, 129.1, 128.0, 127.8,

127.5, 126.9, 123.3 (t, J = 3.0 Hz), 121.1 (t, J = 275.3 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.1 (d, J = 56.2 Hz).

(difluoromethyl)(4-nitrophenyl)sulfane ***(5d)***[15]. Following general procedure **A**, **5d** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (25.1 mg, 61%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 – 8.22 (m, 2H), 7.78 – 7.72 (m, 2H), 6.97 (t, J = 55.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.3, 135.0 (t, J = 2.9 Hz), 134.4, 124.2, 119.6 (t, J = 276.8 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.2 (d, J = 55.9 Hz).

(difluoromethyl)(perchlorophenyl)sulfane ***(5e)***. Following general procedure **A**, **5e** was purified by silica gel chromatography (EtOAc/PE=30/1) as a white solid (45.9 mg, 69%), m.p. 64.3-66.8 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.93 (t, J = 57.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.1, 136.9, 132.8, 126.3 (t, J = 3.8 Hz), 119.5 (t, J = 280.2 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.7 (d, J = 57.0 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_7H_2Cl_5F_2S$: 330.8283, 332.8253, 334.8224. Found: 330.8282, 332.8253, 334.8223.

N-(4-((difluoromethyl)thio)phenyl)acetamide ***(5f)***[19a]. Following general procedure **A**, **5f** was purified by silica gel chromatography (EtOAc/PE=4/1) as a white solid (41.3 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (br, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.38 (t, J = 56.1 Hz, 1H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.2, 141.5, 136.6, 121.5 (t, J = 273.1 Hz), 120.1, 118.3 (t, J = 2.7 Hz), 24.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -92.4 (d, J = 56.2 Hz).

2-((difluoromethyl)thio)pyridine ***(5g)***[18a]. Following general procedure **A**, **5g** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (24.5 mg, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (d, J = 4.6 Hz, 1H), 7. 72 (t, J = 56.3 Hz, 1H), 7.64 (t, J = 7.7 Hz, 2H), 7.30 (d, J = 7.7 Hz, 1H), 7.21 – 7.14 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.2 (t, J = 3.6 Hz), 150.1, 137.2, 124. 4 (t, J = 2.4 Hz), 121.8, 121.3 (t, J = 270.9 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.2 (d, J = 56.4 Hz).

2-((difluoromethyl)thio)pyrimidine ***(5h)***. Following general procedure **A**, **5h** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (19.2 mg, 59%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.61 (d, J = 4.9 Hz, 2H), 7.81 (t, J = 55.9 Hz, 1H), 7.14 (t, J = 4.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.9 (t, J = 6.1 Hz), 157.8, 120.6 (t, J = 270.2 Hz), 118.3. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -99.6 (d, J = 55.8 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_5H_5F_2N_2S$: 163.0136. Found: 163.0136.

2-((difluoromethyl)thio)thiophene ***(5i)***. Following general procedure **A**, **5i** was purified by silica gel chromatography (PE) as a colorless oil (30.3 mg, 91%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (dd, J = 5.4, 1.1 Hz, 1H), 7.39 (dd, J = 3.6, 1.0 Hz, 1H), 7.13 (dd, J = 5.4, 3.6 Hz, 1H), 6.75 (t, J = 57.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.3, 133.0, 128.3, 122.5 (t, J = 3.8 Hz), 120.4 (t, J = 277.7 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -93.5 (d, J = 57.1 Hz). HRMS (ESI-TOF) m/z: $(M+H)^+$ Calcd for $C_5H_5F_2S_2$: 166.9795. Found: 166.9796.

2-((difluoromethyl)thio)-1H-benzo[d]imidazole ***(5j)***[19b] Following general procedure **A**, **5j** was purified by silica gel chromatography (EtOAc/PE=10/1) as a white solid (25.3 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (brs, 1H), 7.85 (t, J = 55.3 Hz, 1H), 7.59 (brs, 2H), 7.28 – 7.21 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 143.9 (br), 140.5 (t, J = 4.6 Hz), 123.3 (br), 121.2 (t, J = 274.5 Hz), 111.9 (br). ^{19}F NMR (376 MHz, DMSO-d_6) δ -92.1 (d, J = 55.2 Hz).

2-((difluoromethyl)thio)benzo[d]oxazole ***(5k)***[19b]. Following general procedure **A**, **5k** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (40.0 mg, 99%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (t, J = 55.7 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.57 – 7.49 (m, 1H), 7.40 – 7.33 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.2 (t, J = 6.2 Hz), 151.7, 141.2, 125.2, 125.0, 119.8 (t, J = 276.6 Hz), 119.4, 110.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -93.2 (d, J = 55.8 Hz).

2-((difluoromethyl)thio)benzo[d]thiazole ***(5l)***[19b]. Following general procedure **A**, **5l** was purified by silica gel chromatography (EtOAc/PE=30/1) as a colorless oil (42.1 mg, 97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 8.2 Hz, 1H), 7.85 (dd, J = 7.6, 0.8 Hz, 1H), 7.67 (t, J = 56.0 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.47 – 7.38 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1 (t, J = 4.3 Hz), 152.90, 136.0, 126.7, 125.6, 122.9, 121.2, 120.3 (t, J = 277.0 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -93.2 (d, J = 55.9 Hz).

General procedure for the synthesis of GRN-529[9c]**.** *4-Difluoromethoxy-3-iodo-benzoic Acid Methyl Ester (4n)*: Methyl 4-hydroxy-3-iodobenzoate **2n** (1.39 g, 5.0 mmol), LiOH (0.263 g, 2.2 equiv., 11.0 mmol) and fluorobenzene (20 mL) were added into a flame-dried Schlenk tube under argon atmosphere and stirred at room temperature for 30 min. Then **1** (2.484g, 1.2 equiv., 6.0 mmol) was added into the mixtures directly, and the reaction was stirred under an atmosphere of argon at room temperature overnight. After filtering through celite and removing the solvent in vacuum, the residue was purified by flash column chromatography on silica gel (eluting with ethyl acetate/hexane = 1:30) to obtain the pure product **4n** (1.135 g, 69%).

Methyl 4-(Difluoromethoxy)-3-(pyridin-2-ylethynyl)-benzoate (7). 2-Ethynylpyridine (**6**) (0.288 g, 1.01 equiv, 2.791 mmol) was charged to a solution of **4n** (0.906 g, 1.00 equiv, 2.763 mmol), CuI (0.011 g, 0.020 equiv, 0.055 mmol) and $Pd(PPh_3)_2Cl_2$ (0.020 g, 0.010 equiv, 0.028 mmol) in N-methylpyrrolidinone (NMP) (20 mL). The mixture was degassed by evacuating and refilling via nitrogen bleed three times, and the mixture was heated to 40 °C. Next, ammonium hydroxide (28% solution) (1.312 g, 8 equiv) was added in one portion, The reaction was held in this range for 6 h. After the reaction was completed, the mixture was cooled to room temperature, and Water (150 g, 150 mL) was added over a period of 45 min, and the suspension was cooled to 5 °C. After 1 h at this temperature, the solids were filtered and washed consecutively with water (60 mL), Finally, the crystals (0.807 g, 96.4% yield) were dried under vacuum. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.02 (dd, J = 8.7, 2.2 Hz, 1H), 7.69 (td, J = 7.7, 1.8 Hz, 1H), 7.54 (dt, J = 7.8, 1.0 Hz, 1H), 7.29 – 7.23 (m, 2H), 6.73 (t, J = 72.8 Hz, 1H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.4, 154.7 (t, J = 2.7 Hz), 150.2, 142.7, 136.2, 135.7, 131.7, 127.5, 127.3, 123.3, 119.0, 115.6 (t, J = 263.0 Hz), 115.4, 94.2, 82.6, 52.4. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -81.9 (d, J = 72.8 Hz).

4-(Difluoromethoxy)-3-(pyridin-2-ylethynyl)benzoic Acid ***(8)***. To a mixture of **7** (0.766 g, 1.00 equiv, 2.53 mmol) in Water (10 mL) and methanol (10 mL) at 40−45 °C was added a solution of 50% NaOH (0.122 g, 3.04 mmol, 1.2 equiv), keeping the temperature in the range of 40−45 °C approximately 3 h. The reaction were diluted with 30 mL of

water and warmed to 45 °C. A solution of HOAc (1.0 mL) in water (10 mL) was slowly added over a period of 1 h. After addition of the acetic acid solution, the mixture was cooled to 20 °C and held for one hour, and the solid was collected and washed with water (50 mL) and dried under vacuum provide **8** as a white powder (0.700 g, 95.8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (br, 1H), 8.65 (d, J = 4.6 Hz, 1H), 8.18 (d, J = 2.3 Hz, 1H), 8.07 (dd, J = 8.7, 1.8 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.50 (t, J = 73.0 Hz, 1H), 7.46 (t, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.2, 154.9 (t, J = 3.2 Hz), 150.7, 142.3, 137.4, 135.2, 132.6, 128.2, 128.1, 124.4, 118.3, 116.6 (t, J = 260 Hz), 114.0, 94.4, 82.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -82.4 (d, J = 72.8 Hz).

(4-Difluoromethoxy-3-pyridin-2-ylethynyl-phenyl)- (5,7-dihydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone ***(GRN-529)***. Into a flame-dried Schlenk tube was charged **8** (289 mg, 1.00 equiv, 1.0 mmol) followed by NMP (5.0 mL) and N,N-diisopropylethylamine (DIPEA) (200 µL, 1.2 equiv, 1.2 mmol). This reaction mixture was stored at room temperature. Into a 15 mL Schlenk tube at 25 °C was charged NMP (5.0 mL) followed by 1,1-carbonyldiimidazole (CDI) (178 mg, 1.10 equiv, 1.1 mol). This mixture was stirred to dissolve. The solution of (**8**) was charged at room temperature to the Schlenk tube over a period of 30 min and stirred at room temperature for another 2 h to generate the activated intermediate.

Into a 50 mL flame-dried Schlenk tube was charged NMP (5.0 mL) followed by 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine dihydrobromide (**9**) (203 mg, 1.05 equiv, 1.05 mol). To this was charged DIPEA (302 µL, 1.83 equiv, 1.83 mmol) over a period of 25 min and keeping the temperature below 35 °C. The contents from the 15 mL Schlenk tube were transferred at ambient temperature to the 50 mL Schlenk tube over a period of 30 min. The reaction was held at ambient temperature for a minimum of 4 h. Once the reaction was deemed complete, water (100 mL) was added over a period of 2 h to the mixture at 30 °C. If needed, an additional charge of water (50 mL) may be added to aid in crystallization if crystals are not observed after 1h. The mixture was held at 25 °C overnight and filtered. The cake was washed with water (50 mL) and allowed to dry on the filter overnight. The solids were weighed to provide **GRN-529** as a white powder (328 mg, 83.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6, Rotomeric mixture) δ 8.64 (d, J = 4.8 Hz, 1H), 8.47 (dd, J = 9.5, 4.9 Hz, 1H), 7.98 (s, 1H), 7.89 (t, J = 7.6 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.75 (dd, J = 27.7, 7.8 Hz, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.47 (t, J = 72.3 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 4.90 (d, J = 12.8 Hz, 2H), 4.84 (d, J = 4.4 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.8, 157.8, 152.8, 150.7, 149.3, 142.3, 137.4, 133.8, 133.2, 131.7, 131.1, 130.5, 128.1, 124.4, 123.0, 119.0, 116.7 (t, J = 262 Hz), 114.2, 94.4, 83.1, 54.81, 52.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -82.7 (d, J = 73.0 Hz).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data, ^{1}H, ^{13}C, ^{19}F NMR spectra, and HRMS (PDF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: gkliu@szu.edu.cn.

ORCID

Guo-Kai Liu: 0000-0001-7617-4267

Henry N. C. Wong: 0000-0002-3763-3085

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by the Natural Science Foundation of Shenzhen (JCYJ20170818143001461 and KQJSCX20180328095508144). We thank the Instrumental Analysis Center of Shenzhen University (Xili Campus) for analytical work.

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