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Ph_2S/selectfluor-promoted deoxydifluorination of aldehydes

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ABSTRACT

The installation of a HCF_2 group is a research area that has received increasing attention, and deoxydifluorination of aldehydes have served as an attractive protocol due to the wide availability of aldehydes. Herein we describe a Ph_2S/Selectfluor-promoted deoxydifluorination of aldehydes under mild conditions. Compared with previous deoxydifluorination methods, which usually use hazardous reagents such as SF_4, DAST and Deoxo-Fluor, this protocol is quite attractive because of the safe and convenient operations, and the use of easily available reagents.

1. Introduction

The difluoromethyl group (HCF_2) is of great interest in pharmaceutical chemistry and agrochemistry due to its unique properties, such as the ability to act as a lipophilic hydrogen bond donor and a bioisostere of hydroxyl or thiol groups [1]. A number of HCF_2-containing pharmaceuticals and agrochemicals have emerged, such as Glecaprevir, Deracoxib and Dithiopyr. Therefore, great efforts have been directed towards the development of efficient methods for the installation of a HCF_2 group. Two strategies have been well established, deoxydifluorination of aldehydes and direct difluoromethylation [2]. Direct difluoromethylation is a straightforward strategy and many difluoromethylation reagents have been developed [3]. However, it is still highly desirable to develop mild and effective methods for deoxydifluorination of aldehydes since aldehydes are widely available and are structural motifs commonly found in biologically active molecules.

Deoxydifluorination of aldehydes is a research area that has received increasing interest. In 1960, Hasek discovered that SF_4 was an effective reagent for deoxofluorination of alcohols, aldehydes, and so on [4]. Although SF_4 is a hazardous and highly toxic gas, this pioneering work has stimulated the development of various "S–F" type reagents for deoxyfluorination, such as DAST (diethylaminosulfur trifluoride) [5], Deoxo-Fluor (*bis*(2-methoxyethyl) aminosulfur trifluoride) [6], Xtal-Fluor [7] and Fluolead [8] (Scheme 1a). All of these reagents are able to convert aldehydes into a HCF_2 group. DAST tends to explode when being heated above 40–50 °C, and Deoxo-fluor decomposes slowly on heating. Both DAST and Deoxo-fluor hydrolyze readily to give HF. Special precautions must be taken when handling DAST or Deoxo-fluor. Compared with liquid DAST and Deoxo-Fluor, crystalline Xtal-Fluor reagents exhibit enhanced thermal stability, but their preparations require the use of hazardous SF_4, DAST or Deoxo-Fluor. Fluolead, a crystalline solid developed by Umemoto, shows much higher stability over DAST and Deoxo-Fluor on contact with water, but slow hydrolysis does occur. Furthermore, Fluolead would react with glass slowly even when pure, and thus must be stored in flasks made of fluoropolymer [8b]. Besides the "S–F" type reagents, other "*N*-CF_2" type reagents have also been developed, such as DFI (2,2-difluoro-1,3-

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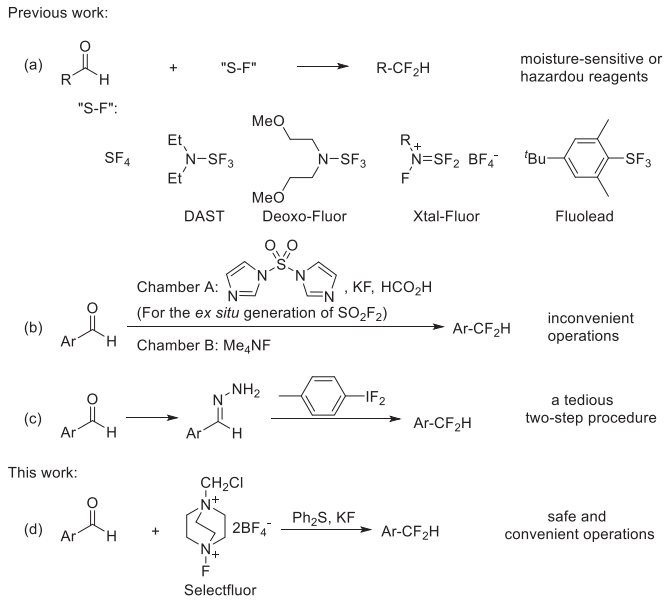


Scheme 1. Deoxydifluorination of aldehydes.

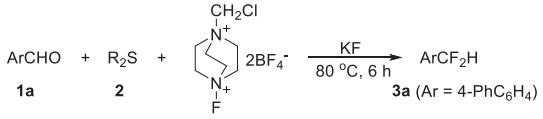
dimethylimidazolidine) [9] and DFMBA (*N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine) [10]. Although these "*N*-CF_2" reagents are also effective for deoxydifluorination of aldehydes, the use of a hazardous reagent, such as $COCl_2$ or SF_4, is usually necessary for their preparations. Recently, Sanford described a mild deoxydifluorination method by using SO_2F_2/Me_4NF for the conversion of aldehyde group (Scheme 1b) [11]. A wide substrate scope was demonstrated, but this process requires using a two-chamber reaction vessel for the *ex situ* generation of SO_2F_2 and the deoxydifluorination reaction, respectively. Aldehydes could first be transformed into hydrazones, which could act as precursors of diazo compounds for difluorination (Scheme 1c) [12]. Moderate to good yields were obtained for difluorination, but the applicability of this general method may be limited due to the tedious two-step procedure.

Our group has been interested in the exploration of new synthetic utilities of phosphonium salts and sulfonium salts [13]. Since our previous studies in phosphonium-salt-promoted dehydroxylative fluorination of alcohols and deoxy-dichlorination/-dibromination of aldehydes [14], we have kept thinking how to efficiently achieve sulfonium-salt-promoted deoxyfluorination. Herein we describe the Ph_2S/Selectfluor-promoted deoxydifluorination of aldehydes under mild conditions (Scheme 1d). All reagents are easily available and shelf-stable. The reaction may proceed via the generation of a reactive sulfonium salt, $[Ph_2S^+\text{-}F]$ X^-, for the activation of aldehydes.

2. Results and discussion

In our previous investigations of phosphonium-salt-promoted deoxy-functionalizations, a trivalent phosphorus was oxidized to a phosphonium salt, which can efficiently enable the deoxygenation by the formation of a strong P═O bond [14]. We speculated that a divalent sulfur compound may also promote deoxydifluorination of aldehydes via the oxidation of the sulfur compound and the subsequent formation of a strong S═O bond. Therefore, we first screened various divalent sulfur compounds (Table 1, entries 1–5). Selectfluor was used as the oxidant because we reasoned that the divalent sulfur may be oxidized to $[R_2S^+\text{-}F]$ X^- species, which is like the above "S–F" type reagents. To our delight, the use of Ph_2S gave the expected product, albeit in a low yield (entry 1). Other diaryl sulfurs led to lower yields (entry 2). No desired product was observed by using dialkyl sulfur compounds (entries 3–4). Since KF and CsF were equally effective (entry 1 vs entry 6), KF was used for further optimization. CH_3CN/$PhCH_3$ as mixed solvents increased the yield slightly (entry 7), but other mixed solvents had no positive effect (entries 8–9). The reaction temperature played an important role (entries 10–13), and a 48% yield was obtained at 110 °C (entry 12). The loadings of various reagents were screened, and the yield was increased to 65% when the molar ratio of Ph_2S: Selectfluor: KF was 1.5:3:1.5 (entry 17).

Table 1
The optimization of reaction conditions.

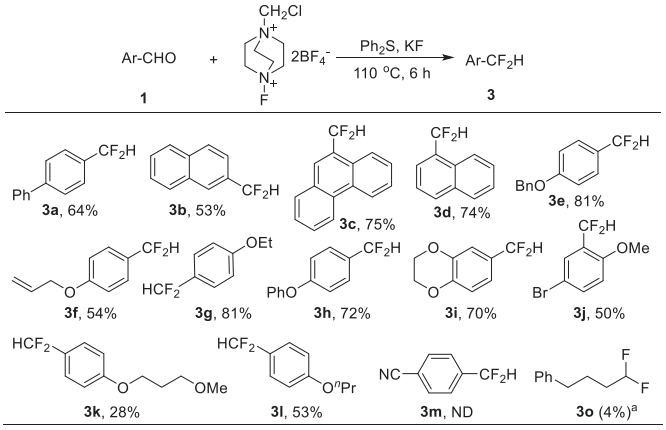


Entry	R_2S	Ratio[a]	Solvent	Yield (%)[b]
1[c]	Ph_2S	5:3:2	CH_3CN	18
2[c]	$(p\text{-}MeOC_6H_4)_2S$	5:3:2	CH_3CN	5
3[c]	$(C_2H_5)_2S$	5:3:2	CH_3CN	ND
4[c]	$(CH_2)_4S$	5:3:2	CH_3CN	ND
5[c]	PhSH	5:3:2	CH_3CN	ND
6	Ph_2S	5:3:2	CH_3CN	18
7	Ph_2S	5:3:10	CH_3CN/$PhCH_3$	28
8	Ph_2S	5:3:10	CH_3CN/$CHCl_3$	ND
9	Ph_2S	5:3:10	CH_3CN/$Cl(CH_2)_2Cl$	15
10[d]	Ph_2S	5:3:10	CH_3CN/$PhCH_3$	5
11[e]	Ph_2S	5:3:10	CH_3CN/$PhCH_3$	40
12[f]	Ph_2S	5:3:10	CH_3CN/$PhCH_3$	48
13[g]	Ph_2S	5:3:10	CH_3CN/$PhCH_3$	46
14[f]	Ph_2S	5:2:10	CH_3CN/$PhCH_3$	38
15[f]	Ph_2S	5:5:5	CH_3CN/$PhCH_3$	59
16[f h]	Ph_2S	1.5:2.5:1.5	CH_3CN/$PhCH_3$	58
17[f h]	Ph_2S	1.5:3:1.5	CH_3CN/$PhCH_3$	65

Reaction conditions: substrate **1a** (0.2 mmol), R_2S, Selectfluor and KF in solvent (2 mL) (If mixed solvents were used, 1 mL of each solvent was used) at 80 °C for 6 h under a N_2 atmosphere. ND = Not Detected.
[a] Molar ratio of R_2S: Selectfluor: KF relative to 1 equiv of substrate **1a**.
[b] The yields were determined by ^{19}F NMR spectroscopy.
[c] CsF was used instead of KF.
[d] The reaction temperature was 60 °C.
[e] The reaction temperature was 100 °C.
[f] The reaction temperature was 110 °C.
[g] The reaction temperature was 120 °C.
[h] The reaction scale was increased to 0.4 mmol (substrate **1a**).

With the optimal reaction conditions in hand, we then investigated the substrate scope of the deoxydifluorination of aldehydes. As shown in Scheme 2, electron-neutral and -rich aryl aldehydes could be converted into the desired products in moderate to good yields. Alkoxyl substituents have interesting effects on the reactions. If the alkoxy group was directly attached to the aryl group, good yields were obtained (**3e**-**3j**). But if not, the yield was dramatically decreased (**3k**). That may be partially because the alkyl ether may compete with the aldehyde group for the coordination with the reactive sulfonium species generated in situ, $[Ph_2S^+\text{-}F]$ X^-. The competitive coordination might suppress the activation of the aldehyde group. If the oxygen atom is attached to an aryl ring, a conjugation effect would lead to the loss of the coordination ability of the oxygen atom. Electron-deficient aryl aldehydes seemed to be inert towards this deoxydifluorination (**3m**). Alkyl aldehydes cannot be well converted under these conditions (**3o**).

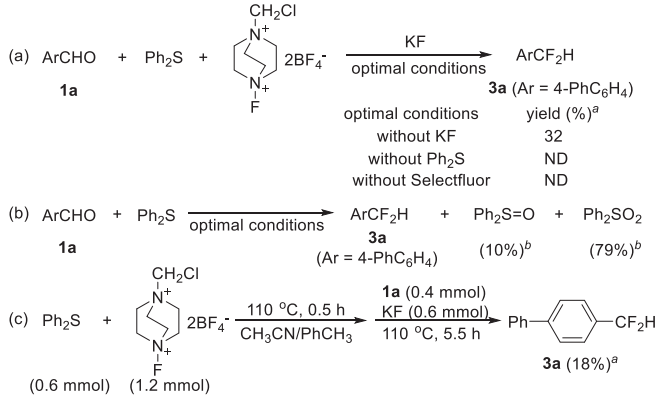
Both Ph_2S and Selectfluor are essential for the deoxydifluorination of aldehydes. No desired product was produced



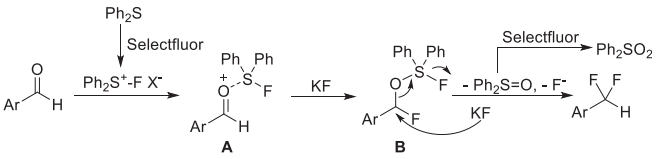
Scheme 2. Deoxydifluorination of aldehydes. Reaction conditions: substrate **1** (0.4 mmol), Ph_2S (0.6 mmol), Selectfluor (1.2 mmol) and KF (0.6 mmol) in CH_3CN/$PhCH_3$ (1 mL/1 mL) at 110 °C for 6 h under a N_2 atmosphere. [a]The yield of **3o** was determined by ^{19}F NMR spectroscopy.

without the presence of any one of them (Scheme 3a). Both Selectfluor and KF are the fluorine sources, as evidenced by the 32% yield without the use of KF (Scheme 3a). The fluorine atoms in Selectfluor may come from the N–F and BF_4 moieties [15]. For the deoxydifluorination of aldehyde **1a**, Ph_2SO and Ph_2SO_2 were isolated in 10% and 79% yields, respectively (Scheme 3b). Ph_2S should be oxidized by Selectfluor to generate a reactive sulfonium salt, which could activate the aldehyde group. Indeed, stirring the mixture of Selectfluor with Ph_2S at 110 °C for 0.5 h led to the complete conversion of Selectfluor, and a new ^{19}F NMR signal at −189.6 ppm was observed. This signal may correspond to the Ph_2S^+-F species according to the ^{19}F NMR signal of a known salt, Me_2S^+- F X^-, which appears at −190 ppm [16]. The subsequent addition of substrate **1a** and KF gave the desired product in 18% yield, further supporting our proposal (Scheme 3c). The low yield may be because the Ph_2S^+-F species would readily undergo side reactions when no substrate is present.

Based on the above results, the plausible reaction mechanism is proposed as shown in Scheme 4. Ph_2S is oxidized by Selectfluor to generate a sulfonium salt, [Ph_2S^+-F] X^-, which can act as a Lewis acid to coordinate with the aldehyde group (intermediate **A**). The activation of the aldehyde group allows for the nucleophilic attack of the fluoride to provide intermediate **B**. The strong S=O bond drives the cleavage of the C–O bond and the formation of Ph_2S=O. The simultaneous attack of a fluoride anion delivers the final



Scheme 3. Experimental evidence. [a]The yield was determined by ^{19}F NMR spectroscopy; [b]Isolated yields were calculated based on substrate **1a**.



Scheme 4. The plausible reaction mechanism.

product. Ph_2S=O would be easily oxidized by Selectfluor to afford Ph_2SO_2. The oxidation consumes Selectfluor and thus Selectfluor has to be used in excess.

3. Conclusion

In summary, we have described a Ph_2S/Selectfluor-promoted deoxydifluorination of aldehydes under mild conditions. The oxidation of Ph_2S by Selectfluor generates a reactive sulfonium salt, [Ph_2S^+-F] X^-, which activates the aldehyde group and drives the deoxydifluorination process. Compared with previous deoxydifluorination methods, this protocol is quite attractive due to the safe and convenient operations, and the use of easily available reagents.

4. Experimental section

4.1. General information

^1H, ^{13}C and ^{19}F NMR spectra were detected on a 400 MHz NMR spectrometer. Data for ^1H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, coupling constant(s) in Hz). Mass spectra were obtained on GC-MS (EI). High resolution mass data were recorded on a high-resolution mass spectrometer in the EI mode. The mass analyzer types for HRMS-EI is time-of-flight mass spectrometer.

4.2. General procedure for deoxydifluorination of aldehydes

Into a sealed tube was added aldehyde **1** (0.4 mmol), KF (35 mg, 0.6 mmol), Selectfluor (425 mg, 1.2 mmol), CH_3CN/$PhCH_3$ (1 mL/1 mL) and Ph_2S (112 mg, 0.6 mmol) under a N_2 atmosphere. The tube was sealed and the reaction mixture was stirred at 110 °C for 6 h. Water (10 mL) was added to quench the reaction, and the product was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried with Na_2SO_4 and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford the desired product **3**.

4.3. Characterization of the products

4.3.1. 4-(difluoromethyl)-1,1′-biphenyl (3a) [3]

52 mg, 64%, white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.64–7.60 (m, 4H), 7.49 (t, J = 7.4 Hz, 2H), 7.42 (tt, J = 7.3 Hz, 1.2 Hz, 1H), 6.73 (t, J = 56.5 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.39 (d, J = 56.5 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (t, J = 2.0 Hz), 140.2 (s), 133.2 (t, J = 22.4 Hz), 128.9 (s), 127.9 (s), 127.4 (s), 127.2 (s), 126.0 (t, J = 6.0 Hz), 114.7 (t, J = 238.5 Hz). GC-MS (EI) calcd. For $C_{13}H_{10}F_2$ [M]$^+$: 204.1; Found: 204.1.

4.3.2. 2-(difluoromethyl)naphthalene (3b) [3]

38 mg, 53%, yellow solid. ^1H NMR (400 MHz, Acetone) δ 8.16 (s, 1H), 8.11–7.97 (m, 3H), 7.69 (d, J = 8.6 Hz, 1H), 7.67–7.60 (m, 2H), 7.08 (t, J = 56.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.37 (d, J = 56.1 Hz, 2F). ^{13}C NMR (101 MHz, Acetone) δ 134.4 (t, J = 1.4 Hz),

132.7 (s), 132.0 (t, J = 22.2 Hz), 128.9 (s), 128.5 (s), 127.9 (s), 127.5 (s), 126.9 (s), 126.0 (t, J = 7.7 Hz), 122.0 (t, J = 4.8 Hz), 115.4 (t, J = 236.1 Hz). GC-MS (EI) calcd. For $C_{11}H_8F_2$ $[M]^+$: 178.1; Found: 178.1.

4.3.3. 9-(difluoromethyl)phenanthrene (3c) [17]

68 mg, 75%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 7.7 Hz, 1H), 8.67 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 7.3 Hz, 1H), 7.95 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.77–7.57 (m, 4H), 7.14 (t, J = 55.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.80 (d, J = 55.0 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4 (s), 130.8 (s), 130.1 (s), 129.5 (s), 128.3 (s), 128.0 (t, J = 20.8 Hz), 127.9 (t, J = 1.9 Hz), 127.2 (s), 127.16 (s), 127.14 (s), 126.8 (t, J = 9.3 Hz), 124.5 (t, J = 1.7 Hz), 123.2 (s), 122.6 (s), 115.6 (t, J = 238.6 Hz). GC-MS (EI) calcd. For $C_{15}H_{10}F_2$ $[M]^+$: 228.1; Found: 228.1.

4.3.4. 1-(difluoromethyl)naphthalene (3d) [17]

53 mg, 74%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.7 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 5.7 Hz, 1H), 7.64–7.44 (m, 3H), 7.13 (t, J = 55.2 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.88 (d, J = 55.2 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (s), 131.5 (t, J = 1.6 Hz), 129.7 (t, J = 2.5 Hz), 129.5 (t, J = 20.8 Hz), 128.8 (s), 127.1 (s), 126.3 (s), 124.8 (t, J = 8.7 Hz), 124.6 (s), 123.5 (t, J = 1.4 Hz), 115.4 (t, J = 238.4 Hz). GC-MS (EI) calcd. For $C_{11}H_8F_2$ $[M]^+$: 178.1; Found: 178.1.

4.3.5. 1-(benzyloxy)-4-(difluoromethyl)benzene (3e) [17]

76 mg, 81%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.31 (m, 7H), 7.02 (d, J = 8.7 Hz, 2H), 6.59 (t, J = 56.7 Hz, 1H), 5.09 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.17 (d, J = 55.8 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (t, J = 1.8 Hz), 136.5 (s), 128.7 (s), 128.2 (s), 127.5 (s), 127.2 (t, J = 6.0 Hz), 127.0 (t, J = 22.0 Hz), 115.0 (s), 114.9 (t, J = 237.5 Hz), 70.1 (s). GC-MS (EI) calcd. For $C_{14}H_{12}F_2O$ $[M]^+$: 234.1; Found: 234.0.

4.3.6. 1-((allyloxy)-4-(difluoromethyl)benzene (3f)

40 mg, 54%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.58 (t, J = 56.8 Hz, 1H), 6.08–5.98 (m, 1H), 5.40 (dq, J = 17.3, 1.5 Hz, 1H), 5.29 (dq, J = 10.5, 1.3 Hz, 1H), 4.55 (dt, J = 5.2, 1.3 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.99 (d, J = 56.6 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (t, J = 1.8 Hz), 132.7 (s), 127.1 (t, J = 5.9 Hz), 126.7 (t, J = 22.7 Hz), 118.0 (s), 114.8 (t, J = 237.4 Hz), 114.7 (s), 68.8 (s). IR (neat) v = 2963, 1647, 1517, 1411, 1252, 1071, 1020, 929, 861, 833, 658. HRMS (EI): calcd. for $C_{10}H_{10}F_2O$ $[M]^+$: 184.0700; Found: 184.0703.

4.3.7. 1-(difluoromethyl)-4-ethoxybenzene (3g) [17]

56 mg, 81%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 6.58 (t, J = 56.8 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.18 (d, J = 56.8 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7 (t, J = 1.6 Hz), 127.0 (t, J = 5.9 Hz), 126.5 (t, J = 22.8 Hz), 114.9 (t, J = 237.3 Hz), 114.5 (s), 63.6 (s), 14.7 (s). GC-MS (EI) calcd. For $C_9H_{10}F_2O$ $[M]^+$: 172.1; Found 172.1.

4.3.8. 1-(difluoromethyl)-4-phenoxybenzene (3h) [18]

63 mg, 72%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 7.42–7.33 (m, 2H), 7.16 (tt, J = 7.7, 1.04 Hz, 1H), 7.08–7.01 (m, 4H), 6.62 (t, J = 56.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.97 (d, J = 56.6 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (t, J = 1.9 Hz), 156.2 (s), 130.0 (s), 128.9 (t, J = 22.8 Hz), 127.3 (t, J = 5.9 Hz), 124.1 (s), 119.6 (s), 118.2 (s), 114.6 (t, J = 238.0 Hz). GC-MS (EI) calcd. For $C_{13}H_{10}F_2O$ $[M]^+$: 220.1; Found 220.1.

4.3.9. 6-(difluoromethyl)-2,3-dihydrobenzo[b][1,4]dioxine (3i) [19]

52 mg, 70%, yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–6.86 (m, 3H), 6.54 (t, J = 56.7 Hz, 1H), 4.27 (s, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.37 (d, J = 56.8 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5 (t, J = 1.8 Hz), 143.6 (s), 127.7 (t, J = 22.8 Hz), 118.7 (t, J = 6.2 Hz), 117.5 (s), 114.8 (t, J = 6.1 Hz), 114.5 (t, J = 237.9 Hz), 64.4 (s), 64.2 (s). IR (neat) v = 2933, 1687, 1602, 1582, 1462, 1391, 1315, 1290, 1166, 1064, 919, 888, 818, 792. HRMS (EI): calcd. for $C_9H_8F_2O_2$ $[M]^+$: 186.0492; Found: 186.0498.

4.3.10. 4-Bromo-2-(difluoromethyl)-1-methoxybenzene (3j)

47 mg, 50%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 1.7 Hz, 1H), 7.50 (dd, J = 8.8 Hz, 1.7 Hz, 1H), 6.86 (t, J = 55.3 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.06 (d, J = 55.3 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (t, J = 5.8 Hz), 134.6 (t, J = 1.9 Hz),129.2 (t, J = 6.2 Hz), 124.4 (t, J = 23.4 Hz), 112.80 (s), 112.79 (s), 110.6 (t, J = 236.9 Hz), 55.9 (s). IR (neat) v = 2944, 1601, 1492, 1412, 1382, 1270, 1179, 1091, 812, 653, 549. HRMS (EI): calcd. for $C_8H_7F_2OBr$ $[M]^+$: 235.9648; Found: 235.9653.

4.3.11. 1-(difluoromethyl)-4-(3-methoxypropoxy)benzene (3k)

24 mg, 28%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.58 (t, J = 56.8 Hz, 1H), 4.07 (t, J = 6.3 Hz, 2H), 3.54 (t, J = 6.1 Hz, 2H), 3.34 (s, 3H), 2.04 (p, J = 6.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.23 (d, J = 56.8 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (t, J = 1.5 Hz), 127.0 (t, J = 6.0 Hz), 126.6 (t, J = 22.7 Hz), 114.9 (t, J = 237.3 Hz), 114.5 (s), 69.0 (s), 64.8 (s), 58.4 (s), 29.5 (s). IR (neat) v = 2930, 1616, 1518, 1383, 1253, 1176, 1119, 1070, 1019, 835, 642. HRMS (EI): calcd. for $C_{11}H_{14}F_2O_2$ $[M]^+$: 216.0962; Found: 216.0966.

4.3.12. 1-(difluoromethyl)-4-propoxybenzene (3l)

39 mg, 53%, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.60 (t, J = 56.7 Hz, 1H), 3.94 (t, J = 6.2 Hz, 2H), 1.87–1.76 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.48 (d, J = 56.7 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (t, J = 1.6 Hz), 127.0 (t, J = 5.9 Hz), 126.5 (t, J = 22.7 Hz), 114.9 (t, J = 237.3 Hz), 114.5 (s), 69.6 (s), 22.4 (s), 10.4 (s). IR (neat) v = 2913, 1719, 1617, 1482, 1457, 1246, 1048, 1005, 819, 548. HRMS (EI): calcd. for $C_{10}H_{12}F_2O$ $[M]^+$: 186.0856; Found: 186.0863.

Declaration of competing interest

All authors declare that No conflict of interest exists.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131963.

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