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Synthesis of α,α-difluorobenzoyl oxygen heterocycles via the radical reaction of 2-iodo-2,2-difluoroacetophenones with unsaturated acids or unsaturated alcohols

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ABSTRACT

A convenient and facile method for the direct synthesis of α,α-difluorobenzoyl lactones or cyclic ethers via the radical cyclization reaction of 2-iodo-2,2-difluoroacetophenone with unsaturated acids or alcohols was reported.

1. Introduction

Molecules containing an α,α-difluoroketone unit are valuable for developing novel drugs in medicinal chemistry because they could be readily formed into hydrates and mimic tetrahedral intermediates involved in peptide hydrolysis [1]. Several α,α-difluoroketones have been reported to serve as drugs and biological probes, such as lubiprostone, GABA agonist and inhibitor of HIV-1 aspartic protease. Meanwhile, the α,α-difluoroketones can be used as fluorinated building blocks for further functionalization [2]. Despite the importance of α,α-difluoroketone derivatives, more efficient and general synthetic methods are still needed [3].

Recent reports show that the methodologies for the synthesis of α,α-difluoroketone derivatives mainly rely on direct fluorination methods and building block fluorination. Radical addition of polyfluoroalkyl iodides to unsaturated compounds could be an alternative strategy for polyfluoroalkylated derivatives [4], 2-iodo-2,2-difluoroacetophenones could also be used as free radicals to introduce α,α-difluorobenzoyl group to diverse compounds. However, the radical addition of 2-iodo-2,2-difluoroacetophenones has not been fully investigated. Burton reported the addition of 2-iodo-2,2-difluoroacetophenones to olefins using UV irradiation or Pd catalyst [5], while copper catalyst was used for the addition of 2-iodo-2,2-difluoroacetophenones to alkenes by Chai [6].

Our group is interested in constructing polyfluoroalkylated oxygen heterocycles due to their wide application in both natural and synthetic products with various bioactivities [7] and has reported their preparation by polyfluoroalkylation of unsaturated acid or alcohol with different polyfluoroalkyl iodides [8]. However, some of the reactions only afforded the adduct products and the sequent cyclization to give the desired polyfluoroalkylated oxygen heterocycles is needed. As part of our continued research in expanding the structural diversity of the fluoroalkylated oxygen heterocycles, we tried to synthesize α,α-difluorobenzoyl oxygen heterocycles by using difluoromethyl acetophenones as difluoroacetylation agent. Herein, we report the direct synthesis of α,α-difluorobenzoyl lactones and α,α-difluorobenzoyl cyclic ethers via the radical reaction of 2-iodo-2,2-difluoroacetophenone with unsaturated acids or unsaturated alcohols initiated by 2,2-azobisisobutyronitrile (AIBN) (Scheme 1).

2. Results and discussion

Our group has previously reported that the reaction of 2-iodo-2,2-difluoroacetophenones with 4-pentenoic acids or 5-hexenoic acid could directly give the cyclic products α,α-difluorobenzoyl γ-butyrolactones or δ-valerolactones by using AIBN as initiator in CH_3CN without any base (Table 1) [9].

We envisioned that the reaction of 2-iodo-2,2-difluoroacetophenones with unsaturated alcohols could also afford the cyclic ethers under a similar reaction condition. However, only low yield of cyclic ether **5a** was obtained when 2,2-difluoro-2-iodo-1-phenylethanone **1a** reacted with pent-4-en-1-ol **4a**, and a large amount of the starting material **1a** was recovered (Table 2, entry 1). The change of solvents has no significant impact on the yield of compound **5a** (entry 2). The result might be ascribed to the different nucleophilic ability between carboxyl and hydroxyl

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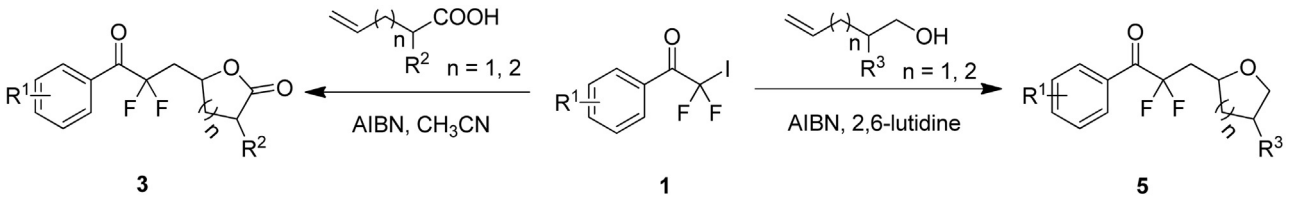


Scheme 1. Radical addition of 2-iodo-2,2-difluoroacetophenones to unsaturated acids and alcohols.

group. Therefore, 2,2-difluoro-2-iodo-1-phenylethanone **1a** and pent-4-en-1-ol **4a** were used as model reactants for the second optimization of the free radical cyclization reaction conditions, and the results are shown in Table 2. Initially, the experiments were conducted in the presence of different initiators or catalysts at 60 °C under a solvent-free condition (entries 3–11). Among several initiators/catalysts tested, AIBN turned out to be the suitable one for the reaction (entry 11), while others, such as Pd, Ni or Cu catalyst, were ineffective and less cyclic product **5a** could be detected (entries 3–10).

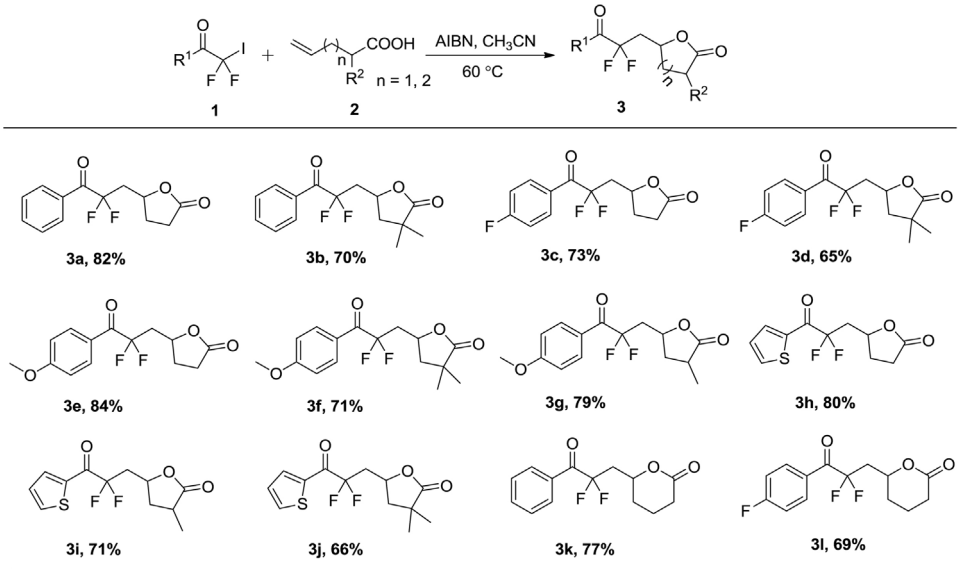
It's worth noting that, the addition of base into the reaction could deprotonate the alcohols [10]. Screening of bases was investigated (entries 12–18) and the result revealed that 2,6-lutidine was the most efficient base for the reaction (entry 18). Moreover, increasing reaction temperature to 80 °C gave higher yield of product **5a** while decreasing reaction temperature obviously diminished the yield (entries 18–20). When the amount of AIBN was increased to 30 mol%, the target compound **5a** was obtained in higher yield (entry 21). However, the yield would be lower when the amount of 2,2-difluoro-2-iodo-1-phenylethanone **1a** was reduced to 1 equiv of **4a** (entry 22).

Having established the optimized method (entry 21), we next probe the generality and scope of this radical cyclization reaction. Several 2-iodo-2,2-difluoroacetophenones and different unsaturated alcohols, such as γ- and δ- hydroxyl olefins, were examined under the optimized reaction conditions (Table 3). Overall, the radical addition reaction proceeded smoothly to furnish the α,α-difluorobenzoyl cyclic ethers in moderate to high yields, and no primary adduct β-iodo(difluoroalkyl)-alkanoic alcohol was observed. The results showed that 2-iodo-2,2-difluoroacetophenones, which have electron-donating groups in the benzene ring give higher yield of the corresponding cyclic ethers than those having halogen atoms, such as fluorine, chlorine. Most remarkably, 2-iodo-2,2-difluoroacetophenone bearing methoxy group reacted with pent-4-en-1-ol to afford 2,2-difluoro-1-(4-methoxyphenyl)-3-(tetrahydrofuran-2-yl) propan-1-one **5g** with yield as high as 90%. Furthermore, the substrates 2,2-difluoro-1-(naphthalen-2-yl)-3-(tetrahydrofuran-2-yl)propan-1-one **1h** and 2,2-difluoro-3-(tetrahydrofuran-2-yl)-1-(thiophen-2-yl)propan-1-one **1i**, which contain heterocyclic groups, could also afford the cyclic compounds with lower yield than those from α,α-difluoroacetophenones. While electron-withdraw group-substituted iododifluoromethyl acetophenone 2,2-difluoro-2-iodo-1-(4-(trifluoromethyl)phenyl) ethanone was employed in this reaction, the reaction efficiency was very poor with no specific product and most of the starting material was recovered. Furthermore, allyl alcohol was subjected to the addition reaction aiming at the corresponding epoxy propane. However, no target compound was obtained and only the reduction product difluoromethyl compound was observed.

3. Conclusion

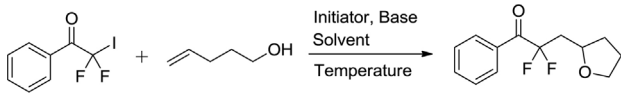
In summary, a convenient and facile approach for α,α-difluorobenzoyl oxygen heterocycles via the radical cyclization reaction of 2-iodo-2,2-difluoroacetophenones with unsaturated acids or alcohols has been developed. The reaction of unsaturated acids was initiated by AIBN in CH_3CN for the synthesis of α,α-difluorobenzoyl lactones, while the reaction of unsaturated alcohols initiated by AIBN proceeded well only in the presence of base 2,6-lutidine to afford α,α-difluorobenzoyl cyclic ethers. Further application of 2-iodo-2,2-difluoroacetophenones for radical reactions to synthesize structurally diverse α,α-difluoroketones are in progress and will be reported in due course.

Table 1
Reaction scope of 2-iodo-2,2-difluoroacetophenones and unsaturated acids [a,b].



[a] Reaction condition: **1** (1.5 mmol), **2** (1.0 mmol), AIBN (30 mol%), CH_3CN (10 mL).
[b] Isolated yield.

Table 2
Optimization of reaction conditions for the synthesis of compound **5a**[a].

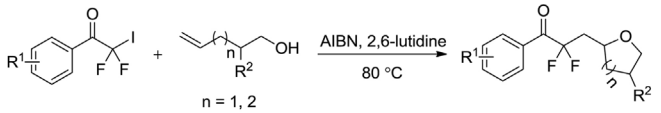


1a **4a** **5a**

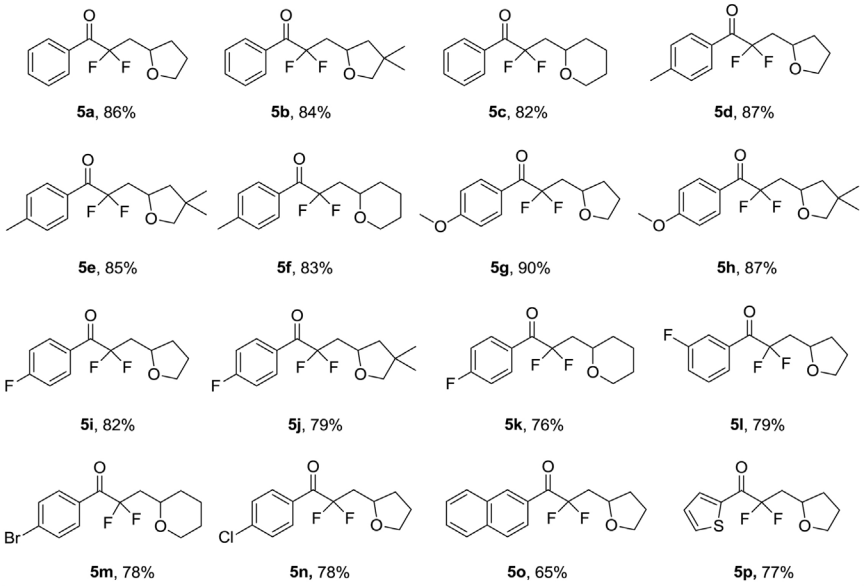
Entry	Initia./Catal. (mol%)	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	AIBN	–	CH_3CN	60	12
2	AIBN	–	CH_3CN + H_2O/$ClCH_2CH_2Cl$/THF/DMF/DMSO/1,4-dioxane	60	15–30
3	$Pd(PPh_3)_4$	–	–	60	23
4	$Pd(OAc)_2$	–	–	60	25
5	$PdCl_2(PPh_3)_2$	–	–	60	trace
6	$Pd(PCy_3)_2Cl_2$	–	–	60	10
7	$NiCl_2$	–	–	60	trace
8	$Ni(acac)_2$	–	–	60	24
9	$(PPh_3)_2NiCl_2$	–	–	60	trace
10	$Ni(dppf)Cl_2$	–	–	60	trace
11	AIBN		–	60	50
12	AIBN	Cs_2CO_3	–	60	19
13	AIBN	$NaHCO_3$	–	60	53
14	AIBN	NaOH	–	60	28
15	AIBN	K_2CO_3	–	60	22
16	AIBN	Et_3N	–	60	trace
17	AIBN	pyridine	–	60	23
18	AIBN	2,6-lutidine	–	60	63
19	AIBN	2,6-lutidine	–	80	76
20	AIBN	2,6-lutidine	–	40	trace
21	AIBN (30 mol%)	2,6-lutidine	–	80	90
22	AIBN (30 mol%)	2,6-lutidine	–	80	65

[c]The ratio of **1a** to **4a** is 1:1.
[a] Reaction condition: **1a** (1.5 mmol), **4a** (1.0 mmol), initiator/catalyst (20 mol%), base (1.5 mmol).
[b] Yields determined by GC analysis and based on **4a**.

Table 3
Reaction scope of 2-iodo-2,2-difluoroacetophenones and unsaturated alcohols[a,b].



1 **4** **5**



5a, 86% **5b**, 84% **5c**, 82% **5d**, 87%

5e, 85% **5f**, 83% **5g**, 90% **5h**, 87%

5i, 82% **5j**, 79% **5k**, 76% **5l**, 79%

5m, 78% **5n**, 78% **5o**, 65% **5p**, 77%

[a] Reaction condition: **1** (1.5 mmol), **4** (1.0 mmol), AIBN (30 mol%), 2,6-lutidine (1.5 mmol).
[b] Isolated yield.

4. Experimental

4.1. General

All reagents were of analytical grade, and obtained from commercial suppliers and used without further purification. All NMR spectra were recorded on a Bruker Avance 500 (resonance frequencies 500 MHz for ^{1}H and 125 MHz for ^{13}C) equipped with a 5 mm inverse broadband probe head with z-gradients at 295.8 K with standard Bruker pulse programs. The samples were dissolved in 0.6 mL $CDCl_3$ (99.8% D.TMS). Chemical shifts were given in values of δ_H and δ_C referenced to residual solvent signals (δ_H 7.26 for 1H, δ_C 77.0 for ^{13}C in $CDCl_3$). The ^{19}F NMR spectra were obtained using a 500 spectrometer (470 MHz) using trifluorotoluene as external standard. High resolution mass spectra (HRMS) were recorded on a Bruker solan X 70 FT-MS (samples was dissolved in CH_3OH and the ion source was ESI), and the energy was 22.5 eV at MS/MS. High resolution mass spectra (HRMS) (Compounds **1c-f**, **1i**, **5o** and **5p**) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. Melting points are uncorrected.

4.2. Preparation of 2-iodo-2,2-difluoroacetophenone *1a-i*

The 2-iodo-2,2-difluoroacetophenone **1a-i** were prepared according to the reported procedure [11]. As shown in Scheme 2, the intermediates enols were obtained from the reaction of ethyl 2,2,2-trifluoroacetate and ketones. The enols reacted with Selectfluor® to form fluorinated *gem*-diols, which then reacted with I_2 to afford 2-iodo-2,2-difluoroacetophenone **1a-i** using the trifluoroacetate release conditions (Scheme 2). The data of NMR and HRMS of new compounds **1c-f** and **1i** were as follows.

4.2.1. 2,2-Difluoro-1-(4-fluorophenyl)-2-iodoethanone (*1c*)

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24–8.22 (m, 2H), 7.24–7.20 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −54.4 (s, 2F), −110.5 (s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$), δ 180.9 (t, $^2J_{C\text{-}F}$ = 22.5 Hz), 166.7 (d, $^{1'}J_{C\text{-}F}$ = 257.5 Hz), 133.8 (d, $^{4'}J_{C\text{-}F}$ = 8.8 Hz), 130.3 (d, $^{3'}J_{C\text{-}F}$ = 10.0 Hz), 116.4 (d, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 29.7 (t, $^1J_{C\text{-}F}$ = 43.8 Hz) ppm. HRMS (EI): calcd for $C_8H_4F_3IO$ [M]+: 299.9259, found: 299.9257.

4.2.2. 2,2-Difluoro-1-(3-fluorophenyl)-2-iodoethanone (*1d*)

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–7.85 (m, 2H), 7.54–7.53 (m, 1H), 7.43–7.37 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ-54.9 (s, 2F), −110.3 (s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$), δ 181.2 (t, $^2J_{C\text{-}F}$ = 22.5 Hz), 162.5 (d, $^{1'}J_{C\text{-}F}$ = 247.5 Hz), 130.7 (d, $^{3'}J_{C\text{-}F}$ = 7.5 Hz), 126.6, 122.3 (d, $^{2'}J_{C\text{-}F}$ = 21.2 Hz), 117.6 (d, $^{2''}J_{C\text{-}F}$ = 23.8 Hz), 95.0 (t, $^1J_{C\text{-}F}$ = 323.8 Hz) ppm. HRMS (EI): calcd for $C_8H_4F_3IO$ [M]+: 299.9259, found: 299.9261.

4.2.3. 1-(4-Bromophenyl)-2,2-difluoro-2-iodoethanone (*1e*)

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04–8.03 (m, 2H), 7.70–7.68 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$): δ-54.7 (s, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.5 (t, $^2J_{C\text{-}F}$ = 23.8 Hz), 132.4, 132.2, 130.8, 127.1, 95.2 (t, $^1J_{C\text{-}F}$ = 325.0 Hz) ppm. HRMS (EI): calcd for $C_8H_4BrF_2IO$ [M]+: 361.8438, found: 361.8442.

4.2.4. 2,2-Difluoro-2-iodo-1-(4-methoxyphenyl)ethanone (*1f*)

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17–8.16 (m, 2H), 7.00–6.99 (m, 2H), 3.93(s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −53.27 (s, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.1 (t, $^2J_{C\text{-}F}$ = 22.5 Hz), 165.0, 133.4, 120.9, 114.3, 95.5 (t, $^1J_{C\text{-}F}$ = 306.3 Hz), 55.7 ppm. HRMS (EI): calcd for $C_9H_7F_2IO_2$ [M]+: 311.9459, found: 311.9460.

4.2.5. 2,2-Difluoro-2-iodo-1-(thiophen-2-yl)ethanone (*1i*)

Light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06–7.87 (m, 2H), 7.26–7.24 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ-54.5 (s, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6 (t, $^2J_{C\text{-}F}$ = 25.0 Hz), 137.7, 136.7, 133.7, 129.1, 29.7 (t, $^1J_{C\text{-}F}$ = 300.0 Hz) ppm. HRMS (EI): calcd for $C_6H_3F_2IOS$ [M]+: 287.8917, found: 287.8918.

4.3. The synthesis of α,α-difluorobenzoyl latones *3a-l*

The synthetic method and spectral data of α,α-difluorobenzoyl latones **3a-l** see reference 9.

4.4. General procedure for the synthesis of compounds *5a-p*

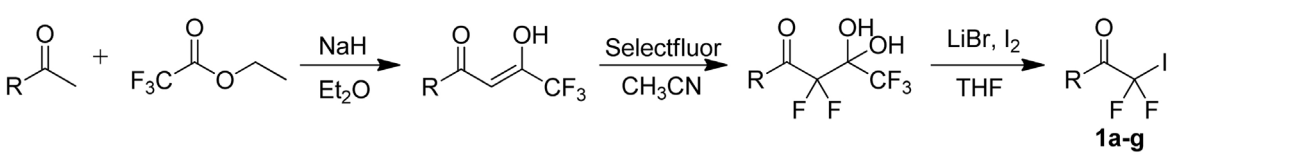
To a solution of 2-iodo-2,2-difluoroacetophenones **1a-i** (1.5 mmol) was added unsaturated alcohol **4** (1 mmol), AIBN (50 mg, 30 mol%) and 2,6-lutidine (160 mg, 1.5 mmol) at room temperature, the mixture was then heated to 80 °C and stirred for 20 h (TLC). After the completion of reaction, the reaction was quenched with H_2O. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/ethyl acetate (20:1) as eluent to afford the corresponding compounds **5**.

4.4.1. 2,2-Difluoro-1-phenyl-3-(tetrahydrofuran-2-yl)propan-1-one (*5a*)

Yellow oily liquid, yield: 86%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11–7.49 (m, 5H), 4.23–4.18 (m, 1H), 3.79 (dd, *J* = 14.7, 7.5 Hz, 1H), 3.71 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.67–2.53 (m, 1H), 2.45–2.35 (m, 1H), 2.17–2.10 (m, 1H), 1.98–1.84 (m, 2H), 1.65–1.58 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −99.05 (AB, *J* = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.4 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 134.0, 132.4, 130.0 (t, $^3J_{C\text{-}F}$ = 3.1 Hz), 128.6, 119.0 (t, $^1J_{C\text{-}F}$ = 251.9 Hz), 73.1 (t, $^{3'}J_{C\text{-}F}$ = 4.4 Hz), 67.6, 40.0 (t, $^{2'}J_{C\text{-}F}$ = 21.9 Hz), 32.0, 25.4 ppm. IR (KBr) ν_{max}: 2977, 2871, 1703, 1598, 1450, 1275, 1176, 1104, 1039, 1027, 917, 714, 687, 612, 423 cm^{-1}. HRMS calcd for $C_{13}H_{14}F_2O_2$ $(M+Na)^+$: 263.0859, found: 263.0854.

4.4.2. 3-(4,4-Dimethyltetrahydrofuran-2-yl)-2,2-difluoro-1-phenylpropan-1-one (*5b*)

Yellow oily liquid, yield: 84%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08–7.47 (m, 5H), 3.80–3.74 (m, 2H), 3.72 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.44–2.24 (m, 2H), 1.78–1.69 (m, 2H), 1.07 (s, 3H), 0.95 (s, 3H); ^{19}F



1a, R = Ph; **1b,** R = 4-CH_3-Ph; **1c,** R = 4-F-Ph;
1d, R = 3-F-Ph; **1e,** R = 4-Br-Ph; **1f,** R = 4-CH_3O-Ph;
1g, R = 4-Cl-Ph; **1h**, R= naphthalene; **1i,** R= thiophene

Scheme 2. Synthesis of 2-iodo-2,2-difluoroacetophenone **1a-i**.

NMR (470 MHz, $CDCl_3$): δ −98.91 (AB, J = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.8 (t, $^2J_{C\text{-}F}$ = 42.5 Hz), 133.8, 132.6, 130.0 (t, $^3J_{C\text{-}F}$ = 3.1 Hz), 128.5, 119.5 (t, $^1J_{C\text{-}F}$ = 251.9 Hz), 80.3 (t, $^{3'}J_{C\text{-}F}$ = 3.8 Hz), 65.7, 41.0, 40.3, 35.4 (t, $^{2'}J_{C\text{-}F}$ = 21.9 Hz), 25.0, 21.5 ppm. HRMS calcd for $C_{15}H_{18}F_2O_2$ $(M+Na)^+$: 291.1173, found: 291.1179.

4.4.3. 2,2-Difluoro-1-phenyl-3-(tetrahydro-2H-pyran-2-yl)propan-1-one (5c)

Yellow oily liquid, yield: 82%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07–7.47 (m, 5H), 3.78–3.76 (m, 1H), 3.66–3.62 (m, 1H), 3.31–3.26 (m, 1H), 2.59–2.47 (m, 1H), 2.34–2.28 (m, 1H), 1.84–1.81 (m, 1H), 1.68–1.65 (m, 1H), 1.54–1.48 (m, 2H), 1.46–1.44 (m, 1H), 1.38–1.34 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.95 (AB, J = 272.6 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.8 (t, $^2J_{C\text{-}F}$ = 30.6 Hz), 133.7, 132.9, 129.9 (t, $^3J_{C\text{-}F}$ = 2.5 Hz), 128.5, 119.0 (t, $^1J_{C\text{-}F}$ = 251.3 Hz), 72.2 (t, $^{3'}J_{C\text{-}F}$ = 5.0 Hz), 68.1, 41.6 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 32.0, 25.4, 23.2 ppm. IR (KBr) ν_{max}: 2938, 2856, 1703, 1599, 1450, 1263, 1092, 806, 721, 701 cm^{-1}. HRMS calcd for $C_{14}H_{16}F_2O_2$ $(M+Na)^+$: 277.1016, found: 277.1018.

4.4.4. 2,2-Difluoro-3-(tetrahydrofuran-2-yl)-1-(p-tolyl)propan-1-one (5d)

Yellow oily liquid, yield: 87%.^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.27 (m, 4H), 4.20–4.14 (m, 1H), 3.78 (dd, J = 14.7, 7.4 Hz, 1H), 3.68 (dd, J = 14.3, 7.8 Hz, 1H), 2.64–2.52 (m, 1H), 2.41 (s, 3H), 2.38–2.27 (m, 1H), 2.14–2.07 (m, 1H), 1.95–1.81 (m,2H), 1.62–1.55 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.94 (AB, J = 282.00 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.0 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 145.2, 130.2 (t, $^3J_{C\text{-}F}$ = 3.1 Hz), 129.3, 119.0 (t, $^1J_{C\text{-}F}$ = 251.3 Hz), 73.1 (t, $^{3'}J_{C\text{-}F}$ = 4.4 Hz), 67.7, 40.1 (t, $^{2'}J_{C\text{-}F}$ = 21.9 Hz), 32.1, 25.5, 23.3, 21.7 ppm. IR (KBr) ν_{max}: 2978, 2871, 1748, 1698, 1608, 1275, 1197, 1177, 1036, 824, 756, 742, 594, 482 cm^{-1}. HRMS calcd for $C_{14}H_{16}F_2O_2$ $(M+Na)^+$: 277.1016, found: 277.1017.

4.4.5. 3-(4,4-Dimethyltetrahydrofuran-2-yl)-2,2-difluoro-1-(p-tolyl) propan-1-one (5e)

Yellow oily liquid, yield: 85%.^1H NMR (500 MHz, $CDCl_3$): δ 8.02–7.28 (m, 4H), 3.83–3.71 (m, 2H), 3.72 (d, J = 9.5 Hz, 1H), 2.43 (s, 3H), 2.37–2.24 (m, 2H), 1.80–1.70 (m, 2H), 1.08 (s, 3H), 0.95 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.85 (AB, J = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.3 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 145.0, 130.2 (t, $^3J_{C\text{-}F}$ = 2.5 Hz), 128.6, 128.6, 119.5 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 80.3 ($^{3'}J_{C\text{-}F}$ = 2.5 Hz), 65.7, 41.0, 40.4, 35.3 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 25.0, 21.8, 21.5 ppm. IR (KBr) ν_{max}: 2965, 2874, 1698, 1608, 1467, 1178, 1121, 1107, 918, 753 cm^{-1}. HRMS calcd for $C_{16}H_{20}F_2O_2$ $(M+Na)^+$: 305.1392, found: 305.1326.

4.4.6. 2,2-Difluoro-3-(tetrahydro-2H-pyran-2-yl)-1-(p-tolyl)propan-1-one (5f)

Yellow oily liquid, yield: 83%. ^1H NMR (500 MHz, $CDCl_3$): δ 7.98–7.28 (m, 4H), 3.81–3.79 (m, 1H), 3.66–3.62 (m, 1H), 3.33–3.28 (m, 1H), 2.57–2.47 (m, 1H), 2.44 (s, 3H), 2.34–2.24 (m, 1H), 1.84–1.82 (m,1H), 1.67 (d, J = 12.80 Hz, 1H), 1.56–1.49 (m, 2H), 1.47–1.44 (m, 1H), 1.41–1.33 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.79 (AB, J = 277.3 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.3 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 144.8, 130.2, 130.1 (t, $^3J_{C\text{-}F}$ = 2.5 Hz), 129.3, 119.1 (t, $^1J_{C\text{-}F}$ = 251.3 Hz), 72.2 (t, $^{3'}J_{C\text{-}F}$ = 5.0 Hz), 68.2, 41.6 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 32.0, 25.5, 23.3, 21.8 ppm. IR (KBr) ν_{max}: 2959, 2922, 2851, 1716, 1464, 1457, 1317, 1247, 1195, 1178, 1133, 1082, 1048, 1013, 966, 816 cm^{-1}. HRMS calcd for $C_{15}H_{18}F_2O_2$ $(M+Na)^+$: 291.1173, found: 291.1173.

4.4.7. 2,2-Difluoro-1-(4-methoxyphenyl)-3-(tetrahydrofuran-2-yl)propan-1-one (5 g)

Yellow oily liquid, yield: 90%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07–6.91 (m, 4H), 4.16–4.11 (m, 1H), 3.83 (s, 3H), 3.76 (q, J = 7.3 Hz, 1H), 3.66 (dd, J = 14.2, 8.0 Hz, 1H), 2.60–2.48 (m, 1H), 2.40–2.29 (m, 1H), 2.11–2.04 (m, 1H), 1.90–1.80 (m, 2H), 1.59–1.53 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.51 (AB, J = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.7 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 164.3, 132.6 (t, $^3J_{C\text{-}F}$ = 3.8 Hz), 119.1 (t, $^1J_{C\text{-}F}$ = 251.3 Hz), 113.9, 73.1 (t, $^{3'}J_{C\text{-}F}$ = 3.8 Hz), 67.6, 55.5, 40.0 (t, $^{2'}J_{C\text{-}F}$ = 21.3 Hz), 39.3, 32.1, 25.4, 23.2 ppm. IR (KBr) ν_{max}: 2846, 1698, 1601, 1573, 1515, 1463, 1427, 1317, 1266, 1251, 1179, 1137, 1059, 975, 872, 833, 554 cm^{-1}. HRMS calcd for $C_{14}H_{16}F_2O_3$ $(M+Na)^+$: 293.0965, found: 293.0933.

4.4.8. 3-(4,4-Dimethyltetrahydrofuran-2-yl)-2,2-difluoro-1-(4-methoxyphenyl)propan-1-one (5 h)

Yellow oily liquid, yield: 87%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.13–6.97 (m, 4H), 3.91 (s, 3H), 3.85–3.78 (m, 2H), 3.73 (dd, J = 7.6, 3.9 Hz, 1H), 2.36–2.27 (m, 2H), 1.79–1.73 (m, 2H), 1.09 (s, 3H), 0.96 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.46(AB, J = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.1 (t, $^2J_{C\text{-}F}$ = 32.5 Hz), 164.1, 132.6, 119.6 (t, $^1J_{C\text{-}F}$ = 250.6 Hz), 117.2, 80.3 (t, $^{3'}J_{C\text{-}F}$ = 3.1 Hz), 65.8, 55.5, 41.1, 40.5, 35.2 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 24.9, 23.5, 21.5 ppm. IR (KBr) ν_{max}: 2962, 1693, 1602, 1513, 1465, 1316, 1264, 1173, 1027, 845, 770 cm^{-1}. HRMS calcd for $C_{16}H_{20}F_2O_3$ $(M+H)^+$: 299.1459, found: 299.1469.

4.4.9. 2,2-Difluoro-1-(4-fluorophenyl)-3-(tetrahydrofuran-2-yl)propan-1-one (5i)

Yellow oily liquid, yield: 82%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.15–7.15 (m, 4H), 4.20–4.17 (m, 1H), 3.78 (dd, J = 14.7, 7.5 Hz, 1H), 3.69 (dd, J = 14.3, 7.9 Hz, 1H), 2.64–2.52 (m, 1H), 2.44–2.33 (m, 1H), 2.15–2.09 (m, 1H), 1.94–1.83 (m, 2H), 1.64–1.57 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.80 (AB, J = 282.0 Hz, 2F), −102.92 (s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.0 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 166.2 (d, $^{1'}J_{C\text{-}F}$ = 255.0 Hz), 132.9 (dt, $^{3'}J_{C\text{-}F}$ = 2.5 Hz, $^3J_{C\text{-}F}$ = 8.8 Hz), 128.7, 119.0 (t, $^1J_{C\text{-}F}$ = 251.9 Hz), 115.9 (d, $^{2''}J_{C\text{-}F}$ = 21.9 Hz), 73.0 (t, $^{3''}J_{C\text{-}F}$ = 4.4 Hz), 67.7, 39.9 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 32.1, 25.4 ppm. IR (KBr) ν_{max}: 2977, 2872, 1705, 1600, 1508, 1239, 850, 815, 768, 618, 593 cm^{-1}. HRMS calcd for $C_{13}H_{13}F_3O_2$ $(M+Na)^+$: 281.0765, found: 281.0765.

4.4.10. 3-(4,4-Dimethyltetrahydrofuran-2-yl)-2,2-difluoro-1-(4-fluorophenyl)propan-1-one (5j)

Yellow oily liquid, yield: 79%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.14–7.14 (m, 4H), 3.80–3.72 (m, 2H), 3.69 (dd, J = 9.9, 1.6 Hz, 1H), 2.41–2.22 (m, 2H), 1.78–1.69 (m, 2H), 1.07 (s, 3H), 0.94 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.69 (AB, J = 282.0 Hz, 2F), −103.13 (s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.3 (t, $^2J_{C\text{-}F}$ = 30.6 Hz), 166.1 (d, $^{1'}J_{C\text{-}F}$ = 255.0 Hz), 132.9 (dt, $^{3'}J_{C\text{-}F}$ = 2.5 Hz, $^3J_{C\text{-}F}$ = 8.8 Hz), 128.9, 119.5 (t, $^1J_{C\text{-}F}$ = 251.9 Hz), 115.8 (d, $^{2''}J_{C\text{-}F}$ = 22.5 Hz), 80.3 (t, $^{3''}J_{C\text{-}F}$ = 2.5 Hz), 65.7, 41.0, 40.3, 35.3 (t, $^{2'}J_{C\text{-}F}$ = 21.88 Hz), 25.0, 21.5 ppm. IR (KBr) ν_{max}: 2925, 2853, 1717, 1604, 1510, 1275, 1231 cm^{-1}. HRMS calcd for $C_{15}H_{17}F_3O_2$ $(M+Na)^+$: 309.1078, found: 309.1075.

4.4.11. 2,2-Difluoro-1-(4-fluorophenyl)-3-(tetrahydro-2H-pyran-2-yl) propan-1-one (5k)

Yellow oily liquid, yield: 76%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.10–7.13 (m, 4H), 3.74–3.72 (m, 1H), 3.63–3.59 (m, 1H), 3.25 (t, J = 9.6 Hz,1H), 2.56–2.44 (m, 1H), 2.33–2.23 (m, 1H), 1.82–1.81 (m, 1H), 1.64 (d, J = 12.9 Hz, 1H), 1.52–1.47 (m, 1H), 1.45–1.44 (m, 1H), 1.44–1.38 (m, 1H), 1.35 (s, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.82 (AB, J = 277.3 Hz, 2F), −103.49 (s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2 (t, $^2J_{C\text{-}F}$ = 29.4 Hz), 166.0 (d, $^{1'}J_{C\text{-}F}$ = 255.0 Hz), 132.7 (dt, $^{3'}J_{C\text{-}F}$ = 2.5 Hz, $^3J_{C\text{-}F}$ = 8.8 Hz), 129.3, 119.0 (t, $^1J_{C\text{-}F}$ = 250.6 Hz), 115.7 (d, $^{2''}J_{C\text{-}F}$ = 21.3 Hz), 72.1 (t, $^{3'2}J_{C\text{-}F}$ = 2.5 Hz), 68.1, 41.6 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 31.9, 25.4, 23.2 ppm. IR (KBr) ν_{max}: 2943, 2859, 1705, 1600, 1581, 1509, 1239, 850, 840, 768 cm^{-1}. HRMS calcd for $C_{14}H_{15}F_3O_2$ $(M+Na)^+$: 295.0922, found: 295.0918.

4.4.12. 2,2-Difluoro-1-(3-fluorophenyl)-3-(tetrahydrofuran-2-yl)propan-1-one (5l)

Light yellow oily liquid, yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.30 (m, 4H), 4.20–4.15 (m, 1H), 3.74 (dd, J = 15.0, 7.5 Hz, 1H), 3.67 (dd, J = 14.0, 7.5 Hz, 1H), 2.64–2.52 (m, 1H), 2.43–2.33 (m, 1H), 2.14–2.07 (m, 1H), 1.92–1.83 (m, 2H), 1.63–1.56 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −99.22 (AB, J = 286.7 Hz, 2F), −111.47(s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.4 (t, $^2J_{C\text{-}F}$ = 31.6 Hz), 162.5 (d, $^{1'}J$ = 246.3 Hz), 137.8, 134.3 (d, $^3J_{C\text{-}F}$ = 2.5 Hz), 130.3 (d, $J_{C\text{-}F}$ = 3.8 Hz), 125.8 (d, $J_{C\text{-}F}$ = 1.9 Hz), 121.0 (d, $J_{C\text{-}F}$ = 10.6 Hz), 119.0 (t, $^1J_{C\text{-}F}$ = 251.9 Hz), 73.0 (t, $^{3'}J_{C\text{-}F}$ = 4.4 Hz), 67.7, 39.9 (t, $^{2'}J_{C\text{-}F}$ = 21.9 Hz), 32.0, 25.4 ppm. IR (KBr) ν_{max}: 2876, 1711,1588, 1486, 1443, 1251, 1132, 1057, 831, 758 cm^{-1}. HRMS calcd for $C_{13}H_{13}F_3O_2$ $(M+Na)^+$: 281.0765, found: 281.0779.

4.4.13. 1-(4-Bromophenyl)-2,2-difluoro-3-(tetrahydro-2H-pyran-2-yl) propan-1-one (5m)

Yellow oily liquid, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90–7.60 (m, 4H), 3.70 (dd, J = 10.80, 3.00 Hz, 1H), 3.61–3.57 (m, 1H), 3.27–3.19 (m, 1H), 2.56–2.43 (m, 1H), 2.32–2.22 (m, 1H), 1.81–1.80 (m, 1H), 1.63 (d, J = 12.9 Hz, 1H), 1.50–1.45 (m, 2H), 1.44–1.41 (m, 1H), 1.38–1.32 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −99.10 (AB, J = 272.6 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.0 (t, $^2J_{C\text{-}F}$ = 29.4 Hz), 131.9, 131.8, 131.3 (t, $^3J_{C\text{-}F}$ = 3.8 Hz), 129.0, 121.0, 119.0 (t, $^1J_{C\text{-}F}$ = 251.3 Hz), 72.1 (t, $^{3'}J_{C\text{-}F}$ = 3.8 Hz), 68.0, 41.7 (t, $^{2'}J_{C\text{-}F}$ = 22.5 Hz), 31.8, 25.4, 23.2 ppm. IR (KBr) ν_{max}: 2977, 2871, 1705, 1586, 1566, 1397, 1315, 824, 759, 473, 421 cm^{-1}. HRMS calcd for $C_{14}H_{15}BrF_2O_2$ $(M + Na)^+$: 355.0121, found: 355.0127.

4.4.14. 1-(4-Chlorophenyl)-2,2-difluoro-3-(tetrahydrofuran-2-yl)propan-1-one (5n)

Yellow oily liquid, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03–7.45 (m, 4H), 4.20–4.14 (m, 1H), 3.75 (dd, J = 15.0, 8.0 Hz, 1H), 3.67 (dd, J = 14.0, 8.0 Hz, 1H), 2.63–2.51 (m, 1H), 2.43–2.33 (m, 1H), 2.14–2.08 (m, 1H), 1.94–1.82 (m, 2H), 1.63–1.56 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −99.04 (AB, J = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.4 (t, $^2J_{C\text{-}F}$ = 30.6 Hz), 140.6, 131.4 (t, $^3J_{C\text{-}F}$ = 3.1 Hz), 130.7, 129.4, 129.0, 118.9 (t, $^1J_{C\text{-}F}$ = 251.9 Hz), 73.0 (t, $^{3'}J_{C\text{-}F}$ = 4.4 Hz), 67.7, 39.9 (t, $^{2'}J_{C\text{-}F}$ = 21.9 Hz), 32.0, 25.4 ppm. IR (KBr) ν_{max}: 2978, 2873, 1706, 1589, 1489, 1403, 1192, 1177, 1093, 1015, 917, 844, 825, 761 cm^{-1}. HRMS calcd for $C_{13}H_{13}ClF_2O_2$ $(M+Na)^+$: 297.0470, found: 297.0471.

4.4.15. 2,2-Difluoro-1-(naphthalen-2-yl)-3-(tetrahydrofuran-2-yl)propan-1-one (5o)

Yellow oily liquid, yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.11-7.80 (m, 3H), 7.67–7.58 (m, 2H), 4.26–4.23 (m, 1H), 3.81 (dd, J = 15.0, 10.0 Hz, 1H), 3.72 (dd, J = 15.0, 10.0 Hz, 1H), 2.78–2.60 (m, 1H), 2.54–2.40 (m, 1H), 2.20–2.10 (m, 1H), 1.99–1.85 (m, 1H), 1.70–1.56 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.4 (AB, J = 282.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.4 (t, $^2J_{C\text{-}F}$ = 30.0 Hz), 135.9, 132.5 (t, $^3J_{C\text{-}F}$ = 3.8 Hz), 132.3, 130.0, 129.7, 128.5, 127.8, 126.9, 124.7 (d, $^{4'}J_{C\text{-}F}$ = 1.3 Hz), 119.2 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 73.2 (t, $^{3'}J_{C\text{-}F}$ = 5.0 Hz), 67.7, 40.1 (t, $^{2'}J_{C\text{-}F}$ = 21.3 Hz), 32.1, 25.5 ppm. IR (KBr) ν_{max}: 3715, 3649, 2959, 2917, 1698, 1627, 1170, 778, 473 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{16}F_2O_2$ $[M]^+$: 290.1118, found: 290.1119.

4.4.16. 2,2-Difluoro-3-(tetrahydrofuran-2-yl)-1-(thiophen-2-yl)propan-1-one (5p)

Yellow oily liquid, yield: 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–8.03 (m, 1H), 7.80–7.79 (m, 1H), 7.22–7.20 (m, 1H), 4.23–4.10 (m, 1H), 3.82 (dd, J = 10.0, 5.0 Hz, 1H), 3.71(dd, J = 10.0, 5.0 Hz, 1H), 2.66–2.55 (m, 1H), 2.45–2.32 (m, 1H), 2.17–2.09 (m, 1H), 1.99–1.85 (m, 1H), 1.67–1.58 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −101.1(AB, J = 277.3 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$), δ 182.8 (t, $^2J_{C\text{-}F}$ = 28.8 Hz), 138.4, 136.1, 135.6, 128.7, 121.6 (d, $^3J_{C\text{-}F}$ = 6.3 Hz), 119.6 (t, $^1J_{C\text{-}F}$ = 252.5 Hz), 73.0 (t, $^{3'}J_{C\text{-}F}$ = 3.8 Hz), 67.7, 39.9 (t, $^{2'}J_{C\text{-}F}$ = 21.3 Hz), 32.0, 25.4 ppm. IR (KBr) ν_{max}: 2978, 2869, 2852, 1678, 1598, 1515, 1462, 1412, 1357, 1185, 1132, 839, 727 cm^{-1}. HRMS (EI): calcd for $C_{11}H_{12}F_2O_2S$ $[M]^+$: 246.0526, found: 246.0525.

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