Supporting Information

Copper Catalyzed One-Pot Difluoroalkylation and Lactonization of Unsaturated Carboxylic Acids

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1. General Information

All experiments were conducted under argon atmosphere. Toluene, DMF, DMSO and acetonitrile were dried and distilled by the standard methods. Other commercially available reagents were purchased and used without further purification, unless otherwise stated. Flash chromatographic separations were carried out on 200-300 mesh silica gel. Reactions were monitored by TLC and GC analysis of reaction aliquots. GC analysis was performed on an Agilent 7890 Gas Chromatography using a HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film). 1H, 13C and 19F NMR spectra were recorded in CDCl3 on a Bruker AVANCE III spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI) through a Bruker Daltonics - micrOTOF-Q II.

2. Preliminary Mechanistic Studies

To gain some mechanistic insight into the reaction, the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.5 equiv) was added to the mixtures of 2a and 1a in standard reactions. The formation of 3aa was inhibited and the yield of 13% of 2a-TEMPO adduct was detected by GC.

1H, 13C, and 19F NMR spectra of 2a-TEMPO
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.34 (q, $J$ = 7.1 Hz, 2H), 1.58-1.53 (m, 6H), 1.35 (t, $J$ = 7.1 Hz, 3H), 1.18-1.15 (m, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 160.85 (t, $J$ = 42.6 Hz), 115.65 (t, $J$ = 271.6 Hz), 63.11, 61.50, 40.33, 33.53 (t, $J$ = 4.3 Hz), 20.86, 17.03, 14.03; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -73.47 (s, 2F).
The GC Spectrum of 2a-TEMPO:
GC analysis of TEMPO Experiment:

\[ \text{OH} + \text{BisCO}_2\text{EI} \xrightarrow{\text{standard condition TEMPO(1.5 equiv.)}} \text{CF}_3\text{CO}_2\text{EI} + \text{CF}_3\text{CO}_2\text{EI} \]

1a 2a 3a trace 2a-TEMPO, 13%
3. Experimental Procedures and NMR Data

General Procedure for the Preparation of Substrates

**Method A:**
To an oven dried 100mL round bottom flask containing succinic anhydride (1.0 g, 10 mmol) and arene (11 mmol, 1.1 equiv) in DCM (33 mL) was added AlCl₃ (22 mmol, 2.2 equiv) portion-wise at room temperature over 5 minutes and allowed to stir until completion. The reaction was poured over 1N HCl in ice, extracted with ether (66 mL) and washed with 1N HCl (3 x 15 mL). The organic layer was dried (Na₂SO₄) and concentrated to give the product as a solid that was subsequently washed with hexanes and vacuum filtered to afford the crude product 1g-1k, 1m, 1r.

**Method B:**
Into a solution of phthalic anhydride (1.48 g, 10 mmol) in toluene (6.4 mL), anhydrous AlCl₃ (2.67 g, 20 mmol) was added slowly. The reaction was stirred at 50 °C for 4 h, and then, it was diluted with 10% sulfuric acid. The precipitate was collected by filtration to provide 1q as a white solid.

**Method C:**
To a flask equipped with a Dean-Stark trap, phthalic anhydride (1.48 g, 10 mmol) were charged and dissolved in chlorobenzene (6 mL). Aluminum chloride (4.0 g, 30 mmol) was added to the above solution under stirring in the presence of nitrogen protection. The reaction mixture was refluxed and stirred for 4 h at 75–80 °C. Upon cooling, the resulting mixture was poured into diluted HCl, agitated. At the beginning, white deposition was created, then the deposition dissolved and the resulting mixture became yellow and phase separation. 1.5 mL 40 % KOH was added to the obtained organic layer. Moved the water layer and acidified it with a large amount of 10 % HCl water solution to precipitate the product 1o.

**Method D:**
To a two neck round-bottom flask equipped with a reflux condenser and addition funnel was added 1.2 mL (1.08 g, 10 mmol) anisole, 30 mL nitrobenzene (as a solvent) and 1.85 g (12.5 mmol) phthalic anhydride. To the additional funnel was added a solution of 3.33 g (25 mmol) of powdered anhydrous aluminum chloride and 8 mL nitrobenzene. This solution, at rt, was dropwise added to the flask during 10 m. The contents of the flask were stirred at rt for 5.5 h. After this time the reaction mixture was added to a solution of 150 mL HCl 20 % and 100 g ice and mixed throughly, extracted with ether. This phase was washed with H₂O, and extracted with saturated NaHCO₃. This solution was then washed with ether. The aqueous solution was transfer to a large beaker and acidified with HCl. The white percpipitate formed and was collected by filtration through to give 1p.

Method E:[5]

To a solution of Mg (6.0 mmol, 144 mg) in THF (3 mL) was added dropwise a solution of aryl bromide derivatives (6 mmol) and THF (8 mL) for 24 h. The mixture was then added to a solution of succinic anhydride (5 mmol) in THF (5 mL) at -90 °C. The mixture was stirred at room temperature over 6 h. After the reaction, the mixture was quenched with an aqueous solution of 1N HCl (5 mL). The aqueous layer was extracted with Et₂O and the organic phase was combined, dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by recrystallization (hexane/CH₂Cl₂ or toluene) to give II.

General Procedure for the preparation of compounds IV[6]

To a suspension of methyltriphenylphosphonium bromide (3.91 g, 11.0 mmol, 1.0 equiv) in THF (20 mL) was added sodium tert-butoxide (2.1 g, 22.0 mmol, 2.0 equiv) at 0 °C. The mixture was then stirred for 30 min. Keto-acid III (8.5 mmol, 0.85 equiv) was then added to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure, and diluted with dichloromethane (50 mL) and NaOH (1 N, 50 mL). The aqueous layer was washed with CH₂Cl₂ (20 mL×2) and acidified with HCl (12 N) until it reached ca. pH 2. The aqueous layer was then extracted with CH₂Cl₂ (30 mL×3), dried (MgSO₄), and filtered. The resultant solution was concentrated under reduced
pressure and the crude product that was purified by flash column chromatography (Hexanes/EtOAc 1: 1) to give alkenoic acid IV.

**General Procedure for Copper Catalyzed One-Pot Difluoroalkylation and Lactonization of Unsaturated Carboxylic Acids**
To a 25 mL of Schlenk tube was added CuBr (0.05 mmol, 10 mol %), Na₂S₂O₅ (0.1 mmol, 20 mol %), unsaturated carboxylic acids I (0.5 mmol, 1.0 equiv) under air and then evacuated and backfilled with Ar (3 times). DMSO (5 mL), PMDETA (1.0 mmol, 2.0 equiv) and ethyl bromodifluoroacetate (1.5 equiv) or perfluoroalkyl iodide (1.5 equiv) was added subsequently. The reaction mixture was heated to 85 °C (oil bath). After stirring for 10 h, the reaction was cooled to room temperature. The reaction mixture was quenched with 50 ml of water and then extracted with ethyl acetate (3×60 ml). The combined organic extracts were washed with brine (50 mL) dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified with silica gel chromatography to give the desired product.

**¹H, ¹³C, and ¹⁹F NMR Spectra:**

**Ethyl 2,2-difluoro-3-(5-oxotetrahydrofuran-2-yl)propanoate (3aa).** The product was purified by silica gel column chromatography (PE/EA = 5/1). Yield, 83%, 93.6 mg, light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.77-4.70 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.69-2.33 (m, 5H), 2.03-1.93 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 176.01, 163.48 (t, J = 252.9, 250.1 Hz, 1C), 114.36 (dd, J = 23.3 Hz, 1C), 74.18 (dd, J = 6.5, 3.3 Hz, 1C), 63.54, 40.31 (t, J = 23.3 Hz, 1C), 28.44, 28.38, 13.96; ¹⁹F NMR (376 MHz, CDCl₃) δ -104.72 (dd, J = 1765.6, 265.8 Hz, 2F); HRMS (ESI): m/z calcd. for C₉H₁₂F₂NaO₄⁺ [M + Na⁺]: 245.0596, found: 245.0590.

**Ethyl 2,2-difluoro-3-(2-isopropyl-5-oxotetrahydrofuran-2-yl)propanoate (3ba).** The product was purified by silica gel column chromatography (PE/EA = 5/1). Yield,
65%, 84.8 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.40-4.24 (m, 2H), 2.78-2.61 (m, 2H), 2.54-2.45 (m, 1H), 2.41-2.30 (m, 1H), 2.26-2.11 (m, 2H), 2.08-2.01 (m, 1H), 1.34 (t, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H) ; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.87, 163.77 (t, $J = 31.7$ Hz, 1C), 115.45 (dd, $J = 253.1$, 249.4 Hz, 1C), 86.92 (dd, $J = 5.9$, 1.2 Hz, 1C), 63.54, 40.57 (dd, $J = 23.6$, 21.4 Hz, 1C), 37.07 (d, $J = 1.5$ Hz, 1C), 28.61, 27.24 (d, $J = 3.4$ Hz, 1C), 16.62, 16.39, 13.89; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.98 (dd, $J = 2165.7$, 266.7 Hz, 2F); HRMS (ESI): m/z calcd. for C$_{12}$H$_{18}$F$_{2}$NaO$_4$+ [M + Na$^+$]: 287.1065, found: 287.1064.

**Ethyl 2,2-difluoro-3-(6-oxotetrahydro-2H-pyran-2-yl)propanoate (3ca).** The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 60%, 71.2 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.62-4.55 (m, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 2.67-2.53 (m, 2H), 2.48-2.28 (m, 2H), 2.03-1.82 (m, 3H), 1.69-1.59 (m, 1H), 1.36 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.03, 163.69 (t, $J = 31.9$ Hz, 1C), 114.45 (dd, $J = 252.9$, 242.9 Hz, 1C), 74.37 (dd, $J = 7.0$, 3.4 Hz, 1C), 63.47, 40.93 (t, $J = 23.6$ Hz, 1C), 29.26, 27.96, 18.43, 13.99; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -104.62 (dd, $J = 2173.1$, 263.3 Hz, 2F); HRMS (ESI): m/z calcd. for C$_{10}$H$_{14}$F$_{2}$NaO$_4$+ [M + Na$^+$]: 259.0752, found: 259.0759.

**Ethyl 2,2-difluoro-3-(2-methyl-5-oxotetrahydrofuran-2-yl)propanoate (3da).** The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 67%, 79.7 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.39-4.26 (m, 2H), 2.63-2.48 (m, 4H), 2.35-2.27 (m, 1H), 2.11-2.04 (m, 1H), 1.50 (d, $J = 1.1$ Hz, 3H), 1.34 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.44, 163.66 (t, $J = 31.7$ Hz, 1C), 114.70 (dd, $J = 252.5$, 250.4 Hz, 1C), 82.56 (t, $J = 3.3$ Hz, 1C), 63.56, 44.28 (t, $J = 22.8$ Hz, 1C), 33.68 (d, $J = 2.1$ Hz, 1C), 28.45, 26.81 (d, $J = 2.7$ Hz, 1C), 13.90; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -102.02 (q, $J = 265.9$ Hz, 2F); HRMS (ESI): m/z calcd. for C$_{10}$H$_{14}$F$_{2}$NaO$_4$+ [M + Na$^+$]: 259.0752, found: 259.0750.
Ethyl 2,2-difluoro-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)propanoate (3ea).\(^7\)
The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 55%, 74.1 mg, light yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.92 (d, \(J = 7.7\) Hz, 1H), 7.72 (t, \(J = 7.5\) Hz, 1H), 7.58 (t, \(J = 7.5\) Hz, 1H), 7.51 (d, \(J = 7.7\) Hz, 1H), 5.69 (dd, \(J = 9.0, 3.1\) Hz, 1H), 4.45-4.34 (m, 2H), 2.84-2.72 (m, 1H), 2.65-2.51 (m, 1H), 1.38 (t, \(J = 7.2\) Hz, 3H); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.40, 163.42 (t, \(J = 31.6\) Hz, 1C), 148.19, 134.58, 129.95, 126.16, 125.80, 122.10, 114.28 (dd, \(J = 253.8, 251.2\) Hz, 1C), 74.84 (dd, \(J = 7.1, 3.6\) Hz, 1C), 63.66, 40.42 (t, \(J = 23.8\) Hz, 1C), 13.99; \(^1\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -104.21 (dd, \(J = 1740.5, 265.9\) Hz, 2F).

Ethyl 2,2-difluoro-3-(5-oxo-2-phenyltetrahydrofuran-2-yl)propanoate (3fa).\(^7\) The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 76%, 112.9 mg, light yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.30 (m, 5H), 4.27-4.11 (m, 2H), 2.95-2.34 (m, 6H), 1.30 (t, \(J = 7.1\) Hz, 3H); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 175.28, 163.47 (t, \(J = 31.6\) Hz, 1C), 141.79, 128.81 (2C), 128.39, 124.70 (2C), 114.33 (t, \(J = 252.0\) Hz, 1C), 84.73 (t, \(J = 4.4\) Hz, 1C), 63.44, 45.66 (t, \(J = 23.1\) Hz, 1C), 34.56, 28.03, 13.86; \(^1\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -101.08 (t, \(J = 14.5\) Hz, 2F).

Ethyl 2,2-difluoro-3-(2-(4-methoxyphenyl)-5-oxotetrahydrofuran-2-yl)propanoate (3ga).\(^7\) The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 90%, 146.9 mg, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.23 (d, \(J = 7.8\) Hz, 2H), 6.86 (d, \(J = 7.8\) Hz, 2H), 4.23-4.08 (m, 2H), 3.77 (s, 3H), 2.85-2.76 (m,
2H), 2.66-2.47 (m, 3H), 2.41-2.34 (m, 1H), 1.27 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.38, 163.50 (t, $J = 31.9$ Hz, 1C), 159.58, 133.50, 126.18 (2C), 114.36 (t, $J = 252.0$ Hz, 1C), 114.09 (2C), 84.74 (t, $J = 4.2$ Hz, 1C), 63.43, 55.45, 45.90 (t, $J = 22.6$ Hz, 1C), 34.45, 28.18, 13.89; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.12 (t, $J = 14.7$ Hz, 2F).

![Ethyl 2,2-difluoro-3-(5-oxo-2-(p-tolyl)tetrahydrofuran-2-yl)propanoate (3ha).][7]

The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 85%, 133.1 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23 (d, $J = 8.3$ Hz, 2H), 7.17 (d, $J = 8.3$ Hz, 2H), 4.26-4.09 (m, 2H), 2.93-2.76 (m, 2H), 2.73-2.65 (m, 1H), 2.61-2.48 (m, 2H), 2.43-2.36 (m, 1H), 2.33 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.39, 163.45 (t, $J = 31.5$ Hz, 1C), 138.79, 138.27, 129.47 (2C), 124.70 (2C), 114.38 (t, $J = 252.0$ Hz, 1C), 84.83 (t, $J = 4.4$ Hz, 1C), 63.43, 45.78 (t, $J = 23.1$ Hz, 1C), 34.49, 28.13, 21.12, 13.89; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.02 (t, $J = 14.6$ Hz, 2F).

![Ethyl 3-(2-(2,5-dimethylphenyl)-5-oxotetrahydrofuran-2-yl)-2,2difluoropropanoate (3ia).][7]

The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 86%, 139.8 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.17 (s, 1H), 6.98 (dd, $J = 17.8$, 7.5 Hz, 2H), 4.21-4.05 (m, 2H), 2.93-2.68 (m, 3H), 2.62-2.47 (m, 2H), 2.42-2.35 (m, 1H), 2.31 (s, 3H), 2.23 (s, 3H), 1.24 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.28, 163.50 (t, $J = 31.6$ Hz, 1C), 139.86, 135.85, 132.70, 130.19, 129.05, 125.76, 114.62 (t, $J = 251.9$ Hz, 1C), 85.40 (t, $J = 4.3$ Hz, 1C), 63.40, 43.83 (t, $J = 22.9$ Hz, 1C), 33.59, 27.95, 21.17, 21.02, 13.83; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -100.42-102.91 (m, 2F); HRMS (ESI): m/z calcd. for C$_{17}$H$_{20}$F$_2$NaO$_4$ $^+$ [M + Na$^+$]: 349.1222, found: 349.1219.
Ethyl 3-(2-(4-bromophenyl)-5-oxotetrahydrofuran-2-yl)-2,2-difluoropropanoate (3ja). The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 69%, 129.3 mg, yellow oil. 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52 (d, $J = 8.6$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 2H), 4.31-4.16 (m, 2H), 2.87-2.80 (m, 2H), 2.75-2.59 (m, 2H), 2.52-2.37 (m, 2H), 1.32 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.84, 163.44 (t, $J = 31.7$ Hz, 1C), 140.92, 132.02 (2C), 126.57 (2C), 122.61, 114.20 (t, $J = 252.3$ Hz, 1C), 84.29 (t, $J = 4.4$ Hz, 1C), 63.61, 45.56 (t, $J = 23.1$ Hz, 1C), 34.73, 27.94, 13.92; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -100.39-102.04 (m, 2F).

Ethyl 3-(2-(4-chlorophenyl)-5-oxotetrahydrofuran-2-yl)-2,2-difluoropropanoate (3ka). The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 72%, 118.7 mg, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J = 8.7$ Hz, 2H), 7.29 (d, $J = 8.7$ Hz, 2H), 4.31-4.16 (m, 2H), 2.88-2.80 (m, 2H), 2.76-2.59 (m, 2H), 2.52-2.37 (m, 2H), 1.32 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.88, 163.42 (t, $J = 31.5$ Hz, 1C), 140.34, 134.43, 129.01 (2C), 126.25 (2C), 114.20 (t, $J = 252.2$ Hz, 1C), 84.26 (t, $J = 4.2$ Hz, 1C), 63.56, 45.56 (t, $J = 23.1$ Hz, 1C), 34.77, 27.91, 13.88; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.22 (q, $J = 267.6$ Hz, 2F).

Ethyl 2,2-difluoro-3-(5-oxo-2-(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)-propanoate (3la). The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 66%, 119.6 mg, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66.
(d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 4.32-4.16 (m, 2H), 2.91-2.84 (m, 2H), 2.79-2.61 (m, 2H), 2.54-2.39 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 174.65, 163.41 (t, J = 31.1 Hz, 1C), 145.93, 131.10 (dd, J = 62.8, 29.9 Hz, 1C), 125.92 (dd, J = 7.5, 3.8 Hz, 1C), 125.27 (2C), 122.55, 114.16 (t, J = 252.5 Hz, 1C), 84.18 (t, J = 4.1 Hz, 1C), 63.65, 45.47 (t, J = 23.3 Hz, 1C), 34.94, 27.82, 13.89; 19F NMR (376 MHz, CDCl3) δ -62.78 (d, J = 13.2 Hz, 3F), -101.27 (q, J = 269.1 Hz, 2F); HRMS (ESI): m/z calcd. for C16H15F5NaO4 [M + Na+]: 389.0783, found: 389.0782.

Ethyl 2,2-difluoro-3-(5-oxo-2-(thiophen-2-yl)tetrahydrofuran-2-yl)propanoate (3ma). The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 50%, 76.4 mg, yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.30 (dd, J = 5.0, 1.3 Hz, 1H), 7.01 (dd, J = 3.6, 1.3 Hz, 1H), 6.97 (dd, J = 5.0, 3.6 Hz, 1H), 4.29-4.13 (m, 2H), 3.03-2.86 (m, 2H), 2.80-2.72 (m, 1H), 2.67-2.51 (m, 3H), 1.31 (t, J = 7.2 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 174.84, 163.34 (t, J = 31.6 Hz, 1C), 145.22, 127.23, 126.08, 124.85, 114.15 (t, J = 251.9 Hz, 1C), 83.37 (t, J = 4.5 Hz, 1C), 63.56, 46.21 (t, J = 23.2 Hz, 1C), 34.83, 28.54, 13.90; 19F NMR (376 MHz, CDCl3) δ -100.53-102.03 (m, 2F); HRMS (ESI): m/z calcd. for C13H14F2NaO4S+ [M + Na+] 327.0473, found: 327.0476.

Ethyl 2,2-difluoro-3-(2-(naphthalen-1-yl)-5-oxotetrahydrofuran-2-yl)propanoate (3na). The product was purified by silica gel column chromatography (PE/EA = 4/1). Yield, 61%, 107.6 mg, yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.88-7.82 (m, 4H), 7.52-7.51 (m, 2H), 7.41-7.39 (m, 1H), 4.19-4.01 (m, 2H), 3.05-2.88 (m, 2H), 2.82-2.75 (m, 1H), 2.66-2.60 (m, 2H), 2.48-2.38 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 175.37, 163.49 (t, J = 31.6 Hz, 1C), 138.80, 132.91, 132.89,128.92, 128.43, 127.67, 126.93, 126.88, 123.75, 122.50, 114.38 (t, J = 252.1 Hz, 1C), 84.85 (t, S12
$J = 4.3$ Hz, 1C), 63.14, 45.52 (t, $J = 23.3$ Hz, 1C), 34.47, 28.01, 13.76; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -100.15-101.74 (m, 2F); HRMS (ESI): m/z calcd. for C$_{19}$H$_{18}$F$_2$NaO$_4^+$ [M + Na$^+$]: 371.1065, found: 371.1062.

Ethyl 3-(1-(4-chlorophenyl)-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2,2-difluoropropanoate (3oa). The product was purified by silica gel column chromatography (PE/EA = 5/1). Yield, 87%, 165.8 mg, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J = 7.6$ Hz, 1H), 7.73-7.69 (m, 1H), 7.60-7.54 (m, 2H), 7.46-7.43 (m, 2H), 7.35-7.33 (m, 2H), 4.33-4.21 (m, 2H), 3.45-3.34 (m, 1H), 3.18-3.08 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.52, 163.43 (t, $J = 31.3$ Hz, 1C), 150.82, 138.38, 134.95, 134.67, 130.02, 129.25 (2C), 126.41, 126.26 (2C), 124.96, 122.69, 113.91 (dd, $J = 254.9$, 251.9 Hz, 1C), 84.73 (dd, $J = 6.3$, 3.5 Hz, 1C), 63.67, 44.04 (t, $J = 23.6$ Hz, 1C), 13.90; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.31 (dd, $J = 1045.9$, 268.5 Hz, 2F).

Ethyl 2,2-difluoro-3-(1-(4-methoxyphenyl)-3-oxo-1,3-dihydroisobenzofuran-1-yl) propanoate (3pa). The product was purified by silica gel column chromatography (PE/EA = 5/1). Yield, 85%, 161.2 mg, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J = 7.6$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.59-7.52 (m, 2H), 7.40-7.36 (m, 2H), 6.89-6.85 (m, 2H), 4.32-4.19 (m, 2H), 3.78 (s, 3H), 3.48-3.37 (m, 1H), 3.19-3.09 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.90, 163.43 (t, $J = 31.3$ Hz, 1C), 159.87, 151.23, 134.38, 131.74, 129.70, 126.28 (2C), 126.18, 125.24, 122.89, 114.30 (2C), 114.03 (dd, $J = 254.9$, 251.0 Hz, 1C), 85.25 (dd, $J = 6.7$, 2.9 Hz, 1C), 84.73 (dd, $J = 6.3$, 3.5 Hz, 1C), 63.67, 44.04 (t, $J = 23.6$ Hz, 1C), 13.90; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.31 (dd, $J = 1045.9$, 268.5 Hz, 2F).
63.56, 55.44, 44.08 (t, $J = 23.6$ Hz, 1C), 13.87; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.29 (dd, $J = 1298.9$, 267.7 Hz, 2F); HRMS (ESI): m/z calcd. for C$_{20}$H$_{18}$F$_2$NaO$_5^+$ [M + Na$^+$]: 399.1015, found: 399.1012.

**Ethyl 2,2-difluoro-3-(3-oxo-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanoate (3qa).**[7] The product was purified by silica gel column chromatography (PE/EA = 5/1). Yield, 94%, 169.7 mg, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88 (d, $J = 7.6$ Hz, 1H), 7.70-7.66 (m, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.17 (d, $J = 8.1$ Hz, 2H), 4.32-4.19 (m, 2H), 3.49-3.38 (m, 1H), 3.22-3.12 (m, 1H), 2.31 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.93, 163.50 (t, $J = 31.5$ Hz, 1C), 151.28, 138.72, 136.88, 134.43, 129.66 (3C), 126.11, 125.03, 124.61 (2C), 122.81, 114.03 (dd, $J = 255.2$, 251.7 Hz, 1C), 85.25 (dd, $J = 6.5$, 3.3 Hz, 1C), 63.53, 43.97 (t, $J = 23.6$ Hz, 1C), 21.05, 13.84; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.22 (dd, $J = 1218.8$, 267.8 Hz, 2F).

5-(2,2-difluoro-3-(indolin-1-yl)-3-oxopropyl)dihydrofuran-2(3H)-one (3ab). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 83%, 122.3 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.16 (d, $J = 8.0$ Hz, 1H), 7.25-7.21 (m, 2H), 7.13-7.09 (m, 1H), 4.92-4.86 (m, 1H), 4.34 (t, $J = 8.3$ Hz, 2H), 3.20 (t, $J = 8.3$ Hz, 2H), 2.80-2.46 (m, 5H), 2.07-1.98 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.50, 160.55 (t, $J = 29.6$ Hz, 1C), 142.45, 131.90, 127.61, 125.43, 124.87, 117.95 (t, $J = 256.6$ Hz, 1C), 117.88, 74.96 (t, $J = 4.2$ Hz, 1C), 47.85 (t, $J = 7.6$ Hz, 1C), 39.92 (t, $J = 22.9$ Hz, 1C), 29.02, 28.67, 28.58; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -101.50 (q, $J = 288.7$ Hz, 2F). HRMS (ESI): m/z calcd. for C$_{15}$H$_{15}$F$_2$NNaO$_3^+$ [M + Na$^+$]: 318.0912, found: 318.0917.
2,2-difluoro-3-(5-oxotetrahydrofuran-2-yl)-N-phenylpropanamide (3ac). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 80%, 108.9 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.13 (s, 1H), 7.57 (d, $J$ = 7.9 Hz, 2H), 7.37 (t, $J$ = 7.9 Hz, 2H), 7.21 (t, $J$ = 7.4 Hz, 1H), 4.84-4.77 (m, 1H), 2.74-2.44 (m, 5H), 2.06-1.95 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.43, 161.40 (t, $J$ = 27.7 Hz, 1C), 135.92, 129.32 (2C), 125.92, 120.63 (2C), 116.41 (t, $J$ = 255.4 Hz, 1C), 74.44 (t, $J$ = 3.7 Hz, 1C), 39.51 (t, $J$ = 23.3 Hz, 1C), 28.59, 28.35; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -102.82-104.48 (m, 2F); HRMS (ESI): m/z calcd. for C$_{13}$H$_{13}$F$_2$NNaO$_3$+ [M + Na$^+$]: 292.0756, found: 292.0761.

N-cyclohexyl-2,2-difluoro-3-(5-oxotetrahydrofuran-2-yl)propanamide (3ad). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 75%, 103.7 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.40 (s, 1H), 4.74-4.67 (m, 1H), 3.77-3.70 (m, 1H), 2.61-2.38 (m, 5H), 2.00-1.90 (m, 3H), 1.72-1.69 (m, 2H), 1.62-1.58 (m, 1H), 1.38-1.29 (m, 2H), 1.24-1.13 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.28, 162.49 (t, $J$ = 27.8 Hz, 1C), 116.29 (t, $J$ = 253.9 Hz, 1C), 74.49 (t, $J$ = 4.6 Hz, 1C), 48.83, 39.52 (t, $J$ = 23.5 Hz, 1C), 32.59, 32.47, 28.52, 28.30, 25.32, 24.75 (2C); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -104.58 (q, $J$ = 258.9 Hz, 2F); HRMS (ESI): m/z calcd. for C$_{13}$H$_{19}$F$_2$NNaO$_3$+ [M + Na$^+$]: 298.1225, found: 298.1231.

5-(3-(benzo[d]oxazol-2-yl)-2,2-difluoro-3-oxopropyl)dihydrofuran-2(3H)-one (3ae). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 84%, 112.7 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83-7.81 (m, 1H), 7.65-7.63 (m, 1H), 7.51-7.42 (m, 2H), 4.98-4.91 (m, 1H), 3.13-2.99 (m, 1H), 2.87-
2.74 (m, 1H), 2.63-2.49 (m, 3H), 2.13-2.03 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$
176.05, 157.17 (t, $J = 32.8$ Hz, 1C), 150.81, 139.92, 127.33, 125.64, 121.49, 115.14 (t, $J = 242.2$ Hz, 1C), 111.67, 74.44 (t, $J = 3.9$ Hz, 1C), 41.48 (t, $J = 23.3$ Hz, 1C), 28.94, 28.55; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -96.63 (dd, $J = 1016.5$, 281.7 Hz, 2F); HRMS (ESI): m/z calcd. for C$_{13}$H$_{11}$F$_2$NNaO$_3^+$ [M + Na$^+$]: 290.0599, found: 290.0603.

5-(2,2-difluoro-3-oxo-3-(piperidin-1-yl)propyl)dihydrofuran-2(3H)-one (3af). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 79%, 102.7 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.86-4.80 (m, 1H), 3.64-3.61 (m, 2H), 3.56-3.53 (m, 2H), 2.71-2.41 (m, 5H), 2.04-1.93 (m, 1H), 1.70-1.56 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.57, 161.07 (t, $J = 28.1$ Hz, 1C), 118.32 (t, $J = 256.7$ Hz, 1C), 75.20 (t, $J = 4.4$ Hz, 1C), 46.92 (t, $J = 6.5$ Hz, 1C), 44.60, 40.62 (t, $J = 23.1$ Hz, 1C), 29.11, 28.65, 26.55, 25.67, 24.46; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -97.87 (dd, $J = 670.3$, 285.7 Hz, 2F); HRMS (ESI): m/z calcd. for C$_{12}$H$_{17}$F$_2$NNaO$_3^+$ [M + Na$^+$]: 284.1069, found: 284.1067.

Methyl (2,2-difluoro-3-(5-oxotetrahydrofuran-2-yl)propanoyl)-D-phenylalaninamide ($dr = 1:1.8$) (3ag). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 78%, 137.9 mg, light yellow oil.

**Major isomer:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25-7.16 (m, 3H), 7.07-7.05 (m, 2H), 6.90-6.85 (m, 1H), 4.86-4.78 (m, 1H), 4.39-4.32 (m, 1H), 3.70 (s, 3H), 3.21-2.98 (m, 2H), 2.55-2.20 (m, 5H), 1.90-1.76 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.21, 170.91, 163.05 (t, $J = 28.6$ Hz, 1C), 135.34, 129.31 (2C), 128.78 (2C), 127.41, 116.07 (t, $J = 254.1$ Hz, 1C), 74.31-74.14 (m, 1C), 53.19, 52.79, 39.49 (t, $J = 23.3$ Hz, 1C),
37.68, 28.50, 28.35; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -104.50 (dd, $J = 32.2$, 227.4 Hz, 2F).

**Minor isomer:** $^1$H NMR (400 MHz, CDCl$_3$) δ 7.25-7.16 (m, 3H), 7.07-7.05 (m, 2H), 6.90-6.85 (m, 1H), 4.86-4.78 (m, 1H), 4.63-4.56 (m, 1H), 3.68 (s, 3H), 3.21-2.98 (m, 2H), 2.55-2.20 (m, 5H), 1.90-1.76 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.17, 170.91, 163.05 (t, $J = 28.6$ Hz, 1C), 135.22, 129.27 (2C), 128.82 (2C), 127.48, 116.04 (t, $J = 254.4$ Hz, 1C), 74.31-74.14 (m, 1C), 53.25, 52.73, 39.40 (t, $J = 23.2$ Hz, 1C), 37.52, 28.50, 28.35; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -106.04 (dd, $J = 317.3$, 147.5 Hz, 2F).

HRMS (ESI): m/z calcd. for C$_{17}$H$_{19}$F$_2$NNaO$_5$+ [M + Na$^+$]: 378.1124, found: 378.1120.

5-(2,2-difluoro-3-morpholino-3-oxopropyl)dihydrofuran-2(3H)-one (3ah). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 75%, 98.4 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.87-4.80 (m, 1H), 3.74-3.62 (m, 8H), 2.72-2.42 (m, 5H), 2.06-1.94 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.44, 161.37 (t, $J = 28.7$ Hz, 1C), 118.18 (t, $J = 256.5$ Hz, 1C), 74.90 (t, $J = 4.3$ Hz, 1C), 66.82, 66.75, 46.57 (t, $J = 6.2$ Hz, 1C), 43.55, 40.41 (t, $J = 22.8$ Hz, 1C), 29.06, 28.59; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -97.79 (q, $J = 288.3$ Hz, 2F); HRMS (ESI): m/z calcd. for C$_{11}$H$_{15}$F$_2$NNaO$_4$+ [M + Na$^+$]: 286.0861, found: 286.0863.

$N,N$-diethyl-2,2-difluoro-3-(5-oxotetrahydrofuran-2-yl)propanamide (3ai). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 63%, 80.1 mg, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.87-4.80 (m, 1H), 3.52 (q, $J = 7.0$ Hz, 2H), 3.38 (q, $J = 7.1$ Hz, 2H), 2.72-2.42 (m, 5H), 2.05-1.94 (m, 1H), 1.21 (t, $J = 7.0$ Hz, 3H), 1.16 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.57, 162.16 (t, $J = 28.2$ Hz, 1C), 118.30 (t, $J = 256.6$ Hz, 1C), 75.22 (t, $J = 4.4$ Hz, 1C), 41.95 (t, $J = 6.2$ Hz, 1C), 41.72, 40.63 (t, $J = 23.2$ Hz, 1C), 29.13, 28.61, 14.35, 12.39; $^{19}$F NMR
(376 MHz, CDCl₃) δ -98.44 (dd, J = 677.2, 285.5 Hz, 2F); HRMS (ESI): m/z calcd. for C₁₁H₁₇F₂NNaO₃⁺ [M + Na⁺]: 272.1069, found: 272.1065.

5-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)dihydrofuran-2(3H)-one (3aj). The product was purified by silica gel column chromatography (PE/EA = 3/1). Yield, 41%, 64.9 mg, light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.89-4.83 (m, 1H), 2.74-2.32 (m, 5H), 2.08-1.98 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 175.77, 73.22, 36.68 (t, J = 21.2 Hz, 1C), 29.03, 28.41; ¹⁹F NMR (376 MHz, CDCl₃) δ -81.02 (tt, J = 9.3, 2.9 Hz, 3F), -112.90-113.02 (m, 2F), -124.49 (dt, J = 12.8, 9.1 Hz, 2F), -125.92-126.02 (m, 2F). HRMS (ESI): m/z calcd. for C₉H₇F₉NaO₂⁺ [M + Na⁺]: 341.0195, found: 341.0193.

References.

3ba

3ba

S21
3ac

3ac
3ah

-99.04

-98.27

-97.31

-96.55

3ah