Pd-catalyzed \textit{para}-Selective C-H Difluoromethylation of Aryl Carboxyls

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I. General

The reagents and solvents were purchased from commercial suppliers and used without further purification unless noted. $^1$H NMR and $^{13}$C NMR spectra were obtained on a Bruker AVANCE III 500 instrument in CDCl$_3$ using TMS as an internal standard, operating at 500 MHz and 125 MHz, respectively. Chemical shifts ($\delta$) are expressed in ppm and coupling constants $J$ are given in Hz. For CDCl$_3$ or DMSO-$d_6$ solutions the chemical shifts are reported as parts per million (ppm) to residual protium or carbon of the solvents; CHCl$_3$ $\delta$H (7.26 ppm) and CDCl$_3$ $\delta$C (77.03 ppm); DMSO$\delta$H (2.51 ppm) and DMSO-$d_6$ $\delta$C (39.52 ppm). $^{19}$F NMR were recorded on a Bruker ascend500. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet. GC experiments were carried out using Agilent 7890B GC. GC-MS experiments that used dodecane as an internal standard were performed with a Thermo DSQ II, Trace GC Ultra. High-resolution mass spectra (HRMS (ESI-TOF)) were obtained on an Agilent 6545 Q-TOF LCMS spectrometer equipped with an ESI source.

II. Preparation of starting materials

1a-1n, 1p, 1q and 4a-4g were purchased from commercial suppliers and used without further purification. 1o and 1r were prepared according to the literature procedure. $^{[1]}$ 1s were prepared according to the literature procedure. $^{[2]}$ 1t and 4h were prepared following the procedures. These compounds 1o, 1r, 1s, 1t and 4h were known.

**Preparation of (2-methoxy-4-(octyloxy)phenyl)(phenyl)methanone (1f):** A flask (50 mL) was added Octabenzone (1.63g, 5.0 mmol, 1.0 equiv), K$_2$CO$_3$ (1.38 g, 10.0 mmol, 2.0 equiv), DMF (25 mL) and CH$_3$I (1.42 g, 10.0 mmol, 2.0 equiv) at room temperature. The mixture was maintained at 60 °C for 15 h. After cooling to room temperature, the reaction mixture was diluted by water (50 mL) and was extracted with EtOAc (100 mL). The organic layer was washed with brine (50 mL) three times. The collected EtOAc layer was concentrated and the residue was purified by column chromatography on silica gel to obtain the corresponding product 1t as a colorless oil (1.27 g, 75%).
Preparation of galactopyranose derivative 4h: 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (0.78 g, 3.0 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (20 mL). To the mixture was dropwise added benzoyl chloride (0.63 g, 4.5 mmol, 1.5 equiv) and Et₃N (0.45 g, 4.5 mmol, 1.5 equiv) at 0 °C. The solution was stirred at room temperature for 6 h and then quenched by addition of saturated NaHCO₃ solution. The mixture was stirred for an additional 30 min., diluted with CH₂Cl₂ and washed with HCl (1 M), brine and then water. The organic layer concentrated and the residue was purified by column chromatography on silica gel to obtain the corresponding product 4h as a colorless oil (0.60 g, 55%)

III. Optimization of reaction conditions

**Table S1.** Optimization of reaction conditions[^a]

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<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
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<th>Ligand</th>
<th>Additive</th>
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28 Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ Mn(OAc)₂ 27
29 Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ Fe₂(SO₄)₃ 39
30 Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ FeCl₂ 30
31 Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ Fe(OEt)₂ 22
32 Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ Fe(OAc)₂ 26
33 Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ / Fe(OAc)₂ 46
34 [c] Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ Fe(OAc)₂ 50
35 [d] Pd(CH₂CN)₂Cl₂ DCE K₂CO₃ P(Cy)₃HBF₄ Fe(OAc)₂ 67
36 [d] Pd[P(Cy)₃]₂Cl₂ DCE K₂CO₃ / Fe(OAc)₂ 74
37 [d][e] Pd[P(Cy)₃]₂Cl₂ DCE K₂CO₃ / Fe(OAc)₂ 55
38 [d][e][f] Pd[P(Cy)₃]₂Cl₂ DCE K₂CO₃ / Fe(OAc)₂ 55
39 / DCE K₂CO₃ / / 0

[a] Reaction conditions: 1a (0.1 mmol), 2 (2.0 equiv), [Pd] (10 mol%), Base (2.0 equiv), Ligand (15 mol%), Additive (5 mol%), Solvent (1.0 mL), 110 ºC, under N₂, 24 h, GC-MS yield (unless otherwise noted); [b] the selectivity of para (4 equiv), K₂CO₃ (6.0 equiv); [c] 2 (4.0 equiv), K₂CO₃ (6.0 equiv); [d] 2 (4.0 equiv), K₂CO₃ (6.0 equiv), 48 h; [e] 0.3 mmol scale, DCE (2.0 mL); [f] Reaction at 125 ºC.

IV. General procedures for the para-difluoromethylation of aryl carbonyls

A mixture of 1 or 3 (0.3 mmol, 1.0 equiv), BrCF₂CO₂Et (0.16 mL, 1.2 mmol, 4.0 equiv), Pd[P(Cy)₃]₂Cl₂ (22.1 mg, 0.03 mmol, 10 mol%), K₂CO₃ (248.4 mg, 1.8 mmol, 6.0 equiv) and Fe(OAc)₂ (2.6 mg, 0.015 mmol, 5 mol%) in a 25 mL Schlenk tube was added the DCE (2.0 mL) under N₂ atmosphere. Then the tube was sealed with a Teflon-lined screw cap and heated at 110 ºC for 48 h. The reaction mixture cooled to room temperature, diluted with CH₂Cl₂ and was filtered through a small pad of Celite followed by washing with CH₂Cl₂. The resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to give the desired products 3a-3t, 5a-5h.

Ethyl 2,2-difluoro-2-(4-(4-methylbenzoyl)phenyl)acetate (3a): ^1H NMR (500 MHz, CDCl₃): δ = 7.84 (d, J = 8.5 Hz, 2H), 7.73-7.71 (m, 4H), 7.29 (d, J = 7.9 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ^13C NMR (125 MHz, CDCl₃): δ = 195.42, 163.72 (t, J = 34.9 Hz), 143.90, 140.39, 136.08 (t, J = 25.6 Hz), 134.21, 130.31 (2C), 129.93 (2C), 129.16 (2C), 125.52 (t, J = 6.0 Hz, 2C), 113.01 (t, J = 252.8 Hz), 63.38, 21.65, 13.85 ppm; ^19F NMR (471 MHz, CDCl₃): δ = -104.27 ppm; HRMS: Calcd. for C₁₆H₁₆F₂O₅[M+Na⁺]: 341.0960, found: 341.0969.
Ethyl 2-(4-benzoylphenyl)-2,2-difluoroacetate (3b): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.87$ (d, $J = 8.4$ Hz, 2H), 7.81-7.79 (m, 2H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 1.32 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 194.23$, 165.70 (d, $J = 255.4$ Hz), 163.68 (t, $J = 34.8$ Hz), 139.92, 136.44 (t, $J = 25.6$ Hz), 133.16 (d, $J = 3.0$ Hz), 132.75 (d, $J = 9.2$ Hz, 2C), 129.90 (2C), 125.71 (t, $J = 6.1$ Hz, 2C), 115.72 (d, $J = 22.0$ Hz, 2C), 112.95 (t, $J = 252.9$ Hz), 63.45, 13.87 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.32$ ppm; HRMS: Calcd. for C$_{17}$H$_{14}$F$_2$O$_3$ [M+Na$^+$]: 327.0803, found: 327.0809.

Diethyl 2,2'-(carbonylbis(4,1-phenylene))bis(2,2-difluoroacetate) (3b'): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.87$ (d, $J = 8.1$ Hz, 4H), 7.75 (d, $J = 8.4$ Hz, 4H), 4.33 (q, $J = 7.1$ Hz, 4H), 1.32 (t, $J = 7.2$ Hz, 6H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 194.89$, 163.65 (t, $J = 34.7$ Hz, 2C), 139.20 (2C), 136.93 (t, $J = 25.6$ Hz, 2C), 130.16 (4C), 125.84 (t, $J = 6.1$ Hz, 4C), 112.89 (t, $J = 252.9$ Hz, 2C), 63.52 (2C), 13.87 (2C) ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.38$ ppm; HRMS: Calcd. for C$_{21}$H$_{18}$F$_4$O$_5$ [M+Na$^+$]: 449.0983, found: 449.0988.

Ethyl 2,2-difluoro-2-(4-(4-fluorobenzoyl)phenyl)acetate (3c): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.86-7.82$ (m, 4H), 7.74 (d, $J = 8.5$ Hz, 2H), 7.19-7.16 (m, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 1.29 (t, $J = 7.2$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 194.23$, 165.70 (d, $J = 255.4$ Hz), 163.68 (t, $J = 34.8$ Hz), 139.92, 136.44 (t, $J = 25.6$ Hz), 133.16 (d, $J = 3.0$ Hz), 132.75 (d, $J = 9.2$ Hz, 2C), 129.90 (2C), 125.71 (t, $J = 6.1$ Hz, 2C), 115.72 (d, $J = 22.0$ Hz, 2C), 112.95 (t, $J = 252.9$ Hz), 63.45, 13.87 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.32$, -104.82 ppm; HRMS: Calcd. for C$_{17}$H$_{13}$F$_3$O$_3$ [M+Na$^+$]: 345.0709, found: 345.0710.

Ethyl 2-(4-acetylphenyl)-2,2-difluoroacetate (3d): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.02$ (d, $J = 8.6$ Hz, 2H), 7.71 (d, $J = 8.5$ Hz, 2H), 4.30 (q, $J = 7.2$ Hz, 2H), 2.62 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H) ppm;
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 197.17, 163.62$ (t, $J = 34.8$ Hz), 139.09, 137.05 (t, $J = 25.6$ Hz), 128.51 (2C), 125.92 (t, $J = 6.1$ Hz, 2C), 112.93 (t, $J = 252.8$ Hz), 63.40, 26.71, 13.82 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.53$ ppm; HRMS: Calcd. for C$_{12}$H$_{12}$F$_2$O$_3$ [M+Na$^+$]: 265.0647, found: 265.0651.

**Ethyl 2-(4-acetyl-3-methylphenyl)-2,2-difluoroacetate (3e)**: $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.72$ (d, $J = 8.1$ Hz, 1H), 7.51-7.48 (m, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.61 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 201.43, 163.79$ (t, $J = 34.8$ Hz), 140.12, 138.68, 135.32 (t, $J = 25.5$ Hz), 129.11, 128.85 (t, $J = 5.9$ Hz), 122.94 (t, $J = 6.1$ Hz), 112.88 (t, $J = 252.6$ Hz), 63.34, 29.71, 21.32, 13.85 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.57$ ppm; HRMS: Calcd. for C$_{13}$H$_{14}$F$_2$O$_3$ [M+Na$^+$]: 279.0803, found: 279.0802.

**Ethyl 2-(4-acetyl-3-methoxyphenyl)-2,2-difluoroacetate (3f)**: $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.75$ (d, $J = 8.0$ Hz, 1H), 7.23-7.19 (m, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.95 (s, 3H), 2.61 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 199.24, 163.70$ (t, $J = 35.0$ Hz), 158.65, 137.54 (t, $J = 25.3$ Hz), 130.69, 130.58, 117.69 (t, $J = 6.2$ Hz), 112.81 (t, $J = 253.0$ Hz), 108.81 (t, $J = 6.4$ Hz), 63.40, 55.83, 31.69, 13.87 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.54$ ppm; HRMS: Calcd. for C$_{13}$H$_{14}$F$_2$O$_4$ [M+Na$^+$]: 295.0752, found: 295.0760.

**Ethyl 2-(4-acetyl-3-fluorophenyl)-2,2-difluoroacetate (3g)**: $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.94$ (t, $J = 7.7$ Hz, 1H), 7.47-7.40 (m, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 2.66 (d, $J = 4.8$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 195.01$ (d, $J = 3.4$ Hz), 163.18 (t, $J = 34.3$ Hz), 161.71 (d, $J = 256.2$ Hz), 138.98 (td, $J_1 = 26.2$ Hz, $J_2 = 8.4$ Hz), 131.31 (d, $J = 2.6$ Hz), 127.80 (d, $J = 12.9$ Hz), 121.58 (td, $J_1 = 6.0$ Hz, $J_2 = 3.7$ Hz), 114.61 (dt, $J_1 = 27.1$ Hz, $J_2 = 6.3$ Hz), 112.11 (td, $J_1 = 253.5$ Hz, $J_2 = 1.7$ Hz), 63.63, 31.39 (d, $J = 7.4$ Hz), 13.85 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -104.53, -107.87$ ppm; HRMS: Calcd. for C$_{12}$H$_{11}$F$_3$O$_3$ [M+Na$^+$]: 283.0552, found: 283.0557.
Ethyl 2-(4-acetyl-2-methylphenyl)-2,2-difluoroacetate (3h): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.84-7.80 (m, 2H), 7.68 (d, J = 8.1 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 2.47 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 197.50, 163.63 (t, J = 34.4 Hz), 138.80, 137.10 (t, J = 3.1 Hz), 135.47 (t, J = 23.2 Hz), 131.46, 126.66 (t, J = 8.8 Hz), 125.84, 113.74 (t, J = 252.6 Hz), 63.37, 26.75, 19.73, 13.86 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta$ = -102.06 ppm; HRMS: Calcd. for C$_{13}$H$_{14}$F$_2$O$_3$ [M+Na$^+$]: 279.0803, found: 279.0809.

Ethyl 2-(4-acetyl-2-methoxyphenyl)-2,2-difluoroacetate (3i): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.73 (d, J = 8.0 Hz, 1H), 7.61 (dd, J$_1$ = 7.9 Hz, J$_2$ = 1.1 Hz, 1H), 7.52 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 2.62 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 197.13, 163.46 (t, J = 33.5 Hz), 157.02 (t, J = 4.6 Hz), 140.59, 126.77 (t, J = 7.5 Hz), 126.43 (t, J = 24.1 Hz), 121.14, 111.76 (t, J = 249.3 Hz), 110.06, 62.84, 55.95, 26.71, 13.89 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta$ = -103.51 ppm; HRMS: Calcd. for C$_{13}$H$_{14}$F$_2$O$_4$ [M+Na$^+$]: 295.0752, found: 295.0752.

Ethyl 2-(4-acetyl-2-fluorophenyl)-2,2-difluoroacetate (3j): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.83 (dd, J$_1$ = 8.1 Hz, J$_2$ = 1.2 Hz, 1H), 7.78-7.75 (m, 1H), 7.72-7.69 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 195.80, 162.7 (t, J = 33.1 Hz), 159.90 (dt, J$_1$ = 253.8, J$_2$ = 3.8 Hz), 141.40 (d, J = 6.3 Hz), 127.76 (td, J$_1$ = 6.9 Hz, J$_2$ = 2.1 Hz), 125.42-124.96 (m), 124.06 (d, J = 3.8 Hz), 115.87 (d, J = 21.8 Hz), 111.23 (d, J = 251.3 Hz), 63.62, 26.74, 13.82 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta$ = -102.65 (d, J = 6.7 Hz), -112.86 (t, J = 7.4 Hz) ppm; HRMS: Calcd. for C$_{12}$H$_{11}$F$_3$O$_3$ [M+Na$^+$]: 283.0552, found: 283.0555.

Ethyl 2-(4-acetyl-2-chlorophenyl)-2,2-difluoroacetate (3k): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.99 (s, 1H), 7.93 (dd, J$_1$ = 8.1 Hz, J$_2$ = 1.3 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.63 (s,
7H), 1.31 (t, J = 7.1 Hz, 3H) ppm; \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)); \(\delta = 195.85, 162.58\) (t, J = 33.5 Hz), 140.14, 135.27 (t, J = 24.5 Hz), 132.79 (t, J = 4.2 Hz), 130.27, 127.87 (t, J = 8.4 Hz), 126.57, 111.84 (t, J = 251.8 Hz), 63.58, 26.70, 13.78 ppm; \(^{19}\text{F}\) NMR (471 MHz, CDCl\(_3\)); \(\delta = -102.90\) ppm; HRMS: Calcd. for C\(_{12}\)H\(_{11}\)ClF\(_2\)O\(_3\)\([\text{M+Na}^+\]): 299.0257, found: 299.0257.

![Image of 3l](image_url)

**Ethyl 2-(4-(cyclohexanecarbonyl)phenyl)-2,2-difluoroacetate (3l):** \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)); \(\delta = 8.00\) (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.27-3.21 (m, 1H), 1.89-1.82 (m, 4H), 1.76-1.72 (m, 4H), 1.53-1.34 (m, 4H), 1.31-1.23 (m, 4H) ppm; \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)); \(\delta = 203.00, 163.68\) (t, J = 34.9 Hz), 138.52, 136.64 (t, J = 25.5 Hz), 128.45 (2C), 125.90 (t, J = 6.0 Hz, 2C), 112.97 (t, J = 252.8 Hz), 63.36, 45.91, 29.26 (2C), 25.88, 25.74 (2C), 13.84 ppm; \(^{19}\text{F}\) NMR (471 MHz, CDCl\(_3\)); \(\delta = -104.45\) ppm; HRMS: Calcd. for C\(_{17}\)H\(_{20}\)F\(_2\)O\(_3\)\([\text{M+Na}^+\]): 333.1273, found: 333.1275.

![Image of 3m](image_url)

**Ethyl 2-(4-(cyclopentanecarbonyl)phenyl)-2,2-difluoroacetate (3m):** \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)); \(\delta = 8.03\) (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.73-3.66 (m, 1H), 1.94-1.88 (m, 4H), 1.75-1.62 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H) ppm; \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)); \(\delta = 201.92, 163.70\) (t, J = 34.8 Hz), 139.04, 136.63 (t, J = 25.5 Hz), 128.66 (2C), 125.83 (t, J = 6.0 Hz, 2C), 112.99 (t, J = 252.7 Hz), 63.38, 46.65, 29.86 (2C), 26.27 (2C), 13.85 ppm; \(^{19}\text{F}\) NMR (471 MHz, CDCl\(_3\)); \(\delta = -104.42\) ppm; HRMS: Calcd. for C\(_{19}\)H\(_{18}\)F\(_2\)O\(_3\)\([\text{M+Na}^+\]): 319.1116, found: 319.1125.

![Image of 3n](image_url)

**Ethyl 2-(4-(cyclopropanecarbonyl)phenyl)-2,2-difluoroacetate (3n):** \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)); \(\delta = 8.08\) (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 2.68-2.63 (m, 1H), 1.31-1.26 (m, 5H), 1.11-1.07 (m, 2H) ppm; \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)); \(\delta = 199.92, 163.72\) (t, J = 34.8 Hz), 140.09, 136.67 (t, J = 25.5 Hz), 128.23 (2C), 125.84 (t, J = 6.1 Hz, 2C), 113.01 (t, J = 252.8 Hz), 63.39, 17.53, 13.86, 12.07 (2C) ppm; \(^{19}\text{F}\) NMR (471 MHz, CDCl\(_3\)); \(\delta = -104.49\) ppm; HRMS: Calcd. for C\(_{14}\)H\(_{14}\)F\(_2\)O\(_3\)\([\text{M+Na}^+\]): 291.0803, found: 291.0808.
Methyl 4-(4-(2-ethoxy-1,1-difluoro-2-oxoethyl)phenyl)-4-oxobutanoate (3o): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.05 (d, $J$ = 8.5 Hz, 2H), 7.71 (d, $J$ = 8.5 Hz, 2H), 4.30 (q, $J$ = 7.1 Hz, 2H), 3.70 (s, 3H), 3.32 (t, $J$ = 6.5 Hz, 2H), 2.78 (t, $J$ = 6.5 Hz, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 197.40, 173.25, 163.61 (t, $J$ = 34.7 Hz), 138.54, 137.18 (t, $J$ = 25.6 Hz), 128.28 (2C), 125.97 (t, $J$ = 6.1 Hz, 2C), 112.90 (t, $J$ = 252.9 Hz), 63.43, 51.91, 33.61, 27.91, 13.82 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta$ = -104.59 ppm; HRMS: Calcd. for C$_{15}$H$_{16}$F$_2$O$_5$ [M+Na$^+$]: 337.0858 found: 337.0861.

Ethyl 2,2-difluoro-2-(4-(2-phenylacetyl)phenyl)acetate (3p): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.08 (d, $J$ = 8.6 Hz, 2H), 7.71 (d, $J$ = 8.6 Hz, 2H), 7.35-7.32 (m, 2H), 7.28-7.25 (m, 3H), 4.32-4.27 (m, 4H), 1.30 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 196.77, 163.60 (t, $J$ = 34.5 Hz), 138.60, 137.07 (t, $J$ = 25.6 Hz), 133.93, 129.40 (2C), 128.82 (2C), 128.80 (2C), 127.12, 125.98 (t, $J$ = 6.1 Hz, 2C), 112.89 (t, $J$ = 251.4 Hz), 63.41, 45.76, 13.84 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta$ = -104.61 ppm; HRMS: Calcd. for C$_{18}$H$_{16}$F$_2$O$_3$ [M+Na$^+$]: 341.0960, found: 341.0965.

Ethyl 2,2-difluoro-2-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetate (3q): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.10 (d, $J$ = 8.1 Hz, 1H), 7.54-7.52 (m, 2H), 4.31 (q, $J$ = 7.2 Hz, 2H), 3.02 (t, $J$ = 6.1 Hz, 2H), 2.70-2.68 (m, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 197.42, 163.73 (t, $J$ = 34.6 Hz), 144.77, 137.18 (t, $J$ = 25.2 Hz), 134.46, 127.72, 126.07 (t, $J$ = 6.0 Hz), 123.73, 112.95 (t, $J$ = 253.0 Hz), 63.40, 39.05, 29.71, 23.01, 13.88 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta$ = -104.60 ppm; HRMS: Calcd. for C$_{14}$H$_{14}$F$_2$O$_3$ [M+Na$^+$]: 291.0803, found: 291.0805.
Methyl 2-(3-(4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoyl)phenyl)propanoate (3r): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.86\) (d, \(J = 8.5\) Hz, 2H), 7.76-7.73 (m, 3H), 7.66 (dt, \(J = 7.5\) Hz, \(J_2 = 1.4\) Hz, 1H), 7.57 (dt, \(J_1 = 7.7\) Hz, \(J_2 = 1.2\) Hz, 1H), 7.46 (t, \(J = 7.7\) Hz, 1H), 4.33 (q, \(J = 7.1\) Hz, 2H), 3.81 (q, \(J = 7.2\) Hz, 3H), 1.54 (d, \(J = 7.2\) Hz, 3H), 1.33 (t, \(J = 7.2\) Hz, 3H ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 195.49, 174.45, 163.73\) (t, \(J = 34.6\) Hz), 141.15, 139.92, 137.25, 136.47 (t, \(J = 25.6\) Hz), 132.08, 130.13 (2C), 129.24, 129.11, 128.77, 125.67 (t, \(J = 6.0\) Hz, 2C), 113.00 (t, \(J = 252.5\) Hz), 63.46, 52.21, 45.30, 18.54, 13.90 ppm; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)): \(\delta = -104.33\) ppm; HRMS: Calcd. for C\(_{21}\)H\(_{20}\)F\(_2\)O\(_5\)[M+Na\(^+\)]: 413.1171, found: 413.1179.

Isopropyl 2-(4-(4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoyl)phenoxy)-2-methylpropanoate (3s): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.81-7.71\) (m, 6H), 6.88-6.85 (m, 2H), 5.08 (p, \(J = 6.3\) Hz, 1H), 4.32 (q, \(J = 7.1\) Hz, 2H), 1.66 (s, 6H), 1.32 (t, \(J = 7.1\) Hz, 3H), 1.20 (d, \(J = 6.3\) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 194.63, 173.08, 163.78\) (t, \(J = 34.7\) Hz), 160.07, 140.62, 135.94 (t, \(J = 25.6\) Hz), 132.16 (2C), 129.86, 129.76 (2C), 125.54 (t, \(J = 6.1\) Hz, 2C), 117.32 (2C), 113.02 (t, \(J = 252.7\) Hz), 79.51, 69.42, 63.41, 25.37 (2C), 21.51 (2C), 13.88 ppm; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)): \(\delta = -104.29\) ppm; HRMS: Calcd. for C\(_{24}\)H\(_{26}\)F\(_2\)O\(_6\)[M+Na\(^+\)]: 471.1590, found: 471.1600.

Ethyl 2,2-difluoro-2-(4-(2-methoxy-4-(octyloxy)benzoyl)phenyl)acetate (3t): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.81-7.71\) (m, 6H), 6.88-6.85 (m, 2H), 5.08 (p, \(J = 6.3\) Hz, 1H), 4.32 (q, \(J = 7.1\) Hz, 2H), 1.66 (s, 6H), 1.32 (t, \(J = 7.1\) Hz, 3H), 1.20 (d, \(J = 6.3\) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 194.53, 163.80\) (t, \(J = 34.7\) Hz), 163.61, 159.92, 141.54, 135.91 (t, \(J = 25.3\) Hz), 132.63, 129.56 (2C), 125.24 (t, \(J = 6.1\) Hz, 2C), 120.57, 113.13 (t, \(J = 252.5\) Hz), 105.45, 99.21, 64.39, 63.28, 55.48, 31.79, 29.32, 29.21, 29.16, 26.01, 22.64, 14.07, 13.84 ppm; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)): \(\delta = -104.25\) ppm; HRMS: Calcd. for C\(_{26}\)H\(_{32}\)F\(_2\)O\(_5\)[M+Na\(^+\)]: 485.2110, found: 485.2120.

Methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (5a): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.12\) (d, \(J = 8.5\) Hz, 2H), 7.69 (d, \(J = 8.5\) Hz, 2H), 4.30 (q, \(J = 7.1\) Hz, 2H), 3.94 (s, 3H), 1.29 (t, \(J = 7.1\) Hz, 3H ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 166.13, 163.68\) (t, \(J = 34.7\) Hz), 137.05 (t, \(J = 25.5\) Hz), 132.66, 129.87 (2C), 125.69 (t, \(J = 6.1\) Hz, 2C), 112.98 (t, \(J = 252.9\) Hz), 63.38, 52.43, 13.84 ppm; \(^{19}\)F NMR
Methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methylbenzoate (5b): \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.96 \) (d, \( J = 8.5 \) Hz, 1H), 7.47 (d, \( J = 7.3 \) Hz, 2H), 4.30 (q, \( J = 7.1 \) Hz, 2H), 3.91 (s, 3H), 2.63 (s, 3H), 1.30 (t, \( J = 7.1 \) Hz, 3H) ppm; \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta = 167.27, 163.80 \) (t, \( J = 34.7 \) Hz), 140.69, 135.90 (t, \( J = 25.4 \) Hz), 132.19, 130.85, 128.56 (t, \( J = 6.0 \) Hz), 122.85 (t, \( J = 6.1 \) Hz), 112.93 (t, \( J = 252.7 \) Hz), 63.32, 52.12, 21.65, 13.85 ppm; \( ^{19}F \) NMR (471 MHz, CDCl\(_3\)): \( \delta = -104.65 \) ppm; HRMS: Calcd. for C\(_{12}\)H\(_{12}\)F\(_2\)O\(_4\) [M+Na\(^+\)]: 281.0596, found: 281.0596.

Methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-fluorobenzoate (5c): \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.92 \) (d, \( J = 8.1 \) Hz, 1H), 7.78 (d, \( J = 10.8 \) Hz, 1H), 7.73 (t, \( J = 7.6 \) Hz, 1H), 4.35 (q, \( J = 7.1 \) Hz, 2H), 3.95 (s, 3H), 1.31 (t, \( J = 7.1 \) Hz, 3H) ppm; \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta = 165.00 \) (d, \( J = 2.5 \) Hz), 162.70 (t, \( J = 33.5 \) Hz), 159.55 (dt, \( J_1 = 253.9 \) Hz, \( J_2 = 4.4 \) Hz), 135.00 (d, \( J = 7.8 \) Hz), 127.42 (td, \( J_1 = 6.9 \) Hz, \( J_2 = 1.9 \) Hz), 125.35 (d, \( J = 3.6 \) Hz), 125.21 (td, \( J_1 = 25.7 \) Hz, \( J_2 = 12.7 \) Hz), 117.42 (d, \( J = 22.6 \) Hz), 111.23 (t, \( J = 252.1 \) Hz), 63.58, 52.71, 13.79 ppm; \( ^{19}F \) NMR (471 MHz, CDCl\(_3\)): \( \delta = -102.64 \) (d, \( J = 6.4 \) Hz), -113.35 (t, \( J = 7.4 \) Hz) ppm; HRMS: Calcd. for C\(_{13}\)H\(_{14}\)F\(_3\)O\(_4\) [M+Na\(^+\)]: 295.0502, found: 295.0754.

Methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3-methoxybenzoate (5d): \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.74-7.70 \) (m, 2H), 7.59 (s, 1H), 4.32 (q, \( J = 7.1 \) Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 1.28 (t, \( J = 7.1 \) Hz, 3H) ppm; \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta = 166.13, 163.53 \) (t, \( J = 33.6 \) Hz), 156.74 (t, \( J = 4.8 \) Hz), 134.02, 126.56 (t, \( J = 7.5 \) Hz), 126.29 (t, \( J = 24.1 \) Hz), 121.90, 112.16, 111.81 (t, \( J = 249.2 \) Hz), 62.82, 56.01, 52.48, 13.91 ppm; \( ^{19}F \) NMR (471 MHz, CDCl\(_3\)): \( \delta = -103.50 \) ppm; HRMS: Calcd. for C\(_{13}\)H\(_{14}\)F\(_2\)O\(_5\) [M+Na\(^+\)]: 311.0702, found: 311.0705.
Methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3,5-dimethoxybenzoate (5e): ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 6H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 165.98, 164.13 (t, J = 32.8 Hz), 159.06 (t, J = 2.5 Hz, 2C), 133.91, 113.74 (t, J = 23.4 Hz), 112.76 (t, J = 250.4 Hz), 105.95 (2C), 62.60, 56.47 (2C), 52.59, 14.01 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ = -98.96 ppm; HRMS: Calcd. for C₁₄H₁₆F₂O₆ [M+Na⁺]: 341.0807, found: 341.0813.

Butyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (5f): ¹H NMR (500 MHz, CDCl₃): δ = 8.12 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 4.35 (t, J = 6.6 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.79-1.73 (m, 2H), 1.52-1.44 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 165.71, 163.71 (t, J = 34.7 Hz), 136.93 (t, J = 25.6 Hz), 133.05, 129.83 (2C), 125.65 (t, J = 6.1 Hz, 2C), 113.01 (t, J = 252.8 Hz), 65.30, 63.38, 30.74, 19.26, 13.86, 13.73 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ = -104.49 ppm; HRMS: Calcd. for C₁₅H₁₈F₂O₄ [M+Na⁺]: 323.1065, found: 323.1071.

Ethyl 2,2-difluoro-2-(1-oxoisochroman-6-yl)acetate (5g): ¹H NMR (500 MHz, CDCl₃): δ = 8.17 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 4.56 (t, J = 6.0 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.12 (t, J = 6.0 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 163.98, 163.48 (t, J = 34.5 Hz), 140.04, 137.74 (t, J = 25.5 Hz), 130.88, 127.70, 124.84 (t, J = 6.0 Hz), 124.57 (t, J = 6.1 Hz), 112.68 (t, J = 253.3 Hz), 67.19, 63.55, 27.80, 13.85 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ = -104.65 ppm; HRMS: Calcd. for C₁₃H₁₂F₂O₄ [M+Na⁺]: 293.0596, found: 293.0604.

1,2:3,4-Bis-0-(1-methylethylidene)-α-D-galactopyranose 6-(4-(2-ethoxy-1,1-difluoro-2-oxoethyl))benzoate (5h): ¹H NMR (500 MHz, CDCl₃): δ = 8.13 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 5.56 (d, J = 4.9 Hz, 1H), 4.65 (dd, J₁ = 7.9 Hz, J₂ = 2.5 Hz, 1H), 4.54 (dd, J₁ = 11.6 Hz, J₁ = 4.6 Hz, 1H), 4.45 (dd, J₁ = 11.5 Hz, J₂ = 7.7 Hz, 1H), 4.35 (dd, J₁ = 5.0 Hz, J₂ = 2.5 Hz, 1H), 4.33-
4.27 (m, 3H), 4.19-4.17 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.30 (t, \( J = 7.1 \) Hz, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 165.51, 163.68 (t, \( J = 34.8 \) Hz), 137.10 (t, \( J = 25.5 \) Hz), 132.58, 129.99 (2C), 125.68 (t, \( J = 5.9 \) Hz, 2C), 112.97 (t, \( J = 252.7 \) Hz), 109.80, 108.85, 96.35, 71.15, 70.78, 70.53, 64.37, 63.39, 26.02, 25.99, 13.85 ppm; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)): \( \delta = -104.58 \) ppm; HRMS: Calcd. for C\(_{23}\)H\(_{28}\)F\(_2\)O\(_9\) [M+Na\(^{+}\)]: 509.1594, found: 509.1600.

V. Post-synthetic modification of difluoroacetate 3a

![Scheme S1](image)

**Scheme S1.** Post-synthetic modification of difluoroacetate 3a.

**Procedure for preparation of 6** \(^{[1]}\): In a 10 mL glass vial, a mixture of 3a (0.1 mmol, 1.0 equiv), NaBH\(_4\) (15.0 equiv), EtOH (2 mL) was stirred for 3 h at room temperature. The reaction was then poured into 1 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (3 \( \times \) 25 mL), washed with water (100 mL), dried over MgSO\(_4\) and concentrated in vacuo. The product was purified by flash chromatography on silica gel with PE / EA = 3 / 1 as the eluent.

![Scheme S1](image)

**2,2-Difluoro-2-(4-(hydroxy(p-tolyl)methyl)phenyl)ethan-1-ol (6):** \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.47-7.43 \) (m, 4H), 7.23 (d, \( J = 8.1 \) Hz, 2H), 7.15 (d, \( J = 7.9 \) Hz, 2H), 5.80 (s, 1H), 3.90 (t, \( J = 13.4 \) Hz, 2H), 2.51-2.27 (m, 5H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 146.18, 140.47, 137.71, 133.47 (t, \( J = 25.6 \) Hz), 129.35 (2C), 126.56 (2C), 126.52 (2C), 125.66 (t, \( J = 6.1 \) Hz, 2C), 120.57 (t, \( J = 243.8 \) Hz), 75.68, 65.91 (t, \( J = 32.6 \) Hz), 21.10 ppm; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)): \( \delta = -106.90 \) ppm; HRMS: Calcd. for C\(_{16}\)H\(_{16}\)F\(_2\)O\(_2\) [M+Na\(^{+}\)]: 301.1011, found: 301.1013.

**Procedure for preparation of 7** \(^{[1]}\): In a 10 mL glass vial, a mixture of 3a (0.1 mmol, 1.0 equiv) and morpholine (1.0 mL) was stirred for 6 h at 60 °C. The reaction was then poured into saturated NH\(_4\)Cl solution, and the aqueous phase was extracted with EtOAc (3 \( \times \) 25 mL), washed with water (100 mL), dried over MgSO\(_4\) and concentrated in vacuo. The product was purified by flash chromatography on silica gel with

PE / EA = 3 / 1 as the eluent.
2,2-Difluoro-2-(4-(4-methylbenzoyl)phenyl)-1-morpholinoethan-1-one (7): ¹H NMR (500 MHz, CDCl₃): δ = 7.86 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.72 (d, J = 5.2 Hz, 4H), 3.58 (s, 4H), 2.45 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 195.42, 161.74 (t, J = 30.2 Hz), 143.95, 140.29, 136.83 (t, J = 24.6 Hz), 134.24, 130.35 (2C), 130.05 (2C), 129.21 (2C), 125.39 (t, J = 5.9 Hz, 2C), 115.64 (t, J = 252.8 Hz), 66.70, 66.49, 46.70, 43.63, 21.71 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ = -95.44 ppm; HRMS: Calcd. for C₂₀H₁₉F₂NO₃ [M+Na⁺]: 382.1225, found: 382.1232.

Procedure for preparation of 8[¹]: In a 10 mL glass vial, a mixture of 3a (0.2 mmol, 1.0 equiv), MeOH (10 mL) and 1 M K₂CO₃ aq. (10 mL) was stirred for 6 h at 60 °C. The reaction was then poured into 1 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (3 × 50 mL), washed with water (100 mL), dried over MgSO₄ and concentrated in vacuo. The product was purified by flash chromatography on silica gel with (CH₂Cl₂ / CH₃OH = 10 / 1) as the eluent.

2,2-Difluoro-2-(4-(4-methylbenzoyl)phenyl)acetic acid (8): ¹H NMR (500 MHz, DMSO-d₆): δ = 7.86 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H) ppm; ¹³C NMR (125 MHz, DMSO-d₆): δ = 194.70, 164.53 (t, J = 32.9 Hz), 143.66, 139.75, 135.96 (t, J = 25.2 Hz), 133.74, 129.97 (2C), 129.83 (2C), 129.24 (2C), 125.43 (t, J = 5.8 Hz, 2C), 113.21 (t, J = 251.1 Hz), 21.16 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ = -102.94 ppm; HRMS: Calcd. for C₁₆H₁₂F₂O₃ [M+Na⁺]: 313.0647, found: 313.0647.

Procedure for preparation of 9[¹]: In a 10 mL glass vial, a mixture of 3a (0.2 mmol, 1.0 equiv), AgNO₃ (6.8 mg, 20 mol %), Selectflour (140.0 mg, 2.0 equiv), acetone (1.0 mL) and H₂O (1.0 mL) was stirred for 3 h at 55 °C. The mixture was concentrated in vacuo. The product was purified by flash chromatography on silica gel with PE / EA = 20 / 1 as the eluent.

p-Tolyl(4-(trifluoromethyl)phenyl)methanone (9): ¹H NMR (500 MHz, CDCl₃): δ = 7.87 (d, J = 8.0 Hz, 2H), 7.73 (dd, J₁ = 13.4 Hz, J₂ = 8.1 Hz, 4H), 7.31 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 195.23, 144.07, 141.14, 134.09, 133.50 (q, J = 32.7 Hz), 130.32 (2C), 129.99
(2C), 129.22 (2C), 125.27 (q, $J = 3.9$ Hz, 2C), 123.71 (q, $J = 272.4$ Hz), 21.69 ppm; $^{19}$F NMR (471 MHz, CDCl$_3$): $\delta = -75.90$ ppm.

VI. Gram scale difluoromethylation of 1a

$$\begin{align*}
\text{1a} & \quad \text{2 (4.0 equiv)} \\
\begin{array}{c}
\text{Pd}[\text{P(Cy}_3\text{)}]^2\text{Cl}_2 (5 \text{ mol\%}) \\
\text{Fe(OAc)}_2 (5 \text{ mol\%}) \\
\text{K}_2\text{CO}_3 (6.0 \text{ equiv})
\end{array} & \quad \text{DCE}, 110 \degree \text{C}, 48 \text{ h}, \text{N}_2 \\
\text{3a} & \quad 0.2 \text{ g 66\%} \\
& \quad 0.5 \text{ g 60\%}
\end{align*}$$

To a mixture of 1a (0.2 g or 0.5 g, 1.0 equiv), BrCF$_2$CO$_2$Et 2 (4.0 equiv), Pd[P(Cy)$_3$]$_2$Cl$_2$ (5 mol%), K$_2$CO$_3$ (6.0 equiv) and Fe(OAc)$_2$ (5 mol%) in a 100 mL Schlenk tube was added the DCE (6 mL or 13 mL) under N$_2$ atmosphere. Then the tube was sealed with a Teflon-lined screw cap and heated at 110 $\degree$C for 48 h. The reaction mixture was cooled to room temperature, diluted with CH$_2$Cl$_2$ and filtered through a small pad of Celite followed by washing with CH$_2$Cl$_2$. The resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to give the desired products 3a.

VII. Preliminary mechanistic study

a) para-Difluoromethylation of benzaldehyde

$$\begin{align*}
\text{10} & \quad \text{2 (4.0 equiv)} \\
\begin{array}{c}
\text{Pd}[\text{P(Cy}_3\text{)}]^2\text{Cl}_2 (x \text{ mol\%}) \\
\text{Fe(OAc)}_2 (5 \text{ mol\%}) \\
\text{K}_2\text{CO}_3 (6.0 \text{ equiv})
\end{array} & \quad \text{DCE (0.15 M), 110 \degree \text{C}, 48 h, N}_2 \\
\text{11} & \quad x = 10 \text{ mol\%, 65\%, 11 / 12 = 4 : 3} \\
& \quad x = 0 \text{ mol\%, 0\%}
\end{align*}$$

b) Deuterium experience

$$\begin{align*}
\text{1d-d$_5$, 93\% D} & \quad \text{2 (4.0 equiv)} \\
\begin{array}{c}
\text{Pd}[\text{P(Cy}_3\text{)}]^2\text{Cl}_2 (10 \text{ mol\%}) \\
\text{Fe(OAc)}_2 (5 \text{ mol\%}) \\
\text{K}_2\text{CO}_3 (6.0 \text{ equiv}), \text{H}_2\text{O (2.0 equiv)}
\end{array} & \quad \text{DCE (0.15 M), 110 \degree \text{C}, 24 h, N}_2 \\
\text{3d-d$_4$, 92.5\% D} & \quad 45\%
\end{align*}$$

c) Control experiment with 2,6-diblocked aryl ketone

$$\begin{align*}
\text{13} & \quad \text{2 (4.0 equiv)} \\
\begin{array}{c}
\text{Pd}[\text{P(Cy}_3\text{)}]^2\text{Cl}_2 (10 \text{ mol\%}) \\
\text{Fe(OAc)}_2 (5 \text{ mol\%}) \\
\text{K}_2\text{CO}_3 (6.0 \text{ equiv})
\end{array} & \quad \text{DCE (0.15 M), 110 \degree \text{C}, 48 h, N}_2 \\
\text{14} & \quad 45\%
\end{align*}$$

Scheme S2. Mechanistic experiences.
**General procedure for a):** A mixture of 10 (0.3 mmol, 1.0 equiv), BrCF₂CO₂Et (0.16 mL, 1.2 mmol, 4.0 equiv), Pd[P(C₅H₃)₂Cl₂ (10 mol% or 0 mol%), K₂CO₃ (248.4 mg, 1.8 mmol, 6.0 equiv) and Fe(OAc)₂ (2.6 mg, 0.015 mmol, 5 mol%) in a 25 mL Schlenk tube was added the DCE (2.0 mL) under N₂ atmosphere. Then the tube was sealed with a Teflon-lined screw cap and heated at 110 °C for 48 h. The reaction mixture cooled to room temperature, diluted with CH₂Cl₂ and was filtered through a small pad of Celite followed by washing with CH₂Cl₂. The resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to give the mixture of products 11 and 12, which was difficult to isolate. The value of the mono- and di-addition products is determined by ¹H NMR spectrum.

**The ¹H NMR spectrum of 11 and 12:**

![NMR spectrum of 11 and 12]

**General procedure for 1d-d₅:** Compound 1d-d₅ was synthesized via a modified procedure according to a previous report. Benzene-d₆ (0.6 mL, 6.4 mmol), AlCl₃ (1.07 g, 8.0 mmol), and anhydrous CS₂ (1.5 mL) were added to a 10-mL flask under argon atmosphere. To the mixture was dropwise added a solution of acetyl chloride (0.628 g, 8.05 mmol) in anhydrous CS₂ (2.5 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 5 h. Upon complete, the resulting mixture was poured out to ice water and extracted with CH₂Cl₂ (3 × 30 mL). The organic layer was washed with saturated aqueous Na₂CO₃ (20 mL) and brine (20 mL) and then dried over Na₂SO₄. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel to give 1d-d₅ as a colorless oil (0.62 g, 78%).

**General procedure for b):** A mixture of 1d-d₅ (0.3 mmol, 1.0 equiv), BrCF₂CO₂Et (0.16 mL, 1.2 mmol, 4.0 equiv), Pd[P(C₅H₃)₂Cl₂ (10 mol% or 0 mol%), K₂CO₃ (248.4 mg, 1.8 mmol, 6.0 equiv) and
Fe(OAc)_2 (2.6 mg, 0.015 mmol, 5 mol%) in a 25 mL Schlenk tube was added the DCE (2.0 mL) under N_2 atmosphere. Then the tube was sealed with a Teflon-lined screw cap and heated at 110 °C for 24 h. The reaction mixture cooled to room temperature, diluted with CH_2Cl_2 and was filtered through a small pad of Celite followed by washing with CH_2Cl_2. The resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to give the product 3d-d_4.

The ^1H NMR spectrum of 1d-d_5:

![NMR spectrum of 1d-d_5](image)

1d-d_5, 93% D

The ^1H NMR spectrum of 3d-d_4:

![NMR spectrum of 3d-d_4](image)
General procedure for c): A mixture of 13 (0.3 mmol, 1.0 equiv), BrCF₂CO₂Et (0.16 mL, 1.2 mmol, 4.0 equiv), Pd[P(Cy)₃]Cl₂ (10 mol% or 0 mol%), K₂CO₃ (248.4 mg, 1.8 mmol, 6.0 equiv) and Fe(OAc)₂ (2.6 mg, 0.015 mmol, 5 mol%) in a 25 mL Schlenk tube was added to DCE (2.0 mL) under N₂ atmosphere. Then the tube was sealed with a Teflon-lined screw cap and heated at 110 °C for 48 h. The reaction mixture cooled to room temperature, diluted with CH₂Cl₂ and was filtered through a small pad of Celite followed by washing with CH₂Cl₂. The resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to give the product 14.

Ethyl 2-(4-acetyl-3,5-difluorophenyl)-2,2-difluoroacetate (14): ¹H NMR (500 MHz, CDCl₃): δ = 7.24-7.20 (m, 2H), 4.33 (q, J₁ = 7.8 Hz, J₂ = 7.1 Hz, 2H), 2.61 (t, J = 1.6 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 193.70, 162.75 (t, J = 34.1 Hz), 159.82 (dd, J₁ = 256.1 Hz, J₂ = 7.5 Hz, 2C), 137.61-137.18 (m), 120.63-120.43 (m), 111.59 (t, J = 254.1 Hz), 110.07 (dq, J₁ = 22.4 Hz, J₂ = 6.3 Hz, 2C), 63.83, 32.30, 13.83 ppm; ¹⁹F NMR (471 MHz, CDCl₃): δ = -104.64, -109.40 ppm; HRMS: Calcd. for C₁₂H₁₀F₄O₃ [M+Na⁺]: 301.0458, found: 301.0458.

VII. References

VIII. NMR spectra
3g
65