Supporting Information

Synthesis of $^{18}$F-Difluoromethylarenes Using Aryl Boronic Acids, Ethyl bromofluoroacetate and $[^{18}F]$Fluoride

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S1: General Information

All chemicals purchased from commercial sources were used without further purification prior to use. All NMR spectra were recorded at a temperature of 298.15 K on Bruker AV400, or AV500 spectrometers. Appropriate deuterated solvents were used as an internal reference depending on the compound measured. All corresponding compound peaks were referenced to the residual solvent peak and reported in parts per million (ppm) using the Bruker internal referencing procedure (edlock). $^{19}$F NMR spectral peaks were referenced to CFCl$_3$. All coupling constants are denoted as $J$ and reported in Hz. The following abbreviations were used to define peak multiplicities $s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, pent =$pentet, sept=$septet, br = broad, $m =$ multiplet. All NMR spectra were processed using Mestrenova 11.0 software. Mass spectra were recorded on Micromass GCT (CI) or Autospec-oaTof instruments. IR spectra were recorded as thin films on Bruker Tensor 27 FT-IR spectrometer. IR absorption are reported in wavenumbers (cm$^{-1}$). All reactions which required anhydrous conditions were carried out in flame-dried glassware under an inert atmosphere of nitrogen or argon. When dry solvents were used these were purified $a$ $priori$ on an alumina column using standard procedures. All reactions were monitored by TLC using Merck Kieselgel 60 F254 plates. High resolution mass spectra (HRMS, $m/z$) were recorded on a Bruker MicroTOF spectrometer using negative or positive electrospray ionization (ESI). Melting point measurements were recorded using a Griffin melting point apparatus.
**S2: Optimisation of the Cu-catalysed cross coupling reaction**

**General Screening Procedure:**
To a 4 mL vial containing a magnetic stir bar was added ligand (if solid), boronic acid, copper source and base. The vial was then evacuated and refilled with N\(_2\) three times. Solvent (0.5 mL) and ligand (if liquid) were then added before heating the reaction mixture to 100 °C and stirring for 18 hours. The resulting solution was cooled to 0 °C before 0.1 mmol of PhCF\(_3\) was added as an internal standard, the corresponding sample was then diluted with CDCl\(_3\). Yields were calculated by quantitative \(^{19}\)F NMR and referenced to PhCF\(_3\). **Note:** All screening reactions were run on a 0.1 mmol scale, isolations were performed on 0.3 mmol scale and in some cases scaled up to illustrate scalability.

**Table 1.** Optimisation of Cu-catalysed cross-coupling of (hetero)aryl boronic acids with ethyl 2-bromo-2-fluoroacetate towards 2-fluoro-2-(hetero)arylacetic acids.

| Entry | Solvent     | Cu-Source | Ligand | Product | Yield\(^a\) |
|-------|-------------|-----------|--------|---------|-------------|
| 1\(^b\) | Dioxane (0.2 M) | Cul | L1  | 7a | 7% |
| 2\(^b\) | Dioxane (0.2 M) | Cul | L2  | 7a | 58% |
| 3 | Toluene (0.2 M) | Cul | L3  | 7a | 63% |
| 4\(^c\) | Toluene (0.4 M) | Cul | L3  | 7a | 82%\(^d\) |
| 5\(^c\) | Toluene (0.4 M) | Cul | L3  | 8a | 75%\(^d,e\) |
| 6\(^c\) | Toluene (0.4 M) | Cul | - | 7a | 0% |
| 7\(^c\) | Toluene (0.4 M) | - | - | 7a | 0% |
| 8\(^c\) | Toluene (0.4 M) | CuCl\(_2\) | L2 | 7a | 0% |
| 9\(^c\) | DMF or DMSO (0.2 M) | Cul | L3 | 7a | 0% |

Screening reactions performed on 0.1 mmol scale. \(^a\)Yield determined by \(^{19}\)F-NMR using PhCF\(_3\) as internal standard. \(^b\)Reactions with 2 equiv. of 6a and 1 equiv. of 2-bromo-2-fluoroacetate. \(^c\)Reactions with 1 equiv. of 6a and 2 equiv. of 2-bromo-2-fluoroacetate. \(^d\)Yield of isolated product. \(^e\)One-pot procedure.
S3: Preliminary Fluorodecarboxylation Experiments

A. Competition studies evaluating the effect of fluorine substitution on fluorodecarboxylation.

An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N₂. Mn(tmp)Cl Catalyst (2.2 mg, 0.0025 mmol, 2.5 mol%), 2-([1,1'-biphenyl]-4-yl)-2-fluoroacetic acid (23.0 mg, 0.1 mmol), 2-([1,1'-biphenyl]-4-yl)acetic acid (21.2 mg, 0.1 mmol, 1 equiv.), Et₃N·3HF (200 µL, 0.12 mmol, 1.2 equiv.) were then added, followed by 1.0 mL of MeCN. The reaction mixture was then heated to 50 °C. Under a stream of N₂, iodosylbenzene (73 mg, 0.33 mmol, 3.3 equiv.) was added slowly to the reaction mixture in solid form over a period of 1.5 hours. After the addition of iodosylbenzene, the solution was cooled to r.t, 0.1 mmol of PhCF₃ was added as internal standard and conversion was measured by ¹⁹FNMR.
B. Reaction with sub-stoichiometric fluoride.

An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N\textsubscript{2}. Mn(tmp)Cl Catalyst (2.0 mg, 0.0020 mmol, 2 mol%), 2-((1,1'-biphenyl)-4-yl)-2-fluoroacetic acid, (23.0 mg, 0.1 mmol) TBAF (1M in THF) (10 \mu L, 0.01 mmol, 0.1 equiv.) were then added, followed by 1.0 mL of MeCN. The reaction mixture was then heated to 50 °C. Under a stream of N\textsubscript{2}, iodosylbenzene (11.1 mg, 0.05 mmol, 0.5 equiv.) was added slowly to the reaction mixture in solid form over a period of 20 minutes. After the addition of iodosylbenzene, the solution was cooled to r.t, diluted with H\textsubscript{2}O (5 mL) and extracted with EtOAc (3 x 5 mL). The organic extracts was dried over MgSO\textsubscript{4} and concentrated under vacuum, prior to silica gel column chromatography.

C. Reaction of iodine(III) complex 5a with sub-stoichiometric fluoride.

2-((1,1'-biphenyl)-4-yl)-2-fluoroacetic acid (0.2 mmol, 10 equiv.), PhIO (0.1 mmol, 5 equiv.) were added to a 4 mL vial containing a stir magnetic stir bar. d\textsubscript{3}-CH\textsubscript{3}CN (2 mL) was then added to the reaction mixture and the mixture was stirred for 10 minutes at 50 °C. The solvent removed under vacuum. The residue was redissolved in d\textsubscript{3}-CH\textsubscript{3}CN (2 mL). Mn(tmp)Cl (0.04 mmol, 2 equiv.) and TBAF (0.02 mmol, 1 equiv.) were then added to the reaction mixture, which was subsequently stirred for a further 10 minutes before cooling to 0 °C. 0.1 mmol of PhCF\textsubscript{3} was then added as internal standard. The yield was determined by quantitative \textsuperscript{19}F NMR (99 %, based on TBAF).
TBAF (1 mmol, 1 equiv., 1.0 M in THF) and anhydrous CH\textsubscript{3}CN (2 mL) were added to a vial containing a magnetic stir bar. 2-fluoro-2-(4-phenoxyphenyl)acetic acid (1 mmol, 10 equiv.) and PhIO (5 mmol, 5 equiv.) were added to the solution (Note: PhIO dissolves as it reacts with 2-fluoro-2-(4-phenoxyphenyl)acetic acid). The mixture was stirred for 2 minutes at 50 °C before Mn(tmp)Cl (2 mmol, 2 equiv.) was added to the solution. The mixture was stirred for another 18 minutes at 50 °C before it was cooled to r.t and analysed by GC-MS (LRMS) to obtain an impurity profile, the products obtained are outlined (Scheme SI-1).
S5: Synthetic Procedures and Characterisation of Compounds

General Procedure (GP) 1: Synthesis of α-aryl-α-fluoroacetic acids.

To a flame-dried pear-shaped round bottomed flask were added CuI (20 mol%), 4,4′,4″-Tri-tert-butyl-2,2’:6’,2″-terpyridine (20 mol%), boronic acid (1 equiv.) and Cs₂CO₃ (2 equiv.), followed by argon degassed toluene (1.5 mL). The reaction mixture is stirred for 18 hours at 100 °C. The reaction mixture is cooled to r.t, solvent removed under reduced pressure. The resulting suspension was then dissolved in a 2:1 MeOH and aqueous K₂CO₃ (10 equiv.) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). MeOH was then removed under reduced pressure. The aqueous suspension was then washed with Et₂O (3 x 10 mL), acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et₂O (3 x 10 mL) and washed with Brine (2 x 10 mL). The organic extracts were then dried over MgSO₄ and concentrated under vacuum and washed with pentane, resulting in an off-white solid. The resulting crude 2-fluoro-2-phenylacetic acids were then subjected to column chromatography (gradient of hexane/ethyl acetate with acetic acid (1%) to ethyl acetate/MeOH with acetic acid (1%)). *Note: Alternatively, the α-(hetero)aryl-α-fluoroacetates can be purified via column chromatography and then hydrolysed without subsequent column chromatography of the carboxylic acid (GP 2).*

General Procedure (GP) 2: Synthesis of α-(hetero)aryl-α-fluoroacetate and subsequent hydrolysis

To a flame-dried pear-shaped round bottomed flask were added CuI (20 mol%), 4,4′,4″-Tri-tert-butyl-2,2’:6’,2″-terpyridine (20 mol%), boronic acid (1 equiv.) and Cs₂CO₃ (2 equiv.).
followed by argon degassed toluene (1.5 mL). The reaction mixture is stirred for 18 hours at 100 °C. The mixture is cooled to r.t, solvent removed under reduced pressure. The residue is then diluted with EtOAc and filtered through a plug of celite. EtOAc is then removed under reduced pressure. The resulting oil is purified by silica gel chromatography (EtOAc/Hexane), resulting in a clear colourless oil. This oil was then dissolved in a 2:1 MeOH and aqueous K$_2$CO$_3$ (5 equiv.) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). The resulting mixture was then acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et$_2$O (3 x 10 mL) and washed with Brine (2 x 10 mL). The organic extracts were dried using MgSO$_4$ and were then concentrated under vacuum and washed with pentane.

**General Procedure (GP) 3: Synthesis of (difluoromethyl)arenes reference compounds**

A flame-dried two-necked round-bottomed flask was charged with a stir-magnetic stir bar and a starting material (if solid). To this flask was added anhydrous DCM and a drop of EtOH. The resulting mixture was cooled to 0 °C and DAST (1.5 equiv.) was added dropwise. The resulting mixture was stirred at 0 °C for a further 10 minutes before it was allowed to warm to r.t. The resulting reaction mixture was stirred until TLC showed all starting material had been consumed. The reaction mixture was then quenched with NaHCO$_3$ until gas evolution stopped and then purified by column chromatography (eluent: n-pentane/DCM). Note: electron rich title compounds such as 1-(difluoromethyl)-2-methoxybenzene and 1-(difluoromethyl)-4-phenoxybenzene are unstable when neat in standard glassware. When removing solvent these compounds should be transferred into a falcon tube and stored in a freezer. In case of decomposition, the compound will turn deep purple, but can be recovered if it is passed through a plug of silica.
General Procedure (GP) 4: Synthesis of (difluoromethyl)arenes reference compounds

An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N\(_2\). Mn(tmp)Cl Catalyst (2.5 mol%) substrate (0.1 mmol) and DCE were then added, followed by Et\(_3\)N·3HF (1.2 equiv.). The reaction mixture was then heated to 50 °C. Under a stream of N\(_2\), iodosylbenzene (3.3 equiv.) was added slowly to the reaction mixture in solid form over a period of 1.5 hours. After the addition of iodosylbenzene, the reaction was stirred until completion.

**Synthesis of α-aryl-α-fluoroacetic acids**

2-((1,1'-Biphenyl)-4-yl)-2-fluoroacetic acid\(^2\)

The title compound was prepared following GP1 using [1,1'-biphenyl]-4-ylboronic acid (59.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs\(_2\)CO\(_3\) (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-tert-butyl-2,2',6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (51.8 mg, 75% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 75%). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.74 (d, \(J = 7.8\) Hz, 2H), 7.70 – 7.66 (m, 2H), 7.56 – 7.52 (m, 2H), 7.48 (dd, \(J = 8.4, 6.9\) Hz, 2H), 7.42 – 7.37 (m, 1H), 6.04 (d, \(J = 47.5\) Hz, 1H). \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 170.2 (d, \(J = 27.4\) Hz), 141.7 (d, \(J = 2.3\) Hz), 140.0, 134.6 (d, \(J = 19.6\) Hz), 129.5, 128.3, 128.0 (d, \(J = 6.0\) Hz), 127.5, 127.3, 89.8 (d, \(J = 183.2\) Hz); \(^{19}\)F NMR (376 MHz, DMSO-\(d_6\)) \(\delta\) -175.73 (d, \(J = 47.5\) Hz). The physical data were identical in all respects to those previously reported.\(^2\)
2-Fluoro-2-(4-phenoxyphenyl)acetic acid

The title compound was prepared following General Procedure GP1 using (4-phenoxyphenyl)boronic acid (64.2 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (51.0 mg, 69% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 69%). Mp: 86 – 88 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.45 (d, J = 9.4 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.23 – 7.12 (m, 1H), 7.10 – 6.99 (m, 5H), 5.82 (d, J = 47.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ: 173.45 (d, J = 28.6 Hz), 159.25 (d, J = 5.6 Hz), 127.74, 124.22, 119.76, 118.69, 88.59 (d, J = 186.4 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ: -177.21 (d, J = 47.7 Hz); Found, 245.06156; IR (film, cm⁻¹) v 3038, 2917, 1768, 1589, 1243; HRMS (ESI) m/z calculated for C₁₄H₁₀FO₃ [M – H] 245.06195, found, 245.06156.

2-(3,5-Dimethylphenyl)-2-fluoroacetic acid

The title compound was prepared following General Procedure GP1 using (3,5-dimethylphenyl)boronic acid (45.0 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (34.4 mg, 63% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 63%). Mp: 68 – 70 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.04 – 6.96 (m, 3H), 5.67 (d, 1H, J = 48.9 Hz), 2.26 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ: 173.37 (d, J = 27.8 Hz), 138.70, 133.21 (d, J = 20.3 Hz), 131.65 (d, J = 2.4 Hz), 124.50 (d, J = 5.9 Hz), 88.99 (d, J = 186.0 Hz), 21.23. ¹⁹F NMR (376 MHz, CDCl₃) δ: -179.17 (d, J = 47.4 Hz). IR (film, cm⁻¹) v: 3038, 2917, 2166, 1725, 1066. HRMS (ESI) m/z calculated for C₁₀H₁₀FO₂ [M – H] 181.06703, found, 181.06673.
2-(2,5-Dimethylphenyl)-2-fluoroacetic acid

![Structural formula of 2-(2,5-Dimethylphenyl)-2-fluoroacetic acid]

The title compound was prepared following General Procedure GP1 (3-iodophenyl)boronic acid (74.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), Cul (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol%). The title compound (42.0 mg, 52% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 52%). **Mp:** 85 – 88 °C; **¹H NMR** (400 MHz, CDCl₃) δ: 7.22 (d, 1H, J = 10.9 Hz), 7.10 (s, 2H), 5.98 (d, 1H, J = 47.2 Hz), 2.38 (s, 3H), 2.31 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ: 174.49 (d, J = 28.7 Hz), 136.13, 133.41 (d, J = 3.9 Hz), 131.68 (d, J = 19.1 Hz), 130.93, 130.72 (d, J = 2.5 Hz), 127.76 (d, J = 6.7 Hz), 86.64 (d, J = 185.6 Hz), 20.88, 18.68; **¹⁹F NMR** (376 MHz, CDCl₃) δ: -180.02 (d, J = 47.2 Hz); **IR** (film, cm⁻¹) v. 3024, 2929, 2845, 1708, 1243; **HRMS** (ESI) m/z calculated for C₁₀H₁₀FO₂ [M–H] 181.06703, found, 181.06680.

2-(4-(tert-Butyl)phenyl)-2-fluoroacetic acid³

![Structural formula of 2-(4-(tert-Butyl)phenyl)-2-fluoroacetic acid]

The title compound was prepared following General Procedure GP1 using (4-(tert-butyl)phenyl)boronic acid (53.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), Cul (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (44.2 mg, 70% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 70%). **¹H NMR** (400 MHz, CDCl₃) δ: 7.41 – 7.29 (m, 4H), 5.73 (d, J = 47.9 Hz, 1H), 1.25 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ: 173.9 (d, J = 27.8 Hz), 153.3 (d, J = 2.0 Hz), 130.4 (d, J = 20.5 Hz), 126.6 (d, J = 5.7 Hz), 125.9, 88.7 (d, J = 185.4 Hz), 34.8, 31.2; **¹⁹F NMR** (376 MHz, CDCl₃) δ -179.1 (d, J = 48.2 Hz). The physical data were identical in all respects to those previously reported.³
2-Fluoro-2-(2-methoxyphenyl)acetic acid

![Chemical Structure]

The title compound was prepared following General Procedure GP1 using (2-methoxyphenyl)boronic acid (45.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol%). The title compound (38.1 mg, 30% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 30%). ¹H NMR (400 MHz, CDCl₃) δ: 7.36 (t, J = 7.8 Hz, 1H), 7.05 (m, 1H), 7.02 (m, 1H), 6.99 - 6.94 (m, 1H), 5.84 (d, J = 46.9 Hz, 1H), 3.88 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ: 173.66 (d, J = 28.8 Hz), 157.64 (d, J = 3.0 Hz), 132.17 (d, J = 2.8 Hz), 129.80 (d, J = 5.3 Hz), 122.62 (d, J = 19.2 Hz), 121.47 (d, J = 1.6 Hz), 111.81 (d, J = 1.0 Hz), 85.31 (d, J = 183.7 Hz), 56.27; ¹⁹F NMR (376 MHz, CDCl₃) δ: -178.49 (d, J = 46.4 Hz). The physical data were identical in all respects to those previously reported.

1-(1-Fluoro-2-hydroperoxy-2l2-ethyl)-3-methoxybenzene

![Chemical Structure]

The title compound was prepared following General Procedure GP1 using (3-methoxyphenyl)boronic acid (45.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (32.6 mg, 56% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 56%). ¹H NMR (400 MHz, CDCl₃) δ: 7.52 (bs, 1H), 7.30 – 7.21 (m, 1H), 7.02 – 6.91 (m, 2H), 6.88 (ddt, J = 8.3, 2.3, 1.0 Hz, 1H), 5.72 (d, J = 47.9 Hz, 1H), 3.75 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 173.6 (d, J = 27.5 Hz), 159.9, 134.8 (d, J = 20.4 Hz), 130.00, 118.9 (d, J = 6.2 Hz) 115.7 (d, J = 1.4 Hz), 111.8 (d, J = 6.3 Hz), 88.6 (d, J = 186.8 Hz), 55.3; ¹⁹F NMR (376 MHz, CDCl₃) δ: -181.19 (d, J = 48.2 Hz). The physical data were identical in all respects to those previously reported.

1-(1-Fluoro-2-hydroperoxy-2l2-ethyl)-4-(trifluoromethyl)benzene
The title compound was prepared following General Procedure GP1 using (4-(trifluoromethyl)phenyl)boronic acid (57.0 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (40.0 mg, 60% yield) was isolated as a yellow solid.

Physical appearance: Yellow solid (yield: 60%). Mp: 80 – 83 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.66 – 7.51 (m, 4H), 5.83 (d, J = 47.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ: 173.2 (d, J = 27.3 Hz), 133.5 – 131.1 (m), 127.7, 126.7 (d, J = 6.7 Hz), 125.9 (q, J = 3.8 Hz), 88.0 (d, J = 178.2 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ: -62.9 (s), -185.2 (d, J = 47.2 Hz); IR (neat, cm⁻¹) ν 2853, 1739, 1418, 1321, 1119, 1066. HRMS (ESI) m/z calculated for C₉H₅F₄O₂ [M – H]⁻, 221.02312. found, 221.02290.

Ethyl 2-fluoro-2-(3-formyl-4-methoxyphenyl)acetate

The title compound was prepared following General Procedure GP2 (3-formyl-4-methoxyphenyl)boronic acid (111.1 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol%).

Physical appearance: Colourless Oil. ¹H NMR (400 MHz, CDCl₃) δ 10.45 (s, 1H), 7.91 (t, J = 2.0 Hz, 1H), 7.67 (ddd, J = 8.7, 2.5, 1.0 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 5.74 (d, J = 47.5 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.96 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 188.99, 168.25 (d, J = 27.9 Hz), 162.51 (d, J = 2.0 Hz), 134.05 (d, J = 5.4 Hz), 127.48 (d, J = 5.7 Hz), 126.84 (d, J = 21.5 Hz), 124.73, 112.29, 88.53 (d, J = 185.8 Hz), 61.97, 55.93, 14.04. ¹⁹F NMR (376 MHz, CDCl₃) δ -177.89 (d, J = 47.6 Hz). IR (neat, cm⁻¹) ν 2921, 2159, 1978, 1758, 1644. HRMS (ESI) m/z calculated for C₁₂H₁₄FO₄ [M + H]⁺, 241.0876, found, 241.0875.

2-Fluoro-2-(3-formyl-4-methoxyphenyl)acetic acid
Physical appearance: yellow solid (yield: 53% based on two steps). Mp: Decomposes between 120 – 150 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.61 (s, 1H), 7.39 – 7.30 (m, 1H), 7.12 – 6.92 (m, 3H), 5.80 (d, \(J = 47.5\) Hz, 1H), 3.83 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 173.58 (d, \(J = 27.9\) Hz), 159.89, 134.77 (d, \(J = 20.5\) Hz), 130.00, 118.91 (d, \(J = 6.3\) Hz), 115.71 (d, \(J = 2.0\) Hz), 111.84 (d, \(J = 6.6\) Hz), 88.67 (d, \(J = 187.2\) Hz), 55.37; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -181.18 (d, \(J = 47.5\) Hz); IR (film, cm\(^{-1}\)) \(\nu\) 2918, 2850, 1756, 1643, 1604, 1256, 1223; HRMS (ESI) \(m/z\) calculated for C\(_{10}\)H\(_8\)FO\(_4\) [M – H]\(^-\), 211.04121, Found, 211.04101.

2-(Dibenzo[b,d]furan-4-yl)-2-fluoroacetic acid

The title compound was prepared following General Procedure GP1 using dibenzo[b,d]furan-4-ylboronic acid (63.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs\(_2\)CO\(_3\) (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (38.1 mg, 52% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 52%). Mp: 96 – 98 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 13.70 (bs, 1H), 8.36 – 8.21 (m, 2H), 7.80 (d, \(J = 8.2\) Hz, 1H), 7.69 – 7.43 (m, 4H), 6.51 (d, \(J = 48.2\) Hz, 1H); \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\): 169.6 (d, \(J = 2.9\) Hz), 128.6, 127.4 (d, \(J = 5.0\) Hz), 124.8, 123.9 (d, \(J = 0.9\) Hz), 123.7, 123.2 (d, \(J = 2.8\) Hz) 121.9, 119.6 (d, \(J = 20.1\) Hz), 112.3, 85.1 (d, \(J = 179.4\) Hz); \(^{19}\)F NMR (376 MHz, DMSO-\(d_6\)) \(\delta\): -176.0 (d, \(J = 48.5\) Hz); IR (film, cm\(^{-1}\)) \(\nu\) 3041, 1734, 1591, 1450, 743; HRMS (ESI) \(m/z\) calculated for C\(_{14}\)H\(_8\)FO\(_3\) [M – H]\(^-\), 243.04630. Found, 243.04589.

Ethyl 2-fluoro-2-(3-((3-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)acetate
The title compound was prepared following General Procedure GP2 using (3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)boronic acid (84.9 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs$_2$CO$_3$ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%).

Physical appearance: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.44 (dq, $J$ = 2.8, 0.9 Hz, 1H), 7.96 – 7.91 (m, 1H), 7.48 (td, $J$ = 7.9, 0.9 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.32 – 7.29 (m, 1H), 7.21 (ddt, $J$ = 8.1, 2.2, 1.0 Hz, 1H), 7.05 (dt, $J$ = 8.6, 0.7 Hz, 1H), 5.81 (d, $J$ = 47.6 Hz, 1H), 4.34 – 4.18 (m, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.09 (d, $J$ = 27.0 Hz), 165.39 (d, $J$ = 1.0 Hz), 153.39, 145.41 (q, $J$ = 4.4 Hz), 136.83 (q, $J$ = 3.2 Hz), 136.15 (d, $J$ = 20.9 Hz), 124.97, 123.36 (d, $J$ = 6.6 Hz), 122.55 (d, $J$ = 1.9 Hz), 122.27, 121.86 (q, $J$ = 34.3 Hz), 119.56 (d, $J$ = 6.8 Hz), 111.57, 88.72 (d, $J$ = 187.0 Hz), 62.03, 14.03; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -61.71, -182.11 (d, $J$ = 47.6 Hz); IR (film, cm$^{-1}$) $\nu$ 3005, 1751, 1280, 1126, 1064; HRMS (ESI) $m/z$ calculated for C$_{16}$H$_{14}$F$_4$NO$_3$ [M + H]$^+$ 344.09043, Found, 344.09054.

2-Fluoro-2-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)acetic acid

Physical appearance: White Solid (Yield = 70% based on two steps). $^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 8.39 (s, 1H), 7.95 (d, $J$ = 10.8 Hz, 1H), 7.67 – 7.52 (m, 4H), 6.88 (d, $J$ = 8.6 Hz, 1H), 5.89 (d, $J$ = 47.9 Hz, 1H), 3.95 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.27 (d, $J$ = 27.5 Hz), 164.26, 152.25, 145.91 – 142.06 (m), 136.23 (q, $J$ = 3.1 Hz), 134.61 (d, $J$ = 20.8 Hz), 129.28, 123.81, 122.60 (d, $J$ = 6.4 Hz), 121.77 (d, $J$ = 1.7 Hz), 121.34 – 120.82 (m), 118.59 (d, $J$ = 6.7 Hz), 110.83, 87.17 (d, $J$ = 188.1 Hz), 28.68. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -61.68 (s) -182.15 (d, $J$ = 47.7 Hz); IR (film, cm$^{-1}$) $\nu$ 3735, 2361, 2341, 1748, 1329. HRMS (ESI) $m/z$ calculated for C$_{14}$H$_8$F$_4$NO$_3$ [M – H], 316.05913. Found, 316.0591.

Ethyl 2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-2-fluoroacetate
The title compound was prepared following General Procedure GP2 using (4-(2H-1,2,3-triazol-2-yl)phenyl)boronic acid (56.7 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol %) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol %).

Physical appearance: Colourless oil. ^1H NMR (400 MHz, Methanol-d₄) δ 8.17 – 8.10 (m, 2H), 7.93 (s, 2H), 7.65 – 7.59 (m, 2H), 5.98 (d, J = 47.2 Hz, 1H), 4.40 – 4.10 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, Methanol-d₄) δ 170.00 (d, J = 28.0 Hz), 137.32, 135.39 (d, J = 20.6 Hz), 129.14 (d, J = 6.2 Hz), 120.04, 89.90 (d, J = 183.6 Hz), 62.99, 14.31. ^19F NMR (376 MHz, Methanol-d₄) δ -180.95 (d, J = 47.2 Hz). IR (neat, cm⁻¹) ν 1935, 1556, 1138, 1096; HRMS (ESI) m/z calculated for C₁₂H₁₃FN₃O₂ [M + H]^+ for 250.09863, Found, 250.09874.

2-(4-(2H-1,2,3-Triazol-2-yl)phenyl)-2-fluoroacetic acid

Physical appearance: White solid (yield: 40%, based on two steps). Mp: 140 – 142 °C; ^1H NMR (500 MHz, Acetonitrile-d₃) δ 8.30 (d, J = 8.0 Hz, 2H), 8.09 (s, 2H), 7.82 – 7.75 (m, 2H), 6.12 (d, J = 47.2 Hz, 1H); ^13C NMR (101 MHz, Methanol-d₄) δ 170.41 (d, J = 27.4 Hz), 140.35, 135.86, 134.42 (d, J = 20.7 Hz), 127.67 (d, J = 5.8 Hz), 118.57, 88.45 (d, J = 182.8 Hz); ^19F NMR (470 MHz, Acetonitrile-d₃) δ -178.45 (d, J = 47.2 Hz); IR (neat, cm⁻¹) ν 2849, 1736, 1118, 1066; HRMS (ESI) m/z calculated for C₁₀H₇FN₃O₂ [M − H]⁻, 220.05278, Found, 220.05232.

Ethyl 2-(3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-2-fluoroacetate

The title compound was prepared following General Procedure GP2 using (3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)boronic acid (64.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL,
0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol %) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16 mg, 20 mol %).

**Physical appearance:** Colourless oil. **¹H NMR** (500 MHz, CDCl₃) δ 7.56 (dt, J = 2.5, 1.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.48 – 7.43 (m, 1H), 6.02 (s, 1H), 5.83 (d, J = 47.5 Hz, 1H), 4.33 – 4.17 (m, 2H), 2.34 – 2.28 (m, 6H), 1.27 (t, J = 7.1 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 168.53 (d, J = 27.2 Hz), 149.78, 140.71, 139.86, 135.71 (d, J = 20.7 Hz), 129.92, 125.97 (d, J = 1.9 Hz), 125.38 (d, J = 6.4 Hz), 123.06 (d, J = 6.7 Hz), 107.80, 89.21 (d, J = 186.9 Hz), 62.45, 14.45, 13.90, 12.86. **¹⁹F NMR** (470 MHz, CDCl₃) δ -181.63 (d, J = 47.6 Hz). **IR** (film, cm⁻¹) ʋ 1935, 1710, 1201; **HRMS** (ESI) m/z calculated for C₁₅H₁₇FN₂O₂ [M + H]^+ for 277.13468, Found, 277.13473.

2-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)phenyl)-2-fluoroacetic acid

**Physical appearance:** White solid (yield: 60%, based on two steps). **Mp:** 122 – 125 °C; **¹H NMR** (400 MHz, Methanol-d₄) δ 7.61 – 7.53 (m, 3H), 7.51 (d, J = 2.6 Hz, 1H), 6.09 (1, 1H), 5.97 (d, J = 47.6 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H); **¹³C NMR** (101 MHz, Methanol-d₄) δ 170.18 (d, J = 26.8 Hz), 149.30, 140.51, 139.63, 136.58 (d, J = 20.7 Hz), 129.38, 126.70 – 125.12 (m), 122.97, 106.80, 88.39 (d, J = 183.4 Hz), 11.76, 10.76; **¹⁹F NMR** (376 MHz, Methanol-d₄) δ -181.91 (d, J = 47.7 Hz); **IR** (film, cm⁻¹) ʋ 2917, 2849, 1745, 1148; **HRMS** (ESI) m/z calculated for C₁₃H₁₄FN₂O₂ [M + H]^+, 249.10338, Found, 249.10327.

Ethyl 2-fluoro-2-(4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)acetate
The title compound was prepared following General Procedure GP2 (4-(1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)boronic acid (104 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-tert-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%).

**Physical appearance:** Colourless Oil. ¹H NMR (500 MHz, CDCl₃) δ 7.52 – 7.47 (m, 2H), 7.42 – 7.37 (m, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.14 – 7.12 (m, 2H), 6.75 (s, 1H), 5.82 (d, J = 47.6 Hz, 1H), 4.27 (qq, J = 10.8, 7.1 Hz, 2H), 2.39 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 167.99 (d, J = 27.2 Hz), 144.92, 144.26 – 142.70 (m), 140.22 (d, J = 2.4 Hz), 139.37, 134.30 (d, J = 20.9 Hz), 129.53, 128.68, 127.28 (d, J = 6.4 Hz), 125.60, 124.69 – 117.40 (m), 105.69 (d, J = 2.4 Hz), 88.64 (d, J = 186.8 Hz), 62.09, 29.72, 21.32, 14.03; ¹⁹F NMR (470 MHz, CDCl₃) δ -62.33, -181.94 (d, J = 48.7 Hz); IR (film, cm⁻¹) v 2985, 1759, 1235, 1131; HRMS (ESI) m/z calculated for C₂₁H₁₉F₄N₂O₂ [M + H]^+, 407.13772, Found, 407.13719

2-Fluoro-2-(4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)acetic acid

**Physical appearance:** White solid (yield: 41%, based on two steps). **Mp:** 148 – 152 °C. ¹H NMR (400 MHz, Methanol-d₄) δ 7.46 – 7.40 (m, 2H), 7.31 – 7.24 (m, 2H), 7.09 – 7.02 (m, 4H), 6.77 (s, 1H), 5.82 (d, J = 47.6 Hz, 1H), 2.23 (s, 3H); ¹⁹F NMR (376 MHz, Methanol-d₄) δ -63.77, -181.72 (d, J = 47.9 Hz); ¹³C NMR (101 MHz, Methanol-d₄) δ 170.12 (d, J = 27.1 Hz), 145.49, -142.98 (q, J = 38.5 Hz), 139.96 (d, J = 2.3 Hz), 139.38, 135.72 (d, J = 20.6 Hz), 129.09, 128.59, 127.23 (d, J = 6.2 Hz), 125.92, 125.58, 121.31 (q, J = 290.3 Hz), 105.0, 88.30 (d, J = 183.4 Hz), 19.86; IR (film, cm⁻¹) v 2918, 2360, 1748, 1510, 1475, 1456; HRMS (ESI) m/z calculated for C₁₅H₁₄F₄N₂O₂ [M + H]^+, 379.10642, Found, 379.10639.

2-Fluoro-2-(4-(4-((1-isoproxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)acetic acid
The title compound was prepared following General Procedure GP2 using (4-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)boronic acid (111.1 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol%). The title compound (60.4 mg, 72% yield) was isolated as a brown solid.

Physical appearance: brown solid (yield: 72%). Mp: 140 – 142 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.69 (dd, J = 8.4, 4.2 Hz, 4H), 7.52 (d, J = 7.9 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.82 (d, J = 47.5 Hz, 1H), 5.00 (m, 1H), 1.59 (s, 6H), 1.13 (d, J = 6.2 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ: 195.41, 173.17, 171.80 (d, J = 28.9 Hz), 160.05, 139.18, 137.31 (d, J = 20.4 Hz), 132.32, 130.09, 129.87, 126.27 (d, J = 6.6 Hz), 117.24, 88.35 (d, J = 188.8 Hz), 79.48, 69.49, 25.36, 21.51; ¹⁹F NMR (376 MHz, CDCl₃) δ: -183.28 (d, J = 47.8 Hz); IR (film, cm⁻¹) ν: 2985, 2361, 1718, 1558, 1503, 1252, 1146, 680; HRMS (ESI) m/z calculated for [M + H]⁺, 403.15514, Found, 403.15535.

2-(3-Bromophenyl)-2-fluoroacetic acid

The title compound was prepared following General Procedure GP1 using (3-bromophenyl)boronic acid (60.2 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol%). The title compound (35.0 mg, 58% yield) was isolated as a brown solid.

Physical appearance: Brown Solid (yield: 58%). Mp: 81 – 83 °C; ¹H NMR (400 MHz, CDCl₃) δ: 10.10 (bs, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 8.0, 2.0 Hz, 1H), 7.34 (dd, J = 7.8, 1.5 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 5.71 (d, J = Hz, H); ¹³C NMR (100 MHz, CDCl₃) δ: 173.7 (d, J =27.3 Hz), 135.4 (d, J = 21.2 Hz), 133.0 (d, J = 2.1 Hz), 130.5, 129.5 (d, J =7.1 Hz), 125.1 (d, J = 6.0 Hz), 122.9, 87.3 (d, J = 178.3 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -
183.16 (d, $J = 47.1$ Hz); IR (film, cm$^{-1}$) ν 3035, 1759, 1689, 156, 818; HRMS (ESI) $m/z$ calculated for $C_8H_5BrFO_2$ [M – H$^-]$, 230.94624. Found, 230.94586.

2-(4-Bromophenyl)-2-flouroacetic acid$^3$

![Chemical Structure](image)

The title compound was prepared following General Procedure GP1 using (4-bromophenyl)boronic acid (60.3 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs$_2$CO$_3$ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (36.3 mg, 52% yield) was isolated as a brown solid.

**Physical appearance:** Brown solid (yield: 52%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 10.44 (bs, 1H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 5.80 (d, $J = 47.2$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 173.8 (d, $J = 27.4$ Hz), 132.4 (d, $J = 21.1$ Hz), 132.1, 128.2 (d, $J = 6.1$ Hz), 124.3 (d, $J = 2.9$ Hz), 88.2 (d, $J = 175.4$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -182.3 (d, $J = 47.2$ Hz). The physical data were identical in all respects to those previously reported.$^3$

2-Fluoro-2-(3-iodophenyl)acetic acid

![Chemical Structure](image)

The title compound was prepared following General Procedure GP1 (3-iodophenyl)boronic acid (74.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs$_2$CO$_3$ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (16.6 mg, 20 mol%). The title compound (42.0 mg, 50% yield) was isolated as a white solid.

**Physical appearance:** White Solid (yield: 50%). Mp: 102 – 104 °C; $^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$: 7.83 (s, 1H), 7.77 (d, $J = 8.7$ Hz, 1H), 7.48 (d, $J = 6.8$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 5.83 (d, $J = 47.6$ Hz, 1H). $^{13}$C NMR (101 MHz, Methanol-$d_4$) $\delta$: 171.6 (d, $J = 27.4$ Hz), 139.7, 138.8 (d, $J = 20.6$ Hz), 136.7 (d, $J = 6.4$ Hz), 127.1 (d, $J = 6.1$ Hz), 89.5 (d, $J = 183.2$ Hz); $^{19}$F NMR (376 MHz, Methanol-$d_4$) $\delta$ -181.77 (d, $J = 47.8$ Hz); IR (film, cm$^{-1}$) ν
3021, 2613, 1689, 1766, 1703. **HRMS (ESI)** m/z calculated for C₈H₅FIO₂ [M – H]⁻ for 278.93237, Found, 278.93228.

2-Fluoro-2-(m-tolyl)acetic acid⁴

![2-Fluoro-2-(m-tolyl)acetic acid](image)

The title compound was prepared following General Procedure GP1 using m-tolylboronic acid (40.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (36.3 mg, 74% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 74%). **¹H NMR** (400 MHz, CDCl₃) δ: 10.16 (bs, 1H), 7.26 – 7.12 (m, 4H), 5.70 (d, J = 48.8 Hz, 1H), 2.30 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ: 174.4 (d, J = 28.1 Hz), 138.8, 133.3 (d, J = 20.1 Hz), 130.8 (d, J = 2.4 Hz), 128.8, 127.3 (d, J = 6.1 Hz), 123.9 (d, J = 6.3 Hz), 88.9 (d, J = 186.2 Hz), 21.4; **¹⁹F NMR** (376 MHz, CDCl₃) δ -180.3 (d, J = 48.9 Hz). The physical data were identical in all respects to those previously reported.⁴

2-Fluoro-4-(p-tolyl)acetic acid⁴

![2-Fluoro-4-(p-tolyl)acetic acid](image)

The title compound was prepared following General Procedure GP1 using p-tolylboronic acid (40.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (36.3 mg, 72% yield) was isolated as a white solid.³

**Physical appearance:** White solid (yield: 72%). **¹H NMR** (400 MHz, CDCl₃) δ: 7.11 (d, 2H), 7.30 (d, 2H), 5.45 (d, J = 47.6 Hz, 1H), 2.15 (s, 3H); **¹⁹F NMR** (376 MHz, CDCl₃) δ: 178.4 (d, J = 47.4 Hz); The physical data were identical in all respects to those previously⁴

2-Fluoro-2-(o-tolyl)acetic acid⁵

![2-Fluoro-2-(o-tolyl)acetic acid](image)
The title compound was prepared following General Procedure GP1 using o-tolylboronic acid (40.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), Cul (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (15.1 mg, 30% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 30%). $^1$H NMR (400 MHz, CDCl₃) δ: 7.18-7.28 (m, 4H), 5.48 (d, $J = 48.2$ Hz, 1H), 2.28 (t, 3H); $^{19}$F NMR (376 MHz, CDCl₃) δ: 178.8 (d, $J = 48.4$ Hz). The physical data were identical in all respects to those previously reported.$^5$

**2-Fluoro-2-phenylacetic acid**

![Structure of 2-Fluoro-2-phenylacetic acid](image)

The title compound was prepared following General Procedure GP1 using phenylboronic acid (36.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 µL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), Cul (11.4 mg, 20 mol%) and 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine (24.1 mg, 20 mol%). The title compound (27.3 mg, 59% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 59%). $^1$H NMR (400 MHz, CDCl₃) δ: 8.67 (bs, 1H), 7.46 – 7.31 (m, 5H), 5.75 (d, $J = Hz$, 1H); $^{13}$C NMR (100 MHz, CDCl₃) δ: 173.8 (d, $J = 27.8$ Hz), 133.4 (d, $J = 20.6$ Hz), 130.0 (d $J = 2.2$ Hz), 128.9, 126.7 (d, $J = 5.9$ Hz), 88.8 (d, $J = 186.8$ Hz); $^{19}$F NMR (376 MHz, CDCl₃) δ -180.8 (d, $J = 47.5$ Hz). The physical data were identical in all respects to those previously reported.$^2$

**Ethyl 2-diazo-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate**

![Structure of Ethyl 2-diazo-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate](image)
To a mixture of methyl 2-(4-(6-methoxypyridin-3-yl)phenyl)acetate (10 mmol, 1 equiv.) and p-ABSA (12 mmol, 1.2 equiv.) in anhydrous MeCN (30 mL), DBU (14 mmol, 1.4 equiv.) was added at 0°C. The reaction mixture was stirred at r.t overnight. Upon the complete consumption of the starting materials, the reaction mixture was diluted with distilled water (20 mL), followed by extraction with Et₂O (3 × 10 mL). After washing with 10% NH₄Cl solution (3×10 mL) and brine (3×10 mL), the combined organic extracts were dried over MgSO₄, concentrated and chromatographed EtOAc:Hexane (10:90) to yield the diazoester.

**Physical appearance:** Orange solid. **Mp:** 135 – 137 °C; **¹H NMR** (400 MHz, CDCl₃) δ: 8.39 (dd, J = 2.7, 0.8 Hz, 1H), 7.79 (dd, J = 8.6, 2.6 Hz, 1H), 7.56 (bs, 4H), 6.82 (dd, J = 8.6, 0.7 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ: 165.5, 163.7, 144.8, 137.2, 135.4, 129.3, 127.1, 124.5, 110.9, 53.6, 52.1. **IR** (film, cm⁻¹) ν 3012, 2951, 2094, 1686, 1160, 815. **HRMS** (ESI) m/z calculated for C₁₅H₁₄N₃O₃ [M + H]⁺, 284.10297 Found, 284.10294.

Methyl 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate

![Methyl 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate](image)

In a 20 mL falcon tube was charged with methyl 2-diazo-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate (0.3 mmol) in 2mL of DCM and cooled to 0°C. HF pyridine (70 %) (0.36 mmol) was then added slowly. The reaction was temperature was raised to r.t after gas evolution. The reaction was monitored by TLC until completion. The reaction was then quenched with NaHCO₃ and the organic layer was extracted with DCM (3 x 5 mL). The organic layer was dried over MgSO₄, concentrated and chromatographed EtOAc:Hexane (10:90).

**Physical appearance:** White solid. **Mp:** 64 – 65 °C; **¹H NMR** (400 MHz, CDCl₃) δ: 8.32 (dd, J = 2.6, 0.8 Hz, 1H), 7.71 (dd, J = 8.6, 2.6 Hz, 1H), 7.54 – 7.43 (m, 4H), 6.76 (dd, J = 8.6, 0.7 Hz, 2H), 5.76 (d, J = 48.2 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ: 168.9 (d, J = 27.2 Hz), 163.9, 145.1, 139.4 (d, J = 3.2 Hz), 137.4, 133.1 (d, J =20.0 Hz), 129.2, 127.3 (d, J = 6.2 Hz), 127.1, 111.0, 89.1 (d, J = 184.3 Hz), 53.6, 52.8; **¹⁹F NMR** (376 MHz, CDCl₃) δ -179.9 (d, J = 48.2 Hz); **IR** (film, cm⁻¹) ν 3014, 2949, 1498, 1195, 822; **HRMS** (ESI) m/z calculated for C₁₅H₁₅FNO₃ [M + H]⁺, 276.10305. Found, 276.10293.

2-Fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetic acid
In a 50 mL round bottom flask, methyl 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate (5 mmol, 1.0 equiv.) was added to a mixture of MeOH (15 mL, 0.3 M) and 1 M K₂CO₃ aq. (15 mL) and stirred at r.t until TLC showed consumption of starting material. The reaction was then poured into 1 M HCl aq. to acidify to pH 5, and the aqueous phase was extracted with Et₂O (3 × 10 mL), washed with brine (10 mL), dried over MgSO₄. The resulting gum was then washed with pentane, until a white free-flowing white solid formed.

**Physical appearance:** White solid (yield: 45% (over 3 steps)). **Mp:** 150 – 153 °C; **¹H NMR** (400 MHz, Methanol-­d₄) δ: 8.44 – 8.38 (m, 1H), 7.97 (dd, J = 8.7, 2.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.6 Hz, 1H), 5.91 (d, J = 48.7 Hz, 1H), 3.97 (s, 3H); **¹³C NMR** (100 MHz, Methanol-­d₄) δ: 170.8 (d, J = 27.9 Hz), 163.9, 144.5, 138.7 (d, J = 2.1 Hz), 134.3 (d, J = 20.1 Hz), 127.2 (d, J = 6.1 Hz), 126.5, 110.4, 88.8 (d, J = 180.2 Hz), 52.8; **¹⁹F NMR** (376 MHz, Methanol-­d₄) -179.6 (d, J = 47.9 Hz); **IR** (film, cm⁻¹) v 2360, 1736, 1607, 1041, 825; **HRMS** (ESI) m/z calculated for C₁₄H₁₃FNO₃ [M + H]^+ 262.08740 Found, 262.08731.
2-Fluoro-2-(6-methoxynaphthalen-2-yl)acetic acid

An oven-dried Schlenk tube containing a magnetic stir bar was charged with Pd(OAc)$_2$ (5.6 mg, 0.025 mmol, 5 mol%), PPh$_3$ (26.2 mg, 0.10 mmol, 20 mol%), boronic acid (1.0 mmol, 2.0 equiv.), and K$_3$PO$_4$·3 H$_2$O (400 mg, 1.5 mmol, 3.0 equiv.). The Schlenk tube was sealed with a rubber septum and then evacuated and backfilled with N$_2$ three times. Toluene (5.0 mL) was added through the septum via syringe and the resulting mixture was stirred at r.t for 5 min. Ethyl $\alpha$-bromo-$\alpha$-fluoroacetate (92.5 mg, 0.50 mmol, 1.0 equiv.) was then added dropwise via syringe. The Schlenk tube was sealed and the mixture was heated at 100 °C with vigorous stirring for 3 h. The mixture was then allowed to cool to r.t and quenched with H$_2$O (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (20 mL), dried with MgSO$_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel (Pentane–EtOAc, 50:1) to give the title the ester product. The ester was then dissolved in a 2:1 MeOH and aqueous K$_2$CO$_3$ (5-10 equiv.) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). The resulting mixture was then acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et$_2$O (3 x 20 mL) and washed with Brine (2 x 20 mL). The organic extracts were dried using MgSO$_4$ and were then concentrated under vacuum and washed with pentane, resulting in the title compound as a white solid.

Physical appearance: White solid (yield: 50% over two steps). Mp: 150 – 152 °C; $^1$H NMR (400 MHz, Methanol-$d_4$) δ: 7.78 (t, $J = 2.0$ Hz, 1H), 7.70 (t, $J = 9.4$ Hz, 2H), 7.40 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.16 (d, $J = 2.5$ Hz, 1H), 7.07 (dd, $J = 8.9$, 2.5 Hz, 1H), 5.86 (d, 1H, $J = 47.8$ Hz), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, Methanol-$d_4$) δ: 158.58, 135.19 (d, $J = 1.8$ Hz) 130.03 (d, $J = 20.4$ Hz), 129.29, 128.44, 127.12, 126.40 (d, $J = 6.8$ Hz) 123.95 (d, $J = 5.1$ Hz), 119.09, 105.32, 89.35 (d, $J = 181.3$ Hz) 54.39. $^{19}$F NMR (376 MHz, Methanol-$d_4$) δ: -177.22 (d, $J = 48.0$ Hz); IR (film, cm$^{-1}$) v.3157, 1764, 1703, 1606. 1267, 1234, 1051, 1029, 815; HRMS (ESI) $m/z$ calculated for C$_{13}$H$_{10}$FO$_3$ [M – H]$^-$ for 233.06195, Found, 233.06185.
2-Fluoro-2-(naphthalen-1-yl)acetic acid

Step 1: A flame dried flask containing a solution of arylacetic acid (559 mg, 3.0 mmol, 1.0 equiv.) and TBSCl (1.04 g, 6.90 mmol, 2.3 equiv.) in THF (0.50 M) was cooled to 0 °C. LiHMDS (1.0 M in THF; 2.2 equiv.) was added slowly and the resulting mixture was stirred at 0 °C for 15 min and then warmed to r.t. It was then stirred at r.t over night before volatiles were removed in vacuo. The crude was taken up in hexane and solid LiCl was filtered off. The filtrate was washed with hexane and the combined organic fractions were concentrated to dryness in vacuo.

Step 2: The residue was dissolved in MeCN (0.50 M) and slowly added to a solution of Selectfluor (2.30 g, 6.50 mmol, 1.3 equiv.) in MeCN (30 mL) at r.t. After stirring for 15 min at r.t the reaction mixture was poured into aq. HCl (1.0 M, 10 mL/mmol acid). This solution was extracted with Et₂O (2x) and the combined Et₂O layers were then extracted with NaOH (1.0 M; 2x). The combined aqueous layers were washed with Et₂O (2x), acidified with HCl (6.0 M) until pH = 1 and extracted with Et₂O (3x). The combined organic fractions were dried over MgSO₄ and concentrated to dryness in vacuo to give the desired aryl(fluoro)acetic acid. The title compound (817 mg, 80%) as a white solid.

Physical appearance: White solid (yield: 80%). ¹H NMR (400 MHz, CDCl₃): δ = 9.55 (br s, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.96 -7.89 (m, 2H), 7.64 (d, J = 7.2 Hz, 1H), 7.61 -7.52 (m, 2H), 7.52 -7.47 (m, 1H), 6.42 (d, J = 46.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 174.3 (d, J = 28.6 Hz), 133.9, 130.8 (d, J = 2.2 Hz), 130.5 (d, J = 1.5 Hz), 129.3 (d, J = 18.3 Hz), 128.9, 127.2, 126.9 (d, J = 8.1 Hz), 126.3, 125.0, 123.5 (d, J = 1.5 Hz), 88.0 (d, J = 186.3 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ = -178.7 (d, J = 46.3 Hz); The physical data were identical in all respects to those previously reported.
Ethyl 2-fluoro-2-(4-(1-(4-(methylsulfonyl)phenyl)-1H-pyrazol-5-yl)phenyl)acetate

To a dry screw-cap tube equipped with a magnetic stirrer, 30 mg of 1-(4-(methylsulfonyl)phenyl)-1H-pyrazole (0.13 mmol, 1.1 equiv.), 1.5 mg of Pd(OAc)$_2$ (0.006 mmol, 5 mol%), 5 mg of L-proline (0.012 mmol, 10 mol%), 18 mg of K$_2$CO$_3$ (0.18 mmol, 1.5 equiv.), 17 mg of Ag$_2$CO$_3$ (0.06 mmol, 0.5 equiv.) and 4 mg of PivOH (0.04 mmol, 30 mol%) were added. After 3 cycles of vacuum/nitrogen, ethyl 2-fluoro-2-(4-iodophenyl)acetate (0.12 mmol, 1.0 eq.) and DMA (2 mL) were added. The tube was closed and stirred at 100 °C overnight. The reaction was cooled, diluted with a solution of saturated LiCl and extracted with Et$_2$O (3 x 10 mL), dried over MgSO$_4$. Solvent was removed under reduced pressure and the corresponding crude compound was purified using column chromatography (hexane/EtOAc = 7:3).

**Physical appearance:** Colourless oil (yield: 43%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.00 – 7.96 (m, 2H), 7.58 – 7.52 (m, 4H), 7.34 – 7.30 (m, 2H), 6.84 (s, 1H), 5.84 (d, $J = 47.5$ Hz, 1H), 4.36 – 4.25 (m, 2H), 3.10 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.91 (d, $J = 26.8$ Hz), 144.98 – 144.30 (m), 144.24, 143.15, 140.19, 135.84 (d, $J = 20.6$ Hz), 129.68, 129.16, 128.70, 127.15 (d, $J = 6.5$ Hz), 125.73, 120.86 (q, $J = 269.3$ Hz), 107.13, 88.65 (d, $J = 187.3$ Hz), 62.22, 44.49, 14.09; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.55 (s), -182.97 (d, $J = 47.7$ Hz). IR (film, cm$^{-1}$) $\nu$ 2985, 1756, 1151, 1096; HRMS (ESI) $m/z$ calculated for: C$_{21}$H$_{18}$F$_4$N$_2$O$_4$SNa [M+ Na]$^+$, 493.08156, found, 493.08145.
2-Fluoro-2-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluormethyl)-1H-pyrazol-5-yl)phenyl)acetic acid

Ethyl 2-fluoro-2-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluormethyl)-1H-pyrazol-5-yl)phenyl)acetate (42 mg, 0.1 mmol, 1 equiv.) was dissolved in a 2:1 MeOH and aqueous K$_2$CO$_3$ (5 equiv.) (5 mL) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). The resulting mixture was then acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et$_2$O (3 x 5 mL) and washed with Brine (2 x 5 mL). The organic extracts were dried using MgSO$_4$ and were then concentrated under vacuum and washed with pentane, resulting in the titled compound in 76% yield.

**Physical appearance:** White solid (yield 76%). **Mp** = 158 °C. **^1H NMR** (400 MHz, Methanol-d$_4$) δ 7.97 – 7.85 (m, 2H), 7.55 – 7.46 (m, 2H), 7.42 (dd, $J = 8.2, 1.2$ Hz, 2H), 7.32 – 7.20 (m, 2H), 5.79 (d, $J = 47.7$ Hz, 1H), 3.06 (s, 3H); **^13C NMR** (101 MHz, Methanol-d$_4$) δ 170.22 (d, $J = 26.8$ Hz), 144.89, 143.97 (t, $J = 38.5$ Hz), 143.08, 140.71, 136.65 (d, $J = 20.5$ Hz), 129.61 (d, $J = 2.1$ Hz), 129.11, 128.41, 126.96 (d, $J = 6.1$ Hz), 125.94, 122.52, 119.86, 106.43, 88.50 (d, $J = 183.4$ Hz), 42.77; **^19F NMR** (376 MHz, Methanol-d$_4$) δ -63.94, -181.97 (d, $J = 48.4$ Hz). **IR** (film, cm$^{-1}$) ν 2919, 2361, 1749, 1136, 1095. **HRMS** (ESI) m/z calculated for C$_{19}$H$_{14}$F$_4$N$_2$O$_4$SNa [M+ Na]$^+$, 465.05026, found, 465.05000.
Synthesis of (difluoromethyl)arenes.

4-(Difluoromethyl)-1,1'-biphenyl\(^3\)

![Image of 4-(Difluoromethyl)-1,1'-biphenyl]

The title compound was prepared following General Procedure GP3 using 4-(difluoromethyl)-1,1'-biphenyl (55 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (48 mg, 78% yield) was isolated as a white solid.

**Physical appearance:** White solid (yield: 78 %). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.68 (d, \(J = 8.0\) Hz, 2H), 7.64 – 7.55 (m, 4H), 7.47 (dd, \(J = 8.4, 6.8\) Hz, 2H), 7.44 – 7.34 (m, 1H), 6.70 (t, \(J = 56.2\) Hz, 1H); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -110.35 (d, \(J = 55.9\) Hz). The physical data were identical in all respects to those previously reported.\(^3\)

1-(Difluoromethyl)-4-phenoxybenzene\(^6\)

![Image of 1-(Difluoromethyl)-4-phenoxybenzene]

The title compound was prepared following General Procedure GP3 using 4-phenoxybenzaldehyde (59 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (28 mg, 43% yield) was isolated as a colourless oil.

**Physical appearance:** Colourless oil (yield: 43%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.39 (d, \(J = 8.2\) Hz, 2H), 7.30 (t, \(J = 7.7\) Hz, 2H), 7.09 (t, \(J = 7.4\) Hz, 1H), 6.97 (d, \(J = 8.1\) Hz, 4H), 6.55 (t, \(J = 58.3\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 159.6, 156.2, 130.0, 128.9 (t, \(J = 22.4\) Hz) 127.3 (t, \(J = 6.1\) Hz), 124.1, 119.6, 118.2, 114.6 (t, \(J = 235.8\) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\): -109.0 (d, \(J = 56.4\) Hz). The physical data were identical in all respects to those previously reported.\(^6\)
1-(Difluoromethyl)-3,5-dimethylbenzene\textsuperscript{7}

\[
\begin{array}{c}
\text{Me} \\
\text{CF}_2\text{H} \\
\text{Me}
\end{array}
\]

The title compound was prepared following General Procedure GP3 using 3,5-dimethylbenzaldehyde (40 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (25 mg, 54\%) was isolated as a yellow oil.

**Physical appearance:** Yellow Oil (yield: 54\%). \textsuperscript{7} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.12 (d, \(J = 5.4\) Hz, 3H), 6.58 (t, \(J = 56.6\) Hz, 1H), 2.37 (s, 6H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) -110.17 (d, \(J = 56.6\) Hz); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 138.44, 132.27 (t, \(J = 2.1\) Hz), 123.20 (t, \(J = 6.0\) Hz), 114.99 (t, \(J = 238.4\) Hz), 21.23. The physical data were identical in all respects to those previously reported.\textsuperscript{7}

2-(Difluoromethyl)-1,4-dimethylbenzene\textsuperscript{6}

\[
\begin{array}{c}
\text{Me} \\
\text{CF}_2\text{H} \\
\text{Me}
\end{array}
\]

The title compound was prepared following General Procedure GP3 using 3,5-dimethylbenzaldehyde (40 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (20 mg, 43\%) was isolated as yellow oil.

**Physical appearance:** Yellow oil (yield: 43\%). \textsuperscript{6} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35 (s, 1H), 7.23 – 7.17 (m, 1H), 7.14 (d, \(J = 7.8\) Hz, 1H), 6.76 (t, \(J = 55.6\) Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 135.61, 133.01 (t, \(J = 4.6\) Hz), 131.99 (t, \(J = 20.6\) Hz), 131.21 (d, \(J = 2.2\) Hz), 130.97, 126.35 (t, \(J = 7.3\) Hz), 114.53 (t, \(J = 237.7\) Hz), 20.91, 17.99. \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) -112.87 (d, \(J = 56.0\) Hz); The physical data were identical in all respects to those previously reported.\textsuperscript{6}
1-\((\text{tert-Butyl})-4\)-(difluoromethyl)benzene$^6$

The title compound was prepared following General Procedure GP3 using 4-(tert-butyl)benzaldehyde (49 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (29 mg, 52\%) was isolated as a colourless oil.

**Physical appearance:** Colourless oil (yield: 52\%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.58 – 7.41 (m, 4H), 6.66 (t, $J$ = 56.6 Hz, 1H), 1.36 (s, 9H); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -109.87 (d, $J$ = 56.6 Hz). The physical data were identical in all respects to those previously reported.$^6$

1-(Difluoromethyl)-2-methoxybenzene$^3$

The title compound was prepared following General Procedure GP3 using 2-methoxybenzaldehyde (41 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (19 mg, 40\%) was isolated as a yellow oil.

**Physical appearance:** Yellow oil (yield: 40\%). $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.59 (d, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.4 Hz, 1H), 7.06 (t, $J$ = 7.4 Hz, 1H), 6.99 (t, $J$ = 55.8 Hz, 1H), 6.96 (d, $J$ = 8.5 Hz, 1H), 3.88 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ =157.2 (t, $J$ = 6.0 Hz), 131.9 (t, $J$ = 1.8 Hz), 126.1 (t, $J$ = 6.0 Hz), 122.6 (t, $J$ = 22.2 Hz), 120.5, 111.6 (t, $J$ = 234.9 Hz), 110.8, 55.5; $^{19}$F NMR (376 MHz, CDCl$_3$): δ = -115.3 (d, $J$ = 55.9 Hz). The physical data were identical in all respects to those previously reported.$^3$
1-(Difluoromethyl)-3-methoxybenzene

The title compound was prepared following General Procedure GP3 using 3-methoxybenzaldehyde (41 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (24 mg, 50%) was isolated as a colourless oil.

Physical appearance: Colourless Oil (yield = 50%) \textit{^1}H NMR (400 MHz, CDCl$_3$) $\delta$: $\delta = 7.38$ (t, $J = 7.9$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 7.06 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.63 (t, $J = 56.5$ Hz, 1H), 3.85 (s, 3H); \textit{^13}C NMR (101 MHz, CDCl$_3$): $\delta = 159.8$, 135.7 (t, $J = 22.0$ Hz), 129.8, 117.8 (t, $J = 6.2$ Hz), 116.6 (t, $J = 1.8$ Hz), 114.6 (t, $J = 239.2$ Hz), 110.7 (t, $J = 5.9$ Hz), 55.3; \textit{^19}F NMR (376 MHz, CDCl$_3$): $\delta = -110.7$ (d, $J = 55.9$ Hz). The physical data were identical in all respects to those previously reported.$^3$

1-(Difluoromethyl)-4-(trifluoromethyl)benzene

The title compound was prepared following General Procedure GP3 using 4-(trifluoromethyl)benzaldehyde (52 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (36 mg, 61%) was isolated as a colourless oil.

Physical appearance: Colourless oil (yield: 61%) \textit{^1}H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J = 8.1$ Hz, 2H), 7.56 (d, $J = 8.1$ Hz, 2H), 6.62 (t, $J = 56.0$ Hz, 1H); \textit{^13}C NMR (101 MHz, CDCl$_3$) $\delta$ 137.79 (d, $J = 1.4$ Hz), 132.85 (d, $J = 32.7$ Hz), 126.08 (t, $J = 6.1$ Hz), 125.78 (q, $J = 3.8$ Hz), 122.61 (q, $J = 271.5$ Hz), 113.70 (t, $J = 240.0$ Hz); \textit{^19}F NMR (376 MHz, CDCl$_3$) $\delta$ -63.04 (s), -112.37 (d, $J = 55.8$ Hz); The physical data were identical in all respects to those previously reported.$^6$
5-(Difluoromethyl)-2-methoxybenzaldehyde

![Chemical Structure](attachment:chemical.png)

To a mixture of 2-bromo-4-(difluoromethyl)-1-methoxybenzene (450 mg, 1.9 mmol) in THF (20 mL) at -78 °C was added nBuLi (1.03 mL, 2.47 mmol, 2.4 M in hexanes). The mixture was stirred at -78 °C for 30 min and then DMF (208 mg, 2.85 mmol) was added. The mixture was stirred at -78 °C for an additional 30 min and then quenched with saturated NH₄Cl (20 mL). The mixture was extracted with EtOAc (2x) and the combined organic layers were washed with brine (2x), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate to yield the title compound as a white solid (150 mg, 42% yield).

**Physical appearance:** White solid (yield: 42%).

**¹H NMR** (400 MHz, CDCl₃) δ: 10.40 (s, 1H), 7.89 (dt, J = 2.5, 1.2 Hz, 1H), 7.65 (ddt, J = 8.8, 2.3, 1.1 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.56 (t, J = 56.4 Hz, 1H), 7.65 (ddt, J = 8.8, 2.3, 1.1 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.56 (t, J = 56.4 Hz, 1H), 3.91 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ: 188.87, 163.17, 132.82 (t, J = 5.4 Hz), 127.04, 126.39 (t, J = 6.3 Hz), 124.62, 116.47, 114.10, 112.14, 111.73, 56.00. **¹⁹F NMR** (376 MHz, CDCl₃) δ: -109.59 (d, J = 56.7 Hz). **IR** (film, cm⁻¹) ν: 1980, 1461, 1257, 1180.

4-(Difluoromethyl)dibenzo[b,d]furan

![Chemical Structure](attachment:chemical.png)

The title compound was prepared following General Procedure GP3 using dibenzo[b,d]furan-4-carbaldehyde (59 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (29 mg, 45%) was isolated as a colourless oil.

**Physical appearance:** Colourless oil (yield: 45%).

**¹H NMR** (400 MHz, CDCl₃) δ: 7.91 (d, 1H, J = 7.6 Hz), 7.83 (d, 1H), 7.55 (dd, 1H, J = 7.6 Hz, J = 1.1 Hz), 7.53 (d, 1H J = 7.6 Hz), 7.47 – 7.30 (td, 1H, J = 8.3 Hz, J = 1.1 Hz), 7.33 – 7.21 (m, 1H), 7.11 (t, 1H, J = Hz); **¹⁹F NMR** (376 MHz, CDCl₃) δ: -113.01 (d, J = 54.9 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ: 156.33, 153.03 (t, J = 5.2 Hz), 127.83, 125.17, 123.72 (t, J = 6.2 Hz), 123.37, 123.25, 123.10 (t, J = 1.6 Hz), 122.74, 120.79, 118.47 (t, J = 23.3 Hz), 111.95, 111.91 (t, J = 236.6 Hz). The physical data were identical in all respects to those previously reported.⁶
2-(3-(Difluoromethyl)phenoxy)-5-(trifluoromethyl)pyridine

To trifluoromethyl)pyridin-2-yl)oxy)benzaldehyde (0.3 g, 1.12 mmol) in CH₂Cl₂ (4 mL) was added Deoxo-Fluor (497 mg, 2.25 mmol) and heated at 40 °C for 16 hours. Starting material aldehyde remained and therefore the reaction mixture was charged with additional Deoxo-Fluor (497 mg, 2.25 mmol) and heated at 40 °C for 6 hours, followed by an additional addition of Deoxo-Fluor (497 mg, 2.25 mmol) and heating at 40 °C for 16 hours. Saturated NaHCO₃ was added and the mixture was extracted with CH₂Cl₂ (2x) and the combined organic fraction was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate, followed by purification by preparative reverse-phase HPLC (Column: Gemini-C18, 100*21.2 mm 5 µm; Mobile phase: MeCN-H₂O (0.1% FA); Gradient: 55% to 65%; Flow rate: 25 ml/min) to yield the title compound as a yellow oil (108 mg, 33% yield).

Physical appearance: Yellow oil (yield: 33%). ¹H NMR (400 MHz, CDCl₃) δ: 8.35 (dt, J = 2.6, 1.0 Hz, 1H), 7.85 (dd, J = 8.6, 2.5 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.32 (dp, J = 7.8, 1.2 Hz, 1H), 7.21 – 7.17 (m, 1H), 6.98 (dt, J = 8.7, 0.8 Hz, 1H), 6.59 (t, J = 56.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 165.32, 153.36, 145.40 (q, J = 4.4 Hz), 136.90 (q, J = 3.2 Hz), 136.20 (t, J = 22.7 Hz), 130.22, 123.88 (t, J = 1.8 Hz), 123.50 (q, J = 271.6 Hz), 122.56 (t, J = 6.2 Hz), 118.83 (t, J = 6.2 Hz), 116.36, 113.98, 111.61 (d, J = 3.1 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ: -61.71, -111.43 (d, J = 56.4 Hz); IR (film, cm⁻¹) ν 2916, 1448, 1395, 1030. HRMS (ESI) m/z calculated for C₁₃H₉F₅NO [M + Na]⁺ 290.05988 Found, 290.05998.
2-(4-(Difluoromethyl)phenyl)-2H-1,2,3-triazole

To a mixture of 4-(2H-1,2,3-triazol-2-yl)benzaldehyde (400 mg, 2.3 mmol) in CH₂Cl₂ (10 mL) was added EtOH (21.3 mg, 0.462 mmol) and Deoxo-Fluor (869 mg, 3.93 mmol) and heated at 40 °C for 18 hours. The reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate to yield the title compound as a white solid (131 mg, 29% yield).

**Physical appearance:** White solid (yield: 29%). ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, J = 7.9, 2H), 7.78 (s, 2H), 7.57 (t, J = 8.7 Hz, 2H), 6.63 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 136.05, 133.37, 126.82 (t, J = 6.1 Hz), 119.04, 114.20 (t, J = 239.1 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -110.77 (d, J = 56.3 Hz).

1-(3-(Difluoromethyl)phenyl)-3,5-dimethyl-1H-pyrazole

To a mixture of 3-(3,5-dimethyl-1H-pyrazol-1-yl)benzaldehyde (200 mg, 1 mmol) in CH₂Cl₂ (10 mL) was added EtOH (9.2 mg, 0.20 mmol) and Deoxo-Fluor (376 mg, 1.70 mmol) and heated at 40 °C for 18 hours. The reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate to yield the titled compound as a yellow oil (88 mg, 40% yield).

**Physical appearance:** Yellow oil (yield: 40%). ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.51 (m, 1H), 7.49 – 7.37 (m, 3H), 6.60 (t, J = 56.3 Hz, 1H), 5.94 (s, 1H), 2.24 (d, J = 0.8 Hz, 3H), 2.22 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -111.30 (d, J = 56.2 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 149.53, 140.35, 139.49, 135.48 (t, J = 22.7 Hz), 129.49, 126.46 (t, J = 1.9 Hz), 124.05 (t, J = 6.0 Hz), 121.79 (t, J = 6.3 Hz), 117.62 – 110.90 (m), 107.56, 13.49, 12.46; IR (film, cm⁻¹) ν 2982, 1452, 1275, 1059, 1024. HRMS (ESI) m/z calculated for C₁₂H₁₃F₂N₂[M + H]⁺, 223.10413, Found 223.10418.
Isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate\(^8\)

The title compound was prepared following General Procedure GP 4 using isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate (37.6 mg, 0.1 mmol, 1.0 equiv.), Mn(tmp)Cl (2.5 mol%), PhIO (0.33 mmol, 3.3 equiv.) Et\(_3\)N·3HF (0.12 mmol, 1.2 equiv.) and DCE (1 mL) and purified using column chromatography (DCM/n-pentane)

**Physical appearance:** White solid (yield: 22%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.77 (d, \(J = 7.9\) Hz, 2H), 7.71 (d, \(J = 8.5\) Hz, 2H), 7.56 (d, \(J = 7.6\) Hz, 2H), 6.85 (d, \(J = 8.5\) Hz, 2H), 6.67 (t, \(J = 56.2\) Hz, 1H), 5.56-4.36 (m, 1H), 1.62 (s, 6H), 1.18 (d, \(J = 6.1\) Hz, 6 H); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -111.64 (d, \(J = 56.1\) Hz). The physical data were identical in all respects to those previously reported.\(^8\)

5-(4-(Difluoromethyl)phenyl)-2-methoxypyridine

The title compound was prepared following General Procedure GP 4 using 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetic acid (26.1 mg, 0.1 mmol, 1.0 equiv.), Mn(tmp)Cl (2.5 mol%), PhIO (0.33 mmol, 3.3 equiv.) Et\(_3\)N·3HF (0.12 mmol, 1.2 equiv.) and DCE (1 mL) and purified using column chromatography (DCM/n-pentane)

**Physical appearance:** White Solid (yield: 21%). \(\text{Mp}: 59 – 62\) °C; \(^1\)H NMR (400 MHz, Methanol-\(d_4\)) \(\delta\) 8.47 – 8.27 (m, 1H), 7.96 (dd, \(J = 8.7, 2.6\) Hz, 1H), 7.70 (d, \(J = 8.6\) Hz, 2H), 7.61 (d, \(J = 8.2\) Hz, 2H), 6.89 (d, \(J = 8.6\) Hz, 1H), 6.80 (t, \(J = 52.6\) Hz, 1H), 3.95 (s, 3H); \(^{13}\)C NMR (101 MHz, Methanol-\(d_4\)) \(\delta\) 165.56, 146.12, 141.49, 139.13, 135.22 (t, \(J = 22.4\) Hz), 130.64, 129.53 – 125.64 (m), 116.36 (t, \(J = 236.6\) Hz), 111.94, 54.31; \(^{19}\)F NMR (376 MHz, Methanol-\(d_4\)) \(\delta\) -111.83 (d, \(J = 56.3\) Hz); IR (film, cm\(^{-1}\)) \(\nu\) 3010, 1402, 1256, 1120. HRMS (ESI) \(m/z\) calculated for \(\text{C}_{13}\text{H}_{12}\text{F}_{2}\text{NO} [\text{M} + \text{H}]^+, 236.08924, \text{Found}, 236.08813.

2-(Difluoromethyl)-6-methoxynaphthalene\(^9\)
A dried Schlenk tube was charged with (0.2 mmol), PDFA (356 mg, 1.0 mmol), 1,3-Cyclopentadione (19.6 mg, 0.2 mmol), Ca(OH)$_2$ (59.3 mg, 0.8 mmol), Pd(PPh$_3$)$_4$ (46.2 mg, 0.04 mmol), H$_2$O (9 mg, 0.5 mmol) and p-xylene (2 mL). The mixture was stirred at 90 °C for 3 h under N$_2$ atmosphere. After being cooled to room temperature, the mixture was subjected to flash column chromatography (petroleum ether / dichloromethane) to afford the pure product as a white solid.

**Physical appearance:** White solid (yield: 42%). $^1$H NMR (200 MHz, CDCl$_3$) δ 7.95 – 7.76 (m, 3H), 7.57 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.26 – 7.15 (m, 2H), 6.78 (t, $J = 56.5$ Hz, 1H), 3.95 (s, 3H); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -109.13 (d, $J = 56.5$ Hz). The physical data were identical in all respects to those previously reported.$^9$

1-(Difluoromethyl)naphthalene$^6$

The title compound was prepared following General Procedure GP3 using 1-naphthaldehyde (47 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (27 mg, 55%) was isolated as a white solid.

**Physical appearance:** White solid (yield: 55%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.09 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 1H), 7.85 – 7.81 (m, 1H), 7.65 – 7.57 (m, 1H), 7.56 – 7.39 (m, 3H), 7.05 (s, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -110.88 (d, $J = 55.4$ Hz). The physical data were identical in all respects to those previously reported.$^6$
5-(4-(Difluoromethyl)phenyl)-1-(4-(methylsulfonl)phenyl)-3-(trifluoromethyl)-1H-pyrazole\textsuperscript{8}

\begin{center}
\includegraphics[width=0.2\textwidth]{5-(4-(Difluoromethyl)phenyl)-1-(4-(methylsulfonl)phenyl)-3-(trifluoromethyl)-1H-pyrazole.png}
\end{center}

Synthesised according to a reported procedure.\textsuperscript{8}

**Physical appearance:** Colourless oil (yield: 20\%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.02 – 7.96 (m, 2H), 7.61 – 7.52 (m, 4H), 7.40 – 7.34 (m, 2H), 6.86 (s, 1H), 6.70 (t, 1H), 3.10 (s, 3H); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) δ -62.55, -111.83 (d, J = 56.3 Hz). The physical data were identical in all respects to those previously reported.\textsuperscript{8}

\textbf{(8R,9S,13S,14S)-3-(Difluromethoxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one}\textsuperscript{10}

\begin{center}
\includegraphics[width=0.2\textwidth]{(8R,9S,13S,14S)-3-(Difluromethoxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one.png}
\end{center}

In a 10 mL round-bottomed flask was placed estrone (136 mg, 0.5 mmol, 1.0 equiv.), acetonitrile (1.0 mL) and 6M aqueous KOH (1.0 mL). The mixture was stirred rapidly at r.t and HCF\textsubscript{2}OTf (0.21 mL, 1.5 mmol, 3.0 equiv.) was added at once at 0 °C. The mixture was stirred vigorously for 2 minutes, warmed to r.t and stirred for a further 20 minutes. The reaction was diluted with H\textsubscript{2}O (10 mL) and extracted with ether (2 x 10 mL). The combined organic layers were dried over MgSO\textsubscript{4}, concentrated, and purified by silica gel chromatography.

**Physical appearance:** White solid (yield: 43%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.29 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.5, 1H), 6.88 (s , 1H), 6.50 (t, J = 74.3 Hz, 1H), 2.94 (dd, J = 9.0, 4.3 Hz, 2H), 2.58 – 2.47 (m, 1H), 2.42 – 2.37 (m, 1H), 2.27 (t, J = 10.6 Hz, 1H), 2.1 (ddd, J = 23.7, 13.3, 5.8 Hz, 2H), 1.98 (d, J = 10.4 Hz, 1H), 1.70 – 1.41 (m, 7H), 0.94 (s, 3H).\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) δ -80.36 (d, J = 74.6 Hz). The physical data were identical in all respects to those previously reported.\textsuperscript{10}
Preparation of Boronic Acid Precursors

Boronic acid precursors used in the synthesis towards 8a-8h, 8j and 8p-8v were purchased from commercial vendors.

Boronic acid precursors used in the synthesis towards 8i and 8k-8m were kindly donated by Pfizer inc.

Boronic acid precursors used in the synthesis of 8n and 8o were synthesized according to known literature procedures.

\((4-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)boronic acid\)

Prepared according to a known literature procedure\(^\text{11}\)

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.30 (s, 2H), 7.94 (d, \(J = 7.6\) Hz, 2H), 7.76 – 7.69 (m, 2H), 7.67 – 7.60 (m, 2H), 6.94 – 6.87 (m, 2H), 5.04 – 4.93 (m, 1H), 1.61 (s, 6H), 1.16 (d, \(J = 6.3\) Hz, 6H). \(\text{HRMS (ESI, m/z)}\) calcd [M - H]\(^-\) for 369.15149, Found, 369.15117. The physical data were identical in all respects to those previously reported.\(^\text{11}\) \textbf{Note: if \(^1\text{H NMR} \) is taken in CDCl\(_3\) peaks corresponding to the boroxine trimer may be observed!}

\((4-(1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)boronic acid\)

Prepared according to a known literature procedure\(^\text{12}\)

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.76 (d, \(J = 8.4\) Hz, 2H), 7.21 (d, \(J = 8.4\) Hz, 2H), 7.07-7.15 (m, 5H), 2.21 (s, 3H); \(\text{LRMS: (ESI}, \text{ m/z})\) 347.1 ([M+H]\(^+\), 100%). The physical data were identical in all respects to those previously reported.\(^\text{12}\) \textbf{Note: if \(^1\text{H NMR} \) is taken in CDCl\(_3\) peaks corresponding to the boroxine trimer may be observed!}
In Situ Preparation of Iodine(III) dicarboxylates

In each radiochemical reaction, α-aryl-α-fluoroacetic acid and iodosylbenzene were pre-stirred in acetonitrile, solvent was removed under vacuum a priori to $^{18}$F being dispensed into the reaction vial. To prove that iodine(III) dicarboxylate intermediate is formed during the pre-stirring step, the model radiochemistry substrate 2-fluoro-2-(4-phenoxyphenyl)acetic acid Iodine(III) dicarboxylate was fully characterised. For other substrates where appropriate, the Iodine (III) dicarboxylate intermediate complex formation was confirmed by $^1$H NMR and $^{19}$F NMR to prove a similar reaction mechanism. Notable shifts of both the benzylic alpha proton and fluorine were observed in $^1$H and $^{19}$F NMR respectively. Iodine(III) dicarboxylates diastereoisomer have peaks which stem from the stereogenic centre of the benzylic Ar-CFHCO$_2$H carbon which were made in a racemic fashion (Scheme SI-8).

Scheme SI-8 Synthesis of Iodine(III) dicarboxylates.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, $J = 6.7$ Hz, 2H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.40 (dt, $J = 24.6$, 8.2 Hz, 8H), 7.29 (s, 2H), 7.16 (t, $J = 7.4$ Hz, 2H), 7.04 (d, $J = 1.1$ Hz, 4H), 6.94 (d, $J = 8.4$ Hz, 4H), 5.70 (d, $J = 48.0$ Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.69 (d, $J = 27.1$ Hz), 158.59, 156.58, 134.80, 132.43, 131.33, 130.02, 129.36 (d, $J = 189.0$ Hz), 128.41, 124.01, 122.96, 119.52, 118.60, 88.33 (d, $J = 189.0$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) -173.83 (d, $J = 48.1$ Hz, 1F), -173.85 (d, $J = 48.1$ Hz, 1F); HRMS (ESI) $m/z$ calculated for [M + Na]$^+$, 717.05561, Found, 717.05588. IR (film, cm$^{-1}$) ν: 3062, 1755, 1677, 1232, 1025.
Phenyl- $\lambda^3$-iodanediyl bis(2-[(1,1'-biphenyl)-4-yl]-2-fluoroacetate)

![Chemical structure]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 – 7.89 (m, 2H), 7.56 (dd, $J$ = 11.0, 7.9 Hz, 10H), 7.46 (t, $J$ = 7.5 Hz, 5H), 7.42 – 7.36 (m, 6H), 5.77 (d, 49.0 Hz, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -175.90 (d, $J$ = 48.7 Hz, 2H).

Phenyl- $\lambda^3$-iodanediyl bis(2-fluoro-2-(4-(trifluoromethyl)phenyl)acetate)

![Chemical structure]

$^1$H NMR (400 MHz, Acetonitrile-$d_3$) $\delta$ 8.06 – 7.86 (m, 2H), 7.73 – 7.55 (m, 5H), 7.56 – 7.33 (m, 6H), 5.92 (d, $J$ = 47.9 Hz, 2H). $^{19}$F NMR (376 MHz, Acetonitrile-$d_3$) $\delta$ -178.89 (d, $J$ = 48.0 Hz).

Phenyl- $\lambda^3$-iodanediyl bis(2-fluoro-2-(3-methoxyphenyl)acetate)

![Chemical structure]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 – 7.73 (m, 2H), 7.51 – 7.38 (m, 1H), 7.37 – 7.27 (m, 2H), 7.23 – 7.12 (m, 2H), 6.93 – 6.65 (m, 6H), 5.61 (d, $J$ = 48.4 Hz, 2H), 3.68 (s, 6H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -176.59 (d, $J$ = 48.7 Hz).
Phenyl- $\lambda$3-iodanediyl bis(2-(3,5-dimethylphenyl)-2-fluoroacetate)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J = 11.2$ Hz, 2H), 7.52 – 7.46 (m, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 6.88 (d, $J = 20.8$ Hz, 6H), 5.56 (d, $J = 48.7$ Hz, 2H), 2.20 (s, 12H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -174.65 (d, $J = 48.7$ Hz, 1F), -174.66 (d, $J = 48.7$ Hz, 1F).

Phenyl- $\lambda$3-iodanediyl bis(2-fluoro-2-(2-methoxyphenyl)acetate)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.96 (s, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.37 (dt, $J = 21.5$, 8.1 Hz, 4H), 7.24 – 7.13 (m, 2H), 7.00 – 6.84 (m, 4H), 6.06 (d, $J = 48.0$ Hz, 2H), 3.77 (s, 6H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -173.78 (d, $J = 47.4$ Hz).

Phenyl- $\lambda$3-iodanediyl bis(2-fluoro-2-(6-methoxynaphthalen-2-yl)acetate)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (dq, $J = 8.4$, 1.9, 1.4 Hz, 2H), 7.60 (ddd, $J = 16.7$, 8.6, 2.3 Hz, 6H), 7.33 – 7.24 (m, 3H), 7.11 – 7.01 (m, 6H), 5.75 (d, $J = 48.5$ Hz, 2H), 3.84 (s, 6H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -173.76 (d, $J = 48.7$), -173.75 (d, $J = 48.6$ Hz).
Phenyl-3-iodanediyl bis(2-fluoro-2-(naphthalen-1-yl)acetate)

\[
\begin{align*}
\text{Phenyl-3-iodanediyl bis(2-fluoro-2-(naphthalen-1-yl)acetate)} \\
\end{align*}
\]

\[
^1H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 8.03 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.0 Hz, 4H), 7.46 (ddt, J = 33.1, 24.3, 9.9 Hz, 11H), 7.15 – 7.05 (m, 2H), 6.27 (d, J = 47.6 Hz, 2H). \text{\textsuperscript{19}F NMR (376 MHz, CDCl}_3\text{)} \delta -174.22 (d, J = 47.6 Hz).
\]

Phenyl-3-iodanediyl bis(2-(2,5-dimethylphenyl)-2-fluoroacetate)

\[
\begin{align*}
\text{Phenyl-3-iodanediyl bis(2-(2,5-dimethylphenyl)-2-fluoroacetate)} \\
\end{align*}
\]

\[
^1H \text{ NMR (400 MHz, Acetonitrile-d}_3\text{)} \delta 8.03 – 7.96 (m, 1H), 7.72 – 7.60 (m, 1H), 7.56 – 7.42 (m, 2H), 7.38 – 7.19 (m, 1H), 7.22 – 6.97 (m, 6H), 6.07 – 5.82 (d, J = 48.2 Hz, 2H), 2.26 (s, 6H), 2.22 (s, 6H), 2.26 (s, 6H). \text{\textsuperscript{19}F NMR (376 MHz, Acetonitrile-d}_3\text{)} \delta -174.41 (d, J = 48.1 Hz).
\]

Phenyl-3-iodanediyl bis(2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-2-fluoroacetate)

\[
\begin{align*}
\text{Phenyl-3-iodanediyl bis(2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-2-fluoroacetate)} \\
\end{align*}
\]

\[
^1H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 8.03 (d, J = 8.7 Hz, 4H), 7.94 – 7.88 (m, 2H), 7.83 (s, 4H), 7.53 (d, J = 15.0 Hz, 1H), 7.46 – 7.34 (m, 6H), 5.77 (d, J = 48.3 Hz, 2H). \text{\textsuperscript{19}F NMR (376 MHz, CDCl}_3\text{)} \delta -176.96 (d, J = 48.3 Hz, 1F), -176.98 (d, J = 48.3 Hz, 1F).
\]

Phenyl-3-iodanediyl bis(2-fluoro-2-(3-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)acetate)
^1H NMR (400 MHz, CDCl₃) δ 8.34 (s, 2H), 7.91 – 7.65 (m, 4H), 7.65 – 7.22 (m, 6H), 7.17 – 7.05 (m, 5H), 6.94 (d, J = 8.6 Hz, 2H), 5.67 (d, J = 48.3 Hz, 2H).  

^19F NMR (376 MHz, CDCl₃) δ -61.64 (s), -178.45 (d, J = 48.4 Hz). -178.45 (d, J = 48.4 Hz).

Phenyl-3-iodanediyl bis(2-(dibenzo[b,d]furan-4-yl)-2-fluoroacetate)

^1H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 7.6 Hz, 4H), 7.62 – 7.54 (m, 2H), 7.47 – 7.33 (m, 4H), 7.33 – 7.23 (m, 4H), 7.23 – 7.13 (m, 3H), 6.95 – 6.88 (m, 2H), 6.23 (d, J = 47.8 Hz, 2H).  

^19F NMR (376 MHz, CDCl₃) δ -176.02 (d, J = 47.8 Hz), -176.04 (d, J = 47.8 Hz).

Diisopropyl 2,2'-%((4,4'-((phenyl-3-iodanediyl)bis(oxy))bis(1-fluoro-2-oxoethane-2,1-diyl))bis(benzoyl))bis(4,1-phenylene))bis(oxy))bis(2-methylpropanoate)

^1H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 23.7, 8.2 Hz, 8H), 7.51 (t, J = 7.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 5H), 6.79 (d, J = 8.6 Hz, 4H), 5.73 (d, J = 48.3 Hz, 2H), 5.02 (p, J = 6.4 Hz, 2H), 1.60 (s, 12H), 1.14 (d, J = 6.1 Hz, 12H).  

^19F NMR (376 MHz, CDCl₃) δ -179.56 (d, J = 48.3 Hz), -179.58 (d, J = 48.3 Hz).
Phenyl-\(\underline{3}\)-iodanediyl bis(2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate)

\[\text{Phenyl-3-iodanediyl bis(2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate)}\]

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 8.39\) (d, \(J = 2.3\) Hz, 2H), 7.94 (d, \(J = 8.3\) Hz, 2H), 7.78 (dd, \(J = 8.6, 2.5\) Hz, 2H), 7.61 – 7.52 (m, 2H), 7.48 (d, \(J = 8.1\) Hz, 4H), 7.39 (d, \(J = 8.0\) Hz, 5H), 6.84 (d, \(J = 8.6\) Hz, 2H), 5.76 (d, \(J = 48.4\) Hz, 2H), 3.99 (s, 6H).

\(^{19}\text{F NMR}\) (376 MHz, CDCl\(_3\)) \(\delta -176.27\) (d, \(J = 48.4\) Hz).

Phenyl-\(\underline{3}\)-iodanediyl bis(2-fluoro-2-(((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[\(a\)]phenanthren-3-yl)oxy)acetate)

\[\text{Phenyl-3-iodanediyl bis(2-fluoro-2-(((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[\(a\)]phenanthren-3-yl)oxy)acetate)}\]

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 8.13 – 8.03\) (m, 2H), 7.63 – 7.54 (m, 1H), 7.47 (dd, \(J = 8.5, 7.2\) Hz, 2H), 7.14 (d, \(J = 8.7\) Hz, 2H), 6.81 – 6.62 (m, 4H), 5.80 (dd, \(J = 60.3, 1.1\) Hz, 2H), 2.81 (dd, \(J = 8.9, 4.2\) Hz, 4H), 2.44 (dd, \(J = 18.9, 8.6\) Hz, 2H), 2.36 – 2.27 (m, 2H), 2.19 (d, \(J = 11.1\) Hz, 2H), 2.13 – 1.84 (m, 8H), 1.63 – 1.29 (m, 12H), 0.84 (s, 6H).

\(^{19}\text{F NMR}\) (376 MHz, CDCl\(_3\)) \(\delta -125.93\) (d, \(J = 60.6\) Hz), -125.94 (d, \(J = 60.6\) Hz).

Iodine(III) Dicarboxylates Formation Competition Experiment

\[\begin{align*}
1a & \quad 0.2 \text{ mmol} \\
2a & \quad 0.2 \text{ mmol}
\end{align*}\]

\[\text{1a (0.2 mmol) and 2a (0.2 mmol) were placed in 4 mL vial with PIDA (0.1 mmol), CDCl\(_3\) (2 mL) was added and the reaction was stirred for 20 minutes at 50 °C prior to }^{19}\text{F NMR analysis.}\]
S6: Radiochemistry:

$\text{[}^{18}\text{F}]\text{Fluoride was produced by Alliance Medical (UK) via the } ^{18}\text{O}(\text{p,n})^{18}\text{F reaction and delivered as } ^{18}\text{F}\text{fluoride in } ^{18}\text{O}-\text{enriched-water. Radiosynthesis and azeotropic drying was performed on a NanoTek microfluidic device (Advion).}$

**Procedure for preparation of a solution of $[^{18}\text{F}]\text{TEAF in MeCN:}$**

A solution of tetraethylammonium bicarbonate (9 mg) in 1 mL of MeCN/H$_2$O, 4:1 was freshly prepared. $[^{18}\text{F}]\text{Fluoride (3.0 - 4.0 GBq) was separated from } ^{18}\text{O}-\text{enriched-water using a Chromafix PSHCO3 } ^{18}\text{F separation cartridge (45 mg) and subsequently released with 900 μL (in 6 x 150 μL portions) of the tetraethylammonium bicarbonate solution into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 μL) under a flow of N$_2$ at 105 °C. The dried $[^{18}\text{F}]\text{TEAF residue was re-dissolved in anhydrous MeCN (500 - 1000 μL).}$

**Optimisation**

**Table SI-2 Optimisation studies for the $[^{18}\text{F}]\text{fluorodecarboxylation of 8b}$**

| Entry | Starting Material (mmol) | Protocol | Solvent | PhIO (mmol) | RCC$^a$ ($n =2)^b$ |
|-------|--------------------------|----------|---------|-------------|------------------|
| 1     | $8b$ (0.11)              | A        | MeCN$^c$| 0.33        | 3% ± 1%          |
| 2     | $8b$ (0.11)              | A        | MeCN    | 0.02        | 6% ± 1%          |
| 3     | $8b$ (0.11)              | A        | DMF     | 0.02        | 7% ± 2%          |
| 4     | $8b$ (0.055)             | A        | DMF$^d$ | 0.02        | 22% ± 7%         |
| 5     | $5b$ (0.014)             | B        | DMF$^d$ | -           | $40\% ± 10\%^e$ |
| 6     | $5b$ (0.014)             | B        | DMF$^d$ | -           | 0% ± 0%$^f$      |
Into a 3 mL vial was weighed 9a (0.014 mmol), 5a (0.014 mmol) and manganese catalyst (2 mgs). To this vial was dispensed \[^{18}\text{F}]\text{TEAF} (20–30 MBq) in a solution of anhydrous MeCN. The MeCN was removed at 100 °C under a flow of nitrogen. Upon cooling, DMF (300 µL) was added to the vial and the reaction was stirred at 50 °C for 20 minutes. The reaction was quenched with water (200 µL) and an aliquot was removed for analysis by radioTLC and radioHPLC for radiochemical conversion and product identity. Analysis was performed using a Waters Nova-Pak C18 column (4 µm, 3.9 x 150 mm) at a flow rate 1 mL/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using DCM/MeOH (9:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.

**General Procedure for the Small Scale \[^{18}\text{F}\]-Fluorination of substrates \[^{18}\text{F}]3a – \[^{18}\text{F}]3o, \[^{18}\text{F}]3w – \[^{18}\text{F}]3z, \[^{18}\text{F}]11a:**

Into a 3 mL vial was weighed substrate (0.014 mmol) and manganese catalyst (2 mgs). To this vial was dispensed \[^{18}\text{F}]\text{TEAF} (20–30 MBq) in a solution of anhydrous MeCN. The MeCN was removed at 100 °C under a flow of nitrogen. Upon cooling, DMF (300 µL) was added to the vial and the reaction was stirred at 50 °C for 20 minutes. The reaction was quenched with water (200 µL) and an aliquot was removed for analysis by radioTLC and radioHPLC for radiochemical conversion and product identity. Analysis was performed using a Waters Nova-Pak C18 column (4 µm, 3.9 x 150 mm) at a flow rate 1 mL/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using DCM/MeOH (9:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.
HPLC gradient A for small scale $^{18}$F-Fluorination of substrates $[^{18}$F]$3a - [^{18}$F]$3o$, $[^{18}$F]$3w - [^{18}$F]$3z$, $[^{18}$F]$11a$:

Water/MeCN, 1 mL/min, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm 0 - 1 min (5% MeCN) isocratic 1 - 10 min (5% MeCN to 95% MeCN) linear increase 10 - 14 min (95% MeCN) isocratic 14 - 15 min (95% MeCN to 5% MeCN) linear decrease 15 - 17 min (5% MeCN) isocratic.

Radio-HPLC of substrates $[^{18}$F]$3a - [^{18}$F]$3o$, $[^{18}$F]$3w - [^{18}$F]$3z$, $[^{18}$F]$11a$

Crude Radio-HPLC traces of the crude mixture following the general procedure, with authentic UV references overlaid are shown below. The solid black line indicates the UV trace for cold reference material and the solid red line is the crude radio-HPLC trace. All samples were run using HPLC gradient A.
The radiochemical conversion results are presented in the table below:

| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|--------------------------|
| 1        | 13%       | 10%                      |
| 2        | 14%       | 11%                      |
| 3        | 28%       | 28%                      |
| 4        | 30%       | 30%                      |

The radiochemical conversion + standard deviation is 20% ± 10%.

![Radiochemical Conversion Diagram](image)

**Figure SI-1** HPLC radio-trace of $[^{18}F]3a$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}$F reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 50%       | 50%                     |
| 2        | 37%       | 37%                     |
| 3        | 45%       | 45%                     |
| 4        | 37%       | 37%                     |
| 5        | 46%       | 46%                     |
| 6        | 53%       | 53%                     |
| 7        | 34%       | 34%                     |
| 8        | 22%       | 22%                     |
| 9        | 30%       | 30%                     |
| 10       | 43%       | 43%                     |

Radiochemical Conversion + Standard Deviation \(40\% \pm 9\%\)

**Figure SI-2** HPLC radio-trace of \[^{18}\text{F}]3\text{b}\) (red) overlaid with HPLC UV-trace (\(\lambda = 220\) nm) of \(^{19}\text{F}\) reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|--------------------------|
| 1        | 20%       | 20%                      |
| 2        | 20%       | 20%                      |
| 3        | 21%       | 19%                      |
| 4        | 27%       | 26%                      |

Radiochemical Conversion + Standard Deviation 21% ± 3%

**Figure SI-3** HPLC radio-trace of $[^{18}F]3c$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}F$ reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|--------------------------|
| 1        | 36%       | 34%                      |
| 2        | 33%       | 31%                      |
| 3        | 42%       | 37%                      |
| 4        | 36%       | 32%                      |

Radiochemical Conversion + Standard Deviation \(34\% \pm 3\%\)

Figure SI-4 HPLC radio-trace of \([^{18}\text{F}]3\text{d}\) (red) overlaid with HPLC UV-trace (\(\lambda = 220 \text{ nm}\)) of \(^{19}\text{F}\) reference compound (black).
**Reaction** | **Radio-TLC** | **Radiochemical Conversion**
--- | --- | ---
1 | 33% | 33%
2 | 29% | 29%
3 | 13% | 13%
4 | 36% | 36%
**Radiochemical Conversion + Standard Deviation** | **28% ± 10%**

**Figure SI-5** HPLC radio-trace of \[^{18}\text{F}]3e\) (red) overlaid with HPLC UV-trace (\(\lambda = 220\) nm) of \(^{19}\text{F}\) reference compound (black).
Reaction | Radio-TLC | Radiochemical Conversion
---|---|---
1 | 27% | 23%
2 | 26% | 21%
3 | 15% | 12%
4 | 8% | 7%
Radiochemical Conversion + Standard Deviation | 16% ± 7%

**Figure SI-6** HPLC radio-trace of [\(^{18}\text{F}\)]\(^{3f}\) (red) overlaid with HPLC UV-trace (\(\lambda = 220\) nm) of \(^{19}\text{F}\) reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|--------------------------|
| 1        | 23%       | 21% ± 5%                 |
| 2        | 22%       | 21% ± 5%                 |
| 3        | 26%       | 26% ± 5%                 |
| 4        | 14%       | 14% ± 5%                 |

Radiochemical Conversion + Standard Deviation 21% ± 5%

Figure SI-7 HPLC radio-trace of $[^{18}F]3g$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}$F reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 16%       | 5%                      |
| 2        | 9%        | 3%                      |
|          | Radiochemical Conversion + Standard Deviation | 4% ± 1% |

**Figure SI-8** HPLC radio-trace of $[^{18}\text{F}]3\text{h}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}\text{F}$ reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 10%       | 10%                     |
| 2        | 8%        | 8%                      |
| 3        | 8%        | 8%                      |
| 4        | 10%       | 10%                     |

Radiochemical Conversion + Standard Deviation \( 9\% \pm 1\% \)

**Figure SI-9** HPLC radio-trace of \([^{18}F]3i\) (red) overlaid with HPLC UV-trace \((\lambda = 220 \text{ nm})\) of \(^{19}\text{F}\) reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 27%       | 27%                     |
| 2        | 39%       | 39%                     |
| 3        | 31%       | 26%                     |
| 4        | 43%       | 35%                     |

Radiochemical Conversion + Standard Deviation: 32% ± 6%

![Figure SI-10](image_url) **Figure SI-10** HPLC radio-trace of [18F]3j (red) overlaid with HPLC UV-trace (λ = 220 nm) of 19F reference compound (black).
**Reaction** | **Radio-TLC** | **Radiochemical Conversion**
---|---|---
1 | 23% | 21% 
2 | 16% | 15% 
3 | 16% | 15% 
4 | 14% | 13% 

Radiochemical Conversion + Standard Deviation | **16% ± 4%**

**Figure SI-11** HPLC radio-trace of [\(^{18}\text{F}\)]\(^3\text{k} \) (red) overlaid with HPLC UV-trace (\( \lambda = 220 \text{ nm} \)) of \( ^{19}\text{F} \) reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 18%       | 11%                     |
| 2        | 24%       | 17%                     |
| 3        | 9%        | 9%                      |
| 4        | 8%        | 8%                      |

Radiochemical Conversion + Standard Deviation $12\% \pm 4\%$

Figure SI-12 HPLC radio-trace of $[{^{18}F}]3l$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}$F reference compound (black).
**Figure SI-13** HPLC radio-trace of \[^{18}\text{F}]3m\) (red) overlaid with HPLC UV-trace \((\lambda = 220 \text{ nm})\) of \(^{19}\text{F}\) reference compound (black).
The image contains a table and a diagram. The table shows the radiochemical conversion and standard deviation for different reactions, while the diagram illustrates an HPLC radio-trace of the [\(^{18}\text{F}\)]3n compound overlaid with a UV trace of a reference compound.

### Table: Radiochemical Conversion

| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 30%       | 30%                     |
| 2        | 19%       | 19%                     |
| 3        | 23%       | 23%                     |
| 4        | 12%       | 12%                     |
|          | **21% ± 6%** |                         |

**Figure SI-14.** HPLC radio-trace of [\(^{18}\text{F}\)]3n (red) overlaid with HPLC UV-trace (\(\lambda = 220\) nm) of \(^{19}\text{F}\) reference compound (black).
Reaction | Radio-TLC | Radiochemical Conversion
--- | --- | ---
1 | 23\% | 21\% 
2 | 31\% | 28\% 
3 | 33\% | 26\% 
4 | 26\% | 20\% 

Radiochemical Conversion + Standard Deviation | 23\% ± 3\%

**Figure SI-15** HPLC radio-trace of [\(F^{18}\)]3o (red) overlaid with HPLC UV-trace (\(\lambda = 220 \text{ nm}\)) of \(F^{18}\) reference compound (black).
Reaction | Radio-TLC | Radiochemical Conversion
---|---|---
1 | 30% | 30%
2 | 27% | 27%
3 | 7% | 7%
4 | 31% | 31%
Radiochemical Conversion + Standard Deviation | 24% ± 11%

Figure SI-16 HPLC radio-trace of $^{18}$F]3w (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}$F reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 40%       | 40%                     |
| 2        | 27%       | 27%                     |
| 3        | 22%       | 22%                     |
| 4        | 34%       | 34%                     |

Radiochemical Conversion + Standard Deviation 30% ± 8%

---

**Figure SI-17** HPLC radio-trace of $[^{18}F]3x$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $[^{18}F]$ reference compound (black).
Reaction | Radio-TLC | Radiochemical Conversion
--- | --- | ---
1 | 49% | 47%
2 | 42% | 39%
3 | 23% | 22%
4 | 36% | 34%

Radiochemical Conversion + Standard Deviation | 36% ± 10%

Figure SI-18 HPLC radio-trace of $^{18}$F3y (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}$F reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 18%       | 17%                     |
| 2        | 13%       | 12%                     |
| 3        | 16%       | 15%                     |

Radiochemical Conversion + Standard Deviation 15% ± 2%

**Figure SI-19** HPLC radio-trace of \(^{18}\text{F}3z\) (red) overlaid with HPLC UV-trace (\(\lambda = 220\) nm) of \(^{19}\text{F}\) reference compound (black).
| Reaction | Radio-TLC | Radiochemical Conversion |
|----------|-----------|-------------------------|
| 1        | 18%       | 18%                     |
| 2        | 31%       | 31%                     |
| 3        | 16%       | 16%                     |

Radiochemical Conversion + Standard Deviation **21% ± 6%**

**Figure SI-20** HPLC radio-trace of $[^{18}\text{F}]11\text{a}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of $^{19}\text{F}$ reference compound (black).
Re-optimisation for Large $^{18}$F dose applications:

**Elution Procedure:**

[$^{18}$F]Fluoride was separated from $^{18}$O-enriched-water using an anion exchange cartridge (Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm particle size, Waters) and released with A solution of Mn(tmp)Cl (8 mg) in 600 µL of anhydrous MeOH into a 5 mL V-vial containing a magnetic stir bar in the concentrator.

**Optimisation under Mn(tmp)$^{18}$F Elution Conditions:**

| Entry | Substrate (mmol) (5b) | Solvent | RCC ($n = 2$) |
|-------|------------------------|---------|---------------|
| 1     | 0.014                  | DMF     | 0%            |
| 2     | 0.014                  | CH$_3$CN | 4% ± 1%      |
| 3     | 0.014                  | DCM     | 0%            |
| 4     | 0.014                  | DCE     | 25% ± 6%     |
| 5     | 0.056                  | DCE     | 3% ± 1%      |
| 6$^a$ | 0.056                  | DCE     | 10% ± 1%     |
| 7     | 0.007                  | DCE     | 37% ± 0%     |

$^a$4 mg of Mn(tmp)Cl spiked into reaction mixture.
Re-optimisation for clinically relevant doses of $^{18}\text{F}$:

Elution Procedure:

$[^{18}\text{F}]$Fluoride was separated from $^{18}\text{O}$-enriched-water using an anion exchange cartridge (Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 μm particle size, Waters) and released with a solution of Mn(tmp)Cl (8 mg) in 600 μL of anhydrous MeOH into a 5 mL V-vial containing a magnetic stir bar in the concentrator.

Procedure for the $^{18}\text{F}$-fluorination of 5b under Batch Scale Isolation:

$[^{18}\text{F}]$Fluoride was separated from $^{18}\text{O}$-enriched-water using an anion exchange cartridge (Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 μm particle size, Waters) and released with a solution of Mn(tmp)Cl (8 mg) in 600 μL of anhydrous MeOH into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The methanol was then removed at 80 °C under a flow of $\text{N}_2$. Once dry, the Mn(tmp)$^{18}\text{F}$ was dissolved in DCM (1 mL) and transferred to a 5 mL vial. Upon transfer, the DCM was removed at 80 °C under a flow of $\text{N}_2$. Once dry, substrate (0.007 mmol) dissolved in DCE (300 μL) was added and the reaction stirred at 60 °C for 20 minutes. Upon completion, the DCE was removed at 70 °C under a flow of $\text{N}_2$. The crude material was dissolved in DMF (300 μL). Upon cooling, the crude solution was diluted in H$_2$O (6 mL) and eluted over a C18 SepPak cartridge (preconditioned with 2 mL MeOH followed by 10 mL H$_2$O). The 5 mL vial was rinsed again with 10% MeCN in H$_2$O (2 mL) and passed over the C18 SepPak cartridge. The desired product was then eluted of the C18 SepPak cartridge with MeCN (2 mL) upon with RadioHPLC analysis was carried out to confirm the radiochemical purity of the product. Analysis was performed using a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1 mL/min. The overall synthesis time was 60 minutes.
Starting Activity (MBq) & Eluted (MBq) & Activity after drying MeOH (MBq) & Activity after transfer and DCM drying (MBq) & Activity after C18 (MBq) & RCY (decay corrected) \\
841 & 720 & 704 & 594 & 67 & 12% \\

Molar Activity Calculation:

The Molar Activity of $[^{18}\text{F}]$1-(difluoromethyl)-4-phenoxybenzene was assessed by radio-HPLC, using an analytical Analysis was performed using a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1 mL/min under HPLC gradient A.

\[ y = 9,033,904.7115x + 0.7922 \]
\[ R^2 = 0.9999 \]

| Run          | MA (GBq/μmol) | Activity (MBq) | mmol         | Area (mAu) |
|--------------|---------------|----------------|--------------|------------|
| First injection | 3.22          | 3.07           | 9.52412E-07  | 8.604      |
| Second injection | 2.77         | 2.76           | 9.95915E-07  | 8.997      |
First Injection

\[ y = 9,033,904.7115x + 0.7922 \quad (y = \text{mAu, } x = \text{mmol}) \]
Area measured from isolated sample: 8.604 mAu
Activity of isolated sample: 3.07 MBq = 3.07E-03 GBq
mmol of isolated sample = 8.604/9,033,904 = 9.52412E-07 mmol
9.52412E-07 mmol = 9.52412E-04 µmol
MA = 0.00307/9.52412E-04 = 3.22 GBqµmol⁻¹

Second Injection

\[ y = 9,033,904.7115x + 0.7922 \quad (y = \text{mAu, } x = \text{mmol}) \]
Area measured from isolated sample: 8.997 mAu
Activity of isolated sample: 2.76 MBq = 2.76E-03 GBq
mmol of isolated sample = 8.997/9,033,904 = 9.95915E-07 mmol
9.95915E-07 mmol = 9.95915E-04 µmol
MA = 0.00276/9.95915E-04 = 2.77 GBqµmol⁻¹

Average

M.A = 3.0 GBq/µmol

Attempt at one-pot procedure with the aryl boron reagent, ethyl 1-fluoro-2-bromoacetate and \(^{18}\)F-fluoride

![Chemical reaction diagram]

| Entry | Copper source (0.06 mmol) | Additive (mmol) | Temperature (°C) | RCC (n = 2) |
|-------|---------------------------|-----------------|------------------|------------|
| 1     | CuI                       | TMEDA (0.1)     | r.t.             | 0%         |
| 2     | CuI                       | TMEDA (0.1)     | r.t.             | 0%         |
| 3     | Cu(II)OTf₂(py)₄           | n/a             | r.t.             | 0%         |
| 4     | Cu(II)OTf₂(py)₄           | n/a             | r.t.             | 0%         |
| 5     | [(iPr)CuCl]               | n/a             | r.t.             | 0%         |
| 6a    | [(iPr)CuCl]               | n/a             | r.t.             | 0%         |
| 7     | CuI                       | TMEDA (0.1)     | 90               | 0%         |
| 8     | CuI                       | TMEDA (0.1)     | 90               | 0%         |
References

1) W. Liu and J. T. Groves, Angewandte Chemie, 2013, 125, 6140.
2) S. Mizuta, I. S. Stenhagen, M. O’Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore and M. Huiban, Org. Lett., 2013, 15, 2648.
3) S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Wheelhouse, M. Tredwell and V. Gouverneur, Synlett, 2016, 27, 25.
4) F. Effenberger, S. Oßwald, Tetrahedron: Asymmetry, 2001, 12, 279
5) F. Zhang, J. Z. Song, Tetrahedron Lett., 2006, 47, 7641.
6) Z. Feng, Q. Min, X. Zhang, Org. Lett., 2015, 18, 44.
7) K. Aikawa, H. Serizawa, K. Ishii, K. Mikami, Org. Lett., 2016, 18, 3690.
8) H. Shi, A. Braun, L. Wang, S. H. Liang, N. Vasdev and T. Ritter, Angew. Chem., Int. Ed., 2016, 55, 10786.
9) X. Deng, J. Lin, J. Xiao, Org. Lett., 2016, 18, 4384.
10) P. S. Fier and J. F. Hartwig, Angew. Chem. Int. Ed., 2013, 52, 2092
11) Y. Xiao, Q. Min, C. Xu, R. Wang and X. Zhang, Angew. Chem. Int. Ed., 2016, 55, 5837-5841.
12) Y. Chen, P. R. Murray, A. T. Davies and M. C. Willis, J. Am. Chem. Soc., 2018, 140, 8781.
$	ext{PhO}$

$	ext{CO}_2\text{H}$

$^1\text{H NMR (400 MHz)}$

CDCl$_3$
^{13}C NMR (101 MHz) 
CDCl₃
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^1\text{H NMR (400 MHz)}$

$\text{CDCl}_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)  
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)  
CDCl$_3$
$^{19}$F NMR (376 MHz) 
CDCl$_3$
$^{13}$C NMR (101 MHz)
$CDCl_3$
$^1$H NMR (400 MHz)
$d_6$-DMSO
$^{13}$C NMR (101 MHz)  
$\text{d}_6$-DMSO
$^{19}$F NMR (376 MHz)  
d$_6$-DMSO
$^1$H NMR (400 MHz)
$\text{CDCl}_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)
d$_4$-MeOD

HOD
d$_4$-MeOD
19F NMR (376 MHz)
CDCl₃
$^{13}$C NMR (400 MHz)

$^{13}$C NMR spectrum of a compound in CDCl$_3$. The spectrum shows peaks at various chemical shifts, indicating the presence of different carbon atoms in the molecule.
$^{19}$F NMR (376 MHz)
$d_{a}$-MeOD
$^{13}$C NMR (400 MHz)

d$_3$-CD$_3$CN

A (d) 170.41
B (s) 140.35
C (c) 127.67
D (s) 116.57
E (d) 88.45
$^{19}\text{F NMR (376 MHz)}$

$d_3\text{CD}_2\text{CN}$
$^3$H NMR (400 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$\text{H NMR (400 MHz)}$

d$_2$-MeOD
$^{19}$F NMR (376 MHz)
d$_r$-MeOD
$^1$H NMR (400 MHz) CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)
CDCl$_3$
$^1$H NMR (101 MHz)
$\text{CDCl}_3$
$^{18}$F NMR (376 MHz)
CDCl$_3$
$^1H$ NMR (400 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl₃
$^{19}$F NMR (376 MHz) 
CDCl$_3$
$^1$H NMR (400 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
CDCl$_3$
$^{19}F$ NMR (376 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^{13}$C NMR (101 MHz)
MeOD
$^{13}$C NMR (101 MHz) 
CDCl$_3$
$^{13}$C NMR (101 MHz) 
CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^{1}H$ NMR (101 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)  
$\text{d}_2$-MeOD
$^{13}$C NMR (101 MHz)
$d_2$-MeOD
$^{19}$F NMR (376 MHz)  
$^d_2$-MeOD
$^1$H NMR (400 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^{13}$C NMR (101 MHz)

CDCl$_3$
$^{19}\text{F NMR (376 MHz)}$

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl₃
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^3$H NMR (400 MHz)
Acetonitrile-$d_6$
$^{19}$F NMR (376 MHz)

Acetonitrile-$d_3$
$^1$H NMR (400 MHz)
CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)  
CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)
CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^{19}F$ NMR (376 MHz)

CDCl$_3$
$^1$H NMR (400 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^{19}$F NMR (376 MHz)

CDCl$_3$
$^{19}F$ NMR (376 MHz)

Acetonitrile-$d_3$
$^{19}$F NMR (101 MHz)

CDCl$_3$
