Application of Benzylic C-H Fluorination for the Formal Synthesis of syn-\(\alpha\), \(\beta\)-difluoro-\(\gamma\)-Amino Acid

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SUPPORTING INFORMATION

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1. General Information

New compounds were characterized by $^1$H, $^2$H, $^{13}$C, $^{19}$F, IR, MS, and HRMS. $^1$H, $^2$H, $^{13}$C, and $^{19}$F NMR spectra were recorded on a JEOL FT-NMR spectrometer ($^1$H NMR, 400 MHz; $^2$H NMR, 61 MHz; $^{13}$C NMR, 100 MHz; $^{19}$F NMR, 377 MHz). $^1$H NMR chemical shifts were determined relative to Me$_4$Si (0.0 ppm) as an internal standard. $^{13}$C NMR chemical shifts were determined relative to CDCl$_3$ (77.0 ppm). $^{19}$F NMR chemical shifts were determined relative to PhCF$_3$ (-62.7 ppm) as an external standard. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR Spectrometer. Mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. Melting points were determined on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System. All reactions were carried out under nitrogen. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or aluminum oxide (Merck, 90 active stage I, 0.063–0.200 mm). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel glass plates (Merck silica gel 60 F254, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.
2. Synthetic procedures and characterization of intermediates

Preparation of (R)-N-benzyl-2-fluoro-3-phenylpropan-1-amine 5

The catalyst (S)-2-[bis-(3,5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine (137mg, 0.23mmol) and 3-phenylpropanal 4 (6.16 g, 46mmol) were stirred at ambient temperature in MTBE (60 mL) for 10 min before the addition of N-fluorodibenzenesulfonylimide (NFSI) (14.49 g, 46mmol). The reaction mixture was then stirred for 16 h at ambient temperature. The mixture was then concentrated under reduced pressure to remove most of the organic solvent, diluted with 30 mL n-hexane and filtered through a pad of celite, eluting with MTBE(30 mL). The mixture was then concentrated under reduced pressure to remove most of the organic solvent again. After dilution of the crude mixture with CH₂Cl₂ (60 mL), benzylamine (6.54mL, 60mmol) and anhydrous Na₂SO₄ (3.0g) was added at 25 °C. The reaction mixture was then stirred for 1 h at ambient temperature. The mixture was then concentrated under reduced pressure, the crude mixture was added with MeOH (50mL) and two drops aqueous methyl orange solution. The solution was cooled to 0 °C, followed by the addition of NaBH₄CN (4.40 g, 70 mmol), then aqueous HCl (3N) was added dropwise slowly when the reaction was yellow and stopped added dropwise when the reaction is red. When the yellow no longer appear, the reaction was quenched with aqueous Na₂CO₃ (2M) until the solution was around pH 10 and extracted thrice with EtOAc, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography with silica gel (PE : EA = 4:1) to afford (R)-N-benzyl-2-fluoro-3-phenylpropan-1-amine 5 as a yellow oil (10.38 g, 93%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel® IC, Isocratic 5% i-PrOH/Hexanes, tR (minor) = 9.06 min, tR (major) = 11.11 min).

(S)-N-benzyl-2-fluoro-3-phenylpropan-1-amine 5

$^1$H NMR (400 MHz, CDCl₃) δ (ppm)

7.35–7.15 (m, 10H), 4.83 (dddt, $J = 3.92, 5.45, 7.03, 49.18$ Hz, 1H), 3.82–3.72 (m, 2H), 3.04–2.70 (m, 4H), 1.80 (bs, 1H);

$^{13}$C NMR (100 MHz, CDCl₃): δ 140.1, 137.0 (d, $J = 5.5$ Hz), 129.4, 128.6, 128.5, 128.2, 127.1, 126.7, 94.1(d, $J = 170.9$ Hz), 53.8, 52.4 (d, $J = 21.3$ Hz), 39.5 (d, $J = 21.4$ Hz);

$^{19}$F NMR (367 MHz, CDCl₃) δ = -183.59 (m, 1F). $^{19}$F {$^1$H} NMR (367 MHz, CDCl₃) δ = -183.59 (s, 1F). Reported.

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**data**: IR (neat) 3095, 2929, 1609, 1037 cm\(^{-1}\); \(^1\)H NMR (400.1 MHz, CDCl\(_3\)) \(\delta\) (ppm): 7.28 (m, 10H) 4.85 (dm, \(J = 52.0\) Hz, 1H), 3.81 (m, 2H), 2.75-3.07 (m, 4H), 1.7 (s, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) (ppm): 139.8, 136.7 (d, \(J = 6.0\) Hz), 129.2, 128.4, 128.3, 128.0, 126.9, 126.5, 93.9 (d, \(J = 172.0\) Hz), 53.7, 52.2 (d, \(J = 21.1\) Hz), 39.3 (d, \(J = 21.1\) Hz); \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) (ppm): -181.9; HRMS (TOF, ES+) C\(_{16}\)H\(_{18}\)FN \([\text{M+H}]^+\) calc'd 244.1502, found 244.1501.

Preparation of (R)-N-benzyl-2-fluoro-3-phenylpropan-1-amine

The (S)-N-benzyl-2-fluoro-3-phenylpropan-1-amine \(5\) (2.80g, 11.57mmol) was dissolved in methanol (10mL) and hydrogenolysis was carried out in presence of 10 wt% Pd/C (280mg) and AcOH (1.0mL) under the hydrogen pressure at room temperature. After 24 h, the catalyst was filtered through celite and the celite washed with methanol (3 x 10 mL). The solution was then concentrated under reduced pressure, the crude mixture(the primary amine) was added with phthalic anhydride (1.71g, 11.57 mmol), AcOH (0.92 mL,16 mmol) and toluene(30 mL). The reaction mixture was heated (130 ºC) to reflux for 12 h. The reaction was quenched with aqueous NH\(_2\)Cl and extracted thrice with EtOAc, dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. Purification by flash column chromatography with silica gel ( PE : EA = 10 : 1) to afford (S)-2-(2-fluoro-3-phenylpropyl)isoindoline-1,3-dione \(3\) as a white solid (2.08 g, 64%).

(S)-2-(2-fluoro-3-phenylpropyl)isoindoline-1,3-dione \(3\) \(\text{m.p.}\) 106–109 ºC; \([\alpha]\)\(D\) + 21.8 (c 0.5, CHCl\(_3\)); IR (neat) \(\nu_{\text{max}}\) 3028, 2929, 1958, 1773, 1715, 1497, 1424, 1396, 1320, 1259, 1190, 1026, 1005, 828, 792, 721, 712, 530 (cm\(^{-1}\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.86 (dd, \(J = 3.2, 5.3\) Hz, 2H), 7.72 (dd, \(J = 3.3, 5.5\) Hz, 1H), 7.27 (m, 5H), 5.02 (dddd, \(J = 3.5, 8.0, 11.9, 49.1\) Hz, 1H), 4.03 (td, \(J = 8.7, 14.2\) Hz, 1H), 3.81 (dddd, \(J = 3.5, 14.4, 27.9\) Hz, 1H), 3.01 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 168.0, 136.1 (d, \(J = 3.8\) Hz), 131.9, 128.6, 126.9, 123.3, 90.9 (dd, \(J = 1.7, 177.5\) Hz), 41.5 (d, \(J = 23.1\) Hz), 39.3 (d, \(J = 20.4\) Hz); \(^{19}\)F NMR (367 MHz, CDCl\(_3\)) \(\delta\) = -185.39 (dddd, \(J = 13.3, 18.5, 35.5, 49.5\) Hz, 1F). \(^{19}\)F \({\{^1}\}H\) NMR (367 MHz, CDCl\(_3\)) \(\delta\) = -185.39 (s, 1F). HRMS (ESI) m/z calcd for C\(_{17}\)H\(_{15}\)FNO\(_2^+\) (M+H\(^+\)) 284.1081, found 284.1083.

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Preparation of 2-(3-phenylpropyl)isoindoline-1,3-dione 7

![Diagram](attachment:image.png)

A mixture of 3-phenylpropan-1-amine (2.0g, 14.8 mmol) and phthalic anhydride (2.192g, 14.8 mmol) in chloroform (20 mL) was heated to reflux at 80 °C for 4 h. The reaction was quenched with H2O(10 mL) and extracted thrice with EtOAc, dried over Na2SO4, filtered and concentrated in vacuo. Purification by flash column chromatography with silica gel(PE:EA=14:1) to afford 2-(3-phenylpropyl)isoindoline-1,3-dione 7 as a colorless oil (2.745g, 70%).

2-(3-phenylpropyl)isoindoline-1,3-dione 7

**1H NMR (400 MHz, CDCl3)** δ (ppm) 7.80 (dd, J = 3.13, 5.5 Hz, 2H), 7.67 (dd, J = 2.95, 5.38 Hz, 2H), 7.27–7.09 (m, 5H), 3.73 (t, J = 7.17 Hz, 2H), 2.67 (t, J = 7.51 Hz, 2H), 2.02 (tt, J = 6.54, 7.42 Hz, 2H); **13C NMR (100 MHz, CDCl3)** δ: 168.3, 141.0, 133.8, 132.1, 128.4, 128.3, 125.9, 123.1, 37.8, 33.2, 29.9.

Reported data5: 1H-NMR (300 MHz, CDCl3) δ (ppm): 7.84 (dd, J = 2.3, 4.2 Hz, 2H); 7.72 (dd, J = 2.3, 4.2 Hz, 2H); 7.29-7.26 (m, 2H); 7.23-7.20 (m, 2H); 7.17-7.14 (m, 1H); 3.77 (t, J = 5.4 Hz, 2H); 2.71 (t, J = 6.1 Hz, 2H); 2.08-2.03 (m, 2H).13C-NMR (75 MHz, CDCl3) δ (ppm): 168.4; 141.0; 133.9; 132.1; 128.4; 128.3; 125.9; 123.2; 37.8; 33.2; 29.9.

FT-IR (cm-1): 1704. HRMS: Calculated for C17H15NO2: 265.1103; Found: 265.1091.

**Synthesis of 2-(3-fluoro-3-phenylpropyl)isoindoline-1,3-dione 8 and 2-(3-oxo-3-phenylpropyl)isoindoline-1,3-dione 9**

![Diagram](attachment:image.png)

A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with Selectfluor (1.912 g, 5.4 mmol), xanthone (44 mg, 0.225 mmol) and the 2-(3-phenylpropyl)isoindoline-1,3-dione 7 (1.19 g, 4.5 mmol). Then anhydrous acetonitrile (30 mL) was added. The reaction mixture was strictly degassed five times by freeze-pump-thaw cycles, and irradiated with a 26 W black light bulb at 25 °C for 24 h. The reaction was quenched with H2O (20mL) and extracted thrice with EtOAc, dried over Na2SO4, filtered and concentrated in vacuo. Purification by flash column chromatography with silica gel (petroleum : ethyl acetate = 12 : 1) to afford 2-(3-fluoro-3-phenylpropyl)isoindoline-1,3-dione 8 as a white solid ( 955mg, 75% ) and 2-(3-oxo-3-phenylpropyl)isoindoline-1,3-dione 9 as a colorless oil ( 138mg, 11% ).

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2-(3-fluoro-3-phenylpropyl)isoindoline-1,3-dione 8 \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta (ppm) \):

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Proton Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.81</td>
<td>dd, ( J = 3.1, 5.4)</td>
<td>2H</td>
<td></td>
</tr>
<tr>
<td>7.68</td>
<td>dd, ( J = 3.1, 5.6)</td>
<td>2H</td>
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<tr>
<td>7.38–7.30</td>
<td></td>
<td>5H</td>
<td></td>
</tr>
<tr>
<td>5.54</td>
<td>(ddd, ( J = 4.2, 8.7, 47.9))</td>
<td>1H</td>
<td></td>
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<tr>
<td>3.92–3.86</td>
<td></td>
<td>2H</td>
<td></td>
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<tr>
<td>2.46–2.16</td>
<td></td>
<td>2H</td>
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\( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) ppm:

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<thead>
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<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Proton Count</th>
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<tr>
<td>168.1</td>
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</tr>
<tr>
<td>139.3</td>
<td>(d, ( J = 23.1))</td>
<td>1H</td>
<td></td>
</tr>
<tr>
<td>133.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>132.0</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>128.5</td>
<td></td>
<td></td>
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<tr>
<td>128.4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>125.5</td>
<td>(d, ( J = 6.5))</td>
<td>1H</td>
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<tr>
<td>123.1</td>
<td></td>
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<tr>
<td>92.4</td>
<td>(d, ( J = 174.3))</td>
<td>1H</td>
<td></td>
</tr>
<tr>
<td>35.5</td>
<td>(d, ( J = 23.4))</td>
<td>1H</td>
<td></td>
</tr>
<tr>
<td>34.5</td>
<td>(d, ( J = 4.6))</td>
<td>2H</td>
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\( ^{19}F \) NMR (367 MHz, CDCl\(_3\)) \( \delta \) ppm:

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<tbody>
<tr>
<td>-175.65</td>
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Reported data:

1H NMR (400 MHz, C\(_6\)D\(_6\)) \( \delta \) ppm:

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<th>Multiplicity</th>
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<th>Proton Count</th>
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<tr>
<td>7.43–7.46</td>
<td>(m, 2H)</td>
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<tr>
<td>6.99–7.11</td>
<td>(m, 5H)</td>
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<tr>
<td>6.88–6.91</td>
<td>(m, 2H)</td>
<td></td>
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<tr>
<td>5.28</td>
<td>(ddd, ( J = 47.8, 8.8, 3.9))</td>
<td>1H</td>
<td></td>
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<tr>
<td>3.61–3.76</td>
<td>(m, 2H)</td>
<td></td>
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<tr>
<td>2.12–2.25</td>
<td>(m, 1H)</td>
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<tr>
<td>1.86–2.02</td>
<td>(m, 1H)</td>
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</table>

\( ^{13}C \) NMR (101 MHz, C\(_6\)D\(_6\)): \( \delta \) ppm:

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<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Proton Count</th>
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<tr>
<td>167.8</td>
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<td></td>
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<tr>
<td>140.0</td>
<td>(d, ( J = 19.6))</td>
<td>1H</td>
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</tr>
<tr>
<td>133.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>132.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>128.6</td>
<td></td>
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<tr>
<td>128.4</td>
<td>(d, ( J = 2.0))</td>
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\( ^{19}F \) NMR (376 MHz, C\(_6\)D\(_6\)): \( \delta \) ppm:

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<td>-176.12</td>
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</table>

Synthesis of 10a, 10b and 10c

The 3-phenylpropanal 4 (3.08g, 23mmol) was diluted with MeOH (40mL). NaBH\(_4\) (1.748g, 46mmol) was added slowly at 0°C. The reaction mixture was then stirred for 1 h at ambient temperature. The mixture was then concentrated under reduced pressure to afford 3-phenylpropan-1-ol. The crude 3-phenylpropan-1-ol (1.0g, 7.3mmol) was diluted with CH\(_2\)Cl\(_2\) (20mL), Et\(_3\)N(2.8mL, 20mmol) and R\(_2\)Cl (R=Cl, Et\(_3\)Cl, or Pivaloyl chloride) was
added respectively at 0°C. The reaction mixture was then stirred for 2 h at 40°C. The mixture was filtered through celite (ethyl acetate washed) and the filtrate was concentrated in vacuo. The crude product was subjected to flash column chromatography with silica gel (PE : EA = 50:1) to afford 10a (1.6g, 92%), 10b (1.27g, 98%) and 10c (1.35g, 84%) as a colourless oil.

Synthesis of 11a, 11b and 11c

The catalyst (S)-2-[bis-(3,5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine (137mg, 0.23mmol) and 3-phenylpropanal 4 (3.08g, 23mmol) were stirred at ambient temperature in MTBE (30 mL) for 10 min before the addition of N-fluorodibenzenesulfonimide (NFSI) (7.25g, 23mmol). The reaction mixture was then stirred for 16 h at ambient temperature. The mixture was then concentrated under reduced pressure for remove most of the organic solvent, diluted with 30 mL n-hexane and filtered through a pad of celite, eluting with MTBE(30mL). The mixture was then concentrated under reduced pressure to remove most of the organic solvent again. After dilution of the crude mixture with MeOH (40mL), NaBH₄ (1.748g, 46mmol) was added slowly at 0°C. The reaction mixture was then stirred for 1 h at ambient temperature. The mixture was then concentrated under reduced pressure to afford (S)-2-fluoro-3-phenylpropan-1-ol. The crude (S)-2-fluoro-3-phenylpropan-1-ol (1.0g, 6.5mmol) was diluted with CH₂Cl₂ (20mL), Et₃N(2.8mL, 20mmol) and R₂Cl (7.8 mmol, BzCl 0.905mL, AcCl 0.555mL, Pivaloyl chloride 0.96mL) was added respectively at 0°C. The reaction mixture was then stirred for 2 h at 40°C. The mixture was filtered through celite (ethyl acetate washed) and the filtrate was concentrated in vacuo. The crude product was subjected to flash column chromatography with silica gel (PE : EA = 40:1) to afford 11a (1.2g, 72%), 11b (1.05g, 83%) and 11c (998mg, 65%) as a colourless oil.

(S)-2-fluoro-3-phenylpropyl benzoate 11a [α]D +71.8 (c 0.5, CHCl₃); IR (neat) νmax 2946, 2742, 2696, 1872, 1667, 1640, 1548, 1435, 1073, 1043, 940, 932, 888, 798, 683, 607 (cm⁻¹); ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.07 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 7.6, Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.35–7.22 (m, 5H), 5.02 (ddddd, J = 2.9, 6.2, 8.9, 13.1, 48.2 Hz, 1H), 4.50 (ddd, J = 2.9, 12.6, 25.2 Hz, 1H), 4.37 (ddd, J = 6.2, 12.3,
21.2 Hz, 1H), 3.18–2.98 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.3, 135.9 (d, $J = 5.6$ Hz), 133.3, 129.8, 129.7, 129.4, 128.7, 128.5, 127.0, 91.5 (d, $J = 176.8$ Hz), 65.5 (d, $J = 22.3$ Hz), 38.1 (d, $J = 21.6$ Hz); $^{19}$F NMR (367 MHz, CDCl$_3$) $\delta$ -184.82 (m, 1F). $^{19}$F $^1$H NMR (367 MHz, CDCl$_3$) $\delta$ -184.82 (s, 1F). HRMS (ESI) m/z calcd for C$_{16}$H$_{16}$FO$_2$ (M+H)$^+$ 259.1134, found 259.1139.

(S)-2-fluoro-3-phenylpropyl acetate 11b $[^{[\alpha]}D$ +8.2 (c 0.25, CHCl$_3$); IR (neat) $\nu_{\text{max}}$ 2895, 2587, 1803, 1692, 1688, 1511, 1154, 965, 881, 653, 532 (cm$^{-1}$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.31–7.16 (m, 5H), 4.84 (dddd, $J = 2.7$, 6.5, 8.9, 13.3, 48.5 Hz, 1H), 4.21 (ddd, $J = 2.7$, 12.5, 26.1 Hz, 1H), 4.09 (ddd, $J = 6.4$, 12.4, 21.7 Hz, 1H), 3.05–2.83 (m, 2H), 2.05 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.6, 135.9 (d, $J = 5.4$ Hz), 129.4, 128.7, 127.0, 91.4 (d, $J = 175.3$ Hz), 65.1 (d, $J = 21.9$ Hz), 37.9 (d, $J = 21.5$ Hz), 20.7; $^{19}$F NMR (367 MHz, CDCl$_3$) $\delta$ -185.05 (m, 1F). $^{19}$F $^1$H NMR (367 MHz, CDCl$_3$) $\delta$ -185.04 (s, 1F). HRMS (ESI) m/z calcd for C$_{11}$H$_{14}$FO$_2$ (M+H)$^+$ 197.0978, found 197.0975.

Benzylic C-H fluorination of 10a, 10b, 10c and 11a, 11b, 11c

General procedure for the photolytic benzylic monofluorination reaction. To a 10 mL round-bottom flask with Selectfluor (71mg, 0.2 mmol, 2.0 equiv) was added anhydrous acetonitrile (2 mL), 9-fluorenone (0.005 mmol, 0.9 mg), and the reaction substrate (0.1 mmol, 1.0 equiv) under nitrogen. The reaction mixture was strictly degassed five times by freeze-pump-thaw cycles, and irradiated with a 26 W CFL at 27°C for 48 h. The crude yield was determined by $^{19}$F NMR using benzotri fluorides as an internal standard. The reaction mixture was then poured into diethyl ether (10 mL), filtrated, concentrated and purified by flash column chromatography with silica gel (PE : EA = 20:1) to afford 12a$^{11}$ (61%), 12b$^{9}$ (55%) and 12c (63%) as a colourless oil.

3-fluoro-3-phenylpropyl pivalate $12c$ IR ($\nu_{\text{max}}$ 2972, 2570, 1715, 1691, 1579, 1532, 1287, 1103, 1086, 945, 825, 658, 546 (cm$^{-1}$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.45–7.30 (m, 5H), 5.57 (ddd, $J = 4.4$, 8.4, 48.0 Hz, 1H), 4.30–4.14 (m, 2H), 2.38–2.24 (m, 1H), 2.23–2.06 (m, 1H), 1.21 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.4, 139.5 (d, $J = 19.7$ Hz), 128.6, 125.5, 125.4, 91.5 (d, $J = 171.3$ Hz), 60.4 (d, $J = 5.7$ Hz), 38.8, 36.4 (d, $J = 24.1$ Hz), 27.2; $^{19}$F NMR (367 MHz, CDCl$_3$) $\delta$ = -177.09 (ddd, $J = 15.6$, 30.2, 46.7 Hz, 1F). $^{19}$F {$^1$H} NMR (367 MHz, CDCl$_3$) $\delta$ = -177.09 (s, 1F). HRMS (ESI) m/z calcd for C$_{14}$H$_{20}$FO$_2$+ (M+H)$^+$ 239.1447, found 239.1446.

Preparation of $2$, $14$ and $15$

A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with Selectfluor (6.25g, 17.65mmol), xanthone (346.3mg, 1.76mmol) and the (S)-$2$-(2-fluoro-3-phenylpropyl)isoindoline-$1,3$-dione $3$ (1.0g, 3.53mmol). Then anhydrous acetonitrile (120 mL) was added. The reaction mixture was degassed five times by freeze-pump-thaw cycles, and irradiated with a 26 W black light bulb at 60 °C for 24 h. The reaction was quenched with H$_2$O (20mL) and extracted thrice with EtOAc, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. Purification by flash column chromatography with silica gel (n-hexane : CH$_2$Cl$_2$ : ethyl acetate = 35 : 2 : 2) to afford $2$ as a white solid (457mg, 43%) and $15$ as a colorless oil (50mg, 5%) and a mixture of $14$ (major) and $3$ (minor). Then the mixture of $14$ and $3$ purification by flash column chromatography with silica gel (n-hexane : dioxane = 15 : 1) to afford $14$ as a white solid (297mg, 28%) and recovered starting material $3$ (100mg).

2-((2R,3R)-2,3-difluoro-3-phenylpropyl)isoindoline-$1,3$-dione $2$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.85 (dd, $J = 3.1$, 5.4 Hz, 2H), 7.73 (dd, $J = 3.0$, 5.4 Hz, 2H), 7.45–7.35 (m, 5H), 5.56 (ddd, $J = 4.6$, 19.3, 46.1 Hz, 1H), 5.11 (dddd, $J = 3.6$, 4.5, 9.1, 19.3, 48.3 Hz, 1H), 4.16 (ddd, $J = 9.1$, 11.9, 21.2 Hz, 1H), 3.73 (ddd, $J = 3.6$, 14.7, 29.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.8, 134.2, 131.8, 129.4 (d, $J = 1.9$ Hz), 128.8, 126.6, 126.5, 123.5, 92.4 (dd, $J = 19.8$, 180.5 Hz), 90.1 (dd, $J = 23.0$, 19F, $J = 15.6$, 30.2, 46.7 Hz, 1F).

185.4 Hz), 38.3 (dd, J = 6.4, 23.8 Hz); $^{19}$F NMR (367 MHz, CDCl$_3$) δ = -188.42 (dd, J = 12.7, 19.7, 46.4 Hz, 1F), -199.91 (m, 1F). $^{19}$F $^1$H NMR (367 MHz, CDCl$_3$) δ = -188.42 (d, J = 12.3 Hz, 1F), -199.90 (d, J = 12.9 Hz, 1F).

Reported data$: white solid (0.220 g, 21%); m.p. 111–115 ºC; $[^\alpha]D +14$ (c 0.42, CHCl$_3$); IR (neat) v max (cm$^{-1}$) 1772, 1720, 1715, 1396, 1389; $^1$H NMR (200 MHz, CDCl$_3$) δ 7.86 (m, 2H), 7.73 (m, 2H), 7.44–7.38 (m, 5H), 5.57 (ddd, J = 46.2, 19.2, 4.5 Hz, 1H), 5.12 (dddd, J = 48.2, 19.3, 9.1, 4.5, 3.6 Hz, 1H), 4.17 (ddd, J = 14.5, 12.2, 8.9 Hz, 1H), 3.74 (ddd, J = 28.7, 14.5, 3.6 Hz, 1H); $^{13}$C $^1$H NMR (50 MHz, CDCl$_3$) δ 168.1, 134.8 (dd, J = 20.5, 4.1 Hz), 134.5, 132.1, 129.7 (d, J = 2.0 Hz), 129.0, 126.9 (d, J = 6.4 Hz), 123.8, 92.7 (dd, J = 180.5, 19.4 Hz), 90.4 (d, J = 184.9, 22.7 Hz), 38.6 (dd, J = 28.7, 14.5, 3.6 Hz, 1F); $^{19}$F NMR (282 MHz, CDCl$_3$) δ −188.8 (ddd, J = 46.4, 19.1, 12.4 Hz, 1F), −200.3 (ddddd, J = 48.3, 28.7, 19.2, 11.8, 12.4 Hz, 1F); $^{19}$F $^1$H NMR (282 MHz, CDCl$_3$) δ −188.8 (d, J = 12.4 Hz, 1F), −200.3 (d, J = 12.4 Hz, 1F); MS (APCI, +ve) m/z 282 ([M−HF]+H+, 36%); elemental analysis requires C 67.8, H 4.4, N 4.7, found C 67.8, H 4.2, N 4.7.

2-((2S,3R)-2,3-difluoro-3-phenylpropyl)isoindoline-1,3-dione 14 $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.81 (dd, J = 3.1, 5.6 Hz, 2H), 7.70 (dd, J = 3.1, 5.5 Hz, 2H), 7.44–7.31 (m, 5H), 5.68 (ddd, d, J = 4.3, 12.9, 46.4 Hz, 1H), 5.11 (dddd, J = 3.9, 3.9, 8.5, 16.5 Hz, 1H), 4.16 (ddd, J = 8.8, 13.3, 14.4 Hz, 1H), 3.87 (ddd, J = 3.4, 14.4, 29.3 Hz, 1H); $^{13}$C $^1$H NMR (100 MHz, CDCl$_3$): δ 167.8, 134.1, 131.8, 129.4 (d, J = 1.9 Hz), 128.7, 126.1, 126.0, 123.4, 92.3 (dd, J = 23.0, 177.2 Hz), 90.2 (dd, J = 25.6, 181.7 Hz), 37.4 (dd, J = 6.6, 23.6 Hz); $^{19}$F NMR (367 MHz, CDCl$_3$) δ = -193.10 (dd, J = 16.5, 16.5, 46.5 Hz, 1F), -195.16 (m, 1F). $^{19}$F $^1$H NMR (367 MHz, CDCl$_3$) δ = -193.10 (d, J = 16.5 Hz, 1F), -195.16 (d, J = 16.9 Hz, 1F). {Reported data$: 2-((2R,3S)-2,3-difluoro-3-phenylpropyl)isoindoline-1,3-dione m.p. 104–105 ºC; $[^\alpha]D −31$ (c 0.22, CHCl$_3$); IR (neat) v max 2928, 2855, 1772, 1717, 1486, 1467, 1457, 1419, 1395, 1363, 1279, 1223, 1197, 1172, 1049, 866, 760, 695, 612, 577, 537, 484, 453, 381, 328 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.84 (m, 2H), 7.72 (m, 2H), 7.45–7.34 (m, 5H), 5.70 (ddd, d, J = 46.4, 12.8, 4.3 Hz, 1H), 5.13 (dddd, J = 47.4, 16.4, 8.6, 4.2, 3.6 Hz, 1H), 4.18 (ddd, J = 14.5, 12.6, 8.8, 0.6 Hz, 1H), 3.89 (ddd, J = 19.5, 14.5, 3.5, 0.6 Hz, 1H); $^{13}$C $^1$H NMR (100 MHz, CDCl$_3$): δ 168.2, 134.9 (d, J = 10.6, 4.4 Hz), 134.4, 132.1, 129.4, 129.0, 126.2 (d, J = 7.4 Hz), 123.7, 92.5 (dd, J = 178.6, 22.4 Hz), 90.5 (d, J = 182.2, 26.0 Hz), 37.7 (dd, J = 23.5, 6.5 Hz); $^{19}$F NMR (282 MHz, CDCl$_3$) δ −193.6 (dd, J = 46.4, 16.5, 16.5 Hz, 1F), −195.6 (m, 1F); $^{19}$F $^1$H NMR (282 MHz, CDCl$_3$) δ −193.6 (d, J = 16.5 Hz, 1F), −195.6 (d, J = 16.5 Hz, 1F); HRMS (ESI, +ve) C17H13F2NO2Na+ requires m/z 324.0807, found 324.0808.}

(R)-2-(2-fluoro-3-oxo-3-phenylpropyl)isoindoline-1,3-dione 15 $[^\alpha]D −2.5$ (c 0.4, CHCl$_3$); IR (neat) v max 2928, 2855, 1772, 1717, 1486, 1467, 1457, 1419, 1395, 1363, 1279, 1223,
1188, 1080, 971, 888, 758, 720, 700, 647, 530 (cm\(^{-1}\)); \(^1\)H NMR (400 MHz, CDCl\(\text{3}\)) \(\delta\) (ppm) 8.08 (d, \(J = 7.6\) Hz, 2H), 7.88 (dd, \(J = 3.1, 5.4\) Hz, 2H), 7.75 (dd, \(J = 3.0, 5.5\) Hz, 2H), 7.66–7.60 (m, 1H), 7.55–7.40 (m, 2H), 5.99 (ddd, \(J = 3.4, 9.0, 49.3\) Hz, 1H), 4.35 (ddd, \(J = 8.9, 14.6, 14.6\) Hz, 1H), 4.18 (ddd, \(J = 3.5, 14.8, 30.1\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(\text{3}\)); \(\delta\) 193.7 (d, \(J = 17.3\) Hz), 167.8, 134.3, 133.9, 131.8, 129.1, 129.0, 128.9, 123.5, 89.5 (d, \(J = 188.0\) Hz), 39.4 (d, \(J = 23.1\) Hz); \(^{19}\)F NMR (367 MHz, CDCl\(\text{3}\)) \(\delta\) = -194.0 (ddd, \(J = 14.6, 29.09, 49.4\) Hz, 1F). \(^{19}\)F \(^1\)H NMR (367 MHz, CDCl\(\text{3}\)) \(\delta\) = -194.05 (s, 1F).

HRMS (ESI) m/z calcd for C\(_{17}\)H\(_{13}\)FNO\(_3\)\(^+\) (M+H\(^+\)) 298.0874, found 298.0875.

Synthesis of 4-(1,3-dioxoisindolin-2-yl)-2-fluorobutanoic acid 16\(^4\)

Ruthenium chloride hydrate (4mg, 0.019mmol) was added to a stirred mixture of 4-(1,3-dioxoisindolin-2-yl)-2-fluorobutanoic acid (105mg, 0.31mmol), dichloromethane (2.5mL), acetonitrile (2.5mL), water (3.0mL) and sodium metaperiodate (1.2 g, 5.616 mmol), and the resulting mixture was stirred at room temperature for 24h. The mixture was filtered through celite (ethyl acetate wash) and the filtrate was concentrated in vacuo. The crude product was subjected to flash chromatography eluting with methanol:ethyl acetate (1:4) to give the title compound 16 as a deep yellow oil (63mg, 80%).

4-(1,3-dioxoisindolin-2-yl)-2-fluorobutanoic acid 16 \(^1\)H NMR (400 MHz, CD\(_3\)CN) \(\delta\) (ppm) 7.78 (s, 4H), 5.06 (d, \(J = 48.7\) Hz, 1H), 3.84–3.71 (m, 2H), 2.40–2.13 (m, 2H); \(^{13}\)C NMR (100 MHz, CD\(_3\)CN): \(\delta\) 168.8, 134.8, 132.6, 123.5, 117.8, 34.0 (d, \(J = 3.5\) Hz), 31.4, 31.1; \(^{19}\)F NMR (367 MHz, CD\(_3\)CN) \(\delta\) = -194.32 (d, \(J = 22.4, 29.5, 48.3\) Hz, 1F). \(^{19}\)F \(^1\)H NMR (367 MHz, CD\(_3\)CN) \(\delta\) = -194.32 (s, 1F). \textbf{Reported data}\(^4\): \textit{Anal.} Calc. for C\(_{12}\)H\(_{10}\)FNO\(_4\): C, 57.4; H, 4.0; F, 7.5; N, 5.6. Found: C, 57.5; H, 3.9; F, 7.6; N, 5.6.

Synthesis of 4-amino-2-fluorobutanoic acid hydrochloride 17\(^15\)

A solution of 4-(1,3-dioxoisindolin-2-yl)-2-fluorobutanoic acid (26 mg, 0.1 mmol) and hydrazine hydrate (6.3 \(\mu\)L) was refluxed in ethanol to give the title compound 17 (99%).


mmol) in ethanol (1 mL) was heated at reflux overnight, then cooled and concentrated in vacuo. The residue was triturated in 4 M aq. HCl (2 mL) and filtered through celite. The filtrate was concentrated, then triturated in water (3 mL) and filtered again. The filtrate was concentrated to furnish the title compound 17 as an off-white solid (16 mg, 99%).

4-amino-2-fluorobutanoic acid hydrochloride 17  

$^1$H NMR (400 MHz, D$_2$O) $\delta$ (ppm) 4.97 (ddd, $J = 3.6, 7.7, 48.4$ Hz 1H), 3.04–2.91 (m, 2H), 2.23–1.95 (m, 2H);  

$^{13}$C NMR (100 MHz, D$_2$O): $\delta$ 173.6, 87.8 (d, $J = 182.6$ Hz), 35.7(d, $J = 3.5$ Hz), 29.3(d, $J = 20.6$ Hz);  

$^{19}$F NMR (367 MHz, D$_2$O) $\delta = -190.20$ (dt, $J = 24.1, 47.9$ Hz, 1F).  

$^{19}$F $^1$H NMR (367 MHz, D$_2$O) $\delta = -190.20$ (s, 1F).  

Reported data$^{16}$:  

(R)-4-amino-2-fluorobutanoic acid hydrochloride. $^1$H NMR [499.8 MHz, D$_2$O]: $\delta$ 5.08 (ddd, $J_{H,H} = 4.0$ Hz, $J_{H,F} = 8.0$ Hz, $J_{F,F} = 49.0$ Hz, 2H), 3.10 (m, 2H), 2.09,2.32 (brm, 2H); $^{13}$C NMR [125.7 MHz, D$_2$O]: $\delta$ 173.4 ($^1J_{C,F} = 23.0$ Hz), 87.6 ($^1J_{C,F} = 180.0$ Hz), 36.0 ($^2J_{C,F} = 3.8$ Hz), 29.6 ($^2J_{C,F} = 20.7$ Hz); HRMS (MM: ESI–APCI) calc’d for C$_4$H$_8$FNO$_4$ [M+H]$^+$ 122.0612, found 122.061; $[\alpha]_D^{22} +10.64$ (c=0.5, H$_2$O)).

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3. Spectra of compounds

$^1$H NMR (400 MHz, CDCl$_3$) of 5

$^{13}$C NMR (100 MHz, CDCl$_3$) of 5
$^{19}$F NMR (367 MHz, CDCl$_3$) of 5

$^{19}$F $^1$H NMR (367 MHz, CDCl$_3$) of 5
$^1$H NMR (400 MHz, CDCl₃) of 3

$^{13}$C NMR (100 MHz, CDCl₃) of 3
\[^{19}\text{F} \text{NMR (367 MHz, CDCl}_3\text{) of 3}\]

\[\begin{array}{c}
\text{O} \quad \text{N} \quad \text{O} \\
\text{3}
\end{array}\]

\[^{19}\text{F} \{^1\text{H}\} \text{NMR (367 MHz, CDCl}_3\text{) of 3}\]

\[\begin{array}{c}
\text{O} \quad \text{N} \\
\text{3}
\end{array}\]
$^1$H NMR (400 MHz, CDCl$_3$) of 7

$^{13}$C NMR (100 MHz, CDCl$_3$) of 7
$^1$H NMR (400 MHz, CDCl$_3$) of  8

$^{13}$C NMR (100 MHz, CDCl$_3$) of  8
$^{19}$F NMR (367 MHz, CDCl$_3$) of $8$

$^{19}$F $\{^1$H$\}$ NMR (367 MHz, CDCl$_3$) of $8$

19
$^1$H NMR (400 MHz, CDCl$_3$) of 9

$^{13}$C NMR (100 MHz, CDCl$_3$) of 9
$^1$H NMR (400 MHz, CDCl$_3$) of 11a

$^{13}$C NMR (100 MHz, CDCl$_3$) of 11a
$^{19}$F NMR (367 MHz, CD$_3$CN) of 11a

$^{19}$F ($^1$H) NMR (367 MHz, CD$_3$CN) of 11a
$^1$H NMR (400 MHz, CDCl₃) of 11b

$^{13}$C NMR (100 MHz, CDCl₃) of 11b
$^{19}$F NMR (367 MHz, CD$_3$CN) of 11b

$^{19}$F $^1$H NMR (367 MHz, CD$_3$CN) of 11b
$^1$H NMR (400 MHz, CDCl$_3$) of 11c

$^{13}$C NMR (100 MHz, CDCl$_3$) of 11c
$^{19}$F NMR (367 MHz, CD$_3$CN) of 11c

11c

$^{19}$F $^1$H NMR (367 MHz, CD$_3$CN) of 11c

11c
$^1$H NMR (400 MHz, CDCl$_3$) of 12c

$^{13}$C NMR (100 MHz, CDCl$_3$) of 12c
$^{19}$F NMR (367 MHz, CD$_3$CN) of 12c

$^{19}$F $\{^1$H$\}$ NMR (367 MHz, CD$_3$CN) of 12c
$^1$H NMR (400 MHz, CDCl$_3$) of 2

$^{13}$C NMR (100 MHz, CDCl$_3$) of 2
$^{19}\text{F NMR (367 MHz, CDCl}_3\text{) of 2}$

$^{19}\text{F }{^1\text{H}} \text{ NMR (367 MHz, CDCl}_3\text{) of 2}$
$^1$H NMR (400 MHz, CDCl₃) of 14

$^{13}$C NMR (100 MHz, CDCl₃) of 14
$^{19}$F NMR (367 MHz, CDCl$_3$) of 14

$^{19}$F $^1$H NMR (367 MHz, CDCl$_3$) of 14
$^1$H NMR (400 MHz, CDCl$_3$) of 15

$^{13}$C NMR (100 MHz, CDCl$_3$) of 15
$^{19}$F NMR (367 MHz, CDCl₃) of 15

$^{19}$F $^{1}$H NMR (367 MHz, CDCl₃) of 15
$^1$H NMR (400 MHz, CD$_3$CN) of 16

$^{13}$C NMR (100 MHz, CD$_3$CN) of 16
$^{19}$F NMR (367 MHz, CD$_3$CN) of 16

$^{19}$F $^{1}$H NMR (367 MHz, CD$_3$CN) of 16
$^1$H NMR (400 MHz, D$_2$O) of 17

$^{13}$C NMR (100 MHz, D$_2$O) of 17
$^{19}$F NMR (367 MHz, D$_2$O) of 17

$^{19}$F {$^1$H} NMR (367 MHz, D$_2$O) of 17
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