Supporting Information

Grignard-Mediated Rearrangement of Trifluoroacetyl from Dihydroisoquinoline Enamides to Afford Tertiary Trifluoromethylcarbinols

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General Information

Unless otherwise noted, all reactions were performed under an atmosphere of nitrogen or argon. Dry tetrahydrofuran (THF), dichloromethane, and dimethylformamide (DMF) were obtained by passing these previously degassed solvents through activated alumina columns. All other reagents were used as received, unless stated otherwise. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel F254 plate (Merck, art. 5715) and column chromatography was performed using silica gel (Merck, mesh 230-400). Volatile solvents were removed under reduced pressure with a rotary evaporator. 

$^1$H and $^{13}$C NMR spectra were recorded with Bruker Avance spectrometers operating at 300 and 500 MHz for $^1$H, 125 MHz for $^{13}$C using CDCl$_3$ or other deuterated solvents. Chemical shifts were reported relative to the residual solvent signal ($^1$H NMR: $\delta = 7.26$ (CDCl$_3$); $^{13}$C NMR: $\delta = 77.16$ (CDCl$_3$)). NMR data were reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, hept = heptet, m = multiplet. Melting points were determined in open capillaries using Optimelt apparatus. The IR spectra of compounds were recorded using Smiths FT-IR spectrometer (model: Identify IR). The $\nu_{\text{max}}$ values expressed in cm$^{-1}$ for the main absorption bands. LC/MS analysis was performed on the Waters Acquity UPLC system with SQ Detector2 via electrospray ionization mode using a mixture of solvents as a mobile phase (Water + 0.1% HCOOH and CH$_3$CN + 0.1% HCOOH) and C18 column (Acquity UPLC BEH C18 1.7 $\mu$m). HRMS was measured with electron impact (EI) ionization or fast atom bombardment (FAB) ionization methods via double focusing mass analyzer (magnetic and electric fields) using JMS-700 (JEOL, Tokyo, Japan).
Preparation of Enamides

2,2,2-Trifluoro-1-(7-methoxy-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (2a)

To a solution of 7-methoxy-1-methyl-3,4-dihydroisoquinoline\(^1\) (1a, 100 mg, 0.57 mmol) in THF (1.0 mL) was added trifluoroacetic anhydride (TFAA) (0.20 mL, 1.4 mmol) followed by triethylamine (Et\(_3\)N) (0.20 mL, 1.4 mmol) at rt and the mixture was stirred at rt for 10 min. The reaction mixture was evaporated under vacuum to get crude mixture which was then purified on silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford the title compound 2a (182 mg, 0.67 mmol, 83%); TLC \(R_f = 0.85\) (EtOAc/hexanes = 1/9); white solid; mp 71.9-74.1 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.25 (d, \(J = 1.5\) Hz, 1H), 7.13 (d, \(J = 8.5\) Hz, 1H), 6.92 (dd, \(J = 8.4, 2.5\) Hz, 1H), 6.07 (s, br, 1H), 5.34 (s, br, 1H), 3.95 (t, \(J = 5.3\) Hz, 2H), 3.78 (s, 3H), 2.89 (t, \(J = 6.0\) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 158.4, 155.5 (q, \(J_{C-F} = 35.8\) Hz), 141.1, 132.0, 130.1, 125.7, 116.5 (q, \(J_{C-F} = 288.3\) Hz), 115.6, 108.9, 108.7, 55.3, 44.7, 27.6; IR \(\nu\) 3044, 3015, 2936, 1688, 1567, 1493, 1432, 1200, 1141, 1032, 798 cm\(^{-1}\); LC/MS 272.0 [M + H\(^+\)]; HRMS (EI) \(m/z\) calcd for C\(_{13}\)H\(_{12}\)F\(_3\)NO\(_2\) [M\(^+\)] 271.0820, found 271.0807.

2,2,2-Trifluoro-1-(1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (2b)\(^2\)

To a solution of 1-methyl-3,4-dihydroisoquinoline (1b, 200 mg, 1.38 mmol) in THF (2.0 mL) was added TF\(_3\)A (0.29 mL, 2.07 mmol) followed by Et\(_3\)N (0.38 mL, 2.75 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h, quenched with H\(_2\)O and extracted with EtOAc (2 X 50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), evaporated under vacuum to get a crude mixture, which was then purified, on silica gel column chromatography evaporated using EtOAc/hexanes (1/4) as an eluent to afford 2b (241 mg, 0.99 mmol, 73%); TLC \(R_f = 0.88\) (EtOAc/hexanes = 1/9); white solid; mp 54.3-56.5 °C (lit.\(^2\) mp 55-56 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.59 (d, \(J = 6.3\) Hz, 1H), 7.21-7.31 (m, 2H), 7.14 (d, \(J = 6.8\) Hz, 1H), 5.77 (s, br, 1H), 5.34 (s, br, 1H), 4.05 (s, br, 2H), 3.01 (t, \(J = 5.9\) Hz, 2H), 2.69 (t, \(J = 7.5\) Hz, 1H), 2.38 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 155.6 (q, \(J_{C-F} = 34.9\) Hz), 141.0, 137.2, 133.4, 131.1, 129.1, 126.9, 124.3, 116.5 (q, \(J_{C-F} = 288.1\) Hz), 108.6, 44.3, 28.5; IR \(\nu\) 3124, 3010, 2951, 1679, 1634, 1434, 1357, 1137, 1043, 895, 770, cm\(^{-1}\); LC/MS 242.1 [M + H\(^+\)]; HRMS (EI) \(m/z\) calcd for C\(_{12}\)H\(_{10}\)F\(_3\)NO [M\(^+\)] 241.0714, found 241.0728.
2,2,2-Trifluoro-1-(4-methyl-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (2c)

To a round-bottomed flask capped with a rubber septum were added 1,4-dimethyl-3,4-dihydroisoquinoline⁴ (1c, 200 mg, 1.25 mmol) and a solution of Et₃N (152 mg, 1.51 mmol) in THF (3.0 mL). The mixture was cooled to 0 °C under stirring and a solution of TFAA (0.21 mL, 1.5 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was maintained at rt under stirring and a nitrogen atmosphere for 30 min. Afterwards, the reaction was diluted with EtOAc (10 mL) and washed with distilled water (10 mL). The organic phase was dried over MgSO₄. After filtration, the solvent was evaporated under reduced pressure to afford the crude mixture which was purified by silica gel column chromatography using EtOAc/hexane (1/4) as an eluent to afford 2c (260 mg, 1.02 mmol, 81%); TLC Rf = 0.90 (EtOAc/hexanes = 1/9); colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.58 (d, J = 7.56 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.27-7.21 (m, 2H), 5.74 (s, br, 1H), 5.31 (s, br, 1H), 4.02-3.96 (m, 1H), 3.94-3.89 (m, 1H), 3.15 (sextet, J = 6.69 Hz, 1H), 1.29 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.8 (q, 2J_C-F = 36.3 Hz), 141.29, 138.8, 130.4, 129.3, 128.0, 126.9, 124.2, 116.6 (q, 1J_C-F = 288.4 Hz), 108.0, 50.2, 33.3, 19.9; IR ν 2963, 1687, 1639, 1431, 1297, 1197, 1144, 1032, 965, 770, 751 cm⁻¹; LC/MS 256.1 [M + H⁺]; HRMS (EI) m/z calcd for C₁₃H₁₂F₃NO [M⁺] 255.0871, found 255.0865.

2,2,2-Trifluoro-1-(6-methoxy-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (2d)

To a solution of 6-methoxy-1-methyl-3,4-dihydroisoquinoline (1d, 100 mg, 0.57 mmol) in THF (1.0 mL) was added TFAA (0.08 mL, 0.57 mmol) at 0 °C. The reaction mixture was stirred at rt for 10 min, quenched with H₂O and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford 2d (120 mg, 0.44 mmol, 78%); TLC Rf = 0.86 (EtOAc/hexanes = 1/9); white solid; mp 68.6-70.6 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.64 (s, 1H), 5.62 (s, br, 1H), 5.22 (s, br, 1H), 4.03 (s, br, 2H), 3.80 (s, 3H), 2.98 (t, J = 5.8 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 160.1, 155.6 (q, 2J_C-F = 35.2 Hz), 140.6, 135.0, 125.7, 123.8, 116.5 (q, 1J_C-F = 288.3 Hz), 113.4, 113.2, 106.4, 55.3, 44.2, 28.9; IR ν 3010, 2932, 2835, 1689, 1606, 1495, 1438, 1361, 1279, 1202, 1176, 1133 1037, 898, 877, 807 cm⁻¹; LC/MS 272.2 [M + H⁺]; HRMS (EI) m/z calcd for C₁₃H₁₂F₃NO₂ [M⁺] 271.0820, found 271.0831.
1-(6,7-Dimethoxy-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethan-1-one (2e)

To a solution of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (1e, 205 mg, 1.00 mmol) and pyridine (98.9 mg, 1.25 mmol) in CH$_2$Cl$_2$ (3.1 mL) was added dropwise TFAA (263 mg, 1.25 mmol) in CH$_2$Cl$_2$ (0.75 mL) at -50 °C. The reaction mixture was stirred at -50 °C for 3 h, quenched with water (5 mL), and extracted with CH$_2$Cl$_2$ (2 x 5 mL). The combined organic layers were dried over MgSO$_4$, concentrated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford 2e (226 mg, 0.750 mmol, 75%); TLC R$_f$ = 0.88 (EtOAc/hexanes = 1/9); slightly yellow solid; mp 81.5-83.1 °C (lit. mp 80 °C); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.03 (s, 1H), 6.59 (s, 1H), 5.62 (s, br, 1H), 5.25 (s, br, 1H), 4.08-4.01 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.94 (t, J = 5.6 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.6 (q, $^1$J$_{C-F}$ = 35.8 Hz), 150.1, 148.1, 126.3, 123.4, 116.5 (q, $^2$J$_{C-F}$ = 286.5 Hz), 111.1, 106.8, 106.6, 106.5, 56.0, 55.9, 44.6, 28.4; IR ν 3020, 2965, 2935, 1698, 1608, 1515, 1440, 1340, 1279, 1135 1037, 902, 810 cm$^{-1}$; LC/MS 302.1 [M + H$^+$].

2,2,2-Trifluoro-1-(7-fluoro-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (2f)

To a solution of 7-Fluoro-1-methyl-3,4-dihydroisoquinoline (1f, 200 mg, 1.23 mmol) in THF (2.0 mL) was added Et$_3$N (0.43 mL, 3.06 mmol) followed by TFAA (0.26 mL, 1.84 mmol) at 0 °C and stirred for 10 min at rt. The mixture was quenched with H$_2$O and extracted with EtOAc (2 x 200 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford 2f (241 mg, 0.93 mmol, 76%); TLC R$_f$ = 0.86 (EtOAc/hexanes = 1/9); white solid; mp 50.3-53.1 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ 7.26-7.29 (m, 1H), 7.09-7.14 (m, 1H), 6.95-7.02 (m, 1H), 5.76 (s, br, 1H), 5.41 (s, br, 1H), 4.03 (s, br, 2H), 2.97 (t, J = 6.0 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.5 (d, $^1$J$_{C-F}$ = 245.0 Hz), 155.4 (q, $^2$J$_{C-F}$ = 34.9 Hz), 140.2, 132.6, 130.7, 129.1, 116.4 (d, $^2$J$_{C-F}$ = 21.1 Hz), 116.4 (q, $^2$J$_{C-F}$ = 288.2 Hz), 110.8 (d, $^2$J$_{C-F}$ = 23.2 Hz), 109.6, 44.3, 27.8; IR ν 3071, 3030, 2947, 1684, 1610, 1578, 1488, 1431, 1316, 1270, 1196, 1151, 931, 893, 752 cm$^{-1}$; LC/MS 260.1 [M + H$^+$]; HRMS (El) m/z calcd for C$_{12}$H$_9$F$_4$NO [M$^+$] 259.0620, found 259.0624.
**2,2,2-Trifluoro-1-(1-methylene-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethan-1-one (2g)**

To a solution of 1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole (1g, 100 mg, 0.54 mmol) in THF (1.0 mL) was added TFAA (0.12 mL, 0.81 mmol) followed by Et$_3$N (0.19 mL, 1.36 mmol) at 0 °C. The reaction mixture was stirred at rt for 30 min, quenched with H$_2$O, and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (2/1) as an eluent to afford 2g (85 mg, 0.3 mmol, 56%); TLC $R_f$ = 0.51 (EtOAc/hexanes = 2/1); white solid; mp 154.2-156.8 °C; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 8.38 (s, br, 1H), 7.45 (d, $J$ = 7.7 Hz, 1H), 7.29 (d, $J$ = 8.0 Hz, 1H), 7.21 (t, $J$ = 7.3 Hz, 1H), 7.10 (t, $J$ = 7.7 Hz, 1H), 5.42 (s, br, 2H), 4.06-4.14 (m, 2H), 2.91 (s, br, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 136.9, 128.8, 126.5, 124.1 120.4, 119.1, (q, $J_{CF}$ = 286.3 Hz), 111.2, 103.9, 46.4, 22.2; IR $\nu$ 3329, 3243, 3101, 1700, 1633, 1559, 1418, 1334, 1184, 1067, 727 cm$^{-1}$; LC/MS 281.2 [M + H$^+$], 561.3 [2M + H$^+$]; HRMS (EI) $m/z$ calcd for C$_{14}$H$_{11}$F$_3$N$_2$O [M$^+$] 280.0823, found 280.0832

**2,2,2-Trifluoro-N-(1-(4-methoxyphenyl)vinyl)-N-methylacetamide (2h)**

[Step 1] To a solution of (E)-1-(4-methoxyphenyl)ethan-1-one oxime (500 mg, 3.03 mmol) and TFAA (0.51 mL, 3.63 mmol) in DMF (5.0 mL) was added Fe powder (507 mg, 9.08 mmol), and then the reaction was initiated by adding catalytic amount of TMSCl under nitrogen. The reaction mixture was stirred at rt for 4 h, quenched with H$_2$O, and extracted with EtOAc (2 x 150 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/3) as an eluent to afford 2,2,2-trifluoro-N-(1-(4-methoxyphenyl)vinyl)acetamide (223 mg, 0.91 mmol, 30%); TLC $R_f$ = 0.52 (EtOAc/hexanes = 2/1); white solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53 (s, 1H), 7.32 (d, $J$ = 8.9 Hz, 1H), 6.91 (d, $J$ = 8.1 Hz, 1H), 5.85 (s, 1H), 5.27 (s, 1H), 3.82 (s, 3H); LC/MS 246.1 [M + H$^+$].

[Step 2] To a solution of above 2,2,2-trifluoro-N-(1-(4-methoxyphenyl)vinyl)acetamide (100 mg, 0.41 mmol) in THF (1.0 mL) was added NaH (24.4 mg, 0.61 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and MeI (51 µL, 0.80 mmol) was added. The reaction mixture was stirred at rt for 12 h, quenched with H$_2$O, and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford 2h (38 mg, 0.15 mmol, 36%); TLC $R_f$
= 0.73 (EtOAc/hexanes = 2/8); white solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33 (d, $J$ = 8.1 Hz, 2H), 6.91 (d, $J$ = 8.1 Hz, 2H), 5.62 (s, 1H), 5.19 (s, 1H), 3.83 (s, 3H), 3.11 (s, 3H); LC/MS 260.3 [M + H$^+$].

1-(7-Methoxy-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (2i)

To a solution of 7-methoxy-1-methyl-3,4-dihydroisoquinoline (1a, 100 mg, 0.57 mmol) in THF (1.0 mL) was added Ac$_2$O (146 mg, 1.43 mmol) followed by Et$_3$N (0.19 mL, 1.43 mmol) at rt and stirred for 5 h. The reaction mixture was evaporated under vacuum to get a crude product which was then purified on silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford 2i (108 mg, 0.49 mmol, 87%); TLC $R_f$ = 0.70 (EtOAc/hexanes = 1/9); colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.15 (d, $J$ = 2.7 Hz, 1H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.86 (dd, $J$ = 8.4, 2.7 Hz, 1H), 5.75 (s, 1H), 5.08 (s, br, 1H), 3.99 (t, $J$ = 6.3 Hz, 2H), 3.85 (s, 3H), 2.86 (t, $J$ = 6.3 Hz, 2H), 2.24 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 203.5, 171.3, 157.8, 139.1, 132.9, 130.4, 117.1, 115.1, 100.0, 55.5, 42.3, 31.3, 29.8, 22.7; IR $\nu$ 3288, 2935, 2835, 1677, 1650, 1608, 1434, 1356, 1267, 1216, 1199, 1039, 728 cm$^{-1}$; LC/MS 217.8 [M + H$^+$]. HRMS (EI) $m/z$ calcd for C$_{13}$H$_{15}$NO$_2$ [M$^+$] 217.1103, found 217.1091.

7-Methoxy-1-methylene-3,4-dihydroisoquinolin-2(1H)-yl(phenyl)methanone (2j)

To a solution of 7-methoxy-1-methyl-3,4-dihydroisoquinoline (1a, 300 mg, 1.71 mmol) in THF (3.0 mL) was added Et$_3$N (0.59 mL, 4.28 mmol) followed by addition of benzoyl chloride (0.24 mL, 2.05 mmol) at 0°C and stirred at rt for 30 min. The reaction mixture was quenched with H$_2$O and extracted with EtOAc (2 x 50 mL). The organic layers were washed with H$_2$O and saturated NaCl (aq). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/4) as an eluent to afford 2j (421 mg, 1.51 mmol, 88%); TLC $R_f$ = 0.73 (EtOAc/hexanes = 1/9); yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.45 (d, $J$ = 7.8 Hz, 2H), 7.28-7.42 (m, 3H), 7.15 (d, $J$ = 8.4 Hz, 1H), 7.08 (d, $J$ = 2.1 Hz, 1H), 6.90 (dd, $J$ = 8.4, 2.1 Hz, 1H), 5.42 (s, 1H), 5.55 (s, 1H), 4.13 (t, $J$ = 6.0 Hz, 2H), 3.85 (s, 3H), 3.01 (t, $J$ = 6.0 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 28.5, 42.8, 55.4, 107.4, 108.9, 115.1, 126.9, 127.9, 128.2, 129.9, 130.2, 132.2, 136.1, 142.9, 158.3, 169.9; IR $\nu$ 3055, 2930, 2833, 1719, 1633, 1571, 1490, 1445, 1382, 1291, 1218, 1036, 887, 788, 697 cm$^{-1}$; LC/MS 280.1 [M + H$^+$]; HRMS (EI) $m/z$ calcd for C$_{18}$H$_{17}$NO$_2$ [M$^+$] 279.1259, found 279.1252.
Synthesis of Trifluoromethylcarbinols

1,1,1-Trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1-yl)-2-methylpropan-2-ol (4a)

To a solution of 2a (50.0 mg, 0.18 mmol) in THF (1.0 mL) was added 3.0 M MeMgBr in diethyl ether (0.09 mL, 0.27 mmol) at rt. The reaction mixture was stirred at rt for 10 min and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford the title compound 4a (52 mg, 0.181 mmol, 98%); TLC Rᵋ = 0.50 (EtOAc/hexanes = 2/8); colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 8.09 (s, br, 1H), 7.15 (d, J = 9.0 Hz, 1H), 6.98-6.95 (m, 2H), 3.86 (s, 3H), 3.73-3.65 (m, 2H), 3.15 (d, J = 16.2 Hz, 1H), 2.82 (d, J = 16.5 Hz, 1H), 2.68 (t, J = 7.5 Hz, 2H), 1.45 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 22.7, 24.8, 35.3, 46.1, 55.5, 73.6 (q, JCF = 28 Hz), 110.9, 116.4, 124.7, 126.1 (q, JCF = 284 Hz), 128.6, 129.4, 129.7, 158.7, 166.2; IR ν 3220, 2992, 2947, 2838, 1733, 1605, 1568, 1464, 1431, 1082 cm⁻¹; LC/MS 287.7 [M + H⁺]; HRMS (EI) m/z calcd for C₁₄H₁₆F₃NO₂ [M⁺] 287.1133, found 287.1145.

3-(3,4-Dihydroisoquinolin-1-yl)-1,1,1-trifluoro-2-methylpropan-2-ol (4b)

To a solution of 2b (50.0 mg, 0.21 mmol) in THF (1.0 mL) was added 3.0 M MeMgBr in diethyl ether (0.10 mL, 0.31 mmol) at rt. The reaction mixture was stirred at rt for 10 min and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford 4b (50 mg, 0.2 mmol, 94%); TLC Rᵋ = 0.53 (EtOAc/hexanes = 2/8); colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, br, 1H), 7.38-7.45 (m, 2H), 7.36 (d, J = 7.4 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 3.60-3.75 (m, 2H), 3.17 (d, J = 16.4 Hz, 1H), 2.81 (d, J = 16.4 Hz, 1H), 2.73 (t, J = 7.4 Hz, 2H), 1.46 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 22.8, 25.7, 35.3, 45.7, 73.5 (q, JCF = 27.9 Hz), 124.7, 126.3 (q, JCF = 284 Hz), 127.3, 127.9, 131.5, 137.4, 166.4; IR ν 3375, 3056, 2980, 2759, 1617, 1569, 1294, 1278, 1141, 1093, 865, 758 cm⁻¹; LC/MS 258.1 [M + H⁺]; HRMS (EI) m/z calcd for C₁₃H₁₄F₃NO [M⁺] 257.1027, found 257.1034.
1,1,1-Trifluoro-2-methyl-3-(4-methyl-3,4-dihydroisoquinolin-1-yl)propan-2-ol (4c)

To solution of 2c (200 mg, 0.78 mmol) in THF (5 mL) was added 3.0 M MeMgBr in Et₂O (0.39 mL, 1.17 mmol) at rt and stirred for 30 min. The reaction mixture was treated with sat. NH₄Cl (aq) solution and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The crude product obtained was purified through column chromatography using EtOAC/hexanes (1/3) as an eluent to afford 4c (180 mg, 0.66 mmol, 85%); TLC Rf = 0.58 (EtOAc/hexanes = 2/8); white solid. mp 83.3-85.0 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (s, br, 1H), 7.50-7.48 (m, 2H), 7.38-7.29 (m, 2H), 3.81-3.71 (s, 1H), 3.59-3.46 (s, 1H), 3.24-3.16 (m, 1H), 2.94-2.82 (m, 2H), 1.49 (s, 3H), 1.27 (dd, J = 7.0, 2.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 17.3, 17.5, 22.7, 22.9, 29.6, 29.7, 35.1, 35.2, 52.5, 52.6, 73.7 (q, ²J_C-F = 27.9 Hz), 124.7, 124.7, 126.0, 126.1, 126.4 (q, ¹J_C-F = 284 Hz), 126.9, 127.0, 127.9, 127.9, 131.8, 142.3, 142.4, 166.2; IR ν 3067, 2846, 2777, 1618, 1570, 1464, 1276, 1137, 1089, 1015, 961, 748 cm⁻¹; LC/MS 272.1 [M + H⁺]; HRMS (EI) m/z calcld for C₁₄H₁₆F₃NO [M⁺] 271.1184, found 271.1183

1,1,1-Trifluoro-3-(6-methoxy-3,4-dihydroisoquinolin-1-yl)-2-methylpropan-2-ol (4d)

To a solution of 2d (50.0 mg, 0.18 mmol) in THF (1.0 mL) was added 3.0 M MeMgBr in Et₂O (0.09 mL, 0.28 mmol) at rt and stirred for 10 min. The reaction mixture was quenched with saturated NH₄Cl (aq), extracted with EtOAc (2 x 25 mL), and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford 4d (50 mg, 0.2 mmol, 96%); TLC Rf = 0.56 (EtOAc/hexanes = 2/8); colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.38 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.72 (s, 1H), 3.84 (s, 3H), 3.62-3.69 (m, 2H), 3.10 (d, J = 16.2 Hz, 1H), 2.75 (d, J = 16.5 Hz, 1H), 2.70 (t, J = 7.3 Hz, 2H), 1.45 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 22.8, 26.3, 35.2, 45.5, 55.4, 73.5 (q, ²J_C-F = 27.8 Hz), 112.2, 113.3, 122.4, 126.3 (q, ¹J_C-F = 284 Hz), 126.7, 139.8, 161.8, 165.9; IR ν 3390, 2952, 2765, 2580, 2244, 1604, 1568, 1315, 1251, 1137, 1093, 1026, 961, 748 cm⁻¹; LC/MS 287.9 [M + H⁺]; HRMS (EI) m/z calcld for C₁₄H₁₆F₃NO₂ [M⁺] 287.1133, found 287.1127.
3-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)-1,1,1-trifluoro-2-methylpropan-2-ol (4e)

To a solution of 2e (205 mg, 0.68 mmol) in THF (5 mL) was added 3.0 M MeMgBr in Et₂O (0.33 mL, 0.99 mmol) at rt and stirred for 30 min. The reaction mixture was quenched with saturated NH₄Cl (aq) solution and extracted with EtOAc (2 X 20 mL). The organic layers were washed with water followed by saturated brine solution. The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude mixture was purified through column chromatography using EtOAC/hexanes (1/1) as an eluent to afford 4e (180 mg, 0.57 mmol, 83%); TLC Rₜ = 0.60 (EtOAc/hexanes = 2/8); white solid; mp 107.2-109.0 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.23 (s, br, 1H), 6.92 (s, 1H), 6.72 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.74-3.58 (m, 1H), 3.15-3.09 (m, 1H), 2.79-2.73 (m, 1H), 2.67 (t, J = 7.65 Hz, 2H), 1.48 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 22.7, 25.4, 35.3, 45.6, 56.0, 56.3, 73.5 (q, ²J_C-F = 27.9 Hz), 108.3, 110.5, 121.7, 126.3, (q, ¹J_C-F = 284 Hz), 131.4, 147.7, 151.6, 165.7.; IR ν 3095, 2973, 2781, 1608, 1567, 1465, 1363, 1268, 1211, 1140, 1093, 1031, 967, 865,784 cm⁻¹; LC/MS 318.1 [M + H⁺]; HRMS (EI) m/z calcld for C₁₅H₁₈F₃NO₃ [M⁺] 317.1239, found 317.1237

1,1,1-Trifluoro-3-(7-fluoro-3,4-dihydroisoquinolin-1-yl)-2-methylpropan-2-ol (4f)

To a solution of 2f (80.0 mg, 0.31 mmol) in THF (1.2 mL) was added 3.0 M MeMgBr in Et₂O (0.15 mL, 0.46 mmol) at rt and stirred for 15 min. The reaction mixture was quenched with NH₄Cl (aq) and extracted with EtOAc (2 X 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAC/hexanes (1/2) as an eluent to afford 4f (91 mg, 0.3 mmol, 86%); TLC Rₜ = 0.52 (EtOAC/hexanes = 2/8); colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (s, br, 1H), 7.07-7.21 (m, 3H), 3.66-3.73 (m, 2H), 3.12 (d, J = 16.4 Hz, 1H), 2.76 (d, J = 16.4 Hz, 1H), 2.69 (t, J = 7.5 Hz, 2H), 1.46 (d, J = 0.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 22.8, 35.5, 45.9, 73.6 (q, ²J_C-F = 27.9 Hz), 111.8 (d, J = 22.5 Hz), 118.2 (d, J = 21.1 Hz), 126.2 (q, ¹J_C-F = 284 Hz), 129.2 (d, J = 7.5 Hz), 129.9 (d, J = 6.5 Hz), 132.9 (d, J = 3.0 Hz), 161.7 (d, J = 244.4 Hz), 165.4; IR ν 3317, 2944, 1626, 1578, 1491, 1264, 1147, 1102, 1027, 887, 868,747 cm⁻¹; LC/MS 276.1 [M + H⁺]; HRMS (EI) m/z calcld for C₁₃H₁₈F₄NO [M⁺] 275.0933, found 275.0929.
3-(4,9-Dihydro-3H-pyrido[3,4-b]indol-1-yl)-1,1,1-trifluoro-2-methylpropan-2-ol (4g)

To a solution of 2g (50 mg, 0.18 mmol) in THF (1.0 mL) was added 3.0 M MeMgBr in diethyl ether (0.18 mL, 0.53 mmol) at rt. The reaction mixture was stirred at same temperature for 10 min and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (25 mL x 2) and washed with H₂O. The combined organic layer was dried over Na₂SO₄ and evaporated under vacuum to get a crude product which was purified through silica gel column chromatography using EtOAc/hexanes (2/1) as an eluent to afford 4g (42 mg, 0.14 mmol, 80%); TLC Rₐ = 0.3 (EtOAc/hexanes = 2/1); white solid; mp 144.1-146.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.40 (s, br, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.1 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 5.42 (s, br, 2H), 4.06-4.14 (m, 2H), 2.91 (s, br, 2H); ¹³C NMR (125 MHz, DMSO-d₆) δ 18.9, 21.5, 47.7, 73.2 (q, ²JCF = 27.4 Hz), 112.9, 116.1, 120.2, 120.2, 124.6, 125.1, 126.9 (q, ¹JCF = 284.9 Hz), 129.1, 137.2, 159.1; IR ν 3405, 3105, 2959, 2720, 2510, 1602, 1543, 1369, 1281, 1134, 1092, 863, 727 cm⁻¹; LC/MS 297.11 [M + H⁺], 593.3 [2M + H⁺]; HRMS (EI) m/z calcd for C₁₅H₁₅F₃N₂O [M⁺] 296.1136, found 296.1134

1,1,1-Trifluoro-2-((7-methoxy-3,4-dihydroisoquinolin-1-yl)methyl)butan-2-ol (4h)

To a solution of compound 2a (50.0 mg, 0.18 mmol) in THF (1.0 mL) was added 3.0 M EtMgBr in diethyl ether (0.09 mL, 0.28 mmol) at rt. The reaction mixture was stirred at rt for 10 min and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford the title compound 4h (52 mg, 0.2 mmol, 95%); TLC Rₐ = 0.53 (EtOAc/hexanes = 2/8); colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 8.24 (s, br, 1H), 7.15 (d, J = 8.1 Hz, 1H), 6.95-7.01 (m, 2H), 3.86 (s, 3H), 3.61-3.71 (m, 2H), 3.07 (d, J = 16.2 Hz, 1H), 2.82 (d, J = 16.2 Hz, 1H), 2.67 (t, J = 7.5 Hz, 2H), 1.86-1.95 (m, 1H), 1.59-1.78 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 7.5, 24.8, 28.4, 32.2, 46.0, 55.5, 75.7 (q, ²JCF = 26.4 Hz), 111.1, 116.3, 124.7, 126.8 (q, ¹JCF = 286 Hz), 128.6, 129.4, 129.6, 130.2, 158.7, 166.8; IR ν 3125, 2939, 2836, 1607, 1571, 1461, 1428, 1281, 1262, 1139, 1108, 1044, 987, 814 cm⁻¹; LC/MS 302.0 [M + H⁺]; HRMS (EI) m/z calcd for C₁₅H₁₈F₃NO₂ [M⁺] 301.1290, found 301.1292.
1,1,1-Trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1-yl)-2-phenylpropan-2-ol (4i)

To a solution of compound 2a (50.0 mg, 0.18 mmol) in THF (1.0 mL) was added PhMgBr (0.28 mL, 0.28 mmol) at rt. The reaction mixture was stirred at rt for 2 h and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford the title compound 4i (41 mg, 0.12 mmol, 64%); TLC Rf = 0.57 (EtOAc/hexanes = 2/8); white solid; mp 74.3-75.2 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.62 (d, J = 7.2 Hz, 2H), 7.25-7.35 (m, 3H), 7.06 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.92 (dd, J = 8.2, 2.3 Hz, 1H), 3.83 (s, 3H), 3.42-3.55 (m, 4H), 2.32-2.58 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.7, 35.02, 45.9, 55.6, 76.6 (q, J_C-F = 27.9 Hz), 110.9, 116.3, 125.3 (q, J_C-F = 284 Hz), 128.1, 128.2, 128.6, 129.3, 129.7, 139.1, 158.7, 156.9; IR ν 3020, 2999, 2932, 2832, 1602, 1500, 1444, 1309, 1230, 1140, 1074, 1014, 963, 899, 841, 824 cm⁻¹; LC/MS 350.1 [M + H⁺]; HRMS (EI) m/z calcd for C₁₉H₁₈F₃NO₂ [M⁺] 349.1290, found 349.1297.

2-(4-Chlorophenyl)-1,1,1-trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1-yl)propan-2-ol (4j)

To a solution of compound 2a (50 mg, 0.18 mmol) in THF (1.0 mL) was added 1.0 M 4-chlorophenylphenyl magnesium bromide in diethyl ether (0.28 mL, 0.28 mmol) at rt. The reaction mixture was stirred at rt for 2 h and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford unstable 4j (43 mg, 0.1 mmol, 61%); TLC Rf = 0.55 (EtOAc/hexanes = 2/8); white solid; mp 104.9-105.8 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.59 (s, br, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 1H), 7.04 (s, 1H), 6.97 (d, J = 8.2 Hz, 1H), 3.88 (s, 3H), 3.53-3.60 (m, 2H), 2.54-2.61 (m, 1H), 2.38-2.44 (m, 1H); IR ν 3314, 3117, 2942, 2832, 1602, 1500, 1444, 1309, 1252, 1140, 1074, 1014, 963, 899, 841, 824 cm⁻¹; LC/MS 383.9 [M + H⁺]; HRMS (FAB+) m/z calcd for C₁₉H₁₈ClF₃NO₂ [M⁺] 384.0978, found 384.0992.

*Note: Due to unstable nature of trifluoromethylcarbinols 4j, 4k and 4m at rt, for the purpose of NMR confirmation these compounds were promptly reduced using NaBH₄ to obtain diastereomeric mixtures of stable 1,3-aminoalcohols in good yields.
2-(4-Chlorophenyl)-1,1,1-trifluoro-3-(7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-ol (5j)

To a solution of 4d (40 mg, 0.10 mmol) in MeOH (1.0 mL) was added NaBH₄ (10 mg, 0.26 mmol) and stirred at rt for 10 min. The reaction mixture was quenched with H₂O and the solvent was evaporated under vacuum. The crude mixture was extracted with EtOAc (2 x 25 mL) and washed with saturated NaCl (aq). The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum.

The crude mixture was purified on silica gel column chromatography using EtOAc/hexanes (1/1) as an eluent to afford 5j (39 mg, 0.1 mmol, 98%); TLC Rf = 0.32 (EtOAc/hexanes = 1/1); white solid; mp 118.9-120.7 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 7.9 Hz, 0.5H), 7.52 (d, J = 7.9 Hz, 1.5H), 7.43 (d, J = 7.9 Hz, 0.5H), 7.29 (d, J = 7.9 Hz, 1.5H), 6.99 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.58 (s, 0.8H), 6.38 (s, 0.2H), 4.63 (d, J = 12.3 Hz, 1H), 3.78 (s, 3H), 3.04-3.15 (m, 2H), 2.67-2.71 (m, 2H), 2.37-2.54 (m, 1H), 2.03-2.17 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 27.6, 36.5, 37.4, 37.6, 126.0, 126.2, 127.1, 128.2, 128.7, 128.7, 130.5, 131.9, 133.5, 136.7, 137.9, 139.5, 157.9; IR ν 3316, 2953, 2923, 2829, 1605, 1499, 1490, 1254, 1219, 1305, 1332, 1158, 1132, 1025, 898, 828, 663 cm⁻¹; LC/MS 385.9 [M + H⁺]; HRMS (EI) m/z calcd for C₁₉H₁₉ClF₃NO₂ [M⁺] 385.1056, found 385.1041

1,1,1-Trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1-yl)-2-(4-methoxyphenyl)propan-2-ol (4k)

To a solution of compound 2a (50 mg, 0.18 mmol) in THF (1.0 mL) was added 0.5 M 4-methoxyphenylmagnesium bromide in THF (0.55 mL, 0.28 mmol) at rt. The reaction mixture was stirred at rt for 2 h and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford 4k. The isolated compound was highly unstable. Hence, it was directly used for the next step (46 mg, 0.1 mmol, 66%); TLC Rf = 0.49 (EtOAc/hexanes = 2/8); colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.96 (d, J = 8.5, 2.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.53-3.61 (m, 2H), 3.47 (d, J = 16 Hz, 1H), 3.39 (d, J = 16 Hz, 1H), 2.54-2.60 (m, 1H), 2.38-2.45 (m, 1H); LC/MS 380.1 [M + H⁺].
1,1,1-Trifluoro-3-(7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-(4-methoxyphenyl)propan-2-ol (5k)

To a solution of 4e (45 mg, 0.12 mmol) in MeOH (1.0 mL) was added NaBH₄ (6.7 mg, 0.2 mmol) at 0 °C. The reaction mixture was stirred at rt for 10 min and the solvent was evaporated under vacuum. The solid obtained was dissolved in H₂O and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/1) as an eluent to afford a diastereomeric mixture (50:50 based on LC/MS) of 5k (38 mg, 0.099 mmol, 84%); TLC Rf = 0.26 (EtOAc/hexanes = 1/1); white solid; mp 125.7-126.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.51 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.61 (s, 1H), 4.64 (d, J = 12.4 Hz, 1H), 3.79 (s, 6H), 3.06-3.12 (m, 2H), 2.52-2.70 (m, 3H), 2.09-2.19 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 27.7, 37.3, 39.0, 52.5, 55.2, 55.4, 111.8, 112.7, 113.4, 126.0, 126.6 (q, JCF = 286 Hz), 126.8, 130.4, 133.1, 138.3, 157.9, 159.2; IR ν 3303, 3012, 2943, 2843, 2024, 1607, 1496, 1457, 1281, 1162, 1139, 1031, 912, 884 cm⁻¹; LC/MS 381.9 [M + H⁺]; HRMS (FAB⁺) m/z calcd for C₂₀H₂₃ClF₃NO₃ [M + H⁺] 382.1630, found 382.1624

2-Benzyl-1,1,1-trifluoro-3-(7-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-ol (4l)

To a solution of compound 2a (50 mg, 0.18 mmol) in THF (1.0 mL) was added 2.0 M benzylmagnesium chloride in THF (0.14 mL, 0.28 mmol) at rt. The reaction mixture was stirred at rt for 2 h and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford 4l (48 mg, 0.1 mmol, 72%); TLC Rf = 0.55 (EtOAc/hexanes = 2/8); white solid; mp 50.2-51.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.57 (s, br, 1H), 7.23-7.29 (m, 5H), 7.06 (d, J = 8.4 Hz, 1H), 6.90 (s, br, 2H), 3.81 (s, 3H), 3.49 (t, J = 6.8 Hz, 2H), 3.23 (d, J = 13.8 Hz, 1H), 3.03 (d, J = 16.4 Hz, 1H), 2.85 (d, J = 13.8 Hz, 1H), 2.60 (d, J = 16.4 Hz, 1H), 2.41-2.62 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.6, 31.9, 41.2, 45.8, 55.5, 76.3 (q, JCF = 26.3 Hz), 111.2, 116.1, 126.5, (q, JCF = 286 Hz), 126.9, 127.7, 128.5, 129.4, 129.5, 131.2, 135.5, 158.6, 166.6; IR ν 3085, 2951, 2835, 2165, 1631, 1573, 1413, 1430, 1281, 1162, 1110, 1043, 1010, 918, 865 cm⁻¹; LC/MS 364.0 [M + H⁺]; HRMS (EI) m/z calcd for C₂₀H₂₂F₂NO₂ [M⁺] 363.1446, found 363.1430
(Z)-1,1,1-trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1(2H)-ylidene)propan-2-one (3a)

To a solution of 2a (50 mg, 0.18 mmol) in THF (1.0 mL) was added iPrMgBr 1.3 M in THF (0.42 mL, 0.54 mmol) at rt and the reaction mixture was stirred for 30 min. The reaction mixture was treated with sat. NH₄Cl (aq) solution and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The crude product obtained was purified through column chromatography using EtOAC/hexanes (1/3) as an eluent to afford 3a (44 mg, 0.16 mmol, 88%); TLC Rf = 0.5 (2:8 EtOAc/hexanes); slightly yellow solid. mp 114.6-116.1 °C; ¹H NMR (500 MHz, CDCl₃) δ 11.60 (s, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 2.6 Hz, 1H), 5.94 (s, 1H), 3.89 (s, 3H), 3.61-3.57 (m, 2H), 2.94 (t, J = 6.8 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 176.3 (q, ²JCF = 32.6 Hz), 162.3, 158.8, 129.4, 128.6, 128.5, 118.5, 118.5, 117.8 (q, ¹JC-F = 286.5 Hz), 111.2, 83.8, 55.6, 39.2, 26.8; IR ν 3184, 2916, 1588, 1564, 1489, 1278, 1231, 1117, 867 cm⁻¹; HRMS (EI) m/z calcd for C₁₃H₁₁F₃NO₂ [M⁺] 271.0820, found 271.0835.

*In case of cyclopentyl and cyclohexyl magnesium bromides, 3a was obtained in 76 and 72% yields, respectively.

1-(7-Methoxy-3,4-dihydroisoquinolin-1-yl)-2-methylpropan-2-ol (4m)

(Z)-1-(7-Methoxy-3,4-dihydroisoquinolin-1(2H)-ylidene)propan-2-one (3b)

To a solution of 2i (50 mg, 0.23 mmol) in THF (1.0 mL) was added 3.0 M MeMgBr in diethyl ether (0.12 mL, 0.35 mmol) at rt. The reaction mixture was stirred at rt for 2 h and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (2 x 25 mL) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford 4m (30 mg, 0.1 mmol, 55%); TLC Rf = 0.52 (EtOAc/hexanes = 3/7); colorless oil; and 3b (17.5 mg, 0.08 mmol, 35%); TLC Rf = 0.31 (EtOAc/hexanes = 3/7); yellow solid; mp 76.9-78.1 °C; Unstable 4m had a tendency to be transformed to DHIQ 1a during purification. Basification of silica gel and running column chromatography expeditiously could overcome this conversion.
4m: ^1^H NMR (300 MHz, CDCl₃) δ 7.13 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 8.4, 2.4 Hz, 1H), 3.85 (s, 3H), 3.67-3.72 (m, 2H), 2.81 (s, 2H), 2.66 (t, J = 2.6 Hz, 1H), 1.34 (s, 6H); LC/MS 233.9 [M + H]^+.

3b: ^1^H NMR (500 MHz, CDCl₃) δ 11.25 (s, br, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.97 (dd, J = 8.3, 2.6 Hz, 1H), 5.62 (s, 1H), 3.87 (s, 3H), 3.43-3.47 (m, 2H), 2.86 (t, J = 6.6 Hz, 2H), 2.18 (s, 3H); ^13^C NMR (125 MHz, CDCl₃) δ 22.7, 29.4, 38.7, 55.4, 89.9, 110.4, 116.9, 128.9, 129.2, 129.9, 156.8, 158.5, 195.7; IR ν 3056, 2963, 2836, 1661, 1597, 1550, 1490, 1319, 1248, 1137, 1030, 979 cm⁻¹; LC/MS 218.1 [M + H]^+; HRMS (EI) m/z calcld for C₁₃H₁₅NO₂ [M⁺] 217.1103, found 217.1120.

1-(7-Methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-methylpropan-2-ol (5m)

To a solution of 4m (30 mg, 0.13 mmol) in MeOH (1.0 mL) was added NaBH₄ (6.7 mg, 0.2 mmol) at 0 °C. The reaction mixture was stirred at rt for 10 min and the solvent was evaporated under vacuum. The solid obtained was dissolved in H₂O and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified on silica gel column chromatography using EtOAc/hexanes (1/1) as an eluent to afford diastereomeric mixture (50:50 based on LC/MS) of 5m (26 mg, 0.11 mmol, 85%); TLC Rₜ = 0.25 (EtOAc/hexanes = 1/1); white solid; ^1^H NMR (300 MHz, CDCl₃) δ 6.98 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.52 (s, 1H), 4.28 (d, J = 12.0 Hz, 1H), 3.78 (s, 3H), 3.19-3.08 (m, 2H), 2.68 (s, 2H), 1.99 (t, J = 13.0 Hz, 1H), 1.68-1.66 (m, 1H), 1.40 (s, 3H), 1.22 (s, 3H); ^13^C NMR (125 MHz, CDCl₃) δ 28.1, 28.4, 31.7, 37.9, 45.5, 52.9, 55.3, 70.4, 111.5, 112.3, 126.6, 130.4, 140.1, 157.8; IR ν 3279, 2961, 2916, 2832, 1608, 1500, 1420, 1249, 1146, 1120, 1037, 849, 771, 663 cm⁻¹; LC/MS 235.9 [M + H]^+; HRMS (EI) m/z calcld for C₁₄H₂₁NO₂ [M⁺] 235.1572, found 235.1556.

(Z)-2-(7-Methoxy-3,4-dihydroisoquinolin-1(2H)-ylidene)-1-phenylethan-1-one (3c)

To a solution of compound 2j (50.0 mg, 0.18 mmol) in THF (1.0 mL) was added 3.0 M MeMgBr in Et₂O (0.18 mL, 0.54 mmol) at rt. The reaction mixture was stirred at rt for 2 h and quenched with saturated NH₄Cl (aq). The mixture was extracted with EtOAc (25 mL x 2) and washed with H₂O. The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to get a crude mixture which was purified through silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford 3c (29 mg, 0.1 mmol, 58%); TLC Rₜ = 0.36 (EtOAc/hexanes = 3/7); yellow oil; ^1^H NMR (300 MHz, CDCl₃) δ...
MHz, CDCl$_3$) $\delta$ 11.81 (s, br, 1H), 7.92-7.95 (m, 2H), 7.41-7.45 (m, 3H), 7.33 (d, $J = 2.5$ Hz, 1H), 7.17 (d, $J = 8.3$ Hz, 1H), 6.99 (dd, $J = 8.3$, 2.5 Hz, 1H), 3.87 (s, 3H), 3.50-3.56 (m, 2H), 2.89 (t, $J = 6.6$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.8, 158.6, 158.4, 140.9, 130.5, 130.3, 129.2, 128.9, 128.2, 126.9, 116.8, 111.0, 86.9, 55.5, 38.9, 27.6; IR $\nu$ 3053, 2936, 2832, 1595, 1560, 1483, 1315, 1240, 1145, 1061, 1036, 863, 760 cm$^{-1}$; LC/MS 280.1 [M + H$^+$]; HRMS (EI) $m/z$ calcd for C$_{18}$H$_{17}$NO$_2$ [M$^+$] 279.1259, found 279.1254.

(Z)-1,1,1-Trifluoro-3-(6-methoxy-3,4-dihydroisoquinolin-1(2H)-ylidene)propan-2-one (3d)

To a solution of 6-methoxy-1-methyl-3,4-dihydroisoquinoline (1d, 1.0 g, 5.7 mmol) in THF (10 mL) was added TF$_2$A (2.0 mL, 14 mmol) followed by Et$_3$N (2.40 mL, 17.1 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 min, quenched with H$_2$O and extracted with EtOAc (2 X 100 mL). The combined organic layer was dried over Na$_2$SO$_4$ and evaporated under vacuum to get a crude product which was purified through silica gel column chromatography using EtOAc/Hexanes (1/2) as an eluent to afford 3d. Geometric isomerism was unambiguously determined based on the x-ray crystallography structure of 3d (1.4 g, 5.2 mmol, 90%); TLC $R_f = 0.31$ (EtOAc/hexanes = 3/7); white solid; mp 167.4-168.5 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.52 (s, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 1H), 6.76 (s, 1H), 5.88 (s, 1H), 3.87 (s, 3H), 3.55-3.59 (s, 2H), 2.95 (t, $J = 6.8$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 27.9, 38.9, 55.5, 83.2, 113.3, 118.0 (q, $^1$J$_{C,F} = 286.5$ Hz), 120.1, 128.4, 138.9, 162.4, 163.1, 175.4 (q, $^2$J$_{C,F} = 32.1$ Hz); IR $\nu$ 3188, 2967, 2918, 1610, 1587, 1490, 1455, 1319, 1245, 1093, 1040, 855, 775 cm$^{-1}$; LC/MS 272.1 [M + H$^+$]; HRMS (EI) $m/z$ calcd for C$_{13}$H$_{12}$F$_3$NO$_2$ [M$^+$] 271.0820, found 271.0829

One-Pot Synthesis of 4a

1,1,1-Trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1-yl)-2-methylpropan-2-ol (4a)

To a solution of a 1a (50 mg, 0.28 mmol) in THF (3 mL) was added TFAA (0.04 mL, 0.31 mmol) at 0 °C. The resulting mixture was stirred at rt for 10 min. TLC analysis showed the complete disappearance of starting material. The reaction mixture was then concentrated to remove THF to afford crude 2a as a yellow oil. To a solution of crude 2a in THF (3 mL) was added 3.0 M MeMgBr in diethyl ether (0.14 mL, 0.42 mmol) at rt. The resulting mixture was stirred at rt for 10 min. The reaction was quenched NH$_4$Cl (aq), water and then extracted with EtOAc (2 X 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under vacuum. The crude mixture was purified on silica gel column chromatography
using EtOAc/Hex (1/2) as an eluent to afford 4a (51 mg, 0.18 mmol, 64%); TLC $R_f = 0.50$ (EtOAc/hexanes = 2/8); colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 (s, br, 1H), 7.13 (d, $J = 9.0$ Hz, 1H), 6.99–6.92 (m, 2H), 3.83 (s, 3H), 3.79–3.56 (m, 3H), 3.13 (d, $J = 16.4$ Hz, 1H), 2.79 (d, $J = 16.4$ Hz, 1H), 2.66 (t, $J = 7.5$ Hz, 2H), 1.46 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 22.7, 24.8, 35.3, 46.1, 55.5, 73.6 (q, $^2$J$_{C\cdot F} = 28$ Hz), 110.9, 116.4, 124.7, 126.1 (q, $^1$J$_{C\cdot F} = 284$ Hz), 128.6, 129.4, 129.7, 158.7, 166.2; LC/MS 287.7 [M + H$^+$].

Alternate Procedure for the Synthesis of 4a

1,1,1-Trifluoro-3-(7-methoxy-3,4-dihydroisoquinolin-1-yl)-2-methylpropan-2-ol (4a)

To a solution of a 2a (50 mg, 0.18 mmol) in THF (1.0 mL) was added 3.0 M MeLi in diethoxymethane (0.090 mL, 0.27 mmol) at 0 °C. The resulting mixture was stirred at rt for 1 h. The reaction was quenched with NH$_4$Cl (aq), water and then extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under vacuum. The crude mixture was purified on silica gel column chromatography using EtOAc/Hex (1/2) as an eluent to afford 4a (29 mg, 0.10 mmol, 57%); TLC $R_f = 0.50$ (EtOAc/hexanes = 2/8); colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.09 (s, br, 1H), 7.15 (d, $J = 9.0$ Hz, 1H), 6.98-6.95 (m, 2H), 3.86 (s, 3H), 3.73-3.65 (m, 2H), 3.15 (d, $J = 16.2$ Hz, 1H), 2.82 (d, $J = 16.5$ Hz, 1H), 2.68 (t, $J = 7.5$ Hz, 2H), 1.45 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 22.7, 24.8, 35.3, 46.1, 55.5, 73.6 (q, $^2$J$_{C\cdot F} = 28$ Hz), 110.9, 116.4, 124.7, 126.1 (q, $^1$J$_{C\cdot F} = 284$ Hz), 128.6, 129.4, 129.7, 158.7, 166.2; 73.6 (q, $^2$J$_{C\cdot F} = 28$ Hz), 110.9, 116.4, 124.7, 126.1 (q, $^1$J$_{C\cdot F} = 284$ Hz), 128.6, 129.4, 129.7, 158.7, 166.2; LC/MS 287.7 [M + H$^+$].
Crossover experiment

To a mixture of 2b (50 mg, 0.21 mmol) and 2i (45 mg, 0.21 mmol) in THF (3 mL) was added 3.0 M MeMgBr in diethyl ether (0.24 mL, 0.72 mmol) at rt. The resulting mixture was stirred at rt for 10 min. LC/MS analysis showed new peaks corresponding to 4b, 4m, and 3d in addition to unreacted 2i. There were no peaks matching with molecular weights of 4o, 4a, and 3e. The reaction was quenched with NH₄Cl (aq) and then extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under vacuum. The crude mixture was purified on silica gel column chromatography using EtOAc/Hex (1/2) as an eluent to afford 4b (38 mg, 0.15 mmol, 72%), 4m (5.0 mg, 0.021 mmol, 10%), 3d (1.2 mg, 5.5 μmol, 3%), and recovered 2i (28 mg, 0.13 mmol, 62%).

References
X-ray Crystallography Analysis of 4g

CCDC-1532366 contains the supplementary crystallographic data for 4g. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Crystal data and structure refinement for 4g

Identification code 20150901lt_0m
Empirical formula C_{15} H_{15} F_3 N_2 O
Formula weight 296.29
Temperature 100(1) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)/n
Unit cell dimensions
\[ a = 6.92630(10) \, \text{Å} \quad \alpha = 90^\circ. \]
\[ b = 8.72380(10) \, \text{Å} \quad \beta = 95.2920(10)^\circ. \]
\[ c = 22.5349(4) \, \text{Å} \quad \gamma = 90^\circ. \]
Volume 1355.84(3) Å³
Z 4
Density (calculated) 1.452 Mg/m³
Absorption coefficient 0.120 mm⁻¹
F(000) 616
Crystal size 0.28 x 0.18 x 0.08 mm³
Theta range for data collection 1.82 to 26.00°
Index ranges -8≤h≤8, 0≤k≤10, 0≤l≤27
Reflections collected 2669
Independent reflections 2669 [R(int) = 0.0000]
Completeness to theta = 26.00° 100.0 %
Absorption correction Multi-scan
Max. and min. transmission 0.9904 and 0.9671
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2669 / 0 / 190
Goodness-of-fit on F² 1.067
Final R indices [I>2sigma(I)] R1 = 0.0347, wR² = 0.0847
R indices (all data) R1 = 0.0382, wR² = 0.0876
Largest diff. peak and hole 0.398 and -0.482 e.Å⁻³
**X-ray Crystallography Analysis of 3a**

CCDC-1819355 contains the supplementary crystallographic data for 3a. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
Crystal data and structure refinement for 3a.

Identification code 20170922
Empirical formula C13 H12 F3 N O2
Formula weight 271.24
Temperature 296(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group C2/c
Unit cell dimensions a = 17.9537(9) Å \( \alpha = 90^\circ \),
b = 7.1369(3) Å \( \beta = 112.706(3)^\circ \),
c = 21.8227(14) Å \( \gamma = 90^\circ \).
Volume 2579.5(2) Å\(^3\)
Z 8
Density (calculated) 1.397 Mg/m\(^3\)
Absorption coefficient 0.123 mm\(^{-1}\)
F(000) 1120
Crystal size 0.50 x 0.40 x 0.20 mm\(^3\)
Theta range for data collection 2.51 to 29.89°.
Index ranges -24<=h<=22, -10<=k<=0, -30<=l<=21
Reflections collected 3711
Independent reflections 3711 [R(int) = 0.0000]
Completeness to theta = 29.89° 99.7 %
Absorption correction None
Max. and min. transmission 0.9758 and 0.9411
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 3711 / 0 / 200
Goodness-of-fit on F\(^2\) 1.027
Final R indices [I>2sigma(I)] R1 = 0.0596, wR2 = 0.1685
R indices (all data) R1 = 0.0842, wR2 = 0.1903
Largest diff. peak and hole 0.257 and -0.205 e.Å\(^{-3}\)
X-ray Crystallography Analysis of 3d

CCDC-1532365 contains the supplementary crystallographic data for 3d. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Crystal data and structure refinement for 3d

Identification code 20150722_0m
Empirical formula C13 H12 F3 N O2
Formula weight 271.24
Temperature 296(1) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)/c
Unit cell dimensions
a = 7.8606(2) Å  α = 90°
b = 8.5158(2) Å  β = 98.771(1)°
c = 18.6068(4) Å  γ = 90°

Volume 1230.96(5) Å³
Z 4
Density (calculated) 1.464 Mg/m³
Absorption coefficient 0.129 mm⁻¹
F(000) 560
Crystal size 0.56 x 0.20 x 0.12 mm³
Theta range for data collection 2.21 to 28.28°
Index ranges -9<=h<=10, -11<=k<=10, -24<=l<=24
Reflections collected 19921
Independent reflections 3068 [R(int) = 0.0221]
Completeness to theta = 28.28° 99.9%
Absorption correction Multi-scan
Max. and min. transmission 0.9847 and 0.9314
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3068 / 0 / 200
Goodness-of-fit on F² 1.029
Final R indices [I>2sigma(I)] R1 = 0.0439, wR2 = 0.1087
R indices (all data) R1 = 0.0581, wR2 = 0.1199
Largest diff. peak and hole 0.147 and -0.242 e.Å⁻³
$^{1}$H & $^{13}$C NMR Spectra

$^{1}$H NMR (300 MHz, DMSO-$d_6$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

precursor of 2h

$^1$H NMR (300 MHz, CDCl$_3$)

2h
$^{1}$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
\( ^1HNMR (300 \text{ MHz, DCI}_3) \)

\( ^{13}C\text{NMR (125 MHz, DCI}_3) \)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, DMSO-$d_6$)
$^1\text{H NMR (300 MHz, CDCl}_3\text{)}$

$^{13}\text{C NMR (125 MHz, CDCl}_3\text{)}$
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

4j

$^1$H NMR (300 MHz, CDCl$_3$)

5j
$^{13}$C NMR (125 MHz, CDCl$_3$)

$^1$H NMR (300 MHz, CDCl$_3$)

S46
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^{1} \text{H NMR (500 MHz, CDCl}_3\text{)}$

$^{13} \text{C NMR (125 MHz, CDCl}_3\text{)}$
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^{1}$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
LC/MS of Crossover Experiment