Copper (I) Reagent-Promoted Hydroxytrifluoromethylation of Enamides: Flexible Synthesis of Substituted-3-hydroxy-2-aryl-3-(2,2,2-trifluoro-1-arylethyl)isoindolin-1-one

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1. General information.

Unless otherwise noted, all reactions were carried out open to air in the oven-dried glass tubes with magnetic stirring. All reagents and solvents were purchased for commercial suppliers. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 aluminum plates and visualized with UV light (254nm). The pure products were obtained by means of column chromatography which was performed on silica gel (200-300 mesh).

2. Instrumentation.

The $^1$H NMR (400 MHz), $^{13}$C NMR (101 MHz), $^{19}$F NMR (376MHz) spectra were recorded at 23$^\circ$C with DMSO-d6/CDCl$_3$ as solvents on a Bruker 400 spectrometer and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in ppm from internal TMS ($\delta$), all coupling constants ($J$ values) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were obtained on a TOF machine (ESI-TOF). Multiplicities are recorded as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br s = broad singlet, m = multiplet.

3. Experimental Procedures

3.1 Preparation of 3-methyleneisoindolin-1-one (1a),[1]

A oven-dried Schlenk tube charged with a magnetic stirring bar was added 2-bromobenzylamide (1.380 g, 5 mmol), CuI (95 mg, 0.5 mmol), L-proline (180 mg, 1.5 mmol) and potassium carbonate (1.380 g, 1 0 mmol), and the tube was evacuated and backfilled with argon (3 times), and then phenylacetylene (830 µl, 7.5 mmol), and i-PrOH (10 mL) were added. The reaction mixture was stirred at 80 $^\circ$C for 16h. After removal of i-PrOH, the residues were filtrated with 20 ml water (3 times). The products were purified by regular column chromatography.

This template for synthesis of other substituted 3-methyleneisoindolin-1-one.
3.2 Preparation of 3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3a).

To a reaction tube equipped with a magnetic stirring bar were added 3-benzylidene-2-phenylisoindolin-1-one (1a) (297 mg, 1 mmol), CF$_3$SO$_2$Na (2) (474 mg, 3 mmol), CuBr (28.7 mg, 0.2 mmol) and K$_2$S$_2$O$_8$ (1082 mg, 4 mmol), and then CH$_3$CN (6 mL) and H$_2$O (3 mL) were added. The reaction mixture was stirred at room temperature for 30 min before being quenched by water (20 mL). Extract with ethyl acetate for three times (60 mL) and the organic phase was concentrated in vacuo and purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 6:1) to give the corresponding product 3a.

This template for synthesis of other substituted 3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one.

4. Characterization data

3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3a).

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 276 mg (72%); $^{1}$H NMR (400 MHz, DMSO-d$_6$) δ 7.98 (s, 1H), 7.91 (d, $J = 7.7$ Hz, 1H), 7.87 – 7.81 (m, 1H), 7.68 (dd, $J = 8.8$, 6.9 Hz, 2H), 7.40 (t, $J = 7.0$ Hz, 4H), 7.32 (d, $J = 3.3$ Hz, 1H), 7.21 (t, $J = 7.4$ Hz, 1H), 7.05 (t, $J = 7.7$ Hz, 2H), 4.12 (q, $J = 10.5$ Hz, 1H); $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ -59.31 (major), -59.89 (minor); $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ165.39, 144.58, 135.78, 133.29, 132.04, 130.81, 130.48, 129.07, 129.06, 128.85, 128.44, 128.23, 127.05, 126.65, 124.90 (q, $J = 6.6$ Hz), 123.35, 92.96, 55.95 (q, $J = 25.5$ Hz); HRMS (ESI-TOF): [M+Na]$^+$ m/z calcld for C$_{22}$H$_{16}$F$_3$NO$_2$Na$: 406.1031, found: 406.1029.

3-hydroxy-2-(m-tolyl)-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3b)
Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 258 mg (65%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.94 (s, 1H), 7.84 (t, $J = 7.2$ Hz, 1H), 7.69 (dd, $J = 13.5$, 7.1 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.24 (dd, $J = 15.4$, 7.9 Hz, 2H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.10 – 7.02 (m, 3H), 6.42 (d, $J = 7.4$ Hz, 2H), 4.11 (q, $J = 10.4$ Hz, 1H), 2.29 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.43 (major), -60.01 (minor); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 164.95, 144.11, 137.43, 132.74, 131.70, 130.50, 130.30, 129.71, 128.57, 128.14, 127.66, 127.27, 127.21, 124.49 (q, $J = 6.1$ Hz), 123.29, 122.84, 92.34, 55.59 (q, $J = 25.7$ Hz), 21.12; HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{23}$H$_{18}$F$_3$NO$_2$Na$^+$: 420.1187, found: 420.1184.

3-hydroxy-2-(p-tolyl)-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3c)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 298 mg (75%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.92 (s, 1H), 7.85 – 7.80 (m, 1H), 7.66 (t, $J = 6.5$ Hz, 2H), 7.33 (d, $J = 4.8$ Hz, 1H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.22 (dd, $J = 12.4$, 7.8 Hz, 3H), 7.06 (t, $J = 7.5$ Hz, 2H), 6.45 (d, $J = 7.4$ Hz, 2H), 4.09 (q, $J = 10.5$ Hz, 1H), 2.35 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.24 (major), -59.98 (minor); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$164.87, 157.74, 144.15, 135.93, 132.67, 132.55, 131.71, 130.26, 130.06, 129.66, 129.12, 128.87, 128.56, 127.73, 126.27, 124.43 (q, $J = 6.9$ Hz), 122.79, 92.40, 55.41 (q, $J = 25.7$ Hz), 20.68 (s); HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{23}$H$_{18}$F$_3$NO$_2$Na$^+$: 420.1187, found: 420.1193.

3-hydroxy-2-(4-methoxyphenyl)-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3d)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 322 mg (78%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.89 (d, $J = 7.4$ Hz, 1H), 7.85 (s, 1H), 7.69 – 7.63 (m, 2H), 7.24 (dd, 4H), 7.07 (t, $J = 7.7$ Hz, 2H), 6.98 (d, $J = 9.0$ Hz, 2H), 6.46 (d, $J = 7.5$ Hz, 2H), 4.05 (q, $J = 10.5$ Hz, 1H), 3.80 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.29 (major), -59.98 (minor); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$164.90, 157.74, 144.15, 132.60, 131.78, 130.48, 130.25, 130.11, 129.73, 128.57, 128.05, 127.75, 127.56, 124.41 (q, $J = 6.5$ Hz), 122.75, 113.58, 92.16, 55.44 (q, $J = 25.1$ Hz), 55.23; HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{23}$H$_{18}$F$_3$NO$_2$Na$^+$: 436.1136, found: 436.1143.

2-(4-fluorophenyl)-3-hydroxy-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3e)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 269 mg (67%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.00 (s, 1H),
7.93 (d, J = 7.5 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.37 (dd, J = 8.6, 5.1 Hz, 2H), 7.29 (d, J = 9.8 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.07 (t, J = 7.6 Hz, 2H), 6.47 (d, J = 7.4 Hz, 2H), 4.15 (q, J = 10.4 Hz, 1H); 19F NMR (376 MHz, DMSO-d6) δ -59.46 (major), -59.73 (minor), -114.98 (major), -115.21 (minor).; 13C NMR (101 MHz, DMSO-d6) δ164.95, 160.31 (d, J = 244.0 Hz), 144.10, 132.86, 131.48, 131.40 (d, J = 2.7 Hz), 130.36, 130.05, 129.64, 128.62, 128.37 (d, J = 8.4 Hz), 127.91, 127.79, 124.52 (q, J = 6.1 Hz), 122.91, 115.18 (d, J = 22.3 Hz), 92.31, 55.49 (q, J = 27.3 Hz); HRMS (ESI-TOF): [M+Na]+ m/z calcd for C22H15F4NO2Na+: 424.0937, found: 424.0935.

2-(2-chlorophenyl)-3-hydroxy-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one(3f)

Diastereomeric ratio (major: minor = 10:1) was determined by 19F NMR analysis of the unpurified product mixture. Faint yellow solid, 250 mg (60%); 1H NMR (400 MHz, CDCl3) δ 8.50 (d, J = 6.6 Hz, 1H), 8.05 (s, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.52 (t, J = 6.8 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.36 (dd, J = 5.0, 1.7 Hz, 3H), 7.12 (td, J = 7.9, 1.4 Hz, 1H), 5.14 (q, J = 8.4 Hz, 1H); 19F NMR (376 MHz, CDCl3) δ -60.56 (minor), -65.94 (major); 13C NMR (101 MHz, CDCl3) δ194.22, 165.98, 137.76, 135.62, 134.38, 131.81, 130.89, 130.24, 129.22, 129.13, 129.09, 127.96, 127.29, 125.49, 125.31, 124.21, 123.24, 122.70, 122.00, 59.33 (q, J = 26.3 Hz); HRMS (ESI-TOF): [M+Na]+ m/z calcd for C22H15ClF3NO2Na+: 440.0641, found: 440.0631.

2-(3-chlorophenyl)-3-hydroxy-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3g)

Diastereomeric ratio (major: minor = 10:1) was determined by 19F NMR analysis of the unpurified product mixture. Faint yellow solid, 250 mg (60%); 1H NMR (400 MHz, DMSO) δ 8.12 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.40 (dd, J = 5.0, 2.3 Hz, 1H), 7.31 (s, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.7 Hz, 2H), 6.44 (d, J = 7.5 Hz, 2H), 4.26 (q, J = 10.3 Hz, 1H); 19F NMR (376 MHz, DMSO) δ -59.55 (major), -59.62 (minor), -65.94 (major); 13C NMR (101 MHz, DMSO) δ165.40, 144.44, 137.25, 133.58, 133.05, 131.68, 130.96, 130.73, 130.44, 130.02, 129.47, 129.14, 128.23, 126.82, 126.21, 125.05, 124.68, 123.51, 93.06, 56.01 (q, J = 25.2 Hz); HRMS (ESI-TOF): [M+H]+ m/z calcd for C22H16ClF3NO2+: 418.0822, found: 418.0819.

3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-(p-tolyl)ethyl)isoindolin-1-one (3h)

Diastereomeric ratio (major: minor = 10:1) was determined by 19F NMR analysis of the unpurified product mixture. Faint yellow solid, 294 mg (74%); 1H NMR (400 MHz, DMSO-d6) δ 7.95 (s, 1H),
7.90 (d, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 6.5$ Hz, 1H), 7.67 (dd, $J = 8.5$, 6.8 Hz, 2H), 7.46 – 7.39 (m, 4H), 7.35 – 7.32 (m, 1H), 6.85 (d, $J = 7.8$ Hz, 2H), 6.29 (d, $J = 7.6$ Hz, 2H), 4.04 (q, $J = 10.6$ Hz, 1H), 2.17 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.34 (major), -59.99 (minor); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 165.41, 144.64, 138.45, 135.77, 133.24, 132.09, 130.76, 129.97, 129.04, 128.85, 128.80, 127.42, 127.08, 126.76, 124.91 (d, $J = 6.1$ Hz), 123.34, 93.04, 55.56 (q, $J = 25.4$ Hz), 20.98; HRMS (ESI-TOF): [M+H]$^+$ m/z calcd for C$_{23}$H$_{19}$F$_3$NO$_2$: 398.1368, found: 398.1327.

3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-(m-tolyl)ethyl)isoindolin-1-one (3i)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 302 mg (76%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.02 (s, 1H), 7.95 (d, $J = 7.5$ Hz, 1H), 7.84 (t, $J = 7.2$ Hz, 1H), 7.72 (d, $J = 7.2$ Hz, 1H), 7.68 (d, $J = 7.3$ Hz, 1H), 7.48 – 7.41 (m, 4H), 7.36 – 7.32 (m, 1H), 7.04 (d, $J = 7.5$ Hz, 1H), 6.93 (t, $J = 7.6$ Hz, 1H), 6.29 – 6.12 (m, 2H), 4.10 (q, $J = 10.5$ Hz, 1H), 2.03 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.31 (major), -59.88 (minor).; $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 164.94, 144.16, 136.79, 135.46, 132.70, 131.70, 130.24, 129.78, 129.08, 128.82, 128.56, 128.47, 127.55, 126.72, 126.50, 126.17, 124.48 (q, $J = 6.5$ Hz), 122.78, 92.57, 55.67 (q, $J = 25.5$ Hz), 20.66; HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{23}$H$_{18}$F$_3$NO$_2$Na$: 420.1187, found: 420.1196.

3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)isoindolin-1-one (3j)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 314 mg (76%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.93 (s, 1H), 7.89 (d, $J = 7.7$ Hz, 1H), 7.86 – 7.80 (m, 1H), 7.70 – 7.65 (m, 2H), 7.44 – 7.39 (m, 4H), 7.35 – 7.31 (m, 1H), 6.61 (d, $J = 8.9$ Hz, 2H), 6.31 (d, $J = 8.2$ Hz, 2H), 4.02 (q, $J = 10.6$ Hz, 1H), 3.64 (s, 3H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.53 (major), -59.88 (minor); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 164.95, 159.17, 144.15, 135.30, 132.76, 131.62, 130.82, 130.30, 128.38, 126.61, 126.30, 124.45 (q, $J = 6.4$ Hz), 122.88, 121.79, 119.76, 113.13, 92.59, 54.95, 54.67 (q, $J = 25.4$ Hz); HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{23}$H$_{18}$F$_3$NO$_3$Na$: 436.1136, found: 436.1136.

3-(1-(2-chlorophenyl)-2,2,2-trifluoroethyl)-3-hydroxy-2-phenylisoindolin-1-one (3k)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 175 mg (42%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.06 (s, 1H), 7.89 (d, $J = 3.8$ Hz, 2H), 7.84 (d, $J = 7.4$ Hz, 1H), 7.76 (dd, $J = 7.8$, 3.9 Hz, 2H), 7.51 (dd, $J = 20.8$,
13.0 Hz, 1H), 7.31 (d, J = 7.5 Hz, 4H), 7.07 (d, J = 7.4 Hz, 2H), 6.22 (d, J = 7.8 Hz, 1H), 4.78 (q, J = 9.7 Hz, 1H); \(^{19}\text{F NMR}\) (376 MHz, DMSO-d6) \(\delta\) -60.81 (major), -61.20 (minor); \(^{13}\text{C NMR}\) (101 MHz, DMSO-d6) \(\delta\) 164.84, 143.67, 136.56, 134.81, 133.16, 132.70, 131.72, 130.68, 130.51, 129.44, 128.66, 128.37, 127.68, 126.81, 126.13, 124.62 (q, J = 6.9 Hz), 123.15, 120.03, 92.04, 51.20 (q, J = 26.3 Hz); HRMS (ESI-TOF): [M+Na]\(^+\) m/z calcd for C\(_{22}\)H\(_{15}\)ClF\(_3\)NO\(_2\)Na\(^+\): 440.0641, found: 440.0645.

3-(1-(3-chlorophenyl)-2,2,2-trifluoroethyl)-3-hydroxy-2-phenylisoindolin-1-one (3l)

Diastereomeric ratio (major: minor = 10:1) was determined by \(^{19}\text{F NMR}\) analysis of the unpurified product mixture. Faint yellow solid, 267 mg (64%); \(^1\text{H NMR}\) (400 MHz, DMSO-d6) \(\delta\) 8.07 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.78 – 7.66 (m, 3H), 7.44 – 7.38 (m, 4H), 7.31 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.42 (d, J = 10.2 Hz, 2H), 4.28 (q, J = 10.3 Hz, 1H); \(^{19}\text{F NMR}\) (376 MHz, DMSO-d6) \(\delta\) -59.46 (major), -59.63 (minor); \(^{13}\text{C NMR}\) (101 MHz, DMSO-d6) \(\delta\) 164.92, 143.93, 135.28, 132.94, 132.34, 132.21, 131.42, 130.72, 130.49, 129.91, 129.52, 128.56, 128.39, 126.81, 126.65, 126.08, 124.44 (q, J = 6.9 Hz), 122.94, 92.22, 54.98 (q, J = 25.2 Hz); HRMS (ESI-TOF): [M+H]\(^+\) m/z calcd for C\(_{22}\)H\(_{16}\)ClF\(_3\)NO\(_2\): 418.0822, found: 418.0823.

3-(1-(4-chlorophenyl)-2,2,2-trifluoroethyl)-3-hydroxy-2-phenylisoindolin-1-one (3m)

Diastereomeric ratio (major: minor = 10:1) was determined by \(^{19}\text{F NMR}\) analysis of the unpurified product mixture. Faint yellow solid, 234 mg (56%); \(^1\text{H NMR}\) (400 MHz, DMSO-d6) \(\delta\) 8.04 (s, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.3 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 6.8 Hz, 3H), 7.36 – 7.32 (m, 1H), 6.91 (t, J = 8.6 Hz, 2H), 6.53 – 6.44 (m,
2H), 4.23 (q, J = 10.3 Hz, 1H); 19F NMR (376 MHz, DMSO-d6) δ -59.60 (major), -60.12 (minor), -112.97 (major), -113.91 (minor); 13C NMR (101 MHz, DMSO-d6) δ164.94, 161.98 (d, J = 246.1 Hz), 143.98, 135.32, 132.87, 132.54, 131.68, 130.96 (d, J = 112.3 Hz), 128.43, 126.78, 126.59, 126.35, 126.13, 124.46 (q, J = 6.1 Hz), 122.95, 114.70 (d, J = 21.5 Hz), 92.43, 54.65 (q, J = 25.4 Hz); HRMS (ESI-TOF): [M+Na]+ m/z calcd for C22H15F4NO2Na+: 424.0937, found: 424.0935.

3-hydroxy-5-methyl-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3o)

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\text{Diastereomeric ratio (major: minor = 10:1) was determined by } \text{19F NMR analysis of the unpurified product mixture. Faint yellow solid, 317 mg (80%); } \text{1H NMR (400 MHz, DMSO-d6) } \delta 7.92 (s, 1H), 7.70 (s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.38 (dd, J = 9.8, 7.2 Hz, 4H), 7.34 – 7.30 (m, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.7 Hz, 2H), 6.42 (d, J = 7.6 Hz, 2H), 4.10 (q, J = 10.5 Hz, 1H), 2.54 (s, 3H); 19F NMR (376 MHz, DMSO-d6) δ -59.30 (major), -59.83 (minor); 13C NMR (101 MHz, DMSO-d6) δ165.39, 144.98, 143.55, 135.91, 131.51, 130.52, 130.11, 129.62, 129.04, 128.78, 128.20, 126.90, 126.60, 125.22 (q, J = 6.1 Hz), 124.85 123.26, 92.73, 55.99 (q, J = 25.5 Hz), 22.16; HRMS (ESI-TOF): [M+Na]+ m/z calcd for C23H18F3NO2Na+: 420.1187, found: 420.1200.

3-hydroxy-6-methyl-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3p)

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\text{Diastereomeric ratio (major: minor = 10:1) was determined by } \text{19F NMR analysis of the unpurified product mixture. Faint yellow solid, 330 mg (83%); } \text{1H NMR (400 MHz, DMSO-d6) } \delta 7.90 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.53 (s, 1H), 7.40 (d, J = 5.3 Hz, 4H), 7.34 – 7.32 (m, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.06 (t, J = 7.6 Hz, 2H), 6.43 (d, J = 7.6 Hz, 2H), 4.10 (q, J = 10.5 Hz, 1H), 2.46 (s, 3H); 19F NMR (376 MHz, DMSO-d6) δ -59.30 (major), -59.83 (minor); 13C NMR (101 MHz, DMSO-d6) δ165.52, 141.89, 140.65, 135.93, 134.00, 132.31, 130.62, 130.08, 129.00, 128.78, 128.21, 126.93, 126.58, 124.74 (q, J = 6.1 Hz), 123.51, 92.84, 56.04 (q, J = 25.5 Hz), 21.31; HRMS (ESI-TOF): [M+Na]+ m/z calcd for C23H18F3NO2Na+: 420.1187, found: 420.1181.

3-hydroxy-4-methyl-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3q)

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\text{white solid, 254 mg (64%); } \text{1H NMR (400 MHz, DMSO-d6) } \delta 7.92 (s, 1H), 7.59 – 7.49 (m, 3H), 7.37 (d, J = 7.2 Hz, 2H), 7.30 – 7.21 (m, 3H), 7.13 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 7.7 Hz, 2H), 6.64 (d, J = 7.5 Hz, 2H), 4.41 (q, J = 10.3 Hz, 1H), 2.70 (s, 3H); 19F NMR (376 MHz, DMSO-d6) δ -60.35 (s); 13C NMR (101 MHz, DMSO-d6) δ165.72, 143.58, 136.53, 135.90, 134.82, 134.08, 131.73, 131.09, 130.41,
5-chloro-3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3r)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. Faint yellow solid, 175 mg (42%); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.16 (s, 1H), 7.87 (s, 1H), 7.75 (d, $J$ = 9.8 Hz, 2H), 7.41 (d, $J$ = 5.6 Hz, 4H), 7.33 (d, $J$ = 2.6 Hz, 1H), 7.23 (t, $J$ = 7.3 Hz, 1H), 7.08 (t, $J$ = 7.5 Hz, 2H), 6.49 (d, $J$ = 7.5 Hz, 2H), 4.20 (q, $J$ = 10.4 Hz, 1H); $^{19}$F NMR (376 MHz, DMSO-d$_6$) $\delta$ -59.35 (major), -59.42 (minor).; $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 163.90, 146.18, 137.61, 135.09, 130.69, 130.31, 129.73, 129.62, 128.87, 128.75, 126.76, 126.58, 126.11, 124.83, 124.38 (q, $J$ = 6.8 Hz), 92.01, 55.30 (q, $J$ = 25.9 Hz); HRMS (ESI-TOF): [M+H]$^+$ m/z calcd for C$_{22}$H$_{18}$F$_3$NO$_2$: 398.0822, found: 398.0835.

6-chloro-3-hydroxy-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3s)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. white solid, 142 mg (34%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 (dd, $J$ = 8.2, 1.1 Hz, 1H), 7.65 (dd, $J$ = 8.2, 2.0 Hz, 1H), 7.20 – 7.11 (m, 5H), 7.11 – 7.05 (m, 2H), 6.95 (t, $J$ = 7.8 Hz, 2H), 6.21 (d, $J$ = 7.7 Hz, 2H), 4.92 (s, 1H), 3.95 (q, $J$ = 10.0 Hz, 1H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.58 (major), -61.62 (minor).; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.07, 141.65, 136.79, 134.21, 133.13, 132.80, 129.27, 128.88, 128.77, 128.36, 128.26, 127.94, 127.00, 125.73 (q, $J$ = 6.7 Hz), 125.62, 123.21, 93.13, 55.60 (q, $J$ = 26.7 Hz); HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{22}$H$_{15}$ClF$_3$NO$_2$Na$: 440.0641, found: 440.0631.

3-hydroxy-6-methoxy-2-phenyl-3-(2,2,2-trifluoro-1-phenylethyl)isoindolin-1-one (3t)

Diastereomeric ratio (major: minor = 10:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. white solid, 343 mg (83%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.74 (d, $J$ = 8.3 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.18 – 7.10 (m, 6H), 6.91 (t, $J$ = 7.7 Hz, 2H), 6.66 (d, $J$ = 2.4 Hz, 1H), 6.20 (d, $J$ = 7.7 Hz, 2H), 4.95 (s, 1H), 3.94 (q, $J$ = 10.1 Hz, 1H), 3.77 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.63 (major), -61.85 (minor).; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.21, 161.18, 135.44, 134.82, 132.99, 129.72, 129.22, 129.01, 128.63, 128.25, 127.74, 126.54, 125.95, 125.51, 125.38 (q, $J$ = 6.4 Hz), 106.12, 93.05, 55.65 (q, $J$ = 26.4 Hz), 55.52; HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{23}$H$_{19}$F$_3$NO$_3$Na$: 436.1136, found: 436.1131.
3-hydroxy-2-phenyl-3-(1,1,1-trifluorohexan-2-yl)isoindolin-1-one(3u)

Diastereomeric ratio (major: minor = 1:1) was determined by $^{19}$F NMR analysis of the unpurified product mixture. White solid, 309 mg (85%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.68 (d, $J = 7.7$ Hz, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.59 (dd, $J = 6.7$, 1.1 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.43 (dd, $J = 6.6$, 3.2 Hz, 2H), 7.40 (dd, $J = 6.1$, 3.5 Hz, 2H), 7.33 – 7.27 (m, 5H), 7.25 – 7.19 (m, 3H), 7.15 (d, $J = 7.5$ Hz, 1H), 4.97 (major, 1H), 4.76 (minor, 1H), 2.74 – 2.59 (m, 2H), 2.36 (dt, $J = 13.7$, 6.0 Hz, 1H), 1.78 (ddd, $J = 22.3$, 15.0, 7.8 Hz, 2H), 1.11 – 0.76 (m, 12H), 0.67 (t, $J = 7.2$ Hz, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -61.30 (major), -65.54 (minor). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.03 (major), 166.93 (manor), 144.36 (major), 144.15 (minor), 134.71 (major), 134.69 (minor), 132.92 (major), 132.36 (minor), 130.76 (major), 130.29 (minor), 130.05 (major), 130.00 (minor), 128.92 (major), 128.72 (minor), 127.27 (major), 126.88 (minor), 126.63 (major), 126.40 (minor), 123.74 – 123.55 (m), 123.44 (major), 123.17 (minor), 93.39 (major, d, $J = 1.7$ Hz), 91.45 (minor, d, $J = 2.0$ Hz), 49.33 – 46.47 (m), 31.94 (major), 31.60 (minor), 30.37 (major), 29.71 (minor), 25.49 (major), 24.91 (minor), 22.63 (major), 22.60 (minor), 17.77 (major), 13.60 (minor); HRMS (ESI-TOF): [M+Na]$^+$ m/z calcd for C$_{20}$H$_{20}$F$_3$NO$_2$Na$: 386.1344, found: 386.1350.

(3,3,3-trifluoroprop-1-ene-1,1-diyl)dibenzene

Oil, 75%, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (dd, $J = 6.1$, 2.6 Hz, 3H), 7.43 – 7.37 (m, 3H), 7.33 (ddd, $J = 6.2$, 3.9, 2.1 Hz, 4H), 6.21 (q, $J = 8.3$ Hz, 1H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -55.56 (s). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 152.69 (q, $J = 5.5$ Hz), 140.34 (s), 137.48 (s), 129.61 (s), 129.32 (q, $J = 1.7$ Hz), 128.70 (s), 128.69 (s), 128.25 (s), 128.18 (s), 128.32 (q, $J = 270.6$ Hz), 115.65 (q, $J = 33.9$ Hz).

5. References:
[1]. Li,L.; Wang,M.; Zhang,X,J.; Jiang,Y,W.; Ma,D,W. Org. Lett. 2009, 11, 1309.
6. NMR spectra.

3a
3n
3p
3s
3u
(3,3,3-trifluoroprop-1-ene-1,1-diyl)dibenzene
4a-HRMS
