Supplementary Information

Cobalt-Catalyzed C(sp^2)–H/C(sp^3)–H Coupling via Directed C–H Activation and 1,5-Hydrogen Atom Transfer

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**Materials and Methods**

**General.** All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash column chromatography was performed using 40-63µm silica gel (Si 60, Merck). 

$^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV-300 (300 MHz), AV-500 (500 MHz) or BBFO-400 (400 MHz) NMR spectrometers. $^1$H and $^{13}$C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm). $^{19}$F NMR spectra are referenced to external CF$_3$CO$_2$H (~76.55 ppm). Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a glass capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 µm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-Tof Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected.

**Materials.** Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous CoBr$_2$ (> 98%) and 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr•HCl) were purchased from Alfa Aesar and used as received. THF and 1,2-dimethoxyethane (DME) were distilled over Na/benzophenone. Grignard reagents were prepared from the corresponding alkyl halides and magnesium turnings in anhydrous THF, and titrated before use.
Preparation of Starting Materials

Preparation of Aryl Imines

All imines (see below) were synthesized according to the literature procedures,¹ and purified by recrystallization or distillation. Spectral data for these compounds showed good agreement with the literature data.²

![Imine Structures](image)

**Preparation of N-(2-Bromobenzyl)amines**

Cyclic amines were alkylated with 2-bromobenzyl bromide using the method reported by Li (2-bromobenzyl bromide/KOH/EtOH).³ Acyclic amines were alkylated with 2-bromobenzyl bromide using the method reported by Mugesh (2-bromobenzyl bromide/TEA/toluene).⁴ Spectral data for 2a,⁵ 2c,⁶ 2d,⁷ and 2f⁸ showed good agreement with the literature data.

![Amine Structures](image)
1-(2-Bromobenzyl)piperidine (2b): Obtained in 74% yield as a light yellow oil. \( R_f \) 0.44 (hexane/EtOAc = 10/1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.53-7.49 (m, 2H), 7.29-7.25 (m, 1H), 7.09 (td, \( J = 7.6, 1.6 \) Hz, 1H), 3.55 (s, 2H), 2.47-2.44 (m, 4H), 1.62-1.56 (m, 4H), 1.48-1.42 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 138.2, 132.5, 130.6, 128.0, 127.1, 124.5, 62.5, 54.6, 26.0, 24.3; HRMS (ESI) Calcd for C\(_{12}\)H\(_{17}\)NBr [M + H]\(^+\) 254.0544, found 254.0536.

1-(2-Bromobenzyl)azepane (2e): Obtained in 71% yield as a light yellow oil. \( R_f \) 0.35 (hexane/EtOAc = 10/1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.56-7.51 (m, 2H), 7.30-7.26 (m, 1H), 7.08 (td, \( J = 7.6, 1.6 \) Hz, 1H), 3.71 (s, 2H), 2.70-2.67 (m, 4H), 1.64-1.62 (m, 8H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 139.4, 132.5, 130.4, 127.9, 127.1, 124.2, 61.7, 55.8, 28.4, 27.1; HRMS (ESI) Calcd for C\(_{13}\)H\(_{19}\)NBr [M + H]\(^+\) 268.0701, found 268.0703.

\( N\)-(2-Bromobenzyl)-N-butylbutan-1-amine (2g): obtained in 70% yield as a light yellow oil. \( R_f \) 0.67 (hexane/EtOAc = 10/1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.59-7.50 (m, 2H), 7.30-7.26 (m, 1H), 7.08 (td, \( J = 7.6, 1.4 \) Hz, 1H), 3.63 (s, 2H), 2.46 (t, \( J = 7.3 \) Hz, 4H), 1.50-1.42 (m, 4H), 1.31 (sextet, \( J = 7.4 \) Hz, 4H), 0.89 (t, \( J = 7.3 \) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 139.8, 132.4, 130.5, 127.8, 127.1, 124.0, 58.3, 54.0, 29.4, 20.6, 14.1; HRMS (ESI) Calcd for C\(_{15}\)H\(_{25}\)NBr [M + H]\(^+\) 298.1170, found 298.1170.
Cobalt-Catalyzed C(sp²)–H/C(sp³)–H Coupling between Aryl Imines and N-(2-Bromobenzyl)amines

Table S1. Formation of Byproducts

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aThe reaction was performed using 0.3 mmol of 1a (c = 0.3 M) and 0.6 mmol of 2a. bThe yield of 3aa was determined by ¹H NMR. The yields of 4–8 were estimated by GC using n-tridecane as an internal standard. cThe amount of sec-BuMgBr was 2.2 equiv. dThe reaction was performed using 0.4 mmol of 1a and 0.2 mmol of 2a (c = 0.2 M) at 0 °C.

Typical Procedure: 1-(2-(1-Benzylpyrrolidin-2-yl)phenyl)ethan-1-one (3aa). In a 10 ml Schlenk tube were placed 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol), (E)-N-(4-methoxyphenyl)-1-phenylethanol-imine (1a, 90.1 mg, 0.40 mmol), 1,3-bis(2,6-
diisopropylphenyl)imidazolinium chloride (SIPr•HCl, 8.5 mg, 0.020 mmol), a freshly prepared THF solution of CoBr$_2$ (0.10 M, 0.20 mL, 0.020 mmol), and DME (0.50 ml). The resulting solution was cooled in an ice bath, followed by the addition of a THF solution of sec-BuMgBr (1.34 M, 0.30 ml, 0.40 mmol). The resulting mixture was stirred in the ice bath for 12 h, and then quenched by the addition of 3 N HCl (1.0 ml). The resulting mixture was stirred at room temperature for 1 h, and then neutralized with 3 N NaOH (2.0 ml) and extracted with EtOAc (3 x 10 ml). The combined organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1) to afford the title compound as a light yellow oil (27.4 mg, 49%).

$R_f$ 0.32 (hexane/EtOAc = 10/1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.11 (d, $J$ = 7.8 Hz, 1H), 7.59 (dd, $J$ = 7.7, 0.7 Hz, 1H), 7.55-7.51 (m, 1H), 7.32-7.21 (m, 6H), 3.92 (t, $J$ = 8.2 Hz, 1H), 3.81 (d, $J$ = 13.1 Hz, 1H), 3.14-3.08 (m, 1H), 3.10 (d, $J$ = 13.2 Hz, 1H), 2.61 (s, 3H), 2.51-2.42 (m, 1H), 2.24 (q, $J$ = 8.9 Hz, 1H), 1.93-1.75 (m, 2H), 1.70-1.61 (m, 1H), $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.4, 144.2, 139.7, 139.0, 131.7, 128.5, 128.0 (two signals overlapped), 127.9, 126.6, 126.1, 65.3, 58.5, 53.3, 35.0, 30.2, 22.7; HRMS (ESI) Calcd for C$_{19}$H$_{22}$NO $[M + H]^+$ 280.1701, found 280.1699.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-methylphenyl)ethan-1-one (3ba): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(p-tolyl)ethan-1-imine (1b, 95.7 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as a brown oil (28.2 mg, 48%).

$R_f$ 0.23 (hexane/EtOAc = 10/1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.91 (s, 1H), 7.53 (d, $J$ = 7.9 Hz, 1H), 7.31-7.28 (m, 4H), 7.24-7.19 (m, 1H), 7.09 (d, $J$ = 7.6 Hz, 1H), 3.95 (t, $J$ = 8.2 Hz, 1H), 3.77 (d, $J$ = 13.0 Hz, 1H), 3.11-3.03 (m, 1H), 3.05 (d, $J$ = 13.0 Hz, 1H), 2.58 (s, 3H), 2.49-2.40 (m, 1H), 2.42 (s, 3H), 2.22 (q, $J$ = 8.9 Hz, 1H), 1.89-1.73 (m, 2H), 1.63-1.54 (m, 1H); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.7, 144.7, 142.4, 139.9, 135.9, 128.8, 128.6, 128.5, 128.1, 126.6, 126.7, 65.3, 58.7, 53.4, 34.9, 30.0, 22.7, 21.7; HRMS (ESI) Calcd for C$_{20}$H$_{24}$NO
1-(2-(1-Benzylpyrrolidin-2-yl)-4-fluorophenyl)ethan-1-one (3ca): The typical procedure was applied to (E)-1-(4-fluorophenyl)-N-(4-methoxyphenyl)ethan-1-imine (1c, 97.3 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a white solid (30.4 mg, 51%).

$R_f$ 0.35 (hexane/EtOAc = 10/1); m.p. 92.9-95.9 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (dd, $J$ = 11.0, 2.7 Hz, 1H), 7.66 (dd, $J$ = 8.6, 5.7 Hz, 1H), 7.31-7.27 (m, 4H), 7.25-7.19 (m, 1H), 6.96 (td, $J$ = 8.1, 2.7 Hz, 1H), 4.03 (td, $J$ = 8.0, 1.4 Hz, 1H), 3.76 (d, $J$ = 13.1 Hz, 1H), 3.14-3.07 (m, 1H), 3.13 (d, $J$ = 13.1 Hz, 1H), 2.58 (s, 3H), 2.52-2.42 (m, 1H), 2.25 (q, $J$ = 8.9 Hz, 1H), 1.89-1.75 (m, 2H), 1.60-1.51 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 200.3, 165.1 ($^1$J$_{C,F}$ = 250.5 Hz), 149.6 (d, $^3$J$_{C,F}$ = 7.6 Hz), 139.6, 134.3 (d, $^4$J$_{C,F}$ = 2.6 Hz), 131.2 (d, $^3$J$_{C,F}$ = 8.8 Hz), 128.6, 128.1, 126.8, 114.8 (d, $^2$J$_{C,F}$ = 22.8 Hz), 113.1 (d, $^2$J$_{C,F}$ = 22.1 Hz), 65.0, 58.8, 53.5, 35.0, 29.9, 22.9; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -106.7; HRMS (ESI) Calcd for C$_{19}$H$_{21}$NOF [M + H]$^+$ 298.1607, found 298.1616.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-chlorophenyl)ethan-1-one (3da): The typical procedure was applied to (E)-1-(4-chlorophenyl)-N-(4-methoxyphenyl)ethan-1-imine (1d, 103.9 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 40/1) of the crude product afforded the title compound as a light yellow oil (24.8 mg, 39%).

$R_f$ 0.33 (hexane/EtOAc = 10/1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.11 (d, $J$ = 2.1 Hz, 1H), 7.54 (d, $J$ = 8.3 Hz, 1H), 7.31-7.19 (m, 6H), 3.93 (t, $J$ = 8.1 Hz, 1H), 3.74 (d, $J$ = 13.0 Hz, 1H), 3.14-3.07 (m, 1H), 3.13 (d, $J$ = 13.0 Hz, 1H), 2.57 (s, 3H), 2.49-2.40 (m, 1H), 2.25 (q, $J$ = 8.9 Hz, 1H).
Hz, 1H), 1.89-1.72 (m, 2H), 1.62-1.53 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 200.9, 147.4, 139.4, 138.2, 136.6, 129.8, 128.6, 128.3, 128.1, 126.8, 126.3, 64.9, 58.8, 53.5, 35.0, 30.0, 22.9; HRMS (ESI) Calcd for C$_{19}$H$_{21}$NOCl [M + H]$^+$ 314.1312, found 314.1316.

1-(3-(1-Benzylpyrrolidin-2-yl)-[1,1'-biphenyl]-4-yl)ethan-1-one (3ea): The typical procedure was applied to (E)-1-((1,1'-biphenyl]-4-yl)-N-(4-methoxyphenyl)ethan-1-imine (1e, 120.6 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as a white solid (23.5 mg, 33%).

$R_f$ 0.27 (hexane/EtOAc = 10/1); m.p. 98.5-101.5 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.38 (d, $J$ = 1.7 Hz, 1H), 7.70-7.65 (m, 3H), 7.52 (dd, $J$ = 8.0, 1.8 Hz, 1H), 7.47 (t, $J$ = 7.5 Hz, 2H), 7.39 (t, $J$ = 7.3 Hz, 1H), 7.32-7.27 (m, 4H), 7.20 (t, $J$ = 6.9 Hz, 1H), 4.03 (t, $J$ = 8.1 Hz, 1H), 3.85 (d, $J$ = 13.2 Hz, 1H), 3.17-3.11 (m, 1H), 3.15 (d, $J$ = 13.3 Hz, 1H), 2.63 (s, 3H), 2.54-2.45 (m, 1H), 2.27 (q, $J$ = 8.9 Hz, 1H), 1.92-1.75 (m, 2H), 1.70-1.61 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 201.8, 145.4, 144.4, 140.3, 139.8, 137.3, 129.1, 128.9, 128.5, 128.1, 127.9, 127.3, 126.7 (two signals overlapped), 124.7, 65.4, 58.7, 53.6, 35.1, 30.1, 22.8; HRMS (ESI) Calcd for C$_{25}$H$_{26}$NO [M + H]$^+$ 356.2014, found 356.2014.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-methoxyphenyl)ethan-1-one (3fa): The typical procedure was applied to (E)-N,1-bis(4-methoxyphenyl)ethan-1-imine (1f, 102.1 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 8/1) of the crude product afforded the title compound as a light yellow oil (18.4 mg, 30%).

$R_f$ 0.17 (hexane/EtOAc = 10/1); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.77 (d, $J$ = 2.7 Hz, 1H), 7.70 (d, $J$ = 8.6 Hz, 1H), 7.32-7.27 (m, 4H), 7.23-7.19 (m, 1H), 6.79 (dd, $J$ = 8.7, 2.7 Hz, 1H), 4.16
(t, J = 8.1 Hz, 1H), 3.88 (s, 3H), 3.80 (d, J = 13.2 Hz, 1H), 3.12-3.07 (m, 1H), 3.09 (d, J = 13.2 Hz, 1H), 2.57 (s, 3H), 2.54-2.47 (m, 1H), 2.24 (q, J = 8.9 Hz, 1H), 1.84-1.75 (m, 2H), 1.58-1.50 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 199.8, 162.8, 148.9, 140.1, 131.9, 130.5, 128.4, 128.1, 126.6, 112.3, 111.8, 65.4, 58.7, 55.4, 53.5, 34.7, 29.5, 22.9; HRMS (ESI) Calcd for C20H24NO2 [M + H]+ 310.1807, found 310.1805.

1-(2-(1-Benzylpyrrolidin-2-yl)-4-(trifluoromethyl)phenyl)ethan-1-one (3ga): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)ethan-1-imine (1g, 117.3 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyprrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (14.5 mg, 21%).

Rf 0.33 (hexane/EtOAc = 10/1); 1H NMR (500 MHz, CDCl3): δ 8.36 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.28-7.19 (m, 5H), 3.85 (t, J = 8.1 Hz, 1H), 3.69 (d, J = 12.9 Hz, 1H), 3.17-3.09 (m, 1H), 3.16 (d, J = 12.9 Hz, 1H), 2.60 (s, 3H), 2.46-2.39 (m, 1H), 2.29 (q, J = 8.9 Hz, 1H), 1.91-1.75 (m, 2H), 1.65-1.58 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 201.8, 145.5, 141.9, 139.1, 133.1 (q, JCF = 31.7 Hz), 128.7, 128.2, 127.8, 126.9, 125.4, 123.8 (q, JCF = 272.0 Hz), 123.1, 65.1, 58.8, 53.6, 35.3, 30.4, 22.9; 19F NMR (376 MHz, CDCl3): δ -63.0; HRMS (ESI) Calcd for C20H21NOF3 [M + H]+ 348.1575, found 348.1578.

1-(2-(1-Benzylpyrrolidin-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3ha): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyprrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (42.1 mg, 61%).

Rf 0.40 (hexane/EtOAc = 10/1); 1H NMR (500 MHz, CDCl3): δ 8.22 (d, J = 8.3 Hz, 1H), 7.77
(s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.29-7.20 (m, 5H), 3.92 (t, J = 8.2 Hz, 1H), 3.71 (d, J = 13.1 Hz, 1H), 3.16-3.10 (m, 1H), 3.15 (d, J = 13.1 Hz, 1H), 2.62 (s, 3H), 2.49-2.41 (m, 1H), 2.27 (q, J = 8.9 Hz, 1H), 1.91-1.76 (m, 2H), 1.64-1.56 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 201.1, 148.8, 139.2 (two signals overlapped), 128.9, 128.6 (q, \(^2J_{C-F}\) = 32.5 Hz), 128.5, 128.1 (two signals overlapped), 126.8, 124.6 (q, \(^3J_{C-F}\) = 3.3 Hz), 123.8 (q, \(^1J_{C-F}\) = 270.7 Hz), 65.1, 58.6, 53.5, 35.2, 30.2, 22.9; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): δ –62.5; HRMS (ESI) Calcd for C\(_{20}\)H\(_{21}\)NOF \([\text{M} + \text{H}]^+\) 348.1575, found 348.1582.

1-\((2-(1-Benzylpyrrolidin-2-yl)-5-chlorophenyl)ethan-1-one\) (3ia): The typical procedure was applied to (E)-1-(3-chlorophenyl)-N-(4-methoxyphenyl)ethan-1-imine (1i, 103.9 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/Et\(_2\)O = 20/1) of the crude product afforded the compound 3ia in a pure form (14.2 mg, 23%) as a light yellow oil and a mixture of 3ia and N-(1-(3-chlorophenyl)ethyl)-4-methoxyaniline (reduced product of 1i; 16.3 mg, 26%, ratio = 5:1 as determined by \(^1\)H NMR) as a yellow oil. Characterization data of 3ia are given below.

\(R_f\) 0.46 (hexane/EtOAc = 10/1); \(^1\)H NMR (400MHz, CDCl\(_3\)): δ 8.01 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.46 (dd, J = 8.5, 2.2 Hz, 1H), 7.30-7.19 (m, 5H), 3.82 (t, J = 8.1 Hz, 1H), 3.73 (d, J = 13.1 Hz, 1H), 3.10-3.06 (m, 1H), 3.09 (d, J = 13.0 Hz, 1H), 2.57 (s, 3H), 2.44-2.35 (m, 1H), 2.22 (q, J = 8.9 Hz, 1H), 1.89-1.72 (m, 2H), 1.62-1.53 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 201.1, 142.9, 140.3, 139.5, 131.9, 131.6, 129.8, 128.5, 128.1, 127.7, 126.8, 64.9, 58.5, 53.4, 35.1, 30.2, 22.8; HRMS (ESI) Calcd for C\(_{19}\)H\(_{21}\)NOCl \([\text{M} + \text{H}]^+\) 314.1312, found 314.1310.

1-\((2-(1-Benzylpyrrolidin-2-yl)-3-fluorophenyl)ethan-1-one\) (3ja): The typical procedure was applied to (E)-1-(3-fluorophenyl)-N-(4-methoxyphenyl)ethan-1-imine (1j, 97.3 mg, 0.40
mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: Hex/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow oil (31.6 mg, 53%).

R_f: 0.17 (hexane/EtOAc = 10/1); ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.18 (m, 6H), 7.07 (t, J = 9.3 Hz, 1H), 3.97 (t, J = 8.5 Hz, 1H), 3.76 (d, J = 13.6 Hz, 1H), 3.23 (d, J = 13.6 Hz, 1H), 3.01-2.98 (m, 1H), 2.51 (s, 3H), 2.34 (q, J = 8.8 Hz, 1H), 2.28-2.21 (m, 1H), 2.04-1.86 (m, 2H), 1.75-1.68 (m, 1H); ^13C NMR (100 MHz, CDCl_3): δ 202.8 (d, J_C-F = 2.0 Hz), 161.1 (d, J_C-F = 247.0 Hz), 143.6 (d, J_C-F = 3.0 Hz), 137.8, 129.3, 128.6 (d, J_C-F = 3.0 Hz), 128.1, 128.0, 126.8, 121.8 (d, J_C-F = 23.0 Hz), 60.5, 58.0, 52.8, 32.6, 31.7, 23.1; ^19F NMR (376 MHz, CDCl_3): δ −114.4; HRMS (ESI) Calcd for C_{19}H_{21}NOF [M + H]^+ 298.1607, found 298.1612.

1-(2-(1-Benzylpyrrolidin-2-yl)phenyl)propan-1-one (3ka): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-phenylpropan-1-imine (1k, 95.7 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol) for 24 h. Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (12.4 mg, 21%).

R_f: 0.35 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, J = 7.5 Hz, 1H), 7.51-7.48 (m, 2H), 7.30-7.26 (m, 5H), 7.24-7.19 (m, 1H), 3.78 (d, J = 13.1 Hz, 1H), 3.72 (t, J = 8.2 Hz, 1H), 3.10-2.80 (m, 4H), 2.44-2.35 (m, 1H), 2.20 (q, J = 8.9 Hz, 1H), 1.91-1.72 (m, 2H), 1.69-1.60 (m, 1H), 1.21 (t, J = 7.3 Hz, 3H); ^13C NMR (100 MHz, CDCl_3): δ 206.1, 143.6, 139.7, 139.6, 131.2, 128.6, 128.1, 127.9, 126.9, 126.7, 126.2, 65.6, 58.4, 53.3, 35.7, 35.3, 22.7, 8.4; HRMS (ESI) Calcd for C_{20}H_{24}NO [M + H]^+ 294.1858, found 294.1860.

8-(1-Benzylpyrrolidin-2-yl)-3,4-dihyronaphalen-1(2H)-one (3la): The typical
procedure was applied to (E)-N-(4-methoxyphenyl)-3,4-dihydropyridine-1(2H)-imine (11, 100.5 mg, 0.40 mmol) and 1-(2-bromobenzyl)pyrrolidine (2a, 48.0 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow oil (27.1 mg, 44%).

Rf 0.20 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, CDCl₃): δ 8.12 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.33-7.29 (m, 4H), 7.21 (t, J = 6.8 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 4.41 (t, J = 8.0 Hz, 1H), 3.78 (d, J = 13.1 Hz, 1H), 3.11-3.05 (m, 1H), 3.07 (d, J = 13.1 Hz, 1H), 2.98-2.94 (m, 2H), 2.76-2.55 (m, 3H), 2.24 (q, J = 8.8 Hz, 1H), 2.16-2.05 (m, 2H), 1.84-1.76 (m, 2H), 1.53-1.44 (m, 1H); 13C NMR (100 MHz, CDCl₃): δ 200.2, 148.2, 145.3, 140.2, 132.9, 131.5, 128.5, 128.1, 127.0, 126.6, 125.9, 65.5, 59.0, 53.5, 41.2, 34.2, 31.1, 22.94, 22.90; HRMS (ESI) Calcd for C₂₁H₂₄NO [M + H]⁺ 306.1858, found 306.1859.

1-(2-(1-Benzylpiperidin-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hb): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and 1-(2-bromobenzyl)piperidine (2b, 50.8 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 60/1) of the crude product afforded the title compound as a light yellow oil (15.9 mg, 22%).

Rf 0.38 (hexane/EtOAc = 10/1); 1H NMR (500 MHz, CDCl₃): δ 8.17 (d, J = 8.7 Hz, 1H), 7.73-7.71 (m, 2H), 7.29-7.19 (m, 5H), 3.66 (dd, J = 10.4, 2.5 Hz, 1H), 3.59 (d, J = 13.5 Hz, 1H), 2.97 (d, J = 11.5 Hz, 1H), 2.84 (d, J = 13.6 Hz, 1H), 2.63 (s, 3H), 1.99-1.92 (m, 2H), 1.79 (d, J = 12.5 Hz, 1H), 1.64-1.36 (m, 4H); 13C NMR (75 MHz, CDCl₃): δ 201.8, 148.9, 139.6, 139.2, 129.2, 128.7 (q, JCF = 32.8 Hz), 128.4, 128.1, 127.8 (q, 3JCF = 3.3 Hz), 126.8, 124.1 (q, JCF = 4.0 Hz), 123.7 (q, JCF = 270.5 Hz), 63.8, 60.1, 53.2, 36.5, 30.7, 25.8, 24.9; 19F NMR (376 MHz, CDCl₃): δ –62.5; HRMS (ESI) Calcd for C₂₁H₂₃NOF₃ [M + H]⁺ 362.1732, found 362.1730.
1-(2-(4-Benzylmorpholin-3-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hc): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and 4-(2-bromobenzyl)morpholine (2c, 51.2 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a light yellow oil (12.4 mg, 17%).

Rf 0.22 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, CDCl3): δ 8.21 (d, J = 8.2 Hz, 1H), 7.79-7.76 (m, 2H), 7.31-7.21 (m, 5H), 4.01-3.96 (m, 2H), 3.86 (d, J = 11.2 Hz, 1H), 3.71-3.62 (m, 2H), 3.35 (t, J = 11.8 Hz, 1H), 2.93 (d, J = 13.3 Hz, 1H), 2.79 (d, J = 11.8 Hz, 1H), 2.66 (s, 3H), 2.32 (td, J = 11.8, 3.3 Hz, 1H); 13C NMR (100MHz, CDCl3): δ 200.9, 143.1, 140.6, 137.9, 129.9, 129.6 (q, 2JCF = 32.7 Hz), 128.6, 128.3, 127.9 (q, 3JCF = 3.3 Hz), 127.1, 124.6 (q, 3JCF = 3.7 Hz), 123.6 (q, 1JCF = 270.7 Hz), 72.9, 67.4, 62.7, 59.6, 51.8, 30.3; 19F NMR (376 MHz, CDCl3): δ –62.7; HRMS (ESI) Calcd for C20H21NO2F3 [M + H]+ 364.1524, found 364.1520.

1-(2-(1-Benzyl-1,2,3,4-tetrahydroquinolin-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hd): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and 1-(2-bromobenzyl)-1,2,3,4-tetrahydroquinoline (2d, 60.4 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 60/1) of the crude product afforded the title compound as a light yellow solid (16.4 mg, 20%).

Rf 0.42 (hexane/EtOAc = 10/1); m.p. 126.7-129.5 °C; 1H NMR (400 MHz, CDCl3): δ 7.94 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.30-7.27 (m, 2H), 7.24-7.20 (m, 1H), 7.17 (d, J = 7.2 Hz, 2H), 7.07-7.02 (m, 2H), 6.65 (t, J = 7.2 Hz, 1H), 6.57 (d, J = 8.2 Hz, 1H), 5.43-5.41 (m, 1H), 4.63 (d, J = 17.2 Hz, 1H), 4.08 (d, J = 17.2 Hz, 1H), 2.69-2.49 (m, 5H),
2.45-2.36 (m, 1H), 2.13-2.07 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 200.2, 148.9, 145.1, 137.9, 137.2, 129.4, 129.3 (q, $^2$J$_{C-F}$ = 32.8 Hz), 128.9, 128.7, 128.0 (q, $^3$J$_{C-F}$ = 3.5 Hz), 127.6, 126.9, 126.4 (two signals overlapped), 123.6 (q, $^1$J$_{C-F}$ = 270.8 Hz), 122.1, 116.2, 110.8, 58.1, 53.3, 29.8, 28.4, 23.7; $^1$H NMR (376 MHz, CDCl$_3$): δ –62.6; HRMS (ESI) Calcd for C$_{25}$H$_{23}$NOF$_3$ [M + H]$^+$ 410.1732, found 410.1732.

1-(2-(1-Benzylazepan-2-yl)-5-(trifluoromethyl)phenyl)ethan-1-one (3he): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and 1-(2-bromobenzyl)azepane (2e, 53.6 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 50/1) of the crude product afforded the title compound as a light yellow oil (48.4 mg, 64%).

R$_f$ 0.52 (hexane/EtOAc = 10/1); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.13 (d, $J$ = 8.6 Hz, 1H), 7.70-7.68 (m, 2H), 7.25-7.15 (m, 5H), 4.23-4.21 (m, 1H), 3.51 (d, $J = 13.8$ Hz, 1H), 3.45 (d, $J = 13.8$ Hz, 1H), 2.99-2.79 (m, 2H), 2.53 (s, 3H), 1.97-1.82 (m, 3H), 1.73-1.47 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 201.6, 151.5, 139.7, 138.7, 129.1, 128.6, 128.3 (q, $^2$J$_{C-F}$ = 32.3 Hz), 128.1, 127.2 (q, $^3$J$_{C-F}$ = 3.3 Hz), 126.7, 124.3 (q, $^3$J$_{C-F}$ = 3.7 Hz), 123.8 (q, $^1$J$_{C-F}$ = 270.7 Hz), 64.7, 59.3, 50.3, 35.4, 30.3, 29.1, 27.2, 26.4; $^{19}$F NMR (376 MHz, CDCl$_3$): δ –62.5; HRMS (ESI) Calcd for C$_{22}$H$_{25}$NOF$_3$ [M + H]$^+$ 376.1888, found 376.1885.

1-(2-(1-(Benzyl(ethyl)amino)ethyl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hf): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and N-(2-bromobenzyl)-N-ethylethanamine (2f, 48.4 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 30/1) of the crude product afforded the title compound as a light yellow oil (40.5 mg, 58%).
$R_f$ 0.42 (hexane/EtOAc = 10/1); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.80 (d, $J = 8.1$ Hz, 1H), 7.65 (d, $J = 8.3$ Hz, 1H), 7.62 (s, 1H), 7.28-7.19 (m, 5H), 4.50 (q, $J = 6.6$ Hz, 1H), 3.52 (d, $J = 17.3$ Hz, 1H), 3.45 (d, $J = 17.2$ Hz, 1H), 2.62-2.45 (m, 5H), 1.37 (d, $J = 6.5$ Hz, 3H), 0.88 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.4, 148.7, 141.1, 139.9, 128.7 (two signals overlapped), 128.2, 128.1, 126.8, 126.7 (q, $^3J_{C-F} = 3.7$ Hz), 123.8 (q, $^1J_{C-F} = 270.7$ Hz), 123.4 (q, $^3J_{C-F} = 3.7$ Hz), 55.2, 54.3, 43.6, 30.5, 16.2, 11.0; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –62.5; HRMS (ESI) Calcd for C$_{20}$H$_{23}$NOF$_3$ [M + H]$^+$ 350.1732, found 350.1729.

![Chemical structure](image)

1-(2-(1-(BenzyI(butyl)amino)butyl)-5-(trifluoromethyl)phenyl)ethan-1-one (3hg): The typical procedure was applied to (E)-N-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (1h, 117.3 mg, 0.40 mmol) and N-(2-bromobenzyl)-N-buty1butan-1-amine (2g, 59.7 mg, 0.20 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 60/1) of the crude product afforded the title compound as a light yellow oil (35.7 mg, 44%).

$R_f$ 0.65 (hexane/EtOAc = 10/1); $^1$H NMR (400 MHz, d$_6$-acetone): $\delta$ 7.94 (s, 1H), 7.90 (d, $J = 8.2$ Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.28-7.19 (m, 5H), 4.53 (dd, $J = 8.8, 5.5$ Hz, 1H), 3.69 (d, $J = 13.9$ Hz, 1H), 3.42 (d, $J = 13.9$ Hz, 1H), 2.62 (s, 3H), 2.57-2.50 (m, 1H), 2.36-2.29 (m, 1H), 2.03-1.94 (m, 1H), 1.89-1.80 (m, 1H), 1.39-1.04 (m, 6H), 0.91 (t, $J = 7.3$ Hz, 3H), 0.75 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.3, 145.8, 142.1, 140.3, 128.8, 128.6 (q, $^2J_{C-F} = 32.7$ Hz), 128.5, 128.1, 126.7, 126.4 (q, $^3J_{C-F} = 3.7$ Hz), 123.8 (q, $^1J_{C-F} = 270.3$ Hz), 123.6 (q, $^3J_{C-F} = 3.7$ Hz), 59.1, 54.7, 50.0, 32.8, 30.6, 28.7, 20.5, 19.8, 14.3, 13.9; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –62.6; HRMS (ESI) Calcd for C$_{24}$H$_{31}$NOF$_3$ [M + H]$^+$ 406.2358, found 406.2361.
Transformation of Product 3aa

1-(2-(1-Benzylpyrrolidin-2-yl)phenyl)-2-diazoethan-1-one (9): To a solution of LiHMDS (1.0 M, 2.49 mL) in 5.0 mL THF was added 1-(2-(1-benzylpyrrolidin-2-yl)phenyl)ethan-1-one (3aa, 642 mg, 2.30 mmol) in THF (4.6 mL) over 1 min at –78 °C. The resulting mixture was stirred at the same temperature for 30 min, followed by the addition of trifluoroethyl trifluoroacetate (541.1 mg, 2.76 mmol) over 2-3 min. After additional stirring for 3 h, the reaction mixture was allowed to warm to room temperature, stirred overnight and then poured into a separatory funnel together with Et₂O (20 mL) and sat. NH₄Cl (20 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure to afford a yellow oil. The oil was placed in a dry 50 mL 3-necked round-bottomed flask under a nitrogen atmosphere and dissolved in acetonitrile (9.3 mL). To this solution was added water (0.02 mL) and NEt₃ (0.23 mL), followed by the dropwise addition of p-acetamidobenzenesulfonyl azide (402.5 mg, 1.68 mmol) in acetonitrile (9.3 mL). The resulting solution was stirred at ambient temperature for 24 h, and then poured into a separatory funnel with Et₂O (20 mL). The organic layer was washed with 5% NaOH aqueous solution (3 x 10 mL), water (3 x 10 mL), and brine. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 8/1-1/1) to afford the desired product as a yellow oil (127.4 mg, 32 % based on recovered 3aa) along with recovery of 3aa (275.3 mg).

Rᶠ 0.67 (hexane/EtOAc = 1/1); ¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.35-7.19 (m, 7H), 5.59 (brs, 1H), 3.85 (brs, 1H), 3.79 (d, J = 13.1 Hz, 1H), 3.11-3.06 (m, 2H), 2.44-2.35 (m, 1H), 2.21 (q, J = 8.9 Hz, 1H), 1.89-1.61 (m, 3H); ¹³C NMR (100 MHz, CD₃CN): δ 191.2, 143.9, 140.7, 139.8, 132.1, 129.5 (2C), 129.1 (2C), 128.6, 127.7, 127.5, 66.0, 58.9, 54.0, 36.3, 23.4; HRMS (ESI) Calcd for C₁₀H₂ₐN₃O [M + H]⁺ 306.1606, found 306.1602.
1'-Benzyldi[spiro[1,2'-indene]-1,2'-pyrrolidin]-3(2H)-one (10): A solution of 1-(2-(1-benzylpyrrolidin-2-yl)phenyl)-2-diazoethan-1-one (9, 127.4 mg, 0.42 mmol) in dichloromethane (20 mL) was added dropwise to a suspension of Rh₂(OAc)₄ in dichloromethane (9.3 mg, 0.02 mmol, 42 ml) at room temperature over a period of 6 h using a syringe pump. The resulting mixture was stirred for additional 20 h and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 12/1) to afford the desired product as a light yellow oil (78.7 mg, 68 %).

Rf 0.24 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.75 (t, J = 7.1 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.3 Hz, 1H), 7.30-7.21 (m, 5H), 3.35 (d, J = 13.0 Hz, 1H), 3.17-3.09 (m, 2H), 2.93 (d, J = 18.7 Hz, 1H), 2.51-2.47 (m, 2H), 2.28-2.21 (m, 1H), 2.08-1.90 (m, 3H); ¹³C NMR (100 MHz, CD₃CN): δ 204.7, 159.1, 140.9, 138.5, 136.1, 129.7, 129.2, 129.1, 127.7, 126.0, 123.2, 70.5, 53.7, 51.9, 43.1, 42.1, 22.4; HRMS (ESI) Calcd for C₁₉H₂₀NO [M + H]⁺ 278.1545, found 278.1545.
Reference


