Micelle enabled C(sp^2)-C(sp^3) cross-electrophile coupling in water *via* synergistic nickel and copper catalysis

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Contents

Materials and Methods

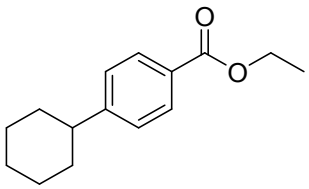
General. All chemicals, reagents, and solvents were purchased from commercial sources and were used without further purification unless otherwise noted. ^{1}H NMR data are reported relative to residual solvent signals, and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet;q, quartet; m, multiplet; br, broad. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at frequencies of 400 and 100 MHz respectively, using DMSO-d^6,or $CDCl_3$. Unless otherwise notice, all the ^{1}H NMR experimets are performed at room temperature (298 K) and 16 times of scans by default; all the ^{13}C NMR experimets are performed at room temperature (298 K) and 1024 times of scans by default. HRMS were obtained on Waters ACQUITY UPLC/Xevo G2 QTOF SYSTEM. UPLC analysis was performed on Agilent 1290 Infinity LC System.

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, J&K Scientific Ltd., and other commercial suppliers and were used as received.

General procedure

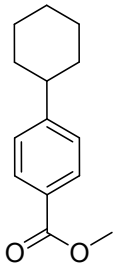
Preparation of the catalyst/ligand solution: In a 10 mL flask in glove box was added $Ni(OAc)_2{\cdot}4H_2O$ (3.15 mg. 2.5 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (35 mg, 3 mol%) and then 2 wt% aqueous TPGS-750-M (5 mL) was added. The resulting mixture was stirred at r.t. for 10 min to obatin a clear pink solution to be directly used in the following step.

General procedure for the reaction: In a 40 mL flask in glove box was added aryl bromide (5 mmol, 1 equiv.), alkyl iodide (7.5 mmol, 1.5 equiv.), 2-MeTHF (10 mL) and 2 wt% aqueous TPGS-750-M (5 mL) solution. Then the above prepared catalyst pink solution was added, followed by adding Cu_2O (5.3 mg, 0.75 mol%) and zinc (821 mg, 12.6 mmol, 2.5 equiv.). The resulting mixture was stirred at 45 ^{o}C for 16 h and the progress was moniterd by HPLC analysis. Upon reaction completion, the zinc dust was romoved by filtration and a two layer solution was collected. Layer separation to collect upper organic layer and the aqueous layer was extracted once by EtOAc (20 mL). The combined organic layers were concentrated in vacuo and the crude material was further purified *via* silica gel chromatography.

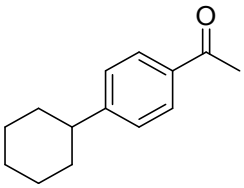


Ethyl 4-cyclohexylbenzoatecarboxylate (3aa)[1]: white solid (X = Br, X' = I, 89% yield; X = I, X' = I, 94% yield; X = Br, X' = Br, 35% yield; Protocol A, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 4.29 (q, J = 8.0 Hz, 2H), 2.60 – 2.54 (m, 1H), 1.81 – 1.76 (m, 4H), 1.74 – 1.66 (m, 1H), 1.47 – 1.33 (m, 4H), 1.31 (t, J = 8.0 Hz, 3H), 1.25 – 1.21 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1,

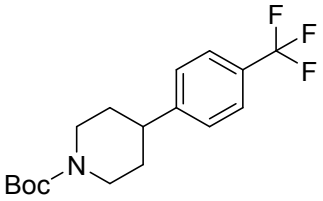
153.6, 129.7, 128.0, 127.5, 60.9, 44.2, 34.0, 26.7, 25.9, 14.7. HRMS (ESI) Calcd for $C_{15}H_{21}O_2^+$ $[M + H]^+$ 233.1541, found 233.1542.



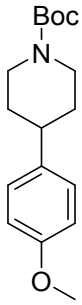
Methyl 4-cyclohexylbenzoate(3ba)[2]: white soild (91% yield, eluent = hexane/MTBE(10:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.31 – 7.23 (m, 2H), 3.89 (s, 3H), 2.55 (m, *J* = 11.5, 6.9, 3.4 Hz, 1H), 1.87 (m, *J* = 10.4, 5.2 Hz, 4H), 1.75 (m, *J* = 10.8, 4.4, 3.0, 1.5 Hz, 1H), 1.49 – 1.32 (m, 4H), 1.31 – 1.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 153.5, 129.7, 127.8, 126.9, 51.9, 44.7, 34.2, 26.8, 26.1. HRMS (ESI) Calcd for $C_{14}H_{19}O_2^+$ $[M + H]^+$ 219.1380, found 219.1364.



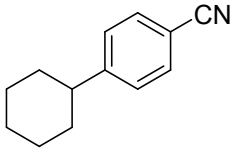
1-(4-Cyclohexylphenyl)ethan-1-one (3ca)[3]: white soild (85% yield, eluent = hexane/MTBE (50:1)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 2.58 (s, 3H), 2.55 (dd, *J* = 8.1, 3.3 Hz, 1H), 1.88 – 1.85 (m, 4H), 1.80 – 1.72 (m, 1H), 1.50 – 1.34 (m, 4H), 1.32 – 1.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 153.8, 135.1, 128.6, 127.1, 44.7, 34.1, 26.7, 26.6, 26.0. HRMS (ESI) Calcd for $C_{14}H_{19}O^+$ $[M + H]^+$ 203.1436, found 203.1436.



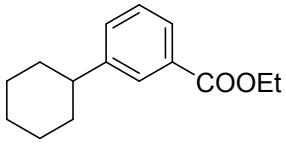
***tert*-Butyl 4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (3db)[4]:** colorless oil (83% yield, eluent = hexane/MTBE (30:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.25 (br, 2H), 2.82 – 2.73 (m, 2H), 2.74 – 2.64 (m, 1H), 1.80 (d, *J* = 13.0 Hz, 2H), 1.61 – 1.60 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 149.8, 128.7 (q, $^2J_{C\text{-}F}$ = 32.0 Hz), 127.2, 125.5 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 271.0 Hz), 79.5, 44.2, 42.6, 32.9, 28.4. HRMS (ESI) Calcd for $C_{13}H_{15}F_3NO_2^+$ $[M – t\text{-Bu+ H}]^+$ 274.1055, found 274.1055.



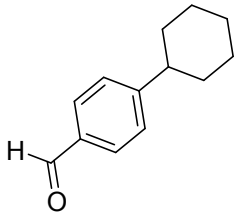
***tert*-Butyl 4-(4-methoxyphenyl)piperidine-1-carboxylate(3eb)[5]:** colorless oil (65% yield with protocol A, eluent = hexane/MTBE(10:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 2H), 6.92 – 6.77 (m, 2H), 4.23 (s, 2H), 3.79 (s, 3H), 2.79 (t, *J* = 13.1 Hz, 2H), 2.66 – 2.52 (m, 1H), 1.79 (d, *J* = 13.1 Hz, 2H), 1.58 (m, *J* = 12.7, 4.4 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 154.9, 138.0, 127.6, 113.9, 79.4, 55.3, 41.9, 33.5, 28.5. HRMS (ESI) Calcd for C13H18NO_3^+ [M – *t*-Bu+ H]$^+$ 236.1281, found 236.1283.



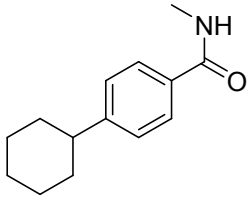
4-Cyclohexylbenzonitrile(3fa)[2]: colorless oil (74% yield, eluent = hexane/MTBE (50:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 2.59 – 2.53 (m, 1H), 1.92 – 1.81 (m, 4H), 1.79 – 1.75 (m, 1H), 1.45 – 1.35 (m, 4H), 1.31– 1.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 132.2, 127.7, 119.2, 109.6, 44.8, 34.0, 26.6, 25.9. HRMS (ESI) Calcd for $C_{13}H_{16}N^+$ [M + H]$^+$ 186.1277, found 186.1284.



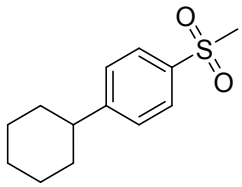
Ethyl 3-cyclohexylbenzoate(3ga): colorless oil (76% yield, eluent = hexane/MTBE (50:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.9 Hz, 1H), 7.87 – 7.84 (m, 1H), 7.43 – 7.30 (m, 2H), 4.38 (q, *J* = 8.0 Hz, 2H), 2.60 – 2.52 (m, 1H), 1.91 – 1.84 (m, 4H), 1.80 – 1.72 (m, 1H), 1.47 – 1.44 (m, 2H), 1.43 – 1.37 (m, 5H), 1.27 – 1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 148.3, 131.4, 130.5, 128.3, 128.0, 127.1, 60.9, 44.4, 34.3, 26.8, 26.1, 14.4. HRMS (ESI) Calcd for $C_{15}H_{21}O_2^+$ [M + H]$^+$ 233.1536, found 233.1531.



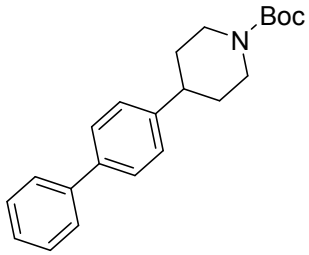
4-Cyclohexylbenzaldehyde(3ha)[6]: white soild (83% yield, eluent = hexane/MTBE (20:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.62 – 2.59 (m, 1H), 1.89 – 1.84 (m, 4H), 1.79 – 1.75 (m, 1H), 1.51 – 1.34 (m, 4H), 1.29 – 1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 155.4, 134.6, 130.0, 127.5, 44.9, 34.1, 26.7, 26.0. HRMS (ESI) Calcd for $C_{13}H_{17}O^+$ $[M + H]^+$ 189.1274, found 189.1266.



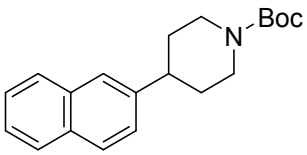
4-Cyclohexyl-*N*-methylbenzamide(3ia)[2]: white soild (76% yield, eluent = hexane/EtOAc (2:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.14 (s, 1H), 3.00 (d, *J* = 8.0 Hz, 3H), 2.57 – 2.51 (m, 1H), 1.89 – 1.82 (m, 4H), 1.79 – 1.72 (m, 1H), 1.49 – 1.33 (m, 4H), 1.29 – 1.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 151.7, 132.2, 127.0, 126.9, 44.5, 34.2, 26.8 (two signals overlapped), 26.1. HRMS (ESI) Calcd for $C_{14}H_{20}NO^+$ $[M + H]^+$ 218.1540, found 218.1546.



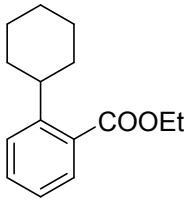
1-Cyclohexyl-4-(methylsulfonyl)benzene (3ja)[7]: white solid (74% yield, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 3.19 (s, 3H), 2.65 – 2.60 (m, 1H), 1.82 – 1.78 (m, 4H), 1.75 – 1.66 (m, 1H), 1.49 – 1.34 (m, 4H), 1.31 – 1.17 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.0, 138.9, 128.1, 127.5, 44.2, 44.1, 34.0, 26.6, 25.9. HRMS (ESI) Calcd for $C_{13}H_{19}O_2S^+$ $[M + H]^+$ 239.1101, found 239.1092.



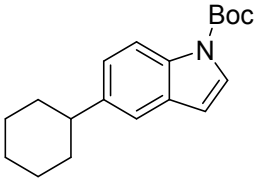
***tert*-Butyl 4-([1,1'-biphenyl]-4-yl)piperidine-1-carboxylate(3ka)[8]:** yellow soild (68% yield with protocol A, eluent = hexane/MTBE (50:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 4H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.23 (d, *J* = 4.0 Hz, 2H), 4.24 (s, 2H), 2.83 – 2.76 (m, 2H), 2.69 – 2.63 (m, 1H), 1.83 (d, *J* = 12.0 Hz, 2H), 1.68 – 1.55 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 144.9, 141.0, 139.3, 128.7, 127.3, 127.2, 127.1, 127.0, 79.5, 44.4, 42.4, 33.2, 28.5. HRMS (ESI) Calcd for $C_{18}H_{20}NO_2^+$ $[M – t\text{-Bu+ H}]^+$ 282.1489, found 282.1499.



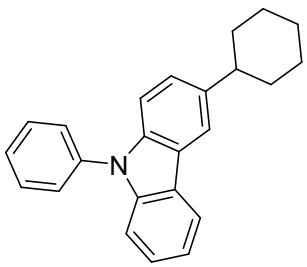
***tert*-Butyl 4-(naphthalen-2-yl)piperidine-1-carboxylate(3la):** yellow soild (62% yield, eluent = hexane/MTBE (20:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 3H), 7.66 – 7.61 (m, 1H), 7.50 – 7.40 (m, 2H), 7.36 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.29 (br, 2H), 2.98 – 2.74 (m, 3H), 1.92 (d, *J* = 13.1 Hz, 2H), 1.76 – 1.57 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 143.3, 133.6, 132.3, 128.1, 127.6, 127.6, 126.0, 125.8, 125.4, 124.8, 79.5, 44.6, 42.8, 33.2, 28.5. HRMS (ESI) Calcd for $C_{16}H_{18}NO_2^+$ [M – *t*-Bu+ H]$^+$ 256.1327, found 256.1318.



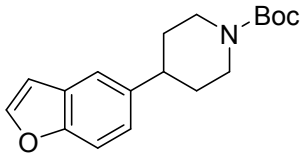
Ethyl 2-cyclohexylbenzoate(3ma)[9]: colorless oil (55% yield, eluent = hexane/MTBE (20:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.37 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.23 – 7.21 (m, 1H), 4.37 (q, *J* = 8.0 Hz, 2H), 3.29 – 3.26 (m, 1H), 1.94 – 1.81 (m, 4H), 1.80 – 1.72 (m, 1H), 1.47 – 1.37 (m, 7H), 1.29 – 1.24 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 148.3, 131.4, 130.6, 129.7, 126.8, 125.4, 60.9, 40.3, 34.4, 27.0, 26.3, 14.3. HRMS (ESI) Calcd for $C_{15}H_{21}O_2^+$ [M + H]$^+$ 233.1536, found 233.1531.



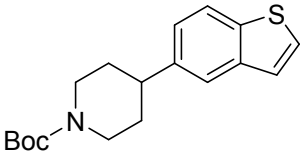
***tert*-Butyl 5-cyclohexyl-1H-indole-1-carboxylate (3na)[7]:** colorless oil (57% yield, eluent = hexane/MTBE (2:1)) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 3.7 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.18 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.63 (d, *J* = 3.7 Hz, 1H), 2.59 – 2.53 (m, 1H), 1.84 – 1.67 (m, 5H), 1.61 (s, 9H), 1.50 – 1.30 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.6, 142.7, 133.5, 130.8, 126.5, 123.9, 119.0, 114.9, 108.0, 84.0, 44.1, 34.91, 28.2, 26.9, 26.1. HRMS (ESI) Calcd for $C_{15}H_{18}NO_2^+$ [M – *t*-Bu + H]$^+$ 244.1332, found 244.1337.



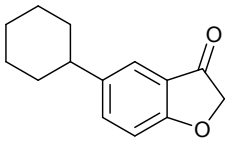
3-Cyclohexyl-9-phenyl-9H-carbazole(3oa): yellow oil (72% yield, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 1.7 Hz, 1H), 7.64 – 7.53 (m, 4H), 7.49 – 7.40 (m, 1H), 7.40 – 7.32 (m, 3H), 7.31 – 7.26 (m, 2H), 2.77 – 2.63 (m, 1H), 2.04 – 1.95 (m, 2H), 1.93 – 1.89 (m, 2H), 1.86 – 1.76 (m, 1H), 1.66 – 1.57 (m, 1H), 1.53 – 1.42 (m, 2H), 1.35 – 1.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.1, 139.5, 138.0, 129.8, 127.2, 127.0, 125.7, 125.3, 123.5, 123.4, 120.2, 119.7, 117.9, 109.7, 109.5, 44.7, 35.3, 27.2, 26.3. HRMS (ESI) Calcd for $C_{24}H_{24}N$ $[M + H]^+$ 326.1903, found 326.1907.



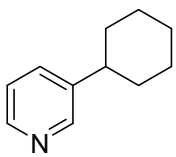
***tert*-Butyl 4-(benzofuran-5-yl)piperidine-1-carboxylate(3pa):** white soild (68% yield, eluent = hexane/MTBE (15:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.0 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.14 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 4.26 (br, 2H), 2.95 – 2.64 (m, 3H), 1.87 – 1.84 (m, 2H), 1.76 – 1.60 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 153.8, 145.3, 140.5, 127.6, 123.4, 118.8, 111.2, 106.5, 79.4, 44.6, 42.7, 33.8, 28.5. HRMS (ESI) Calcd for $C_{14}H_{16}NO_3^+$ $[M – t\text{-Bu} + H]^+$ 246.1125, found 246.1135.



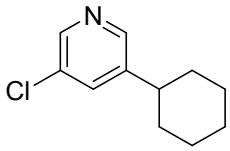
***tert*-Butyl 4-(benzo[b]thiophen-5-yl)piperidine-1-carboxylate (3qa):** white solid (75% yield, eluent = hexane/MTBE (3:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.40 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.22 – 3.96 (m, 2H), 2.83 – 2.75 (m, 3H), 1.84 – 1.75 (m, 2H), 1.60 – 1.51 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4, 142.6, 140.3, 137.5, 127.9, 124.4, 124.3, 122.9, 121.7, 79.0, 42.1, 33.6, 31.7, 28.6. HRMS (ESI) Calcd for $C_{14}H_{16}NO_2S^+$ $[M – t\text{-Bu} + H]^+$ 262.0896, found 262.0906.



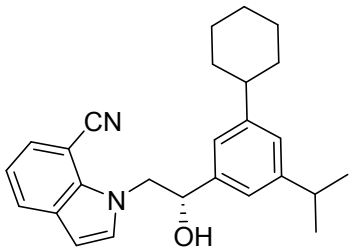
5-Cyclohexylbenzofuran-3(2H)-one (3ra): orange oil (81% yield, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 4.77 (s, 2H), 2.59 – 2.54 (m, 1H), 1.80 – 1.76 (m, 4H), 1.74 – 1.65 (m, 1H), 1.47 – 1.29 (m, 4H), 1.28 – 1.18 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 200.2, 172.4, 142.0, 137.7, 121.3, 120.8, 113.8, 75.5, 43.3, 34.4, 26.8, 25.9. HRMS (ESI) Calcd for $C_{14}H_{17}O_2$ $[M + H]^+$ 217.1223, found 217.1238.



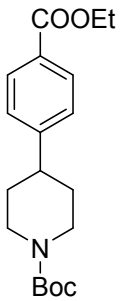
3-Cyclohexylpyridine(3sa)[10]**:** yellow oil (62% yield, eluent = hexane/EtOAc(1:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.4 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 2.55 – 2.49 (m, 1H), 1.89 – 1.84 (m, 4H), 1.79 – 1.73 (m, 1H), 1.46 – 1.37 (m, 4H), 1.29 – 1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.3, 142.9, 134.0, 123.3, 42.0, 34.1, 26.7, 26.0. HRMS (ESI) Calcd for $C_{11}H_{16}N^+$ $[M + H]^+$ 162.1277, found 162.1269.



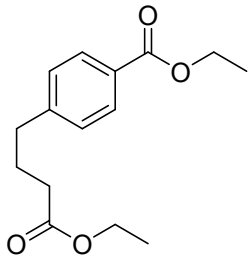
3-Chloro-5-cyclohexylpyridine (3ta): colorless oil (59% yield, eluent = hexane/MTBE (4:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, *J* = 4.0 Hz, 2H), 7.76 (s, 1H), 2.60 – 2.53 (m, 1H), 1.79 – 1.71 (m, 4H), 1.69 – 1.66 (m, 1H), 1.43 – 1.27 (m, 4H), 1.23 – 1.19 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.4, 146.1, 145.0, 134.3, 131.5, 41.2, 33.7, 26.6, 25.7. HRMS (ESI) Calcd for $C_{11}H_{15}ClN^+$ $[M + H]^+$ 196.0888, found 196.0896.



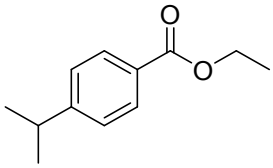
(*S*)-1-(2-(3-Cyclohexyl-5-isopropylphenyl)-2-hydroxyethyl)-1*H*-indole-7-carbonitrile(3ua): white soild (55% yield, eluent = hexane/EA(5:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.16 – 7.09 (m, 3H), 7.01 (d, *J* = 1.6 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 5.18 – 5.15 (m, 1H), 4.82 (dd, *J* = 16.0, 4.0 Hz, 1H), 4.57 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.50 – 2.48 (m, 1H), 2.09 (t, *J* = 4.0 Hz, 1H), 1.84 (d, *J* = 8.6 Hz, 4H), 1.75 (d, *J* = 12.6 Hz, 1H), 1.45 – 1.33 (m, 4H), 1.22 (d, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 148.6, 140.5, 134.3, 132.0, 130.5, 128.5, 126.4, 125.3, 121.9, 121.6, 119.2, 119.1, 102.3, 93.8, 74.2, 54.5, 44.7, 34.5, 34.2, 26.9, 26.2, 24.0. HRMS (ESI) Calcd for $C_{26}H_{31}N_2O$ $[M + H]^+$ 387.2431, found 387.2419.



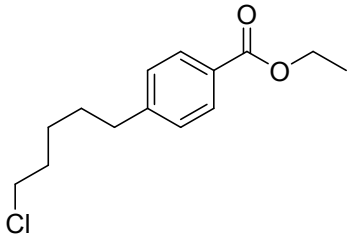
***tert*-Butyl 4-(4-(ethoxycarbonyl)phenyl)piperidine-1-carboxylate (3ab)**[11]**:** colorless oil (82% yield, eluent = hexane/EtOAc (20:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.36 (q, *J* = 8.0 Hz, 2H), 4.25 (br, 2H), 2.80 – 2.74 (m, 2H), 2.70 – 2.67 (m, 1H), 1.84 – 1.80 (m, 2H), 1.67 – 1.57 (m, 2H), 1.48 (s, 9H), 1.38 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 154.8, 151.0, 129.9, 128.7, 126.8, 79.6, 60.8, 44.3, 42.8, 32.9, 28.5, 14.4. HRMS (ESI) Calcd for $C_{15}H_{20}NO_4^+$ [M – *t*-Bu + H]$^+$ 278.1387, found 278.1392.



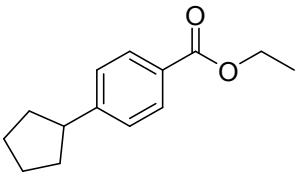
Ethyl 4-(4-ethoxy-4-oxobutyl)benzoate (3ac)[12]**:** colorless oil (71% yield, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.34 (dd, *J* = 8.0, 4.0 Hz, 2H), 4.29 (q, *J* = 8.0 Hz, 2H), 4.04 (q, *J* = 8.0 Hz, 2H), 2.65 (dd, *J* = 8.0, 4.0 Hz, 2H), 2.30 – 2.23 (m, 2H), 1.87 – 1.79 (m, 2H), 1.30 (t, *J* = 8.0 Hz, 3H), 1.16 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.0, 166.1, 147.7, 129.7, 129.1, 128.1, 61.0, 60.2, 34.7, 33.3, 26.3, 14.6, 14.5. HRMS (ESI) Calcd for $C_{15}H_{21}O_4^+$ [M + H]$^+$ 265.1435, found 265.1437.



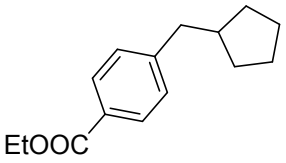
Ethyl 4-isopropylbenzoate (3ad)[11]**:** colorless oil (75% yield, eluent = hexane/MTBE (20:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.38 (dd, *J* = 8.0, 4.0 Hz, 2H), 4.30 (q, *J* = 8.0 Hz, 2H), 2.96 (hept, *J* = 6.9 Hz, 1H), 1.31 (t, *J* = 8.0 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 154.5, 129.7, 128.1, 127.1, 60.9, 34.0, 23.9, 14.6. HRMS (ESI) Calcd for $C_{12}H_{17}O_2^+$ [M + H]$^+$ 193.1223, found 193.1228.



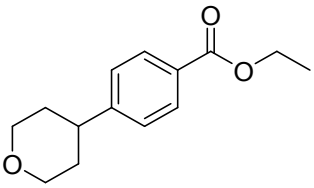
Ethyl 4-(5-chloropentyl)benzoate (3ae)[13]**:** colorless oil (71% yield, eluent = hexane/MTBE (50:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.36 (q, *J* = 8.0 Hz, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.72 – 1.61 (m, 2H), 1.53 – 1.43 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 147.7, 129.7, 128.4, 128.2, 60.8, 44.9, 35.8, 32.4, 30.4, 26.5, 14.4. HRMS (ESI) Calcd for $C_{14}H_{20}ClO_2^+$ [M + H]$^+$ 255.1152, found 255.1152.



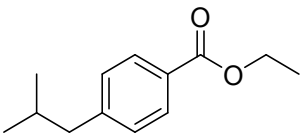
Ethyl 4-cyclopentylbenzoate (3af)[12]**:** colorless oil (81% yield, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.27 (q, *J* = 8.0 Hz, 2H), 3.04 (pent, *J* = 6.9 Hz, 1H), 2.06 – 2.00 (m, 2H), 1.99 – 1.70 (m, 2H), 1.69 – 1.59 (m, 2H), 1.58 – 1.51 (m, 2H), 1.31 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 152.3, 129.6, 127.9, 127.8, 60.9, 45.7, 34.6, 25.6, 14.7. HRMS (ESI) Calcd for $C_{14}H_{19}O_2^+$ $[M + H]^+$ 219.1385, found 219.1384.



Ethyl 4-(cyclopentylmethyl)benzoate(3ag)[14]**:** colorless oil (77% yield, eluent = hexane/MTBE (50:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.66 (d, *J* = 7.6 Hz, 2H), 2.18 – 2.00 (m, 1H), 1.76 – 1.60 (m, 4H), 1.58 – 1.46 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.25 – 1.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 147.8, 129.5, 128.8, 128.0, 60.7, 42.1, 41.8, 32.4, 24.9, 14.4. HRMS (ESI) Calcd for $C_{15}H_{21}O_2^+$ $[M + H]^+$ 233.1536, found 233.1531.

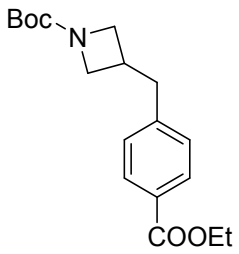


Ethyl 4-(tetrahydro-2H-pyran-4-yl)benzoate (3ah)[14]**:** white solid (54% yield, eluent = hexane/MTBE (10:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.40 (dd, *J* = 8.0, 4.0 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.97 – 3.92 (m, 2H), 3.50 – 3.37 (m, 2H), 2.92 – 2.77 (m, 1H), 1.73 – 1.59 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 151.9, 129.8, 128.4, 127.5, 67.7, 61.0, 41.1, 33.6, 14.6. HRMS (ESI) Calcd for $C_{14}H_{19}O_3^+$ $[M + H]^+$ 235.1329, found 235.1344.

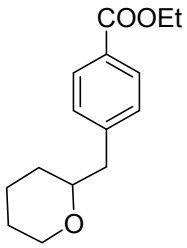


Ethyl 4-isobutylbenzoate (3ai)[15]**:** colorless oil (72% yield, eluent = hexane/MTBE (50:1)); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.51 (d, *J* = 8.0 Hz, 2H), 1.99 – 1.81(m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

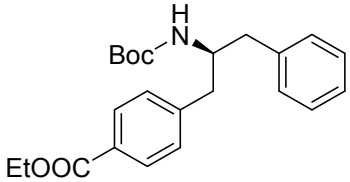
166.2, 147.4, 129.7, 129.5, 128.0, 60.9, 44.9, 30.0, 22.5, 14.6. HRMS (ESI) Calcd for $C_{13}H_{19}O_2^+$ $[M + H]^+$ 207.1380, found 207.1382.



***tert*-Butyl 3-(4-(ethoxycarbonyl)benzyl)azetidine-1-carboxylate (3aj):** colorless oil (61% yield, eluent = hexane/EA(10:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.98 (t, *J* = 8.4 Hz, 2H), 3.63 (dd, *J* = 8.4, 5.4 Hz, 2H), 2.94 (d, *J* = 8.0 Hz, 2H), 2.83 – 2.77(m, 1H), 1.42 (s, 9H), 1.37 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 156.4, 144.6, 129.9, 128.8, 128.4, 79.4, 60.9, 54.3, 40.20, 29.6, 28.4, 14.3. HRMS (ESI) Calcd for $C_{14}H_{18}NO_4^+$ $[M –t\text{-Bu} + H]^+$ 264.1231, found 264.1234.

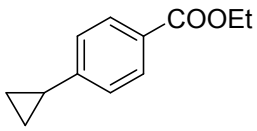


Ethyl 4-((tetrahydro-2H-pyran-2-yl)methyl)benzoate (3ak): colorless oil (63% yield, eluent = hexane/EA(20:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.98 – 3.93 (m, 1H), 3.53 – 3.45 (m, 1H), 3.38 – 3.35 (m, 1H), 2.89 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.71 (dd, *J* = 13.7, 5.8 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.62 – 1.54 (m, 2H), 1.52 – 1.40 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.34 – 1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 144.3, 129.5, 129.4, 128.5, 78.3, 68.6, 60.7, 43.1, 31.6, 26.0, 23.5, 14.3. HRMS (ESI) Calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1485, found 249.1496.



Ethyl (*S*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl)benzoate(3al): yellow soild (55% yield, eluent = hexane/EtOAc(10:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.26 – 7.24 (m, 3H), 7.18 – 7.17 (m, 2H), 4.39 – 4.34 (m, 3H), 4.13 (s, 1H), 2.90 – 2.76 (m, 4H), 1.39 (t, J = 7.2 Hz, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 155.2, 143.7, 137.9, 129.7, 129.38 (two signals overlapped), 128.8, 128.5,

126.5, 79.4, 77.2, 60.9, 52.5, 40.4, 28.3, 14.4. HRMS (ESI) Calcd for $C_{19}H_{23}NO_4^+$ [M –*t*-Bu+ H]$^+$ 328.1544, found 328.1527.



Ethyl 4-cyclopropylbenzoate (3am)[11]**:** colorless oil (68% yield, eluent = hexane/EA(20:1)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.94 (m, *J* = 8.3, 5.0 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.10 – 0.98 (m, 2H), 0.76 (m, *J* = 6.8, 4.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.64, 149.75, 129.59, 127.68, 125.33, 60.66, 15.66, 14.33, 10.06. HRMS (ESI) Calcd for $C_{12}H_{15}O_2$ [M + H]$^+$ 191.1067, found 191.1076.

Reference:

1. P. Klumphu, and B. H. Lipshutz, *J. Org. Chem.,* 2014, **79**, 888–900.
2. D. Liu, Y. Li, C. Liu, A. Lei, X. Qi, Y. Lan, *Org. Lett.,* 2015, **17**, 998–1001.
3. E. Watanabe, Y. Chen, O. May, S. V. Ley, *Chem. −Eur. J.,* 2020, **26**, 186−191.
4. X. Zhang, D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2016, **138**, 13862–13865.
5. G. A. Molander, K. M. Traister, B. T. Oneill, *J. Org. Chem.,* 2014, **79**, 5771–5780.
6. R. Martin-Montero, V. R. Yatham, H. Yin, J. Davies, R. Martin, *Org. Lett.,* 2019, **21**, 2947–2951.
7. I. B. Perry, T. F. Brewer, P. J. Sarver, D. M. Schultz, D. A. DiRocco, D. W. C. MacMillan, *Nature,* 2018, **560**, 70–75.
8. H. Yue, C. Zhu, L. Shen, Q. Geng, K. J. Hock, T. Yuan, L. Cavallo, M. Rueping, *Chem. Sci.,* 2019, **10**, 4430–4435.
9. J. Liu, Y. Deng, H. Wang, H. Zhang, G. Yu, B. Wu, H. Zhang, Z. Yang, A. Lei, *Org. Lett.,* 2008, 10, 2661–2664.
10. E. C. Hansen, C. Li, S. Yang, D. Pedro, D. J. Weix, *J. Org. Chem.,* 2017, **82**, 7085–7092.
11. T. B. Hamby, C. S. Sevov, B. L. Truesdell, *J. Am. Chem. Soc.,* 2020, **142**, 5884–5893.
12. R. J. Perkin, A. J. Hughes, D. J. Weix, E. C. Hansen, *Org. Process Res. Dev.,* 2019, **23**, 1746–1751.
13. C. Duplais, A. Krasovkiy, B. H. Lipshutz, *Organometallics,* 2011, **30**, 6090–6097.
14. I. Abdiaj, A. Fontana, M. V. Gomez, A. de la Hoz, J. Alcázar, *Angew. Chem. Int. Ed.,* 2018, **57**, 8473–8477.
15. S. Biswas, B. Qu, J.-N. Desrosiers, Y. Choi, N. Haddad, N. K. Yee, J. H. J. Song, and C. H. Senanayake, *J. Org. Chem.,* 2020, **85**, 8214−8220.