Supplementary Material (ESI) for Chemical Communications

Supporting Information

Efficient Cu-catalyzed oxidative Mannich reaction between tertiary amines and methyl ketones

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General information:

All solvents and reagents were purchased from the suppliers and used without further purification. Yields reported are for isolated yields unless otherwise stated. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ at room temperature on a Varian INOVA-400 spectrometer. The chemical-shift scale is based on internal TMS. MS spectra were performed on a Agilent 1100 series mass spectrometer. HRMS analyses were performed on a Shimadzu QP-2000 mass spectrometer. IR spectra were recorded by Thermo Electron Nicolet FTIR-6700 instrument. TLC analyses were performed on silica gel plates and column chromatography was conducted over silica gel (mesh 200-300).

Representative procedure:

1-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-butan-2-one and 3-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-butan-2-one

In a 10 mL round-bottom flask equipped with a balloon filled with molecular oxygen was placed 5 mmol% CuI (9.5 mg, 0.05 mmol), 2-butanone (0.17 ml, 3 mmol), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (209 mg, 1 mmol), acetic acid (0.2 ml, 3 mmol), 4 Å molecular sieves (50 mg). Product formation was sensitive to the stirring efficiency. The mixture was stirred under molecular oxygen at 80 ^{0}C for 6 h before it was cooled to room temperature. The mixture was diluted with ether and quenched with saturated NaCl solution. The ether layer was separated and the aqueous layer was further extracted three times with ether. The organic phases were combined, dried over $MgSO_4$, and concentrated via vacua. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 30:1) to afford the 200 mg of the desired product in 72% yield.

Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, J = 8.4 Hz, 2H), 7.03 – 7.00 (m, 4H), 6.83 – 6.83 (t, J = 7.6 Hz, 2H), 6.65 (t, J = 7.2 Hz, 1H), 5.31 (t, J = 6.4 Hz, 1H), 3.55 – 3.38 (m, 2H), 2.93 – 2.88 (m, 2H), 2.74 – 2.65 (m, 2H), 2.28 – 2.11 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.88, 148.76, 138.29, 134.37, 129.27 (2 C), 128.57, 126.78, 126.70, 126.16, 118.02, 114.49 (2 C), 55.00, 48.86, 41.83, 37.19, 27.19, 7.44; IR (neat) 1709 cm^{-1} (C=O); MS (CI) m/z: 280 $[M+1]^+$; HRMS (EI) calcd for $C_{19}H_{21}NO$ $[M]^+$ 279.3761, found 279.3768; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.15 – 7.00 (m, 6H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.70 – 6.66 (m, 1H), 4.76 (d, *J* = 9.6 Hz, 1H), 3.74 – 3.66 (m, 1 H), 3.62 – 3.56 (m, 1H), 3.04 – 2.98 (m, 1H), 2.95 – 2.87 (m, 1H), 2.73 - 2.67 (m, 1H), 2.02 (s, 3H), 1.06 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.32, 148.44, 134.43, 133.87, 128.16 (2 C), 128.13, 127.20, 126.07, 124.37, 117.89, 114.95 (2 C), 60.07, 51.46, 41.42, 27.17, 4.57, 14.08; IR (neat) 1708 cm^{-1} (C=O); MS (CI) m/z: 280 $[M+1]^+$; HRMS (EI) calcd for $C_{19}H_{21}NO$ $[M]^+$ 279.3761, found 279.3764.

1-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-propan-2-one

Yield: 68%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.15 (m, 2H), 7.10 – 7.05 (m, 4H), 6.87 – 6.83 (m, 2H), 6.72 – 6.69 (m, 1H), 5.33 (t, *J* = 6.0 Hz, 1H), 3.59 – 3.46 (m, 2H), 3.01 – 2.96 (m, 2H), 2.78 – 2.74 (m, 2H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.22, 147.87, 137.28, 133.42, 128.33 (2 C), 127.65, 125.85, 125.78, 125.27, 117.25, 113.77 (2 C), 53.78, 49.21, 41.05, 30.07, 26.21; IR (neat) 1701 cm^{-1} (C=O); MS (CI) m/z: 266 $[M+1]^+$; HRMS (EI) calcd for $C_{18}H_{19}NO$ $[M]^+$ 265.3496, found 265.3485.

4-(*N*-methyl-*N*-(4-methylphenyl)amino)-butan-2-one

Yield: 70%. ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2 H), 3.53 (t, *J* = 7.2 Hz, 2H), 2.81 (s, 3H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.18 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.11, 145.65, 128.79 (2 C), 125.09, 112.00 (2 C), 46.67, 39.15, 37.67, 29.59, 19.19; IR (neat) 1708 cm^{-1} (C=O); MS (CI) m/z: 192 $[M+1]^+$; HRMS (EI) calcd for $C_{12}H_{17}NO$ $[M]^+$ 191.2695, found 191.2694.

1-[1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-isoquinolinyl]-propan-2-one

Yield: 73%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.03 (m, 4H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.75 – 6.72 (m, 2H), 5.18 (t, *J* = 6.0 Hz, 1H), 3.67 (s, 3H), 3.47 – 3.40 (m, 2H), 2.96 – 2.89 (m, 2H), 2.73 – 2.68 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.28, 152.54, 137.04, 133.18, 127.93 (2 C), 127.70, 125.75, 125.68, 125.23, 117.58, 113.64 (2 C), 55.11, 54.59, 48.89, 42.24, 29.84, 25.65; IR (neat) 1716 cm^{-1} (C=O); MS (CI) m/z: 296 $[M+1]^+$; HRMS (EI) calcd for $C_{19}H_{21}NO_2$ $[M]^+$ 295.3755, found 295.3767.

1-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-pentan-2-one

Yield: 62%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.13 (m, 2H), 7.06 – 7.03 (m, 4H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.69 – 6.66 (m, 1H), 5.34 (t, *J* = 6.4 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.47 – 3.40 (m, 1H), 3.00 – 2.90 (m, 2H), 2.77 – 2.65 (m, 2H), 2.24 – 2.09 (m, 2H), 1.47 – 1.40 (m, 2H), 0.75 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.45, 147.80, 137.40, 133.38, 128.29 (2 C), 127.58 125.83, 125.72, 125.19, 117.03, 113.53 (2 C), 53.84, 48.21, 44.95, 40.91, 26.27, 15.88, 12.60; IR (neat) 1707 cm^{-1} (C=O); MS (CI) m/z: 294 $[M+1]^+$; HRMS (EI) calcd for $C_{20}H_{23}NO$ $[M]^+$ 293.4027, found 293.4039.

1-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-hexan-2-one

Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.12 (m, 2H), 7.06 – 7.01 (m, 4H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.66 (t, *J* = 7.2 Hz, 1H), 5.33 (t, *J* = 6.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.41 – 3.32 (m, 1H), 2.97 – 2.88 (m, 2H), 2.72 – 2.60 (m, 2H), 2.24 – 2.10 (m, 2 H), 1.39 – 1.34 (m, 2H), 1.34 – 1.12 (m, 2H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.56, 147.79, 137.38, 133.37, 128.28 (2 C), 127.57, 125.82, 125.71, 125.18, 117.02, 113.50 (2 C), 53.84, 48.17, 42.74, 40.91, 26.27, 24.50, 21.15, 12.79; IR (neat) 1708 cm^{-1} (C=O); MS (CI) m/z: 308 $[M+1]^+$; HRMS (EI) calcd for $C_{21}H_{25}NO$ $[M]^+$ 307.4293, found 307.4295.

1-[1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-isoquinolinyl]-hexan-2-one

Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 7.05 (m, 4H), 6.85 – 6.82 (m, 2H), 6.74 – 6.72 (m, 2H), 5.21 (t, *J* = 6.4 Hz, 1H), 3.67 (s, 3H), 3.48 – 3.45 (m, 1H), 3.41 – 3.35 (m, 1H), 2.95 – 2.88 (m, 2H), 2.70 – 2.61 (m, 2H), 2.20 – 2.19 (m, 2H), 1.39 – 1.37 (m, 2H), 1.15 – 1.13 (m, 2H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.74, 152.12, 142.65, 137.46, 133.26, 127.86, 125.84, 125.56, 125.12, 117.11 (2 C), 113.61 (2 C), 55.02, 54.60, 47.96, 42.62, 41.68, 25.89, 24.55, 21.19, 12.80; IR (neat) 1708 cm^{-1} (C=O); MS (CI) m/z: 338 $[M+1]^+$; HRMS (EI) calcd for $C_{22}H_{27}NO_2$ $[M]^+$ 337.4553, found 337.4570.

1-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-heptan-2-one

Yield: 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.14 (m, 2H), 7.06 – 7.04 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.68 (t, *J* = 7.2 Hz, 1H), 5.34 (t, *J* = 6.0 Hz, 1H), 3.57 – 3.53 (m, 1H), 3.48 – 3.41 (m, 1H), 3.02 – 2.92 (m, 2H), 2.78 – 2.66 (m, 2H), 2.26 – 2.13 (m, 2H), 1.42 – 1.39 (m, 2H), 1.19 – 1.09 (m, 6H), 0.77 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.67, 147.79, 137.39, 133.39, 128.29 (2 C), 127.58, 125.85, 125.72, 125.20, 117.03, 113.51 (2 C), 53.87, 48.20, 43.08, 40.92, 30.51, 27.72, 26.27, 22.39, 21.42, 12.99; IR (neat) 1709 cm^{-1} (C=O); MS (CI) m/z: 336 $[M+1]^+$; HRMS (EI) calcd for $C_{23}H_{29}NO$ $[M]^+$ 335.4825, found 335.4827.

2-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-1-phenylethanone

Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.76 (m, 2H), 7.47 – 7.43 (m, 2H), 7.35 – 7.31 (m, 2H), 7.19 – 7.15 (m, 2H), 7.09 – 7.02 (m, 3H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.68 (t, *J* = 7.2 Hz, 1H), 5.59 (t, *J* = 6.8 Hz, 1H), 3.61 – 3.56 (m, 2H), 3.55 – 3.49 (m, 1H), 3.36 – 3.29 (m, 1H), 3.08 – 3.01 (m, 1H), 2.89 – 2.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.61, 147.72, 137.50, 136.23, 133.46, 132.06, 128.32 (2 C), 127.52 (2 C), 127.07 (2 C), 126.10, 125.79, 125.23, 116.89, 114.75, 113.28 (2 C), 53.99, 44.32, 41.12, 26.54; IR (neat) 1680 cm^{-1} (C=O); MS (CI) m/z: 328 $[M+1]^+$; HRMS (EI) calcd for $C_{23}H_{21}NO$ $[M]^+$ 327.4189, found 327.4176.

2-[1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-isoquinolinyl]-1-phenylethanone

Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.42 (m, 1H), 7.34 – 7.31 (m, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.07 – 7.04 (m, 3H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.46 (t, *J* = 6.4 Hz, 1H), 3.66 (s, 3H), 3.52 –

3.45 (m, 3H), 3.26 – 3.20 (m, 1H), 3.04 – 2.96 (m, 1H), 2.79 – 2.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.78, 151.94, 142.53, 137.52, 136.25, 133.26, 131.96, 127.80, 127.46 (2 C), 127.06 (2 C), 126.02, 125.62, 125.09, 116.77 (2 C), 113.60 (2 C), 55.20, 54.58, 43.85, 41.67, 26.18; IR (neat) 1676 cm^{-1} (C=O); MS (CI) m/z: 358 $[M+1]^+$; HRMS (EI) calcd for $C_{24}H_{23}NO_2$ $[M]^+$ 357.4449, found 357.4452.

2-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-1-*p*-tolylethanone

Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.12 (m, 3H), 7.09 – 7.07 (m, 2H), 7.05 – 7.04 (m, 2 H), 7.02 – 6.99 (m, 1H), 6.88 – 6.86 (m, 2H), 6.66 – 6.62 (m, 1H), 5.57 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.55 – 3.52 (m, 2H), 3.51 – 3.41 (m, 1H), 3.29 – 3.23 (m, 1H), 3.04 – 2.96 (m, 1H), 2.84 – 2.79 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.18, 147.69, 142.86, 137.55, 133.70, 133.41, 128.28 (2 C), 128.16 (2 C), 127.46, 127.17 (2 C), 126.07, 125.72, 125.17, 116.76, 113.17 (2 C), 53.94, 44.12, 41.04, 26.51, 20.56; IR (neat) 1676 cm^{-1} (C=O); MS (CI) m/z: 342 $[M+1]^+$; HRMS (EI) calcd for $C_{24}H_{23}NO$ $[M]^+$ 341.4455, found 341.4451.

2-[1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-isoquinolinyl]-1-*p*-tolylethanone

Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.10 (m, 3H), 7.07 – 7.05 (m, 3H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.44 (t, *J* = 6.0 Hz, 1H), 3.65 (s, 3H), 3.51 – 3.42 (m, 3H), 3.23 – 3.17 (m, 1H), 3.04 – 2.96 (m, 1H), 2.78 – 2.73 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.34, 151.88, 142.77, 142.56, 137.61, 133.79, 133.23, 128.15 (2 C), 127.77, 127.21 (2 C), 126.04, 125.58, 125.07, 116.65 (2 C), 113.62 (2 C), 55.16, 54.59, 43.71, 41.65, 26.20, 20.59; IR (neat) 1675 cm^{-1} (C=O); MS (CI) m/z: 372 $[M+1]^+$; HRMS (EI) calcd for $C_{25}H_{25}NO_2$ $[M]^+$ 371.4715, found 371.4721.

2-[1,2,3,4-Tetrahydro-2-phenyl)-1-isoquinolinyl]-1-(4-methoxyphenyl)ethanone

Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.8 Hz, 2H), 7.15 – 7.11 (m, 3H), 7.04 – 7.03 (m, 2H), 7.01 – 6.98 (m, 1H), 6.88 – 6.86 (m, 2H), 6.76 – 6.74 (m, 2H), 6.64 (d, *J* = 7.2 Hz, 1H), 5.55 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.70 (s, 3H), 3.54 – 3.50 (m, 2H), 3.43 – 3.38 (m, 1H), 3.26 – 3.20 (m, 1H), 3.03 – 2.96 (m, 1H), 2.84 – 2.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.03, 162.43, 147.70, 137.58, 133.41, 129.35 (2 C), 129.26, 128.28 (2 C), 127.46, 126.08, 125.71, 125.15, 116.72, 113.14 (2 C), 112.62 (2 C), 54.37, 54.04, 43.83, 41.04, 26.52; IR (neat) 11670 cm^{-1} (C=O); MS (CI) m/z: 358 $[M+1]^+$; HRMS (EI) calcd for $C_{24}H_{23}NO_2$ $[M]^+$ 357.4449, found 357.4443.

2-[1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-isoquinolinyl]-1-(4-methoxyphenyl)-ethanone

Yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.07 – 7.04 (m, 3H), 6.88 – 6.85 (m, 2H), 6.80 – 6.78 (m, 2H), 6.73 – 6.71 (m, 2H), 5.44 (t, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.51 – 3.46 (m, 2H), 3.45- 3.39 (m, 1H), 3.20 – 3.15(m, 1H), 3.04 – 2.96 (m, 1H), 2.79 – 2.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.24, 162.39, 151.88, 142.60, 137.66, 133.25, 133.41,

129.39 (2 C), 127.75, 126.07, 125.57, 125.06, 116.63 (2 C), 113.64 (2 C), 112.60 (2 C), 55.28, 54.62, 54.42, 43.46, 41.68, 26.25; IR (neat) 1716 cm^{-1} (C=O); MS (CI) m/z: 388 $[M+1]^+$; HRMS (EI) calcd for $C_{25}H_{25}NO_3$ $[M]^+$ 387.4709, found 387.4714.

2-[1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-isoquinolinyl]-pentan-3-one

Yield: 24%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.06 (m, 6H), 6.87 – 6.85 (m, 2H), 6.70 – 6.66 (m, 1H), 5.06 – 4.78 (m, 1H), 3.67 – 3.52 (m, 2H), 3.05 – 2.98 (m, 2H), 2.93 – 2.87 (m, 1H), 2.30 – 1.80 (m, 2H), 1.10 – 1.00 (m, 3H), 0.87 – 0.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.97, 212.93, 148.85, 148.43, 137.25, 134.70, 133.89, 133.53, 128.17 (2 C), 128.10 (2 C), 128.00, 127.61, 127.36, 126.04, 125.94, 125.67 (2 C), 124.99, 124.34, 117.64, 116.26, 114.64,112.66 (2 C), 60.37, 58.48, 52.07, 50.26, 41.41, 41.37, 36.73, 33.89, 25.70, 24.85, 14.52, 14.33, 6.63, 6.32; IR (neat) 1713 cm^{-1} (C=O); MS (CI) m/z: 294 $[M+1]^+$; HRMS (EI) calcd for $C_{20}H_{23}NO$ $[M]^+$ 293.4027, found 293.4026.