Supporting Information

Unprecedented Copper-Mediated Oxidative Demethylation of Propionamides via Bidentate-Chelation Assistance

Table of Contents

I. General Information ................................................................. S2
II. Preparation of Propionamides ............................................. S3-S9
III. General Experimental Procedures, Spectral Data ........... S10-S20
IV. References ............................................................................. S21
V. NMR Spectra ........................................................................... S22-S61
I. General Information

a). Materials

Unless otherwise noted, all the reactions were carried out in anhydrous solvents under O$_2$ atmosphere (purity $\geq$99.995%). Cu(OAc)$_2$(98%) was purchased from Sigma-Aldrich. Anhydrous solvents (DMF, DMSO, NMP) were purchased from Acros and used without further purification. K$_2$CO$_3$ and Na$_2$CO$_3$ were purchased from Sinopharm Chemical Reagent Co., Ltd and used as received. The following reagents were purchased from commercial sources: Ag$_2$O(99%, Alfa), Ag$_2$CO$_3$(99%, Acros), AgOAc(99%, Stream), (BOC)$_2$O(95%, TCI), TMSOAc(98%, J&K), Cs$_2$CO$_3$(99.5%, Acros).

All the other reagents and solvents mentioned in this text were purchased from commercial sources and used without purification.

b). Analytical Methods

$^1$H-NMR, $^{13}$C-NMR and $^{19}$F-NMR spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature in CDCl$_3$ unless otherwise noted; Data for $^1$H-NMR are reported as follows: chemical shift ($\delta$ ppm), multiplicity, integration, and coupling constant (Hz). Data for $^{13}$C-NMR are reported in terms of chemical shift ($\delta$ ppm), multiplicity, and coupling constant (Hz). Gas chromatographic (GC) analysis was acquired on a Shimadzu GC-2014 Series GC System equipped with a flame-ionization detector. GC-MS analysis was performed on Thermo Scientific AS 3000 Series GC-MS System. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Flash column chromatographic purification of products was accomplished using forced-flow chromatography on Silica Gel (200-300 mesh).
II. Preparation of Propionamides

Starting materials:

1a)

a. Starting materials 1a-d, 2u were prepared according to literature [1]. Starting materials 3, 1o, 1p, 1q, 4, 5 were synthesized according to literature [2]. Substrate 1s was synthesized according to literature [3]. Substrates 1e and 1u were synthesized according to literature [4]. Substrate 6 was synthesized according to literature [5].
**b)** General procedure for the synthesis of 1f-1n, 1t[1].

To a solution of carboxylate ester (20 mmol) in THF (20 mL) at -78 °C, LDA (2.0 M THF solution, 11 mL) was added dropwise and the mixture was stirred at this temperature for 1 h. Alkyl halide (20 mmol) was then added dropwise to the solution at -78 °C. After the addition, the mixture was warmed to room temperature and stirred overnight. Then the mixture was quenched with water, extracted with Et₂O (40 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄, and then evaporated in vacuo to give the crude ester.

To the ester was added NaOH (60 mmol) and methanol (50 mL). The mixture was stirred overnight at 80 °C. After removal of methanol in vacuo, the pH of the mixture was adjusted to 2 with 3.0 M HCl. The mixture was then saturated with NaCl and extracted with Et₂O (40 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄, and then evaporated in vacuo to give the crude carboxylic acid, which was used directly for the next step without further purification.

Oxalyl chloride (3.5 mL, 40 mmol) was added slowly to a stirred solution of the carboxylic acid in CH₂Cl₂ (40 mL) and DMF (0.2 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and another 16 h at room temperature, and evaporated in vacuo. The residue was then dissolved in toluene (5 mL), evaporated in vacuo twice, to give the crude acid chloride, which was used directly for the next step without further purification.

The acid chloride was added dropwise to a solution of 8-aminoquinoline (2.0 g, 14 mmol) and NEt₃ (3.8 mL, 28 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred overnight at room temperature. Then the mixture was diluted with CH₂Cl₂ (50 mL), washed successively with water, and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:100, v/v), to afford corresponding 8-aminoquinolinyl amides 1.

![2-ethyl-2-methyl-N-(quinolin-8-yl)-4-(p-tolyl)butanamide](image)

Compound 1f, yellow oil, was prepared from ethyl 2-methylbutanoate and 1-(2-iodoethyl)-4-methylbenzene.

$^1$H NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H), 8.88 – 8.79 (m, 2H), 8.18 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.60 – 7.43 (m, 3H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 2H), 2.72 – 2.53 (m, 2H), 2.28 (s, 3H), 2.21 – 2.10 (m, 1H), 2.00 – 1.80 (m, 2H), 1.75-1.66 (m, 1H), 1.46 (s, 3H), 0.97 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl₃) δ 175.64, 148.13, 139.31, 138.65, 136.51, 135.18, 134.52, 129.00, 128.29, 127.99, 127.53, 121.54, 121.27, 116.52, 47.71, 42.33, 33.05, 30.77, 20.96, 20.81, 8.95.


![2-ethyl-4-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)butanamide](image)

Compound 1g, yellow oil, was prepared from ethyl 2-methylbutanoate and 1-(2-iodoethyl)-4-
methoxybenzene.

1H NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H), 8.83 (dd, J = 4.9, 3.0 Hz, 2H), 8.18 (dd, J = 8.3, 1.5 Hz, 1H), 7.59 – 7.44 (m, 3H), 7.12 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 3.75 (s, 3H), 2.70 – 2.51 (m, 2H), 2.21 – 2.09 (m, 1H), 1.99 - 1.90 (m, 1H), 1.89 – 1.78 (m, 1H), 1.75-1.60 (m, 1H), 1.46 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 175.65, 157.69, 148.12, 138.62, 136.54, 134.49, 129.29, 127.99, 127.54, 121.54, 121.28, 116.53, 113.72, 55.23, 47.69, 42.41, 33.05, 30.29, 20.79, 8.95.

HRMS calcd for C_{23}H_{26}N_2O_2 (M+ H⁺): 363.2067, Found: 363.2068.

F 2-ethyl-4-(4-fluorophenyl)-2-methyl-N-(quinolin-8-yl)butanamide

Compound 1h, yellow oil, was prepared from ethyl 2-methylbutanoate and 1-fluoro-4-(2-iodoethyl)benzene.

1H NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H), 8.84-8.82 (m, 2H), 8.18 (dd, J = 8.3, 1.5 Hz, 1H), 7.60 – 7.43 (m, 3H), 7.18-7.12 (m, 2H), 6.91 (t, J = 8.7 Hz, 2H), 2.80 – 2.62 (m, 2H), 2.24 – 2.12 (m, 1H), 2.01 – 1.77 (m, 2H), 1.75-1.65 (m, 1H), 1.46 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H).

19F NMR (376 MHz, CDCl₃) δ -117.89.

13C NMR (101 MHz, CDCl₃) δ 175.46, 148.21, 138.73, 137.95 (d, J = 4 Hz), 136.44, 134.47, 129.74 (d, J = 7 Hz), 127.98, 127.49, 121.59, 121.34, 116.39, 115.01 (d, J = 21 Hz), 47.68, 42.24, 33.07, 30.45, 20.79, 8.95.

HRMS calcd for C_{22}H_{23}FN_2O (M+ H⁺): 351.1867, Found: 351.1865.

2-ethyl-2-methyl-N-(quinolin-8-yl)-4-(4-(trifluoromethyl)phenyl)butanamide

Compound 1i, yellow oil, was prepared from ethyl 2-methylbutanoate and 1-(2-iodoethyl)-4-(trifluoromethyl)benzene.

1H NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H), 8.86 – 8.76 (m, 2H), 8.19 (dd, J = 8.3, 1.5 Hz, 1H), 7.60 – 7.44 (m, 5H), 7.31 (d, J = 8.0 Hz, 2H), 2.81 – 2.62 (m, 2H), 2.24 – 2.12 (m, 1H), 2.02 – 1.80 (m, 2H), 1.71 (dq, J = 14.8, 7.5 Hz, 1H), 1.48 (s, 3H), 0.99 (t, J = 7.5 Hz, 3H).

19F NMR (376 MHz, CDCl₃) δ -62.27.

13C NMR (101 MHz, CDCl₃) δ 175.28, 148.23, 146.50, 138.70, 136.49, 134.39, 128.75, 128.12 (q, J = 33 Hz), 128.00, 127.50, 125.22 (q, J = 4.0 Hz), 124.33 (q, J = 270 Hz), 121.62, 121.42, 116.44, 47.68, 41.76, 33.12, 31.20, 20.81, 8.94.

HRMS calcd for C_{23}H_{23}F_3N_2O (M+ H⁺): 401.1835, Found: 401.1837.

2-(3-chlorophenyl)-2,2-dimethyl-N-(quinolin-8-yl)butanamide
Supporting Information

Compound 1j, colourless oil, was prepared from methyl isobutyrate and 1-chloro-3-(2-iodoethyl)benzene.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.32 (s, 1H), 8.86-8.80 (m, 2H), 8.17 (dd, $J = 8.3$, 1.6 Hz, 1H), 7.59 – 7.43 (m, 3H), 7.24-7.22 (m, 1H), 7.19 – 7.06 (m, 3H), 2.70 – 2.61 (m, 2H), 2.06 – 1.98 (m, 2H), 1.48 (s, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.89, 148.31, 144.27, 138.77, 136.39, 134.48, 134.03, 129.56, 128.56, 127.96, 127.44, 126.65, 125.95, 121.62, 121.40, 116.36, 43.85, 43.43, 31.30, 25.81.

HRMS calcd for C$_{21}$H$_{21}$ClN$_2$O (M+ H$^+$): 353.1415, Found: 353.1413.

2-ethyl-2-methyl-4-(naphthalen-1-yl)-N-(quinolin-8-yl)butanamide

Compound 1k, yellow oil, was prepared from ethyl 2-methylbutanoate and 1-(2-iodoethyl)naphthalene.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.37 (s, 1H), 8.91 (ddd, $J = 7.5$, 1.1 Hz, 1H), 8.82 (dd, $J = 4.2$, 1.5 Hz, 1H), 8.19 (dd, $J = 8.3$, 1.4 Hz, 1H), 8.04 (dd, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.67 (dd, $J = 7.0$, 2.1 Hz, 1H), 7.62 – 7.28 (m, 7H), 3.25 – 2.99 (m, 2H), 2.40 – 2.23 (m, 1H), 2.06 – 1.87 (m, 2H), 1.74 (dq, $J = 14.7$, 7.4 Hz, 1H), 1.57 (s, 3H), 1.01 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.57, 148.25, 138.26, 138.56, 136.39, 134.57, 133.84, 131.76, 128.65, 127.99, 127.54, 126.59, 126.05, 125.79, 125.58, 125.38, 123.83, 121.57, 121.31, 116.37, 47.92, 41.65, 33.20, 28.49, 20.73, 9.00.

HRMS calcd for C$_{26}$H$_{26}$N$_2$O (M+ H$^+$): 383.2118, Found: 383.2115.

2-ethyl-2-methyl-N-(quinolin-8-yl)oct-7-enamide

Compound 1l, yellow oil, was prepared from ethyl 2-methylbutanoate and 6-iodohex-1-ene.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.22 (s, 1H), 8.84 – 8.79 (m, 2H), 8.15 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.57 – 7.40 (m, 3H), 5.76 (ddt, $J = 16.9$, 10.2, 6.7 Hz, 1H), 4.98 – 4.84 (m, 2H), 2.07 – 1.99 (m, 2H), 1.92-1.81 (m, 2H), 1.70 – 1.53 (m, 2H), 1.47 – 1.29 (m, 7H), 0.94 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.03, 148.20, 138.89, 138.80, 136.30, 134.64, 127.95, 127.48, 121.51, 121.14, 116.20, 114.28, 47.62, 39.80, 33.59, 32.91, 29.51, 24.11, 20.75, 8.99.

HRMS calcd for C$_{20}$H$_{20}$N$_2$O (M+ H$^+$): 311.2118, Found: 311.2114.

(E)-2-ethyl-2-methyl-N-(quinolin-8-yl)oct-5-enamide

Compound 1m, yellow oil, was prepared from ethyl 2-methylbutanoate and (E)-1-iodohex-3-ene.
Supporting Information

\[ ^1H \text{ NMR} \ (400 \text{ MHz}, \text{ CDCl}_3) \delta 10.23 \ (s, \ 1H), \ 8.82 \ (dt, \ J = 5.5, \ 1.5 \text{ Hz}, \ 2H), \ 8.15 \ (dd, \ J = 8.3, \ 1.7 \text{ Hz}, \ 1H), \ 7.57 – 7.41 \ (m, \ 3H), \ 5.51 – 5.29 \ (m, \ 2H), \ 2.13 – 1.97 \ (m, \ 2H), \ 1.96 – 1.86 \ (m, \ 4H), \ 1.68-1.60 \ (m, \ 2H), \ 1.38 \ (s, \ 3H), \ 0.97-0.88 \ (m, \ 6H). \]

\[ ^{13}C \text{ NMR} \ (101 \text{ MHz}, \text{ CDCl}_3) \delta 175.82, \ 148.21, \ 138.82, \ 136.27, \ 134.63, \ 132.25, \ 128.73, \ 127.94, \ 127.46, \ 121.51, \ 121.15, \ 116.20, \ 47.50, \ 39.94, \ 32.92, \ 27.82, \ 25.52, \ 20.65, \ 13.80, \ 8.97. \]

HRMS calcd for C\textsubscript{20}H\textsubscript{26}N\textsubscript{2}O (M+H\textsuperscript{+}): 311.2118, Found: 311.2115.

2,2-dimethyl-N-(quinolin-8-yl)hept-6-enamide

Compound 1n, yellow oil, was prepared from methyl isobutyrate and 5-iodopent-1-ene.

\[ ^1H \text{ NMR} \ (400 \text{ MHz}, \text{ CDCl}_3) \delta 10.25 \ (s, \ 1H), \ 8.83 – 8.78 \ (m, \ 2H), \ 8.15 \ (dd, \ J = 8.3, \ 1.7 \text{ Hz}, \ 1H), \ 7.56 – 7.41 \ (m, \ 3H), \ 5.78 \ (ddt, \ J = 16.9, \ 10.2, \ 6.7 \text{ Hz}, \ 1H), \ 5.03 – 4.88 \ (m, \ 2H), \ 2.12 – 2.03 \ (m, \ 2H), \ 1.76 – 1.69 \ (m, \ 2H), \ 1.51 – 1.42 \ (m, \ 2H), \ 1.38 \ (s, \ 6H). \]

\[ ^{13}C \text{ NMR} \ (101 \text{ MHz}, \text{ CDCl}_3) \delta 176.56, \ 148.19, \ 138.80, \ 138.58, \ 136.32, \ 134.65, \ 127.95, \ 127.46, \ 121.21, \ 116.25, \ 114.63, \ 43.72, \ 41.03, \ 34.19, \ 25.65, \ 24.25. \]

HRMS calcd for C\textsubscript{18}H\textsubscript{22}N\textsubscript{2}O (M+H\textsuperscript{+}): 283.1805, Found: 283.1801.

2-cyclohexyl-2-methyl-N-(quinolin-8-yl)propanamide

Compound 1t, yellow oil, was prepared from methyl 2-cyclohexylacetate and iodomethane.

\[ ^1H \text{ NMR} \ (400 \text{ MHz}, \text{ CDCl}_3) \delta 10.24 \ (s, \ 1H), \ 8.86 – 8.79 \ (m, \ 2H), \ 8.17 \ (dd, \ J = 8.3, \ 1.6 \text{ Hz}, \ 1H), \ 7.58 – 7.42 \ (m, \ 3H), \ 1.82 – 1.65 \ (m, \ 6H), \ 1.36 – 1.26 \ (m, \ 8H), \ 1.17 – 1.10 \ (m, \ 3H). \]

\[ ^{13}C \text{ NMR} \ (101 \text{ MHz}, \text{ CDCl}_3) \delta 177.25, \ 148.09, \ 138.64, \ 136.55, \ 134.55, \ 128.00, \ 127.56, \ 121.49, \ 121.21, \ 116.52, \ 47.05, \ 46.24, \ 27.85, \ 26.86, \ 26.57, \ 22.22. \]

HRMS calcd for C\textsubscript{19}H\textsubscript{24}N\textsubscript{2}O (M+H\textsuperscript{+}): 297.1961, Found: 297.1963.

c) General procedure for the synthesis of 1r and 5-(2,5-dimethylphenoxy)-2,2-dimethyl-N-(quinolin-8-yl)pentanamide (9)\textsuperscript{/2}.

Oxalyl chloride (3.5 mL, 40 mmol) was added slowly to a stirred solution of 2,2-dimethylbutanoic acid (20 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (40 mL) and DMF (0.2 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and another 16 h at room temperature, and evaporated in vacuo to give the crude acid chloride, which was used directly for the next step without further purification.

The acid chloride was added dropwise to a solution of 5-methoxyquinolin-8-amine (2.0 g, 14 mmol) and NEt\textsubscript{3} (3.8 mL, 28 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL). The mixture was stirred overnight at room temperature. Then the mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (50 mL), washed successively with water, and brine. The organic layer was dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:100, v/v), to afford corresponding 8-aminoquinolinyl amides 1r (yellow oil).

S7
N-(5-methoxyquinolin-8-yl)-2,2-dimethylbutanamide

Compound 1r, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.00 (s, 1H), 8.82 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.73 (d, $J$ = 8.5 Hz, 1H), 8.56 (dd, $J$ = 8.4, 1.7 Hz, 1H), 7.43 (dd, $J$ = 8.4, 4.3 Hz, 1H), 6.83 (d, $J$ = 8.6 Hz, 1H), 3.98 (s, 3H), 1.76 (q, $J$ = 7.5 Hz, 2H), 1.38 (s, 6H), 0.95 (t, $J$ = 7.5 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.21, 150.04, 148.66, 139.45, 131.20, 128.14, 120.62, 120.44, 116.29, 104.38, 55.76, 43.89, 34.15, 25.13, 9.34.

HRMS calcd for C$_{16}$H$_{20}$N$_2$O$_2$ (M+ H$^+$): 273.1598, Found: 273.1601.

5-(2,5-dimethylphenoxy)-2,2-dimethyl-N-(quinolin-8-yl)pentanamide (9)

Compound 9, Colourless oil. It was prepared from Gemfibrozil and 8-aminoquinoline.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.29 (s, 1H), 8.83 – 8.78 (m, 2H), 8.15 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.57 – 7.42 (m, 3H), 6.95 (d, $J$ = 7.5 Hz, 1H), 6.61 (d, $J$ = 7.5 Hz, 1H), 6.57 (s, 1H), 3.94 (t, $J$ = 5.9 Hz, 2H), 2.25 (s, 3H), 2.13 (s, 3H), 1.97 – 1.83 (m, 4H), 1.46 (s, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.35, 156.91, 148.15, 138.65, 136.44, 136.39, 134.54, 130.20, 127.96, 127.47, 123.54, 121.52, 121.31, 120.61, 116.40, 111.92, 67.91, 43.58, 37.94, 25.66, 25.18, 21.36, 15.76.

HRMS calcd for C$_{24}$H$_{28}$N$_2$O$_2$ (M+ H$^+$): 377.2224, Found: 377.2221.

d) General procedure for the synthesis of 7,7-dimethyl-8-oxo-8-(quinolin-8-ylamino)octyl acetate (7).[1]

To a solution of methyl isobutyrate (20 mmol) in THF (20 mL) at -78 °C, LDA (2.0 M THF solution, 11 mL) was added dropwise and the mixture was stirred at this temperature for 1 h. ((6-iodohexyl)oxy)trimethylsilane (15 mmol) was then added dropwise to the solution at -78 °C. After the addition, the mixture was warmed to room temperature and stirred overnight. Then the mixture was quenched with water, extracted with Et$_2$O (40 mL x 3). The combined organic layers were washed with brine, dried over MgSO$_4$, and then evaporated in vacuo to give the crude ester.

To the ester was added NaOH (60 mmol) and methanol (50 mL). The mixture was stirred overnight at 80 °C. After removal of methanol in vacuo, the pH of the mixture was adjusted to 2 with 3.0 M HCl. The mixture was then extracted with CH$_2$Cl$_2$ (40 mL x 3). The combined organic layers were washed with brine, dried over MgSO$_4$, and then evaporated in vacuo to give the crude ester.
carboxylic acid, which was used directly for the next step without further purification.

To a solution of the crude carboxylic acid in 20 mL pyridine, Ac₂O (30 mmol) was added dropwise and the mixture was stirred at room temperature for 10 h. Then the mixture was quenched with 2.0 M HCl, extracted with CH₂Cl₂ (40 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄, and then evaporated in vacuo to give the crude carboxylic acid.

Oxalyl chloride (3.5 mL, 40 mmol) was added slowly to a stirred solution of the carboxylic acid in CH₂Cl₂ (40 mL) and DMF (0.2 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and another 16 h at room temperature, and evaporated in vacuo. The residue was then dissolved in toluene (5 mL), evaporated in vacuo twice, to give the crude acid chloride, which was used directly for the next step without further purification.

The acid chloride was added dropwise to a solution of 8-aminoquinoline (2.0 g, 14 mmol) and NEt₃ (3.8 mL, 28 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred overnight at room temperature. Then the mixture was diluted with CH₂Cl₂ (50 mL), washed successively with water, and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:50, v/v), to afford corresponding 8-aminoquinolinyl amide (yellow oil).

**7,7-dimethyl-8-oxo-8-(quinolin-8-ylamino)octyl acetate**

Compound 7, yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 10.24 (s, 1H), 8.84 – 8.77 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.57 – 7.41 (m, 3H), 4.00 (t, J = 6.7 Hz, 2H), 2.01 (s, 3H), 1.73-1.69 (m, 2H), 1.62 – 1.53 (m, 2H), 1.40 (s, 6H), 1.38 – 1.30 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 176.62, 171.19, 148.20, 138.79, 136.35, 134.66, 127.96, 127.48, 121.54, 121.22, 116.24, 64.55, 43.77, 41.51, 29.79, 28.55, 25.77, 25.67, 24.84, 20.99.

HRMS calcd for C₂₁H₂₇N₂O₃ (M+ H⁺): 357.2173, Found: 357.2169.
III. General Experimental Procedures, Spectral Data

Experimental Procedures for Examples Described in Table 1.

\[
\begin{array}{cccccc}
\text{Entry} & \text{Catalyst} & \text{Base} & \text{Additive} & \text{Solvent} & \text{Yield} \\
1 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & - & \text{DMSO} & 21 \\
2 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & \text{Ag}_2\text{O} & \text{DMSO} & 20 \\
3 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & \text{Ag}_2\text{CO}_3 & \text{DMSO} & 16 \\
4 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & \text{AgOAc} & \text{DMSO} & 41 \\
5 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & \text{Ac}_2\text{O} & \text{DMSO} & 24 \\
6 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & (\text{BOC})_2\text{O} & \text{DMSO} & 22 \\
7 & \text{Cu(OAc)}_2 & \text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 38 \\
8 & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 45 \\
9 & \text{Cu(OAc)}_2 & \text{Cs}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 40 \\
10 & \text{Cu(OAc)}_2 & \text{Li}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 36 \\
11 & \text{Cu(OAc)}_2 & \text{NaOAc} & \text{TMSOAc} & \text{DMSO} & 8 \\
12 & \text{Cu(OAc)}_2 & \text{KOAc} & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
13 & \text{Cu(OAc)}_2 & \text{Na}_2\text{PO}_4 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
14 & \text{Cu(OAc)}_2 & \text{K}_2\text{PO}_4 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
15 & \text{Cu(OAc)}_2 & \text{Na}_3\text{HPO}_4 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
16 & \text{Cu(OAc)}_2 & \text{K}_2\text{HPO}_4 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
17 & \text{Cu(OAc)}_2 & \text{PhCOOK} & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
18 & \text{Cu(OAc)}_2 & \text{PhCOONa} & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
19^\text{[c]} & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 48 \\
20^\text{[c]} & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 56 \\
21^\text{[c]} & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMF} & 32 \\
22^\text{[c]} & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{NMP} & 19 \\
23^\text{[c]} & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 72(70^\text{[b]}) \\
24^\text{[c]} & \text{Cu(OTf)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
25^\text{[c]} & \text{CuCl}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
26^\text{[c]} & \text{CuBr}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
27^\text{[c]} & \text{Pd(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
28^\text{[c]} & \text{Cu(OAc)}_2 & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & 54 \\
29^\text{[c]} & - & \text{K}_2\text{CO}_3\cdot\text{Na}_2\text{CO}_3 & \text{TMSOAc} & \text{DMSO} & \text{trace} \\
\end{array}
\]

[a] Reaction conditions: 1a (0.1 mmol), Cu catalyst (0.1 mmol), base (0.3 mmol), additive (0.4 mmol) in 1 mL solvent for at 150°C 16h under O2. Yields (average of two runs) were determined by GC with triphenylmethane as the internal standard. [b] Isolated yields. [c]
The reaction was conducted with K$_2$CO$_3$ (0.2 mmol) and Na$_2$CO$_3$ (0.1 mmol). [d] Cu(OAc)$_2$ (0.2 mmol) was added. [e] 4A-MS (30 mg) was added. [f] Pd(OAc)$_2$ (10% mmol) was added. (BOC)$_2$O = di-tert-butyl dicanonate, TMSOAc = trimethylsilyl acetate.

To a 15 mL Schlenk tube Cu catalyst (0.20 mmol), Base (0.3 mmol), 1a (0.10 mmol), 4A-MS (30 mg) and a stir bar were added. The vessel was then evacuated and filled with O$_2$ (three cycles). Additive (0.40 mmol, if additive is a solid, it was added along with the Cu catalyst) and solvent (1.0 mL) were added in turn under O$_2$. The reaction mixture was stirred at the mentioned temperature for the indicated amount of time. After that, the reaction mixture was diluted with EtOAc, filtered through silica gel with copious washings (EtOAc). Triphenylmethane (24.4 mg, 0.10 mmol) was added and the product yield was determined by GC analysis.

**General Procedures for Examples Described in Table 2.**

To a 15 mL Schlenk tube Cu(OAc)$_2$ (36.2 mg, 0.20 mmol), K$_2$CO$_3$ (27.6 mg, 0.20 mmol), Na$_2$CO$_3$ (10.6 mg, 0.1 mmol), propionamide (0.10 mmol), 4A-MS (30 mg) and a stir bar were added. The vessel was then evacuated and filled with O$_2$ (three cycles). TMSOAc (0.40 mmol) and DMSO (1.0 mL) were added in turn under O$_2$. The reaction mixture was stirred at 150°C for 16h. After that, the reaction mixture was diluted with EtOAc, filtered through silica gel with copious washings (EtOAc), concentrated, and purified by column chromatography (EtOAc/hexane = 1/100 to 1/50, v/v).

**2-ethyl-N-(quinolin-8-yl)butanamide (2a)**

Following the general procedure, colourless liquid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.86 (s, 1H), 8.89 – 8.78 (m, 2H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.56 – 7.41 (m, 3H), 2.39 – 2.26 (m, 1H), 1.88 – 1.75 (m, 2H), 1.72 – 1.58 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.77, 148.14, 138.43, 136.35, 134.53, 127.95, 127.45, 121.54, 121.32, 116.47, 52.64, 25.87, 12.12.

HRMS calcld for C$_{15}$H$_{18}$N$_2$O (M+H$^+$): 243.1492, Found: 243.1491.

**2-methyl-N-(quinolin-8-yl)butanamide (2b)**

Following the general procedure, yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.88 (s, 1H), 8.84 – 8.79 (m, 2H), 8.16 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.58 – 7.40 (m, 3H), 2.61 – 2.49 (m, 1H), 1.94 – 1.80 (m, 1H), 1.67-1.57 (m, 1H), 1.33 (d, $J = 6.9$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.40, 148.10, 138.41, 136.43, 134.58, 127.96, 127.48, 121.55, 121.32, 116.50, 44.57, 27.50, 17.57, 11.95.

HRMS calcld for C$_{14}$H$_{16}$N$_2$O (M+H$^+$): 229.1335, Found: 229.1333.
Supporting Information

N-(quinolin-8-yl)isobutyramide (2c)
Following the general procedure, yellow liquid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.91 (s, 1H), 8.83 – 8.78 (m, 2H), 8.16 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.58 – 7.42 (m, 3H), 2.78 (hept, $J$ = 6.9 Hz, 1H), 1.36 (d, $J$ = 6.9 Hz, 6H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.79, 148.13, 138.48, 136.41, 127.96, 127.48, 121.57, 121.32, 116.44, 37.16, 19.75.
HRMS calcd for C$_{13}$H$_{14}$N$_2$O (M+H$^+$): 215.1179, Found: 215.1178.

2-methyl-4-phenyl-N-(quinolin-8-yl)butanamide (2d)
Following the general procedure, yellow liquid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.88 (s, 1H), 8.88 – 8.77 (m, 2H), 8.17 (dd, $J$ = 8.2, 1.4 Hz, 1H), 7.57-7.45 (m, 3H), 7.30 – 7.17 (m, 5H), 2.83 – 2.56 (m, 3H), 2.24-2.19 (m, 1H), 1.90-1.83 (m, 1H), 1.36 (d, $J$ = 8.0 Hz, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.04, 148.11, 141.75, 138.42, 136.43, 134.51, 128.51, 128.40, 127.96, 127.48, 125.88, 121.59, 121.44, 116.58, 42.27, 36.04, 33.63, 18.25.
HRMS calcd for C$_{20}$H$_{20}$N$_2$O (M+H$^+$): 305.1648, Found: 305.1646.

2-ethyl-4-phenyl-N-(quinolin-8-yl)butanamide (2e)
Following the general procedure, yellow liquid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.89 (s, 1H), 8.91 – 8.78 (m, 2H), 8.18 (d, $J$ = 8.2 Hz, 1H), 7.58-7.45 (m, 3H), 7.31 – 7.14 (m, 5H), 2.82 – 2.72 (m, 1H), 2.69-2.62 (m, 1H), 2.47-2.40 (m, 1H), 2.24 – 2.11 (m, 1H), 1.91-1.84 (m, 2H), 1.71 – 1.61 (m, 1H), 1.00 (t, $J$ = 7.4 Hz, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.48, 148.06, 141.84, 138.80, 138.30, 136.52, 134.38, 128.52, 128.38, 127.99, 127.51, 125.84, 121.58, 121.48, 116.68, 50.12, 34.46, 33.76, 26.41, 12.01.
HRMS calcd for C$_{21}$H$_{22}$N$_2$O (M+H$^+$): 319.1805, Found: 319.1804.

2-ethyl-N-(quinolin-8-yl)-4-(p-tolyl)butanamide (2f)
Following the general procedure, yellow liquid.
Supporting Information

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.87 (s, 1H), 8.90 – 8.77 (m, 2H), 8.19 (d, $J = 8.2$ Hz, 1H), 7.62 – 7.41 (m, 3H), 7.09 (q, $J = 8.1$ Hz, 4H), 2.78 – 2.56 (m, 2H), 2.46-2.39 (m, 1H), 2.30 (s, 3H), 2.21 – 2.10 (m, 1H), 1.92 – 1.77 (m, 2H), 1.70-1.60 (m, 1H), 0.99 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.55, 148.04, 138.73, 138.30, 136.52, 135.27, 134.40, 129.05, 128.40, 127.99, 127.51, 121.56, 121.45, 116.70, 50.11, 34.57, 33.31, 26.42, 21.00, 12.00.


![Structure of 2-ethyl-4-(4-methoxyphenyl)-N-(quinolin-8-yl)butanamide (2g)](image)

Following the general procedure, yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.86 (s, 1H), 8.90 – 8.76 (m, 2H), 8.18 (dd, $J = 8.2$, 1.4 Hz, 1H), 7.60 – 7.43 (m, 3H), 7.13 (d, $J = 8.5$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 3.77 (s, 3H), 2.77 – 2.66 (m, 1H), 2.65 – 2.54 (m, 1H), 2.43-2.31 (m, 1H), 2.20 – 2.08 (m, 1H), 1.92 – 1.78 (m, 2H), 1.68-1.60 (m, 1H), 0.99 (t, $J = 7.4$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -117.73.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.34, 157.77, 148.11, 138.39, 136.42, 134.43, 133.87, 129.41, 127.97, 127.48, 121.59, 121.44, 116.58, 113.77, 55.23, 50.08, 34.68, 32.84, 26.43, 12.03.

HRMS calcd for C$_{22}$H$_{24}$N$_2$O$_2$ (M+H$^+$): 349.1911, Found: 349.1909.

![Structure of 2-ethyl-4-(4-fluorophenyl)-N-(quinolin-8-yl)butanamide (2h)](image)

Following the general procedure, yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.85 (s, 1H), 8.89 – 8.77 (m, 2H), 8.19 (d, $J = 7.2$ Hz, 1H), 7.60 – 7.43 (m, 3H), 7.20-7.11 (m, 2H), 6.94 (t, $J = 8.7$ Hz, 2H), 2.78 – 2.57 (m, 2H), 2.40 (ddd, $J = 13.9$, 9.4, 4.9 Hz, 1H), 2.22 – 2.09 (m, 1H), 1.92 – 1.79 (m, 2H), 1.71 – 1.63 (m, 1H), 1.00 (t, $J = 7.4$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -117.73.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.34, 161.33(d, $J = 242$ Hz), 148.13, 138.35, 137.39(d, $J = 4$ Hz), 136.49, 134.35, 129.83(d, $J = 8$ Hz), 128.00, 127.50, 121.62, 121.53, 116.64, 115.10 (d, $J = 21$ Hz), 50.05, 34.52, 32.95, 26.45, 12.02.

HRMS calcd for C$_{21}$H$_{21}$N$_2$O$_2$ (M+H$^+$): 337.1711, Found: 337.1710.

![Structure of 2-ethyl-N-(quinolin-8-yl)-4-(4-(trifluoromethyl)phenyl)butanamide (2i)](image)

Following the general procedure, yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.88 (s, 1H), 8.92 – 8.77 (m, 2H), 8.20 (d, $J = 7.8$ Hz, 1H), 7.63 – 7.43 (m, 5H), 7.32 (d, $J = 7.9$ Hz, 2H), 2.88 – 2.65 (m, 2H), 2.50 – 2.37 (m, 1H), 2.26 – 2.11 (m, 1H), 1.95 – 1.80 (m, 2H), 1.70 – 1.59 (m, 1H), 1.01 (t, $J = 7.4$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.26.
Supporting Information

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.09, 148.22, 145.92, 138.42, 136.42, 134.31, 128.84, 128.24 (q, $J = 32$ Hz), 127.99, 127.45, 125.31 (q, $J = 4.0$ Hz), 124.36 (q, $J = 270$ Hz), 121.68, 121.61, 116.58, 50.07, 34.03, 33.63, 26.52, 12.00.

HRMS calcd for C$_{22}$H$_{21}$N$_2$F$_3$O (M+H$^+$): 387.1679, Found: 387.1680.

4-(3-chlorophenyl)-2-methyl-N-(quinolin-8-yl)butanamide (2j)

Following the general procedure, yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.90 (s, 1H), 8.87-8.812 (m, 2H), 8.19 (dd, $J = 8.3$, 1.5 Hz, 1H), 7.60 – 7.43 (m, 3H), 7.24-7.08 (m, 4H), 2.80 – 2.58 (m, 3H), 2.24-2.15 (m, 1H), 1.89-1.80 (m, 1H), 1.36 (d, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.78, 148.11, 143.79, 138.31, 136.58, 134.36, 134.13, 129.64, 128.63, 127.98, 127.50, 126.71, 126.10, 121.62, 121.55, 116.71, 42.16, 35.78, 33.31, 18.31.

HRMS calcd for C$_{20}$H$_{19}$ClN$_2$O (M+H$^+$): 339.1259, Found: 339.1257.

2-ethyl-4-(naphthalen-1-yl)-N-(quinolin-8-yl)butanamide (2k)

Following the general procedure, orange liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.94 (s, 1H), 8.91 (dd, $J = 7.5$, 1.5 Hz, 1H), 8.82 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.17 (dd, $J = 8.3$, 1.7 Hz, 1H), 8.09 – 8.03 (m, 1H), 7.85 – 7.79 (m, 1H), 7.69 (p, $J = 3.1$ Hz, 1H), 7.61 – 7.33 (m, 7H), 3.30-3.23 (m, 1H), 3.12-3.05 (m, 1H), 2.58 – 2.47 (m, 1H), 2.36-2.27 (m, 1H), 2.05-1.96 (m, 1H), 1.92 – 1.81 (m, 1H), 1.70 – 1.63 (m, 1H), 1.01 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.41, 148.16, 143.79, 138.42, 138.00, 136.41, 134.44, 133.88, 131.80, 128.68, 127.98, 127.48, 126.69, 126.16, 125.83, 125.53, 125.43, 123.88, 121.59, 116.63, 50.64, 33.75, 31.11, 26.55, 12.04.


2-ethyl-N-(quinolin-8-yl)oct-7-enamide (2l)

Following the general procedure, yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.85 (s, 1H), 8.87 – 8.79 (m, 2H), 8.16 (dd, $J = 8.3$, 1.6 Hz, 1H), 7.57 – 7.43 (m, 3H), 5.77 (ddt, $J = 16.9$, 10.2, 6.7 Hz, 1H), 5.02 – 4.82 (m, 2H), 2.45 – 2.34 (m, 1H), 1.86-1.76 (m, 2H), 1.88 – 1.75 (m, 2H), 1.69 – 1.60 (m, 2H), 1.47 – 1.37 (m, 4H), 1.00 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.85, 148.15, 138.90, 138.44, 136.44, 134.51, 127.96, 127.48, 121.57, 121.35, 116.50, 114.33, 50.97, 33.61, 32.72, 29.02, 27.14, 26.27, 12.13.

Following the general procedure, yellow liquid.

\[ \text{HNMR (400 MHz, CDCl}_3\text{)} \delta 9.85 \text{ (s, 1H), 8.89 – 8.77 (m, 2H), 8.16 (dd, } J = 8.3, 1.6 \text{ Hz, 1H), 7.57 – 7.43 (m, 3H), 5.56 – 5.33 (m, 2H), 2.46-2.38 (m, 1H), 2.14-1.79 (m, 6H), 1.67-1.61 (m, 2H), 1.00 (t, } J = 7.4 \text{ Hz, 2H), 0.94 (t, } J = 7.5 \text{ Hz, 3H).} \]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 174.76, 148.12, 138.43, 136.36, 134.51, 133.08, 128.27, 127.96, 127.48, 121.56, 121.35, 116.49, 50.12, 32.64, 30.56, 26.29, 25.57, 13.88, 12.11. \]

HRMS calcd for C\textsubscript{19}H\textsubscript{24}N\textsubscript{2}O (M+H\textsuperscript{+}): 297.1961, Found: 297.1960.

Following the general procedure, orange liquid.

\[ \text{HNMR (400 MHz, CDCl}_3\text{)} \delta 9.80 \text{ (s, 1H), 8.78 – 8.70 (m, 2H), 8.09 (dd, } J = 8.3, 1.7 \text{ Hz, 1H), 7.50 – 7.35 (m, 3H), 5.73 (ddt, } J = 16.9, 10.2, 6.7 \text{ Hz, 1H), 4.97 – 4.84 (m, 2H), 2.54 (dt, } J = 13.7, 6.9 \text{ Hz, 1H), 2.07 – 1.99 (m, 2H), 1.85 – 1.74 (m, 1H), 1.55 – 1.42 (m, 3H), 1.26 (d, } J = 6.9 \text{ Hz, 3H).} \]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 175.30, 148.10, 138.43, 136.36, 134.55, 127.94, 127.45, 121.54, 121.33, 116.48, 114.67, 42.89, 33.94, 33.75, 26.73, 18.00. \]

HRMS calcd for C\textsubscript{17}H\textsubscript{20}N\textsubscript{2}O (M+H\textsuperscript{+}): 269.1648, Found: 269.1646.

Following the general procedure, yellow liquid.

\[ \text{HNMR (400 MHz, CDCl}_3\text{)} \delta 9.76 \text{ (s, 1H), 8.86 – 8.73 (m, 2H), 8.15 (dd, } J = 8.3, 1.6 \text{ Hz, 1H), 7.59 – 7.41 (m, 3H), 3.46 – 3.34 (m, 1H), 2.57 – 2.42 (m, 2H), 2.37–2.29 (m, 2H), 2.11 – 1.94 (m, 2H).} \]

\[ \text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 173.78, 148.10, 138.43, 136.40, 134.58, 127.96, 127.48, 121.56, 121.30, 116.41, 41.40, 25.51, 18.18. \]

HRMS calcd for C\textsubscript{14}H\textsubscript{14}N\textsubscript{2}O (M+H\textsuperscript{+}): 227.1179, Found: 227.1178.

Following the general procedure, yellow liquid.

\[ \text{HNMR (400 MHz, CDCl}_3\text{)} \delta 9.88 \text{ (s, 1H), 8.84 – 8.74 (m, 2H), 8.16 (dd, } J = 8.2, 1.3 \text{ Hz, 1H), 7.57 – 7.40 (m, 3H), 3.02 – 2.88 (m, 1H), 2.11-1.94 (m, 4H), 1.88 – 1.79 (m, 2H), 1.72-1.64 (m, 2H).} \]
N-(quinolin-8-yl)cyclohexanecarboxamide (2q)
Following the general procedure, yellow liquid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.90 (s, 1H), 8.85 – 8.75 (m, 2H), 8.16 (dd, $J = 8.3$, 1.6 Hz, 1H), 7.61 – 7.39 (m, 3H), 2.53-2.45 (m, 1H), 2.15 – 2.02 (m, 2H), 1.94 – 1.83 (m, 2H), 1.75 – 1.61 (m, 3H), 1.48 – 1.20 (m, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.93, 148.07, 138.45, 136.44, 134.63, 127.96, 127.49, 121.54, 121.26, 116.48, 46.91, 29.77, 25.79, 25.76.
HRMS calcd for C$_{16}$H$_{18}$N$_2$O (M+H$^+$): 255.1492, Found: 255.1495.

N-(5-methoxyquinolin-8-yl)-2-methylbutanamide (2r)
Following the general procedure, yellow liquid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.62 (s, 1H), 8.82 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.73 (d, $J = 8.5$ Hz, 1H), 8.57 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.44 (dd, $J = 8.4$, 4.2 Hz, 1H), 6.84 (d, $J = 8.6$ Hz, 1H), 3.99 (s, 3H), 2.57 – 2.45 (m, 1H), 1.94 – 1.80 (m, 1H), 1.67 – 1.55 (m, 1H), 1.32 (d, $J = 6.9$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.92, 150.13, 148.58, 139.17, 131.27, 128.08, 120.65, 120.46, 116.58, 104.43, 55.78, 44.50, 27.55, 17.61, 11.98.
HRMS calcd for C$_{16}$H$_{18}$N$_2$O$_2$ (M+H$^+$): 259.1441, Found: 259.1439.

2,3-dimethyl-N-(quinolin-8-yl)butanamide (2s)
Following the general procedure, yellow liquid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.85 (s, 1H), 8.85 – 8.77 (m, 2H), 8.16 (dd, $J = 8.3$, 1.6 Hz, 1H), 7.58 – 7.41 (m, 3H), 2.40 – 2.27 (m, 1H), 2.09-2.01 (m, 1H), 1.31 (d, $J = 6.9$ Hz, 3H), 1.05-1.02 (m, 6H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.23, 148.14, 138.46, 136.40, 134.57, 127.96, 127.49, 121.56, 121.31, 116.45, 49.95, 31.75, 21.18, 19.62, 14.99.
HRMS calcd for C$_{16}$H$_{18}$N$_2$O (M+H$^+$): 243.1492, Found: 243.1490.

2-cyclohexyl-N-(quinolin-8-yl)propanamide (2t)
Supporting Information

Following the general procedure, yellow liquid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.84 (s, 1H), 8.87 – 8.77 (m, 2H), 8.16 (dd, \(J = 8.2, 1.0\) Hz, 1H), 7.59 – 7.41 (m, 3H), 2.41 – 2.31 (m, 1H), 1.96-1.88 (m, 1H), 1.84 – 1.74 (m, 2H), 1.71-1.64 (m, 3H), 1.34 – 1.24 (m, 6H), 1.13 – 0.97 (m, 2H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 175.33, 148.12, 138.42, 136.43, 134.53, 127.97, 127.50, 121.56, 121.32, 116.47, 49.17, 41.31, 31.52, 30.02, 26.40, 26.34, 26.29, 15.03.

HRMS calcd for C\(_{18}\)H\(_{22}\)N\(_2\)O (M+H\(^+\)): 283.1805, Found: 283.1804.

\(2u\) and \(2u'\) were isolated as an inseparable yellow oil (42%). The yields were determined by \(^1\)H NMR analysis in comparison with literature reports (\(2u^{[1]} : 2u'^{[4]} = 1 : 0.7\)). \(2u\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.82 (s, 1H), 8.85 – 8.79 (m, 2H), 8.17 (d, \(J = 8.2\) Hz, 1H), 7.57 – 7.43 (m, 3H), 2.42 (q, \(J = 7.0\) Hz, 1H), 1.29 (d, \(J = 7.0\) Hz, 3H), 1.09 (s, 9H).

\(2u'\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.84 – 8.81 (m, 1H), 8.53 – 8.47 (m, 1H), 8.10 (dd, \(J = 8.3, 1.8\) Hz, 1H), 7.56 – 7.42 (m, 2H), 7.40-7.35 (m, 1H), 4.50 (d, \(J = 8.0\) Hz, 1H), 4.11 (d, \(J = 8.0\) Hz, 1H), 1.46 (s, 3H), 1.10 (s, 9H).

General procedure for examples described in scheme 2
General procedure for example described in **scheme 2a**: To a 15 mL Schlenk tube Cu(OAc)$_2$ (36.2 mg, 0.20 mmol), K$_2$CO$_3$ (27.6 mg, 0.2 mmol), Na$_2$CO$_3$ (10.6 mg, 0.1 mmol), propionamide 6 (0.10 mmol), 4A-MS (30 mg) and a stir bar were added. The vessel was then evacuated and filled with O$_2$ (three cycles). TMSOAc (0.40 mmol) and DMSO (1.0 mL) were added in turn under O$_2$. The reaction mixture was stirred at 150°C for 16h. After that, the reaction mixture was diluted with EtOAc, filtered through silica gel with copious washings (EtOAc), concentrated, and purified by column chromatography (EtOAc/hexane = 1/100 to 1/50, v/v ) to give 2a in 62% yield.

General procedure for example described in **scheme 2b**: To a 15 mL Schlenk tube Cu(OAc)$_2$ (36.2 mg, 0.20 mmol), K$_2$CO$_3$ (27.6 mg, 0.2 mmol), Na$_2$CO$_3$ (10.6 mg, 0.1 mmol), propionamide 7 (0.10 mmol), 4A-MS (30 mg) and a stir bar were added. The vessel was then evacuated and filled with O$_2$ (three cycles). TMSOAc (0.40 mmol) and DMSO (1.0 mL) were added in turn under O$_2$. The reaction mixture was stirred at 150°C for 16h. After that, the reaction mixture was diluted with EtOAc, filtered through silica gel with copious washings (EtOAc), concentrated, and purified by column chromatography (EtOAc/hexane = 1/100 to 1/50, v/v ).

**7-methyl-8-oxo-8-(quinolin-8-ylamino)octyl acetate (7a)**
Following the general procedure, orange liquid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.87 (s, 1H), 8.85 – 8.78 (m, 2H), 8.17 (dd, $J = 8.3$, 1.5 Hz, 1H), 7.60 – 7.42 (m, 3H), 4.02 (t, $J = 6.7$ Hz, 2H), 2.67 – 2.54 (m, 1H), 2.02 (s, 3H), 1.90 – 1.80 (m, 1H), 1.65 – 1.53 (m, 3H), 1.42 – 1.30 (m, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.36, 171.20, 148.08, 138.39, 136.42, 134.53, 127.94, 127.46, 121.54, 121.33, 116.50, 64.53, 42.98, 34.38, 29.27, 28.52, 27.33, 25.77, 20.97, 18.04.

HRMS calcd for C$_{20}$H$_{26}$N$_2$O$_3$ (M+H$^+$): 343.2016, found: 343.2014.

**2-methyl-2-(quinolin-8-ylcarbamoyl)octane-1,8-diyl diacetate (8)**
Following the general procedure, yellow liquid.
1H NMR (400 MHz, CDCl₃) δ 10.44 (s, 1H), 8.84 – 8.77 (m, 2H), 8.17 (dd, J = 8.3, 1.7 Hz, 1H), 7.58 – 7.44 (m, 3H), 4.37 (d, J = 11.1 Hz, 1H), 4.21 (d, J = 11.1 Hz, 1H), 4.00 (t, J = 6.7 Hz, 2H), 2.15 (s, 3H), 2.01 (s, 3H), 1.70 – 1.51 (m, 3H), 1.44 (s, 3H), 1.42 – 1.29 (m, 6H).

13C NMR (101 MHz, CDCl₃) δ 173.51, 171.17, 170.82, 148.18, 138.77, 136.41, 134.55, 128.00, 127.47, 121.61, 121.54, 116.56, 69.45, 64.46, 47.08, 36.69, 29.72, 25.71, 24.05, 20.98, 20.93, 19.85.


General procedure for examples described in scheme 4

General procedure for examples described in scheme 4: To a 15 mL Schlenk tube Cu(OAc)₂ (36.2 mg, 0.20 mmol), K₂CO₃ (27.6 mg, 0.2 mmol), Na₂CO₃ (10.6 mg, 0.1 mmol), propionamide 9 (0.10 mmol), 4A-MS (30 mg) and a stir bar were added. The vessel was then evacuated and filled with O₂ (three cycles). TMSOAc (0.40 mmol) and DMSO (1.0 mL) were added in turn under O₂. The reaction mixture was stirred at 150°C for 16h. After that, the reaction mixture was diluted with EtOAc, filtered through silica gel with copious washings (EtOAc), concentrated, and purified by column chromatography (EtOAc/hexane = 1/100 to 1/50, v/v ) to give 10 in 52% yield.

General procedure for removal of 8-aminoquinoline [6]: Propionamide 10 (0.3 mmol) and NaOH (1.8 mmol) were heated in 2 mL EtOH for 12h at 100°C. Then the reaction mixture was diluted with water and extracted with ether (20 mL). The aqueous layer was acidified with 3.0 M HCl until pH~2 and extracted with ether (20 mL x 3). The orgaic phases was combined, dried over Na₂SO₄ and evapored to afford the alkyl carboxylic acid 11.

5-(2,5-dimethylphenoxy)-2-methyl-N-(quinolin-8-yl)pentanamide (10)

Compound 10, colourless liquid.
1H NMR (400 MHz, CDCl₃) δ 9.94 (s, 1H), 8.86 – 8.75 (m, 2H), 8.17 (dd, J = 8.3, 1.5 Hz, 1H), 7.58 – 7.42 (m, 3H), 6.98 (d, J = 7.4 Hz, 1H), 6.69 – 6.56 (m, 2H), 4.06 – 3.89 (m, 2H), 2.80-2.75 (m, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 2.10 – 1.99 (m, 1H), 1.98 – 1.87 (m, 2H), 1.86 – 1.75 (m, 1H), 1.38 (d, J = 6.9 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 175.13, 156.95, 148.05, 138.34, 136.53, 136.45, 134.49, 130.28, 127.98, 127.50, 123.64, 121.56, 121.44, 120.70, 116.66, 112.01, 67.58, 42.64, 31.05, 27.30, 21.38, 19.85.

HRMS calcd for C₂₃H₂₆N₂O₂ (M+H⁺): 363.2067, found: 363.2062.
Supporting Information

5-(2,5-dimethylphenoxy)-2-methylpentanoic acid (11)

Compound 11, yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.00 (d, $J$ = 7.3 Hz, 1H), 6.66 (d, $J$ = 7.5 Hz, 1H), 6.62 (s, 1H), 3.96 (dt, $J$ = 5.8, 3.8 Hz, 2H), 2.64 – 2.51 (m, 1H), 2.31 (s, 3H), 2.17 (s, 3H), 1.93 – 1.80 (m, 3H), 1.74 – 1.63 (m, 1H), 1.24 (d, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 181.88, 156.90, 136.48, 130.32, 123.62, 120.75, 111.94, 67.37, 38.93, 30.15, 27.03, 21.40, 16.98, 15.78.

IV. References

[1] X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, Nat. Chem. 2015, 6, 1-10.


V. NMR Spectra
Supporting Information