Supplementary Information

Synthesis of 3-(Aminomethyl)pyridine by Traceless C3-Selective Umpolung of 1-Amidopyridin-1-ium Salts

Pingsheng Tang\textsuperscript{a,b}, Dehai Xiao,*\textsuperscript{a} Bo Wang*\textsuperscript{a}

\textsuperscript{a}Key Lab of Synthetic Polymer of the Chinese Academy of Sciences, Green Chemistry and Process Laboratory, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, P. R. China.

\textsuperscript{b}University of Chinese Academy of Sciences, Beijing 100049, P. R. China.

*E-mail: wangbo@ciac.ac.cn; dhxiao@ciac.ac.cn

Contents

General information 2
Synthesis and characterization data 2-9
References 9
\textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra of products 10-37
HPLC-HRMS spectrum of reaction mixture (experiment entry 8, Table 2 in main text) 38-39
References on the total synthesis of huperzine A 40
General information

Unless otherwise mentioned, all reactions were carried out under anhydrous conditions, and all commercially available reagents were used as received. 1-amidopyridin-1-ium salts\(^1\) and aminals\(^2\) were synthesized according to literature reports. Anhydrous solvents were obtained from a Pure Solvent purification system from Innovative Technology. Reactions were monitored by thin layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60 F\(_{254}\)) and visualized by UV fluorescence (254 nm) and one of the following: phosphomolybdic acid, ninhydrin, \(p\)-anisaldehyde. Column chromatography was performed over Silicycle P\(_{60}\) silica gel (230–400 mesh). NMR spectra were recorded on Bruker AVANCE III 300, AVANCE III 400 and AVANCE III HD500 instruments using residual CHCl\(_3\) as internal references (\(\delta_H = 7.26 \text{ ppm and } \delta_C = 77.16 \text{ ppm}\)). The following abbreviations were used to designate multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), m (multiplet), br (broad). High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF-QII mass spectrometer using electrospray ionization. Melting points were recorded on a WRS-1B melt point apparatus (Shanghai Shenguang Instrument Co., LTD) and were uncorrected.

Synthesis and characterization data

General procedure for reaction conditions optimization

\[
\begin{align*}
\text{1a to 1f} & \quad + \quad \text{2a} \\
\begin{array}{c}
\text{1a to 1f} \\
\text{2a}
\end{array} & \quad \xrightarrow{1. \text{ Solvent}} \quad \text{3a}
\end{align*}
\]

To a solution of 1-amidopyridin-1-ium iodide 1a to 1f (0.2 mmol) in designated solvent (1.0 mL) was added designated amount of aminal 2a, and the mixture was stirred at designated temperature and monitored by TLC till 1a to 1f disappeared. The mixture was cooled to room temperature, and zinc powder (130.8 mg, 2.0 mmol) and glacial acetic acid (1.0 mL) were added and stirred for 5 min. The reaction was quenched with saturated NaHCO\(_3\) solution and extracted with CH\(_2\)Cl\(_2\). The combined organic extracts was washed with brine, dried over anhydrous MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash chromatography using CH\(_2\)Cl\(_2\)/MeOH to give product 3a.

General procedure for synthesis of pyridine 3b to 3w

\[
\begin{align*}
\text{1f} & \quad + \quad \text{2b to 2w} \\
\begin{array}{c}
\text{1f} \\
\text{2b to 2w}
\end{array} & \quad \xrightarrow{1. \text{ CH}_3\text{CN}} \quad \text{3b to 3w}
\end{align*}
\]
To a solution of 1-amido(pyridin-1-ium) iodide 1f (76.8 mg, 0.2 mmol) in CH$_3$CN (1.0 mL) was added aminal 2b to 2w (0.44 mmol), and the mixture was stirred in a 90 ºC oil bath, and monitored by TLC till 1f disappeared. The mixture was cooled to room temperature, and zinc powder (130.8 mg, 2.0 mmol) and glacial acetic acid (1.0 mL) were added and stirred for 5 min. The reaction was quenched with saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The combined organic extracts was washed with brine, dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using CH$_2$Cl$_2$/MeOH to give products 3b to 3w.

4-(phenyl(pyridine-3-yl)methyl)morpholine (3a): 45.6 mg (90% yield), white solid, m.p. 102 – 104 ºC. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.64 (d, $J = 2.2$ Hz, 1H), 8.41 (dd, $J = 4.8$, 1.7 Hz, 1H), 7.72 (ddd, $J = 7.9$, 2.0 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.32 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 4.23 (s, 1H), 3.68 (t, $J = 4.7$ Hz, 4H), 2.36 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 149.8, 148.8, 141.3, 137.9, 135.5, 128.9, 128.0, 127.6, 123.7, 74.3, 67.2, 52.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{19}$N$_2$O 255.1492; Found 255.1500.

4-((4-methoxyphenyl)(pyridine-3-yl)methyl)morpholine (3b): 43.7 mg (77% yield), white solid, m.p. 109 – 110 ºC. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.64 (s, 1H), 8.42 (d, $J = 3.9$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.28 (d, $J = 8.7$ Hz, 2H), 7.20 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 2H), 4.20 (s, 1H), 3.74 (s, 3H), 3.69 (t, $J = 4.6$ Hz, 4H), 2.45 – 2.28 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.0, 149.5, 148.5, 138.3, 135.4, 133.2, 129.1, 123.7, 114.2, 73.5, 67.1, 55.3, 52.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{21}$N$_2$O$_2$ 285.1598; Found 285.1604.

4-(pyridin-3-yl(p-tolyl)methyl)morpholine (3c): 46.8 mg (87% yield), white solid, m.p. 106 – 108 ºC. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.66 (d, $J = 1.5$ Hz, 1H), 8.42 (dd, $J = 4.7$, 1.3 Hz, 1H), 7.74 (ddd, $J = 7.8$, 1.8 Hz, 1H), 7.27 (d, $J = 7.9$ Hz, 2H), 7.19 (dd, $J = 7.9$, 4.8 Hz, 1H), 7.09 (d, $J = 7.9$ Hz, 2H), 4.22 (s, 1H), 3.70 (t, $J = 4.7$ Hz, 4H), 2.36 (m, 4H), 2.28 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.6, 148.6, 138.1, 137.3, 135.4, 129.6, 127.9, 123.7, 74.0, 67.1, 55.3, 52.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{21}$N$_2$O 269.1648; Found 269.1653.

4-((2-fluorophenyl)(pyridin-3-yl)methyl)morpholine (3d): 49.6 mg (91% yield), white solid, m.p. 113 – 114 ºC. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.67 (d, $J = 1.2$ Hz, 1H), 8.44 (dd, $J = 4.7$, 1.4 Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.57 (ddd, $J = 7.4$, 1.9 Hz, 1H), 7.24 – 7.06 (m, 3H), 6.97 (ddd, $J = 9.5$, 8.0, 1.3 Hz, 1H), 4.71 (s, 1H), 3.70 (t, $J = 4.7$ Hz, 4H), 2.41 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.7 (d, $^3$J(C-F) = 246.4 Hz), 149.9, 148.7, 136.8, 135.8, 128.9 (d, $^3$J(C-F) = 8.4 Hz), 128.7 (d, $^3$J(C-F) = 3.8 Hz), 128.0 (d, $^3$J(C-F) = 12.5 Hz), 124.6 (d, $^3$J(C-F) = 3.5 Hz), 123.7, 115.8 (d, $^3$J(C-F) = 22.4 Hz), 67.1, 65.1 (d, $^3$J(C-F) = 2.1 Hz), 52.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{18}$FN$_2$O 273.1398; Found 273.1406.
4-((4-chlorophenyl)(pyridin-3-yl)methyl)morpholine (3e): 46.1 mg (80% yield), white solid, m.p. 118 – 120 °C. \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.62 (d, \(J = 1.6\) Hz, 1H), 8.44 (dd, \(J = 4.7, 1.4\) Hz, 1H), 7.69 (dd, \(J = 7.9, 1.8\) Hz, 1H), 7.33 (d, \(J = 8.5\) Hz, 2H), 7.25 (d, \(J = 8.5\) Hz, 2H), 7.20 (dd, \(J = 7.9, 4.9\) Hz, 1H), 4.23 (s, 1 H), 3.69 (t, \(J = 4.6\) Hz, 4H), 2.36 (m, \(J = 7.3\) Hz, 4H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 149.5, 148.9, 139.7, 137.3, 135.5, 133.3, 129.3, 129.1, 123.8, 73.5, 67.0, 52.5. \textbf{HRMS} (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\textsubscript{16}H\textsubscript{18}ClN\textsubscript{2}O 289.1102; Found 289.1109.

4-((3-bromophenyl)(pyridin-3-yl)methyl)morpholine (3f): 57.5 mg (86% yield), white solid, m.p. 127 – 128 °C. \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.62 (d, \(J = 1.7\) Hz, 1H), 8.45 (dd, \(J = 4.7, 1.4\) Hz, 1H), 7.70 (ddd, \(J = 7.9, 1.7\) Hz, 1H), 7.55 (dd, 1H), 7.34 (d, \(J = 1.4\) Hz, 1H), 7.31 (d, \(J = 1.6\) Hz, 1H), 7.21 (dd, \(J = 7.8, 4.8\) Hz, 1H), 7.15 (dd, \(J = 8.1, 7.5\) Hz, 1H), 4.21 (s, 1H), 3.70 (t, \(J = 4.6\) Hz, 4H), 2.53 – 2.18 (m, \(J = 4.4\) Hz, 4H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 149.6, 149.0, 143.7, 137.1, 135.6, 130.8, 130.8, 130.6, 126.6, 123.8, 123.0, 73.7, 67.0, 52.6. \textbf{HRMS} (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\textsubscript{16}H\textsubscript{18}BrN\textsubscript{2}O 333.0597; Found 333.0604.

4-((2-bromophenyl)(pyridin-3-yl)methyl)morpholine (3g): 61.5 mg (92% yield), white solid, m.p. 132 – 133 °C. \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.74 (d, \(J = 1.7\) Hz, 1H), 8.44 (dd, \(J = 4.7, 1.5\) Hz, 1H), 7.77 (ddd, \(J = 8.1, 1.7\) Hz, 2H), 7.49 (dd, \(J = 8.0, 1.1\) Hz, 1H), 7.32 (ddd, \(J = 8.1, 7.2, 0.9\) Hz, 1H), 7.20 (dd, \(J = 7.8, 4.8\) Hz, 1H), 7.06 (ddd, \(J = 7.8, 1.5\) Hz, 1H), 4.83 (s, 1H), 3.69 (t, \(J = 4.7\) Hz, 4H), 2.55 – 2.40 (m, 2H), 2.40 – 2.28 (m, 2H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 150.3, 148.8, 140.1, 136.2, 136.1, 133.4, 129.3, 128.9, 128.1, 124.6, 123.6, 71.2, 67.1, 52.6. \textbf{HRMS} (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\textsubscript{16}H\textsubscript{18}BrN\textsubscript{2}O 333.0597; Found 333.0600.

4-(morpholino(pyridin-3-yl)methyl)benzonitrile (3h): 47.1 mg (84% yield), white solid, m.p. 143 – 145 °C. \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.59 (d, \(J = 1.8\) Hz, 1H), 8.44 (d, \(J = 4.5, 1.2\) Hz, 1H), 7.67 (ddd, \(J = 7.8, 1.8\) Hz, 1H), 7.58 (d, \(J = 8.5\) Hz, 2H), 7.53 (d, \(J = 8.5\) Hz, 2H), 7.22 (dd, \(J = 7.8, 4.8\) Hz, 1H), 4.31 (s, 1H), 3.69 (m, 4H), 2.35 (m, 4H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 149.5, 149.2, 146.8, 136.4, 135.6, 132.8, 128.6, 123.9, 118.6, 111.5, 73.7, 66.9, 52.5. \textbf{HRMS} (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\textsubscript{17}H\textsubscript{18}N\textsubscript{3}O 280.1444; Found 280.1452.

methyl 4-(morpholino(pyridin-3-yl)methyl)benzoate (3i): 49.5 mg (79% yield), white solid, m.p. 91 – 92 °C. \textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.63 (d, \(J = 1.5\) Hz, 1H), 8.44 (dd, \(J = 4.5, 1.2\) Hz, 1H), 7.95 (d, \(J = 8.3\) Hz, 2H), 7.71 (ddd, \(J = 8.1, 1.8, 1.5\) Hz, 1H), 7.48 (d, \(J = 8.3\) Hz, 2H), 7.20 (dd, \(J = 7.8, 4.8\) Hz, 1H), 4.31 (s, 1H), 3.86 (s, 3H), 3.70 (t, \(J = 4.6\) Hz, 4H), 2.37 (m, \(J = 4.3\) Hz, 4H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 166.7, 149.6, 149.0, 146.4, 137.0, 135.6, 130.3, 129.5, 127.9, 123.8, 73.9, 67.0, 52.5, 52.2. \textbf{HRMS} (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}O\textsubscript{3} 313.1547; Found 313.1554.
4-((1-bromonaphthalen-2-yl)(pyridin-3-yl)methyl)morpholine (3j): 71.2 mg (93% yield), white solid, m.p. 159 – 160 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.87 (d, $J$ = 1.8 Hz, 1H), 8.45 (dd, $J$ = 4.8, 1.5 Hz, 1H), 8.29 (d, $J$ = 8.4 Hz, 1H), 7.92 (d, $J$ = 8.7 Hz, 1H), 7.86 (ddd, $J$ = 7.8, 1.8 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.61 – 7.44 (m, 2H), 7.20 (dd, $J$ = 7.8, 4.8 Hz, 1H), 5.22 (s, 1H), 3.80 – 3.60 (m, 4H), 2.60 – 2.36 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 150.2, 148.9, 138.2, 136.4, 135.9, 133.9, 132.6, 128.5, 128.1, 127.8, 127.7, 126.9, 125.8, 124.6, 123.6, 71.9, 67.1, 52.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{20}$H$_{20}$BrN$_2$O 383.0754; Found 383.0754.

4-(pyridin-3-yl(pyridin-4-yl)methyl)morpholine (3k): 88.0 mg (69% yield), white solid, m.p. 90 – 92 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.59 (d, $J$ = 1.5 Hz, 1H), 8.49 (d, $J$ = 5.7 Hz, 2H), 8.47 – 8.38 (m, 1H), 7.65 (d, $J$ = 7.9 Hz, 1H), 7.32 (d, $J$ = 5.7 Hz, 2H), 7.20 (dd, $J$ = 7.9, 4.8 Hz, 1H), 4.23 (s, 1H), 3.67 (t, $J$ = 4.6 Hz, 4H), 2.34 (q, $J$ = 4.6 Hz, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.0, 147.5, 145.0, 133.8, 132.9, 130.1, 119.8, 119.2 mg (94% yield), white solid, m.p. 86 – 88 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.61 (s, 1H), 8.44 (d, $J$ = 4.8 Hz, 1H), 7.68 (d, $J$ = 7.9 Hz, 1H), 7.40 – 7.15 (m, 6H), 4.44 (s, 1H), 2.67 (s, 8H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 149.6, 148.5, 140.8, 137.6, 135.4, 128.7, 128.0, 127.4, 133.5, 73.4, 53.5, 28.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_9$N$_2$S 271.1264; Found 271.1267.

1-methyl-4-(phenyl(pyridin-3-yl)methyl)piperazine (3m): 119.2 mg (89% yield), white solid, m.p. 105 – 107 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.65 (d, $J$ = 2.2 Hz, 1H), 8.42 (dd, $J$ = 4.8, 1.7 Hz, 1H), 7.71 (ddd, $J$ = 7.9, 2.0 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.33 – 7.23 (m, 2H), 7.22 – 7.09 (m, 2H), 4.27 (br s, 1H), 2.46 (s, 8H), 2.29 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 149.6, 148.5, 141.6, 138.2, 135.4, 128.8, 127.9, 127.4, 133.6, 73.7, 55.3, 51.7, 45.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{22}$N$_2$ 268.1808; Found 268.1812.

3-(phenyl(piperdin-1-yl)methyl)pyridine (3n): 75.1 mg (60% yield), white solid, m.p. 87 – 88 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.63 (d, $J$ = 2.2 Hz, 1H), 8.43 (dd, $J$ = 4.8, 1.7 Hz, 1H), 7.72 (d, $J$ = 7.9 Hz, 1H), 7.37 (m, 2H), 7.30 (m, 2H), 7.20 (m, 2H), 4.29 (s, 1H), 2.30 (m, 4H), 1.57 (m, 4H), 1.44 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 149.7, 148.3, 142.0, 138.7, 135.5, 128.6, 128.0, 127.2, 123.5, 74.2, 53.1, 26.2, 24.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{21}$N$_2$ 253.1699; Found 253.1701.

$N,N$-dimethyl-1-phenyl-1-(pyridin-3-yl)methanamine (3o): 58.6 mg (55% yield), white solid, m.p. 82 – 84 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.65 (d, $J$ = 2.4 Hz, 1H), 8.44 (dd, $J$ = 4.8, 1.5 Hz, 1H), 7.76 (ddd, $J$ = 7.8, 2.0 Hz, 1H), 7.40 (m, 2H), 7.30 (m, 2H), 7.20 (m, 2H), 4.13 (s, 1H), 2.20 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 149.6, 148.5, 142.4, 138.9, 135.2, 128.8, 127.8, 127.4, 123.6, 75.4, 44.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{14}$H$_{17}$N$_2$ 213.1386; Found 213.1389.
**N-benzyl-N-methyl-1-phenyl-1-(pyridin-3-yl)methanamine (3p):** 114.2 mg (79% yield), white solid, m.p. 119 – 121 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.73 (d, \(J = 2.2\) Hz, 1H), 8.45 (dd, \(J = 4.8, 1.7\) Hz, 1H), 7.84 (ddd, \(J = 7.9, 2.0\) Hz, 1H), 7.58 – 7.18 (m, 11H), 4.56 (s, 1H), 3.57 (d, \(J = 13.5\) Hz, 1H), 3.47 (d, \(J = 13.5\) Hz, 1H), 2.10 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 149.8, 148.5, 141.7, 139.4, 138.4, 135.6, 128.8, 128.6, 128.4, 128.1, 127.5, 127.0, 123.6, 72.7, 59.7, 40.2. HRMS (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\(_{26}\)H\(_{23}\)N\(_2\) 289.1699; Found 289.1703.

**N,N-dibenzyl-1-phenyl-1-(pyridin-3-yl)methanamine (3q):** 40.9 mg (22% yield), white solid, m.p. 166 – 168 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.72 (s, 1H), 8.54 (d, \(J = 2.7\) Hz, 1H), 7.73 (d, \(J = 7.9\) Hz, 1H), 7.54 – 7.14 (m, 16H), 5.04 (s, 1H), 3.59 (d, \(J = 14.1\) Hz, 2H), 3.58 (d, \(J = 14.1\) Hz, 2H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 150.8, 148.6, 139.2, 138.9, 136.7, 136.0, 129.3, 128.7, 128.6, 128.5, 127.6, 127.2, 123.2, 65.1, 53.9. HRMS (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\(_{36}\)H\(_{33}\)N\(_2\)O 562.2375; Found 562.2364.

**4-(pyridin-3-ylmethyl)morpholine (3r):** 22.0 mg (25% yield), pale yellow oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.52 (d, \(J = 1.5\) Hz, 1H), 8.48 (dd, \(J = 4.7, 1.3\) Hz, 1H), 7.66 (dd, \(J = 7.8\) Hz, 1H), 7.23 (dd, \(J = 7.8, 5.0\) Hz, 1H), 3.68 (m, 4H), 3.48 (s, 2H), 2.42 (m, 4H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 150.6, 148.8, 136.9, 133.3, 123.5, 67.0, 60.7, 53.6. HRMS (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\(_{10}\)H\(_{15}\)N\(_2\)O 179.1179; Found 179.1182.

**3,5-bis(morpholinomethyl)pyridine (3r'):** 90.6 mg (65% yield), pale yellow oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.40 (d, \(J = 2.2\) Hz, 1H), 7.61 (dd, \(J = 2.2\) Hz, 1H), 3.66 (m, 8H), 3.47 (s, 4H), 2.40 (m, 8H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.3, 137.4, 132.8, 66.8, 60.4, 53.4. HRMS (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\(_{15}\)H\(_{24}\)N\(_2\)O 278.1863; Found 278.1866.

**1,1'-(pyridine-3,5-diyl)bis(N,N-dibenzylmethanamine) (3s):** 212.5 mg (85% yield), pale yellow solid, m.p. 146 – 148°C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.47 (br s, 2H), 7.86 (s, 1H), 7.49 – 7.22 (m, 20H), 3.59 (s, 8H), 3.58 (s, 4H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 149.0, 139.4, 136.7, 134.9, 128.8, 128.4, 127.2, 58.2, 55.2. HRMS (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\(_{33}\)H\(_{36}\)N\(_3\) 498.2904; Found 498.2909.

**1,1'-(pyridine-3,5-diyl)bis(N-benzyl-N-methylmethanamine) (3t):** 143.3 mg (83% yield), pale yellow solid, m.p. 121 – 124 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.49 (d, \(J = 2.1\) Hz, 2H), 7.74 (d, \(J = 2.1\) Hz, 1H), 7.51 – 7.02 (m, 10H), 3.55 (s, 4H), 3.54 (s, 4H), 2.21 (s, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 149.1, 138.9, 137.0, 134.3, 128.9, 128.3, 127.1, 61.9, 58.9, 42.2. HRMS (ESI-TOF) \(m/z\): [M + H]\(^+\) Calcd for C\(_{23}\)H\(_{28}\)N\(_3\) 346.2278; Found 346.2284.

**N,N'-pyridine-3,5-diylbis(methylene))bis(N-butylbutan-1-amine) (3u):** 57.0 mg (32% yield), pale yellow oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.37 (d, \(J = 2.1\) Hz, 2H), 7.60 (s, 1H), 3.51 (s, 4H), 2.48 – 2.23 (t, \(J = 7.2\) Hz, 8H), 1.50 – 1.34 (m, 8H), 1.34 – 1.17 (m, 8H), 0.84 (t, \(J = 7.3\) Hz, 12H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 148.8, 137.1,
\[ \text{HRMS (ESI-TOF) } m/z: [M + H]^+ \text{ Calcd for C}_{23}H_{44}N_3 362.3530; \text{ Found 362.3535.} \]

\[ \text{N,N'}-(\text{pyridine-3,5-diylbis(methylene)})\text{bis(\text{ethylethanamine}) (3v): 82.3 mg (66\% yield), pale yellow oil.} \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta 8.37 \text{ (s, 2H), 7.64 \text{ (s, 1H), 3.54 \text{ (s, 4H), 2.48 \text{ (q, } J = 7.1 \text{ Hz, 8H), 0.99 \text{ (t, } J = 7.1 \text{ Hz, 12H).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta 149.1, 137.5, 134.4, 54.7, 46.8, 11.6. \]

\[ \text{HRMS (ESI-TOF) } m/z: [M + H]^+ \text{ Calcd for C}_{15}H_{28}N_3 250.2278; \text{ Found 250.2284.} \]

\[ \text{N,N'}-(\text{pyridine-3,5-diylbis(methylene)})\text{bis(\text{N-methylpropan-2-amine}) (3w): 75.5 mg (61\% yield), pale yellow oil.} \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta 8.39 \text{ (s, 2H), 7.66 \text{ (s, 1H), 3.50 \text{ (s, 4H), 2.88 \text{ (hept, } J = 6.6 \text{ Hz, 2H), 2.12 \text{ (s, } J = 6.6 \text{ Hz, 12H).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta 149.1, 137.2, 134.8, 54.8, 53.4, 36.8, 17.9. \]

\[ \text{HRMS (ESI-TOF) } m/z: [M + H]^+ \text{ Calcd for C}_{15}H_{28}N_3 250.2277; \text{ Found 250.2277.} \]

**Procedure for synthesis of 1-((N,4-dimethylphenyl)sulfonamido)-3-(morpholino(phenyl) methyl) pyridin-1-ium iodide**

To a solution of 1-((N-methyltoluenesulfonamido)pyridin-1-ium iodide (39.4 mg, 0.1 mmol) in CH\(_2\)Cl\(_2\) (2.0 mL) was added benzaldehyde (12.1 mg, 0.11 mmol) and morpholine (10.2 mg, 0.11 mmol). The mixture was stirred in a 50 °C oil bath for 18 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by gravity chromatography to give the titled product as yellow solid. 24.9 mg (44% yield), m.p. 142 – 143 °C. \[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta 8.99 \text{ (s, 1H), 8.85 \text{ (d, } J = 6.5 \text{ Hz, 1H), 8.67 \text{ (d, } J = 8.1 \text{ Hz, 1H), 7.46 – 7.27 \text{ (m, 9H), 4.92 \text{ (s, 1H), 3.80 \text{ (s, 3H), 3.74 – 3.65 \text{ (m, 4H), 2.49 \text{ (s, 3H), 2.46 \text{ (s, 4H).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta 148.3, 147.2, 145.9, 144.6, 143.8, 136.3, 131.3, 129.5, 129.0, 128.9, 128.9, 126.9, 71.2, 66.9, 51.7, 40.2, 22.2. \]

\[ \text{HRMS (ESI-TOF) } m/z: [M – I]^+ \text{ Calcd for C}_{24}H_{28}N_3O_3S 438.1846; \text{ Found 438.1851.} \]

**Procedure for synthesis of N-ethyl-4-methoxy-N-(5-(phenyl(pyrrrolidin-1-yl)methyl)-2-(pyrrrolidin-1-yl) pyridin-1(2H)-yl)benzamide (4).**

To a solution of 1f (77.0 mg, 0.2 mmol) in CH\(_2\)CN (1.0 mL) was added aminal 2x (101.5 mg, 0.44 mmol). The mixture was stirred at room temperature for 1 h then a yellow precipitate was formed. The mixture was filtrated, washed with cold CH\(_2\)CN and dried in vacuo to give 4 as yellow powder (72.3 mg 74% yield). \[ ^1H \]
NMR (500 MHz, CDCl₃) δ 7.71 (d, J = 8.5 Hz, 2H), 7.37 (s, 1H), 7.21 – 7.02 (m, 5H), 6.89 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 11.5 Hz, 1H), 6.34 – 6.19 (m, 2H), 4.37 (s, 1H), 4.10 (dq, 1H), 4.01 (dq, 1H), 3.83 (s, 3H), 3.27 (m, 4H), 2.40 (m, 2H), 2.33 (m, 2H), 1.99 – 1.89 (m, 4H), 1.73 (d, J = 6.5 Hz, 4H), 1.18 (t, J = 7.0 Hz, 3H).<br>

13C NMR (75 MHz, CDCl₃) δ 169.7, 160.7, 146.1, 144.4, 143.6, 138.9, 131.8, 129.0, 127.8, 126.2, 126.1, 112.7, 112.6, 98.0, 68.1, 55.5, 53.5, 49.3, 36.4, 25.5, 23.9, 11.9.<br>

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C₃₀H₃₉N₄O₂ 487.3068; Found 487.3063.<br>

Procedure for synthesis of 3,5-bis(morpholinomethyl)pyridine 3s' from 1g<br>

To a solution of 1g (92.7 mg, 0.2 mmol) in CH₃CN (1.0 mL) was added aminal 2r (82.2 mg, 0.44 mmol), and the mixture was stirred in a 90 °C oil bath for 4 h. The mixture was cooled to room temperature, and zinc powder (65.4 mg, 1.0 mmol) and glacial acetic acid (1.0 mL) were added and stirred for 5 min. The reaction was quenched with saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic extracts was washed with brine, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography using CH₂Cl₂/MeOH to give products 3s' as pale yellow oil (36.6 mg, 66% yield).<br>

Procedure for synthesis of N-(5-bromo-2-morpholinopyridin-1(2H)-yl)-N-ethyl-4-methoxybenzamide (5)<br>

To a solution of 1g (92.6 mg, 0.2 mmol) in CH₃CN (1.0 mL) was added 2a (115.5 mg, 0.44 mmol). The mixture was stirred at room temperature for 1 h, then the solvent was removed in vacuo and the residue was purified by flash chromatography to give 5 as yellow powder (71.4 mg, 85% yield).<br>

Procedure for synthesis of 1-(N-ethyl-4-methoxybenzamido)-3-(morpholino(phenyl)methyl) pyridin-1-ium iodide (7').
A solution of 1g (92.9 mg, 0.2 mmol) and 2a (115.5 mg, 0.44 mmol) in CH$_3$CN (1.0 mL) was stirred in a 90 °C oil bath for 30 min. The solvent was removed in vacuo and the residue was purified by gravity chromatography to give 7' as yellow foam (88.5 mg, 79% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.66 (d, $J = 6.2$ Hz, 1H), 9.56 (s, 1H), 8.74 (d, $J = 8.1$ Hz, 1H), 8.33 (dd, $J = 7.2$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.48 – 7.18 (m, 5H), 6.91 (d, $J = 8.4$ Hz, 2H), 5.01 (s, 1H), 4.39 (q, $J = 7.2$ Hz, 2H), 3.81 (s, 3H), 3.77 – 3.57 (m, 4H), 2.49 (m, 2H), 2.35 (m, 2H), 1.21 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.4, 162.9, 146.8, 146.5, 145.9, 137.4, 130.9, 129.9, 129.5, 128.6, 128.4, 122.4, 114.3, 77.4, 70.7, 66.7, 55.6, 51.7, 50.8, 13.4. HRMS (ESI-TOF) m/z: [M – I$^-$]$^+$ Calcd for C$_{26}$H$_{30}$N$_3$O$_3$$^+$ 432.2282; Found 432.2280.

References

\(^1\)H NMR and \(^{13}\)C NMR spectra of products

\(^1\)H NMR of \(3a\), 300 MHz in CDCl\(_3\)

\(^{13}\)C NMR of \(3a\), 75 MHz in CDCl\(_3\)
$^{1}$H NMR of 3b, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3b, 100 MHz in CDCl$_3$
$^1$H NMR of 3c, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3c, 100 MHz in CDCl$_3$
$^1$H NMR of 3d, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3d, 100 MHz in CDCl$_3$
$^{13}$C NMR of 3e, 100 MHz in CDCl$_3$
1H NMR of 3f, 300 MHz in CDCl₃

13C NMR of 3f, 100 MHz in CDCl₃
$^1$H NMR of 3g, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3g, 100 MHz in CDCl$_3$
\[ ^1H \text{ NMR of } 3h, 300 \text{ MHz in CDCl}_3 \]

\[ ^{13}C \text{ NMR of } 3h, 100 \text{ MHz in CDCl}_3 \]
$^1$H NMR of 3i, 300 MHz in CDCl$_3$

$^1$C NMR of 3i, 100 MHz in CDCl$_3$
$^{1}H$ NMR of 3j, 300 MHz in CDCl$_3$

$^{13}C$ NMR of 3j, 75 MHz in CDCl$_3$
$^{1}$H NMR of 3k, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3k, 75 MHz in CDCl$_3$
\( ^1H \text{ NMR of } 3l, 300 \text{ MHz in CDCl}_3 \)

\( ^13C \text{ NMR of } 3l, 75 \text{ MHz in CDCl}_3 \)

21
$^1$H NMR of 3m, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3m, 75 MHz in CDCl$_3$
$^1$H NMR of 3n, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3n, 75 MHz in CDCl$_3$
$^1$H NMR of 3o, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3o, 75 MHz in CDCl$_3$
$^1$H NMR of 3p, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3p, 75 MHz in CDCl$_3$
$^{13}$C NMR of 3q, 75 MHz in CDCl$_3$
$^1$H NMR of $3r$, 300 MHz in CDCl$_3$

$^{13}$C NMR of $3r$, 100 MHz in CDCl$_3$
\[ \text{H NMR of } 3r', 300 \text{ MHz in CDCl}_3 \]

\[ \text{C NMR of } 3r', 100 \text{ MHz in CDCl}_3 \]
$^{1}H$ NMR of 3s, 300 MHz in CDCl$_3$

$^{13}C$ NMR of 3s, 75 MHz in CDCl$_3$
\[ \text{H NMR of 3t, 300 MHz in CDCl}_3 \]

\[ \text{C NMR of 3t, 75 MHz in CDCl}_3 \]
H NMR of 3u, 300 MHz in CDCl₃

C NMR of 3u, 75 MHz in CDCl₃
$^{13}$C NMR of 3v, 75 MHz in CDCl$_3$
$^{1}$H NMR of 3w, 300 MHz in CDCl$_3$

$^{13}$C NMR of 3w, 75 MHz in CDCl$_3$
$^1$H NMR, 300 MHz in CDCl$_3$

$^1$C NMR, 75 MHz in CDCl$_3$
**$^1$H NMR of 4, 500 MHz in CDCl$_3$**

**$^{13}$C NMR of 4, 75 MHz in CDCl$_3$**
$^1$H NMR of 5, 300 MHz in CDCl$_3$

$^{13}$C NMR of 5, 75 MHz in CDCl$_3$
$^1$H NMR of 7', 300 MHz in CDCl$_3$

$^{13}$C NMR of 7', 75 MHz in CDCl$_3$
HPLC-HRMS spectrum of reaction mixture
(experiment entry 8, Table 2 in main text)
<table>
<thead>
<tr>
<th>Observed</th>
<th>Calculated</th>
<th>Cation</th>
<th>Formula</th>
<th>Assigned Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>88.0754</td>
<td>88.0757</td>
<td>[M + H]$^+$</td>
<td>C$<em>4$H$</em>{10}$NO$^+$</td>
<td></td>
</tr>
<tr>
<td>135.0445</td>
<td>135.0441</td>
<td>M$^+$</td>
<td>C$_3$H$_2$O$_2$$^+$</td>
<td>MeO-Ph</td>
</tr>
<tr>
<td>168.0814</td>
<td>168.0808</td>
<td>M$^+$</td>
<td>C$<em>{12}$H$</em>{10}$N$^+$</td>
<td></td>
</tr>
<tr>
<td>176.1076</td>
<td>176.1070</td>
<td>M$^+$</td>
<td>C$_{11}$H$_4$NO$^+$</td>
<td></td>
</tr>
<tr>
<td>211.1237</td>
<td>211.1230</td>
<td>[M + H]$^+$</td>
<td>C$<em>{14}$H$</em>{15}$N$_2$$^+$</td>
<td></td>
</tr>
<tr>
<td>237.1605</td>
<td>237.1598</td>
<td>M$^+$</td>
<td>C$<em>{13}$H$</em>{21}$N$_2$O$_2$$^+$</td>
<td></td>
</tr>
<tr>
<td>257.1295</td>
<td>257.1285</td>
<td>M$^+$</td>
<td>C$<em>{15}$H$</em>{17}$N$_2$O$_2$$^+$</td>
<td></td>
</tr>
<tr>
<td>298.1914</td>
<td>298.1914</td>
<td>M$^+$</td>
<td>C$<em>{18}$H$</em>{24}$N$_3$$^+$</td>
<td>NHEt</td>
</tr>
<tr>
<td>344.1966</td>
<td>344.1969</td>
<td>[M + H]$^+$</td>
<td>C$<em>{19}$H$</em>{26}$N$_3$O$_3$$^+$</td>
<td>MeO-Ph</td>
</tr>
<tr>
<td>347.1751</td>
<td></td>
<td></td>
<td></td>
<td>unknown</td>
</tr>
<tr>
<td>432.2267</td>
<td>432.2282</td>
<td>M$^+$</td>
<td>C$<em>{26}$H$</em>{30}$N$_3$O$_3$$^+$</td>
<td>MeO-Ph</td>
</tr>
</tbody>
</table>
References on the total synthesis of huperzine A