Electronic Supplementary Information

Highly chemoselective, sterically sensitive NHC-catalysed amine acylation with pyridil

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1. General

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent; CDCl$_3$ and DMSO-d$_6$ and referenced relative to residual CHCl$_3$ (δ = 7.26 ppm) and DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE, EXSY and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F254 slides and visualized by UV irradiation and KMnO4 staining. Anhydrous acetonitrile (CH$_3$CN), dichloromethane (CH$_2$Cl$_2$) and tetrahydrofuran (THF) were obtained by using Pure Solv MD-4EN Solvent Purification System. Unless otherwise noted, all commercially available compounds were used as provided, without any further purification. DBU and all other amines were distilled over calcium hydride under argon before use.
2. Synthesis of 4-Ethyl-1-methyl-1\textit{H}-1,2,4-triazol-4-ium iodide (3)

\[
\begin{array}{c}
\text{N=NNH} \\
\text{Na(s)} \quad \text{MeOH (2.0 M)} \quad \text{MeI (1 equiv.)} \\
\text{S1 39\%} \\
\end{array} \quad \begin{array}{c}
\text{EtI (2.2 equiv.)} \\
\text{3 23\%} \\
\end{array}
\]

1-Methyl-1\textit{H}-1,2,4-triazole (S1)

To an oven-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged MeOH (80 mL) and sodium (3.30 g). The solution was stirred for 5 minutes before 1,2,4-triazole (10 g, 155.0 mmol) was added and the mixture stirred at room temperature until the solid dissolved. The vessel was then placed under a protective atmosphere of argon and cooled to 0 °C in an ice bath. Iodomethane (9.04 mL, 20.61 g, 155.0 mmol) was added dropwise \textit{via} syringe. Stirring was continued for 5 minutes at 0 °C before warming to room temperature and stirring for a further 2 hours under argon before refluxing at 60 °C for 20 h. Upon cooling, the solvent was removed in vacuo and H\textsubscript{2}O (60 mL) was added. The product was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 50 mL), the combined organic layers were dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo} to yield S1 as a yellow liquid (4.67 g, 39\%) that was dried under vacuum for several hours.

Spectral data for this compound were consistent with those in the literature.\textsuperscript{1}

\[\delta_H (400 \text{ MHz}, \text{CDCl}_3): \quad 7.93 \text{ (1 H, s), 7.78 (1 H, s), 3.80 (3 H, s)}.\]

HRMS (\textit{m/z} - ESI): Found: 84.0564 (M+H)\textsuperscript{+} C\textsubscript{3}H\textsubscript{6}N\textsubscript{3} Requires: 84.0562.

4-Ethyl-1-methyl-1\textit{H}-1,2,4-triazol-4-ium iodide (3)

To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged 1-methyl-1\textit{H}-1,2,4-triazole (S1, 4.2 g, 50.5 mmol). The vessel was placed under a
protective atmosphere of argon and ethyl iodide (8.9 mL, 111 mmol) was added via syringe. The flask was covered with aluminium foil and the reaction mixture stirred for 96 h at room temperature under argon. The resulting precipitate was filtered, washed with Et₂O (3 x 20 mL) and recrystallised from 1% Et₂O/MeOH to yield 3 as a white crystalline solid (3.07g, 23%).

Spectral data for this compound were consistent with those in the literature.¹

δ_H (400 MHz, DMSO-d₆): 10.03 (1 H, s), 9.18 (1 H, s), 4.2 (2 H, q, J 7.3), 4.03 (3 H, s), 1.41 (3 H, t, J 7.3).

HRMS (m/z - ESI): Found: 112.0874 (M)+ \text{C}_5\text{H}_{10}\text{N}_3 \text{Requires: 112.0875.}

3. Synthesis of amines and diamines: procedures

Synthesis of (E)-3-phenylprop-2-en-1-amine (S3)

![Synthesis of (E)-3-phenylprop-2-en-1-amine (S3)](image)

2-cinnamylisoindoline-1,3-dione (S2)

![2-cinnamylisoindoline-1,3-dione (S2)](image)

To an oven-dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged THF (12 mL) and cinnamyl alcohol (0.77 mL, 6.0 mmol) under an atmosphere of argon. Triphenylphosphine (2.05 g, 7.8 mmol), and phthalimide (1.32 g, 9.0 mmol) was added to the reaction mixture at 0 °C. DIAD (1.6 mL, 7.8 mmol) was added to the flask over 10 minutes at 0 °C. The reaction mixture was stirred at 0 °C for 1 h after which time the flask was warmed to room temperature and stirred overnight. The resulting mixture was concentrated in vacuo and the residue was purified by flash column chromatography, eluting
in gradient from 100% hexanes to 12:1 EtOAc:hexanes. The residue obtained after the initial
flash column chromatography was dissolved in EtOAc (25 mL) and KOH (1 M, 25 mL). The
aqueous phase was extracted into EtOAc (3 x 20 mL). The combined organic layers were
dried over MgSO₄ and the solvent was removed under reduced pressure to yield S2 as a white
solid (0.94 g, 60%). M.p. 152-154 °C (lit.,² M.p. 154-155 °C).

Spectral data for this compound were consistent with those in the literature.²

δ_H (400 MHz, CDCl₃): 7.87 (2H, dd, J 5.5, 3.1), 7.72 (2H, dd, J 5.5, 3.1), 7.37-7.32 (2
H, m), 7.31-7.27 (2H, m), 7.24-7.21 (1H, m), 6.66 (1H, d, J 15.8), 6.26 (1H, dt, J 15.8, 6.5), 4.45 (2H, dd, J 6.5, 1.1).

(E)-3-phenylprop-2-en-1-amine (S3)

To a solution of 2-cinnamylisoindoline-1,3-dione (S2, 0.94 g, 3.6 mmol) in MeOH (60 mL),
was charged hydrazine monohydrate (0.72 mL, 14.4 mmol) at room temperature. The mixture
was stirred overnight at room temperature after which time the mixture was concentrated in vacuo. The resulting residue was diluted with CH₂Cl₂ (30 mL) and KOH (1 M, 30 mL). The
aqueous phase was extracted into EtOAc (3 x 30 mL). The combined organic layers were
dried over MgSO₄ and the solvent was removed under reduced pressure to yield S3 as a pale-
yellow oil (0.21 g, 44%) which was used without further purification.

Spectral data for this compound were consistent with those in the literature.²

δ_H (400 MHz, CDCl₃): 7.42-7.16 (5H, m), 6.51 (1H, d, J 15.8), 6.33 (1H, dt, J 15.8,
5.8), 3.49 (2H, d, J 5.8), 1.40 (2H, br. s).

HRMS (m/z - ESI): Found: 134.0956 (M+H)⁺ C₉H₁₂N Requires: 134.0970.
Synthesis of diamines S8 and S9

\[
\begin{align*}
\text{RNH}_2 (20 \text{ equiv.)} & \quad \text{reflux} \\
\text{S6} \quad R=\text{CH}_2\text{CH}_3, 91\% & \quad \text{S7} \quad R=\text{CH}({\text{CH}_3})_2, 97\%
\end{align*}
\]

*tert*-butyl (3-hydroxypropyl)(methyl)carbamate (S4)

To a stirred solution of 3-methylamino-1-propanol (2.20 mL, 22.6 mmol) and triethylamine (3.50 mL, 24.9 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (200 mL), was charged a solution of di-*tert*-butyl dicarbonate (5.97 g, 27.2 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (25 mL) dropwise at 0˚C, under an atmosphere of argon. After 1 h at 0˚C the reaction mixture was warmed to room temperature and stirred overnight. The mixture was washed sequentially with brine (150 mL), a saturated citric acid solution (150 mL), a saturated sodium hydrogen carbonate solution (150 mL) and water (150 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to yield the S4 as a colourless oil (4.05 g, 94%).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{3}

\[\delta_H (400 \text{ MHz, CDCl}_3): \quad 3.63 (2 \text{ H, m}), 3.38 (2 \text{ H, t, } J 5.9), 2.83 (3 \text{ H, s}), 1.74-1.63 (2 \text{ H, m}), 1.45 (9\text{H, s}).\]

HRMS (m/z - ESI): Found: 212.1261 (M+Na)\textsuperscript{+} C\textsubscript{9}H\textsubscript{19}NNaO\textsubscript{3} Requires: 212.1257.
A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with tert-butyl (3-hydroxypropyl)(methyl)carbamate (S4, 5.67 g, 30.0 mmol), CH$_2$Cl$_2$ (60 mL) and triethylamine (9.5 mL, 65.9 mmol). The flask was cooled to 0°C followed by the addition of tosyl chloride (6.28 g, 33.0 mmol) and DMAP (0.37 g, 3.0 mmol). The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with a saturated ammonia chloride solution (50 mL) and extracted into CH$_2$Cl$_2$ (3 x 50 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent was removed in vacuo. The resulting residue was purified by flash column chromatography, eluting in gradient from 100% hexanes to 10% EtOAc in hexanes to yield S5 as a colourless oil (3.6 g, 35%).

Spectral data for this compound were consistent with those in the literature.$^3$

$\delta$ (400 MHz, CDCl$_3$): 7.79 (2H, d, $J$ 8.2), 7.34 (2 H, d, $J$ 8.2), 4.04 (2 H, t, $J$ 6.4), 3.24 (2 H, t, $J$ 6.4), 2.79 (3 H, s), 2.45 (3 H, s), 1.87 (2 H, quin., $J$ 6.4), 1.42 (9H, s).

HRMS ($m/z$ - ESI): Found: 366.1353 (M+Na)$^+$ C$_{16}$H$_{25}$NNaO$_5$S Requires: 366.1346.

**tert-butyl (3-(ethylamino)propyl)(methyl)carbamate (S6)**

To a 50 mL round-bottomed flask containing a magnetic stirring bar was added 3-((tert-butoxycarbonyl)(methyl)amino)propyl 4-methylbenzenesulfonate (S5, 3.01 g, 8.78 mmol) and ethylamine (66% solution in H$_2$O, 19 mL). The reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC analysis),
the reaction was quenched with a saturated sodium hydrogen carbonate solution (20 mL) and extracted into CH$_2$Cl$_2$ (3 x 50 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent was removed in vacuo to give the product, S6 as a colourless oil (1.74 g, 91%). The product was used without further purification.

$\delta_H$ (400 MHz, DMSO-d$_6$): 3.19 (2 H, t, $J$ 7.0), 2.76 (3 H, br. s), 2.58 (2 H, quart., $J$ 7.1), 2.51 (2 H, m), 1.61 (2 H, quint., $J$ 7.0), 1.39 (9 H, s), 1.03 (3 H, t, $J$ 7.1).

$\delta_C$ (100 MHz, DMSO-d$_6$): 155.4 (C=O), 78.8 (q), 66.6, 46.9, 46.8, 46.6, 46.3, 46.0, 43.7, 34.3, 28.5, 27.8, 27.2, 14.8.

*There are an unexpected number of carbon signals observed with this compound due to it being a rotameric molecule. Although this is not observed in the 1H NMR spectrum, it is confirmed by analysis of HSQC and EXSY spectra.

$\nu_{max}$ (neat)/cm$^{-1}$: 2970, 2930, 1687 (C=O), 1481, 1454, 1392, 1365, 1311, 1251, 1157, 1050, 878, 771, 641.

HRMS (m/z - ESI): Found: 217.1843 (M+H)$^+$ C$_{11}$H$_{24}$N$_2$O$_2$ Requires: 217.1838

$\text{N}^1$-ethyl-$\text{N}^3$-methylpropane-1,3-diamine (39)

A 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged tert-butyl (3-(ethylamino)propyl)(methyl)carbamate (S6, 2.12 g, 9.69 mmol) and CH$_2$Cl$_2$ (50 mL). To this stirring solution trifluoroacetic acid (15 mL, 96.9 mmol) was added. The reaction mixture was stirred for 4 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with Et$_2$O until a white precipitate was observed. This precipitate (2.67 g, 7.75 mmol) was stirred in CH$_2$Cl$_2$ and K$_2$CO$_3$ (5.22 g, 31.0 mmol) for 2 h (the progress of this reaction can be monitored by $^{19}$F NMR spectroscopy). After complete consumption of starting material, the resulting suspension was filtered, and the precipitate was washed with Et$_2$O (3 x 10 mL). The filtrate was concentrated in vacuo (care was taken when removing the solvent as the diamine produced is volatile) to yield 39 (0.79 g, 88%) as a colourless oil which was used without further purification.
$\delta_H$ (400 MHz, CDCl$_3$): 2.72-2.61 (6 H, m), 2.44 (3 H, s), 1.69 (2 H, app. quin., $J$ 7.1), 1.31 (2 H, br. s), 1.11 (3 H, t, $J$ 7.1).

$\delta_C$ (100 MHz, CDCl$_3$): 50.6, 48.3, 44.2, 36.6, 30.4, 15.3.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3378 (NH), 2965, 2932, 2799, 1449, 1378, 1305, 1117, 1054, 747.

LRMS ($m/z$ - ESI): Found: 59.1 (M+2H)$^+$, C$_6$H$_{18}$N$_2$ Requires: 59.1.

**tert-butyl (3-(isopropylamino)propyl)(methyl)carbamate (S7)**

![Chemical Structure](image)

To a 10 mL round-bottomed flask containing a magnetic stirring bar was added 3-((tert-butoxycarbonyl)(methyl)amino)propyl 4-methylbenzenesulfonate (S5, 0.55 g, 1.57 mmol), EtOH (2 mL) and isopropylamine (2.7 mL, 31.4 mmol). The reaction mixture was heated at reflux for 16 h. After complete consumption of the starting material (monitored by TLC analysis), the reaction mixture was quenched with a saturated sodium hydrogen carbonate solution (20 mL) and extracted into CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were dried over MgSO$_4$ and the solvent was removed in vacuo to furnish the product, S7, as a colourless oil (0.35 g, 97%) which was used without further purification.

$\delta_H$ (400 MHz, DMSO-d$_6$): 3.19 (2 H, t, $J$ 7.0), 2.78-2.70 (4 H, m), 2.48 (2 H, t, $J$ 7.0), 1.58 (2 H, app. quint., $J$ 7.0), 1.39 (9 H, s), 0.98 (6 H, d, $J$ 6.2).

$\delta_C$ (100 MHz, DMSO-d$_6$): 154.6 (C=O), 78.0 (q), 47.9, 43.5, 40.7, 33.5, 27.9, 27.5, 22.1.

*The carbon signal at 40.7 ppm is not observed in the $^{13}$C spectra attached as it is distorted by the DMSO-d$_6$ signal, however, it is observed by analysis of HSQC spectra.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2967, 2932, 1689 (C=O), 1479, 1454, 1392, 1365, 1308, 1223, 1157, 988, 876, 771, 664.

HRMS ($m/z$ - ESI): Found: 231.2073 (M+H)$^+$, C$_{12}$H$_{27}$N$_2$O$_2$ Requires: 231.2067.
\( N^1\text{-isopropyl-N}^3\text{-methylpropane-1,3-diamine (37)} \)

\[
\text{NH} \quad \text{NHH}
\]

To a 25 mL round-bottomed flask equipped with a magnetic stirring bar was charged tert-butyl (3-(isopropylamino)propyl)(methyl)carbamate (S7, 0.58 g, 2.53 mmol) and \( \text{CH}_2\text{Cl}_2 \) (12 mL). To this stirring solution trifluoroacetic acid (2 mL, 25.3 mmol) was added. The reaction mixture was stirred for 4 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with \( \text{Et}_2\text{O} \) until a white precipitate was observed. This precipitate (0.60 g, 1.67 mmol) was stirred in \( \text{CH}_2\text{Cl}_2 \) and \( \text{K}_2\text{CO}_3 \) (0.97 g, 6.68 mmol) for 2 h (the progress of this reaction can be monitored by \( ^{19}\text{F} \text{NMR spectroscopy} \)). After complete consumption of starting material, the resulting suspension was filtered, and the precipitate was washed with \( \text{Et}_2\text{O} \) (3 x 10 mL). The filtrate was concentrated in vacuo (care was taken when removing the solvent as the diamine produced is volatile) to yield the title compound, 37 (0.16 g, 72%) as a colourless oil which was used without further purification.

\( \delta_H \) (400 MHz, CDCl\(_3\)): 2.78 (1 H, sept., \( J \) 6.2), 2.69-2.59 (4 H, m), 2.43 (3 H, s), 1.67 (2 H, app. quint., \( J \) 7.2), 1.55 (2 H, br. s), 1.05 (6 H, d, \( J \) 6.2).

\( \delta_C \) (100 MHz, CDCl\(_3\)): 50.7, 48.8, 45.9, 36.4, 30.1, 22.8.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1} \): 3299 (NH), 3107, 3069, 2962, 2933, 2852, 2796, 1745, 1691, 162, 1547, 1472, 1447, 1363, 1169, 1126, 818, 704.

HRMS (\( m/z \) - APCI): Found: 131.1549 (M+H)\(^+\) \( \text{C}_7\text{H}_{19}\text{N}_2 \) Requires: 131.1543.

4. Table 1: Experimental data

**General procedure 1:** Substrate evaluation in the NHC-catalysed oxidative amidation between 2,2’-pyridil and various primary and secondary amines (Table 1).

An oven dried 10 mL round-bottomed flask, equipped with a magnetic stirring bar was evacuated and put under an atmosphere of argon repeatedly. The flask was fitted with a septum seal and argon-filled balloon. 2,2’-pyridil (212.2 mg, 1 mmol), phenazine (180.2 mg, 1 mmol) and catalyst 3 (35.9 mg, 15 mol%, 0.15 mmol), were charged to the flask.
sequentially. The flask was again evacuated and put under an atmosphere of argon repeatedly. The flask was re-fitted with a septum seal and argon-filled balloon. THF (0.4 M) was charged to the flask followed sequentially by freshly distilled DBU (165 µL, 1.1 mmol) and the relevant freshly distilled amine (1 mmol) in rapid succession. The reaction was stirred at room temperature for 24 h. The residue obtained was purified by flash column chromatography to furnish the desired product

**Pyridin-2-yl(pyrrrolidin-1-yl)methanone (22)**

![Pyridin-2-yl(pyrrrolidin-1-yl)methanone](image)

Prepared according to general procedure 1 using 2,2'-pyridil (212.2 mg, 1 mmol) and pyrrolidine (84 µL, 1 mmol). Purified by flash chromatography, eluting in gradient from 1% MeOH to 10% MeOH in CH2Cl2, to isolate 22 a brown oil (176.4 mg, 93%).

Spectral data for this compound were consistent with those in the literature.4

δH (400 MHz, CDCl3): 8.57 (1 H, d, J 4.0), 7.86-7.74 (2 H, m), 7.36-7.30 (1 H, m), 3.77-3.64 (4 H, m), 1.98-1.86 (4 H, m).


**Piperidin-1-yl(pyridin-2-yl)methanone (23)**

![Piperidin-1-yl(pyridin-2-yl)methanone](image)

Prepared according to general procedure 1 using 2,2’-pyridil (212.3 mg, 1 mmol) and piperidine (99 µL, 1 mmol). Purified by flash chromatography, eluting in gradient from 1% MeOH to 10% MeOH in CH2Cl2, to isolate 23 a brown oil (166.3 mg, 94%).

Spectral data for this compound were consistent with those in the literature.5
\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 8.59 (1 \text{ H, d, } J 4.0), 7.81-7.75 (1 \text{ H, m}), 7.57 (1 \text{ H, d, } J 7.8), 7.35-7.29 (1 \text{ H, m}), 3.78-3.71 (2 \text{ H, m}), 3.43 (2 \text{ H, t, } J 5.6), 1.73-1.64 (4 \text{ H, m}), 1.61-1.52 (2 \text{ H, m}). \]

HRMS (m/z - ESI): Found: 213.1010 (M+Na)\(^+\) \(\text{C}_{11}\text{H}_{14}\text{N}_2\text{NaO}\) Requires: 213.0998.

**N-isobutylpicolinamide (19)**

\[
\begin{align*}
\text{N} & \text{-isobutylpicolinamide (19)}  \\
& \\
\end{align*}
\]

Prepared according to general procedure 1 using 2,2’-pyridil (212.3 mg, 1 mmol) and isobutyl amine (100 \(\mu\text{L}, 1\) mmol). Purified by flash chromatography, eluting in gradient from 100\% hexanes to 30\% EtOAc in hexanes, to isolate 19 a colourless oil (165.1 mg, 93\%).

Spectral data for this compound were consistent with those in the literature.\(^6\)

\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 8.55 (1 \text{ H, d, } J 4.7), 8.20 (1 \text{ H, d, } J 7.7), 8.13 (1 \text{ H, br. s}), 7.84 (1 \text{ H, t, } J 7.7), 7.44-7.39 (1 \text{ H, m}), 3.31 (2 \text{ H, t, } J 6.6), 1.92 (1 \text{ H, dt, } J 13.4, 6.7), 0.99 (6 \text{ H, d, } J 6.7). \]

HRMS (m/z - APCI): Found: 179.1179 (M+H)\(^+\) \(\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}\) Requires: 179.1179.

**N-isopropylpicolinamide (20)**

\[
\begin{align*}
\text{N} & \text{-isopropylpicolinamide (20)}  \\
& \\
\end{align*}
\]

Prepared according to general procedure 1 using 2,2’-pyridil (212.1 mg, 1 mmol) and isopropyl amine (100 \(\mu\text{L}, 1\) mmol). Purified by flash chromatography, eluting in gradient from 100\% hexanes to 30\% EtOAc in hexanes to isolate 20 as a pale-yellow oil (136.2 mg, 83\%).

Spectral data for this compound were consistent with those in the literature.\(^7\)
\[ \delta_H (400 \text{ MHz, CDCl}_3): \] 8.53 (1 H, d, J 4.7), 8.20 (1 H, d, J 7.8), 7.91-7.81 (1 H, m), 7.43-7.38 (1 H, m), 4.34-4.21 (1 H, m), 1.29 (6 H, d, J 6.6).

HRMS (\(m/z\) - APCI): Found: 165.1018 (M+H)+ \(C_9H_{13}N_2O\) Requires: 165.1022.

\(N,N\)-dipropylpicolinamide (25)

![N,N-dipropylpicolinamide (25)](image)

Prepared according to general procedure 1 using 2,2’-pyridil (212.2 mg, 1 mmol) and dipropyl amine (137 \(\mu\)L, 1 mmol). Purified by flash chromatography, eluting in gradient from 10:1 v/v to 1:1 v/v, \(\text{CH}_2\text{Cl}_2\) : EtOAc to isolate 25 as a pale yellow oil (135.0 mg, 65%).

\[ \delta_H (400 \text{ MHz, CDCl}_3): \] 8.59 (1 H, d, J 4.8), 7.78 (1 H, td, J 7.7, 1.7), 7.57 (1 H, d, J 7.7), 7.34-7.30 (1 H, m), 3.49 (2 H, t, J 7.6), 3.33 (2 H, t, J 7.6), 1.74 (2 H, app. sextet), 1.58 (2 H, app. sextet), 1.00 (3 H, t, J 7.4), 0.75 (3 H, t, J 7.4).

\[ \delta_C (100 \text{ MHz, CDCl}_3): \] 169.0 (C=O), 155.4 (q), 148.3, 136.8, 124.0, 123.2, 50.4, 47.4, 22.1, 20.8, 11.5, 11.1.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 2964, 2933, 2875, 1628 (C=O), 1484, 1458, 1437, 1114, 809, 748, 618.

HRMS (\(m/z\) - ESI): Found: 207.1484 (M+H)+ \(C_{12}H_{19}N_2O\) Requires: 207.1492.

\(N\)-cinnamylpicolinamide (17)

![\(N\)-cinnamylpicolinamide (17)](image)

Prepared according to general procedure 1 using 2,2’-pyridil (212.2 mg, 1 mmol) and \((E)\)-3-phenylprop-2-en-1-amine (83, 159.7 mg, 1 mmol). Purified by flash chromatography, eluting
in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate 17 as a colourless oil (237.3 mg, 99%).

δ_H (400 MHz, CDCl₃): 8.58 (1 H, d, J 4.8), 8.25 (1 H, d, J 7.7), 7.89 (1 H, app. td, J 7.7, 1.7), 7.45 (1 H, ddd, J 7.7, 4.8, 1.7), 7.42-7.36 (2 H, m), 7.36-7.30 (2 H, m), 7.28-7.23 (1 H, m), 6.64 (1 H, d, J 15.8), 6.33 (1 H, dt J 15.8, 6.2), 4.30 (2 H, td, J 6.2, 1.5).

δ_C (100 MHz, CDCl₃): 164.2 (C=O), 149.8 (q), 148.1, 137.4, 136.6 (q), 132.2, 128.6, 127.7, 126.4, 126.3, 125.4, 122.4, 41.5.

ν_max (neat)/cm⁻¹: 3384, 3057, 3026, 2921, 1668 (C=O), 1515, 1434, 1161, 964, 745, 692, 620.


_N-allylpicolinamide (16)_

![N-allylpicolinamide (16)](image)

Prepared according to general procedure 1 using 2,2’-pyridil (212.3 mg, 1 mmol) and allyl amine (75 µL, 1 mmol). Purified by flash chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate 16 as a brown oil (136.2 mg, 83%).

Spectral data for this compound were consistent with those in the literature.⁸

δ_H (400 MHz, CDCl₃): 8.55 (1 H, d, J 4.8), 8.20 (1 H, d, J 7.7), 8.14 (1 H, br. s), 7.86 (1 H, app. td, J 7.7, 1.7), 7.42 (1 H, ddd, J 7.7, 4.8, 1.7), 5.95 (1H, ddd, J 17.1, 10.3, 5.5), 5.31-5.24 (1 H, m), 5.20-5.15 (1 H, m), 4.14-4.08 (2 H, m).

**N-(prop-2-yn-1-yl)picolinamide (18)**

![Image of N-(prop-2-yn-1-yl)picolinamide](image)

Prepared according to general procedure 1 using 2,2’-pyridil (212.2 mg, 1 mmol) and propargyl amine (64 µL, 1 mmol). Purified by flash chromatography, eluting in gradient from 100% hexanes to 10:1 v/v hexanes:EtOAc to isolate 18 as an off-white solid (127.1 mg, 79%).

Spectral data for this compound were consistent with those in the literature.\(^9\)

\[\delta_H\] (400 MHz, CDCl\(_3\)): 8.55 (1 H, d, \(J\) 4.7), 8.27-8.16 (2 H, m), 7.87-7.81 (1 H, m), 7.45-7.40 (1 H, m), 4.26 (2 H, dd, \(J\) 5.6, 2.4), 2.26 (1H, t, \(J\) 2.4).

HRMS (m/z - APCI): Found: 161.0712 (M+H)\(^+\) C\(_9\)H\(_9\)N\(_2\)O Requires: 161.0709.

**1-picolinoylpiperidine-4-carbonitrile (24)**

![Image of 1-picolinoylpiperidine-4-carbonitrile](image)

Prepared according to general procedure 1 using 2,2’-pyridil (212.2 mg, 1 mmol) and piperidine-4-carbonitrile (112 µL, 1 mmol). Purified by flash chromatography, eluting in gradient from 1% MeOH to 10% MeOH in CH\(_2\)Cl\(_2\) to isolate 24 as a colourless oil (147.3 mg, 68%).

\[\delta_H\] (400 MHz, CDCl\(_3\)): 8.55 (1 H, d, \(J\) 4.8), 7.82 (1 H, td, \(J\) 7.7, 1.7), 7.67 (1 H, d, \(J\) 7.7), 7.37 (1H, dd, \(J\) 7.7, 4.8), 4.04-3.95 (1 H, m), 3.84-3.74 (2 H, m), 3.62-3.53 (1 H, m), 2.99-2.94 (1 H, m), 2.10-1.88 (4 H, m).

\[\delta_C\] (100 MHz, CDCl\(_3\)): 167.5 (C=O), 153.7 (q), 148.3, 137.2, 124.8, 124.0, 120.9 (CN), 45.3, 40.5, 29.1, 28.3, 26.5.
\( \nu_{\text{max}} \text{ (neat)/cm}^{-1}: \) 2962, 2925, 2236 (CN), 1639 (C=O), 1577, 1308, 1047, 806, 760, 719, 655, 618.

HRMS (m/z - ESI): Found: 216.1129 (M+H)+ \text{C}_{12}\text{H}_{14}\text{N}_{3}\text{O} Requires: 216.1131.

\textit{N-benzylpicolinamide (15)}

Prepared according to general procedure 1 using 2,2'-pyridil (212.2 mg, 1 mmol) and benzylamine (110 \( \mu \text{L}, \) 1 mmol). Purified by flash chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate 15 as a pale yellow solid (194.0 mg, 91%). M.p. 86-89 °C (lit.,\textsuperscript{10} M.p. 85-87 °C).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{10}

\( \delta_H \) (400 MHz, CDCl\textsubscript{3}): 8.53 (1 H, d, \( J \) 4.6), 8.38 (1 H, br. s), 8.24 (1 H, d, \( J \) 7.8), 7.86 (1 H, td, \( J \) 7.8, 1.6), 7.45-7.41 (1 H, m), 7.40-7.32 (4H, m), 7.31-7.28 (1 H, m), 4.68 (2 H, d, \( J \) 6.1).

\textit{N-(1-phenylethyl)picolinamide (21)}

Prepared according to general procedure 1 using 2,2'-pyridil (212.3 mg, 1 mmol) and \( \alpha \)-methyl benzylamine (129 \( \mu \text{L}, \) 1 mmol). Purified by flash chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate 21 as a white solid (183.0 mg, 81%).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{11}

\( \delta_H \) (400 MHz, CDCl\textsubscript{3}): 8.54 (1 H, d, \( J \) 4.4), 8.33 (1 H, br. s), 8.20 (1 H, d, \( J \) 7.7), 7.84 (1 H, td, \( J \) 7.7, 1.7), 7.45-7.28 (6 H, m), 5.37-5.28 (1 H, m), 1.63 (3 H, d, \( J \) 6.9).
HRMS (m/z - APCI): Found: 227.1172 (M+H)⁺ C₁₄H₁₅NO Requires: 227.1179.

*N-benzyl-N-methylpicolinamide (26)*

**Prepared according to general procedure 1 using 2,2’-pyridil (212.1 mg, 1 mmol) and methyl benzylamine (130 µL, 1 mmol). Purified by flash chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate 26 as a colourless oil (150.2 mg, 66%).**

Spectral data for this compound were consistent with those in the literature.¹²

*An apparent degenerate mix of rotamers is observed in the ¹H spectrum of this compound.*

δH (400 MHz, DMSO-d₆): Rotamer (a): 8.61-8.53 (1 H, m), 7.95-7.86 (1 H, m), 7.62-7.57 (1 H, m), 7.50-7.42 (1 H, m), 7.40-7.20 (5 H, m), 4.68 (2 H, s), 2.87 (3 H, s).

Rotamer (b): 8.61-8.53 (1 H, m), 7.95-7.86 (1 H, m), 7.62-7.57 (1 H, m), 7.50-7.42 (1 H, m), 7.40-7.20 (5 H, m), 4.54 (2 H, s), 2.83 (3 H, s).


**5. Table 2: Experimental data**

**General procedure 2: Substrate evaluation in the NHC-catalysed oxidative amidation between 2,2’-pyridil and various diamines (Table 2).**

An oven dried 10 mL round-bottomed flask, equipped with a magnetic stirring bar was evacuated under high vacuum and put under an atmosphere of argon repeatedly. The flask was fitted with a septum seal and argon-filled balloon. 2,2’-pyridil, phenazine (180.2 mg, 1 mmol) and catalyst 3 (35.9 mg, 15 mol%, 0.15 mmol), were charged to the flask sequentially. The flask was again evacuated and put under an atmosphere of argon repeatedly. The flask was re-fitted with a septum seal and argon-filled balloon. THF (0.4 M) was charged to the
flask followed sequentially by freshly distilled DBU (165 µL, 1.1 mmol) and the relevant freshly distilled amine (1 mmol) in rapid succession. The reaction was stirred at room temperature for 24 h. The residue obtained was purified by flash column chromatography to furnish the desired product.

*N-(piperidin-2-ylmethyl)picolinamide (30)*

Prepared according to general procedure 2 using 2,2'-pyridil (106.1 mg, 0.5 mmol) and 2-(aminomethyl)piperidine (29, 146 µL, 1.0 mmol). Purified by flash chromatography, eluting in 96:3:1 CH₂Cl₂:MeOH:NEt₃ to isolate 30 as an orange oil (206.8 mg, 94%).

δ<sub>H</sub> (400 MHz, CDCl₃): 8.53 (1 H, d, J 4.4), 8.45 (1 H, br. s), 8.16 (1 H, d, J 7.7), 7.83 (1 H, t, J 7.7), 7.44-7.38 (1 H, m), 4.08 (1 H, br. s), 3.67-3.57 (1 H, m), 3.56-3.46 (1 H, m), 3.24 (1 H, d, J 12.1), 3.07-2.98 (1 H, m), 2.73 (1 H, td, J 12.0, 2.0), 1.93-1.76 (2 H, m), 1.74-1.64 (1 H, m), 1.63-1.32 (3 H, m).

δ<sub>C</sub> (100 MHz, CDCl₃): 165.1 (C=O), 149.7 (q), 148.1, 137.4, 126.2, 122.3, 56.4, 46.3, 44.7, 29.6, 25.4, 23.8.

ν<sub>max</sub> (neat)/cm<sup>-1</sup>: 3346, 2929, 2796, 1655 (C=O), 1589, 1568, 1528, 1434, 1222, 1087, 1054, 746, 670, 618, 579.

HRMS (m/z - ESI): Found: 220.1444 (M+H)<sup>+</sup> C₁₂H₁₈N₃O Requires: 220.1444.

*N-(3-(methylamino)propyl)picolinamide (32)*

Prepared according to general procedure 2 using 2,2'-pyridil (212.2 mg, 1.0 mmol) and N-methyl-1,3-propanediamine (31, 104 µL, 1.0 mmol). Purified by flash chromatography, eluting in 96:3:1 CH₂Cl₂:MeOH:NEt₃ to isolate 32 as an orange oil (190.2 mg, 98%).
\( \delta_H (400 \text{ MHz, CDCl}_3): \) 8.55 (1 H, d, \( J \) 4.7), 8.39 (1 H, br. s), 8.20 (1 H, d, \( J \) 7.8), 7.85 (1 H, td, \( J \) 7.8, 1.7), 7.42 (1 H, ddd, \( J \) 7.8, 4.7, 1.7), 3.58 (2 H, q, \( J \) 6.4), 3.29 (2 H, br. s), 2.79 (2 H, t, \( J \) 6.4), 2.51 (3 H, s), 1.90 (2 H, quin., \( J \) 6.4).

\( \delta_C (100 \text{ MHz, CDCl}_3): \) 164.6 (C=O), 150.0 (q), 148.1, 137.3, 126.1, 122.2, 49.1, 37.5, 35.9, 29.1.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}'): \) 3313, 3058, 2936, 1656 (C=O), 1589, 1568, 1568, 1524, 134, 1378, 1288, 1167, 1147, 1088, 997, 821, 749, 692, 619.

HRMS (\( m/z \) - ESI): Found: 194.1296 (M+H)\(^+\) \( C_{10}H_{16}N_3O \) Requires: 194.1288.

**N-(2-aminopropyl)picolinamide (33)**

\[
\text{\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{O} \\
\text{NH}_2 \\
\end{array}}
\]

Prepared according to general procedure 2 using 2,2'-pyridil (106.1 mg, 1.0 mmol) and 1,2-diaminopropane (8, 100 \( \mu \)L, 1.0 mmol). Purified by flash chromatography, eluting in 96:3:1 CH\(_2\)Cl\(_2\)::MeOH:NEt\(_3\) to isolate 33 as an orange oil (190.2 mg, 98%).

\( \delta_H (400 \text{ MHz, CDCl}_3): \) 8.58 (1 H, d, \( J \) 4.6), 8.39 (1 H, br. s), 8.21 (1 H, d, \( J \) 7.7), 7.88 (1 H, app. td, \( J \) 7.7, 1.7), 7.44 (1 H, ddd, \( J \) 7.7, 4.6, 1.7), 3.57-3.49 (1 H, m), 3.45-3.25 (1 H, m), 3.25-3.15 (1 H, m), 1.46 (2 H, br. s), 1.19 (3 H, d, \( J \) 6.3).

\( \delta_C (100 \text{ MHz, CDCl}_3): \) 164.6 (C=O), 150.0 (q), 148.1, 137.3, 126.1, 122.3, 47.4, 46.9, 21.8.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}'): \) 3302, 3058, 2971, 2931, 1656 (C=O), 1589, 1569, 1522, 1464, 1434, 1381, 1289, 1145, 1089, 997, 821, 748, 691, 620.

HRMS (\( m/z \) - ESI): Found: 180.1136 (M+H)\(^+\) \( C_{9}H_{14}N_3O \) Requires: 180.1131.
**N-(3-(isopropylamino)propyl)-N-methylpicolinamide (37)**

![Chemical Structure](image)

Prepared according to general procedure 2 using 2,2'-pyridil (212.2 mg, 1.0 mmol) and 36 (157.9 mg, 1.0 mmol). Purified by flash chromatography, eluting in 96:3:1 CH$_2$Cl$_2$:MeOH:NEt$_3$ to isolate 37 as an orange oil (215.5 mg, 92%).

*An apparent degenerate mix of rotamers is observed in the $^1$H and $^{13}$C NMR spectra of this compound.*

δ$_H$ (400 MHz, CDCl$_3$): Rotamer (a): 8.59 (1 H, dd, $J$ 7.7, 4.8), 7.80 (1 H, td, $J$ 7.7, 1.6), 7.66-7.59 (1 H, m), 7.36-7.32 (1 H, m), 3.65 (2 H, t, $J$ 7.0), 3.13 (3 H, s), 2.83 (1 H, q, $J$ 6.3), 2.76-2.69 (2 H, m), 1.90 (2 H, quin., $J$ 6.3), 1.09 (6 H, d, $J$ 6.3).

Rotamer (b): 8.59 (1 H, dd, $J$ 7.7, 4.8), 7.80 (1 H, td, $J$ 7.7, 1.6), 7.66-7.59 (1 H, m), 7.36-7.32 (1 H, m), 3.51 (2 H, t, $J$ 7.2), 3.06 (3 H, s), 2.76-2.69 (1 H, m), 2.51 (2 H, q, $J$ 6.9), 1.82 (2 H, quin., $J$ 7.2), 1.00 (6 H, d, $J$ 6.2).

δ$_C$ (100 MHz, CDCl$_3$): Rotamer (a): 169.1 (C=O), 154.8 (q), 148.3, 137.0, 124.3, 123.7, 48.8, 45.8, 44.3, 33.4, 27.5, 22.9.

Rotamer (b): 168.9 (C=O), 154.7 (q), 148.1, 136.9, 124.2, 123.4, 48.9, 48.6, 44.2, 36.9, 29.0, 22.8.

ν$_{max}$ (neat)/cm$^{-1}$: 3413, 2964, 1624 (C=O), 1588, 1566, 1496, 1452, 1426, 1404, 1382, 1315, 1174, 1086, 751, 711, 674, 651, 618, 569.

HRMS ($m$/z - ESI): Found: 236.1757 (M+H)$^+$ C$_{13}$H$_{22}$N$_3$O Requires: 236.1757.
N-(3-(isopropylamino)propyl)-N-methylpicolinamide (38)

Prepared according to general procedure 2 using 2,2'-pyridil (212.2 mg, 1 mmol) and 39 (130.4 mg, 1.0 mmol). Purified by flash chromatography, eluting in gradient from 100:1:1 to 90:10:1 CH₂Cl₂:MeOH:NEt₃ to isolate 40 as an pale yellow oil (208.4 mg, 94%).

*An apparent degenerate mix of rotamers is observed in the ¹H and ¹³C NMR spectra of this compound.

δ_H (400 MHz, CDCl₃): Rotamer (a): 8.53-8.47 (1 H, m), 7.75-7.68 (1 H, m), 7.57-7.49 (1 H, m), 7.29-7.23 (1 H, m), 3.57 (2 H, t, J 7.1), 3.04 (3 H, s), 2.69-2.56 (4 H, m), 1.87-1.78 (2 H, m), 1.51 (1 H, br. s), 1.05 (3 H, t, J 7.1).

Rotamer (b): 8.53-8.47 (1 H, m), 7.75-7.68 (1 H, m), 7.57-7.49 (1 H, m), 7.29-7.23 (1 H, m), 3.41 (2 H, t, J 7.1), 2.97 (3 H, s), 2.54-2.40 (4 H, m), 1.78-1.70 (2 H, m), 1.51 (1 H, br. s), 0.97 (3 H, t, J 7.1).

δ_C (100 MHz, CDCl₃): Rotamer (a): 169.0 (C=O), 154.7 (q), 148.2, 136.9, 124.2, 123.5, 48.9, 46.7, 44.1, 36.8, 28.6, 15.2.

Rotamer (b): 168.8 (C=O), 154.6 (q), 148.1, 136.9, 124.2, 123.3, 46.5, 45.7, 44.0, 33.3, 27.3, 15.2.

ν_max (neat)/cm⁻¹: 3432, 2935, 1622 (C=O), 1587, 1566, 1492, 1454, 1424, 1405, 1302, 1083, 1045, 994, 808, 750, 651, 618.

HRMS (m/z - ESI): Found: 222.1601 (M+H)⁺ C₁₂H₂₀N₃O Requires: 222.1601.
**N-((1R,2R)-2-aminocyclohexyl)picolinamide (35)**

![N-((1R,2R)-2-aminocyclohexyl)picolinamide (35)](image)

Prepared according to general procedure 2 using 2,2'-pyridil (160.0 mg, 0.5 mmol) and (1R,2R)-cyclohexane-1,2-diamine (34, 137.0 mg, 1.0 mmol). Purified by flash chromatography, eluting in gradient from 100:1:1 to 97:3:1 CH₂Cl₂:MeOH:NEt₃ to isolate 35 as an orange oil (169.1 mg, 77%).

δ_H (400 MHz, CDCl₃): 8.58 (1 H, d, J 4.7), 8.23 (1 H, d, J 7.7), 7.99 (1 H, d, J 7.7), 7.88 (1 H, app. td, J 7.7, 1.2), 7.45 (1 H, ddd, J 7.7, 4.7, 1.2), 3.78-3.71 (1 H, m), 2.58 (1 H, td, J 10.7, 4.1), 2.10-2.03 (2 H, m), 1.83-1.77 (2 H, m), 1.58 (2 H, br. s), 1.47-1.24 (4 H, m).

δ_C (100 MHz, CDCl₃): 164.5 (C=O), 150.0 (q), 148.0, 137.4, 126.2, 122.4, 56.4, 55.7, 35.3, 32.5, 25.2, 25.1.

ν_max (neat)/cm⁻¹: 3266, 2923, 2851, 1650 (C=O), 1535, 1447, 956, 925, 851, 820, 755, 681, 618, 587.


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**6. Protection of secondary amides using di-tert-butyl dicarbonate**

*tert*-butyl benzyl(picolinoyl)carbamate (46)

![tert*-butyl benzyl(picolinoyl)carbamate (46)](image)

To a 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged N-benzylpicolinamide (15, 0.196 g, 0.922 mmol), DMAP (0.0563 g, 0.461 mmol), NEt₃ (0.2 mL, 1.38 mmol) and CH₃CN (0.92 mL). The flask was placed under an atmosphere of argon using an argon filled balloon and septum. To the flask di-tert-butyl dicarbonate (0.391 g, 1.83
mmol) was added and the flask was equipped with a reflux condenser. The reaction mixture was heated to reflux and allowed to stir until complete consumption of the starting material was detected by TLC analysis of the crude reaction mixture. At the end of the reaction, the solvent was removed in vacuo and the product was purified via flash column chromatography, eluting in gradient from 100% hexanes to 7:3 v/v hexanes:EtOAc to isolate 46 as a colourless oil (0.267 g, 93%).

$$\delta_H (400 \text{ MHz}, \text{CDCl}_3): \quad 8.61 \ (1 \ H, \ d, J 4.8), \ 7.83 \ (1 \ H, \ \text{app. td}, J 7.8, 1.6), \ 7.72 \ (1 \ H, \ d, J 7.8), \ 7.48 \ (2 \ H, \ d, J 7.3), \ 7.44-7.39 \ (1 \ H, \ m), \ 7.35 \ (2 \ H, \ t, J 7.3), \ 7.31-7.25 \ (1 \ H, \ m), \ 5.05 \ (2H, \ s), \ 1.17 \ (9 \ H, \ s).$$

$$\delta_C (100 \text{ MHz}, \text{CDCl}_3): \quad 171.4 \ (\text{C}=\text{O}), \ 154.5 \ (\text{C}=\text{O}) \ 153.2 \ (\text{q}), \ 148.1, \ 137.5 \ (\text{q}), \ 136.9, \ 128.4, \ 127.9, \ 127.3, \ 125.2, \ 122.9, \ 83.2 \ (\text{q}), \ 48.8, \ 27.3.$$

$$\nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: \quad 2927, \ 2853, \ 2119, \ 1733 \ (\text{C}=\text{O}), \ 1684 \ (\text{C}=\text{O}), \ 1497, \ 1439, \ 1416 \ 1380, \ 1343, \ 1256, \ 1233, \ 1173, \ 1146, \ 996, \ 985, \ 845, \ 747, \ 736, \ 624.$$

HRMS ($m/z$ - ESI): Found: 335.1376 (M+Na)$^+$ C$_{18}$H$_{20}$N$_2$NaO$_3$ Requires: 335.1366.

**tert-butyl (3-((tert-butoxycarbonyl)(methyl)amino)propyl)(picolinoyl)carbamate (48)**

![Chemical structure](image)

To a 5 mL round-bottomed flask equipped with a magnetic stirring bar was charged N-(3-(methylamino)propyl)picolinamide (32, 0.033 g, 0.171 mmol), DMAP (0.042 g, 0.342 mmol), NEt$_3$ (0.24 mL, 1.71 mmol) and THF (0.7 mL). The flask was placed under an atmosphere of argon using an argon filled balloon and septum. To the flask di-tert-butyl dicarbonate (0.448 g, 2.05 mmol) was added and the flask was equipped with a reflux condenser. The reaction mixture was heated to reflux and allowed to stir until complete consumption of the starting material was detected by TLC analysis of the crude reaction mixture. At the end of the reaction, the solvent was removed in vacuo and the product was
purified via flash column chromatography, eluting in 1:1 v/v hexanes:EtOAc to isolate 48 as a colourless oil (0.061 g, 93%).

$$\delta_H (400 \text{ MHz, CDCl}_3):$$ 8.58 (1 H, d, $J = 4.7$), 7.82 (1 H, td, $J = 7.8, 1.6$), 7.67 (1 H, d, $J = 7.8$), 7.43-7.37 (1 H, m), 3.85 (2 H, t, $J = 7.5$), 3.41-3.29 (2 H, m), 2.89 (3 H, s), 1.95 (2 H, quint., $J = 7.4$), 1.47 (9 H, s), 1.20 (9 H, s).

$$\delta_C (100 \text{ MHz, CDCl}_3):$$ 171.5 (C=O), 155.7 (C=O), 154.8 (C=O), 153.1 (q), 148.1, 136.9, 125.2, 122.7, 83.0 (q), 79.3 (q), 46.8, 43.4, 34.0, 28.5, 27.4, 27.1.

$$\nu_{\text{max}} (\text{neat})/\text{cm}^{-1}:$$ 2977, 2932, 1736 (C=O), 1687 (C=O), 1671 (C=O), 1479, 1431, 1392, 1365, 1289, 1141, 1059, 995, 871, 858, 772, 748, 669, 619.

HRMS ($m/z$ - ESI): Found: 416.2156 (M+Na)$^+$ C$_{20}$H$_{31}$N$_3$NaO$_5$ Requires: 416.2156.

**Other conditions for Boc-protection of 15 and 32**

*Note:* The protection of 15 and 32 to render 48 and 50 respectively can be carried out with varying solvents, temperatures, equivalents of (Boc)$_2$O and reaction times. While the reaction conditions in this communication utilise relatively large equivalents of (Boc)$_2$O and elevated temperatures, it is possible to carry out this protection using milder conditions albeit with longer reaction times and possible with reduced yields. These conditions are shown below.

- (Boc)$_2$O (2 equiv.), reflux, CH$_3$CN, 9 h, 43% conversion by $^1$H NMR spectroscopy (using $p$-iodoanisole as the internal standard).
- Additional (Boc)$_2$O (2 equiv.), reflux, CH$_3$CN, 18 h, 93% isolated yield.
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<th>temperature (°C)</th>
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<th>Time (h)</th>
<th>yield (*) (%)</th>
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<td>60</td>
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</table>

*aConversion determined by $^1$H NMR spectroscopy using $p$-iodoanisole as the internal standard. *bIsolated yield determined after flash column chromatography.

*Note: Alternatively, BocCl can be used to carry out this transformation.
7. Reductive cleavage of \(N\)-substituted pyridoyl amides

**General procedure 3: Reductive cleavage of \(N\)-substituted pyridoyl amides using NaBH\(_4\)**

To an oven dried 10 mL round-bottomed flask, equipped with a magnetic stirring bar was charged the appropriate \(N\)-substituted pyridoyl amide (1 equiv.) and EtOH (0.12 M). NaBH\(_4\) (2 equiv.) was charged to the flask in one portion and the reaction mixture was stirred at room temperature for 2 h after which time the reaction mixture was diluted with acetone (1 mL) and stirred for a further 1 h. The crude mixture was concentrated *in vacuo* and the resulting residue dissolved in Et\(_2\)O (10 mL). The organic layer was washed sequentially with KHSO\(_4\) (1 M, 3 x 5 mL), a saturated sodium hydrogen carbonate solution (3 x 5 mL) and brine (3 x 5 mL). The organic layer was dried over anhydrous MgSO\(_4\) and concentrated under reduced pressure to provide the boc-protected amine which requires no further purification.

**tert-butyl benzyl(methyl)carbamate (47)**

Prepared according to general procedure 3 using tert-butyl benzyl(picolinoyl)carbamate (46, 110.0 mg, 0.352 mmol), NaBH\(_4\) (28.5 mg, 0.704 mmol) and EtOH (2.8 mL) to isolate 47 as a colourless oil (65.5 mg, 90%).

Spectral data for this compound were consistent with those in the literature.\(^{13}\)

\[\delta_H (400 MHz, CDCl_3): \quad 7.63-7.23 (5 H, m), 4.82 (1 H, br. s), 4.32 (2 H, d, J 5.0), 1.46 (9 H, s).\]
HRMS (m/z - ESI): Found: 230.1152 (M+Na)\(^+\) C\(_{12}\)H\(_{17}\)N\(_{3}\)NaO\(_{2}\) Requires: 230.1151.

**tert-butyl (3-((tert-butoxycarbonyl)amino)propyl)(methyl)carbamate (49)**

![Chemical Structure](image)

Prepared according to general procedure 3 using tert-butyl (3-((tert-butoxycarbonyl)(methyl)amino)propyl)(picolinoyl)carbamate (48, 83.8 mg, 0.221 mmol), NaBH\(_4\) (17.0 mg, 0.442 mmol) and EtOH (1.8 mL) to isolate 49 as a colourless oil (51.7 mg, 81%).

\(\delta_H (400\ \text{MHz, CDCl}_3):\) 3.27 (2 H, t, \(J\ 6.5\)), 3.13-3.05 (2 H, m), 2.82 (3 H, s), 1.71-1.59 (3 H, m), 1.46 (9 H, s), 1.44 (9 H, s).

\(\delta_C (100\ \text{MHz, CDCl}_3):\) 156.1 (C=O), 155.7 (C=O), 79.5 (q), 79.0 (q), 45.9, 45.3, 37.2, 34.0, 28.4.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3357 (NH), 2976, 2931, 1679 (C=O), 1509, 1454, 1365, 1307, 1248, 1152, 1084, 872, 772, 640, 592.

HRMS (m/z - ESI): Found: 311.1953 (M+Na)\(^+\) C\(_{14}\)H\(_{28}\)N\(_{2}\)NaO\(_{4}\) Requires: 311.1941.
8. Deprotection studies

**General procedure 4: Alkylation of secondary and tertiary amides.**

An oven dried 25 mL capacity sealed tube equipped with a magnetic stirring bar was charged with the appropriate amide (1.0 equiv.), 2-iodoethanol (1.5 equiv.) and acetonitrile (1.0 M). The flask was sealed and the reaction mixture was heated to 120 °C and stirred for 18 h after which time the contents of the sealed tube were cooled, concentrated and purified *via* and flash column chromatography.

**2-(benzyl(methyl)carbamoyl)-1-(2-hydroxyethyl)pyridin-1-ium iodide (S8)**

![Chemical structure of S8](attachment:image)

Prepared according to general procedure 4 using *N*-benzyl-*N*-methylpicolinamide (26, 191.0 mg, 0.844 mmol) and 2-iodoethanol (100 µL, 1.27 mmol). Purified by flash chromatography, eluting in gradient from 100% CH₂Cl₂ to 5% methanol in CH₂Cl₂ to isolate S8 as a pale-yellow oil (332.1 mg, 98%).

*A non-degenerate mix of rotamers is observed in the ¹H NMR and ¹³C spectra of this compound. The NMR spectra of this compound are recorded at 60°C for more defined resonance signals.*

δ_H (600 MHz, DMSO-d₆): Major rotamer. 9.12 (1 H, d, J 6.0), 8.74 (1 H, t, J 7.8), 8.33-8.19 (2 H, m), 7.47-7.30 (4 H, m), 7.30-7.25 (1 H, m), 5.28 (1 H, t, J 5.3), 4.77 (2 H, s), 4.70-4.58 (2 H, m), 3.95-3.83 (2 H, m), 2.88 (3 H, s).

Minor rotamer. 9.07 (1 H, d, J 6.0), 8.69 (1 H, t, J 7.9), 8.33-8.19 (2 H, m), 7.47-7.30 (4 H, m), 7.30-7.25 (1 H, m), 5.28 (1 H, t, J 5.3), 4.70-4.58 (2 H, m), 4.50 (2 H, s), 3.95-3.83 (2 H, m), 3.05 (3 H, s).

δ_C (100 MHz, DMSO-d₆): Major rotamer. 161.4 (C=O), 148.3 (q), 147.2, 136.2 (q), 129.4, 129.3, 128.6, 128.5, 128.2, 127.1, 61.5, 60.0, 50.7, 36.8.
Minor rotamer. 161.5 (C=O), 148.5 (q), 148.3, 147.2, 135.5 (q), 129.4, 128.4, 128.3, 127.9, 126.6, 61.4, 59.9, 54.2, 33.3.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3000 (OH), 3028, 2928, 1646 (C=O), 1617, 1581, 1492, 1451, 1409, 1263, 1073, 926, 739, 697, 609.

HRMS ($m/z$ - ESI): Found: 271.1448 (M)$^+$ \text{C}_{16}\text{H}_{19}\text{N}_{2}\text{O}_{2}$ Requires: 271.1441.

1-oxo-3,4-dihydro-$1H$-pyrido[2,1-$c$][1,4]oxazin-5-ium iodide (42)

Prepared according to general procedure 4. Upon complete conversion of 26 to S8, determined by analysis of $^1$H NMR spectra, CSA (0.392 g, 1.69 mmol, 2.2 equiv.) was added to the reaction mixture and the reaction was stirred for a further 2 h at 120 °C after which time the reaction mixture was cooled and filtered to obtain 42 as a pale yellow solid (278.8 mg, 68%).

$\delta$$_H$(600 MHz, DMSO-$d_6$): 9.20 (1 H, d, $J$ 5.8), 8.82 (1 H, app. t, $J$ 7.9), 8.69 (1 H, d, $J$ 7.9), 8.42 (1 H, app. t, $J$ 5.8), 5.07-5.02 (2 H, m), 4.98-4.94 (2 H, m).

$\delta$$_C$ (100 MHz, DMSO-$d_6$): 157.1 (C=O), 147.8, 145.7, 139.2 (q), 131.3, 129.7, 65.7, 52.6.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2987, 1744 (C=O), 1623 (C=O), 1399, 1282, 1137, 1040, 759, 669, 636.

HRMS ($m/z$ - ESI): Found: 150.0554 (M)$^+$ \text{C}_8\text{H}_8\text{NO}_2$ Requires: 150.0550.
2-((3-((tert-butoxycarbonyl)(ethyl)amino)propyl)(methyl)carbamoyl)-1-(2-hydroxyethyl)pyridin-1-ium iodide (44)

An oven dried 25 mL capacity sealed tube equipped with a magnetic stirring bar was charged with \(N\)-(3-(isopropylamino)propyl)-\(N\)-methylpicolinamide (38, 40.9 mg, 0.185 mmol), di-\(tert\)-butyl dicarbonate (69.9 mg, 0.277 mmol) and CH\(_3\)CN (0.2 mL). The flask was sealed and heated to 120 °C until complete protection of 40 was detected by \(^1\)H NMR spectroscopy using \(p\)-iodoanisole as an internal standard. Upon complete boc-protection of 38, 2-iodoethanol (22 \(\mu\)L, 0.277 mmol) was charged to the flask. The reaction mixture was heated to 120 °C and stirred for 12 hours after which time the contents of the sealed tube were concentrated and purified via flash column chromatography eluting in gradient from 100% CH\(_2\)Cl\(_2\) to 5% MeOH in CH\(_2\)Cl\(_2\) to isolate 44 as an orange oil (81.7 mg, 90%).

* A non-degenerate mix of rotamers is observed in the \(^1\)H NMR and \(^{13}\)C spectra of this compound at 25 °C, however when the \(^1\)H NMR spectrum of this compound was recorded at 80°C only the major rotamer was detected.

\[\delta_{\text{H}} (400 \text{ MHz, DMSO-\(d_6\))} 9.11 \text{ (1 H, app. d), 8.73 (1 H, t, } J 7.8), 8.30-8.20 (2 H, m), 5.22 (1 H, br. s), 4.74-4.56 (2 H, m), 3.98-3.83 (2 H, m), 3.54 (2 H, app. t), 3.31-3.18 (4 H, m), 2.94 (3 H, s), 1.94-1.77 (2 H, m), 1.44 (9 H, s), 1.13-1.04 (3 H, m).\]

\[\delta_{\text{C}} (100 \text{ MHz, DMSO-\(d_6\))}: \text{ Major rotamer: 160.9 (C=O), 160.7 (C=O), 148.8 (q), 148.0, 147.1, 126.9, 126.3, 79.7 (q), 61.4, 60.1, 46.2, 43.8, 42.0, 37.1, 28.6, 25.7, 13.6.}\]

\[\text{Major rotamer: 160.8 (C=O), 160.6 (C=O), 148.7 (q), 148.1, 147.2, 128.4, 126.6, 78.9 (q), 61.5, 59.9, 46.2, 46.1, 41.8, 34.3, 28.5, 26.9, 12.6.}\]
$$\nu_{\text{max}} \text{(neat)/cm}^{-1}: \quad 3334 \text{ (OH), 2974, 2932, 1648 (C=O), 1619, 1481, 1453, 1418, 1293, 1253, 1161, 1074, 963, 872, 775, 748.}$$

HRMS (m/z - ESI): Found: 366.2399 (M)$^+$ C$_{19}$H$_{32}$N$_3$O$_4$ Requires: 366.2387.

**Alkylation optimisation**

*Note*: This reaction was optimised using the less reactive electrophile, TBS-protected 2-iodoethanol. The optimal reaction conditions for this reaction were then employed in the alkylation of 26 with 2-iodoethanol. It is envisaged that using other solvents at lower temperatures will allow for 26 to be alkylated by 2-iodoethanol in high yields.

![Chemical structure](image)

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$^a$Conversion determined by $^1$H NMR spectroscopy using p-iodoanisole as the internal standard. $^b$Isolated yield determined after flash column chromatography.

*Note:* In order to develop a successful methodology for highly chemoselective amine protection and subsequent deprotection, a library of substituted-benzil derivates were synthesised and screened. However, 2,2-pyridil was found to achieve optimal results in this
reaction. Several other electrophiles were also screened in the alkylation of 2,2-pyridil, with 2-iodoethanol carrying out this transformation in the highest yields and shortest reaction times. The libraries of substituted-benzils and electrophiles are shown below.

**Library of substituted benzils screened**

![Substituted benzils](image1)

**Library of electrophiles screened**

![Electrophiles](image2)
9. NMR spectra

**tert-butyl (3(ethylamino)propyl)(methyl)carbamate**

**N**<sup>1</sup>-**ethyl-N**<sup>3</sup>-methylpropane-1,3-diamine
*tert*-butyl (3-(isopropylamino)propyl)(methyl)carbamate
$N^1$-isopropyl-$N^3$-methylpropane-1,3-diamine
$N,N$-dipropylpicolinamide
$N$-cinnamylpicolinamide
1-picolinoylpiperidine-4-carbonitrile
N-(piperidin-2-ylmethyl)picolinamide

\[
\begin{align*}
\text{N} & \quad \text{(piperidin-2-ylmethyl)picolinamide} \\
\end{align*}
\]
$N$-(3-(methylamino)propyl)picolinamide
$N$-(2-aminopropyl)picolinamide
$N$-(3-(isopropylamino)propyl)-$N$-methylpicolinamide
$N$-(3-(isopropylamino)propyl)-$N$-methylpicolinamide
$N\text{-}((1R,2R)\text{-}2\text{-}\text{aminocyclohexyl})\text{picolinamide}$
2-(benzyl(methyl)carbamoyl)-1-(2-hydroxyethyl)pyridin-1-ium iodide
2-((3-((tert-butoxycarbonyl)(ethyl)amino)propyl)(methyl)carbamoyl)-1-(2-hydroxyethyl)pyridin-1-ium iodide
1-oxo-3,4-dihydro-1H-pyrido[2,1-c][1,4]oxazin-5-ium iodide
tert-butyl benzyl(picolinoyl)carbamate
*tert*-butyl (3-((*tert*-*butoxycarbonyl*)(methyl)amino)propyl)(picolinoyl)carbamate
**tert-butyl (3-((tert-butoxycarbonyl)amino)propyl)(methyl)carbamate**

![Chemical Structure](image)

**NMR Spectrum**

![NMR Spectrum](image)
10. Proposed mechanism

Note: the acylation is carried out using pyridil, however the Breslow intermediate which is formed alongside the amide product can revert to pyridine-2-carboxaldehyde, which can take part in the acylation via benzoin condensation to pyridoin and oxidation to pyridil.

11. References


