

ENGINEERING CHEMISTRY: INTEGRATED CONTROL
STRATEGIES AND INTERNET-ENABLED TOOLS FOR
CHEMICAL SYNTHESIS

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This dissertation is submitted for the degree of Doctor of Philosophy

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Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

It does not exceed the word limit of 60,000 as prescribed by the Degree Committee for Physics and Chemistry, University of Cambridge.

Daniel E. Fitzpatrick

July 2017

Acknowledgements

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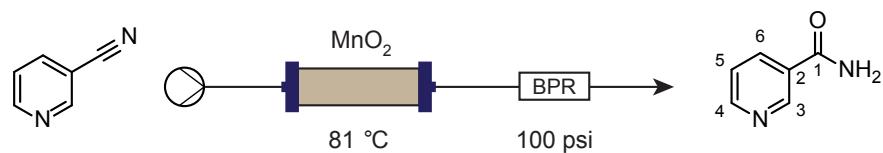
My PhD journey wouldn't have been possible without my colleagues in the Innovative Technology Centre (ITC). Drs Lucie Guetzoyan, Claudio Battilocchio, Nikzad Nikbin, Richard Ingham, Ricardo Labes and Robbie Mutton - thank you for patiently answering my endless questions in the lab. Particular thanks must go to Dr Ben Bhawal who was always happy to demonstrate experimental and workup procedures new to me. Helen, Jo and Jacqui thank you for keeping the group organised and on track. To Nick and Naomi, your efforts keeping the ITC and Whiffen labs in working order are very much appreciated.

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Chapter 1 – Development of a laboratory process control system

Pyridine-3-carboxamide (2)



A solution of 3-cyanopyridine (0.292 g, 2.80 mmol) in a 1:1 (*v/v*) water/isopropyl alcohol solvent mixture (0.28 M, 10 mL) was pumped at 0.194 mL min⁻¹ through an Omnifit column (\varnothing 10 mm, 100 mm length) heated to 81 °C. The column was packed with 2.0 g manganese dioxide, and small plugs of celite were placed at both ends of the column. Pressure was provided by a 100 psi back pressure regulator. Crude reaction mixture was concentrated under reduced pressure and purified over silica (DCM/MeOH gradient elution, 0 % for 1 CV, 0 – 10 % over 5 CV, 10 % for 20 CV) to afford the title compound (0.281 g, 2.30 mmol, 82 %) as a semi-transparent white solid.

M_p: 128 – 130 °C (H₂O) [literature: 128 – 130 °C (H₂O)];⁸⁰

IR (neat) ν/cm^{-1} : 3351 (m), 3145 (bm), 2507 (bw), 2159 (m), 2031 (m), 1976 (m), 1674 (s), 1613 (m), 1592 (m), 1574 (m), 1485 (m), 1421 (m), 1392 (s), 1339 (m), 1201 (m), 1124 (m), 1028 (s), 828 (m); 776 (m), 700 (s);

¹H NMR (600 MHz, DMSO-*d*₆) δ/ppm = 9.04 (s, 1H, H-3), 8.69 (d, *J* = 4.8 Hz, 1H, H-4), 8.21 (d, *J* = 7.9 Hz, 1H, H-6), 8.18 (bs, 1H, NH₂), 7.62 (bs, 1H, NH₂), 7.48 (dd, *J* = 7.9, 4.8 Hz, 1H, H-5);

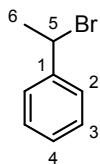
¹³C NMR (150 MHz, DMSO-*d*₆) δ/ppm = 166.51 (C-1), 151.90 (CH, C-4), 148.69 (CH, C-3), 135.16 (CH, C-6), 129.68 (C-2), 123.40 (CH, C-5);

HRMS *m/z* calc. for C₆H₇N₂O [M + H]⁺ 123.0558, found 123.0563, Δ = 4.1 ppm;

Microanalysis calc. (found) for C₆H₇N₂O C 59.01% (58.85%), N 22.94% (22.80%), H 4.95% (4.81%).

Recorded data were consistent with those reported previously.⁸⁰

1-Bromoethylbenzene (4)



The equipment layout for this flow procedure is shown in Figure 1.23a (pg. 45).

Solutions of tetrabromomethane (1.446 g, 4.36 mmol, 0.87 eq.) in acetonitrile (MeCN) (0.5 M, 8.72 mL), 1-phenylethanol (0.6 mL, 5.00 mmol) in MeCN (0.5 M, 10 mL) and triphenylphosphine (2.256 g, 8.6 mmol, 1.72 eq.) in MeCN (0.25 M, 34.4 mL) were prepared and connected to three HPLC pumps. These solutions were pumped at 0.337 mL min⁻¹, 0.388 mL min⁻¹ and 1.338 mL min⁻¹, respectively, through tee-junctions where they were mixed with 0.261 mL min⁻¹ of MeCN pumped by an HPLC pump. The combined stream flowed through a 10 mL reactor coil heated to 111 °C. System pressure was provided by a 100 psi back pressure regulator. Crude reaction mixture was concentrated under reduced pressure and purified over silica (hexane/ethyl acetate gradient elution, 0 % for 1 CV, 0 – 20 % over 10 CV, 20 % for 10 CV) to afford the title compound (0.562 g, 4.6 mmol, 92 %) as yellow/brown liquid.

IR (neat) ν/cm^{-1} : 2468 (bw), 2158 (m), 2033 (m), 1977 (m), 1494 (w), 1454 (m), 1376 (w), 1211 (m), 1178 (m), 1044 (m), 1025 (m), 963 (m), 911 (w), 760 (s), 693 (s);

¹H NMR (600 MHz, CDCl₃) δ/ppm = 7.45 (d, J = 7.2 Hz, 2H, H-2), 7.36 (t, J = 7.5 Hz, 2H, H-3), 7.30 (t, J = 7.2 Hz, 1H, H-4), 5.23 (q, J = 7.0 Hz, 1H, H-5), 2.06 (d, J = 7.0 Hz, 3H, H-6);

¹³C NMR (150 MHz, CDCl₃) δ/ppm = 143.19 (C-1), 128.63 (C-3), 128.30 (C-4), 126.76 (C-2), 49.53 (C-5), 26.79 (C-6);

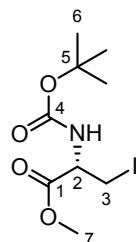
HRMS m/z calc. for C₈H₈Br [M - H]⁺ 182.9809, found 182.9806, Δ = -1.6 ppm;

Microanalysis calc. (found) for C₈H₉Br C 51.92% (51.94%), H 4.90% (4.86%), Br 43.18% (42.62%).

Recorded NMR data were consistent with those reported previously.³¹⁴

Chapter 2 – Synthesis of AZ82 & the integration of batch and flow techniques

Methyl (2*S*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (8)



Polymer supported triphenylphosphine (3.75 g, 2.0 mmol/g loading, 1.25 eq.) and imidazole (0.51 g, 7.5 mmol, 1.25 eq.) were added to DCM (40 mL). After the imidazole had completely dissolved, the mixture was cooled to 0 °C and iodine (1.90 g, 7.5 mmol, 1.25 eq.) was added slowly in three portions. The mixture was stirred at room temperature for 10 minutes before being cooled to 0 °C. Methyl (*tert*-butoxycarbonyl)-D-serinate (1.31 g, 6.0 mmol) was dissolved in DCM (10 mL) and added dropwise to the previous mixture which was left to stir for 1 hour at 0 °C then 1.5 hours at room temperature. The product mixture was filtered through a glass sinter before being purified over silica (hexane/ethyl acetate gradient elution, 0 – 25 % over 15 CV) to give the title compound (1.619 g, 4.92 mmol, 82 %) as a light yellow oil that solidified in the refrigerator.

LC-MS $t_R = 4.63$ min, m/z 170.28;

IR (neat) ν/cm^{-1} : 3349 (m), 2982 (w), 1732 (s), 1690 (s), 1522 (s), 1438 (m), 1394 (m), 1368 (m), 1314 (s), 1273 (s), 1249 (m), 1222 (s), 1206 (m), 1156 (s), 1141 (s), 1059 (s), 1010 (m), 980 (m), 863 (m), 791 (m);

$^1\text{H NMR}$ (600 MHz, CDCl_3) $\delta/\text{ppm} = 5.35$ (d, $J = 6.2$ Hz, 1H, NH), 4.38 – 4.57 (m, 1H, H-2), 3.79 (s, 3H, H-7), 3.53 – 3.59 (m, 2H, H-3), 1.45 (s, 9H, H-6);

$^{13}\text{C NMR}$ (150 MHz, CDCl_3) $\delta/\text{ppm} = 170.02$ (C-1), 154.80 (C-4), 80.47 (C-5), 53.65 (C-2), 52.98 (C-7), 28.25 (C-6), 7.83 (C-3);

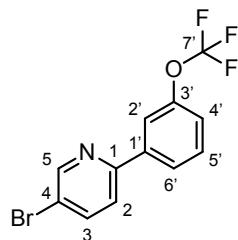
HRMS m/z calc. for $\text{C}_9\text{H}_{17}\text{INO}_4$ $[\text{M} + \text{H}]^+$ 330.0202, found 330.0192, $\Delta = -3.0$ ppm;

$[\alpha]_D^{28.0} = -41.5$ (c 1.0 in CHCl_3);

Microanalysis calc. (found) for $\text{C}_9\text{H}_{16}\text{INO}_4$ C 32.84% (32.84%), H 4.90% (4.82%), N 4.26% (4.14%).

Recorded NMR data were consistent with those reported previously.¹²⁹

5-Bromo-2-(3-(trifluoromethoxy)phenyl)pyridine (11)



5-Bromo-2-iodopyridine (0.142 g, 0.5 mmol), sodium carbonate (3.0 eq., 0.159 g), (3-(trifluoromethoxy)phenyl)boronic acid (1.0 eq., 0.103 g) and tetrakis(triphenylphosphine)palladium(0) (5 mol%, 0.029 g) were added to a 20 mL microwave vial containing ethanol (7 mL), distilled water (3 mL) and distilled toluene (5 mL). The resulting mixture was degassed by purging with nitrogen for 15 minutes before being heated to 70 °C under microwave irradiation for 20 minutes. Following extraction with ethyl acetate (3 x 50 mL), the organic phase was purified over silica (hexane/ethyl acetate gradient elution, 0 – 7 % over 15 CV, 7 % for 5 CV) to yield the title compound (0.128 g, 92 %) as a colourless oil which solidified in the refrigerator.

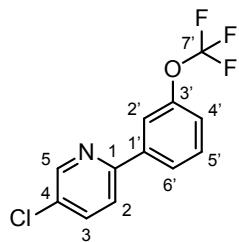
LC-MS $t_R = 5.43$ min, m/z 320.19 321.19 (1:1) ($[M + H]^+$);

IR (neat) ν/cm^{-1} : 1589 (w), 1571 (w), 1553 (w), 1457 (m), 1440 (w), 1362 (w), 1248 (s), 1213 (s), 1157 (s), 1097 (m), 1004 (m), 943 (w), 832 (m), 794 (m), 747 (m), 701 (m);

¹H NMR (600 MHz, CDCl₃) $\delta/\text{ppm} = 8.75$ (d, $J = 2.1$ Hz, 1H, H-5), 7.91 – 7.88 (m, 2H, C-3, H-6'), 7.78 (s, 1H, H-2'), 7.62 (d, $J = 8.5$ Hz, 1H, H-2), 7.50 (t, $J = 8.0$ Hz, 1H, H-5'), 7.28 (d, $J = 8.0$ Hz, 1H, H-4');

¹³C NMR (150 MHz, CDCl₃) $\delta/\text{ppm} = 154.15$ (C-1), 150.91 (C-5), 149.87 (C-3'), 140.30 (C-1'), 139.48 (C-3), 130.20 (C-5'), 124.91 (C-2), 121.61 (C-4'), 121.60 (C-6'), 120.08 (C-4), 120.47 (centre of quartet, C-7'), 119.41 (C-2');

HRMS m/z calc. for C₁₂H₈BrF₃NO [M + H]⁺ 317.9741, found 317.9750, $\Delta = 2.8$ ppm.

5-Chloro-2-(3-(trifluoromethoxy)phenyl)pyridine (23)

Prepared and isolated following the same procedure as for compound **11**, substituting 2-bromo-5-chloropyridine for 2,5-dibromopyridine. The title compound (0.135 g, 99 %) was collected as a light yellow/green oil.

LC-MS $t_R = 5.43$ min, m/z 274.29 276.27 (3:1) ($[M + H]^+$);

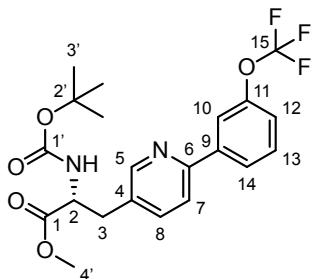
IR (neat) ν/cm^{-1} : 1576 (w), 1558 (w), 1458 (m), 1442 (w), 1372 (w), 1248 (s), 1213 (s), 1155 (s), 1113 (s), 1011 (m), 943 (w), 833 (m), 794 (m), 751 (m), 704 (m);

¹H NMR (400 MHz, CDCl_3) $\delta/\text{ppm} = 8.65$ (d, $J = 2.3$ Hz, 1H, H-5), 7.87 – 7.89 (m, 2H, H-2', H-6'), 7.75 (dd, $J = 8.5, 2.3$ Hz, 1H, H-3), 7.67 (d, $J = 8.5$ Hz, 1H, H-2), 7.49 (t, $J = 8.0$ Hz, 1H, H-5'), 7.28 (d, $J = 8.0$ Hz, 1H, H-4');

¹³C NMR (100 MHz, CDCl_3) $\delta/\text{ppm} = 153.79$ (C-1), 149.85 (C-3'), 148.70 (C-5), 136.60 (C-1'), 131.36 (C-3), 130.17 (C-4), 124.94 (C-5'), 121.52 (C-2 or C-6'), 121.51 (C-2 or C-6'), 121.09 (C-2'), 119.45 (C-4'), 120.52 (centre of quartet, C-7');

HRMS m/z calc. for $\text{C}_{12}\text{H}_8\text{ClF}_3\text{NO}$ $[M + H]^+$ 274.0168, found 274.0177, $\Delta = 3.3$ ppm.

Methyl (2*R*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-(trifluoromethoxy)phenyl)pyridin-3-yl)propanoate (12)



To a stirred mixture of zinc dust (1.51 g, 10 mmol, 4.0 eq.) cleaned according to the procedure described by Newman and Evans¹⁴⁰ and anhydrous DMF (10 mL) under nitrogen was added iodine (45 mg). Alkyl halide **8** (0.823 g, 2.5 mmol) was dissolved in anhydrous DMF (10 mL) and added dropwise to this mixture. Tris(dibenzylideneacetone)dipalladium(0) (69 mg, 3 mol%), tri(*o*-tolyl)phosphine (68 mg, 9 mol%) and aryl bromide **11** (0.795 g, 2.5 mmol, 1.0 eq.) were added and the mixture was heated to 50 °C for 6 hours under nitrogen. After filtration through a pad of silica using ethyl acetate, volatiles within the product mixture were removed under reduced pressure. The residue was washed with water containing lithium chloride (5 wt.%, 150 mL) and extracted with ethyl acetate (3 x 100 mL). The organic phase was concentrated *in vacuo* and purified over silica (hexane/ethyl acetate gradient elution, 0 – 30 % over 20 CV, 30 - 50 % over 10 CV, 50 % for 8 CV) to afford the title compound (0.754 g, 68 %) as a brown oil.

LC-MS $t_R = 5.23$ min, m/z 385.30 ($[M - C_4H_9 + H]^+$);

IR (neat) ν/cm^{-1} : 2980 (bw), 1740 (m), 1713 (m), 1599 (w), 1564 (w), 1496 (w), 1471 (m), 1440 (w), 1367 (m), 1249 (s), 1216 (s), 1156 (s), 1049 (m), 1026 (m), 943 (w), 842 (m), 795 (m), 761 (m), 693 (m);

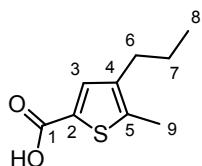
¹H NMR (600 MHz, CDCl₃) δ/ppm = 8.46 (s, 1H, H-5), 7.89 (d, J = 8.0 Hz, 1H, H-14), 7.87 (s, 1H, H-10), 7.66 (d, J = 8.1 Hz, 1H, H-7), 7.57 (dd, J = 8.1, 2.1 Hz, 1H, H-8), 7.48 (t, J = 8.0 Hz, 1H, H-13), 7.25 – 7.27 (m, 1H, H-12), 5.11 (bd, J = 7.5 Hz, 1H, NH), 4.65 (bd, J = 6.6 Hz, 1H, H-2), 3.75 (s, 3H, H-4'), 3.07 – 3.24 (bm, 2H, H-3), 1.42 (s, 9H, H-3');

¹³C NMR (150 MHz, CDCl₃) δ/ppm = 171.71 (C-1), 154.96 (C-1'), 154.51 (C-6), 150.51 (C-5), 149.78 (C-11), 141.11 (C-9), 137.76 (C-8), 130.94 (C-4), 130.03 (C-7), 124.95 (C-13), 121.18 (C-14), 120.45 (centre of quartet, C-15), 120.21 (C-10), 119.43 (C-12), 80.22 (C-2'), 54.07 (C-2), 52.49 (C-4'), 35.35 (C-3), 28.23 (C-3');

HRMS m/z calc. for $C_{21}H_{24}F_3N_2O_5$ $[M + H]^+$ 441.1637, found 441.1648, $\Delta = 2.5$ ppm;

$[\alpha]_D^{28.0} = -40.3$ (c 1.0 in $CHCl_3$);

5-Methyl-4-propylthiophene-2-carboxylic acid (16)



Batch procedure

Anhydrous dimethyl formamide (DMF) (1.0 mL, 13 mmol, 1.3 eq.) was mixed with anhydrous dichloromethane (DCM) (3.0 mL) in a 20 mL microwave vial under nitrogen and cooled to 0 °C before neat phosphorous oxychloride (0.935 mL, 10 mmol, 1.0 eq.) was added dropwise. The mixture was then allowed to warm to room temperature and left to stir for 30 minutes. Hexan-2-one (1.065 mL, 10 mmol) was combined with anhydrous DCM (3.0 mL) and added dropwise to the stirred mixture at room temperature. The resulting mixture was heated to 80 °C for 40 minutes under microwave irradiation, after which time the vial was left to cool to room temperature. Crude reaction mixture was transferred into a 50 mL round bottom flask held in an ice bath before an aqueous solution of sodium acetate (4.3 M, 10 mL) was added slowly. Having been stirred for 30 minutes, the product was extracted into DCM (3 x 10 mL) and the organic layers combined and dried over sodium sulfate. Solvent was then removed under reduced pressure and the resulting viscous oil carried forward into the next step without further purification.

Sodium (0.322 g, 14 mmol, 1.4 eq.) was added to ethanol (30 mL) and stirred vigorously until it was no longer visible. The stirred mixture was cooled to 0 °C before a solution of ethyl 2-mercaptoproacetate (1.42 mL, 13 mmol, 1.3 eq.) in tetrahydrofuran (THF) (5 mL) was added dropwise. The mixture was heated to reflux for 8 hours, after which time an aqueous solution of potassium hydroxide (KOH) (2.0 M, 20 mL) was added. Having been left to stir at reflux overnight, all solvent was removed from the reaction mixture under reduced pressure. Residues were dissolved in H₂O (40 mL) and stirred before concentrated hydrochloric acid (HCl) (37 %) was added dropwise until a very cloudy suspension formed. After extraction with ethyl acetate (3 x 20 mL), the combined organic layers were concentrated *in vacuo* and purified over silica (DCM/MeOH gradient elution, 0 % for 5 CV, 0 - 5 % over 10 CV, 0 - 7 % over 10 CV, 7 % for 5 CV) to afford the title compound (0.534 g, 29 %) as an off-white solid.

Integrated batch-flow procedure

The equipment layout for this procedure is shown in Figure 2.14 (pg. 71).

Neat phosphorous oxychloride (2.24 mL, 24 mmol, 1.4 eq.) was added at 0.5 mL min^{-1} by syringe pump to a mixture of 2 mL anhydrous DMF in 10 mL anhydrous DCM at 0°C , and stirred vigorously in a 50 mL integrated batch flask. The mixture was allowed to warm to room temperature, then left to stir for 35 minutes. The product mixture was pumped at 0.5 mL min^{-1} through a tee-junction where it met a solution of 0.5 mL min^{-1} hexan-2-one (2.12 mL, 17.3 mmol) in DCM (12 mL), before passing through a 10 mL reactor coil held at 90°C . On exiting the coil, the product mixture met an aqueous solution of sodium acetate (4.3 M) pumped at 1.0 mL min^{-1} by an HPLC pump, and a dilution stream of DCM at 1.0 mL min^{-1} via an HPLC pump.

The resulting mixture passed through a length of tubing (2.5 mL, PTFE), before entering a gravity separation column. The organic layer was collected and stored in a reservoir, while the aqueous layer was discarded as waste. Organic solution stored in this column was removed at 1.0 mL min^{-1} using a peristaltic pump and mixed with an ethanol stream (1.0 mL min^{-1} , HPLC pump), before flowing into a distillation column, held at 90°C . Ethanol-enriched product mixture was removed from this column at 1.05 mL min^{-1} by peristaltic pump into a reservoir held above a 100 mL integrated batch vessel.

Sodium (0.7 g, 30.4 mmol, 1.75 eq.) was added to 30 mL ethanol at 0°C in a 100 mL integrated batch vessel, and left to stir until it had reacted completely (approx. 1 hour). Neat ethyl 2-mercaptoacetate (2.85 mL, 26 mmol, 1.5 eq.) was added at 0.5 mL min^{-1} by syringe pump before the solution was allowed to warm to room temperature and left to stir for 60 minutes. The ethanol-enriched mixture from the previous step was added dropwise (by gravity) before the reaction flask was heated to 90°C , and stirred vigorously under reflux for 2 hours. An aqueous solution of potassium hydroxide (2.0 M, 50 mL) was added dropwise (by gravity) and the resulting mixture left to stir for 4 hours.

All solvent was removed from the reaction mixture under reduced pressure. Residues were dissolved in H_2O (40 mL) and stirred before concentrated hydrochloric acid (HCl) (37 %) was added dropwise until a very cloudy suspension formed. After extraction with ethyl acetate ($3 \times 50 \text{ mL}$), the combined organic layers were concentrated *in vacuo* and purified over silica (DCM/MeOH gradient elution, 0 % for 5 CV, 0 - 5 % over 10 CV, 0 - 7 % over 10 CV, 7 % for 5 CV) to afford

the title compound (0.967 g, 5.25 mmol, 30 %) as an off-white solid.

M_p: 89 – 90 °C (CH₂Cl₂);

LC-MS $t_R = 4.62$ min, m/z 167.37;

IR (neat) ν/cm^{-1} : 2961 (m), 2928 (m), 2857 (w), 2524 (w), 1645 (s), 1522 (m), 1444 (s), 1374 (w), 1307 (s), 1273 (s), 1231 (m), 1199 (m), 1160 (m), 1121 (m), 1064 (m), 1049 (m), 944 (m), 894 (m), 866 (w), 843 (w), 785 (w), 760 (s), 716 (m), 645 (m);

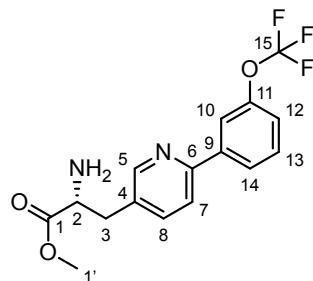
¹H NMR (600 MHz, DMSO-*d*₆) $\delta/\text{ppm} = 12.75$ (bs, 1H, OH), 7.46 (s, 1H, H-3), 2.45 (t, $J = 7.4$ Hz, 2H, H-6), 2.35 (s, 3H, H-9), 1.52 (sextet, $J = 7.4$ Hz, 2H, H-7), 0.87 (s, $J = 7.4$ Hz, 3H, H-8);

¹³C NMR (150 MHz, DMSO-*d*₆) $\delta/\text{ppm} = 162.87$ (C-1), 140.84 (C-5), 139.35 (C-4), 134.82 (C-3), 129.34 (C-2), 29.36 (C-6), 22.92 (C-7), 13.58 (C-9), 13.15 (C-8);

HRMS m/z calc. for C₉H₁₃O₂S [M + H]⁺ 185.0636, found 185.0639, $\Delta = 1.6$ ppm;

Microanalysis calc. (found) for C₉H₁₂O₂S C 58.67% (58.63%), H 6.56% (6.42%).

Methyl (2*R*)-2-amino-3-(6-(3-(trifluoromethoxy)phenyl)pyridin-3-yl)propanoate (13)



Boc-protected amine **12** (0.661 g, 1.50 mmol) was added to anhydrous DCM (10 mL) and cooled to 0 °C. Trifluoroacetic acid (TFA) (0.46 mL, 6.0 mmol, 4.0 eq.) was added dropwise to the solution after which time the mixture was allowed to warm to room temperature and left to stir for 60 minutes. Having removed solvent and excess TFA under reduced pressure, a saturated solution of sodium bicarbonate (20 mL) was added and the mixture stirred vigorously. Following extraction with DCM (5 x 10 mL), the organic layers were combined and dried over magnesium sulfate. Purification over silica (DCM/MeOH gradient elution, 0 % for 1 CV, 0 – 10 % over 10 CV, 10 % for 20 CV) afforded the title compound (0.381 g, 1.12 mmol, 75 %) as a brown oil.

LC-MS $t_R = 4.19$ min, m/z 281.41;

IR (neat) ν/cm^{-1} : 2988 (bw), 1735 (m), 1678 (w), 1597 (w), 1564 (w), 1471 (m), 1441 (w), 1393 (w), 1375 (w), 1248 (s), 1214 (s), 1156 (s), 1047 (m), 1027 (m), 943 (w), 829 (m), 795 (m), 760 (m), 691 (m);

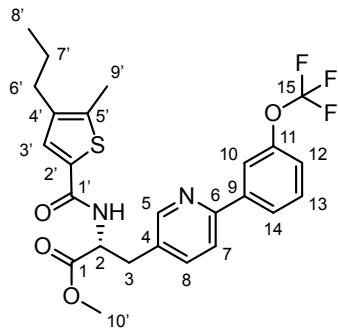
¹H NMR (600 MHz, CDCl₃) δ/ppm = 8.54 (s, 1H, H-5), 7.89 (d, J = 8.0 Hz, 1H, H-14), 7.87 (s, 1H, H-10), 7.67 (d, J = 8.1 Hz, 1H, H-7), 7.63 (dd, J = 8.1, 2.1 Hz, 1H, H-8), 7.47 (t, J = 8.0 Hz, 1H, H-13), 7.25 (d, J = 8.0 Hz, 1H, H-12), 3.75 – 3.77 (m, 1H, H-2), 3.74 (s, 3H, H-1'), 2.91 – 3.12 (bm, 2H, H-3);

¹³C NMR (150 MHz, CDCl₃) δ/ppm = 175.03 (C-1), 154.33 (C-6), 150.52 (C-5), 149.76 (C-11), 141.17 (C-9), 137.74 (C-8), 132.07 (C-4), 130.01 (C-7), 124.92 (C-13), 121.10 (C-14), 120.40 (centre of quartet, C-15), 120.17 (C-10), 119.40 (C-12), 55.42 (C-2), 52.15 (C-1'), 37.75 (C-3);

HRMS m/z calc. for C₁₆H₁₆F₃N₂O₃ [M + H]⁺ 341.1113, found 341.1113, Δ = 0.0 ppm;

$[\alpha]_D^{28.0} = -40.1$ (*c* 1.0 in CHCl₃);

Methyl (2*R*)-2-(5-methyl-4-propylthiophene-2-carboxamido)-3-(6-(3-(trifluoro methoxy)phenyl)pyridin-3-yl)propanoate (17)



To a stirred solution of amine **13** (0.340 g, 1.0 mmol) in DMF (10 mL) was added a solution of carboxylic acid **16** (0.184 g, 1.0 mmol, 1.0 eq.) in DMF (5 mL). The mixture was cooled to 0 °C and 1-hydroxybenzotriazole hydrate (HOEt) (0.184 g, 1.2 mmol, 1.2 eq.) in DMF (5 mL) was added slowly. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (0.20 mL, 1.2 mmol, 1.2 eq.) and diisopropylethylamine (DIPEA) (0.52 mL, 3.0 mmol, 3.0 eq.) were added dropwise to the mixture and the resulting solution left to stir at room temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate (40 mL) and an aqueous solution of lithium chloride (0.5 M, 40 mL), the phases were separated after vigorous mixing and the aqueous phase further extracted with ethyl acetate (40 mL). Removal of solvent from the combined organic layer under reduced pressure and purification of residues over silica (hexane/ethyl acetate, 0 % for 2 CV, 0 – 40 % over 30 CV) afforded the title compound (0.485 g, 0.958 mmol, 96%) as a brown oil.

LC-MS $t_R = 5.45$ min, m/z 507.36 [M + H]⁺;

IR (neat) ν/cm^{-1} : 2958 (w), 2932 (w), 2161 (bw), 2024 (w), 1978 (w), 1742 (m) 1624 (m), 1562 (m), 1525 (m), 1470 (m), 1445 (m), 1250 (s), 1212 (s), 1157 (s) 1056 (m), 1026 (m), 1002 (m), 943 (m), 843 (m), 795 (m), 753 (m), 692 (m);

¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.45 (s, 1H, H-5), 7.88 (d, J = 8.0 Hz, 1H, H-14), 7.86 (s, 1H, H-10), 7.65 (d, J = 8.1 Hz, 1H, H-7), 7.57 (dd, J = 8.1, 2.3 Hz, 1H, H-8), 7.47 (t, J = 8.0 Hz, 1H, H-13), 7.24 – 7.26 (m, 2H, H-12, H-3'), 6.44 (d, J = 7.2 Hz, 1H, NH), 5.05 – 5.09 (m, 1H, H-2), 3.79 (s, 3H, H-10'), 3.21 – 3.38 (m, 2H, H-3), 2.45 (t, J = 7.4 Hz, 2H, H-6'), 2.37 (s, 3H, H-9'), 1.56 (sextet, J = 7.4 Hz, 2H, H-7'), 0.92 (t, J = 7.4 Hz, 3H, H-8');

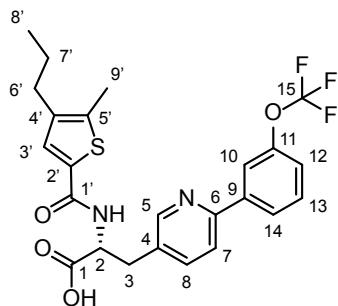
¹³C NMR (100 MHz, CDCl₃) δ/ppm = 171.56 (C-1), 161.57 (C-1'), 154.58 (C-6), 150.44 (C-5), 149.78 (C-11), 141.07 (C-9), 139.55 (C-4' or C-5'), 139.53 (C-4' or C-5'), 137.87 (C-8), 132.21

(C-4), 130.88 (C-3'), 130.82 (C-2'), 130.03 (C-7), 124.97 (C-13), 121.21 (C-14), 120.48 (centre of quartet, C-15), 120.25 (C-10), 119.45 (C-12), 53.17 (C-2), 52.69 (C-10'), 34.92 (C-3), 30.15 (C-6'), 23.44 (C-7'), 13.77 (C-9'), 13.44 (C-8');

HRMS m/z calc. for $C_{25}H_{26}F_3N_2O_4S$ [M + H]⁺ 507.1565, found 507.1577, $\Delta = 2.4$ ppm;

$[\alpha]_D^{28.0} = -60.9$ (*c* 1.0 in CHCl₃);

(2*R*)-2-(5-Methyl-4-propylthiophene-2-carboxamido)-3-(6-(3-(trifluoromethoxy)phenyl)pyridin-3-yl)propanoic acid (18)



Methyl ester **17** (0.037 g, 0.072 mmol) was mixed with THF (2.0 mL) and cooled to 0 °C. A solution of lithium hydroxide (1.0 M, 1.5 mL) dropwise and the mixture was allowed to warm to room temperature. Having been left to stir for 1.5 hours, all solvent was removed under reduced pressure and water (3.0 mL) added to solubilise residues. The solution was acidified with hydrochloric acid solution (1.0 M), and the product extracted with ethyl acetate (3 x 5 mL). Removal of solvent from the combined organic layer under reduced pressure gave the title compound (0.035 g, 0.071 mmol, 99 %) as a light brown oil that solidified in the refrigerator.

LC-MS $t_R = 5.30$ min, m/z 493.38 [M + H]⁺;

IR (neat) ν/cm^{-1} : 2960 (w), 2932 (w), 2871 (w), 2544 (bw), 2160 (w), 2019 (w), 1976 (w), 1729 (m), 1608 (m), 1556 (m), 1528 (m), 1446 (m), 1385 (m), 1250 (s), 1213 (s), 1158 (s), 849 (m), 769 (m), 752 (m), 689 (m);

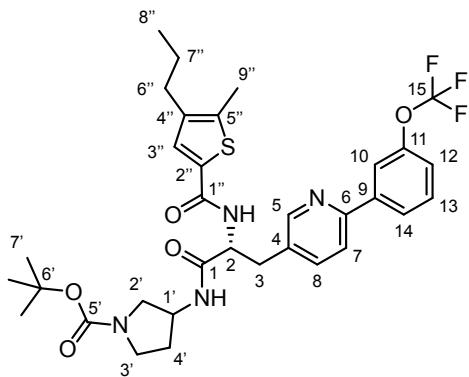
¹H NMR (400 MHz, CDCl₃) $\delta/\text{ppm} = 8.86$ (s, 1H, H-5), 8.19 (bs, 1H, H-8 or H-7 or H-14), 7.93 (bd, $J = 7.0$ Hz, 1H, H-8 or H-7 or H-14), 7.79 (bd, $J = 6.4$ Hz, 1H, H-8 or H-7 or H-14), 7.72 (s, 1H, H-10), 7.54 (t, $J = 8.0$ Hz, 1H, H-13), 7.42 (s, 1H, H-3'), 7.33 (d, $J = 8.0$ Hz, 1H, H-12), 5.04 (bs, 1H, H-2), 3.52 – 3.59 (m, 2H, H-3), 2.34 (t, $J = 6.4$ Hz, 2H, H-6'), 2.27 (s, 3H, H-9'), 1.43 – 1.50 (m, 2H, H-7'), 0.83 (t, $J = 7.4$ Hz, 3H, H-8');

¹³C NMR (100 MHz, CDCl₃) $\delta/\text{ppm} = 175.49, 173.47, 162.48, 149.76, 145.69, 139.81, 139.67, 132.13, 131.50, 130.98, 126.25, 123.33, 123.12, 120.32$ (centre of quartet, C-15), 120.24, 60.41, 53.475, 50.55, 34.09, 30.08, 23.35, 20.66, 13.72, 13.32;

HRMS m/z calc. for C₂₄H₂₄F₃N₂O₄S [M + H]⁺ 493.1409, found 493.1413, $\Delta = 0.8$ ppm;

$[\alpha]_D^{28.0} = -70.3$ (*c* 1.0 in CHCl₃);

tert-Butyl (3*R*)-3-((2*R*)-2-(5-methyl-4-propylthiophene-2-carboxamido)-3-(6-(3-(trifluoromethoxy)phenyl)pyridin-3-yl)propanamido)pyrrolidine-1-carboxylate (20)



Carboxylic acid **18** (0.390 g, 0.792 mmol) and (*3R*)-*tert*-Butyl 3-aminopyrrolidine-1-carboxylate (0.186 g, 1.0 mmol, 1.26 eq.) were mixed with DMF (15 mL) and cooled to 0 °C. The mixture was cooled to 0 °C and HOBr (0.146 g, 0.95 mmol, 1.2 eq.) in DMF (5 mL) was added slowly. EDC (0.16 mL, 0.95 mmol, 1.2 eq.) and DIPEA (0.41 mL, 2.37 mmol, 3.0 eq.) were added dropwise to the mixture and the resulting solution left to stir at room temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate (40 mL) and an aqueous solution of lithium chloride (0.5 M, 40 mL), the phases were separated after vigorous mixing and the aqueous phase further extracted with ethyl acetate (40 mL). Removal of solvent from the combined organic layer under reduced pressure and purification of residues over silica (hexane/ethyl acetate, 0 % for 2 CV, 0 – 100 % over 15 CV, 100 % for 10 CV) afforded the title compound (0.383 g, 0.580 mmol, 73%) as a light brown oil.

LC-MS $t_R = 5.52$ min, m/z 661.59 [M + H]⁺;

IR (neat) ν/cm^{-1} : 3280 (w), 2963 (w), 2928 (w), 1694 (m), 1615 (m), 1560 (m), 1533 (m), 1470 (m), 1446 (m), 1394 (m), 1366 (m), 1252 (s), 1218 (s), 1161 (s), 1130 (s), 876 (w), 834 (w), 754 (s), 691 (w);

¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.54 (s, 1H, H-5), 7.87 (d, J = 8.0 Hz, 1H, H-14), 7.85 (s, 1H, H-10), 7.63 (d, J = 8.1 Hz, 1H, H-8), 7.60 (d, J = 8.1 Hz, 1H, H-7), 7.45 (t, J = 8.0 Hz, 1H, H-13), 7.23 – 7.24 (m, 2H, H-3'', H-12), 6.69 (bs, 1H, NH), 4.86 (s, 1H, NH), 4.35 – 4.38 (m, 1H, H-2), 3.59 (bs, 1H, H-1'), 3.36 (bs, 2H), 3.03 – 3.22 (m, 4H), 2.43 (t, J = 7.4 Hz, 2H, H-6''), 2.34 (s, 3H, H-9''), 2.17 (s, 1H), 2.06 – 2.08 (m, 1H), 1.55 (sextet, J = 7.4 Hz, 2H, H-7''), 1.42 – 1.46 (m, 9H, H-7'), 0.91 (t, J = 7.4 Hz, 3H, H-8'');

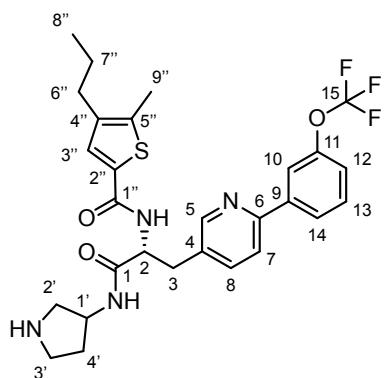
¹³C NMR (100 MHz, CDCl₃) δ/ppm = 162.54, 162.11, 154.36, 154.29, 150.52, 149.72, 141.07,

139.66, 137.77, 132.25, 131.28, 130.78, 129.94, 124.94, 121.04, 119.39, 119.18, 79.49, 54.18, 51.04, 43.75, 41.30, 36.47, 34.08, 30.13, 28.38, 23.40, 22.58, 14.02, 13.76;

HRMS m/z calc. for $C_{33}H_{40}F_3N_4O_5S$ $[M + H]^+$ 661.2672, found 661.2676, $\Delta = 0.6$ ppm;

$[\alpha]_D^{28.0} = +2.2$ (c 1.0 in $CHCl_3$);

5-Methyl-N-((*R*)-1-oxo-1-((*R*)-pyrrolidin-3-ylamino)-3-(6-(3-(trifluoromethoxy)phenyl)pyridin-3-yl)propan-2-yl)-4-propylthiophene-2-carboxamide (6)



Boc-protected amine **20** (0.352 g, 0.533 mmol) was added to anhydrous DCM (10 mL) and cooled to 0 °C. Trifluoroacetic acid (TFA) (0.16 mL, 2.13 mmol, 4.0 eq.) was added dropwise to the solution after which time the mixture was allowed to warm to room temperature and left to stir for 60 minutes. Having removed solvent and excess TFA under reduced pressure, a saturated solution of sodium bicarbonate (20 mL) was added and the mixture stirred vigorously. A precipitate formed during this time, which was collected *via* filtration. The filter cake was washed with water (30 mL) and dried to afford the title compound (0.272 g, 0.485 mmol, 91 %) as a light yellow-white solid.

M_p: 177 – 180 °C (H₂O);

LC-MS $t_R = 4.74$ min, m/z 561.44;

IR (neat) ν/cm^{-1} : 3284 (w), 2931 (w), 2871 (w), 1616 (m), 1562 (m), 1528 (m), 1470 (m), 1445 (m), 1392 (m), 1250 (s), 1214 (s), 1157 (s), 1026 (m), 1002 (w), 943 (w), 841 (m), 794 (m), 760 (m), 690 (m);

¹H NMR (400 MHz, MeOH-*d*₄) δ/ppm = 8.56 (s, 1H, H-5), 7.91 (d, J = 8.0 Hz, 1H, H-14), 7.86 (s, 1H, H-10), 7.77 – 7.84 (m, 2H, H-7, H-8), 7.54 (t, J = 8.0 Hz, 1H, H-13), 7.49 (s, 1H, H-3’’), 7.31 (d, J = 8.0 Hz, 1H, H-12), 4.77 – 4.81 (m, 1H, H-1’), 4.22 – 4.28 (m, 1H, H-2), 3.21 – 3.26 (m, 1H), 3.12 – 3.17 (m, 1H), 3.01 – 3.06 (m, 1H), 2.92 – 2.98 (m, 1H), 2.83 – 2.89 (m, 1H), 2.53 – 2.57 (m, 1H), 2.46 (t, J = 7.4 Hz, 2H, H-6’’), 2.32 (s, 3H, H-9’’), 2.01 – 2.10 (m, 1H), 1.63 – 1.71 (m, 1H), 1.57 (sextet, J = 7.4 Hz, 2H, H-7’’), 0.91 (t, J = 7.4 Hz, 3H, H-8’’);

¹³C NMR (100 MHz, MeOH-*d*₄) δ/ppm = 173.14 (C-1), 164.48 (C-1’’), 155.52 (C-6), 151.61 (C-5), 151.20 (C-11), 142.55 (C-9), 141.29 (C-4’ or C-5’’), 140.95 (C-4’ or C-5’’), 139.89 (C-8), 134.31 (C-3’’), 134.19 (C-2’’), 132.43 (C-4), 131.70 (C-7), 126.66 (C-13), 122.50 (C-14), 122.13

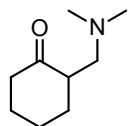
(C-10), 121.96 (centre of quartet, C-15), 120.56 (C-12), 56.20 (C-2), 53.32 (C-1'), 51.86 (C-2'), 46.28 (C-3'), 36.12 (C-3), 33.23 (C-4'), 31.24 (C-6''), 24.70 (C-7''), 14.24 (C-9''), 13.44 (C-8'');

HRMS m/z calc. for $C_{28}H_{32}N_4O_3F_3S$ $[M + H]^+$ 561.2147, found 561.2172, $\Delta = 4.5$ ppm;

$[\alpha]_D^{28.0} = +69.0$ (c 1.0 in CHCl₃).

Chapter 3 – Around-the-world synthesis

2-((Dimethylamino)methyl)cyclohexan-1-one (36)



To a stirred solution of cyclohexanone (10.0 g, 102 mmol) in ethanol (200 mL) was added dimethylamine hydrochloride (24.9 g, 306 mmol, 3.0 eq.) and paraformaldehyde (9.8 g). Concentrated hydrochloric acid (37 %, 2.5 mL) was added slowly before the resulting mixture was heated to 90 °C for 18 hours. Having been allowed to cool to room temperature, reaction solvent was removed under reduced pressure and residues dissolved in water (200 mL). An aqueous solution of sodium hydroxide (1.0 M) was added slowly until the pH of the solution rose to 10 (by indicator paper). The mixture was extracted with diethyl ether (3 x 100 mL) and the combined organic layers dried over magnesium sulfate. Removal of organic solvent under reduced pressure afforded the title compound (8.08 g, 52.0 mmol, 51 %) as a yellow oil.

IR (neat) ν/cm^{-1} : 2937 (m), 2860 (m), 2819 (m), 2765 (m), 1708 (s), 1449 (m), 1384 (w), 1309 (w), 1264 (w), 1219 (m), 1179 (w), 1157 (w), 1127 (m), 1042 (m), 1028 (m), 963 (w), 876 (m), 829 (w), 810 (m);

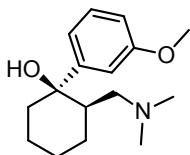
¹H NMR (600 MHz, CDCl₃) δ/ppm = 2.66 – 2.69 (m, 1H), 2.47 – 2.48 (m, 1H), 2.38 – 2.41 (m, 1H), 2.28 – 2.33 (m, 1H), 2.19 – 2.22 (m, 8H), 2.00 – 2.03 (m, 1H), 1.84 – 1.87 (m, 1H), 1.62 – 1.73 (m, 2H), 1.36 – 1.43 (m, 1H);

¹³C NMR (150 MHz, CDCl₃) δ/ppm = 211.63 (C=O), 58.53 (CH₂), 48.42 (CH), 45.27 (CH₃), 41.36 (CH₂), 31.94 (CH₂), 27.54 (CH₂), 24.01 (CH₂);

HRMS m/z calc. for C₉H₁₈NO [M + H]⁺ 156.1388, found 156.1388, Δ = 0.0 ppm;

Microanalysis calc. (found) for C₈H₁₇NO C 69.63% (69.31%), N 9.02% (6.97%), H 11.04% (11.22%).

Recorded data were consistent with those reported previously.^{315–317}

(1*S*,2*S*)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexan-1-ol (38)

The equipment layout for this flow procedure is shown in Figure 3.6 (pg. 89).

A solution of ketone **36** (0.776 g, 5.0 mmol) in anhydrous THF (0.5 M, 10 mL) was pumped at 0.703 mL min⁻¹ to a tee junction (PTFE) where it mixed with a stream of (3-methoxyphenyl)-magnesium bromide solution (1.691 g, 8.0 mmol, 1.6 eq.) in THF (0.5 M, 16 mL) pumped at 1.125 mL min⁻¹. The combined solution was directed through two 10 mL reactor coils heated to 41 °C. System pressure was maintained using a 40 psi back pressure regulator.

Crude reaction mixture was partitioned between a mixture of ice and saturated aqueous ammonium chloride solution (25 mL), and diethyl ether (25 mL). The layers were separated following vigorous mixing. Following extraction of the aqueous layer with diethyl ether (3 x 25 mL), the combined organic phase was dried over magnesium sulfate before being concentrated under reduced pressure. Residues were dissolved in toluene (25 mL) and mixed with distilled water (25 mL). An aqueous solution of hydrochloric acid (1.0 M) was added slowly until the pH of the aqueous layer lowered to 3 (by indicator paper). Following phase separation, the aqueous layer was washed with toluene (3 x 20 mL), and the organic layers discarded. The pH of the aqueous solution was adjusted to 9 (by indicator paper) by slow addition of aqueous sodium hydroxide solution (1.0 M) before ethyl acetate was added (20 mL). Following vigorous mixing, the organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound (1.133 g, 4.3 mmol, 86 % by ¹H NMR with internal standard, 4:1 *S/R* ratio) as a brown oil.

LC-MS t_R = 3.06 min, m/z 264.3;

IR (neat) ν/cm^{-1} : 2935 (m), 2857 (m), 2830 (m), 2783 (w), 1599 (m), 1583 (m), 1483 (m), 1461 (s), 1430 (m), 1286 (m), 1250 (s), 1164 (m), 1092 (m), 1044 (s), 991 (s), 961 (m), 861 (m), 832 (m), 779 (s), 700 (s);

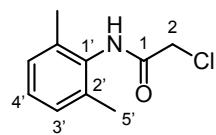
¹H NMR (600 MHz, CDCl₃) δ/ppm = 7.20 – 7.23 (m, 1H), 7.14 (bs, 1H), 7.02 (bs, 1H), 6.71 – 6.73 (m, 1H), 3.78 (s, 3H), 2.36 – 2.39 (m, 1H), 2.00 – 2.10 (m, 9H), 1.56 – 1.85 (m, 6H), 1.46 – 1.49 (m, 1H), 1.30 – 1.37 (m, 1H);

¹³C NMR (150 MHz, CDCl₃) δ/ppm = 159.49, 152.01, 128.90, 117.35, 111.21, 110.94, 76.04, 61.58, 55.15, 47.77, 44.76, 41.30, 27.92, 26.86, 22.27;

HRMS *m/z* calc. for C₁₆H₂₆NO₂ [M + H]⁺ 264.1964, found 264.1952, Δ = -4.0 ppm;

Microanalysis calc. (found) for C₁₆H₂₅NO₂ C 72.97% (70.84%), N 5.32% (5.07%), H 9.57% (9.30%).

2-Chloro-*N*-(2,6-dimethylphenyl)acetamide (42)



The equipment layout for this flow procedure is shown in Figure 3.12 (pg. 96).

Triethylamine (TEA) (1.74 mL, 12.5 mmol, 1.25 eq.) and 2,6-dimethylaniline (1.23 mL, 10 mmol) were added to anhydrous DCM (1.0 M 2,6-dimethylaniline, 7.03 mL). This solution was pumped at 1.342 mL min⁻¹ to a tee junction where it mixed with a solution of chloroacetyl chloride (1.58 mL, 19.8 mmol, 1.98 eq.) in anhydrous DCM (1.0 M, 18.2 mL) pumped at 2.658 mL min⁻¹. The combined stream passed through two 10 mL reactor coils heated to 105 °C. System pressure was maintained using a 250 psi back pressure regulator.

Crude reaction mixture collected from the system was mixed vigorously with a saturated aqueous solution of ammonium chloride (30 mL). The organic phase was dried over magnesium sulfate and solvent removed under reduced pressure. DCM was slowly added until residues had dissolved completely, after which time the mixture was left until solvent had evaporated. Crystals of title compound (1.720 g, 8.7 mmol, 87 %) were collected as colourless needles.

M_p 148 – 149 °C (DCM) [Lit. 148 – 150 °C];³¹⁸

LC-MS *t*_R = 3.58 min, *m/z* 198.1;

IR (neat) *v*/cm⁻¹: 3215 (bw), 3036 (w), 2973 (w), 1681 (w), 1643 (m), 1533 (m), 1476 (m), 1431 (m), 1376 (m), 1323 (m), 1249 (m), 1207 (m), 1147 (m), 980 (m), 795 (w), 760 (s), 708 (s), 663 (s);

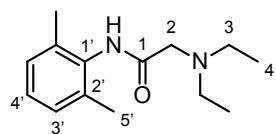
¹H NMR (600 MHz, CDCl₃): *δ*/ppm = 7.86 (s, 1H, NH), 7.13 – 7.16 (m, 1H, H-4'), 7.10 (d, *J* = 7.5 Hz, 2H, H-3'), 4.24 (s, 2H, H-2), 2.24 (s, 6H, H-5');

¹³C NMR (150 MHz, CDCl₃): *δ*/ppm = 164.30 (C-1), 135.29 (C-1'), 132.64 (C-2'), 128.31 (C-3'), 127.82 (C-4'), 42.73 (C-2), 18.24 (C-5');

HRMS *m/z* calc. for C₁₀H₁₃NOCl [M + H]⁺ 198.0686, found 198.0688, Δ = 1.0 ppm;

Microanalysis calc. (found) for C₁₀H₁₂NOCl C 60.77% (60.78%), N 7.09% (7.00%), H 6.12% (6.08%), Cl 17.93% (17.92%).

All recorded data were consistent with those reported previously.³¹⁹

2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide (44)

The equipment layout for this flow procedure is shown in Figure 3.14 (pg. 99).

A solution of compound **42** (0.988 g, 5.0 mmol) in DMF (0.5 M, 10 mL) was pumped at 0.570 mL min⁻¹ to a tee junction where it mixed with a solution of diethylamine (2.02 mL, 19.5 mmol, 3.9 eq.) and TEA (2.72 mL, 19.5 mmol, 3.9 eq.) in DMF (2.0 M diethylamine, 5.01 mL) pumped at 0.556 mL min⁻¹. The mixture was directed through two 10 mL reactor coils heated to 99 °C. System pressure was maintained using a 100 psi back pressure regulator.

Crude reaction mixture was diluted with distilled water (25 mL) and DCM (25 mL) before it was agitated vigorously. The organic phase was washed with distilled water (3 x 10 mL) before volatiles were removed under reduced pressure. Residues were purified *via* flash column chromatography on silica (100 % ethyl acetate) to afford the title compound (1.148 g, 4.9 mmol, 98 %) as a light yellow solid.

M_p: 67 – 68 °C (EtOAc) [Lit. 66 - 68 °C];³²⁰

LC-MS *t*_R = 2.81 min, *m/z* 235.2;

IR (neat) *v*/cm⁻¹: 3256 (bw), 2968 (m), 2923 (w), 2800 (w), 1737 (w), 1663 (s), 1594 (w), 1492 (s), 1423 (m), 1373 (m), 1292 (m), 1207 (m), 1165 (m), 1121 (m), 1091 (m), 1072 (m), 987 (m), 764 (s);

¹H NMR (600 MHz, CDCl₃) δ/ppm = 8.92 (s, 1H, NH), 7.07 – 7.11 (m, 3H, H-3', H-4'), 3.22 (s, 2H, H-2), 2.69 (q, *J* = 7.2 Hz, 4H, H-3), 2.23 (s, 6H, H-5'), 1.14 (t, *J* = 7.2 Hz, 6H, H-4);

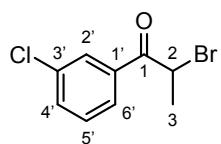
¹³C NMR (150 MHz, CDCl₃) δ/ppm = 170.21 (C-1), 135.03 (C-1'), 133.94 (C-2'), 128.17 (C-3'), 127.00 (C-4'), 57.50 (C-2), 48.92 (C-3), 18.53 (C-5'), 12.63 (C-4);

HRMS *m/z* calc. for C₁₄H₂₃N₂O [M + H]⁺ 235.1810, found 235.1814, Δ = 1.7 ppm;

Microanalysis calc. (found) for C₁₄H₂₂N₂O C 71.76% (71.56%), N 11.95% (11.76%), H 9.46% (9.59%).

All recorded data were consistent with those reported previously.³²¹

2-Bromo-1-(3-chlorophenyl)propan-1-one (47)



The equipment layout for this flow procedure is shown in Figure 3.17 (pg. 104).

A solution of 1-(3-chlorophenyl)propan-1-one (0.843 g, 5.0 mmol) in DCM (0.5 M, 10 mL) was pumped at 0.500 mL min⁻¹ into a tee junction where it mixed with a solution of bromine (0.256 mL, 5.0 mmol, 1.0 eq.) in DCM (0.5 M, 10 mL) pumped at 0.500 mL min⁻¹. The combined solutions were directed through two 10 mL reactor coils heated to 44 °C. System pressure was maintained using a 75 psi back pressure regulator.

Collected reaction mixture was quenched with a saturated solution of sodium metabisulfite (30 mL), and the organic layer dried over magnesium sulfate. Removal of solvent afforded the title compound (1.238 g, 5.0 mmol, >99 %) as a colourless oil.

LC-MS $t_R = 4.54$ min, m/z 155.3;

IR (neat) ν/cm^{-1} : 1687 (s), 1570 (m), 1473 (w), 1442 (m), 1422 (m), 1376 (w), 1333 (m), 1230 (s), 1160 (m), 1076 (m), 996 (m), 959 (m), 901 (m), 801 (m), 786 (m), 738 (s), 696 (s), 672 (s);

¹H NMR (600 MHz, CDCl₃) δ/ppm = 7.99 (s, 1H, H-2'), 7.89 (d, J = 7.9 Hz, 1H, H-6'), 7.56 (d, J = 7.9 Hz, 1H, H-4'), 7.43 (t, J = 7.9 Hz, 1H, H-5'), 5.22 (q, J = 6.7 Hz, 1H, H-2), 1.90 (d, J = 6.7 Hz, 3H, H-3);

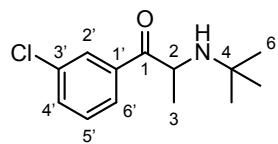
¹³C NMR (150 MHz, CDCl₃) δ/ppm = 192.03 (C-1), 135.62 (C-1'), 135.08 (C-3'), 133.55 (C-4'), 130.00 (C-2'), 128.96 (C-5'), 126.93 (C-6'), 41.24 (C-2), 19.95 (C-3);

HRMS m/z calc. for C₉H₉BrClO [M + H]⁺ 246.9525, found 246.9524, Δ = -0.4 ppm;

Microanalysis calc. (found) for C₉H₈BrClO C 43.67% (43.67%), H 3.23% (3.10%).

Recorded data were consistent with those reported previously.³²²

2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one (48)



Single flow reaction

The equipment layout for this flow procedure is shown in Figure 3.19 (pg. 108).

A solution of compound **47** (0.619 g, 2.5 mmol) in *N*-methyl-2-pyrrolidone (NMP) (0.25 M, 10 mL) was pumped at 0.25 mL min⁻¹ to a tee junction where it was mixed with a solution of *tert*-butylamine (0.788 mL, 7.5 mmol, 3.0 eq.) in NMP (0.25 M, 29.2 mL) pumped at 0.75 mL min⁻¹. The resulting solution was heated to 90 °C in two 10 mL reactor coils. System pressure was maintained using a 100 psi back pressure regulator.

Water (25 mL) was added to crude reaction mixture and the resulting solution extracted with diethyl ether (3 x 25 mL). The combined organic phases were washed with water (5 x 25 mL) before being dried over magnesium sulfate. Removal of solvent under reduced pressure following purification over silica (DCM/MeOH gradient elution, 0 % for 1 CV, 0 – 10 % over 5 CV, 10 % for 25 CV) afforded the title compound (0.479 g, 2.0 mmol, 80 %) as a yellow oil that solidified in the refrigerator.

Telescopied flow preparation

The equipment layout for this flow procedure is shown in Figure 3.22 (pg. 112). The parameters described herein are for steady state operation.

A solution of 1-(3-chlorophenyl)propan-1-one in DCM (0.5 M) was pumped at 0.5 mL min⁻¹ to a tee junction where it mixed with a solution of bromine in DCM (0.5 M) pumped at 0.5 mL min⁻¹ via peristaltic pump. The combined solution was directed through a 10 mL reactor coil held at 44 °C. System pressure was maintained using a 100 psi back pressure regulator.

Eluting crude reaction mixture was mixed with 2.0 mL min⁻¹ (HPLC pump) of sodium metabisulfite solution in water (2.0 M) and passed through an Omnifit column (100 mm length, \varnothing 10 mm) filled with eight magnetic stirrer bars which was placed on top of a stirrer plate. Phases were

separated in a vertical Omnifit column (100 mm length, \varnothing 10 mm) from which the organic layer was removed at an average rate of 0.500 mL min⁻¹ via peristaltic pump and mixed with a stream of NMP at 0.500 mL min⁻¹ (HPLC pump) at a tee junction.

The combined solution was passed into a distillation column held at 110 °C from which solution was drawn at 0.610 mL min⁻¹ via peristaltic pump and mixed with 0.390 mL min⁻¹ of *tert*-butylamine solution in NMP (1.928 M). The resulting mixture was directed through two 10 mL reactor coils heated to 90 °C. System pressure was maintained using a 100 psi back pressure regulator.

Solvent was removed from a 10 mL sample of crude reaction mixture under reduced pressure and residues were purified using the process described above for the single flow reaction to afford the title compound (0.479 g, 2.0 mmol, 80 %) as a yellow oil that solidified in the refrigerator.

LC-MS t_R = 3.43 min, m/z 240.2;

IR (neat) ν/cm^{-1} : 2967 (m), 1684 (s), 1571 (m), 1454 (m), 1424 (m), 1365 (m), 1298 (m), 1206 (s), 1142 (m), 1078 (m), 991 (m), 974 (m), 902 (w), 800 (m), 766 (m), 730 (s), 695 (m), 674 (s);

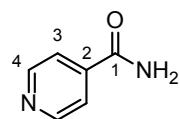
¹H NMR (600 MHz, CDCl₃) δ/ppm = 7.96 (s, 1H, H-2'), 7.87 (d, J = 7.9 Hz, 1H, H-6'), 7.55 (d, J = 7.9 Hz, 1H, H-4'), 7.44 (t, J = 7.9 Hz, 1H, H-5'), 4.29 (q, J = 7.2 Hz, 1H, H-2), 2.31 (s, 1H, NH), 1.25 (d, J = 7.2 Hz, 3H, H-3), 1.04 (s, 9H, H-6);

¹³C NMR (150 MHz, CDCl₃) δ/ppm = 203.80 (C-1), 136.64 (C-1'), 135.15 (C-3'), 133.18 (C-4'), 130.09 (C-2'), 128.42 (C-5'), 126.36 (C-6'), 52.22 (C-2), 50.80 (C-4), 29.73 (C-6), 22.48 (C-3);

HRMS m/z calc. for C₁₃H₁₉NClO [M + H]⁺ 240.1150, found 240.1142, Δ = -3.3 ppm;

Microanalysis calc. (found) for C₁₃H₁₉NCl₂O C 56.53% (56.55%), N 5.07% (5.07%), H 6.93% (6.95%), Cl 25.67% (25.42%). Note: elemental analysis of the hydrochloric salt of compound 48 was performed owing to instability of the free base.

All recorded data were consistent with those reported previously.^{323–325}

Isonicotinamide (57)

The equipment layout for this flow procedure is shown in Figure 3.19 (pg. 108).

A solution of pyridine-4-carbonitrile (1.041 g, 10 mmol) in IPA/H₂O (0.5 M, 20 mL, 1:1 *v/v*) was pumped at 0.278 mL min⁻¹ through an Omnifit column (100 mm length, \varnothing 10 mm) heated to 117 °C. The column was packed with 2.5 g manganese dioxide, and small plugs of celite were placed at both ends of the column. Pressure was provided by a 40 psi back pressure regulator. Crude reaction mixture was concentrated under reduced pressure and purified over silica (DCM/MeOH gradient elution, 0 % for 1 CV, 0 – 10 % over 5 CV, 10 % for 25 CV) to afford the title compound (1.110 g, 9.1 mmol, 91 %) as a white solid.

M_p: 129 – 131 °C (DCM) [Lit. 128 – 130 °C];⁸⁰

LC-MS *t*_R = 0.33 min, *m/z* 123.0;

IR (neat) *v/cm*⁻¹: 3312 (m), 3058 (bm), 2520 (bw), 2159 (m), 1978 (m), 1677 (s), 1619 (s), 1599 (s), 1553 (s), 1490 (m), 1395 (s), 1223 (s), 1149 (m), 1129 (m), 1061 (m), 1001 (s), 845 (s), 817 (s), 758 (s), 672 (s);

¹H NMR (600 MHz, DMSO-*d*₆) *δ*/ppm = 8.71 (dd, *J* = 4.4, 1.6 Hz, 1H, H-4), 8.24 (s, 1H, NH₂), 7.76 (dd, *J* = 4.4, 1.6 Hz, 1H, H-3), 7.72 (s, 1H, NH₂);

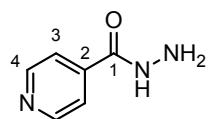
¹³C NMR (150 MHz, DMSO-*d*₆) *δ*/ppm = 166.29 (C-1), 150.19 (C-4), 141.26 (C-2), 121.38 (C-3);

HRMS *m/z* calc. for C₆H₇N₂O [M + H]⁺ 123.0553, found 123.0551, Δ = -1.62 ppm;

Microanalysis calc. (found) for C₆H₇N₂O C 59.01% (58.76%), N 22.94% (22.88%), H 4.95% (4.90%).

All recorded data were consistent with those reported previously.^{80,326,327}

Pyridine-4-carbohydrazide (50)



The equipment layout for this flow procedure is shown in Figure 3.30 (pg. 123).

A solution of amide **57** (0.611 g, 5.0 mmol) in MeOH (0.4 M, 12.5 mL) was pumped at 0.333 mL min⁻¹ to a tee junction where it was mixed with a solution of hydrazine monohydrate (1.21 mL, 25.0 mmol, 5.0 eq.) in MeOH (2.0 M, 12.5 mL) pumped at 0.333 mL min⁻¹. The resulting mixture was heated to 150 °C in two 10 mL reactor coils. System pressure was maintained using a 100 psi back pressure regulator.

Solvent was removed from crude reaction mixture under reduced pressure and residues were purified over silica (DCM/MeOH gradient elution, 0 % for 1 CV, 0 – 10 % over 15 CV, 10 % for 20 CV) to afford the title compound (0.343 g, 2.5 mmol, 50 %) as a white solid.

M_p: 171 – 173 °C (DCM) [Lit. 171 – 173 °C];³²⁸

LC-MS t_R = 1.40 min, m/z 138.1;

IR (neat) ν/cm^{-1} : 3104 (bm), 1549 (bs), 1459 (bs), 1411 (s), 1305 (bs), 1220 (m), 1138 (bm), 994 (s), 952 (m), 887 (m), 844 (s), 815 (m), 740 (m), 670 (s);

¹H NMR (600 MHz, DMSO-*d*₆) δ/ppm = 10.09 (s, 1H, NH), 8.70 (dd, J = 4.4, 1.6 Hz, 2H, H-4), 7.72 (dd, J = 4.4, 1.6 Hz, 2H, H-3), 4.62 (s, 2H, NH₂);

¹³C NMR (150 MHz, DMSO-*d*₆) δ/ppm = 163.85 (C-1), 150.18 (C-4), 140.23 (C-2), 120.97 (C-3);

HRMS m/z calc. for C₆H₈N₃O [M + H]⁺ 138.0662, found 138.0659, Δ = -2.02 ppm;

Microanalysis calc. (found) for C₆H₇N₃O C 52.55% (52.25%), N 30.64% (30.43%), H 5.15% (5.15%).

All recorded data were consistent with those reported previously.³²⁹

Chapter 4 – Development of a semi-continuous inline chromatography system

1-Bromoethylbenzene (4)

Batch preparation

Triphenylphosphine (2.098 g, 8.0 mmol, 0.8 eq.) was dissolved in MeCN (50 mL) and the solution cooled to 0 °C. Carbon tetrabromide (3.316 g, 10.0 mmol, 1.0 eq.) was added slowly and the mixture left to stir at room temperature for 10 minutes before being cooled to 0 °C. 1-Phenylethanol (1.21 mL, 10.0 mmol) was added dropwise to the solution, and the resulting mixture left to stir at 0 °C for 60 minutes. The reaction mixture was allowed to warm to room temperature, and stirred for an additional 1.5 hours.

A sample of 2 mL crude reaction mixture was purified using the supercritical fluid chromatography (SFC) unit described in Chapter 4, to recover 81 % of the title compound (92 % purity, by HPLC, NMR) in the crude mixture as a yellow/brown liquid.

Methyl (2*S*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (8)

Batch preparation

Triphenylphosphine (3.147 g, 12.0 mmol, 1.2 eq.) and imidazole (0.817 g, 12.0 mmol, 1.2 eq.) were dissolved in DCM (50 mL) and the solution cooled to 0 °C. Iodine (3.046 g, 12.0 mmol, 1.2 eq.) was added slowly and the stirred mixture stirred at room temperature for 10 minutes. During this time a yellow suspension was observed to form. The mixture was cooled to 0 °C before a solution of methyl (*tert*-butoxycarbonyl)-D-serinate (2.190 g, 10.0 mmol) in DCM (2.0 M, 5.0 mL) was added dropwise. The solution was left to stir at 0 °C for 60 minutes, then room temperature for 1.5 hours.

A sample of 1.0 mL crude reaction mixture was diluted with DCM (1.0 mL) and then purified using the SFC unit described in Chapter 4, to recover 89 % of the title compound (>99 % purity by HPLC, NMR) from the crude mixture as a light yellow oil that solidified in the refrigerator.

Pyridine-4-carbohydrazide (50)

Telescopied flow preparation

The equipment layout for this flow procedure is shown in Figure 4.24 (pg. 162). The parameters described herein are for steady state operation.

A solution of pyridine-4-carbonitrile in IPA/H₂O (0.5 M, 1:1 *v/v*) was pumped at 0.278 mL min⁻¹ through an Omnifit column (100 mm length, \varnothing 10 mm) heated to 117 °C. The column was packed with 2.5 g manganese dioxide, and small plugs of celite were placed at both ends of the column. Pressure was provided by a 75 psi back pressure regulator. The amide product was isolated inline using the SFC unit described in Chapter 4, and directed into a holding reservoir at a rate of 6.022 mL min⁻¹ in MeOH (0.011 M).

Solution in this holding reservoir was pumped at 6.022 mL min⁻¹ (HPLC pump) into a tee junction where it mixed with a solution of hydrazine monohydrate in MeOH (1.32 M) pumped at 0.500 mL min⁻¹ by HPLC pump. The combined solution was directed through seven 20 mL reactor coils held at 130 °C. System pressure was provided by a 150 psi back pressure regulator.

Solvent was removed from a 100 mL sample of crude reaction mixture under reduced pressure and residues were purified over silica (DCM/MeOH gradient elution, 0 % for 1 CV, 0 – 10 % over 15 CV, 10 % for 20 CV) to afford the title compound (0.079 g, 0.575 mmol, 27 %) as a white solid.