Use of Lithium Diisopropylamide in Flow: Operability and Safety Challenges Encountered on Multigram Scale

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Supporting information

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General information

1.0 Materials and analysis

Materials

Reagents were obtained commercially, from Combi-Blocks and Sigma-Aldrich, and used as received. Solvents were used wet unless otherwise stated, and reactions were *not* performed under an inert atmosphere unless otherwise stated.

Wheaton vial details, Item# 224882 & W242710

High performance liquid chromatography (HPLC)

These data were recorded on an Agilent HPLC system, equipped with a Waters X-select CSH C18 (30 mm length × 2.0 mm internal diameter, 2.5 μm packing particle size) at 40 °C.

The solvents employed were:

A = Water + 0.05% TFA

B = Acetonitrile + 0.05% TFA

The gradient employed was as follows:

Time (min)	Flow rate (mL/min)	% A / %	% B / %
0	1.0	97	3
3.7	1.0	5	95
4.00	1.0	5	95
4.01	1.0	97	3
5.5	1.0	97	3

The UV response was monitored at a wavelength of 220 nm.

Method 1 used throughout unless otherwise stated.

Low resolution liquid chromatography mass spectrometry (LCMS) method 1.

These data were recorded using a Waters Acquity UPLC, equipped with a CSH C18 column (50 mm × 2.1 mm internal diameter, 1.7 μm packing diameter) at 40 °C.

The solvents employed were:

A = 10 mM ammonium bicarbonate in water, adjusted to pH 10 with ammonia solution.

B = acetonitrile

The gradient employed was as follows:

Time / min	Flow rate / mL min^{-1}	% A / %	% B / %
0	1	97	3
0.05	1	97	3
1.5	1	5	95
1.9	1	5	95
2.0	1	97	3

The UV detection was an averaged signal from wavelength of 210 nm to 350 nm and mass spectra were recorded on a Waters ZQ mass spectrometer using alternate-scan positive and negative electrospray ionization (ES).

Low resolution liquid chromatography mass spectrometry (LCMS) method 2.

These data were recorded using a Waters Acquity UPLC, equipped with a Acquity UPLC BEH C18 (50 mm × 3.0 mm internal diameter, 1.7 μm packing diameter) at 50 °C.

The solvents employed were:

A = water 0.1% formic acid

B = acetonitrile 0.1% formic acid

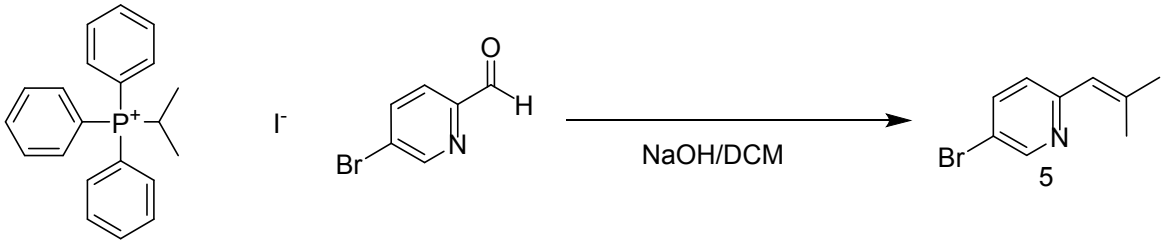
The gradient employed was as follows:

Time / min	Flow rate / mL min^{-1}	% A / %	% B / %
0	0.8	95	5
1.4	0.8	0	100
1.9	0.8	0	100
2.0	0.8	95	5

The UV detection was an averaged signal from wavelength of 210 nm to 350 nm and mass spectra were recorded on a Waters ZQ mass spectrometer using alternate-scan positive and negative electrospray ionization (ES).

2.0 Synthesis

Synthesis of 5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **5**

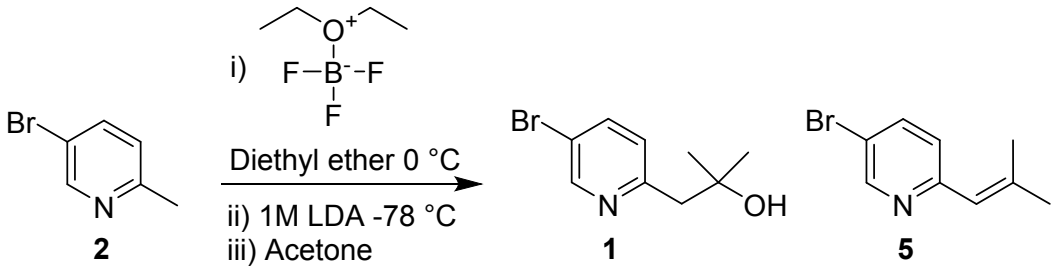


A mixture of 5-bromopicolinaldehyde (100 mg, 0.538 mmol), isopropyltriphenylphosphonium iodide (256 mg, 0.591 mmol) and sodium hydroxide (0.806 mL, 1.613 mmol) in Dichloromethane (DCM) (4 mL) were stirred at room temperature for 18 hrs. Additional sodium hydroxide (0.806 mL, 1.613 mmol) was added and stirred at room temperature for 4hr, after which time sodium hydroxide (0.806 mL, 1.613 mmol) was added and stirred at room temperature for a further 18 hrs.

DCM (4 mL) and water (4 mL) were added the layers were separated. Organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*, . The crude was purified by normal phase column chromatography (gradient 0 to 5% Cyclohexane/EtOAc) to give 70 mg of title compound 5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **4.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (d, *J*=1.00 Hz, 3H), 2.08 (d, *J*=1.01 Hz, 3H), 6.27-6.28 (m, 1H), 7.22 (d, *J*=8.34 Hz, 1H), 7.95 (dd, *J*=8.34, 2.53 Hz, 1H), 8.62 (d, *J*=2.53 Hz, 1H); .LC/MS, 1.41 min (ES+) m/z (relative intensity) 212/214 ([M + H]+.,95) method 2.

NOTE: 5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **5** is volatile, evaporation process was carried out without heating.

Synthesis of 5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **5**



To a solution of 5-bromo-2-methylpyridine **2** (200 mg, 1.163 mmol) in diethyl ether (7 mL) under Argon at 0 °C was added boron trifluoride etherate (0.158 mL, 1.279 mmol). The resulting suspension was stirred at 0ºC for 10 minutes. It was cooled to -78ºC and lithium diisopropylamide, 1.0 M in THF (1.628 mL, 1.628 mmol) was dropwise added to the reaction mixture. After 20 min, Acetone (0.256 mL, 3.49 mmol) was added, and the solution was brought to room temperature.

After 1hr, LC-MS showed a mixture of **2**, **1** and major peak corresponding with dehydration product (5-bromo-2-(2-methylprop-1-en-1-yl)pyridine) **5**.

The reaction mixture was quenched with water and it was extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, during concentration step material lost. The crude product was purified by normal phase column chromatography (cyclohexane/ ethyl acetate gradient 0-50%). To give the title compound 5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **5** 8 mg and recovered 5-bromo-2-methylpyridine **2** 86 mg**.** No 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** isolated.

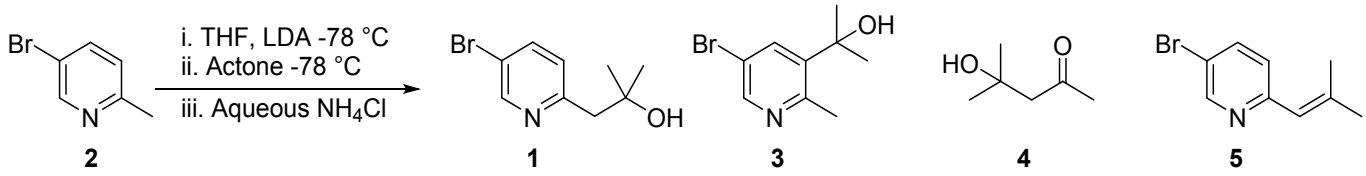
Note fractions concentrated *in vacuo* without heat.

5-Bromo-2-(2-methylprop-1-en-1-yl)pyridine **5** 8 mg ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (d, *J*=1.00 Hz, 3H), 2.08 (d, *J*=1.01 Hz, 3H), 6.27-6.28 (m, 1H), 7.22 (d, *J*=8.34 Hz, 1H), 7.95 (dd, *J*=8.34, 2.53 Hz, 1H), 8.62 (d, *J*=2.53 Hz, 1H)

5-Bromo-2-methylpyridine **2** 86 mg ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 7.26 (d, *J*=8.37 Hz, 1H), 7.91 (dd, *J*=8.37, 2.46 Hz, 1H), 8.55 (d, *J*=2.46 Hz, 1H)

Stability study

Synthesis of 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1**



2 **1** **3** **4** **5**

Dry acetone: Calcium sulfate (80 g, 588 mmol) was added to acetone (1800 mL), mixture was allowed to stand at room temperature overnight.

5-bromo-2-methylpyridine **2** (50 g, 291 mmol) was dissolved in dry Tetrahydrofuran (THF, 1000 ml)

Reactor system cooled to -70 °C, see Figure 15 in manuscript

Reactor flushed under at the flowing flow rates for 6min.

2M LDA in THF 1.3 ml/min

Feedline 5.98 g/min (THF)

Dry acetone 1.22ml/min

After initial 6 min changed to

2M LDA in THF 1.3 ml/min

Feedline 5.98 g/min 5-bromo-2-methylpyridine **2** in THF

Dry acetone 1.22ml/min

After a further 6 min, blockage on LDA line, LDA frozen in T-mixer

2M LDA replaced with 1M LDA in THF/Hexanes (1:7)

1M LDA 1.3 ml/min

Feedline 5.98 g/min 5-bromo-2-methylpyridine **2** in THF

Dry acetone 1.22 ml/min

Sampled every 3min during start up, see Figure S1

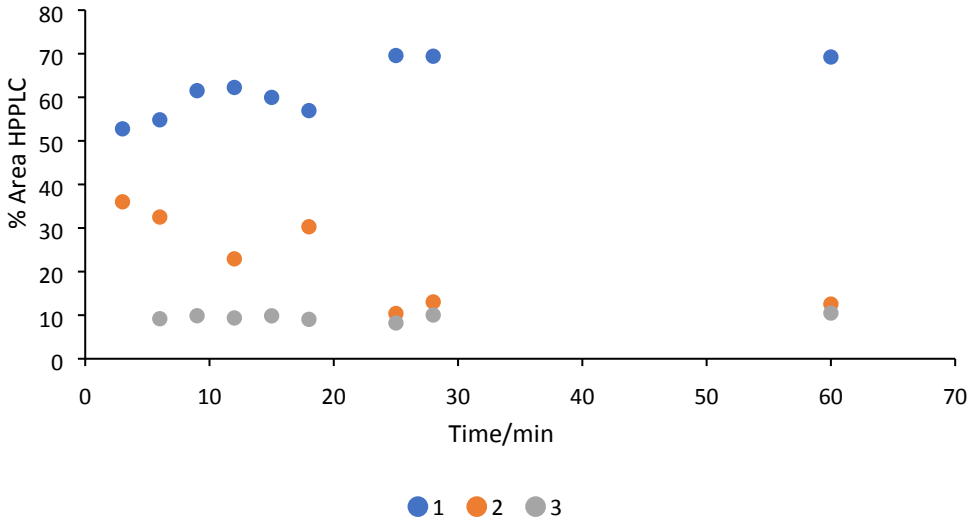
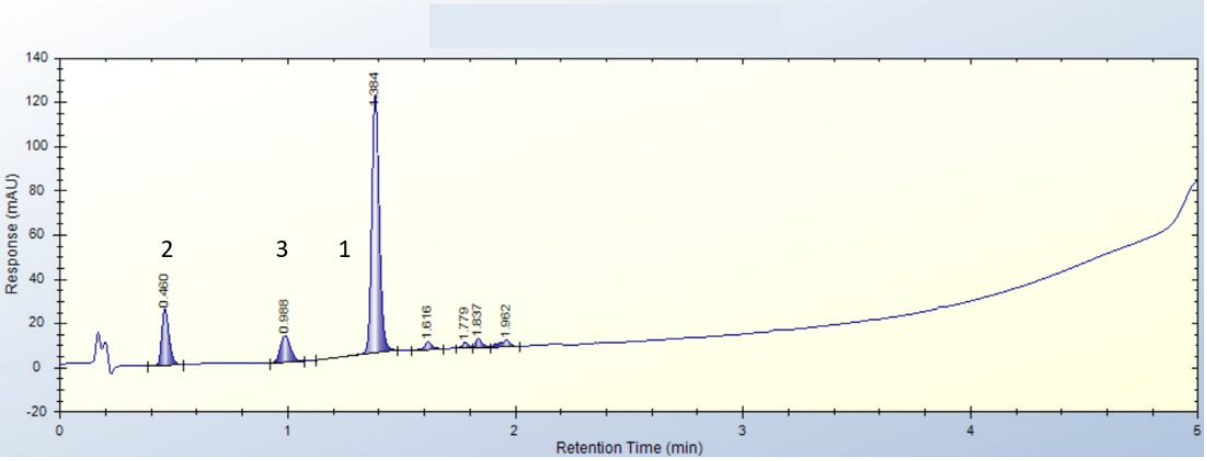


Figure S1. Reaction profile during start-up

After 18 min eq of LDA increased to 2.1eq, conversion increased to 69% however impurities increased after 28 min LDA eq returned to 1.4 eq and held at this for 1.5 hr, out flow collected for 1.5 hr to give 820 g of solution.

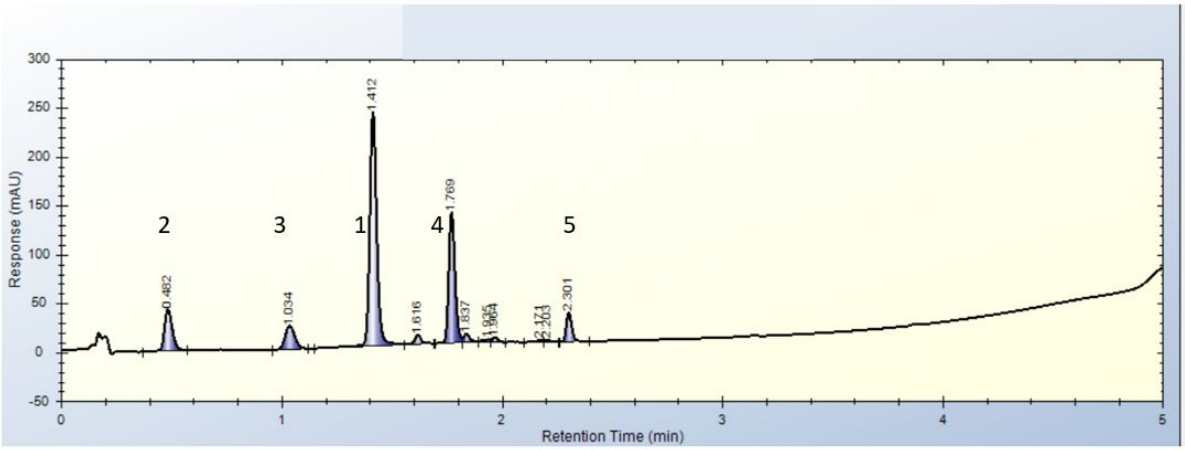
HPLC of bulk 67.9% **1**



Time (min)	%	Compound
0.46	14.24	2
0.99	9.58	3
1.38	67.94	1
1.62	2.15	Unknown
1.78	1.23	Unknown
1.84	2.08	Unknown
1.96	2.75	Unknown

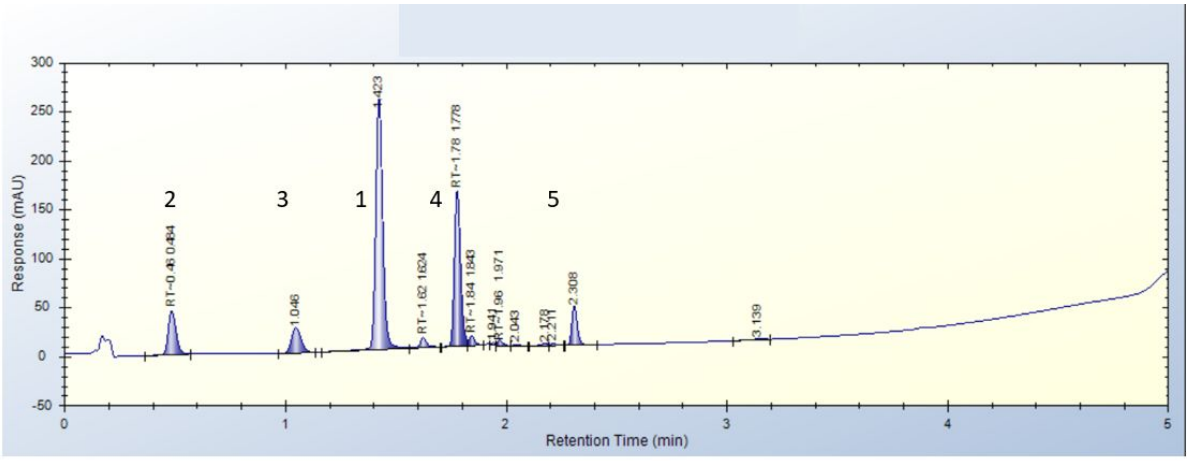
Bulk held at room temperature for 5 days,

HPLC of bulk after 2 days



Time (min)	%	Compound
0.48	9.62	2
1.03	6.74	3
1.42	49.10	1
1.62	1.93	Unknown
1.77	24.35	4
1.84	1.51	Unknown
1.93	0.46	Unknown
1.96	0.80	Unknown
2.17	0.46	Unknown
2.20	0.309	Unknown
2.30	4.71	5

HPLC of bulk after 5 days



Time (min)	%	Compound
0.48	9.28	2
1.05	6.57	3
1.42	46.90	1
1.62	1.85	Unknown
1.78	25.90	4
1.84	1.51	Unknown
1.97	0.76	Unknown
2.04	0.237	Unknown
2.18	0.388	Unknown
2.21	0.285	Unknown
2.31	5.73	5
3.14	0.299	Unknown

~200 mL of the bulk was taken and washed with ~150 mL of conc NH_4Cl and ~150 mL of sat NaCl. The organic solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain 8 g of crude material.

The crude was purified by chromatographic column (100 g Biotage column, Heptane:EtOAc 0-30%) to give. the title compound 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** as a

yellow oil 4.037 g and 2-(5-bromo-2-methylpyridin-3-yl)propan-2-ol **3 as** yellow waxy solid 751 mg.

1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** as a yellow oil 4.037 g

1H NMR (400 MHz, DMSO-d6) δ 1.09 (s, 7H), 2.80 (s, 2H), 3.26-3.37 (m, 1H), 4.55 (s, 1H), 7.20-7.39 (m, 1H), 7.88-7.98 (m, 1H), 8.55-8.65 (m, 1H); HPLC: tR = 1.30 min (TFA) (100% purity by UV); .LC/MS, 0.68 min (ES^+) m/z (relative intensity) 230.01/231.98 ($[M + H]^+$.,85).

2-(5-bromo-2-methylpyridin-3-yl)propan-2-ol **3** a yellow waxy solid 751 mg

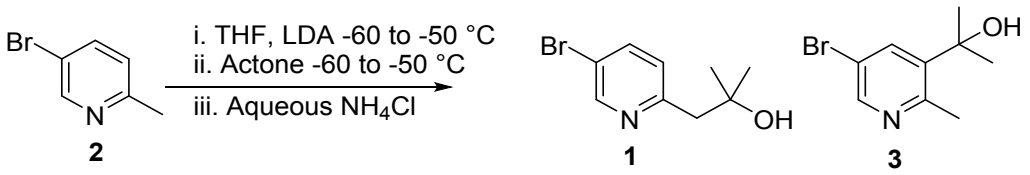
1H NMR (400 MHz, DMSO-d6) δ 1.58 (s, 6H), 2.44 (s, 3H), 3.32 (s, 2H), 5.46 (s, 1H), 7.65 (s, 1H), 8.48 (s, 1H) ; HPLC: tR = 1.30 min (TFA) (100% purity by UV); .LC/MS, 0.54 min (ES+) m/z (relative intensity) 230.02/232.01 ([M + H]+.,90).

4-hydroxy-4-methylpentan-2-one **4** not isolated.

5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **5** not isolated**, 5** is volatile at 40 ºC believed to have been removed during the concentration step.

In addition to confirm the non-volatility of 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** , it was subjected to 10 mbar at 40ºC on evaporator for 2 hr, no change in weight. However **1** observed to co-distil with solvents.

Synthesis of 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol monohydrochloride **1**



Dry acetone: Calcium sulfate (80 g, 588 mmol) was added to acetone (1800 mL), mixture was allowed to stand at room temperature overnight.

5-bromo-2-methylpyridine **2** (50 g, 291 mmol) was dissolved in dry Tetrahydrofuran (THF, 1000 ml)

Bottle to bottle variance of the same batch of 1M LDA in THF:Hexanes (1:7) had been observed, before any flow runs the bottle of LDA is use tested in small scale batch reactions.

1 mL 5-bromo-2-methylpyridine **2** in THF cooled to -70C 1.1 to 2.5 eq LDA added stirred for 2 min then quenched with 1 mL dry acetone added HPLC taken then quenched with 100 ul sat NH_4Cl soln. See Figure S2 for results

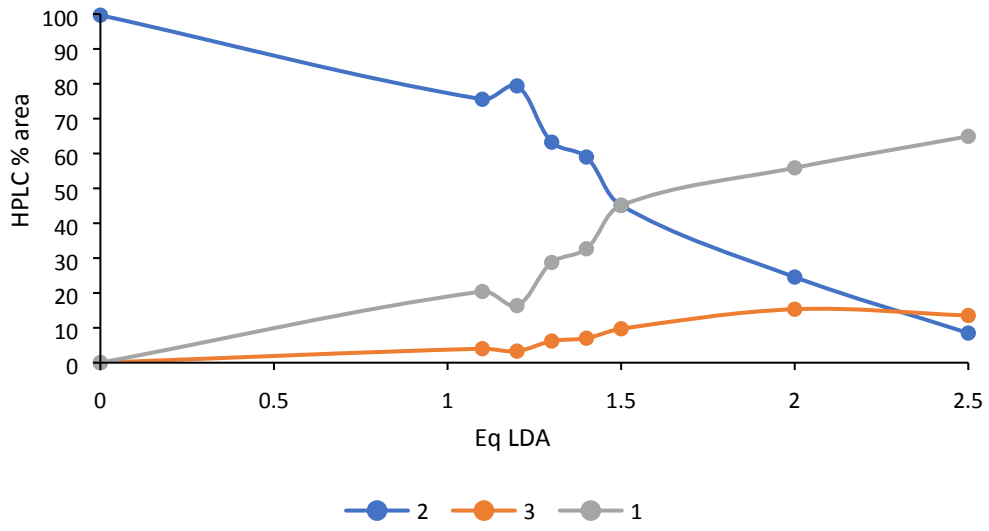


Figure S2. Eq LDA vs conversion to **1**

System cooled to -60 °C, flowed onto NH_4Cl quench

Start at 1.8 eq LDA, for 36min

1M LDA in THF:Heaxanes (1:7) 3.15 g/min
Feedline 7.85 g/min 5-bromo-2-methylpyridine **2** THF solution
Acetone 1.61 ml/min

2.1 eq for 30min
1M LDA in THF:Heaxanes (1:7) 3.51 g/min
Feedline 7.49 g/min 5-bromo-2-methylpyridine **2** THF solution
Acetone 1.53 ml/min

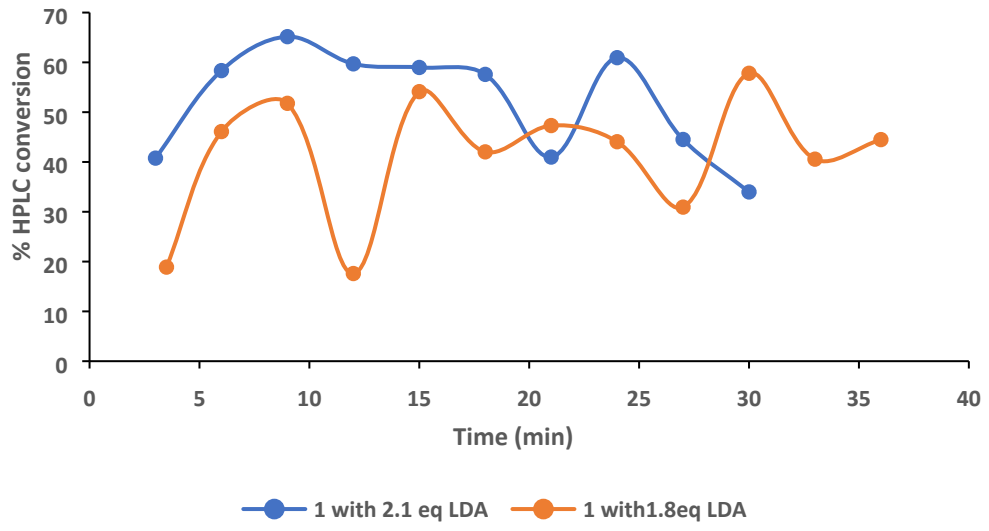


Figure S3. Conversion monitored over 30 min 1.8 eq LDA vs 2.1 eq LDA

~900 ml collected between the both runs, 643 ml 5-bromo-2-methylpyridine **2** THF solution (183.62 mmol) processed max yield of 42.25 g

Organic and aqueous separated.

Wgt of organic 771.02 g, d= 0.8362, 922.05 mL, HPLC 52.07% **1**, 32.72% **2**, 7.45% **3**

Concentrated *in vacuo* (130 mbar 40 °C) to give a brown oil 62.09 g, loaded onto a 50 g Biotage column, followed by a 340 g Biotage column (Heptane:EtOAc 0-30%).

Relevante fractions concentrated *in vacuo* (108 mbar 40 °C).

Recovered 5-bromo-2-methylpyridine **2** 7.75 g

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 7.26 (d, *J*=8.37 Hz, 1H), 7.91 (dd, *J*=8.37, 2.46 Hz, 1H), 8.55 (d, *J*=2.46 Hz, 1H)

Adjusting processed material for recovered **2** 183.62-45= 138.62 mmol max adjusted yield of **1** 31.897 g

Relevant fractions concentrated *in vacuo* (88 mbar 40 °C).

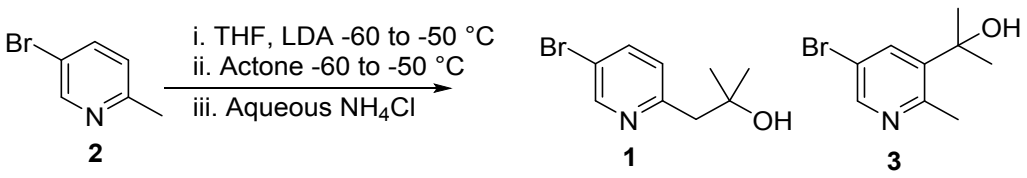
1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** to give a yellow oil, 20.48 g transferred a smaller flask with MeOH, and concentrated to give 15.34 g

NMR (DMSO-d6) trace MeOH, **1**: 4-hydroxy-4-methyl-2-pentanone (bpt 22 °C) 2.6:1

Note: 4-Hydroxy-4-methyl-2-pentanone, comes from the aldol of acetone with its self in the presence of LDA, further evaporation indicates that **1** co-distils with solvent.

Impure **1** dissolved in 10 ml EtOAc to this mixture was added 40 mL 2M HCl in ether an off white solid drops out of solution stirred at room temperature for 30 min, filtered, cake washed on funnel with 15 mL EtOAc, dried on high vac at 45 °C overnight. To give the title compound 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** as the monohydrochloride salt 13.9770 g. 38% 1H NMR (400 MHz, DMSO-d6) δ 1.11 (s, 6H), 2.88 (s, 2H), 7.38-7.52 (m, 1H), 7.77 (br s, 1H), 8.05-8.23 (m, 1H), 8.65-8.84 (m, 1H); HPLC: tR = 1.31 min (TFA) (99.09% purity by UV);

Synthesis of 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** final processing run



Bottle to bottle variance of the same batch of 1M LDA in THF:Hexanes (1:7) had been observed, before any flow runs the 500 mL bottles of LDA were use tested in small scale batch reactions.

1 mL 5-bromo-2-methylpyridine **2** (50 mg) in THF cooled to -70 °C 1.1 to 2.1 eq LDA added stirred for 2 min then quenched with 1 mL dry acetone added HPLC taken then quenched with 100 ul sat NH_4Cl soln. See **Figure S4** for results

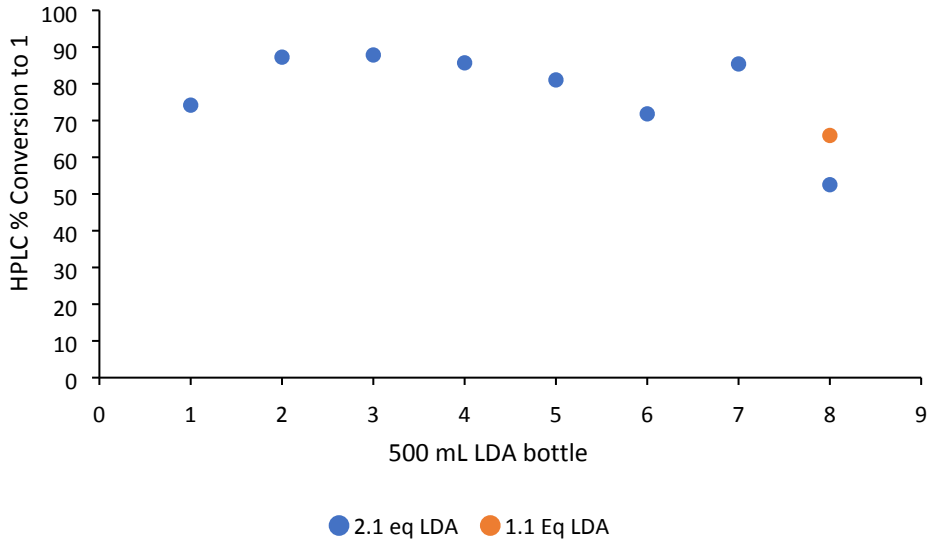


Figure S4. Results of use test of 500 mL bottles of LDA in THF:hexanes from the same batch.

Details of processing runs in main manuscript.

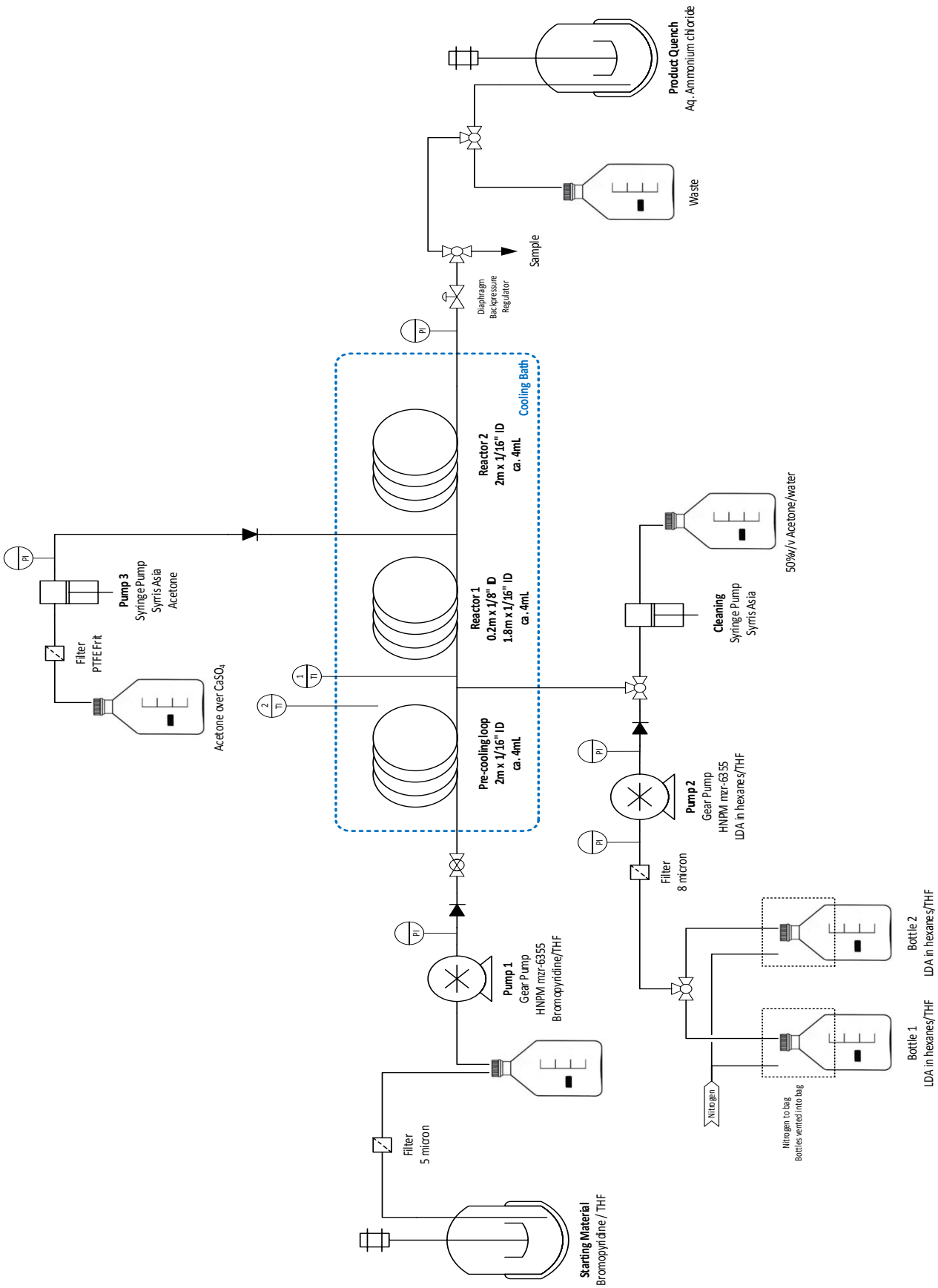


Figure S5. Final equipment diagram for flow synthesis of **1**.

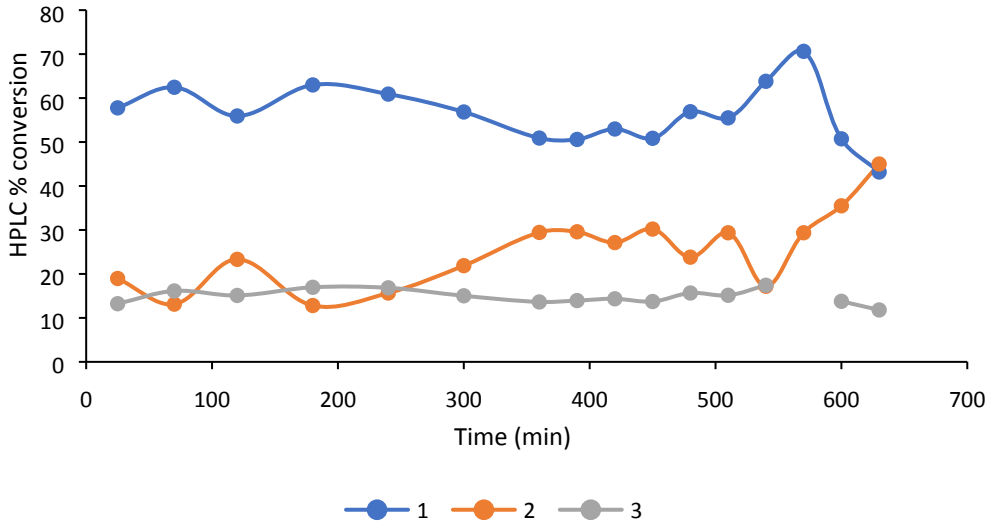
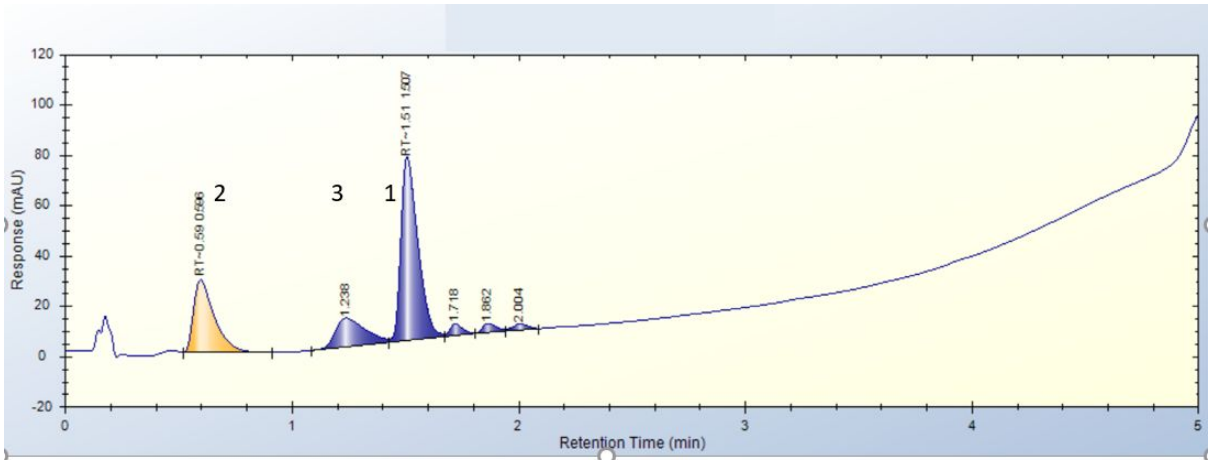


Figure S6. Reaction profile over 10 hr processing 300 g **2** figure 19 in manuscript.

HPLC of bulk from processing 300 g **2**



Note: Peaks are broad due defective guard column

Time (min)	%	Compound
0.59	25.9	2
1.24	14.5	3
1.51	53.4	1
1.72	2.5	Unknown
1.86	2.08	Unknown
2.00	1.64	Unknown

Results

Solution d=0.8275

Vessel weight 7.98 kg

Vessel tare 2.66 kg

Solution weight 5.32 kg

Solution volume 6.43 L

Solution volume 6429.61 mL

Solution assay of **1** 119795.9331 mg

Solution assay of **1** 119.80 g 30 %

Concentrated in vacuo (130 mbar 40 °C) to give a brown oil 1105 g, 498 g loaded onto a 3 kg Biotage column (Heptane:EtOAc 0-40%, two 498 g batches purified). **Note** Part of batch (109 g, ~ 15 g of **1**) lost during an attempt at distilling the crude product.

Relevante fractions concentrated *in vacuo* (100 mbar 40 °C).

To remaining solution 250 ml 4M HCl in dioxane added, an off white solid drops out of solution stirred at room temperature for 30 min, filtered, cake washed on funnel with 150 mL EtOAc, dried on high vac at 45 °C overnight.

To give the title compound 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1** in two batches as the monohydrochloride salt.

Batch 1 66.4 g 14.3%

Batch 2 64.7 g 13.9%

1H NMR (400 MHz, DMSO-d6) δ 1.11 (s, 6H), 2.88 (s, 2H), 7.38-7.52 (m, 1H), 7.77 (br s, 1H), 8.05-8.23 (m, 1H), 8.65-8.84 (m, 1H)

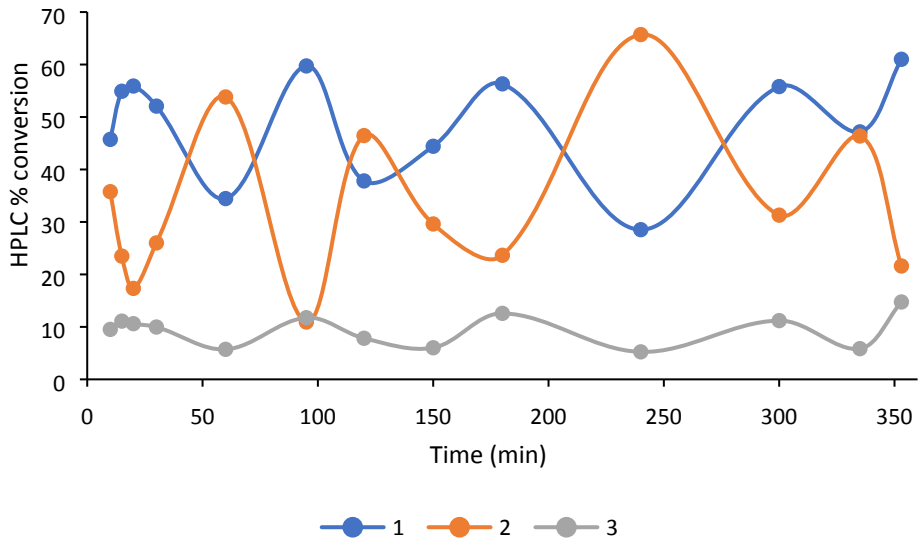
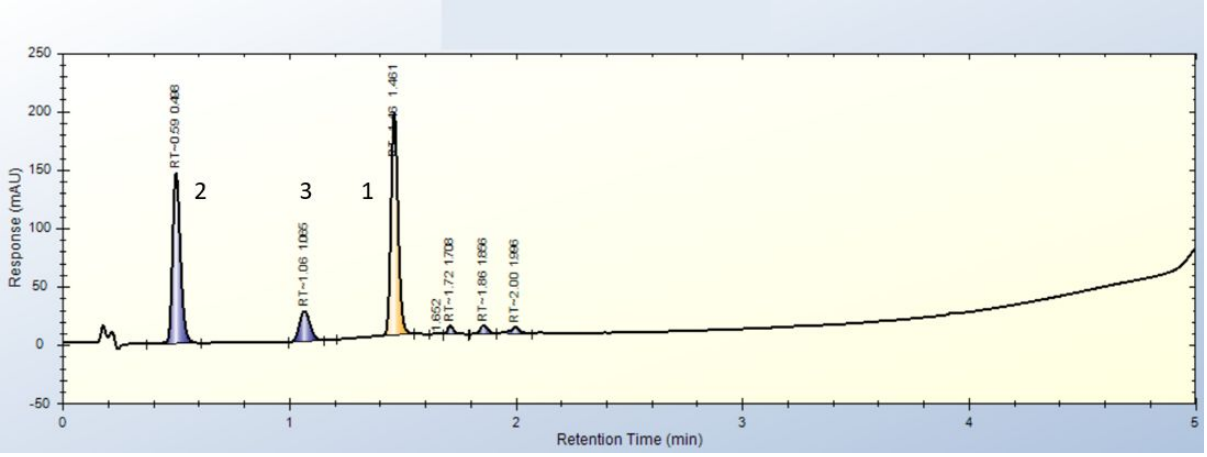


Figure S7. Reaction profile over 6 hr processing 200 g **2**, shape of graph is due to LDA filter blinding over time, figure 21 in manuscript..

HPLC of bulk from processing 200 g **2**



Time (min)	%	Compound
0.59	39.1	2
1.24	9.4	3
1.51	45.8	1
1.72	1.7	Unknown
1.86	2.0	Unknown
2.00	1.8	Unknown

Vessel weight 6.69 kg

Vessel tare 2.66 kg

Solution weight 4.03 kg

Solution volume 4.87 L

Solution volume 4868.88 mL

Solution assay of **1** 89733.31 mg

Solution assay of **1** 89.73 g 33.5%

Concentrated in vacuo (130 mbar 40 °C) to give a brown oil 317 g, loaded onto a 1.5 kg Biotage column (Heptane:EtOAc 0-30%).

Relevante fractions concentrated in vacuo (100 mbar 40 °C).

To remaining solution 100 ml 4M HCl in dioxane added, an off white solid drops out of solution stirred at room temperature for 30 min, filtered, cake washed on funnel with 100 mL EtOAc, dried on high vac at 45 °C overnight.

To give the title compound 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol 1 in two batches as the monohydrochloride salt, 95.42 g, 30.8 %

1H NMR (400 MHz, DMSO-d6) δ 1.11 (s, 6H), 2.88 (s, 2H), 7.38-7.52 (m, 1H), 7.77 (br s, 1H), 8.05-8.23 (m, 1H), 8.65-8.84 (m, 1H)

Photos of 2M LDA in THF/heptane/ethylbenzene after cooling to <-60°C

Figure S8 supports Table 1 in main manuscript.

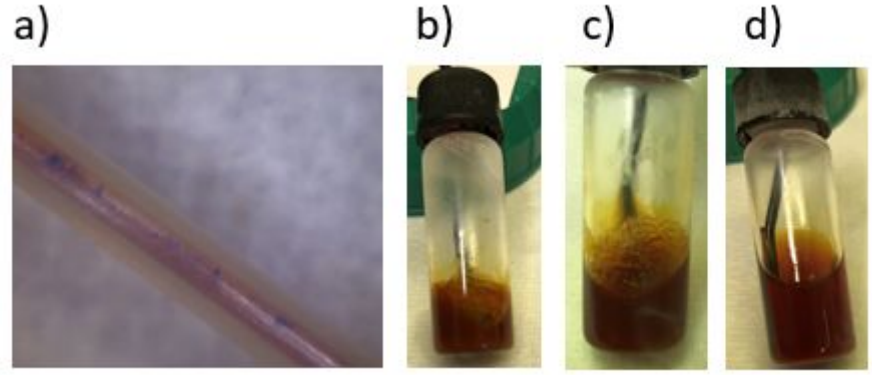
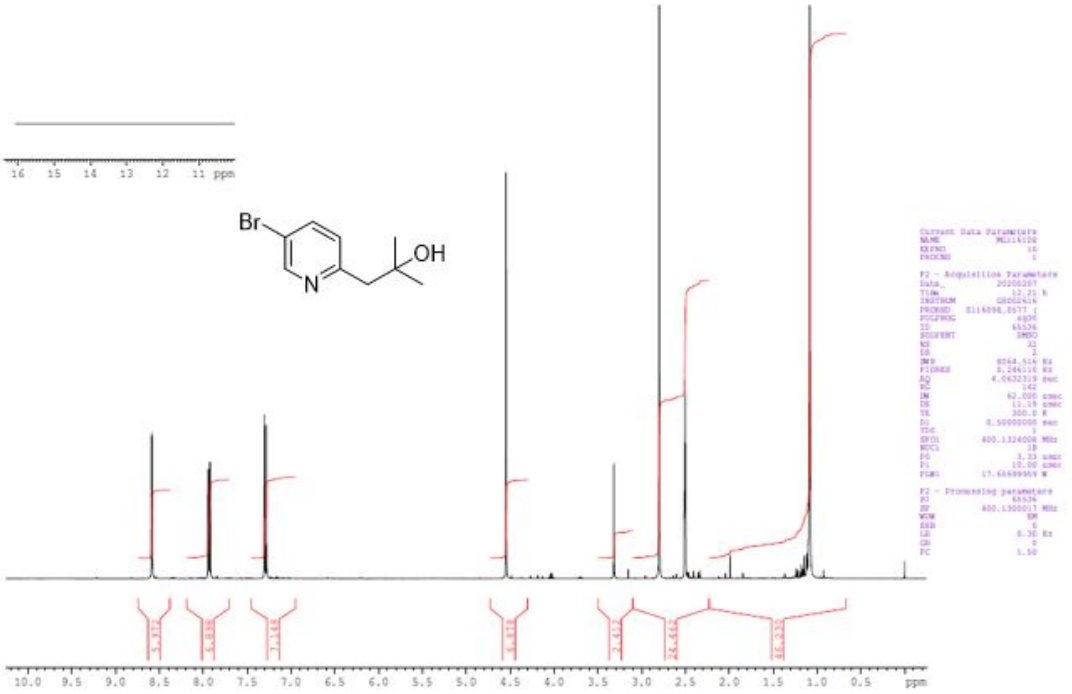


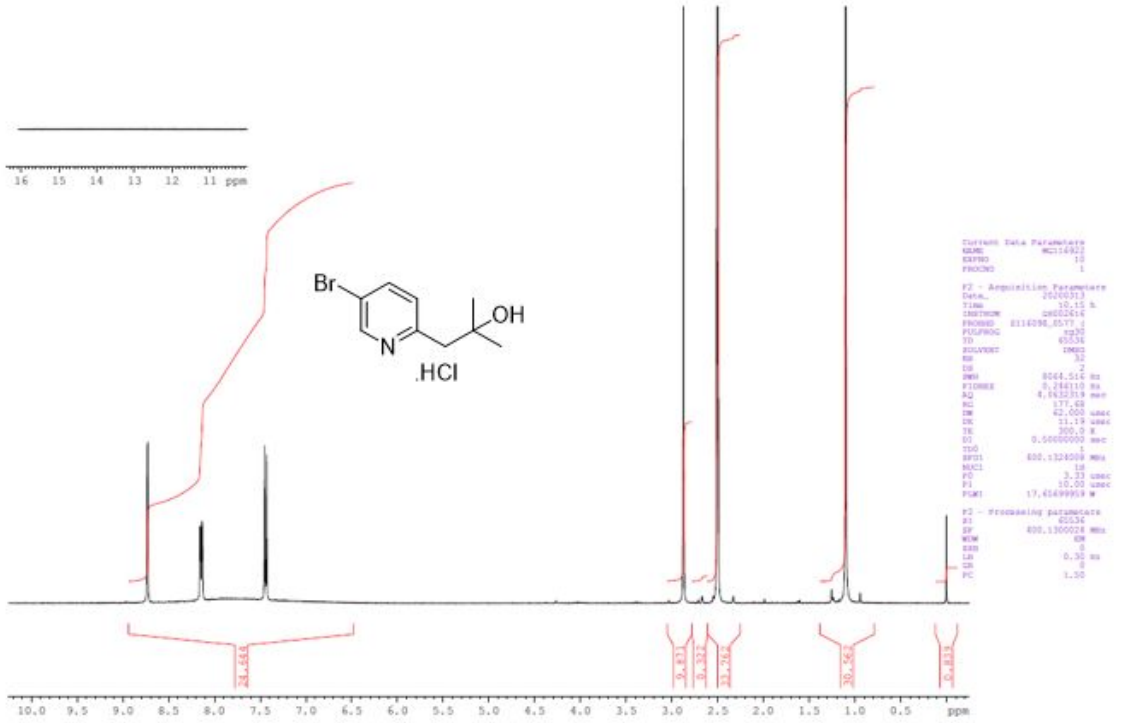
Figure S8. a) 2M LDA in THF/heptane/ethylbenzene in 1/32th ID tubing held at -70 °C solids in tubing, b) 2M LDA in THF/heptane/ethylbenzene in 4 ml Wheaton vial at -66 °C frozen solid, c) 1.538M LDA in THF/heptane/ethylbenzene in 4 ml Wheaton vial at -67 °C, semi-solid, d) 2M LDA in THF/heptane/ethylbenzene in 4 ml Wheaton vial at -68.1 °C solution.

NMR Spectra

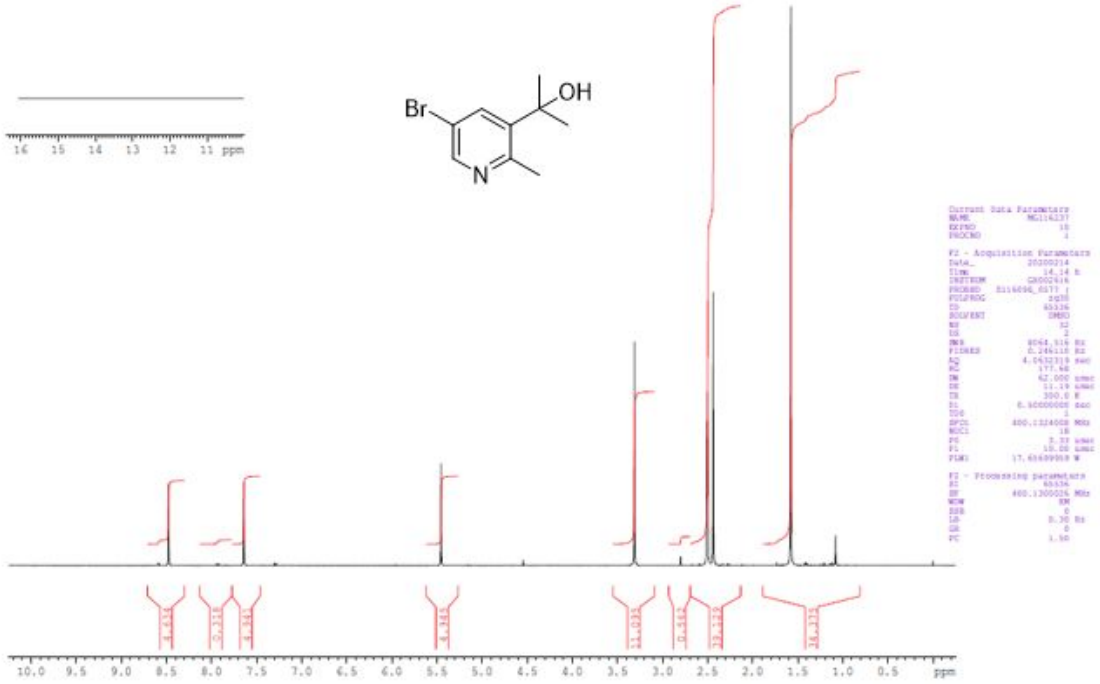
^{1}H NMR DMSO 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol **1**



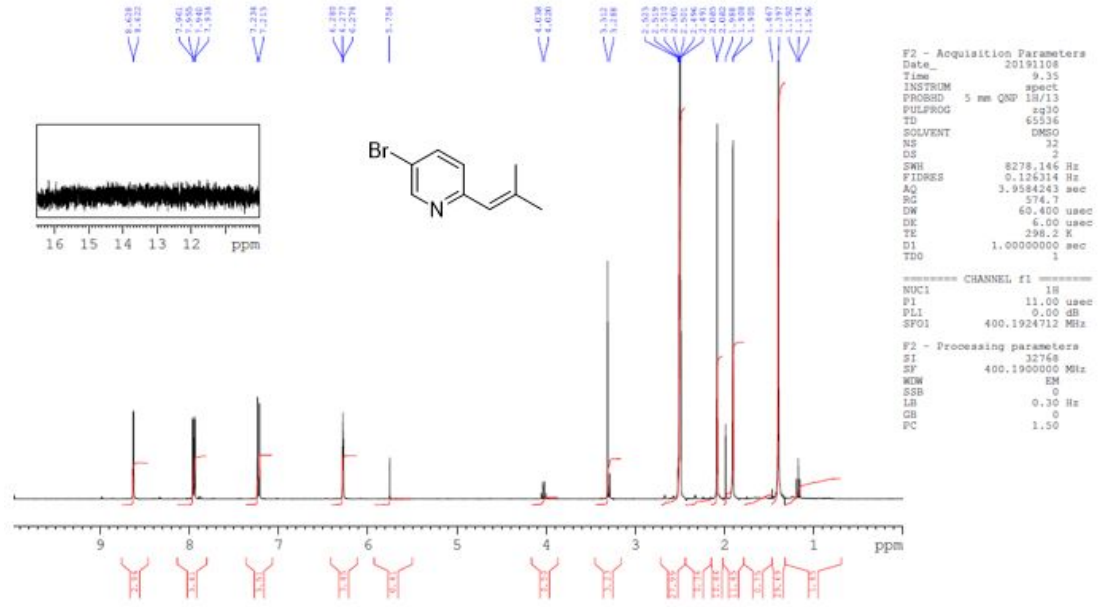
^{1}H NMR DMSO 1-(5-bromopyridin-2-yl)-2-methylpropan-2-ol monohydrochloride **1**



^{1}H NMR DMSO 2-(5-bromo-2-methylpyridin-3-yl)propan-2-ol **3**

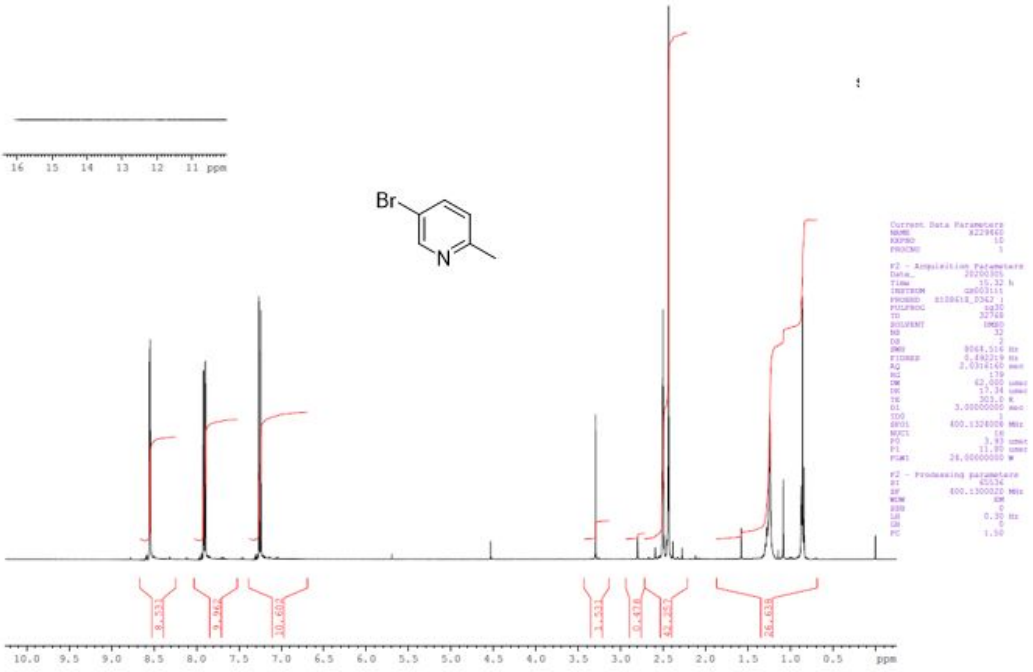


^{1}H NMR DMSO 5-bromo-2-(2-methylprop-1-en-1-yl)pyridine **5**



Note: NMR contains cyclohexane (1.40 ppm), trace DCM and trace ethyl acetate.

[1]H NMR DMSO 5-bromo-2-methylpyridine **2**



Note: NMR contains heptane.