Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Electronic Supplementary Information

Rapid formation of 2-lithio imidazole derivatives and their reaction with a range of electrophiles in flow

Simeng Wang, Jenny-Lee Panayides, Darren Riley, Chris Tighe, Klaus Hellegardt, Mimi Hii and Philip W. Miller

1 Batch Reactions

1.1 General procedure

All starting materials, reagents, and solvents were purchased from commercial suppliers (and used as received). Reactions requiring inert condition were performed using Schlenk technique. NMR spectra were recorded at 400 MHz for ^{1}H and 101 MHz for ^{13}C on a Bruker AV-400 spectrometer at room temperature in DMSO-d_6 or $CDCl_3$. The spectra were analysed using MestReNova 14.1.0. High-resolution mass spectrometry (HRMS) data was obtained via Electrospray (ES) or Atmospheric Pressure Chemical Ionisation (APCI) on a Thermo Scientific Q-Exactive system. FTIR measurements were performed on a Bruker Alpha P spectrometer with DGTS detector and diamond ATR accessory.

1.2 2-Substitution reaction procedures in batch

1.2.1 1-Tritylimidazole (2)

Under vigorous stirring, imidazole (34 g, 0.5 mmol) and trityl chloride (140 g, 0.5 mol) was mixed with 500 mL of dichloromethane at 0 °C. At the same temperature, triethylamine (70 mL, 0.5 mol) was added via a dropping funnel over 30 minutes. The reaction was warmed up to room temperature and stirred for 12 hours. The white suspension formed was dissolved after the addition of 200 mL of water. Dichloromethane was removed *in-vacuo* to yield an off-white slurry in water. The slurry was filtered and dried over 6 hours to form a white cake as the crude product. The crude product was recrystallised in ethanol to yield 1-tritylimidazole as a white needle-like crystal (147 g, 0.474 mol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.46 (t, *J* = 1.2 Hz, 1H), 7.37 – 7.30 (m, 9H), 7.18 – 7.11 (m, 6H), 7.07 (t, *J* = 1.2 Hz, 1H), 6.83 (t, *J* = 1.4 Hz, 1H). MS (ES+): *m*/*z* calcd for $C_{22}H_{18}N_2 + H^+$: 437. 1543 $[M+H]^+$; found: 311.1554;

1.2.2 2-Methyl-1-(triphenylmethyl)imidazole (4a)

1-Tritylimidazole (0.5 g, 1.67 mmol) was dissolved in 10 mL of anhydrous THF in a dry flask under nitrogen and cooled to -78 °C. A solution of n-butyllithium (1.6 M, 1.1 mL, 1.75 mmol, 1.05 equiv) was added dropwise. The reaction mixture was stirred at this temperature for 1 hour. A solution of methyl iodide in anhydrous THF (0.5 M, 3.7 mL, 1.84 mmol, 1.05 equiv) was added slowly. The reaction was allowed to gradually warm up to room temperature and stirred for 2 hours. Under vigorous stirring, 0.5 mL of triethylamine was added to the reaction. The mixture was passed through a short layer of celite in ethyl acetate. The filtrate was concentrated *in vacuo* to yield a pale yellow solid. The crude solid was purified with column chromatography (silica, petroleum ether/EtOAc 1:1) to yield the pure product as a white solid (461 mg, 1.42 mmol, 85 %). ^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.40 – 7.28 (m, 10H), 7.20 – 7.06 (m, 6H), 6.90 (d, *J* = 1.5 Hz, 1H), 6.71 (d, *J* = 1.5 Hz, 1H), 1.64 (s, 3H).

1.2.3 2-Chloro-1-(triphenylmethyl)imidazole (5a)

1-Tritylimidazole (2.0 g, 6.68 mmol) was dissolved in 50 mL of anhydrous THF in a dry flask under nitrogen to yield a colourless solution. This solution was cooled to -78 °C and a solution of n-butyllithium (1.6 M, 4.5 mL, 7.2 mmol, 1.08 equiv) was added dropwise. The reaction mixture was stirred at this temperature for 1 hour and the reaction gradually turned red. At the same temperature, trichloroisocyanuric acid was added (0.62 g, 2.67 mmol, 0.4 equiv). The light brown solution obtained was allowed to gradually warm up to room temperature and stirred for 12 hours. The mixture was passed through a short layer of celite in ethyl acetate. The pale solution obtained was concentrated *in vacuo* to yield a yellow solid. The crude solid was purified with column chromatography (silica, petroleum ether/EtOAc 1:1) to yield the pure product as a white crystal (1.41 g, 4.07 mmol, 61 %). ^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.43 – 7.27 (m, 10H), 7.20 – 7.08 (m, 7H), 6.94 (d, *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 1.7 Hz, 1H). HRMS (ES+): *m*/*z* calcd for $C_{22}H_{17}N_2Cl$ +H^+: 345.1159 [*M*+H]$^+$; found: 345.1169;

1.2.4 2-Bromo-1-(triphenylmethyl)imidazole (6a)

1-Tritylimidazole (0.5 g, 1.67 mmol) was dissolved in 10 mL of anhydrous THF in a dry flask under nitrogen and cooled to -78 °C. A solution of n-butyllithium (1.6 M, 1.15 mL, 1.84 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at this temperature for 1 hour. A solution of N-bromosuccinimide (327 mg, 1.84 mmol, 1.1 equiv) in 5 mL of anhydrous THF was added slowly. The yellow solution obtained was allowed to gradually warm up to room temperature and stirred for 12 hours. 1 mL of water was added to the reaction, followed by 10 mL of saturate sodium sulphite solution. The product was extracted with 20 mL of ethyl acetate and washed twice with 20 mL of brine. The organic layer was dried over magnesium sulphate and concentrated *in vacuo* to yield a yellow solid. The solid was purified with column chromatography (silica, petroleum ether/EtOAc 1:1) to yield the pure product as a white crystal (377 mg, 0.97 mmol, 58 %). ^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.42 – 7.29 (m, 9H), 7.20 – 7.09 (m, 6H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H). HRMS (APCI): *m*/*z* calcd for $C_{22}H_{17}IN_2$ +H^+: 389.0648 [*M*+H]$^+$; found: 389.0638;

1.2.5 2-Iodo-1-(triphenylmethyl)imidazole (7a)

1-Tritylimidazole (0.5 g, 1.67 mmol) was dissolved in 10 mL of anhydrous THF in a dry flask under nitrogen to yield a colourless solution. This solution was cooled to -78 °C and a solution of n-butyllithium (1.6 M, 1.2 mL, 1.92 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 10 minutes and warmed up to -10 °C for 30 minutes. The reaction gradually turned red during this time. The reaction was cooled to -78 °C and a solution of iodine (0.42 g, 1.67 mmol) in 5 mL of anhydrous THF was added slowly. The light brown solution obtained was allowed to gradually

warm up to room temperature and stirred for 12 hours. Under vigorous stirring, 1 mL of water was added to the reaction, followed by 10 mL of saturate sodium sulphite solution until the reaction turned pale yellow. The product was extracted with 20 mL of ethyl acetate and washed twice with 20 mL of brine. The organic layer was dried over magnesium sulphate and concentrated *in vacuo* to yield a yellow solid. The solid was purified with column chromatography (silica, petroleum ether/EtOAc 1:1) to yield the pure product as a white crystal (474 mg, 1.09 mmol, 65 %). ^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.39 – 7.34 (m, 9H), 7.21 – 7.17 (m, 6H), 7.04 (d, *J* = 1.5 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H). HRMS (APCI): *m*/*z* calcd for $C_{22}H_{17}IN_2$ +H$^+$: 437.0509 [*M*+H]$^+$; found: 437.0504.

1.3 General procedure for deprotection reactions in batch

100 mg of the 2-substituted products were dissolved in 5 mL of MeOH in a sealed vial. 0.25 mL of glascial acetic acid was added and the reaction was heated at 60 °C for 12 hours. After cooling to room temperature, the volatiles were removed. 5 mL of water was added to the residues and the mixture was sonicated for 5 minutes before being filtered. The filtrate was concentrated *in vacuo* to yield the deprotected product.

2-Methylimidazole (4b): product isolated as a white solid (23.5 mg, 0.287 mmol, 93%)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.65 (s, 1H), 6.83 (s, 2H), 2.25 (s, 3H). HRMS (ES+): *m*/*z* calcd for $C_4H_6N_2$ +H$^+$: 83.0609 [*M*+H]$^+$; found: 83.0613;

2-Chloroimidazole (5b): product isolated as a white crystalline solid (26.2 mg, 0.255 mmol, 88%)
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 7.03 (s, 2H). HRMS (APCI): *m*/*z* calcd for $C_{22}H_{17}IN_2$ +H$^+$: 437.0509 [*M*+H]$^+$; found: 437.0504;

2-Bromoimidazole (6b): product isolated as a pale yellow solid (28.7 mg, 0.195 mmol, 76%)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.38 (br, 1H), 7.05 (s, 2H).

2-Iodoimidazole (7b): product isolated as a white solid (35.1 mg, 0.181 mmol, 79%)
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.04 (s, 2H). HRMS (APCI): *m*/*z* calcd for $C_3H_2IN_2$ +H$^+$: 194.9414 [*M*+H]$^+$; found: 194.9409;

2 Flow Reactions

2.1 General procedures

The flow reactions were performed with NewEra ER-1000 Syringe Pumps. Reagents were loaded to Norm-Ject Luer Lock Plastic Syringe. The sizes of syringes used include 10 mL (diameter 15.90 cm),

20 mL (diameter 20.05 cm) and 50 mL (diameter 29.20 cm). FEP tubings were used at the channel (ID = 1 mm) and T-junction (ID = 2 mm) was used to connected the channels.

Prior to the reactions, the reaction channels were rinsed with 50 mL of acetone and dried by passing through nitrogen gas over 30 minutes. The channels were further rinsed with 50 mL of anhydrous THF before loading the reagents. The samples were collected after the reagents were equilibrated in the channel for at least 5 channel volumes.

2.2 Lithiation flow condition optimisation (Set-up A and B)

2.2.1 Procedure

20 mL of 0.16 M 1-tritylimidazole solution and 20 mL of THF (only for Set-up B) were loaded onto a 20 mL Luer-lock syringes while 4 mL of 1.6 M n-butyllithium in hexane was loaded onto a 10 mL Luer-lock syringe. 2 mL of MeI (0.5M in THF) solutions were added in a sealed vial with a magnetic stirrer under nitrogen. The sample were collected in the vial with stirring. The system was constructed as described in figure S1.

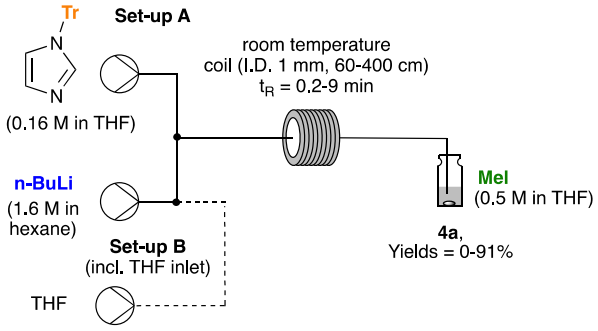


Figure S1. Flow Set-up A and B for optimisation of lithiation condition.

2.2.2 NMR Sample preparation

To the samples obtained from the flow reaction, 1 mL of triethylamine were added with stirring. The mixture was filtered through a short layer of celite and rinsed with 2 mL of ethyl acetate to remove the white precipitates. 50 µL of freshly prepared 1,3,5-trimethoxybenzene solution was added to the samples (0.041 mmol, 138 mg/mL in ethyl acetate). The mixtures were concentrated in-vacuo and dried under vacuum for 1 hour. 0.8 mL of chloroform-*d* was added to yield a clear solution for the analysis.

2.2.3 Result analysis

The NMR conversion and yield were calculated with reference to the internal standard. The decomposition was estimated from the difference between the number of moles of the expected product and the sum of product and unreacted starting materials.

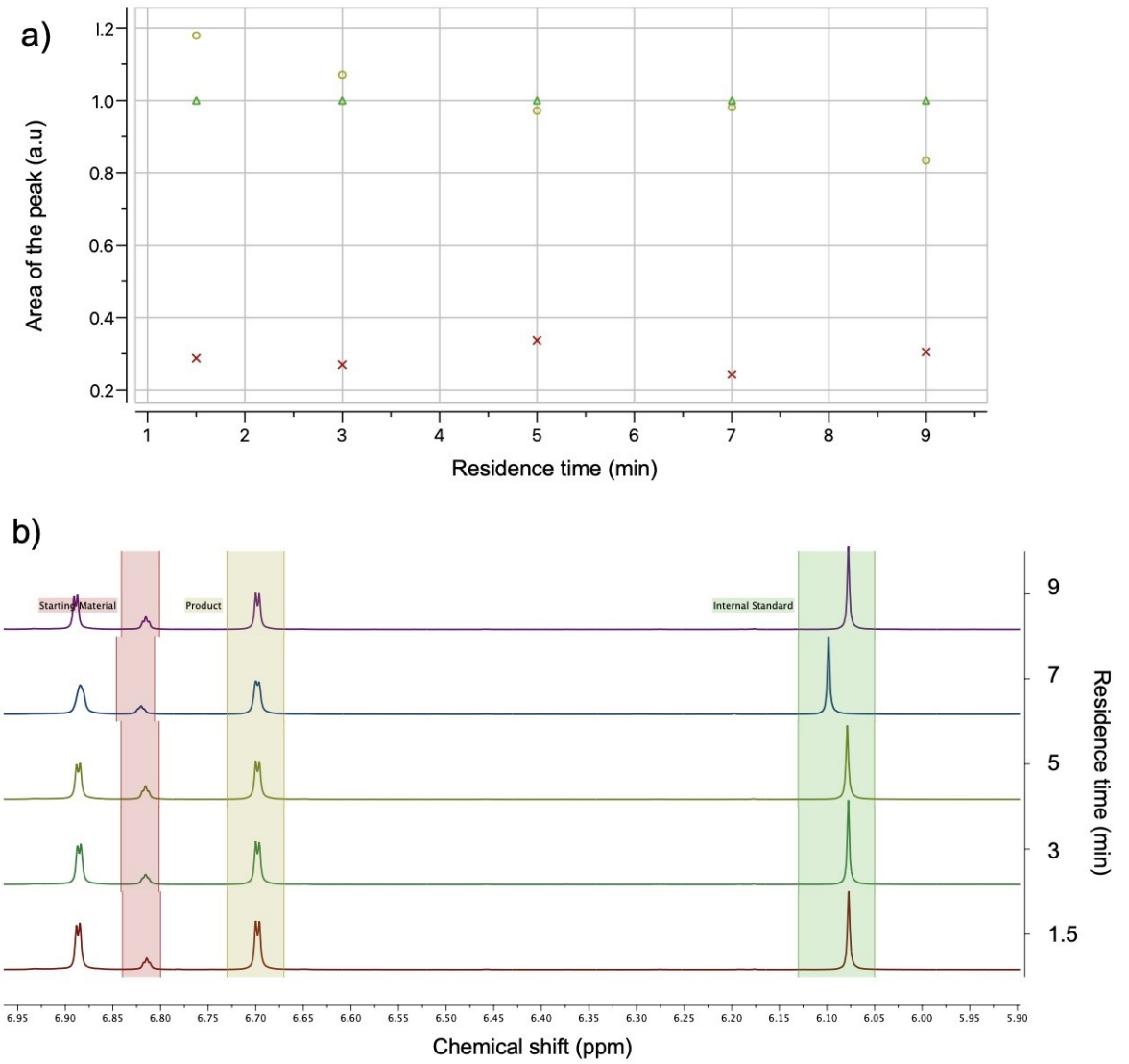


Figure S2. NMR analysis of the sample obtained from set-up A, revealing the decomposition of the starting materials. a)area under curve against the residence time, b) NMR traces against the chemical shifts. Starting material – 1-tritylimidazole, product – 2-methyl-1-tritylimidazole, internal standard – 1,3,5-trimethoxybenzene.

t^R /min	Starting material			Product			Decomposition	
	Integral	**n /mmol**	**%**	**Integral**	**n /mmol**	**%**	**n /mmol**	**%**
1.5	0.287	0.035	18%	1.179	0.145	75%	0.013	7%
3	0.27	0.033	17%	1.07	0.132	68%	0.028	15%
5	0.337	0.041	21%	0.972	0.120	62%	0.032	17%
7	0.242	0.030	15%	0.981	0.121	62%	0.043	22%
9	0.305	0.038	19%	0.834	0.103	53%	0.053	27%

Table S1. The data of the NMR analysis showing the percentage conversion, yield and decomposition.

2.3 Electrophile screening in flow (Set-up C)

2.3.1 Procedure

20 mL of 0.16 M 1-tritylimidazole solution and 20 mL of THF were loaded onto a 20 mL Luer-lock syringes, 4 mL of 1.6 M n-butyllithium in hexane and 10 mL of electrophile solution was loaded onto a 10 mL Luer-lock syringe. The sample were collected in the vial loaded with 5 mL distill water with a magnetic stirrer. The system was constructed as described in figure S3.

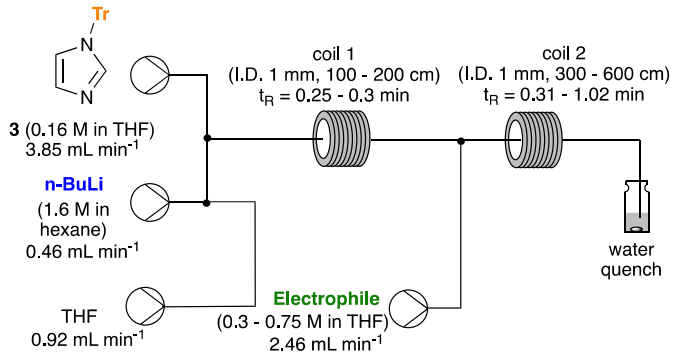


Figure S3. Flow set-up C used for all substrate testing

Entry	Electrophile	t_R / min		coil length / cm		Electro.	Electro.	Flow Rate / mLmin^{-1}			
		Lith.	Subs.	coil 1	coil 2	equiv.	conc / M	nBuLi	THF	3	Electro.
1	MeI	0.3	0.31	200	300	1.2	0.3	0.46	0.92	3.85	2.46
2	C_2Cl_6	0.3	0.51	200	500	1.2	0.3	0.46	0.92	3.85	2.46
3	$C_2Br_2Cl_4$	0.3	0.51	200	500	1.2	0.3	0.46	0.92	3.85	2.46
4	I_2	0.3	0.31	200	300	1.2	0.3	0.46	0.92	3.85	2.46
5	EtI	0.25	1.02	100	600	1.8	0.45	0.28	0.55	2.31	1.48
6	BuI	0.25	1.02	100	600	1.8	0.45	0.28	0.55	2.31	1.48
7	4-methoxy benzyl iodide	0.3	0.31	200	300	1.2	0.3	0.46	0.92	3.85	2.46
8	DMF	0.3	0.31	200	300	3.0	0.75	0.46	0.92	3.85	2.46
9	2-octanone	0.3	0.61	200	600	1.2	0.3	0.46	0.92	3.85	2.46
10	$ClCO_2Et$	0.3	0.61	200	600	1.2	0.3	0.46	0.92	3.85	2.46
11	diphenyl disulfide	0.3	0.61	200	600	1.2	0.3	0.46	0.92	3.85	2.46
12	TMSCl	0.3	0.31	200	300	1.2	0.3	0.46	0.92	3.85	2.46
13	TIPSCl	0.3	0.61	200	600	1.2	0.3	0.46	0.92	3.85	2.46

Table S2. Set-up details for substrate screening for all electrophiles. Lith. – lithiation, Subs. – subsitution, Electro. – electrophile.

2.4 10 min flow scale-up reaction with MeI (Set-up C)

50 mL of 0.16 M 1-tritylimidazole solution and 40 mL of MeI solution (0.3 M in THF) were loaded onto 50 mL Luer-lock syringes. 6 mL of 1.6 M n-butyllithium in hexane onto a 10 mL Luer-lock syringe while 20 mL of THF was loaded onto a 20 mL syringe. The system was constructed as described in figure S3. The sample were collected in a conical flask loaded with 50 mL distill water with a magnetic stirrer. The collection began after the system was equilibrated for 1 minute.

2.5 Characterisation of products from flow reactions

2.5.1 2-Ethyl-1-tritylimidazole (8)

^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.37 – 7.28 (m, 9H), 7.16 – 7.09 (m, 6H), 6.97 (d, *J* = 1.5 Hz, 1H), 6.67 (d, *J* = 1.5 Hz, 1H), 1.90 (q, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ = 151.7, 142.6, 129.9, 129.8, 128.0, 127.8, 125.34, 121.0, 23.9, 11.7. HRMS (ES+): *m*/*z* calcd for $C_{24}H_{22}N_2$ +H^+: 339.1861 [*M*+H]$^+$; found: 339.1857;

2.5.2 2-Butyl-1-tritylimidazole (9)

^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.38 – 7.28 (m, 9H), 7.21 – 7.08 (m, 6H), 6.95 (d, *J* = 3.6 Hz, 1H), 6.67 (d, *J* = 3.7 Hz, 1H), 1.96 – 1.84 (m, 2H), 1.25 – 1.16 (m, 2H), 1.02 – 0.88 (m, 2H), 0.62 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.7, 129.9, 128.0, 127.7, 125.4, 120.9, 30.4, 29.6, 22.5, 13.7. HRMS (ES+): *m*/*z* calcd for $C_{26}H_{26}N_2$ +H^+: 367.2174 [*M*+H]$^+$; found: 367.2177;

2.5.3 2-(1,2-Bis(4-methoxyphenyl)ethyl)-1-tritylimidazole (10)

^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.30 – 7.15 (m, 10H), 7.11 – 7.03 (m, 6H), 6.93 – 6.80 (m, 2H), 6.70 (d, *J* = 1.5 Hz, 1H), 6.55 (tdd, *J* = 8.0, 2.6, 1.0 Hz, 2H), 6.40 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.10 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.03 (dt, *J* = 7.6, 1.3 Hz, 1H), 5.96 (dd, *J* = 2.6, 1.5 Hz, 1H), 3.54 (d, *J* = 7.2 Hz, 7H), 3.13 – 3.02 (m, 1H), 2.84 (dd, *J* = 13.1, 4.4 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ = 158.9, 158.4, 142.4, 129.9, 128.5, 128.1, 128.0, 127.8, 122.1, 121.6, 121.4, 114.6, 114.0, 112.0, 111.9, 55.0, 55.0, 47.8, 44.6. HRMS (ES+): *m*/*z* calcd for $C_{38}H_{34}N_2O_2$ +H^+: 551.2699 [*M*+H]$^+$; found: 551.2704;

2.5.4 1-(Triphenylmethyl)-imidazole-2-carboxaldehyde (11)

^{1}H NMR (400 MHz, Chloroform-*d*): δ = 9.25 (s, 1H), 7.40 – 7.32 (m, 9H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.17 – 7.10 (m, 6H), 7.06 – 7.02 (m, 1H). HRMS (ES−): *m*/*z* calcd for $C_{23}H_{18}N_2O$ −H^+: 337.1341 [*M*−H]$^-$; found: 337.1333;

2.5.5 2-(1-Hydroxy-1-methylheptyl)-1-(triphenylmethyl)imidazole (12)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.28 (m, 9H), 7.24 – 7.17 (m, 6H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.71 (d, *J* = 1.5 Hz, 1H), 1.56 – 1.43 (m, 2H), 1.32 – 0.95 (m, 14H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 144.2, 129.7, 127.6, 127.4, 124.4, 122.5, 77.2, 76.8, 76.5, 74.4, 44.2, 31.6, 29.4, 29.2, 23.3, 22.4, 13.9. HRMS (ES+): *m*/*z* calcd for $C_{30}H_{34}N_2O$ +CH_3CN+Na^+: 502.2834 [*M*+CH_3CN+Na]$^+$; found: 502.2833;

2.5.6 2-(Phenylsulfanyl)-1-(triphenylmethyl)imidazole (14)

^{1}H NMR (400 MHz, Chloroform-*d*): δ = 7.29 – 7.24 (m, 9H), 7.21 – 7.16 (m, 6H), 7.13 (d, *J* = 1.5 Hz, 1H), 7.11 – 7.05 (m, 3H), 6.96 – 6.91 (m, 3H). HRMS (ES+): *m*/*z* calcd for $C_{28}H_{22}N_2O$ +H^+: 419.1582 [*M*+H]$^+$; found: 419.1588;

3 Solubility Test

10 mL of ethereal solvent was added to 1 g of 1-tritylimidazole in a sealed vial. The mixture was stirred for 12 hours. The saturate solution was removed from the vial via a syringe and filtered. 1 mL of the filtrate was transferred into a pre-weighed vial and concentrated *in vacuo*. The solid was further dried under vacuum and weighed to give the mass of 1-tritylimidazole dissolved in 1 mL of solvent.

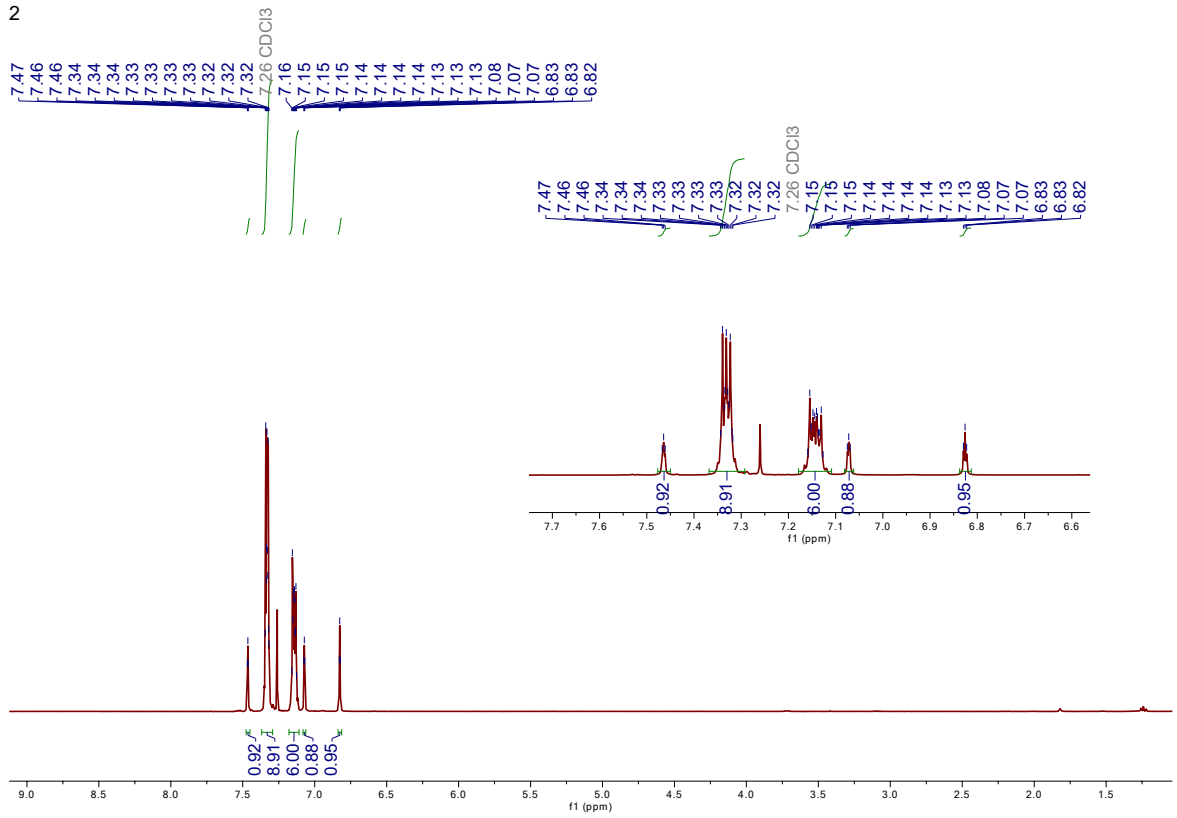
Solvent	**Molar solubility (mol/L)**
Tetrahydrofuran (THF)	0.21
Dimethoxyethane (DME)	0.05
1,4-Dioxane	0.13

Table S3. Molar solubilities of 1-tritylimidazole in ethereal solvents.

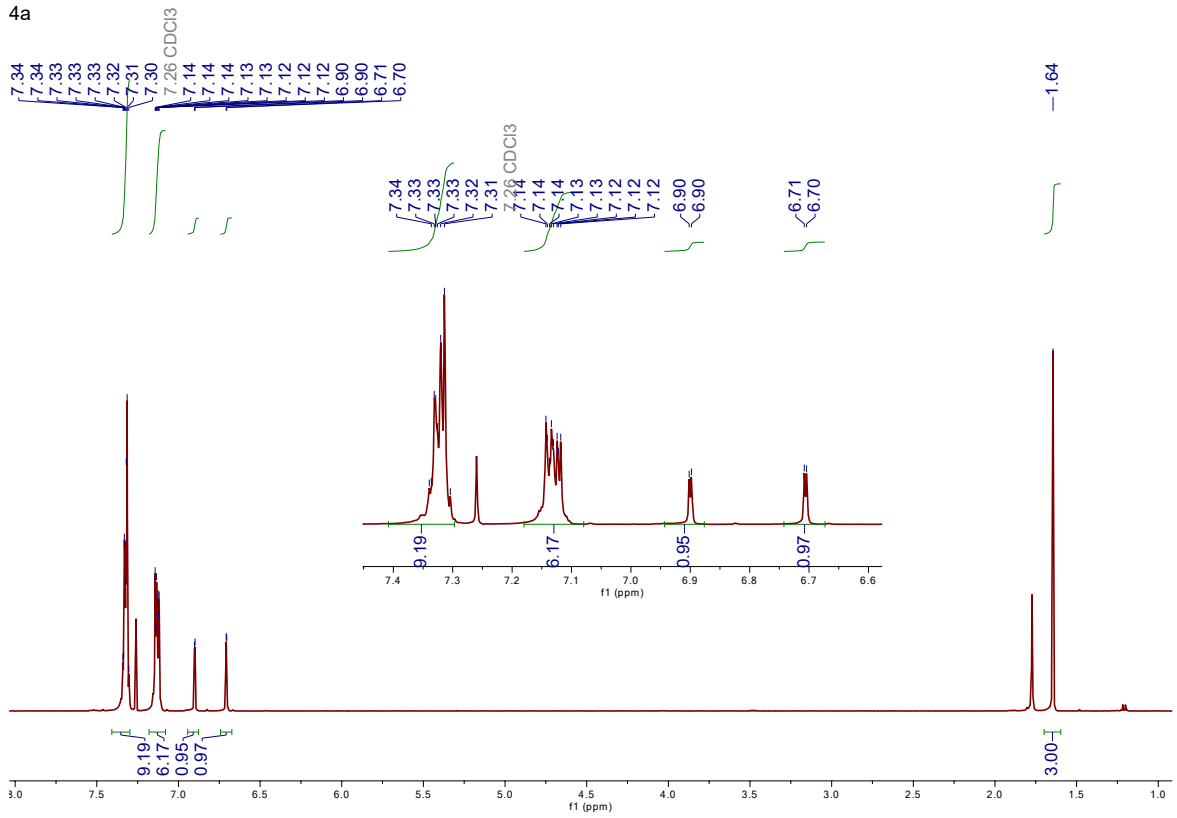
4 NMR Spectra

4.1 Batch reactions

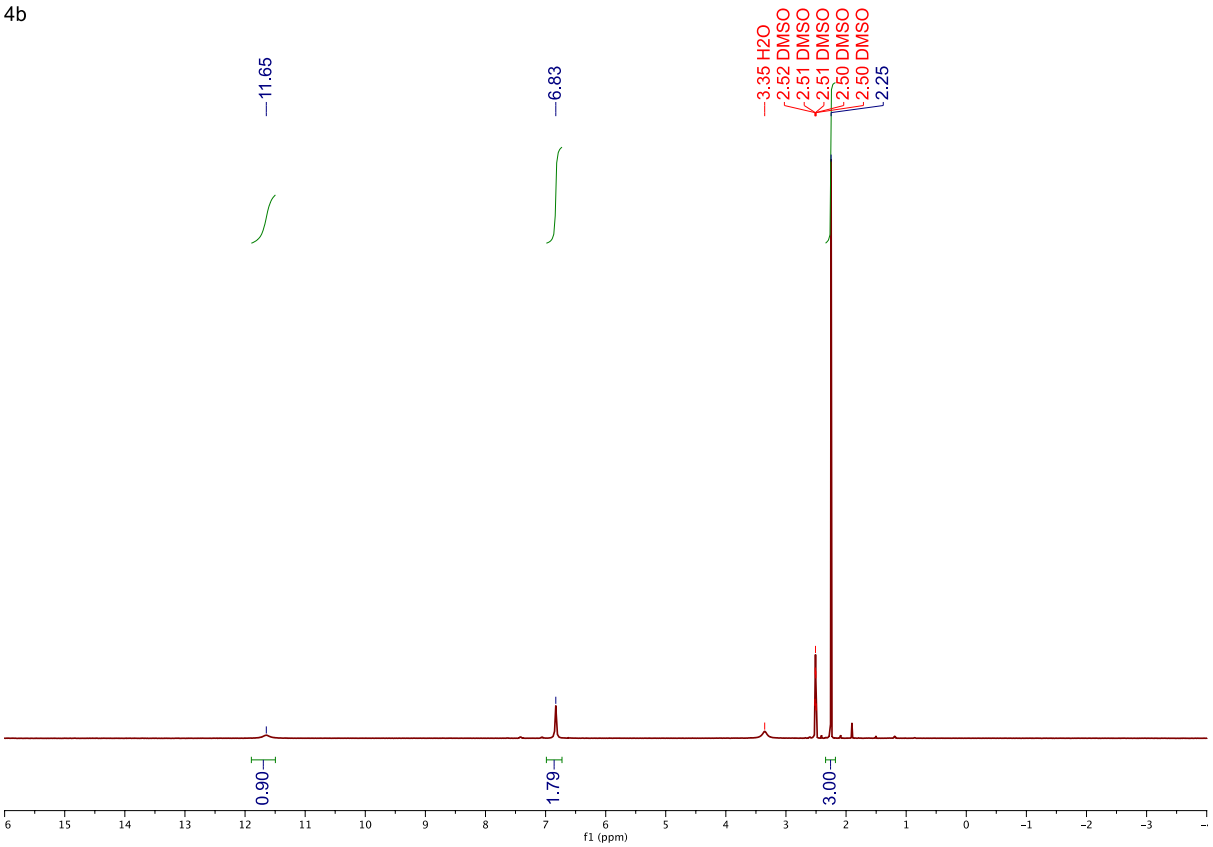
4.1.1 1-Triphenylmethylimidazole (2)



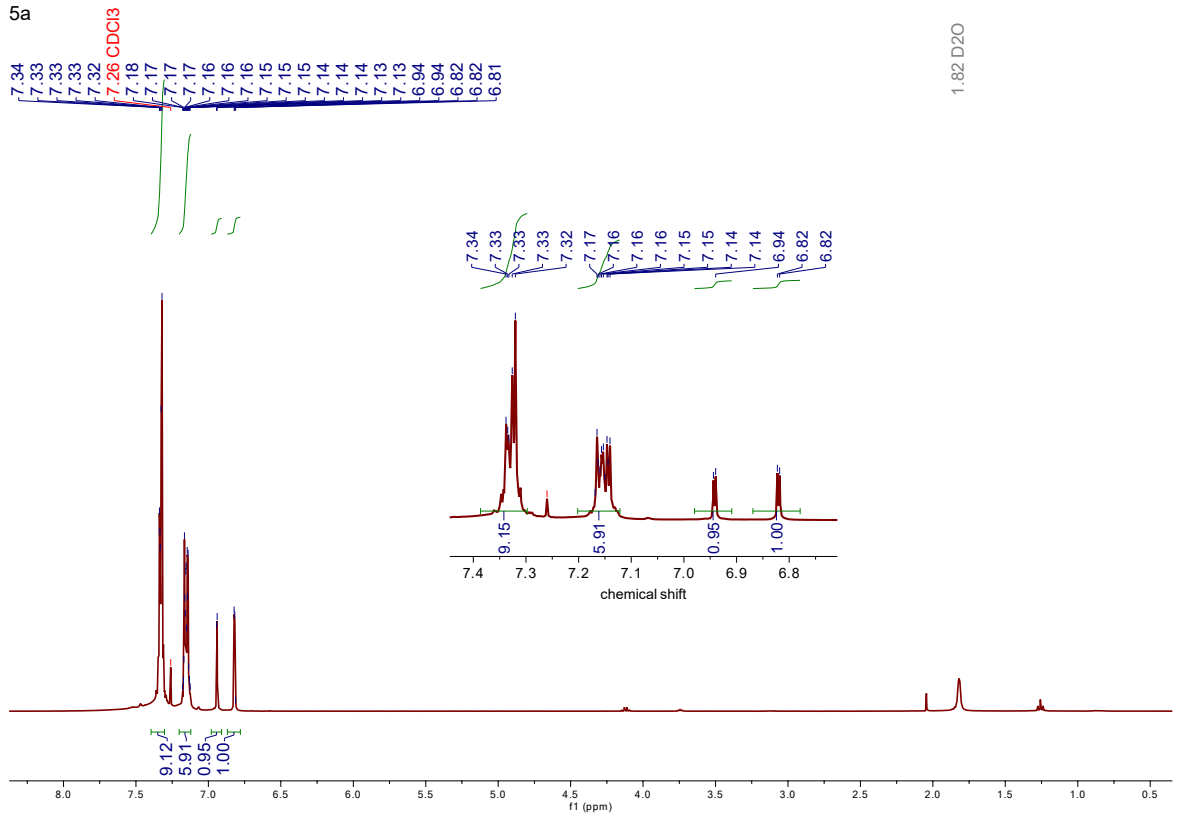
4.1.2 2-Methyl-1-(triphenylmethyl)imidazole (4a)



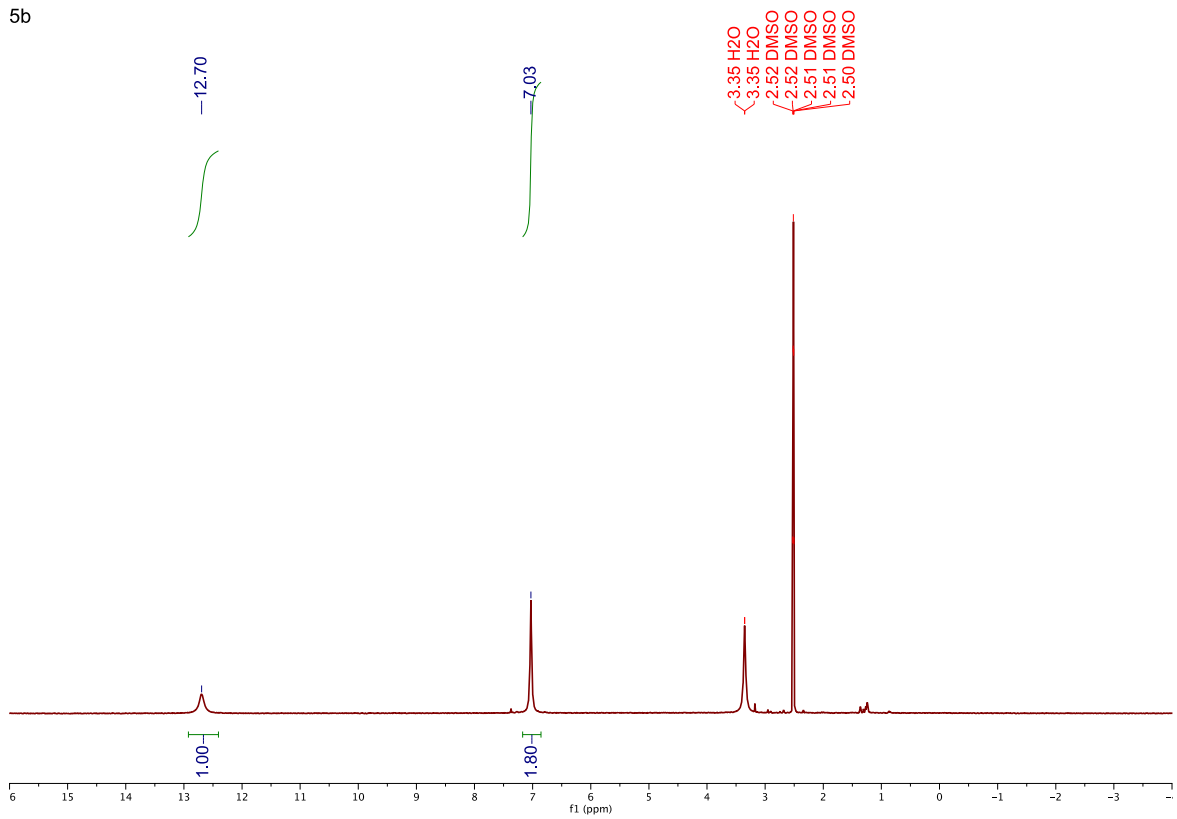
4.1.3 2-Methylimidazole (4b)



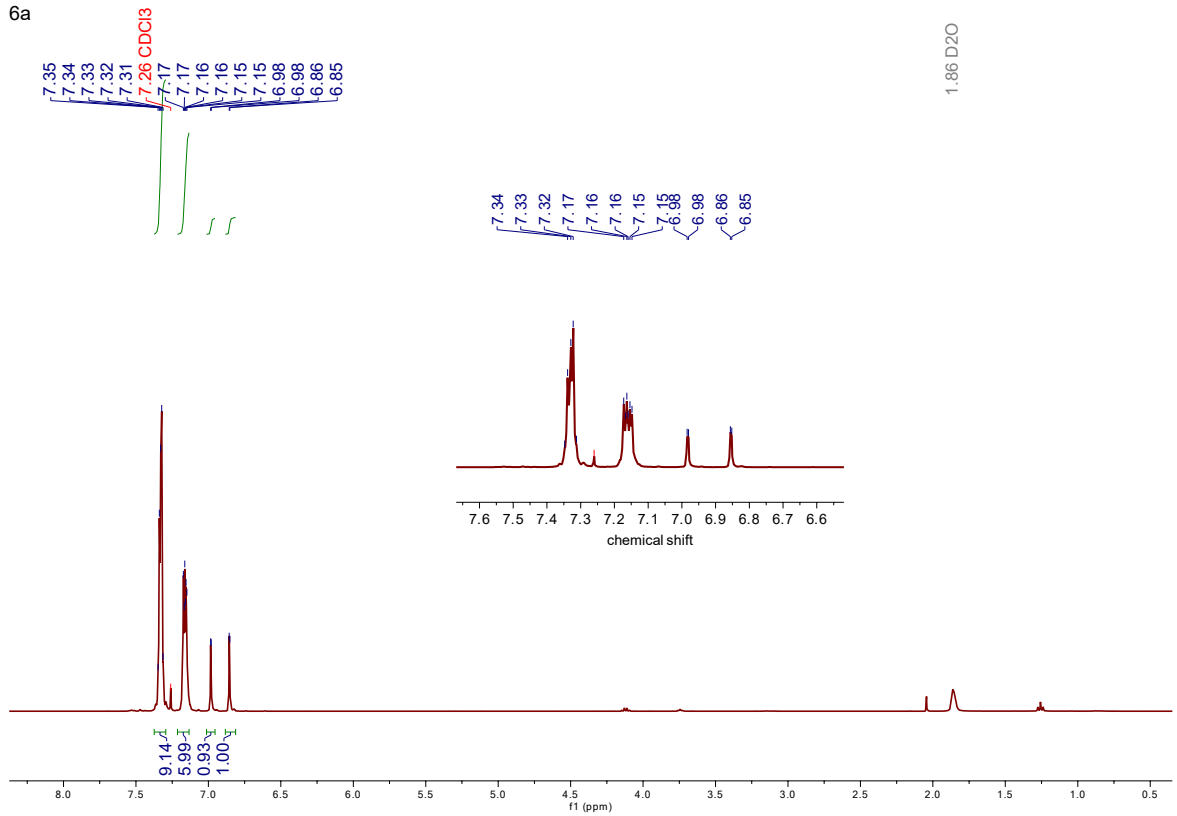
4.1.4 2-Chloro-1-(triphenylmethyl)imidazole (5a)



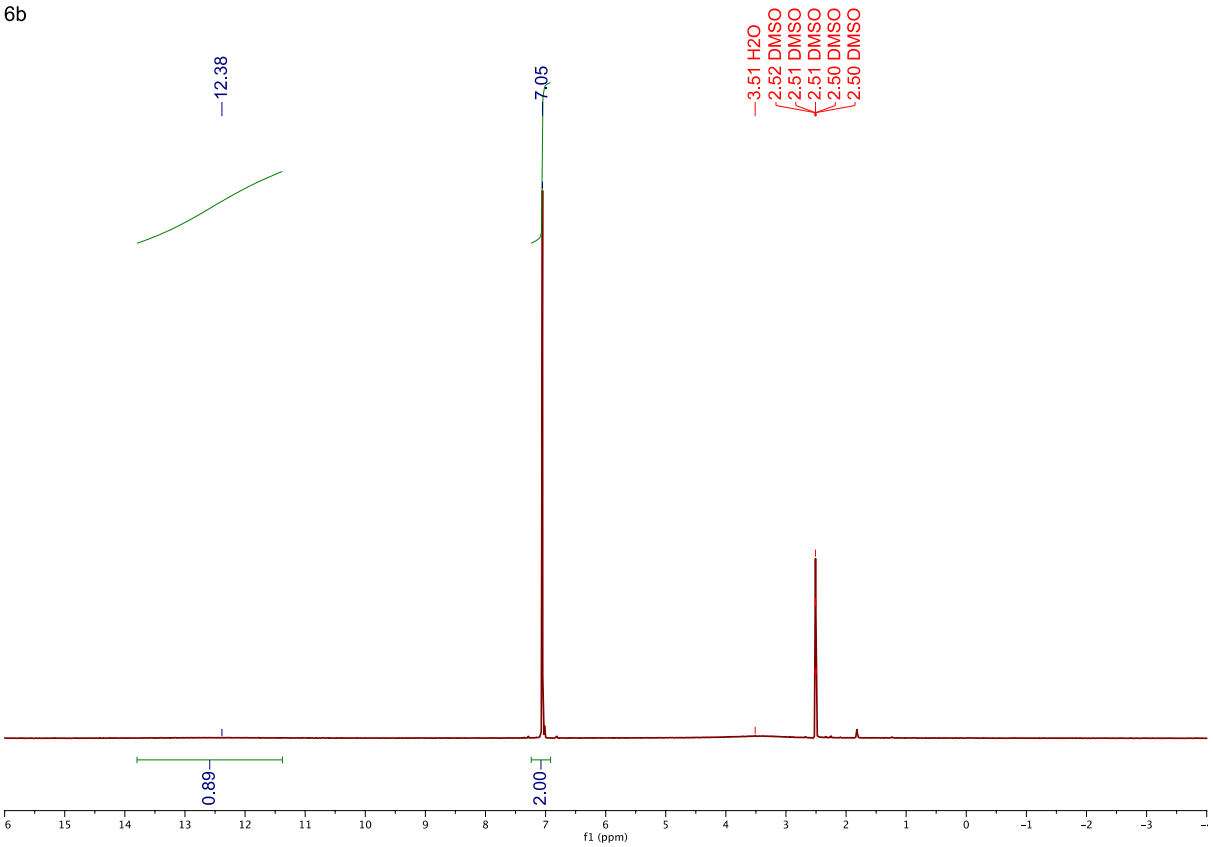
4.1.5 2-Chloroimidazole (5b)



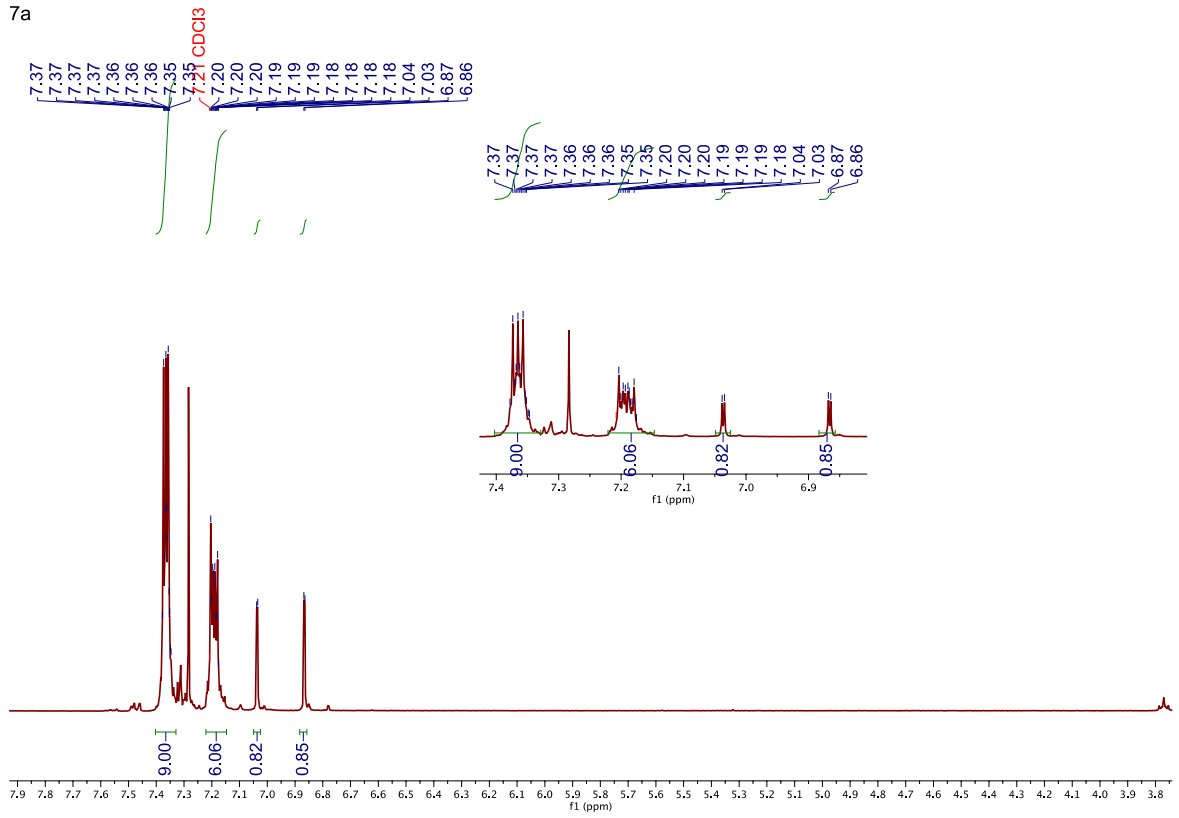
4.1.6 2-Bromo-1-(triphenylmethyl)imidazole (6a)



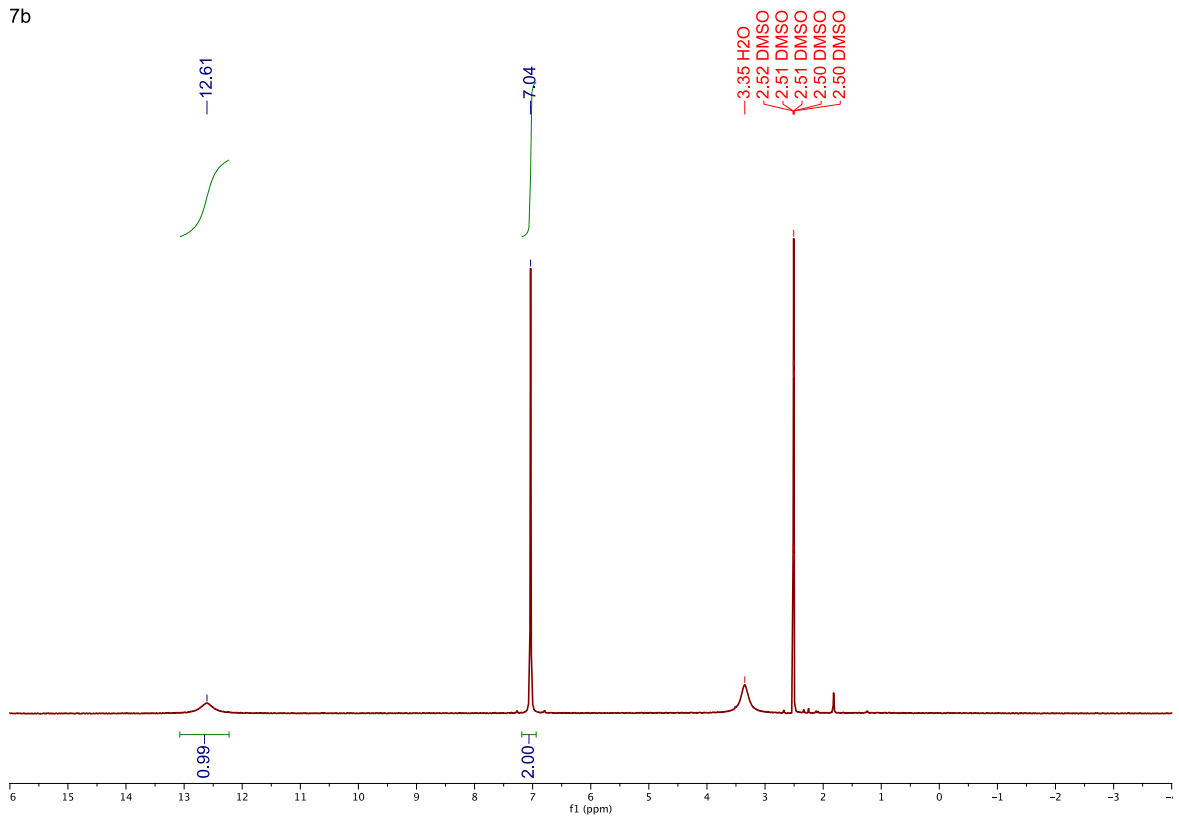
4.1.7 2-Bromoimidazole (6b)



4.1.8 2-Iodo-1-(triphenylmethyl)imidazole (7a)

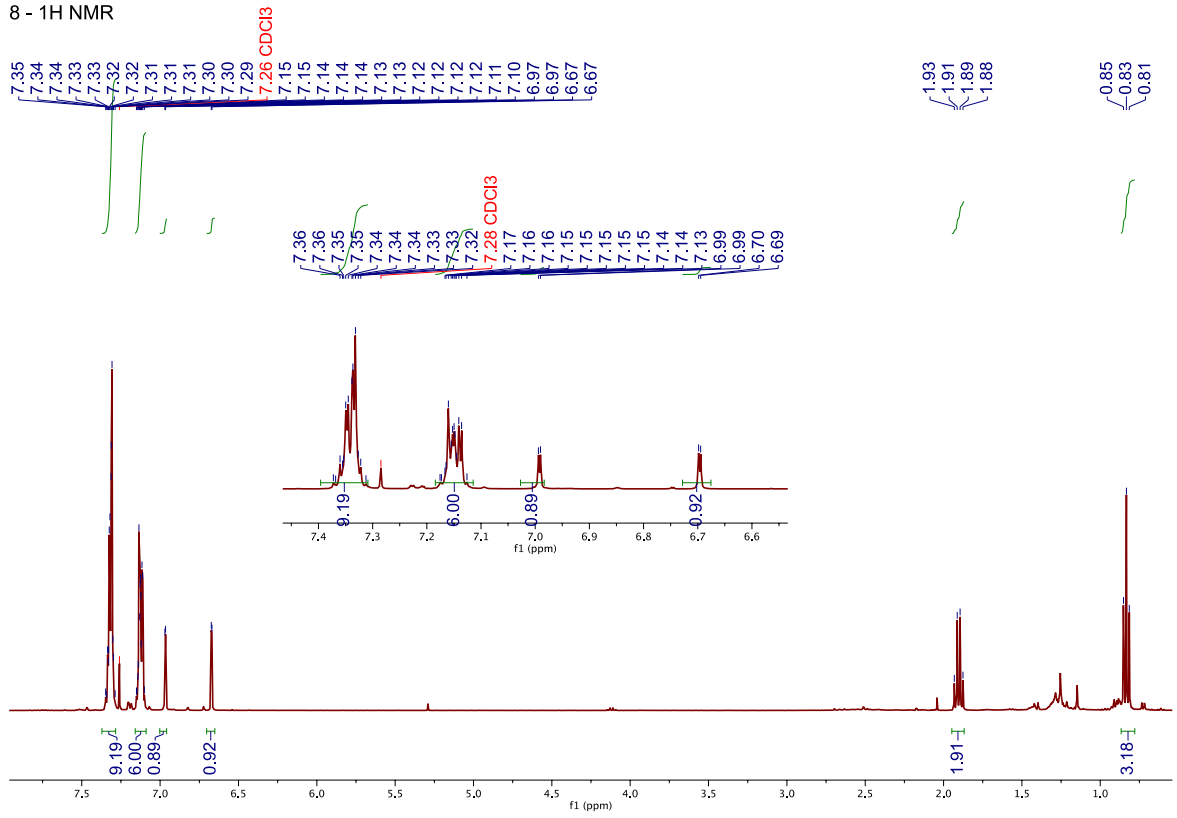


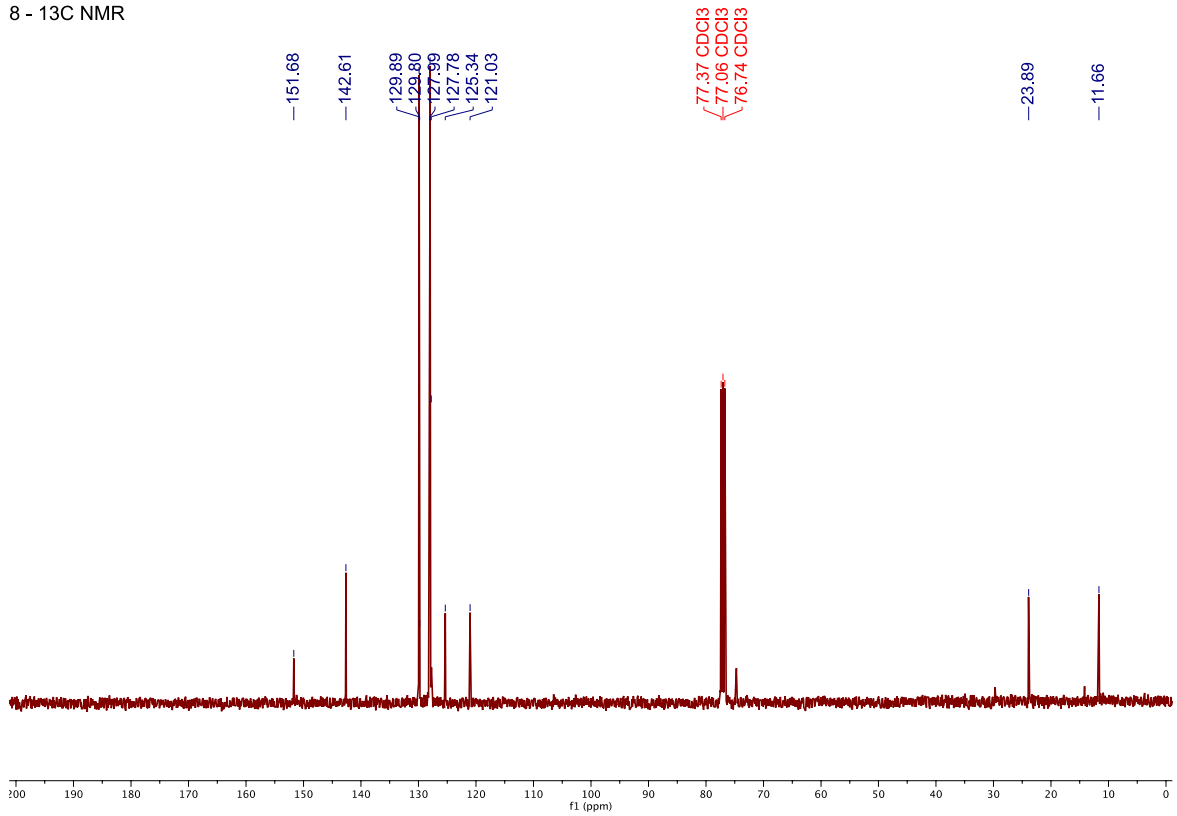
4.1.9 2-Iodoimidazole (7b)



4.2 Flow reactions

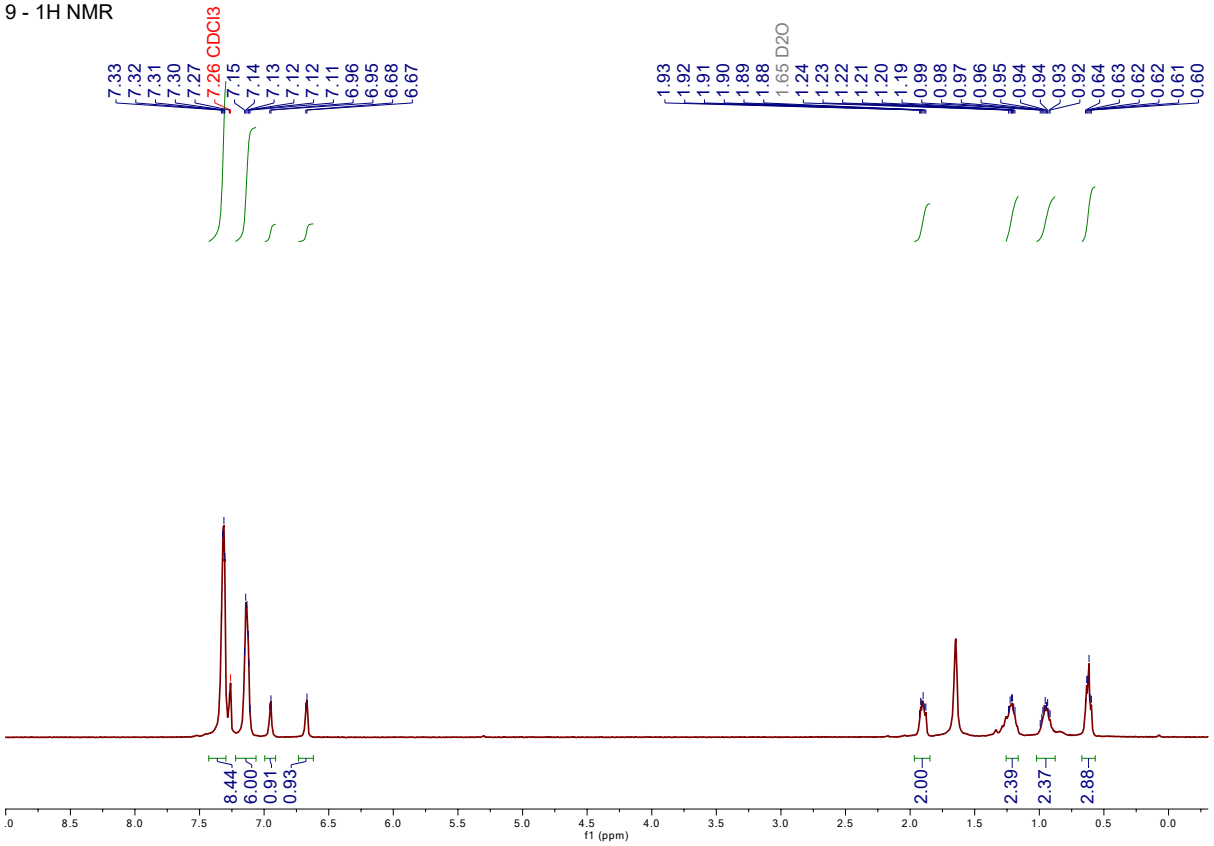
4.2.1 2-Ethyl-1-(triphenylmethyl)imidazole (8)



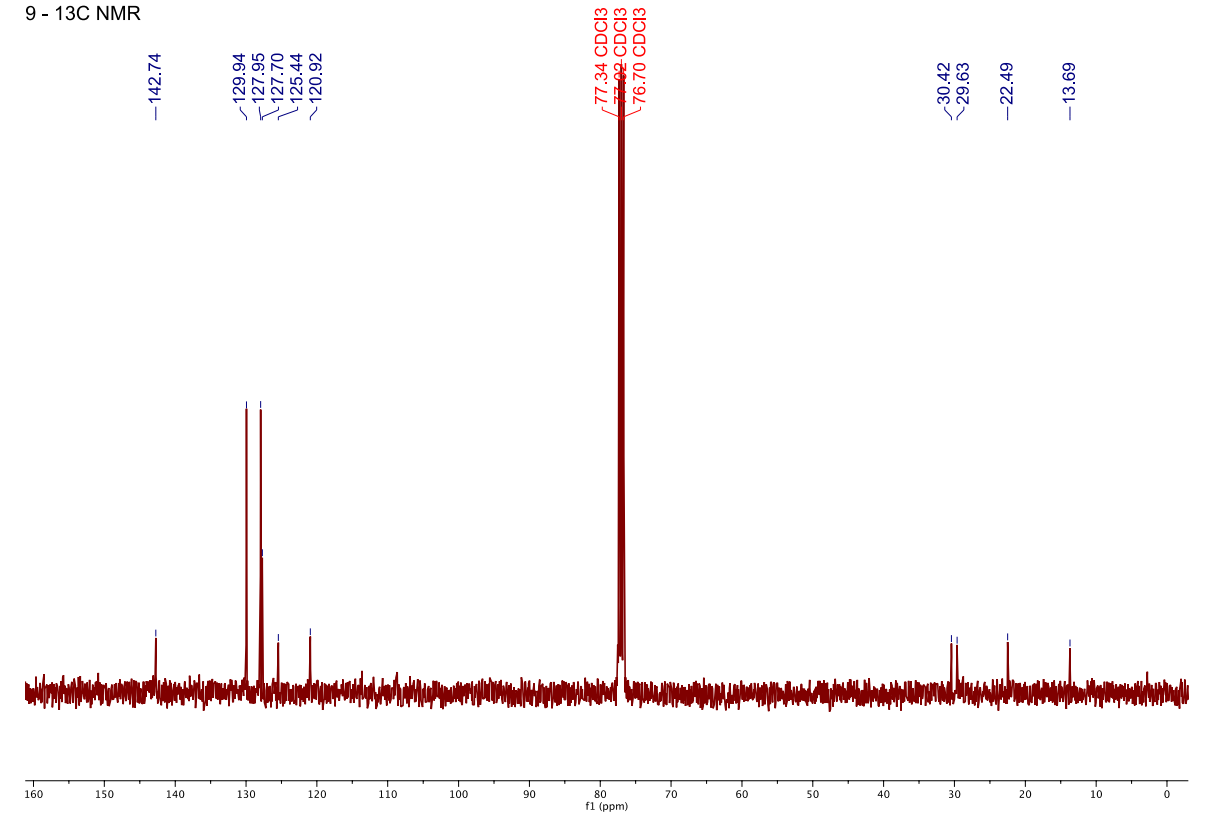


4.2.2 2-Butyl-1-(triphenylmethyl)imidazole (9)

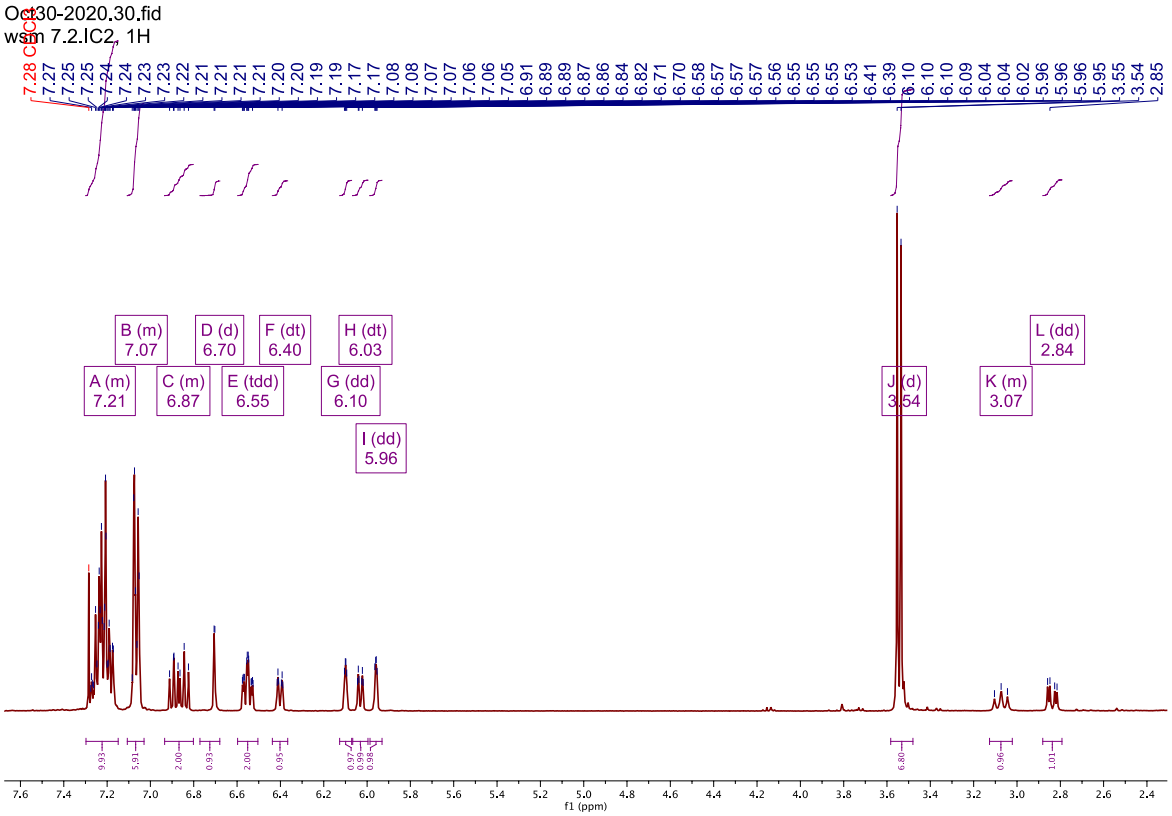
9 - 1H NMR

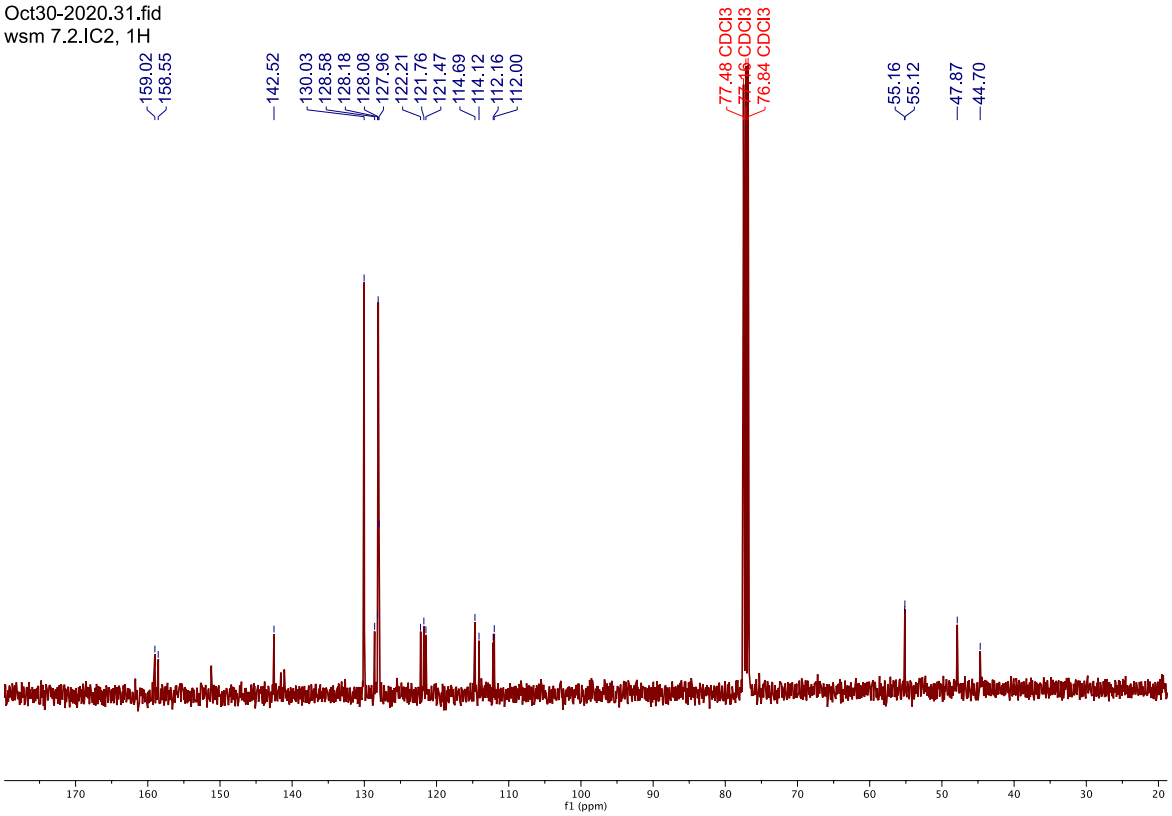


9 - 13C NMR

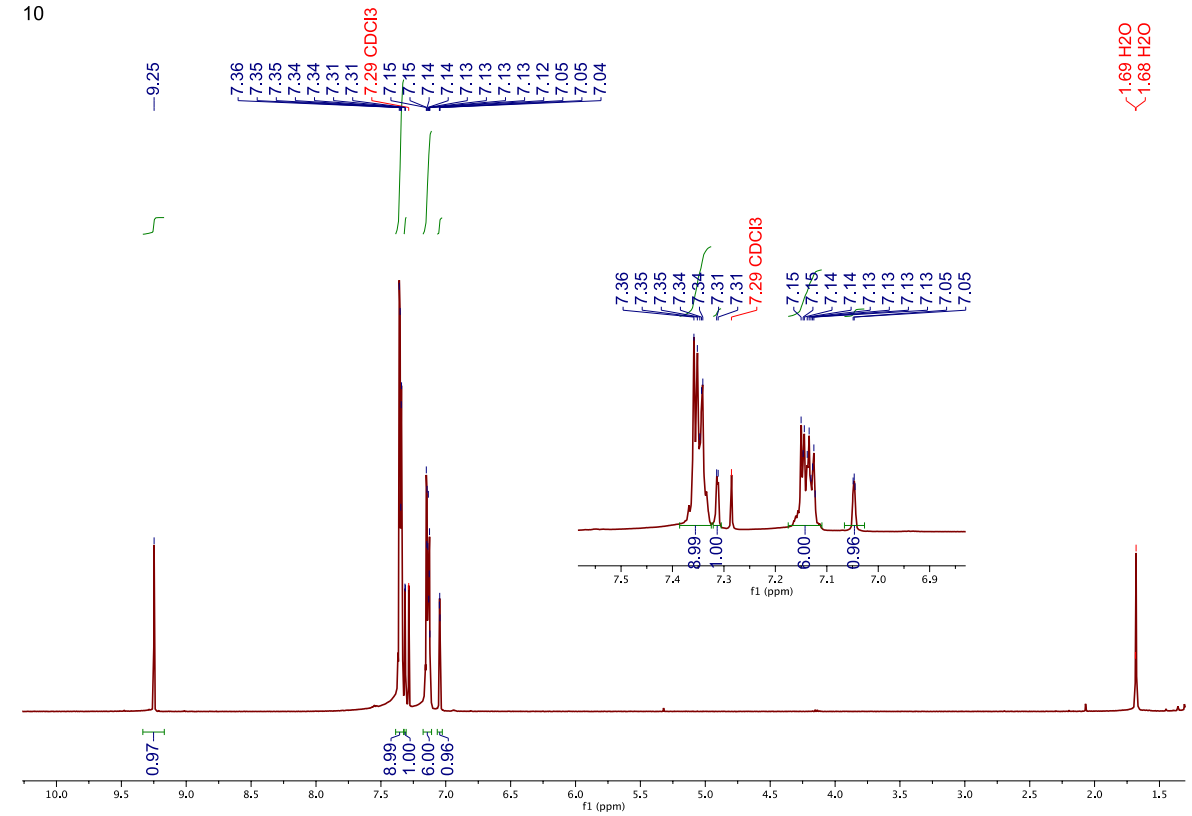


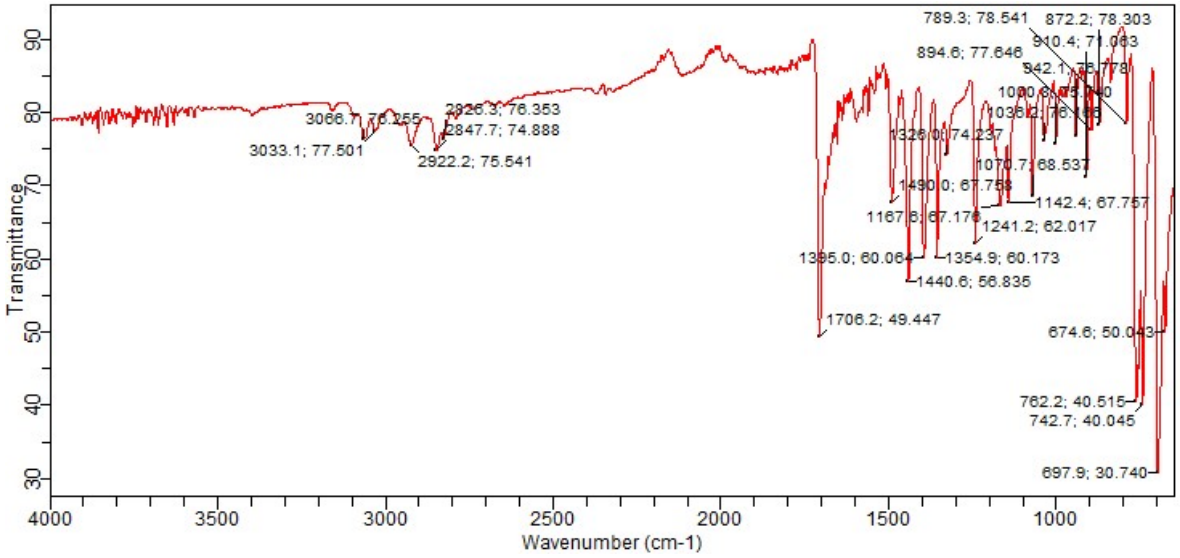
4.2.3 2-(1,2-Bis(4-methoxyphenyl)ethyl)-1-tritylimidazole (10)



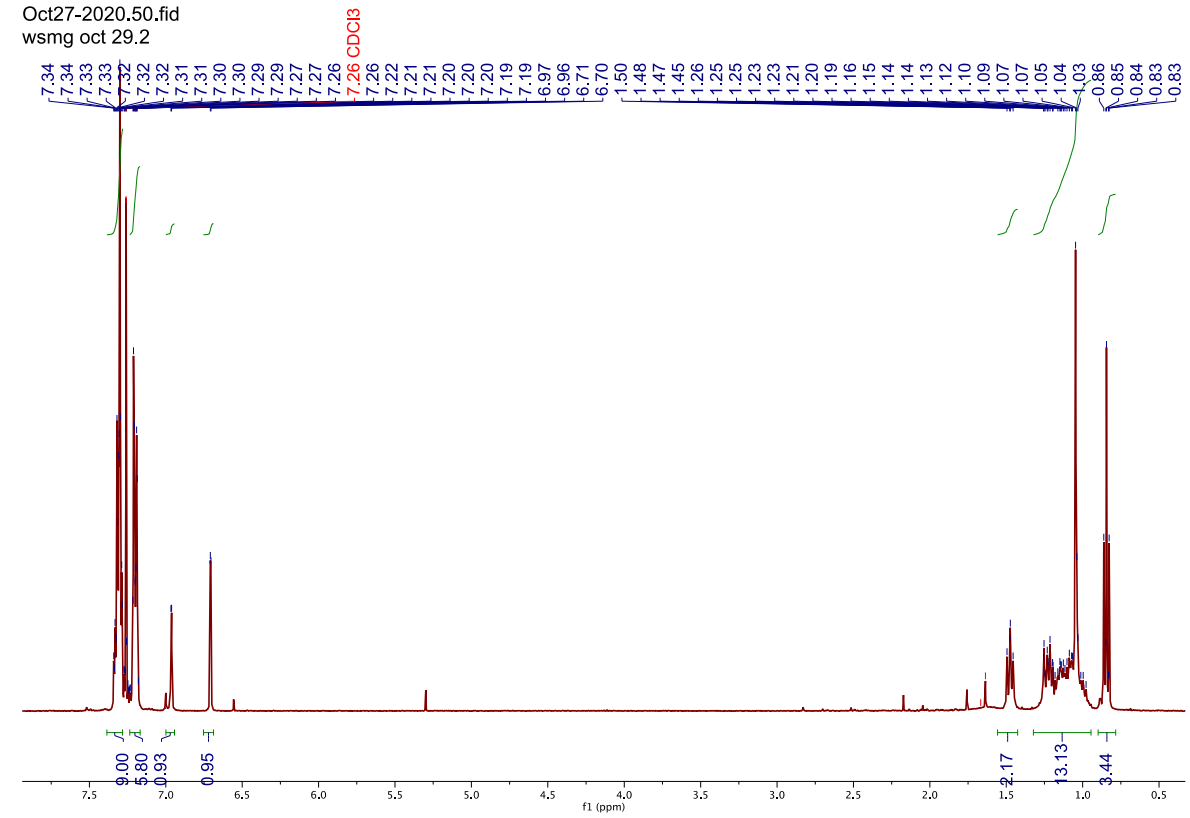


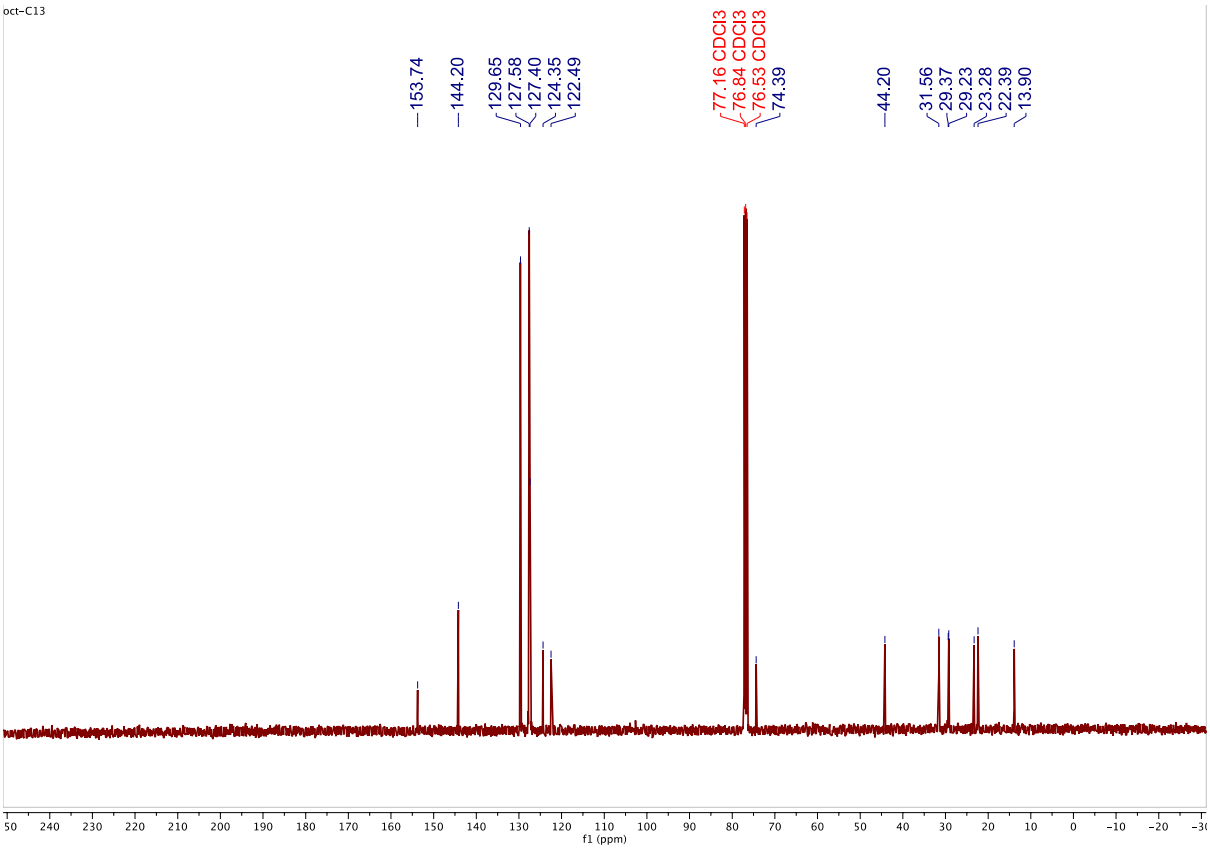
4.2.4 1-(Triphenylmethyl)-imidazole-2-carboxaldehyde (11)





4.2.5 **2-(1-Hydroxy-1-methylheptyl)-1-(triphenylmethyl)imidazole** (12)





4.2.6 2-(Phenylsulfanyl)-1-(triphenylmethyl)imidazole (14)