Electronic Supporting Information

Development of a Multistep Electrochemical Flow Platform for Automated Catalyst Screening

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1 General Experimental Information

Unless otherwise noted, all reagents were obtained from commercial sources and used without purification.

Anhydrous acetonitrile was acquired from a Dow-Grubbs solvent purification system, where it was passed over activated alumina to remove water, a copper catalyst to remove oxygen, and molecular sieves to remove any remaining water. It was then degassed by purging with argon.

NMR spectroscopic data were obtained on either a Bruker A500 (CH dual cryoprobe) or Bruker Ascend 400 spectrometer. ^{1}H and $^{13}C\{1H\}$ NMR chemical shifts are reported in ppm and are referenced against residual solvent peaks. Spin-spin coupling constants *J* are given in Hz and refer to apparent multiplicities rather than true coupling constants. Data is reported as: chemical shift, multiplicity and integration. Carbon shifts are reported to the nearest 0.1 ppm. Carbons in an identical environment giving one signal are not indicated further.

References to spectroscopic data are given for known compounds.

The flow setup consists of PFA tubing of an 0.8 mm ID (K6A0079040X, Polyflon) and stainless-steel tubing of an 0.762 mm ID (20553, Sigma Aldrich).

Reactions were either monitored by $^{1}H\{^{13}C\}$ NMR spectroscopy or HPLC (Agilent Infinity 1260 with InfinityLab Poroshell 120 EC-C18 column).

An ASX-7000 Series Autosampler was used with ligand precursors being prepared in microwave vials under an inert atmosphere.

A SyrDos™ Syringe Dosing Pump was used for the electrochemical reactor, and a Jasco Pu-980 for the reactants.

The injector and autosampler were controlled through a custom-built MATLAB interface through a USB connection. Details of the control syntax can be found at Brochure_ASX-7000_series.pdf (teledynecetac.com) and Universal Electric Actuator Instruction Manual (vici.com).

2 Electrochemical Reaction

2.1 Electrochemical Reactor

The reactor consists of stainless steel plates at the top and bottom , PTFE spacers and copper electrodes similar to previous reactors developed in the group (Figure S1, Table S1).[1] The reactor has a 4.8 cm diameter. The stainless-steel plates enhance structural stability and are bolted together. The electrodes and PTFE spacers are stacked in the middle. The stainless-steel plates exhibit an inlet and outlet with ¼-28 threads for standard fittings (1). All elements, the stainless-steel plates, the spacers and the electrodes have three big holes for the M5 bolts (2), and two small ones (3) to align all elements while stacking. Two of the holes for the bolts are slotted on the spacers and electrodes (2 in Figure S3D). For aligning the elements drill bits (3.8 mm) are inserted into the bottom stainless-steel plate, then the reactor is assembled and bolted together, and then the bits removed. PTFE spacers are 1 mm thick and have cut in channels to direct the liquid flow (4). The electrodes have a lip to connect to the power supply (5) and a hole for the reaction mixture to flow through to the next PTFE spacer (6). Depending on the number of spacers and electrodes the volume of the reactor can be changed, each spacer exhibits a flow channel with a 0.464 mL volume. If not otherwise mentioned, in this work two spacers and three copper electrodes have been used resulting in a 0.928 mL volume. The reactor can be attached to a power supply through lips on the electrodes.

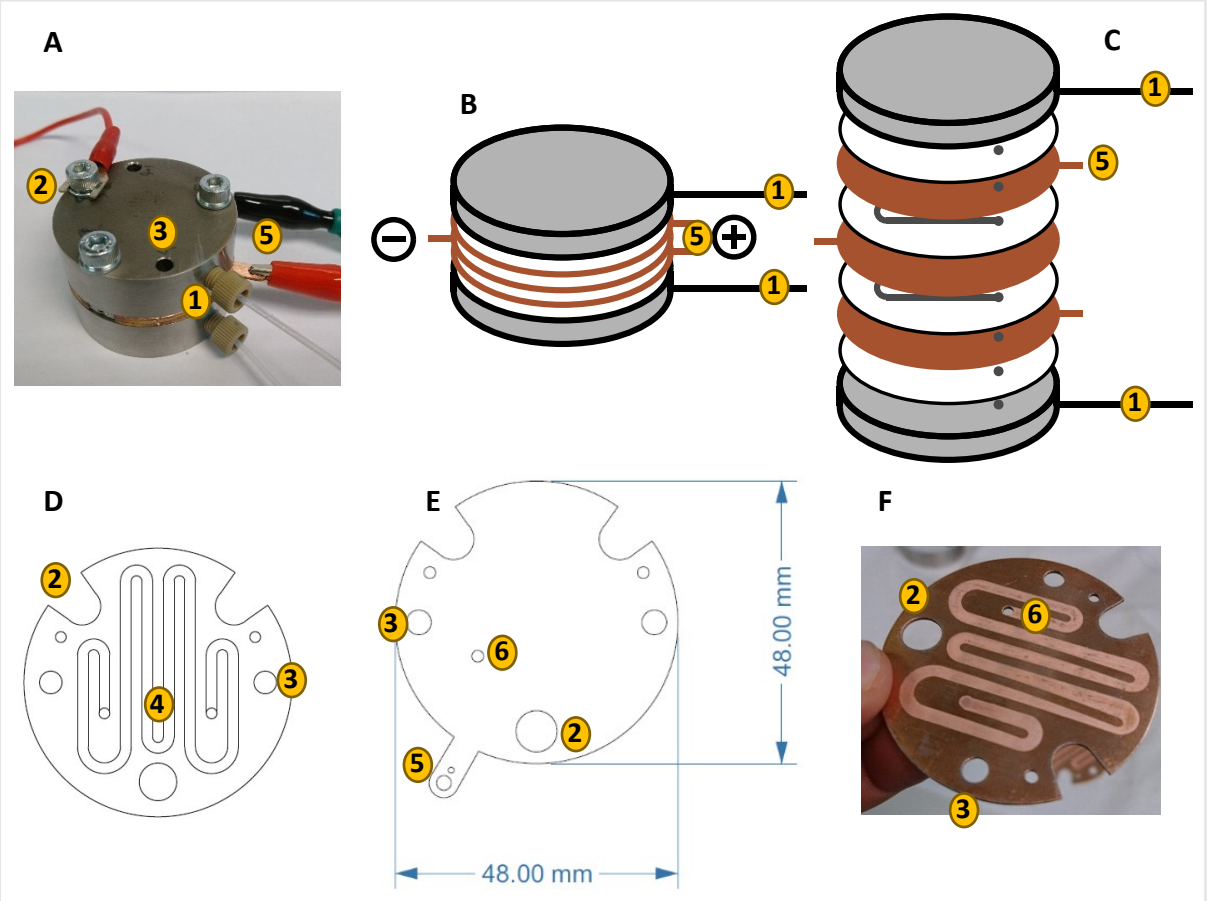


Figure S1: Continuous electrochemical reactor, A: picture of the assembled reactor, B: drawing of the assembled reactor, C: drawing of the elements of the reactor, D: spacer drawing, E: electrode drawing, F: picture of the electrode, 1: inlet and outlet, 2: holes for bolts, 3: holes for allignment, 4: flow channel, 5: connection lip, 6: hole for flow through.

Table S1: Parts of the electrochemical reactor.

Part	Supplier	Part number
Stainless steel plates	Machined internally	Stainless Steel 304
Copper plates	Laser cut	C160 grade, 0.9 mm thickness
PTFE spacers	Laser cut	Virgin grade PTFE, 1 mm thickness
Screws (M5)	RS	4838281
Nuts (M5)	RS	525931
Drill bits (3.8 mm)	RS	7683012
Power supply	Tenma	72-10480

If not otherwise mentioned, the reactor was assembled with two spacers (0.926 mL) and three copper electrodes.

2.2 Cleaning of the Electrochemical Reactor

The reactor was taken apart and all parts rinsed with acetone. The spacers were submerged in 3 M aqueous HCl solution and sonicated for 5 min. After washing with water and acetone, the spacers were dried on the bench. The electrodes were sanded (P1200 grade), wiped with 3 M aqueous HCl solution and rinsed with acetone before leaving on the bench to dry.

2.3 Alternating Polarity

Alternating polarity usually refers to a square wave in potential by reversing the direction of current (Figure S2). The use of alternating polarity means that the potential is constant within intervals maintaining the selectivity of the system in the context of a synthetic reaction. Alternating polarity is used in this research.

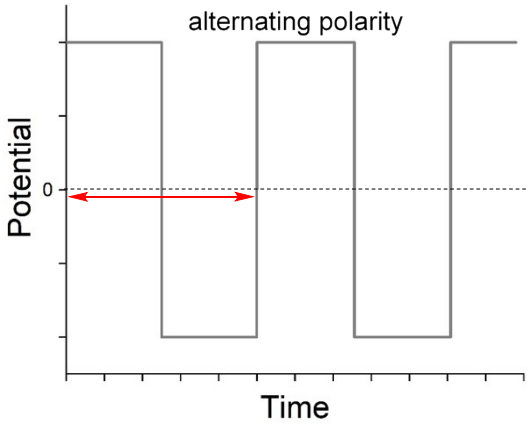
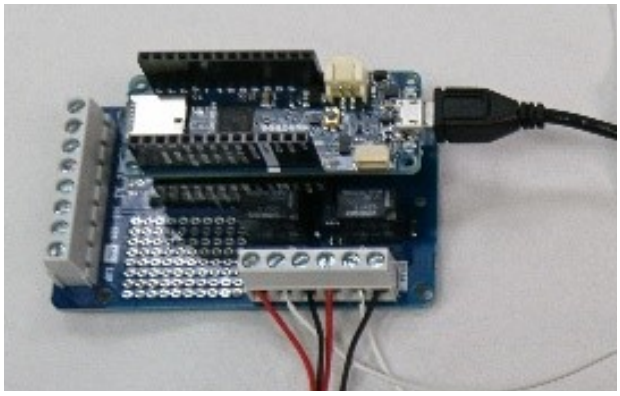


Figure S2. Alternating Polarity with the period shown with red arrow.

The alternating polarity controller (APM, Figure S3) consists of an Arduino MKR ZERO (1697584) with an Arduino MKR Relay Proto Shield (1697588) with a micro-USB power supply

(131-4662) all purchased from RS. The relay clicks between different positions to afford the alternating polarity (Figure S4). Coding supplied with the data.



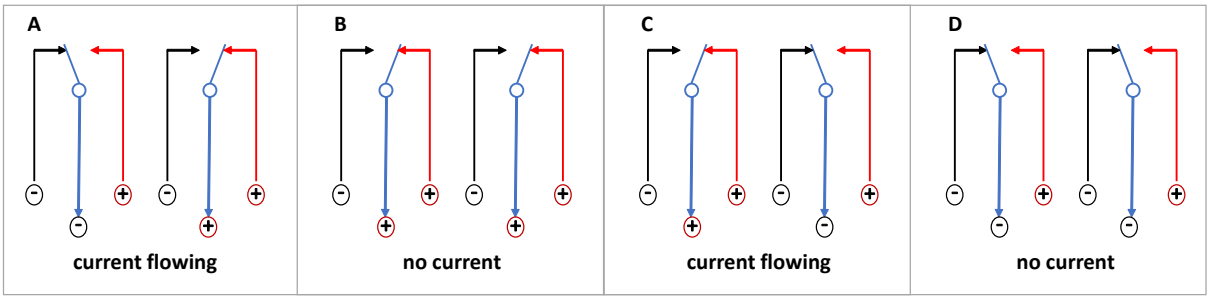
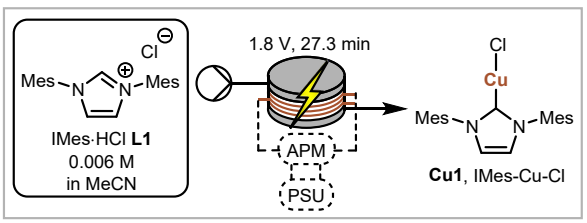


Figure S3 Alternating polarity controller (APM).

Figure S4: Relay principle, red and black from power supply, blue to reactor (white wire in Figure S4).

2.4 Electrochemical Optimisation

A solution of 1,3-dimesityl-1H-imidazolium choride (IMes·HCl, **L1**) (0.006 M) in anhydrous MeCN was prepared under argon. The reactor was assembled with two spacers and three copper electrodes before programming the APM and connecting to the power supply. The flow setup assembled according to Scheme S1. The reactor was filled with the solution and the pump started at 0.034 mL min^{-1} (27.3 min residence time). The power supply was then switched on at the desired potential to start the reaction. After waiting for steady state (1 h), a sample was collected for 15 min into a round bottom flask under air. The solvent was removed under reduced pressure and the sample taken up in $CDCl_3$ for ^1H NMR analysis. The results are given in Figure S5 and Table S2.



Scheme S1: Setup electrochemical optimisation.

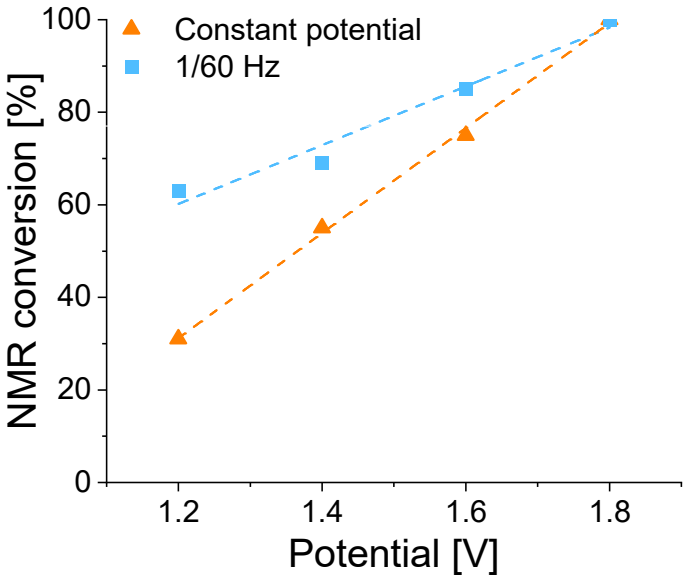


Figure S5: Single sweep voltammetry at constant potential (orange) and 1/60 Hz (blue), ^{1}H NMR conversions.[2]

Table S2: Data for the single sweep voltammetry in Figure S10[2]

entry	frequency [Hz]	potential [V]	conversion [%]	C [mA]	F [mol^{-1}]
1	-	1.2	31	0.3	0.7
2	-	1.4	55	0.3	1.0
3	-	1.6	75	0.5	1.5
4	-	1.8	100	1.1	3.3
5	1/60	1.2	63	0.4	1.2
6	1/60	1.4	69	0.5	1.4
7	1/60	1.6	85	0.6	1.8
8	1/60	1.8	100	0.8	2.4

2.5 Long Term Stability

The reactions were prepared as in the optimisation studies with the APM at 1/60 Hz or at a constant potential of 1.8 V.

A solution of 1,3-dimesityl-1H-imidazolium choride (IMes·HCl, **L1**) (0.006 M) in anhydrous MeCN was prepared under argon. The setup was prepared by programming the APM and assembling according to Scheme S1. The reactor was filled with the solution and the pump started at 0.034 mL min^{-1} (27.3 min residence time). The power supply was then switched on at the desired potential to start the reaction. The reaction output was collected in aliquots into a round bottom flask under air. The solvent was removed under reduced pressure and the sample taken up in $CDCl_3$ for ^{1}H NMR analysis. The results are given in Figure S6, with the time points referring to the stop of the collection for that respective aliquot. The reaction was stopped after 6 h.

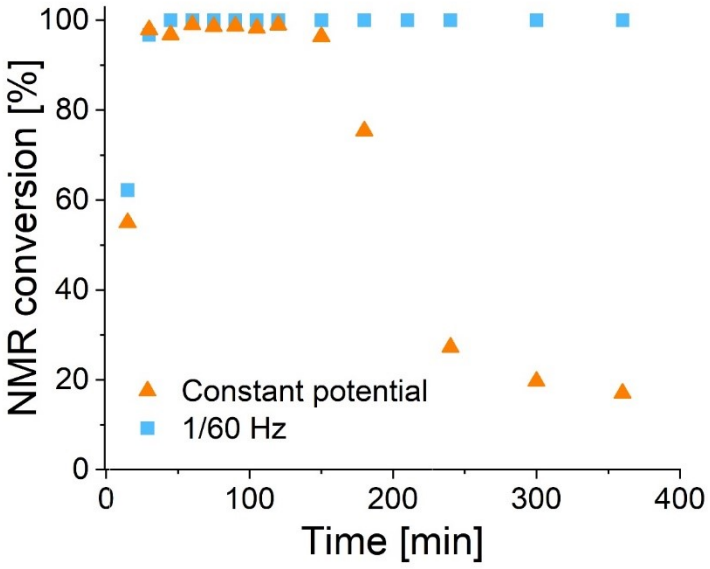


Figure S6: Long term stability with (blue) and without (orange) APM, ^{1}H NMR conversion measured over 6 h.

2.6 Electrochemical Analysis

Reactions were typically analysed *via* ^{1}H NMR spectroscopy, measuring conversions, or HPLC, measuring yields. For the calculation of NMR conversions, the peaks of the starting material (IMes·HCl, **L1**) and product (IMes-Cu-Cl, **Cu1**) were compared.

SM(**L1**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.90 (s, 4H), 2.43 (s, 6H), 1.68 (s, 12H).

P(**Cu1**): ^{1}H NMR (501 MHz, $CDCl_3$) δ 11.07 (s, 1H), 7.56 (s, 2H), 7.04 (s, 4H), 2.35 (s, 6H), 2.20 (s, 12H).

Figure S7 shows a typical NMR spectrum obtained. The starting material peak at 7.56 ppm was integrated to 2H. The peaks around 7 ppm were then integrated. Product peaks were typically observed higher in the crude NMR spectra than in the spectra of recrystallised material. The starting material peak at 7.05 ppm and the product peak at 7.01 overlap (7.05 and 7.02 ppm in Figure S7), the peak corresponding to the product peak at 6.90 ppm was taken to calculate the conversion (7.00 ppm in Figure S7).

In this case the conversion X can be calculated as:

$$X = \frac{\frac{I_P}{H_P}}{\frac{I_P}{H_P} + \frac{I_{SM}}{H_{SM}}} \cdot 100\% = \frac{\frac{1.15}{4}}{\frac{1.15}{4} + \frac{2}{2}} \cdot 100\% = 22\%$$

I_P: integration for product peak

I_{SM}: integration for starting material peak

H_P: number of protons for product peak

H_{SM}: number of protons for starting material peak

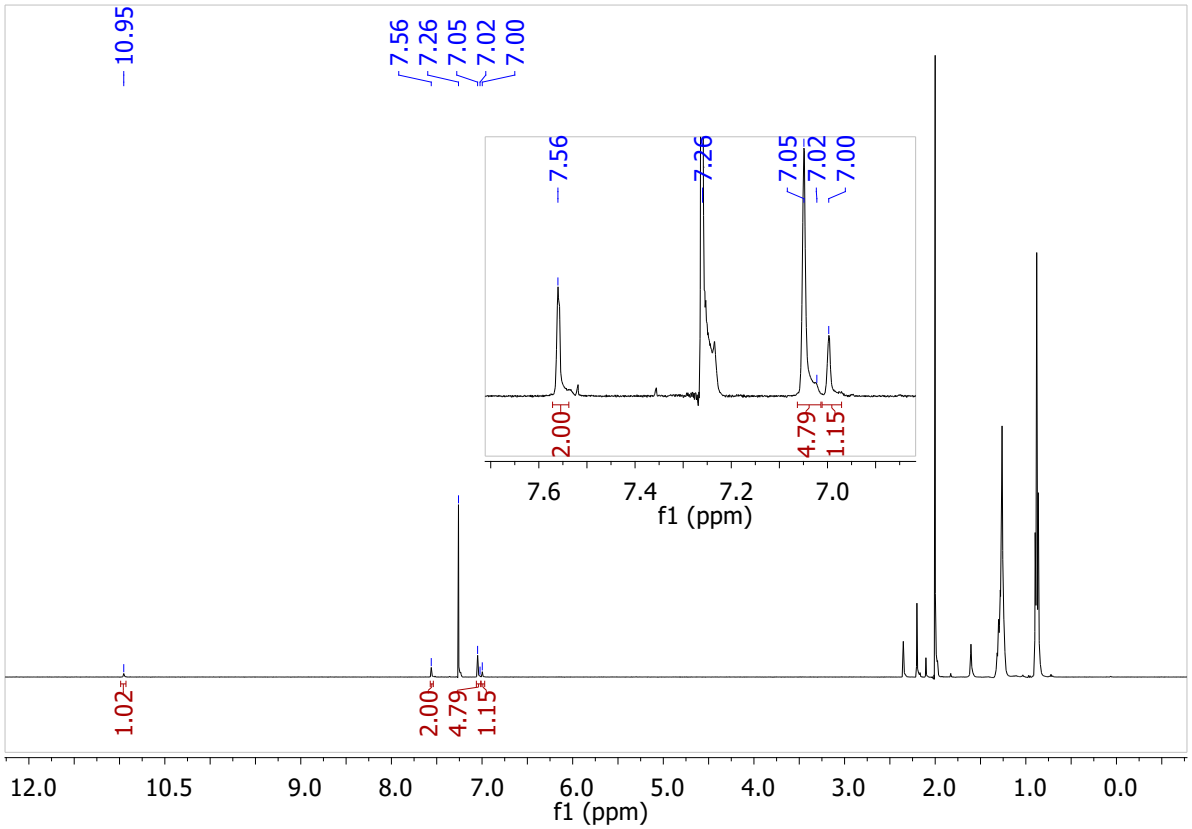


Figure S7: Typical ^{1}H NMR spectrum (501MHz, $CDCl_3$) for the electrochemical reaction of IMes·HCl (**L1**) to IMes-Cu-Cl (**Cu1**).

2.7 Substrate Scope

The reactions were prepared in a similar fashion to the optimisation studies.

A solution of the starting imidazolium salt (0.006 M) in anhydrous MeCN was prepared under argon. The setup was prepared by programming the APM to 1/60 Hz and assembling according to Scheme S1. The reactor was filled with the solution and the pump started at 0.034 mL min^{-1} (27.3 min residence time). The power supply was then switched on at 1.8 V to start the reaction. After waiting for steady state (1 h), a sample was collected for 15 min into a round bottom flask under air. The solvent was removed under reduced pressure and the sample taken up in $CDCl_3$ for ^{1}H NMR analysis. The conversions were calculated by comparing starting material and product peaks (Figure S8).

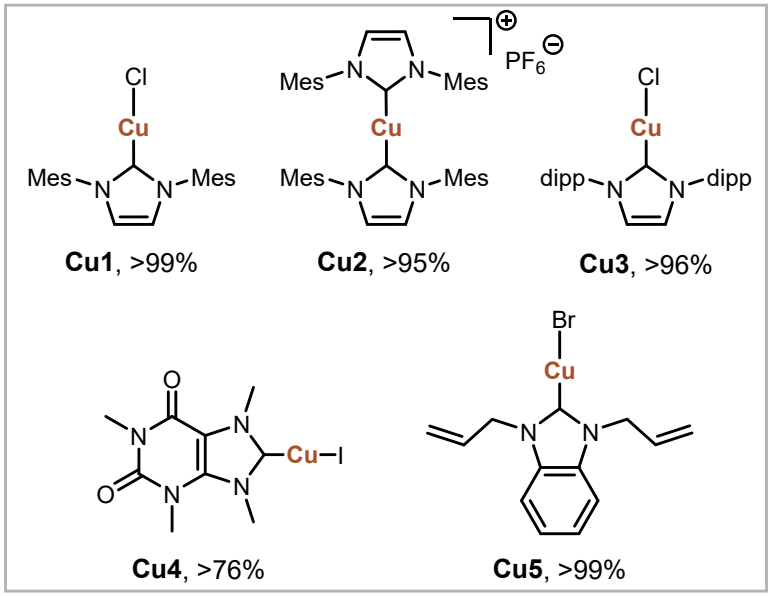


Figure S8: Substrate Scope, ^{1}H NMR conversions.

Cu1:[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.90 (s, 4H), 2.43 (s, 6H), 1.68 (s, 12H).

Cu2:[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 4H), 7.00 (s, 8H), 2.35 (s, 12H), 2.10 (s, 24H).

Cu3:[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 4H), 7.13 (s, 2H), 2.57 (hept, *J* = 6.8 Hz, 4H), 1.30 (d, *J* = 6.9 Hz, 12H), 1.23 (d, *J* = 6.9 Hz, 12H).

Cu4:

^{1}H NMR (400 MHz, DMSO) δ 4.16 (s, 3H), 3.99 (s, 3H), 3.72 (s, 3H), 3.23 (s, 3H).

Cu5:[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.41 – 7.36 (m, 2H), 6.04 (ddd, *J* = 15.9, 11.0, 5.7 Hz, 2H), 5.39 – 5.23 (m, 4H), 5.09 – 5.01 (m, 4H).

3 Click Reaction

3.1 Continuous Protocol

The setup was assembled as shown in Figure S9 **B** with a 5 mL sample loop and a 2 mL tubular reactor submerged in an oil bath. The oil bath was heated to 120 °C and the setup filled with acetonitrile before setting the pump to 0.1 mL/min. While waiting for the reactor to heat up, a solution of benzyl azide (0.1 M, 0.5 mmol, 0.06 mL), phenyl acetylene (0.11 M, 0.55 mmol, 0.06 mL, 1.1 equiv.) and copper catalyst (1 mol%, 0.001 M, 0.05 mmol) in acetonitrile (5 mL) was prepared. The solution was injected into the system and a sample taken after waiting 40 min for steady state. The sample was filtered through silica to remove the catalyst and then the solvent was removed under reduced pressure. The sample was taken up in $CDCl_3$ for ^1H NMR analysis to determine the conversion of benzyl azide into the triazole product.

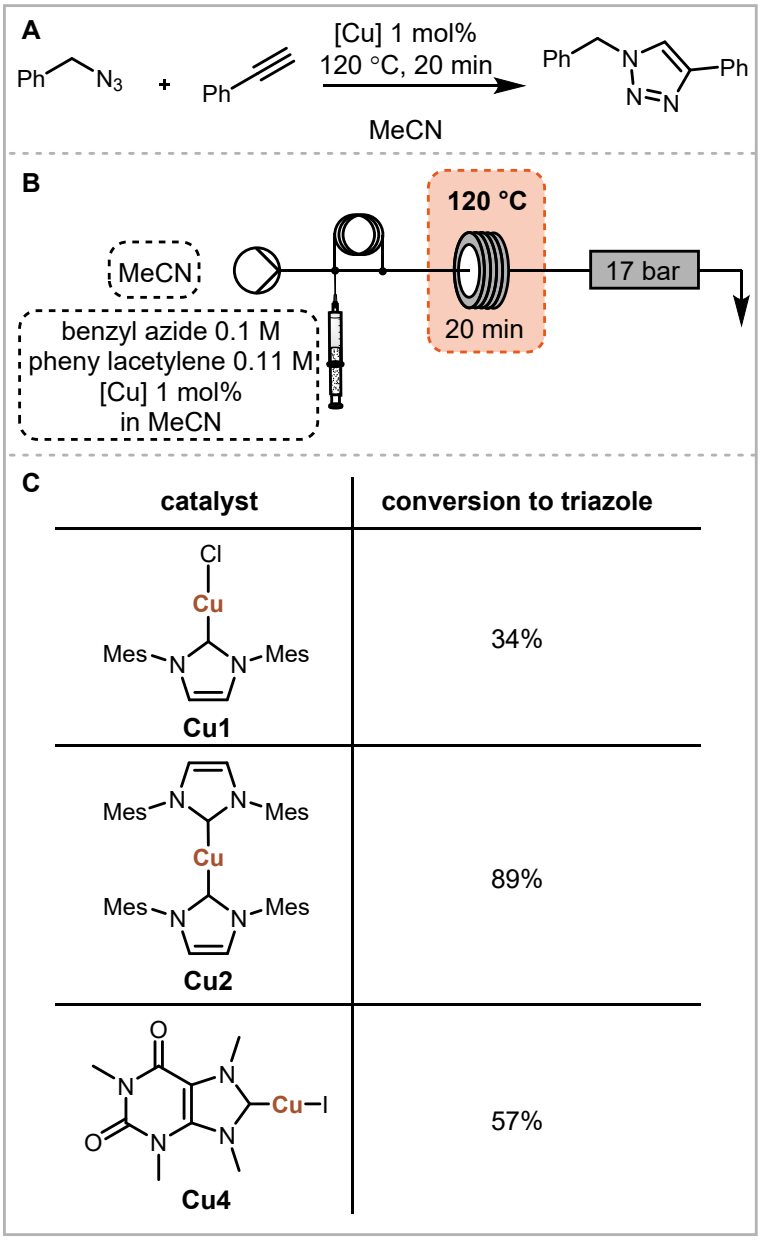
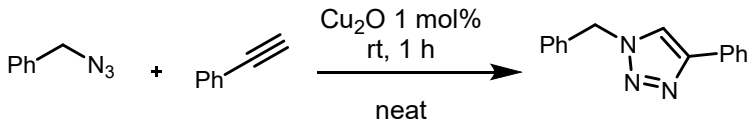


Figure S9: Model click reaction with benzyl azide and phenyl acetylene, **A**: reaction scheme; **B**: flow setup; **C**: catalyst screen, ^1H NMR spectroscopic triazole conversions.

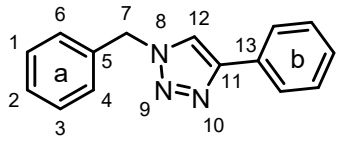
3.2 Large scale synthesis

1-benzyl-4-phenyl-1H-1,2,3-triazole



Benzyl azide (1.43 g, 10.8 mmol), phenyl acetylene (1.3 mL, 11.8 mmol, 1.1 equiv) and copper (I) oxide (15 mg, 0.11 mmol, 1 mol%) were stirred neat at room temperature. After 20 min the mixture had completely turned solid. The reaction was left for another 30 min, then taken up in EtOAc (100 mL) and washed with water (50 mL). The product was extracted from the aqueous layer twice more (50 mL EtOAc). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting cream solid was recrystallised in warm EtOAc. After cooling down the solid was filtered off and washed with hexane to yield the product as a colourless solid (2.0295 g, 8.6 mmol, 80%).

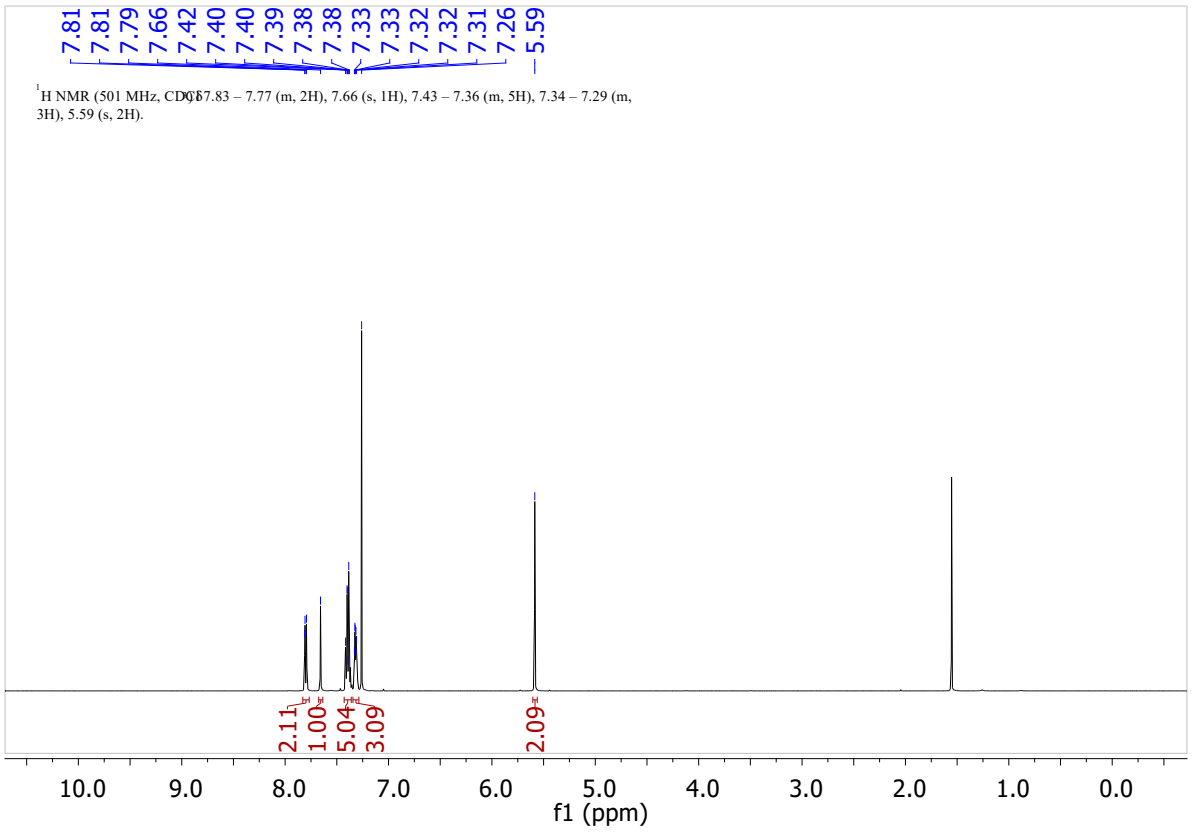
The data is consistent with the literature.[4]



^{1}H NMR (501 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H, $ArH^{1,3}$), 7.66 (s, 1H, ArH^{12}), 7.43 – 7.36 (m, 5H, ArH^{b}), 7.34 – 7.29 (m, 3H, $ArH^{2,4,6}$), 5.59 (s, 2H, CH_2^{7}).

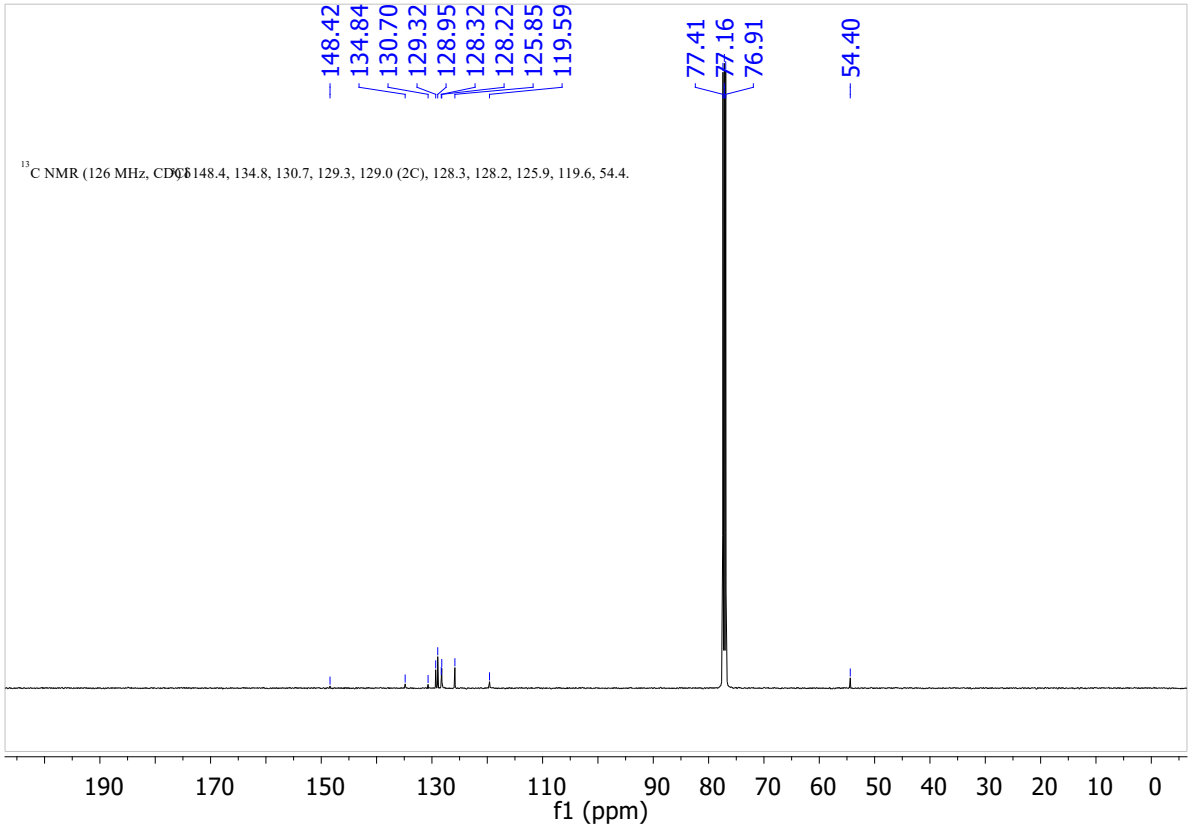
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4 (ArC^{14}), 134.8 (ArC^{5}), 130.7 (ArC^{11}), 129.3 ($ArCH^{b}$), 129.0 (2x $ArCH^{b}$), 128.3 ($ArCH^{2}$), 128.2 ($ArCH^{4,6}$), 125.9 ($ArCH^{1,3}$), 119.6 ($ArCH^{12}$), 54.4 (CH_2^{7}).

HRMS (ESI^+): measured $[M+H]^+$ 236.1192, calculated $[M+H]^+$ 236.1182.



^{1}H NMR (501 MHz, CDCl$_3$) δ 7.83 – 7.77 (m, 2H), 7.66 (s, 1H), 7.43 – 7.36 (m, 5H), 7.34 – 7.29 (m, 3H), 5.59 (s, 2H).

^{1}H NMR spectrum (501 MHz, $CDCl_3$) of 1-benzyl-4-phenyl-1H-1,2,3-triazole.



^{13}C NMR (126 MHz, CDCl$_3$) δ 148.4, 134.8, 130.7, 129.3, 129.0 (2C), 128.3, 128.2, 125.9, 119.6, 54.4.

13C NMR spectrum (126 MHz, $CDCl_3$) of 1-benzyl-4-phenyl-1H-1,2,3-triazole.

3.3 HPLC monitoring

3.3.1 UV spectra

The UV spectra for the internal standard (biphenyl), the product and both starting materials were recorded to determine optimum wavelengths for monitoring.

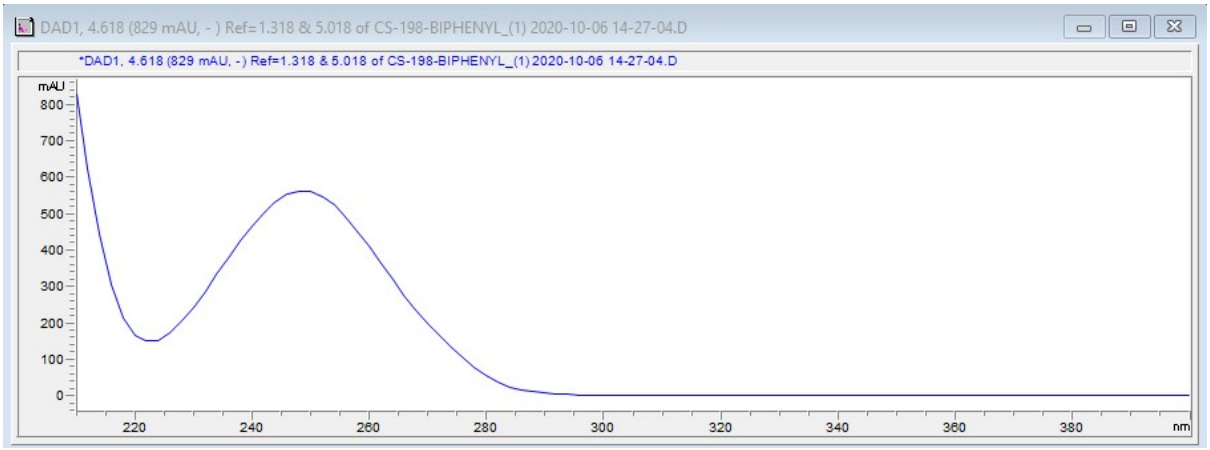


Figure S10: UV/Vis spectrum of biphenyl as internal standard (IS), maximum absorption at 250 nm.

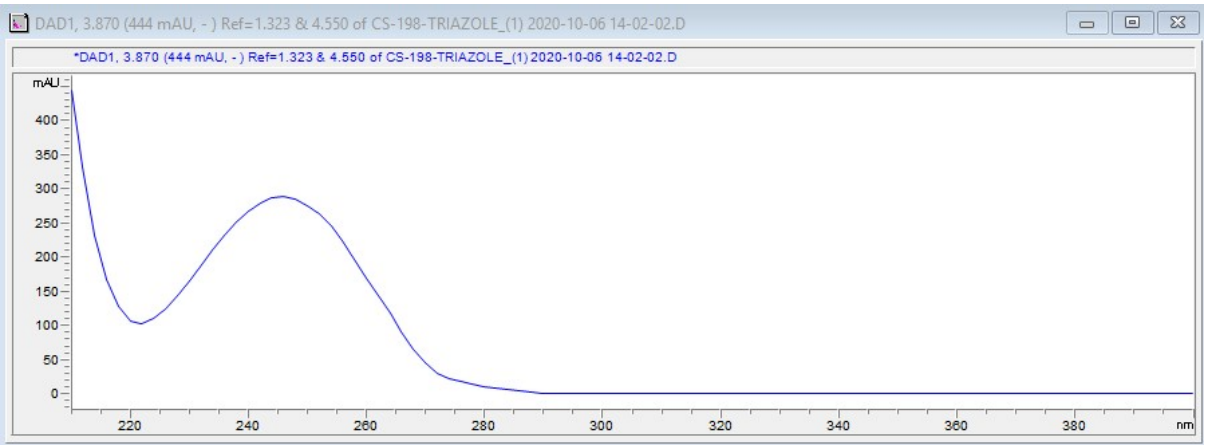


Figure S11: UV/Vis spectrum of the triazole product (P), maximum absorption at 250 nm.

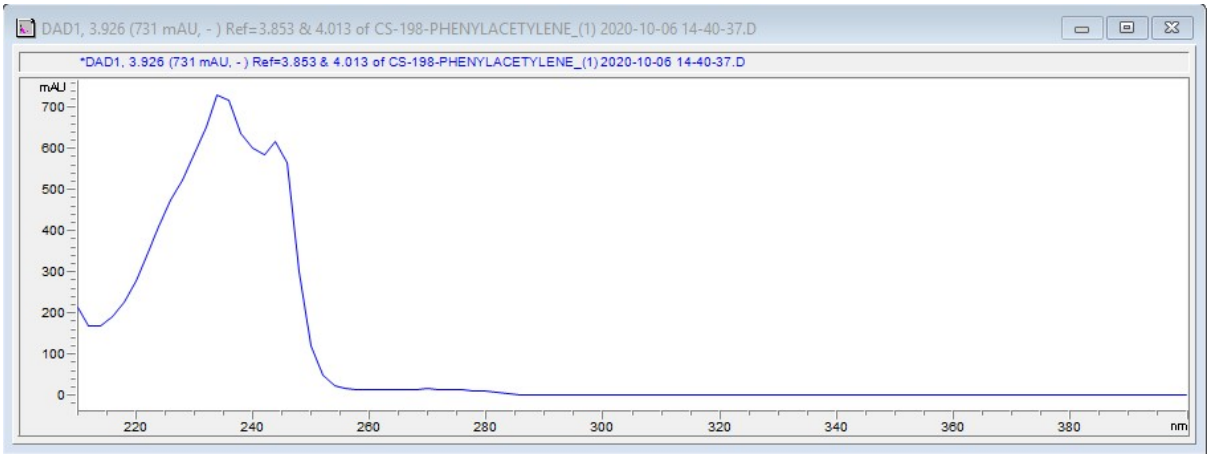


Figure S12: UV/Vis spectrum of the first starting material (SM1, phenyl acetylene), maximum absorption at 230 nm.

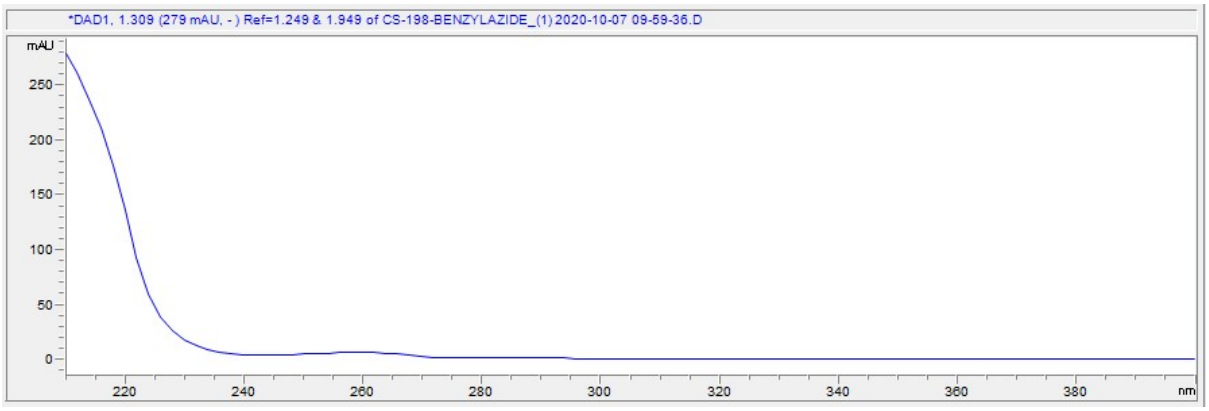


Figure S13: UV/Vis spectrum of the second starting material (SM2,benzylazide), maximum absorption at 210 nm.

3.3.2 HPLC Method

Solvent A: H_2O 0.1% TFA

Solvent B: MeCN 0.1% TFA

Table S3: HPLC method used in this study.

Time/ min	Solvent A/ %	Solvent B/ %	Flowrate/ mL/min	comment
0.0	45	55	0.3	idle conditions
3.0	45	55	1.5	start method, keep eluent composition
4.0	5	95	1.5	gradient eluent composition
4.5	5	95	1.5	keep eluent composition
4.8	45	55	1.5	gradient back to initial composition
5.0	45	55	1.5	keep eluent composition

After method optimisation, the method shown in Table S3 was used throughout this work.

3.3.3 HPLC Calibration

The following solutions were prepared:

Biphenyl 0.01 M, 100 mL.

SM1+SM2: biphenyl 0.01 M, phenylacetylene 0.01 M, benzylazide 0.01 M, 500 mL.

P: biphenyl 0.01 M, triazole 0.01 M, 25 mL.

A solution gradient was prepared by diluting the solutions SM1+SM2 and P with the biphenyl solution.

For each resulting solution the sample valve (500 nL) was charged manually with a syringe and the HPLC triggered by switching the valve through Matlab (2.5 s opening time). The ratio between the area of the internal standard and the area of the substrate was calculated (Table S4 and S5).

Table S4: Results for product dilution.

	concentration P	conc/ conc IS	area biphenyl	area P	ratio
P_100	0.01	1	867	947.01	1.09
P_50	0.005	0.5	873	478.07	0.55
P_100	0.01	1	871.6	951.7	1.09
P_90	0.009	0.9	877.0220337	861.8562	0.98
P_60	0.006	0.6	874.8873901	577.857	0.66
P_30	0.003	0.3	876.5029907	284.1147	0.32
P_20	0.002	0.2	878.4638062	190.2973	0.22
P_10	0.001	0.1	865.5672607	97.79453	0.11

Table S5: Results for starting material dilution.

	concentration SM	conc/ conc IS	area biphenyl	area SM1	ratio 1	area SM2	ratio 2
SM_10	0.001	0.1	868.4806519	65.72755	0.08	48.52849	0.06
SM_20	0.002	0.2	866.8311157	129.2338	0.15	90.12675	0.10
SM_30	0.003	0.3	711.9088745	154.1808	0.22	107.7243	0.15
SM_50	0.005	0.5	867.1869507	335.0421	0.39	220.4573	0.25
SM_60	0.006	0.6	801.84729	368.2478	0.46	239.8771	0.30
SM_90	0.009	0.9	712.6252441	482.3609	0.68	314.8731	0.44
SM_100	0.01	1	751.9749756	583.2283	0.78	383.3643	0.51

The ratio of the areas was plotted against the ratio of the concentrations. The slope of the linear trend line (forced through 0) represents the calibration factor (Figure S14).

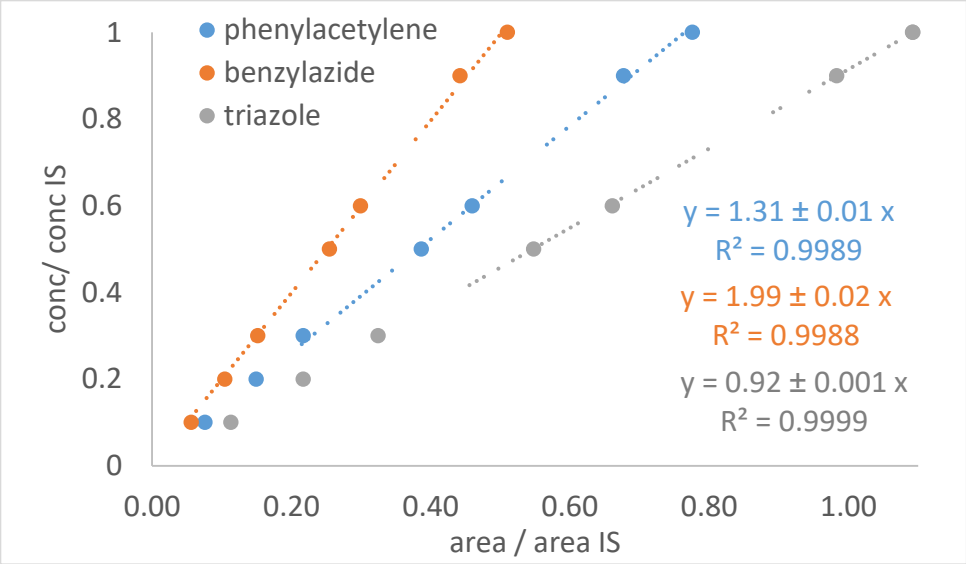


Figure S14: Calibration for SM1, SM2 and P.

4 Telescoped Reaction

4.1 Without Autosampler

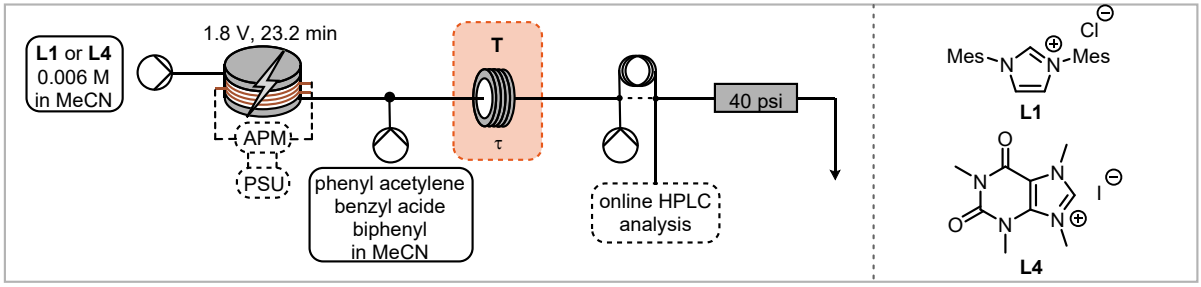
The electrochemical reactor was assembled with two spacers (0.926 mL) and three copper electrodes and the APM set to 1/60 Hz. The flow setup was assembled according to Figure S15.

A solution of IMes·HCl **L1** (0.006 M, 204 mg, 0.6 mmol) in dry and degassed MeCN (100 mL) was prepared in a flame dried ampoule under argon.

Another solution of benzylazide (0.1 M, 1.25 mL, 1.33 g, 10 mmol), phenylacetylene (0.1 M, 1.10 mL, 1.02 g, 10 mmol) and biphenyl (0.1 M, 1.54 g, 10 mmol) in MeCN (100 mL) was prepared in a volumetric flask.

10 mL of the first solution was transferred to a flame dried Schlenk tube under argon. The Schlenk tube was equipped with an argon filled balloon and the inlet of the first pump inserted through a Suba seal. The solution was pumped through the setup at 0.5 mL/min testing for leaks. Once the reactor was full, the flow rate was switched to 0.040 mL/min (23.2 min residence time). The HPLC was set up to sample every 6 min *via* a 0.6 nL Vici valve (2.5 s opening time).

The second solution was equipped with a Suba seal and the inlet of the second pump inserted. The reactor was filled with solution and the second pump was set to 0.24 mL/min. The reaction was started by switching on the Eurotherm heating control, the power supply (1.8 V) and starting the HPLC measurements.



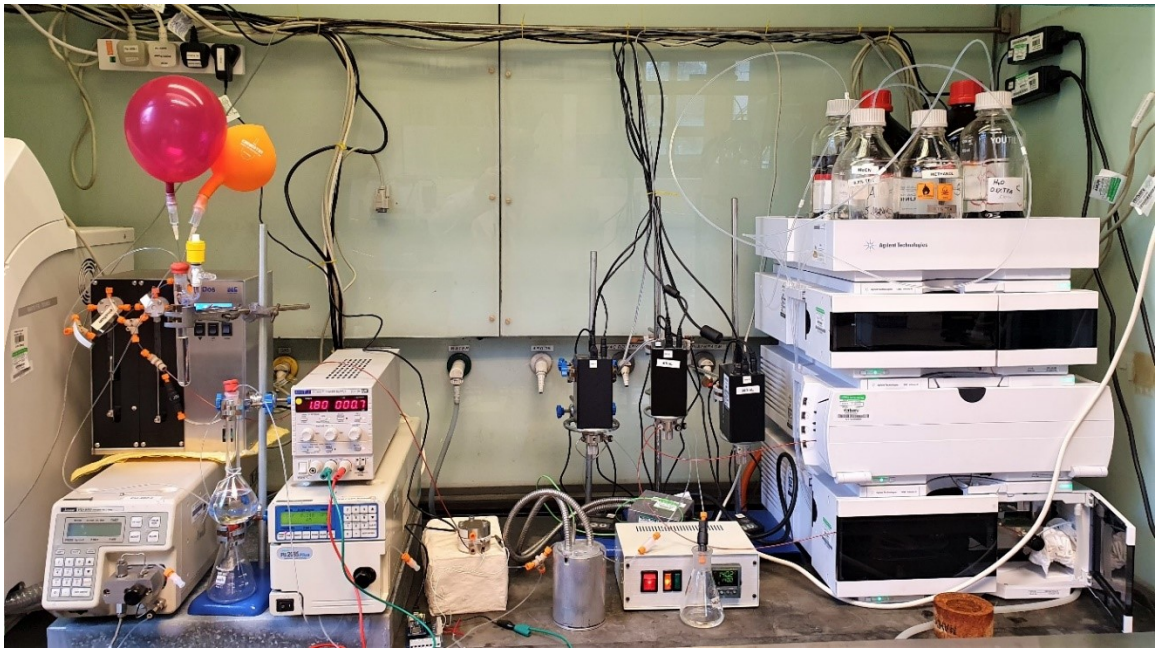


Figure S15: Telescoped reaction setup.

Table S6: Optimisation of the telescoped reaction

entry	catalyst precursor	mol%	residence time/ min	T/ °C	triazole yield/ %
1	L1	1	7.14	120	6
2	L1	2	12.5	120	19
3	L1	2	12.5	140	22
4	L1	3	16.7	120	42
5	L4	3	16.7	120	77

4.2 With Autosampler, no cleaning

The electrochemical reactor was assembled with two spacers (0.926 mL) and three copper electrodes and the APM set to 1/10 Hz. The flow setup was assembled according to Figure S16 with a 4.56 mL sample loop for the autosampler.

A solution of IMes·HCl (0.006 M, 204 mg, 0.6 mmol) in dry and degassed MeCN (100 mL) was prepared in a flame dried ampoule under argon. 10 mL of this solution was transferred to a sealed and flame dried microwave vial under argon.

Another solution of benzylazide (0.1 M, 1.25 mL, 1.33 g, 10 mmol), phenylacetylene (0.1 M, 1.10 mL, 1.02 g, 10 mmol) and biphenyl (0.1 M, 1.54 g, 10 mmol) in MeCN (100 mL) was prepared in a volumetric flask.

Acetonitrile and the second solution were pumped through the setup according to Figure S16 at 0.5 mL/min and 1 mL/min to fill the reactors and test for leaks before switching to the desired flowrates of 0.040 mL/min and 0.24 mL/min (23.2 min and 7.15 min residence time). The HPLC was set up to sample every 6 min *via* a 500 nL Vici valve (2.5 s opening time).

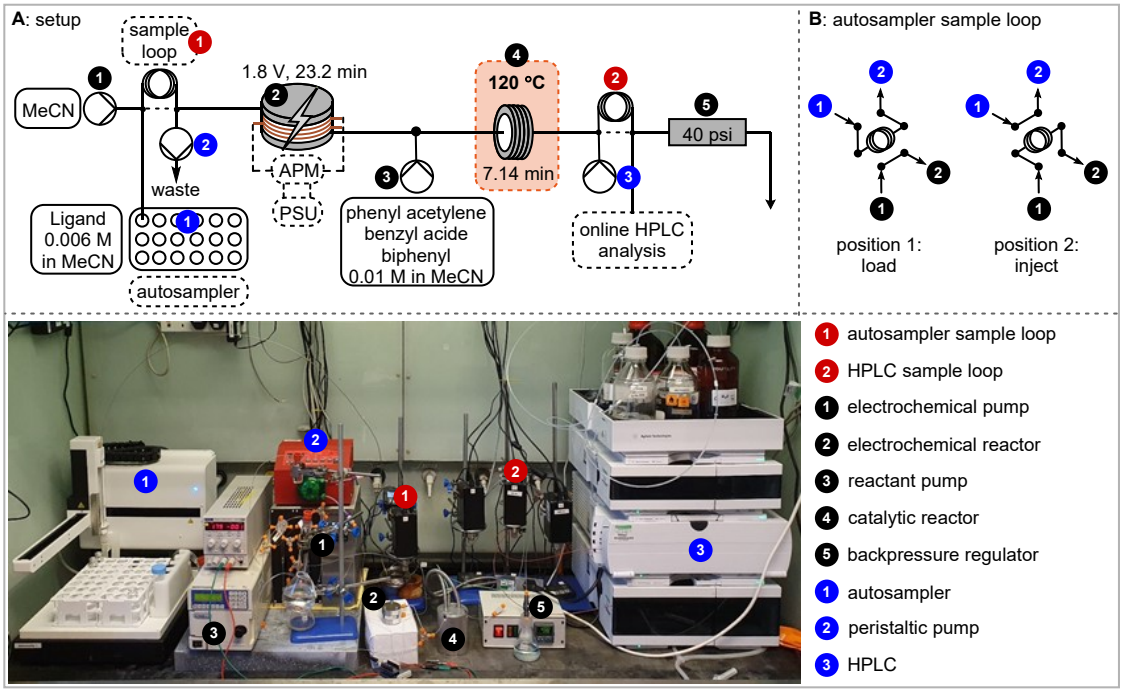


Figure S16: **A**: Telescoped reaction setup with autosampler; **B**: sample loop configuration.

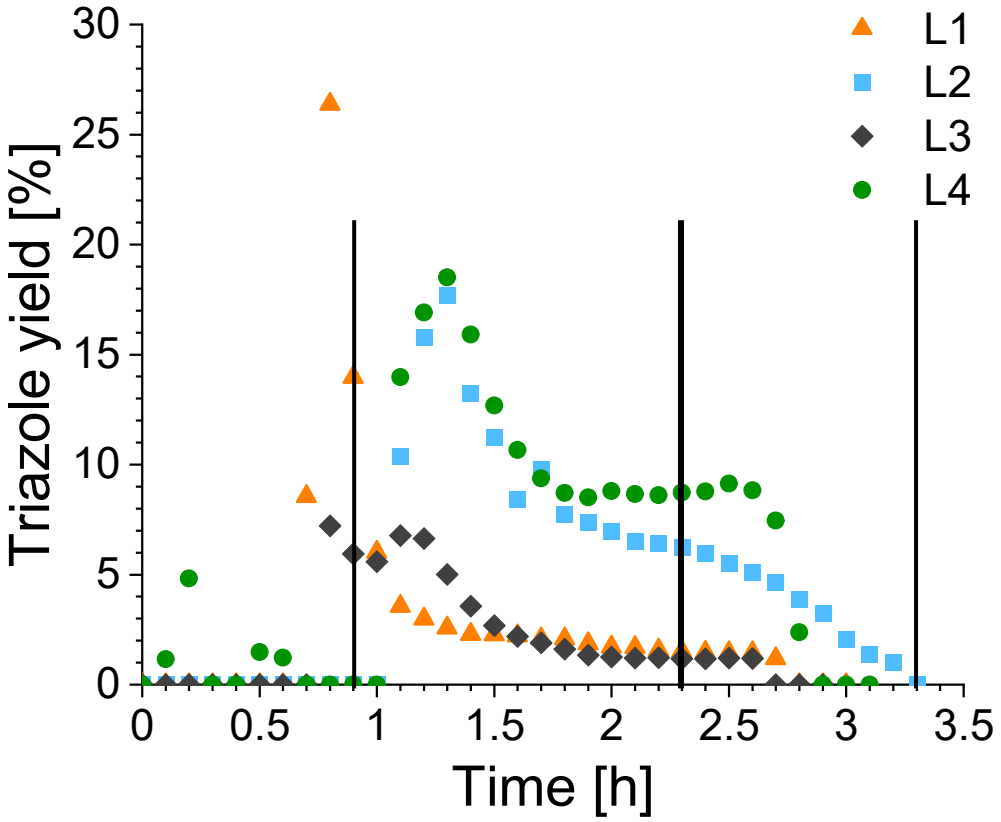


Figure S17: Results from the autosampler injection of different ligands without cleaning, bold line: steady state yield taken, dotted lines: calculated aliquot beginning and end.

Table S7: Results from the autosampler injection of different ligands without cleaning.

	ligand	Triazole yield/ %
L1	IMes·HCl	2
L2	IMes·HPF_6	8
L3	IPr·HCl	2
L4	Xanthinium iodide	9

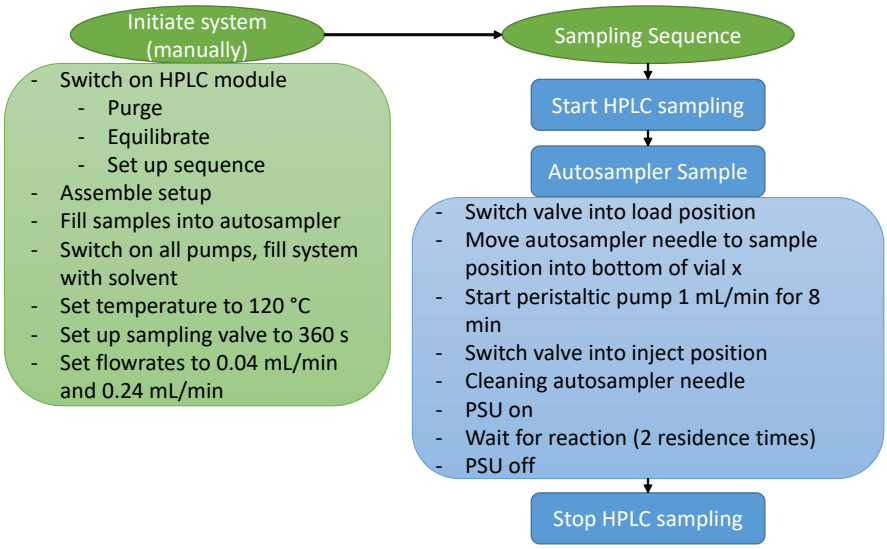


Figure S18: Autosampler sequence for injection of different ligands without cleaning.

4.3 Calculations sample loop size reduction

Total residence time: 40 min.

Calculated beginning aliquot: 48 min (total residence time + 8 min autosampler).

Calculated end aliquot 162 min.

Earliest stable point at 108 min, visual analysis.

Latest stable point 156 min.

Aliquot time: 162 min – 48 min = 114 min.

Stable time: 156 min – 108 min = 48 min.

Minimum aliquot time: 114 min – 48 min = 66 min.

Minimum aliquot volume: 66 min * 0.04 mL/ min = 2.64 mL.

3.0 mL, 75 min, 6.6 m 1/16” SS tubing.

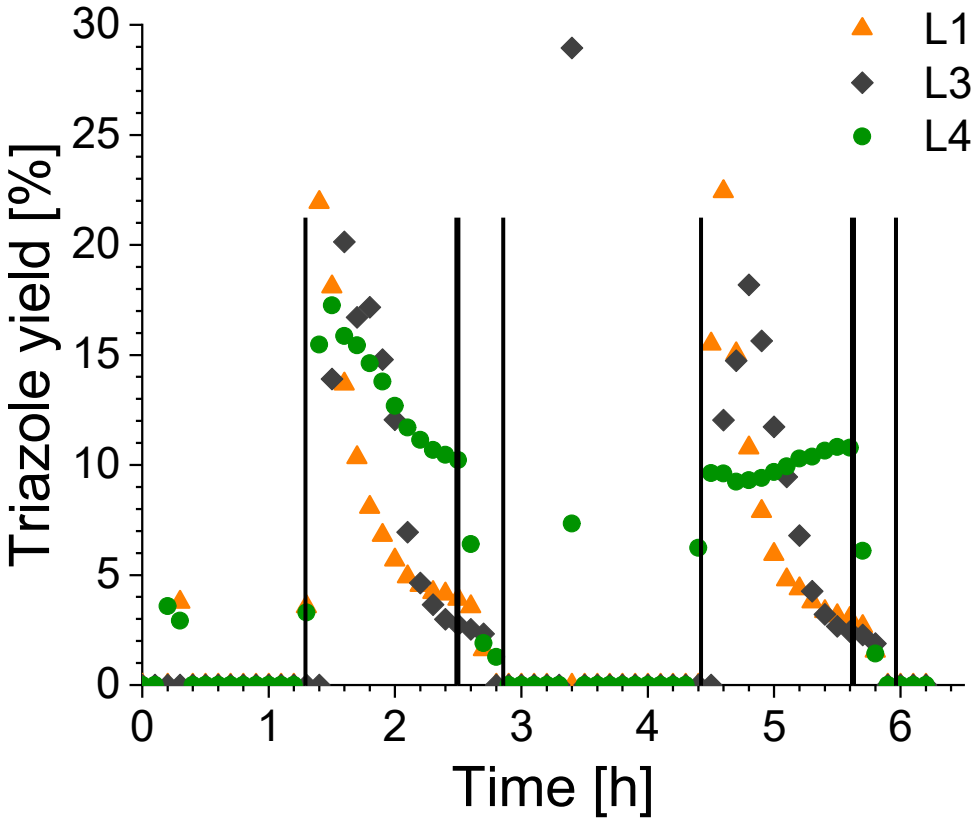
4.4 Integration of cleaning

The electrochemical reactor was assembled with two spacers (0.926 mL) and three copper electrodes and the APM set to 1/10 Hz. The flow setup was assembled according to Figure S16 with a 3 mL sample loop for the autosampler.

A solution of IMes·HCl (0.006 M, 204 mg, 0.6 mmol) in dry and degassed MeCN (100 mL) was prepared in a flame dried ampoule under argon. 10 mL of this solution was transferred to a sealed and flame dried microwave vial under argon.

Another solution of benzylazide (0.1 M, 1.25 mL, 1.33 g, 10 mmol), phenylacetylene (0.1 M, 1.10 mL, 1.02 g, 10 mmol) and biphenyl (0.1 M, 1.54 g, 10 mmol) in MeCN (100 mL) was prepared in a volumetric flask.

Acetonitrile and the second solution were pumped through the setup according to Figure S16 at 0.5 mL/min and 1 mL/min to fill the reactors and test for leaks before switching to the desired flowrates of 0.040 mL/min and 0.24 mL/min (23.2 min and 7.15 min residence time). The HPLC was set up to



sample every 6 min *via* a 500 nL Vici valve (2.5 s opening time).

Figure S19: Results from the autosampler injection of different ligands with cleaning, bold line: steady state yield taken, dotted lines: calculated aliquot beginning and end.

Table S8: Results from the autosampler injection of different ligands with cleaning.

	ligand	Triazole yield/ %	
		Injection 1	Injection 2
L1	IMes·HCl	3.9	3.0
L3	IPr·HCl	2.3	2.3
L4	Xanthinium iodide	10.2	10.8

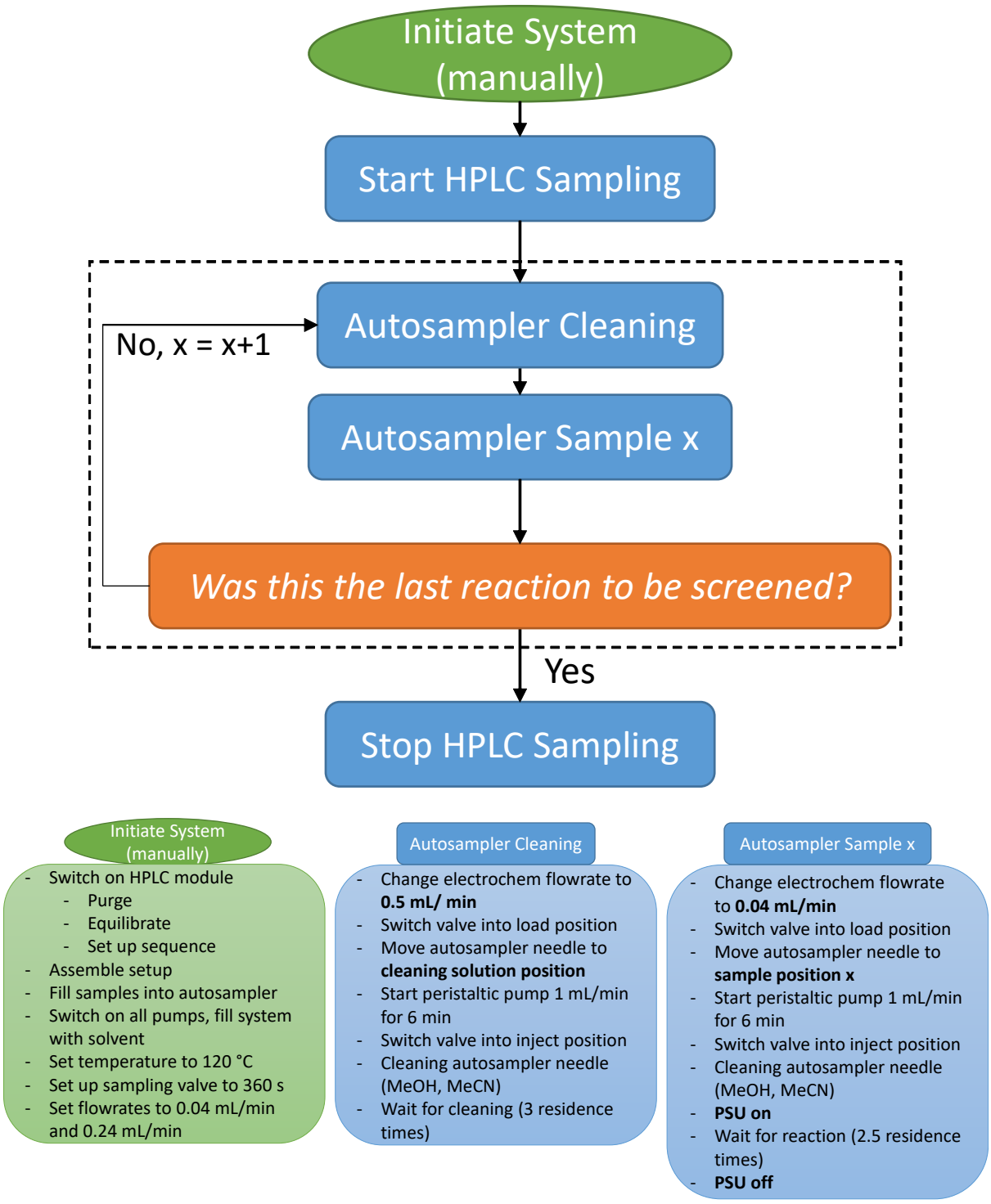


Figure S20: Autosampler sequence for injection of different ligands with cleaning.

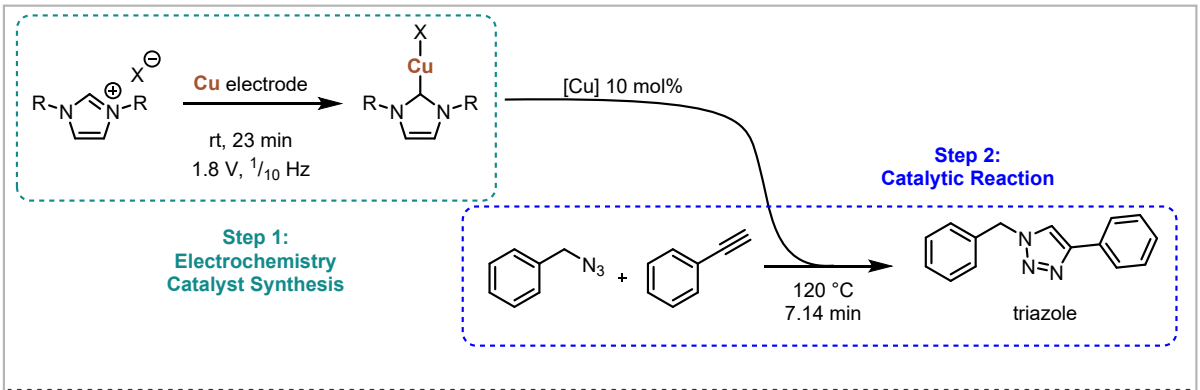
4.5 Ligand Screen

The electrochemical reactor was assembled with two spacers (0.926 mL) and three copper electrodes and the APM set to 1/10 Hz. The flow setup was assembled according to Figure S16 with a 3 mL sample loop for the autosampler.

A solution of the desired ligand (0.006 M) in dry and degassed MeCN (20 mL) was prepared in a flame dried microwave vial under argon.

Another solution of benzylazide (0.1 M, 1.25 mL, 1.33 g, 10 mmol), phenylacetylene (0.1 M, 1.10 mL, 1.02 g, 10 mmol) and biphenyl (0.1 M, 1.54 g, 10 mmol) in MeCN (100 mL) was prepared in a volumetric flask.

Acetonitrile and the second solution were pumped through the setup according to Figure S16 at 0.5 mL/min and 1 mL/min to fill the reactors and test for leaks before switching to the desired flowrates of 0.040 mL/min and 0.24 mL/min (23.2 min and 7.15 min residence time). The HPLC was set up to sample every 6 min *via* a 500 nL Vici valve (2.5 s opening time).



catalyst	triazole yield	catalyst	triazole yield	catalyst	triazole yield
Cu1	3%	**Cu7**	5%	**Cu11**	38%
Cu3	2%	**Cu8**	19%	**Cu12**	36%
Cu4	11%	**Cu9**	0%	**Cu13**	25%
Cu6	23%	**Cu10**	34%	**Cu14**	53%

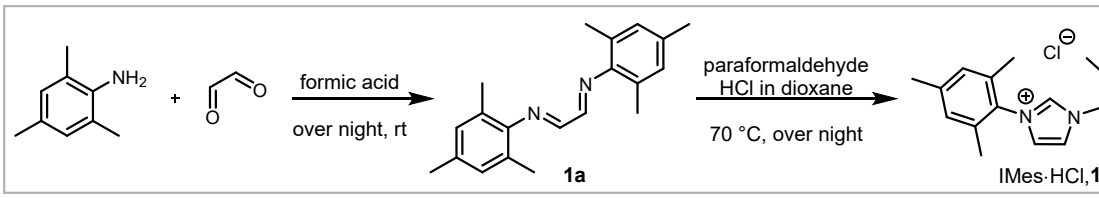
Figure S21: Ligand screen using the full flow setup. Triazole yield by HPLC using biphenyl as an internal standard.

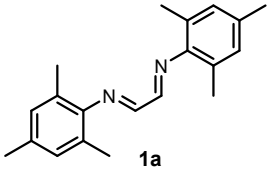
Table S9: Triazole yield and turnover frequency using catalysts shown in Figure S21.

catalyst	triazole yield [%]	catalyst TOF [10^{-3} s^{-1}]
Cu1	3	0.70
Cu3	2	0.47
Cu4	11	2.6
Cu6	23	5.4
Cu7	5	1.2
Cu8	19	4.4
Cu9	0	0
Cu10	34	7.9
Cu11	38	8.9
Cu12	36	8.4
Cu13	25	5.8
Cu14	53	12

5 Synthesis of Starting Materials

5.1 L1, 1,3-Dimesityl-1H-imidazolium choride (IMes·HCl)

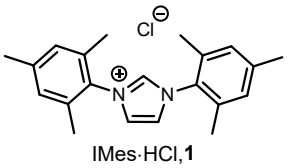




To a solution of 2,4,6-trimethylaniline (23.2 mL, 164 mmol, 2 equiv) in EtOH (150 mL) was added glyoxal (40% in water, 9.6 mL, 84 mmol, 1.02 equiv) and 20 drops of formic acid. After a few minutes a yellow precipitate formed and the reaction solution was left to stir overnight. The solid was filtered off and washed with EtOH and MeOH to yield the product, *N*,*N*-dimesitylethane-1,2-diimine, as a bright yellow solid (78%, 18.95 g, 64 mmol). The diimine was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 2H), 6.91 (s, 4H), 2.30 (s, 6H), 2.16 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 147.6, 134.4, 129.1, 126.7, 20.9, 18.4.



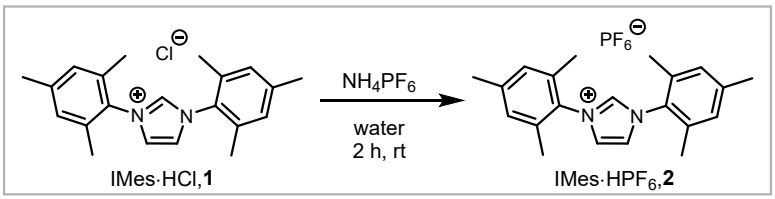
A solution of *N*,*N*-dimesitylethane-1,2-diimine (11.0 g, 37.5 mmol) and paraformaldehyde (1.2 g, 41 mmol, 1.1 equiv) in anhydrous toluene (300 mL) was prepared under N_2 and then heated up to 100 °C till mostly dissolved (about 30 min). After cooling to 40 °C HCl in dioxane (4 M, 10.3 mL, 41 mmol, 1.1 equiv) was added slowly turning the reaction mixture red. The reaction solution was then stirred at 70 °C overnight forming a precipitate in a dark brown solution. The precipitate was filtered off, washed with EtOAc until the filtrate ran clear yielding the crude product as a pale brown solid. The solid was then triturated from MeCN and Et_2O, filtered and washed with Et_2O to give the product, 1,3-dimesityl-1H-imidazolium chloride **L1**, as an off-white solid (37%, 4.67 g, 13.7 mmol).

^{1}H NMR (501 MHz, $CDCl_3$) δ 11.07 (s, 1H), 7.56 (s, 2H), 7.04 (s, 4H), 2.35 (s, 6H), 2.20 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6, 140.4, 134.2, 130.8, 130.1, 124.3, 21.3, 17.9.

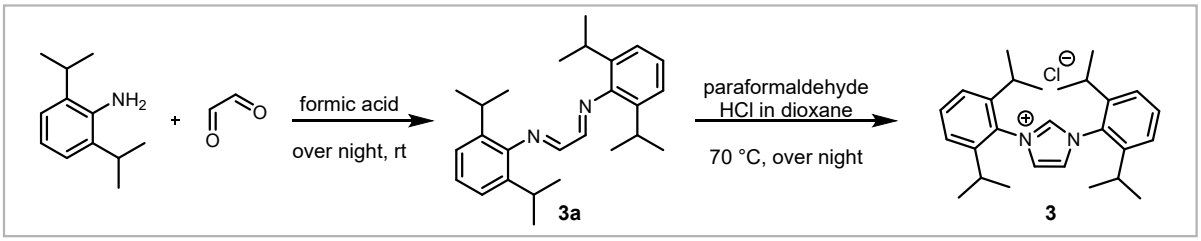
The data is consistent with the literature.[5]

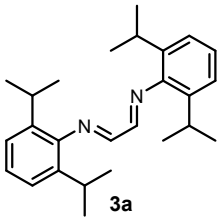
5.2 L2, 1,3-Dimesityl-1H-imidazolium hexafluorophosphate (IMes·HPF_6)



The product was prepared following a known literature procedure.[1]

5.3 L3, 1,3-Bis(2,6-diisopropylphenyl)-1H-imidazolium chloride

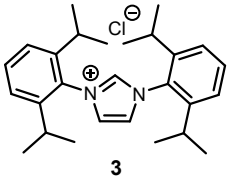




To a solution of 2,6-diisopropylaniline (10.6 mL, 10 g, 56 mmol, 2.1 equiv) in MeOH (50 mL) was added glyoxal (40% in water, 3.2 mL, 28 mmol) and 2 drops of formic acid. The reaction solution was left to stir overnight forming a yellow precipitate. The precipitate was filtered and washed with MeOH yielding the product (8.2 g, 22 mmol, 78%). The product was used without further purification (*N*,*N*-bis(2,6-diisopropylphenyl)ethane-1,2-diimine, **3a**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 2H), 7.22 – 7.15 (m, 6H), 2.95 (hept, *J* = 6.9 Hz, 4H), 1.21 (d, *J* = 6.9 Hz, 24H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 148.2, 136.9, 125.3, 123.3, 28.2, 23.5.



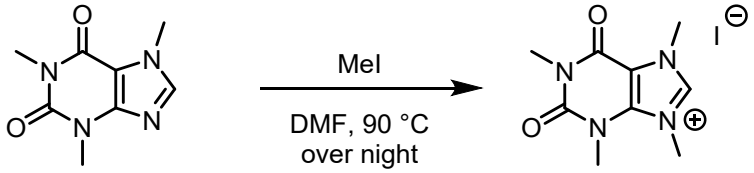
A solution of the diimine **3a** (5 g, 13 mmol) and paraformaldehyde (0.40 g, 13 mmol) in toluene (100 mL) was heated up to 100 °C till mostly dissolved (about 30 min). After cooling to 40 °C HCl in dioxane (4 M, 3.3 mL, 13 mmol) was added slowly turning the reaction mixture red. The reaction solution was then stirred at 70 °C overnight forming a precipitate. The precipitate was washed with EtOAc until the filtrate ran clear. The solid was then triturated from MeOH and Et_2O, filtered and washed with Et_2O to give the product, 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium **3**, as a beige solid (32%, 1.78 g, 4.2 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.15 (s, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 2.44 (hept, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.7 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 138.7, 132.3, 130.0, 126.9, 124.9, 29.3, 24.9, 24.0.

The data is consistent with the literature.[5]

5.4 L4, 1,3,7,9,-tetramethylxanthinium iodide



Following a modified literature procedure,[6] an ampoule was equipped with caffeine (4.5 g, 23.2 mmol), methyl iodide (7.55 mL, 121 mmol, 5.3 equiv) and *N, N*'-dimethyl formamide (25 mL). The mixture was stirred at 90 °C over night. The caffeine dissolved once the reaction mixture reached temperature which turned red over time. After cooling down to room temperature, EtOAc (50 mL) was added to the clear solution, precipitating the product. The precipitate was washed with

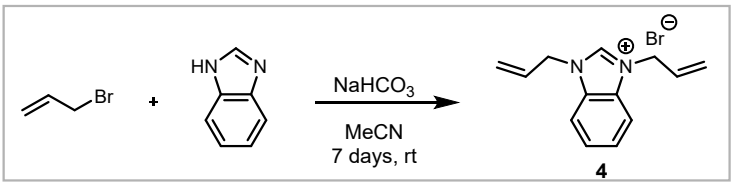
EtOAc until the filtrate ran clear (~2 x 10 mL). The crude product was further purified *via* trituration from warm MeCN (100 mL, 60 °C) and Et_2O (100 mL). The solid was washed with Et_2O and dried under vacuum yielding the product as a colourless solid (5.9 g, 75%, 17.5 mmol).

The data is consistent with previous reported data.[6]

^{1}H NMR (400 MHz, DMSO) δ 9.28 (d, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 2.3 Hz, 3H), 4.05 (s, 3H), 3.74 (s, 3H), 3.27 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 153.29, 150.18, 139.61, 139.27, 107.74, 36.86, 35.62, 31.35, 28.40.

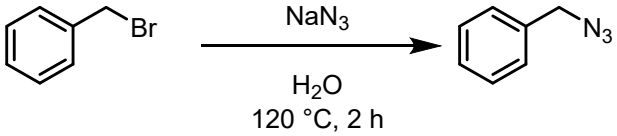
5.5 L5, 1,3-Diallyl-1H-benzimidazolium bromide



4

The product was prepared according to a known literature procedure.[3]

5.6 Benzylamide

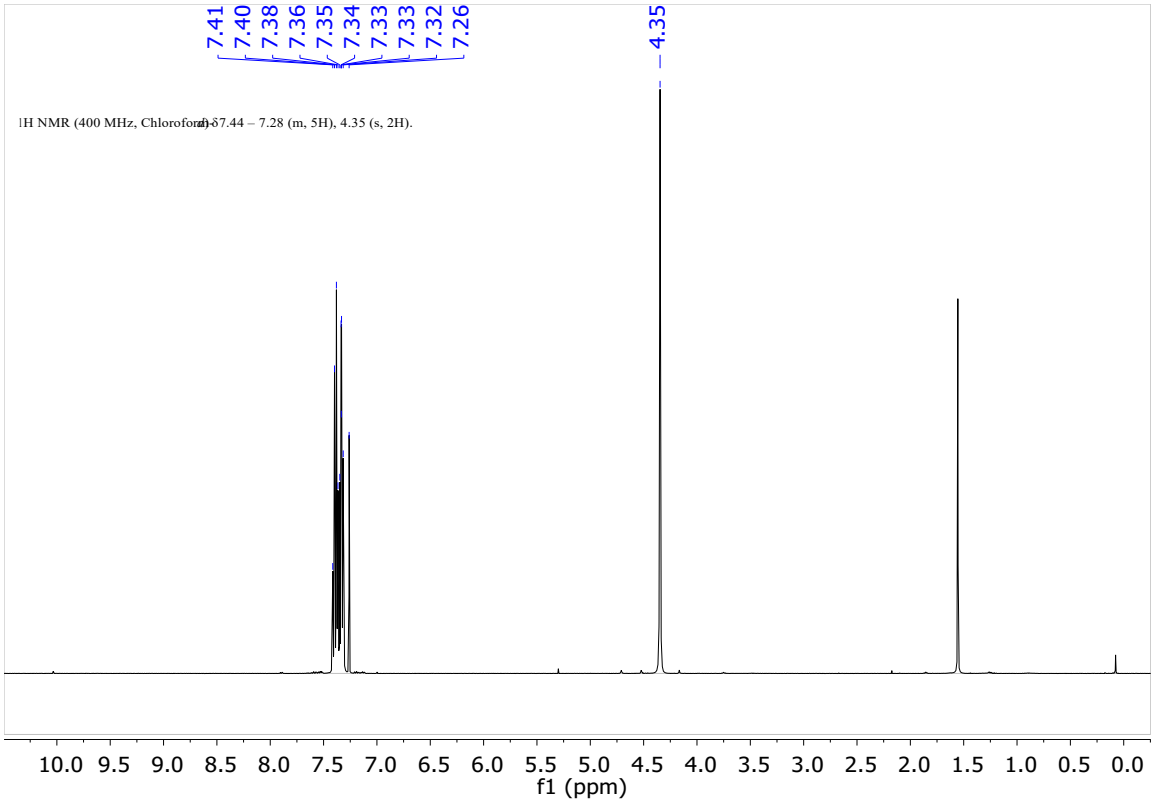


A 250 mL round bottomed flask was charged with benzylbromide (5.9 mL, 50 mmol), sodium azide (8.13 g, 125 mmol, 2.5 equiv.) and water (50 mL) and closed with a Suba seal. The mixture was stirred at 120 °C for 2 h. After cooling down to room temperature, the reaction mixture was diluted with water (50 mL) and the product extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield the product (6.165 g, 46 mmol, 92%).

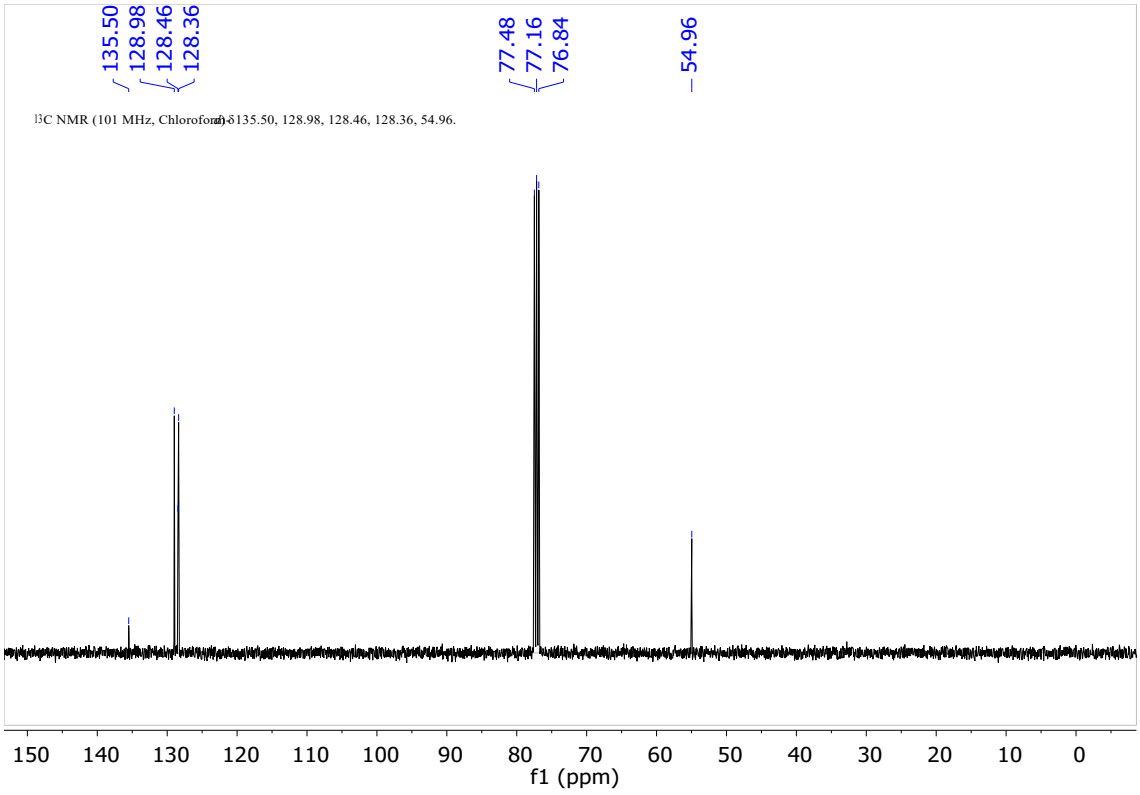
The data is consistent with the literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 4.35 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.50, 128.98, 128.46, 128.36, 54.96.



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of benzylamide.



^{13}C NMR spectrum (101 MHz, $CDCl_3$) of benzylamide.

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