Shedding light on the use of Cu(II)-salen complexes in the A^3 coupling reaction

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Contents

Materials.

All reagents were purchased from Sigma Aldrich, Fluorochem, Tokyo Chemical Industry, Apollo Scientific, Fischer Scientific or Alfa Aesar and used without further purification. Experiments were performed under aerobic or nitrogen conditions. The petroleum ether used was of the fraction that boils between 40 and 60 °C.

Instrumentation.

NMR spectra were recorded with a Varian VNMRS 500 or Varian VNMRS 600 at 30 °C on solution-state samples in Chloroform-d or DMSO-d_6. Chemical shifts are quoted in parts per million (ppm). Coupling constants (J) are recorded in units of Hz. FT-IR spectra were recorded over the range of 4000–650 cm^{-1} on a PerkinElmer Spectrum One FT-IR spectrometer fitted with a UATR polarisation accessory. HRMS data were obtained with a Bruker Daltonics Fourier Transform (FTMS) Apex II spectrometer with electrospray ionisation (ESI) and methanol as solvent. ESI-MS data were obtained on a VG Autospec Fissions instrument (EI at 70 eV) and carried out by Dr A. K. Abdul-Sada at the University of Sussex. Molecular ions are reported as mass/charge (m/z) ratios. LCMS Reactions were monitored with the assistance of liquid chromatography-mass spectrometry. All products were analysed using the following conditions: Column - Waters XSelect CSH C18 5 μm 4.6 x 50 mm @ 50 °C. Flow Rate - 1.7 ml/min. Eluents A - Water, B – Acetonitrile, both with +0.1% TFA. Gradient - 0.0 min 5% B, 0.4-3 min 5-98% B, 3-3.5 min 98%B, 3.5-3.6 min 98-5% B, 3.6-4 min 5% B. Method - ES positive. Thermogravimetric analysis was carried out with a Thermogravimetric analyser Q-50 V20.13 using a platinum pan, in a nitrogen atmosphere from 25 – 792 °C, at a scan rate of 10 °C/min. UV−Vis measurements (280-750 nm) were performed at room temperature (20˚C) using a Thermo Scientific Evolution 300 UV-Vis spectrophotometer equipped with 5mm path length quartz cells, and the collected data were processed using the Vision Pro software. CD spectra were collected using a Jasco J-715 spectropolarimeter with a Peltier temperature control

system at 21 °C. Samples were placed into 1 mm path length quartz cuvettes (Hellma) and scanned from 180-850 nm. The parameters were set as the following: a pitch of 0.1 nm, a scan speed 50 nm min^{-1}, response time 4 s, slit widths 1 nm and with standard sensitivity. Each set of data was collected in duplicate. Spectra were converted to molar ellipticity per residue (MER). Elemental analysis was performed at London Metropolitan University. The synthesis reporting microwave irradiation was performed in a Biotage Initiator Robot Sixty in pressure-rated 5 mL Biotage glass vials. Purification of compounds with normal-phase silica flash column chromatography was conducted in a Biotage Isolera with UV detection at 254 nm, and the solvent mixture of diethyl ether/petroleum ether (fraction 40-60) was used as the gradient eluent (0:100-30:70 v/v).

Electrochemistry.

Electrochemical measurements were carried out using an Autolab 302N potentiostat interfaced through Nova 2.0 software to a personal computer. Electrochemical measurements were performed in a glovebox under oxygen levels of less than 5 ppm using solvent that had been purified by passing through an alumina-based purification system. Diamond-polished glassy carbon electrodes of 3 mm diameter were employed for cyclic voltammetry (CV) scans. CV data were evaluated using standard diagnostic criteria for diffusion control and chemical and electrochemical reversibility. The experimental reference electrode was a silver wire coated with anodically deposited silver chloride. The electrochemical potentials in this article are referenced to the ferrocene/ferrocenium couple. The ferrocene potential was obtained by its addition to the analyte solution.

Ligand synthesis.

The ligand 6,6'-((1E,1'E)-((1S,2S)-cyclohexane-1,2-diylbis(azanylylidene)) bis(methanylylidene))bis(2,4-di-tert-butylphenol) (H_2L^S) was synthesized by reflux using a round-bottomed flask equipped with a reflux condenser and a magnetic stir bar. The round

bottom flask was charged with 4.70 g (20.0 mmol) of 3,5-di-tert-butylsalicylaldehyde in 90 mL of EtOH absolute. A solution of 1.14 g of (1*S*,2*S*)-(−)-1,2-Diaminocyclohexane (10.0 mmol) in 10 mL of EtOH absolute was added. The flask was heated at reflux for 2 hours with the appearance of the Schiff base as a bright yellow precipitate. Yield = 97%, based on (1*S*,2*S*)-(−)-1,2-Diaminocyclohexane**.**

Catalysts synthesis and characterisation.

[Cu(II)L^S] (**1S**) was synthesized by the following procedure: H_2L^S (0.1 mmol, 55 mg), $Cu(OTF)_2$ (0.1 mmol, 36 mg) and Et_3N (0.2 mmol, 27 μL) were added in methanol (20ml), using a round-bottomed flask equipped with a reflux condenser and a magnetic stir bar. The resulting mixture was refluxed for 1 hour. The solution mixture was filtered, and the filtrate was then collected and underwent slow evaporation, forming brown needle-shaped crystals after two days. Yield = 85%, based on Cu^{II}. Elemental analysis for $CuC_{36}H_{52}N_2O_2$: C 71.13, H 8.63, N 4.61; found C 71.03, H 8.57, N 4.67.

Synthesis of compound 6.

The ligand 2-(((1S, 2S)-2-(3,5-di-tert-butyl-2-hydroxybenzylamino)cyclohexylamino)-methyl)-4,6-di-tert-butylphenol ($H_2L_2^S$) was synthesized following the reported procedure.[1] Yield = 90%, based on (H_2L^S). [Cu(II)L_2^S] (**6**) was synthesized by the following procedure: $H_2L_2^S$ (0.1 mmol, 55 mg), $Cu(OTF)_2$ (0.1 mmol, 36 mg) and Et_3N (0.2 mmol, 27 μL) were added in methanol (20ml), using a round-bottomed flask equipped with a reflux condenser and a magnetic stir bar. The resulting mixture was refluxed for 1 hour, and green oil was formed after the evaporation of the solvent. Yield = 80%, based on Cu^{II}. The identity of compound 6 was confirmed by ESI-MS (Figure S12).

FT-IR

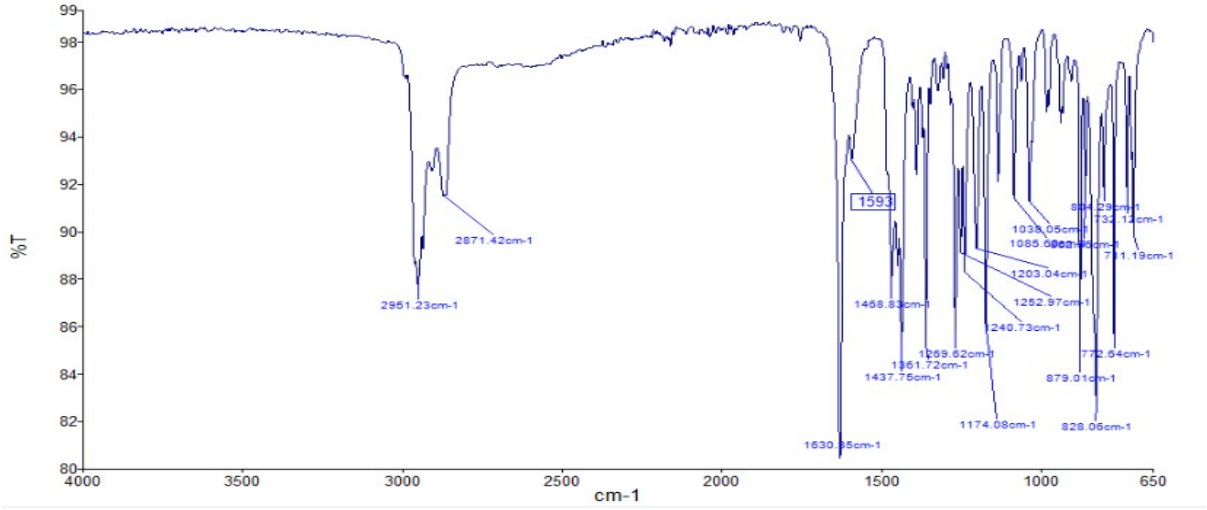


Figure S1. FT-IR of the ligand (**H_2L^S**).

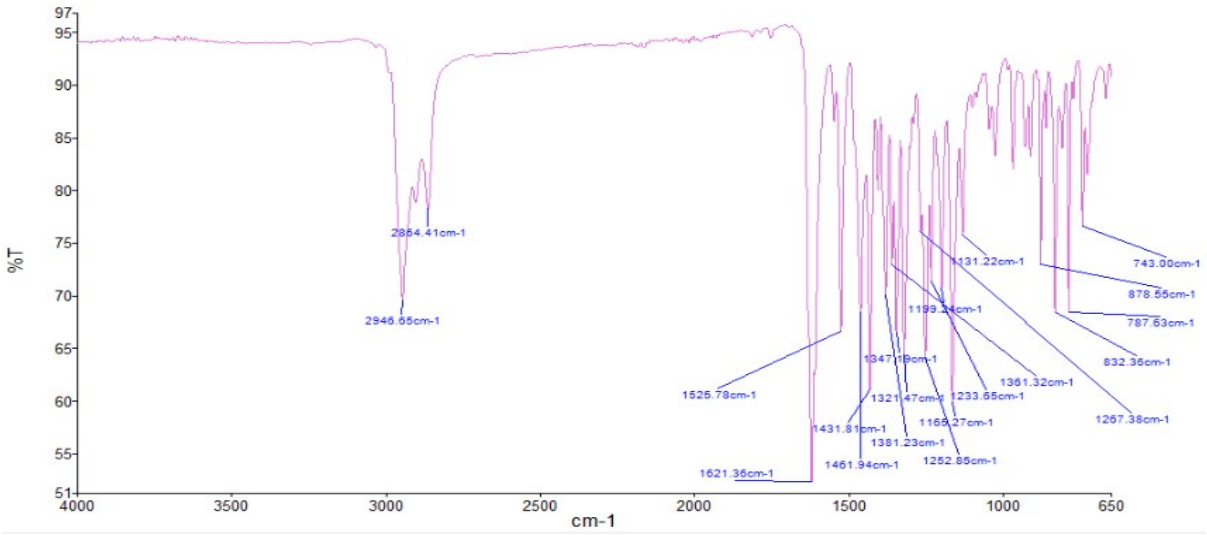


Figure S2. FT-IR of the catalyst (**1S**).

ESI-FTMS

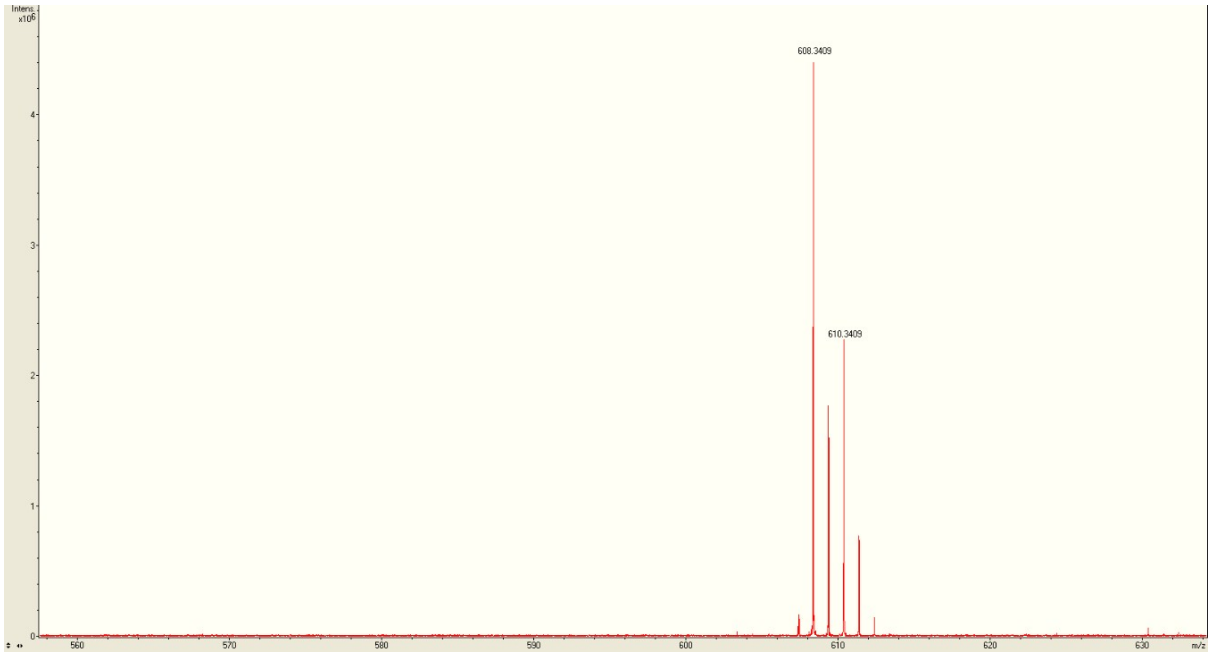


Figure S3. ESI-FTMS of the catalyst (**1S**). m/z: ([M + H]$^+$) calcd for $CuC_{36}H_{53}N_2O_2$, 608.3402; found, 608.3409.

Circular Dichroism

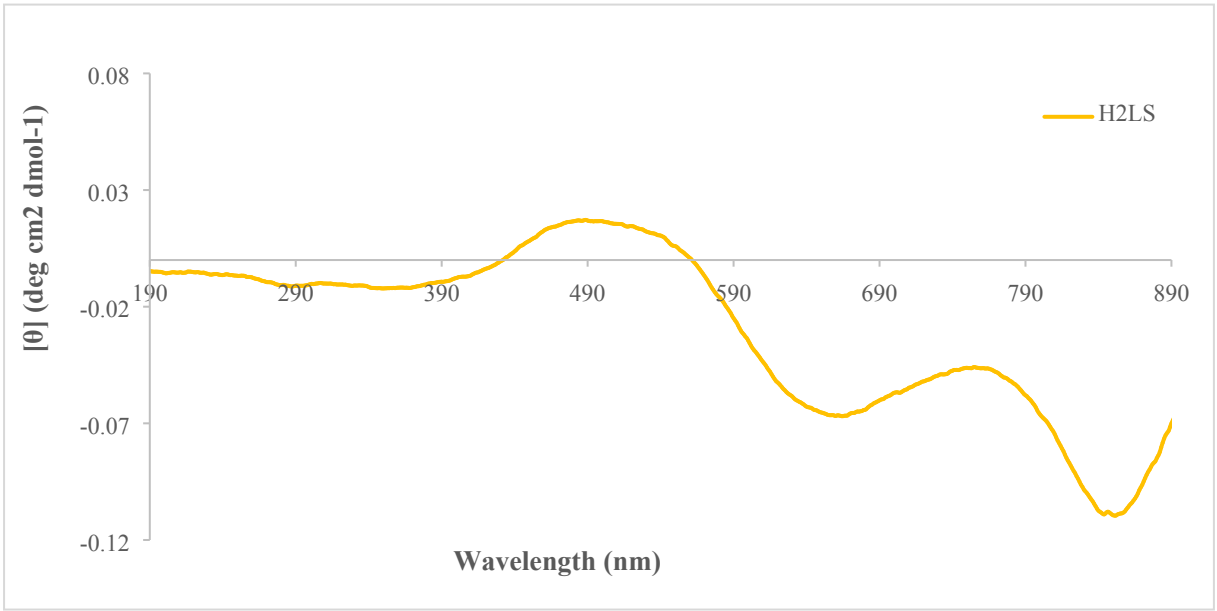


Figure S4. The CD spectrum of H_2L^S in DCM (1 mM) at 0˚.

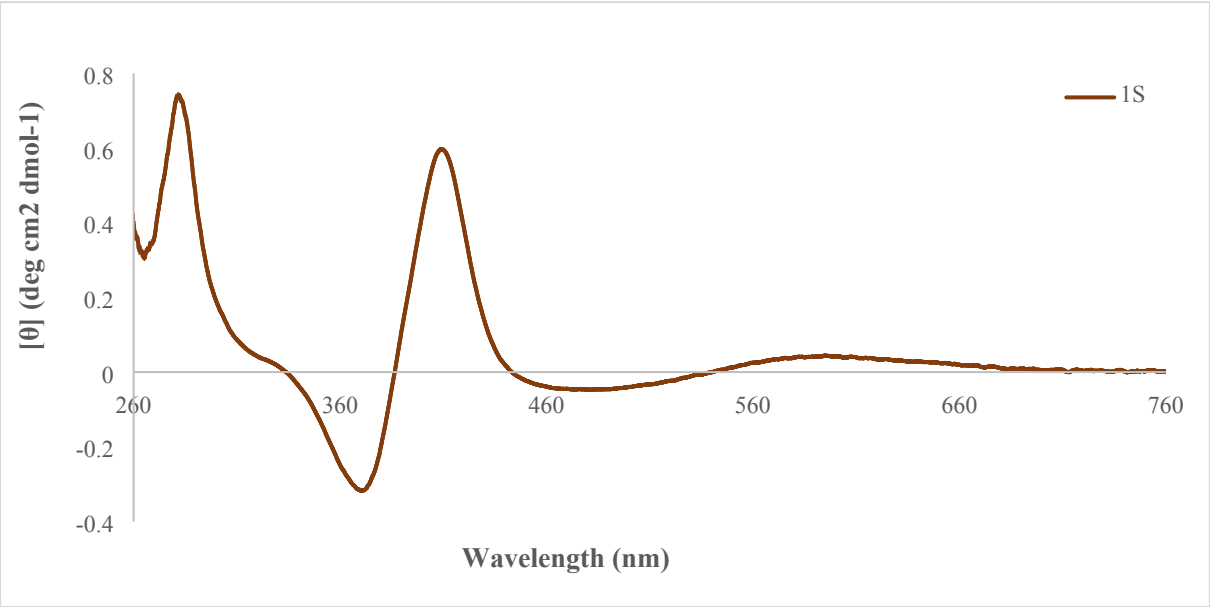


Figure S5. The CD spectrum of **1S** in DCM (1 mM) at 0˚.

TGA

Thermal studies for **1S** and recovered **1S,** were conducted up to1000 and 800 °C respectively. For **1S**.CH_3CN (Figure S7) a continuous mass loss occurs from room temperature up to 140 °C, corresponding to the loss of the lattice solvent molecule. The remaining core is then immediately subjected to a further mass loss. The analysis for **1S** (Figure S7) shows an initial mass loss which begins from 300˚C and agrees to one acetonitrile molecule (calc.: 4.7%, theor.: 4.8%). Decomposition of **1S** to CuO follows at 330˚C (CuO residue calc.: 12.2%, theor.: 12.2%). The recovered compound **1S.**$2CH_2Cl_2$ shows an initial mass loss which occurs at 212 °C and corresponds in good agreement to the loss of two lattice dichloromethane molecules (calc.:9.8%, theor.: 10.2%). Subsequently, the complex undergoes another mass loss starting from 330 ˚C due to the gradual decomposition (calc.: 90.0%, theor.: 89.9%).

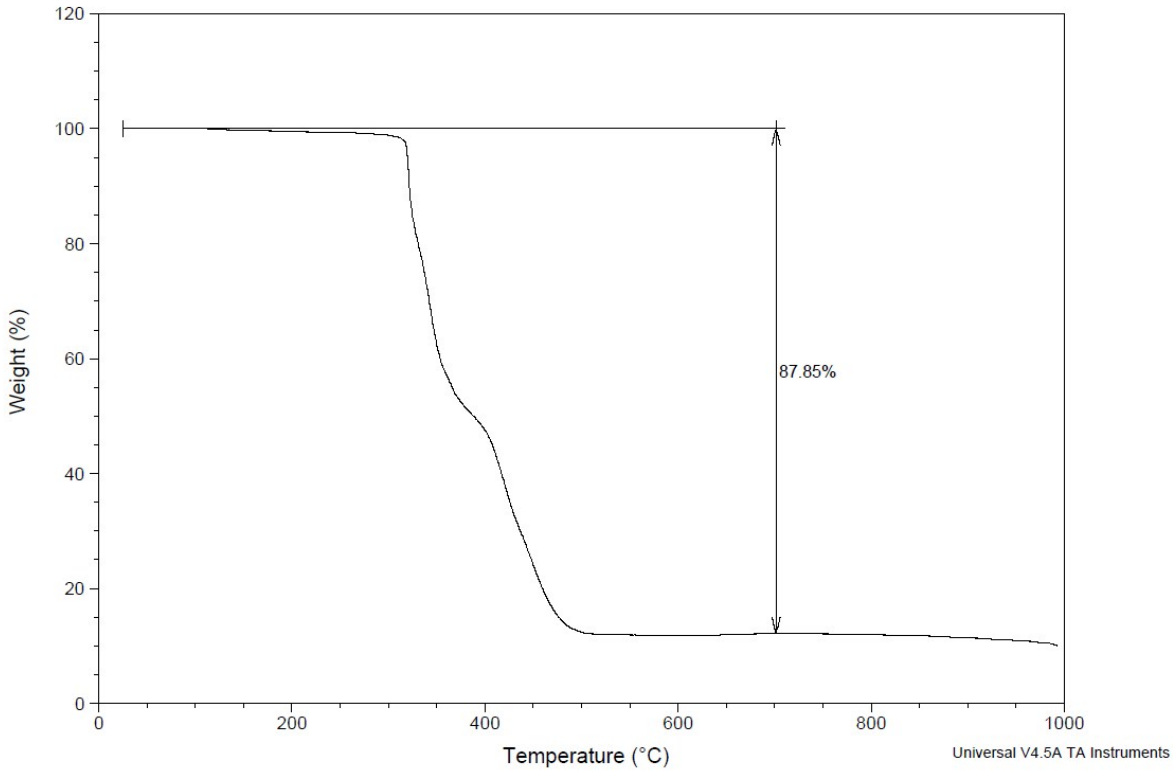


Figure S6. TGA of compound **1S** (20-1000˚C).

UV-Vis

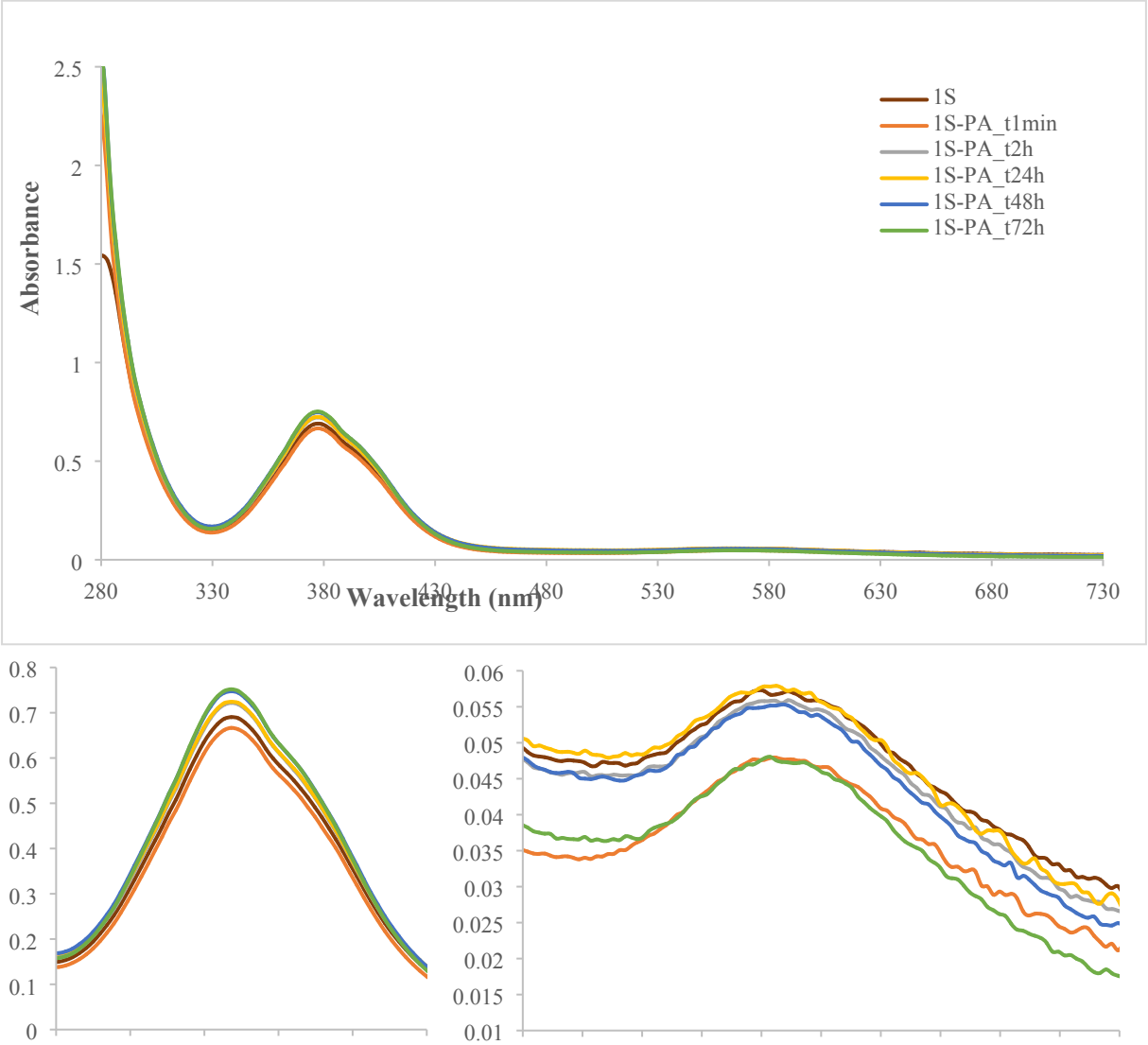


Figure S7. UV-Vis time study of the catalyst (**1S**) (0.1 mM) upon addition of phenylacetylene (PA) in DCM, in the region of 280-750 nm. The ratio of **1S**:PA is equal to 1:50. The maxima at 381 nm correspond to MLCT, and the maxima at 562 nm are attributed to the Cu(II) centre of **1S** and show time dependent interaction with phenylacetylene.

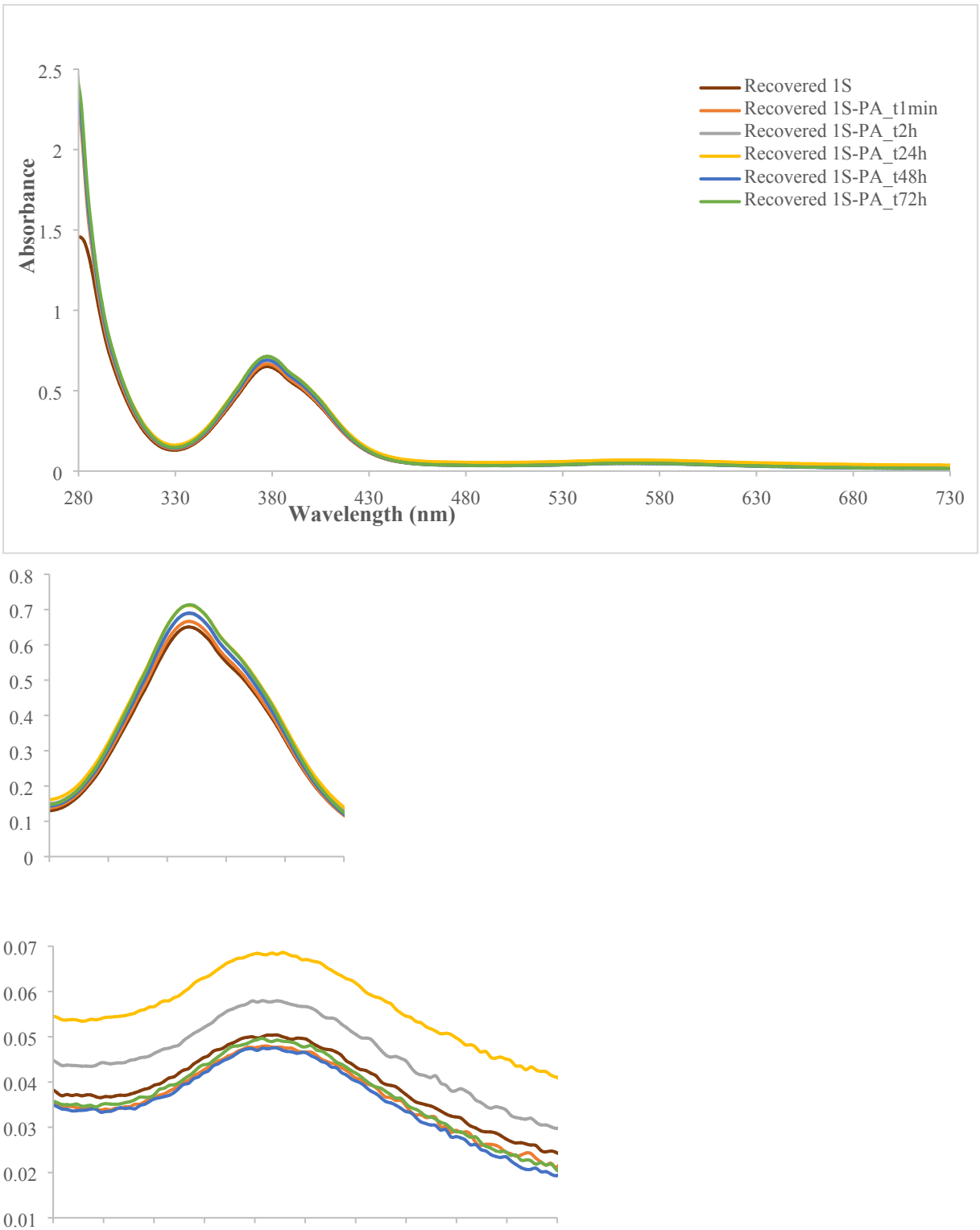


Figure S8. UV-Vis time study of the recovered catalyst (recovered **1S**) (0.1 mM), after the first catalytic cycle, upon addition of phenylacetylene (PA) in DCM, in the region of 280-750 nm.

The ratio of recovered**1S**:PA is equal to 1:50. The maxima at 562 nm are attributed to the Cu(II) centre of the recovered **1S** and show time-dependent interaction with phenylacetylene.

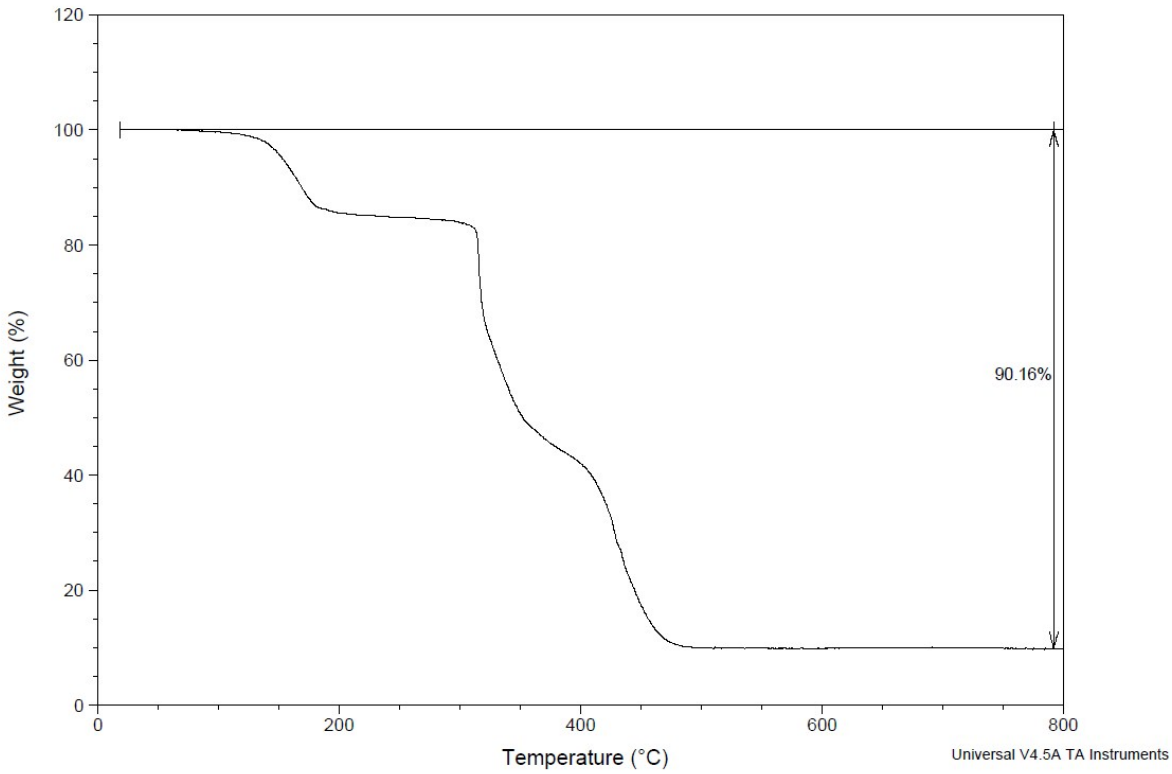


Figure S9. TGA of the recovered compound **1S** after the fifth catalytic cycle (20-800˚C).

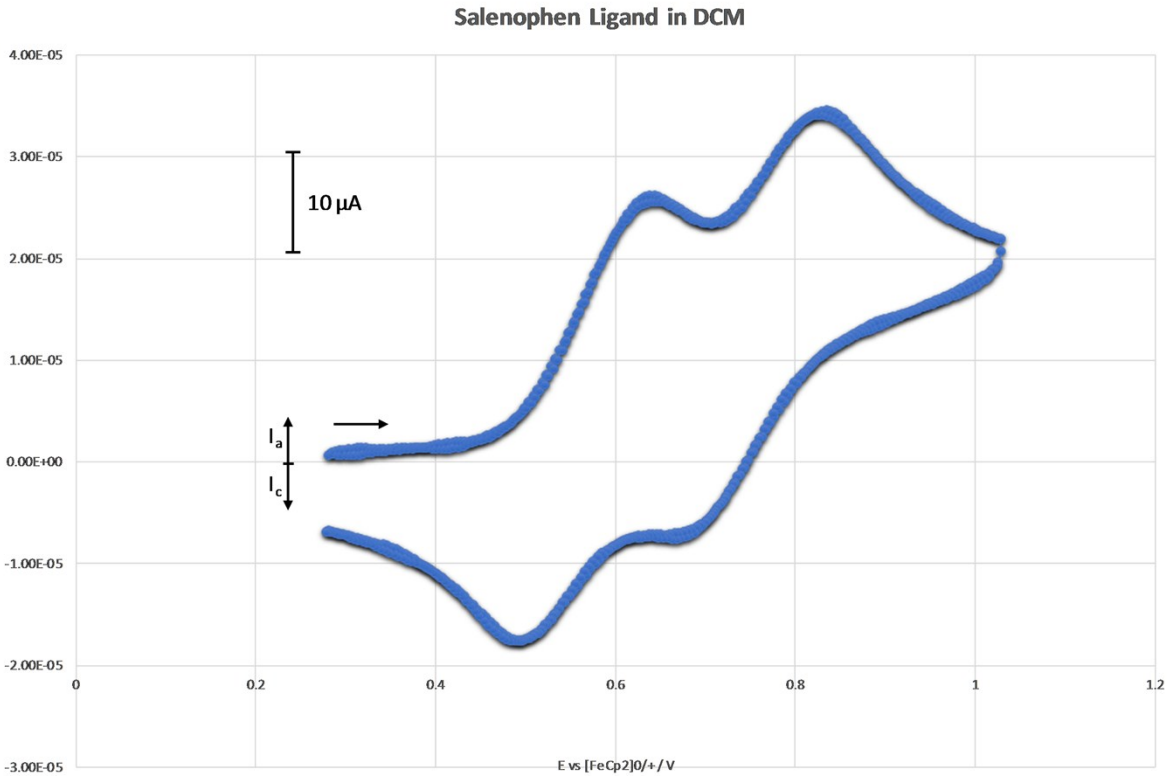


Figure S10. The CV of the free Ligand (H_2L)

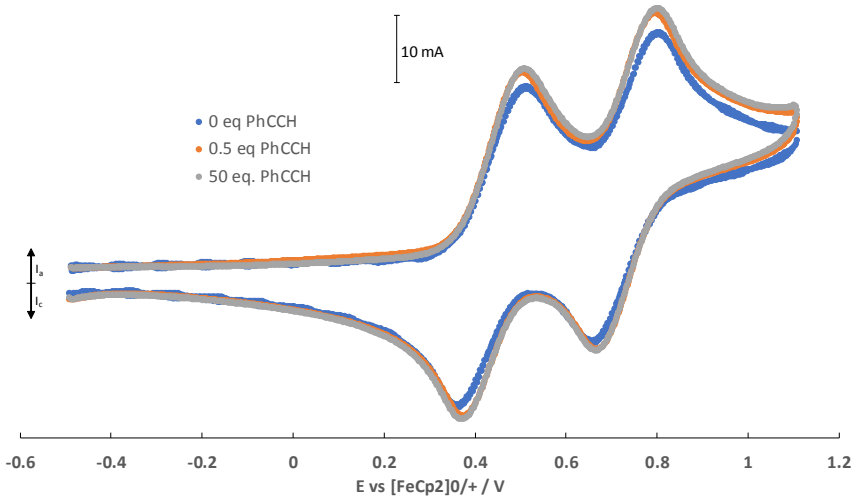


Figure S11. (upper) The redox CV of **1S** in the presence of phenylacetylene. **1S'** gave a similar pattern. (lower)

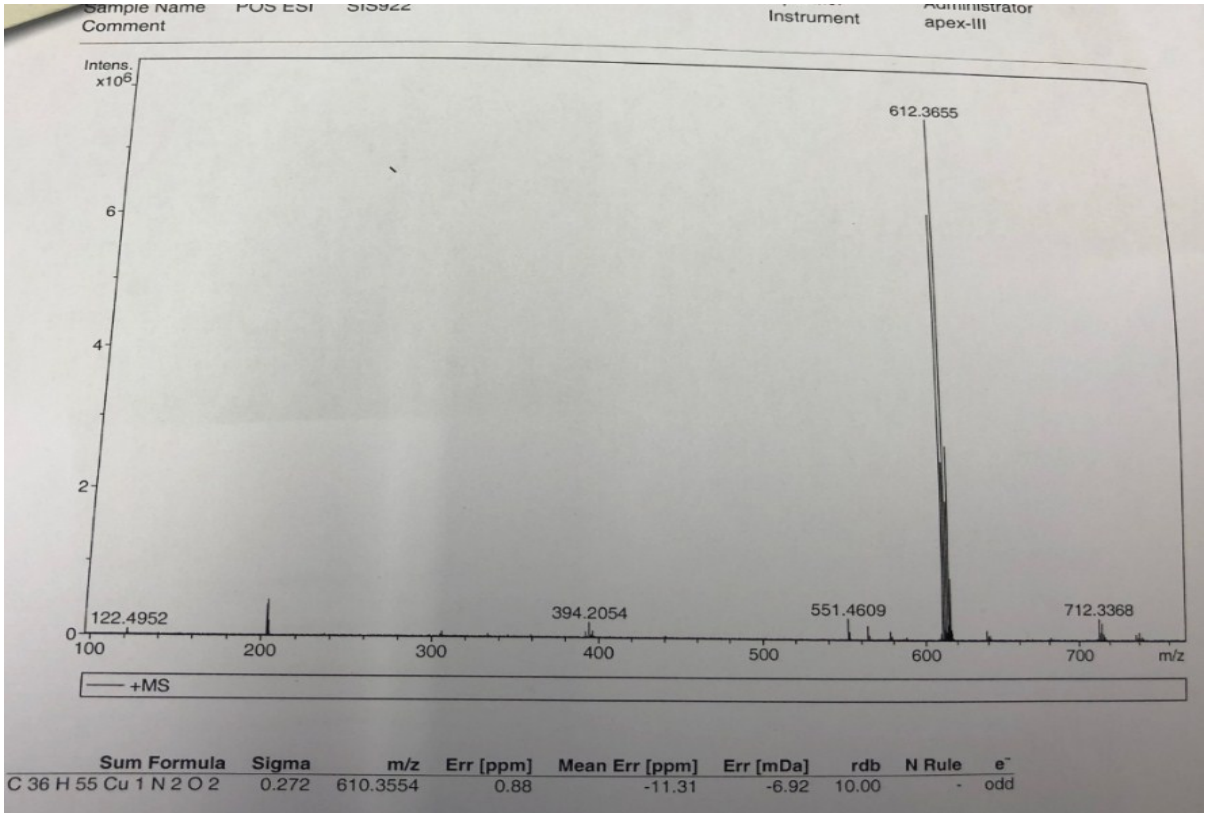
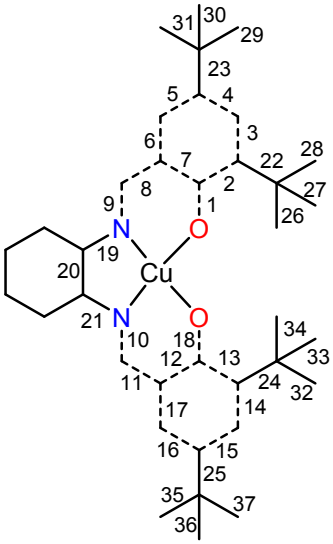


Figure S12. ESI-FTMS of the compound [**6**]. m/z: ($[M+H]^+$) calcd for $CuC_{36}H_{57}N_2O_2$, 612.3715; found, 612.3655.

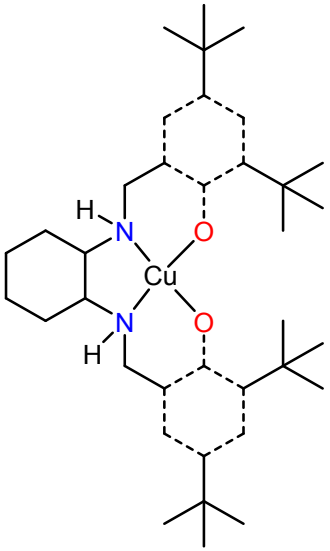
X-Ray crystallography

Data for **1S** and **1S'** were collected at the National Crystallography Service, University of Southampton.[2] Single pale brown, rod-shaped crystals of **1S** were supplied. A suitable crystal (0.15×0.02×0.02) mm^3 was selected and mounted on a MITIGEN holder in perfluoro ether oil on a Rigaku FRE+ equipped with HF Varimax confocal mirrors and an AFC12 goniometer and HG Saturn 724+ detector. Single light yellow rod-shaped crystals of **1S'** were supplied. A suitable crystal 0.24×0.03×0.03 mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000 detector. The crystals were kept at a steady T = 100(2) K during data collection. The data were processed with CrysAlisPro and solved by intrinsic phasing methods with SHELXT.[3] All crystal structures were then refined on Fo^2 by full-matrix least-squares refinements using SHELXL.[3] Geometric/crystallographic calculations were performed using PLATON,[4]Olex2,[5] and WINGX[6] packages; graphics were prepared with Crystal Maker.[7] Structures **1S** and **1S'** have been given CCDC deposition numbers 1954036- 1954037, respectively

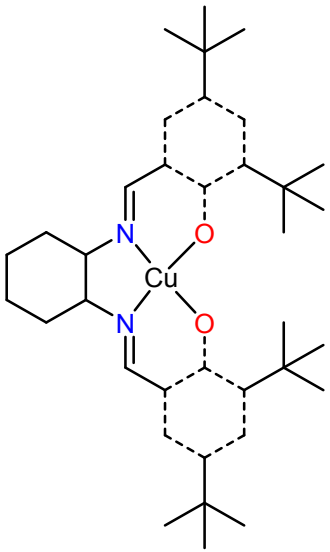
Table S1. Bond distances of Cu based compounds build with similar salen frameworks and different oxidation states black (II), red (III).[8–11]



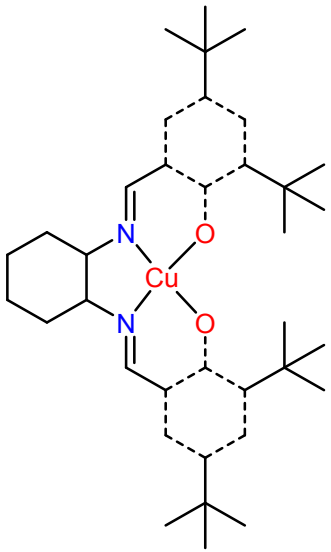
MODEL



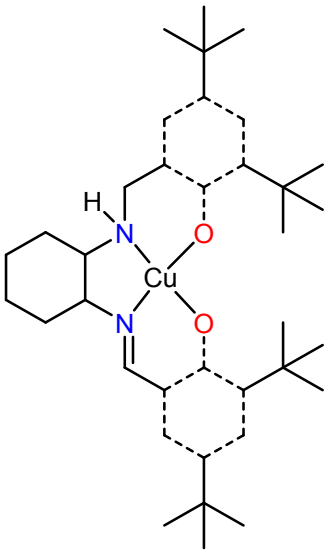
CIYHAV



DAHBET



SONMAK

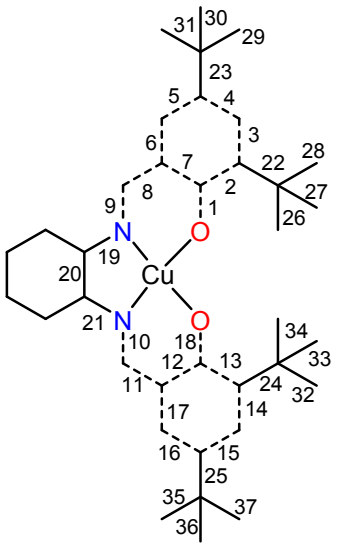


YEKJUW

Bond	Compound 1S (100K)		1S' (100K)		CIYHAV (100K)	DAHBET (160K)	SONMAK (173K)	SONMAK (173K)	YEKJUW (173K)	
Cu – N1	1.916(8)	1.920(8)	**1.940(6)**	1.920(5)	1.992	1.904	1.875	1.879	1.960	1.978
Cu – N2	1.935(8)	1.928(8)	1.935(6)	1.926(5)	1.991	1.915	1.874	1.877	1.930	1.944
Cu – O1	1.902(7)	1.896(7)	1.900(5)	1.889(5)	1.887	1.887	1.839	1.837	1.884	1.864
Cu – O2	1.893(7)	1.879(7)	**1.910(5)**	1.882(5)	1.894	1.885	1.859	1.831	1,907	1.878
1	1.307(13)	1.332(12)	1.300(9)	1.328(9)	1.331	1.299	1.307	1.318	1.327	1.330
2	1.445(14)	1.420(13)	1.447(10)	1.439(10)	1.423	1.443	1.422	1.444	1.428	1.454
3	1.359(15)	1.372(14)	**1.400(10)**	1.384(11)	1.398	1.372	1.388	1.376	1.442	1.393
4	1.406(14)	1.409(14)	1.414(10)	1.395(10)	1.400	1.398	1.400	1.428	1.393	1.421
5	1.370(14)	1.375(14)	1.361(10)	1.378(10)	1.376	1.375	1.377	1.369	1.382	1.352
6	1.402(15)	1.432(15)	1.401(11)	1.436(10)	1.399	1.410	1.423	1.405	1.367	1.402
7	1.434(14)	1.418(14)	1.440(10)	1.405(10)	1.418	1.423	1.423	1.406	1.394	1.397
8	1.432(14)	1.409(14)	**1.468(8)**	1.443(10)	1.496	1.431	1.404	1.449	1.495	1.476
9	1.297(12)	1.305(12)	1.292(10)	1.296(9)	1.474	1.283	1.294	1.292	1.450	1.372
10	1.255(13)	1.265(12)	**1.284(10)**	1.292(9)	1.471	1.281	1.281	1.289	1.323	1.265

11	1.451(14)	1.453(14)	**1.472(8)**	1.440(10)	1.488	1.436	1.407	1.426	1.441	1.453
12	1.444(15)	1.424(14)	1.433(10)	1.419(10)	1.409	1.424	1.398	1.434	1.413	1.444
13	1.462(14)	1.430(14)	**1.438(9)**	1.435(9)	1.422	1.429	1.436	1.437	1.420	1.416
14	1.397(15)	1.399(15)	1.395(11)	1.377(10)	1.400	1.378	1.367	1.392	1.353	1.345
15	1.419(14)	1.429(14)	1.407(10)	1.416(10)	1.398	1.403	1.415	1.399	1.403	1.416
16	1.359(14)	1.365(15)	1.352(10)	1.380(10)	1.362	1.366	1.364	1.380	1.379	1.351
17	1.393(15)	1.418(15)	1.421(11)	1.413(11)	1.399	1.402	1.433	1.404	1.410	1.447
18	1.287(13)	1.305(13)	1.308(9)	1.326(9)	1.329	1.302	1.332	1.317	1.305	1.304
19	1.477(10)	1.483(9)	1.468(8)	1.482(7)	1.482	1.506	1.507	1.467	1.482	1.492
20	1.531(10)	1.516(10)	1.529(7)	1.518(9)	1.500	1.518	1.514	1.496	1.537	1.514
21	1.490(9)	1.487(10)	1.472(8)	1.481(7)	1.487	1.491	1.476	1.478	1.460	1.460
22	1.535(14)	1.533(14)	1.538(9)	1.535(10)	1.539	1.535	1.556	1.514	1.521	1.535
23	1.535(16)	1.529(14)	1.535(10)	1.538(10)	1.541	1.528	1.505	1.556	1.565	1.549
24	1.529(14)	1.550(14)	1.548(10)	1.545(9)	1.542	1.535	1.533	1.531	1.522	1.546
25	1.537(15)	1.524(15)	1.541(9)	1.545(10)	1.532	1.522	1.537	1.526	1.525	1.521
26	1.551(13)	1.540(12)	1.542(10)	1.526(11)	1.540	1.522	1.512	1.492	1.525	1.514
27	1.548(14)	1.549(13)	1.536(9)	1.533(9)	1.531	1.531	1.546	1.544	1.542	1.524
28	1.513(14)	1.547(14)	1.536(10)	1.551(10)	1.533	1.540	1.579	1.545	1.544	1.535
29	1.557(13)	1.538(13)	1.539(10)	1.530(10)	1.531	1.517	1.517	1.517	1.512	1.492
30	1.520(14)	1.508(15)	1.518(11)	1.533(10)	1.532	1.530	1.551	1.518	1.522	1.510
31	1.543(15)	1.558(13)	1.549(9)	1.554(10)	1.512	1.537	1.558	1.555	1.542	1.542
32	1.539(13)	1.526(12)	1.552(9)	1.545(9)	1.526	1.529	1.530	1.508	1.527	1.515
33	1.546(14)	1.536(14)	1.537(10)	1.528(10)	1.526	1.531	1.542	1.538	1.537	1.523
34	1.541(13)	1.534(14)	1.532(10)	1.523(10)	1.527	1.539	1.558	1.543	1.545	1.532
35	1.530(13)	1.546(14)	1.540(10)	1.541(10)	1.528	1.524	1.536	1.512	1.543	1.537
36	1.534(13)	1.536(13)	1.542(9)	1.535(9)	1.535	1.528	1.540	1.526	1.554	1.542
37	1.542(14)	1.525(14)	1.528(10)	1.533(9)	1.549	1.532	1.550	1.545	1.561	1.563

Table S2. Bond distances comparison of **1S** prior and post catalysis (**1S'**)



MODEL

Bond	1S		1S'	
Cu – N1	1.916(8)	1.920(8)	**1.940(6)**	1.920(5)
Cu – N2	1.935(8)	1.928(8)	1.935(6)	1.926(5)
Cu – O1	1.902(7)	1.896(7)	1.900(5)	1.889(5)
Cu – O2	1.893(7)	1.879(7)	**1.910(5)**	1.882(5)
1	1.307(13)	1.332(12)	1.300(9)	1.328(9)
2	1.445(14)	1.420(13)	1.447(10)	1.439(10)
3	1.359(15)	1.372(14)	**1.400(10)**	1.384(11)
4	1.406(14)	1.409(14)	1.414(10)	1.395(10)
5	1.370(14)	1.375(14)	1.361(10)	1.378(10)
6	1.402(15)	1.432(15)	1.401(11)	1.436(10)
7	1.434(14)	1.418(14)	1.440(10)	1.405(10)
8	1.432(14)	1.409(14)	**1.468(8)**	**1.443(10)**
9	1.297(12)	1.305(12)	1.292(10)	1.296(9)
10	1.255(13)	1.265(12)	**1.284(10)**	**1.292(9)**
11	1.451(14)	1.453(14)	**1.472(8)**	**1.440(10)**
12	1.444(15)	1.424(14)	1.433(10)	1.419(10)
13	1.462(14)	1.430(14)	**1.438(9)**	1.435(9)
14	1.397(15)	1.399(15)	1.395(11)	1.377(10)
15	1.419(14)	1.429(14)	1.407(10)	1.416(10)
16	1.359(14)	1.365(15)	1.352(10)	1.380(10)
17	1.393(15)	1.418(15)	**1.421(11)**	1.413(11)
18	1.287(13)	1.305(13)	**1.308(9)**	**1.326(9)**
19	1.477(10)	1.483(9)	1.468(8)	1.482(7)
20	1.531(10)	1.516(10)	1.529(7)	1.518(9)
21	1.490(9)	1.487(10)	1.472(8)	1.481(7)
22	1.535(14)	1.533(14)	1.538(9)	1.535(10)
23	1.535(16)	1.529(14)	1.535(10)	1.538(10)
24	1.529(14)	1.550(14)	1.548(10)	1.545(9)
25	1.537(15)	1.524(15)	1.541(9)	1.545(10)
26	1.551(13)	1.540(12)	1.542(10)	1.526(11)
27	1.548(14)	1.549(13)	1.536(9)	1.533(9)
28	1.513(14)	1.547(14)	1.536(10)	1.551(10)
29	1.557(13)	1.538(13)	1.539(10)	1.530(10)
30	1.520(14)	1.508(15)	1.518(11)	1.533(10)
31	1.543(15)	1.558(13)	1.549(9)	1.554(10)
32	1.539(13)	1.526(12)	1.552(9)	1.545(9)
33	1.546(14)	1.536(14)	1.537(10)	1.528(10)
34	1.541(13)	1.534(14)	1.532(10)	1.523(10)
35	1.530(13)	1.546(14)	1.540(10)	1.541(10)
36	1.534(13)	1.536(13)	1.542(9)	1.535(9)
37	1.542(14)	1.525(14)	1.528(10)	1.533(9)

Table S3. Bond Valence Sum analysis for **1S** prior and post catalysis (**1S'**).[12]

Prior 1S												
	Entity 1							**Entity 2**				
	1.902	1.6790	-0.2230	-0.6027	0.54733			1.896	1.6790	-0.2170	-0.58649	0.556278	
	1.893	1.6790	-0.214	-0.57838	0.560807			1.879	1.6790	-0.2	-0.54054	0.582433	
2+	1.916	1.7510	-0.165	-0.44595	0.640218	2.356528	**2+**	1.92	1.7510	-0.169	-0.45676	0.633334	2.391834
	1.935	1.7510	-0.184	-0.4973	0.608172			1.928	1.7510	-0.177	-0.47838	0.619788	
	1.902	1.6790	-0.2230	-0.6027	0.54733			1.896	1.6790	-0.2170	-0.58649	0.556278	
	1.893	1.6790	-0.214	-0.57838	0.560807			1.879	1.6790	-0.2	-0.54054	0.582433	
1+	1.916	1.5950	-0.321	-0.86757	0.419972	1.927059	**1+**	1.92	1.5950	-0.325	-0.87838	0.415456	1.960737
	1.935	1.5950	-0.34	-0.91892	0.39895			1.928	1.5950	-0.333	-0.9	0.40657	
Post 1S												
	Entity 1							**Entity 2**				
	1.9	1.6790	-0.2210	-0.5973	0.550297			1.889	1.6790	-0.2100	-0.56757	0.566903	
	1.91	1.6790	-0.231	-0.62432	0.535623			1.882	1.6790	-0.203	-0.54865	0.57773	
2+	1.94	1.7510	-0.189	-0.51081	0.600009	2.294101	**2+**	1.92	1.7510	-0.169	-0.45676	0.633334	2.401114
	1.935	1.7510	-0.184	-0.4973	0.608172			1.926	1.7510	-0.175	-0.47297	0.623147	
	1.9	1.6790	-0.2210	-0.5973	0.550297			1.889	1.6790	-0.2100	-0.56757	0.566903	
	1.91	1.6790	-0.231	-0.62432	0.535623			1.882	1.6790	-0.203	-0.54865	0.57773	
1+	1.94	1.5950	-0.345	-0.93243	0.393595	1.878465	**1+**	1.92	1.5950	-0.325	-0.87838	0.415456	1.968862
	1.935	1.5950	-0.34	-0.91892	0.39895			1.926	1.5950	-0.331	-0.89459	0.408773	

Table S4. Crystallographic data collections for three different crystals from each sample

	1S			**1S'**		
a	9.8640(2)	9.8842(2)	9.8778(2)	9.8707(4)	9.8532(4)	9.8859(4)
b	13.6012(4)	13.5926(3)	13.5731(2)	13.5816(6)	13.589(10)5	13.5894(5)
c	14.8446(3)	14.8655(4)	14.8563(2)	14.8795(8)	14.8669(7)	14.8650(4)
Alpha	62.802(3)	62.813(2)	62.862(2)	62.815(5)	62.901(6)	62.850(3)
Beta	73.297(2)	73.287(2)	73.333(2)	73.314(4)	73.467(4)	73.292(4)
Gamma	78.658(2)	78.682(2)	78.744(2)	78.760(3)	78.768(5)	78.707(4)
Volume	1691.65(8)	1696.57(8)	1693.23(6)	1694.92(16)	1693.92(19)	1697.05(12)

General Catalytic protocol for the synthesis of propargylamines.

Compounds 5aaa-5fda.

A mixture of aldehyde (1 mmol), amine (1.1 mmol), alkyne (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Methodology **A**) stirred at room temperature for 72 hours (Methododology **B**) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method **B**) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamines were obtained as red or yellow oils, which solidified on standing.

Reactions with TEMPO.

A mixture of cyclohexanecarboxaldehyde (1 mmol), pyrrolidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), 2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical (TEMPO, 10mol% based on aldehyde) and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours. The reaction was monitored by thin-layer chromatography (TLC). After completion, the slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to the remaining mixture. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and is filtrated through filter paper (to withhold the recovered catalyst).

Subsequently, the excess of TEMPO is removed from the reaction mixture by filtration through silica gel using diethyl ether as eluent. The ^{1}H NMR of the crude reaction mixture does not indicate the formation of the product.

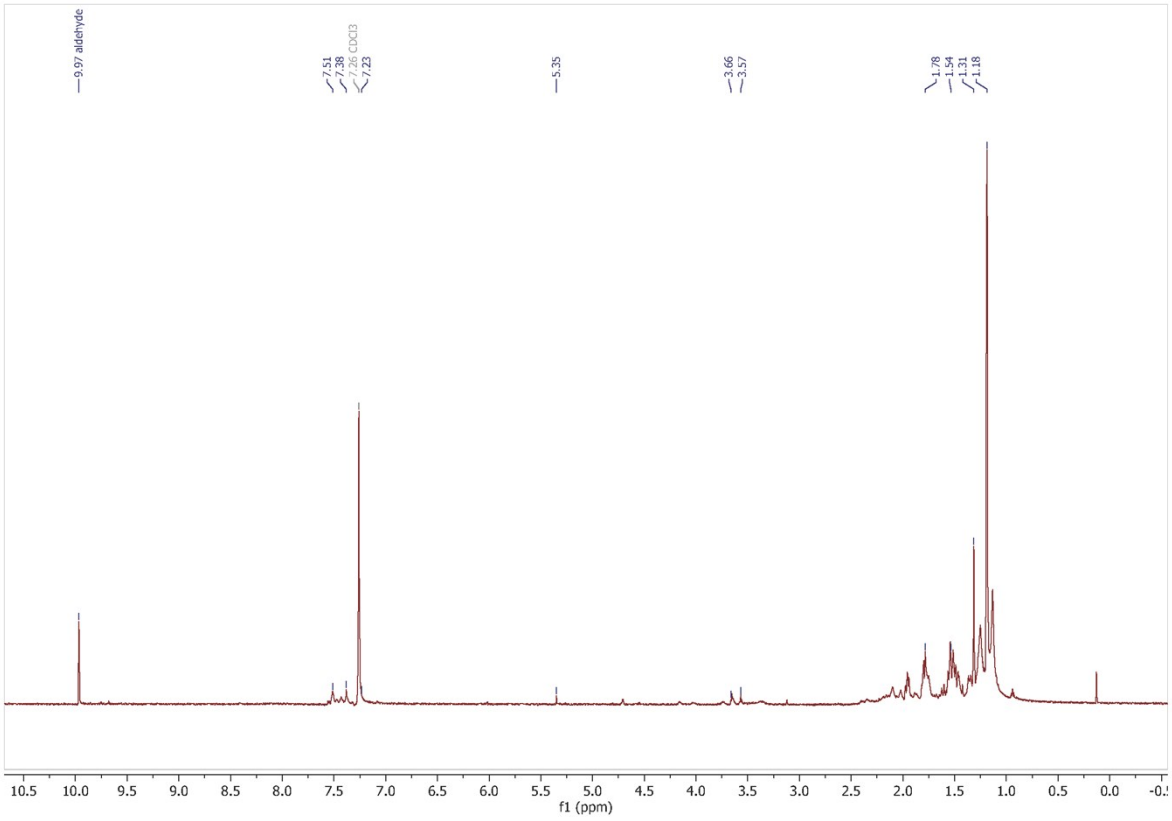


Figure S13. Crude ^{1}H NMR spectrum of the test reaction in the presence of TEMPO. The spectrum shows only the existence of starting materials in the reaction mixture.

Theoretical Calculations

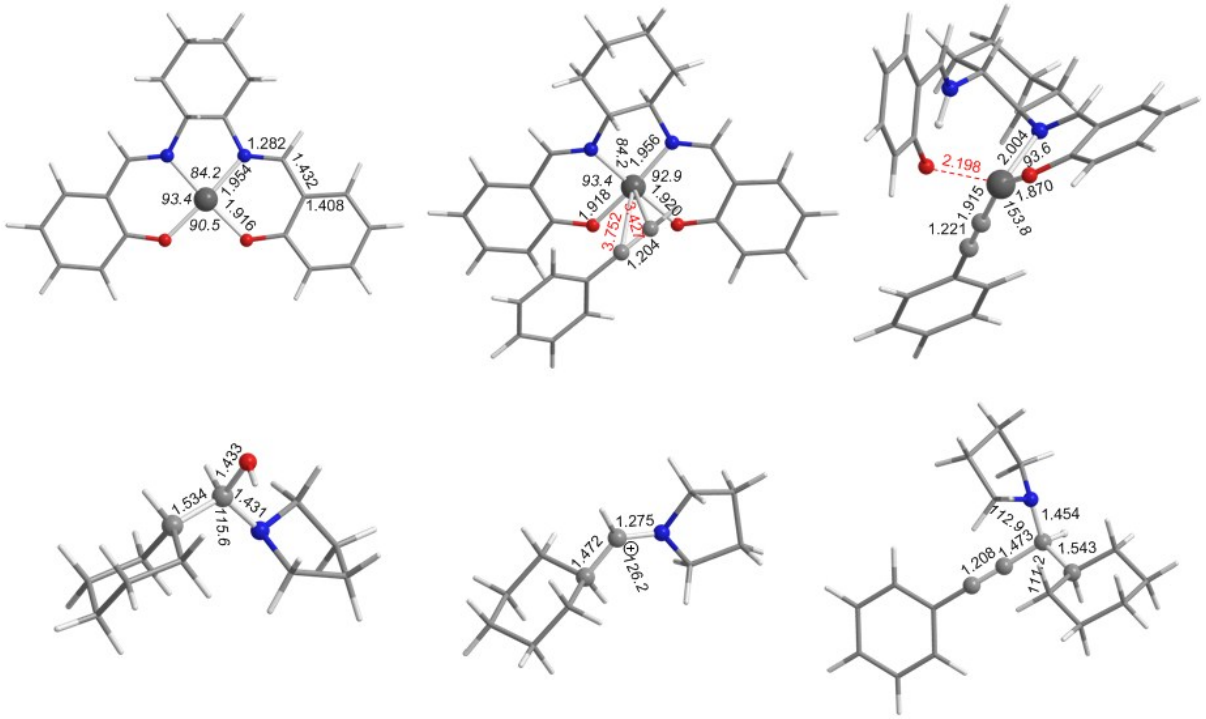


Figure S14. Geometrical structures of all reactants, intermediates and products directly optimised in solution phase employing the PBE0/Def2-TZVP/PCM computational protocol.

Table S5. Cartesian coordinates and energies of ll reactants, intermediates and products calculated by PBE0/Def2-TZVP/PCM computational protocol.

$C_6H_{11}CH(OH)(NC_4H_8)$

C,0,-7.8379379357,1.820186779,0.5948027504
C,0,-7.7421086898,0.6105416503,1.5210650485
C,0,-6.2660781802,0.1945107542,1.4481192572
N,0,-5.7086114579,0.9308056584,0.3099930802
C,0,-6.8109706957,1.482224369,-0.4664464942
C,0,-3.2209849964,-0.9552110498,1.2820334298
C,0,-1.7952579571,-1.0811665498,1.8095372109
C,0,-1.3094952106,0.2288918989,2.415049014
C,0,-1.429920295,1.3742969943,1.4191184546
C,0,-2.8467231278,1.4876634862,0.8712000871
C,0,-3.3162378811,0.1739033963,0.2550816525
C,0,-4.6607743381,0.3396188796,-0.4654086173
O,0,-5.0390036603,-0.8739770282,-1.1271705916
H,0,-7.5423579139,2.7332694199,1.119192171
H,0,-8.8394442399,1.968631036,0.1880388681
H,0,-8.375560828,-0.1943941457,1.1400701323
H,0,-8.0630412346,0.8238157232,2.5416266462
H,0,-6.185150805,-0.8932003476,1.3268111389

H,0,-5.7302397413,0.456134667,2.3658927977
H,0,-6.472779917,2.3510565728,-1.0384195134
H,0,-7.229049123,0.7515671153,-1.1777376273
H,0,-3.8913027,-0.7621611128,2.1248252555
H,0,-3.5248425444,-1.9140232012,0.8461904988
H,0,-1.1304089641,-1.3677578561,0.9850952905
H,0,-1.7412639077,-1.8854461269,2.5494198287
H,0,-0.2748207838,0.1280213593,2.7569042683
H,0,-1.9121026588,0.4585527341,3.3029826559
H,0,-0.7341337409,1.203359367,0.5880029015
H,0,-1.1310990327,2.3174386748,1.8869304864
H,0,-2.902235144,2.2878400958,0.1253407885
H,0,-3.5329985983,1.7676184155,1.6782504882
H,0,-2.6116596974,-0.0831904955,-0.5484760448
H,0,-4.4832062924,1.0349176372,-1.2922510344
H,0,-5.0108137072,-1.5909427704,-0.4865802789

Sum of electronic and zero-point Energies= -561.020927
Sum of electronic and thermal Energies= -561.007929
Sum of electronic and thermal Enthalpies= -561.006985
Sum of electronic and thermal Free Energies= -561.060496

$[C_6H_{11}CH(NC_4H_8)]^+$

C,0,-8.7736870725,0.0563341242,0.0679824452
C,0,-8.0128192623,-0.3622161724,-1.1851501047
C,0,-6.5845626702,-0.5368257698,-0.6925712713
N,0,-6.4801208797,0.4069710523,0.4425327857
C,0,-7.8004288896,1.0003896089,0.7455171779
C,0,-3.5823445534,-0.5920786067,2.1265418486
C,0,-2.1649087674,-1.1115752478,1.9312148039
C,0,-1.2116128584,-0.0003338037,1.5161339292
C,0,-1.7089838478,0.7138383564,0.2677436641
C,0,-3.1234044418,1.2465614827,0.4495376799
C,0,-4.0814109191,0.1099425646,0.8515117075
C,0,-5.419432019,0.6723264624,1.09853373
H,0,-8.9706027284,-0.8073407716,0.7073427068
H,0,-9.7215349128,0.545881095,-0.149770886
H,0,-8.0571343032,0.4287984526,-1.9369339311
H,0,-8.3923968301,-1.278974993,-1.6333164354
H,0,-5.8257969009,-0.3030946087,-1.4372712381
H,0,-6.4074340826,-1.5423702745,-0.3066471847
H,0,-7.9179697655,1.0951866774,1.8229954926
H,0,-7.8275730214,1.9928419026,0.2902267746
H,0,-3.602794609,0.1212646358,2.9585378366
H,0,-4.2583734676,-1.4102896103,2.3872674555
H,0,-2.1701653558,-1.8951697528,1.1645122392
H,0,-1.8251150232,-1.5817669894,2.8578195616
H,0,-0.2116012691,-0.4070489856,1.3434462308

H,0,-1.1206271401,0.723247074,2.3352431826
H,0,-1.6912896769,0.0214385438,-0.5819930519
H,0,-1.0450814466,1.543528333,0.0107201779
H,0,-3.4768218802,1.7199360661,-0.4698344467
H,0,-3.1318759318,2.014161715,1.2317307236
H,0,-4.1228725286,-0.6204254492,0.0396986659
H,0,-5.531322945,1.3837628886,1.91459773

Sum of electronic and zero-point Energies= -485.102753
Sum of electronic and thermal Energies= -485.091229
Sum of electronic and thermal Enthalpies= -485.090285
Sum of electronic and thermal Free Energies= -485.141099

[Cu(Salen)]

Cu,0,-0.0020249074,1.1114850555,0.1745477685
O,0,-0.8742930878,2.2803369687,1.4177827697
O,0,0.8634658914,2.6087487061,-0.6515496695
N,0,-1.0509164007,-0.4438225775,0.7211414027
N,0,1.0528471321,-0.1974419687,-0.8208236484
C,0,-1.7360579087,1.9563669615,2.3241943161
C,0,-2.2081847679,2.9602104898,3.205513052
C,0,-3.1249491671,2.6866179035,4.1922253562
H,0,-3.4561223768,3.4883034304,4.8444592033
C,0,-3.6377903172,1.3946542895,4.3676255004
C,0,-3.2034117473,0.3993846302,3.5272388067
H,0,-3.5866631211,-0.6106991198,3.6383568873
C,0,-2.2643368047,0.6420712865,2.5069627551
C,0,-1.8962856488,-0.4713668226,1.6849069778
H,0,-2.4012023454,-1.4094378534,1.9211923416
C,0,-0.7485517831,-1.6122367347,-0.1006447755
H,0,-1.2629748091,-1.4572499472,-1.0601351521
C,0,-1.1600114707,-2.9636777529,0.4554605517
H,0,-2.2426487241,-3.0017639123,0.600805416
H,0,-0.6951511911,-3.1092428182,1.4379749522
C,0,-0.7362905407,-4.0805289908,-0.4904274313
H,0,-1.0086941535,-5.0470111761,-0.0588286852
H,0,-1.2932532938,-3.9887349477,-1.4301970926
C,0,0.7550870978,-4.0317359028,-0.7802537135
H,0,1.0314516765,-4.8185557666,-1.4867239753
H,0,1.3122930678,-4.2294629391,0.1429011545
C,0,1.1732610661,-2.6771776561,-1.338732049
H,0,2.2559592358,-2.6642318279,-1.4879862007
H,0,0.7083896426,-2.517169967,-2.3189903076
C,0,0.7562597842,-1.5625594775,-0.3960526733
H,0,1.2707002837,-1.706271847,0.5651875131
C,0,1.8975274536,0.0748394304,-1.7464004604
H,0,2.4064078141,-0.7437913057,-2.2578647275
C,0,2.2598286177,1.3879219316,-2.1885694447
C,0,3.199084021,1.4729179126,-3.2337329973

H,0,3.5869645486,0.5468612369,-3.6478194304
C,0,3.6279630627,2.6793284501,-3.7298032674
C,0,3.1090867849,3.8535628594,-3.1686114723
H,0,3.43585097,4.8176938876,-3.5447317061
C,0,2.1920882156,3.808376842,-2.1458992906
C,0,1.725636687,2.5810981877,-1.6133476373
H,0,-1.8152627956,3.9623096428,3.0744577393
H,0,-4.3606265964,1.1873198317,5.1466842946
H,0,4.3510617822,2.7232884137,-4.5345450469
H,0,1.7945891237,4.7206729631,-1.715247904

Sum of electronic and zero-point Energies= -2673.307896
Sum of electronic and thermal Energies= -2673.287347
Sum of electronic and thermal Enthalpies= -2673.286403
Sum of electronic and thermal Free Energies= -2673.357758

[Cu(Salen)(HC≡CPh]

Cu	0.5942	0.01044	-0.8066
O	-1.09572	-0.35696	-1.63645
O	1.19078	-1.76932	-1.20937
N	0.03031	1.76775	-0.16721
N	2.36056	0.56919	-0.18007
C	-2.09913	0.44737	-1.75666
C	-3.23372	0.01788	-2.48882
C	-4.33642	0.82105	-2.65497
H	-5.18162	0.44879	-3.22504
C	-4.38698	2.10744	-2.10188
C	-3.30483	2.55289	-1.38367
H	-3.31774	3.54468	-0.9412
C	-2.15735	1.75926	-1.19504
C	-1.0962	2.32658	-0.41928
H	-1.29575	3.32146	-0.01809
C	1.04761	2.38912	0.67671
H	0.98127	1.89338	1.65629
C	0.9383	3.88921	0.88534
H	-0.00941	4.13882	1.3691
H	0.94805	4.39296	-0.08875
C	2.09126	4.39403	1.74426
H	2.01741	5.47913	1.85238
H	2.0024	3.97196	2.75208
C	3.43883	4.01168	1.15381
H	4.24929	4.35173	1.80351
H	3.57318	4.52105	0.19241
C	3.55175	2.50679	0.94426
H	4.51203	2.27556	0.47599
H	3.53011	1.99207	1.9125
C	2.40799	2.00486	0.08122
H	2.47147	2.49367	-0.90165
C	3.35944	-0.20837	0.02621

H	4.27922	0.20729	0.44063
C	3.3956	-1.61196	-0.25419
C	4.57846	-2.30047	0.07609
H	5.38314	-1.73828	0.541
C	4.73298	-3.64129	-0.17506
C	3.67709	-4.33173	-0.7855
H	3.78068	-5.3913	-0.99637
C	2.50974	-3.69131	-1.12495
C	2.31272	-2.31074	-0.87098
H	-3.20155	-0.97717	-2.91842
H	-5.26019	2.7335	-2.2362
H	5.64947	-4.15396	0.08889
H	1.69654	-4.23109	-1.59734
C	-3.38801	-0.97236	2.82472
C	-4.75366	-1.14679	2.67626
C	-5.24631	-2.04517	1.73849
C	-4.36606	-2.77126	0.94669
C	-2.99892	-2.60302	1.08828
C	-2.49628	-1.70031	2.03051
C	-1.09035	-1.52285	2.17484
C	0.09921	-1.3726	2.28925
H	-3.00069	-0.27206	3.55509
H	-5.43712	-0.57791	3.29589
H	-6.31581	-2.17867	1.62419
H	-4.74636	-3.47232	0.21282
H	-2.30959	-3.16462	0.4696
H	1.15272	-1.24736	2.39408

Sum of electronic and zero-point Energies= -2981.328467
Sum of electronic and thermal Energies= -2981.299990
Sum of electronic and thermal Enthalpies= -2981.299045
Sum of electronic and thermal Free Energies= -2981.391841

Cu(II) intermediate

Cu,0,-0.6250773318,-0.014652409,-0.8920952308
O,0,-0.0389230274,0.9155653994,-2.4051944214
O,0,0.666329269,-1.7707198092,-1.1714629209
N,0,0.0178698781,1.393975583,0.3802298144
N,0,1.8267732148,-0.5814363463,0.8759033529
C,0,0.157788464,2.1947106585,-2.4895152672
C,0,0.2731579493,2.7829566881,-3.7686602733
C,0,0.4803352057,4.1337716519,-3.9253672231
H,0,0.5525319547,4.5453365278,-4.9267619996
C,0,0.6024592094,4.9806199113,-2.8178144017
C,0,0.5156276544,4.432947859,-1.5609012672
H,0,0.6235235721,5.065127767,-0.6847363248
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H,0,3.33534046,-2.8236759399,-4.6128747072
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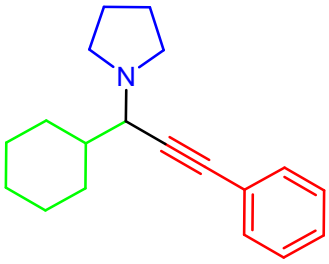
H,0,1.0719208838,-1.173160925,0.5080223658

Sum of electronic and zero-point Energies= -2981.295048
Sum of electronic and thermal Energies= -2981.265980
Sum of electronic and thermal Enthalpies= -2981.265036
Sum of electronic and thermal Free Energies= -2981.359749

Characterisation data for the A3 Coupling products - ^{1}H NMR, ^{13}C NMR, LCMS, HRMS and MS.

1-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)pyrrolidine (5aaa)



A mixture of cyclohexanecarboxaldehyde (1 mmol), pyrrolidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to the remaining mixture. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5aaa was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 – 7.41 (m, 2H), 7.29 (dd, *J* = 5.3, 2.0 Hz, 2H), 3.36 (d, *J* = 8.4 Hz, 1H), 2.79 – 2.62 (m, 4H), 2.12 – 2.06 (m, 0H), 1.95 (d, *J* = 13.0 Hz, 0H), 1.78 (d, *J* = 5.8 Hz, 5H), 1.68 (d, *J* = 12.1 Hz, 0H), 1.63 – 1.54 (m, 1H), 1.32 – 1.04 (m, 3H).

^{13}C NMR (151 MHz, cdcl$_3$) δ 131.9, 128.3, 127.9, 123.8, 61.4, 50.2, 41.5, 30.9, 30.4, 26.8, 26.4, 26.4, 23.7.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{26}N$, 268.2; found, 268.2, R_t = 2.37 min.

(Method A) isolated yield = 259 mg, 97%, (method B) isolated yield = 264 mg, 97%.

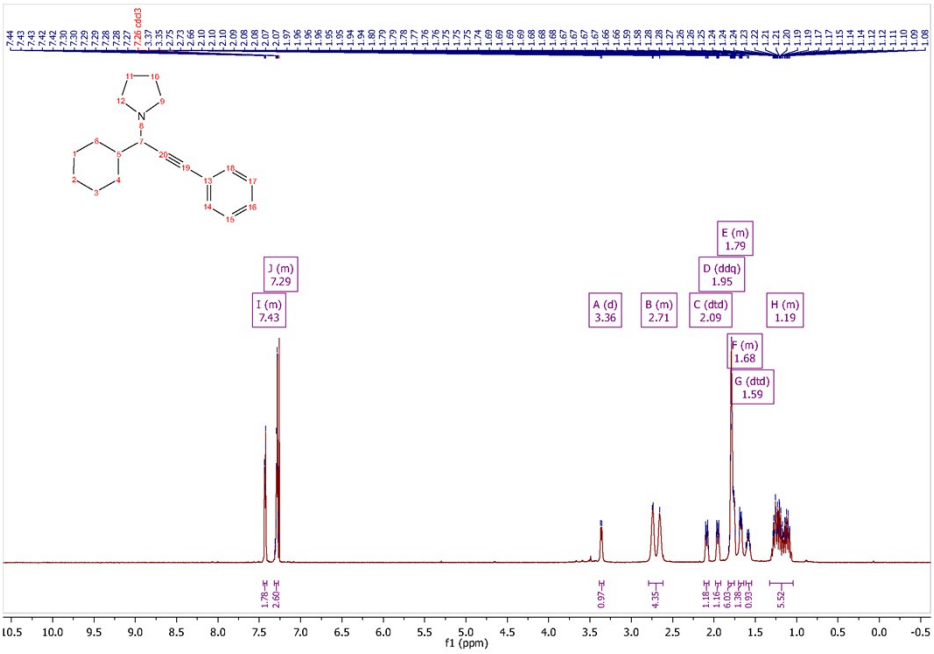


Figure S15. ^{1}H NMR spectrum of propargylamine **5aaa**.

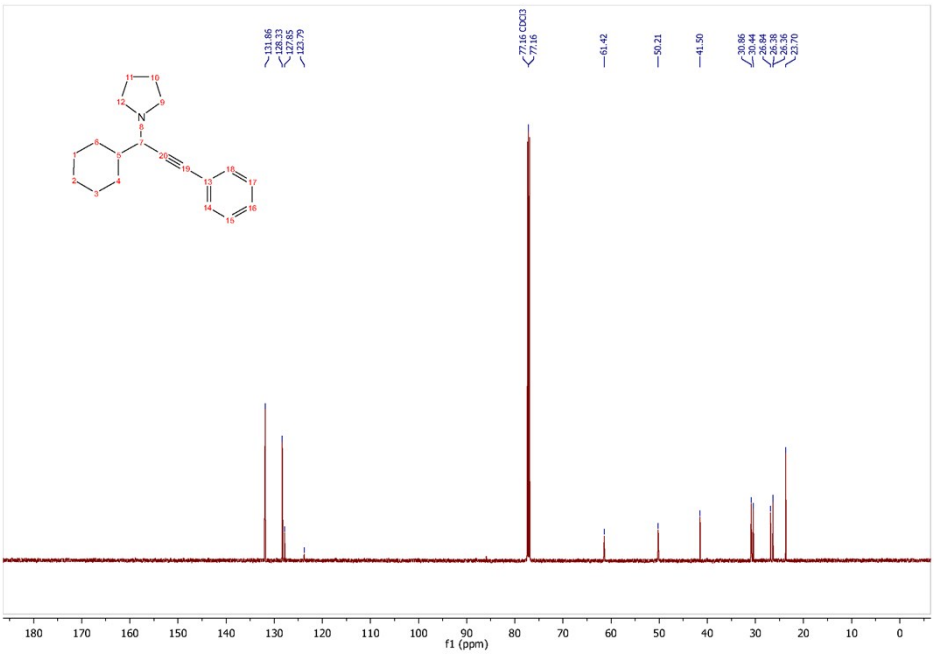


Figure S16. ^{13}C NMR spectrum of propargylamine **5aaa**.

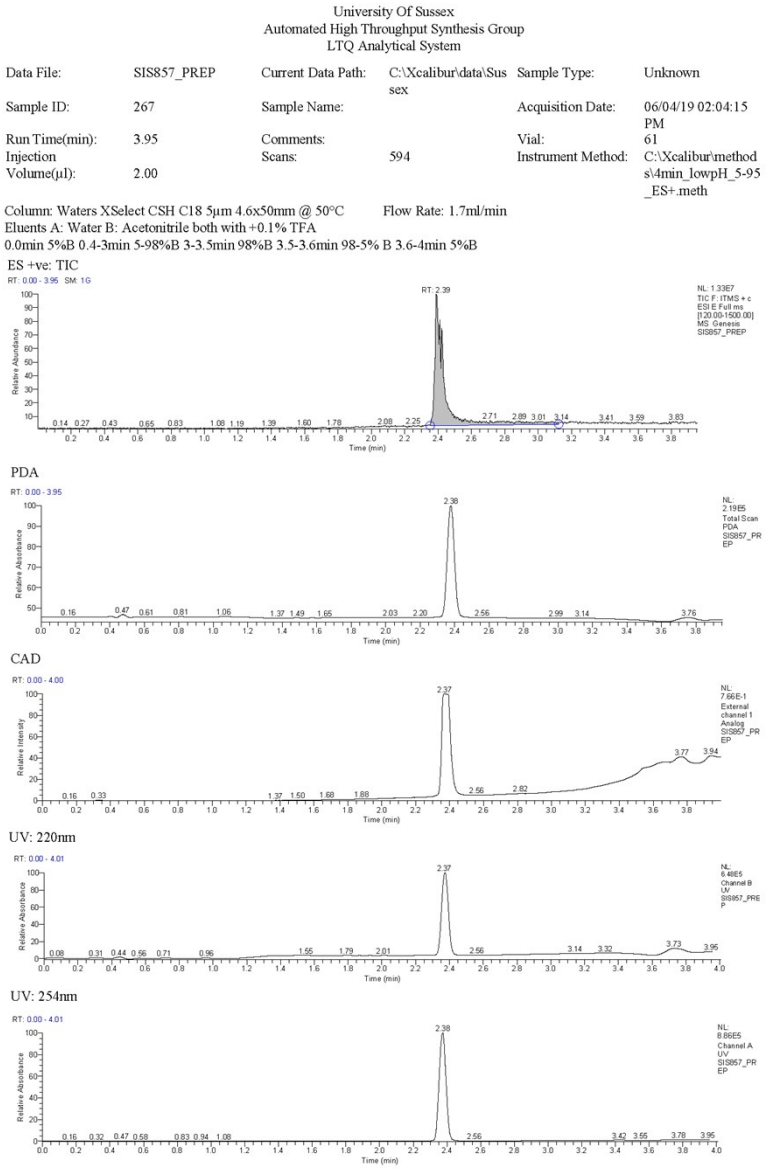


Figure S17. LCMS spectrum of propargylamine **5aaa**.

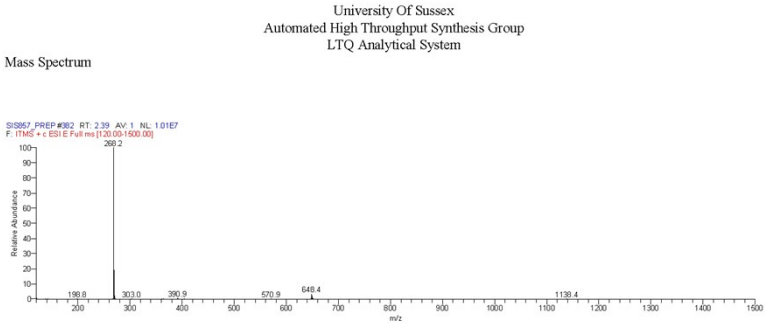
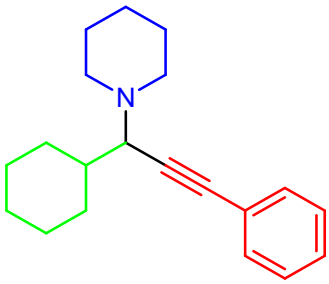


Figure S18. MS spectrum of propargylamine **5aaa**.

1-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)piperidine (5aba)



A mixture of cyclohexanecarboxaldehyde (1 mmol), pipperidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was

(Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5aba was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 7.33 – 7.22 (m, 3H), 3.11 (d, *J* = 9.8 Hz, 1H), 2.63 (s, 2H), 2.41 (s, 2H), 2.13 – 2.06 (m, 1H), 2.03 (ddt, *J* = 13.6, 4.0, 2.0 Hz, 1H), 1.80 – 1.72 (m, 2H), 1.67 – 1.52 (m, 6H), 1.43 (dd, *J* = 15.0, 8.9 Hz, 2H), 1.36 – 1.11 (m, 3H), 1.09 – 0.88 (m, 2H). ^{13}C NMR (151 MHz, Chloroform-d) δ 131.9, 128.3, 127.8, 123.9, 87.9, 86.3, 64.5, 50.9, 39.7, 31.5, 30.6, 26.9, 26.4, 26.3, 24.8, 22.7.

MS (LCMS) m/z: ($[M + H]^+$) calcd for $C_{20}H_{28}N$, 282.1; found, 282.1, R_t = 2.50 min.

(Method A) isolated yield = 275 mg, 97%, (method B) isolated yield = 280 mg, >99%.

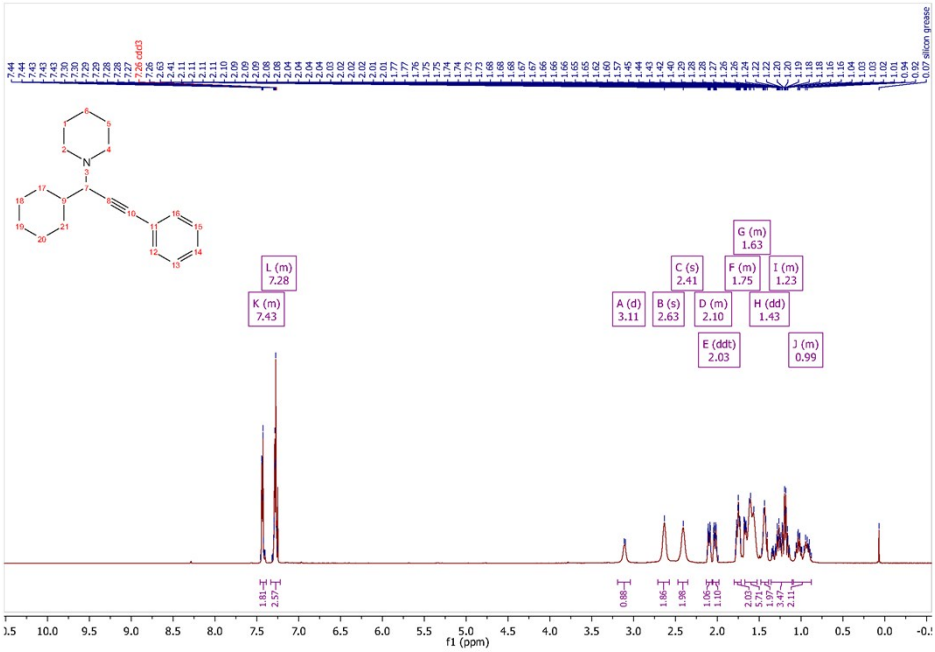


Figure S19. [1]H NMR spectrum of propargylamine **5aba**.

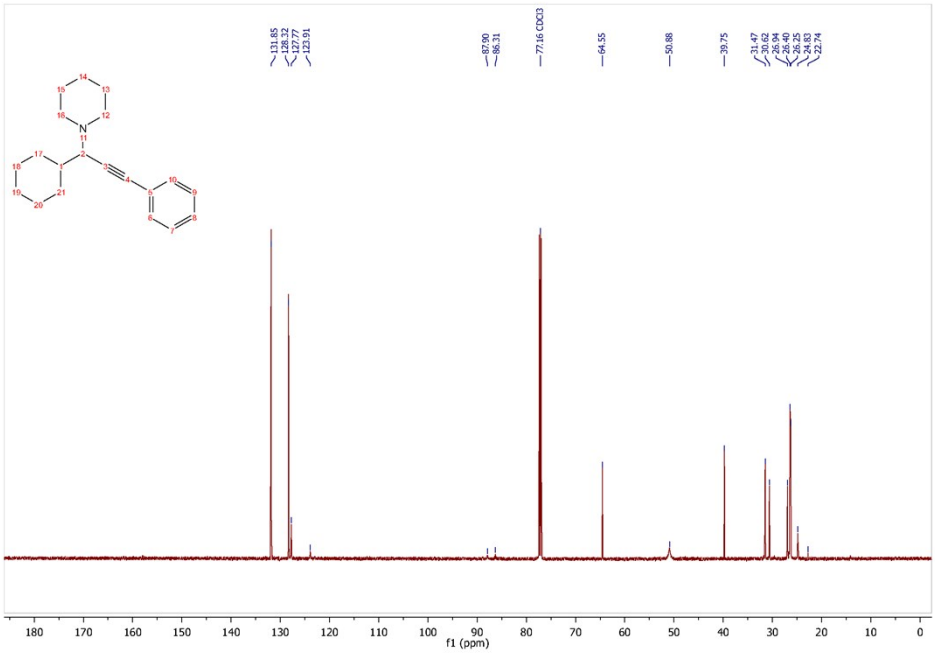


Figure S20. [13]C NMR spectrum of propargylamine **5aba**.

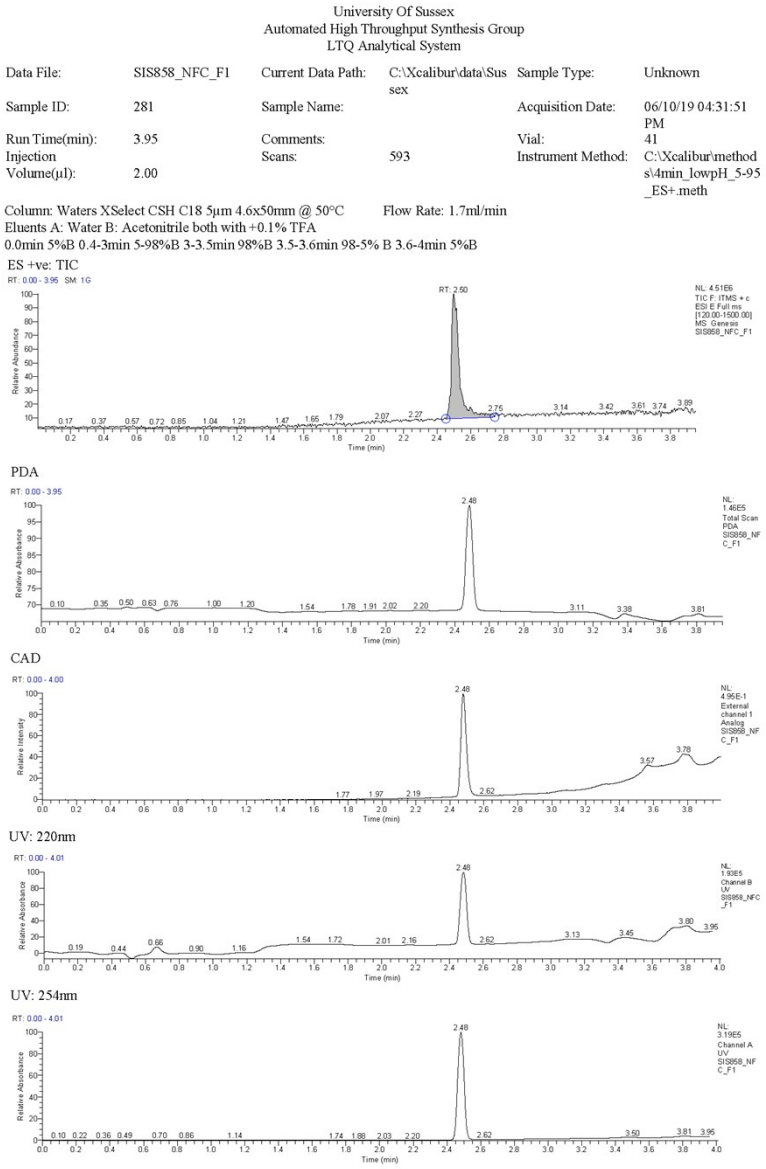


Figure S21. LCMS spectrum of propargylamine **5aba**.

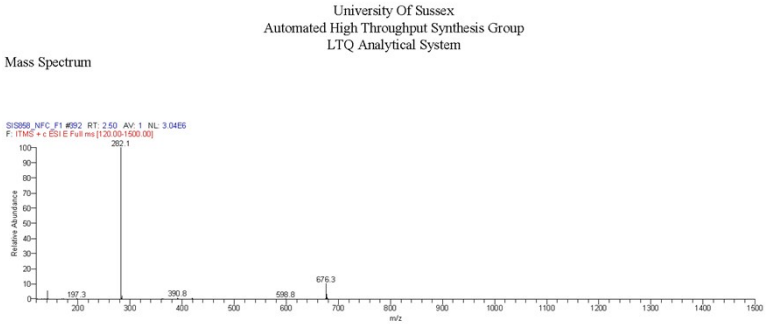
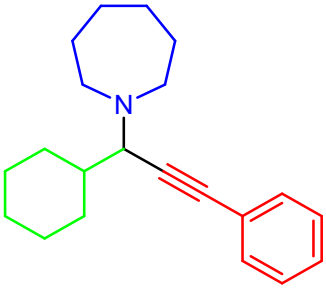


Figure S22. MS spectrum of propargylamine **5aba**.

1-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)azepane (5aca)



A mixture of cyclohexanecarboxaldehyde (1 mmol), azepane (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5aca was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 2H), 7.33 – 7.23 (m, 3H), 3.16 (d, *J* = 10.1 Hz, 1H), 2.80 (ddd, *J* = 12.9, 6.9, 3.6 Hz, 2H), 2.57 (ddd, *J* = 12.6, 7.5, 4.3 Hz, 2H), 2.20 – 2.06 (m, 2H), 1.80 – 1.70 (m, 3H), 1.70 – 1.51 (m, 9H), 1.33 – 1.13 (m, 3H), 1.05 – 0.86 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 131.8, 128.3, 127.6, 124.1, 89.1, 85.0, 77.4, 76.9, 65.4, 52.8, 41.0, 31.3, 30.8, 29.4, 27.3, 27.0, 26.4, 26.2.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{21}H_{30}N$, 296.2; found, 296.2, R_t = 2.47 min.

(Method A) isolated yield = 275 mg, 93%, (method B) isolated yield = 280 mg, 95%.

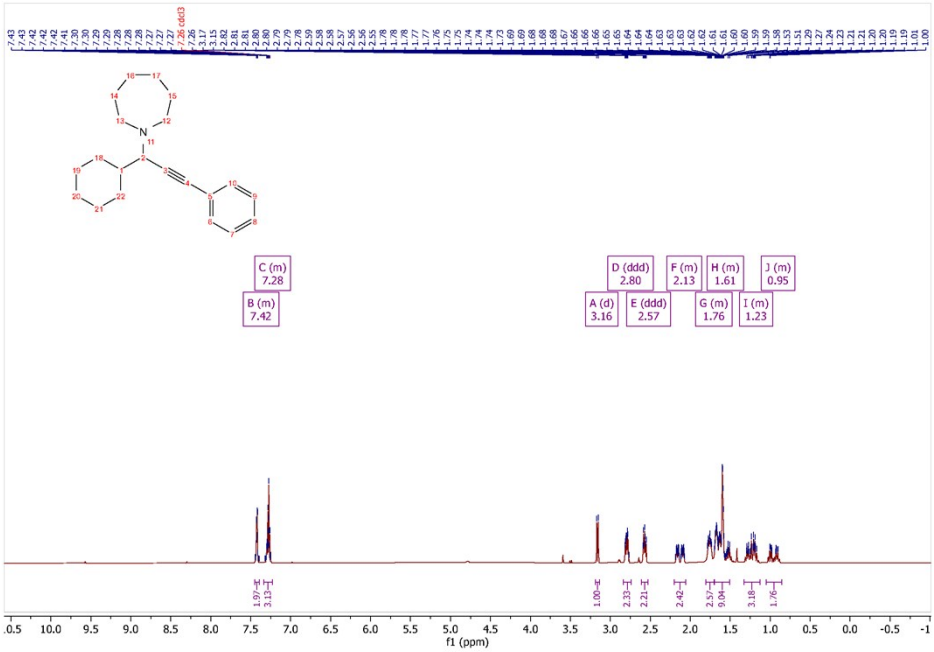


Figure S23. ^{1}H NMR spectrum of propargylamine **5aca**.

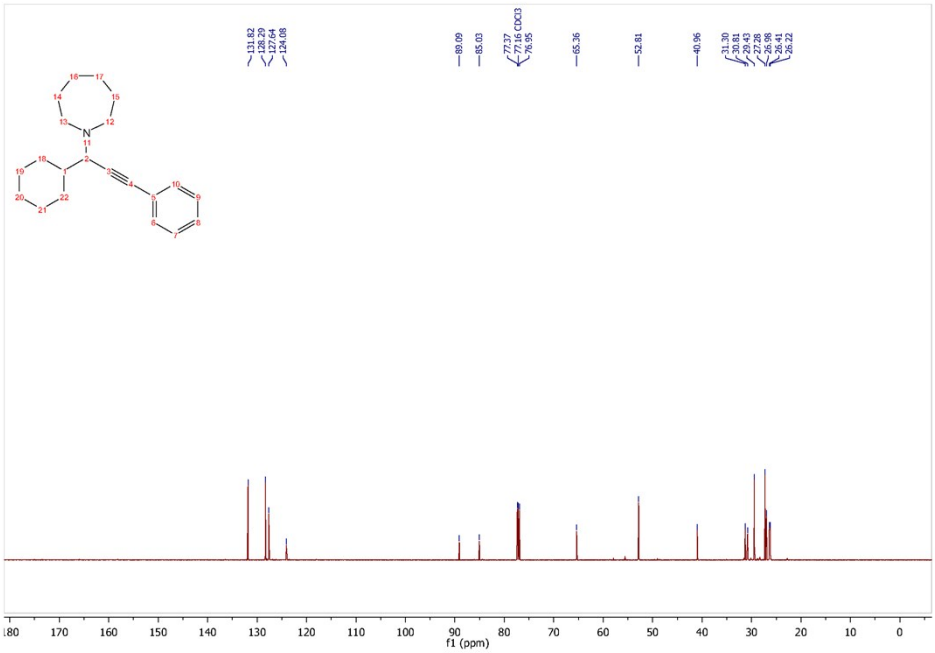


Figure S24. ^{13}C NMR spectrum of propargylamine **5aca**.

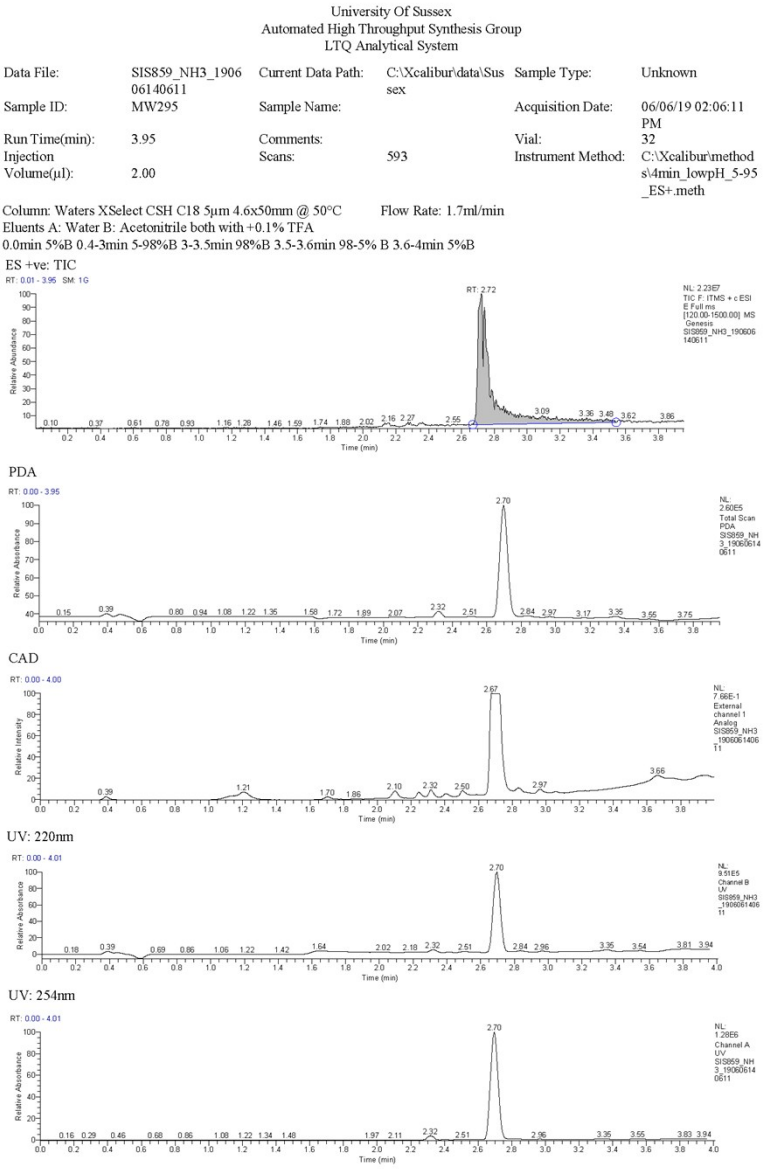


Figure S25. LCMS spectrum of propargylamine **5aca**.

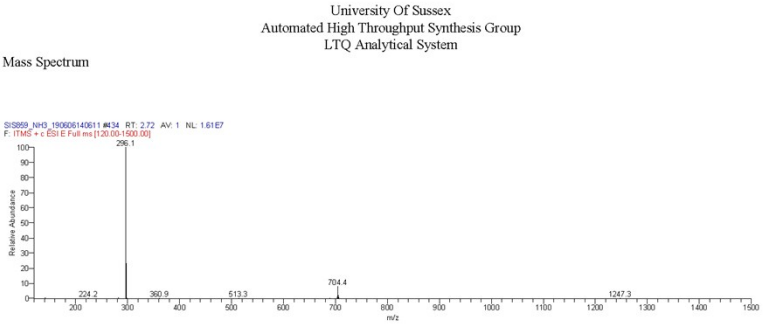
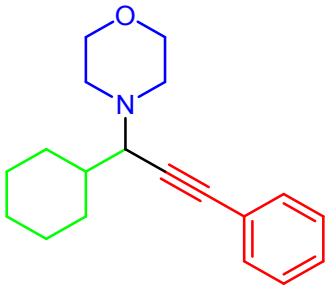


Figure S26. MS spectrum of propargylamine **5aca**.

4-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)morpholine (5ada)



A mixture of cyclohexanecarboxaldehyde (1 mmol), morpholine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was

(Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5ada was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 2H), 7.33 – 7.27 (m, 3H), 3.79 – 3.69 (m, 4H), 3.13 (d, J = 9.8 Hz, 1H), 2.75 – 2.67 (m, 2H), 2.52 (ddd, J = 11.2, 6.3, 2.9 Hz, 2H), 2.14 – 2.01 (m, 2H), 1.81 – 1.56 (m, 4H), 1.33 – 1.14 (m, 3H), 1.02 (ddd, J = 49.8, 11.8, 3.5 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 131.8, 128.4, 128.0, 123.6, 86.9, 86.8, 67.4, 64.1, 50.1, 39.3, 31.5, 31.1, 30.5, 29.6, 26.9, 26.3, 26.2.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{26}NO$, 284.1; found, 284.1, R_t = 2.60 min.

(Method A) isolated yield = 272 mg, 96%, (method B) isolated yield = 281 mg, 99%.

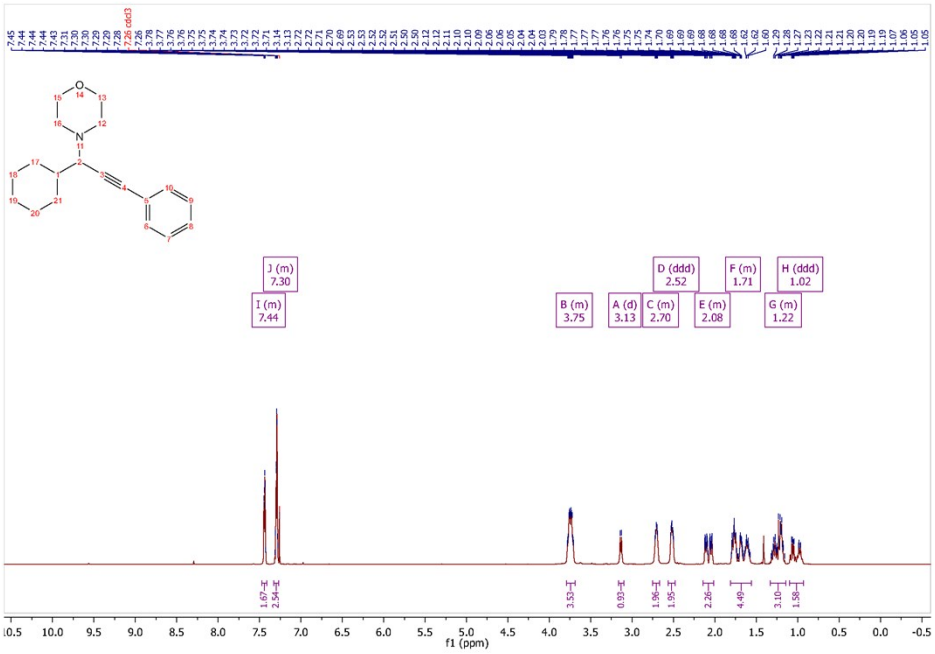


Figure S27. ^{1}H NMR spectrum of propargylamine **5ada**.

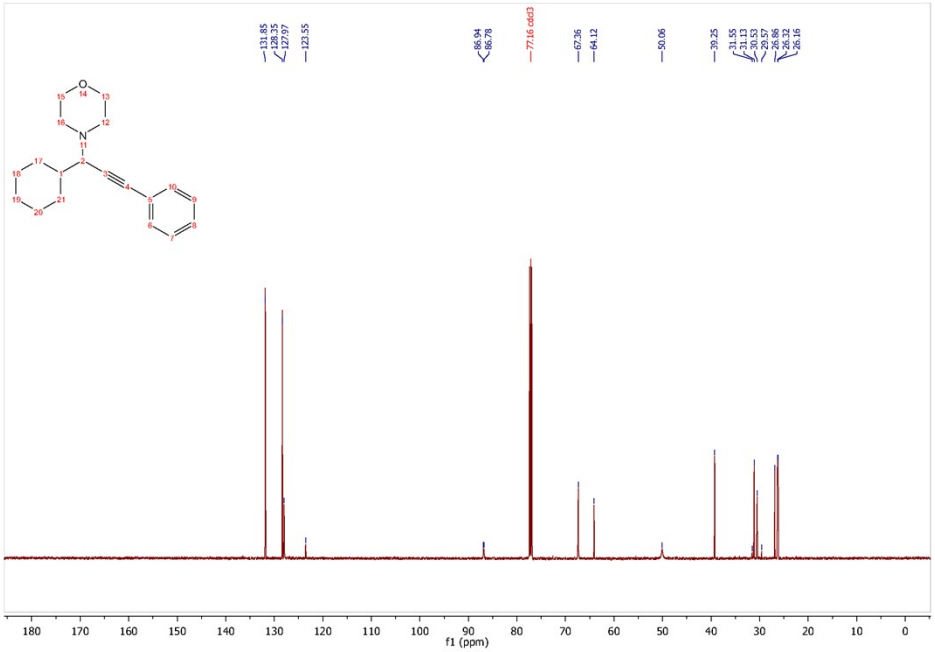


Figure S28. ^{13}C NMR spectrum of propargylamine **5ada**.

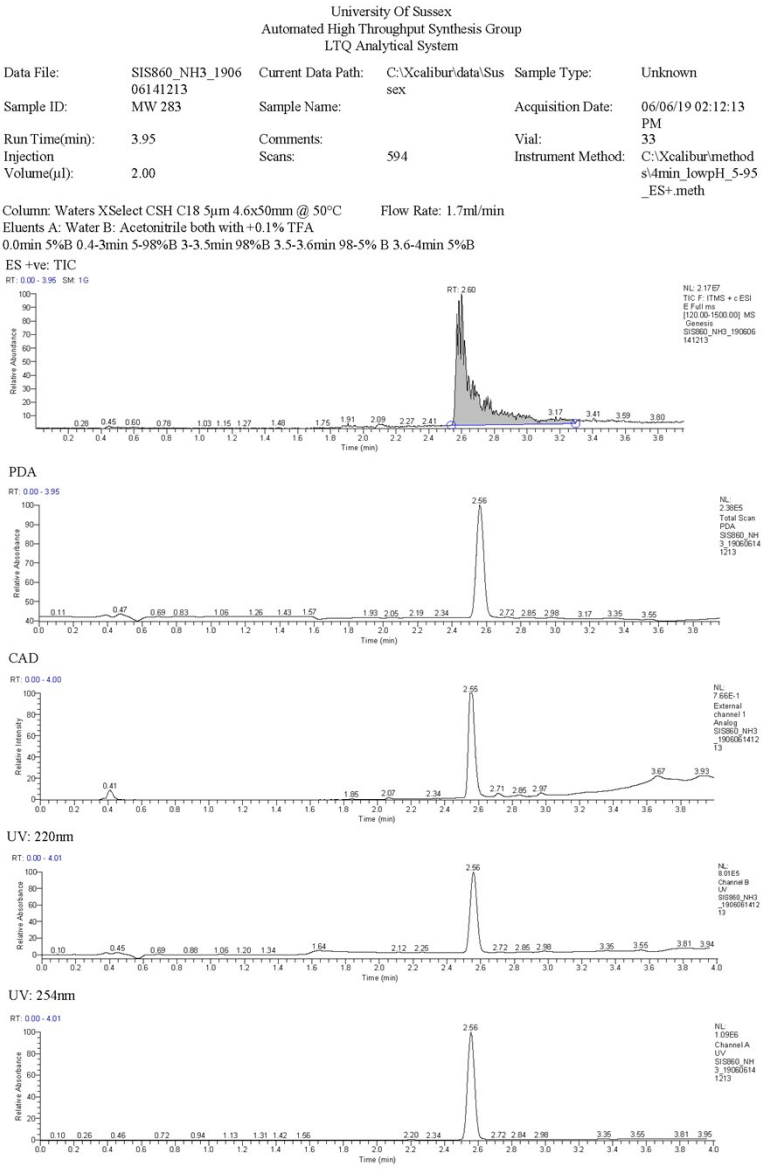


Figure S29. LCMS spectrum of propargylamine **5aca**.

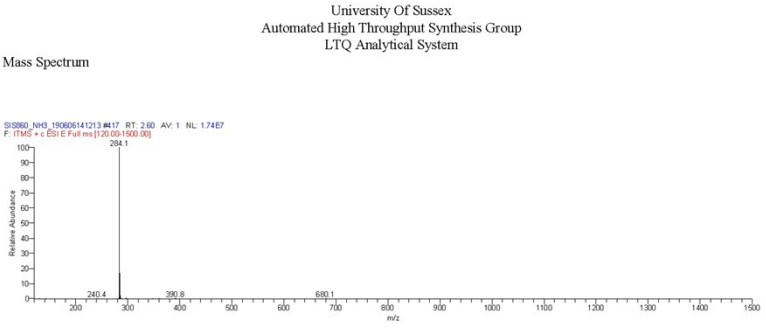
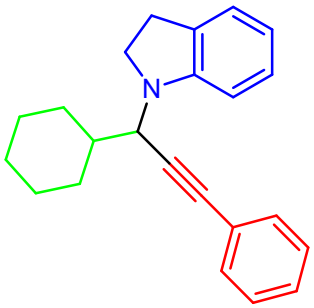


Figure S30. MS spectrum of propargylamine **5ada**.

1-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)indoline (5afa)



A mixture of cyclohexanecarboxaldehyde (1 mmol), indoline (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine **5afa** was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.34 (dd, *J* = 6.8, 2.9 Hz, 2H), 7.25 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.09 (t, *J* = 7.2 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.15 (d, *J* = 10.0 Hz, 1H), 3.55 – 3.43 (m, 2H), 3.00 (tt, *J* = 15.2, 10.8 Hz, 2H), 2.22 (dtd, *J* = 12.4, 4.0, 2.2 Hz, 1H), 2.11 (dtd, *J* = 13.6, 4.6, 4.1, 2.3 Hz, 1H), 1.88 – 1.69 (m, 4H), 1.40 – 1.13 (m, 5H).

^{13}C NMR (151 MHz, Chloroform-d) δ 151.8, 131.9, 130.2, 128.2, 128.0, 127.3, 124.5, 123.4, 118.0, 107.8, 87.1, 85.3, 55.4, 48.4, 41.2, 31.6, 31.1, 30.3, 29.6, 28.5, 26.7, 26.2, 26.1.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{23}H_{26}N$, 316.2; found, 316.0, R_t = 3.64 min.

(Method A) isolated yield = 230 mg, 73%, (method B) isolated yield = 277 mg, 88%.

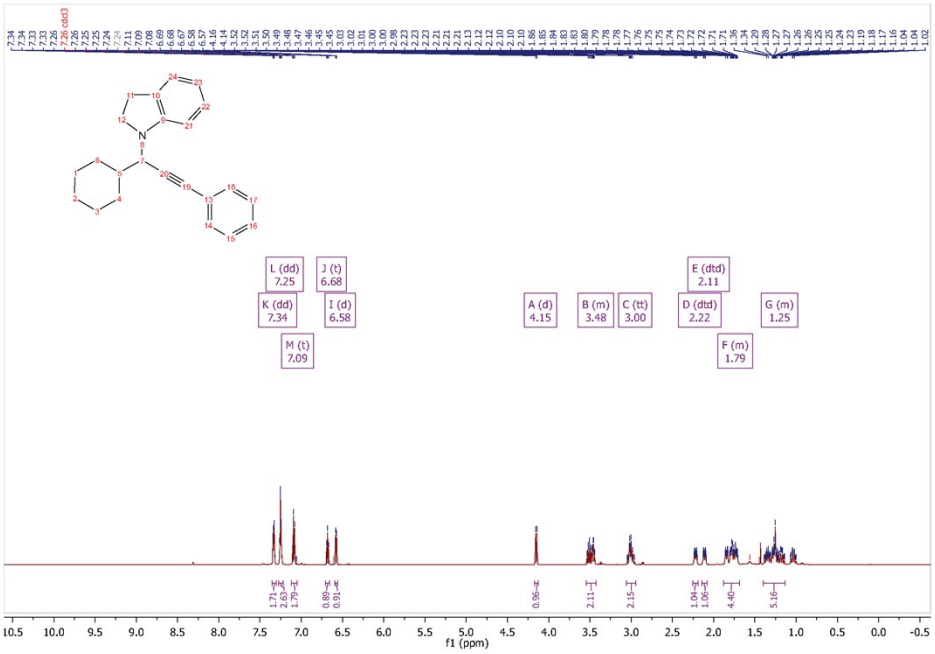


Figure S31. ^{1}H NMR spectrum of propargylamine **5afa**.

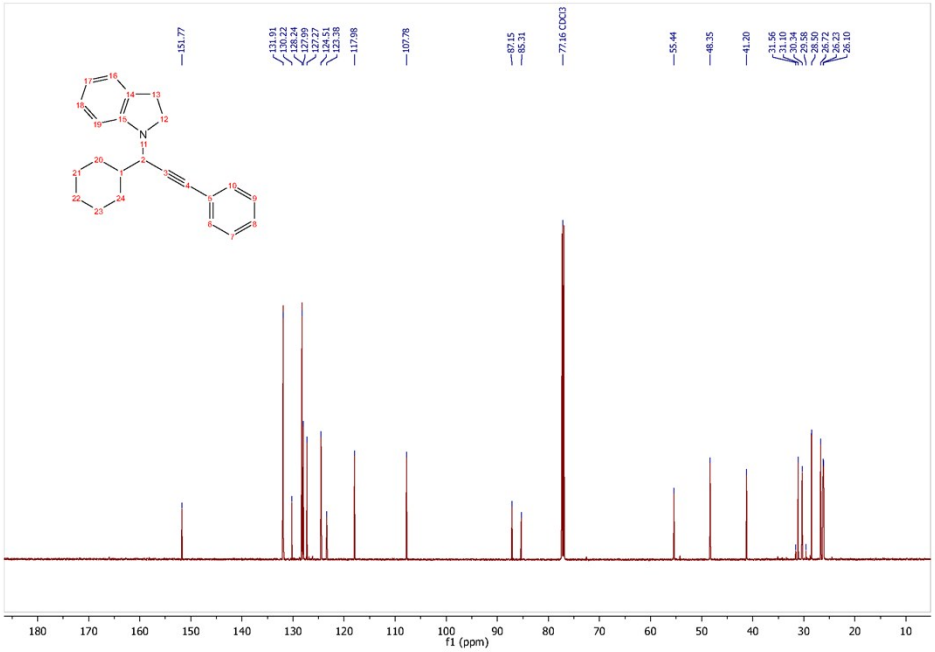


Figure S32. ^{13}C NMR spectrum of propargylamine **5afa**.

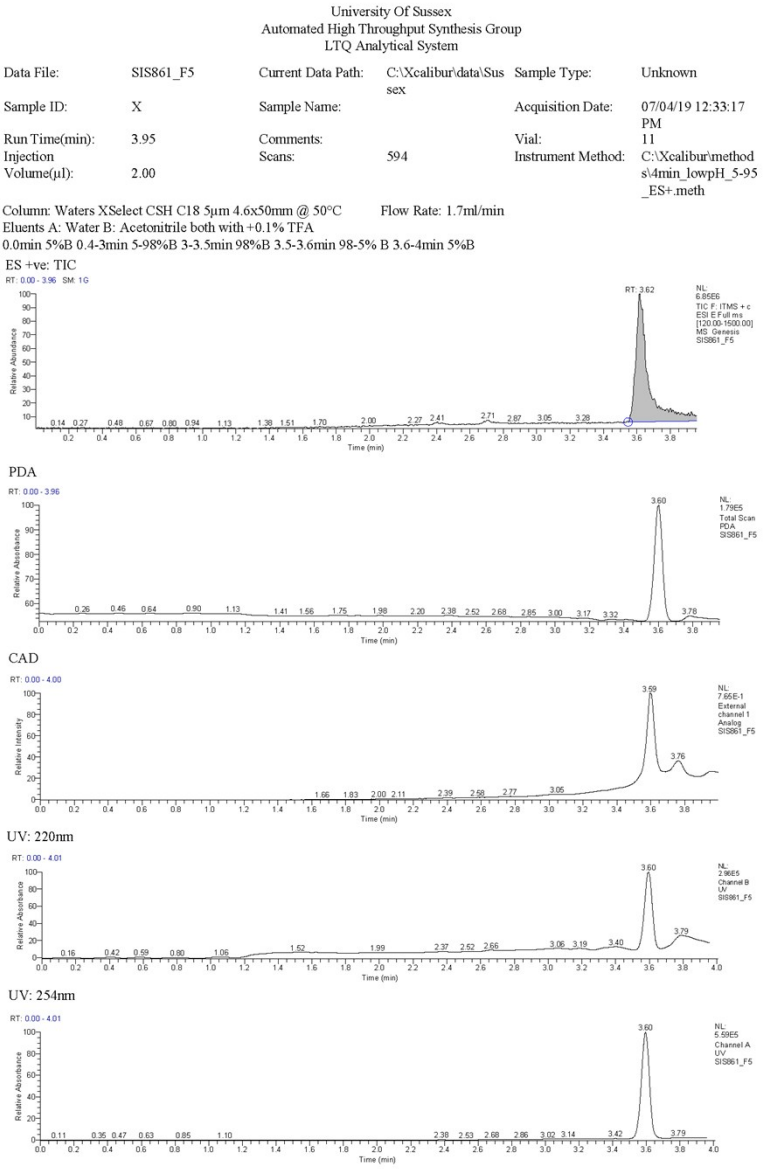


Figure S33. LCMS spectrum of propargylamine **5afa**.

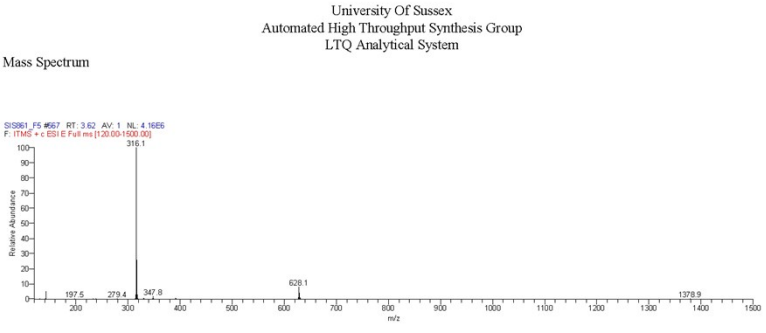
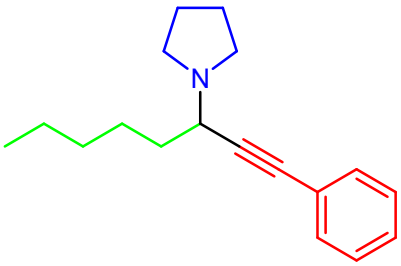


Figure S34. MS spectrum of propargylamine **5afa**.

1-(1-phenyloct-1-yn-3-yl)pyrrolidine (5baa)



A mixture of hexanal (1 mmol), pyrrolidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5baa was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 – 7.38 (m, 2H), 7.27 (dd, *J* = 5.1, 2.0 Hz, 3H), 3.65 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.75 (qd, *J* = 6.7, 3.2 Hz, 2H), 2.67 (qd, *J* = 7.0, 6.5, 2.9 Hz, 2H), 1.81 – 1.77 (m, 4H), 1.75 – 1.65 (m, 3H), 1.57 (dddd, *J* = 12.0, 8.4, 6.5, 3.5 Hz, 1H), 1.50 – 1.45 (m, 1H), 1.32 (ddd, *J* = 7.6, 5.7, 3.5 Hz, 3H), 0.90 – 0.89 (m, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 131.9, 128.3, 127.9, 123.7, 88.5, 85.4, 55.3, 54.7, 49.9, 46.7, 45.7, 35.2, 31.8, 26.6, 23.7, 22.7, 14.2.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{18}H_{26}N$, 256.2; found, 256.2, R_t = 2.41 min.

(Method A) isolated yield = 202 mg, 79%, (method B) isolated yield = 202 mg, 79%.

Figure S35. ^{1}H NMR spectrum of propargylamine **5baa**.

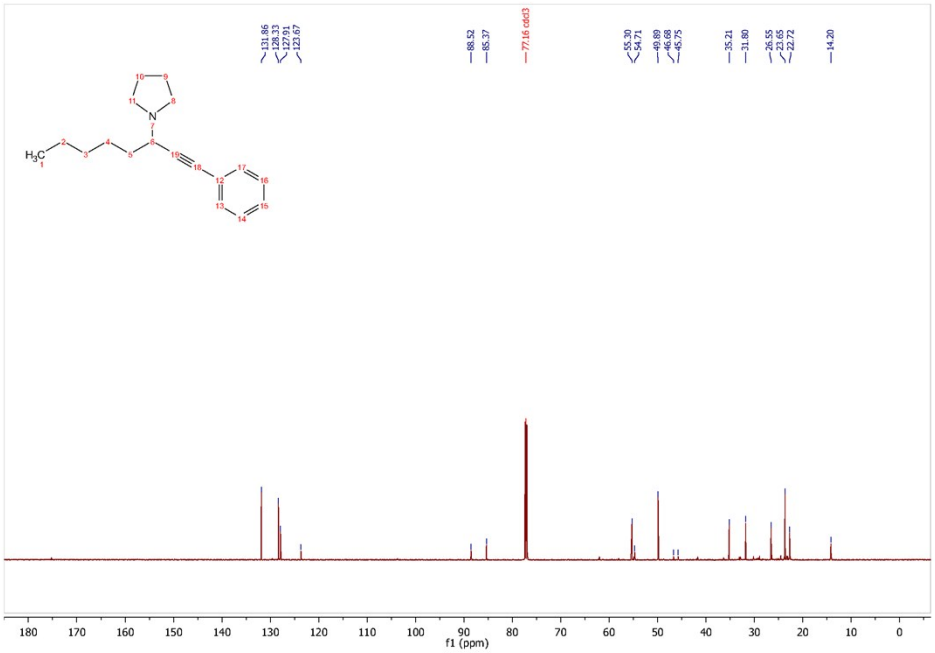


Figure S36. ^{13}C NMR spectrum of propargylamine **5baa**.

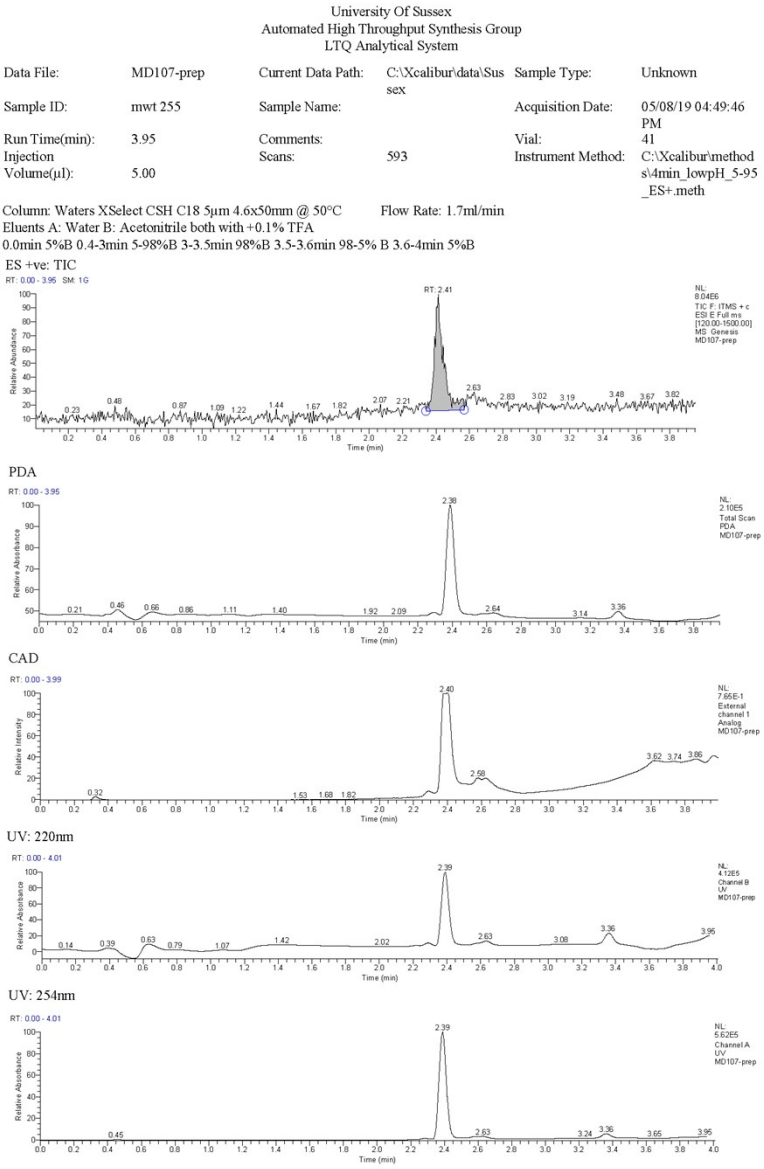


Figure S37. LCMS spectrum of propargylamine **5baa**.

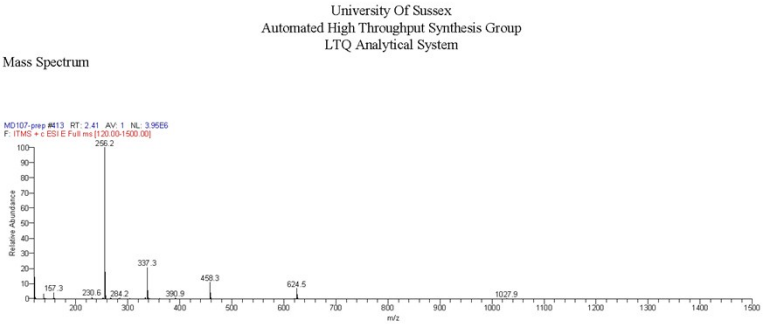
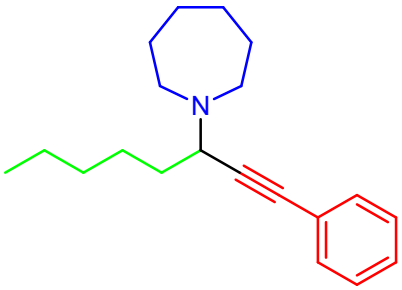


Figure S38. HRMS spectrum of propargylamine **5baa**.

1-(1-phenyloct-1-yn-3-yl)azepane (5bca)



A mixture of cyclohexanecarboxaldehyde (1 mmol), azepane (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method

A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5bca was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m, 2H), 7.32 – 7.23 (m, 3H), 3.52 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.82 (ddd, *J* = 12.7, 7.1, 3.6 Hz, 2H), 2.63 (ddd, *J* = 12.5, 7.8, 3.9 Hz, 2H), 1.75 – 1.57 (m, 9H), 1.56 – 1.40 (m, 2H), 1.33 (tt, *J* = 6.0, 2.7 Hz, 4H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 131.7, 128.1, 127.6, 123.7, 89.5, 84.2, 59.0, 52.5, 50.8, 34.3, 31.6, 29.0, 27.0, 26.4, 25.3, 25.1, 22.6, 14.0.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{30}N$, 284.1; found, 284.1, R_t = 2.55 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{30}N$, 284.2378; found, 284.2378.

(Method A) isolated yield = 224 mg, 79%, (method B) isolated yield = 255 mg, 90%.

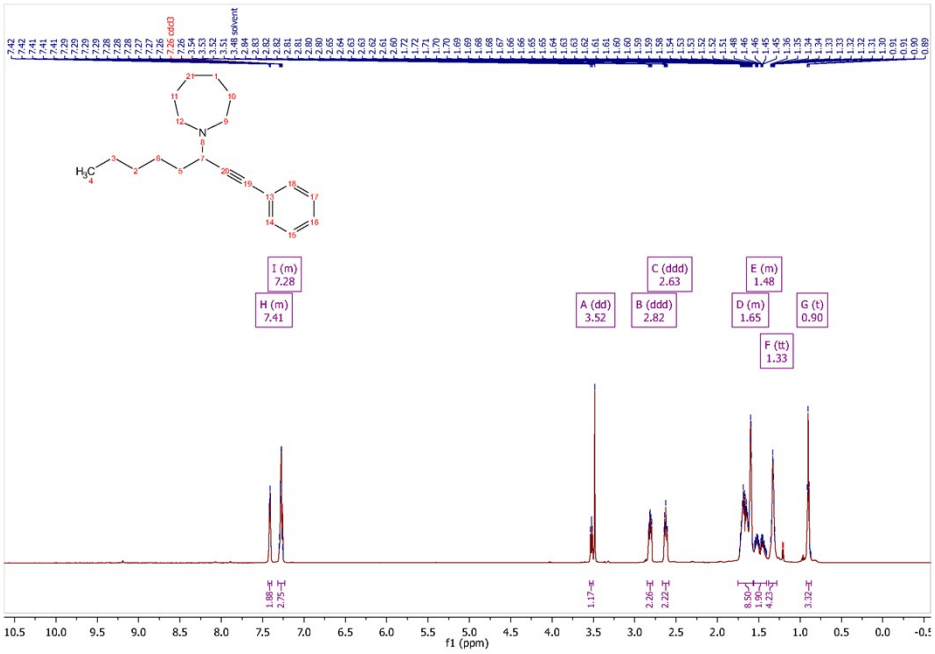


Figure S39. ^{1}H NMR spectrum of propargylamine **5bca**.

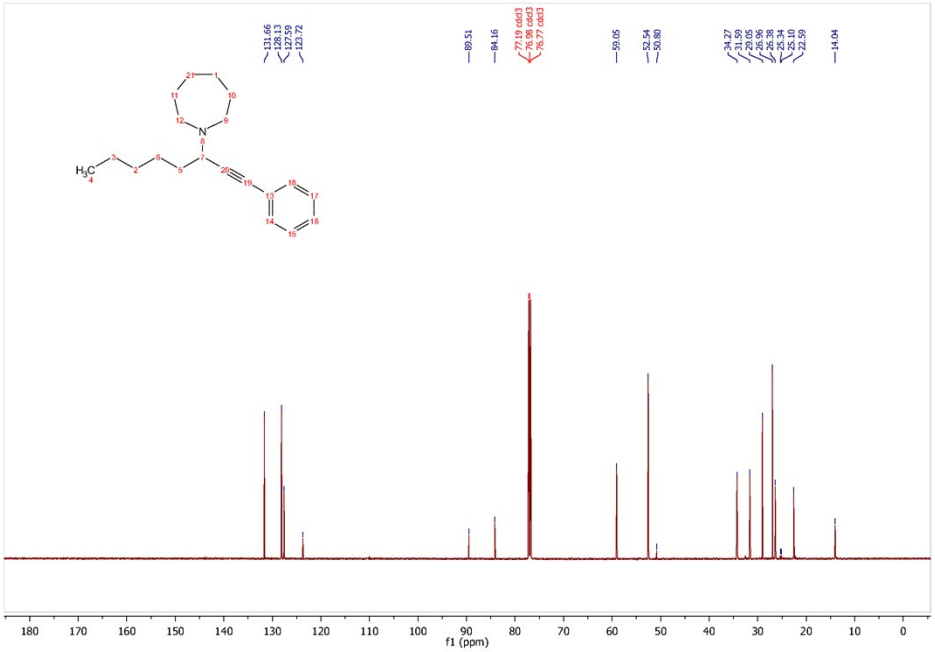


Figure S40. ^{13}C NMR spectrum of propargylamine **5bca**.

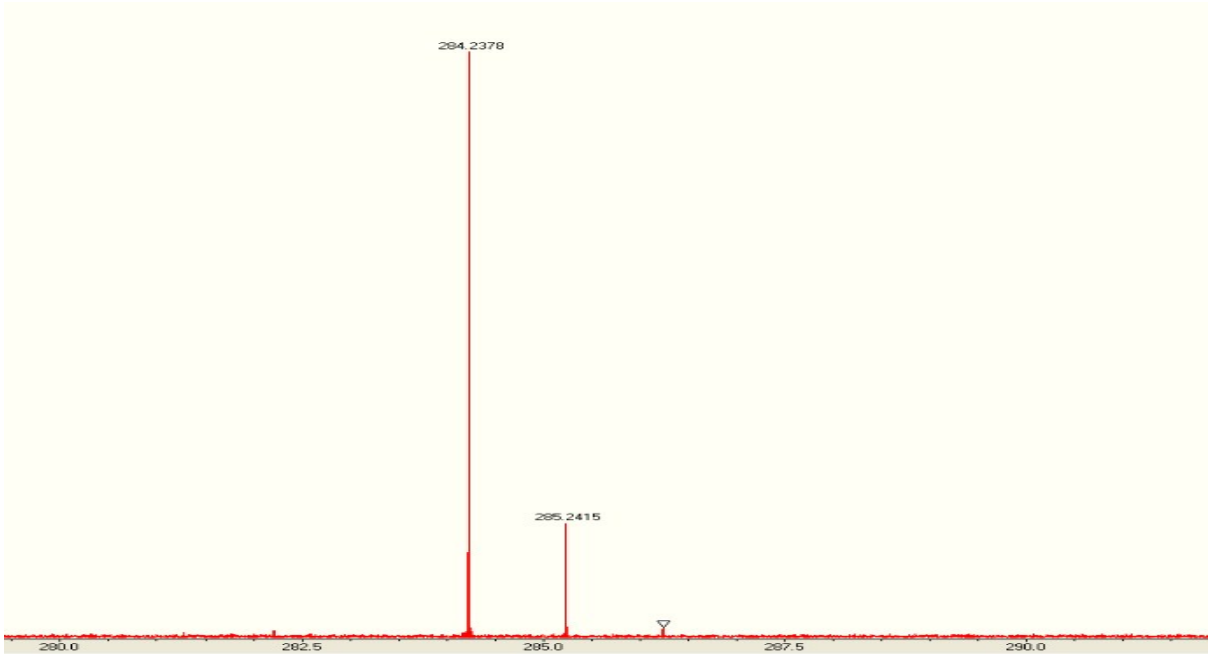


Figure S41. 5bca: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{30}N$, 284.2378; found, 284.2378.

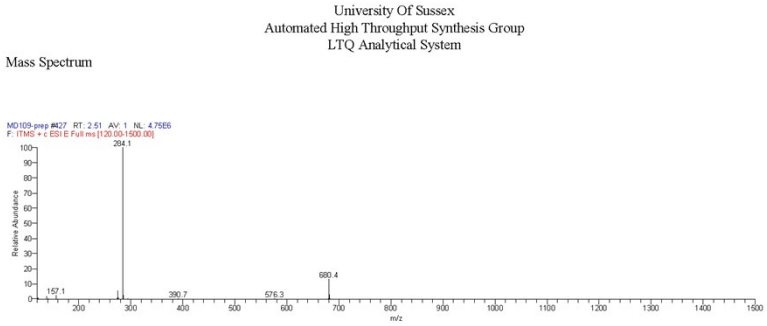


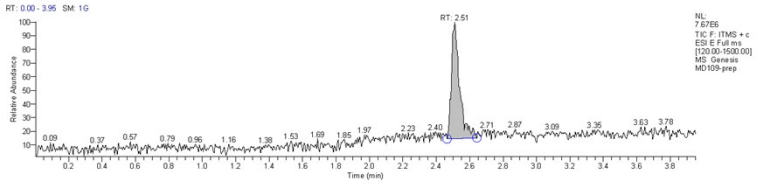
Figure S42. MS spectrum of propargylamine **5bca**.

University Of Sussex
Automated High Throughput Synthesis Group
LTQ Analytical System

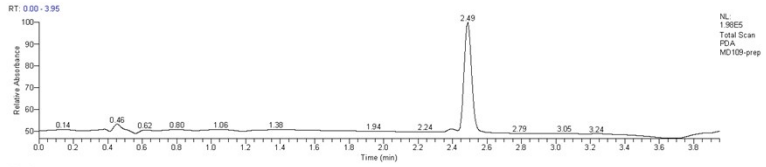
Data File:	MD109-prep	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	mwt 283	Sample Name:		Acquisition Date:	05/08/19 04:56:01 PM
Run Time(min):	3.95	Comments:		Vial:	42
Injection Volume(µl):	5.00	Scans:	593	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

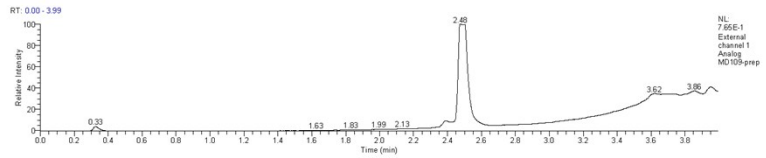
ES +ve: TIC



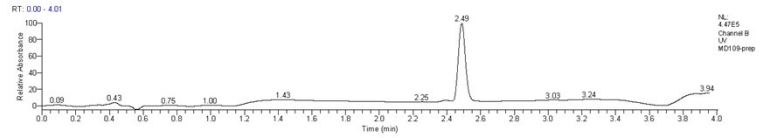
PDA



CAD



UV: 220nm



UV: 254nm

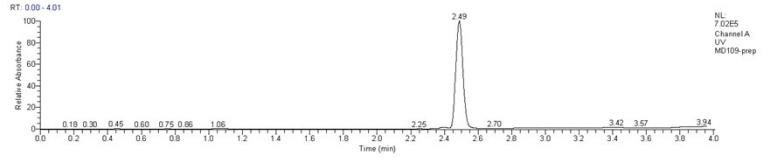
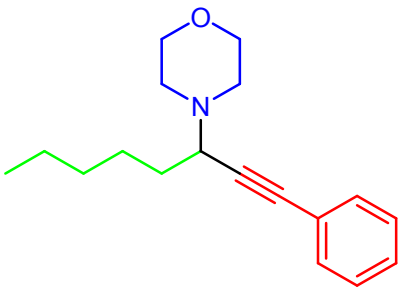


Figure S43. LCMS spectrum of propargylamine **5bca**.

4-(1-phenyloct-1-yn-3-yl)morpholine (5bda)



A mixture of hexanal (1 mmol), morpholine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5bda was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 7.29 (q, *J* = 2.8 Hz, 3H), 3.76 (s, 4H), 3.50 (s, 1H), 2.76 (s, 2H), 2.58 (s, 2H), 1.60 – 1.50 (m, 2H), 1.46 (tt, *J* = 16.6, 8.8 Hz, 2H), 1.36 – 1.30 (m, 4H), 0.93 – 0.86 (m, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 131.9, 130.1, 128.4, 85.6, 85.2, 83.0, 41.0, 34.0, 31.6, 28.6, 26.4, 24.0, 22.7, 20.9, 17.6, 17.4, 14.8, 14.2, 8.1.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{18}H_{26}NO$, 272.2; found, 272.0, R_t = 2.40 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{18}H_{26}NO$, 272.2014; found, 272.2016.

(Method A) isolated yield = 255 mg, 94%, (method B) isolated yield = 269 mg, 99%.

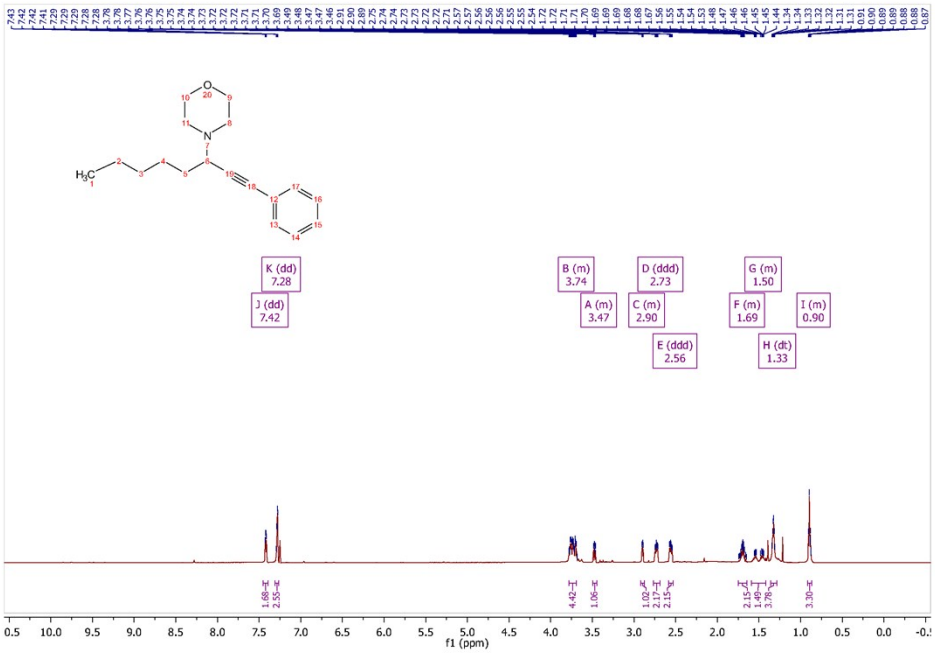


Figure S44. ^{1}H NMR spectrum of propargylamine **5bda**.

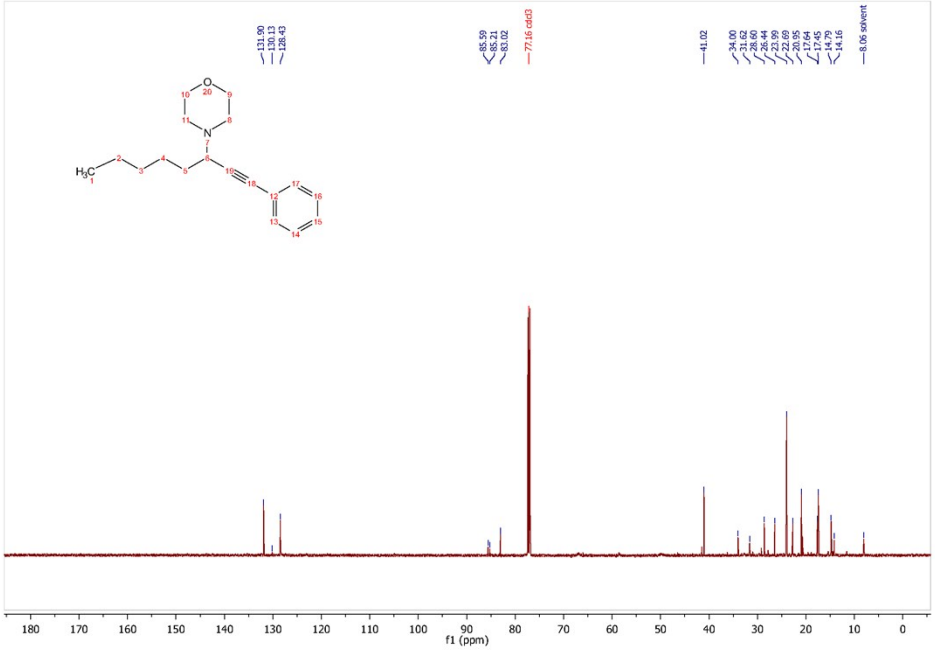


Figure S45. ^{13}C NMR spectrum of propargylamine **5bda**.

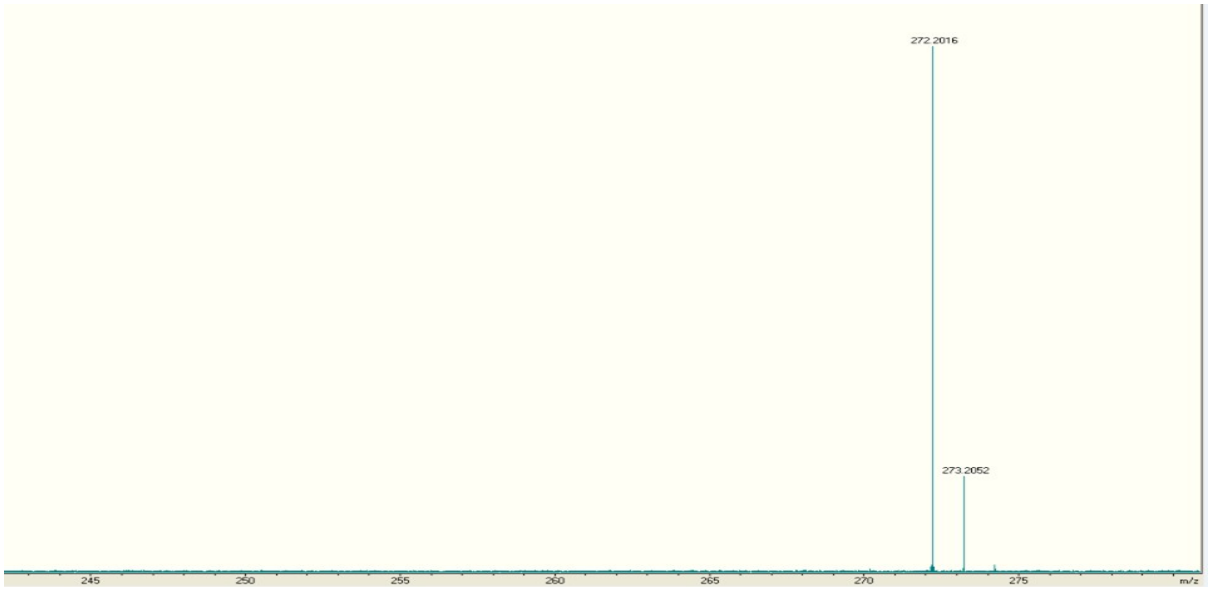


Figure S46. 5bda: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{18}H_{26}NO$, 272.2014; found, 272.2016.

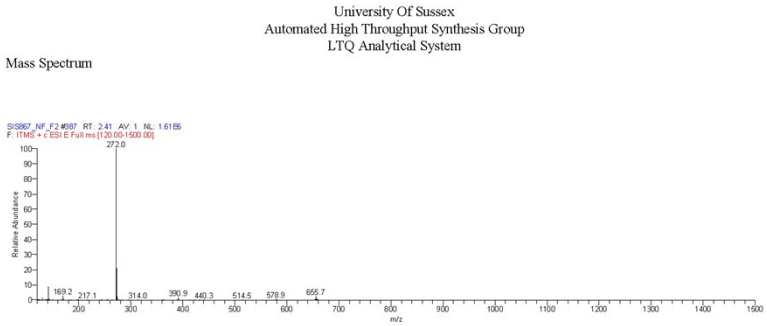


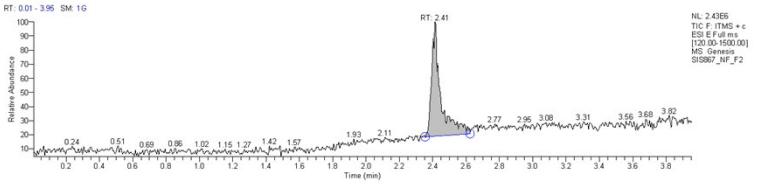
Figure S47. MS spectrum of propargylamine **5bda**.

University Of Sussex
Automated High Throughput Synthesis Group
LTQ Analytical System

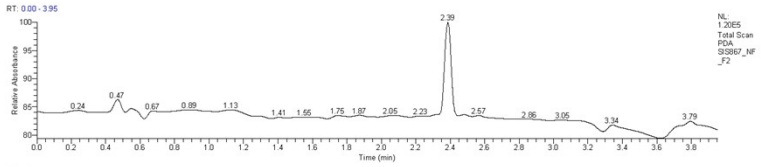
Data File:	SIS867_NF_F2	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	MWt271	Sample Name:		Acquisition Date:	06/07/19 04:39:36 PM
Run Time(min):	3.95	Comments:		Vial:	33
Injection Volume(µl):	2.00	Scans:	593	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

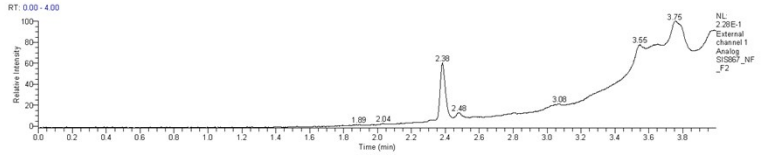
ES +ve: TIC



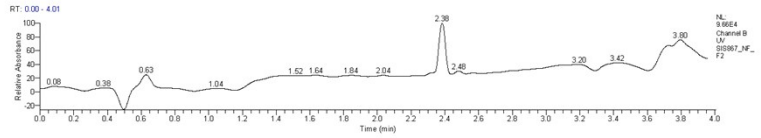
PDA



CAD



UV: 220nm



UV: 254nm

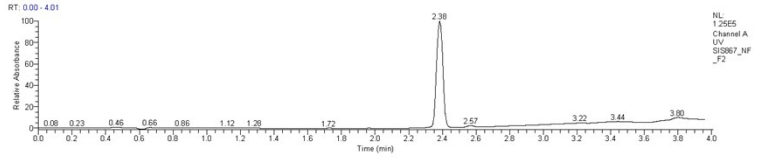
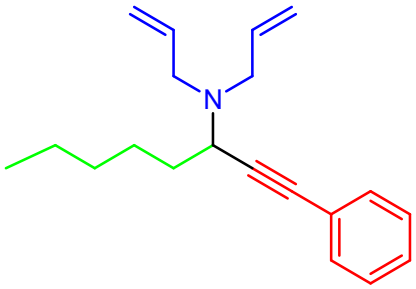


Figure S48. LCMS spectrum of propargylamine **5bda**.

N,N-diallyl-1-phenyloct-1-yn-3-amine (5bea)



A mixture of hexanal (1 mmol), diallylamine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5bea was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.49 – 7.44 (m, 2H), 7.36 – 7.28 (m, 2H), 5.90 (dddd, *J* = 17.6, 10.1, 7.9, 4.7 Hz, 2H), 5.28 (dq, *J* = 17.1, 1.7 Hz, 2H), 5.16 (dd, *J* = 10.1, 1.9 Hz, 2H), 3.76 (t, *J* = 7.6 Hz, 1H), 3.38 (ddd, *J* = 14.2, 4.5, 2.1 Hz, 2H), 3.04 (dd, *J* = 14.2, 7.9 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.58 – 1.46 (m, 2H), 1.36 (dddd, *J* = 12.6, 9.2, 6.7, 3.7 Hz, 4H), 0.94 (t, *J* = 7.0 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 136.8, 131.8, 128.3, 127.9, 123.7, 117.1, 88.5, 85.1, 76.9, 54.1, 53.2, 34.0, 31.7, 26.4, 22.7, 14.2.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}N$, 272.2; found, 282.1, R_t = 2.56 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}N$, 282.2014; found, 282.2223.

(Method A) isolated yield = 247 mg, 91%, (method B) isolated yield = 260 mg, 96%.

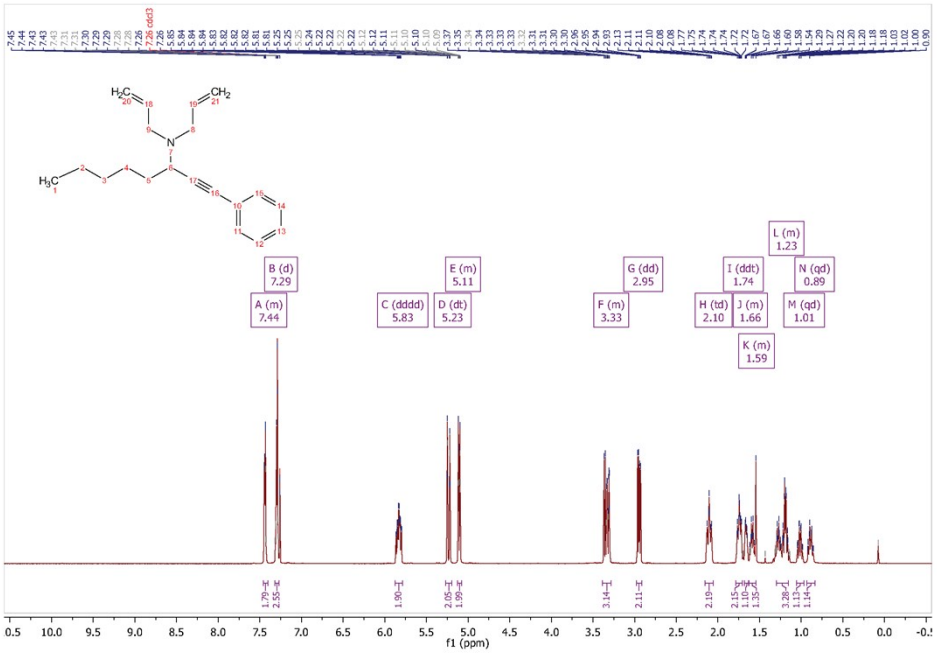


Figure S49. ^{1}H NMR spectrum of propargylamine **5bea**.

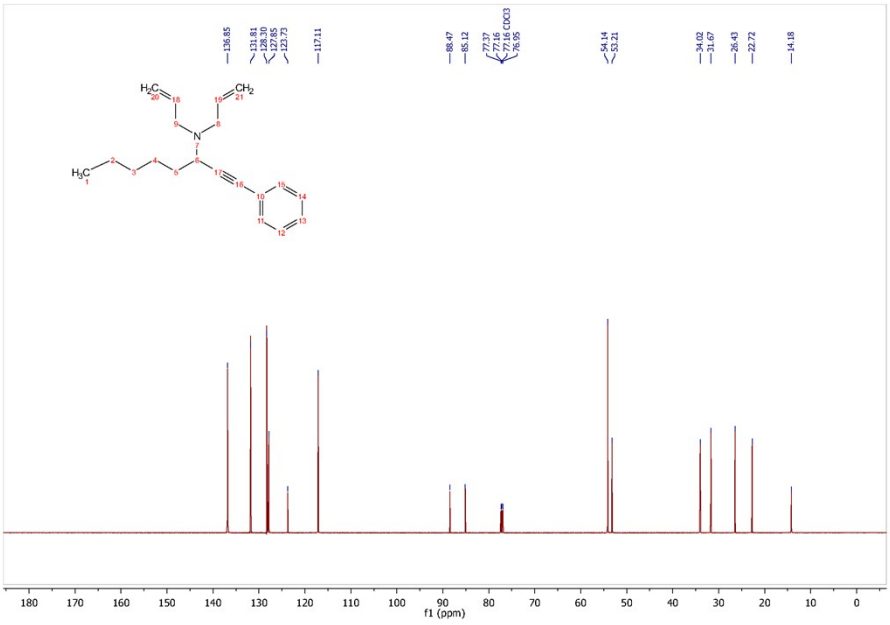


Figure S50. ^{13}C NMR spectrum of propargylamine **5bea**.

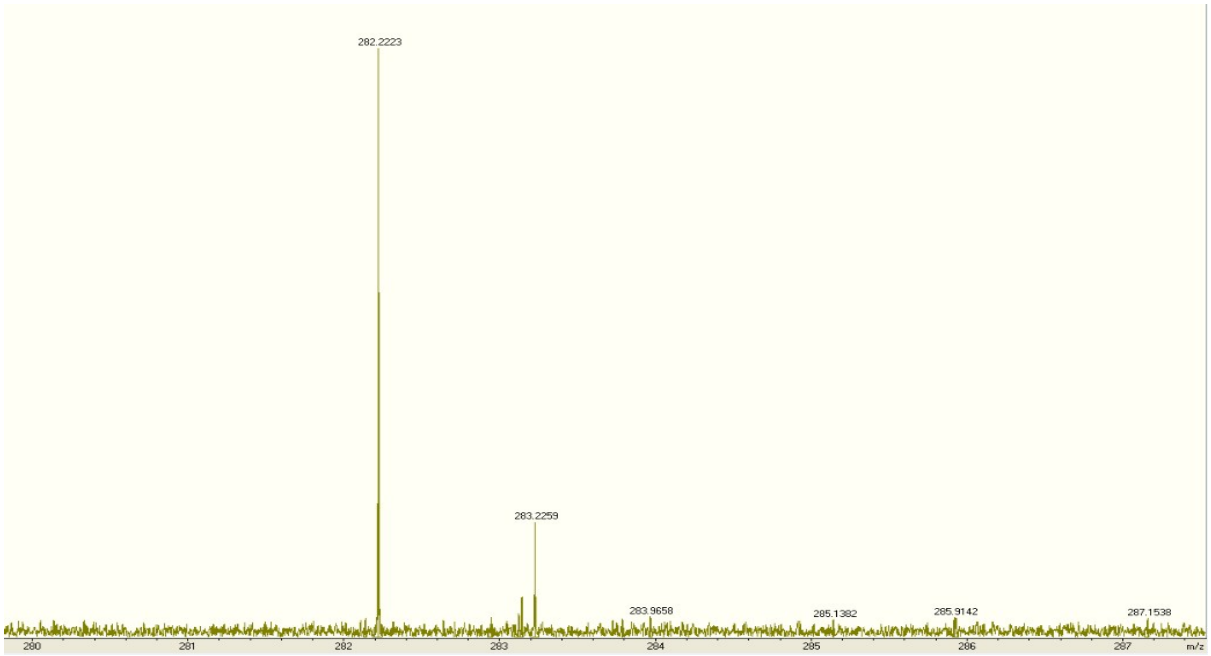


Figure S51. 5bea: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}N$, 272.2014; found, 272.2223.

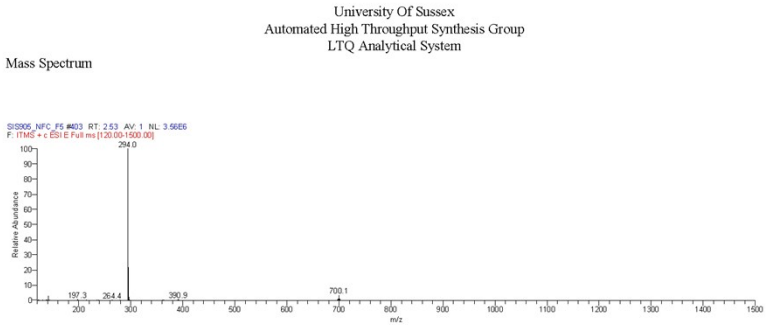


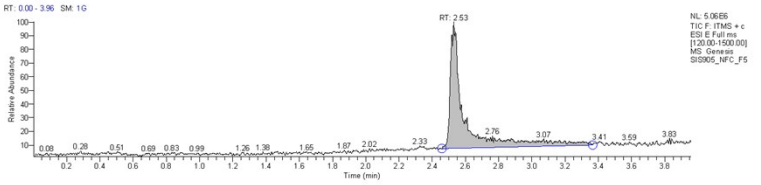
Figure S52. MS spectrum of propargylamine **5bea**.

University Of Sussex
Automated High Throughput Synthesis Group
LTQ Analytical System

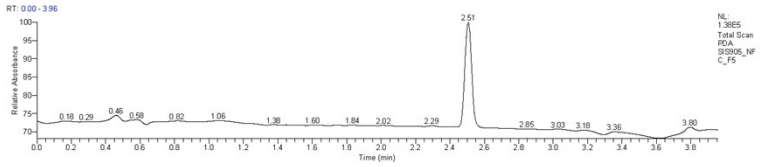
Data File:	SIS905_NFC_F5	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	SIS905 OR 4	Sample Name:		Acquisition Date:	06/20/19 10:46:52 AM
Run Time(min):	3.95	Comments:		Vial:	21
Injection Volume(µl):	2.00	Scans:	594	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

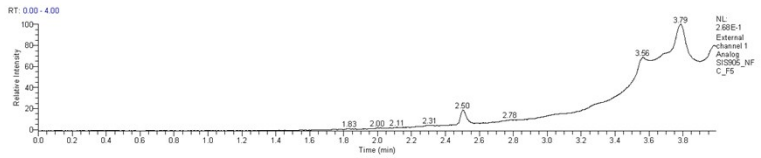
ES +ve: TIC



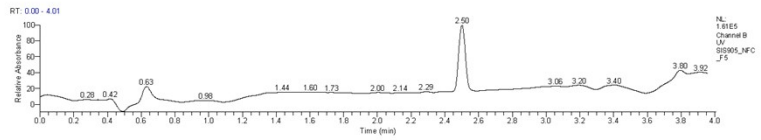
PDA



CAD



UV: 220nm



UV: 254nm

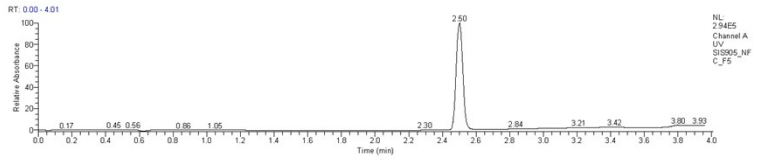
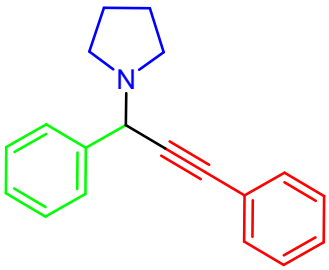


Figure S53. LCMS spectrum of propargylamine **5bea**.

1-(1,3-diphenylprop-2-yn-1-yl)pyrrolidine (5caa)



A mixture of benzaldehyde (1 mmol), pyrrolidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5caa was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.64 – 7.60 (m, 2H), 7.51 – 7.47 (m, 2H), 7.36 (dd, *J* = 8.3, 6.8 Hz, 2H), 7.33 – 7.28 (m, 4H), 4.94 (s, 1H), 2.73 (tq, *J* = 7.0, 3.0 Hz, 4H), 1.82 (pd, *J* = 5.2, 4.2, 3.1 Hz, 4H).

^{13}C NMR (151 MHz, Chloroform-d) δ 139.3, 131.9, 131.6, 129.8, 128.5, 128.4, 128.3, 128.1, 127.8, 123.3, 87.2, 86.6, 59.2, 50.3, 23.6.

MS (LCMS) m/z: ($[M + H]^+$) calcd for $C_{19}H_{20}N$, 262.2; found, 261.9, R_t = 2.23 min.

(Method A) isolated yield = 165 mg, 63%, (method B) isolated yield = 227 mg, 87%.

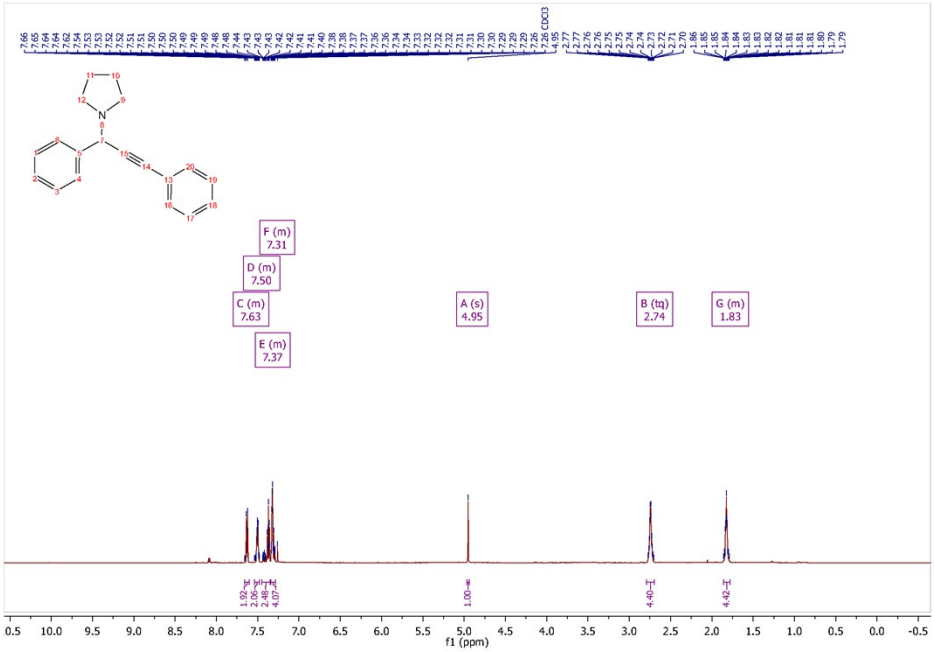


Figure S54. [1]H NMR spectrum of propargylamine **5caa**.

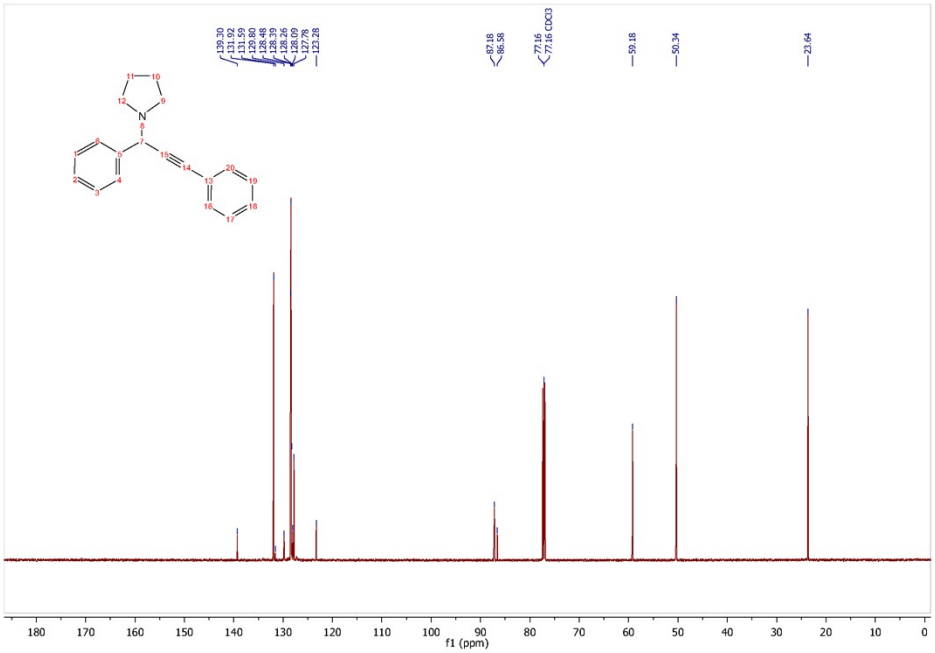


Figure S55. [13]C NMR spectrum of propargylamine **5caa**.

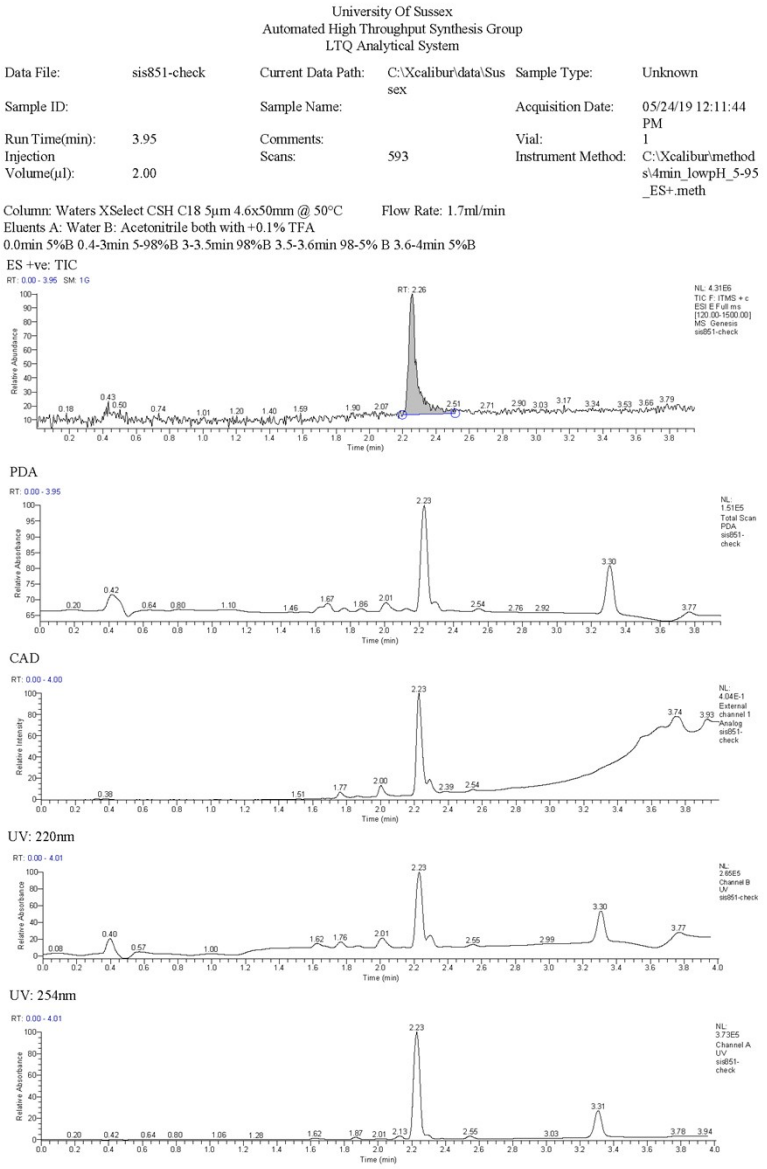


Figure S56. LCMS spectrum of propargylamine **5caa**.

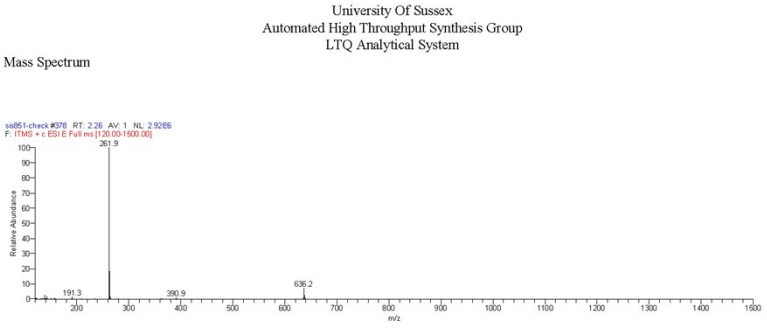
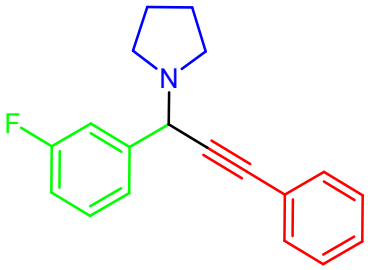


Figure S57. MS spectrum of propargylamine **5caa**.

1-(1-(3-fluorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (5daa)



A mixture of 3-fluorobenzaldehyde (1 mmol), pyrrolidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5daa was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.50 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.38 (dd, *J* = 9.9, 2.1 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.00 (td, *J* = 8.4, 2.6 Hz, 1H), 5.01 (s, 1H), 2.82 – 2.72 (m, 4H), 1.87 – 1.79 (m, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.8 (d, $^{1}J_{F,C}$= 245.5 Hz), 141.2, 131.8, 129.8 (d, $^{3}J_{F,C}$= 8.0 Hz), 128.4, 128.3, 123.9 (d, $^{4}J_{F,C}$= 3.1 Hz), 122.7, 115.3, (d, $^{2}J_{F,C}$= 22.4 Hz), 114.8 (d, $^{2}J_{F,C}$= 20.8 Hz), 87.8, 85.0, 58.5 (d, $^{4}J_{F,C}$= 2.2 Hz), 55.8, 50.1, 24.0.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{19}NF$, 280.2; found, 280.0, R_t = 2.26 min.

(Method A) isolated yield = 170 mg, 61%, (method B) isolated yield = 237 mg, 85%.

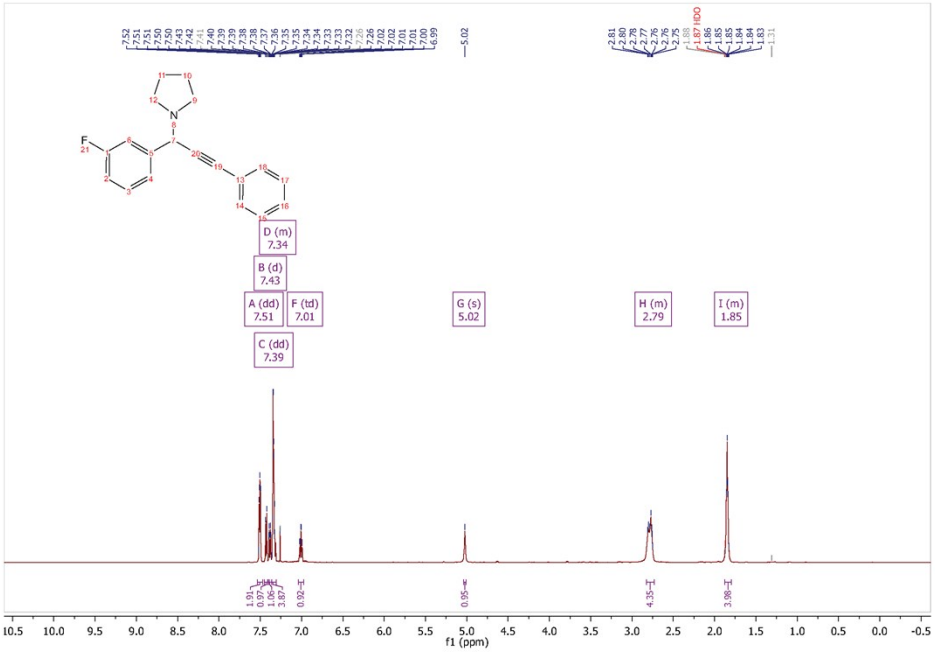


Figure S58. ^{1}H NMR spectrum of propargylamine **5daa**.

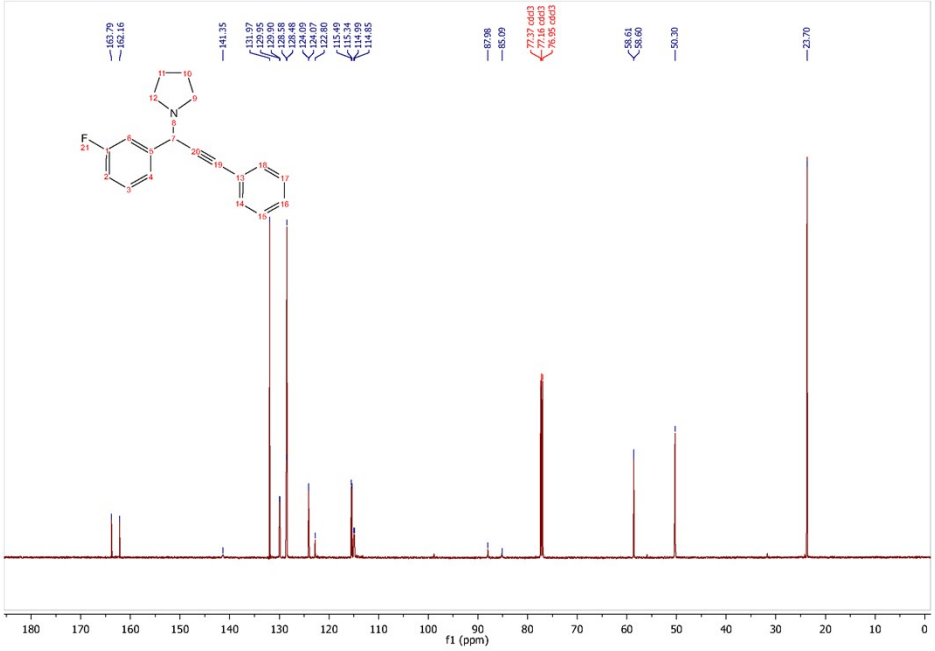


Figure S59. ^{13}C NMR spectrum of propargylamine **5daa**.

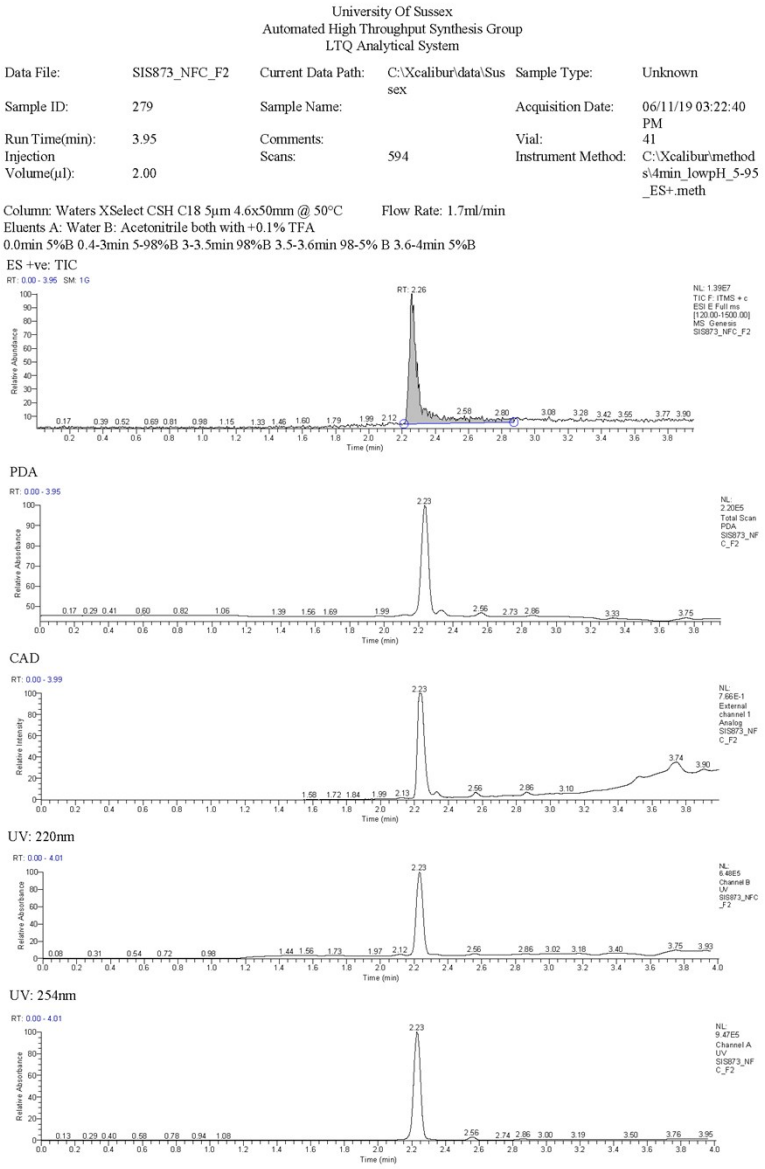


Figure S60. LCMS spectrum of propargylamine **5daa**.

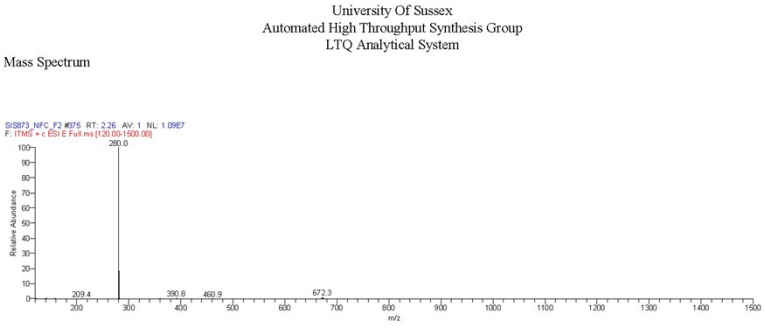
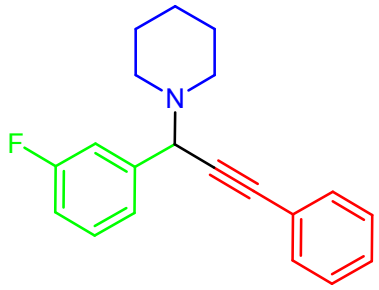


Figure S61. MS spectrum of propargylamine **5daa**.

1-(1-(3-fluorophenyl)-3-phenylprop-2-yn-1-yl)piperidine (5dba)



A mixture of 3-fluorobenzaldehyde (1 mmol), pipperidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5cba was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.55 – 7.49 (m, 2H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.39 (dt, *J* = 10.2, 2.0 Hz, 1H), 7.35 – 7.32 (m, 4H), 6.98 (td, *J* = 8.4, 2.5 Hz, 1H), 4.80 (s, 1H), 2.56 (s, 4H), 1.69 – 1.41 (m, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.8 (d, $^{1}J_{F,C}$= 244.4 Hz), 141.5, 131.8, 129.4 (d, $^{3}J_{F,C}$= 8.0 Hz), 128.3, 128.2, 124.0, 123.0, 115.3 (d, $^{2}J_{F,C}$= 23.1 Hz), 114.3 (d, $^{2}J_{F,C}$= 19.9 Hz), 88.2, 85.2, 61.9 (d, $^{4}J_{F,C}$= 1.8 Hz), 50.6, 26.1, 24.3.

MS (LCMS) m/z: ([M + H]$^{+}$) calcd for $C_{20}H_{21}NF$, 294.2; found, 294.0, R_t = 2.43 min.

(Method A) isolated yield = 173 mg, 59%, (method B) isolated yield = 229 mg, 78%.

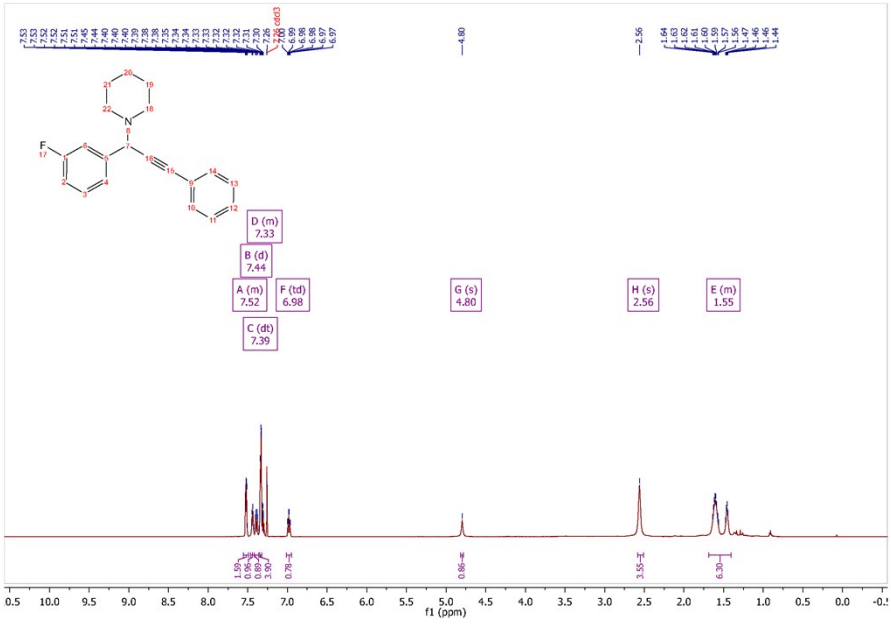


Figure S62. ^{1}H NMR spectrum of propargylamine **5dba**.

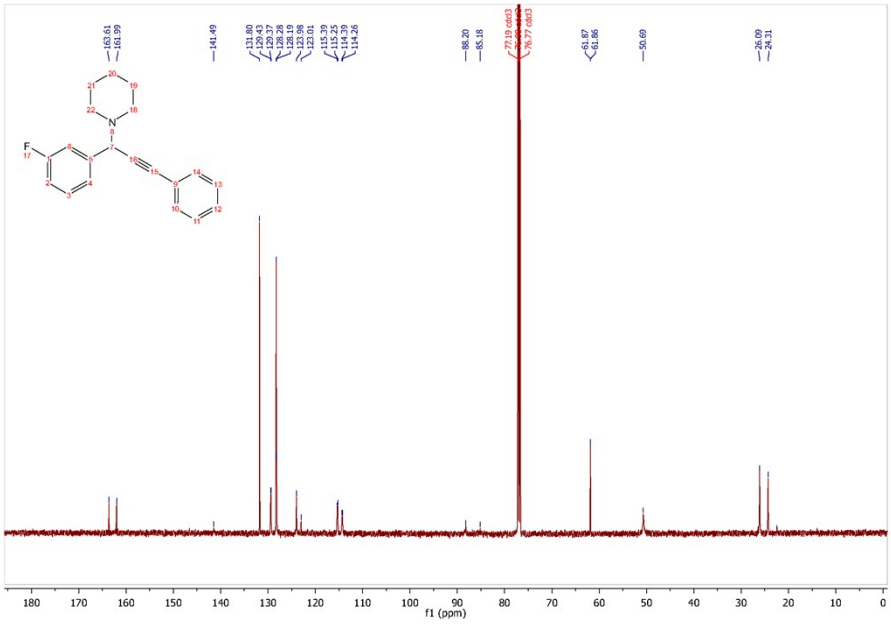


Figure S63. ^{13}C NMR spectrum of propargylamine **5dba**.

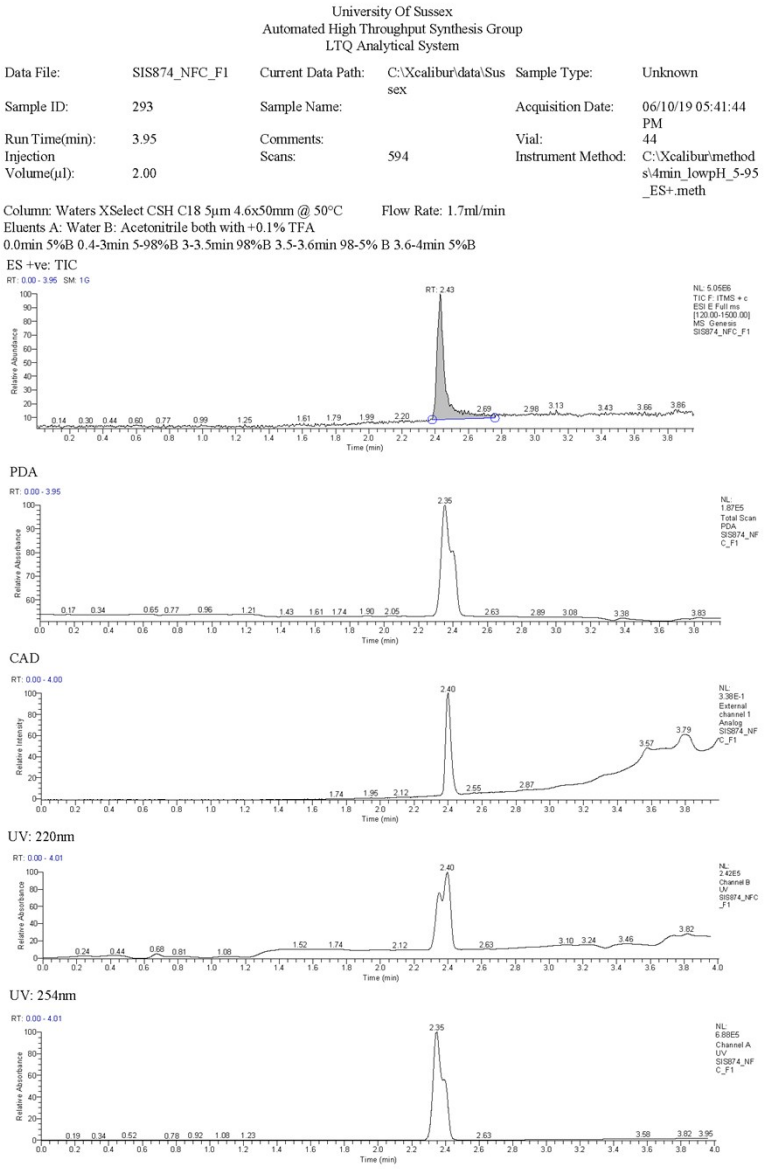


Figure S64. LCMS spectrum of propargylamine **5dba**.

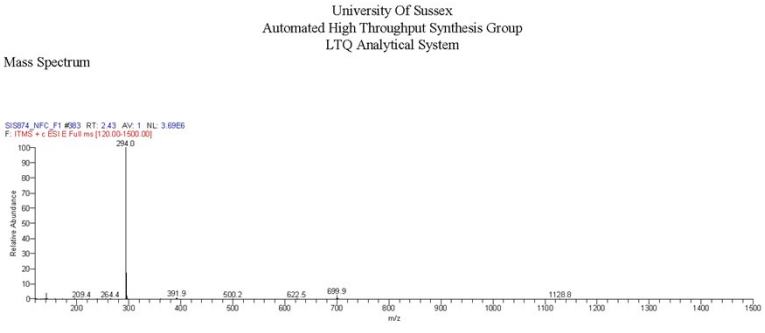
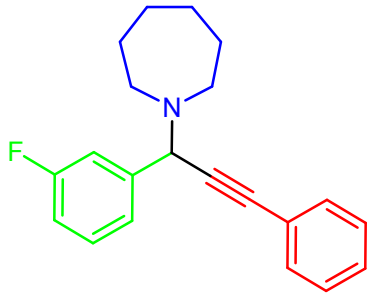


Figure S65. MS spectrum of propargylamine **5dba**.

1-(1-(3-fluorophenyl)-3-phenylprop-2-yn-1-yl)azepane (5dca)



A mixture of 3-fluorobenzaldehyde (1 mmol), azepane (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5dca was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.51 (dd, J = 6.6, 3.1 Hz, 2H), 7.49 (d, J = 6.7 Hz, 1H), 7.44 (d, J = 10.0 Hz, 1H), 7.36 – 7.27 (m, 4H), 6.97 (s, 1H), 4.88 (s, 1H), 2.72 (s, 4H), 1.68 (d, J = 12.5 Hz, 2H), 1.61 (s, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.8 (d, $^{1}J_{F,C}$= 245.5 Hz), 131.8, 129.4 (d, $^{3}J_{F,C}$= 9.1 Hz), 128.3, 128.2, 123.8 (d, $^{4}J_{F,C}$= 2.6 Hz), 123.1, 115.2 (d, $^{2}J_{F,C}$= 22.1 Hz), 114.3 (d, $^{2}J_{F,C}$= 20.5 Hz), 87.6, 86.1, 62.3, 62.3 (d, $^{4}J_{F,C}$= 1.8 Hz), 52.7, 28.8, 26.9.

MS (LCMS) m/z: ([M + H]$^{+}$) calcd for $C_{21}H_{23}NF$, 308.2; found, 308.0, R_t = 2.39 min. HRMS (ESI-FTMS) m/z: ([M + H]$^{+}$) calcd for $C_{21}H_{23}NF$, 308.1814; found, 308.1817.

(Method A) isolated yield = 190 mg, 62%, (method B) isolated yield = 215 mg, 70%.

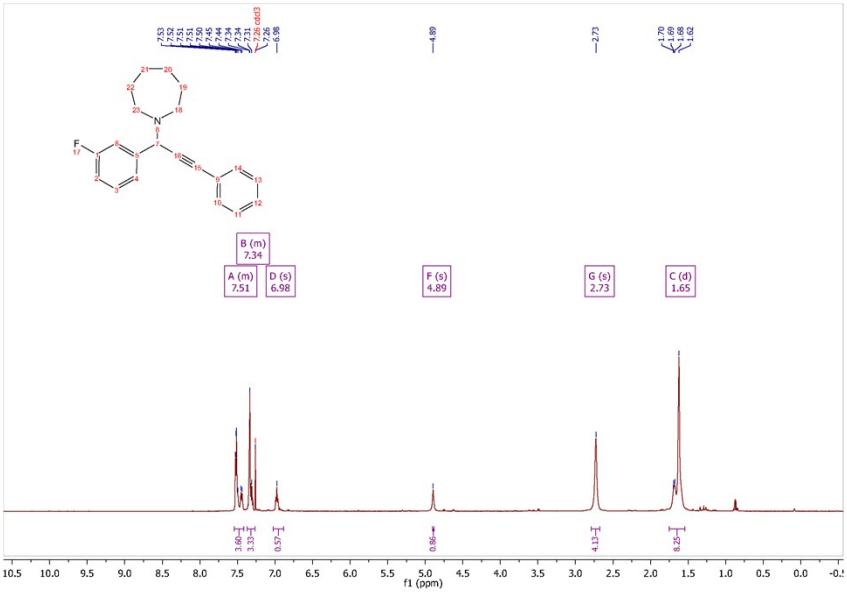


Figure S66. ^{1}H NMR spectrum of propargylamine **5dca.**

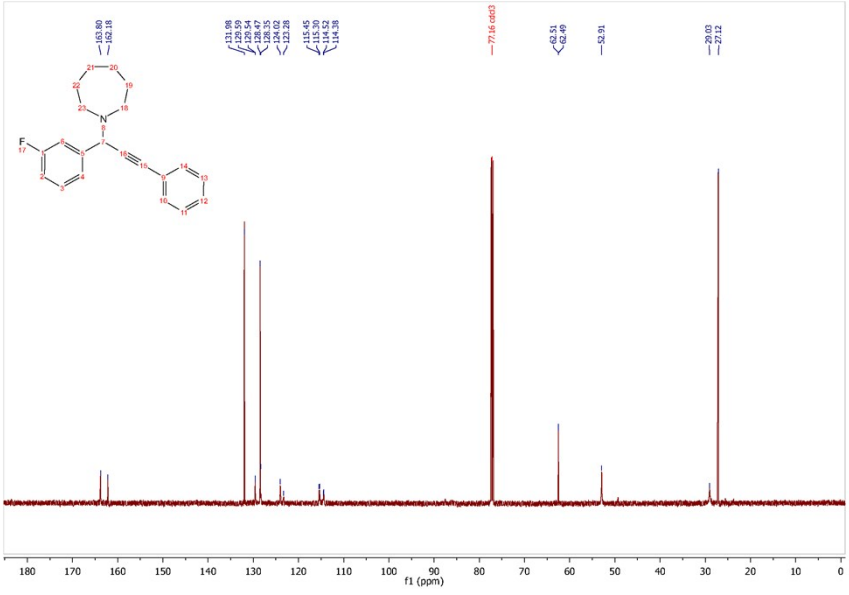


Figure S67. ^{13}C NMR spectrum of propargylamine **5dca**.

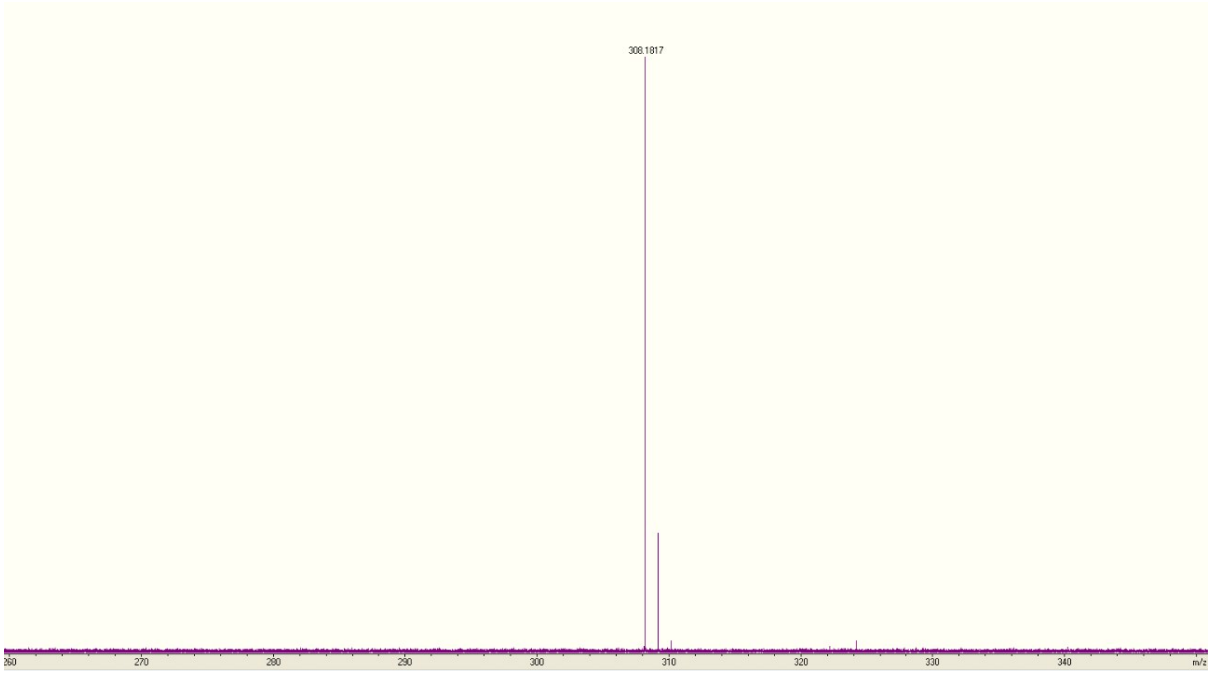


Figure S68. 5dca: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{21}H_{23}NF$, 308.1814; found, 308.1817.

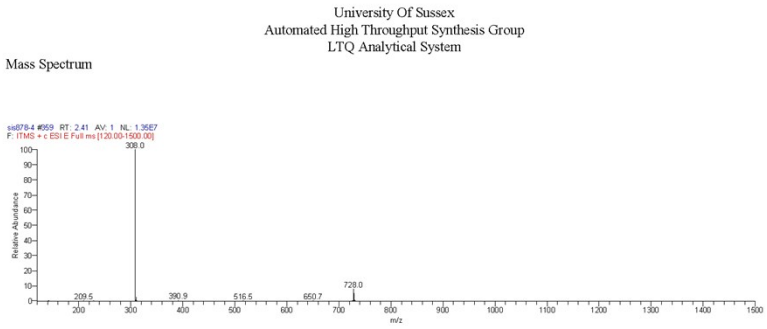


Figure S69. MS spectrum of propargylamine **5dca**.

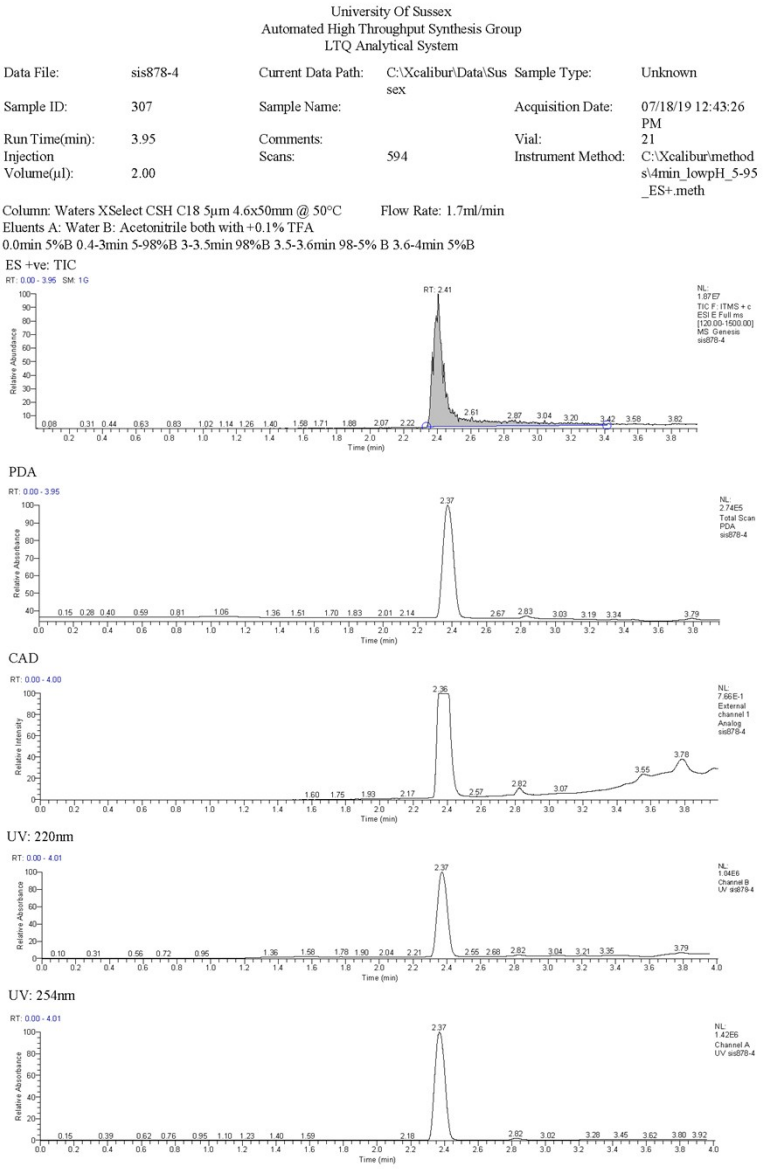
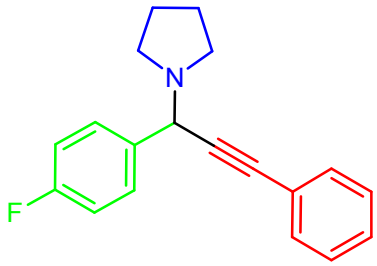


Figure S70. LCMS spectrum of propargylamine **5dca**.

1-(1-(3-fluorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (5eaa)



A mixture of 4-fluorobenzaldehyde (1 mmol), pyrrolidine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5eaa was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.64 – 7.58 (m, 2H), 7.51 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.34 (p, *J* = 3.7 Hz, 3H), 7.10 – 7.03 (m, 2H), 4.89 (s, 1H), 2.70 (ddt, *J* = 9.4, 6.2, 3.3 Hz, 4H), 1.86 – 1.77 (m, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.3 (d, $^{1}J_{F,C}$= 246.0 Hz), 136.9, 135.5 (d, $^{4}J_{F,C}$= 3.2 Hz), 131.9, 129.9 (d, $^{3}J_{F,C}$= 7.9 Hz), 128.4, 128.3, 123.2, 117.2, 15.1 (d, $^{2}J_{F,C}$= 21.5 Hz), 87.3, 86.5, 58.4, 54.1, 50.3, 23.6.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{19}FN$, 280.1; found, 280.0, R_t = 2.26 min.

(Method A) isolated yield = 53 mg, 19%, (method B) isolated yield = 87 mg, 31%.

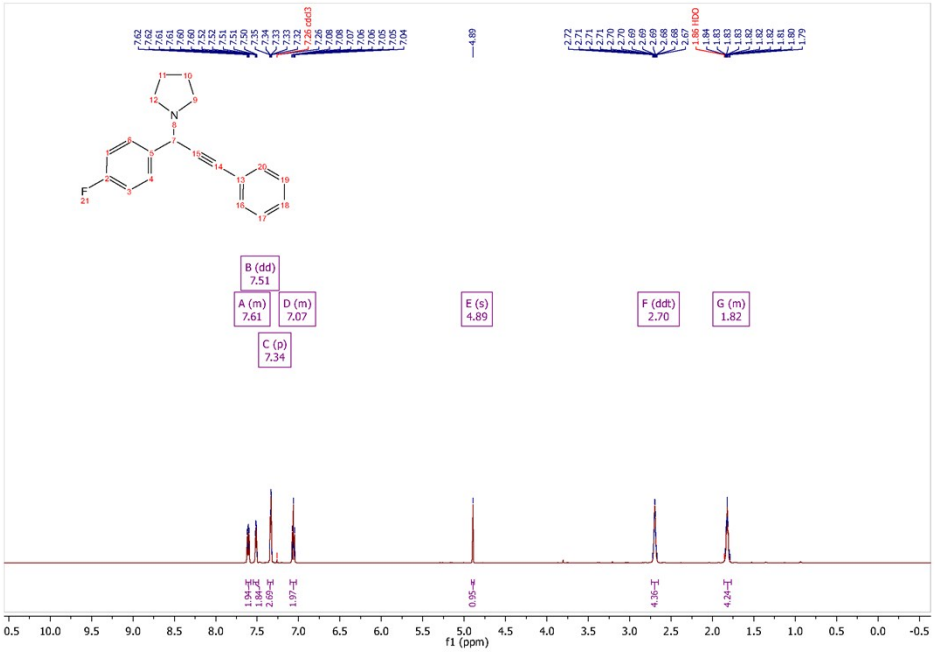


Figure S71. ^{1}H NMR spectrum of propargylamine **5eaa.**

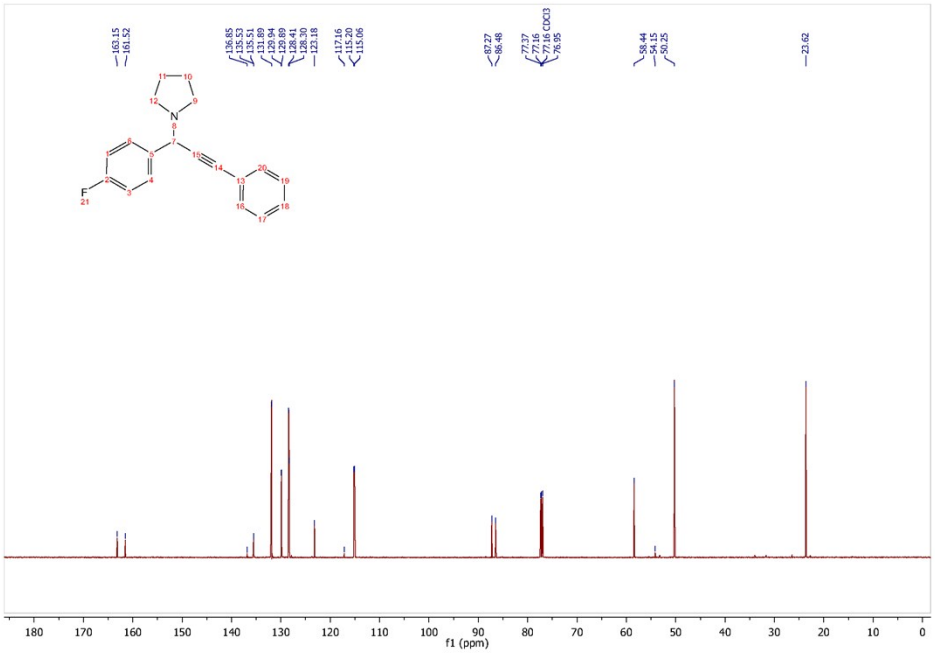


Figure S72. ^{13}C NMR spectrum of propargylamine **5eaa**.

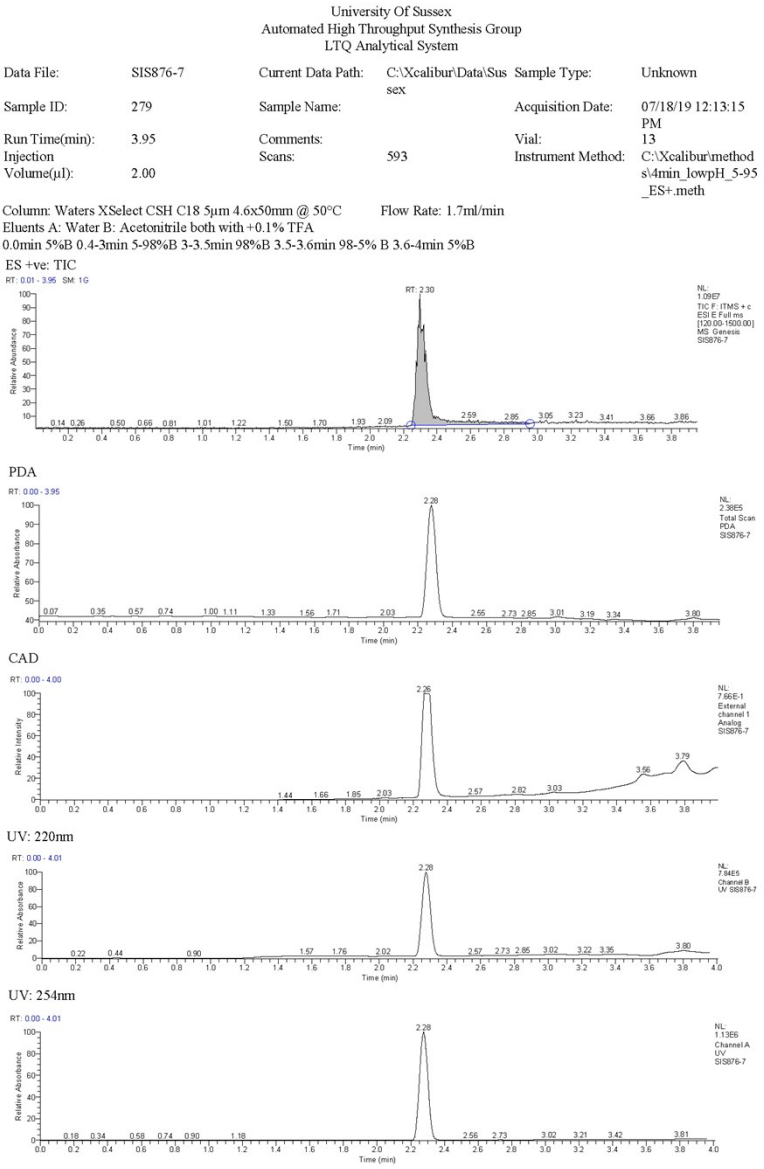


Figure S73. LCMS spectrum of propargylamine **5eaa**.

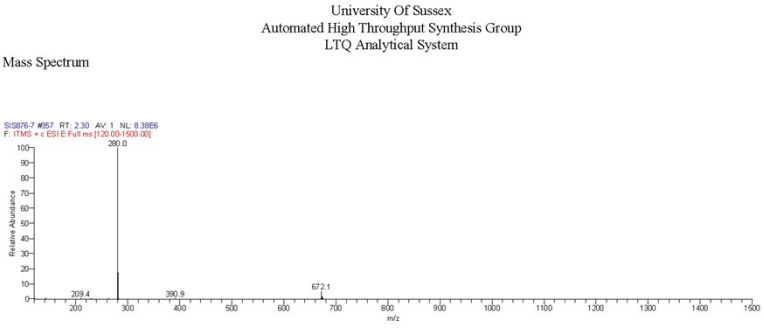
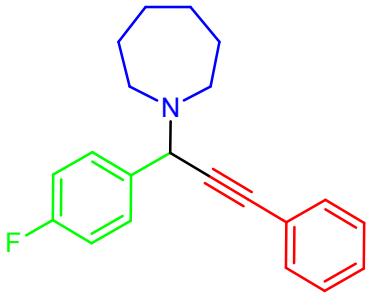


Figure S74. MS spectrum of propargylamine **5eaa**.

1-(1-(4-fluorophenyl)-3-phenylprop-2-yn-1-yl)azepane (5eca)



A mixture of 4-fluorobenzaldehyde (1 mmol), azepane (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (**1S**, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method

A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5eca was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.74 – 7.68 (m, 2H), 7.58 – 7.53 (m, 2H), 7.40 – 7.34 (m, 3H), 7.11 – 7.04 (m, 2H), 4.91 (s, 1H), 2.76 (ddd, J = 7.1, 4.6, 2.3 Hz, 6H), 1.76 – 1.70 (m, 1H), 1.71 – 1.58 (m, 5H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.2 (d, $^{1}J_{F,C}$= 245.5 Hz), 135.7 (d, $^{4}J_{F,C}$= 3.1 Hz), 131.9, 129.9 (d, $^{3}J_{F,C}$= 7.8 Hz), 128.4, 128.2, 123.4, 114.8, 114.8 (d, $^{4}J_{F,C}$= 21.3 Hz), 87.4, 86.6, 62.2, 52.7, 29.2, 27.1.

MS (LCMS) m/z: ([M + H]$^{+}$) calcd for $C_{21}H_{23}NF$, 308.2; found, 308.0, R_t = 2.39 min.

HRMS (ESI-FTMS) m/z: ([M + H]$^{+}$) calcd for $C_{21}H_{23}NF$, 308.1814; found, 308.1820.

(Method A) isolated yield = 49 mg, 16%, (method B) isolated yield = 92 mg, 30%.

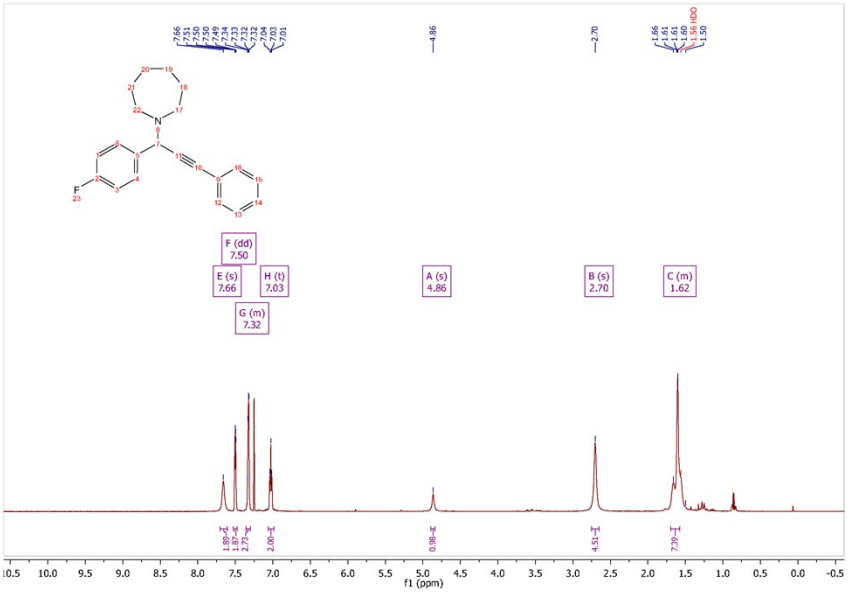


Figure S75. ^{1}H NMR spectrum of propargylamine **5eca.**

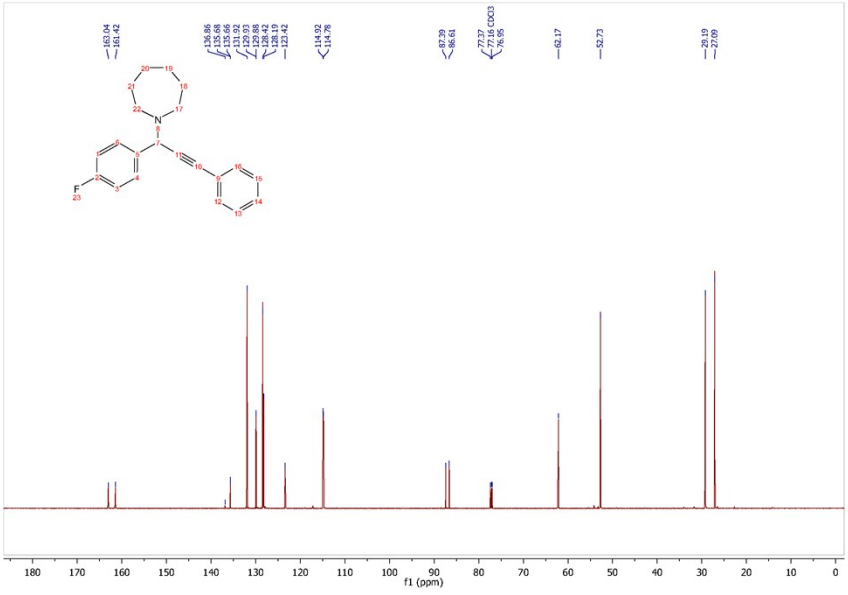


Figure S76. ^{13}C NMR spectrum of propargylamine **5eca**.

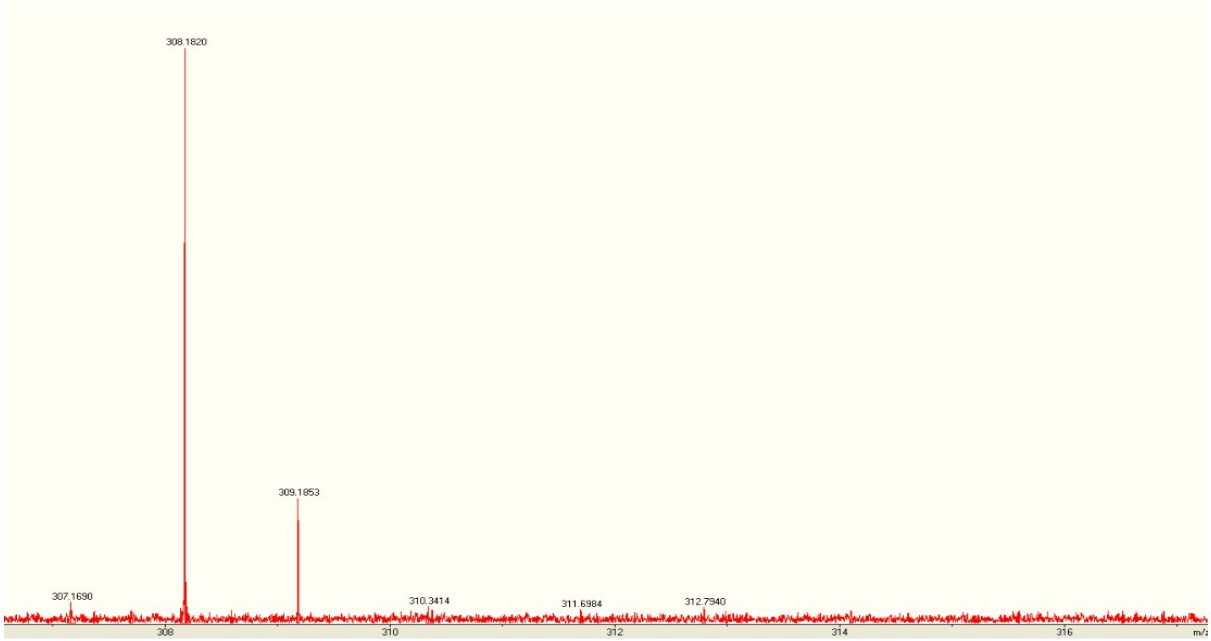


Figure S77. 5eca: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{21}H_{23}NF$, 308.1814; found, 308.1820.

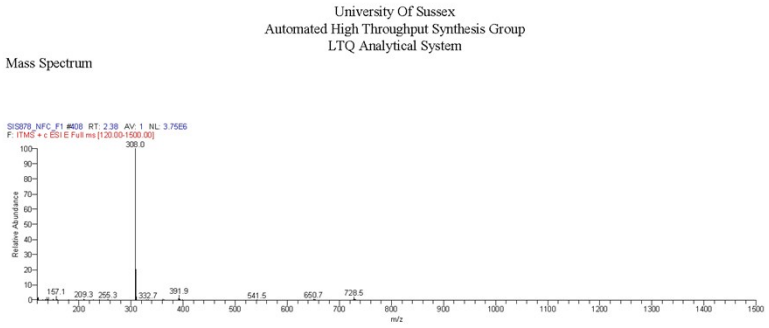


Figure 78. MS spectrum of propargylamine **5eca**.

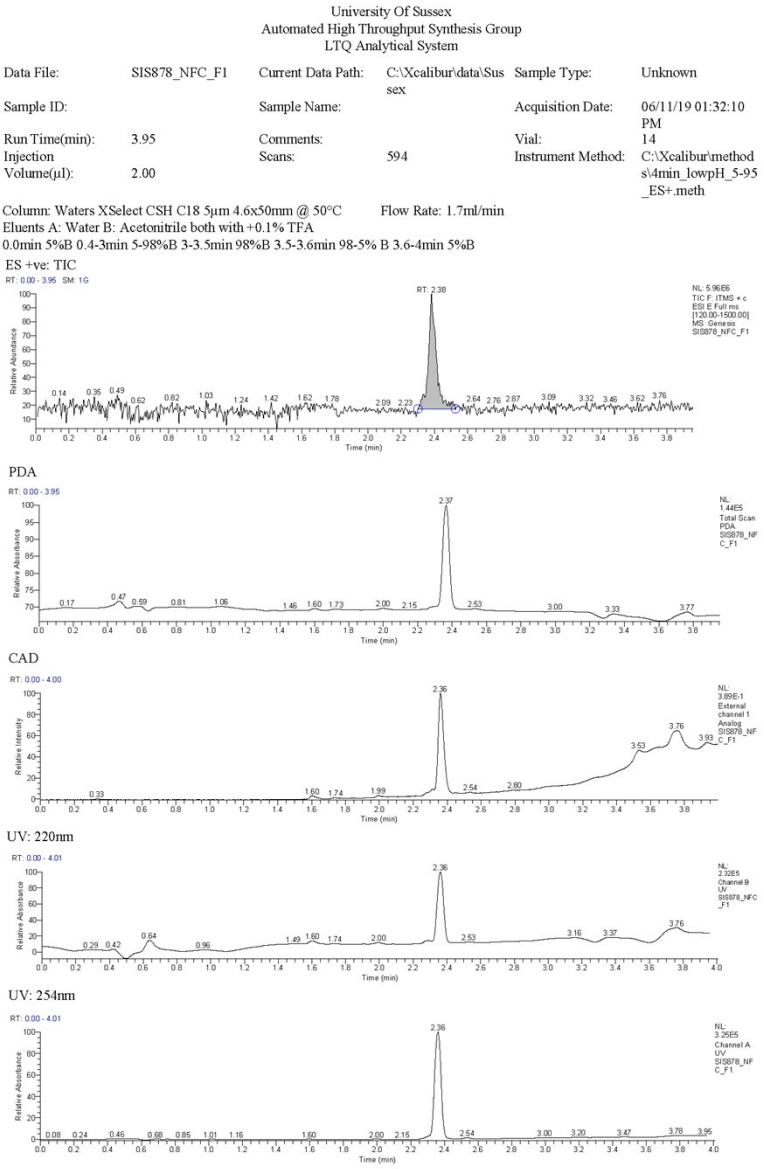
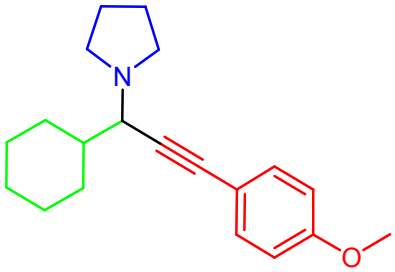


Figure S79. LCMS spectrum of propargylamine **5eca**.

1-(1-cyclohexyl-3-(4-methoxyphenyl)prop-2-yn-1-yl)pyrrolidine (5aab)



A mixture of cyclohexanecarboxaldehyde (1 mmol), pyrrolidine (1.1 mmol), 4-ethynylanisole (1.2 mmol), Cu catalyst (1S, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was

(Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5aab was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 2H), 6.86 – 6.79 (m, 2H), 3.80 (s, 2H), 3.33 (d, J = 8.3 Hz, 1H), 2.72 (t, J = 7.0 Hz, 2H), 2.64 (p, J = 5.8 Hz, 2H), 2.11 – 2.04 (m, 1H), 1.98 – 1.91 (m, 1H), 1.78 (q, J = 4.1, 2.6 Hz, 4H), 1.71 – 1.64 (m, 1H), 1.57 (tdt, J = 11.6, 8.2, 3.4 Hz, 1H), 1.32 – 1.04 (m, 4H).

^{13}C NMR (151 MHz, Chloroform-d) δ 159.3, 133.2, 116.0, 114.0, 86.4, 85.7, 61.5, 55.4, 50.2, 41.5, 30.9, 30.4, 26.9, 26.4, 26.4, 23.7.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}NO$, 298.2; found, 298.1, R_t = 2.42 min.

(Method A) isolated yield = 288 mg, 97%, (method B) isolated yield = 288 mg, 97%.

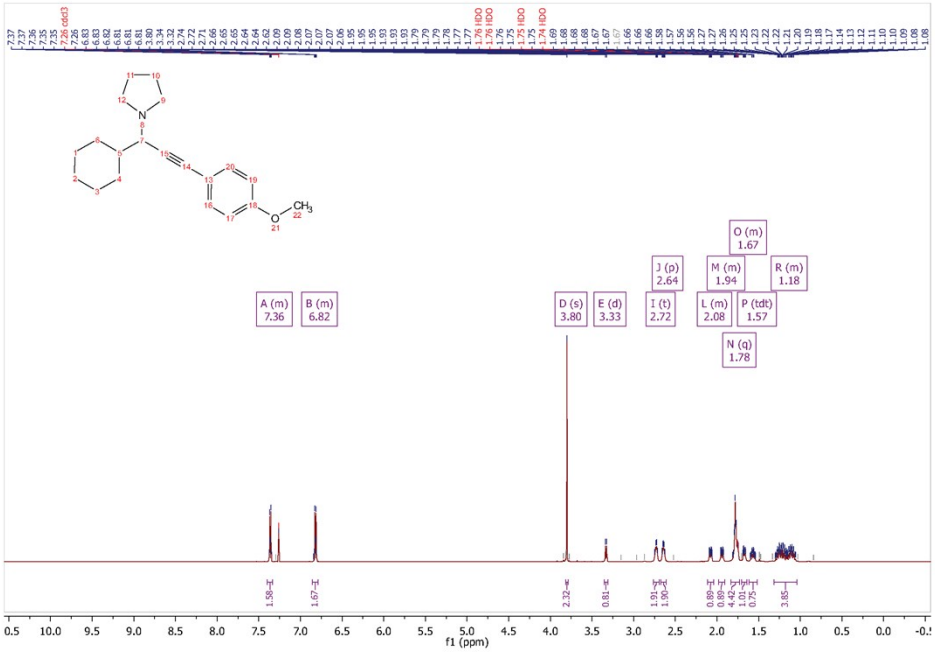


Figure S80. ^{1}H NMR spectrum of propargylamine **5aab.**

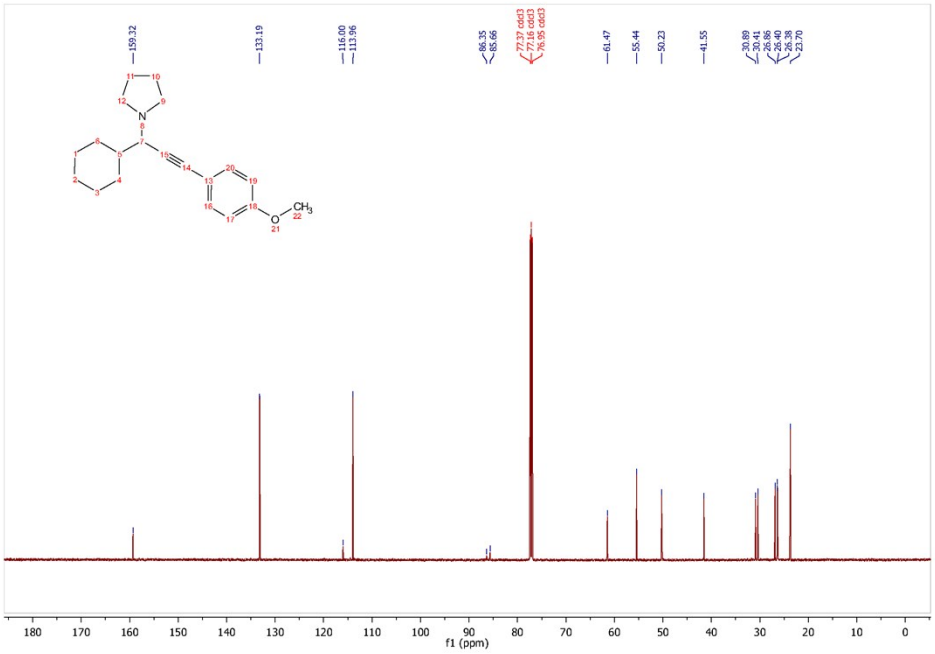


Figure S81. ^{13}C NMR spectrum of propargylamine **5aab**.

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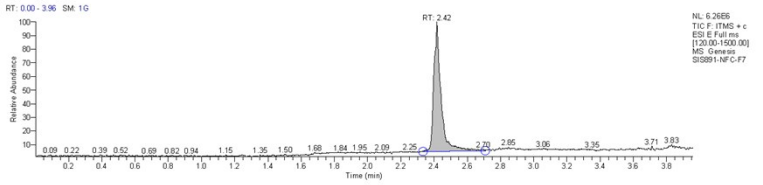
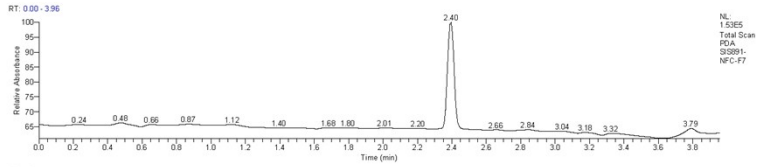
Data File:	SIS891-NFC-F7	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	SIS891_F7	Sample Name:		Acquisition Date:	07/02/19 04:51:56 PM
Run Time(min):	3.95	Comments:		Vial:	42
Injection Volume(µl):	2.00	Scans:	594	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

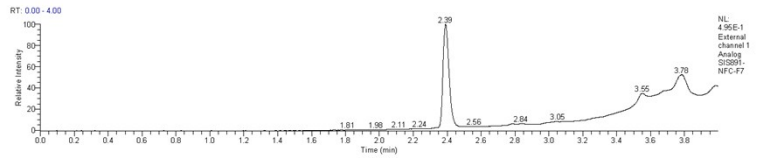
ES +ve: TIC



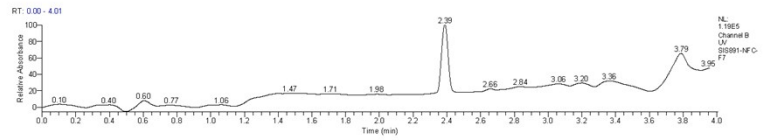
PDA



CAD



UV: 220nm



UV: 254nm

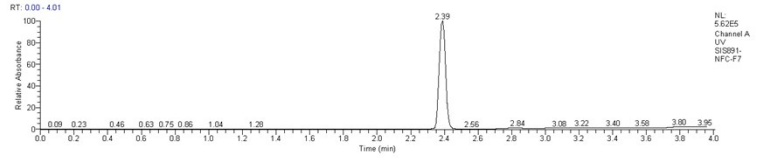


Figure S82. LCMS spectrum of propargylamine **5aab**.

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Mass Spectrum

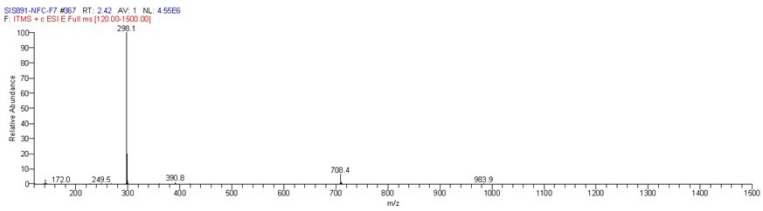
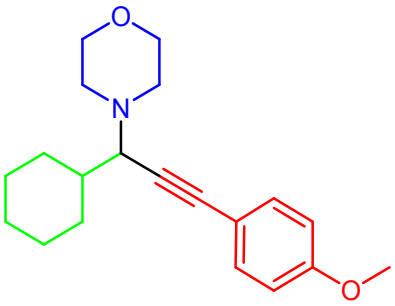


Figure S83. MS spectrum of propargylamine **5aab**.

4-(1-cyclohexyl-3-(4-methoxyphenyl)prop-2-yn-1-yl)morpholine (5adb)



A mixture of cyclohexanecarboxaldehyde (1 mmol), morpholine (1.1 mmol), 4-ethynylanisole (1.2 mmol), Cu catalyst (1S, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was

(Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5adb was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 – 7.34 (m,2H), 6.84 – 6.79 (m, 2H), 3.80 (s, 3H), 3.78 – 3.68 (m, 4H), 3.10 (d, J = 9.7 Hz, 1H), 2.68 (d, J = 18.6 Hz, 1H), 2.68 (s, 1H), 2.49 (s, 1H), 2.49 (d, J = 18.3 Hz, 1H), 2.12 – 1.99 (m, 2H), 1.76 (td, J = 12.1, 11.4, 5.6 Hz, 2H), 1.58 (d, J = 14.3 Hz, 2H), 1.32 – 1.14 (m, 3H), 1.08 – 1.00 (m, 1H), 0.95 (d, J = 12.1 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.4, 133.2, 115.7, 114.0, 110.2, 86.7, 85.1, 67.4, 64.2, 55.4, 50.1, 39.3, 31.1, 30.6, 26.9, 26.3, 26.2.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}NO_2$, 314.2; found, 314.0, R_t = 2.33 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}NO_2$, 314.2119; found, 314.2119.

(Method A) isolated yield = 298 mg, 95%, (method B) isolated yield = 313 mg, >99%.

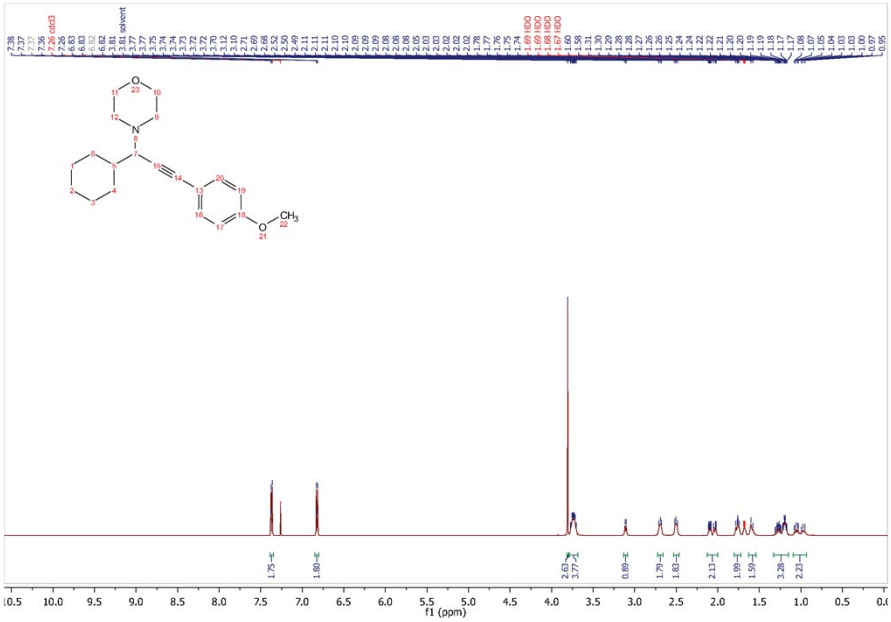


Figure S84. ^{1}H NMR spectrum of propargylamine **5adb**.

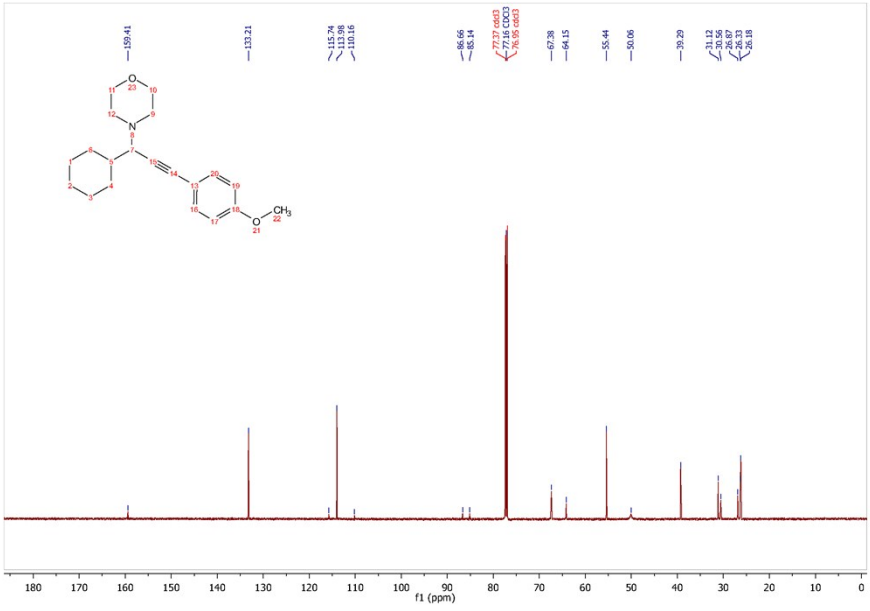


Figure S85. ^{13}C NMR spectrum of propargylamine **5adb**.

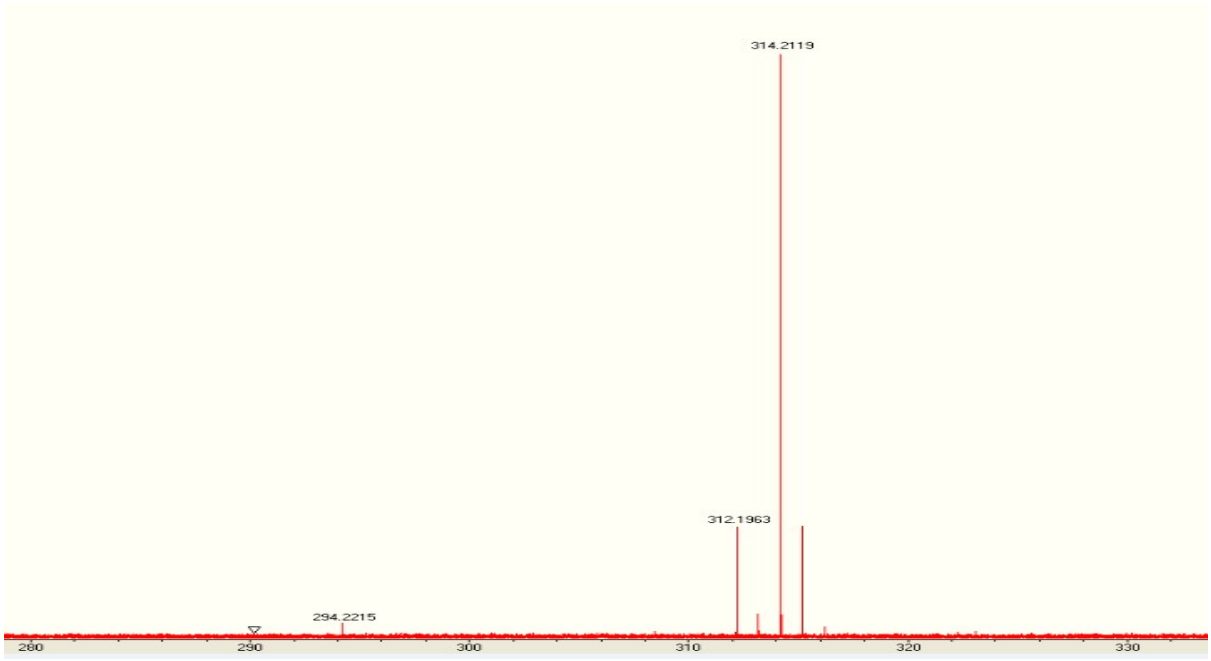


Figure S86. 5adb: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{20}H_{28}NO_2$, 314.2119; found, 314.2119.

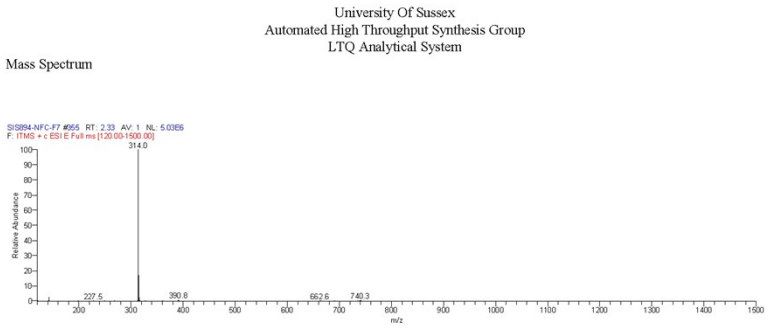


Figure S87. MS spectrum of propargylamine **5adb**.

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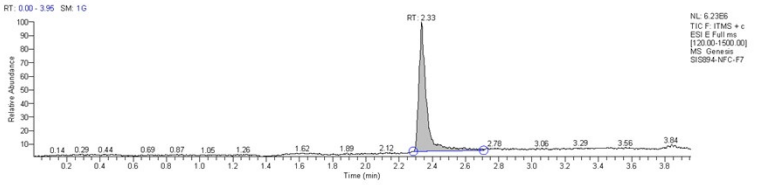
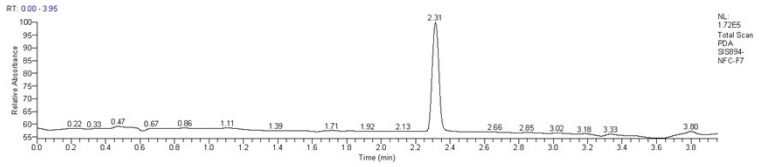
Data File:	SIS894-NFC-F7	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	313	Sample Name:		Acquisition Date:	07/02/19 05:45:04 PM
Run Time(min):	3.95	Comments:		Vial:	51
Injection Volume(µl):	2.00	Scans:	594	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

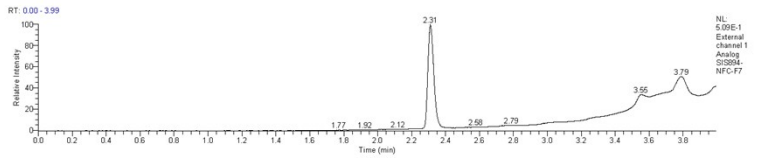
ES +ve: TIC



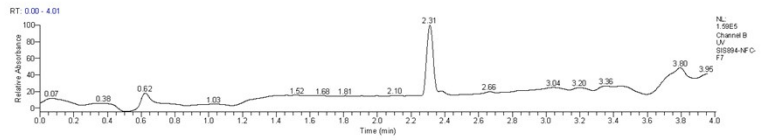
PDA



CAD



UV: 220nm



UV: 254nm

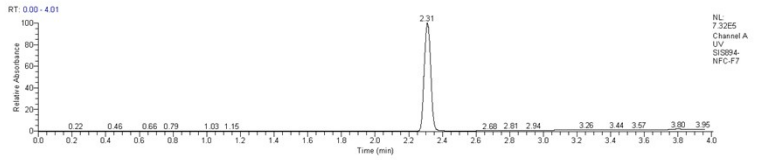
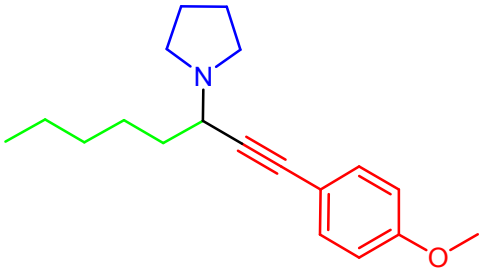


Figure S88. LCMS spectrum of propargylamine **5adb**.

1-(1-(4-methoxyphenyl)oct-1-yn-3-yl)pyrrolidine (5bab)



A mixture of hexanal (1 mmol), pyrrolidine (1.1 mmol), 4-ethynylanisole (1.2 mmol), Cu catalyst (1S, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5bab was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 – 7.34 (m, 2H), 6.85 – 6.81 (m, 2H), 3.81 – 3.79 (m, 3H), 2.97 (s, 1H), 1.95 – 1.84 (m, 4H), 1.75 – 1.66 (m, 2H), 1.46 (s, 2H), 1.36 – 1.25 (m, 6H), 0.93 – 0.81 (m, 5H).

^{13}C NMR (151 MHz, Chloroform-d) δ 159.9, 133.4, 114.1, 56.0, 55.5, 50.3, 49.9, 39.6, 34.2, 31.5, 26.4, 23.9, 22.6, 14.1.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{28}NO$, 286.2; found, 286.0, R_t = 2.43 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{28}NO$, 286.2170; found, 286.2171.

(Method A) isolated yield = 225 mg, 79%, (method B) isolated yield = 240 mg, 84%.

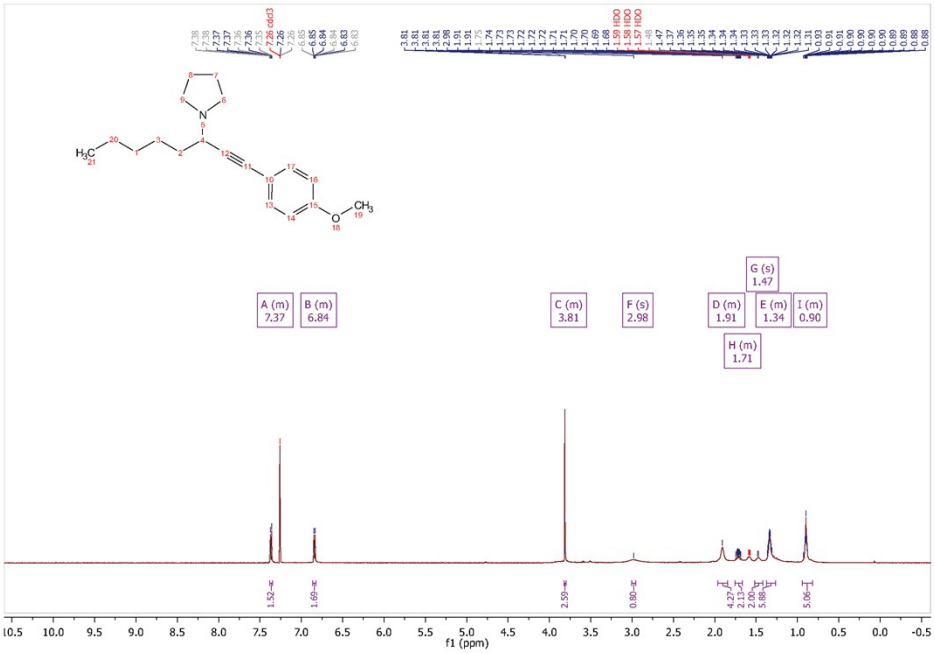


Figure S89. ^{1}H NMR spectrum of propargylamine **5bab**.

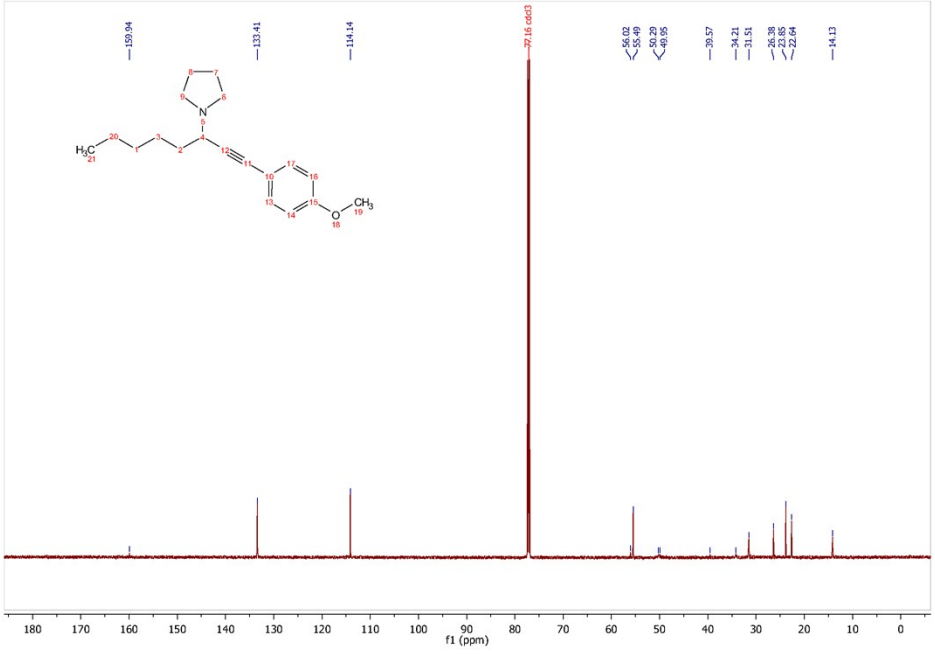


Figure S90. ^{13}C NMR spectrum of propargylamine **5bab**.

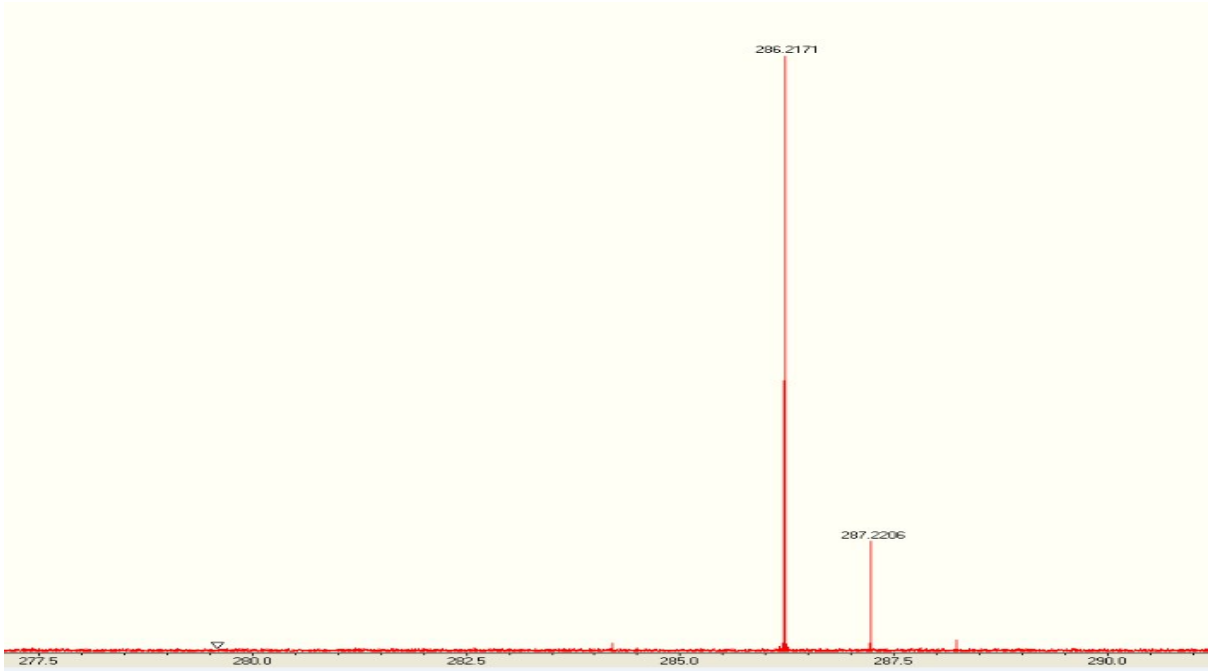


Figure S91. 5bab: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{28}NO$, 286.2170; found, 286.2171.

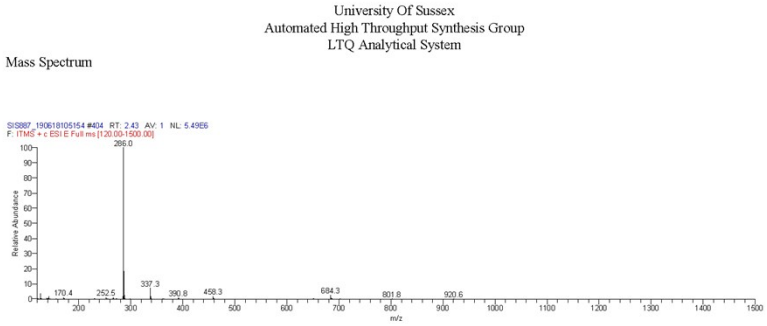


Figure S92. MS spectrum of propargylamine **5bad**.

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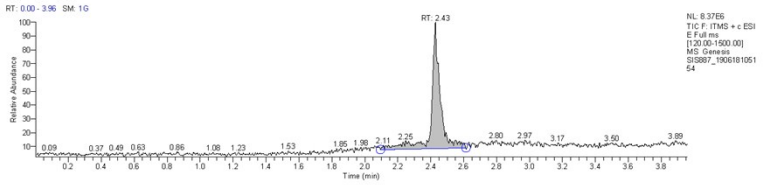
LTQ Analytical System

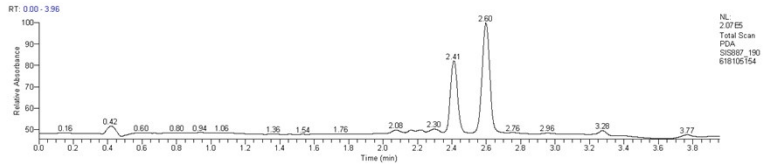
Data File:	SIS887_190618105154	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	285	Sample Name:		Acquisition Date:	06/18/19 10:51:54 AM
Run Time(min):	3.95	Comments:		Vial:	11
Injection Volume(µl):	2.00	Scans:	594	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

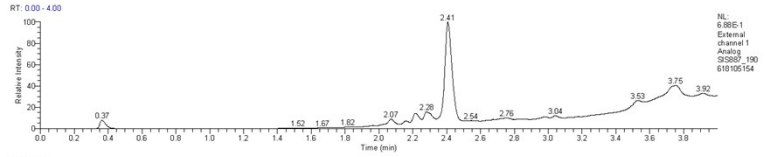
ES +ve: TIC



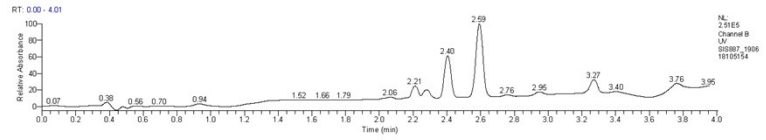
PDA



CAD



UV: 220nm



UV: 254nm

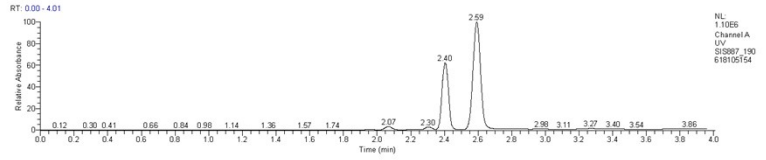
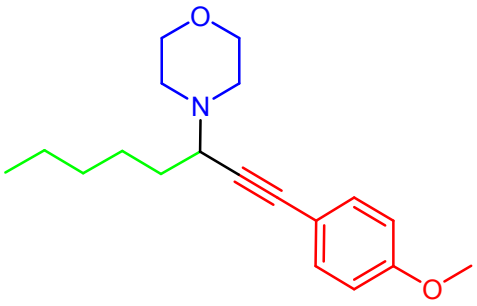


Figure S93. LCMS spectrum of propargylamine **5bad**.

4-(1-(4-methoxyphenyl)oct-1-yn-3-yl)morpholine (5bdb)



A mixture of hexanal (1 mmol), morpholine (1.1 mmol), 4-ethynylanisole (1.2 mmol), Cu catalyst (1S, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was (Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5bdb was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 – 7.33 (m, 2H), 6.85 – 6.79 (m, 2H), 3.80 (s, 3H), 3.68 (s, 4H), 3.48 (s, 1H), 2.74 (s, 2H), 2.57 (s, 2H), 1.62 – 1.50 (m, 3H), 1.45 (dp, J = 14.4, 7.6 Hz, 1H), 1.33 (dt, J = 8.5, 4.0 Hz, 4H), 0.93 – 0.84 (m, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 133.3, 114.0, 67.2, 58.5, 55.5, 49.9, 33.0, 31.7, 26.4, 22.7, 14.2.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{28}NO_2$, 302.2; found, 301.9, R_t = 2.40 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{28}NO_2$, 302.2119; found, 302.2119.

(Method A) isolated yield = 271 mg, 90%, (method B) isolated yield = 280 mg, 93%.

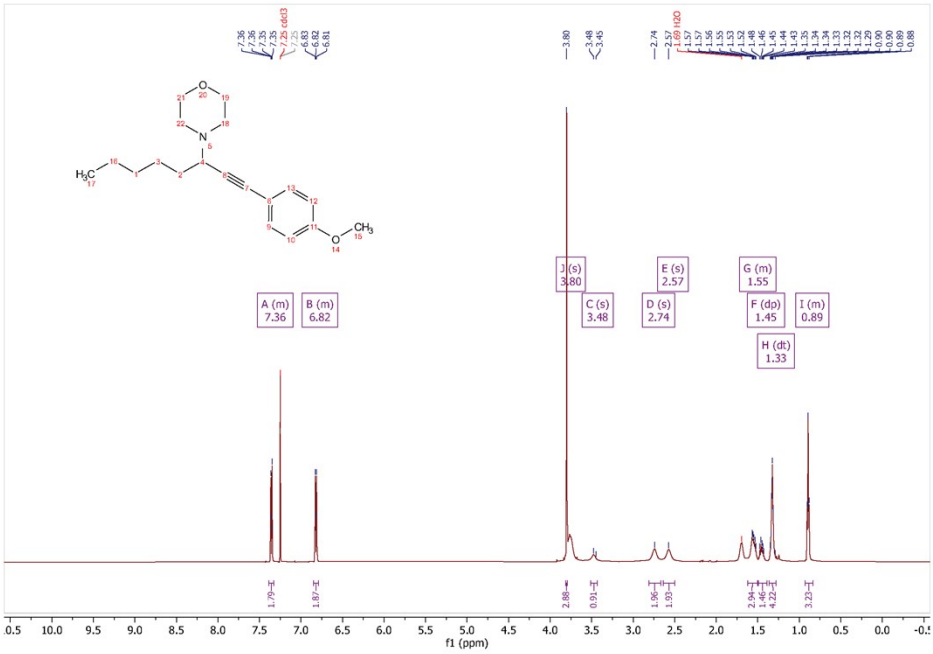


Figure S94. ^{1}H NMR spectrum of propargylamine **5bdb**.

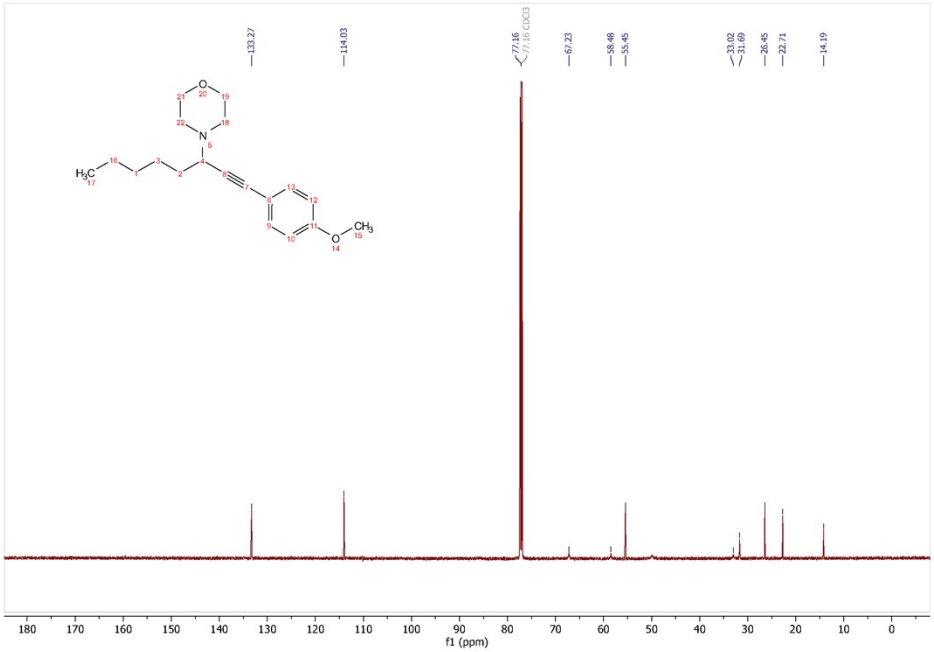


Figure S95. ^{13}C NMR spectrum of propargylamine **5bdb**.

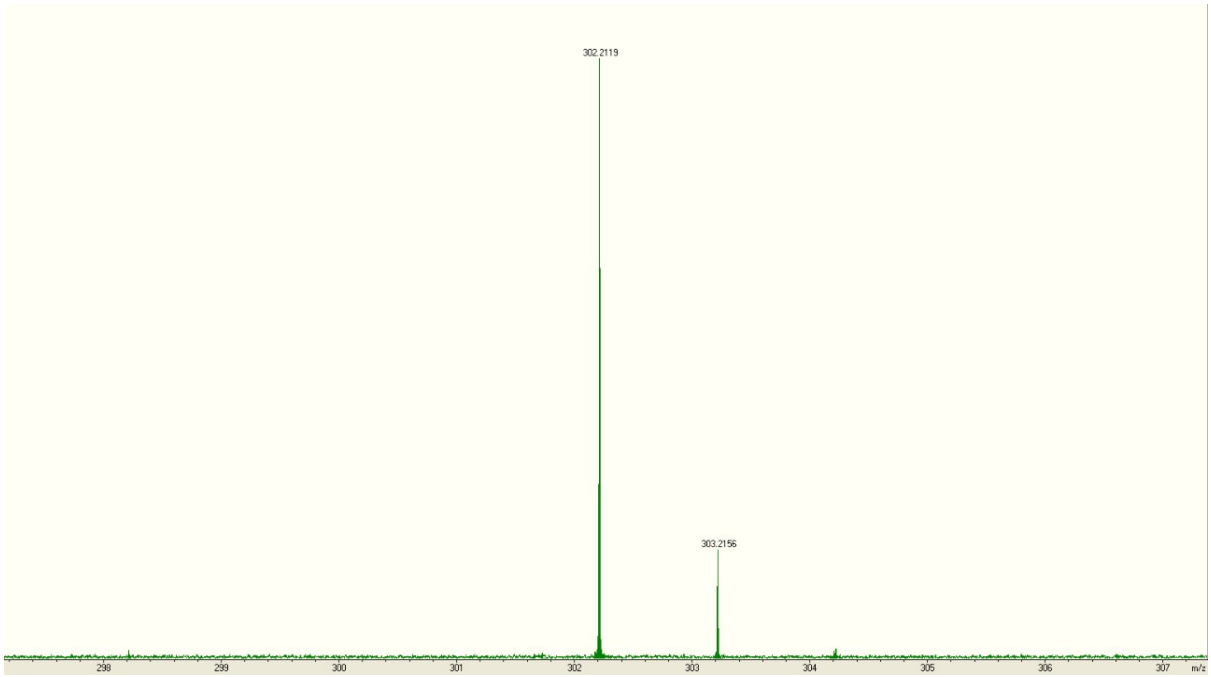


Figure S96. 5bdb: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{19}H_{28}NO_2$, 302.2119; found, 302.2119.

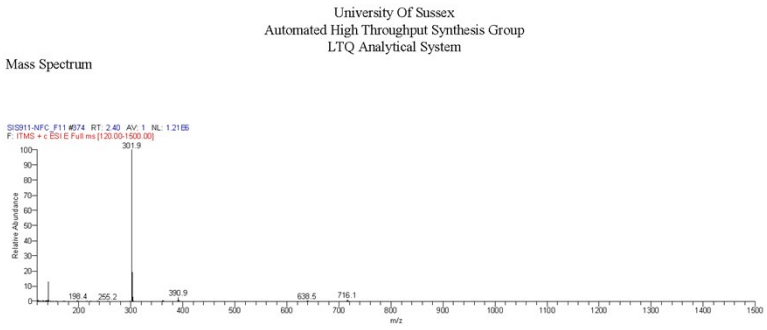


Figure S97. MS spectrum of propargylamine **5bdb**.

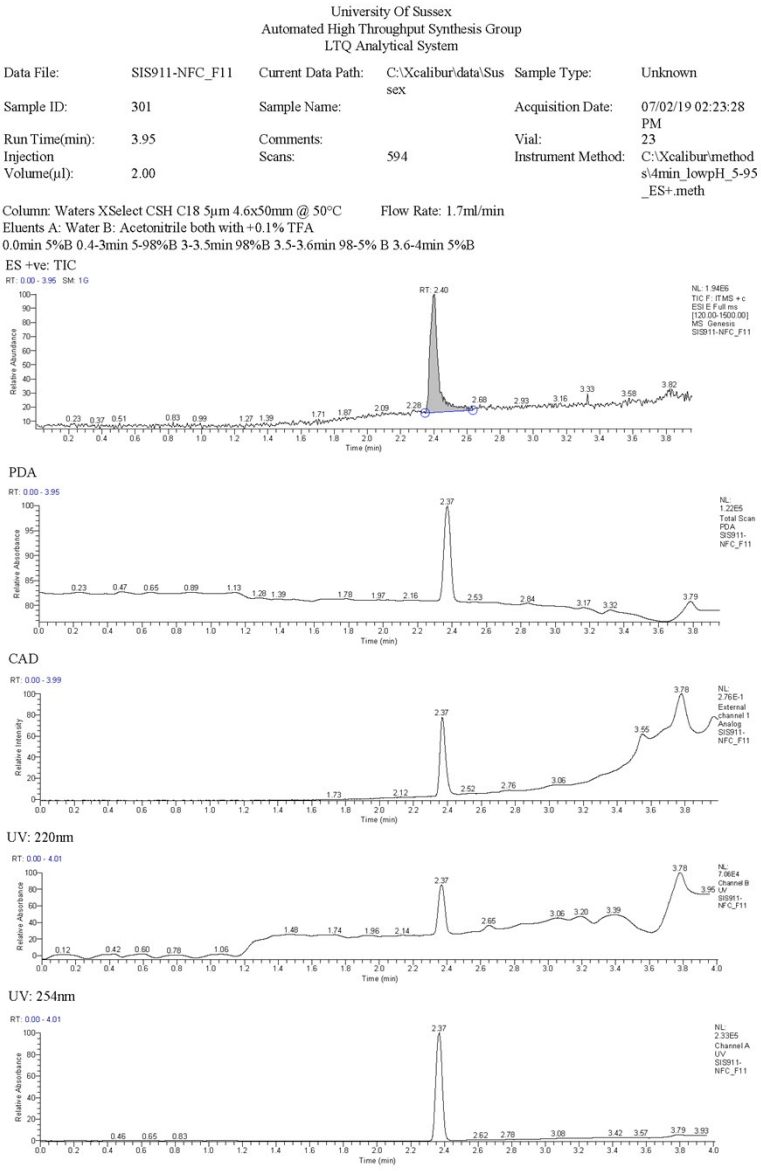
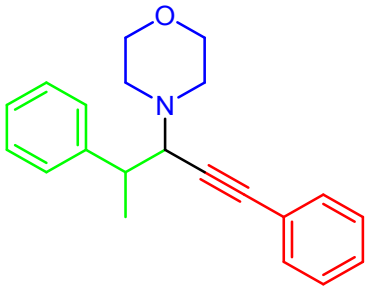


Figure S98. LCMS spectrum of propargylamine **5bdb**.

4-(1,4-diphenylpent-1-yn-3-yl)morpholine (5fda)



A mixture of 2-phenylpropionaldehyde (1 mmol), morpholine (1.1 mmol), phenylacetylene (1.2 mmol), Cu catalyst (1S, 2 mol%, based on aldehyde), and CH_2Cl_2 (dry, 2 mL) was placed in a sealed tube equipped with 4 Å molecular sieves (50 mg) and magnetic stir bar and was

(Method A) stirred at room temperature for 72 hours (Method B) exposed to microwave irradiation at 80˚C for 30 mins. The reaction was monitored by thin-layer chromatography (TLC). After completion, the (cooled to ambient temperature, in the case of method B) slurry is filtered through filter paper (to withhold the molecular sieves), the filtrate is evaporated under vacuum and ^{i}PrOH is added to it. The reaction mixture stands for one hour at 5˚C towards precipitation of the catalyst and subsequently is filtrated through filter paper (to withhold the recovered catalyst). The resultant solution is concentrated under reduced pressure, and the residue is then loaded into a flash column chromatography. The product is isolated through silica gel using a diethyl ether/petroleum ether (fraction 40-60) mixture as the gradient eluent (01:99-30:70 v/v). Propargylamine 5fda was obtained by each method as a yellow oil. Method B provided the sample whose purity is documented.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 – 7.52 (m, 2H), 7.50 – 7.47 (m, 2H), 7.45 – 7.27 (m, 16H), 4.64 (d, J = 5.9 Hz, 1H), 4.58 (d, J = 5.3 Hz, 1H), 4.02 – 3.92 (m, 6H), 3.60 (p, J = 6.9 Hz, 1H), 3.53 (td, J = 7.0, 5.3 Hz, 1H), 1.60 (d, J = 6.9 Hz, 3H), 1.52 (d, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 141.2, 140.6, 132.1, 131.9, 130.1, 130.0, 129.2, 129.0, 128.8, 128.8, 128.6, 128.2, 128.2, 127.3, 120.6, 120.6, 93.5, 93.4, 78.3, 78.0, 66.0, 65.4, 63.9, 54.4, 42.4, 41.4, 40.2, 20.3, 19.5.

MS (LCMS) m/z: ([M + H]$^+$) calcd for $C_{21}H_{24}NO$, 306.2; found, 306.1, R_t = 2.32 min. HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{21}H_{24}NO$, 306.1857; found, 306.1855.

(Method A) isolated yield = 217 mg, 71%, (method B) isolated yield = 262 mg, 62%.

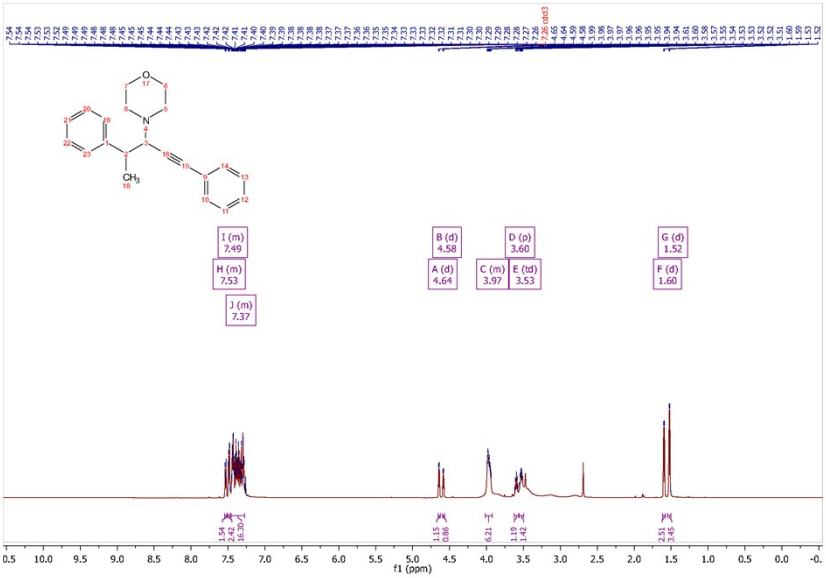


Figure S99. ^{1}H NMR spectrum of propargylamine **5fda**.

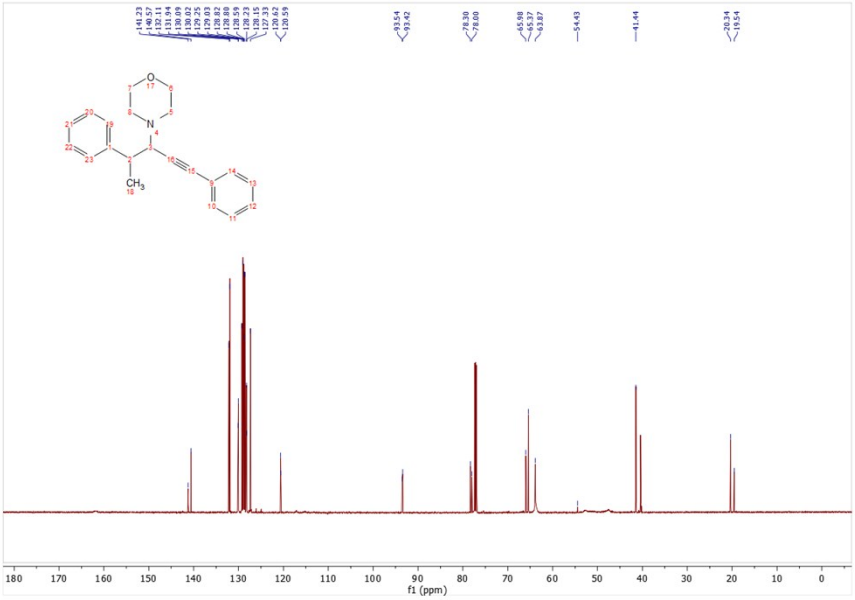


Figure S100. ^{13}C NMR spectrum of propargylamine **5fda**.

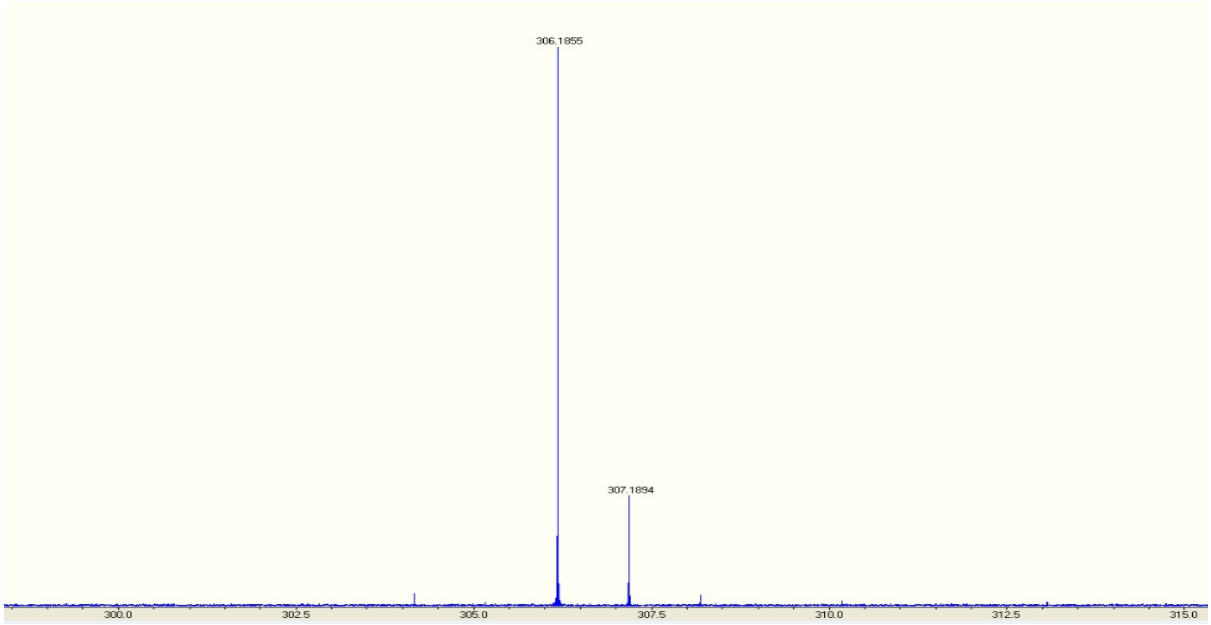


Figure S101. 5fda: HRMS (ESI-FTMS) m/z: ([M + H]$^+$) calcd for $C_{21}H_{24}NO$, 306.1857; found, 306.1855.

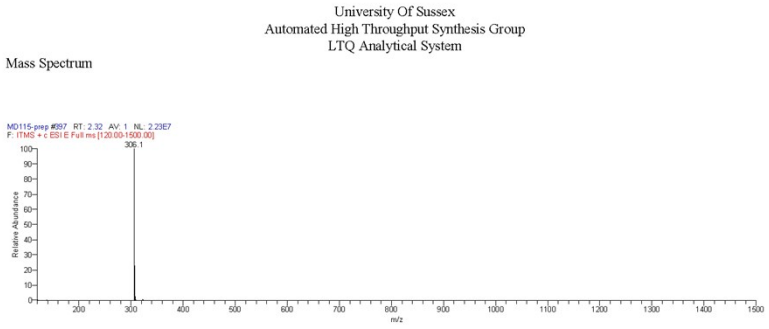


Figure S102. MS spectrum of propargylamine **5fda**

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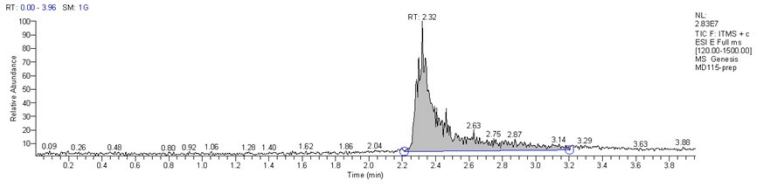
LTQ Analytical System

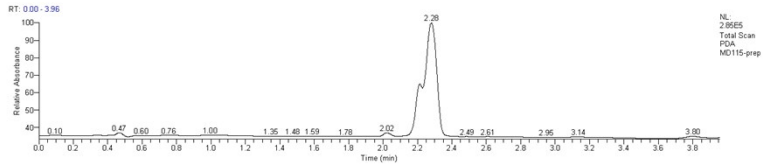
Data File:	MD115-prep	Current Data Path:	C:\Xcalibur\data\Sussex	Sample Type:	Unknown
Sample ID:	mwt 305	Sample Name:		Acquisition Date:	05/09/19 03:16:28 PM
Run Time(min):	3.95	Comments:		Vial:	5
Injection Volume(µl):	5.00	Scans:	594	Instrument Method:	C:\Xcalibur\methods\4min_lowpH_5-95_ES+.meth

Column: Waters XSelect CSH C18 5µm 4.6x50mm @ 50°C Flow Rate: 1.7ml/min
Eluents A: Water B: Acetonitrile both with +0.1% TFA
0.0min 5%B 0.4-3min 5-98%B 3-3.5min 98%B 3.5-3.6min 98-5% B 3.6-4min 5%B

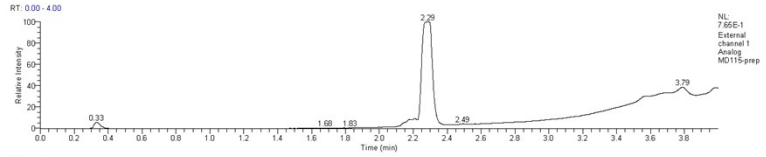
ES +ve: TIC



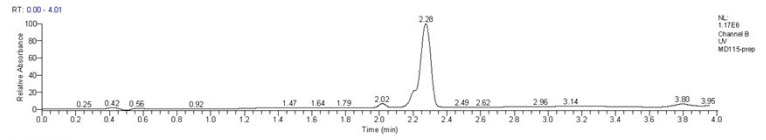
PDA



CAD



UV: 220nm



UV: 254nm

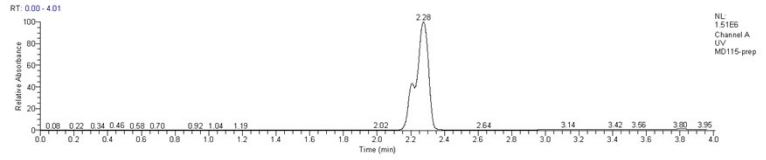


Figure S103. LCMS spectrum of propargylamine **5fda**.

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