Electronic Supplementary Material (ESI) for Green Chemistry.

SUPPORTING INFORMATION

Continuous Niobium Phosphate Catalysed Skraup Reaction for Quinoline Synthesis from Solketal

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1. General Information

Reagent and solvents were used as received without further purification unless otherwise specified. Glycerol, Solketal, and aniline were purchased from Aldrich and toluene from Fisher. Water was distilled and MilliQ grade. The ^{1}H and ^{13}C NMR spectra were recorded on a 300, 400 or 500 MHz Bruker DPX spectrometer. ^{1}H NMR chemical shifts were reported in ppm using tetramethylsilane (TMS, $\delta = 0.00$ ppm) as the internal standard and in $CDCl_3$ (^{1}H, $\delta = 7.26$ ppm, ^{13}C, $\delta = 77.2$ ppm). The data of ^{1}H NMR was reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J* value) in Hz and integration. GC/FID analysis were run on a Shimadzu GC/FID-2014 spectrometer using and Restek Rtx-1 capillary column (L=30 m, Ø=0.32 mm, film=0.25 µm). The following conditions were used. Carrier gas: N2; flow rate: 5.0 mL/min; split ratio: 1:10; initial T: 50 °C (3 min), ramp rate: 15 °C/min; final T: 240 °C (10 min). X-ray crystal analysis was collected at 120 K with a monochromatic wavelength of 1.54184 with a GV1000, Atlas diffractometer. Thermogravimetric analysis was performed on a TGA Q500 V20.13 Build 39, with a maximum temperature of 1000 °C, under air flow, and heating rate of 10 °C/min. Column chromatography were performed using silica gel 40-63 µm purchased from Aldrich. Mass spectrometry analysis was run on a Bruker MicroTOF equipped with an Electron Spray Ionization technique. The catalysts employed here was niobium phosphate $NbOPO_4$ (NbP), supplied by Companhia Brasileira de Metalurgia e Mineração (CBMM) in powder form and used without any treatment.

2. The Continuous Flow apparatus

The continuous flow experiments were carried out under high pressure and high temperature represented in Figure S1. The reactor system consists of two ¼'' tubes used as the pre-mixer and reactor, stainless steel tubing, including 1/16'' pipes with appropriate Swagelok fittings and a series of liquid pumps and taps. The scale-up of the reaction was investigated by adopting a different configuration. The mixer and the reactor were replaced by a 4 tubular reactors in series (Stainless steel tube, ¼" o.d., and 75 mm in length) as shown in Figure S2 and detailed in previous work.[1] The first tube was filled with sand (**Mixer**) and the three remaining tubes with 3.6 g (3 x 1.2g) of NbP (Reactor, **Rb**). A single aluminum block, with four heating cartridges, was used to heat the multiple reactors.

The CO_2 was pumped by a Jasco PU-1580-CO_2 pump, and-the organic reagents were introduced into the system by Jasco PU-980 HPLC pumps. All the organics and the CO_2 were pumped through the 1/16'' stainless steel piping into the pre-mixer, where they were preheated and mixed. Then the mixed reagents flowed into the reactor where the reaction took place. Both the pre-mixer and the reactor were heated by Eurotherm 2616 heaters, and the temperature was monitored by a Picologger. To protect from overheating a temperature trip (Eurotherm 2122) was introduced to the system. After the reactor the mixture was real-time analyzed by a Shimadzu GC-2010 spectrometer. The pressure of the whole system was controlled by a Jasco BP-1580-81 back pressure regulator (BPR), and monitored by a pressure sensor placed before the pre-mixer.

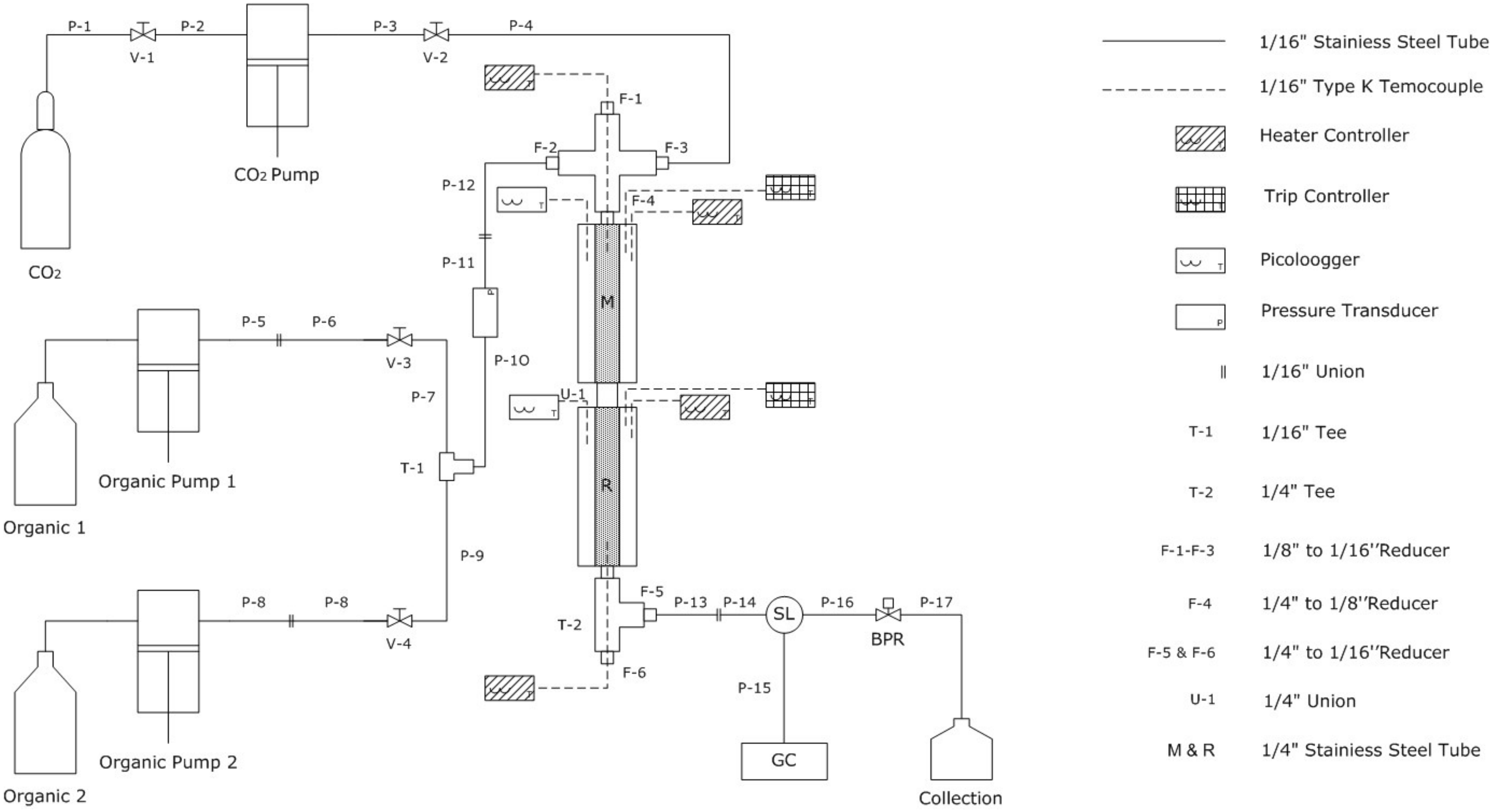


Figure S1. Schematic of the high pressure continuous flow apparatus used for the niobium catalysed Skraup quinoline synthesis. Organic were introduced into the system using JascoPU-980 HPLC pumps 1 and 2 reaching first mixer M then flowed into the reactor(s) (**Ra** in this scheme or **Rb** for the triple reactor design) heated via temperature controlled aluminium blocks. Back pressure regulator (BPR) Jasco BP-1580-81 controls the pressure of the system. Thermocouples: monitor reactor temperature internally and externally. Pressure Transducer: monitors systems. Temperature and pressure trips were introduced to the system.

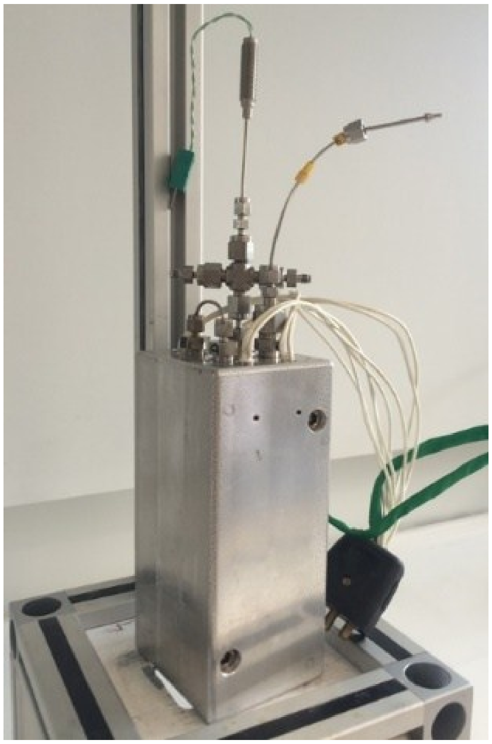


Figure S2. Photograph of constructed multi-pass tubular reactor consisting of 4 stainless ¼” tubes (¼” o.d., 75 mm in length, 1 mm wall thickness) that are held in place and sealed with Swadgelok fittings and frits. A single heating block allows the heating using four heating cartridges.

3. Operating Procedures

CAUTION !!! HIGH PRESSURE AND TEMPERATURE REQUIRE THE IMPLEMENTATION OF TRIPS AND SENSORS LINKED TO A TRIPBOX. OVER AND UNDER LIMITS MUST BE SET TO AVOID OVERHEATING OR OVERPRESSURE OCCURING.

3.1. Start-up Procedure

1. The solutions were prepared in advance and used toluene as solvent.
2. The reactor was filled with Niobium phosphate hydride (approximately 1.2 g), and then the tube was resealed into the flow system. The reactor had sieves on both ends of the tube to avoid the catalyst powder being washed away.
3. Leak detection was performed by setting the BPR to a desired pressure, pumping CO_2 into the system, and using Snoop™ leak detection liquid to test the leak proofness of every fitting.

4. If all fittings were pressure-tight, both the pre-mixer and the reactor were coated by the heating blocks, meantime making sure that the heating block controllers, temperature trips and Picologger cables were appropriately connected.
5. Then the system pressure and temperature trips were checked. Both the pressure trip and temperature trips were set at a higher level than the experiment maximum.
6. The overpressure of the CO_2 pump was set a bit higher than the other pressure trips to make sure CO_2 could be pumped through the system if the other trips were initiated.
7. The starting conditions (organics flow rates and temperature) for the experiment were set as desired.
8. First the CO_2 pump was started, and then the heating controllers were turned on.
9. Then the organics were pumped against closed corresponding taps to ensure that the pump head was not vacated by carbon dioxide when the tap was opened.
10. After that the appropriate taps were opened to allow the organics to be pumped into the system.
11. Before proceeding the system was allowed to reach an equilibration state with the organics (approximately 10-20 minute).
12. The online GC spectrometer was turned on and connected to the desktop computer. Then GC Solutions™ was opened. A batch file was created in GC solutions software to collect multiple chromatographs. It was started simultaneously with the data logging software (Picologg Recorder).
13. By using the MATLAB GUI (see A. J. Parrott PhD thesis for full details reference), the organic pumps, the CO_2 pump, the heating controllers and the BPR were programmed to change at various times throughout the experiment, exploring different reaction conditions.
14. The system is ready to carry out an automated experiment.

3.2. System shutdown and cleaning.

Once the experiment was complete, the aluminum blocks were set to cool down at r.t. while pure methanol (50 ml at 0.5 mL/min) was delivered to the system. Immediately after, CO_2 was pumped to flush the methanol away. Afterward, the system was vented to the atmospheric pressure and the reactor emptied.

4. Continuous Flow Skraup reaction over niobium phosphate (NbP)

4.1. Preliminary procedure

The substrates (aniline or solketal or glycerol or acetone) solutions were prepared using toluene or water as solvent at these following concentrations: 0.275, 0.550 and 0.825 M. The **Mixer** was filled with sand and the **Reactor** (**Ra**) with 1.2 g of NbP. Prior to the reaction, a leak detection was performed by filling the system with 100 bar of CO_2 and checking all the fitting with a liquid leak detector.

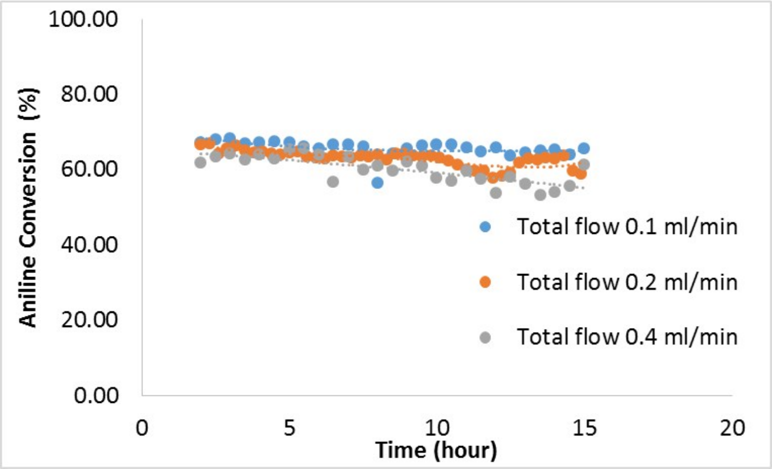
4.2. General procedure

A preliminary conditioning of the apparatus was carried out by delivering the two reactants solutions to the system at flow rates in the range of 0.05-0.2 mL/min for a minimum of 5 minutes. Afterwards, the **BPR** was set to the operating pressure (from atmospheric to 100 bar). When the pressure was stabilized, both the **Mixer** and the Reactor (**R_a** or **R_b**) were heated at the working temperature (225-300 °C). Then, the reaction mixture was analyzed by the in-line GC/FID at regular intervals (usually every 30 min) for 24-72 h. As an example: The reaction was carried out using solutions of aniline and solketal in toluene (0.275 M), were allowed to react at 0.1 mL/min over 1.2 g of NbP at 250 °C and 100 bar for 1 hours. The brown oily residue was purified by flash column chromatography (FCC) using cyclohexane:ethyl acetate (CyHex:AcOEt) and characterized by ^1H, ^{13}C NMR and HRMS-ESI analysis.

5. Effect of the flow rate on the Skraup reaction over niobium phosphate (NbP)

The total flow rate effect on the Skraup reaction between aniline and solketal has been carried out at 250 °C and 10 MPa. As depicted in Figure S3, tests proved that the flow rate had a minor effect, if any, on the conversion of aniline. The latter remained substantially steady at 55-60% for the first 10-15 h of reaction (Figure S3a). Then, if the experiments were prolonged, the higher flow rates (0.2 mL/min and 0.4 mL/min) showed a slight decrease of the conversion to 55% during the first 15 hours. The selectivity towards quinoline (approx. 55%) was also not affected by the flow rate when this was set in the range of 0.1-0.2 mL/min; though, as for the conversion, the selectivity decreased to 40 % at 0.4 mL/min (Figure S3b).

a)



b)

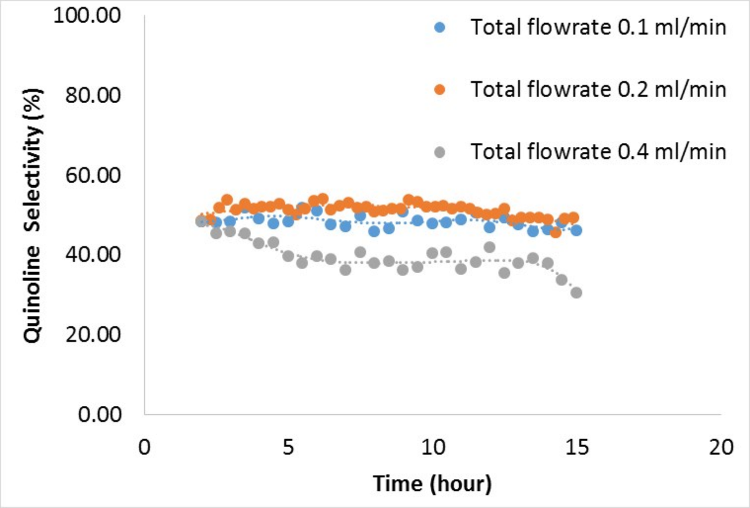


Figure S3. Influence of the residence time. a) Aniline conversion and b) quinoline selectivity of three sets of experiments with the mixer and reactor heated at 250 °C. Several flow rate set for both the two 0.275 M solketal and aniline solutions in toluene and 10 MPa system pressure.

6. Products characterization

6.1.1. Synthesis of quinoline (3a)

The reaction was carried out accordingly to the general procedure 5.2. The purification of quinoline 3a was undertaken with 85:15 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.92 (dd, *J*=4.2, 1.7Hz, 1H), 8.19 – 8.09 (m, 2H), 7.85-7.80 (m, 1H), 7.72 (ddd, *J*=8.5, 6.9, 1.5Hz, 1H), 7.55 (ddd, *J*=8.1, 6.9, 1.2Hz, 1H), 7.40 (dd, *J*=8.3, 4.2Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 150.5, 148.4, 136.2, 129.6, 129.6, 128.4, 127.9, 126.7, 121.2. **HRMS-ESI** for C_9H_8N $[M]^+$ calculated 130.0657, found: 130.0653.

6.1.2. Synthesis of 3-methyl-1H-indole (3b)

The reaction was carried out accordingly to the general procedure. The purification of 3-methyl-1H-indole **3b** was carried out with 80:20 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm: 7.59 (dd, *J* 7.8, 1.1 Hz, 1H), 7.35 (dd, *J*=8.0, 0.9 Hz, 1H), 7.19 (ddd, *J*=8.2,7.0,1.3 Hz, 1H), 7.12 (ddd, *J*=7.9,7.0,1.0Hz, 1H), 6.97 (dd, *J*=2.3,1.2Hz, 1H), 2.34 (d, *J*=1.1Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 136.4, 128.4, 122.0, 121.7, 119.2, 119.0, 111.9, 111.1, 9.8. **HRMS-ESI** for C_9H_9N $M^{+\cdot}$ calculated 130.0813, found 130.0654.

6.1.3. Synthesis of 2,4-dimethylquinoline (4a)

The reaction was carried out accordingly to the general procedure. The purification of 2,4-dimethylquinoline **4a** was carried out with 50:50 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* 8.5, 1H), 7.95 (dd, *J* 8.3, 1.4 Hz, 1H), 7.67 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.50 (ddd, *J* 8.2, 6.9, 1.3 Hz, 1H), 7.14 (d, *J* 1.1 Hz, 1H), 2.70 (s, 3H), 2.67 (d, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm: 158.8, 147.8, 144.3, 129.3, 129.2, 126.7, 125.5, 123.7, 122.9, 25.4, 18.7. **HRMS-ESI** for $C_{11}H_{12}N$ $[M+H]^+$ calculated 158.0970, found 158.0961.

6.1.4. Synthesis of 2,2,4-trimethyl-1,2-dihydroquinoline (4b)

The reaction was carried out accordingly to the general procedure. The purification of 2,2,4-trimethyl-1,2-dihydroquinoline **4b** was carried out with 50:50 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm: 7.07 (dd, *J*=7.6, 1.5Hz, 1H), 6.99 (td, *J*=7.6,1.5Hz, 1H), 6.67 (td, *J*=7.5, 1.3Hz, 1H), 6.53–6.49 (d, 1H), 5.32 (d, *J*=1.5 Hz, 1H), 1.99 (d, *J*=1.4Hz, 3H), 1.30 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm: 142.6, 128.8, 128.5, 128.5, 123.9, 122.1, 117.9, 113.6, 52.2, 30.8, 18.7. **HRMS-ESI** for $C_{12}H_{16}N$ $[M+H]^+$ calculated 174.1283, found 174.1287.

6.1.5. Synthesis of 6-methoxyquinoline (5a)

The reaction was carried out accordingly to the general procedure. The purification of 6-methoxyquinoline **5a** was carried out with a gradient of polarity from 85:15 to 50:50 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm: 8.78 (dd, *J*=4.3,1.7Hz, 1H), 8.12–8.07 (m, 1H), 8.07–8.02 (m, 1H), 7.43–7.36 (m, 2H), 7.09 (d, *J*=2.8Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl^3$) δ ppm: 157.9, 147.7, 144.2, 135.3, 130.7, 129.5, 122.6, 121.5, 105.2, 55.7. **HRMS-ESI** for $C_{10}H_{10}NO$ $[M+H]^+$ calculated 160.0762, found 160.0766.

6.1.6. Synthesis of 4-methoxy-N-methylaniline (5b)

The reaction was carried out accordingly to the general procedure. The purification of,4-methoxy-N-methylaniline **5b** was carried out with a gradient of polarity from 85:15 to 50:50 (v/v)of CyHex:AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm: 6.84–6.78 (m, 2H), 6.69–6.62 (m, 2H), 3.76 (s, 3H), 2.82 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm: 152.7, 142.9, 115.1, 114.4, 55.9, 32.2. **HRMS-ESI** for $C_8H_{12}NO$ $[M+H]^+$ calculated 138.0919, found 138.0919.

6.1.7. Synthesis of N-ethyl-4-methoxyaniline (5c)[2]

The reaction was carried out accordingly to the general procedure. The purification of N-ethyl-4-methoxyaniline **5c** was carried out with a gradient of polarity from 85:15 to 50:50 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm: 6.78 (m, 2H), 6.62–6.55 (m, 2H), 3.75 (s, 3H), 3.11 (q, *J*=7.1Hz, 2H), 1.24 (t, *J*=7.1Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm: 152.2, 142.9, 115.0, 114.2, 55.98, 39.6, 15.16. **HRMS-ESI** for $C_{19}H_{14}NO$ $[M+H]^+$ calculated 152.1075, found 152.1077.

6.1.8. Synthesis of 4-(quinolin-6-yl methyl)aniline (6a)

The reaction was carried out accordingly to the general procedure. The purification of 4-(quinoline-6-yl methyl)aniline **6a** was carried out with a gradient of polarity from 80:20 to 30:70 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.85 (dd, *J*=4.3,1.7Hz, 1H), 8.07 (dd, *J*=8.3,1.8Hz, 1H), 8.01 (d, J=9.2Hz, 1H), 7.58–7.54 (m, 2H), 7.36 (dd, *J*=8.3,4.2Hz, 1H), 7.02 (d, *J*=8.3Hz, 2H), 6.67–6.63 (m, 2H), 4.06 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 149.9, 147.3, 144.9, 140.7, 135.9, 131.4, 130.6, 130.1, 129.5, 128.5, 126.6, 121.2, 115.5, 41.2. **HRMS-ESI** for $C_{16}H_{15}N_2$ $[M+H]^+$ calculated 235.1235, found 235.1245.

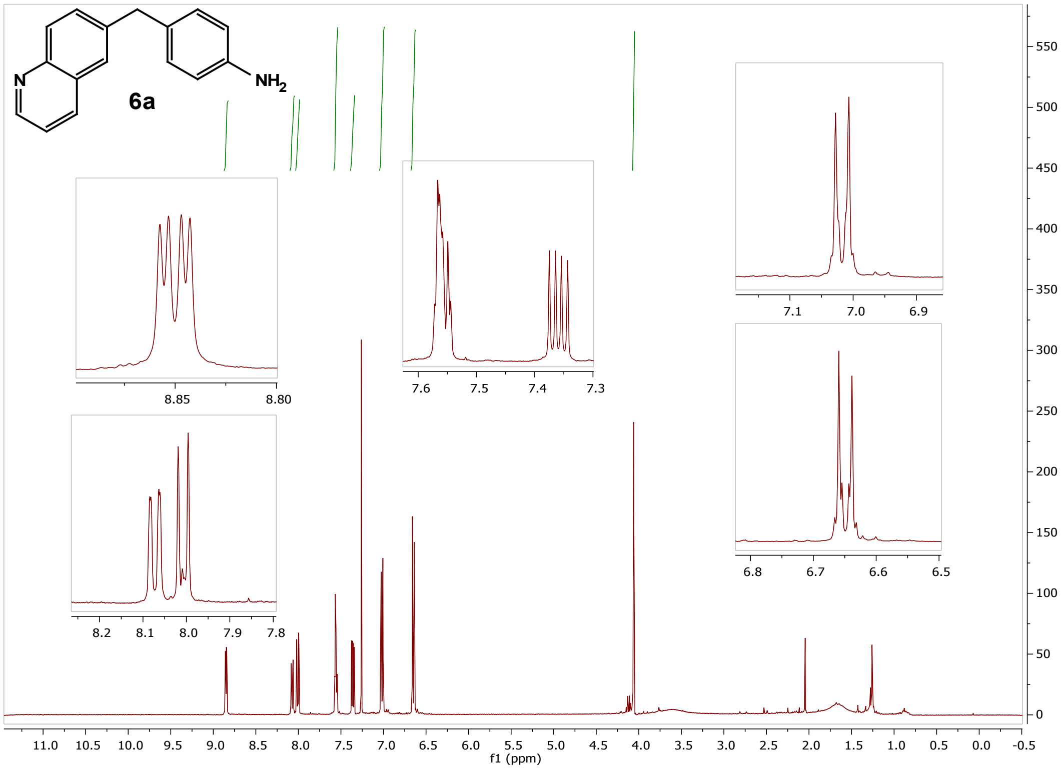


Figure S4. ^{1}H NMR spectra of **6a**

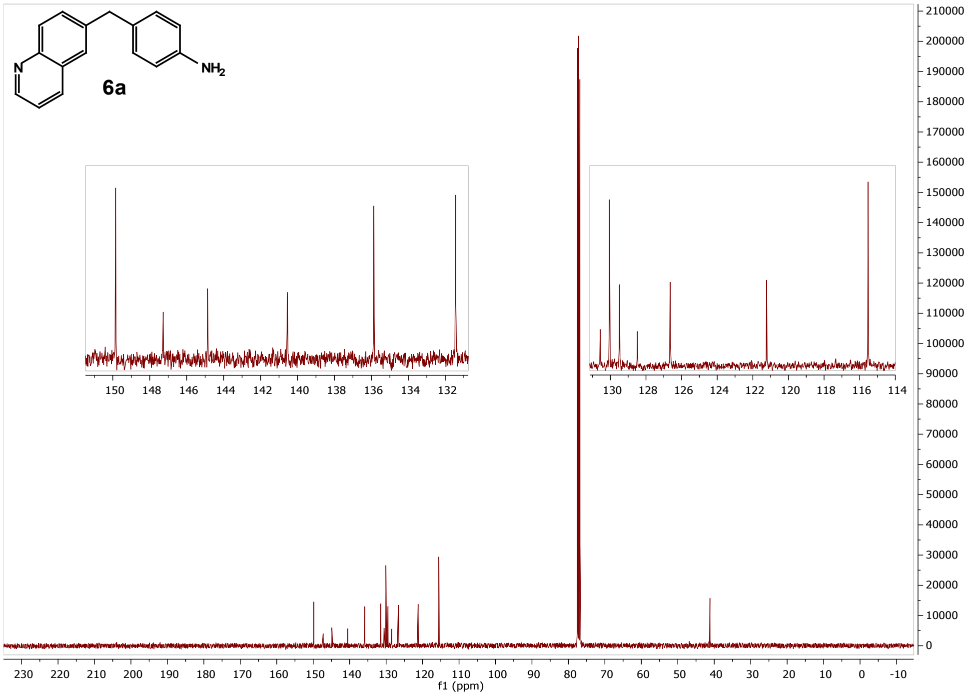


Figure S5. ^{13}C NMR spectra of **6a**

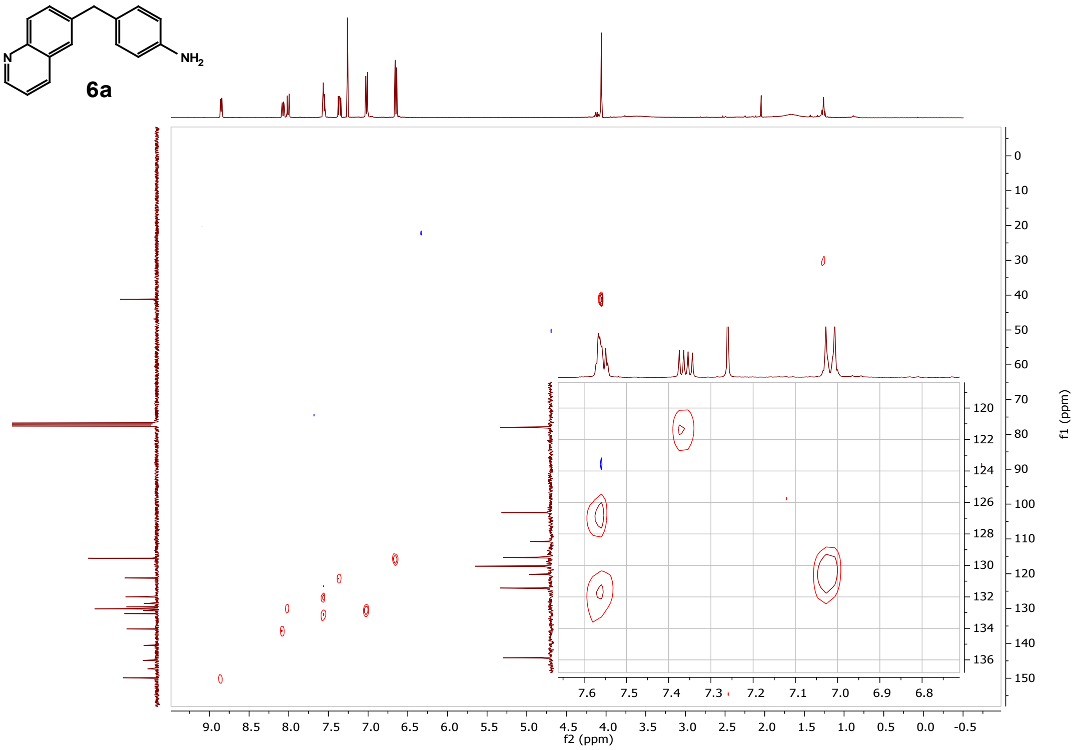


Figure S6. HMQC spectra of **6a**

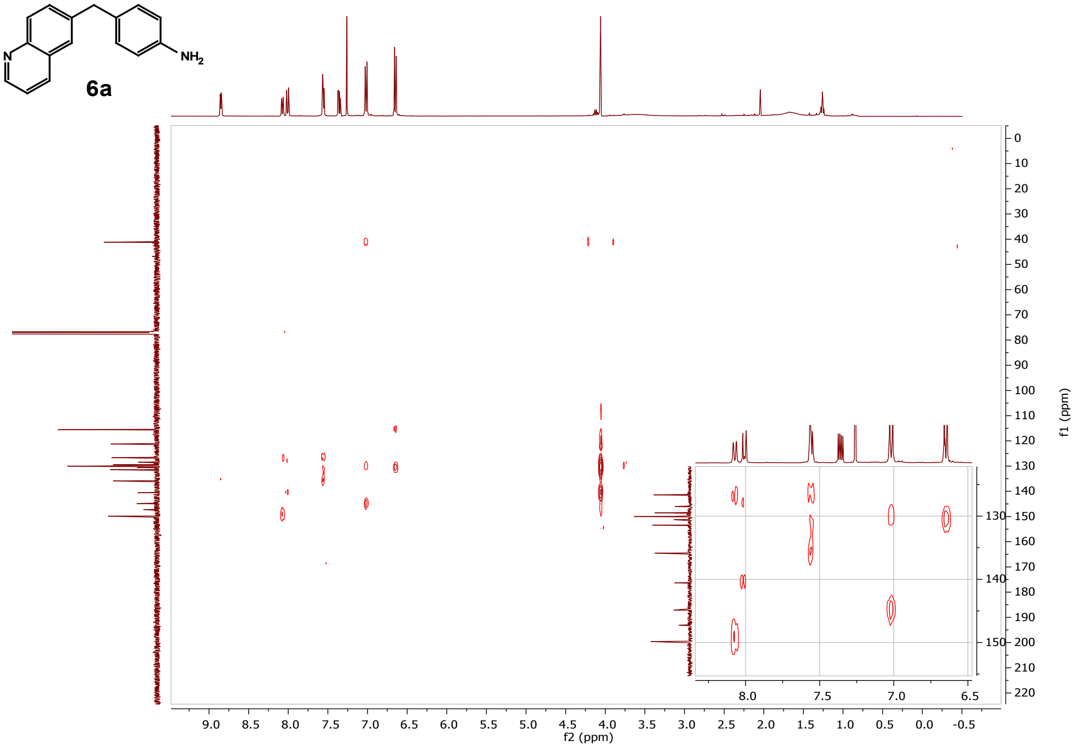


Figure S7. HMBC spectra of **6a**

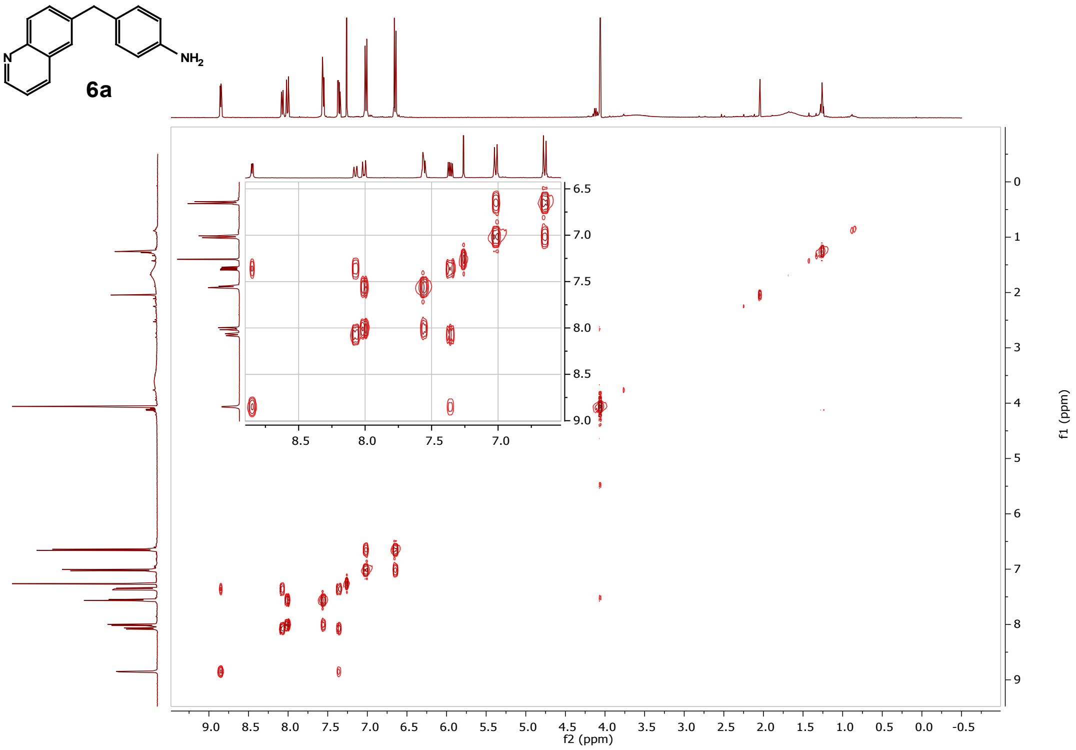
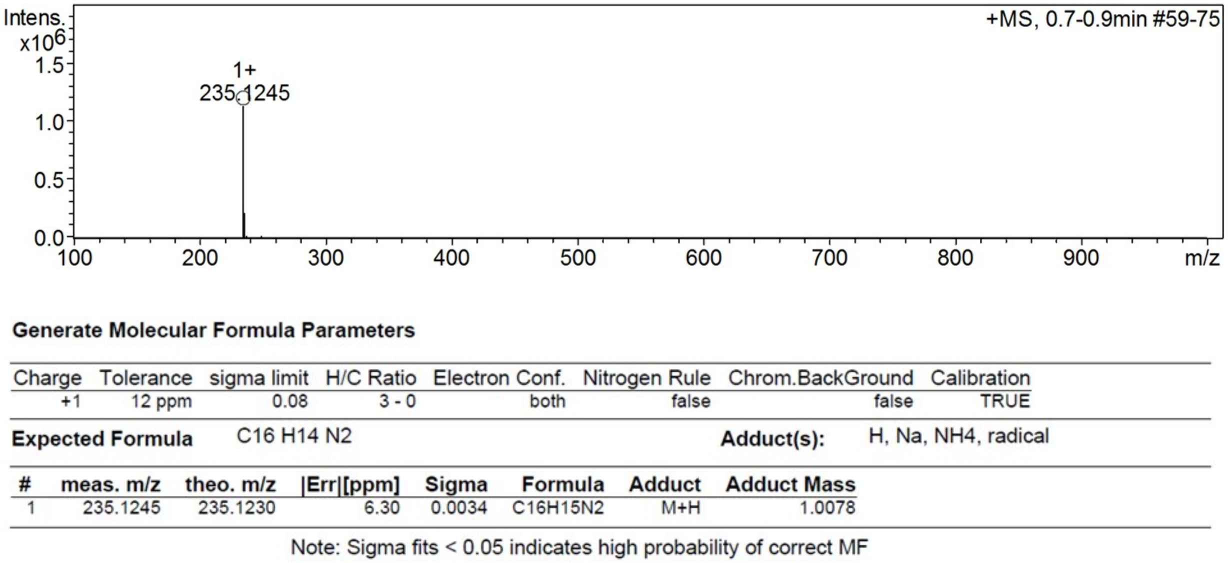


Figure S8. COSY spectra of **6a**



Generate Molecular Formula Parameters

Charge	Tolerance	sigma limit	H/C Ratio	Electron Conf.	Nitrogen Rule	Chrom.BackGround	Calibration
+1	12 ppm	0.08	3 - 0	both	false	false	TRUE

Expected Formula C16 H14 N2 **Adduct(s):** H, Na, NH4, radical

#	meas. m/z	theo. m/z	|Err|[ppm]	Sigma	Formula	Adduct	Adduct Mass
1	235.1245	235.1230	6.30	0.0034	C16H15N2	M+H	1.0078

Note: Sigma fits < 0.05 indicates high probability of correct MF

Figure S9. HRMS-ESI of **6a**

6.2. Synthesis of di(quinolin-6-yl)methane (6b)

The reaction was carried out accordingly to the general procedure. The purification of di(quinolin-6-yl)methane **6b** was carried out with a gradient of polarity from 80:20 to 30:70 (v/v) of CyHex:AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm: 8.91 (dd, *J*=4.3,1.7Hz, 2H), 8.09 (m, 4H), 7.70-7.57 (m, 4H), 7.41 (dd, *J*=8.3,4.2Hz, 2H), 4.39 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 150.1, 147.3, 138.9, 135.7, 131.2, 129.8, 128.4, 127.1, 121.3, 41.8. **HRMS-ESI** for $C_{19}H_{15}N_2$ as $[M+H]^+$ calculated 271.1235, found 271.1245 calculated.

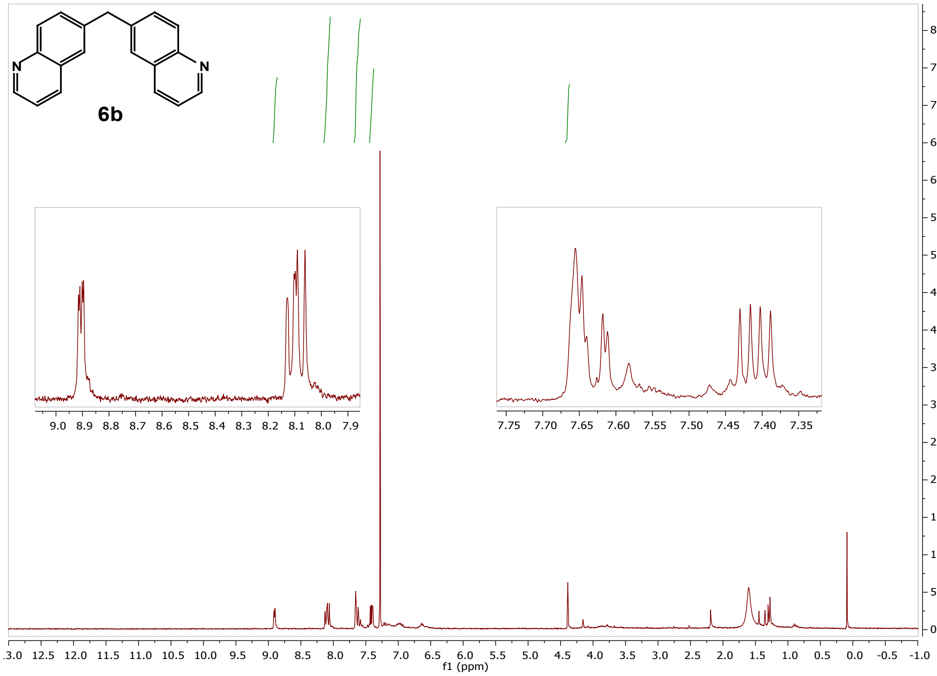


Figure S10. ^{1}H NMR spectra of **6b**

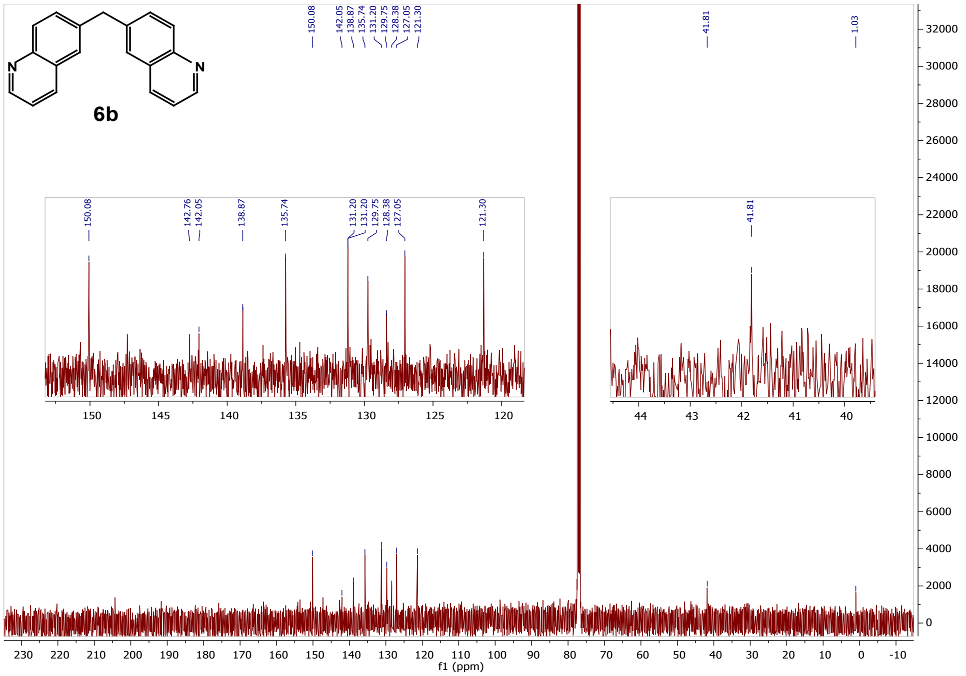


Figure S11.^{13}C NMR spectra of **6b**

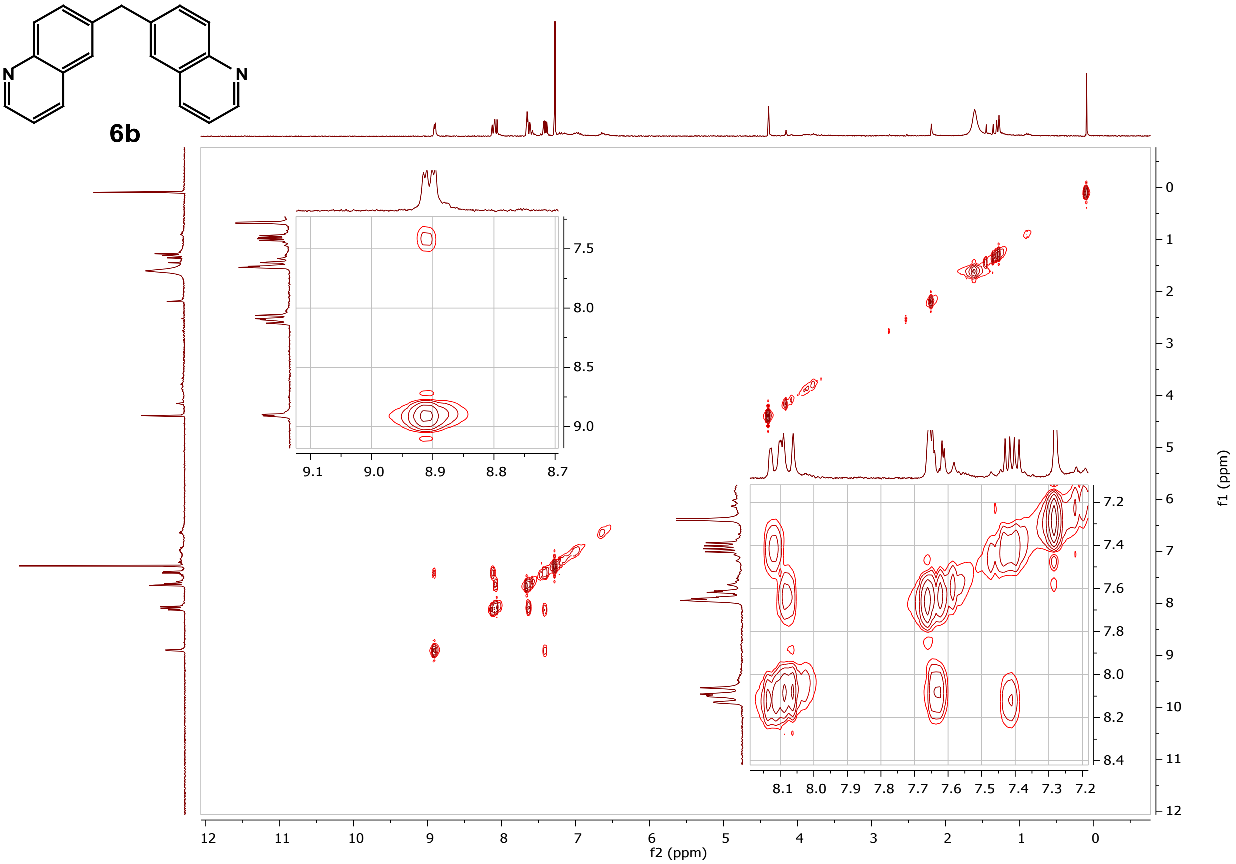
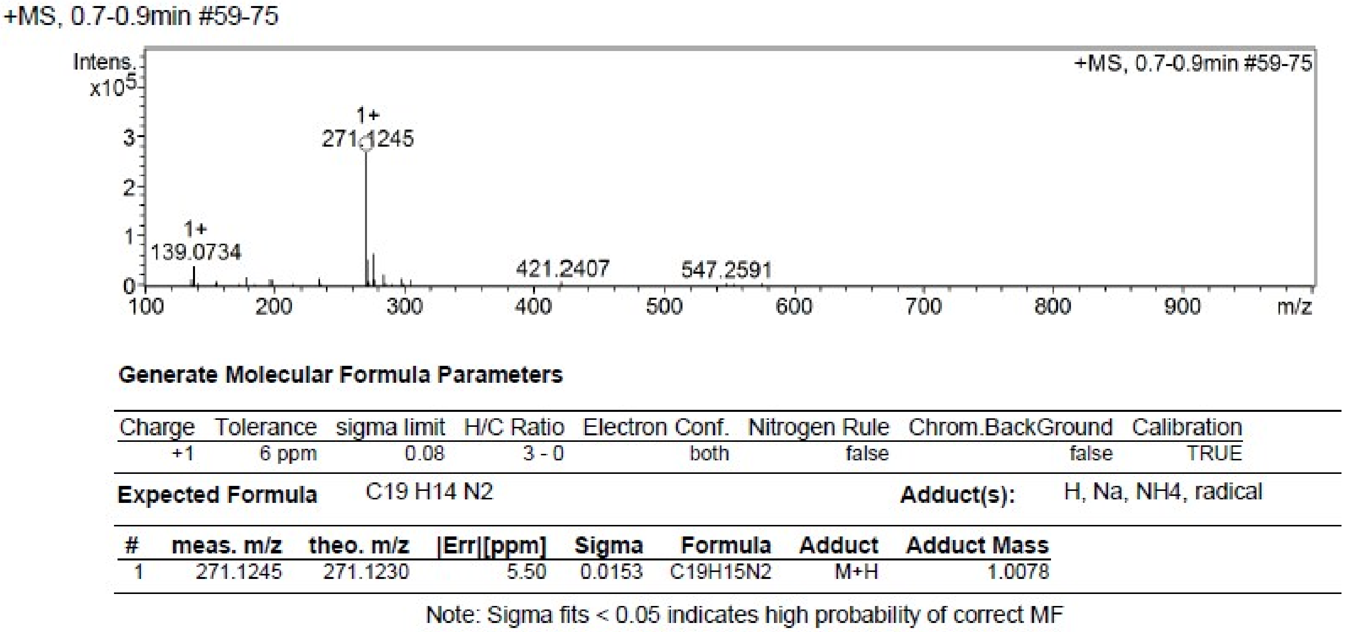


Figure S12. COSY spectra of **6b**



Generate Molecular Formula Parameters

Charge	Tolerance	sigma limit	H/C Ratio	Electron Conf.	Nitrogen Rule	Chrom.BackGround	Calibration
+1	6 ppm	0.08	3 - 0	both	false	false	TRUE

Expected Formula C19 H14 N2 **Adduct(s):** H, Na, NH4, radical

#	meas. m/z	theo. m/z	|Err|[ppm]	Sigma	Formula	Adduct	Adduct Mass
1	271.1245	271.1230	5.50	0.0153	C19H15N2	M+H	1.0078

Note: Sigma fits < 0.05 indicates high probability of correct MF

Figure S13. HRMS-ESI of **6b**

7. X-ray crystallographic structure of compound 6b

Single crystals of $C_{16}H_{14}N_2$ 4-(quinolin-6-yl methyl)aniline **6a** were grown. A suitable crystal was selected and mounted in fomblin film on a micromount on a GV1000, Atlas diffractometer giving the crystal structure shown in Figure S14.

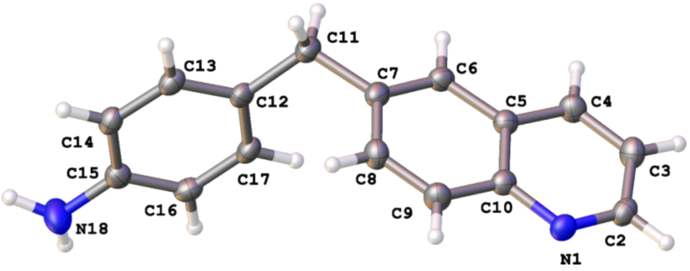


Figure S14. X-ray crystallographic structure of compound **6a**.

Table S1. Crystal data and structure refinement for compound 6b

Empirical formula	$C_{16}H_{14}N_2$
Formula weight	234.29
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.0024(9)
b/Å	6.9487(7)
c/Å	17.5896(15)
α/°	90
β/°	98.794(9)
γ/°	90
Volume/Å^3	1208.2(2)
Z	4
ρ_{calc}g/cm^3	1.288
μ/mm^{-1}	0.594
F(000)	496.0
Crystal size/mm^3	0.354 × 0.17 × 0.164
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.178 to 147.092
Index ranges	$-12 \le h \le 12$, $-8 \le k \le 8$, $-11 \le l \le 21$
Reflections collected	4597
Independent reflections	2356 [R_{int} = 0.0226, R_{sigma} = 0.0265]
Data/restraints/parameters	2356/0/169
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0395, wR_2 = 0.1042
Final R indexes [all data]	R_1 = 0.0451, wR_2 = 0.1091
Largest diff. peak/hole / e Å^{-3}	0.19/-0.20

8. Thermogravimetric analysis

Figure S15 shows the thermogravimetric analysis of a) the fresh NbP catalyst. The total weight loss is about 13 % observed from 50 °C to 450 °C probably corresponding to loss of physically absorbed and hydrous water molecules. For the used NbP catalyst, the weight loss overall 32 % in two stages (Figure S15).The initial weight loss is again attributed to water just before 420 °C (around 13 %). The second weight loss occurs between 450 – 600 °C which we attribute to coke burning off the surface (around 19 %).

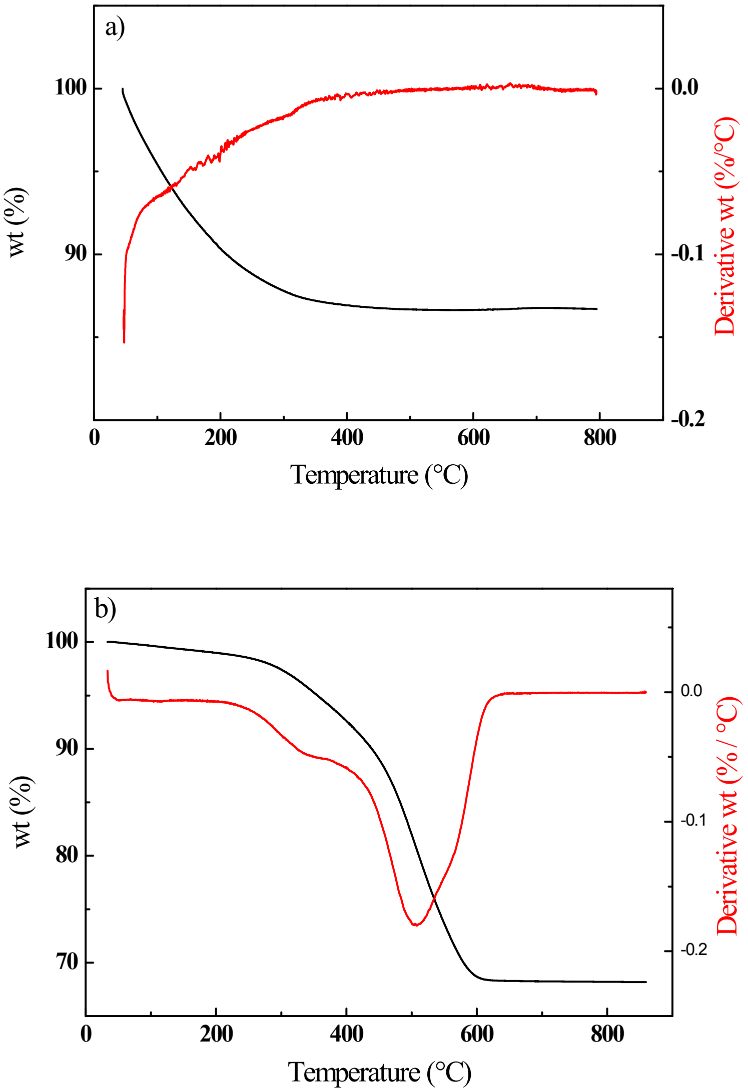


Figure S15. TGA analysis of the a) fresh NbP and b) used NbP catalyst.

9. References

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