Electronic Supplementary Information

Nitrous oxide as diazo transfer reagent: the synthesis of triazolopyridines

Iris R. Landman, Farzaneh Fadaei-Tirani and Kay Severin*

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland.

* E-mail: kay.severin@epfl.ch

Content **Page**

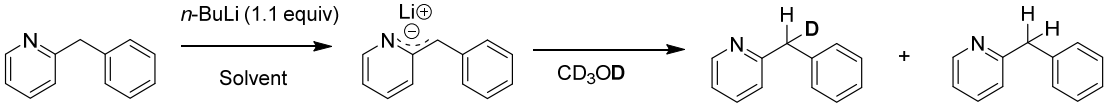
1. Materials and methods

Caution: *Although we have not experienced any accidents, diazo compounds and other nitrogen containing compounds are potentially explosive and toxic compounds.*[1] *In addition, alkyllithium reagents (e.g. t-BuLi) are pyrophoric reagents. Accordingly, their use, handling and storage should be carried out with appropriate precautions.*

Unless stated otherwise, all reactions were carried out under inert atmosphere of dry N_2 using Schlenk or glovebox techniques. All reagents were purchased from commercial suppliers (Sigma Aldrich, Acros, TCI, VWR, Fluorochem, ABCR) and used without additional purification. Starting materials were synthesized accordingly.[2–5] Concentration of organolithium compounds: *n*-BuLi (2.5 M in hexanes), *s*-BuLi (1.4 M in cyclohexane) and *t*-Bu (1.6 M in pentanes). *NMR spectra* were recorded at ambient temperature on Bruker spectrometers: Avance III 400 MHz Prodigy probe 5 mm ICONNMR ATMA, Avance 400 MHz BBIz 5mm ATMA or Avance III HD 600 MHz CPTCIz 5 mm. Chemical shifts in ppm were aligned with respect to the residual peak of deuterated solvent.[6] *Electronspray-ionisation HRMS* data were acquired on a Q-Tof Ultima mass spectrometer (Waters) or a Q-Tof 6530 Accurate mass spectrometer (Agilent) operated in the positive ionization mode and fitted with a standard Z-spray ion source equipped with the Lock-Spray interface. Data from the Lock-Spray were used to calculate a correction factor for the mass scale and provide accurate mass information of the analyte. Data were processed using the MassLynx 4.1 software. *Column chromatography* was performed on a CombiFlash NextGen from Teledyne ISCO, using RediSep columns. *RP-HPLC,* Agilent 1260 Infinity LC, using a Kinetex 5u EVO 18 100 A column.

2. Optimization of the reaction conditions

Examining lithiation efficiency

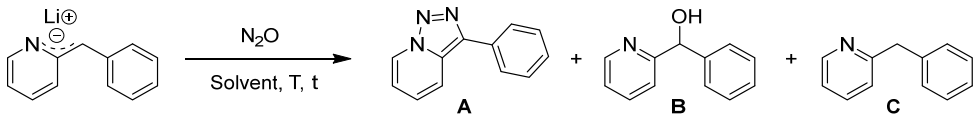


In a 250 ml oven-dried Schlenk flask: 2-Benzylpyridine (1 mmol) was dissolved in THF or diethyl ether (10 ml), which was cooled to –78 °C or 0 °C, respectively. Subsequently, *n*-BuLi was added and a red suspension formed. The mixture was stirred for 30 min at –78 °C or 0 °C, followed by allowing to warm up to rt and stirring for additional 1.5 h. The solvent was removed under vacuum, yielding a brick-red solid.

A small amount of the lithiated salt was dissolved in dry d_4-methanol. The lithiation efficiency was calculated by comparing the CH_2 vs CHD ^{1}H NMR signal. For both, Et_2O and THF, the lithiation was nearly complete under the given conditions.

Et_2O (0.1 M), 0 °C to rt, 1 h	>95% lithiated
THF (0.1 M), –78 °C to rt, 2 h	>95% lithiated

N_2O conversion optimization



An initial optimization was performed (Table S2.1) by varying the reaction conditions and analyzing the crude reaction mixture by ^{1}H NMR (CD_2Cl_2) by comparing the α-H signal of the pyridyl group of product **A** (8.76 ppm), side-product **B** (8.55 ppm), and starting material **C** (8.50 ppm). In the glovebox, in an oven-dried microwave vial: Lithiated benzylpyridine (50 mg) was dissolved in THF (0.048 – 0.1 M). Next, the flask was subjected to an N_2O atmosphere (3x N_2O/*vac* cycles). The reaction mixture was placed in a pre-heated oil-bath. After the given time, the reaction was quenched with water, the product was extracted with ethyl acetate, and the solvent was removed under vacuum. For the scale-up reactions, a 250 ml oven-dried Schlenk was used, which was sealed with a metal clip.

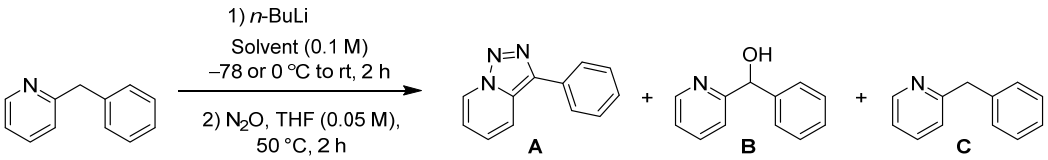
Table S2.1. Screening of reaction conditions

Entry	T (°C)	Conc. (M)	Time (h)	Conversion (%)		
				A	B	C
1	rt	0.048	1	52	48	0
2	0	0.048	1	23	67	10
3	40	0.024	1	>95	2	<5
4	50	0.024	1	>95	0	<5
5 [a]	50	0.048	2	>95	0	<5
6 [b,c]	50	0.1	1	93[a]	3	4
7 [b,c]	50	0.1	2	>95[a]	0	<5

[a] 350 mg instead of 50 mg. [b] 200 mg instead of 50 mg. [c] New set of signals appeared.

The initial screening indicated that at rt and 0 °C (entry 1 and 2), the reaction does not go to full completion. Increasing the temperature to 50 °C (entry 4) was beneficial for the conversion. For reactions at higher concentration (0.1 M, entry 6 and 7), a new side-product was detected, which was not identified. We have chosen the conditions given under entry 5 (50 °C for 2 h) for further studies.

Reaction in two steps, one pot



In a 250 ml oven-dried Schlenk flask: 2-Benzylpyridine (0.161 ml, 1 mmol) was dissolved in THF or diethyl ether (10 ml), which was cooled to –78 °C or 0 °C, respectively. Next, *n*-BuLi was added and a red suspension formed. The mixture was stirred for 30 min at –78 °C or 0 °C, followed by allowing to warm up to rt and stirring for additional 1.5 h. The solvent was removed under vacuum, yielding a brick-red solid. The solid was redissolved in THF (20 ml), subjected to an N_2O atmosphere (3x N_2O/*vac* cycles) and heated at 50 °C for 2 h in a pre-heated oil bath. The solvent was removed under vacuum and water was added to quench the reaction. The product was extracted with ethyl acetate (100 ml). For the reaction screening (Table S2.2), an aliquot of the organic phase was evaporated and the ratio of product and side-products was determined by ^{1}H NMR (CD_2Cl_2).

Table S2.2. Screening of reaction conditions, two-step reaction, one-pot.

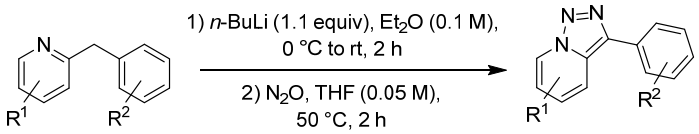
Entry	*n*-BuLi (equiv)	Solvent	*T* (°C)	Conversion (%)		
				A	B	C
1	1.5	THF	–78	88	5	7
2	2	THF	–78	55	40	5
3	4	THF	–78	*Mixture of signals*		
4	1.1	Et_2O	0	>95	<5	<5
5 [a]	1.1	Et_2O	0	*Mixture of signals*		

[a] N_2O reaction overnight instead of 2 h.

Starting with THF as solvent (entry 1–3), the increase in equivalents of *n*-BuLi did not lead to a higher conversion into the desired product. In case of 4 equiv (entry 3), there was a mixture of signals, suggesting some side-reactions had taken place. Switching to Et_2O and 1.1 equiv (entry 4) gave the desired clean conversion, which was selected as the optimal reaction condition. Heating overnight also produced side-products (entry 5).

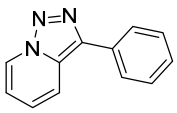
3. Synthesis of the triazoles 1–10

General procedure



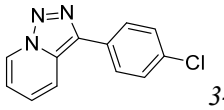
In a 250 ml oven-dried Schlenk flask: 2-Benzylpyridine (1 mmol) was dissolved in diethyl ether (10 ml). The reaction mixture was cooled to 0 °C and *n*-BuLi (1.1 equiv) was added, forming a red suspension. It was stirred for 30 min at 0 °C, followed by allowing to warm up to rt and stirring for additional 1.5 h. The solvent was removed under vacuum, yielding a brick-red solid. The solid was redissolved in THF (20 ml) and the solution was subjected to an N_2O atmosphere (3x N_2O/*vac* cycles) and heated at 50 °C for 2 h in a pre-heated oil bath. The solvent was removed under vacuum, water (50 ml) was added, and the product was extracted with ethyl acetate (100 ml). The organic phase was washed with brine and dried over $MgSO_4$, filtered, and the solvent was evaporated. The resulting product was washed with diethyl ether/hexane and dried under vacuum.

Scope



3-Phenyl-[1,2,3]triazolo[1,5-a]pyridine (**1**)

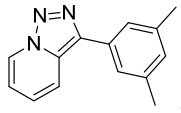
Triazolopyridine **1** was prepared from 2-benzylpyridine (1 mmol), following the general procedure. Yield (yellow solid): 160 mg (82%). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.76 (dt, *J* = 7.1, 1.1 Hz, 1H), 8.02 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.99 – 7.92 (m, 2H), 7.52 (dd, *J* = 8.5, 7.1 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.34 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.03 (td, *J* = 6.8, 1.2 Hz, 1H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 137.48, 131.63, 130.42, 128.91, 127.67, 126.39, 125.71, 125.57, 118.25, 115.26, 53.76, 53.58, 53.40, 53.22, 53.04. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{10}N_3^+$ 196.0869; Found 196.0872. The spectra are in agreement with what has been reported in the literature.[7]



3-(4-Chlorophenyl)-[1,2,3]triazolo[1,5-a]pyridine (**2**)

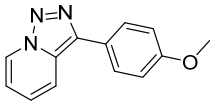
Triazolopyridine **2** was prepared from 2-(4-chlorobenzyl)pyridine (1 mmol), following the general procedure. Yield (orange solid): 206 mg (90%). For the upscale synthesis, the reaction was performed with 5.12 mmol of 2-(4-chlorobenzyl)pyridine in a 1 L Schlenk flask. After evaporation of THF, the yellow precipitate was triturated with water and filtered. The yellow solid was washed with hexane and then freeze-dried in pentane. Yield (orange solid): 879 mg (74%). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.77 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.99 (dt, *J*

= 9.0, 1.2 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.53 – 7.49 (m, 2H), 7.37 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.05 (td, *J* = 6.9, 1.2 Hz, 1H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 136.38, 133.29, 130.41, 130.24, 129.07, 127.61, 126.09, 125.69, 118.01, 115.41, 53.76, 53.58, 53.40, 53.22, 53.04. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_9ClN_3^+$ 230.0480; Found 230.0481. The spectra are in agreement with what has been reported in the literature.[7]



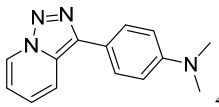
3-(3,5-Dimethylphenyl)-[1,2,3]triazolo[1,5-a]pyridine (**3**)

Triazolopyridine **3** was prepared from 2-(3,5-dimethylbenzyl)pyridine (0.41 mmol), following the general procedure. Yield (yellow solid): 62 mg (67%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.02 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.59 (dt, *J* = 1.5, 0.7 Hz, 2H), 7.30 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.07 – 7.03 (m, 1H), 7.00 (td, *J* = 6.8, 1.2 Hz, 1H), 2.42 (d, *J* = 0.8 Hz, 6H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 138.58, 137.76, 131.32, 130.38, 129.39, 125.52, 125.44, 124.19, 118.46, 115.21, 53.76, 53.58, 53.40, 53.22, 53.04, 21.10. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3^+$ 224.1182; Found 224.1187. The spectra are in agreement with what has been reported in the literature.[7]



3-(4-Methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine (**4**)

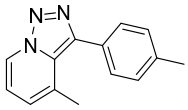
Triazolopyridine **4** was prepared from 2-(4-methoxybenzyl)pyridine (0.62 mmol), following the general procedure. Additional purification was performed by flash column chromatography, hexane/ethyl acetate (2:1 to 3:2). Yield (off-white solid): 78 mg (55%). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.73 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.97 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.93 – 7.81 (m, 2H), 7.30 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.11 – 7.03 (m, 2H), 7.00 (td, *J* = 6.9, 1.3 Hz, 1H), 3.87 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 159.57, 137.65, 130.15, 127.85, 125.60, 125.32, 124.34, 118.42, 115.26, 114.49, 55.41, 54.04, 53.77, 53.50, 53.23, 52.96. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}N_3O^+$ 226.0975; Found 226.0978. The spectra are in agreement with what has been reported in the literature.[7]



4-([1,2,3]Triazolo[1,5-a]pyridin-3-yl)-N,N-dimethylaniline (**5**)

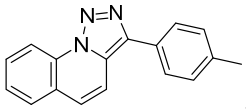
Triazolopyridine **5** was prepared from *N*,*N*-dimethyl-4-(pyridin-2-ylmethyl)aniline (0.53 mmol), following the general procedure. Additional purification was performed by flash column chromatography, hexane/ethyl acetate (2:1 to 3:2). Yield (yellow solid): 126 mg (49%). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.78 – 8.62 (m, 1H), 7.97 (dd, *J* = 9.1, 1.3 Hz, 1H), 7.88 – 7.73 (m, 2H), 7.32 – 7.18 (m, 1H), 6.97 (t, *J* = 7.0 Hz, 1H), 6.90 – 6.80 (m, 2H), 3.02 (s, 6H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 150.23, 138.23, 129.66, 127.27, 125.33, 124.58, 119.42,

118.57, 115.02, 112.48, 53.76, 53.58, 53.40, 53.22, 53.04, 40.18. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}N_4^+$ 239.1291; Found 239.1292. New compound.



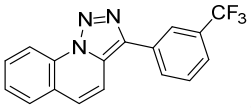
4-Methyl-3-(p-tolyl)-[1,2,3]triazolo[1,5-a]pyridine (**6**)

Triazolopyridine **6** was prepared from 3-methyl-2-(4-methylbenzyl)pyridine (1.15 mmol), following the general procedure. Yield (red/brown solid): 212 mg (91%). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.60 (d, *J* = 7.0 Hz, 1H), 7.54 – 7.39 (m, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 6.98 (dt, *J* = 6.8, 1.2 Hz, 1H), 6.90 (t, *J* = 6.8 Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 139.30, 138.04, 131.22, 130.25, 129.49, 129.32, 128.65, 124.68, 123.04, 115.18, 53.76, 53.58, 53.40, 53.22, 53.04, 20.96, 19.29. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3^+$ 224.1182; Found 224.1187. New compound.



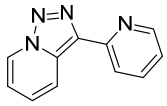
3-(p-Tolyl)-[1,2,3]triazolo[1,5-a]quinoline (**7**)

Triazoloquinoline **7** was prepared from 2-(4-methylbenzyl)quinoline (0.79 mmol), following the general procedure. Yield (yellow solid): 178 mg (86%). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.79 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.95 – 7.85 (m, 3H), 7.84 – 7.76 (m, 2H), 7.68 – 7.57 (m, 2H), 7.40 – 7.32 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 139.52, 137.78, 131.85, 129.87, 129.41, 128.36, 128.27, 127.94, 126.88, 126.51, 126.39, 123.79, 115.80, 115.10, 53.56, 53.38, 53.20, 53.02, 52.84, 20.78. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}N_3^+$ 260.1182; Found 260.1184. New compound.



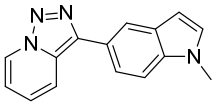
3-(3-(Trifluoromethyl)phenyl)-[1,2,3]triazolo[1,5-a]quinoline (**8**)

Triazoloquinoline **8** was prepared from 2-(3-(trifluoromethyl)benzyl)quinoline (0.76 mmol), following the general procedure. Yield (yellow solid): 219 mg (93%). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.82 (d, *J* = 8.3 Hz, 1H), 8.29 (s, 1H), 8.21 (ddd, *J* = 5.9, 3.7, 1.8 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.75 – 7.64 (m, 4H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 137.99, 132.31, 131.85, 131.15, 130.26, 129.71, 129.40, 128.48, 128.42, 127.62, 127.19, 125.39, 124.23, 124.19, 123.78, 123.15, 123.11, 115.94, 114.47, 53.74, 53.47, 53.20, 52.93, 52.66. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{11}F_3N_3^+$ 314.0900; Found 314.0887. New compound.



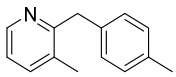
3-(Pyridin-2-yl)-[1,2,3]triazolo[1,5-a]pyridine (**9**)

Triazoloquinoline **9** was prepared from di(pyridin-2-yl)methane (0.53 mmol), following the general procedure. Heated under N_2O atmosphere for 19 hours. It was purified by flash column chromatography, petroleum ether/ ethyl acetate (10:1 to 1:1). Yield (white solid): 39 mg (37%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 – 8.72 (m, 2H), 8.69 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.38 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.83 (td, *J* = 7.8, 1.8 Hz, 1H), 7.49 – 7.34 (m, 1H), 7.31 – 7.18 (m, 1H), 7.06 (td, *J* = 6.7, 1.3 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.83, 149.11, 137.17, 132.18, 126.70, 125.41, 122.23, 121.40, 120.81, 116.12. **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{11}H_9N_4^+$ 197.0822; Found 197.0818. The spectra are in agreement with what has been reported in the literature.[7]



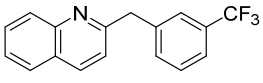
3-(1-Methyl-1H-indol-5-yl)-[1,2,3]triazolo[1,5-a]pyridine (**10**)

Triazolopyridine **10** was prepared from 1-methyl-5-(pyridin-2-ylmethyl)-1*H*-indole (0.51 mmol), following the general procedure. The reaction mixture was stirred for 4 h at 50 °C under N_2O atmosphere. Yield (yellow solid): 54 mg (44%). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.74 (dt, *J* = 7.1, 1.1 Hz, 1H), 8.13 (dd, *J* = 1.7, 0.7 Hz, 1H), 8.08 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.84 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.30 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.19 – 7.11 (m, 1H), 7.01 (td, *J* = 6.8, 1.2 Hz, 1H), 6.57 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.85 (s, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 138.87, 136.23, 129.91, 129.55, 128.61, 125.18, 124.68, 122.58, 120.45, 118.58, 118.42, 114.89, 109.59, 100.90, 53.56, 53.38, 53.20, 53.02, 52.84, 32.63. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}N_4^+$ 249.1135; Found 249.1140. New compound.



3-Methyl-2-(4-methylbenzyl)pyridine

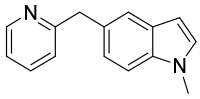
3-Methyl-2-(4-methylbenzyl)pyridine was synthesized according to literature procedure.[2] With TMP, yield (yellow oil): 206 mg (65%). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.36 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.6, 1.9, 0.9 Hz, 1H), 7.07 (s, 5H), 4.11 (s, 2H), 2.29 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 158.93, 146.42, 137.49, 136.03, 135.34, 131.32, 128.71, 128.35, 121.26, 53.74, 53.67, 53.47, 53.20, 52.93, 52.66, 41.25, 20.43, 18.45. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}N^+$ 198.1277; Found 198.1279. New compound.



2-(3-(Trifluoromethyl)benzyl)quinoline

2-(3-(Trifluoromethyl)benzyl)quinoline was synthesized according to literature procedure.[2] With TMP, yield (yellow oil): 217 mg (47%). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.10 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.03 (dt, *J* = 8.4,

1.0 Hz, 1H), 7.81 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.62 (t, *J* = 1.7 Hz, 1H), 7.52 (tdd, *J* = 7.8, 5.2, 3.9 Hz, 3H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 4.38 (s, 2H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 160.08, 147.97, 140.51, 136.60, 132.72, 130.65, 130.33, 129.47, 129.00, 128.93, 127.53, 126.80, 126.06, 125.81, 125.77, 125.73, 125.69, 125.61, 123.27, 123.23, 123.19, 123.15, 122.91, 121.37, 53.94, 53.87, 53.67, 53.40, 53.13, 52.86, 45.00. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{13}F_3N^+$ 288.0995; Found 288.0998. New compound.

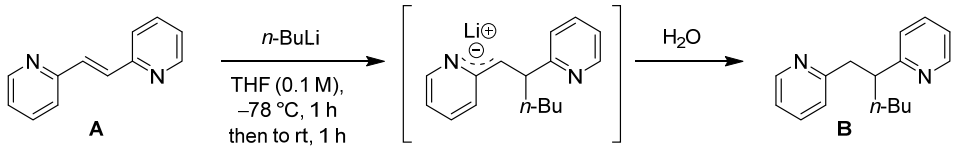


1-Methyl-5-(pyridin-2-ylmethyl)-1H-indole

1-Methyl-5-(pyridin-2-ylmethyl)-1H-indole was synthesized by *N*-methylation of 5-bromoindole,[3] and then cross-coupling according to literature procedure.[4] Yield (pale orange solid): 113 mg (31%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (dt, *J* = 5.1, 1.5 Hz, 1H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.30 – 7.19 (m, 3H), 7.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.04 (d, *J* = 3.1 Hz, 1H), 6.43 (dd, *J* = 3.1, 0.9 Hz, 1H), 4.39 (s, 2H), 3.77 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.22, 146.66, 138.96, 135.86, 129.43, 128.98, 128.95, 124.33, 123.10, 121.88, 121.38, 109.70, 100.87, 77.37, 77.16, 76.95, 43.35, 33.02. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2^+$ 223.1230; Found 223.1234. New compound.

4. Synthesis of the triazoles 11–15

Examining lithiation efficiency



The lithiation was performed as described by Stentzel and Klumpp.[8]

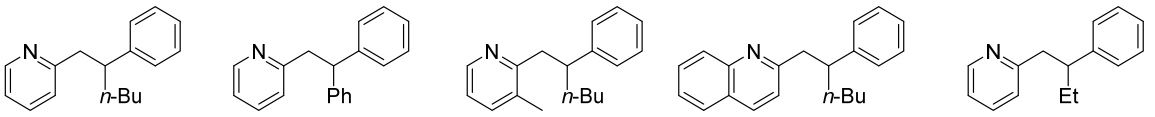
The substrate (0.05 mmol) was dissolved in THF (0.5 ml) and the respective additive was added (for entry 3 and 4). The mixture was cooled to –78 °C and *n*-BuLi (1.5 equiv) was added. The red mixture was stirred for 1 h at –78 °C, after which it was taken out of the cold bath, and allowed to warm up to room temperature over 1 h. Then, the solvent was evaporated and protonation was achieved with a few drops of water. The internal standard, trimethoxybenzene, was added and the yields were calculated by integration of selected ^{1}H NMR signals (Table S4.1).

Table S4.1. Screening of lithiation conditions.

Entry	Additive	*n*-BuLi (equiv)	Conversion (%)	
			A	B
1	-	1.5	<5	83
2 [a]	-	7	<5	<5
3	TMEDA (1 equiv)	1.5	<5	86
4	HMPA (1 equiv)	1.5	5	72

[a] Mixture of signals.

Other substrates, conditions of entry 1; ^{1}H NMR yields.



90% 55% 79% 78% <5% (From EtMgBr, 1.5 eq)

Reaction in two steps, one pot

Next, the reaction was optimized over 2 steps on a 0.3 mmol scale (Table S4.2). After performing the lithiation, the solvent was evaporated *in situ* and fresh THF (0.05 M) was added. Subsequently, the reaction was subjected to N_2O. The solvent was evaporated, yielding a yellow oil. It was redissolved in ethyl acetate (10 ml). An aliquot of 0.5 ml was taken and the solvent was evaporated to which the internal standard trimethoxybenzene was added. The yield was calculated by integration of selected ^{1}H NMR signals.

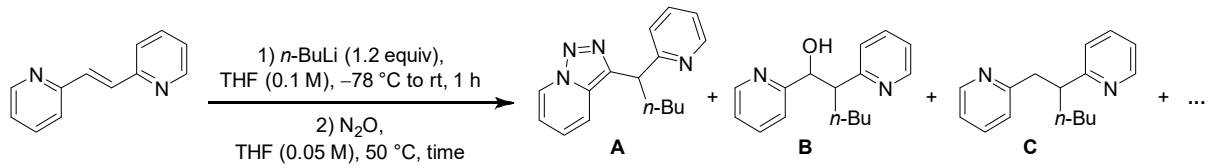


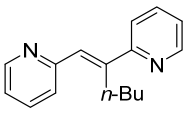
Table S4.2. Screening of reaction conditions, two-step reaction, one-pot.

Entry	Schlenk flask size	Additive	Time (h)	Conversion (%)		
				A	B	C
1a	250 ml	-	2	25 [a]	47 [a]	29 [a]
1b	250 ml	-	3.5	38 [a]	45 [a]	17 [a]
1c	250 ml	-	16	67 [a]	18 [a]	15 [a]
1d	250 ml	-	24	68	<5	-
2	100 ml	-	24	60	10	-
3	500 ml	-	24	44	<5	-
4	250 ml	TMEDA (1 equiv)	24	61	<5	-

[a] NMR yield calculated based on the ratio of the three products instead of an internal standard.

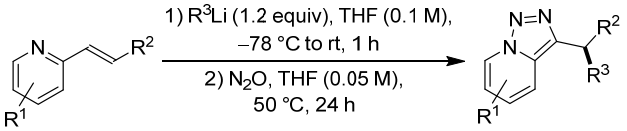
First, the reaction under N_2O was followed over time (entry 1a–d) indicating that prolonged reaction times were beneficial for the yield. Then, changing the size of the flask (entry 2 and 3) or adding TMEDA (entry 4) did not lead to higher yields.

The following side-product was identified by HRMS:



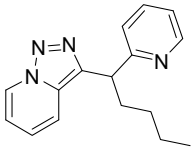
HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2^+$ 239.1543; Found 239.1550.

General procedure



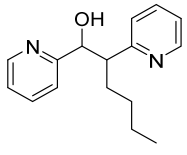
In a 250 ml oven-dried Schlenk flask: The olefinic pyridine or quinoline (0.3 mmol) was dissolved in THF (0.1 M). The reaction mixture was cooled to –78 °C and RLi (1.2 equiv) was added. The reaction was allowed to warm up over 1 h. While the mixture was still cold, the solvent was removed under vacuum. The residue was redissolved in THF (0.05 M), subjected to an N_2O atmosphere (3x N_2O/*vac* cycles) and heated at 50 °C for 24 h in a pre-heated oil bath. The solvent was removed under vacuum. In case olefinic dipyridines, the crude product was purified by reversed phase C18 column chromatography (gradient of 3–30% ACN/H_2O with 0.1v% formic acid). For the 2-styryl quinolines, the crude product was purified by column chromatography with 10% ethyl acetate/hexane.

Scope



3-(1-(Pyridin-2-yl)pentyl)-[1,2,3]triazolo[1,5-a]pyridine (**11**)

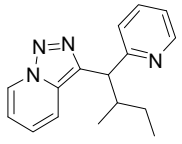
Triazolopyridine **11** was prepared from (*E*)-1,2-di(pyridin-2-yl)ethene (0.3 mmol) and *n*-BuLi, following the general procedure. Yield (yellow oil): 43 mg (54%). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.61 (dt, *J* = 7.1, 1.1 Hz, 1H), 8.50 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.76 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.35 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.16 – 7.03 (m, 2H), 6.88 (td, *J* = 6.8, 1.3 Hz, 1H), 4.56 (t, *J* = 7.9 Hz, 1H), 2.46 – 2.24 (m, 2H), 1.44 – 1.16 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 162.55, 148.75, 139.74, 136.19, 131.27, 124.77, 123.62, 122.29, 121.23, 118.37, 114.78, 53.56, 53.38, 53.20, 53.02, 52.84, 45.75, 33.78, 29.77, 22.32, 13.51. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_4^+$ 267.1604; Found 267.1605. New compound.



1,2-di(Pyridin-2-yl)hexan-1-ol

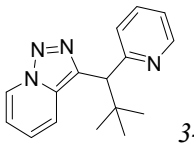
Side-product from the reaction of triazolopyridine **11**, isolated by RP-HPLC. Based on the ^{1}H NMR spectra, diastereomers were found in a ratio of 1.8:1 (**A**:**B**). Yield (yellow oil): 5 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (ddt, *J* = 4.9, 1.7, 0.9 Hz, 2H, **A**), 8.53 – 8.42 (m, 2H, **B**), 7.70 (dtd, *J* = 11.0, 7.7, 1.8 Hz, 2H, **A**), 7.56 (d, *J* = 7.9 Hz, 1H, **A**), 7.48 (dtd, *J* = 9.8, 7.7, 1.8 Hz, 2H, **B**), 7.32 – 7.16 (m, 4H, 3H, **A**, 1H, **B**), 7.09 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H, **B**), 7.03 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H, **B**), 6.89 (d, *J* = 7.8 Hz, 1H, **B**), 5.16 (d, *J* = 3.0 Hz,

1H, **A**), 5.12 (d, *J* = 3.4 Hz, 1H, **B**), 3.48 – 3.41 (m, 1H, **B**), 3.36 (d, *J* = 10.9 Hz, 1H, **B**), 2.03 (ddt, *J* = 8.9, 6.0, 3.4 Hz, 1H, **A**), 1.85 (dddd, *J* = 13.5, 11.0, 9.9, 5.2 Hz, 1H, **A**), 1.49 – 1.26 (m, 2H, **A**, 2H, **B**), 1.26 – 1.05 (m, 2H, **A**), 1.03 – 0.91 (m, 2H, **B**), 0.88 (t, *J* = 7.2 Hz, 3H, **B**), 0.72 (t, *J* = 7.3 Hz, 3H, **A**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.79, 163.60, 162.58, 161.66, 148.52, 148.42, 148.33, 148.10, 137.07, 136.73, 136.65, 136.34, 124.77, 124.45, 122.11, 122.01, 121.72, 121.65, 121.44, 120.59, 77.48, 77.36, 77.32, 77.16, 76.84, 76.32, 51.47, 51.27, 33.29, 29.97, 29.72, 27.73, 22.88, 22.72, 14.13, 13.95. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O^+$ 257.1648; Found 257.1649. New compound.



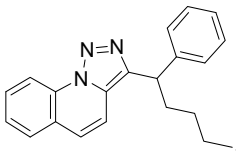
3-(2-Methyl-1-(pyridin-2-yl)butyl)-[1,2,3]triazolo[1,5-a]pyridine (**12**)

Triazolopyridine **12** was prepared from (*E*)-1,2-di(pyridin-2-yl)ethene (0.3 mmol) and *s*-BuLi, following the general procedure. Yield (yellow oil): 19 mg (29%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (dq, *J* = 7.1, 1.1 Hz, 1H), 8.51 (dq, *J* = 4.7, 1.6 Hz, 1H), 8.04 (ddt, *J* = 8.9, 3.8, 1.2 Hz, 1H), 7.61 (dq, *J* = 6.3, 2.2 Hz, 2H), 7.13 (dddt, *J* = 10.9, 8.3, 5.0, 1.3 Hz, 2H), 6.89 (td, *J* = 6.8, 1.2 Hz, 1H), 4.42 (t, *J* = 10.3 Hz, 1H), 2.75 (dddd, *J* = 10.3, 8.7, 6.8, 3.8 Hz, 1H), 1.47 – 1.26 (m, 1H), 1.23 – 1.03 (m, 1H), 0.96 – 0.73 (m, 6H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 161.56, 161.49, 147.27, 138.71, 137.28, 131.70, 131.66, 124.70, 123.82, 123.80, 123.71, 121.55, 121.52, 118.75, 114.91, 53.56, 53.38, 53.20, 53.02, 52.84, 50.97, 38.19, 38.07, 27.07, 26.77, 16.75, 16.48, 10.47, 10.31. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_4^+$ 267.1604; Found 267.1608. New compound.



3-(2,2-Dimethyl-1-(pyridin-2-yl)propyl)-[1,2,3]triazolo[1,5-a]pyridine (**13**)

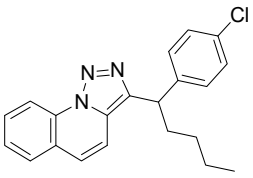
Triazolopyridine **13** was prepared from (*E*)-1,2-di(pyridin-2-yl)ethene (0.25 mmol) and *t*-BuLi, following the general procedure. Yield (pale yellow solid): 25 mg (38%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 – 8.59 (m, 1H), 8.56 – 8.49 (m, 1H), 8.01 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.97 – 7.90 (m, 1H), 7.62 (td, *J* = 7.7, 1.9 Hz, 1H), 7.21 – 7.08 (m, 2H), 6.90 (td, *J* = 6.8, 1.3 Hz, 1H), 4.53 (s, 1H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.63, 148.03, 138.52, 136.17, 132.95, 125.46, 125.07, 124.15, 121.74, 119.34, 115.13, 56.11, 36.41, 28.67. **HRMS** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_4^+$ 267.1604; Found 267.1605. New compound.



3-(1-Phenylpentyl)-[1,2,3]triazolo[1,5-a]quinoline (**14**)

Triazoloquinoline **14** was prepared from (*E*)-2-styrylquinoline (0.3 mmol) and *n*-BuLi, following the general procedure. The resulting yellow solid was washed with pentane and dried by vacuum. Yield (yellow solid): 43.6

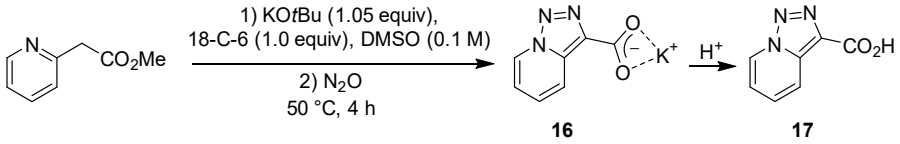
mg (46%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.4 Hz, 1H), 7.77 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.34 (d, *J* = 9.3 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.15 (m, 2H), 4.34 (t, *J* = 7.8 Hz, 1H), 2.52 (dddd, *J* = 13.3, 9.5, 7.8, 5.7 Hz, 1H), 2.24 (dddd, *J* = 13.5, 9.0, 7.7, 6.0 Hz, 1H), 1.48 – 1.18 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.90, 143.22, 132.16, 129.95, 129.18, 128.68, 128.49, 128.10, 127.06, 126.63, 125.52, 124.11, 116.40, 114.88, 43.24, 35.39, 30.29, 22.78, 14.18. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}N_3^+$ 316.1808; Found 316.1811. New compound.



3-(1-(4-Chlorophenyl)pentyl)-[1,2,3]triazolo[1,5-a]quinoline (**15**)

Triazoloquinoline **15** was prepared from (*E*)-2-(4-chlorostyryl)quinoline (0.3 mmol) and *n*-BuLi, following the general procedure. The resulting yellow solid was washed with pentane and dried by vacuum. Yield (pale yellow solid): 40.0 mg (38%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.75 – 7.59 (m, 2H), 7.48 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.31 – 7.27 (m, 3H), 7.19 (dt, *J* = 6.4, 2.2 Hz, 2H), 7.12 (d, *J* = 9.4 Hz, 1H), 4.24 (t, J = 7.8 Hz, 1H), 2.51 – 2.29 (m, 1H), 2.23 – 2.03 (m, 1H), 1.40 – 1.08 (m, 4H), 0.79 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.64, 142.42, 132.36, 132.16, 130.08, 129.46, 129.14, 128.80, 128.55, 127.16, 125.81, 124.10, 116.42, 114.57, 77.48, 77.36, 77.16, 76.84, 42.60, 35.48, 30.22, 22.73, 14.14. **HRMS** (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}ClN_3^+$ 350.1419; Found 350.1417. New compound.

5. Synthesis of triazole 17



A quick optimization was performed (Table S5.1). In DMSO and in THF, oligomers were formed, which hampered the conversion (entry 1 and 4). Addition of 18-crown-6 did prevent the formation of oligomers (entry 2 and 5), whereas TMEDA was not suited (entry 3). The conversion was followed by ^{1}H NMR in d_6-DMSO (entry 2) and d_8-THF (entry 5). In d_8-THF, a mixture of products was observed. In d_6-DMSO, the conversion was clean and a more detailed ^{1}H NMR study was performed.

Table S5.1. Screening of reaction conditions

Entry	Solvent	Additive	T	Result
1	DMSO	-	rt	Oligomers
2	DMSO	18-crown-6	rt	Dissolved → followed by NMR
3	DMSO	TMEDA	rt	Oligomers
4	THF	-	rt	Oligomers
5	THF	18-crown-6	rt, 50 °C for 1 h	Dissolved → followed by NMR: Mixture of products

In a J-Young's NMR tube, methyl 2-pyridylacetate (3 µl) was dissolved in d_3-DMSO/DMSO (1:1, 0.5 ml) and KO*t*Bu (1.05 eq) and 18-crown-6 (1.0 eq) were added. A blank measurement was taken after which the sample was subjected to an N_2O atmosphere (3x N_2O/*vac* cycles) and heated at 50 °C. The conversion was followed by ^{1}H NMR over time (Figure S5.1).

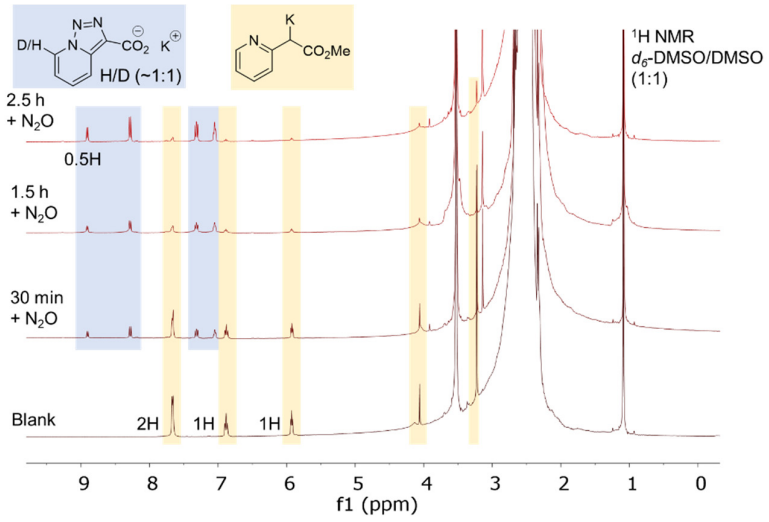
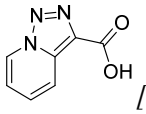


Figure S5.1. ^{1}H NMR spectra for the conversion of metalated methyl 2-pyridylacetate into **16** using the conditions given in entry 2, table S5.1.

According to the ^{1}H NMR measurements, the deprotonation by KO*t*Bu was quantitative. After 2.5 h, the reaction was nearly complete. Under basic conditions, H/D exchange of acidic protons can occur in d_6-DMSO.[9,10] The proton next to the N-atom in the ring of the triazolopyridine is known to be acidic, and partial H/D exchange was observed. The formation of salt **16** was corroborated by X-ray diffraction. Single crystals of **16** were obtained within 2 weeks after layering the DMSO sample with ethyl acetate (see ESI, 6. X-ray crystallography).

Potassium [1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (**16**)

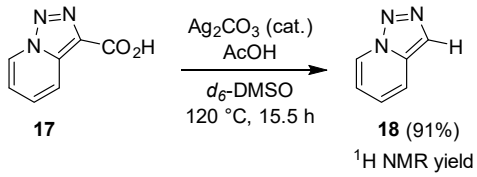
In a 100 ml oven-dried Schlenk flask: Methyl 2-(pyridin-2-yl)acetate (0.5 mmol) was dissolved in DMSO (5 ml) and KO*t*Bu (1.05 equiv) and 18-crown-6 (1.0 equiv) were added. The reaction mixture was subjected to N_2O (3x N_2O/*vac* cycles) and heated at 50 °C for 4 h in a pre-heated oil bath. After cooling down, the reaction mixture was poured slowly into a round bottom flask with toluene (50 ml). The resulting precipitate was isolated by filtration and washed with several portions of toluene and pentane. The brown residue was triturated with pentane and then dried under vacuum. Traces of 18-crown-6 and DMSO remained despite repeated washings. Yield (red/brown solid): 92 mg (91%). **^{1}H NMR** (400 MHz, CD_3OD) δ 8.88 (dt, *J* = 7.1, 1.1 Hz, 1H), 8.33 (dt, *J* = 8.9, 1.3 Hz, 1H), 7.49 (ddd, *J* = 9.0, 6.7, 1.0 Hz, 1H), 7.17 (td, *J* = 6.8, 1.3 Hz, 1H). **^{13}C NMR** (101 MHz, CD_3OD) δ 168.86, 137.11, 135.36, 128.35, 126.56, 121.21, 117.26, 71.33 (18-crown-6), 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36.



[1,2,3]Triazolo[1,5-a]pyridine-3-carboxylic acid (**17**)

Further work-up was performed by dissolving **16** in a minimal amount of water while heating. The pH of the solution was lowered to pH 2 with HCl. The reaction mixture was concentrated and the liquid was removed. The remaining solid was washed with water, pentane, and freeze-dried in pentane. Yield (light brown solid): 73 mg (89%). **^{1}H NMR** (400 MHz, CD_3OD) δ 9.05 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.27 (dt, *J* = 8.9, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.9, 6.7, 1.0 Hz, 1H), 7.32 (td, *J* = 6.9, 1.3 Hz, 1H). **^{13}C NMR** (151 MHz, CD_3OD) δ 164.08, 136.32, 131.03, 130.67, 127.52, 120.11, 118.20, 49.42, 49.28, 49.27, 49.14, 49.13, 49.00, 48.99, 48.86, 48.85, 48.72, 48.70, 48.57, 48.56. **HRMS** (APPI/LTQ-Orbitrap) *m/z*: $[M]^+$ Calcd for $C_7H_5N_3O_2^+$ 163.0376; Found 163.0384.

*Decarboxylation of **17***



17 **18** (91%)
^{1}H NMR yield

We have investigated the removal of the CO_2H group via Ag(I)-catalysis to give the plain triazole **18**.[11] In a J-Young NMR tube, 4 mg of **17** was dissolved in d_6-DMSO (0.5 ml) and trimethoxybenzene was added as internal standard. A blank spectrum was recorded. Subsequently, Ag_2CO_3 (15 mol%) and acetic acid (1 µl) were added and the reaction mixture was heated for 15.5 h at 120 °C. A nearly clean conversion was observed and the ^{1}H NMR yield of [1,2,3]triazolo[1,5-*a*]pyridine **18** was 91 %. Note that triazolopyridines will decompose at higher temperatures and release N_2.[1]

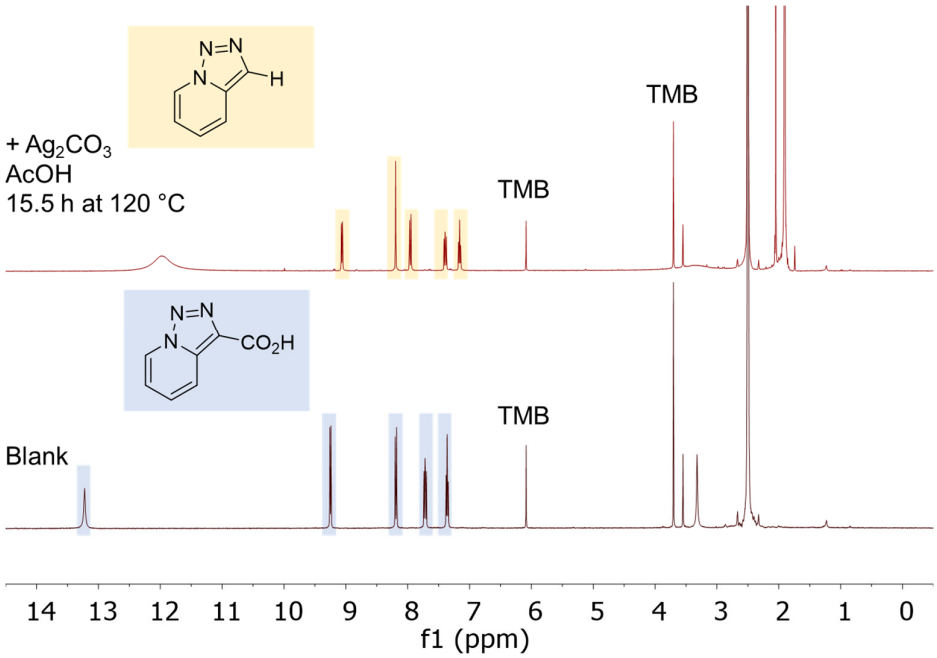


Figure S5.2. ^{1}H NMR spectra for the protodecarboxylation of **17** to **18** in d_6-DMSO. TMB = trimethoxybenzene.

6. X-ray crystallography

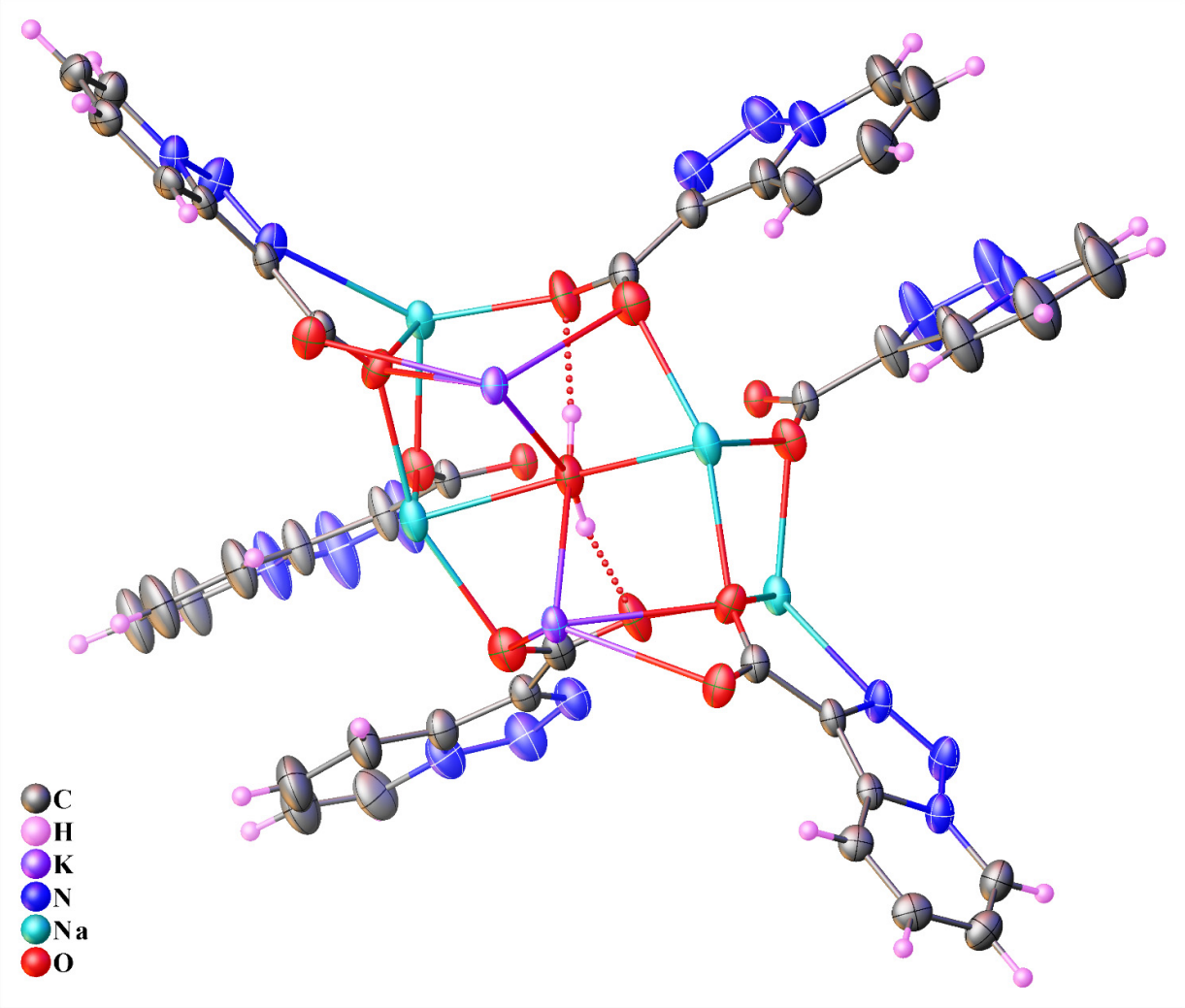


Figure S6.1. Molecular structure of **16** in the crystal (thermal ellipsoids are drawn at 50%).

Table S6.1. Crystallographic data of **16**.

Compound	**16**
Formula	$C_{42}H_{26}K_2N_{18}Na_4O_{13}$
$D_{calc.}$/ g cm^{-3}	1.661
μ/mm^{-1}	2.948
Formula Weight	1160.97
Colour	colourless
Shape	prism-shaped
Size/mm^3	0.09×0.06×0.02
T/K	140.00(10)
Crystal System	monoclinic
Space Group	$P2/n$
a/Å	14.2718(7)
b/Å	6.5810(3)
c/Å	24.714(3)
α/°	90
β/°	90.107(7)
γ/°	90
V/Å^3	2321.2(3)
Z	2
Z'	0.5
Wavelength/Å	1.54184
Radiation type	Cu$K\alpha$
Θ_{min}/°	3.573
Θ_{max}/°	77.339
Measured Refl's.	22718
Indep't Refl's	4567
Refl's I≥2σ(I)	3099
R_{int}	0.0655
Parameters	360
Restraints	655
Largest Peak/e Å^{-3}	0.715
Deepest Hole/e Å^{-3}	-0.579
GooF	1.042
wR_2 (all data)	0.1704
wR_2	0.1545
R_1 (all data)	0.1061
R_1	0.0634
CCDC number	2094800

Experimental. Colourless prism-shaped crystals of **16** were grown within 2 weeks by layering a solution of **16** in DMSO with ethyl acetate. A suitable crystal with dimensions 0.09 × 0.06 × 0.02 mm^3 was selected and mounted on a XtaLAB Synergy R, DW system, HyPix-Arc 150 diffractometer. The crystal was kept at a steady T = 140.00(10) K during data collection. The structure was solved with the ShelXT 2018/2[10]solution program using dual methods and by using Olex2 1.3[11] as the graphical interface. The model was refined with ShelXL 2018/3[12] using full matrix least squares minimisation on $|F|^2$.

Structure Quality Indicators

Reflections:	d min (Cu\a) 2θ=154.7° 0.79	I/σ(I) CIF 13.2	Rint CIF 6.55%	Full 135.4° 93% to 154.7 99.8
Refinement:	Shift CIF 0.000	Max Peak CIF 0.7	Min Peak CIF -0.6	GooF CIF 1.042

Data were measured using ω scans using Cu$K\alpha$ radiation. The diffraction pattern was indexed and the total number of runs and images was based on the strategy calculation from the program CrysAlis^{Pro} 1.171.41.110a.[13] The maximum resolution achieved was Θ = 77.339° (0.79 Å). The unit cell was refined using CrysAlis^{Pro} 1.171.41.110a on 6064 reflections, 27% of the observed reflections.

Data reduction, scaling and absorption corrections were performed using CrysAlis^{Pro} 1.171.41.110a.[13] The final completeness is 99.80 % out to 77.339° in Θ. A Gaussian absorption correction was performed using CrysAlis^{Pro} 1.171.41.110a. Numerical absorption correction based on Gaussian integration over a multifaceted crystal model. Empirical absorption correction using spherical harmonics as implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient μ of this material is 2.948 mm^{-1} at this wavelength (λ = 1.54184Å) and the minimum and maximum transmissions are 0.802 and 1.000.

The structure was solved and the space group $P2/n$ (# 13) determined by the ShelXT 2018/2[10]structure solution program using using dual methods and refined by full matrix least squares minimisation on $|F|^2$ using version 2018/3 of ShelXL[12]. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model. Most hydrogen atom positions were calculated geometrically and refined using the riding model, but the hydrogen atom bound to O7 was found in a difference map and refined freely.

The value of Z' is 0.5. This means that only half of the formula unit is present in the asymmetric unit, with the other half consisting of symmetry equivalent atoms.

Crystallographic and refinement data are summarized in Table S6.1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre and correspond to the CCDC number of 2094800. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

7. NMR Spectra

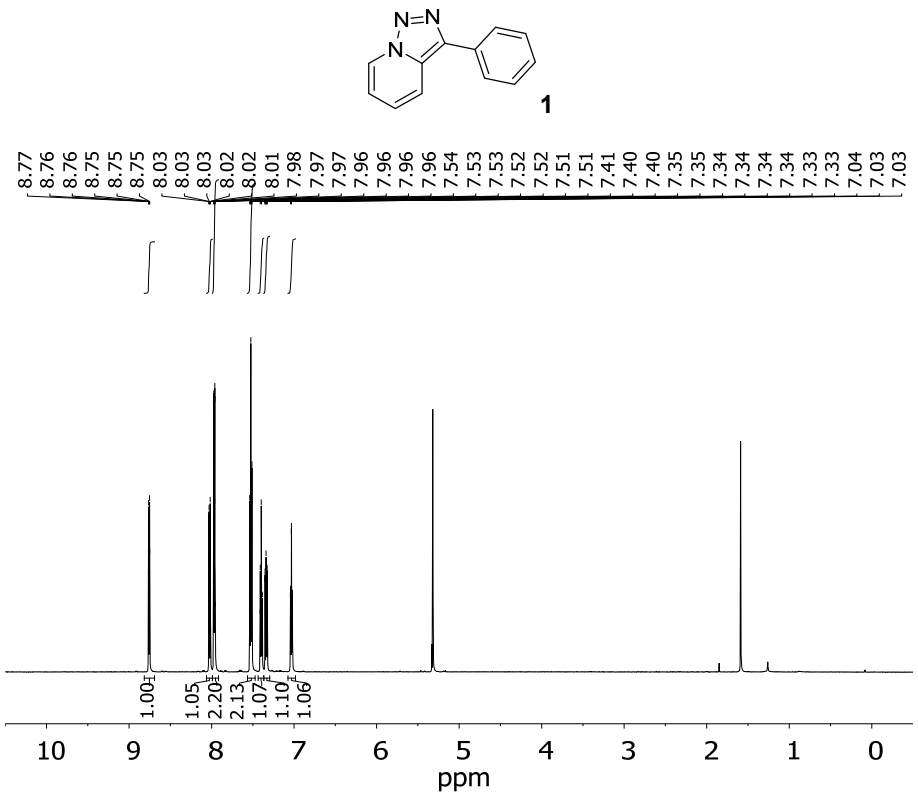


Figure S7.1. ^{1}H NMR spectrum of **1** (400 MHz, CD_2Cl_2).

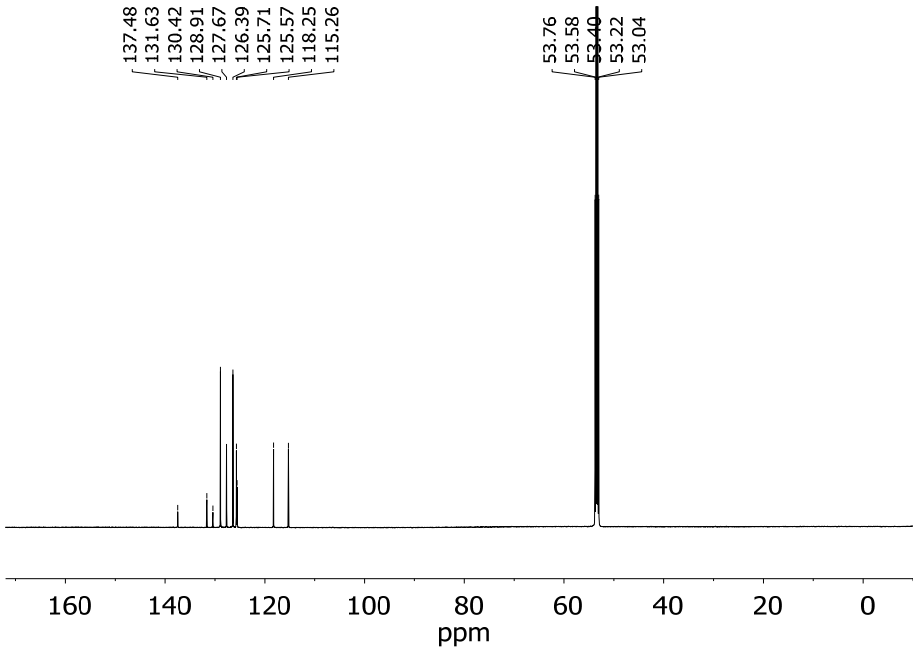


Figure S7.2. ^{13}C NMR spectrum of **1** (151 MHz, CD_2Cl_2).

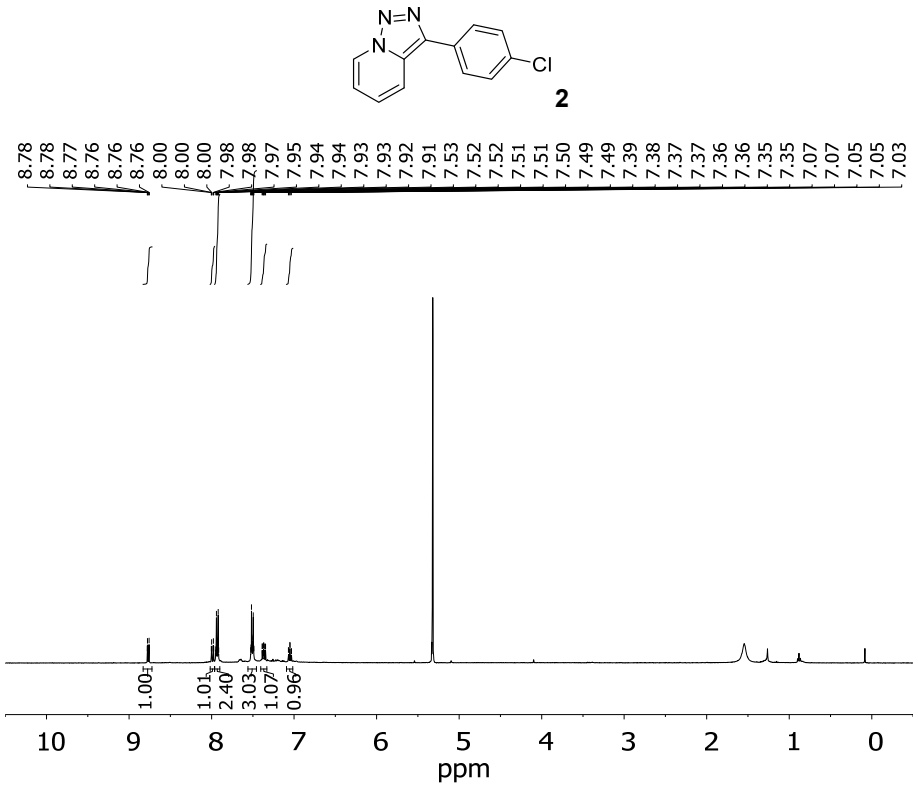


Figure S7.3. ^{1}H NMR spectrum of **2** (400 MHz, CD_2Cl_2).

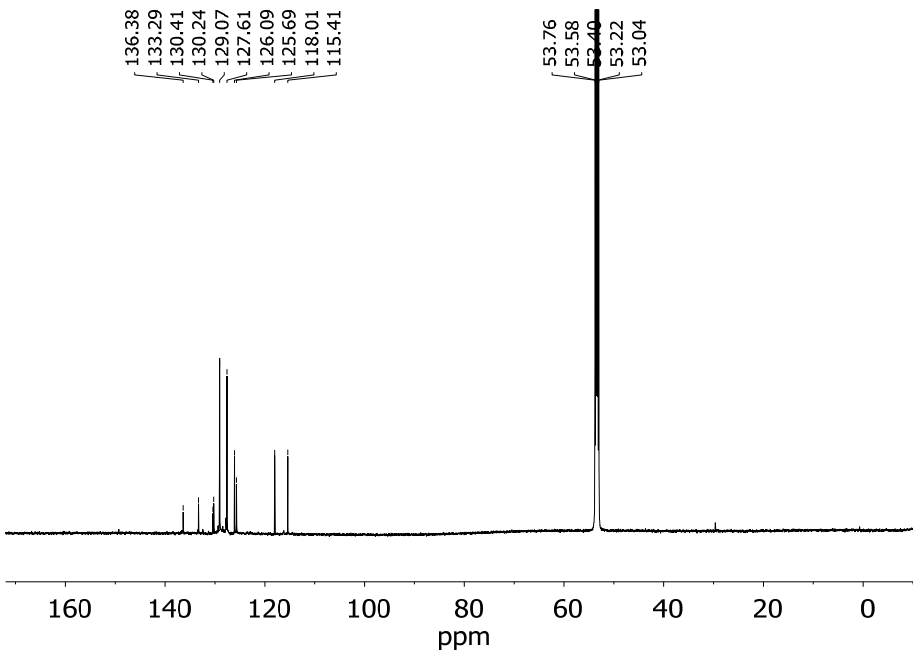


Figure S7.4. ^{13}C NMR spectrum of **2** (151 MHz, CD_2Cl_2).

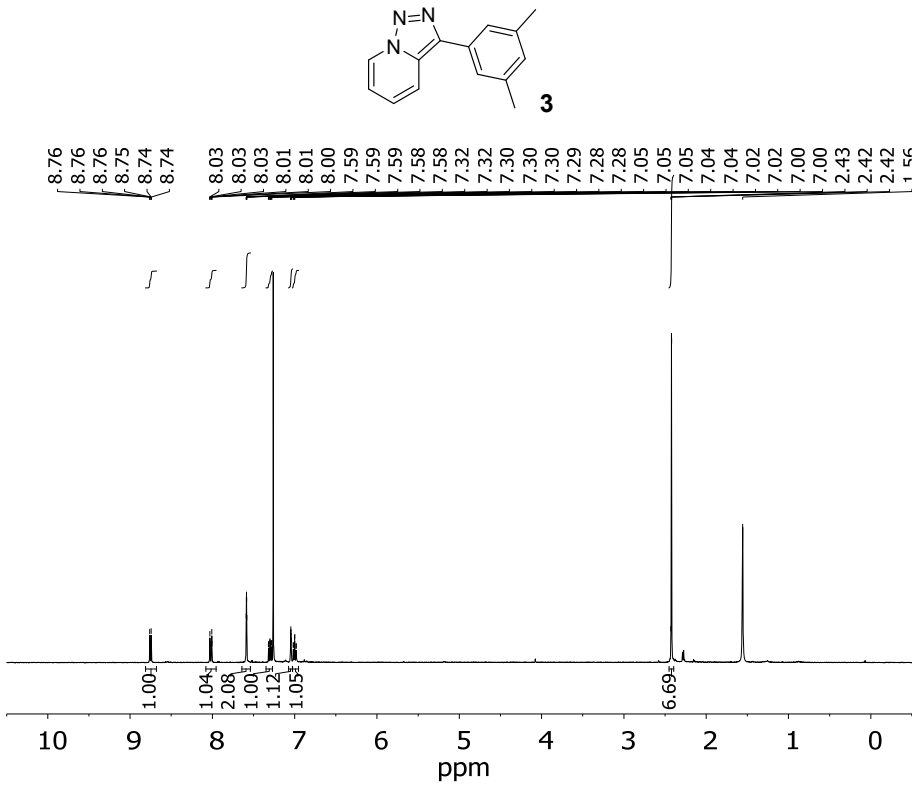


Figure S7.5. ^{1}H NMR spectrum of **3** (400 MHz, $CDCl_3$).

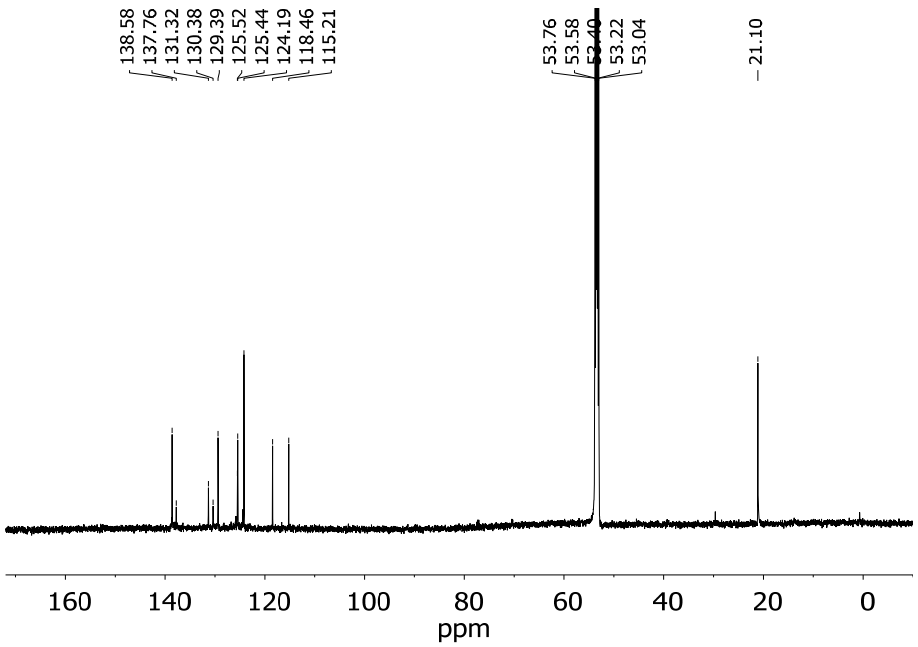


Figure S7.6. ^{13}C NMR spectrum of **3** (CD_2Cl_2).

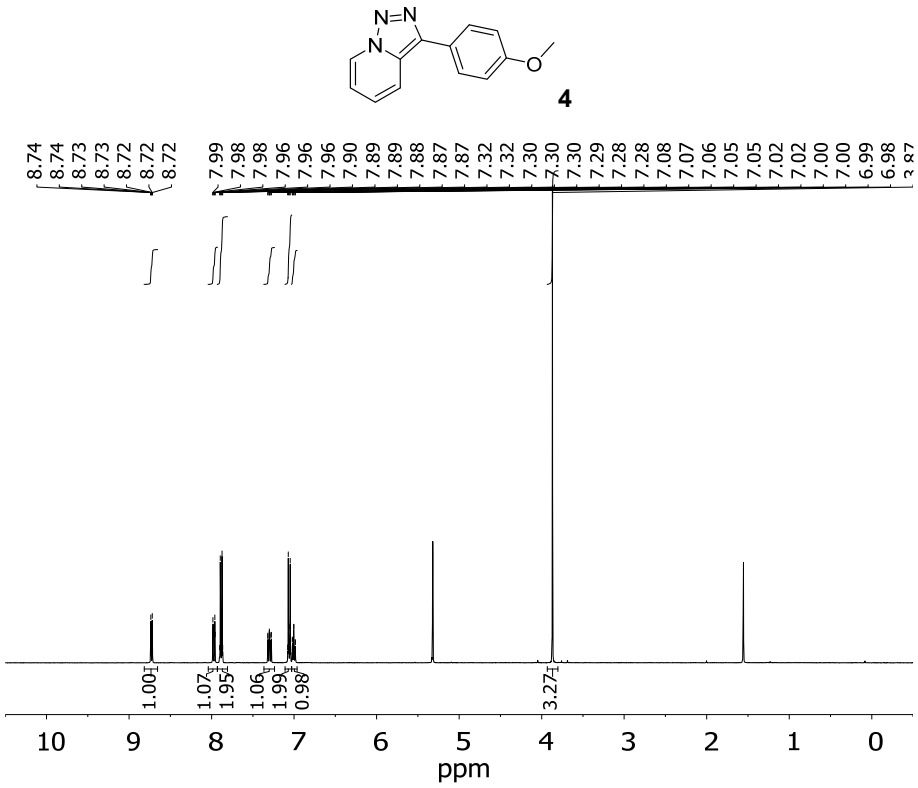


Figure S7.7. ^{1}H NMR spectrum of **4** (400 MHz, CD_2Cl_2).

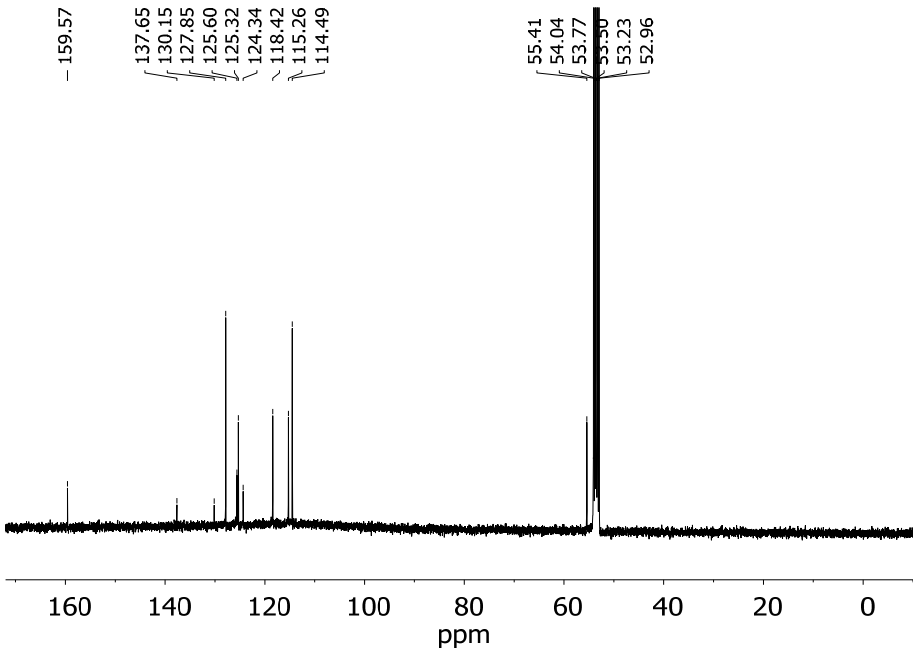


Figure S7.8. ^{13}C NMR spectrum of **4** (101 MHz, CD_2Cl_2).

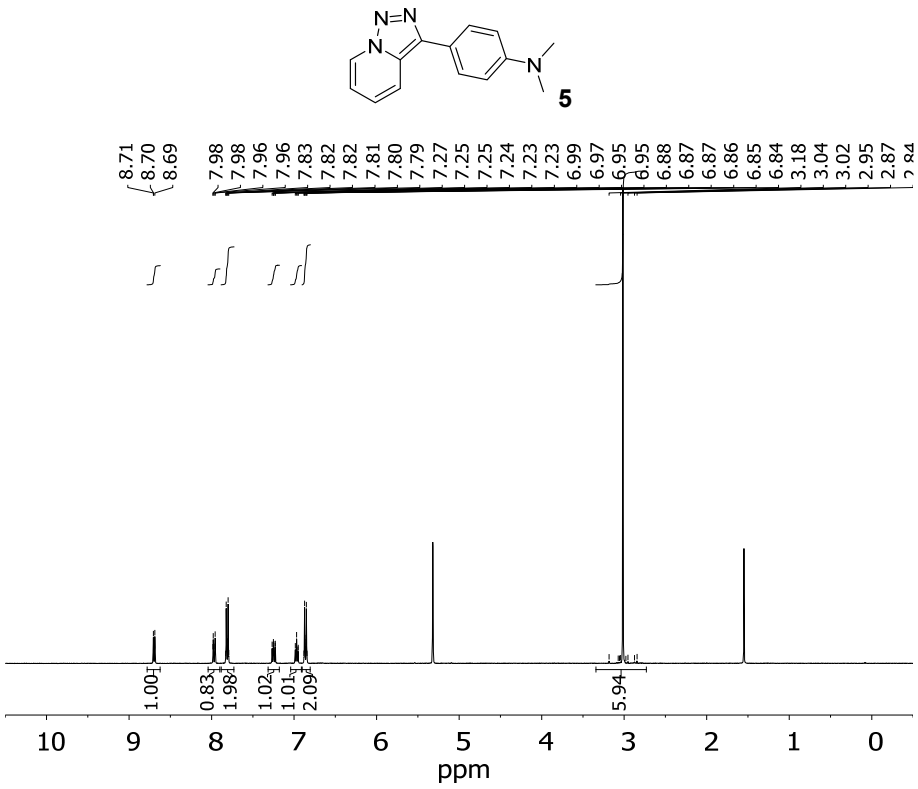


Figure S7.9. ^{1}H NMR spectrum of **5** (400 MHz, CD_2Cl_2).

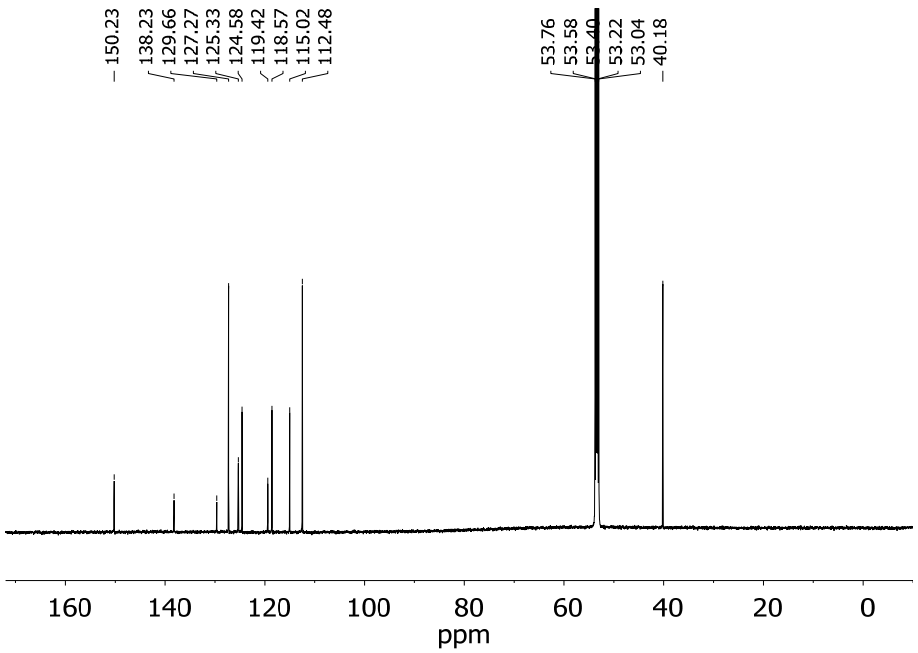


Figure S7.10. ^{13}C NMR spectrum of **5** (151 MHz, CD_2Cl_2).

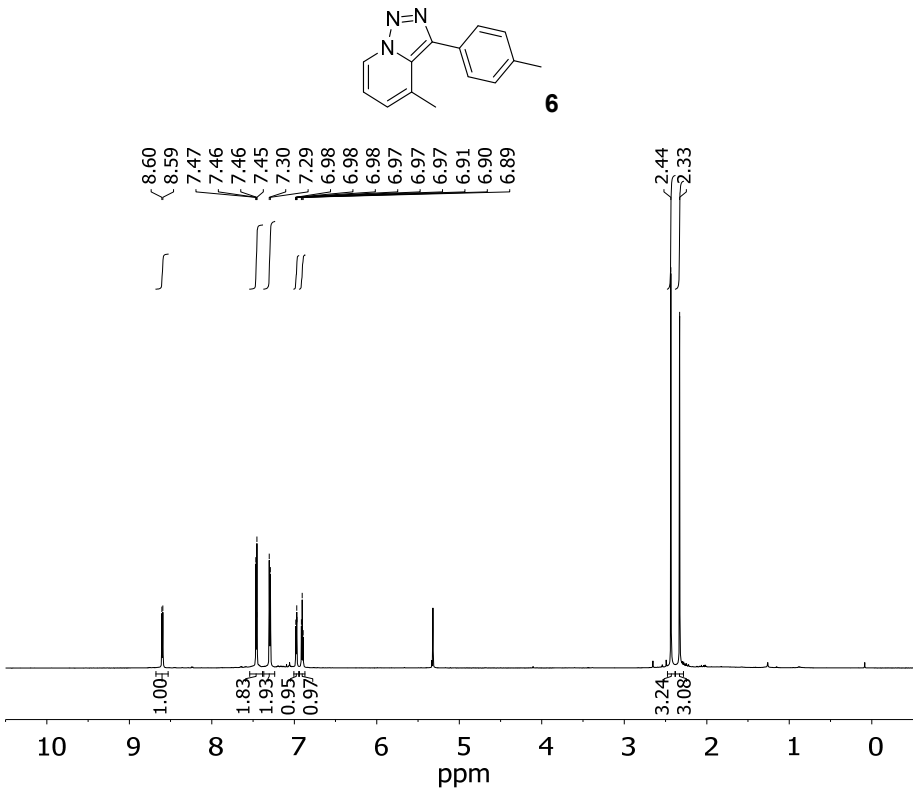


Figure S7.11. ^{1}H NMR spectrum of **6** (400 MHz, CD_2Cl_2).

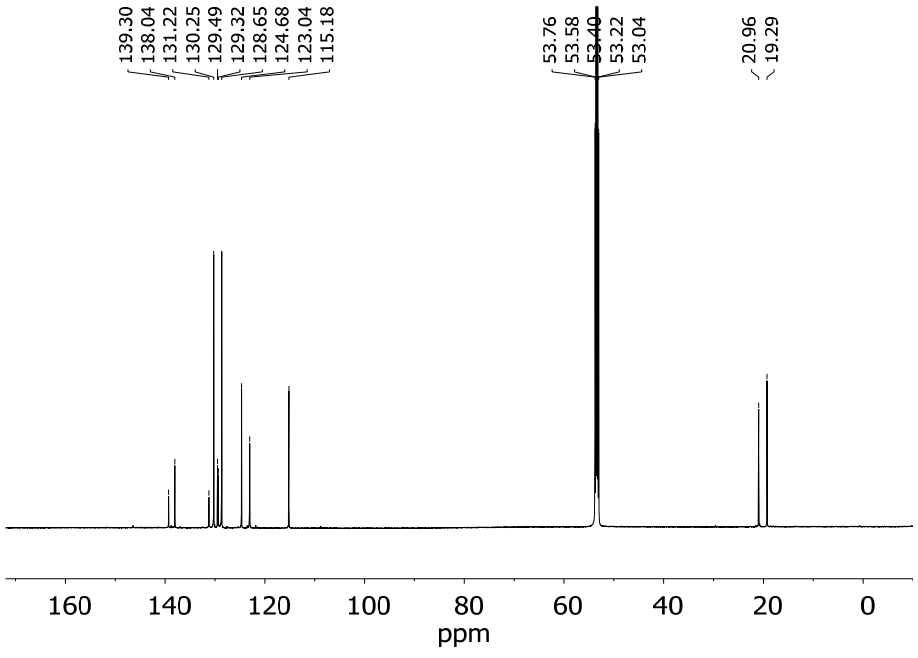


Figure S7.12. ^{13}C NMR spectrum of **6** (CD_2Cl_2).

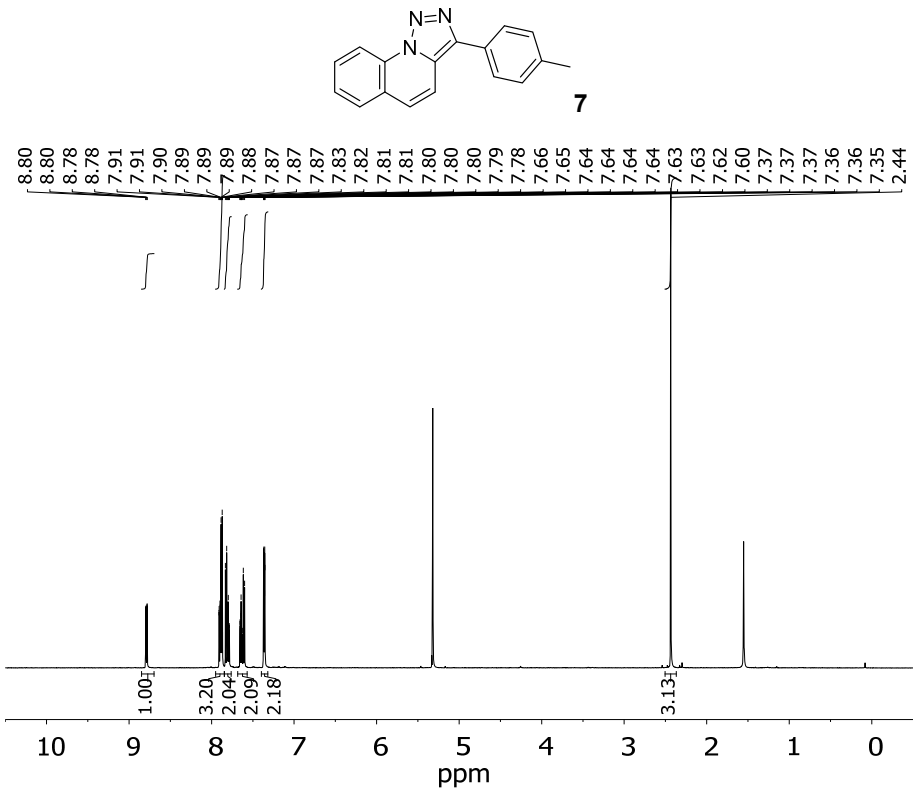


Figure S7.13. ^{1}H NMR spectrum of **7** (600 MHz, CD_2Cl_2).

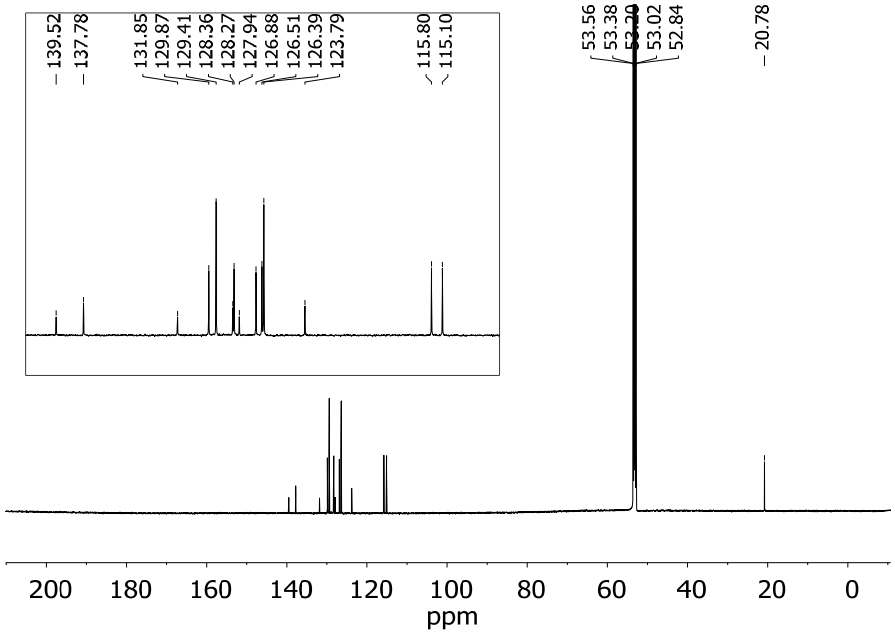


Figure S7.14. ^{13}C NMR spectrum of **7** (151 MHz, CD_2Cl_2).

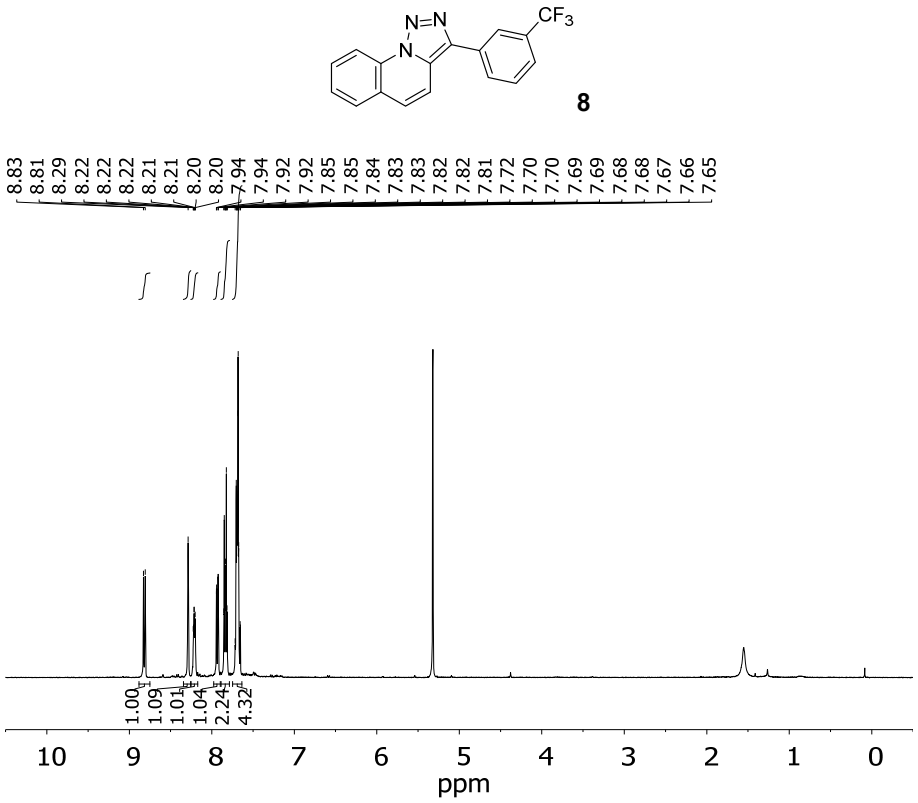


Figure S7.15. ^{1}H NMR spectrum of **8** (400 MHz, CD_2Cl_2).

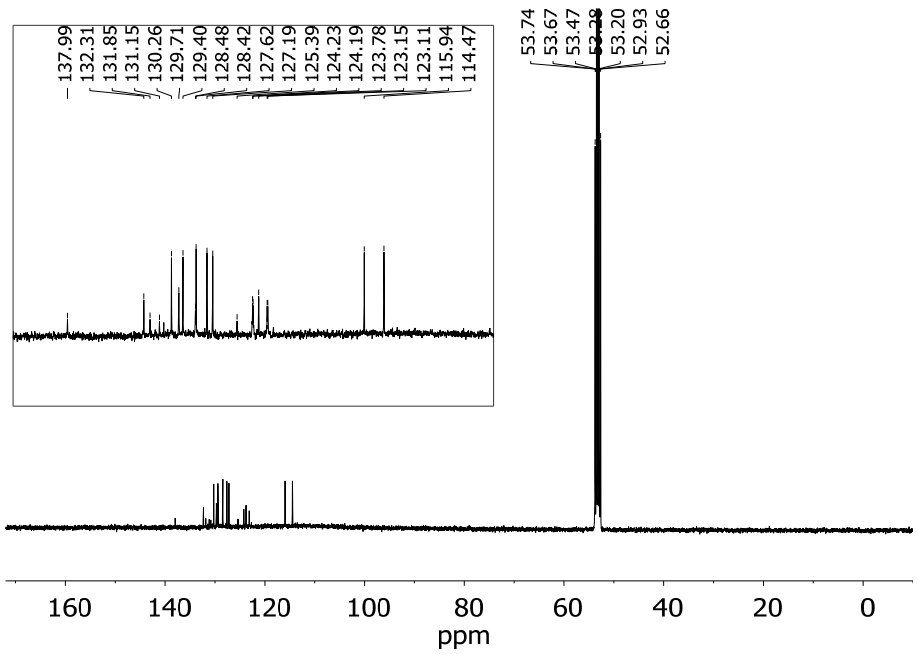


Figure S7.16. ^{13}C NMR spectrum of **8** (101 MHz, CD_2Cl_2)

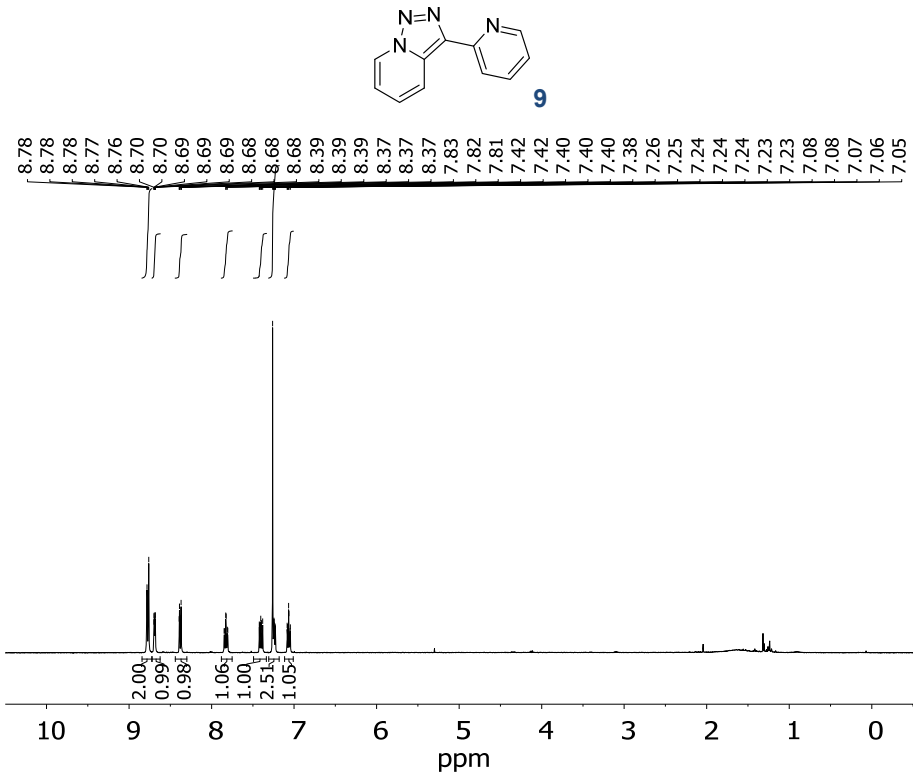


Figure S7.17. ^{1}H NMR spectrum of **9** (400 MHz, $CDCl_3$).

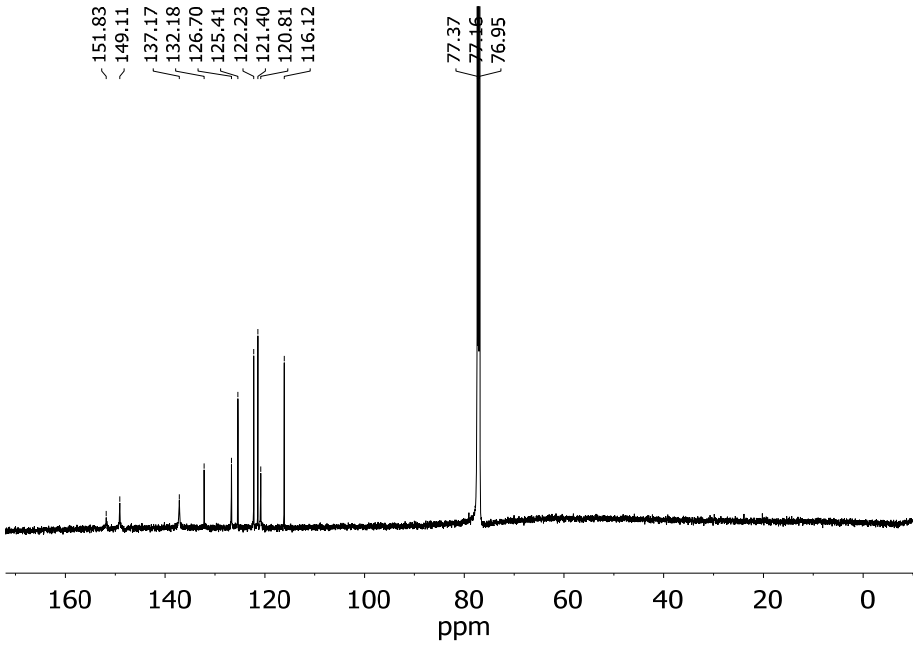


Figure S7.18. ^{13}C NMR spectrum of **9** (101 MHz, $CDCl_3$).

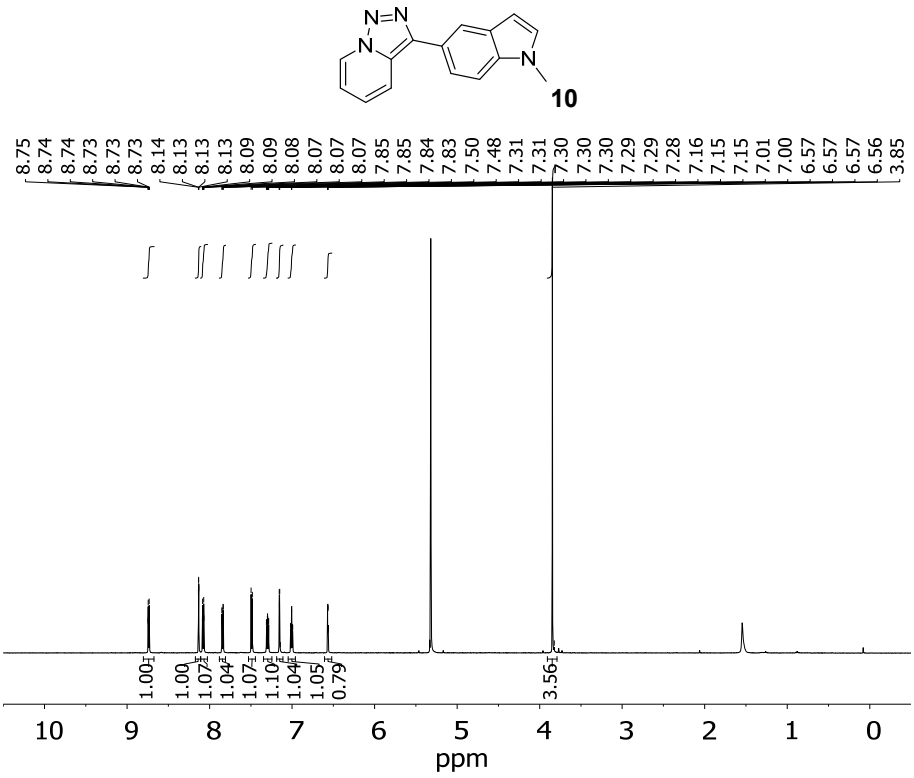


Figure S7.19. ^{1}H NMR spectrum of **10** (600 MHz, CD_2Cl_2).

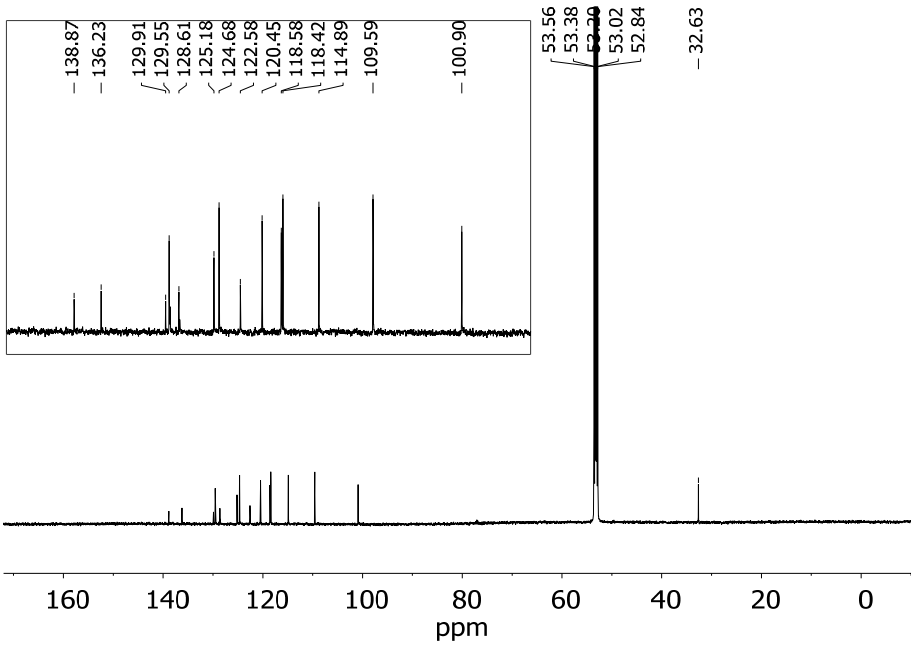


Figure S7.20. ^{13}C NMR spectrum of **10** (101 MHz, CD_2Cl_2).

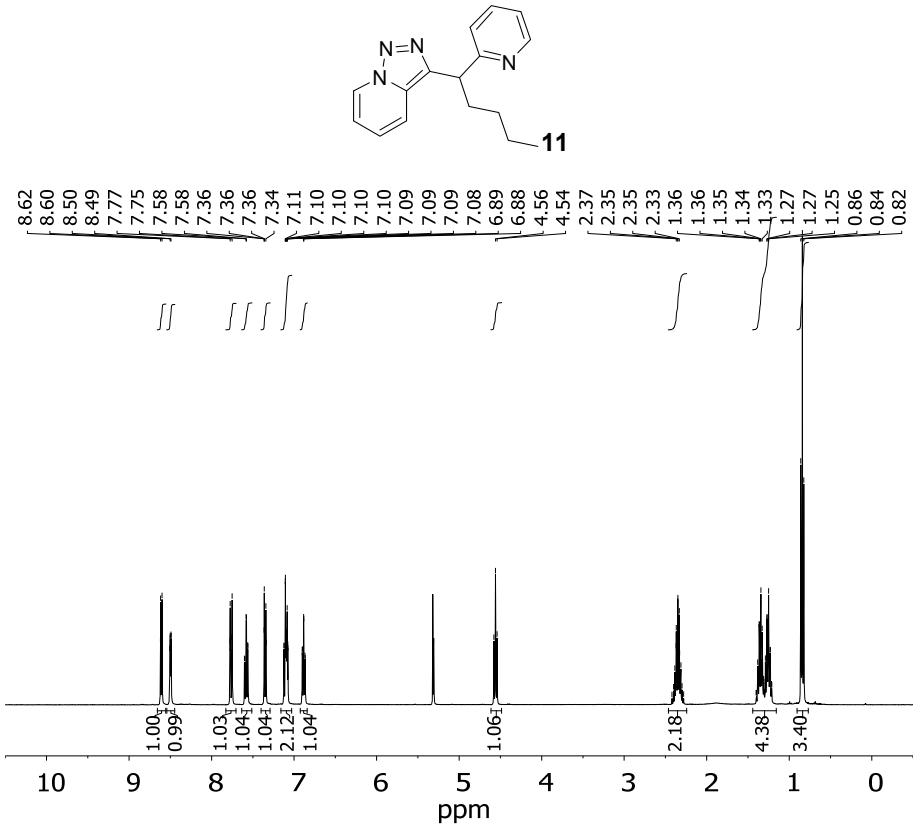


Figure S7.21. ^{1}H NMR spectrum of **11** (600 MHz, CD_2Cl_2).

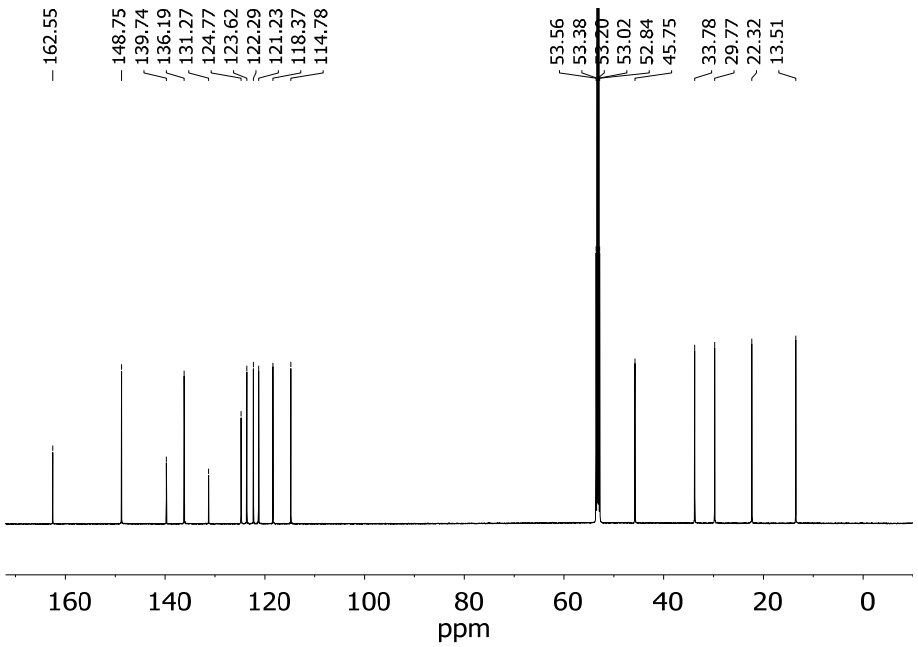


Figure S7.22. ^{13}C NMR spectrum of **11** (101 MHz, CD_2Cl_2).

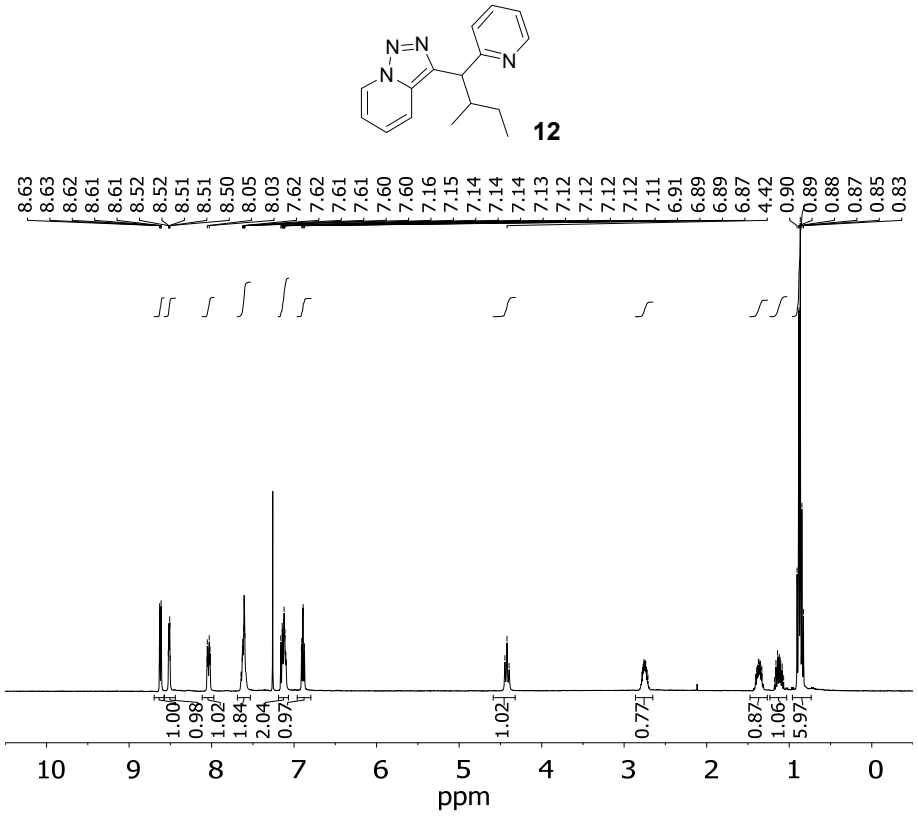


Figure S7.23. ^{1}H NMR spectrum of **12** (400 MHz, $CDCl_3$).

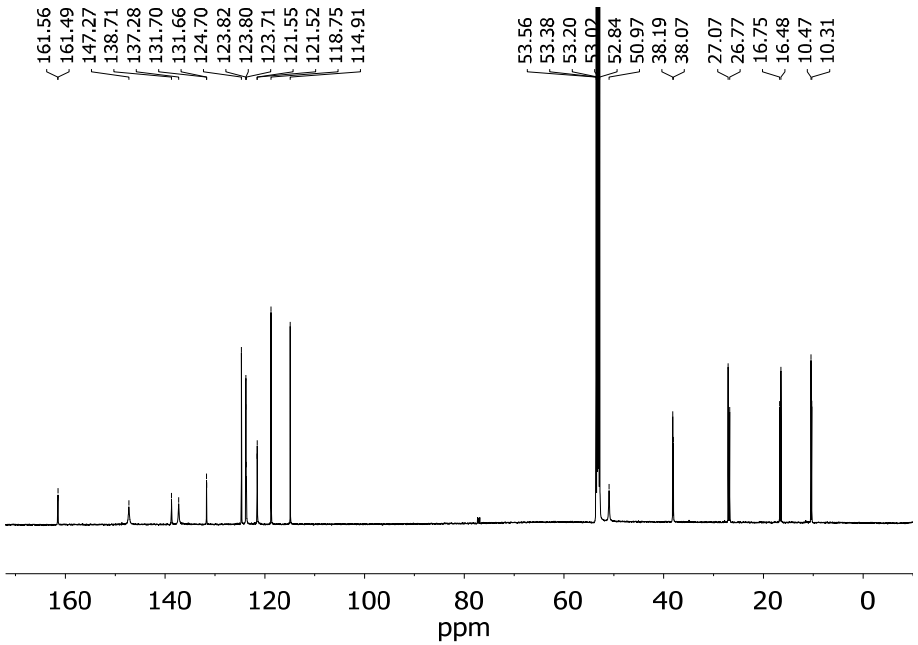


Figure S7.24. ^{13}C NMR spectrum of **12** (101 MHz, CD_2Cl_2).

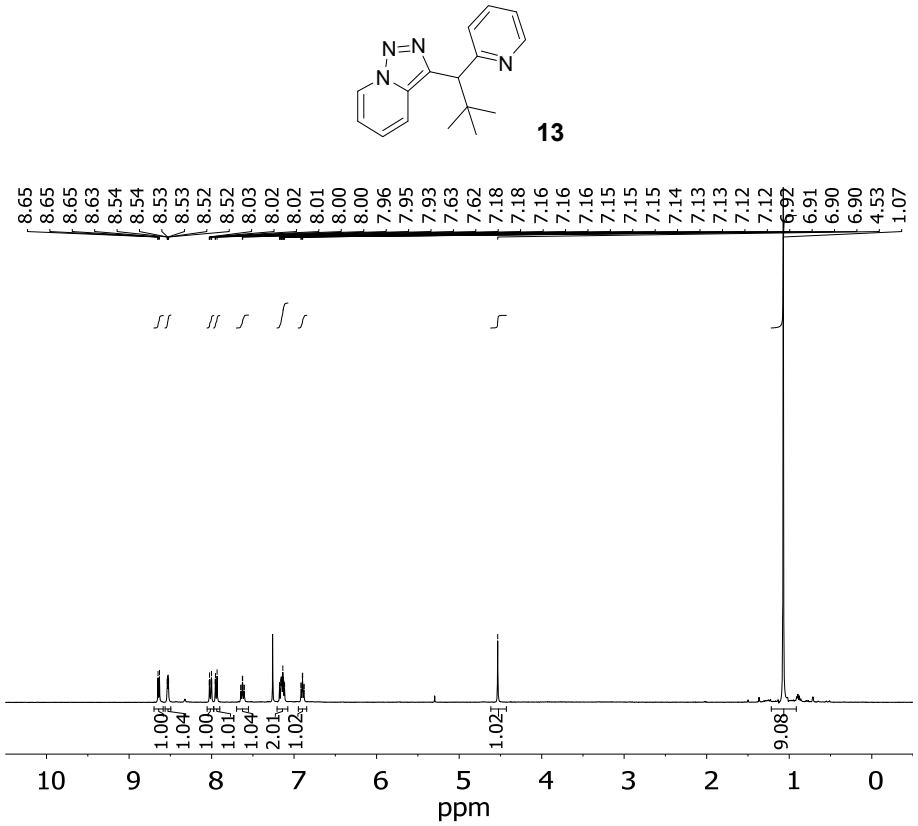


Figure S7.25. ^{1}H NMR spectrum of **13** (400 MHz, $CDCl_3$).

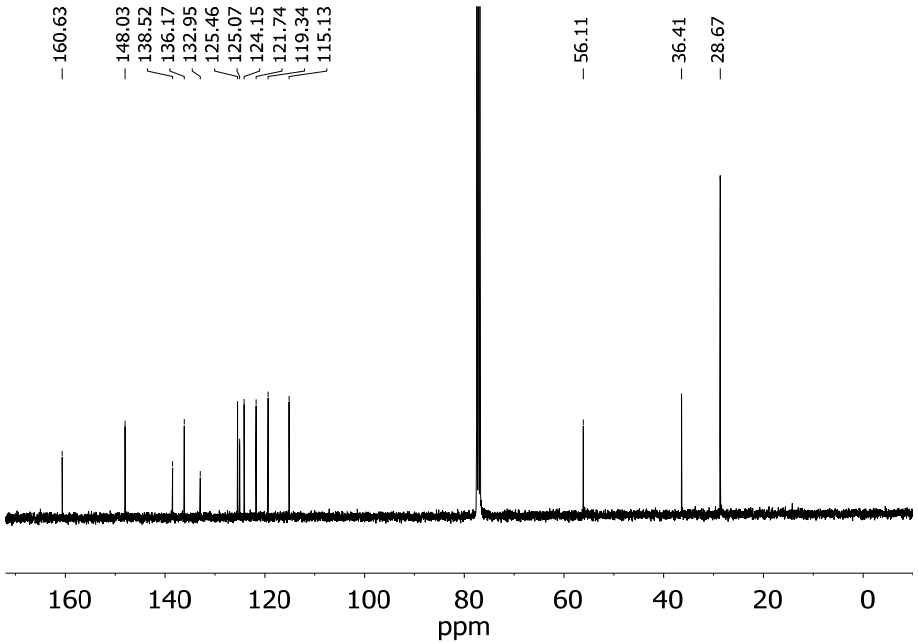


Figure S7.26. ^{13}C NMR spectrum of **13** (101 MHz, $CDCl_3$).

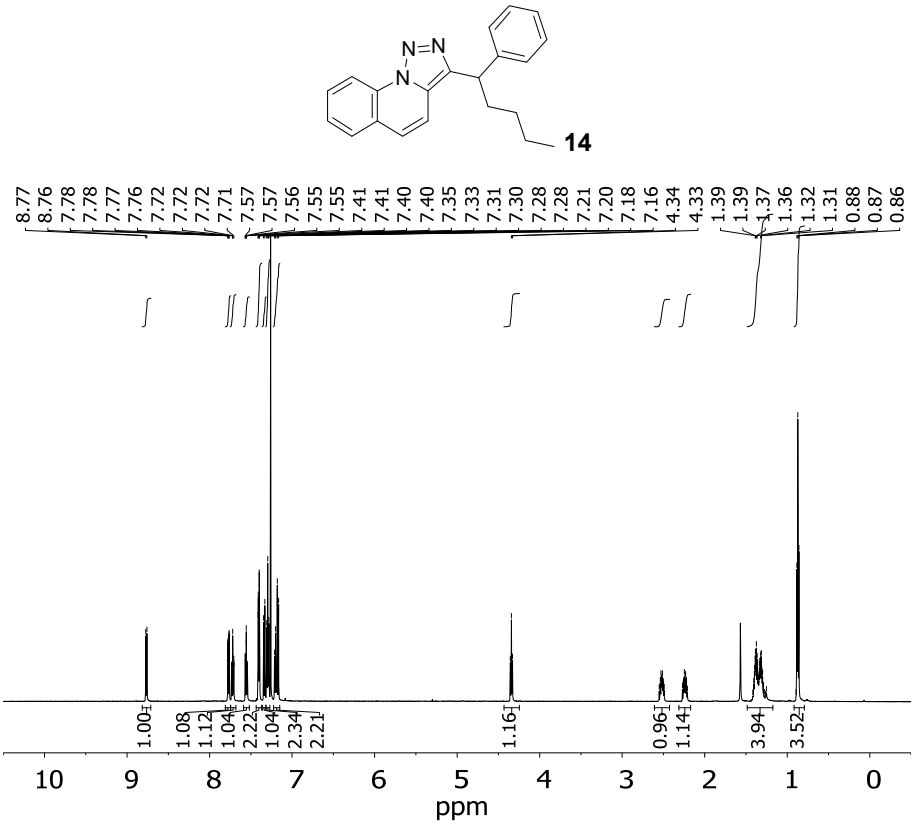


Figure S7.27. ^{1}H NMR spectrum of **14** (600 MHz, $CDCl_3$).

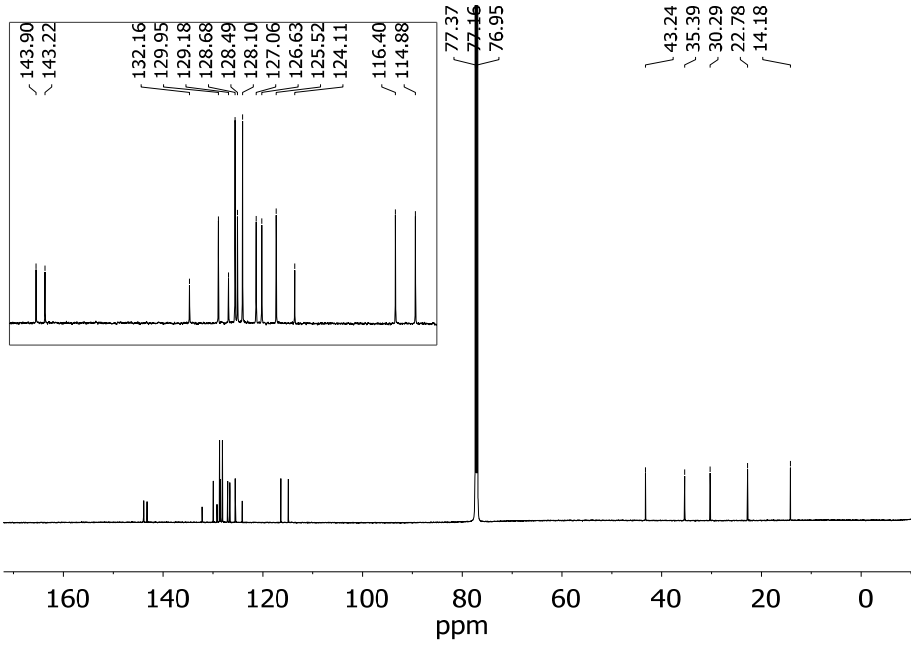


Figure S7.28. ^{13}C NMR spectrum of **14** (101 MHz, $CDCl_3$).

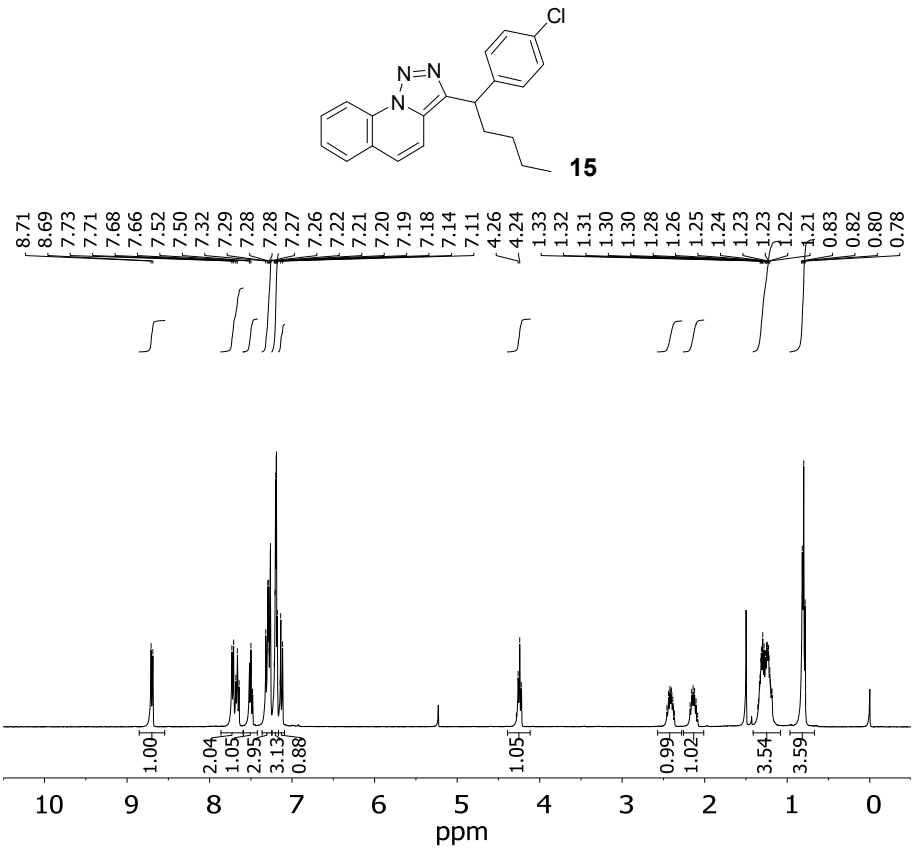


Figure S7.29. ^{1}H NMR spectrum of **15** (400 MHz, $CDCl_3$).

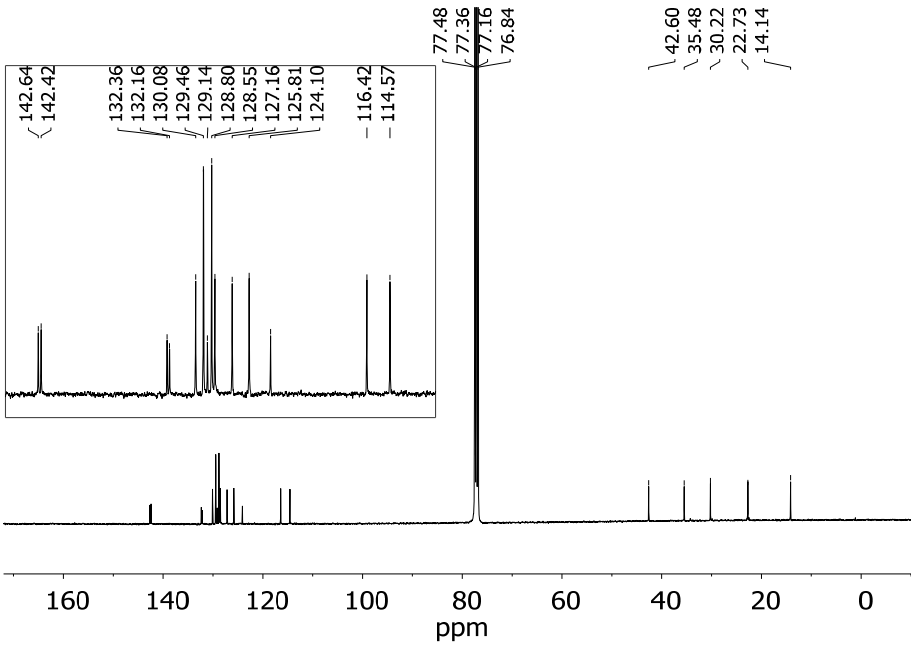


Figure S7.30. ^{13}C NMR spectrum of **15** (101 MHz, $CDCl_3$).

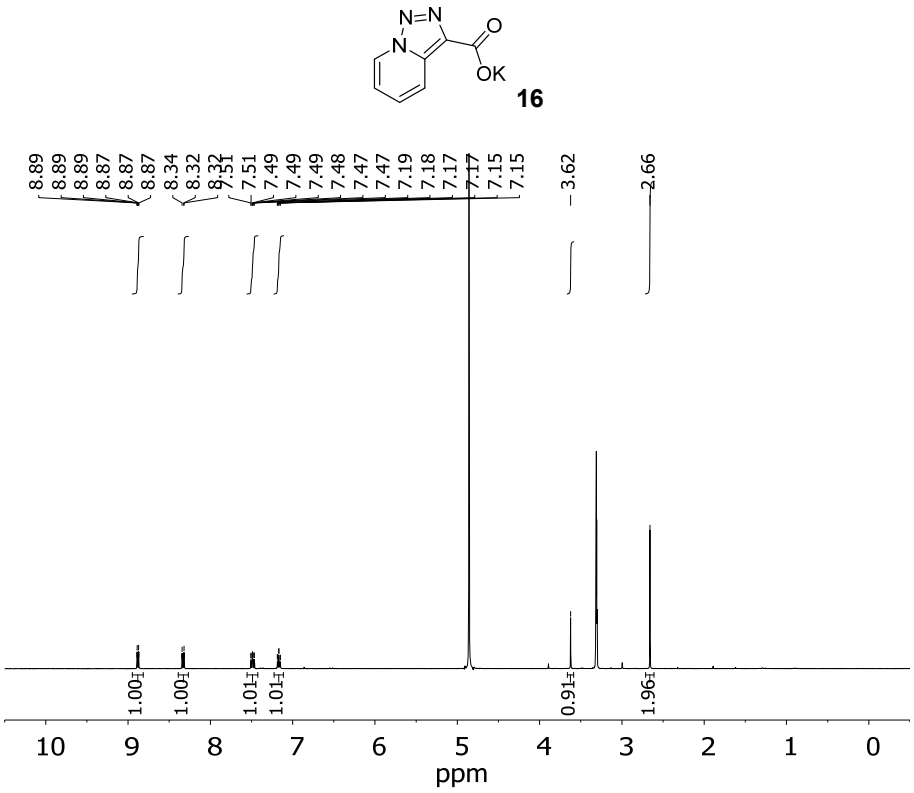


Figure S7.31. ^{1}H NMR spectrum of **16**. The signals at 2.66 and 3.62 ppm correspond to remaining DMSO and 18-crown-6 (400 MHz, CD_3OD).

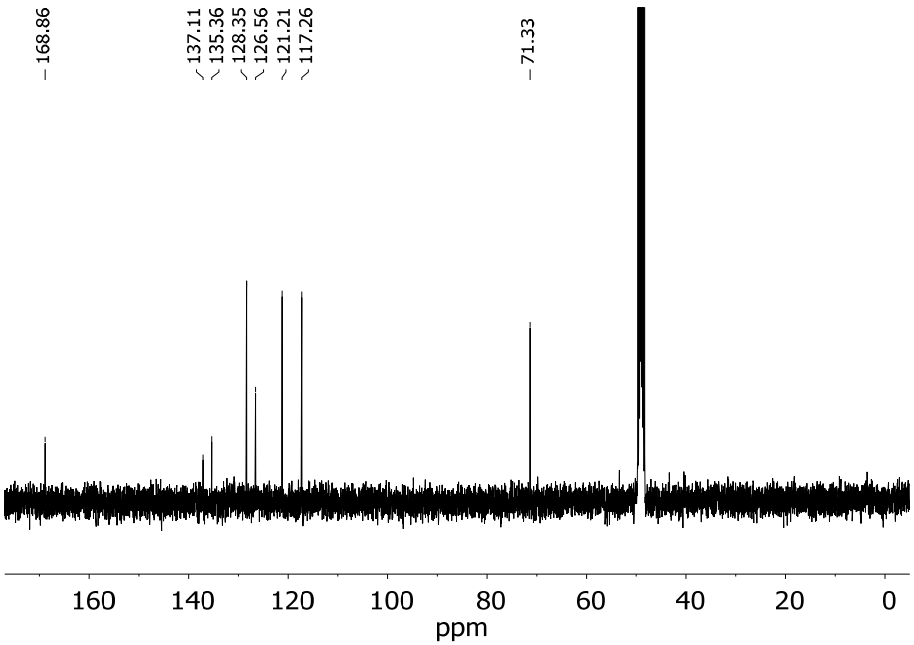


Figure S7.32. ^{13}C NMR spectrum of **16**. The signal at 71.33 ppm corresponds to remaining 18-crown-6 (101 MHz, CD_3OD).

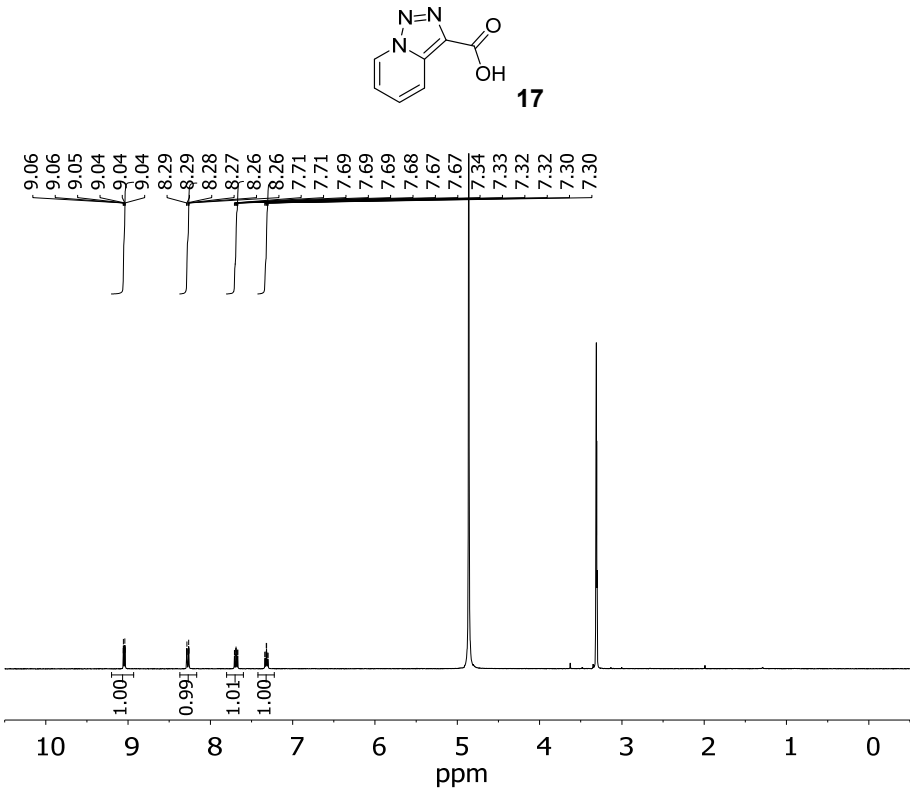


Figure S7.33. ^{1}H NMR spectrum of **17** (400 MHz, CD_3OD).

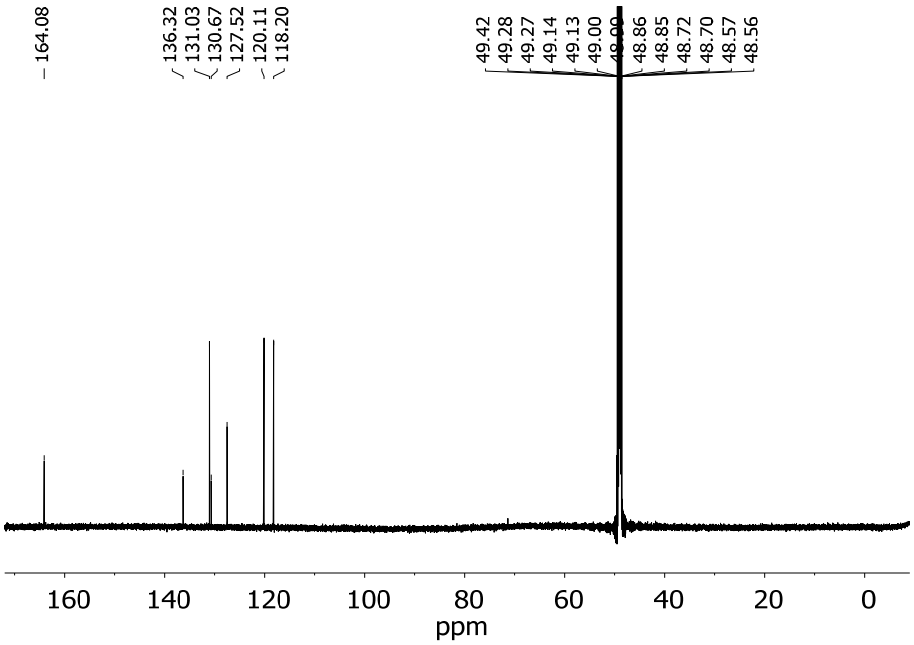


Figure S7.34. ^{13}C NMR spectrum of **17** (151 MHz, CD_3OD).

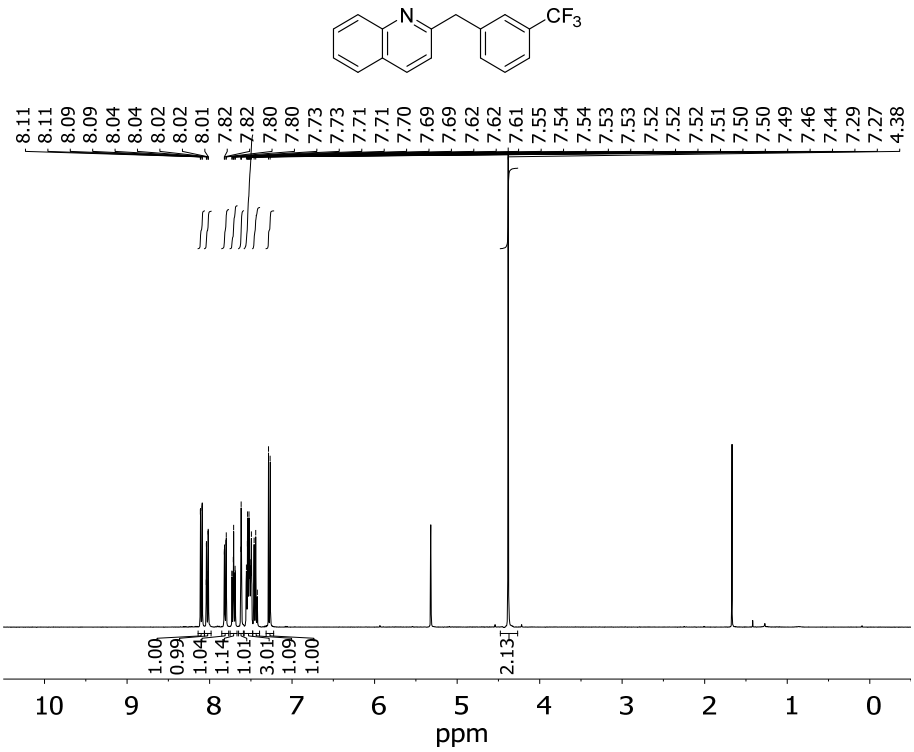


Figure S7.35. ^{1}H NMR spectrum of *2-(3-(trifluoromethyl)benzyl)quinoline* (400 MHz, CD_2Cl_2).

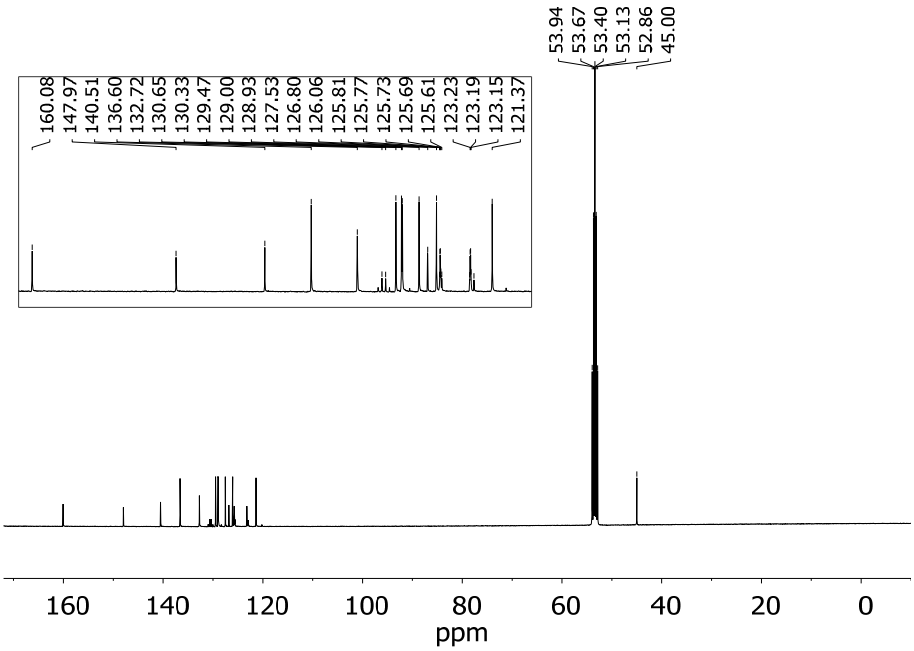


Figure S7.36. ^{13}C NMR spectrum of *2-(3-(trifluoromethyl)benzyl)quinoline* (101 MHz, CD_2Cl_2).

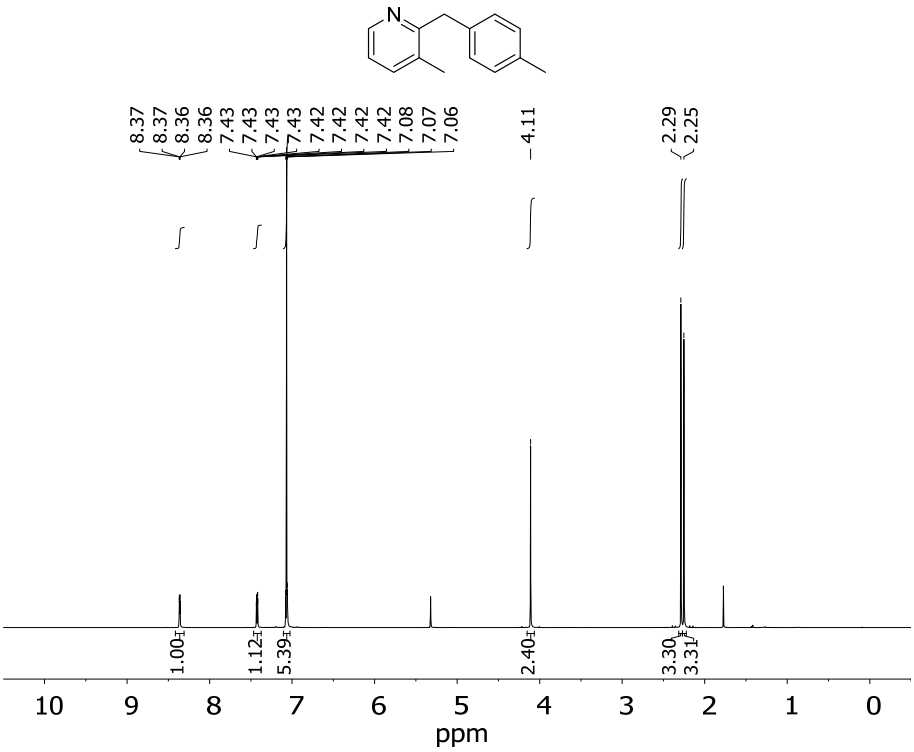


Figure S7.37. [1]H NMR spectrum of *3-methyl-2-(4-methylbenzyl)pyridine* (600 MHz, CD_2Cl_2).

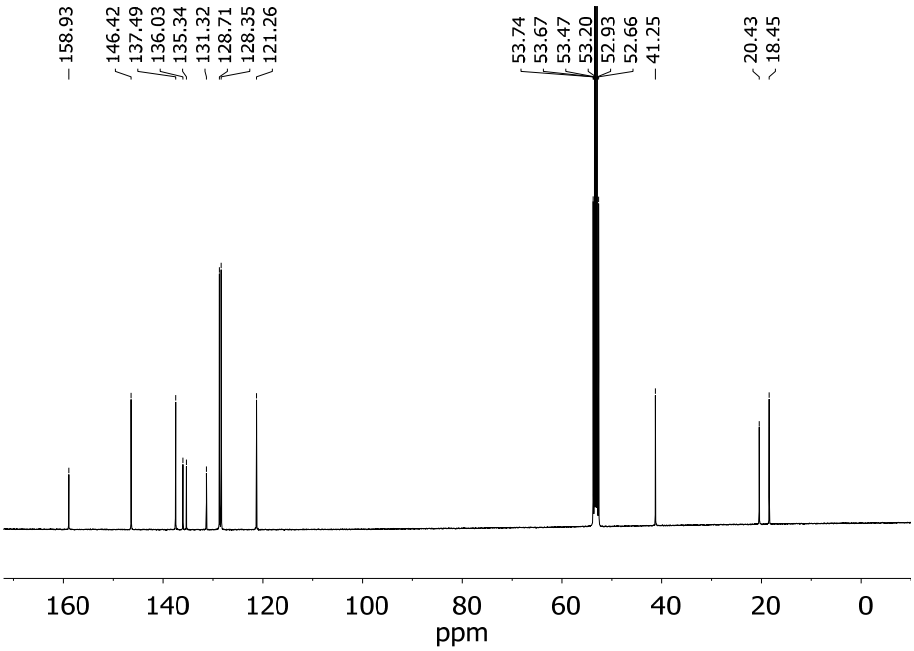


Figure S7.38. [13]C NMR spectrum of *3-methyl-2-(4-methylbenzyl)pyridine* (101 MHz, CD_2Cl_2).

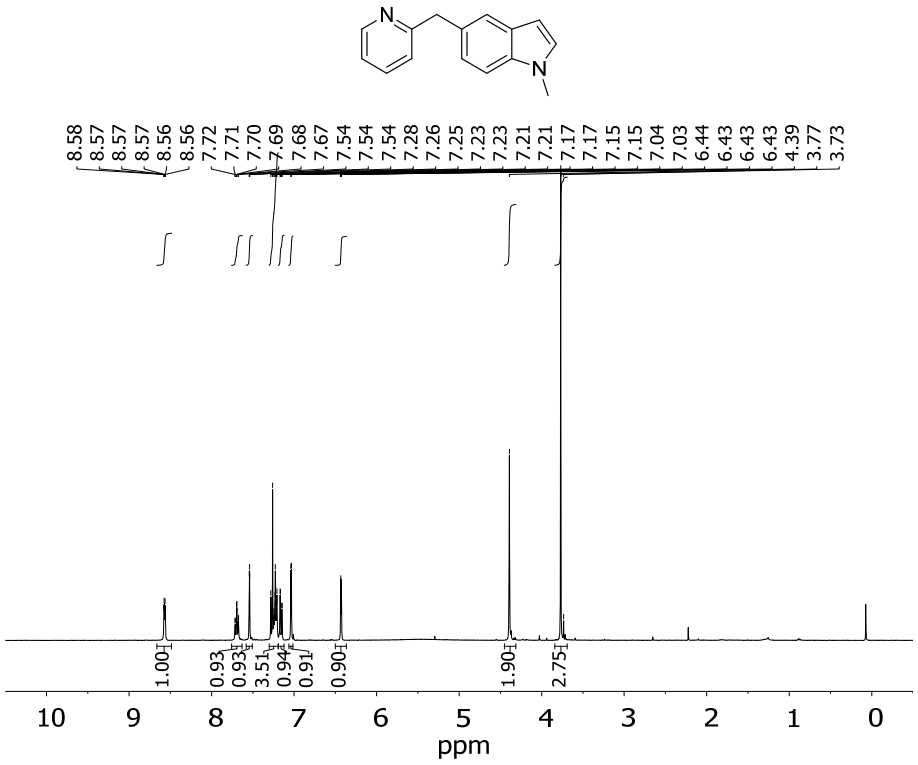


Figure S7.39. ^{1}H NMR spectrum of *1-methyl-5-(pyridin-2-ylmethyl)-1H-indole* (600 MHz, $CDCl_3$).

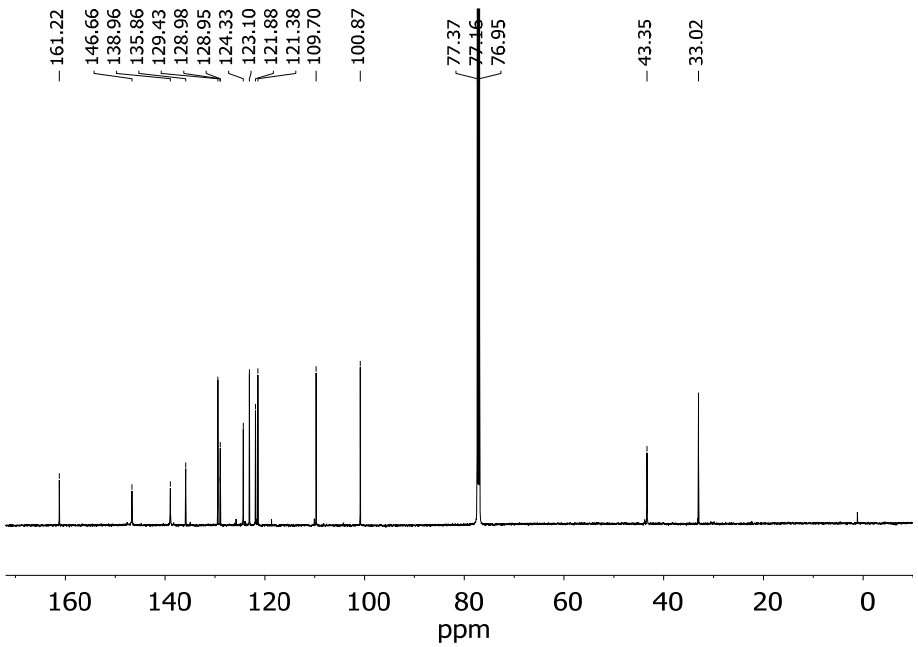


Figure S7.40. ^{13}C NMR spectrum of *1-methyl-5-(pyridin-2-ylmethyl)-1H-indole* (101 MHz, $CDCl_3$).

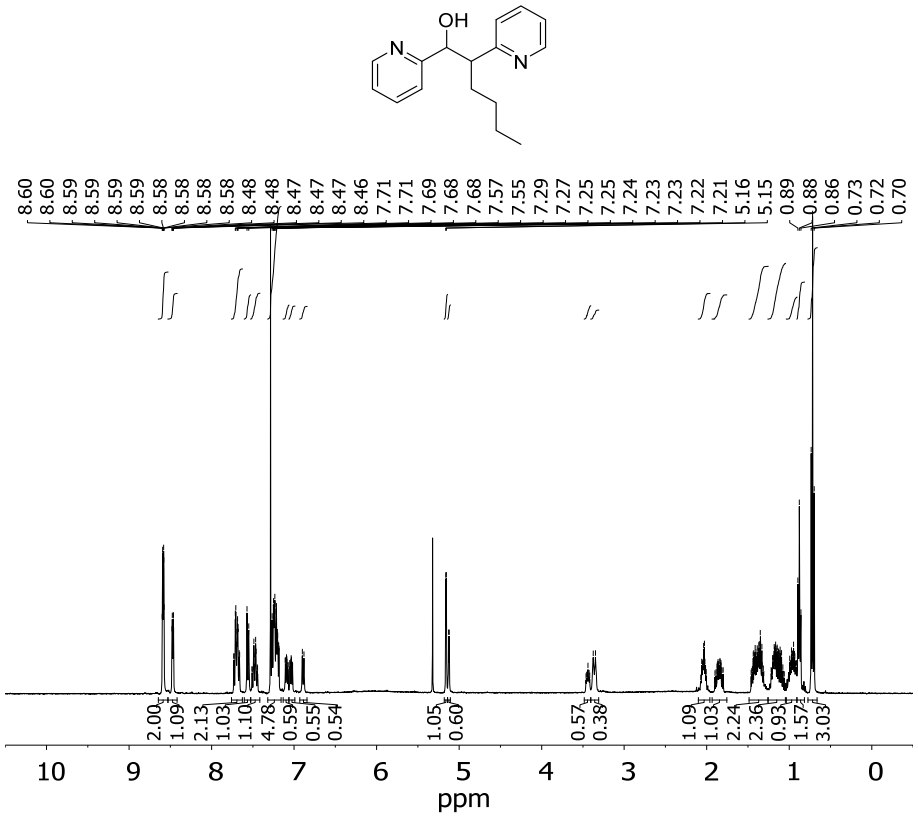


Figure S7.41. ^{1}H NMR spectrum of *1,2-di(pyridin-2-yl)hexan-1-ol* (400 MHz, $CDCl_3$).

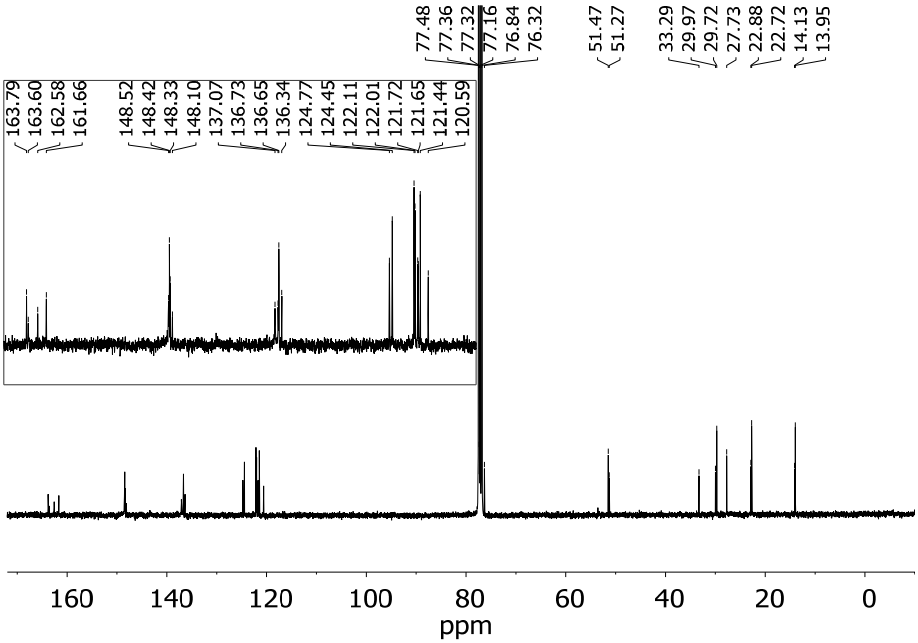


Figure S7.42. ^{13}C NMR spectrum of *1,2-di(pyridin-2-yl)hexan-1-ol* (101 MHz, $CDCl_3$).

8. References

1 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67–84.

2 S. Duez, A. K. Steib, S. M. Manolikakes and P. Knochel, *Angew. Chem. Int. Ed.*, 2011, **50**, 7686–7690.

3 X. Jiang, A. Tiwari, M. Thompson, Z. Chen, T. P. Cleary and T. B. K. Lee, *Org. Process Res. Dev.*, 2001, **5**, 604–608.

4 W. Jin, P. Zheng, W. T. Wong and G. L. Law, *Adv. Synth. Catal.*, 2017, **359**, 1588–1593.

5 T. B. Nguyen, T. M. Nguyen and P. Retailleau, *Chem. Eur. J.*, 2020, **26**, 4682–4689.

6 G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176–2179.

7 G. Jiang, Y. Lin, M. Cai and H. Zhao, *Synthesis*, 2019, **51**, 4487–4497.

8 M. R. Stentzel and D. A. Klumpp, *J. Org. Chem.*, 2020, **85**, 12740–12746.

9 L. Tie, X. H. Shan, J. P. Qu and Y. B. Kang, *Org. Chem. Front.*, 2021, **8**, 2981–2984.

10 M. Patel, R. K. Saunthwal and A. K. Verma, *ACS Omega*, 2018, **3**, 10612–10623.

11 P. Lu, C. Sanchez, J. Cornella and I. Larrosa, *Org. Lett.*, 2009, **11**, 5710–5713.