Supporting Information

Identification of N- or O-Alkylation of Aromatic Nitrogen Heterocycles and *N*-Oxides Using ^{1}H–^{15}N HMBC NMR Spectroscopy

Kevin J. Sheehy, Lorraine M. Bateman, Niko T. Flosbach, Martin Breugst,* and Peter A. Byrne*

Contents

1. General Experimental

Commercial diazines and alkylating agents were obtained from Fluorochem, Sigma-Aldrich and Alfa Aesar.

CH_2Cl_2, MeCN, CD_3CN, THF, Et_2O, DMSO-d_6 and DMSO were dried over activated 3 Å molecular sieves and stored under an atmosphere of nitrogen in flasks with grease-free J. Young's valves. Molecular sieves (10 weight percent per unit volume of compound to be dried) were activated by flame drying (open to the ambient atmosphere) in the storage flask(s) for 5 – 10 minutes (depending on quantity of sieves to be dried). After flame-drying, the storage flask was immediately connected to a Schlenk line, sealed off from the external atmosphere, and subjected to vacuum (between 1 and 5×10^{-3} mbar), and allowed to stand until the sieves had cooled. The flask was then subjected to several vacuum/refill cycles to establish a nitrogen atmosphere inside,[1] and the solvent/compound to be dried was then added against a flow of nitrogen.

Solvents that were used in relative bulk (MeCN, CH_2Cl_2, Et_2O, THF) were stored in a specialised flask with two J. Young's valves, one of which was modified to facilitate easy access of a needle to the body of the flask through the side-arm of the valve. When accessing the dry solvent, the angled side-arm was sealed with a rubber septum, and the small volume contained between the septum and the sealed tap of the J. Young's valve was flushed with a stream of nitrogen gas for a minimum of five minutes prior to opening the valve. The solvent required several days after commencing drying to reach maximal dryness (analysis by Karl Fischer titration for all but DMSO and DMSO-d_6), but was dry enough for most purposes after one day. Solvents stored in this manner were found to retain water contents of less than 10 ppm for more than one year.

For all reactions conducted using Schlenk glassware, the Schlenk flask was dried in an oven, then attached to vacuum via Schlenk manifold and placed under vacuum ($\leq 5 \times 10^{-3}$ mbar). The flask was then filled with nitrogen gas by the pump and fill technique (three repeats of the following cycle: evacuation to $\leq 5 \times 10^{-3}$ mbar, re-fill with nitrogen gas).[1] Solids and reagents were then introduced to the flasks under fast nitrogen flow.

NMR spectra were recorded on Bruker Avance III 600, Bruker Avance I 400 and Bruker Avance III 300 NMR spectrometers. ^{1}H NMR spectra (600 MHz, 400 MHz and 300 MHz respectively),^{13}C{^{1}H} NMR spectra (proton decoupled mode; 150 MHz, 100 MHz and 75 MHz, respectively), COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC NMR spectra were acquired at 293 K on the 300 MHz instrument and 300 K on the 400 MHz and 600 MHz instruments. Tetramethylsilane (TMS) was employed as the external chemical shift reference standard for these. ^{1}H-^{15}N HMBC NMR spectra were recorded on a Bruker Avance III 600 NMR spectrometer [600.1 MHz (^{1}H), 60.8 MHz (^{15}N)], equipped with Bruker BBFO cryoprobe at 300 K and referenced externally to ammonia (at 0 ppm), the value of which was uncorrected. ^{1}H-^{15}N HMBC NMR spectra were acquired using the Bruker hmbcqpndqf pulse program (2D H-1/X correlation via heteronuclear zero and double quantum coherence optimised on long range couplings), with 4 scans and spectral width of 600–650 ppm. Spectra recorded in non-deuterated solvents were acquired using the Bruker NOESY presat (noesygppr) solvent suppression pulse sequence, using presaturation during the mixing time and relaxation delay. Chemical shifts (δ) are expressed as parts per million (ppm). Coupling

constants (*J*) are expressed in Hertz (Hz). Splitting patterns in ^{1}H-NMR spectra are designated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), td (triplet of doublets), q (quartet), quin (quintet) and m (multiplet). Infrared spectra were measured using a FTIR UATR2 spectrometer – samples were prepared as thin films in acetonitrile. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). All spectra were run at University College Cork.

General Procedures

Procedure A: Removal of solvent while maintaining an inert atmosphere

The following procedure was used to remove the solvent and volatile reagents from a Schlenk flask containing a completed reaction mixture while maintaining an inert atmosphere. A Schlenk manifold connected to a rotary vane vacuum pump *via* a liquid nitrogen cold trap (and a nitrogen supply) was connected to a second vacuum trap, which was also attached to the reaction flask (closed, and containing a solution in a volatile solvent under nitrogen atmosphere). The trap and tubing connecting it to the Schlenk manifold and reaction flask were placed under vacuum ($\leq 5 \times 10^{-3}$ mbar). The vacuum trap was then filled with nitrogen gas by the pump and fill technique (see description above, and reference 1). The trap was then placed under vacuum and then cooled with liquid N_2. At this point the tap on the Schlenk flask is opened and volatile solvent is removed and collected in the trap. After approximately 30 minutes, the entirety of the trap and the Schlenk flask are re-filled with nitrogen gas through the Schlenk manifold and the tap of the Schlenk flask is closed. The trap is removed and the flask is re-attached directly to the Schlenk manifold. This procedure is repeated when removing excess Et_2O after conducting an Et_2O wash in some experiments (see below).

Procedure B: Preparation of samples for NMR spectroscopy under inert atmosphere

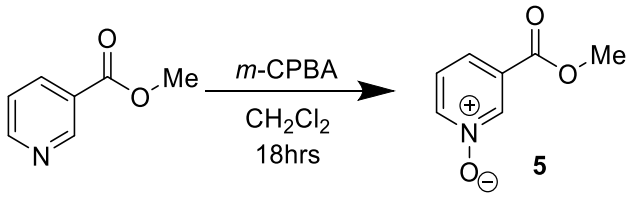
The following procedure was used to place the products of the alkylation reactions (dissolved in an appropriate solvent) into NMR tubes while maintaining an inert atmosphere. The products were formed in an N_2-filled Schlenk flask using inert atmosphere techniques. The appropriate solvent (specified for individual reactions below) was introduced to the Schlenk flask by syringe and *ca.* 10 – 20 mg of the product was dissolved. An empty NMR tube was placed in a long, tube shaped Schlenk flask before being evacuated and re-filled with nitrogen ≥ 3 times, creating an inert atmosphere inside the flask. The solution to be examined (in dry DMSO, DMSO-d_6 or CH_2Cl_2) was added to the inert NMR tube by syringe under nitrogen. The NMR tube was then sealed by a rubber septum cap while inside the long Schlenk flask (using a tweezers to insert the septum), and wrapped with PTFE tape. The septum was then covered with Parafilm and the tube transferred to the appropriate spectrometer for analysis.

Procedure C: Preparation of benzhydryl adducts of heterocycles and *N*-oxides

The following procedure was used to synthesise the benzhydryl adducts of the heterocycles discussed in the main article. 4-Methylbenzhydryl chloride (1 equivalent) was weighed into a reaction vessel and transferred into a glove box containing a nitrogen atmosphere. Dry CD_2Cl_2 (0.85 ml) was added,

followed by the heterocycle or *N*-oxide (1 equivalent). AgOTf (1.1 – 1.2 equivalents) was then added, causing the immediate precipitation of AgCl. The reaction vessel was sealed, agitated for 15 minutes, and then filtered (removing AgCl) through a syringe filter into an NMR tube. The NMR tube was sealed using a rubber septum. The seal was then wrapped with PTFE tape and Parafilm. Finally, the NMR tube was placed in a long Schlenk flask and removed from the glove box and brought to the NMR spectrometer. All products underwent relatively rapid decomposition (hydrolysis) on exposure to moisture, and hence were only characterized by inert atmosphere NMR spectroscopy.

2. Preparation of 3-(methoxycarbonyl)pyridine *N*-oxide (methyl nicotinate *N*-oxide)



Preparation of *N*-oxides was achieved using a modification of an established literature procedure.[2]

Methyl nicotinate (2.094 g, 15.3 mmol) was dissolved in CH_2Cl_2 (70 ml). 3-Chloroperbenzoic acid (2.59 g, 15.0 mmol) was added in one portion and the solution was stirred for 18 hrs. The mixture was filtered through a Büchner funnel to remove any precipitated 3-chlorobenzoic acid. The organic solvent was washed once with a saturated sodium sulfite solution and once with a solution of brine. The solvent was then removed under reduced pressure. The residue was purified by column chromatography using mixtures of EtOAc and cyclohexane, with progressively smaller amounts of cyclohexane being employed. The column fractions containing pure **5** were combined, and the solvent was removed under vacuum, yielding **5** as a pale yellow solid (0.7166 g, 32%). Many eluted fractions contained both *N*-oxide **5** and 3-chlorobenzoic acid, which led to the low isolated yield. The pure *N*-oxide produced was stored under nitrogen gas in a glove box due to its hygroscopic properties.

^{1}H NMR (300 MHz, $CDCl_3$, 27 °C) δ 8.80 – 8.75 (m, 1H), 8.34 (ddd, J = 6.5, 1.8, 1.1 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.37 (dd, J = 7.7, 6.7 Hz, 1H), 3.97 (s, 3H). [3]

Note: The 3-chloroperbenzoic acid used is a solid consisting of ≤77% *m*-CPBA.

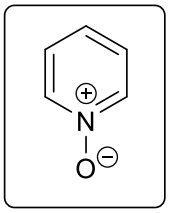
3. NMR Spectral data for Starting Compounds 1 – 6

Observation of ^{15}N NMR Chemical Shifts Using the ^{1}H-^{15}N HMBC NMR Spectroscopic Technique

^{15}N NMR chemical shifts values were measured using ^{1}H-^{15}N HMBC NMR spectroscopy. These values were compared with extant ^{14}N and ^{15}N values found in the literature (see below and main article).

Note: The spectra were recorded using non-deuterated solvents, with the signals of the solvent suppressed during acquisition, as described in the General Experimental section above.

3.1. NMR Spectral Data for Starting Materials in DMSO/DMSO-d_6

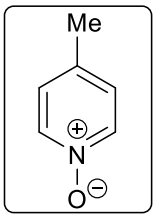


Pyridine *N*-Oxide (4)

Pyridine *N*-oxide (**4**) (0.052 g) was dissolved in dry DMSO (0.65 ml) in a N_2-filled Schlenk flask and placed in an NMR tube by syringe under nitrogen, which was then sealed by a rubber septum cap and wrapped with PTFE tape. The product was analysed by ^{1}H-^{15}N HMBC NMR spectroscopy.

^{1}H NMR (600 MHz, DMSO, 27 °C) δ 8.19 (d, *J* = 6.0 Hz, 2H), 7.37 (t, *J* = 7.1 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H). [4]

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 295.1. [5]



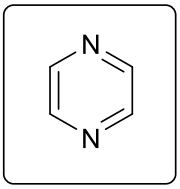
4-Methylpyridine *N*-Oxide (6)

4-Methylpyridine- *N*-oxide (**6**) (0.052 g, 0.48 mmol) was dissolved in dry DMSO-d_6 (0.65 ml) in a N_2-filled Schlenk flask and placed in an NMR tube by syringe under nitrogen, which was then sealed by a rubber septum cap and wrapped with PTFE tape. The product was analysed by ^{1}H-^{15}N HMBC NMR spectroscopy.

^{1}H NMR (600 MHz, DMSO-d_6, 27 °C) δ 8.09 (d, *J* = 6.9 Hz, 2H), 7.23 (d, *J* = 6.5 Hz, 2H), 2.27 (s, 3H). [4]

^{15}N NMR (60.8 MHz, DMSO-d_6, 27 °C): δ 284.3. [6]

3.2. NMR Spectral Data for Starting Materials in CH_2Cl_2

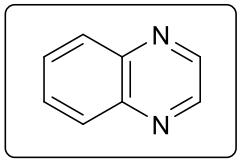


Pyrazine (1)

Pyrazine (**1**) (0.063 g) was dissolved in dry CH_2Cl_2 (0.65 ml) in a N_2-filled Schlenk flask and placed in an NMR tube by syringe under nitrogen, which was then sealed by a rubber septum cap and wrapped with PTFE tape. The product was analysed by ^{1}H-^{15}N HMBC NMR spectroscopy.

^{1}H NMR (600 MHz, CH_2Cl_2, 27 °C) δ 8.54 (s, 4H).

^{15}N NMR (60.8 MHz, CH_2Cl_2, 27 °C): δ 333.0



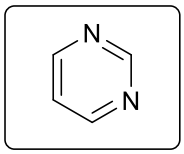
Quinoxaline (2)

Quinoxaline (**2**) (0.052 g) was dissolved in dry CH_2Cl_2 (0.65 ml) in a N_2-filled Schlenk flask and placed in an NMR tube by syringe under nitrogen, which was then sealed by a rubber septum cap and wrapped with PTFE tape. The product was analysed by ^{1}H-^{15}N HMBC NMR spectroscopy.

^{1}H NMR (600 MHz, CH_2Cl_2, 27 °C) δ 8.81 (s, 2H), 8.09 (dt, *J* = 6.6, 3.3 Hz, 2H), 7.80 – 7.73 (m, 2H).

^{15}N NMR (60.8 MHz, CH_2Cl_2, 27 °C): δ 329.0

Pyrimidine (3)

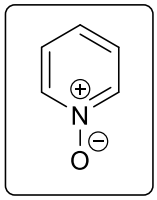


Pyrimidine (**3**) (0.045 g) was dissolved in dry CH_2Cl_2 (0.65 ml) in a N_2-filled Schlenk flask and placed in an NMR tube by syringe under nitrogen, which was then sealed by a rubber septum cap and wrapped with PTFE tape. The product was analysed by ^{1}H-^{15}N HMBC NMR spectroscopy.

^{1}H NMR (600 MHz, CH_2Cl_2, 27 °C) δ 9.15 (s, 1H), 8.69 (d, *J* = 4.9 Hz, 2H), 7.29 (td, *J* = 4.9, 1.4 Hz, 1H).

^{15}N NMR (60.8 MHz, CH_2Cl_2, 27 °C): δ 294.4

Pyridine *N*-Oxide (4)



Pyridine *N*-oxide (**4**) (0.096 g) was dissolved in dry CH_2Cl_2 (0.65 ml) in a N_2-filled Schlenk flask and placed in an NMR tube by syringe under nitrogen, which was then sealed by a rubber septum cap and wrapped with PTFE tape. The product was analysed by ^{1}H-^{15}N HMBC NMR spectroscopy.

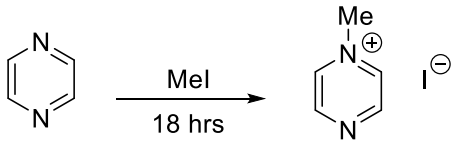
^{1}H NMR (600 MHz, CH_2Cl_2, 27 °C) δ 8.13 – 8.06 (m, 1H), 7.25 – 7.15 (m, 2H).

^{15}N NMR (60.8 MHz, CH_2Cl_2, 27 °C): δ 294.0. [5]

4. Reactions of Diazines and *N*-oxides with Alkylating Agents

Preparation of *N*-methylpyrazinium iodide (7a)

Pyrazine (**1**) (0.089 g, 1.11 mmol) was placed in a N_2-filled Schlenk flask. Methyl iodide (0.21 ml, 0.48g, 3.38 mmol) was added by syringe to the flask, which was wrapped in aluminium foil to protect the contents from light. The MeI was removed under vacuum by Procedure A after stirring of the reaction mixture for 18 hours, and the yellow solid product (**7a**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 ml each) were used in this manner to wash the product (yield = 0.049 g, 20%). A sample of **7a** in dry DMSO was then prepared for ^1H and ^1H-^{15}N HMBC NMR spectroscopic characterisation by Procedure B. Note: An initial attempt to dissolve the product in CH_2Cl_2 was unsuccessful, and a residual amount of this solvent can be seen in the spectrum.



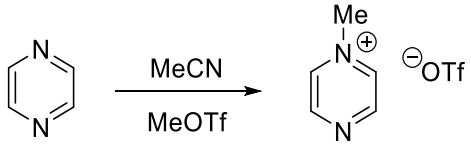
1 **7a**

^{1}H NMR (600 MHz, DMSO, 27 °C) δ 9.49 (app. S, 2H), 9.11 (d, *J* = 3.0 Hz, 2H), 4.37 (s, 3H).[7]

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 357.6, 221.0

Copies of the NMR spectra are shown in Section 5.

Preparations of *N*-Methylpyrazinium triflate (7b)

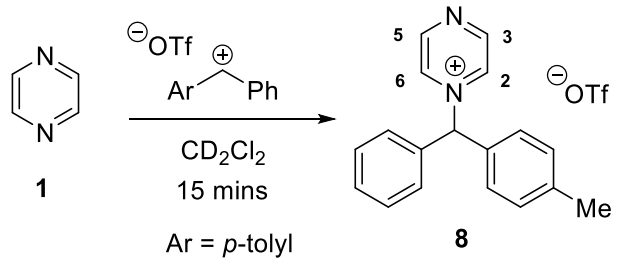


1 **7b**

See procedures and NMR spectral details in the experimental section of the main article. Copies of the NMR spectra are shown in Section 5 below.[7]

Preparation of 8

Pyrazine (**1**) (0.016 g, 0.20 mmol), 4-methylbenzhydryl chloride (0.041 g, 0.19 mmol) and silver triflate (0.054 g, 0.21 mmol) were combined by the process described in Procedure C to produce **8** in CD_2Cl_2. This product decomposes by hydrolysis if exposed to the ambient atmosphere. Consequently, the product was not isolated. Instead, the reaction mixture (in CD_2Cl_2) was analysed directly by NMR spectroscopy using Procedure B. The signals in the NMR spectra of the reaction mixture assigned to **8** are reported below.



^{1}H NMR (600 MHz, CD_2Cl_2, 27 °C) δ 9.42 (s, 2H, H-3 & H-5), 8.83 (s, 2H, H-2 & H-6), 7.67 (s, 1H, PhTolC*H*), 7.54 – 7.09 (m, 9H, Phenyl H-2, H-3, H-4, H-5 & H-6. Tolyl H-2, H-3, H-5 & H-6), 2.38 (s, 3H, CH_3).

The peak assigned to the starting material **1** is seen at 8.57 ppm. 4H of this compound integrates for 1.75 with respect to 1H of **8**; *i.e*. 1H of **1** = 0.44 with respect to 1H of **8**.

Peaks assigned to hydrolysis products are seen at 6.14ppm and 5.37ppm. The aromatic protons of these products also contribute to the integration of the multiplet at 7.54 – 7.09 ppm.

^{13}C NMR (150 MHz, CD_2Cl_2, 27 °C) δ 151.7 (C-3 & C-5), 141.6 (Tolyl C-4), 136.4 (C-2 & C-5), 134.2 (Phenyl C-1), 130.9 (Tolyl C-3 & C-5), 130.2 (Phenyl C-3 & C-5), 129.6 (Tolyl C-2 & C-6), 129.5 (Tolyl C-1), 129.3 (Phenyl C-2 & C-6), 79.6 (PhTol*C*H), 21.3 (*C*H_3).

A ^{13}C NMR signal assigned to the *C*$F_3SO_3^-$ ion is seen at δ 121.1 (q, J = 321 Hz).

^{15}N NMR (60.8 MHz, CD_2Cl_2, 27 °C): δ 364.4, 240.6.

A peak assigned to the starting material **1** appears at 332.0 ppm.

Conversion Calculation (based on consumption of 4-methylbenzhydrylium ion):

2H of Compound **8** corresponds to 2.00, therefore 1H = 1.00.

For the hydrolysis product at 6.14 ppm, 1H = 0.27

For the bis(benzhydryl) ether hydrolysis product signal at 5.37 ppm ($Ar_2CH)_2O$), 2H = 0.09.

$$\text{Conversion} = \frac{1.00}{1.00 + 0.27 + 0.09} \times 100 = 74\%$$

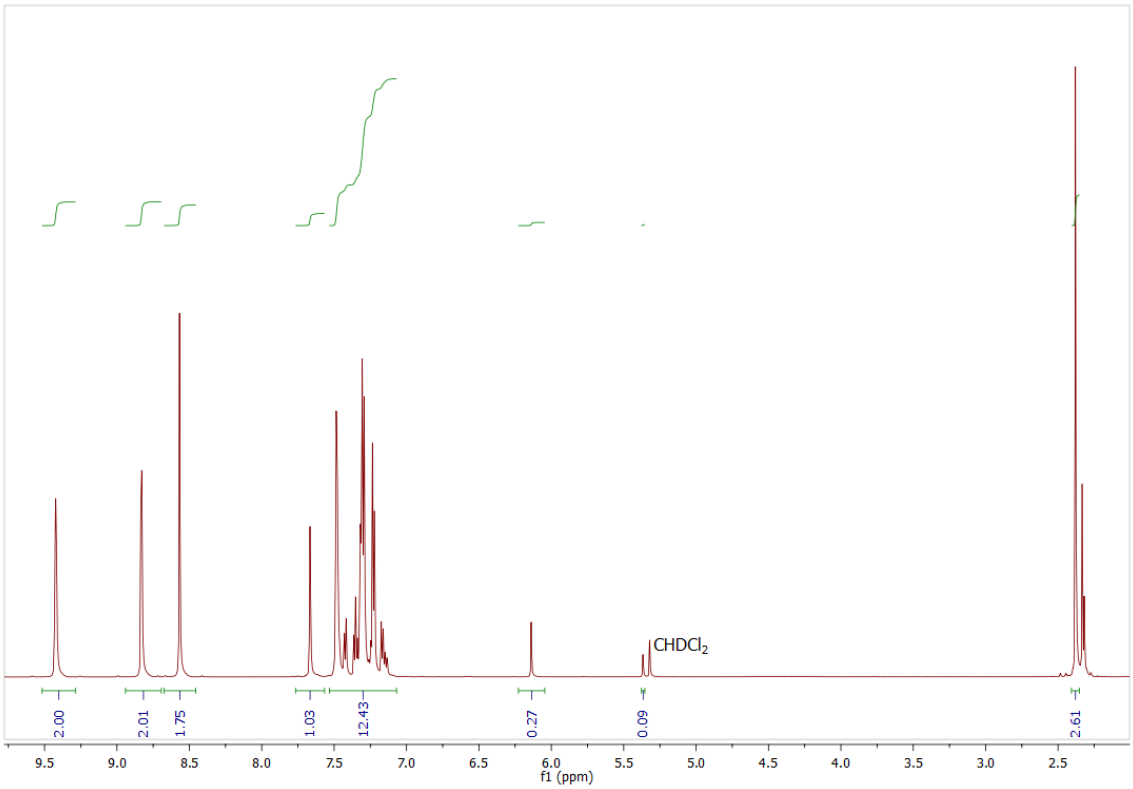
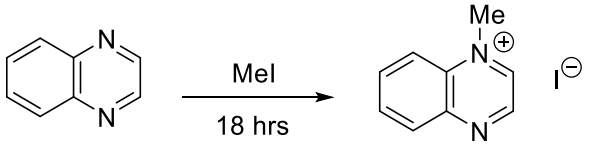


Figure S1: ^{1}H NMR spectrum of **8**. Note: Copies of full NMR spectra are shown in Section 5.

Preparation of *N*-Methylquinoxalinium iodide (9a)

Quinoxaline (**2**) (0.131 g, 1.01 mmol) was placed in a N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl iodide (0.19 ml, 0.43 g, 3.03 mmol) was added by syringe to the flask. The MeI was removed under vacuum by Procedure A after stirring of the reaction mixture for 18 hours, and the orange oil product (**9a**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 ml each) were used in this manner to wash the product (yield = 0.117 g, 43%). A sample of **9a** in dry DMSO was then prepared for ^1H and ^1H-^{15}N HMBC NMR spectroscopic characterisation using Procedure B. Note: An initial attempt to dissolve the product in CH_2Cl_2 was unsuccessful, and a residual amount of this solvent can be seen in the spectrum.



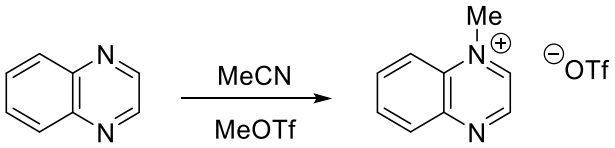
2 **9a**

^{1}H NMR (600 MHz, DMSO, 27 °C) δ 9.68 (d, J = 2.8 Hz, 1H), 9.58 (d, J = 2.6 Hz, 1H), 8.59 (d, J = 8.7 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.36 – 8.30 (m, 1H), 8.27 (t, J = 7.7 Hz, 1H), 4.69 (s, 3H). [8]

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 355.5, 208.6

Copies of the NMR spectra are shown in Section 5.

Preparation of *N*-Methylquinoxalinium triflate (9b)



2 **9b**

(a) Quinoxaline (**2**) (0.242 g, 1.86 mmol) was dissolved in dry MeCN (5 ml) in a N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl triflate (0.304 g, 1.85 mmol) was subsequently added dropwise. After *ca.* 18 hours, the MeCN was removed under vacuum by Procedure A and the solid product (**9b**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (0.5 ml each) were used in this manner to wash the product (yield = 0.537 g, 98%; product contained *ca*. 2% (**2**), therefore yield = 98% × 0.98= <u>96%</u>). A sample of **9b** in dry DMSO-d_6 was then prepared for ^1H NMR spectroscopic characterisation using Procedure B.

^{1}H NMR (400 MHz, DMSO-d_6, 27 °C) δ 9.71 (d, J = 2.8 Hz, 1H), 9.61 (d, J = 2.6 Hz, 1H), 8.64 (d, J = 8.7 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.39 – 8.33 (m, 1H), 8.29 (t, J = 7.4 Hz, 1H), 4.77 (s, 3H). [8]

Copies of the NMR spectra are shown in Section 5.

(b) Quinoxaline (**2**) (0.096 g, 0.74 mmol) was dissolved in dry MeCN (5 ml) in a N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl triflate (0.087 g, 0.53 mmol) was subsequently added dropwise. After *ca.* 30 minutes, the MeCN was removed under vacuum by Procedure A and the solid product (**9b**) was washed with dry Et_2O (3 × 0.4 ml portions) as described above. The product was analysed by ^1H and ^1H-^{15}N HMBC NMR spectroscopy by Procedure B in DMSO.

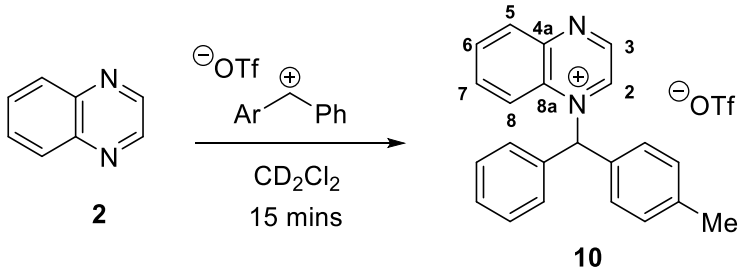
^{1}H NMR (600 MHz, DMSO, 27 °C) δ 9.68 (d, *J* = 2.8 Hz, 1H), 9.57 (d, *J* = 2.5 Hz, 1H), 8.60 (d, *J* = 8.7 Hz, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.33 (t, *J* = 7.3 Hz, 1H), 8.26 (t, *J* = 7.7 Hz, 1H), 4.72 (s, 3H). [8]

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 356.6, 208.7.

Copies of the NMR spectra are shown in Section 5.

Preparation of 10

Quinoxaline (**2**) (0.019 g, 0.015 mmol), 4-methylbenzhydryl chloride (0.030 g, 0.14 mmol) and silver triflate (0.045 g, 0.18 mmol) were combined by the process described in Procedure C to produce **10** in CD_2Cl_2. This product decomposes by hydrolysis if exposed to the ambient atmosphere. Consequently, the product was not isolated. Instead, the reaction mixture (in CD_2Cl_2) was analysed directly by NMR spectroscopy using Procedure B. The signals in the NMR spectra of the reaction mixture assigned to **10** are reported below.



^{1}H NMR (600 MHz, CD_2Cl_2, 27 °C) δ 9.60 (d, *J* = 3.0 Hz, 1H, H-4), 8.74 (d, *J* = 3.0 Hz, 1H, H-2), 8.60 – 8.55 (m, 1H, H-5), 8.55 – 8.50 (m, 1H, H-8), 8.21 – 8.11 (m, 3H, C*H*PhTol, H-6 & H-7), 7.49 – 7.44 (m, 3H, Phenyl H-3, H-4 & H-5), 7.39 – 7.11 (m, 6H, Phenyl H-2 & H-6, Tolyl H-2, H-3, H-5 & H-6), 2.37 (s, 3H, CH_3).

Signals assigned to the starting material **2** are seen at 8.87 ppm, within the multiplet at 8.21 – 8.11 ppm and 7.83 ppm. 2H of this compound corresponds to an integration of ~0.40 relative to 1H of **10**.

The multiplet at 8.21-8.11 ppm contains 1H each of C*H*PhTol, H-6 & H-7. Also included is 1H of the starting material **2**.

Signals assigned to hydrolysis products are seen at 6.14 ppm and 5.37 ppm. The aromatic protons of these products also contribute to the integration of the multiplet at 7.39 – 7.11 ppm.

^{13}C NMR (150 MHz, CD_2Cl_2, 27 °C) δ 147.7 (C-3), 147.4 (C-4a), 141.4 (Tolyl C-4), 137.7 (C-2), 137.3 (C-7), 134.4 (C-6), 134.4 (Phenyl C-1), 132.6 (C-8), 131.1 (Tolyl C-3 & C-5), 130.9 (C-8a), 130.6 (Phenyl C-4), 130.3 (Phenyl C-3 & C-5), 129.6 (Tolyl C-2 & C-6), 129.5 (Tolyl C-1), 129.2 (Phenyl C-2 & C-6), 120.4 (C-5), 75.2 (*C*HPhTol), 21.3 (CH_3).

A ^{13}C NMR signal assigned to the $CF_3SO_3^-$ ion is seen at 121.1 (q, J = 321 Hz).

^{15}N NMR (60.8 MHz, CD_2Cl_2, 27 °C): δ 363.7, 225.3

A peak assigned to the starting material **2** may also be seen at 324.0 ppm.

Conversion Calculation (based on consumption of 4-methylbenzhydrylium ion):

1H of Compound **10** corresponds to 1.00.

For the benzhydrol hydrolysis product at 6.14 ppm, 1H = 0.12

For the bis(benzhydryl) ether hydrolysis product signal at 5.37 ppm ($Ar_2CH)_2O$), 2H = 0.11.

$$\text{Conversion} = \frac{1.00}{1.00 + 0.12 + 0.11} \times 100 = 81\%$$

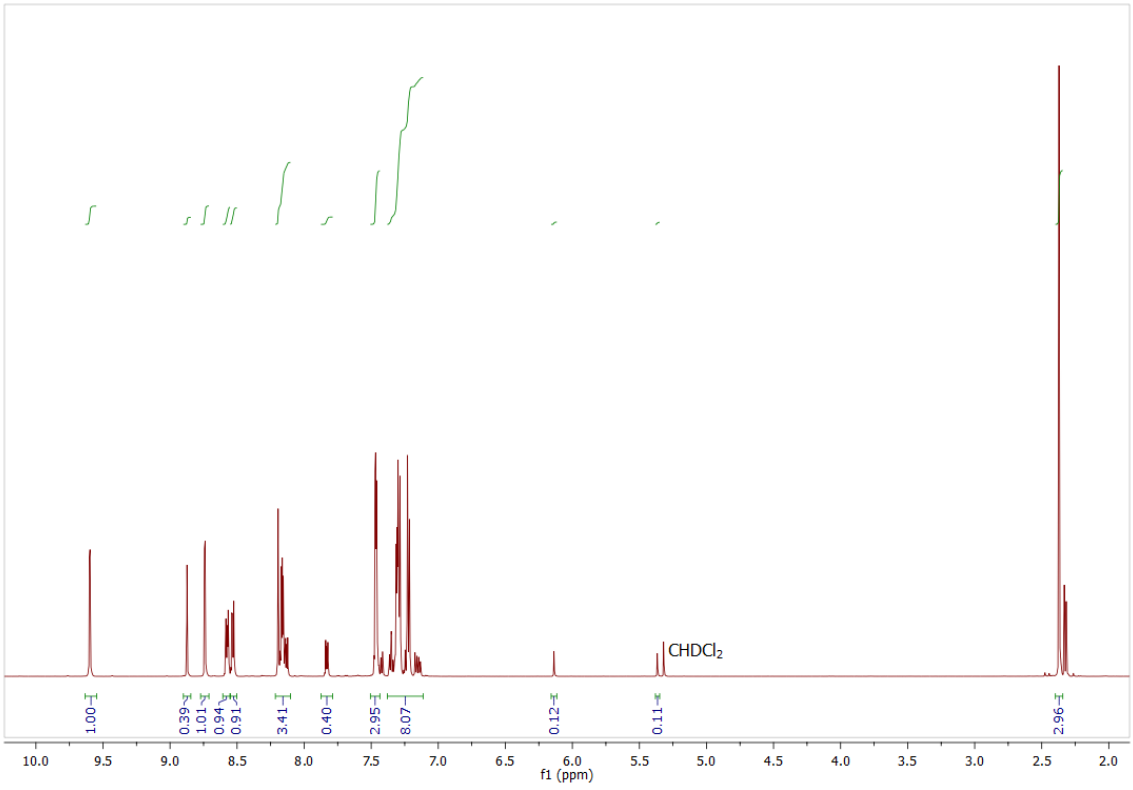
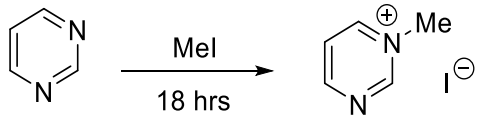


Figure S2: ^{1}H NMR spectrum of **10**. The full spectrum is shown in Section 5.

Preparation of *N*-Methylpyrimidinium iodide (11a)

Pyrimidine (**3**) (0.089 g, 1.11 mmol) was placed in a N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl iodide (0.21 ml, 0.48g, 3.38 mmol) was added by syringe to the flask. The MeI was removed under vacuum by Procedure A after stirring of the reaction mixture for 18 hours, and the yellow solid product (**11a**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 ml each) were used in this manner to wash the product (yield = 0.150 g, 61%). A sample of **11a** in dry DMSO was then prepared for ^1H and ^1H-^{15}N HMBC NMR spectroscopic characterisation using Procedure B.



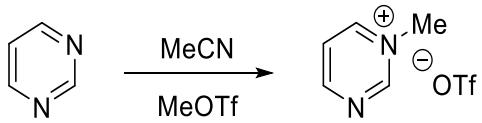
3 **11a**

^{1}H NMR (600 MHz, DMSO, 27 °C) δ 9.77 (s, 1H), 9.41 (dd, J = 4.9, 1.7 Hz, 1H), 9.35 (d, J = 6.3 Hz, 1H), 8.26 (t, *J* = 5.6 Hz, 1H), 4.26 (s, 3H). [7]

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 298.7, 199.5

Copies of the NMR spectra are shown in Section 5.

Preparation of *N*-Methylpyrimidinium triflate (11b)



3 **11b**

(a) Pyrimidine (**3**) (0.138 g, 1.72 mmol) was dissolved in dry MeCN (5 ml) in an inert N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl triflate (0.282 g, 1.73 mmol) was subsequently added dropwise. After *ca.* 18 hours, the MeCN was removed under vacuum by Procedure A and the solid product (**11b**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (2 ml each) were used in this manner to wash the product (yield = 0.337 g, 80%. Product contained *ca*. 2% (**3**), therefore yield = 80% × 0.98= <u>78%</u>). A sample of **11b** in dry DMSO-d_6 was then prepared for ^1H NMR spectroscopic characterisation using Procedure B.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.43 (d, *J* = 4.9 Hz, 1H), 9.34 (d, *J* = 5.7 Hz, 1H), 8.25 (t, *J* = 5.5 Hz, 1H), 4.31 (app. d, *J* = 1.9 Hz, 3H). [7]

It is not clear whether the apparent small splitting of the signal at δ 4.31 is an artefact particular to the acquisition of this spectrum, or whether it is a consequence of ^1H-^{15}N coupling. The corresponding signal in other spectra of the same compound does appear as a singlet (see below).

(b) Pyrimidine (**3**) (0.111 g, 1.38 mmol) was dissolved in dry MeCN (5 ml) in a N_2-filled Schlenk flask which was wrapped in aluminium foil to protect the product from light. Methyl triflate (0.159 g, 0.97 mmol) was subsequently added dropwise. After *ca.* 30 minutes, the MeCN was removed under vacuum by Procedure A and the solid product (**11b**) was washed with dry Et_2O (3 × 2 ml portions) as described above. The product was analysed by ^1H and ^1H-^{15}N HMBC NMR spectroscopy by Procedure B in DMSO.

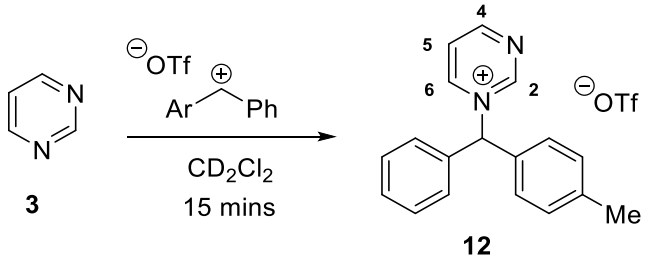
^{1}H NMR (600 MHz, DMSO, 27 °C) δ 9.73 (s, 1H), 9.39 (dd, *J* = 4.9, 1.6 Hz, 1H), 9.30 (d, *J* = 6.3 Hz, 1H), 8.22 (t, *J* = 5.5 Hz, 1H), 4.27 (s, 3H). [7]

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 299.9, 199.4.

Copies of the NMR spectra are shown in Section 5.

Preparation of 12

Pyrimidine (**3**) (0.009 g, 0.11 mmol), 4-methylbenzhydryl chloride (0.024 g, 0.11 mmol) and silver triflate (0.028 g, 0.11 mmol) were combined by the process described in Procedure C to produce **12** in CD_2Cl_2. This product decomposes by hydrolysis if exposed to the ambient atmosphere. Consequently, the product was not isolated. Instead, the reaction mixture (in CD_2Cl_2) was analysed directly by NMR spectroscopy using Procedure B. The signals in the NMR spectra of the reaction mixture assigned to **12** are reported below.



3 12

^{1}H NMR (600 MHz, CD_2Cl_2, 27 °C) δ 9.54 (s, 1H, H-2), 9.41 (d, *J* = 3.5 Hz, 1H, H-4), 9.06 (dd, *J* = 4.7, 1.7 Hz, 1H, H-6), 8.18 (t, *J* = 5.6 Hz, 1H, H-5), 7.60 (s, 1H, C*H*PhTol), 7.49 – 7.44 (m, 3H, Phenyl H-3, H-4 & H-5), 7.38 – 7.10 (m, 6H, Phenyl H-2 & H-6. Tolyl H-2, H-3, H-5 & H-6), 2.37 (s, 3H, CH_3).

A peak assigned to a hydrolysis product is seen at 5.36 ppm. The aromatic protons of this product also contribute to the integration of the multiplet at 7.38 – 7.10 ppm.

^{13}C NMR (150 MHz, CD_2Cl_2, 27 °C) δ 165.7 (C-4), 153.7 (C-2), 151.9 (C-6), 141.4 (Tolyl C-4), 134.5 (Phenyl C-1), 131.0 (Tolyl C-1), 130.9 (Tolyl C-3 & C-5), 130.6 (Phenyl C-4), 130.2 (Phenyl C-3 & C-5), 129.5 (Tolyl C-2 & C-6), 129.2 (Phenyl C-2 & C-6), 124.7 (C-5), 76.6 (*C*HPhTol), 21.3 (*C*H_3).

A ^{13}C NMR signal assigned to the *C*$F_3SO_3^-$ ion is seen at δ 120.9 (q, *J* = 320 Hz).

^{15}N NMR (60.8 MHz, CD_2Cl_2, 27 °C): δ 298.8, 218.6

Conversion Calculation (based on consumption of 4-methylbenzhydrylium ion):

1H of Compound **12** corresponds to 1.00.

For the bis(benzhydryl) ether hydrolysis product signal at 5.36 ppm ($Ar_2CH)_2O$), 2H = 0.11.

$$\text{Conversion} = \frac{1.00}{1.00 + 0.11} \times 100 = 90\%$$

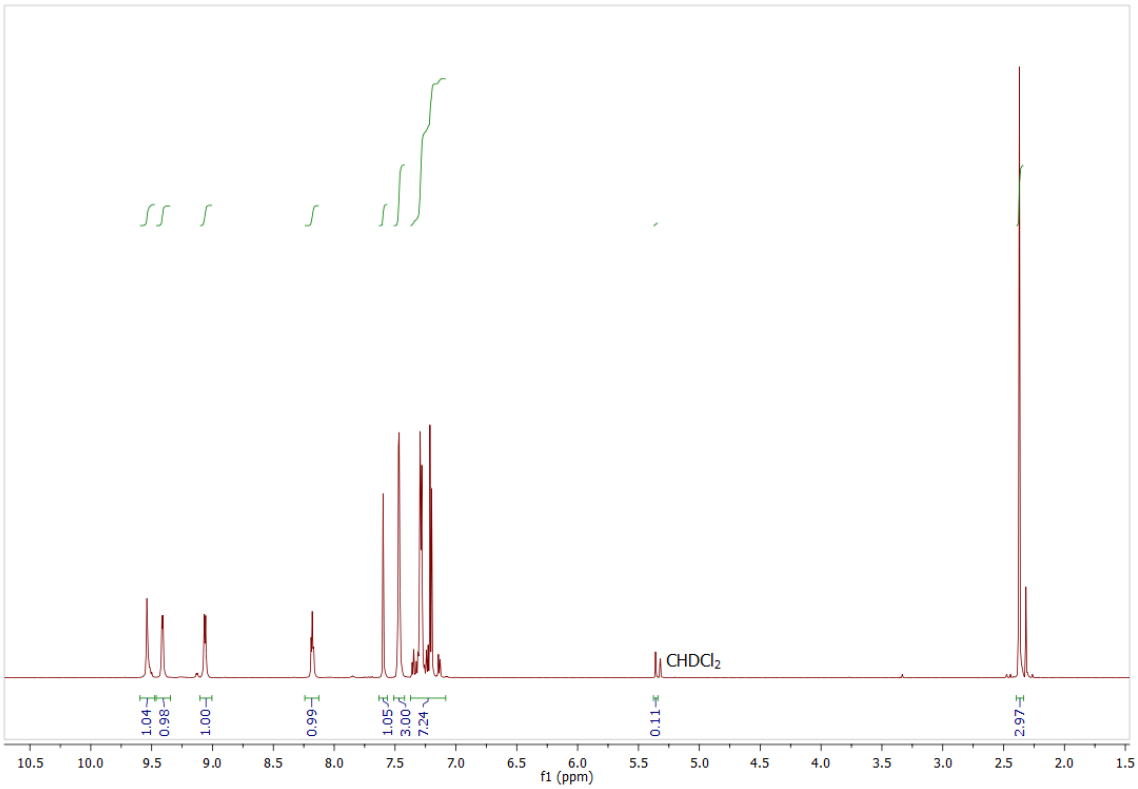
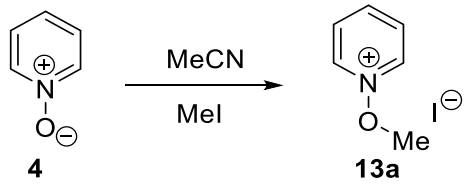


Figure S3: ^{1}H NMR spectrum of **12**. The full spectrum is shown in Section 5.

Preparation of *N*-Methoxypyridinium iodide (13a)



4 **13a**

(a) Pyridine *N*-oxide (**4**) (0.485 g, 5.1 mmol) was added to a N_2-filled Schlenk flask. Methyl iodide (6.84 g, 48.2 mmol) was subsequently added dropwise *via* syringe. The MeI was removed under vacuum by Procedure A after stirring of the reaction mixture for 40 hours, and the resulting yellow solid product (**13a**) was washed by addition of dry THF, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry THF (3 ml each) were used in this manner to wash the product (yield = 0.665 g, 59%). A sample of **13a** in dry DMSO-d_6 was then prepared for ^{1}H and ^{1}H-^{15}N HMBC NMR spectroscopic characterisation using Procedure B.

^{1}H NMR (300 MHz, DMSO-d_6, 27 °C) δ 9.51 – 9.46 (m, 2H), 8.68 – 8.58 (m, 1H), 8.31 – 8.23 (m, 2H), 4.45 (s, 3H). [4]

A copy of the ^{1}H NMR spectrum is shown in Section 5.

(b) Pyridine *N*-oxide (**4**) (0.056 g, 0.59 mmol) was dissolved in dry MeCN (5 ml) in a N_2-filled Schlenk flask. Methyl iodide (0.25 g, 1.76 mmol) was subsequently added dropwise *via* syringe. The MeI was removed under vacuum by Procedure A after stirring of the reaction mixture for 18 hours, and the yellow solid product (**13a**) was analysed by ^{1}H and ^{1}H – ^{15}N HMBC NMR spectroscopy using Procedure B in DMSO. Note: The reaction did not go to completion and hence the ^{1}H and ^{1}H – ^{15}N HMBC NMR spectra contain significant amounts of the starting material (**4**).

^{1}H NMR (600 MHz, DMSO, 27 °C)

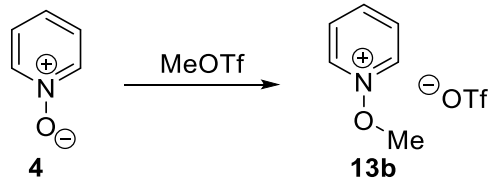
Signals assigned to **13a**: δ 9.46 (d, *J* = 6.1 Hz, 2H), 8.61 (t, *J* = 7.7 Hz, 1H), 8.24 (t, *J* = 7.3 Hz, 2H), 4.42 (s, 3H). [4]

Signals assigned to **4**: δ 8.17 (d, *J* = 6.1 Hz, 2H), 7.38 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H).

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 256.8 (Also appearing: 295.1, ^{15}N signal of **4**)

Copies of the NMR spectra are shown in Section 5.

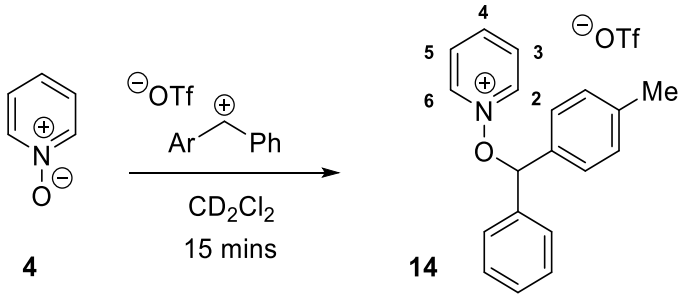
Preparations of *N*-Methoxypyridinium triflate (13b)



See procedures in Experimental section of main article. Copies of the NMR spectra are shown in Section 5 below.[9]

Preparation of 14

Pyridine *N*-oxide (**4**) (0.015 g, 0.16 mmol), 4-methylbenzhydryl chloride (0.031 g, 0.14 mmol) and silver triflate (0.048 g, 0.19 mmol) were combined by the process described in Procedure C to produce **14** in CD_2Cl_2. This product decomposes by hydrolysis if exposed to the ambient atmosphere. Consequently, the product was not isolated. Instead, the reaction mixture (in CD_2Cl_2) was analysed directly by NMR spectroscopy using Procedure B. The signals in the NMR spectra of the reaction mixture assigned to **14** are reported below.



^{1}H NMR (600 MHz, CD_2Cl_2, 27 °C) δ 8.93 (d, *J* = 6.1 Hz, 2H, H-3 & H-5), 8.36 (t, *J* = 7.8 Hz, 1H, H-4), 7.97 (t, *J* = 7.3 Hz, 2H, H-2 & H-6), 7.50 (app. dd, *J* = 6.4, 3.0 Hz, 2H, Phenyl H-2 & H-6), 7.44 – 7.10 (m, 7H, Phenyl H-3, H-4 & H-5, Tolyl H-2, H-3, H-5 & H-6), 6.91 (s, 1H, C*H*PhTol), 2.33 (s, 3H, C*H*$_3$).

A signal of the starting material **4** appears at δ 8.17 ppm (2H of **4**). This signal integrates for 0.30 relative to 1H of **14**, and hence 1H of **4** = 0.15 relative to 1H of **14**. Other signals are obscured.

^{13}C NMR (150 MHz, CD_2Cl_2) δ 145.4 (C-4), 142.3 (C-3 & C-5), 140.9 (Tolyl C-4), 135.2 (Phenyl C-1), 131.8 (Tolyl C-1), 130.3 (Tolyl C-3 & C-5), 130.2 (Phenyl C-4), 129.7 (C-2 & C-6), 129.5 (Phenyl C-3 & C-5), 128.8 (Phenyl C-2 & C-6), 128.5 (Phenyl C-2 & C-6), 97.1 (*C*HPhTol), 21.3 (*C*H$_3$).

A ^{13}C NMR signal assigned to the *C*$F_3SO_3^-$ ion is seen at δ 121.3 (q, *J* = 321 Hz).

^{15}N NMR (60.8 MHz, CD_2Cl_2, 27 °C): δ 246.0

Conversion Calculation (based on consumption of 4-methylbenzhydrylium ion):

2H of Compound **14** corresponds to 2.00, therefore 1H = 1.00.

For the benzhydrol hydrolysis product at 6.14 ppm, 1H = 0.04

For the bis(benzhydryl) ether hydrolysis product signal at 5.36 ppm ($Ar_2CH)_2O$), 2H = 0.09.

$$\text{Conversion} = \frac{1.00}{1.00 + 0.04 + 0.09} \times 100 = 88\%$$

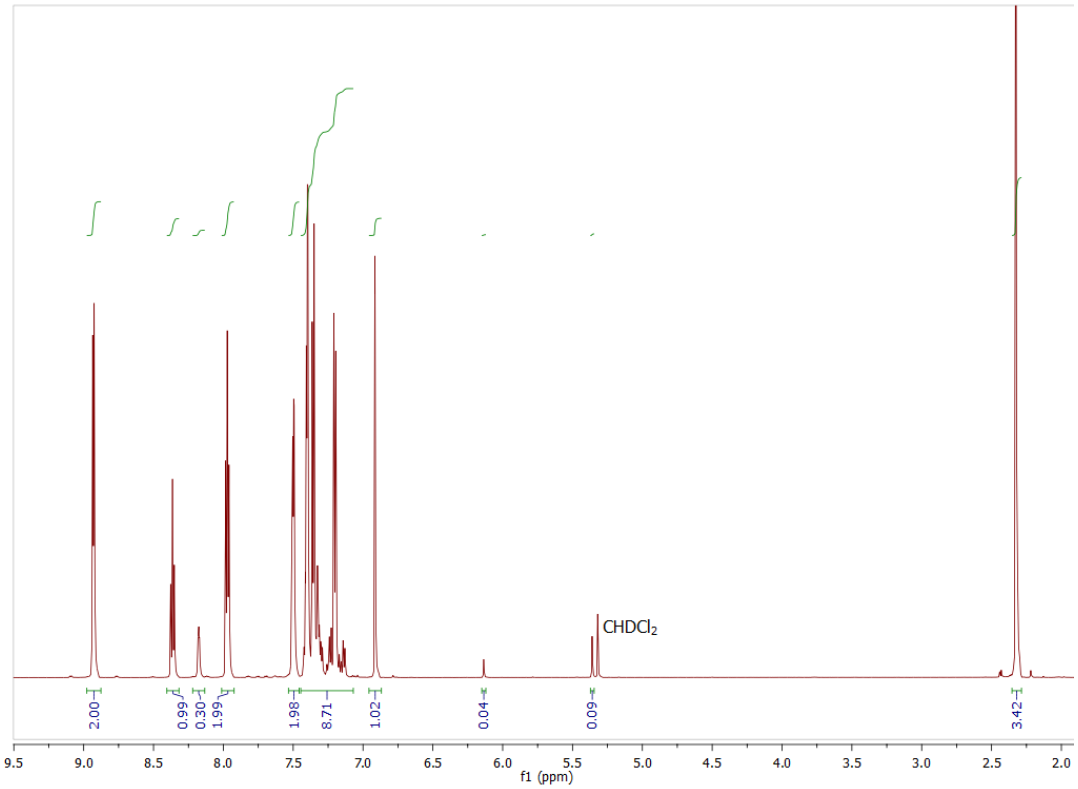
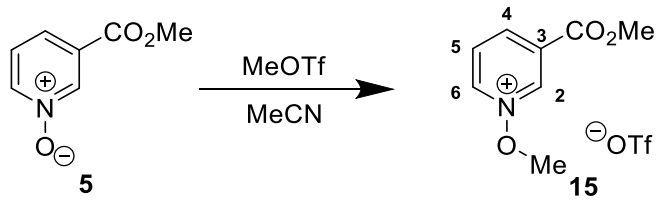


Figure S4: ^{1}H NMR spectrum of **14**. The full spectrum is shown in Section 5.

Preparation of *N*-Methoxy-3-(methoxycarbonyl)pyridinium triflate (15)

3-(methoxycarbonyl)pyridine *N*-oxide (**5**) (0.054 g, 0.35 mmol) was dissolved in dry MeCN (5 ml) in an inert N_2-filled Schlenk flask. Methyl triflate (0.069 g, 0.42 mmol) was subsequently added dropwise. After *ca.* 48 hours, the MeCN was removed under vacuum by Procedure A and the yellow solid product (**15**) was washed by addition of dry Et_2O, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry Et_2O (3 ml each) were used in this manner to wash the product (yield = 0.045 g, 40%; product contains a small quantity of starting material **5**). A sample of **15** in dry DMSO-d_6 was then prepared for ^{1}H and ^{1}H-^{15}N HMBC NMR spectroscopic characterisation using Procedure B.



^{1}H NMR (300 MHz, DMSO-d_6, 27 °C) δ 9.98 (t, J = 1.6 Hz, 1H, H-2), 9.65 (ddd, J = 6.6, 2.0, 1.1 Hz, 1H, H-6), 9.03 – 8.96 (m, 1H, H-4), 8.40 – 8.33 (m, 1H, H-5), 4.49 (s, 3H, COOCH_3), 4.00 (s, 3H, NOCH_3).

^{13}C NMR (75 MHz, DMSO-d_6, 27 °C) δ 160.0 (*C*OOCH$_3$), 143.0 (C-4), 142.7 (C-6), 140.9 (C-2), 129.8 (C-3), 128.0 (C-3), 68.5 (NO*C*H$_3$), 52.1 (COO*C*H$_3$).

^{15}N NMR (60.8 MHz, DMSO-d_6, 27 °C): δ 252.4

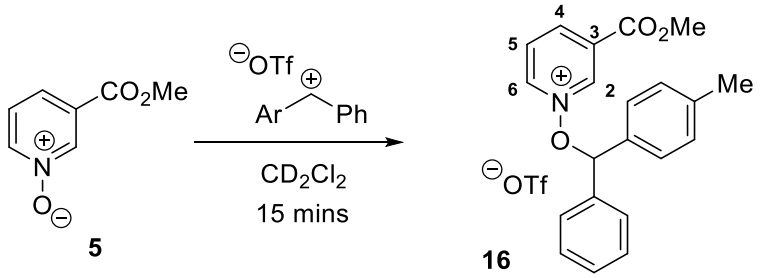
IR (ATR-FTIR), cm^{-1}: 3078 (w), 1740 (s), 1441 (w), 1256 (s), 1156 (s), 1029 (s), 637 (s).

Several attempts at recording HRMS data (by electrospray ionisation in positive mode) for this compound proved unsuccessful, which we ascribe to decomposition of the compound under the different experimental conditions employed.

Copies of the NMR spectra are shown in Section 5.

Preparation of 16

3-(methoxycarbonyl)pyridine *N*-oxide (**5**) (0.0188 g, 0.12 mmol), 4-methylbenzhydryl chloride (0.0266 g, 0.12 mmol) and silver triflate (0.039 g, 0.15 mmol) were combined by the process described in Procedure C to produce **16** in CD_2Cl_2. This product decomposes by hydrolysis if exposed to the ambient atmosphere. Consequently, the product was not isolated. Instead, the reaction mixture (in CD_2Cl_2) was analysed directly by NMR spectroscopy using Procedure B. The signals in the NMR spectra of the reaction mixture assigned to **16** are reported below.



^{1}H NMR (600 MHz, CD_2Cl_2, 27 °C) δ 9.30 – 9.27 (m, 1H, H-6), 9.05 (t, J = 1.7 Hz, H-2 overlaps with signal of **5**), 8.84 (d, J = 8.0 Hz, 1H, H-4), 8.23 – 8.16 (m, 1H, H-5), 7.54 – 7.50 (m, 2H, Phenyl H-2 & H-6), 7.45 – 7.20 (m, 7H, Phenyl H-3, H-4 & H-5, Tolyl H-2, H-3, H-5 & H-6), 6.95 (s, 1H, C*H*PhTol), 3.99 (s, 3.3H, overlapping signals of CO_2CH_3 of **5** and **16**), 2.34 (s, contains 3.3H, overlapping signals of Tolyl CH_3 of **5** and **16**).

Signals of the bis(benzhydryl) ether hydrolysis product appear at δ 7.32 (4H), 7.14 (4H), and 5.37 (2H). The integration of 1H of this hydrolysis product = 0.07 relative to 1H of **16**. Aromatic protons of this product also contribute to the integration of the multiplet at 7.27 – 7.19 ppm.

Small signals of **5** appear at δ 9.03 (overlaps with signal of **16**), 8.74, 8.32, 7.73 (1H each), each integrating for 0.10 relative to 1H of **16**.

^{13}C NMR (150 MHz, CD_2Cl_2, 27 °C) δ 160.9 (*C*OOCH$_3$), 145.8 (C-6), 145.3 (C-4), 142.7 (C-2), 141.2 (Tolyl C-4), 135.1 (Phenyl C-1), 132.0 (C-3), 131.7 (Tolyl C-1), 130.4 (C-5), 130.3 (Phenyl C-4), 130.3 (Tolyl C-3 & C-5), 129.5 (Phenyl C-3 & C-5), 128.8 (Tolyl C-2 & C-6, 128.5 (C-2 & C-6), 97.8 (*C*HPhTol), 54.4 (COO*C*H$_3$), 21.3 (*C*H$_3$).

A ^{13}C NMR signal assigned to the *C*F$_3$SO$_3^-$ ion is seen at δ 121.0 (q, J = 320 Hz).

^{15}N NMR (60.8 MHz, DMSO, 27 °C): δ 248.3

<u>Conversion Calculation</u> (based on consumption of 4-methylbenzhydrylium ion):

1H of Compound **16** corresponds to 1.00.

For the bis(benzhydryl) ether hydrolysis product signal at 5.37ppm (Ar$_2$C*H*)$_2$O), 2H = 0.14.

$$\text{Conversion} = \frac{1.00}{1.00 + 0.14} \times 100 = 88\%$$

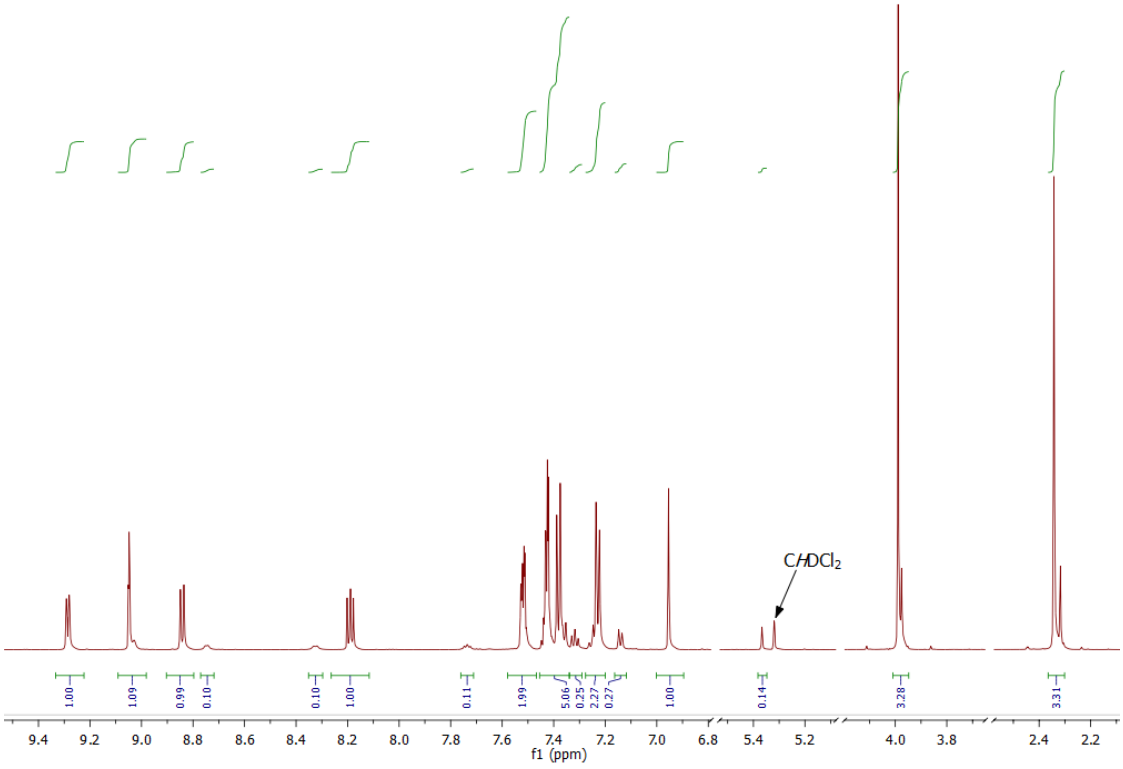
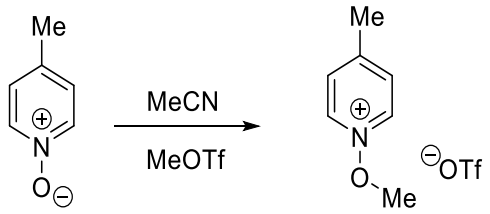


Figure S5: ^{1}H NMR spectrum of **16**. The full spectrum is shown in Section 5.

Preparation of *N*-methoxy-4-methylpyridinium triflate (17)



6 **17**

(a) 4-Methylpyridine-*N*-oxide (**6**) (0.251 g, 2.30 mmol) was dissolved in dry MeCN (10 ml) in an inert N_2-filled Schlenk flask. Methyl triflate (0.495 g, 2.53 mmol) was subsequently added dropwise. The MeCN was removed under vacuum after 72 hours by Procedure A and the solid product (**17**) was washed by addition of dry THF, which was removed by cannula filtration (under inert atmosphere). Three aliquots of dry THF (3 ml each) were used in this manner to wash the product. A sample of **15** in dry DMSO-d_6 was then prepared for ^{1}H and ^{1}H-^{15}N HMBC NMR spectroscopic characterisation using Procedure B. The conversion was observed to be 93% from the integrations in the ^{1}H NMR spectrum. Copies of the NMR spectra are shown in Section 5.

^{1}H NMR (600 MHz, DMSO-d_6, 27 °C)

Signals assigned to **17**: δ 9.30 (d, *J* = 7.0 Hz, 2H), 8.08 (d, *J* = 6.7 Hz, 2H), 4.39 (s, 3H), 2.63 (s, 3H). [10]

Signals assigned to **6**: δ 8.14 (d, *J* = 6.8 Hz, 1H), 7.28 (d, *J* = 6.5 Hz, 1H), 2.30 (s, 1H).

^{15}N NMR (60.8 MHz, DMSO-d_6, 27 °C): δ 247.3. [11]

(b) 4-Methylpyridine-*N*-oxide (**6**) (59 mg, 0.54 mmol) was dissolved in $CDCl_3$ (0.6 ml) in an inert atmosphere glove box. Methyl triflate (89 mg, 0.54 mmol) was added to this solution dropwise (over *ca.* 3 minutes) while agitating the solution. The formation of a small amount of precipitate or emulsion was noted (i.e. the product has only limited solubility in $CDCl_3$). A portion of this solution (0.2 ml) was transferred to a NMR tube, and further $CDCl_3$ (0.5 ml) was added. The NMR tube was sealed with a rubber septum. ^{1}H NMR spectroscopic analysis indicated conversion of 92% (i.e. there remained 8% of starting material **6**). The solution in the NMR tube was re-combined with the reaction mixture (open to ambient atmosphere), and the solvent was removed under vacuum, giving a colourless oil. This oil was washed with five portions of diethyl ether (*ca.* 2 ml each). Each portion of ether was decanted off carefully. After the fourth wash, the oil solidified, giving a white solid. This solid was dissolved in the minimum possible amount of boiling $CHCl_3$, and a small number of drops of boiling diethyl ether was added, causing an oil to separate from the solution. The solution was decanted off from the oil, and further ether (*ca.* 2 ml) was added to the remaining oil, causing is to form a white solid almost instantly. The ether was decanted off, and three further ether washes (2 ml each) of the solid were carried out. The white solid was then dried under vacuum (125 mg, 84% yield). ^{1}H NMR spectroscopic analysis of this solid in DMSO-d_6 showed it to be product **17**.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 – 9.25 (m, 2H), 8.09 (app d, *J* = 6.7 Hz, 2H), 4.39 (s, 3H), 2.64 (s, 3H).[10] A copy of the ^{1}H NMR spectrum is shown in Section 5.

5. Copies of NMR Spectra of Compounds Reported in Section 4

7a in DMSO (From Pyrazine (1) + MeI)

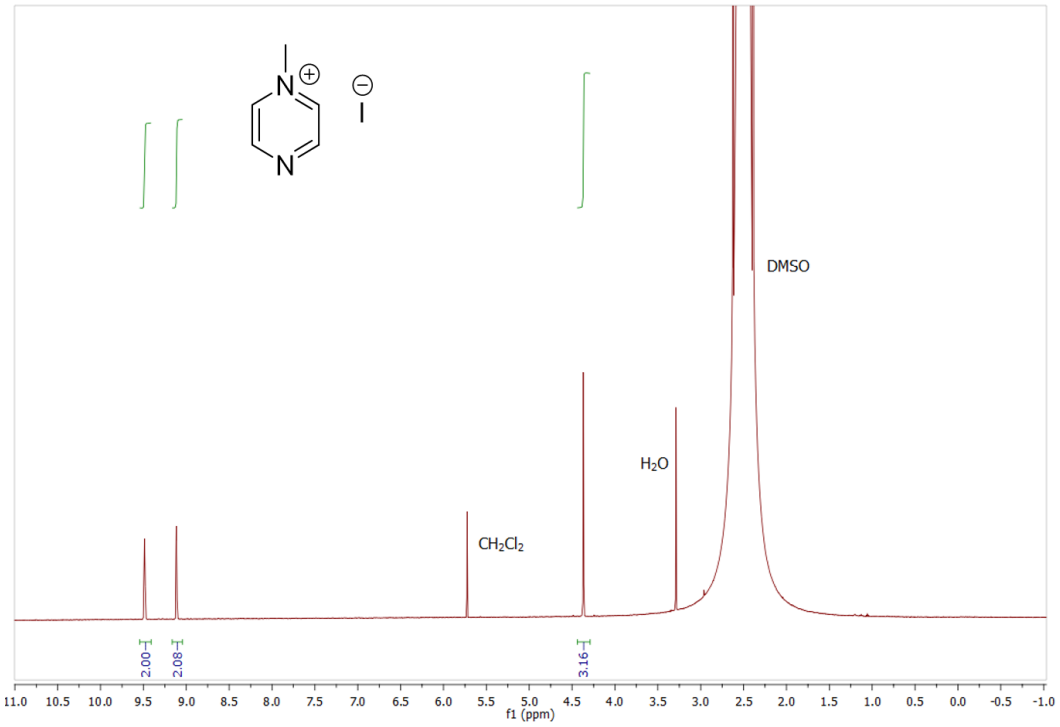


Figure S6: Full ^{1}H NMR spectrum of **7a** in DMSO

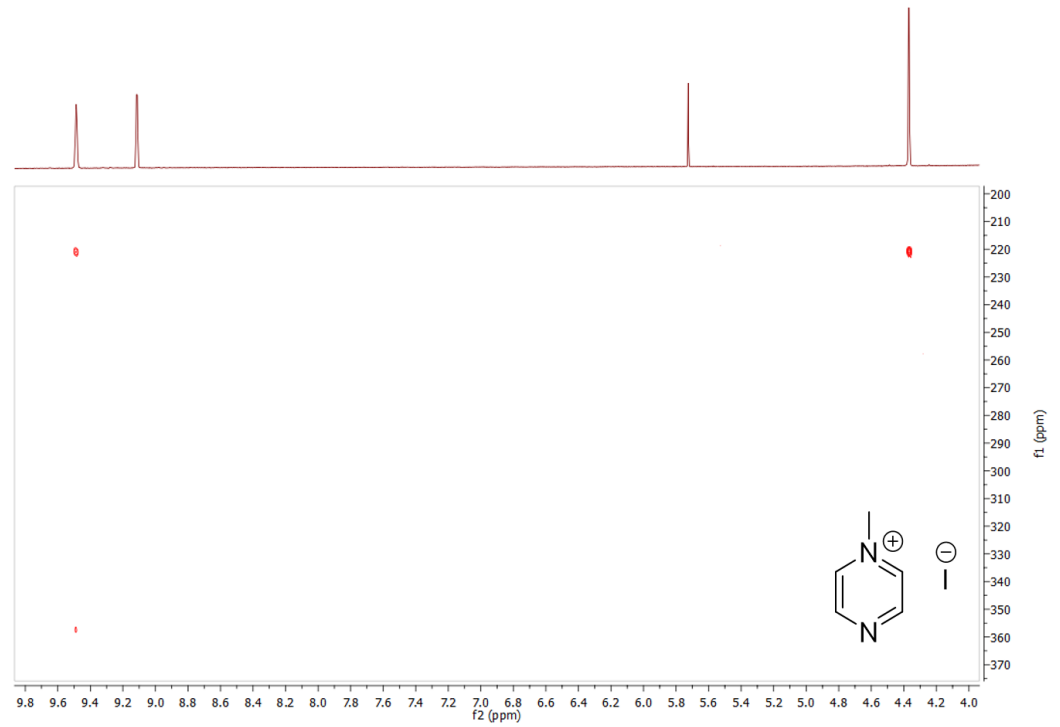


Figure S7: ^{1}H-^{15}N HMBC NMR spectrum of **7a** in DMSO.

7b in DMSO-d_6 (From Pyrazine (1) + MeOTf in MeCN)

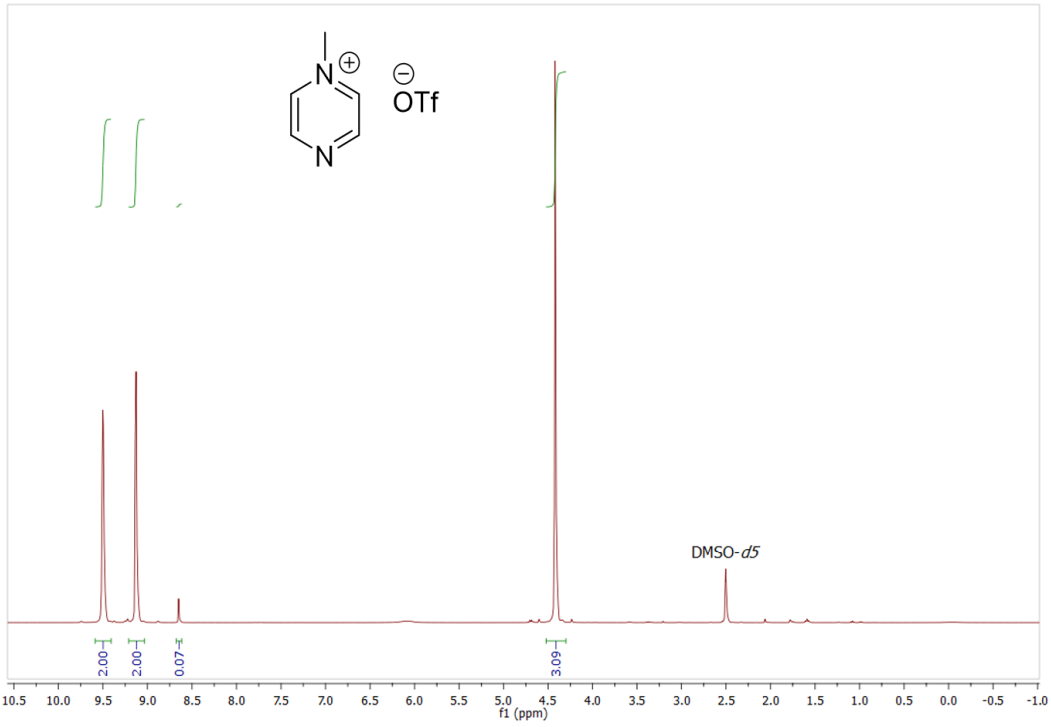


Figure S8: Full ^{1}H NMR spectrum of **7b** in DMSO-*d6*.

7b in DMSO (From Pyrazine (1) + MeOTf in MeCN)

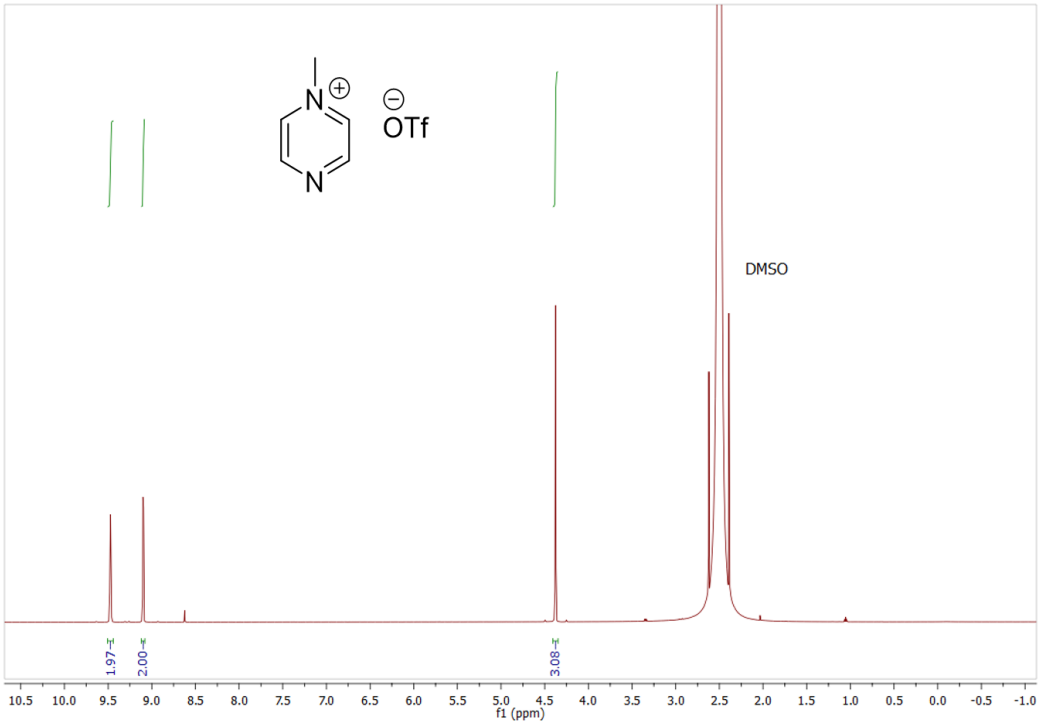


Figure S9: Full ^{1}H NMR spectrum of **7b** in DMSO.

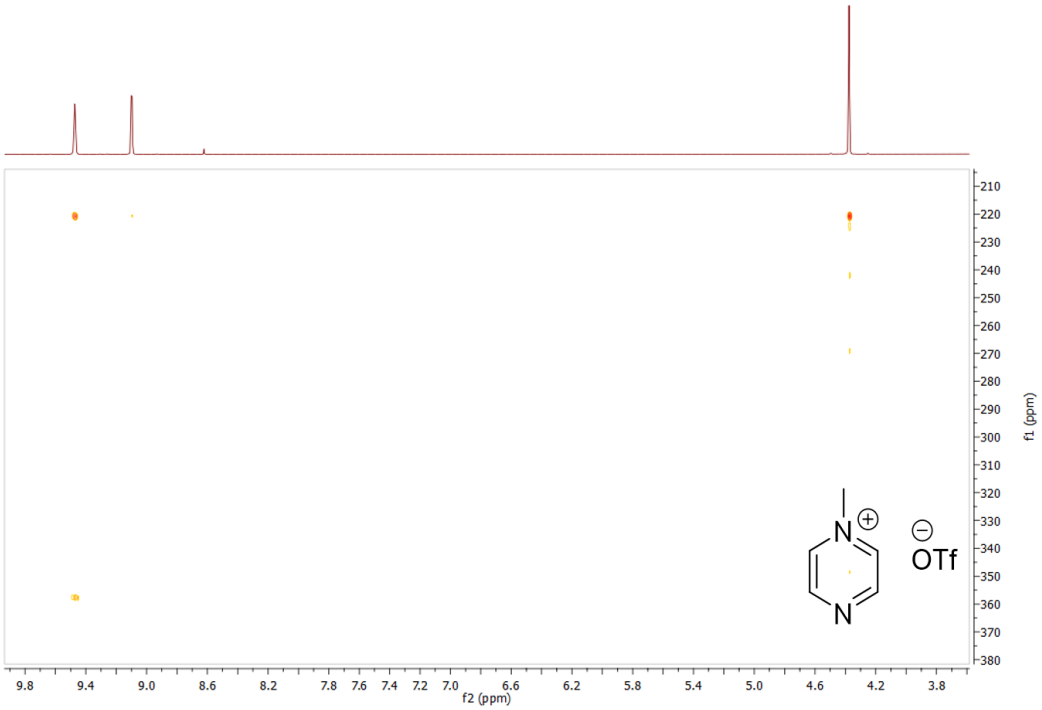


Figure S10: ^{1}H-^{15}N HMBC NMR spectrum of **7b** in DMSO.

8 in CD_2Cl_2 (From Pyrazine (1) + 4-methylbenzhydrylium ion (19) in CD_2Cl_2)

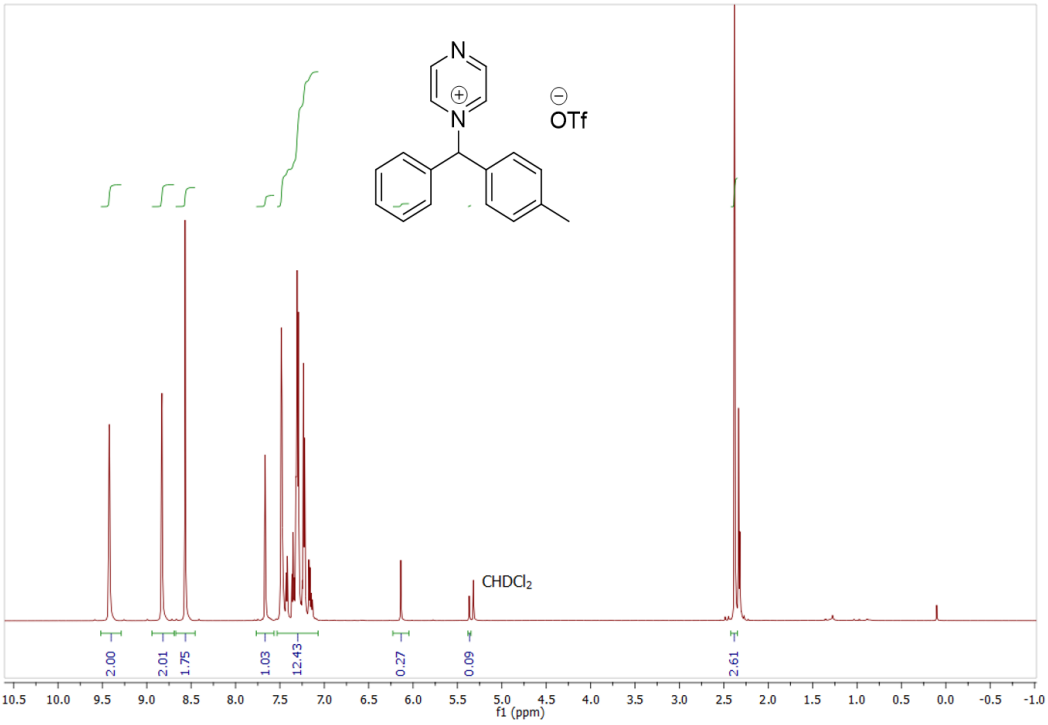


Figure S11: Full ^{1}H NMR spectrum of **8** in CD_2Cl_2.

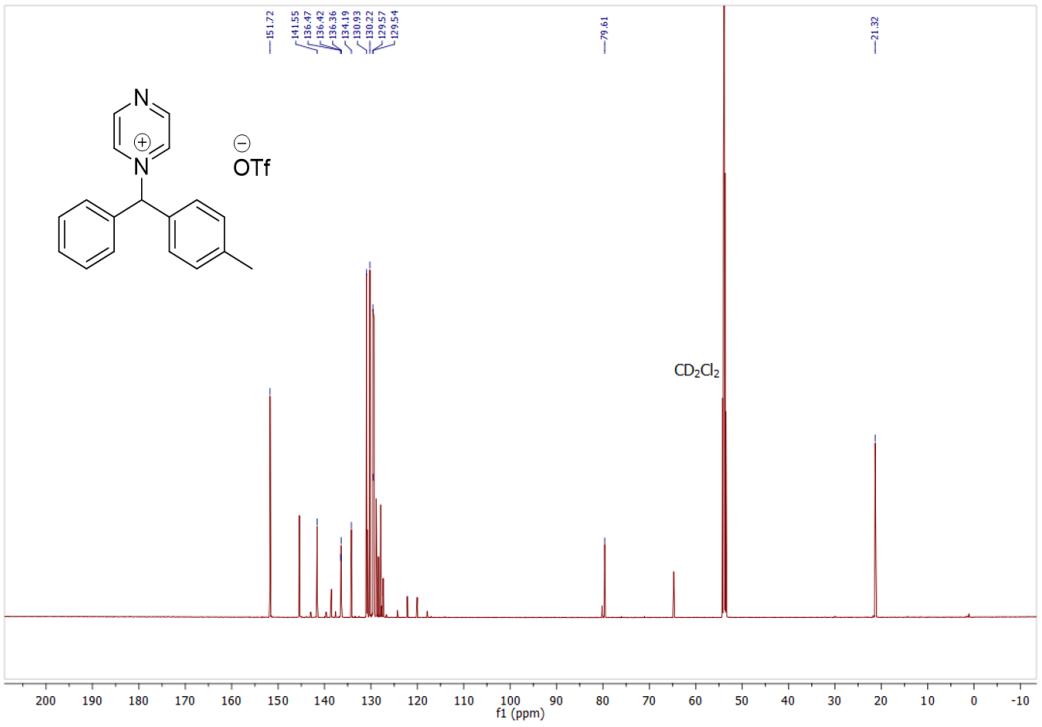


Figure S12: ^{13}C spectrum of **8** in CD_2Cl_2.

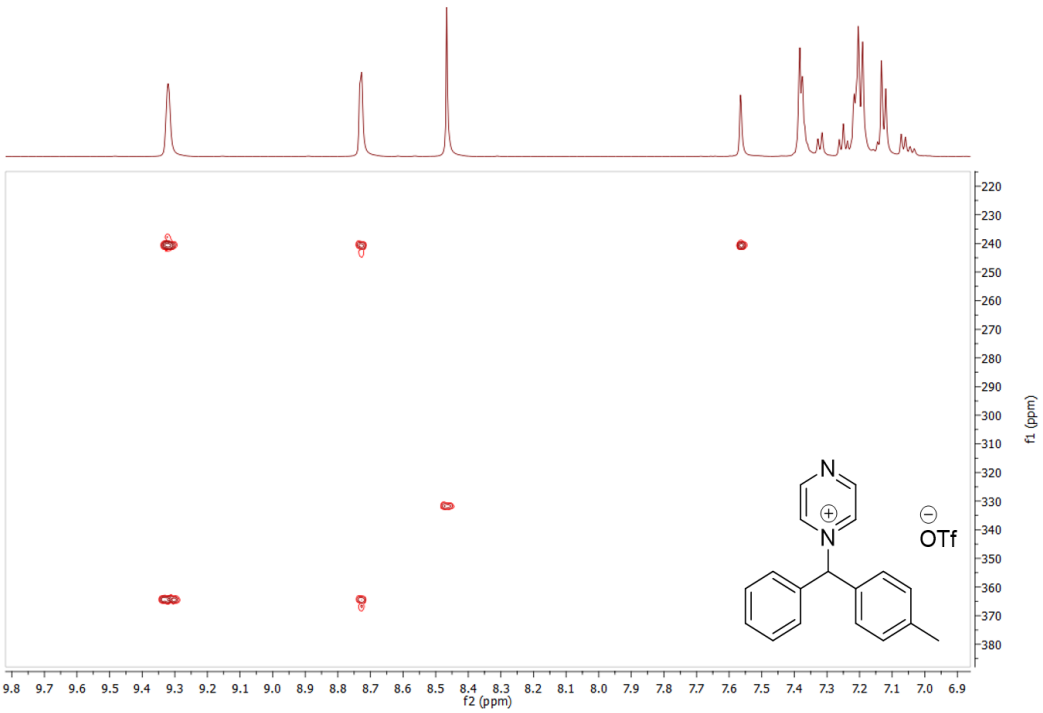


Figure S13: ^{1}H-^{15}N HMBC NMR spectrum of **8** in CD_2Cl_2.

9a in DMSO (From quinoxaline (2) + MeI)

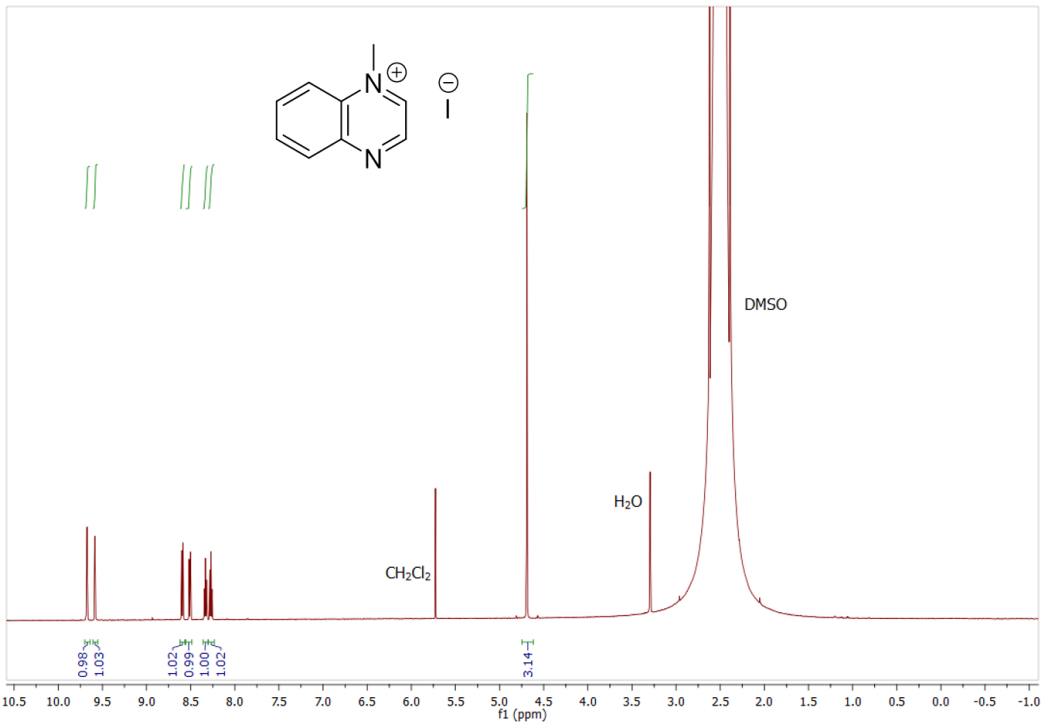


Figure S14: Full ^{1}H NMR spectrum of **9a** in DMSO

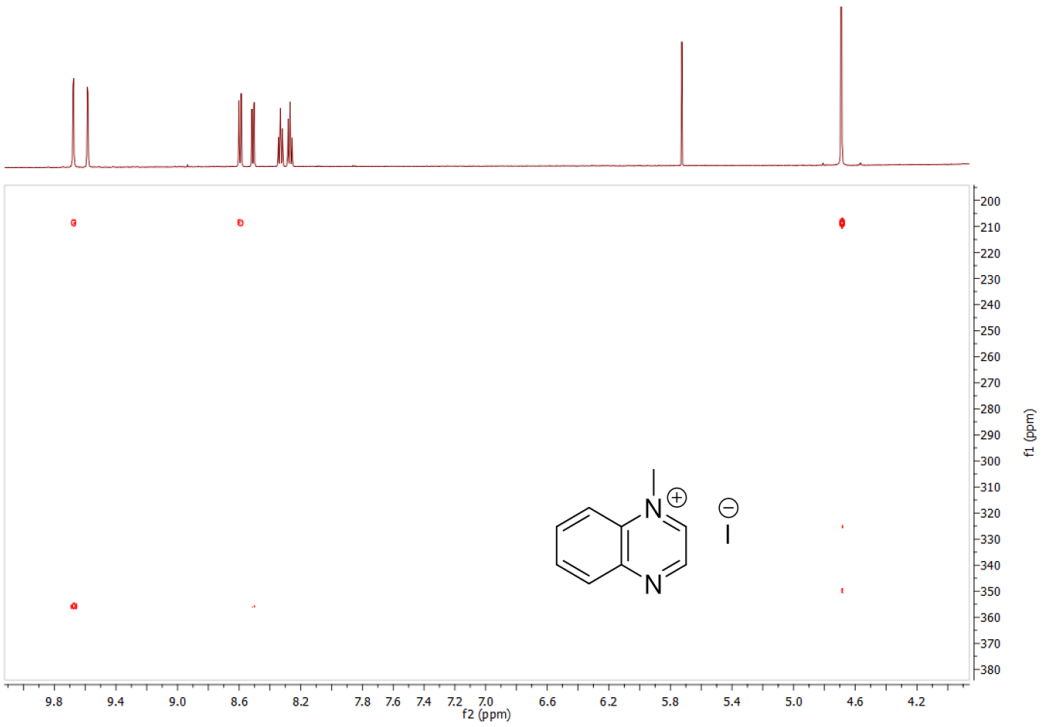


Figure S15: ^{1}H-^{15}N HMBC NMR spectrum of **9a** in DMSO

9b in DMSO-d_6 (From quinoxaline (2) + MeOTf in MeCN)

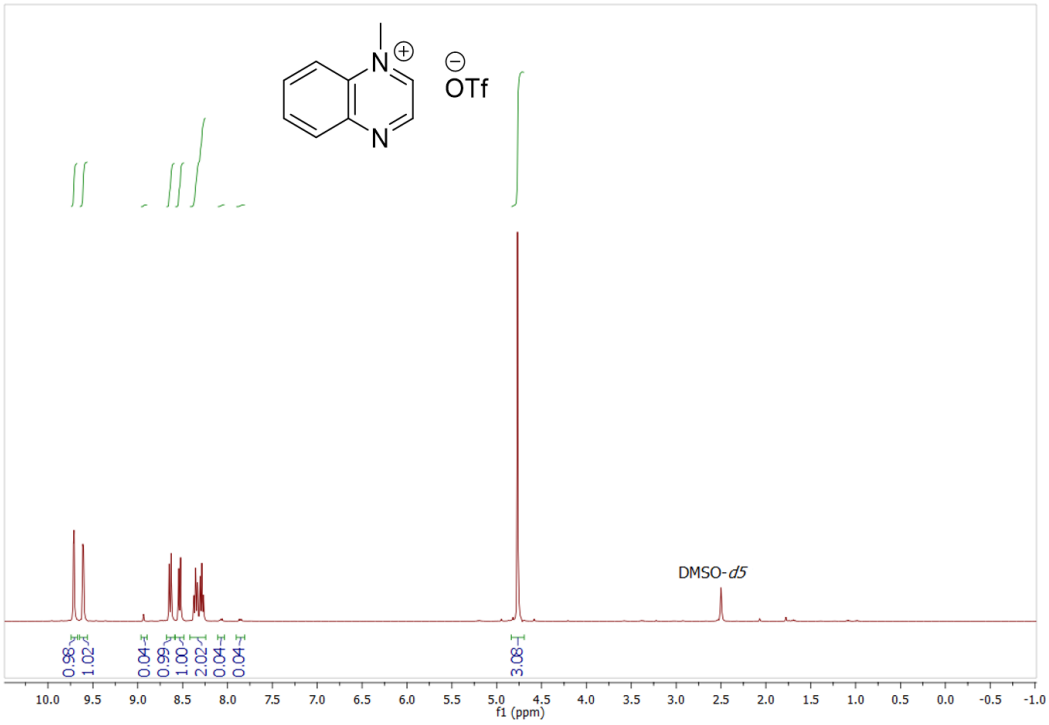


Figure S16: Full ^{1}H NMR spectrum of **9b** in DMSO-d_6

9b in DMSO (From quinoxaline (2) + MeOTf in MeCN)

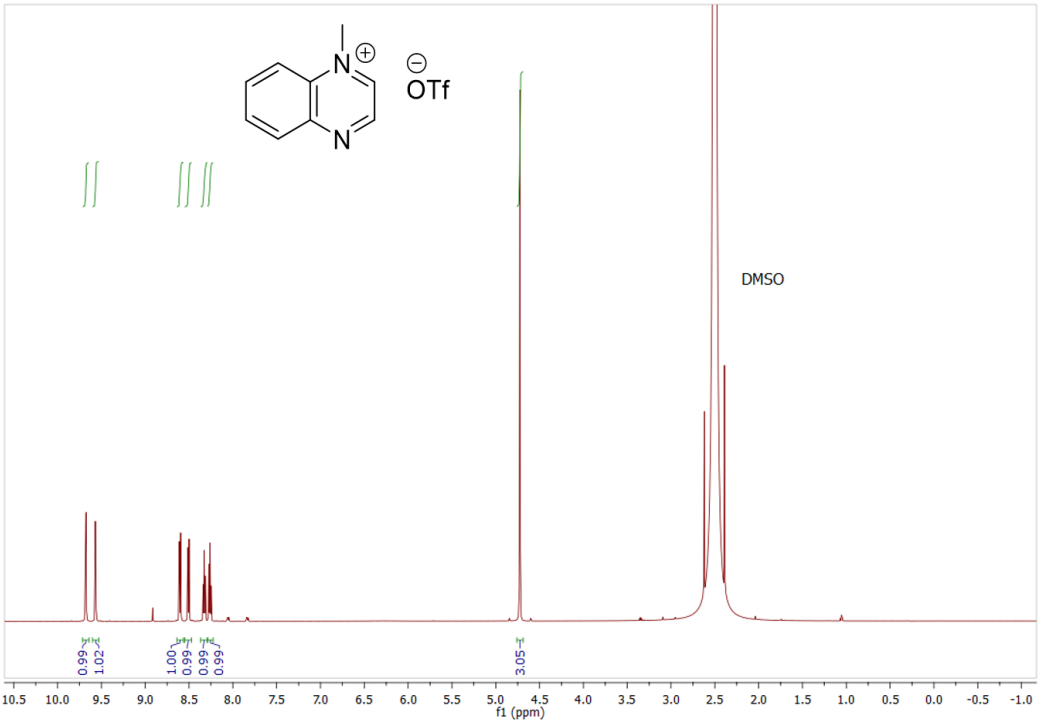


Figure S17: Full ^{1}H NMR spectrum of **9b** in DMSO.

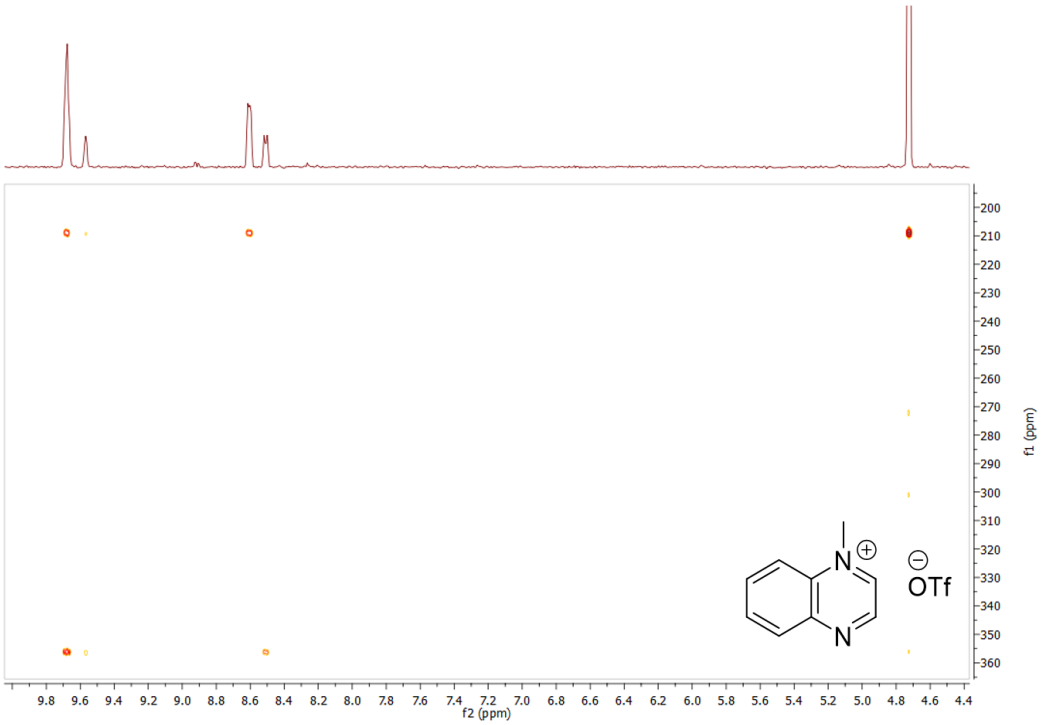


Figure S18: ^{1}H-^{15}N HMBC NMR spectrum of **9b** in DMSO.

10 in CD_2Cl_2 (From quinoxaline (2) +4-methylbenzhydrylium ion (19) in CD_2Cl_2)

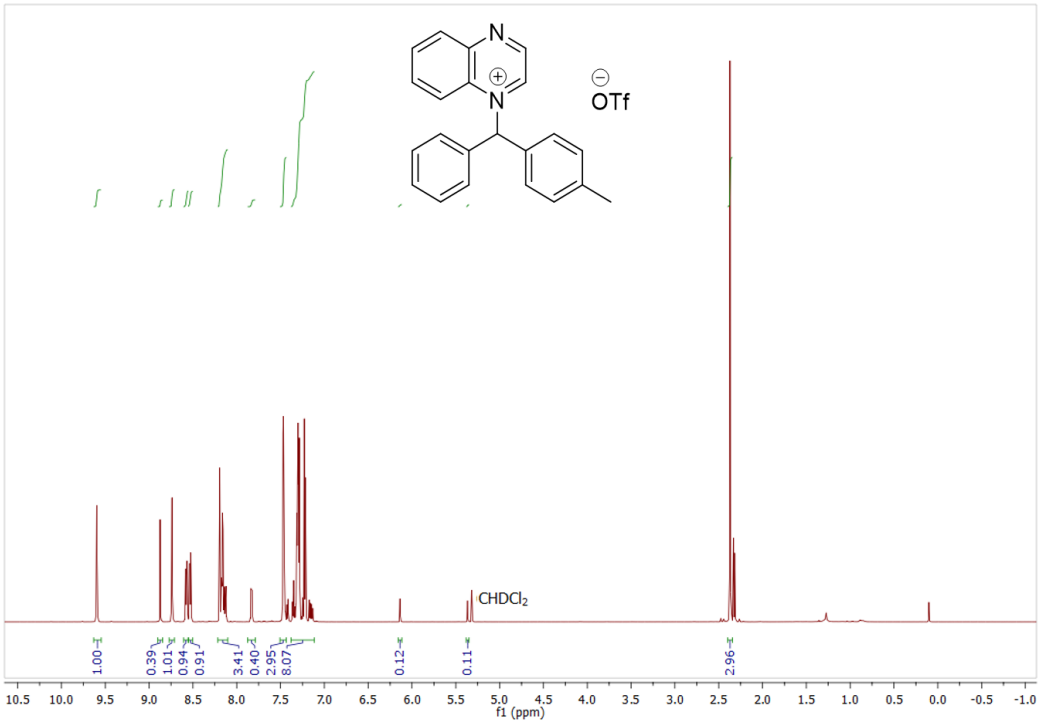


Figure S19: Full ^{1}H NMR spectrum of **10** in CD_2Cl_2.

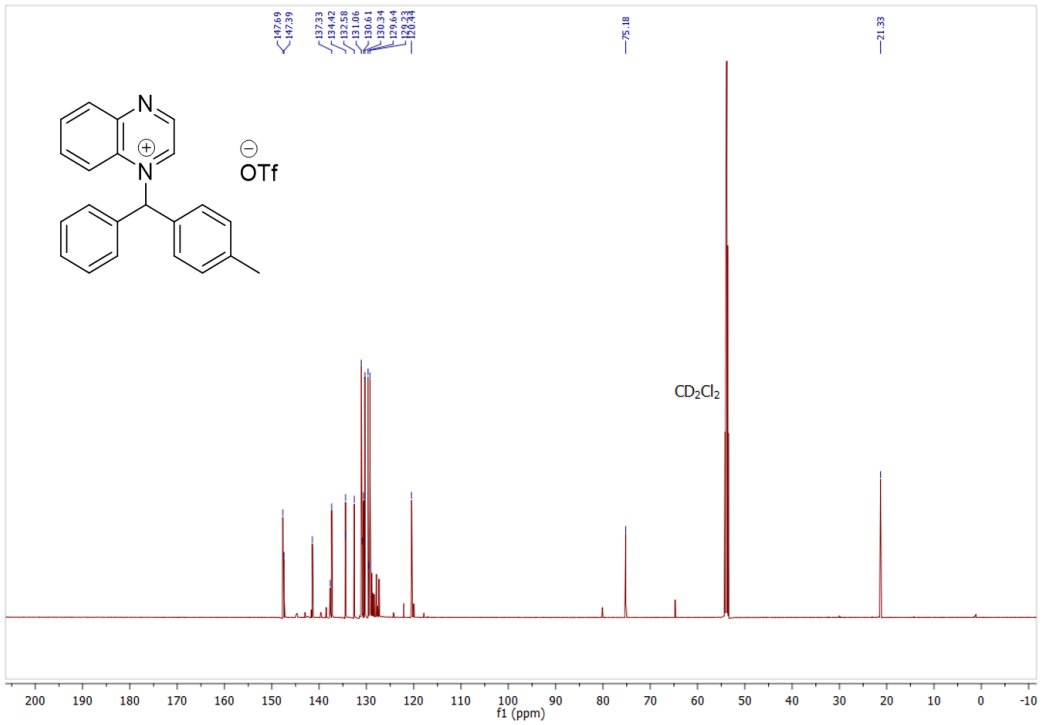


Figure S20: ^{13}C spectrum of **10** in CD_2Cl_2.

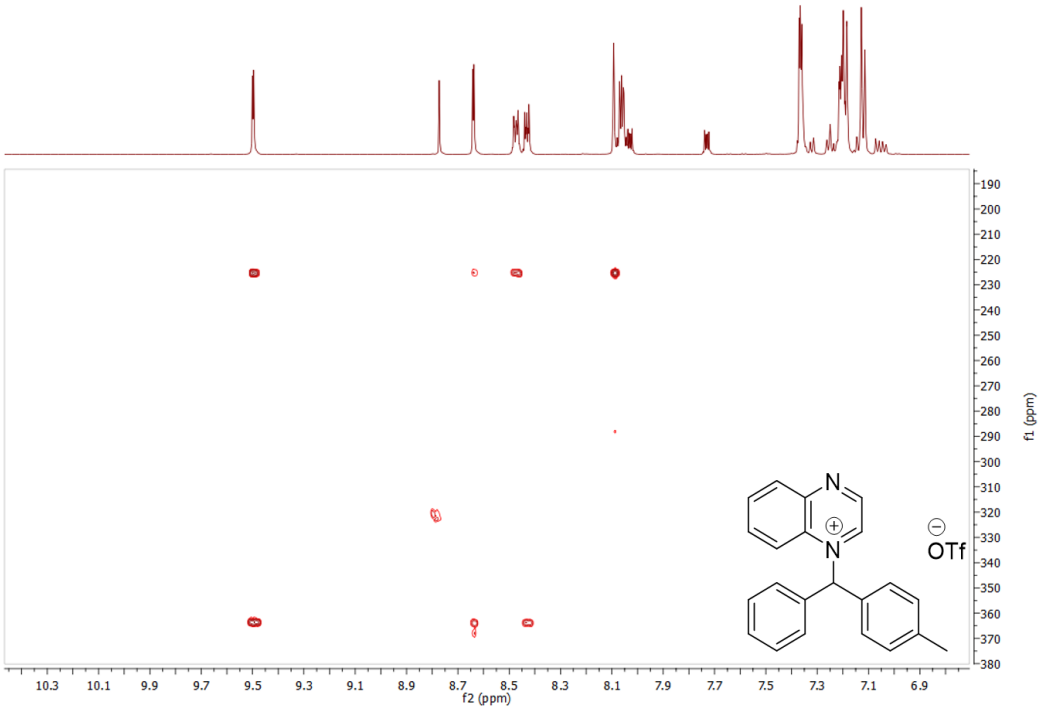


Figure S21: ^{1}H-^{15}N HMBC NMR spectrum of **10** in CD_2Cl_2.

11a in DMSO (From Pyrimidine (3) + MeI)

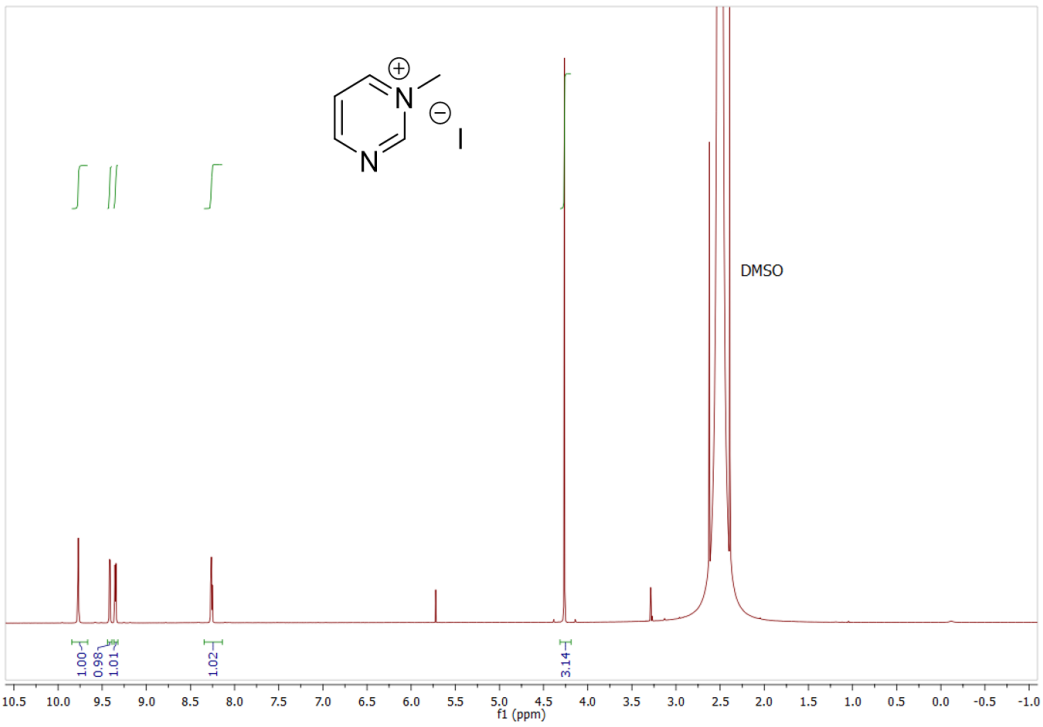


Figure S22: Full ^{1}H NMR spectrum of **11a** in DMSO.

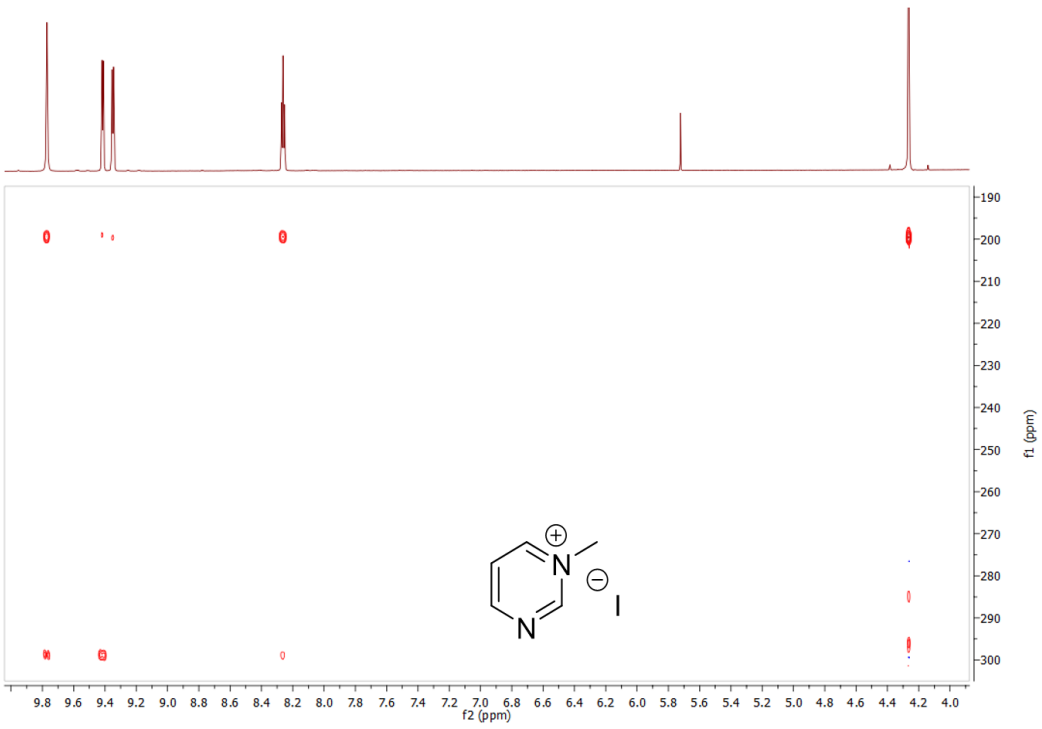


Figure S23: ^{1}H-^{15}N HMBC NMR spectrum of **11a** in DMSO.

11b in DMSO-d_6 (From Pyrimidine (3) + MeOTf in MeCN)

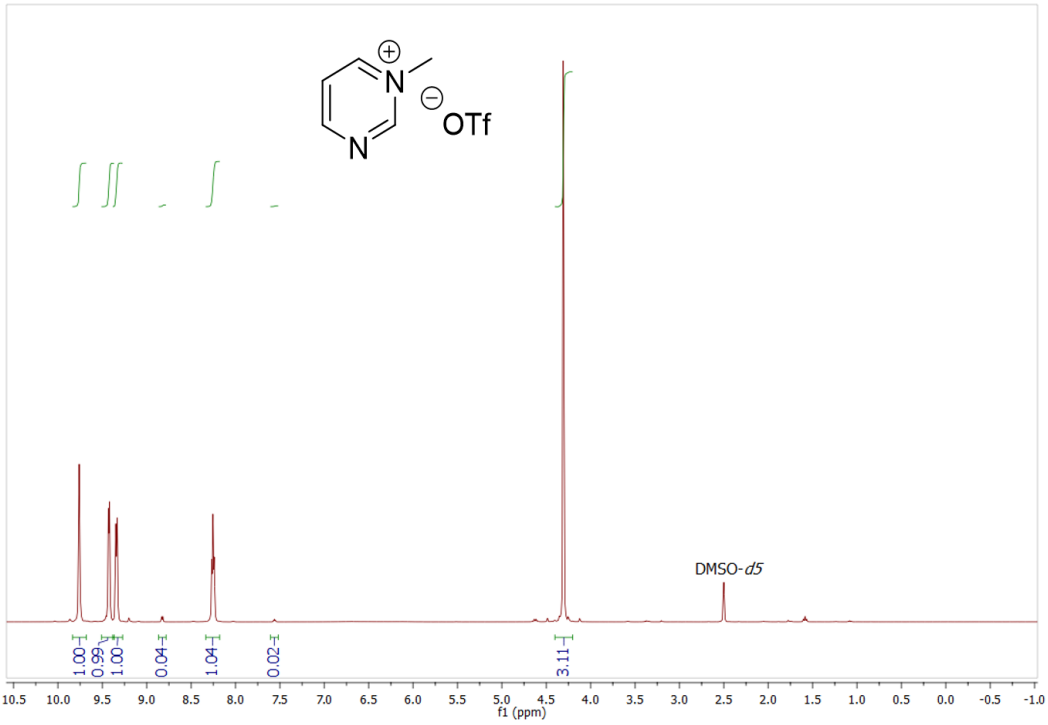


Figure S24: Full ^{1}H NMR spectrum of **11b** in DMSO-d_6.

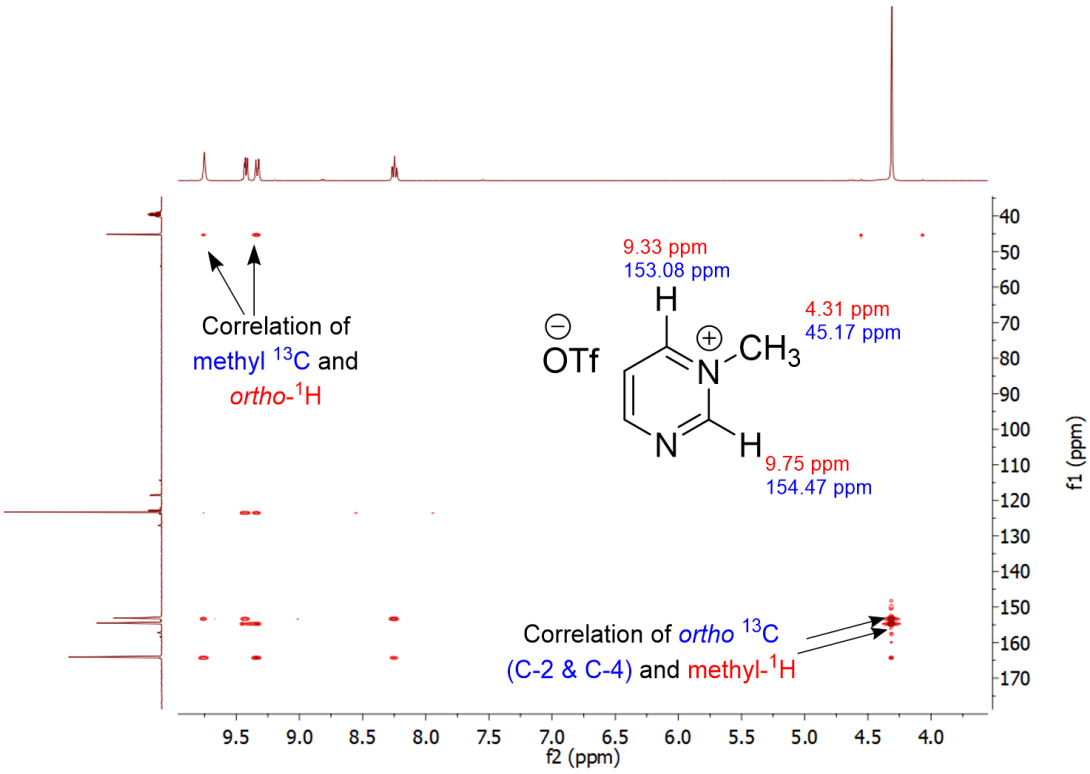


Figure S25: Section of ^{1}H – ^{13}C HMBC NMR spectrum of **11b** in DMSO-d_6, showing the correlation between *N*-methyl signals and ring signals.

11b in DMSO (From Pyrimidine (3) + MeOTf in MeCN)

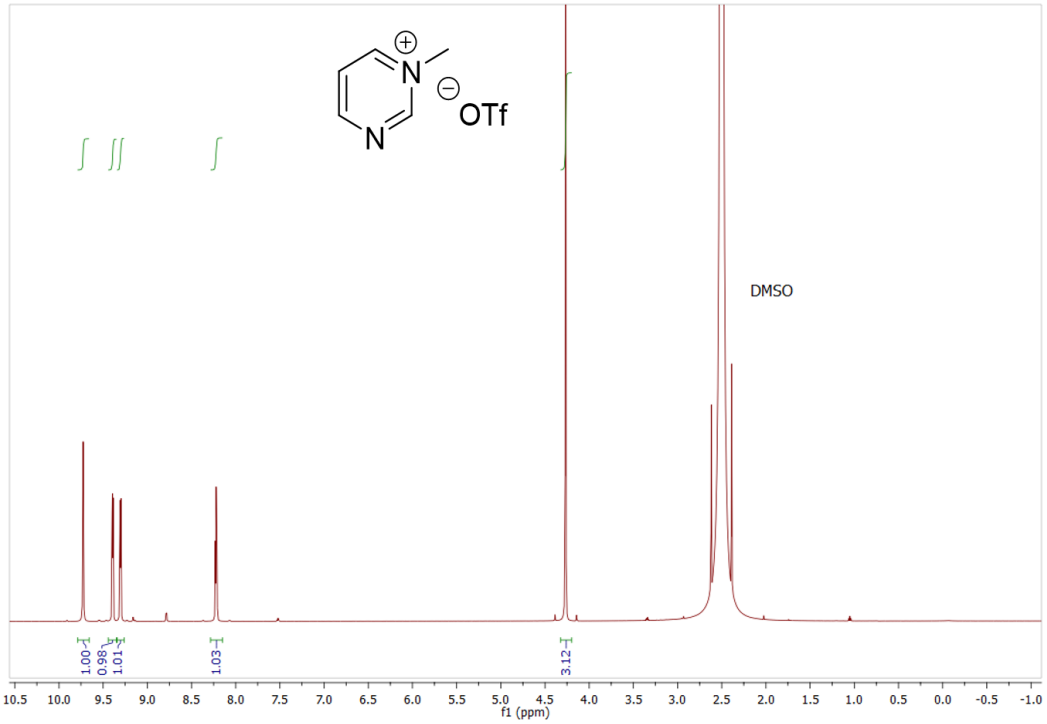


Figure S26: Full ^{1}H NMR spectrum of **11b** in DMSO.

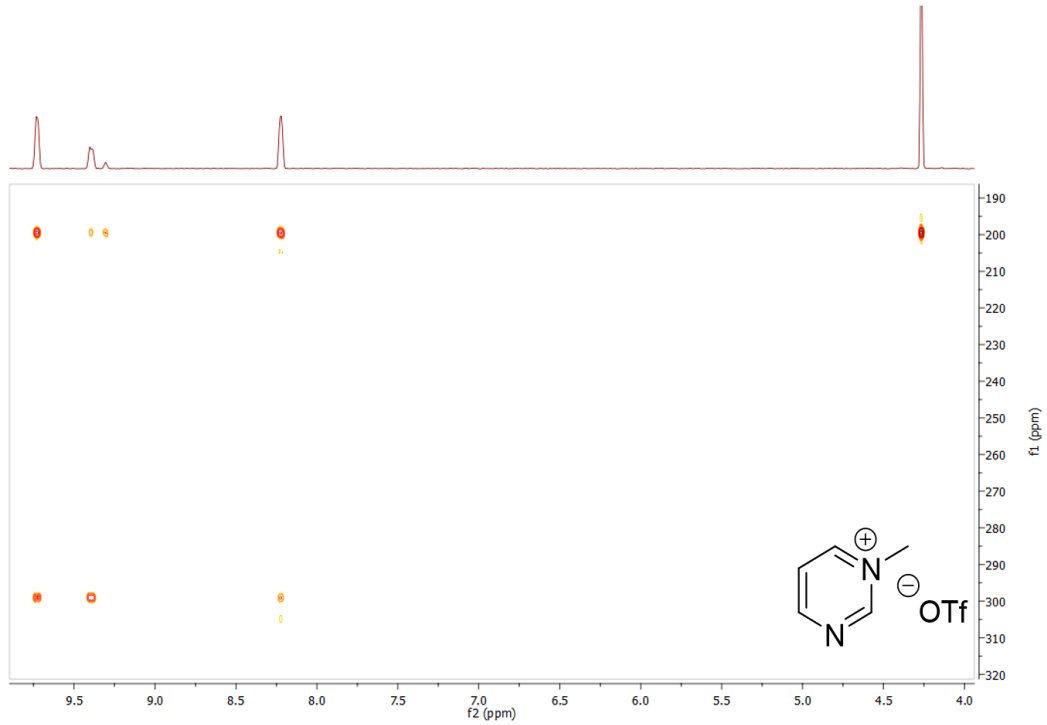


Figure S27: ^{1}H-^{15}N HMBC NMR spectrum of **11b** in DMSO.

12 in CD_2Cl_2 (From pyrimidine (3) + 4-methylbenzhydrylium ion (19) in CD_2Cl_2)

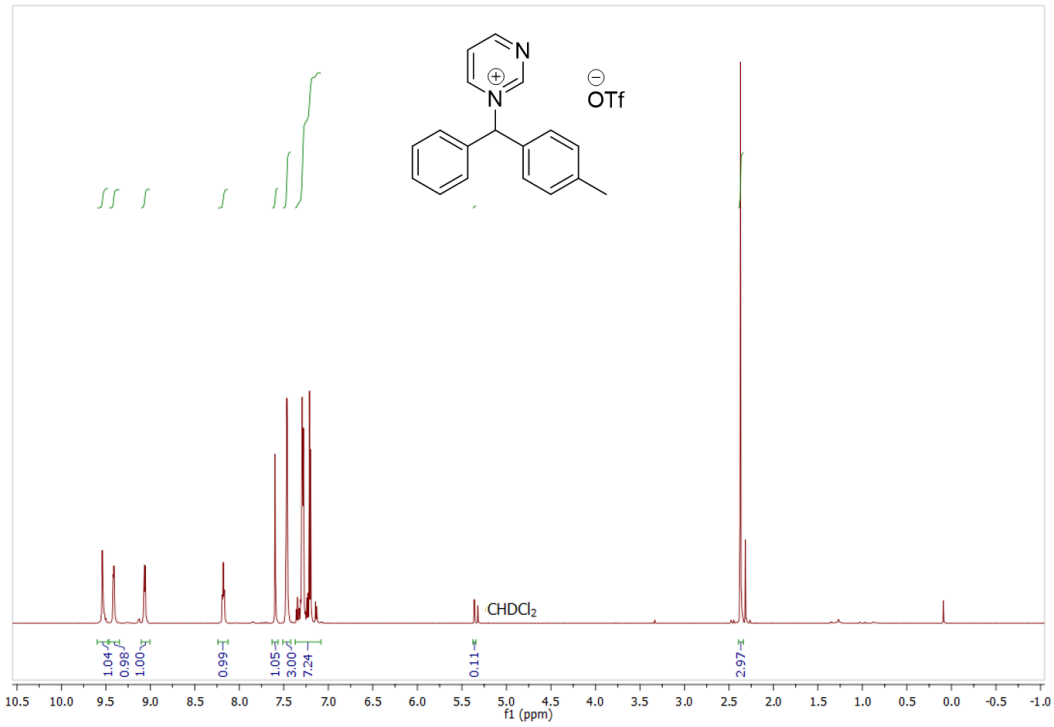


Figure S28: Full ^{1}H NMR spectrum of **12** in CD_2Cl_2.

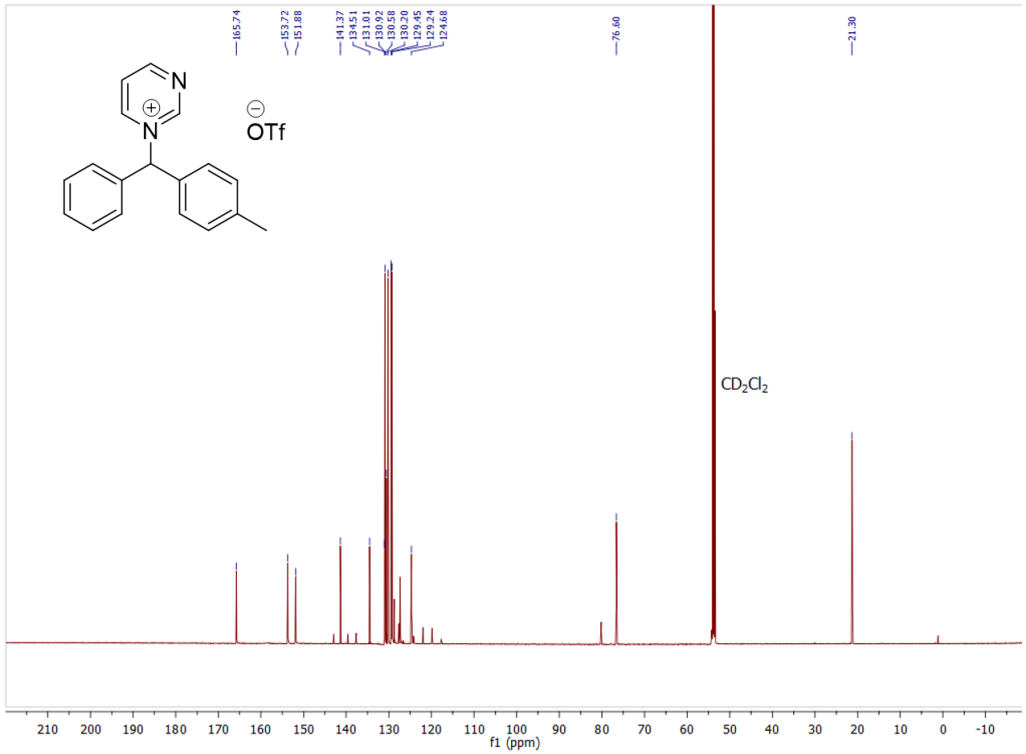


Figure S29: ^{13}C spectrum of **12** in CD_2Cl_2.

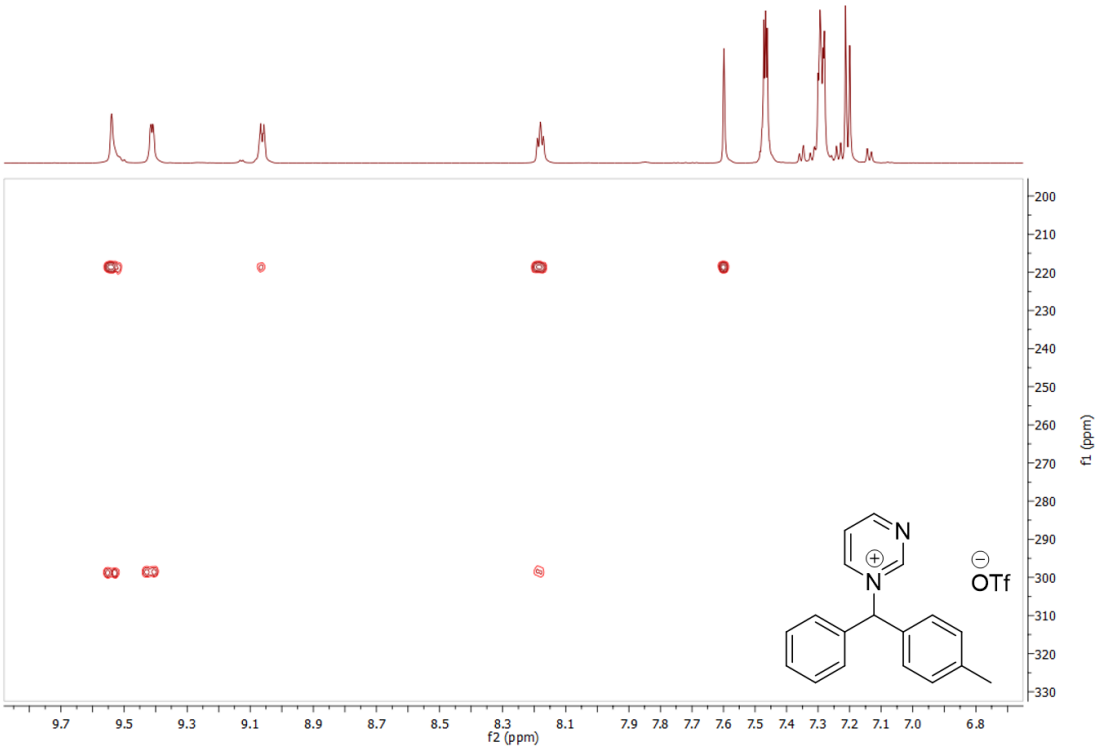


Figure S30: ^{1}H-^{15}N HMBC NMR spectrum of **12** in CD_2Cl_2.

13a in DMSO-*d*$_6$ (From Pyridine *N*-oxide (4) + MeI)

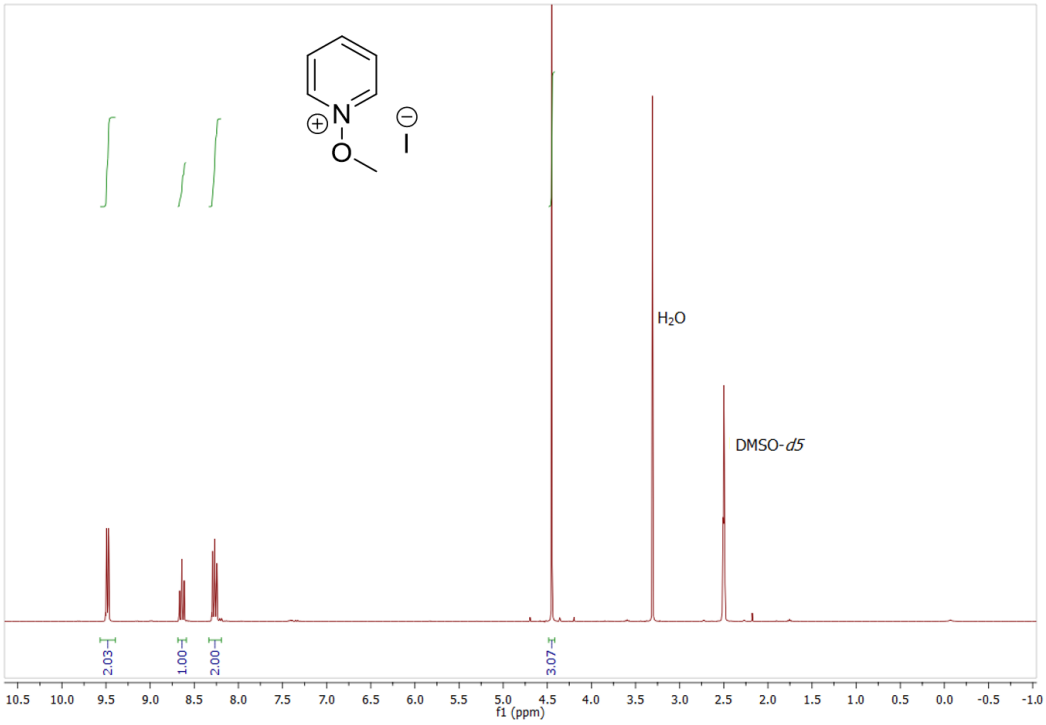


Figure S31: Full ^{1}H NMR spectrum of **13a** in DMSO-*d*$_6$.

13a in DMSO (From Pyridine *N*-oxide (4) + MeI in MeCN)

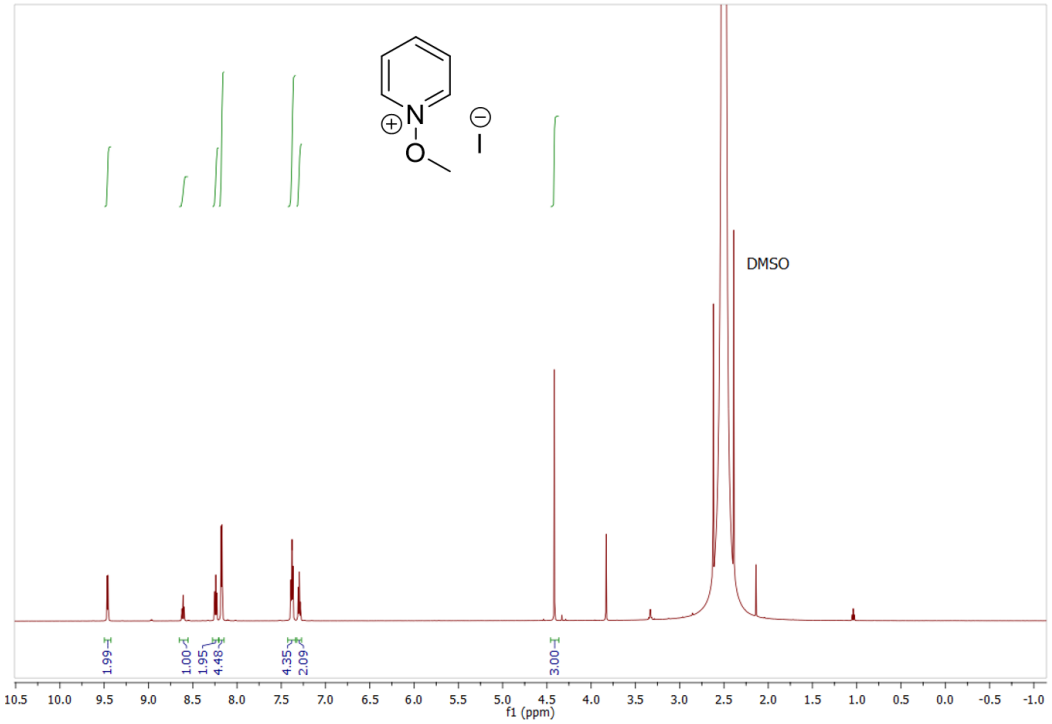


Figure S32: Full ^{1}H NMR spectrum of **13a** and **4** in DMSO

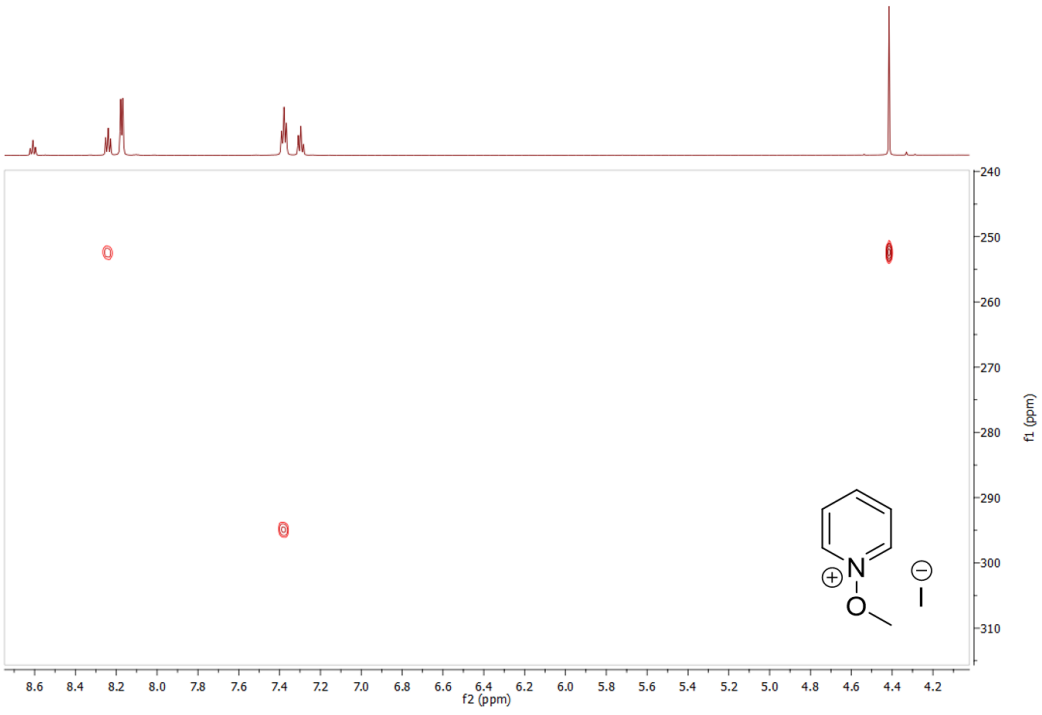


Figure S33: ^{1}H-^{15}N HMBC NMR spectrum of **13a** and **4** in DMSO.

13b in DMSO-d_6 (From Pyridine *N*-oxide (4) + MeOTf in MeCN)

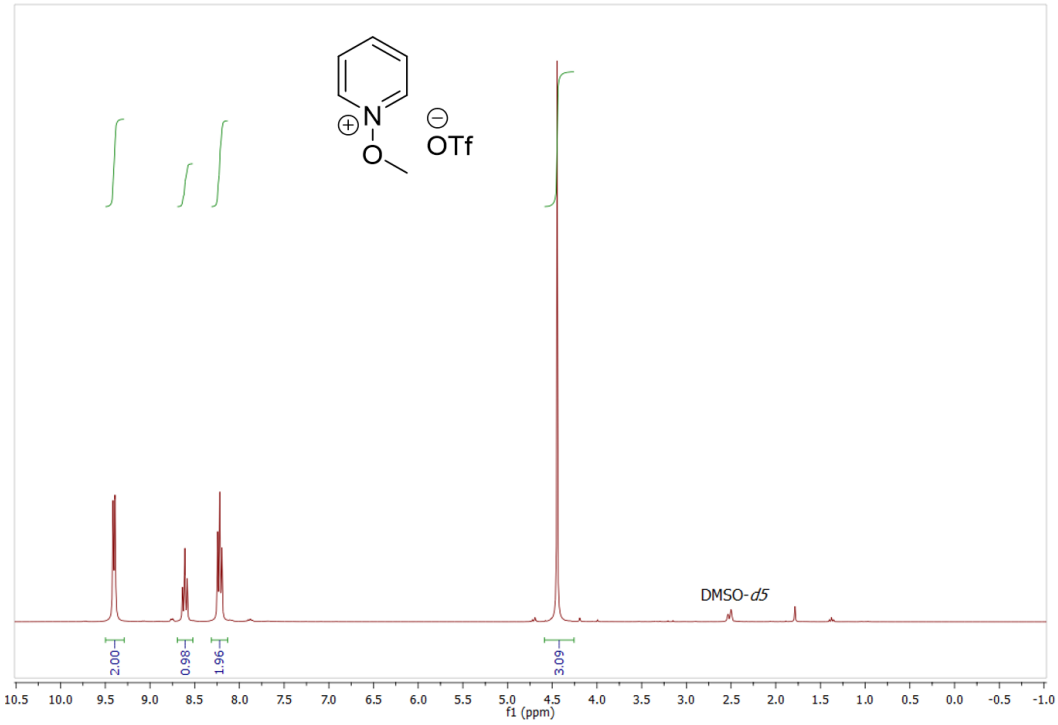


Figure S34: Full ^{1}H NMR spectrum of **13b** in DMSO-d_6.

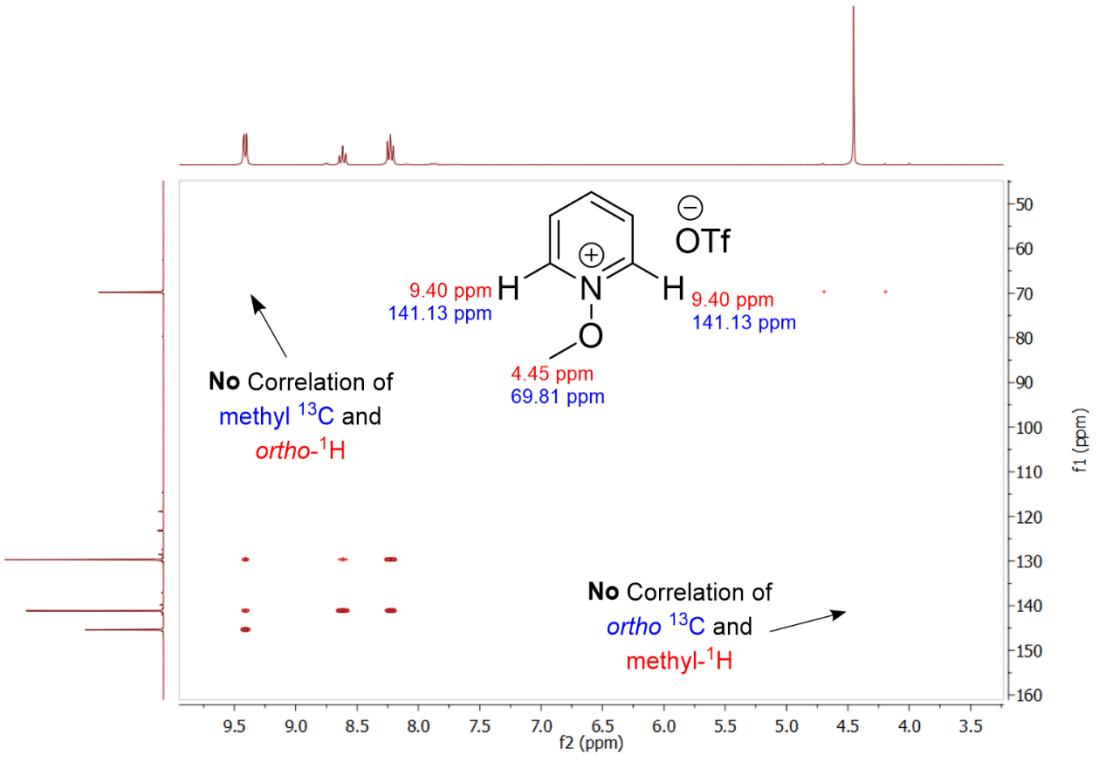


Figure S35: Section of ^{1}H – ^{13}C HMBC NMR spectrum of **13b** in DMSO-d_6, showing no correlation between *O*-methyl signals and ring signals.

13b in DMSO (From Pyridine *N*-oxide (4) + MeOTf in MeCN)

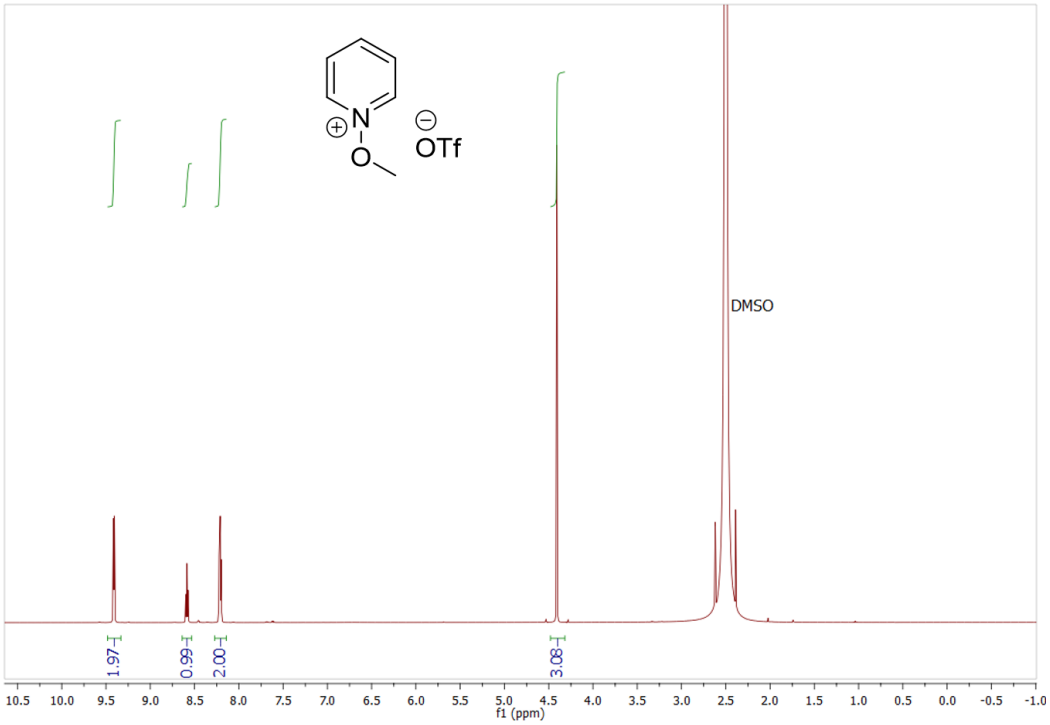


Figure S36: Full ^{1}H NMR spectrum of **13b** in DMSO.

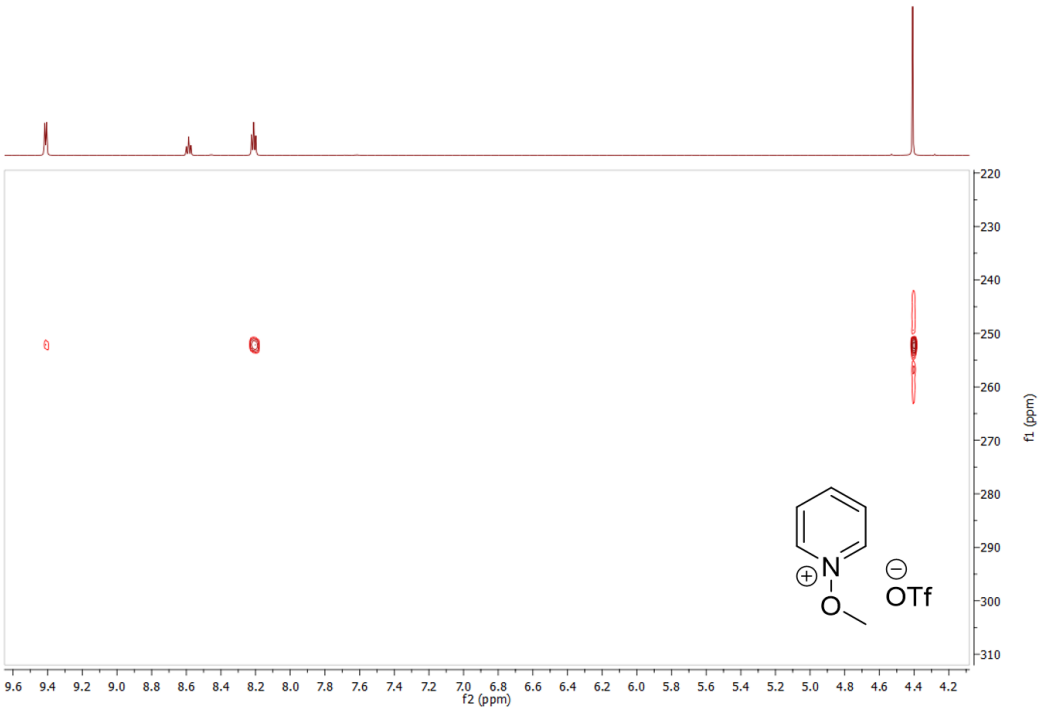


Figure S37: ^{1}H-^{15}N HMBC NMR spectrum of **13b** in DMSO.

13b in CH_2Cl_2 (From Pyridine *N*-oxide (4) + MeOTf in CH_2Cl_2)

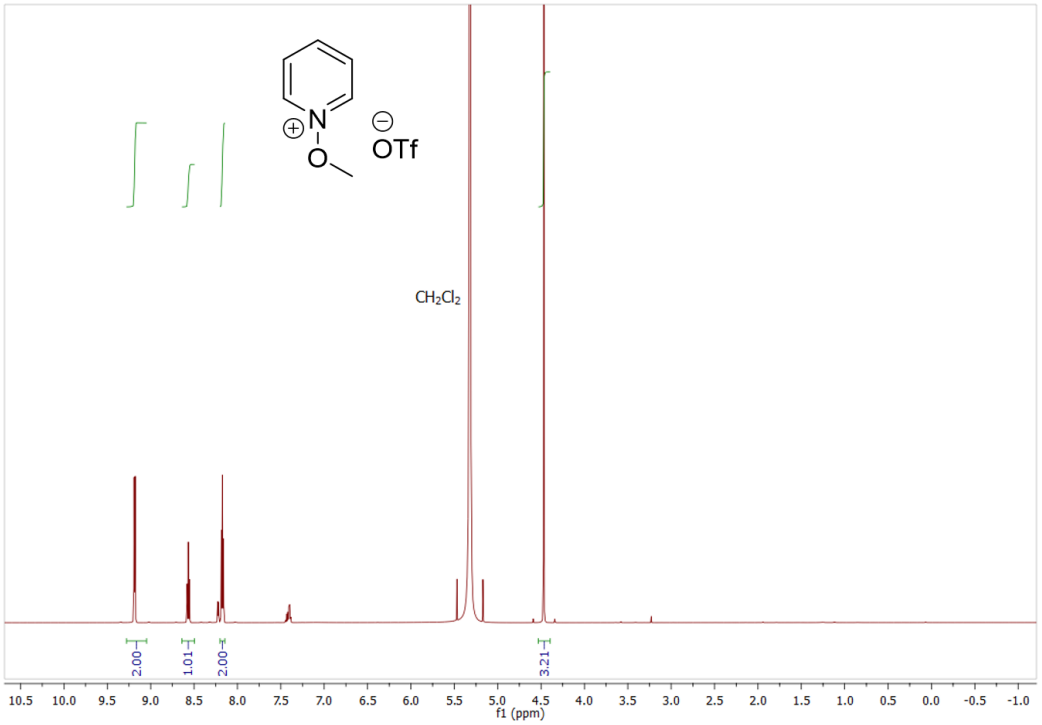


Figure S38: Full ^{1}H NMR spectrum of **13b** in CH_2Cl_2

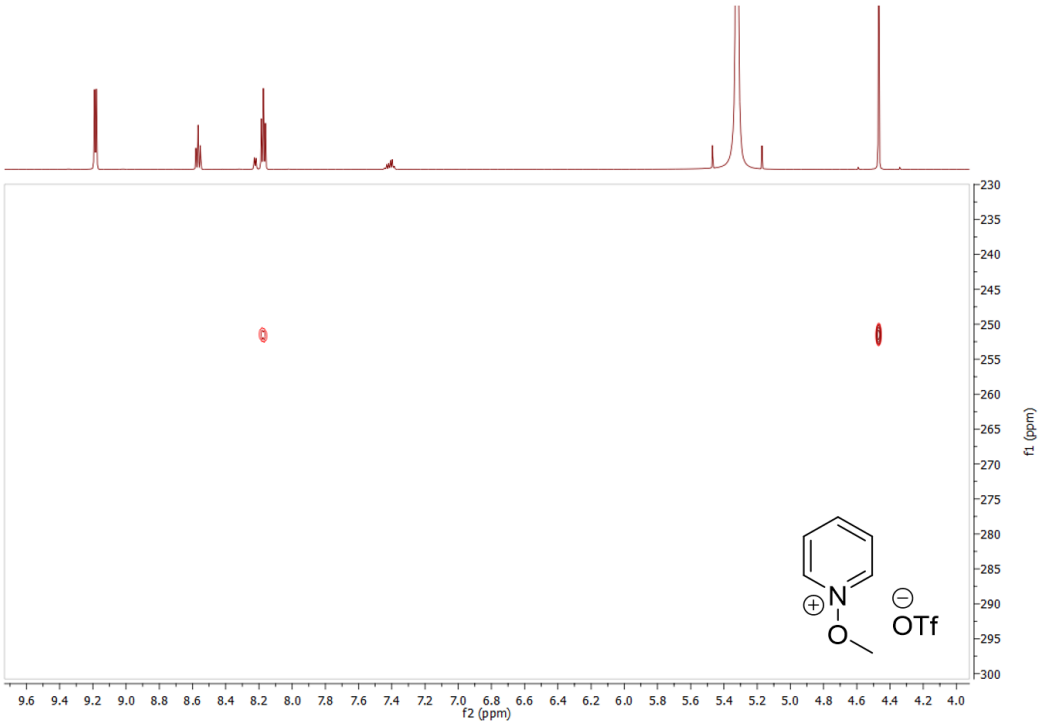


Figure S39: ^{1}H-^{15}N HMBC NMR spectrum of **13b** in CH_2Cl_2.

14 in CD_2Cl_2 (From pyridine *N*-oxide (4) + 4-methylbenzhydrylium ion (19) in CD_2Cl_2)

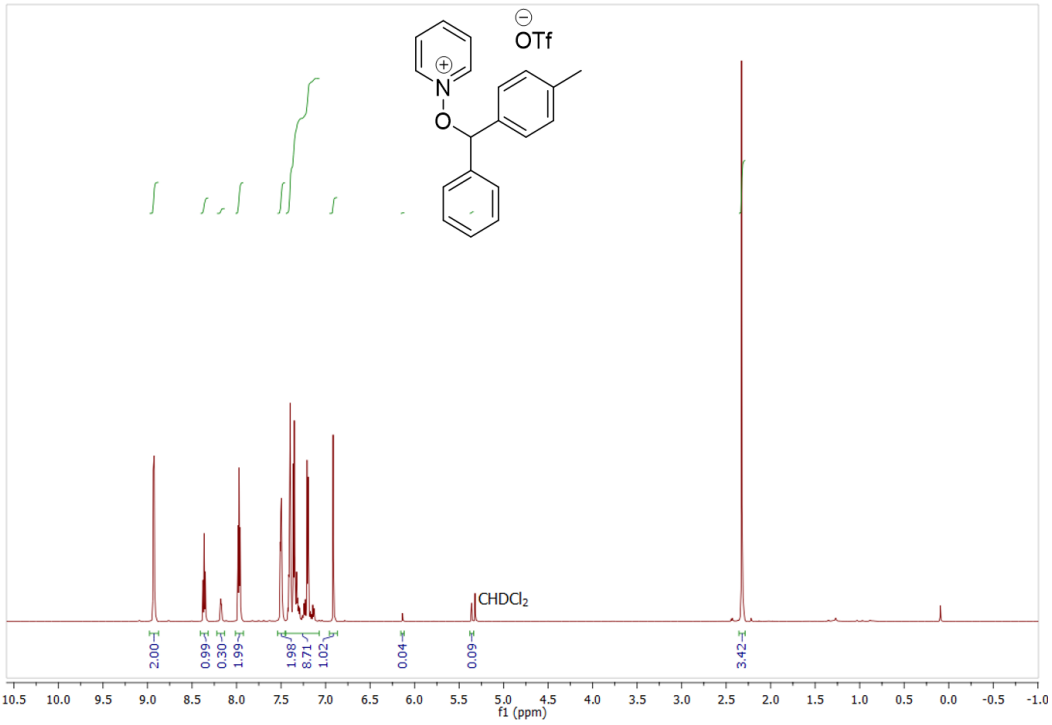


Figure S40: Full ^{1}H NMR spectrum of **14** in CD_2Cl_2.

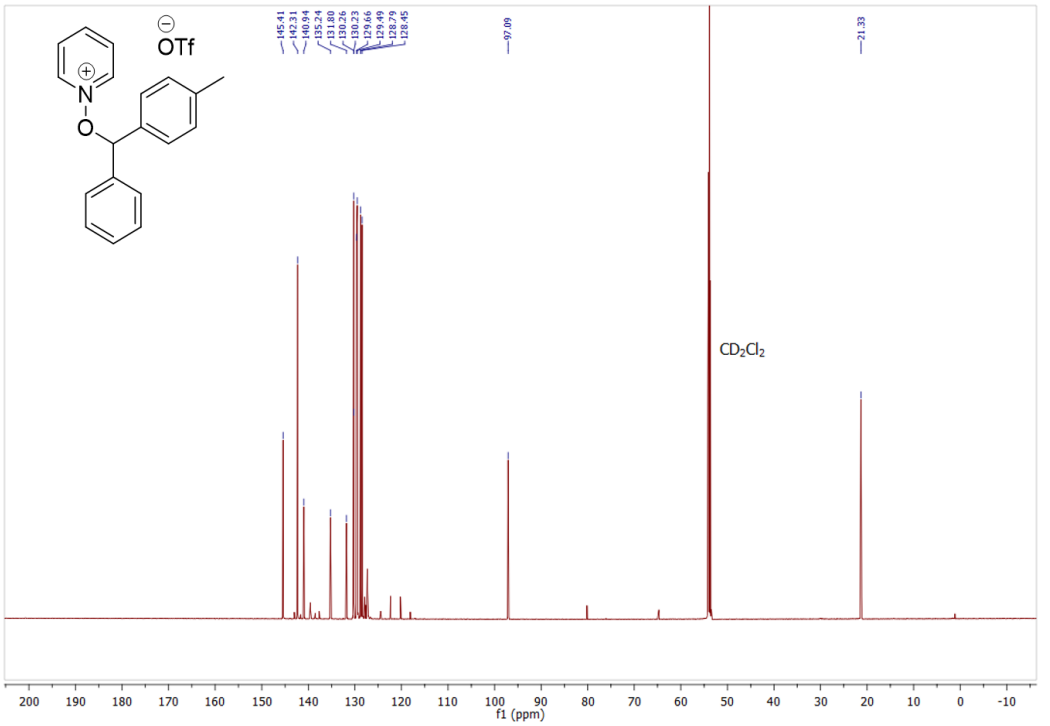


Figure S41: ^{13}C spectrum of **14** in CD_2Cl_2.

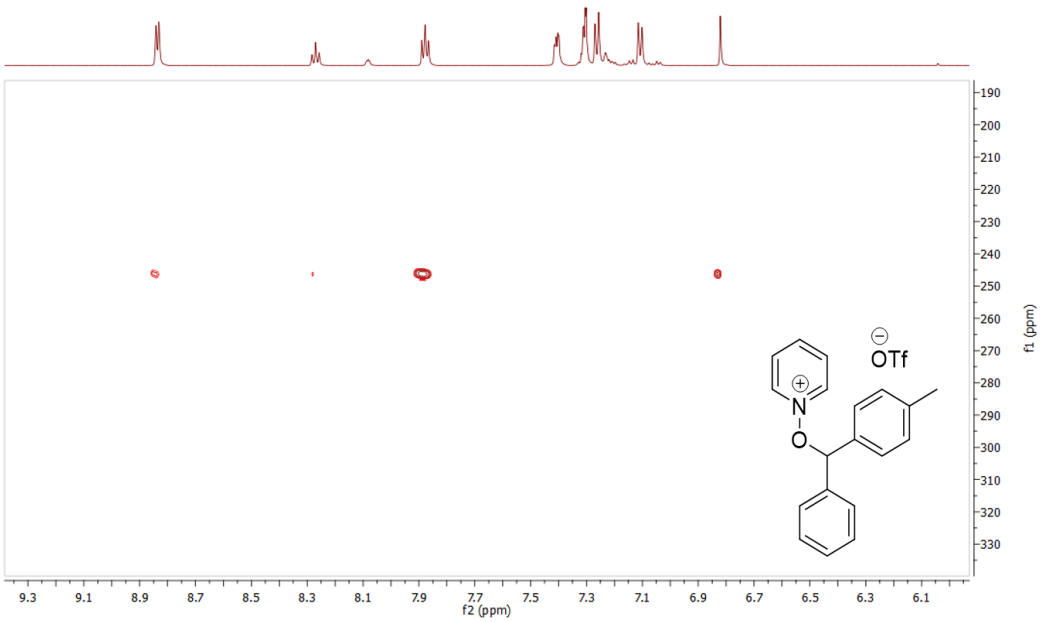


Figure S42: ^{1}H-^{15}N HMBC NMR spectrum of **14** in CD_2Cl_2.

15 in DMSO-d_6 (From 5 + MeOTf in MeCN)

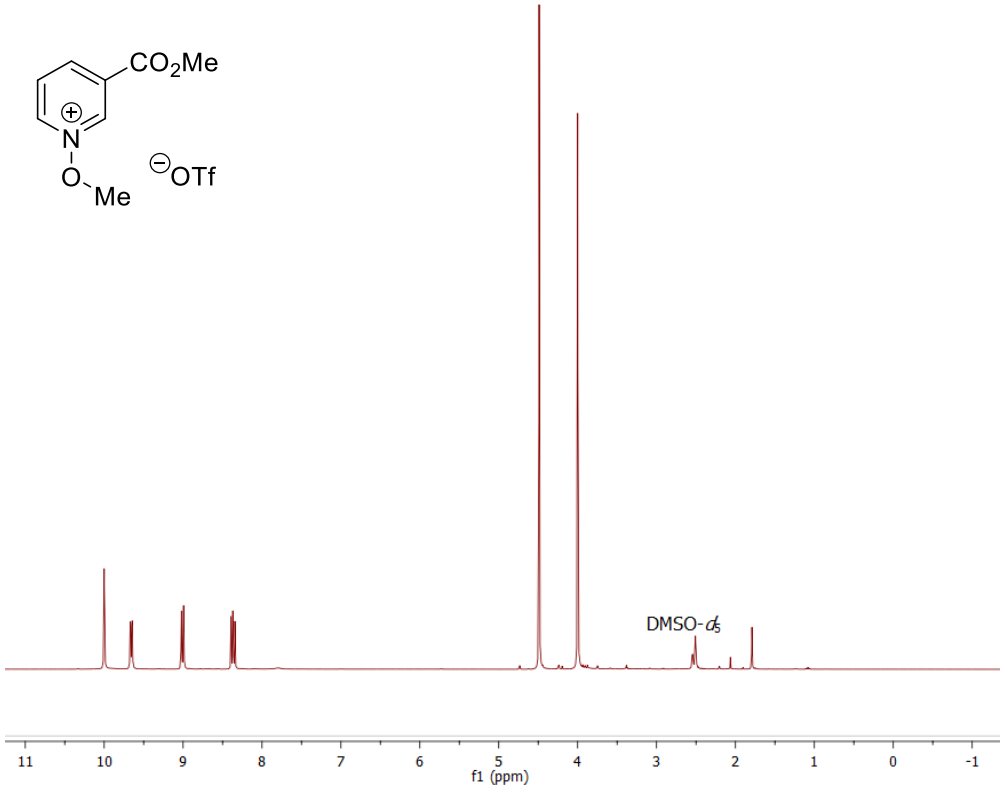


Figure S43: Full ^{1}H NMR spectrum of **15** in DMSO-d_6.

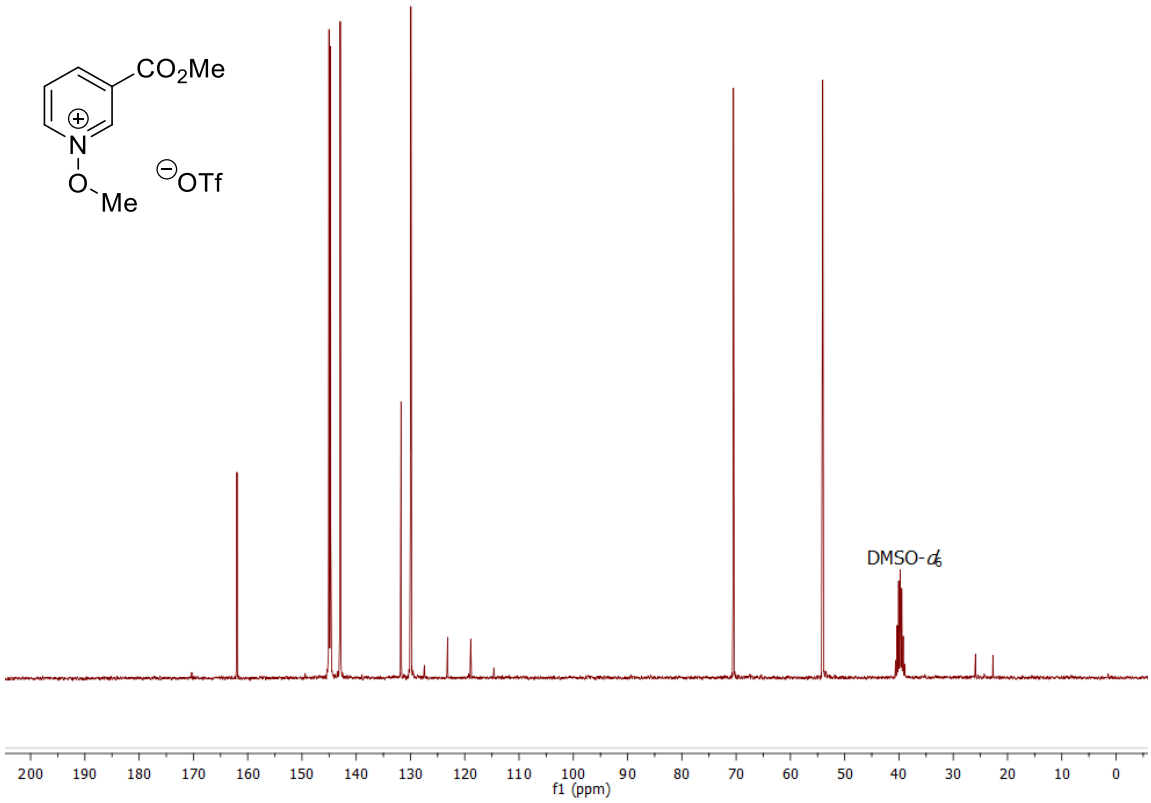


Figure S44: ^{13}C NMR spectrum of **15** in DMSO-d_6.

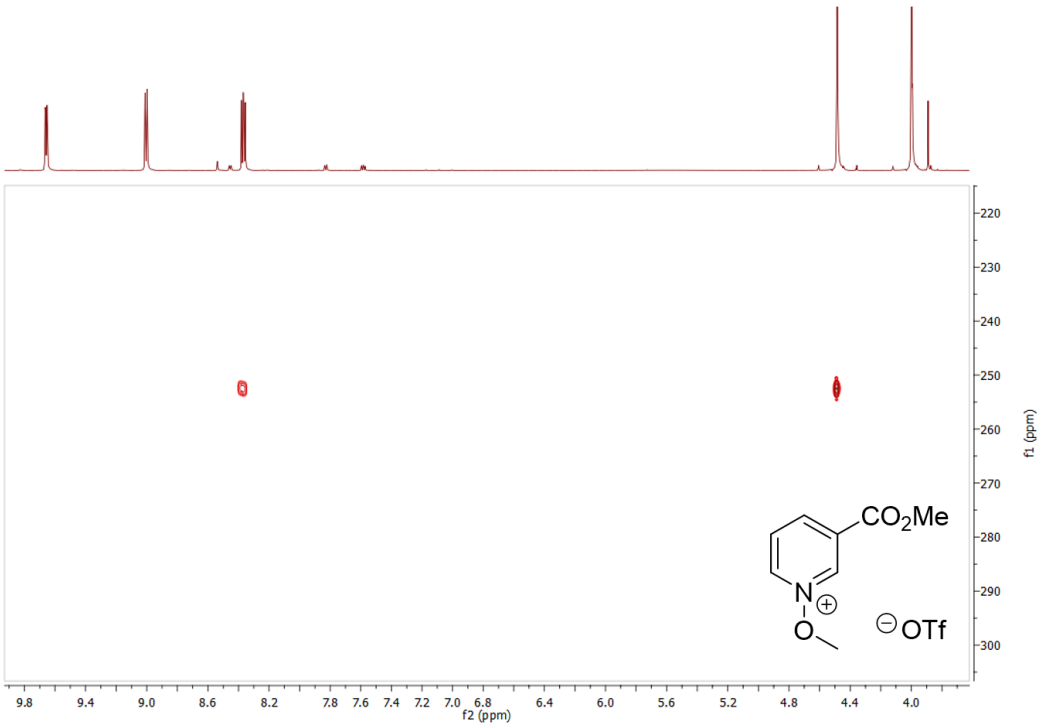


Figure S45: ^{1}H-^{15}N HMBC NMR spectrum of **15** in DMSO-d_6.

16 in CD_2Cl_2 (from 5 + 4-methylbenzhydrylium ion (19) in CD_2Cl_2)

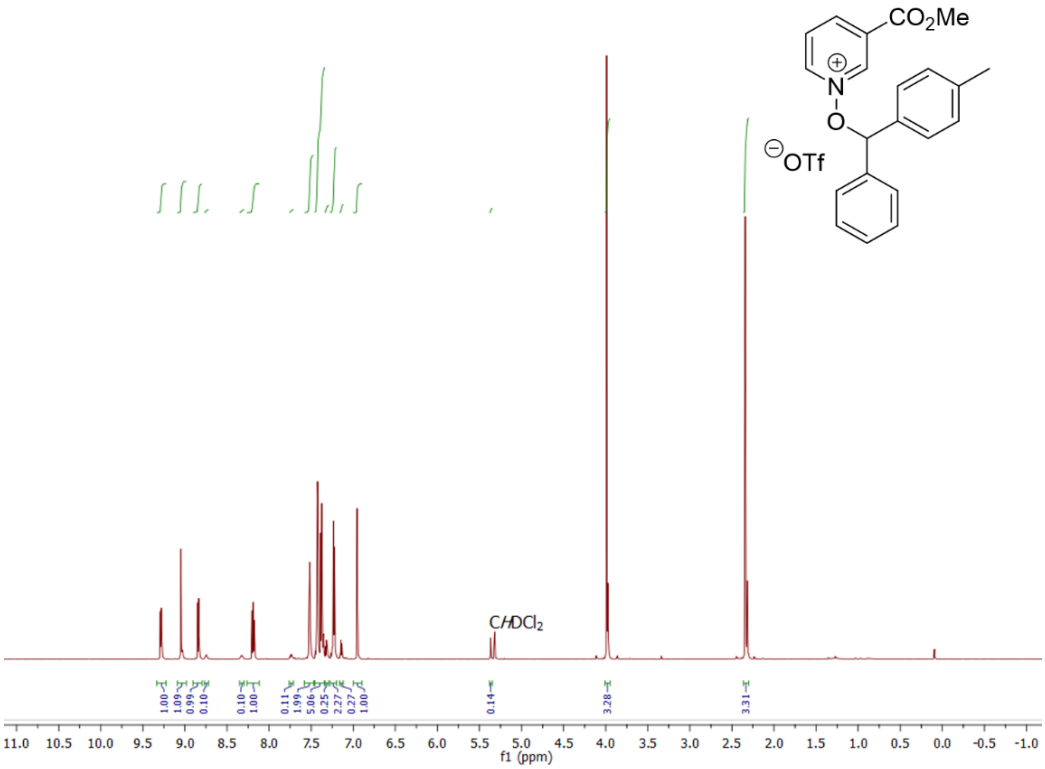


Figure S46: Full ^{1}H NMR spectrum of **16** in CD_2Cl_2.

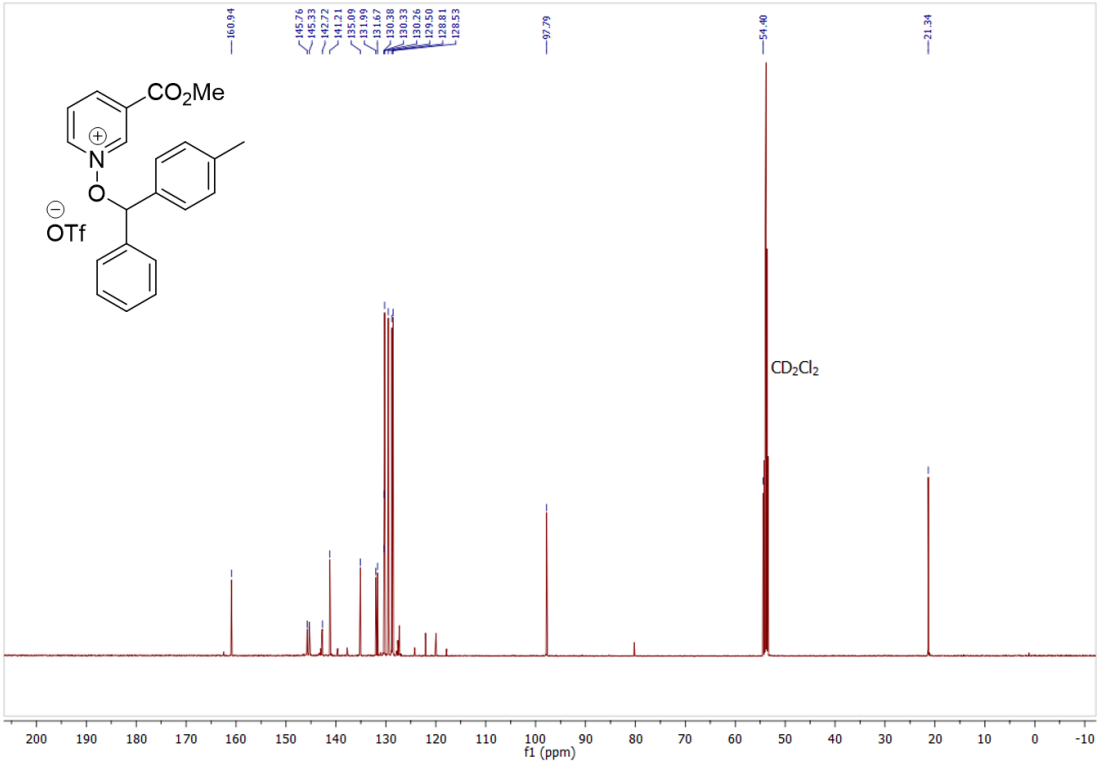


Figure S47: ^{13}C NMR spectrum of **16** in CD_2Cl_2.

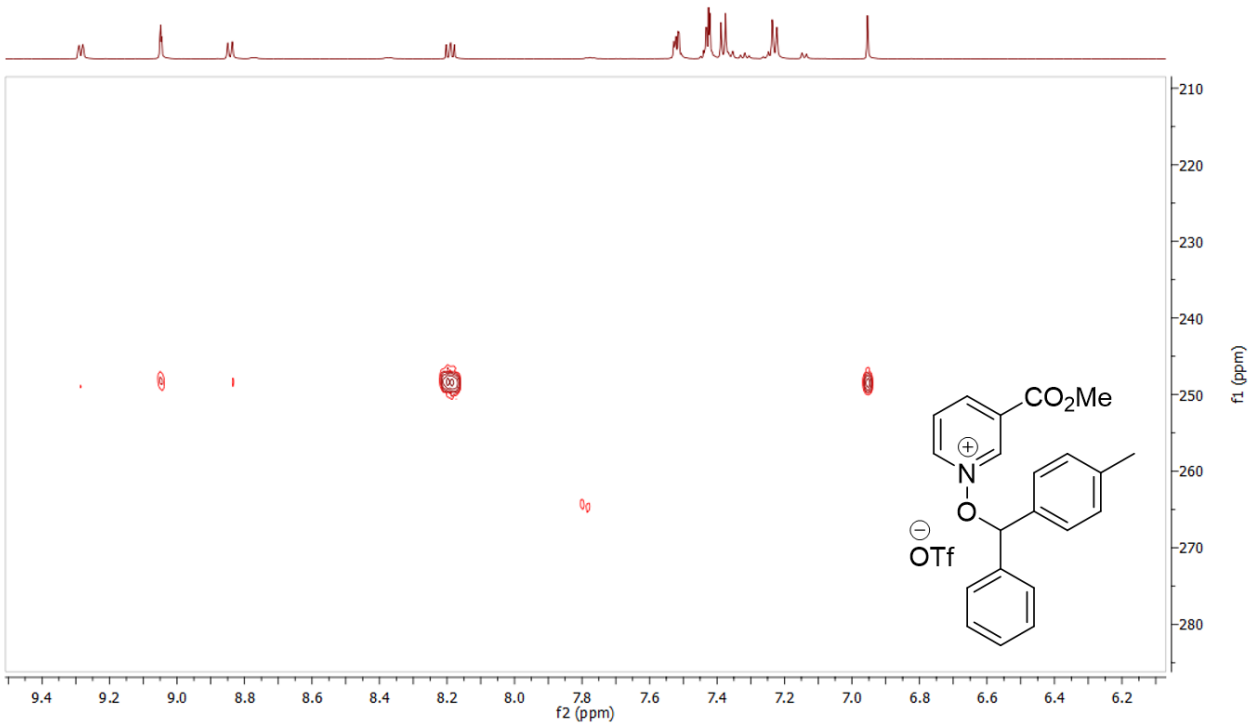


Figure S48: ^{1}H-^{15}N HMBC NMR spectrum of **16** in CD_2Cl_2.

17 in DMSO-d_6 (From 4-methylpyridine-*N*-oxide (6) + MeOTf in MeCN)

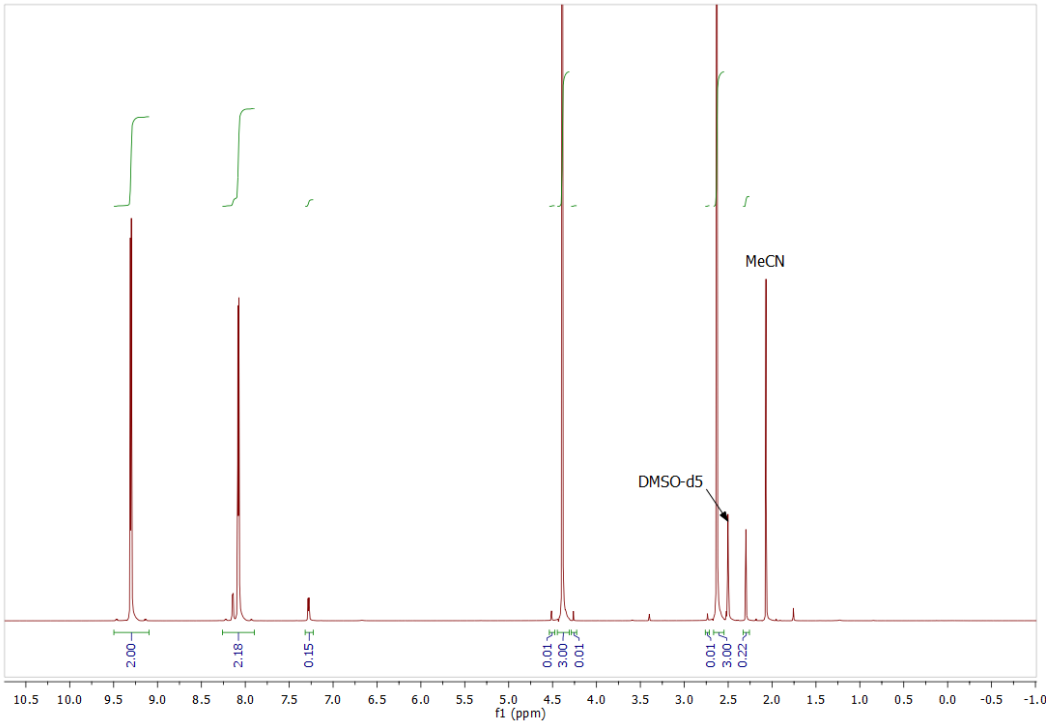


Figure S49: Full ^{1}H NMR spectrum of **17** in DMSO-d_6.

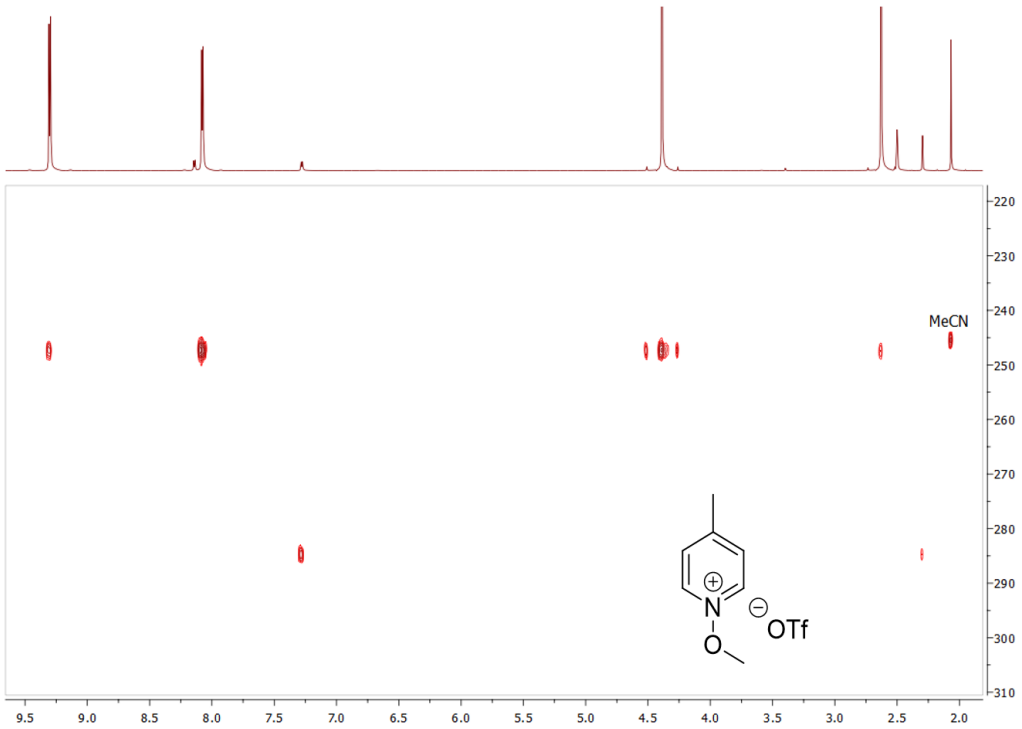


Figure S50: ^{1}H-^{15}N HMBC NMR spectrum of **17**, containing signals assigned to **6** in DMSO-d_6.

17 in DMSO-d_6 (From 4-methylpyridine-*N*-oxide (6) + MeOTf in $CDCl_3$)

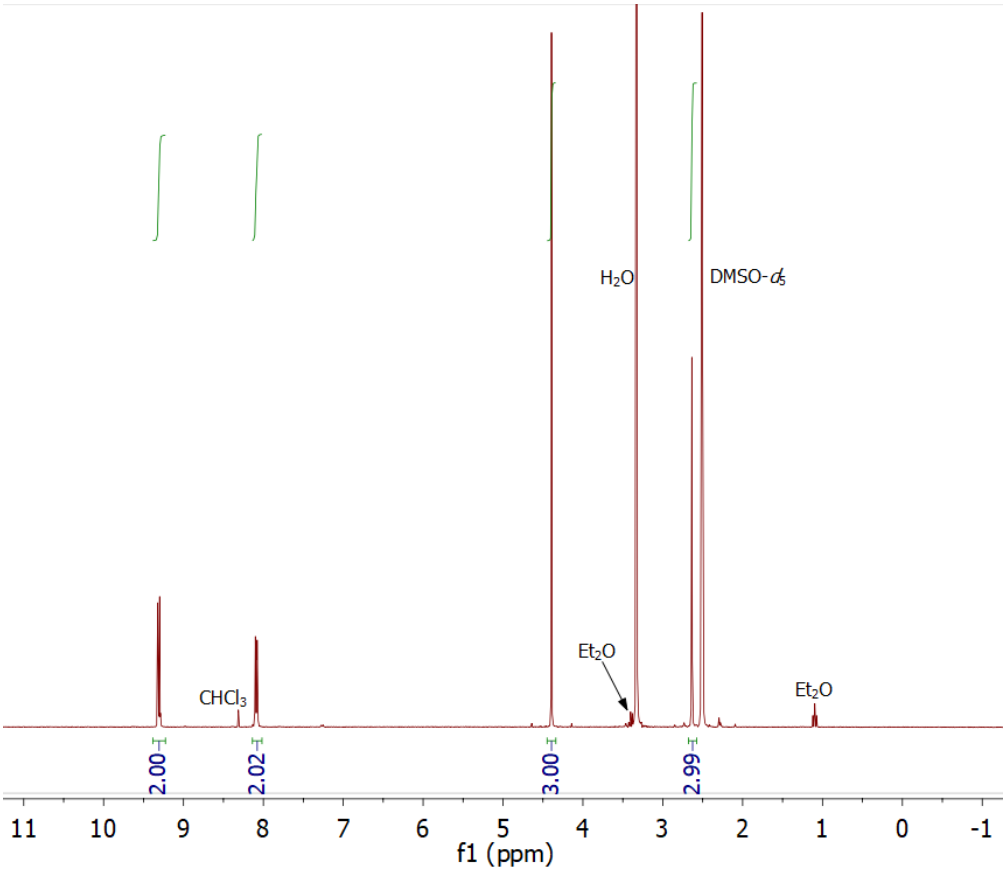
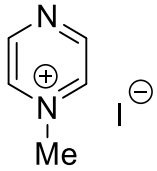
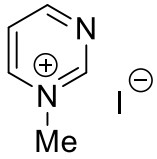
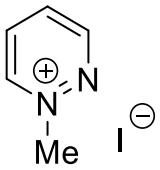
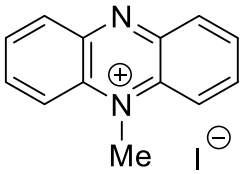
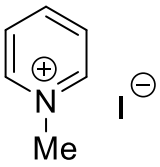
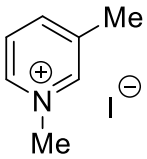
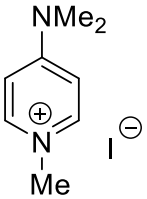
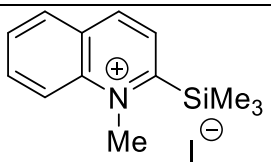


Figure S51: Full ^{1}H NMR spectrum of **17** in DMSO-d_6. [12]

6. Tables of ^{13}C NMR Spectroscopic Data

Table S1. ^{13}C NMR chemical shift (δ_C) values of N^+—CH_3 carbon nuclei of selected *N*-methylated aromatic N-heterocycles. Most of the references cited in the table contain multiple examples – only a representative selection has been included here.

Entry	Compound	Solvent	δ_C (ppm)	Reference
1		CD_3CN	50.32	7
2		DMSO-*d*$_6$	45.17	7
3		DMSO-*d*$_6$	52.07	7
4		D_2O	38.66	13
5		DMSO-*d*$_6$	48.1	14
6		DMSO-*d*$_6$	47.6	14
7		DMSO-*d*$_6$	43.92	15
8		DMSO-*d*$_6$	45.77	16

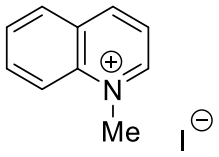
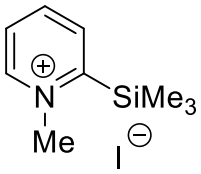
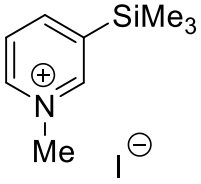
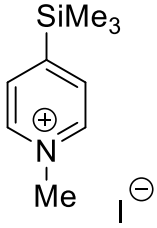
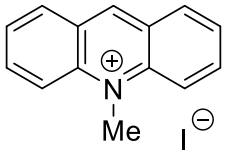
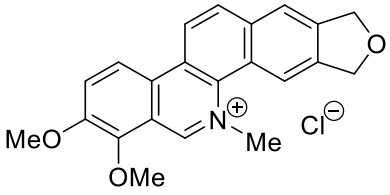
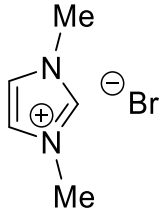
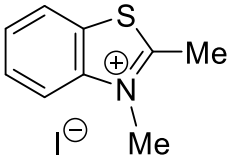
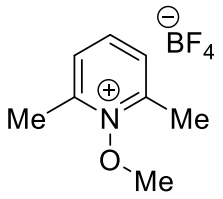
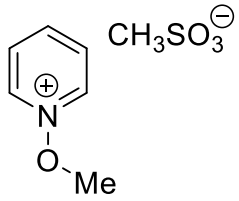
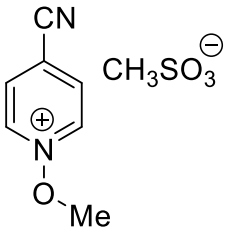
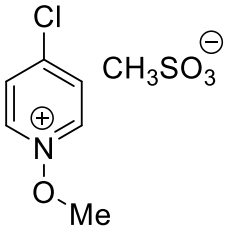
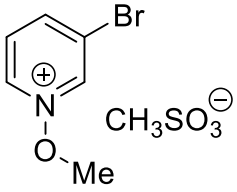
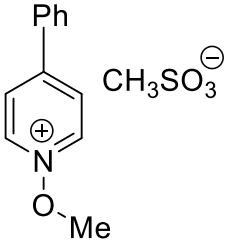
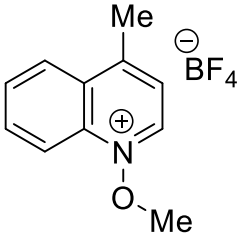
9		DMSO-d_6	45.37	16
10			49.49	16
11			47.77	16
12			47.61	16
13		DMSO-d_6	38.6	17
14			52.17	18
15		CD_2Cl_2	36.7	19
16		DMSO-d_6	36.91	20

Table S2. ^{13}C NMR chemical shift (δ_C) values of N^+—O*C*H_3 carbon nuclei of selected *O*-methylated adducts of aromatic *N*-oxides. Most of the references cited in the table contain multiple examples – only a representative selection has been included here.

Entry	Compound	Solvent	δ_C (ppm)	Reference
1		DMSO-*d*$_6$	67.4	9
2		DMSO-*d*$_6$	69.9	9
3		DMSO-*d*$_6$	70.0	9
4		DMSO-*d*$_6$	70.2	9
5		DMSO-*d*$_6$	70.4	9
6		DMSO-*d*$_6$	74.7	9
7		DMSO-*d*$_6$	69.5	10

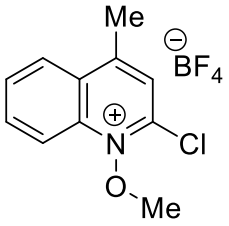
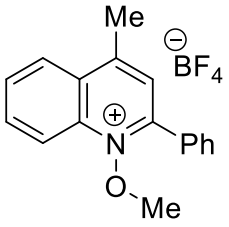
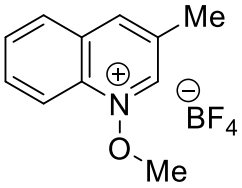
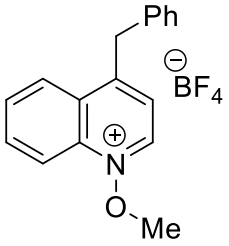
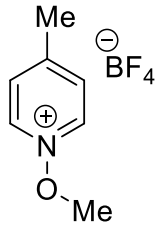
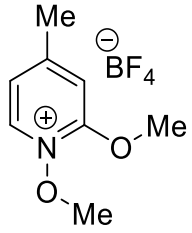
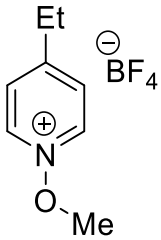
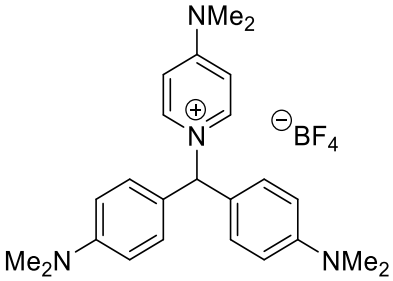
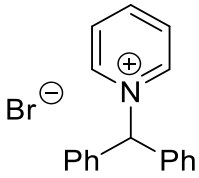
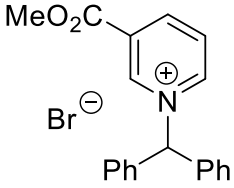
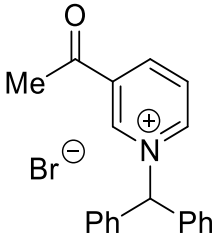
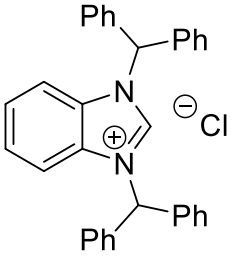
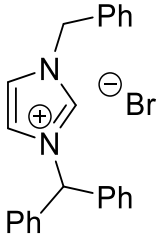
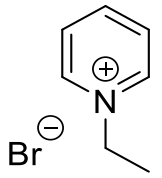
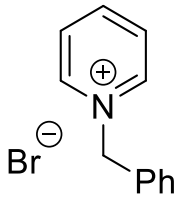
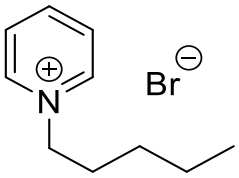
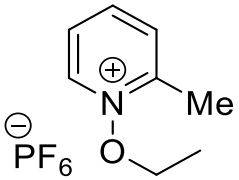
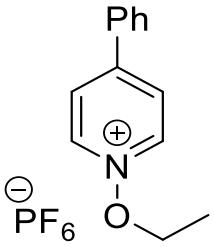
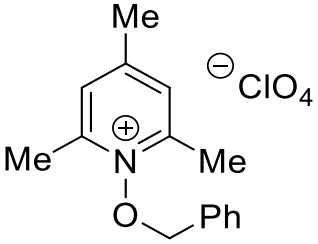
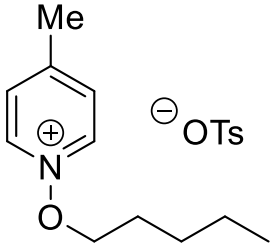
8		DMSO-d_6	62.6	10
9		DMSO-d_6	67.0	10
10		DMSO-d_6	69.6	10
11		CD_3OD	72.9	10
12		CD_3OD	69.8	10
13		CD_3OD	68.6	10
14		CD_3OD	69.4	10

Table S3. ^{13}C NMR chemical shift (δ_C) values of N^+—*C* and O—*C* carbons in selected N- and O-alkylation adducts of aromatic N-heterocycles and *N*-oxides. Note: No O-benzhydryl adducts of aromatic *N*-oxides have been characterised prior to this article. Many of the references cited in the table contain multiple examples – only a representative selection has been included here.

Entry	Compound	Solvent	δ_C (ppm)	Reference
1		$CDCl_3$	73.8	21
2		DMSO-*d*$_6$	75.4	22
3		DMSO-*d*$_6$	76.2	23
4		DMSO-*d*$_6$	76.0	24
5		CD_3OD	67.6	25
6		DMSO-*d*$_6$	65.8	26

7		DMSO-d_6	56.0	22
8		DMSO-d_6	62.6	22
9		$CDCl_3$	61.6	27
10		DMSO-d_6	78.58	28
11		DMSO-d_6	81.05	29
12		CD_2Cl_2	82.01	30
13		CD_2Cl_2	83.92	31

7. References

1. Shriver, D. F.; Drezdon, M.A, *The Manipulation of Air-Sensitive Compounds*, 2nd Edition. John Wiley & Sons: New York; 1986.

2. Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K., Reduction of Amine *N*-Oxides by Diboron Reagents. *J. Org. Chem.* **2011**, *76* (19), 7842 – 7848.

3. Vasta, J. D.; Raines, R. T. *Bioorgan. Med. Chem.* **2015**, *23*, 3081 – 3090.

4. ^{1}H NMR spectral characterisation of pyridine *N*-oxide (**4**) and 4-methylpyridine *N*-oxide (**6**) in DMSO-d_6, and of *N*-(methoxy)pyridinium iodide (**13a**) and *N*-(methoxy)-4-methylpyridinium iodide in $CDCl_3$: Andreev, V. P. *Chem. Heterocycl. Compd.* **2010**, *46*, 184 – 195.

5. ^{14}N NMR chemical shift values for pyridine *N*-oxide (**4**) of 85.64 ppm (in DMSO) and 85.66 ppm (in CH_2Cl_2), referenced to nitromethane at 0 ppm, were reported in: Witanowski, M.; Sicinska, W.; Biernat, S.; Webb, G. A. *J. Magn. Reson.* **1989**, *83*, 351 – 357. These literature δ_N values equate to 294.6 and 294.5 ppm, respectively, when re-referenced to ammonia at 0 ppm.

6. A similar δ_N value (285.2 ppm, relative to nitromethane at 380.2 ppm) was determined for 4-methylpyridine *N*-oxide (**6**) in $CDCl_3$ solvent: Sanz, D.; Perona, A.; Claramunt, R. M.; Elguero, J. *Tetrahedron* **2005**, *61*, 145 – 154.

7. ^{1}H NMR spectral characterisation of *N*-methylpyrazinium iodide (**7a**) and *N*-methylpyrimidinium iodide (**11a**) in CD_3CN: Newmark, R. A.; Tucker, A.; Hardy, L. C. *Magn. Reson. Chem.* **1996**, *34*, 728 – 729.

8. ^{1}H NMR spectral characterisation of *N*-methylquinoxalinium iodide (**9a**) in DMSO-d_6: Leblanc, N.; Sproules, S.; Pasquier, C.; Auban-Senzier, P.; Raffy, H.; Powell, A. K. *Chem. Commun.* **2015**, *51*, 12740 – 12743.

9. ^{1}H NMR spectral characterisation of *N*-(methoxy)pyridinium iodide (**13b**) in DMSO – d_6: Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2016**, *138*, 8718 – 8721.

10. ^{1}H NMR spectral characterisation of *N*-(methoxy)-4-methylpyridinium tetrafluoroborate in DMSO-d_6: Gao, X.; Han, S.; Zheng, M.; Liang, A.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *J. Org. Chem.* **2019**, *84*, 4040 – 4049.

11. ^{15}N NMR chemical shift data for *N*-(methoxy)-4-methylpyridinium iodide in CH_3OH: Dega-Szafran, Z.; Szafran, M.; Sitkowski, J.; Stefaniak, L. *J. Phys. Org. Chem.* **1996**, *9*, 746 – 750.

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

13. Mortzfeld, F. B.; Pietruszka, J.; Baxendale, I. R. *Eur. J. Org. Chem.* **2019**, 5424 – 5433.

14. Chaumeil, H.; Jacques, P.; Diemer, V.; Nouën, D. L.; Carré, C. *J. Mol. Struct.* **2011**, *1002*, 70 – 75.

15. Jun, D.; Paar, M.; Binder, J.; Marek, J.; Pohanka, M.; Stodulka, P.; Kuca, K. *Lett. Org. Chem.* **2009**, *6*, 500 – 503.

16. Lukevics, E.; Leipiņš, E.; Segal, I.; Fleisher, M. *J. Organomet. Chem.* **1991**, *406*, 283 – 298.

17. Eberhard, J.; Peuntinger, K.; Fröhlich, R.; Guldi, D. M.; Mattay, J. *Eur. J. Org. Chem.* **2018**, 2682 – 2700.

18. Marek, R.; Toušek, J.; Dostál, J.; Slavík, J.; Dommisse, R.; Sklenář, V. *Magn. Reson. Chem.* **1999**, *37*, 781 – 787.

19. Brünig, T.; Krekić, K.; Bruhn, C.; Pietschnig, R. *Chem. Eur. J.* **2016**, *22*, 16200 – 16212.

20. Feng, G.; Luo, X.; Lu, X.; Xie, S.; Deng, L.; Kang, W.; He, F.; Zhang, J.; Lei, C.; Lin, B.; Huang, Y.; Nie, Z.; Yao, S. *Angew. Chem. Int. Edit.* **2019**, *58*, 6590 – 6594.

21. Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem–Eur. J.* **2007**, *13*, 336 – 345.

22. Katritzky, A. R.; Dega-Szafran, Z. *Magn. Reson. Chem.* **1989**, *27*, 1090 – 1093.

23. Bennasar, M. L. s.; Roca, T.; Monerris, M.; Juan, C. l.; Bosch, J. *Tetrahedron* **2002**, *58*, 8099 – 8106.

24. Bennasar, M. L. s.; Roca, T.; Zulaica, E.; Monerris, M. *Tetrahedron* **2004**, *60*, 6785 – 6789.

25. Huang, W.; Guo, J.; Xiao, Y.; Zhu, M.; Zou, G.; Tang, J. *Tetrahedron* **2005**, *61*, 9783 – 9790.

26. Sabbah, M.; Soulère, L.; Reverchon, S.; Queneau, Y.; Doutheau, A. *Bioorgan. Med. Chem.* **2011**, *19*, 4868 – 4875.

27. Balaban, T. S.; Tămăşan, I.; Deleanu, C. *Liebigs Ann. Chem.* **1992**, 173 – 175.

28. Kabatc, J.; Kostrzewska, K.; Dobosz, R.; Orzeł, Ł.; Jurek, K. *J. Polym. Sci. A1.* **2017**, *55*, 2840 – 2850.

29. Shukla, D.; Adiga, S. P.; Ahearn, W. G.; Dinnocenzo, J. P.; Farid, S. *J. Org. Chem.* **2013**, *78*, 1955 – 1964.

30. Fuentes, A., Martínez-Palou, R.; Jiménez-Vázquez, H. A.; Delgado, F.; Reyes, A.; Tamariz, J. *Monatsh. Chem.* **2005**, *136*, 177 – 192.

31. Kim, I.; Park, B.; Kang, G.; Kim, J.; Jung, H.; Lee, H.; Baik, M.-H.; Hong, S. *Angew. Chem. Int. Edit.* **2018**, *57*, 15517 – 15522.