SUPPORTING INFORMATION

C – H Arylation of Heterocyclic *N*-Oxides Through *In-Situ* Diazotisation Of Anilines Without Added Promoters: A Green And Selective Coupling Process

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1. GENERAL EXPERIMENTAL

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material, unless otherwise stated.

HPLC Method: HPLC analysis was conducted on a Hewlett Packard series 1100 using a Phenomenex Luna C18 column (50 mm x 2.1mm i.d. 3.0 µm packing diameter) at 40 °C.
Eluent A = Water + 0.05%*v/v* trifluoroacetic acid
Eluent B = Acetonitrile + 0.05%*v/v* trifluoroacetic acid
Gradient:

Time (min)	Flow rate (mL/min)	% A	% B
0	1.0	100	0
8	1.0	5	95
8.5	1.0	5	95
8.6	1.0	100	0
10.0	1.0	100	0

The UV detection was performed at 305 nm.

LC/MS Method: HPLC analysis was conducted on a Waters ZQ using a Phenomenex Luna C18 column (50 mm x 2.1 mm i.d. 3.0 µm packing diameter) at 40 °C.
Eluent A = Water + 0.05% *v/v* trifluoroacetic acid
Eluent B = Acetonitrile + 0.05% *v/v* trifluoroacetic acid
Gradient:

Time (min)	Flow rate (mL/min)	% A	% B
0	1.0	100	0
8	1.0	5	95
8.5	1.0	5	95
8.6	1.0	100	0
10.0	1.0	100	0

The UV detection was a summed signal of the range 205 nm to 400 nm.
Mass Spectrometry was conducted on a Waters ZQ.
Ionisation mode: Positive Electrospray
Scan Range: 100 to 1000 AMU
Scan Time: 0.5 second
Inter scan Delay: 0.05 seconds

Silica gel chromatography
Unless otherwise stated, silica gel chromatography purification were performed on a Biotage SP4, using pre-packed Biotage silica cartridges (KP-Sil) monitored by UV.

Nuclear magnetic resonance spectrometry
Unless otherwise stated, 400 MHz ^{1}H NMR spectra were recorded on Brucker AV 400 NMR spectrometers. Signals are reported as: chemical shift δ/ppm (multiplicity, number of protons, coupling constants). Chemical shifts are reported to the nearest 0.01 ppm and coupling constant to the nearest 0.1 Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, a = apparent). 100 MHz ^{13}C spectra were recorded on the same spectrometers.

High-Resolution Mass Spectrometry: High Resolution Mass Spectrometry was carried out by the Mass Spectrometry Service of GlaxoSmithKline, Stevenage.

Differential Scanning Calorimetry analysis

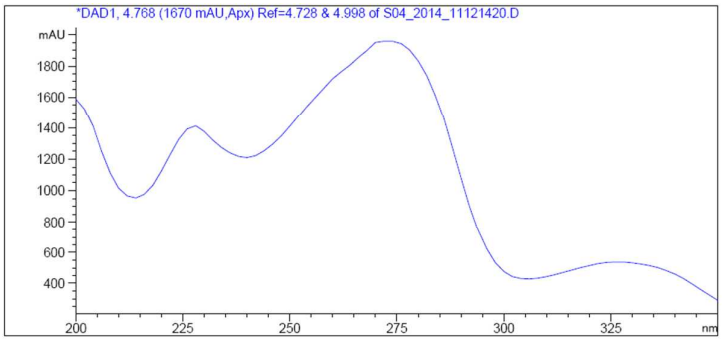
Samples were run in high pressure gold 40 µL crucibles from 20 °C to 350 °C at 2 °C/min on a Mettler Toledo DSC823e device.

2. CALIBRATION CURVE USED FOR COMPOUND 23

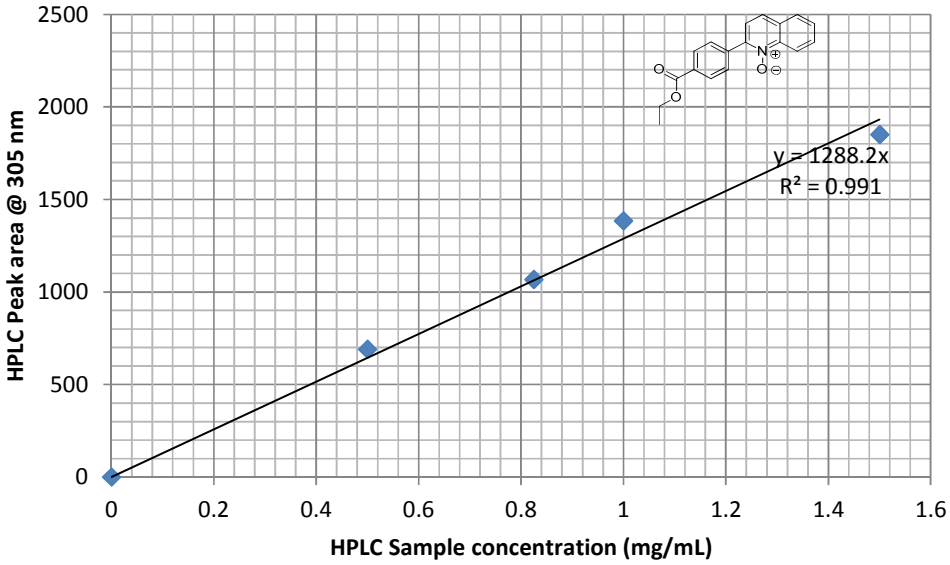
Solutions (in acetonitrile + 0.1% TFA *v/v*) were preparing by dissolving the corresponding amount of material in 25 mL volumetric flasks followed by analysis by HPLC.

Sample concentration (mg/mL)	HPLC Peak area (305 nm)
0	0
0.5	690.655
0.825	1067.759
1.0	1383.025
1.5	1850.923

Results table used for the calibration curve



UV spectrum of 23

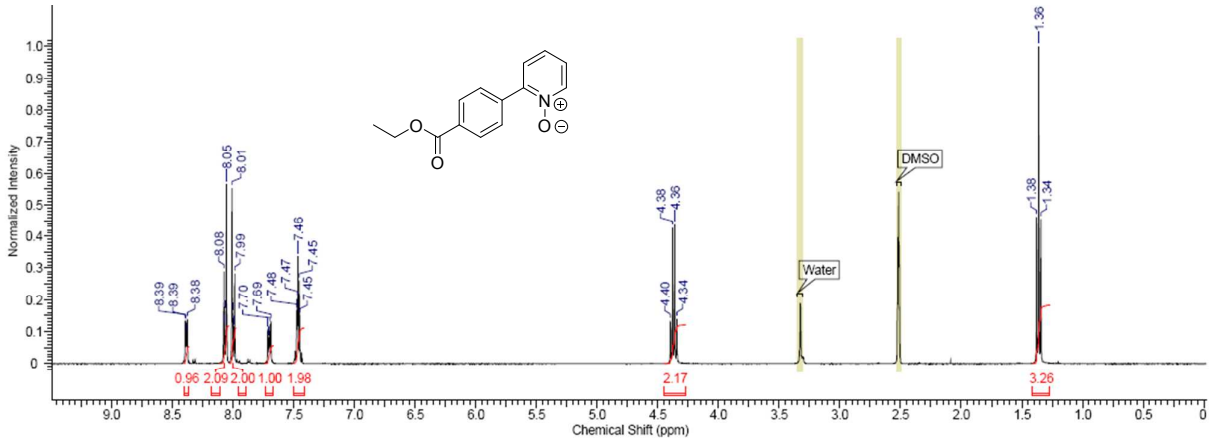


3. GENERAL PROCEDURE FOR THE SCREENING OF *N*-OXIDE HETEROCYCLES AND SOLVENTS

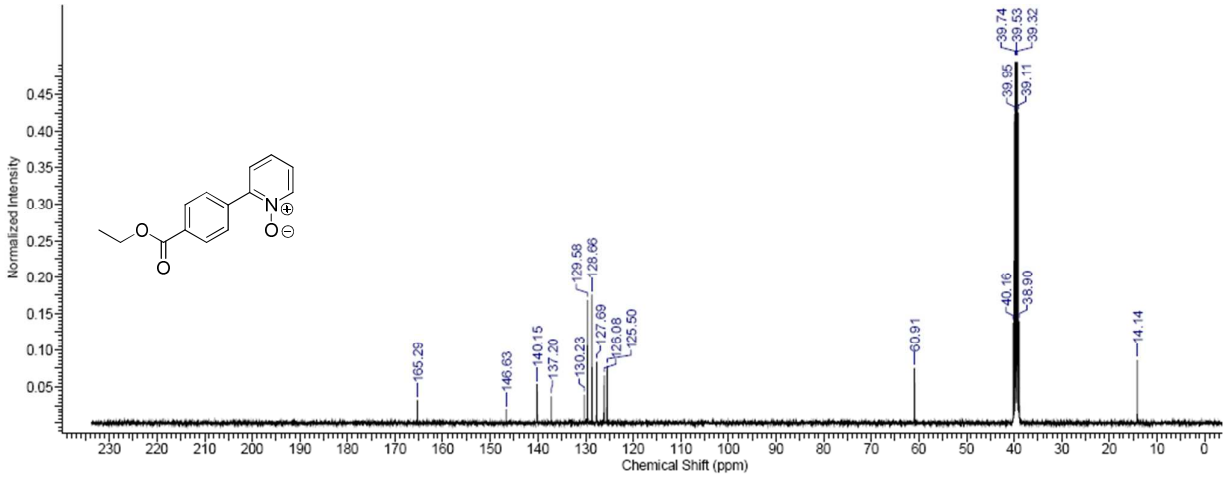
To a round bottom flask containing ethyl 4-aminobenzoate **7** (250 mg, 1.513 mmol), *N*-oxide heterocycle (3.03 mmol) and L-ascorbic acid **35** (27 mg, 0.151 mmol) under a nitrogen atmosphere was added degassed solvent (12.5 mL), followed by *tert*-butyl nitrite (0.240 mL, 1.816 mmol) and the reaction mixture was stirred for 17 hours at 20 °C. After this time, reaction mixture was evaporated to dryness and the crude product was purified by silica gel chromatography eluting with either heptane/ethyl acetate or CH_2Cl_2/MeOH mixtures to yield the target compound.

2-(4-(Ethoxycarbonyl)phenyl)pyridine *N*-oxide (19): Orange solid (81 mg, 22% yield), Mp: 119–120 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.39-8.38 (m, 1H), 8.07 (d, 2H, *J* = 8.6 Hz), 8.00 (d, 2H, *J* = 8.6 Hz), 7.72-7.67 (m, 1H), 7.45-7.48 (m, 2H), 4.37 (q, 2H, *J* = 7.1 Hz), 1.36 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.3 (C_{IV}), 146.6 (C_{IV}), 140.2, 137.2 (C_{IV}), 130.2 (C_{IV}), 129.6, 128.7, 127.7, 126.1, 125.5, 60.9, 14.1 ppm. HRMS (ESI$^+$): calculated for $C_{14}H_{14}NO_3$ $[M + H]^+$ 244.0960, found 244.0968.

400 MHz ^{1}H NMR spectrum in DMSO-d_6:

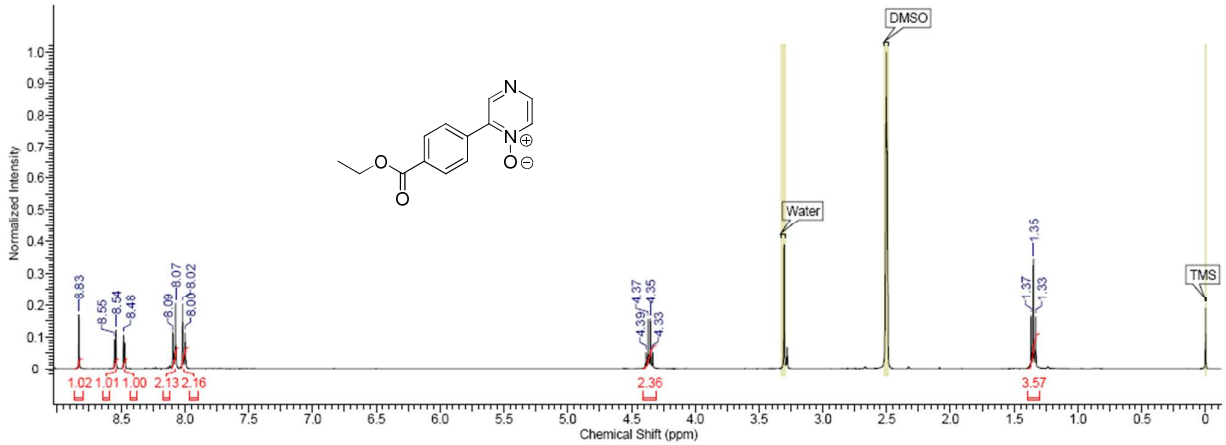


100 MHz ^{13}C NMR spectrum in DMSO-d_6:

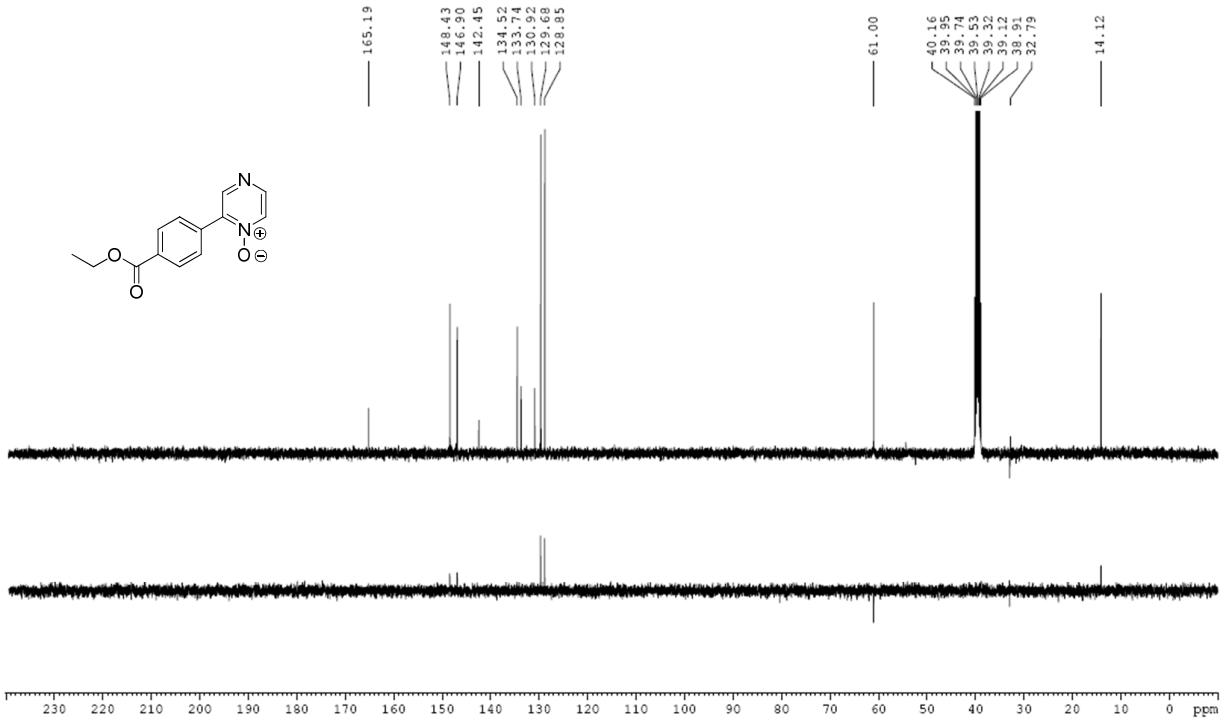


2-(4-(Ethoxycarbonyl)phenyl)pyrazine *N*-oxide (20): Orange solid (69 mg, 19% yield), Mp: 154–159 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.83 (s, 1H), 8.55 (d, 1H, *J* = 4.1 Hz), 8.48 (d, 1H, *J* = 4.1 Hz), 8.08 (d, 2H, *J* = 8.5 Hz), 8.01 (d, 2H, *J* = 8.5 Hz), 4.36 (q, 2H, *J* = 7.1 Hz), 1.35 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.2 (C_{IV}), 148.4, 146.9, 142.5 (C_{IV}), 134.5, 133.7 (C_{IV}), 130.9 (C_{IV}), 129.7, 128.9, 61.0, 14.1 ppm. HRMS (ESI$^+$): calculated for $C_{13}H_{13}N_2O_3$ $[M + H]^+$ 245.0924, found 245.0921.

400 MHz ^{1}H NMR spectrum in DMSO-d_6:

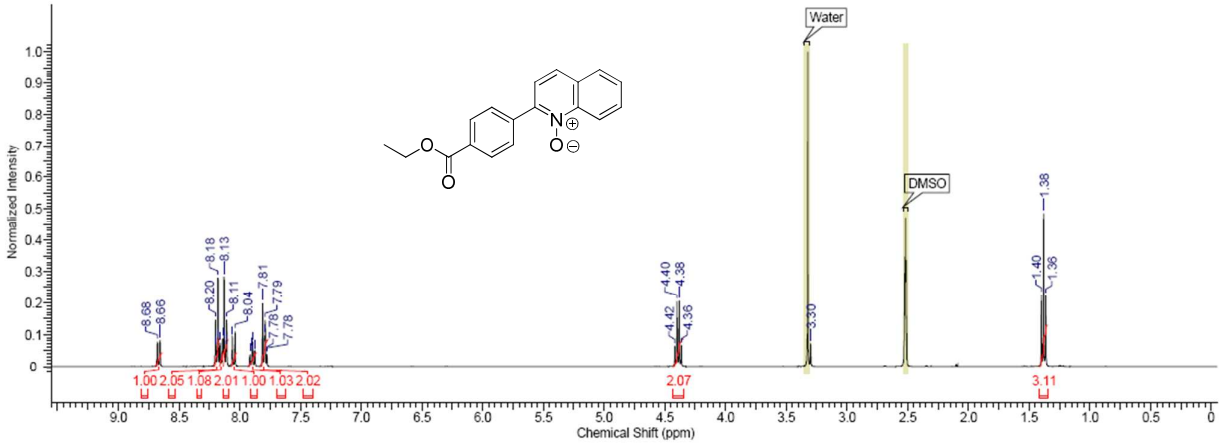


100 MHz ^{13}C NMR and DEPT135 spectra in DMSO-d_6:

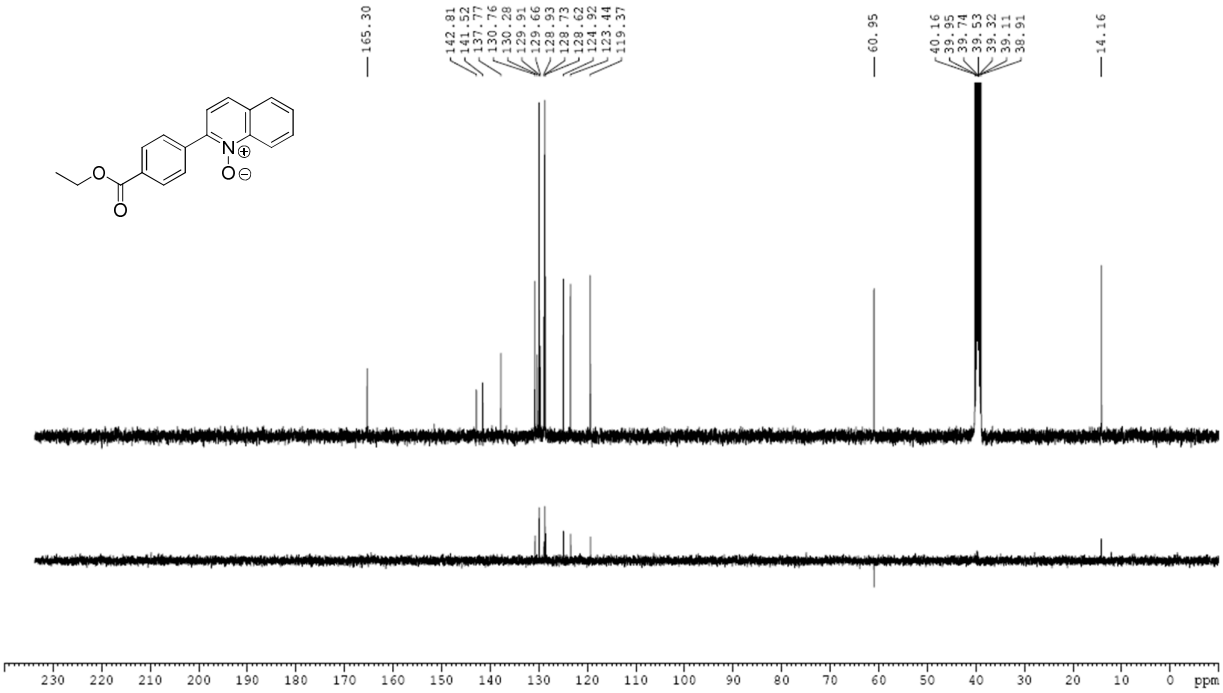


2-(4-(Ethoxycarbonyl)phenyl)quinoline *N*-oxide (23): Pale pink solid (264 mg, 60% yield), Mp: 196–200 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.67 (d, 1H, *J* = 8.8 Hz), 8.19 (d, 2H, *J* = 8.6 Hz), 8.15 (d, 1H, *J* = 8.7 Hz), 8.12 (d, 2H, *J* = 8.6 Hz), 8.05 (d, 1H, *J* = 8.5 Hz), 7.90 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.5 Hz), 7.81-7.78 (m, 2H), 4.39 (q, 2H, *J* = 7.1 Hz), 1.38 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.3 (C_{IV}), 142.8 (C_{IV}), 141.5 (C_{IV}), 137.8 (C_{IV}), 130.8, 130.3 (C_{IV}), 129.9, 129.7 (C_{IV}), 128.9, 128.7, 128.6, 124.9, 123.4, 119.4, 61.0, 14.2 ppm. HRMS (ESI$^+$): calculated for $C_{18}H_{16}NO_3$ $[M + H]^+$ 294.1127, found 294.1125.

400 MHz ^{1}H NMR spectrum in DMSO-d_6:

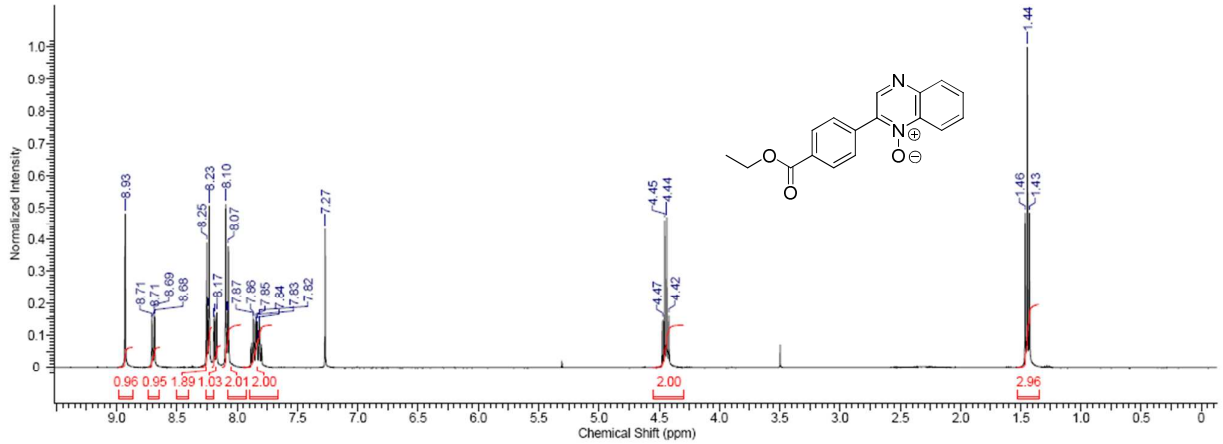


100 MHz ^{13}C NMR and DEPT135 spectra in DMSO-d_6:

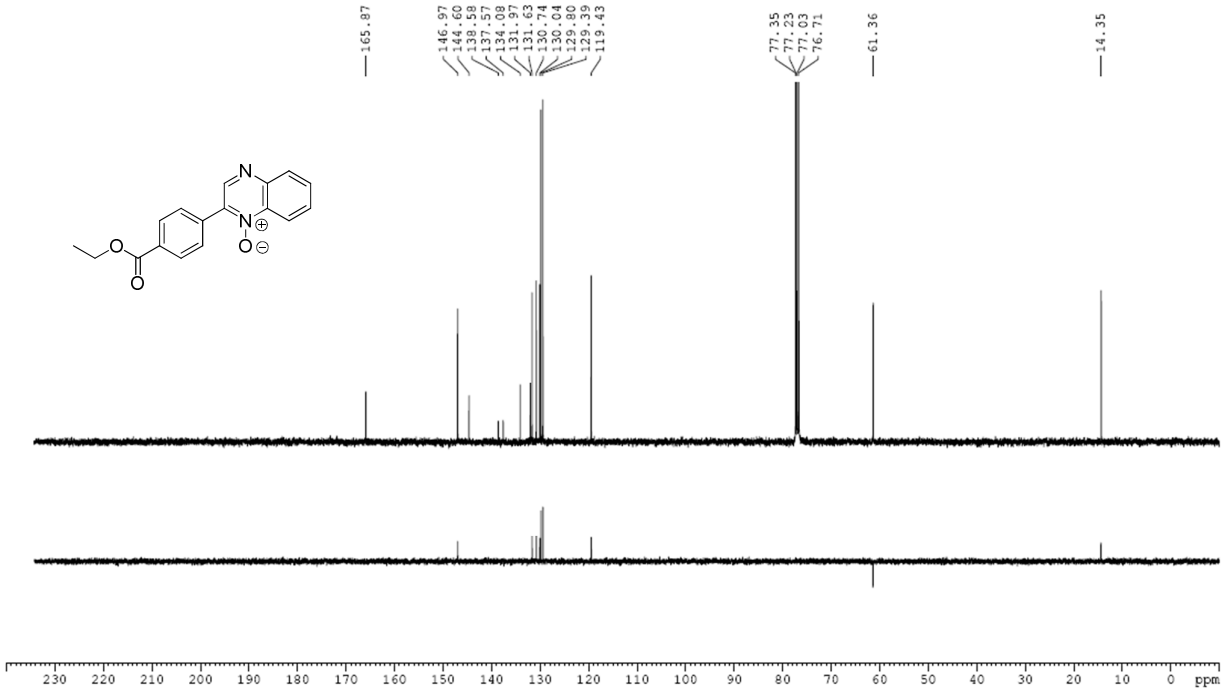


2-(4-(Ethoxycarbonyl)phenyl)quinoxaline *N*-oxide (24): Beige solid (317 mg, 71% yield), Mp: 212–215 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.93 (s, 1H), 8.70 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 8.24 (d, 2H, J = 8.5 Hz), 8.18 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.4 Hz), 8.09 (d, 2H, J = 8.5 Hz), 7.89-7.80 (m, 2H), 4.45 (q, 2H, J = 7.2 Hz), 1.44 (t, 3H, J = 7.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9 (C_{IV}), 147.0, 144.6 (C_{IV}), 138.6 (C_{IV}), 137.6 (C_{IV}), 134.1 (C_{IV}), 132.0 (C_{IV}), 131.6, 130.7, 130.0, 129.8, 129.4, 119.4, 61.4, 14.4 ppm. HRMS (ESI$^+$): calculated for $C_{17}H_{15}N_2O_3$ $[M + H]^+$ 295.1076, found 295.1077.

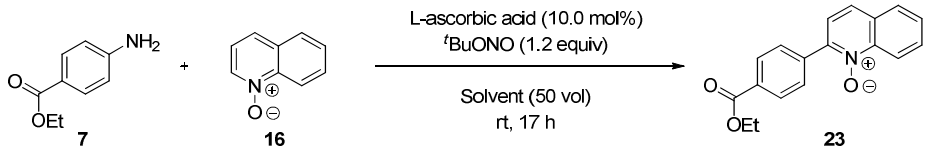
400 MHz ^{1}H NMR spectrum in $CDCl_3$:



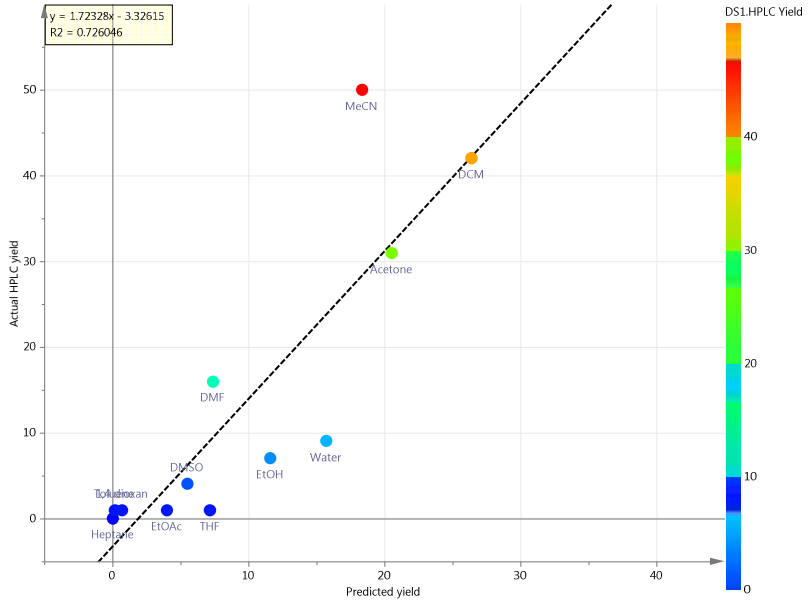
100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

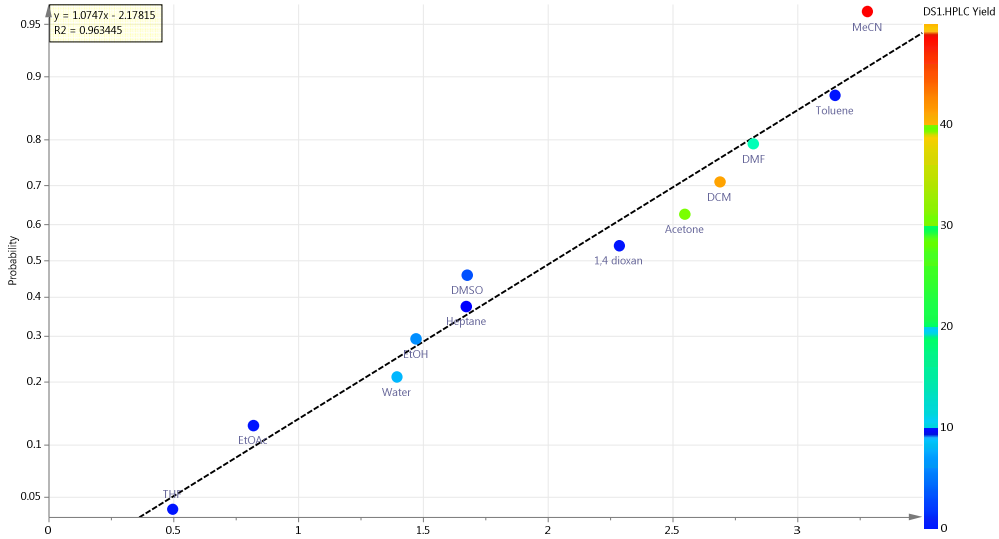


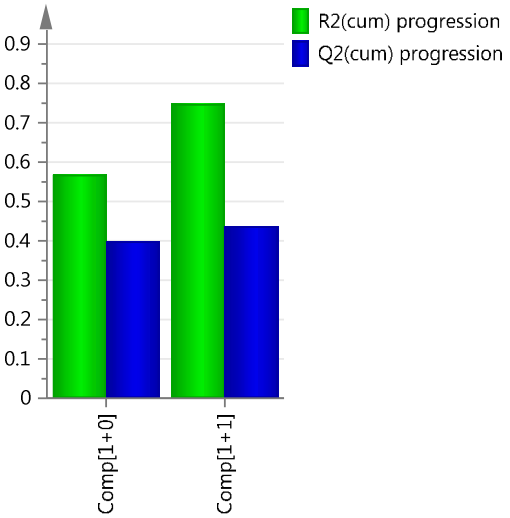
4. ORTHOGONAL PARTIAL LEAST SQUARE REGRESSION MODEL

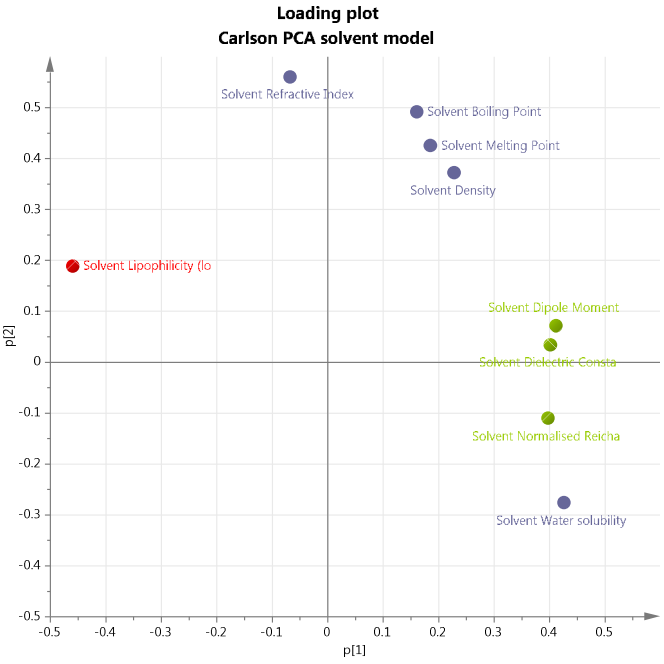


Entry	Solvent	HPLC Yield	Isolated Yield
1	Heptane	0%	Not isolated
2	Toluene	1%	Not isolated
3	1,4-dioxane	1%	Not isolated
4	THF	1%	Not isolated
5	EtOAc	1%	Not isolated
6	DMSO	4%	Not isolated
7	EtOH	7%	Not isolated
8	Water	9%	Not isolated
9	DMF	16%	19%
10	Acetone	31%	33%
11	CH_2Cl_2	42%	40%
12	MeCN	50%	60%

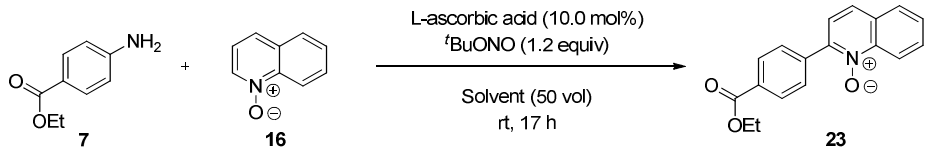



y = 1.0747x - 2.17815
R2 = 0.963445
Probability
DS1.HPLC Yield
MeCN
Toluene
DMF
DCM
Acetone
1,4 dioxan
DMSO
Heptane
EtOH
Water
EtOAc
THF


R2(cum) progression
Q2(cum) progression
Comp[1+0]
Comp[1+1]


Loading plot
Carlson PCA solvent model
Solvent Refractive Index
Solvent Boiling Point
Solvent Melting Point
Solvent Density
Solvent Lipophilicity (lo
Solvent Dipole Moment
Solvent Dielectric Consta
Solvent Normalised Reicha
Solvent Water solubility
p[1]
p[2]

5. DESIGN OF EXPERIMENT STUDY AND RESULTS



To a round bottom flask containing ethyl 4-aminobenzoate **7** (250 mg, 1.513 mmol, 1.0 equiv.), quinoline *N*-oxide hydrate **16** (80% w/w, desired number of equivalents) and L-ascorbic acid **35** (desired loading) under a nitrogen atmosphere was added degassed acetonitrile (desired volume), followed by *tert*-butyl nitrite (0.240 mL, 1.816 mmol) and the reaction mixture was stirred for 17 hours at the desired temperature. The reaction mixture was then diluted in a 50 mL volumetric flask with ethyl acetate to dissolve the solids and the solution was analysed by HPLC by diluting 250 µL into 1250 µL of acetonitrile. Yields were calculated from a calibration curve.

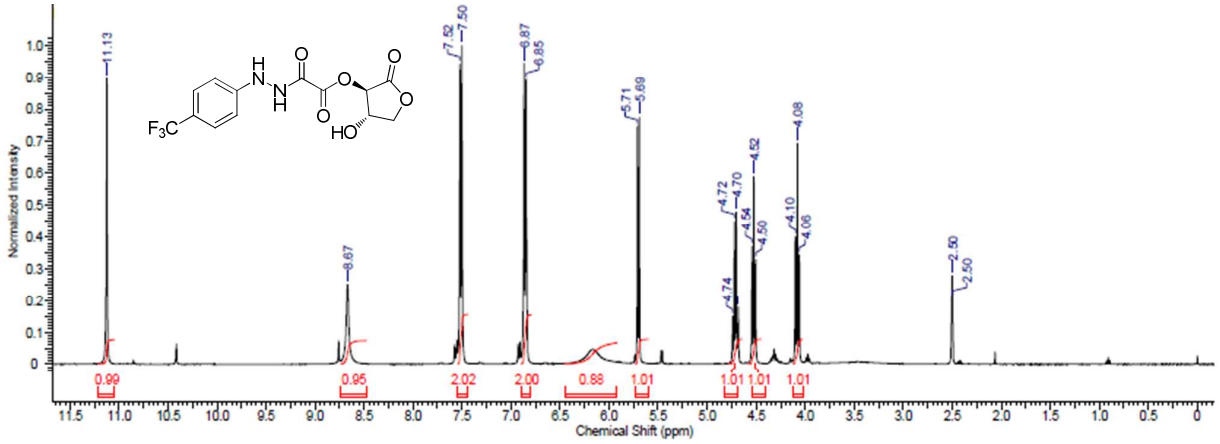
Run	Ascorbic Acid Loading (mol%)	Quinoline *N*-Oxide Equivalents (eq.)	Solvent Volumes (mL/g of **13**)	Temperature (°C)	Yield
1	20	3	10	40	48
2	1	3	10	0	14
3	10.5	2	55	20	44
4	1	1	10	0	18
5	1	3	100	40	50
6	20	3	100	40	52
7	1	1	100	0	24
8	1	3	100	0	1
9	10.5	2	55	20	46
10	20	3	100	0	2
11	10.5	2	55	20	46
12	1	1	100	40	38
13	1	3	10	40	50
14	20	1	10	0	34
15	20	1	100	40	38
16	20	1	100	0	39
17	20	1	10	40	36
18	1	1	10	40	38
19	10.5	2	55	20	37
20	20	3	10	0	1

6. PROCEDURE FOR THE SYNTHESIS OF HYDRAZINE DERIVATIVE 37

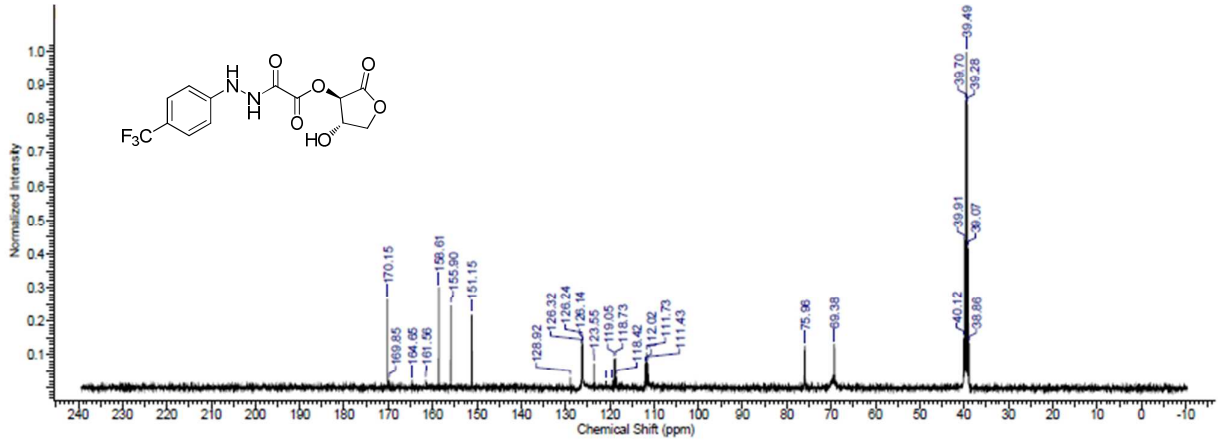
L-ascorbic acid **35** (346 mg, 1.96 mmol) was added to a round bottom flask containing 4-(trifluoromethyl)benzenediazonium tetrafluoroborate **34** (510 mg, 1.96 mmol) dissolved in a mixture of acetonitrile (1 mL) and water (7.5 mL) and the resulting mixture was stirred at room temperature for 30 minutes. A precipitate was formed and was filtered off the reaction mixture to give the hydrazine derivative **37** as a white solid (575 mg, 1.65 mmol, 84% yield).

(*3R,4S*)-4-hydroxy-2-oxotetrahydrofuran-3-yl-2-(2-(4-(trifluoromethyl)phenyl)hydrazinyl)-2-oxoacetate (37): White solid (575 mg, 84% yield), Mp 195–200 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.13 (s, 1H), 8.67 (s, 1H), 7.51 (d, 2H, *J* = 8.5 Hz), 6.86 (d, 2H, *J* = 8.5 Hz), 6.17 (bs, 1H), 5.70 (d, 1H, d = 7.8 Hz), 4.71 (aq, 1H, *J* = 7.6 Hz), 4.52 (at, 1H, *J* = 8.0 Hz), 4.08 (at, 1H, *J* = 8.3 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 170.2 (C_{IV}), 158.6 (C_{IV}), 155.9 (C_{IV}), 155.2 (C_{IV}), 126.4, 126.3, 124.9 (C_{IV}, q, *J* = 270.3 Hz), 118.9 (C_{IV}, q, *J* = 31.8 Hz), 111.7 (at, *J* = 29.5 Hz), 76.0, 69.4 ppm. HRMS (ESI$^+$): Calculated for $C_{13}H_{12}F_3N_2O_6$ $[M + H]^+$ 349.0642, found 349.0653

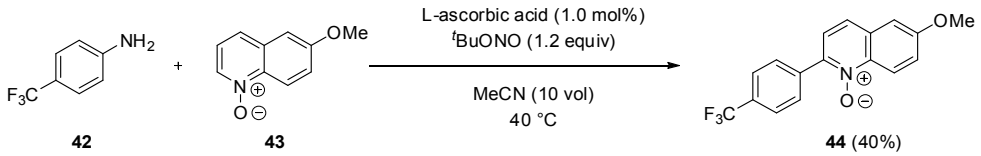
400 MHz ^{1}H NMR spectrum in DMSO-d_6:



100 MHz ^{13}C NMR spectrum in DMSO-d_6:



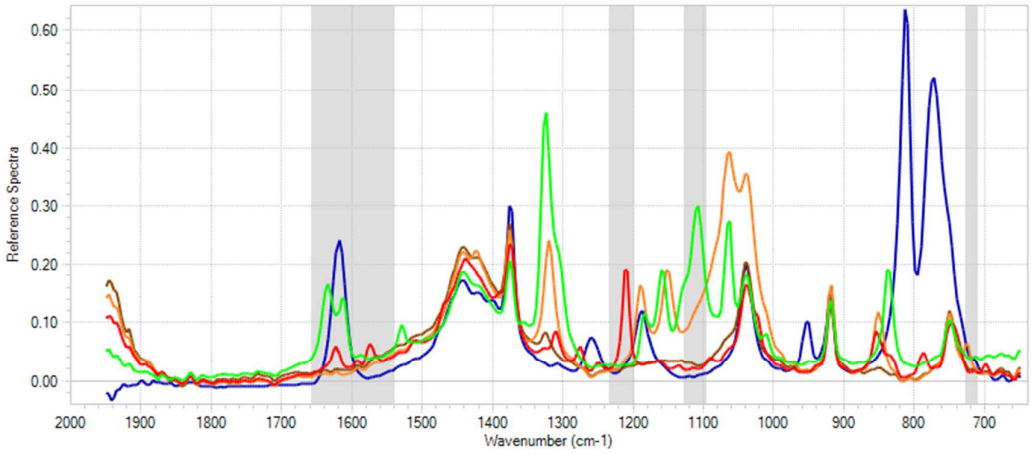
7. PROCEDURE FOR REACTIR AND LCMS MONITORING



42 **43** **44** (40%)

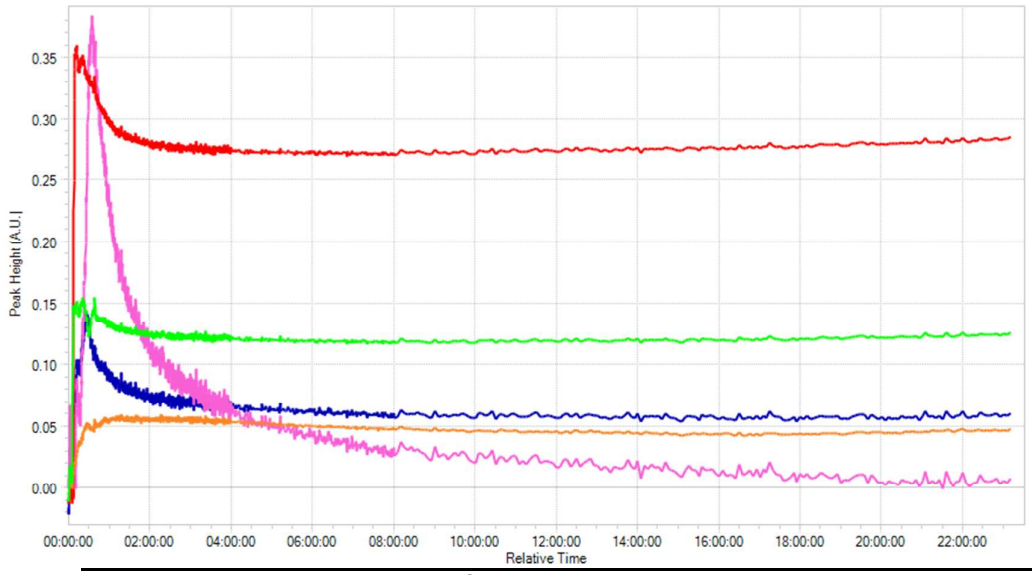
To a 400 mL EasyMax 402 (Mettler Toledo) reactor fitted with an IR probe (Mettler Toledo ReactIR iC 10 with MCT detector using HappGenzel apodization fitted with a DiComp (Diamond) probe connected with AgX 6mm x 2m Fiber (Silver Halide)) under a nitrogen atmosphere was charged L-ascorbic acid **35** (6 mg, 0.31 mmol) diluted in previously degassed acetonitrile (100 mL), followed by 6-methoxyquinoline *N*-oxide **43** (10.87 g, 62.1 mmol) and 4-(trifluoromethyl)aniline **42** (3.91 mL, 31.0 mmol). The resulting mixture was stirred at 40 °C and monitored by IR and LC/MS for 21 hours. 6-methoxy-2-(4-trifluoromethylphenyl)quinoline *N*-oxide **44** precipitated spontaneously during the course of the reaction and was isolated by filtration to give a beige solid (3.92 g, 12.3 mmol, 40% yield).

IR absorption spectra of reaction components in acetonitrile:



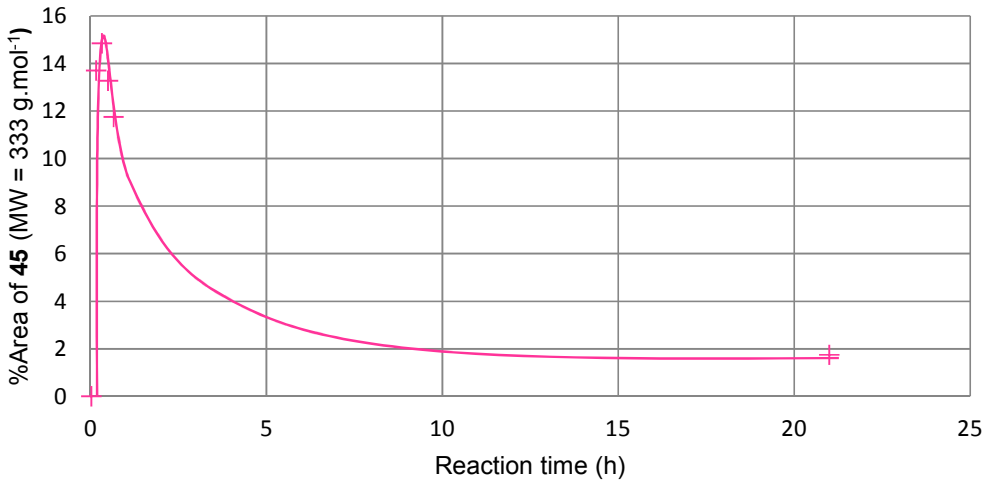
Entry	Component	Wavenumber
1	4-(Trifluoromethyl)aniline **42**	1125 to 1097 cm^{-1}
2	4-(Trifluoromethyl)benzenediazonium **34**	725 to 711 cm^{-1}
3	6-Methoxyquinoline *N*-oxide **43**	1232 to 1199 cm^{-1}
4	*tert*-Butyl nitrite	1656 to 1540 cm^{-1}
5	2-(4-(Trifluoromethyl)phenyl)-6-methoxyquinoline *N*-oxide **44**	No characteristic band observed

Reaction profile with simulated intermediate:

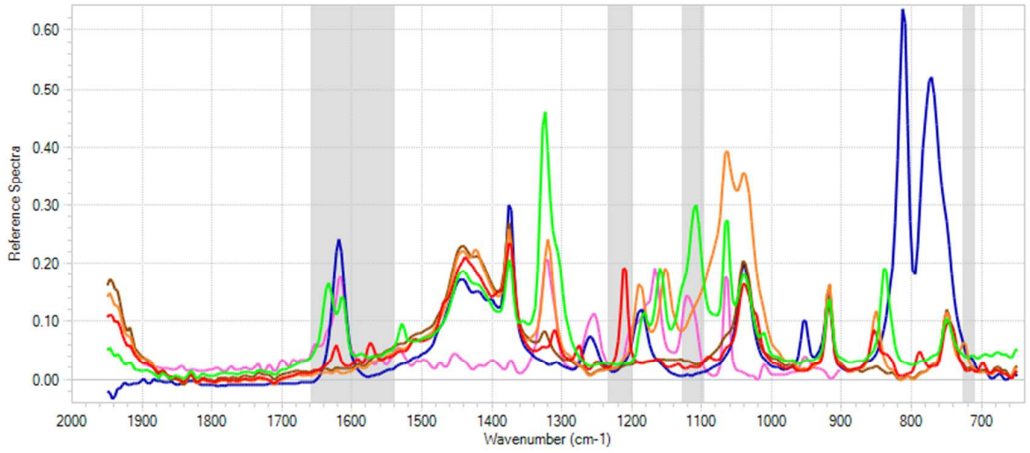


Entry	Component	Wavenumber
1	4-(Trifluoromethyl)aniline **42**	1125 to 1097 cm^{-1}
2	4-(Trifluoromethyl)benzenediazonium **34**	725 to 711 cm^{-1}
3	6-Methoxyquinoline *N*-oxide **43**	1232 to 1199 cm^{-1}
4	*tert*-Butyl nitrite	1656 to 1540 cm^{-1}
5	Simulated intermediate	Calculated

LCMS monitoring of the intermediate:



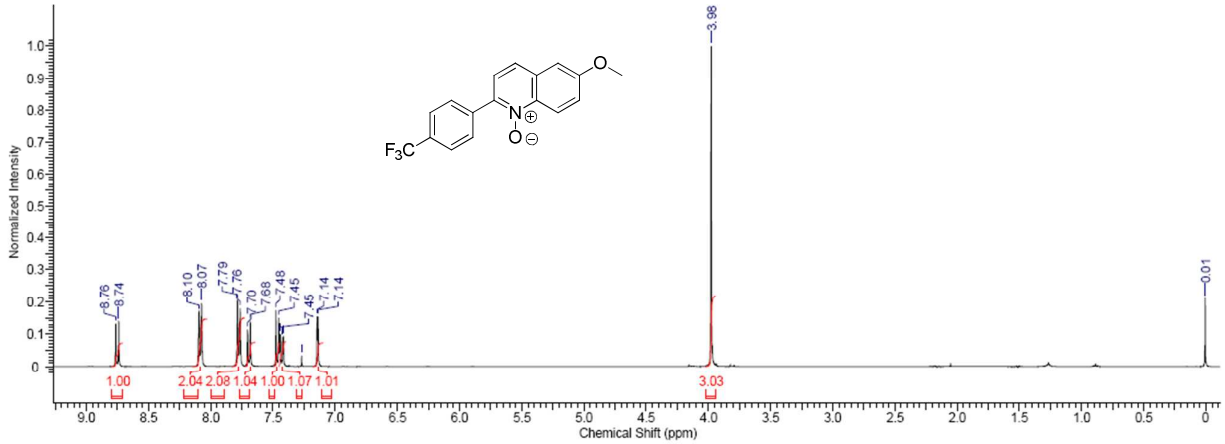
IR absorption spectra of reaction components in acetonitrile with simulated intermediate:



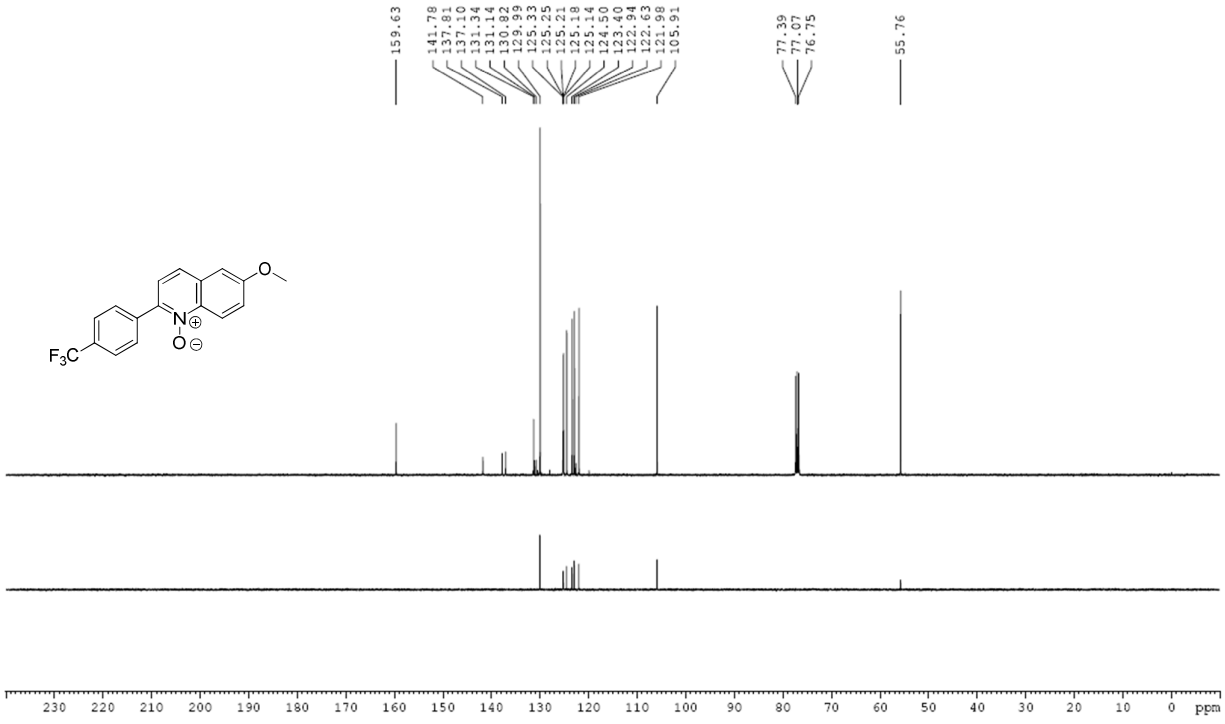
Entry	Component	Wavenumber
1	4-(Trifluoromethyl)aniline **42**	1125 to 1097 cm^{-1}
2	4-(Trifluoromethyl)benzenediazonium **34**	725 to 711 cm^{-1}
3	6-Methoxyquinoline *N*-oxide **43**	1232 to 1199 cm^{-1}
4	*tert*-Butyl nitrite	1656 to 1540 cm^{-1}
5	2-(4-(Trifluoromethyl)phenyl)-6-methoxyquinoline *N*-oxide **44**	No characteristic band observed
6	Simulated intermediate	Calculated

6-Methoxy-2-(4-(trifluoromethyl)phenyl)quinoline *N*-oxide (44): Beige solid (3.92 g, 40% yield), Mp 218–223 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, 1H, J = 9.5 Hz), 8.09 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.3 Hz), 7.69 (d, 1H, J = 8.6 Hz), 7.46 (d, 1H, J = 8.6 Hz), 7.43 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.14 (d, 1H, J = 2.4 Hz), 3.98 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6 (C_{IV}), 141.8, 137.80, 137.1, 131.3, 131.0 (q, J = 32.6 Hz), 130.0, 125.2 (q, J = 3.8 Hz), 124.5, 124.0 (q, J = 272.2 Hz), 123.40, 122.9, 122.0, 105.9, 55.8 ppm. HRMS (ESI$^+$): Calculated for $C_{17}H_{13}F_3NO_2$ $[M + H]^+$ 320.0893, found 320.0895.

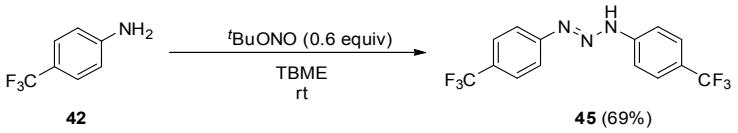
400 MHz ^{1}H NMR spectrum in $CDCl_3$:



100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:



8. PREPARATION OF TRIAZENE 45

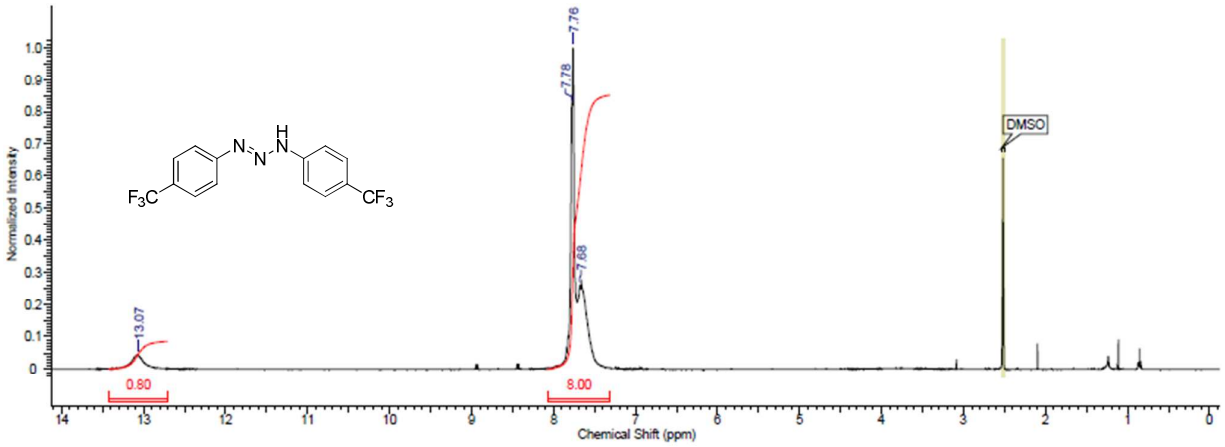


42 **45** (69%)

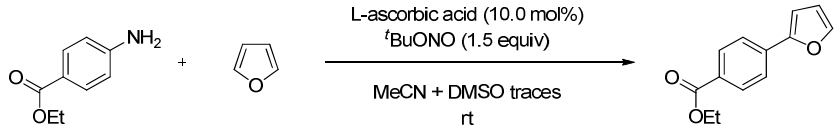
To a round bottom flask containing a stir bar and 4-(trifluoromethyl)aniline **42** (0.195 mL, 1.552 mmol) in TBME (5 mL) was added *tert*-butyl nitrite (0.123 mL, 0.931 mmol) and the resulting mixture was stirred for 2 hours at room temperature. The solvent was then removed under reduced pressure and the resulting solid was triturated in heptane. Filtration of the slurry afforded 1,3-bis(4-(trifluoromethyl)phenyl)triazene (**45**) (178 mg, 0.534 mmol, 69 % yield) as an orange solid.

1,3-Bis(4-(trifluoromethyl)phenyl)triazene (45): Orange solid (178 mg, 69% yield), Mp 114–116 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.07 (bs, 1H), 7.78-7.60 (m, 8H) ppm. HRMS (ESI^{+}): Calculated for $C_{14}H_{10}F_6N_3$ $[M + H]^+$ 334.0773, found 334.0773

400 MHz ^{1}H NMR spectrum in DMSO-d_6:



9. CONTROL REACTIONS



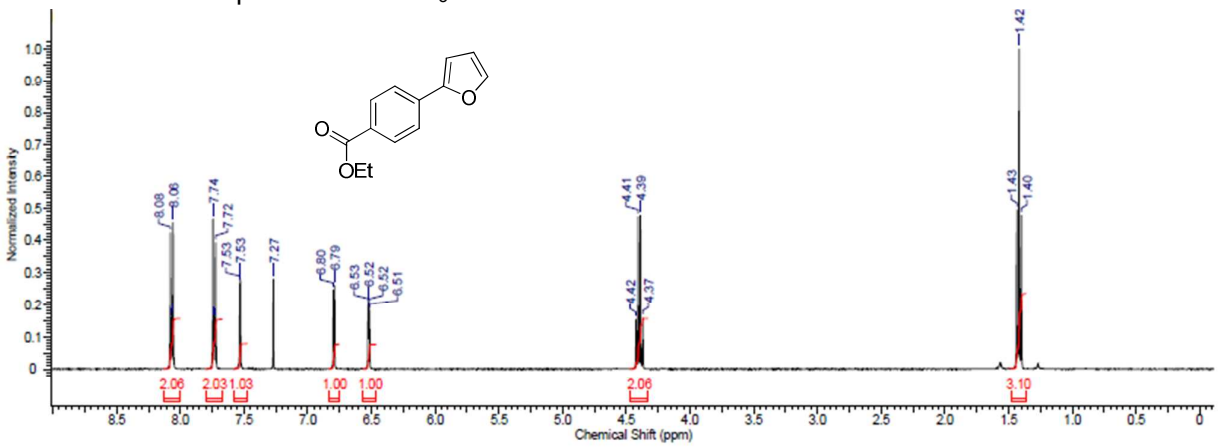
7 (1.0 equiv) **8** (10.0 equiv) **9**

Entry	Conditions	Yield
1	Literature[34]	64%
2	With ascorbic acid	52%
3	Without ascorbic acid	53%

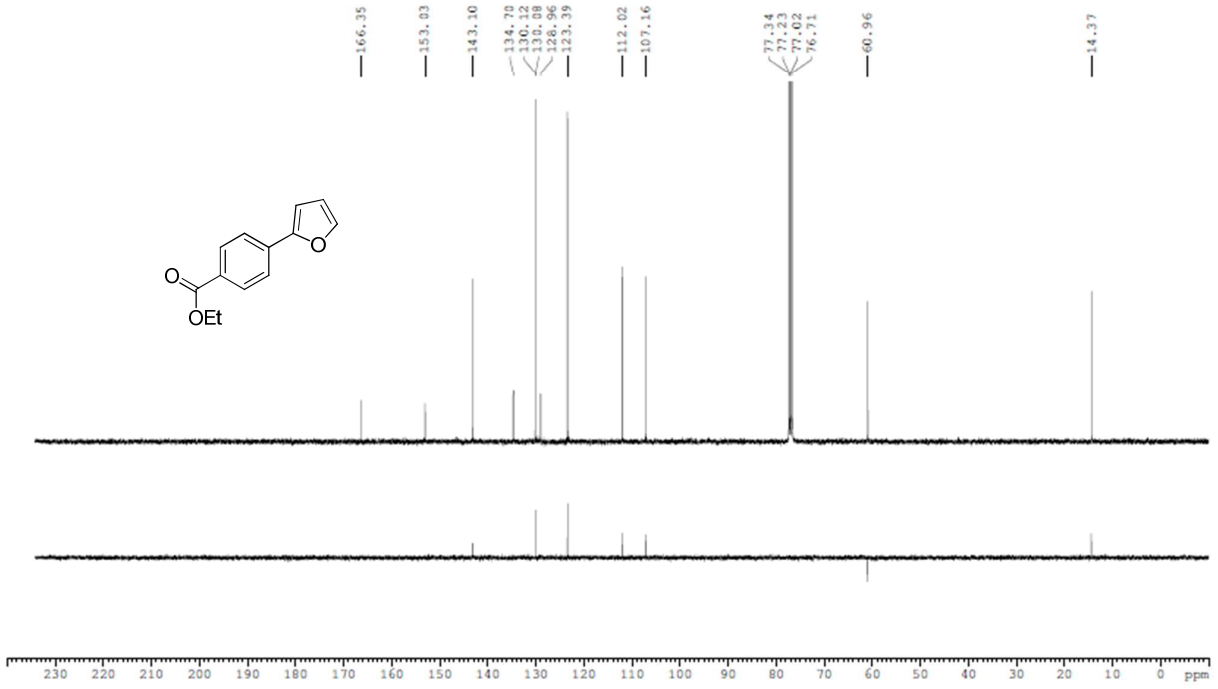
To a glass tube containing benzocaine **7** (83 mg, 0.5 mmol) under a nitrogen atmosphere was added previously degassed acetonitrile (5 mL), followed by furan **8** (0.36 mL, 5.00 mmol), *tert*-butyl nitrite (0.1 mL, 0.750 mmol) and a previously prepared solution of DMSO (0.1 mL) with or without L-ascorbic acid **35** (0.88 mg, 5.0 µmol). The resulting mixture was stirred for 14 hours at room temperature and was evaporated to dryness under reduced pressure. The crude product was then purified by silica gel chromatography eluting with heptane/ethyl acetate to give ethyl 4-(furan-2-yl)-benzoate **9** (56 mg, 0.26 mmol, 52% yield with L-ascorbic acid **35**, 57 mg, 0.27 mmol, 53% yield without L-ascorbic acid **35**) as a white solid.

Ethyl 4-(furan-2-yl)benzoate (9): White solid (56 mg, 52% yield with L-ascorbic acid **35**; 57 mg, 53% yield without L-ascorbic acid **35**), Mp 57–60 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, 2H, J = 8.6 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.53 (d, 1H, J = 1.3 Hz), 6.80 (d, 1H, J = 3.4 Hz), 6.52 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.7 Hz), 4.40 (q, 2H, J = 7.1 Hz), 1.42 (t, 3H, J = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4 (C_{IV}), 153.0 (C_{IV}), 143.1, 134.7 (C_{IV}), 130.1, 129.0 (C_{IV}), 123.4, 112.0, 107.2, 61.0, 14.4 ppm. HRMS (ESI$^+$): Calculated for $C_{13}H_{13}O_3$ $[M + H]^+$ 217.0859, found 217.0852.

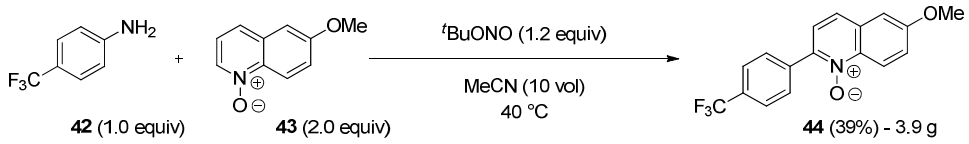
400 MHz ^{1}H NMR spectrum in $CDCl_3$:



100 MHz ^{13}C NMR and DEPT135 spectrum in $CDCl_3$:



10. CALORIMETRY STUDY



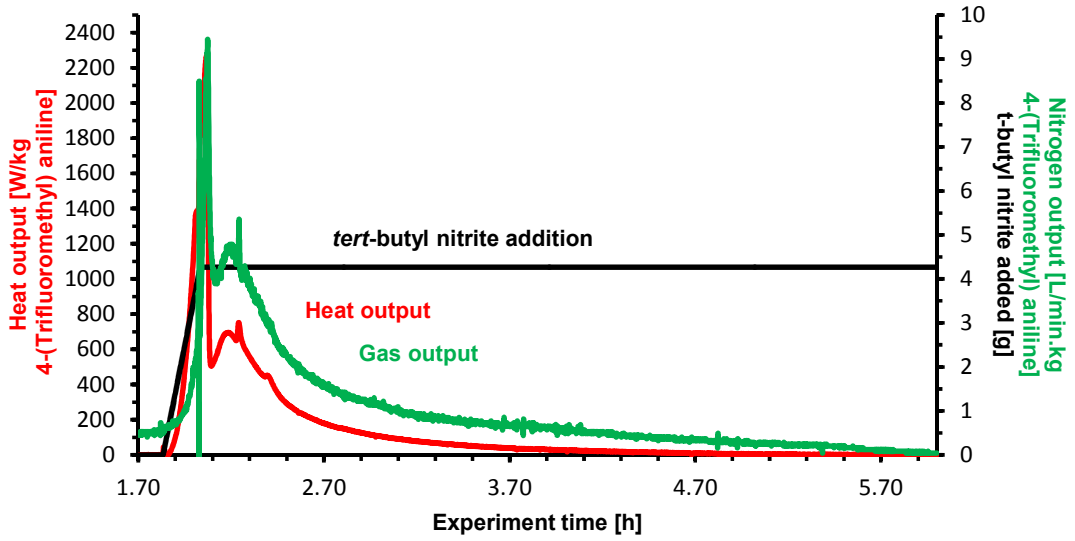
42 (1.0 equiv) **43** (2.0 equiv) **44** (39%) - 3.9 g

To a 100 mL Reaction Calorimetry 1 (RC 1, Mettler Toledo) reactor under a nitrogen atmosphere was charged 6-methoxyquinoline *N*-oxide **43** (10.87 g, 62.1 mmol), followed by previously degassed acetonitrile (50 mL). The solution was then stirred at 40°C and a first calibration was performed (Cp = 2221 J/[Kg.K]).

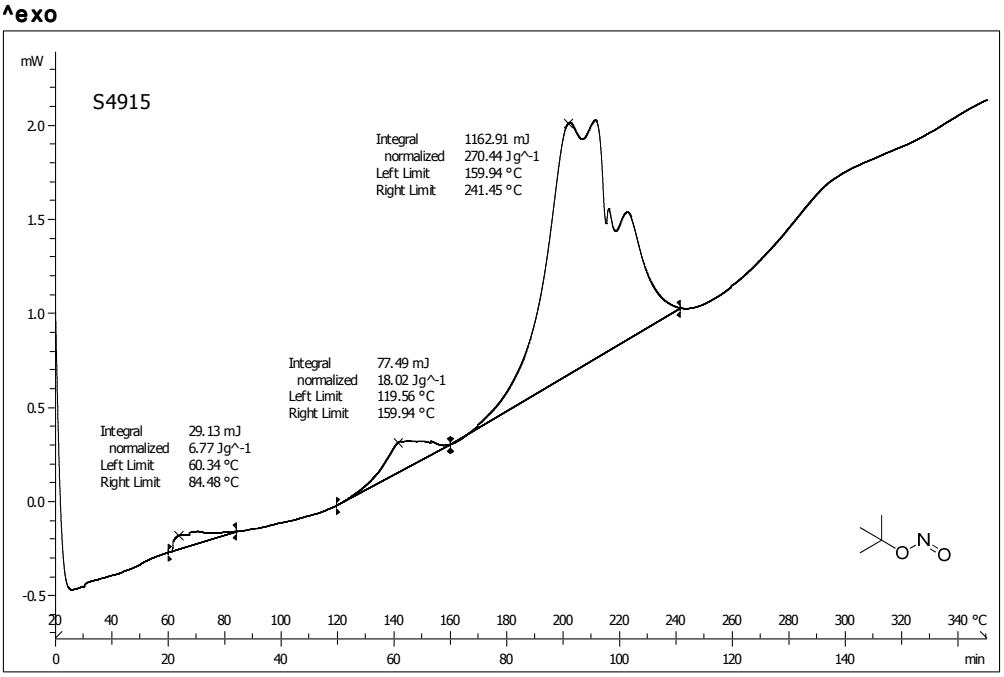
Aniline addition: 4-(trifluoromethyl)aniline **42** (3.91 mL, 31.0 mmol) was added dropwise with a syringe pump over 10 minutes to the previous solution at 40°C and a second calibration was performed (Cp = 1948 J/[Kg.K]). The RC 1 instrument indicated a total heat output of 0.33 kJ and a predicted adiabatic temperature rise of 3 °C. No gas output was observed during the addition of the 4-(trifluoromethyl)aniline **42**.

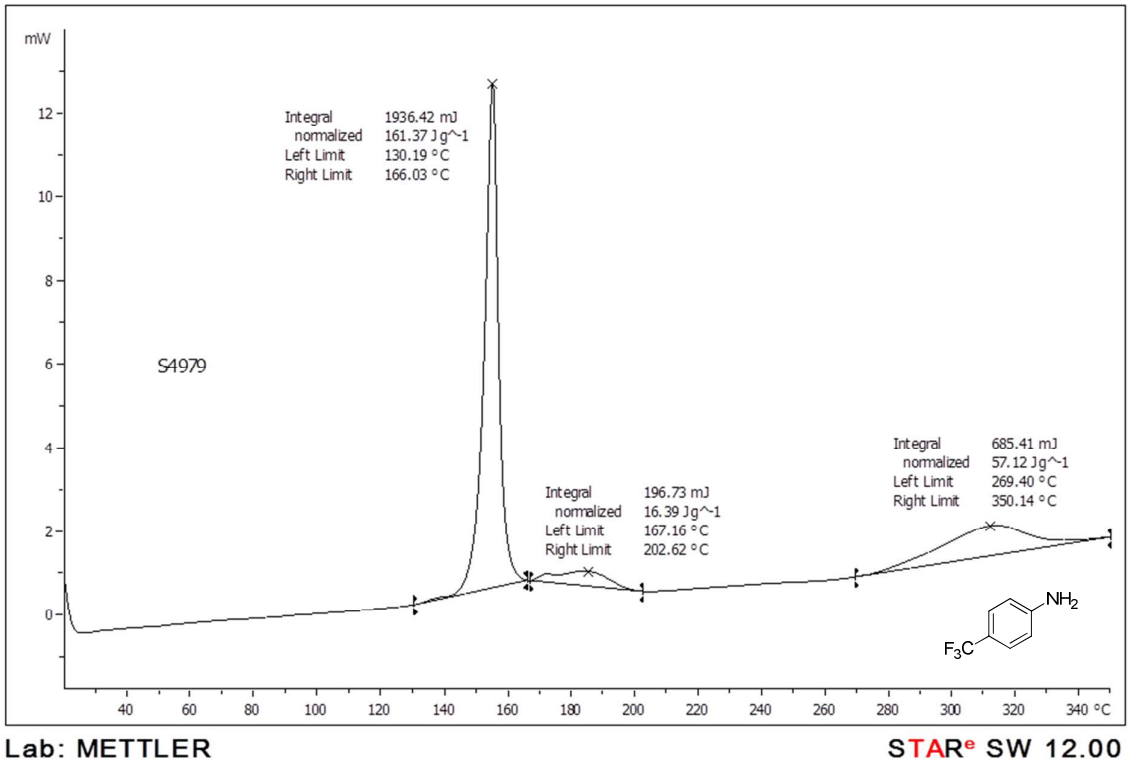
tert-Butyl nitrite addition: *tert*-butyl nitrite (4.92 mL, 37.2 mmol) was then added dropwise with a syringe pump over 10 minutes to the previous reaction mixture under nitrogen at 40°C and a third calibration was performed (Cp = 2170 J/[Kg.K]) after 19 hours. The RC 1 instrument indicated a total heat output of 10.4 kJ and a predicted adiabatic temperature rise of 81°C.

Work-up / isolation: The slurry was then stirred for 17 hours at 40°C under nitrogen before being cooled down to 20 °C. 6-Methoxy-2-(4-(trifluoromethyl)phenyl)quinoline *N*-oxide **44** precipitated spontaneously during the course of the reaction and was isolated by filtration to give a beige solid (3.88 g, 12.15 mmol, 39% yield).

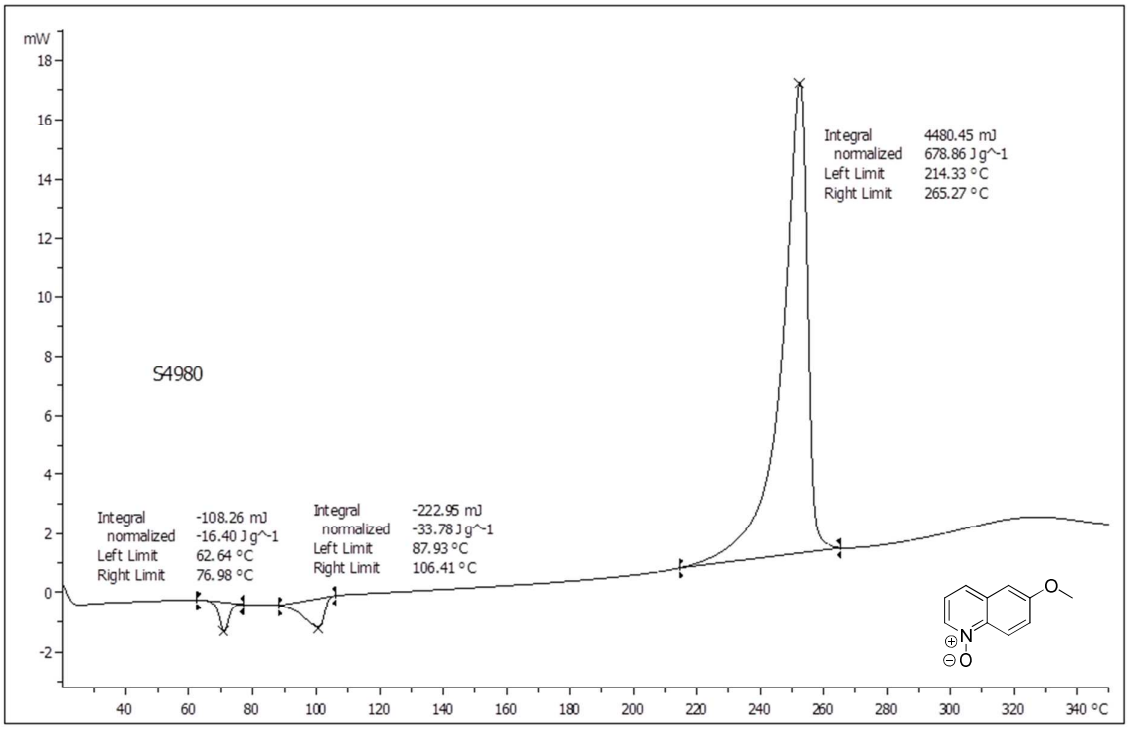


Differential Scanning Calorimetry data:



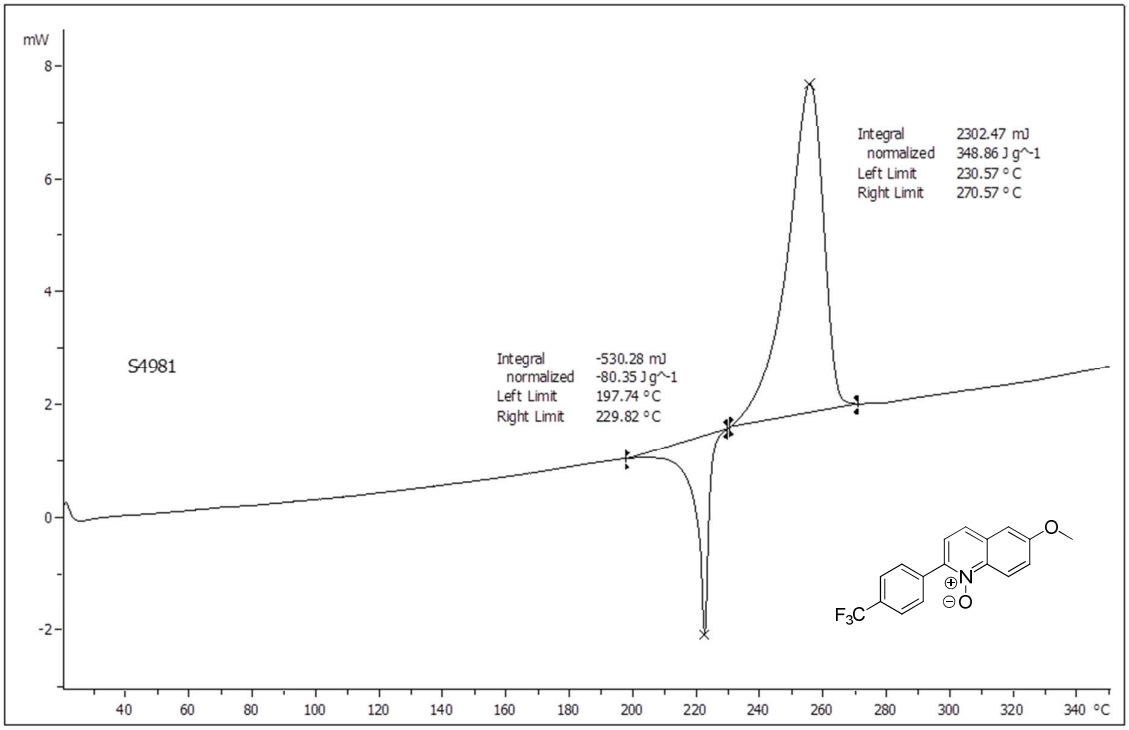


^exo



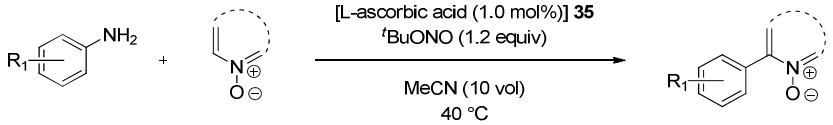
Lab: METTLER STARe SW 12.00

^exo



Lab: METTLER STARe SW 12.00

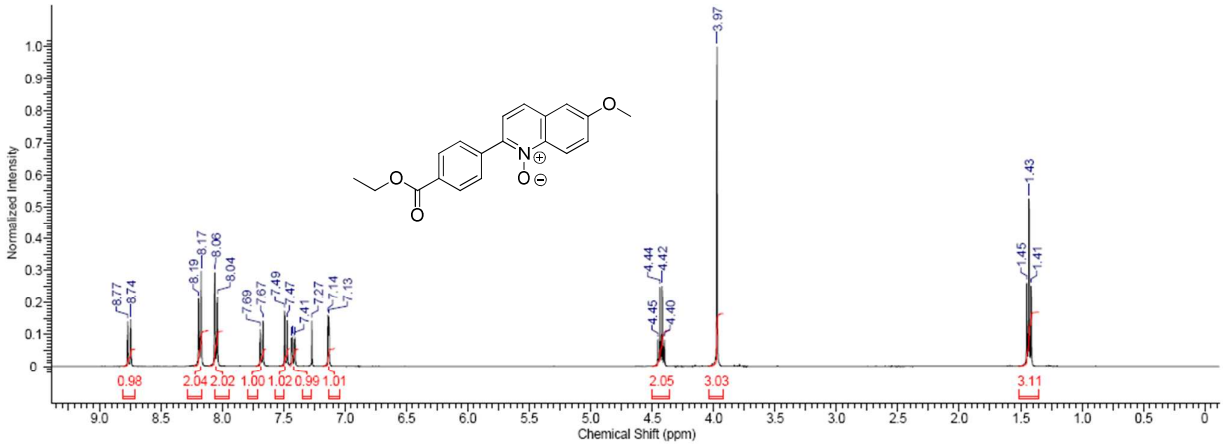
11. SCOPE OF THE REACTION



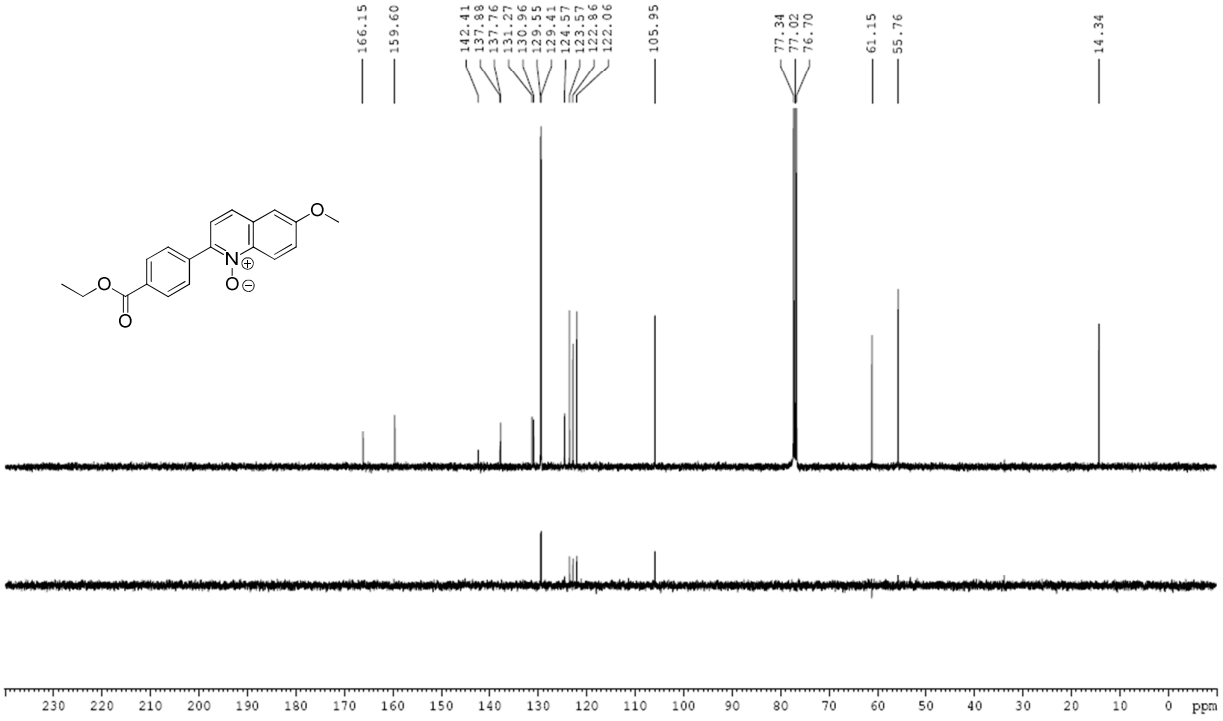
To a glass tube containing the aniline (1.0 equiv) and the *N*-oxide heterocycle (2.0 equiv) [L-ascorbic acid **35** (1.0 mol%) when required] under a nitrogen atmosphere was added degassed acetonitrile (10 volumes), followed by *tert*-butyl nitrite (1.2 equiv.) and the reaction mixture was stirred for 17 hours at 40 °C. The reaction mixture was then evaporated to dryness and the crude product was purified by silica gel chromatography eluting with either heptane/ethyl acetate or CH_2Cl_2/MeOH mixtures to yield the target compound.

2-(4-(Ethoxycarbonyl)phenyl)-6-methoxyquinoline *N*-oxide (57): Beige solid (244 mg, 50% yield), Mp: 201–204 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.76 (d, 1H, J = 9.5 Hz), 8.18 (d, 2H, J = 8.4 Hz), 8.05 (d, 2H, J = 8.5 Hz), 7.68 (d, 1H, J = 8.5 Hz), 7.48 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.14 (d, 1H, J = 2.5 Hz), 4.43 (q, 2H, J = 7.1 Hz), 3.97 (s, 3H), 1.43 (t, 3H, J = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2 (C_{IV}), 159.6 (C_{IV}), 142.4 (C_{IV}), 137.9 (C_{IV}), 137.8 (C_{IV}), 131.3 (C_{IV}), 131.0 (C_{IV}), 129.6, 129.4, 124.6, 123.6, 122.9, 122.1, 106.0, 61.2, 55.8, 14.3 ppm. HRMS (ESI$^+$): calculated for $C_{19}H_{18}NO_4$ $[M + H]^+$ 324.1232, found 324.1230.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

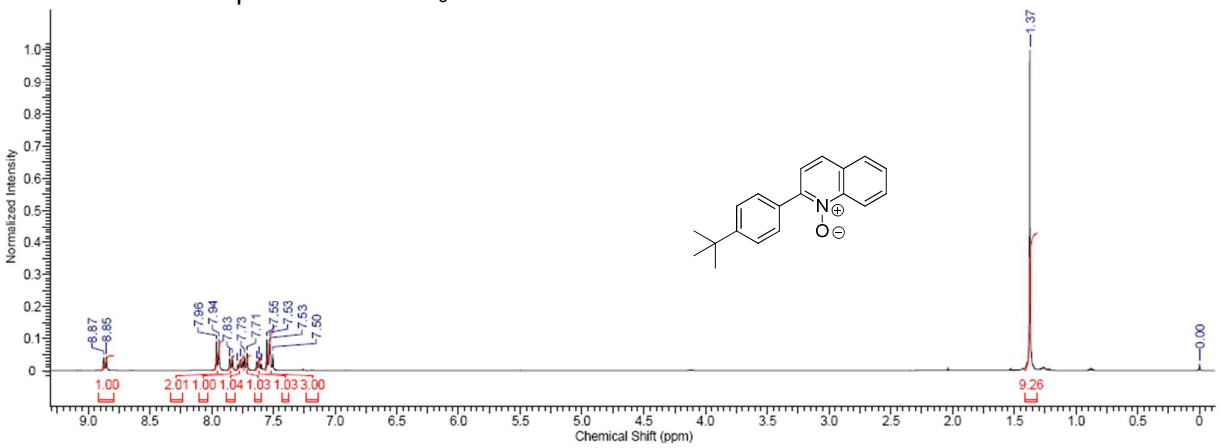


100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

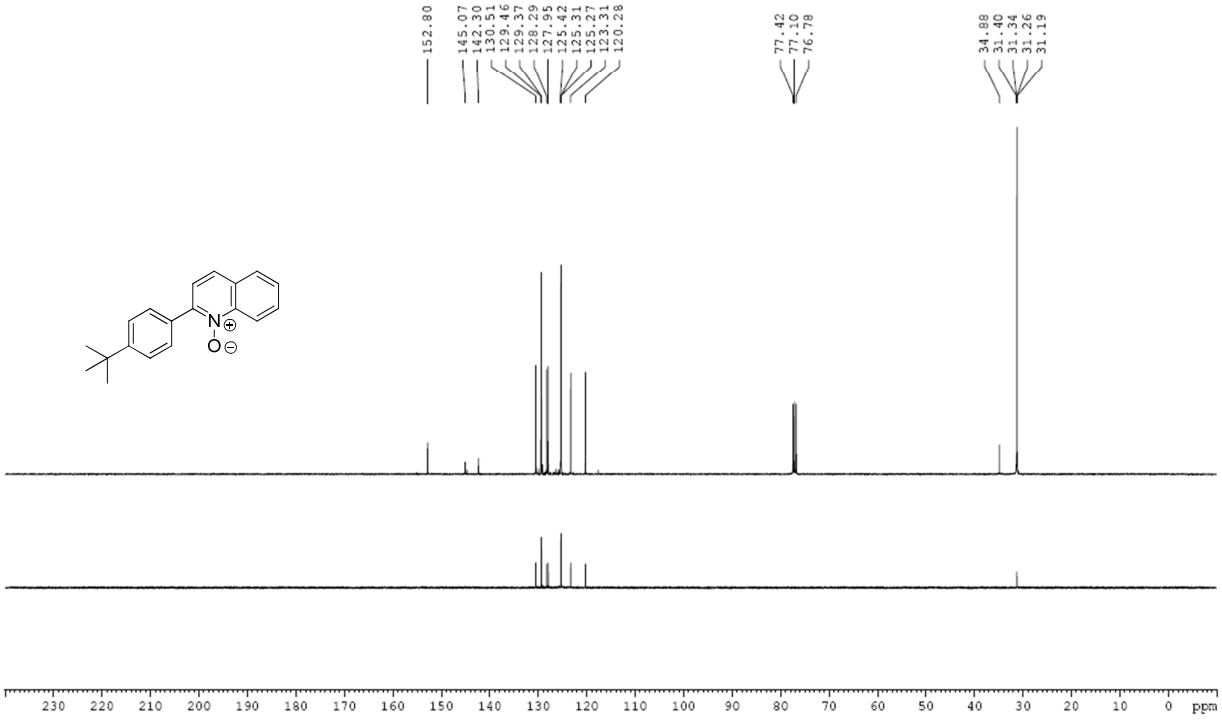


2-(4-(*tert*-Butyl)phenyl)quinoline *N*-oxide (58): Red solid (255 mg, 55% yield without L-ascorbic acid **35**; 238 mg, 51% yield with L-ascorbic acid **35**), Mp 156–160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, 1H, *J* = 8.5 Hz), 7.95 Hz (d, 2H, *J* = 8.1 Hz), 7.84 (d, 1H, *J* = 8.1 Hz), 7.77-7.75 (m, 1H), 7.72 (d, 1H, *J* = 8.8 Hz), 7.62-7.59 (m, 1H), 7.55-7.50 (m, 3H), 1.37 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8 (C_{IV}), 145.1 (C_{IV}), 142.3 (C_{IV}), 130.5, 129.5, 129.4, 128.3, 128.0, 125.4, 125.3, 125.3, 123.3, 120.3, 34.9 (C_{IV}), 31.3 ppm. HRMS (ESI$^+$): calculated for $C_{19}H_{20}NO$ [M + H]$^+$ 278.1539, found 278.1544.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

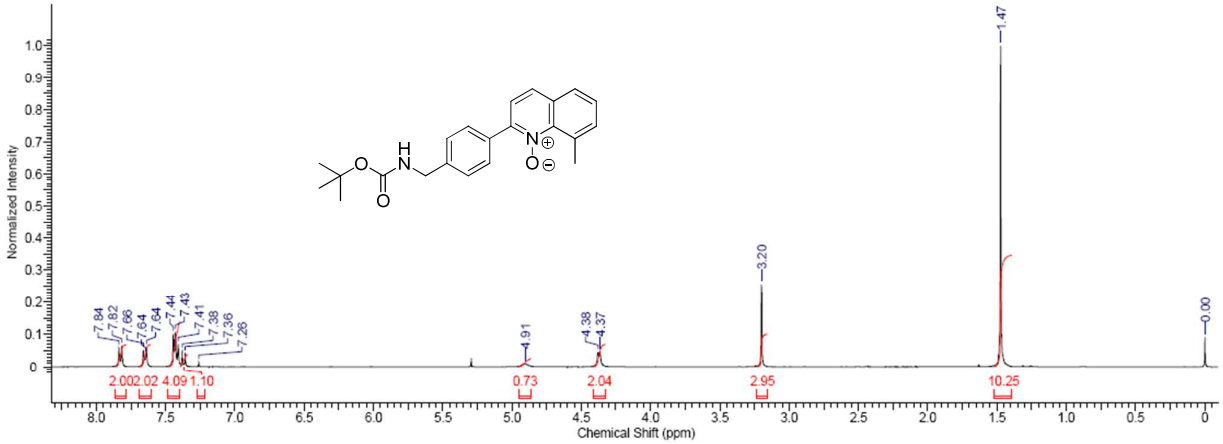


100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

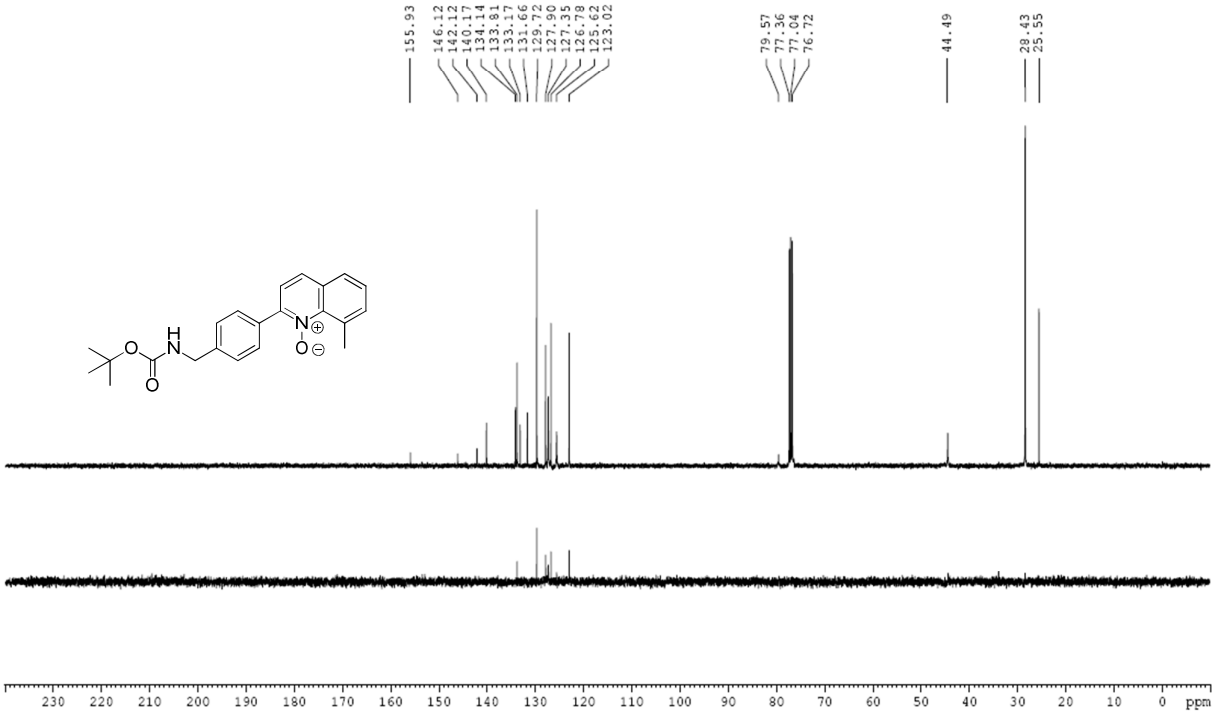


2-(4-((*N*-Boc)aminomethyl)phenyl)-8-methylquinoline *N*-oxide (59): Orange solid (107 mg, 44% yield without L-ascorbic acid **35**; 236 mg, 58% yield with L-ascorbic acid **35**), Mp 119–123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 2H, *J* = 8.2 Hz), 7.65 (d, 2H, *J* = 9.0 Hz), 7.44-7.41 (m, 4H), 7.37 (d, 1H, *J* = 8.6 Hz), 4.91 (bs, 1H), 4.38 (d, 2H, *J* = 5.7 Hz), 3.20 (s, 3H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9 (C_{IV}), 146.1 (C_{IV}), 142.1 (C_{IV}), 140.2 (C_{IV}), 134.1 (C_{IV}), 133.8, 133.2 (C_{IV}), 131.7, 129.7, 127.9, 127.4, 126.8, 125.6 (C_{IV}), 123.0, 79.6 (C_{IV}), 44.5, 28.4, 25.6 ppm. HRMS (ESI$^+$): calculated for $C_{22}H_{25}N_2O_3$ $[M + H]^+$ 365.1860, found 365.1875.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

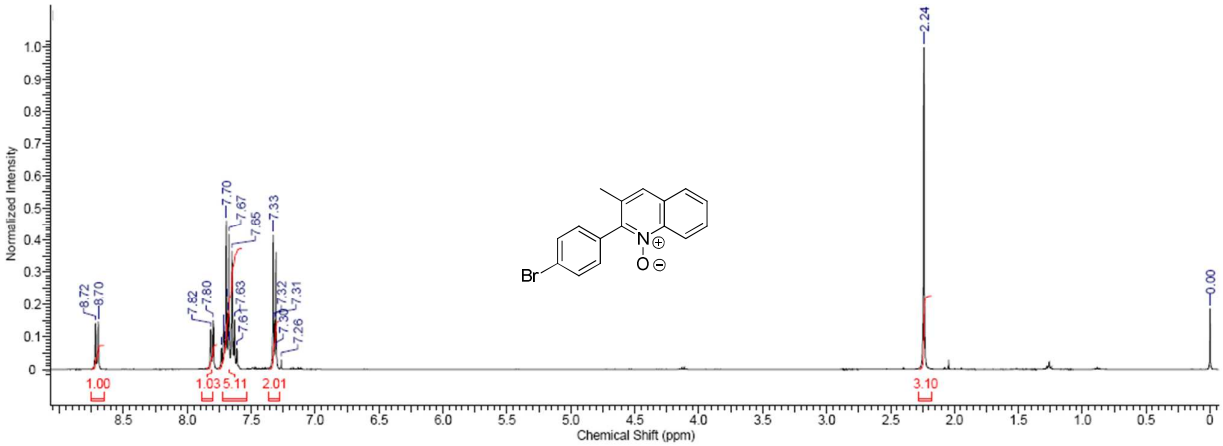


100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

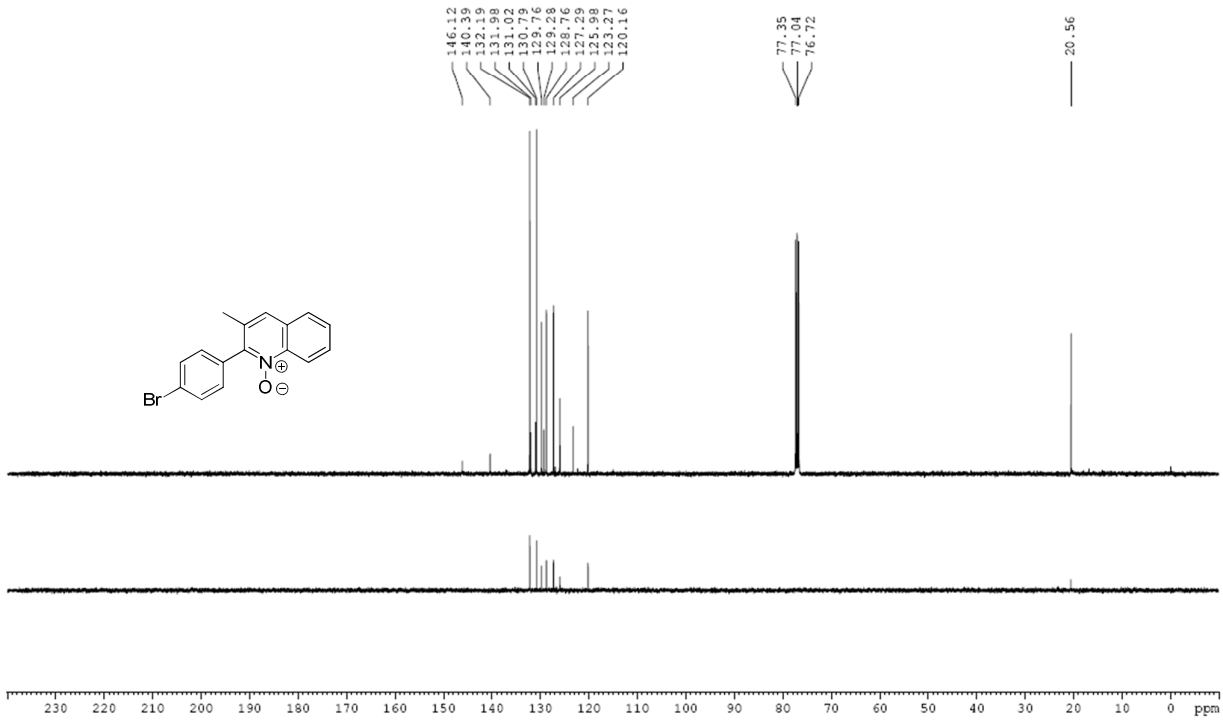


2-(4-Bromophenyl)-3-methylquinoline *N*-oxide (60): Beige solid (235 mg, 52% yield without L-ascorbic acid **35**; 233 mg, 51% yield with L-ascorbic acid **35**), Mp 140–143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (d, 1H, *J* = 8.5 Hz), 7.81 (d, 1H, *J* = 7.6 Hz), 7.73-7.60 (m, 5H), 7.32 (d, 2H, *J* = 8.6 Hz), 2.24 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.1 (C_{IV}), 140.4 (C_{IV}), 132.2, 132.0 (C_{IV}), 131.0 (C_{IV}), 130.8, 129.8, 129.3 (C_{IV}), 128.8, 127.3, 126.0, 123.3 (C_{IV}), 120.2, 20.6 ppm. HRMS (ESI$^+$): calculated for $C_{16}H_{13}{}^{79}BrNO$ $[M + H]^+$ 314.0175, found 314.0188.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

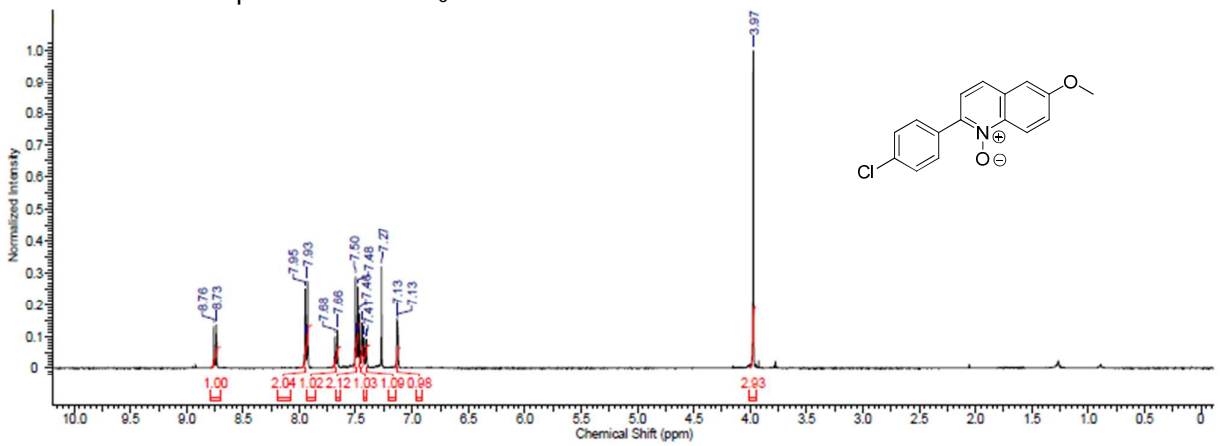


100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

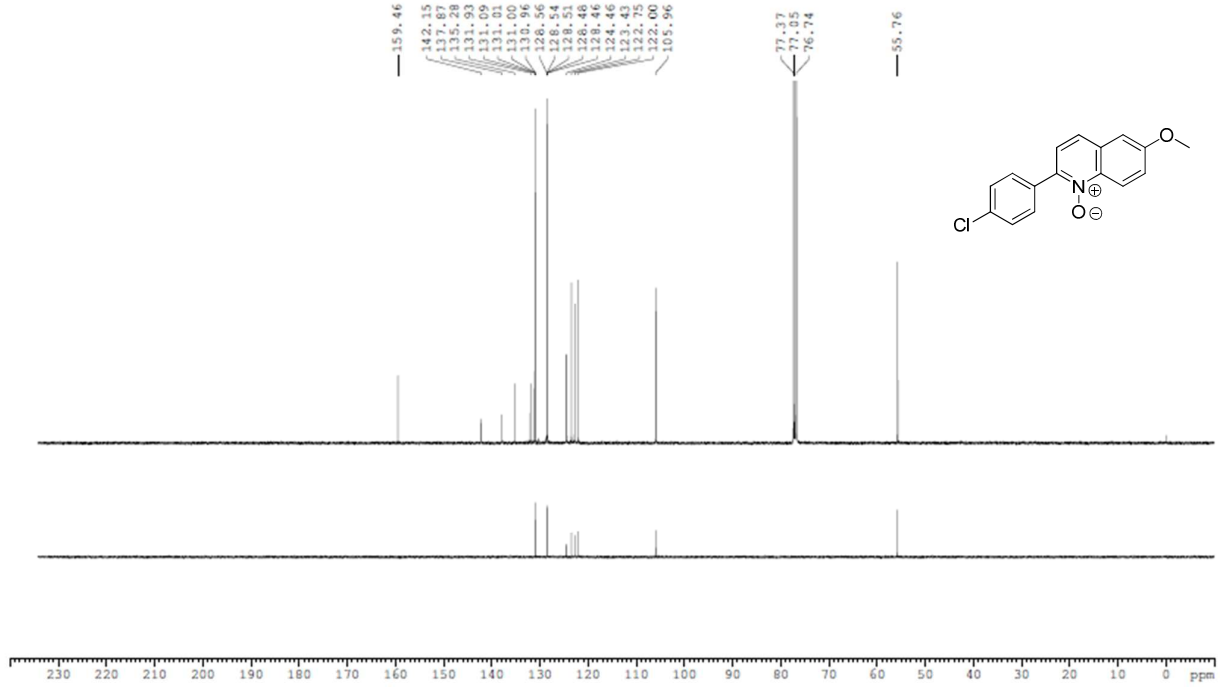


6-Methoxy-2-(4-chlorophenyl)quinoline *N*-oxide (61): Beige solid (294 mg, 53% yield without L-ascorbic acid **35**; 286 mg, 51% yield with L-ascorbic acid **35**), Mp 140–143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, 1H, *J* = 9.6 Hz), 7.94 (d, 2H, *J* = 8.6 Hz), 7.68 (d, 1H, *J* = 8.6 Hz), 7.51 (d, 2H, *J* = 8.5 Hz), 7.47 (d, 1H, *J* = 8.8 Hz), 7.44 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.13 (d, 1H, *J* = 2.7 Hz), 3.97 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5 (C_{IV}), 142.1(C_{IV}), 137.8 (C_{IV}), 135.2 (C_{IV}), 131.9 (C_{IV}), 131.0 (C_{IV}), 130.9, 128.5, 124.4, 123.4, 122.7, 122.0, 105.9, 55.7 ppm. HRMS (ESI$^+$): Calculated for $C_{16}H_{13}{}^{35}ClNO_2$ $[M + H]^+$ 286.0629, found 286.0633.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

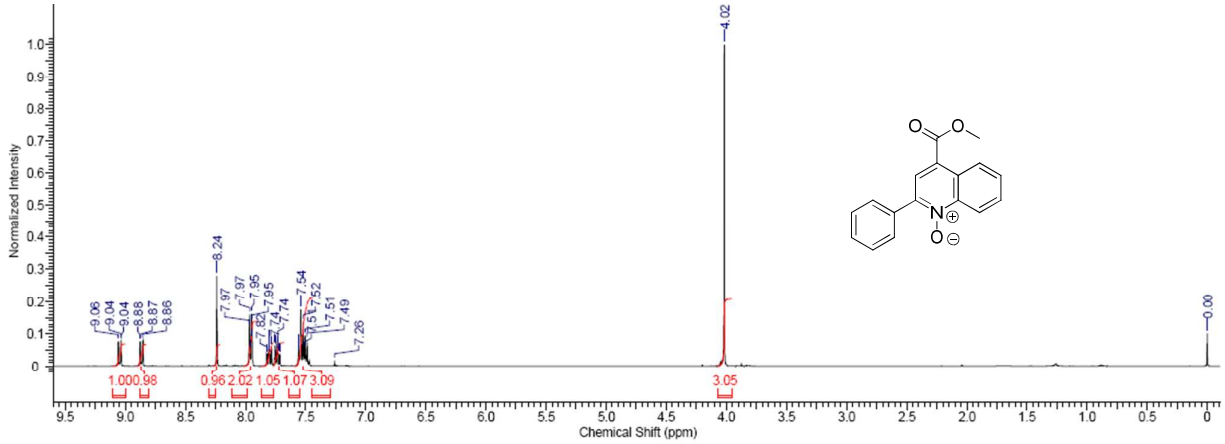


100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

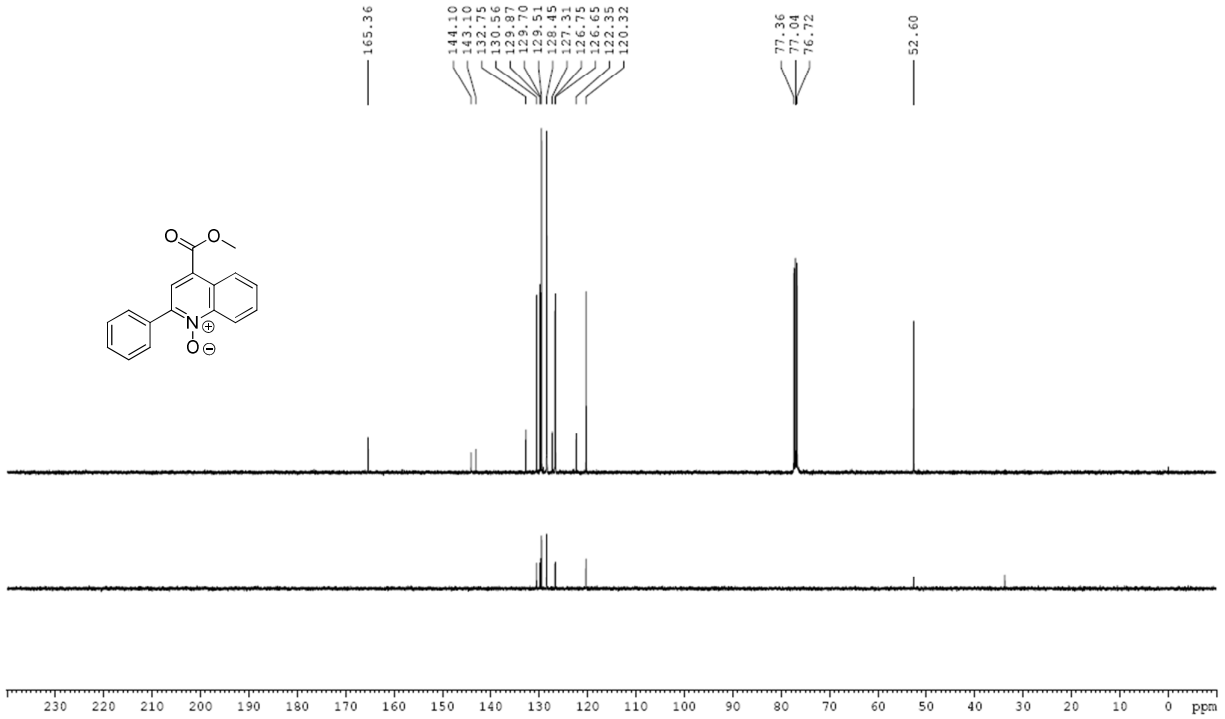


4-(Methoxycarbonyl)-2-phenylquinoline *N*-oxide (62): Orange solid (251 mg, 70% yield without L-ascorbic acid **35**; 351 mg, 65% yield with L-ascorbic acid **35**), Mp 112–117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.05 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.0 Hz), 8.87 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.0 Hz), 8.24 (s, 1H), 7.96 (dd, 2H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.80 (ddd, 1H, J_1 = 8.3 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz), 7.74 (ddd, 1H, J_1 = 8.3 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz), 7.57-7.46 (m, 3H), 4.02 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4 (C_{IV}),144.1 (C_{IV}), 143.1 (C_{IV}), 132.8 (C_{IV}), 130.6, 129.9, 129.7, 129.5, 128.5, 127.3 (C_{IV}), 126.8, 126.7, 122.4 (C_{IV}), 120.3, 52.6 ppm. HRMS (ESI$^+$): calculated for $C_{17}H_{14}NO_3$ $[M + H]^+$ 280.0968, found 280.0976.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

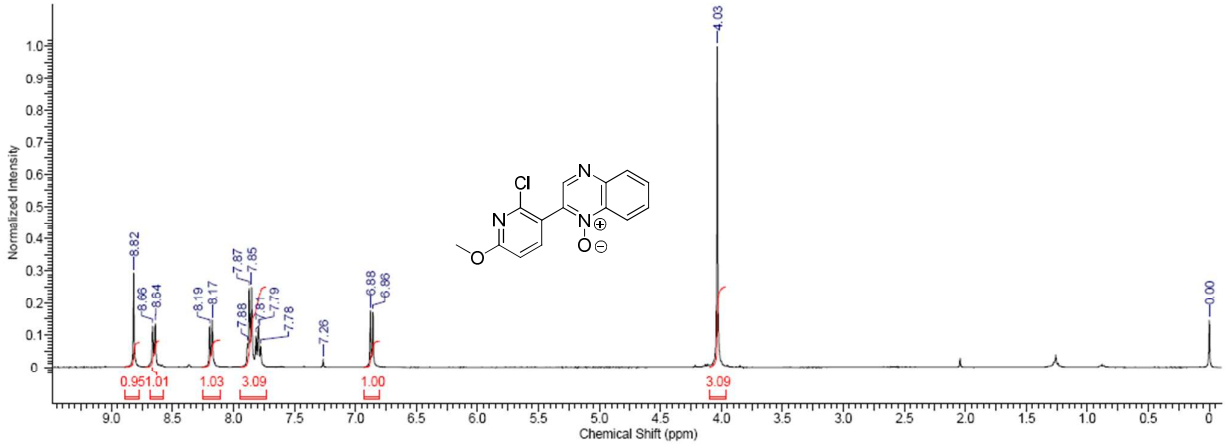


100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:

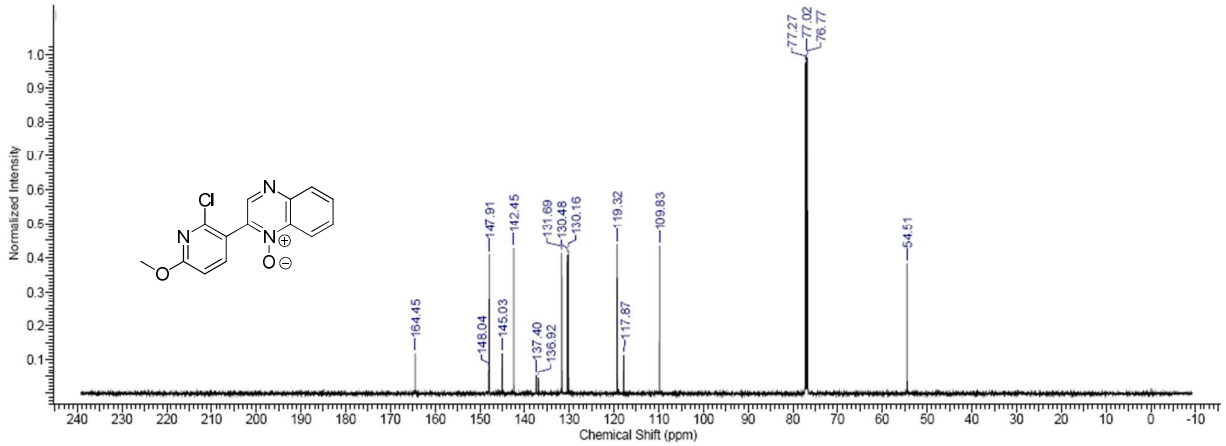


2-(2-Chloro-6-methoxypyridin-3-yl)quinoxaline *N*-oxide (63): Brown solid (58 mg, 15% yield without L-ascorbic acid **35**; 117 mg, 22% yield with L-ascorbic acid **35**), Mp 174–180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, 1H), 8.65 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 1H, *J* = 8.3 Hz), 7.89-7.76 (m, 3H), 6.87 (d, 1H, *J* = 8.9 Hz), 4.03 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5 (C_{IV}), 148.0 (C_{IV}), 147.9, 145.0 (C_{IV}), 142.5, 137.4 (C_{IV}), 136.9 (C_{IV}), 131.7, 130.5, 130.2, 119.3, 117.9 (C_{IV}), 109.8, 54.5 ppm. HRMS (ESI$^+$): calculated for $C_{14}H_{11}{}^{35}ClN_3O_2$ $[M + H]^+$ 288.0534, found 288.0544.

400 MHz ^{1}H NMR spectrum in $CDCl_3$:

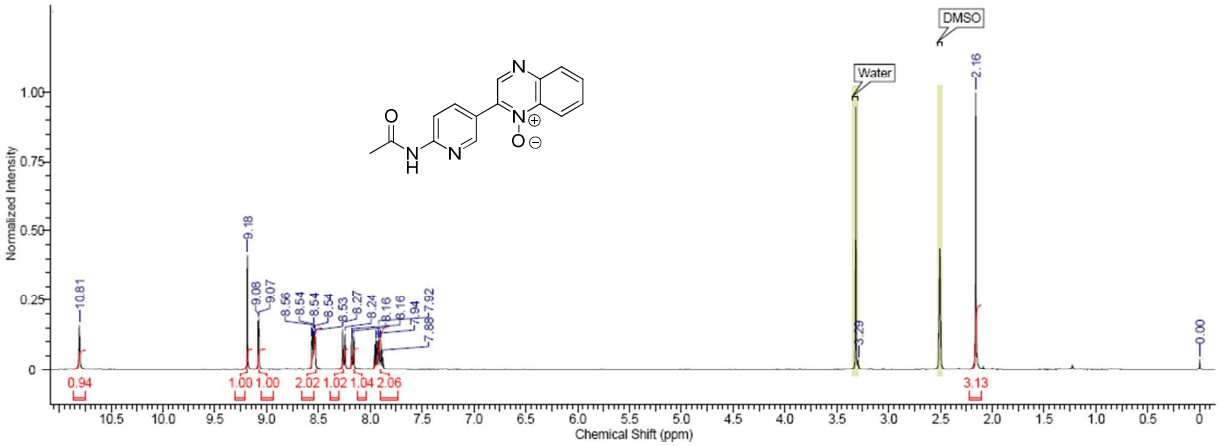


125 MHz ^{13}C NMR in $CDCl_3$:

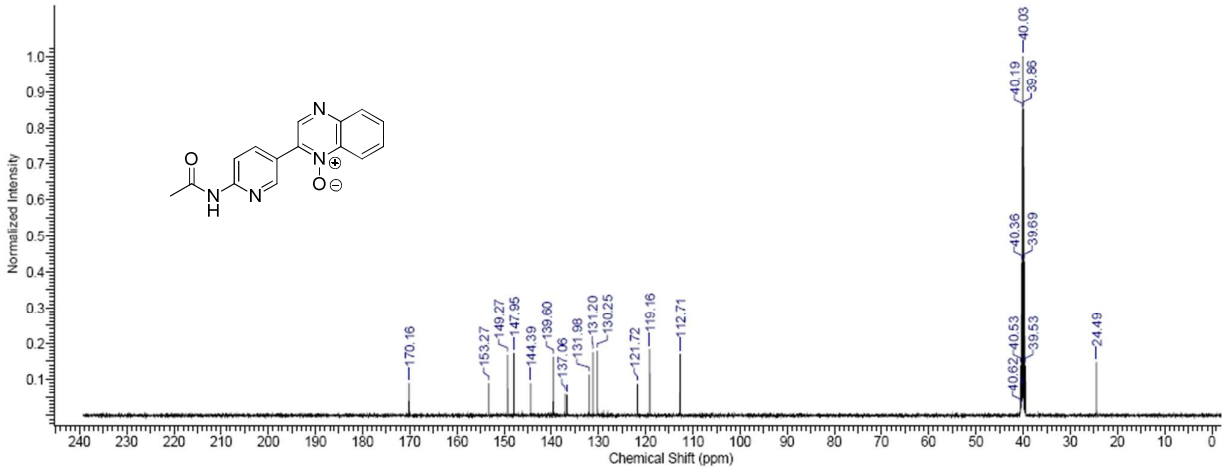


2-(6-(Acetamido)pyridin-3-yl)quinoxaline *N*-oxide (64): White solid (201 mg, 43% yield without L-ascorbic acid **35**; 99 mg, 43% yield with L-ascorbic acid **35**), Mp 245–250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.81 (s, 1H), 9.18 (s, 1H), 9.08 (d, 1H, J = 2.0 Hz), 8.56-8.53 (m, 2H), 8.26 (d, 1H, J = 8.8 Hz), 8.17 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.4 Hz), 7.96-7.88 (m, 2H), 2.16 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 170.2 (C_{IV}), 153.3 (C_{IV}), 149.3, 148.0, 144.4 (C_{IV}), 139.6, 137.1 (C_{IV}), 136.7 (C_{IV}), 132.0, 131.2, 130.3, 121.7 (C_{IV}), 119.2, 112.7, 24.5 ppm. HRMS (ESI$^+$): calculated for $C_{15}H_{13}N_4O_2$ $[M + H]^+$ 281.1033, found 281.1034.

400 MHz ^{1}H NMR spectrum in DMSO-d_6:

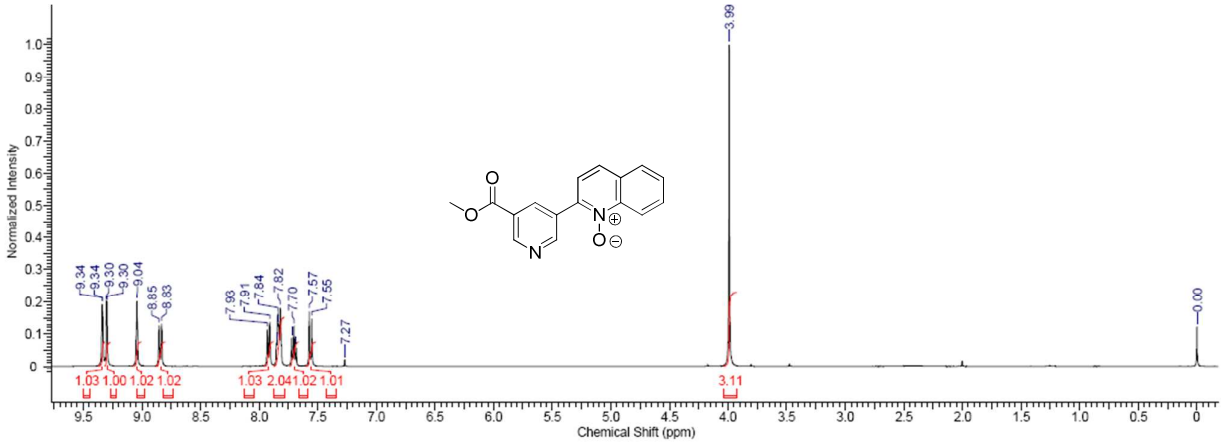


125 MHz ^{13}C NMR spectrum in DMSO-d_6:

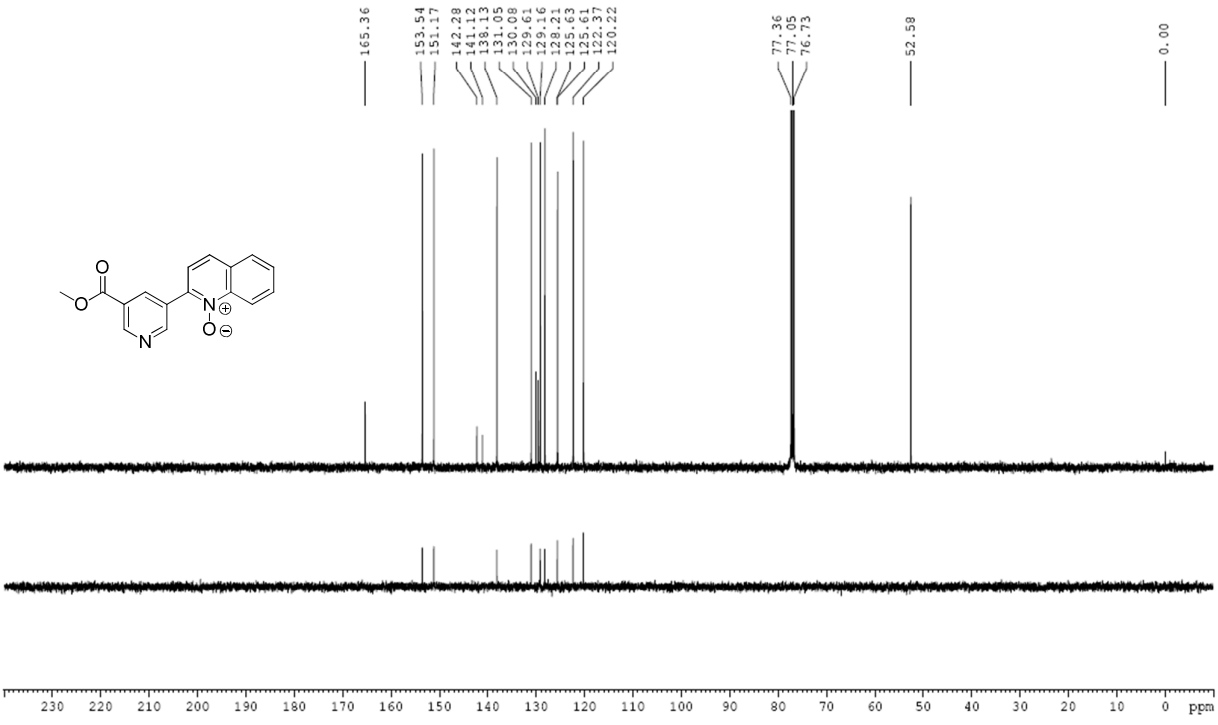


2-(5-(Methoxycarbonyl)pyridin-3-yl)quinoline *N*-oxide (65): White solid (162 mg, 35% yield without L-ascorbic acid **35**; 158 mg, 34% yield with L-ascorbic acid **35**), Mp 180–183 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.34 (d, 1H, *J* = 1.9 Hz), 9.30 (d, 1H, *J* = 1.4 Hz), 9.04 (s, 1H), 8.84 (d, 1H, *J* = 8.8 Hz), 7.92 (d, 1H, *J* = 8.1 Hz), 7.85-7.80 (m, 2H), 7.72-7.68 (m, 1H), 7.56 (d, 1H, *J* = 8.6 Hz), 3.99 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4 (C_{IV}), 153.5, 151.2, 142.3 (C_{IV}), 141.1 (C_{IV}), 138.1, 131.1, 130.1, 129.6, 129.2, 128.2, 125.6, 122.4, 120.2, 52.6 ppm. One quaternary carbon peak is missing. HRMS (ESI$^+$): calculated for $C_{16}H_{13}N_2O_3$ $[M + H]^+$ 281.0921, found 281.0923.

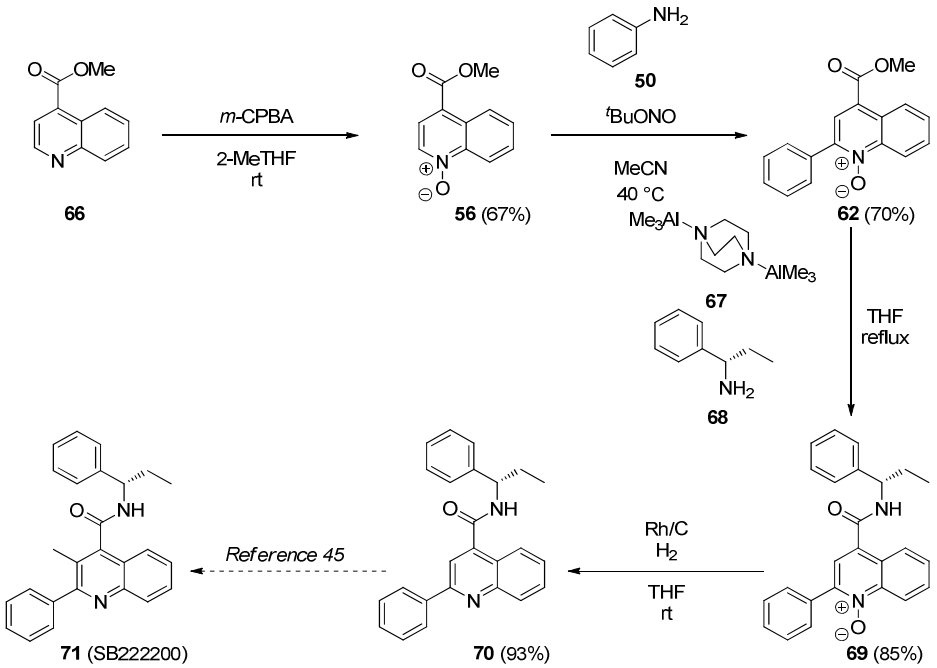
400 MHz ^{1}H NMR spectrum in $CDCl_3$:



100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:



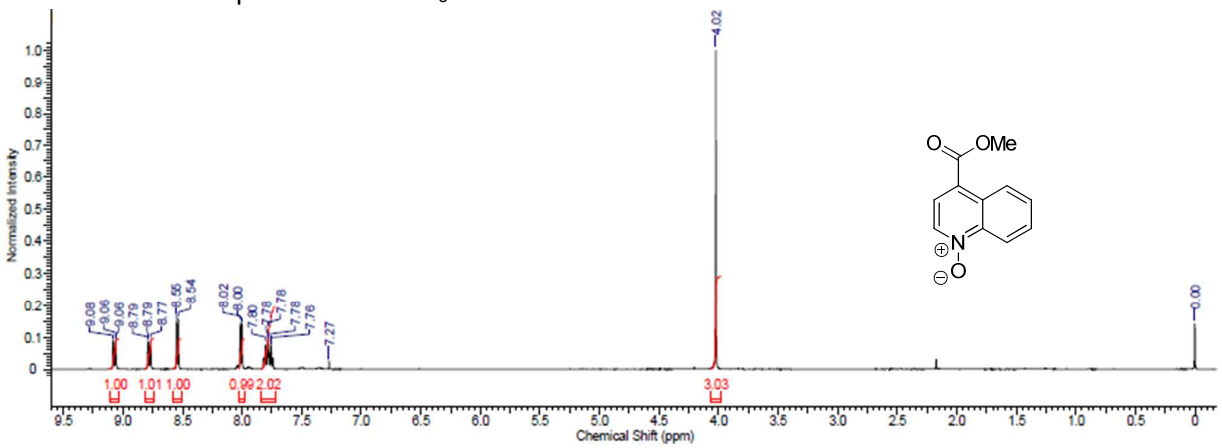
12. FORMAL SYNTHESIS OF SB222200



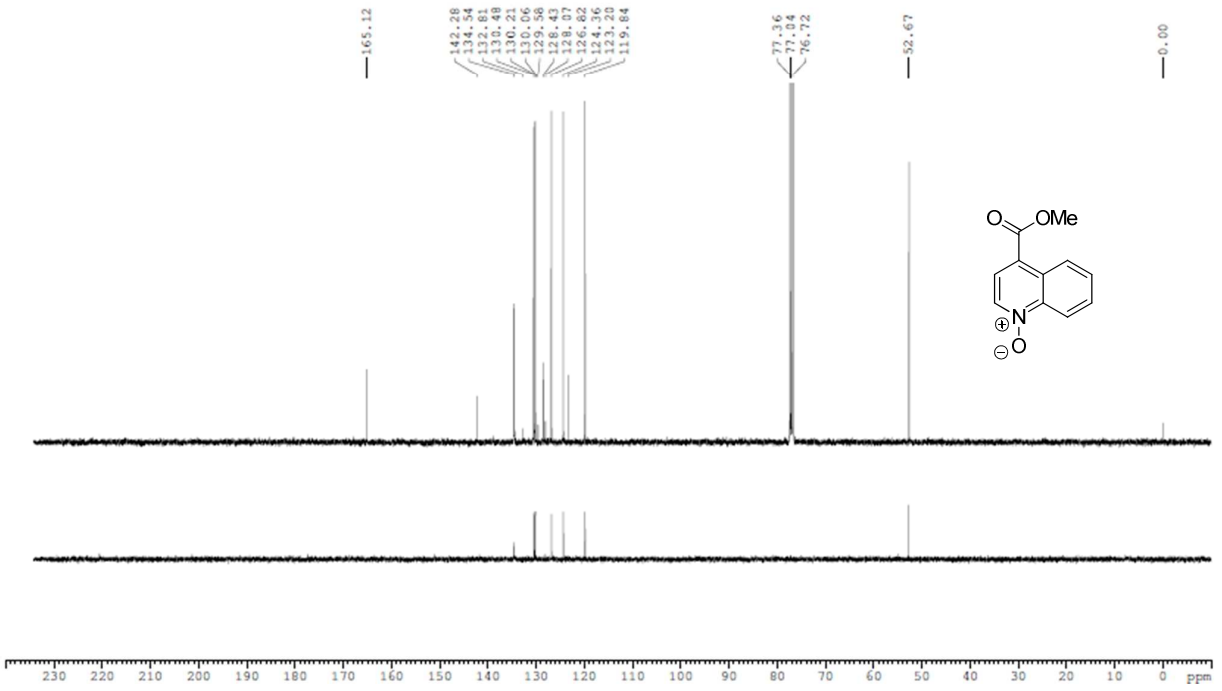
Synthesis of 4-(methoxycarbonyl)quinoline *N*-oxide 56: To a solution of methyl quinoline-4-carboxylate **66** (1.94 g, 10.36 mmol) in 2 MeTHF (100 mL) at room temperature under air was added portionwise *m*-CPBA (1.967 g, 11.40 mmol). The resulting solution was stirred for 24 hours at room temperature and the solvent was removed under reduced pressure. The crude product was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ and the organic layer was dried over anhydrous Na_2SO_4 before being concentrated in vacuo. The crude product was then purified by silica gel chromatography eluting with dichloromethane/acetone to give 4-(methoxycarbonyl)quinoline *N*-oxide **56** (1.40 g, 6.89 mmol, 67% yield) as a white solid.

4-(Methoxycarbonyl)quinoline *N*-oxide (56): White solid (1.40 g, 67% yield), Mp 152–153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.07 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 8.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 8.55 (d, 1H, J = 6.4 Hz), 8.01 (d, 1H, J = 6.4 Hz), 7.82 7.70 (m, 2H), 4.02 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.1 (C_{IV}), 142.3 (C_{IV}), 134.4, 130.4, 130.2, 128.4 (C_{IV}), 126.8, 124.4, 123.0 (C_{IV}), 119.8, 52.6 ppm. HRMS (ESI$^+$): Calculated for $C_{11}H_{10}NO_3$ [M + H]$^+$ 204.0655, found 204.0653

400 MHz ^{1}H NMR spectrum in $CDCl_3$:



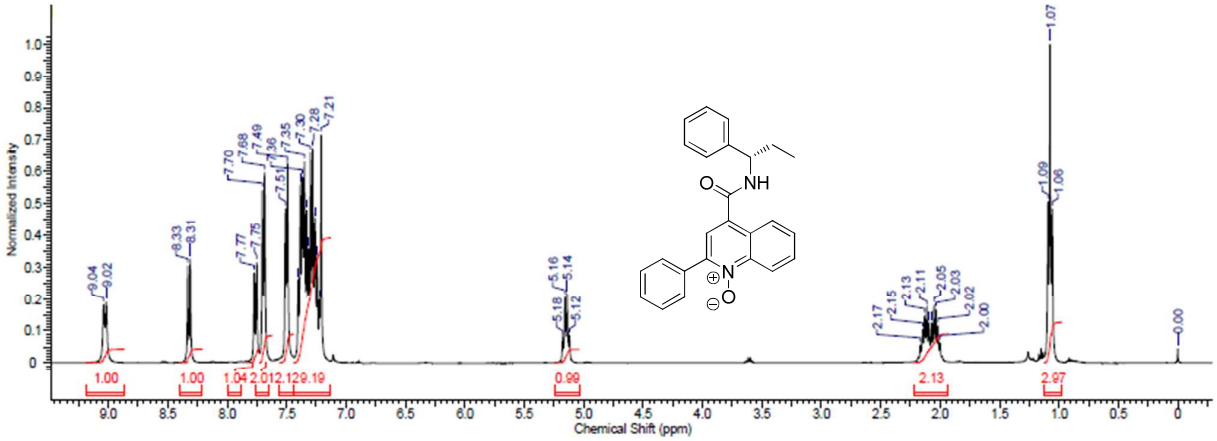
100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:



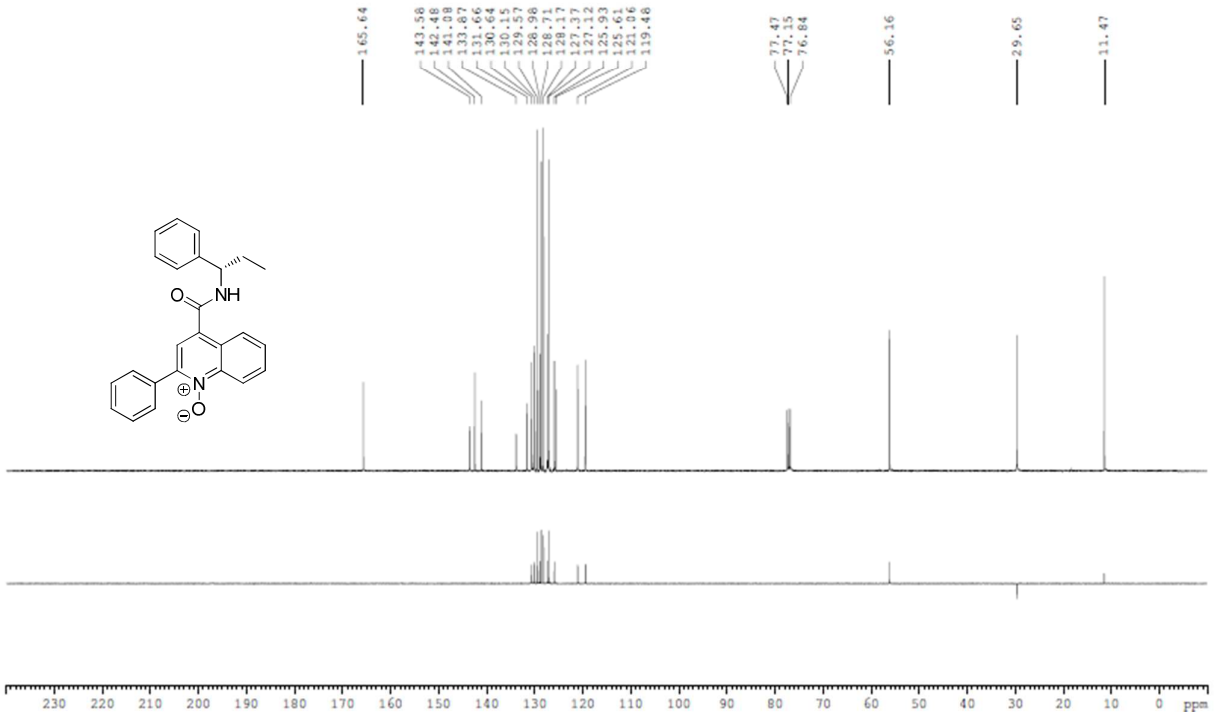
Synthesis of 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide (69): To a stirred solution of DABAL-Me_3 **67** (193 mg, 0.75 mmol) in anhydrous THF at room temperature under nitrogen was added (*S*)-α-ethylbenzylamine **68** (0.108 mL, 0.75 mmol) and the resulting solution was stirred at 40°C for 1 hour. To this mixture 4-(methoxycarbonyl)-2-phenylquinoline *N*-oxide **62** (140 mg, 0.50 mmol) was added and the reaction was stirred at reflux for 22 hours. The reaction mixture was cooled to ambient temperature and quenched with aqueous HCl (2 M) dropwise and was extracted with ethyl acetate. The organic phase was separated and evaporated to dryness under reduced pressure. The crude product was then purified by silica gel chromatography eluting with heptane/ethyl acetate to give 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide (**69**) (162 mg, 0.42 mmol, 85 % yield) as an off-white solid.

2-Phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide (69): Off-white solid (162 mg, 85% yield), Mp 90–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.03 (d, 1H, *J* = 8.3 Hz), 8.32 (d, 1H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 8.1 Hz), 7.69 (d, 2H, *J* = 7.5 Hz), 7.50 (d, 2H, *J* = 7.1 Hz), 7.40-7.21 (m, 9H), 5.15 (q, 1H, *J* = 7.8 Hz), 2.20-2.00 (m, 2H), 1.07 (t, 3H, *J* = 7.4 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6 (C_{IV}), 143.6 (C_{IV}), 142.5 (C_{IV}), 141.1 (C_{IV}), 133.9 (C_{IV}), 131.7 (C_{IV}), 130.6, 130.2, 129.6, 129.0, 128.7, 128.2, 127.4, 127.1, 125.9, 125.6 (C_{IV}), 121.1, 119.5, 56.2, 29.7, 11.5 ppm. HRMS (ESI$^+$): Calculated for $C_{25}H_{23}N_2O_2$ $[M + H]^+$ 383.1754, found 383.1761

400 MHz ^{1}H NMR spectrum in $CDCl_3$:



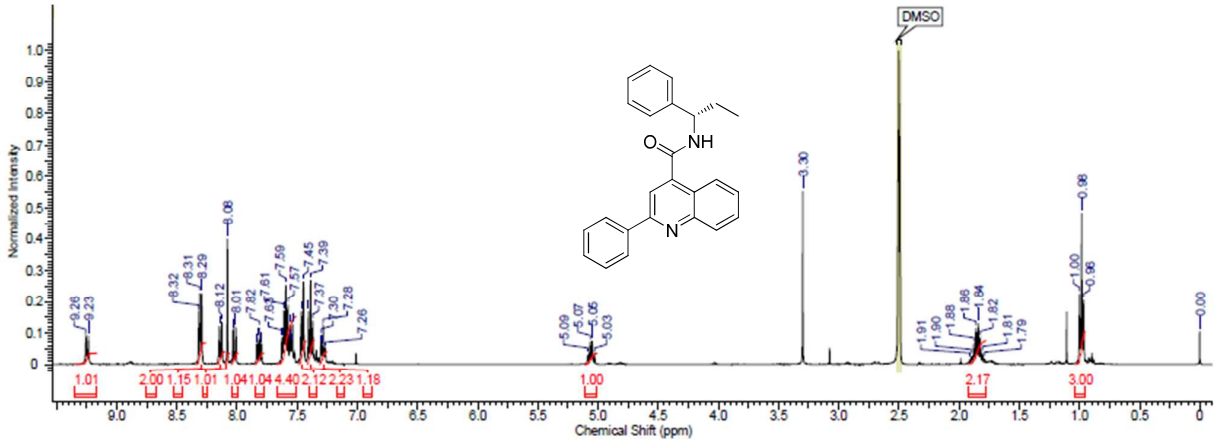
100 MHz ^{13}C NMR and DEPT135 spectra in $CDCl_3$:



Synthesis of 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline (70): 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide **69** (147 mg, 0.38 mmol,), Johnson Matthey 5% rhodium on charcoal type 20A paste, 60% wet (99 mg, 0.02 mmol) and THF (3.5 mL) were added to a hydrogenation reactor which was purged 3 times with 5 bar of nitrogen and then 3 times with 3 bar of hydrogen. The reaction was then stirred at room temperature under 3 bar of hydrogen for 2 hours and was stopped by flushing the hydrogenation reactor with nitrogen. The reaction mixture was then filtered through a plug of Celite to remove the catalyst and the filtrate was evaporated in vacuo. The crude product was then purified by silica gel chromatography eluting with heptane/ethyl acetate to give 2-phenyl-4-(carboxy-(S)-α-ethylbenzylamine)quinoline (**70**) (131 mg, 0.36 mmol, 93 % yield) as a stable white foam.

2-Phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline (70): Off-white solid (162 mg, 85% yield), Mp 140–150 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.25 (d, 1H, *J* = 8.5 Hz), 8.30 (d, 2H, *J* = 6.9 Hz), 8.13 (d, 1H, *J* = 8.1 Hz), 8.08 (s, 1H), 8.02 (dd, 1H, J_1 = 8.6 Hz, J_2 = 0.8 Hz), 7.82 (dd, 1H, J_1 = 7.1 Hz, J_2 = 0.5 Hz), 7.63-7.54 (m, 4H), 7.46 (d, 2H, *J* = 7.1 Hz), 7.38 (d, 2H, *J* = 7.6 Hz), 7.28 (at, 1H, *J* = 7.3 Hz), 5.06 (q,1H, *J* = 6.6 Hz), 1.91-1.79 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 166.7 (C_{IV}), 156.3 (C_{IV}), 148.4 (C_{IV}), 143.9 (C_{IV}), 143.8 (C_{IV}), 138.8 (C_{IV}), 130.6, 130.3, 130.0, 129.4, 128.8, 127.8, 127.6, 127.3, 127.0, 125.6, 123.9 (C_{IV}), 116.9, 55.5, 29.7, 11.7 ppm. HRMS (ESI$^+$): Calculated for $C_{25}H_{23}N_2O$ $[M + H]^+$ 367.1805, found 367.1806

400 MHz ^{1}H NMR spectrum in DMSO-d_6:



100 MHz ^{13}C NMR spectrum in DMSO-d_6: