Electronic Supplementary Material (ESI) for ChemComm.

SUPPORTING INFORMATION

Experimental and Mechanistic Analysis of the Palladium-Catalyzed Oxidative C8-Selective C–H Homocoupling of Quinoline *N*-Oxides

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General Procedures

Materials and methods: All quinoline *N*-oxides were synthesized from respective quinolines according to the typical oxidation procedures.[1] Silver phosphate was prepared according the published procedure.[2]

Ethyl 6-methoxy-4-phenylquinoline-2-carboxylate was prepared according to the published procedure.[3] All chemicals were used as commercially available. All thermal reactions were conducted with continuous magnetic stirring under an atmosphere of argon in 2 dram vials (6 mL, FisherBrand).

Reactions were monitored by TLC until deemed complete using silica gel-coated glass plates (Merck Kieselgel 60 F254). Plates were visualized under UV light (254 nm).

Purification: Column chromatography was performed using CombiFlash Rf-200 (Teledyne-Isco) automated flash chromatography system with hand-packed RediSep columns.

Characterization: ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded at 500 (^{1}H), 125 and (^{13}C), and 282 MHz (^{19}F) on Varian Mercury VX 300 and Agilent Inova 500 instruments in $CDCl_3$ solutions. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) in Hz. Proton multiplicity is assigned

using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (quart.), quintet (quint.), septet (sept.), multiplet (m), broad (br).

Infrared measurements were carried out neat on a Bruker Vector 22 FT-IR spectrometer fitted with a Specac diamond attenuated total reflectance (ATR) module.

Preparation of silver acetate[4]

To a solution of silver nitrate (25.5 g, 150 mmol) and acetic acid (1.0 mL) in deionized water (250 mL) at 23 °C was added a solution of sodium acetate (14.7 g, 180 mmol, 1.2 equiv.) in deionized water (150 mL). The solids were filtered and washed with small amounts of water, hexanes, and acetone before being dried under reduced pressure (0.5mbar) for 4 h at 50 °C to yield silver acetate (22.5 g, 91 %) that was stored in the dark.

General procedure 1 for the reaction development experiments (GP1)

A 6 mL vial was charged with quinoline *N*-oxide (29 mg, 0.2 mmol), palladium salt (10 mol %, 0.02 mmol) silver salt (0.10–1 mmol, 0.5–4 equiv), acetic acid (15 or 30 equiv.) and an appropriate amount of deionized water (0–5 equiv). The vial was sealed, and the reaction mixture was stirred at 120 °C (thermal conditions) for 12h. Work up was performed according to the general procedure 2.

General procedure 2 for the work-up of kinetic and reaction development experiments (GP2)

After completion of a reaction carried out with 0.2 mmol of quinoline *N*-oxide, the reaction mixture was charged with a 0.05M solution of 1,4-dimethoxybenzene (0.05 or 0.1 mmol) in dichloromethane (0.5 or 1 mL), and the mixture was stirred at room temperature for 5 min. Then a 1:3 v/v mixture of 50% aq. ammonia solution and saturated aq. solution of ammonium chloride (2 mL) was added, and the stirring was continued for 15 min. The organic phase was separated, dried over sodium sulfate and concentrated under reduced pressure. The conversion of the substrate to the C8-dimeric product was determined from the ^{1}H NMR spectrum of the crude product in

$CDCl_3$ by integration of the 2-H peak of the 8,8'-biquinolyl 1,1'-dioxide and 1,4-dimethoxybenzene (6.82 ppm, 1 H, s).

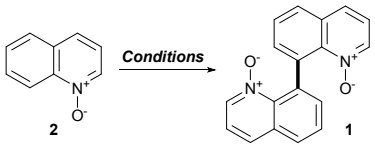
General Procedure 3 (GP3) for the synthesis of 4, 9, 10

A substituted quinoline *N*-oxide (0.20 mmol, 1 equiv.), palladium salt (5 mg, 0.02 mmol, 10 mol %), silver acetate (132 mg, 0.80 mmol, 4 equiv.) or silver phosphate, acetic acid (173 μL, 3.0 mmol, 15 equiv.), and deionized water (17 μL, 1.0 mmol, 5 equiv.). The vials were degassed and heated at 120 °C for the specified time. The vials were cooled to 23 °C and concentrated on Celite under reduced pressure. The crude product was then purified by column chromatography [dichloromethane/EtOAc-EtOH (1:1), neutral alumina] to yield the desired compound.

General Procedure 4 (GP4) for the synthesis of 1, 3, 5, 6, 8, 11, 12:

A substituted quinoline *N*-oxide (0.20 mmol, 1 equiv.), palladium salt (5 mg, 0.02 mmol, 10 mol %), silver acetate (132 mg, 0.80 mmol, 5 equiv.), acetic acid (57 μL, 1.0 mmol, 5 equiv.), and deionized water (6 μL, 0.30 mmol, 1.5 equiv.). The vials were degassed and heated at 120 °C for the specified time. The vials were cooled to 23 °C and concentrated on Celite under reduced pressure. The crude product was then purified by column chromatography [dichloromethane/EtOAc-EtOH (1:1), neutral alumina] to yield the desired compound.

Table S1. Oxidative C–H homocoupling of quinoline *N*-oxide (**2**) (Additional experiments).[a]

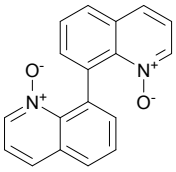


Entry	Silver salt (equiv)	Co-Solvent	Solvent (equiv.)	Yield, %
1	AgOAc (4)	–	AcOH/H_2O (15/5)	57
2	AgOAc (4)	–	AcOH/H_2O (30/10)	45
3	AgOAc (2)	–	AcOH/H_2O (30/10)	43
4	AgOAc (4)	–	AcOH/H_2O (83/28)	15
5	AgOAc (4)	PhMe (0.5M)	AcOH/H_2O (15/5)	27
6	AgOAc (4)	DMF (0.5 M)	AcOH/H_2O (15/5)	0
7	AgOAc (2)	–	AcOH/H_2O (5/1.5)	81
8	AgOAc (4)	–		61
9[b]	AgOAc (4)	-	AcOH/H_2O (15/5)	0

[a] Reaction conditions: quinoline *N*-oxide (0.50 mmol), $Pd(OAc)_2$ (10 mol%) 120 °C, 18 h, under Ar;

[b] quinolone *N*-oxide (0.50 mmol), $Pd(OAc)_2$ (0 mol%), 120 °C, 18 h, under argon.

8,8'-Biquinoline 1,1'-dioxide (1)

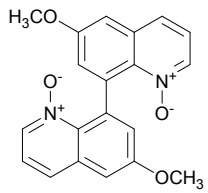


Synthesis from quinoline 1-oxide: According to GP4, a mixture of quinoline *N*-oxide (1.05 g, 7.24 mmol), silver acetate (4.81 g, 28.96 mmol, 4 equiv.), palladium acetate (162 mg, 0.724 mmol, 10 mol %), acetic acid (2.10 mL) and deionized water (210 μL) was heated to 120 °C for 24 h. The crude product was purified by column chromatography to yield **1** (871 mg, 83 %).

Synthesis from 2-carboxyquinoline 1-oxide: According to GP3, a mixture of 2-carboxyquinoline 1-oxide (76 mg, 0.4 mmol), silver phosphate (334 mg, 0.80 mmol, 2 equiv.), palladium acetate (10 mg, 0.04 mmol, 10 mol %), acetic acid (360 μL) and deionized water (36 μL) was heated to 120 °C for 24 h. The crude product was purified by column chromatography to yield **1** (41 mg, 71 %).– m.p.:207-212 °C. - ^{1}H NMR (500 MHz): 7.22 (2 H, dt, *J* = 2.5, 6 Hz), 7.40 (2 H, dd, *J* = 1.5, 7 Hz), 7.57 (2 H, t, *J* = 8 Hz), 7.75 (2 H, d, *J* = 8 Hz), 7.82 (2 H, dd, *J* = 1.5, 8.5 Hz), 8.20 (2 H, dd, *J* = 1, 6 Hz) ppm. – ^{13}C NMR (125 MHz): 126.1, 126.2, 127.2, 127.3, 128.3 (m), 129.9, 130.0, 131.0, 136.0,

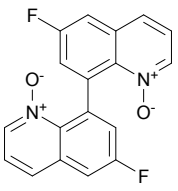
137.3, 140.7 ppm. – IR: 1101, 1246, 1303, 1380, 1424, 1575, 2900, 2934, 3110, 3389 cm^{-1}. – MS (ESI): 288.9, calcd: 289.0972, HRMS: 289.0962 [$M+H^+$].

6,6'-Dimethoxy-8,8'-biquinoline 1,1'-dioxide (3)



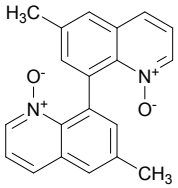
According to GP4, 6-methoxyquinoline *N*-oxide (88 mg, 0.50 mmol), silver acetate (332 mg, 2.0 mmol, 4 equiv.), palladium acetate (11 mg, 0.05 mmol, 10 mol %), acetic acid (144 μL), and water (14 μL) was heated to 120 °C for 12h. The crude product was purified by column chromatography to yield **3** (56 mg, 63 %). – m.p.: 200-206 °C - ^{1}H NMR (500 MHz): 3.92 (6 H, s), 7.04–7.06 (4 H, m), 7.16 (2 H, dd, *J* = 6, 8.5 Hz), 7.62 (2 H, dd, *J* = 1, 4.5 Hz), 8.08 (2 H, dd, *J* = 1, 6 Hz) ppm. – ^{13}C NMR (125 MHz): 55.5, 104.7, 121.4, 122.3, 125.1, 132.4, 134.2, 138.4, 157.5 ppm. IR: 1032, 1167, 1271, 1365, 1466, 1578, 1656, 2842, 3005, 3073, 3368 cm^{-1}– MS (ESI): 348.9, calcd: 349.1183, HRMS: 349.1166 [$M+H^+$]

6,6'-Difluoro-8,8'-biquinoline 1,1'-dioxide (4)



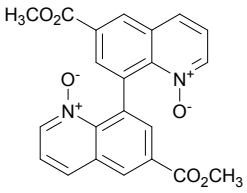
According to GP3, 6-fluoroquinoline *N*-oxide (65 mg, 0.40 mmol), silver acetate (200 mg, 1.2 mmol, 4 equiv.), palladium acetate (10 mg, 0.04 mmol, 10 mol %), acetic acid (360 μL), and water (36 μL) were heated to 120 °C for 18 h. The crude product was purified by column chromatography to yield **4** (45 mg, 69 %). – m.p.: 162-168 °C. - ^{1}H NMR (500 MHz): 7.17 (2 H, dd, *J* = 3.0, 8.5 Hz), 7.20–7.28 (2 H, m), 7.44 (2 H, dd, *J* = 2.5, 8 Hz), 7.67 (2 H, d, *J* = 8.5 Hz), 8.18 (2 H, d, *J* = 6 Hz) ppm. – ^{13}C NMR (125 MHz): 110.4 (d, *J* = 12.5 Hz), 110.6 (d, *J* = 12.5 Hz), 119.7 (d, *J* = 9.1 Hz), 120.0 (d, *J* = 9.1 Hz), 122.1, 122.2, 125.5 (d, *J* = 2.8 Hz), 125.6 (d, *J* = 2.8 Hz), 128.1–128.3 (m), 131.9, 132.0, 135.4, 137.8, 139.1, 139.1 ppm. – ^{19}F NMR (282 MHz): – 111.8 (t) ppm. – MS (ESI): 325.0, calcd: 325.0783, HRMS: 325.0642 [$M+H^+$].

6,6'-Dimethyl-8,8'-biquinoline 1,1'-dioxide (5)



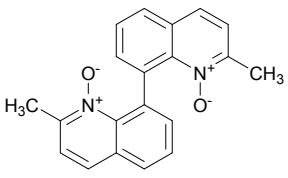
According to GP4, 6-methylquinoline *N*-oxide (80 mg, 0.50 mmol), silver acetate (342 mg, 2 mmol, 4 equiv.), palladium acetate (11 mg, 0.05 mmol, 10 mol %), acetic acid (144 μL), and water (14 μL) were heated to 120 °C for 18 h. The crude product was purified by column chromatography to yield **5** (56 mg, 70 %). – m.p.: 167-170 °C. - ^{1}H NMR (500 MHz): 2.54 (6 H, s), 7.17 (2 H, dd, *J* = 4, 8.5 Hz), 7.25 (2 H, s), 7.59 (2 H, s), 7.66 (2 H, d, *J* = 8.5 Hz), 8.18 (2 H, d, *J* = 6 Hz) ppm. – ^{13}C NMR (125 MHz): 21.3, 21.4, 120.8, 120.9, 125.6, 125.7, 128.3 (m), 131.2, 132.3, 132.4, 135.8, 137.0, 137.1, 139.4 ppm. – IR: 1203, 1301, 1372, 1436, 1575, 2853, 2930, 3038, 3312 cm^{-1}. – MS (ESI): 316.9, calcd: 317.1284, HRMS: 317.1285 [M+H^{+}].

6,6'-Bis(methoxycarbonyl)-8,8'-biquinoline 1,1'-dioxide (6)



According to GP4, 6-methoxylcarbonylquinoline *N*-oxide (101 mg, 0.50 mmol), silver acetate (342 mg, 2 mmol, 4 equiv.), palladium acetate (22 mg, 0.1 mmol, 20 mol %), acetic acid (144 μL), and water (14 μL) were heated to 120 °C for 18 h. The crude product was purified by column chromatography to yield **6** (61 mg, 61 %). – ^{1}H NMR (500 MHz): 3.96 (6 H, s), 7.29–7.32 (2 H, dd, *J* = 2.5, 6 Hz), 7.86 (2 H, d, *J* = 3.5 Hz), 7.99 (2 H, d, *J* = 2 Hz), 8.25 (2 H, d, *J* = 1.5 Hz), 8.58 (2 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 52.6, 121.8, 127.1, 128.8, 129.1, 130.3., 130.5, 137.1, 137.5, 142.2, 165.7 ppm. – IR: 1102, 1195, 1276, 1302, 1442, 1575, 1663, 1720, 2856, 2952, 3168, 3367 cm^{-1}. – MS (ESI): 404.9, calcd: 405.1081, HRMS: 405.0670 [M+H^{+}].

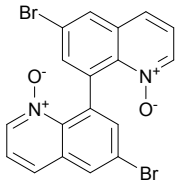
2,2'-Dimethyl-8,8'-biquinoline 1,1'-dioxide (7)



According to GP3, 2-methyl quinoline *N*-oxide (64 mg, 0.40 mmol) was reacted with palladium acetate (10 mg, 0.04 mmol, 10 mol %), silver phosphate (330 mg, 0.8 mmol, 2 equiv.), acetic acid (360 μL), and deionized water (36 μL) at 150 °C for 24 h. The crude product was purified by column chromatography to yield **7** (50 mg,

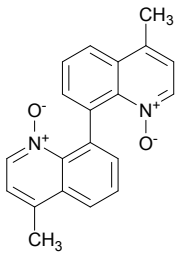
78%). – ^{1}H NMR (500 MHz): 2.43 (6 H, s), 7.24–7.38 (4 H, m), 7.51 (2 H, t, *J* = 8 Hz), 7.64 (2 H, d, *J* = 8.5 Hz), 7.77 (2 H, dd, *J* = 1, 8 Hz) ppm. – ^{13}C NMR (125 MHz): 19.2, 122.9, 125.2, 126.2, 127.0, 129.9, 130.1, 137.6, 140.4, 145.5 ppm. – IR: 1107, 1210, 1307, 1399, 1436, 1521, 2852, 2920, 2978, 3339 cm^{-1}. – MS (ESI): 316.9, calcd: 317.1285, HRMS: 317.1271 [M+H^{+}].

6,6'-Dibromo-8,8'-biquinoline 1,1'-dioxide (8)



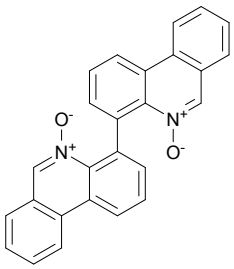
According to GP4, 6-bromoquinoline *N*-oxide (112 mg, 0.50 mmol), palladium acetate (11 mg, 0.05 mmol, 10 mol %), silver acetate (342 mg, 2.0 mmol, 4 equiv.), acetic acid (144 μL), and deionized water (14 μL) were reacted for 12 h. The crude product was purified by column chromatography to yield **8** (63 mg, 56 %). – ^{1}H NMR (500 MHz): 7.24–7.27 (2 H, m), 7.47 (2 H, d, *J* = 2 Hz), 7.66 (2 H, d, *J* = 8 Hz), 7.99 (2 H, d, *J* = 2 Hz), 8.21 (2 H, d, *J* = 6 Hz) ppm. – ^{13}C NMR (125 MHz): 121.4, 122.1, 125.1, 129.4, 131.8, 132.8, 136.2, 137.5, 139.5 ppm. – IR: 1110, 1245, 1323, 1445, 1517, 1621, 2989, 3025, 3122, 3317 cm^{-1}. – MS (ESI): 444.8, calcd: 444.9182, HRMS: 444.9181 [M+H^{+}].

4,4'-Dimethyl-8,8'-biquinoline 1,1'-dioxide (9)



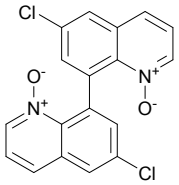
According to GP3, 4-methylquinoline *N*-oxide (64 mg, 0.40 mmol) was reacted with palladium acetate (10 mg, 0.04 mmol, 10 mol %), silver acetate (265 mg, 1.60 mmol, 4 equiv.), acetic acid (360 μL), and deionized water (36 μL), at 120 °C for 24 h. The crude product was purified by column chromatography to yield **9** (47 mg, 74 %). – m.p.: 200-206 °C. - ^{1}H NMR (500 MHz): 2.70 (6 H, s), 7.06 (2 H, d, *J* = 6 Hz), 7.41 (2 H, d, *J* = 7 Hz), 7.61 (2 H, t, *J* = 8.5 Hz), 7.92 (2 H, dd, *J* = 1, 8.5 Hz), 8.10 (2 H, d, *J* = 6 Hz) ppm. – ^{13}C NMR (125 MHz): 19.1, 121.6, 123.4, 127.0, 129.4, 130.1, 134.3, 135.2, 138.2, 139.9 ppm. – IR: 1047, 1250, 1374, 1559, 1647, 2832, 2894, 2999, 3070, 3418 cm^{-1}. – MS (ESI): 316.9, calcd: 317.1285, HRMS: 317.1269 [M+H^{+}].

4,4'-Biphenanthridine 5,5'-dioxide (10)



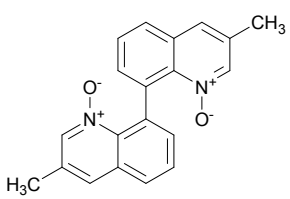
According to GP3, phenanthridine *N*-oxide (98 mg, 0.50 mmol), palladium acetate (11 mg, 0.05 mmol, 10 mol %), silver acetate (332 mg, 2.0 mmol, 4 equiv.), acetic acid (450 μL), and deionized water (45 μL) were heated to 120 °C for 18 h. The crude product was purified by column chromatography to yield **10** (41 mg, 42 %). – m.p.: 230-235 °C. - ^{1}H NMR (500 MHz): 7.67 (2 H, dt, *J* = 1, 8 Hz), 7.75 (2 H, dt, *J* = 1, 8 Hz), 7.79 (2 H, d, *J* = 8 Hz), 7.82–7.84 (2 H, m), 8.51 (2 H, d, *J* = 8 Hz), 8.59 (2 H, dd, *J* = 2, 8 Hz), 8.90 (2 H, s), 8.93 (2 H, dd, *J* = 2, 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 120.7, 122.1, 122.7, 126.1, 126.6, 126.7, 128.9, 129.3, 129.5, 129.6, 134.6, 139.4 ppm. – IR: 1042, 1153, 1371, 1514, 1656, 2922, 3022, 3179, 3375 cm^{-1}. – MS (ESI): 389.0, calcd: 389.1285, HRMS: 389.0877 [M+H^{+}].

6,6'-Dichloro-8,8'-biquinoline 1,1'-dioxide (11)



According to GP4, 6-chloroquinoline *N*-oxide (90 mg, 0.50 mmol), palladium acetate (11 mg, 0.05 mmol, 10 mol %), silver acetate (342 mg, 2.0 mmol, 4 equiv.), acetic acid (144 μL), and deionized water (14 μL) were heated to 120 °C for 18 h. The crude product was purified by column chromatography to yield **11** (67 mg, 74 %). – ^{1}H NMR (500 MHz): 7.24–7.37 (4 H, m), 7.66 (2 H, d, *J* = 8.5 Hz), 7.82 (2 H, s), 8.18 (2 H, d, *J* = 6 Hz) ppm. – ^{13}C NMR (125 MHz): 122.2, 125.1, 126.0, 130.3, 131.5, 133.2, 136.1, 137.8, 139.3 ppm. – IR: 1109, 1232, 1445, 2893, 2992, 3025 cm^{-1}. – MS (ESI): 355.0 [M^{-}], calcd: 357.0192, HRMS: 357.0152 [M+H^{+}].

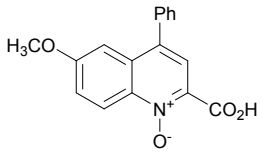
3,3'-Dimethyl-8,8'-biquinoline 1,1'-dioxide (12)



According to GP4, 3-methylquinoline *N*-oxide (80 mg, 0.50 mmol), palladium acetate (11 mg, 0.05 mmol, 10 mol %), silver acetate (342 mg, 2.0 mmol, 4 equiv.), acetic acid (144 μL), and deionized water (14 μL) were heated to 120 °C for 18 h. The

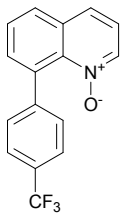
crude product was purified by column chromatography to yield **12** (72 mg, 90 %). – m.p.: 170-173 °C. - ^{1}H NMR (500 MHz): 2.36 (6 H, s), 7.31 (2 H, dd, *J* = 1, 7.5 Hz), 7.49–7.52 (4 H, m), 7.70 (2 H, dd, *J* = 1, 8 Hz), 8.07 (2 H, s) ppm. – ^{13}C NMR (125 MHz): 18.4, 125.9, 126.6, 127.2, 129.1, 130.7, 130.9, 137.1, 137.3, 139.0 ppm. – IR: 1063, 1160, 1273, 1320, 1444, 1574, 1649, 2921, 304, 3363 cm^{-1}. – MS (ESI): 317.0, calcd: 317.1285, HRMS: 317.1284 [M+H^{+}].

2-Carboxy-6-methoxy-4-phenylquinoline 1-oxide (14)



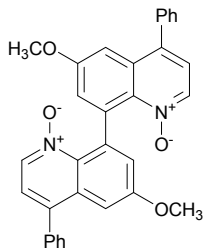
To a solution of ethyl 6-methoxy-4-phenylquinoline-2-carboxylate[5] (377 mg, 1.23 mmol) in dichloromethane (2 mL) was added sodium trimethylsilanolate (208 mg, 1.85 mmol, 1.5 equiv.) at 23 °C. After 2 h methanesulfonic acid (120 μL, 1.84 mmol, 1.5 equiv.) was added and the reaction allowed to stir an additional 1 h. The reaction was diluted with deionized water (7 mL) and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and washed with hexanes (3 x 2 mL) to yield the intermediate. The isolated compound was dissolved in chloroform (2.5 mL) and *meta*-chloroperoxybenzoic acid was added (259 mg, 0.75 mmol, 1.5 equiv., 50% by mass) and the reaction allowed to stir at 23 °C for 12 h. After 12 h the reaction was diluted with deionized water (10 mL) and the aqueous layer extracted with chloroform (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [dichloromethane/EtOAc-EtOH (1:1), silica gel] to yield **14** (138 mg, 71%). –^{1}H NMR (500 MHz): 3.85 (3 H, s), 7.40–7.60 (5 H, m), 7.99 (1 H, dd, *J* = 1, 7 Hz), 8.08 (1 H, s), 8.30 (1 H, s), 8.78 (1 H, d, *J* = 8 Hz) 11.21–11.38 (1 H, br s) ppm. – ^{13}C NMR (125 MHz): 55.8, 105.0, 121.7, 123.1, 124.6, 129.1, 129.5, 129.9, 130.2, 131.0, 133.8, 134.7, 162.3, 170.5 ppm. – IR: 913, 1026, 1145, 1263, 1370, 1575, 1616, 2549, 2657, 2885, 2973, 3072 cm^{-1}. – MS ESI: 296.0, calcd: 296.0917, HRMS: 296.0858 [M+H^{+}].

8-(4-(Trifluoromethyl)phenyl)quinoline 1-oxide (15)[2]



Three 2 mL vials, with magnetic stir bar, were degassed with argon for 1 min. To each vial was added 2-carboxyquinoline 1-oxide (**13)** (38 mg, 0.2 mmol), silver phosphate (123 mg, 0.30 mmol, 0.5 equiv.), palladium acetate (6.6 mg, 0.03 mmol, 5 mol %). Degassed acetic acid (1.80 mL, 18.0 mmol, 30 equiv.), degassed water (430 μL, 24.0 mmol, 40 equiv.) and 4-(trifluoromethyl)iodobenzene (264 μL, 1.80 mmol, 3 equiv.) were added in order and the reaction heated in a microwave at 180 °C for 50 min. The reactions were cooled to 23 °C, combined, and diluted with 5 mL of a 1:3 v/v mixture of 30% aq. ammonia solution and saturated aq. solution of ammonium chloride. The aqueous layer was extracted with dichloromethane (5 x 5 mL), the organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography [dichloromethane/EtOAc–EtOH (1:1), silica gel] to yield the desired 8-arylquinoline *N*-oxide **15** (49 mg, 85 %). – m.p.: 122–124 °C. – ^{1}H NMR (500 MHz): 7.32 (1 H, dd, *J* = 2, 6 Hz), 7.43 (2 H, d, *J* = 8.5 Hz), 7.50 (1 H, dd, *J* = 1, 7 Hz), 7.62–7.67 (3 H, m), 7.79 (1 H, 8.5 Hz), 7.93 (1 H, dd, *J* = 2, 8.5 Hz), 8.35 (1 H, 6 Hz) ppm. – ^{13}C NMR (125 MHz): 121.5, 123.4, 123.8 (quart., *J* = 2.5 Hz), 125.6, 126.2, 127.7, 128.0, 128.3, 129.1, 132.0, 134.0, 134.8, 136.8, 138.8 ppm. – ^{19}F NMR (282 MHz): –62.2 ppm. – IR: 1018, 1149, 1243, 1322, 1405, 1509, 2981, 3092 cm^{-1}.

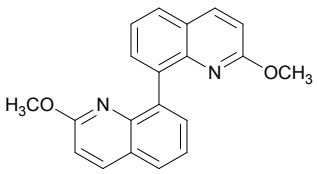
6,6'-Dimethoxy-4,4'-diphenyl-8,8'-biquinoline 1,1'-dioxide (16)



According to GP3, **14** (150 mg, 0.5 mmol), silver phosphate (418 mg, 1 mmol, 2 equiv.), palladium acetate (11 mg, 0.05 mmol, 10 mol %), acetic acid (450 μL) and deionized water (45 μL) were heated to 150 °C for 18 h. The crude product was then purified by column chromatography to yield **16** (55 mg, 44 %). – ^{1}H NMR (500 MHz): 3.76 (6 H, s), 6.63 (2 H, s), 7.10–7.15 (4 H, m), 7.50–7.60 (10 H, m), 8.07 (2 H, d, *J* = 9 Hz) ppm. – ^{13}C NMR (125 MHz): 55.8, 103.7, 120.5, 121.6, 122.4, 128.6, 128.9, 129.1, 129.3, 130.8, 136.7, 152.7, 154.9, 161.3 ppm. – IR: 1133, 1218, 1258, 1380, 1451,

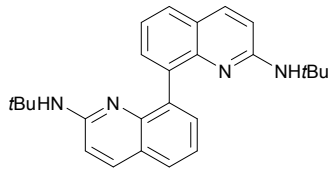
1637, 2873, 2981, 3006, 3250 cm^{-1}. – MS (ESI): 501.0, calcd: 501.1809, HRMS: 501.1799 [M+H^+].

2,2'-Dimethoxy-8,8'-biquinoline (17)



Quinoline *N*-oxide dimer **1** (50 mg, 0.17 mmol) in methanol (2.5 mL) was added *p*-toluenesulfonic chloride (50 mg, 0.26 mmol, 1.5 equiv.) at 23 °C. The reaction mixture was allowed to stir for 15 min before triethylamine (50 μL, 0.35 mmol, 2 equiv.) was added and the reaction was allowed to stir 12 h. The reaction mixture was diluted with a 1M HCl (5 mL) and dichloromethane (5 mL). The layers were separated and the organic layer washed with a saturated aqueous solution of sodium carbonate. The aqueous layers were combined and extracted with dichloromethane (4 x 5 mL), the organic layers combined, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [silica gel, hexanes/dichloromethane] to yield **17** (40 mg, 74 %). – ^{1}H NMR (500 MHz): 3.52 (6 H, s), 6.86 (2 H, d, *J* = 8.5 Hz), 7.48 (2 H, t, *J* = 8 Hz), 7.77 (2 H, dd, *J* = 1.5, 8 Hz), 7.89 (2 H, dd, *J* = 1.5, 8 Hz), 8.03 (2 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 52.8, 112.2, 123.1, 125.0, 126.8, 131.9, 137.0, 138.8, 144.9, 161.2 ppm. – IR: 1154, 1204, 1351, 1497, 1648, 2841, 3025 cm^{-1}. – MS (ESI): 317.0, calcd: 317.1285, HRMS: 317.1284 [M+H^+].

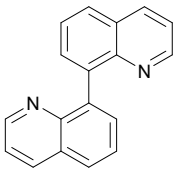
***N*^{2},*N*$^{2'}$-Di-*tert*-butyl-8,8'-biquinoline-2,2'-diamine (18)**



Quinoline *N*-oxide dimer **1** (129 mg, 0.45 mmol) and *tert*-butylamine (283 μL, 2.7 mmol, 6 equiv.) in trifluorotoluene (4.5 mL) at 0 °C was added *p*-toluenesulfonic anhydride (308 mg, 0.945 mmol, 2.1 equiv.) in 3 portions. The reaction mixture was allowed to stir at 0 °C for 1.5 h before being diluted with a saturated aqueous solution of sodium bicarbonate (5 mL). The aqueous layer was extracted with dichloromethane (4 x 5 mL), the organic layers combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexanes/EtOAc] to yield **18** (120 mg, 67 %). – ^{1}H

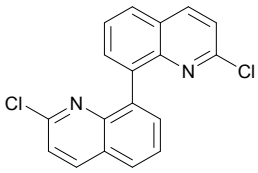
NMR (500 MHz): 0.89 (18 H, s), 6.36 (2 H, d, *J* = 8.5 Hz), 7.23–7.25 (2 H, m), 7.56 (4 H, d, *J* = 7 Hz), 7.73 (2 H, d, *J* = 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 28.4, 50.9, 110.0, 112.5, 120.9, 122.3, 126.1, 129.6, 136.2, 138.9, 155.1 ppm. – IR: 1109, 1214, 1335, 1434, 2898, 2900, 3201 cm^{-1}. – MS (ESI): 399.2, calcd: 399.2543, HMRS: 399.2499 [M+H^{+}].

8,8'-Biquinoline[6] (19)



To a solution of *N*-oxide dimer **1** (25 mg, 0.09 mmol) in acetic acid (1 mL) and deionized water (100 μL) was added hypophosphorous acid (350 μL). The reaction was heated to 120 °C for 12 h, then diluted with a saturated aqueous solution of sodium carbonate (10 mL), and the aqueous layer was extracted with ethyl acetate (5 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes/EtOAc-EtOH (1:1), neutral alumina] to yield **19** (21 mg, 90 %). – m.p. 205-207 ◦C. - ^{1}H NMR (500 MHz): 7.37 (2 H, dd, *J* = 4, 8.5 Hz), 7.69 (2 H, dd, *J* = 7, 8 Hz), 7.82 (2 H, dd, *J* = 1.5, 7 Hz), 7.91 (2 H, dd, *J* = 1.5, 8 Hz), 8.25 (2 H, dd, *J* = 2, 8.5 Hz), 8.79 (2 H, dd, *J* = 7, 1.5 Hz) ppm. – ^{13}C NMR (125 MHz): 121.0, 126.2, 128.1, 128.8, 131.9, 136.4, 139.4, 147.4, 150.3 ppm. – IR: 1101, 1210, 1305, 1372, 1454, 1592, 16115, 2989, 3025 cm^{-1}. – MS (ESI): 257.0, calcd: 257.1 [M+H+].

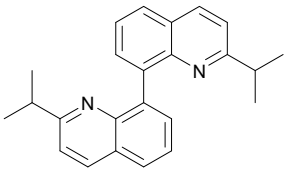
2,2'-Dichloro-8,8'-biquinoline (20)



Quinoline *N*-oxide dimer **1** (100 mg, 0.35 mmol) in thionyl chloride (3.5 mL) was heated at 50 °C for 12 h. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography [hexanes/EtOAc-EtOH (1:1), neutral alumina] to yield **20** (95 mg, 84%). – m.p.: 214-217 ◦C. - ^{1}H NMR (500 MHz): 7.35 (2 H, d, *J* = 8.5 Hz), 7.67 (2 H, t, *J* = 7.5 Hz), 7.88 (4 H, t, *J* = 7.5 Hz), 8.14 (2 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 122.2, 126.2, 127.2, 127.6, 133.5, 137.0, 138.9, 146.5, 150.0 ppm.

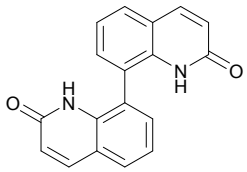
– IR: 1107, 1273, 1325, 1416, 1564, 2854, 2927, 3045 cm^{-1}. – MS (ESI): 325.8, calcd: 326.0367, HRMS: 326.0366 [M+2H$^+$].

2,2'-Diisopropyl-8,8'-biquinoline (21)



To a degassed vial was added *N*-oxide dimer **1** (50 mg, 0.17 mmol), copper chloride (2 mg, 0.02 mmol, 10 mol %), magnesium chloride (43 mg, 0.43 mmol, 2.5 equiv.), and diethyl ether (1 mL). Isopropylmagnesium chloride (150 μL, 0.43 mmol, 2.5 equiv., 3 M in 2-methyltetrahydrofuran) was added to the vial and the reaction allowed to stir for 12 h. After 12 h the reaction was diluted with a saturated aqueous solution of ammonium chloride (2 mL) and the aqueous layer extracted with dichloromethane (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes/EtOAc-EtOH (1:1), neutral alumina] to yield **21** (40 mg, 69 %). – ^{1}H NMR (500 MHz): 1.07 (6 H, d, *J* = 7 Hz), 2.97 (1 H, sept., *J* = 7 Hz), 7.24–7.28 (2 H, m), 7.57 (2 H, dt, *J* = 0.5, 8 Hz), 7.81 (2 H, d, *J* = 8 Hz), 7.93 (2 H, dd, *J* = 0.5, 8 Hz), 8.10 (2 H, d, *J* = 8 Hz ppm. – ^{13}C NMR (125 MHz): 22.0, 36.6, 118.9, 124.6, 126.7, 126.8, 131.8, 135.9, 138.6, 146.5, 165.8 ppm. – IR: 1092, 1362, 1456, 1498, 1558, 1668, 2923, 2960, 3038 cm^{-1}. – MS ESI: 340.1, calcd: 340.1939, HRMS: 340.1960 [M].

8,8'-Biquinoline-2,2'(1*H*,1'*H*)-dione (22)



A solution of **1** (100 mg, 0.347 mmol) in trifluoroacetic acid (4.5 mL) was divided into three 2 dram vials and heated to 70 °C. After 12 h the reactions were combined, concentrated under reduced pressure, and purified by column chromatography [dichloromethane/EtOAc-EtOH(1:1), neutral alumina] to yield **22** (73 mg, 73 %). – ^{1}H NMR (500 MHz): 6.68 (2 H, d, *J* = 10 Hz), 7.35–7.38 (2 H, m), 7.45 (2 H, dd, *J* = 1.5, 8 Hz), 7.72 (2 H, d, *J* = 8 Hz), 7.85 (2 H, dd, *J* = 1.5, 10 Hz), 8.20–8.34 (2 H, br s) ppm. – ^{13}C NMR (125 MHz): 120.7, 121.1, 122.7, 123.0, 129.3, 132.23, 136.4, 140.78, 162.2

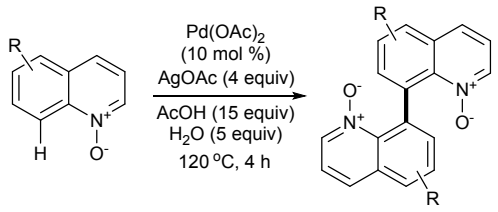
ppm. – IR: 1032, 1137, 1206, 1325, 1406, 1568, 1642, 2924, 3048, 3157, 3543 cm^{-1}. – MS (ESI): 289.0, calcd: 2894.0972, HRMS: 289.0971 [M+H$^+$].

Kinetic isotope effect study

An argon-flushed 6 mL vial was charged with a degassed solution of quinoline *N*-oxide (15 mg, 0.2 mmol) or 2,8-d_2-quinoline *N*-oxide (15 mg, 0.1 mmol) in glacial acetic acid or CD_3COOD (0.18 mL), palladium acetate (10 mol %, 4.4 mg, 0.02 mmol) silver acetate (4 equiv, 134 mg, 0.8 mmol), degassed and deionized water (5 equiv., 18 μL, 1 mmol) or D_2O (5 equiv., 20 μL, 1 mmol). The vial was sealed, and the reaction mixture was stirred at 120 °C for 4 h. A 1:3 v/v mixture of 30% aq. ammonia solution and saturated aq. solution of ammonium chloride (2 mL) was added, and the reaction mixture was extracted with chloroform. The organic phase was separated, dried over sodium sulfate and concentrated under reduced pressure. The experiment was carried out in triplicate for quinoline *N*-oxide and 2,8-d_2-quinoline *N*-oxide, and the conversion was determined by ^{1}H NMR.

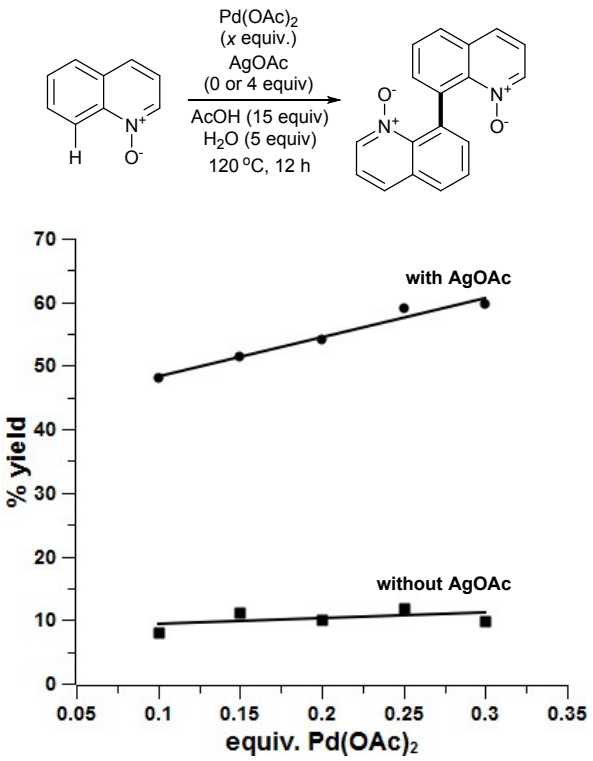
Table S2. Hammett correlation study for the oxidative C8–H homocoupling of 5- and 6-substituted quinoline *N*-oxides.

entry	Substituent	σ	log(conv.X/conv.H)
1	*m*-(6)-CH_3	-0.07	0.0826
2	H	0	0
3	*m*-(6)-CH_3O	0.12	-0.223
4	*p*-(5)-Br	0.23	-0.272
5	*m*-(6)-F	0.34	-0.468
6	*m*-(6)-Cl	0.37	-0.476



An argon-flushed 2 mL vial was charged with the respective 5- or 6-substituted quinoline *N*-oxide (0.2 mmol), palladium acetate (4.4 mg, 0.02 mmol, 10 mol %) silver acetate (134 mg, 0.8 mmol, 4 equiv), a degassed mixture of glacial acetic acid (0.18 mL, 3.0 mmol, 15 equiv.) and deionized water (0.018 mL, 1 mmol, 5 equiv). The vial was sealed, and the reaction mixture was stirred at 120 °C for 4 h. Work up was performed according to the general procedure GP2. Each experiment was carried out in triplicate. Values of log(conv.X/conv.H) are derived from the average of three runs for each substituted quinoline *N*-oxide and reported in Table S2.

Experiments with varied amounts of $Pd(OAc)_2$ in the absence and in the presence of AgOAc



Experiments in the absence of AgOAc: An argon-flushed 2 mL vial was charged with quinoline *N*-oxide (0.2 mmol), palladium acetate (0.02, 0.03, 0.04, 0.05, 0.06 mmol; 0.1, 0.15, 0.2, 0.25, 0.3 equiv), a degassed mixture of glacial acetic acid (0.18 mL, 3.0 mmol, 15 equiv.) and deionized water (0.018 mL, 1 mmol, 5 equiv). The vial was sealed, and the reaction mixture was stirred at 120 °C for 12 h. Work up was performed according to the general procedure GP2. Each experiment was carried out in triplicate. Values of yield of dimer **1** are derived from the average of three runs for each amount of $Pd(OAc)_2$ and reported in Table S3.

Experiments in the presence of AgOAc: An argon-flushed 2 mL vial was charged with quinoline *N*-oxide (0.2 mmol), palladium acetate (0.02, 0.03, 0.04, 0.05, 0.06 mmol; 0.1, 0.15, 0.2, 0.25, 0.3 equiv) silver acetate (134 mg, 0.8 mmol, 4 equiv), a degassed mixture of glacial acetic acid (0.18 mL, 3.0 mmol, 15 equiv.) and deionized water (0.018 mL, 1 mmol, 5 equiv). The vial was sealed, and the reaction mixture was stirred at 120 °C for 12 h. Work up was performed according to the general procedure GP2. Each experiment was carried out in triplicate. Values of yield of dimer **1** are derived from the average of three runs for each amount of $Pd(OAc)_2$ and reported in Table S3.

Table S3. Influence of amounts of $Pd(OAc)_2$ on the yield of dimer 1 in the absence and in the presence of AgOAc.

entry	equiv $Pd(OAc)_2$	yield of **1** without AgOAc, %	yield of **1** with AgOAc, %
1	0.1	8.1	48.0
2	0.15	11.2	51.4
3	0.2	10.1	54.1
4	0.25	11.9	59.0
5	0.3	9.9	59.8

Table S4. Single crystal X-ray crystallographic data for 8,8'-biquinoline 1,1'-dioxide (1)

CCDC Nr: CCDC 1037965

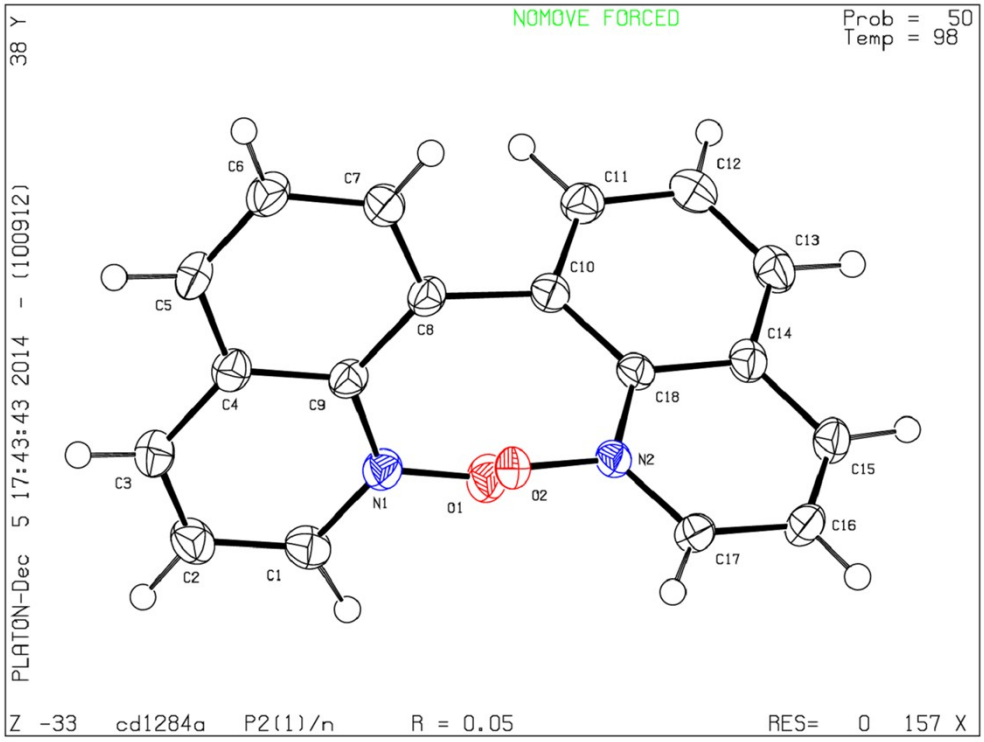
Bond precision:	C–C = 0.0029 A	Wavelength = 0.71073	
Cell:	*a* = 7.720(5)	*b* = 21.073(12)	*c* = 8.161(5)
	α = 90	β = 92.202(10)	γ = 90
Temperature:	98 K		
	Calculated		
	Reported Volume		
	1326.7(14)		
	1326.7(14) Space group	P 21/n	
	P2(1)/n Hall group	-P 2yn	
	-P 2yn		
Moiety formula	$C_{18}H_{12}N_2O_2$	$C_{18}H_{12}N_2O_2$	
Sum formula	$C_{18}H_{12}N_2O_2$	$C_{18}H_{12}N_2O_2$	
Mr	288.30	288.30	
Dx, g cm^{-3}	1.443	1.443	
Z	4	4	
Mu (mm^{-1})	0.096	0.096	
F000	600.0	600.0	
F000'	600.26		
h,k,l_{max}	9,25,9	9,25,9	
N_{ref}	2471	2464	
T_{min},T_{max}	0.983, 0.993	0.811, 1.000	
T_{min}'	0.981		

Correction method= MULTI-SCAN

Data completeness= 0.997 Theta(max)= 25.500

R(reflections)= 0.0483 (2132) wR2(reflections) = 0.1219 (2464) S = 1.000

N_{par} = 235



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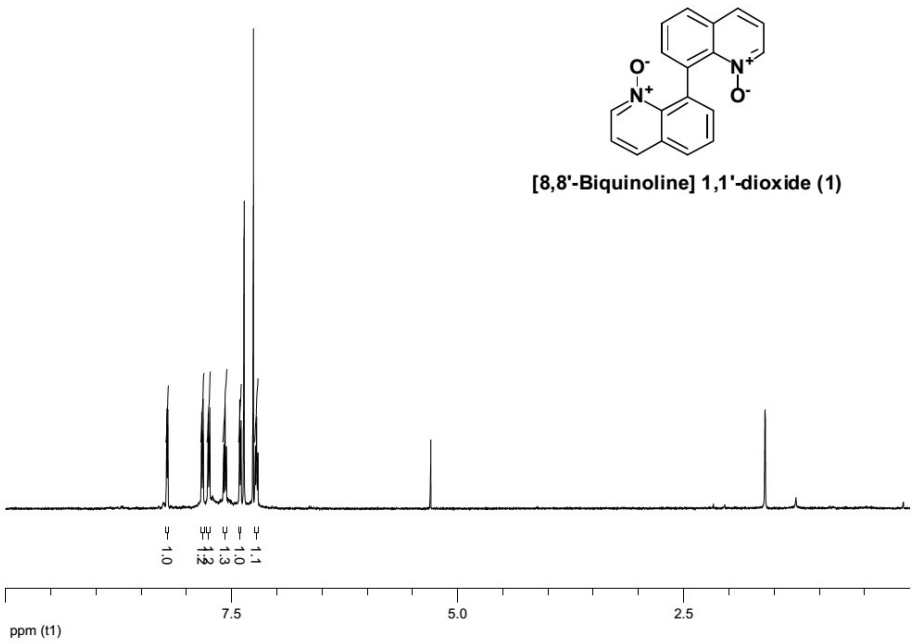
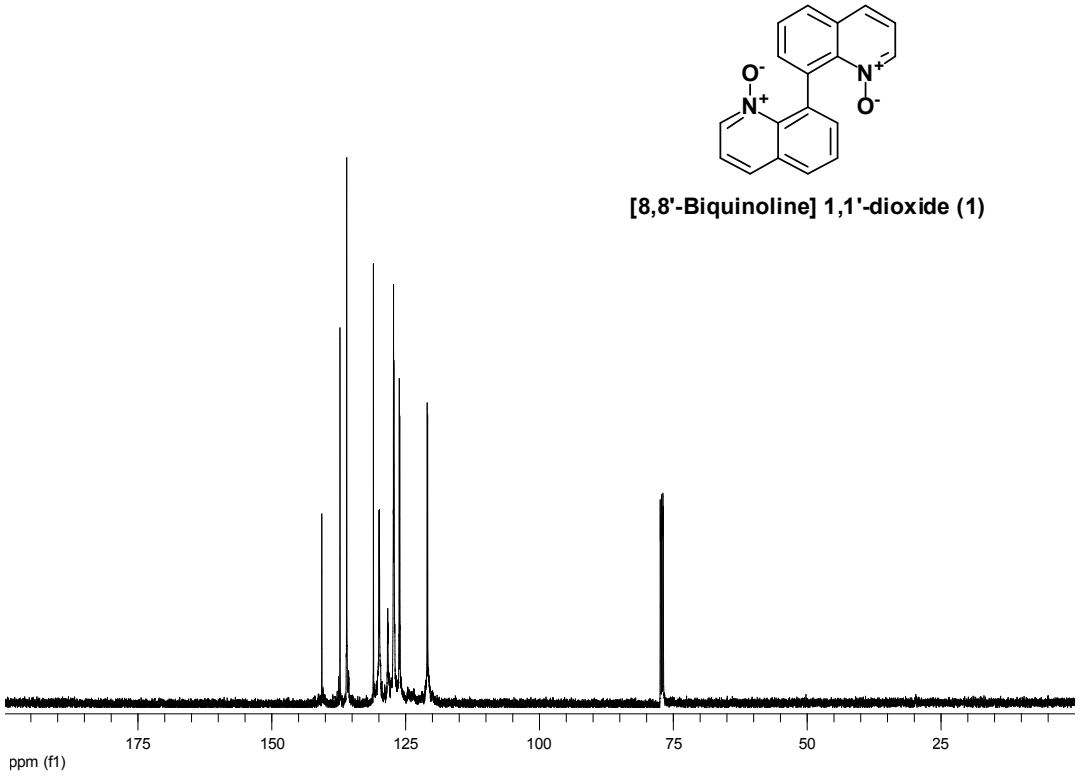
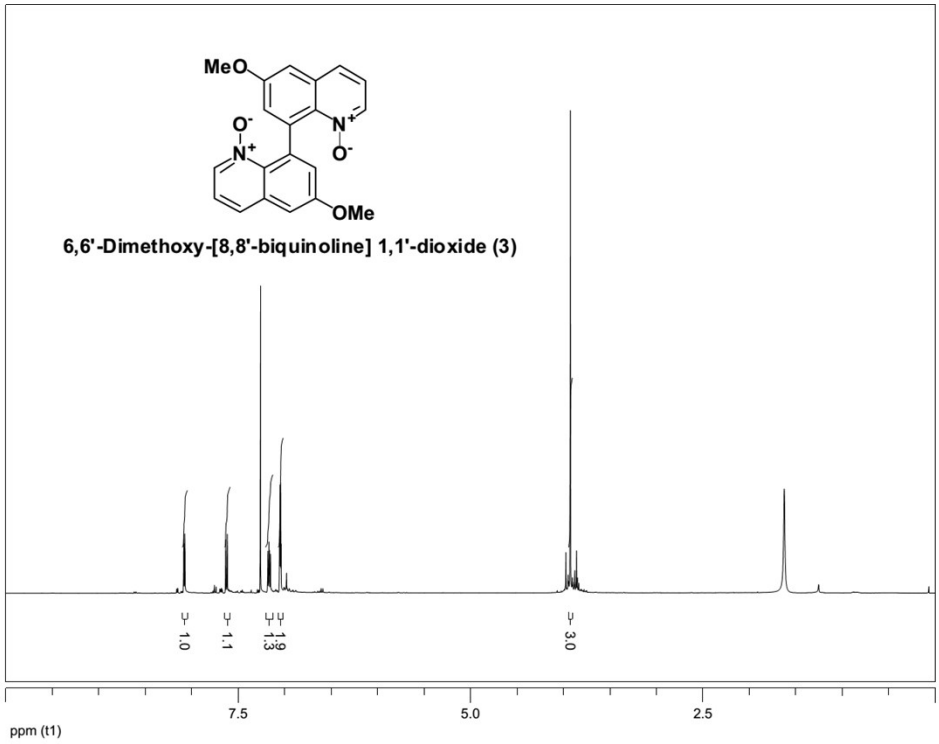
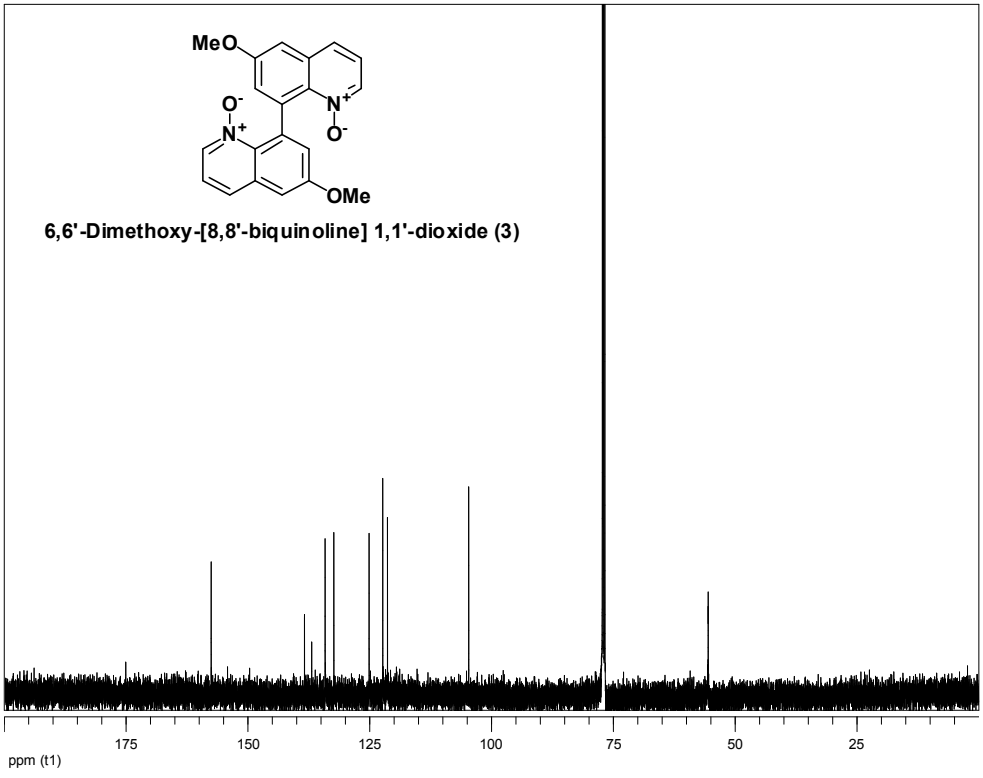
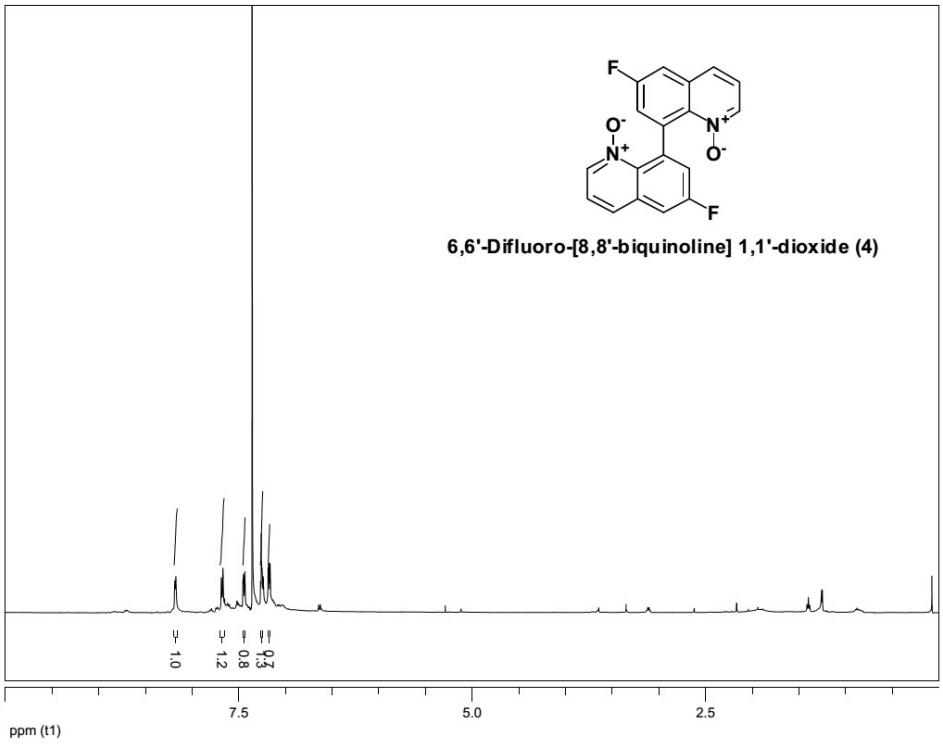
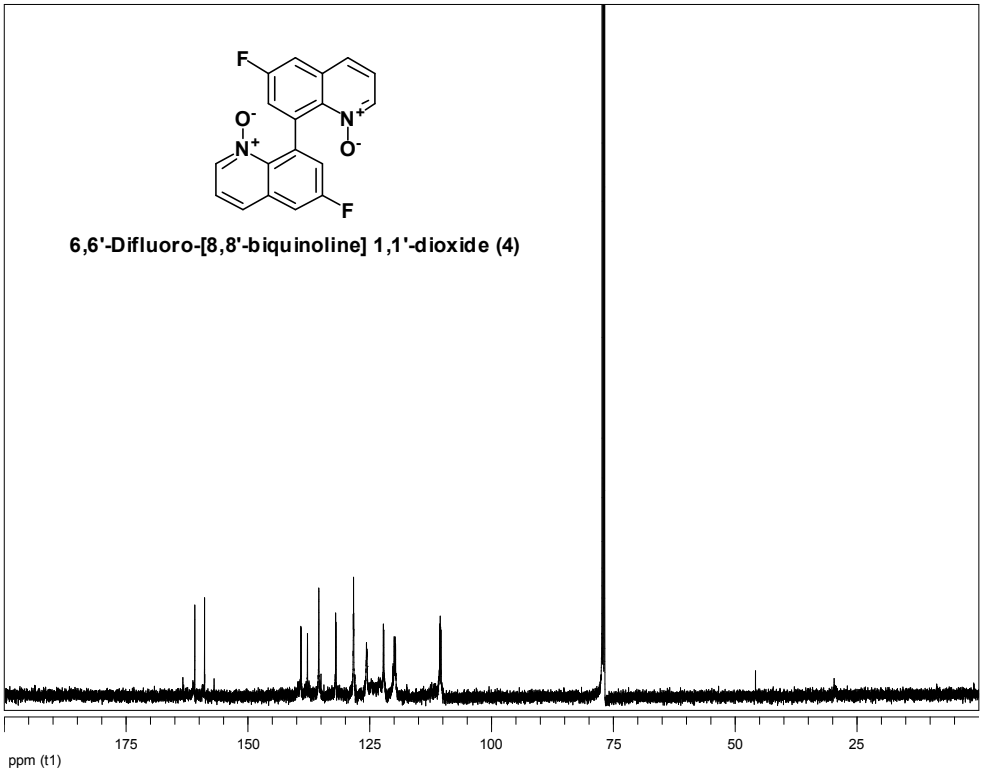

[8,8'-Biquinoline] 1,1'-dioxide (1)
1.0
1.2
1.3
1.0
1.1
7.5
5.0
2.5
ppm (t1)

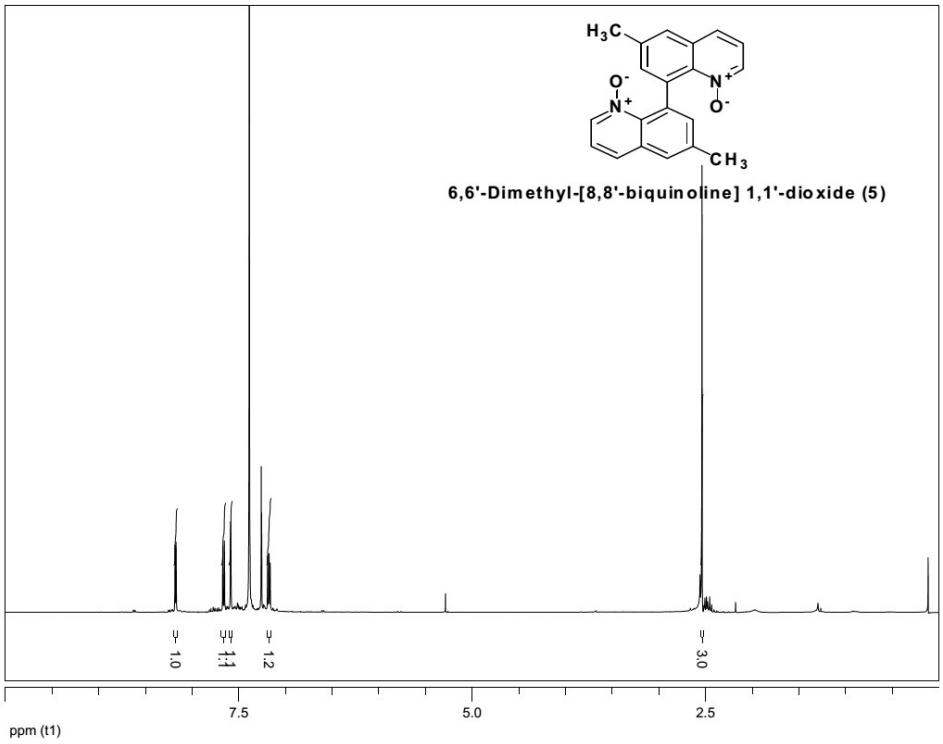

[8,8'-Biquinoline] 1,1'-dioxide (1)
175
150
125
100
75
50
25
ppm (f1)

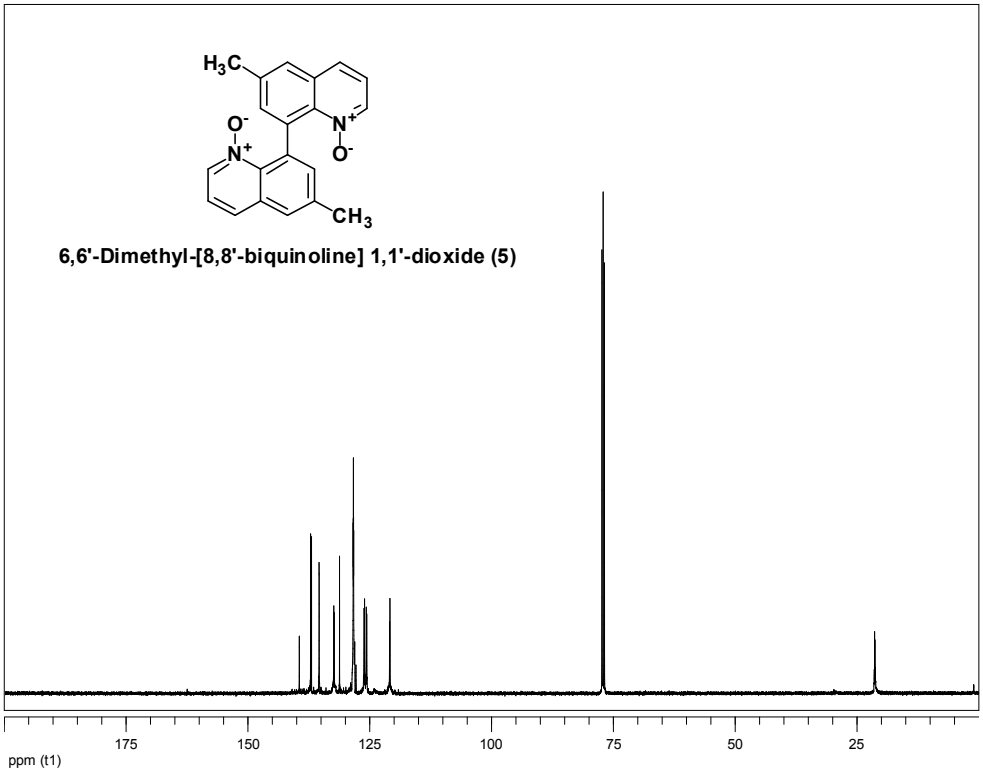

MeO
O-
N+
N+
O-
OMe
6,6'-Dimethoxy-[8,8'-biquinoline] 1,1'-dioxide (3)
1.0
1.1
1.3
1.9
3.0
7.5
5.0
2.5
ppm (t1)

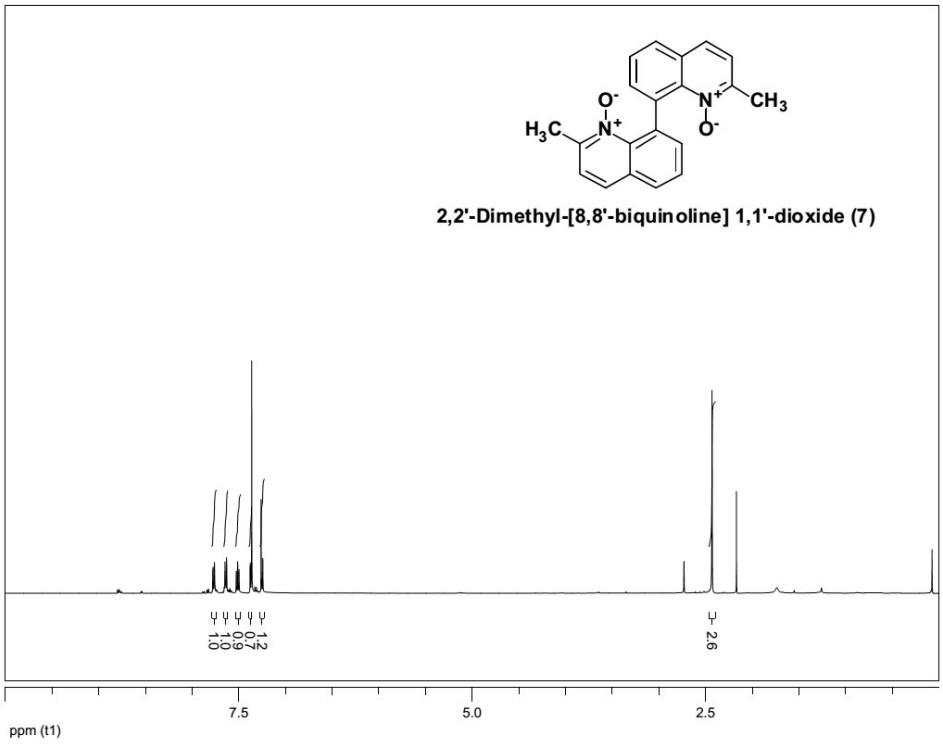

MeO
O-
N+
N+
O-
OMe
6,6'-Dimethoxy-[8,8'-biquinoline] 1,1'-dioxide (3)
175
150
125
100
75
50
25
ppm (t1)

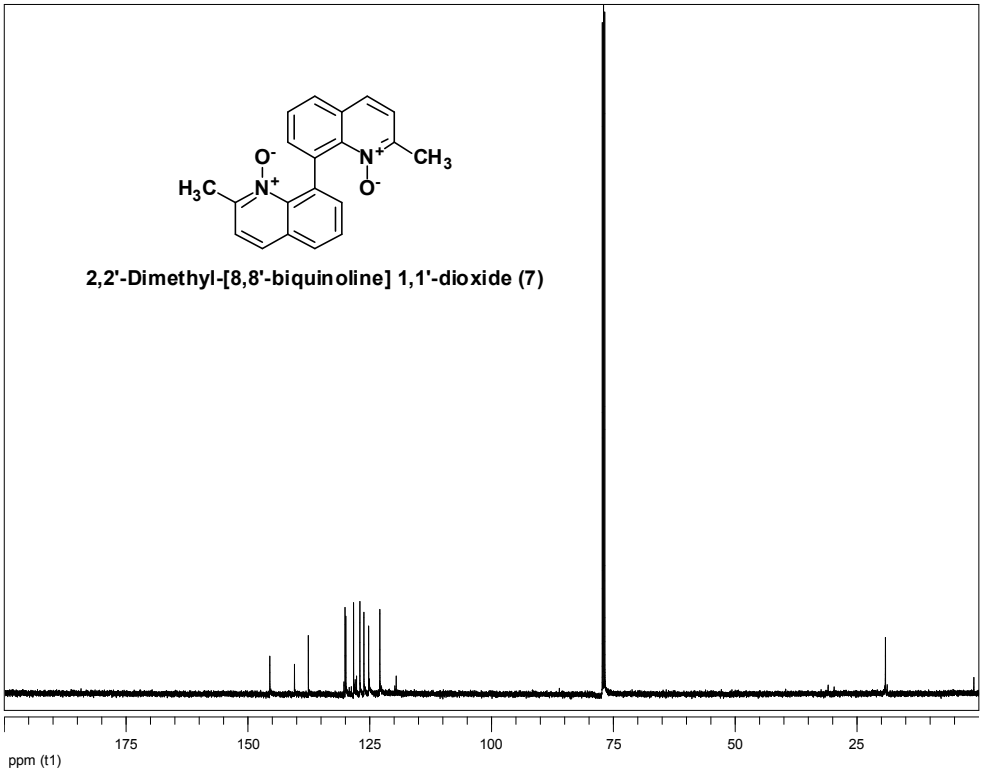

F
O-
N+
N+
O-
F
6,6'-Difluoro-[8,8'-biquinoline] 1,1'-dioxide (4)
1.0
1.2
0.8
0.7
0.3
7.5
5.0
2.5
ppm (t1)

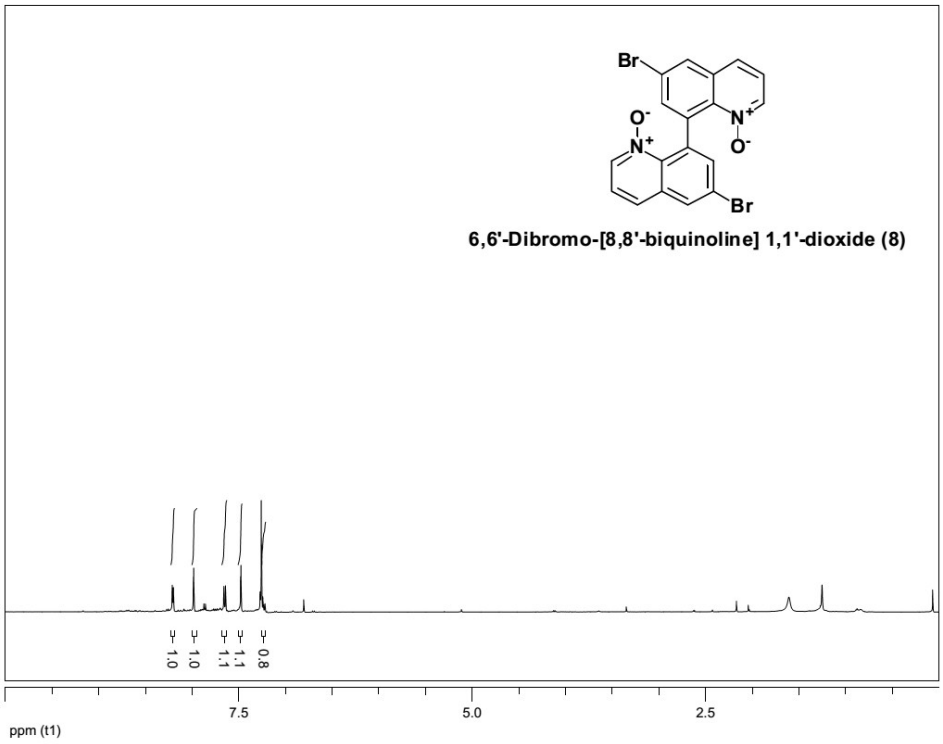

F
O-
N+
N+
O-
F
6,6'-Difluoro-[8,8'-biquinoline] 1,1'-dioxide (4)
175
150
125
100
75
50
25
ppm (t1)

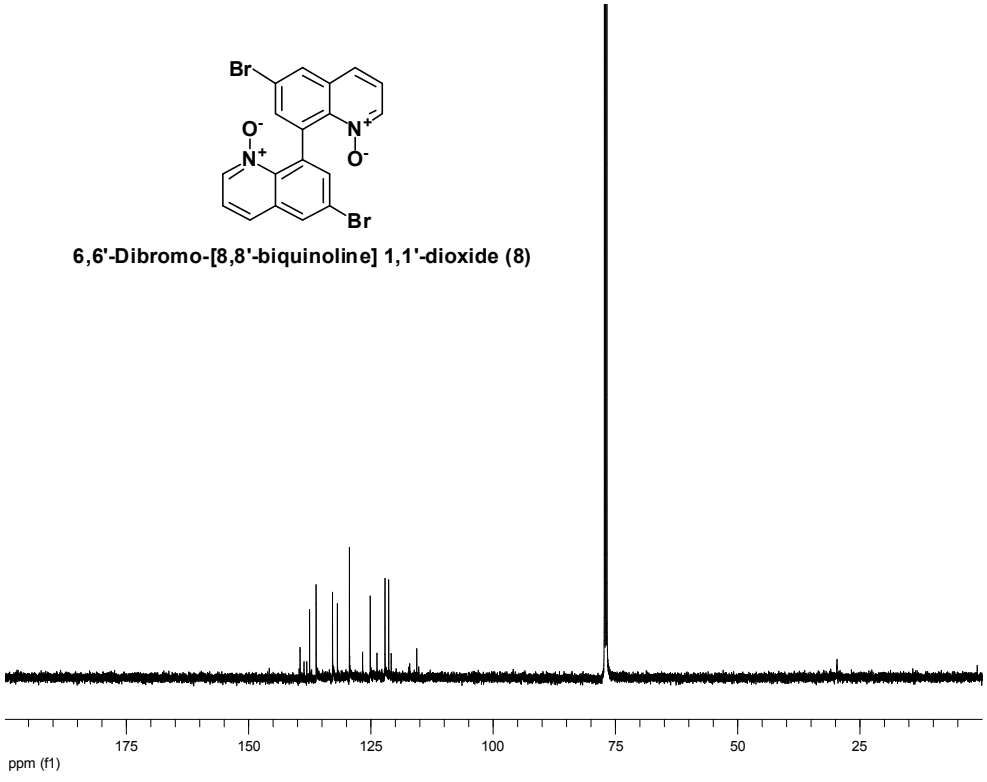

6,6'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (5)
1.0
1.1
1.2
3.0
7.5
5.0
2.5
ppm (t1)

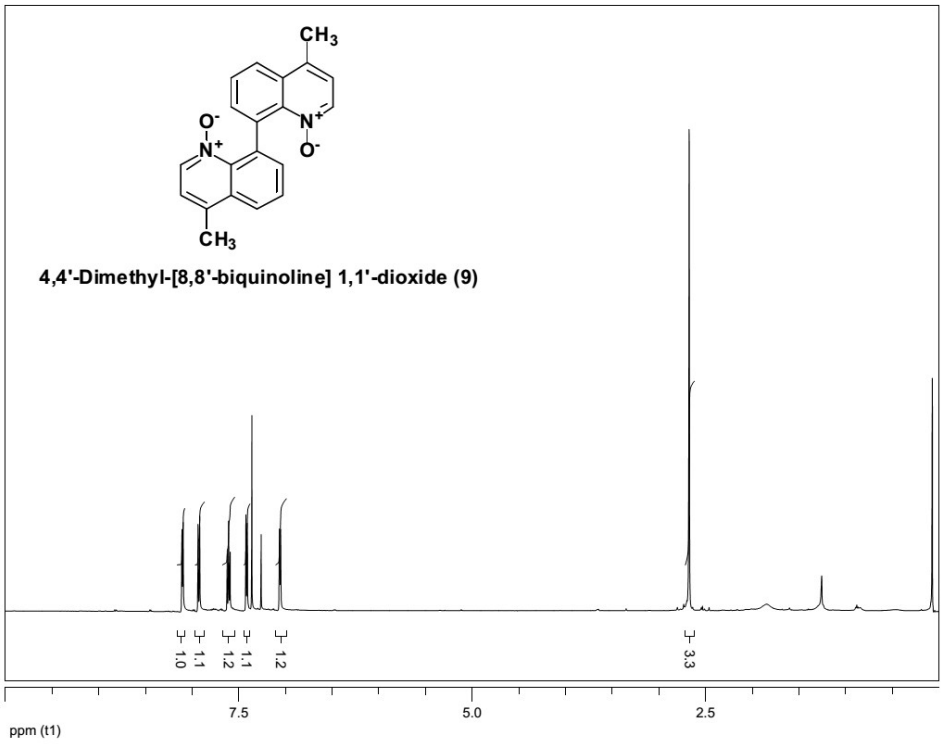

6,6'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (5)
175
150
125
100
75
50
25
ppm (t1)

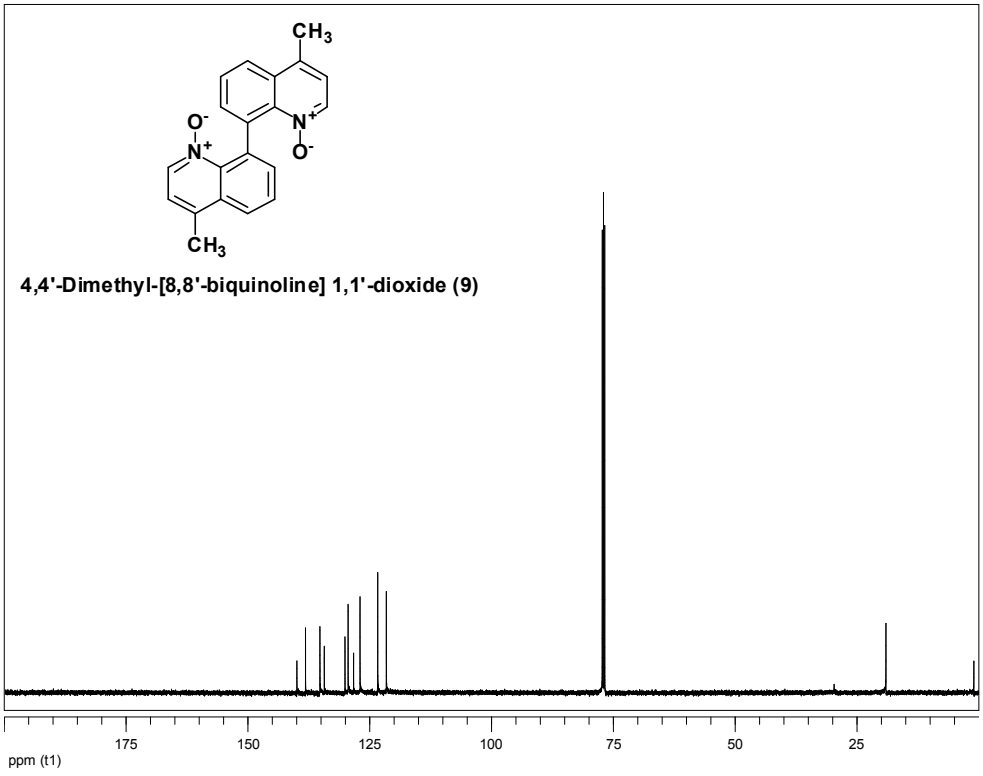

2,2'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (7)
1.10
1.06
1.09
1.12
2.26
7.5
5.0
2.5
ppm (t1)

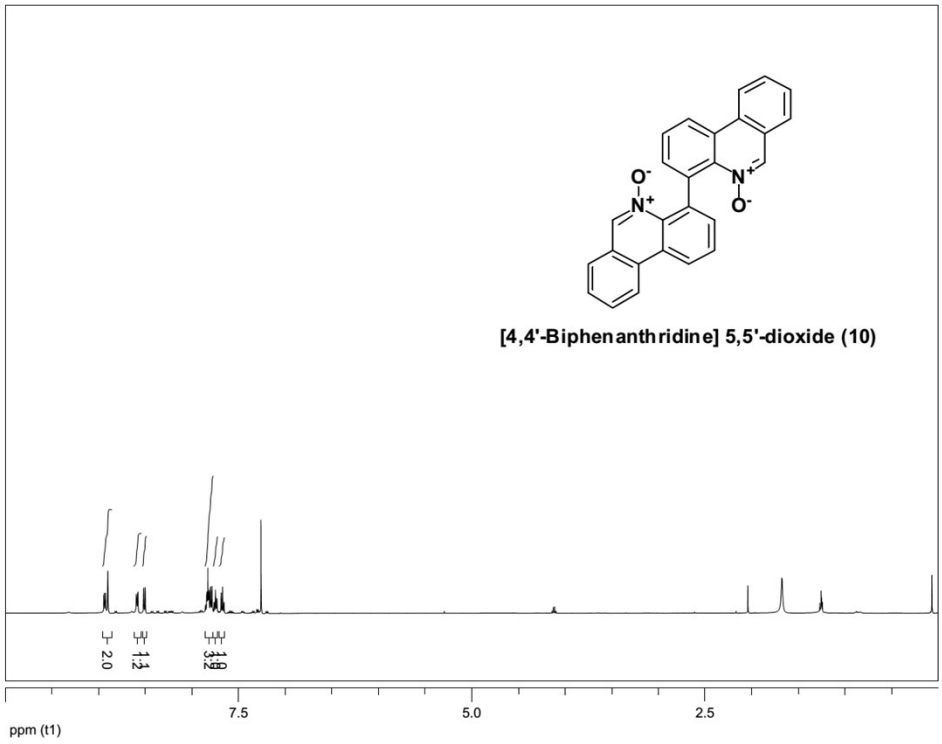

2,2'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (7)
175
150
125
100
75
50
25
ppm (t1)

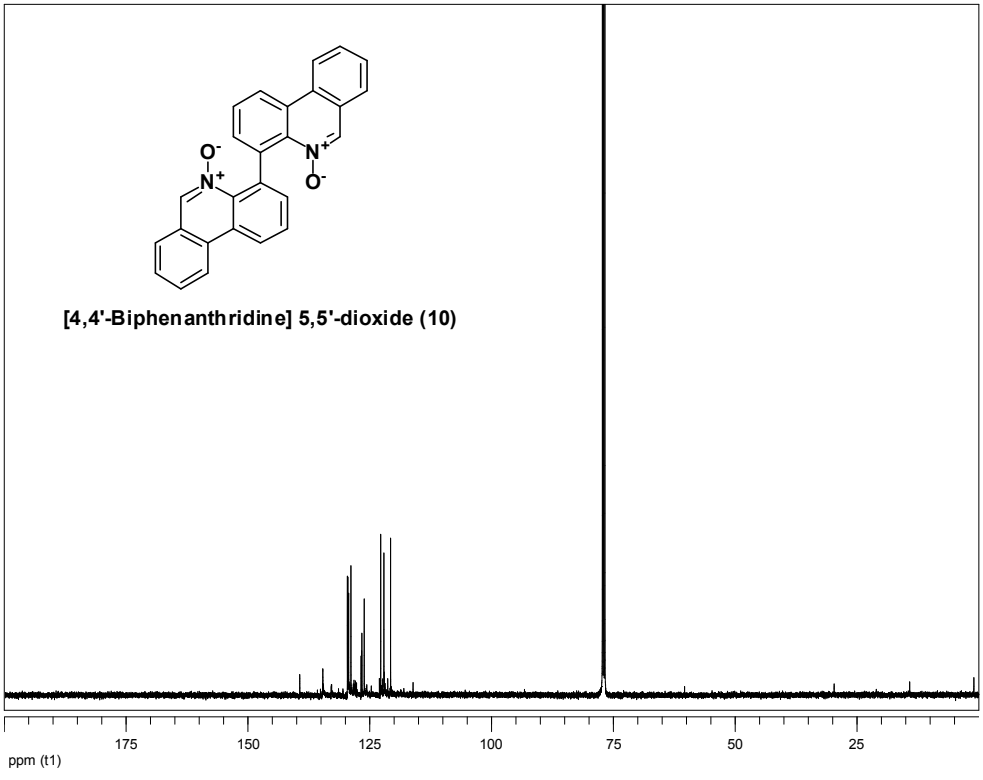

Br
O-
N+
N+
O-
Br
6,6'-Dibromo-[8,8'-biquinoline] 1,1'-dioxide (8)
1.0
1.0
1.1
1.1
0.8
7.5
5.0
2.5
ppm (t1)

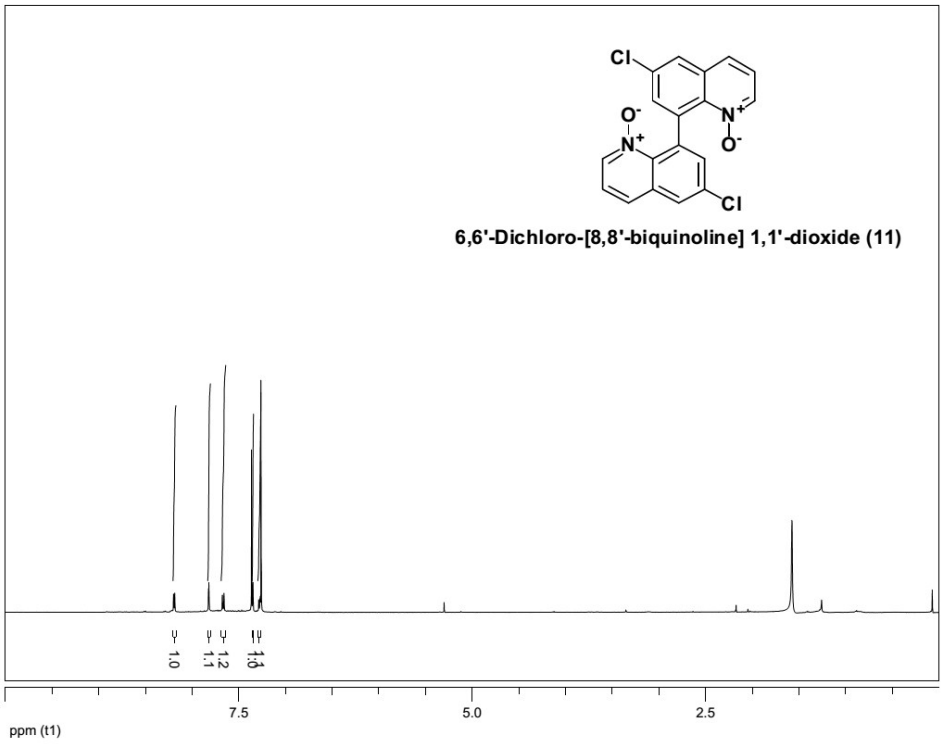

Br
O-
N+
N+
O-
Br
6,6'-Dibromo-[8,8'-biquinoline] 1,1'-dioxide (8)
175
150
125
100
75
50
25
ppm (f1)

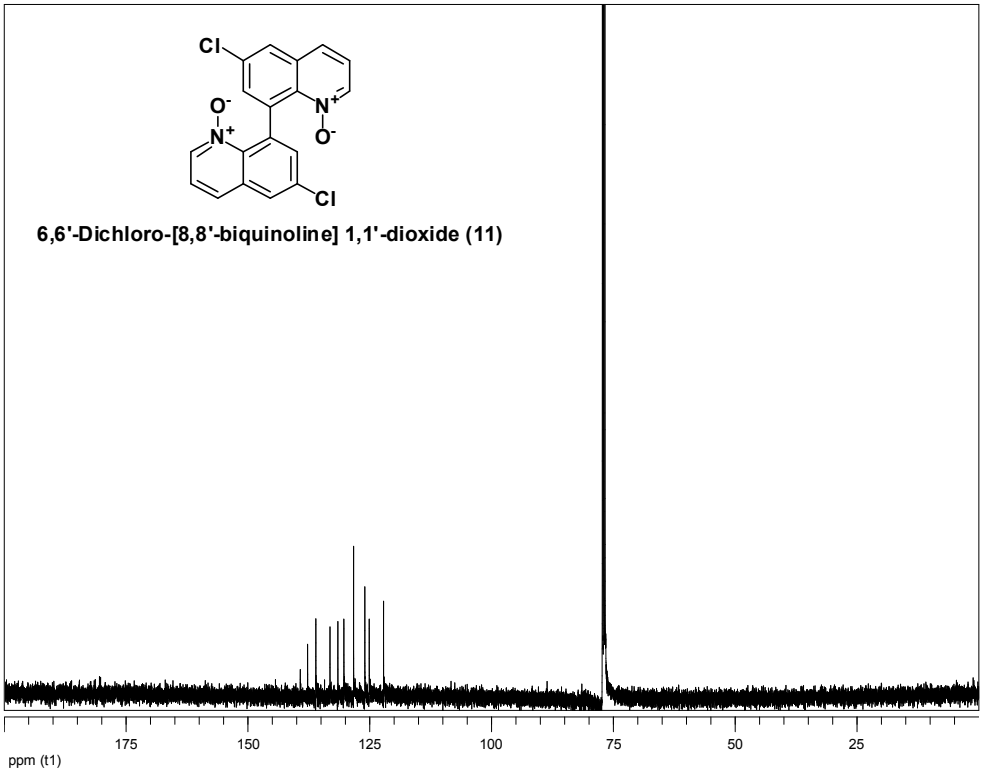

4,4'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (9)
1.0
1.1
1.2
1.1
1.2
3.3
7.5
5.0
2.5
ppm (t1)

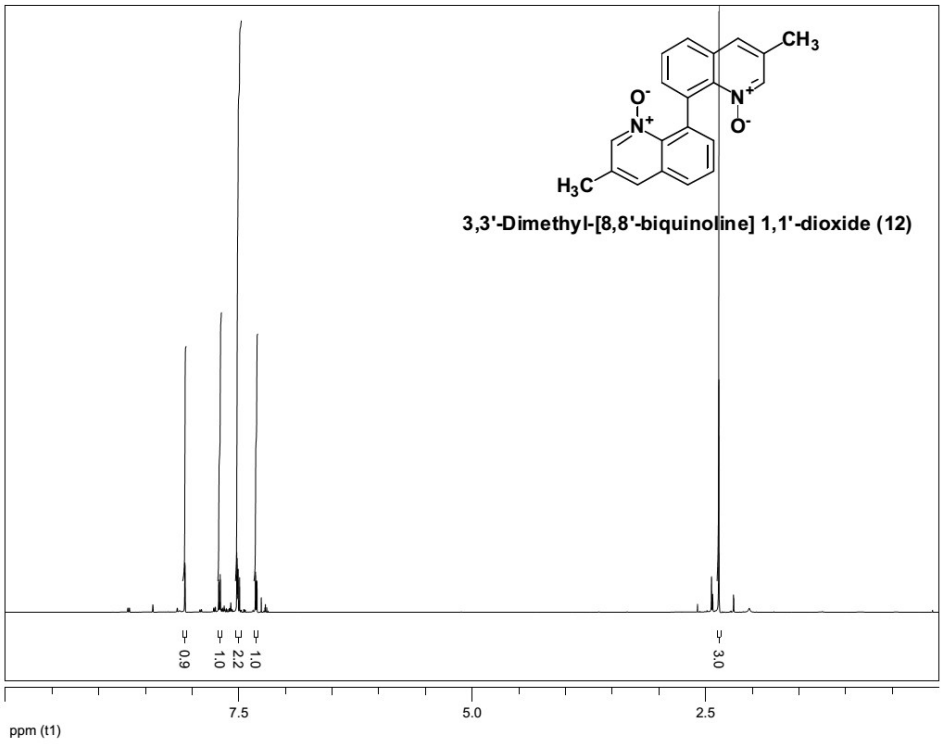

4,4'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (9)
175
150
125
100
75
50
25
ppm (t1)

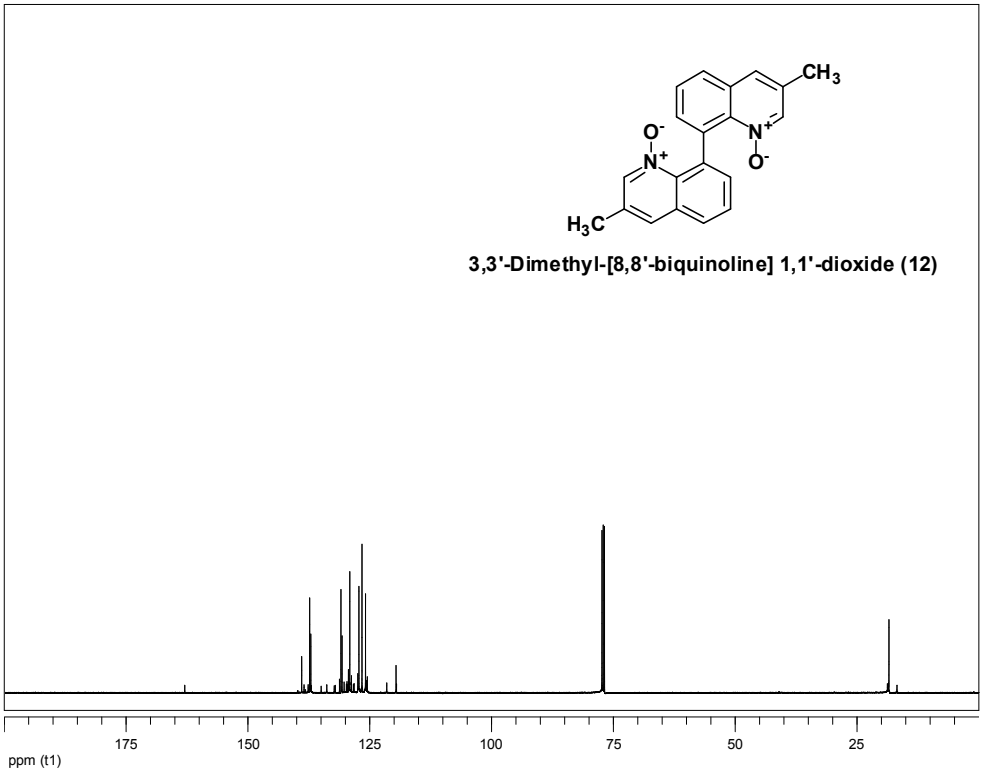

[4,4'-Biphenanthridine] 5,5'-dioxide (10)
2.0
1.1
1.2
3.1
3.2
7.5
5.0
2.5
ppm (t1)

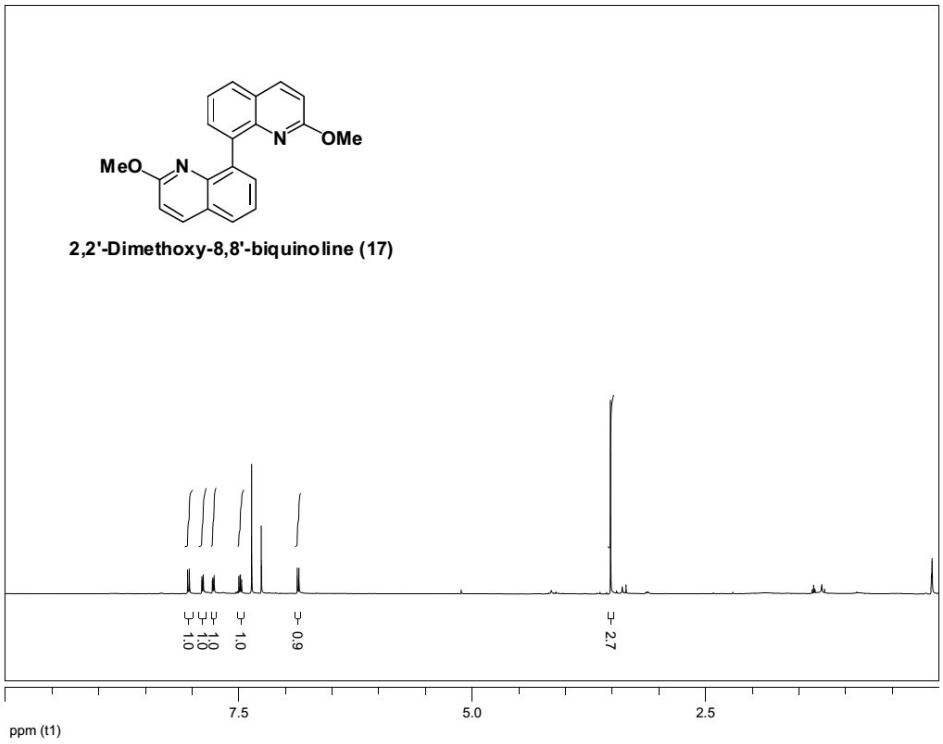

[4,4'-Biphenanthridine] 5,5'-dioxide (10)
175
150
125
100
75
50
25
ppm (t1)

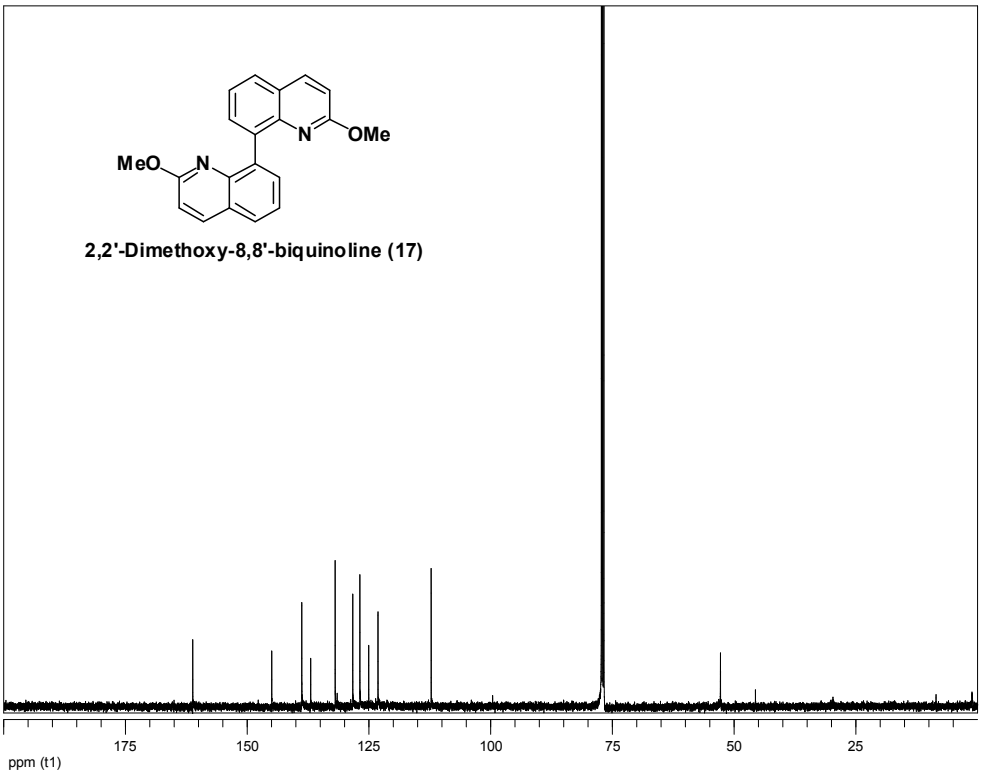

Cl
O-
N+
N+
O-
Cl
6,6'-Dichloro-[8,8'-biquinoline] 1,1'-dioxide (11)
1.0
1.1
1.2
1.3
7.5
5.0
2.5
ppm (t1)

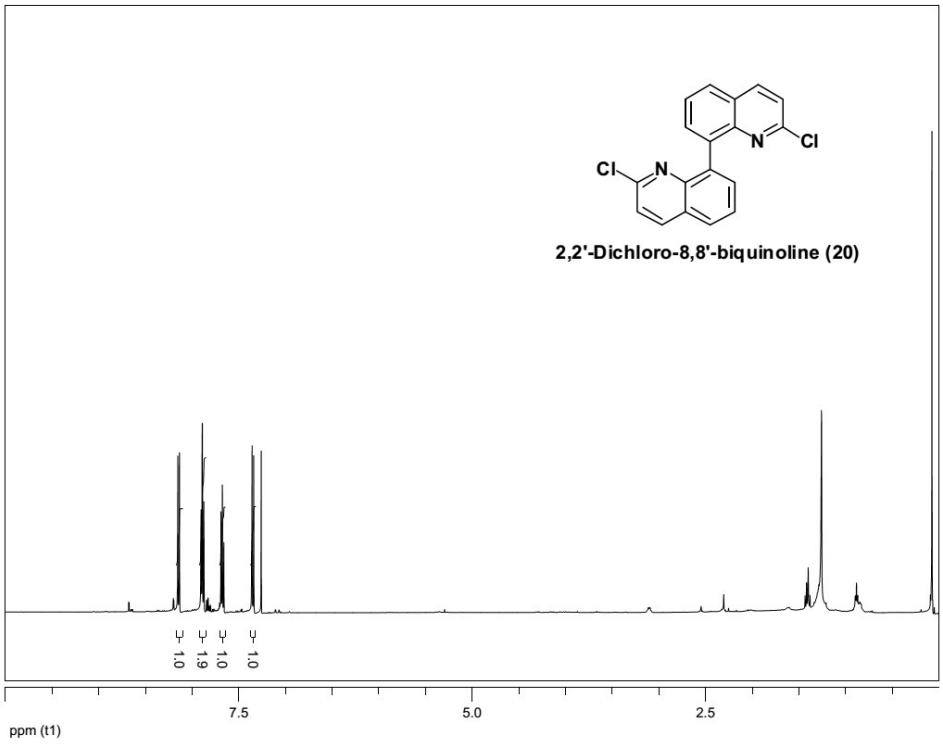

Cl
O-
N+
N+
O-
Cl
6,6'-Dichloro-[8,8'-biquinoline] 1,1'-dioxide (11)
175
150
125
100
75
50
25
ppm (t1)

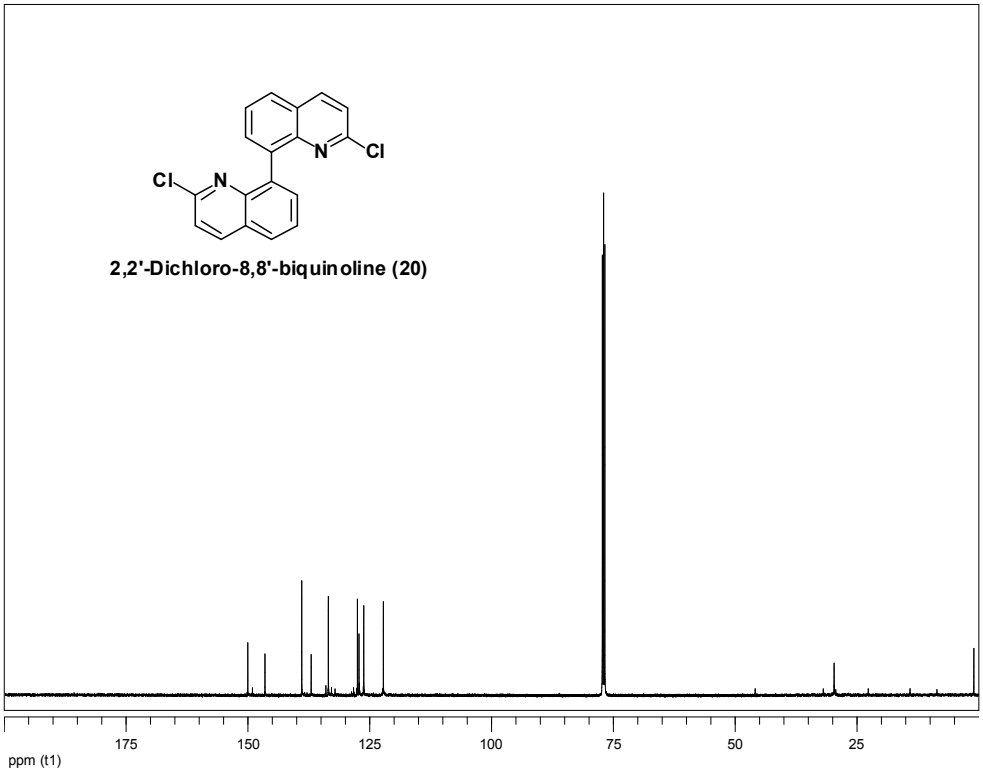

CH3
O-
N+
N+
O-
H3C
3,3'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (12)
0.9
1.0
2.2
1.0
3.0
7.5
5.0
2.5
ppm (t1)

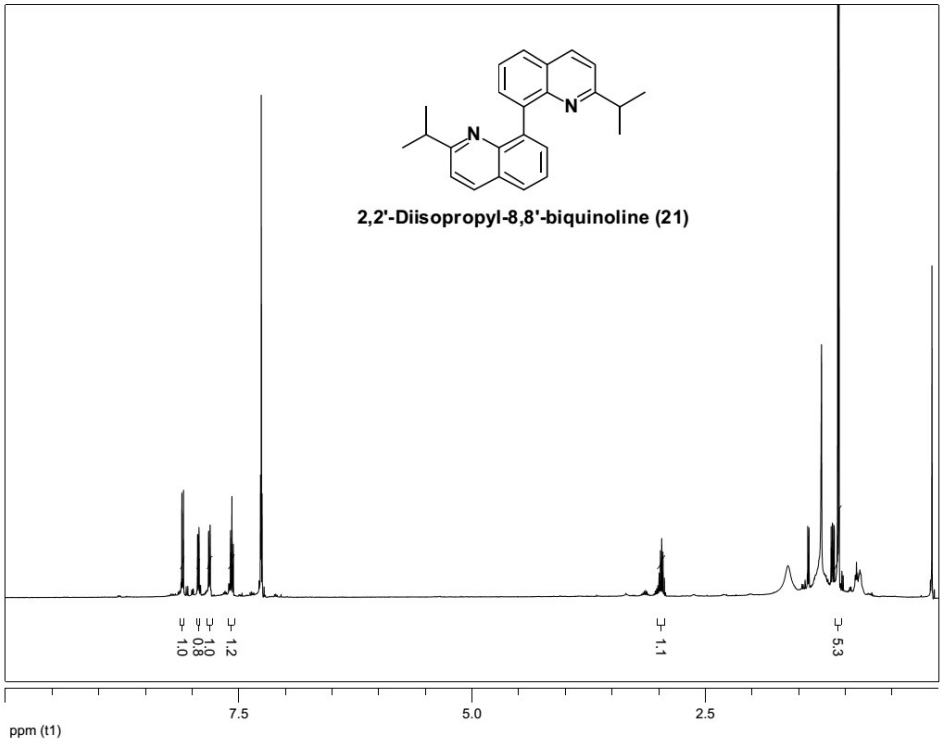

CH3
O-
N+
N+
O-
H3C
3,3'-Dimethyl-[8,8'-biquinoline] 1,1'-dioxide (12)
175
150
125
100
75
50
25
ppm (t1)

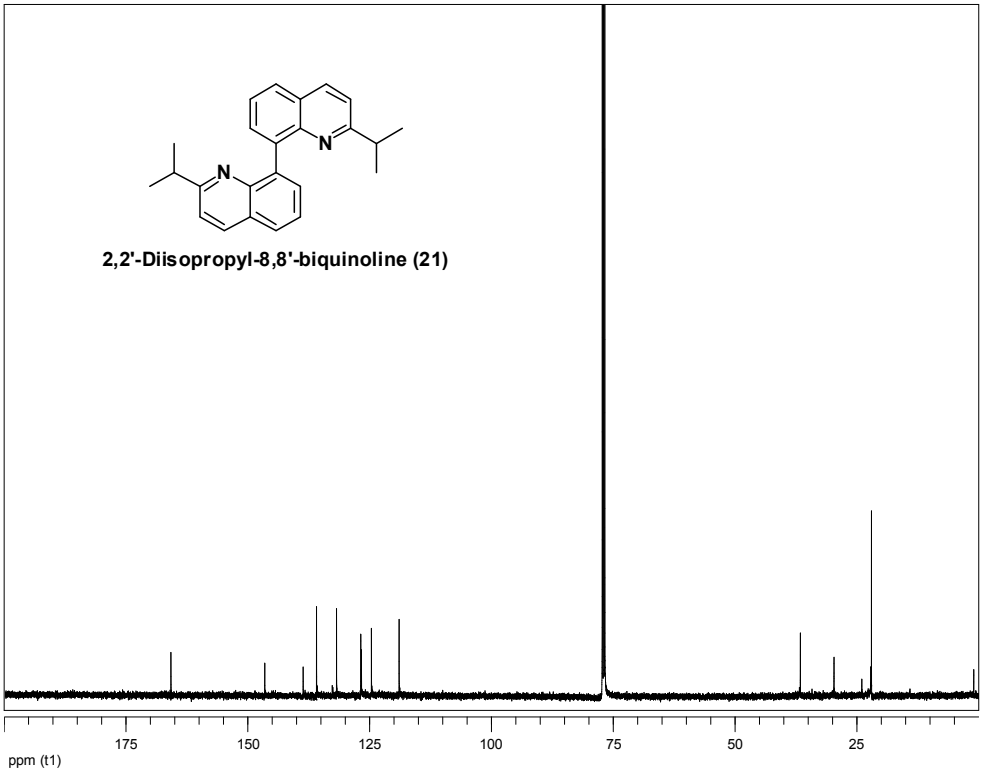

MeO
N
N
OMe
2,2'-Dimethoxy-8,8'-biquinoline (17)
1.0
1.0
1.0
0.9
2.7
7.5
5.0
2.5
ppm (t1)

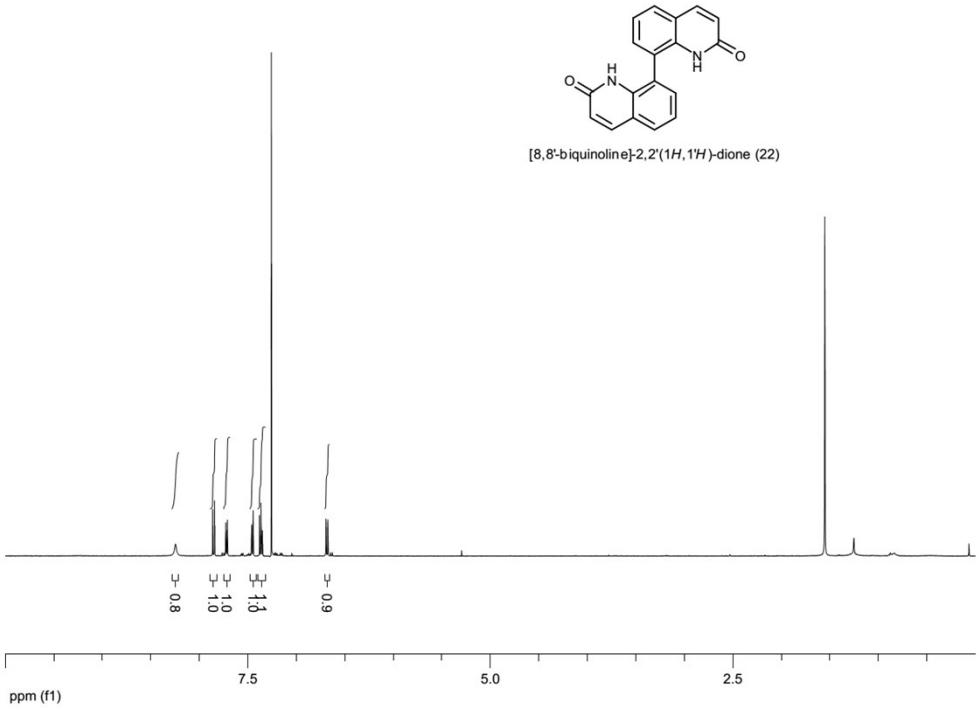

MeO
N
N
OMe
2,2'-Dimethoxy-8,8'-biquinoline (17)
175
150
125
100
75
50
25
ppm (t1)

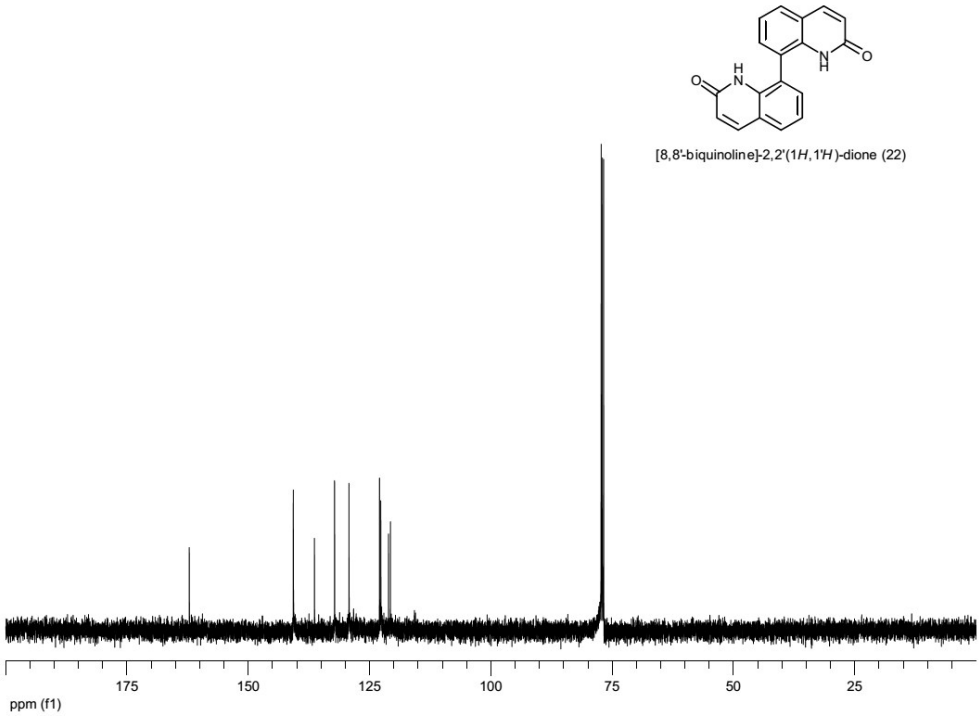

Cl
N
N
Cl
2,2'-Dichloro-8,8'-biquinoline (20)
1.0
1.9
1.0
1.0
7.5
5.0
2.5
ppm (t1)


Cl
N
N
Cl
2,2'-Dichloro-8,8'-biquinoline (20)
175
150
125
100
75
50
25
ppm (t1)


2,2'-Diisopropyl-8,8'-biquinoline (21)
1.0
0.8
1.0
1.2
1.1
5.3
7.5
5.0
2.5
ppm (t1)


2,2'-Diisopropyl-8,8'-biquinoline (21)
175
150
125
100
75
50
25
ppm (t1)


[8,8'-biquinoline]-2,2'(1H,1'H)-dione (22)
0.8
1.0
1.0
1.1
1.1
0.9
7.5
5.0
2.5
ppm (f1)


[8,8'-biquinoline]-2,2'(1H,1'H)-dione (22)
175
150
125
100
75
50
25
ppm (f1)