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A NOVEL SOLID-PHASE SYNTHESIS OF QUINOLINES

E Tang,^{1,2,*} Deshou Mao,³ Wen Li,² Zhangyong Gao,² and Pengfei Yao²

¹Key Laboratory of Medicinal Chemistry of Natural Resource (Yunnan University), Ministry of Education, P. R. of China. ²School of Chemical Science and Technology, Yunnan University, No 2 Green Lake North Road, Kunming 650091, P. R. of China. ³Research Center of Hongta Group, No 118 Hongta Road, Yuxi 653100, Yunnan Province, P. R. of China

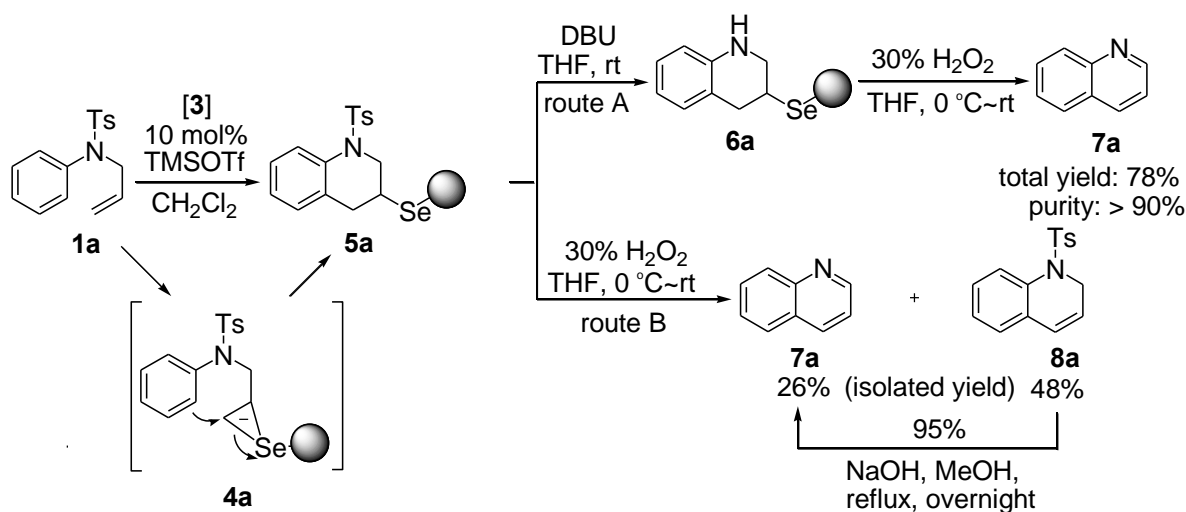
e-mail: tange@ynu.edu.cn

Abstract – A method for synthesizing substituted-quinolines using TMSOTf-catalyzed polystyrene-supported succinimidyl selenide-induced intramolecular seleno-arylation of tethered alkenes as a key step has been developed. The catalytic process provides an efficient method for the stereoselective and regioselective synthesis of tetrahydroquinoline possessing a seleno-functionality, followed by deprotection of tosyl group and *syn*-elimination of selenoxides to provide quinolines in good yields and purities.

The regioselective and stereoselective solid-phase synthesis of heterocycles and its application to the generation of drug-like molecules has attracted widespread attention.¹ Various Lewis acid-catalyzed carbon-carbon bond forming reactions have been adapted to solid-phase synthesis as a way of constructing a wide range of heterocyclic structures.² Quinolines are one of the major classes of heterocycles and the quinoline ring system is found in many natural products.³ Substituted quinolines are widely used in medicinal chemistry particularly as antituberculosis,⁴ antimalaria,⁵ anticancer⁶ and antiviral⁷ agents. Quinoline derivatives also find significant applications as agrochemicals⁸ and dyes.⁹ Numerous literatures have grown up relating to preparation of combinatorial library of quinolines. Most of them are focused on the intermolecular reaction to form supported tetrahydroquinolines¹⁰ and subsequent oxidation reaction with oxidants¹¹ to give quinolines. The solid-phase synthesis of quinolines based on the Friedländer reaction between the resin-bound azomethine and a ketone has been developed, the yields are high and the polymer-bound aniline moiety of the azomethine is easily recycled.¹² Quinolines have also been prepared by modification of quinoline skeleton.¹³ However, few solid-phase synthesis of quinolines by intramolecular cyclization reaction has been reported.¹⁴ In recent years, we

the reaction flask. PSSS was then treated in turn with 10 mol% TMSOTf and **1a** in dry CH₂Cl₂ at -78 °C for 2 h. And then the reaction mixture was kept at -20 °C for 8 h to afford 3-polystyrene-supported selenotetrahydroquinoline (**5a**). The treatment of **5a** with H₂O₂ in THF at 0 °C to room temperature gave a mixture of quinoline (**7a**) in 26% isolated yield and 1-tosyl-1, 2-dihydroquinoline (**8a**) in 48% isolated yield. However, **7a** could be obtained in the yield of 95% by the treatment of **8a** with sodium hydroxide in methanol. Therefore, the intermediate resin **5a** was firstly deprotected with 1, 8-diazabicyclo[5, 4, 0]undec-7-ene (DBU) in THF at room temperature to give 3-polystyrene-supported selenotetrahydroquinoline (**6a**). The reaction was monitored by FT-IR. The strong peak of the sulfonyl absorption at 1321 cm⁻¹ disappeared in the FT-IR spectrum of resulting resin **6a**. Then, the treatment of **6a** with H₂O₂ at 0 °C to room temperature afforded quinoline (**7a**) in 78% total yield (Scheme 2).

In the step to afford **5a**, a range of cyclization reaction conditions involving **1a** and PSSS (**3**) were explored. The results are depicted in Table 1. The employment of 10 mol% BF₃·Et₂O, AlCl₃, FeCl₃ and



Scheme 2. Solid-phase synthesis of quinoline **7a**

Table 1. Optimization of solid-phase conditions of cyclization

Entry	Lewis acid	Amount of catalyst (mol%)	Total yield of 7a (%) ^a	Purity of 7a (%) ^b
1	none	-	nr	-
2	TiCl ₄	10	nr	-
3	Sm(OTf) ₃	10	nr	-
4	AgOTf	10	nr	-
5	BF ₃ ·Et ₂ O	10	<5	-
6	AlCl ₃	10	<5	-

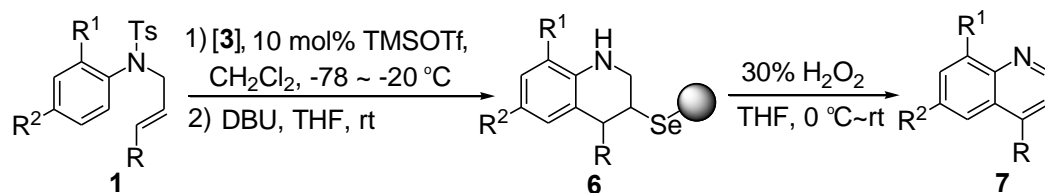
7	FeCl ₃	10	<5	-
8	ZnCl ₂	10	<5	-
9	TMSOTf	10	78	> 90
10	TMSOTf	5	50	> 70
11	TMSOTf	20	76	> 90

^a Yields of the crude products based on the loading of polystyrene-supported selenenyl bromide (Br, 0.99 mmol/g); nr = no reaction; **7a** was synthesized by route A.

^b Determined by HPLC analysis.

ZnCl₂ afforded the product in very low yield when the cyclization reaction was performed at -78 °C for 2 h and then -20 °C for 8 h in dry CH₂Cl₂ (Table 1, entries 5-8). Addition of double dose of TMSOTf did not improve the yield of **7a** (Table 1, entries 11). The yield and the purity of **7a** decreased when 5 mol% of TMSOTf was employed (Table 1, entries 10). No product was obtained when other Lewis acids such as TiCl₄, Sm(OTf)₃, and AgOTf were used (Table 1, entries 2-4). It is noteworthy that substrate **1a** did not undergo any reaction with PSSS (**3**) in the absence of a Lewis acid (Table 1, entry 1).

Table 2. Solid-phase synthesis of quinolines **7** by route A



Entry	R	R ¹	R ²	Product	Total yield (%) ^a	Purity (%) ^b
1 ^c	H	H	H	7a	78	> 90
2	H	H	MeO	7b	82	> 95
3	Me	H	H	7c	75	> 90
4	Me	Me	H	7d	76	> 90
5	Me	MeO	H	7e	81	> 90
6	Me	H	MeO	7f	82	> 95
7	Me	H	Cl	7g	75	> 90
8	Me	H	Br	7h	73	> 90
9	Ph	H	H	7i	78	> 90
10	Ph	H	MeO	7j	85	> 95
11	4 [?] -MeC ₆ H ₄	H	H	7k	78	> 90

12	2'-Me-4'-MeOC ₆ H ₃	H	H	7l	80	> 90
13	4'-ClC ₆ H ₄	H	H	7m	75	> 90
14	2'-MeC ₆ H ₄	H	H	7n	76	> 90
15	4'-MeOC ₆ H ₄	H	H	7o	79	> 90
16	H	CHO	H	7p	-	-

^a Yields of the crude products based on the loading of polystyrene-supported selenenyl bromide (Br, 0.99 mmol/g);

^b Determined by HPLC analysis;

^c Also see entry 9 in Table 1.

Then the polystyrene-supported selenium-mediated cyclization reactions of a series of substituted *N*-allyl-toluene-4-sulfonanilides **1** in the one-pot procedure were studied. The products **7** were obtained in good yields and high purities by route A. The results are summarized in Table 2. It was quite obvious that when R¹ and R² were H, electron-donating substituents such as alkoxy and alkyl and halide substituents, the carbon-based ring-closure reaction proceeded smoothly to give cyclized compounds (Table 2, entries 1-6, 9-15). Good results were also obtained when R was H, alkyl, phenyl, and electron-donating group substituted phenyl (Table 2). No cyclized products were obtained when R¹ and R² were electron-withdrawing substituents such as formyl (Table 2, entry 16). It is interesting that the TMSOTf-catalyzed PSSS-mediated cyclization reaction of compounds **1** and the subsequent deprotection of *p*-toluenesulfonyl group gave rise to the six-membered cyclic compounds **6** as a result of *6-endo-trig* cyclization of compounds **1**. The five-membered cyclic compounds were not obtained.

In conclusion, we have developed a highly regioselective selenium-mediated intramolecular Friedel-Crafts alkylation of substituted *N*-allyl-toluene-4-sulfonanilides using polymer-supported organoselenium reagent as a selenium source. Among the catalysts investigated, TMSOTf was found to be the best one. The target products were obtained in good yields and purities by the cleavage of the selenium linker. Furthermore, the easy workup procedure and easily prepared substrates provide an approach that is well-suited for building the parallel libraries upon the basis of further transformation of polymer-supported tetrahydroquinoline **6**. The further modifications of resin **6** are still underway.

EXPERIMENTAL

Melting points were measured with a X-6 micro-melting apparatus and were uncorrected. ¹H NMR (300 MHz or 400MHz) and ¹³C NMR (75 MHz or 100 MHz) spectra were recorded on a Bruker Avance 300 or 400 spectrometer in CDCl₃ with TMS as the internal standard; chemical shifts were quoted in ppm and J values were given in Hz. IR spectra were recorded on a Thermo Nicolet Avatar 360 spectrometer. HRMS were performed on an Agilent LC/Msd TOF instrument. HPLC were run on an Agilent 1100

High performance liquid chromatograph with a tunable UV detector. Dry CH_2Cl_2 and DMF were distilled from CaH_2 . Dry THF was distilled from Na. Purities and yields of the products are determined by the crude products and NMR, HRMS, FTIR, are determined by the purified products (the crude products were subjected to TLC on silica gel with ethyl acetate and light petroleum (1:4-1:25) as eluent to give the purified products).

Typical procedure for the preparation of allyl polystyrene-supported selenide (2): To a suspension of the swollen polystyrene-supported selenenyl bromide (Br: 0.99 mmol/g, 2.5 g) in dry THF/DMF (V/V=5:1, 30 mL) was added NaBH_4 (5 mmol) under nitrogen atmosphere at 40 °C. After stirring for 8 h at 40 °C, allyl bromide (5.5 mmol) was added dropwise under nitrogen atmosphere, and stirred for another 12 h. The resin **2** was collected by filtration, washed with THF (20 mL \times 2), MeOH (20 mL \times 2) and CH_2Cl_2 (20 mL \times 2) and dried in vacuum. IR (KBr): ν_{max} = 3068, 3019, 2847, 1565, 1415, 1185, 1016, 907, 751, 694 cm^{-1} .

General procedure for the preparation of 3-polystyrene-supported seleno-1-tosyl-1, 2, 3, 4-tetrahydroquinolines (5): To a suspension of the swollen resin **2** (1.0 g) in dry CH_2Cl_2 (15 mL) was added NCS (0.668 g, 5.0 mmol) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and 2 h at room temperature. After filtrating and washing with dry CH_2Cl_2 (15 mL \times 3), resin **3** was suspended with dry CH_2Cl_2 (15 mL) and cool at -78 °C. Trimethylsilyl trifluoromethanesulfonate (0.022 g, 0.10 mmol) was added. After stirring for 0.5 h at -78 °C, substituted *N*-allyltoluene-4-sulfonanilide **1** (5.0 mmol) was added under nitrogen atmosphere. The suspension was stirred for another 2 h at -78 °C and then stored in a freezer at -20 °C for 8 h. Saturated aqueous NaHCO_3 (5 mL) was poured into the flask to quench reaction mixture. The resin **5** was collected by filtration, washed with THF (20 mL \times 2), ether (20 mL \times 2), THF/ H_2O (3:1) (20 mL \times 2), H_2O (20 mL \times 2), THF (20 mL \times 2), MeOH (20 mL \times 2), and CH_2Cl_2 (20 mL \times 2), and dried under vacuum.

Typical procedure for the preparation of quinoline (7a) by route B: The washed resin **5** was suspended in THF (15 mL). To the mixture was added 30% aqueous H_2O_2 (1.2 mL) and stirred for 1 h at 0 °C, and then stirred for another 20 min at room temperature. The mixture was filtered and the resin was washed with CH_2Cl_2 (15 mL \times 2). The filtrate was washed with H_2O (30 mL \times 2), dried over MgSO_4 . After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt (V/V) =10:1) to give 33.3 mg (26% isolated yield) of quinoline (**7a**) and 135.6 mg (48% isolated yield) of 1-tosyl-1, 2-dihydroquinoline (**8a**). A mixture of **8a** (135.6 mg, 0.475 mmol), 2.4 mL of aq NaOH, and 10 mL MeOH was refluxed overnight. The reaction was quenched by water and the mixture was extracted with CH_2Cl_2 . Combined extracts were washed with brine and dried over MgSO_4 . After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt (V/V) =10:1) to give 58.3 mg (95% isolated yield) of **7a**.

General procedure for the preparation of quinolines 7 by route A: The washed resin **5** was suspended in THF (15 mL). To the mixture was added 1,8-diazabicyclo[5, 4, 0]undec-7-ene (DBU) (2.0 mL) and stirred for 24 h at room temperature. The resin **6** was collected by filtration, washed with THF/H₂O (3:1) (20 mL×2), H₂O (20 mL×2), THF (20 mL×2), MeOH (20 mL×2), and CH₂Cl₂ (20 mL×2), and dried under vacuum. The washed resin **6** was suspended in THF (15 mL). To the mixture was added 30% aqueous H₂O₂ (1.2 mL) and stirred for 1 h at 0 °C, and then stirred for another 20 minutes at room temperature. The mixture was filtered and the resin was washed with CH₂Cl₂ (15 mL×2). The filtrate was washed with H₂O (30 mL×2), dried over MgSO₄, and evaporated to dryness in vacuum to afford quinolines **7**.

Quinoline (7a)²²: ¹H NMR (300 MHz, CDCl₃): δ = 8.92 (d, *J* = 4.2 Hz, 1H), 8.14 (t, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.39 (dd, *J*₁ = 8.2 Hz, *J*₂ = 4.2 Hz, 1H). IR (KBr): ν_{max} = 1620, 1597, 1529, 1315, 1118 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₉H₇N 129.0578; found 129.0577.

6-Methoxyquinoline (7b)²²: ¹H NMR (300 MHz, CDCl₃): δ = 8.75 (dd, *J*₁ = 4.2 Hz, *J*₂ = 1.5 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.38–7.33 (m, 2H), 7.06 (d, *J* = 2.7 Hz, 1H), 3.93 (s, 3H); IR (KBr): ν_{max} = 1618, 1600, 1427, 1388, 1255, 1130 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₀H₉NO 159.0684; found 159.0688.

4-Methylquinoline (7c)²³: ¹H NMR (300 MHz, CDCl₃): δ = 8.75 (d, *J* = 4.2, 1H), 8.15–8.05 (m, 1H), 7.93 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.4, 1H), 7.68–7.63 (m, 1H), 7.52–7.47 (m, 1H), 7.15 (d, *J* = 4.2, 1H), 2.64 (s, 3H); IR (film): ν_{max} = 1598, 1525, 1454, 1311, 1253 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₀H₉N 143.0735; found 143.0732.

4,6-Dimethylquinoline (7d)²³: ¹H NMR (300 MHz, CDCl₃): δ = 8.70 (d, *J* = 4.2 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.76–7.72 (m, 1H), 7.52 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H), 7.16 (d, *J* = 4.2 Hz, 1H), 2.70 (s, 3H), 2.60 (s, 3H); IR (film): ν_{max} = 1620, 1586, 1528, 1500, 1457, 1383, 1256 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₁H₁₁N 157.0891; found 157.0892.

8-Methoxy-4-methylquinoline (7e)²⁴: ¹H NMR (300 MHz, CDCl₃): δ = 8.75 (d, *J* = 4.5 Hz, 1H), 8.00 (d, *J* = 6.0 Hz, 1H), 7.45 (t, *J* = 6.0 Hz, 1H), 7.25–7.18 (m, 2H), 3.89 (s, 3H), 2.68 (s, 3H); IR (KBr): ν_{max} = 1618, 1522 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₁H₁₁NO 173.0841; found 173.0840.

6-Methoxy-4-methylquinoline (7f)²⁴: ¹H NMR (300 MHz, CDCl₃): δ = 8.60 (d, *J* = 4.2 Hz, 1H), 8.00 (d, *J* = 9.3 Hz, 1H), 7.34 (dd, *J* = 2.7, 9 Hz, 1H), 7.14–7.20 (m, 2H), 3.92 (s, 3H), 2.63 (s, 3H); IR (KBr): ν_{max} = 1619, 1497 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₁H₁₁NO 173.0841; found 173.0844.

6-Chloro-4-methylquinoline (7g)²⁴: ¹H NMR (300 MHz, CDCl₃): δ = 8.76 (d, *J* = 3.3 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.65 (dd, *J*₁ = 9.0 Hz, *J*₂ = 2.4 Hz, 1H), 7.26 (d, *J* = 3.3 Hz, 1H), 2.69 (s, 3H); IR (KBr): ν_{max} = 1603, 1506 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₀H₈ClN 177.0345; found

177.0343.

6-Bromo-4-methylquinoline (7h)²⁴: ¹H NMR (300 MHz, CDCl₃): δ = 8.80 (d, *J* = 4.5 Hz, 1H), 8.17 (d, *J* = 2.1 Hz, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 7.79 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.31 (d, *J* = 4.5 Hz, 1H), 2.69 (s, 3H); IR (KBr): ν_{max} = 1625, 1512 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₁H₈BrN 220.984; found 220.987.

4-Phenylquinoline (7i)²⁴: ¹H NMR (300 MHz, CDCl₃): δ = 8.95 (d, *J* = 4.5, 1H), 8.23–8.13 (m, 1H), 7.95–7.88 (m, 1H), 7.75–7.68 (m, 1H), 7.56–7.44 (m, 6H), 7.32 (d, *J* = 4.5, 1H); IR (KBr): ν_{max} = 1588, 1495, 1393 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₅H₁₁N 205.0891; found 205.0893.

6-Methoxy-4-phenylquinoline (7j): ¹H NMR (400 MHz, CDCl₃): δ = 8.80 (d, *J* = 4.8 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.46–7.56 (m, 5H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 4.5 Hz, 1H), 7.21 (s, 1H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 157.85, 147.46, 147.05, 144.75, 138.29, 131.19, 129.25, 128.61, 128.30, 127.65, 121.69, 121.62, 103.68, 55.35; IR (neat): ν_{max} = 1620, 1585, 1495, 1429, 1256 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₆H₁₃NO 235.0997; found 235.0997.

4-(*p*-Tolyl)quinoline (7k): ¹H NMR (300 MHz, CDCl₃): δ = 8.95 (d, *J* = 4.5 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.74 (m, 1H), 7.47–7.55 (m, 1H), 7.39–7.47 (m, 2H), 7.31–7.41 (m, 3H), 2.49 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 149.7, 148.5, 148.2, 138.1, 134.7, 129.6, 129.1, 128.9, 128.9, 128.7, 126.6, 126.2, 125.7, 121.1, 21.1; IR (neat): ν_{max} = 1616, 1586, 1504, 1461, 1422, 1391 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₆H₁₃N 219.1048; found 219.1051.

4-(4-Methoxy-2-methylphenyl)quinoline (7l): ¹H NMR (400 MHz, CDCl₃): δ = 8.91 (d, *J* = 4.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.62–7.71 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 4.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.4 Hz, 1H), 3.83 (s, 3H), 2.00 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 159.7, 150.2, 148.5, 148.5, 137.6, 130.9, 129.9, 129.9, 129.4, 127.8, 126.8, 126.2, 122.1, 115.7, 111.3, 55.4, 20.5. IR (neat): ν_{max} = 1609, 1496, 1388, 1297, 1240 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₇H₁₅NO 249.1154; found 249.1155.

4-(4-Chlorophenyl)quinoline (7m): ¹H NMR (400 MHz, CDCl₃): δ = 8.92 (d, *J* = 4.4 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.72 (m, 1H), 7.40–7.52 (m, 5H), 7.29 (d, *J* = 4.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 149.99, 148.74, 147.15, 136.41, 134.69, 130.86, 130.04, 129.49, 128.89, 126.89, 126.53, 125.49, 121.27. IR (neat): ν_{max} = 1616, 1588, 1460, 1425 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₅H₁₀ClN 239.0502; found 239.0500.

4-(2-Tolyl)quinoline (7n): ¹H NMR (400 MHz, CDCl₃): δ = 8.92 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.71–7.60 (m, 1H), 7.47 (dd, *J*₁ = 8.8 Hz, *J*₂ = 2.0 Hz, 1H), 7.25–7.44 (m, 4H), 7.25 (d, *J* = 4.4 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 2.00 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 150.1, 148.7, 148.5, 137.5, 136.2, 130.2, 130.0, 129.6, 129.6, 128.6, 127.4, 126.7, 126.2, 126.0, 121.5, 20.0; IR (neat): ν_{max} = 1615, 1586, 1502, 1461, 1420, 1390 cm⁻¹; HRMS *m/z* [M]⁺ calcd for C₁₆H₁₃N 219.1048; found 219.1047.

4-(4-Methoxyphenyl)quinoline (7o): ¹H NMR (400 MHz, CDCl₃): δ = 8.94 (d, *J* = 4.4 Hz, 1H), 8.18 (d,

$J = 8.4$ Hz, 1H), 7.99 (d, $J = 8.4$ Hz, 1H), 7.70–7.76 (m, 1H), 7.44–7.55 (m, 2H), 7.34 (d, $J = 4.2$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 159.92, 150.08, 148.81, 148.26, 130.86, 130.34, 129.90, 129.31, 127.01, 126.55, 125.97, 121.34, 114.12, 55.48$; IR (neat): $\nu_{\text{max}} = 2930, 2849, 1617, 1495, 1238, 1110$ cm^{-1} ; HRMS m/z $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{NO}$ 235.0997; found 235.0994.

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