Ball-Milling Synthesis of Sulfonyl Quinolines via Coupling of Haloquinolines with Sulfonic Acids

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1. General information

Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. $^1$H NMR spectra were recorded at 400 MHz and $^{13}$C NMR spectra were recorded at 101 MHz by using a Bruker Avance 400 spectrometer. Chemical shifts were calibrated using residual undeuterated solvent as an internal reference ($^1$H NMR: CDCl$_3$ 7.26 ppm, $^{13}$C NMR: CDCl$_3$ 77.0 ppm). The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet. Mass spectra were performed on a spectrometer operating on ESI-TOF.

2. Experimental Section

**General procedure for the preparation of sulfonyl quinolines**

\[
\text{N} \quad \text{X} \quad \text{N} \\
\begin{array}{c}
1 \\
2 \\
3
\end{array}
\]

\(X = \text{Cl, Br, I}\)

A mixture of halogenated quinolines 1 (0.5 mmol) and sulfonic acids 2 (0.65 mmol) were milled in a stainless steel jar charged with 1 ball (10 mm) at 20Hz for 10 – 20 min. The resulting powder was direct purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired products sulfonyl quinolines 3.

**Gram-scale synthesis of 3aa**

\[
\begin{array}{c}
1a, 10\text{mmol} \\
\text{ball milling} \\
3aa, 2.55\text{g, 88%}
\end{array}
\]

A mixture of 2-chloroquinoline 1a (1.63 g, 10 mmol) and 4-methylbenzenesulfinic acid 2a (2.03 g, 13 mmol) were milled in a stainless steel jar charged with 1 ball (10 mm) of the same material at 20Hz for 10 min. After completion, the resulting powder was direct purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give 2.55 gram of 3aa, isolated yield 88%.

**One pot synthesis of 4-quinolinyl ether**

\[
\begin{array}{c}
1j, 2\text{mmol} \\
\text{1) TsH, ball milling, r.t.} \\
\text{2) 1-Phenylethanol, t-BuOK} \\
\text{DMF, r.t.} \\
4a, 0.37\text{g, yield 75%}
\end{array}
\]

A mixture of halogenated 4-chloroquinoline 1j (0.33 g, 2 mmol) and 4-methylbenzenesulfonic acid 2a (0.41 g, 2.6 mmol) was milled in a stainless steel jar charged with 1 ball (10 mm) of the same material at 20Hz for 10 min, the resulting powder was then dissolved in DMF (6mL) and transferred to a round bottom flask, 1-phenylethanol (0.29 g, 2.4mmol) and t-BuOK (1M in THF, 2.4 mmol) were added, the mixture was stirred for about 2 hours. After completion, the resulting mixture was extracted with EtOAc (10 mL×3) and the organic phase was then removed under vacuum. The residue was purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give 0.37 gram of 4a, total yield 75%.
Synthesis of sulfonated cloquintocet-mexyl (3wa)

A solution of cloquintocet-mexyl 4b (0.67 g, 2.0 mmol) in DCM (20 mL) was stirred at 0 °C for 5 min, then 3-chloroperbenzoic acid (m-CPBA, 3.0 mmol) was added to the solution in three portions. The mixture was stirred at 25 °C for 12 h and a saturated aqueous NaHCO₃ solution (20 mL) was added. The resulting solution was extracted with DCM (10 mL × 2). Then it was dried by anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude product cloquintocet-mexyl N-oxide and used without further purification.

The above-synthesized crude product cloquintocet-mexyl N-oxide was added to a solution of POCl₃ (0.31 g, 2 mmol), and DMF (0.15 g, 2 mmol) in DCM (10 mL) at 0 - 5 °C. The reaction was allowed to stir at room temperature for 6h, after completion, the reaction was quenched with 2M Na₂CO₃ solution (20 mL) and the resulting mixture was extracted with DCM (10 mL × 3). The organic layer was combined and then removed under vacuum. The residue was purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give 0.20 gram of 3wa. 1H NMR (400 MHz, Chloroform-d) δ 8.47 (d, J = 8.8 Hz, 1H), 7.51 (dd, J = 11.8, 8.6 Hz, 2H), 6.93 (d, J = 8.5 Hz, 1H), 5.09 – 4.97 (m, 1H), 4.92 (d, J = 2.0 Hz, 2H), 1.57 (dd, J = 13.1, 5.0 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.26 – 1.20 (m, 9H), 0.85 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz, Chloroform-d) δ 168.1, 152.1, 150.9, 140.1, 136.0, 126.5, 126.0, 124.0, 123.4, 111.2, 72.8, 66.5, 35.7, 31.5, 24.9, 22.5, 19.9, 13.9; HRMS (ESI) m/z calcd. for C₁₈H₁₂Cl₁₄NO₃[M+H]⁺: 370.0971, found 370.0966.

A mixture of 2-chlorocloquintocet-mexyl 1w (0.19 g, 0.5 mmol) and 4-methylbenzenesulfonic acid 2a (0.10 g, 0.65 mmol) were milled in a stainless steel jar charged with 1 ball (10 mm) of the same material at 20Hz for 10 min. After completion, the resulting powder was directly purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give 0.20 gram of 3wa, isolated yield 82%. 1H NMR (400 MHz, Chloroform-d) δ 8.72 (d, J = 8.8 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.4 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.85 (s, 2H), 2.40 (s, 3H), 1.58 (dq, J = 12.3, 6.1, 5.2 Hz, 1H), 1.47 (dt, J = 14.0, 7.0 Hz, 1H), 1.28 – 1.20 (m, 9H), 0.85 (t, J = 6.7 Hz, 3H); 13C NMR (101 MHz, Chloroform-d) δ 168.1, 158.0, 153.4, 145.0, 140.2, 136.1, 135.6, 129.8, 129.3, 128.8, 127.7, 123.9, 118.6, 114.2, 72.6, 67.6, 35.7, 31.5, 24.9, 22.5, 21.6, 13.9; HRMS (ESI) m/z calcd. for C₂₉H₂₆Cl₂NO₅S[M+H]⁺: 490.1449, found 490.1446.

Characterization data of products

2-tosylquinoline (3aa)¹

White solid; 93% yield; ¹H NMR (400 MHz, Chloroform-d) δ 8.36 (d, J = 8.6 Hz, 1H), 8.18 (t, J = 8.2 Hz, 2H), 8.02 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.2 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.65 (t, J = 7.1 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 2.39 (s, 3H); ¹³C NMR (101 MHz, Chloroform-d) δ 158.3, 147.4, 144.8, 138.7, 136.1, 130.9, 130.4, 129.7, 129.1, 129.0, 128.7, 127.6, 117.6, 21.6.

2-(phenylsulfonyl)quinoline (3ab)²

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White solid; 82% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.39 (d, $J = 8.5$ Hz, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 8.17 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.76 (t, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 7.9$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.26 – 7.21 (m, 1H), 2.55 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 158.1, 147.1, 139.0, 138.6, 137.0, 133.9, 132.4, 130.9, 130.5, 130.3, 129.1, 128.8, 127.7, 126.3, 117.7, 20.7.

2-(o-tolylsulfonyl)quinoline (3ac)

White solid; 83% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.39 (d, $J = 8.5$ Hz, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 8.17 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.76 (t, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 7.9$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.26 – 7.21 (m, 1H), 2.55 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 158.1, 147.1, 139.0, 138.6, 137.0, 133.9, 132.4, 130.9, 130.5, 130.3, 129.1, 128.8, 127.7, 126.3, 117.7, 20.7.

2-(m-tolylsulfonyl)quinoline (3ad)

White solid; 84% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.37 (d, $J = 8.6$ Hz, 1H), 8.18 (t, $J = 8.3$ Hz, 2H), 7.92 (d, $J = 6.1$ Hz, 2H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.80 – 7.74 (m, 1H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.39 (d, $J = 7.7$ Hz, 2H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 158.0, 147.3, 139.3, 138.8, 138.7, 134.5, 130.9, 130.3, 129.1, 129.1, 128.9, 128.7, 127.6, 126.1, 117.7, 21.2.

2-((3-bromophenyl)sulfonyl)quinoline (3ae)

White solid; 87% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.41 (dd, $J = 8.5$, 2.7 Hz, 1H), 8.31 – 8.25 (m, 1H), 8.24 – 8.13 (m, 2H), 8.08 (d, $J = 7.8$ Hz, 1H), 7.89 (dd, $J = 8.0$, 3.5 Hz, 1H), 7.80 (q, $J = 6.6$ Hz, 1H), 7.70 (dt, $J = 12.7$, 6.4 Hz, 2H), 7.41 (td, $J = 7.9$, 3.6 Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 157.4, 147.4, 140.9, 138.9, 136.8, 131.8, 130.6, 130.4, 129.4, 128.9, 127.7, 127.7, 123.0, 117.6.

2-((4-(tert-butyl)phenyl)sulfonyl)quinoline (3af)

White solid; 92% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.37 (d, $J = 8.5$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 2H),
8.06 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.2 Hz, 1H), 7.79 (t, J = 8.4 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.6 Hz, 2H), 1.30 (s, 9H); $^{13}$C NMR (101 MHz, Chloroform-d) δ 158.3, 157.6, 147.4, 138.7, 136.1, 130.9, 130.4, 129.1, 128.8, 128.7, 127.2, 117.8, 35.2, 31.0.

2-((4-methoxyphenyl)sulfonyl)quinoline (3ag)

White solid; 82% yield; $^1$H NMR (400 MHz, Chloroform-d) δ 8.36 (d, J = 8.5 Hz, 1H), 8.17 (dd, J = 8.5, 4.2 Hz, 2H), 7.86 (d, J = 8.2 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-d) δ 163.8, 147.4, 138.6, 131.2, 130.9, 130.4, 130.3, 129.0, 128.7, 127.6, 117.5, 114.3, 55.6.

2-((4-fluorophenyl)sulfonyl)quinoline (3ah)

White solid; 86% yield; $^1$H NMR (400 MHz, Chloroform-d) δ 8.39 (d, J = 8.5 Hz, 1H), 8.23 – 8.10 (m, 4H), 7.88 (d, J = 8.2 Hz, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.5 Hz, 2H); $^{13}$C NMR (101 MHz, Chloroform-d) δ165.9 (d, J_{C-F} = 257.6 Hz), 157.8, 147.3, 138.8, 134.9 (d, J_{C-F} = 4.0 Hz), 131.9 (d, J_{C-F} = 10.1 Hz), 131.1, 130.2, 129.3, 128.8, 127.7, 117.4, 116.4 (d, J_{C-F} = 23.2 Hz); $^{19}$F NMR (376 MHz, Chloroform-d) δ -103.3.

2-((4-chlorophenyl)sulfonyl)quinoline (3ai)

White solid; 88% yield; $^1$H NMR (400 MHz, Chloroform-d) δ 8.39 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.08 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.1 Hz, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H); $^{13}$C NMR (101 MHz, Chloroform-d) δ 157.6, 147.4, 140.5, 138.9, 137.4, 131.1, 130.5, 130.2, 129.4, 129.3, 128.8, 127.7, 117.4.

2-((4-bromophenyl)sulfonyl)quinoline (3aj)

White solid; 87% yield; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.40 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 7.4 Hz, 1H), 7.72 – 7.65 (m, 3H); $^{13}$C NMR (101 MHz, Chloroform-d) δ 157.6, 147.4, 138.9, 138.0, 132.4, 131.1, 130.6, 130.3, 129.4, 129.2, 128.9, 127.7, 117.5.

2-((4-(trifluoromethyl)phenyl)sulfonyl)quinoline (3ak)

White solid; 82% yield; 

2-(4-methoxyphenyl)sulfonyl)quinoline (3ag)

White solid; 82% yield; $^1$H NMR (400 MHz, Chloroform-d) δ 8.36 (d, J = 8.5 Hz, 1H), 8.17 (dd, J = 8.5, 4.2 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.2 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-d) δ 158.3, 157.6, 147.4, 138.7, 136.1, 130.9, 130.4, 129.1, 128.8, 128.7, 127.7, 117.8, 35.2, 31.0.
White solid; 81% yield; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.42 (d, $J = 8.5$ Hz, 1H), 8.28 (d, $J = 8.3$ Hz, 2H), 8.24 (s, 1H), 8.13 (d, $J = 8.6$ Hz, 1H), 7.89 (d, $J = 8.2$ Hz, 1H), 7.79 (dt, $J = 7.0$, 2.7 Hz, 3H), 7.67 (t, $J = 7.5$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 157.2, 147.4, 142.6, 139.0, 135.2 (q, $J_{C-F} = 33.3$ Hz), 131.2, 130.2, 129.6, 129.5, 128.9, 127.7, 126.1 (q, $J_{C-F} = 3.0$ Hz), 123.1 (q, $J_{C-F} = 273.7$ Hz), 117.5; $^{19}$F NMR (376 MHz, Chloroform-$d$) δ -63.2.

ethyl 4-(quinolin-2-ylsulfonyl)benzoate (3al)

White solid; 83% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.40 (d, $J = 8.5$ Hz, 1H), 8.26 – 8.16 (m, 5H), 8.14 (d, $J = 8.6$ Hz, 1H), 7.89 (d, $J = 8.2$ Hz, 1H), 7.79 (t, $J = 7.7$ Hz, 1H), 7.67 (t, $J = 7.5$ Hz, 1H), 4.39 (s, 2H), 1.38 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 165.0, 157.5, 147.4, 142.7, 138.9, 135.0, 131.1, 130.3, 130.1, 129.4, 129.1, 128.9, 127.7, 117.6, 61.7, 14.2.

2-([1,1'-biphenyl]-4-ylsulfonyl)quinoline (3am)

White solid; 80% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.40 (d, $J = 8.5$ Hz, 1H), 8.24 (d, $J = 8.5$ Hz, 1H), 8.22 – 8.18 (m, 3H), 7.89 (d, $J = 8.2$ Hz, 1H), 7.80 (ddd, $J = 8.4$, 6.9, 1.4 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.67 (t, $J = 7.5$ Hz, 1H), 7.61 – 7.54 (m, 2H), 7.48 – 7.36 (m, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 158.2, 147.5, 146.7, 139.2, 138.8, 137.6, 131.0, 130.4, 129.6, 129.2, 129.0, 128.9, 128.6, 127.7, 127.4, 117.7.

2-(naphthalen-2-ylsulfonyl)quinoline (3an)

White solid; 84% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.75 (s, 1H), 8.38 (dd, $J = 8.3$, 3.4 Hz, 1H), 8.27 (d, $J = 8.5$ Hz, 1H), 8.22 – 8.18 (m, 3H), 8.16 (d, $J = 9.9$ Hz, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 8.03 – 7.91 (m, 2H), 7.92 – 7.82 (m, 2H), 7.81 – 7.71 (m, 1H), 7.70 – 7.55 (m, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 158.1, 147.4, 138.8, 138.7, 136.0, 135.3, 132.1, 131.0, 130.8, 130.3, 129.5, 129.3, 129.2, 128.8, 127.9, 127.7, 127.5, 123.7, 117.8.

2-((3,5-dichlorophenyl)sulfonyl)quinoline (3ao)

White solid; 81% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.42 (d, $J = 8.8$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 8.16 (d, $J = 9.3$ Hz, 1H), 8.01 (d, $J = 1.9$ Hz, 2H), 7.90 (dd, $J = 8.2$, 1.1 Hz, 1H), 7.81 (ddd, $J = 8.5$, 6.9, 1.5 Hz, 1H), 7.69 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H), 7.54 (t, $J = 1.9$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 156.8, 147.4, 141.8, 139.1, 135.9, 133.7, 131.3, 130.3, 129.6, 129.0, 127.7, 127.3, 117.5.

2-((3-chloro-4-fluorophenyl)sulfonyl)quinoline (3ap)

White solid; 81% yield; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.42 (d, $J = 8.8$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 8.16 (d, $J = 9.3$ Hz, 1H), 8.01 (d, $J = 1.9$ Hz, 2H), 7.90 (dd, $J = 8.2$, 1.1 Hz, 1H), 7.81 (ddd, $J = 8.5$, 6.9, 1.5 Hz, 1H), 7.69 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H), 7.54 (t, $J = 1.9$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 156.8, 147.4, 141.8, 139.1, 135.9, 133.7, 131.3, 130.3, 129.6, 129.0, 127.7, 127.3, 117.5.
White solid; 87% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.41 (d, $J = 8.5$ Hz, 1H), 8.24 – 8.18 (m, 2H), 8.15 (d, $J = 8.6$ Hz, 1H), 8.06 (ddd, $J = 8.6$, 4.4, 2.3 Hz, 1H), 7.90 (d, $J = 8.2$ Hz, 1H), 7.81 (t, $J = 7.7$ Hz, 1H), 7.68 (t, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 8.5$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 161.3 (d, $J_{C-F} = 259.6$ Hz), 157.3, 147.4, 139.0, 135.9 (d, $J_{C-F} = 3.9$ Hz), 132.0 (d, $J_{C-F} = 1.6$ Hz), 131.2, 130.2, 129.8 (d, $J_{C-F} = 8.9$ Hz), 129.4, 128.9, 127.7, 122.5 (d, $J_{C-F} = 19.0$ Hz), 117.4 (d, $J_{C-F} = 22.6$ Hz), 117.3; $^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -105.5.

3-methyl-2-tosylquinoline (3ba)$^8$

White solid; 82% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.05 (s, 1H), 7.96 – 7.89 (m, 3H), 7.75 (d, $J = 7.9$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 157.0, 144.7, 144.5, 139.8, 135.8, 129.9, 129.7, 129.4, 129.1, 128.9, 128.5, 126.6, 21.7, 18.8.

4-methyl-2-tosylquinoline (3ca)$^9$

White solid; 83% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.17 (d, $J = 8.4$ Hz, 1H), 8.07 – 7.98 (m, 4H), 7.76 (t, $J = 7.7$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 2H), 2.86 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 157.9, 147.9, 147.2, 144.7, 136.2, 131.0, 130.5, 129.7, 129.0, 128.8, 128.7, 123.8, 118.1, 118.1, 21.6, 19.2.

4-chloro-2-tosylquinoline (3da)$^1$

White solid; 86% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.28 (s, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 8.2$ Hz, 2H), 7.83 (t, $J = 7.1$ Hz, 1H), 7.75 (t, $J = 7.3$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 2.41 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 158.1, 148.1, 145.2, 135.5, 131.7, 130.8, 130.1, 129.9, 129.1, 127.0, 124.2, 117.9, 21.7.

6-methoxy-2-tosylquinoline (3ea)$^2$

White solid; 81% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.21 (d, $J = 8.5$ Hz, 1H), 8.14 (d, $J = 8.6$ Hz, 1H), 8.05 (d, $J = 9.3$ Hz, 1H), 8.00 (d, $J = 8.3$ Hz, 2H), 7.41 (dd, $J = 9.3$, 2.7 Hz, 1H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 2.7$ Hz, 1H), 3.94 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 159.7, 155.7, 144.6, 143.6, 136.8, 136.5, 131.8, 130.3, 129.7, 128.9, 124.2, 118.2, 104.5, 55.7, 21.6.

6-fluoro-2-tosylquinoline (3fa)$^{10}$
White solid; 84% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.30 (d, $J = 8.6$ Hz, 1H), 8.21 – 8.11 (m, 2H), 7.99 (d, $J = 8.2$ Hz, 2H), 7.55 – 7.43 (m, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 2.37 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 161.7 (d, $J = 253.5$ Hz), 157.7, 144.9, 144.3, 138.0 (d, $J = 5.9$ Hz), 135.8, 132.9 (d, $J = 9.5$ Hz), 129.7, 129.6 (d, $J = 11.1$ Hz), 128.9, 121.5 (d, $J = 26.3$ Hz), 118.4, 110.7 (d, $J = 22.1$ Hz), 21.5; $^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -108.3.

6-chloro-2-tosylquinoline (3ga)$^1$

White solid; 84% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.3 (d, $J = 8.6$ Hz, 1H), 8.2 (d, $J = 8.6$ Hz, 1H), 8.1 (d, $J = 9.1$ Hz, 1H), 8.0 (d, $J = 8.3$ Hz, 2H), 7.9 (d, $J = 2.2$ Hz, 1H), 7.3 (d, $J = 8.1$ Hz, 2H), 2.4 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 158.6, 145.7, 145.0, 137.7, 135.7, 135.2, 132.0, 131.9, 129.8, 129.3, 129.1, 126.3, 118.6, 21.7.

6-bromo-2-tosylquinoline (3ha)$^7$

White solid; 82% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.28 (d, $J = 8.6$ Hz, 1H), 8.21 (d, $J = 8.6$ Hz, 1H), 8.05 – 8.01 (m, 3H), 7.99 (s, 1H), 7.84 (dd, $J = 9.0$, 2.1 Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 2.41 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 158.7, 145.9, 145.0, 137.6, 135.7, 134.5, 131.9, 129.8, 129.3, 129.1, 123.5, 118.6, 21.7.

8-bromo-2-tosylquinoline (3ia)$^3$

White solid; 81% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.29 (d, $J = 8.5$ Hz, 1H), 8.20 – 8.13 (m, 1H), 8.06 (d, $J = 8.0$ Hz, 2H), 7.99 (t, $J = 7.4$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 2H), 2.35 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 159.3, 145.0, 144.4, 139.2, 135.2, 134.5, 129.9, 129.8, 129.5, 129.3, 127.4, 125.8, 117.7, 21.7.

1-tosylisoquinoline (3ja)$^3$

White solid; 85% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.20 – 9.13 (m, 1H), 8.43 (d, $J = 5.5$ Hz, 1H), 7.97 (d, $J = 8.2$ Hz, 2H), 7.94 – 7.86 (m, 1H), 7.80 – 7.72 (m, 3H), 7.35 (d, $J = 8.1$ Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 157.3, 144.7, 140.5, 137.7, 136.0, 131.1, 129.6, 129.2 (d, $J = 5.1$ Hz), 127.5, 125.3, 124.9, 124.3, 77.3, 77.0, 76.7, 21.7.

4-tosylquinoline (3ka)$^{11}$

White solid; 90% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.11 (d, $J = 4.3$ Hz, 1H), 8.65 (d, $J = 8.4$ Hz, 1H), 8.22 – 8.11 (m, 2H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.77 (t, $J = 8.2$ Hz, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 2.38 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 149.6, 149.3, 145.1, 145.1, 137.1, 130.5, 130.3, 130.1,
White solid; 88% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.07 (d, $J = 4.4$ Hz, 1H), 8.31 (d, $J = 10.2$, 2.7 Hz, 1H), 8.19 (dd, $J = 10.2$, 5.0 Hz, 2H), 7.87 (d, $J = 8.3$ Hz, 2H), 7.54 (dd, $J = 9.3$, 7.9, 2.8 Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 2H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 161.3 (d, $J_{C-F} = 253.5$ Hz), 148.9 (d, $J_{C-F} = 3.0$ Hz), 146.6, 145.4, 144.8 (d, $J_{C-F} = 253.5$ Hz), 136.7, 133.1 (d, $J_{C-F} = 10.1$ Hz), 130.2, 128.0, 123.1 (d, $J_{C-F} = 11.1$ Hz), 121.8, 120.8 (d, $J_{C-F} = 25.3$ Hz), 108.5 (d, $J_{C-F} = 25.3$ Hz), 21.6; $^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -106.9.

6-bromo-4-tosylquinoline (3ma)

White solid; 85% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.10 (d, $J = 4.4$ Hz, 1H), 8.86 (d, $J = 1.8$ Hz, 1H), 8.14 (d, $J = 4.3$ Hz, 1H), 8.05 (d, $J = 9.0$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.84 (dd, $J = 9.0$, 2.0 Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 149.9, 147.8, 145.5, 145.4, 136.7, 134.1, 132.0, 130.2, 128.1, 126.7, 123.5, 123.1, 121.7, 21.7.

7-chloro-4-tosylquinoline (3na)

White solid; 81% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.10 (d, $J = 4.4$ Hz, 1H), 8.62 (d, $J = 9.2$ Hz, 1H), 8.17 (d, $J = 2.0$ Hz, 1H), 8.10 (d, $J = 4.4$ Hz, 1H), 7.86 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 2.38 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 150.8, 149.7, 145.5, 145.4, 136.8, 136.5, 130.1, 129.7, 129.4, 128.0, 125.6, 121.0, 120.5, 21.6.

7-bromo-4-tosylquinoline (3oa)

White solid; 88% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.09 (d, $J = 4.4$ Hz, 1H), 8.54 (d, $J = 9.1$ Hz, 1H), 8.36 (d, $J = 2.0$ Hz, 1H), 8.13 (d, $J = 4.4$ Hz, 1H), 7.86 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 150.7, 149.8, 145.4, 136.8, 132.7, 130.2, 128.0, 125.6, 124.8, 121.2, 120.8, 21.6.

6,7-dimethoxy-4-tosylquinoline (3pa)

White solid; 94% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.87 (d, $J = 4.6$ Hz, 1H), 7.99 (d, $J = 4.6$ Hz, 1H), 7.93 – 7.80 (m, 3H), 7.45 (s, 1H), 7.29 (d, $J = 8.1$ Hz, 2H), 4.11 – 3.93 (m, 6H), 2.37 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 152.7, 151.1, 147.2, 147.1, 145.0, 142.7, 137.4, 129.9, 127.7, 118.9, 118.2, 108.7, 101.9, 56.2, 56.1, 21.6.

4-(1-phenylethoxy)quinoline (4a)
White solid; 75% yield; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.58 (d, $J = 5.3$ Hz, 1H), 8.38 (d, $J = 9.3$ Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.71 (ddd, $J = 8.4, 6.9, 1.4$ Hz, 1H), 7.55 (ddd, $J = 8.1, 7.0, 1.1$ Hz, 1H), 7.42 – 7.32 (m, 4H), 7.29 (t, $J = 7.1$ Hz, 1H), 6.57 (d, $J = 5.3$ Hz, 1H), 5.58 (q, $J = 6.4$ Hz, 1H), 1.81 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 160.4, 151.0, 149.1, 141.7, 128.8, 128.7, 127.9, 125.6, 125.2, 122.0, 121.7, 102.6, 76.7, 24.3.

4. References
5. $^1$H and $^{13}$C NMR spectra of products

$^1$H spectrum of 3aa

$^{13}$C spectrum of 3aa
$^1$H spectrum of 3ab

$^{13}$C spectrum of 3ab
$3^1$H spectrum of 3ac

$^{13}$C spectrum of 3ac
$^{1}H$ spectrum of 3ad

$^{13}C$ spectrum of 3ad
$^{1}H$ spectrum of 3ae

$^{13}C$ spectrum of 3ae
$\text{H spectrum of 3af}$

$\text{C spectrum of 3af}$

$\text{H spectrum of 3af}$

$\text{C spectrum of 3af}$
$^1$H spectrum of 3ah

$^{13}$C spectrum of 3ah
$^1$H spectrum of 3ai
$^{13}$C spectrum of 3ai

$^1$H spectrum of 3aj
$^{13}$C spectrum of 3aj

$^1$H spectrum of 3ak
$^{13}$C spectrum of 3ak

$^{19}$F spectrum of 3ak
\(^1^H\) spectrum of 3al

\(^{13}\)C spectrum of 3al
$^{1}H$ spectrum of 3am

$^{13}C$ spectrum of 3am
$^1$H spectrum of 3ap

$^{13}$C spectrum of 3ap
$^1$H spectrum of 3ba

$^1$F spectrum of 3ap
$^{13}$C spectrum of 3ba

$^1$H spectrum of 3ca
$^{13}\text{C}$ spectrum of 3ca

$^1\text{H}$ spectrum of 3da
$^{13}$C spectrum of 3fa

$^{19}$F spectrum of 3fa
$^1$H spectrum of 3ga

$^{13}$C spectrum of 3ga
$^1$H spectrum of 3ia

$^{13}$C spectrum of 3ia
$^1$H spectrum of 3ja

$^{13}$C spectrum of 3ja
$\text{H spectrum of 3ka}$

$\text{C spectrum of 3ka}$
$\text{H spectrum of 3la}$

$\text{C spectrum of 3la}$

$\text{H spectrum of 3la}$

$\text{C spectrum of 3la}$
$^{19}$F spectrum of 3la

$^1$H spectrum of 3ma
$^{13}$C spectrum of 3ma

$^1$H spectrum of 3na
$^{13}$C spectrum of 4a

$^1$H spectrum of 1w
$^{13}$C spectrum of 3wa