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# $Sc(OTf)_3$ mediated one pot synthesis of 2,3-disubstituted quinolines from anilines and epoxides

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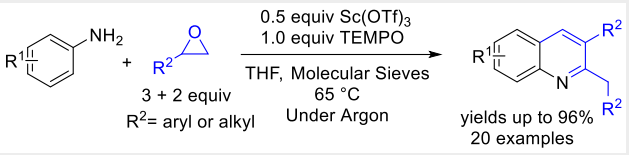
**ABSTRACT:** Here, we report the first synthesis of 2,3-disubstituted quinolines from anilines and aromatic or aliphatic epoxides. This reaction utilizes $Sc(OTf)_3$ as a Lewis acid and TEMPO as an oxygen scavenger. A wide variety of highly substituted quinolines were obtained with moderate to excellent yields (up to 96%).



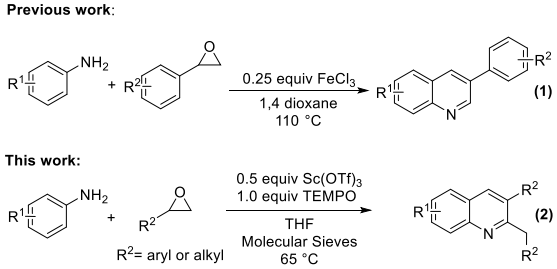

## ■ INTRODUCTION

Quinoline is one of the privileged scaffolds due to its wide abundance in biologically active natural products.[1] Compounds containing quinoline scaffolds play a significant role in wide range of therapeutic areas[2] including anti-malarial,[3] anti-microbial,[4] CNS,[5] anti-inflammatory,[6] anti-cancer agents[7] and potentially recent SARS-CoV-2 treatment.[8] Substituted quinoline derivatives have also been used as building blocks and catalysts.[9] In addition, quinoline scaffolds have applications in agrochemicals,[10] as anti-foaming agents[11] in refineries and as ligands to prepare phosphorescent complexes in sensors.[12]

Several classical approaches to synthesize quinolines including the Skraup reaction, Conrad-Limpach-Knorr reaction, Friedlander reaction, Combes reaction, Doebner-von Miller reaction, Povarov reaction and the Pfitzinger reaction, which have been well documented in the literature.[13] However, these existing methods suffer from one or more limitations including the need for high temperatures, low yields, harsh reaction conditions, limited availability of substrates, poor regioselectivity and tedious multistep procedures, which require isolation of intermediates. Several recent modifications have been made to address some of these limitations.[14] However, the synthesis of 2,3-disubstituted quinolines using readily available starting materials such as aldehydes, ketones, alkenes, alkynes, cyclobutanes or allyl alcohols is still limited to a few reports.[15] We present herein the utilization of readily available epoxides as a new approach to access 2,3-disubstituted quinolines.

In a previous report, Wang and co-workers examined the addition of epoxides and anilines in presence of $FeCl_3$ to form 3-substituted quinolines (eq 1, **Scheme 1**).[16] In their mechanism, the authors proposed a radical mediated C-C bond cleavage, resulting in de-alkylation and isolation of exclusively the C-3 substituted quinolines. Inspired by their proposed mechanism, we report herein a one pot quinoline synthesis from epoxides and anilines, using $Sc(OTf)_3$ and TEMPO, to provide the 2,3-disubstituted quinolines in yields up to 96% (eq 2, **Scheme 1**).

**Scheme 1: Synthesis of quinolines from epoxides and aromatic amines.**




## ■ RESULTS AND DISCUSSION

We commenced our investigations by treating 1 equivalent of 3,4,5-trimethoxyaniline (**1a**) with 2 equivalents of styrene oxide (**2a**), in presence of 0.1 equivalent of different Lewis acids in dichloromethane (DCM) at room temperature (**Table S1**). Lewis acids included: aluminium chloride ($AlCl_3$), silver triflate (AgOTf), gold (I) chloride (AuCl), gold (III) chloride ($AuCl_3$), gold (III) chloride trihydrate ($HAuCl_4.3H_2O$), boron trifluoride diethyl etherate ($BF_3.OEt_2$), scandium (III) triflate ($Sc(OTf)_3$), and others (**Table S1**). Among the Lewis acids tested, $AuCl_3$, $HAuCl_4.3H_2O$ and $Sc(OTf)_3$ provided the best yields of our desired 2,3-substituted quinoline **Q1**. In addition, we investigated the reactions with a few

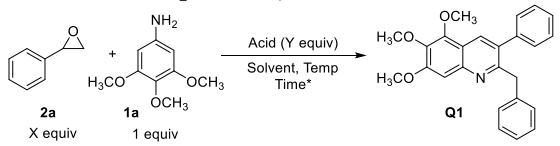
Brønsted acids, including phosphoric acid ($H_3PO_4$), trifluoroacetic acid (TFA) and triflic acid (TfOH); the latter of which was also found to be a good mediator of 2,3-disubstituted quinoline formation (**Table S1**). It is important to note that the reaction did not show any product formation in the absence of acid, under basic (2,6-lutidine or triethylamine) nor under neutral condition (**Table S1**). These studies demonstrated that the reaction requires acidic conditions to proceed. From here, we chose our best acids ($AuCl_3$, $HAuCl_4.3H_2O$, $Sc(OTf)_3$ and TfOH) for additional optimization of the reaction conditions.

The reaction was further optimized by changing the equivalents of epoxide, amine and acids (**Table S2**) and which indicated that an increase of epoxide (to 3 equivalents) and higher catalyst loading raise product formation. A further increase in the epoxide resulted in lower product formation, likely due to undesirable interactions among epoxides. From this, two sets of conditions were selected for optimization studies: (a) 3 equivalents of epoxide with 0.5 equivalents of $Sc(OTf)_3$, and (b) 4 equivalents of epoxide with 1 equivalent of TfOH.

After optimization of the Lewis acids, we evaluated various solvents and the effects of temperature on product formation. Of the solvents screened (acetonitrile (MeCN), tetrahydrofuran (THF), chloroform ($CHCl_3$), toluene, acetone and water, THF provided the best yield, possibly via a scandium-THF complex (**Table S3**). In THF, 2 extra equivalents of epoxide were added, which increased the isolated yield to 81% of quinoline product. There was a direct correlation observed between temperature and product yield, as high temperature provided more product, whereas at -78 °C no product was observed (**Table 1**). To further investigate higher temperatures, some additional solvents, including dichloroethane (DCE), 1,4-dioxane, dimethyl sulfoxide (DMSO) and 2-methyl tetrahydrofuran were screened. Interestingly, at 80 °C in 2-methyl tetrahydrofuran, product formation declined. Additionally, further temperature increases in other solvents dropped yield significantly. We observed an induction of C-2 de-alkylation, forming the 3-substituted quinolines, upon higher temperatures. The reaction pathway (**Scheme 3**) likely involved an intermediate imine, which let us to add molecular sieves (4Å), which further increased the yield to 85%.

Previous reports indicate that Fe or Cu initiate a radical mediated dealkylation of the C-2 position.[14(a),16] Although $Sc(OTf)_3$ is not anticipated to invoke radial formation, to prevent inadvertent C-2 de-alkylation, the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was added to our previously optimized conditions, which further increased yield to 91% (Scheme 2, **Q1**). This outcome suggests that 1 equivalent of radical scavenger prevents unwanted oxidation by trapping any radical formed in the reaction vessel. Additional equivalents of TEMPO did not improve product formation. The optimized conditions, (3+2 equivalents of epoxide, 0.5 equivalents of $Sc(OTf)_3$ and 1.0 equivalent of TEMPO in THF at 65 °C) were used to explore substrate scope of this reaction using various epoxides and anilines.

**Table 1: Optimization of quinoline synthesis (solvent and temperature)**




| X epoxide | Solvent | Acid | Y Acid | Temp °C | Q1 % Yield |
|---|---|---|---|---|---|
| 3 | DCM | $Sc(OTf)_3$ | 0.5 | rt | 43 |
| 3 | MeCN | $Sc(OTf)_3$ | 0.5 | rt | 36 |
| 3 | THF | $Sc(OTf)_3$ | 0.5 | rt | 44 |
| 3 | $CHCl_3$ | $Sc(OTf)_3$ | 0.5 | rt | 41 |
| 3 | THF | $Sc(OTf)_3$ | 0.5 | 65 | 48 |
| 3 | THF | $Sc(OTf)_3$ | 0.5 | 0 | 26 |
| 3 | THF | $Sc(OTf)_3$ | 0.5 | -40 | 10 |
| 3 | THF | $Sc(OTf)_3$ | 0.5 | -78 | 0 |
| 2[c] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 42 |
| 2+0.5[a,c] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 56 |
| 3+2[a] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 81 |
| 3+2[a,b] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 59 |
| 3[c] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 51 |
| 3+2[a,c] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 85 |
| **3+2[a,c,d]** | **THF** | **$Sc(OTf)_3$** | **0.5** | **65** | **91** |
| 3+2[a,c,e] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 56 |
| 3+1[a,c] | THF | $Sc(OTf)_3$ | 0.5 | 65 | 75 |
| 4 | THF | $Sc(OTf)_3$ | 0.5 | 65 | 77 |
| 5 | THF | $Sc(OTf)_3$ | 0.5 | 65 | 69 |
| 4+2[a] | THF | TfOH | 1 | 65 | 64 |
| 4+2[a] | THF | TfOH | 0.5 | 65 | 68 |
| 3+2[a] | 2-Me THF | $Sc(OTf)_3$ | 0.5 | 80 | 65 |
| 3+2[a] | DCE | $Sc(OTf)_3$ | 0.5 | reflux | 39 |

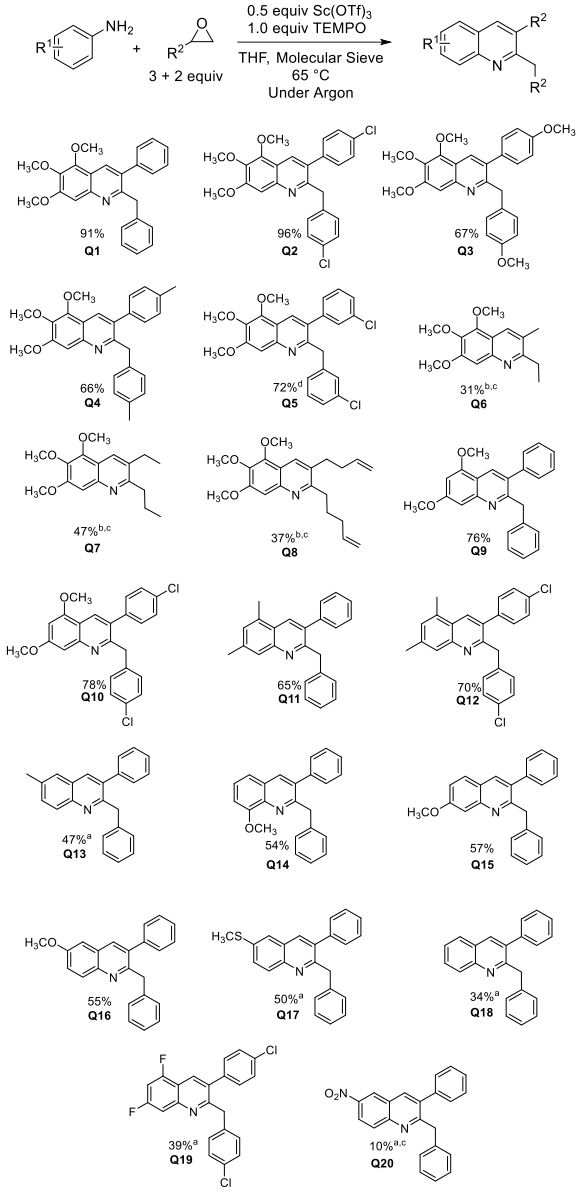
| | | | | | |
|---|---|---|---|---|---|
| 3+2[a] | 1,4-dioxane | $Sc(OTf)_3$ | 0.5 | reflux | 51 |
| 3+2[a] | DMSO | $Sc(OTf)_3$ | 0.5 | 140 | 45 |

rt=room temperature. *All reaction above rt ran for 18 h, otherwise 24 h. [a]Additional equivalents of epoxide was added after 6 h. [b]0.1mL $H_2O$ was added at the beginning. [c]4Å molecular sieve was added. [d]1 equivalent TEMPO was added. [e]5 equivalent TEMPO was added.

Initially, 3,4,5-trimethoxy aniline (**1a**) was screened with different substituted styrene oxides (**2**). As shown in **Scheme 2**, both electron donating and electron withdrawing groups were well tolerated and the corresponding quinolines were obtained in 66-96% yields (**Q2-Q5**). Epoxides with electron withdrawing group (4-chlorostyrene oxide) provided the best yield 96% (**Q2**), likely due to the reduction of oxidative C-2 de-alkylation.[17] In addition to aromatic epoxides, a few aliphatic epoxides were examined. Propylene oxide, butylene oxide and 1,2-epoxy-5-hexene all moderately reacted with **1a** to provide the highly substituted quinolines (**Q6-Q8**) in 31-47% yield.

Next, various aromatic amines (**1**) bearing different substituents, including electron-withdrawing and electron-donating groups, were reacted with styrene oxide (**2a**) or 4-chlorostyrene oxide. It was found that reduction of the electron density in the aromatic amine directly impacted product yields. Removing one methoxide from 3,4,5-trimethoxy aniline (**1a**) to 3,5-dimethoxyaniline provided 76% and 78% of quinoline **Q9** and **Q10**, respectively. A similar trend was observed with alkyl substituted aromatic amines, which provided quinolines **Q11-Q13** in 47-70% yields. Anilines with one methoxy group on their ortho-, meta-, or para-position provided quinolines **Q14-Q16,** in similar yield of 54-57%. It should be noted that, only one regioisomer (**Q15**) was isolated, when *m*-methoxy aniline was used as starting aniline. As anticipated from the previous trend, treatment of aniline with **2a** gave 34% of the quinoline product (**Q18**). Only 10% product (**Q20**) was isolated when we used most electron deficient group ($-NO_2$) at the para position of the aromatic amine. In addition, a gram scale reaction was conducted with styrene oxide (**2a**) and 3,4,5-trimethoxy aniline (**1a**) and the quinoline product **Q1** was obtained with 78% yield (See Supplemental, Page S5).

**Scheme 2: Substrate scope of the reaction**

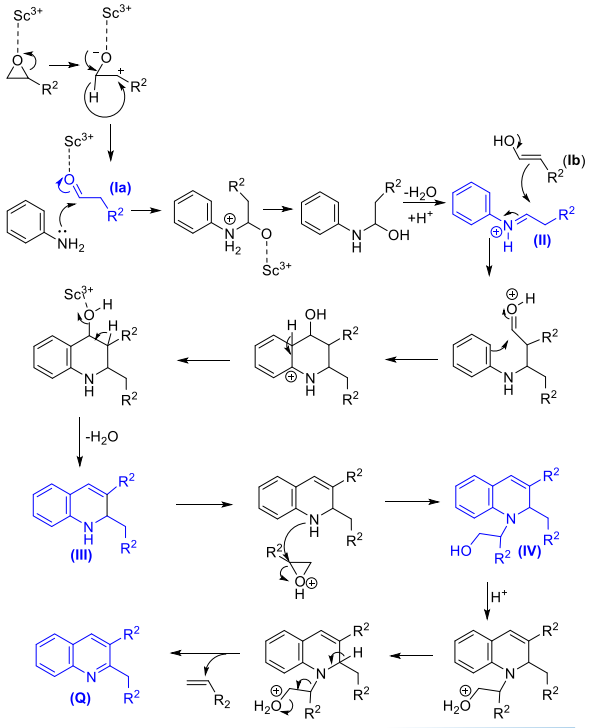



[a]Additional 1 equivalent of epoxide was added at 12 h and reaction ran for 24 h. [b]Reaction ran with a total of 3 equivalents of epoxide. [c]Reaction ran without TEMPO. [d]Temperature at 60 °C.

A plausible mechanism consistent with the observed results (see also supplemental information), is proposed in **Scheme 3**. The reaction is initiated following the rapid *in situ* generation of aldehyde **Ia** (observed by NMR within 5 minutes, see supplemental *Mechanistic Experiment-3*) by $Sc^{3+}$, to form iminium **II** (observed in MS, Fig. S1). A second equivalent of the enol tautomer of aldehyde **Ib** reacts with iminium **II**, which undergoes cyclization with aryl group to form the 1,2-dehydroquinoline **III** (observed in MS, Fig. S1). Oxidation of the

dihydroquinoline **III** can be envisioned, following the addition of another epoxide to **III**, to render intermediate **IV** (observed in MS, Fig. S2 and Fig. S3), to yield the desired quinoline **Q**. In further support of this mechanism, the product is also formed upon addition of phenylacetaldehyde albeit in significantly lower yield (Supplemental: Mechanistic investigation 1).

**Scheme 3: Proposed mechanism of the reaction**



## ■ CONCLUSIONS

In summary, we have developed a new method for the synthesis of 2,3-disubstituted quinolines from epoxides and aromatic amines. This reaction tolerates a variety of electron donating aromatic amines with both aliphatic and aromatic epoxides to provide the quinoline scaffold in moderate to excellent yields.

## ■ EXPERIMENTAL SECTION

**General information.** Commerically available reagents were used without additional purification. All reactions were performed under an argon atmosphere with commerical-grade reagents. THF was dried under 3Å molecular sieve and checked for any water content before using in the reaction. Molecular sieve (3Å and 4Å) was freshly activated before use. All flasks were oven-dried overnight and cooled under argon. All NMR spectra were recorded on a 500 MHz spectrometer. Mass spectrometer ionization method was ESI with a Quadrupole detector and infrared specta were recorded on a Jasco Series 6600 FTIR spectrometer.

**Method to synthesize gram scale *2-benzyl-5,6,7-trimethoxy-3-phenylquinoline* (Q1).** To a solution of dry tetrahydrofuran (THF) (40 mL) in a 100 mL dry round bottom flask, styrene oxide (3 equiv, 15 mmol) was added, followed by $Sc(OTf)_3$ (0.5 equiv, 2.5 mmol) at room temperature. Then 3,4,5-trimethoxy aniline (1 equiv, 5 mmol) was added at room temperature. The reaction was placed under argon gas and was stirred for 6 hours at 65 °C in oil bath. Then, another 2 equiv (10 mmol) of styrene oxide was added dropwise and the reaction was continued to stir for additional 12 hours. After that, the reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure. Then 40 mL of dichloromethane and 40ml saturated $NaHCO_3$ solution was added and the solution was extracted with 3×40 mL of dichloromethane. The combined organic layers were collected and evaporated under reduced pressure and product was purified using automated CombiFlash chromatography (silica gel, 20-40 microns, gradient 7.5% ethyl acetate in hexane). Yield: 1.497gm (78%).

**General method to synthesize of 2,3-substituted quinoline (Q).** To a solution of dry tetrahydrofuran (THF) (10 mL) in a 50 mL dry round bottom flask, different substituted epoxides (3 equiv, 0.75 mmol) were added, followed by $Sc(OTf)_3$ (0.5 equiv, 0.125 mmol) at room temperature. Then different substituted aromatic amines (1 equiv, 0.25 mmol), followed by TEMPO (1 equiv, 0.25 mmol) was added at room temperature. The reaction was placed under argon gas and was stirred for 6 hours at 65 °C in sand bath (Compound Q1, Q5, Q7 and Q19 in oil bath). Then, another 2 equiv of the same epoxide was added dropwise and the reaction was allowed to stir for additional 12 hours. After that, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. Then 10mL of dichloromethane and 10ml saturated $NaHCO_3$ solution was added and the solution was extracted with 3×10mL of dichloromethane. The combined organic layers were collected and evaporated under reduced pressure and the crude products were purified using automated CombiFlash chromatography (silica gel, 20-40 microns, gradient 1.5-20% ethyl acetate in hexane).

*2-benzyl-5,6,7-trimethoxy-3-phenylquinoline* (**Q1**). Colorless oil (88mg, 91%). Isolated with 7.5% ethyl acetate in hexane. IR: 3058, 3027, 2936, 1616, 1591, 1563, 1480, 1370, 1101 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.19 (s, 1H), 7.42 (m, 3H), 7.32 – 7.30 (m, 2H), 7.26 (s, 1H), 7.23 – 7.08 (m, 3H), 7.0 (d, *J* = 7.0 Hz, 2H), 4.28 (s, 2H), 4.05 (s, 3H), 4.03 (s, 3H), 3.96 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ

158.1, 156.1, 146.9, 145.1, 140.7, 140.2, 140.1, 133.6, 131.1, 129.6, 128.8, 128.2, 128.0, 127.3, 125.8, 117.6, 103.7, 61.5, 61.0, 56.0, 42.1. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{25}H_{24}NO_3^+$) 386.1751; Found 386.1756.

*2-(4-chlorobenzyl)-3-(4-chlorophenyl)-5,6,7-trimethoxyquinoline* (**Q2**). Colorless oil (108mg, 96%). Isolated with 7.5% ethyl acetate in hexane. IR: 3060, 3026, 2917, 1600, 1585, 1493, 1073, 760, 695 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.14 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 4.20 (s, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 157.3, 156.4, 146.9, 145.1, 140.8, 138.6, 138.3, 133.4, 132.2, 131.6, 131.3, 130.9, 130.2, 128.3, 128.1, 117.6, 103.6, 61.5, 61.0, 56.1, 41.6. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{25}H_{22}Cl_2NO_3^+$) 454.0971; Found 454.0986.

*5,6,7-trimethoxy-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)quinoline* (**Q3**). Colorless oil (30mg, 67%; ran with 0.1mmol of aromatic amine as 1 equiv). Isolated with 10% ethyl acetate in hexane. IR: 3062, 3031, 2933, 1611, 1510, 1371, 1210, 1101, 1033 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.16 – 8.11 (m, 1H), 7.24 (s, 1H), 7.23 – 7.20 (m, 2H), 6.99 – 6.89 (m, 4H), 6.75 – 6.69 (m, 2H), 4.20 (s, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H), 3.74 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 159.1, 158.7, 157.8, 156.0, 146.9, 144.9, 140.6, 133.2, 132.5, 132.1, 131.1, 130.7, 129.7, 117.6, 113.5, 113.4, 103.6, 61.5, 61.0, 56.0, 55.3, 55.1, 41.2. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{27}H_{28}NO_5^+$) 446.1962; Found 446.1973.

*5,6,7-trimethoxy-2-(4-methylbenzyl)-3-(p-tolyl)quinoline* (**Q4**). Colorless oil (27mg, 66%; ran with 0.1mmol of aromatic amine as 1 equiv). Isolated with 7.5% ethyl acetate in hexane. IR: 3051, 3019, 2935, 1616, 1480, 1370, 1101 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.17 (s, 1H), 7.27 – 7.21 (m, 5H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 4.23 (s, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.96 (s, 3H), 2.44 (s, 3H), 2.28 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 158.4, 156.0, 146.9, 145.0, 140.7, 137.3, 137.2, 137.1, 135.3, 133.5, 131.1, 129.5, 128.8, 128.7, 128.6, 117.6, 103.6, 61.5, 61.0, 56.0, 41.5, 20.9, 20.7.HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{27}H_{28}NO_3^+$) 414.2064; Found 414.2074.

*2-(3-chlorobenzyl)-3-(3-chlorophenyl)-5,6,7-trimethoxyquinoline* (**Q5**). Colorless oil (82mg, 72%). Isolated with 7.5% ethyl acetate in hexane. IR: 3059, 2936, 1615, 1475, 1369, 1104, 1037, 783, 683 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.17 (s, 1H), 7.42 – 7.35 (m, 2H), 7.26 (s, 1H), 7.23 (t, *J* = 1.8 Hz, 1H), 7.18 – 7.11 (m, 3H), 6.98 (s, 1H), 6.90 – 6.86 (m, 1H), 4.22 (s, 2H), 4.05 (s, 3H), 4.04 (s, 3H). 3.96 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 156.9, 156.5, 146.9, 145.2, 141.8, 140.9, 133.9, 133.7, 132.0, 131.3, 129.6, 129.5, 129.4, 128.8, 127.8, 127.5, 127.3, 127.1, 126.1, 117.6, 103.6, 61.5, 61.0, 56.1, 42.1. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{25}H_{22}Cl_2NO_3^+$) 454.0971; Found 454.0980.

*2-ethyl-5,6,7-trimethoxy-3-methylquinoline* (**Q6**). Colorless solid (20mg, 31%). Isolated with 15% ethyl acetate in hexane. MP: 95-97 °C. IR: 3017, 2964, 2925, 1604, 1484, 1389, 1238, 1093, 1002 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.04 (s, 1H), 7.17 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 2.93 (q, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 1.33 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 162.2, 155.1, 146.5, 144.1, 140.2, 130.0, 127.0, 117.8, 103.4, 61.4, 60.9, 55.9, 28.9, 18.7, 12.3. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{15}H_{20}NO_3^+$) 262.1438; Found 262.1449.

*3-ethyl-5,6,7-trimethoxy-2-propylquinoline* (**Q7**). Colorless oil (34mg, 47%). Isolated with 20% ethyl acetate in hexane. IR: 3010, 2961, 2937, 1601, 1479, 1373, 1236, 1094, 1001 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.05 (s, 1H), 7.14 (s, 1H), 4.04 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H), 2.91 – 2.87 (m, 2H), 2.82 (q, *J* = 7.5 Hz, 2H), 1.81 (dd, *J* = 15.5, 7.5 Hz, 2H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 161.0, 155.1, 146.6, 144.1, 140.1, 133.1, 128.1, 117.8, 103.5, 61.4, 60.9, 55.9, 37.4, 25.2, 22.6, 14.6, 14.1. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{17}H_{24}NO_3^+$) 290.1751; Found 290.1758.

*3-(but-3-en-1-yl)-5,6,7-trimethoxy-2-(pent-4-en-1-yl)quinoline* (**Q8**). Colorless oil (32mg, 37%). Isolated with 12% ethyl acetate in hexane. IR: 3074. 3001, 2934, 1616, 1566, 1481, 1243, 1093 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.05 (s, 1H), 7.15 (s, 1H), 6.04 – 5.85 (m, 2H), 5.18 – 4.98 (m, 4H), 4.04 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 2.95 – 2.86 (m, 4H), 2.48 – 2.43 (m, 2H), 2.23 (q, *J* = 7.3 Hz, 2H), 1.90 (dt, *J* = 15.4, 7.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 160.8, 155.2, 146.5, 144.3, 140.2, 138.7, 137.9, 130.7, 129.2, 117.6, 115.0, 114.5, 103.5, 61.4, 61.0, 55.9, 34.7, 34.6, 33.8, 31.7, 28.5. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{21}H_{28}NO_3^+$) 342.2064; Found 342.2066.

*2-benzyl-5,7-dimethoxy-3-phenylquinoline* (**Q9**). Yellow solid (68mg, 76%). Isolated with 6.5% ethyl acetate in hexane. MP: 80-82 °C. IR: 3059, 3019, 2920, 1628, 1575, 1493, 1382, 1204, 1117, 1044 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.27 (s, 1H), 7.44 – 7.37 (m, 3H), 7.32 – 7.29 (m, 2H), 7.21 – 7.15 (m, 2H), 7.13 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.08 – 6.95 (m, 3H), 6.54 (d, *J* = 2.1 Hz, 1H), 4.28 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 161.4, 159.3, 156.1, 149.4, 140.2, 140.0, 132.9, 131.5, 129.6, 128.8, 128.1, 128.0, 127.2, 125.8, 115.0, 99.2, 97.8, 55.8, 55.6, 42.2. HRMS (ESI-TOF) m/z:

[(M+H)+] calcd for ($C_{24}H_{22}NO_2^+$) 356.1645; Found 356.1653.

*2-(4-chlorobenzyl)-3-(4-chlorophenyl)-5,7-dimethoxyquinoline* (**Q10**). Light yellow oil (83mg, 78%). Isolated with 7.5% ethyl acetate in hexane. IR: 3063, 3007, 2931, 1621, 1575, 1490, 1379, 1204, 1014, 809, 732, 673 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.23 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.17 (dd, *J* = 17.2, 8.4 Hz, 4H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 1.8 Hz, 1H), 4.20 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 161.6, 158.5, 156.1, 149.5, 138.6, 138.3, 133.3, 131.7, 131.6, 131.4, 130.9, 130.2, 128.3, 128.1, 115.0, 99.2, 98.0, 55.8, 55.7, 41.7. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{24}H_{20}Cl_2NO_2^+$) 424.0866; Found 424.0846.

*2-benzyl-5,7-dimethyl-3-phenylquinoline* (**Q11**). Colorless oil (53mg, 65%). Isolated with 4% ethyl acetate in hexane. IR: 3026, 2960, 2919, 1622, 1595, 1494, 1257, 1073, 1007 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.09 (s, 1H), 7.72 (s, 1H), 7.42 – 7.39 (m, 3H), 7.32 – 7.29 (m, 2H), 7.24 (s, 1H), 7.13 (dd, *J* = 13.3, 7.0 Hz, 3H), 6.98 (d, *J* = 7.0 Hz, 2H), 4.31 (s, 2H), 2.64 (s, 3H), 2.54 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 158.3, 147.8, 140.3, 139.9, 139.3, 134.6, 134.2, 133.2, 129.6, 129.0, 128.8, 128.2, 128.0, 127.4, 126.0, 125.8, 124.2, 42.3, 21.5, 18.3. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{24}H_{22}N^+$) 324.1747; Found 324.1756.

*2-(4-chlorobenzyl)-3-(4-chlorophenyl)-5,7-dimethylquinoline* (**Q12**). Colorless oil (69mg, 70%). Isolated with 4% ethyl acetate in hexane. IR: 3045, 2972, 2916, 1621, 1591, 1489, 1369, 1263, 1015, 807, 712, 667 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.08 (s, 1H), 7.74 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 4.26 (s, 2H), 2.64 (s, 3H), 2.55 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 157.5, 147.9, 139.7, 138.6, 138.2, 134.3, 133.5, 133.4, 133.2, 131.6, 130.9, 130.2, 129.3, 128.4, 128.1, 126.0, 124.1, 41.8, 21.6, 18.2. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{24}H_{20}Cl_2N^+$) 392.0967; Found 392.0944.

*2-benzyl-6-methyl-3-phenylquinoline* (**Q13**). Light yellow oil (36mg, 47%). Isolated with 3% ethyl acetate in hexane. IR: 3025, 2915, 1601, 1489, 1368, 1073, 1030 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 7.98 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.20 – 7.08 (m, 3H), 6.98 (d, *J* = 7.4 Hz, 2H), 4.31 (s, 2H), 2.56 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 158.0, 145.8, 139.9, 139.8, 136.2, 136.0, 135.9, 131.5, 129.4, 128.8, 128.4, 128.2, 128.0, 127.4, 126.9, 126.2, 125.8, 42.4, 21.3. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{23}H_{20}N^+$) 310.1590; Found 310.1599.

*2-benzyl-8-methoxy-3-phenylquinoline* (**Q14**). Light yellow oil (44mg, 54%). Isolated with 5% ethyl acetate in hexane. IR: 3058, 3025, 2926, 1614, 1594, 1564, 1494, 1272, 1113, 1030 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 7.97 (s, 1H), 7.50 – 7.47 (m, 1H), 7.43 – 7.39 (m, 4H), 7.28 – 7.25 (m, 2H), 7.16 – 7.09 (m, 4H), 6.96 – 6.91 (m, 2H), 4.36 (s, 2H), 4.10 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 157.6, 155.3, 139.9, 139.7, 139.1, 136.7, 136.4, 129.3, 128.7, 128.2, 128.1, 128.0, 127.5, 126.5, 125.7, 119.2, 107.8, 56.0, 42.5. HRMS (ESI-TOF) m/z: [(M+H)$^+$] calcd for ($C_{23}H_{20}NO^+$) 326.1539; Found 326.1542.

*2-benzyl-7-methoxy-3-phenylquinoline* (**Q15**). Light yellow oil (46mg, 57%). Isolated with 5% ethyl acetate in hexane. IR: 3058, 3026, 2927, 1619, 1601, 1492, 1375, 1209, 1026 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_3OD$) δ 8.00 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.34 (m, 3H), 7.23 – 7.18 (m, 3H), 7.10 – 7.05 (m, 3H), 6.85 – 6.81 (m, 2H), 4.28 (s, 2H), 3.97 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_3OD$) δ 161.4, 158.9, 148.2, 139.3, 139.1, 137.4, 134.1, 129.2, 128.7, 128.2, 128.0, 127.8, 127.3, 125.7, 122.3, 119.5, 105.1, 54.7, 41.5. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{23}H_{20}NO^+$) 326.1539; Found 326.1545.

*2-benzyl-6-methoxy-3-phenylquinoline* (**Q16**). Light yellow oil (45mg, 55%). Isolated with 5% ethyl acetate in hexane. IR: 3058, 3030, 2921, 1622, 1492, 1224, 1028 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 7.98 (d, *J* = 9.2 Hz, 1H), 7.91 (s, 1H), 7.45 – 7.40 (m, 3H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.19 – 7.08 (m, 4H), 7.02 – 6.95 (m, 2H), 4.28 (s, 2H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 157.7, 156.4, 143.3, 140.0, 139.9, 136.2, 135.6, 130.2, 129.4, 128.8, 128.2, 128.0, 127.8, 127.4, 125.8, 121.9, 104.8, 55.5, 42.2. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{23}H_{20}NO^+$) 326.1539; Found 326.1544.

*2-benzyl-6-(methylthio)-3-phenylquinoline* (**Q17**). Light yellow oil (43mg, 50%). Isolated with 3% ethyl acetate in hexane. IR: 3025, 2917, 1600, 1585, 1493, 1261, 1073, 823, 728 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 7.97 (d, *J* = 8.9 Hz, 1H), 7.89 (s, 1H), 7.60 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.44 – 7.41 (m, 3H), 7.30 – 7.27 (m, 2H), 7.17 – 7.11 (m, 3H), 7.00 – 6.95 (m, 2H), 4.29 (s, 2H), 2.60 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 158.2, 145.4, 139.7, 139.7, 137.1, 136.5, 135.4, 129.4, 129.0, 128.8, 128.7, 128.2, 128.0, 127.5, 127.4, 125.8, 122.0, 42.3, 15.5. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{23}H_{20}NS^+$) 342.1311; Found 342.1318.

*2-benzyl-3-phenylquinoline* (**Q18**). Light yellow oil (25mg, 34%). Isolated with 1.5% ethyl acetate in hexane. IR: 3025, 2922, 1601, 1592, 1486, 1410, 1073 $cm^{-1}$. $^1H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.10 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.58-7.56 (dd, *J* = 7.0 Hz, *J* = 8.1

Hz, 1H), 7.46 – 7.40 (m, 3H), 7.32 – 7.29 (m, 2H), 7.19 – 7.11 (m, 3H), 6.99 (d, *J* = 7.4 Hz, 2H), 4.34 (s, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 159.1, 147.2, 139.7, 139.7, 136.7, 136.0, 129.4, 129.3, 128.8, 128.8, 128.2, 128.0, 127.5, 127.5, 126.9, 126.3, 125.8, 42.5. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{22}H_{18}N^+$) 296.1434; Found 296.1444.

*2-(4-chlorobenzyl)-3-(4-chlorophenyl)-5,7-difluoroquinoline* (**Q19**). White solid (39mg, 39%). Isolated with 1.5% ethyl acetate in hexane. MP: 62-63 °C. IR: 3059, 3026, 2917, 1639, 1573, 1443, 1373, 1233, 1133, 1052, 1004, 854, 755, 696 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.18 (s, 1H), 7.61 – 7.55 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.15 (m, 4H), 7.10 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 4.26 (s, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 161.5 (dd, *J* = 248, 14 Hz), 160.9 (dd, *J* = 256, 15 Hz), 157.4, 148.0 (dd, *J* = 14, 4.5 Hz), 137.4, 137.3, 134.3 (dd, *J* = 6, 3 Hz), 134.0, 131.9, 130.8, 130.3, 130.2 (dd, *J* = 3.5, 2 Hz), 128.6, 128.2, 114.6 (dd, *J* = 15, 2 Hz), 108.7 (dd, *J* = 21, 4.5 Hz), 102.0 (dd, *J* = 21, 6 Hz), 42.0. m/z: [(M+H)+] calcd for ($C_{22}H_{14}Cl_2F_2N^+$) 400.0466; Found 400.0445.

*2-benzyl-6-nitro-3-phenylquinoline* (**Q20**). Light yellow oil (9mg, 10%). Isolated with 3% ethyl acetate in hexane. IR: 3025, 2921, 1601, 1575, 1520, 1494, 1403, 1021 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CD_2Cl_2$) δ 8.81 (s, 1H), 8.48 (d, *J* = 9.2 Hz, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.18 (s, 1H), 7.48 (s, 3H), 7.31 – 7.30 (m, 2H), 7.18 – 7.16 (m, 3H), 7.00 – 6.98 (m, 2H), 4.37 (s, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CD_2Cl_2$) δ 163.5, 152.2, 144.1, 138.7, 138.5, 138.1, 137.9, 130.6, 129.3, 128.9, 128.5, 128.1, 128.1, 126.2, 125.7, 124.4, 122.6, 42.8. HRMS (ESI-TOF) m/z: [(M+H)+] calcd for ($C_{22}H_{17}N_2O_2^+$) 341.1285; Found 341.1292.

## ■ ASSOCIATED CONTENT

**Supporting Information** Detailed experimental procedures and spectroscopy data for all compounds synthesized is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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