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One-Step Catalytic Synthesis of Alkyl-Substituted Quinolines

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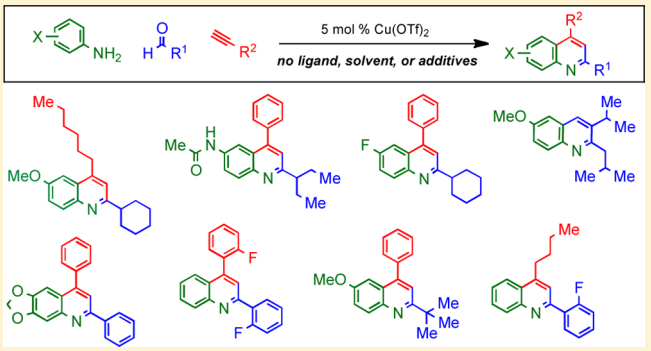
Supporting Information

ABSTRACT: Difficult-to-access alkyl-substituted quinolines are formed directly from commercially available anilines, aldehydes, and alkynes bearing a variety of substituents. Copper(II) triflate catalyzes this three-component coupling without ligand, cocatalyst, solvent, or inert atmosphere. In addition, a two-component Povarov reaction forms 2,3-dialkyl quinolines under the same green conditions that enable the selective three-component synthesis of 2-alkyl quinolines as well as more common aryl quinolines.



Quinolines are valued as luminescent materials, tunable ligands, natural products, and medicines.[1−8] As in classic Skraup,[2] Friedlander,[3] Doebner-Von Miller, Pfitzinger, Conrad−Limpach, and Combes reactions, a multitude of quinoline syntheses developed over the past 130 years utilize a starting material with two or three functional groups.[4] For example, an aryl amine bearing a carbonyl condenses and cyclizes with a separate carbonyl substrate in the Friedländer quinoline synthesis.[3−5] Quinolines bearing aryl and other sp^2 groups are readily accessed by these methods. Additional groups must be incorporated during the synthesis of the bifunctional starting material as only the simplest variants tend to be commercially available.[4−6]

Figure 1 shows a small sampling of the alkyl-substituted quinolines that display activity against malaria, inflammation,

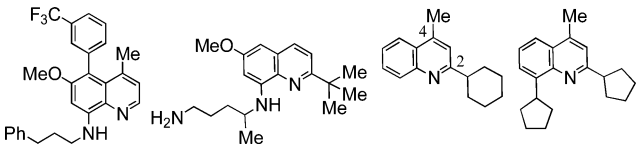


Figure 1. Alkyl quinolines with therapeutic indicators.

cancer, and tuberculosis.[7,8] The greater activity imparted by alkyl groups, particularly by those at C-2 adjacent to the quinoline nitrogen, is credited to an overall increase in lipophilicity, which increases cell permeability.[8] However, Friedländer annulation of 2-amino benzaldehydes with alkyl ketones can result in mixtures of 2-alkyl versus 2,3-dialkyl quinolines due to nonregioselective enolate formation.[5] Thus, access to alkyl-substituted quinolines is a challenge medicinal chemists continue to approach by alkylation of an advanced quinoline starting material or by multistep procedures involving nitroarene reduction.[7−9]

Multicomponent coupling reactions are a powerful tool for the synthesis of a variety of heterocycles.[10] This mode of heterocycle construction allows for variation in each component while eliminating waste generated in multistep syntheses. So-called A^3 (Aldehyde-Amine-Alkyne) three-component coupling reactions allow for maximum variability in product structures as hundreds of aldehyde, aniline, and alkyne starting materials are commercially available.[11,12] A^3 couplings begin with the condensation of an aldehyde and an amine to produce an imine electrophile, and attack by the acetylide nucleophile formed from a terminal alkyne produces a propargylamine. *N*-Aryl propargylamines can be converted to heteroaromatic compounds.[12]

In 2002, a copper-catalyzed A^3 coupling of aniline **1**, benzaldehyde **2**, and alkyne **3** was reported.[13] Condensation to imine **4** is followed by alkynylation to propargylamine **5** as well as in situ cyclization and oxidation to quinoline **6**. A loading of 30 mol % CuCl provides 9−48% yield of propargylamine **5** and 31−48% yield of quinoline **6**. These product mixtures are attributed to the reduction of imine **4** during oxidation of **5** to **6**, which also produces *N*-benzylaniline **7** (Scheme 1).

In 2008, Xiao et al. showed that 5 mol % $AuCl_3$ could be applied to convert propargylamines into 2,4-diaryl quinolines in 65−87% yield.[14] However, no alkyl aldehydes were incorporated, and propargylamines similar to **5**, lacking an aryl group on the alkyne, did not convert into the desired quinoline in 3 days. In contrast, if 5 mol % $AuCl_3$ is combined with 30 mol % CuBr, this dual catalyst A^3 forms 2,4-diaryl quinolines directly from aryl aldehydes, anilines, and phenylacetylene derivatives.[15] A number of groups have applied Lewis acid, acidic resin, and microwave methods for better conversion of aryl aldehydes to

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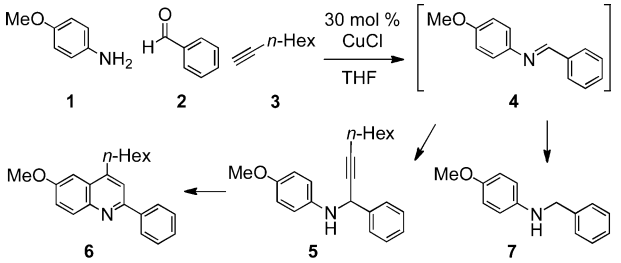
Scheme 1. A^3 Forms Propargylamine and 2-Aryl Quinoline along with Reduced Imine

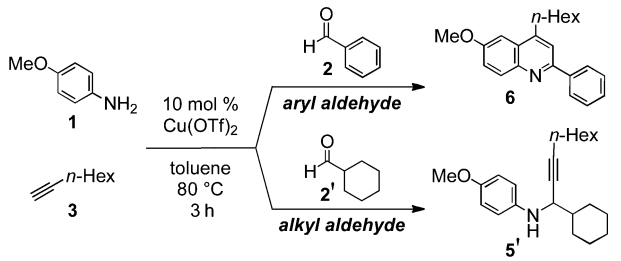


aryl-substituted quinolines.[16] In contrast, alkyl aldehydes are rarely reported in A^3 syntheses of quinolines: as they are more acidic than terminal alkynes, alkyl aldehydes enolize and produce side-products via Povarov reactions.[17,18]

Herein, we present a solvent-free copper-catalyzed A^3 reaction capable of producing a wide variety of quinolines substituted with alkyl as well as aryl, fluorine, ether, thioether, and amide groups in excellent yields under an ambient atmosphere.

Copper(II) trifluoromethanesulfonate, $Cu(OTf)_2$, is sufficiently active to catalyze the formation of propargylamines from either electron-poor *p*-toluenesulfonamide or electron-rich alkyl amines.[19] When *p*-anisidine (**1**), benzaldehyde (**2**), and 1-octyne (**3**) are treated with 10 mol % $Cu(OTf)_2$ in toluene at 80 °C, conversion to 4-alkyl quinoline **6** is complete in 3 h (Scheme 2). In contrast with the results from Scheme 1 in the presence of 30 mol % CuCl,[13] intermediate propargylamine **5** is not observed in the presence of 10 mol % $Cu(OTf)_2$.

Scheme 2. Aryl Aldehyde Forms Quinoline while Alkyl Aldehyde Halts at Propargylamine under the Same Conditions



The bottom equation in Scheme 2 highlights the obstacle presented when incorporation of an alkyl aldehyde is attempted. If cyclohexanecarboxaldehyde **2′** is substituted for benzaldehyde **2** under identical conditions, propargylamine **5′** forms rather than the corresponding quinoline. Therefore, the barrier to cyclize and oxidize to a 2-alkyl quinoline appears significantly higher than to a 4-alkyl quinoline: uncyclized propargylamine **5′** remains, whereas conversion to 2-aryl-4-alkyl quinoline **6** is complete in 3 h. Heating the reaction mixture containing **5′** to 100 °C results in incomplete cyclization and oxidation to the desired quinoline. As quinoline **6** and propargylamine **5′** are produced cleanly without concurrent imine reduction, these conditions presented an improved platform from which to optimize the efficient one-step synthesis of 4-alkyl and 2-alkyl quinolines.

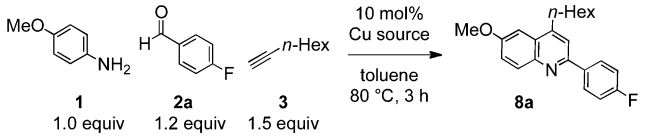
To ascertain whether copper(II) triflate is the optimal catalyst for the A^3 synthesis of quinolines, both Cu(I) and Cu(II) sources were reexamined in the formation of **8a** (Table 1) from *p*-anisidine, *p*-fluorobenzaldehyde, and 1-octyne. A range of copper(I) and copper(II) acetate and halide salts did not catalyze this A^3 reaction beyond the formation of imine (entries 1–5). Trace product formed with 10 mol % CuBr or $CuBr{\cdot}Me_2S$ (Table 1, entries 6 and 7). Superior activity was observed with $Cu(OTf)_2$, CuOTf, and $Cu(ClO_4)_2$ as catalysts (Table 1, entries 8–10). Thus, the highest yields are obtained with catalysts bearing less coordinating, nonhalide counterions.

At 80 °C, conversion drops when the catalyst loading is reduced to 5 mol %, but switching from toluene to chloroform as the solvent improves conversion and provides 78% yield of quinoline **8a** in 12 h. Note that the byproduct of this reaction is 1 equiv of water. Under an ambient atmosphere, nitrogen, or argon and with up to 10 equiv of water added, this A^3 coupling of aldehydes, anilines, and alkynes proceeds with nearly identical GC yields. It has been shown that the air-oxidation of dihydroquinoline to quinoline is extremely rapid;[14] thus, it is likely that oxidation occurs as soon as the reaction is sampled.

This lower 5 mol % catalyst loading with $CHCl_3$ as the solvent also serves when 1-octyne is replaced with phenylacetylene for A^3 reactions with anilines and aryl aldehydes (Scheme 3). Under Procedure A, aniline and *p*-anisidine react in $CHCl_3$ at 80 °C to form quinolines **8b** and **8c** in 87% and 78% yield, respectively. 5-Aminobenzodioxole and 4-aminobiphenyl provide good yields of **8d** and **8e** under Procedure A in 12–20 h.

Because of an interest in solvent-free green chemistry,[20,21] the reaction of *p*-toluidine to form 6-methyl-2,4-diphenyl-

Table 1. Copper Triflate and Perchlorate Are the Most Active Catalysts for A^3 Synthesis of 4-Alkyl Quinoline 8a[a]



entry	Cu source	GC yield (%)	entry	Cu source	GC yield (%)
1	$Cu(OAc)_2$	0	6	CuBr	5
2	CuOAc	0	7	$CuBr{\cdot}Me_2S$	7
3	$CuCl_2$	0	8	$Cu(OTf)_2$	72
4	CuI	0	9	CuOTf	69
5	$CuBr_2$	0	10	$Cu(ClO_4)_2$	72

[a]Corrected GC yield (%) of reactions carried out in toluene under an ambient atmosphere with 1.0 equiv of aniline, 1.2 equiv of aldehyde, 1.2 equiv of alkyne, and dodecane as the internal standard.

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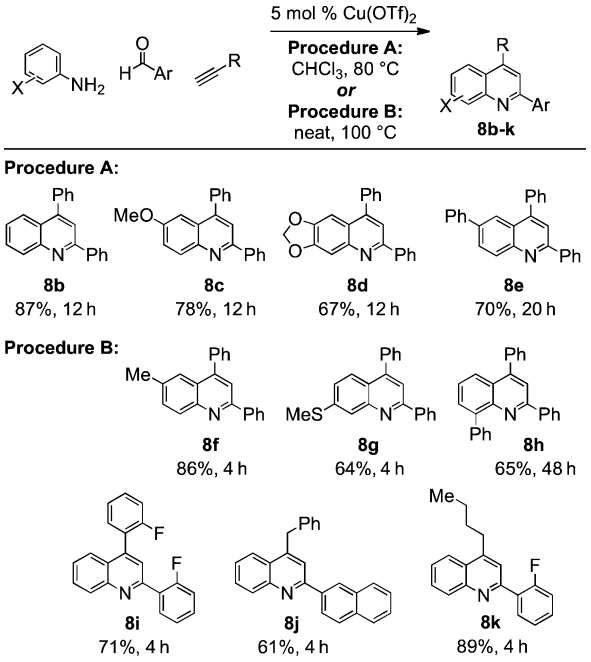
Scheme 3. Efficient A^3 Reaction of Various Anilines with Benzaldehydes and Alkynes under Conditions A or B[a]



[a]Isolated yield (%) of reactions carried out under an ambient atmosphere with 1.0 equiv of aniline, 1.2 equiv of aldehyde, and 1.2 equiv of alkyne under conditions indicated by Procedure A or B.

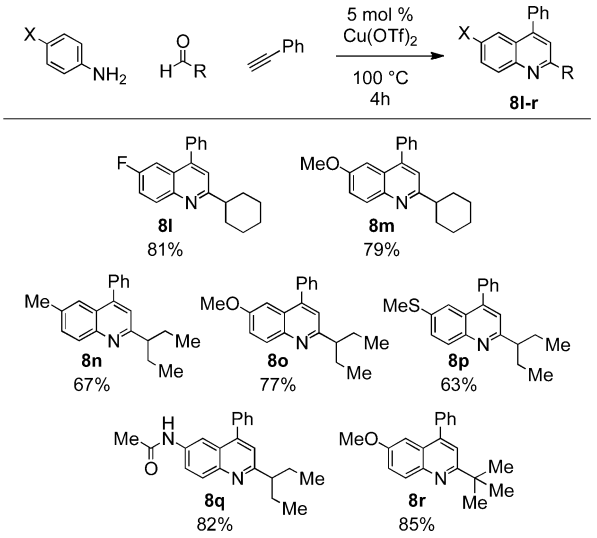
quinoline **8f** was tested without $CHCl_3$. The combination of solvent-free conditions and raising the temperature to 100 °C was required for complete conversion in only 4 h, and quinoline **8f** is isolated in 86% yield under Procedure B. 3-(Methylthio)aniline and 2-aminobiphenyl convert to sulfide-containing **8g** and hindered 2,4,8-triphenyl quinoline **8h** under solvent-free conditions. 2-Fluorobenzaldehyde and aniline rapidly react with 1-hexyne to give an 89% yield of 4-alkyl quinoline **8k** (Scheme 3). Thus, a variety of aldehydes and alkynes can be incorporated simply by heating the starting materials with 5 mol % $Cu(OTf)_2$ in a capped vial or tube.

The true test of this method is in the incorporation of problematic alkyl aldehydes like cyclohexanecarboxaldehyde for the formation of 2-alkyl quinolines. Fluoro- and methoxy-substituted anilines produce 2-cyclohexyl quinolines in nearly identical yield (Scheme 4, **8l** and **8m**). 2-Ethylbutyraldehyde combines with phenylacetylene and anilines bearing 4-methyl, 4-methoxy, 4-methylthio, and 4-acetamide groups to produce **8n**, **8o**, **8p**, and **8q** in up to 82% yield. Note that 6-acetamide **8q** provides a handle to tether quinolines to other functional groups. Hindered 2-*tert*-butyl quinoline **8r** is formed in 4 h in 85% yield under an ambient atmosphere and without solvent.

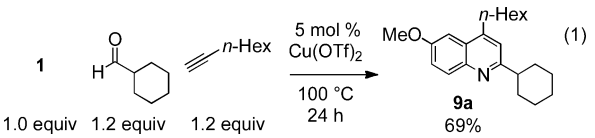
Thus, these greener solvent-free conditions are the key to the A^3 synthesis of alkyl-substituted quinolines. This operationally simple method applies to the previously recalcitrant combination of *p*-anisidine **1**, cyclohexanecarboxaldehyde, and 1-octyne from Scheme 2: 2-cyclohexyl-4-*n*-hexyl quinoline **9a** is isolated in 69% yield after 24 h (eq 1). Note that groups synthesizing 2,4-dialkyl quinolines will need to heat their desired substrates with 5 mol % $Cu(OTf)_2$ for at least 24 h and monitor conversion to product.

If aldehydes without branching at the α-carbon are utilized, a mixture of quinoline products is observed in the competition between acetylide and enolate nucleophiles.[14] α-Deprotonation

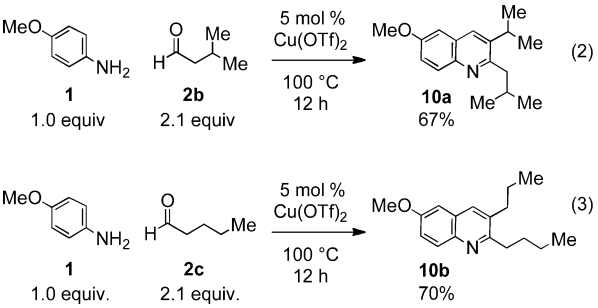
Scheme 4. Solvent-Free Conditions Required for Complete Conversion of α-Branched Alkyl Aldehydes to Quinolines[a]



[a]Isolated yield (%) of reactions carried out neat under an ambient atmosphere with 1.0 equiv of aniline, 1.2 equiv of aldehyde, and 1.2 equiv of alkyne.



is kinetically favored for less-hindered aldehydes like isovaleraldehyde (**2b**) and valeraldehyde (**2c**) in eqs 2 and 3 below.



Without branching adjacent to the carbonyl, a competing Povarov reaction forms 2,3-dialkyl quinolines.[17] By replacing the terminal alkyne with an additional equivalent of isovaleraldehyde or valeraldehyde, 2,3-dialkyl quinolines **10a** and **10b** are isolated in 67% and 70% yield, respectively.

This method for the multicomponent synthesis of quinolines maximizes diversity by the direct use of commercially available starting materials. Simply mixing and heating inexpensive anilines, aldehydes, and alkynes with 5 mol % $Cu(OTf)_2$ provides the first efficient A^3 route to a range of substituted quinolines that includes 2-alkyl quinolines. Heating the same catalyst with *p*-anisidine and a valeraldehyde produces 2,3-dialkyl quinolines via a two-component Povarov reaction. These robust solvent-free processes complement the many methods for making aryl-substituted quinolines, operate under an ambient atmosphere, and tolerate water.

By choosing the appropriate starting aldehyde, aniline, and alkyne, this mode of construction allows maximum variation in

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the substituents on the quinoline while eliminating the waste generated in multistep syntheses. In fact, the byproduct of this reaction is 1 equiv of water. In addition to the incorporation of alkyl or aryl aldehydes, both electron-rich and electron-poor anilines react efficiently in these three-component couplings. One-step variation of the substituents available on the quinoline scaffold should allow other groups to rapidly tune their properties, including solubility, luminescence, and biological activity.

EXPERIMENTAL SECTION

General Methods. All reactions were set up on the benchtop in test tubes equipped with magnetic stir bars and closed with screw caps. Column chromatography was performed using silica gel. Copper(II) trifluoromethanesulfonate was purchased from Alfa Aesar and used as supplied.

General Analytical Information. ^{1}H and ^{13}C NMR spectra were measured on a 400 MHz spectrometer using $CDCl_3$ as a solvent at room temperature. Some spectra include tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet, and br - broad. Gas chromatography spectra were obtained using dodecane as an internal standard. For IR spectra, attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm^{-1}). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the crystal and the solid material. Mass spectrometric data were recorded on a ToF instrument using direct injection of samples in acetonitrile into the electrospray source (ESI) and either positive or negative ionization.

General Procedure A. To a test tube equipped with a magnetic stir bar was added 5 mol % $Cu(OTf)_2$, $CHCl_3$ (1 mL), aniline (1.0 equiv), aldehyde (1.2 equiv), and alkyne (1.2 equiv), and the reaction was stirred at 80 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop a wet-packed silica gel column. Chromatography with diethyl ether (Et_2O) or ethyl acetate (EtOAc) in hexanes as eluent afforded the product, identified by its bright blue UV activity on TLC.

General Procedure B. To a test tube equipped with a magnetic stir bar was added 5 mol % $Cu(OTf)_2$, aniline (1.0 equiv), aldehyde (1.2 equiv), and alkyne (1.2 equiv), and the reaction was stirred at 100 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop a wet-packed silica gel column. Chromatography with diethyl ether (Et_2O) or ethyl acetate (EtOAc) in hexanes as eluent afforded the product, identified by its bright blue UV activity on TLC.

*2-(4-Fluorophenyl)-4-hexyl-6-methoxyquinoline (**8a**).* Prepared according to general procedure A: *p*-Anisidine (124 mg, 1.0 mmol), 4-fluorobenzaldehyde (127 μL, 1.2 mmol), *n*-octyne (177 μL, 1.2 mmol), $Cu(OTf)_2$ (18 mg, 5 mol %), and $CHCl_3$ (1.0 mL) were stirred at 80 °C for 12 h to afford the title compound as a yellow oil in 78% yield (0.232 g, 0.78 mmol) after column chromatography on silica gel (0−2−4% Et_2O in hexanes). IR (film) 3075, 2959, 2928, 1599, 1495, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.16−8.04 (m, 3H), 7.61 (s, 1H), 7.41−7.34 (dd, J = 8.0, 4.0 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.23−7.15 (m, 2H), 3.95 (s, 3H), 3.09−2.97 (m, 2H), 1.81 (dt, J = 15.4, 7.6 Hz, 2H), 1.54−1.42 (m, 2H), 1.43−1.29 (m, 4H), 0.98−0.85 (t, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 163.6 (d, J = 248.4 Hz), 157.6, 153.7, 148.1, 144.4, 136.2, 131.9, 129.2 (d, J = 8.3 Hz), 127.4, 121.5, 118.6, 115.7 (d, J = 21.4 Hz), 102.0, 55.6, 32.8, 31.8, 29.7, 29.5, 22.7, 14.2. HRMS (ESI) m/z calcd for $C_{22}H_{23}FNO$ requires 336.1764, found 336.1756.

*2,4,-Diphenylquinoline (**8b**).* Prepared according to general procedure A: Aniline (92 μL, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), $Cu(OTf)_2$ (18 mg, 5 mol %), and $CHCl_3$ (1.0 mL) were stirred at 80 °C for 12 h to afford the title compound as a pale yellow solid in 87% yield (0.245 g, 0.87 mmol) after column chromatography on silica gel (0−2−4% Et_2O in hexanes). IR (film) 3055, 3028, 2920, 1589, 1546, 1488, 1444 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.24 (d, J = 8.5 Hz, 1H), 8.19 (dd, J = 12.5, 4.1 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.56−7.46 (m, 7H), 7.43 (t, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 156.9, 149.2, 148.9, 139.7, 138.5, 130.3, 129.6, 129.6, 129.4, 128.9, 128.7, 128.5, 127.7, 126.4, 125.8, 125.7, 119.4. HRMS (ESI) m/z calcd for $C_{21}H_{16}N$ requires 282.1283, found 282.1287.

*6-methoxy-2,4-diphenylquinoline (**8c**).* Prepared according to general procedure A: *p*-Anisidine (124 mg, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), $Cu(OTf)_2$ (18 mg, 5 mol %), and $CHCl_3$ (1.0 mL) were stirred at 80 °C for 12 h to afford the title compound as a yellow oil in 78% yield (0.290 g, 0.93 mmol) after column chromatography on silica gel (0−1% Et_2O in hexanes). IR (film) 3059, 2927, 1621, 1590, 1548, 1490, 1471, 1450 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.22−8.20 (m, 1H), 8.18 (d, J = 3.7 Hz, 1H), 7.80 (s, 1H), 7.63−7.40 (m, 10H), 7.23 (d, J = 2.8 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 157.9, 154.7, 147.9, 145.0, 139.8, 138.8, 131.7, 129.4, 129.0, 128.9, 128.8, 128.4, 127.4, 126.7, 121.9, 119.7, 103.7, 55.5. HRMS (ESI) m/z calcd for $C_{22}H_{18}NO$ requires 312.1388, found 312.1393.

*6,8-Diphenyl-[1,3]dioxolo[4,5-g]quinoline (**8d**).* Prepared according to general procedure A: 5-Aminobenzodioxole (138 mg, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), $Cu(OTf)_2$ (18 mg, 5 mol %), and $CHCl_3$ (1.0 mL) were stirred at 80 °C for 12 h to afford the title compound as a pale yellow solid in 67% yield (0.220 g, 0.67 mmol) after column chromatography on silica gel (0−2−4% Et_2O in hexanes). IR (film) 2893, 1616, 1558, 1487, 1457 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.18−8.13 (m, 2H), 7.67 (s, 1H), 7.61−7.38 (m, 9H), 7.16 (s, 1H), 6.10 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 155.1, 150.7, 148.2, 148.1, 147.3, 139.9, 139.0, 129.5, 129.1, 128.9, 128.8, 128.4, 127.4, 122.8, 118.0, 106.6, 101.8, 101.2. HRMS (ESI) m/z calcd for $C_{22}H_{15}NO_2$ requires 325.1103, found 325.1102.

*2,4,6-Triphenylquinoline (**8e**).* Prepared according to general procedure A: 4-Aminobiphenyl (170 mg, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), $Cu(OTf)_2$ (18 mg, 5 mol %), and $CHCl_3$ (1.0 mL) were stirred at 80 °C for 20 h to afford the title compound as a pale yellow solid in 70% yield (0.250 g, 0.70 mmol) after column chromatography on silica gel (0−2% Et_2O in hexanes). IR (film) 3029, 1738, 1716, 1589, 1543, 1484, 1444 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.38 (d, J = 8.7 Hz, 1H), 8.29−8.22 (m, 2H), 8.14 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 8.7, 2.1 Hz, 1H), 7.88 (s, 1H), 7.70−7.42 (m, 12H), 7.42−7.34 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 156.8, 149.6, 148.2, 140.7, 139.5, 139.2, 138.5, 130.6, 129.7, 129.6, 129.4, 129.0, 128.8, 128.6, 127.7, 127.5, 126.0, 123.5, 119.9 [2 peaks overlapped]. HRMS (ESI) m/z calcd for $C_{27}H_{18}N$ requires 356.1434, found 356.1433.

*6-Methyl-2,4-diphenylquinoline (**8f**).* Prepared according to general procedure B: *p*-Toluidine (108 mg, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow solid in 86% yield (0.254 g, 0.86 mmol) after column chromatography on silica gel (0−2−4% Et_2O in hexanes). IR (film) 3054, 2915, 1588, 1544, 1488, 1449 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.27−8.15 (m, 3H), 7.79 (s, 1H), 7.66 (s, 1H), 7.61−7.44 (m, 9H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 156.0, 149.1, 147.0, 139.3, 138.6, 136.7, 132.2, 129.7, 129.5, 129.0, 128.8, 128.6, 127.8, 127.7 125.9, 124.6, 119.7, 22.0. HRMS (ESI) m/z calcd for $C_{22}H_{18}N$ requires 296.1439, found 296.1429.

*7-(Methylthio)-2,4-diphenylquinoline (**8g**).* Prepared according to general procedure B: 3-(Methylthio)aniline (124 μL, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow solid in 64% yield (0.209 g, 0.64 mmol) after column chromatography on silica gel (0−2−4−6%

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Et_2O in hexanes). IR (film) 3056, 3030, 2918, 1733, 1603, 1584, 1571, 1484, 1420 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.18 (dd, J = 5.3, 3.3 Hz, 2H), 8.00 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.74 (s, 1H), 7.59−7.44 (m, 8H), 7.33 (dd, J = 8.8, 2.0 Hz, 1H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 157.4, 149.5, 149.3, 141.8, 139.5, 138.3, 129.6, 129.0, 128.8, 128.6, 127.8, 127.7, 125.9, 125.7, 123.6, 123.4, 118.7, 15.2. HRMS (ESI) m/z calcd for $C_{22}H_{17}NS$ requires 327.1082, found 327.1084.

*2,4,8-Triphenylquinoline (**8h**).* Prepared according to general procedure B: 2-Aminobiphenyl (170 mg, 1.0 mmol), benzaldehyde (122 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 48 h to afford the title compound as a pale yellow solid in 65% yield (0.232 g, 0.65 mmol) after column chromatography on silica gel (0−1% Et_2O in hexanes). IR (film) 3059, 3024, 1554, 1485, 1443 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.18 (dd, J = 9.5, 2.6 Hz, 2H), 7.94−7.84 (m, 4H), 7.80 (dd, J = 7.1, 1.4 Hz, 1H), 7.63−7.50 (m, 8H), 7.50−7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 155.5, 149.8, 146.0, 141.2, 140.0, 139.3, 139.0, 131.3, 130.6, 129.8, 129.6, 128.9, 128.8, 128.5, 127.8, 127.6, 127.3, 126.5, 126.3, 125.5, 118.7. HRMS (ESI) m/z calcd for $C_{27}H_{20}N$ requires 358.1596, found 358.1605.

*2,4-Bis(2-fluorophenyl)quinoline (**8i**).* Prepared according to general procedure B: Aniline (92 μL, 1.0 mmol), 2-fluorobenzaldehyde (127 μL, 1.2 mmol), 2-fluorophenylacetylene (136 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a greenish crystalline solid in 71% yield (0.225 g, 0.71 mmol) after column chromatography on silica gel (2−4−6−8−10% Et_2O in hexanes). IR (film) 3056, 2926, 1615, 1594, 1582, 1486, 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.29 (d, J = 8.4 Hz, 1H), 8.17 (td, J = 7.8, 1.7 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.82−7.69 (m, 2H), 7.59−7.38 (m, 4H), 7.39−7.15 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 160.9 (d, J = 251.5 Hz), 159.8 (d, J = 248.5 Hz), 153.6, 148.6, 143.0, 131.9, 131.7, 131.1 (d, J = 8.4 Hz), 130.7 (d, J = 7.8 Hz), 130.2, 129.8, 127.8 (d, J = 11.9 Hz), 127.0, 126.0, 125.8, 125.7, 124.8, 124.5 (d, J = 2.5 Hz), 123.6 (d, J = 8.0 Hz), 116.4 (d, J = 23.1 Hz), 116.1 (d, J = 22.2 Hz). HRMS (ESI) m/z calcd for $C_{21}H_{13}F_2N$ requires 317.1016, found 317.1017.

*4-Benzyl-2-(naphthalen-2-yl)quinoline (**8j**).* Prepared according to general procedure B: Aniline (92 μL, 1.0 mmol), 2-naphthaldehyde (188 μL, 1.2 mmol), 3-phenyl-1-propyne (150 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 24 h to afford the title compound as a pale yellow solid in 61% yield (0.21 g, 0.61 mmol) after column chromatography on silica gel (0−2% Et_2O in hexanes) and correction for benzyl impurity. IR (film) 3055, 3022, 1595, 1553, 1492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.61 (s, 1H), 8.42 (d, J = 6.7 Hz, 1H), 8.29 (dd, J = 8.6, 1.6 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.98 (t, J = 7.5 Hz, 2H), 7.90−7.84 (m, 1H), 7.81 (s, 1H), 7.75 (t, J = 7.3 Hz, 1H), 7.58−7.47 (m, 3H), 7.36−7.29 (m, 2H), 7.29−7.20 (m, 3H), 4.54 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 156.7, 148.5, 147.7, 143.6, 138.6, 135.9, 134.1, 133.5, 130.2, 129.8, 129.1, 129.0, 128.8, 127.8, 127.1, 126.9, 126.8, 126.6, 125.4, 125.2, 124.0, 123.7, 120.4, 38.8. HRMS (ESI) m/z calcd for $C_{26}H_{19}N$ requires 345.1517, found 345.1501.

*4-n-Butyl-2-(2-fluorophenyl)quinoline (**8k**).* Prepared according to general procedure B: Aniline (92 μL, 1.0 mmol), 2-fluorobenzaldehyde (127 μL, 1.2 mmol), *n*-hexyne (173 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellowish-green solid in 89% yield (0.248 g, 0.89 mmol) after column chromatography on silica gel (0−2−4% Et_2O in hexanes). IR (film) 3075, 2959, 2928, 1599, 1495, 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.22 (d, J = 8.3 Hz, 1H), 8.14−8.01 (m, 2H), 7.77−7.67 (m, 2H), 7.56 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.46−7.38 (m, 1H), 7.32 (td, J = 7.5, 1.1 Hz, 1H), 7.20 (ddd, J = 11.1, 8.2, 1.0 Hz, 1H), 3.18−3.07 (m, 2H), 1.80 (tt, J = 7.8, 6.7 Hz, 2H), 1.50 (dq, J = 14.7, 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 160.8 (d, J = 249.7 Hz), 153.8, 149.0, 148.5, 131.7, 130.8 (d, J = 8.3 Hz), 130.5, 129.3, 128.2 (d, J = 12.3 Hz), 126.7, 126.4, 124.8 (d, J = 2.2 Hz), 123.6, 122.2 (d, J = 7.4 Hz), 116.3 (d, J = 22.9 Hz), 32.3, 32.2, 22.9, 14.0. HRMS (ESI) m/z calcd for $C_{19}H_{17}FN$ requires 278.1345, found 278.1343.

*2-Cyclohexyl-6-fluoro-4-phenylquinoline (**8l**).* Prepared according to general procedure B: 4-Fluoroaniline (95 μL, 1.0 mmol), cyclohexanecarboxaldehyde (146 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a pale yellow solid in 81% yield (0.247 g, 0.81 mmol) after column chromatography on silica gel (0−2% Et_2O in hexanes). IR (film) 3066, 3027, 2923, 1623, 1596, 1557, 1513, 1489, 1467 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.12 (dd, J = 9.1, 5.5 Hz, 1H), 7.59−7.37 (m, 7H), 7.29 (s, 1H), 2.95 (tt, J = 12.0, 3.3 Hz, 1H), 2.07 (d, J = 11.8 Hz, 2H), 1.95−1.84 (m, 2H), 1.79 (d, J = 12.6 Hz, 1H), 1.66 (ddd, J = 24.9, 12.5, 3.0 Hz, 2H), 1.56−1.40 (m, 2H), 1.40−1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 165.7, 160.3 (d, J = 246.0 Hz), 148.3, 145.4, 138.1, 131.7 (d, J = 8.8 Hz), 129.4, 128.8, 128.6, 126.3 (d, J = 9.6 Hz), 120.6, 119.2 (d, J = 25.7 Hz), 109.0 (d, J = 22.8 Hz), 47.5, 32.9, 26.6, 26.2. HRMS (ESI) m/z calcd for $C_{22}H_{22}FN$ requires 306.1658, found 306.1659.

*2-Cyclohexyl-6-methoxy-4-phenylquinoline (**8m**).* Prepared according to general procedure B: *p*-Anisidine (124 mg, 1.0 mmol), cyclohexanecarboxaldehyde (146 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow oil in 79% yield (0.250 g, 0.79 mmol) after column chromatography on silica gel (0−2−4−6−8−10% Et_2O in hexanes). IR (film) 2924, 2851, 1620, 1593, 1491, 1473, 1445 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.04 (d, J = 9.2 Hz, 1H), 7.59−7.42 (m, 5H), 7.35 (dd, J = 9.2, 2.7 Hz, 1H), 7.23 (s, 1H), 7.16 (d, J = 2.7 Hz, 1H), 3.76 (s, 3H), 2.93 (tt, J = 11.9, 3.1 Hz, 1H), 2.07 (d, J = 11.9 Hz, 2H), 1.89 (d, J = 12.9 Hz, 2H), 1.78 (d, J = 12.7 Hz, 1H), 1.65 (ddd, J = 24.8, 12.5, 2.8 Hz, 2H), 1.48 (ddd, J = 15.8, 11.3, 3.1 Hz, 2H), 1.39−1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.0, 157.4, 147.5, 144.3, 138.9, 130.8, 129.4, 128.7, 128.3, 126.3, 121.3, 120.2, 103.9, 55.5, 47.4, 33.1, 26.7, 26.2. HRMS (ESI) m/z calcd for $C_{22}H_{22}NO$ requires 316.1701, found 316.1708.

*6-Methyl-2-(pentan-3-yl)-4-phenylquinoline (**8n**).* Prepared according to general procedure B: *p*-Toluidine (108 mg, 1.0 mmol), 2-ethylbutyraldehyde (148 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow solid in 67% yield (0.194 g, 0.67 mmol) after column chromatography on silica gel (0−1.5% Et_2O in hexanes). IR (film) 3055, 2959, 2928, 1592, 1557, 1489, 1449 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.08 (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 7.58−7.46 (m, 6H), 7.18 (s, 1H), 2.90−2.77 (m, 1H), 2.46 (s, 3H), 1.83 (p, J = 7.4 Hz, 4H), 0.88 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.5, 148.0, 146.8, 138.8, 135.7, 131.4, 129.7, 129.2, 128.6, 128.3, 125.6, 124.5, 120.5, 52.2, 28.4, 21.8, 12.4. HRMS (ESI) m/z calcd for $C_{21}H_{22}N$ requires 288.1752, found 288.1760.

*6-Methoxy-2-(3-pentanyl)-4-phenylquinoline (**8o**).* Prepared according to general procedure B: *p*-Anisidine (124 mg, 1.0 mmol), 2-diethylbutyraldehyde (148 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow oil in 77% yield (0.235 g, 0.77 mmol) after column chromatography on silica gel (0−2−4−6% Et_2O in hexanes). IR (film) 2960, 2930, 1621, 1491 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.08 (d, J = 9.2 Hz, 1H), 7.60−7.42 (m, 5H), 7.37 (dd, J = 9.2, 2.8 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 7.18 (s, 1H), 3.77 (s, 3H), 2.81 (p, J = 7.2 Hz, 1H), 1.83 (p, J = 7.4 Hz, 4H), 0.88 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 163.0, 157.4, 147.2, 144.4, 138.9, 131.0, 129.5, 128.7, 128.3, 126.3, 121.2, 120.8, 103.9, 55.5, 52.0, 28.3, 12.3 (d, J = 5.2 Hz). HRMS (ESI) m/z calcd for $C_{21}H_{24}NO$ requires 306.1858, found 306.1853.

*6-Methylthio-2-(3-pentanyl)-4-phenylquinoline (**8p**).* Prepared according to general procedure B: 4-(Methylthio)aniline (125 μL, 1.0 mmol), 2-diethylbutyraldehyde (148 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow solid in 63% yield (0.201 g, 0.63 mmol) after column chromatography on silica gel (0−2% Et_2O in hexanes). IR (film) 3057, 2959, 2922, 1737, 1587, 1552, 1481, 1455 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.08 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.9, 2.1 Hz, 1H), 7.57−7.44 (m, 5H), 7.19 (s, 1H), 2.88−2.77 (m, 1H), 2.45

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(s, 3H), 1.82 (p, J = 7.4 Hz, 4H), 0.87 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.8, 147.5, 146.5, 138.3, 136.3, 129.7, 129.6, 128.8, 128.7, 128.5, 126.0, 121.6, 121.1, 52.1, 28.3, 16.1, 12.3. HRMS (ESI) m/z calcd for $C_{21}H_{22}NS$ requires 320.1473, found 320.1465.

*N-[2-(3-Pentanyl)-4-phenyl-6-quinolinyl]acetamide (**8q**).* Prepared according to general procedure B: 4-Aminoacetanilide (151 mg, 1.0 mmol), diethylbutyraldehyde (148 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a white solid in 82% yield (0.271 g, 0.82 mmol) after column chromatography on silica gel (10−20−30−40−50% Et_2OAc in hexanes). IR (film) 3062, 2960, 2929, 1737, 1695, 1655, 1621, 1604, 1552, 1516, 1501, 1459 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.19−8.09 (m, 2H), 8.00 (s, 1H), 7.88 (dd, J = 9.1, 1.8 Hz, 1H), 7.55−7.39 (m, 5H), 7.19 (s, 1H), 2.84 (dt, J = 14.3, 7.2 Hz, 1H), 2.16 (s, 3H), 1.88−1.72 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 168.8, 164.5, 148.7, 145.0, 138.3, 136.0, 129.6, 128.8, 128.7, 126.0, 123.6, 120.9, 114.6, 114.5, 52.0, 28.3, 24.7, 12.4. HRMS (ESI) m/z calcd for $C_{22}H_{23}N_2O$ requires 331.1810, found 331.1809.

*2-tert-Butyl-6-methoxy-4-phenylquinoline (**8r**).* Prepared according to general procedure B: *p*-Anisidine (124 mg, 1.0 mmol), pivaldehyde (131 μL, 1.2 mmol), phenylacetylene (132 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4 h to afford the title compound as a yellow oil in 85% yield (0.246 g, 0.85 mmol) after column chromatography on silica gel (0−2% Et_2O in hexanes). IR (film) 3059, 2957, 2903, 1621, 1491, 1470 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.05 (d, J = 9.0 Hz, 1H), 7.61−7.45 (m, 5H), 7.42 (s, 1H), 7.36 (dd, J = 9.2, 2.8 Hz, 1H), 7.17 (d, J = 2.8 Hz, 1H), 3.79 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 166.5, 157.4, 147.1, 144.1, 139.3, 131.4, 129.5, 128.7, 128.2, 125.8, 121.1, 118.9, 103.7, 55.6, 38.0, 30.4. HRMS (ESI) m/z calcd for $C_{20}H_{22}NO$ requires 292.1701, found 292.1709.

*2-Cyclohexyl-6-methoxy-4-n-hexylquinoline (**9a**).* Prepared according to general procedure B: *p*-Anisidine (124 mg, 1.0 mmol), cyclohexanecarboxaldehyde (146 μL, 1.2 mmol), *n*-octyne (178 μL, 1.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 24 h to afford the title compound as a clear oil in 69% yield (0.225 g, 0.69 mmol) after column chromatography on silica gel (0−2−4% Et_2O in hexanes). IR (film) 2924, 1620, 1593, 1491, 1450 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.03 (d, J = 9.1 Hz, 1H), 7.33 (dd, J = 9.2, 2.7 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (s, 1H), 3.93 (s, 3H), 3.04−2.94 (m, 2H), 2.90 (dd, J = 15.4, 8.3 Hz, 1H), 2.01 (d, J = 11.5 Hz, 2H), 1.88 (d, J = 12.8 Hz, 2H), 1.76 (dt, J = 15.4, 7.6 Hz, 4H), 1.61 (ddd, J = 24.6, 12.4, 2.8 Hz, 2H), 1.54−1.40 (m, 4H), 1.33 (dd, J = 9.7, 6.1 Hz, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.0, 157.2, 148.1, 143.4, 130.8, 127.2, 121.0, 119.4, 102.2, 55.7, 47.2, 33.1, 32.7, 31.8, 29.7, 29.5, 26.7, 26.2, 22.7, 14.2. HRMS (ESI) m/z calcd for $C_{22}H_{30}NO$ requires 324.2327, found 324.2322.

*2-Isobutyl-6-methoxy-3-isopropylquinoline (**10a**).* Prepared according to general procedure B: *p*-Anisidine (124 mg, 1.0 mmol), isovaleraldehyde (236 μL, 2.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 12 h to afford the title compound as a yellow oil in 70% yield (0.180 g, 0.70 mmol) after column chromatography on silica gel (0−2−5% Et_2O in hexanes). IR (film) 2957, 1624, 1599, 1512, 1491, 1464 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.96 (d, J = 9.2 Hz, 1H), 7.88 (s, 1H), 7.27 (dd, J = 9.1, 2.7 Hz, 1H), 7.03 (d, J = 2.8 Hz, 1H), 3.91 (s, 3H), 3.30 (m, 1H), 2.90 (d, J = 7.3 Hz, 2H), 2.33−2.14 (m, 1H), 1.32 (d, J = 6.8 Hz, 6H), 0.99 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 158.1, 157.4, 141.9, 141.2, 131.1, 129.7, 128.3, 121.3, 104.8, 55.6, 43.8, 29.6, 28.9, 24.0, 22.7. HRMS (ESI) m/z calcd for $C_{17}H_{23}NO$ requires 257.1780, found 257.1782.

*6-Methoxy-2-(2-methylpropyl)-3-(2-propanyl)quinoline (**10b**).* Prepared according to general procedure B: *p*-Anisidine (124 mg, 1.0 mmol), valeraldehyde (234 μL, 2.2 mmol), and $Cu(OTf)_2$ (18 mg, 5 mol %) were stirred at 100 °C for 12 h to afford the title compound as a yellow oil in 67% yield (0.173 g, 0.67 mmol) after column chromatography on silica gel (0−4−6−10% Et_2O in hexanes). IR (film) 2956, 2930, 1625, 1492, 1465 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.93 (d, J = 9.2 Hz, 1H), 7.75 (s, 1H), 7.31−7.23 (m, 1H), 7.00 (d, J = 2.8 Hz, 1H), 3.90 (s, 3H), 2.95 (dd, J = 9.5, 6.6 Hz, 2H), 2.81−2.70 (m, 2H), 1.81−1.66 (m, 4H), 1.49 (dq, J = 14.8, 7.4 Hz, 2H), 1.08−1.01 (m, 3H), 1.01−0.93 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 159.7, 157.3, 142.4, 137.8, 134.3, 129.8, 128.2, 121.1, 104.7, 55.6, 35.4, 34.5, 32.1, 23.8, 23.2, 14.2, 14.2. HRMS (ESI) m/z calcd for $C_{17}H_{23}NO$ requires 257.1780, found 257.1784.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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