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Note

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Synthesis of Quinolines through Three-Component Cascade Annulation of Aryl Diazonium Salts, Nitriles, and Alkynes

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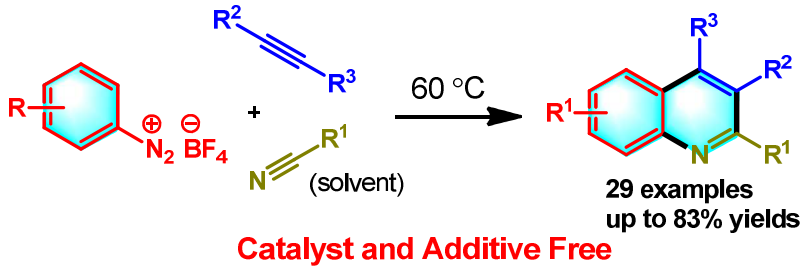


ABSTRACT: An efficient and rapid synthesis of multiply substituted quinolines is described. This method is enabled by a three-component cascade annulation of readily available aryl diazonium salts, nitriles, and alkynes. This reaction is catalyst- and additive-free. Various aryl diazonium salts, nitriles, and alkynes can participate in this transformation, and the yields are up to 83%.

Quinolines represent one of the ubiquitous heterocycles in the natural alkaloids displaying a wide variety of pharmacological properties, such as tumoricidal, angina pectoris, antihypertensive, and antibacterial activities.[1] Furthermore, their structures and properties have made them widely applicable in the functional materials[2] and asymmetric catalysts.[3] The synthesis of the structural core of quinolines has well been established.[4] The most popular strategy for the construction of quinolone core is based on the condensation of aniline derivatives with various carbonyl compounds,[4, 5] e.g., Combes synthesis, Conrad-Limpach-Knorr synthesis, and Friedlander synthesis. Recently, transition-metal-catalyzed couplings have merged as powerful tools for the efficient and rapid synthesis of quinolines.[4b, 6] Despite these advances, a clean, efficient, and economic technology is still needed to obtain useful polyfunctionalized quinolines from readily available starting materials.

Cycloaddition of *N*-arylnitrilium salts (**I**) with alkynes can compete with classical syntheses in the efficacy and rapidity of the quinoline construction (Figure 1). Compared to well-established annulation of iminium salts with alkynes followed by oxidation to quinolines,[7] annulation of nitrilium salts with alkynes can give quinolines directly without oxidation. In 1992, Jochims and co-workers reported that *N*-arylnitrilium salts (**I**) could be prepared by Beckmann rearrangement of the corresponding oximes (**II**) or abstraction of chloride from the corresponding imidoyl chlorides (**III**).[8] The preformed nitrilium salts (**I**) could undergo polar [4 + 2] cycloaddition with alkynes to give

substituted quinolines (Figure 1A). Recently, Chen and co-workers found that *N*-arylnitrilium salts (**I**) could be generated *in situ* by copper-catalyzed aryl group transfer from diaryliodonium salts (**IV**) to nitriles, followed by annulation with alkynes to give quinolines (Figure 1B).[6a]

Encouraged these elegant reports, we sought to make a modified approach for the synthesis of quinolines via cascade annulation of aryl diazonium salts, nitriles, and alkynes.[9] It is known that diazonium salts decompose on warming into aryl cation with the release of N_2. The inherent electrophilicity of dizonium salts offers a pathway to introduce cyano group into an aromatic ring to yield *N*-arylnitrilium salts (**I**). As demonstrated by Jochims and Chen, this *N*-arylnitrilium salts can undergo [4 + 2] cycloaddition with alkynes to provide polysubstituted quinolines (Figure 1C). Herein, we would like to report a rapid and efficient method to synthesize quinolines from three easily accessible precursors, saying aryl diazonium salts, nitriles, and alkynes. This method presented here is catalyst and additive-free, economic, and environmentally benign.

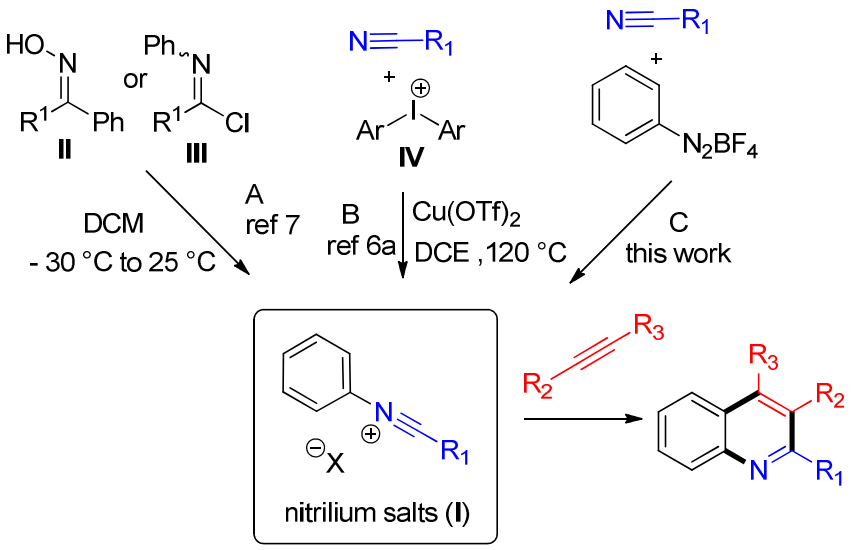
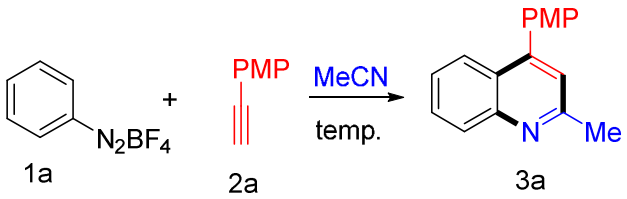


Figure 1. Syntheses of quinolines by cycloaddition of *N*-arylnitrilium salts with alkynes

At the outset of this investigation, we explored the cascade reaction of aryl diazonium salt **1a** and *p*-methoxyphenylacetylene (**2a**) using acetonitrile as the solvent. We were pleased to find that when a mixture of aryl diazonium salt **1a** (0.3 mmol) and *p*-methoxyphenylacetylene (**2a,** 0.6 mmol) in 3 mL of anhydrous acetonitrile was stirred at room temperature for 30 h, the desired quinoline **3a** was obtained in a 55% isolated yield (Table 1, entry 1). When the reaction mixture was slightly warned up to 40 ºC, the reaction can go to completion in 6 h with 82% isolated yield (entry 2). The concentration of the reaction mixture had significant impact on the chemical yields (entries 3-6). More concentrated or diluted reaction mixture led to lower isolated yields. Higher temperature could accelerate the reaction with comparable yields (entries 7-8). The reaction could finish in one hour at 60 ºC and half an hour at 80 ºC. The dosage of alkyne **2a** can

be reduced to 1.2 and 1.5 equivalents with 79% and 83% isolated yields respectively at 60 °C (entries 11-12).

Table 1. Optimization of the Reaction Conditions[a]



entry	MeCN	temp	time	yield/%[b]
1	3 mL	25 °C	30 h	55
2	3 mL	40 °C	6 h	82
3	1 mL	40 °C	6 h	76
4	2 mL	40 °C	6 h	80
5	6 mL	40 °C	6 h	72
6	9 mL	40 °C	6 h	66
7	2 mL	60 °C	1 h	84
8	2 mL	80 °C	0.5 h	83
9[c]	2 mL	40 °C	6 h	72
10[d]	2 mL	40 °C	6 h	74
11[c]	2 mL	60 °C	1 h	79
12[d]	**2 mL**	**60 °C**	**1 h**	**83**

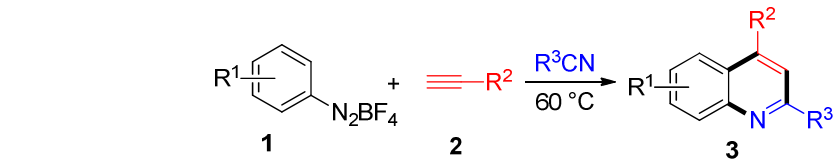
[a]Reaction conditions: A solution of **1a** (0.3 mmol), **2a** (0.6 mmol) in anhydrous acetonitrile was stirred at the indicated temperature. [b]Isolated yields. [c]1.2 equiv

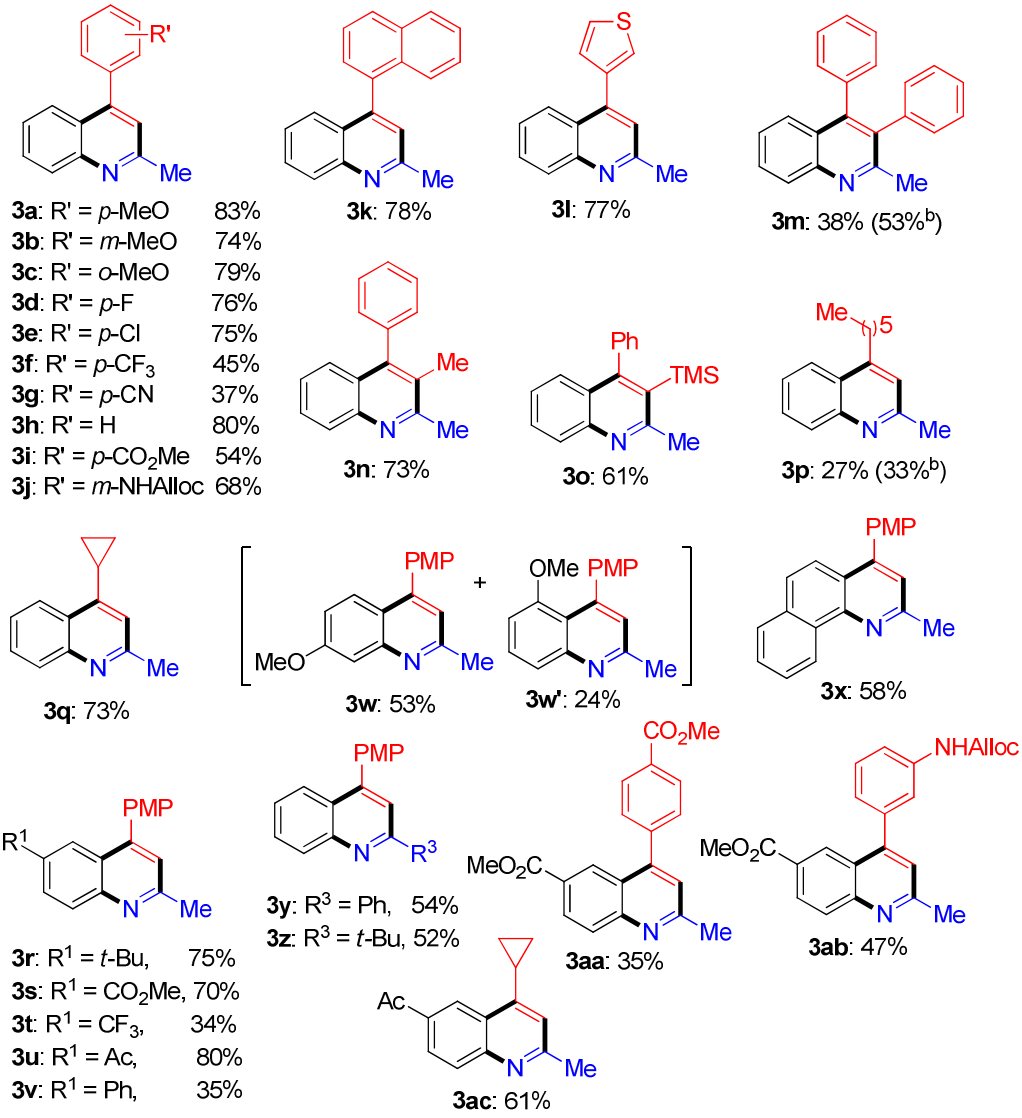
of **2a** (0.36 mmol) was used. [d]1.5 equiv of **2a** (0.45 mmol) was used. PMP = *para*-methoxyphenyl

After the reaction parameter was established, we next explored the scope and limitation of this reaction (Scheme 1). First, a variety of alkynes reacted with diazonium salt **1a** in acetonitrile. Electron-rich and neutral phenylacetylene derivatives went through this smoothly with 68-83% yields while electron-deficient phenylacetylene derivatives were less reactive with 37-54% yields. Naphthalene- and thiophene-derived terminal alkynes could also undergo this transformation frequently to provide the quinolines **3k** and **3l** in 78% and 77% yields respectively. To our delight, internal aromatic alkynes were also suitable reaction partners to give the corresponding quinolines **3m**-**3o** in reasonable isolated yields (53-73%). The reaction with linear aliphatic alkyne (1-octyne) was sluggish and only 33% desired quinolone **3p** could be isolated even through 3.0 equivalents of 1-octyne were employed. However, ethynylcyclopropane was a good reaction partner and 73% yield of quinoline **3q** could be obtained under optimal conditions. Then, various functionalized aryl diazonium salts reacted with *para*-methoxyphenylacetylene (**2a**) in acetonitrile. Functional groups, such as ester (**3s**), ether (**3w**), trifluoromethyl (**3t**), ketone (**3u**), and naphthalene (**3x**), could be tolerated. When *meta*-methoxyphenyl diazonium salt was used, two regioisomers **3w** and **3w'** were obtained with 81% combined yield. Annulation of phenyl diazonium salt (**1a**) and *para*-methoxyphenylacetylene (**2a**) in benzonitrile and pivalonitrile was also

feasible. The corresponding quinolines **3y** and **3z** were isolated in 54% and 52% yields respectively. Finally, multiple functionalized quinolines **3aa**-**3ac** could be also prepared in acceptable yields by means of this method. In the cases of low yields, the major by-products were the amides, which were generated from the hydrolysis of the corresponding nitrilium intermediates.

Scheme 1. Substrate Scope[a]



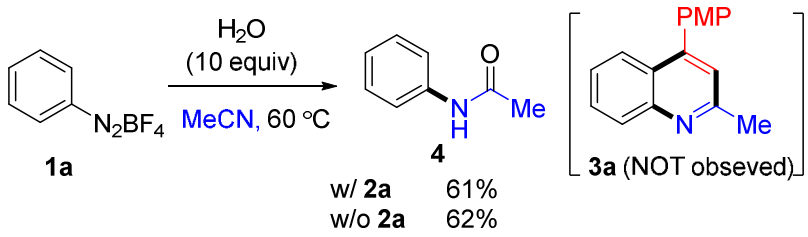


[a]Reaction conditions: A solution of **1** (0.3 mmol), **2** (0.45 mmol) in anhydrous nitrile (2 mL) was stirred at 60 °C for 1 h. [b]3.0 equiv of **2** was used.

In order to gain insights into the mechanism of this transformation, some control experiments were carried out (Scheme 2). When 10 equivalents of distilled water was introduced into the model reaction mixture, no quinoline **3a**

was observed. Instead, the *N*-phenylacetamide (**4**) was obtained in a 61% yield based on the crude ^{1}H NMR analysis. Furthermore, when alkyne **2a** was removed from the reaction mixture, the similar result was obtained. These findings suggests that the nitrilium salt is the key intermediate of this reaction.[6a, 10]

Scheme 2. Control Experiments



On the basis of control experiments and the previous reports,[6a, 7] a plausible mechanism is proposed (Figure 2). Upon heating, the aryl diazonium salt **1a** decomposes into the aryl cation **5** with concomitant releasing of N_2. Acetonitrile works as a nucleophile to attack the aryl cation **5**, resulting in the formation of nitrilium cation **6**. There are two possible pathways to form quinoline **3a**. In the path A, nitrilium cation reacts with alkyne **2a** through a concerted Diels-Alder reaction to give the intermediate **8**. After deprotonation, the intermediate **8** can convert to quinoline **3a**. Alternatively, quinoline **3a** can be generated in a stepwise manner (path B). The intermediate **6** is attacked by alkyne **2a** to give the vinyl cation **9** following by Friedel-Crafts-type cyclization to give the desired quinoline **3a**.

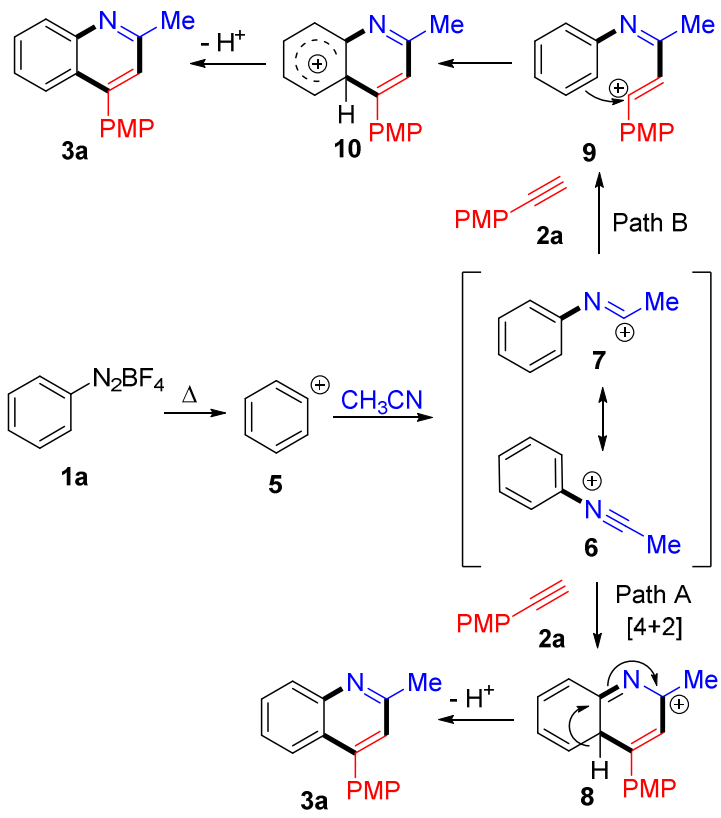


Figure 2. Proposed mechanism

In summary, we have described an efficient and rapid synthesis of multiply functionalized quinolines from three components, saying aryl diazonium salts, alkynes, and nitriles. The reaction can finish in one hour at 60 °C and the yield was up to 83%. Furthermore, neither catalyst nor additive is necessary. This economic, and environmentally benign procedure should benefit the future development of potential industrial processes and makes this protocol particularly attractive for the chemical community.

Experimental Section

General information. All reagents were used without further purification. Thin layer chromatography (TLC) was performed on precoated plates (silica gel

60 F254, Art 5715) and visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid or potassium permanganate, respectively. Column chromatography was performed on Silica Gel 60 (300–400 Mesh) using a forced flow of 0.5–1.0 bar. ^{1}H NMR (400 M Hz), ^{13}C NMR (101 M Hz) and ^{19}F (376 M Hz) were measured on a 400 M NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) with respect to the residual solvent peak. Coupling constants are reported as Hertz (Hz), signal shapes and splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on an IR spectrophotometer and are reported as wavenumber (cm^{-1}).

General Procedure for the preparation of aryl diazonium tetrafluoroborates.[11] The appropriate aniline (10 mmol) was dissolved in a mixture of 3.4 mL of hydrofluoroboric acid (50%) and 4 mL of distilled water. The reaction mixture was cooled down to 0°C using an ice-water bath, and then sodium nitrite ($NaNO_2$) solution (0.69 g in 1.5 mL) was added drop wise. The resulting reaction mixture was stirred for 40 min at 0-5 °C and the obtained precipitate was collected by filtration, dried and re-dissolved in a minimum amount of acetone. Diethyl ether was added until precipitation of diazonium tetrafluoroborate, which is filtered, washed several times with small portions of diethyl ether and dried under vacuum.

General procedure for synthesis of quinolones. A 10 mL round bottom flask equipped with a rubber septum and magnetic stir bar was charged with aryl diazonium salt **1a** (0.3 mmol, 1.0 equiv). Then *p*-MeO phenylacetylene **2a** (0.45 mmol, 1.5 equiv)

and CH_3CN (2.0 mL) were added with a syringe. The mixture was placed in an oil bath preheated to 60 °C. After the reaction was complete (as judged by TLC analysis), the mixture was poured into a separatory funnel containing 20 mL of H_2O and 20 mL of Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The crude product was purified by flash chromatography on silica gel to afford the desired product **3a**.

*4-(4-methoxyphenyl)-2-methylquinoline (**3a**)*:[12] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3a** as a white solid (62.1 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.45-7.41 (m, 3H), 7.21 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 158.5, 148.5, 148.3, 130.8, 130.4, 129.3, 129.0, 125.7, 125.6, 125.3, 122.2, 114.0, 55.4, 25.4.

*4-(3-methoxyphenyl)-2-methylquinoline (**3b**):* Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3b** as a yellow solid (55.6 mg, 74%). Mp 72-73 ºC. IR (film, cm^{-1}): 1581; 1464; 1038; 887; 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.88 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.68 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.44-7.40 (m, 2H), 7.23 (s, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.03-7.00 (m, 2H), 3.85 (s, 3H), 2.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.5, 148.41, 148.35, 139.5, 129.6, 129.4, 129.0, 125.8, 125.7, 125.1, 122.1, 121.9, 115.1, 113.8, 55.4, 25.4. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{17}H_{15}NO$: 250.1226; found: 250.1226.

*4-(2-methoxyphenyl)-2-methylquinoline (**3c**):* Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3c** as a yellow solid (59.3 mg, 79%). Mp 105-106 ºC. IR (film, cm^{-1}): 1592; 1487; 1023; 873; 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.64 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.55-7.53 (m, 1H), 7.45 (td, *J* = 8.3, 1.7 Hz, 1H), 7.38-7.34 (m, 1H), 7.24 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.22 (s, 1H), 7.08 (dt, *J* = 8.3, 4.1 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 3.69 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.8, 148.0, 146.0, 131.2, 129.9, 129.1, 128.8, 127.0, 126.1, 125.8, 125.4, 123.0, 120.7, 111.1, 55.5, 25.4. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{17}H_{15}NO$: 250.1226; found: 250.1225.

*4-(4-fluorophenyl)-2-methylquinoline (**3d**)*:[12] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3d** as a yellow solid (54.3 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.68 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.47-7.41 (m, 3H), 7.23-7.18 (m, 3H), 2.77 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.40. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 248.0 Hz), 158.5, 148.4, 147.5, 134.1, 134.1, 131.2 (d, *J* = 8.2 Hz), 129.3 (d, *J* = 30.9 Hz), 125.9, 125.36, 125.1, 122.3, 115.6 (d, *J* = 21.6 Hz), 25.3.

*4-(4-chlorophenyl)-2-methylquinoline (**3e**)*:[13] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3e** as a yellow solid (56.7 mg, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.70-7.66 (m, 1H), 7.49-7.40 (m, 5H), 7.19 (s, 1H), 2.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 148.3, 147.3, 136.5, 134.6, 130.8, 129.5, 129.1, 128.8, 126.0, 125.3, 124.8, 122.2, 25.3.

2-methyl-4-(4-(trifluoromethyl)phenyl)quinolone ***(3f)***:[12] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3f** as a yellow solid (38.4 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.80-7.69 (m, 4H), 7.61 (d, *J* = 7.7 Hz, 2H), 7.41-7.43 (m, 1H), 7.22 (s, 1H), 2.79 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.57. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 148.4, 147.0, 141.8, 130.6 (q, *J* = 32.6 Hz), 129.9, 129.6, 129.2, 128.2, 126.2, 125.5 (q, *J* = 3.6 Hz), 124.6, 124.1 (q, *J* = 272.3 Hz), 122.2, 25.3.

4-(2-methylquinolin-4-yl)benzonitrile ***(3g)***:[12] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3g** as a yellow solid (27.0 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.74-7.70 (m, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.49-7.45 (m, 1H), 7.22 (s, 1H), 2.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 148.4, 146.4, 142.9, 132.4, 130.3, 129.8, 129.3, 126.4, 124.8, 124.3, 122.1, 118.5, 112.4, 25.4.

2-methyl-4-phenylquinoline ***(3h)***:[12] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3h** as a yellow solid (52.6 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.69-7.64 (m, 1H), 7.51-7.45 (m, 5H), 7.42-7.38 (m, 1H), 7.21 (s, 1H), 2.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 148.6, 148.4, 138.2, 129.5, 129.3, 129.0, 128.5, 128.3, 125.8, 125.7, 125.1, 122.2, 25.4.

Methyl 4-(2-methylquinolin-4-yl)benzoate ***(3i)***: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3i** as a yellow solid (44.6 mg, 54%). Mp 110-111 ºC. IR (film, cm^{-1}): 1700; 1432; 1019; 858; 758 cm^{-1}. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.44 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.23 (s, 1H), 3.98 (s, 3H), 2.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 158.5, 148.4, 147.4, 142.8, 130.1, 129.8, 129.6, 129.5, 129.2, 126.1, 125.2, 124.6, 122.1, 52.3, 25.4. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{18}H_{15}NO_2$: 278.1176; found: 278.1173.

*Allyl (3-(2-methylquinolin-4-yl)phenyl)carbamate (**3j**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3j** as a white solid (64.9 mg, 68%). Mp 166-167 ºC. IR (film, cm^{-1}): 1717; 1432; 1104; 858; 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.84 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.65 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.55-7.51 (m, 3H), 7.42-7.37 (m, 2H), 7.19 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 5.94 (ddt, *J* = 17.0, 10.5, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.66 (d, *J* = 5.7 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 153.5, 148.3, 148.2, 139.0, 138.4, 132.4, 129.4, 129.2, 128.9, 125.8, 125.6, 125.0, 124.6, 122.2, 119.7, 118.6, 118.2, 65.9, 25.2. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{20}H_{18}N_2O_2$: 319.1441; found: 319.1441.

*2-methyl-4-(naphthalen-1-yl)quinolone (**3k**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3k** as a white solid (63.0 mg, 78%). Mp 164-165 ºC. IR (film, cm^{-1}): 1597; 1505; 1020; 764; 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 11.0, 8.4 Hz, 2H), 7.67-7.63 (m, 1H), 7.58-7.54 (m, 1H), 7.49-7.42 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.31-7.24 (m, 3H),

2.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 148.1, 147.5, 135.8, 133.5, 131.97, 129.5, 128.9, 128.7, 128.3, 127.3, 126.5, 126.4, 126.22, 126.16, 126.0, 125.8, 125.3, 123.4, 25.5. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{20}H_{15}N$: 270.1277; found: 270.1277.

*2-methyl-4-(thiophen-3-yl)quinolone (**3l**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3l** as a yellow solid (52.2 mg, 77%). Mp 101-102 ºC. IR (film, cm^{-1}): 1596; 1414; 1022; 796; 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.69-7.65 (m, 1H), 7.47-7.41 (m, 3H), 7.30 (dd, *J* = 3.5, 2.9 Hz, 1H), 7.25 (s, 1H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 148.4, 143.2, 138.6, 129.4, 129.1, 128.9, 126.2, 125.9, 125.5, 125.1, 124.8, 122.0, 25.3. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{14}H_{11}NS$: 226.0685; found: 226.0684.

*2-methyl-3,4-diphenylquinoline (**3m**)*:[14] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3m** as a yellow solid (46.8 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.70-7.66 (m, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.26-7.14 (m, 6H), 7.10-7.05 (m, 4H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 147.1, 146.6, 138.7, 136.8, 134.1, 130.13, 130.07, 129.1, 128.7, 127.9, 127.7, 127.2, 126.9, 126.6, 126.3, 125.9, 25.47.

*2,3-dimethyl-4-phenylquinoline (**3n**)*:[15] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3n** as a yellow solid (50.9 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.59 (dt, *J* = 8.4, 4.1 Hz, 1H), 7.53-7.44 (m, 3H), 7.31 (d, *J* = 3.7 Hz, 2H), 7.24-7.22 (m, 2H), 2.75 (s, 3H), 2.17 (s, 3H). ^{13}C NMR

(101 MHz, $CDCl_3$) δ 158.9, 146.3, 146.1, 137.7, 129.4, 128.5, 128.5, 128.2, 127.7, 127.5, 126.9, 126.1, 125.5, 24.6, 17.0.

*2-methyl-4-phenyl-3-(trimethylsilyl)quinolone (**3o**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3o** as a white solid (53.7 mg, 61%). Mp 77-78 ºC. IR (film, cm^{-1}): 1562; 1480; 1019; 761; 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.59 (ddd, *J* = 8.3, 5.5, 2.7 Hz, 1H), 7.44-7.42 (m, 3H), 7.29-7.22 (m, 4H), 2.89 (s, 3H), 0.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 154.0, 145.0, 137.9, 128.3, 128.2, 127.6, 126.2, 126.02, 125.99, 124.4, 124.0, 123.4, 26.6, 0.0. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{19}H_{21}NSi$: 292.1516; found: 292.1515.

*4-hexyl-2-methylquinoline (**3p**)*:[16] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3p** as a white solid (18.1 mg, 27%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 19.8, 8.2 Hz, 2H), 7.68-7.63 (m, 1H), 7.51-7.47 (m, 1H), 7.13 (s, 1H), 3.03-3.00 (m, 2H), 2.71 (s, 3H), 1.74 (dt, *J* = 15.5, 7.6 Hz, 2H), 1.43 (dd, *J* = 14.8, 6.9 Hz, 2H), 1.37-1.32 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 148.8, 148.0, 129.3, 129.0, 125.9, 125.4, 123.4, 121.6, 32.2, 31.7, 30.1, 29.4, 25.3, 22.6, 14.1.

*4-cyclopropyl-2-methylquinoline (**3q**)*:[12] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3q** as a yellow oil (40.1 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.68-7.64 (m, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 6.92 (s, 1H), 2.68 (s, 3H), 2.40-2.33 (m, 1H), 1.14-1.11 (m, 2H),

0.84-0.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 149.4, 147.7, 129.1, 127.0, 125.4, 123.8, 118.0, 25.4, 12.0, 7.6.

*6-(tert-butyl)-4-(4-methoxyphenyl)-2-methylquinoline (**3r**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3r** as a brown solid (68.8 mg, 75%). IR (film, cm^{-1}): 1608; 1461; 1032; 831; 768 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.8 Hz, 1H), 7.87 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.18 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.99 (m, 3H), 2.74 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157.7, 148.3, 148.1, 146.9, 130.73, 130.67, 128.5, 128.1, 124.7, 122.2, 120.6, 114.0, 55.4, 35.0, 31.2, 25.2. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{21}H_{23}NO$: 306.1852; found: 306.1852.

*Methyl 4-(4-methoxyphenyl)-2-methylquinoline-6-carboxylate (**3s**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3s** as a white solid (64.5 mg, 70%). Mp 89-90 ºC. IR (film, cm^{-1}): 1716; 1464; 1026; 855; 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.7 Hz, 1H), 8.26 (dd, *J* = 8.8, 1.8 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.45-7.43 (m, 2H), 7.27 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 161.0, 160.1, 150.4, 149.6, 130.8, 129.7, 129.3, 129.0, 128.8, 127.3, 124.5, 122.9, 114.3, 55.4, 52.3, 25.5. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{19}H_{17}NO_3$: 308.1281; found: 308.1280.

*4-(4-methoxyphenyl)-2-methyl-6-(trifluoromethyl)quinolone (**3t**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3t** as a yellow solid (32.3 mg, 34%). Mp 61-62 ºC. IR (film, cm^{-1}): 1609; 1468; 1031; 832; 780 cm^{-1}. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.85 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.31 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 3.92 (s, 3H), 2.80 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.04. ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.2, 149.5, 149.2, 130.7, 130.2, 129.4, 127.5 (q, *J* = 32.4 Hz), 125.0 (q, *J* = 3.0 Hz), 124.5, 124.2 (q, *J* = 272.3 Hz) , 123.8 (q, *J* = 4.5 Hz), 123.3, 114.4, 55.4, 25.5. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{18}H_{14}F_3NO$: 318.1100; found: 318.1099.

*1-(4-(4-methoxyphenyl)-2-methylquinolin-6-yl)ethan-1-one (**3u**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3u** as a white solid (69.5 mg, 80%). Mp 109-110 ºC. IR (film, cm^{-1}): 1675; 1454; 1270; 1021; 880 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.8 Hz, 1H), 8.22 (dd, *J* = 8.8, 1.9 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.46-7.44 (m, 2H), 7.28 (s, 1H), 7.09-7.07 (m, 2H), 3.91 (s, 3H), 2.78 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 161.1, 160.2, 150.5, 149.7, 134.1, 130.8, 129.6, 129.5, 128.0, 127.6, 124.5, 122.9, 114.3, 55.4, 26.7, 25.6. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{19}H_{17}NO_2$: 292.1332; found: 292.1331.

*4-(4-methoxyphenyl)-2-methyl-6-phenylquinoline (**3v**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3v** as a brown oil (33.7 mg, 35%). IR (film, cm^{-1}): 1604; 1487; 1245; 1028; 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.62-7.60 (m, 2H), 7.49-7.41 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35-7.32 (m, 1H), 7.23 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 3.90 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 159.8, 158.5, 148.5, 147.9, 140.8, 138.4, 130.8, 130.4, 129.5, 128.9, 128.9, 127.5, 127.4, 125.4, 123.6, 122.6, 114.1, 55.4, 25.4. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{23}H_{19}NO$: 326.1539; found: 326.1538.

7-methoxy-4-(4-methoxyphenyl)-2-methylquinoline ***(3w)****;* *7-methoxy-4-(4-methoxyphenyl)-2-methylquinoline* ***(3w')***: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded as a white solid **3w** (44.4 mg, 52%), **3w'** (20.0mg, 24%). **3w**: Mp 96-97 ºC. IR (film, cm^{-1}): 1584; 1463; 1029; 878; 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 9.2 Hz, 1H), 7.44-7.40 (m, 3H), 7.08 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 159.8, 158.8, 150.3, 148.2, 130.7, 130.6, 126.8, 120.2, 120.1, 118.5, 114.0, 107.2, 55.5, 55.4, 25.3. HRMS (DART Positive) ($[M+H]^+$) Calcd for $C_{18}H_{17}NO_2$: 280.1332; found: 280.1331. **3w'**: Mp 71-72 ºC. 1607; 1465; 1032; 872; 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.58 (t, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.06 (s, 1H), 6.94-6.91 (m, 2H), 6.78 (d, *J* = 7.7 Hz, 1H), 3.88 (s, 3H), 3.55 (s, 3H), 2.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 158.1, 156.5, 150.0, 147.8, 135.1, 129.5, 129.4, 124.3, 121.6, 117.3, 112.4, 105.6, 55.4, 55.3, 24.9. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{18}H_{17}NO_2$: 280.1332; found: 280.1331.

4-(4-methoxyphenyl)-2-methylbenzo[h]quinoline ***(3x)***: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3x** as a white solid (51.8 mg, 58%). Mp 111-112 ºC. IR (film, cm^{-1}): 1589; 1497; 1033; 837; 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 1H), 7.78 (d,

J = 9.1 Hz, 1H), 7.72-7.62 (m, 3H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.29 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 2.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157.1, 148.1, 146.5, 133.5, 131.6, 130.9, 128.0, 127.5, 126.8, 126.4, 124.9, 123.1, 122.7, 122.5, 114.0, 55.4, 25.4. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{21}H_{17}NO$: 300.1383; found: 300.1382.

*4-(4-methoxyphenyl)-2-phenylquinoline (**3y**)*:[17] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3y** as a white solid (50.3 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.20-8.18 (m, 2H), 7.95 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.79 (s, 1H), 7.72 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.54-7.44 (m, 6H), 7.08 (d, *J* = 8.7 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 157.0, 148.9, 139.8, 130.9, 130.7, 130.2, 129.5, 129.3, 128.9, 127.6, 126.3, 126.0, 125.7, 119.4, 114.1, 55.5.

*2-(tert-butyl)-4-(4-methoxyphenyl)quinoline (**3z**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3z** as a yellow oil (45.4 mg, 52%). IR (film, cm^{-1}): 1609; 1496; 1245; 1033; 832 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.67-7.63 (m, 1H), 7.46-7.39 (m, 4H), 7.05 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 159.7, 148.1, 147.9, 131.2, 130.9, 129.8, 128.9, 125.6, 125.5, 125.3, 118.5, 114.0, 55.4, 38.2, 30.2. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{20}H_{21}NO$: 292.1696; found: 292.1695.

*Methyl 4-(4-(methoxycarbonyl)phenyl)-2-methylquinoline-6-carboxylate (**3aa**)*: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3aa** as a

white solid (35.5 mg, 35%). Mp 188-189 ºC. IR (film, cm^{-1}): 1715; 1563; 1277; 1103; 857 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.5 Hz, 1H), 8.29 (dd, *J* = 8.8, 1.7 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.31 (s, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 161.0, 150.3, 148.7, 142.0, 130.5, 130.0, 129.6, 129.5, 129.2, 128.4, 127.6, 123.9, 122.9, 52.37, 52.36, 25.6. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{20}H_{17}NO_4$: 336.1230; found: 336.1231.

*Methyl 4-(3-(((allyloxy)carbonyl)amino)phenyl)-2-methylquinoline-6-carboxylate **(3ab)***: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3ab** as a white solid (52.5 mg, 47%). Mp 83-84 ºC. IR (film, cm^{-1}): 1721; 1593; 1278; 1050; 845 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.7 Hz, 1H), 8.26 (dd, *J* = 8.8, 1.9 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.59 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 7.20-7.17 (m, 1H), 7.06 (s, 1H), 5.96 (ddt, *J* = 16.1, 10.5, 5.7 Hz, 1H), 5.36 (ddd, *J* = 17.2, 2.9, 1.4 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.68 (d, *J* = 5.7 Hz, 2H), 3.91 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 161.0, 153.2, 150.3, 149.4, 138.40, 138.38, 132.3, 129.5, 129.4, 129.0, 128.9, 127.39, 124.7, 124.3, 123.0, 119.5, 118.9, 118.5, 66.0, 52.3, 25.6. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{22}H_{20}N_2O_4$: 377.1496; found: 377.1496.

*1-(4-cyclopropyl-2-methylquinolin-6-yl)ethan-1-one **(3ac)***: Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **3ac** as a white solid (41.1 mg, 61%). Mp 88-89 ºC. IR (film, cm^{-1}): 1670; 1596; 1257; 1063; 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 8.8, 1.9 Hz, 1H), 8.05 (d,

J = 8.8 Hz, 1H), 6.97 (s, 1H), 2.75 (s, 3H), 2.71 (s, 3H), 2.48 (ddd, *J* = 13.7, 8.3, 5.4 Hz, 1H), 1.23 (ddd, *J* = 8.4, 6.3, 4.5 Hz, 2H), 0.91-0.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 161.5, 151.3, 149.8, 133.8, 129.6, 127.6, 126.3, 125.7, 118.58, 26.8, 25.6, 11.9, 8.3. HRMS (DART-FTICI Positive) ($[M+H]^+$) Calcd for $C_{15}H_{15}NO$: 226.1226; found: 226.1226.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publication website at DOI:

Characterization of products (copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra)

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