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Access to Quinolines through Gold-Catalyzed Intermolecular Cycloaddition of 2-Aminoaryl Carbonyls and Internal Alkynes

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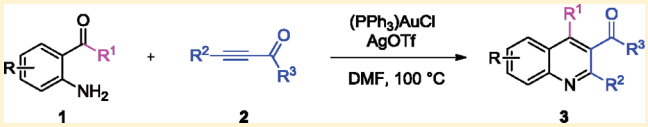
Supporting Information

ABSTRACT: A facile and general method leading to polyfunctionalized quinolines was developed. In the presence of a highly efficient combination encompassing $(PPh)_3AuCl$ and AgOTf, the reactions between 2-aminocarbonyls and an array of internal alkynes proceeded smoothly to afford quinoline derivatives in good to excellent yields (up to 93%).



Judging from the extensive reports surrounding quinolines,[1] the generation of an efficient platform for their expedient synthesis has, indubitably, been of great interest for decades. Apart from their wide presence in various natural products (Figure 1) and pharmaceutical compounds,[2] quinoline

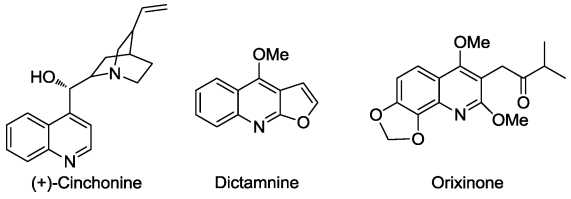


Figure 1. Examples of quinoline-containing natural products.

derivatives have been reported to possess biological properties such as antibacterial,[3a] anti-inflammatory,[3b] and antimicrobial activities.[3c] Therefore, the benefits associated with them justify the continual search for strategies to develop their synthesis.

Pioneering work on the construction of quinolines by Koenigs[4] in 1879 drew the attention of researchers and prompted a widespread search to increase the preparative value as the initial method required harsh conditions.[5]

Among the methods described over the years, prominent conventional examples include Friedländer synthesis, Skarup reactions, as well as Doebner–Miller reactions.[6] However, a recent upsurge of reports on synthesizing quinolines has demonstrated that new cycloadditions of suitable precursors through acid catalysis[7] and novel metal-catalyzed coupling–cyclization reactions[8] could compete and surpass conventional strategies in terms of celerity and efficacy. One prominent example is the recent work done by Li and co-workers, in which they reported an elegant work on the use of terminal ynones with aminoaryls to synthesize 3-carbonyl quinolines through Fe-catalyzed Michael addition–cycloaddition approach.[9]

Alkyne moieties have been ubiquitously employed in many organic syntheses. In particular, metal-catalyzed intermolecular alkyne reactions have been extremely popular in cycloadditions as they provide a convenient approach to the acquirement of cyclic compounds.[10] Our group has been actively developing new synthetic routes to heterocycles through efficacious methodologies.[11] One current example is the microwave-assisted three-component synthesis of pyrimidinones, catalyzed by copper(II) triflate.[12] Inspired by the immense opportunities presented by alkyne moieties and our growing interests in the assembly of heterocycles, we envisioned the use of alkyne in the construction of an array of quinoline derivatives.

Although there have been various reports on the synthesis of quinolines using alkynes,[9,13] the strategies often employ terminal alkynes with a rather limited substrate applicability. Internal alkynes, in contrast to terminal alkynes, allow integration of more functional groups into quinolines, increasing their possible applications and employability. Encouraged by the seemingly sparse report on using internal alkynes to construct quinolines, we sought to develop a novel method for the reaction of internal ynoates report successful applications of a variety of 2-aminoaryl carbonyls and internal alkynes in the synthesis of quinoline derivatives.

Preliminary studies were conducted with the aim to locate a suitable catalyst to promote the reaction between 2-aminobenzaldehyde **1a** and ethyl 3-phenylpropiolate **2a**. $Ni(cod)_2$ was chosen as the initial experimental catalyst due to reports demonstrating nickel's successful applications in such addition reactions.[14] However, the catalyst failed to produce the desired product. On top of that, no reaction was observed for $Sc(OTf)_3$ after heating at 100 °C for 24 h (Table 1, entries 1 and 2). Following the failure of preceding catalysts, attention was then directed to gold catalysts. Gold catalysts provide huge possibilities in organic reactions and ubiquitous reports have acknowledged their potentials, especially in cycloaddition reactions of alkyne as they preferentially coordinates to alkyne bonds.[15] In addition, gold catalysts have also been reported to aid substantially to the synthesis of quinolines[16] and isoquino-

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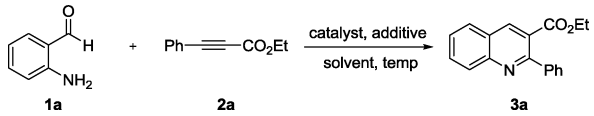
Table 1. Optimization of Quinoline 3a



1a 2a 3a

entry[a]	catalyst	ligand/additive	solvent	temp (°C)	time (h)	yield (%)
1	$Ni(cod)_2$	PPh_3	DMF	100	24	
2	$Sc(OTf)_3$		DMF	100	24	nr
3	$AuCl_3$		DMF	100	4	30
4	$(Ph_3P)AuCl$	AgOTf	DMF	100	2	88
5[b]	RAuCl	AgOTf	DMF	100	3	72
6[c]	$(Ph_3P)AuCl$	$AgNO_3$	DMF	100	24	<10
7	$(Ph_3P)AuCl$	Ag_2CO_3	DMF	100	24	nr
8	$(Ph_3P)AuCl$	AgOTf	ACN	reflux	12	58
9	$(Ph_3P)AuCl$	AgOTf	THF	60	12	47
10[c]	$(Ph_3P)AuCl$	AgOTf	CH_2Cl_2	reflux	24	<10
11	$(Ph_3P)AuCl$	AgOTf	DMF	50	5	66
12[d]	$(Ph_3P)AuCl$	AgOTf	DMF	100	8	82
13[e]	$(Ph_3P)AuCl$	AgOTf	DMF	100	1	80

[a]Unless specified, reactions were carried out by treating **1a** (1 equiv) and **2a** (1.5 equiv) with catalyst (10 mol %) and ligand/additive (10 mol %) in solvent (2 mL). [b]R = [P(*t*-Bu)$_2$(*o*-biphenyl)]. [c]More than 80% of the starting materials were recovered. [d]Reaction was carried out with catalyst (5 mol %) and additive (5 mol %). [e]Reaction was carried out with catalyst (20 mol %) and additive (20 mol %).

lines.[17] To our delight, successful acquirement of the desired product when catalytic amount of $AuCl_3$ was employed validated our prediction, albeit the yield was only 30% (Table 1 entry 3). Silver additives have been known to complement gold catalysts by increasing the electrophilicity of the gold center through halide abstraction.[18] Hence, the reaction was further examined by the incorporation of silver additive. Interestingly, the yield was raised significantly to 88% and the time was shortened to 2 h when $AuCl_3$ was replaced by $(Ph_3P)AuCl$, with AgOTf as additive. Further attempt to alternate the catalyst to [P(*t*-Bu)$_2$(*o*-biphenyl)]AuCl gave a less satisfactory result (72% yield, Table 1 entry 5). These outcomes showcases the suitability of $(Ph_3P)AuCl$ for this reaction and prompted a search for an additive most compatible with $(Ph_3P)AuCl$. After screening various additives including $AgNO_3$ and Ag_2CO_3, it was apparent that the combination of $(Ph_3P)AuCl$ with AgOTf gave the best yield (Table 1, entries 4, 6, and 7). Subsequent examination of the solvent effect reveals DMF to be the optimal solvent in comparison to ACN, THF and CH_2Cl_2 (Table 1, entries 8−10). The reaction temperature was fixed at 100 °C as longer reaction times were required and lower yields were obtained when the temperature was reduced to 50 °C (Table 1, entry 11). In the final part of the studies, the catalyst and additive loadings were investigated. Although there were no significant effects of the loadings on the yields, observable changes in the reaction times were documented (Table 1, entries 12−13). When the loadings were decreased to 5 mol %, the reaction time was prolonged to 8 h. Increase of the loadings to 20 mol % did not shorten the reaction time significantly, therefore 10 mol % of catalyst loading and additive loading were chosen as the most favorable loading amounts. Through the optimization studies, a set of optimal conditions was defined. With 10 mol % $(Ph_3P)AuCl$, 10 mol % AgOTf in DMF at 100 °C, the reaction proceeded smoothly, providing a high yield of 88% in 2 h.

Elucidation of the optimal set of conditions allowed continual investigation of the reaction scope and flexibility. To examine the adaptability of the reaction, a wide array of 2-aminoaryl carbonyls **1** were employed. From Table 2, it was worthy of note that most of the 2-aminoaryl carbonyls **1** provided the desired compound in good to excellent yields (80−91%). A closer examination of the results revealed that in contrast to the 5-Cl-, 5-NO_2-, 4′-Cl-, and 4′-Br-substituted 2-aminobenzophenones, the 4-Me- and 4′-Me-substituted benzophenones produced observable higher yields (Table 2, entries 4−9, **3d−i**). This led to the speculation that electron-donating substituents perform better than electron-withdrawing substituents. In particular, when strong electron-withdrawing 5-NO_2-substituted 2-aminobenzophenone was subjected to the same conditions, the reaction could not be completed even after 48 h and the 38% yield (**3f**) obtained was comparatively inferior to other products (Table 2, entry 6). In addition, when 2-aminobenzophenone was substituted with 5-Cl and 2′-F, the yield was slightly lower (80%), presumably due to the presence of two electron-withdrawing substituents (Table 2, entry 10). Encouraged by the success of aryl substituents, the focus was directed to the possibility of incorporating alkyl substituents in the system. Notably, the reaction proceeded smoothly in the presence of 2-aminoacetophenone, providing an excellent yield of 91% (Table 2, entry 2, **3b**). Increasing the alkyl chain did not affect the yield, and compound **3k** was also produced with an exceptional yield (Table 2, entry 11).

Extension of the preliminary studies on the substrate scope (Table 3) was essential, and exploration using a range of alkyne substituents **2** was therefore crucial. Gratifyingly, good to excellent yields (80−90%) were obtained in the presence of electron-donating or electron-withdrawing substituents on the aryl ring of the alkyne (Table 3, entries 1−4, **3l−o**). Although there was a slight decrease in the yields for electron-withdrawing substituents as compared to electron-donating substituents, the difference is less significant and good yields were acquired even for NO_2-substituted aryl alkynes. Furthermore, bulky substituent (naphthalene) on the aryl alkyne did not hinder the reaction and **3p** was obtained in high yield of 88% (Table 3, entry 5). Smooth progression of the reaction also occurred for alkyl alkyne, providing excellent yields between 88% to 91% (Table 3, entries 6−8, **3q−s**). Subsequently, the ethoxy group in the alkyne was replaced with

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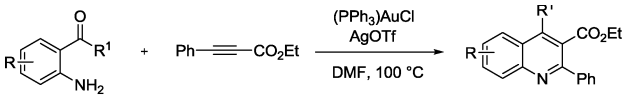
Table 2. Substrate Scope: An Insight to the Flexibility of the Reaction through Various 2-Aminoaryl Carbonyls 1



1 2a 3

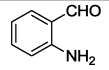
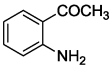
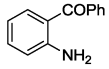
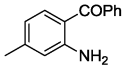
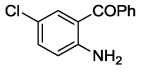
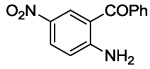
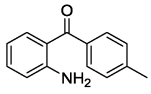
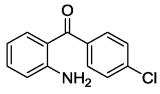
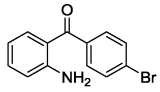
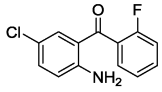
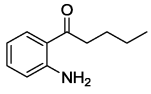
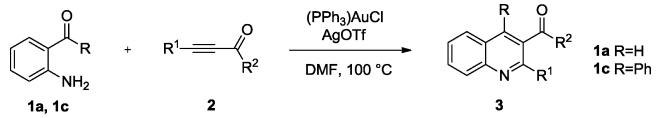
entry[a]	1		3	yield (%)
1	1a		3a	88
2	1b		3b	91
3	1c		3c	91
4	1d		3d	90
5	1e		3e	83
6	1f		3f	38
7	1g		3g	88
8	1h		3h	82
9	1i		3i	83
10	1j		3j	80
11	1k		3k	91

Table 3. Substrate Scope: An Insight to the Flexibility of the Reaction through Various Internal Alkyne Substituents 2



1a, 1c 2 3

entry[a]	1	2		3	yield (%)
1	1a	2b	R^1 = 4- CH_3Ph, R^2 = CO_2Et	3l	90
2	1a	2c	R^1 = 4-OCH_3Ph, R^2 = CO_2Et	3m	93
3	1a	2d	R^1 = 4-BrPh, R^2 = CO_2Et	3n	85
4	1a	2e	R^1 = 4-NO_2Ph, R^2 = CO_2Et	3o	80
5	1a	2f	R^1 = naphthalene, R^2 = CO_2Et	3p	88
6[b]	1c	2g	R^1 = CH_3, R^2 = CO_2Et	3q	90
7[b]	1c	2h	R^1 = $CH_2CH_2CH_3$, R^2 = CO_2Et	3r	91
8[b]	1c	2i	R^1 = $(CH_2)_5CH_3$, R^2 = CO_2Et	3s	88
9	1a	2j	R^1 = Ph, R^2 = piperidine	3t	75
10	1a	2k	R^1 = Ph, R^2 = CH_3	3u	65

[a]Reactions carried out by treating **1a** (1 equiv) and **2** (1.5 equiv) with $(Ph_3P)AuCl$ (10 mol %) and AgOTf (10 mol %) in DMF (2 mL) at 100 °C. [b]Reactions with **1c** (1 equiv).

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piperidine, and a relatively good yield of 75% was obtained for **3t** (Table 3, entry 9). Rounding up on investigation of the substrate scope, a ketone-substituted alkyne was employed and the reaction was able to give a reasonable yield of 65% (Table 3, entry 10, **3u**). This further exemplifies the diversity of the reaction and provides a favorable conclusion to our investigations.

In summary, an expedient methodology for the facile synthesis of quinolines was demonstrated with the aid of $(PPh_3)AuCl$ catalyst and AgOTf additive. This intermolecular cyclization of internal alkynes allowed the efficient integration of more functional groups into quinolines. In addition, the adaptability of this strategy was displayed by the good to excellent yields obtained for a large array of substrates. The importance of quinolines extends beyond being components of natural products; they have also been acknowledged for their wide applications in biological and pharmaceutical fields.[1−3] Therefore, the success of this strategy provides immediate access to an extensive library of quinolines, contributing significantly to the research sector.

EXPERIMENTAL SECTION

All reactions were conducted under an atmosphere of nitrogen, unless otherwise indicated. All reagents and solvents were obtained from commercial suppliers and used without further purification. Product purification by flash column chromatography was accomplished using silica gel (0.010−0.063 mm). Technical grade solvents were used for chromatography and distilled prior to use. IR spectra were recorded and reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on an ion trap mass spectrometer, coupled with the HPLC system and the CE system. Accurate masses are reported for the molecular ion $[M + H]^+$ or a suitable fragment ion. NMR spectra were recorded at room temperature on a 400 MHz NMR spectrometer. The residual solvent signals were taken as the reference (7.26 ppm for ^1H NMR spectroscopy and 77.0 ppm for ^{13}C NMR spectroscopy). Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from triethylsilane. Chemical shift (δ) is referred in terms of ppm, coupling constants (J) are given in Hz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or unresolved.

2-Aminoaryl carbonyls **1b−j** and internal alkynes **2a,g−i** were obtained from commercial suppliers and used without further purification. Other 2-aminoaryl carbonyls **1a**[19a] and **1k**[19b] and internal alkynes **2b−f**,[20a] **2j**,[20b] **2k**[20c] were prepared from the standard literature procedures.

General Procedure for the Synthesis of Quinolines. To a solution of 2-aminobenzaldehyde **1a** (10.0 mg, 0.08 mmol, 1.0 equiv), $(PPh_3)AuCl$ (0.4 mg, 0.008 mmol, 0.1 equiv), and AgOTf (0.2 mg, 0.008 mmol, 0.1 equiv) in DMF (2 mL) was added ethyl 3-phenylpropiolate **2a** (15.0 μL, 0.09 mmol, 1.1 equiv). The reaction mixture was stirred at 100 °C for 2 h (TLC monitored). The resulting mixture was then diluted with EtOAc and filtered through Celite. The filtrate was washed with water (2 × 20 mL) and brine (2 × 20 mL), and the organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude residue as a dark yellow oil. The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3a** (20.1 mg, 0.07 mmol, 88% yield) as a yellow oil.

*Ethyl 2-Phenylquinoline-3-carboxylate (**3a**).* R_f = 0.34 (EtOAc/Hex 20/80). ^1H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.83−7.79 (m, 1H), 7.65−7.59 (m, 3H), 7.50−7.44 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 158.1, 148.4, 140.8, 139.0, 131.5, 129.5, 128.6, 128.5, 128.2(2), 127.2, 125.8, 125.5, 61.5, 13.7. FT-IR (neat):: ν_{max} 3063, 2986, 2901, 1721, 1620, 1597, 1451, 1234, 1096, 833 cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{15}NO_2$ $[M + H]^+$ 278.1103, found 278.1181.

*Ethyl 4-Methyl-2-phenylquinoline-3-carboxylate (**3b**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3b** (19.6 mg, 0.07 mmol, 91% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex 20/80). ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.70−7.68 (m, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.48−7.43 (m, 3H), 4.15 (q, J = 7.2 Hz, 2H), 2.76 (s, 3H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 156.2, 147.2, 142.7, 140.6, 130.3, 128.6, 128.3, 127.4, 126.9, 126.0, 124.1, 61.5, 15.6, 13.6. FT-IR (neat): ν_{max} 3063, 2986, 1721, 1644, 1582, 1497, 1450, 1296, 1234 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{17}NO_2$ $[M + H]^+$ 292.1259, found 292.1338.

*Ethyl 2,4-Diphenylquinoline-3-carboxylate (**3c**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3c** (16.3 mg, 0.05 mmol, 91% yield) as a yellow solid. R_f = 0.34 (EtOAc/Hex 20/80). Mp: 89−91 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.3 Hz, 1H), 7.79−7.75 (m, 3H), 7.62 (d, J = 8.3 Hz, 1H), 7.52−7.41 (m, 9H), 3.87 (q, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 156.0, 147.8, 147.1, 140.2, 135.5, 130.4, 129.8, 129.4, 129.1, 128.8, 128.6, 128.5, 128.4, 128.2, 127.2, 127.0, 126.5, 125.5, 61.2, 13.4. FT-IR (neat): ν_{max} 3063, 2978, 2893, 1728, 1612, 1551, 1481, 1443, 1296, 1227, 1103 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{19}NO_2$ $[M + H]^+$ 354.1416, found 354.1494.

*Ethyl 7-Methyl-2,4-diphenylquinoline-3-carboxylate (**3d**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3d** (15.7 mg, 0.04 mmol, 90% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex 20/80). ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.75−7.73 (m, 2H), 7.51−7.40 (m, 9H), 7.31 (d, J = 8.7 Hz, 1H), 3.86 (q, J = 7.2 Hz, 2H), 2.57 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 156.0, 148.1, 146.9, 141.0, 140.4, 135.8, 129.4, 129.3, 128.8, 128.7, 128.5, 128.4(2), 128.2, 126.4, 126.2, 123.5, 61.2, 21.8, 13.4. FT-IR (neat): ν_{max} 3063, 2978, 2932, 2870, 1728, 1620, 1551, 1489, 1450, 1412, 1288, 1227, 1173 cm^{-1}. HRMS (ESI): m/z calcd for $C_{25}H_{21}NO_2$ $[M + H]^+$ 368.1572, found 368.1650.

*Ethyl 6-Chloro-2,4-diphenylquinoline-3-carboxylate (**3e**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3e** (13.8 mg, 0.04 mmol, 83% yield) as a yellow oil. R_f = 0.35 (EtOAc/Hex 20/80). ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 9.0 Hz, 1H), 7.76−7.73 (m, 2H), 7.70 (dd, J = 2.2, 9.0 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.52−7.46 (m, 6H), 7.46−7.39 (m, 2H), 3.88 (q, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 156.2, 146.3, 146.2, 139.8, 134.8, 133.0, 131.4, 129.3, 129.1, 128.8, 128.5(2), 128.4, 127.9, 126.3, 125.3, 61.4, 13.4. FT-IR (neat): ν_{max} 3063, 2986, 2932, 1728, 1643, 1551, 1474, 1443, 1296, 1219, 1111, 756, 702 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{18}ClNO_2$ $[M + H]^+$ 388.1026, found 388.1104.

*Ethyl 6-Nitro-2,4-diphenylquinoline-3-carboxylate (**3f**).* The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **3f** (6.2 mg, 0.02 mmol, 38% yield) as a yellow solid. R_f = 0.31 (EtOAc/Hex 20/80). Mp: 126−128 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 2.4 Hz, 1H), 8.53 (dd, J = 2.4, 9.2 Hz, 1H), 8.34 (d, J = 9.2 Hz, 1H), 7.79−7.77 (m, 2H), 7.57−7.56 (m, 3H), 7.51−7.49 (m, 3H), 7.43−7.41 (m, 2H), 3.91 (q, J = 7.1 Hz, 2H), 0.84 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 159.4, 149.8, 149.1, 145.9, 138.3, 134.0, 131.7, 129.7, 129.4, 129.3, 128.9, 128.7, 128.6(2), 124.9, 123.9, 123.6, 61.7, 13.3. FT-IR (neat): ν_{max} 1728, 1643, 1558, 1528, 1481, 1443, 1342, 1288, 1219, 1111, 1088 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{18}N_2O_4$ $[M + H]^+$ 399.1267, found 399.1345.

*Ethyl 2-Phenyl-4-p-tolylquinoline-3-carboxylate (**3g**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3g** (15.3 mg, 0.04 mmol, 88% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex 20/80). ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.4 Hz, 1H), 7.78−7.74 (m, 3H), 7.65 (d, J = 8.4 Hz, 1H), 7.50−7.45 (m, 4H), 7.31 (s, 4H), 3.88 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 0.83 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 156.0, 147.8, 147.3, 140.3, 138.3, 132.5,

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130.4, 129.8, 129.3, 128.9, 128.8, 128.6, 128.4, 126.9, 126.6, 125.7, 61.2, 21.4, 13.4. FT-IR (neat): ν_{max} 2978, 2924, 1728, 1636, 1551, 1489, 1458, 1296, 1227, 1103 cm^{-1}. HRMS (ESI): m/z calcd for $C_{25}H_{21}NO_2$ $[M + H]^+$ 368.1572, found 368.1650.

*Ethyl 4-(4-Chlorophenyl)-2-phenylquinoline-3-carboxylate (**3h**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3h** (13.7 mg, 0.04 mmol, 82% yield) as a yellow solid. R_f = 0.35 (EtOAc/Hex 20/80). Mp: 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.4 Hz, 1H), 7.80−7.73 (m, 3H), 7.57−7.56 (m, 1H), 7.52−7.45 (m, 6H), 7.37 (d, J = 8.4 Hz, 2H), 3.90 (q, J = 7.1 Hz, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 156.0, 147.8, 156.8, 140.1, 134.8, 133.9, 130.8, 130.6, 129.9, 128.9, 128.5(2), 128.4, 127.3, 127.2, 126.2, 125.3, 61.4, 13.4. FT-IR (neat): ν_{max} 3017, 2986, 1721, 1636, 1574, 1551, 1481, 1404, 1219, 1103, 756, 664 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{18}ClNO_2$ $[M + H]^+$ 388.1026, found 388.1104.

*Ethyl 4-(4-Bromophenyl)-2-phenylquinoline-3-carboxylate (**3i**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3i** (13.0 mg, 0.03 mmol, 83% yield) as a yellow solid. R_f = 0.35 (EtOAc/Hex 20/80). Mp: 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.4 Hz, 1H), 7.80−7.73 (m, 3H), 7.65 (d, J = 8.4 Hz, 2H), 7.58−7.45 (m, 5H), 7.30 (d, J = 8.4 Hz, 2H), 3.90 (q, J = 7.1 Hz, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 156.0, 147.8, 145.8, 140.1, 134.4, 131.5, 131.1, 130.6, 129.9, 128.9, 128.5, 128.4, 127.3, 127.1, 126.2, 125.2, 123.0, 61.4, 13.4. FT-IR (neat): ν_{max} 3071, 2986, 2932, 1728, 1636, 1551, 1481, 1443, 1296, 1227, 1103, 694, 664 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{18}BrNO_2$ $[M + H]^+$ 432.0521, found 432.0599.

*Ethyl 6-Chloro-4-(2-fluorophenyl)-2-phenylquinoline-3-carboxylate (**3j**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3j** (13.0 mg, 0.03 mmol, 80% yield) as a yellow oil. R_f = 0.35 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 9.0 Hz, 1H), 7.76−7.70 (m, 3H), 7.54−7.46 (m, 5H), 7.34−7.25 (m, 3H), 3.90 (q, J = 7.1 Hz, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 160.9, 158.5, 156.5, 146.1, 140.9, 139.8, 133.4, 131.7, 131.5, 131.3, 131.2, 129.1, 128.5(2), 126.2, 124.8, 124.3(2), 122.6, 116.0, 115.8, 61.5, 13.4. FT-IR (neat): ν_{max} 3017, 2986, 2940, 1728, 1636, 1574, 1551, 1474, 1450, 1296, 1219, 1111, 756, 664 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{17}FClNO_2$ $[M + H]^+$ 406.0932, found 406.1010.

*Ethyl 4-Butyl-2-phenylquinoline-3-carboxylate (**3k**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3k** (17.1 mg, 0.05 mmol, 91% yield) as a yellow oil. R_f = 0.42 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.69−7.67 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.48−7.42 (m, 3H), 4.13 (q, J = 7.1 Hz, 2H), 3.15−3.11 (m. 2H), 1.80−1.73 (m, 2H), 1.52 (sext, J = 7.4 Hz, 2H), 1.03−0.97 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 156.4, 147.7, 147.4, 140.7, 130.5, 130.2, 128.6, 128.4, 128.3, 126.9(2), 125.3, 124.1, 61.4, 33.2, 29.7, 23.3, 13.8, 13.6. FT-IR (neat): ν_{max} 3063, 2955, 2924, 2870, 1721, 1620, 1574, 1497, 1458, 1404, 1288, 1234, 1165, 1103 cm^{-1}. HRMS (ESI): m/z calcd for $C_{22}H_{23}NO_2$ $[M + H]^+$ 334.1729, found 334.1807.

*Ethyl 2-p-Tolylquinoline-3-carboxylate (**3l**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3l** (21.6 mg, 0.07 mmol, 90% yield) as a yellow oil. R_f = 0.34 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.28−7.26 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 158.1, 148.5, 138.9, 138.5, 137.8, 131.4, 129.5, 128.9, 128.5, 128.2, 127.0, 125.8, 125.5, 61.5, 21.3, 13.8. FT-IR (neat): ν_{max} 3017, 2932, 1721, 1620, 1458, 1427, 1219, 1096 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{17}NO_2$ $[M + H]^+$ 292.1259, found 292.1338.

*Ethyl 2-(4-Methoxyphenyl)quinoline-3-carboxylate (**3m**).* The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **3m** (23.6 mg, 0.08 mmol, 93% yield) as a yellow oil. R_f = 0.21 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.60−7.56 (m, 1H), 7.00 (d, J = 8.6 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 160.2, 157.7, 148.4, 138.9, 133.2, 131.4, 130.1, 129.4, 128.2, 127.0, 125.7, 125.5, 113.7, 61.6, 55.4, 13.9. FT-IR (neat): ν_{max} 3017, 2978, 2940, 2839, 1721, 1612, 1558, 1512, 1458, 1420, 1250, 1219, 1096, 1034 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{17}NO_3$ $[M + H]^+$ 308.1208, found 308.1287.

*Ethyl 2-(4-Bromophenyl)quinoline-3-carboxylate (**3n**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3n** (24.9 mg, 0.07 mmol, 85% yield) as a pale yellow solid. R_f = 0.35 (EtOAc/Hex 20/80). Mp: 86−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.64−7.60 (m, 3H), 7.52 (d, J = 8.3 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 157.0, 148.4, 139.7, 139.4, 131.8, 131.3, 130.3, 129.5, 128.3, 127.5, 125.9, 125.0, 123.0, 61.7, 13.8. FT-IR (neat): ν_{max} 3017, 2986, 1721, 1620, 1597, 1558, 1481, 1450, 1420, 1265, 1227, 1096 cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{14}BrNO_2$ $[M + H]^+$ 356.0208, found 356.0286.

*Ethyl 2-(4-Nitrophenyl)quinoline-3-carboxylate (**3o**).* The crude residue was then purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford compound **3o** (21.3 mg, 0.07 mmol, 80% yield) as a yellow solid. R_f = 0.23 (EtOAc/Hex 20/80). Mp: 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.34 (d, J = 8.5 Hz, 2H), 8.18 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.68 (t, J = 8.0 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 156.2, 148.4, 147.8, 147.3, 140.0, 132.2, 129.7, 129.6, 128.4, 128.1, 126.2, 124.4, 123.3, 61.8, 13.9. FT-IR (neat): ν_{max} 3017, 2986, 1721, 1620, 1597, 1558, 1481, 1450, 1420, 1373, 1265, 1227, 1096 cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{14}N_2O_4$ $[M + H]^+$ 323.0954, found 323.1032.

*Ethyl 2-(Naphthalen-2-yl)quinoline-3-carboxylate (**3p**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3p** (23.8 mg, 0.07 mmol, 88% yield) as a pale yellow oil. R_f = 0.34 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.94−7.84 (m, 3H), 7.67 (t, J = 7.6 Hz, 1H), 7.60−7.52 (m, 3H), 7.46 (t, J = 7.0 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 3.85 (q, J = 7.1 Hz, 2H), 0.60 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 158.1, 148.7, 139.5, 139.1, 133.4, 131.9, 131.8, 129.6, 128.5(2), 128.3, 127.5, 126.4, 126.3(2), 125.7, 125.2, 125.1, 61.1, 13.1. FT-IR (neat): ν_{max} 3055, 2978, 2932, 1721, 1620, 1597, 1558, 1489, 1458, 1427, 1250, 1234, 1204, 1072 cm^{-1}. HRMS (ESI): m/z calcd for $C_{22}H_{17}NO_2$ $[M + H]^+$ 328.1259, found 328.1338.

*Ethyl 2-Methyl-4-phenylquinoline-3-carboxylate (**3q**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3q** (13.3 mg, 0.05 mmol, 90% yield) as a yellow solid. R_f = 0.42 (EtOAc/Hex 20/80). Mp: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1H), 7.74−7.70 (m, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.50−7.47 (m, 3H), 7.45−7.41 (m, 1H), 7.38−7.35 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.79 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 154.6, 147.7, 146.2, 135.7, 130.2, 129.4, 128.9, 128.4, 128.2, 127.4, 126.5, 126.4, 125.2, 31.3, 23.8, 13.6. FT-IR (neat): ν_{max} 2978, 2932, 1728, 1566, 1489, 1443, 1404, 1296, 1227, 1180, 1065 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{17}NO_2$ $[M + H]^+$ 292.1259, found 292.1338.

*Ethyl 4-Phenyl-2-propylquinoline-3-carboxylate (**3r**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3r** (14.7 mg, 0.05 mmol, 91% yield) as a pale yellow solid. R_f = 0.42 (EtOAc/Hex 20/80). Mp: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 1H),

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7.73−7.69 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.50−7.35 (m, 6H), 4.04 (q, J = 7.2 Hz, 2H), 3.02−2.98 (m, 2H), 1.88 (sext, J = 7.4 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 158.3, 147.8, 146.3, 135.8, 130.1, 129.4, 129.0, 128.4, 128.2, 127.4, 126.4, 126.3, 125.1, 61.2, 39.2, 23.1, 14.2, 13.6. FT-IR (neat): ν_{max} 3017, 2963, 2870, 1721, 1566, 1481, 1458, 1404, 1219, 1065 cm^{-1}. HRMS (ESI): m/z calcd for $C_{21}H_{21}NO_2$ $[M + H]^+$ 320.1572, found 320.1650.

*Ethyl 2-Hexyl-4-phenylquinoline-3-carboxylate (**3s**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3s** (16.1 mg, 0.04 mmol, 88% yield) as a pale yellow oil. R_f = 0.42 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 1H), 7.73−7.69 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.49−7.35 (m, 6H), 4.04 (q, J = 7.2 Hz, 2H), 3.04−3.00 (m, 2H), 1.89−1.81 (m, 2H), 1.45 (t, J = 7.2 Hz, 2H), 1.34−1.30 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 158.5, 147.8, 146.3, 135.9, 130.1, 129.4, 129.0, 128.4, 128.2, 127.3, 126.4, 126.3, 125.1, 61.2, 37.3, 31.7, 29.8, 29.4, 22.5, 14.0, 13.6. FT-IR (neat): ν_{max} 3024, 2955, 2932, 2862, 1721, 1643, 1556, 1489, 1458, 1404, 1219, 1173, 1065 cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{27}NO_2$ $[M + H]^+$ 362.2042, found 362.2120.

*(2-Phenylquinolin-3-yl)(piperidin-1-yl)methanone (**3t**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3t** (19.6 mg, 0.06 mmol, 75% yield) as a yellow oil. R_f = 0.03 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.90−7.85 (m, 3H), 7.77 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.51−7.45 (m, 3H), 3.72−3.66 (m, 1H), 3.53−3.47 (m, 1H), 2.93−2.86 (m, 1H), 2.73−2.67 (m, 1H), 1.58−1.50 (m, 1H), 1.44−1.30 (m, 3H), 1.18−1.09 (m, 1H), 0.62−0.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 155.2, 148.0, 139.4, 136.0, 130.5, 130.1, 129.6, 129.2(2), 128.5, 127.7, 127.1, 126.5, 47.7, 42.5, 25.2, 24.9, 24.1. FT-IR (neat): ν_{max} 3017, 2947, 2862, 1620, 1474, 1443, 1219, 1026 cm^{-1}. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_2O$ $[M + H]^+$ 317.1576, found 317.1654.

*1-(2-Phenylquinolin-3-yl)ethanone (**3u**).* The crude residue was then purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford compound **3u** (15.2 mg, 0.06 mmol, 65% yield) as a yellow oil. R_f = 0.17 (EtOAc/Hex 20/80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.79−7.75 (m, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.56−7.47 (m, 3H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 156.6, 148.0, 137.2, 136.7, 133.7, 132.2, 131.0, 130.1, 128.7, 128.6, 128.1, 126.6, 125.2, 24.2. FT-IR (neat): ν_{max} 3061, 3019, 2958, 1663, 1568 cm^{-1}. HRMS (ESI): m/z calcd for $C_{17}H_{13}NO$ $[M + H]^+$ 248.0997, found 248.1075.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **3a−u**. This material is available free of charge via the Internet at http://pubs.acs.org.

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