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Copper-catalyzed tandem reaction of enamino esters with ortho-halogen aromatic carbonyls: one pot approach to functionalized quinolines

Fei Peng,[a] Jin Liu,[a] Lili Li [a] and Zhiwei Chen*[a]

Abstract: A novel, efficient, and practical approach for the synthesis of functionalized quinolines has been developed through the copper-catalyzed C–C bond formation and C–N coupling of enamino esters with *ortho*-halogen aromatic carbonyls. By using this methodology, a series of quinolines can be easily obtained in moderate to good yields with favorable functional group tolerance. A gram-scale reaction was also performed to demonstrate the scaled-up applicability of this methodology.

Introduction

The quinoline skeleton is a core structure in various natural products and pharmaceuticals (Figure 1).[1] Quinoline derivatives play an important role in medicinal chemistry, which exhibit a diverse range of biological properties, such as anticancer,[2] antimicrobial,[3] anti-parasitic,[4] and antipsychotic activities.[5] Accordingly, the development of new reliable and practical synthetic approaches to prepare quinolines from readily available starting materials is of great interest.

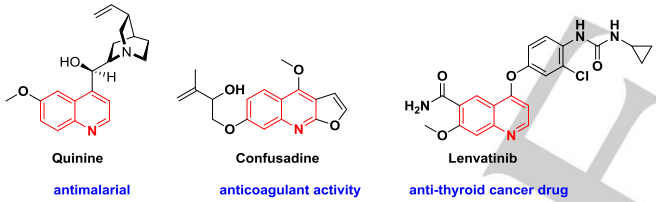
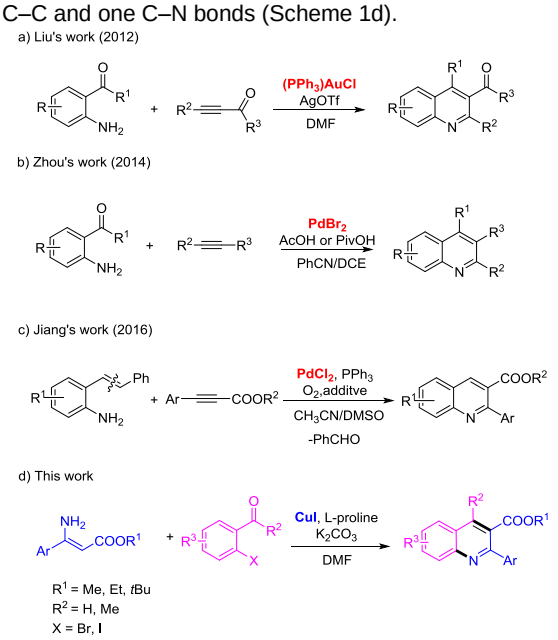


Figure 1. Selected examples bearing the quinoline core structure.

Recently, transition-metal-catalyzed C–H functionalization has emerged as an efficient and versatile method for accessing various heterocycles and carbocycles.[6] In this context, various methodologies have been developed to produce versatile quinolines via transition-metal-catalyzed C–H functionalization. In 2012, Liu and co-workers described the Au-catalyzed [4 + 2] cyclization of 2-aminoaryl carbonyls and alkynes to form 3-acyl quinolines (Scheme 1a).[7] Similarly, an elegant work reported by Zhou group disclosed an efficient approach for the preparation of quinolines through Pd^{II}-catalyzed syntheses from 2-amino aromatic ketones and alkynes (Scheme 1b).[8] Recently, Jiang group developed an efficient method for the synthesis of functionalized quinolines through C–C double bond cleavage (Scheme 1c).[9] In addition, syntheses of quinolines via Ru-catalyzed cyclization process have also been reported by Kapur,[10] Sun[11] and Hu[12] groups, respectively. However, all these methods employed precious metals as the catalysts, and in terms of sustainability and practicability, thus it is highly desirable to exploit efficient methods to access these structural motifs using inexpensive and widely abundant metals as catalyst.[13] In this concern, copper is an extremely diverse and earth-abundant transition metal that has received increasing attention for the construction of various bonds in organic synthesis during the past years.[14] Copper-catalyzed Ullmann C–N coupling has made great progress towards the construction of N-heterocycles.[15] Recently, Kaeobamrung group reported the copper-catalyzed 2-halobenzaldehydes and cyclic enaminones to accomplish dihydroacridines, and acyclic enaminones to achieve quinolines,[15g] our work was focused on the chain enamino esters formation of functionalized quinolines which can be used to complement Kaeobamrung's work. On the other hand, enamino esters are useful synthons showing prevalent application in organic synthesis and have been discovered with widespread application in the construction of N-containing heterocyclic compounds such as pyrroles,[16] pyridines[17], pyrazoles[18] and oxazoles.[19] During our continuous research in constructing nitrogenous heterocyclic compounds using enamino esters[20], a copper-catalyzed tandem approach is designed for the synthesis of quinolines via cascade formation of one C–C and one C–N bonds (Scheme 1d).



Scheme 1. Different protocols for the synthesis of quinolines.

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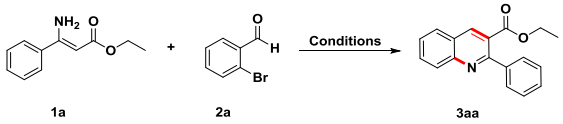
Results and Discussion

The model substrates initially used to evaluate the domino reaction were ethyl 3-amino-3-phenylacrylate (**1a**) and 2-bromobenzaldehyde (**2a**) (Table 1). After exploring a set of copper salts, CuI turned out to be the optimal catalyst, leading to the desired product **3a** in 76% yield. Next, various solvents, such as toluene, dioxane and CH_3CN, were examined, while DMF gave the highest yield (entries 5–8). Subsequently, effect of bases was investigated (entries 9–12), stronger bases did not afford higher yields (entries 11 and 12), and K_2CO_3 provided the best result (entry 5). Changing the ligand to 2, 2'-bipyridine or 1, 10-phen was also observed to be detrimental leading to a slight drop in the yields (entries 13 and 14). No reaction occurred in the absence of copper catalyst (entry 15), whereas a decrease in yield was observed in the absence of ligand or base (entries 16 and 17). Finally, the screening of reaction temperatures indicated that the reaction gave the best result at 120 °C (entries 5, 18 and 19). Hence, the most optimal conditions of 10 mol% CuI, 20 mol% L-proline and 3.0 eq. of K_2CO_3 in DMF at 120 °C were simultaneously used for further investigation.

Table 1. Optimization of Reaction Conditions for Synthesis of quinolines. [a]

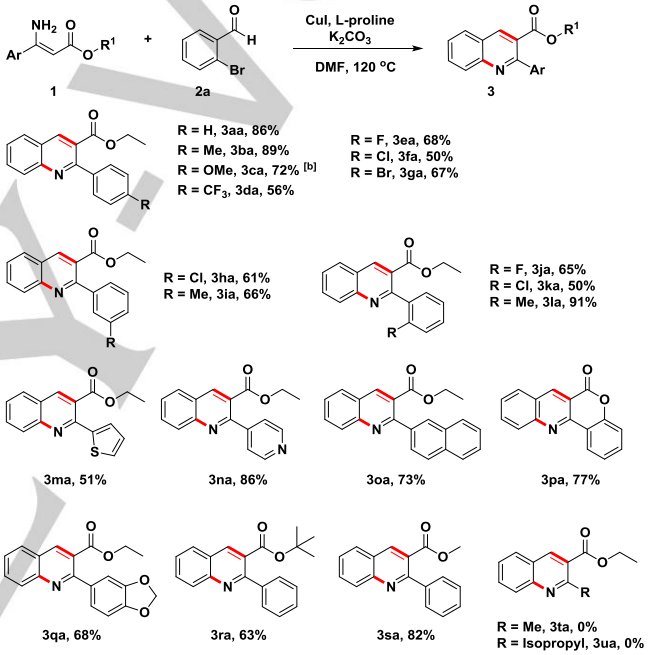


1a 2a 3aa

Entry	Catalyst	Base	Ligand	Solvent	Yield (%) [b]
1	CuCl	K_2CO_3	L-Proline	DMSO	61
2	CuBr	K_2CO_3	L-Proline	DMSO	55
3	CuI	K_2CO_3	L-Proline	DMSO	76
4	Cu_2O	K_2CO_3	L-Proline	DMSO	60
5	***CuI***	***K_2CO_3***	***L-Proline***	***DMF***	***86***
6	CuI	K_2CO_3	L-Proline	Toluene	77
7	CuI	K_2CO_3	L-Proline	dioxane	59
8	CuI	K_2CO_3	L-Proline	CH_3CN	74
9	CuI	Na_2CO_3	L-Proline	DMF	80
10	CuI	K_3PO_4	L-Proline	DMF	48
11	CuI	Cs_2CO_3	L-Proline	DMF	78
12	CuI	t-BuONa	L-Proline	DMF	63
13	CuI	K_2CO_3	2, 2'-bipyridine	DMF	81
14	CuI	K_2CO_3	1, 10-Phen	DMF	76
15	-	K_2CO_3	-	DMF	N.R.
16	CuI	K_2CO_3	-	DMF	67
17	CuI	-	L-Proline	DMF	47
18 [c]	CuI	K_2CO_3	L-Proline	DMF	75
19 [d]	CuI	K_2CO_3	L-Proline	DMF	84

[a] Reaction conditions: ethyl-3-amino-3-phenylacrylate **1a** (0.5 mmol), 2-bromobenzaldehyde **2a** (0.6 mmol), copper catalyst (0.05 mmol), base (1.5 mmol), ligand (0.1 mmol), 2.0 mL solvent, 120 °C, 18 h, nitrogen atmosphere, in sealed Schlenk tube. [b] Isolated yield based on **1a**. [c] At 110 °C. [d] At 130 °C. N. R. = no reaction.

Having identified the optimized reaction conditions, we next investigated the scope of enamino esters **1**, as the tandem reaction partner with 2-bromobenzaldehyde **2a**. As shown in scheme 2, a broad range of electron-withdrawing and electron-donating substituents at the aryl *para*- and *ortho*- position of enamino esters were well tolerated, and the corresponding products (**3aa**–**3ga** and **3ja**–**3la**) were delivered in moderate to good yields. It was worth noting that the reaction yield was dependent on electronic effects of substitutes at the aryl segments of enamino esters, as the aryl *para*- and *ortho*-position of enamino esters with electron-donating substituents showed higher yield than those with electron-withdrawing groups (**3ba**, **3ca** *vs.* **3da** and **3ja**, **3ka** *vs.* **3la**). In addition, *meta*-chloro and methyl substituted substrates reacted smoothly and resulted in the target quinolines (**3ha** and **3ia**) in 61–66% yields. Satisfyingly, thienyl- **1m** and pyridy- **1n** enamino esters proceeded well to afford desired products **3ma** in 51% and **3na** 86% yield, respectively. Fused aryl enamino esters were also compatible with the reaction and gave products **3oa**, **3pa** and **3qa** in moderate yields. This reaction was also applicable to substrates possessing bulky *tert*-butyl ester and methyl ester groups (**3ra** and **3sa**), steric hindrance of *tert*-butyl might result in the lower yield of **3ra**. However, no reaction occurred when the aliphatic enamino esters **1t** and **1u** were used as the substrates.

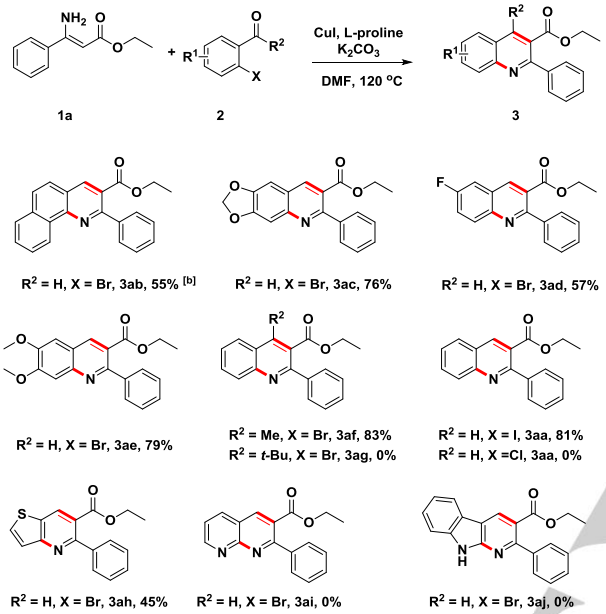


Scheme 2. The tandem reaction of enamino esters with 2-bromobenzaldehyde. [a]

[a] Reaction conditions: enamino esters **1** (0.5 mmol), 2-bromobenzaldehyde **2a** (0.6 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), L-Proline (0.1 mmol), 2.0 mL DMF, 120 °C, 18 h, nitrogen atmosphere, in sealed Schlenk tube. [b] The reaction was performed for 24 h.

To further evaluate the versatility and compatibility of the present protocol, attention was next turned toward exploring the scope of *ortho*-halogen aromatic carbonyls. As shown in scheme 3, various substituted *ortho*-bromine aromatic aldehydes **2** were coupled with ethyl 3-amino-3-phenylacrylate **1a** under the current reaction conditions to deliver the structurally diverse quinoline motifs in 55–79% yields (**3ab**–**3ae**). A number of electron-donating groups and halogen groups were well tolerated. Notably, the *ortho*-bromoacetophenone could also participate smoothly in the reaction, leading to the corresponding product **3af** in high yield, steric hindrance of *tert*-butyl ketone can not participate in the reaction to give the product **3ag**. For *ortho*-iodobenzaldehyde, similar reactivity was observed (X = I, **3aa**, 81%). However, *ortho*-chlorobenzaldehyde was not

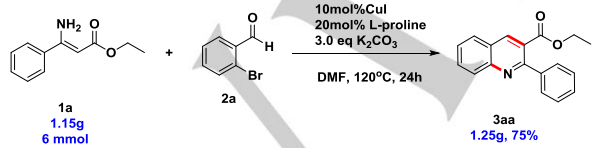
reactive and no desired product was observed (X = Cl, **3aa**, 0%). Furthermore, the method was also tested for the synthesis of thieno[3,2-b]pyridine derivatives, which are useful bioactive compounds and possess a diverse range of biological functions such as urotensin-II receptor antagonists,[21] Src kinase inhibitor,[22] and RON receptor tyrosine kinase inhibitor.[23] To our delight, desired ethyl 5-phenylthieno[3,2-b]pyridine-6-carboxylate **3ah** was successfully synthesized in moderate yield. We also tried to synthesize 1,8-naphthyridine **3ai** and pyridoindole structures **3aj**, but unfortunately we did not get the product.



Scheme 3. The tandem reaction of *ortho*-halogen aromatic carbonyls with ethyl-3-amino-3-phenylacrylate. [a]

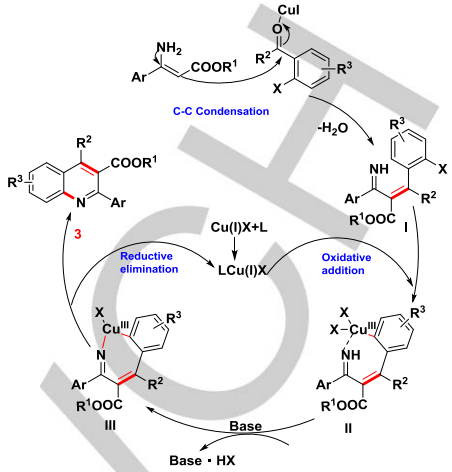
[a] Reaction conditions: ethyl-3-amino-3-phenylacrylate **1a** (0.5 mmol), *ortho*-halogen aromatic carbonyls **2** (0.6 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), L-Proline (0.1 mmol), 2.0 mL DMF, 120 °C, 18 h, nitrogen atmosphere, in sealed Schlenk tube. [b] The reaction was performed for 24 h.

To examine the practicality of the reaction system, the copper-catalyzed tandem annulation reaction was conducted on a gram scale, and the desired product **3aa** was obtained in a good yield of 75%, thus highlighting the synthetic utility of this methodology (Scheme 4).



Scheme 4. Gram-scale experiment

On the basis of the above experimental results and previously published results,[16–20] a plausible mechanism for the tandem reaction is depicted in Scheme 5. Initially, the reaction of enamino esters **1** and *ortho*-halogen aromatic carbonyls **2** gives intermediate **I** via C–C bond formation. The intermediate **I** would then undergo oxidative addition to give intermediate **II**. In the presence of base, **II** would lead to **III**. The resulting intermediate **III** on reductive elimination would give quinolines **3** via copper-catalyzed Ullmann C–N coupling.



Scheme 5. Possible mechanism

Conclusions

In conclusion, we have developed a novel, efficient, and practical copper-catalyzed tandem method for construction of functionalized quinolines. The protocol uses cheap and readily available CuI as the catalyst, substituted enamino esters and *ortho*-halogen aromatic carbonyls as the starting materials, and the corresponding quinolines were obtained in moderate to good yields. The thienopyridine skeleton also has been constructed, this method would provide a new and useful strategy for constructing of fused aza-heterocyclic compound.

Experimental Section

Materials and general experimental details

All reagents were obtained from commercial sources (purity > 99%) and used without further purification, unless otherwise indicated. Silica gel for column chromatography was purchased from Qingdao Haiyang Chemical Co., Ltd. Reactions were stirred using Teflon-coated magnetic stir bars. Thin-layer chromatography (TLC)

Melting points were determined using a Büchi B-540 capillary melting point apparatus. ^{1}H NMR and ^{13}C NMR were recorded with Bruker Avance III instruments at 600 and 150 MHz in $CDCl_3$ using tetramethylsilane (TMS, δ = 0 ppm) as internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), respectively. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. High resolution mass spectral (HRMS) analyze was measured on an Agilent 1290-6540 UHPLC Q-Tof HR-MS System ESI spectrometer.

General procedure for the synthesis of quinolines 3. A 25 mL sealed Schlenk tube was charged with enamine **1** (0.5 mmol), *ortho*-halogen aromatic carbonyls **2** (0.6 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), K_2CO_3 (1.5 mmol) and DMF (2 mL) under nitrogen atmosphere. The reaction was performed at 120 °C for 18-24 h. The resulting mixture was

cooled to room temperature and queous NH_4Cl (30 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combineid organc extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding products **3**.

Ethyl 2-phenylquinoline-3-carboxylate (3aa). Yellow oil (119 mg, 86% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.82 (t, *J* = 8.4 Hz, 1H), 7.64 – 7.60 (m, 3H), 7.49 – 7.44 (m, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 158.2, 148.4, 140.8, 139.1, 131.6, 129.6, 128.6 (2), 128.2 (2), 127.3, 125. 9, 125.6, 61.6, 13.7. HRMS (ESI): m/z: calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$ 278.1176, found: 278.1178.

Ethyl 2-(p-tolyl)quinoline-3-carboxylate (3ba). Yellow oil (129 mg, 89% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.80 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.61 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 158.1, 148.4, 138.9, 138.5, 137.8, 131.5, 129.5, 128.9, 128.6, 128.2, 127.1, 125.8, 125.5, 61. 6, 21.4, 13.8. HRMS (ESI): m/z: calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1332, found: 292.1334.

Ethyl 2-(4-methoxyphenyl)quinoline-3-carboxylate (3ca). Yellow oil (110 mg, 72% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.80 (ddd, J = 8.4, 7.8, 1.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.58 (ddd, J = 8.4, 7.8, 1.2 Hz, 1H), 7.00 (d, J = 6.0 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 (150 MHz, $CDCl_3$) δ 168.3, 160.2, 157.5, 148.4, 139.0, 133.1, 131.5, 130.1, 129.4, 128.2, 127.0, 125.7, 125.5, 113.7, 61.6, 55.4, 13.9. HRMS (ESI): m/z: calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1281, found: 308.1282.

Ethyl 2-(4-(trifluoromethyl)phenyl)quinoline-3-carboxylate (3da). White solid (97 mg, 56% yield). mp 114-116 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.74 (s, 4H), 7.65 (t, *J* = 7.2 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 156.9, 148.4, 144.5, 139.8, 132.0, 130.6($J_{C\text{-}F}$ = 132.0 Hz), 129.6, 129.1, 128.4, 127.7, 126.1, 125.1 ($J_{C\text{-}F}$ = 24.0, 18.0 Hz), 124.9, 123.3, 61.7, 13.7. HRMS (ESI): m/z: calcd for $C_{19}H_{15}F_3NO_2$ $[M + H]^+$ 346.1048, found: 346.1041.

Ethyl 2-(4-fluorophenyl)quinoline-3-carboxylate (3ea). White solid (100 mg, 68% yield). mp 76-77 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.68 – 7.58 (m, 3H), 7.22 – 7.13 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 164.0, 162.4, 157.1, 148.4, 139.3, 136.8 ($J_{C\text{-}F}$ = 3.0 Hz), 131.7, 130.5 ($J_{C\text{-}F}$ = 9.0 Hz), 129.5, 128.3, 127.4, 125.9, 125.2, 115.3($J_{C\text{-}F}$ = 22.5 Hz), 61.6, 13.8. HRMS (ESI): m/z: calcd for $C_{18}H_{15}FNO_2$ $[M + H]^+$ 296.1081, found: 296.1082.

Ethyl 2-(4-chlorophenyl)quinoline-3-carboxylate (3fa). White solid (78 mg, 50% yield). mp 88-89 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.16 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.82 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.61 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.59 – 7.56 (m, 2H), 7.47 – 7.43 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 157.0, 148.4, 139.4, 139.2, 134.8, 131.8, 130.1, 129.5, 128.4, 128.3, 127.5, 125.9, 125.1, 61.7, 13.8. HRMS (ESI): m/z: calcd for $C_{18}H_{15}ClNO_2$ $[M + H]^+$ 312.0786, found: 312.0791.

Ethyl 2-(4-bromophenyl)quinoline-3-carboxylate (3ga). White solid (119 mg, 67% yield). mp 81-82 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.83 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.53 – 7.49 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 157.0, 148.4, 139.7, 139.5, 131.8, 131.3, 130.3, 129.5, 128.3, 127.5, 125.9, 125.0, 123.1, 61.7, 13.8. HRMS (ESI): m/z: calcd for $C_{18}H_{15}BrNO_2$ $[M + H]^+$ 356.0281, found: 356.0282.

Ethyl 2-(3-chlorophenyl)quinoline-3-carboxylate (3ha). Yellow oil (95 mg, 61% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.86 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.51 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.47 – 7.40 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 156.7, 148.3, 142.5, 139.6, 134.1, 131.9, 129.6, 129.4, 128.8, 128.62, 128.3, 127.6, 126.9, 126.0, 125.1, 61.7, 13.8. HRMS (ESI): m/z: calcd for $C_{18}H_{15}ClNO_2$ $[M + H]^+$ 312.0786, found: 312.0783.

Ethyl 2-(m-tolyl)quinoline-3-carboxylate (3ia). Yellow oil (96 mg, 66% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 7. 8Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.49 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.26 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 158.3, 148.4, 140.7, 138.9, 137.9, 131.5, 129.6, 129.4, 129.2, 128.2, 128.1, 127.2, 125.9, 125.8, 125.7, 61.5, 21.5, 13.7. HRMS (ESI): m/z: calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1332, found: 292.1333.

Ethyl 2-(2-fluorophenyl)quinoline-3-carboxylate (3ja). Yellow oil (96 mg, 65% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.19 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.83 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.72 (td, *J* = 7.2, 1.8 Hz, 1H), 7.63 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.43 (m, 1H), 7.32 (td, *J* = 7.2, 1.2 Hz, 1H), 7.11 (ddd, *J* = 10.2, 8.4, 1.2 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 160.9, 159.3, 153.4, 148.8, 139.5, 131.8, 130.9 ($J_{C\text{-}F}$ = 3.0 Hz), 130.5 ($J_{C\text{-}F}$ = 7.5 Hz), 129.6, 129.1 ($J_{C\text{-}F}$ = 15.0 Hz), 128.5, 127.6, 125.9 ($J_{C\text{-}F}$ = 106.5 Hz), 124.5 ($J_{C\text{-}F}$ = 3.0 Hz), 115.0 ($J_{C\text{-}F}$ = 21.0 Hz), 61.5, 13.8. HRMS (ESI): m/z: calcd for $C_{18}H_{15}FNO_2$ $[M + H]^+$ 296.1081, found: 296.1076.

Ethyl 2-(2-chlorophenyl)quinoline-3-carboxylate (3ka). Yellow oil (78 mg, 50% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.70 – 7.65 (m, 1H), 7.55 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.47 – 7.39 (m, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 156.7, 148.6, 140.5, 139.8, 132.6, 131.9, 130.3, 129.6, 129.5, 129.0, 128.6, 127.7, 126.9, 126.4, 125.1, 61.5, 13.7. HRMS (ESI): m/z: calcd for $C_{18}H_{15}ClNO_2$ $[M + H]^+$ 312.0786, found: 312.0789.

Ethyl 2-(o-tolyl)quinoline-3-carboxylate (3la). Yellow oil (132 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.85 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.38 – 7.32 (m, 1H), 7.30 – 7.21 (m, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.19 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 159.3, 148.5, 141.0, 139.4, 135.5, 131.7, 129.9, 129.5, 128.5, 128.2, 128.2, 127.9, 127.3, 126.0, 125.5, 61.4, 19.7, 13.6. HRMS (ESI): m/z: calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1332, found: 292.1339.

Ethyl 2-(thiophen-2-yl)quinoline-3-carboxylate (3ma). Yellow oil (72 mg, 51% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.76 (m, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.48 (dd, *J* = 5.4, 0.6 Hz, 1H), 7.41 (dd, *J* = 3.6, 0.6 Hz, 1H), 7.11 (dd, *J* = 4.8, 3.6 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 150.1, 148.2, 143.1, 138.2, 131.5, 129.3, 128.5, 128.1, 128.0, 127.6, 127.2, 125.6, 125.1, 61.9, 14.0. HRMS (ESI): m/z: calcd for $C_{16}H_{14}NO_2S$ $[M + H]^+$ 284.0740, found: 284.0745.

Ethyl 2-(pyridin-4-yl)quinoline-3-carboxylate (3na). Yellow solid (119 mg, 86% yield), mp 111-113 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.73 (d, *J* = 5.4 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 8.4 Hz,

1H), 7.86 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.66 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.54 (dd, *J* = 4.2, 1.8 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 155.8, 149.5, 148.7, 148.4, 139.9, 132.1, 129.6, 128.4, 128.0, 126.3, 124.6, 123.3, 61.8, 13.7. HRMS (ESI): m/z: calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.1128, found: 279.1130.

Ethyl 2-(naphthalen-2-yl)quinoline-3-carboxylate (3oa). Yellow oil (119 mg, 73% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.94 – 7.88 (m, 4H), 7.85 – 7.79 (m, 1H), 7.76 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.60 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.54 – 7.48 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 158.0, 148.5, 139.2, 138.2, 133.3, 133.2, 131.6, 129.6, 128.6, 128.3, 128.2, 127.8, 127.7, 127.3, 126.5, 126.4, 126.3, 125.9, 125.7, 61.6, 13.8. HRMS (ESI): m/z: calcd for $C_{22}H_{18}NO_2$ $[M + H]^+$ 328.1332, found: 328.1337.

6H-chromeno[4,3-b]quinolin-6-one (3pa). Yellow solid (95 mg, 77 % yield). mp 222-224 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.79 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.92 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.46 – 7.41 (m, 1H), 7.39 (dd, *J* = 8.4, 0.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 152.7, 151.1, 149.6, 141.1, 133.4, 132.4, 129.6, 129.4, 127.4, 127.3, 125.3, 125.0, 119.7, 117.4, 115.8. HRMS (ESI): m/z: calcd for $C_{16}H_{10}NO_2$ $[M + H]^+$ 248.0706, found: 248.0709.

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)quinoline-3-carboxylate (3qa). Yellow solid (109 mg, 68 % yield). mp 94-96 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.20 (s, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.02 (s, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 157.3, 148.2, 147.7, 139.0, 134.7, 131.5, 129.4, 128.2, 127.2, 125.8, 125.5, 122.9, 109.3, 108.2, 101.3, 61.6, 29.7, 13.9. HRMS (ESI): m/z: calcd for $C_{19}H_{16}NO_4$ $[M + H]^+$ 322.1074, found: 322.1076.

Tert-butyl 2-phenylquinoline-3-carboxylate (3ra). Yellow oil (96 mg, 63% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.80 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.48 – 7.44 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 158.2, 148.2, 141.2, 138.8, 131.3, 129.5, 128.8, 128.4, 128.2, 127.2, 127.1, 126.02, 82.3, 27.6. HRMS (ESI): m/z: calcd for $C_{20}H_{20}NO_2$ $[M + H]^+$ 306.1489, found: 306.1496.

Methyl 2-phenylquinoline-3-carboxylate (3sa). Yellow oil (108 mg, 82% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.50 – 7.43 (m, 3H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 158.0, 148.4, 140.5, 139.3, 131.7, 129.5, 128.7, 128.6, 128.3, 127.3, 125.8, 125.1, 52.5. HRMS (ESI): m/z: calcd for $C_{17}H_{14}NO_2$ $[M + H]^+$ 264.1019, found: 264.1022.

Ethyl 2-phenylbenzo[h]quinoline-3-carboxylate (3ab). Yellow solid (90 mg, 55 % yield). mp 107-108 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (dd, *J* = 6.0, 3.6 Hz, 1H), 8.63 (s, 1H), 7.94 – 7.91 (m, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.72 (m, 5H), 7.53 – 7.45 (m, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 156.7, 147.0, 140.9, 138.3, 134.5, 131.2, 129.2, 129.0, 128.6, 128.5, 128.1, 127.9, 127.3, 125.6, 125.3, 124.9, 124.0, 61.6, 13.8. HRMS (ESI): m/z: calcd for $C_{22}H_{18}NO_2$ $[M + H]^+$ 328.1332, found: 328.1339.

Ethyl 6-phenyl-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate (3ac). Yellow oil (122 mg, 76% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.59 – 7.56 (m, 2H), 7.46 – 7.41 (m, 4H), 7.13 (s, 1H), 6.15 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 156.5, 152.5, 148.5, 147.2, 140.9, 137.7, 128.6, 128.3, 128.10, 123.5, 123.0, 106.0, 102.9, 102.1, 61.4, 13.7. HRMS (ESI): m/z: calcd for $C_{19}H_{16}NO_4$ $[M + H]^+$ 322.1074, found: 322.1075.

Ethyl 6-fluoro-2-phenylquinoline-3-carboxylate (3ad). Yellow solid (84 mg, 57 % yield). mp 73-74 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.18 (dd, *J* = 9.0, 5.4 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.58 (ddd, *J* = 9.0, 8.4, 2.4 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.4 Hz, 1H), 7. 49 – 7.45 (m, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 161.61, 159.95, 157.5 ($J_{C\text{-}F}$ = 3.0 Hz), 145.5, 140.4, 138.2 ($J_{C\text{-}F}$ = 4.5 Hz), 132.1 ($J_{C\text{-}F}$ = 9.0 Hz), 128.69, 128.55, 128.25, 126.5 ($J_{C\text{-}F}$ = 10.5 Hz), 126.39, 121.8 ($J_{C\text{-}F}$ = 25.5 Hz), 111.1 ($J_{C\text{-}F}$ = 22.5 Hz), 61.71, 13.68. HRMS (ESI): m/z: calcd for $C_{18}H_{15}FNO_2$ $[M + H]^+$ 296.1081, found: 296.1084.

Ethyl 6,7-dimethoxy-2-phenylquinoline-3-carboxylate (3ae). Yellow solid (133 mg, 79 % yield). mp 154-156 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.61 – 7.56 (m, 2H), 7.51 (s, 1H), 7.47 – 7.40 (m, 3H), 7.14 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 3H), 4.04 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 156.6, 154.3, 150.4, 145.9, 141.2, 137.3, 128.6, 128.2, 128.1, 123.4, 121.6, 108.1, 105.2, 61.3, 56.4, 56.2, 13.7. HRMS (ESI): m/z: calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$ 338.1387, found: 338.1390.

Ethyl 4-methyl-2-phenylquinoline-3-carboxylate (3af). Yellow oil (121 mg, 83% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.73 – 7.69 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.50 – 7.45 (m, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.79 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 156.3, 147.2, 142.8, 140.6, 130.4, 130.3, 128.8, 128.7, 128.4, 127.5, 127.0, 126.1, 124.1, 61.6, 15.7, 13.6. HRMS (ESI): m/z: calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1332, found: 292.1333.

Ethyl 5-phenylthieno[3,2-b]pyridine-6-carboxylate (3ah). Yellow oil (63 mg, 45% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.94 (d, *J* = 5.4 Hz, 1H), 7.66 (d, *J* = 5.4 Hz, 1H), 7.58 – 7.55 (m, 2H), 7.47 – 7.43 (m, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 157.1, 157.0, 140.7, 134.4, 133.0, 130.9, 128.6, 128.4, 128.1, 125.3, 122.8, 61.5, 13.7. HRMS (ESI): m/z: calcd for $C_{16}H_{14}NO_2S$ $[M + H]^+$ 284.0740, found: 284.0741.

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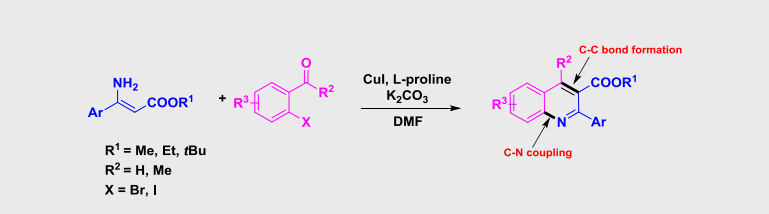

Copper-catalyzed tandem reaction for efficient synthesis of functionalized quinolines via C–C bond formation and C–N coupling of enamino esters with *ortho*-halogen aromatic carbonyls has been demonstrated. The success of gram-scale reaction and thieno[3,2-b]pyridine derivatives synthesis have been used to extend the application.

* Functionalized quinolines, Copper-catalyzed

Key Topic*

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Page No. – Page No.

Copper-catalyzed tandem reaction of enamino esters with ortho-halogen aromatic carbonyls: one pot approach to functionalized quinolines