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Access to C4-Functionalized Quinolines via Copper-Catalyzed Tandem Annulation of Alkynyl Imines with Diazo Compounds

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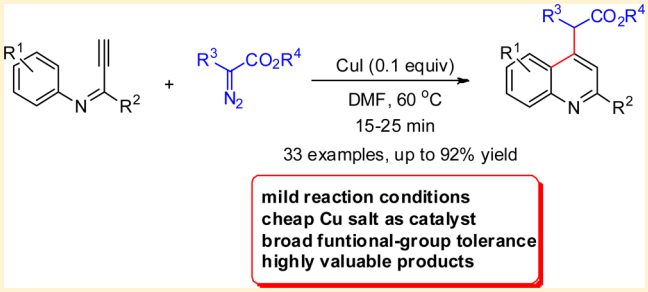
Supporting Information

ABSTRACT: An efficient synthesis of C4-functionalized quinolines through copper-catalyzed tandem annulation of alkynyl imines with diazo compounds is described. This transformation involves an *in situ* formation of allene and intramolecular electrocyclization, which features high efficiency, mild reaction conditions, easy operation, and broad functional-group tolerance. A wide variety of C4-functionalized quinolines were provided in up to 92% yield for 33 examples.



INTRODUCTION

Quinoline derivatives are receiving continuing attention owing to their promising biological and pharmaceutical activities, including antimalarial, anti-inflammatory, and antibacterials.[1] Thus, it is highly desirable to develop novel and efficient methods for the synthesis of such highly valuable molecules. Classical methods have been frequently employed in the synthesis of quinolines since the late 1800s, including Skraup,[2] Doebner−von Miller,[3] Combes,[4] Friedländer,[5] Pfitzinger,[6] and Conrad−Limpach[7] syntheses. However, there still remains some challenges, such as harsh reaction conditions, tedious workup procedures, and narrow scopes.

Recently, transition-metal-catalyzed tandem reactions have become an efficient strategy for the construction of structurally complex molecules in organic synthesis,[8] which has been successfully applied in the preparation of substituted quinolines.[9] For example, Shi,[9a] Xia,[9b] Xu,[9c] Li,[9d] and Chen[9g] have reported impressive procedures to substituted quinolines starting from azide-methylenecyclopropanes, 1,7-enynes, alkyne-tethered diazo compounds, *o*-cyanoarylacrylamides, and *N*-aryl azoles, respectively. Recently, we have described a copper-catalyzed cascade reaction for the synthesis of 4-sulfonamidoquinolines from alkynyl imines and sulfonyl azides.[10a] In our continuing efforts to develop heterocycle-forming protocols,[10] herein, we report a highly practical protocol to build C4-functionalized quinolines, in which the copper-catalyzed allene formation and intramolecular electrocyclization were involved (Scheme 1).

RESULTS AND DISCUSSION

We began our study with the model reaction of alkynyl imine **1a** with phenyl diazoacetate **2a** in the presence of 10 mol % CuCl in acetonitrile (MeCN) at 60 °C. To our delight, the desired product **3aa** was isolated in 41% yield (Table 1, entry 1). Inspired by the preliminary result, various reaction parameters were valued, including copper salts, solvents, and temperature. The copper salts were examined first (entries 1−6). CuI gave the best result, affording **3aa** in 80% yield (entry 3). CuBr, $CuBr_2$, and $Cu(OAc)_2$ afforded lower yields (entries 2, 4, and 5). No desired product was detected with $Cu(OTf)_2$ as the catalyst (entry 6). Then the influence of the solvents was investigated, showing that polar aprotic solvents favored this transformation (entries 7−14). NMP and DMF could give 82% and 87% yields, respectively (entries 9 and 10). When the reaction proceeded at 50 or 70 °C, **3aa** was provided in 60% and 53% yields, respectively (entries 15 and 16). Reducing catalyst loading resulted in a lower yield of 44% (entry 17). In addition, when the amount of **2a** was decreased to 1.2 equiv, the yield was decreased to 42% (entry 18). Finally, the optimized reaction conditions were identified as follows: **1a** (0.2 mmol), **2a** (0.3 mmol), CuI (0.1 equiv), DMF (1 mL), 60 °C.

Under the optimal reaction conditions, we started our investigation on the scope of alkynyl imines **1a−r** with phenyl diazoacetate **2a** (Table 2). Both of the electron-donating and electron-withdrawing groups on the *N*-aryl ring of the alkynyl imines were well tolerated and provided the corresponding quinolines in appreciable yields (65−90%, entries 1−10). *m*-Methylphenyl alkynylimine **1h** gave 1:1 regioisomeric mixture in 80% yield (entry 8). Notably, steric hindrance did not obviously influence the transformation. The *ortho* methyl on the *N*-aryl ring gave higher yield compared to the corresponding substrates with *para* or *meta* methyl on the *N*-aryl ring (entry 9 vs 2 and 8). Meanwhile, *ortho* chloro-substituted substrate gave similar yield to the corresponding

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Scheme 1

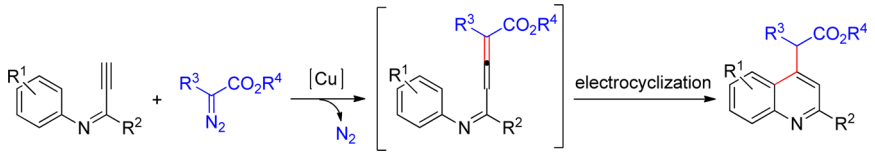
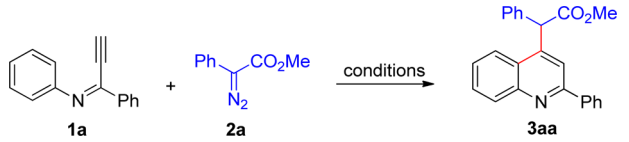


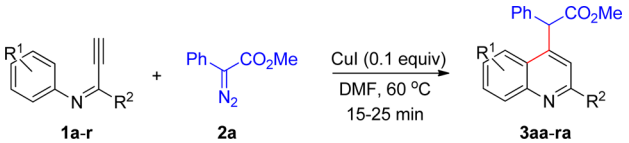
Table 1. Screening the Reaction Conditions for the Reaction of Alkynyl Imine 1a with Phenyl Diazoacetate 2a[a]



entry	catalyst	solvent	yield[b] (%)
1	CuCl	MeCN	41
2	CuBr	MeCN	20
3	CuI	MeCN	80
4	$CuBr_2$	MeCN	65
5	$Cu(OAc)_2$	MeCN	52
6	$Cu(OTf)_2$	MeCN	—
7	CuI	MeOH	33
8	CuI	THF	24
9	CuI	NMP	82
10	CuI	DMF	87
11	CuI	DCE	19
12	CuI	dioxane	11
13	CuI	DMSO	17
14	CuI	toluene	trace
15[c]	CuI	DMF	60
16[d]	CuI	DMF	53
17[e]	CuI	DMF	44
18[f]	CuI	DMF	42

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), copper salt (0.1 equiv), solvent (1 mL), 60 °C. [b]Isolated yield. [c]50 °C. [d]70 °C. [e]0.05 equiv of CuI. [f]**2a** (0.24 mmol). DMF = *N*,*N*-dimethylformamide, NMP = *N*-methyl-2-pyrrolidone.

Table 2. Reactions of Various Alkynyl Imines 1a−r with Phenyl Diazoacetate 2a[a]



entry	1	R^1	R^2	3	yield[b] (%)
1	**1a**	H	Ph	**3aa**	87
2	**1b**	4-Me	Ph	**3ba**	70
3	**1c**	4-OMe	Ph	**3ca**	85
4	**1d**	4-*i*Pr	Ph	**3da**	65
5	**1e**	4-F	Ph	**3ea**	83
6	**1f**	4-Cl	Ph	**3fa**	76
7	**1g**	4-Br	Ph	**3ga**	72
8	**1h**	3-Me	Ph	**3ha**[1],**3ha**[2]	80[c]
9	**1i**	2-Me	Ph	**3ia**	90
10	**1j**	2-Cl	Ph	**3ja**	74
11	**1k**	4-CF_3	Ph	**3ka**	60
12	**1l**	H	4-MeC_6H_4	**3la**	82
13	**1m**	H	4-*t*BuC_6H_4	**3ma**	89
14	**1n**	H	4-ClC_6H_4	**3na**	83
15	**1o**	H	4-$OMeC_6H_4$	**3oa**	83
16	**1p**	H	3-MeC_6H_4	**3pa**	82
17	**1q**	H	2-Thienyl	**3qa**	61
18	**1r**	H	*t*Bu	**3ra**	84

[a]Reaction conditions: **1a-r** (0.2 mmol), **2a** (0.3 mmol), CuI (0.1 equiv), DMF (1 mL), 60 °C. [b]Isolated yield. [c]Products were obtained as 1:1 regioisomeric mixture.

substrate with *para* chloro (entry 10 vs 6). 60% Yield was obtained when R^1 was trifluoromethyl (entry 11). The substituted scope on imine carbon was then examined. Diversely structural quinolines were afforded in 61% to 89% yields (entries 12−18). Interestingly, thienyl-substituted substrate **1q** was also applicable to this reaction system and gave the product **3qa** in 61% yield (entry 17). In addition, excellent yield was obtained when R^2 was *tert*-butyl group (84%, entry 18).

Next, the scope of diazo compounds **2b−p** was investigated (Table 3). Generally, the diazo compounds containing either electron-rich or electron-deficient aryl groups gave the corresponding products in good to excellent yields (66−92%, entries 1−8). It is worth noting that diazo compound containing Bpin group provided the corresponding product in 40% yield (entry 9). When R^4 was ethyl, isopropyl, and benzyl, the reaction could proceed smoothly and gave the corresponding products in 88%, 60%, and 82% yields, respectively (entries 10−12). Gratifyingly, aliphatic diazo compounds were also applicable to this reaction system, affording the corresponding products in 63% and 66% yields, respectively (entries 13 and 14). Benzyl diazoacetate could give the desired product in 60% yield (entry 15).

Based on the results obtained and literature reports, a plausible mechanism for this transformation is depicted in Scheme 2. Initially, the reaction of alkynyl imine **1** with diazo compound **2** catalyzed by copper gave intermediate **a**, which might provide the allene intermediate **b**.[11] Then, 6π-electrocyclization of **b** was triggered, followed by [1,3]-H shift, to render the target product **3**.[12]

CONCLUSION

In conclusion, we have developed an efficient procedure for the preparation of C4-functionalized quinolines. An *in situ* formation of allene and sequential intramolecular electrocyclization reaction were involved in this tandem procedure. This strategy features high efficiency, mild reaction conditions, easy operation, and broad functional-group tolerance. A variety of useful quinoline derivatives were afforded in good to excellent yields.

EXPERIMENTAL SECTION

General Information. All commercial materials and solvents were used directly without further purification. Melting points were determined on a melting point apparatus and were uncorrected. ^1H and $^{13}C\{^1H\}$ NMR spectra were measured on a 400 MHz spectrometer (^1H 400 MHz, ^{13}C 100 MHz) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room

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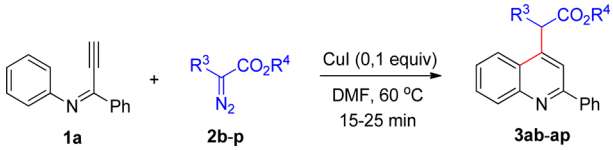
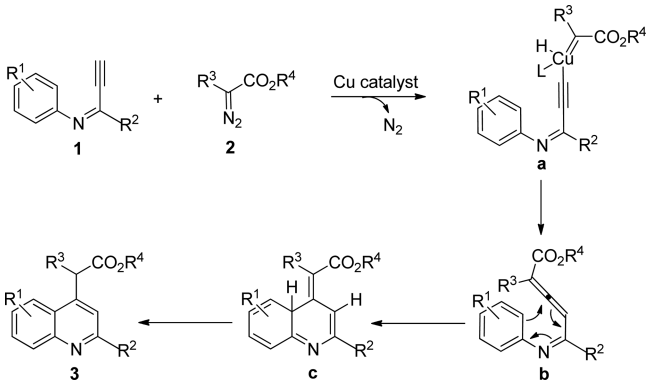
Table 3. Reactions of Alkynyl Imine 1a with Various Diazo Compounds 2b–p[a]



entry	2	R^3	R^4	3	yield[b] (%)
1	**2b**	4-FC_6H_4	Me	**3ab**	87
2	**2c**	4-ClC_6H_4	Me	**3ac**	84
3	**2d**	4-BrC_6H_4	Me	**3ad**	86
4	**2e**	4-$MeOC_6H_4$	Me	**3ae**	92
5	**2f**	4-MeC_6H_4	Me	**3af**	84
6	**2g**	2-ClC_6H_4	Me	**3ag**	88
7	**2h**	3-ClC_6H_4	Me	**3ah**	66
8	**2i**	3-MeC_6H_4	Me	**3ai**	79
9	**2j**	4-$BpinC_6H_4$	Me	**3aj**	40
10	**2k**	Ph	Et	**3ak**	88
11	**2l**	Ph	*i*Pr	**3al**	60
12	**2m**	Ph	Bn	**3am**	82
13	**2n**	H	Et	**3an**	63
14	**2o**	Me	Et	**3ao**	66
15	**2p**	Bn	Et	**3ap**	60

[a]Reaction conditions: **1a** (0.2 mmol), **2b–p** (0.3 mmol), CuI (0.1 equiv), DMF (1 mL), 60 °C. [b]Isolated yield.

Scheme 2. Proposed Reaction Mechanism



temperature. HRMS ESI spectra were obtained on Q-TOF spectrometer.

Compounds 1a–q,[10a] **1r,**[12d] **2a–m,**[13a] **2o,**[13a] **and 2p.**[13b] These compounds were prepared according to the literatures.

General Procedure for Synthesis of C4-Functionalized Quinolines 3. The corresponding alkynyl imines **1** (0.2 mmol), diazo compounds **2** (0.3 mmol), CuI (0.02 mmol), and 1 mL of DMF were added to a 5 mL Schlenk tube equipped with magnetic stirring, and the reaction mixture was stirred at 60 °C under air atmosphere. After completing reaction, the mixture was diluted with dichloromethane (20 mL) and washed with brine (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated, and the residue was purified by silica gel column chromatography with EA/petroleum ether (1:40) as the eluent to afford the products **3**.

*Methyl 2-Phenyl-2-(2-phenylquinolin-4-yl)acetate (**3aa**).* (61 mg, 87%); yellow solid; mp 103–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.13–8.06 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 2.9 Hz, 1H), 7.67–7.61 (m, 1H), 7.49–7.42 (m, 3H), 7.41–7.23 (m, 6H), 5.80 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 156.9, 148.5, 144.3, 139.4, 136.3, 130.6, 129.3, 129.3, 128.8, 128.7, 128.7, 127.8, 127.4, 126.6, 125.7, 122.6, 118.6, 52.9, 52.6; HRMS m/z (ESI) calcd for $C_{24}H_{20}NO_2$ $(M + H)^+$ 354.1489, found 354.1497.

*Methyl 2-(6-Methyl-2-phenylquinolin-4-yl)-2-phenylacetate (**3ba**).* (51 mg, 70%); yellow solid; mp 142–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.04 (m, 3H), 7.76 (s, 1H), 7.74 (s, 1H), 7.56–7.52 (m, 1H), 7.51–7.45 (m, 2H), 7.45–7.41 (m, 1H), 7.40–7.30 (m, 5H), 5.80 (s, 1H), 3.79 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 156.2, 147.2, 143.6, 139.6, 136.7, 136.5, 131.7, 130.4, 129.2, 128.9, 128.8, 128.7, 127.9, 127.4, 125.8, 121.7, 118.7, 52.9, 52.7, 22.1; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1653.

*Methyl 2-(6-Methoxy-2-phenylquinolin-4-yl)-2-phenylacetate (**3ca**).* (63 mg, 85%); yellow solid; mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 9.2 Hz, 1H), 8.07–8.03 (m, 2H), 7.75 (s, 1H), 7.50–7.45 (m, 2H), 7.44–7.40 (m, 1H), 7.40–7.35 (m, 5H), 7.35–7.31 (m, 1H), 7.20 (d, J = 2.6 Hz, 1H), 5.69 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 157.9, 154.7, 144.6, 142.9, 139.6, 136.3, 132.1, 128.9, 128.9, 128.9, 128.7, 127.9, 127.3, 126.7, 121.7, 118.9, 101.4, 55.4, 53.6, 52.7; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_3$ $(M + H)^+$ 384.1594, found 384.1600.

*Methyl 2-(6-Isopropyl-2-phenylquinolin-4-yl)-2-phenylacetate (**3da**).* (51 mg, 65%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 7.1 Hz, 2H), 7.78 (d, J = 1.3 Hz, 1H), 7.74 (s, 1H), 7.64–7.59 (m, 1H), 7.48 (t, J = 7.3 Hz, 2H), 7.45–7.36 (m, 5H), 7.35–7.30 (m, 1H), 5.80 (s, 1H), 3.80 (s, 3H), 3.13–3.02 (m, 1H), 1.35–1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 156.3, 147.5, 147.3, 144.0, 139.7, 136.5, 130.5, 129.3, 129.2, 128.9, 128.7, 127.9, 127.5, 125.7, 119.0, 118.6, 53.2, 52.7, 34.3, 23.9; HRMS m/z (ESI) calcd for $C_{27}H_{26}NO_2$ $(M + H)^+$ 396.1958, found 396.1960.

*Methyl 2-(6-Fluoro-2-phenylquinolin-4-yl)-2-phenylacetate (**3ea**).* (62 mg, 83%); yellow solid; mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.16 (m, 1H), 8.09–8.01 (m, 2H), 7.84 (s, 1H), 7.61–7.56 (m, 1H), 7.52–7.42 (m, 4H), 7.42–7.36 (m, 4H), 7.36–7.30 (m, 1H), 5.66 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 160.6 (d, J = 248.3 Hz), 156.5 (d, J = 2.7 Hz), 145.8, 143.9 (d, J = 5.7 Hz), 139.2, 136.0, 133.2 (d, J = 9.2 Hz), 129.4, 129.1, 128.8, 128.8, 128.1, 127.4, 126.6 (d, J = 9.4 Hz), 119.5 (d, J = 25.5 Hz), 119.4, 106.7 (d, J = 23.1 Hz), 53.1, 52.8; HRMS m/z (ESI) calcd for $C_{24}H_{19}FNO_2$ $(M + H)^+$ 372.1394, found 372.1400.

*Methyl 2-(6-Chloro-2-phenylquinolin-4-yl)-2-phenylacetate (**3fa**).* (59 mg,76%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 9.0 Hz, 1H), 8.09–8.02 (m, 2H), 7.96 (d, J = 2.1 Hz, 1H), 7.84 (s, 1H), 7.65–7.60 (m, 1H), 7.51–7.43 (m, 3H), 7.42–7.31 (m, 5H), 5.71 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 157.2, 146.9, 143.6, 138.9, 136.0, 132.6, 132.2, 130.3, 129.6, 129.1, 128.8, 128.7, 128.1, 127.5, 126.5, 121.9, 119.5, 52.8, 52.8; HRMS m/z (ESI) calcd for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1092.

*Methyl 2-(6-Bromo-2-phenylquinolin-4-yl)-2-phenylacetate (**3ga**).* (62 mg, 72%); yellow solid; mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.06 (d, J = 8.5 Hz, 3H), 7.83 (s, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.53–7.44 (m, 3H), 7.42–7.32 (m, 5H), 5.72 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 157.4, 147.2, 143.6, 139.0, 136.0, 132.9, 132.4, 129.7, 129.1, 128.9, 128.8, 128.1, 127.5, 127.0, 125.2, 120.9, 119.5, 52.9, 52.8; HRMS m/z (ESI) calcd for $C_{24}H_{19}BrNO_2$ $(M + H)^+$ 432.0594, found 432.0600.

*Methyl 2-(7-Methyl-2-phenylquinolin-4-yl)-2-phenylacetate (**3ha**[1]) and Methyl 2-(5-Methyl-2-phenylquinolin-4-yl)-2-phenylacetate (**3ha**[2]).* (59 mg, 80%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.03 (m, 3H), 8.00 (s, 0.5H), 7.88–7.83 (m, 1H), 7.74 (s, 0.5H), 7.59–7.52 (m, 1H), 7.51–7.46 (m, 2H), 7.46–7.42 (m, 1H), 7.38–7.35 (m, 2H), 7.34–7.29 (m, 2H), 7.23–7.16 (m, 1H), 6.36 (s, 0.5H), 5.78 (s, 0.5H), 3.78 (d, J = 1.4 Hz, 3H), 2.87 (s, 1.5H), 2.54 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.2, 157.1, 155.7, 150.6, 148.8, 144.6, 144.1, 139.7, 139.6, 138.9, 138.1, 136.5, 133.5, 130.8, 130.1, 129.7, 129.4, 129.3, 128.9, 128.9, 128.9, 128.9, 128.8, 128.8, 128.7, 127.9, 127.6, 127.5, 127.4, 126.3, 123.8, 122.5, 120.9, 117.9, 54.3, 53.1, 52.7, 52.7, 25.4, 21.6; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1653.

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*Methyl 2-(8-Methyl-2-phenylquinolin-4-yl)-2-phenylacetate (**3ia**).* (66 mg, 90%); yellow solid; mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.14 (m, 2H), 7.82 (t, J = 3.9 Hz, 2H), 7.55 (d, J = 6.9 Hz, 1H), 7.49 (t, J = 7.3 Hz, 2H), 7.45−7.38 (m, 2H), 7.36 (d, J = 4.4 Hz, 4H), 7.34−7.28 (m, 1H), 5.81 (s, 1H), 3.78 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 155.1, 147.5, 144.4, 139.7, 138.7, 136.7, 129.6, 129.3, 128.9, 128.9, 128.7, 127.8, 127.5, 126.4, 125.7, 120.6, 117.9, 53.2, 52.7, 18.4; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1651.

*Methyl 2-(8-Chloro-2-phenylquinolin-4-yl)-2-phenylacetate (**3ja**).* (57 mg, 74%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.16 (m, 2H), 7.92−7.85 (m, 2H), 7.81 (d, J = 7.4 Hz, 1H), 7.52−7.43 (m, 3H), 7.42−7.30 (m, 6H), 5.78 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 156.9, 144.9, 144.8, 138.9, 136.2, 135.0, 129.8, 129.6, 129.0, 128.8, 128.8, 128.0, 127.6, 127.2, 126.4, 121.8, 119.1, 53.2, 52.8; HRMS m/z (ESI) calcd for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1104.

*Methyl 2-Phenyl-2-(2-phenyl-6-(trifluoromethyl)quinolin-4-yl)-acetate (**3ka**).* (51 mg, 60%); white solid; mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 7.0 Hz, 2H), 7.93 (d, J = 12.9 Hz, 2H), 7.71−7.48 (m, 4H), 7.48−7.38 (m, 4H), 5.85 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 159.1, 149.7, 145.5, 138.8, 135.8, 131.8, 130.0, 129.2, 128.9, 128.8, 128.2, 128.2 (q, J = 32.1 Hz), 127.7, 125.2 (q, J = 2.9 Hz), 124.9, 124.0 (q, J = 272.4 Hz), 120.8 (q, J = 4.5 Hz), 119.8, 52.9, 52.9; HRMS m/z (ESI) calcd for $C_{25}H_{19}F_3NO_2$ $(M + H)^+$ 422.1362, found 422.1367.

*Methyl 2-Phenyl-2-(2-(p-tolyl)quinolin-4-yl)acetate (**3la**).* (60 mg, 82%); yellow solid; mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 8.9 Hz, 3H), 7.79 (s, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40−7.33 (m, 4H), 7.33−7.27 (m, 3H), 5.80 (s, 1H), 3.78 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 157.0, 148.6, 144.2, 139.5, 136.7, 136.5, 130.6, 129.5, 129.3, 128.9, 128.8, 127.9, 127.4, 126.5, 125.7, 122.7, 118.6, 53.0, 52.7, 21.3; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1651.

*Methyl 2-(2-(4-(tert-Butyl)phenyl)quinolin-4-yl)-2-phenylacetate (**3ma**).* (73 mg, 89%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H), 7.72−7.66 (m, 1H), 7.54−7.47 (m, 3H), 7.40−7.35 (m, 4H), 7.35−7.29 (m, 1H), 5.80 (s, 1H), 3.78 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 157.1, 152.6, 148.7, 144.2, 136.8, 136.5, 130.7, 129.3, 128.9, 128.9, 127.9, 127.3, 126.6, 125.8, 125.7, 122.7, 118.8, 53.1, 52.7, 34.7, 31.2; HRMS m/z (ESI) calcd for $C_{28}H_{28}NO_2$ $(M + H)^+$ 410.2115, found 410.2122.

*Methyl 2-(2-(4-Chlorophenyl)quinolin-4-yl)-2-phenylacetate (**3na**).* (64 mg, 83%); yellow solid; mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 8.06−7.96 (m, 3H), 7.76 (s, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.55−7.50 (m, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.41−7.29 (m, 5H), 5.81 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 155.7, 148.6, 144.6, 137.9, 136.4, 135.6, 130.7, 129.6, 128.9, 128.9, 128.8, 127.9, 126.9, 125.8, 122.8, 118.3, 52.9, 52.8; HRMS m/z (ESI) calcd for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1106.

*Methyl 2-(2-(4-Methoxyphenyl)quinolin-4-yl)-2-phenylacetate (**3oa**).* (64 mg, 83%); yellow solid; mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.71−7.65 (m, 1H), 7.52−7.46 (m, 1H), 7.37 (s, 5H), 7.02 (d, J = 8.0 Hz, 2H), 5.80 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 160.8, 156.6, 148.6, 144.1, 136.4, 132.0, 130.5, 129.4, 128.9, 128.9, 128.9, 127.9, 126.4, 125.5, 122.7, 118.3, 114.1, 55.4, 53.0, 52.8; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_3$ $(M + H)^+$ 384.1594, found 384.1599.

*Methyl 2-Phenyl-2-(2-(m-tolyl)quinolin-4-yl)acetate (**3pa**).* (60 mg, 82%); yellow solid; mp 90−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.84−7.78 (m, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.54−7.48 (m, 1H), 7.43−7.29 (m, 6H), 7.28−7.22 (m, 1H), 5.81 (s, 1H), 3.79 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 157.3, 148.6, 144.2, 139.5, 138.5, 136.4, 130.7, 130.2, 129.4, 128.9, 128.8, 128.7, 128.2, 127.9, 126.7, 125.7, 124.7, 122.8, 118.9, 52.9, 52.8, 21.5; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1653.

*Methyl 2-Phenyl-2-(2-(thiophen-2-yl)quinolin-4-yl)acetate (**3qa**).* (44 mg, 61%); white solid; mp 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.71 (s, 1H), 7.70−7.64 (m, 1H), 7.61 (d, J = 3.3 Hz, 1H), 7.50−7.43 (m, 2H), 7.41−7.30 (m, 5H), 7.13−7.09 (m, 1H), 5.76 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 152.0, 148.4, 145.1, 144.3, 136.3, 130.2, 129.6, 128.9, 128.8, 128.8, 128.0, 127.9, 126.6, 126.2, 125.8, 122.8, 117.4, 52.9, 52.8; HRMS m/z (ESI) calcd for $C_{22}H_{18}NO_2S$ $(M + H)^+$ 360.1053, found 360.1059.

*Methyl 2-(2-(tert-Butyl)quinolin-4-yl)-2-phenylacetate (**3ra**).* (56 mg, 84%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.64−7.57 (m, 1H), 7.48−7.39 (m, 2H), 7.35−7.23 (m, 5H), 5.74 (s, 1H), 3.74 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.8, 147.7, 143.2, 136.6, 130.3, 128.7, 127.7, 126.0, 125.0, 122.5, 117.8, 53.1, 52.5, 38.1, 29.9; HRMS m/z (ESI) calcd for $C_{22}H_{23}NO_2$ $(M + H)^+$ 334.1802, found 334.1800.

*Methyl 2-(4-Fluorophenyl)-2-(2-phenylquinolin-4-yl)acetate (**3ab**).* (65 mg, 87%); yellow solid; mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.2 Hz, 2H), 7.94 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.74−7.68 (m, 1H), 7.55−7.48 (m, 3H), 7.48−7.43 (m, 1H), 7.38−7.31 (m, 2H), 7.10−7.01 (m, 2H), 5.78 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 162.3 (d, J = 247.3 Hz), 157.1, 148.6, 144.2, 139.4, 132.2 (d, J = 3.3 Hz), 130.8, 130.5 (d, J = 8.2 Hz), 129.5, 129.5, 128.8, 127.5, 126.9, 125.6, 122.7, 118.5, 115.9 (d, J = 21.6 Hz), 52.8, 52.3; HRMS m/z (ESI) calcd for $C_{24}H_{19}FNO_2$ $(M + H)^+$ 372.1394, found 372.1400.

*Methyl 2-(4-Chlorophenyl)-2-(2-phenylquinolin-4-yl)acetate (**3ac**).* (65 mg, 84%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.2 Hz, 1H), 8.13−8.07 (m, 2H), 7.92 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.73−7.67 (m, 1H), 7.51 (t, J = 7.2 Hz, 3H), 7.47−7.42 (m, 1H), 7.35−7.28 (m, 4H), 5.77 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 157.1, 148.7, 143.8, 139.4, 134.9, 133.9, 130.8, 130.2, 129.6, 129.5, 129.1, 128.8, 127.5, 126.9, 125.5, 122.6, 118.5, 52.9, 52.4; HRMS m/z (ESI) calcd for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1105.

*Methyl 2-(4-Bromophenyl)-2-(2-phenylquinolin-4-yl)acetate (**3ad**).* (74 mg, 86%); yellow solid; mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 1H), 8.12−8.07 (m, 2H), 7.92 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H), 7.74−7.68 (m, 1H), 7.53−7.43 (m, 6H), 7.26 (s, 1H), 7.25−7.22 (m, 1H), 5.75 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 157.1, 148.7, 143.7, 139.4, 135.5, 132.1, 130.8, 130.5, 129.6, 129.5, 128.8, 127.5, 126.9, 125.5, 122.6, 122.1, 118.5, 52.9, 52.5; HRMS m/z (ESI) calcd for $C_{24}H_{19}BrNO_2$ $(M + H)^+$ 432.0594, found 432.0600.

*Methyl 2-(4-Methoxyphenyl)-2-(2-phenylquinolin-4-yl)acetate (**3ae**).* (70 mg, 92%); yellow solid; mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.2 Hz, 1H), 8.12−8.07 (m, 2H), 7.98 (d, J = 8.3 Hz, 1H), 7.81 (s, 1H), 7.72−7.66 (m, 1H), 7.53−7.47 (m, 3H), 7.46−7.40 (m, 1H), 7.30 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.75 (s, 1H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 159.1, 157.1, 148.6, 144.7, 139.5, 130.7, 129.9, 129.4, 129.3, 128.8, 128.4, 127.5, 126.7, 125.8, 122.8, 118.6, 114.3, 55.2, 52.7, 52.3; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_3$ $(M + H)^+$ 384.1594, found 384.1601.

*Methyl 2-(2-Phenylquinolin-4-yl)-2-(p-tolyl)acetate (**3af**).* (62 mg, 84%); yellow solid; mp 82−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 1H), 7.82 (s, 1H), 7.73−7.66 (m, 1H), 7.53−7.46 (m, 3H), 7.46−7.40 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.77 (s, 1H), 3.77 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 157.1, 148.6, 144.6, 139.5, 137.7, 133.4, 130.7, 129.6, 129.4, 129.3, 128.8, 128.7, 127.6, 126.7, 125.8, 122.8, 118.7, 52.7, 29.7, 21.1; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1653.

*Methyl 2-(2-Chlorophenyl)-2-(2-phenylquinolin-4-yl)acetate (**3ag**).* (68 mg, 88%); yellow solid; mp 115−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.3 Hz, 1H), 8.14−8.08 (m, 2H), 7.87 (d, J = 8.3 Hz, 1H), 7.73−7.67 (m, 2H), 7.54−7.43 (m, 5H), 7.28−7.23 (m, 1H), 7.21−7.13 (m, 2H), 6.25 (s, 1H), 3.83 (s, 3H); ^{13}C NMR

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(100 MHz, $CDCl_3$) δ 171.6, 157.0, 148.7, 143.5, 139.4, 134.6, 134.1, 130.7, 130.2, 129.8, 129.6, 129.5, 129.3, 128.8, 127.6, 127.2, 126.9, 125.6, 122.8, 118.6, 52.9, 50.2; HRMS m/z (ESI) calcd for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1104.

*Methyl 2-(3-Chlorophenyl)-2-(2-phenylquinolin-4-yl)acetate (**3ah**).* (51 mg, 66%); yellow solid; mp 89−91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.2 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.75−7.69 (m, 1H), 7.55−7.49 (m, 3H), 7.49−7.44 (m, 1H), 7.37 (s, 1H), 7.31−7.27 (m, 2H), 7.27−7.24 (m, 1H), 5.78 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 157.1, 148.7, 143.6, 139.4, 138.4, 134.8, 130.8, 130.1, 129.6, 129.5, 129.0, 128.9, 128.2, 127.6, 127.0, 126.9, 125.6, 122.6, 118.6, 52.9, 52.6; HRMS m/z (ESI) calcd for $C_{24}H_{19}ClNO_2$ $(M + H)^+$ 388.1099, found 388.1104.

*Methyl 2-(2-Phenylquinolin-4-yl)-2-(m-tolyl)acetate (**3ai**).* (58 mg, 79%); yellow solid; mp 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.2 Hz, 2H), 7.99 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.56−7.42 (m, 4H), 7.29−7.24 (m, 1H), 7.22−7.09 (m, 3H), 5.78 (s, 1H), 3.79 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 157.0, 148.4, 144.6, 139.4, 138.7, 136.2, 130.6, 129.5, 129.5, 129.4, 128.8, 128.8, 127.6, 126.8, 125.8, 122.8, 118.8, 52.9, 52.8, 21.5; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1652.

*Methyl2-(2-Phenylquinolin-4-yl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (**3aj**).* (38 mg, 40%); white solid; mp 175−177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.1 Hz, 2H), 7.97 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 7.9 Hz, 2H), 7.77 (s, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.55−7.47 (m, 3H), 7.45 (d, J = 7.0 Hz, 1H), 7.43−7.37 (m, 2H), 5.83 (s, 1H), 3.79 (s, 3H), 1.34 (d, J = 9.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 157.1, 148.5, 144.2, 139.4, 135.4, 130.7, 129.5, 129.4, 128.8, 128.3, 127.6, 126.8, 125.8, 122.7, 118.9, 83.9, 53.3, 52.8, 24.8, 24.8; HRMS m/z (ESI) calcd for $C_{30}H_{31}BNO_4$ $(M + H)^+$ 480.2341, found 480.2349.

*Ethyl 2-Phenyl-2-(2-phenylquinolin-4-yl)acetate (**3ak**).* (65 mg, 88%); yellow solid; mp 99−101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.1 Hz, 2H), 8.00 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.53−7.46 (m, 3H), 7.45−7.42 (m, 1H), 7.41−7.28 (m, 5H), 5.79 (s, 1H), 4.31−4.21 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 157.0, 148.6, 144.5, 139.5, 136.6, 130.7, 129.4, 129.3, 128.9, 128.8, 128.8, 127.8, 127.5, 126.7, 125.9, 122.8, 118.7, 61.7, 53.2, 14.1; HRMS m/z (ESI) calcd for $C_{25}H_{22}NO_2$ $(M + H)^+$ 368.1645, found 368.1652.

*Isopropyl 2-Phenyl-2-(2-phenylquinolin-4-yl)acetate (**3al**).* (46 mg, 60%); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 1H), 8.13−8.06 (m, 2H), 8.00 (d, J = 8.3 Hz, 1H), 7.81 (s, 1H), 7.73−7.67 (m, 1H), 7.53−7.41 (m, 4H), 7.41−7.28 (m, 5H), 5.75 (s, 1H), 5.22−5.08 (m, 1H), 1.25 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 157.0, 148.6, 144.7, 139.5, 136.6, 130.7, 129.4, 129.3, 128.9, 128.9, 128.8, 127.8, 127.5, 126.6, 125.9, 122.9, 118.7, 69.3, 53.4, 21.6, 21.6; HRMS m/z (ESI) calcd for $C_{26}H_{24}NO_2$ $(M + H)^+$ 382.1802, found 382.1806.

*Benzyl 2-Phenyl-2-(2-phenylquinolin-4-yl)acetate (**3am**).* (70 mg, 82%); yellow solid; mp 91−93 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 7.0 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.49−7.40 (m, 4H), 7.37−7.25 (m, 10H), 5.83 (s, 1H), 5.31−5.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.0, 148.6, 144.2, 139.4, 136.4, 135.2, 130.7, 129.4, 129.3, 128.9, 128.7, 128.5, 128.5, 128.4, 127.9, 127.5, 126.7, 125.7, 122.9, 118.6, 67.4, 53.2; HRMS m/z (ESI) calcd for $C_{30}H_{24}NO_2$ $(M + H)^+$ 430.1802, found 430.1810.

*Ethyl 2-(2-Phenylquinolin-4-yl)acetate (**3an**).* (37 mg, 63%); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23−8.11 (m, 3H), 7.99 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H), 7.75−7.69 (m, 1H), 7.58−7.49 (m, 3H), 7.48−7.40 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 157.0, 148.5, 140.7, 139.4, 130.4, 129.5, 129.3, 128.8, 127.5, 126.5, 126.4, 123.4, 120.5, 61.3, 38.7, 14.1; HRMS m/z (ESI) calcd for $C_{19}H_{18}NO_2$ $(M + H)^+$ 292.1332, found 292.1337.

*Ethyl 2-(2-Phenylquinolin-4-yl)propanoate (**3ao**).* (40 mg, 66%); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.18−8.12 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.75−7.70 (m, 1H), 7.58−7.50 (m, 3H), 7.49−7.43 (m, 1H), 4.52 (q, J = 7.1 Hz, 1H), 4.22−4.10 (m, 2H), 1.71 (d, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 157.2, 148.6, 146.9, 139.6, 130.7, 129.4, 129.3, 128.8, 127.5, 126.5, 125.6, 122.8, 117.1, 61.2, 41.2, 17.8, 14.0; HRMS m/z (ESI) calcd for $C_{20}H_{20}NO_2$ $(M + H)^+$ 306.1489, found 306.1496.

*Ethyl 3-Phenyl-2-(2-phenylquinolin-4-yl)propanoate (**3ap**).* (46 mg, 60%); yellow solid; mp 91−92 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.18−8.12 (m, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.75−7.69 (m, 1H), 7.57−7.50 (m, 3H), 7.49−7.43 (m, 1H), 7.28−7.16 (m, 5H), 4.76−4.64 (m, 1H), 4.17−4.02 (m, 2H), 3.70−3.59 (m, 1H), 3.26−3.14 (m, 1H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 157.1, 148.7, 145.1, 139.5, 138.6, 130.7, 129.4, 129.4, 128.8, 128.8, 128.5, 127.6, 126.7, 126.5, 125.6, 122.7, 117.6, 61.3, 48.8, 39.1, 13.9; HRMS m/z (ESI) calcd for $C_{26}H_{24}NO_2$ $(M + H)^+$ 382.1802, found 382.1808.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01227.

Copies of ^1H NMR and ^{13}C NMR for all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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