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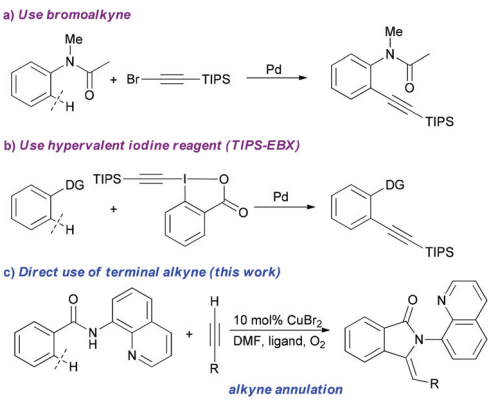
# Directed arene/alkyne annulation reactions *via* aerobic copper catalysis†

Yi Zhang,[a] Qian Wang,[a] Huidong Yu*[b] and Yong Huang*[a]

We describe a straightforward protocol for a smooth dehydrogenative annulation reaction between various arenes and terminal alkynes using a catalytic amount of $CuBr_2$ and molecular oxygen. 3-Methyleneisoindoline derivatives are prepared in high yields.

## Introduction

Cross coupling reactions between an inert $sp^2$ C–H and a sp C–H bond, the C–H Sonogashira reactions, have drawn significant attention because of the synthetic versatility of alkynyl arenes.[1] Arene alkynylation using terminal acetylenes have been studied extensively for heterocycles, polyfluoroarenes and phenols using Pd, Cu and Ga, which relies on the electronic characteristics of aromatic substrates to control site selectivity.[2] On the other hand, the complementary arene/alkyne coupling reaction using a directing group to accomplish precise regioselectivity has been significantly more challenging, despite the recent studies on directed C–H functionalization reactions.[3] Chatani and co-workers first reported an anilide directed alkynylation reaction using oxidative alkynyl bromides and Pd.[4] Subsequently, Chatani and Yu reported $sp^3$ C–H alkynylation using alkynyl bromides and Pd through either Pd(II)/Pd(IV) or Pd(0)/Pd(II) mechanisms.[5] Very recently, Loh, Li and Glorius independently reported the use of hypervalent iodine reagents and Rh for the directed *ortho*-alkynylation of arenes.[6] Most of these reactions only work for specific substrates having a silicon atom next to the triple bond. Furthermore, the direct use of terminal alkynes remains scarce.[7] Inspired by the recent progress in direct coupling reactions between terminal alkynes and heteroatoms using copper catalysis,[8] we decided to explore the feasibility of affecting the coupling of arenes and terminal alkynes using this cheap industrial metal as a catalyst.[9] Herein, we report a highly efficient arene/alkyne annulation reaction using a copper catalyst under aerobic oxidation conditions. This method offers a complementary approach towards substituted 3-methyleneisoindolin-1-one derivatives (Scheme 1).[10]




**Scheme 1** Directed arene/alkyne cross coupling reactions.

## Results and discussion

We started our initial exploration by treating 8-aminoquinoline *p*-methyl-benzamide **1a** with phenylacetylene **2a** using various metal catalysts.[11] Common transition metals, such as Rh, Ru, Pd, Ir, failed to promote the C–H arene/alkyne coupling reaction. In most cases, the dimerization of the terminal alkyne was a serious side reaction. Gratifyingly, CuI, in combination with a base and NMO as the oxidant, was quickly identified as an effective metal for this transformation. The reaction did not proceed in the absence of either copper or the oxidant. Various bases were tolerated for the $sp^2$–sp dehydrogenative annulation reaction with CsOAc being the most effective. The highest conversions were obtained in highly polar solvents, such as DMF. Then, various copper salts were examined (Table 1). Most Cu(I) and Cu(II) salts catalyzed the desired annulation reaction with good catalytic efficiency (10 mol%). We were pleased to find that atmosphere molecular oxygen was a very

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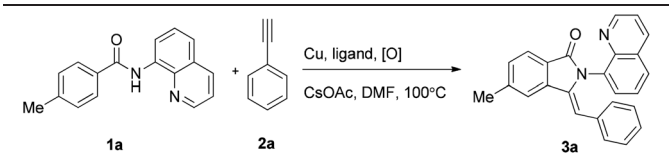
**Table 1** Reaction condition survey for the C–H arene/alkyne annulation reaction[a]




| Entry | Catalyst | Oxidant | Ligand | Yield[b] (%) |
|---|---|---|---|---|
| 1 | CuI | NMO | 1,10-Phenanthroline | 78.8 |
| 2 | CuBr | NMO | 1,10-Phenanthroline | 97.2 |
| 3 | $Cu(OAc)_2$ | NMO | 1,10-Phenanthroline | 88.9 |
| 4 | $CuCl_2$ | NMO | 1,10-Phenanthroline | 71.9 |
| 5 | $CuBr_2$ | NMO | 1,10-Phenanthroline | >99 |
| 6 | $CuBr_2$ | $O_2$ | 1,10-Phenanthroline | 94.3 |
| 7 | $CuBr_2$ | $O_2$ | 2,9-Dichloro-1,10-phenanthroline | 63.9 |
| **8**[c] | **$CuBr_2$** | **$O_2$** | **Neocuproine** | **>99** |

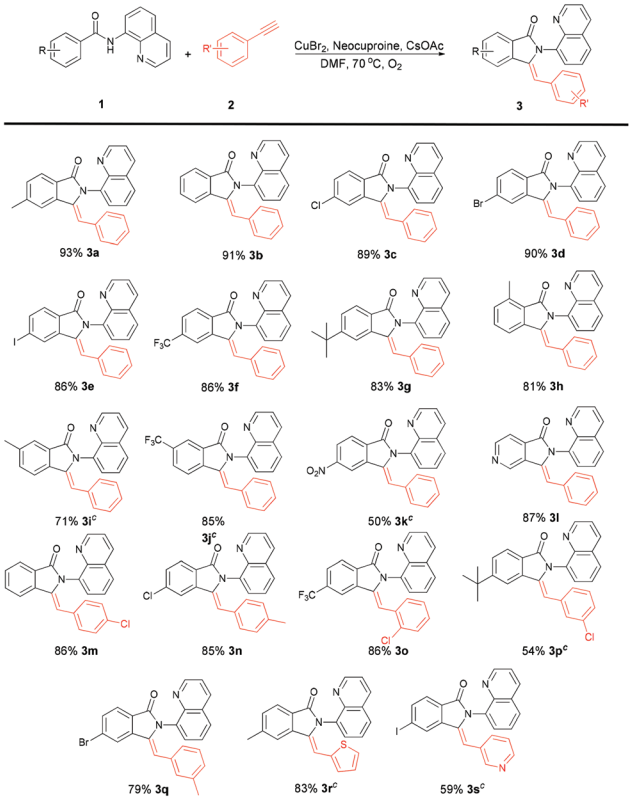
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), ligand (0.04 mmol), Cu catalyst (0.02 mmol), CsOAc (0.24 mmol), oxidant (0.6 mmol), in 1 mL DMF at 100 °C for 20 hours. [b] Yield determined by GC using biphenyl as the internal standard. [c] The reaction was carried out at 70 °C.

effective oxidant for the formation of **3a**. Ligands had a high impact on the conversion, and neocuproine led the quantitative conversion to **3a** at 70 °C (Table 1, entry 8).

With the optimized reaction conditions, we explored the substrate scope for the C–H arene/alkyne annulation reaction (Table 2). Arenes bearing either electron-rich (**1a**, **1g**, **1h**) or electron-poor (**1c**, **1d**, **1f**, **1k**) substituents were equally competent substrates, and the corresponding substituted 3-methyleneisoindolin-1-one products were isolated in good yields. The reaction tolerates various functional groups, such as alkyl, chloride, bromide, iodide, trifluoromethyl, and nitro. *ortho*-, *meta*- and *para*-Substitution were compatible, although sterically more demanding substrates required a longer reaction time (36–48 h). Notably, heteroarene (*e.g.* pyridine) substrates reacted to yield a high conversion (Table 2, product **3l**). Various terminal alkynes were also investigated. Aryl acetylenes, including heteroaryl ones (Table 2, product **3r**, **3s**), underwent this dehydrogenative coupling/cyclization cascade reaction to provide good yields. Products from these substrates were isolated as single double bond isomers. Unfortunately, alkyl substituted alkynes led to low conversions and messy product mixtures.

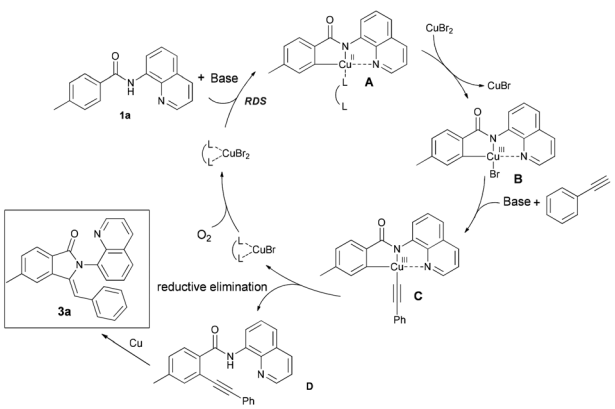
Mechanistic studies were carried out. Isotope experiments revealed that the arene C–H cleavage is the rate limiting step. Because copper acetylide is easily generated when a terminal alkyne is mixed with copper and a base, we investigated whether it was a reaction intermediate. When independently synthesized copper acetylide was treated with the substrate **1a**, only small amounts of the desired product **3a** were obtained (<10%), suggesting that copper acetylide is not involved in this reaction. The turnover of the catalyst is accomplished by molecular oxygen because the reaction did not proceed under Ar atmosphere.

**Table 2** Substrate scope for the C–H arene/alkyne annulation[a,b]

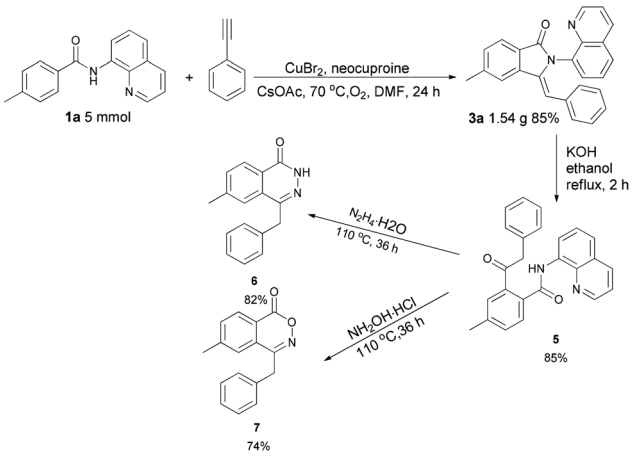



[a] Reaction condition: **1** (0.2 mmol), **2** (0.3 mmol), neocuproine (0.04 mmol), $CuBr_2$ (0.02 mmol), CsOAc (0.24 mmol), $O_2$ balloon, in 1 mL DMF for 20 hours. [b] Isolated yield. [c] The reaction time was extended to 48 hours.

Based on the previous reports on C–H activation reactions involving Cu(II) and Cu(III) intermediates,[12] a plausible reaction mechanism is proposed in Scheme 2. First, the base assisted Cu(II) insertion to NH is followed by OAc-mediated C–H insertion to give Cu(II) metallocycle **A**; second, the disproportionation of Cu(II) generates the arylcopper(III) intermediate **B**; third, a ligand exchange occurs between **B** and the terminal alkyne




**Scheme 2** Control experiments and proposed mechanism.




Scheme 3 A large scale reaction and synthetic applications.

in the presence of a base to give **C**; finally, the deductive elimination of **C** affords the alkynylated product **D**, which is known to undergo facile cyclization to give product **3a**. The ligand is believed to facilitate the aerobic oxidation of Cu(I) to Cu(II).

This C–H arene/alkyne annulation reaction could be extended to the gram scale without compromising yields. Hydrolysis of the product afforded the corresponding keto benzamide,[5] which was further transformed to the pharmacologically relevant compounds **6**[13] and **7**[14] using a hydroxylamine or hydrazine hydrate mediated cyclization reaction (Scheme 3).[13]

## Conclusions

In summary, we identified a simple protocol for the direct C–H annulation reaction between arenes and terminal alkynes. The substrate scope is extended beyond the previously reported silicon substituted alkynes and is general regardless of the electronic nature of the arene. The use of catalytic amounts of copper and the aerobic nature of this method represents a major advancement in the employment of terminal alkynes in directed C–H functionalization reactions.

## Experimental

### Representative procedure for the synthesis of *N*-(quinolin-8-yl)-benzamides

8-Aminoquinoline (0.72 g, 5 mmol) and triethylamine (0.9 mL, 6.5 mmol) were dissolved in anhydrous $CH_2Cl_2$ (10 mL) in a 50 mL round-bottom flask, and followed by the dropwise addition of a suspension of 4-methylbenzoyl chloride (2.71 g, 6.5 mmol) in 25 mL of $CH_2Cl_2$ *via* a syringe. The reaction mixture was stirred overnight. After completion, the reaction mixture was diluted with $CH_2Cl_2$ (25 mL), and washed with aqueous HCl (10 mL, 1 N), $NaHCO_3$ (saturated aqueous solution, 10 mL), brine (20 mL), and finally dried over $MgSO_4$. The organic solvent was removed by evaporation. Purification by column chromatography afforded the desired amide as an off-white solid.

**4-Methyl-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.88 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.73 (s, 1H), 8.95 (dd, $J$ = 7.5, 1.3 Hz, 1H), 8.85 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.17 (dd, $J$ = 8.3, 1.5 Hz, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 7.59 (t, $J$ = 7.9 Hz, 1H), 7.53 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.46 (dd, $J$ = 8.3, 4.2 Hz, 1H), 7.36 (s, 1H), 7.33 (s, 1H), 2.45 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.60, 148.39, 142.49, 138.90, 136.51, 134.81, 132.45, 129.60, 128.12, 127.61, 127.44, 121.80, 121.68, 116.59, 21.70.

***N*-(Quinolin-8-yl)benzamide.** $R_f$ = 0.87 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.76 (s, 1H), 8.96 (dd, $J$ = 7.4, 1.5 Hz, 1H), 8.86 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.19 (dd, $J$ = 8.3, 1.6 Hz, 1H), 8.15–8.05 (m, 2H), 7.68–7.52 (m, 5H), 7.48 (dd, $J$ = 8.3, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.62, 148.43, 138.91, 136.54, 135.29, 134.72, 131.99, 128.94, 128.13, 127.61, 127.44, 121.84, 116.68.

**4-Chloro-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.88 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.72 (s, 1H), 8.91 (dd, $J$ = 7.1, 1.8 Hz, 1H), 8.85 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.19 (dd, $J$ = 8.3, 1.6 Hz, 1H), 8.05–8.03 (m, 1H), 8.03–7.99 (m, 1H), 7.64–7.45 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.46, 148.49, 138.83, 138.25, 136.59, 134.46, 133.64, 129.19, 128.86, 128.12, 127.58, 122.04, 121.90, 116.73.

**4-Bromo-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.89 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.73 (s, 1H), 8.92 (dd, $J$ = 7.0, 1.9 Hz, 1H), 8.86 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.21 (dd, $J$ = 8.3, 1.6 Hz, 1H), 8.01–7.96 (m, 1H), 7.96–7.93 (m, 1H), 7.74–7.70 (m, 1H), 7.70–7.66 (m, 1H), 7.65–7.54 (m, 2H), 7.50 (dd, $J$ = 8.3, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.59, 148.50, 138.85, 136.60, 134.45, 134.13, 132.18, 129.04, 128.13, 127.60, 126.75, 122.06, 121.91, 116.75, 77.57, 77.15, 76.73.

**4-Iodo-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.91 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.73 (s, 1H), 8.91 (dd, $J$ = 7.0, 1.9 Hz, 1H), 8.86 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.21 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.94–7.87 (m, 2H), 7.84–7.81 (m, 1H), 7.80 (d, $J$ = 1.9 Hz, 1H), 7.65–7.54 (m, 2H), 7.50 (dd, $J$ = 8.3, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.78, 148.50, 138.85, 138.16, 136.59, 134.72, 134.44, 129.00, 128.13, 127.59, 122.06, 121.90, 116.76, 99.08.

**4-(*tert*-Butyl)-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.91 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.75 (s, 1H), 8.95 (d, $J$ = 7.4 Hz, 1H), 8.85 (d, $J$ = 3.1 Hz, 1H), 8.23–8.09 (m, 1H), 8.09–7.90 (m, 2H), 7.67–7.35 (m, 5H), 1.39 (d, $J$ = 2.2 Hz, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.61, 155.49, 148.37, 138.92, 136.50, 134.85, 132.48, 128.13, 127.62, 127.29, 125.88, 121.79, 121.65, 116.58, 35.15, 31.33.

**2-Methyl-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.91 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.23 (s, 1H), 8.96 (dd, $J$ = 7.3, 1.2 Hz, 1H), 8.78 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.18 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.75–7.66 (m, 1H), 7.66–7.52 (m, 2H), 7.43 (ddd, $J$ = 8.8, 7.3, 2.9 Hz, 2H), 7.33 (t, $J$ = 7.0 Hz, 2H), 2.62 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.37, 148.42, 138.74, 136.83, 136.77, 136.51, 134.86, 131.52, 130.47, 128.14, 127.57, 127.41, 126.16, 121.93, 121.82, 116.66, 20.37.

**3-Methyl-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.92 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.72 (s, 1H), 8.95 (d, $J$ = 7.4 Hz, 1H), 8.85 (d, $J$ = 4.1 Hz, 1H), 8.17 (d, $J$ = 8.2 Hz, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.65–7.51 (m, 2H), 7.47 (dd, $J$ = 8.5, 4.9 Hz, 2H), 7.40 (t, $J$ = 5.7 Hz, 1H), 2.49 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.84, 148.42, 138.91, 138.81, 136.52, 135.28, 134.77, 132.75, 128.79, 128.20, 128.12, 127.60, 124.36, 121.81, 121.78, 116.67, 21.64.

***N*-(Quinolin-8-yl)isonicotinamide.** $R_f$ = 0.66 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.81 (s, 1H), 8.97–8.81 (m, 4H), 8.19 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.90 (dd, $J$ = 4.5, 1.6 Hz, 2H), 7.64–7.53 (m, 2H), 7.49 (dd, $J$ = 8.3, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 163.39, 150.97, 148.65, 142.17, 138.76, 136.63, 133.95, 128.09, 127.51, 122.59, 122.04, 121.14, 117.02.

**4-Nitro-*N*-(quinolin-8-yl)benzamide.** $R_f$ = 0.91 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.83 (s, 1H), 8.98–8.82 (m, 2H), 8.47–8.34 (m, 2H), 8.30–8.20 (m, 3H), 7.68–7.58 (m, 2H), 7.53 (dd, $J$ = 8.3, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 163.32, 149.88, 148.68, 140.73, 138.77, 136.70, 134.03, 128.60, 128.13, 127.55, 124.19, 122.64, 122.09, 116.99.

***N*-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide.** $R_f$ = 0.91 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.78 (s, 1H), 8.99–8.87 (m, 1H), 8.85 (d, $J$ = 2.9 Hz, 1H), 8.27–8.04 (m, 3H), 7.81 (d, $J$ = 7.9 Hz, 2H), 7.60 (dd, $J$ = 11.7, 4.9 Hz, 2H), 7.49 (dd, $J$ = 8.2, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.18, 148.60, 138.84, 138.53, 136.64, 134.29, 133.5 (d, $J$ = 32.5 Hz), 128.14, 127.90, 127.57, 126.01 (dd, $J$ = 3.6 Hz), 122.35, 123.88 (dd, $J$ = 270.9 Hz), 122.00, 116.89.

***N*-(Quinolin-8-yl)-3-(trifluoromethyl)benzamide.** $R_f$ = 0.91 (3 : 1 hexane–ethyl acetate). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.78 (s, 1H), 8.92 (d, $J$ = 6.8 Hz, 1H), 8.86 (d, $J$ = 3.9 Hz, 1H), 8.36 (s, 1H), 8.23 (dd, $J$ = 14.8, 8.0 Hz, 2H), 7.85 (d, $J$ = 7.7 Hz, 1H), 7.69 (t, $J$ = 7.8 Hz, 1H), 7.65–7.54 (m, 2H), 7.50 (dd, $J$ = 8.2, 4.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.03, 148.60, 138.82, 136.61, 136.10, 134.26, 131.55 (d, $J$ = 32.5), 130.38, 129.54, 128.56, 128.52, 128.11, 127.54, 124.71 (dd, $J$ = 4.5 Hz), 123.89 (dd, $J$ = 270.1 Hz), 122.30, 121.97, 116.89.

## General procedure for the direct arene/alkyne annulation reactions

A 1 dram vial equipped with a magnetic stir bar was charged with amide 1 (0.2 mmol, 1 equiv.), cupric bromide (0.02 mmol, 0.1 equiv.), 2,9-dimethyl-1,10-phenanthroline (0.04 mmol, 0.2 equiv.), and CsOAc (0.24 mmol, 1.2 equiv.). Anhydrous DMF (1.0 mL), alkyne 2 (0.3 mmol, 1.5 equiv.) were added to the mixture, and then transferred to preheated oil bath for an indicated amount of time under an oxygen balloon. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (2 mL). The suspension was filtered through a pad of Celite and the solid phase was washed with ethyl acetate (3 × 20 mL). The filtrate was then washed with brine and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel followed by an appropriate solvent to elute the products.

**(*Z*)-3-Benzylidene-5-methyl-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.66 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.85 (d, $J$ = 2.8 Hz, 1H), 8.01–7.91 (m, 1H), 7.88 (d, $J$ = 7.7 Hz, 1H), 7.69 (s, 1H), 7.57 (d, $J$ = 8.2 Hz, 1H), 7.52–7.43 (m, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.33–7.23 (m, 2H), 6.77 (s, 1H), 6.68 (t, $J$ = 6.5 Hz, 1H), 6.62–6.46 (m, 4H), 2.56 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.22, 150.32, 144.47, 142.94, 139.10, 136.22, 135.76, 134.38, 133.70, 130.23, 130.05, 128.86, 128.27, 128.16, 126.29, 125.97, 125.94, 125.64, 123.79, 121.18, 119.99, 106.90, 22.21.

**(*Z*)-3-Benzylidene-5-chloro-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.67 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.83 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.00–7.89 (m, 2H), 7.86 (d, $J$ = 1.4 Hz, 1H), 7.58 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.53 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.48 (dd, $J$ = 7.4, 1.3 Hz, 1H), 7.34–7.26 (m, 2H), 6.78 (s, 1H), 6.69 (dt, $J$ = 12.7, 4.3 Hz, 1H), 6.56 (dd, $J$ = 10.3, 2.8 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.16, 150.40, 144.23, 140.22, 138.71, 135.83, 135.07, 133.88, 133.07, 130.00, 129.47, 128.86, 128.55, 128.10, 126.67, 126.37, 126.30, 125.66, 125.22, 121.31, 120.07, 108.61.

**(*Z*)-3-Benzylidene-5-bromo-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.78 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.05 (d, $J$ = 1.2 Hz, 1H), 7.98 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.86 (d, $J$ = 8.1 Hz, 1H), 7.70 (dd, $J$ = 8.1, 1.6 Hz, 1H), 7.60 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.48 (dd, $J$ = 7.4, 1.4 Hz, 1H), 7.34–7.28 (m, 2H), 6.78 (s, 1H), 6.72–6.66 (m, 1H), 6.55 (d, $J$ = 4.5 Hz, 4H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 167.20, 150.34, 144.35, 140.47, 135.71, 135.11, 134.02, 133.17, 132.25, 130.04, 128.90, 128.46, 128.15, 127.18, 127.02, 126.37, 126.27, 125.62, 125.37, 123.03, 121.25, 108.48.

**(*Z*)-3-Benzylidene-2-(quinolin-8-yl)-5-(trifluoromethyl)isoindolin-1-one.** $R_f$ = 0.68 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.82 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.15 (s, 1H), 8.10 (d, $J$ = 7.9 Hz, 1H), 7.96 (dd, $J$ = 8.3, 1.4 Hz, 1H), 7.82 (d, $J$ = 7.9 Hz, 1H), 7.59 (d, $J$ = 8.2 Hz, 1H), 7.50 (dd, $J$ = 7.3, 1.3 Hz, 1H), 7.29 (dt, $J$ = 6.8, 5.0 Hz, 2H), 6.89 (s, 1H), 6.70 (dt, $J$ = 8.8, 4.3 Hz, 1H), 6.55 (t, $J$ = 6.5 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.77, 150.43, 144.12, 138.91, 135.85, 135.07, 134.28, 133.96, 133.68, 132.85, 131.01, 130.00, 128.86, 128.72, 128.07, 126.43, 126.39, 125.85 (dd, $J$ = 4 Hz), 125.66, 124.59, 121.38, 117.16 (dd, $J$ = 4 Hz) 109.30.

**(*Z*)-3-Benzylidene-5-(*tert*-butyl)-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.79 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (dd, $J$ = 4.2, 1.6 Hz, 1H), 7.99–7.87 (m, 3H), 7.63 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.57 (dd, $J$ = 8.2, 1.1 Hz, 1H), 7.50 (dd, $J$ = 7.3, 1.2 Hz, 1H), 7.34–7.24 (m, 2H), 6.84 (s, 1H), 6.71–6.61 (m, 1H), 6.60–6.47 (m, 4H), 1.46 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.14, 156.22, 150.30, 144.44, 138.65, 136.45, 135.77, 134.35, 133.68, 130.14, 128.86, 128.31, 128.14, 126.86, 126.25, 125.91, 125.66, 123.62, 121.17, 116.25, 106.77, 35.59, 31.46.

**(*Z*)-3-Benzylidene-7-methyl-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.80 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.88 (dd, $J$ = 4.2, 1.7 Hz, 1H), 7.99 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.72 (d, $J$ = 7.7 Hz, 1H), 7.62–7.49 (m, 2H), 7.45 (dd, $J$ = 7.4, 1.4 Hz, 1H), 7.31 (dt, $J$ = 14.5, 6.1 Hz, 3H), 6.77 (s, 1H), 6.67 (t, $J$ = 7.0 Hz, 1H), 6.55 (dt, $J$ = 13.0, 7.5 Hz, 4H), 2.78 (s, 3H).

$^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.04, 150.57, 144.62, 139.34, 138.18, 136.12, 135.96, 134.45, 133.92, 131.90, 131.22, 130.16, 128.95, 128.31, 126.40, 126.03, 125.76, 125.65, 121.30, 117.22, 106.59, 17.73.

**(*Z*)-3-Benzylidene-6-methyl-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.62 (1 : 1 hexane–ethyl acetate) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.85 (d, $J$ = 3.1 Hz, 1H), 7.96 (d, $J$ = 8.1 Hz, 1H), 7.80 (s, 1H), 7.77 (d, $J$ = 7.9 Hz, 1H), 7.57 (d, $J$ = 8.2 Hz, 1H), 7.53–7.43 (m, 2H), 7.34–7.24 (m, 2H), 6.75 (s, 1H), 6.67 (t, $J$ = 6.8 Hz, 1H), 6.60–6.49 (m, 4H), 2.52 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 168.19, 150.20, 144.45, 139.30, 136.28, 136.19, 135.62, 134.36, 133.69, 133.21, 129.99, 128.78, 128.50, 128.16, 128.12, 126.19, 125.79, 125.52, 123.90, 121.07, 119.39, 106.46, 21.46.

**(*Z*)-3-Benzylidene-2-(quinolin-8-yl)-6-(trifluoromethyl)isoindolin-1-one.** $R_f$ = 0.69 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.83 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.28 (s, 1H), 8.03–7.89 (m, 3H), 7.61 (dd, $J$ = 8.2, 1.2 Hz, 1H), 7.51 (dd, $J$ = 7.3, 1.3 Hz, 1H), 7.35–7.28 (m, 2H), 6.91 (s, 1H), 6.76–6.67 (m, 1H), 6.57 (dd, $J$ = 10.4, 2.8 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.79, 150.44, 144.13, 141.46, 135.86, 135.14, 133.67, 132.86, 131.32 (dd, $J$ = 33 Hz) 130.01, 128.97 (dd, $J$ = 3 Hz), 128.88, 128.71, 128.67, 128.06, 126.49, 126.41, 125.68, 123.91 (dd, $J$ = 270 Hz), 121.4 (dd, $J$ = 4 Hz), 120.37, 109.88.

**(*Z*)-3-Benzylidene-5-nitro-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.61 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.83 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.77 (d, $J$ = 1.6 Hz, 1H), 8.43 (dd, $J$ = 8.3, 1.9 Hz, 1H), 8.16 (d, $J$ = 8.3 Hz, 1H), 8.00 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.64 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.52 (dd, $J$ = 7.4, 1.3 Hz, 1H), 7.36–7.30 (m, 2H), 6.97 (s, 1H), 6.73 (dd, $J$ = 8.6, 4.9 Hz, 1H), 6.58 (dd, $J$ = 7.1, 6.4 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 165.97, 150.80, 150.51, 143.96, 139.49, 135.91, 134.58, 133.45, 132.69, 132.51, 129.91, 128.89, 128.08, 126.69, 126.48, 125.69, 125.16, 123.96, 121.47, 115.57, 110.43.

**(*Z*)-3-Benzylidene-2-(quinolin-8-yl)-2,3-dihydro-1*H*-pyrrolo-[3,4-*c*]pyridin-1-one.** $R_f$ = 0.48 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.35 (s, 1H), 8.92 (d, $J$ = 5.0 Hz, 1H), 8.89 (dd, $J$ = 4.1, 1.6 Hz, 1H), 8.05 (dd, $J$ = 8.3, 1.5 Hz, 1H), 7.94 (dd, $J$ = 5.0, 0.7 Hz, 1H), 7.68 (dd, $J$ = 8.2, 1.0 Hz, 1H), 7.55 (dd, $J$ = 7.3, 1.1 Hz, 1H), 7.42–7.34 (m, 2H), 7.02 (s, 1H), 6.77 (dt, $J$ = 8.7, 4.5 Hz, 1H), 6.62 (d, $J$ = 4.4 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.50, 150.52, 149.53, 144.08, 142.62, 135.87, 134.85, 134.19, 133.54, 133.13, 132.74, 129.98, 128.88, 128.83, 128.07, 126.53, 126.43, 125.68, 121.45, 117.39, 109.98.

**(*Z*)-3-Benzylidene-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.67 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.92 (dd, $J$ = 4.1, 1.5 Hz, 1H), 8.05 (dd, $J$ = 11.2, 4.5 Hz, 2H), 7.96 (d, $J$ = 7.7 Hz, 1H), 7.76 (t, $J$ = 7.3 Hz, 1H), 7.70–7.59 (m, 2H), 7.55 (d, $J$ = 7.3 Hz, 1H), 7.41–7.34 (m, 2H), 6.88 (s, 1H), 6.75 (t, $J$ = 6.6 Hz, 1H), 6.68–6.55 (m, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.13, 150.36, 144.45, 138.73, 136.13, 135.78, 134.26, 133.58, 132.24, 130.06, 129.09, 128.87, 128.37, 128.34, 128.16, 126.31, 126.02, 125.65, 123.95, 121.22, 119.66, 107.33.

**(*Z*)-3-Benzylidene-5-iodo-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.79 (1 : 1 hexane–ethyl acetate) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.85 (dd, $J$ = 4.1, 1.5 Hz, 1H), 8.28 (s, 1H), 7.99 (dd, $J$ = 8.3, 1.5 Hz, 1H), 7.93 (dd, $J$ = 8.0, 1.0 Hz, 1H), 7.74 (d, $J$ = 8.0 Hz, 1H), 7.61 (d, $J$ = 8.2 Hz, 1H), 7.49 (dd, $J$ = 7.3, 1.1 Hz, 1H), 7.37–7.29 (m, 2H), 6.79 (s, 1H), 6.71 (dt, $J$ = 8.6, 4.4 Hz, 1H), 6.57 (t, $J$ = 6.6 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.44, 150.38, 144.23, 140.30, 138.06, 135.78, 134.81, 133.84, 133.12, 129.99, 129.04, 128.85, 128.51, 128.09, 127.65, 126.35, 126.27, 125.64, 125.35, 121.29, 108.56, 99.15.

**(*Z*)-3-(4-Chlorobenzylidene)-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.60 (1 : 1 hexane–ethyl acetate) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.83 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.02 (dd, $J$ = 11.7, 4.8 Hz, 2H), 7.87 (d, $J$ = 7.7 Hz, 1H), 7.75–7.63 (m, 2H), 7.58 (t, $J$ = 7.5 Hz, 1H), 7.51 (dd, $J$ = 7.3, 1.3 Hz, 1H), 7.40–7.29 (m, 2H), 6.72 (s, 1H), 6.45 (d, $J$ = 9.1 Hz, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.14, 150.55, 144.42, 138.55, 136.89, 136.01, 134.21, 132.50, 132.12, 131.93, 130.27, 129.44, 129.40, 129.02, 128.63, 128.41, 126.38, 125.91, 124.15, 121.55, 119.82, 105.90.

**(*Z*)-5-Chloro-3-(4-methylbenzylidene)-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.63 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (dd, $J$ = 4.2, 1.7 Hz, 1H), 7.99 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.92 (d, $J$ = 8.1 Hz, 1H), 7.86 (d, $J$ = 1.5 Hz, 1H), 7.61 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.52 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.47 (dd, $J$ = 7.4, 1.4 Hz, 1H), 7.36–7.28 (m, 2H), 6.76 (s, 1H), 6.42 (d, $J$ = 7.9 Hz, 2H), 6.34 (d, $J$ = 7.9 Hz, 2H), 2.01 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.11, 150.37, 144.34, 140.29, 138.63, 136.01, 135.65, 134.78, 134.07, 130.06, 129.98, 129.31, 128.88, 128.22, 127.99, 127.01, 126.63, 125.67, 125.20, 121.31, 119.98, 108.80, 20.89.

**(*Z*)-3-(2-Chlorobenzylidene)-2-(quinolin-8-yl)-5-(trifluoromethyl)isoindolin-1-one.** $R_f$ = 0.68 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.20 (s, 1H), 8.12 (d, $J$ = 7.9 Hz, 1H), 7.95 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.85 (d, $J$ = 7.9 Hz, 1H), 7.58 (dd, $J$ = 7.8, 1.8 Hz, 2H), 7.32 (ddd, $J$ = 8.4, 5.8, 4.0 Hz, 2H), 6.85 (d, $J$ = 7.5 Hz, 1H), 6.79 (s, 1H), 6.69–6.59 (m, 1H), 6.35 (d, $J$ = 7.4 Hz, 1H), 6.18 (t, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.75, 150.75, 144.13, 138.52, 136.17, 135.75, 134.30 (dd, $J$ = 33), 133.19, 132.93, 131.71, 131.21, 130.22, 129.85, 128.84, 128.65, 127.99, 127.89, 126.21 (dd, $J$ = 4), 125.63, 124.63, 124.33, 123.86 (dd, $J$ = 271.4), 121.42, 117.46 (dd, $J$ = 4), 105.99, 105.00.

**(*Z*)-5-(*tert*-Butyl)-3-(4-chlorobenzylidene)-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.80 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.86 (dd, $J$ = 4.1, 1.6 Hz, 1H), 8.00 (dd, $J$ = 8.3, 1.5 Hz, 1H), 7.92 (d, $J$ = 8.1 Hz, 1H), 7.88 (d, $J$ = 0.9 Hz, 1H), 7.68–7.57 (m, 2H), 7.50 (dd, $J$ = 7.3, 1.2 Hz, 1H), 7.38–7.28 (m, 2H), 6.71 (s, 1H), 6.64 (d, $J$ = 7.4 Hz, 1H), 6.56–6.45 (m, 3H), 1.45 (s, 9H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.07, 156.40, 150.52, 144.21, 138.38, 137.40, 135.98, 135.56, 134.11, 132.35, 129.99, 129.04, 128.63, 128.49, 127.43, 127.15, 126.39, 125.95, 125.93, 125.78, 123.70, 121.41, 116.32, 104.79, 35.60, 31.44.

**(*Z*)-5-Bromo-3-(3-methylbenzylidene)-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.68 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.88 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.03 (d, $J$ = 1.5 Hz, 1H), 8.01 (d, $J$ = 1.7 Hz, 1H), 7.85 (d, $J$ = 8.1 Hz, 1H), 7.69 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.59 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.43 (dd, $J$ = 7.4, 1.4 Hz, 1H), 7.33 (dd, $J$ = 8.3, 4.2 Hz, 1H), 7.30–7.25 (m, 1H), 6.76 (s, 1H), 6.61–6.44 (m, 3H), 6.26 (d, $J$ = 0.4 Hz, 1H), 1.66 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.26,

150.48, 144.27, 140.44, 136.06, 135.85, 134.84, 134.04, 132.98, 132.23, 129.69, 129.30, 128.92, 128.44, 127.16, 127.05, 127.02, 126.49, 125.64, 125.37, 125.28, 123.00, 121.33, 108.84, 20.64.

**(*Z*)-5-Methyl-2-(quinolin-8-yl)-3-(thiophen-2-ylmethylene)isoindolin-1-one.** $R_f$ = 0.60 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (dd, $J$ = 4.0, 1.3 Hz, 1H), 8.09 (dd, $J$ = 8.3, 1.2 Hz, 1H), 7.86 (d, $J$ = 7.7 Hz, 1H), 7.75 (d, $J$ = 8.2 Hz, 1H), 7.68–7.58 (m, 2H), 7.45 (t, $J$ = 7.8 Hz, 1H), 7.40–7.29 (m, 2H), 6.75 (d, $J$ = 5.0 Hz, 1H), 6.71 (s, 1H), 6.29–6.24 (m, 1H), 5.96 (d, $J$ = 3.4 Hz, 1H), 2.54 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.26, 150.65, 145.00, 143.06, 139.08, 135.99, 135.92, 135.76, 134.23, 130.30, 130.18, 129.00, 128.60, 128.22, 125.92, 125.70, 125.62, 123.86, 121.45, 119.94, 99.43.

**(*Z*)-5-Iodo-3-(pyridin-3-ylmethylene)-2-(quinolin-8-yl)isoindolin-1-one.** $R_f$ = 0.51 (1 : 1 hexane–ethyl acetate) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.79 (dd, $J$ = 4.1, 1.6 Hz, 1H), 8.26 (s, 1H), 7.94 (ddd, $J$ = 13.1, 8.1, 1.3 Hz, 2H), 7.89–7.78 (m, 2H), 7.71 (d, $J$ = 8.0 Hz, 1H), 7.63 (dd, $J$ = 8.2, 1.0 Hz, 1H), 7.57 (dd, $J$ = 7.3, 1.1 Hz, 1H), 7.39 (t, $J$ = 7.8 Hz, 1H), 7.30 (dd, $J$ = 8.3, 4.2 Hz, 1H), 6.75 (d, $J$ = 7.8 Hz, 1H), 6.62 (s, 1H), 6.40 (dd, $J$ = 7.7, 4.9 Hz, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.34, 150.57, 148.55, 147.04, 143.83, 139.74, 138.54, 136.59, 135.93, 134.83, 133.28, 130.27, 129.32, 129.22, 129.00, 128.85, 127.63, 125.94, 125.40, 121.63, 120.96, 103.99, 99.45.

### Synthesis of 4-methyl-2-(2-phenylacetyl)-*N*-(quinolin-8-yl)-benzamide (5)

A solution of 145 mg of (*Z*)-3-benzylidene-5-methyl-2-(quinolin-8-yl)isoindolin-1-one in 10 mL of 10% ethanolic potassium hydroxide was refluxed for 2 hours. The reaction mixture was concentrated under reduced pressure, diluted with 20 mL EA, washed with brine and saturated $NaHCO_3$ and then extracted with EA for three times. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatograph to give 4-methyl-2-(2-phenylacetyl)-*N*-(quinolin-8-yl)benzamide (**5**) 129 mg (85%).[15]

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.82 (dd, $J$ = 4.2, 1.6 Hz, 1H), 8.10 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.85–7.70 (m, 2H), 7.51–7.36 (m, 2H), 7.36–7.22 (m, 6H), 7.22–7.16 (m, 1H), 7.10 (t, $J$ = 7.9 Hz, 1H), 6.13 (dd, $J$ = 7.6, 0.8 Hz, 1H), 3.75 (dd, $J$ = 35.4, 13.6 Hz, 2H), 2.51 (s, 3H).

### Synthesis of 4-benzyl-6-methylphthalazin-1(2*H*)-one (6)

A solution of 150 mg of **5** in 2 mL of ethanolic and 50 μL of hydrazine hydrate was added, and the reaction mixture was stirred at 110 °C. After completion, the reaction mixture was concentrated under reduced pressure, diluted with 20 mL EA, washed with brine. The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatograph to give compound **6** 82.1 mg (82%).

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.55 (s, 1H), 8.42 (d, $J$ = 8.6 Hz, 1H), 7.62 (d, $J$ = 6.8 Hz, 2H), 7.43–7.23 (m, 5H), 4.36 (s, 2H), 2.54 (s, 3H).

### Synthesis of 4-benzyl-6-methyl-1*H*-benzo[*d*][1,2]oxazin-1-one (7)

A solution of 150 mg of **5** in 2 mL of ethanolic and 0.25 mL of pyridine was treated with 0.25 g of hydroxylamine hydrochloride, and the reaction mixture was stirred at 110 °C for 36 hours. After completion, the reaction mixture was concentrated under reduced pressure, diluted with 20 mL EA, washed with 1 N HCl and brine, and then extracted with EA for three times. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatograph to give compound **7** 74.4 mg (74%).

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.0 Hz, 1H), 7.56 (d, $J$ = 8.0 Hz, 1H), 7.42 (s, 1H), 7.38–7.28 (m, 4H), 7.28–7.20 (m, 1H), 4.26 (s, 2H), 2.45 (s, 3H).

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## Notes and references

1 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; (*b*) J. Liu, J. W. Y. Lam and B. Z. Tang, *Chem. Rev.*, 2009, **109**, 5799; (*c*) H. K. Bisoyi and S. Kumar, *Chem. Soc. Rev.*, 2010, **39**, 264.

2 For a recent review, see: (*a*) S. Messaoudi, J.-D. Brion and M. Alami, *Eur. J. Org. Chem.*, 2010, 6495. For recent examples, see: (*b*) K. Kobayashi, M. Arisawa and M. Yamaguchi, *J. Am. Chem. Soc.*, 2002, **124**, 8528; (*c*) A. S. Dudnik and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2010, **49**, 2096; (*d*) I. V. Seregin, V. Ryabova and V. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 7742; (*e*) N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 4156; (*f*) Y. Wei, H. Zhao, J. Kan, W. Su and M. Hong, *J. Am. Chem. Soc.*, 2010, **132**, 2522.

3 For selected reviews, please see: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (*c*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*d*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2011, **45**, 814; (*e*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*f*) N. Yoshikai, *Synlett*, 2011, 1047; (*g*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2009, **110**, 624; (*h*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (*i*) B.-J. Li and Z.-J. Shi, *Chem. Soc. Rev.*, 2012, **41**, 5588; (*j*) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369.

4 M. Tobisu, Y. Ano and N. Chatani, *Org. Lett.*, 2009, **11**, 3250.

5 (*a*) Y. Ano, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 12984; (*b*) J. He, M. Wasa, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 3387.

6 (*a*) C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2014, **53**, 2722; (*b*) F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780; (*c*) K. D. Collins, F. Lied and F. Glorius, *Chem. Commun.*, 2014, **50**, 4459.

7 For direct use of terminal alkynes using Mn and Ru catalysts, see: (*a*) B. Zhou, H. Chen and C. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 1264; (*b*) R. He, Z.-T. Huang, Q.-Y. Zheng and C. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4950; (*c*) K. Cheng, B. Yao, J. Zhao and Y. Zhang, *Org. Lett.*, 2008, **10**, 5309.

8 (*a*) J. Li and L. Neuville, *Org. Lett.*, 2013, **15**, 1752; (*b*) L. Wang, H. Huang, D. L. Priebbenow, F.-F. Pan and C. Bolm, *Angew. Chem., Int. Ed.*, 2013, **52**, 3478; (*c*) A. Laouiti, M. M. Rammah, M. B. Rammah, J. Marrot, F. Couty and G. Evano, *Org. Lett.*, 2011, **14**, 6; (*d*) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2009, **132**, 28; (*e*) Y. Gao, G. Wang, L. Chen, P. Xu, Y. Zhao and L.-B. Han, *J. Am. Chem. Soc.*, 2009, **131**, 7956; (*f*) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833.

9 For examples of copper catalyzed C–H functionalization reactions, see: (*a*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (*b*) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 3354; (*c*) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237. Immediately prior to submission of this manuscript, You and co-workers published a similar $sp^2$/sp C–H annulation reaction using 3 equivalent of copper, possible through a different reaction mechanism, see: *Org. Lett.*, 2014, **16**, 2884.

10 L. Li, M. Wang, X. Zhang, Y. Jiang and D. Ma, *Org. Lett.*, 2009, **11**, 1309.

11 (*a*) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (*b*) J. Roane and O. Daugulis, *Org. Lett.*, 2013, **15**, 5842.

12 (*a*) P. J. Chmielewski, L. Latos-Grażyński and I. Schmidt, *Inorg. Chem.*, 2000, **39**, 5475; (*b*) H. Furuta, H. Maeda and A. Osuka, *J. Am. Chem. Soc.*, 2000, **122**, 803; (*c*) M. Pawlicki, I. Kańska and L. Latos-Grażyński, *Inorg. Chem.*, 2007, **46**, 6575; (*d*) H. Zhang, B. Yao, L. Zhao, D.-X. Wang, B.-Q. Xu and M.-X. Wang, *J. Am. Chem. Soc.*, 2014, **136**, 6326; (*e*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062.

13 (*a*) K. G. Byler, M. Brito-Arias, A. Marquez-Navarro, B. Nogueda-Torres, L. G. Torres-Bustillos and K. Martinez-Mayorga, *Bioorg. Med. Chem.*, 2012, **20**, 2587; (*b*) A. H. F. Abd El-Wahab, H. M. Mohamed, A. M. El-Agrody, M. A. El-Nassag and A. H. Bedair, *Pharmaceuticals*, 2011, **4**, 1158.

14 J. Fuska, A. Fuskova and B. Proksa, *Neoplasma*, 1985, **32**, 407.

15 V. Scartoni and T. Tognetti, *J. Heterocycl. Chem.*, 1984, **21**, 1499.

 