JOC The Journal of Organic Chemistry



Note

# Copper(II)-Mediated ortho-Selective C(sp2)–H Tandem Alkynylation/Annulation and ortho-Hydroxylation of Anilides with 2-Aminophenyl-1H-pyrazole as A Directing Group

Wan-Chen Cindy Lee, Wei Wang, and Jie Jack Li

*J. Org. Chem.*, **Just Accepted Manuscript** • Publication Date (Web): 15 Jan 2018



## Just Accepted



ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

1

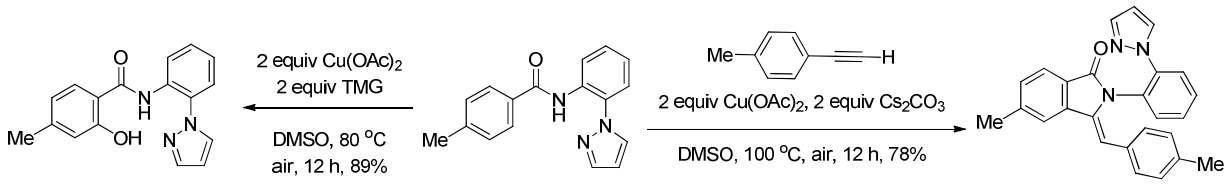
# Copper(II)-Mediated *ortho*-Selective C($sp^2$)–H Tandem Alkynylation/Annulation and *ortho*-Hydroxylation of Anilides with 2-Aminophenyl-1H-pyrazole as A Directing Group

Wan-Chen Cindy Lee,[†] Wei Wang,[‡] and Jie Jack Li[†*]

[†]Department of Chemistry, University of San Francisco, 2130 Fulton Street, San Francisco, CA 94117, USA; [‡]Pfizer La Jolla, 10770 Science Center Drive, San Diego, CA 92121, USA.

[*]Email: lijiejackli@hotmail.com

**Abstract:**




2-Aminophenyl-1*H*-pyrazole has been identified as a viable directing group to promote copper(II)-mediated *ortho*-selective $sp^2$ C–H bond tandem alkynylation/annulation of anilides with terminal alkynes to offer arylmethylene isoindolinones. Meanwhile, copper(II)-mediated *ortho*-selective $sp^2$ C–H hydroxylation of anilides has also been optimized as the major reaction pathway by using $Cu(OAc)_2$ as the promoter and 1,1,3,3-tetramethylguanidine as an organic base. Recovery of the directing group was achieved by hydrazinolysis for arylmethylene isoindolinones and basic hydrolysis for the hydroxylation products, respectively.

---

Isoindolinones are present in natural products such as fumaridine (**1** in Fig. 1),[1] an arylmethylene isoindolinone alkaloid.[1] They are also important pharmacophores. For instance, lenalidomide (Revlimid, **2**),[2] a thalidomide derivative, is a potent tumor necrosis factor (TNF)-α inhibitor for the treatment of multiple myeloma. On the other hand, phthalazin-1(2*H*)-ones are present in several drugs as represented by olaparib (Lynparza, **3**), as a poly-adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitor for the treatment of ovarian cancer.[3] Herein, we report a synthesis of isoindolinone derivatives employing a copper(II)-mediated $sp^2$ C–H bond alkynylation/annulation of anilides with terminal alkynes, employing 2-aminophenyl-1*H*-pyrazole (2-APP) as a new directing group, to furnish arylmethylene isoindolinones, which may be conveniently converted to phthalazin-1(2*H*)-ones via hydrazinolysis (*vide infra*).

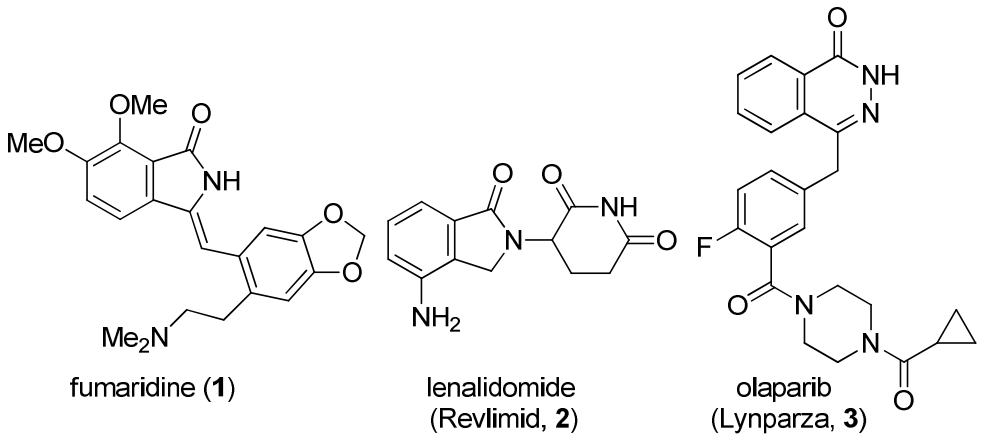
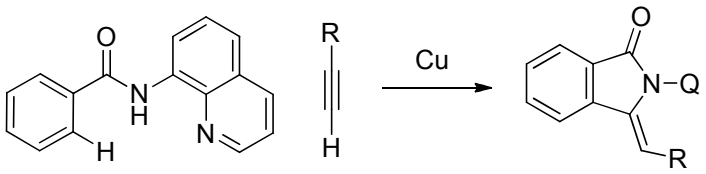



**Fig. 1.** Bioactive isoindolinones and phthalazin-1(2*H*)-one

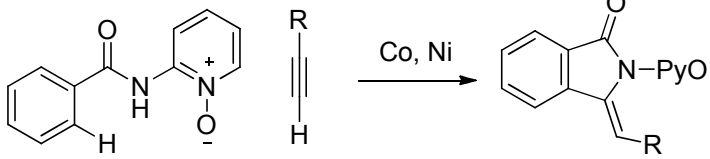
In 2014, You[4] first described a copper-mediated tandem oxidative $sp^2$ C–H alkynylation/annulation with terminal alkynes to afford the 3-methyleneisoindolinone scaffold although removal of the 2-aminoquinoline (Q) directing group was not successful [eq (1)]. Similar methodology on copper-mediated C($sp^2$)–H/C($sp$)–H couplings was reported by Huang[5] in 2014 and Liu[6] in 2015, respectively. The two latter papers described the removal of the directing group via hydrazinolysis to prepare phthalazin-1(2*H*)-ones. Subsequently, Zhang extended the substrate scope to aliphatic amides to produce pyrrolidones.[7] Meanwhile, Niu and Song's group employed Co(II)- and Ni(II)-catalysts and pyridine oxide (PyO) as an auxiliary to realize an $sp^2$ C–H tandem alkynylation/annulation using silver acetate as an oxidant to gain access to 3-methylene isoindolin-1-one structures [eq (2)].[8] In 2016, we discovered that 2-aminophenyl-1*H*-pyrazole (2-APP) as a new removable directing group was efficient in facilitating C–H carbon–nitrogen,[9] carbon–chlorine,[10] and carbon–carbon bond[11] formations. We then proceeded to explore 2-APP's utility as a directing group for promoting the C($sp^2$)–H/C($sp$)–H couplings to produce 3-methyleneisoindolin-1-ones [eq (3), PP = 1-phenyl-1*H*-pyrazole]. In comparison to existing directing groups such as 8-aminoquinoline and 2-aminophenyloxazoline, 2-APP is less expensive, especially in comparison to the latter.[9]

*You, 2014:*



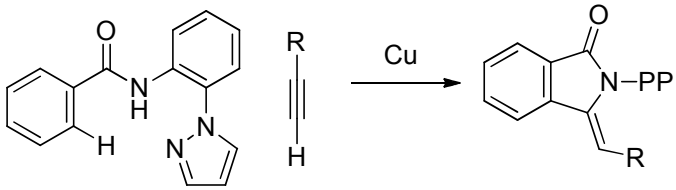

(1)

*Niu & Song, 2015:*




(2)

*This work:*

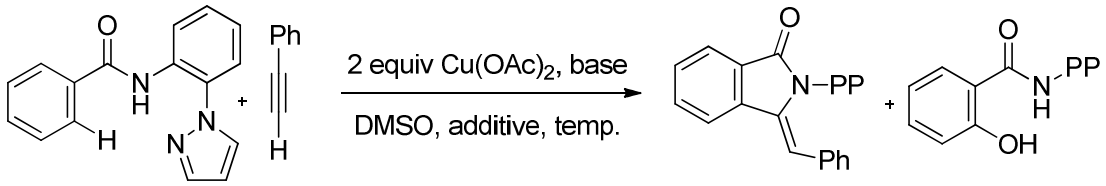



(3)

After experimentations employing anilide **4** as the substrate with 2-APP as the directing group, we discovered that $Cu(OAc)_2$ was the promoter of choice and DMSO the optimal solvent for facilitating the $sp^2$ C–H bond cascade alkynylation/annulation. As shown in Table 1, when anilide **4** in DMSO was heated with 2 equiv of $Cu(OAc)_2$, along with $Cs_2CO_3$ as the base in open air, arylmethylene isoindolinone **6** was formed in 62% yield, along with 18% of the hydroxylation product **7a** (entry 1). Formation of phenol **7** is consistent with our previous observations for $Cu(OAc)_2$-mediated C($sp^2$)–H amidation.[9] As far as the base is concerned, both 1,1,3,3-tetramethylguanidine (TMG, entry 2) and CsOAc (entry 3) proved to be inferior to $Cs_2CO_3$ for the production of **6** although the latter seemed to promote the hydroxylation product **7** with higher efficiency. A few additives that accelerated other C–H bond functionalizations in the literature were tested for our method, but pyridine, tetrabutylammonium iodide (TBAI), and N-methylmorpholine N-oxide (NMO) did not show much advantages (entries 4–6). With regard to reaction temperature, when the reaction was run at 120 $^oC$, the yield dropped (entry 7), and 100 $^oC$ was found to be optimal (entry 8). When the reaction was run under nitrogen (entry 9), the yields for **6** and **7** were both suppressed, indicating the reaction is indeed an aerobic oxidation process. Not surprisingly, the reaction run under an oxygen atmosphere favors the hydroxylation, producing 70% of the hydroxylation product **7** (entry 10) as the major product.

Table 1. Optimization of $Cu(OAc)_2$-Mediated Oxidative C($sp^2$–H) Bond Alkynylation/Annulation[a]

4




**4a** **5a** **6a** **7a**

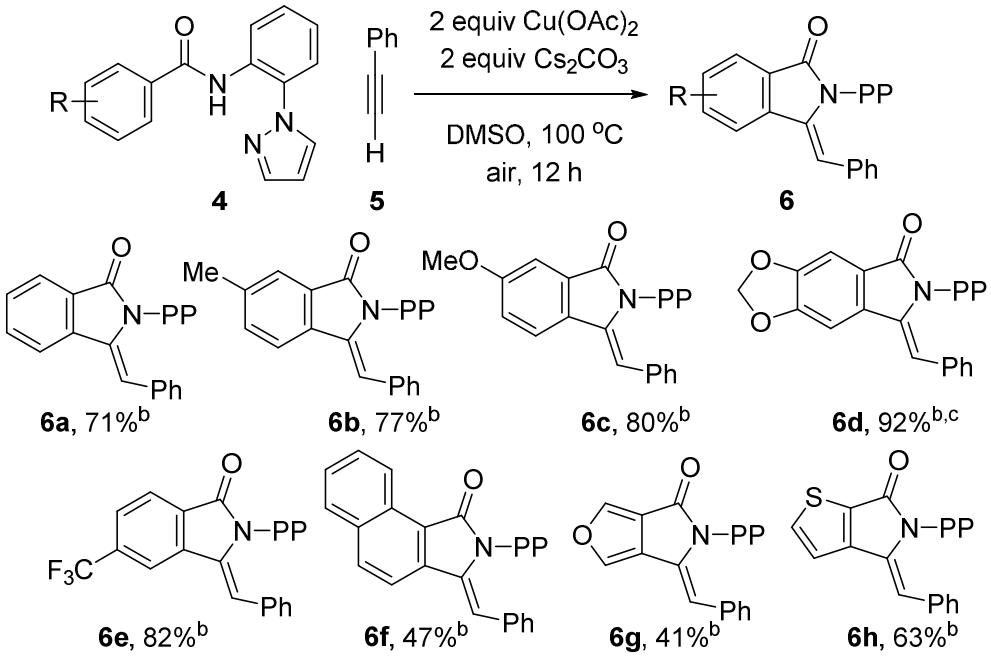
| Entry | Base | Additive | Temp. (ºC) | **6**, Yield (%)[b] | **7**, Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | – | 80 | 62 | 18 |
| 2 | TMG | – | 80 | 36 | 10 |
| 3 | $Cs_2CO_3$ | – | 80 | 23 | 74 |
| 4 | $Cs_2CO_3$ | pyridine | 80 | 25 | 6 |
| 5 | $Cs_2CO_3$ | TBAI | 80 | 32 | 6 |
| 6 | $Cs_2CO_3$ | NMO | 80 | 65 | 24 |
| 7 | $Cs_2CO_3$ | – | 120 | 45 | 0 |
| 8 | $Cs_2CO_3$ | – | 100 | **78** | **18** |
| 9 | $Cs_2CO_3$ | $N_2$ | 80 | 38 | 5 |
| 10 | $Cs_2CO_3$ | $O_2$ | 80 | 25 | 70 |

[a]The reactions were run with 2 equiv of $Cu(OAc)_2$, base, and additive in DMSO in open air for 12 h. [b]The yield determined by $^1H$ NMR analysis of crude reaction product using $CH_2Br_2$ as an internal standard.

After securing the optimal reaction conditions, we probed the scope of substrates. As shown in Table 2, this methodology accommodates substrates with both electron-donating substituents (**6a**–**6d**) and electron-withdrawing substituent (**6e**). In addition, the naphthalenyl substrate offered the isoindolinone derivative **6f** in moderate yield. Gratifyingly, this method also worked for heterocyclic substrates, giving rise to the corresponding furan- and thiophene-derivatives **6g** and **6h** in 41% and 63% yield, respectively.

Table 2. Substrate Scope for $Cu(OAc)_2$-Mediated Oxidative Alkynylation/Annulation[a]

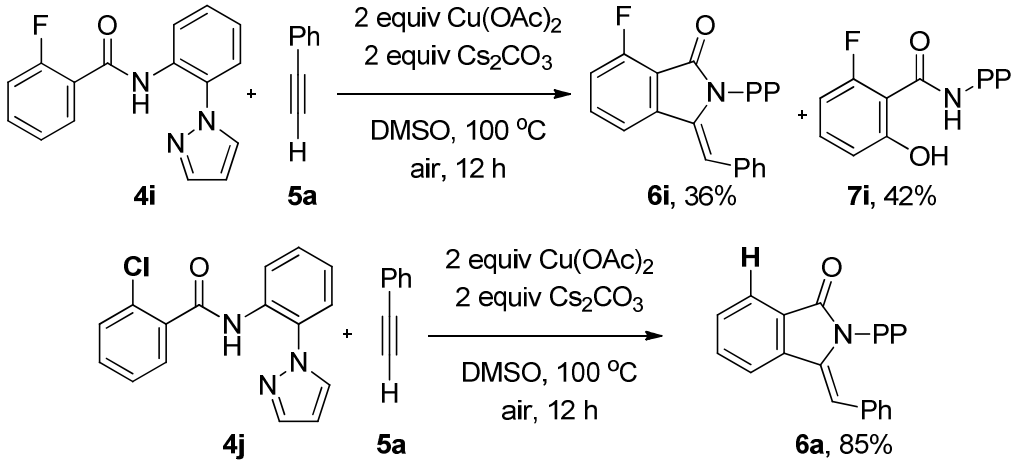
5




[a]Reaction conditions: Substrate **4** (0.19 mmol), phenylacetylene (**5a**, 3 equiv), $Cu(OAc)_2$, (2 equiv), $Cs_2CO_3$ (2 equiv) in DMSO at 100 °C overnight in open air. [b]Isolated yield.; [c]A mixture of 1:1 regioisomers onto the methylenedioxybenzene ring.

Interestingly, as shown in Scheme 1, when fluorine-substituted substrate **4i** was subjected to the standard reaction conditions, the hydroxylation product **7i** was isolated in 42% yield while the alkynylation/annulation product **6i** in only 36% yield. Indeed, we observed in the past that fluorine-substituted substrates are especially accommodating the aerobic oxidation reaction. Furthermore, when chlorine-substituted substrate **4j** was subjected to the standard reaction conditions, the dechlorinated isoindolinone **6a** was isolated as the predominant product. We speculate that the *ortho*-C–Cl bond on **4j** was much more readily activated (Scheme 1) in comparison to the *ortho*-C–H bond under the standard reaction conditions.

**Scheme 1.** Anomalies of the Methodology[a,b]

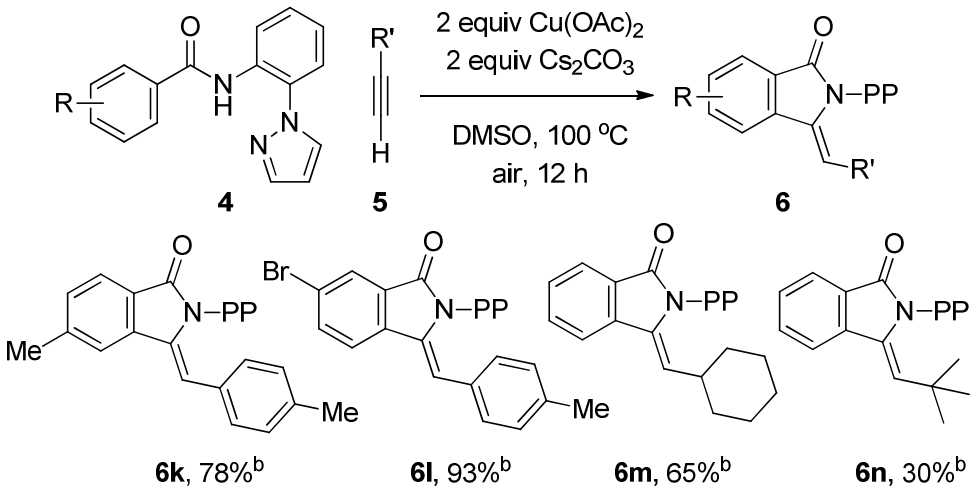


6

[a]Reaction conditions: Substrate **4** (0.19 mmol), phenylacetylene (**5**, 3 equiv), $Cu(OAc)_2$ (2 equiv), $Cs_2CO_3$ (2 equiv) in DMSO at 100 °C overnight in open air; [b]Isolated yield.

We also set out to gauge the scope for the terminal acetylenes. As shown in Table 3, the reaction works well for both aromatic acetylenes (**6k** and **6l**) and aliphatic acetylenes such as ethynylcyclohexane (**6m**). Intriguingly, when 3,3-dimethylbut-1-yne was used as the coupling partner, the alkynylation/annulation product **6n** was isolated only in 30% yield while the hydroxylation product **7a** was isolated as the major product in 62% yield. This outcome did not come as a complete surprise because the *tert*-butyl is so bulky and the steric hindrance retarded the annulation process thus allowing oxidation to proceed more rapidly.

Table 3. Terminal Acetylene Scope for $Cu(OAc)_2$-Mediated Alkynylation/Annulation[a]




[a]Reaction conditions: Substrate **4** (0.19 mmol), phenylacetylene (**5**, 3 equiv), $Cu(OAc)_2$ (2 equiv), $Cs_2CO_3$ (2 equiv) in DMSO at 100 °C overnight in open air; [b]Isolated yield.

Intrigued by the appearance of hydroxylation product **7**, we set out to optimize *its* production in the absence of terminal acetylenes. While Mother Nature can carry out chemo-, regio-, and stereoselective C–H hydroxylation with stunning precision using chromosome P450s,[12] C–H hydroxylation in the laboratory remains in its infancy. In 2006, Yu's group revealed a Cu(II)-catalyzed aryl C–H bond hydroxylation.[13] In 2014, Shi and coworkers disclosed a copper-mediated hydroxylation of arenes and heteroarenes directed by a removable bidentate auxiliary, 2-(pyridine-2-yl-isopropylamine (PIPamine, see Fig. 2).[14] In 2015, Yu's and Jiao's groups accomplished a similar feat using 2-(4,5-dihydrooxazol-2-yl)aniline (Oxa)[15] and oxime ether,[16] respectively, as the removable directing groups. More recently, chemists from groups of Wang and Li produced 2-(phenylthio)phenols using disulfide to direct C–H hydroxylation.[17] Finally, Yu's group described that monodentate oxazoline could serve as a

ligand to promote copper-mediated *ortho*-C–H hydroxylation and amination.[18] Intriguingly, Baidya et al. disclosed a copper-mediated etherification of arenes with alkoxysilane employing 2-APP as the removable directing group[19] shortly after our report on 2-APP-directed *ortho*-C–H amidation.[9] Remarkably, with an exception of reference 17 where palladium was the catalyst, all other metal-mediated *ortho*-C–H hydroxylation was carried out using *copper* salts.[20]

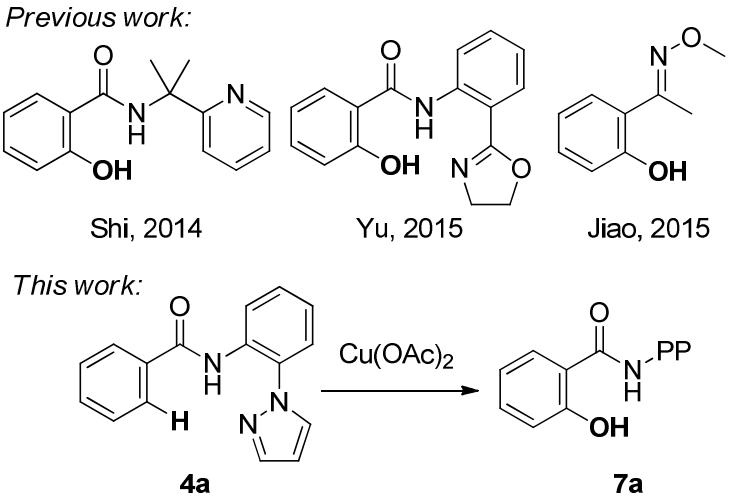
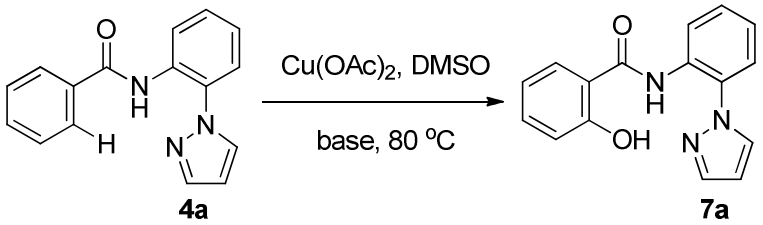



**Fig. 2.** *ortho*-C($sp^2$)–H hydroxylation directed by a removable auxiliary

Optimization for *ortho*-C–H hydroxylation of substrate **4a** was straightforward. As shown in Table 4, it was rapidly established that $Cu(OAc)_2$ and DMSO were the promoter and solvent of choice, respectively. In contrast to what we observed for **4a**'s C–H alkynylation/annulation, TMG now delivered the highest yield of phenol **7a**.

Table 4. Optimization of $Cu(OAc)_2$-Mediated Oxidative C($sp^2$–H) Bond Hydroxylation[a,b]



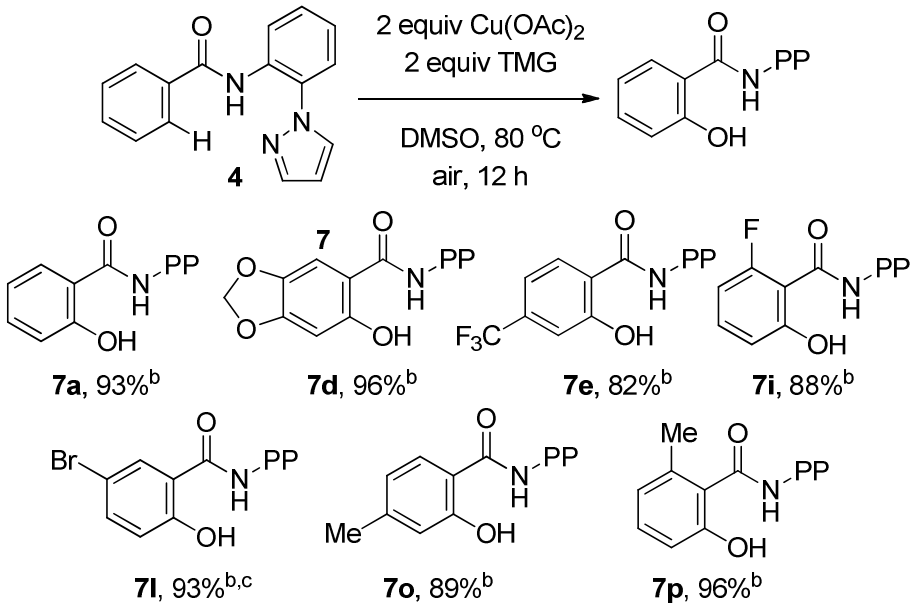

| Entry | Equiv $Cu(OAc)_2$ | Base (2 equiv) | Additive | **6**, Yield (%) |
|---|---|---|---|---|
| 1 | 1 | $Cs_2CO_3$ | – | 7 |
| 2 | 1 | TMG | – | 37 |
| 3 | 1 | TMG | NMO | 65 |
| 4 | 1 | TMG | $O_2$ | 52 |
| 5 | 2 | CsOAc | – | 90 |
| **6** | **2** | **TMG** | **–** | **97** |

8

[a]The yield determined by $^1$H NMR analysis of crude reaction product using $CH_2Br_2$ as an internal standard. [b]The reactions were run with 2 equiv of $Cu(OAc)_2$ and base in DMSO in open air for 12 h at 80 °C.

Under optimal hydroxylation conditions, arene substrates **4** were oxidized to the corresponding phenol **7** in good to excellent yield (82–96%, see Table 5) with the *o*-methoxyl-substituted substrate as an exception, giving rise to phenol **7a** in 51% yield. Unfortunately, heteroarene substrates containing furan, thiophene and pyridine core structures failed to be hydroxylated despite our extensive efforts.

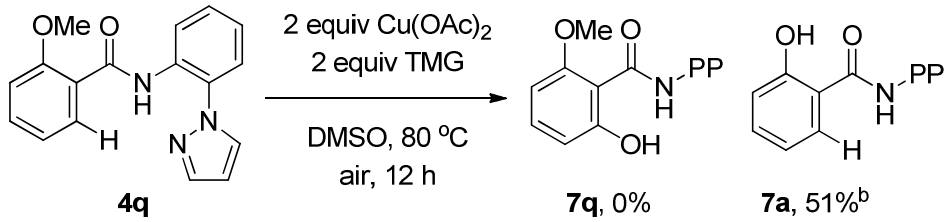
Table 5. Substrate Scope for $Cu(OAc)_2$-Mediated Oxidative *o*-Hydroxylation[a,b]




[a]Reaction conditions: Substrate **4** (0.19 mmol), $Cu(OAc)_2$, (2 equiv), TMG (2 equiv) in DMSO at 80 °C overnight in open air. [b]Isolated yield. [c]A mixture of 4:1 regioisomers of the two *ortho*-positions with the one shown (**7l**) as the major product.

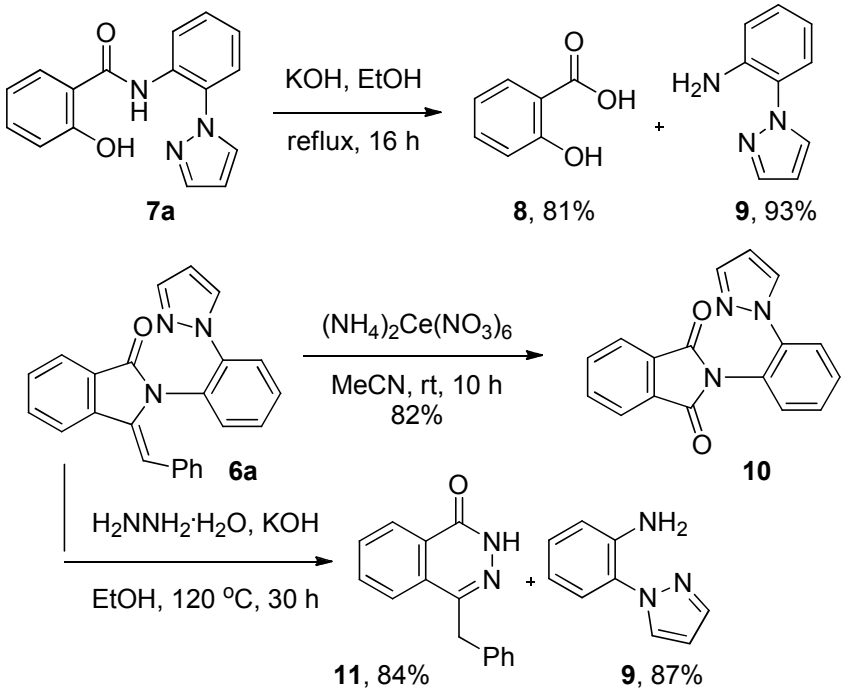
An intriguing reaction was observed in the process of evaluating $Cu(OAc)_2$-mediated oxidative *o*-hydroxylation. When substrate **4q** was subjected to our optimal reaction conditions for *ortho*-hydroxylation, no anticipated hydroxylation product **7q** was observed. Instead, as shown in Scheme 2, demethylation product **7a** was isolated in 51% yield.

**Scheme 2.** Demethylation in place of hydroxylation.




Removal of the 2-APP directing groups was an interesting journey. Indeed, as shown in Scheme 3, basic hydrolysis[21] of amide **7a** proceeded uneventfully to deliver salicyclic acid **8** in 81% yield, along with recovered auxiliary 2-APP **9** in 93% yield. Releasing the 2-APP directing groups from arylmethylene isoindolinone **6a** proved to be not trivial. No reaction was observed under strong acidic and basic hydrolysis conditions. Attempt using oxidative cleavage with cerium ammonium nitrate (CAN) gave rise to phthalidmide **10** in 82% yield, an interesting transformation worth noting on its own right. Hydrazinolysis[5,6] of **6a** recovered the 2-APP directing group in 87% yield along with phthalazin-1(2*H*)-one **11** in 84% yield.

**Scheme 3.** Removal of the directing group.




In summary, we discovered that 2-APP may serve as a viable bidentate directing group for copper-mediated aerobic oxidative C($sp^2$–H) bond alkynylation/annulation with terminal alkynes to produce arylmethylene isoindolinones. Meanwhile, in the absence terminal alkynes, a similar methodology has been developed to maximize *ortho*-selective C–H hydroxylation using $Cu(OAc)_2$ as the promoter and TMG as the base. Recovery of the 2-APP directing group was achieved by hydrazinolysis of the arylmethylene isoindolinones and basic hydrolysis for the hydroxylation products.

## Experimental Section

General procedures for the preparation of anilide substrates and data for most of **4** may be found in references 9 and 10 with exception of the following compounds:

***N*-(2-(1*H*-Pyrazol-1-yl)phenyl)-4-(trifluoromethyl)benzamide (4e)**

White solid, 1.49 g, 90% yield, mp: 103.9–104.4 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:6→1:3), $R_f$ = 0.62 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 11.58 (s, 1H), 8.72 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 2H), 7.90 (dd, *J* = 11.1, 2.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.43 (ddd, *J* = 16.5, 7.8, 1.4 Hz, 2H), 7.25 (td, *J* = 7.8, 1.4 Hz, 1H), 6.55 (t, *J* = 2.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.9, 141.2, 133.8–133.0 (q, *J* = 32.69 Hz), 131.3, 130.2, 129.0, 128.1, 127.7, 125.8–125.7 (q, *J* = 3.87 Hz), 126.9–120.4 (q, *J* = 272.1 Hz), 124.5, 122.9, 121.9, 107.4. $^{19}$F NMR (470 MHz, $CDCl_3$) δ –63.0. HRMS (ESI, m/z) calcd for $C_{17}H_{12}F_3N_3O$ [M+H]: 332.1004, found: 332.1002.

***N*-(2-(1*H*-Pyrazol-1-yl)phenyl)furan-3-carboxamide (4g)**

White solid, 1.09 g, 86% yield, mp: 137.4–138.3 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:6→1:3), $R_f$ = 0.33 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 11.06 (s, 1H), 8.66 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.04 (d, *J* = 1.3 Hz, 1H), 7.88 (dt, *J* = 3.5, 1.5 Hz, 2H), 7.48 (q, *J* = 1.6 Hz, 1H), 7.44–7.34 (m, 2H), 7.23–7.15 (m, 1H), 6.78 (t, *J* = 1.5 Hz, 1H), 6.54 (q, *J* = 1.9 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.6, 145.4, 143.9, 141.0, 131.5, 130.3, 128.6, 128.1, 123.9, 123.7, 122.7, 122.0, 108.4, 107.3. HRMS (ESI, m/z) calcd for $C_{14}H_{11}N_3O_2$ [M+H]: 254.0923, found: 254.0921.

***N*-(2-(1*H*-Pyrazol-1-yl)phenyl)-2-methoxybenzamide (4q)**

White solid, 1.19 g, 81% yield, mp: 84.4–85.7 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:6→1:3), $R_f$ = 0.37 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.63 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.81 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.45 (dddd, *J* = 8.6, 7.0, 5.0, 1.7 Hz, 2H), 7.30 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12–7.03 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.50 (t, *J* = 2.2 Hz, 1H), 4 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.8, 157.3, 140.9, 133.2, 133.2, 132.4, 130.8, 130.5, 128.8, 125.0, 124.0, 123.8, 121.9, 121.1, 111.2, 106.9, 55.7. HRMS (ESI, m/z) calcd for $C_{17}H_{15}N_3O_2$ [M+H]: 294.1236, found: 294.1235.

**General Procedures for the C–H Alkynylation/Annulation**

A 10 mL microwave vial was charged with the substrate **4** (0.19 mmol), then was added the arylacetylene **5** (0.57 mmol), copper acetate (0.38 mmol) and $Cs_2CO_3$ (0.38 mmol). After adding the solvent DMSO (2 mL), the reaction was heated at 100 °C open to air. After stirring at 100 °C for 12 h, the reaction was judged complete by TLC, the reaction mixture was filtered.

The filtrate was washed with saturated ammonium chloride, and brine, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired product **6**.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-benzylideneisoindolin-1-one (6a)**

Yellow solid, 0.049 g, 71% yield, mp: 216.3–217.1 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.45 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, $J$ = 7.6 Hz, 1H), 7.76 (d, $J$ = 7.7 Hz, 1H), 7.65 (t, $J$ = 7.5 Hz, 1H), 7.57–7.48 (m, 2H), 7.45 (d, $J$ = 2.4 Hz, 1H), 7.31–7.17 (m, 3H), 7.12 (td, $J$ = 7.6, 1.6 Hz, 1H), 7.04–6.93 (m, 5H), 6.65 (s, 1H), 6.28 (t, $J$ = 2.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.1, 140.9, 138.8, 137.5, 134.1, 132.9, 132.4, 130.7, 129.9, 129.6, 129.1, 129.0, 128.7, 127.5, 127.4, 127.1, 126.6, 125.0, 123.9, 119.4, 107.6, 106.6. HRMS (ESI, m/z) calcd for $C_{24}H_{17}N_3O$ [M+H]: 364.1444, found: 364.1452.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-benzylidene-6-methylisoindolin-1-one (6b)**

Yellow solid, 0.055 g, 77% yield, mp: 121.8–123.3 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.38 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.63 (d, $J$ = 7.9 Hz, 1H), 7.51 (d, $J$ = 1.6 Hz, 1H), 7.45 (dd, $J$ = 6.9, 1.9 Hz, 2H), 7.31–7.27 (m, 1H), 7.26–7.16 (m, 2H), 7.12 (td, $J$ = 7.7, 1.5 Hz, 1H), 7.02–6.90 (m, 5H), 6.59 (s, 1H), 6.27 (t, $J$ = 2.1 Hz, 1H), 2.50 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.2, 140.9, 139.4, 137.5, 136.4, 134.2, 133.5, 133.1, 130.7, 130.0, 129.6, 129.2, 129.1, 128.7, 127.7, 127.38, 127.1, 126.5, 125.0, 124.0, 119.3, 106.9, 106.6, 21.6. HRMS (ESI, m/z) calcd for $C_{25}H_{19}N_3O$ [M+H]: 378.1600, found: 378.1602.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-benzylidene-6-methoxyisoindolin-1-one (6c)**

Yellow solid, 0.060 g, 80% yield, mp: 150.6–152.1 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.31 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, $J$ = 8.5 Hz, 1H), 7.52 (d, $J$ = 1.7 Hz, 1H), 7.45 (d, $J$ = 2.4 Hz, 1H), 7.36 (d, $J$ = 2.5 Hz, 1H), 7.27–7.16 (m, 4H), 7.11 (td, $J$ = 7.6, 1.5 Hz, 1H), 7.01–6.90 (m, 5H), 6.53 (s, 1H), 6.28 (t, $J$ = 2.2 Hz, 1H), 3.91 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.1, 160.9, 140.9, 137.4, 134.0, 133.1, 131.7, 130.7, 123.0, 129.6, 129.01, 128.7, 128.7, 128.6, 128.5, 127.4, 127.1, 126.5, 125.0, 121.23, 120.8, 106.6, 105.9, 55.8. HRMS (ESI, m/z) calcd for $C_{25}H_{19}N_3O_2$ [M+H]: 394.1549, found: 394.1550.

**(*Z*)-6-(2-(1*H*-Pyrazol-1-yl)phenyl)-7-benzylidene-6,7-dihydro-5*H*-[1,3]dioxolo[4,5-*f*]isoindol-5-one (6d)**

Yellow solid, 0.071 g, 92% yield (a mixture of 1:1 regioisomers onto the methylenedioxybenzene ring), mp: 93.7–95.8 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.19 [ethyl acetate/hexanes (1: 2)] (a mixture of 1:1 regioisomers) $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, $J$ = 10.0, 1.7 Hz, 2H), 7.51–7.45 (m, 2H), 7.43 (d, $J$ = 2.4 Hz, 1H), 7.23–7.15 (m, 3H), 7.14–7.09 (m, 3H), 6.99–6.96 (m, 2H), 6.95–6.92 (m, 5H), 6.69 (s, 1H), 6.43 (s, 1H), 6.29 (dt, $J$ = 11.2, 2.1 Hz, 2H), 6.21 (s, 2H), 6.12 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.7, 167.4, 152.2, 151.8, 149.3, 140.9, 140.8, 137.4, 137.4, 135.0, 134.0, 133.2, 132.9, 131.6, 130.7, 130.6, 130.0, 129.9, 129.6, 129.6, 129.1, 129.0, 128.7, 128.6, 127.4, 127.4, 127.01, 127.1, 126.6, 126.6, 125.0, 125.0, 122.6, 122.1, 120.6, 118.9, 111.7, 109.1, 107.1, 106.6, 106.5, 103.1, 102.7, 102.2, 99.6. HRMS (ESI, m/z) calcd for $C_{25}H_{17}N_3O_3$ [M+H]: 408.1342, found: 408.1341.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-benzylidene-5-(trifluoromethyl)isoindolin-1-one (6e)**

Yellow solid, 0.067 g, 82% yield, mp: 79.2–82.2 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.47 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, $J$ = 11.2 Hz, 2H), 7.77 (dd, $J$ = 8.0, 1.3 Hz, 1H), 7.47–7.43 (m, 1H), 7.38 (d, $J$ = 2.4 Hz, 1H), 7.23 (qd, $J$ = 8.1, 7.6, 1.5 Hz, 3H), 7.16 (td, $J$ = 7.5, 1.8 Hz, 1H), 7.07–6.92 (m, 5H), 6.71 (s, 1H), 6.29 (t, $J$ = 2.0 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.8, 141.2, 139.0, 137.1, 134.6– 133.8 (q, $J$ = 32.51 Hz), 133.1, 132.3, 130.7, 130.2, 129.6, 129.6, 129.1, 129.0, 128.6, 127.6, 127.12, 127.01, 125.8–125.7 (q, $J$ = 3.6 Hz), 124.8, 124.6, 122.7, 116.9–116.8 (q, $J$ = 4.0 Hz), 109.2, 106.7. $^{19}$F NMR (470 MHz $CDCl_3$) δ –62.5. HRMS (ESI, m/z) calcd for $C_{25}H_{16}F_3N_3O$ [M+H]: 432.1317, found: 432.1320.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-benzylidene-2,3-dihydro-1*H*-benzo[*e*]isoindol-1-one (6f)**

Yellow solid, 0.037 g, 47% yield, mp: 167.3–168.5 ºC, flash chromatography eluting with dichloromethane/hexanes (1:4), $R_f$ = 0.33 ($CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, $J$ = 8.3 Hz, 1H), 8.08 (d, $J$ = 8.5 Hz, 1H), 7.96 (d, $J$ = 8.2 Hz, 1H), 7.79 (d, $J$ = 8.5 Hz, 1H), 7.70 (ddd, $J$ = 8.3, 6.8, 1.3 Hz, 1H), 7.61 (ddd, $J$ = 8.2, 6.9, 1.3 Hz, 1H), 7.46 (dd, $J$ = 9.9, 2.1 Hz, 2H), 7.32 (td, $J$ = 7.8, 1.7 Hz, 1H), 7.30–7.23 (m, 2H), 7.20 (td, $J$ = 7.5, 1.8 Hz, 1H), 7.07–6.94 (m, 5H), 6.73 (s, 1H), 6.23 (t, $J$ = 2.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.0, 140.9, 138.8, 137.6, 134.4, 133.7, 133.1, 132.9, 131.0, 130.0, 129.6, 129.2, 129.1, 128.7, 128.5, 128.2, 127.4, 127.1, 126.9, 125.1, 124.5, 121.3, 116.8, 109.4, 106.6. HRMS (ESI, m/z) calcd for $C_{28}H_{19}N_3O$ [M+H]: 414.1600, found: 414.1601.

**(*Z*)-5-(2-(1*H*-Pyrazol-1-yl)phenyl)-6-benzylidene-5,6-dihydro-4*H*-furo[3,4-*c*]pyrrol-4-one (6g)**

Yellow solid, 0.028g, 41% yield, mp: 76.4–77.8 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.09 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, $J$ = 14.5, 1.9 Hz, 2H), 7.51–7.43 (m, 2H), 7.39–7.28 (m, 3H), 7.23–7.16 (m, 1H), 7.12 (dd, $J$ = 8.3, 6.8 Hz, 2H), 7.05 (d, $J$ = 2.0 Hz, 1H), 6.98–6.88 (m, 2H), 6.53 (s, 1H), 6.29 (t, $J$ = 2.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.2, 159.8, 146.4, 143.6, 140.9, 138.0, 134.7, 131.8, 131.7, 129.9, 129.5, 129.0, 128.6, 127.6, 127.6, 125.5, 114.8, 107.8, 107.2, 98.0. HRMS (ESI, m/z) calcd for $C_{22}H_{15}N_3O_2$ [M+H]: 354.1236, found: 354.1233.

**(*Z*)-5-(2-(1*H*-Pyrazol-1-yl)phenyl)-4-benzylidene-4,5-dihydro-6*H*-thieno[2,3-*c*]pyrrol-6-one (6h)**

Yellow solid, 0.044 g, 63% yield, mp: 172.9–174.0 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.15 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, $J$ = 5.1 Hz, 1H), 7.57 (d, $J$ = 1.7 Hz, 1H), 7.53–7.44 (m, 2H), 7.36 (dp, $J$ = 8.7, 4.6 Hz, 1H), 7.30 (d, $J$ = 4.4 Hz, 2H), 7.24 (d, $J$ = 5.1 Hz, 1H), 7.21–7.17 (m, 1H), 7.12 (t, $J$ = 7.5 Hz, 2H), 6.96–6.90 (m, 2H), 6.62 (s, 1H), 6.28 (s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.3, 145.3, 145.3, 140.9, 138.0, 134.9, 134.3, 131.7, 131.6, 123.0, 129.5, 129.2, 128.9, 128.4, 127.6, 127.5, 125.5, 124.5, 107.2, 105.0. HRMS (ESI, m/z) calcd for $C_{22}H_{15}N_3OS$ [M+H]: 370.1008, found: 370.1011.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-benzylidene-7-fluoroisoindolin-1-one (6i)**

Yellow solid, 0.026 g, 36% yield (the hydroxylation product **7i** was isolated in 42% while the alkynylation/annulation product **6i** in 36% yield, respectively), mp: 203.7–206.9 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.37 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.07–8.00 (m, 1H), 7.63–7.49 (m, 4H), 7.44 (d, $J$ = 2.4 Hz, 1H), 7.26–7.23 (m, 2H), 7.22–7.20 (m, 1H), 7.18–7.12 (m, 2H), 6.99–6.93 (m, 3H), 6.65 (s, 1H), 6.29 (t, $J$ = 2.1 Hz, 1H). $^{19}$F NMR (470 MHz, $CDCl_3$) δ –116.4. HRMS (ESI, m/z) calcd for $C_{24}H_{16}FN_3O$ [M+ H]: 382.1349, found: 382.1351.

**General Procedures for the Alkynylation/Annulation with various terminal alkynes**

A 10 mL microwave vial was charged with substrate **4** (0.19 mmol), then was added terminal alkyne **5** (0.57 mmol), copper acetate (0.38 mmol) and $Cs_2CO_3$ (0.38 mmol). After adding the solvent DMSO (2 mL), the reaction was heated at 100 °C open to air. After stirring at 100 °C for 12 h, the reaction was judged complete by TLC, the reaction mixture was filtered. The filtrate was washed with saturated ammonium chloride, and brine, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired product **6**.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-5-methyl-3-(4-methylbenzylidene)isoindolin-1-one (6k)**

Yellow solid, 0.058 g, 78% yield, mp: 118.8–120.0 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.33 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, $J$ = 7.8 Hz, 1H), 7.55–7.50 (m, 2H), 7.45–7.41 (m, 2H), 7.34–7.28 (m, 2H), 7.26–7.19 (m, 2H), 6.83–6.74 (m, 4H), 6.58 (s, 1H), 6.26 (t, $J$ = 2.0 Hz, 1H), 2.52 (s, 3H), 2.21 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.3, 143.1, 140.8, 139.4, 139.3, 136.4, 133.6, 132.4, 130.7, 130.1, 129.7, 129.2, 129.2, 129.0, 128.5, 127.8, 127.4, 125.1, 123.8, 119.7, 107.6, 106.6, 22.2, 21.2. HRMS (ESI, m/z) calcd for $C_{26}H_{21}N_3O$ [M+H]: 392.1757, found: 392.1755.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-6-bromo-3-(4-methylbenzylidene)isoindolin-1-one (6l)**

Yellow solid, 0.081 g, 94% yield, mp: 166.4–170.1 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.53 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, $J$ = 1.7 Hz, 1H), 7.73 (dd, $J$ = 8.2, 1.8 Hz, 1H), 7.59 (d, $J$ = 8.2 Hz, 1H), 7.47 (d, $J$ = 1.7 Hz, 1H), 7.38 (d, $J$ = 2.4 Hz, 1H), 7.29–7.20 (m, 3H), 7.16 (ddd, $J$ = 8.3, 6.4, 2.4 Hz, 1H), 6.82 (d, $J$ = 7.9 Hz, 2H), 6.76 (d, $J$ = 7.9 Hz, 2H), 6.57 (s, 1H), 6.27 (t, $J$ = 2.1 Hz, 1H), 2.21 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.6, 141.0, 137.6, 137.3, 136.8, 135.2, 132.9, 130.6, 129.9, 129.6, 129.6, 129.2, 129.0, 128.7, 127.9, 127.5, 126.9, 125.0, 122.7, 121.0, 108.7, 106.6, 21.2. HRMS (ESI, m/z) calcd for $C_{25}H_{18}BrN_3O$ [M+H]: 456.0705, found: 456.0705.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-(cyclohexylmethylene)isoindolin-1-one (6m)**

Yellow solid, 0.046 g, 65% yield, mp: 133.2–135.7 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.46 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91–7.80 (m, 2H), 7.66–7.55 (m, 5H), 7.52–7.41 (m, 3H), 6.21 (t, $J$ = 2.2 Hz, 1H), 5.39 (d, $J$ = 10.8 Hz, 1H), 1.65–1.53 (m, 3H), 1.42–1.30 (m, 3H), 1.00–0.85 (m, 4H), 0.70 (dddd, $J$ = 16.4, 13.1, 8.2, 3.7 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.4, 141.0, 139.6, 138.5, 132.3, 132.2, 130.8, 130.3, 130.1, 129.7, 128.4, 128.1, 127.4, 126.0, 123.6, 119.2, 116.6, 107.3, 34.6, 33.2, 33.0, 25.7, 25.6, 25.5. HRMS (ESI, m/z) calcd for $C_{24}H_{23}N_3O$ [M+H]: 370.1913, found: 370.1912.

**(*Z*)-2-(2-(1*H*-Pyrazol-1-yl)phenyl)-3-(2,2-dimethylpropylidene)isoindolin-1-one (6n)**

Yellow solid, 0.045 g, 69% yield, mp: 175.4–177.0 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:3), $R_f$ = 0.41 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92–7.80 (m, 2H), 7.68–7.64 (m, 2H), 7.64–7.53 (m, 3H), 7.51–7.40 (m, 3H), 6.23 (t, $J$ = 2.1 Hz, 1H), 5.70 (s, 1H), 0.86 (s, 9H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.5, 140.9, 140.8, 139.4, 132.4, 132.4, 131.8, 131.3, 130.1, 129.7, 128.4, 127.8, 126.4, 126.1, 123.8, 121.3, 119.0, 107.2, 32.5, 31.3. HRMS (ESI, m/z) calcd for $C_{22}H_{21}N_3O$ [M+H]: 344.1757, found: 344.1755.

**General Procedures for the C–H Hydroxylation**

A 10 mL microwave vial was charged with the substrate **4** (0.19 mmol) in DMSO (2 mL), then was added the copper acetate (0.38 mmol) and 1,1,3,3,-tetramethylguanidine(TMG) (0.38 mmol). The reaction was heated at 80 °C open to air. After stirring at 80 °C for 12 h, the reaction was judged complete by TLC, the reaction mixture was filtered. The filtrate was washed with saturated ammonium chloride and brine, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash chromatography to give the desired product **7**.

***N*-(2-(1*H*-Pyrazol-1-yl)phenyl)-6-hydroxybenzo[*d*][1,3]dioxole-5-carboxamide (7d)**

White solid, 0.059 g, 96% yield, mp: 202.4–203.4 ºC, flash chromatography eluting with dichloromethane/hexanes (4:1), $R_f$ = 0.53 ($CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$) δ 12.28 (s, 1H), 11.53 (s, 1H), 8.55–8.50 (m, 1H), 7.90 (t, *J* = 2.7 Hz, 2H), 7.42 (dd, *J* = 9.4, 7.2 Hz, 2H), 7.29–7.25 (m, 2H), 6.58–6.48 (m, 2H), 6.08 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.5, 152.4, 146.8, 141.2, 135.0, 130.6, 130.2, 129.4, 127.9, 124.6, 123.4, 122.1, 120.9, 111.5, 107.4, 102.4, 100.6. HRMS (ESI, m/z) calcd for $C_{17}H_{13}N_3O_4$ [M+H]: 324.0978, found: 324.0976.

***N*-(2-(1*H*-Pyrazol-1-yl)phenyl)-2-hydroxy-4-(trifluoromethyl)benzamide (7e)**

White solid, 0.054 g, 82% yield, mp: 120.2–121.0 ºC, flash chromatography eluting with dichloromethane/hexanes (4:1), $R_f$ = 0.66 ($CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$) δ 12.41 (s, 1H), 11.93 (s, 1H), 8.57 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.93 (dd, *J* = 3.9, 2.2 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.44 (ddd, *J* = 7.4, 4.0, 2.5 Hz, 2H), 7.32–7.26 (m, 2H), 7.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.57 (t, *J* = 2.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.6, 162.2, 141.2, 136.2–135.4 (q, *J* = 32.9 Hz), 130.2, 130.1, 129.4, 127.9, 126.8, 126.5–120.0 (q, *J* = 273.1 Hz), 125.2, 123.5, 121.8, 117.7, 116.1–116.0 (q, *J* = 3.9 Hz), 115.3–115.2 (q, *J* = 3.57 Hz), 107.6. $^{19}$F NMR (470 MHz, $CDCl_3$) δ –63.7. HRMS (ESI, m/z) calcd for $C_{17}H_{12}F_3N_3O_2$ [M+H]: 348.0954, found: 348.0955.

***N*-(2-(1*H*-Pyrazol-1-yl)phenyl)-5-bromo-2-hydroxybenzamide (7l)**

White solid, 0.063 g, 93% yield (a mixture of 4:1 regioisomers of the two *ortho*-positions with the one (**7l**) as the major product), mp: 164.4–166.8 ºC, flash chromatography eluting with dichloromethane/hexanes (4:1), $R_f$ = 0.71 ($CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$) δ 12.21 (s, 1H), 11.95 (s, 1H), 8.59 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 1.8 Hz, 1H), 7.95–7.89 (m, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.51 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.43 (td, *J* = 8.2, 3.5 Hz, 2H), 7.28 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.59 (t, *J* = 2.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.4, 161.1, 141.3, 137.0, 130.2, 130.1, 129.0, 127.9, 125.0, 124.9, 123.1, 121.7,

120.6, 119.5, 110.5, 107.7. HRMS (ESI, m/z) calcd for $C_{16}H_{12}BrN_3O_2$ [M+H]: 358.0185, found: 358.0186.

**_N_-(2-(1_H_-Pyrazol-1-yl)phenyl)-2-hydroxy-4-methylbenzamide (7o)**

White solid, 0.050 g, 89% yield, mp: 120.6–121.6 ºC, flash chromatography eluting with dichloromethane/hexane (4:1), $R_f$ = 0.59 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 12.21 (d, $J$ = 0.7 Hz, 1H), 11.53 (s, 1H), 8.54 (dd, $J$ = 8.2, 1.3 Hz, 1H), 7.90 (dd, $J$ = 10.5, 2.2 Hz, 2H), 7.54 (d, $J$ = 8.2 Hz, 1H), 7.46–7.38 (m, 2H), 7.24 (ddd, $J$ = 8.4, 7.5, 1.4 Hz, 1H), 6.84–6.80 (m, 1H), 6.76 (dd, $J$ = 8.3, 1.6 Hz, 1H), 6.54 (s, 1H), 2.36 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.7, 162.2, 145.6, 141.2, 130.7, 130.2, 129.5, 127.9, 125.9, 124.6, 123.5, 122.1, 120.2, 118.8, 112.3, 107.4, 21.7. HRMS (ESI, m/z) calcd for $C_{17}H_{15}N_3O_2$ [M+H]: 294.1236, found: 294.1233.

**_N_-(2-(1_H_-Pyrazol-1-yl)phenyl)-2-hydroxy-6-methylbenzamide (7p)**

White solid, 0.053 g, 96% yield, mp: 136.3–137.3 ºC, flash chromatography eluting with dichloromethane/hexane (4:1), $R_f$ = 0.28 ($CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 10.27 (s, 1H), 8.53 (dd, $J$ = 8.3, 1.3 Hz, 1H), 7.83 (d, $J$ = 2.4 Hz, 1H), 7.75 (d, $J$ = 1.9 Hz, 1H), 7.45 (ddd, $J$ = 8.6, 7.5, 1.5 Hz, 1H), 7.38 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.27–7.22 (m, 2H), 6.84 (d, $J$ = 8.2 Hz, 1H), 6.76 (d, $J$ = 7.5 Hz, 1H), 6.50 (t, $J$ = 2.2 Hz, 1H), 2.58 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.7, 159.8, 141.5, 136.1, 132.5, 130.6, 130.1, 129.9, 128.0, 125.0, 123.9, 122.9, 122.8, 118.7, 115.4, 107.5, 21.6. HRMS (ESI, m/z) calcd for $C_{17}H_{15}N_3O_2$ [M+H]: 294.1236, found: 294.1233.

**Procedures for Removal of the Directing Group**

To a solution of the **7a** (0.21 mmol) and KOH (2.10 mmol) was added EtOH (3 mL). After refluxing for 16 h, the reaction was judged complete by TLC. After filtration via a pad of Celite, the filtrate was washed with 1M HCl and saturated brine, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired acid **8** as a white solid. **2-Hydroxybenzoic acid (8)** White solid, 0.024g, 81% yield, mp: 159.5–160.1 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:6→1:2), $R_f$ = 0.41 [ethyl acetate/hexanes (1:2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.95 (dd, $J$ = 8.0, 1.7 Hz, 1H), 7.54 (ddd, $J$ = 8.8, 7.1, 1.8 Hz, 1H), 7.03 (dd, $J$ = 8.4, 1.0 Hz, 1H), 6.96 (ddd, $J$ = 8.2, 7.2, 1.1 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.9, 162.2, 137.0, 131.0, 119.6, 117.8, 111.3. HRMS (ESI, m/z) calcd for $C_7H_6O_3$ [M+H]: 139.0389, found: 139.0394.

**2-(2-(1_H_-Pyrazol-1-yl)phenyl)isoindoline-1,3-dione (10)**

To a solution of the **6a** (0.13 mmol) and CAN (1.30 mmol) was added MeCN (2 mL). After stirring for 10 h, the reaction was judged complete by TLC. The filtrate was extracted with $NH_4Cl$ and saturated brine, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired product **10** as a pale yellow solid, 0.031 g, 82% yield, mp: 130.3–132.0 ºC, flash chromatography eluting with ethyl acetate/hexanes (1:8→1:2), $R_f$ = 0.35 [ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, $J$ = 5.5, 3.0 Hz, 2H), 7.76 (dd, $J$ = 5.5, 3.1 Hz, 2H), 7.70 (d, $J$ = 2.4 Hz, 1H), 7.63–7.57 (m, 2H), 7.57–7.52 (m, 1H), 7.52 – 7.42 (m, 2H), 6.33 (t, $J$ = 2.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.0, 141.5, 137.76, 134.1, 132.1, 130.9, 130.1, 129.6, 128.31, 125.8, 125.2, 123.8, 107.1. HRMS (ESI, m/z) calcd for $C_{17}H_{11}N_3O_2$ [M+H]: 290.0923, found: 290.0922.

**4-Benzylphthalazin-1(2*H*)-one (11)**

To a solution of the **6a** (0.13 mmol), $N_2H_4$•$H_2O$ (1.30 mmol) and KOH (1.30 mmol) was added EtOH (3 mL). After stirring at 120 ºC for 30 h, the reaction was judged complete by TLC. The filtrate was washed with 1 M HCl and saturated brine, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired product **11** as a pale yellow solid, 0.026g, 84% yield, mp: 194.2–195.6 ºC flash chromatography eluting with ethyl acetate/hexanes (1:8→1:1), $R_f$ = 0.18 ([ethyl acetate/hexanes (1: 2)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 11.08 (s, 1H), 8.53–8.45 (m, 1H), 7.81–7.70 (m, 3H), 7.30 (d, $J$ = 4.4 Hz, 4H), 7.25–7.21 (m, 1H), 4.33 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.8, 146.4, 137.6, 133.4, 131.3, 129.8, 128.7, 128.5, 128.3, 127.0, 126.8, 125.4, 38.9. HRMS (ESI, m/z) calcd for $C_{15}H_{12}N_2O$ [M+H]: 237.1022, found: 237.1018.

**Supporting Information**

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

**References**

1. Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2003,** *59*, 6615.
2. Muller, G. W.; Chen, R.; Huang, S. H.; Corral, L. G.; Wong, L. M.; Patterson, R. T.; Chen, Y.; Kaplan, G.; Stirling, D. I. *Bioorg. Med. Chem. Lett*. **1999,** *9*, 1625.
3. Menear, K. A.; Adcock, C.; Boulter, R.; Cockcroft, X.-l.; Copsey, L.; Cranston, A.; Dillon, K. J.; Drzewiecki, J.; Garman, S.; Gomez, S.; Javaid, H.; Kerrigan, F.; Knights, C.; Lau, A.; Loh, Jr.; V. M.; Mathews, I. T. W.; Moore, S.; O'Connor, M. J.; Smit, G. C.

18
M.; Matin, N. M. B. *J. Med. Chem.* **2008,** *51*, 6581.
4. Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014,** *16,* 2884.
5. Zhang, Y.; Wang, Q.; Yu, H.; Huang, Y. *Org. Biomol. Chem.* **2014,** *12*, 8844.
6. Zhu, W.; Wang, B.; Zhou, S.; Liu, H. *Beilstein J. Org. Chem.* **2015,** *11*, 1624.
7. (a) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc*. **2015,** *137*, 12990. (b) Zhang, J.; Li, Z.; Chen, H.; Wang, B.; Liu, Z. *Adv. Synth. Catal.* **2016,** *358*, 792. (c) Lin, C.; Zhang, J.; Chen, Z.; Liu, Y.; Zhang, Y. *Adv. Synth. Catal.* **2016,** *358*, 1778.
8. (a) Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. *Angew. Chem. Int. Ed*. **2015,** *54*, 10012. (b) Zheng, X.-X.; Du, C.; Zhao, X.-M.; Zhu, X.; Suo, J.-F.; Hao, X.-Q.; Niu, J.-L.; Song, M.-P. *J. Org. Chem*. **2016,** *81*, 4002. (c) Hao, X.-Q.; Du, C.; Zhu, X.; Li, P.-X.; Zhang, J.-H.; Niu, J.-L.; Song, M.-P. *Org. Lett*. **2016,** *18*, 3610.
9. Lee, W. C. C.; Shen, Y.; Gutierrez, D. A.; Li, J. J. *Org. Lett.* **2016**, *18*, 2660.
10. Lee, W.-C. C.; Tehrani, A.; Li, J. J. *Synthesis* **2017,** *49,* 2865.
11. Shen, Y.; Lee, W. C. C.; Gutierrez, D. A.; Li, J. J. *J. Org. Chem.* **2017**, in press.
12. Ortiz de Montellano, P. R. *Chem. Rev.* **2010,** *110*, 932.
13. Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006,** *128*, 6790.
14. Li, X.; Liu, Y.-H.; Gu, W.-J.; Li, B.; Chen, F.-J.; Shi, B.-F. *Org. Lett.* **2014,** *16,* 3904.
15. Sun, S.-Z.; Shang, M.; Wang, H.-L.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. *J. Org. Chem.* **2015,** *80,* 8843.
16. Liang, Y.-F.; Wang, X.; Yuan, Y.; Liang, Y.; Li, X.; Jiao, N. *ACS Catal.* **2015,** *5,* 6148.
17. Wang, L.; Xie, Y.-B.; Huang, N.-Y.; Zhang, N.-N.; Li, D.-J.; Hu, Y.-L.; Liu, M.-G.; Li, D.-S. *Adv. Synth. Catal.* **2017,** *359*, 779.
18. Shang, M.; Shao, Q.; Sun, S.-Z.; Chen, Y.-Q.; Xu, H.; Dai, H.-X.; Yu, J.-Q. *Chem. Sci.* **2017,** *8,* 1469.
19. Selvakumar, J.; Grandhi, G. S.; Sahoo, H.; Baidya, M. *RSC Adv.* **2016,** *6,* 79361.
20. (a) Ahmad, N. M. *Copper-Mediated C–H Activation*. In *C-H Bond Activation in Organic Synthesis*; Li, J. J., Ed.; CRC: Boca Raton, FL, 2015, pp. 175–215. (b) Cai, X.-h.; Xie, B. *Synthesis* **2015,** *47*, 737–759. (c) Evano, G.; Blanchard, N. *Copper-Mediated Cross-Coupling Reactions*; Wiley: Hoboken, NJ, 2013.
21. Basic hydrolysis to remove directing groups: (a) Truong, T.; Klimovica, K.; Daugulis,

O. *J. Am. Chem. Soc.* **2013,** *135*, 9342. (b) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016,** *138*, 4601. (c) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014,** *136*, 3354.