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Copper-Mediated Tandem Oxidative C(sp^2)−H/C(sp)−H Alkynylation and Annulation of Arenes with Terminal Alkynes

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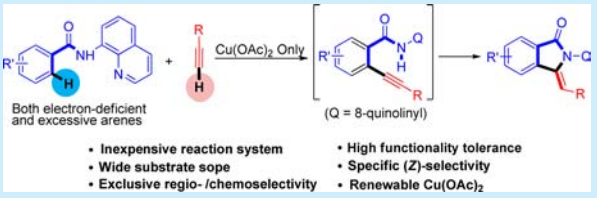
Supporting Information

ABSTRACT: The copper-mediated tandem oxidative C(sp^2)−H/C(sp)−H cross-coupling and intramolecular annulation of arenes with terminal alkynes has been developed, which offers a highly efficient approach to the 3-methyleneisoindolin-1-one scaffold. In this oxidative coupling process, $Cu(OAc)_2$ acts as both the promoter and the terminal oxidant. This protocol features a wide substrate scope; high functional group tolerance; exclusive chemo-, regio-, and stereoselectivity; and simple, easily available, and inexpensive reaction system. The transformation has demonstrated for the first time that $Cu(OAc)_2$ can be renewable after undergoing an oxidative reaction.



Over the past years, the transition-metal-catalyzed oxidative C−H/C−H cross-coupling reactions have emerged as a powerful tool for the formation of C−C bonds and have become one of the hottest research topics in synthetic organic chemistry.[1] In general, these types of transformations require high-priced precious metal catalysts such as Rh, Pd, and Ru in combination with a stoichiometric amount of metal oxidant including copper and silver salt. From a practical and industrial viewpoint, it would be highly appealing and desirable to explore inexpensive and abundant alternatives that are endowed with high catalytic performance, versatility, and excellent and complementary chemo- and regioselectivity. Recently, Miura and Yu independently disclosed the stoichiometric copper-promoted oxidative cross-coupling reactions between two (hetero)arenes through a 2-fold C(sp^2)−H cleavage to forge the (hetero)aryl−(hetero)aryl scaffolds without the assistance of other precious metal catalysts.[2] Lei described the stoichiometric silver-promoted oxidative C(sp^3)−H/C(sp)−H functionalization of 1,3-dicarbonyl compounds with terminal alkynes for the construction of polysubstituted furans and pyrroles.[3] These pioneering works have demonstrated that a stoichiometric amount of copper or silver salt can serve as both the promoter and the terminal oxidant. Undoubtedly, these less expensive and easily available stoichiometric systems would pave a new pathway for innovating oxidative C−H/C−H cross-coupling reactions. Nevertheless, this realm is still in its infancy, and the issues of diversity and efficiency remain to be addressed.

The synthesis of arylacetylenes is among the most fundamental and important synthetic transformations due to the unique reactivity of acetylenes including addition, oxidation, reduction, and in particular cyclization.[4] To date, the introduction of acetylenic groups into aromatic scaffolds mostly relies on the Sonogashira reactions[5] and the recently emerged direct alkynylation of aromatic C−H bonds with alkynyl halides or pseudohalides.[6] Doubtlessly, the direct oxidative coupling between arenes and terminal alkynes via double C−H bond cleavage is a more straightforward approach to these molecules. Although a few heteroarenes could smoothly undergo oxidative C(sp^2)−H/C(sp)−H cross-coupling with terminal alkynes,[7] the application of this strategy to simple arenes is still largely underdeveloped.[7b,8] In 2010, Nevado, Su, and Miura independently revealed the gold- or copper-catalyzed oxidative alkynylation of simple arenes via 2-fold C−H bond cleavage. However, the scope of arenes was limited to extremely electron-excessive polyalkoxybenzenes or electron-deficient polyfluoroarenes. Inspired by aromatic *ortho*-C−H activation via a double coordination strategy,[2d,6c,9,10] we herein wish to disclose the copper-mediated tandem transformation involving sequential oxidative C(sp^2)−H/C(sp)−H alkynylation and intramolecular annulation of unactivated arenes with terminal alkynes with the assistance of 8-aminoquinoline, which not only tolerates a broad range of arenes and terminal alkynes but also offers a highly effective strategy to synthesize biologically important 3-methyleneisoindolin-1-ones (Scheme 1).[11]

We initially focused our investigation on the copper-mediated cross-coupling of *N*-(quinolin-8-yl)benzamide **1a** with phenylacetylene **2a** (Table 1). Gratifyingly, (*Z*)-3-benzylidene-2-(quinolin-8-yl)isoindolin-1-one **3a** was obtained in 25% yield when a stoichiometric amount of $Cu(OAc)_2{\cdot}H_2O$ was employed in toluene at 140 °C for 24 h (Table 1, entry 1). Due to the existence of excess **2a** and Cu(II) salt, the homocoupling of **2a** was inevitable to give **2aa**. Further optimization of solvents showed *t*-AmylOH was the best choice

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Scheme 1. Tandem Oxidative C(sp²)−H/C(sp)−H Cross-Coupling and Intramolecular Annulation of Arenes with Terminal Alkynes

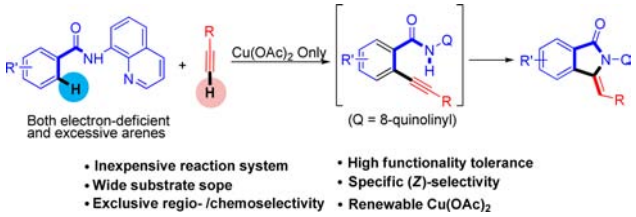
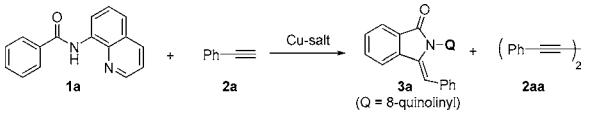


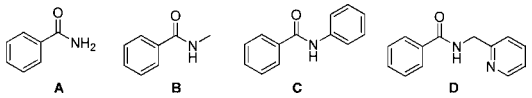
Table 1. Optimization of Reaction Conditions[a]



entry	Cu-salt (equiv)	solvent	yield (%) 3a[b]/2aa[c]
1	$Cu(OAc)_2·H_2O$ (4.0)	toluene	25/35
2	$Cu(OAc)_2·H_2O$ (4.0)	*t*-AmylOH	57/60
3	$CuCl_2$ (4.0)	*t*-AmylOH	trace/8
4	CuI (4.0)	*t*-AmylOH	n.d./2
5[d]	$Cu(OAc)_2$ (3.0)	*t*-AmylOH	89/46
6[d,e]	$Cu(OAc)_2$ (3.0)	*t*-AmylOH	91/44
7[d,f]	$Cu(OAc)_2$ (3.0)	*t*-AmylOH	77/53
8[d,g]	$Cu(OAc)_2$ (3.0)	*t*-AmylOH	31/52

[a]Reactions were carried out using **1a** (0.25 mmol), **2a** (0.75 mmol, 3.0 equiv), and copper salt in 2.0 mL of dry solvent for 24 h at 140 °C under an N_2 atmosphere. [b]Isolated yields. [c]Yields determined with GC-MS by using naphthalene as an internal standard. [d]120 °C. [e]2.5 equiv of **2a**. [f]2.0 equiv of **2a**. [g]0.5 mmol of **1a** and 0.25 mmol of **2a**.

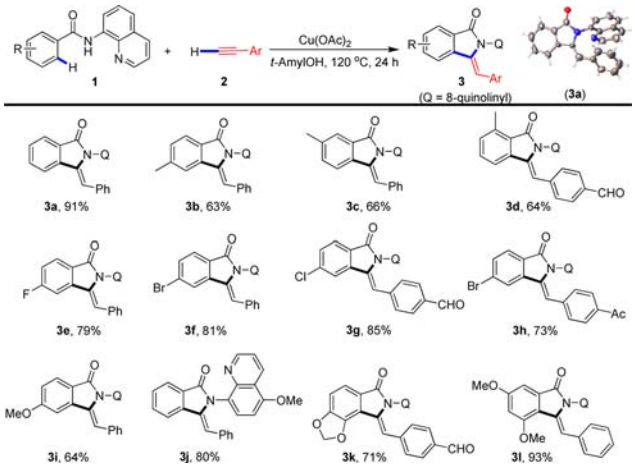
unsuccessful substrates



(Table 1, entry 2). $Cu(OAc)_2$ proved to be the most efficient oxidant and promoter (Table 1, entry 5), whereas $CuCl_2$ gave a trace amount of product **3a**, and CuI was totally ineffective. Subsequently, other reaction parameters including the loading of phenylacetylene, the ratio of two substrates, and the reaction temperature were investigated (Table 1, entries 5−8). Finally, the best result was observed when 2.5 equiv of phenylacetylene **2a** was used in combination with $Cu(OAc)_2$ (3.0 equiv) in *t*-AmylOH at 120 °C for 24 h (for a detailed optimization study, see the Supporting Information). Under the optimized conditions, a series of structurally similar benzamides **A**−**D** were examined, but no cross-coupled product was observed except for the nearly quantitative formation of **2aa**. These control experiments showed the indispensable role of the 8-aminoquinoline moiety for this reaction.

Next, we set out to explore the scope of *N*-(quinolin-8-yl)benzamide partners as summarized in Scheme 2. To our delight, the reaction system could accelerate the tandem reaction of a wide array of *N*-(quinolin-8-yl)benzamides with terminal alkynes, delivering a series of functionalized 3-methyleneisoindolin-1-ones in moderate to excellent yields. The positions of substituent on arenes had a negligible effect on the transformation. No matter whether the substituent was installed on the *ortho*-, *meta*-, or *para*-position of arenes, the reaction proceeded smoothly (Scheme 2, **3b**−**d**). *N*-(Quinolin-8-yl)benzamides bearing the chloro or bromo group on the aromatic ring selectively underwent the oxidative alkynylation reaction, and the competitive Sonagashira reaction did not take place (Scheme 2, **3f**−**h**). Moreover, the reaction performed well when the quinoline ring had a methoxyl group at the 5-position (Scheme 2, **3j**). In addition, single-crystal X-ray diffraction of **3a** (Scheme 2) and 2D NMR spectrum of **3b** demonstrated that the product was formed in the *Z*-type.[12]

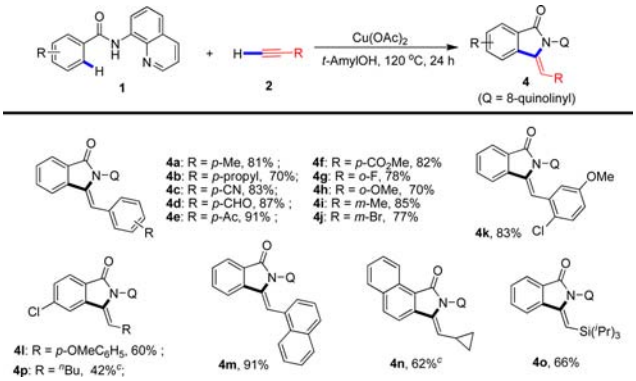
Scheme 2. Scope of *N*-(Quinolin-8-yl)benzamides[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.625 mmol, 2.5 equiv), $Cu(OAc)_2$ (3.0 equiv), and *t*-AmylOH (2.0 mL) at 120 °C for 24 h. [b]Isolated yields.

Subsequently, we turned our attention to test the generality of terminal alkynes (Scheme 3). Aryl alkynes bearing both

Scheme 3. Scope of Terminal Alkynes[a,b]



[a]For reaction conditions see Scheme 2. [b] Isolated yields. [c] 3.0 equiv of terminal alkynes, 140 °C.

electron-withdrawing groups (Scheme 3, **4c**−**g** and **4j**) and electron-donating groups (Scheme 3, **4a**, **4b**, **4h**, **4i**, and **4l**) were all successfully engaged in this transformation. Functional groups such as ester, aldehyde, acyl, nitrile, fluorine, chlorine, and bromine could be tolerated under the current conditions, which may allow high diversity in the synthesis of functionalized 3-methyleneisoindolin-1-ones. An alkyne containing a naphthalene moiety could also be employed without any difficulty (Scheme 3, **4m**). In addition to aryl alkynes, cyclopropyl acetylene, 1-hexyne, and (triisopropylsilyl)-acetylene could also be compatible in the transformation, delivering **4n**, **4p**, and **4o** in acceptable yields, respectively.

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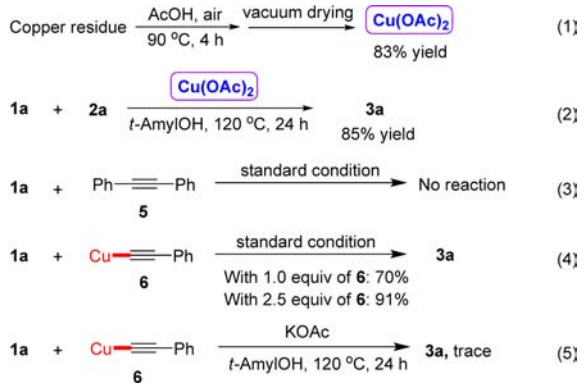
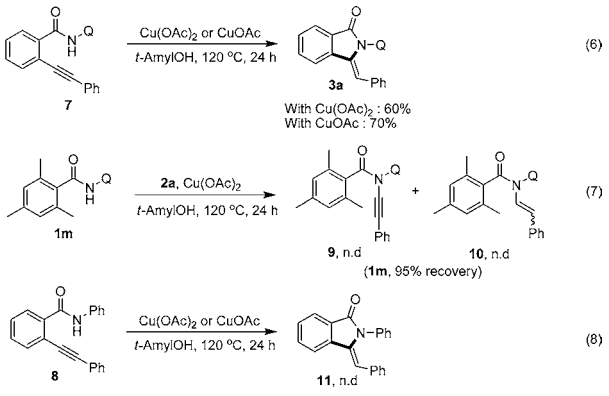
Although $Cu(OAc)_2$ is one of the cheapest metal oxidants, we tried to recycle the copper to further reduce the cost and waste after the reaction. Indeed, $Cu(OAc)_2$ could be regenerated after simple treatment of copper residue with bubbles of air in acetic acid solution and subsequent vacuum drying (eq 1). The regenerated $Cu(OAc)_2$ could smoothly promote the tandem reaction (eq 2).



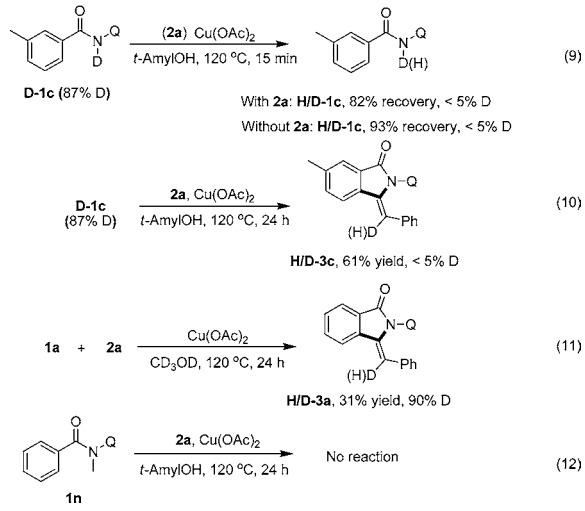
To get some insights into the mechanism of this tandem reaction, a series of controlled experiments were performed. First, a stoichiometric amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), frequently used as radical scavenger in transition-metal-mediated reactions, had a negligible effect on the reaction between **1a** and **2a**, which indicated that a free-radical pathway might be ruled out (Table S1, entry 18). Next, we found that no reaction occurred when terminal alkyne **2a** was replaced by internal alkyne **5** (eq 3). Notably, copper phenylacetylide **6** could give rise to the desired product **3a** (eq 4). These observations suggested that the Cu(I)-alkynyl intermediate might serve as a reactive species. However, the addition of extra $Cu(OAc)_2$ as a terminal oxidant was essential to achieve this oxidative $C(sp^2)$–H/C(sp)–H cross-coupling reaction. Only a trace amount of **3a** was observed in the absence of $Cu(OAc)_2$ (eq 5).

Subsequently, we found that *ortho*-alkynyl benzamide **7** could smoothly be transformed to the target molecule **3a** in the presence of either $Cu(OAc)_2$ or CuOAc (eq 6). To exclude the



possibility of the reaction between N–H and C(sp)–H bonds, *ortho*-blocked benzamide **1m** was treated with phenylacetylene **2a**. Neither the N-alkynylation product **9** nor the N-alkenlation product **10** was detected, and **1m** was recovered in 95% yield (eq 7). These factors demonstrated that the domino reaction first underwent the direct oxidative $C(sp^2)$–H/C(sp)–H cross-coupling followed by the intramolecular annulation to form the isoindolinone skeleton, although attempts to isolate the coupled *ortho*-alkynyl benzamides failed. In addition, *N*-phenyl-2-(phenylethynyl)benzamide **8** failed to undergo the annulation reaction (eq 8), which suggested that the acidity of the N–H bond in benzamide was vital to the transformation.[2d,13]

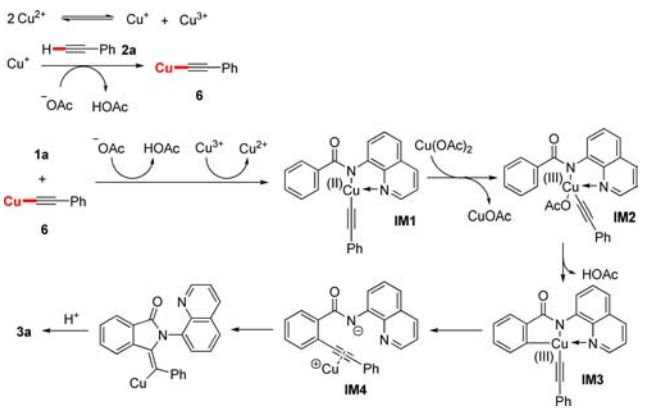
We finally investigated whether the N–H bond cleavage occurred during the formation of some metallic species. Treatment of N-deuterated benzamide **D-1c** with or without **2a** under the optimized conditions for 15 min both led to a significant loss of deuterium content (eq 9). When the reaction



time was extended to 24 h, the product **3c** was obtained in 61% yield with <5% deuterium remaining at the alkenyl position (eq 10). When **1a** reacted with **2a** in MeOH-d_4, 90% deuterium was incorporated at the alkenyl position (eq 11). In addition, when the N–H bond was blocked by a methyl group, no cross-coupled product was found (eq 12). These outcomes hinted that the N–H bond cleavage might be involved in the formation of cyclometallic intermediates.

On the basis of the above observations, a tentative mechanism is proposed in Scheme 4. First, the disproportionation of Cu(II) gives Cu(III) and Cu(I). Next, the acetate-ligand-assisted cupration of **2a** with Cu(I) generates copper phenylacetylide **6**, which undergoes a bidentate chelation process with **1a** to deliver intermediate **IM1** with the assistance of a Cu(III) species and acetate ion (comproportionation reaction).[2b,d,14] Subsequently, the $Cu(OAc)_2$-promoted oxida-

Scheme 4. Proposed Mechanism



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tion of **IM1** affords **IM2**, followed by an acetate-assisted intramolecular C−H cupration of the phenyl ring to furnish the key intermediate **IM3**. The following reductive elimination and intramolecular annulation form **3a**.[15] The above assumptions also demonstrate why 3 equiv of $Cu(OAc)_2$ must be required to achieve a good conversion.

Finally, we attempted the removal of the quinolinyl group from the products. All attempts failed to give the deprotected products. Subsequently, we installed a methoxyl group on the C5 position of quinoline ring and tried to remove the quinoline moiety via the oxidation of ceric ammonium nitrate (CAN) in CH_3CN/H_2O solution.[16] Unfortunately, the deprotected product was still not detected. In comparison to *N*-arylated aliphatic lactam, it seemed to be more difficult to remove the N-aryl group from benzolactam.

In summary, by taking advantage of the bidentate-chelation assistance of an 8-aminoquinoline residue, we have disclosed for the first time the copper-mediated tandem oxidative $C(sp^2)-H/C(sp)-H$ cross-coupling and intramolecular annulation of unactivated arenes with terminal alkynes, delivering a wide array of functionalized 3-methyleneisoindolin-1-ones. In the oxidative cross-coupling process, $Cu(OAc)_2$ serves as both the promoter and the terminal oxidant. The transformation has demonstrated for the first time that $Cu(OAc)_2$ can be renewable after undergoing an oxidative reaction. The present protocol exhibits the following features: (1) a simple, easily available, and inexpensive reaction system; (2) no extra ligand, base, and additive is required; (3) wide substrate scope; (4) excellent functional group tolerance; and (5) exclusive chemo-, regio-, and stereoselectivities. Our findings offer an alternative method for the efficient synthesis of a 3-methyleneisoindolin-1-one scaffold and shed more light on nonprecious metal-mediated oxidative cross-coupling reactions.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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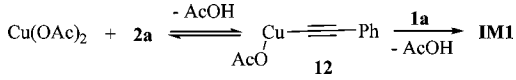
(12) For detailed 2D NMR spectra of **3b**, **3c**, and **3k**, see Supporting Information.

(13) The ^1H NMR chemical shifts of NH in **7** and **8** are 11.22 and 9.20 ppm, respectively ($CDCl_3$, 25 °C).

(14) At this stage, we cannot completely exclude the following possible pathway to intermediate **IM1**: cupration of **2a** with Cu(II) to generate **12** and subsequent ligand exchange with **1a** to form **IM1**, although attempts to capture intermediate **12** failed. For a similar mechanism proposed by Miura et al., see refs 2b and 2d.



(15) After the reductive elimination, the triple bond in situ coordinates with Cu(I) to form **IM4**. The N^- anion of benzamide then attacks the alkyne moeity from the opposite side of copper(I), followed by the protonation to deliver the specific *Z*-type product **3a**. However, at this moment, it is unclear why this reaction shows predominant preference for the formation of the five-membered ring over the six-membered ring.

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