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Cu(II)-Catalyzed Coupling of Aromatic C−H Bonds with Malonates

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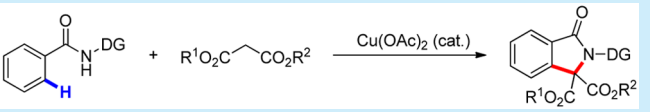
Supporting Information

ABSTRACT: A new Cu(II)-catalyzed oxidative coupling of arenes with malonates has been developed using an amide-oxazoline directing group. The reaction proceeds via C(sp^2)−H activation and malonate coupling, followed by intramolecular oxidative N−C bond formation. A variety of arenes bearing different substituents are shown to be compatible with this reaction.

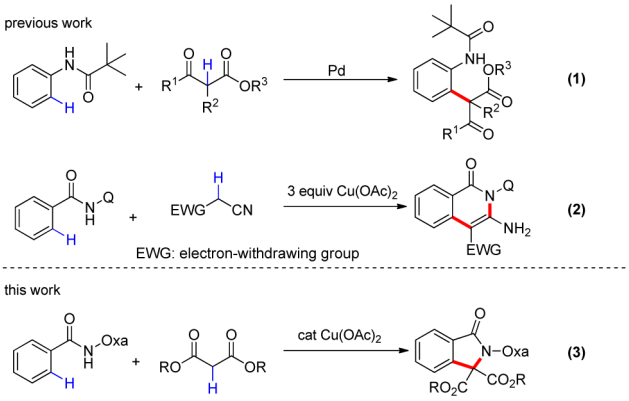


Over the past several decades, transition-metal-catalyzed C−H functionalization reactions have emerged as powerful tools for the construction of C−C and C−X bonds in organic synthesis.[1] In this context, the extensively utilized Heck reaction and Stille, Suzuki, Negishi, and Hiyama couplings have provided inspiration for the development of analogous transformations using C−H bonds in lieu of aryl or alkyl halides as the reaction partners. Most notably, Pd-catalyzed C−H olefination has undergone substantial progress in terms of both catalyst development and mechanistic understanding since 1967.[2] On the other hand, the coupling of C−H bonds with organometallic reagents and other nucleophiles via Pd(II)/Pd(0) redox catalysis has been far less developed. The difficulty associated with transfer of a nucleophilic carbon fragment via transmetalation or direct displacement to the Pd(II) intermediate, as well as the subsequent reductive elimination, has historically proven to be a significant challenge. Despite a series of developments in Pd-catalyzed C−H coupling with organometallic reagents,[3] the coupling of C−H bonds with a malonate nucleophile remains challenging. Such a coupling was previously realized in the context of allylic C−H activation.[4] More recently, Pd(II)/Mn(III)-mediated *ortho*-C−H coupling of anilide with *β*-keto esters via a radical mechanism was accomplished for the first time, although the substrates were limited to the electron-rich anilides (Scheme 1, eq 1).[5]

During the course of our studies, a Cu(II)-mediated [3 equiv of $Cu(OAc)_2$] oxidative coupling of benzamide with ethyl cyanoacetate using 8-aminoquinoline as a directing group was also discovered (eq 2).[6]

Herein, we describe a copper-catalyzed, direct oxidative coupling of aromatic C−H bonds with malonates using an amide-oxazoline as the directing group. The initially formed coupling products undergo intramolecular C−N bond formation leading to isoindolinone scaffolds (eq 3).

Scheme 1. Transition-Metal-Catalyzed Coupling of Aromatic C−H Bonds with Malonates



Cu-catalyzed C−H functionalizations have attracted an increasing amount of attention in recent years.[7−11] Encouraged by new reports detailing Cu-mediated C−H functionalizations using an amide−oxazoline directing group,[11] we began to investigate whether this auxiliary could be exploited in the coupling of C−H bonds with malonate nucleophiles. As such, we found that oxidative coupling of *N*-arylbenzamide substrate **1a** with 2 equiv of dimethyl malonate **2a** proceeded in the presence of 20 mol % of $Cu(OAc)_2$, 1.5 equiv of Ag_2O, and 2.0 equiv of Na_2CO_3 in DMSO at 80 °C to afford desired product **3a** in 38% yield (Table 1, entry 1). To improve this reaction, an extensive screening of reaction parameters was conducted. Various bases were investigated, and it was discovered that Li_2CO_3 produced the highest yield of 52% (Table 1, entries 2−8). Furthermore, DMSO and Ag_2CO_3 also proved to be optimal choices after evaluation of different solvents (see

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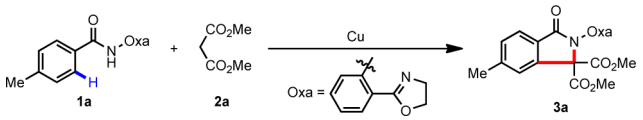
Table 1. Optimization of Reaction Conditions[a]



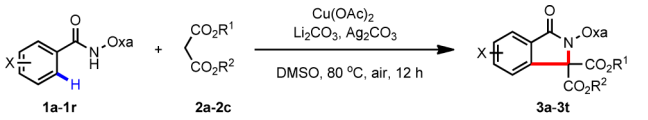
entry	$Cu(OAc)_2$ (mol %)	[Ag]	base (equiv)	yield (%)[b]
1	20	Ag_2O	Na_2CO_3 (2.0)	38
2	20	Ag_2O	Li_2CO_3 (2.0)	52
3	20	Ag_2O	K_2CO_3 (2.0)	9
4	20	Ag_2O	LiOAc (2.0)	14
5	20	Ag_2O	$NaHCO_3$ (2.0)	29
6	20	Ag_2O	$KHCO_3$ (2.0)	27
7	20	Ag_2O	K_2HPO_4 (2.0)	47
8	20	Ag_2O	KH_2PO_4 (2.0)	46
9	20	Ag_2CO_3	Li_2CO_3 (2.0)	57
10	20	AgOAc	Li_2CO_3 (2.0)	27
11	20	$AgNO_3$	Li_2CO_3 (2.0)	41
12[c]	20	Ag_2CO_3	Li_2CO_3 (2.0)	79
13[c]	30	Ag_2CO_3	Li_2CO_3 (2.0)	78
14[c]	10	Ag_2CO_3	Li_2CO_3 (2.0)	63
15[c]	0	Ag_2CO_3	Li_2CO_3 (2.0)	n.r.
16[c]	**20**	**Ag_2CO_3**	**Li_2CO_3 (1.0)**	**79(69)[d]**
17[c]	20	Ag_2CO_3	Li_2CO_3 (0)	55
18[c,e]	20	Ag_2CO_3	Li_2CO_3 (1.0)	52
19[c,f]	20	Ag_2CO_3	Li_2CO_3 (1.0)	68

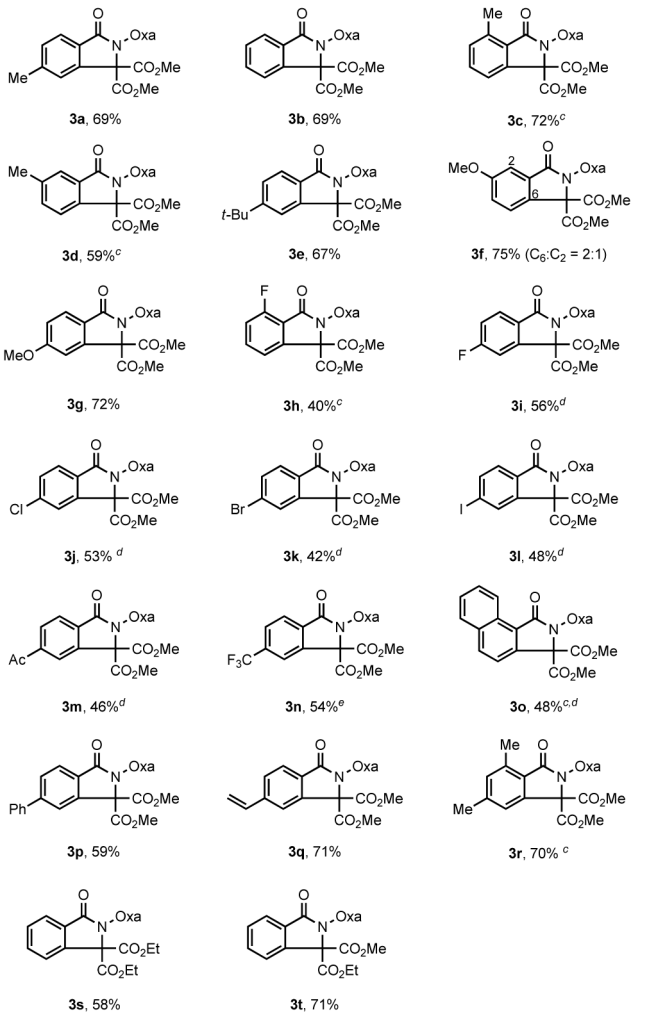
[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (20 mol %), base (0.2 mmol), [Ag] (0.15 mmol), DMSO (1.0 mL), air, 80 °C, 12 h. [b]Yields were determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c]DMSO (4.0 mL). [d]Isolated yield. [e]70 °C. [f]90 °C.

Supporting Information) and oxidants, respectively (Table 1, entries 9−11). The use of molecular oxygen as the sole oxidant gave poor yields (<10%). Notably, the yield was increased to 79% when the reaction was run at lower concentrations (Table 1, entry 12). A variety of copper salts are also reactive, albeit lower yields were obtained when compared to $Cu(OAc)_2$ (see Supporting Information). Reducing the quantity of $Cu(OAc)_2$ to 10 mol % lowered the yield to 63% (Table 1, entry 14). It should also be noted that in the absence of copper no reactivity is observed (Table 1, entry 15). Additionally, altering the amount of Ag_2CO_3 and **2a** does not seem to have any beneficial impact on the yield (see Supporting Information). Interestingly, reducing the amount of Li_2CO_3 to 1.0 equiv had a negligible impact on the observed reactivity (Table 1, entry 16). Finally, increasing the reaction temperature to 90 °C, or reducing the reaction temperature to 70 °C, did not further increase the yield (Table 1, entries 18−19).

With these optimized conditions in hand, we proceeded to examine the substrate scope of this oxidative coupling cyclization reaction (Scheme 2). In general, both electron-donating and -withdrawing substituents on the benzene ring of benzamides were well-tolerated under the current conditions. Oxidative coupling/cyclization of electron-rich methyl-, *tert*-butyl-, and methoxy-substituted arenes proceeded smoothly to provide the corresponding products in 59−75% yields (**3a**−**3g**). It is noteworthy that when benzamides **1d** and **1f**, bearing *meta* substituents on the benzene ring, were subjected to this C−H functionalization protocol, the regioselectivity of the reaction favored the formation of less sterically hindered products (**3d, 3f**). Electron-deficient arenes bearing halides, acetyl, and trifluoromethyl groups also proceeded well,

Scheme 2. Scope of Substrates[a,b]





[a]Reaction conditions: **1a**−**1r** (0.10 mmol), **2a**−**2c** (0.2 mmol), $Cu(OAc)_2$ (20 mol %), Li_2CO_3 (0.1 mmol), Ag_2CO_3 (0.15 mmol), DMSO (4.0 mL), air, 80 °C, 12 h. [b]Isolated yield. [c]$Cu(OAc)_2$ (50 mol %). [d]70 °C. [e]60 °C.

affording their corresponding products in moderate yields (**3h**−**3n**, 40−56% yield). Vinyl substrate **1q** was also cyclized to provide **3q** in 71% yield. Halogen (**3h**−**3l**) and vinyl (**3q**) substituents in the products are useful handles for further synthetic elaborations. As expected, oxidative coupling/cyclization of substrate **1b** with malonates **2b** and **2c** can also be converted into desired products of **3s** and **3t** in 58% and 71% yield, respectively. The structure of **3s** was unambiguously determined by X-ray diffraction analysis (see Supporting Information).

Interestingly, we found that coupling of benzamide substrate **1a** with 3-oxobutanoate **4** afforded methyl 3,6-dimethyl-1-oxo-1*H*-isochromene-4-carboxylate **5**, derived from enolate *O*-acylation following oxidative C−H coupling, in 34% yield (Scheme 3). No corresponding isoindolinone products were detected. Apparently, the newly installed enolate assisted the removal of the amide directing group. The structure of **5** was

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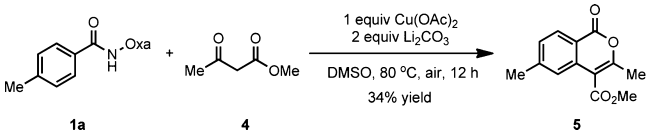
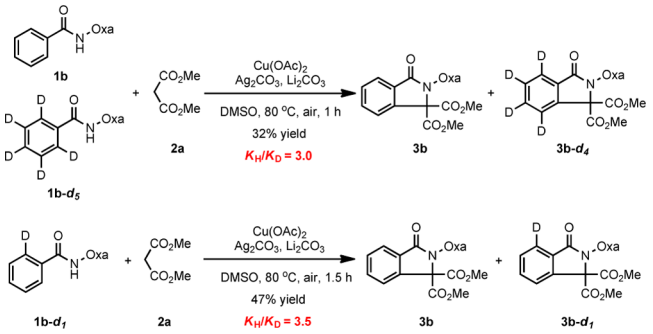
Scheme 3. Coupling of Benzamides Substrate 1a with 3-Oxobutanoate



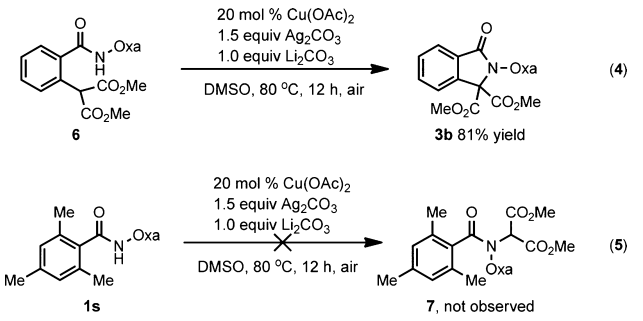
also unambiguously established by X-ray diffraction analysis (see Supporting Information).

To obtain insights into the mechanism of this cascade reaction, both intra- and intermolecular kinetic isotope effect (KIE) experiments were conducted with the deuterium labeled substrates **1b**-d_1 and **1b**-d_5 (Scheme 4). Significant KIEs were

Scheme 4. Kinetic Isotope Effect Experiments



observed, suggesting that C−H cleavage could potentially be the rate-limiting step. In addition, two potential intermediates **6** and **1s** were synthesized and evaluated under standard conditions (eqs 4 and 5). We found that the benzamide **6** could be smoothly converted to the target product **3b** in 81% yield, while *ortho*-blocked benzamide **1s** failed to provide potential initial N−C coupled intermediate **7** and instead resulted in 96% recovery of **1s**. These results suggest that this oxidative coupling cyclization reaction first underwent the direct oxidative C(sp^2)−H/C(sp^3)−H cross-coupling followed by intramolecular N−H/C(sp^3)−H cross-coupling to form the isoindolinone scaffold.



In conclusion, we have developed a Cu-catalyzed direct oxidative coupling reaction of aromatic *ortho*-C−H bonds with malonates. This new copper-catalyzed oxidative cyclization reaction displayed good functional group tolerance and provided an alternative method for preparing isoindolinones which is a privileged moiety and ubiquitous in natural products and pharmaceuticals. Further development of a readily removable directing group to effect this transformation is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of all new compounds. 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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