Organic LETTERS
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Cu(OAc)$_2$-Catalyzed Coupling of Aromatic C−H Bonds with Arylboron Reagents

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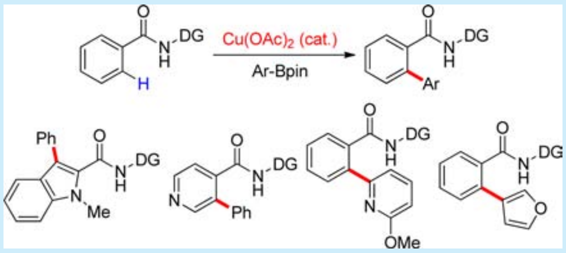
S *Supporting Information*

ABSTRACT: Cu-catalyzed coupling of aryl C−H bonds with arylboron reagents was accomplished using a readily removable directing group, which provides a useful method for the synthesis of biaryl compounds. The distinct transmetalation step in this Cu-catalyzed C−H coupling with aryl borons provides unique evidence for the formation of an aryl cupperate intermediate.



Scheme 1. Transition-Metal-Catalyzed C−H Coupling with Organometallic Reagent

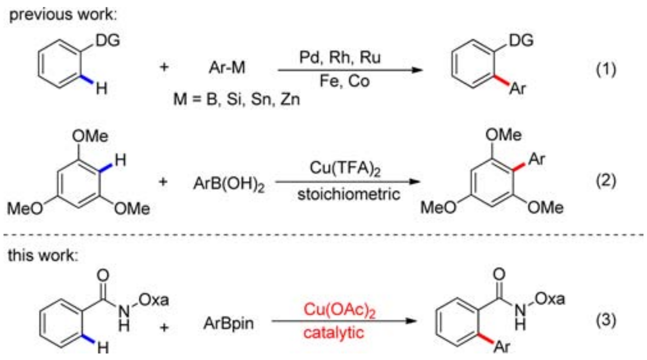
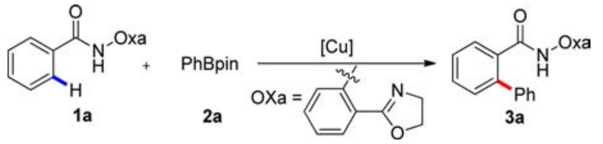


Table 1. Reaction Development[a]



1a 2a 3a

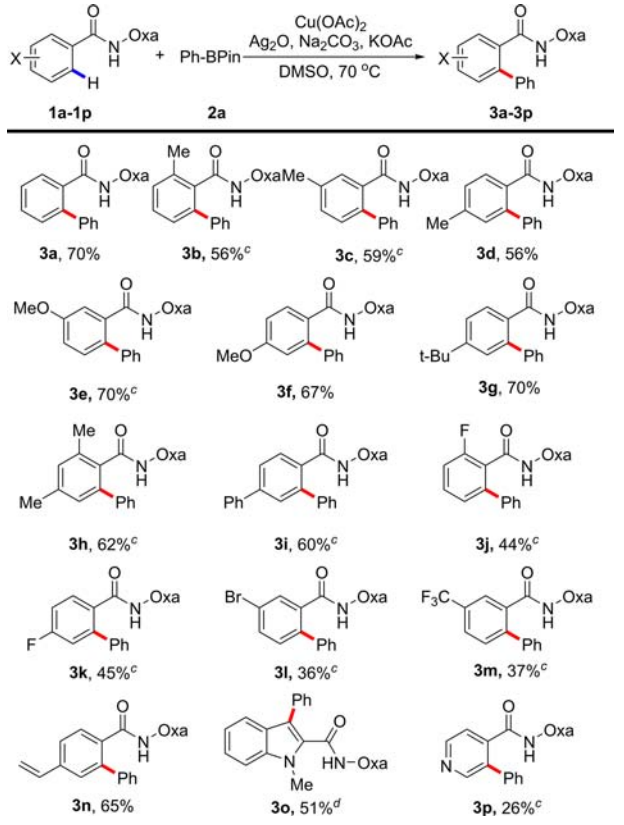
entry	Cu(OAc)$_2$ (mol %)	[Ag] (equiv)	base	yield[b] (%)
1	20	AgOAc (1.0)	Na_2CO_3	21
2	20	Ag_2CO_3 (1.0)	Na_2CO_3	30
3	20	$AgNO_3$ (1.0)	Na_2CO_3	29
4	20	Ag_2O (1.0)	Na_2CO_3	50
5	20	Ag_2O (1.0)	K_2CO_3	33
6	20	Ag_2O (1.0)	KOAc	25
7	20	Ag_2O (1.0)	NaOAc	22
8[c]	20	Ag_2O (1.0)	Na_2CO_3	55
9[c]	30	Ag_2O (1.0)	Na_2CO_3	62
10[c]	30	Ag_2O (1.5)	Na_2CO_3	66
11[c]	30	Ag_2O (2.0)	Na_2CO_3	63
12[c,d]	30	Ag_2O (1.5)	Na_2CO_3	65
13[c,d]	30	Ag_2O (1.5)	Na_2CO_{3+} KOAc[e]	69
14[c,d,f]	30	Ag_2O (1.5)	Na_2CO_{3+} KOAc[e]	73

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), base (0.2 mmol), DMSO (1.0 mL), 80 °C, Ar, 12 h. [b]Yield determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c]**2a** (0.25 mmol). [d]4 h. [e]Na_2CO_3 (0.2 mmol), KOAc (0.2 mmol). [f]70 °C.

Despite the remarkable success of Pd(0)-catalyzed cross-coupling reactions of aryl halides,[1] development of Pd(II)-catalyzed cross-coupling of C−H bonds with organometallic reagents[2] has remained a great challenge due to the lack of reactivity of C−H bonds and difficulty in closing the oxidative catalytic cycle. From a historical perspective, the direct coupling of C−H bonds with organometallic reagents has long attracted the attention of organic chemists.[3−6] In 1998, Oi et al. reported the first catalytic cross-coupling of 2-arylpyridines with arylstannanes using $RhCl(Ph_3P)_3$ as a catalyst.[4a] In 2003, Murai et al. reported a ruthenium(0)-catalyzed ortho-arylation of aromatic ketones with arylboronates.[5a] Inspired by Pd(0)-catalyzed cross-coupling reactions, we embarked on the development of a series of Pd(II)-catalyzed oxidative cross-couplings of C−H bonds with organotin and organoboron reagents.[2a−d] While this newly established catalytic cycle has gained considerable interest,[2,3] the use of Cu(II) catalysts for catalytic C−H activation reactions could be complementary and sometimes desir-

Received: September 16, 2014
Published: October 17, 2014

Scheme 2. Scope of Benzamide Substrates[a,b]

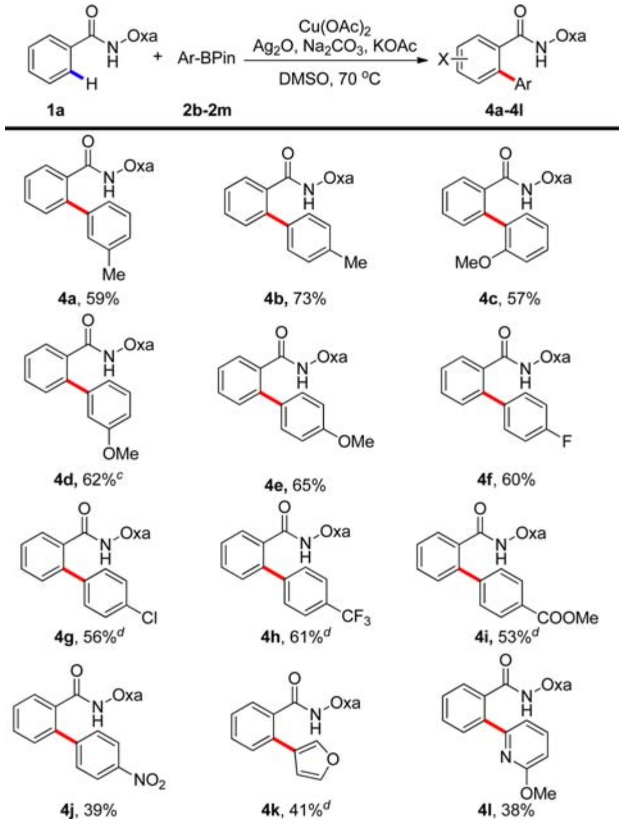


[a]Reaction conditions: **1a−1p** (0.1 mmol), **2a** (0.25 mmol), $Cu(OAc)_2$ (0.03 mmol), Ag_2O (0.15 mmol), Na_2CO_3 (0.2 mmol), KOAc (0.2 mmol), DMSO (1.0 mL), 70 °C, Ar, 4 h. [b]Isolated yield. [c]**2a** (0.4 mmol), $Cu(OAc)_2$ (0.04 mmol), 12 h. [d]$Cu(OAc)_2$ (0.02 mmol).

able.[7−10] We and others have previously reported a diverse range of $Cu(OAc)_2$-catalyzed or -mediated C−H activation reactions using directing groups.[7−10] Interestingly, a single example of C−H coupling of an electron-rich trimethoxyarene with arylboronic acids using stoichiometric $Cu(TFA)_2$ was also reported by Itami.[11] Herein, we report the first example of Cu(II)-catalyzed cross-coupling of inert aryl C−H bonds with organoboron reagents using a readily removable directing group.

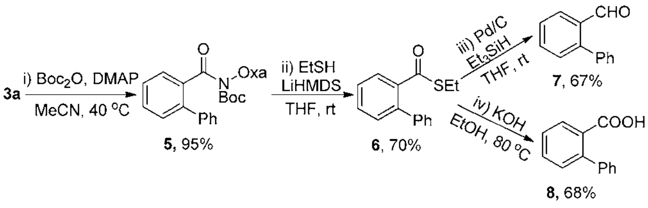
In our initial report on the Cu(II)-catalyzed C−H functionalization of 2-phenylpyridine, we demonstrated the feasibility of forging C−N and C−C bonds using nucleophilic amines and cyanides,[7a] though subsequent efforts to develop Cu(II)-catalyzed C−H couplings with organoboron reagents using this directing group proved unsuccessful. However, our recent discovery of a superior, easily removable amide−oxazoline directing group for Cu(II)-mediated aminations[9a] prompted us to revisit this subject (Scheme 1). Encouragingly, we found that substrate **1a** was arylated with 21% yield in the presence of 2 equiv of PhBpin, 20 mol % of $Cu(OAc)_2$, 1 equiv of AgOAc, and 2 equiv of Na_2CO_3 at 80 °C (Table 1, entry 1). The yield was improved to 50% when Ag_2O was used as oxidant (Table 1, entries 2−4), which is similar to our Pd-catalyzed C−H coupling reactions in which Ag_2O was found to promote transmetalation in addition to reoxidizing the low-valent metal.[2b,d] After a brief screening of bases, Na_2CO_3 remained the optimal choice (Table 1, entries 5−7). Alternative copper salts proved to be ineffective for this transformation

Scheme 3. Scope of Arylboronates[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2b−2m** (0.25 mmol), $Cu(OAc)_2$ (0.03 mmol), Ag_2O (0.15 mmol), Na_2CO_3 (0.2 mmol), KOAc (0.2 mmol), DMSO (1.0 mL), 70 °C, Ar, 4 h. [b]Isolated yield. [c]12 h. [d]**2** (0.4 mmol), $Cu(OAc)_2$ (0.04 mmol), 12 h

Scheme 4. Synthetic Elaboration of the Directing Group



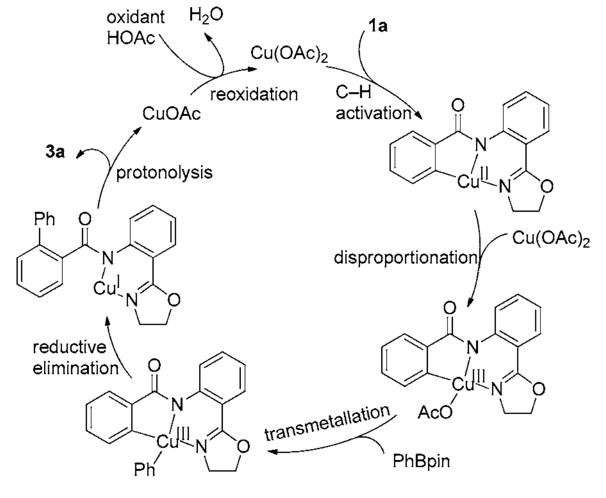


Figure 1. Plausible catalytic cycle.

(see the Supporting Information). A moderate improvement in yield was also obtained by increasing the amount of PhBpin to 2.5 equiv (Table 1, entry 8). The coupling reaction proceeded in the presence of 30 mol % of $Cu(OAc)_2$ and 1.5 equiv of Ag_2O to afford the product in 66% yield (Table 1, entries 9–11). Additionally, the reaction time could be shortened to 4 h without affecting the yield (Table 1, entry 12). The use of a combination of Na_2CO_3 and KOAc as the bases and decreasing the reaction temperature to 70 °C further improved the yield to 73%.

The scope of this reaction with respect to the benzamide substrate was examined under these conditions. As shown in Scheme 2, electron-rich methyl-, methoxy-, *tert*-butyl-, 2,4-dimethyl-, and phenyl-substituted arenes undergo C–H arylation well, affording the desired products in good yields (**3b–i**, 56–70% yields). Electron-deficient halogen and trifluoromethyl substituents are tolerated (**3j–m**), although lower yields were observed. In these cases, a majority of the starting materials were recovered and a small amount of ortho-hydroxylated side products were obtained. Arylation of the vinylated arene produced the desired product in 65% yield (**3n**). Indole and pyridine substrates are also arylated in 51% and 26% yields, respectively (**3o**,**p**).

A variety of arylboronates were investigated as coupling partners using **1a** as the substrate (Scheme 3). The coupling of **1a** with electron-rich arylboronates afforded the arylated products in 57–73% yields (**4a–e**). Arylboron reagents containing electron-withdrawing groups such as fluoro, chloro, trifluoromethyl, and methoxycarbonyl moieties are also compatible, providing the coupling products in 53–61% yields (**4f–i**). The presence of a nitro group reduced the yield to 39% (**4j**). Coupling with heterocyclic arylboronates also proceeds, albeit in moderate yields (**4k**,**l**).

To improve the synthetic applicability of this reaction, we treated the Boc-protected product **5** with EtSH in the presence of LiHMDS at room temperature to give the thioester **6** (Scheme 4).[12] The thioester **6** can be readily converted to the corresponding aldehyde **7** and carboxyl acid **8** in good yields.

Despite the rapid development of Cu-catalyzed various C–H activation reactions,[7−10] evidence for the involvement of a C–H cupperation intermediate remains scarce (Figure 1). The distinct catalytic cycle of C–H coupling with aryl borons proceeding through a transmetalation step supports the formation of an aryl cupperate intermediate, although the involvement of Cu(III) remains to be elucidated. In addition, the intra- (k_H/k_D = 3.3) and intermolecular (k_H/k_D = 4.3) kinetic isotope effects also ruled out an electrophilic aromatic substitution pathway (S_EAr) (see the Supporting Information).

In summary, we have developed a copper(II)-catalyzed cross-coupling reaction of aryl C–H bonds using a readily removable directing group. Both the benzamide substrates and the coupling partners tolerate a wide range of functional groups. This finding paves the way for developing Cu-catalyzed cross-coupling of C–H bonds with organometallic reagents using directing groups.

■ 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, NSFC-21121062, and The Recruitment Program of Global Experts for financial support. We gratefully acknowledge The Scripps Research Institute, for financial support. This work was supported by NSF under the CCI Center for Selective C–H Functionalization, CHE-1205646.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Table 1 has been corrected to include the reaction equation, which was inadvertently omitted due to production error. The revised version was re-posted on November 7, 2014.