

Cu(II)-Catalyzed Functionalizations of Aryl C–H Bonds Using O₂ as an Oxidant

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The development of transition-metal-catalyzed C–H activation reactions directed by functional groups has witnessed substantial progress in the past three decades.^{1,2} A wide range of metal catalysts, including Ru, Rh, Pt, and Pd, has been exploited with varying degrees of success. From the viewpoint of the practicality of these types of reactions in laboratory synthesis and industrial applications, tremendous challenges lie ahead in controlling selectivity and identifying inexpensive oxidants and metal catalysts. In light of the remarkable progress made in the development of Cu-catalyzed C–heteroatom bond forming reactions that were previously catalyzed predominantly by Pd^{II} catalysts,³ we turned our attention to Cu-catalyzed C–H functionalization reactions. H-abstraction of allylic C–H bonds using Cu(I)/*tert*-butyl hydroperoxide has been successfully exploited in peroxidation⁴ and alkylation reactions.⁵ Since the pyridyl group has been extensively used to direct C–H activation reactions,^{1,6} we launched our effort to develop C–H functionalization reactions directed by a pyridyl group (Py) using Cu(II) catalysts. Herein, we report a Cu(II)-catalyzed acetoxylation and halogenation of aryl C–H bonds. This newly discovered reaction is also shown to be applicable to cyanation, amination, etherification, and thioetherification of C–H bonds.

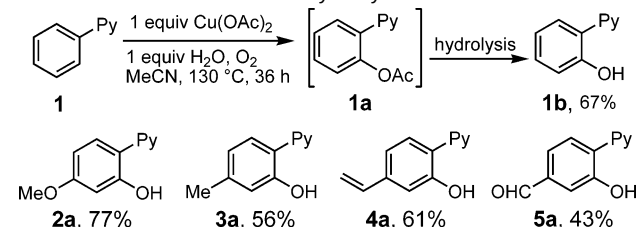
We initiated our investigations by examining whether pyridyl can direct Cu-catalyzed *ortho*-selective C–H functionalizations. We discovered that the reaction of 2-phenylpyridine with 1 equiv of Cu(OAc)₂ and 1 equiv of H₂O in MeCN under O₂ (1 atm) at 130 °C for 36 h gave hydroxylated product **1b** in 67% yield (Scheme 1).⁷ Labeling experiments using H₂¹⁸O in the absence of O₂ showed that the oxygen atom from Cu(OAc)₂ was incorporated into product **1b**.⁸ The rapid hydrolysis of the corresponding acetate **1a** under the reaction conditions led us to propose that the first step involves the formation of the acetoxyated product, which undergoes hydrolysis catalyzed by the intramolecular pyridyl group.⁹

We were delighted to find that reactions of 2-arylpyridines **2**–**5** give the monohydroxylated products **2a**–**5a** in moderate yields under the same conditions (Scheme 1). The high monoselectivity is most likely due to the binding of the hydroxyl group and the nitrogen in the product to Cu(II), which prevents further reaction. In particular, the tolerance of the double bond and carbonyl functional groups and the use of O₂ as the oxidant are significant advantages compared to our recently reported Pd-catalyzed C–H functionalization reactions.¹⁰

While the selective formation of the monohydroxylated product is a synthetically useful feature, this product inhibits the reaction and prevents catalytic turnover. This problem was circumvented by adding Ac₂O to the reaction to acetylate **1b**. As a result, the Cu loading was reduced to 10 mol % in the presence of O₂, albeit resulting in significant diacetoxylation (Scheme 2).

During the screening of reaction conditions for this acetoxylation reaction, we found that the reaction of **1** with 20 mol % of Cu(OAc)₂ in Cl₂CHCHCl₂ gave dichlorinated product **1d** in 92% isolated yield.^{11,12} Analysis of the reaction mixture using ¹H NMR and pH measurements indicated that Cl₂CHCHCl₂ was partially con-

Scheme 1. Formation of Monohydroxylated Products



Scheme 2. Cu(II)-Catalyzed Acetoxylation of Aryl C–H Bonds

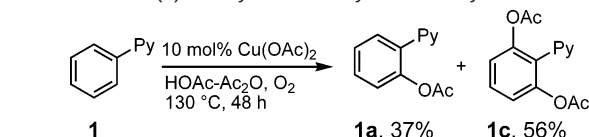


Table 1. Cu(II)-Catalyzed Chlorination of Aryl C–H Bonds^a

entry	substrate	product	yield	entry	substrate	product	yield
1			92%	8			81%
2			63% ^b	9			91%
3			93%	10			92%
4			86%	11			91%
5			51%	12			55%
6			82%	13			90%
7			42%	14			30%
			20%				65%

^a With 20 mol % of CuCl₂, Cl₂CHCHCl₂, O₂ (1 atm), 130 °C, 24 h.

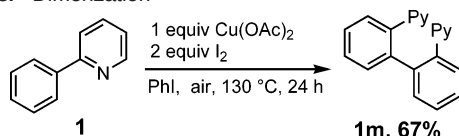
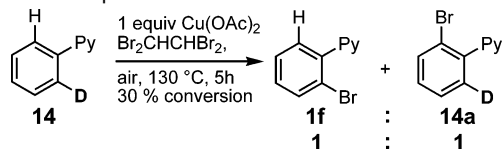
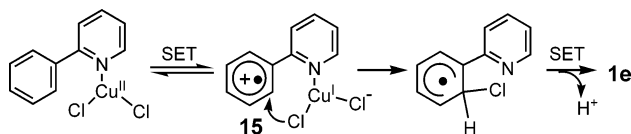
^b At 100 °C; 23% dichlorinated product was also obtained.

verted to Cl₂C=CHCl and HCl that provided the Cl[−] anion source (see Supporting Information). The reaction of a wide range of 2-arylpyridines (**1**–**13**) with 20 mol % of CuCl₂ in Cl₂CHCHCl₂ afforded chlorinated products in excellent yields (Table 1). In the presence of an *ortho*-substituent on the pyridine (entry 11), the monochlorinated product was obtained as a major product, which indicates that the steric hindrance around the N atom of the pyridyl group prevents further chlorination. It is also observed that electron-withdrawing groups attached to the aryl ring resulted in lower conversion (entry 7). Pleasingly, monoselectivity was also improved by carrying

Table 2. Cu(II)-Mediated Diverse C–H Functionalizations^a

entry	anion source	solvent	product (X)	yield
1	—	Br ₂ CHCHBr ₂	Br, 1f	65% ^d
2	I ₂	ClCH ₂ CH ₂ Cl	I, 1g	61% ^{b,d}
3	TMSCN	MeCN	CN, 1h	42%
4	—	MeNO ₂	CN, 1h	67%
5	TsNH ₂	MeCN	TsNH, 1i	74%
6	<i>p</i> -CN-PhOH	MeCN	<i>p</i> -CN-PhO, 1j	35%
7	PhSH	DMSO	PhS, 1k	40%
8	MeSSMe	DMSO	MeS, 1l	51% ^d
9	H ₂ O	DMSO	OH, 1b	22% ^c

^a With 1 equiv of Cu(OAc)₂, air, solvent, 130 °C, 24 h. ^b At 100 °C, 8 h. ^c With 1 equiv of CuF₂. ^d Difunctionalized products (10–20%) were also obtained.

Scheme 3. Dimerization**Scheme 4.** Isotope Effect**Scheme 5.** Possible Mechanism

out the reaction at a lower temperature (100 °C, entry 2).

The initial success prompted us to test whether the use of other copper sources, CuX₂, or a combination of Cu(OAc)₂ and nucleophilic anions could be equally effective, thereby introducing different types of functionality onto the aryl ring. Remarkably, this reactivity was extended to cyanation, amination, etherification, and thioetherification reactions by using a combination of Cu(OAc)₂ and various nucleophilic anions (Table 2). The monofunctionalized products are obtained as major products. Direct cyanation is a valuable transformation in heterocycle synthesis since the conversion of CN into tetrazole is frequently used in drug syntheses.¹³ The use of MeNO₂ as a CN source for cyanation is practically convenient (entry 4).¹⁴ We also identified TsNH₂ as a nitrogen anion source to achieve the first direct amination of aryl C–H bonds (entry 5). The formation of the hydroxylated product using CuF₂ and H₂O is practically attractive if the yield can be further improved (entry 9).

By running the iodination reaction (entry 2) at 130 °C using PhI as a solvent, the dimerized product **1m** was obtained in 67% yield (Scheme 3). Presumably, the initially formed iodinated product **1g** underwent Ullmann coupling to give **1m**.

To achieve catalytic turnover in these reactions, we carried out mechanistic investigations and obtained a number of insights. First, no isotope effect was observed in an intramolecular competition experiment using substrate **14** (Scheme 4). This result suggests that the reaction mechanism is different from the Pd-catalyzed functionalization reactions, in which substantial isotope effects are usually observed.^{10a} Second, the chlorination reaction was found to be

first order in both substrate **1** and CuCl₂. Third, electron-withdrawing groups decrease the reaction rates (see Supporting Information).

On the basis of Kochi's seminal work on Co(TFA)₃-mediated oxidation of aryl C–H bonds,¹⁵ we invoked a radical–cation pathway to explain the data obtained from our mechanistic studies (Scheme 5). A single electron transfer (SET) from the aryl ring to the coordinated Cu(II) leading to the cation–radical intermediate **15** is the rate-limiting step. The lack of reactivity of biphenyl suggests that the coordination of Cu(II) to the pyridine is necessary for the SET process. The observed *ortho*-selectivity is explained by an intramolecular anion transfer from a nitrogen-bound Cu(I) “ate” complex **15**.¹⁶

In summary, we have discovered Cu(II)-catalyzed diverse C–H functionalization reactions. The use of inexpensive Cu catalysts and O₂ as the stoichiometric oxidant is a significant practical advantage. The tolerance of alkene, alkoxy, and aldehyde functionality is a synthetically useful feature. Identification of new conditions to achieve catalytic turnover for the amination, cyanation, etherification, and thioetherification reactions is underway.

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Supporting Information Available: Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) An alternative mechanism: an electrophilic attack of the pyridyl-coordinated Cu(II) on the aryl ring could take place in a manner similar to that of the Pb(TFA)₄-mediated oxidation of aryl C–H bonds.¹⁵ The subsequent loss of a proton would give an unusual cyclometalated aryl Cu(II) complex that could undergo reductive elimination to give the functionalized products and Cu(0).
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