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Cu(II)-Catalyzed Functionalizations of Aryl C−H Bonds Using O_2 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 peroxidation[4] 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.

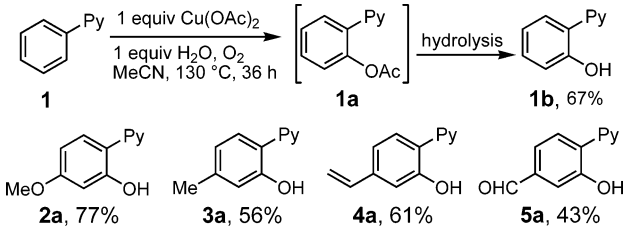
We initiated our investigations by examining whether pyridyl can direct Cu-catalyzed *ortho*-selective C−H functionalizations. We discovered that the reaction of 2-phenylpyridine with 1 equiv of $Cu(OAc)_2$ and 1 equiv of H_2O in MeCN under O_2 (1 atm) at 130 °C for 36 h gave hydroxylated product **1b** in 67% yield (Scheme 1).[7] Labeling experiments using $H_2{}^{18}O$ in the absence of O_2 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 acetoxylated 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 O_2 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 Ac_2O to the reaction to acetylate **1b**. As a result, the Cu loading was reduced to 10 mol % in the presence of O_2, 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 $Cl_2CHCHCl_2$ gave dichlorinated product **1d** in 92% isolated yield.[11,12] Analysis of the reaction mixture using ^1H NMR and pH measurements indicated that $Cl_2CHCHCl_2$ was partially converted to $Cl_2C{=}CHCl$ 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 $CuCl_2$ in $Cl_2CHCHCl_2$ 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

Scheme 1. Formation of Monohydroxylated Products



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

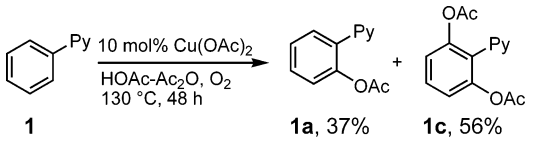
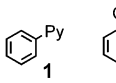
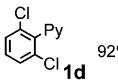
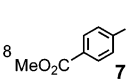
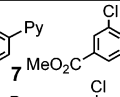
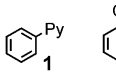
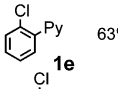
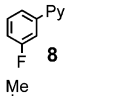
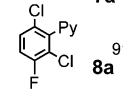
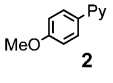
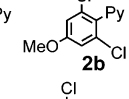
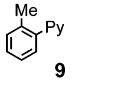
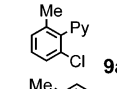
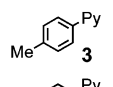
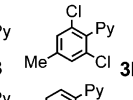
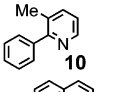
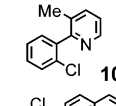
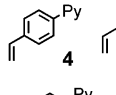
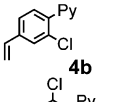
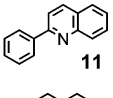
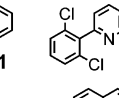
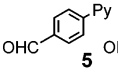
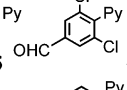
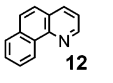
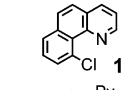
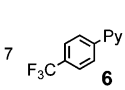
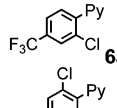
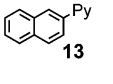
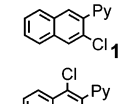


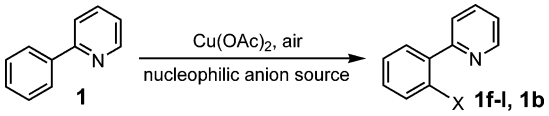
Table 1. Cu(II)-Catalyzed Chlorination of Aryl C−H Bonds[a]

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% 20%	14			30% 65%

[a] With 20 mol % of $CuCl_2$, $Cl_2CHCHCl_2$, O_2 (1 atm), 130 °C, 24 h. [b] At 100 °C; 23% dichlorinated product was also obtained.

10.1021/ja061715q CCC: $33.50

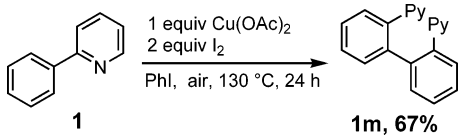
Table 2. Cu(II)-Mediated Diverse C−H Functionalizations[a]



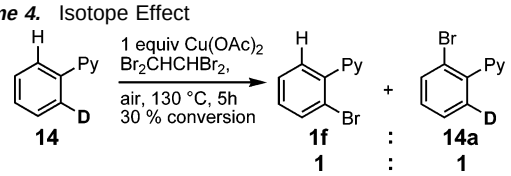
entry	anion source	solvent	product (X)	yield
1	−	$Br_2CHCHBr_2$	Br, **1f**	65%[d]
2	I_2	$ClCH_2CH_2Cl$	I, **1g**	61%[b,d]
3	TMSCN	MeCN	CN, **1h**	42%
4	−	$MeNO_2$	CN, **1h**	67%
5	$TsNH_2$	MeCN	TsNH, **1i**	74%
6	*p*-CN-PhOH	MeCN	*p*-CN-PhO, **1j**	35%
7	PhSH	DMSO	PhS, **1k**	40%
8	MeSSMe	DMSO	MeS, **1l**	51%[d]
9	H_2O	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 CuF_2. [d] Difunctionalized products (10−20%) were also obtained.

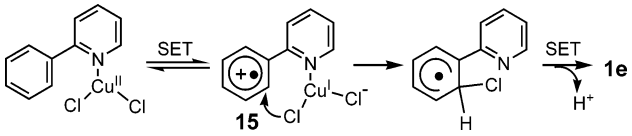
Scheme 3. Dimerization



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, CuX_2, 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 $MeNO_2$ as a CN source for cyanation is practically convenient (entry 4).[14] We also identified $TsNH_2$ 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 CuF_2 and H_2O 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 $CuCl_2$. 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 O_2 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.

Acknowledgment. We thank Brandeis University for financial support, and the Camille and Henry Dreyfus Foundation for a New Faculty Award. We thank Professor Peter Beak (University of Illinois, Urbana−Champaign) for helpful discussions about the mechanism.

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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(14) The mechanism of the formation of the cyanation product in the absence of CN^- remains to be elucidated.
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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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