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Copper(II)-Catalyzed Ortho-Acyloxylation of the 2-Arylpyridines sp^2 C−H Bonds with Anhydrides, Using O_2 as Terminal Oxidant

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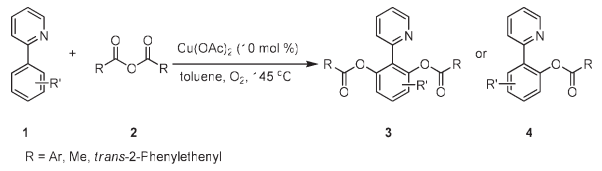

A chelation-assisted copper(II)-catalyzed ortho-acyloxylation of the 2-arylpyridine sp^2 C−H bond with anhydride is described. The procedure tolerates various functional groups, such as carbomethoxyl, methoxyl, fluoro, bromo, chloro, and cyano groups, affording the mono- or diacyloxylated products in moderate to good yields. Importantly, this procedure uses O_2 as a clean terminal oxidant.

Immense effort has been directed toward the development of efficient strategies for the direct functionalization of the C−H bond using transition metal catalysis.[1] Notable progress has been made predominantly with Pd,[2] Ru,[3] and Rh[4] catalysts which allow atom-economical transformations of the C−H bonds into C−C and C−heteroatom bonds. Recently, the development of regioselective C−O bond formation via C−H cleavage has attracted much attention.[5] We also have developed an efficient rhodium-catalyzed *o*-benzoxylation of the sp^2 C−H bond.[6] However, most reports on such transformations have been limited to acetoxylation,[7] and have used relatively expensive palladium or rhodium catalysts. From the synthetic point of view, it is more cost-efficient to replace the expensive transition metal catalyst with a cheaper one. Employing copper as the catalyst, which is not commonly used in C−H functionalization reactions,[8] is particularly attractive due to its low cost and toxicity. In 2006, Yu described an elegant example of $Cu(OAc)_2$-catalyzed oxidative acetoxylation of arene C−H bonds in $HOAc/Ac_2O$ using oxygen as a clean oxidant at an elevated temperature (Scheme 1, eq 1).[9] In 2005, Yu also reported a Pd-catalyzed

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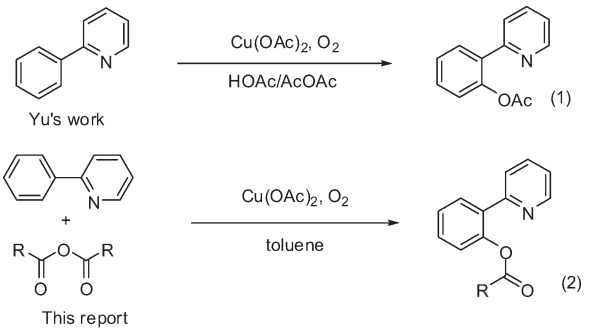
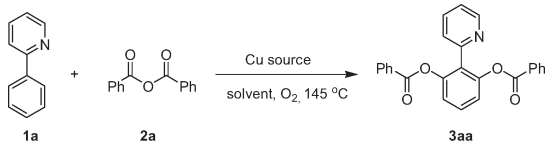
SCHEME 1. Copper-Catalyzed Acyloxylation of the 2-Phenylpyridine C−H Bond



stereoselective oxidation of methyl groups by carboxylic anhydrides.[10] Our interest in C−H functionalization[6,11] led us to explore the possibility of using readily available anhydrides as the reaction partners catalyzed by copper for such transformations. Herein, we report a chelation-assisted copper(II)-catalyzed ortho-acyloxylation of the sp^2 C−H bond of 2-arylpyridine employing O_2 as the terminal oxidant (Scheme 1, eq 2).

TABLE 1. Selected Results of Screening the Optimal Conditions[a]



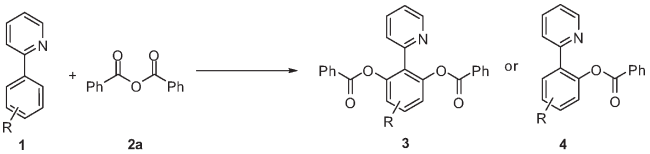
entry	Cu source (mol %)	solvent	yield (%)
1	$Cu(OAc)_2$(30)	NMP	< 5
2	$Cu(OAc)_2$(30)	DMF	< 5
3	$Cu(OAc)_2$(30)	DCE	36
4	$Cu(OAc)_2$(30)	xylene	77
5	$Cu(OAc)_2$(30)	1,4-dioxane	< 5
6	$Cu(OAc)_2$(30)	CH_3CN	12
7	$Cu(OAc)_2$(30)	toluene	85
8	$Cu(OAc)_2$(20)	toluene	85
9	$Cu(OAc)_2$(10)	toluene	84 (79[b], 73[c])
10	$Cu(OAc)_2$(5)	toluene	78
11	$Cu(OAc)_2$(10)	toluene	53[d]
12	$Cu(OAc)_2$(10)	toluene	< 5[e]
13	$Cu(OTf)_2$(10)	toluene	< 5
14	$CuBr_2$(10)	toluene	< 5
15	$Cu(acac)_2$(10)	toluene	49
16	CuO(10)	toluene	11
17	$CuCl_2$(10)	toluene	75

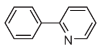
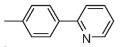
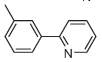
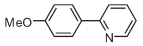
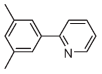
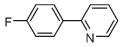
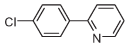
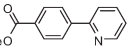
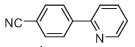
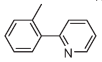
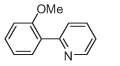
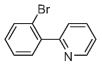
[a]2-Phenylpyridine (0.2 mmol), benzoic anhydride (0.6 mmol), Cu source in dry solvent in a sealed tube, 145 °C, 24 h, under O_2. [b]Benzoic anhydride (0.5 mmol). [c]Benzoic anhydride (0.7 mmol). [d]Under air. [e]Under N_2.

We initiated our investigation by examining the reaction of benzoic anhydride and 2-phenylpyridine using $Cu(OAc)_2$ as the catalyst in a sealed tube (Table 1). The results suggested that the solvent was crucial for this transformation. Polar solvents such as NMP and DMF inhibited the reaction (Table 1, entries 1 and 2). Among the low-polar solvents screened, toluene was the best, affording the diacyloxylated product in 85% yield (Table 1, entry 7). Several copper sources were also examined. $Cu(OAc)_2$ and $CuCl_2$ showed better catalytic reactivity. In addition, the amount of $Cu(OAc)_2$ had little effect on the reaction (Table 1, entries 7−10). To reduce the catalyst loading, we finally chose 10 mol % of $Cu(OAc)_2$ as the catalyst. Increasing or decreasing the amount of benzoic anhydride slightly decreased the yield (Table 1, entry 9).

Under air, the yield of **3aa** sharply decreased to 53% (Table 1, entry 11). Under N_2, only a trace of the product was formed (Table 1, entry 12), which indicated that O_2 may act as the terminal oxidant in the procedure. Particularly, the use of O_2 as an oxidant in C−H bond functionalization showed practical advantages compared to other oxidants, such as $PhI(OAc)_2$, Oxone, $K_2S_2O_8$, BQ, and TBHP. Benzoic acid was subjected to the reaction, and the yield of **3aa** decreased to 34%. Replacing Ac_2O with benzoic anhydride in Yu's protocol resulted in the formation of acetoxylated product along with a trace of the benzoxylated product. The reaction temperature was also crucial for the reaction, with lower yields obtained at temperatures below 145 °C.

TABLE 2. Ortho-Acyloxylation of 2-Arylpyridines with Benzoic Anhydride[a]



entry	2-aryl pyridine 1		product	yield (%)
1		1a	3aa	84
2		1b	3ba	87
3		1c	4ca	61
4		1d	3da	79
5		1e	4ea	54[b]
6		1f	3fa	49[b]
7		1g	3ga	56
8		1h	3ha	60[b]
9		1i	4ia	31[b]
10		1j	4ja	85
11		1k	4ka	91
12		1l	4la	33

[a]2-Arylpyridine (0.2 mmol), benzoic anhydride (0.6 mmol), $Cu(OAc)_2$ (10 mol %) in dry toluene (2 mL) in a sealed tube, O_2, 145 °C, 24 h. [b]48 h.

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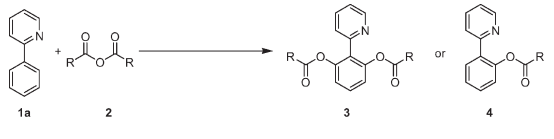
Finally, the optimized conditions were defined as follows: under O_2, 10 mol % of $Cu(OAc)_2$ as the catalyst, and a 1:3 mol ratio of 2-arylpyridine and anhydride in dry toluene at 145 °C.

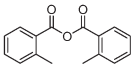
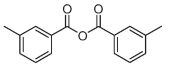
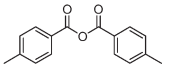
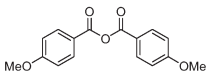
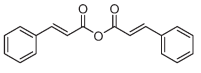
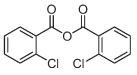
With the optimized reaction conditions in hand, the scope of 2-arylpyridines was investigated (Table 2). The electronic property of the substituent significantly affected the reaction. The electron-donating functional groups attached to the aryl ring gave higher yields than those with electron-withdrawing groups (Table 2, entries 2, 3, 4, 10, 11 vs 6, 7, 8, 9). Notably, the procedure tolerated a range of functional groups, such as cyano, chloro, bromo, and carbomethoxyl groups. Importantly, the selectivity of mono- and diacyloxylation may be dominated by the hindrance on the aryl ring. For example, the meta-substituted substrates **1c** and **1e** solely produced the monoacyloxylated product in moderate yields (Table 2, entries 3 and 5). Furthermore, the monoacyloxylated product was obtained when one ortho-position of phenyl was blocked. For example, 2-*o*-tolylpyridine **1j** and 2-(2-methoxyphenyl)pyridine **1k** provided monoacyloxylated products in 85% and 91% yields, respectively (Table 2, entries 10 and 11). Aryl bromide was also a reaction partner, albeit the acyloxylation product ***4l*a** was isolated in 33% yield, along with the recovery of starting material. This was notable as on one hand the aryl bromide substrates are often very reactive in $Pd^{0/II}$ catalytic cycles, and on the other hand the bromo products could be easily further modifiable (Table 2, entry 12).

Next, we explored the reaction of a variety of anhydrides with 2-phenylpyridine as shown in Table 3. These results indicated that steric hindrance on the aryl ring of the anhydrides had little effect on the transformation (Table 3, entry 1 vs entry 3). Acetic anhydride produced the monoacetoxylated product **4af** as a major product in moderate yield. In particular, *trans*-cinnamic anhydride **2g** was subjected to the reaction, affording the product **3ag** in 40% yield with longer reaction time (Table 3, entry 6). Disappointingly, the feasibility of access to trifluoromethanesulfonated product by use of trifluoromethanesulfonic anhydride failed.

A competition reaction was conducted under the standard conditions, and **3aa** was isolated in 58% yield along with 38% of **3′aa**, indicating that it was the benzoyloxyl that preferably transferred to the ortho-acyloxylation product (Scheme 2).

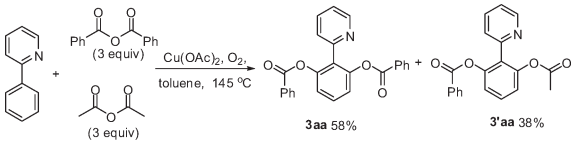
TABLE 3. Ortho-Acyloxylation of 2-Phenylpyridine with Anhydrides[a]



entry	anhydride **2**		product	yield (%)
1		**2b**	**3ab**	85
2		**2c**	**3ac**	80
3		**2d**	**3ad**	83
4		**2e**	**3ae**	81
5		**2f**	**4af**	42
6		**2g**	**3ag**	40[b]
7		**2h**	**3ah**	48[b]

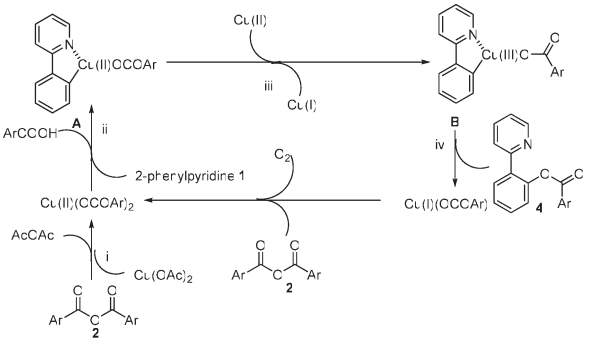
[a]2-Phenylpyridine (0.2 mmol), anhydride (0.6 mmol), $Cu(OAc)_2$ (10 mol %) in dry toluene (2 mL) in a sealed tube, O_2, 145 °C, 24 h. [b]48 h.

SCHEME 2. Competition Reaction of Anhydride with 2-Phenylpyridine



Radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2 mol %) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 2 mol %) were added to the standard procedure, respectively. However, product **3aa** was isolated in 81% and 85% yields, respectively. This result ruled out the possibility of a radical-mediated mechanism.[9]

SCHEME 3. Plausible Mechanism



On the basis of the experimental results and Stahl's seminal work on mechanistic study of copper-catalyzed aerobic oxidative coupling of arylboronic esters and methanol,[12] a plausible mechanism for this transformation is outlined in Scheme 3. In step i, the reation of $Cu(OAc)_2$ with benzoic anhydride **2** affords Cu(II) benzoate and acetic anhydride as a byproduct. Step ii involves the electrophilic attack of Cu(II) on phenyl ring of 2-arylpyridine to afford a cyclometalated Cu(II) intermediate **A**. The fact that the 2-arylpyridine possessing electron-donating groups showed higher reactivity is consistent with this step. Then, the Cu(II) intermediate **A** is oxidized to a Cu(III) intermediate **B** in the presence of Cu(II). In the final step, the reductive elimination of Cu(III) intermediate **B** takes place immediately to deliver the product **4** along with a Cu(I) species, which is oxidized by O_2 to

(12) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.

regenerate the Cu(II) benzoate in the presence of benzoic anhydride **2**.

In conclusion, we have developed an efficient chelation-assisted copper-catalyzed ortho-acyloxylation reaction of the 2-arylpyridine sp^2 C−H bond, affording mono- or diacyloxylation products in moderate to good yields. The use of inexpensive copper catalysts and O_2 as the terminal oxidant provides a significant practical advantage for this transformation. The reaction showed remarkably broad substrate scope and good functional group tolerance.

Experimental Section

General Procedure for Ortho-Acyloxylation of the 2-Arylpyridines. Under O_2 atmosphere, a sealed tube was charged with 2-arylpyridine (0.2 mmol), anhydrides (0.6 mmol), $Cu(OAc)_2$ (10 mol %), and dry toluene (2 mL). The mixture was stirred at 145 °C for 24 h. Then the solvent was concentrated in vacuo and the residue was purified by flash column chromatography on a silica gel to give the desired product.

2-(Pyridin-2-yl)-1,3-phenylene bis(3-methylbenzoate) (3ac): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (d, J = 3.9 Hz, 1H), 7.73 (d, J = 9.9 Hz, 4H),7.58−7.52 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.36−7.24 (m, 6H), 7.10 (m, 1H), 2.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.8, 152.0, 149.4, 149.2, 138.2, 136.2, 134.3, 133.7, 130.6, 129.5, 128.9, 128.3, 127.2, 125.3, 122.5, 120.6, 21.2; IR (prism, cm^{-1}) ν 3061, 2923, 1735, 1457, 1426, 1269; HRMS (EI) calcd for $C_{27}H_{21}NNaO_4$ $(M+Na)^+$ 446.1368, found 446.1348.

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Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.