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Copper(II)-catalyzed *ortho*-functionalization of 2-arylpyridines with acyl chlorides†

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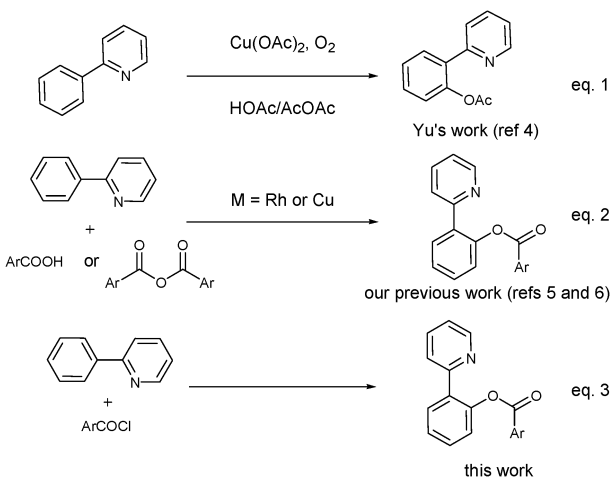
Copper-catalyzed *ortho*-benzoxylation of 2-arylpyridine sp^2 C–H bonds with acyl chloride is described. Notably, switching the base from *t*-BuOK to Li_2CO_3 causes chlorination of the C–H bond to take place.

The direct conversion of carbon–hydrogen bonds into carbon–carbon, carbon–halogen, carbon–nitrogen and carbon–sulfur bonds is a very powerful methodology for building complex molecules.[1] Recently, carbon–oxygen bond formation *via* C–H bond functionalization has attracted much attention.[2] In 2005, Yu reported a Pd-catalyzed stereoselective oxidation of methyl groups by carboxylic anhydrides.[3] 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 (Scheme 1, eq (1)).[4] In 2009, we developed an efficient rhodium-catalyzed *ortho*-benzoxylation of an sp^2 C–H bond (Scheme 1, eq (2)).[5] Subsequently, we demonstrated a copper-catalyzed *ortho*-acyloxylation reaction of an sp^2 C–H bond (Scheme 1, eq (2)).[6] However, transition-metal-catalyzed benzoxylation of a C–H bond is not common, and sometimes, the carboxylic anhydrides are not commercially available. Thus, the need for new methodology for such a transformation still exists. Our interest in C–H functionalization led us to explore the possibility of using readily available acyl chlorides as the reaction partners for such transformations.[5–7] Herein, we report a chelation-assisted copper(II)-catalyzed *ortho*-acyloxylation of the sp^2 C–H bond of 2-arylpyridine by acyl chloride, employing O_2 as the terminal oxidant (Scheme 1, eq (3)).[8]

Initial studies were performed using the reaction of 2-*o*-tolylpyridine with benzoyl chloride under oxygen as the model reaction, employing $Cu(OAc)_2$ as the catalyst in a sealed tube (Table 1). The results suggested that the base was important for this transformation and *t*-BuOK appeared to be the best among the screened bases, delivering the product in 85% yield (Table 1, entry 7). Under air, the yield dramatically decreased to 57%, while no desired product was detected under nitrogen (Table 1, entry 7). These results suggested that the oxygen played a significant role in the reaction. In addition, the amount of $Cu(OAc)_2$ had little effect on the reaction (Table 1, entries 7, 9 and 10). To reduce the catalyst loading, we finally chose 20 mol% of $Cu(OAc)_2$ as the catalyst. Several copper sources were also examined, however, the use of $Cu(OTf)_2$, $Cu(acac)_2$, CuO, and $CuCl_2$ as the catalyst precursors resulted in trace formation of **3aa** (Table 1, entries 11, 12, 14 and 15). The solvent was also crucial for this transformation and the low-polar solvent toluene was the best. Increasing the amount of benzoyl chloride slightly did not change the yield obviously (Table 1, entry 8). The reaction conducted on a 1 mmol scale provided **3aa** in an acceptable 78% yield.

Encouraged by these results, we further pursued the scope of the process with respect to acyl chlorides. As expected, the reaction proceeded smoothly, with yields ranging from moderate to good, and tolerated various functional groups, such as ethoxyl, chloro, fluoro and trifluoromethyl groups. The hindrance on the phenyl of acyl chloride had some effect on the reaction. For example, **3ac** and **3ad** were isolated in 90% and 87% yields, respectively (Table 2, entries 3 and 4), while **3ab** was obtained in 72% yield (Table 2, entry 2). The electronic effect of the substituent on the phenyl of the acyl chloride is not obvious in the reaction. Evidently, the regioselectivity of the *meta*-substituted substrates was dominated by steric effects, and the less hindered *ortho*-position of



Scheme 1 Acyloxylation of the 2-phenylpyridine C–H bond.

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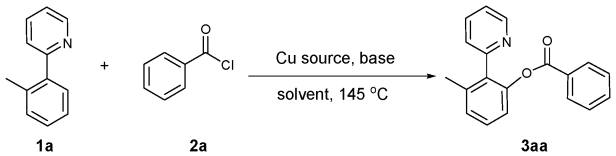
Table 1 Selected results of reaction parameters screening[a]



1a 2a 3aa

Entry	Cu source (equiv.)	Base	Solvent	Yield (%)
1	$Cu(OAc)_2$ (0.3)	$NaHCO_3$	toluene	56
2	$Cu(OAc)_2$ (0.3)	$KHCO_3$	toluene	81
3	$Cu(OAc)_2$ (0.3)	Na_2CO_3	toluene	66
4	$Cu(OAc)_2$ (0.3)	Ag_2CO_3	toluene	80
5	$Cu(OAc)_2$ (0.3)	Li_2CO_3	toluene	<5
6	$Cu(OAc)_2$ (0.3)	NaOAc	toluene	<5
7	$Cu(OAc)_2$ (0.3)	*t*-BuOK	toluene	85 (57[b], <5[c])
8	$Cu(OAc)_2$ (0.3)	*t*-BuOK	toluene	86[d]
9	$Cu(OAc)_2$ (0.2)	*t*-BuOK	toluene	83
10	$Cu(OAc)_2$ (0.1)	*t*-BuOK	toluene	80
11	$Cu(OTf)_2$ (0.2)	*t*-BuOK	toluene	<5
12	$Cu(acac)_2$ (0.2)	*t*-BuOK	toluene	<5
13	CuI (0.2)	*t*-BuOK	toluene	60
14	CuO (0.2)	*t*-BuOK	toluene	<5
15	$CuCl_2$ (0.2)	*t*-BuOK	toluene	<5
16	$Cu(OAc)_2$ (0.2)	*t*-BuOK	xylene	76
17	$Cu(OAc)_2$ (0.2)	*t*-BuOK	DMF	<5
18	$Cu(OAc)_2$ (0.2)	*t*-BuOK	NMP	<5
19	$Cu(OAc)_2$ (0.2)	*t*-BuOK	chlorobenzene	59
20	$Cu(OAc)_2$ (0.2)	*t*-BuOK	CH_3CN	18

[a] Reaction conditions: 2-*o*-tolylpyridine (0.2 mmol), benzoyl chloride (0.4 mmol), base (2 equiv.), Cu source in dry solvent (2 mL) in a sealed tube, 145 °C, 48 h, under O_2. Isolated yield. [b] Under air. [c] Under N_2. [d] Benzoyl chloride (0.6 mmol).

Table 2 *Ortho*-chlorination of 2-arylpyridines with acyl chlorides[a]

1 2 3

Entry	R^1, R^2	R^3	Yield[b] (%)
1	R^1 = 2-Me, R^2 = H (**1a**)	H (**2a**)	83 (**3aa**)
2	**1a**	2-Me (**2a**)	72 (**3ab**)
3	**1a**	3-Me (**2c**)	90 (**3ac**)
4	**1a**	4-Me (**2d**)	87 (**3ad**)
5	**1a**	4-F (**2e**)	83 (**3ae**)
6	**1a**	2-Cl (**2f**)	60 (**3af**)
7	**1a**	3-CF_3 (**2g**)	89 (**3ag**)
8	**1a**	2-OEt (**2h**)	86 (**3ah**)
9	R^1 = 2-OMe, R^2 = H (**1b**)	H (**2a**)	76 (**3ba**)
10	R^1 = 3-Me, R^2 = H (**1c**)	H (**2a**)	54 (**3ca**)
11	R^1 = 3,5-Me, R^2 = H (**1d**)	H (**2a**)	52 (**3da**)
12	R^1 = H, R^2 = Me (**1e**)	H (**2a**)	81 (**3ea**)

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (20 mol%), and *t*-BuOK (0.4 mmol) in dry toluene (2 mL) under O_2 at 145 °C for 48 h. [b] Isolated yield.

2-arylpyridine was acylated with good selectivity (>95 : 5). Meanwhile, presumably as a result of steric hindrance, the monofunctionalized product was observed using substrate **1e** (Table 2, entry 12).[9] Disappointingly, the feasibility of accessing the acetoxylated product using acetyl chloride was poor. In comparison with our previous work, this methodology is more practical since most acyl chlorides are commercially available.

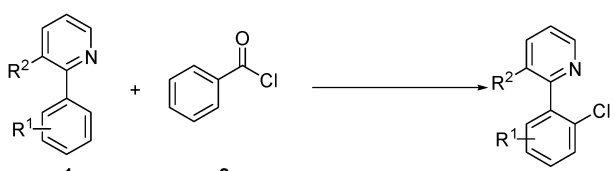
Interestingly, when Li_2CO_3 was used in the procedure instead of *t*-BuOK, *ortho*-chlorination of 2-arylpyridine occurred (Table 3). For **1f**, the reaction gave the dichlorinated product in 99% yield with a longer reaction time. However, if we blocked one *ortho* position of 2-arylpyridine or increased the hindrance either on the phenyl or pyridinyl ring, the mono-chlorination took place smoothly using the procedure. Obviously, the chloride source was derived from the benzoyl chloride. In 2009, Dong reported a similar work in the palladium-catalyzed C–H bond functionalization with aryl-sulfonyl chlorides.[10] It is a novel approach of providing chlorinated arylpyridine.[4,10,11]

During the reaction, carboxylic anhydride was detected by GC-MS. The acyl chloride may readily form carboxylic anhydride in the presence of a base and moisture.[12] Moreover, $PhCOO^tBu$, which may be formed by the reaction of acyl chloride with *t*-BuOK, was subjected to the procedure, and no benzoxylation product was formed. Based on the experimental results and our previous work,[6] we reasoned carboxylic anhydride was the intermediate in this tranformation.

A plausible mechanism for this transformation is outlined in Scheme 2. In step (i), carboxylic anhydride was formed *in situ* from acyl chloride in the presence of a base and moisture.[12] In fact, the reaction is inhibited in the presence of molecular sieves. This result is consistent with step (i). In step (ii), the reaction of $Cu(OAc)_2$ with benzoic anhydride **5** affords Cu(II) benzoate and acetic anhydride as a byproduct. Step (iii) involves the electrophilic attack of Cu(II) on the phenyl ring of **1** to afford a cyclometallated Cu(II) intermediate **A**. Then, the Cu(II) intermediate **A** is oxidized to a Cu(III) intermediate **B** in the presence of Cu(II).[13] In the final step, the reductive elimination of Cu(III) intermediate **B** takes place immediately to deliver the product **3** along with a Cu(I) species, which is oxidized by O_2 to regenerate the Cu(II) benzoate in the presence of benzoic anhydride **5**.

In conclusion, we have developed a copper-catalyzed *ortho*-benzoxylation of 2-arylpyridine C–H bonds using the commercially available acyl chlorides. The procedure tolerates a series of functional groups, such as ethoxyl, chloro, fluoro and trifluoromethyl groups. Notably, switching the base from

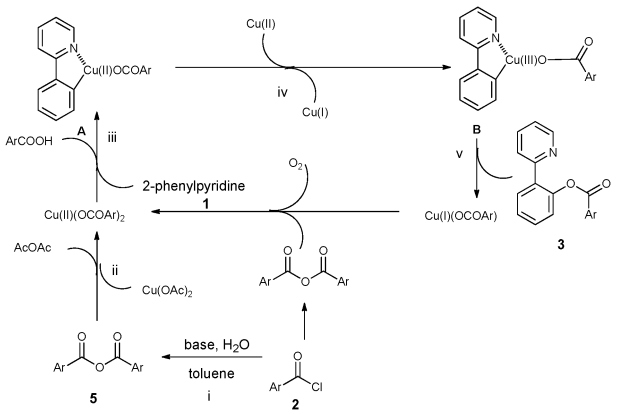
Table 3 *Ortho*-chlorination of 2-arylpyridines with acyl chlorides[a]



1 2a 4

Entry	1	Yield[b] (%)
1	**1a**	80 (**4aa**)
2	**1b**	77 (**4ba**)
3	**1d**	65 (**3da**)
4	**1e**	51 (**3ea**)
5	R^1 = H, R^2 = H (**1f**)	99 (**3fa**)[c]

[a] Reaction conditions: 2-arylpyridine **1** (0.2 mmol), benzoyl chloride **2a** (0.6 mmol), Li_2CO_3 (0.4 mmol) and $Cu(OAc)_2$ (20 mol%) in dry toluene (2 mL) in a sealed tube, 145 °C, 48 h, under O_2. [b] Isolated yield. [c] 60 h.



Scheme 2 A possible mechanism for the transformation *via* Cu(II) (**A**) and Cu(III) (**B**) intermediates.

t-BuOK to Li_2CO_3 causes chlorination of the C–H bond to take place. Ongoing work seeks to gain further insights into the mechanism of this reaction and to expand the scope to the acylation of unactivated sp^3 C–H bonds.

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