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Copper(II)-catalyzed *ortho*-Benzoxylation of 2-Arylpyridines with Sodium Carboxylates

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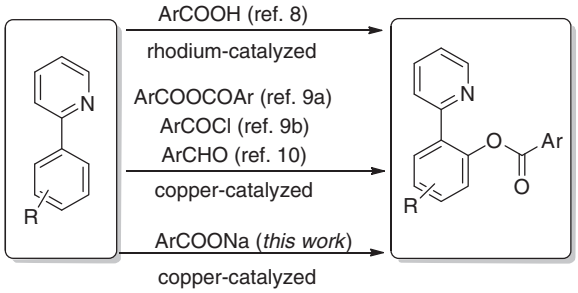
Copper-catalyzed *ortho*-benzoxylation of an sp^2 C–H bond by sodium carboxylates is described. The procedure tolerates carbomethoxy, formyl, bromo, and chloro groups, providing the benzoxylated products in moderate to good yields.

The ester functionality is a ubiquitous structural moiety in natural products, pharmaceuticals, and functional materials. Thus, the need for ester compounds will never lessen.[1] Extensive efforts in transition-metal-catalyzed esterification have shown encouraging progress during the past decade.[2] In the past few years, selective functionalization of C–H bonds has emerged as a powerful tool in modern organic synthesis.[3] The C–H activation strategy has also been applied in ester formation.[4] Among them, great interest has been focused on C–H acetoxylation of pyridine- or imine-directing groups.[5] For example, Sanford discovered palladium-catalyzed *ortho*-acetoxylation of 2-arylpyridines using $PhI(OAc)_2$ as an oxidant.[6] In 2005, Yu reported Pd-catalyzed stereoselective oxidation of methyl groups in 2-oxazolines using lauroyl or benzoyl peroxide as the stoichiometric oxidant.[7] Subsequently, Yu described the $Cu(OAc)_2$-catalyzed oxidative acetoxylation of arene C–H bonds in HOAc/Ac_2O using oxygen as a clean oxidant.[8] However, most reports on such transformations have been limited to acetoxylation. In 2009, we developed *ortho*-benzoxylation of 2-arylpyridines with benzoic acid using expensive rhodium as the catalyst.[9] Subsequently, we demonstrated a copper-catalyzed *ortho*-benzoxylation reaction of an sp^2 C–H bond with anhydride or acyl chloride.[10] However, the carboxylic anhydrides as benzoxylation partner are not commercially available in most cases and acyl chlorides are usually susceptible to moisture. More recently, Huang developed a copper-catalyzed domino oxidation–acyloxylation reaction of 2-arylpyridines with aldehydes or methylarenes affording relative lower yields.[11] Thus, it is highly desirable to develop a dependable benzoxylation partner.

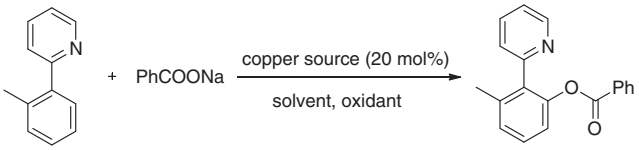
Sodium carboxylates are widely used in traditional cross-coupling reactions in ester synthesis due to their superior features such as high air- and moisture-stability.[12] Our interest in transition-metal-catalyzed C–H functionalization spurred us to explore the possibility of using readily available sodium carboxylates as the benzoxylation partners for such transformations.[9,10] Herein, we report the chelation-assisted copper(II)-catalyzed *ortho*-benzoxylation of 2-arylpyridine with sodium carboxylates (Scheme 1).

To begin our study, the effect of the various reaction parameters on the reaction of 2-*o*-tolylpyridine (**1a**) with sodium benzoate (**2a**) was examined using $Cu(OTf)_2$ as the catalyst (Table 1). The results suggested that the oxidant had a dramatic effect on the reaction. Among the oxidants tested, only 15% of **3aa** was obtained using O_2, which had practical advantages in our early reports[9] (Table 1, Entry 1). No reaction was observed using



Scheme 1. *ortho*-Benzoxylation of 2-arylpyridine.

Table 1. Screening for the optimum conditions[a]



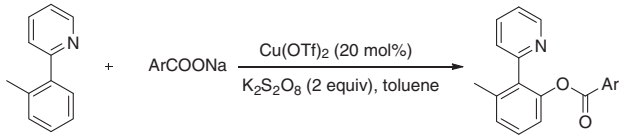
1a **2a** **3aa**

Entry	Cu sources	Oxidant	Solvent	Yield/%[b]
1	$Cu(OTf)_2$	O_2	toluene	15
2	$Cu(OTf)_2$	DDQ	toluene	<5
3	$Cu(OTf)_2$	$PhI(OAc)_2$	toluene	31
4	$Cu(OTf)_2$	TBHP	toluene	44
5	$Cu(OTf)_2$	$K_2S_2O_8$	toluene	82 (69)[c], (28)[d]
6	$Cu(OAc)_2$	$K_2S_2O_8$	toluene	26
7	$CuCl_2$	$K_2S_2O_8$	toluene	51
8	CuF_2	$K_2S_2O_8$	toluene	44
9	CuI	$K_2S_2O_8$	toluene	<5
10	CuCl	$K_2S_2O_8$	toluene	47
11	$CuBr_2$	$K_2S_2O_8$	toluene	49
12	CuBr	$K_2S_2O_8$	toluene	36
13	$Cu(OTf)_2$	$K_2S_2O_8$	NMP	<5
14	$Cu(OTf)_2$	$K_2S_2O_8$	DCE	<5
15	$Cu(OTf)_2$	$K_2S_2O_8$	DMF	10
16	$Cu(OTf)_2$	$K_2S_2O_8$	1,4-dioxane	<5
17	$Cu(OTf)_2$	$K_2S_2O_8$	toluene	50[e]
18	$Cu(OTf)_2$	$K_2S_2O_8$	toluene	55[f]

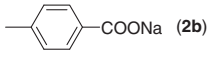
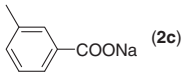
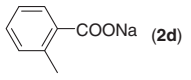
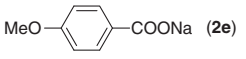
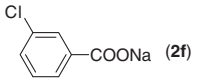
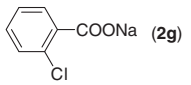
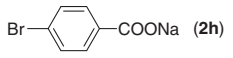
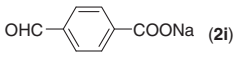
[a]All reactions were run with 2-*o*-tolylpyridine (0.3 mmol), sodium benzoate (0.2 mmol), copper source (20 mol %), oxidant (2 equiv) in 2 mL of solvent under air at 130 °C for 24 h. See Supporting Information (SI) for details.[14] [b]Isolated yield. [c]$K_2S_2O_8$ (1 equiv). [d]Under N_2. [e]10 mol % $Cu(OAc)_2$. [f]110 °C.

DDQ as oxidizing reagent (Table 1, Entry 2). The yield could be improved when TBHP was employed in the reaction (Table 1, Entry 4). To our delight, the reaction afforded the product **3aa** in 82% yield in the presence of $K_2S_2O_8$ (Table 1, Entry 5). Decreasing the amount of $K_2S_2O_8$ to 1 equiv lowered the yield

Table 2. *ortho*-Benzoxylation reaction of 2-*o*-tolylpyridine with sodium carboxylates[a]

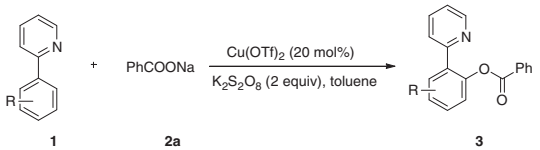


1a **2** **3**

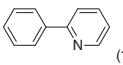
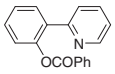
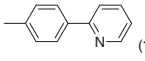
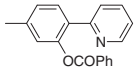
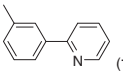
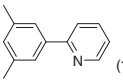
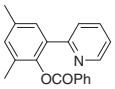
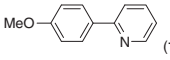
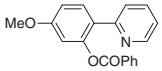
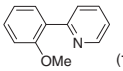
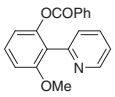
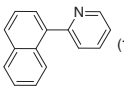
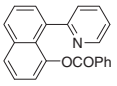
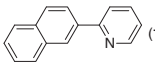
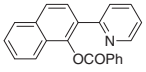
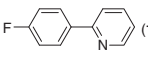
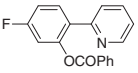
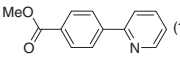
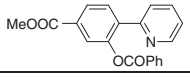
Entry	Substrate **2**	Product **3**	Yield/%[b]
1	 (**2a**)	**3aa**	82
2	 (**2b**)	**3ab**	75
3	 (**2c**)	**3ac**	60
4	 (**2d**)	**3ad**	50
5	 (**2e**)	**3ae**	86
6	 (**2f**)	**3af**	60
7	 (**2g**)	**3ag**	36
8	 (**2h**)	**3ah**	85
9	 (**2i**)	**3ai**	35

[a]All reactions were run with 2-*o*-tolylpyridine (0.3 mmol), sodium carboxylates (0.2 mmol), $Cu(OTf)_2$ (20 mol %), $K_2S_2O_8$ (2 equiv) in 2 mL of toluene under air at 130 °C for 24 h. See SI for details.[14]
[b]Isolated yield.

Table 3. *ortho*-Benzoxylation reaction of arylpyridine with sodium benzoate[a]



1 **2a** **3**

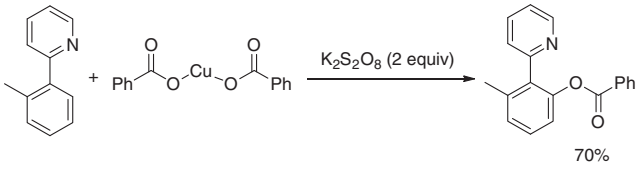
Entry	Substrate **1**	Product **3**	Yield/%[b]
1	 (**1b**)	 (**3ba**)	65
2	 (**1c**)	 (**3ca**)	75
3	 (**1d**)	(**3da**)	62[c]
4	 (**1e**)	 (**3ea**)	52
5	 (**1f**)	 (**3fa**)	52
6	 (**1g**)	 (**3ga**)	85
7	 (**1h**)	 (**3ha**)	67
8	 (**1i**)	 (**3ia**)	62
9	 (**1j**)	 (**3ja**)	50
10	 (**1k**)	 (**3ka**)	35

[a]All reactions were run with 2-arylpyridine (0.3 mmol), sodium benzoate (0.2 mmol), $Cu(OTf)_2$ (20 mol %), $K_2S_2O_8$ (2 equiv) in 2 mL of toluene under air at 130 °C for 24 h. See SI for details.[14]
[b]Isolated yield. [c]The ratio of 2- and 6-benzoxylation product was 1:8.3, determined by ^{1}H NMR.

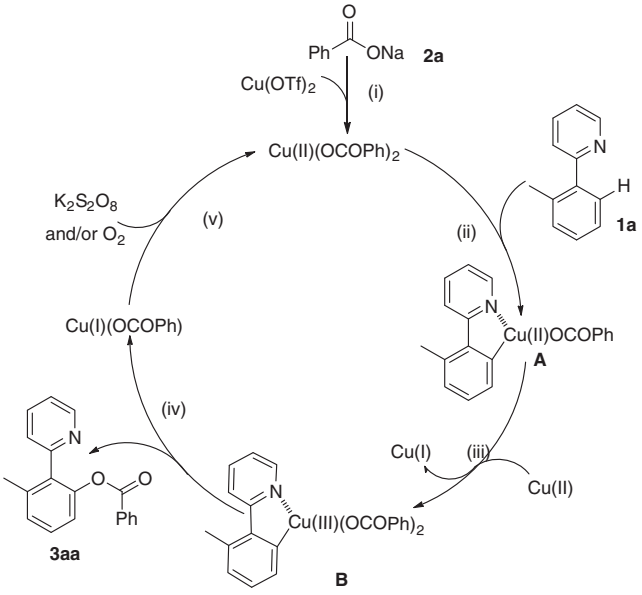
slightly, while 28% of **3aa** was detected under nitrogen (Table 1, Entry 5). Further study revealed that the source of copper had a dramatic effect on the reaction and $Cu(OTf)_2$ was the best (Table 1, Entries 5–12). In addition, the amount of $Cu(OTf)_2$ had obvious effect on the reaction (Table 1, Entry 5 vs. 17). The yield was decreased to 50% when using 10 mol % $Cu(OTf)_2$ (Table 1, Entry 17). Only 55% yield was obtained when the temperature was decreased to 110 °C (Table 1, Entry 18). Replacing toluene with other solvents such as NMP, DCE, DMF, and 1,4-dioxane significantly decreased the yields (Table 1, Entries 13–16). Thus, the best results were obtained in the presence of $Cu(OTf)_2$ (20 mol %) in combination with two equivalents of $K_2S_2O_8$ as the oxidant in toluene at 130 °C for 24 h. The reaction conducted on a 1 mmol scale provided **3aa** in an acceptable 78% yield. It is interesting that no product was detected when PhCOOH instead of PhCOONa was used.

With the optimized conditions in hand, the scope of sodium carboxylates was next investigated (Table 2). As expected, sodium carboxylates worked well under the reaction conditions. It was found that this method was quite general, as diverse substrates possessing methoxy, formyl, chloro, and bromo groups were perfectly tolerated under these reaction conditions and produced the corresponding products **3** in moderate to good yields. However, steric hindrance affected the efficiency. For example, 75% of **3ab** was isolated, while the yield of **3ad** decreased to 50% (Table 2, Entries 2 and 4). In particular, when sodium 4-bromobenzoate (**2h**) was subjected to the reaction, the product **3ah** was isolated in 85% yield, leaving the C–Br bond intact (Table 2, Entry 8). Disappointingly, the feasibility of accessing the acetoxylated product using sodium acetate failed.

Next, we promptly examined the scope of the arylpyridine moiety in the *ortho*-benzoxylation process (Table 3). As expected, the 2-phenylpyridine derivatives bearing various substitutents at the *para*, *meta*, or *ortho* position on the phenyl ring reacted smoothly to afford the desired monofunctionalized



Scheme 2. Stoichiometric reactions of copper(II) benzoate with 2-*o*-tolylpyridine.



Scheme 3. Plausible mechanism.

products in 35–85% yields. Evidently, the regioselectivity of the *meta*-substituted substrates was dominated by steric effects, and the less hindered *ortho*-position of 2-arylpyridine was acyloxylated with good selectivity (Table 3, Entry 3). Naphthalene substrates were also successfully benzoxylated in good yields and with excellent regioselectivity (Table 3, Entries 7 and 8). The use of substrates containing strong electron-withdrawing groups, such as ester was found to give the desired products in 35% yield (Table 3, Entry 10).

More experiments were carried out to gain a preliminary insight into reaction mechanism. When the stoichiometric reaction of 2-*o*-tolylpyridine (**1a**) with copper(II) benzoate was conducted, 3-methyl-2-(pyridin-2-yl)phenyl benzoate (**3aa**) was isolated in 70% yield (Scheme 2). This result showed copper(II) benzoate may be the intermediate. A working mechanism was proposed as outlined in Scheme 3. In step (i), the reaction of copper(II) trifluoromethanesulfonate with sodium benzoate forms copper(II) benzoate. Step (ii) involves the electrophilic attack of copper(II) benzoate on the phenyl ring of **1a** 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 a Cu(I) species, which is oxidized by $K_2S_2O_8$ to regenerate the copper(II) benzoate.

In summary, we have developed the copper-catalyzed *ortho*-benzoxylation of 2-arylpyridine C–H bonds employing the facile prepared sodium carboxylates and afforded the benzoxylation products in moderate to good yields. The reaction showed remarkably broad substrate scope with good functional group tolerance.

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References and Notes

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