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Rhodium-Catalyzed *ortho*-Benzoxylation of sp^2 C−H Bond

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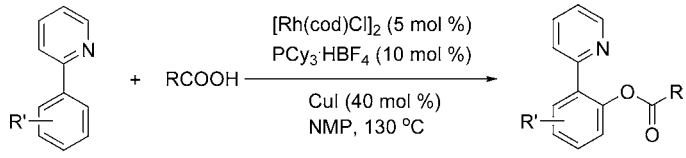
ABSTRACT



A rhodium-catalyzed *ortho*-benzoxylation of the sp^2 C−H bond by carboxylic acids is described. The procedure tolerates carbomethoxy, formyl, bromo, chloro, and nitro groups, providing the benzoxylated products in moderate to good yields. Importantly, no external oxidant was required for the transformation.

Selective functionalization of the C−H bond is a longstanding goal in organic synthesis because it obviates the prefunctionalization of substrates.[1] Combinations of transition metals and directing groups are useful strategies to facilitate the cleavage of the C−H bond, affording valuable transformations of an sp^2-hybridized C−H bond to C−C,[2] C−X,[3] and C−N bonds.[4] Recently, much attention has been paid to the development of regioselective C−O bond formation via C−H cleavage. For example, Sanford, Crabtree, Wang, and Stock demonstrated acetoxylation of an sp^2 C−H bond employing $PhI(OAc)_2$,[5] Oxone,[6] $K_2S_2O_8$,[7] and other reagents[8] as terminal oxidants. The Pd-catalyzed sp^3 C−H bond acetoxylation reactions[9] were also developed by Yu, Corey, and Sanford, respectively. However, most of the reports on

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(1) For representative reviews on C−H functionalization, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879, and references therein. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699. (c) Ritleng, V.; Sirlin, C.; Preffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (g) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, DOI: 10.1021/cr900005n. (i) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (j) Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, 949. (k) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (l) Diaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (m) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, DOI: 10.1021/ar9000058. (n) Dyker, G. *Handbook of C-H Transformations. Applications in Organic Synthesis*; Wiley-VCH; Weinheim, 2005. (o) Murai, S. *Activation of Unreactive Bonds and Organic Synthesis*; Springer: Berlin, 1999; pp 48−78. (p) Chatani, N. *Directed Metallation*; Springer: Berlin, 2008; Vol. 24.

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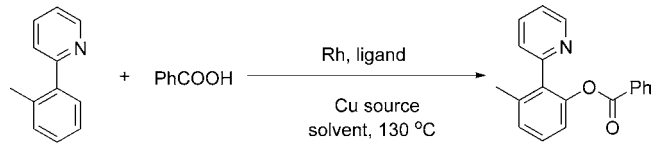
Table 1. Effects of Rh Source, Cu Sources, Ligands, and Solvents



1a 2a 3aa

entry	Rh source	Cu source (equiv)	ligand	solvent	yield (%)[a]
1	$Rh(CO)_2(C_5H_7O_2)$	$Cu(OAc)_2$ (0.3)		NMP	<5
2	$Rh(CO)_2(C_5H_7O_2)$	CuBr (0.3)		NMP	29
3	$Rh(CO)_2(C_5H_7O_2)$	CuCl (0.3)		NMP	26
4	$Rh(CO)_2(C_5H_7O_2)$	Cu_2O (0.3)		NMP	20
5	$Rh(CO)_2(C_5H_7O_2)$	CuI (0.3)		NMP	36
6	$Rh(CO)_2(C_5H_7O_2)$	CuI (0.3)	binap	NMP	46
7	$Rh(CO)_2(C_5H_7O_2)$	CuI (0.1)	binap	NMP	<5
8	$Rh(CO)_2(C_5H_7O_2)$	CuI (0.4)	binap	NMP	53
9	$Rh(CO)_2(C_5H_7O_2)$	CuI (0.5)	binap	NMP	50
10	$Rh(CO)_2(C_5H_7O_2)$	CuI (1.0)	binap	NMP	51
11	$Rh(PPh_3)_3Cl$	CuI (0.4)	binap	NMP	62
12	$[Rh(cod)Cl]_2$	CuI (0.4)	binap	NMP	63
13	$[Rh(cod)Cl]_2$	CuI (0.4)	PPh_3	NMP	43
14	$[Rh(cod)Cl]_2$	CuI (0.4)	$P(1\text{-Nap})_3$	NMP	49
15	$[Rh(cod)Cl]_2$	CuI (0.4)	$i\text{-Pr}_2\text{N-PPh}_2$	NMP	40
16	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	NMP	66
17	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	DMF	20
18	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	1,4-dioxane	<5
19	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	toluene	<5
20	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	xylene	<5
21	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	NMP	72[b]
22	$[Rh(cod)Cl]_2$	CuI (0.4)	$PCy_3{\cdot}HBF_4$	NMP	69[b,c]

[a] 2-*o*-Tolylpyridine (0.2 mmol), benzoic acid (0.4 mmol), Rh source (5 mol %), Cu source, and ligand (7.5 mol %) in solvent, 130 °C, 36 h. Isolated yield. [b] 2-*o*-Tolylpyridine (0.4 mmol) and benzoic acid (0.2 mmol). [c] Under N_2.

such transformations via transition-metal-catalyzed C−H bond cleavage are almost limited to acetoxylation,[10] and a stoichiometric oxidant is required to fulfill the catalytic cycle. In 2005, the elegant Pd-catalyzed sp^3 C−H bond acetoxylation reaction employing peroxide oxidant MeCOOOtBu[11] was developed by Yu, in which aliphatic carboxylic acids were incorporated by using anhydrides. In 2006, Yu demonstrated the Cu(II)-catalyzed acetoxylation of an aryl C−H bond using O_2 as a clean oxidant.[3d] Herein, we wish to report rhodium-catalyzed *ortho*-benzoxylation of an sp^2 C−H bond. Importantly, no external oxidant was required in the procedure.

Our investigation started with the reaction of benzoic acid and 2-*o*-tolylpyridine using $Rh(CO)_2(acac)$ as the catalyst

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(10) The direct benzoxylation of the arene C−H bond other than acetoxylation, see: (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974.

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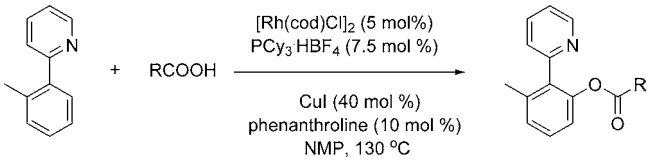
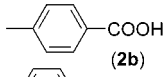
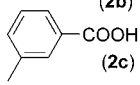
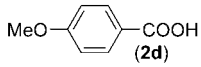
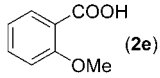
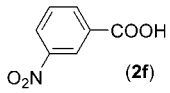
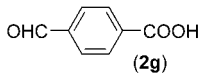
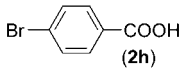
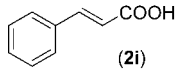
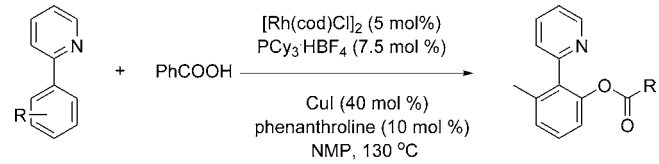
Table 2. *ortho*-Benzoxylation Reaction of 2-*o*-Tolylpyridine with Carboxylic Acids

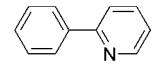
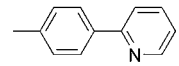
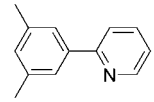
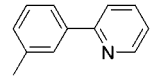
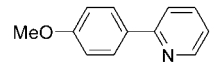
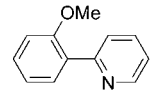
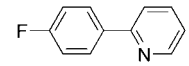
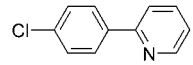
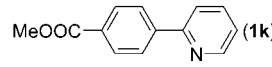


1a	2		3
entry	carboxylic acids **2**	product **3**	yield (%)[a]
1	 (**2b**)	**3ab**	76
2	 (**2c**)	**3ac**	79
3	 (**2d**)	**3ad**	80
4	 (**2e**)	**3ae**	61
5	 (**2f**)	**3af**	58
6	 (**2g**)	**3ag**	40
7	 (**2h**)	**3ah**	57
8	 (**2i**)	**3ai**	44
9	CH_3COOH (**2j**)	**3aj**	45

[a] 2-*o*-Tolylpyridine (0.4 mmol), carboxylic acid (0.2 mmol), $[Rh(cod)Cl]_2$ (5 mol %), CuI (40 mol %), and PCy_3·HBF_4 (7.5 mol %) in NMP, 130 °C, 36 h. Isolated yield.

Table 3. *ortho*-Benzoxylation Reaction of 2-Aryl Pyridines with Benzoic Acid



1	2a		3
entry	substrate **1**	product **3**	yield (%)[a]
1	 (**1b**)	**3ba**	69
2	 (**1c**)	**3ca**	65
3	 (**1d**)	**3da**	85
4	 (**1e**)	**3ea**	63[b]
5	 (**1f**)	**3fa**	70
6	 (**1g**)	**3ga**	81
7	 (**1i**)	**3ha**	48
8	 (**1j**)	**3ia**	43
9	 (**1k**)	**3ja**	53

[a] 2-*o*-Tolylpyridine (0.2 mmol), benzoic acid (0.4 mmol), $[Rh(codCl)]_2$ (5 mol %), CuI (40 mol %), and PCy_3·HBF_4 (7.5 mol %) in NMP, 130 °C, 36 h. Isolated yield. [b] The ratio of 2- and 6-benzoxylation product was 4:15, determined by ^1H NMR.

(Table 1). The results suggested that the copper sources used had a dramatic effect on the yields. Among the copper sources screened, CuI turned out to be the best (entry 5, Table 1), while $Cu(OAc)_2$ was not effective at all (entry 1, Table 1). Remarkably, the yield of **3aa** could be increased to 46% in the presence of binap (entry 6, Table 1). Unfortunately, decreasing the amount of CuI to 10 mol % resulted in no reaction (entry 7, Table 1), while increasing the amount of CuI to 40 mol % greatly improved the yield of **3aa** to 53% (entry 8, Table 1). Several rhodium sources were also examined. The Rh(cod)Cl dimer and Wilkinson's catalyst showed better catalytic activity (entries 11 and 12, Table 1). The ligand was also crucial for this transformation. The preligand, PCy_3·HBF_4, was the best, affording **3aa** in 66% yield (entry 16, Table 1). Next, we studied the solvent effect and found that *N*-methyl-2-pyrrolidone (NMP) was superior to dioxane, toluene, xylene, or DMF. Notably, the yield was improved to 72% by changing the ratio of benzoic acid and 2-*o*-tolylpyridine (entry 21, Table 1). When conducted under a N_2 atomsphere, **3aa** was obtained in 69% yield. The comparable result indicated O_2 was not essential for this transformation.

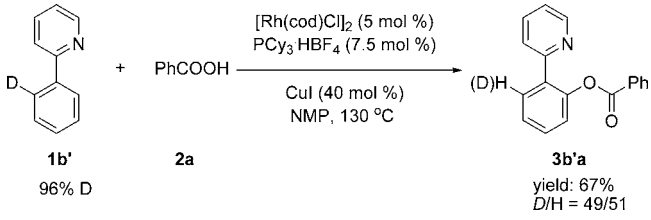
With a highly active catalytic system in hand, the scope of carboxylic acids was next investigated (Table 2). As expected, various substrates worked well under the reaction conditions. A range of functional groups, such as bromo, methoxy, formyl, and nitro groups, were tolerated in this procedure. However, steric hindrance affected the efficiency. For example, 80% of **3ad** was isolated, while the yield of **3ae** was decreased to 61% (entries 3 and 4, Table 2). The electron-donating substituents on the phenyl ring of carboxylic acids were beneficial for the transformation, whereas an electron-withdrawing group decreased the efficiency. Notably, **2h** underwent C−H bond benzoxylation leaving

the C−Br bond intact, which is attractive for further synthetic elaboration. It is noteworthy that an alkyl acid, such as acetic acid, also underwent the direct acetoxylation with **1a**, forming **3aj** in 45% yield (entry 9, Table 2). Particularly, the acrylic acid derivative, cinnamic acid **2i**, was subjected to the reaction, affording the product **3ai** in 44% yield (entry 8, Table 2).

Next, we explored the reaction of a variety of 2-aryl pyridines with benzoic acid as shown in Table 3. Steric hindrance on the aryl ring of 2-aryl pyridines did not inhibit the transformation. 2-(3,5-Dimethylphenyl)pyridine, for example, reacted smoothly to afford the corresponding product **3da** in 85% yield (entry 3, Table 3). The arenes possessing electron-donating functional groups were found to be more reactive and gave slightly higher yields than those of electron-withdrawing groups (entries 3, 4, 5, and 6 vs 8 and 9 Table 3). Fortunately, the chloro group was compatible with the reaction conditions (entry 8, Table 3). As for substrates containing a *meta* substituent on the aromatic ring (entry 4, Table 3), modest selectivity was observed for benzoxylation of the less sterically hindered *o*-C−H bond.

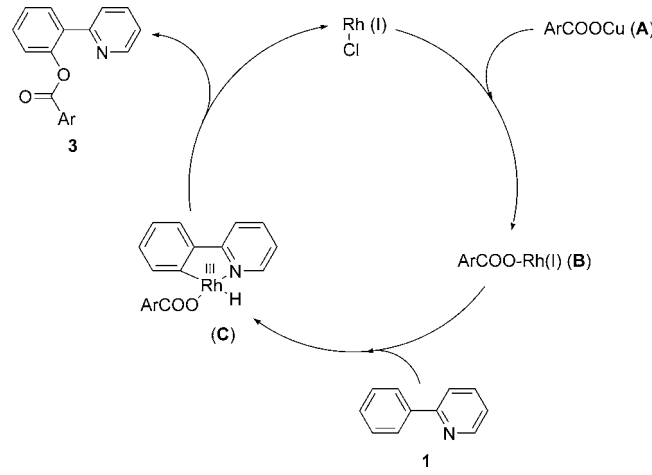
The intramolecular isotope kinetic effects of 2-phenylpyridine were studied. As shown in Scheme 1, interestingly, the k_H/k_D was found to be 51/49.

Scheme 1. Kinetic Isotope Effect Study



A plausible mechanism for this transformation is outlined in Scheme 2. First, rhodium(I) species react with the Cu-mediated benzoxylation product to produce intermediate **B**. Second, oxidative addition of the *ortho*-C−H bond of arylpyridine with rhodium(I) **B** species occurs to form Rh(III) intermediate **C**.[12] Finally, reductive elimination of intermediate **C** produces the desired product **3**[13] and regenerates the rhodium(I) catalyst.

Scheme 2. Plausible Mechanism



In conclusion, we have developed an efficient method for rhodium-catalyzed *ortho*-benzoxylation of the sp^2 C−H bond affording the benzoxylation products in moderate to good yields. The reaction showed remarkably broad substrate scope and good functional group tolerance. Efforts to expand the benzoxylation to an sp^3 C−H bond and elucidate the mechanism in detail are underway in our laboratory.

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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.

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(12) For the rhodium-catalyzed C−H functionalization without external oxidant, see: (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (b) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439. In these reactions, as suggested, insertion of an Rh(I) complex into an sp^2 C−H bond leads to H−Rh(III)−Ar species which undergoes further reaction.

(13) The reductive elimination to form the C−O bond on Rh(III), see: Haarman, H. F.; Kaagman, J. F.; Smeets, W. J. J.; Spek, A. L.; Vrieze, K. *Inorg. Chim. Acta* **1998**, *270*, 34.