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Palladium-catalyzed decarboxylative cross-coupling of 3-pyridyl and 4-pyridyl carboxylates with aryl bromides

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ABSTRACT

Decarboxylative cross-coupling of 3-pyridyl and 4-pyridyl carboxylates with aryl bromides is reported. Using a bimetallic system of Cu_2O and $Pd(PPh_3)_4$, the scope of the reaction is demonstrated by the synthesis of 27 pyridine-containing biaryls in moderate to good yields.

Pyridine-containing heterobiaryls represent privileged structural units and are frequently found in pharmaceuticals, natural products, bioactive molecules, and organic ligands.[1] The 3- or 4-aryl-substituted pyridine motifs are a subclass of heterobiaryls and are present in a number of important pharmaceuticals and small molecules (Fig. 1).

Stoichiometric pyridyl organometallic reagents have been extensively employed to prepare pyridine-containing biaryl motifs. In this context, 3- and 4-pyridyl organometallics used in cross-coupling reactions have proven to be more challenging than simple aryl organometallics. This difficulty is presumably due to the instability and slow rate of transmetalation,[1b] attributed to the electron deficiency of the pyridine ring. In spite of these hurdles, transition-metal-catalyzed cross-coupling methods such as Suzuki,[2] Stille,[3] and others[4–6] exist for the use of these 3- and 4-pyridyl organometallics in coupling reactions. A major limitation with the aforementioned approaches is the stoichiometric synthesis of a reactive metal species. Notable alternative methods have recently emerged such as direct arylation of pyridine through C–H bond activation.[7] While this approach would be ideal from an atom economy perspective, the regioselectivity remains a significant limitation. Decarboxylative cross-coupling provides a catalytic approach to the synthesis of biaryls, which would additionally obviate the regioselectivity issue. The extrusion of carbon dioxide is not as atom economical, but it is a gaseous waste that does not need to be separated from the desired product.[8] Several groups such as those of Goossen,[9] Forgione,[10] and others[11] have demonstrated the synthesis of biaryls and heterobiaryls via decarboxylative cross-coupling. Studies by Myers[12] and others[13] also highlight the synthetic utility of related decarboxylative reactions. Although decarboxylative coupling has been utilized in organic synthesis, only a few reports are available which employ pyridine carboxylic acids as coupling partners. More recently, Wu[14a] and Stoltz[14b]

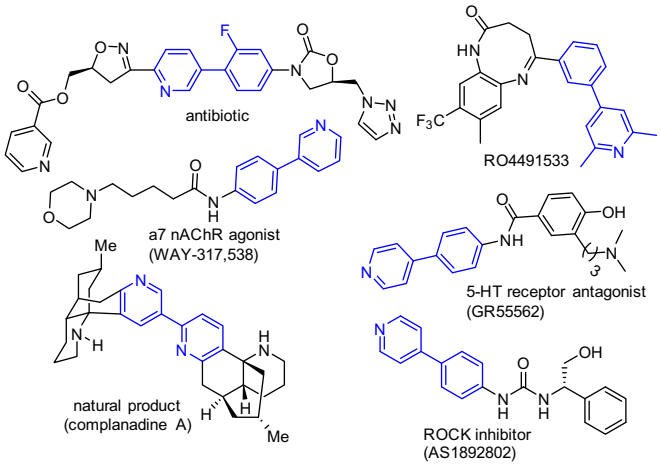

Figure 1. Bioactive 3-aryl and 4-aryl pyridine derivatives.

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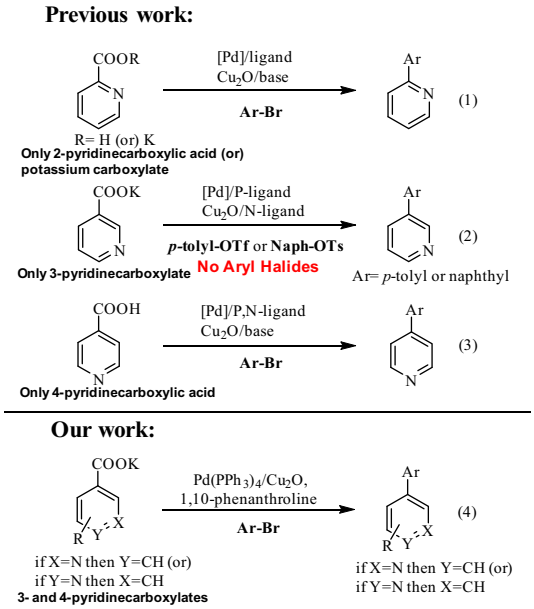
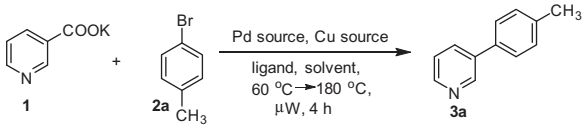


Scheme 1. Decarboxylative cross-coupling reactions of pyridine carboxylic acids.

independently reported the decarboxylative cross-coupling between pyridine-2-carboxylic acid (or) potassium pyridine-2-carboxylate and aryl bromides (Scheme 1, Eq. 1). Goossen et al. demonstrated the decarboxylative cross-coupling of potassium pyridine-3-carboxylate with an aryl triflate[9c] or aryl tosylate[9h] (Scheme 1, Eq. 2). However, to the best of our knowledge, an example of the decarboxylative cross-coupling of pyridine-3-carboxylic acid with aryl halides has not been reported, and that of pyridine-4-carboxylic acid is rare (Scheme 1, Eq. 3).[15] Herein, we report a more general method for the decarboxylative cross-coupling of both 3-pyridyl and 4-pyridyl carboxylates with aryl bromides for the synthesis of 3- or 4-arylpyridines (Scheme 1, Eq. 4), which are of interest in medicinal chemistry (Fig. 1).

Our study began by testing the Pd-catalyzed decarboxylative coupling of potassium pyridine-3-carboxylate with 4-bromotoluene (Table 1). Initial results using a similar bimetallic catalyst system reported by Wu and co-workers,[14a] $PdCl_2$ and Cu_2O with BINAP as a ligand in DMA under microwave irradiation, provided a 22% yield of the desired product (Table 1, entry 1). Switching the palladium precatalyst ($PdCl_2$) to the palladium catalyst [$Pd(PPh_3)_4$] improved the yield to 30% (Table 1, entry 2). Interestingly, decreasing the Pd-catalyst loading from 5 mol % to 2.5 mol % did not alter significantly the yield (Table 1, compare entries 2 and 3). Other bidentate and monodentate phosphine ligands such as Xantphos and X-phos were evaluated but failed to improve the yields (Table 1, entries 4 and 5). Although phosphines such as BINAP are known to be effective ligands for copper(I),[14a,16] and the exact mechanism of the reaction is not clearly understood, we hypothesized that nitrogen-containing ligands might help to facilitate decarboxylation.[17] Both mono and bidentate ligands were screened. The monodentate ligand pyridine gave a comparable yield to the phosphine ligands (35% yield, Table 1, entry 6). Bidentate N-ligands such as 2,2′-bipyridine and 1,10-phenanthroline provided a marked improvement with yields of 53% and 72%, respectively (Table 1, entries 7 and 8). This result indicates that the bite angle plays a critical role in the decarboxylation. To explore the potential effect of the phosphine ligand on these optimized conditions, other Pd(0) and Pd(II) sources in combination with a phosphine ligand (10 mol %) as an additive were screened. No improvement was observed providing a range of yields of 30–58% (Table 1, entries 9–13). Replacing Cu_2O with other Cu salts such as CuI or CuBr gave much lower yields (Table 1, compare entries 8 with 14 and 15). The influence of several polar

Table 1
Optimization of the reaction conditions[a]



Entry	Additive	Pd source	Ligand	Solvent	Yield[b] (%)
1[c]	Cu_2O	$PdCl_2$	BINAP	DMA	22
2[c]	Cu_2O	$Pd(PPh_3)_4$	BINAP	DMA	30
3	Cu_2O	$Pd(PPh_3)_4$	BINAP	DMA	28
4	Cu_2O	$Pd(PPh_3)_4$	Xantphos	DMA	17
5	Cu_2O	$Pd(PPh_3)_4$	XPhos	DMA	12
6	Cu_2O	$Pd(PPh_3)_4$	Pyridine	DMA	35
7	Cu_2O	$Pd(PPh_3)_4$	2,2′-Bipyridine	DMA	53
8	**Cu_2O**	**$Pd(PPh_3)_4$**	**1,10-Phenanthroline**	**DMA**	**72**
9[d]	Cu_2O	$Pd_2(dba)_3$+PPh_3	1,10-Phenanthroline	DMA	30
10[d]	Cu_2O	$PdCl_2$+PPh_3	1,10-Phenanthroline	DMA	55
11[d]	Cu_2O	$Pd(OAc)_2$+PPh_3	1,10-Phenanthroline	DMA	35
12[d]	Cu_2O	$Pd(acac)_2$+PPh_3	1,10-Phenanthroline	DMA	58
13[d]	Cu_2O	$Pd(acac)_2$+XPhos	1,10-Phenanthroline	DMA	30
14	CuI	$Pd(PPh_3)_4$	1,10-Phenanthroline	DMA	15
15	CuBr	$Pd(PPh_3)_4$	1,10-Phenanthroline	DMA	24
16	Cu_2O	$Pd(PPh_3)_4$	1,10-Phenanthroline	NMP	36
17	Cu_2O	$Pd(PPh_3)_4$	1,10-Phenanthroline	DMF	48
18	Cu_2O	$Pd(PPh_3)_4$	1,10-Phenanthroline	Diglyme	28
19	Cu_2O	$Pd(PPh_3)_4$	1,10-Phenanthroline	DMSO	12

Values in bold face indicate best optimized reaction conditions employed to study substrate scope.
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), Cu (0.15 mmol), Pd (2.5 mol %), ligand (10 mol %), solvent (3.0 mL), 60–180 °C, μw, 4 h.
[b] Isolated yield based on **1**.
[c] 5 mol % palladium catalyst.
[d] 10 mol % P-ligand.