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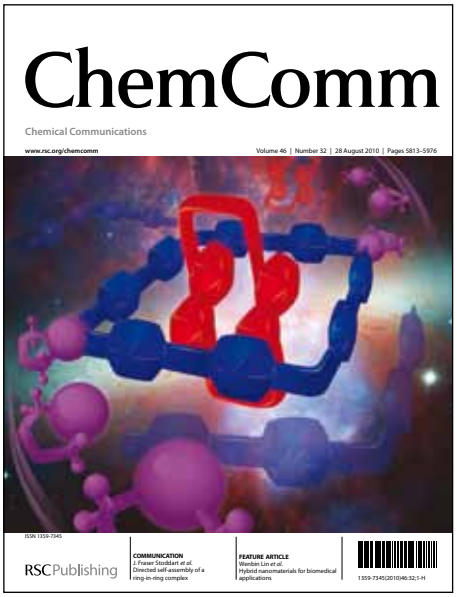

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ARTICLE TYPE

Arylation of 2- Substituted pyridines via Pd-Catalyzed Decarboxylative Cross-Coupling Reactions of 2-Picolinic acid

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The novel palladium-catalyzed decarboxylative cross-coupling reactions of 2-picolinic acid with aryl and heteroaryl bromides including benzenes, naphthalenes, pyridines and quinolines for C-C bond formation has been successfully achieved.

Derivatives of 2-arylpyridine are among the most important heterocyclic structural motifs and are found in a large number of natural products, pharmaceuticals, materials and ligands.[1] Some cross-coupling reactions have been applied for the synthesize of 2-arylpyridines with a wide range of aryl halides and organometallics. But due to the instability and the synthetic difficulty of 2-pyridyl organometallics, their application is severely limited. For example, the Suzuki-Miyaura coupling of 2-pyridyl boron derivatives is probably the most widely used.[2] However, the inherent instability of 2-pyridyl boronic acid makes very few examples of 2-pyridyl boronates serving as the nucleophile source included in cross-coupling reactions.[3-5] Until recently, Burke's group firstly reported the identified 2-pyridyl N-methyliminodiacetic acid (MIDA) boronate which is both air stable and can be isolated in a chemically pure form.[5e,5f]

Since Nilsson first reported the transition-metal mediated decarboxylative biaryl coupling,[6] the exciting breakthroughs have been achieved by Myers,[7] Goossen,[8] and others[9] as an attractive alternative to typical cross-coupling reactions. Liu *et al.* developed the excellent procedures for the copper-catalyzed decarboxylative coupling of polyfluorobenzoic acids.[10] Meanwhile some sliver-catalyzed aryl acid decarboxylation was described by Su *et al.* and others.[11, 12] Although decarboxylative coupling has been utilized in organic synthesis, only a few reports of heteroarylcarboxylic acids including oxazole, thiophene and furan carboxylic acid is available.[9d,9g] As the substrate of a powerful alternative to the conventional organometallic building blocks, picolinic acids represent a kind of cheap, stable and readily available structures. However, examples of the cross-coupling of 2-picolinic acid with aryl halides have not been reported.

The decarboxylative cross-coupling reaction of 2-picolinic acids was considered not favored comparing to the decarboxylative cross-coupling of similar benzene acids based on the literature presence.[13-15] However, the occurrence possibility of this reaction is exist and it was worth to be investigated. Salvador Conejero and co-workers reported a simple, general route to a 2-pyridylidene transition metal complexes.[16] This result encouraged us to study the decarboxylative cross-coupling reaction of 2-picolinic acid with aryl- and heteroaryl-bromides.

Firstly, the decarboxylative cross-coupling reaction of 2-picolinic acid (**1a**) and 4-bromobenzonitrile (**2a**) was investigated as the model reaction as shown in Table 1. We investigated various Pd source (5 mol% loading) and ligands initially (Table 1, entries 1-14). When BINAP was used as the ligand, 75% yield of the desired decarboxylative cross-coupling product was obtained (Table 1, entry 10). Obviously, the BINAP was more effective than the other ligands in this reaction (Table 1, entries 1-9). We speculated the bidentate ligand with a rigid angle like BINAP must be fitting for the cross-coupling and reducing the Ullmann-type products due to steric hindrance around the metal.[17] Moreover, BINAP is the ligand of copper (I)[18] stabilizing 2-pyridyl metal compounds.[8]

Secondly, the additives were investigated. Copper (I) as an additive shows an excellent result in this reaction (Table 1, entries 10, 15-17). Owing to the facile protonation of pyridine α-position and the speed of oxidative addition of aryl halides to palladium, the Ullmann reaction[19] and decarboxy coupling reaction are the competing reactions. Cu_2O was then selected and found to be the optimal additive for the current reaction (Table 1, entry 10). Other copper salts were also investigated with no better than Cu_2O (Table 1, entries 16-20). Su and co-workers reported the Ag-promoted decarboxylation.[12] So we tried the reaction with Ag_2CO_3, but it resulted in much worse than Cu_2O (Table 1, entry 21). The main reason is due to the fast decarboxylation which leads to the protonation of pyridine α-position other than the cross-coupling reaction. To investigate our hypothesis, 5-phenylpicolinic acid was selected as the decarboxylative cross-coupling reaction substrate. The reaction was monitored by GC-MS. When we replaced copper (I) with Ag_2CO_3, the decarboxylation-protonation product, 3-phenylpyridine, was

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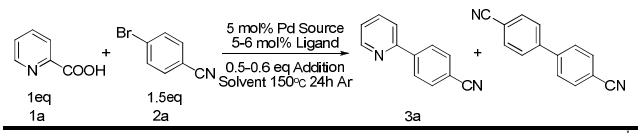
Table 1 Screen of Catalysts, Ligands and Additive for the Cross-coupling of 2-Picolinic acid with 4-Bromobenzonitrile[a]

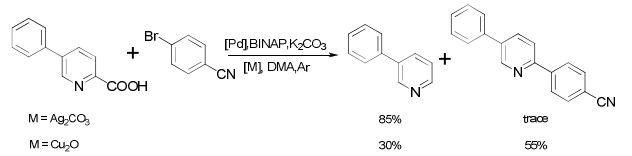


Entry	Pd Source	Ligand	Additive	Yield[b] [%]
1	$PdCl_2$	$P(Cy)_3$	Cu_2O	20
2	$PdCl_2$	Ph_3P	Cu_2O	52
3	$PdCl_2$	CyJohnPhos	Cu_2O	40
4	$PdCl_2$	DavePhos	Cu_2O	46
5	$PdCl_2$	SPhos	Cu_2O	48
6	$PdCl_2$	XPhos	Cu_2O	57
7	$PdCl_2$	RuPhos	Cu_2O	38
8	$PdCl_2$	Xantphos	Cu_2O	64
9	$PdCl_2$	DPPF	Cu_2O	31
10	***$PdCl_2$***	***BINAP***	***Cu_2O***	***75***
11	$PdBr_2$	BINAP	Cu_2O	74
12	$Pd_2(dba)_3$	BINAP	Cu_2O	40
13	$Pd(acac)_2$	BINAP	Cu_2O	trace
14	$Pd(AcO)_2$	BINAP	Cu_2O	trace
15	$PdCl_2$	BINAP	CuI	43
16	$PdCl_2$	BINAP	CuBr	28
17	$PdCl_2$	BINAP	CuCl	trace
18	$PdCl_2$	BINAP	$CuBr_2$	trace
19	$PdCl_2$	BINAP	$CuCO_3$	trace
20	$PdCl_2$	BINAP	$Cu(CH_3COO)_2$	trace
21	$PdCl_2$	BINAP	Ag_2CO_3	trace

[a] Reaction conditions: 0.6 mmol **1a**, 0.9 mmol **2a**, 5 mol% catalyst, 6 mol% ligand, 1.8 mmol K_2CO_3, 3.5 mL DMA, 0.3 mmol addition, 150 ℃, 24 h, argon atmosphere, 200mg 3Å MS.

[b] Isolated yields based on **1a**.

found as a major product with no desired decarboxylation-cross-coupling product detected (Scheme 1).

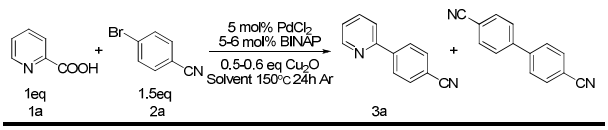


Scheme 1 Decarboxylative Coupling Reaction of 5-Phenylpicolinic Acid with 4-Bromobenzonitrile

Thirdly, the influence of various bases for this transformation was studied in the presence of Cu_2O. K_2CO_3 and K_3PO_4 were found to give good yield of the desired decaboxylation-cross-coupling product (Table 2, entries 1-7). KOAc was known as an inhibitor in the Ullmann-type coupling of aryl halides.[20] But KOAc did not result in better result in this reaction. It was also important to point out that the solvent played a critical role for this reaction (Table 2, entry 1, 8-11). The desired product was obtained in 75% yield when DMA was used as solvent (Table 2, entry 1). When the reaction temperature was reduced to 120℃, the isolated yields were also reduced. The conclusion for this study is that the combination of 5 mol% $PdCl_2$, 6 mol % BINAP in DMA in the presence of K_2CO_3 or K_3PO_4 and Cu_2O at 150 ℃ is the optimum condition.

Under the optimized reaction conditions, a wide range of aryl bromides were investigated for this reaction. It was found that both electron-rich and electron-poor aryl bromides could be successfully converted to the corresponding products in moderate

Table 2 Screen of the Base and Solvents for the Cross-coupling of 2-Picolinic Acid with 4-Bromobenzonitrile[a]



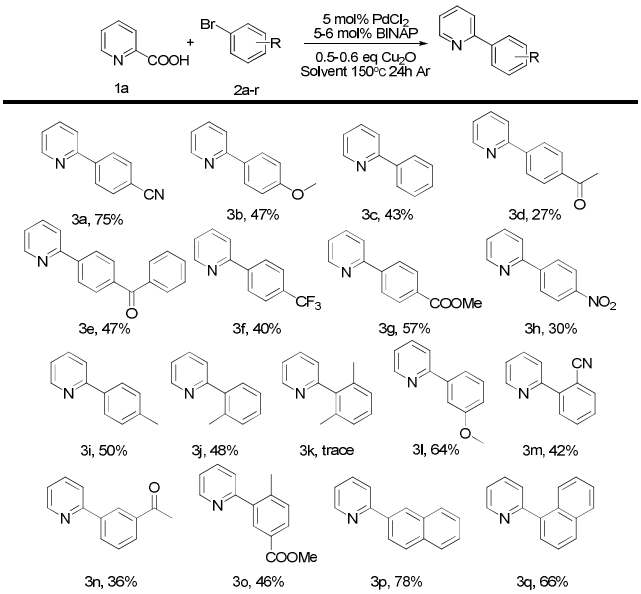
Entry	base	solvent	Tem.[℃]	Yield[b] [%]
1	***K_2CO_3***	***DMA***	***150***	***75***
2	Cs_2CO_3	DMA	150	trace
3	K_3PO_4	DMA	150	74
4	Na_2CO_3	DMA	150	39
5	t-BuOK	DMA	150	no
6	NEt_3	DMA	150	no
7	KOAc	DMA	150	66
8	K_2CO_3	NMP	150	20
9	K_2CO_3	DMF	150	35
10	K_2CO_3	DMAB	150	43
11	K_2CO_3	DMA:DMSO(40:1)	150	33
12	K_2CO_3	DMA	120	56

[a] Reaction conditions: 0.6 mmol **1a**, 0.9 mmol **2a**, 5 mol% $PdCl_2$, 6 mol% BINAP, 1.8 mmol base, 3.5 mL Solvent, 0.3 mmol Cu_2O, 24 h, argon atmosphere, 200 mg 3Å MS.

[b] Isolated yields based on **1a**.

to good yields. As shown in Table 3, the reaction condition could be compatible to a wide range of functional groups such as ethers, ketones, esters, nitriles, trifluoromethyl, alkyls and nitro groups. It was conjectured that the lower yield of 2-(acetyl-phenyl) pyridine is due to the carbonyl oxygen coordination role with copper (I). Furthermore, the functional groups of aryl bromides positions were not more of an impact (Table 3: **3a**, **3m**; **3b**, **3l**; **3d**, **3n**; **3i**, **3j**.), but steric hindrance of aryl bromides had a great effect on products yields (Table 3, **3k**). For bromo-naphthalene,

Table 3 The Palladium-catalyzed Decarboxylative Cross-coupling Reactions of 2-Picolinic Acid with Aryl bromides[a]



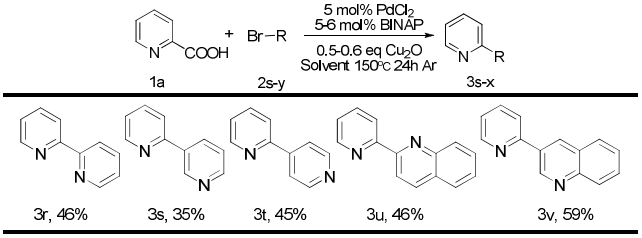
[a] Reaction conditions: 0.6 mmol **1a**, 0.9 mmol **2**, 5 mol% $PdCl_2$, 6 mol% BINAP, 1.8 mmol K_2CO_3, 3.5 mL DMA, 0.3 mmol Cu_2O, 150 ℃, 24 h, argon atmosphere, 200 mg 3Å MS.

[b] Isolated yields based on **1a**.

both α-bromonaphthalene and β-bromonaphthalene gave the desired products in good yields (Table 3, **3p**, **3q**). The reaction of 2-picolinic acid with iodobenzene and chlorobenzene were investigated. In case of iodobenzene, only 28% yield was obtained due to the homo-coupling of iodobenzene. Chlorobenzene was so inactive that only trace product was monitored by GC-MS in the reaction.

To extend the reaction scope, we proceeded to study the cross-coupling reactions of picolinic acid with heteroaryl bromides under the optimized reaction conditions. The results are summarized in Table 4. At first, a variety of bromo-pyridines as cross-coupling partners were examined. 2-bromopyridine, 3-bromopyridine and 4-bromopyridine afforded the corresponding dipyridine in 46%, 35% and 45% yields respectively. Both 2-bromoquinoline and 3-bromoquinoline were all the selectable substrate, and affording the corresponding product **3u** and **3v** separately in 46% and 59% yields.

Table 4 The palladium-catalyzed decarboxylative cross-coupling reactions of 2-picolinic acid with heteroaryl bromides[a].



[a] Reaction conditions: 0.6 mmol **1a**, 0.9mmol **2**, 5 mol% $PdCl_2$, 6 mol% BINAP, 1.8 mmol K_2CO_3, 3.5 mL DMA, 0.3 mmol Cu_2O, 150 ℃, 24 h, argon atmosphere, 200 mg 3Å MS.

[b] Isolated yields based on **1a**.

In order to further conjecture the probable reason of the low chemical yields, the reaction of 2-picolinic acid (**1a**) and 1-bromo-4-methoxybenzene (**2b**) was detected by GC-MS and HPLC，HPLC showed that the 2-picolinic acid was consumed totally and pyridine(38%) was detected. Meanwhile, 1-bromo-4-methoxybenzene (**2b**) was not exist, except the expected product, 4,4'-dimethoxybiphenyl was found as mainly by-product. So the protonation of **1a** and the Ullmann-type reaction of **2b** produced the low chemical yields.

In conclusion, a novel synthetic route to 2-aryl- and heteroaryl-pyridines was discovered and developed *via* the palladium-catalyzed decarboxylative cross-coupling reactions of 2-picolinic acid with aryl- and heteroaryl-bromides. In this reaction, an efficient new catalytic system has been developed. Both the catalyst and ligand are commercially available. In addition, cheap and stable 2-picolinic acid has been used. We believe that the process combined with the condition would be attractive and beneficial for its further development. Further exploration of this reaction is currently under investigation in our lab.

Acknowledgement

We are grateful to the Natural Science Foundation of China (20772114, 21172200), the Research Program of Fundamental and Advanced Technology of Henan Province (122300413203) for financial support.

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