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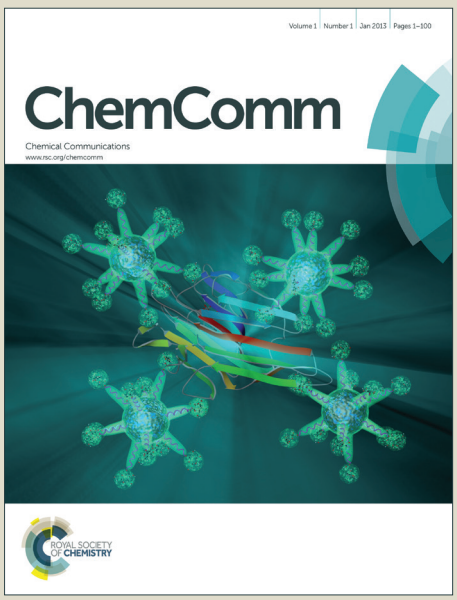

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Cite this: DOI: 10.1039/c0xx00000x

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COMMUNICATION

Copper-catalyzed direct C-H arylation of pyridine *N*-oxides with arylboronic esters: one-pot synthesis of 2-arylpyridines

Yan Shen, Jiuxi Chen,* Miaochang Liu, Jinchang Ding, Wenxia Gao, Xiaobo Huang and Huayue Wu*

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

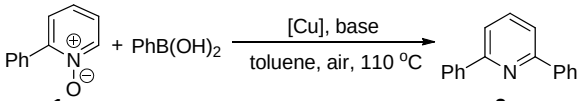
DOI: 10.1039/b000000x

The first example of the copper-catalyzed direct C−H arylation of pyridine *N*-oxides with arylboronic esters has been developed, leading to a wide range of 2-arylpyridines in a one-pot synthesis with moderate to good yields without additional reductant. This transformation allows for rapid access to a variety of 2-arylpyridines using an inexpensive catalytic system that would be more difficult to access with traditional methods. Thus, this method represents a simple and practical procedure to access 2-arylpyridines.

Pyridines are among the most prevalent heterocyclic structural motifs that occur in a wide variety of bioactive natural products, pharmaceuticals, functional materials, ligands, organo-catalysts and synthetic building blocks.[1] The 2-arylpyridines, as a typical class of C-H bond activation partners, have become increasingly important in the past few years because they are good substrates for cyclometallation.[2] 2-Arylpyridines are generally synthesized by the use of 2-halopyridines[3] or 2-pyridyl organometallics[4] as a coupling partner. The fundamental work of Fagnou and co-workers on the palladium-catalyzed direct arylation of pyridine *N*-oxides with aryl bromides provided attractive and valuable routes for the synthesis of 2-arylpyridines.[5] Other improved methods have also been reported for constructing 2-arylpyridines by the use of pyridine *N*-oxides[6] as coupling partners, with palladium-catalyzed direct arylation via C−H activation representing the major strategy.[7] However, to realize the synthesis of the desired 2-arylpyridines, reducing agents[8] were required to reduce the *N*-oxide products in these transformations. Several groups[9] have reported the use of Minisci-type reactions for the synthesis of 2-arylpyridines by a free-radical mechanism. Recently, Wu and co-workers developed a novel synthetic route to 2-arylpyridines via the palladium-catalyzed decarboxylative cross-coupling reactions.[10] The arylation using Grignard reagents[11] is also a powerful tool for the construction of 2-arylpyridines.

To the best of our knowledge, C–H functionalization of pyridine *N*-oxides (or pyridine derivatives) with inexpensive copper catalysts has rarely been reported,[12] even though copper was the first transition metal shown to promote C–H arylation.[13,14] We therefore considered that organoboron reagents[15] might serve as both arylation coupling reagents and as reductants in the copper-catalyzed C-H activation reaction, achieving a one-pot synthesis of 2-arylpyridines. As part of the continuing efforts in our laboratory toward the development of novel transition metal-catalyzed coupling reactions with organoboron reagents,[16] herein we report copper-catalyzed direct C-H arylation of pyridine *N*-oxides with arylboronic esters for the one-pot synthesis of 2-arylpyridines.

Table 1 Selected results of screening the optimal conditions[a]



1a **3aa**

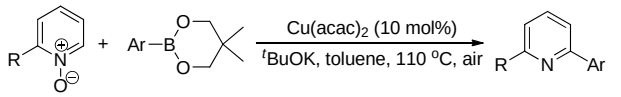
entry	Cu source	base	yield (%)[b]
1	CuI	KOH	trace
2	CuI	^{t}BuOK	28
3	CuBr	^{t}BuOK	34
4	CuCl	^{t}BuOK	32
5	CuCN	^{t}BuOK	41
6	CuSCN	^{t}BuOK	39
7	CuOAc	^{t}BuOK	37
8	CuOTf	^{t}BuOK	35
9	$CuCl_2$	^{t}BuOK	32
10	$CuBr_2$	^{t}BuOK	37
11	$CuSO_4$	^{t}BuOK	trace
12	$Cu(OAc)_2$	^{t}BuOK	51
13	$Cu(OTf)_2$	^{t}BuOK	49
14	$Cu(acac)_2$	^{t}BuOK	79
15	$Cu(acac)_2$	^{t}BuONa	41
16	$Cu(acac)_2$	^{t}BuOLi	19
17	$Cu(acac)_2$	EtOK	trace
18	$Cu(acac)_2$	EtONa	trace
19	$Cu(acac)_2$	CaH_2	trace
20	$Cu(acac)_2$	$NaNH_2$	trace
21	$Cu(acac)_2$	KOH	trace
22	$Cu(acac)_2$	K_3PO_4	0
23	$Cu(acac)_2$	Cs_2CO_3	0
24	$Cu(acac)_2$	Et_3N	0
25	$Cu(acac)_2$	DBACO	0
26	$Cu(acac)_2$	^{t}BuOK	87[c]

[a] *Reaction conditions*: **1a** (0.5 mmol), phenylboronic acid (1.0 mmol), Cu source (10 mol %), base (1.5 mmol), toluene (5 mL), 110 °C, 2 h, air. [b] Isolated yield. [c] Using phenylboronic ester (**2a**) as the arylation reagent.

Our preliminary studies focused on the reaction between 2-phenylpyridine *N*-oxide (**1a**) and phenylboronic acid to obtain the optimal reaction conditions (Table 1). Through a screening process, no target product was detected using Cs_2CO_3 as the base

with a variety of palladium or copper catalysts. To our delight, a trace amount of the desired product 2,6-diphenylpyridine (**3a**) was observed by GC/MS (EI) analysis using KOH as the base in the presence of CuI (entry 1). However, we were pleased to find that the yield of the desired product **3a** could be improved to 28% in toluene under an air atmosphere after the base was changed to the stronger ^{t}BuOK base (entry 2). Encouraged by this promising result, a series of trial experiments were performed in the presence of copper catalysts and with adjustments to the reaction parameters in order to obtain more satisfactory results. First, we investigated copper catalysts. Among the copper sources used, $Cu(acac)_2$ exhibited the highest catalytic reactivity in 79% yield (entries 2−14). Screening revealed that the use of ^{t}BuOK as the base achieved the best result (entries 15-25). The best solvent is toluene, and other solvents were ineffective for the reaction (see Table S1 in ESI†). We also investigated the influences of material ratio, catalyst amount, and reaction temperature on the arylation yield (see Table S1 in ESI†). Other organoboron reagents (see entries 1-5 Table S2 in ESI†) were used for this reaction under the same conditions and phenylboronic ester (**2a**) showed the best result (87%, entry 26) whereas alkylboronic acids (e.g. isobutylboronic acid and benzylboronic acid) were unreactive (see entries 6 and 7 Table S2 in ESI†). Therefore, we performed all the subsequent reactions using arylboronic esters.

Table 2 Copper-catalyzed reaction of 2-arylpyridine *N*-oxides[a]



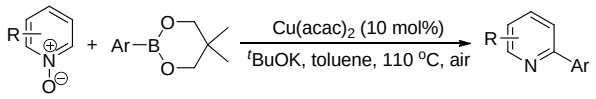
1 **2** **3**

entry	R (**1**)	Ar (**2**)	product	yield (%)[b]
1	Ph (**1a**)	Ph (**2a**)	**3aa**	87
2	Ph (**1a**)	*p*-(Me)C_6H_4 (**2b**)	**3ab**	84
3	Ph (**1a**)	*o*-(Me)C_6H_4 (**2c**)	**3ac**	41
4	Ph (**1a**)	*m*-(Me)C_6H_4 (**2d**)	**3ad**	89
5	Ph (**1a**)	*p*-(OMe)C_6H_4 (**2e**)	**3ae**	65
6	Ph (**1a**)	*o*-(OMe)C_6H_4 (**2f**)	**3af**	18
7	Ph (**1a**)	*p*-(CF_3)C_6H_4 (**2g**)	**3ag**	71
8	Ph (**1a**)	*p*-(CN)C_6H_4 (**2h**)	**3ah**	51
9	Ph (**1a**)	*p*-(F)C_6H_4 (**2i**)	**3ai**	79
10	Ph (**1a**)	*p*-(Cl)C_6H_4 (**2j**)	**3aj**	73
11	Ph (**1a**)	*m*-(Cl)C_6H_4 (**2k**)	**3ak**	64
12	Ph (**1a**)	*p*-(Br)C_6H_4 (**2l**)	**3al**	81
13	Ph (**1a**)	*p*-(I)C_6H_4 (**2m**)	**3am**	43
14	Ph (**1a**)	*p*-(Ph)C_6H_4 (**2n**)	**3an**	71
15	Ph (**1a**)	*p*-(CH_2=CH)C_6H_4 (**2o**)	**3ao**	62
16	*p*-(Me)C_6H_4 (**1b**)	Ph (**2a**)	**3ba**	79
17	*p*-(OMe)C_6H_4 (**1c**)	Ph (**2a**)	**3ca**	83
18	*p*-(F)C_6H_4 (**1d**)	Ph (**2a**)	**3da**	81

[a] *Reaction conditions*: **1** (0.5 mmol), **2** (1.0 mmol), $Cu(acac)_2$ (10 mol %), ^{t}BuOK (1.5 mmol), toluene (5 mL), 110 °C, 2 h, air. [b] Isolated yields.

Having the optimized reaction conditions in hand, we next explored the scope and generality of the arylation reaction using various 2-arylpyridine *N*-oxides (**1a-1d**) and arylboronic esters (**2**) (Table 2). First, the reaction between 2-phenylpyridine *N*-oxide (**1a**) and various arylboronic esters (**2b**−**2o**) was investigated under standard conditions. The steric effects of substituents had an obvious impact on the yield of the reaction. For example, arylation of **1a** with *para*-, *meta*- and *ortho*-tolylboronic ester (**2b**-**2d**) provided 84% of **3ab** and 89% of **3ad**, while the yield of **3ac** was decreased to 41% (entries 2–4). The same phenomenon was observed in the reaction of **1a** with *para*- and *ortho*-methoxyphenylboronic ester (entries 5 and 6). The electronic properties of the substituents on the phenyl ring of the arylboronic esters had little effect on the reaction. In general, the arylboronic esters bearing an electron-withdrawing substituent (e.g., −CF_3) produced a slightly higher yield of products than those analogues bearing an electron-donating substituent (e.g., −OMe) (entries 5 and 7). However, substrate **2h**, bearing a cyano group, was treated with **1a** to afford slightly lower yields of **3ah** (entry 8). It is noteworthy that the chloro, fluoro, bromo, and iodo moieties (commonly used for cross-coupling reactions) in arylboronic esters were all tolerated and afforded several halogen-containing products **3i**–**3m** in moderate to good yields, leading to a useful handle for further cross-coupling reactions (entries 8-12). We observed moderate yield of **3an** when **2n** was used as the substrate (entry 13). Moreover, (4-vinylphenyl)boronic ester (**2o**), possessing a functionalized vinyl group, was tolerated well and afforded the product **3ao** in 62% yield (entry 14). In addition, several 2-arylpyridine *N*-oxides were examined. The electronic properties of the groups on the phenyl ring moiety of the arylpyridine *N*-oxides had little effect on the reaction. For example, the reaction of **1a** with *p*-methylphenylpyridine *N*-oxide (**1b**), *p*-methoxyphenylpyridine *N*-oxide (**1c**), and *p*-fluorophenylpyridine *N*-oxide (**1d**) resulted in the formation of the corresponding desired products **3ba**, **3ca**, and **3da** in 79%, 83%, and 81% yields, respectively (entries 15-17).

Table 3 Copper-catalyzed reaction of 2-unsubstituted pyridine *N*-oxides[a]



1 **2** **3**

entry	R (**1**)	Ar (**2**)	product	yield (%)[b]
1	H (**1e**)	Ph (**2a**)	**3ea**	81
2	H (**1e**)	*p*-(Me)C_6H_4 (**2b**)	**3eb**	78
3	H (**1e**)	*o*-(Me)C_6H_4 (**2c**)	**3ec**	32
4	H (**1e**)	*m*-(Me)C_6H_4 (**2d**)	**3ed**	83
5	H (**1e**)	*p*-(OMe)C_6H_4 (**2e**)	**3ee**	68
6	H (**1e**)	*p*-(CF_3)C_6H_4 (**2g**)	**3eg**	64
7	H (**1e**)	*p*-(CN)C_6H_4 (**2h**)	**3eh**	52
8	H (**1e**)	*p*-(F)C_6H_4 (**2i**)	**3ei**	72
9	H (**1e**)	*p*-(Cl)C_6H_4 (**2j**)	**3ej**	67
10	H (**1e**)	*m*-(Cl)C_6H_4 (**2k**)	**3ek**	58
11	H (**1e**)	*p*-(Br)C_6H_4 (**2l**)	**3el**	74
12	H (**1e**)	*p*-(Ph)C_6H_4 (**2n**)	**3en**	79
13	H (**1e**)	*p*-(CH_2=CH)C_6H_4 (**2o**)	**3eo**	72
14	4-Me (**1f**)	Ph (**2a**)	**3fa**	74
15	4-CN (**1g**)	Ph (**2a**)	**3ga**	35
16	4-Ph (**1h**)	Ph (**2a**)	**3ha**	67
17	3-Ph (**1i**)	Ph (**2a**)	**3ia**	68

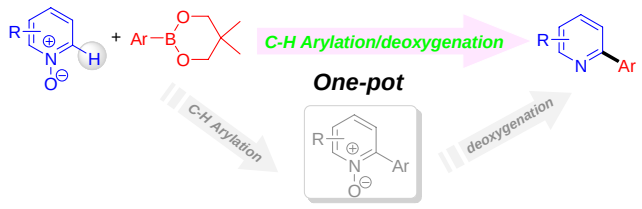
[a] *Reaction conditions*: **1** (0.5 mmol), **2** (1.0 mmol), $Cu(acac)_2$ (10 mol %), ^{t}BuOK (1.5 mmol), toluene (5 mL), 110 °C, 2 h, air. [b] Isolated yields.

Next, we turned our attention to the effect of the reactions of various 2-unsubstituted pyridine *N*-oxides (**1e-1i**) and arylboronic esters (**2**) under standard conditions (Table 3). The reactions proceeded smoothly with high selectivity and tolerated a wide range of functional groups, including methoxy, fluoro, chloro, bromo, trifluoromethyl, cyano, and vinyl groups. Steric effects of substituents had an obvious

impact on the yield of the reaction. Substrate *p*-tolylboronic ester (**2b**) bearing a *p*-methyl group, for example, was treated with **1e** to afford 81% yield of **3eb**, while the yield of **3ee** was decreased to 32% with the *o*-tolylboronic ester (**2c**) possessing an *o*-methyl group (entries 2 and 3). The electronic properties of groups on the phenyl ring moiety of the arylboronic esters had some effects on the reaction (entries 5-13). We also examined the effect of substitution on the pyridine *N*-oxide. The presence of both electron-donating and electron-withdrawing groups was tolerated, as exemplified by the successful coupling of both 4-methylpyridine *N*-oxide (**1f**) and 4- or 3-phenylpyridine *N*-oxide (**1h**-**1i**) (entries 14, 16 and 17). However, pyridine *N*-oxides containing a strong electron-withdrawing group on the pyridine ring, such as 4-cyanopyridine *N*-oxide (**1g**), reduced the yield of the corresponding product **3ga** (entry 15).

To elucidate the mechanism of formation of 2-arylpyridines, we undertook control experiments (see Scheme S1-S5 in ESI†). The product **3aa** could not be detected and when 2-phenylpyridine was treated with **2a** under standard conditions, almost 90% of 2-phenylpyridine was recovered. We found that **3aa** was obtained in 59% yield when the reaction of 2,6-diphenylpyridine *N*-oxide (**4a**) with **2a** was performed in toluene. These results showed that **2a** could serve as a reductant in the transformation. In addition, no or only trace amounts of the desired product was observed when the procedure was carried out under N_2 atmosphere or in the absence of copper catalyst.

On the basis of the above experimental results, we proposed a possible reaction pathway for the formation of 2-arylpyridines (Scheme 1). The first step may involve the arylation of pyridine *N*-oxides with arylboronic esters. Then deoxygenation of the arylated pyridine *N*-oxides by using organoboron reagent as a reductant delivers the corresponding 2-aryl pyridines as the products. It is worth mentioning that the arylation depends on copper catalyst, base and oxygen. Whereas the deoxygenation is independent of the arylation and does not depend on copper catalyst and base. However, details of the mechanism of the formation of the 2-arylpyridines remain unclear at the current stage.



Scheme 1 Possible reaction pathway.

Kinetic isotope competition experiments were also carried out under the reaction conditions to reveal the intermolecular kinetic isotope effects (k_H/k_D) being 2.9 (see Scheme S6 in ESI†). The result indicated that the C-H cleavage might be involved in the rate-determining step.

In summary, we have developed a new protocol for the one-pot direct synthesis of 2-arylpyridines in moderate to good yields via copper-catalyzed C-H arylation of pyridine *N*-oxides with arylboronic esters. Further efforts to explore the detailed mechanism and extend the applications of the transformation are currently underway in our laboratories.

Financial support was provided by the National Natural Science Foundation of China (Nos. 21102105 and 21072153).

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College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. China.
E-mail: jiuxichen@wzu.edu.cn; huayuewu@wzu.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b000000x/

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