Silver-Catalyzed 2-Pyridyl Arylation of Pyridine *N*-Oxides with Arylboronic Acids at Room Temperature

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Abstract: A novel direct arylation of pyridine *N*-oxides with arylboronic acids through C–H functionalization has been developed. This new reaction is performed at room temperature using catalytic silver(I) nitrate in the presence of potassium persulfate and give 2-pyridyl arylation derivatives of pyridine *N*-oxides.

Key words: silver, pyridine *N*-oxides, arylation

Palladium-catalyzed C–H bond activation for the C–C cross-coupling reaction has emerged as a powerful method for the preparation of biaryls.[1] In particular, reactions involving Pd-catalyzed aryl halides with aromatic C–H bond activation have been extensively investigated.[2] In this area of research, various functional groups containing heteroatoms such as acetyl, pyridyl, and imino groups were needed as directing groups (DG) for C–H activation chemistry.[3] Using aryl boronic acids as coupling partners with the direct C-arylation of aromatic rings under very mild, room-temperature conditions remain rare.[4] Most of the successful reactions employ a combination of a palladium catalyst with silver or copper salts as oxidants and require high reaction temperature.

Pyridine moiety is an important component of natural products, materials, and medicinal chemistry.[5] Substituted pyridines are usually synthesized from metalated or halopyridyl compounds. However, this route needs extra preparation steps and is inevitably accompanied with problems such as expensive reagents and more waste. Since Fagnou reported the palladium-catalyzed regioselective direct arylation of pyridine *N*-oxides with aryl bromides,[6] this method has been studied and developed for the preparation of substituted pyridines and other heterocycles. Recently, palladium-catalyzed C–H functionalization of pyridine *N*-oxides with unactivated arenes was reported by Chang's group.[7] More recently, Ackermann and co-worker reported direct arylations of pridine *N*-oxides with aryl or alkenyl tosylates and mesylates,[8] Tzschucke reported the synthesis of unsymmetrically substitued bipyridines by a palladium-catalyzed direct C–H arylation of pyridine *N*-oxides.[9] However, these processes suffer either from high reaction temperatures or expensive phosphine ligands and co-oxidants (Scheme 1, equations 1–3), which limit their potential application.

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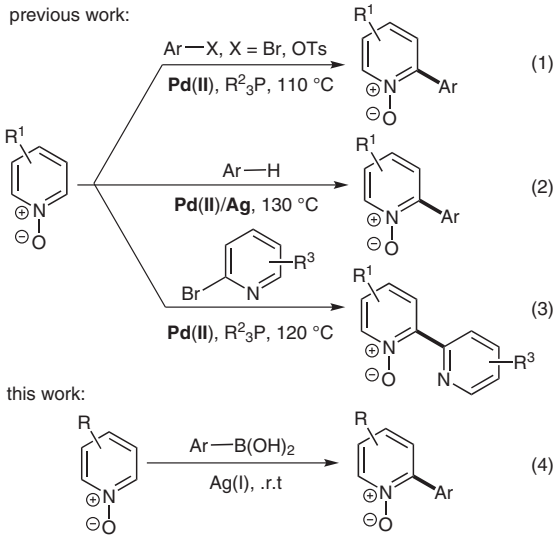
Though Baran and co-workers have reported that the catalyst system $AgNO_3$–$K_2S_2O_8$ was effective for the coupling between electron-deficient heterocycles and arylboronic acids,[10] one equivalent of trifluoroacetic acid must be needed to block the nitrogen atom of pyridine to reduce the electron density and to increase the nucleophilicity of the 2-position of the pyridine. In addition, the tertiary butyl group must be blocked at the 4-position of pyridine, otherwise two or three regioisomers were obtained. Thereby, we studied the C–H bond activation using pyridine *N*-oxides as platforms for the 2-arylpyridines. Described herein is a new approach for the C–C bond formation of pyridine *N*-oxides – a regioselective direct cross-coupling with arylboronic acids catalyzed by silver salt at room temperature (Scheme 1, equation 4).

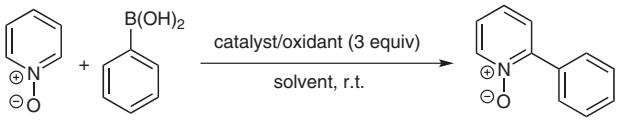


Scheme 1 Comparison of previous works with this work

We initiated an investigation of the C–H coupling using pyridine *N*-oxides (**1a**) with phenylboronic acid (**2a**) in the presence of 10 mol% of $AgNO_3$ and three equivalents of $K_2S_2O_8$ at room temperature, and product **3aa** was obtained in 41% yield (Table 1, entry 1). The yield was increased to 69% when 20 mol% of $AgNO_3$[14] were loaded (Table 1, entry 2). Other metals such as $Cu(OAc)_2$,[14] $CuCl_2$,[14] and $FeCl_3$[14] were ineffective for this reaction even at 90 °C (Table 1, entries 3–6). When BPO was used as oxidant, no desired product was obtained (Table 1, entry 10). For other solvent mixtures, THF–H_2O (1:1, v/v) and DMSO–H_2O (1:1, v/v) were found not to be better

than CH_2Cl_2/H_2O, maybe due to solvability and extractability. The yield was slightly reduced when the $(NH_4)_2S_2O_8$ was used as an oxidant (Table 1, entry 11).

Table 1 Screening of Reaction Conditions[a]



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

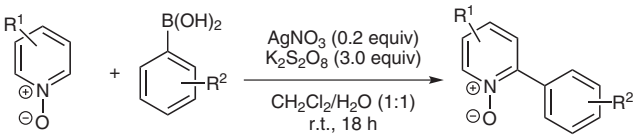
Entry	Catalyst (mol%)	Oxidant	Solvent (1:1)	Yield (%)[b]
1	$AgNO_3$ (10)	$K_2S_2O_8$	CH_2Cl_2/H_2O	41
2	$AgNO_3$ (20)	$K_2S_2O_8$	CH_2Cl_2/H_2O	69
3[c]	$Cu(OAc)_2$ (10)	$K_2S_2O_8$	CH_2Cl_2/H_2O	trace
4[d]	$CuCl_2$ (10)	$K_2S_2O_8$	CH_2Cl_2/H_2O	trace
5[e]	$CuCl_2$ (100)	$K_2S_2O_8$	CH_2Cl_2/H_2O	11
6	$FeCl_3$ (20)	$K_2S_2O_8$	CH_2Cl_2/H_2O	0
7	–	$K_2S_2O_8$	CH_2Cl_2/H_2O	0
8	$AgNO_3$ (20)	$K_2S_2O_8$	THF–H_2O	43
9	$AgNO_3$ (20)	$K_2S_2O_8$	DMSO–H_2O	37
10	$AgNO_3$ (20)	BPO	CH_2Cl_2/H_2O	0
11	$AgNO_3$ (20)	$(NH_4)_2S_2O_8$	CH_2Cl_2/H_2O	60

[a] Conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), catalyst (10–100%), oxidant (3.0 mmol), solvent (30 mL, 1:1) at r.t. for 18 h.
[b] Isolated yield based on **2a**.
[c] At 70 °C.
[d] At 70 °C.
[e] At 90 °C.

The standard conditions were applied to a series of substituted pyridine *N*-oxides and arylboronic acids as shown in Table 2. Pyridine *N*-oxides **1a** with 4-methoxyphenylboronic acid (**2d**) gave the coupling product in 56% yield (Table 2, entry 4), while a moderate yield (69%) was obtained when phenylboronic acid (**2a**) was reacted with **1a** (Table 2, entry 1). Pyridine *N*-oxide with an electron-withdrawing group, for example, cyano in the 4-position, gave slightly higher yield (Table 2, entries 11 and 12) than those without electron-withdrawing substituents (Table 2, entries 1 and 4). Products **3ab** and **3bb** were obtained in moderate to good yields though 2-methoxyphenylboronic acid (**2b**) has an *ortho* substituent (Table 2, entries 2 and 9). When pyrazine N^1-oxide **3c** was used as substrate, the reaction proceeded smoothly and products **3ca** and **3cf** were obtained in high yields (Table 2, entries 7 and 8). 1-Naphthaleneboronic acid (**2f**) coupled with 3-cyanopyridine *N*-oxide (**3e**) gave 2-substituted and 6-substituted products **3ef** and **3ef′** with a ratio of 1:2, and the overall yield was 77% (Table 2, entry 13). It should be mentioned that this process for the direct cross-coupling through C–H activation was operationally very easy.[13]

As shown in Scheme 2, based on Baran's study,[10] if there is no oxide on pyridine ring, a mixture of C2 and C4 coupling products were obtained in a 2:1 ratio together with some bisarylation product. In our work, only the C2 arylation product was found (Table 2, entry 1). Similarly, only 30% yield of product was obtained when pyrazine coupled with *p*-methyphenylboronic acid directly.

Table 2 Scope of the Coupling of Arylboronic Acids to Substituted Pyridine *N*-Oxide **1**[a]



1a–e **2a–f** **3aa–3ef**

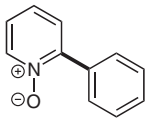
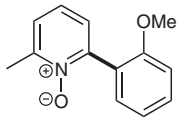
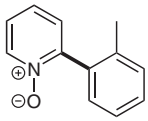
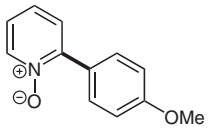
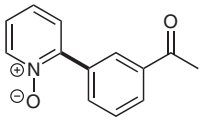
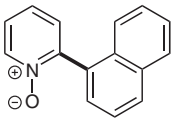
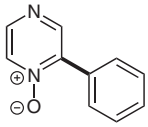
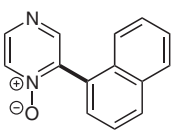
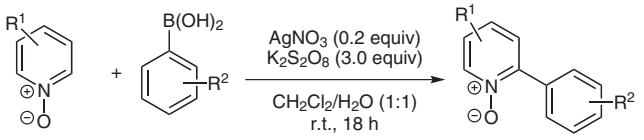
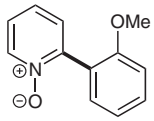
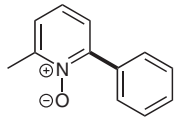
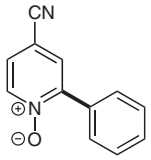
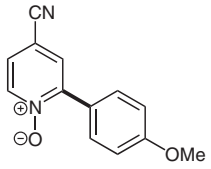
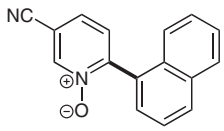
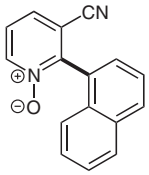
Entry	Product	Yield (%)[b]
1	 **3aa**	69
2	 **3bb**	62
3	 **3bc**	58
4	 **3ad**	56
5	 **3ae**	64
6	 **3af**	42
7	 **3ca**	80
8	 **3cf**	87

Table 2 Scope of the Coupling of Arylboronic Acids to Substituted Pyridine *N*-Oxide **1**[a] (continued)



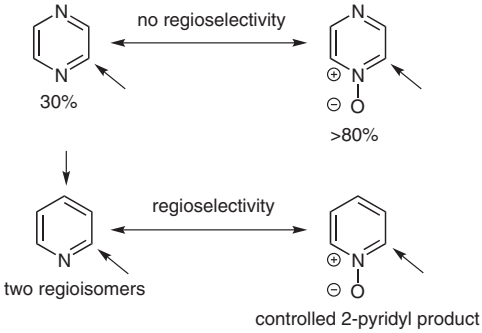
1a–e **2a–f** **3aa–3ef**

Entry	Product	Yield (%)[b]
9	 **3ab**	75
10	 **3ba**	55
11	 **3da**	76
12	 **3dd**	66
13	 **3ef** and  **3ef′**	77 (**3ef**/**3ef′** = 1:2)

[a] Conditions: 1.5 mmol **1** and 1.0 mmol **2** were used.
[b] Isolated yields after column chromatography were based on **2**.

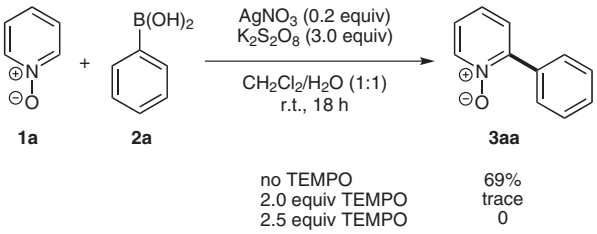
In our work, using pyrazine N^1-oxide as substrate, product **3ca** could be obtained in 80% isolated yield (Table 2, entry 7). These observations led us to conclude that the introduction of oxide to pyridine could increase the reactivity and selectivity of the reaction.

The mechanism of the reaction was also tested by us, based on Baran's and Li's work,[11] and a radical pathway was postulated here. Persulfate anion disproportionates



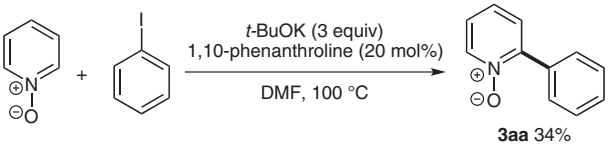
Scheme 2 Comparison of previous studies with this work

into sulfate radical anion in the presence of silver(I) salts. This radical could induce the arylboronic acid to provide an aryl radical which is an important intermediate in this reaction. This was indeed supported by experiments performed in the presence of radical scavenger. When two equivalents of tetramethylpiperidine *N*-oxide (TEMPO) was added under the same conditions, a trace of the desired product was observed. As shown in Scheme 3, the reaction was completely shut off when 2.5 equivalents of TEMPO were added, which indicated that a radical intermediate was involved in this transformation.



Scheme 3 A radical pathway test

To study the mechanism of the reaction deeply, we did another reaction to testify if an aryl radical was produced here. It is well known that phenyl iodide or phenyl bromide could produce a phenyl radical in the presence of potassium *tert*-butoxide.[12] As shown in Scheme 4, it is interesting to note that product **3aa** was also obtained in 34% yield when phenyl iodide was used as a substrate in the presence of potassium *tert*-butoxide. It could provide some evidence for the mechanism of this reaction.



Scheme 4

In summary, a novel, room-temperature approach to a silver-catalyzed direct 2-pyridyl arylation of pyridine *N*-oxides with arylboronic acids has been developed. In view of the importance of pyridine *N*-oxide derivatives in medical chemistry as well as their easy deoxygenation to the more important pyridine derivatives, this novel method will

find broad use in organic synthesis. Extending the scope of the novel method to other heterocyclic *N*-oxides is in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(13) **General Procedure for this Reaction**
A 50 mL vial was charged with a magnetic stir bar, pyridine *N*-oxide (**1a**, 1.5 mmol), phenylboronic acid (**2a**, 1.0 mmol), $AgNO_3$ (0.2 mmol), $K_2S_2O_8$ (3.0 mmol), followed by CH_2Cl_2 and deionized H_2O (1:1, v/v, 30 mL in total). After stirring at r.t. for 18 h, the reaction mixture was filtered through Celite (washed with MeOH and CH_2Cl_2), extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, then evaporated under reduced pressure, and the isolated yield was obtained by flash chromatography column on silica gel (gradient eluent of MeOH in CH_2Cl_2: 1–5%, v/v).

(14) The metal sources used here [$AgNO_3$, $Cu(OAc)_2$, $CuCl_2$, $FeCl_3$] were all purchased from Aladdin Company in Shanghai. AR grade of $AgNO_3$ (>99.8%), AR grade of $Cu(OAc)_2$ (anhyd, >99.0%), AR grade of $CuCl_2$ (anhyd, >98.0%), AR grade of $FeCl_3$ (anhyd, >97.5%).
2-Phenylpyridine *N*-Oxide (3aa)[6]
^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ = 7.26–7.33 (m, 1 H), 7.41–7.45 (m, 1 H), 7.47–7.53 (m, 4 H), 7.80–7.83 (m, 2 H), 8.48 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K): δ = 149.4, 140.6, 132.6, 129.7, 129.3, 128.3, 127.5, 126.0, 124.6. Mp 144–146 °C (CH_2Cl_2).
2-(2-Methoxyphenyl)-6-methylpyridine *N*-Oxide (3bb)
^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ = 7.40–7.45 (t, *J* = 8.4 Hz, 1 H), 7.35–7.37 (d, *J* = 7.6 Hz, 1 H), 7.16–7.25 (m, 3 H), 6.99–7.06 (m, 2 H), 3.80 (s, 3 H), 2.57 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K): δ = 157.3, 149.5, 147.9, 130.7, 125.9, 125.2, 124.1, 122.9, 120.5, 111.2, 55.8, 18.4. ESI-MS: *m/z* = 216.0 $[M + 1]^+$. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}NO_2^+$: 216.1025; found: 216.1021.
2-(2-Methylphenyl)pyridine *N*-Oxide (3bc)[6]
^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ = 8.37 (d, *J* = 4.8 Hz, 1 H), 7.36–7.40 (m, 1 H), 7.24–7.32 (m, 6 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K): δ = 150.8, 140.1, 137.8, 132.9, 130.1, 129.6, 129.3, 128.0, 125.9, 125.4, 125.0, 19.5. Mp 107–109 °C (CH_2Cl_2).
2-(4-Methoxyphenyl)pyridine *N*-Oxide (3ad)[6]
^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ = 8.35 (d, *J* = 6.4 Hz, 1 H), 7.80 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.21 (t, *J* = 6.4 Hz, 1 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 3.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K):

δ = 160.7, 149.2, 140.6, 130.9, 127.1, 126.7, 124.6, 123.9, 113.8, 55.4. Mp 120–122 °C (CH_2Cl_2).

2-(3-Acetylphenyl)pyridine *N*-Oxide (3ae)

^{1}H NMR (400 MHz, $CDCl_3$, 293 K): δ = 8.35–8.39 (m, 2 H), 8.07 (t, *J* = 8.0 Hz, 2 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 6.0 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.26–7.31 (m, 1 H), 2.65 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K): δ = 197.6, 148.3, 140.5, 137.1, 133.9, 133.0, 129.3, 128.6, 127.4, 126.2, 125.2, 26.7. ESI-MS: *m/z* $[M + 1]^+$ = 214.1. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{13}H_{12}NO_2^+$: 214.0868; found: 214.0866.