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Original article

Arylation of pyridine *N*-oxides *via* a ligand-free Suzuki reaction in water

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ABSTRACT

We report a practical and highly efficient protocol for the arylation of pyridine *N*-oxides with arylboronic acid through palladium-catalyzed Suzuki reaction in water. This ligand-free Suzuki reaction is performed in the presence of diisopropylamine and gives 2- or 3-arylated pyridyl *N*-oxide derivatives in good to excellent yields within 1 h.

1. Introduction

Given the importance of pyridine *N*-oxide derivatives in medical chemistry as well as their easy deoxygenation to the more important pyridine derivatives, methods for the synthesis of pyridine *N*-oxide derivatives continue to attract considerable interest in organic synthesis [1–5]. Fagnou *et al.* reported the palladium-catalyzed regioselective direct arylation of pyridine *N*-oxides with aryl bromides, which was used for the preparation of substituted pyridines and other heterocycles [6,7]. Recently, the C–H bond activation approach using pyridine *N*-oxides was served as an attractive platform for the 2-functionalization of pyridine species [8–14]. However, these methods require harsh conditions and long reaction time.

In 1999, Lohse *et al.* reported a catalytic system of DME/H_2O/K_2CO_3/5%Pd(PPh_3)$_4$ for the Suzuki cross-coupling reaction between 2- or 4-chloropyridine *N*-oxide and arylboronic acid, affording 65%–70% isolated yield of the desired products, which provided an alternative for the synthesis of aryl-substituted pyridine *N*-oxide derivatives [15]. To the best of our knowledge, this is the only example of the arylation of pyridine *N*-oxides *via* the Suzuki reaction. The palladium-catalyzed Suzuki reaction of aryl halides with arylboronic acids is one of the most versatile and powerful tools to form biaryls, which has been extensively used in the synthesis of pharmaceuticals, herbicides, natural products and advanced functional materials [16,17]. However, *N*-heteroaryl halides are generally inactive substrates for the Suzuki reaction due to the potential coordination of the nitrogen to the active palladium species [18]. So far, a lot of achievements have been made to activate these substrates, including the development of ligand-promoted protocols as Lohse *et al.* did [15]. Our group has reported ligand-free approaches to activate 2-bromopyridine derivatives successfully in ethylene glycol or EtOH/H_2O [19,20]. At the moment, we are interested in activating 2-bromopyridine derivatives for the palladium-catalyzed Suzuki reaction in water without any additional ligand.

The use of water as sole reaction medium has several advantages, such as abundance, non-toxic, non-corrosiveness and improved safety [21–25]. Developing organic reaction in pure water is one of the latest challenges for modern chemists. Herein, we report an efficient method for the Pd(OAc)$_2$-catalyzed Suzuki reaction of 2- or 3-bromopyridine *N*-oxides in pure water without any ligand.

2. Experimental

Aryl halides and arylboronic acids were purchased from Alfa Aesar. Other chemicals were obtained commercially and used without purification. ^{1}H NMR spectra were recorded on a Bruker AvanceII 400 spectrometer using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal

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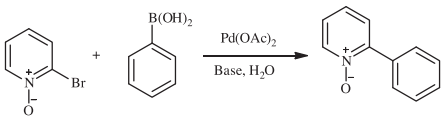
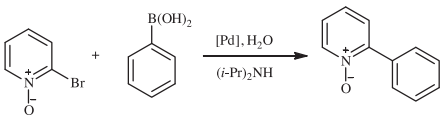
Table 1
Effects of bases on the Suzuki cross-coupling reaction of 2-bromopyridine *N*-oxide with phenylboronic acid.[a]



Entry	Base	Yield (%)[b]
1	$K_3PO_4{\cdot}3H_2O$	86
2	NaOH	88
3	K_2CO_3	90
4	*i*-$PrNH_2$	Trace
5	$(i\text{-Pr})_2NH$	94
6	Et_3N	90
7	$(i\text{-Pr})_2NEt$	57
8	DABCO	92
9	Morpholine	45
10	Dicyclohexylamine	47
11	Piperazine	13

[a] *Reaction conditions*: 2-Bromopyridine *N*-oxide (0.5 mmol), phenylboronic acid (0.75 mmol), 0.25 mol% $Pd(OAc)_2$, base (1.0 mmol), H_2O (1.0 mL), 100 °C, 30 min, in air.
[b] Isolated yield.

Table 2
Effects of palladium species on the cross-coupling of 2-bromopyridine *N*-oxide with phenylboronic acid.[a]



Entry	[Pd]	Yield (%)[b]
1	$Pd(OAc)_2$	92
2	$PdCl_2$	89
3	$PdCl_2(CH_3CN)_2$	47
4	$Pd_2(dba)_3$	91
5	Pd/C	Trace

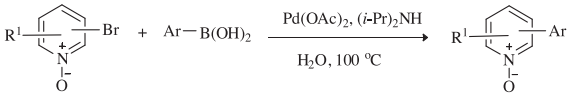
[a] *Reaction conditions*: 2-Bromopyridine *N*-oxide (0.5 mmol), phenylboronic acid (0.75 mmol), 0.25 mol% [Pd], $(i\text{-Pr})_2NH$ (1.0 mmol), H_2O (1.0 mL), 100 °C, 10 min, in air.
[b] Isolated yield.

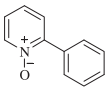
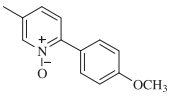
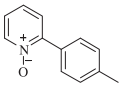
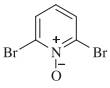
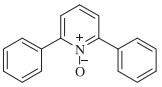
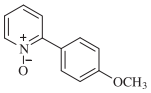
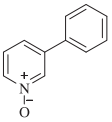
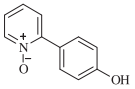
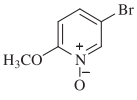
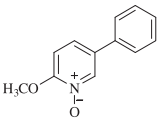
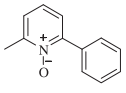
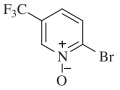
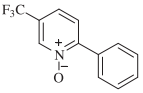
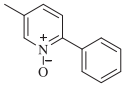
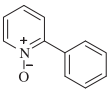
standard. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted.

For this study, pyridine *N*-oxides were synthesized according to the following general procedures: pyridyl halides (1.0 equiv.) and *m*-chloroperoxybenzoic acid (1.1 equiv.) are dissolved in dry methylene dichloride. The reaction is allowed to stir at room temperature overnight. The solvent is then evaporated under reduced pressure and the crude reaction mixture is purified by column chromatography on silica gel with CH_2Cl_2 or CH_2Cl_2/MeOH mixtures.

All Suzuki reactions were carried out under air atmosphere. A mixture of bromopyridine *N*-oxide (0.5 mmol), arylboronic acid (0.75 mmol), $(i\text{-Pr})_2NH$ (1.0 mmol), $Pd(OAc)_2$ (0.25 mol%), H_2O (1.0 mL) was allowed to react at 100 °C. The reaction mixture was added to brine (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The solvent was concentrated under vacuum and the product was isolated by short chromatography on a silica gel (200–300 mesh) column.

Table 3
The Suzuki reaction of bromopyridine *N*-oxides with arylboronic acids.[a]



Entry	*N*-oxide	Product	Yield (%)[b]	Entry	*N*-oxide	Product	Yield (%)[b]
1			96	7			67
2			92	8			90
3			61	9			93
4			57	10			96
5			85	11			35
6			95	12			35

[a] *Reaction conditions*: 2-Bromopyridine *N*-oxide (0.5 mmol), arylboronic acid (0.75 mmol), 0.25 mol% $Pd(OAc)_2$, $(i\text{-Pr})_2NH$ (1.0 mmol), H_2O (1.0 mL), 100 °C, 1 h, in air.
[b] Isolated yield.

The characterization and spectra of all products are available in the Supporting information.

3. Results and discussion

Initially, the cross-coupling of 2-bromopyridine *N*-oxide with phenylboronic acid was chosen as a model reaction for screening bases. The experimental data presented in Table 1.

Water-soluble inorganic bases gave comparative yields (Table 1, entries 1–3), which were better than the results of cross-coupling of 4-bromoanisole with arylboronic acid as we reported [26]. The reason for this is supposed due to the highly solubility of 2-bromopyridine *N*-oxide in water. Several organic bases were examined and $(i\text{-Pr})_2NH$, Et_3N, DABCO (1,4-diazabicyclo[2.2.2]octane) (Table 1, entries 5, 6 and 8) provided relatively high yields compared to the other bases. The results show that $(i\text{-Pr})_2NH$ (Table 1, entry 5) is the best choice, which provided a 94% isolated yield in 30 min.

The palladium source employed in the Suzuki reaction is also important to the catalytic efficiency. As shown in Table 2, the palladium sources have dramatic effects on the reaction activity under the present conditions. The results indicated that $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2$ exhibited high catalytic activity. $PdCl_2(CH_3CN)_2$ gave relatively low yields. Pd/C just provided trace yield in 10 min. It is supposed that $PdCl_2(CH_3CN)_2$ and Pd/C might have a long activation period in the present catalytic system. We chose $Pd(OAc)_2$ as the catalyst for the following study.

We further investigated the scope of direct arylation of bromopyridine *N*-oxides under the conditions of 0.25 mol% $Pd(OAc)_2$ and two equivalents of $(i\text{-Pr})_2NH$ at 100 °C in water. The results are shown in Table 3. The cross-coupling of 2-bromopyridine *N*-oxide with phenylboronic acid or 4-methylphenlyboronic acid could afford above 92% isolated yields in 1 h (Table 3, entries 1 and 2), which were more efficient than the previous report that 2-tolylpyridine *N*-oxide was obtained in 91% isolated yield overnight from the reaction between pyridine *N*-oxide and 4-bromotoluene [7]. The reaction between 2-bromopyridine *N*-oxide and 4-methoxylphenylboronic acid or 4-hydroxyphenylboronic acid provided a lower isolated yield of 61% and 57% in 1 h (Table 3, entries 3 and 4). Methylpyridine *N*-oxides could be activated by this catalytic system, affording 67%–95% isolated yield (Table 3, entries 5–7). The cross-coupling of 2,6-dibromopyridine *N*-oxide with phenylboronic acid performed efficiently, providing a 90% isolated yield in 1 h (Table 3, entry 8). The arylation of 3-bromopyridine *N*-oxide or 2-methoxyl-5-bromopyridine *N*-oxide proceeded very quickly with the yields of 93% and 96%, respectively (Table 3, entries 9 and 10). However, the cross-coupling of 2-bromo-5-(trifluoromethyl)-pyridine *N*-oxide or 2-chloropyridine *N*-oxide with phenylboronic acid was carried out slowly than that of 2-bromopyridine *N*-oxide (Table 3, entries 11 and 12).

4. Conclusion

In summary, we have developed an efficient protocol for the arylation of pyridine *N*-oxides with arylboronic acid. In view of the importance of pyridine *N*-oxide derivatives in medical chemistry, the Suzuki reaction will find a broad use in organic synthesis. Extending the scope of Suzuki reaction to other heterocyclic *N*-oxides is in progress in our laboratory.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.09.019.

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