

# A Simple Copper Salt Catalyzed N-Arylation of Amines, Amides, Imides, and Sulfonamides with Arylboronic Acids

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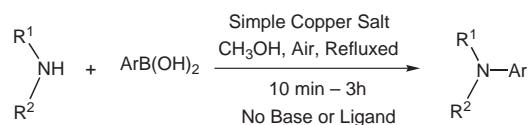
**Abstract:** A simple copper salt catalyzed N-arylation reaction with arylboronic acids is reported. In the presence of a catalytic amount of a simple copper salt, the coupling of arylboronic acids with imides was performed in MeOH to give N-arylimides in excellent yields; a variety of amines, amides and sulfonamides could also be successfully coupled with arylboronic acids to give corresponding N-arylated products in moderate yields.

**Key words:** N-arylation, copper salt, boronic acid, coupling, Ullmann reaction

The copper-mediated N-arylation reaction is an important transformation and has been developed to include a wide range of substrates. The classical copper-mediated Ullmann reaction has underpinned the research community when functionalities of these sorts are required.<sup>1</sup> However, the harsh reaction conditions led to severe limitations in the general use of this reaction, especially on a large scale. In recent years, a few approaches have also been developed by using aryllead,<sup>2</sup> arylbismuth,<sup>3</sup> arylstannane,<sup>4</sup> arylsilane<sup>5</sup> reagents as the aryl donor in the presence of Cu(OAc)<sub>2</sub> and base. The recent introduction of arylboronic acids as reaction partners has been a significant improvement over previous methods.<sup>6</sup> In 1997, the copper-mediated heteroatom arylation reaction with the use of arylboronic acids was discovered independently by Chan, Evans and Lam.<sup>6,7</sup> A more important discovery by Collman has demonstrated that the N-arylation reaction of imidazoles with arylboronic acids can be rendered when a catalytic amount of copper complex was used.<sup>8</sup> Based on these studies, further improvements to the catalytic variation of boronic acid cross coupling have been reported.<sup>9</sup> However, all these reactions are carried out with either Et<sub>3</sub>N or pyridine as base, or with the use of copper complex in halogenated hydrocarbon. These reactions are normally slow, which generally need 18 hours–13 days to proceed to complete. Moreover, the use of excess arylboronic acids is also a major limitation of the method. Therefore, it is necessary to develop more general and efficient catalytic systems for N-arylation of a variety of substrates.

Recently, we have carried out the N-arylation reaction of imidazole with arylboronic acids using only 5% mol of a simple copper salt, without any additives in protic solvent,

obtaining corresponding N-arylimidazoles in almost quantitative yields.<sup>10</sup> The successful N-arylation reaction of imidazole with arylboronic acids encouraged us further to explore the generality of this procedure, and we found that the simple copper salt can also catalyze the N-arylation reaction of a variety of amines, amides, imides and sulfonamides in protic solvent in the absence of additional ligands or bases to give corresponding N-arylated products in moderate to excellent yields (Scheme 1). N-Arylation reaction of amines, amides, imides and sulfonamides with arylboronic acids has recently gained considerable attention, because of their potential application in pharmaceutical, agrochemical industries.<sup>6,7,9,11</sup> To the best of our knowledge, N-arylation of amines, amides, imides and sulfonamides with arylboronic acids conducted in protic solvent with the use of simple copper salts has not been explored previously; this represents an advance over the use of complex copper salts together with a substantial amount of base in non-protic solvent.



**Scheme 1** A simple copper salt catalyzed N-arylation reaction.

Treatment of 1.4–2 mmol of N-H containing substrate with 1 mmol of arylboronic acid in the presence of catalytic amount of a simple copper salt in MeOH at reflux temperature was found to lead to coupling products. In preliminary study, CuCl was evaluated for the desired reactivity. Excellent yields of cross-coupled products were obtained for imides (Table 1, entries 1 and 7), whereas amines, amides and sulfonamides were afforded in poor yields. When Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was used as copper source, satisfactory results were obtained with amines, amides, imides and sulfonamides.

A series of arylboronic acids were employed for the coupling reaction with imides under the conditions outlined in Table 1. It was found that 10% mol of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was sufficient for imides. It is worth mentioning that the coupling reaction with phenylboronic acid was complete in 2 hours, and the corresponding N-arylation products were obtained in excellent yields (Table 1, entries 1, 7), which are superior to previous work.<sup>7d,9c</sup> A variety of substituted phenylboronic acids and naphthylboronic acid were also

subjected to coupling with phthalimide and succinimide respectively. Good results were obtained with *p*- and *m*-substituted phenylboronic acids and naphthylboronic acid (Table 1, entries 2–4 and 8–11). It should be noted

**Table 1** Cu(OAc)<sub>2</sub>·H<sub>2</sub>O-Catalyzed N-Arylation Reaction of Imides with Arylboronic Acids<sup>a</sup>

Entry	Imides	ArB(OH) <sub>2</sub>	Product	Yield <sup>b</sup> (%)
1				96,96 <sup>c</sup>
2				94
3				93
4				90
5				20
6				trace
7				88,86 <sup>c</sup>
8				86
9				87
10				85
11				72
12				19
13				trace

<sup>a</sup> Reaction conditions: 1.4 mmol imides, 1 mmol arylboronic acid, and 10% mol of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O in 10 mL anhyd MeOH were stirred drastically, air bubbled in and refluxed 10 min–3 h. The reaction was judged complete by TLC. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography to give N-arylated product.

<sup>b</sup> Isolated yield, purity confirmed by HPLC, MS and <sup>1</sup>H NMR.

<sup>c</sup> 10% mol of CuCl was used.

that *o*-substituted phenylboronic acids afforded the desired compounds in very poor yields (Table 1, entries 5, 6, 12, 13). These low yields appear to be a result of steric hindrance.

The application of this reaction to the coupling of amines, amides and sulfonamides with phenylboronic acid was also briefly explored. Such coupling was found to give the desired N-arylation products in moderate yields, as shown in Table 2. The amount of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O can be quite dependent on the nature of the substrate. 10% mol of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was sufficient for amines (Table 2, entries 1–7). The use of 40% mol of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O is suitable for amides and *p*-tolylsulfonamide (Table 2, entries 8–10). Especially for the latter, the yield increased while the amount of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O increased. The conditions used in Table 2 were unoptimized, and it is likely that further optimization of conditions for the coupling reaction could result in higher yields. It is interesting that bis-arylated products were never detected during the course of the coupling reactions, which is consistent with Buchwald's report.<sup>9a</sup>

**Table 2** Cu(OAc)<sub>2</sub>·H<sub>2</sub>O-Catalyzed N-Arylation Reaction of Amines, Amides and Sulfonamides with Phenylboronic Acid<sup>a</sup>

Entry	Substrate	Product	Yield <sup>b</sup> (%)
1			78
2			76
3			52
4			74
5			56
6			39
7			43
8			51 <sup>c</sup>
9			40 <sup>c</sup>
10			50, <sup>c</sup> 73 <sup>d</sup>

<sup>a,b</sup> See Table 1, except 2 mmol of N-H containing substrate was used.

<sup>c</sup> 40% mol of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was used.

<sup>d</sup> 100% mol of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was used.

It is essential to add base or ligand in the coupling reaction of arylboronic acids in previous work, except for the recent report by Quach and Batey<sup>12</sup>. We found that neither base nor ligand was necessary for the catalyzed system of

simple copper salts. Moreover, the coupling reaction is very fast. It took only 10 minutes–3 hours to complete transformation to arylated product, which is much faster than that reported previously. To the best of our knowledge, the majority of previously reported reaction conditions tend to use the N-H containing substrate as the limiting agent and the boronic acid in excess. Our procedure actually has the boronic acid as the limiting agent with the N-H containing substrate in excess, this could account for the seemingly lower yields when compare with the work of Buchwald<sup>9c</sup> as well as Quach and Batey.<sup>12</sup>

In summary, we have developed a simple copper salt catalyzed coupling of arylboronic acids with amines, amides, imides and sulfonamides in moderate to excellent yields. The further work including the study on mechanism is being in progress.

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