

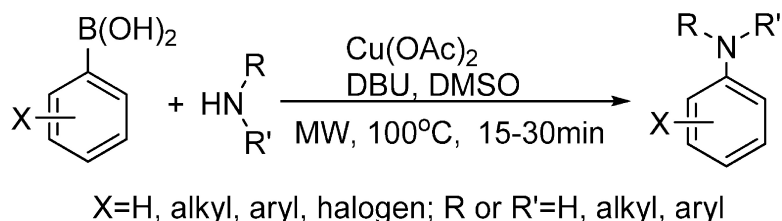
Report

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## Microwave-Assisted Efficient Copper-Promoted N-Arylation of Amines with Arylboronic Acids

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Amination of arylboronic acids is one of the most important reactions in the synthesis of essential intermediates and targets of numerous pharmaceutical agents, agrochemicals, natural products, and industrial materials containing the N-aryl moiety.<sup>1</sup> One of the traditional methods to create the C–N bond is the transition-metal-catalyzed arylation of nucleophiles with aryl halides, that is, the Ullmann or Goldberg condensations.<sup>2</sup> Recently, significant progress has been achieved in C–N bond formation; for example, Ullmann coupling has led to the emergence of several protocols based on copper or iron–copper catalysis.<sup>3</sup> Chan and Lam<sup>4</sup> reported the preparation of C–N bonds via Cu-mediated coupling of amines with arylboronic acids under milder conditions, where arylboronic acids are used as arylating agents instead of aryl halides.<sup>5</sup> Although these methods are highly effective, there is still much room for improvement, for example, these methods usually require high temperatures, long reaction times, and complex ligands, and some of them suffer from a relatively narrow scope of substrates, especially for aniline derivatives.

Microwave-assisted organic reactions have been applied to a wide range of reaction types, including aromatic nucleophilic substitution, cycloaddition, and organometallic reactions.<sup>6</sup> It accelerates a variety of synthetic transformations via time- and energy-saving protocols. Das and Basu reported that the construction of arylamines units with microwave oven;<sup>5c</sup> however, these reactions are only limited to the primary amines, and the secondary amines and nitrogen-containing aromatic heterocycles were found to be unreactive. Herein, we wish to explore a more effective microwave-assisted method to give amination of arylboronic acids with various amines based on the promotion of Cu(OAc)<sub>2</sub>, especially containing the aniline moiety. In comparison with

the current methods of the C–N bond formation, our approach displays particular advantages: (i) it proceeds faster and gives moderate to good yield; (ii) it requires only the inexpensive Cu(OAc)<sub>2</sub>; and (iii) it is applicable to a broader substrate scope (primary and secondary alkylamines, substituted anilines, nitrogen heterocycles, and differently substituted arylboronic acids).

All of the microwave-assisted reactions were performed in an Initiator EXP microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation.

Initially we found that the N-arylation of morpholine using phenylboronic acid could be efficiently promoted in the presence of Cu(OAc)<sub>2</sub> and organic base under the microwave (MW) irradiation. The nature of bases had a pronounced impact on the process. DBU turned out to be better than NEt<sub>3</sub>, while pyridine was ineffective, although they were very good bases under Chan–Lam's conditions. Using phenylboronic acid and morpholine as model substrates, we further optimized the reaction conditions by testing several parameters, such as different bases, various solvents, reaction temperatures, reaction times, and different amounts of Cu(OAc)<sub>2</sub> and DBU. The process was carried out by microwave irradiation of the sample in a sealed tube to afford 4-phenylmorpholine. The results are summarized in Table 1. The optimum results were usually obtained when 0.5 M amine and 0.75 M arylboronic acid were allowed to react with 2.0 equiv of Cu(OAc)<sub>2</sub> and 2.0 equiv of DBU stirred in DMSO at 100 °C for 15 min.

Using the optimized conditions in hand, we subjected a series of amines and substituted anilines to the copper-promoted arylation with phenylboronic acid to explore the generality and scope of the process. As shown in Table 2, we were pleased to find that this method was applicable to a broad substrate scope on substituted anilines. The results indicated that the aliphatic amines were obtained in good to excellent yields, albeit the anilines and heterocyclic amines gave moderate yields (entries 3–13, Table 2), relatively. For

**Table 1.** Procedure Optimization of the Reaction of Morpholine with Phenylboronic Acid<sup>a</sup>

entry	solvent	base	T (°C)	time (min)	yield (%) <sup>d</sup>
1	DMF	DBU	100	15	61
2	dioxane	DBU	100	15	59
3	DMSO	DBU	100	15	95
4 <sup>b</sup>	DMSO	DBU	100	15	0
5	DMSO	NEt <sub>3</sub>	100	15	75
6	DMSO	<i>t</i> -BuOK	100	15	68
7 <sup>c</sup>	DMSO	DBU	80	15	80
8 <sup>c</sup>	DMSO	DBU	100	15	82
9 <sup>c</sup>	DMSO	DBU	120	15	73
10	DMSO	DBU	100	10	85
11	DMSO	DBU	100	20	79

<sup>a</sup> Reaction conditions: 1.5 mmol of phenylboronic acid, 1 mmol of amine, 2.0 mmol of diacetoxycopper, 2.0 mmol of base, 2 mL of dry solvent. <sup>b</sup> In the absence of diacetoxycopper. <sup>c</sup> 1.5 mmol of diacetoxycopper was added as the catalyst. <sup>d</sup> Isolated yield.

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**Table 2.** Coupling of Phenylboronic Acid with Different Amines<sup>a</sup>

$$\text{PhB(OH)}_2 + \text{HNR}_1\text{R}_2 \xrightarrow[\text{MW, 100}^\circ\text{C}]{\text{Cu(OAc)}_2, \text{DBU}} \text{Ph-NR}_1\text{R}_2$$

Entry	HNR <sub>1</sub> R <sub>2</sub>	Product	Yield (%) <sup>c</sup>
1			<b>3a</b> 96
2			<b>3b</b> 95
3			<b>3c</b> 89
4			<b>3d</b> 48
5 <sup>b</sup>			<b>3e</b> 66
6 <sup>b</sup>			<b>3f</b> 86
7 <sup>b</sup>			<b>3g</b> 83
8 <sup>b</sup>			<b>3h</b> 30
9 <sup>b</sup>			<b>3i</b> 58
10 <sup>b</sup>			<b>3j</b> 54
11 <sup>b</sup>			<b>3k</b> 29
12 <sup>b</sup>			<b>3l</b> 68
13 <sup>b</sup>			<b>3m</b> 66

<sup>a</sup> Reaction conditions: 1.5 mmol of phenylboronic acid, 1 mmol of amine, 2.0 mmol of diacetoxy copper, 2.0 mmol of DBU, 2 mL of dry DMSO. <sup>b</sup> Reaction time is 30 min. <sup>c</sup> Isolated yield.

example, propan-2-amine and morpholine afforded 96% and 95% of **3a** and **3b**, respectively (entries 1 and 2, Table 2), and 48% and 66% of **3d** and **3e**, respectively, were isolated when indole and aniline reacted with phenylboronic acid (entries 4 and 5, Table 2). Anilines containing various electron-donating and -withdrawing substituents were carried out under the optimal reaction conditions. As shown, the anilines bearing chloro-, methyl-, and methoxyl-substitutions were well tolerated (entries 6, 7, 12 and 13, Table 2), although those containing an electron-withdrawing group typically gave lower yields (entries 9–12, Table 2). Steric effects were also observed that the *para*- and *meta*-substituted anilines proceeded in good yields (entries 6, 7, 9 and 10,

**Table 3.** Coupling of Anilines with Different Arylboronic Acids<sup>a</sup>

$$\text{PhNH}_2 + \text{ArB(OH)}_2 \xrightarrow[\text{MW, 100}^\circ\text{C}]{\text{Cu(OAc)}_2, \text{DBU}} \text{PhNHAr}$$

Entry	ArB(OH) <sub>2</sub>	Product	Yield (%) <sup>b</sup>
1			<b>3e</b> 66
2			<b>3f</b> 69
3			<b>3g</b> 58
4			<b>3h</b> 29
5			<b>3i</b> 70
6			<b>3j</b> 70
7			<b>3k</b> 38
8			<b>3l</b> 87
9			<b>3m</b> 71

<sup>a</sup> Reaction conditions: 1.5 mmol of substituted boronic acid, 1 mmol of aniline, 2.0 mmol of diacetoxy copper, 2.0 mmol of DBU, 2 mL of dry DMSO, 30 min. <sup>b</sup> Isolated yield.

Table 2), while more steric *ortho*-substituted anilines are less reactive (entries 8 and 11, Table 2).

The scope of the process with respect to arylboronic acids was then investigated (Table 3). The coupling reactions of aniline with arylboronic acids containing various electron-donating and electron-withdrawing substituents were also carried out under the optimal reaction conditions. As expected, the corresponding *N*-arylation products were obtained in moderate to good yields. No significant electronic effects were observed for the electron-rich and -poor substituted arylboronic acids (entries 1, 2, 5, 8, and 9, Table 3). Reactions of *para*- or *meta*-substituted arylboronic acids occurred in good yields (entries 2, 3, 5, and 6, Table 3), while more steric *ortho*-substituted boronic acids are less reactive (entries 4 and 7, Table 3). *o*-Methoxyl-substitutions, either on the aryl amine or the arylboronic acid gave lower yields (entry 8, Table 2; entry 4, Table 3), suggesting that concurrent steric hindrance from both substrates is compatible in the current system.

In summary, we described a rapid, efficient, and convenient protocol for the preparation of *N*-arylated amines by coupling of arylboronic acids with amines in the presence of inexpensive Cu(OAc)<sub>2</sub> and DBU. Compared with the former Ullmann reaction conditions, this methodology developed a much faster way to construct C–N bonds under microwave irradiation without using expensive ligand and

palladium. Furthermore, the procedure used commercially available reagents and equipment, and a variety of substrates could participate in the process with higher purities and yields. The short reaction times and simple reaction conditions render this method particularly attractive for the efficient construction of library synthesis and preparation of biologically and medicinally interesting molecules.

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**Supporting Information Available.** Reaction procedures and characterization data of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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