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## A simple and efficient N-arylation of amines and sulfonamides with $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$

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### ABSTRACT

N – arylation of amines and sulfonamides with aryl boronic acids in presence of  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$  has been carried out at room temperature. The remarkable selectivity under mild and neutral conditions, commercially available inexpensive catalyst is an attractive feature of this method.

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### KEYWORDS

Amines;  
Sulfonamides;  
Boronic acid.

### INTRODUCTION

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds is in great demand.

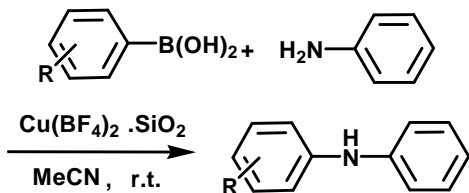
The formation of C-N bond via cross coupling reaction represents an important addition to the synthetic methodologies for the preparation of nitrogen containing compounds in pharmaceuticals,<sup>[1,2]</sup> crop-protection chemicals and material sciences. In contrast to the powerful C-C bond cross coupling reactions of Suzuki and Stille, a need remains for mild (weak base and room temperature) and general C – N bond cross coupling reactions for a wide variety of N – H containing substrates.

In recent years Buchwald<sup>[3a]</sup> and Hatwing<sup>[3b]</sup> have pioneered a valuable Palladium catalyzed C-N cross coupling of aryl halides with amines, anilines, mono nitrogen azoles and carbamates, in general involving either a base (t-BuONa) or elevated temperature. Aryl bismuths<sup>[3c-d]</sup> and aryl leads<sup>[3e]</sup> have been demonstrated to undergo copper promoted N-arylation at elevated

temperature. Subsequently, Copper catalyzed amination was also achieved<sup>[4]</sup> by adding 1 – 10 phenanthroline as a ligand to conduct coupling at lower temperature than the classical Ullmann condensation.<sup>[4a]</sup> More recently, copper promoted N – arylation with aryl boronic acids for diverse N-H containing substrates was discovered by Chan<sup>[5]</sup> and Lam.<sup>[6]</sup> This methodology was further extended to include aryl stannanes<sup>[7]</sup> with limited success. However these reactions are generally slow (18 hr – 13 days to proceed to completion) and carried out with either  $\text{Et}_3\text{N}$  or pyridine as base in dichloromethane. In all cases, the use of excess of aryl boronic acids is also a major limitation of the methods. Although the reaction conditions in these powerful new methods are significant improvements over classical Ullmann condensation conditions, still there is room for improvement.

However, many of these reported methods suffer from one or more disadvantages such as harsh experimental procedure and reagents that are expensive, moisture sensitive, or highly toxic in nature. Consequently, there is an opportunity for further development towards mild conditions to increased variation of the subsequent

in the components and for better yields (Scheme 1).



R: Alkyl, heteroaryl

Scheme 1

## RESULTS AND DISCUSSION

The catalytic activity of the cupric fluoroborate ( $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$ ) for N-arylation of aniline (2 mmole)

TABLE 1: Reactions of aniline with benzene boronic acid under various conditions

Entry	Solvent	$\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$ (mmol)	Time (min)	Yield (%) <sup>a</sup>
1.	Neat	---	90	10
2.	THF	0.1	40	55
3.	$\text{CH}_3\text{Cl}_2$	0.1	40	65
4.	$\text{CHCl}_3$	0.1	40	70
5.	$\text{Et}_2\text{O}$	0.1	40	70
6.	EtOAc	0.1	40	80
7.	DMF	0.1	40	80
8.	$\text{CH}_3\text{CN}$	0.1	20	92
9.	$\text{CH}_3\text{CN}$	0.15	20	92
10.	$\text{CH}_3\text{CN}$	0.2	20	92
11.	$\text{CH}_3\text{CN}$	0.05	40	82

<sup>a</sup> Isolated yield of the corresponding diphenylamine

with Boronic acid (2 mmol) at room temperature was studied and it was found that application of less than 0.1 mmol (30mg) of ( $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$ ) in acetonitrile (5ml) a moderate yield of the corresponding diphenylamine (TABLE 1, entries-11), whereas use of more than 0.1 mmol (30mg) obtained an excellent yields (TABLE 1, entries-9-10). The reaction in THF,  $\text{CH}_3\text{CN}$ ,  $\text{CHCl}_3$ ,  $\text{Et}_2\text{O}$ , EtOAc, DMF (TABLE 1, entries -1-7) were found less effective. Since we have carried out the reaction in presence of  $\text{CH}_3\text{CN}$  solvent to get the excellent yield (92%, entries 8)

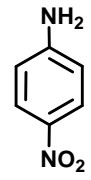
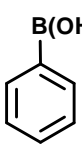
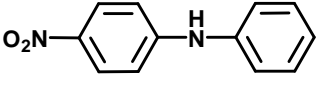
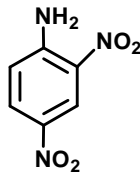
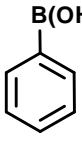
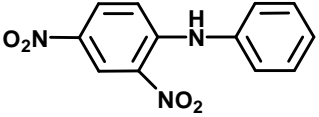
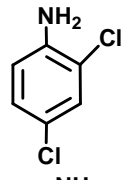
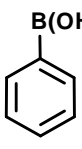
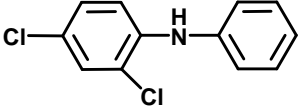
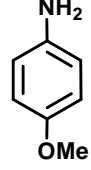
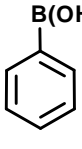
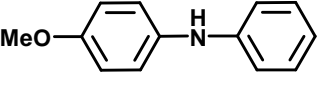
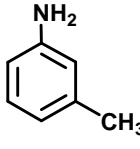
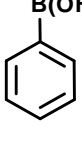
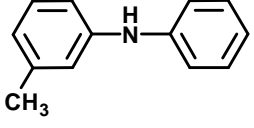
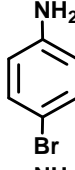
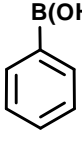
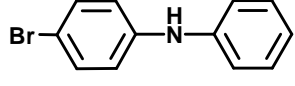
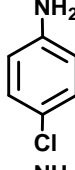
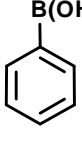
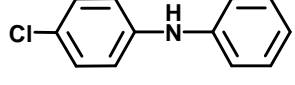
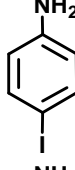
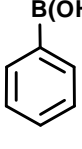
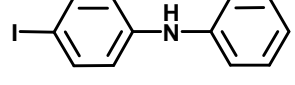
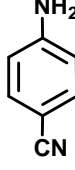
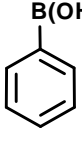
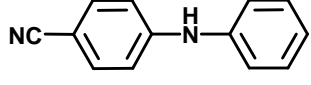
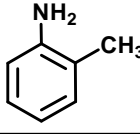
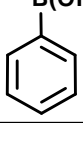
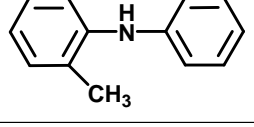
A variety of aromatic, aliphatic, and heterocyclic amines were converted to corresponding N-arylation using  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$  in excellent yields at room temperature and in short reaction times. Furthermore, the reaction conditions are very mild and no by-products were observed. The results are summarized in TABLE 2. All aromatic amines carrying electron donating or withdrawing substituents reacted well and gave excellent yields (TABLE 2 1-21). Aliphatic amines produced N-arylation in good yields (TABLE 2, 23-25). The nitro substituted aryl amines required slightly longer reaction times to produce comparable yields than those of their simple and electron-rich counterparts (TABLE 2, entries 4,5,16,17). The reaction responded well with various aryl / hetero aryl boronic acids with various electron donating and withdrawing aniline analogs, furnishing good yield of products in short reaction time (TABLE 2, 15-21, 24, 25).

TABLE 2: N-arylation of amines using  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$

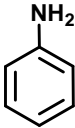
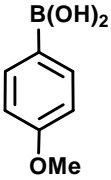
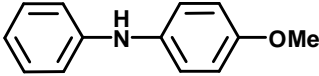
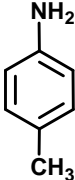
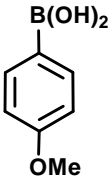
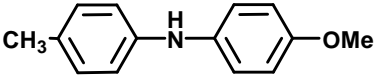
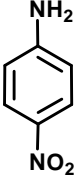
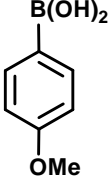
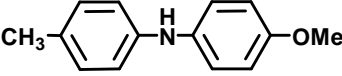
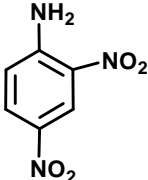
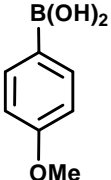
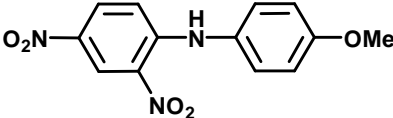
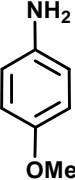
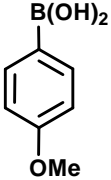
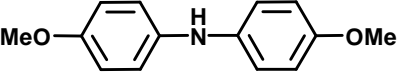
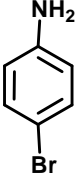
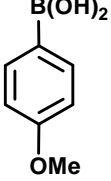
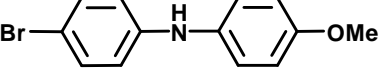
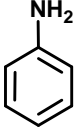
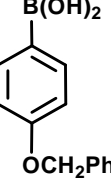
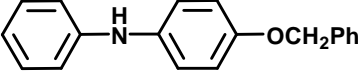
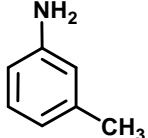
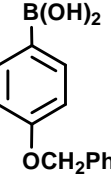
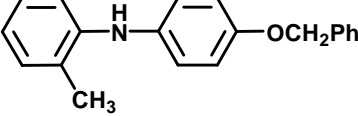
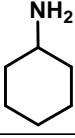
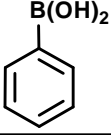
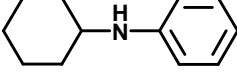
Entry	Amines <sup>a</sup>	Boronic Acid	Product <sup>b</sup>	Time (min)	Yield <sup>c</sup> (%)
1.				20	92
2.				20	92
3.				20	91

(Continued)

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Entry	Amines <sup>a</sup>	Boronic Acid	Product <sup>b</sup>	Time (min)	Yield <sup>c</sup> (%)
4.				40	80
5.				50	70
6.				20	83
7.				20	88
8.				20	90
9.				20	86
10.				20	85
11.				20	86
12.				20	86
13.				20	80

(Continued)

Entry	Amines <sup>a</sup>	Boronic Acid	Product <sup>b</sup>	Time (min)	Yield <sup>c</sup> (%)
14.				20	85
15.				20	90
16.				40	81
17.				50	72
18.				20	91
19.				20	87
20.				20	88
21.				20	85
22.				20	90

(Continued)

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Entry	Amines <sup>a</sup>	Boronic Acid	Product <sup>b</sup>	Time (min)	Yield <sup>c</sup> (%)
23.				20	88
24.				20	90
25.				20	85

<sup>a</sup> The substrate was treated with boronic acid (2 mmol) by using 0.1 mmol of  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$  in the presence of acetonitrile under neat conditions at room temperature.

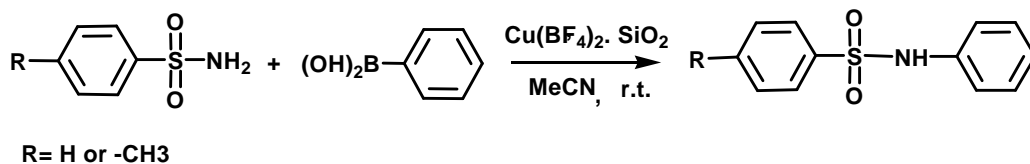
<sup>b</sup> All products were identified by their IR and <sup>1</sup>H NMR spectra.

<sup>c</sup> Isolated yields.

Sulfonamides are extremely useful pharmaceutical compounds because they exhibit a wide range of biological activities such as anticancer, anti-inflammatory and antiviral functions<sup>[8]</sup>. More recently N-arylation of sulfonamides are reported in the literature.<sup>[9-11]</sup> However use of oxidant, drastic conditions, long reaction

time and low to moderate yields are the limitations associated with these methods.

Encouraged by these results, we further treated aryl boronic acids with benzene / p-toluene sulfonamides at room temperature to yield N-arylated products of corresponding sulfonamides at short reaction time (Scheme 2).



Scheme 2

A variety of aryl, heteroaryl boronic acids reacted smoothly with sulfonamides at room temperature to fur-

nish the corresponding N-arylated sulfonamides in good yields. (TABLE 3).

TABLE 3: N-arylation of sulfonamide using  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$

Entry	Amide <sup>a</sup>	Boronic acid	Product <sup>b</sup>	Time (min)	Yield <sup>c</sup> (%)
1.				20	92
2.				20	90

(Continued)

Entry	Amide <sup>a</sup>	Boronic acid	Product <sup>b</sup>	Time (min)	Yield <sup>c</sup> (%)
3.				20	92
4.				20	89
5.				20	91
6.				20	89

<sup>a</sup> The sulfonamide (2 mmol) was treated with boronic acid (2 mmol) by using 0.1 mmol of  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$  in the presence of acetonitrile under neat conditions at room temperature.

<sup>b</sup> All products were identified by their IR and <sup>1</sup>H NMR spectra

<sup>c</sup> Isolated yields.

## CONCLUSION

In conclusion, this manuscript describes a method in which  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$  is a highly efficient catalyst for N-arylation of amines and sulfonamides. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields. The remarkable selectivity under mild and neutral conditions, of this commercially available inexpensive catalyst is an attractive feature of this method.

## EXPERIMENTAL

### General procedure for the N-arylation of amines from aryl boronic acids

To a mixture of benzene boronic acid (2 mmol), sodium (or potassium) carbonate (2 mmol) and aniline (2

mmol),  $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$  (100 mg, 50 mol %) was stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction, diethyl ether (20 ml) was added and the organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum to furnish the crude product, which was further purified by column chromatography (Pet. Ether : Ethyl acetate = 9:1). In all the cases, the product obtained after the usual work up gave satisfactory spectral data.

### Spectral data for selected compounds

N, N-Biphenyl amine (1b) : White solid; mp. 52°C; IR (KBr) : 3365, 2626, 1599, 1495, 1177, 1024, 844, 746  $\text{cm}^{-1}$

<sup>1</sup>H NMR (200 MHz,  $\text{CDCl}_3$ ): 5.65(brs, 1H), 6.87-7.08 (m, 5H), 7.21 – 7.31 (m, 5H);

<sup>13</sup>C NMR (50 MHz,  $\text{CDCl}_3$ ): d 117.67, 120.83, 129.23, 142.96; EIMS m/z 169 (M);

Anal. Calcd for  $\text{C}_{12}\text{H}_{11}\text{N}$ : C, 85.14; H, 8.54; N, 8.30. Found: C, 85.28; H, 6.63; N, 8.42.

**Full Paper****REFERENCES**

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