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# An Efficient Base-Free *N*-Arylation of Imidazoles and Amines with Arylboronic Acids Using Copper-Exchanged Fluorapatite

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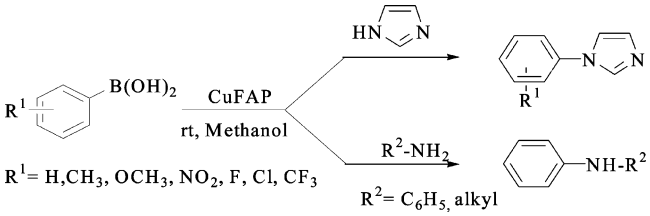
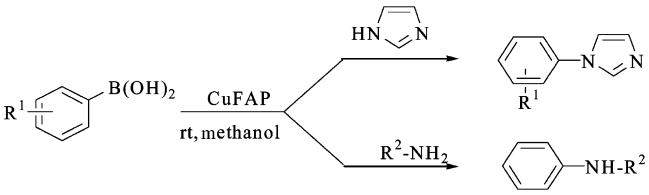



*N*-Arylation of imidazoles and amines with arylboronic acids was accomplished with copper-exchanged fluorapatite (CuFAP) in methanol at room temperature. The products *N*-arylimidazoles and *N*-arylamines were isolated in good to excellent yields. A variety of arylboronic acids were converted to the corresponding *N*-arylimidazoles and *N*-arylamines, demonstrating the versatility of the reaction.

C−N bond formation via transition metal catalysis is currently a subject of great interest, and intensive research is being carried out to ensure useful organic transformations.[1] The synthesis of *N*-arylimidazoles and other *N*-arylamines has attracted significant interest because of the frequent occurrence of these structural units in biologically active inhibitors.[2] The most straightforward route to *N*-arylimidazoles involves the direct formation of the aryl−nitrogen bond. However, the standard practice for carrying out such reactions involves nucleophilic aromatic substitution[3] and traditional Ullmann reactions[4] as well as the coupling of imidazoles with aryllead, arylbismuth, arylborane, and arylsilane reagents.[5] Chan and Lam established

**SCHEME 1**




an efficient approach to *N*-arylimidazoles via $Cu(OAc)_2$-mediated coupling of imidazoles with readily available arylboronic acids.[6]

Later, Collman and co-workers reported using Cu(II) complexes with nitrogen-chelating bidentate ligands in the coupling of imidazoles at room temperature.[7] Very recently, Xie and co-workers have shown the simple copper salt catalyzed coupling of imidazoles with arylboronic acids in protic solvent without any base.[8] The development of mild and cost-effective catalytic procedures for *N*-arylation of imidazoles and amines still remains an active research area.[9] Recently, calcium hydroxyapatite has been used as a heterogeneous support for transition metals, and the supported hydroxyapatite is used for organic transformations.[10] In this direction, we recently performed an efficient *N*-arylation of imidazoles and other heterocycles with chloro- and fluoroarenes using basic copper apatite catalysts.[11]

Herein, we report the facile *N*-arylation of imidazoles and amines catalyzed by heterogeneous basic copper fluorapatite (CuFAP) (Scheme 1) at room temperature. Various arylboronic acids were examined for the synthesis of *N*-arylimidazoles and *N*-arylamines.

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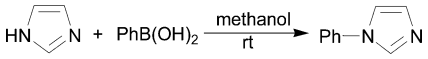
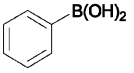
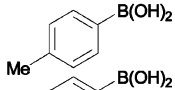
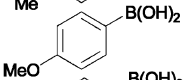
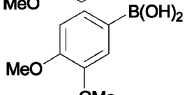
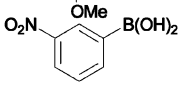
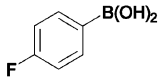
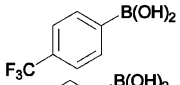
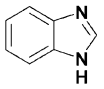
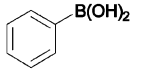
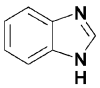
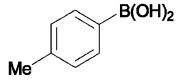
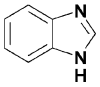
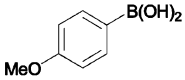
**TABLE 1.** ***N*-Arylation of Imidazoles Using Different Copper Catalysts**[a]




| entry | catalyst | time (h) | yield (%)[b] |
|---|---|---|---|
| 1 | $Cu(OAc)_2$ | 6 | 25 |
| 2 | CuI | 6 | 30 |
| 3 | Cu powder | 6 | 25 |
| 4 | CuHAP | 6 | 20 |
| 5 | CuFAP | 6 | 88, 82[c] |
| 6 | none | 24 | 0 |

[a] Conditions: imidazole (1.2 mmol), phenylboronic acid (1 mmol), methanol (3 mL), rt. [b] Isolated yields. [c] Yield after fourth cycle.

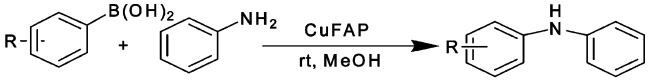
**TABLE 2.** ***N*-Arylation of Imidazoles with Different Arylboronic Acids**[a]

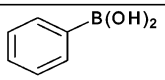
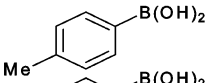
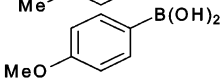
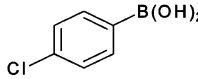
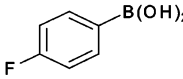
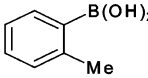
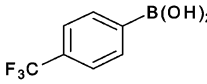
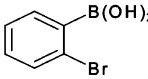
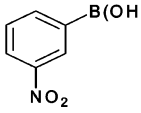
| entry | imidazole | arylboronic acid | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 5 | 88 (25)[c], 80[d] |
| 2 |  |  | 4 | 86 |
| 3 |  |  | 5 | 90 |
| 4 |  |  | 5 | 85 |
| 5 |  |  | 8 | 78 |
| 6 |  |  | 5 | 85 |
| 7 |  |  | 8 | 80 |
| 8 |  |  | 12 | 88 (25)[c], 83[d] |
| 9 |  |  | 12 | 85 |
| 10 |  |  | 12 | 86 |

[a] Conditions: imidazole (1.2 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), methanol (4 mL), rt. [b] Isolated yields. [c] $Cu(OAc)_2$ homogeneous reaction under identical conditions. [d] Yield after fourth cycle.

In an effort to evolve a better catalytic system, various catalysts were screened for *N*-arylation of imidazole and phenylboronic acid in methanol at room temperature. The results are summarized in Table 1. Homogeneous Cu catalyst, $Cu(OAc)_2$ and CuI, gave very low yield (Table 1, entries 1 and 2). Copper-exchanged hydroxyapatite (CuHAP) also gave a very low yield (Table 1, entry 4), while CuFAP afforded a very good yield (Table 1, entry 5). Moreover, the controlled *N*-arylation reaction conducted under identical conditions devoid of CuFAP gave no coupled product despite prolonged reaction time (Table 1, entry 6). CuFAP was recovered quantitatively by simple filtration and was reused several times, with consistent activity even after the fourth cycle (Table 1, entry 5). The absence of copper in the filtrate was confirmed by atomic absorption spectroscopy, which confirms no leaching of copper during the reaction and provides evidence for heterogeneity throughout the reaction.

**TABLE 3.** ***N*-Arylation of Aniline with Various Arylboronic Acids**[a]




| entry | arylboronic acid | time (h) | yield (%)[b] |
|---|---|---|---|
| 1 |  | 3 | 90 |
| 2 |  | 4 | 93 |
| 3 |  | 4 | 90 |
| 4 |  | 3 | 87 |
| 5 |  | 3 | 87 |
| 6 |  | 3 | 89 |
| 7 |  | 4 | 90 |
| 8 |  | 2 | 91 |
| 9 |  | 6 | 79 |

[a] Conditions: aniline (1.5 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), methanol (4 mL). [b] Isolated yields.

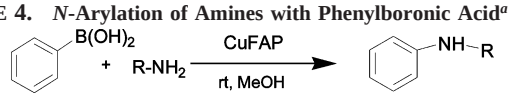
Our method was successfully amenable to a wide range of arylboronic acids, allowing preparation of *N*-arylimidazoles and *N*-arylbenzimidazoles in high yield, and the results are shown in Table 2. Phenylboronic acids with an electron-donating group afforded better yields (Table 2, entries 2−4) than did those with electron-withdrawing groups (Table 2, entries 5−7). Similar observation was made when benzimidazoles were used in place of imidazoles to obtain the corresponding *N*-arylbenzimidazoles (Table 2, entries 8−10), but the reactions took longer time compared to that in the reactions of imidazoles.

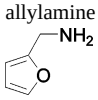
After achieving excellent results with imidazoles, we further applied this catalytic system for the *N*-arylation of aromatic amines and aliphatic amines. The results are shown in Tables 3 and 4. Table 3 shows the results of *N*-arylation of aniline with several arylboronic acids.

It is clear from Table 3 that *N*-arylation proceeds very effectively and affords the corresponding *N*-arylated products in good to excellent yields under very mild conditions.[12] No spectacular electronic effects were observed in the *N*-arylation of aniline; only a slight decrease in the reaction rate was noted with the 3-nitrophenylboronic acid. Next we examined the *N*-arylation of various primary amines, such as aliphatic,

(12) Chiang, G. C. H.; Olsson, T. *Org. Lett.* **2004**, *6*, 3079.

**TABLE 4.** ***N*-Arylation of Amines with Phenylboronic Acid**[a]




| entry | amines | time (h) | yield (%)[b] |
|---|---|---|---|
| 1 | *n*-butylamine | 3 | 93 |
| 2 | *n*-hexylamine | 4 | 90 |
| 3 | *n*-heptylamine | 4 | 92 |
| 4 | *n*-octylamine | 4 | 95 |
| 5 | benzylamine | 2 | 90 |
| 6 | cyclohexylamine | 3 | 88 |
| 7 | allylamine | 4 | 87 |
| 8 |  | 2 | 90 |



[a] Conditions: amine (1.5 mmol), arylboronic acid (1 mmol), CuFAP (100 mg), methanol (4 mL). [b] Isolated yields.

cyclohexyl, and heterocyclic amines, with phenylboronic acid using CuFAP catalyst at room temperature, and the results are listed in Table 4. All the reactions proceeded very efficiently at room temperature and yielded the corresponding *N*-arylated products. It was interesting to note that the formation of the conceivable diarylated product is not observed in our conditions.

In conclusion, we have developed a heterogeneous CuFAP-catalyzed *N*-arylation of imidazoles and amines under mild conditions. The following features make this process attractive: (1) base-free *N*-arylation; (2) the reaction is carried out at room temperature; (3) the procedure works well with a variety of imidazoles and amines, affording good to excellent yields; and (4) reusability of the catalyst.

## Experimental Section

**A Typical Procedure for *N*-Arylation of Imidazole with Phenylboronic Acid at Ambient Conditions:** In a typical experimental procedure, CuFAP (100 mg) was added to a mixture of imidazole (1.2 mmol) and phenylboronic acid (1 mmol) in methanol (3 mL) at room temperature, and the mixture was stirred for 5 h. The progress of the reaction was monitored by TLC, and on completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 70/30) to afford the *N*-phenylimidazole. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.83 (s, 1H), 7.50−7.30 (m, 5H), 7.25 (br s, 1H), 7.18 (br s, 1 H). EI-MS: 144 (100%), 117, 77, 51. IR (thin film/neat, $cm^{-1}$): 3424, 3117, 1600, 1509, 1304, 1253, 1110, 1058, 908, 760, 690, 659, 520.

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**Supporting Information Available:** Detailed experimental procedures and compound characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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