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New Aryl/Heteroaryl C-N Bond Cross-coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation

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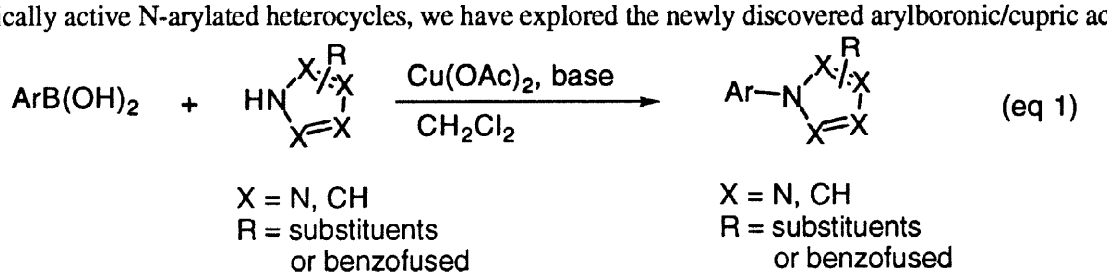
Abstract: A new aryl/heteroaryl C-N bond cross-coupling reaction via the arylboronic acid/cupric acetate arylation of N-H containing heteroarenes has been discovered. This new methodology is mild, proceeds at room temperature exposed to air, and works for many heteroarenes and arylboronic acids providing good yields of N-arylated heteroarenes.

Aryl/aryl C-C bond cross-coupling reactions, such as Suzuki[1] and Stille[2] reactions, are important and powerful methodologies in organic synthesis. However, the corresponding aryl/heteroaryl C-N bond cross-coupling reactions are not common[3], especially ones that involve mild conditions and are applicable to a wide spectrum of heteroarenes and aryl partners. Traditional procedures, such as the Ullmann reaction[4], usually require very high temperatures and give variable yields. On the other hand, arylation of amines and anilines using aryl halides/palladium or nickel catalyst has been well documended[5] by Hartwig and Buchwald. Recently, arylation of N-H containing heteroarenes has been shown to work with catalytic cupric acetate/*p*-tolyllead triacetate[3] or catalytic cupric trifluoroacetate/triphenylbismuth bistrifluoroacetate[6]. The aryllead reaction is a significant improvement over previous methods. However, only *p*-tolyllead was reported for the aryllead reaction, which in general requires elevated temperature (90°C, except for indazole). This reaction aslo involves relatively toxic organolead byproducts. The arylbismuth reaction is limited to indole-like heteroarenes. Both of these reactions are also limited by the very small number of commercially available organolead or organobismuth substrates, which is an important factor in making heterocycle-containing libraries. In our search for a general and mild methodology for the aryl/heteroaryl C-N bond cross-coupling reaction towards the synthesis of biologically active N-arylated heterocycles, we have explored the newly discovered arylboronic/cupric acetate



(eq 1)

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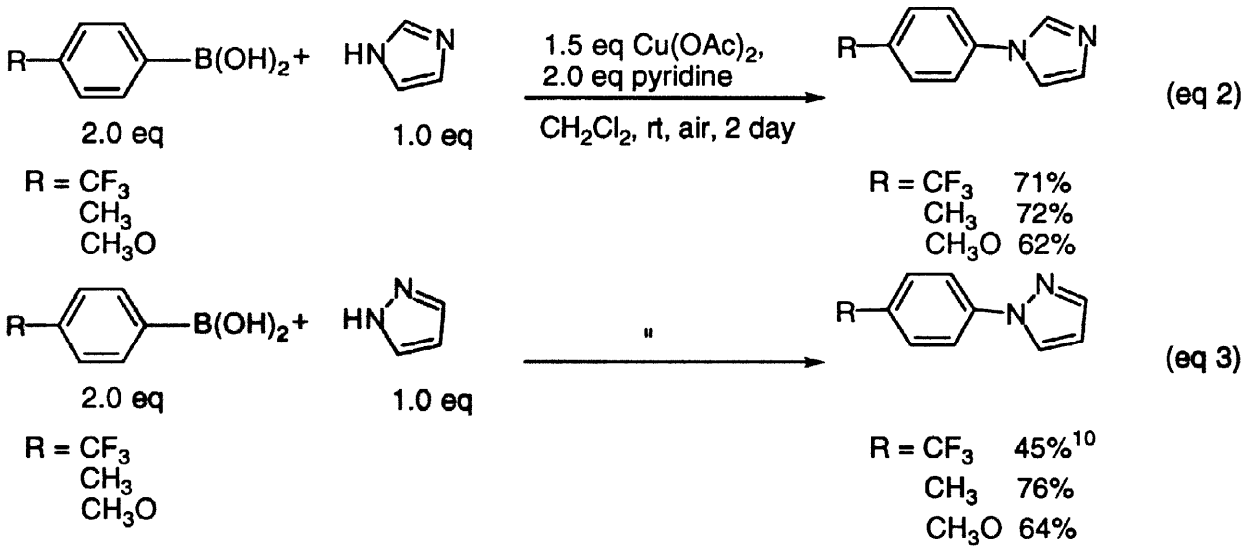
arylation reaction[7]. This reaction is applicable to the arylation of phenols[8], anilines, anilides, imides, cyclic carbamates, sulfonamides and ureas. We have discovered that the arylboronic/cupric acetate arylation reaction is also a powerful methodology to perform aryl/heteroaryl C-N bond cross-coupling for the arylation of a variety of standard N-H containing heteroarenes (eq 1).

The general conditions for this coupling reaction involve the addition of 2.0 equivalents of arylboronic acid and 2.0 equivalents of base (pyridine) to 1.0 equivalent of heteroarene in methylene chloride, followed by 1.5 equivalent of anhydrous cupric acetate and 4Å molecular seives[9]. The reaction mixture is stirred open to air at room temperature for 2 days . The mixture is chromatographed on silica gel to give the desired N-arylated heteroarene.

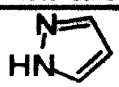
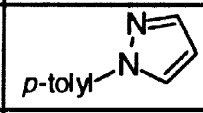
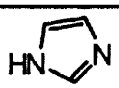
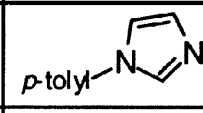
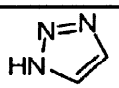
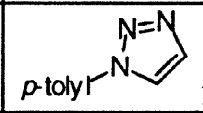
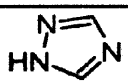
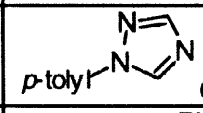
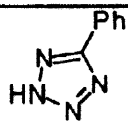
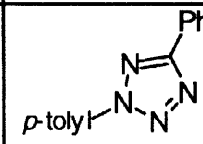
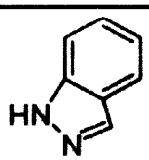
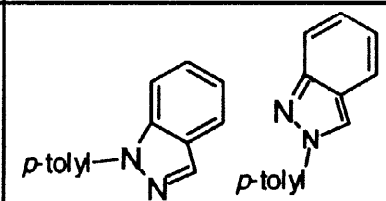
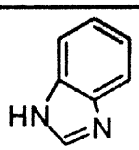
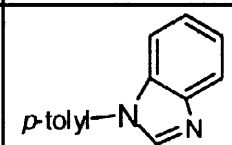


Keeping the heteroarenes constant as imidazole (eq 2) and pyrazole (eq 3), three different arylboronic acids (*p*-trifluoromethylphenyl, *p*-tolyl and *p*-methoxyphenyl) ranging from electron-deficient to electron-rich rings were attempted. The yields are in general good, indicating that this reaction can tolerate arylboronic acids of various electronic nature.

A standard set of heteroarenes, containing different numbers of nitrogens, were explored using *p*-tolylboronic acid to determine the synthetic scope of this coupling reaction. In general, the yields of these reactions are good (67% to 88%) for the more nucleophilic heterocycles like pyrazole, imidazole, indazole and benzimidazole. For the less nucleophilic heterocycles, such as triazoles and tetrazole, the yields are low. In these cases, large amounts of *p*-cresol and *p*-tolyl ether were obtained. We believe this is because when the C-N coupling reaction is slow, the competing conversion of *p*-tolylboronic acid to *p*-cresol by cupric acetate and the subsequent arylation of *p*-cresol took place. Phenyltetrazole was used instead of the parent tetrazole since the parent tetrazole gave no product because of poor solubility in organic solvents. Pyrrole and indole were tried, but very little desired product (<~3%) can be isolated from the complex reaction mixture. The reason for this poor reaction is currently being investigated.

For the heteroarenes capable of forming regioisomers, it was found that in most cases (entry 3-6), one major regioisomer (determined by nOe experiment) predominates, the minor regioisomer is either of low yield or undetectable (<5%). Use of more than 1.5 equivalents of cupric acetate[11] or more than 2.0 equivalents of base did not appear to increase the yield. Methylene chloride, 1,4-dioxane, N-methylpyrrolidinone, THF and

Table 1. Cross-coupling reaction[a] of *p*-tolylboronic acid with diverse N-H containing heteroarenes.

Entry	Heteroarene substrate	Product and isolated yield
1		 76%
2[b]		 72%
3[c]		 11%
4[c]		 6%
5[c,d]		 26%
6		 9 : 2 88%
7		 67%

[a]Conditions: 1.0 eq. heteroarene + 2.0 eq. *p*-tolylboronic acid + 2.0 eq. pyridine + 1.5 eq. anhydrous $Cu(OAc)_2$ + 4Å molecular sieves in methylene chloride. The spectral data for the new compounds are in accord with the structures assigned.

[b]Use of pyridine or triethylamine as base gives similar yields.

[c]Pyridine, triethylamine, N-methylmorpholine and 1,8-diazabicyclo[5.4.0]undecane were used as base. Pyridine gives the best yield. Regioechemistry was determined by nOe experiments.

[d]Five equivalents of pyridine gave 24% yield.

DMF as solvents are preferred over ethyl acetate, toluene and DMSO. Use of methanol resulted in no product formation. We have also bubbled oxygen during the phenyltetrazole reaction and observed no improvement in yield compared with under air.

We hypothesize that the mechanism of the reaction involves cupric acetate forming a complex with the heterocycle and transmetallating with arylboronic acid. Reductive elimination of the resulting heterocycle/copper/aryl complex[12] affords the N-arylated heterocycle. The mechanism of the reaction is being investigated[13].

In summary, we have discovered an important aryl/heteroaryl C-N bond cross-coupling reaction capable of forming a wide range of N-arylated heteroarenes. This methodology is currently being applied to the N-arylation of N-H containing saturated heterocycles. We have also demonstrated that aryltrialkylstannanes can replace arylboronic acids in cupric acetate promoted N-arylation reactions. However, the yields are much lower than the corresponding arylboronic acid reactions and further optimization is in progress. The mild conditions of this general N-arylation methodology in terms of pyridine base, room temperature, air and diverse substrate tolerance make it an ideal reaction for the generation of heterocycle-containing libraries. We are currently exploring the different aspects of this methodology in order to expand its potential scope.

Representative procedure: A 20 mL vial is charged with a magnetic stirrer bar, *4*-tolylboronic acid (90 mg, 0.667 mmol, 2.0 eq), benzimidazole (39 mg, 0.333 mmol, 1.0 eq), anhydrous cupric acetate (91 mg, 0.500 mmol, 1.5 eq), 250 mg activated 4 Å molecular sieves, pyridine (1.0 mL of 0.67M solution in dichloromethane, 0.67 mmol, 2.0 eq), and 4 mL dichloromethane. The reaction is stirred under air at ambient temperature in a loosely capped vial for 2 days. The reaction is judged complete by TLC analysis of an aliquot. The reaction is filtered through Celite, washed with methanol and purified by silica gel chromatography (eluent 15% ethyl acetate/hexane with 1% MeOH) to give 46 mg (67%) of 1-*p*-tolyl-1*H*-benzimidazole.

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9. Suggestion of D. A. Evans. See ref 8. In general, the yields are the same or slightly better with the addition of 4Å molecular sieves.
10. This trifluoromethylphenyl analog is volatile under high vacuum. The yield is probably higher than 45%.
11. For the benzimidazole reaction, $Cu(OTf)_2$, instead of $Cu(AcO)_2$, also promotes the reaction, but not $CuCl_2$. Since this reaction is formally an oxidative-coupling reaction, we have replaced cupric acetate with ferric chloride in the imidazole reaction. However, no product was observed.
12. (a) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tet. Lett.* **1987**, *28*, 887-890. (b) Wipf, P. *Syn.* **1993**, 537-557.
13. We have recently discovered that this reaction works well also for the 1,3-propanediol cyclic ester of boronic acid.