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CUPRIC ACETATE MEDIATED N-ARYLATION BY ARYLBORONIC ACIDS : A PRELIMINARY INVESTIGATION INTO THE SCOPE OF APPLICATION

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Abstract: A range of NH substrates of varying nucleophilicity were reacted with a selection of electronically diverse aryl boronic acids in the presence of cupric acetate in order to evaluate the generality of a previously described *N*-arylation procedure. The results of that investigation are discussed.

The *N*-arylation of NH-containing substrates under mild conditions has been described by a relatively small number of researchers. Notably the work of Buchwald[1-3] and Hartwig[4] describes procedures which permit the catalytic cross coupling of a variety of primary amines with both electron rich and electron poor aryl bromides by employing $Pd_2(dba)_3$/BINAP. However the arylation of other NH substrates is less developed, with only a handful of examples in which heterocyclic nitrogen participates[3,5] and fewer still when the nitrogen atom is deactivated by an adjacent group such as carbonyl.[6] More recently however, Chan and co-workers[7] reported the efficient *N*-arylation of a wide range of NH substrates by their reaction with the corresponding boronic acid in the presence of cupric acetate and either triethylamine or pyridine. In this report moderate to excellent yields were afforded for the *p*-tolylation of primary and secondary amines and more interestingly for poorly nucleophilic substrates such as amides, imides, ureas, carbamates and sulfonamides.

As a wide variety of electronically diverse boronic acids are available either commercially or synthetically we were interested to explore the generality of this procedure, by examining the efficiency of the *N*-arylation across a selection of substrates of varied NH basicity/nucleophilicty.

For this investigation, the reaction conditions used were essentially the same as that described by Chan[7,8] with an extension of reaction time in some cases. Furthermore, in consideration of the report by Evans *et al.*[9] concerning the possibility of the role of oxygen in the copper promoted arylation of phenols with aryl boronic acid, no attempt was made to exclude atmospheric oxygen.(Scheme 1, Table 1).

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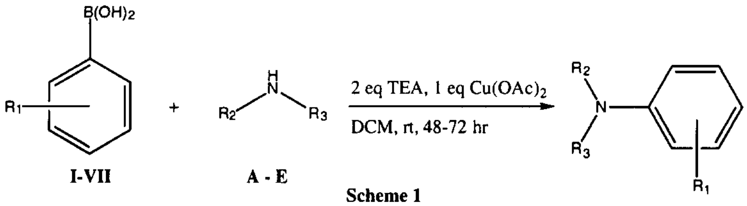
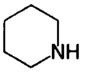
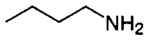
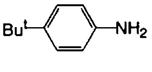
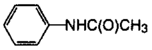
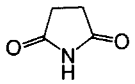


Scheme 1

Table 1: Yields of N-Arylated Products‡ by Cupric Acetate Mediated Coupling of NH-Substrates with Arylboronic Acids.

NH Substrate **Arylboronic Acid§**	**A** 	**B** 	**C** 	**D** 	**E** 
I.[10] R_1 = 4-N(CH$_3$)$_2$	0%	0%	na	11%	0%
II.[11] R_1 = 4-OCH$_3$	82%[12]	39%[13]	na	na	0%
III.[11] R_1 = 2-OCH$_3$	14%[14]	17%[13]	0%	0%	0%
IV. R_1 = 4-CH$_3$	58%[12]	43%	56%	12%[16]	69%[15]
V. R_1 = H	0%	6%	42%	0%	72%[15]
VI. 3-CF$_3$	0%	21%	10%	53%[17]	65%
VII. 3-NO$_2$	11%	na	<10%	18%[18]	36%

‡ Products identified by ^{1}H nmr and GC/MS

§ Commercially unavailable aryl boronic acids were prepared by the reaction of trimethyl borate with either the corresponding aryl Grignard or lithio intermediate, followed by an acidic quench under standard conditions.[19]

In an attempt to rationalise reactivity trends among coupling partners, Table 1 was presented such that the NH substrates **A-E** were arranged in order of decreasing basicity. Likewise the arylboronic acids **I-VII** were ranked according to decreasing σ values of the substituents.[20] Treatment of the data in this fashion however, did not reveal any obvious trends for either the electron rich or electron poor aryl boronic acids in their reactivity with the NH substrates.

The lower yields afforded by the *ortho-* *vs.* *para*-substituted methoxyboronic acids may be attributed to the steric congestion at the reaction center. Evans *et al.*[9] also reported depressed yields in the arylation of phenols by *ortho*-heteroatom substituted boronic acids. Curiously, the data also suggests that across this spectrum of NH substrates the *p*-tolyl substituted boronic acid **(IV)** generally gives higher yields than the unsubstituted phenylboronic acid **(III)**. This was also borne out in the results reported by Chan and co-workers.[7,21]

Despite the obvious utility of this reaction, the results herein highlight the somewhat capricious nature of this reaction. Other workers have reported similarly incongruous results. Lam *et al.*[5] found that while the yields for various arylations of heterocycles such as pyrazole, imidazole, indazole and benzimidazole, were generally high, that of triazoles and tetrazoles were lower while pyrroles and indoles exhibited virtually no reactivity towards arylation. Chan's article[7] also contains entries where the isolated yields for seemingly analogous systems varied markedly. However each of the authors noted that the role of the base used and the solubility of reaction partners had a significant bearing on the outcome.[22]

The present investigation of the cupric acetate mediated *N*-arylation by aryl boronic acids presents a number of preparative examples which may prove useful in the choice of reaction partners, particularly when non-specific *N*-arylation is required. Additionally, it highlights the potential of the method in so much as it demonstrates useful examples of couplings between electronically diverse reactants. However this report emphasises the need for further mechanistic studies in order to improve the method's generality.

Representative Procedure: The resulting dark-blue to turquoise mixture of the NH substrate **(A-E)**(1.0 mmol), aryl boronic acid **(1-7)** (2.0 mmol), anhydrous cupric acetate (1.0 mmol), triethylamine (2.0 mmol) in dry DCM (3-5ml) was stirred at room temperature for 48-72hr and monitored by tlc. Silica gel (3-4g) was added and the solvent removed at reduced pressure. The adsorbed material was loaded onto a pre-packed column of silica and fractions collected by elution. The appropriate fractions were collected and the identity of the products confirmed by ^{1}Hnmr and/or GC/MS examinations.

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