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COMMUNICATION

Copper-Catalyzed, Ceric Ammonium Nitrate Mediated *N*-Arylation of Amines[†]

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Cu-Catalyzed, ligand and base free cross-coupling of aryl boronic acids with primary and secondary amines has been reported. This 'Chan-Evans-Lam' reaction has revealed that at room temperature, catalytic copper(II) acetate and ceric ammonium nitrate (*CAN*) *as an oxidant, N-arylation can result in an effective C-N bond formation. This air stable, practical, robust protocol enables a variety of functional group tolerance on both boronic acid and amine partners.*

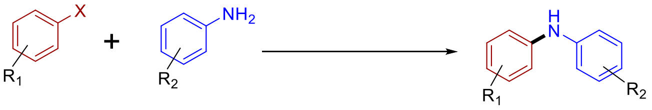
The formation of C-N bonds has been one of the most important transformations in organic synthesis for several decades. Its widespread applications can be found in a variety of fields including the syntheses of pharmaceuticals, agrochemicals, dyes and natural products.[1] Transition-metal catalysis has made this transformation more general and practical. In particular, Buchwald, Hartwig and others have made great contributions through the use of Pd and Cu catalyzed C-N bond formation reactions involving the coupling of electrophilic aryl halides and nucleophilic amines.[2]

In the late 1990's, Cu-mediated cross-coupling of arylboronic acids with amines and phenols was reported by Chan, [3] Evans,[4] and Lam[5] independently and involved stoichiometric amounts of Cu(II) catalyst and an amine base. Collman et al. demonstrated a limited application of a catalytic version (CuOH.TMEDA) of this reaction in the synthesis of substituted indoles.[6] Buchwald has reported the role of the ligand, meristic acid in Cu-catalyzed arylation of anilines, however, inferior results for aliphatic amines were observed.[7]

Recent reports have extended the scope of cross-coupling reactions to include potassium aryl trifluoroborate salts,[8] boronic acid pinacol esters,[9] arylboroxines[10], diarylboronic acids[11] with amines, phenols[12], thioethers[13] and phosphonate diesters as coupling partners.[14,15] It is noteworthy that other transition metals such as Ni,[16,17,18] Mn/Cu bimetallic conditions[19] have exhibited efficacy within this protocol. Another report by Kobayashi et al. described a visible light mediated Cu(II)-catalyzed oxidative cross-coupling reaction (myristic acid/*fac*-[Ir(ppy)$_3$]/2,6-lutidine) between arylboronic acids and anilines.[20] This report was limited to aryl amines and aryl boronic acids. Overall, these reports were usually associated with a ligand, a base, molecular sieves, elevated temperatures or poor yields.

Ceric ammonium nitrate (CAN) with its low cost, low toxicity, air and moisture stable properties, has attracted widespread applications in organic synthesis.[21,22] In particular, this greener oxidant is attractive because of its high reduction potential, Lewis acid nature and especially its role as a single-electron-transfer oxidant.[23] With these advantages, we have hypothesized CAN could be utilized as an oxidant in *N*-arylation of amines in the presence of a Cu-catalyst.[24]

Figure 1. Outline of Preparation of *N*-Aryl amines



Privious work (a) Buchwald-Hartwig: Cat. Pd(II)/phosphine/Base, X = Halides
(b) Chan-Evans-Lam: Stoichiometric Cu(II)/Base,
X = Boronic acids

This work Cu(OAc)$_2$ (10 mol %), CAN (1.5 equiv)/PhMe, r.t); X = Boronic acids

This study reports Cu(OAc)$_2$ catalyzed cross-coupling of arylboronic acids with primary/secondary amines in the absence of a base and a ligand. To the best of our knowledge, there is no report employing CAN mediated Cu-catalyzed cross-coupling of boronic acids with amines.

Our investigation was initiated with cross-coupling of phenylboronic acid (**1a**) with *p*-anisidine (**2a**) using a catalytic amount of Cu(OAc)$_2$ and CAN in CH_2Cl_2 at room temperature (Table 1, entry 1). Gratifyingly, the desired product resulted in good yield. Subsequently, optimization of the catalyst was evaluated. Cu(I) gave low yield, whereas Cu(II) salts resulted in better yields with Cu(OAc)$_2$ being the most desirable (entries 2-8). As depicted in Table 1, in the absence of Cu-catalyst or CAN, low or no cross-

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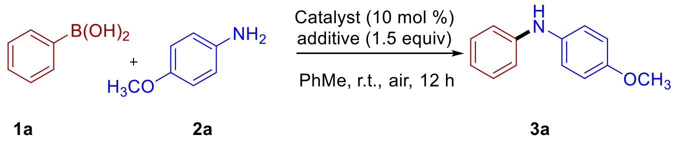
Table 1: Optimization of Reaction Conditions[a]



entry	catalyst	additive	solvent	yield[b]
1	$Cu(OAc)_2$	CAN	CH_2Cl_2	77
2	CuI	CAN	CH_2Cl_2	nd
3	$CuCl_2$	CAN	CH_2Cl_2	45
4	$CuBr_2$	CAN	CH_2Cl_2	nd
5	Cu_2O	CAN	CH_2Cl_2	nr
6	$CuSO_4$	CAN	CH_2Cl_2	nd
7	$Cu(acac)_2$	CAN	CH_2Cl_2	trace
8	$Cu(OAc)_2$	-	CH_2Cl_2	7
9	-	CAN	CH_2Cl_2	nr
10	$Cu(OAc)_2$	CAN	CH_3CN	nd
11	$Cu(OAc)_2$	CAN	PhMe	93
12	$Cu(OAc)_2$	CAN	$PhMe/H_2O$	nd
13	$Cu(OAc)_2$	CAN	THF	nd
14	$Cu(OAc)_2$	CAN	PhMe/50 ºC	nr
15	$Cu(OAc)_2$	CAN	PhMe	61[c]

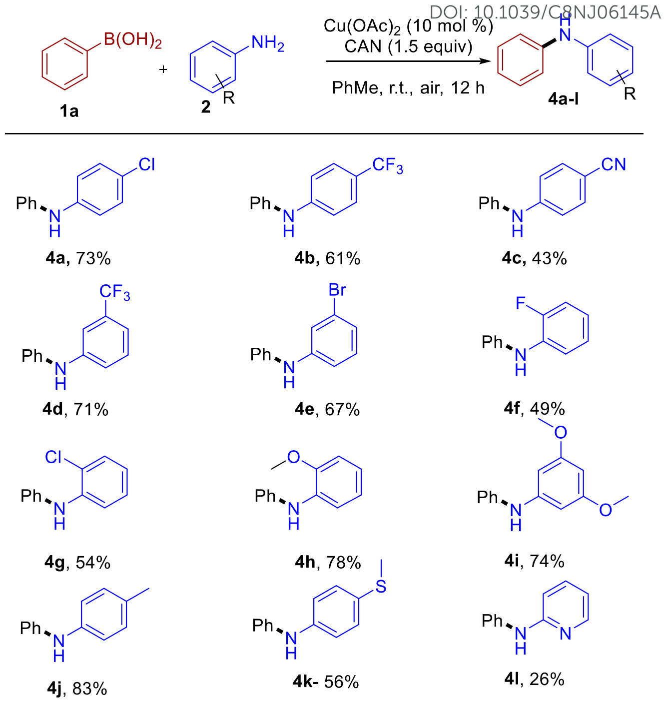
[a]Reaction conditions: $ArB(OH)_2$ (**1**, 1.2 mmol), $ArNH_2$ (**2**, 1 mmol), catalyst (0.1 mmol), additive (1.5 mmol), solvent (5.0 mL), 12 h. [b]Isolated yield. [c]1 Gram scale. nr = No reaction, starting materials recovered. nd = No desired product.

coupling occurred (entries 8,9). Various solvents including CH_2Cl_2, CH_3CN, THF, toluene, toluene/H_2O were examined. Apparently, anhydrous nonpolar solvents such as CH_2Cl_2 and Toluene are preferred with toluene providing the highest yield of the desired product at room temperature (entries 10-14). It was also observed that extended reaction time resulted in homo-coupling of aryl boronic acid.

With optimized reaction conditions in hand, we proceeded to explore the scope of substrate coupling reaction between substituted anilines with phenylboronic acid (Scheme 1). Electron donating and withdrawing substituted anilines were evaluated. Electron withdrawing substituted anilines were generally good-yielding (**4a-g;** 43-73%) however, the electron-rich anilines proved to be greater cross-coupling partners (**3a, 4h-k;** 56-93%). Evaluation of the substituted anilines also revealed that *meta*-substituted electron withdrawing anilines gave the cross-coupled product in high yields (**4d-e;** 67-71%), *ortho*-substituted electron withdrawing groups produced lower yields (**4f-g;** 49-54%), and the *ortho*-substituted methoxy aniline gave an excellent yield (**4h;** 78%). Finally, the electron deficient heterocyclic amine afforded the desired product **4l**.

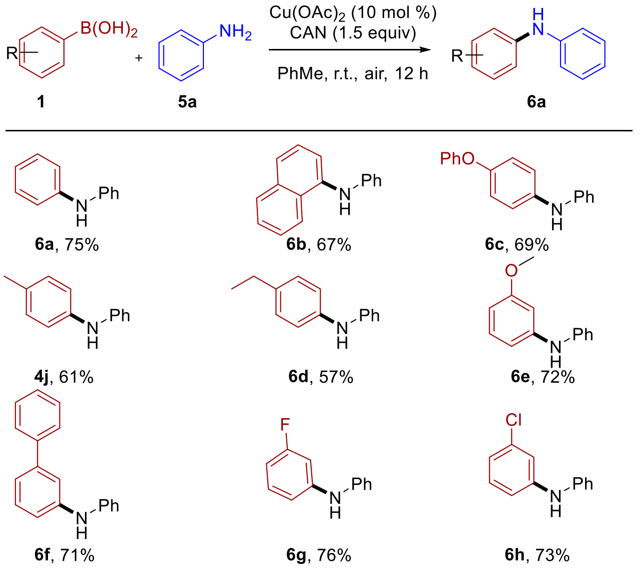
Encouraged by the aforementioned results, various substituted aryl boronic acids were also examined (Scheme 2). Aromatic

Scheme 1: Scope of Substituted Anilines[a]



[a]Reaction conditions: $ArB(OH)_2$ (**1**, 1.2 mmol), $ArNH_2$ (**2**, 1 mmol), $Cu(OAc)_2$ (0.1 mmol), CAN (1.5 mmol), toluene (5 mL), r.t., for 12 h.

Scheme 2: Scope of Substituted Boronic acids[a]



[a]Reaction conditions: $ArB(OH)_2$ (**1**, 1.2 mmol), $ArNH_2$ (**5**, 1 mmol), $Cu(OAc)_2$ (0.1 mmol), CAN (1.5 mmol), toluene (5 mL), and r.t., for 12 h.

boronic acids proceeded well (**6a, b**). In fact, there was no clear difference between electron-rich or electron withdrawing substitution on aryl boronic acid and the corresponding *N*, *N*-diaryl amine products were obtained in good yields (**6c-h**). Further, electron deficient boronic acids were investigated, with halo-substituted boronic acids resulting in excellent yields (**6g** and **6h**).

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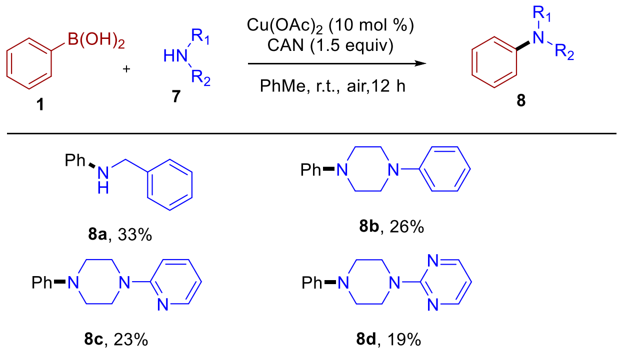
Scheme 3: Scope of Primary and Secondary Amines[a]

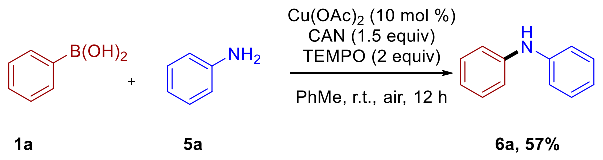


[a]Reaction conditions: ArB(OH)$_2$ (**1**, 1.2 mmol), ArNH$_2$ (**7**, 1 mmol), Cu(OAc)$_2$ (0.1 mmol), CAN (1.5 mmol), toluene (5 mL), and r.t., for 12 h.

This protocol was further extended to *N*-arylation of aliphatic amines (Scheme 3), a procedure we have often employed in our lab.[25] Gratifyingly, the aliphatic amines were also effective under the cross-coupling conditions (**8a-d**) employed. The coupling of benzylamine with substituted aryl boronic acids afforded the desired products in good yields. However, secondary amines **8b**, **8c,** and **8d** resulted in poor yields.

Finally, we further evaluated the utility of the protocol by carrying out a gram scale reaction which resulted in the desired coupled product **3a** in 61% (table 1, entry 15).

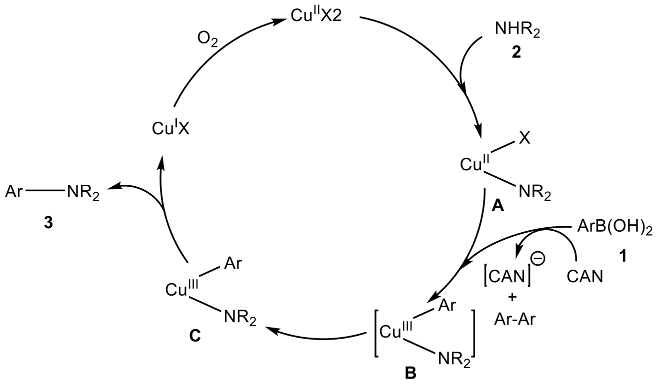
Scheme 4. Controll Experiment with TEMPO



To understand the possible reaction mechanism, control experiment was carried out using the free radical trap (Scheme 4). In the presence of an oxidant, boronic acids have been reported to form the aryl radicals through a single-electron transfer.[26] When the reaction has carried out under standard condition and in the presence of 2,2,6,6-tetramethyl-piperidine-1-oxy (TEMPO), arylated amine product formation was observed. This observation appears to suggest that, this protocol is not proceeding through a free radical mechanism.

Following previous reports by Lam and Watson et al.[27] we have opined a mechanism by which this protocol proceeds as shown in Scheme 5. The cycle could be initiated with coordination between Cu(II) with an amine. The second step could be transmetalation of **A** with boronic acid to form **B**. According to our hypothesis, CAN could oxidize the Cu(II) (**B**) to Cu(III) (**C**) with subsequent reductive elimination offering the desired *N*-aryl product and Cu(I). Oxidation of Cu(I) in the presence of atmospheric-O$_2$ would then complete the catalytic cycle.

Scheme 5. Proposed Reaction Mechanism



In summary, we have developed a useful and practical Cu(II)/CAN mediated protocol for the *N*-arylation of aryl and aliphatic amines. Conventional Chan-Evans-Lam protocol requires stoichiometric amount of catalyst and base, whereas this simple and easy reaction setup at room temperature could produce desired products efficiently in the absence of any base, ligand and catalytic amounts of Cu(OAc)$_2$. This base free condition could also offer arylation of substrates with base-sensitive functional groups.

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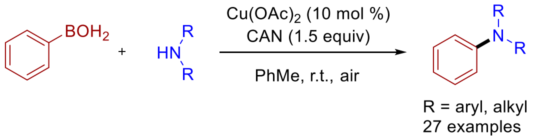

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