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Chemoselective *N*-arylation of Aminobenzamides via Copper Catalysed Chan–Evans–Lam Reactions

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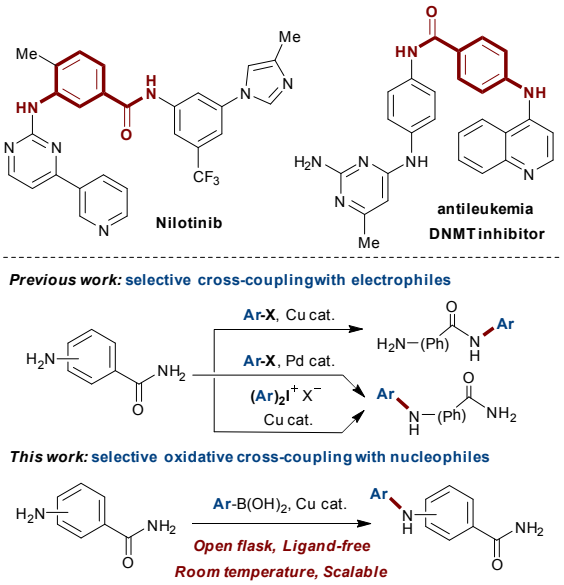
Chemoselective *N*-arylation of unprotected aminobenzamides was achieved via Cu-catalysed Chan–Evans–Lam cross-coupling with aryl boronic acids for the first time. Simple copper catalysts enable the selective arylation of amino groups in ortho/meta/para-aminobenzamides under open-flask conditions. The reactions were scalable and compatible with a wide range of functional groups.

Aromatic C–N bonds are prevalent across a wide range of important organic compounds, including synthetic intermediates, organic materials, pharmaceutical and natural products. Therefore, the development and application of methods to construct C(aryl)–N bonds have long been one of the most important research areas in organic chemistry.

In the last two decades, a plethora of transition-metal-catalysed C–N cross-coupling reactions have achieved remarkable progress and been widely practiced.[1] Among these, the Cu-catalysed Ullmann[2] and Pd-catalysed Buchwald-Hartwig[3] amination reactions generally couple nucleophilic nitrogen atoms with electrophilic partners such as aryl halides. In contrast, Cu-catalysed/mediated Chan–Evans–Lam (CEL)[4] reactions couple two nucleophiles, usually an amino group and an organoboron compound, under oxidative conditions. The CEL reactions were developed independently by Chan, Evans and Lam in 1998, being characterized by low cost of catalysts and ligands, high tolerance towards aerobic environment and simple reaction conditions.[5] This inspired the following intensive investigations and significant improvement in this field, therefore mutually reinforcing the defining characteristics of such reactions. Nowadays, different reaction systems are still being continuously developed to improve the reactive efficiency and broaden the substrate scope.[6]



Scheme 1 Representative bioactive *N,N'*-discriminated diarylated aminobenzamides and strategic synthesis to mono-arylated aminobenzamides

Despite such progress, the CEL reactions have been rarely applied in the chemoselective C–N cross-coupling reactions of aryl dinucleophiles,[7,8] which are usually accomplished by Ullmann and Buchwald-Hartwig reactions.[9] More specifically, the *N,N'*-discriminated diarylated aminobenzamides constitutes a common structural motif in a number of drugs and potential candidate drugs,[10] such as *Nilotinib*, an approved drug for the treatment of chronic myelogenous leukemia. This results in efforts on the selective arylation of unprotected aminobenzamides. In fact, the aminobenzamides could be selectively arylated with electrophilic coupling partners, as demonstrated by Buchwald group[9a] and Zeng group[11], with aryl halides and diaryliodonium salts, separately.

In contrast, although aniline and benzamide have been two of the most widely-used nitrogen sources[4] in CEL reactions separately,

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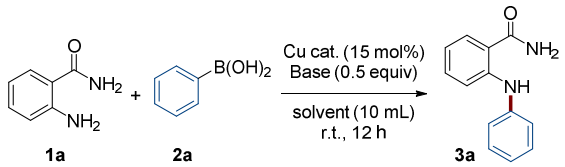
chemoselective CEL cross-coupling between organoboron compounds and the dinucleophilic aminobenzamides have never been realized, to the best of our knowledge. In combination with our ongoing interest in the selective decoration of di- and polynucleophiles,[12] this situation inspired our efforts on selective arylation of aminobenzamides via facile oxidative CEL protocol, which might offer complementary opportunities in decorating such type of feedstock. Herein, we disclose our results on the Cu-catalysed chemoselective CEL *N*-arylation reactions between aminobenzamides and aryl boronic acids. The aniline moiety was consistently preferentially arylated for either *2*-aminobenzamides that benefited from chelation assistance or *3*-/*4*-aminobenzamides. In addition, the reactions could be facilely and efficiently accomplished under ligand-free and aerobic conditions at room temperature.

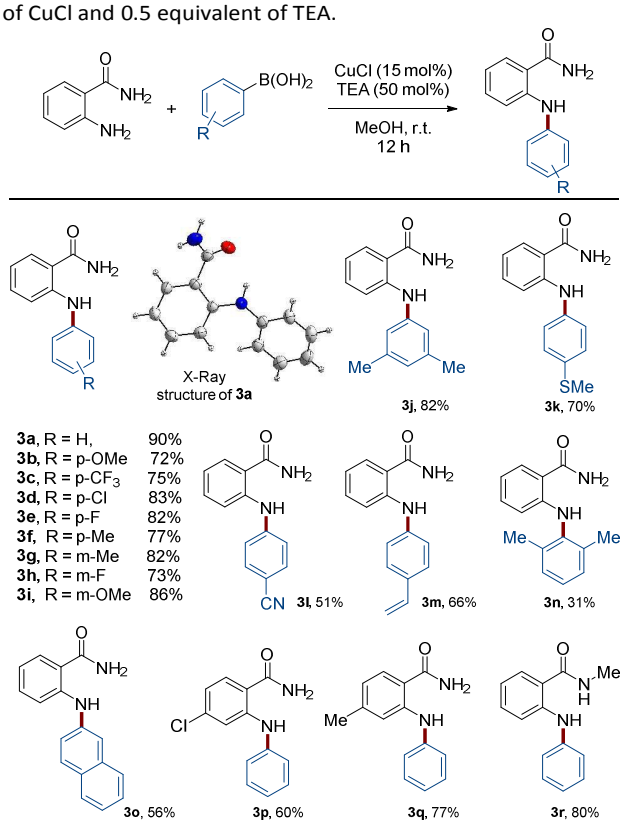
Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yields (%)[b]
1	$Cu(OAc)_2$	TEA	DCM	N.R.
2	$Cu(OTf)_2$	TEA	MeOH	34
3	**CuCl**	**TEA**	**MeOH**	**90**
4	CuCl	-	MeOH	63
5	CuCl	K_2CO_3	MeOH	81
6	CuCl	Na_2CO_3	MeOH	75
7	CuCl	$KHCO_3$	MeOH	68
8	CuCl	DBU	MeOH	68
9	CuCl	TEA	MeOH	66[c]
10	CuCl	TEA	MeOH	24[d]
11	CuCl	TEA	DCM	N.R. (75%)[e]
12	CuCl	TEA	THF	N.R.
13	CuCl	TEA	toluene	N.R.

[a]Reaction conditions: 0.5 mmol **1a** (1.0 equiv.), 0.75 mmol **2a** (1.5 equiv.), 0.075 mmol CuCl (15 mol%), 0.25 mmol bases (0.5 equiv.), r.t., open flask, 12 h. [b]Isolated yields. [c]MeOH (1.0 mL). [d]70 °C. [e]The isolated yield of PhB(aam).

We commenced the studies using *2*-aminobenzamide (anthranilamide, AAM) **1a** and phenylboronic acid **2a** as reaction components (Table 1). Transformations were conducted in open flasks with air as oxidant.[13] Firstly, copper-mediated coupling reactions between **1a** and **2a** were tried, generating a complex mixture that contained *N*-arylation products without obvious chemoselectivity (Table S1, in Supporting Information). The attempts to realize the catalysed C–N cross-couplings all failed due to the easy condensation of $PhB(OH)_2$ with *2*-aminobenzamide, which afforded PhB(aam) as the main product. Using MeOH as solvent, $Cu(OTf)_2$ as catalyst and triethylamine (TEA) as base, the reaction provided the arylated product of aniline moiety **3a** other than PhB(aam) in 34% yield (Table 1, entry 2). The structure of the obtained product was confirmed by NMR and X-ray diffraction analysis (**Scheme 2**, CCDC: 1563817). The yield of **3a** was improved to 90% upon utilizing CuCl as catalyst (Table 1, entry 3). Further screening of other reactive parameters led to no better results. Other solvents such as DCM and THF turned out to be invalid for this transformations (Table 1, entries 1, 11-13). Notably, concentrated solution and elevated temperature were detrimental, decreasing the yield of target **3a** (Table 1, entries 9, 10). In brief, 90% of chemoselective *N*-arylated product **3a**, was isolated when *2*-aminobenzamide was stirred with 1.5 equivalent of phenylboronic acid in aerobic MeOH at room temperature for 12 hours, using simple 15 mol% of CuCl and 0.5 equivalent of TEA.



Scheme 2 Reactions between *2*-aminobenzamides and aryl boronic acids

Under the optimized reaction conditions, various aryl boronic acids were reacted with *2*-aminobenzamide, and the results were illustrated in Scheme 2. Both electron-rich and -deficient boronic acids were compatible with such conditions. Reactions of *3*- or *4*-substituted compounds bearing methyl, halides, methoxy and trifluoromethyl groups afforded target products **3a**-**3k** in 70-86% yields. This cross-coupling also well tolerated cyano- and vinyl-substituted phenyl boronic acids (**3l** and **3m**). The compatibility towards these functional groups enabled the potential application for further transformations. 2,6-Disubstituted compound could also be employed in spite of the significantly decreased yield due to the steric effect (**3n**, 31%). Moreover, *2*-aminobenzamide bearing -Me and -Cl substituents also furnished the corresponding products **3p** and **3q** selectively. Substitution on *N* atom of the amide group was

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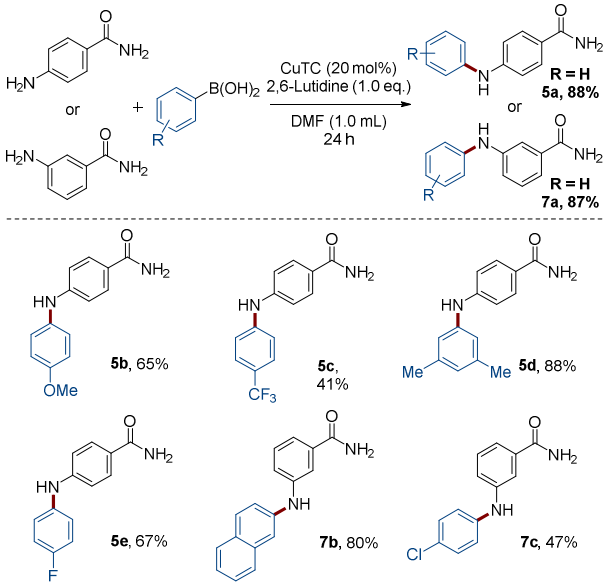
also tolerated, affording **3r** in slightly lower yield compared with the formation of **3a**.

Next, selective arylation of *3*- or *4*-aminobenzamide was explored. In the beginning, the reaction between *4*-aminobenzamide and phenyl boronic acid was performed under the previously optimized conditions. Unfortunately, no arylated product of aniline was observed. This result indicated the presence of a chelation assistance effect in the reaction between *2*-aminobenzamide and aryl boronic acids under the optimized conditions. Copper cyclometalated species might be formed due to the chelation effect of the adjacent amino and amide groups and enabled the following catalytic transformations, like a recent result from Baidya group.[6b]

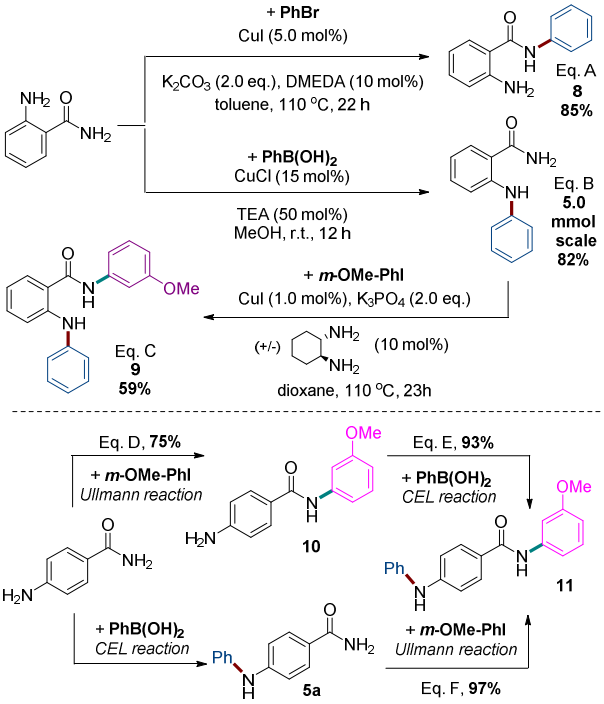
This situation necessitated the further exploration of another reaction system for *3*- and *4*-aminobenzamide. *4*-aminobenzamide **4a** and phenyl boronic acid **2a** were used as reaction components. Screening of reactive parameters revealed that the combination of copper thiophene carboxylate (CuTC, 20 mol%), 2,6-lutidine (1.0 equiv.) and DMF (1.0 mL) gave the best result (Details of screening were listed in Table S2 in Supporting information). The chemoselective *N*-arylated product **5a** was obtained in 88% yield (**Scheme 3**). In addition, this reaction system was also suitable for the *3*-aminobenzamide, whose product **7a** was obtained in 87% yield. The optimized system was then applied for other substrates. The application of electron-rich 4-methoxy- and 3,5-dimethyl-phenyl boronic acid would give **5b** and **5d**, in 65% and 88% yields, separately. Electron-withdrawing groups such as Cl, CF_3 would affect the efficiency of cross-coupling reaction, leading to decreased yields. 2-Naphthylboronic acid also worked well, giving aim product **7b** in 80% yield.



Scheme 3 Reactions between *3*- or *4*-aminobenzamides and arylboronic acids

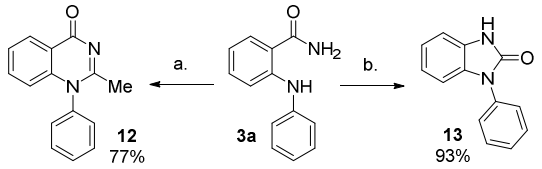
As mentioned above, in the Cu-catalysed Ullmann reactions between aminobenzamides and aryl halides, the arylation occurred selectively at the amide groups. Therefore, this CEL coupling protocol might complement such reactivity, which rendered the selective arylation of amino or amide group feasible both by the catalysis of cheap copper salts (**Scheme 4, Eq. A and D**). It should be noted this easily-handled and low-cost CEL reaction could be directly scaled up to gram scale with only slightly reduced yield (**Scheme 4, Eq. B**).

In addition, the synthesis of unsymmetrically diarylated aminobenzamides was accomplished through sequential Cu-catalysed C–N cross-coupling reactions. For example, **3a** and **5a** were both competent nucleophiles for the Ullmann reactions, leading to diarylated aminobenzamides in 59% and 97% yield, separately (**Scheme 4, Eq. C and F**). The Ullmann/CEL sequence was also feasible, as exemplified by Eq. D and Eq. E in Scheme 4.[9a]



Scheme 4 The applications of the selective CEL reactions

Taking advantage of the adjacent arylamino and amide groups in 2-arylamino benzamide, aryl-substituted heterocycles could be readily accessible. When **3a** was treated with acetyl chloride in acetic acid, 1-phenylquinazolin-4(1*H*)-one **11** was isolated in 77% yield.[14] Cyclic ureas such as 1-phenyl-benzo[*d*]imidazol-2-one **12** was generated in 93% yield via iodosylbenzene-induced Hofmann rearrangement of **3a**.[15]



Scheme 5 The synthesis of aryl-substituted heterocycles. Reaction conditions: a. 0.3 mmol **3a** (1.0 equiv.), 0.9 mmol acetyl chloride (3.0 equiv.), acetic acid (1.0 mL), r.t, open flaks, 3 h; b. 0.3 mmol **3a** (1.0 equiv.), 0.45 mmol iodosylbenzene (1.5 equiv.), dichloromethane (1.5 mL), r.t, open flaks, 2 h.

In conclusion, we have shown for the first time that *2*-/*3*-/*4*-aminobenzamides can be efficiently chemoselectively arylated by virtue of Cu-catalysed oxidative CEL aryl–amino cross-coupling

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reactions, with readily available boronic acids. This low-cost protocol tolerates a wide range of functional groups and can be handled at room temperature under open-flask conditions. Additionally, in the reactions of *2*-aminobenzamides, uncommon chelation assistance plays vital role in determining the catalytic activity. This protocol has been successfully utilized in the synthesis of unsymmetrically diarylated aminobenzamides and substituted heterocycles. Further extended exploration and utilization of this protocol are underway in our laboratory.

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Conflicts of interest

There are no conflicts of interest to declare.

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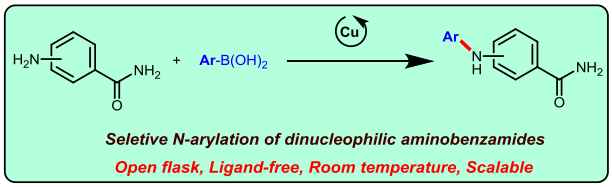

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