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Copper Catalyzed N-Arylation of Amidines with Aryl Boronic Acids and One-Pot Synthesis of Benzimidazoles by a Chan–Lam–Evans N-Arylation and C–H Activation/C–N Bond Forming Process

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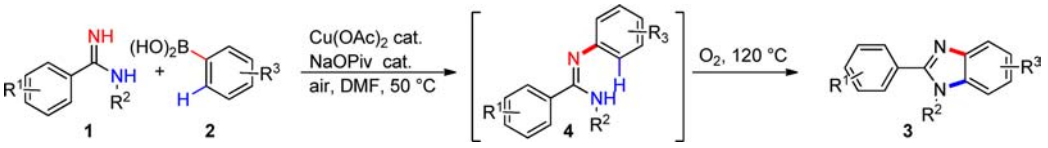
ABSTRACT



Mono-N-arylation of benzamidines 1 with aryl boronic acids 2 was effectively achieved in the presence of a catalytic amount of $Cu(OAc)_2$ and NaOPiv under mild aerobic conditions. Combining this step with an intramolecular direct C–H bond functionalization, catalyzed by the same catalytic system but under oxygen at 120 °C, afforded benzimidazoles 3 in good to excellent yields.

Benzimidazoles are valuable synthetic targets due to their presence in compounds ranging from pharmaceuticals to materials.[1] It is therefore not surprising that many synthetic methods have been developed to reach this bicyclic ring system.[2] Traditionally these compounds are prepared by a condensation of substituted *ortho*-phenylenediamines with carbonyl derivatives. Following the development of metal-catalyzed C–N bond forming reactions,[3] alternative strategies relying on the use of *ortho*-functionalized aryl halides have emerged.[4,5] More recently, metal-catalyzed C–H activation[6]/cyclization processes starting from simple N-arylated precursors have been developed.[7]

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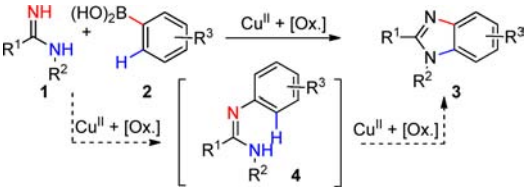
N-Arylated amidines, an important strutural unit in medicinal chemistry,[8] have often been used as starting materials for the synthesis of benzimidazoles.[4] Domino processes combining the *in situ* formation of amidines with subsequent cyclization have also been developed for the synthesis of benzimidazoles.[9]

We have been involved in the development of metal-catalyzed domino processes,[10] including sequences containing a direct aromatic C−H functionalization step.[11] In addition, we recently extended the Chan−Lam−Evans reaction to the cyclopropylation of nitrogen containing heterocycles.[12] Subsequent to this work, we became interested in developing a domino copper-catalyzed synthesis of benzimidazoles from boronic acids and amidines (Scheme 1). Whereas developing such a sequence might appear trivial since the second step has been established by Buchwald,[7a] several potential pitfalls existed: (1) The Cham−Lam−Evans reaction has been extended to numerous functionalities,[13] but not to unprotected amidines.[14] (2) Copper-promoted N-arylations involving boronic acids are known to occur under basic or neutral conditions while the importance of acid has been established for the copper-catalyzed intramolecular cyclization involving the C−H functionalization step.[7a,d] Herein, we report the realization of this domino process for the synthesis of benzimidazoles from easily available aryl boronic acids and amidines by a sequence involving Chan−Lam−Evans N-arylation, C−H activation, and C−N bond formation.

Scheme 1. Prospected Sequence for the Synthesis of Benzimidazoles



To explore the feasibility of our planned domino process, we first targeted the synthesis of N-arylated amidine **4a** (R_1 = Ph, R_2 = H, R_3 = 4-methyl), and the survey of reaction conditions is summarized in Table 1. Treatment of benzimidamide (**1a**) with *p*-tolylboronic acid (**2a**) in the presence of an excess of $Cu(OAc)_2$ under argon in DMF at rt furnished the desired mono-N-arylated amidine **4a** in 77% yield (Table 1, entry 1). Pleasingly, under catalytic conditions [$Cu(OAc)_2$ (0.2 equiv), air], **4a** was formed in 44% yield (entry 2). Heating the reaction at 80 °C in DMF or at reflux in methanol only marginally improved the yield, and higher temperatures proved to be deleterious (entries 3−5). Among the additives/ligands that were evaluated [1,10-phenantroline (Phen), bipyridine (Bipy), tetramethylethylenediamine (TMEDA), triphenylphosphine oxide, sodium pivalate (NaOPiv), thiophene carboxylate (TC)], triphenyl phosphine oxide and sodium pivalate significantly improved the process (entries 6−12). N,N′-Bis-arylated amidine **5a** was observed in all reactions, but could be suppressed by reducing the stoichiometry of the arylboronic acid from 2.0 to 1.2 equiv (entries 11 and 12).

The scope of this new Cu-catalyzed N-arylation reaction was briefly examined (Figure 1). Arylboronic acids including pyridin-4-yl boronic acid, bearing an electron-withdrawing or -donating group at the *para* position, furnished the expected mono-N-arylated amidines in good to excellent yields (**4a**−**c**). *Ortho*-substitution was also tolerated affording the corresponding product (**4d**) in good yield (62%) if an excess of amidine (1.5 equiv) was used. Potassium aryltrifluoroborates could also be used instead of boronic acids, albeit with slightly reduced yields.

The reaction was not limited to primary amidines as *N*-(*p*-tolyl)- and *N*-(isopropyl)-benzimidamides **1b** and **1c** were effectively arylated, furnishing the corresponding *N*,*N*′-adducts **5a** and **5c**, respectively. Notably, unsymmetrical N,N′-bisarylation of amidines could be accomplished upon sequential addition of two different arylboronic acids

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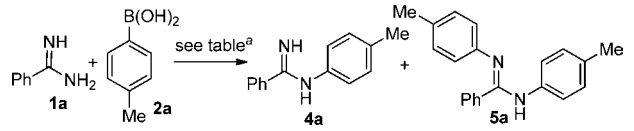
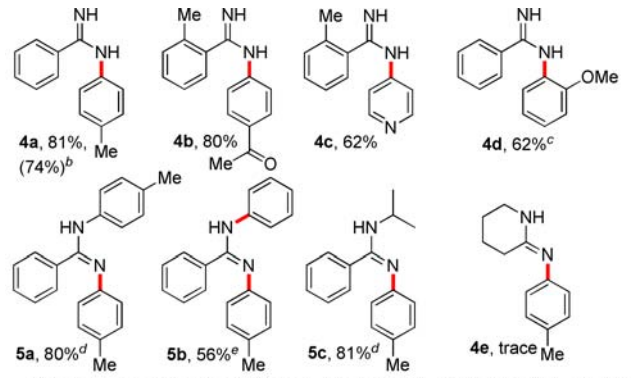
Table 1. Survey of Reaction Conditions for the Mono-N-arylation of Amidines



entry	catalyst/additive	atm, temp (°C)	solv	yield (%)[b]
1[c]	$Cu(OAc)_2$	argon, rt	DMF	77
2	$Cu(OAc)_2$	air, rt	DMF	42(26)
3	$Cu(OAc)_2$	air, 80	DMF	48(13)
4	$Cu(OAc)_2$	air, 130	DMF	29(15)
5	$Cu(OAc)_2$	air, refux	MeOH	46(7)
6	$Cu(OAc)_2$/Bipy	air, rt	DMF	35
7	$Cu(OAc)_2$/TMEDA	air, rt	DMF	44
8	$Cu(OAc)_2$/Phen	air, rt	DMF	48
9	$Cu(OAc)_2$/Ph_3PO	air, rt	DMF	60
10[d]	Cu(TC)	air, rt	DMF	63
11[d,e]	$Cu(OAc)_2$/NaOPiv	air, rt	DMF	81 (<5)
12[d]	$Cu(OAc)_2$/Ph_3PO	air, rt	DMF	77 (<5)

[a] Conditions: catalyst (0.2 equiv), additive (0.2 equiv), amidine (1.0 equiv), *p*-TolB$(OH)_2$ (2 equiv), 24 h. [b] Isolated yield; the yield in parentheses refers to compound **5a**. [c] Catalyst (2 equiv). [d] 1.2 equiv of PhB$(OH)_2$. [e] 0.4 equiv of NaOPiv.



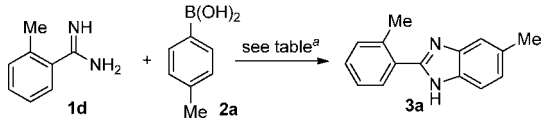
[a] General conditions: $Cu(OAc)_2$ (0.2 equiv), PivONa (0.4 equiv), ArB$(OH)_2$ (1.2 equiv), amidine (1.0 equiv), air, in DMF at 50 °C, 24 h. [b] $ArBF_2K$ (1.2 equiv) was used, at 70 °C. [c] ArB$(OH)_2$ (1.0 equiv), amidine (1.5 equiv). [d] ArB$(OH)_2$ (1.5 equiv). [e] PhB$(OH)_2$ (1.0 equiv), 24 h, then *p*-TolB$(OH)_2$ (1.5 equiv), 48 h.

Figure 1. Scope of the copper-catalyzed N-arylation of amidines.[a]

as illustrated by a three-component synthesis of **5b** (56% yield). It should be mentioned that 1.5 equiv of the second arylboronic acid was necessary to ensure the optimal yield of the N,N′-bisarylated amidine. The conditions were however not suitable for the N-arylation of *C*-alkylamidines furnishing only a trace amount of **4e**.

The intermolecular N-arylation step being established, we next focused our attention to the synthesis of benzimidazoles (Table 2). We quickly learned that performing the reaction under oxygen significantly improved the C−H activation/C−N functionalization event (entry 1 vs 2).

Table 2. Survey of Reaction Conditions for the One-Pot Synthesis of Benzimidazoles



entry	1a (equiv)	2a (equiv)	temp (°C)	*t* (h)	atm	additives	yield (%)[b]
1	1	1.2	rt/120	48/40	air/air	Ph_3PO	29
2	1	1.2	rt/120	24/24	air/O_2	Ph_3PO	44
3	1	1.2	50/120	12/13	air/O_2	Ph_3PO	52
4[c]	1	1.2	50120	12/12	air/O_2	NaOPiv	53
5[c]	1.5	1	50/120	12/6	air/O_2	NaOPiv	85
6	1.5	1	50120	12/6	air/O_2	Ph_3PO	75
7[c,d]	1.5	1	50/120	12/6	air/O_2	NaOPiv	82
8[c]	1.5	1	120	8	O_2	NaOPiv	73

[a] Conditions: $Cu(OAc)_2$ (0.2 equiv), additive (0.2 equiv), oxidant, DMF. [b] Isolated yield. [c] NaOPiv (0.4 equiv). [d] DMSO as solvent.

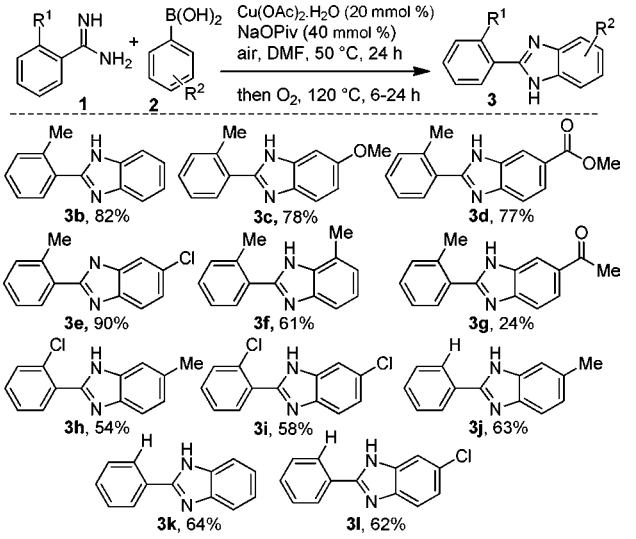
A combination of copper(II) acetate with either Ph_3PO or NaOPiv furnished comparable results (entries 3 and 4).[15] The yield could be improved to a useful level by adjusting here again the stoichiometry between the amidine and the arylboronic acid (entries 5−8). It should be noted that the sequence could be performed in DMSO without significantly affecting the yields (entry 5 vs 7). Interestingly, when the above reaction was performed at 120 °C in the presence of $Cu(OAc)_2$ and NaOPiv the annulation reaction took place to directly afford the benzimidazole **3a** in 73% yield (entry 8).

The scope of the present annulation protocol was next examined under the following optimized conditions: $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv), NaOPiv (0.4 equiv), air, DMF, 50 °C, 24 h, then O_2, 120 °C, 4−24 h; the results are presented in Schemes 2 and 3.

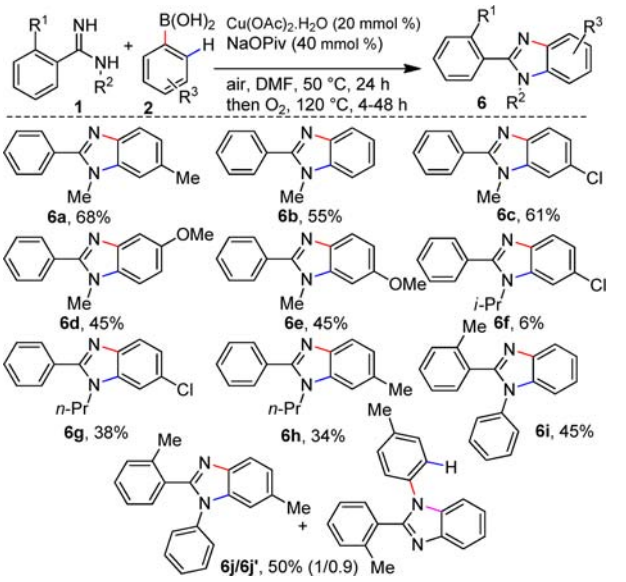
The electronic nature of the substituent at the aryl boronic acid only weakly influenced the outcome of the reaction, as **3a**−**e** could be isolated in excellent yields. However, while groups such as hydrogen, alkyl, ether, halogen, or ester were well tolerated, **3g** bearing a ketone function was isolated in a modest 24% yield. Substitution was not limited to the *para* postion, and interestingly, use of *para*- or *meta*- (methoxyphenyl)-boronic acid afforded the same compound **3c** in similar yields. *Ortho*-substitution on the arylboronic acid was also compatible as demonstrated by the formation of **3f**. The reaction was not limited to the use of 2-methylbenzimidamide (**1d**), as 2-chlorobenzimidamide (**1e**) furnished the corresponding benzimidazoles **3h** and **3i** in 54% and 58% yield, respectively. Interestingly, benzimidamide **1a** lacking an *ortho*-substituent participated well in this domino process (**3j**−**3l**) in sharp

(15) The presence of a Lewis basic oxygen in Pivalate or Ph_3PO could play a role in (1) the activation of the boronic acid and (2) the cleavage of the CH bond; see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126.

Scheme 2. Scope of the Copper-Catalyzed Synthesis of Benzimidazoles from Primary Benzamidines



Scheme 3. Scope of the Copper-Catalyzed Synthesis of Benzimidazoles from Secondary Benzamidines



contrast to a previous report on the cyclization of *N*-arylbenzamides.[16]

Synthesis of 1,2-disubstituted benzimidazoles from *N*-substituted benzimidamides was also examined, and the results are presented in Scheme 3. Benzimidazoles **6a**−**e** could be isolated in moderate to good yield when *N*-methyl substituted benzamide **1f** was used as a coupling partner. It should be highlighted that the reaction was selective, allowing 5- or 6-substituted *N*-methylbenzimidazoles **6d** and **6e** to be built by simply changing the boronic acid from the *meta*-substituted to *para*-subtituted aryl donor. Whereas *N*-*n*-propyl benzimidazoles (**6f**−**g**) could be isolated in modest yields, *N*-isopropyl was not tolerated in the reaction. In each case, the benzimidazole **3a** was also isolated in a variable amount, probably generated through a competitive *N*-dealkylation reaction known to occur under oxidative conditions.[17] Finally, we were able to synthesize N-arylated benzimidazoles using N-arylated benzamidines. When 2-methyl-*N*-phenylbenzimidamide (**1h**) was reacted with *p*-tolylboronic acid (**5a**), an inseparable mixture of regioisomers **6j** and **6j′** (0.9/1 ratio) was isolated in 58% overall yield.

In summary, we have developed a mild copper-catalyzed mono-N-arylation of amidines using arylboronic acids under aerobic conditions. The process has been extended to a one-pot synthesis of benzimidazoles involving a sequence of intermolecular C−N bond formation and an intramolecular C−H functionalization/C−N bond-forming event. The ready accessibility of starting materials and the low cost of the catalytic system made this process a valuable alternative for the construction of these interesting heterocycles.

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Supporting Information Available. Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) According to ref 7a., intramolecular cyclization required the presence of an *ortho*-substitution on the benzamidine.

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The authors declare no competing financial interest.