C–H Functionalization

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C–H Functionalization/C–N Bond Formation: Copper-Catalyzed Synthesis of Benzimidazoles from Amidines**

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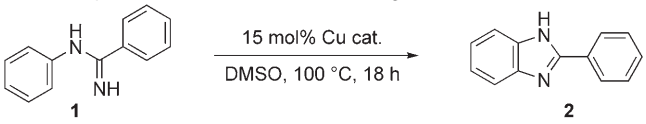
An immense effort has been made to develop efficient strategies for the direct functionalization of C–H bonds using transition-metal catalysis.[1] For the most part, ruthenium-,[2] rhodium-,[3] and palladium-based[4] catalysts have been applied to effect either C–C or C–Het (Het = heteroatom) bond formation by replacement of a C–H bond. Few examples have been described that employ copper as catalysts,[5] which is particular attractive due to its low cost and low toxicity. Herein, we disclose a new $Cu(OAc)_2$-catalyzed synthesis of benzimidazoles from amidines through a C–H functionalization/C–N bond-forming process that uses oxygen as the oxidant and generates water as the only direct waste product.

Recently, we reported that carbazoles could be formed by intramolecular C–H bond functionalization.[6] We were eager to extend our approach to the synthesis of other classes of heterocycles, such as benzimidazoles, which are of considerable importance in medicinal chemistry.[7] Brain's palladium-catalyzed *N*-arylation of (*ortho*-bromophenyl)amidines to give benzimidazoles[8] inspired us to use amidines as our starting materials. The cyclization of amidines by oxidative means had been reported earlier. However, the use of stoichiometric amounts of reagents, such as $Pb(OAc)_4$,[9] and iodine(III) compounds,[10] and a rather narrow functional-group scope—only examples with Me, Cl, and Br substituents were reported—are major disadvantages. NaOCl is known to promote the cyclization as well via *N*-chlorinated amidines.[11] Although the low cost of NaOCl is an appealing feature, low to moderate yields were obtained for amidines bearing functional groups, and as mentioned in one report,[11b] chlorinated side products might be anticipated when this method is applied. Altogether, these drawbacks prompted us to reinvestigate this transformation.

We started our study by examining the conversion of *N*-phenylbenzamidine (**1**) into 2-phenylbenzimidazole (**2**). After an initial screen of palladium and copper catalysts, solvents, and reaction temperatures, we found that the use of 15 mol% $Cu(OAc)_2$ in DMSO at 100 °C under an oxygen atmosphere produced **2** after 18 h in 19% yield with a low conversion of **1** (Table 1, entry 1). Using 5 equivalents of pyridine or triethylamine as a basic additive, the conversion was enhanced, but the yield of **2** was not greatly affected (Table 1, entries 2, 3). A satisfactory result was obtained when 5 equivalents of acetic acid were used in lieu of a base additive; a 74% yield of benzimidazole **2** and almost complete conversion of **1** were observed (Table 1, entry 4). We subsequently tested other copper(II) salts and acids (Table 1, entries 5–9). Only Cu(isobutyrate)$_2$ and propionic acid provided comparable results. Catalytic activity was also found under an air atmosphere, though the formation of **2** was slower (Table 1, entry 10).

Table 1: Optimization of the initial screening results.



1 **2**

Entry	Cu catalyst	Additive (5 equiv)	Gas atm	Conv. [%]	Yield [%][a]
1	$Cu(OAc)_2$	-	O_2	37	19
2	$Cu(OAc)_2$	pyridine	O_2	57	25
3	$Cu(OAc)_2$	NEt_3	O_2	72	23
4	$Cu(OAc)_2$	HOAc	O_2	96	74 (63)[b]
5	$CuCl_2$	HOAc	O_2	29	15
6	$CuSO_4$	HOAc	O_2	85	68
7	Cu(isobutyrate)$_2$	HOAc	O_2	92	71
8	$Cu(OAc)_2$	formic acid	O_2	39	19
9	$Cu(OAc)_2$	propionic acid	O_2	89	68
10	$Cu(OAc)_2$	HOAc	air	70	44

[a] GC yield vs. internal standard; reactions conducted on a 0.2 mmol scale. [b] Yield of isolated compounds; average of two runs on a 1.0 mmol scale.

Using the optimized conditions, we next explored the scope and generality of the process. Amidines were prepared through the addition of an aniline to a carbonitrile derivative following known procedures.[12] We were surprised to find that functionalized amidines derived from aryl nitriles without *ortho* substituents showed little conversion into the desired benzimidazole and mainly the formation of decomposition products which seemed to inhibit the catalytic cycle. However, clean formation of substituted 2-phenylbenzimidazoles was observed when the amidine was derived from a 2-substituted aryl nitrile.[13] As shown in Table 2, a variety of *ortho* substituents, such as Me, CF_3, OMe, Cl, or TBS can be used. In addition, several functional groups including halo-

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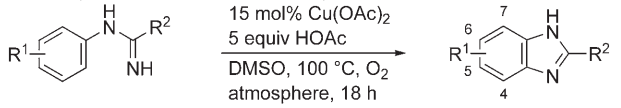
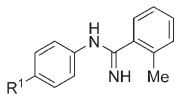
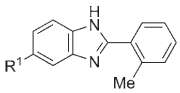
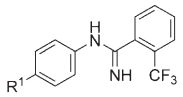
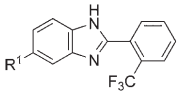
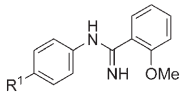
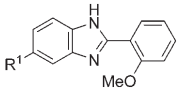
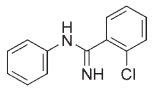
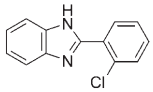
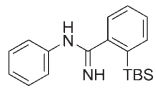
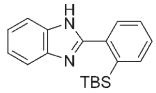
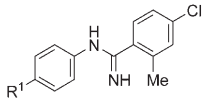
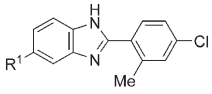
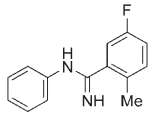
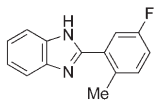
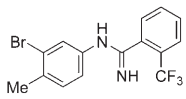
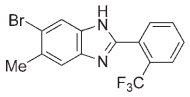
Table 2: Synthesis of substituted 2-arylbenzimidazoles.



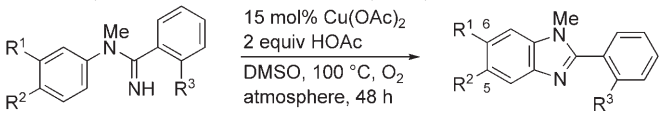
Entry	Substrate	Product	R^1	Yield [%][a]
1			H	89
2			OMe	70
3			F	86
4			Cl	89
5			Br	89
6			H	87
7			OMe	74[b]
8			CO_2tBu	88[c,d]
9			I	89
10			H	68
11			Cl	75
12				81
13				80[e]
14			H	85
15			Br	88
16				89
17				80[c,f]

[a] Yield of isolated compounds; average of two runs on a 1.0 mmol scale. [b] Reaction also conducted with the *meta* substituted amidine to give mainly the same product; 74% yield of isolated compound; 19:1 regioselectivity (GC). [c] Reaction time 36 h. [d] Reaction also conducted with the *meta* substituted amidine to give the same product; 69% yield of isolated compound; no regioisomer detected. [e] Reaction conducted on a 0.5 mmol scale instead of 1.0 mmol. [f] 14:1 regioselectivity (HPLC).

gens and electron-donating or electron-withdrawing substituents are tolerated well on the *N*-aryl ring of the amidine. The ability to incorporate the whole range of halogen substituents makes this method particularly appealing, since these substituents can be used for further synthetic manipulations. As for substitution patterns, high yields were obtained when the substituents are in the 5- and 6-positions of the benzimidazole. Only low conversions were observed for cyclizations leading to 4-substituted or 4,6-disubstituted products.

The method can be extended to the preparation of *N*-methylated 2-phenylbenzimidazoles, a feature which was not reported for the older methods (Table 3).[9–11] Using our approach, the reaction conditions had to be modified only

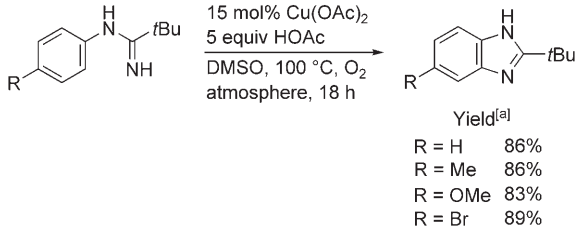
Table 3: Synthesis of substituted *N*-methyl-2-arylbenzimidazoles.



Entry	R^1	R^2	R^3	Yield [%][a]
1	H	H	Me	68
2	H	H	Cl	69
3	H	Br	Cl	84
4	Br	H	Cl	54[b]

[a] Yield of isolated compounds; average of two runs on a 1.0 mmol scale. [b] 5:1 regioselectivity (HPLC); yield corresponds to the major isomer shown above.

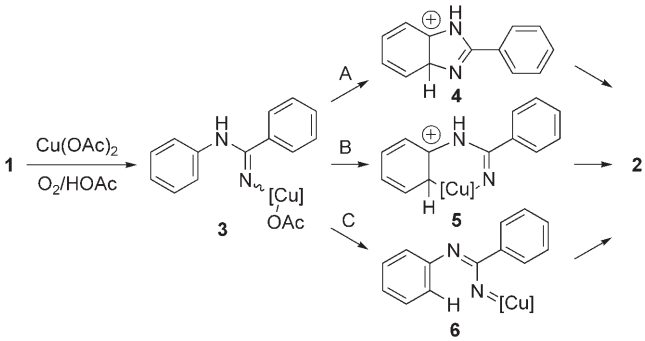
slightly with respect to the amount of acetic acid and reaction time to obtain high yields. Further investigations also revealed that 2-alkylated benzimidazoles can be obtained (Scheme 1). However, compared to the older methods[9–11]



Scheme 1. Synthesis of substituted 2-*tert*-butylbenzimidazoles. [a] Yield of isolated compounds; average of two runs on a 1.0 mmol scale.

our method is limited to amidines bearing a bulky *tert*-butyl group. In attempts to cyclize amidines with a smaller ethyl, isopropyl, or benzyl substituent, only decomposition of the starting material was observed.

We currently are unsure of the mechanistic course of the benzimidazole-forming process. Scheme 2 outlines possible pathways suggested by literature precedent of related processes. The reaction of **1** with $Cu(OAc)_2$ presumably leads



Scheme 2. Possible reaction pathways for the conversion of **1** into **2**.

first to a Cu–N adduct **3**[10] with copper either in oxidation state II or III.[14] In pathway A the *N*-aryl ring attacks the amidine moiety in a fashion similar to an electrophilic aromatic substitution to form **4** with concurrent release of a reduced copper species. Rearomatization then provides **2**. In pathway B the *N*-phenyl ring attacks the copper center in **3** to give a metallacycle **5**.[15] Product **2** is subsequently formed through rearomatization and reductive elimination of the metal. Pathway C involves a copper nitrene **6**.[16] A concerted insertion of the nitrogen into a C–H bond or an electrocyclic ring closure and a final [1,3]-shift of a hydrogen would then lead to **2**.[9]

To probe the action of an electrophilic aromatic substitution mechanism, we treated an unsubstituted amidine and amidines substituted with either an electron-donating (OMe) or electron-withdrawing group (CO_2tBu) in the *para* or *meta* position of the aniline-derived part of **1**. We then measured and compared their conversions into the corresponding benzimidazoles after 2, 4, 6, and 8 h.[17] The highest reactivity was observed for the amidine with an OMe in the *meta* position, the lowest for the amidine with a CO_2tBu group in the same position. This result is consistent in direction, but not in magnitude, with the ability of these substituents to stabilize the carbocation in **4** or **5**. A thorough mechanistic study is needed to unravel the mechanistic intricacies of this process.

In conclusion, an efficient copper-catalyzed C–H functionalization/C–N bond-forming approach providing benzimidazoles in good to very good yields from readily available amidines has been developed. The new method requires only inexpensive reagents, such as copper(II) acetate, acetic acid, and oxygen, and tolerates a variety of useful functional groups.

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Keywords: C–H functionalization · C–N bond formation · copper · heterocycles · homogeneous catalysis

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[17] See Supporting Information for data and a more detailed discussion.

