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Copper-Catalyzed Aerobic Oxidative Intramolecular C−H Amination Leading to Imidazobenzimidazole Derivatives

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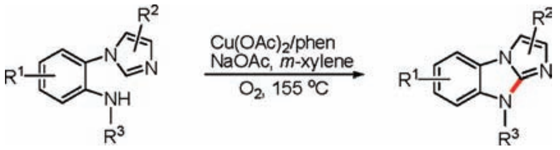
ABSTRACT



A highly efficient copper-catalyzed aerobic oxidative intramolecular C−H amination has been developed using substituted 2-(1*H*-imidazol-1-yl)-*N*-alkylbenzenamines as the starting materials, and the corresponding imidazobenzimidazole derivatives were obtained in excellent yields. This is an economical and practical method for the construction of *N*-heterocycles.

Compounds containing nitrogen widely occur in natural products and synthetic drugs. In fact, the synthetic drugs generally contain more nitrogen than the natural products because nitrogen can carry a positive charge, and act as a hydrogen bond donor and/or acceptor that strongly influences the interaction between the medicinal agent and its target.[1] In addition, the pK_a values of amines are often in the range of physiological pH, a physical property essential for improving the bioavailability of drugs.[2] Therefore, the development of novel C−N bond forming methodologies is of the utmost importance. For over a century, N-arylation of amines has attracted wide attention, and the copper-catalyzed Ullmann/Goldberg-type N-arylations[3−5] and palladium-catalyzed Buchwald−Hartwig couplings[6] are popular methods thus far. However, the methods need previously functionalized substrates (such as aryl halides and tosylates). Obviously, the direct catalytic transformation of carbon−hydrogen bonds to carbon−nitrogen bonds is more economical and environmentally friendly because such

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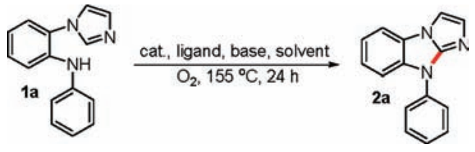
reactions do not require the presence of functional groups in the substrates.[7] Over the past decade, there has been great progress in the direct functionalization of C−H bonds,[8] and some *N*-heterocycles, such as benzimidazoles,[9] indazoles,[10] indolines,[11] carbazoles,[12] and *N*-methoxylactams,[13] have been made through a C−H activation/C−N bond-forming strategy, but expensive palladium-, rhodium-, and ruthenium-based catalysts are usually required. Recently, some inexpensive copper-catalyzed sp^2 C−H aminations/amidations have been developed,[2,14] and the heterocycles have been constructed via a copper-catalyzed sp^2 C−H activation strategy[15] using dioxygen as the oxidant.[16] The synthesized imidazobenzimidazole derivatives exhibit various biological and pharmacological activity. For example, they are used as inhibitors of p53[17a] and β-lactamases,[17b] corticotropin-releasing factor 1 receptor antagonists,[17c] and analgetic agents.[17d] They also show antioxidant, radioprotector, antiarrythmic, spasmolytic, antiaggregant, anticalmodulin, and antisecretory activities, and some substances exhibit the properties of phosphodiesterase inhibitors, decrease calcium ion transport through membranes, increase myocardium resistance to hypoxia, and reduce the arterial pressure.[17e−g] Couplings of substituted

Table 1. Copper-Catalyzed Intramolecular C−H Amination of *N*-(2-(1*H*-Imidazol-1-yl)phenyl)benzenamine (**1a**) Leading to 9-Phenylimidazo[1,2-*a*]benzimidazole (**2a**) under Oxygen: Optimization of Conditions[a]



entry	cat.	ligand	base	solvent	yield (%)[b]
1	$Cu(OAc)_2$	–	NaOAc	*m*-xylene	52
2	$CuBr_2$	–	NaOAc	*m*-xylene	5
3	CuO	–	NaOAc	*m*-xylene	15
4	CuI	–	NaOAc	*m*-xylene	6
5	CuBr	–	NaOAc	*m*-xylene	8
6	CuCl	–	NaOAc	*m*-xylene	49
7	$Cu(OAc)_2$	–	NaOAc	DMSO	trace
8	$Cu(OAc)_2$	–	NaOAc	DMF	trace
9	$Cu(OAc)_2$	PPh_3	NaOAc	*m*-xylene	76
10	$Cu(OAc)_2$	PPh_3	Na_2CO_3	*m*-xylene	72
11	$Cu(OAc)_2$	PPh_3	K_2CO_3	*m*-xylene	48
12	$Cu(OAc)_2$	PPh_3	Cs_2CO_3	*m*-xylene	5
13	$Cu(OAc)_2$	PPh_3	K_3PO_4	*m*-xylene	37
14	$Cu(OAc)_2$	PPh_3	$NaHCO_3$	*m*-xylene	35
15	**$Cu(OAc)_2$**	**phen**	**NaOAc**	***m*-xylene**	**93**
16	$Cu(OAc)_2$	DMEDA	NaOAc	*m*-xylene	65
17	$Cu(OAc)_2$	proline	NaOAc	*m*-xylene	51
18	$Cu(OAc)_2$	phen	NaOAc	*o*-xylene	86
19	$Cu(OAc)_2$	phen	NaOAc	*p*-xylene	88
20	$Cu(OAc)_2$	phen	NaOAc	*m*-xylene	65[c]
21	$Cu(EH)_2$	–	NaOAc	*m*-xylene	46[d]

[a] Reaction conditions: *N*-(2-(1*H*-imidazol-1-yl)phenyl)benzenamine (**1a**) (0.3 mmol), catalyst (0.06 mmol), ligand (0.12 mmol), base (1.2 mmol), solvent (1 mL), reaction temperature (155 °C), reaction time (24 h) in a Schlenk tube under oxygen balloon (1 atm). [b] Isolated yield. [c] Under air. [d] EH = 2-ethylhexanoate.

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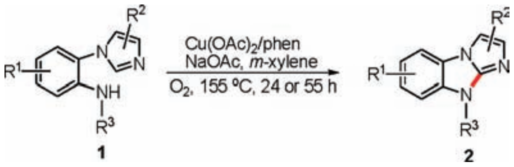
Table 2. Copper-Catalyzed Aerobic Oxidative Intramolecular C−H Amination Leading to Imidazobenzimidazole Derivatives[a]



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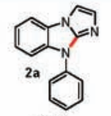
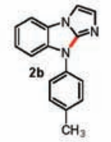
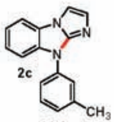
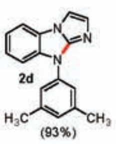
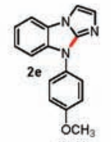
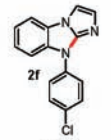
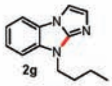
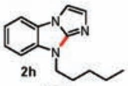
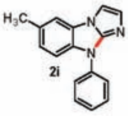
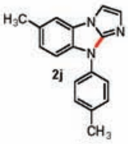
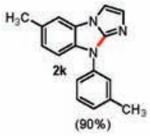
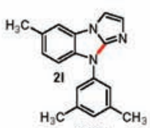
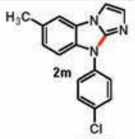
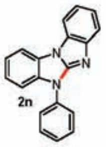
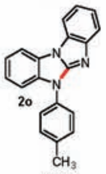
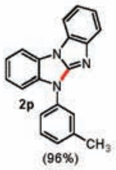
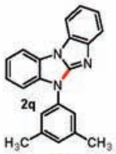
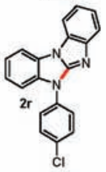
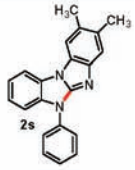
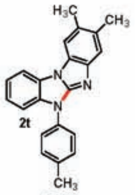
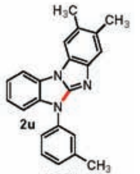
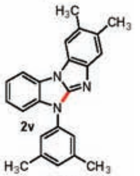
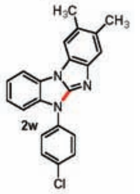
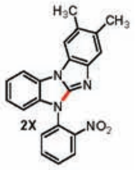
1	24	 2a (93%)
2	24	 2b (93%)
3	24	 2c (95%)
4		 2d (93%)
5	55	 2e (93%)
6	24	 2f (92%)
7	55	 2g (82%)
8	55	 2h (90%)
9	55	 2i (90%)
10	55	 2j (91%)
11	55	 2k (90%)
12	55	 2l (92%)
13	55	 2m (92%)
14	55	 2n (81%)
15	55	 2o (93%)
16	55	 2p (96%)
17	55	 2q (90%)
18	55	 2r (82%)
19	55	 2s (90%)
20	55	 2t (91%)
21	55	 2u (93%)
22	55	 2v (97%)
23	55	 2w (95%)
24	55	 2X (92%)

[a] Reaction conditions: **1** (0.3 mmol), Cu(OAc)$_2$ (0.06 mmol), 1,10-phen (0.12 mmol), NaOAc (1.2 mmol), *m*-xylene (1 mL), reaction temperature (155 °C), reaction time (24 or 55 h) in a Schlenk tube using an oxygen balloon (1 atm). [b] Isolated yield.

2-aminobenzimidazoles with 1-bromoalkan-2-ones are common methods,[17] but the prefunctionalization approaches are not economical. Herein, we report a novel copper-catalyzed aerobic oxidative intramolecular C−H amination leading to imidazobenzimidazole derivatives under oxygen.

Here, *N*-(2-(1*H*-imidazol-1-yl)phenyl)benzenamine (**1a**) was used as the model substrate to optimize reaction conditions including catalysts, ligands, bases, and solvents under oxygen (1 atm). As shown in Table 1, six copper salts (0.2 equiv) were screened in the presence of 4 equiv of

NaOAc (relative to amount of **1a**) in *m*-xylene at 155 °C (entries 1−6), and $Cu(OAc)_2$ afforded the highest yield (entry 1). Only a trace amount of product was observed when DMSO and DMF were used as the solvents (entries 7 and 8). The yields obviously increased when PPh_3 was applied as the ligand (entry 9). Various bases were determined (entries 10−14), and NaOAc showed the highest efficiency (entry 9). Other ligands were also investigated (entries 15−17), and 1,10-phenanthroline (phen) provided the highest yield (93%) (entry 15). We attempted *o*-xylene and *p*-xylene as the solvents. Surprisingly, they were inferior to *m*-xylene (compare entries 15, 18, and 19). The reaction under air gave a 65% yield (entry 20). When copper(2-ethylhexanoate)$_2$ was used as the catalyst in the presence of ligand, the target product was obtained in 46% yield (entry 21).

As shown in Table 2, the scope of copper-catalyzed aerobic oxidative intramolecular C−H amination of **1** leading to imidazobenzimidazole derivatives (**2**) was investigated under the optimized conditions (using 20 mol % of $Cu(OAc)_2$ as the catalyst, 40 mol % phen as the ligand, 4 equiv of NaOAc as the base (relative to amount of **1**), and *m*-xylene as the solvent). The reactions provided the corresponding target products in excellent yields. The copper-catalyzed intramolecular C−H amination showed tolerance of some functional groups in the substrates including ether (entry 5), C−Cl bond (entries 6, 13, 18 and 23), nitro (entry 24) and *N*-heterocycles.

In order to ascertain structures of the newly synthesized imidazobenzimidazole derivatives (**2**), a single crystal of **2m** was prepared, and its structure was unambiguously confirmed by X-ray diffraction analysis (Figure 1) (see Supporting Information for details).

A possible mechanism for copper-catalyzed aerobic oxidative synthesis of imidazobenzimidazole derivatives (**2**) is suggested in Scheme 1. Coordination of 1,10-phenanthroline (phen) with $Cu(OAc)_2$ first forms complex $L_nCu(OAc)_2$. Treatment of substrate (**1**) with $L_nCu(OAc)_2$ provides intermediate **I** in the presence of base (NaOAc), and reductive elimination of **I** affords the target product (**2**) leaving the Cu(II)L_n catalyst under oxygen.[14d,e]

In summary, we have developed a highly efficient copper-catalyzed aerobic oxidative intramolecular sp^2 C−H amination leading to imidazobenzimidazole derivatives. The protocol uses inexpensive $Cu(OAc)_2$ as the catalyst, 1,10-phenanthroline as the ligand, NaOAc as the base, and economical and environment friendly oxygen as the oxidant, and the corresponding *N*-heterocycles were obtained in excellent yields. This method should provide a new and useful strategy for the construction of *N*-heterocycles.

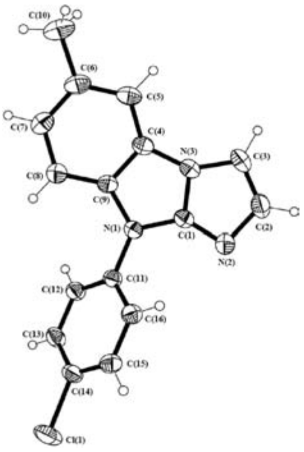
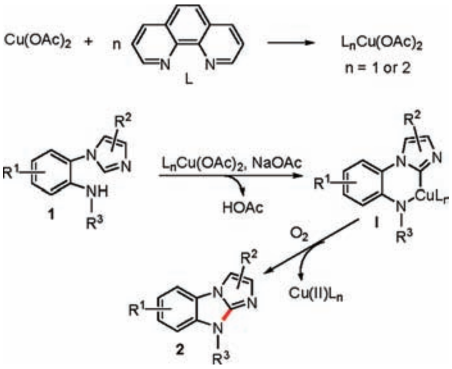


Figure 1. Crystal structure of compound **2m**.

Scheme 1. Possible Mechanism for Copper-Catalyzed Aerobic Oxidative Intramolecular C−H Amination Leading to Imidazobenzimidazole Derivatives (**2**)



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Supporting Information Available. Synthetic procedures, characterization data, and ^{1}H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.