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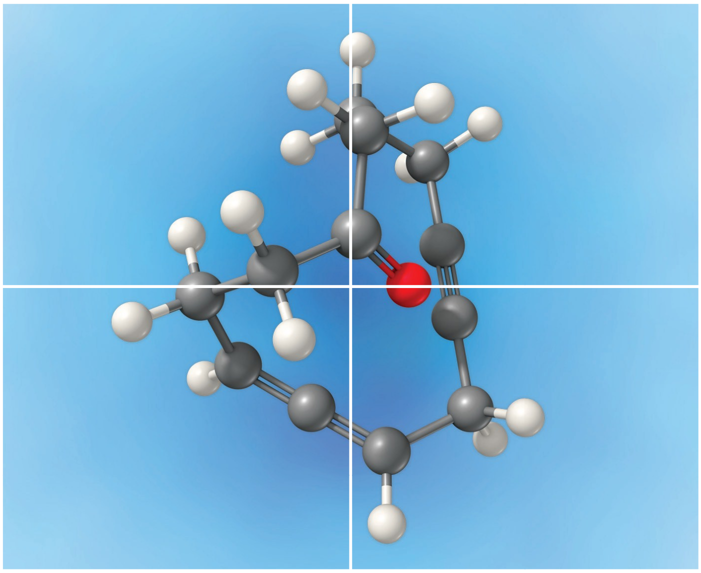

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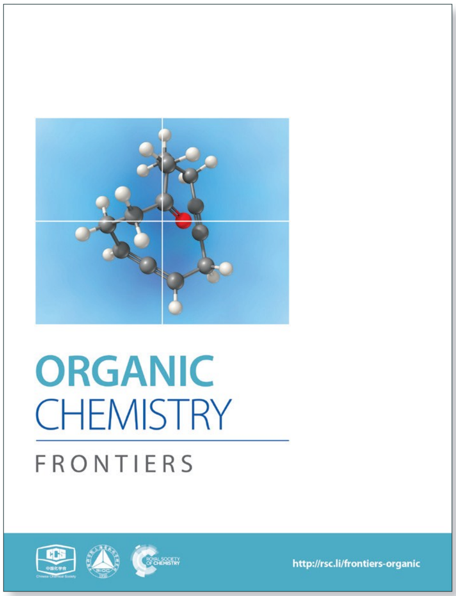

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Copper-Catalyzed Oxidative Coupling Reaction of *α, β*-Unsaturated Aldehydes with Amidines: Synthesis of 1, 2, 4-Trisubstituted-1*H*-Imidazole-5-Carbaldehydes

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A practical and highly functional group-compatible synthesis of 1, 2, 4-trisubstituted-1*H*-imidazole-5-carbaldehydes has been developed via copper-catalyzed oxidative coupling of amidines and *α, β*-unsaturated aldehydes, which features aldehyde reserved, cheap catalysts, as well as high atom economy and mild conditions.

Introduction

The imidazole core is an important scaffold that could be found in a large number of natural products (Figure 1 a),[1] pharmaceuticals (Figure 1 b and c),[2] and advanced materials[3]. Thus, the development of synthetic protocols for imidazole derivatives has always been an active area of research.[4] The Bredereck synthesis,[5] Van Leusen reaction,[6] Debus-Radziszewski reaction,[7] and the reaction of *R*-haloketones with amidines[8] are well documented as traditional methods to build imidazole rings. However, these procedures generally involve a strong base or relatively high temperature.

With the rapid development of transition metal-catalysis in the past decades, using simple *N*-arylated substrates as precursors for the synthesis of various imidazole derivatives has stimulated great research efforts.[9] Among these, Cu-catalyzed oxidative synthesis of imidazole derivatives has become increasingly popular for their high efficiency.[10] Typically, the group of Chiba has developed a series of strategies to afford various azaheterocycles under Cu-catalyzed oxidative conditions in the past few years.[10b-g]

Aldehyde is one of the most important groups in functional group transformation, such as Aldol reaction and Mannich reaction. As a potentially versatile synthetic intermediate, the aldehyde-substituted imidazoles contain an important reactive center for facile derivatization.[11] For example, Qiao's group synthesized novel functional materials, Schiff-base linked poly-meric imidazoles (SLPI),[11i] which are developed by aldehyde-substituted imidazoles. Based on previous studies on other and our groups,[9j,9t,10j,12] we report a copper-catalyzed oxidative coupling of *α, β*-unsaturated aldehydes with amidines to construct 1, 2, 4-trisubstituted-1*H*-imidazole-5-carbaldehydes under mild conditions with H_2O as the sole byproduct.

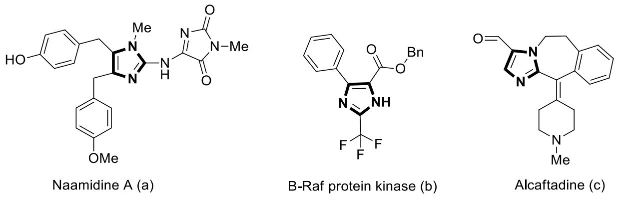

Figure 1. Examples of compounds with imidazole skeleton

Results and discussion

We initiated the investigation by using *N*-phenylbenzamidine (**1a**) and cinnamaldehyde (**2a**) as model substrates for optimization of this process, and the effects of all reaction parameters were systematically examined (Table 1). When the reaction was carried out in the presence of CuI (10 mol%), DABCO (1, 4-diazabicyclo-[2.2.2]octane) (20 mol%) and PhCl (chlorobenzene) (2 mL) at 100 ^{o}C for 36 h under air atmosphere, the desired product **3aa** was isolated in 26% yield (entry 1). It was found that two equivalents of MnO_2 under N_2 atmosphere increased the reactivity, producing the corresponding product **3aa** in 75% yield (entry 3). Other oxidants were inefficient in the presence of N_2 (entries 4-6). Among various copper catalysts that we screened, CuI gave the highest yield (entries 7-9). The replacement of DABCO with other ligands did not promote the efficiency of the reaction (entries 10–12). An evaluation of solvents revealed that PhCl

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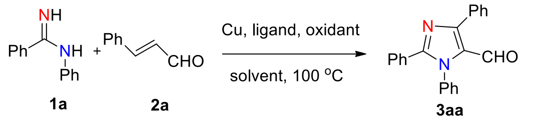
Table 1. Optimization of Reaction Conditions[a]



Entry	Catalyst	Ligand	Oxidant	Solvent	Yield [%][b]
1	CuI	DABCO	air	PhCl	26%
2[c]	CuI	DABCO	MnO_2	PhCl	48%
3	**CuI**	**DABCO**	**MnO_2**	**PhCl**	**75%**
4	CuI	DABCO	$K_2S_2O_8$	PhCl	27%
5	CuI	DABCO	TBHP	PhCl	20%
6	CuI	DABCO	$AgCO_3$	PhCl	15%
7	CuBr	DABCO	MnO_2	PhCl	20%
8	$CuBr_2$	DABCO	MnO_2	PhCl	32%
9	$CuCl_2$	DABCO	MnO_2	PhCl	54%
10	CuI	Bipy	MnO_2	PhCl	53%
11	CuI	TMEDA	MnO_2	PhCl	25%
12	CuI	PPh_3	MnO_2	PhCl	21%
13	CuI	DABCO	MnO_2	DCE	24%
14	CuI	DABCO	MnO_2	DMF	trace
15	CuI	DABCO	MnO_2	dioxane	36%
16[d]	CuI	DABCO	MnO_2	PhCl	30%
17[e]	CuI	DABCO	MnO_2	PhCl	68%
18[f]	CuI	DABCO	MnO_2	PhCl	55%
19[g]	CuI	DABCO	MnO_2	PhCl	45%
20[h]	CuI	DABCO	MnO_2	PhCl	59%
21[i]	CuI	DABCO	MnO_2	PhCl	63%

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (10 mol%), ligand (20 mol%), oxidant (2 equiv.), N_2, solvent (2 mL), 100 °C, 36 h. [b]Isolated yield. [c]Under air atmosphere. [d]The ratio of **1a**/**2a** = 1.5:1. [e]CuI (20 mol%), DABCO (40 mol%). [f]140 °C. [g]70 °C. [h]MnO_2 (1 equiv.). [i]MnO_2 (3 equiv.).

was the optimal choice, while other solvents such as DCE (1, 2-dichloroethane), DMF (N, N-dimethylformamide) and 1, 4-dioxane showed inferior results (entries 13–15). In addition, lower yields of **3aa** were obtained when we attempted to change the ratio of **1a**/**2a**, catalyst loading and temperature (entries 16–19). When varying the amounts of MnO_2, we found that the reaction with two equivalents of MnO_2 offered the best yield (entry 4 vs. entries 20 and 21). The structure of **3aa** was confirmed by X-ray crystallography (Figure 2).[13]

With the optimized conditions in hand, we proceeded to examine the substrate scope (Scheme 1). First, we studied the R^1-substituted arylamidines. Electron-rich-substituted arylamidines such as *p*-Me and *p*-OMe gave reaction products in excellent yields (**3ba**, 80%; **3ca**, 82%). When both aromatic rings were substituted with electron-rich groups, the product was isolated in optimal yield (**3na**, 88%). Electron-deficient arylamidines bearing halide (F-, Cl-, Br-) and trifluoromethyl groups reacted under the standard conditions to afford the desired products in moderate yields (**3da**-**3ha**, 38%-62%).

We next examined the substrate scope of this reaction using R^2-substituted arylamidines. The *p*-Me-substituted arylamidine delivered **3ja** in good yield (81%), while the *p*-Cl-substituted arylamidine afforded **3ia** in lower yield (50%). *O*-substituted arylamidines showed slightly lower reactivity than *p*-substituted arylamidine (**3ja**, 81%; **3ka**, 62%), indicating that

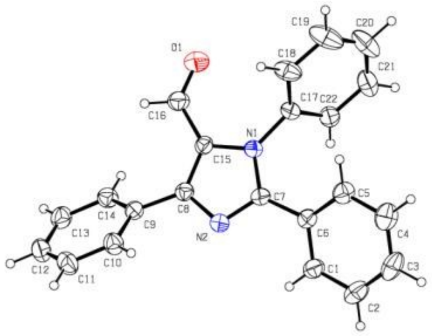
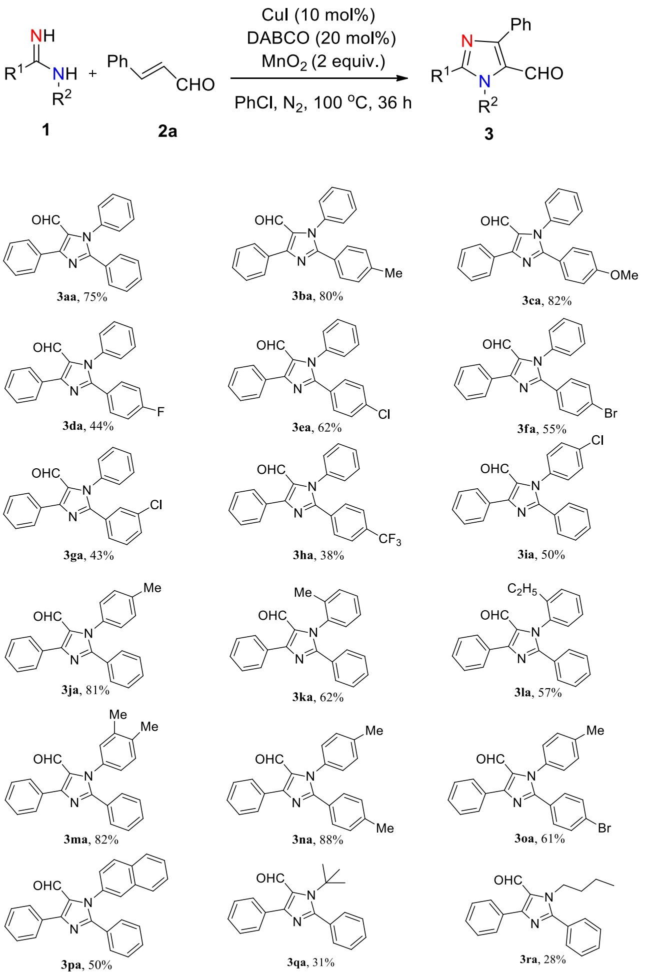
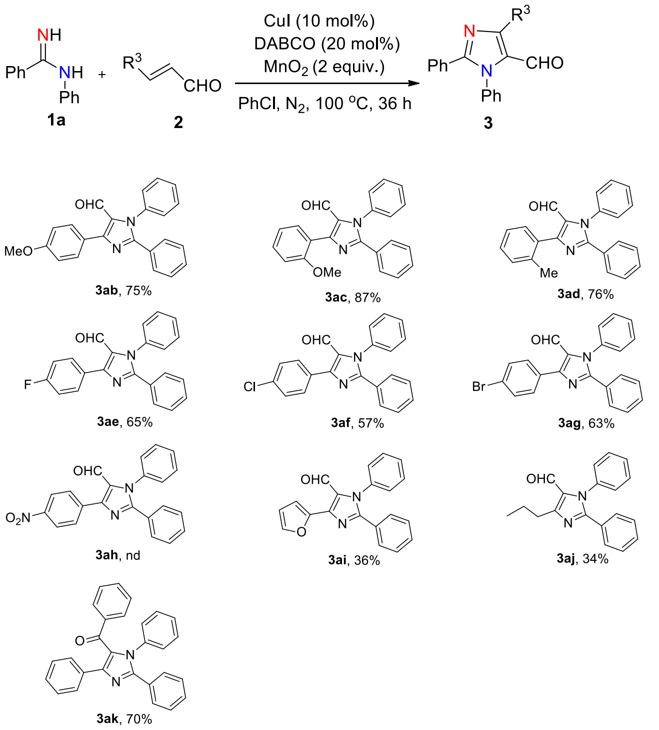


Figure 2. X-ray structure of **3aa.**

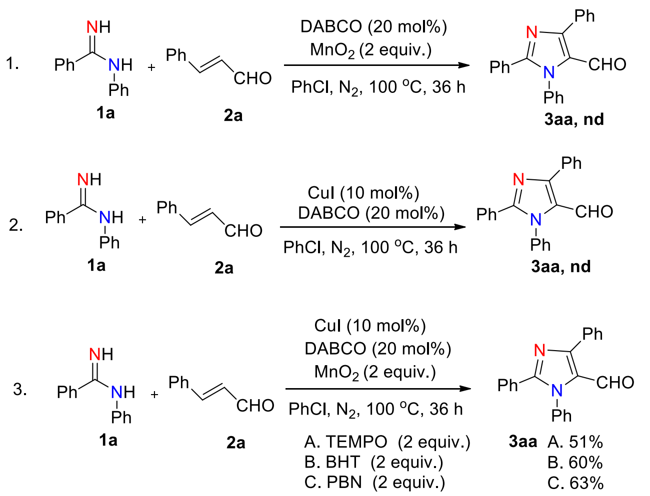


Scheme 1. The scope of amidines. Isolated yields are given. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), CuI (10 mol%), DABCO (20 mol%), MnO_2 (2 equiv.), N_2 , PhCl (2 mL), 100 °C, 36 h.

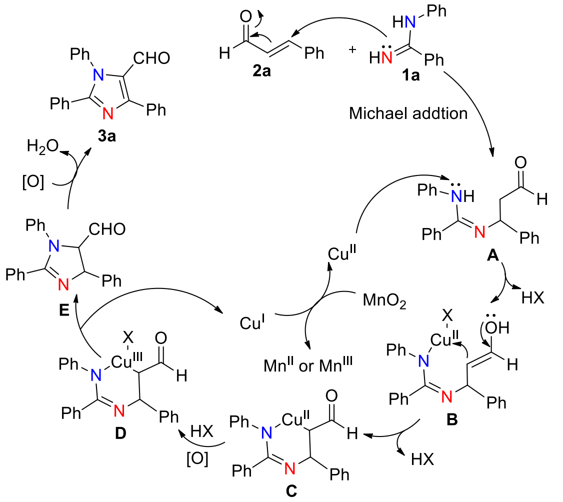
steric factors had a negative influence on this conversion. Furthermore, *N*-(naphthalen-2-yl)benzimidamide, *N*-(tert-butyl)benzimidamide and *N*-butylbenzimidamide were tolerated, affording the corresponding products in low yields (**3pa**, 50%; **3qa**, 31%; **3ra**, 28%).



Scheme 2. The scope of α, β-unsaturated aldehydes. Isolated yields are given. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), CuI (10 mol%), DABCO (20 mol%), MnO_2 (2 equiv.), N_2, PhCl (2 mL), 100 °C, 36 h.



Scheme 3. Controlled Experiments



Scheme 4. Proposed mechanism

The scope of α, β-unsaturated aldehydes was also examined (Scheme 2). Substrates bearing electron-donating groups (methyl and methoxyl) at the aromatic ring produced the corresponding products in good yields (**3ab–3ad**, 75–87%). The presence of electron-withdrawing substituents (F-, Cl-, Br-) at para position reduce the efficiency of the reaction, as the corresponding products could be isolated in slightly lower yields (**3ae–3ag**, 57–65%). Additionally, substrates bearing a furan and an *n*-propyl were also compatible, albeit providing lower yields (**3ai**, 36%; **3aj**, 34%). Unfortunately, the reaction with *p*-nitro-substituted α, β- unsaturated aldehyde did not afford the desired product **3ah** under the standard reaction conditions. Futhermore, we also tried chalcone with **1a** under the standard reaction conditions, which afforded the corresponding product (**3ak**) in 70% yield.

To understand the possible mechanism of this reaction, several control experiments were investigated (Scheme 3). Firstly, the reaction between **1a** and **2a** without using catalyst or oxidant was carried out, but no desired product was detected (Scheme 3 Eq. 1 and 2). Moreover, when 2 equiv. 2, 2, 6, 6-tetramethyl-1-piperidinyloxl (TEMPO) was added into the standard reaction, the isolated yield of **3aa** reduced from 75% to 51% (Scheme 3 Eq. 3 A), in which it may be the weak oxidizing effect of TEMPO affected the reaction. We also tried other radical traps such as BHT (2, 6-di-tert-butyl-4-methylphenol) (Scheme 3 Eq. 3 B) and PBN (*N*-benzylidene-tert-butylamine *N*-oxid) (Scheme 3 Eq. 3 C), which produced **3aa** in 60% and 63% respectively, indicating that this transformation might not proceed via a radical pathway.

Based on previous studies and control experiments, a plausible reaction mechanism is proposed as shown in Scheme 4.[14] Initially, a Michael addition of *N*-arylbenzamidines (**1a**) to the cinnamaldehyde (**2a**) took place to form the corresponding Michael adduct **A**.[14a-d] Subsequently, the nitrogen atom that connected to the benzene ring bound with Cu(II) salts to produce the intermediate **B** which simultaneously reacted with the enol to form the cyclic Cu(II) intermediate **C**.[14e] Then intermediate **C** on oxidation by the oxidant formed the intermediate **D** in which copper was in the +III oxidation state.[14f] Finally, the intermediate **D** through reductive elimination to afford intermediate **E**, which on rapid oxidative aromatization under oxidizing conditions leads to the tandem product **3aa**.Reoxidation of the Cu^I to the Cu^{II} by MnO_2 completed the catalytic cycle.

Conclusions

In summary, an efficient copper-catalyzed oxidative coupling of α, β-unsaturated aldehydes with amidines for the synthesis of 1, 2, 4-trisubstituted-1*H*-imidazole-5-carbaldehydes was developed, which shows a high atom economy, cheap catalysts and mild conditions. Further studies on the application of this transformation are underway.

Experimental

Typical Procedure for the Preparation of 3: **1** (0.20 mmol), **2** (0.40 mmol), CuI (3.8 mg, 10 mol%), DABCO (4.5 mg, 20 mol%), MnO$_2$ (34.8 mg, 2.0 equiv.), and PhCl (2 mL) were added to a flask with a magnetic stirring bar under N$_2$ atmosphere. The mixture was stirred at 100 °C for 36 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to get the crude product, which was further purified by silica gel chromatography to give product **3**. The identity and purity of the products was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis.

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