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CuI/$BF_3 \cdot Et_2O$ Cocatalyzed Aerobic Dehydrogenative Reactions of Ketones with Benzylamines: Facile Synthesis of Substituted Imidazoles

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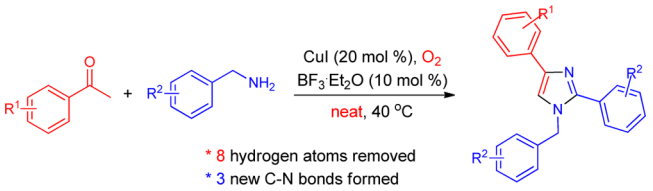
ABSTRACT



A novel CuI/$BF_3 \cdot Et_2O$/O_2-mediated reaction utilizing ketones and benzylamines for the construction of substituted imidazoles in one step under mild conditions has been demonstrated. This protocol involved the removal of eight hydrogen atoms, the functionalization of four C(sp^3)–H bonds and three new C–N bond formations.

Direct C–N bond formation has been considered an effective and practical strategy for the construction of heterocycles.[1] Some excellent results about C–N bond formations with copper catalysts have been achieved.[2] For example, Buchwald's,[2g,3] Hartwig's[2h,4] and Ma's groups[2j] have reported a series of leading works in this area to establish C–N bonds via cross-coupling reactions using organic halide substrates with amines. Since the pioneering research work by Buchwald in 2005,[5] an increasing number of N-heterocycles has been constructed by the C–N bond-forming strategy through intramolecular amination via C–H activation.[6] From both environmental and economical points of view, O_2 is the ideal oxidant[7] because of its abundance, low cost, and lack of toxic byproduct. Therefore, using a copper/O_2 catalyst system to construct heterocycles and drugs from simple and readily accessible

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substrates is compatible with the increasing requirements for green chemistry and efficient process.

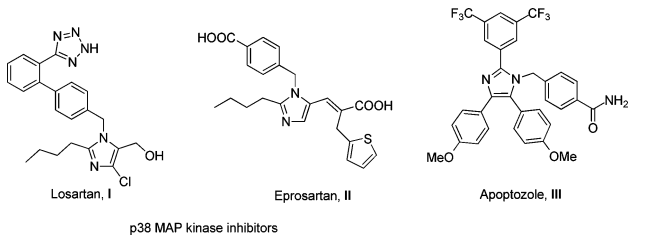
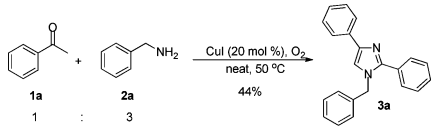


Figure 1. Selected imidazoles.

The preparation of highly substituted imidazoles is one of the most important fields in organic synthesis, which is regarded as a privileged heterocyclic motif in many bioactive natural products and pharmaceutical compounds,[1] such as inhibitors of p38 MAP kinase (e.g., Losartan **I**, Eprosartan **II**, Figure 1),[8] glucagon receptors,[9] plant growth regulators,[10] therapeutic agent,[11] antibacterial,[12] antitumor,[13] and also pesticides.[14] Recently, Shin's group[15] reported the Apoptozole (**III**, Figure 1), which has high cellular potency to promote membrane trafficking of mutant CFTR and its chloride channel activity in cystic fibrosis cells. Therefore, methods for the preparation of highly substituted imidazoles as the basic scaffold are necessary.[16] Despite many reported approaches[17,18] available for preparing the imidazole derivatives, the direct, region-defined synthesis of highly substituted imidazoles from commercially available starting materials has remained as one of the most challenging tasks. Herein, we report a novel $CuI/BF_3 \cdot Et_2O$[19] cocatalyzed aerobic oxidative reaction of ketones with benzylamines to the synthesis of highly substituted imidazoles in the presence of O_2 through aerobic oxidation[20−25] and dehydrogenative annulation of ketone with benzylmaines.

Initially, we treated **1a** (1.0 equiv) and **2a** (3.0 equiv) with CuI and O_2 (O_2 balloon, 1 atm) under neat conditions at 50 °C for 24 h. Surprisingly, trisubstitued imidazole **3a** was formed in 44% yield (LC yield) instead of other products such as imine, enamine, α-ketoamide[26] or indole derivative[27] (Scheme 1). The structure of **3a** was confirmed by spectroscopic analysis and further confirmed by single-crystal X-ray analysis.[28]

Scheme 1. Reaction of **1a** and **2a**



In order to improve the yield of **3a**, we further screened different copper salts, solvents (see the Supporting In-

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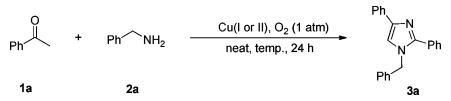
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	cat. (mol %)	additive (mol %)	temp [°C]	yield [%][a]
1	**CuI (20)**	**none**	**50**	**44**
2	CuBr (20)	none	50	<5
3	$CuBr_2$ (20)	none	50	n.r.
4	CuI (20)	2,2′-bipyridine (20)	40	67
5	CuI (20)	4,4′-di-*tert*-butyl-2,2′-bipyridine (20)	40	62
6	CuI (20)	1,10-phenanthroline (20)	40	37
7	CuI (20)	I_2 (20)	40	62
8	CuI (20)	$BF_3 \cdot Et_2O$ (20)	40	75
9	**CuI (20)**	**$BF_3 \cdot Et_2O$ (10)**	**40**	**83 [71][b]**

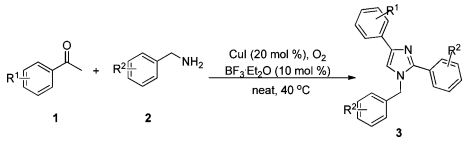
[a] Reaction conditions: **1a** (2 mmol), **2a** (6 mmol), neat, O_2 (1 atm). The yields were determined by LC analysis using biphenyl as the internal standard. [b] Isolated yield.

formation), and reaction temperatures as well as additives. As presented in Table 1, CuI showed higher catalytic reactivity than other copper salts such as CuBr and $CuBr_2$ for this reaction (Table 1, entries 1−3). It was found that the use of *N*,*N*-ligands such as 2,2′-bipyridine and 4,4′-di-*tert*-butyl-2,2′-bipyridine as additives could promote the reaction, and the yields of **3a** were increased to 67% (LC yield) and 62% (LC yield), respectively (Table 1, entries 4 and 5). In view of the effects of the ligands, we turned our attention to the cheap Lewis acid as the additive instead of the expensive ligands. When 20 mol % I_2 or 20 mol % $BF_3 \cdot Et_2O$ was used as the additive, the desired product could be obtained in 62% (LC yield) and 75% (LC yield) yields, respectively (Table 1, entries 7 and 8). After screening the amount of $BF_3 \cdot Et_2O$, it was observed that 10 mol % $BF_3 \cdot Et_2O$ as additive gave the best result and **3a** could be produced in 83% LC yield and 71% isolated yield (Table 1, entry 9).

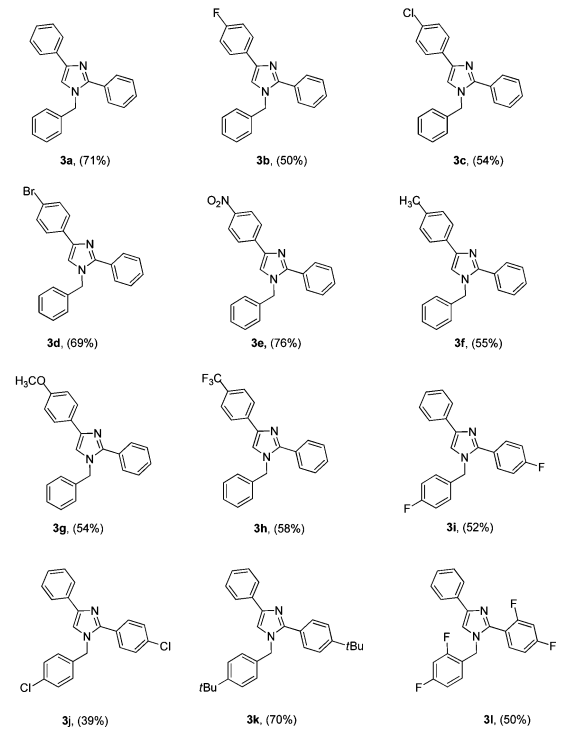
With the optimized conditions in hand, we next examined the scope of this oxidative reaction. The results were summarized in Table 2. In most cases, moderate to good yields of the corresponding imidazoles were delivered under the optimized conditions. Notably, good yield of 1,2,4-trisubstitued imidazole **3e** was obtained for substrate **1e** bearing a strong electron-withdrawing group (76% yield). In addition, when 1-(4- methoxyphenyl)-one **1g** containing electron-donating group was subjected to this transformation, a moderate yield (54%) of the desired product **3g** was achieved as well. The structure of product **3g** was also confirmed by single-crystal X-ray analysis.[28] When other 1-phenylethanone derivatives bearing F, Cl, Br, CH_3, CF_3 groups were applied to the reaction, the desired products (**3b**, **3c**, **3d**, **3f**, **3h**) were also obtained in moderate yields.

Reactions of a variety of substituted benzylamines **2** with acetophenone **1a** were also surveyed. It was found

Table 2. Imidazole Synthesis from Ketones with Benzyl-Amine[a]



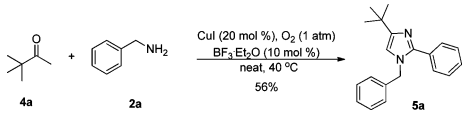
1 2 3



[a] Reaction conditions: **1** (2 mmol), **2** (6 mmol), CuI (20 mol %), $BF_3 \cdot Et_2O$ (10 mol %), O_2 (1 atm), 40 °C, 24 h.

that substrate **2k** possessing *tert*-butyl substituent at the 4-position of the aryl ring provided the desired imidazole product **3k** in 70% yield. When (2,4-difluorophenyl)-methanamine **2l** was treated with acetophenone **1a** under the analogous reaction conditions, 1,2,4-trisubstitued imidazole **3l** was obtained in 50% yield. When aliphatic ketone 3,3-dimethylbutan-2-one **4a** instead of **1a** was subjected to the reaction with **2a** under the optimized reaction conditions, the desired imidazole derivative **5a** could also be obtained in 56% yield (Scheme 2).

Scheme 2. Reaction of **4a** and **2a**

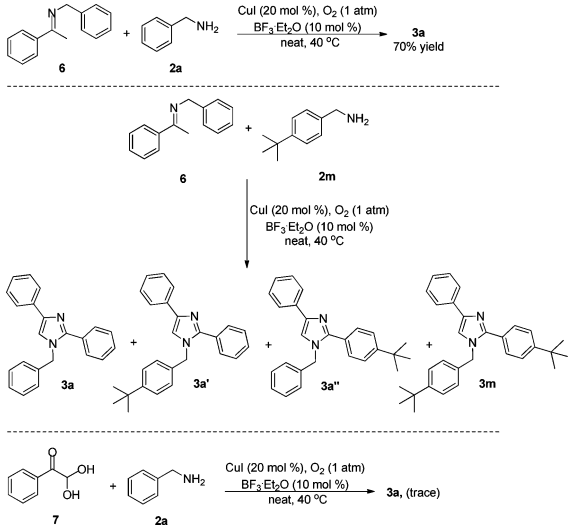


4a 2a 5a

To better understand the mechanism of this reaction, some control experiments were carried out (Scheme 3). The reaction of imine **6** with **2a** under the $CuI/BF_3 \cdot Et_2O/O_2$ conditions generated **3a** in 70% yield (Scheme 3).

Similar reaction of **6** and **2m** under the standard conditions afforded the mixture of **3a**, **3a′**, **3a″** and **3m**, which was determined by the LC−MS analysis.

Scheme 3. Control Experiments

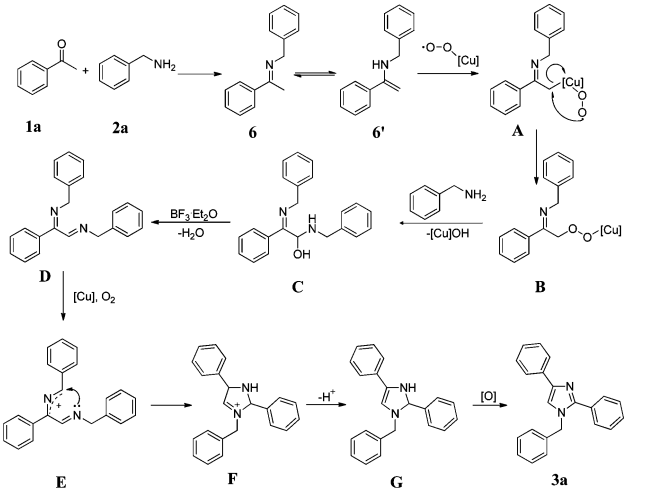


Both these results suggested that there was an equilibrium between imine **6** with the mixture of **1a** and **2a** under the reaction conditions and imine **6** was the intermediate for this reaction. Furthermore, the reaction of 2,2-dihydroxy-1-phenylethanone (**7**)[29] with **2a** under the standard conditions was investigated, respectively.[30] It was found that only trace of the desired product was detected by LC−MS. This result implied that 2,2-dihydroxy-1-phenylethanone was not the intermediate of the reaction.

On the basis of the above-mentioned results and the literature reports,[21,25,29,30] we proposed a plausible mechanism for the reaction (Scheme 4). Enamine **6′** generated via tautomerization of imine **6** from **1a** and **2a** would be oxidized to **B**.[25] Subsequently, the intermediate **B** was attacked by another molecule of **2a** to give intermediate **C**. After the dehydration of **C** under Lewis acidic conditions, the intermediate **D** was generated. Finally, intermediate **D** underwent an annulation to give intermediate **E** followed by the ensuing proton elimination to afford **G**. Upon further oxidation of **G**, the desired product **3a** was yielded eventually.

In conclusion, we have described a novel and efficient approach for the preparation of highly substituted imidazoles in one step by using ketones and benzylamines catalyzed by commercially available $CuI/BF_3 \cdot Et_2O$ in the atmosphere of O_2. $BF_3 \cdot Et_2O$ showed high reactivity as a cocatalyst combined with CuI. In addition, this reaction provides a simple, easy-handling, and atom-economic way to the synthesis of polysubstituted imidazoles under mild conditions. This protocol involved the removal of eight hydrogen atoms, the functionalization of four $C(sp^3)$−H bonds and three new C−N bond formations in one manipulation. Currently, studies toward enlarging the scope of the $CuI/BF_3 \cdot Et_2O$ catalyst system to the synthesis of other useful compounds via aerobic oxidative C−H amination and further understanding the mechanism of the reaction are ongoing.

Scheme 4. Proposed Mechanism



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Supporting Information Available. Experimental procedures, CIF files for **3a** and **3g**, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) When we were preparing this manuscript, Jiao's group reported the preparation of oxazoles by the reaction of amines and aryl acetaldehydes mediated by 1.5 equiv of $CuBr_2$ using O_2 as oxidant via C−H functionalization: Xu, Z.-J.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367.

The authors declare no competing financial interest.