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Copper(I) Iodide/Boron Trifluoride Etherate-Cocatalyzed Aerobic Dehydrogenative Reactions Applied in the Synthesis of Substituted Heteroaromatic Imidazo[1,2-*a*]pyridines

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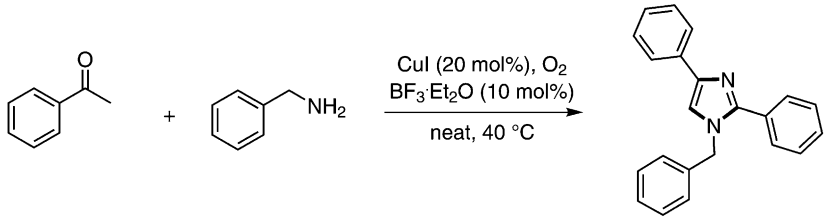
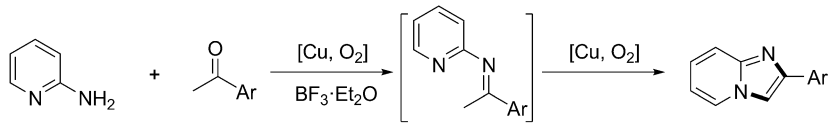
Abstract: Compared with the well-known palladium-catalyzed oxidative dehydrogenation coupling reactions, similar transforms initiated by copper/oxygen have attracted more and more attention. We have investigated a novel construction of heteroaromatic imidazo[1,2-*a*]pyridines through copper(I) iodide/boron trifluoride etherate/oxygen-mediated dehydrogenative reactions of aryl alkyl or alkyl alkyl ketones with 2-aminopyridines. Four hydrogen atoms are removed and two new C–N bonds are formed in one step *via* the imine formation and oxidative C(sp^3)–H functionalization.

Keywords: C(sp^3)–H functionalization; copper; dehydrogenative coupling; imidazo[1,2-*a*]pyridines; oxygen

The construction of N-heterocycles *via* direct C–H amination[1] is one of the most attractive and challenging fields in organic chemistry. This strategy provides a route without relying on prefunctionalization of the compounds to the corresponding organic halides and features high bond-formation efficiencies and atom economy. Recently, several reports were focused on the synthesis of, especially, pyrroles *via* the so-called "borrowing hydrogen" methodology.[2] Compared to the classical precious metal-catalyzed C–H functionalization,[3] the copper-catalyzed dehydrogenative functionalization, especially C–H amination, have attracted considerable attention due to its efficiency, inexpensiveness, readily available starting materials, insensitivity to air, and easy handling advantages.[4] With the advances in aerobic dehydrogenative reactions, O_2 has been considered as the powerful and ideal oxidant for its natural, inexpensive, and environmentally friendly characteristics.[5] From both environmental and economic points of view, it is a challenge to construct heterocycles and drugs from simple and readily accessible substrates using a copper/O_2 catalyst system *via* direct C–H amination.[6] More recently, we have reported the construction of substituted imidazoles (Scheme 1) *via* aerobic oxidative C–H amination under the CuI/BF_3·Et_2O/O_2 catalyst system.[7] It was found that the copper/O_2 catalyst system could activate the α-position of imines followed by other reactions such as cyclizations. In light of these considerations, we reasoned that the CuI/BF_3·Et_2O/O_2 catalyst system could also activate the α-position of *N*-(arylethylidene)pyridin-2-amine *via* an aerobic oxidative C–H amination strategy for the construction of new heterocyclic rings. To our delight, imidazo[1,2-*a*]pyridine derivatives could be obtained by the reaction of pyridin-2-amine with ketones under the action of the CuI/BF_3·Et_2O/O_2 catalyst system (Scheme 2).



Scheme 1. Our previous work on the construction of substituted imidazoles.



Scheme 2. The strategy for the construction of imidazo[1,2-*a*]pyridines.

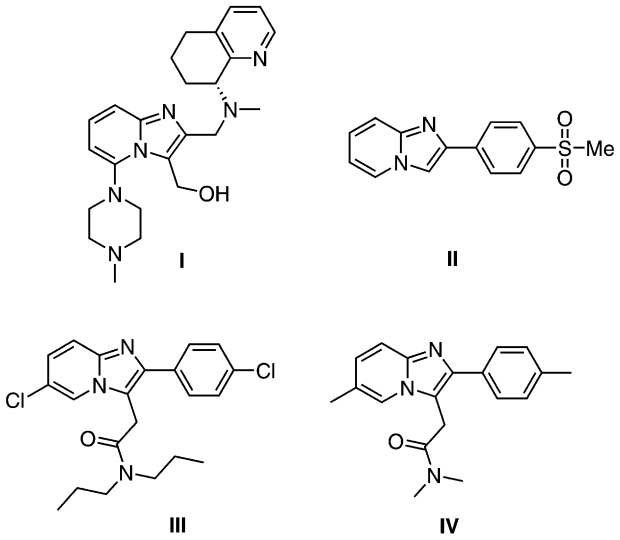
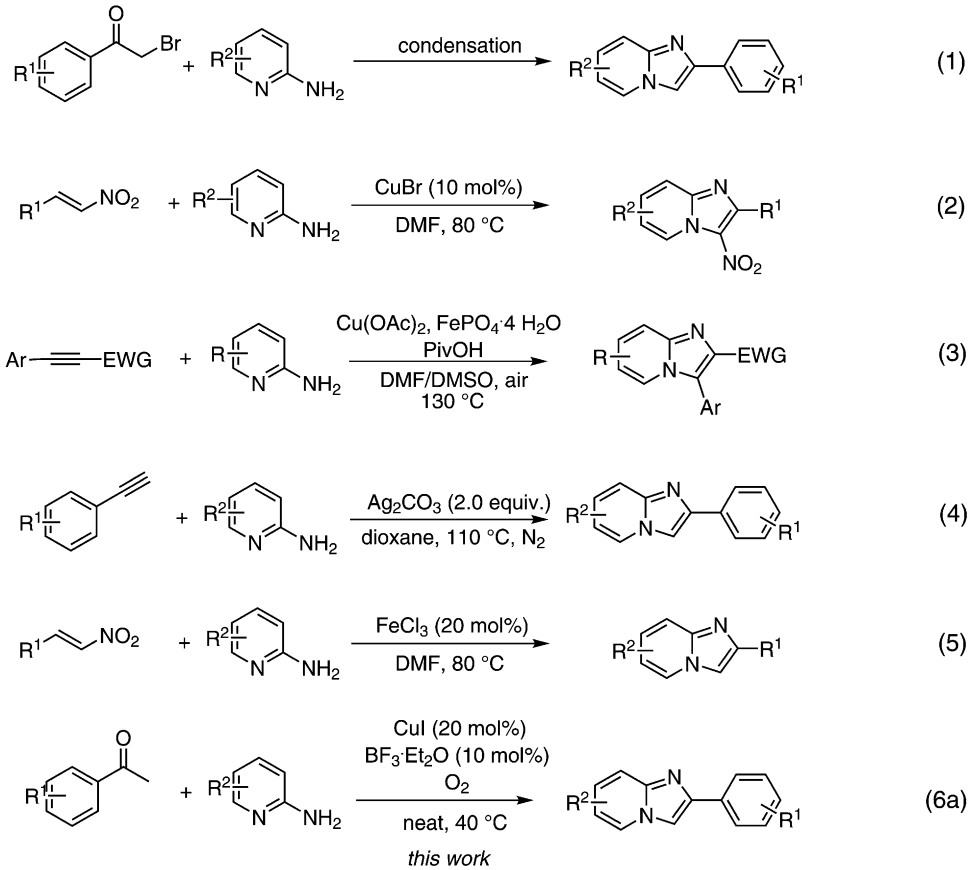


Figure 1. Selected imidazo[1,2-*a*]pyridines.

The imidazo[1,2-*a*]pyridine ring system[8] is the core structure of many commercially available drugs, some of which show antibacterial,[9] antitumor,[10] and antiviral activities.[11] For example, the optically active GSK812397 (Figure 1, **I**) is a drug for the treatment of HIV infection.[12] Zolimidine, alpidem, zolpidem (Figure 1, **II**, **III**, **IV**) are used as antiulcer, anxiolytic, and hypnotic drugs, respectively.[13–15]

Numerous methods have been developed for the formation of variously substituted imidazo[1,2-*a*]pyridines.[16] The traditional approach for the preparation of substituted imidazo[1,2-*a*]pyridines is the condensation reaction of 2-aminopyridines with α-halocarbonyl compounds which has found wide applications in medicinal chemistry and drug synthesis [Scheme 3, Eq. (1)].[17] Recently, Liang and co-workers have developed a copper-catalyzed method for the preparation of imidazo[1,2-*a*]pyridines with aminopyridines and nitroolefins using air as oxidation [Scheme 3, Eq.



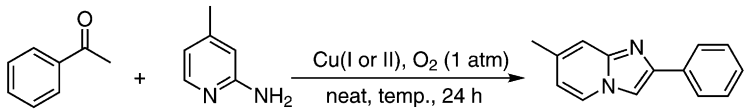
Scheme 3. The construction of imidazo[1,2-*a*]pyridines from 2-aminopyridines.

(2)].[18] A facile synthesis of imidazo[1,2-*a*]pyridines catalyzed by copper(II) and iron(III) has been reported by Liu's group [Scheme 3, Eq. (3)].[19] Lei's group reported that the reaction of 2-aminopyridines and terminal alkynes catalyzed by 2.0 equiv. of Ag_2CO_3 could form imidazo[1,2-*a*]pyridines easily [Scheme 3, Eq. (4)].[20] Meanwhile, Hajra and co-workers reported the synthesis of imidazo[1,2-*a*]pyridines by the iron(III)-catalyzed one-pot cascade reaction between nitroolefins and 2-aminopyridine [Scheme 3, Eq. (5)].[21] However, efficient and straightforward strategies for constructing these scaffolds from simple, readly accessible and inexpensive materials are still highly attractive topics. Herein, we report the update study of CuI/BF_3·Et_2O/O_2-mediated reactions utilizing ketones with 2-aminopyridines for the construction of heteroaromatic imidazo[1,2-*a*]pyridines in one step.[22]

Our study was initiated by treating 1.0 equiv. acetophenone **1a** and 1.0 equiv. 4-methylpyridin-2-amine **2a** with CuI (20 mol%), BF_3·Et_2O (10 mol%) in the presecne of O_2 (O_2 balloon, 1 atm) under neat conditions at 40 °C for 24 h. To our delight, 7-methyl-2-phenylimidazo[1,2-*a*]pyridine **3a** was formed in 36% yield (GC yield). The structure of **3a** was confirmed by spectroscopic analysis and further confirmed by a single-crystal X-ray analysis.[23] This interesting one-step transformation to the heteroaromatic imidazo-[1,2-*a*]pyridines encouraged us to further screen different proportions, copper salts, solvents (see the Supporting Information), reaction temperature as well as additives. By screening the temperature, it was found that **3a** could be produced in 54% and 80% (GC yield) at room temperature and 60 °C, respectively (Table 1, entries 3and 4). It was noted that CuI showed higher catalytic reactivity than other copper salts such as CuBr and $Cu(OTf)_2$ for this reaction (Table 1, entries 6–8). The N,N-ligands such as 1,10-phenanthroline, 2,2′-bipyridine and 4,4′-di-*tert*-butyl-2,2′-bipyridine could improve the yields up to 60% (GC yield) (Table 1, entries 9–11). To our delight, **3a** could be obtained in 70% isolated yield (81% GC yield) (Table 1, entry 2) under catalysis by CuI (20 mol%) and BF_3·Et_2O (10 mol%) in the presecne of O_2 (O_2 balloon, 1 atm) under neat conditions at 40 °C, when the ratio of **1a** and **2a** was changed to 1:2.[24]

With the optimized conditions in hand, we further investigated the scope of this protocol. As presented in Table 2, a series of substituted imidazo[1,2-*a*]pyridines could be prepared directly from different ketones and 2-aminopyridines in moderate to good yields. products **3b** and **3c** could be obtained in 51% and 52% yields, when 2-aminopyridine was reacted with 1-(4-methoxyphenyl)ethanone **1b** and 1-(*p*-tolyl)-ethanone **1c**, respectively. Meanwhile, acetophenones with methyl substituents at the *ortho* and *meta* positions of the aromatic ring could react smoothly to afford the desired products **3d** and **3e** in moderate yields, respectively. The halogen-containing imidazo-[1,2-*a*]pyridines (**3g**, **3h**, **3i**, **3j**) could also be observed in good yields under the identical conditions, which opens the possibility for further functionalization. Moreover, when 1-[4-(trifluoromethyl)phenyl]ethanone **1m** bearing a strong electron-withdrawing group was subjected to this transformation, a good yield (72%) of the desired product **3m** was achieved as

Table 1. Optimization of the reaction conditions.

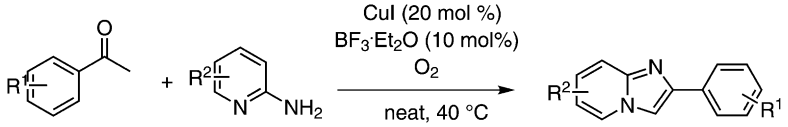


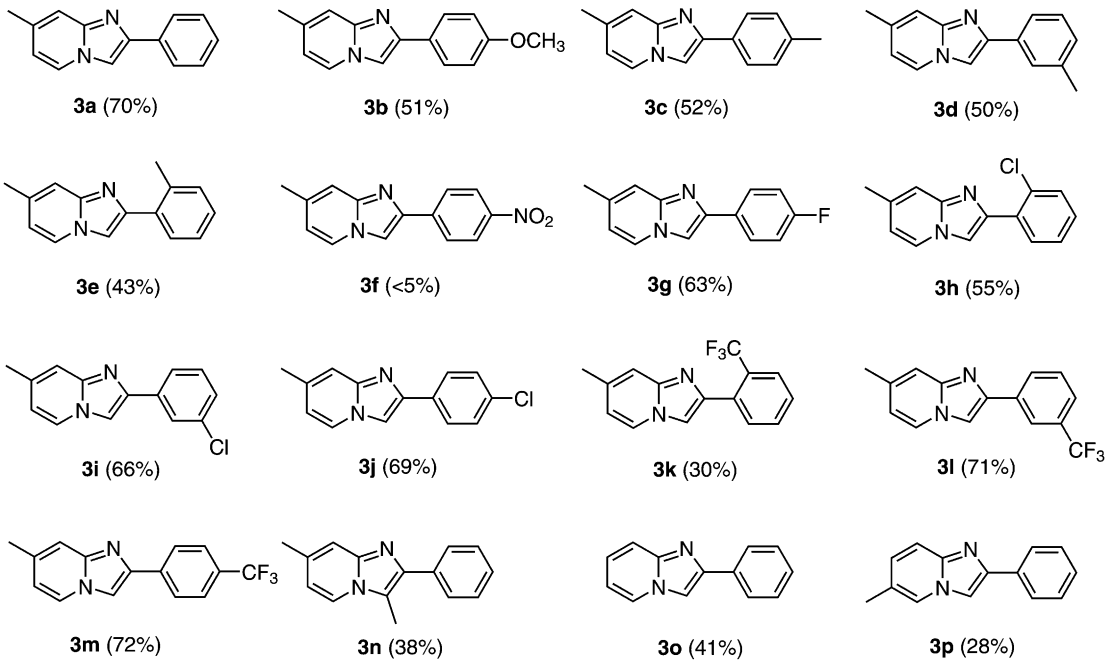
1a **2a** **3a**

Entry	**1a**:**2a**	Catalyst (mol%)	Additive (mol%)	Temperature [°C]	Yield [%][a]
1	1:1	CuI (20)	BF_3·Et_2O (10)	40	36
2	1:2	CuI (20)	BF_3·Et_2O (10)	40	81 (70)[b]
3	1:2	CuI (20)	BF_3·Et_2O (10)	r.t.	54
4	1:2	CuI (20)	BF_3·Et_2O (10)	60	80
5	1:2	CuI (10)	BF_3·Et_2O (10)	40	75
6	1:2	CuBr (20)	BF_3·Et_2O (10)	40	<5
7	1:2	$CuBr_2$ (20)	BF_3·Et_2O (10)	40	n.r.
8	1:2	$Cu(OTf)_2$ (20)	BF_3·Et_2O (10)	40	n.r.
9	1:2	CuI (20)	2,2′-bipyridyl (20)	40	60
10	1:2	CuI (20)	1,10-phenanthroline (20)	40	53
11	1:2	CuI (20)	4,4′-di-*tert*-butyl-2,2′-dipyridyl (20)	40	29

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

Table 2. Substrate scope for the reaction of ketones and 2-aminopyridines.[a]





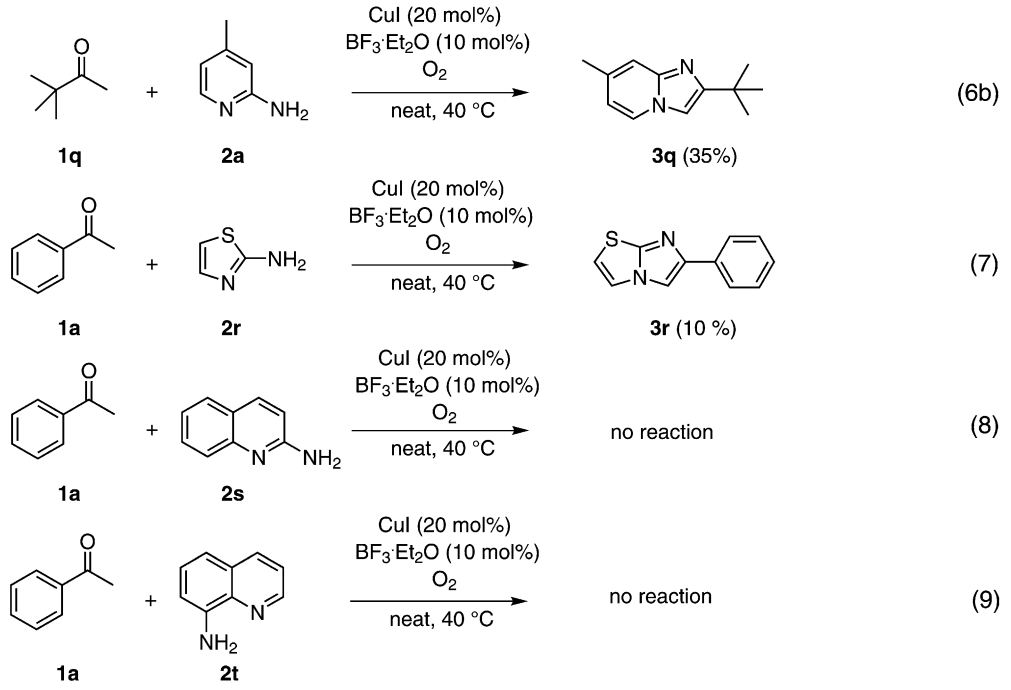
[a] *Reaction conditions:* **1** (2 mmol), **2** (6 mmol), CuI (20 mol%), $BF_3{\cdot}Et_2O$ (10 mol%), O_2 (1 atm), 40 °C, 24 h.

well. However, the reaction with 1-(4-nitrophenyl)-ethanone afforded the desired product **3f** in a poor yield. Notably, the reaction with propiophenone could also proceed to furnish the desired product **3n** in 38% isolated yield. In addition, when methyl was substitued at the 5-position of 2-aminopyridine, the transformation resulted in a lower yield (28%) due to the effect of steric hindrance.

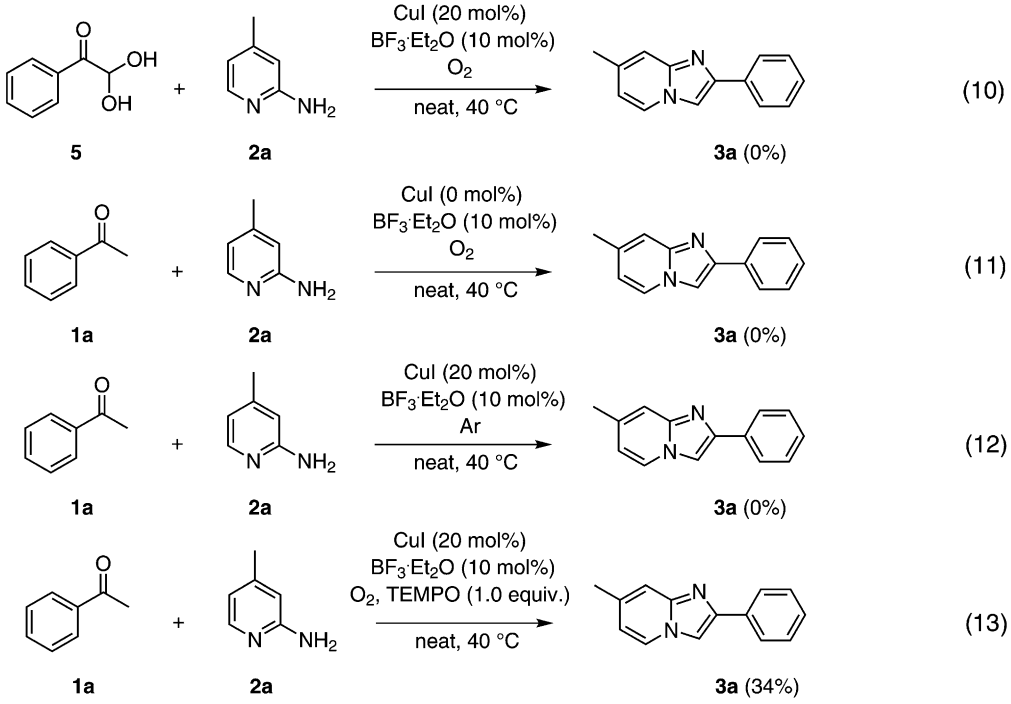
When the aliphatic ketone 3,3-dimethylbutan-2-one **1q** instead of **1a** was subjected to the reaction with **2a** under the optimized reaction conditions, the desired imidazole derivative **3q** could also be obtained in 35% yield [Scheme 4, Eq. (6b)]. However, when thiazol-2-amine was applied to this reaction instead of 2-aminopyridine, the corresponding 6-phenylimidazo-[2,1-*b*]thiazole could be isolated in 10% yield only [Scheme 4, Eq. (7)]. By the way, when quinolin-2-amine (**2s**) or quinolin-8-amine (**2t**) was treated with acetophenone (**1a**), respectively, under the optimized reaction conditions, we could not isolate any desired product [Scheme 4, Eqs. (8) and (9)].

Meanwhile, some control experiments were carried out in order to further understand the mechanism of the reactions (Scheme 5). When 2,2-dihydroxy-1-phenylethanone (**5**) instead of **1a** was treated with **2a** under the standard conditions, we could not isolate the desired **3a**, thus indicating that the 2,2-dihydroxy-1-phenylethanone (**5**) should not be a plausible intermediate for the reaction. Therefore, it would be an important factor which leads to the result that our reaction differs from that described by Wu and coworkers,[25] who reported the synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*]pyridines promoted by 1.5 equiv. I_2. Moreover, no desired **3a** was formed when the reaction of **1a** and **2a** was run under the modified conditions without CuI [Scheme 5, Eq. (11)]. Furthermore, the reaction of **1a** with **2a** under anatmosphere of argon was also investigated, and it failed to give **3a** [Scheme 5, Eq. (12)]. Interestingly, when 1.0 equiv. TEMPO was added to the reaction of **1a** and **2a** under the optimized conditions, it was found that **3a** could still be produced in 34% GC yield [Scheme 5, Eq. (13)].

Based on the results of control experiments and the works reported by Buchwald, Chiba, Hajra and others,[6,24] a plausible reaction mechanism for this transform is presented in Scheme 6. Enamine **4′** is formed *via* tautomerization of imine **4** from the con-



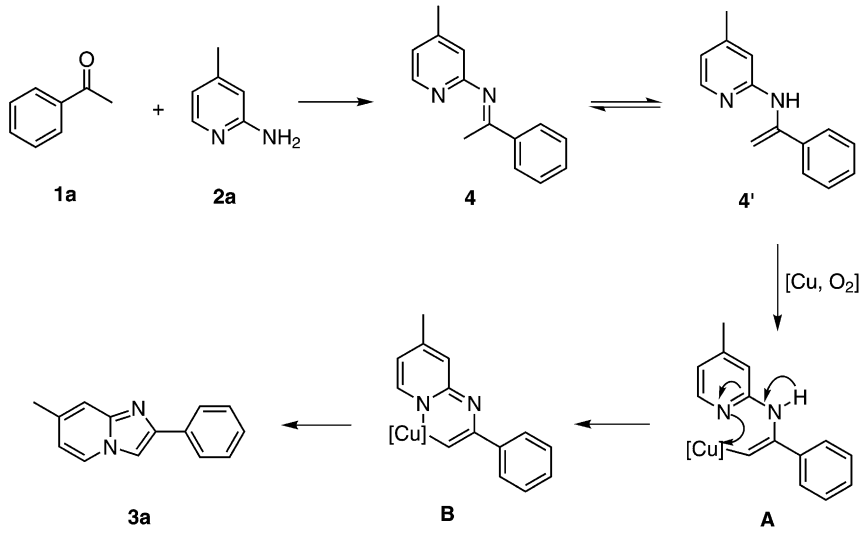
Scheme 4. Expanding experiments.



Scheme 5. Control experiments.

densation reaction of **1a** and **2a** in the presence of $BF_3{\cdot}Et_2O$. In the process of oxidative addition catalyzed by copper/O_2, enamine **4′** would be converted into **B** through the intermediate **A**. Finally, the desired product **3a** would be generated through the reductive elimination of **B**.

In summary, we have applied CuI/$BF_3{\cdot}Et_2O$-cocatalyzed aerobic dehydrogenative reactions to synthesis of imidazo[1,2-*a*]pyridines from readily available 2-aminopyridines and ketones through the oxidative C(sp^3)–H functionalization under mild conditions. Promoted only by copper species, diversified imidazo-



Scheme 6. A plausible mechanism.

[1,2-*a*]pyridines are generated in moderate to good yields through 2-aminopyridines reacting smoothly with various ketones. Oxygen showed high reactivity as an oxidative agent in this transform. This approach could open a new way to the synthesis of various imidazo[1,2-*a*]pyridines, which have potentially biological activities. Further studies about the construction of N-heterocycles *via* direct C–H amination catalyzed by the copper/O_2 system are currently underway in our laboratory.

Experimental Section

Typical Procedure for the Synthesis of 7-methyl-2-phenylimidazo[1,2-*a*]pyridine (3a)

A Schlenk tube equipped with a stirrer bar was charged with acetophenone (**1a**, 2 mmol, 0.2401 g), 4-methylpyridin-2-amine (**2a**, 6 mmol, 0.6424 g), CuI (0.4 mmol, 0.0759 g, 20 mol%), and $BF_3{\cdot}Et_2O$ (0.2 mmol, 0.0284 g). The Schlenk tube was quickly evacuated, closed under vacuum, and then refilled with oxygen using an oxygen balloon. The resulting mixture was stirred at 40 °C for 24 h. After the completion of reaction, the residue was directly purified by flash column chromatography using ethyl acetate and petroleum ether as eluents to afford the pure product **3a**.

Acknowledgements

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[23] For details see the Supporting Informantion.

[24] When the reaction was conducted with a highly pure copper iodide (99.9998% which was purchased from Sigma) under the standard conditions, **3a** could be obtained in 68% isolated yield, this is simliar to the result of entry 2 (Table 1) which would confirm the activity of CuI.

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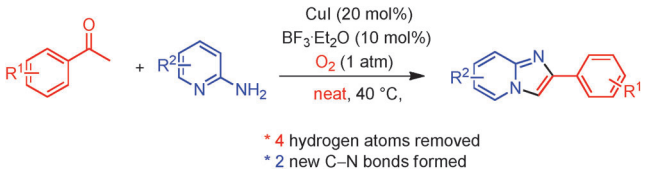
8 Copper(I) Iodide/Boron Trifluoride Etherate-Cocatalyzed Aerobic Dehydrogenative Reactions Applied in the Synthesis of Substituted Heteroaromatic Imidazo[1,2-*a*]pyridines



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