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Copper-Catalyzed Synthesis of Imidazo[1,2-*a*]pyridines through Tandem Imine Formation-Oxidative Cyclization under Ambient Air: One-Step Synthesis of Zolimidine on a Gram-Scale

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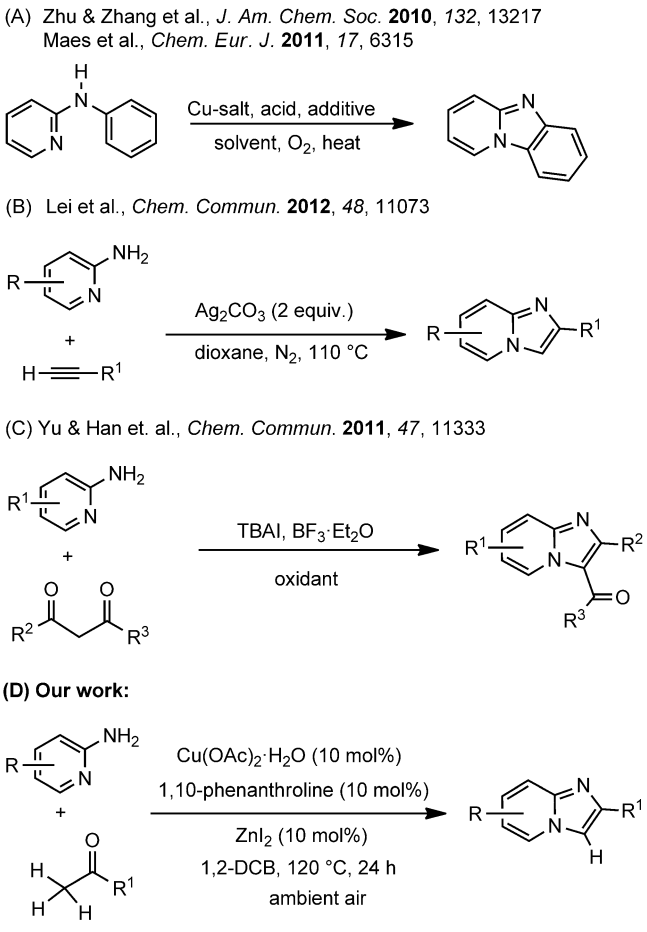
Abstract: A new copper-catalyzed oxidative cyclization *via* C–H amination between 2-aminopyridines and methyl aryl/heteroaryl ketones has been developed under ambient air. Imidazo[1,2-*a*]pyridines containing a wide range of functional groups have been synthesized from basic and easily available starting materials. This simple, one-pot reaction protocol is applicable for the direct preparation of zolimidine (a marketed antiulcer drug) on a large scale.

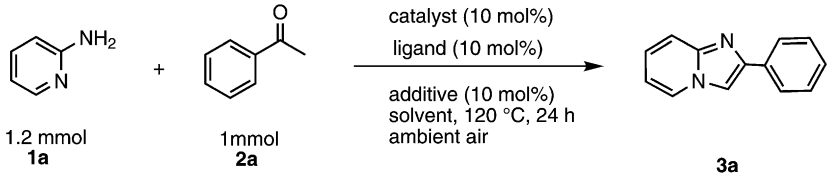
Keywords: ambient air; copper; cyclization; imidazo[1,2-*a*]pyridines; oxidative amination; zolimidine

The transition metal-catalyzed oxidative C–H bond amination has attracted great interest in recent times of synthetic organic chemists. Various priviledged heterocyclic scaffolds have been synthesized using inter- or intramolecular amination *via* C–H fuctionalization.[1] C–H functionalization and subsequently C–N bond formation is more preferable than the conventional synthetic methods due to atom efficiency and environmentally benign conditions.[2] Additionally, these types of reactions are very useful as the pre-functionalization of the substrate is not required, so avoiding the multistep synthesis, and contribute to changing the way chemists think about chemical reactivity and planning chemical syntheses. Direct C–N bond formation through C–H bond functionalization is commonly catalyzed by Pd[3] or Cu.[4] Many reagents such as TBHP, DTBP, $PhI(OAc)_2$, H_2O_2, O_2, *m*CPBA etc. are used as common oxidants among which O_2 is most preferable due to its inexpensive, inexhaustible and environmentally benign features. In this context, some efficient approaches have been developed employing less expensive copper catalysts and O_2 as the oxidant for the synthesis of biologically important moieties *via* oxidative couplings.[5] So the



Scheme 1. Synthetic strategies to imidazo[1,2-*a*]pyridines *via* oxidative C–H amination.

Table 1. Optimization of the reaction conditions.



Entry	Catalyst	Ligand	Additive	Solvent	Yield (%)[a]
1	$Cu(OAc)_2{\cdot}H_2O$	1,10-phenanthroline	—	DCB[b]	50
2	**$Cu(OAc)_2{\cdot}H_2O$**	**1,10-phenanthroline**	**ZnI_2**	**DCB**	**84**
3	$Cu(OAc)_2{\cdot}H_2O$	—	ZnI_2	DCB	60
4	$Cu(OAc)_2{\cdot}H_2O$	bipyridine	ZnI_2	DCB	78
5	$Cu(OAc)_2{\cdot}H_2O$	TMEDA[c]	ZnI_2	DCB	80
6	$Cu(OAc)_2{\cdot}H_2O$	DMEDA[d]	ZnI_2	DCB	82
7	$Cu(OAc)_2{\cdot}H_2O$	8-hydroxyquinoline	ZnI_2	DCB	75
8	$Cu(OAc)_2{\cdot}H_2O$	1,10-phenanthroline	ZnI_2	DMSO	70
9	$Cu(OAc)_2{\cdot}H_2O$	1,10-phenanthroline	ZnI_2	DMF	62
10	$Cu(OAc)_2{\cdot}H_2O$	1,10-phenanthroline	ZnI_2	toluene	65
11	CuI	1,10-phenanthroline	ZnI_2	DCB	75
12	CuBr	1,10-phenanthroline	ZnI_2	DCB	74
13	CuCl	1,10-phenanthroline	ZnI_2	DCB	70
14	$CuBr_2$	1,10-phenanthroline	ZnI_2	DCB	72
15	$CuCl_2$	1,10-phenanthroline	ZnI_2	DCB	64
16	$Cu(OTf)_2$	1,10-phenanthroline	ZnI_2	DCB	62
17	$Pd(OAc)_2$	1,10-phenanthroline	ZnI_2	DCB	66
18	$PdCl_2$	1,10-phenanthroline	ZnI_2	DCB	59

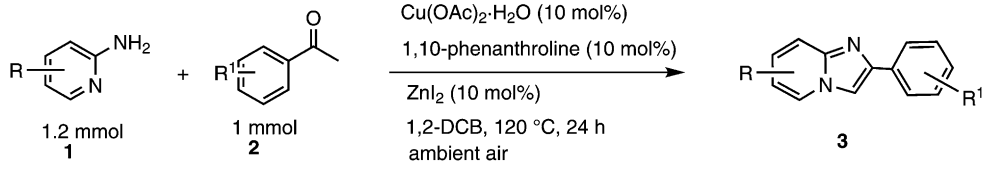
[a] Yields of isolated products.
[b] 1,2-Dichlorobenzene.
[c] Tetramethylethylenediamine.
[d] Dimethylethylenediamine.

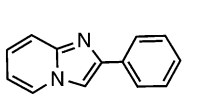
synthesis of biologically and medicinally active heterocyclic compounds using copper salts under aerobic conditions is an emerging field of organic synthesis in respect of economical as well as ecological points of view.

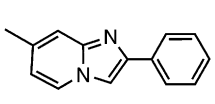
The imidazopyridine nuclei, in particular the imidazo[1,2-*a*]pyridines, constitute an important class of biologically active nitrogen-containing heterocycles and exhibit a wide range of biological activities.[6] Imidazo[1,2-*a*]pyridine scaffolds are present in a number of commercial drugs such as zolpidem,[7a] alpidem,[7a] olprinone,[7b] zolimidine,[7c] necopidem and saripidem.[7d] Some of these heterocyclic moieties display excited-state intramolecular proton transfer.[7e]

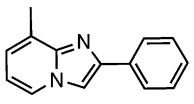
Considering their wide range of activities, the syntheses of imidazo[1,2-*a*]pyridines are getting much attraction in recent times. Various methods have been developed to construct the imidazo[1,2-*a*]pyridines.[8] A simple method is the condensation of 2-aminopyridines with α-halo ketones.[7e] Three-component coupling is also another way to construct these moieties.[8a] Recently, we have synthesized imidazo[1,2-*a*]pyridines by a tandem cyclization between 2-aminopyridine and nitroolefins.[8i] But only a few approaches are reported based on metal catalyzed C–H activation (Scheme 1, A and B).[9] However, although existing methods (*via* C–H activation) are quite useful, the construction of the imidazo[1,2-*a*]pyridine moiety through direct amination from readily available and simple starting materials employing inexpensive metal catalysts with environmentally benign oxidants is highly desirable. Although ketones having electron-withdrawing groups have been used previously (Scheme 1, C),[8g,h] simple acetophenones have not yet

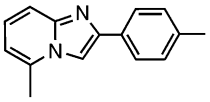
Table 2. Substrate scopes of aminopyridines.[a]

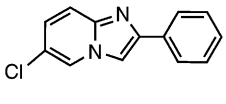


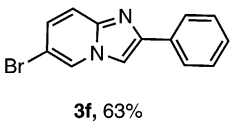

3a, 84%

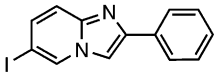

3b, 80%


3c, 81%


3d, 30%


3e, 60%


3f, 63%


3g, 69%

[a] Yields of isolated products.

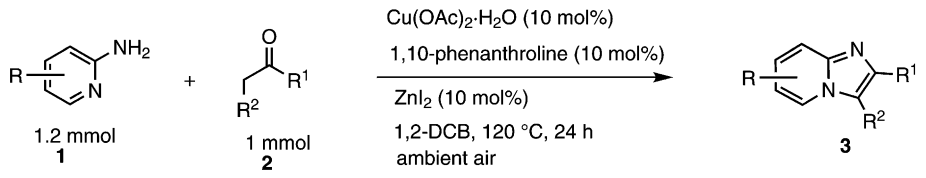
been explored as an oxidative coupling partner for intramolecular C–N bond formation/cyclization. Oxidative amination is quite feasible for β-keto esters/ketones due to the easy formation of enamines while it is not so easy for simple methyl aryl ketones due to the non-isolable enamine. Herein, we report a direct approach for the synthesis of imidazo[1,2-*a*]pyridines from readily available 2-aminopyridines and methyl aryl/heteroaryl ketones using a copper salt as the catalyst under aerobic conditions *via* oxidative C–H amination (Scheme 1, D).

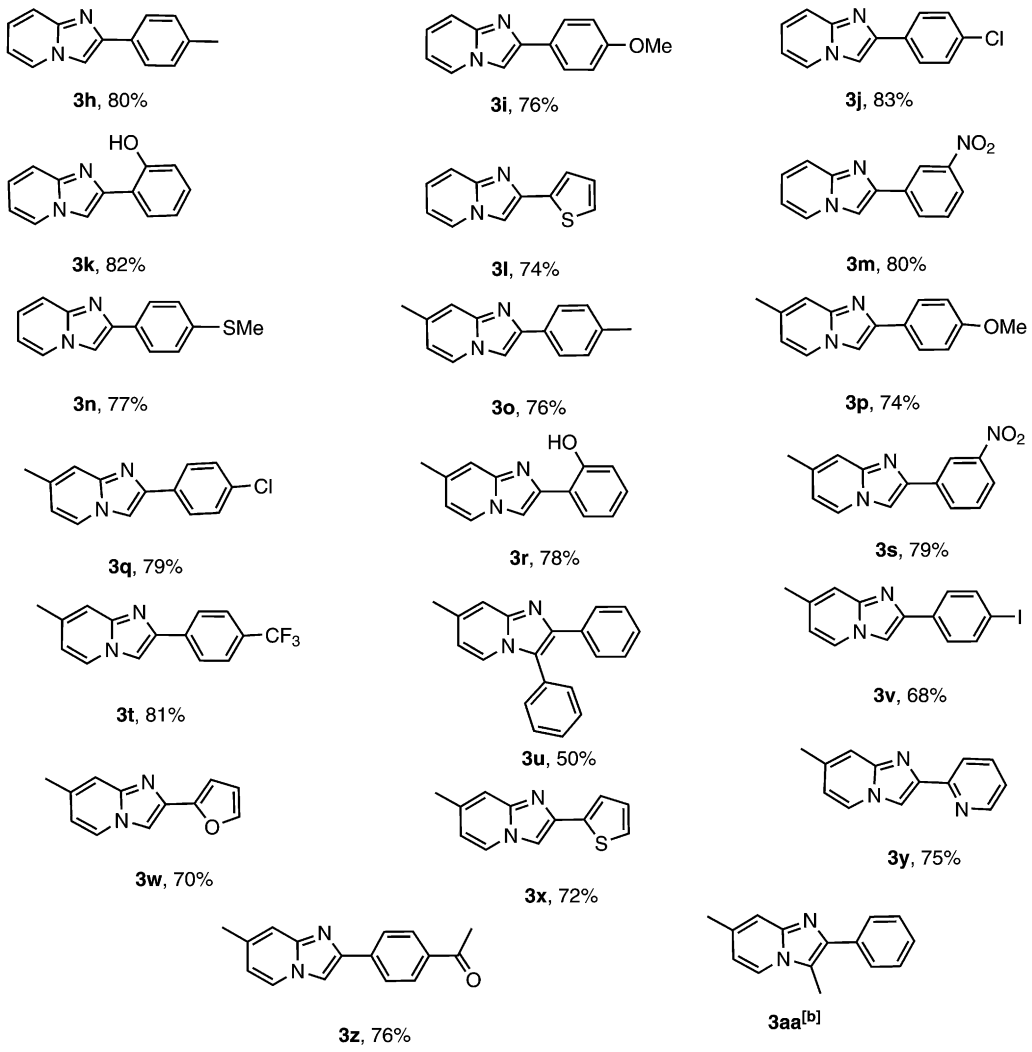
For the optimization of the reaction conditions, reaction between 2-aminopyridine **1a** and acetophenone **2a** was carried out using different metal catalysts and solvents (Table 1). Initially the reaction was performed using $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), 1,10-phenanthroline (10 mol%) in 1,2-dichlorobenzene at 120 °C under aerobic conditions (Table 1, entry 1) and a moderate yield (50%) was obtained under these conditions. To improve the yield a soft Lewis acid, ZnI_2 (10 mol%) was used as additive[11] (Table 1, entry 2) whereby an 84% isolated yield of desired product was obtained. In this context, it is worthy to mention that recently Nagasawa et al. reported oxidative coupling between 2-aminopyridines and benzonitriles where ZnI_2 was found to be a very effective additive for the cyclization.[11] Other additives such as $ZnCl_2$, molecular sieves, TBAB etc. were studied, but these are not so effective as ZnI_2. Ligands such as bipyridine, TMEDA, DMEDA, 8-hydroxyquinoline (Table 1, entries 4–7) produced lower yields. However, in the absence of any ligand (Table 1, entry 3) only 60% yields were obtained. Use of other common solvents such as DMSO, DMF, and toluene (Table 1, entries 8, 9 and 10) did not improve the yields. Various other copper catalysts like CuI, CuBr, CuCl, $CuBr_2$, $CuCl_2$, $Cu(OTf)_2$ (Table 1, entries 11–16) could catalyze the reaction also. However, palladium salts [$Pd(OAc)_2$, $PdCl_2$] were not so effective (Table 1, entries 17 and 18) and produced lower amounts of products. Thus a combination of $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), 1,10-phenanthroline (10 mol%), and ZnI_2 (10 mol%) in 1,2-dichlorobenzene at 120 °C was found to represent the optimized reaction conditions affording 84% isolated yield (Table 1, entry 2) under ambient air.

The scope and limitations of the optimized reaction conditions were examined by employing various 2-aminopyridines and acetophenone (Table 2). First, the effect of substituents on the 2-aminopyridine moiety was tested. Methyl substituents at 3- and 4-positions afforded high yields of the products (**3b**, **3c**). But with a methyl group at the 6-position on the pyridine ring the reaction proceeded sluggishly (**3d**). We were pleased to notice that under the stated conditions, aminopyridines substituted with halogens such as Cl, Br, I (**3e**, **3f**, and **3g**) smoothly reacted with acetophenone without forming any dehalogenated products. Further functionalization on imidazo[1,2-*a*]pyridine containing I and Br substituents could be possible *via* cross-coupling reactions.

Then our attention was turned to the use of substituted acetophenones as well as heteroaryl ketones to prove the general applicability of the reaction conditions. A library of imidazo[1,2-*a*]pyridines was synthesized by reacting aminopyridine with substituted ace-

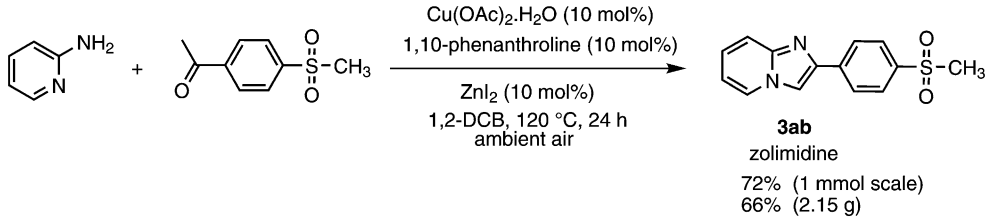
Table 3. Substrate scopes of ketones.[a]



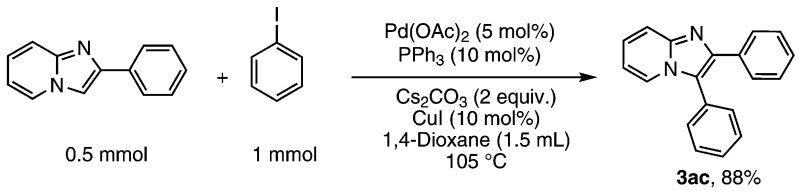


[a] Yield of isolated products.
[b] Inseparable mixture.

tophenones (Table 3). Acetophenones bearing electron-withdrawing as well as electron-donating groups afforded the corresponding imidazo[1,2-*a*]pyridines with high to excellent yields. Functional groups like Me (**3h**, **3o**), OMe (**3i**, **3p**), Cl (**3j**, **3q**), OH (**3k**, **3r**), NO_2 (**3m**, **3s**) were unaffected under the reaction conditions and the desired products were obtained in 74–83% yields. Interestingly, 4-iodoacetophenone also afforded the imidazo[1,2-*a*]pyridine (**3v**) in high yield. Heteroaryl ketones reacted well without accompanying self-condensation or ring cleavage (**3w**, **3x**, **3y**). An acetophenone containing a strong electron-withdrawing group such as CF_3 also produced the product (**3t**) with excellent yield. 1,4-Diacetylbenzene reacted only with one equivalent aminopyridine to afford the product (**3z**) having an unreacted acetyl group. 2-Hydroxyacetophenone on reaction with 2-aminopyridine afforded the product (**3k**) which displays excited-state intramolecular proton transfer (ESIPT).[7e] 4′-(Methylthio)acetophenone produced the corresponding imidazo[1,2-*a*]pyridine (**3n**) which is a precursor of the drug zolimidine.[9c] 2-Phenylacetonephenone af-



Scheme 2. One-pot synthesis of zolimidine.



Scheme 3. Functionalization of 3-unsubstituted imidazopyridine.

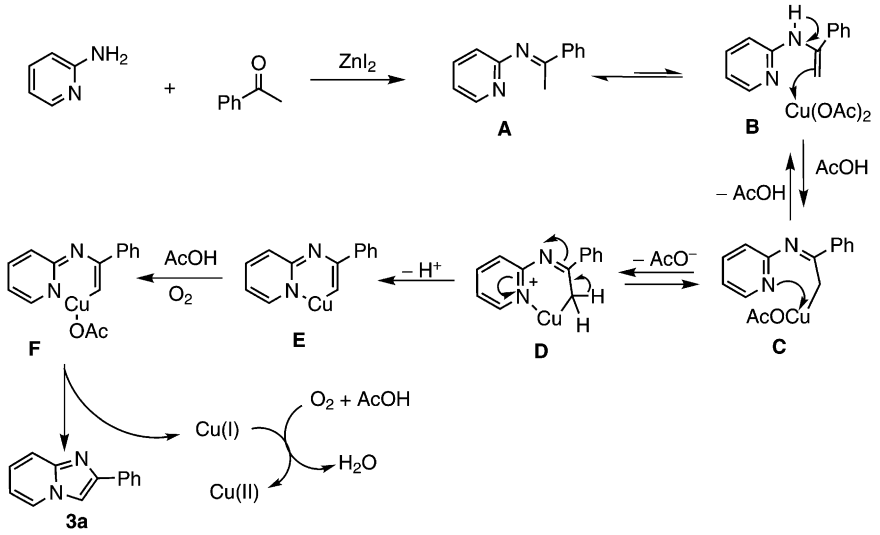
forded 2,3-disubstituted imidazo[1,2-*a*]pyridine (**3u**) in moderate yield. However, propiophenone produced an inseparable mixture of products (**3aa**).

A most important achievement of our protocol is the synthesis of the marketed drug zolimidine (an antiulcer drug) in one-pot (Scheme 2). Reaction between 2-aminopyridine and commercially available 4′-(methylsufonyl)acetophenone produced zolimidine in a single step with 72% yield. The preparation of the drug is also applicable on the gram-scale affording 66% of isolated product.

Further functionalization has been carried out to construct the highly substituted imidazo[1,2-*a*]pyridines through C–H activation employing a modified method (Scheme 3).[10] The reaction proceeded very well affording high yields.

Although detailed experimental evidence is still pending, a probable mechanism is shown in Scheme 4. Initially, imine **A** is formed by the reaction of aminopyridine and acetophenone under the present reaction conditions. The imine after tautomerization to enamine **B** reacted with $Cu(OAc)_2$ to form the adduct **C**[12] which is readily converted into the intermediate **D**.[9a,11] Intermediate **D** [Cu(II)] is converted into **E** which is then oxidized to the reactive intermediate **F** [Cu(III)].[13] The intermediate **F** afforded the product **3a** through reductive elimination along with Cu(I) species which is oxidized by the aerobic oxygen to complete the catalytic cycle.

In summary, we have developed a copper-catalyzed direct oxidative cyclization *via* C–H amination between 2-aminopyridines and methyl aryl/heteroaryl ketones under ambient air. A library of functionalized



Scheme 4. Probable reaction mechanism.

imidazo[1,2-*a*]pyridines has been synthesized from basic and easily available starting materials. Operational simplicity, less expensive metal catalyst, aerobic reaction conditions and tolerance of a wide range of functional groups make this reaction a highly practical and reliable method. This one-pot simple reaction protocol has been utilized for the direct preparation of zolimidine, a marketed antiulcer drug on a large scale. We believe that our findings will gain much importance in synthetic community. Further study to explore the mechanistic path of this oxidative transformation is currently ongoing in our laboratory.

Experimental Section

Typical Procedure for Synthesis of 2-Phenylimidazo-[1,2-*a*]pyridine (3a)

A mixture of 2-aminopyridine (**1a**, 1.2 mmol), acetophenone (**2a**, 1 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), 1,10-phenanthroline (0.1 mmol) and ZnI_2 (0.1 mmol) in 1,2-dichlorobenzene (2 mL) was stirred at 120 °C for 24 h under ambient air. After cooling the reaction mixture, it was filtered and washed with dichloromethane. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent.

Acknowledgements

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