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Cu(I)-Catalyzed Transannulation of *N*-Heteroaryl Aldehydes or Ketones with Alkylamines via C(sp^3)−H Amination

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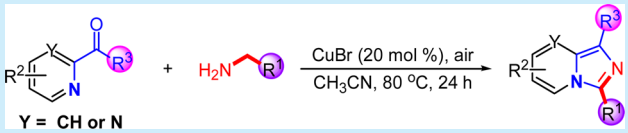
Supporting Information

ABSTRACT: A copper(I)-catalyzed direct transannulation of *N*-heteroaryl aldehydes or ketones with alkylamines via C_{sp^3}−H amination has been achieved using molecular oxygen as a sole oxidant. *N*-Heteroarenes are employed as the amine source. This transformation provides a rapid and concise access to multifunctional imidazo[1,5-*a*]pyridines.



A transition-metal-catalyzed direct C−H amination strategy has attracted extensive attention due to its atom and step economy.[1] Recently, remarkable progress has been achieved based on C(sp^2)−H bond activation/amination to form C(sp^2)−N bonds.[2] Meanwhile, more challenging metal-catalyzed unactivated C(sp^3)−H aminations via nitrene insertion,[3] as well as a C(sp^3)−H activation/C−N coupling process,[4] pioneer another unique access to site-selectively construct C−N bonds on a C_{sp^3} atom. In this regard, several major amino sources including arylamines and aliphatic amines,[4b] amides,[4a,c,5] azides,[4d,6] haloamines, etc.[7] have been extensively investigated for constructing the C(sp^3)−N bond using transition-metal catalysts. However, employing *N*-heteroarenes as amino sources to couple with the C(sp^3) atom via metal-catalyzed C(sp^3)−H amination is rarely reported,[8] although this strategy potentially results in the rapid assembly of structurally diverse *N*-heterocycles which commonly occur in synthetic molecules.

Imidazo[1,5-*a*]pyridine nuclei belong to an important class of building blocks in both material chemistry and pharmaceutical industry.[9] Based on the traditional Vilsmeier-type protocol,[10] alternative synthetic methods have been successfully developed to construct imidazo[1,5-*a*] *N*-heterocycles in which an excess amount of activating reagents such as iodine, S_8, etc. were employed.[11] Therefore, the development of an atom-economic synthetic method for these *N*-heteroarenes is in strong demand. Recently, Zhu reported that a Cu(II)-catalyzed direct intramolecular C−N formation reaction of *N*-aryl-2-aminopyridines via C(sp^2)−H activation/amination could efficiently construct pyrido[1,2-*a*]benzimidazoles using *N*-heterarenes as amino sources.[2b] Inspired by this work, and in combination with our continuing efforts to explore efficient reactions starting from imines to rapidly construct *N*-heterocycles,[12] we expect that a

Scheme 1. Cu(I)-Catalyzed Direct C_{sp^3}−H Amination

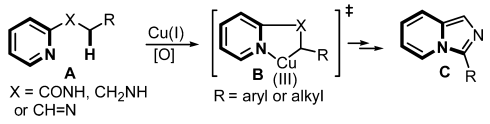
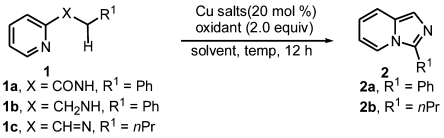


Table 1. Optimization of the Reaction Parameters[a]



entry	pyridines	Cu salts	oxidant	solvent	yield (%)[b]
1	**1a**	CuOAc	air	EtOAc	**2a**, nr[c]
2	**1b**	CuOAc	air	EtOAc	**2a**, trace
3	**1c**	CuOAc	air	EtOAc	**2b**, 8
4	**1c**	CuCl	air	EtOAc	**2b**, 28
5	**1c**	CuBr	air	EtOAc	**2b**, 47
6	**1c**	CuI	air	EtOAc	**2b**, 25
7	**1c**	CuCN	air	EtOAc	**2b**, 25
8	**1c**	$Cu(OAc)_2$	air	EtOAc	**2b**, nr[c]
9	**1c**	$CuBr_2$	air	EtOAc	**2b**, nr[c]
10	**1c**	CuBr	O_2	EtOAc	**2b**, 64
11	**1c**	CuBr	Ar	EtOAc	**2b**, nr[c]
12	**1c**	CuBr	MnO_2	EtOAc	**2b**, nr[c]
13	**1c**	CuBr	AgOAc	EtOAc	**2b**, nr[c]
14	**1c**	CuBr	BQ	EtOAc	**2b**, <5
15	**1c**	CuBr	air	toluene	**2b**, 22
16	**1c**	CuBr	air	CH_3CN	**2b**, 75
17	**1c**	CuBr	air	CH_3CN	**2b**, nr[c,d]
18	**1c**	CuBr	air	CH_3CN	**2b**, 31[e]
19	**1c**	CuBr	air	CH_3CN	**2b**, 56[f]
20	**1c**	CuBr	air	CH_3CN	**2b**, 81[g]

[a]Unless otherwise noted, all the reactions were carried out using pyridines (**1**) (0.10 mmol) and oxidant (0.20 mmol) with a Cu catalyst (20 mol %) in solvent (2.0 mL) at 80 °C for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield. [c]nr = no reaction. [d]60 °C of reaction temperature. [e]100 °C of reaction temperature. [f]10 mol % of CuBr was used. [g]**1c** was generated in situ by using 0.1 mmol of *n*-$BuNH_2$ and 0.1 mmol of 2-formylpyridine as starting material under standard conditions.

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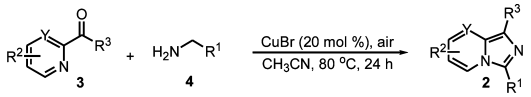
Table 2. Cu(I)-Catalyzed Sequential One-Pot Synthesis of Imidazo[1,5-*a*]pyridines *via* C(sp^3)−H Amination[a]



3 + 4 → 2

entry	heteroarene **3**	amine **4**	product **2**	yield (%)[b]
1	**3a**	**4a**	**2a**	85
2	**3b**	**4a**	**2c**	80
3	**3c**	**4a**	**2d**	68
4	**3d**	**4a**	**2e**	63
5	**3e**	**4a**	**2f**	67
6	**3f**	**4a**	**2g**	87
7	**3g**	**4a**	**2h**	42
8	**3i**	**4a**	**2i**	74
9	**3a**	**4b**	**2j**	72
10	**3a**	**4c**	**2k**	77
11	**3a**	**4d**	**2l**	52
12	**3a**	**4e**	**2m**	58
13	**3a**	**4f**	**2n**	66
14	**3a**	**4g**	**2o**	83
15	**3a**	**4i**	**2p**	71
16	**3a**	**4j**	**2q**	74
17	**3a**	**4k**	**2r**	77
18	**3a**	**4l**	**2s**	nr[c]
19	**3a**	**4m**	**2t**	42
20	**3a**	**4n**	**2u**	56
21	**3a**	**4o**	**2v**	62

[a]All the reactions were carried out using aldehyde (**3**) (0.10 mmol) and amine (**4**) (0.10 mmol) with the CuBr catalyst (10 mol %) in CH_3CN (2.0 mL) at 80 °C for 24 h under air in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield. [c]nr = no reaction.

metallcyclic species (**B**) could be possibly formed via alkyl C(sp^3)−H activation using pyridine derivative **A** as starting material and also could be oxidized to the high oxidation state of species **B** which will result in the formation of heterocycles **C** through reductive elimination if additional coupling partners such as alkynes, arylboronic acids, etc. are avoided in reaction systems (Scheme 1).[12c] To identify this hypothesis, herein we describe a novel Cu(I)-catalyzed C(sp^3)−H amination using *N*-heteroarenes as an amino source to construct an imidazo[1,5-*a*] *N*-heterocyclic skeleton under atmospheric oxygen.

Initially, we tried to design and synthesize 2-substituted pyridines including **1a**, **1b**, and **1c** which contain various linking spacers X (X = CONH, CH_2NH, and CH═N) to investigate the effect of substrate type on the CuOAc-catalyzed intramolecular C_{sp^3}−H amination in ethyl acetate (2.0 mL) at 80 °C for 12 h under an air atmosphere (Table 1, entries 1−3), and we quickly found butyl-pyridin-2-ylmethylene amine **1c** could afford an 8% yield of the desired imidazo[1,5-*a*]pyridine **2b** (entry 3). Although the yield of **2b** is too low, this positive result stimulated us to further optimize the reaction conditions for achieving satisfying yields. Then, we employed **1c** as a model substrate to investigate the effect of various copper salts on this transformation. Among the tested copper catalysts (entries 3−9), Cu(I) salts, especially CuBr, afforded an improved **2b** yield (entry 5, 47% yield). In contrast, Cu(II) salts such as $Cu(OAc)_2$ and $CuBr_2$ could not provide the desired target product **2b**. Subsequently, the reaction conditions were further optimized by screening a series of oxidants and various solvents, and we found the CuBr/air/CH_3CN reaction system could afford a 75% yield of **2b** at 80 °C for 12 h (entries 10−16). Notably, poorer

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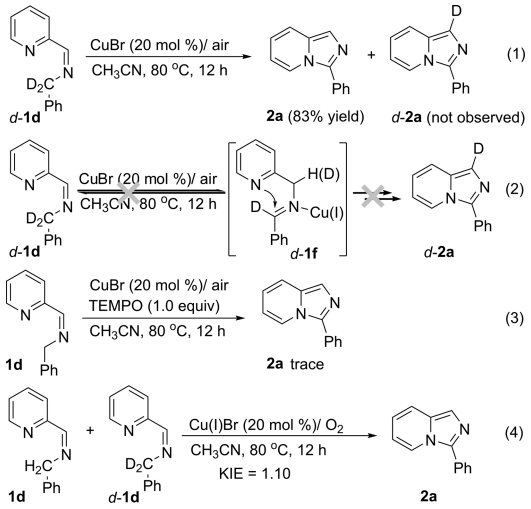
conversions of **2b** were observed when lowering and increasing the reaction temperature to 60 and 100 °C, respectively (compare entries 17 and 18 with 16), and employing 10 mol % of the CuBr catalyst also resulted in a lower yield (56% yield; compare entry 19 with 16). Finally, the best yield (81% yield of **2b**) was obtained by directly using 0.1 mmol of *n*-$BuNH_2$ and 0.1 mmol of 2-formylpyridine as starting material which led to the in situ formation of **1c** under optimized conditions (compare entry 20 with 16).

On the basis of these promising screening results, we next investigated the scope of the current procedure by testing various pyridine derivatives and amines via the Cu(I)-catalyzed one-pot C(sp^3)−H amination/cyclization. First, different substitutions at the 5-position of 2-formylpyridine **3** was examined in the C(sp^3)−H amination reaction with benzylamine **4a**. As summarized in Table 2, electron-donating groups such as a 5-methyl group facilitated the reaction and led to an 80−85% yield of the imidazo[1,5-*a*]pyridine (entries 1 and 2). In contrast, changing the substituted groups from 5-methyl to the electron-withdrawing 5-CO_2Et, 5-Cl, and 5-Br group resulted in an ∼15% decrease in yield (compare entries 3−5 with 2). In addition, other *N*-heteroaryl aledhydes such as 2-quinolinecarbaldehyde **3f** and 2-formylpyrimidine **3i** also exhibited excellent reactivity and could furnish quinoline derivatives **2g** and **2j** in excellent yields (entries 6 and 9). Gratifyingly, when we attempted to use the 2-pyridyl ketones as substrates under our reaction conditions, we found this transformation tolerated phenyl-pyridin-2-yl-methanone (**3g**), which could be smoothly converted to the corresponding 1,3-disubstituted imidazo[1,5-*a*]pyridines **2h** in 42% yield (entry 7).

Subsequently, we further examined the scope of amines that participate in this C(sp^3)−H amination with 2-formylpyridine **3a**. The results in Table 2 show that this protocol tolerated a variety of electron-rich and -poor benzylamines (**4a**−**4f**); common functional groups on the benzene rings including an alkyl, hydroxyl, halogen, and trifluoromethyl group were all compatible with this transformation and gave moderate to good yields of the desired imidazo[1,5-*a*]pyridines (entries 9−13). Moreover, various aliphatic amines also allowed for this transformation and afforded the corresponding 3-alkyl-imidazo[1,5-*a*]-pyridines in good yields (71−83% yield, entries 14−17), regardless of whether the steric hindrance of the alkyl groups [such as $Ph(CH_2)_3$, isobutyl, etc.] is large or not (compare entries 14 and 17 with 16). Most importantly, the present C(sp^3)−H amination method could be successfully applied to a wide range of heteroarylmethylene amines (**4m**, **4n**, and **4o**) which could be readily employed to construct the corresponding 3-(2-pyridyl), 3-(2-furyl), and 3-(2-thienyl)-substituted imidazo-[1,5-*a*]pyridines (**2t**, 42% yield; **2u**, 56% yield; **2v**, 62% yield) in moderate yields (entries 19−21). Unfortunately, the reactivity of the electron-deficient cyanomethylene amine **4l** was observed to be very low and did not produce the desired *N*-heteroarene **2s** (entry 18).

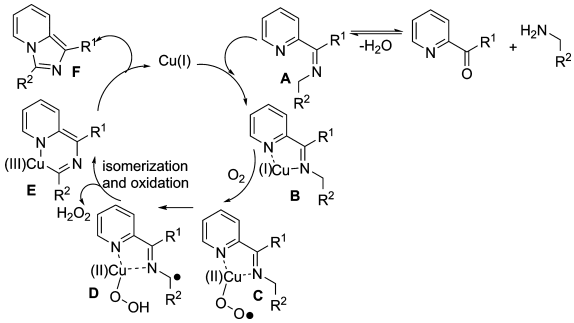
To further investigate the primary mechanism of the present Cu(I)-catalyzed C(sp^3)−H amination, several controlled reactions were carried out. First, employing deuterated pyridine derivative *d*-**1d** as starting material under our reaction conditions only furnished an 83% yield of **2a**; no deuterated *d*-**2a** was observed by ^{1}H NMR and GC-MS methods (Scheme 2, eq 1). This fact ruled out the possibility that imine *d*-**1d** could be isomerized to *d*-**1f** via 1,3-H shift under CuBr/air/CH_3CN system, and then Cu(I) salts enhanced this transformation via a Lewis acid catalyzed nucleophilic addition/oxidation cascade

Scheme 2. Preliminary Mechanistic Studies



(eq 2). Next, addition of 1.0 equiv of TEMPO to the CuBr/air reaction system remarkably inhibited the intramolecular C(sp^3)−H amination of **1d** (eq 3), revealing that radical intermediates were possibly involved in this reaction. Finally, the intramolecular isotope effect (K_H/K_D = 1.10) further indicated that the C(sp^3)−H bond breaking was not the rate-limiting step of the reaction (eq 4). Based on the above observations and relevant reactions regarding the Cu(I)−dioxygen catalytic system,[13] we depict a plausible catalytic cycle in Scheme 3. The

Scheme 3. Proposed Catalytic Cycle



transformation is first triggered by the coordination of the Cu(I) ion with the pyridine N-atom and imine N-atom from **A**, which could enable the [Cu(II)−O−O·] **C** formation from Cu(I) **B** under an oxygen atmosphere.[14] Subsequently, the corresponding Cu(II)-superoxo radical **C** would abstract the intramolecular H atom from the coordinated imine to produce Cu(II) intermediate **D**,[13c] which could be further led to the formation of a six-membered Cu(III) species **E** via isomerization/oxidation processes. Finally, the reductive elimination of Cu(III) intermediate **E** led to the formation of imidazo[1,5-*a*]pyridine **F** with regeneration of the Cu(I) catalyst.[15]

In conclusion, we have developed the first Cu(I)-catalyzed direct C_{sp^3}−H amination of 2-acylpyridines with aliphatic amines to construct multifunctional imidazo[1,5-*a*]pyridines[16] via a one-pot tandem process employing aerial oxygen as the green oxidant, in which *N*-heteroarenes were used as amine sources. This transformation is compatible with electron-rich or -poor 2-acylpyridines and aliphatic amines. More detailed mechanistic studies and further applications of this transformation in the synthesis of complex molecules are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Analytical data for all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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