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Modular Pyridine Synthesis from Oximes and Enals through Synergistic Copper/Iminium Catalysis

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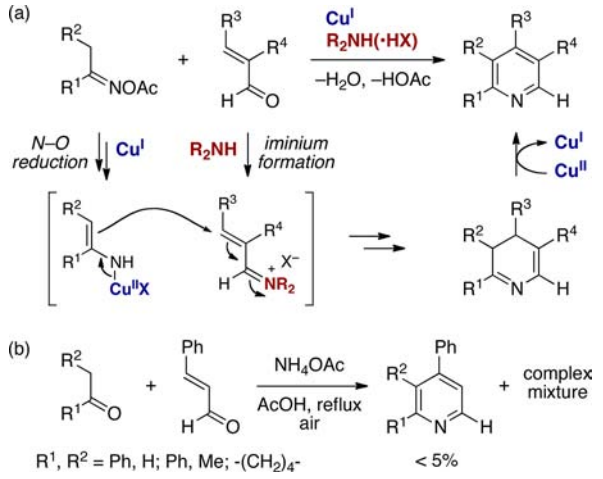
Supporting Information

ABSTRACT: We describe here a [3+3]-type condensation reaction of *O*-acetyl ketoximes and α,β-unsaturated aldehydes that is synergistically catalyzed by a copper(I) salt and a secondary ammonium salt (or amine). This redox-neutral reaction allows modular synthesis of a variety of substituted pyridines under mild conditions with tolerance of a broad range of functional groups. The reaction is driven by a merger of iminium catalysis and redox activity of the copper catalyst, which would initially reduce the oxime N−O bond to generate a nucleophilic copper(II) enamide and later oxidize a dihydropyridine intermediate to the pyridine product.

Synergistic catalysis has attracted increasing interest in the field of chemical synthesis because it potentially enables a previously unknown type of transformation or provides a known reaction with unprecedented efficiency or chemo-, regio-, and stereoselectivity.[1a] Among various catalyst combinations, the combination of transition metal and organic catalysts is attractive, where the complementary modes of substrate activation could lead to diverse transformations.[1] In particular, the combination of transition metal and secondary amine catalysts has been extensively practiced in carbonyl α-functionalizations, where enamine catalysis is merged with various modes of electrophile activation with transition metal catalysts.[2] In comparison, the use of secondary amines for metal/iminium synergistic catalysis has thus far been limited to asymmetric conjugate addition of silicon, boron, and carbon nucleophiles to α,β-unsaturated aldehydes, where the organometallic nucleophiles are activated uniformly through transmetalation.[3] Here, we report on a copper(I)/secondary amine-catalyzed [3+3]-type condensation reaction of *O*-acetyl oximes and enals that features a unique merger of iminium catalysis and redox copper catalysis, allowing modular synthesis of a variety of substituted pyridines under mild conditions (Scheme 1a). The copper catalyst presumably plays roles (1) to reduce the oxime N−O bond[4,5] and generate a nucleophilic copper(II) enamide, and (2) to oxidize a dihydropyridine intermediate to the pyridine product. As such, the overall transformation is redox-neutral and produces water and acetic acid as the only byproducts.

The development of the present condensation reaction was conceived originally from our need for a convenient method for preparing pyridine derivatives for other purposes.[6] While oxidative condensation of a ketone, an enal, and ammonia

Scheme 1



appeared straightforward, in our hands, reactions of simple ketones such as acetophenone, propiophenone, and cyclohexanone with cinnamaldehyde and ammonium acetate all failed to afford the desired pyridine products in more than 5% yield but produced complex mixtures (Scheme 1b). This was not at all surprising, because the scope of the classical pyridine synthesis based on carbonyl condensation is severely limited due to the difficulty in controlling multiple reaction steps, such as imine/enamine formation and Michael addition, while suppressing many undesirable competing pathways.[7,8] We reasoned that this intrinsic difficulty might be removed by preinstalling a nitrogen atom as well as an internal oxidant in the reactant instead of using a ketone, an ammonia source, and an external oxidant separately.

With the above conjecture and the ability of copper(I) to reduce oxime N−O bonds,[4,5] we chose acetophenone *O*-acetyl oxime **1a** and cinnamaldehyde **2a** as model substrates and screened copper salts and other reaction conditions (Table 1).[9] With only CuI (20 mol %), the reaction in DMSO at 60 °C produced 2,4- and 2,6-diphenylpyridines **3aa** and **3aa′** in low yield (11%) with a ca. 1:1 ratio (entry 1). The addition of pyrrolidinium perchlorate (20 mol %) dramatically accelerated the reaction and improved the regioselectivity, affording **3aa** as the sole product in 78% yield (entry 2). Similar effects were observed with ammonium salts of piperidine, morpholine, and

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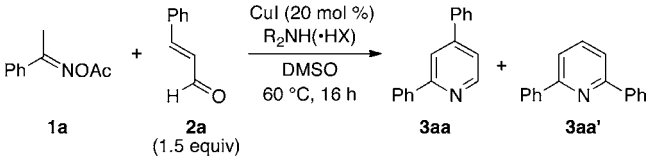
Table 1. Screening of Reaction Conditions[a]



entry	$R_2NH(\cdot HX)$	GC yield (%)[b]	3aa:3aa′[b]
1	none	11	53:47
2	pyrrolidine·$HClO_4$ (20 mol %)	78[c]	>99:1
3	piperidine·$HClO_4$ (20 mol %)	46	>99:1
4	morpholine·$HClO_4$ (20 mol %)	65	>99:1
5	$Et_2NH\cdot HClO_4$ (20 mol %)	72	>99:1
6	$iPr_2NH\cdot HClO_4$ (20 mol %)	8	>99:1
7[d]	pyrrolidine·$HClO_4$ (20 mol %)	0	–
8	pyrrolidine (20 mol %)	23	>99:1
9[d]	pyrrolidine (2 equiv)	1	>99:1
10	iPr_2NH (20 mol %)	55	>99:1
11	iPr_2NH (2 equiv)	91[c]	99:1

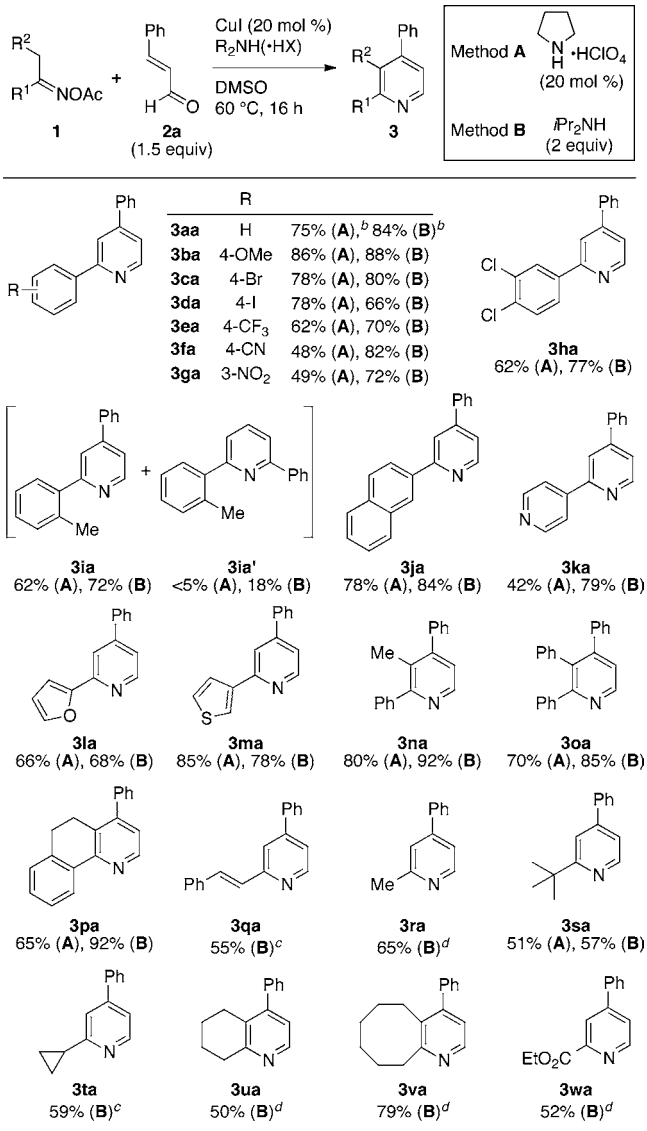
[a]Reaction was performed on a 0.2 mmol scale. [b]Determined by GC using *n*-tridecane as an internal standard. [c]Isolated yield. [d]CuI was omitted from the reaction.

Et_2NH (entries 3–5), while the ammonium salt of iPr_2NH was not very effective (entry 6). The ammonium salt alone did not catalyze the reaction (entry 7). Among other copper salts, CuBr·SMe_2 showed a comparable catalytic activity, while $Cu(OAc)_2$ and CuOTf were less effective.[9]

Upon further examination, we noted that pyrrolidine itself was not a very effective cocatalyst (entry 8). The use of 2 equiv of pyrrolidine almost completely shut down the reaction (entry 9). In contrast, iPr_2NH, in its neutral form, showed a significant positive effect, affording **3aa** in 55% and 91% yield with 20 mol % and 2 equiv loadings, respectively (entries 10 and 11). We speculate that coordination of pyrrolidine to the copper catalyst killed its catalytic activity, while bulky iPr_2NH did not cause such interference. Note that the use of *O*-pentafluorobenzoyl oxime or free oxime instead of **1a** resulted in a lower yield or no reaction, respectively.

Based on the above optimization study, we defined the methods using pyrrolidinium salt (20 mol %) and iPr_2NH (2 equiv) as methods A and B, respectively, and explored their scope in the condensation of various oximes with **2a** (Table 2). A variety of oximes derived from aryl methyl ketones participated in the reaction with both of the methods, affording the corresponding 2,4-disubstituted pyridines **3aa**–**3ma**, with tolerance of functional groups, including bromo, iodo, cyano, and nitro groups as well as pyridine, furan, and thiophene heterocycles. The reaction of the parent acetophenone oxime **1a** could be scaled up to 10 mmol scale without a problem. While most of the oximes exclusively afforded the 2,4-disubstituted pyridines, reaction of the oxime derived from 2′-methylacetophenone was accompanied by the 2,6-disubstituted isomer **3ia′**. Oximes derived from other aryl ketones such as propiophenone, 2-phenylacetophenone, and tetralone afforded the products **3na**–**3pa**, respectively, in good yields. The difference in the scope of methods A and B became clear upon further exploration. Thus, oximes derived from benzylideneacetone, acyclic and cyclic aliphatic ketones, and ethyl pyruvate afforded the pyridine derivatives **3qa**–**3wa** in moderate to good yields with method B, while method A was much less effective (<20% yield except for **3sa**).

Table 2. Condensation of Various Oximes with Cinnamaldehyde



[a]Unless otherwise noted, the reaction was performed on a 0.2 mmol scale. [b]10 mmol scale. [c]Method A afforded ca. 20% yield (GC). [d]Method A afforded less than 10% yield (GC).

We next explored the scope of α,β-unsaturated aldehydes (Table 3). As was the case with cinnamaldehyde, β-aryl enals were amenable to the condensation reaction using both methods A and B, affording 2,4-diarylpyridines **3ab**–**3ae**, **3bf**, **3bg**, and **3ah** in good yields. Method B showed a better performance than method A in the reaction of methacrolein (see **3pi**), and also allowed acrolein to take part in the reaction, albeit in a modest yield (see **3pj**). In contrast, β-alkyl and α,β-disubstituted enals exclusively produced the expected pyridine derivatives **3pk** and **3pl**, respectively, with method A, while substantial amounts of their regioisomers were observed with method B (see the Supporting Information). α,β-Unsaturated ketones such as benzylideneacetone and chalcone reacted rather sluggishly with both methods A and B, affording the corresponding pyridine products in less than 5% yield.

Control experiments supported the intermediacy of an iminium ion in the present reaction (with method A). Thus, the reaction of **1a** and iminium salt **4a** (1.5 equiv) derived from

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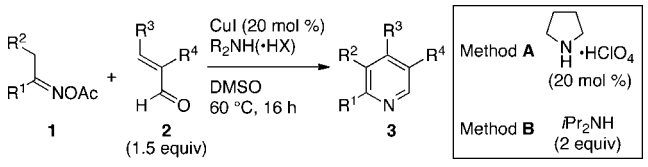
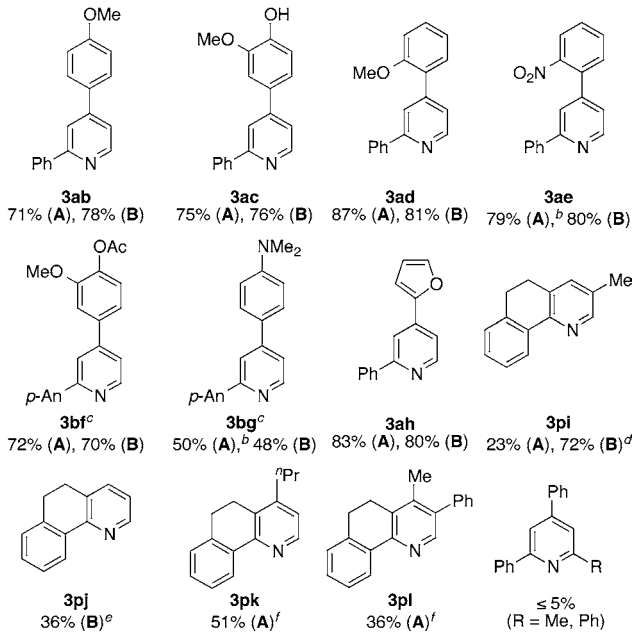
Table 3. Condensation with Various Enals[a]

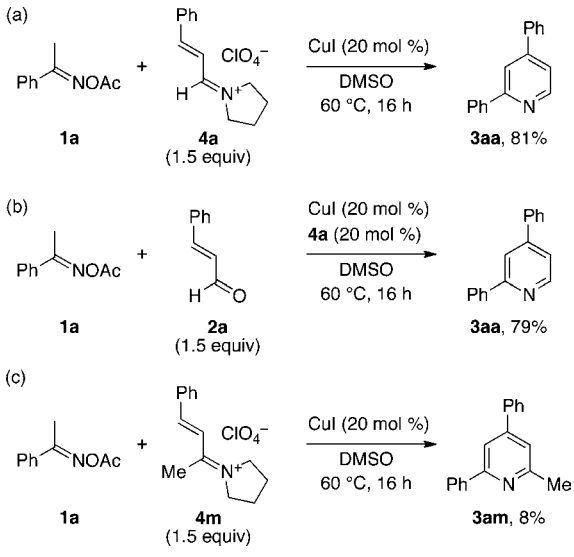




[a]The reaction was performed on a 0.2 mmol scale. [b]40 mol % of CuI was used. [c]*p*-An = 4-MeOC$_6$H$_4$. [d]2 equiv of methacrolein was used. [e]5 equiv of acrolein was used. Not examined with method A. [f]3 equiv of enal was used. Method B produced a mixture of regioisomers (see the Supporting Information).

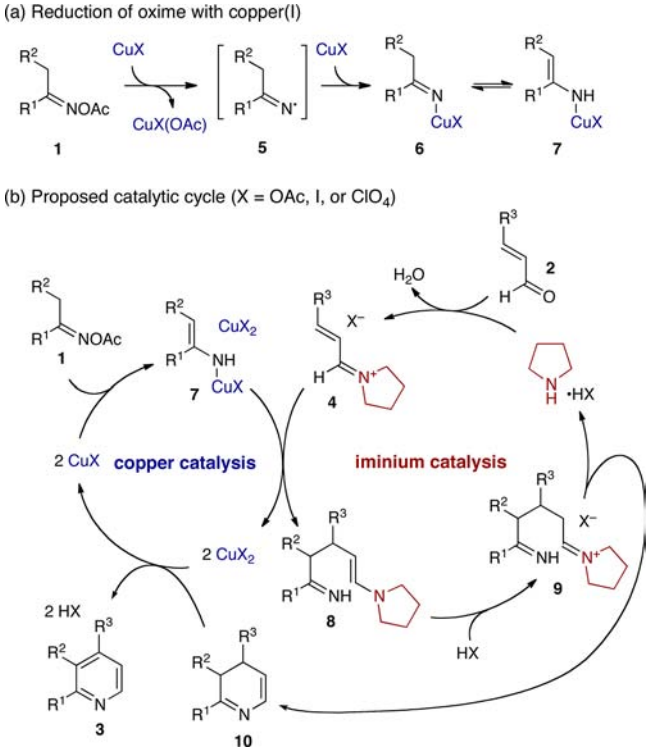
cinnamaldehyde and pyrrolidine, in the presence of 20 mol % CuI, afforded **3aa** in 81% yield (Scheme 2a). No pyridine product was obtained in the absence of CuI. Iminium salts derived from piperidine and morpholine also participated in the reaction, albeit in lower yields (57% and 55%, respectively). In addition, the iminium salt **4a** served as a cocatalyst for the condensation of **1a** and **2a**, affording **3aa** in 79% yield (Scheme 2b). Note that the reaction of the iminium salt of benzylideneacetone (**4m**) was rather sluggish (Scheme 2c), which was consistent with the poor reactivity of enones in the present reaction (vide supra). Unfortunately, the same control experiments could not be performed for the reaction with method B because attempts to prepare the corresponding isolated iminium salt of *i*Pr$_2$NH were unsuccessful with conventional and other methods.[10]

Scheme 2. Control Experiments Using Iminium Salt



It is natural to assume that the oxime and the copper catalyst give rise to a nucleophilic reaction partner for the iminium ion. On the basis of previous studies on copper catalysis of oxime derivatives,[4,5d,e] we consider that oxime **1** and CuI produce an iminylcopper(II) species **6** through a sequential single-electron reduction of the N−O bond (Scheme 3a).[11] Tautomerization

Scheme 3. (a) Possible Pathway for the Activation of Oxime with Copper(I) Catalyst and (b) Proposed Mechanism Involving Copper(I)/Iminium Catalysis



of **6** would then give a copper(II) enamide **7**,[5e,12] which would serve as a nucleophile toward the iminium ion. With this speculation, we formulate a possible mechanism as illustrated in Scheme 3b for the reaction with method A. Michael addition of **7** to the iminium ion **4** produces an enamine intermediate **8**,[13] which is then protonated to give an iminium ion **9**. Deaminative cyclization of **9** affords dihydropyridine **10** and regenerates the ammonium catalyst. Oxidation of **10** with copper(II) furnishes the pyridine product **3** along with acetic acid (HX), while regenerating the copper(I) catalyst. Thus, the synchronized and intersecting copper and iminium catalytic cycles represent a signature of synergistic catalysis.[1a] The formation of the pyridine regioisomer **3′** (see Table 2, **3ia′**) may result from Michael addition of the N atom of **7** (or **6**) to **4** (see Scheme S1 in the Supporting Information).

We speculate that the reaction with method B also involves the same type of iminium activation mechanism. The much

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improved reactivity with iPr$_2$NH than with its ammonium salt (see entries 6 and 10 in Table 1) may suggest that the concentration of neutral amine is more crucial than that of active proton for the formation of an iminium ion from this bulky and less nucleophilic secondary amine.

In summary, we have successfully combined the redox activity of copper and the iminium activation strategy to construct pyridines from *O*-acetyl oximes and α,β-unsaturated aldehydes. With the operational simplicity, modularity, and functional group compatibility, the present reaction has substantially expanded the scope of pyridine derivatives accessible from readily available carbonyl compounds. Furthermore, in light of the accessible substitution patterns, the present method not only effectively complements other existing and emerging methods for pyridine synthesis[14−18] but also enables, in combination with methods for the direct functionalization of the pyridine core,[19] the construction of a diverse array of polysubstituted pyridines. Further improvement and extension of this synergistic catalysis are currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and characterization data. 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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