A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201704378
Angew. Chem. 10.1002/ange.201704378

Link to VoR: http://dx.doi.org/10.1002/anie.201704378
http://dx.doi.org/10.1002/ange.201704378

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Angewandte Chemie International Edition 10.1002/anie.201704378

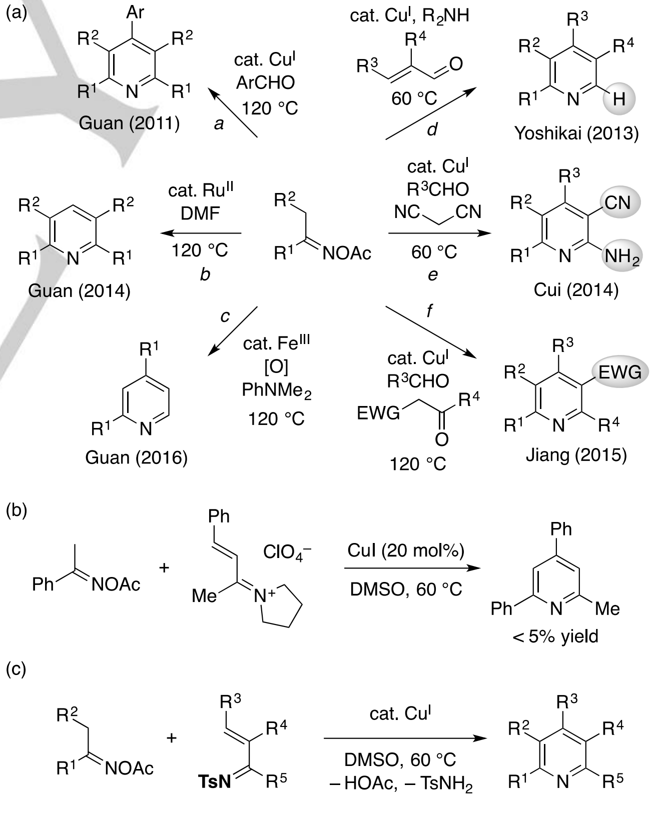
Synthesis of Highly Substituted Pyridines via Copper-Catalyzed Condensation of Oximes and α,β-Unsaturated Imines**

Wei Wen Tan, Yew Jin Ong, and Naohiko Yoshikai*[a]

Abstract: A copper-catalyzed condensation reaction of oxime acetates and α,β-unsaturated ketimines into pyridine derivatives is reported. The reaction features mild conditions, high functional group compatibility, and high regioselectivity with respect to unsymmetrical oxime acetates, thus allowing for the preparation of a wide range of polysubstituted pyridines, many of which are not readily accessible by conventional condensation methods.

The pyridine ring frequently occurs as a core structural element in natural products and synthetic pharmaceuticals and plays pivotal role in coordination chemistry, catalysis and materials science. Consequently, the development of methods for the efficient and regioselective of this compound class has been among significant tasks in heterocyclic chemistry.[1] Besides conventional methods based on the condensation of carbonyl compounds and amines, a number of alternative approaches, those catalyzed by transition metals in particular, have been actively pursued to date.[2-4]

In the above context, oxime derivatives have emerged as readily accessible and versatile starting materials for transition metal-catalyzed synthesis of pyridines[5,6] as well as many other nitrogen-containing heterocycles owing to the ability of the oxime functionality to undergo reductive N–O bond cleavage[7-9] and/or to serve as a directing group for C–H activation.[10,11] While α,β-unsaturated oxime derivatives have been employed as C3N1 units for pyridine synthesis using alkenylboronic acids,[5a] alkynes,[5b-e] or alkenes[5f,g] as C2 reaction partners, oxime acetates bearing α-protons have also found a use as C2N1 units for pyridine synthesis (Scheme 1a).[6] Guan and coworkers developed a series of metal-catalyzed pyridine-forming reactions wherein two molecules of oxime acetates are condensed with a C1 source such as aldehyde, dimethylformamide, and dimethylaniline (Scheme 1a, *a*–*c*).[6a-c] Our group developed a [3 + 3] pyridine synthesis from oxime acetates and α,β-unsaturated aldehydes promoted synergistically by a copper catalyst and a secondary amine (Scheme 1a, *d*).[6d] Later, Cui and Jiang independently reported copper-catalyzed three-component pyridine synthesis from oxime esters, aldehydes, and active methylene compounds such as malononitrile or β-ketoesters (Scheme 1a, *e* and *f*).[6e,f] The methods *d*–*f* are considered to involve the reaction between a nucleophilic copper(II) enamide formed via reduction of the oxime acetate by copper(I) and an activated Michael acceptor formed via carbonyl–amine condensation or Knoevenagel condensation, and are attractive for the preparation of unsymmetrically substituted pyridines. However, this approach does not allow the use of ordinary unactivated enones, which substantially limits the accessible substitution patterns of pyridines. In fact, even a preformed iminium salt derived from an enone failed to participate in our previous pyridine-forming reaction (Scheme 1b). In our effort to remove this limitation, we have developed a copper-catalyzed pyridine synthesis from oxime acetates and α,β-unsaturated ketimines, which is reported herein (Scheme 1c). The method features simple and mild reaction conditions and allows regioselective synthesis of a broad range of multisubstituted pyridines, including those not readily accessible by conventional condensation approaches.



Scheme 1. Oximes as C2N1 units for pyridine synthesis.

Given the failure of enones as substrates for the copper/secondary amine catalytic system,[6d] the present study initially focused on the exploration of enone equivalents for the condensation with oxime acetates. Screening experiments along this line led to the finding of clean transformation of propiophenone oxime acetate (**1a**, 0.24 mmol, 1.2 equiv) and

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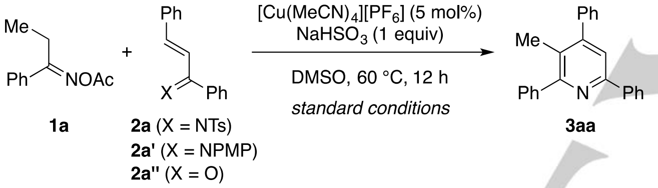
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) chalcone *N*-tosyl imine (**2a**, 0.2 mmol) into the desired tetrasubstituted pyridine **3aa** in the presence of [Cu(MeCN)$_4$][PF$_6$] (5 mol%) and NaHSO$_3$ (1 equiv) in DMSO at 60 °C (Table 1, entry 1). The same reaction could be performed on a 5 mmol scale in 95% yield. Note also that the reaction proceeded quantitatively even under air using undistilled DMSO. Other copper salts could be used in place of the cationic catalyst, albeit with somewhat lower yields of **3aa** (entries 2–4). The yield of **3aa** dropped significantly in the absence of NaHSO$_3$ (entry 5).[12] The reaction became sluggish when using DMF instead of DMSO as the solvent (entry 6). Notably, chalcone *N*-PMP (*p*-methoxyphenyl) imine (**2a'**) also participated in the condensation with **1a** under otherwise identical conditions to afford **3aa**, albeit in a moderate yield (entry 7). This reaction was further improved by increasing the catalyst loading and the reaction temperature to 10 mol% and 90 °C, respectively (entry 8). In contrast, the reaction using parent chalcone (**2a''**) afforded only a trace amount of **3aa** (entry 9). Note that the reaction of **2a'**, when performed using a large excess (> 2 equiv) of **1a**, was accompanied by homocoupling of **1a** to produce 2,5-diphenyl-3,4-dimethylpyrrole as a byproduct,[9c] while this homocoupling was not observed at all in the optimized reaction systems (entries 1 and 8).

Table 1. Effect of reaction conditions.[a]

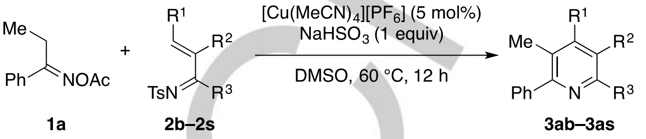


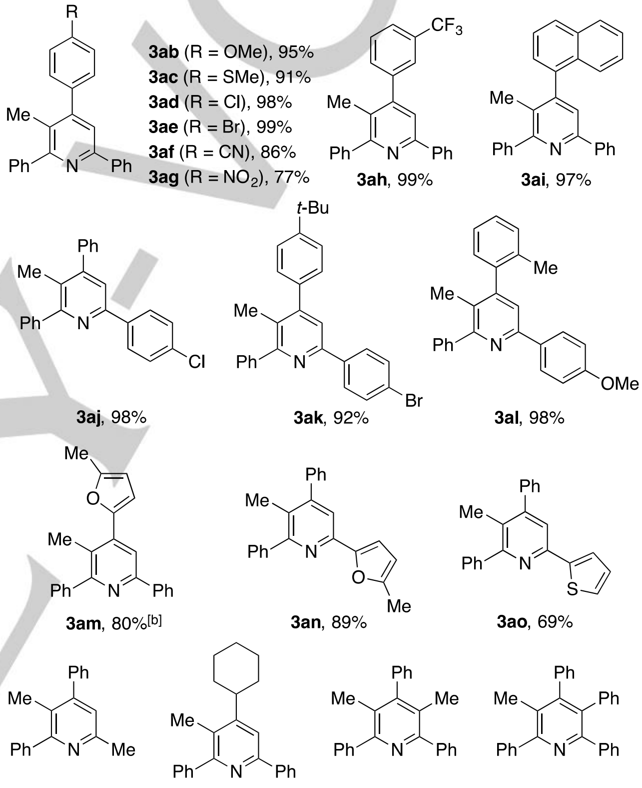
Entry	X	Deviation from standard conditions	Yield [%][b]
1	NTs	None	99 (95)[c]
2	NTs	CuCl instead of [Cu(MeCN)$_4$][PF$_6$]	84
3	NTs	CuBr instead of [Cu(MeCN)$_4$][PF$_6$]	85
4	NTs	CuI instead of [Cu(MeCN)$_4$][PF$_6$]	84
5	NTs	NaHSO$_3$ omitted	10
6	NTs	DMF instead of DMSO	68
7	NPMP	None	75
8	NPMP	10 mol% catalyst, *T* = 90 °C	87
9	O	None	< 5

[a] The reaction was performed using 0.24 mmol (1.2 equiv) of **1a** and 0.2 mmol of **2a** under N$_2$ atmosphere. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. The result for a 5 mmol-scale reaction is shown in the parentheses.

Having identified the viable enone equivalent and the optimal reaction conditions, we explored the scope of the present pyridine synthesis. Table 2 summarizes the results of condensation of **1a** with a variety of unsaturated ketimines. Unsaturated imines derived from substituted chalcones smoothly participated in the reaction with **1a**, affording the desired pyridines **3ab**–**3al** in good to excellent yields with tolerance of functional groups such as methylthio, bromo, cyano, nitro, and trifluoromethyl groups. The reaction also tolerated unsaturated ketimines bearing furyl, thienyl, or alkyl substituents (see **3am**–**3aq**). A pentasubstituted pyridines **3ar** and **3as** could also be synthesized via the condensation of **1a** and the corresponding α,β-disubstituted unsaturated ketimines.

Table 2. Condensation of **1a** with various α,β-unsaturated ketimines.[a]



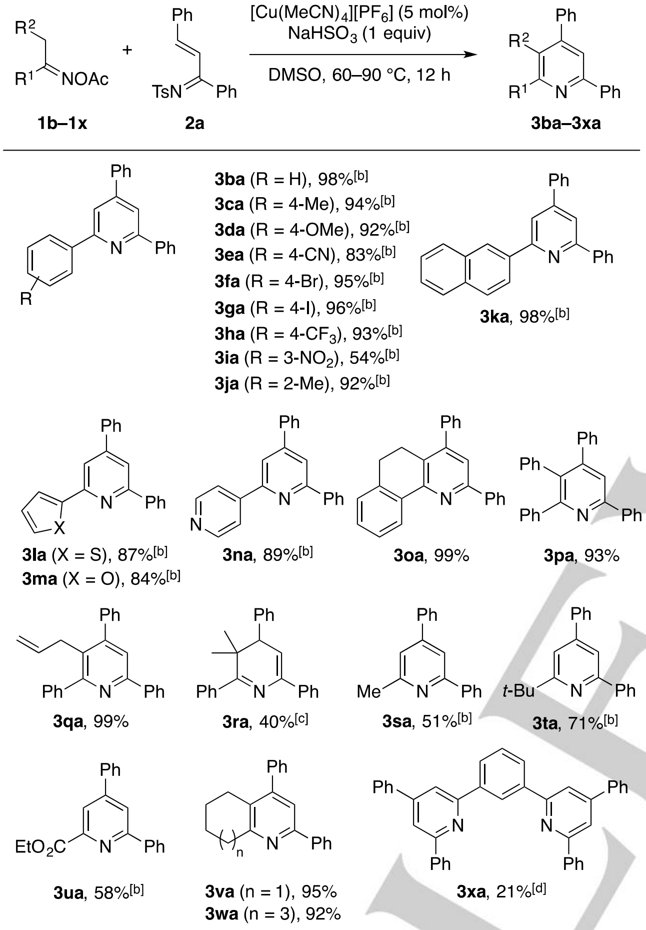


3ab (R = OMe), 95%
3ac (R = SMe), 91%
3ad (R = Cl), 98%
3ae (R = Br), 99%
3af (R = CN), 86%
3ag (R = NO$_2$), 77%
3ah, 99%
3ai, 97%
3aj, 98%
3ak, 92%
3al, 98%
3am, 80%[b]
3an, 89%
3ao, 69%
3ap, 63%[b]
3aq, 55%
3ar, 52%
3as, 44%[c]

[a] Unless otherwise noted, the reaction was performed under the conditions in Table 1, entry 1. [b] N-PMP imine was employed, and the reaction was performed under the conditions in Table 1, entry 8. [c] The reaction was performed at 90 °C.

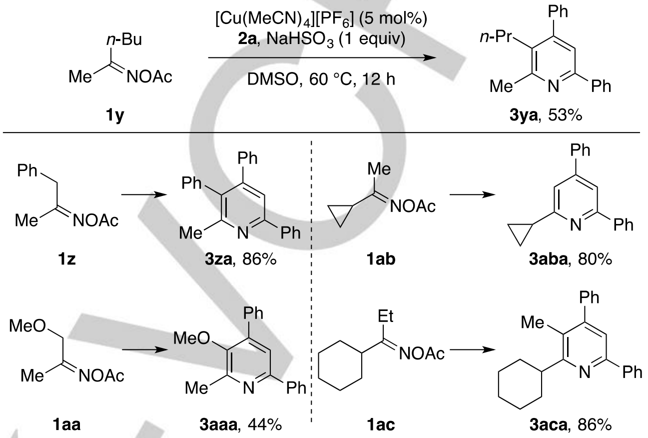
Next, we examined the reaction of various oxime acetates bearing only one type of enolizable α-position, using **2a** as the reaction partner (Table 3). The reaction of acetophenone-derived oxime acetate **1b** was somewhat sluggish under the conditions optimized for **1a**, affording 2,4,6-triphenylpyridine (**3ba**) in 76% yield. Nevertheless, the reaction could be improved by increasing the equivalence of **1b** (1.6 equiv) and the reaction temperature (90 °C), resulting in the formation of **3ba** in near quantitative yield. This modified set of conditions proved highly reliable for efficient preparation of a series of 2,4,6-triarylpyridines using oximes derived from aryl methyl ketones (see **3ba**–**3na**). Aryl alkyl oximes derived from tetralone, 2-phenylacetophenone, and phenyl 3-butenyl ketone smoothly took part in the reaction with **2a** under the original conditions, affording the desired products **3oa**–**3qa** in excellent yields. Interestingly, oxime derived from isobutyrophenone afforded 3,4-dihydorpyridine derivative **3ra** as a result of C–C bond formation at the tertiary carbon center, albeit in a modest yield. Besides the aryl alkyl oximes, oximes derived from acetone, pinacolone, ethyl pyruvate, and cycloalkanones were all amenable to the present condensation (see **3sa**–**3wa**). A bis-oxime derived from 1,3-diacetylbenzene participated in twofold condensation with **2a** to afford the pyridine product **3xa** albeit in a low yield.

Table 3. Condensation of various oxime acetates with **2a**.[a]



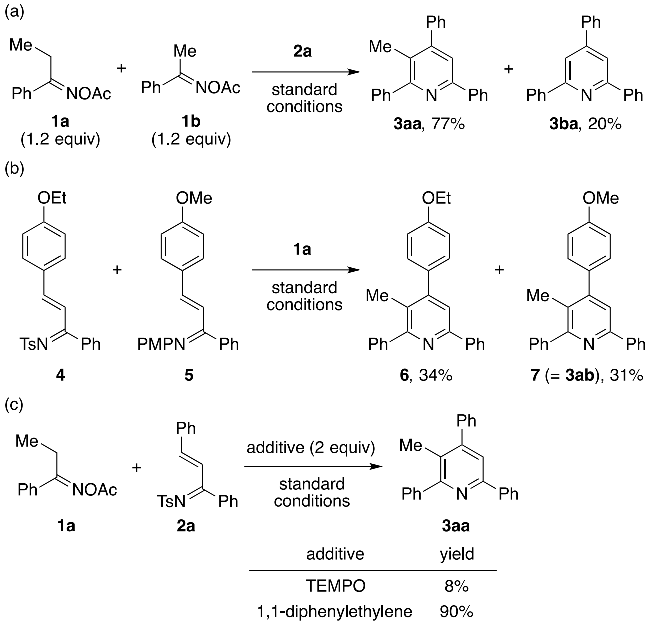
[a] Unless otherwise noted, the reaction was performed under the conditions shown in Table 1, entry 1. [b] The reaction was performed using 1.6 equiv of oxime at 90 °C. [c] Oxime acetate derived from isobutyrophenone was used. [d] Oxime acetate derived from 1,3-diacetylbenzene and 2 equiv of **2a** were used at 90 °C.

To further clarify the scope of the present pyridine synthesis, we examined the reaction of a series of oxime acetates that have two distinct enolizable α-positions (Scheme 2). The reaction of oxime derived from 2-hexanone with **2a** resulted in C–C bond formation at the α-position of the butyl group to afford tetrasubstituted pyridine **3ya** in 53% yield, while formation of the other possible regioisomer was not detected. Likewise, oximes derived from phenylacetone and methoxyacetone also underwent regioselective C–C bond formation at the methylene position to afford the corresponding products **3za** and **3aaa**, respectively, while the one derived from cyclopropyl methyl ketone produced 2,4,6-trisubstituted pyridine **3aba** via C–C bond formation at the methyl group. The regioselectivity observed in these reactions may be associated with the thermodynamic stability of the copper enamide intermediates (vide infra). On the other hand, oxime derived from cyclohexyl ethyl ketone afforded tetrasubstituted pyridine **3aca** in good yield via regioselective C–C bond formation at the ethyl group.



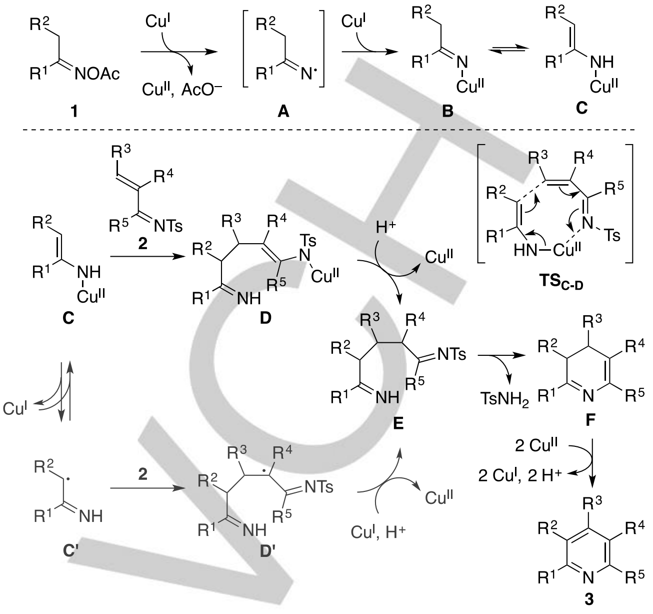
Scheme 2. Regioselective formation of pyridine derivatives from oximes bearing two distinct α-positions. See the Supporting Information for the detail of the reaction conditions.

To gain mechanistic insight, competition and control experiments were performed (Scheme 3). First, a competition between propiophenone oxime **1a** and acetophenone oxime **1b** toward **2a** resulted in preferential reaction of **1a** (Scheme 3a). This observation is in line with the milder reaction conditions required for **1a** than that required for **1b**. Second, a competition experiment was performed using N-Ts imine **4** and N-PMP imine **5**, which were derived from electronically similar chalcone derivatives (Scheme 3b). On the contrary to the better reactivity of N-Ts imine in individual reactions (Table 1), the competition resulted in the formation of the pyridine products **6** and **7** in a near 1:1 ratio. Lastly, the reaction of **1a** with **2a** was largely suppressed by the addition of TEMPO, while the addition of 1,1-diphenylethylene did not interfere with the pyridine formation (Scheme 3c). This may suggest that electron transfer processes involving the copper catalyst (vide infra) are inhibited by TEMPO,[13] but not by 1,1-diphenylethylene.



additive	yield
TEMPO	8%
1,1-diphenylethylene	90%

Scheme 3. Competition and control experiments. The yields were determined by GC analysis.



Scheme 4. Proposed reaction pathways.

On the basis of previous studies on copper catalysis of oximes[5a,6,7b,9] and the above observations, we are tempted to propose reaction pathways shown in Scheme 4. Sequential single-electron reduction with two equivalents of Cu^I would convert the oxime **1** to an iminyl radical **A** and then to an iminylcopper(II) species **B**. The species **B** would tautomerize to generate a copper(II) enamide **C**.[6,14] Conjugate addition of **C** to the unsaturated N-Ts imine **2** and subsequent intramolecular cyclization would liberate $TsNH_2$ and give a dihydropyridine intermediate **F** (cf. product **3ra** in Table 3), which would be oxidized by Cu^{II} to furnish the pyridine product **3**. While low-lying LUMO of the Michael acceptor appears essential for the previously developed oxime/enal and oxime/aldehyde/ketoester condensations (Scheme 1a), we speculate that coordination of the imine nitrogen to copper assists the C–C bond-forming step of the present pyridine synthesis (see $\mathbf{TS_{C\text{-}D}}$). This may also account for the competence of N-PMP imine, which features less electrophilic β-position and more coordinating nitrogen, as a Michael acceptor for the present reaction (*cf.* Table 1 and Scheme 3b). Besides the ionic pathway for the C–C bond formation, we may not exclude an alternative pathway involving an α-imino radical **C'**, which can be formed via homolytic N–Cu cleavage of **C**. Note that the radical **C'** and its dimerization were proposed for the copper-catalyzed pyrrole-forming homocoupling reaction of oxime acetate.[9c] Addition of **C'** to **2** and reduction/protonation of the resulting radical **D'** with Cu^I/H^+ would eventually lead to the same pyridine product.

In summary, we have developed a copper-catalyzed condensation reaction of oxime acetates and α,β-unsaturated ketimines for the regioselective synthesis of highly substituted pyridines. The scope of the reaction covers a particularly broad range of oxime acetates, derived from aryl alkyl- and dialkyl, acyclic and cyclic ketones, thus allowing access to various multisubstituted pyridines including those not readily accessible by conventional condensation methods such as the Kröhnke synthesis and its variants.

Acknowledgements

This work was supported by the Singapore Ministry of Education (RG3/15, RG114/15) and Nanyang Technological University.

Keywords: pyridines • synthetic methods • condensation • oximes • copper

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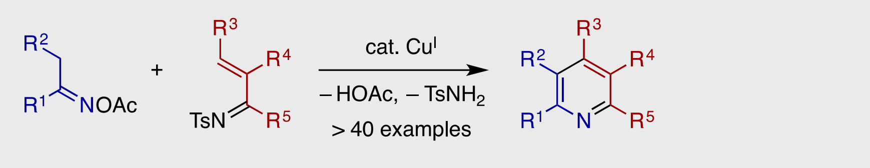
COMMUNICATION



A copper-catalyzed condensation reaction of oxime acetates and α,β-unsaturated ketimines into pyridine derivatives is reported. The reaction features mild conditions, high functional group compatibility, and high regioselectivity with respect to unsymmetrical oxime acetates, thus allowing for the preparation of a wide range of polysubstituted pyridines, many of which are not readily accessible by conventional condensation methods.

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Synthesis of Highly Substituted Pyridines via Copper-Catalyzed Condensation of Oximes and α,β-Unsaturated Imines