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# Copper(I)-Catalyzed Ketenimine Formation/Aza-Claisen Rearrangement Cascade for Stereoselective Synthesis of α-Allylic Amidines

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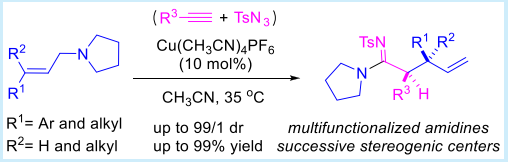
**ABSTRACT:** A copper-catalyzed three-component reaction of terminal alkynes, $TsN_3$, and tertiary allylic amines is developed toward the one-pot synthesis of α-allylic amidines. The product was synthesized on gram scale under 1 mol % of catalyst loading. Transformations of products into alkenyl amine and other nitrogen-containing compounds are demonstrated without any loss of stereochemical information.

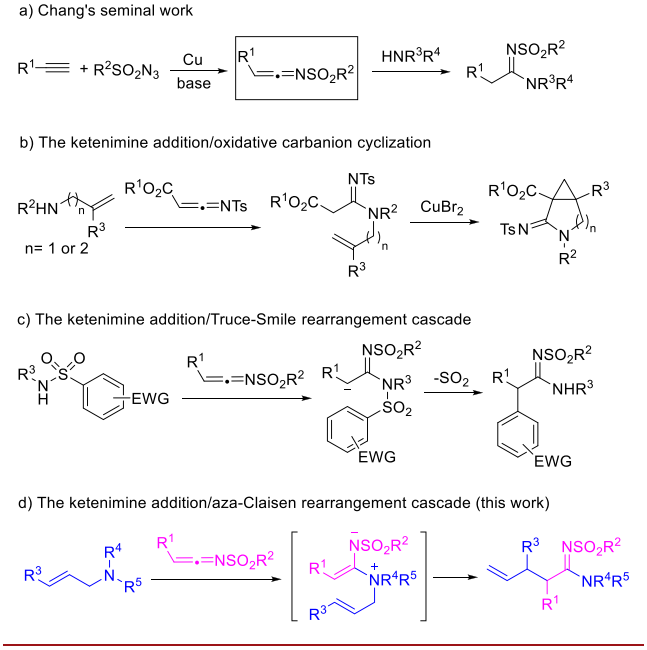





The multicomponent reaction (MCR) represents one of the powerful tools to assemble complex molecules to reach high efficiency and operational simplification.[1] MCRs are also particularly practical for the rapid construction of successive stereocenters in total synthesis and drug development. For example, Cu-catalyzed azide−alkyne cycloaddition[2] (CuAAC) and triazole coupling cascade has become an important strategy for the synthesis of important triazole derivatives.[3] When azides containing a strong electron-withdrawing group (e.g., sulfonyl) at the N1 atom, the triazolyl copper intermediate facilely undergoes a ring-opening rearrangement/nitrogen-release process and the resultant electrophilic ketenimine intermediate[4] could couple with various nucleophilic reagents to produce carbonyl derivative, such as amides,[5] amidines,[6] ketones,[7] imines,[8] and *N*-containing heterocycles.[9] In Chang's pioneering work,[6a,b] the Cu-catalyzed three-component reaction of alkynes, *N*-Ts azides, and primary/secondary amines provided a direct access to amidines (Scheme 1a). In this context, the ketenimine addition of secondary (homo)allylic amines, followed by an oxidative carbanion cyclization, was demonstrated toward cyclopropane-fused cyclic amidines[10] (Scheme 1b). Recently, the ketenimine addition of 4-nitrobenzenesulfonamides and Truce−Smile rearrangement cascade was reported to construct α-aryl amidines[11] (Scheme 1c). However, the ketenimine addition of tertiary amines remain challenging. The related coupling reaction of trialkyl amines and *N*-sulfonyl ketenimine only gave dealkylation products.[12]

In past decades, the Claisen rearrangement has become one of most powerful methods for the C−C bond formation and stereoselective synthesis of α-allylic carbonyl derivatives.[13] We envisioned that the coupling of an allylic substituted tertiary amine and the *N*-Ts ketenimine might form the zwitterion intermediate that is allowed to undergo the aza-Claisen rearrangement (Scheme 1d). Such a three-component reaction not only enables the step- and atom-economic synthesis of functionalized amidines but also generates multiple carbon

**Scheme 1. CuAAC-Ketenimine Formation and Reaction with Amines**

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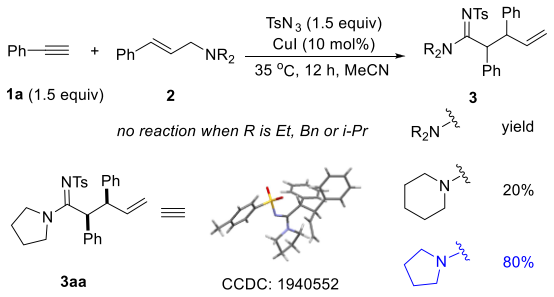
stereocenters. Although Xu and Shen et al. demonstrated an elegant Cu-mediated amino enyne cyclization/aza-Claisen rearrangement cascade to construct cyclic $\alpha$-allylic amidines,[14] the intermolecular ketenimine addition/Claisen rearrangement is still unknown. Herein, a Cu-catalyzed three-component coupling reaction of tertiary allylic amines, alkynes, and azides is reported to provide access to acyclic $\alpha$-allylic amidines.[15]

To test the feasibility, several allylic tertiary amines were chosen to react with ethynylbenzene (**1a**) and $TsN_3$ in the presence of CuI (10 mol %) (Scheme 2). Pleasingly, cinnamyl

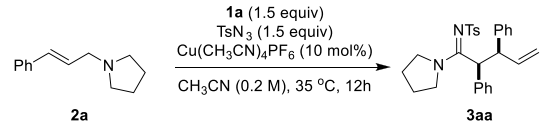
**Scheme 2. Initial Attempts**




pyrrolidine (**2a**) was able to couple with the in situ generated ketenimine and transformed into the rearrangement product (**3aa**) as single diastereomeric isomer. The *syn* configuration of **3aa** was confirmed by the X-ray diffraction analysis and the observed stereochemical outcome is consistent with that of the ketene−Claisen reaction.[13c] During the further reaction condition optimization, **3aa** was obtained in excellent yield (94%) in the presence of $Cu(CH_3CN)_4PF_6$ (10 mol %) with $CH_3CN$ as the solvent at 35 °C for 12 h (Table 1, entry 1). The yield was slightly decreased when any reaction parameter was changed (entries 2−7). None of the target was observed in the absence of copper salt (entry 8).

With the optimal conditions in hand, the scope of terminal alkynes was evaluated. A broad range of arylalkynes, depicted in Scheme 3, reacted with $TsN_3$ and cinnamyl pyrrolidine to form homoallylic amidines with excellent stereoselectivities. Electron-rich arylalkynes, bearing a *p*-Me, *p*-OMe, *o*-OMe, or *p*-$^t$Bu substituent, were quite reactive and transformed into

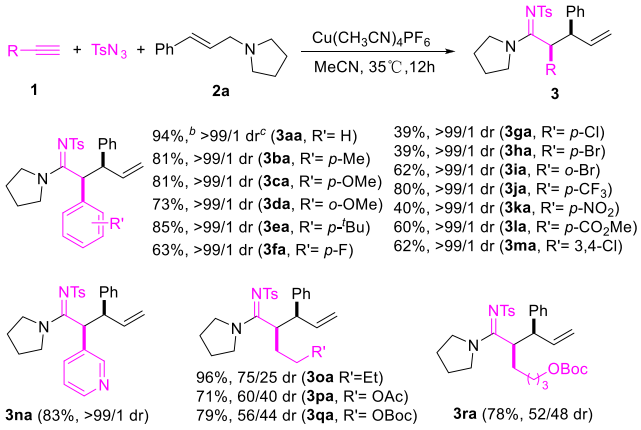
**Table 1. Reaction Conditions Evaluation**[a]




| entry | changes of reactions conditions | yield (%)[b] | dr[c] |
|---|---|---|---|
| 1 | none | 94 | >99/1 |
| 2 | CuI instead of $Cu(CH_3CN)_4PF_6$ | 80 | >99/1 |
| 3 | $Cu(OTf)_2$ instead of $Cu(CH_3CN)_4PF_6$ | 74 | >99/1 |
| 4 | THF instead of $CH_3CN$ | 62 | >99/1 |
| 5 | DCM instead of $CH_3CN$ | 87 | >99/1 |
| 6 | 25 °C instead of 35 °C | 80 | >99/1 |
| 7 | 45 °C instead of 35 °C | 81 | >99/1 |
| 8 | without copper | 0 | |

[a]All reactions were performed under argon using **1** (0.3 mmol), $TsN_3$ (0.3 mmol), **2a** (0.2 mmol), catalyst (10 mol %) in 1 mL of the solvent. [b]The isolated yield. [c]Determined by $^1$H NMR of the crude product.

**Scheme 3. Scope of Terminal Alkynes**[a]




[a]All reactions were performed under argon using **1** (0.3 mmol), $TsN_3$ (0.3 mmol), **2a** (0.2 mmol), and $Cu(CH_3CN)_4PF_6$ (0.02 mmol) in 1.0 mL of MeCN for 12h. [b]Isolated yield. [c]Determined by $^1$H NMR of the crude product.

**3ba**-**3ea** in high yields (73−85%). The electron-deficient arylalkynes gave moderate to good yields. For example, *p*-F, *p*-$CF_3$ and *p*-COOMe substituted ethynylbenzenes were readily transformed into **3fa** (63%), **3ja** (80%) and **3la** (60%) in good yields, while the three-component reaction with *p*-Cl-, *p*-Br-, *o*-Br-, and *p*-$NO_2$-substituted ethynylbenzenes gave moderate yields. In particular, 3,4-dichloro-4-ethynylbenzene and 3-ethynylpyridine were allowed to undergo the three-component reaction, providing **3ma** (62%) and **3na** (83%) in good yields with excellent diastereoselectivities. In the next investigation, hex-1-yne- or OAc/OBoc-tethered alkynes were reactive to undergo the Cu-catalyzed cascade, affording $\alpha$-alkyl-substituted homoallylic amidines (**3oa**−**3ra**) in high yields (71−96%) with moderate diastereoselectivities. The low stereoselectivities for products (**3oa**−**3ra**) might result from their less sterically hindered R group that leading the ketenimine reacts less selectively with the allylic amine **2a** between path *a* and *b*; thus, the formed mixture of *E*- and *Z*-ethene-1,1-diamine intermediates undergo the stereospecific rearrangement and produce two diastereoisomers less selectively (Figure 1).

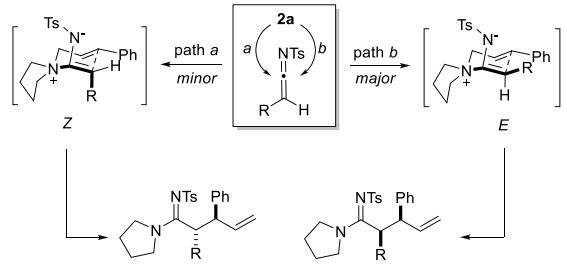



**Figure 1.** Proposed mechanism.

The next investigation was focused on the scope of allylic tertiary amines. (Table 2) The electronic properties of aryl groups on cinnamyl pyrrolidine substrates (**2b**−**2h**) has little effect on reactivity and stereoselectivity of the reaction. Electron-deficient cinnamyl amines bearing a F, Cl, Br, or $NO_2$ substituent reacted smoothly to form **3ad**−**3ag** in high yields (82−99%). The furan-derived allylic amine (**2i**) was


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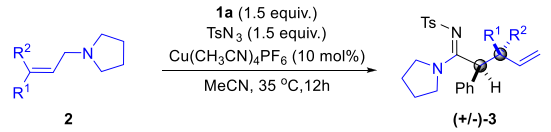
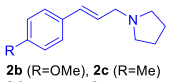
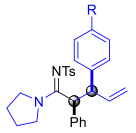
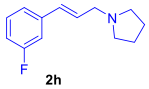
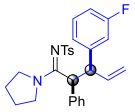
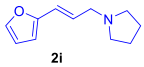
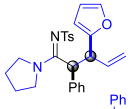
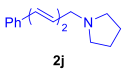
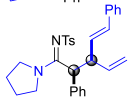
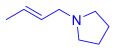
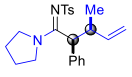
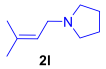
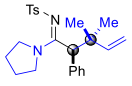
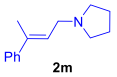
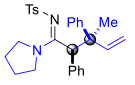
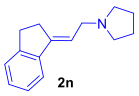
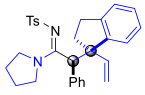
**Table 2. Scope of Allylic Amines**[a]



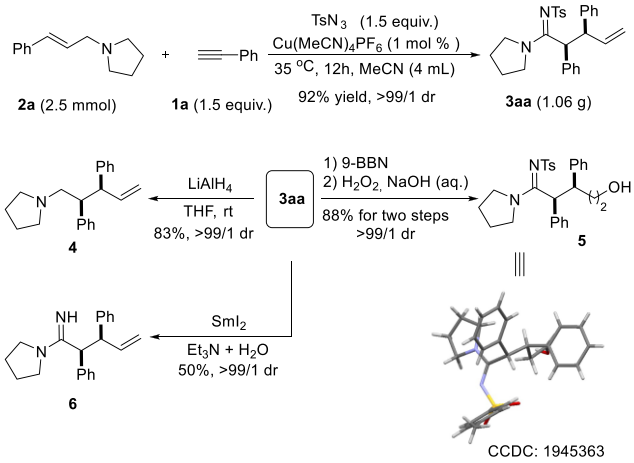

| Entry | 2 | 3 | yield,[b] dr [c] |
|---|---|---|---|
| 1 |  **2b** (R=OMe), **2c** (R=Me) **2d** (R=F), **2e** (R=Cl) **2f** (R=Br), **2g** (R=$NO_2$) |  | 99%, >99/1 dr (**3ab**) 95%, >99/1 dr (**3ac**) 95%, >99/1 dr (**3ad**) 99%, >99/1 dr (**3ae**) 90%, >99/1 dr (**3af**) 82%, >99/1 dr (**3ag**) |
| 2 |  **2h** |  | 98%, >99/1 dr (**3ah**) |
| 3 |  **2i** |  | 99%, >99/1 dr (**3ai**) |
| 4 |  **2j** |  | 91%, >99/1 dr (**3aj**) |
| 5 |  **2k** |  | 63%, >99/1 dr (**3ak**) |
| 6 |  **2l** |  | 73%, (**3al**) |
| 7 |  **2m** |  | 66%, >99/1 dr (**3am**) |
| 8 |  **2n** |  | 65%, >99/1 dr (**3an**) |

[a]All reactions were performed under argon using **1a** (0.3 mmol), $TsN_3$ (0.3 mmol), **2** (0.2 mmol), and $Cu(CH_3CN)_4PF_6$ (0.02 mmol) in 1.0 mL of MeCN for 12h. [b]Isolated yield. [c]Determined by $^1H$ NMR of the crude product.

smoothly transformed into *syn*-homoallylic amidines (**3ai**). Divinyl and crotyl pyrrolidines (**2j** and **2k**) also showed high reactivities as well as excellent stereoselectivities. (Table 2, entries 4 and 5) Allylic amines with trisubstituted olefinic groups (**2l**−**2n**) were exposed to the catalytic system and reacted smoothly to produce expected three-component adducts (**3al**−**3an**) with excellent drs. Yields were slightly eroded (65−73%) owing to the partial decomposition of zwitterionic 1,5-diene intermediates.

To demonstrate the application of this Cu-catalyzed MCR, the scale-up reaction with 2.5 mmol of the allylic amine (**2a**) was performed. The reaction proceeded smoothly under 1 mol % of catalyst loading, giving 1.06 g of **3aa** (92% yield) (Scheme 4). Some transformations of the product were carried out to construct *N*-containing molecules. For example, the selective reduction of **3aa** to olefinic amine (**4**) with $LiAlH_4$ proceeded smoothly in good yield (83%). The selective transformation of olefinic group by a sequential hydroboration and oxidation was successful to give a multifunctionalized amidine (**5**) in 88% yield. And the *N*-Ts group of **3aa** was readily removed by $SmI_2$

**Scheme 4. Gram-Scale Synthesis and Transformations of 3aa**




reduction to afford **6**.[16] It is worth noticing that all products were obtained without any loss of diastereoselectivities.

In conclusion, a new approach toward the synthesis of $\alpha$-allylic amidines was accomplished by merging Cu-catalyzed ketenimine formation/aza-Claisen rearrangement cascade. Allylic tertiary amines were employed and successfully incorporated into $\alpha$-allylic amidines bearing tertiary/quaternary carbon centers. The method features good tolerance of functional groups, easy scale-up, and easy operation. The research on asymmetric synthesis of functionalized amidines is currently ongoing.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01012.

Experimental procedures, spectroscopic data, and NMR spectra of all products (PDF)

### Accession Codes

CCDC 1940552 and 1945363 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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