Copper-Catalyzed Cyclization/aza-Claisen Rearrangement Cascade Initiated by Ketenimine Formation: An Efficient Stereocontrolled Synthesis of α-Allyl Cyclic Amidines**

Hua-Dong Xu, Zhi-Hong Jia, Ke Xu, Mei Han, Sai-Nan Jiang, Jing Cao, Jia-Cheng Wang, and Mei-Hua Shen**

Abstract: *An efficient and convenient synthesis of α-allyl cyclic amidines has been achieved by applying a novel cascade reaction. Copper(I)-mediated in situ N-sulfonyl ketenimine formation from the reaction of a terminal alkyne with sulfonyl azide is followed by an intramolecular nucleophilic attack on the central carbon atom by an allylic tertiary amine, and then an aza-Claisen rearrangement takes place through a chair transition state to furnish the titled amidines with complete stereocontrol.*

Studies of reactive species comprise a large part of research in organic chemistry and contribute continually to the development of new chemistry because transformations of such energetic entities are typically exothermic and have a significant thermodynamic driving force.[1] Very often, interception of these reactive species by other functionalities has proved to be an efficient strategy for reaction discovery.[2] By comparison with their oxygen congeners, ketenes,[3] the ketenimine class of reactive intermediates (Figure 1; **A**, **B**,
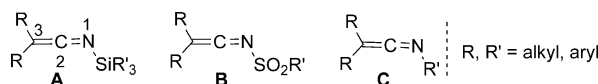

Figure 1. Three types of ketenimines.

and **C**) has an additional N1 substitution site, and therefore has demonstrated more diverse and tunable reactivity.[4] The nature of the N substitution plays a pivotal role in ketenimine reactivity. While the silyl ketenimine **A** is well known for its

strong C3 nucleophilicity,[5] the reactivity of the *N*-sulfonyl ketenimine **B** is mainly characterized by initial nucleophilic attack on C2 of the ketenimines,[6] and the ketenimines **C** bearing N-alkyl/aryl groups are frequently observed in concerted processes.[7] Although great advances have been made in ketenimine chemistry recently, we anticipated there was new reactivity to explore.

The amidine moiety exhibits a unique structure which is present in numerous bioactive natural products and medicinal compounds.[8] This functional group also finds broad applications in catalysis,[9] metal ligation,[10] and chemical biology.[11] Herein we report an unprecedented reaction model of a ketenimine featuring an intramolecular ketenimine capture[12]/aza-Claisen cascade[13] to provide an efficient method for preparing functionalized cyclic amidines.

The tertiary amino enyne **1a** was reacted with tosyl azide in the presence of a catalytic amount of copper(I) thiophene-2-carboxylate (CuTc) in anhydrous toluene at room temperature, and the substrate was consumed in 30 minutes (TLC) and two compounds, the triazole **3a** and amidine **2a**, were isolated in 40 and 44% yield, respectively (Figure 2).
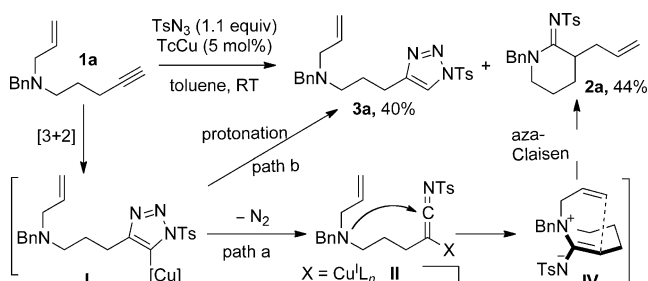

Figure 2. Proposed divergent pathways for the formation of triazole and amidine. Ts = 4-toluenesulfonyl.

According to the elegant protocol from Chang and co-workers on *N*-tosyl ketenimine formation from the terminal alkyne/sulfonyl azide combination,[14] we reasoned that these interesting outcomes derived from two competing pathways, as shown in Figure 2. The initial [3+2] adduct **I** is protonated to give **3a** (path b). In contrast, **I** can further decompose to the sulfonyl ketenimine **III**, and then cyclize by virtue of a tethered nitrogen nucleophile to acquire the cyclic zwitterion **IV**. Finally, sequential aza-Claisen rearrangement gives rise to **2a** (path a). The conversion of **I** into the N-tosyl ketenime **II** must be facilitated by the basicity of the tertiary

[*] Dr. H. Xu, Z. Jia,[+] K. Xu,[+] M. Han, S. Jiang, J. Cao, J. Wang, Dr. M. Shen
School of Pharmaceutical Engineering and Life Science
Changzhou University, First Middle Gehu Road
Changzhou, Jiangsu Province, 213164 (China)
E-mail: huadongxu@gmail.com
meihuashen@gmail.com

[+] These authors contributed equally to this work.

amine in the substrate since previous mechanistic studies have proved the necessity of a tertiary amine for *N*-sulfonyl ketenime formation.[15] The novelty of both the reaction itself and the structure of **2a** motivated us to carry out further investigations on path a.

Efforts to improve the selectivity by changing the reaction medium and the copper(I) source were not fruitful (entries 1–4, Table 1). Reactions carried out in tetrahydrofuran (THF),

Table 1: Optimization of reaction conditions for the metal-catalyzed reaction of **1a** with TsN$_3$.[a]

Entry	Cat.	Base	Solvent	Yield [%][b]	3a/2a
1	CuTc	none	toluene	84	1.0:1.1
2	CuTc	none	CH$_2$Cl$_2$	85	1.0:1.1
3	CuTc	none	THF	86[c]	1.0:1.2
4	CuI	none	THF	87	1.0:1.5
5	CuI	DIPEA (1 equiv)	THF	65	1.0:3.0
6	CuI	DIPEA (3 equiv)	THF	82	1.0:12
7	CuI	DIPEA (5 equiv)	THF	88	0:1.0
8	CuI	Et$_3$N	THF	76	0:1.0
9	CuI	Py	THF	78	0:1.0
10	CuI	2,6-lutidine	THF	78	0:1.0
11	CuTc	DIPEA	THF	75	0:1.0
12	Cu(OTf)$_2$	DIPEA	THF	69[d]	0:1.0
13	AgOTf	DIPEA	THF	38[e]	0:1.0
14	CuI	DIPEA	CHCl$_3$	73	0:1.0
15	CuI	DIPEA	toluene	72	0:1.0
16	CuI	DIPEA	DMSO	70	0:1.0
17	CuI	DIPEA	MeCN	74	0:1.0
18	CuI	DIPEA	*t*BuOH	68	0:1.0
19	CuI	DIPEA	CH$_2$Cl$_2$	83	0:1.0

[a] Reaction conditions: **1a** (1.0 equiv, 0.1 M), TsN$_3$ (1.1 equiv), DIPEA, and metal catalyst (5 mol%) were stirred in solvent at RT for half an hour. [b] Yield of isolated product. [c] Reaction performed at 60°C. [d] Recovered 25% starting material. [e] Complex reaction mixture. DMSO = dimethyl sulfoxide, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.

CH$_2$Cl$_2$, and toluene all gave **2a** and **3a**, largely in equal amounts, and catalysis by CuI instead of CuTc slightly favored path a (entry 4). The use of higher temperature did not afford a significant change (entry 3). As expected, the introduction of an external organic base shifts the reaction course to path a substantially (entries 5–10), and the use of 5 equivalents of base completely excluded the formation of **3a**. While other organic bases function well, diisopropylethyl amine (DIPEA) proved to be the best in terms of the yield. Several other catalysts were tested under these reaction conditions but were found to be inferior to CuI. For example, 5 mol% Cu(OTf)$_2$ is not sufficient for full conversion of the starting material and AgOTf delivered a complex reaction mixture (entries 11–13). Although THF is the optimum solvent among those tested, the reaction tolerates various types of solvent, even with nucleophilic DMSO and *tert*-butyl alcohol offering 70 and 68% yield, respectively. The current optimal reaction conditions involve reacting the enyne **1** with the sulfonyl azide (1.1 equiv) in the presence of DIPEA (5.0 equiv) at room

Table 2: The reaction of **1a** or **4a** with various sulfonyl azides under optimal reaction conditions.

Mbs = *p*-methoxybenzenesulfonyl, Mts = mesitylenesulfonyl, Nos = 4-nitrobenzenesulfonyl, PMB = *para*-methoxybenzyl, SES = 2-[(trimethyl)-ethyl]sulfonyl.

temperature using CuI (5 mol%) as the catalyst and anhydrous THF as the solvent.

The impact of the sulfonyl azide on this reaction was inspected under the optimal reaction conditions (Table 2). Sulfonyl azides with different electronic and steric properties reacted with the benzylamino enyne **1a** or *p*-methoxybenzyl-amino enyne **4a** to form the corresponding six- or five-membered cyclic amidines reliably in excellent yields.

Replacement of the benzyl group in **1a** or the *p*-methoxybenzyl moiety in **4a** with other substituents resulted in an array of substrates (**1b–f** and **4b–i**, Table 3), which were subjected to the optimal reaction conditions. The electronic nature of the *para* substituent on the benzyl group has a negligible effect, if any, on the reaction yield. Substrates with either electron-donating or electron-withdrawing groups gave more than 90% yields (**2b–e**; **10a–e**). Other N-alkyl groups such as the carboethoxymethyl and hexyl groups provided almost equally high yields (**2f, 10f–g**), thus demonstrating the scope of compatible N-alkyl substituents. Interestingly, the benzyl amine **4i**, bearing an *ortho*-hydroxy group, unlike the prototype **1a**, does not react at room temperature without an external base, however, it proceeds smoothly at 60°C to produce the non-aza-Claisen product **10i** in 86% yield. We assumed that intramolecular hydrogen bonding masks the basic nitrogen center at low temperature and **10i** is formed by 1,4-elimination of *o*-quinone methide[16] (**13**) from the cyclized zwitterion **IV$_{4i}$** (Figure 3a). Removal of this interaction by acylation of the phenolic group brought **4h** back into the desired reaction manifold.

Next, variations on the allyl segment were examined, thus leading to the discovery that substitution on each of the three positions is well tolerated with respect to yields (**1g–m→2g–m**; **4j–l→10j–l**, Table 3) as clean reactions and high yields were obtained without exception (85–95%). Normally difficult quaternary carbon centers are constructed with ease by this method (**10j–k, 2g**). Substrates of bis(allyl) amino enynes such as **1l** and **1m** raise the issue of chemoselectivity. The fact that almost equal amounts of the cyclic amidines **2l** and **2l′** were obtained indicates that conjugation to the ester carbonyl

Table 3: Reactions of various tertiary amino enyne with TsN₃.[a,b]

Substrate	Product	Substrate	Product	Substrate	Product
4a: X = OMe, n = 2 **4b**: X = H, n = 2 **1a**: X = H, n = 3 **1b**: X = OMe, n = 3 **4c**: X = Cl, n = 2 **1c**: X = Cl, n = 3 **4d**: X = CF₃, n = 2 **1d**: X = CF₃, n = 3 **4e**: X = NO₂, n = 2 **1e**: X = NO₂, n = 3	**10a**, 96% **10b**, 85% **2a**, 88% **2b**, 94% **10c**, 96% **2c**, 93% **10d**, 94% **2d**, 95% **10e**, 91% **2e**, 93%	**1h**	**2h**, 93%	**4n**[d]: R = Et, 82% **4o**[d]: R = Me, 18%	**10n**: R = Et **10o**: R = Me 95%[e]
4f: n = 2 **1f**: n = 3	**10f**, 88% **2f**, 90%	**1i**	**2i**, 92%	**1o**	**2o**, 91%, d.r.: 4/1[f] 85%, d.r.: 1/0[g]
4g	**10g**, 86%	**1j**	**2j**, 92%	**1p**	**2p**, R = Et, 29% **2p'**, R = iPr, 58%
4h: R = Ac	**10h**, 93%	**4l**: n = 0 **1k**: n = 1	**10l**, 93% **2k**, 95%	**1q**	**2q**, 89%
4i: R = H	**10i**[c], 86%	**1l**	**2l**: R/R', CO₂Et/H, 42% **2l'**: R/R', H/CO₂Et, 43%	**11**	**12**, 90%
4j: n = 0 **1g**: n = 1	**10j**, 86% **2g**, 93%	**1m**	**2m**, 84%	**4p**	**10p**, 94%
4k	**10k**, 85%	**1n**	**2n**, 90%	**4q**	**10q**, R = Et, 36% **10q'**, R = iPr, 57%
		4m	**10m**, 96%	**1r**	**2r**, 55%

[a] All reactions were carried out on 25–100 mg scale under optimal reaction conditions unless otherwise mentioned. [b] Yield of isolated product. [c] Heating to 60°C without DIPEA. [d] Inseparable mixture of **4o/4p**. [e] Combined yield. [f] The d.r. value was determined by NMR spectroscopy. [g] Reaction carried out at 0°C in the presence of 1.5 equivalents of DIPEA. PMP = *para*-methoxyphenyl.
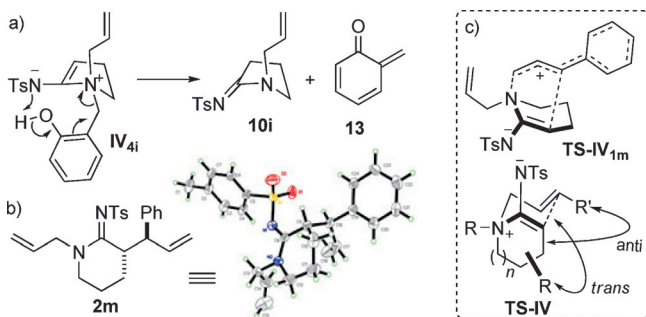

Figure 3. a) Explanation of the formation of **10i**. b) X-ray crystal structure of **2m**.[18] c) Proposed transition states **TS-IV₁ₘ** and **TS-IV**.

in **1l** does not interfere with the reaction profile, whereas the resonance effect of a phenyl ring on the double bond has pronounced influence on the reaction outcome as, in our

hands, **2m** was isolated as the sole product. Although the reason for these intriguing phenomena is not clear at this stage, we rationalized that the aza-Claisen rearrangement of intermediate **IV** (Figure 3c, top) proceeds through the transition-state **TS-IV₁ₘ**, characterized by a benzylic carbon atom bearing significant positive charge. This transition state, therefore, is stabilized by the conjugation to the aromatic ring. Single-crystal X-ray structure analysis established the *anti* configuration of **2m**, and the same relative stereochemistry was assigned to other congeners by analogy. The exclusive observation of the single epimers **2j–m** and **10l** demonstrates the outstanding diastereoselectivity of this reaction.

Further efforts have been devoted to exploring the substrate scope with regard to diversity of the alkyne. Substitution with an alkyl or a carboxy group on each methylene group provides excellent substrates for this reaction as five- or six-membered cyclic amidines were

obtained in exceptionally high yields (**1n–o**→**2n–o, 4m–o**→ **10m–o**, Table 3). The two-dimensional ^{1}H-^{1}H NOESY experiments have been performed on **10n** and **2o** to reveal their relative configuration to be *trans*, thus illustrating the high stereoselectivity of this reaction. It is worth noting that under standard reaction conditions, an inseparable mixture of diastereomers **2o** (d.r.: 4:1) was obtained from the substrate **1o**. However, by reducing the amount of external base to 1.5 equivalents and the reaction temperature to 0 °C, the same reaction provides 100 % diastereoselectivity. The compound **1p**, with one-carbon elongation of the alkyne linkage, gave rise to the linear amidine **2p**, a product of intermolecular attack on the nascent ketenimine **III$_{1p}$** by DIPEA instead of attack by the intramolecular competitor. However, **1q** afforded the seven-membered cyclic amidine **2q**, thus smoothly reflecting the prominent template effect of a ring. In contrast, the reaction of the propargyl amine **11** with tosyl azide under identical reaction conditions delivered a 90 % yield of **12**, the product of a cyclization/β-elimination cascade, a process which has been observed very recently by the group of Talukdar.[17]

Overall, we consider that the aza-Claisen reaction proceeds through the chairlike transition-state **TS-IV** (Figure 3c, bottom), which explains both the *anti* selectivity attained during the C3−C4 bond formation and the *trans*-stereoselectivity controlled by the R group on the nascent ring.

Finally, we draw attention to the divergent results presented by the close homologues **4p,q** and **1r**. The *p*-methoxyphenyl amino enyne **4p** underwent the cyclization/ aza-Claisen rearrangement smoothly to furnish the cyclic amidine **10p** in 94 % yield. In contrast, its comparatively less-electron-rich tolyl counterpart **4q** gave the noncylization products **10q/10q′** in a combined yield of 93 %. The observation that such a subtle change in nucleophilicity can confer so remarkable a divergence in the reaction courses is amazing. Furthermore, with the *p*-methoxyphenyl amine **1r** as a substrate, only the intermolecular product **2r** was obtained with 55 % yield, thus testifying to the sensitivity of the reaction to the tether length.

In summary, a new ketenimine reaction mode has been established and thus provides a convenient copper-catalyzed protocol for cyclic amidine synthesis with high yield under mild reaction conditions. By using this method, tertiary allyl enynes, with broad substitution patterns, can be converted stereoselectively into α-allyl cyclic amidines bearing multiple functionalities for potential elaboration.

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