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Lewis Acid Catalyzed [1,3]-Sigmatropic Rearrangement of Vinyl Aziridines

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Abstract

This communication details the copper catalyzed ring expansion of vinyl aziridines to 3-pyrrolines. Broad substrate scope (24 examples) using tosyl and phthalimide protected vinyl aziridine substrates is observed. Cu(hfacac)₂ was determined to be superior to all other catalysts tested.

3-Pyrrolines (2,5-dihydropyrroles), while important in their own right, are synthetically versatile heterocycles which allow ready access to pyrrolidines and pyrroles.¹ Collectively these ring systems occur in countless natural products and pharmaceuticals.² Not surprisingly, a number of different synthetic approaches toward pyrrolines have been developed but the most popular are Birch reduction of pyrroles,³ [3+2] cyclization,⁴ and ring closing metathesis.⁵ Despite these and other creative approaches, a requisite exists for a simple and selective method which allows access to structurally complex 3-pyrrolines. Herein, we demonstrate that vinyl aziridines can be efficiently converted to 3-pyrrolines using commercially available copper(II) catalysts.

Analogous to the vinyl cyclopropane rearrangement,⁶ the thermolysis of vinyl aziridines to 3-pyrrolines was first observed in the late 1960's.⁷ Harsh thermal conditions were employed and little substrate scope was observed. Since these initial experiments, several attempts have been

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Supporting Information **Available:** Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

made to investigate the reaction further, but limitations such as competing side reactions and the necessity of additional functionality were found.⁸ Therefore, applications of this rearrangement to the synthesis of complex molecules have been lacking.^{9,10} Clearly, there is a need to develop conditions that expand the scope of the rearrangement and allow functional group compatibility.

Vinyl aziridines are most easily synthesized by one of three methods: the addition of a nitrene to a diene, the addition of an allylic ylide to an imine or the cyclization of unsaturated amino alcohols.¹¹ Each method has limitations often directly related to the nitrogen protecting group. This paper focuses on the p-toluenesulfonyl (Ts) and phthalimido (Phth) protecting groups. Tosyl aziridines are easily accessed by employing an aziridination protocol developed by Sharpless¹² or by catalytic decomposition of N-phenyliodinanes.¹³ Although phthalimide substituted aziridines are less commonly used, they offer an attractive option based on their ease of synthesis utilizing a stabilized singlet nitrene and broader substrate scope.¹⁴

Vinyl aziridine **1** was chosen as a model substrate due to the growing interest in dehydropyrolines.¹⁵ Based on previous work by our group on the catalytic ring expansion of vinyl oxiranes and vinyl thiiranes,¹⁶ copper catalysts were tested (Table 1). The more electrophilic copper(II) hexafluoroacetylacetonate (entries 14-18) proved far superior to other commercially available and synthetic catalysts. Interestingly, the reaction proceeds faster and with a higher yield when the Cu(hfacac)₂ hydrate is dried prior to use. Optimized reaction conditions were found to be 150 °C, 0.1 M [substrate], and 5 mol % catalyst loading.

Table 2 displays the results of applying these optimized conditions to a variety of phthalimide and tosyl protected vinyl aziridines. These products can be readily deprotected to give the N-H pyrrolines.¹⁷ Simple substrates (Entries 1-11) demonstrate that all substitution patterns are well tolerated resulting in excellent yields. Entries 4, 5, and 8 display an important synthetic aspect of this rearrangement, as each 3-pyrroline can originate from two regioisomeric vinyl aziridine precursors or even from their mixture. Some of the simple substrates can rearrange thermally at more extreme temperatures and often at dramatically diminished yield. However, the thermal rearrangement of more complex substrates is either nonexistent or very poor.

The copper catalyzed rearrangement has been shown to be quite functional group tolerant. These groups include enol ethers, esters, protected alcohols, sulfonamides, and imides. This compatibility is important because some of these functional groups likely coordinate to the electrophilic copper center and yet do not prevent the reaction from occurring. Next, fused and bridged bicyclic compounds (entries 15-23) can be rearranged to create complex ring systems. With respect to protecting groups, we observe that in general the more electron rich phthalimide aziridines rearrange faster than the corresponding tosyl protected aziridines. Product yields vary between protecting groups but only phthalimide aziridines are competent for very strained systems (entries 17-20).¹⁸ Entries 23 and 24 are particularly noteworthy, since they establish the potential for diastereoselective rearrangements.¹⁹ Lastly, the diastereomer of the substrate in entry 18 and the Z-isomer of the substrate in entry 10 do not rearrange under a variety of conditions tested. These substrates display the importance of the conformation and sterics of the substrate when it is bound to the catalyst.

Investigation into this reaction has revealed that the rearrangement is copper specific and with a few exceptions distinct to copper(II) acetylacetonate ligands. Determination of the mechanism has proved elusive but the synthesis of two new catalysts has probed what the active copper species might be. The substrate from entry 3 was chosen as a model system for investigation and the results are shown in Figure 1. The reaction was conducted in sealed NMR tubes under the standard reaction conditions (0.1 M of vinyl aziridine, 5 mol % catalyst) except CDCl₃ was used as the solvent. The reactions with Cu(hfacac)₂ (**3**) have a characteristic sigmoidal shape

suggesting an autocatalytic process. When the catalyst loading is changed a dramatic effect on the rate is observed. When a mixed acac catalyst is used, Cu(dbm)(hfacac) (**4**)²⁰, a slightly slower reaction is observed with a similar profile. Careful analysis of the slope of the line suggests the maximum rate of the reaction is higher than that of Cu(hfacac)₂. This suggests that a more active catalyst species is produced during the course of the reaction. The reaction profile of Cu(hfacac)(TMEDA)Br (**5**)²¹ is completely different with little to no induction period or autocatalytic behavior. This suggests that the catalyst is already in its most active form unlike Cu(hfacac)₂. This catalyst is inferior likely due to a less electrophilic copper(II) center. The mixed complexes, **4** and **5**, are peculiar since no other catalysts have even approached the effectiveness of Cu(hfacac)₂ as demonstrated in Table 1. Finally, similar kinetic experiments were performed in benzene and those experiments confirmed the same behavior; however improved solubility in CDCl₃ created more reproducible results.

Using all results obtained during this investigation we have produced a catalytic cycle shown in Scheme 1. We propose that substrate (**7**) binds in the axial site of Cu(hfacac)₂ to form complex **8**. The substrate induces disproportionation of the Cu(hfacac)₂ to form cationic copper (II) complex **9** and anionic copper(II) complex **X**⁻, which serves as a counterion for the active cationic complex. This *in situ* generated cationic copper(II) catalyst through a Lewis acid activation weakens the C-N bond of the aziridine. During the ring expansion, it is possible the copper center may chelate to the nearby olefin producing the transition state **10**. We believe that an ordered transition state, without complete heterolysis or homolysis of the C-N bond, is necessary to account for the diastereoselectivity observed in the rearrangement of substrates **23** and **24**. The rearrangement produces complex **11**, which then associatively undergoes an interchange with more substrate to reform complex **9**. Complexes **9** and **11** constitute the autocatalytic cycle that we propose is in good agreement with the observed kinetics presented in Figure 2. Complexes **9** and **11** cannot be observed during the course of the reaction because of the paramagnetic behavior of copper(II).

This proposed mechanism accounts for a number of other experimental observations not yet mentioned. First, product **12** was found to inhibit the reaction dramatically. Second, **X**⁻ was found to not be catalytically competent when synthesized independently.²² Also, reactions with cationic copper(II) complex **5** do not possess an induction period because it mimics the structure of **9** which is the active catalyst. Next, copper(II) species are observable (UV-Vis. Spectroscopy, NMR) throughout the reaction but no copper(I) intermediates could be detected nor were copper(I) catalysts competent in the rearrangement. Finally, using Singleton's method²³ we have obtained preliminary kinetic isotope results for two different vinyl aziridine substrates. These studies show significant heavy atom isotope effects at all three carbon centers involved in the rearrangement suggesting the reaction is concerted in nature.

In summary, we have demonstrated that 3-pyrrolines can be readily accessed from vinyl aziridines using commercially available copper(II) catalysts. The scope of this new catalytic rearrangement is very broad, providing access to a greater range of diverse products than other currently available 3-pyrroline forming methods. Mechanistic analysis revealed unique autocatalytic behavior and can be summarized as a Lewis Acid catalyzed [1,3]-Sigmatropic rearrangement. New catalysts were synthesized based on these mechanistic insights. These catalysts approach the effectiveness of Cu(hfacac)₂ but allow more options for electronic tuning and induction of asymmetry. Further studies on the mechanism and scope of this ring expansion are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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18. The substrates in entries 11, 13, and 24 under the thermal conditions form azomethine ylides and products from this intermediate are observed. In the reactions of entries 19 and 20 the pyrroles can be isolated from the retro Diels-Alder of the products.
19. Unfortunately when compound **1** was synthesized asymmetrically, chirality was not transferred to the product. Compound **1** was transesterified with a chiral alcohol in order to assess enantiomeric purity of the starting material and product. The product was found not to epimerize under the given reaction conditions.
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Figure 1.
Kinetics plot of 2-methyl-N-tosyl-2-vinylaziridine (Entry 3)

Scheme 1.
Proposed Catalytic Cycle

Table 1
Copper Catalyzed Ring Expansion of Vinyl Aziridines

entry	catalyst	time (h)	yield ^a
1	none	16	0% ^b
2	CuI	16	0%
3	Cu[(S,S)-Ph-box]Cl ₂	16	0%
4	Cu[(S,S)-Ph-box]OTf ₂	16	0%
5	Cu(acac) ₂	16	0%
6	Cu(tfacac) ₂	16	0%
7	Cu(dbm) ₂	16	10%
8	Cu(ptfm) ₂	16	0%
9	Cu(acyc) ₂	16	35%
10	Cu(tfaccy) ₂	16	20%.
11	Cu(fod) ₂	16	0%
12	Cu(3-[NO ₂]acac) ₂	16	0%
13	Cu(3-[CO ₂ Et]acac) ₂	16	20%
14	Cu(hfacac) ₂ · H ₂ O	11	70%
15	Cu(hfacac)₂ (dry)	7.5	99%
16	Cu(hfacac) ₂ (dry)	1 ^c	99%
17	Cu(hfacac) ₂ (dry)	22 ^d	99%
18	Cu(hfacac) ₂ (dry)	36 ^e	99%

Conditions: 5 mol % catalyst, toluene, 150 °C, 0.1 M.

{ hf = hexafluoro, acac = acetylacetonate, (S,S)-Ph-box = (S,S)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline), tf = trifluoro, dbm = dibenzoylmethanate, ptfm = 1,3-bis[4-(trifluoromethyl)phenyl]-1,3-propanedione, accy = 2-acetylcyclohexanone, fod = heptafluorobutanoyl pivaloylmethanate, 3-[NO₂]acac = 3-nitroacetylacetonate, 3-[CO₂Et]acac = ethyl diacetoacetate }

^aNMR Yield.

^bDecomposes at 170 °C.

^c5 M.

^d1 mol %.

^e130 °C.

Table 2

3-Pyrroline Synthesis

no.	substrate	product	R	time (h)	yield
1			Ts	5.5 ^c	92%
2			Phth	2 ^c	92%
3			Ts	1 ^c	99%
4			Phth	2 ^c	92%
5			Phth	3 ^c	96%
6			Ts	1 ^c	98%
7			Phth	0.3 ^c	93%
8			Phth	3 ^c	96%
9			Ts	12 ^d	80%
10			Ts	7.5 ^d	98%
11			Phth	0.8 ^d	67% ^k
12			Ts	5 ^c	97%
13			Ts	20 ^e	60%
14			Ts	6 ^e	95% ^k
15			Ts	20 ^d	75% ^f
16			Phth	16 ^d	93% ^{g,h}
17			Phth	12 ^d	94% ^g

no.	substrate	product	R	time (h)	yield
18 ^d			Phth	21 ^d	53%
19			Phth	3 ^d	28% ^k
20			Phth	2 ^d	56%
21			Ts	1 ^d	78%
22			Ts	1.5 ^d	94%
23 ^a			Ts	1 ^d	88% ⁱ
24 ^a			Ts	16 ^d	90% ^j

Conditions: 5 mol % dry Cu(hfacac)₂, 0.1 M.

^a Racemic.

^b Isolated yields.

^c 100 °C Benzene.

^d 150 °C Toluene.

^e 120 °C Toluene.

^f Cu(hfacac)₂ H₂O does not work.

^g 0.2 M.

h_{20} mol % Cu(tfiacac)₂.

$i_{>20:1}$ dr.

$j_{4:1}$ dr.

$k_{\text{Thermal component to reaction (see supporting information)}}$.