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# Copper-Catalyzed Cycloisomerization of Unactivated Allene-Tethered *O*-Propargyl Oximes: A Domino Reaction Sequence toward the Synthesis of Hexahydropyrrolo[3,4-*b*]azepin-5(4*H*)-ones

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Cite This: *Org. Lett.* 2021, 23, 3343−3348 Read Online

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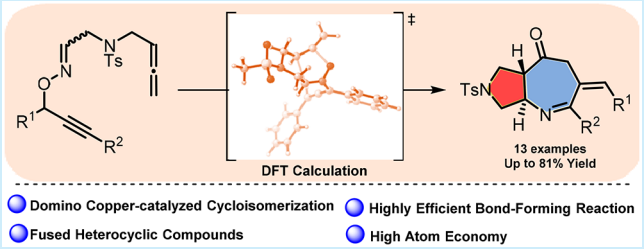
**ABSTRACT:** A novel copper-catalyzed cycloisomerization of unactivated allene-tethered *O*-propargyl oximes has been developed for the synthesis of hexahydropyrrolo[3,4-*b*]azepin-5(4*H*)-ones. This one-pot domino reaction proceeds via a [2,3]-sigmatropic rearrangement, a [3 + 2] cycloaddition, and another [3,3]-sigmatropic rearrangement. The methodology offers a practical and straightforward route for the rapid assembly of both ring components of the fused bicyclic motifs from acyclic precursors by simultaneously forming four new bonds (a C═O, a C═N, and two C−C bonds) in a single step.




Azepine and azepane derivatives are important classes of *N*-heterocycles found in a number of biologically important molecules and numerous natural products (Figure 1).[1,2]

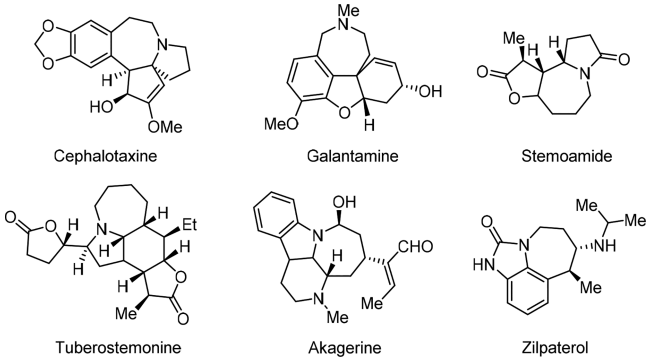



**Figure 1.** Examples of biologically active azepines.

Therefore, in recent years, various synthetic approaches to these valuable heterocyclic compounds have been introduced;[3] however, there are only a few approaches toward their ring-fused analogues, and their synthesis still remains a challenge.[4] Consequently, developing new synthetic strategies that enable the one-step assembly of their ring-fused analogues from readily available acyclic precursors is highly desirable.

In this regard, the transition-metal-catalyzed cycloisomerization of 1,*n*-enynes, 1,*n*-dienes and -diynes, and 1,*n*-allenynes and -allenenes has emerged as a powerful synthetic approach because it facilitates the rapid assembly of different types of complex cyclic compounds.[5] Nevertheless, because the reactive sites of the intermediates in these transformations involve only carbon atoms, mainly carbocyclic compounds are obtained. On the contrary, the cycloisomerization of various unsaturated compounds bearing an oxime moiety can be harnessed as a valuable synthetic building block for the synthesis of heterocyclic frameworks.[6] In this context, recently, there has been growing interest in *O*-propargyl oximes as alternative building blocks in cycloisomerization reactions, which provide efficient protocols for the synthesis of various heterocycles due to their ability to undergo C−O, C═N, and N−O bond-cleavage reactions.[7]

Consequently, intense interest has been directed toward the cycloisomerization reactions of structurally different *O*-propargyl oximes having different oxime groups. The nature of these domino skeletal rearrangement reactions and the possible reaction products depends on the nature of the unsaturated compounds installed on the oxime moiety.

To the best of our knowledge, all previously reported examples of the intramolecular cycloisomerization of *O*-propargyl oximes lead to the formation of single-ring heterocycles. For example, the reaction of *O*-propargyl oximes (**I**) possessing aryl groups in the presence of catalytic amounts of CuBr affords the corresponding azete oxides (**II**) through a domino [2,3]-rearrangement and a 4$\pi$-electrocyclization pathway.[8] Employing *O*-propargyl oximes having alkene moieties in the copper-catalyzed cascade reactions gives rise to the

**Received:** March 10, 2021
**Published:** April 12, 2021



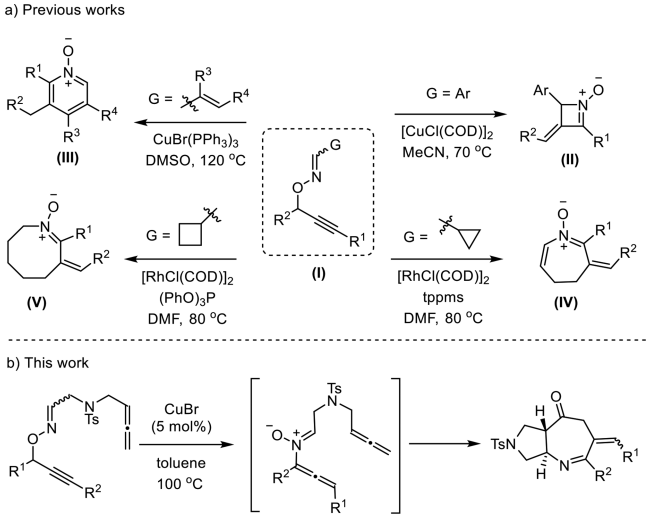




https://doi.org/10.1021/acs.orglett.1c00837
*Org. Lett.* 2021, 23, 3343−3348

corresponding multisubstituted pyridines (**III**) via a cascade, [2,3]-rearrangement and 6$\pi$-electrocyclization.[9] The rhodium-catalyzed cycloisomerization of *O*-propargyl oximes derived from cyclopropane carbaldehyde and cyclobutyl carbaldehyde furnishes the corresponding derivatives of azepine oxide (**IV**) and azocine oxide (**V**), respectively.[10,11] These reactions proceed through [2,3]-rearrangement and ring expansion of the strained cyclopropyl and cyclobutyl substituents (Scheme 1a).

**Scheme 1. (a) Domino Skeletal Rearrangement Reactions of *O*-Propargylic Oximes and (b) Cycloisomerization of Unactivated Allene-Tethered *O*-Propargyl Oximes**

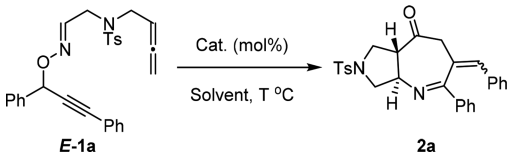



On the basis of our recent work on the rhodium-catalyzed cycloisomerization of 1,6-allenenes,[12] we envisioned that *O*-propargyl oximes having an allene moiety would be interesting substrates in cycloisomerization reactions to construct interesting structurally complex heterocycles. Herein we report the copper-catalyzed cycloisomerization of new, well-designed *O*-propargylic oximes **1** having an allene moiety, which provides easy access to fused, bicyclic hexahydropyrrolo[3,4-*b*]azepin-5(4*H*)-one scaffolds (Scheme 1b).

We commenced our studies with (*E*)-*O*-propargyl allenyloxime ***E*-1a** as the model substrate. Subjecting the substrate ***E*-1a** to 5 mol % of CuCl in toluene at 100 °C for 12 h furnished the hexahydropyrrolo[3,4-*b*]azepin-5(4*H*)-one product **2a** as a mixture of Z and E configurations of the exocyclic double bond of the product **2a** in a 78:22 (Z/E) ratio in 44% yield (entry 1). The structure of the bicyclic compound was unambiguously determined by NMR measurements and X-ray crystallographic analysis.

Optimization of the reaction conditions for the formation of **2a** was achieved by examining the effects of different catalysts and solvents (Table 1). Control experiments mediated by AgOTf, $Ph_3PAuCl$, $AuCl_3$, and $In(OTf)_3$ as catalysts were found to lead to a mixture of unknown decomposition products along with **2a** in 12% yield in the case of the latter (Table 1, entries 2–5). Using other Cu-based catalysts such as CuBr, $[Cu(COD)Cl]_2$, and $Cu(CH_3CN)_4BF_4$ revealed that CuBr is the best catalyst for the domino process, which gave access to the desired product in 69% yield with a E/Z ratio of 79:21 (Table 1, entries 6–8). Further screening of various solvents revealed that the reaction proceeds best in toluene.

**Table 1. Optimization of the Reaction Conditions[a]**




| entry | catalyst | solvent | temp (°C) | yield[b] (%) | Z/E |
|---|---|---|---|---|---|
| 1 | CuCl | toluene | 100 | 44 | 78:22 |
| 2 | AgOTf | toluene | 100 | | |
| 3 | $PPh_3AuCl$ | toluene | 100 | | |
| 4 | $AuCl_3$ | toluene | 100 | | |
| 5 | $In(OTf)_3$ | toluene | 100 | 12 | |
| **6** | **CuBr** | **toluene** | **100** | **69** | **79:21** |
| 7 | $[Cu(COD)Cl]_2$ | toluene | 100 | 64 | 79:21 |
| 8 | $Cu(CH_3CN)_4BF_4$ | toluene | 100 | 55 | 78:22 |
| 9 | CuBr | toluene | 80 | 40 | 79:21 |
| 10 | CuBr | toluene | 120 | 66 | 81:19 |
| 11 | CuBr | MeCN | 100 | 22 | 86:14 |
| 12 | CuBr | THF | 100 | 35 | 80:20 |
| 13 | CuBr | DMF | 100 | 40 | 80:20 |
| 14 | | toluene | 100 | n.r. | |

[a]Reaction conditions: **1a** (0.2 mmol), solvent [0.1 M], catalyst (5 mol %). [b]Isolated yields.

Moreover, the effect of the temperature was also investigated. By lowering the temperature from 100 to 80 °C, the yield was decreased to 40% (Table 1, entry 9). When the reaction temperature was increased from 100 to 120 °C, no improvement in yield was observed (Table 1, entry 10).

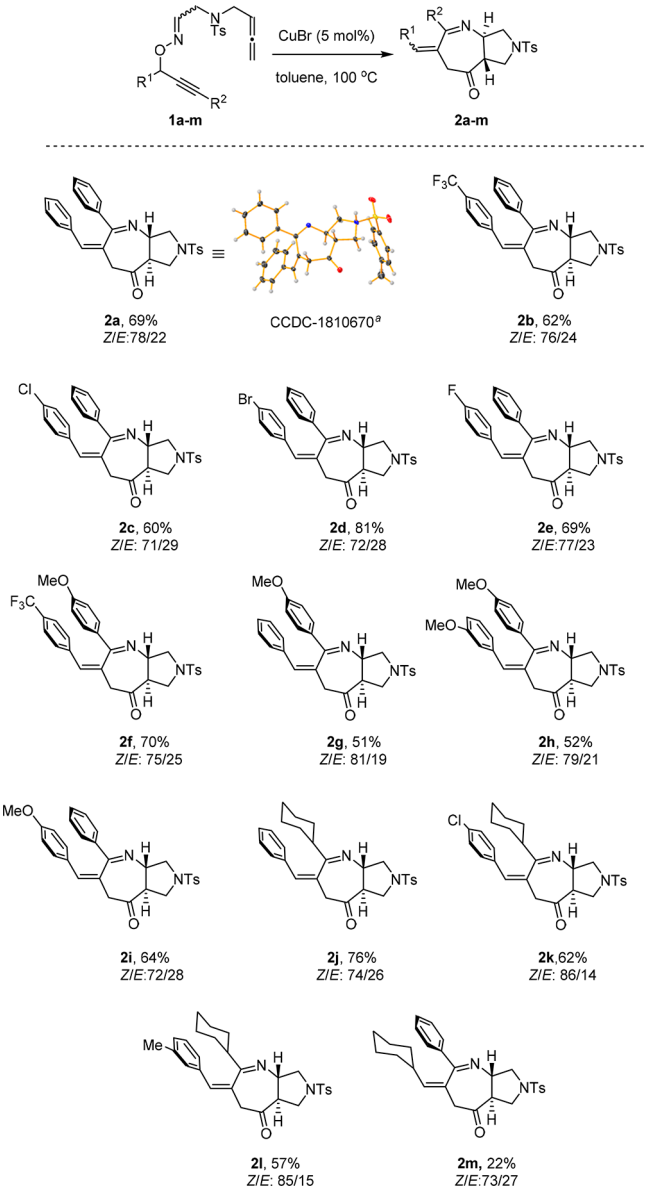
The starting material remained untouched in the absence of the catalyst (Table 1, entry 14). Interestingly, using the Z isomer of the starting material instead of the E isomer under the optimized reaction conditions (5 mol % CuBr in toluene at 100 °C) lead to the desired product in an almost similar yield with similar E/Z ratios (66% yield, 78:22 E/Z). Hence, subjecting a mixture of Z/E isomers of the starting material to the reaction conditions yielded the same result (66% yield, 79:21 Z/E).

With optimal reaction conditions in hand, we proceeded to investigate the substrate scope of this domino cycloisomerization process using various *O*-propargyl allenyloximes. As illustrated in Scheme 2, *O*-propargyl allenyloximes with either electron-poor or electron-rich aryl substituents at the propargylic position lead to the desired product in good to high yields (Scheme 2, **2a–2i**), and both aromatic and aliphatic substituents at the alkyne terminus were tolerated (Scheme 2, **2k** and **2l**). Aliphatic substituents at the propargylic position afforded the corresponding product, albeit in lower yields (Scheme 2, **2m**).

On the basis of the previously described results, our mechanistic hypothesis is described as shown in Figure 2b. First, the $\pi$-activation of the alkyne moiety of the *O*-propargylic oximes **1** by CuBr leads to the formation of *N*-allenyl nitrones ***E*-3** and ***Z*-3** via a well-known [2,3]-sigmatropic rearrangement. These two isomers are in equilibrium with each other under the reaction conditions. Next, the [3 + 2] dipolar cycloaddition (1,3-DC) of the generated *Z*,*E*-nitrone **3** with the allenyl moiety leads to methylene-*N*-allenylisoxazolidine **Int.A**. To gain further mechanism insight into this 1,3-DC reaction as the key step that has a main role in the diastereoselectivity of the reaction, density functional theory (DFT) calculations were


https://doi.org/10.1021/acs.orglett.1c00837
Org. Lett. 2021, 23, 3343–3348

**Scheme 2. Exploration of Substrate Scope**




[a]Ellipsoid probability level of the ORTEP diagram is 50%.

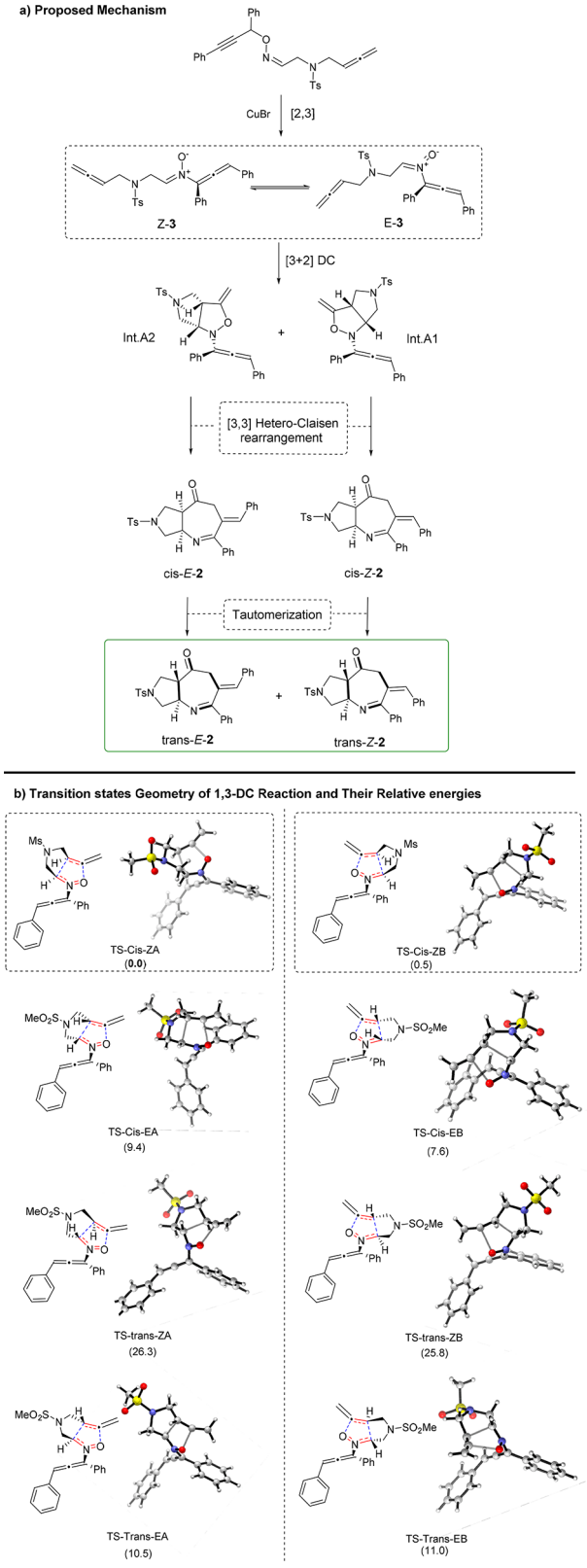



**Figure 2.** (a) Proposed reaction mechanism. (b) Optimized transition-state structures of the DC reaction. The relative Gibbs free energies at the B3LYP/6-311++G(d,p)-PCM(toluene)//B3LYP/6-31G(d,p) level of theory are given in parentheses (in kcal/mol).

carried out at the B3LYP/6-311++G(d,p)-PCM(toluene)//B3LYP/6-31G(d,p) level of theory using the Gaussian 09 package.[13,14]

A mesyl group was used as a model for the tosyl group in intermediate **3** (Figure 2). The relative Gibbs free energy of eight possible transition states (TSs) of the DC reaction showed that the ***Z*-3** isomer is more reactive than the ***E*-3** isomer, and this intramolecular DC primarily proceeds in an exo manner (Figure 2a). The Gibbs free-energy difference between **TS-Cis-ZA** and **TS-Cis-ZB** (0.54 kcal·mol$^{-1}$) well illustrates the ratio of stereoisomers obtained from the reaction. (The calculated Z/E based on Boltzmann populations is 71:29.)

Subsequently, the calculations suggest a unique concerted [3,3]-sigmatropic rearrangement that leads to the selective formation of ***cis*-Z-2** and ***cis*-E-2** (kinetic products)[15] from **Int.A1** and **Int.A2**, respectively (Figure 3, Figure S1, and Scheme 3.) The energy barrier of this [3,3]-sigmatropic rearrangement (12.7 kcal/mol) is lower than that of the prior 1,3-DC reaction (22.2 kcal/mol). Finally, the cis-fused kinetic



https://doi.org/10.1021/acs.orglett.1c00837
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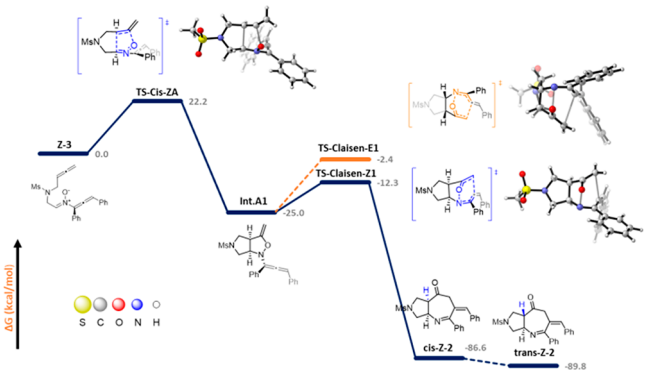
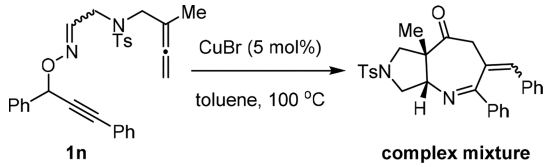



**Figure 3.** Potential energy surface (PES) for the formation of ***trans*-Z-2** as the major isomer. All energies are in kcal/mol

**Scheme 3. Cycloisomerization of 1n under the Optimized Reaction Condition**




products tautomerize to the thermodynamically more stable ***trans*-E-2** and ***trans*-Z-2**.

In summary, we have developed a novel method for the synthesis of a broad range of hexahydropyrrolo[3,4-*b*]azepin-5(4*H*)-ones via copper-catalyzed intermolecular cycloisomerization. Remarkably, this reaction allows the construction of one C═O, one C═N, and two C−C bonds by the cleavage of one C−O, one N−O, and one C═N bond in a single synthetic operation via a [2,3]-sigmatropic rearrangement/[3 + 2] cycloaddition/[3,3]-sigmatropic rearrangement sequence of unactivated allene-tethered *O*-propargyl oximes. This methodology is distinguished by a broad scope, a high yield, low catalyst loadings, and a mild, operationally simple strategy. Reaction selectivity is supported by DFT calculations involving the sequence of a 1,3-dipolar cycloaddition, a novel Claisen-type rearrangement, and a keto−enol tautomerization. Hence, this new intramolecular cyclization has the potential to be used in pharmaceutical exploitation and the total synthesis of natural products containing azepin motifs.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00837.

General experimental procedures, computational details, and $^{1}$H NMR, $^{13}$C NMR, and HR-MS spectra of all compounds (PDF)

### Accession Codes

CCDC 1810670 contains 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.

## ■ ACKNOWLEDGMENTS

We are grateful for a fellowship from the Alexander von Humboldt Foundation for the Research Group Linkage Program financial support. We thank Dr. Daniel Kratzert for the X-ray crystal structure analysis (Institut für anorganische Chemie, Albert-Ludwigs-Universitat Freiburg).

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https://doi.org/10.1021/acs.orglett.1c00837
*Org. Lett.* 2021, 23, 3343−3348