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# Mechanism and the Origins of Stereospecificity in Copper-Catalyzed Ring Expansion of Vinyl Oxiranes: A Traceless Dual Transition-Metal-Mediated Process

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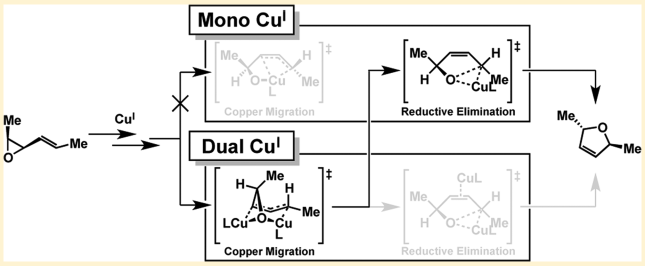
S *Supporting Information*

**ABSTRACT:** Density functional theory computations of the Cu-catalyzed ring expansion of vinyloxiranes is mediated by a traceless dual Cu(I)-catalyst mechanism. Overall, the reaction involves a monomeric Cu(I)-catalyst, but a single key step, the Cu migration, requires two Cu(I)-catalysts for the transformation. This dual-Cu step is found to be a true double Cu(I) transition state rather than a single Cu(I) transition state in the presence of an adventitious, spectator Cu(I). Both Cu(I) catalysts are involved in the bond forming and breaking process. The single Cu(I) transition state is not a stationary point on the potential energy surface. Interestingly, the reductive elimination is rate-determining for the major diastereomeric product, while the Cu(I) migration step is rate-determining for the minor. Thus, while the reaction requires dual Cu(I) activation to proceed, kinetically, the presence of the dual-Cu(I) step is untraceable. The diastereospecificity of this reaction is controlled by the Cu migration step. Suprafacial migration is favored over antarafacial migration due to the distorted Cu $\pi$-allyl in the latter.



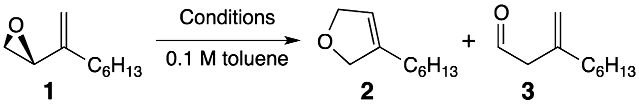
## 1. INTRODUCTION

Cooperative or dual catalysis has become popular in recent literature; dual organocatalyzed,[1] organo- and transition-metal-catalyzed,[2] homobimetallic transition-metal-catalyzed,[3] and even heterobimetallic-catalyzed[4] processes are known.[5] We have previously reported a simple and scalable Cu(II)-catalyzed synthetic method for the preparation of dihydrofurans (DHFs) from vinyloxiranes (VOs)[6a,b] (Table 1),[7] key structural components found in natural products, bulk commodity chemicals, and pharmaceuticals. Herein, we report the complete mechanism and the origins of diastereospecificity for this transformation. Specifically, we propose an unusual, traceless dual catalysis motif. A key step in this reaction requires two Cu(I)-catalysts, but the rate-determining step only requires a single catalyst. Ultimately, this renders the dual catalysis motif kinetically undetectable but crucial for the chemistry.

## 2. EXPERIMENTAL SECTION

As previously reported,[6] $Cu(hfacac)_2$ catalyzes the transformation of vinyloxirane **1** to dihydrofuran **2**. In these reactions, a significant initial induction period was observed, suggesting that a more active catalyst was being formed in situ. We have since discovered that this ring expansion reaction is significantly accelerated by the use of Cu(I) catalysts. This was accomplished using reducing agents such as Sn(II)-2-ethylhexanoate[8a] and cobaltocene,[8b] or alternatively by using preformed Cu(I) catalysts such as Cu(hfacac)(cod).[9] Employing either one of these conditions, significant reaction acceleration was observed, and ring expansions could be run at lower temperatures (Table 1). All conditions perform similarly at 150 °C (entries 1−3), but at 100 or 80 °C the Cu(II) conditions (A) fail (entries 4 and 7), while the new Cu(I) catalyzed conditions successfully ring expand **1** to

Table 1. Copper-Catalyzed Rearrangement of Vinyloxirane 1[a]



| entry | conditions | temp (°C) | time (h) | conv. (%) | DHF:H-shift |
|---|---|---|---|---|---|
| 1 | A | 150 | 0.25 | 100 | 13:1 |
| 2 | B | 150 | 0.25 | 100 | 17:1 |
| 3 | C | 150 | 0.25 | 100 | 15:1 |
| 4 | A | 100 | 4 | no rxn | N/A |
| 5 | B | 100 | 4 | 84 | >20: 1 |
| 6 | C | 100 | 4 | 65 | >20: 1 |
| 7 | A | 80 | 10 | no rxn | N/A |
| 8 | B | 80 | 10 | 89 | >20: 1 |
| 9 | C | 80 | 10 | 70 | >20: 1 |

[a]Conditions: (A) 5 mol % $Cu(hfacac)_2$; (B) 5 mol % $Cu(hfacac)_2$ + 5 mol % $Sn(2\text{-ethylhexanoate})_2$; (C) 5 mol % Cu(hfacac)(COD).

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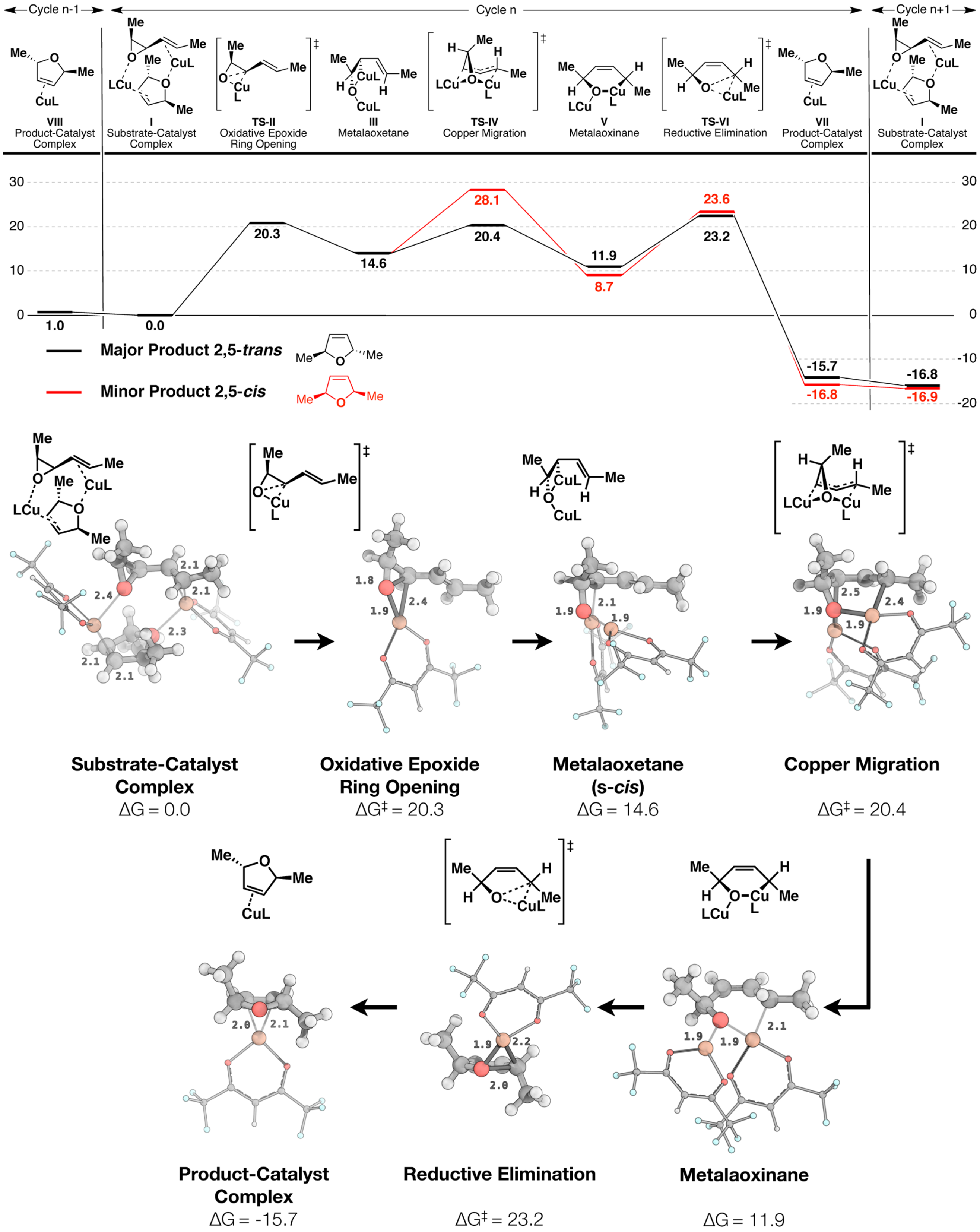


**Figure 1.**[7] Reaction coordinate of Cu(I)-catalyzed ring expansion of *cis*-2,3-epoxy-*trans*-4-hexene (*cis*-2-methyl-*trans*-3-propenoxirane) (above) and structures of stationary points along the reaction coordinate for the formation of the major products (below). All structures, energies, and free energy corrections computed at the B3LYP/def2-SVP level of theory, as implemented in Turbomole.[10a−d] Energies displayed in kcal/mol, and distances in Å. Computed structures rendered using Pymol.[10e]

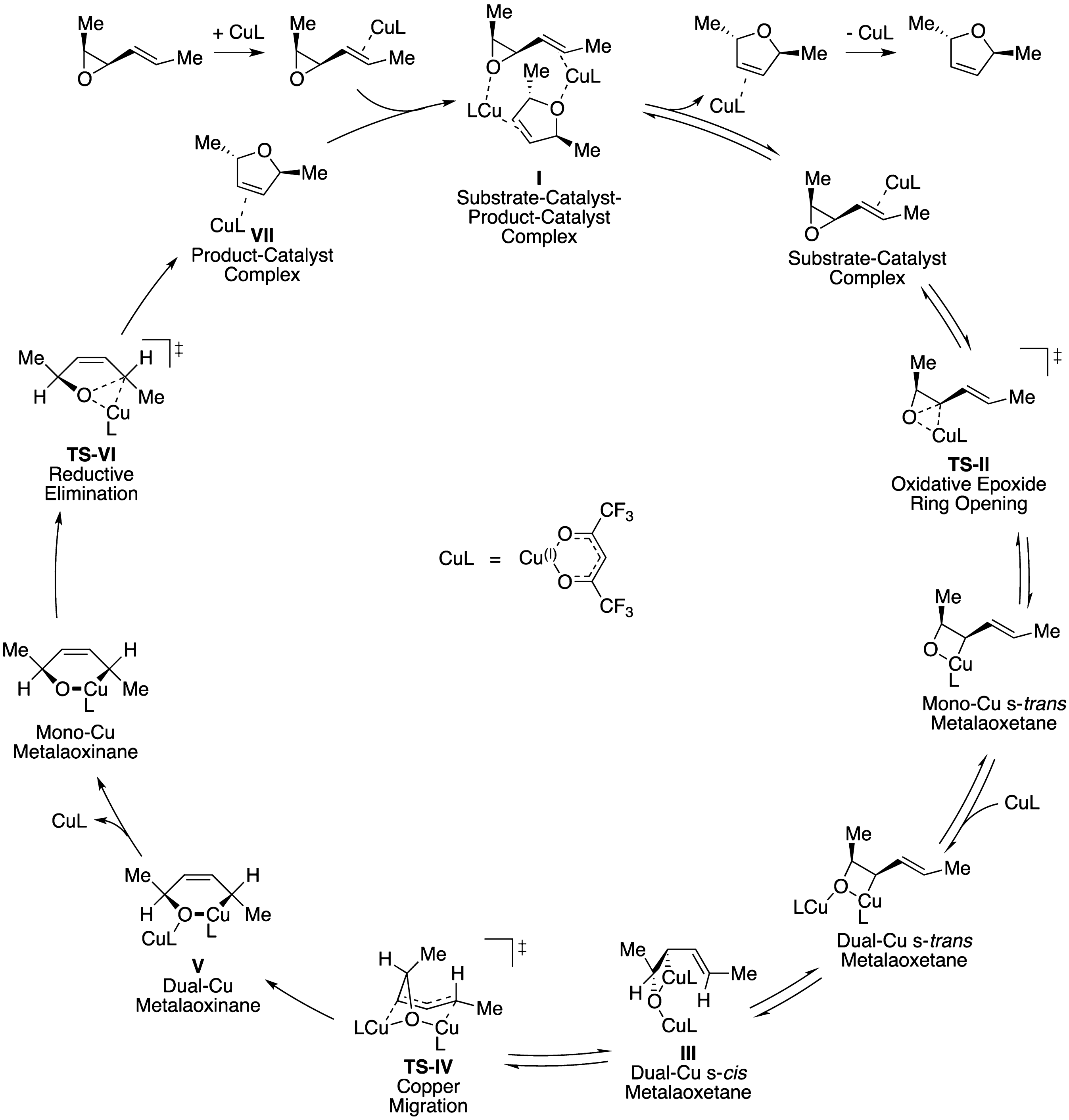


**Figure 2.** Complete catalytic cycle for the Cu(I)-catalyzed stereospecific rearrangement of vinyloxiranes to dihydrofurans.

selectively form **2** (entries 5–6 and 8–9). Equally important evidence in favor of Cu(I)-catalysis was the absence of the initial induction period previously observed in all Cu(hfacac)$_2$ kinetic traces.[6a,7,8a,9] Similar Cu(I) supportive insights were also observed for the analogous vinylaziridine expansion.[9]

## 3. METHODS

The geometries and thermal corrections for all stationary points along the reaction coordinate were computed with the B3LYP and the def2-SVP basis set, as implemented in the Turbomole suite of programs.[10] Manual, exhaustive conformational searches, including all possible single or dual Cu ligation isomers, were performed for all species reported. Stationary points were verified by frequency calculations and wave function stability tests.

## 4. RESULTS AND DISCUSSION

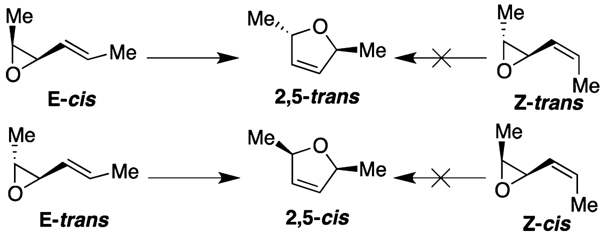
Initially, the entire reaction coordinate involving a single Cu(I)-catalyst was computed. The catalytic cycle begins with the initial exothermic complexation of a free Cu(I) catalyst with a substrate alkene. Oxidative epoxide ring opening affords the s-*trans*-metalaoxetane. Upon isomerization to s-*cis*-metalaoxetane, the copper is poised for migration to the distal olefin carbon. However, computations showed that this key Cu(I)-migration step to form the metalaoxinane is not a stationary point on the potential energy surface with a single Cu(I) catalyst. If the metalaoxinane could be produced, the system would undergo reductive elimination to afford the dihydrofuran product.

In the monocopper migration process, the endocyclic Cu(III) migrates to the distal olefin carbon to form the metalaoxinane directly. However, shortening the Cu−C bond along the expected reaction coordinate results in the reformation of the oxirane ring, reverting back to the starting VO−Cu complex. In sharp contrast, a dual Cu(I)-catalyzed migration step to form the metalaoxinane was a true stationary point along the reaction coordinate. In the dual-copper process, the exocyclic Cu(I) migrates to the distal olefin carbon forming the metalaoxinane. These computational evidence collectively suggest that this dual Cu step is distinctly different from a single Cu mechanism in the presence of an adventitious, spectator Cu(I); the second Cu(I) is essential for this transformation.

This reaction involves both single and dual copper intermediates and transition states (Figures 1 and 2).[12] The reaction coordinate diagram as well as the computed structures for the formation of the major product is shown in Figure 1. The complete detailed catalytic cycle is shown in Figure 2. The resting state of the catalytic process is the cyclic substrate−catalyst−product−catalyst complex **I**. Both Cu(I) catalysts are found to be square pyramidal, coordinating to the $\pi$-systems of a substrate or product and an oxygen of another substrate or product. The dissociation of this complex to the monocopper vinyl oxirane complex is endothermic by 2.3 kcal/mol. In the oxidative epoxide ring opening **TS-II**, the Cu(I)-hfacac inserts into the epoxide C−O bond. The metalaoxetane Cu(III) is also in a square planar configuration, with the coordinating C, O, and the hfacac in the plane. Upon complexation of a free Cu(I) catalyst to the metalaoxetane oxygen, the s-*trans*/s-*cis* isomerization of this species affords the dual-copper s-*cis*-metalaoxetane **III**. In the following copper migration **TS-IV**, the exocyclic Cu(I) migrates to the distal olefin carbon, forming the metalaoxinane, while simultaneously breaking the metalaoxetane C−Cu bond.[13] This metalaoxinane **V** is in an envelope conformation with the newly formed metalaoxinane endocyclic Cu(III) puckered. The dissociation of the exocyclic oxygen bound Cu(I) leads to the reductive elimination of **TS-VI**, closing the ring to produce the DHF product and regenerating the Cu(I) catalyst.

The title reaction is diastereospecific: *E-cis* and *Z-trans* yield the *trans*-DHF product, whereas the *E-trans* and *Z-cis* yield the *cis*-DHF product (Scheme 1).[6a,11] The complete reaction coordinate of the Cu(I)-catalyzed rearrangement involving all VOs shown in Scheme 1 were computed and are included in the Supporting Information. In all cases, computations reproduce the experimental diastereoselectivities.

**Scheme 1. Diastereospecificity of the Title Reaction**[a]



[a] *E-cis* and *Z-cis* yield the *trans*-DHP product, whereas the *E-trans* and *Z-trans* yield the *cis*.[6a,11]

Diastereodifferentiation arises at the copper migration (Figure 3). The migration of the exocyclic Cu(I) to the olefin can be either suprafacial or antarafacial to the breaking endocyclic Cu(III)−C bond. The major pathway proceeds through the energetically preferred suprafacial copper migration, while the minor pathway proceeds through the disfavored antarafacial migration. In all cases, suprafacial rearrangements were energetically more favorable than the antarafacial. In the case shown in Figure 3, the preference for the suprafacial migration was 7.7 kcal/mol. This is because (1) the antarafacial transition structure is destabilized by the loss of conjugation in the nonplanar $\pi$-allyl. This distortion (39° from planarity) is necessary to realize Cu(I)-catalyst migration to the distal prochiral face of the $\pi$-allyl (Figure 3, highlighted in green). Analogous distortion from planarity in the parent allyl anion corresponds to 4.6 kcal/mol of destabilization. (2) The rest of

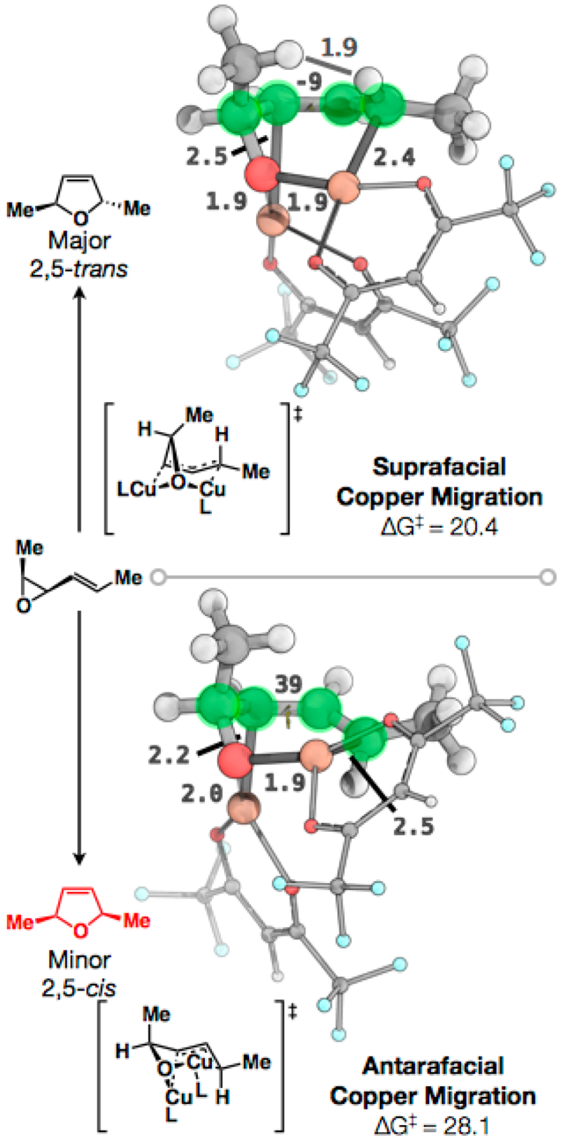


**Figure 3.** Dual Cu(I) migration transition structures leading to the major and minor products, computed at the B3LYP/def2-SVP level of theory, as implemented in Turbomole.[10a−d] $\pi$-allyl atoms are highlighted in green. Energies displayed in kcal/mol, distances in Å, and dihedrals in degrees. Computed structures rendered using Pymol.[10e]

the selectivity most likely arises from the strains in the Cu bonds.

Interestingly, the rate-determining steps are different for the formation of the major and minor diastereomeric products. The computed barriers suggest that the dual-Cu(I) migration step is not rate determining for the formation of the major product (i.e., the necessity of two Cu(I)-catalysts for this transformation is kinetically traceless), but it is in the minor product pathway.

While the existence of d-orbitals and the possibility of other intervening mechanisms complicate the extension of Woodward−Hoffmann rules to transition-metal-catalyzed reactions,[14] the failure of the monomeric Cu(I)-catalyzed process is conspicuously in line with Woodward−Hoffmann rules which predict a forbidden concerted 1,3-suprafacial sigmatropic shift.[15] We hypothesize that the presence of the second intervening Cu(I) circumvents the cyclic $\pi$-orbital alignment restrictions of a concerted, thermal pericyclic process and allows the reaction to proceed.

## 5. CONCLUSION

In summary, we have used computations and experiments to elucidate the complete mechanism and origins of the diastereospecificity of a Cu(I)-catalyzed rearrangement of vinyloxiranes to dihydrofurans. DFT computations reveal that an unusual, traceless dual transition-metal-mediated process is operative. Efforts are underway to capitalize on this milder synthetic procedure and for the design of new synthetic processes with improved selectivities based on these discoveries.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Cartesian coordinates, energies, and reaction coordinate diagrams. Detailed explanation of relative energies between monomeric and dual copper species also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(11) The *Z-cis/trans* substrates afford ketones as the major product, as a result of a competing hydride shift mechanism.

(12) Conversion between monomeric and dual copper species is shown in the Supporting Information.

(13) For the unsubstituted VO the suprafacial Cu migration is stepwise. Cu attacks the allyl, forming a tricyclic intermediate followed by Cu-allyl dissociation to form the metalaoxinane intermediate. In contrast, the antarafacial copper migration is concerted. See Supporting Information.

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