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Mechanistic Studies on Au(I)-Catalyzed [3,3]-Sigmatropic Rearrangements using Cyclopropane Probes

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Abstract

A comparative study of the Au(I)-catalyzed [3,3]-sigmatropic rearrangement of propargylic esters and propargyl vinyl ethers is described. Stereochemically defined cyclopropanes are employed as mechanistic probes to provide new synthetic and theoretical data concerning the reversibility of this type of rearrangement. Factors controlling the structure-reactivity relationship of Au(I)-coordinated allenes have been examined, thereby allowing for controlled access to orthogonal reactivity.

Introduction

Among the large number of reactions disclosed in the past five years in the field of homogenous gold catalysis,[1] the Au(I)-catalyzed rearrangement of propargylic esters has recently gained much attention. This interest is primarily due to the accessibility of the starting materials, the mild reaction conditions required for conversion, and above all the very rich chemistry that derives from the two main reaction manifolds, the Au(I)-catalyzed [2,3] and [3,3]-sigmatropic rearrangements.[2] Evidence for the existence of Au-carbenoid species in the [2,3]-rearrangement has been gathered in an array of ways that include intra-[3] and intermolecular trapping[4] including oxidation[5] of the carbenoid intermediates. In a closely related field, we have recently reported that propargyl vinyl ethers undergo irreversible Au(I)-catalyzed Claisen rearrangements[6] to afford allenes **3** (Scheme 1). These allenes are proposed to result from the Grob-type fragmentation of intermediates **2**.

It has been postulated that Au(I)-catalyzed [3,3]-rearrangements of propargylic esters are reversible processes[7,8] that take place via cationic intermediates related to **4** and subsequent formation of Au(I)-coordinated allenes **5**, which can then undergo further transformations.[9] However, the reversibility of the rearrangement is generally assumed, and validation by direct experimental evidence is lacking. Also, the final products arising from **5** depend heavily on the electronic structure of the metal-bound allene. A diverse pool of reactions[10,11] has been published that take advantage of substituents enforcing the dominance of specific resonance forms of reactive intermediates. Despite these successes, information about the factors dictating which resonance form dominates and relative rates of competing reaction pathways remains largely empirical. A better understanding of the various reactive intermediates in these systems would provide a more robust foundation for the design of future reaction manifolds.

In an effort to gain insight on the nature of these intermediates, we sought to capitalize on the known tendency of cyclopropyl carbinyl cations to undergo rearrangements.[12,13] Phenyl-substituted cyclopropanes have proven valuable mechanistic probes in the identification of cationic mechanisms.[14] To test for cationic reactivity in the Au-bound intermediates, we

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designed substrates incorporating a *cis*-disubstituted cyclopropyl group at the propargylic position. If species evolved exhibiting significant carbocationic character alpha to the cyclopropane, a fast isomerization to the thermodynamically more stable *trans*-cyclopropane should result (structures **7** and **8**, Scheme 2). Additionally, varying the electronic properties of the cyclopropyl substituents themselves should enable modulation of the reactivity prompted by positive charge build-up in the Au-coordinated allenes or other intermediates.

Computational results are presented here in tandem with the experimental data, a combination often used in modern organic chemistry.[15] The theoretical results establish consistency between our specific system and those studied by others, and lend support to many of our mechanistic claims. In this context, the present work describes a comparative study of the Au (I)-catalyzed [3,3]-rearrangement of two different cyclopropyl-substituted systems, propargylic esters and propargyl vinyl ethers.

Results and discussion

1. General reactivity: esters vs. vinyl ethers

An initial test reaction on the model substrate **9** showed that the Au(I)-catalyzed rearrangement of the pivaloate in CH_2Cl_2 afforded, instead of the expected allene, cyclopentene **10** (62%, 75:25 mixture of olefin isomers about the exocyclic double bond) and enyne **11** (32%) after 10 minutes (Scheme 3.1). Employing CH_3NO_2 as the solvent suppressed formation of **11**, affording exclusively the cyclopentene **10** in 75% yield as a mixture of olefins about the exocyclic double bond (86:14 *E*/*Z* ratio), albeit with longer reaction times (8 h). In contrast, using C_6H_6 as the solvent favored formation of the open enyne **11** over **10**. While no allene species were detected during these trials, we present strong evidence that **10** is in fact the product of a cyclopropyl ring expansion from an allene intermediate.[16] In agreement with our previously reported results,[6a] and in contrast to the reaction of **9**, treatment of vinyl ether **12** in CH_2Cl_2 with catalytic $[(Ph_3PAu)_3O]BF_4$ resulted in the exclusive formation of the corresponding allene **13** (Scheme 3.2). The $Ph_3PAuSbF_6$-catalyzed reaction also afforded **13** as the sole reaction product, albeit in lower yield (76%).

2. On the reversibility of the [3,3]-sigmatropic rearrangement

2.1. Experimental evidence—The use of a stereochemically defined starting material provided an opportunity to probe the reversibility of subsequent steps along the reaction pathway. A key observation emerged from ^{1}H NMR analysis of the reaction mixture during the transformation of **9** to **10**: as the reaction progressed, formation of **10** was observed along with gradual scrambling of the stereochemistry of **9** at both propargylic and cyclopropyl positions in the remaining propargyl starting material (eq 1). This scrambling occurred in two separate events. First, the relative stereochemistry at the propargylic position was completely lost after only 2 minutes, suggesting that the first event is a very fast and reversible rearrangement of the pivaloate group. It is known that Au(I) catalyzes the stereoisomerization of allenes[6a,6c,17] and thus this scrambling event is likely to proceed through a reversible [3,3]-sigmatropic rearrangement. Second, a slower *cis*-to-*trans* isomerization of the cyclopropyl moiety took place over 1 h, leaving the *trans*-cyclopropyl isomer (as a 1:1 mixture of diastereomers of propargyl ester) as the predominant form of **9** thereafter.[18] This result implies that the two scrambling events are mechanistically distinct, and allows for the proposal of an intermediate with carbocationic character which is responsible for the *cis*/*trans* cyclopropyl scrambling and which is generated along the propargylic scrambling pathway.

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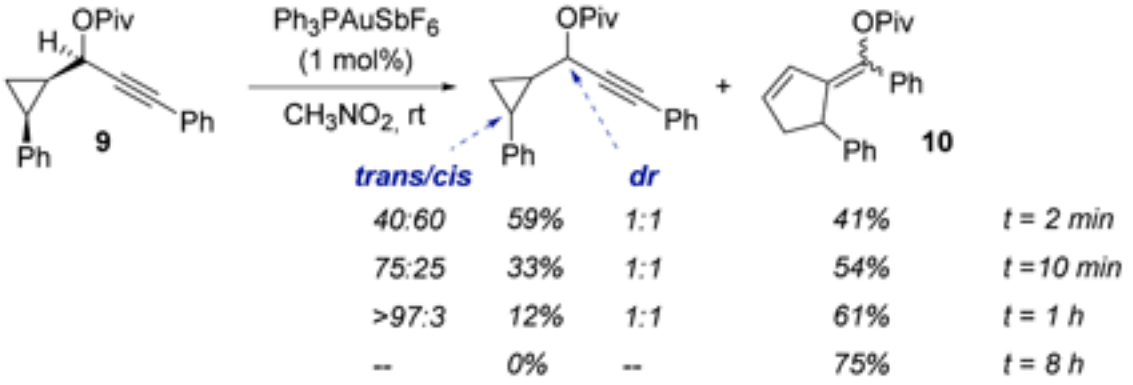

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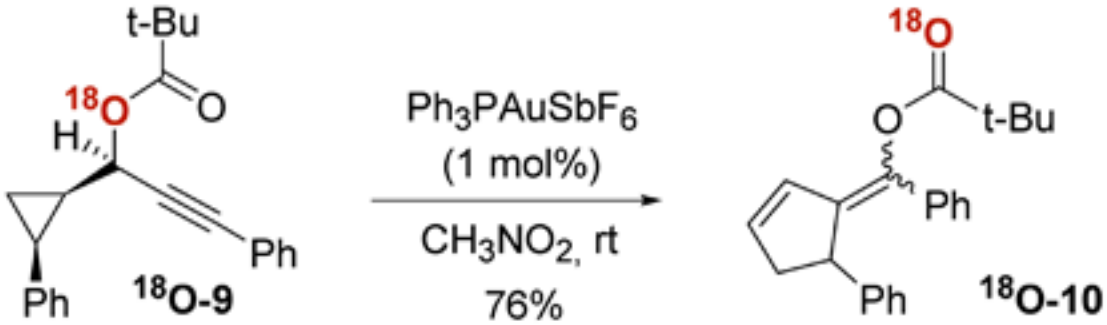
2.2. [3,3]-rearrangement as double [2,3]-migration?—It has been suggested that double [2,3]-acyloxy migrations can also account for net [3,3]-rearrangements.[8,9c] In order to investigate this assertion, an isotopic labeling study was conducted wherein the ^{18}O-enriched ester ^{18}**O-9** was synthesized and subjected to the reaction conditions (eq 2).[19] After 8 hours, cyclopentene ^{18}**O-10** was isolated in 76% yield. Mass and IR spectra showed that the ^{18}O label resided exclusively at the carbonyl oxygen of ^{18}**O-10**. Two conclusions can be drawn from this experiment. First, **10** is exclusively generated from a [3,3]-rearrangement, provided that it is formed directly from a Au(I)-coordinated allene. A double [2,3]-acyloxy migration would place the label at the ester linkage in the allene intermediate and thus also in the ester linkage in ^{18}**O-10**. In apparent contradiction with a previous computational study,[8] the fact that the label does not scramble allowed us to determine that, at least in the case reported herein, the proposed double migration is not operative.[20] Second, stereochemical scrambling at the propargylic position of the substrate is not caused by ionization of the pivaloate moiety. If ionization had occurred then scrambling at the labeled position should have been observed.[21]



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2.3. DFT studies on the reversibility of propargylic esters—A computational study (B3LYP/LACVP**, see Supporting Information for details and coordinates) was undertaken to model the reaction path from the nearly un-simplified model propargylic ester complex **A1** to allene complex **A3** shown in Figure 1. Our studies indicate that **A1**, **A2** and **A3** should rapidly interconvert. These results are qualitatively similar to those obtained for a more simplified system studied by Cavallo and coworkers.[8] The activation barrier ($\Delta G_{STP}^{\ddagger}$ in CH_2Cl_2) corresponding to the cyclization transition state **Ats1** was predicted to be 7.5 kcal/

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mol. Heterocycle **A2** and allene **A3** appear to be isoenergetic and more stable than **A1** by 4.3 kcal/mol.

It is well established experimentally[6a,6c] and theoretically[17] that axially chiral allenes undergo Au-catalyzed racemization. The low-energy structure **A4** was predicted to be accessible from **A3**, which arises from a rotation of approximately 60° about the bond connecting the central allenyl carbon and C1 (resonance forms in Scheme 2). In this configuration the four allenyl substituents are nearly coplanar and thus the allenyl stereochemistry would not be expected to persist. The calculated barrier to rotation from **A3** to **A4** is only 1.9 kcal/mol (5.7 kcal/mol for the reverse process). In conjunction with the reversibility of the [3,3]-rearrangement, this reactivity profile accounts for the experimentally-observed stereochemical scrambling at the propargyl position of **9**, as suggested above.

The *trans*-cyclopropyl allene complex $\mathbf{A3}_{trans}$ was correctly predicted to be slightly more stable than **A3**. Unfortunately no satisfactory, low-energy pathway was located for the conversion of **A3** to $\mathbf{A3}_{trans}$ although several possible routes were investigated. Based on literature precedent[12] concerning an organic system, we suggest a mechanism commencing with a 1,2-methylene shift in the cyclopropyl fragment to form a cyclobutonium intermediate. However, several species along this pathway could not be located and thus alternative mechanisms should be entertained. This issue and one other candidate mechanism are discussed in the Supporting Information.

2.4. DFT studies on the reversibility of propargyl vinyl ethers—To establish appropriate comparisons between reactivity patterns, we performed additional computations employing a model propargyl vinyl ether. As stated above (eq 2), a very clean and fast reaction affording the allenyl *cis*-cyclopropane **13** was observed experimentally. The computed reaction path for the vinyl ether system **B** is shown in Figure 2. The predicted activation barrier for the initial cyclization is considerably lower than that for model system **A**, and the transformation to allene **B3** was found to be much more exothermic, as expected for a carbon-carbon bond forming reaction. There is a qualitative difference, however, in that the cyclic structure B2 was not located as a stationary point on the reaction path. Rather, searching along the reaction coordinate from transition state **Bts1** revealed **B2** as only a shoulder along a concerted pathway to **B3** (Figure 2, insert, electronic energy (*E*) only); no nearby minima or transition states were located. As in model system **A**, the *trans*-cyclopropyl isomer $\mathbf{B3}_{trans}$ was calculated to be slightly more stable than **B3** (by 2 kcal/mol). Additionally, a twisted allene structure (**B4**) was predicted to be accessible, although in this case it is slightly less stable than **B3**. Therefore, scrambling of the stereochemistry in the product allene is predicted for this system, although the irreversibility of the [3,3]-rearrangement dictates that no scrambling of stereochemistry at the propargyl position of the starting substrate should be observed. This prediction is consistent with the findings of a previous study of propargyl vinyl ethers.[6a]

3. Substituents determine η^1- or η^2-allene character of Au(I)-coordinated allenes

3.1. Experimental evidence—We next examined the impact that arylcyclopropyl groups with different electronic properties might exert on product distribution and stereochemistry. Replacement of the phenyl group of **9** with 4-$NO_2C_6H_4$ and 4-$MeOC_6H_4$ had a dramatic effect on the reactivity of both the ester and vinyl ether systems. Specifically, reaction of the electron-deficient analog **15**, bearing a 4-$NO_2C_6H_4$ group, resulted exclusively in rapid scrambling of the stereochemistry at the propargylic position (1:1 ratio after 10 minutes) and *cis*/*trans* cyclopropane isomerization (a 70:30 ratio of *cis*/*trans* isomers was obtained, Scheme 4.1). The fact that a decrease in the cation-stabilizing ability of the cyclopropyl substituent results in incomplete scrambling of the cyclopropyl stereochemistry as well as failure to yield a cyclopentene product indicates that positive charge build-up near the aryl group is an important

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feature of the *cis*/*trans* cyclopropyl isomerization as well as the cyclopropyl ring expansion. Specifically, exposure of propargylic ester **15** (bearing a 4-$MeOC_6H_4$ group) to $Ph_3PAuSbF_6$ afforded cyclopentene **16** in 97% yield after only 10 minutes (Scheme 4.2), indicating that the electron-donating nature of the 4-$MeOC_6H_4$ group and its ability to stabilize nearby positive charge build-up greatly increases the reactivity of the system.

In analogy with propargylic esters, propargyl vinyl ethers bearing 4-$NO_2C_6H_4$ and 4-$MeOC_6H_4$ groups on the cyclopropyl moiety were synthesized. In light of the results obtained for substrate **12** (Scheme 3.2), $[(Ph_3PAu)_3O]BF_4$ was used as the catalyst for this part of our studies. First, reaction of 4-$NO_2C_6H_4$-substituted **17** led exclusively to quantitative formation of allene **18** with complete retention of the cyclopropyl stereochemistry (Scheme 4.3). Conversely, treatment of the 4-$MeOC_6H_4$-substituted propargyl vinyl ether **19** under identical reaction conditions resulted in the very rapid formation of a mixture of species assigned as allenes **20** and **21** (by ^{1}H NMR, Figure 5.4), indicating that *cis*/*trans* cyclopropyl isomerization was now operative. Subsequently, the peaks corresponding to **20** and **21** gradually disappeared while those belonging to cyclopentene **22** gained intensity. After 48 h, **22** was the only observed species, existing as a 75:25 mixture of olefin isomers about the exocyclic double bond. This experiment provides direct evidence that the cyclopropyl ring expansion proceeds only from an allene intermediate.[22] It is reasonable to posit that this holds for the formation of **10** as well, as proposed above.

3.2. The allene-Au bond—The preceding observations reveal that, although the ester and ether systems follow analogous mechanistic pathways, electronic effects play a critical role in the final outcome of the reaction. In the case of propargylic esters, the participation of resonance form **24** (Scheme 5) in the allene intermediate appears to be significant. There apparently is sufficient positive charge build-up at C1 to allow a *cis*/*trans* cyclopropyl scrambling process, even in the presence of a strongly electron-withdrawing group (Ar= 4-$NO_2C_6H_4$) on the cyclopropyl ring. However, it appears that electron-deficient cyclopropyl substitution renders the central allenyl carbon insufficiently nucleophilic for the allene intermediate to undergo pentannulation. Conversely, the electron-donating 4-$MeOC_6H_4$ cyclopropyl substitution stabilizes positive charge build-up in the intermediates along the cyclopropyl scrambling pathway while also rendering the allenyl fragment more electron-rich. Thus, the rates of both cyclopropyl scrambling and pentannulation are accelerated.

The principal structural difference between the ester and ether systems is the presence of the allenyl oxygen. Non-activated systems that do not contain an allenyl oxygen, such as **12** and **17**, do not experience sufficient positive charge build-up at C1 to undergo *cis*/*trans* cyclopropyl isomerization. In other words, the participation of the vinyl-Au(I) resonance form **27** is less important. However, the incorporation of an electron-rich aryl group stabilizes the system to the extent that less cationic character is needed at C1 for the cyclopropyl rearrangements to become operative.

The electronic and structural explanations posited above are supported by computational analysis of the structures of allenes **A3** (Figure 3a) and **B3** (Figure 3b). The most obvious difference between the geometries of the two structures is the nature of the carbon-Au bonds. While the gold center in **A3** is canted strongly towards C2, **B3** appears more like a η^2-coordinated allene[17,23] wherein C1 and C2 both participate in bonding ($\angle$(C1–C2-Au) = 89°, see Figure 3 for other angles).

A Natural Bond Orbital (NBO) analysis suggested that the bonding differences are due to polarization of the C1–C2 and C2–C3 bonds by the ester oxygen in **A3**, which has the effect of placing more electron density at C2 (natural charges are −0.41 and −0.22 for **A3** and **B3**, respectively) and in turn increases the ionic character of the C2-Au bond (d(C2-Au) = 2.13

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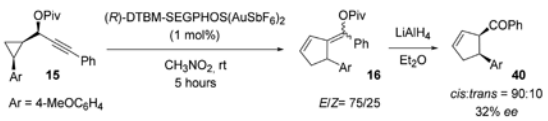
and 2.21 Å for **A3** and **B3**, respectively). The negative charge build-up on C2 of **A3** makes that position more nucleophilic, promoting its attack on the cyclopropyl ring (a process that would result in the concerted formation of the pentannulation product from **A3**/**B3**). While the localized C1–C2 π bond in **A3** is polarized such that 75% of its electron density resides on C2, the analogous polarization is only 63% in **B3**. Therefore, the donor orbital involved in the allene-Au(I) dative bond of **A3** is more like an sp^2-hybridized lone pair than the two-center π bond of **B3**. Surprisingly, C1 recovers enough electron density from the cyclopropyl ring that in both cases its partial (natural) charge is calculated to be near zero; in fact, C1 in **B3** bears a slightly *negative* charge (−0.09). Assuming that the mechanism for *cis*/*trans* cyclopropyl isomerization is dependent on a partial positive charge on C1, the lower charge on C1 of **B3** accounts for its disinclination toward this mode of reactivity. The C1 natural charges associated with the twisted allenes **A4** and **B4** are nearly identical at −0.02, suggesting that these species are not involved in the cyclopropyl *cis/trans* isomerization.

4. Au(I)-coordinated allenes: application to reaction design

Knowledge gained from the experiments discussed above allowed us to rationally design syntheses that display orthogonal reactivity depending on the electronics of the propargyl starting materials. This was accomplished by replacing the arylcyclopropyl groups of the substrates with vinyl-substituted cyclopropanes. In this scenario, two different fates can be envisioned for a vinylcyclopropyl-allenyl intermediate: formation of the cyclopentene analogous to the products described above or a Cope rearrangement involving a η^2-coordinated allene that would lead to the formation of a cycloheptadiene.[24] When we examined the behavior of the diastereomeric ester series **28**–**31** under our standard reaction conditions, we were pleased to observe formation of the corresponding cyclopentenes **32** and **33** in excellent yields and as the sole observed reaction products[25] (Scheme 6.1 and 6.2), in agreement with the system reported by Goeke and coworkers.[16] The cyclopentenes were obtained regardless of the stereochemistry at the cyclopropyl and propargylic positions. It was also observed that the relative stereochemistry of the styryl moiety was retained in all cases. It is worth noting that a similar reactivity pattern can be obtained for **34**, which exhibits a regiochemistry that positions the ester on the opposite side of the allene intermediate (Scheme 6.3).

Conversely, the reaction of vinyl ether **37** with $[(Ph_3PAu)_3O]BF_4$ as the catalyst led to formation of cycloheptadiene **39** (Scheme 6.4). As proposed above, **37** presumably undergoes a Au(I)-catalyzed Claisen rearrangement to yield allene **38**, followed by a thermal Cope rearrangement to form a seven-membered ring. Thus, the activation barrier for the pentannulation is lower than that for the Cope rearrangement from the allenyl esters, but the situation is reversed for the formyl allene which is much less prone to cyclopropyl ring expansion.

We envisioned that if a Au(I) species were involved in this step then induction could be obtained by choosing an appropriate chiral ligand.[11d] Indeed, treatment of **15** with (*R*)-DTBM-SEGPHOS$(AuCl)_2$ and $AgSbF_6$ afforded **16**, which upon reduction with $LiAlH_4$ in diethyl ether resulted in formation of **40** in 32% ee (eq 3). Although this enantiomeric excess is modest, it provides evidence for trapping of a chiral Au(I) intermediate.



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5. Summary of the proposed reaction mechanism

Based on the results presented above, we propose the mechanistic hypothesis outlined in Scheme 7. Starting material **A** enters the catalytic cycle by coordinating to cationic Au(I), forming alkyne complex **B**. The [3,3]-migration then commences, passing through cyclic carbocation **C**. Structure **C** is a long-lived intermediate in the ester system but only a point along the reaction trajectory in the vinyl ether system. A Grob-type fragmentation of **C** results in the formation of allene complex **D**, a process which is irreversible in the vinyl ether case because a strong carbon-carbon bond is formed. Complex **D** can then fragment yielding free allene **E**, or if sufficient positive charge build-up is present at C1 it can ring open[12] and convert to the thermodynamically-favored **D′**. A formyl allene with no electron-donating groups on the cyclopropyl ring apparently has insufficient cationic character at C1 for this process to take place. Alternatively, **D** or **D′** can undergo a ring expansion to irreversibly form cyclopentene complex F by a concerted process. The same electronic factors that facilitate conversion to **D′** lower the activation barrier to the pentannulation reaction, albeit to varying extents. Finally, cyclopentene **G** is released and the cationic Au(I) species re-enters the catalytic cycle. Therefore, the phenylcyclopropylpropargyl vinyl ethers are different from the electron-rich ethers and the esters only in that, in the former case, a larger energy barrier for the formation of **F** is encountered by **D**, and Au(I) decomplexation to form the free allene **E** is faster.

Conclusion—In this work, key mechanistic aspects on the nature of the Au(I)-catalyzed [3,3]-rearrangement of propargylic substrates have been disclosed. Specifically, our studies provide experimental evidence for the reversibility of the rearrangement in the case of propargylic esters. In contrast, the Au(I)-catalyzed [3,3]-rearrangement of propargylic vinyl ethers is irreversible and proceeds through a concerted pathway. We have found that the cationic nature of the Au(I)-coordinated allenes formed after the rearrangement and the electron-donating abilities of the allene substituents heavily influences their structure-reactivity, determining the η^1- or η^2-allene character of Au(I)-coordinated allenes. These findings enable controlled access to Au(I)-coordinated allenes that display orthogonal reactivity patterns. We anticipate that the mechanistic insights provided by this study will enable further developments in this area of catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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18. In agreement with this, *cis* cyclopropanes were never detected over the course of the reaction of the substrate *trans*-9. See Supporting Information for details.

19. For related labeling experiments on phosphatyloxy migrations, see: Schwier T, Sromek AW, Yap DML, Chernyak D, Gevorgyan V. J Am Chem Soc 2007;129:9868. [PubMed: 17658805]

20. Terminal alkynes preferentially undergo a 2,3-migration of the ester fragment, whereas internal alkynes bearing alkyl or phenyl substituents mainly exhibit a 3,3-ester shift. Results obtained in our system employing terminal alkynes are detailed in the Supporting Information. For a computational study on this issue, see: Soriano E, Marco-Contelles J. Chem Eur J 2008;14:6771.

21. See Supporting Information for additional data on the ionization process.

22. Computational evidence for this statement is presented in the Supporting Information.

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25. See Supporting Information for a brief substrate scope on this cyclization process.

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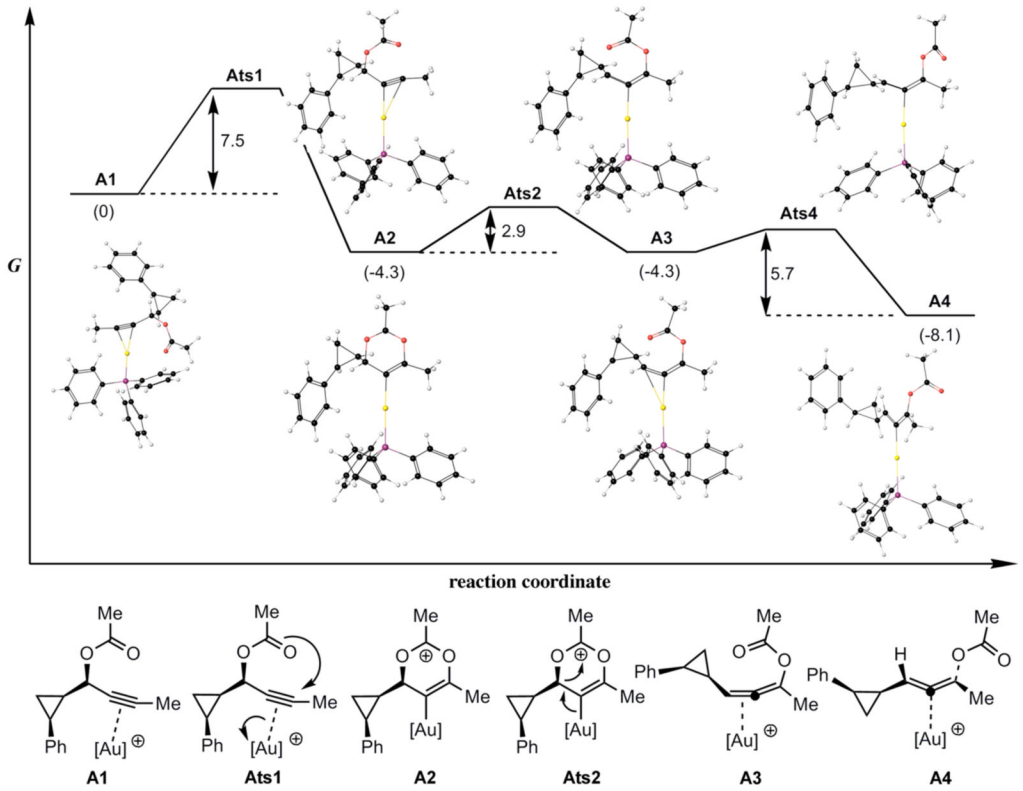

Figure 1.

Reaction coordinate diagram for propargyl ester model system in CH_2Cl_2, relative Gibbs free energies in kcal/mol. Color scheme: C, black; H, grey; O, red; P, purple; Au, yellow.

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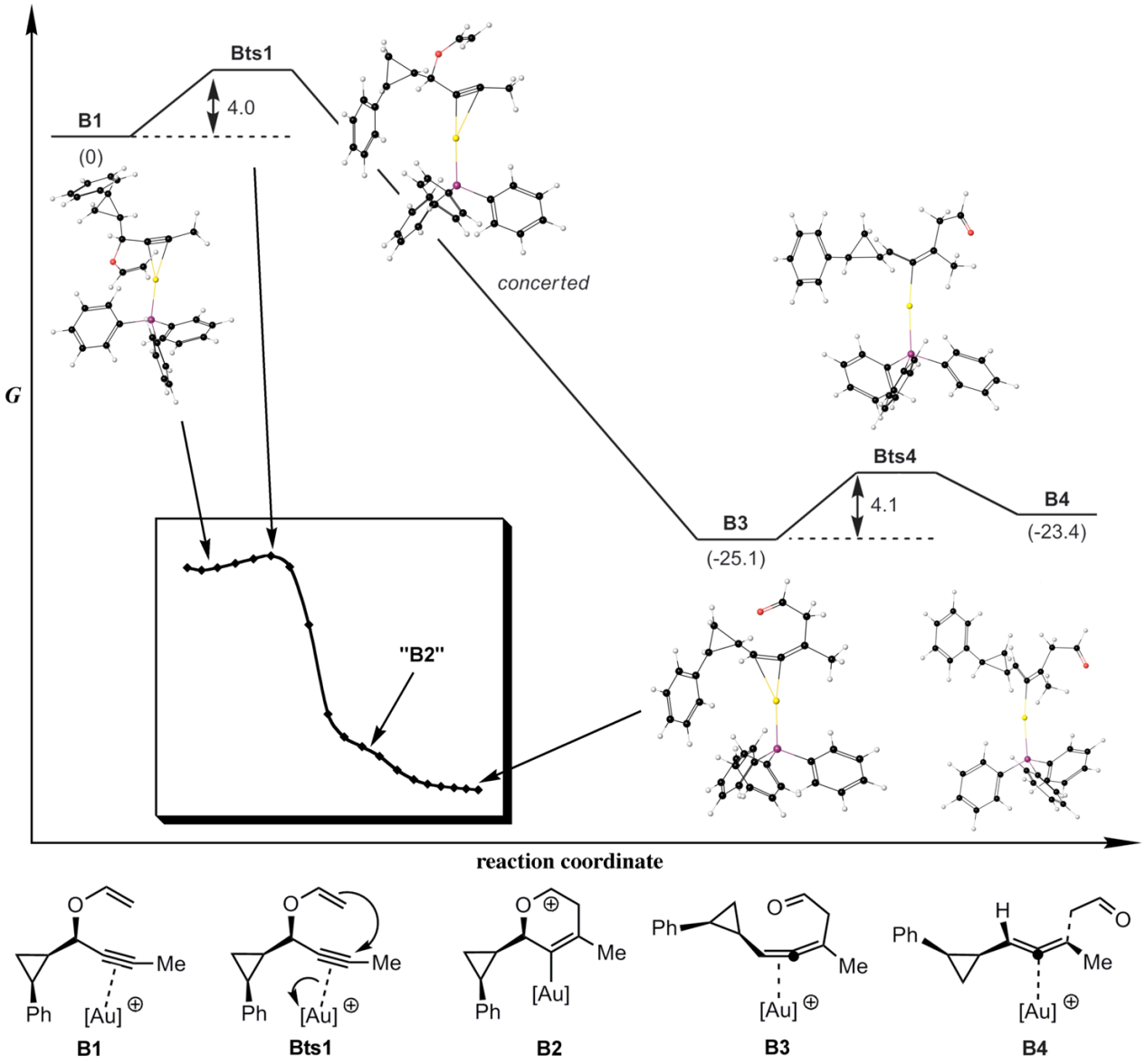

Figure 2.

Reaction coordinate diagram for vinyl propargyl ether model system in CH_2Cl_2, relative Gibbs free energies in kcal/mol. Insert: Computed reaction coordinate profile (electronic E only) about transition state Bts1. Color scheme: C, black; H, grey; O, red; P, purple; Au, yellow.

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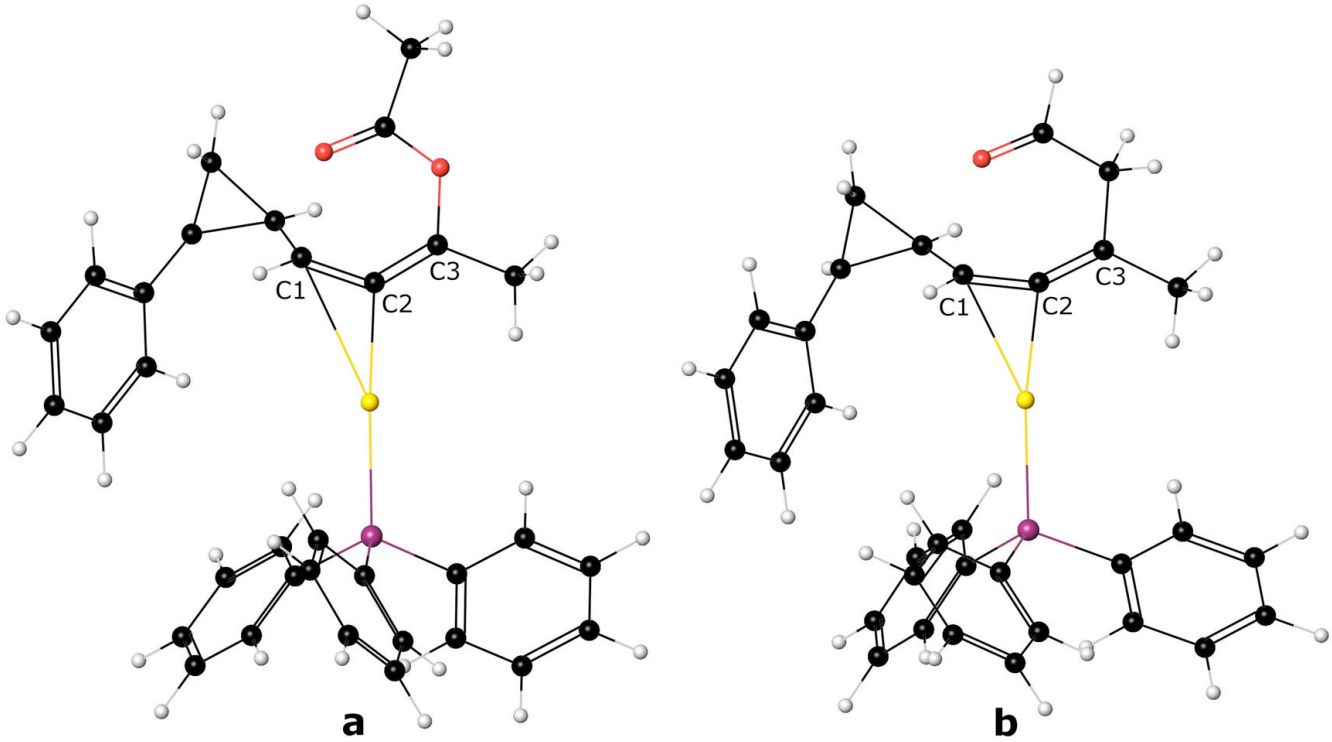
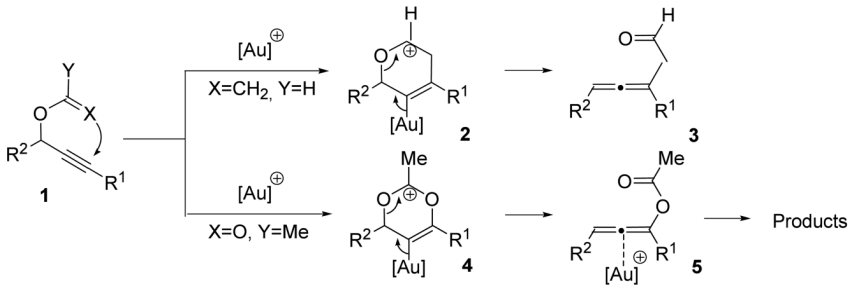


Figure 3.

a. Left: molecular representation of optimized A3: d(C1–C2), 1.40 Å; d(C2–C3), 1.34 Å; d (C1-Au), 2.85 Å; d(C2-Au), 2.13 Å; ∠(C1-C2-C3), 131°; ∠(C1-C2-Au), 106°. NBO charges: C1, 0.04; C2, −0.41; C3, 0.34. b. Right: molecular representation of optimized B3: d(C1–C2), 1.37 Å; d(C2–C3), 1.33 Å; d(C1-Au), 2.58 Å; d(C2-Au), 2.21 Å; ∠(C1-C2-C3), 146°; ∠(C1-C2-Au), 89°. NBO charges: C1, −0.09; C2, −0.22; C3, −0.01. Color scheme: C, black; H, grey; O, red; P, purple; Au, yellow.



Scheme 1.
[3,3]-rearrangements of propargyl vinyl ethers and esters

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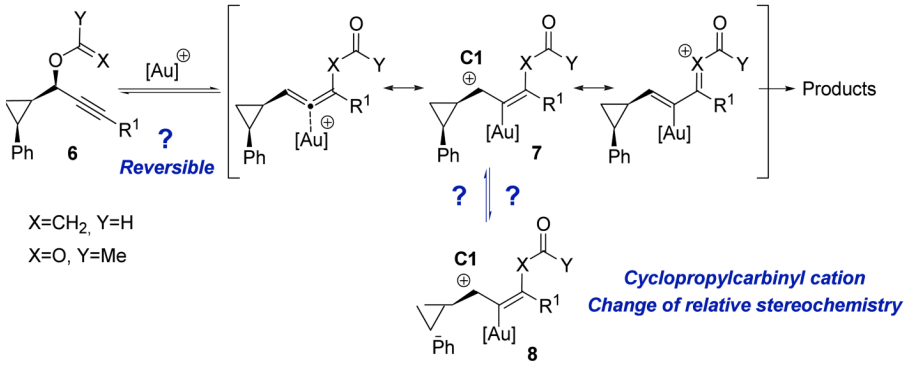

Scheme 2.
Proposed use of cyclopropanes as mechanistic probes

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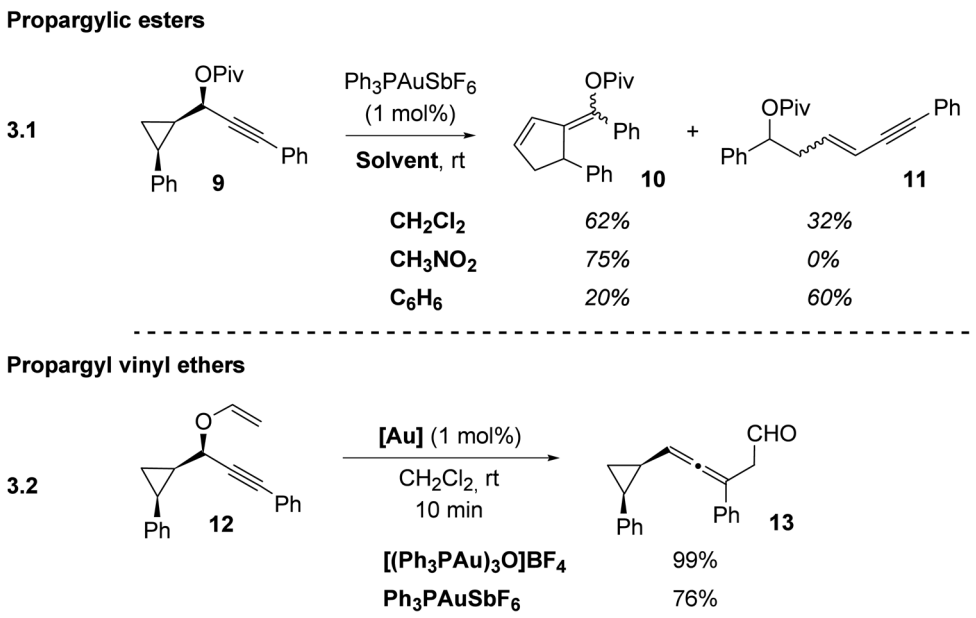

Scheme 3.
General reactivity patterns of cyclopropyl propargylic esters and vinyl ethers

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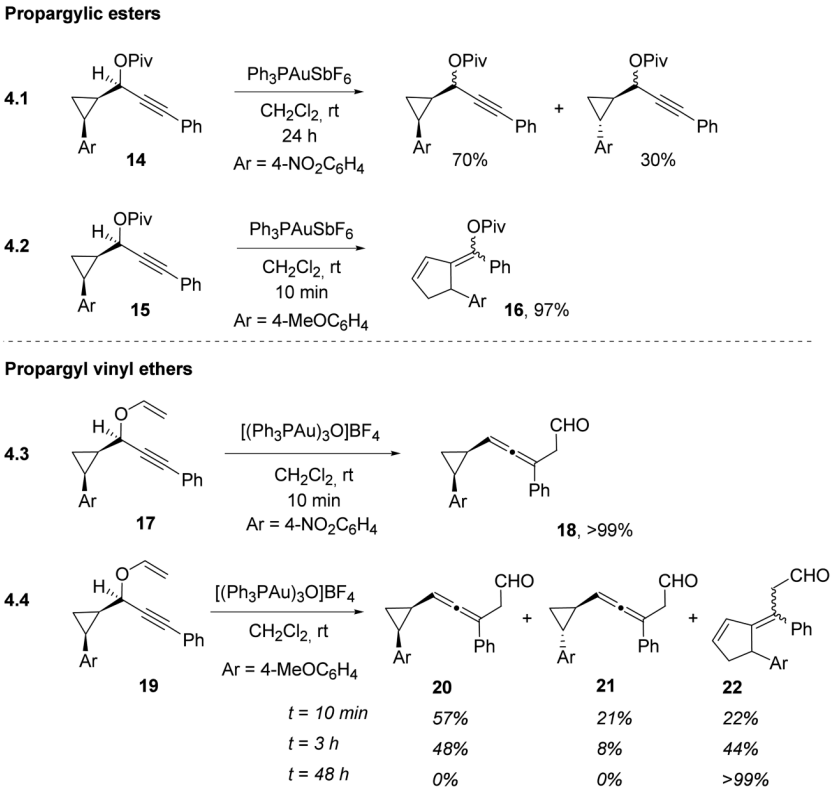

Scheme 4.

Substituent effects on product distribution, direct detection of an allene as the intermediate in the pentannulation reaction.

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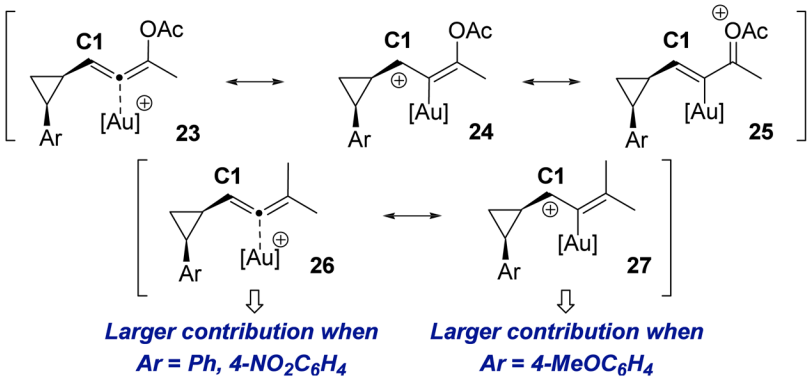

Scheme 5.
Relevant resonance forms for Au(I)-coordinated allenes

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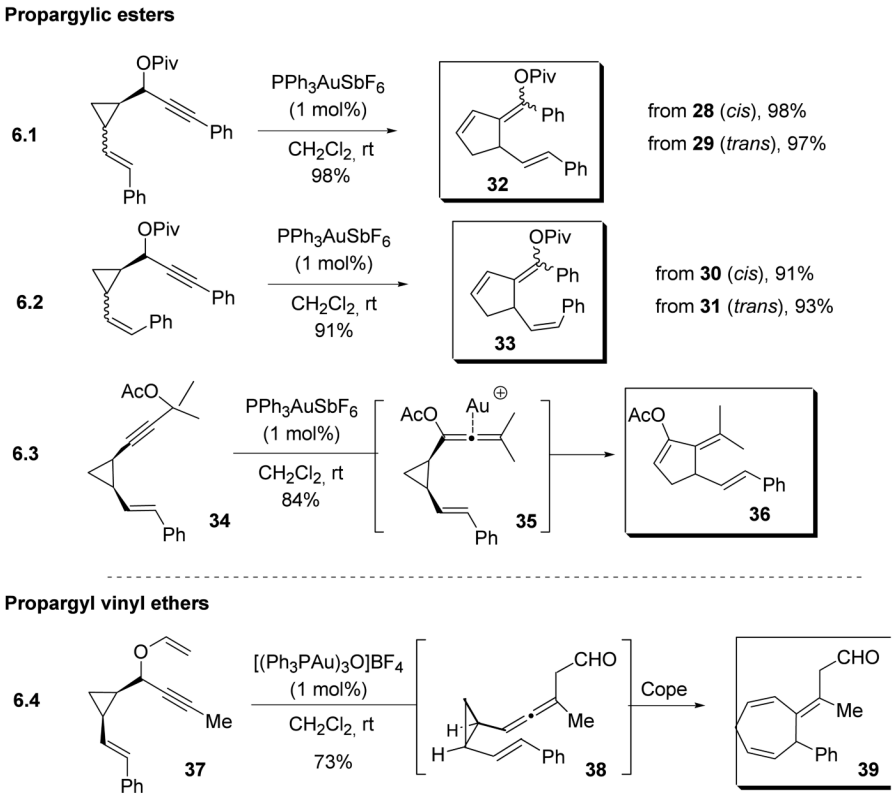

Scheme 6.
Orthogonal reactivity patterns in vinylcyclopropyl-substituted substrates.

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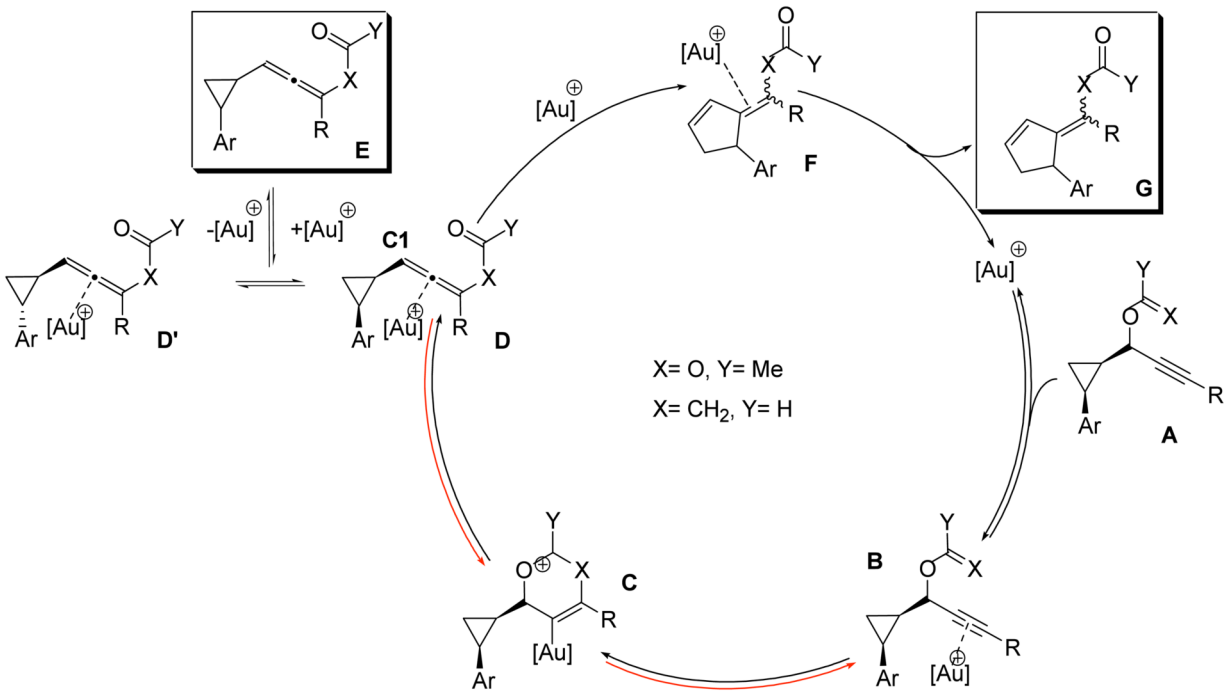

Scheme 7.
Proposed mechanism for the Au(I)-catalyzed pentannulation of propargylic esters.

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