

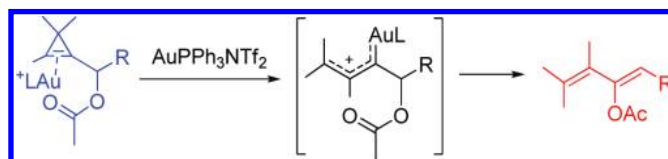
Experimental and Theoretical Investigation into the Gold-Catalyzed Reactivity of Cyclopropenylmethyl Acetates

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ABSTRACT



Cyclopropenylmethyl acetates have been shown to undergo rapid and stereoselective gold catalyzed rearrangement to Z-acetoxydienes in high yield. DFT calculations have shown that while several reaction pathways can be envisaged only a single, ring-opening one operates.

The diverse reactivity of propargyl acetates in the presence of gold catalysts is currently being investigated by several groups.¹ For example, propargyl acetates **1** can undergo gold-catalyzed 1,3- or 1,2-acyl migrations via **2** and **3** to form **4** and **5**, respectively. Intermediates **4** and **5** are poised to react further giving a diverse range of products resulting from allene activation and carbene-type reactivity, respectively (Figure 1).² In this context, we decided that cyclopropenylmethyl acetates, which are highly strained homologues of propargyl esters,

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(1) For reviews on gold-catalyzed reactions of propargyl acetates, see: (a) Marion, N. P.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (b) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718.

(2) For examples of 1,2- and 1,3-shifts of propargyl esters, see refs 3 and 4 within review. 1a For selected more recent examples of 1,2-shifts, see: (a) Blanc, A.; Alix, A.; Weibel, J. M.; Pale, P. *Eur. J. Org. Chem.* **2010**, *9*, 1644. (b) Huang, X. G.; de Haro, T.; Nevado, C. *Chem.–Eur. J.* **2009**, *24*, 5904. For selected recent examples of 1,3-shifts, see: (c) Garayalde, D.; Gomez-Bengoa, E.; Huang, X. G.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720. (d) Yu, M.; Zhang, G. Z.; Zhang, L. M. *Tetrahedron* **2009**, *65*, 1849.

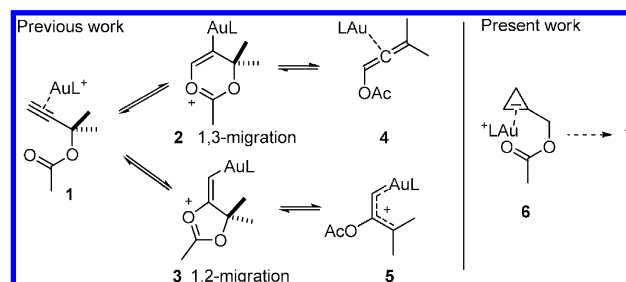


Figure 1. Propargyl acetate and cyclopropenylmethyl acetate activation by gold catalysts.

should also lead to interesting reactivity upon activation by gold salts.³ While cyclopropenes with their π -rich double bond and high strain character would appear to be ideal substrates for activation by gold, there has been relatively little investigation of this aspect of their chemistry. To date, Lee and co-workers have described the gold-catalyzed solvolysis of simple alkyl

cyclopropenes,^{4a} while both Shi and Zhu^{4b} as well as Wang and co-workers^{4c} have demonstrated the cycloisomerization of cyclopropenes to afford indene derivatives. In this paper, we report our combined experimental and theoretical investigation into the reactivity of cyclopropenylmethyl acetates **6**. Their extremely facile transformation into *Z*-acetoxylated dienes by the action of AuPPh₃NTf₂ is demonstrated, and a rationale for both the mechanism and stereoselectivity of this reaction is provided.

We began our experimental investigations by preparing the required cyclopropenylmethyl acetates from tribromocyclopropanes using the method of Baird et al.,⁵ followed by acetylation of the resulting alcohols. Nitrobenzaldehyde-derived cyclopropene **8a** was chosen as our first substrate as its crystalline nature would enable product identification by X-ray analysis if necessary (Table 1). Upon exposure of

examples of thermally induced cyclopropene–carbene rearrangements which provide mixtures of dienes and other products.⁸ It is also of note that Zhang and co-workers have reported a gold-catalyzed rearrangement of propargyl acetates to acetoxylated dienes with high *Z*-selectivity.⁹ Given our promising initial result, we began a catalyst screen to identify optimum conditions for obtaining **9a** in high yield and high *Z*-selectivity, the results of which are summarized in Table 1. It was determined that AuPPh₃NTf₂ was the optimum catalyst for the reaction and that lowering the temperature to –50 °C provided optimum selectivity for the *Z*-diene. An NMR experiment revealed that further lowering the temperature to –78 °C slowed the reaction but did not increase the *Z*-selectivity of the reaction.

With selective diene-forming reaction in hand, we set about exploring the substrate scope of the rearrangement

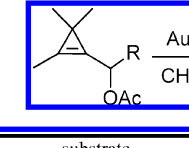
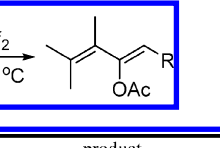
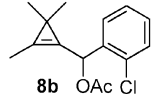
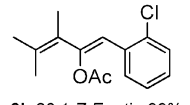
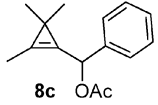
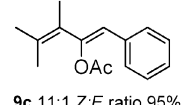
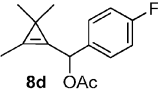
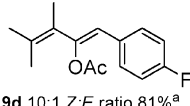
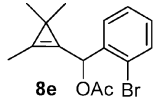
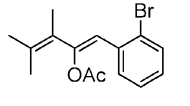
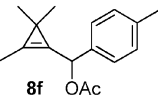
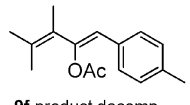
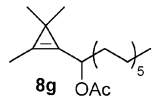
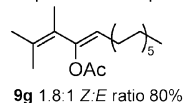
Table 1. Discovery and Optimization of Reaction Conditions for Diene Formation

entry	catalyst ^a	conditions ^b	% yield 9a (<i>Z</i> : <i>E</i>) ^c
1	AuPPh ₃ Cl/AgSbF ₆	DCM, rt, 20 min	66 (4:1)
2 ^d	AuPPh ₃ Cl/AgBF ₄	DCM, rt, 12 h	0
3 ^d	AuCl	DCM, rt, 12 h	7 (4.5:1)
4	AuPrBu ₃ Cl/AgSbF ₆	DCM, rt, 30 min	24 (3.8:1)
5	[(Ph ₃ PAu) ₃ O]BF ₄	DCM, rt, 12 h	23 (3.6:1)
6	IPrAuCl	DCM, rt, 30 min	25 (4:1)
7	Au(III) ^e	DCM, rt, 12 h	28 (3.7:1)
8	PPh ₃ PAuNTf ₂	DCM, rt, 30 min	99 (8:1)
9	PPh ₃ PAuNTf ₂	DCM, –50 °C, 5 min	99 (13:1)^f

^a All reactions run with 5 mol % of catalyst unless otherwise stated. ^b Reactions run at 0.144 M for entries 1–9. ^c NMR yields using MeNO₂ as an internal standard. ^d 15% and 26% of starting material remaining for entries 2 and 3, respectively. ^e Dichloro(2-pyridinecarboxylato)gold. ^f Isolated yield.

8a to the AuPPh₃Cl/AgSbF₆ precatalyst system, we were delighted to find that rearrangement to the *Z*-acetoxylated diene **9a** occurred in 66% yield with a 4:1 *Z*:*E* selectivity (Table 1, entry 1). The stereochemistry of the major *Z* isomer was confirmed unambiguously by X-ray crystallography.⁶ In the context of diene-forming reactions from cyclopropenes, early work by Müller and co-workers reports a single example of a symmetrical cyclopropene ethylcarboxylate forming a diene in the presence of a Rh(III) catalyst.⁷ There are also several early

Table 2. Substrate Scope for the Diene-Forming Reaction

substrate	product
	 9a 13:1 <i>Z</i> : <i>E</i> ratio 99%
	 9b 20:1 <i>Z</i> : <i>E</i> ratio 99%
	 9c 11:1 <i>Z</i> : <i>E</i> ratio 95%
	 9d 10:1 <i>Z</i> : <i>E</i> ratio 81% ^a
	 9e 41:1 <i>Z</i> : <i>E</i> ratio 89% ^a
	 9f product decomp.
	 9g 1.8:1 <i>Z</i> : <i>E</i> ratio 80%

(Table 2). We were pleased to find that a wide selection of aryl-derived cyclopropenylmethyl acetates underwent very

(3) For recent reviews on cyclopropene synthesis and reactivity, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. For a specific example of the reactivity of cyclopropenylmethyl acetates, see: (c) Simaan, S.; Masarwa, A.; Zohar, E.; Stanger, A.; Bertus, P.; Marek, I. *Chem.–Eur. J.* **2009**, *15*, 8449.

(4) (a) Bauer, J. T.; Hadfield, J. T.; Lee, A.-L. *Chem. Commun.* **2008**, 6405. (b) Zhu, Z. B.; Shi, M. *Chem.–Eur. J.* **2008**, *14*, 10219. (c) Li, C. K.; Zeng, T.; Wang, J. B. *Tetrahedron Lett.* **2009**, *50*, 2956.

(5) M. S. Baird, M. S.; Hussain, H. H.; W. Nethercott, W. *J. Chem. Soc., Perkin Trans. 1* **1986**, *1*, 1845.

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(8) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271.

(9) Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740.

selective gold-catalyzed rearrangement to (Z)-2-acyloxy-1,3-dienes **9a–g**. Notably, **9e** bearing an *o*-bromobenzyl group rearranged with an impressive 41:1 *Z:E* selectivity. Also of interest was the reduced *Z:E* selectivity observed for the dodecyl aldehyde derived **9g**. It should also be noted that while electron-rich **9f** underwent rapid rearrangement the resulting diene decomposed before purification could be carried out.

The diene-forming reaction is fascinating in terms of both the mechanism and the observed stereoselectivity, especially when compared to the gold-catalyzed reactions of propargyl esters **1**. A number of mechanistic possibilities can be envisaged following activation of the cyclopropene double bond by gold. Similarly to propargyl esters **1**, both 1,2- and 1,3-migration to form **10** and **13**, respectively, can be envisaged for cyclopropene **6** (Figure 2; pathways a and b).

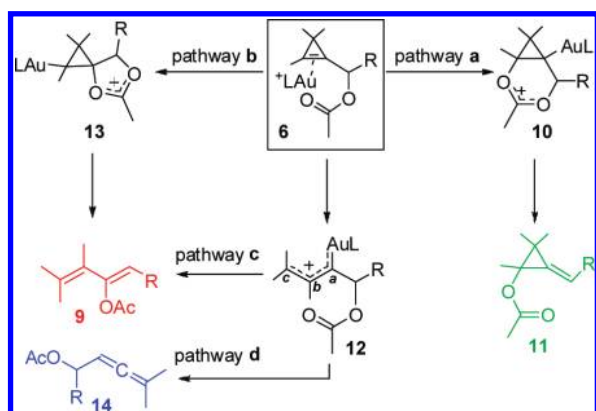


Figure 2. Potential pathways for reaction of gold-coordinated **6**.

Given that diene **9** is the only product observed, pathway a toward methylenecyclopropane **11** cannot be operating. However, pathway b can lead to the observed diene product **9** via 1,2-shift to bicyclic **13** followed by ring opening. On the other hand, Lee and co-workers proposed a ring-opening mechanism to account for the observed allyl ether products in their solvolysis of cyclopropenes.^{4a} In addition, a recent mechanistic study by Fürstner and co-workers has shown that cyclopropenone acetals undergo ring opening in the presence of gold catalysts.¹⁰ Given these reports, we designed two alternative pathways, c and d, that both proceed via initial formation of gold vinyl carbenoid species **12**. Attack of the pendant acetate can then occur at carbon *a* to give the observed diene **9** or at carbon *c* to give allene **14**. These mechanistic possibilities pose four important questions: (1) Does the diene form via the ring-opening–migration pathway c or the migration–ring-opening pathway b. (2) What is the reason that pathways a and d are not operating. (3) What is the origin of the observed high *Z*-selectivity for substrates **9a–f** with R = aryl and the negligible selectivity for **9g** with R = dodecyl. Finally, (4) does the replacement of an aryl group with an alkyl group affect the preferred pathway followed?

(10) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510–2513.

To address these questions, we turned our attention to computational studies, the results of which are now discussed.

In our DFT calculations, we used the model catalyst [AuPMe₃]⁺ in conjunction with reactants bearing R = phenyl and ethyl to model the aryl and alkyl substrates, respectively. Our theoretical studies showed that all four pathways are thermodynamically very favorable; however, they all differ significantly in terms of kinetics. On the basis of our calculations with the substrate R = phenyl, the highest Gibbs free energy points for pathways a, b, c, and d are 17.3, 17.0, 11.8, and 37.5 kcal mol^{−1}, respectively. For R = ethyl, the corresponding Gibbs free energy points for pathways a, b, c, and d are 17.8, 22.9, 11.7, and 35.1 kcal mol^{−1}, respectively. Therefore, the calculations show that regardless of the identity of the R group the ring-opening pathway c is always kinetically favored. As such, the detailed mechanism of pathway c for R = phenyl and ethyl is illustrated in Figure 3, and the other pathways are provided in the Supporting Information.

The preference for this ring-opening mechanism can be explained based on the associated relief of ring strain upon

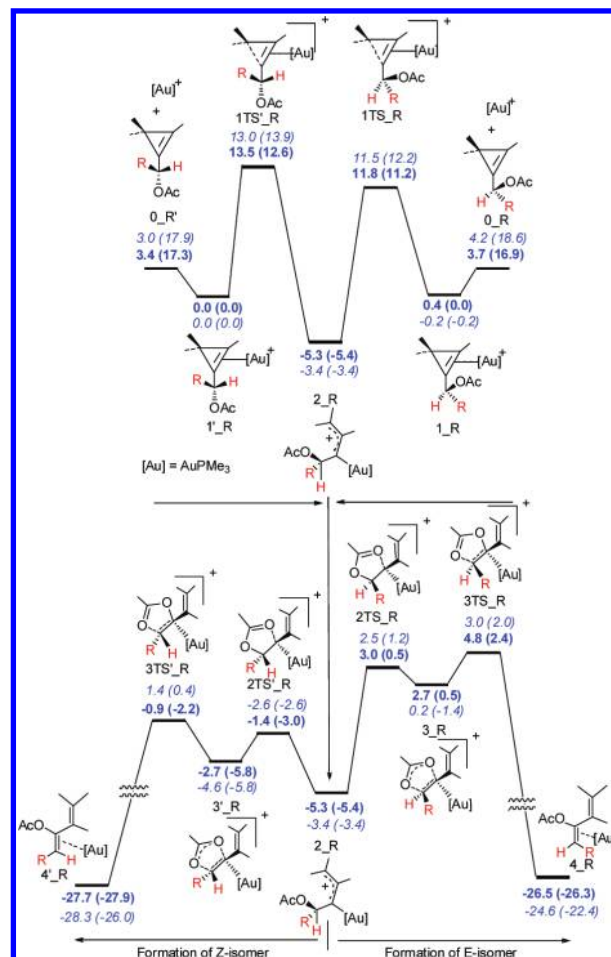


Figure 3. Energy profiles calculated for pathway c of the gold-catalyzed rearrangement of cyclopropenylmethyl acetates. The relative free energies (and electronic energies in parentheses) are given in kcal mol^{−1}. The values in bold refer to R = phenyl, and the italicized values refer to R = ethyl.

formation of **2_R**¹¹ (Figure 3). Although pathway d also proceeds via **2_R**, this pathway is not followed because attack of the pendant acetate on carbon *c* (Figure 2) requires a higher deformation energy in the transition structure resulting in a raised energy barrier. This attack is disfavored because of the greater distance of the acetate from carbon *c*. For example, in **2_R** (R = phenyl) the sp² oxygen is 5.667 Å away from carbon *c* but only 3.895 Å away from carbon *a*. In the favored pathway c, we considered two conformations R and R' of the starting cyclopropene to be reactive toward ring opening. In conformation **0_R'**, the R group is pointing toward the *gem*-dimethyl group, whereas in **0_R** it is pointing away from it. These two conformations undergo initial coordination to the gold to yield adducts **1_R** and **1'_R**, which can both lead to the ring-opened **2_R** intermediate. It is of interest to note that the slightly less stable conformer **0_R** has a lower activation barrier toward ring opening (see top of Figure 3). Following ring opening, the pendant acetate can undergo 1,2-transfer in two steps. Attack of the acetate on carbon *a* (see **12**, Figure 2) occurs first to provide the five-membered ring intermediates **3_R** and **3'_R**, and then breaking of these five-membered rings takes place to give the products **4_R** and **4'_R** (bottom of Figure 3). As illustrated in Figure 1, starting from **2_R** there are two possibilities leading to the *Z* and *E* isomers, respectively. Our calculations show that from **2_R** the energy barrier for the formation of the *Z* diene **4'_R** is significantly lower than that of the *E*-diene **4_R**. The preference for the pathway leading to formation of **4'_R** can be explained by a steric argument. In the pathway leading to the formation of **4_R**, the R group is pointing toward the methylbut-2-ene fragment resulting in an unfavorable steric repulsion; this steric repulsion is absent in the pathway leading to the formation of **4'_R**. It can therefore be seen that the stereoselectivity of the reaction is controlled by a steric interaction between the R group and the methylbut-2-ene fragment (Figure 4). This fits in with the experimental

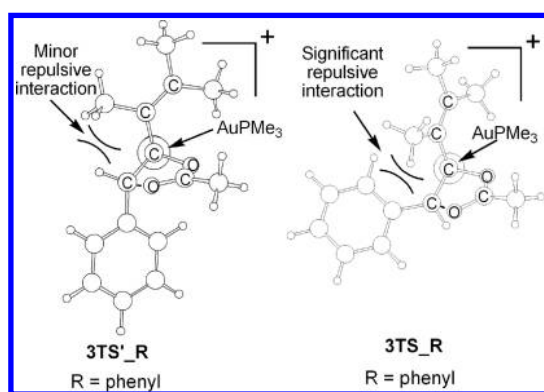


Figure 4. Optimized geometries for **3TS'_R** and **3TS_R** (R = phenyl).

results where the more sterically demanding substrates with R = *o*-chlorophenyl and R = *o*-bromophenyl result in the highest

Z-selectivity (dienes **9b** and **9e**, Table 2). In both pathways shown at the bottom of Figure 1, the energy barrier for the breaking of the five-membered ring (**3TS_R** and **3TS'_R**) is greater than for its formation (**2TS_R** and **2TS'_R**). For both R = phenyl and ethyl, **3TS_R** is higher in energy than **3TS'_R**, but the energy difference for R = ethyl (1.6 kcal mol⁻¹) is significantly smaller than for R = phenyl (5.7 kcal mol⁻¹), resulting in the low *Z*-selectivity observed for R = alkyl (see **9g**) and the high *Z*-selectivity observed for R = aryl (see **9a–e**). The lowered difference in energy between **3TS_R** and **3TS'_R** for R = ethyl is due to the reduced steric effect of the alkyl group compared to an aryl group. The alkyl group has the ability to adopt a conformation where two hydrogens are pointing toward the 2-methylbut-2-ene fragment in **3TS_R**, resulting in a less congested and a lower-energy transition state compared to that of the phenyl group (see Figure S4, Supporting Information). In conclusion, we have developed an efficient and stereoselective synthesis of *Z*-acetoxydienes **9a–g**. On the basis of DFT calculations, we have been able to propose a detailed mechanism for the formation of these dienes. These calculations show that ring opening, followed by intramolecular 1,2-acetate transfer, is the most favorable pathway and that the ring opening is rate determining.

The mechanistic divergence of cyclopropenylmethyl acetates **6** from propargyl acetates **1** is an important aspect of the chemistry uncovered here. In Nolan's elegant computational study,^{1b} he demonstrated that the gold vinyl carbenoid species **5** and the gold allene species **4** are in rapid equilibrium and that the exact product obtained is dependent upon a variety of factors, including precise substrate structure and the nature of the ligand employed. It is significant that in the case of cyclopropenylmethyl acetate **6** reactivity is guided unambiguously toward a ring-opening pathway due to the cyclic nature of the starting material. Cyclopropenes **6** also differ from propargyl acetates in that they afford gold vinyl carbenoid **12**, which is an isomer of gold vinyl carbenoid **5**. We anticipate that the ability to prepare this alternative gold vinyl carbenoid, along with the mechanistic detail presented here, will stimulate further research into the development of new gold-catalyzed reactions of cyclopropenylmethyl acetates. Research is currently underway to further develop the synthetic potential of these substrates and to identify cyclopropenes that will react via the alternative pathways outlined in Figure 2.

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Supporting Information Available: Full computational details, experimental procedures, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) **2_R** is the reactive conformation of structure **12** in Figure 2, and the IRC calculations show that **1TS_R** is directly connected to **2_R**.