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Mechanistic Insights into the Gold-Catalyzed Cycloisomerization of Bromoallenyl Ketones: Ligand-Controlled Regioselectivity

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In recent years, the homogeneous catalysis by gold complexes received increasing attention. Particularly, cyclizations of alkynes and allenes mediated by gold complexes have been widely explored.¹ Along this line, the Gevorgyan group has recently reported a gold-catalyzed regiodivergent cycloisomerization of bromoallenyl ketones **a** into isomeric bromofurans **b** and **c** (Scheme 1).² According to the originally proposed mechanism, products **b** and **c** result from different activation modes of the substrate by gold complexes.² It was thought that more oxophilic Au(III) catalyst³ coordinates to the carbonyl oxygen (**d**), which, via halirenium intermediate **e**, produces the 3-bromofuran **b**, a product of 1,2-Br migration. Alternatively, the more π -philic Au(I) catalyst coordinates to the distal double bond of the allene (**f**), leading to the gold carbenoid intermediate **g**. Subsequent 1,2-hydride shift in the latter forms 2-bromofuran **c** (Scheme 1).² Great interest has been aroused by this important discovery, since not only it opens an unprecedented access to different types of halofurans, but also represents the very first example of reaction, in which employment of gold catalyst in different oxidation states leads to different products.^{1a,c,4,5,6} A more detailed mechanistic investigation of origins of the observed regioselectivity of this cycloisomerization, properties of the key intermediates, as well as profiles of the overall catalytic cycles, may give better understanding on the important transition metal-catalyzed chemistry of alkynes and allenes. This in turn, may provide guide for future design of new catalytic transformations. Herein, we wish to report our theoretical and experimental results on the mechanism of Au(III)- and Au(I)-catalyzed cycloisomerization of bromoallenyl ketones, with the emphasis on the origins of the regiochemistry of 1,2-migrations. Our study indicates that the 1,2-H migration could be assisted by the ligand L of the Au(PR'₃)₃L complex, thus, the regioselectivity of 1,2-migrations can be controlled by ligands at Au-complexes.

Thus, DFT calculations to investigate the above mentioned cycloisomerization have been performed.^{7,8} The computed energy surfaces for the AuCl₃ and Au(PH₃)Cl-catalyzed cycloisomerizations of bromoallenyl ketone **1** are provided in Figure 1. Results of the Au(III)-catalyzed reaction (**I**; Figure 1) indicate that the gold catalyst, upon coordination to the distal double bond of the allene **1**,⁹ instantly gives the cyclic intermediate **2** via a barrierless and highly exergonic process with relative free energies of 32.6 and 33.6 kcal/mol, in the gas phase and in toluene solution, respectively. Next, intermediate **2** undergoes more favorable 1,2-Br migration via the transition state **TS1** to generate the product complex **3** rather than 1,2-H shift through **TS2** to give **4**. Thus, the computed free energy barriers difference of 14.3 kcal/mol for the latter processes is in a good agreement with the experimentally observed nearly exclusive 1,2-Br migration.² Although, the formation of the complex **3** from intermediate **2** is endergonic

(Figure 1), the latter will be transformed into the product **b** irreversibly via a highly exergonic (30.3 kcal/mol) ligand exchange process of **3** with another molecule of substrate, thus, completing the catalytic cycle.¹⁰

Remarkably, it was found that the AuCl₃-catalyzed cycloisomerization of **1** in wet toluene¹¹ leads to the decreased ratio of 1,2-Br vs 1,2-H migration products. This implies that the H-shift could be catalyzed by a trace amount of water present in the system, analogously to the recently reported H₂O-assisted formal 1,2-H shift in the Au⁺-catalyzed carbocyclization.^{8c} This hypothesis was unambiguously confirmed by the calculations and further by reactions performed in the presence of D₂O.¹⁰ Thus, DFT calculations revealed the H₂O-assisted H-shift from **2** to **4** is a stepwise H-abstraction/donation process with an activation free energy of 17.8 kcal/mol in toluene, which is only about 1.4 kcal/mol higher than that for the 1,2-Br migration.¹⁰

The energy surface for the reaction catalyzed by Au(I) (**II**, Figure 1) is quite different from that for Au(III). Coordination of the less electrophilic Au(PH₃)Cl to the distal double bond of **1** gives π -complex **5** with the free energy increased by 20.8 kcal/mol in toluene solution. The latter, via the **TS3** with 10.5 kcal/mol activation energy barrier, transforms into the zwitterionic intermediate **6**. From intermediate **6**, the reaction may proceed through the direct 1,2-migration steps to generate complexes **7** and **8**. Calculations showed that the activation barrier for the direct 1,2-H shift (**TS5**) is 30.1 kcal/mol, while that for the 1,2-Br migration (**TS4**) is only 14.6 kcal/mol, thus contradicting with the experimental results on the observed predominant 1,2-H shift.² However, the major 1,2-H migration pathway can reasonably be rationalized in terms of the stepwise ligand-assisted H-shift process. Thus, as shown in **II** (Figure 1), **6** rotamerizes to a relatively more stable intermediate **9**. Geometries of **6** and **9**, revealed the remarkably prolonged Au-Cl distances, implying quite weak Au-Cl interactions.¹² Consequently, the weakly coordinated chloride is now capable of hydrogen abstraction at C2 via **TS6** with a barrier of 6.3 kcal/mol only to give intermediate **10**. Notably, the HCl moiety is associated with the gold-substituted furan through Cl-H...C3 hydrogen bonding interaction.¹⁰ Gas phase calculations showed that the formation of **10** is slightly exergonic, though a solvation by toluene substantially destabilizes this intermediate. Protodeauration of **10** at C3 via **TS7** leads to the product complex **8**. The activation free energy of this step is 15.7 and 8.7 kcal/mol in the gas phase and in toluene, respectively. Dissociation of **8** is quite favorable with an exergonicity of 26.3 kcal/mol in toluene. Thus, the overall barrier for the chloride-assisted H-migration process from **9** to the complex **8** is 8.7 kcal/mol only.

Based on these results, we hypothesized that if no labile chloride ligand present in a Au(I)-catalyzed cycloisomerization (e.g. using cationic Au(I) or AuCl complexes), reaction may proceed via a predominant 1,2-Br migration. As predicted, our experiments indicated that employment of AuCl or cationic catalysts, such as Au(PPh₃)BF₄ and Au(PPh₃)SbF₆, produced the 1,2-Br migration product **A** as a major or sole isomer (Scheme 2).¹⁰ Unexpectedly, use of Au(PPh₃)OTf lead to exclusive formation of the 1,2-H shift product **B**, thus, exhibiting a dramatic counterion effect on the regioselectivity of the reaction. The DFT calculations shed light on this seeming controversy.^{8d,10} The computations revealed that in both Au(PR₃)⁺ and AuCl-catalyzed reactions, the 1,2-Br migration is more favorable with the activation barrier about 13 kcal/mol. However, 1,2-H shift in Au(PR₃)⁺-catalyzed reactions can be assisted by the counterions. Thus, it was found that the OTf⁻-assisted 1,2-H shift requires an activation free energy of 9.6 kcal/mol only, whereas those for BF₄⁻ and SbF₆⁻ are much higher (20.2 and 29 kcal/mol, respectively), which is in a good agreement with the experiments.

In summary, the mechanism of Au-catalyzed cycloisomerization of bromoallenyl ketones has been investigated through DFT computational and experimental studies. It was found that both Au(I) and Au(III) catalysts¹³ activate distal double bond of the allene to produce cyclic

zwitterionic intermediates, which undergo a kinetically favored 1,2-Br migration. However, in the cases of Au(PR₃)L (L = Cl, OTf) catalysts, the counterion-assisted H-shift is the major process, indicating that the regioselectivity of the Au-catalyzed 1,2-H vs 1,2-Br migration is ligand dependent. The present study may provide better understanding on the reactions of allenes and alkynes activated by Au(I) and Au(III) complexes,^{14,15} different catalytic performance of Au-complexes in different oxidation states, and particularly the ligand effect, which has received limited attention only.^{1c,8d,16}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Our computational studies confirmed possible formation of the originally proposed Au(III)-coordination complex **d** (Scheme 1),² however, neither cyclization transition state nor halirenium intermediate **e** were located.
- See Supporting Information for experimental and computational details.
- Possible involvement of Brønsted acid as a true catalyst was ruled out by control experiments. Besides, addition of TTBP, a proton scavenger, did not inhibit the Au-catalyzed cycloisomerization.¹⁰
- The Au-Cl distances in Au(PH₃)Cl, **5**, **6**, and **9** are 2.327, 2.481, 2.573, and 2.561 Å, respectively. See Supporting Information for bond critical point analysis of the weak interactions.
- Possible involvement of AuCl as a true catalyst in AuCl₃-catalyzed reactions via an in-situ redox process was ruled out by the observed different reactivity patterns of these complexes.¹⁰
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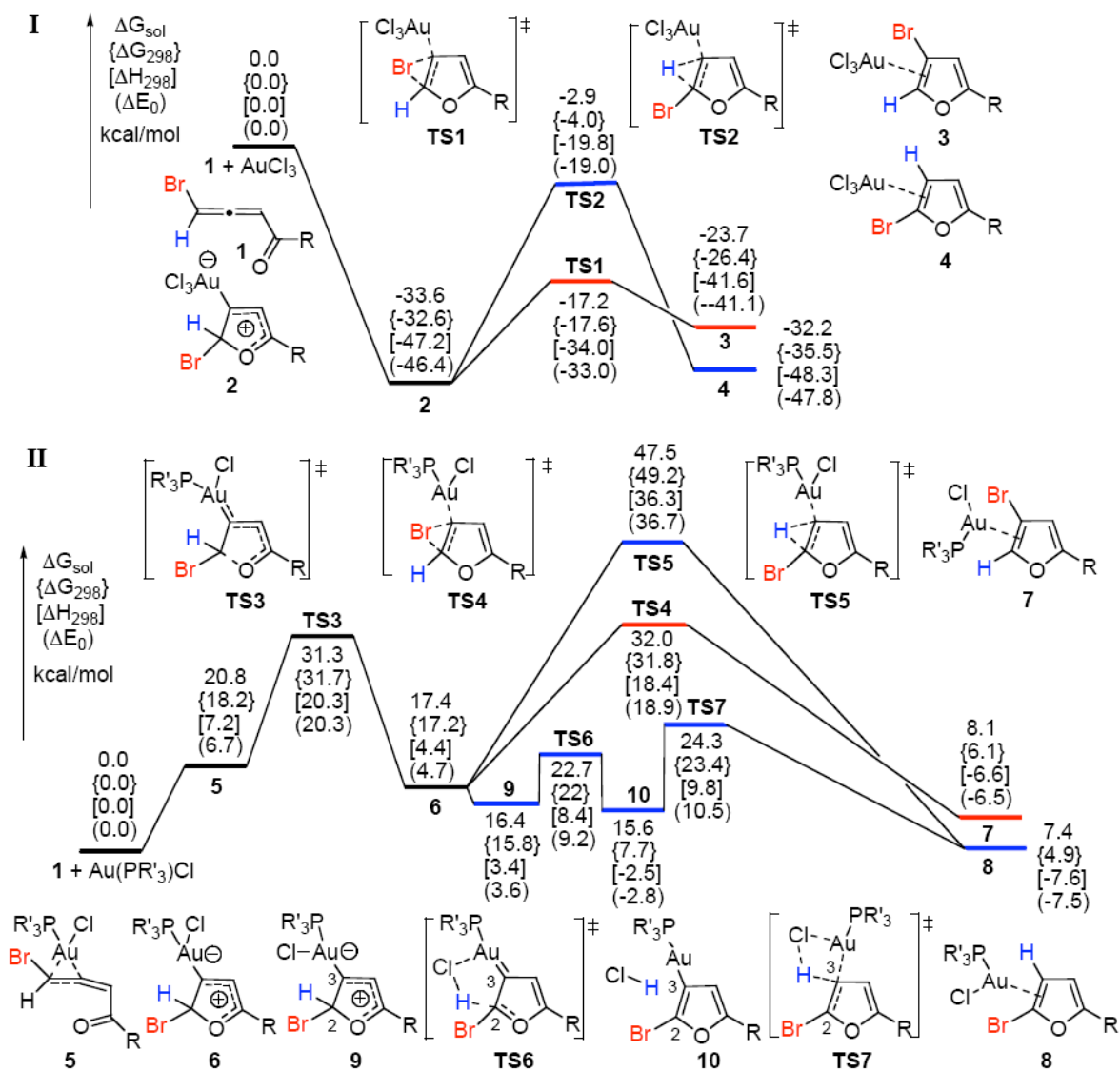
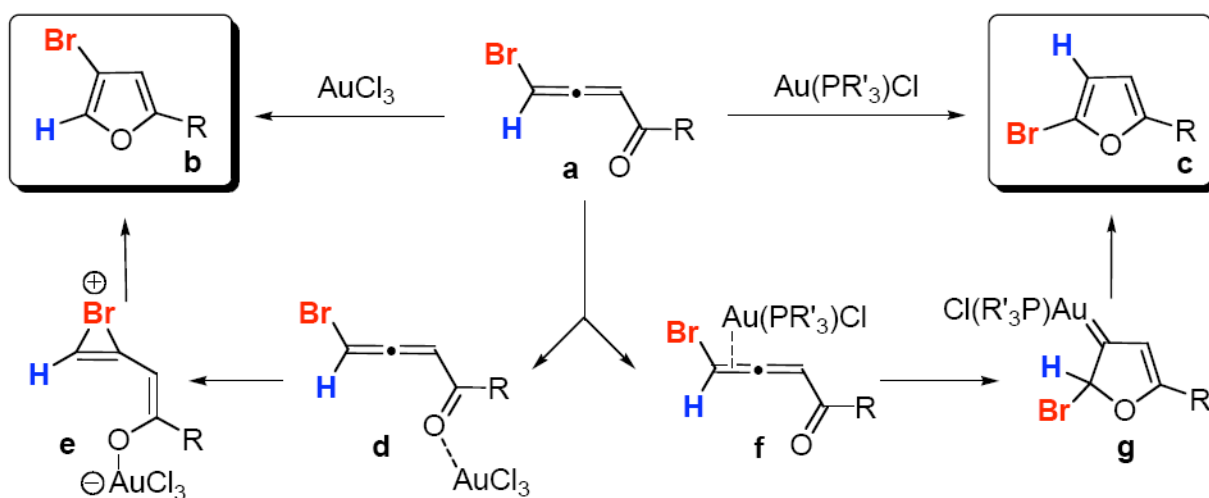
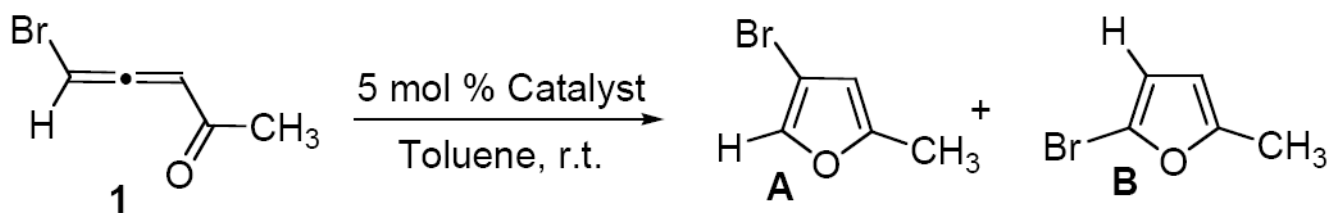


Figure 1. Potential energy surfaces for AuCl_3 - and $\text{Au}(\text{PR}'_3)\text{Cl}$ -catalyzed cycloisomerizations ($\text{R} = \text{CH}_3$, $\text{R}' = \text{H}$).⁷



Scheme 1.
Regiodivergent Au(III)- and Au(I)-catalyzed cycloisomerizations of bromoallenyl ketones.



Catalyst	A : B
Au(PPh ₃)BF ₄	>98 : 2
Au(PPh ₃)SbF ₆	100 : 0
Au(PPh ₃)OTf	0 : 100
AuCl	80 : 20

Scheme 2.
Experimental results of Au(I)-catalyzed reactions.¹⁰