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Reactive Intermediates

Mechanistic Studies on the Rearrangement of 1-Alkenyl-2-alkynylcyclopropanes: From Allylic Gold(I) Cations to Stable Carbocations**

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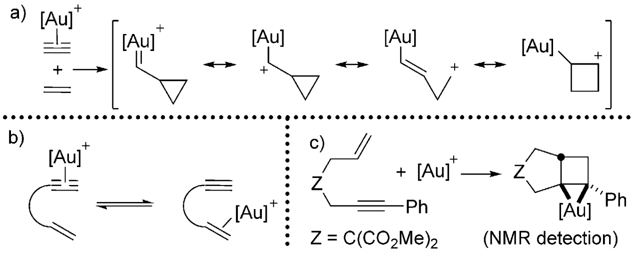
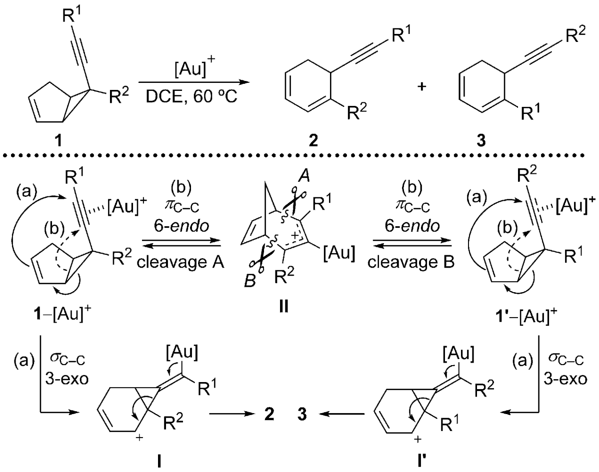
Abstract: *An allylic gold(I) cation, proposed as key intermediate in the gold-promoted rearrangement of 1,5-enynes bearing a fixed conformation, has been detected and characterized by NMR spectroscopy. Moreover, its participation in the overall transformation was confirmed. Computational studies indicate that the gold-catalyzed transformation occurs through an uncommon rearrangement. Additionally, this study led us to isolate and characterize a stable homoantiaromatic carbocation.*

Gold-catalyzed cycloisomerization of 1,*n*-enynes represents a paradigm in gold catalysis.[1] From these substrates, a great variety of products with an increased molecular complexity can be easily accessed by skeletal rearrangements. These transformations involve the nucleophilic attack of the alkene onto the gold-activated alkyne, thus leading to an intermediate which can be depicted with multiple resonance structures (Scheme 1 a).[2] Thus, the reaction outcome has been related to the contribution of these resonance structures, which can be strongly influenced by the enyne structure, catalyst, or reaction conditions. Furthermore, the high reactivity of the proposed intermediates makes their trapping a remarkably challenging task. In this sense, NMR studies have shown that gold(I) coordinates to both the alkene and alkyne to give an equilibrium mixture (Scheme 1 b),[3] while unique experimental evidence of a gold(I) intermediate has been recently reported by Widenhoefer and co-workers in the cycloisomerization of a 1,6-enyne (Scheme 1 c).[4]



Scheme 1. a) Resonance structures in gold(I)-promoted enyne cycloisomerizations. b) Coordination of gold(I) to 1,*n*-enynes. c) NMR evidence of gold(I) intermediates in cycloisomerizations.



Scheme 2. Gold(I)-catalyzed rearrangement of the enyne **1** into the cyclohexadienes **2** and **3** and previously proposed mechanism.

We have recently studied the reactivity of a specific class of 1,5-enynes, that is, the alkynylcyclopropanes **1**, which undergoes a gold-catalyzed rearrangement to the alkynylcyclohexadienes **2** and **3** (Scheme 2).[5] At that stage, a tentative pathway for the formation of **2** and **3** involving a 3-*exo-dig* attack via the intermediates **I** and **I'**, respectively, was suggested. The formation of **2** and **3** was justified assuming an isomerization of **1** through a reversible 6-*endo-dig* attack of the olefin involving intermediate **II**, a formal allylic gold(I) cation. To gain further proof on the existence of intermediates such as **II**, as well as to unravel the reaction pathway, we carried out experimental and computational studies, the results of which are described herein.

Preliminary indications on the participation of **II** were gained by its trapping with alcohols as nucleophiles,[5] and led to the isolation of the compounds **4** and **5** (see Scheme 3)

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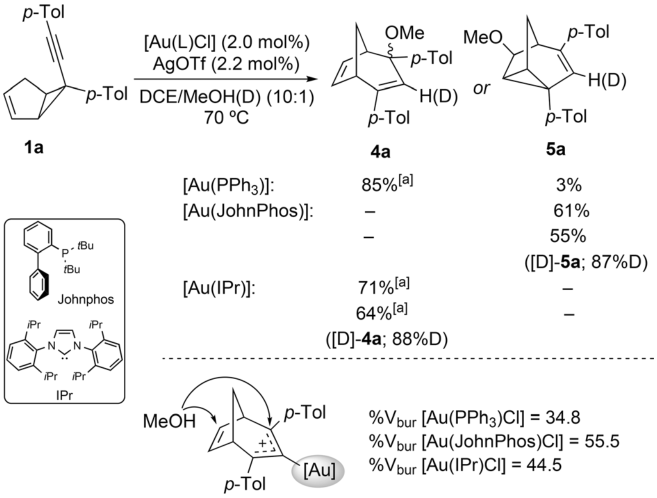
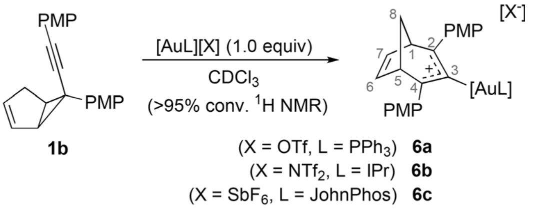


Scheme 3. Gold-catalyzed selective reactions of **1a** with MeOH(D). [a] *exo/endo* ≈ 2:1.

depending to the size of the alcohol.[6] Moreover, we have also found that the outcome in the reaction of the alkynylcyclopropane **1a** and MeOH can be correlated with the percent buried volume (%V$_{bur}$) of the gold complexes (Scheme 3).[7] Thus, while the use of [Au(PPh$_3$)]$^+$ led to **4a**, the bulkier catalyst [Au(JohnPhos)]$^+$ gave rise to **5a**. Besides, the NHC-stabilized gold catalyst [Au(IPr)]$^+$ selectively afforded **4a**. Experiments using MeOD gave rise to either [D]-**4a** or [D]-**5a**, thus providing additional experimental support. These experiments clearly point out the existence of the allylic gold(I) cation structure **II**.

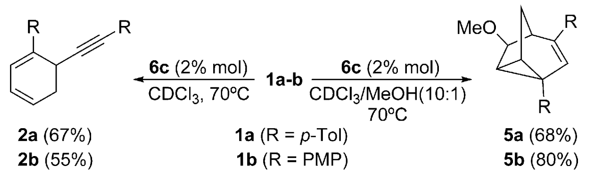
Then, we attempted to detect **II** (Scheme 4). Treatment of **1b** with stoichiometric amounts of [Au(PPh)$_3$Cl]/AgOTf in CDCl$_3$ at −50 °C immediately produced a bright blue solution, thus indicating the formation of a new species. The NMR analysis evidenced the formation of the new symmetrical complex **6a**. Thus, C3 was identified at $\delta = 168.5$ ppm ($^2J_{\text{P-C}} = 108$ Hz), while signals corresponding to C2–C4 were found at $\delta = 202.0$ ppm (selected signals shown in Scheme 4). Unfortunately, **6a** proved unstable and decomposed gradually during the measurement. We then accomplished the study using [Au(IPr)][NTf$_2$], and were also able to generate the gold complex **6b**. The compound **6b** showed a superior stability and it could be characterized by one- and two-dimensional NMR spectroscopy (see the Supporting Information). Signals corresponding to C3 and C2–C4 were located at $\delta = 165.7$ and 201.8 ppm, respectively. Moreover, the complex **6c**, derived from the use of [Au(JohnPhos)(MeCN)][SbF$_6$], was also prepared and characterized by NMR spectroscopy. A mixture of two isomers at −20 °C was observed, with signals at $\delta = 169.1/168.1$ (C3) and 199.8/199.6 ppm (C2-C4) in the ^{13}C NMR (^{31}P decoupled) spectra.[8] Chemical shifts of C2, C3, and C4 in complexes **6a–c** indicate that the positive charge is distributed along the η^1-allyl gold moiety.[9] Besides, the complexes **6a–c** display a structure which might be potentially destabilized by π-electron delocalization with certain homoantiaromatic character.[10] Indeed, the paramagnetic ring current associated to the homoconjugation is reflected in the low-field shifts ($\delta = 15$–20 ppm) of bridged methylene signals observed for C8 in **6a–c** with respect to **4b** ($R^1 = R^2 = p$-MeOC$_6$H$_4$; $\delta = 41.8$, 42.8 ppm, *exo/endo*), obtained as described in Scheme 3.[11]



	C1,C5	C2,C4	C3	C6,C7	C8	PR$_3$
6a	55.2	202.0	168.5	140.6	58.9	39.5
6b	54.7	201.8	165.7	140.5	59.6	-
6c[a]	54.1	199.8	169.1	141.3	60.0	66.0
	54.1	199.6	168.2	141.0	53.9	65.7

Scheme 4. Gold-mediated conversion of **1b** into **6a–c** and selected NMR data. The chemical shifts are given in ppm. [a] Mixture of isomers. PMP = 4-MeOC$_6$H$_4$, Tf = trifluoromethanesulfonyl.

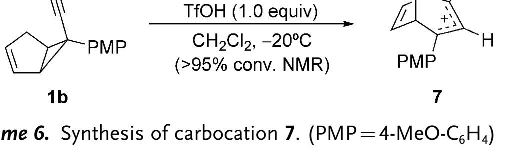
The participation of the allylic gold(I) cations **6** in the catalytic processes was further proved (Scheme 5). Thus, treatment of the cyclopropanes **1a** and **1b** with approximately 2 mol% of **6c** in CDCl$_3$ at 70 °C afforded the expected cyclohexadienes **2a** and **2b**, respectively. Moreover, when the reaction was performed in the presence of MeOH, the corresponding compounds **5a** and **5b** were isolated.



Scheme 5. Catalytic competence of gold complex **6c**.

The characterization η^1-allylic gold(I) cationic species (**6**) constitutes the first experimental evidence on the formation of such complexes. This result is not only relevant to the present transformation. These elusive species have been proposed in other gold(I)-catalyzed reactions but were never characterized.[12–14]

Although X-ray analysis of the complexes **6** failed because of their decomposition, a new species which was identified as the carbocation **7** was detected in these trials (Scheme 6). Indeed, **7** was obtained by treatment of **1b** with trifluoromethane sulfonic acid (TfOH, 1.0 equiv) in CH$_2$Cl$_2$ at −20 °C. Remarkably, TfOH proved unable to catalyze the



Scheme 6. Synthesis of carbocation **7**. (PMP = 4-MeO-C$_6$H$_4$)

rearrangement of **1** into **2**, and **7** could not be converted into **2b** under the many reaction conditions attempted. These results indicated the need of gold to accomplish the transformation of **1** into **2** and **3**. Besides, **7** showed high stability as it could be fully characterized by NMR and X-Ray analysis at room temperature.[15] Homoconjugation in **7** is also significant considering the low-field shift in signals corresponding to H8-H8′ ($\delta = 2.6, 2.9$ ppm).[16] The compound **7** represents a rare example of a stable homoantiaromatic species.[9,10]

We also carried out a computational study (B3PW91-D3/cc-pVDZ-PP//B3PW91/cc-pVDZ-PP level) on the mechanism of the rearrangement of **1c** ($R^1 = R^2 = Ph$) into **2c**, which is depicted in Figure 1 (see the Supporting Information for details). Starting from the species **1c**–[Au], alkyne coordination to gold facilitates the 6-*endo-dig* $\pi_{C\text{-}C}$ attack to give the transition-state **TS1** (+6.2 kcal mol^{-1}). From **TS1**, the intrinsic reaction coordinate (IRC) leads to **TS2** (−0.9 kcal mol^{-1}), which showed an elongation on the C1−C7 bond (1.370 to 1.446 Å) and the imminent formation of the C1−C2 bond (2.217 to 1.590 Å). Since the IRC calculation connects two transition states, there must be a valley-ridge inflection (VRI) or a bifurcation along the IRC.[17] **TS2** can evolve towards the structures **A** (−13.0 kcal mol^{-1}) or **B** (−17.3 kcal mol^{-1}), which resemble the previously observed complexes **6**. Interestingly, we found an energetically plausible reaction pathway which connects **B** with the final structure **2c**–[Au]. Thus, a rare skeleton rearrangement from **B** to the more stable structure **C** (−18.4 kcal mol^{-1}) occurs to overcome the highest energy barrier (23.5 kcal mol^{-1}) through **TS3** (+6.2 kcal mol^{-1}).[18] This step involves a double 1,3-migration as two bonds are being cleaved and two bonds are being created. Finally, the transition-state **TS4** (−3.8 kcal mol^{-1}) connects **C** with **2c**–[Au] (−13.1 kcal mol^{-1}). Thus, this computational study provides a plausible reaction pathway for the conversion of **1** into **2** and **3** through the common intermediate **B**, whose participation has been experimentally proven by spectroscopic observation. The relative energies found for **B** going to either **TS1** or **TS3** (23.5 kcal mol^{-1}, in both cases) indicate that an equilibrium between **C** and **A** is feasible, as it was proposed to explain the formation of isomers.[5] Conversely, the earlier postulated 3-*exo-dig* nucleophilic attack (Scheme 2) seems to be less likely as the calculated structure for the corresponding transition state is higher in energy than **TS1** (+17.8 versus +6.2; see the Supporting Information for the complete calculated pathway).

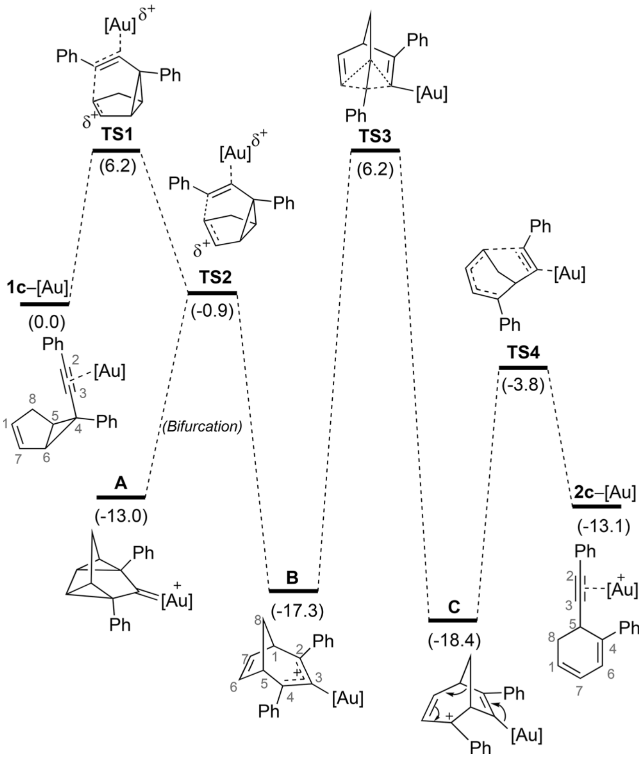


Figure 1. Calculated relative free-energy profile for the rearrangement of **1c** into **2c**. (Carbon numbers were assigned as indicated for complexes **6**; numbers within parentheses indicate ΔG in kcal mol^{-1}; [Au] = $AuPH_3$).

In summary, this study allows us to propose a revised mechanism for the gold-catalyzed rearrangement of enynes (**1**) into the cyclohexadienes **2** and **3**. While examples on the observation of gold intermediates is rare, we were able to detect and, for the first time, characterize by NMR spectroscopy the η^1-allylic gold(I) cationic intermediates **6**. Remarkably, structures like **6** are not only relevant in 1,*n*-enyne cycloisomerizations. In this sense, η^1-allylic gold(I) cationic species have been proposed in the racemization of allenes and their further functionalizations, yet they were never experimentally characterized.[19] Additionally, the computational study provides a reaction pathway connecting **1**→**6**→**2/3**. This study supports the role of **6** in the overall transformation, which undergoes an unusual rearrangement by a double 1,3-migration. Moreover, we were also able to isolate and fully characterize compound **7**, a rare example of stable homoantiaromatic carbocation.

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