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Nature of the Intermediates in Gold(I)-Catalyzed Cyclizations of 1,5-Enynes

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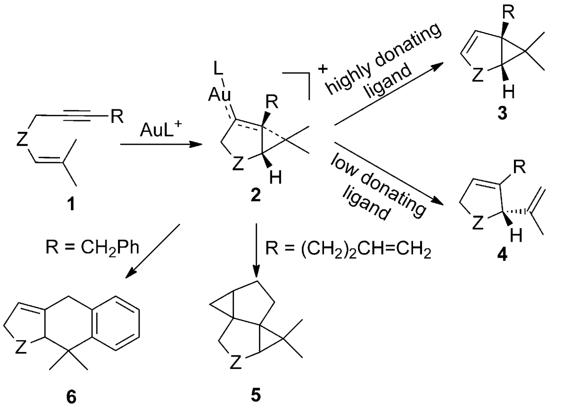
Abstract: The carbene or carbocationic nature of the intermediates in the gold-catalyzed cycloisomerization of 1,5-enynes can be revealed, depending on the ligands on the gold catalysts. Gold complexes with highly electron-donating ligands promote reactions that proceed via intermediates with carbene-like character, leading to products with a bicyclo[3.1.0]hexene skeleton. The intermediate cyclopropyl *endo*-gold carbenes formed in this cyclization have been trapped, for the first time, to give biscyclopropane derivatives in a reaction that proceeds in a concerted fashion, according to DFT calculations.

Keywords: cyclization · density functional theory · enynes · gold · reaction mechanisms

Introduction

In contrast to 1,6-enynes, which usually react by 6-*exo-dig* pathways with gold(I) catalysts,[1] 1,5-enynes **1** almost invariably undergo 5-*endo*-dig cyclizations through intermediates of type **2** to form derivatives **3**,[1–9] since formation of intermediates with a bicyclo[3.1.0]hexane structure is more favorable than formation of the strained bicyclo[2.1.0]pentane system resulting from *exo* cyclization (Scheme 1).[10,11,12]

Ligands play a major role in the control of the regio or site selectivity in gold-catalyzed reactions of 1,6-enynes.[1b,13,14] Thus, reactions of gold complexes with highly electron-donating N-heterocyclic carbene (NHC) ligands proceed via intermediates with more carbene-like character, whereas reactions with phosphite–gold catalysts can be better interpreted as proceeding via carbocationic intermediates.[15,16,17,18] However, the role of ligands in cyclizations of 1,5-enynes has not been examined systematically. Herein, we report the results of a study on the effect of ligands in cyclizations of 1,5-enynes **1**. Of particular mechanistic relevance, we have found the first examples of intramolecular cyclopropanation of *endo*-gold carbenes formed in the cyclization of 1,5-enynes to give products of type **5** (Scheme 1), which proceeded in a concerted manner, according to DFT calculations. We also report the intramolecular opening of intermediates **2** by benzyl groups to give tricyclic compounds **6**.



Scheme 1. Gold-catalyzed cyclization of 1,5-enynes via cyclopropyl gold(I) carbenes **2**.

Results and Discussion

DFT calculations on a series of 1,5-enyne models show that the nature of intermediates **2** depends on the ligand on gold(I) (Figure 1). For comparison, Pt^{II} intermediates **7** and free carbocations **8a** (R=H) and **8b** (R=Me) are also included for this study. Calculations show that metal-stabilized intermediates are significantly different from single homoallylic carbocations **8a**,**b**. Intermediate **2** (L=$P(OPh)_3$) shows the longest bond length (1.688 Å) of the Au^I complexes, but this distance is still 0.3 Å shorter than a classic carbocation, such as **8b** (R=Me). In contrast, intermediate **2** with a strongly electron-donating ligand, such as Cl^-, presents the shortest bond (1.606 Å), which corresponds more closely to a cyclopropyl gold(I) structure. Although the effect is not

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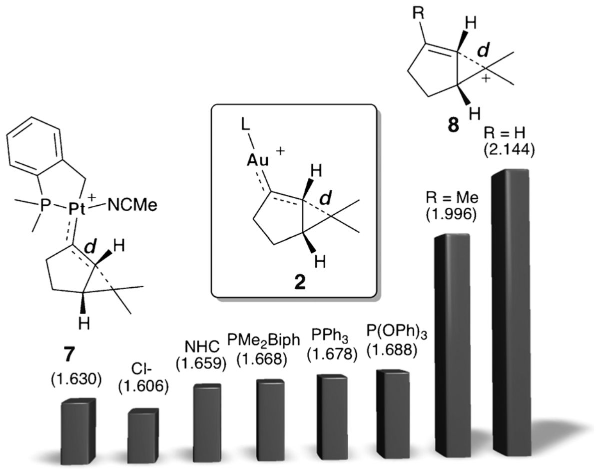
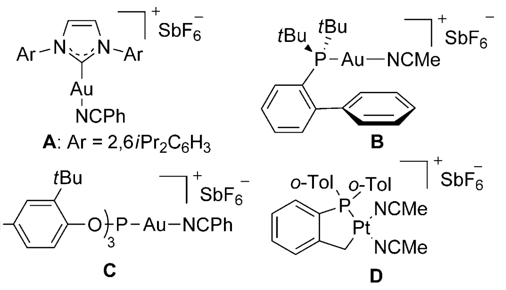


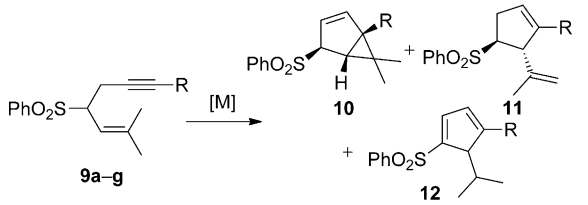
Figure 1. Variation of distance, *d* [Å], in gold intermediates **2** as a function of ligand L (NHC = *N,N'*-diphenylimidazolydene, Biph = biphenyl). Platinum intermediate **7** and carbocations **8** are included for comparison. The scale has originates at 1.4 Å to highlight the relative differences (DFT, B3LYP/6-31G**, LANL2DZ (Au)).

dramatic, the bond lengths increase along the series $Cl^- <$ *N,N'*-diphenylimidazolydene (NHC) $<$ $PMe_2Biph < PPh_3 < P(OPh)_3$, which correlates with the decreasing donor ability of L.



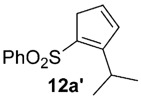
This trend is also observed experimentally for 1,5-enynes **9a–g**, with allylic sulfones, gold complexes **A–C** and platinum complex **D** as catalysts of different electrophilicity. The reaction of **9a** with catalyst **A** (5 mol %) in CH_2Cl_2 at room temperature gave bicyclo[3.1.0]hexene **10a** as the major product (Table 1, entry 1), whereas more electrophilic catalyst **B** led to cyclopentadiene **12a'** (Table 1, entry 2). Extensive decomposition was observed with catalyst **C**, which led to **12a'** in low yield (Table 1, entry 3). The reaction with $AuCl_3$ proceeded at 80 °C in toluene to give 51 % of a 1:1 mixture of **10a** and **11a** (Table 1, entry 4). Platinum(II) complex **D** also led to **10a** as the major product (Table 1, entry 5), whereas a complex mixture was observed with $[PtCl_4]$. The bicyclo[3.1.0]hexane derivatives did not undergo isomerization through vinylcyclopropane rearrangements under the reaction conditions.[19] The reaction of **9b** and **9c** in the presence of catalyst **C** exclusively gave 1,4-dienes **11b** and **11c** (Table 1, entries 6 and 7). As expected, phenyl-substituted enyne **9d** gave rise to **10d** with catalyst **A** (Table 1, entry 8). The reaction of **9d** with catalyst **C** led to **11d** along with **12d** in 25 % yield (Table 1, entry 9). Cyclopentadiene **12d** was obtained as a single isomer that slowly equilibrated to give a 3.6:1:1 mixture of three cyclopentadienes by 1,5-H sigmatropic migration. Cyclization of enynes **9e,f** in the presence of catalyst **C** also gave mixtures of 1,4-dienes **11e,f** and cyclopentadienes **12e,f** (Table 1, entries 10 and 11). In contrast, cyclization of enyne **9g** with catalyst **C** gave **11g** cleanly in 85 % yield (Table 1, entry 12).

Table 1. Cyclization of 1,5-enynes **9a–f** with gold(I) and platinum(II) metal catalysts.[a]



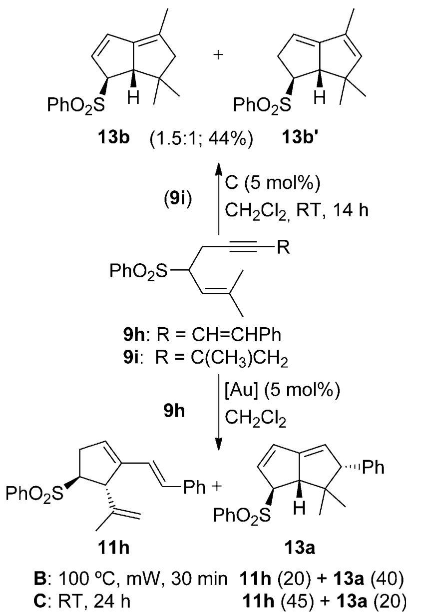
Entry	R (enyne)	Cat.	*T* [°C]	*t* [h]	Product (yield [%])
1	H (**9a**)	**A**	23	16	**10a**+**11a**+**12a'** (10:1:4, 74)
2	H (**9a**)	**B**	100[b]	0.3	**12a'** (87)
3	H (**9a**)	**C**	23	1	**12a'** (23)
4	H (**9a**)	$AuCl_3$	80[c]	14	**10a**+**11a** (1:1, 51)
5	H (**9a**)	**D**	23	16	**10a**+**11a**+**12a'** (10:2:1, 69)
6	Me (**9b**)	**C**	23	24	**11b** (80)
7	Et (**9c**)	**C**	23	24	**11c** (52)
8	Ph (**9d**)	**A**	23	18	**10d** (50)
9	Ph (**9d**)	**C**	23	17	**11d** (67)+**12d** (25)
10	*p*-MeC_6H_4 (**9e**)	**C**	23	16	**11e** (58)+**12e** (21)
11	*p*-$MeOC_6H_4$ (**9f**)	**C**	23	16	**11f** (58)+**12f** (28)
12	*p*-AcC_6H_4 (**9g**)	**C**	23	18	**11g** (85)

[a] 5 mol % catalyst in CH_2Cl_2. [b] Microwave heating. [c] Reaction in toluene.



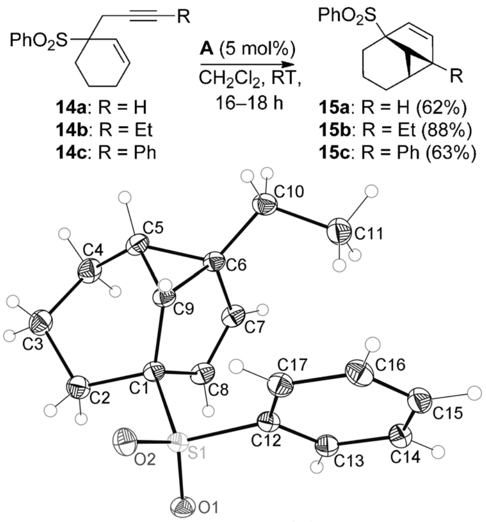
12a'

Vinyl-substituted enynes **9h,i** were also studied. Cyclization of enyne **9h** with catalyst **B** under microwave irradiation led to the expected product **11h** along with **13a** as the major product (Scheme 2). The product ratio was inverted when the reaction was carried out with complex **C** as catalyst at room temperature for 24 h. Tetrahydropentalene **13a** is formed via an intermediate of type **2** (see Scheme 1) and not by gold(I)-catalyzed cyclization of **11h** because heating this triene with catalyst **B** at 100 °C (microwave irradiation) for 30 min failed to give **13a**. Mechanistically, this annulation is related to that occurring in the gold(I)-catalyzed [4+2] cycloaddition of dienynes[13,21] and in the cyclization of 1,8-dien-4-ynes,[8c] in which the pendant alkenes act as the internal nucleophiles. Cyclization of enyne **9i** in the presence of catalyst **C** resulted in the formation of 1.5:1 mixture of bicyclic products **13b**/**13b'** in moderate yield.



Scheme 2. Gold(I)-catalyzed cyclization of dienynes **9h** and **9i**.

Enynes **14a–c**, with different substitution patterns at the alkene, also reacted with catalyst **A** at room temperature to form tricyclic products **15a–c** in good yields (Scheme 3).



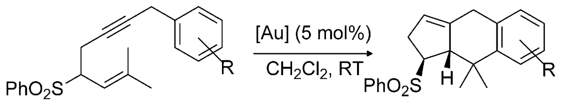
15b

Scheme 3. Gold(I)-catalyzed cyclization of eynes **14a–c** and X-ray crystal structure of **15b**. Ellipsoids are drawn at the 50 % probability level.[20]

The reaction of enyne **14b** was also carried out with catalyst **D** to give **15b** in 78 % yield after 12 h at room temperature. The structure of tricyclic compound **15b** was confirmed by single-crystal X-ray diffraction (Scheme 3).[20]

Benzyl-substituted 1,5-enynes **9j–n** led to compounds **16** (Table 2) through intramolecular cycloaddition reactions reminiscent to those of aryl-substituted 1,6-enynes.[21] In all cases, tricyclic compounds **16** were obtained as single stereoisomers. In general, good yields were obtained with electrophilic catalysts **B** or **C**. Enyne **9n**, substituted at the *meta* position of the aryl ring, led to a mixture of regioisomeric compounds **16e** and **16e′** (Table 2, entries 11 and 12). In this reaction, the aryl ring opens the intermediate cyclopropyl gold(I) carbene in a process related to that occurring in the gold(I)-catalyzed formal [4+2] cycloaddition of arylalkynes with alkenes.[21]

Table 2. Cycloaddition of enynes **9j–n** with gold(I) catalysts.



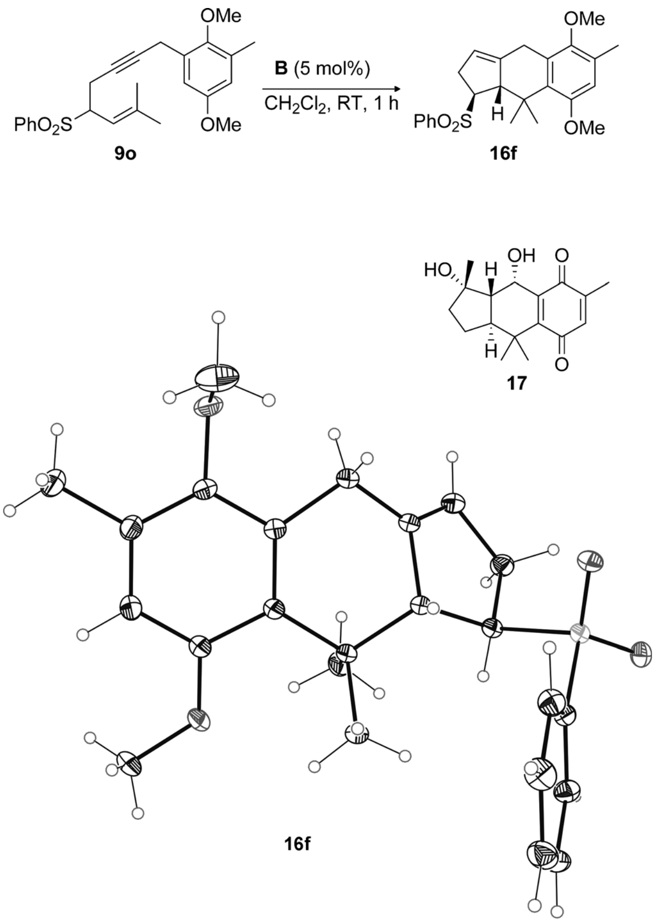
9j–n **16a–e**

Entry	R (enyne)	Cat.	*t* [h]	Product (yield [%])
1	H (**9j**)	**B**	14	**16a** (95)
2	H (**9j**)	**C**	12	**16a** (71)
3	*p*-MeO (**9k**)	**A**	3	**16b** (66)
4	*p*-MeO (**9k**)	**B**	3	**16b** (66)
5	*p*-MeO (**9k**)	**C**	2	**16b** (95)
6	*p*-Ph (**9l**)	**A**	14	**16c** (63)
7	*p*-Ph (**9l**)	**B**	14	**16c** (60)
8	*p*-Ph (**9l**)	**C**	0.2	**16c** (92)
9	2,3,4-$(MeO)_3$ (**9m**)	**B**	14	**16d** (64)
10	2,3,4-$(MeO)_3$ (**9m**)	**C**	0.2	**16d** (45)
11	*m*-MeO (**9n**)	**B**	14	**16e** (55)+**16e′** (12)
12	*m*-MeO (**9n**)	**C**	14	**16e** (57)+**16e′** (31)

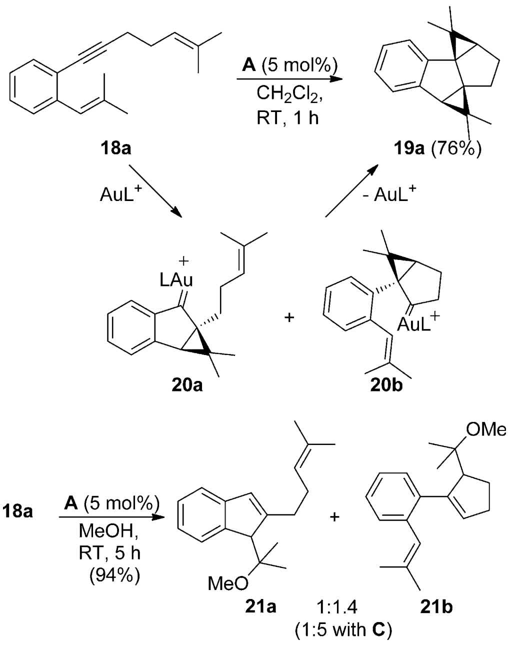
1,5-Enyne **9o** reacted smoothly with catalyst **B** at room temperature to give cycloadduct **16f** in 95 % yield, the structure of which was confirmed by X-ray diffraction (Scheme 4).[22] Tricyclic compound **16f** possesses the tricyclic skeleton of (+)-pycnanthuquinone C (**17**),[23,24] which is a natural compound structurally related to pycnanthuquinones A and B[25] and rossinone.[26]

Intermediates of cyclizations of 1,6-enynes have been trapped by intra-[27] or intermolecular cyclopropanation;[18,28] however, the trapping of intermediates **2** by alkenes in cyclizations of 1,5-enynes was unknown. Therefore, we decided to trap these intermediates in reactions catalyzed by gold complexes, such as **A**, with donating ligands that would enhance their carbene-like character. Thus, dienyne **18a**, which has two alkene groups in a 1,5-relationship to the alkyne, reacted in the presence of catalyst **A** to give pentacyclic biscyclopropane derivative **19a** in 76 % yield (Scheme 5). The relative configuration of **19a** was assigned by NOE experiments.

Interestingly, in this case, the formation of **19a** from **18a** could occur by two parallel pathways via intermediates **20a** and/or **20b**, which would converge to form the same biscyclopropane derivative. Both intermediates are likely to be formed in this transformation, since a similar gold(I)-catalyzed reaction carried out in MeOH led to a 1:1.4 mixture of adducts **21a** and **21b**. In the presence of catalyst **C**, the methoxycyclization reaction gave a 1:5 mixture of **21a** and **21b**.

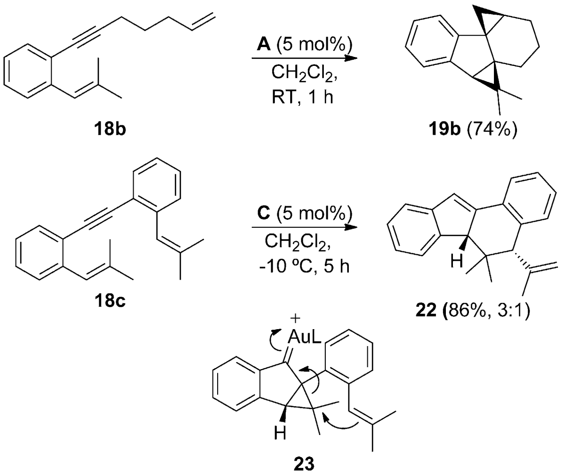


Scheme 4. Gold(I)-catalyzed cyclization of eyne **9o** to give **16f**, which is related to (+)-pycnanthuquinone C. Ellipsoids are drawn at the 50% probability level.[22]



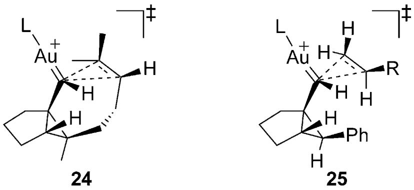
Scheme 5. Gold(I)-catalyzed cyclization of dienyne **18a** to give **19a**.

Enyne **18b** was also cyclized in the presence of catalyst **A** to form biscyclopropane **19b**. In contrast, enyne **20c** gave complex mixtures in the presence of catalyst **A**, whereas tetracyclic compound **22** (3:1 mixture of diastereomers) was obtained in 86% yield using catalyst **C**, presumably via intermediate **23** (Scheme 6).



Scheme 6. Gold(I)-catalyzed cyclization of dienynes **18b** and **18c**.

The cyclopropanation of 1,5-dien-10-ynes proceeds through transition states, such as **24** (Scheme 7), in which the two carbon–carbon bonds are similarly formed (2.23 and 2.10 Å).[27] We found that intermolecular cyclopropanation can occur both in a concerted or in a stepwise fashion, depending on the substituents present on the alkene. Thus, whereas the reaction with ethylene and propene via transition states of type **25** (Scheme 7) is concerted (bond distances 2.1–2.5 Å), cyclopropanation with more-polarized styrene is stepwise.[18] However, in the latter case, formation of the second C–C bond required a very low barrier. As a consequence, although formally stepwise, the cyclopropanation of styrene is also stereospecific.



Scheme 7. Transition states **24** and **25** for the intra- and intermolecular cyclization of 1,6-enynes with alkenes.

We studied the intramolecular cyclopropanation of intermediates **26a**,**b** theoretically to form tetracyclic products **27a**,**b** with PMe_3 and NHC (*N,N'*-dimethylimidazolydene) ligands as models, and for the intramolecular cyclopropanations of 1,5-enynes (Figure 2). Cyclopropanation was found to be concerted in both cases with activation energies of 17–

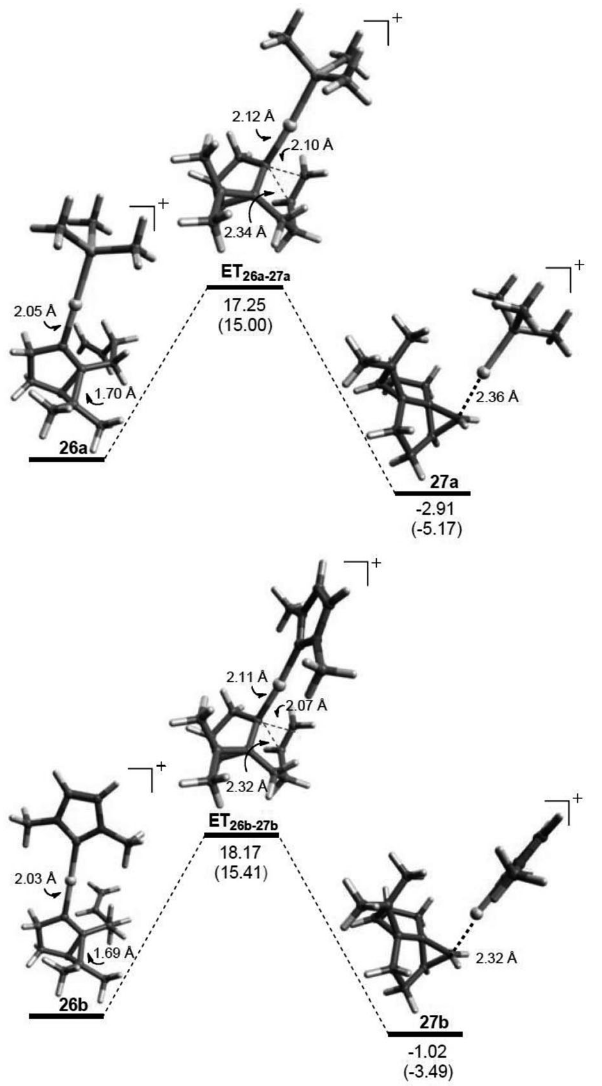
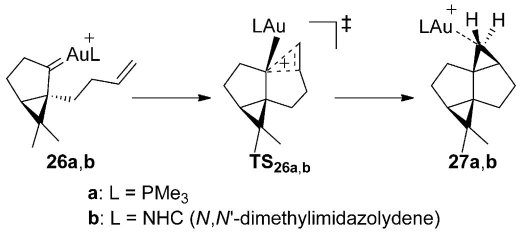


Figure 2. Top: Reaction coordinate (DFT, B3LYP, 6-31G(d) (C, P, H), and SDD (Au) in CH_2Cl_2) for the intramolecular cyclopropanation of **26a** to form corner-metalated **27a**. Bottom: Reaction coordinate (DFT, B3LYP, 6-31G(d) (C, N, H), and SDD (Au) in CH_2Cl_2) for the intramolecular cyclopropanation of **26b** to form corner-metalated **27b**. Free energies in kcal mol^{-1} (ZPE-corrected potential energies are in parentheses).

18 kcal mol^{-1} (free energy in CH_2Cl_2), which were about twice as high as that found for the intermolecular cyclopropanation of a model 1,6-enyne with propene.[18] Transition states $TS_{26a\text{-}27a}$ and $TS_{26b\text{-}27b}$ are asynchronous and the C–C bond between the carbene carbon and C1 is more advanced (2.07–2.10 Å) than that of C2 (2.32–2.34 Å). The reaction proceeds very similarly with $[Au(PMe_3)]^+$ and $[Au(NHC)]^+$, although the activation energy is higher for **26b**, as expected for an intermediate in which the electrophilicity of the carbene is reduced by the more donating NHC ligand. Transition states leading to *anti*-biscyclopropane derivatives were not found.

As the cyclopropanation progresses, the C–Au bond elongates from 2.03–2.05 Å in carbenes **26a**,**b** to 2.11–2.12 Å in transition states $TS_{26a\text{-}27a}$ and $TS_{26b\text{-}27b}$ and, finally, LAu^+ moves to C1 to form corner-metalated cyclopropanes **27a**,**b** (Au–C distance 2.32–2.36 Å) (Scheme 8).



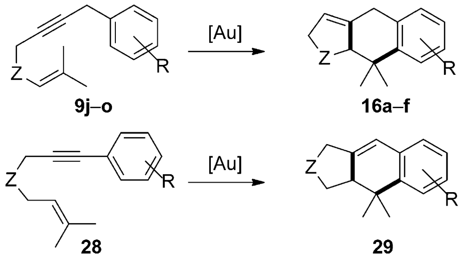
Scheme 8. Mechanism for the conversion of **26a**,**b** into **27a**,**b** via transition state $TS_{26a,b}$.

As shown before in a more simple system,[16] the Au–C carbene bond (2.03 Å) in intermediate **26b** is shorter than that between Au and the NHC ligand (2.08 Å). Additionally, although one of the cyclopropane C–C bonds in intermediates **26a** and **26b** is longer than the other two (1.69–1.70 Å vs. 1.46–1.59 Å), the internal angle (67.75° for **26a**, 67.11° for **26b**) is far more acute that the tetrahedral angle expected for an open carbocation.

Conclusion

Gold complexes with highly electron-donating N-heterocyclic ligands enhanced the carbene-like character of the intermediates in cyclizations of 1,5-enynes in the same manner as that observed before for 1,6-enynes.[13,15,18] These reactions lead to products with a bicyclo[3.1.0]hexene skeleton that retains the cyclopropane ring of the initial intermediate. These intermediates can be opened by aryl groups in substrates **9j–o** in a process that is mechanistic and synthetically similar to the formal [4+2] cycloaddition of dienynes **28** to form tricyclic derivatives **29** (Scheme 9).[21]

The intermediate cyclopropyl *endo*-gold carbenes can be trapped to form biscyclopropane derivatives, which is in agreement with cyclopropanations observed in gold(I)-catalyzed cyclization of vinyl allenes, which proceed through similar intermediates.[29] According to DFT calculation, this intramolecular cyclopropanation from 1,5-enynes proceeds by a concerted process similar to that found before for the



Scheme 9. Comparison between the intramolecular arylation of 1,5-enynes (**9**) with that of 1,6-enynes (**28**).

intra- and intermolecular cyclopropanations observed in reactions of 1,6-enynes.

We have argued before that the representation of the intermediates in gold(I)-catalyzed cyclizations of 1,6-enynes as simple carbocations is simplistic.[13] This work further emphasizes this point by showing that the intermediates in gold(I)-catalyzed cyclizations of 1,5-enynes are significantly stabilized homoallylically and are not open carbocations.

Experimental Section

General procedure for the cyclization of 1,5-enynes: The starting enyne was dried before being used in the reaction by repeated evaporation of a solution of the compound in toluene (10 mg mL^{-1}, 3×) under vacuum. A solution of the 1,5-enynes in CH_2Cl_2 (0.5–1 mL) was added to a solution of gold(I) complexes **A–C** (5 mol %) in CH_2Cl_2 (0.5 mL) and stirred at room temperature until full conversion (as determined by TLC). The crude reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the cyclized products.

Computational details: Calculations were performed with the Gaussian 09 series of programs.[30] The geometries of all complexes were optimized at the DFT level using the B3LYP functional.[31] The LANL2DZ basis set, which included the relativistic effective core potential (ECP) of Hay and Wadt and employed a split-valence (double-ζ) basis set, was used for Au.[31]

Acknowledgements

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