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Carbocations or Cyclopropyl Gold Carbenes in Cyclizations of Enynes

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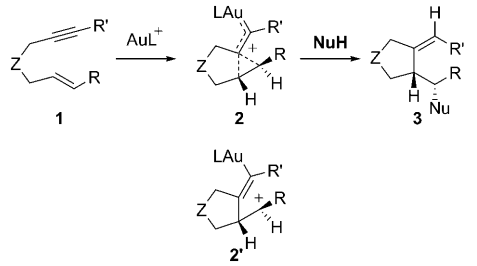
Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday

Abstract: Theoretical and experimental studies on the gold(I)-catalyzed formal [4+2] cycloaddition of dienynes are consistent with a mechanism that proceeds by means of cyclopropyl gold(I) carbenes instead of simple carbocations. This work shows that homoallylic stabilization is significant even for systems in which the tertiary carbocation is stabilized by two methyl groups.

Keywords: carbenes · cyclization · density functional calculations · enynes · gold

Introduction

According to DFT calculations, 1,6-enynes **1** react in the presence of gold(I) catalysts through intermediates **2**[1] that are trapped by hetero- or carbonucleophiles to form addition products **3**[2–10] (Scheme 1). A similar pathway was proposed for related Pt^{II}- and Pd^{II}-catalyzed reactions of enynes.[11,12] Indeed, cyclopropyl metal carbenes were first proposed as intermediates in Pd^{II}-catalyzed cyclizations of 1,6-enynes in the presence of 1,3-dienes.[13] Intermediates **2** are also involved in the skeletal rearrangement of 1,6-enynes,[14] intramolecular cyclopropanations[15] of enynes, and other reactions.[1,16–19] Different trapping experiments support the involvement of intermediates **2** in these transformations.[5,20,21] The intermolecular reaction of alkynes with alkenes catalyzed by gold(I) can also be interpreted as proceeding through related intermediates.[22]



Scheme 1. Gold-catalyzed cyclization of 1,6-enynes by means of cyclopropyl gold(I) carbenes **2**.

Although structures such as **2** are depicted for convenience in a simplified manner as cyclopropyl gold carbenes,[1] DFT calculations reveal that these species have highly distorted structures, which are intermediate between cyclopropyl gold carbenes and gold-stabilized homoallylic carbocations.[4b,7d,9,14a,23] Indeed, we have demonstrated that if the enyne is substituted at the alkene with strongly electron-releasing R groups, skeletal rearrangements and addition reactions catalyzed by gold(I) lose their usual stereospecificity.[9] In these cases, the reactive intermediates are better described as open carbocations **2′**.

The nature of intermediates **2** has been discussed recently and their carbocationic character **2′** has been stressed.[3g,24,25] Actually, the mere involvement of **2** as intermediates in gold(I)-catalyzed cyclizations of substituted enynes has been questioned. Thus, for example, it was proposed that the reported mechanism for the [4+2] cycloaddition of dienynes **4** to give hydrindanes **5** by means of intermediates **6** and **7**[4] could be explained more simply by a cyclization of carbocation **8**[26] (Scheme 2). In favor of this interpretation, it was argued that the more substituted cyclopropyl carbon atom in intermediate **6** should be less reactive towards nucleophilic attack.[26]

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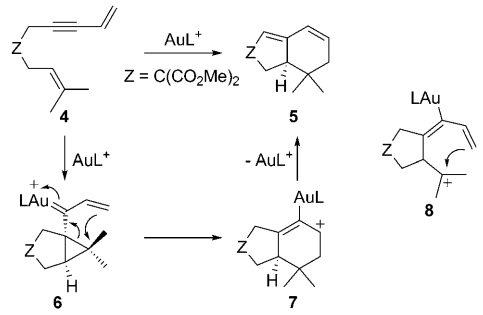
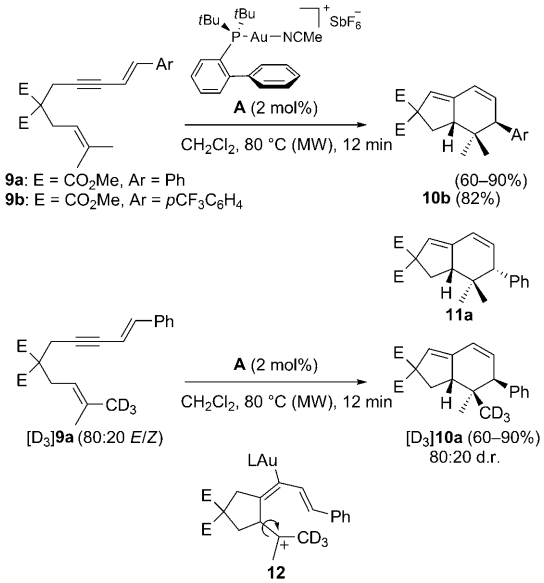


Scheme 2. Original mechanistic proposal for the intramolecular [4+2] cycloaddition of dienynes through intermediate **6**[4] and alternative proposal by means of carbocation **8**.[26]

The original mechanistic proposal for a Nazarov-type cyclization through intermediates **6** and **7** was based on the analogy with the mechanism of the [4+2] cycloaddition of aryl-substituted enynes, which was supported by a theoretical study.[4b] Therefore, since our original interpretation for the cyclization of dienynes has been questioned,[26] we decided to study in detail the mechanism of the gold(I)-catalyzed cyclization of substrates of type **4** with the aim to shed light on the nature of the intermediates involved in this and related gold(I)-catalyzed processes.

Results and Discussion

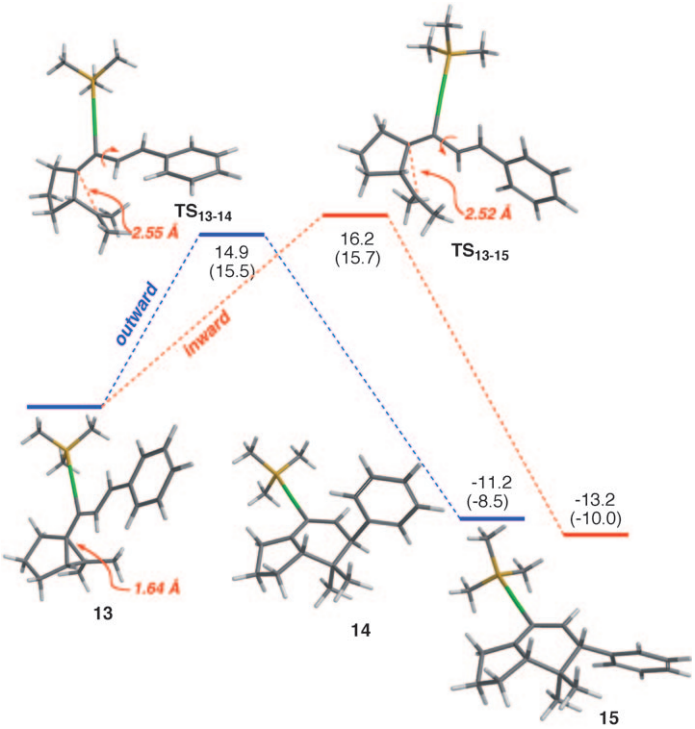
We reported before that the cycloaddition of dienyne **9a** using gold(I) catalyst **A** gave hydrindane **10a** stereoselectively[4] (Scheme 3). Similarly, reaction of dienyne **9b** with an electron-withdrawing group on the aryl group in the presence of cationic gold(I) complex **A** gave exclusively **10b**. The total stereoselectivity observed in these cycloadditions



Scheme 3. Gold-catalyzed cyclization of dienynes **9a**,**b** and [D_3]**9a**.

is noteworthy since calculations (DFT at the B3LYP-6-31G level) predict that **10a** and its diastereomer **10a′** possess the same energy ($\Delta E < 0.1$ kcal mol^{-1}). Importantly, reaction of selectively deuterated dienyne [D_3]**9a** (80:20 *E*/*Z* ratio) with catalyst **A** led to hydrindane [D_3]**10a** with the labeled CD_3 *cis* to the phenyl group. This result shows that a tertiary carbocation such as **12** is either not an intermediate in this reaction or, if **12** is formed, cyclization is faster than bond rotation that would give a 1:1 mixture of deuterated derivatives.

To better define the mechanism of this process, we performed DFT calculations on a model system that lacked the substitution at the tether (Scheme 4). These calculations show that the cycloaddition proceeds through intermediate

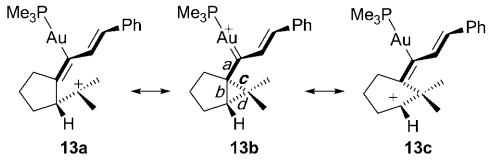


Scheme 4. Energy profile for the key step in the [4+2] cycloaddition of enyne **9** with [$AuPMe_3$]$^+$ in CH_2Cl_2 calculated with the PCM model ($\Delta(E+ZPE)$, kcal mol^{-1}) and calculated distances (in red). Energy differences without solvent effects are given in parentheses.

13 by an outward rotation of the alkenylcarbene by means of transition state $\mathbf{TS_{13-14}}$ to form allyl cation **14**, which corresponds to intermediate **7** in Scheme 2. The alternative inward rotation in intermediate **13** would form **15** through $\mathbf{TS_{13-15}}$ in a less favorable process. Although the differences in energy between $\mathbf{TS_{13-14}}$ and $\mathbf{TS_{13-15}}$ are small, these calculations predict formation of products with the configuration determined experimentally.

According to DFT calculations, cationic gold intermediates **13** are not open carbocations and show instead a quite regular cyclopropyl gold(I) carbene structure with cyclo-

Table 1. Calculated distances [Å] for intermediate **13**.



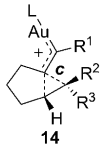
Method	Au–C	*a*	*b*	*c*	*d*
B3LYP	2.076	1.439	1.547	**1.643**	1.483
M06	2.083	1.430	1.537	**1.611**	1.457

propyl bonds (1.55 ± 0.10 Å, Table 1). According to that shown in Scheme 4, the lengthening bond *c* (Table 1) in **13** leads to structures that resemble open carbocations, which are, however, transition states (**TS$_{13–14}$** and **TS$_{13–15}$**) and not intermediates.

A more detailed analysis of intermediates **14** that bear different R^1–R^3 substituents using the B3LYP and M05 functionals is shown in Table 2.[27] For the neutral structures **14a–f** with L = Cl^-, regular cyclopropyl gold(I) carbenes were found in all cases with distances *c* = 1.55–1.64 Å, whereas this bond length was slightly longer in the case of cationic intermediates **14g**,**h** and **14j**,**k** (1.57–1.66 Å). These differences are consistent with the higher donating ability of chloride when compared with phosphine ligands.[28,29] The structures of **14i** and **14l**, with two methyl groups at the terminus, show longer distances (1.76–1.86 Å with B3LYP, 1.67–1.69 Å with M05) that are nevertheless shorter than those found for limiting structures with cyclopropyl or *p*-methoxyphenyl substituents at the terminal carbon atom.[9]

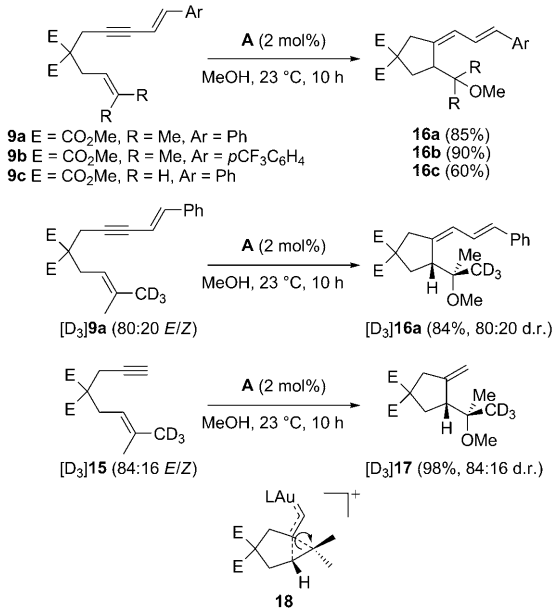
When the gold(I)-catalyzed reaction of dienynes **9a–c** was carried out in methanol, products **16a–c** of methoxycyclization[2] were isolated in 60–90% yield (Scheme 5). These results show that trapping of the intermediates **13** by methanol is faster than the cyclization process. Reaction of dienyne [D_3]**9a** (80:20 *E*/*Z* ratio) with catalyst **A** in methanol as solvent led to [D_3]**16a** as an 80:20 mixture of diastereomers, which demonstrates again that the intermediate species **13** is not a free carbocation that could undergo bond-rotation cyclization to form an equal mixture of both diastereomers.

Table 2. Calculated distances [Å] for intermediates **24**.[a]



14	L	R^1	R^2	R^3	*c*
a	Cl^-	H	H	H	1.555 (1.547)
b	Cl^-	H	Me	H	1.582 (1.572)
c	Cl^-	H	Me	Me	1.630 (1.614)
d	Cl^-	CH=CH_2	H	H	1.582 (1.567)
e	Cl^-	CH=CH_2	Me	H	1.609 (1.590)
f	Cl^-	CH=CH_2	H	Me	1.643 (1.615)
g	PMe_3	H	H	H	1.568 (1.567)
h	PMe_3	H	Me	H	1.614 (1.608)
i	PMe_3	H	Me	Me	1.858 (1.683)
j	PMe_3	CH=CH_2	H	H	1.604 (1.588)
k	PMe_3	CH=CH_2	Me	H	1.661 (1.624)
l	PMe_3	CH=CH_2	Me	Me	1.756 (1.668)

[a] B3LYP/6-31G(d) (C,H,P), LANL2DZ (Au). In parentheses: M05/6-31G(d) (C,H,P), LANL2DZ (Au).



Scheme 5. Gold-catalyzed methoxycyclization of dienynes **9a**,**b**, [D_3]**9a**, and enyne [D_3]**15**.

Furthermore, selectively labeled 1,6-enyne [D_3]**15** (84:16 *E*/*Z* ratio) reacted with catalyst **A** in the presence of methanol to give [D_3]**17** with the same diastereomeric ratio. This result demonstrates that bond rotation around bond *c* in intermediate **18** does not take place. Calculation for structures **14i** and **18** with the M06 functional (Figure 1) show slightly less distorted cyclopropyl gold(I) carbenes than those determined with B3LYP or M05 (Table 2). Importantly, even though atoms-in-molecules (AIM) analysis[30] shows zero electron density at the bond-critical point of bond *c* for structures **14i** and **14l**,[27] the calculated bond angle between bonds *b* and *d* (64.7–65.2°) was much smaller than the tetrahedral angle of 109.5°, in accord with a substantial homoallylic stabilization of the cationic species.

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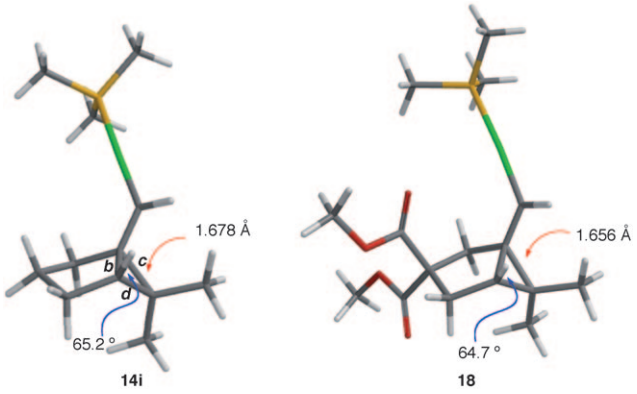

Figure 1. Calculated structure for intermediates **14i** and **18** [M06 6-31G** (C,H,P), LANL2DZ (Au) (Spartan 08)].

Conclusion

Our results show that the gold(I)-catalyzed cyclization of dienynes to form hydrindanes proceeds by means of cyclopropyl gold(I) carbenes as intermediates, which undergo C–C bond formation faster than rotation around the elongated cyclopropane bond. Attack of methanol to these intermediates is also faster than possible rotation around that elongated bond.

Although the depiction of the intermediates in gold(I)-catalyzed cyclizations of 1,6-enynes as simple carbocations has the merit of simplicity and mnemotechnic value, this is nevertheless a simplistic representation. Our work shows that homoallylic stabilization is significant even for systems in which the cation is stabilized by two methyl groups.

This study may be relevant to other transformations of enynes that proceed by annulation/trapping by nucleophiles pendant to the alkyne or alkene terminus of the enynes.[24,31,32] In general, it is important to distinguish processes that occur by an overall *anti* addition of the electrophile (the metal-coordinated alkyne) and the nucleophile to the alkene, such as alkoxycyclizations[2] and polycyclization reactions,[32] from those that occur by an overall *syn* addition. In the first case, in analogy with the Stork–Eschenmoser model for squalene and oxidosqualene cyclizations,[33] reactions might be concerted, although this hypothesis has not yet been substantiated theoretically. It is interesting to note, however, that stepwise mechanisms might be operative even for the reactions catalyzed by different cyclase enzymes.[34] For gold(I)-catalyzed *syn* additions to alkenes, this work, in line with previous theoretical and experimental results,[4b,16b] supports a stepwise mechanism.

Experimental Section

*General Method for the Cyclization of Enynes **9a** and [D$_3$]**9a***

The enyne (50.0 mg, 0,15 mmol) dissolved in dry CH_2Cl_2 (0.5 mL) was added to a solution of cationic Au^I complex **A** (2.2 mg, 0.002 mmol) in dry CH_2Cl_2 (0.5 mL). The reaction was stirred at 80 °C over 12 min in a microwave. The resulting mixture was filtered through Celite and purified by flash chromatography (10% EtOAc in hexanes).

General Procedure for the Methoxycyclization of Enynes

The enyne (0.15 mmol) dissolved in dry MeOH (0.5 mL) was added to a solution of cationic Au^I complex **A** (0.002 mmol) in dry MeOH (0.5 mL). The reaction was stirred at room temperature for 10 h. The resulting mixture was filtered through Celite and purified by flash chromatography (10% EtOAc in hexanes).

Computational Details

Calculations were performed with the Gaussian 03 series of programs.[35] The geometries of all complexes were optimized at the DFT level using the B3LYP functional[36] or the M05/M06 functionals[37] using the standard 6-31G(d) basis set for C, H, and P. The LANL2DZ basis set, which includes the relativistic effective core potential (ECP) of Hay and Wadt and employs a split-valence (double-ζ) basis set, was used for Au.[38] Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE). The starting approximate geometries for the transition states (**TS**) were graphically located. Intrinsic reaction coordinate (IRC) studies were performed to confirm the relation of the transition states with the corresponding minima. Solvent effects were considered by performing single-point calculations in CH_2Cl_2 using the polarized continuum model (PCM) on the optimized structures.

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