VIP Gold Catalysis

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On the Nature of the Reactive Intermediates in Gold-Catalyzed Cycloisomerization Reactions**

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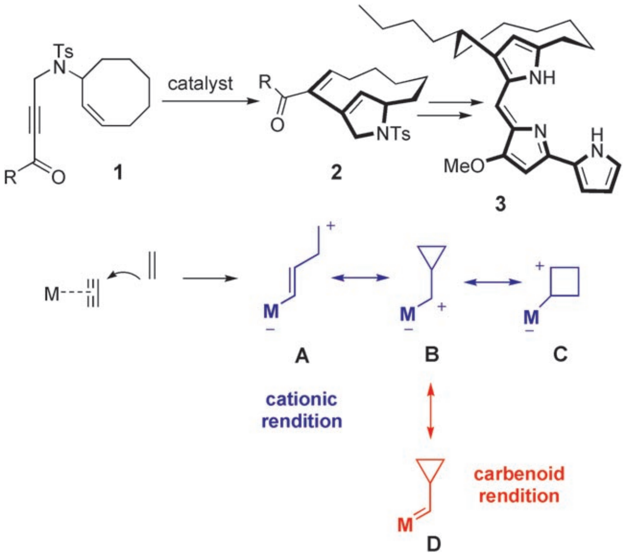
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 75th birthday

Over the course of the last decade, the use of platinum and gold complexes as carbophilic π-acids has evolved from a laboratory curiosity to a blossoming field of catalysis research.[1] This popularity is largely due to the significant increase in molecular complexity and the impressive structural diversity that can be garnered in such inherently atom-economic and user-friendly transformations.

The tremendous preparative success notwithstanding, the mechanistic understanding is still limited, not least because of the lack of secured structural data on pertinent intermediates. It was during the total synthesis of the pyrrole-alkaloid streptorubin (**3**) that our research group had noticed a striking analogy between noble metal catalyzed enyne cycloisomerization reactions and the reactivity pattern generally associated with “nonclassical” carbocations (**A**–**C**, Scheme 1).[2,3] The fact that the transformation of substrate **1** into diene **2** can be brought about by Pt^{II} or Au^{I} as well as by ordinary Lewis or even Brønsted acids enforced this view.[2] In formal terms, however, putative intermediates of type **B** can also be interpreted as electrophilic metal cyclopropylcarbenes **D**, thus rendering the purely “cationic” and the strict “carbene” rendition of the basic mechanism as nothing but the mesomeric extremes of a generic picture (Scheme 1).[1–4]



Scheme 1. Analysis of the key step in a total synthesis of streptorubin (**3**) led to the conclusion that the attack of an alkene upon an alkyne catalyzed by a noble metal results in reactive intermediates that can be described in either cationic or carbenoid terms. M = noble metal, R = butyl, Ts = *para*-toluenesulfonyl.

This initial hypothesis has since accounted for a host of different transformations and was confirmed by numerous computational and experimental studies.[1] Yet, it became fairly common practice to discuss plausible catalytic cycles on the basis of metal carbenes without appreciation for the underlying formalism. Therefore we feel urged to present experimental evidence which suggests that the carbocationic view might actually be more adequate if Ockham’s razor is applied, in particular to the field of gold catalysis.[5]

The notion that “gold carbenes” may have little in common with ordinary metal carbenes of the Fischer or Schrock types is supported by the crystal structure analysis of the known complex **4** (Figure 1).[6] The C–Au bond length falls within the range of a typical single bond between an sp^2-hybridized carbon atom and an Au^{I} center,[7] whereas the C–N bond is surprisingly short.[8] Complex **4** is therefore more accurately depicted as a gold-stabilized iminium cation rather than a gold carbene.

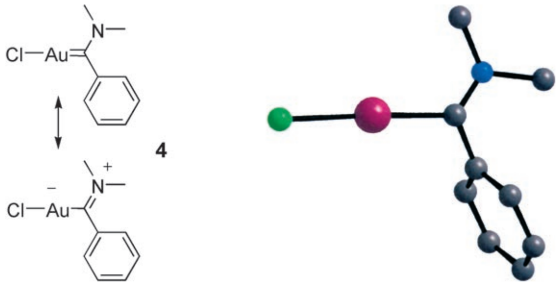


Figure 1. Structure of a Fischer-type “gold carbene”.[6a] Notably, the C–Au bond length (2.02(3) Å) falls within the range for a single bond, whereas the C–N bond (1.262 Å) is even shorter than that of a prototypical imine.[7,8]

To probe the putative cationic character of the reactive gold intermediates more thoroughly, a series of cycloisomerization experiments was designed employing differently sub-

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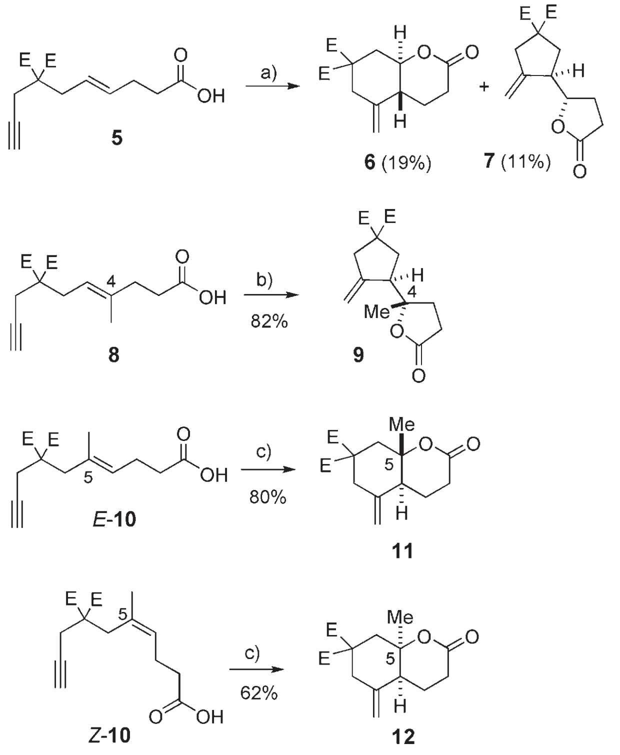
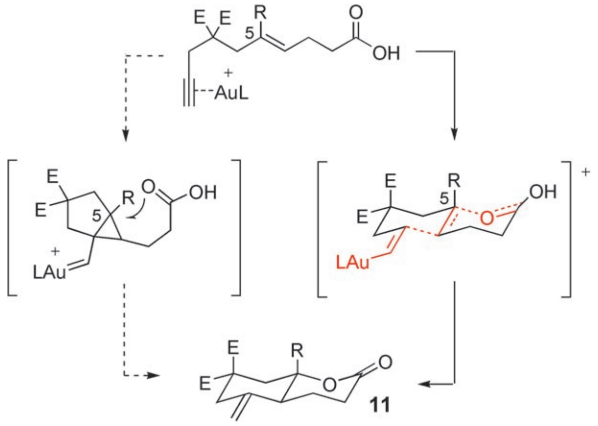
stituted enynes with a pendant carboxylate trap. Gold-catalyzed additions of carboxylic acids to olefins are surprisingly scarce;[9,10] even more remarkably, recent reports showed that carboxylates smoothly add across an alkyne but leave an olefin within proximity unengaged.[10] In view of this literature precedent, it came as no surprise that enyne **5** did not cyclize well on treatment with [AuCl(Ph$_3$P)] and AgSbF$_6$ in CH$_2$Cl$_2$, affording an almost statistical mixture of **6** and **7** in poor yield (Scheme 2).



Scheme 2. Reagents and conditions: [AuCl(Ph$_3$P)], AgSbF$_6$, CH$_2$Cl$_2$, RT: a) 10 mol% of each reagent; b) 3 mol% of each reagent; c) 5 mol% of each reagent. E = COOMe.

A single methyl substituent on the alkyne, however, changes the outcome dramatically (Scheme 2). Thus, the 4-methyl derivative **8** gave butyrolactone **9** as a single isomer in 82% yield, whereas *E*-**10**, in which the methyl group is shifted by one carbon atom, converted exclusively into the annulated bicycle **11**. Similarly informative is the selective transformation of *Z*-**10** into the diastereomeric product **12**.

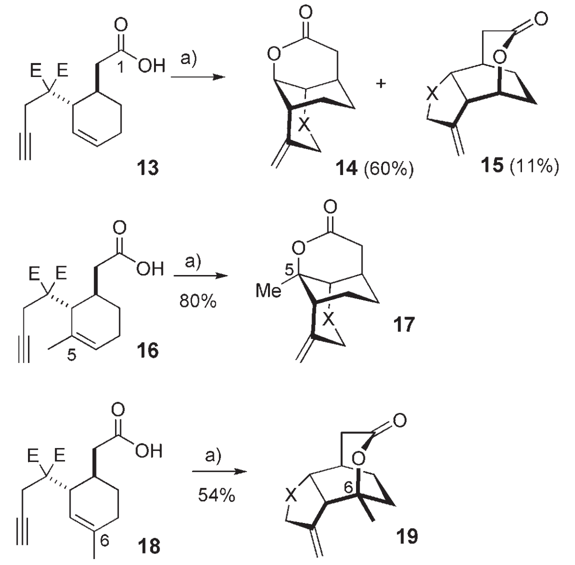
We believe that these results are highly instructive in terms of the mechanism. If the intermediate were an ordinary gold cyclopropylcarbene of type **D** (Scheme 1), as frequently depicted in enyne-cycloisomerization processes, it would be difficult to understand why a methyl group at C5 results in a dramatic increase in efficiency (R = Me versus R = H; Scheme 3). Moreover, it is highly unlikely that substitution would favor attack of the carboxylate onto the then more crowded carbon atom of the cyclopropyl ring. Both experimental observations, however, are readily explained if one assumes that the intermediate (or transition state) largely resembles a carbocation, which is generated by coordination of the gold template to the alkyne moiety. The incipient positive charge at the internal position, generated by slippage of the metal along the axis of the π system,[11,12] engenders a net *anti* addition of the alkyne and the carboxylate to the alkene relay in *E*-**10** to give product **11**, most likely through a highly ordered, chairlike, charge-delocalized transition state of the type characteristic for acid catalyzed polyene cyclizations (Scheme 3).[13–15] The double-bond isomers *E*-**10** and *Z*-**10** react stereospecifically, which is also in excellent accord with the Stork–Eschenmoser paradigm.[13,14] If one assumes cationlike reactive intermediates and/or transition states, the formation of butyrolactone **9** from **8** simply follows from the more stabilized tertiary cation at C4.



Scheme 3. Conceivable intermediates in the gold catalyzed reaction of enyne *E*-**10**. E = COOMe, L = neutral ligand, R = H or Me.

A second set of experiments led to similar conclusions. As expected, the cyclohexenyl derivative **13** afforded a mixture of products, favoring the caged derivative **14** that was formed by attack at C5 by the carboxylate (**14**/**15** ≈ 5.4:1; Scheme 4). Substitution at C5 by a methyl group led to a matched situation, in which the inherent bias and the effect resulting from charge stabilization go hand in hand (**16**→**17**). In the mismatched case of substrate **18**, however, the heteroatom nucleophile exclusively attacks the site where a cationic intermediate is more highly stabilized, even though the trajectory is less favorable in conformational terms. An ordinary gold carbene intermediate hardly explains these divergent pathways, as its overall topology is not determined by the absence or presence of a peripheral methyl substituent. In any case, the structures of the isomeric products **17** and **19** were unambiguously established by X-ray crystallography (Figures 2 and 3).

The concerted nature of cationic polycyclization reactions is known to be dependent on the type of nucleophilic trap.[13,14a] Lower nucleophilicity is thought to engender a less ordered transition state and hence favors formation of a more localized carbocation. To investigate whether this characteristic trait is also reflected in the cycloisomerization chemistry described herein, a representative set of reactions was repeated with alcohol substrates rather than the carboxylic acid series (Scheme 5). In fact, the intrinsic preference of substrate **20a** is opposite to that of its carboxylic acid



Scheme 4. Reagents and conditions: a) [AuCl(Ph$_3$P)] (5 mol%), AgSbF$_6$ (5 mol%), CH$_2$Cl$_2$, RT. E = COOMe, X = C(COOMe)$_2$; arbitrary numbering scheme as shown.

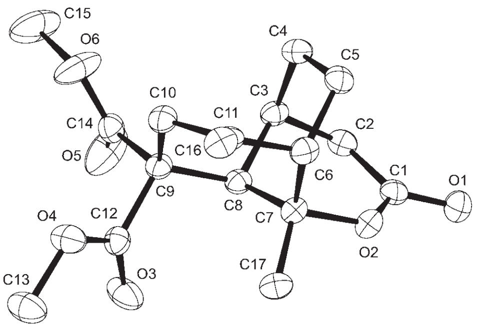


Figure 2. Structure of compound **17** in the solid state.[16]

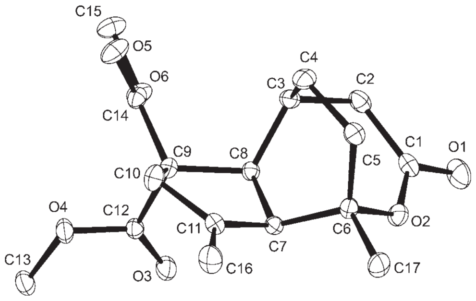
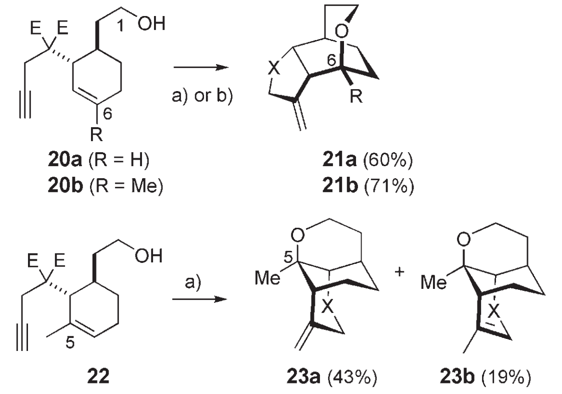


Figure 3. Structure of compound **19** in the solid state.[16]



Scheme 5. Reagents and conditions: a) [AuCl(Ph$_3$P)] (5 mol%), AgSbF$_6$ (5 mol%), CH$_2$Cl$_2$, RT; b) PtCl$_2$ (10 mol%), toluene, RT. E = COOMe, X = C(COOMe)$_2$; arbitrary numbering scheme as shown.

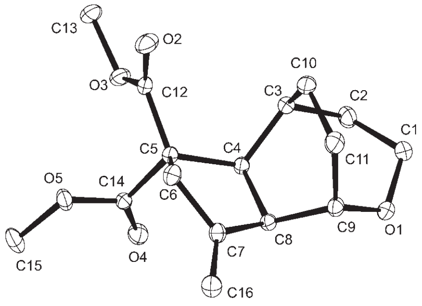


Figure 4. Structure of compound **21a** in the solid state.[16]

congener **13**, with selective attack of the alcohol at C6 of the cyclohexene skeleton to give product **21a** exclusively (Figure 4). As expected, substitution with a methyl group at this site enhanced the reaction efficiency (**20b**→**21b**). Notably, however, this pronounced bias can again be overturned by simply placing the substituent at the adjacent C5 position. As evident from the conversion of **22** into **23**, the cyclization follows this change and occurs again at the site where the developing positive charge is best stabilized.[17]

In summary, it was shown that enyne cycloisomerizations catalyzed by gold exhibits the characteristic attributes commonly associated with cationic polyene cyclization reactions. This consistent picture strongly advocates that the gold intermediates involved are more appropriately described as gold-stabilized carbocations rather than "gold carbenes".[18] This conclusion is supported by the analysis of the crystal structure of a prototype complex as well as by computational studies, which also emphasized that the gold cyclopropyl carbenes must have a very distorted structure and actually resemble the canonical form of a gold-stabilized homoallyl cation.[19] We believe that this notion deserves proper consideration in the discussion of noble-metal catalysis in general.

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[17] Only trace amounts of the regioisomeric compound, arising from attack of the alcohol at C6, were detected.

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