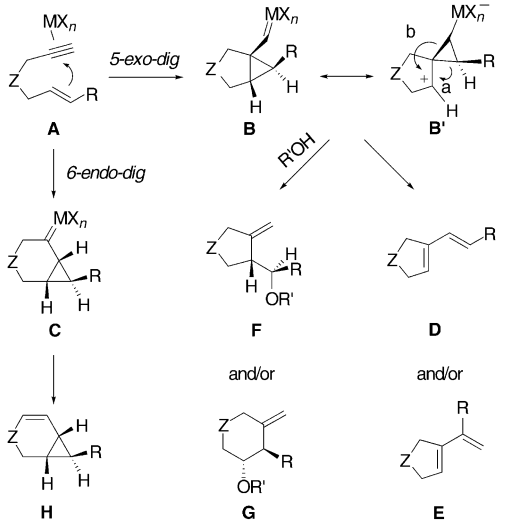


Scheme 1. Mechanism for the skeletal rearrangement and alkoxycyclization of enynes.

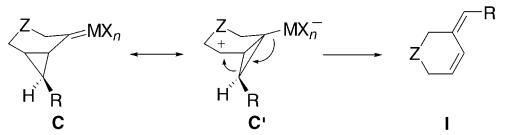
Cyclization Reactions

Cationic Gold(I) Complexes: Highly Alkynophilic Catalysts for the *exo*- and *endo*-Cyclization of Enynes**

*Cristina Nieto-Oberhuber, M. Paz Muñoz, Elena Buñuel, Cristina Nevado, Diego J. Cárdenas, and Antonio M. Echavarren**

A group of synthetically useful transformations of α,ω-enynes are catalyzed by electrophilic transition-metal complexes or halides MX_n to give a variety of carbo- or heterocycles.[1] Coordination of MX_n to the alkyne forms a (η^2-alkyne)metal complex **A**, which evolves to form the metal cyclopropyl carbene complexes **B** (*5-exo-dig*) or **C** (*6-endo-dig*) (Scheme 1).[2] Skeletal rearrangement of α,ω-enynes may proceed via intermediates **B** (best envisioned via canonical form **B′**) to form conjugated dienes **D** (cleavage of bond a) and **E** (cleavage of bond b).[2–5] Alternatively, attack of nucleophiles R′OH (alcohols or water) at **B** gives products of alkoxy- or hydroxycyclization **F** and **G**.[2,6,7] Simultaneous coordination of the metal to the alkyne and the alkene triggers the Alder-ene cycloisomerization[1,8,9a] through metallacyclopentene intermediates.

Products derived from intermediates **C** have been found for substrates where Z = O or NTs. In these cases, β-hydrogen elimination gives **H**,[5b–c,10] although opening of the cyclopropane by R′OH has also been found.[6a] Intriguingly, an skeletal rearrangement (**C** to **I**) by a *6-endo-dig* process has not yet been observed (Scheme 2).



Scheme 2. Mechanism for the *endo*-skeletal rearrangement.

For the skeletal rearrangement of α,ω-enynes, platinum(IV) and cationic platinum(II) catalysts have been reported to be the most reactive transition-metal complexes.[3] Lewis acid $GaCl_3$ also catalyzes these reactions under relatively mild conditions, although larger amounts of catalysts were used (10 mol % $GaCl_3$ versus 2 mol % Pt^{II} salt).[11] Here we report that cationic gold(I) complexes $[Au(PPh_3)]^+ X^-$ are very reactive, yet selective, catalysts for the cyclization of enynes. In particular, these catalysts are the most active for the skeletal rearrangement reaction. We have also found the first examples of a *6-endo-dig* skeletal rearrangement (Scheme 2). Importantly, the $[Au(PPh_3)]^+$ ion, which is isolobal to the H^+ ion,[12] cannot coordinate to the alkene and the alkyne simultaneously and, in consequence, the Alder-ene cycloisomerization does not compete and the cyclizations proceed exclusively through complexes of type **A**.

Using DFT calculations, we first compared the activation exerted by $[Au(PH_3)]^+$ for the intermolecular reaction of propyne with *trans*-2-butene with those of three other catalysts: *trans*-$[Pd(H_2O)Cl_2]$, *trans*-$[Pt(H_2O)Cl_2]$, and $AuCl_3$. The gold(I) complex was found to give the most reactive propyne–metal complex.[13] Likewise, by using (*E*)-6-octen-1-yne as a model substrate for the cyclization (Scheme 3), calculations indicate that upon coordination to $[Au(PH_3)]^+$, a highly polarized (η^1-alkyne)gold complex **J** is formed, which shows substantial electron deficiency at C2. The high polarization of **J** explains the high reactivity

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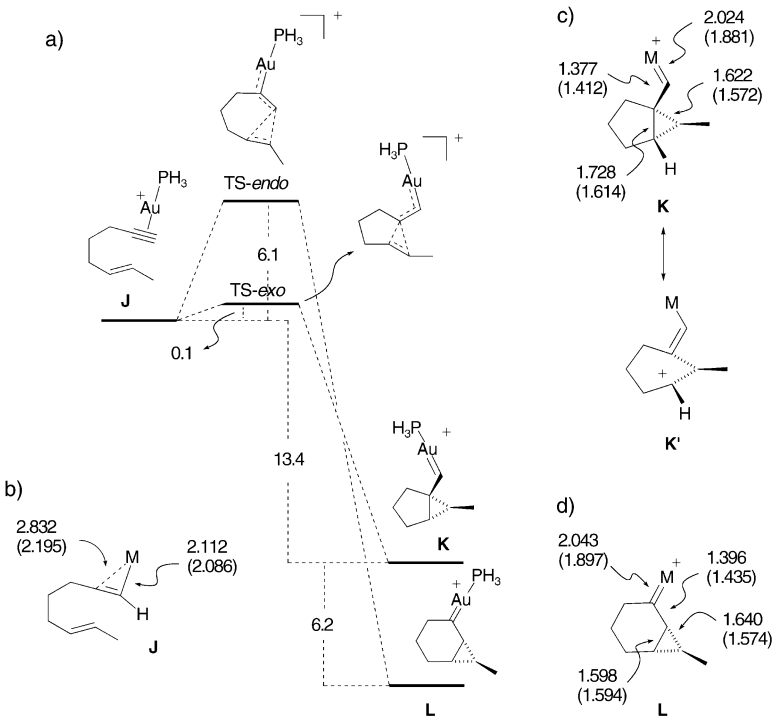


Scheme 3. a) Reaction coordinate for the cyclization of (*E*)-6-octen-1-yne with $[AuPH_3]^+$ at the B3LYP/6-31G(d) and LANL2DZ level (ZPE corrected energies are given in kcal mol^{-1}); b–d) Selected bond lengths (Å) for **J**–**L**. Values in parentheses are for the analogous Pt^{II} complexes (M = *trans*-$[Pt(H_2O)Cl_2]$).[2a,6a]

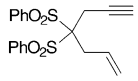
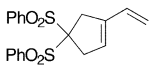
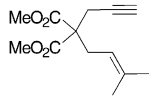
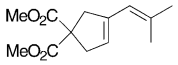
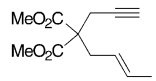
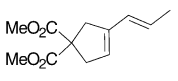
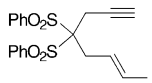
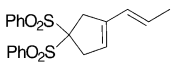
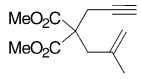
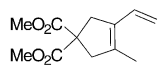
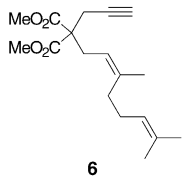
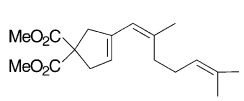
encountered in the hydration[14] and amination of alkynes[15] catalyzed by gold(I) complexes. Complex **J** reacts very readily with the alkene by *exo* cyclization with a very small activation energy ($E_a = 0.1$ kcal mol^{-1}) to give intermediate **K**. This complex shows a very distorted cyclopropyl carbene structure,[2,6c] in which the cyclopropane C–C bonds conjugated with the carbene are particularly long. The structure of this intermediate actually resembles the canonical form **K′** (a gold(I)-stabilized homoallylic carbocation). The activation energy for the *6-endo-dig* process to give carbene **L** is 6.1 kcal mol^{-1}, which suggests that the *exo* cyclization should be favored with gold(I) catalysts, at least for substrates related to (*E*)-6-octen-1-yne. For comparison, the calculated activation energies for the analogous transformation with $[Pt(H_2O)Cl_2]$ are 10.3 and 11.2 kcal mol^{-1} (*exo* and *endo*, respectively), although the transformations promoted by platinum(II) are thermodynamically more favored (19.5 kcal mol^{-1} for the *exo* and 27.6 kcal mol^{-1} for the *endo* cyclizations).[2a,6a]

By using catalysts formed in situ from $[Au(PPh_3)Cl]/AgX$ (X = BF_4 or SbF_6),[16,17] enynes undergo skeletal rearrangements to give products of type **D** (Scheme 1). The rearrangements of enynes **1**–**6** proceed readily at room temperature in CH_2Cl_2 and are completed in less than 1 h to give **7**–**12** (Table 1). No reaction was observed by using $[Au(PPh_3)Cl]$ alone. In addition, the reaction is not catalyzed by Ag^I salts. The reaction does not proceed in solvents such as MeCN or toluene.

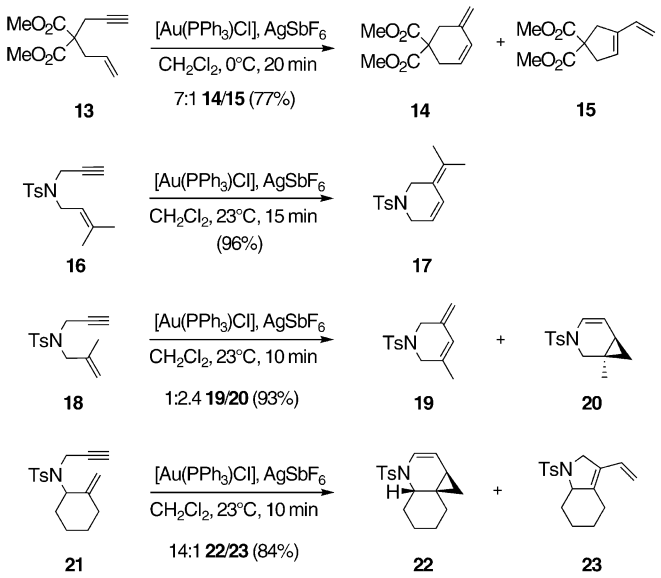
Surprisingly, in contrast with the reaction of **1** (Table 1, entry 1), enyne **13** gives **14** as the major 1,3-diene (Scheme 4). The endocyclic rearrangement depicted in Scheme 2 was evidenced in the clean transformation of enyne **16** into diene **17**. Similarly, enyne **18** gives rearranged **19**,[18,19] along with **20**, the product of a β-hydrogen elimination.[6,10] In the case of **21**, the major endocyclic intermediate evolves to give **22**, along with exocyclic rearranged derivative **23**.

Although cyclization of **6** affords triene **12** (Table 1, entry 6) as the only isolated product, reaction of its *E* isomer **24** gives tetracycle **25** as the major or exclusive product under very mild conditions (Table 2).[20] An active catalyst could also be generated by reaction of $[Au(PPh_3)Me]$ with trifluoroacetic acid (TFA). No reaction was observed in DMF or in the presence of additional PPh_3 (1 equiv). Dienyne **27** reacts similarly to give tetracycle **28**. Analogous transformations have been reported by using ruthenium,

Table 1: Skeletal rearrangements with $[Au(PPh_3)Cl]$ (2 mol%) and a silver salt (2 mol%).

Entry	Enyne	AgX	*T* [°C]	*t* [min]	Product	Yield [%]
1	 **1**	$AgSbF_6$	23	5	 **7**	100
2	 **2**	$AgSbF_6$	23	25	 **8**	91
3	 **3**[a]	$AgBF_4$	23	10	 **9**[a]	96
4	 **4**[a]	$AgBF_4$	23	15	 **10**[a]	100
5	 **5**	$AgBF_4$	23	5	 **11**	76
6	 **6**	$AgSbF_6$	−4	60	 **12**	47

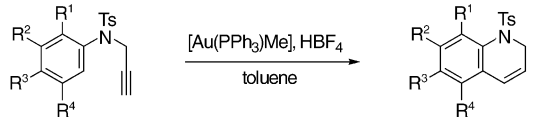
[a] 4:1 *E*/*Z*.



Scheme 4. Endocyclic cyclizations with 2 mol% Au^{I} catalyst.

unusual natural product myliol, and related tetracyclic sesquiterpenes,[23] posses the same carbon skeleton of **25** and **28**, although the fusion of the dimethylcyclopropane unit occurs with the opposite configuration.

The cyclization of *N*-propargyl *N*-tosylanilines **31a–c** is also catalyzed by the cationic complex formed from [Au(PPh$_3$)Me] and HBF_4 (Scheme 6). This intramolecular reaction gives 1,2-dihydroquinolines **32a–c** and proceeds under milder conditions and with better yields than the cyclization catalyzed by Pt^{II}.[24,25]

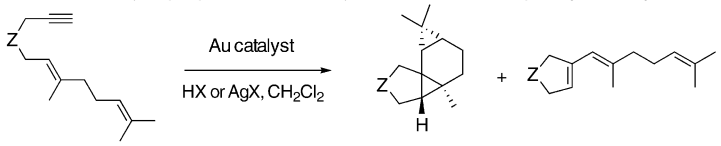


31a $R^1 = R^4 = OMe$, $R^2 = R^3 = H$
31b $R^1 = R^4 = H$, $R^2 = R^3 = OMe$
31c $R^1 = H$, $R^2 = R^3 = R^4 = OMe$

32a (23°C, 4 h, 71%)
32b (50°C, 4 h, 89%)
32c (50°C, 17 h, 92%)

Scheme 6. Cyclization of *N*-propargyl-*N*-tosylanilines with a Au^{I} complex (3 mol%).

Table 2: Intramolecular cyclopropanation of dienynes with a Au^{I} complex (2 mol%).



24 Z = C(CO$_2$Me)$_2$
27 Z = C(SO$_2$Ph)$_2$
29 Z = NTs

25 Z = C(CO$_2$Me)$_2$
28 Z = C(SO$_2$Ph)$_2$
30 Z = NTs

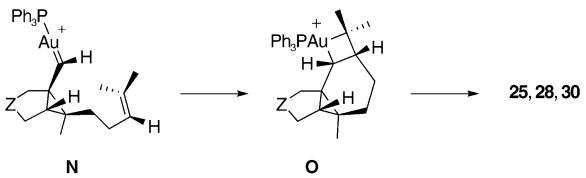
26 R = C(CO$_2$Me)$_2$

Entry	Dienyne	Catalyst	*T* [°C]	*t* [min]	Products (yield [%])
1	**24**	[Au(PPh$_3$)Cl]/AgBF$_4$	−30	20	**25** (78) + **26** (7)
2	**24**	[Au(PPh$_3$)Me]/TFA[a]	23	240	**25** (63)
3	**27**	[Au(PPh$_3$)Cl]/AgSbF$_6$	−4	20	**28** (49)
4	**29**	[Au(PPh$_3$)Cl]/AgSbF$_6$	0	15	**30** (89)

[a] 3 mol% gold(I) catalyst and 6 mol% TFA.

platinum, and rhodium catalysts in toluene at 80°C,[21] although in the case of gold(I) the reactions proceed under milder conditions. Dienyne **29**, with the same substitution pattern of **16**, reacts exclusively by an *exo* pathway to give **30** in good yield (Table 2, entry 4).

Formation of **25**, **28**, and **30** can be explained by evolution of intermediate **N** by intramolecular cyclopropanation via **O** (Scheme 5). The stereoselectivity of the last cyclopropanation appears to be a result of the kinetically controlled trapping of **N**, which presents an antiperiplanar arrangement of the cyclopropane and the metal carbene.[22] Interestingly, the



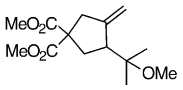
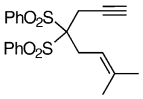
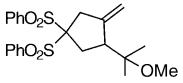
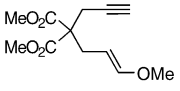
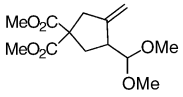
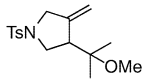
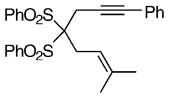
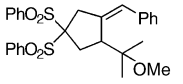
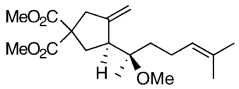
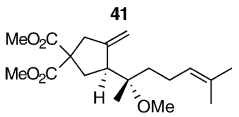
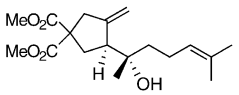
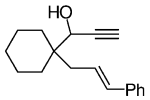
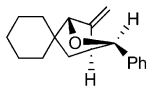
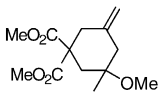
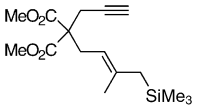
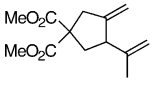
N **O**

Scheme 5. Mechanistic rationale for the stereoselective intramolecular cyclopropanation.

Methoxycyclization of the enynes, instead of skeletal rearrangement, was observed when the reactions were carried out in MeOH with a catalyst formed in situ from [Au(PPh$_3$)Me] and a protic acid, such as HBF_4, phosphotungstic acid trihydrate, or TFA (Table 3). No cyclizations were observed with the protic acids in the absence of the gold(I) species. Addition of PPh_3 or diphosphanes (dppe, dppe, dppf) (3 mol%) led to unreactive gold(I) complexes. However, the reaction could be carried out in the presence of bulky and electron-rich PCy_3 (Table 3, entries 2 and 11). Reactions with gold(I) species usually proceed at room temperature, although the less reactive substrates were cyclized in refluxing methanol (Table 3, entries 5–6, and 11). The cyclization of **36** could be carried out with only 1 mol% of catalyst (Table 3, entry 4). The methoxycyclizations (entries 7–8) and hydroxycyclization (entry 9) show that these reactions proceed with complete stereoselectivity. The hydroxyl group of **44** exerts a complete stereochemical control to give **45** as a result of an intramolecular alkoxycyclization (Table 3, entry 10). In general, the alkoxycyclizations proceed more readily with gold(I) than with platinum(II) catalysts.[2] Allyl silane **47** also reacts to give diene **48**[26] with both cationic and neutral gold(I) complexes (Table 3, entries 12 and 13), although, as expected, milder conditions are required with the cationic gold(I) catalysts (Table 3, entry 12).

Under the conditions of the methoxycyclization, cationic [Au(PPh$_3$)MeOH]$^+$ is presumably formed. The *exo*/*endo* selectivity depends on the gold(I) catalyst. Thus, substrate **16** undergoes skeletal rearrangement by an *endo* pathway with [Au(PPh$_3$)]$^+$ (Scheme 4), while the reaction in MeOH proceeds exocyclically (Table 3, entry 5). Interestingly, the opposite occurs with enyne **5**, which rearranges exocyclically

Table 3: Alkoxy- or hydroxycyclization of enynes with [Au(PPh$_3$)Me] (3 mol%) and a protic acid (6 mol%).

Entry	Enyne	Acid (solvent)	T [°C]	t [h]	Product	Yield [%]
1	**2**	HBF_4 (MeOH)	23	4	 **33**	97
2	 **34**	HBF_4[a] (MeOH)	23	12	 **35**	85
3	 **36**	TFA (MeOH)	23	0.5	 **37**	95
4[c]	**36**	$H_3PW_{12}O_{40}$[b] (MeOH)	23	2	**37**	96
5	**16**	$H_3PW_{12}O_{40}$[b] (MeOH)	65	17	 **38**	85
6	 **39**	$H_3PW_{12}O_{40}$[b] (MeOH)	65	17	 **40**	96
7	**6**	HBF_4 (MeOH)	23	4	 **41**	65
8	**24**	HBF_4 (MeOH)	23	4	 **42**	82
9	**24**	HBF_4 (H_2O/acetone)	23	4	 **43**	63[d]
10	 **44**	$H_3PW_{12}O_{40}$[b] (toluene)	23	3	 **45**	100
11	**5**	(TFA)[a]	65	12	 **46**	48[e]
12	 **47**	HBF_4 (MeOH)	23	12	 **48**	97
13[f]	**47**	(MeOH)	70	12	**48**	97

[a] PCy_3 (3 mol%) was also added. [b] The trihydrate was used. [c] [Au(PPh$_3$)Me] (1 mol%) and protic acid (2 mol%) employed. [d] **25** (22%) and **26** (15%) were also obtained. [e] Based on 97% conversion. [f] Reaction catalyzed by [Au(PPh$_3$)Cl].

(Table 1, entry 5) and reacts in MeOH by an *endo-dig* pathway (Table 3, entry 11).

In summary, although much attention has been recently given to gold(III) species as highly electrophilic catalysts,[6a,27] alkynophilic gold(I) complexes are even more reactive catalysts for the skeletal rearrangement and alkoxycyclization of enynes proceeding through highly polarized (η^1-alkyne)gold(I) complexes. With these catalysts, the first examples of skeletal rearrangement of enynes by the endocyclic cyclization pathway have been documented. The construction of complex molecular architectures under very mild conditions and in short reaction times with gold(I) species augurs well for the implementation of this methodology in diversity-oriented synthesis.

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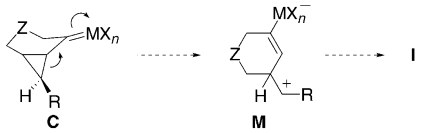

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