Mechanistic Studies

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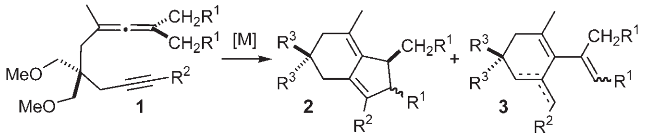
Gold(I)- and Gold(III)-Catalyzed Cycloisomerization of Allenynes: A Remarkable Halide Effect**

Gilles Lemière, Vincent Gandon, Nicolas Agenet, Jean-Philippe Goddard, Ariel de Kozak, Corinne Aubert, Louis Fensterbank,* and Max Malacria**

Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 60th birthday

Electrophilic metal halides, also referred to as π Lewis acids, are exquisite catalysts for the selective and efficient cycloisomerization of polyunsaturated precursors into highly valuable carbo- or heterocyclic derivatives.[1] The diversity of the substrates that have been examined, mainly under platinum(II) and (IV) catalysis,[2] as well as gold(I) and (III) catalysis,[3] not only illustrates the versatility of these processes, but also renders the proposed mechanistic scenarios more plausible. In the case of enynes,[4] electrophilic activation of the alkyne triggers a nucleophilic attack by the alkene to give a metallacyclopropyl carbene intermediate that can evolve along different pathways.[5] Alternatively, metallacyclopentene intermediates have been invoked to give Alder-ene types of products.[6] In this context, because of their high degree of unsaturation, allenynes are very interesting substrates.[7]

Table 1: Reactivity of **1** in the presence of platinum and gold catalysts.[a]



Entry	Catalyst	Conditions	**2** [%]	**3** [%]	*exo/endo*
1a: $R^1=R^2=H$					
1	$PtCl_2$, 5 mol%	toluene, RT, 24 h	80	–[b]	–
2	$PtCl_4$, 5 mol%	toluene, RT, 1 h	80	–[b]	–
3	$AuCl_3$, 1 mol%	CH_2Cl_2, 0°C, 0.5 h	80	–[b]	–
4	$NaAuCl_4$, 1 mol%	CH_2Cl_2, 0°C, 1 h	75	–[b]	–
5	AuCl, 1 mol%	CH_2Cl_2, 0°C, 0.5 h	79	–[b]	–
6	$[Au(PPh_3)SbF_6]$, 1 mol%	CH_2Cl_2, 0°C, 0.25 h	0	70	1:1
7	$[Au(PPh_3)NTf_2]$, 1 mol%	CH_2Cl_2, 0°C, 6 h	5	68	2:1
8	$[Pt(PhCN)_2dppp](BF_4)_2$, 5 mol%	CH_2Cl_2, 35°C, 0.3 h	–[b]	57	3:1
1b: $R^1=Me$, $R^2=H$					
9	$AuCl_3$, 1 mol%	CH_2Cl_2, 0°C, 0.5 h	64[c]	–[b]	–
1c: $R^1=H$, $R^2=SiMe_3$					
10	$AuCl_3$, 1 mol%	CH_2Cl_2, 0°C to RT	no reaction		
11	AuCl, 1 mol%	CH_2Cl_2, 0°C to RT	no reaction		
12	$[Au(PPh_3)SbF_6]$, 1 mol%	CH_2Cl_2, 0°C, 0.25 h	complex mixture of isomers		

[a] $R^3=CH_2OMe$. [b] Traces were observed. [c] Two diastereomers (55:45).

Our initial experiments with $PtCl_2$ and precursors **1** (Tables 1 and 2) gave three types of reaction evolution depending upon the substitution pattern of the starting material.[8] To rationalize the formation of products **2**–**4**, we proposed the intervention of a common platinacyclopentene intermediate. This suggestion was later supported by the DFT calculations of Soriano and Marco-Contelles.[9] Nevertheless, some new data did not completely fit with this mechanistic rationale. For example, we noticed that the formation of hydrindiene **2a** from **1a** could also be promoted by $PtCl_4$ (Table 1, entry 2) in a more rapid reaction than that with $PtCl_2$; this result would imply an unlikely Pt^{IV}–Pt^{VI} catalytic couple if a platinacyclopentene pathway were involved (Table 1, entry 2).[10] Furthermore, although, to the best of our knowledge, auracyclopentenes are unknown species, gold(III) and gold(I) chloride catalysts also afforded hydrindienes **2a** and **2b** in high yield and after short reaction times at 0°C (Table 1, entries 3–5 and 9). Two other observations shed additional light on this transformation. In the presence of a cationic gold(I) complex generated in situ from the reaction of $[AuCl(PPh_3)]$ with $AgSbF_6$, a dramatic change in reactivity occurred, and only the regioisomers **3** were isolated (Table 1, entry 6). This reactivity was further confirmed when we used $[Au(PPh_3)NTf_2]$[11] and $[Pt(PhCN)_2dppp](BF_4)_2$[12] (dppp = 1,3-bis(diphenylphosphanyl)propane, two other cationic halide-free metal catalysts (Table 1, entries 7–8). In general, alkynes with a trimethylsilyl (TMS) substituent react sluggishly in $PtCl_2$-catalyzed processes.[13] Accordingly, allenyne **1c** did not react under $AuCl_3$ or AuCl catalysis (Table 1,

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[*] G. Lemière, Dr. V. Gandon, N. Agenet, Dr. J.-P. Goddard, Dr. C. Aubert, Prof. Dr. L. Fensterbank, Prof. Dr. M. Malacria
Laboratoire de Chimie Organique, UMR CNRS 7611
Institut de Chimie Moléculaire, FR 2769
Université Pierre et Marie Curie, Paris 6, case 229
4, place Jussieu, 75005 Paris (France)
Fax: (+33) 1-4427-7360
E-mail: aubert@ccr.jussieu.fr
fensterb@ccr.jussieu.fr
malacria@ccr.jussieu.fr
Prof. Dr. A. de Kozak
Laboratoire de Chimie de la Matière Condensée
UMR CNRS 7574
Université Pierre et Marie Curie, Paris 6, case 176
4, place Jussieu, 75005 Paris (France)

[**] M.M. is a member of the Institut Universitaire de France (IUF). The authors thank the IUF, the Ministère de la Recherche, and the CNRS for financial support.

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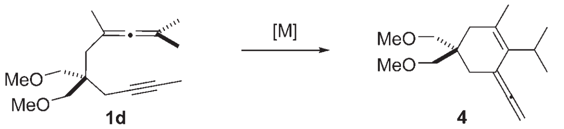
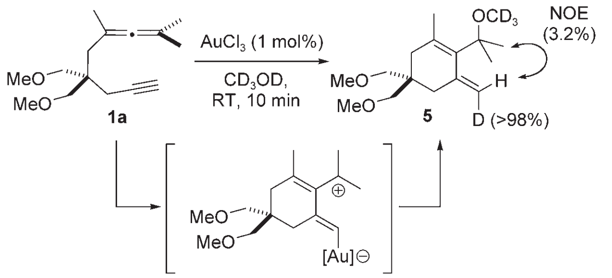
entries 10–11). When a gold(I) source was used instead, a complex mixture of unidentified products resulted (Table 1, entry 12).[14] In contrast, unambiguous reactivity was observed for precursor **1d** in the presence of the previously used catalysts (Table 2). In all cases, vinyl allene **4** was formed in high yield.

Table 2: Formation of vinyl allene **4**.



Entry	Catalyst	Conditions	**4** [%]
1	$PtCl_2$, 5 mol%	toluene, RT, 24–48 h	84
2	$AuCl_3$, 1 mol%	CH_2Cl_2, RT, <5 min	92
3	AuCl, 1 mol%	CH_2Cl_2, RT, <5 min	89
4	$[Au(PPh_3)SbF_6]$, 1 mol%	CH_2Cl_2, RT, <5 min	79

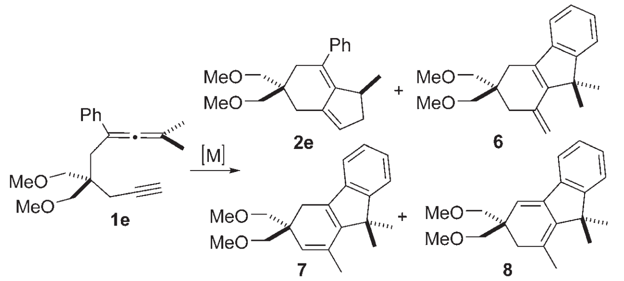
As no metallacyclic pathway could explain these new findings with gold, we suspected the occurrence of a cationic event.[15] To probe this hypothesis, we monitored the reaction of **1a** in CD_3OD in the presence of $AuCl_3$ (1 mol%) by ^1H and ^{13}C NMR spectroscopy. The conversion of **1a** was complete within 10 minutes, and compound **5** was formed as a single diastereomer (Scheme 1). The stereochemical assignment of the exocyclic double bond was based on an NOE experiment. The structure of compound **5** supports the existence of a carbocationic intermediate in which the carbon–gold bond is *anti* to the cationic center.



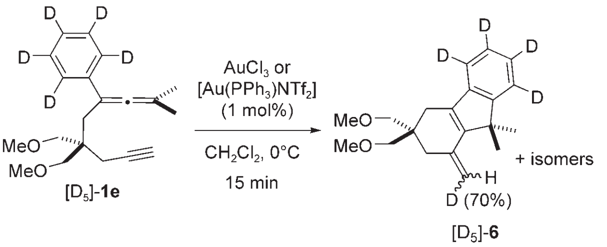
Scheme 1. Trapping of a key intermediate with deuterated methanol.

We also wanted to probe the occurrence of a cationic route in non-oxygenated solvents. Echavarren and co-workers showed that a metallacyclic pathway can be disfavored artificially in the presence of oxygen-containing nucleophilic solvents.[6] Therefore, we introduced a phenyl group at the internal allene position to give **1e** (Table 3). This substrate proved to be highly reactive and provided in good yield the expected Friedel–Crafts product **6** with an exocyclic methylene group, accompanied by the endocyclic isomers **7** and **8**.[16] In the presence of platinum(II) the reaction was much slower, and a large amount of hydrindiene **2e** was formed.

Table 3: Intervention of an aromatic ring.



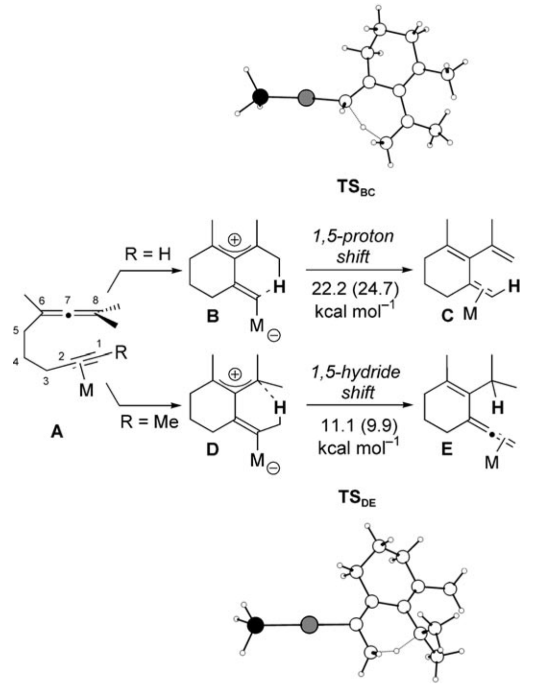
Entry	Catalyst	Cond.	Yield [%]	Products	Ratio
1	$AuCl_3$, 1 mol%	CH_2Cl_2, 0°C, 15 min	98	**6/7/8**	67:27:6
2	$[Au(PPh_3)SbF_6]$, 1 mol%	CH_2Cl_2, 0°C, 15 min	87	**6/7/8**	65:30:5
3	$PtCl_2$, 5 mol%	toluene, RT, 30 h	84	**2e/6/7/8**	38:44:11:7



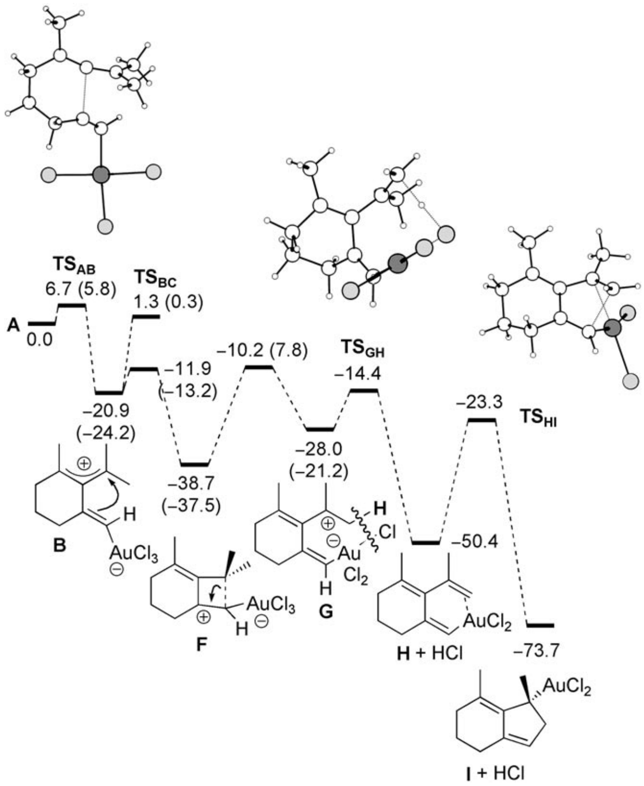
Scheme 2. Deuterium-transfer experiment.

We next performed an isotope-labeling experiment with compound [D_5]-**1e** (Scheme 2). As a result of the facile isomerization of the exocyclic double bond, it was not possible to assign the configuration of compound [D_5]-**6**. However, it was evident from ^1H NMR spectroscopy that a deuterium atom had been transferred from the phenyl ring to the exocyclic double bond.

This valuable set of information drove us to analyze the mechanism in more detail. The reactivity of allenynes toward $AuPH_3^+$ and $AuCl_3$ was studied by means of DFT computations. $AuCl_3$ was chosen as a unique model for gold halide species since it is assumed to be the dominant catalyst after chloride substitution in $AuCl_4^-$ or after the dismutation of AuCl into $AuCl_3$ and Au^0 in CH_2Cl_2.[17] The latter assertion derives from our observation of a brown powder that forms instantaneously when AuCl is added to a solution of any allenyne. An X-ray powder diffraction study confirmed the presence of pure gold(0) unambiguously (see Supporting Information for details). Along with the results of computational studies dealing with the gold-catalyzed cyclization of enynes,[18] we could locate neither auracyclopentenes nor their hypothetical η^4-complexed precursors. Instead, cationic species of type **B** or **D** (Scheme 3) were found and linked to alkyne–gold complexes **A** via reasonably low lying transition states ($\Delta G^{\ddagger}_{298} \approx 5$–$15$ kcal mol^{-1}; see Supporting Information).[19] In all cases, *exo* cyclizations, which lead to a *trans* arrangement of the C2–C7 and C1–M bonds, were found to be favored kinetically over *endo* cyclizations by nearly a factor of two.



Scheme 3. Mechanistic proposal for the formation of Alder-ene and vinyl allene products: $\Delta G^{\ddagger}_{298}$ values were calculated at the DFT/B3LYP/LACVP(d,p) level for M = $AuCl_3$ (and $AuPH_3^+$). Representative geometries of transition states are given for M = $AuPH_3^+$. P (black), Au (dark gray), Cl (light gray).



Scheme 4. Energy profile [kcal mol^{-1}] for the transformation of **A** (R = H, M = $AuCl_3$) into the hydrindiene precursor **I**: Geometries of key transition states are depicted. Energy values for the transformation of **A** into **G** with M = $AuPH_3^+$ are also indicated in parentheses.

The formation of Alder-ene products **C** was only computationally possible when R = H, by a direct 1,5-proton shift. These transformations require a free energy of activation of 22.2 kcal mol^{-1} ($AuCl_3$) or 24.7 kcal mol^{-1} ($AuPH_3^+$) and are exothermic by 27.7 kcal mol^{-1} ($AuCl_3$) or 25.1 kcal mol^{-1} ($AuPH_3^+$). The formation of vinyl allene **E** from **D** (R = Me) is also possible in a single step by a 1,5-hydride shift.[20] Free energies of activation of 11.1 kcal mol^{-1} ($AuCl_3$) and 9.9 kcal mol^{-1} ($AuPH_3^+$) were calculated for these exothermic processes ($\Delta G_{298} = -5.0$ kcal mol^{-1} ($AuCl_3$) and -6.0 kcal mol^{-1} ($AuPH_3^+$)).

To account for the formation of hydrindienes,[21] we noticed that only chloride-containing catalysts could promote this specific cycloisomerization (see Table 1).Therefore, we envisaged a mechanism for the transformation of **B** into **I** that involves isomerization of the vinyl metal moiety followed by the elimination of HCl. From a thermodynamic point of view, the isomerization of **B** into **G** is favorable with $AuCl_3$ ($\Delta G_{298} = -7.1$ kcal mol^{-1} (R = H) and -7.2 kcal mol^{-1} (R = Me)), but not with $AuPH_3^+$ ($\Delta G_{298} = 3.0$ kcal mol^{-1} (R = H) and 1.5 kcal mol^{-1} (R = Me)). Manifold efforts failed to locate a transition state corresponding to the direct transformation of **B** into **G**. However, we were able to find a two-step mechanism for this isomerization (Scheme 4). When R = H and M = $AuCl_3$ (or $AuPH_3^+$), a free energy of activation of 9.0 (11.0) kcal mol^{-1} is sufficient to convert **B** into intermediate **F**, which is more stable than **B** by 17.8 (13.3) kcal mol^{-1}. In this case, the quite low free energies of activation make this step faster than the 1,5-proton shifts described above. On the other hand, when R = Me ($\Delta G^{\ddagger}_{298} = 17.1$ kcal mol^{-1} ($AuCl_3$) and 38.1 kcal mol^{-1} ($AuPH_3^+$)) the 1,5-hydride shift is still the fastest process. Therefore, the rest of the discussion will be restricted to the case R = H. Complexes of type **F** would result from a formal [2+2] cycloaddition of the starting compounds **A**.[22] Although the C1−C8 bond is especially long (≈1.59 Å), ring opening at C1−C8 is kinetically difficult. With $AuCl_3$, a free energy of activation of 28.5 kcal mol^{-1} was found for the endothermic transformation of **F** into **G** ($\Delta G_{298} = 10.7$ kcal mol^{-1}). However, **G** would readily undergo elimination of HCl with concomitant formation of an Au−C bond to give **H** ($\Delta G^{\ddagger}_{298} = 13.6$ kcal mol^{-1}). This step is appreciably exothermic by 22.4 kcal mol^{-1}.

The resulting alkene–gold complex **H** could then undergo a 5-*endo*-trig carboauration to give complex **I**. This transformation requires quite a high free energy of activation of 27.1 kcal mol^{-1} but is also characterized by a large exothermicity of 23.3 kcal mol^{-1}. The last step could then be the cleavage of the Au−C bond by HCl, to liberate the final product and regenerate the catalyst. Overall, the formation of **I** from **A** has a thermodynamic driving force greater than that corresponding to the transformation of **A** into **C** ($\Delta G_{298}(\mathbf{AI}) = -73.7$ kcal mol^{-1}; $\Delta G_{298}(\mathbf{AC}) = -48.6$ kcal mol^{-1}). Thus, with $AuCl_3$, the two-step isomerization of the vinyl metal moiety positions the metal suitably for the elimination of HCl. On the other hand, the isomerization of **B** into **G** is much more difficult with $AuPH_3^+$. Although the first step to give **F** can be quite fast ($\Delta G^{\ddagger}_{298} = 11.0$ kcal mol^{-1}) and thermodynamically favorable ($\Delta G_{298} = -13.3$ kcal mol^{-1}), the energy requirement for the transformation of **F** into **G** seems to be prohibitively high ($\Delta G^{\ddagger}_{298} = 45.3$ kcal mol^{-1}, $\Delta G_{298} = 16.3$ kcal mol^{-1}).[23] As **F** was not found to evolve in any other way, we believe that the formation of the Alder-ene product **C** arises from the 1,5-proton shift described above, despite a higher activation energy (24.7 kcal mol^{-1} for **B**→**C** versus 11.0 kcal mol^{-1} for **B**→**F**). The greater stability of **C** relative to that of **F** (ΔG_{298}(**AF**) $= -37.5$ kcal mol^{-1}; ΔG_{298}(**AC**) $= -49.3$ kcal mol^{-1}) should funnel the reaction toward the Alder-ene product.

Thus, gold catalysis has provided deeper insight into the mechanism of the cycloisomerization of allenynes. Because no standard metallacyclic route could be envisaged, two unusual mechanistic pathways which take into account the presence of cationic intermediates have been proposed: a 1,5-proton shift for the Alder-ene products and a 1,5-hydride shift for the vinyl allenes. We also found evidence for an intriguing halide effect that completely alters the cycloisomerization process (Alder-ene versus hydrindiene products), presumably through the elimination of HCl as a key step for the formation of hydrindienes. Finally, physical evidence has been found for the dismutation of AuCl into Au and $AuCl_3$. A comprehensive experimental and computational study will be reported in due course.

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