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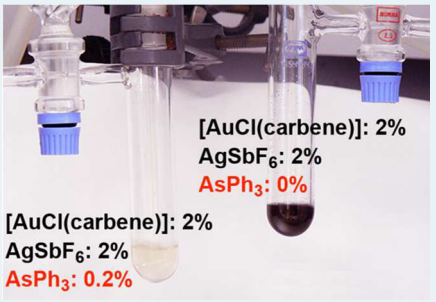
Some Singular Features of Gold Catalysis: Protection of Gold(I) Catalysts by Substoichiometric Agents and Associated Phenomena

Camino Bartolomé, Zoraida Ramiro, Marconi N. Peñas-Defrutos, and Pablo Espinet*

IU CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47071 Valladolid, Spain

Supporting Information

ABSTRACT: This study deals with two striking phenomena: the complete protection against decomposition of hypothetically monocoordinated Au^I intermediates [AuL]Y (L = strongly coordinating ligand; Y^- = poorly coordinating anion) by addition of small substoichiometric amounts (5 mol % relative to Au) of not strongly coordinating ligands (e.g., $AsPh_3$) and the fact that, in contrast, strongly coordinating ligands cannot provide this substoichiometric protection. The two phenomena are explained considering that (i) the existence of real monocoordinated [AuL]Y is negligible in condensed phases and the kinetically efficient existing species are dicoordinated [AuL(W)]Y (W = any very weakly coordinating ligand existing in solution, including OH_2, the solvent, or the Y^- anion) and (ii) these [AuL(W)]Y intermediates give rise to decomposition by a disproportionation mechanism, via polynuclear intermediates formed by associative oligomerization with release of some W ligands. It is also shown that very small concentrations of [AuL(W)]Y are still catalytically efficient and can be stabilized by overstoichiometric adventitious water, so that full decomposition of the catalyst is hardly reached, although eventually the stabilized concentration can be kinetically inefficient for the catalysis. These results suggest that, in cases of gold catalysis requiring the use of a significant quantity of gold catalyst, the turnover numbers can be increased or the concentration of gold catalyst widely reduced, using substoichiometric protection properly tuned to the case.



KEYWORDS: *gold, catalysis, catalyst protection, redox disproportionation, kinetic studies*

INTRODUCTION

Au^I has become an important catalytic metal, whether by itself[1] or in bimetallic[2] catalyzed processes. Abundant formation of metallic gold during some catalysis is not infrequent, although it is not always mentioned. Au^0 can apparently be produced in the absence of any obvious reducing agent, in which case it has been proposed to be formed by disproportionation of 3 Au^I into 2 Au^0 + 1 Au^{III}.[3] In fact this disproportionation reaction has been used stoichiometrically as a synthetic procedure to obtain novel classes of gold(III) carbene based anticancer agents.[4] Previous to these papers, Jones had reported, in a crystallographically oriented work, that [AuXL] complexes with picoline ligands (which additionally show rearrangement equilibria 2[AuXL] = [AuL_2][AuX_2]; X = halide) disproportionate in part into gold(III) and gold(0) when 50% of the halide is extracted in the absence of protecting ligands, as shown in eq 1.[5]

$$4\,[Au^{I}ClL] + 2\,Ag(SbF_6) \longrightarrow [Au^{I}L_2](SbF_6) + [Au^{III}Cl_2L_2](SbF_6) + 2\,Au^0 + 2\,AgCl \quad (1)$$

With these precedents in mind, disproportionation seems a reasonable path for catalyst decomposition and Au^0 formation in catalytic reactions that operate under circumstances very similar to those of eq 1 (although with complete removal of Cl^-). Surprisingly, perhaps because of the very different context of the studies mentioned above, these results have passed unnoticed in the area of gold catalysis, and the corresponding papers have been barely cited in gold catalysis works.

Recently, an interesting article from the group of Hammond and Xu faced the question of decomposition of gold complexes under catalytic conditions, examining the influence on catalyst deactivation of the substrate, the counterion, and the solvent. The authors suggested that unsaturated substrates (e.g., alkynes, alkenes, allenes) might induce disproportionation of Au^I to Au^0 and Au^{III}, playing a key role in the decay of the catalyst.[6,7] In fact they managed to detect Au^I, Au^0, and Au^{III} in XPS spectra not only of samples from solutions of [Au(OTf)-(PPh_3)] with cyclohexene in chloroform but also of samples from the reaction of AuCl with AgOTf without cyclohexene in dichloromethane. Cyclohexene appeared to accelerate the decomposition but remained itself unaltered.

In this context we report here our studies on an intriguing effect we came across with in our catalysis of cyclization of 1,6-enynes with cationic carbene gold complexes generated from [AuCl(carbene)] and $Ag(SbF_6)$.[8,9] These catalysts are very active, but formation of Au^0 was clearly observed during the process.[10] Since we had found a positive stabilizing effect upon addition of excess $AsPh_3$ in Au/Pd bimetallic catalysis,[11] we decided to test the potential gold catalyst stabilization by $AsPh_3$

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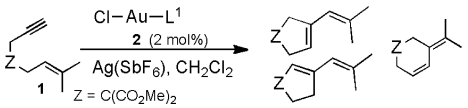
in these cyclizations. To our surprise, total suppression of Au^0 formation was achieved in most cases using *just a very substoichiometric* amount of protector ligand ($AsPh_3$:Au = 1:10).[10]

We explain here how this substoichiometric protection can be understood and what its effect is on the activity of the catalyst. We will see, as we develop our comments, that this behavior is related to disproportionation as the mechanism of formation of Au^0. We will also show that protection by disregarded agents in solution is particularly relevant when working with low gold concentrations, as in gold catalysis. The experimental problem of this study is that working with low catalytic concentrations practically precludes direct observation of the key species in solution. In spite of this, kinetic experiments provide interesting information and allow for some considerations on the complexity of factors influencing these catalytic systems at extremely low concentrations.

RESULTS AND DISCUSSION

Decomposition during Enyne Cyclization. The process examined in this study was the cyclization of enyne **1** catalyzed by the carbene gold complex [AuCl{C(NHAdamantan-1-yl)(NHPy-2)}] (**2**), shown in eq 2. Complex **2** is just one example in a series of other gold complexes with carbenes that behaved similarly for skeletal rearrangement and alkoxycyclization of enynes.[10] For convenience, the carbene ligand C(NHAdamantan-1-yl)(NHPy-2) will be represented as L^1 and the gold complex as [AuClL^1]. For simplicity, L^1 will be used also, in the general discussion, to represent any good coordinating ligand of an initial catalyst [AuClL^1], which remains coordinated throughout the catalytic reaction after the Cl^- ligand has been removed as AgCl using a more soluble silver salt (all reactions were carried out shielded from the light).



(2)

The cyclization in eq 2 is efficient and fast but shows heavy catalyst decomposition (deep purple color) during the process. However, addition of 10 mol % of $AsPh_3$ relative to Au fully prevents the formation of gold(0), while the catalysis remains active, although somewhat slower. The preparative effects of this protection were reported.[10] The dramatic visual effect of a substoichiometric addition of $AsPh_3$ in our catalytic experiments is shown in Figure 1.

Decomposition in the Absence of Enyne. It is worth noting that similar decomposition is observed when the chloro complex **2** is reacted with $Ag(SbF_6)$ in CH_2Cl_2 in the absence of enyne; thus, there is at least one efficient decomposition pathway that does not need to be induced by the presence of any unsaturated reagent or by the operation of the catalytic process. Different decomposition experiments of a similar carbene gold complex, [AuCl{C(NHXylyl)(NMe_2)}] (**3**), in the presence of stoichiometric $Ag(SbF_6)$ were performed (see the Supporting Information). Au^0 was observed upon halide abstraction in all cases, and the bis(carbene) complex [Au{C(NHXylyl)(NMe_2)}$_2$](SbF_6) (**4**), which is catalytically inactive for enyne cyclization, was isolated from the solutions. Figure 2 shows the X-ray structure of **4**.

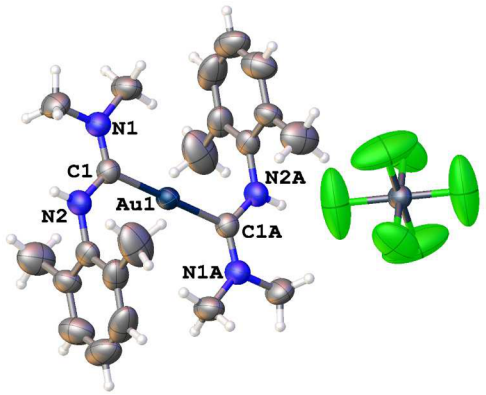


Figure 2. X-ray structure of [Au{C(NHXylyl)(NMe_2)}$_2$](SbF_6) (**4**). Selected bond lengths: (Å): Au(1)–C(1) = 2.051(5); C(1)–N(1) = 1.319(6); C(1)–N(2) = 1.332(6). Selected bond angles (deg): N(1)–C(1)–N(2) = 119.1(4); C(1)–Au(1)–C(1A) = 180.

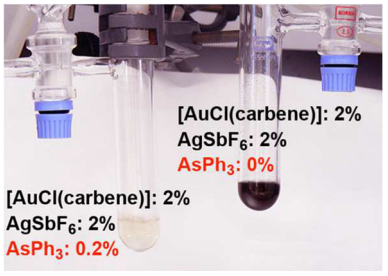


Figure 1. Aspect of the cyclization experiments of eq 2 after the reaction has finished (30 min): (right) without added $AsPh_3$; (left) with added $AsPh_3$.

These results confirm that our catalytic systems behave quite similarly to the decomposition of gold picoline complexes reported by Jones, this meaning that the Au^0 observed originates through a disproportionation reaction. In the case of Jones (eq 1), the Au^{III} complex could be isolated because only half of the halide ligands were extracted with $Ag(SbF_6)$ and the other half were found to be stabilizing the Au^{III} complex as [$Au^{III}Cl_2L_2$](SbF_6). In the case of total extraction of the halide, as in catalysis, the hypothetical [Au^{III}] complex formed might be unstable and lead to [$Au^{I}L_2$](SbF_6), in the presence of reductant agents. This has been the hypothesis proposed by Hammond.[6] The fate of the Au^{III} product is rather intriguing, because it is not easy to find the oxidized products of the potential reductants. In spite of this uncertainty, the above evidence supports reasonably that the most likely decomposition pathway of gold(I) complexes deprived of protecting ligands is disproportionation. Our case of study here is to explain why some circumstances *totally prevent* this decomposition with only substoichiometric protection by an extra second ligand, and we assume in our discussion disproportionation as the mechanism for catalyst decomposition.

Protection vs Decomposition under Catalytic Conditions. Decomposition and catalysis are two competing reactions that follow different pathways, although they may be sharing some intermediates and steps. In general, the step of decomposition and that of formation of the products could occur on different or on identical intermediates but, even if the latter were the case, the two processes would certainly have different transition states (TS) and activation energies. The rates of the two processes will depend on the concentrations of the species involved in the respective rate-determining step

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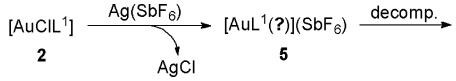
(rds) and on the corresponding rate constant. Any rate expression consists of a rate constant and a product of concentrations with their exponentials. For a reaction to be observed (whether by formation of products or by decomposition), the concentration of the corresponding intermediate initiating the rds should be *sufficient* to produce an observable change in a reasonable time. This *sufficient* concentration depends on the value of the corresponding rate constant of each process (defined by the corresponding activation energy). We will refer to this condition as *kinetically efficient* or *kinetically inefficient* concentration.[12] Even in a hypothetical case where catalysis and decomposition pathways occurred from the same intermediate (hence the concentration of this species is the same for the two processes), it might happen that this concentration was kinetically inefficient for one process (due to a higher activation energy) but kinetically efficient for the other (due to a lower activation energy).

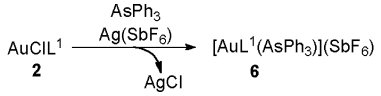
Unlikeliness of a Naked [AuL^1]Y Intermediate. Equation 3 represents the decomposition reaction observed when complex **2** is treated with Ag(SbF$_6$). Devoid of the Cl$^-$ ligand and also lacking any protecting second ligand L^2 added on purpose, catalyst **2** decomposes. We depict for convenience the intermediate **5** with a question mark occupying a coordination position on gold to denote a lack of definition of the unknown species from which decomposition starts.



(3)

The first question to be considered is as follows: what is the probability for a truly naked monocoordinated intermediate to exist in solution? A true monocoordinated Au^I complex should have an unoccupied sp orbital that is extremely low in energy, which is unlikely to remain empty in the presence of other chemical species. As a good indication of this improbability, a DFT calculation (made in another context) of the cost of dissociation of [Au(C$_6$F$_5$)(AsPh$_3$)] into [Au(C$_6$F$_5$)] + (AsPh$_3$) afforded $\Delta G_0 \approx 40.9$ kcal mol^{-1} (equivalent to $K_{dis} \approx 10^{-30}$ at 298.15 K and 1 atm). With solvent correction for CH_2Cl_2, the calculated value is $\Delta G_0(CH_2Cl_2) \approx 34.5$ kcal mol^{-1}, still equivalent to the negligible dissociation constant $K_{dis} \approx 5 \times 10^{-26}$ at room temperature.[13] The dissociation must be even less favorable for cationic monocoordinated species. Considering this information, it looks very unlikely that naked monocoordinated species can exist in *kinetically efficient concentration* in condensed phases. Consequently, we change from now on the formula for **5** from [AuL^1(?)]Y to [AuL^1(W)]Y, with W = any fairly weak ligand.[14] These badly protected complexes represent the likely intermediates from which decomposition can start.

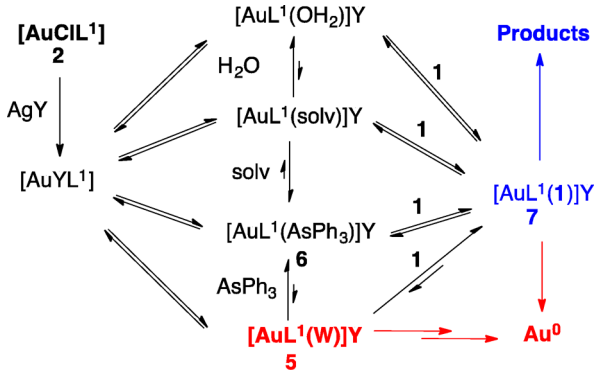
The usual strategy to stabilize these cationic gold complexes with noncoordinating anions is the addition of a protecting ligand to make [AuL^{1}L^2](SbF$_6$). For instance, AsPh$_3$ is a reasonably good ligand for gold(I) (stronger than many other W ligands, but much weaker than PPh$_3$) and we have shown before that, using complex **2** and quantitative AsPh$_3$, a thermally stable complex with mixed ligands, [AuL^1(AsPh$_3$)](SbF$_6$) (**6**), is formed (eq 4).[10] Complex **6** is an efficient cyclization catalyst and does not show any sign of decomposition during catalysis, but it is obvious that quantitative formation of **6** cannot be achieved with just a substoichiometric amount (10 mol %) of AsPh$_3$. Gold protection with substoichiometric AsPh$_3$ requires a different explanation.



(4)

The picture of possible Au^I species in solution is, in general, much more complex than eqs 3 and 4 can represent. A view closer to reality should consider many coexisting equilibria, as proposed in Scheme 1 for the case under study.[15] The picture is

Scheme 1. Plausible Multiple Equilibria under Catalytic Conditions[a]



[a] L^1, **1**, and AsPh$_3$ could be other groups as discussed.

not comprehensive but shows that many chemical species will be in equilibrium once the Cl$^-$ ligand has been removed by a soluble AgY salt to give insoluble AgCl. These can include (a) neutral [AuYL^1] complexes when Y$^-$ can coordinate (in this respect, a reasonable sequence of Y$^-$ coordination ability is halide > OH$^-$ > triflate ≫ SbF$_6^-$) and (b) cationic [AuL^{1}L^2]Y complexes where L^2 can be a coordinating solvent, water in the solvent, an added L^2 ligand producing large equilibrium displacement toward [AuL^{1}L^2]Y (e.g., L^2 = AsPh$_3$), a ligand liberated by catalyst decomposition, a second intra- or intermolecular donor atom in the initial L^1 ligand (e.g., the N atoms in NHCs or NACs),[16] or the reacting substrate (in our case, enyne **1** forming **7**). In addition, remarkably stable neutral OH$^-$ complexes can easily form from cationic water complexes.[17,18] In Scheme 1 we have highlighted [AuL^1(W)]Y (**5**) as the putative intermediate through which gold decomposition step occurs; in principle one or more of the compounds mentioned might play this role. In addition, **7** (accepted in the literature to be the complex from which cyclization occurs) could be this intermediate and yet the two different activation energies would yield different reaction rates toward cyclization and decomposition.

Obviously there is not much hope of obtaining quantitative data for all these species or of monitoring their changing concentrations in a running reaction. Moreover, dealing strictly with the interactions of multiple equilibria, where the concentrations are changing as the reaction progresses, is terribly complex. For this reason we will take a more simple and practical approach which is sufficient for our case.

Let us consider the effect of the incorporation of a second ligand L^2 to gold, replacing a halide that has been extracted as in eq 3. In the presence of sufficient L^2 (L^2:Au ratio ≥1:1), **2** gives [AuL^{1}L^2](SbF$_6$). For L^2 = AsPh$_3$ (eq 4), the dicoordinated complex [AuL^1(AsPh$_3$)](SbF$_6$) (**6**) is catalyti-

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cally active and does not decompose, as found experimentally.[10] In this simple model, since we observe an efficient protecting effect of $AsPh_3$ that prevents the undesired decomposition reaction, the spontaneous $AsPh_3$ dissociation from **6** must be small (the concentration of intermediate **5** leading to decomposition must be *kinetically inefficient*). Otherwise, we should observe decomposition. On the other hand, associative[19] $AsPh_3$ substitution by the enyne reagent (eq 5) must still produce a *kinetically efficient concentration* of **7** in equilibrium with **6**, sufficient as to observe active catalysis. However, if a stronger ligand that is more difficult to substitute (e.g., PPh_3 1:1) is used, it blocks not only the decomposition but also the cyclization reaction, as observed experimentally.[10] This indicates that PPh_3 hinders the formation of a kinetically efficient concentration of complex **7**. In other words, PPh_3 prevents not only the decomposition reaction but also the desired cyclization.

$$[AuL^1(AsPh_3)](SbF_6) \underset{AsPh_3}{\overset{\text{enyne (1)}}{\rightleftharpoons}} [AuL^1(\mathbf{1})](SbF_6) \xrightarrow{\text{cycliz.}} \quad (5)$$
6 **7**

In this simple approach it follows that when there is a defect of stabilizing ligand (L^2:Au < 1:1) or when the coordinating ability of this protector agent is too poor and gives rise to significant L^2 release, the formation of a stable complex $[AuL^1L^2]^+$ should be only partial, and the unprotected fraction in the form of complex **5** (Scheme 1) may reach a *kinetically efficient concentration* to decompose. Obviously, as we advanced before, this model cannot explain how, as in our experiments, a *substoichiometric* ratio of L^2 protects the totality of catalyst from decomposition: the use of 10 mol % of $AsPh_3$ should produce (depending on the dissociation constant) 10 mol % or less of **6** and leave 90 mol % or more of **5** unprotected. Then, how is it that decomposition of the 90 mol % unprotected **5** is not observed at all?

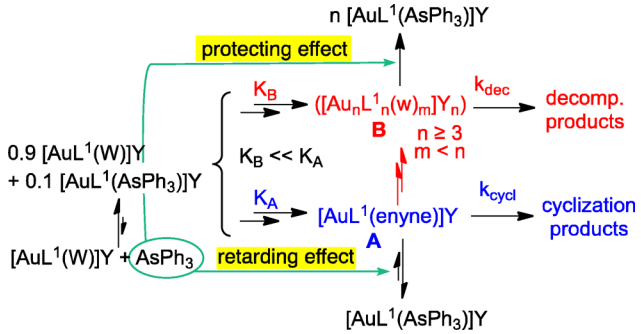
A More Complex Decomposition Pathway. The gold-catalyzed mechanisms for reactions with enynes are well-known[1f,20] and occur on $[AuL^1(enyne)]Y$ mononuclear intermediates (first-order rate dependence on Au concentration). The mechanisms of decomposition of gold(I) complexes are not as well studied, but as discussed above, there are good indications to assume disproportionation. Disproportionation should require at some moments di- or trimolecular or higher molecularity intermediates and transition states to be formed from $[AuL^1(W)]Y$. Considering the high ligand dissociation energy noted above, these oligomerizations should follow an associative mechanism, and formation of the oligomers will give rise to interactions with the otherwise empty orbital, which in part compensate the dissociation of W (eq 6).[21]

$$n\,[AuL^1(W)]Y \rightleftharpoons [Au_nL^1{}_n(W)_m]Y_n + (n-m)\,W \quad (6)$$
W = any poorly protecting ligand

The participation in the decomposition pathway of multinuclear intermediates imposes a radical kinetic change, because it leads to a rate dependence of order 2, 3, or higher on the low concentration of their mononuclear $[AuL^1(W)]Y$ precursors.[22] Or, in other words, the concentration of the putative multinuclear species will be orders of magnitude lower than that for their $[AuL^1(W)]Y$ precursors, and they are directly unobservable. Since decomposition does occur, these lower concentrations are kinetically efficient. However, the very different concentrations of $[AuL^1(enyne)]Y$ and $[Au_nL^1{}_n(W)_m]Y_n$ lead to very different kinetic responses to the addition of external agents. Tuning the percentage of W for efficient protection from decomposition, while keeping a reasonable cyclization rate, should be possible, as shown in some experiments below.

Catalyst Protection by Substoichiometric $AsPh_3$. Scheme 2 depicts how the addition of a substoichiometric amount of $AsPh_3$ can produce only a proportional reduction in rate of the skeletal rearrangement reactions of enynes and be lethal for the formation of oligomers and the decomposition reaction. Let us take, as in Scheme 2, a mixture of $[AuClL^1]$, $Ag(SbF_6)$, $AsPh_3$, and enyne in the proportion 1:1:0.1:excess, in dichloromethane, and let us remove quantitatively the Cl^- ligand by precipitation as AgCl: should $AsPh_3$ be an excellent ligand, it would convert 10 mol % of the gold catalyst in the complex $[AuL^1(AsPh_3)](SbF_6)$. For the other 90 mol % of $[AuL^1(W)](SbF_6)$, the cyclization and decomposition pathways should be competitive, as in the absence of arsine but at 90% rate. However, $AsPh_3$ is not a very good ligand for Au^I and there is a ligand substitution equilibrium from $[AuL^1(AsPh_3)](SbF_6)$ that slightly increases the concentration of $[AuL^1(W)](SbF_6)$ over 90% and, most importantly, produces some concentration of free $AsPh_3$ in solution. This concentration may be small in comparison with the concentration of $[AuL^1(enyne)](SbF_6)$, but it is huge in comparison with the concentration of the multinuclear species, which are destroyed by $AsPh_3$ coordination splitting them. A *kinetically efficient* concentration of the multinuclear species can be made incompatible with a sufficient substoichiometric concentration of $AsPh_3$. Thus, the cyclization rate is only slowed down but the decomposition is quenched.

Scheme 2. Decomposition (Red) vs Cyclization (Blue)[a]



[a] K_A stands for associative reactions leading to coordinated enyne (eq 5). K_B represents a sequence of associative reactions leading to nucleation (eq 6).

It is important to remark that the unusual phenomenon of substoichiometric protection against decomposition is in fact a direct consequence of the multinuclear nature of the decomposition pathway. Consequently, its observation provides a strong support to the proposals of disproportionation as the mechanism operating on gold(I) complexes when they are deprived of a second strongly stabilizing ligand.

Why $AsPh_3$? Will Other Additives Do? As reported before,[10] $[Au(AsPh_3)_2](SbF_6)$ is catalytically active for the cyclization or methoxycyclization of enynes, but $[Au(PPh_3)_2](SbF_6)$ is inactive. This indicates that the cyclization intermediate $[Au(AsPh_3)(enyne)](SbF_6)$ can be formed to a sufficient extent from $[Au(AsPh_3)_2](SbF_6)$, by ligand substitution of an arsine but the enyne cannot displace PPh_3 from $[Au(PPh_3)_2](SbF_6)$ to form a kinetically efficient concentration

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of [Au(PPh$_3$)(enyne)](SbF$_6$). A better estimation of the relative coordinative strength to gold(I) of AsPh$_3$ and PPh$_3$ is provided by the fact that a mixture of [AuCl(AsPh$_3$)] + 20 AsPh$_3$ + 1 PPh$_3$ in CH$_2$Cl$_2$ quantitatively affords [AuCl(PPh$_3$)], while in a mixture of [AuCl(PPh$_3$)] + 21 AsPh$_3$, the PPh$_3$ complex remains unaltered. Thus, the affinity of AuCl for PPh$_3$ is at least 20-fold higher than that for AsPh$_3$.[23]

However, under substoichiometric conditions AsPh$_3$ is a better protecting ligand than PPh$_3$. In fact, no decomposition is observed from the reaction of [AuCl{C(NHXylyl)(NMe$_2$)}] (**3**) and Ag(SbF$_6$) in the presence of 5 mol % of AsPh$_3$, after 9 h at room temperature, but the same amount of PPh$_3$ is less efficient in protecting the system and allows formation of colloidal gold (Figure 3). Why is the weaker AsPh$_3$ ligand better for substoichiometric protection?

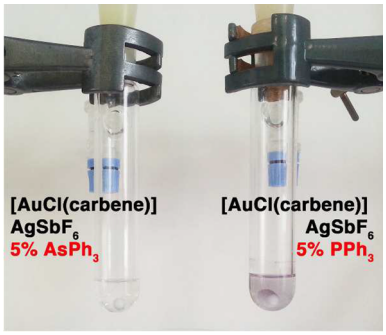


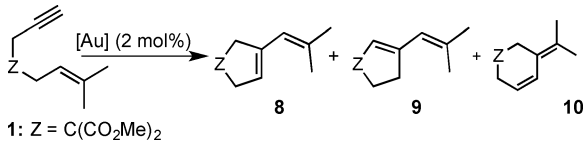
Figure 3. [AuCl(carbene)] in the presence of Ag(SbF$_6$) and 5 mol % of AsPh$_3$ (left) and 5 mol % of PPh$_3$ (right) after 9 h at room temperature in the absence of enyne.

This observation can be easily explained by considering that the protecting effect of a substoichiometric ligand requires, as discussed in Scheme 2, the existence of a small but effective concentration of free ligand (highlighted in a green circle in Scheme 2). This protection is not achieved with PPh$_3$ because the concentration of free PPh$_3$ in solution is negligible (PPh$_3$ is very efficiently retained by the gold complex). An interesting consequence of this analysis is that the protecting ligand must be one that has a reasonable dissociation equilibrium from the dicoordinated Au complex, not large but not too small (we call it a *medium coordinating ability* ligand). In other words, the best ligands are bad substoichiometric protecting agents, because a certain concentration of free ligand must exist in the solution for the protecting effect to be produced. Because of that, ligands of medium coordinating ability are the most efficient. In principle, the protection might be tunable for different needs by simply changing the amount of added AsPh$_3$ or by using another appropriate protecting ligand.

Other Protecting Agents. In light of the previous observations and the reaction/decomposition mechanism proposed in Scheme 2, other effects, reported in the literature[10] or observed in some additional experiments summarized in Table 1, can be understood. The protection can be produced by ligands proceeding from partial self-dissociation of the catalytic complexes, as long as the dissociation equilibrium is not too large or too small. This requirement applies to neutral and anionic ligands in substoichiometric to overstoichiometric proportions, depending on their coordinating ability, as shown in Table 1.

In reactions similar to eq 2 (Table 1), ligands such as AsPh$_3$ and OTf$^-$ are efficient protectors that do not block the

Table 1. Skeletal Rearrangement of 1 under Several Conditions[a]



entry	AgX	additive	time/conversion (Au reduction)	**8**/**9**/**10** (%)
1	Ag(SbF$_6$)		5 min/100 (deep purple)	95/0/0[10]
2	AgOTf		5 min/98	95/0/3
3	AgOAc		24 h/−	0/0/0
4	Ag(SbF$_6$)	NH$_4$OAc[b]	5 min/100 (deep purple)	100/0/0
5	Ag(SbF$_6$)	NH$_4$OAc[c]	5 min/100	100/0/0

[a]Percentages of products **8**−**10** were checked by ^{1}H NMR on the isolated solids. Reactions were carried out in CH$_2$Cl$_2$, at 25 °C with 2 mol % of **2** and 2 mol % of AgY. [b]Reaction carried out with 0.2 mol % of NH$_4$OAc. [c]Reaction carried out in a saturated solution of NH$_4$OAc in CH$_2$Cl$_2$. For the corresponding reported reactions see ref 10.

reactivity when present in stoichiometric proportions, while OAc$^-$ or PPh$_3$ quench the reaction. Note the following, for instance. (i) A reaction that occurs with gold decomposition when Ag(SbF$_6$) is used as Cl$^-$ abstractor (entry 1)[10] runs without gold decomposition, in the lack of any protecting additive, using AgOTf to abstract the halide (entry 2). Obviously this happens because OTf$^-$ is a better coordinating anion than SbF$_6^-$ and its dissociated concentration is acting as a protecting agent. (ii) The use of AgOAc (OAc$^-$ is a much better coordinating anion than OTf$^-$) instead of Ag(SbF$_6$) prevents the decomposition but also quenches the cyclization (entry 3). (iii) Addition of an excess of NH$_4$OAc (this salt is sparingly soluble in CH$_2$Cl$_2$) to the reaction mixture of **2** with Ag(SbF$_6$) totally suppresses the decomposition observed while it keeps the reaction running (entry 5); the catalysis with lower amounts of NH$_4$OAc does not completely inhibit the decomposition (entry 4). All these are examples of protecting anions with different coordinating abilities. We have also checked pyridine and tetrahydrothiophene (tht) as possible neutral ligands in the role of AsPh$_3$, and they are much less effective than AsPh$_3$ (see Figure S1 in the Supporting Information).

The examples just discussed show that there are different grades of protection against decomposition, their efficiency depending on the type of L^1 ligand, the coordinating ability of the anions, and the other species existing in solution. For instance, for L^1 = PPh$_3$ the solutions formed by extraction of the halide with AgOTf in CH$_2$Cl$_2$ are remarkably stable.[6] All these observations fit well with the proposal of an associative mechanism for the oligomerization, since all these factors change the electrophilicity of the [AuL^1(W)]Y intermediates and their propensity toward associative oligomerization.[24]

Survival of the "Unprotected" Catalyst. Weakly coordinating solvents or adventitious water are probably silent protectors in many apparently unprotected reactions. In fact, although the image of catalyst decomposition in Figure 1 is impressive, it is somewhat deceptive as far catalyst activity is concerned, because further experiments reveal that the solution−suspension containing the heavily decomposed catalyst retains activity. Additional experiments provide further interesting details and reveal that, as one gets close to very low but still operative gold catalyst concentrations, the picture

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becomes less clear. Quantifying the problem is not easy, as the effects depend on too many variables not at reach of determination. However, some information on the behavior of the system under catalytic conditions can be obtained in the experiments that follow.

Figure 4 depicts the conversion results, determined by NMR monitoring in CD_2Cl_2, of skeletal rearrangement of enyne **1**

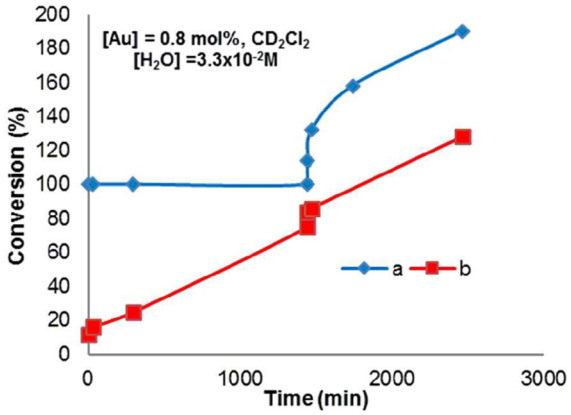

Figure 4. Au-catalyzed cyclization with two successive additions of enyne **1**, monitored by ^{1}H NMR in CD_2Cl_2, with $[\mathbf{1}]_0$ = 0.10 M and $[Au]_0 = 8 \times 10^{-4}$ M: (a) without $AsPh_3$; (b) with 10 mol % $AsPh_3$ relative to Au.

using (a) $[\mathbf{1}]_0$ = 0.10 M and 0.8 mol % of catalyst **2**, in the presence of 0.8 mol % of $Ag(SbF_6)$, without $AsPh_3$ (blue line; we call this case *unprotected* catalyst meaning that no protector $AsPh_3$ ligand has been added on purpose) and (b) $[\mathbf{1}]_0$ = 0.10 M and 0.8 mol % of **2** with 0.08 mol % $AsPh_3$ (10 mol % relative to gold), in the presence of 0.8 mol % of $Ag(SbF_6)$ (red line). The plot shows that, in the first NMR spectrum (about 3 min reaction time), the conversion with the *unprotected* catalyst (without added arsine) has been completed (conversion 100) and much gold decomposition is observed in the tube; in contrast, in the presence of arsine (blue line) no decomposition is observed but the conversion is slow and only after 24 h does it reach 75% conversion.[25] At that moment a new addition of the same amount of enyne **1** to both NMR tubes shows that, in spite of the apparently massive decomposition produced in the tube without $AsPh_3$ protection, there is still active catalyst able to produce conversion, now reaching full conversion (200) in some hours. The remarkable lowering in conversion rate (see the slope of the blue line) for this second step with the unprotected catalyst has to be attributed to the partial (but abundant) catalyst decomposition. On the other hand, the catalyst protected with 10% $AsPh_3$ (red line) shows initially, upon addition of new **1**, some acceleration of the conversion rate (due to the momentary increase in concentration of **1**). Although the conversion rate is initially slower than that for the *unprotected* system, the slope of the line remains identical with that of the previous period, while that of the *unprotected* system has decreased dramatically from that of the initial instantaneous conversion.

These experiments suggest that the apparently massive decomposition of the "unprotected" catalyst observed under synthetic conditions (Figure 1) is not complete, and a small part of the catalyst has been stabilized when it has reached a very small concentration.

A second conversion experiment during catalysis was monitored to determine the rate of decomposition of the gold catalyst. In this experiment the usual amount of catalyst (2%) was reduced to 0.5% and the time between successive additions of enyne was reduced to 15 min, a reasonable time for reactions in the literature. The cationic catalyst was generated from [AuCl{C(NHXylyl)(NMe_2)}] (**3**) and $Ag(SbF_6)$. Figure 5 shows the evolution of the enyne consumption (by conversion to cyclic products).

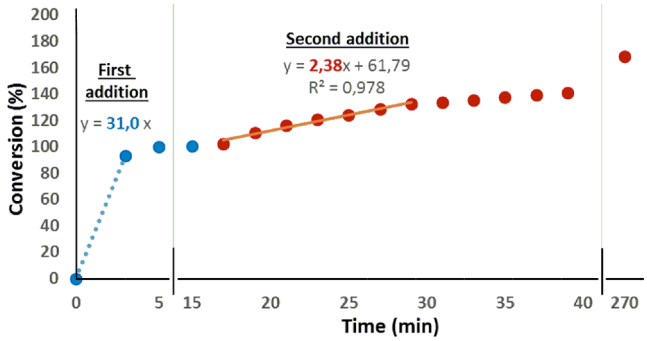

Figure 5. Au-catalyzed cyclization without $AsPh_3$, with two successive additions of enyne **1**, monitored by ^{1}H NMR in CD_2Cl_2, with $[\mathbf{1}]_0$ = 0.10 M and $[Au]_0 = 5.0 \times 10^{-4}$ M (details in Table S2 in the Supporting Information).

Initially, the reaction after the first addition is too fast to allow determination of its initial rate by NMR, but at least it can be concluded that the initial slope should be larger that 31.0 and that 93% conversion has been achieved in 3 min. The evolution shows that 0.5% of gold catalyst is sufficient for total conversion within 15 min (even in 5 min). After the second addition of **1**, the reassumed conversion shows an initial slope of 2.38. Since the enyne concentration has been restored, this rate difference is due to the different concentration of gold catalyst. Consequently we can say that the percentage of catalyst not decomposed in the first run (15 min) is, at most, 7.7% ($2.38/\geq 31 \times 100 \leq 7.7$). The second run is much less efficient, and in 15 min the additional conversion is only 33%. After 270 min the catalyst is still working, very slowly, and the additional conversion has reached only 70%. It is clear that the catalysis observed is molecular, and the conversion of molecules into gold metallic species is quenching the catalysis.

It is interesting to note that in gold catalysis just tiny concentrations (much lower percentages than often used) can be very efficient.[26] On the other hand, the experiments show that, as expected, the catalytic activity of the substoichiometrically protected catalyst is lower than that for the initial *unprotected* catalyst but it is maintained for successive runs, while the catalytic activity of the unprotected catalyst decreases with time.

The previous observations lead us to a scenario that somehow reminds that of Esopo's fable "The tortoise and the hare":[27] here a fast *unprotected* catalyst races versus a protected but slower catalyst. In practical terms the question is as follows: is it better to use the protected or the unprotected catalyst?

To check this, the experiments shown in Figure 6 were carried out. Two identical (except for the protector) cyclization reactions were prepared in NMR tubes, and successive additions of 1 mol equiv of enyne **1** to both tubes were made each time that one of the two tubes had reached almost total conversion or large conversion when rates became slow

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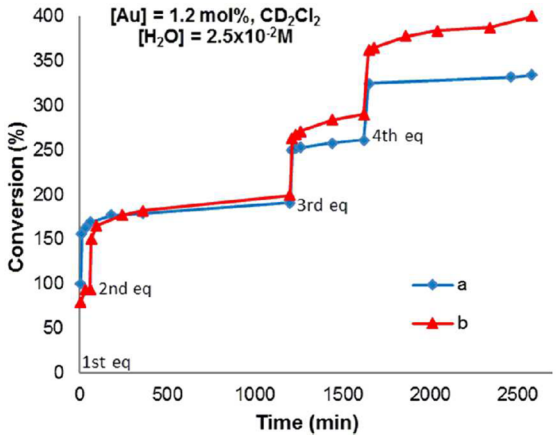

Figure 6. Au-catalyzed cyclization with four successive additions of **1**, monitored by NMR in CD_2Cl_2, with $[\mathbf{1}]_0 = 0.10$ M and $[Au]_0 = 1.2 \times 10^{-3}$ M: (a) without $AsPh_3$; (b) with 10 mol % $AsPh_3$ relative to Au. The reloading with enyne **1** was made when at least one of the curves was close enough to total conversion (details in Table S3 in the Supporting Information). Decomposition was observed only for the unprotected catalyst.

(see Table S3 in the Supporting Information for details). Decomposition was observed only for the *unprotected* catalyst. The curves show that $AsPh_3$ protection of the catalyst yields more in the long term. At variance with Esopo's fable here, we are dealing not only with the different speeds of the two runners, the tortoise (**2** + $Ag(SbF_6)$ protected with 10 mol % $AsPh_3$) and the hare (**2** + $Ag(SbF_6)$) but also with the length of their lives. The former, the tortoise, is slower but its life is longer (comparatively infinite) and in the long term it surpasses what is left of the hare catalyst, which is going slower and slower because its concentration is decaying to a limit of very low (*kinetically inefficient*) concentration.

The experiment was planned to confirm that higher turnover numbers are accessible to the $AsPh_3$ protected catalyst in comparison to the unprotected catalyst, as is the case. The experiment also shows that a minute catalytically active concentration of "unprotected" Au^I survives for several runs. How is it protected?

Water as Protecting Ligand. The formation, in wet organic solvent solutions, of $[Au(PPh_3)(OH_2)](OTf)$ and $[\{Au(PPh_3)\}_2(\mu\text{-}OH)]_2(OTf)_2$, as well as the very stable hydroxo complex $[Au(OH)(PPh_3)]$, and their equilibria and relationships with other related oxo and hydroxo complexes (some of them reported as isolated species) are well documented[17,18,28,29] and have been recently studied.[30] We suspected that, in the previous experiments, water in the solvent might be protecting a low concentration of *unprotected* catalyst in the form of OH_2 or OH^- gold complexes,[31] keeping some gold catalyst active toward subsequent runs. In our catalytic conditions for this part of the study, with unusually low concentration of catalyst, direct NMR observation of these putative complexes is not possible. Moreover, when working at the lowest concentrations of catalyst, we can no longer visually detect even the expected decomposition to Au^0. Thus, evidence of what is going on in the catalysis has to be obtained from kinetic effects in controlled experiments.

The amount of water in the CH_2Cl_2 used cursorily in our catalysis, and in the CD_2Cl_2 we used for NMR kinetic monitoring, was determined by NMR integration versus C_6Me_6 as internal reference. It was further confirmed by Karl Fischer analysis, affording H_2O molar concentrations of 0.78×10^{-4} M in the CH_2Cl_2 used and 330×10^{-4} M in the CD_2Cl_2. For the case of CH_2Cl_2, these values are on the order of the catalyst concentration used and on the order of protecting arsine concentration (only 10% that of the gold complex). They are much higher in the case of CD_2Cl_2. In fact, in comparison with the catalyst concentration used in the ^1H NMR monitoring experiments in Figure 7 (conversions of enyne **1** using **2** as

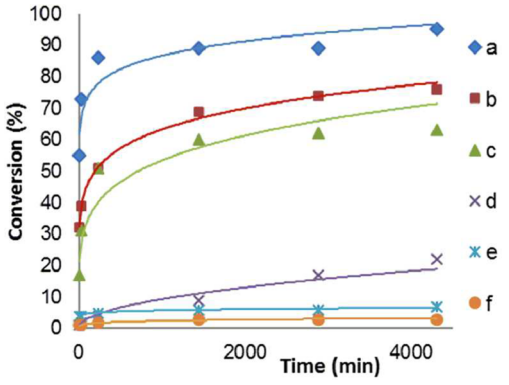

Figure 7. Plot of skeletal rearrangement conversions in CH_2Cl_2 or CD_2Cl_2, using $[\mathbf{1}]_0 = 0.10$ M, $[Au]_0 = 1.0 \times 10^{-4}$ M, $AsPh_3$ (10 mol % of gold concentration except for (f)), and OH_2 as contained in the solvent, leading to the following Au:$AsPh_3$:OH_2 ratios: (a) 1:0.1:0.78; (b) 1:0:330; (c) 1:0:0.78; (d) 1:0.1:330; (e) 1:0:1550; (f) 1:2:330. Note that the continuous lines are not aimed at a mathematical fitting of the points but are meant just as a help to the eye.

precatalyst, [Au] = 1.0×10^{-4} M, and $Ag(SbF_6)$ as halide extractor), the concentration of water in CH_2Cl_2 was a bit smaller than the gold concentration but still 7.8 times that of arsine when used ($[AsPh_3] = 1.0 \times 10^{-5}$ M). In the NMR solvent (CD_2Cl_2) the concentration of water was 330 times higher than that of gold. When the latter solution was saturated adding 1 drop of water, the concentration of water dissolved in CD_2Cl_2 reached a value 1550 times higher than that of the gold catalyst (see the Supporting Information for details). Under these circumstances the high overstoichiometric contents of water produce important stabilizing and rate reaction effects, comparable to those produced by the use of substoichiometric $AsPh_3$, as shown quantitatively in Figure 7. This shows, complementing the analysis done up to now, that a bad ligand (water is a hard ligand, much worse for Au^I than $AsPh_3$), can still be protecting if in highly overstoichiometric proportion.

Since the colloidal gold(0) formed can hardly be visually detected for these concentrations, catalyst decomposition has to be inferred from the decay of conversion. The interpretation of the curves in Figure 7 is not straightforward. However, those that show a deeper fall in slope at still low conversions suggest to be suffering faster catalyst decomposition. Yet, they are the result of two somewhat contradictory influences of the two protecting ligands (water in solvent and $AsPh_3$), which expectedly protect differently against decomposition: they keep the catalyst alive, but they also retard differently the cyclization of enyne. In addition, especially for the reactions having $AsPh_3$, partial decomposition of the catalyst increases the $AsPh_3$:Au^I ratio for the rest, increasing the protection but decreasing the conversion rate.

For curves a–c in Figure 7, the initial conversion rate is very high and eventually approaches zero rate before total conversion has been reached, suggesting that the catalyst has

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decomposed or has become kinetically inefficient after 2500 min (except perhaps for curve a). The best protection and conversion is achieved in curve a, where just 10% of $AsPh_3$ plus 78 mol % of adventitious water, both relative to **2** ($Au:AsPh_3:H_2O$ ratio 1:0.1:0.78), does better as protector than 330 times water. Without $AsPh_3$ added, a smaller content in water (0.78 times, curve c) is fairly effective as protector, but the protection is better with 330 times water (curve b).

The horizontal lines for curves e (with a large overstoichiometric amount of water) and f (with an overstoichiometric amount of $AsPh_3$) in Figure 7 suggest that, at these very low concentrations of gold, both ligands can quench the conversion (since the catalyst must be very well protected, this quenching cannot be assigned to catalyst decomposition).

In curve d in Figure 7, a moderate concentration of water (yet largely overstoichiometric) and only 0.01 mol % arsine (10 mol % relative to Au) allow for catalytic conversion over a long time, although at a very slow rate. We could say that the catalyst is overprotected, which is largely detrimental to the catalytic rate.

The overall effects observed suggest that the protecting effect on the catalyst by $AsPh_3$ and H_2O (or perhaps OH^-) can be prolonged for a long time, once the gold concentrations are very low. The previous experiments also confirm that water in the solvent can act as a protecting agent, which explains the retention of some catalytic activity in heavily decomposed "naked" catalysts and should be a factor to be taken into account when studying gold catalysis. Yet, a substoichiometric amount of $AsPh_3$ protects better than a large overstoichiometric amount of water. In a more general context, overstoichiometric percentages of other bad ligands for Au^I could also protect the catalyst from decomposition, while still allowing for its participation in catalysis.

CONCLUSIONS

The existence of significant concentrations of monocoordinated $[AuL]^+$ intermediates in solution looks extremely unlikely. However, the associative formation from $[AuL(W)]^+$ of *polynuclear intermediates* $[Au_nL^1{}_n(W)_m]^{n+}$, with concomitant release of $n - m$ molecules of the W ligand, provides a satisfactory explanation for the fact that a substoichiometric proportion of a moderate ligand can totally prevent the decomposition of the kind of catalysts formed by extracting Cl^- from $[AuClL^1]$. The existence of this substoichiometric effect is in itself a strong support of disproportionation as the mechanism of catalyst decomposition. The catalyst decomposition mechanism studied here versus the skeletal rearrangement of enynes can be operative in other Au^I catalyses where decomposition occurs. The formulation for the polynuclear intermediates is at the moment speculative and does not exclude that release of some L^1 ligand might be additionally needed to induce disproportionation. Further experiments and DFT calculations are in progress to elucidate their exact nature.

A fascinating experimental result shows that substoichiometric protection can be made much more efficient by using ligands that are not as good ($AsPh_3$ is an example, but others could be used) than by using extremely good ligands (e.g., PPh_3). This striking behavior is a natural consequence of the mechanism of decomposition through polynuclear intermediates and consequently provides additional support to our mechanistic proposal. Additional experiments show that there are other modes of protection of the catalyst (sometimes by silent ligands in solution, such as water) when it reaches very low concentrations.

This is a study of some unusual or less known aspects of gold(I) catalysts that could be utilized to improve the use of these catalysts. Here we have pursued not the optimization of the effects found but the understanding of their mechanistic base. The results here, along with those in our previously reported tests,[10] indicate that there are many possibilities to increase the turnover numbers of gold catalysts, reduce the percentage of catalyst used (one or 2 orders of magnitude below their routine use), or protect them to enable their use at higher temperatures.[10] This will require tuning them for each specific application, using the new better understanding of their behavior.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01825.

General procedures and catalytic and decomposition experiments (PDF)

Crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Author

*P.E.: fax, (+)34 983 423013; e-mail, espinet@qi.uva.es; web, http://cinquima.uva.es.

Notes

The authors declare no competing financial interest.

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(31) Whether coordination of water occurs as a neutral ligand, giving the cationic $[Au(carbene)(OH_2)]^+$, or as OH^-, giving the neutral [Au(OH)(carbene)], we cannot observe experimentally, but the latter possibility looks very plausible considering the expected high acidity of H_2O coordinated to Au^{I} and the studies in ref 30. As a matter of fact, OH^- is a very efficacious protecting anionic ligand but, at variance with Cl^-, for instance, it does not need to dissociate to render the gold complex active: a simple protonation equilibrium with water in the solvent will convert it into an easy to displace OH_2 ligand, thus activating the catalyst. For related possible complexes see ref 18b.

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