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Au(III) catalyzes the cross-coupling between activated methylenes and alkene derivatives

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ABSTRACT

In the last decade substantial efforts were devoted towards the exploitation of the Au(I) as a promising tool to promote C–C bond formation reactions via the activation of unsaturations. Among these efforts, Au(I)/Au(III) cross couplings mediated by a co-oxidant or by photoactivation sit at a privileged position. Au(III) has also shown a rich chemistry but, due to its hardness and lower affinity for unsaturations, it is less often the catalyst of choice in C–C bond forming strategies. Surprisingly, we have recently found two examples of cross-coupling reactions in which the authors report to be adding Au(III) to the reaction flask while claiming that Au(I) is the species responsible for the catalytic events. One of such cases even occurs under oxidizing conditions. Here we present a detailed computational study in which we explore the mechanism behind these C–C forming reactions. Our results suggest that Au(III) can efficiently catalyze these transformations, thus invoking this exotic reduction is not only unnecessary but also energetically unfavourable.

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1. Introduction

Gold catalysis is one of the most captivating topics in Organic Chemistry [1–18]. In recent years, particular attention has been devoted to gold catalyzed C–H bond activations as a strategic tool for the formation of new C–C bonds. On the same lines, the stoichiometric Au(III) activation of C–H bonds towards the formation of new C–C bonds has been known for quite some time [19–23]. Nonetheless, the catalytic version of this transformation is still underdeveloped [11,24–26]. Alternatively, Au(I) cross-coupling reactions have remained a challenge due to the reluctance of this metal to oxidize to Au(III), although this difficulty has been overcome through the use of co-oxidants [27–35].

With such precedents, the past decade has witnessed a renaissance in homogeneous oxidative gold chemistry. Specifically, the group of Tse and coworkers pioneered the use of external oxidants, such as I(III) species, to induce the oxidation of Au(I) to Au(III) as a key step in the gold catalyzed C–C bond formation between two

non-activated organic entities [36]. Later, Zhang [37,38], Nevado, Muñiz, Toste and Lloyd-Jones among others, applied, improved and expanded this protocol in related cross-coupling reactions by introducing alternative oxidant sources [39,37,38,40–50]. Additionally, photoredox catalysis has been proved efficient in this kind of reactions to avoid the use of external oxidants [51–57].

Both common oxidation states in gold, I and III, are reasonably stable in the absence of strong redox agents, and this is why we were shocked finding reports in the literature in which Au(III) is added to the reaction mixture but Au(I) is claimed to be responsible for the catalytic transformation. For example, Li and co-workers [58] presented an atom efficient addition of activated methylene compounds **1** to alkenes **2** leading to branched diketones **3** catalyzed by AuCl₃ in the presence of AgOTf (Fig. 1a). Remarkably, in their thorough exploration of this chemistry, Au(III) was proven to be essential to catalysis since the substitution of Au(III) salts by Au(I) species resulted in only trace amounts of the sought after product. Yet, Au(I) was assumed to be the active catalyst by virtue of a reduction of AuCl₃ by the starting product. This is in stark contradiction to the known compatibility of Au(III) with these functional groups and with the >95% yields the authors report for some reaction products (if we assume the reduction premise, 5%

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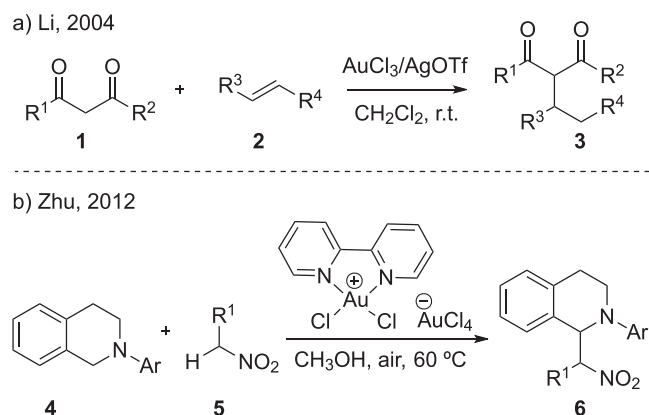


Fig. 1. Gold(III)-mediated oxidative C–C bond formation reactions between a) 1,3-diketones **1** and alkenes **2** and b) tetrahydroisoquinoline derivatives **4** and nitroalkanes **5**.

of the initial diketone **1** had to be oxidized to allow for the catalyst initial reduction). It is worth to note that this Au(III)/Au(I) redox process was no longer proposed in later related works from the same group [59].

In 2012 Zhu et al. reported an example of another highly efficient gold-catalyzed oxidative C–C coupling between different tetrahydroisoquinoline derivatives **4** and a variety of compounds containing activated methylenes [60], mostly nitroalkenes **5**, using a bipyridine–Au(III) complex as catalyst (Fig. 1b). Similarly to the Li proposal, they described the reduction of the Au(III) catalyst to a Au(I) species as a plausible step in the mechanism even though the reaction requires oxidative conditions. Remarkably, they also experimentally demonstrated the inefficiency of PPh_3AuCl as a catalyst in this reaction (Au(I) yielded trace amounts of the desired product and the same results were obtained when using no catalyst at all). The mechanistic proposal accompanying this work also includes a β -elimination step on a Au(I) complex, a reaction that we have recently studied in detail [61] and which was what originally called our attention to this contribution. In our work we show that it is highly unlikely that a β -elimination occurs in a Au(I) complex. It is however feasible when the metal center is Au(III). Other experimental groups have reached similar conclusions [62,63] showing that Au(III) outperforms Au(I) in these elimination processes, and that only under very specific circumstances Au(I) complexes undergo β -elimination reactions.

Triggered by the contrast between these mechanistic proposals and the reported experimental evidences and conditions, we have performed a thorough computational study of the mechanisms of the described reactions. We provide here a critical explanation on the requirement of an oxidative environment for the effectiveness of the second process and draw attention to why invoking a Au(III)/Au(I) reduction process is unnecessary.

2. Results

We therefore evaluated the reaction mechanism for the transformations presented in Fig. 1 in two different scenarios, depending on the oxidation state of gold at the active catalyst: Au(I) or Au(III). For computational efficiency, we performed our calculations considering AuCl (**7**) as catalyst for the Au(I)-catalyzed transformation while AuCl_2OTf (**12**) was used as the active species in the Au(III) catalyzed reaction. Regarding the reactants, 2,4-pentanedione (**1**), styrene (**2**), the *N*-phenyl tetrahydroisoquinoline **4** and nitromethane (**5**) were selected as representative models of these structures used experimentally.

Regarding the coupling between an activated methylene and styrene described by Li, the activation of the diketone **1** by the gold catalyst is the initial common step in both gold-cycles, see Fig. 2. In the Au(I)-mediated mechanism, the activation of **1** consists on the coordination of the metal to the lone pair of the oxygen at one carbonyl group leading to **8** [64]. Once **8** is formed it is proposed to evolve by the oxidative addition of gold into a non-polar and unactivated C–H bond. The barrier we computed for this rare event is consequently very high (165.7 kJ/mol) and it leads to an unstable Au(III)-intermediate, **9** (111.4 kJ/mol, see Fig. 2-left). Following the reported mechanistic proposal, styrene would coordinate onto the Au(III) intermediate **9** leading to a fleeting intermediate **10** which can further progress via a very kinetically and enthalpically favourable process towards **11** (35.9 kJ/mol). During the conversion of **10** into **11** the hydride-like H atom at **10** adds to the terminal carbon atom of the alkene moiety of styrene at **TS2** (129.8 kJ/mol). This is an early transition state characterized by a Au–H bond distance of 1.63 Å, whereas the Au–C bond distance is 2.32 Å. Interestingly at this state the hydrogen atom has already lost its hydride character and bears a charge (derived from the atomic polar tensor, APT) [65,66] of 0.2 a.u. compared to the –0.1 a.u. charge found in **10**. Finally, **11** progresses via a reductive elimination step in which a new C–C σ -bond is formed, yielding product **8** and regenerating the catalyst. This last step takes place via transition structure **TS3** and requires 86.2 kJ/mol.

The alternative Au(III)-catalyzed process that would account for this **1** to **3** transformation is shown in Fig. 2-right. Initially, the more stable intermediate **13** (–99.3 kJ/mol) would be formed by a double π -coordination between AuCl_2^+ , which is formed experimentally by reaction of AuCl_3 with a halogen scavenger (AgOTf), and the C=C bonds of the keto-enol tautomer **1a** and styrene **2**. In contrast to what was found for the Au(I)-cycle, the keto-enol tautomer, **1a**, is the reactive species here. Then, the system can further progress by the nucleophilic addition of the enolate moiety onto the phenyl-substituted carbon atom of the activated alkene unit affording the protonated α -alkyl diketone, **14**. This step involves an energy barrier of 85.2 kJ/mol and the distance of the C–C forming bond is 2.35 Å at **TS4**. A subsequent acid-base reaction between **14** and the OTf^- anion would lead to **15** which, after a protodeauration step, affords product **3** and the initial catalyst, **12**. Our computational results predict that the energy span for the Au(I) and the Au(III) cycles are 187.4 kJ/mol [67] and 85.2 kJ/mol, respectively [68]. In summary, the mechanism in which Au(III) acts as catalyst is more favorable than that catalyzed by Au(I). Remarkably, in the Au(III)-cycle no change of the gold oxidation state takes place along the entire catalytic cycle. As a consequence this C–C coupling reaction between **1** and **2** can proceed without intervention of an uncanny and demanding Au(III)/Au(I) redox step.

We also investigated the reactivity described by Zhu et al. In this work they report a Au(III)-catalyzed C–C coupling between a tertiary amine and an activated methylene in the presence of air as an oxidant source (see Fig. 1-b). It is also proposed that the mechanism ruling this transformation could be initiated by a reduction of Au(III) to Au(I), despite the intentional bubbling of oxidant, followed by a β -hydride elimination step. We computed this elimination step at tetrahydroisoquinoline **4** towards the iminium species **17** and **22** considering AuCl and AuCl_2^+ as catalysts, respectively (see Fig. 3) [69]. As expected, the energy penalty for this process was high (87.7 kJ/mol, **TS5**) for the Au(I) complex and substantially lower (7.7 kJ/mol, **TS8**) for the Au(III) alternative (see Fig. 3). Aiming to shed light on this energy difference, we performed a detailed analysis of these two transition states, obtaining that in **TS5** the Au–C, Au–H and H–C bond distances involved in the H-shift are 3.22, 1.66 and 1.66 Å, respectively,

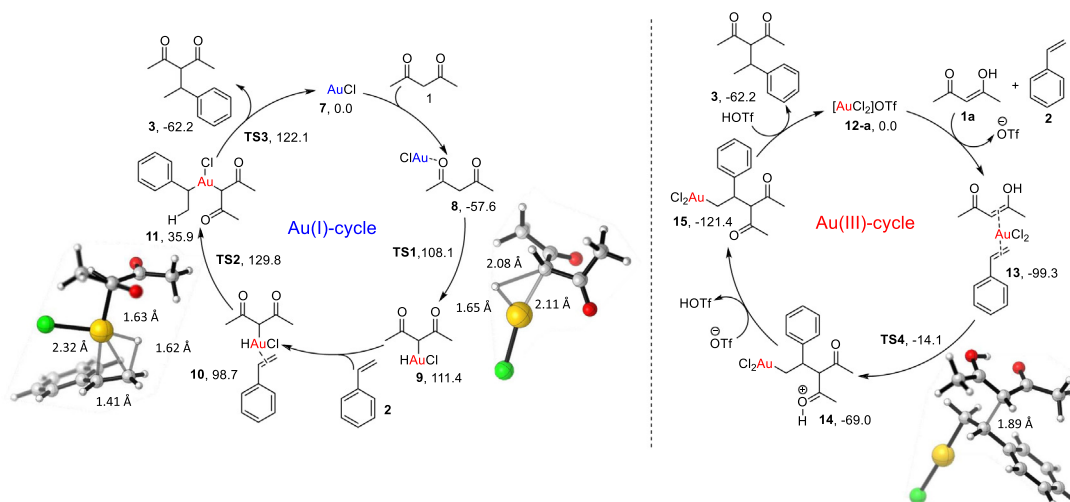


Fig. 2. Proposed mechanism for the gold(I) (left) and gold(III)-mediated (right) formation of diketone **3** through a C–C coupling reaction between **1** and **2** at the PCM(DCM)/M06/Def2-TZVPPD//PCM(DCM) M06/Def2-SVP theoretical level. Gibbs free energies are reported in kJ/mol (1 atm and 298 K), relative to the active catalyst and the reactants considered as separate species. Colors refer to the alternative gold oxidation state: Au(I) (blue) and Au(III) (red).

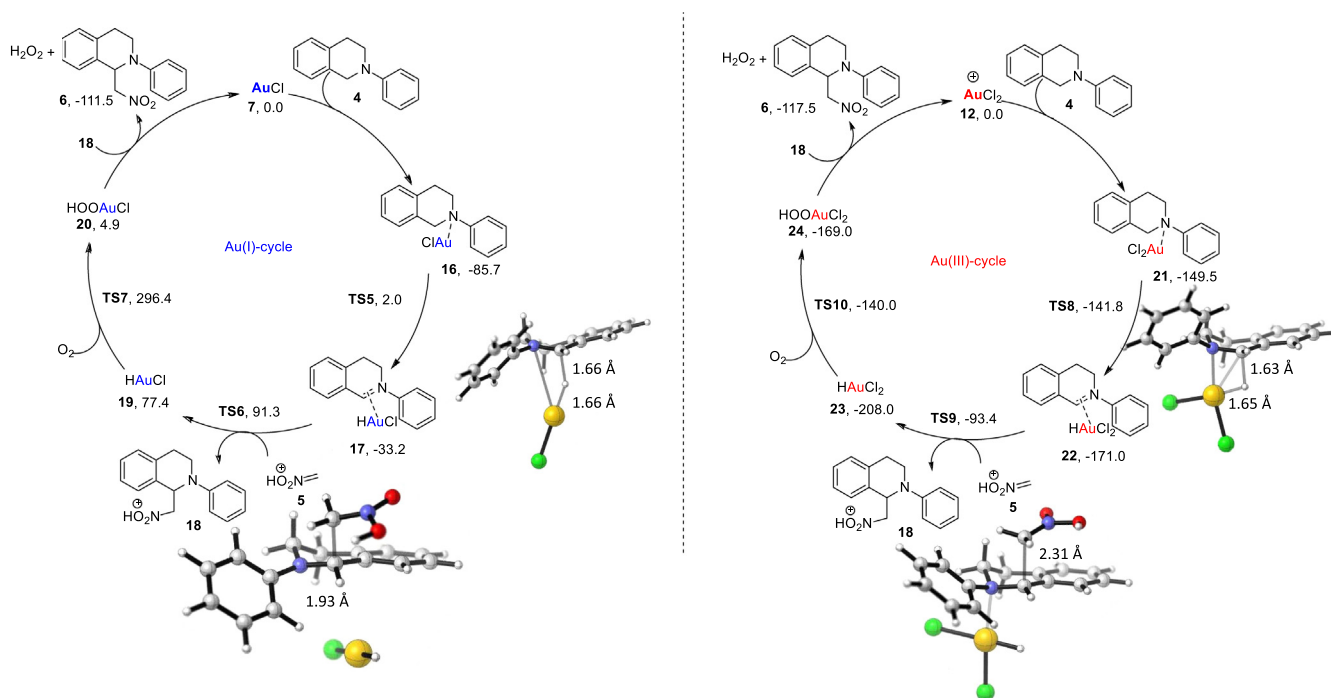


Fig. 3. Proposed mechanism for the gold(I) (left) and gold(III)-mediated (right) formation of the tetrahydroisoquinoline **6** by C–C coupling reaction between **4** and **5** at the PCM(MeOH)/M06/Def2-TZVPPD//PCM(MeOH)/M06/Def2-SVP theoretical level. Gibbs free energies are reported in kJ/mol (1 atm and 298 K), relative to the active catalysts **7** in case of Au(I)-cycle or **12** for Au(III)-cycle. Colors refer to the alternative gold oxidation state: Au(I) (blue) and Au(III) (red).

and the charge at the hydrogen atom is of -0.80 a.u. whereas in **TS8** those distances are slightly shorter of 2.48, 1.65 and 1.63 Å, respectively, and the charge at the hydrogen atom is notably lower (-0.26 a.u.). These structural parameters, and particularly the charges at the hydrogen atoms, justify the lower computed energy barrier for this step when Au(III) is involved. In line with our previous findings for the gold catalyzed β -hydride elimination on different substrates [61], Au(III) can simply accommodate better the negative charge of the migrating hydrogen atom whereas in the Au(I) species strong electron repulsion builds up when the metal center and the hydride approach.

Next, in both gold-cycles, the resulting intermediates **17** and **22** may be trapped by nitromethane. We propose here that the nitro-

methane tautomer **5** is the active species in this process, since a nucleophilic carbon is determining for the evolution of the system towards the formation of **6**. To explain the presence of this *a priori* unstable species - the tautomeric form of nitromethane is 69.2 kJ/mol less stable than nitromethane - [70] we considered first both oxygen and the resulting gold-hydride complexes as potential promoters for the tautomerization (see SI), however we could only find water efficiently assisting this transformation. The energy barrier of this process is 139 kJ/mol which would be accessible at the working temperatures (see SI). This finding is compatible with the use of air instead of pure oxygen in the experimental setup since moisture is present in the former. The nucleophilic additions were computed to proceed overcoming an energy barrier of 124.5 kJ/mol

and 77.6 kJ/mol via transition structures **TS6** (Au(I)-cycle) and **TS9** (Au(III)-cycle), respectively. In both transition structures, nitromethane approaches to the electrophilic carbon center by the opposite side to which the metal is placed. The recovery of the Au(I) and Au(III) catalyst also requires the participation of oxygen, it inserts at the resulting gold-hydride complexes **19** and **23** leads to the peroxide partners **20** and **24**. Remarkably, this step is very costly energetically for the Au(I)-catalyst (219.0 kJ/mol) whereas it only requires 68.0 kJ/mol when Au(III) acts as catalyst. Finally, these two species can evolve via the release of hydrogen peroxide thus allowing the recovery of the initial catalysts.

3. Conclusions

In summary, we have herein revised the mechanisms ruling two gold catalyzed cross-coupling reactions between activated methylenes and alkenes. Our calculations predict that the Au(III) catalyst actually added to the reaction mixture in the experimental setup is effective towards the coupling reaction between 2,4-pentanedione and styrene. The rate-determining step is the coupling step between the 1,3-diketone and the alkene moieties. Likewise, the reaction between tetrahydroisoquinolines and nitromethane is preferably mediated by AuCl₂⁺. In this case, the computed energy barriers of the key β -hydride elimination and the subsequent oxygen insertion steps are notably lower than when AuCl is the active catalyst. This effect has been described in detail in the past, both in computational and experimental work. We have demonstrated that the proposed reduction of Au(III) to Au(I) before the catalytic cycle starts is not necessary since Au(III) is capable of facilitating these transformations.

These are only two examples that captured our attention because of their relevance in the field of homogeneous gold catalysis and their relation to β -elimination steps in their proposed mechanisms (in backwards and forwards directions, respectively), but they can be considered representative of a more general conduct that has become popular recently: Proposing a *plausible mechanism* alongside almost any new discovered reaction. With this work, we would like to pose a word of caution since understanding the mechanism of a reaction is without a doubt of invaluable relevance; it provides the scientific community with key information to further tune, improve and exploit the new reaction. However, when the mechanistic proposal is not supported by adequate data, regardless of whether that data comes from a thorough computational study, kinetic experiments or a combination of both, it can lead to biased conclusions that cannot only undermine the discovery of a reaction but can also prevent or delay its application.

4. Computational methods and general protocols

Computational methods The geometries of all the stationary points were fully optimized by using the Gaussian09 program [71] at the M06/Def2-SVP computational level [72,73]. The associated effective core potential (ECP) was employed to describe the Au atom. This computational method was selected based in its superior performance when simulating homogeneous gold-mediated organic reactions [74–76]. The effect of the solvent (dichloromethane and methanol, respectively) was taken into account using the Polarizable Continuum Model (PCM) [77] with the default parameters implemented in the Gaussian 09 package [71]. Harmonic analysis was performed to characterize minima (0 imaginary frequencies) and transition states (1 imaginary frequency). The wave function stability was confirmed in all stationary points [78,79]. Thermochemical corrections at 298.15 K were calculated for all stationary points from unscaled vibrational frequencies. An energy refinement was performed via single point

energy calculations at optimized geometries computed at the M06/def2-TZVPPD [72,73] theoretical level and were combined with the previous computed thermochemical corrections to obtain Gibbs free energies at 298.15 K. The energies in this work are therefore reported at the PCM(MeOH)/M06/Def2-TZVPPD//PCM(MeOH)/M06/Def2-SVP level.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jcat.2020.09.030>.

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