VIP **Gold Catalysis** *Very Important Paper*

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CO Extrusion in Homogeneous Gold Catalysis: Reactivity of Gold Acyl Species Generated through Water Addition to Gold Vinylidenes**

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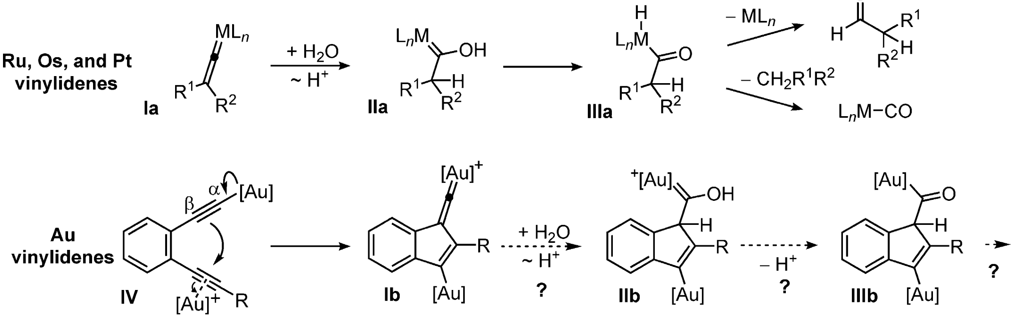
Abstract: *Herein, we describe a new gold-catalyzed decarbonylative indene synthesis. Synergistic σ,π-activation of diyne substrates leads to gold vinylidene intermediates, which upon addition of water are transformed into gold acyl species, a type of organogold compound hitherto only scarcely reported. The latter are shown to undergo extrusion of CO, an elementary step completely unknown for homogeneous gold catalysis. By tuning the electronic and steric properties of the starting diyne systems, this new reactivity could be exploited for the synthesis of indene derivatives in high yields.*

In 2012, Zhang and co-workers and our group independently discovered a dual gold-catalyzed pathway as a new activation mode in homogeneous gold catalysis.[1] Therein, the nucleophilic σ-activation and the electrophilic π-activation of the alkyne units in diyne systems act synergistically to generate gold vinylidene intermediates. Since then, the high reactivity of these species was mostly exploited for insertion reactions into unactivated C–H bonds.[2] So far, only rare reports appeared in which a gold vinylidene is trapped with heteroatom nucleophiles.[1a,3]

On the other hand, such reactions are well known for vinylidene complexes of other metals. For example, the reaction of Ru, Os, or Pt vinylidenes with water leads to hydroxy–carbene derivatives, which can tautomerize to the corresponding metal acyl species. The latter can either eliminate the whole organic fragment as an aldehyde or extrude CO, thereby forming the respective metal carbonyl and an organic product (Scheme 1, upper part).[4]

As part of our ongoing research on new reactive intermediates[5] in homogeneous gold catalysis we wondered if gold vinylidenes generated through the dual catalysis mode in combination with water might enable the synthesis of related gold acyl species as well (Scheme 1, lower part). Only rare examples of acyl complexes of gold are known. All of them are based on stoichiometric reactions that use anionic Fischer carbene complexes as precursors. Their transmetalation onto a gold fragment often leads to gold acyl species that are still coordinated to the original metal fragment.[6] To date, only one free gold acyl complex has been reported.[7] Besides, to the best of our knowledge, no reports on the reactivity of these species exist. Therefore, the addition of water to intermediately formed gold vinylidenes would not only allow a new access to these species without the need for preformed organometallic reagents that require the exclusion of air and moisture, but also enable us to gain first mechanistic insight into the reactivity of these compounds.



Scheme 1. The known formation of metal acyl species from metal vinylidenes and water (upper part) and the envisioned generation of gold acyl species through addition of water to gold vinylidenes (lower part).

Indeed, during our studies of dual gold-catalyzed reactions in the presence of water with substrate **1a**, we observed a transformation to an unexpected product showing a mass loss of 10 u with regard to the starting material. By running the reaction with 1 equivalent of water and 5 mol % of dual activation catalyst **3**,[8] we were able to isolate the product and to characterize it as the indene derivative **2a** (Scheme 2).[9]

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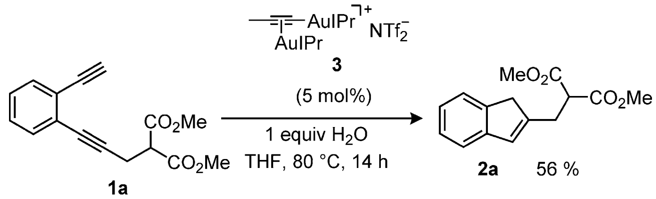


Scheme 2. Dual gold-catalyzed transformation of **1a** in the presence of 1 equiv of water (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethylsulfonyl).

The loss of one carbon atom was unambiguously proven by a crystal structure analysis.[10,11]

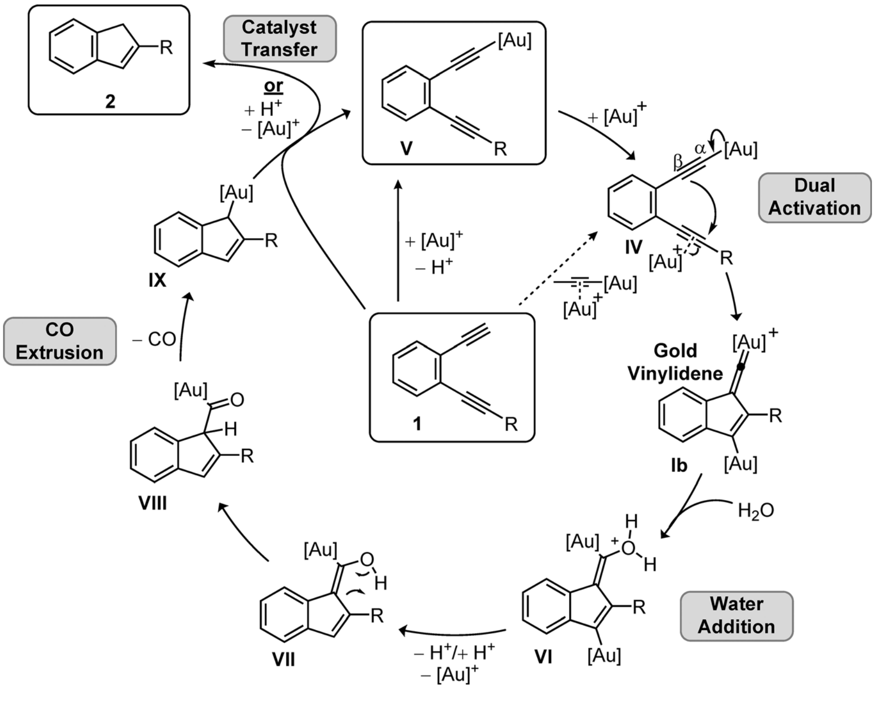
Our mechanistic hypothesis for this unexpected product is indeed based on the formation of a gold acyl complex and its subsequent chemical transformation. We assume that, in accordance to other reported dual gold-catalyzed transformations, the generation of gold vinylidene intermediate **Ib** initiates the reaction cascade (Scheme 3). **Ib** can be trapped with water as a nucleophile leading to species **VI**. Protodemetalation of the sp^2-Au species and transfer of the oxygen-bounded proton onto the conjugated system then led to gold acyl species **VIII**. By extrusion of CO,[12] intermediate **IX** can be formed which, after protodeauration or catalyst transfer onto the next molecule of the starting material, completes the catalytic cycle. Through this pathway two hydrogen atoms from water would be added to the product, whereas the oxygen atom together with one carbon atom from the starting material would be eliminated in the form of CO. In total, this would account for the observed mass loss of 10 u.

Since, to the best of our knowledge, no precedents for a CO extrusion in homogeneous gold catalysis exist, we carried out further investigation on this interesting elementary step. To prove directly the formation of CO in the catalytic cycle, we ran the reaction in a closed vial with septum and injected samples of the gas phase into a GC/MS. At first, we used 5 equivalents of $H_2(^{18}O)$ as nucleophile and indeed we were able to detect the formation of a peak at *m*/*z* 30 corresponding to $C(^{18}O)$ (Figure 1). The simultaneous growth of the peak at *m*/*z* 28 is probably due to diffusion of nitrogen but could also arise in some part from the formation of $C(^{16}O)$ out of residual non-labelled $H_2(^{16}O)$. Nevertheless, this experiment clearly proves the crucial role of water for the reaction and shows that it is really the oxygen atom of the latter that is incorporated into the eliminated carbon monoxide.

Next, we synthesized substrate $[^{13}C]$-**1m** bearing a ^{13}C-label at the terminal alkyne position and followed its transformation in the presence of 5 equivalents of $H_2(^{16}O)$ in a similar fashion (Figure 2). This time, we detected the formation of a peak at *m*/*z* 29 corresponding to ^{13}CO. Again, the peak at *m*/*z* 28 was growing as well. To check, whether this growth is solely due to diffusion of nitrogen or whether it contains a contribution from ^{12}CO, we isolated product **2m**. If ^{12}CO was produced during the reaction, the ^{13}C-label should still be present in the product. Since this was not the case (neither the ^{13}C NMR nor an MS spectrum of **2m** showed any indication of a ^{13}C-label), this experiment clearly proves that selectively the former terminal alkyne carbon and therefore the vinylidene/gold acyl carbon is eliminated as CO during the reaction and that the peak at *m*/*z* 28 can be allocated to N_2.

After the proof of the postulated CO extrusion we set out to investigate the proton transfer steps of the reaction cascade with deuterium labeling experiments.[11] Unfortunately, the presence of water, which could be shown to be essential for the reaction, led to an undesired exchange at the terminal alkyne position of the starting material under the reaction conditions (confirming the involvement of a gold acetylide). Therefore, no conclusions can be drawn from these experiments and a differentiation whether the catalytic cycle is closed by a catalyst transfer step or by protodeauration is not possible either.

Next, we synthesized substrate **1b** in which the symmetry of the backbone is broken by the introduction of an extra methyl group. Its gold-catalyzed transformation in the presence of 5 equivalents of D_2O led to a 1.0:0.8 mixture of the two isomers **2ba** and **2bb** that were assigned with the help of an HMBC NMR spectrum (Scheme 4). The detection of these two isomers suggests that the displacement of the gold catalyst in the allylic fragment of **IX** can happen either directly or by an



Scheme 3. Proposed mechanism for the gold-catalyzed formation of indenes from diyne systems in the presence of water. Counterions are omitted for clarity.

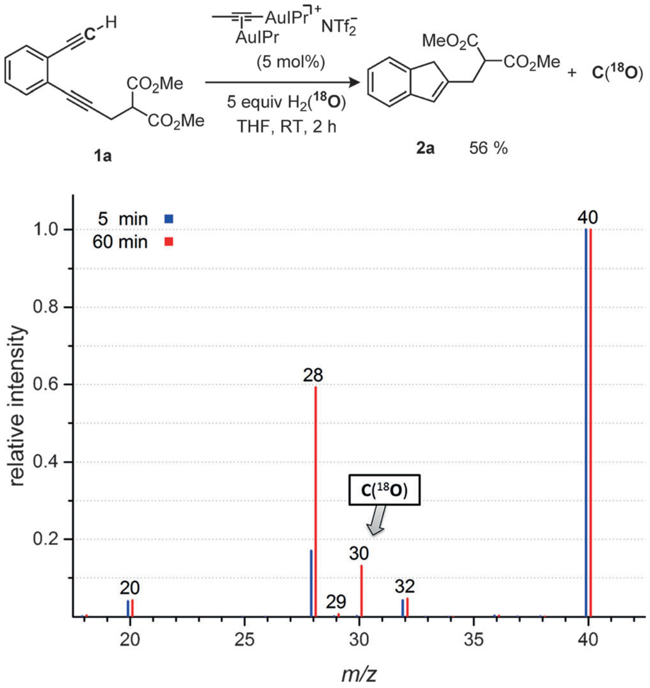


Figure 1. GC/MS spectra of the gas phase of the gold-catalyzed transformation of **1a** in the presence of 5 equiv of $H_2(^{18}O)$. The vial was flushed with argon and the corresponding peak at *m/z* 40 was used as a reference peak.

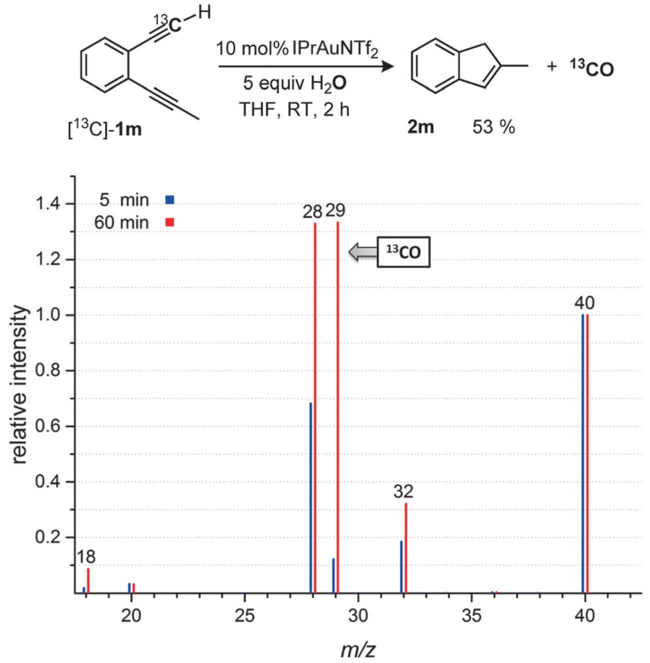
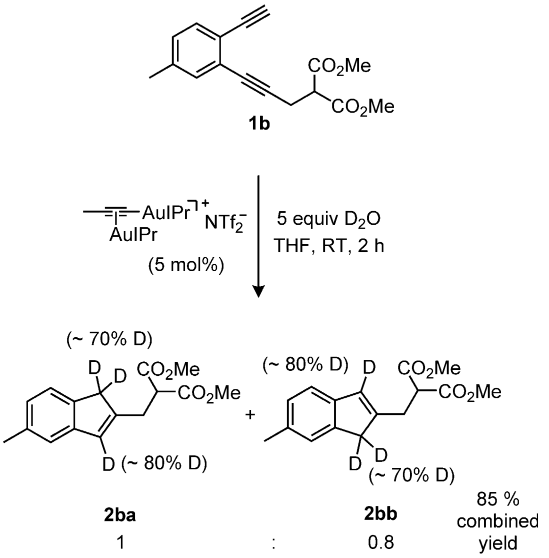


Figure 2. GC-MS spectra of the gas phase of the gold-catalyzed transformation of [^{13}C]-**1m** in the presence of 5 equiv of H_2O. The vial was flushed with argon and the corresponding peak at *m/z* 40 was used as a reference peak.

S_E2' process.[13] In the case of substrates with a symmetrical backbone both pathways lead to the same product.

After the mechanistic investigation, we set out to optimize the reaction conditions[11] and to examine the substrate scope.

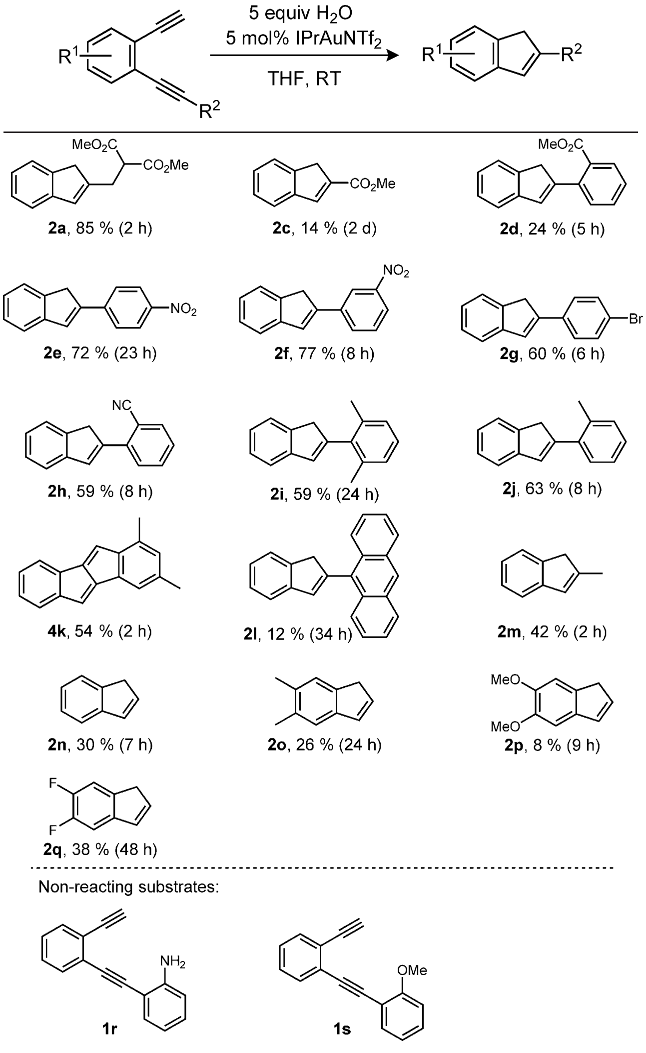


Scheme 4. Gold-catalyzed transformation of **1b** in the presence of 5 equiv of D_2O.

At first, a catalyst screening revealed that $IPrAuNTf_2$ alone led to a faster conversion than the corresponding dual activation catalyst **3**. Next, we screened different auxiliary ligands but none gave better results than IPr. With regard to the counter anions, the pre-activated complex $IPrAuNTf_2$ outperformed the combination of IPrAuCl with different silver salts. A solvent screening showed that THF was the best candidate and among the different amounts of water that were tested 5 equivalents turned out to give the highest yield within the shortest reaction time. No strong effect of the concentration of the organic substrate was observed and the initial molarity of 0.2 M was used for further reactions. Finally, we conducted several control experiments but neither in the presence of only water nor $AgNTf_2$ nor $HNTf_2$ any product formation could be detected.

With these optimized conditions in hand [**1** (200 mM in THF), 5 mol% $IPrAuNTf_2$, 5 equivalents H_2O, room temperature] we started to investigate the substrate scope of the decarbonylating gold-catalyzed indene synthesis. As shown in Table 1, the product **2a**, derived from malonate substrate **1a**, could be isolated in a respectable 85% yield. The attachment of an ester group directly at the triple bond in **1c** resulted in a longer reaction time and only a poor yield of indene **2c**. Next, we examined substrates bearing aryl-substituted internal alkyne units. Since the addition of water to the gold vinylidene is an *inter*molecular reaction, we first applied aryl groups with electron-withdrawing substituents as these turned out to be unreactive in the competing *intra*molecular formation of dibenzopentalenes.[2a] Indeed, nearly all of the substrates delivered the corresponding indene derivatives **2e** to **2h** in good yields; with the *ortho*-benzoate substrate **2d** being the only exception (24%). Two or even only one methyl group in the *ortho*-position also efficiently blocked the intramolecular trapping of the gold vinylidene and the corresponding indene products **2i** and **2j** could be isolated in 59% and 63% yield, respectively. Unfortunately, an *ortho*-NH_2- or OMe-substituent gave no conversion at all. As

Table 1: Substrate scope for the gold-catalyzed indene synthesis.[a]



[a] All reactions were performed in THF (200 mм in **1**) at room temperature. All yields refer to isolated products.

expected, the methyl groups in the *meta*-positions of substrate **1k** could not prevent the intramolecular insertion into one of the *ortho*-C–H bonds and dibenzopentalene **4k** was obtained as the only product in 54% yield. An anthryl substituent restored the indene formation, but a long reaction time was required and the product **2l** was only obtained in low yield. Substrate **1m** with a simple methyl group at the internal alkyne could also be converted although the yield of **2m** was quite poor. Finally, we also investigated *bis*-terminal diyne systems **1n** to **1q**. All of them resulted in poor yields, whereby the dimethoxy-substituted derivate **1p** gave nearly no product at all. This might be due to the presence of two strong electron-donating groups, which reduces the acidity of the terminal alkynes and therefore hampers the formation of the gold acetylide.

In summary, we were able to discover a new reactivity for gold vinylidenes, namely the formation of sparely reported gold acyl species through the addition of water to gold vinylidene intermediates. In addition, we could prove that the latter can undergo an extrusion of CO, an elementary step so far unknown in homogeneous gold catalysis. Following this methodology, various indene derivatives could be synthesized. We could further demonstrate that high yields for these transformations can be achieved if competing intramolecular pathways can be suppressed by tuning the electronic or steric properties of the applied starting materials. Further investigation concerning the formation and reactivity of gold acyl species from vinylidenes are currently underway in our lab. The microscopic reverse reaction, the insertion of CO, might also open entirely new perspectives for gold catalysis.

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[10] CCDC 1027159 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] See the Supporting Information for further details.

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