Gold Catalysis

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Dinuclear Gold Catalysis: Are Two Gold Centers Better than One?**

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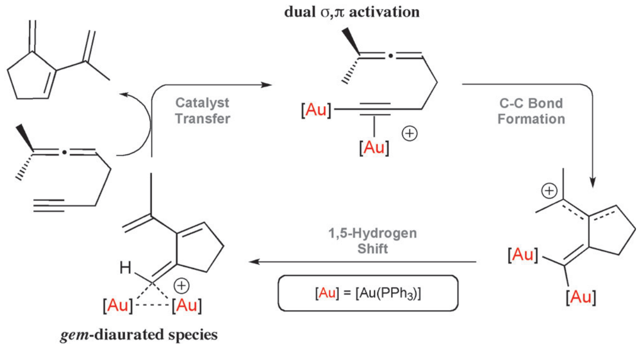
In the ever-expanding field of homogeneous gold catalysis a new era appears to have begun.[1] During the last five years, several topics have dominated the scientific literature on gold catalysis. While most of these topics have been the subject of extensive reviews,[2] little has been said about the chemistry of dinuclear gold species. This reactivity mode has primarily been discussed in the context of 1) the dual σ,π-activation of a single substrate, typically a terminal alkyne, by two gold molecules and 2) the role of the *gem*-diaurated species in catalysis.

In 2008, Toste and co-workers reported, in the course of mechanistic studies dealing with the cycloisomerization of 1,5-allenynes, the first evidence of dual σ,π-activation by a gold catalyst, $[\{Au(PPh_3)\}_3O][BF_4]$ (**1**).[3] In the reported computational studies, which were supported by experimental data, it was found that the most plausible reaction mechanism involved a dual σ,π-type activation of the alkynyl group by two molecules of $[Au(PPh_3)]^+$ generated from the interaction between **1** and the substrate. This reaction sequence was followed by cycloisomerization, generating a *gem*-diaurated species that reacted with a new substrate molecule to release the final product (Scheme 1).[3] The Toste work raised questions about the interactions between Au^I complexes and terminal alkynes, and the mechanism by which gold catalyzes organic transformations. Such reactions often involve active species generated in situ, which renders detailed mechanistic studies difficult. Subsequently, several research groups,[4] including those of Nolan,[4a,b] Widenhoefer,[4c] and Corma,[4d] began to explore dual activation by Au^I complexes. We reported on the synthesis, characterization, and reactivity of digold species of the form $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ (**2**) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene). Since **2** can be formed from [Au(L)Cl]/AgX in aqueous media, it was proposed as the active catalyst in water-containing reactions involving alkynes or nitriles.[4a,b] Mechanistic investigations elucidating the role of the two gold centers in these catalytic transformations have yet to be performed.



Scheme 1. Catalytic cycle proposed by Toste et al.

The Widenhoefer and Corma groups independently reported the dual σ,π-activation of alkynes, shedding light on how a dinuclear gold species can be easily generated in situ from a mononuclear gold complex and a terminal alkyne. While the former focused on the synthesis and stability of σ,π-digold acetylide complexes,[4c] the latter investigated their importance as intermediates in catalytic transformations.[4d] Widenhoefer et al began their studies by reacting well-defined cationic π-acetylide species, such as $[Au(IPr)(\eta^1\text{-}CCPh)][SbF_6]$ (**3**), with 1 equiv of base at low temperatures (Scheme 2). This reaction afforded the dinuclear gold species $[\{Au(IPr)\}_2(\eta^1,\eta^2\text{-}CCPh)][SbF_6]$ (**4**) in short reaction times. Further investigation revealed that **4** could be easily synthesized in very good yields by reacting a mixture of [Au(IPr)Cl]/$AgSbF_6$ with an excess of phenylacetylene at 25 °C for 10 min.[4c] The stability of the σ and π bonds was subsequently investigated. Addition of a two-electron donor ligand, such as pyridine, to a solution of **4** led to a 1:1 mixture of the neutral σ-acetylide species [Au(IPr)(CCPh)] (**5**) and the cationic complex $[Au(IPr)(Py)][SbF_6]$ (**6**) after 10 min at 25 °C. On the other hand, evaluation of the stability of **4** towards protodeauration revealed that σ,π-acetylide species were much more stable towards this process than their mononuclear congeners. Addition of HOTf to a solution of **4** did not afford any product after 12 h at 25 °C, while reaction with **5** led to complete conversion into [Au(IPr)(OTf)] after 10 min at −80 °C.[4c] Formation of **3** also generates 1 equiv of a strong Brønsted acid, whose effect on the reactivity should not be neglected (Scheme 2). Since **3** was easily generated in the

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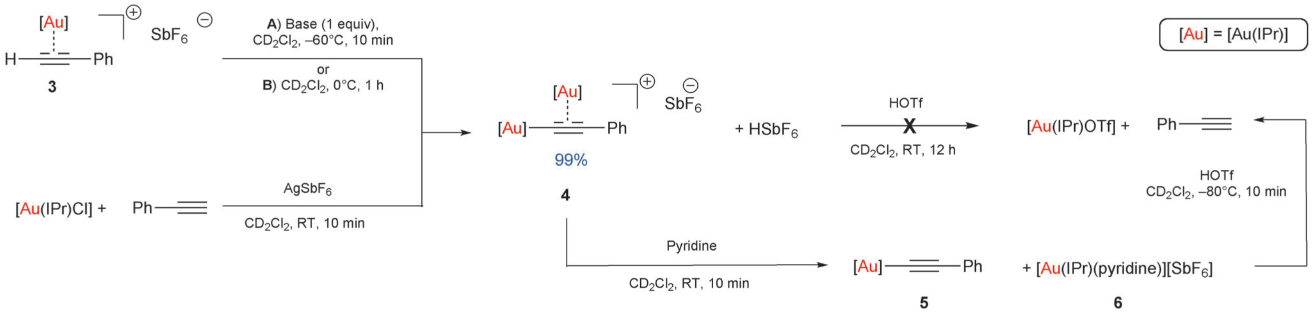


Scheme 2. Synthesis and reactivity of the σ,π-acetylide species reported by Widenhoefer et al.

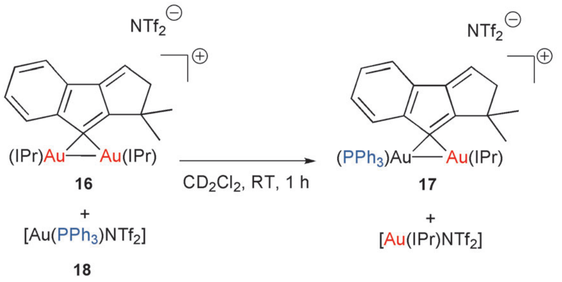
absence of a base, it was suggested that this type of species may be involved in the transformation of terminal alkynes.[4c]

This hypothesis was independently confirmed by the Corma group[4d] while studying the mechanism of the intermolecular [2+2] cycloaddition of alkynes with alkenes reported by Echavarren.[5] During the course of their investigations, Corma et al. observed the formation of a digold species of the type $[\{Au(L)\}_2(\eta^1,\eta^2\text{-}CCPh)][SbF_6]$ (**7**) (L = phosphane ligand), resulting from the reaction involving a cationic gold complex $[Au(L)(NCMe)][SbF_6]$ (**8**) and phenylacetylene.[4d] The use of **7** as a catalyst enhanced the selectivity of the reaction towards the alkene, allowing the use of the alkyne and alkene substrates in a 1:1 ratio rather than the 1:2 ratio described by Echavarren, although **7** has lower activity than **8**.[4d] They also demonstrated the influence of the Brønsted acid generated in situ, as it could either react with the alkene, promoting polymerization of the substrate, or with the final product, thus reducing the selectivity and yields. Although the Corma group demonstrated that σ,π-acetylide species could be active intermediates in catalysis, it is worth mentioning a recent contribution by Gimbert et al. in which a combination of computational and experimental studies has shown the lack of reactivity of such species in the cycloisomerization of 1,6-enynes.[4e]

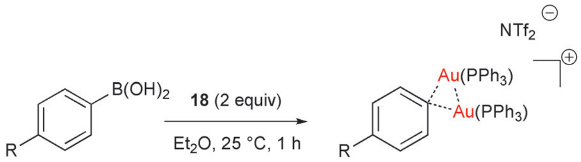
Recently, several reports have focused on the formation and characterization of geminally diaurated unsaturated hydrocarbons, highlighting their significance as a possible catalyst resting state in some Au^I-catalyzed transformations. Several research groups have most notably contributed to our understanding of the chemistry of those species[6] and three contributions deserve special mention. The Gagné group has recently reported on the strong electronic and counterion effects in the formation and reactivity of *gem*-diaurated species.[6b] In their studies, a series of Au^I–aryl complexes were used as models for catalytic vinyl gold intermediates, instead of the corresponding *gem*-diaurated vinyl species because of the low stability of the latter. Three main conclusions can be drawn from their work: 1) the electron density of the aryl and vinyl ligands has a high impact on the reactivity of the digold species, such that the most reactive complexes are those bearing less electron-rich ligands; 2) the tendency to form these species is higher for counterions with poorer coordinating ability; and 3) the presence of gold salts can affect the rate of protodemetalation of mononuclear Au^I–aryl/vinyl species because they can, depending on the nature of the counterion, promote the generation of digold species and thus inhibit this process.[6b] These statements should be taken into account when considering the use of certain catalysts for multistep reactions because less coordinating counterions are typically chosen to accelerate the initiation step, but at the same time these promote the formation of digold intermediate species that are more stable, and thus less reactive.[6b]

Following the work of the Toste group,[3] Hashmi and coworkers have recently extensively reported on this dual activation of diynes leading to *gem*-diaurated intermediates.[7] In early work they performed mechanistic investigations on the α/β-selectivity of a cycloaddition reaction.[7a,b] Several factors could affect the selectivity: the α-isomer was the major product at high catalyst loadings and low temperatures, and the formation of the β-isomer was preferred in the presence of basic additives. The latter result suggested the possible formation of the Au–acetylide species **9** during the catalytic cycle yielding the β-product (Scheme 3). To support this, several reactions of **9** and diyne **10** were performed. Surprisingly, mixing catalytic amounts of **9** and Gagosz's catalyst, $[Au(IPr)(NTf_2)]$[8] (**11**), led to almost complete conversion of **10** into the β-isomer, while the use of stoichiometric amounts of **9** led to no reaction. This suggested that an equilibrium exists between **9**, **10**, and **11**. If **11** reacts with diyne **10** in the absence of additives, the α-product is the major one, while if formation of **9** is favored, for example, by the addition of a base that would further react with **11** to form the dual activated intermediate **12**, then the β-isomer is formed.[7a] Attempts to gain insights into the reaction mechanism resulted in the isolation of Au^I–aryl (**13**) and *gem*-diaurated (**14**) species. Catalytic reaction using 5 mol% of **13** afforded only 5 mol% of the β-isomer, owing to protodemetalation by **10** and formation of acetylide **9**. Addition of **11** afforded the desired product in high yields. On the other hand, the use of 2.5 mol% of **14** afforded the β-isomer in high yields even in the absence of additional catalyst. Further investigations revealed that **14** was involved in an equilibrium with **13** and the free catalyst **11** at high temperatures and is the reason the reaction proceeds.[7a] This makes **14** an excellent "off-cycle" or "reservoir" catalyst for this transformation. Therefore, the catalytic cycle proposed for the β-selectivity is as follows: the initial reaction of **11** with **10**, followed by subsequent addition of benzene affords the aryl–gold species **15**; then protodeauration by diyne **10** forms acetylide **9** and starts the β-selective catalytic cycle (Scheme 3).[7a]

This catalytic cycle could be considered as a general scheme for the reactions involving diyne-type substrates described by Hashmi et al.[7] Their recent follow-up communication deals with the role of this *gem*-diaurated species in the synthesis of benzofulvenes and sheds further light on the role of digold species in catalysis.[7c] The Hashmi group has developed an alternative synthetic protocol to that of the Zhang group,[9] identifying and isolating the *gem*-digold species **16** as an excellent, rapidly activated precatalyst for this reaction type.[7c] When **16** was used as the catalyst, the reaction time could be reduced by a factor of 3![7c] In the course of their studies, the first example of a *gem*-diaurated species bearing two different gold centers (**17**) was isolated. This mixed diaurated species was formed by reacting **16** with 1 equiv of the Gagoz triphenylphosphane complex **18** (Scheme 4).[7c,8] Unfortunately, no studies have yet been performed to determine how the presence of two different gold centers might affect reactivity.



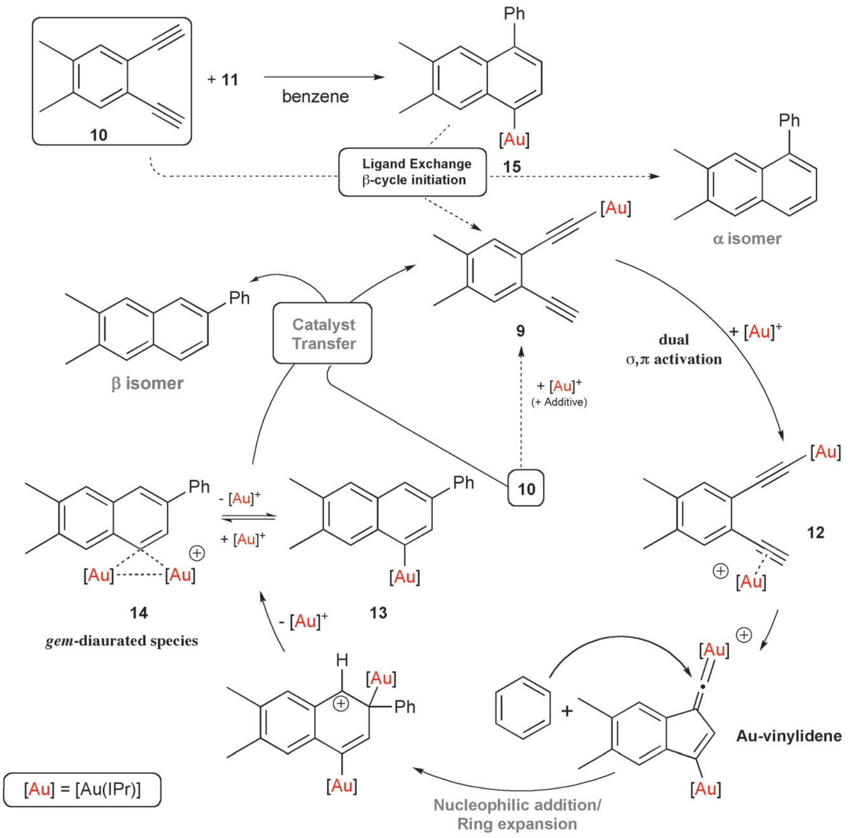
Scheme 4. Mixed *gem*-diaurated species reported by Hashmi et al.



Scheme 5. Synthesis of $[\{Au(PPh_3)\}_2(\mu\text{-aryl})][NTf_2]$ reported by Gray et al.

Recently, Gray and co-workers have reported the first straightforward methodology to obtain aromatic *gem*-diaurated species in high yields under mild conditions.[6g] By reacting 2 equiv of complex **18** with 1 equiv of boronic acid in diethyl ether at 25°C, they were able to isolate several $[\{Au(PPh_3)\}_2(\mu\text{-aryl})][NTf_2]$ complexes (Scheme 5).[6g] Nevertheless, only tentative insight into the reactivity of this exciting type of species has been gained and further studies aiming to expand the scope and to better explain their reactivity are still needed.

We have highlighted key contributions that bring to the fore interesting mechanistic questions in gold catalysis. The role of digold species in many of these transformations cannot be excluded and whenever possible this option should be



Scheme 3. Cataytic cycle prosposed by Hashmi et al.

seriously considered. Much remains to be achieved in gold catalysis to clearly delineate the role of these digold species in the ongoing "gold rush".

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