Gold Catalysis

DOI: 10.1002/anie.200907078

Homogeneous Gold Catalysis Beyond Assumptions and Proposals—Characterized Intermediates

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coordination compounds · gold · organometallic compounds · reaction mechanisms · reactive intermediates

Gold catalysis is a very active area in the field of catalysis research. New reactions are published every week, amazing changes in the connectivity are often observed, the number of applications in total synthesis is increasing …—but what are the mechanisms of these reactions? Sound information can be provided by knowledge about the intermediates of these reactions.

1. Introduction

So far, no homogeneous gold-catalyzed reaction has been reported that could possibly consist of only one elementary reaction, they proceed instead by multistep mechanisms.[1] In almost all of the publications from the field, we find schemes with mechanisms for the reactions, but in most cases these are accompanied by words such as "speculation", "assumption", "conceivable", "suppose", "proposal", "putative", or "rational". Most of these proposed mechanisms are based on either thorough studies of the literature and include analogies to other gold-catalyzed reactions and the mechanisms "proposed" for these or even analogies to reactions catalyzed by other related transition metals.

We must ask what the basis for these suggestions is—where does the experimental evidence end and the speculation start? What do we know about the elementary reactions of gold catalysis on the basis of experiments?

In this Minireview the intermediates identified by *direct* observation and by characterization will be discussed; intermediates suggested only on the basis of *indirect* evidence are excluded.

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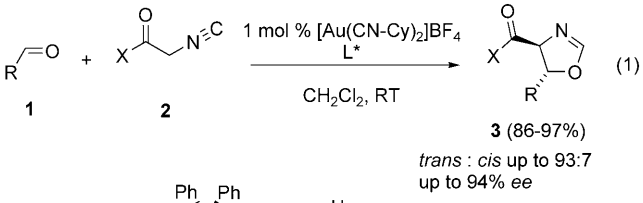
2. Gold Compounds as Intermediates

2.1. Complexes of the Catalyst

While no mechanistic speculations were included in the presumed first paper on homogeneous gold catalysis,[2] a postulate for the intermediate **4** is found in another early example.[3,4] This intermediate, shown in Equation (1), would nicely explain the stereochemical outcome of these enantioselective reactions. However, the catalyst was prepared in situ, and there is no published direct experimental evidence for the tetracoordinated gold complex **1** or a secondary ligand–substrate interaction in these reactions.



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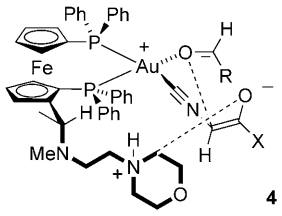
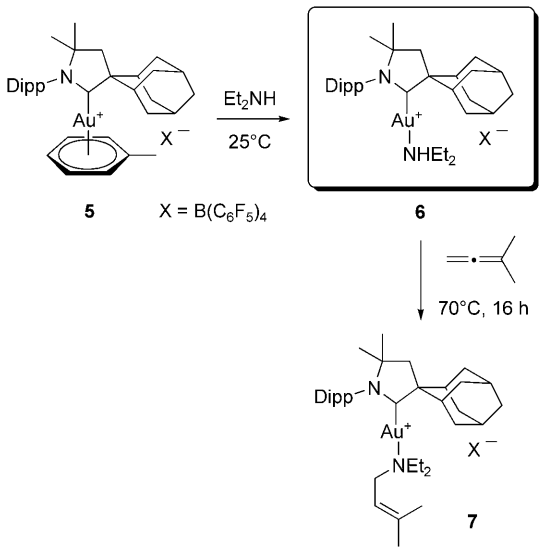


In situ NMR studies confirmed the coordination through the two phosphorus atoms of the ligand, and not the two nitrogen atoms,[5] but did not support a tetracoordinated species. Thus one would have to consider a tricoordinated gold(I) species. This is strongly supported by recent findings in the field of gold(I)-catalyzed hydroamination. When exposed to one equivalent of diethylamine in [D_6]benzene

at room temperature, catalyst **5** delivered the amine complex intermediate **6** in quantitative yield (Scheme 1). On the other hand, **5** does not show any significant interaction with the substrate 1,1-dimethylallene. After 16 h at 70 °C, complex **6** in the presence of an excess of the allene gave complex **7**, which again was isolated in 95% yield and would be formed via a tricoordinated intermediate.[6a] Similar observations were made for ammonia.[6b]



Scheme 1. Conversion of amine complex **6** to **7** via a tricoordinated intermediate. Dipp = di(isopropyl)phenyl.

2.2. Gold Hydrides

Another early conclusion was the low affinity for a β-H elimination reaction,[7] which was assigned to the low stability of gold hydrides.[8,9] While the catalytic experiments[7,10] support this statement, the spectacular recent isolation of the NHC-gold(I) monohydride **9** disproves the general low stability [Eq. (2)].[11]

The reactivity of **9** with regard to typical elementary steps of catalysis reactions has been investigated: normal alkynes such as 1-hexyne and diphenylacetylene do not insert into the

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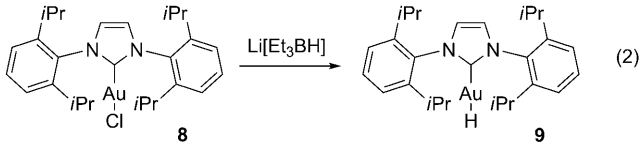
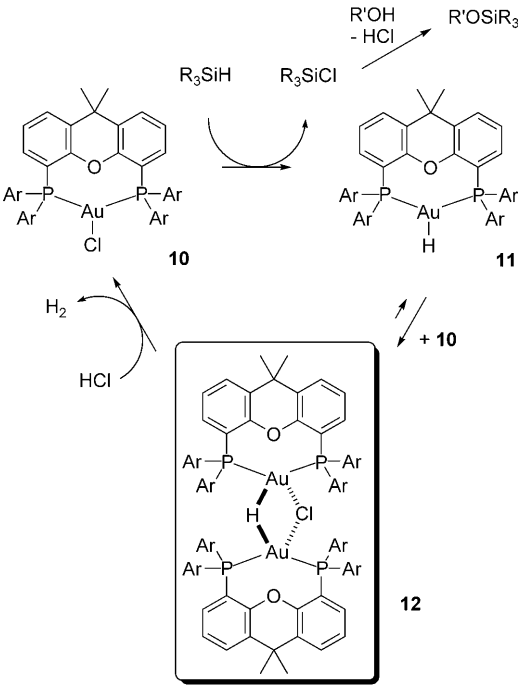


(2)

gold–hydrogen bond, but dimethylacetylenedicarboxylate does. Unexpectedly, a crystal structure analysis showed an *anti* arrangement of the NHC-gold fragment and the hydride; thus neither a radical mechanism nor a *syn* addition/isomerization could be ruled out. In their conclusion, the authors suggest that these results may lead to new opportunities in gold(I) catalysis—in this context one must keep in mind that a) gold(III) monohydrides had already been proposed as intermediates in homogeneous gold-catalyzed hydrogenation reactions, and the reaction pathway was supported by DFT calculations,[12] and b) an active participation of gold(I) hydrides in the dehydrogenative silylation of alcohols was proposed (the reported hydrolysis of **9** would nicely fit that picture).[13] In a more recent study, a gold(I) hydride species **12** was characterized by ^{1}H and ^{31}P NMR measurements and by ESI-MS spectrometry (Scheme 2).[14] NMR spectroscopic and kinetic studies revealed that the reaction mechanism of the dehydrogenative silylation indeed involves the gold(I) hydride species as a key intermediate.

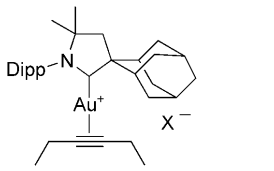


Scheme 2. Gold(I) hydride intermediate **12** in the dehydrogenative silylation of alcohols.

2.3. π Complexes of Unsaturated Substrates

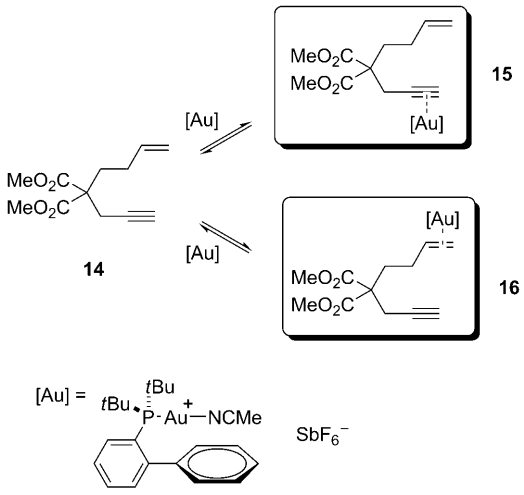
Apart from a few reactions such as these discussed above, most homogeneous gold catalysis reactions are probably initiated by the coordination of C–C multiple bonds to the

gold center. This property of a soft π-philic Lewis acid[1c,k] has been confirmed experimentally with only a few gold complexes of alkynes,[15–17] arenes,[17c] and alkenes,[18] but not yet with allenes. The structural information obtained from these structure analyses is interesting, but again the reactivity is the crucial factor in this context, and only for two of these examples have their intermediacy in catalytic cycles been investigated. An earlier investigation of the addition of water to alkynes at low temperatures detected the presence of different intermediates which showed characteristic ^{1}H and ^{19}F NMR signals; however, since these were always part of complex mixtures, a clear spectroscopic or structural assignment of a specific intermediate was not possible.[17b] Experiments on **13** suggest that ammonia readily substitutes the alkyne and, thus, **13** is not the intermediate in the gold-catalyzed formation of an imine.[6b]



13 X = $B(C_6F_5)_4$

A very important ^{1}H-^{1}H NOESY experiment on the enyne substrate **14** (Scheme 3) carried out at 223 K to avoid a cyclization reaction showed an equilibrium of alkyne (**15**) and



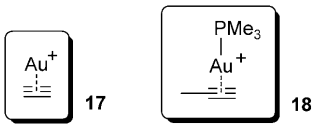
Scheme 3. ^{1}H NMR spectroscopy at low temperatures shows an equilibrium of the two π complexes **15** and **16**.

alkene (**16**) coordination.[17e] There is no exact value mentioned in the publication, but a ratio of the two species (**15** and **16**) close to 1:1 can be deduced from the spectrum shown. Experimentally, the selective addition of nucleophiles such as water to alkynes but not alkenes is thus not based on a preference in the coordination step but on significant differences in the reactivity of these two π complexes.

A neocuproin-gold(I)–styrene adduct could also be detected by in situ ESI-MS studies during the oxidative gold-catalyzed cleavage of alkenes.[19]

2.4. Nucleophilic Attack

The coordination to the gold complex described above activates the C–C multiple bond for the attack of the nucleophile. Two possibilities are conceivable: *syn* and *anti* addition. Early studies on the gold(I)-catalyzed addition of alcohols to alkynes suggested a *syn* addition on the basis of DFT calculations in the gas phase.[20] In this case, the reaction would proceed by an inner-sphere mechanism, the alcohol would become attached to the gold(I)–alkyne complex by an associative mechanism, and then the alcohol and the gold moiety would end up on the same side of the C–C double bond formed in the addition step (in analogy to the hydroamination discussed in Section 2.1, but the amines are much stronger ligands than alcohols or water for gold). On the other hand, subsequent MS studies show that while the gold(I)–alkyne complexes **17** and **18** are easily formed, the nucleophilic addition in the gas phase proceeds at a rate much too low to explain the efficient conversion in solution.[21]



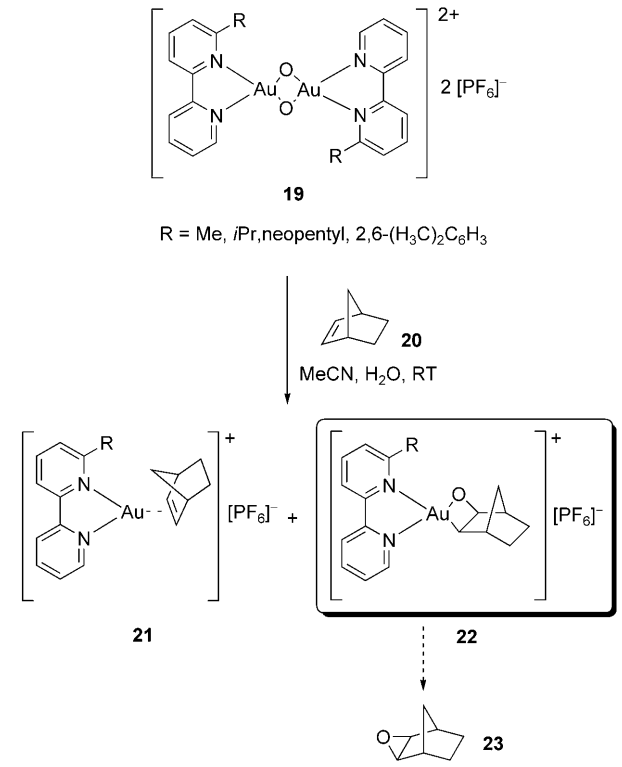
Furthermore, it is quite possible, that the *syn* addition is an artefact of the gas-phase calculation. It is quite clear that the most stable point for attachment of the nucleophile in the gas phase is close to the positively charged gold center. However, this does not necessarily mean that the barrier of activation for a reaction in a solvent composed, for example, of nucleophilic molecules, is lower for the *syn* addition than for the *anti* addition of the same nucleophiles (which in the solution are also present at the back side of the triple bond).

Besides Ref. [6a], there are only a few reports[22] in the literature that suggest a *syn* addition of a gold center and an amine nucleophile to an allene, but the observed stereochemical outcome of the reaction can only be explained in those studies if a subsequent isomerization of a double bond in the intermediate vinylgold species was involved. More straightforward than such a two-step *syn* addition/double-bond isomerization would be a direct *anti* addition, which the authors did not exclude.

Recent results obtained by computational studies on the reaction of oxygen nucleophiles described by Teles et al.[20a] suggest that even a small cluster of six water or alcohol molecules (mimicking the solvent) makes the *anti* addition the more efficient process.[23]

The only proof for the feasibility of a *syn* oxyauration originates from stoichiometric organogold chemistry. The reaction of the bridged gold(III)–oxo complex **19** with

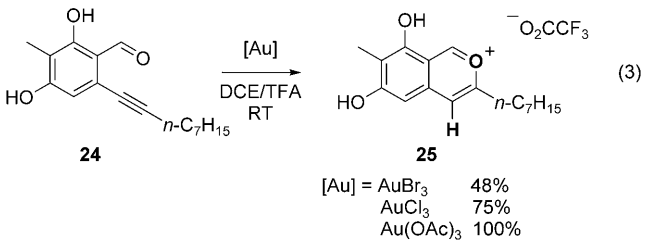
norbornene (**20**) delivers the stable (!) auraoxetane **22**, which has even been characterized by an X-ray crystal-structure analysis (Scheme 4).[24] However, one has to keep in mind that



Scheme 4. Auraoxetane **22** is accessible from the dinuclear gold(III) complex **19** and norbornene.

the oxygen and gold atoms are already tightly connected in the starting material and that norbornene is a very special olefin, which is activated by ring strain and offers only one π face for reactions (the *endo* face is sterically inaccessible). Thus, one would expect to observe a *syn* addition with norbornene if the energy of activation is not too high for that process.

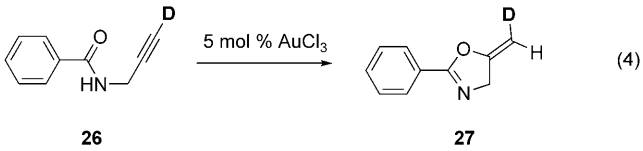
In fact, all experimental evidence from other systems points towards an *anti* addition. This is true for both oxidation states of the precatalysts. In the case of gold(III), there is an example of the formation of benzopyrylium salts **25** which can only proceed by an *anti* addition [Eq. (3)].[25] The products **25** are protonated analogues of intermediates of gold-catalyzed conversions of *o*-alkynylbenzaldehydes.[26]



(3)

Similar results that indicate an *anti* addition were obtained for the hydroarylation of electron-deficient alkynes in both intra- and intermolecular cases, which included deuterium-labeling and cross-over experiments.[27] These results do not rule out an equilibration after a *syn* addition, thereby leading to the thermodynamically more stable *E* diastereoisomer in the acyclic case. Similar results were reported for the gold-catalyzed cyclizations of substituted (*Z*)-2-en-4-yn-1-ols.[28] Only for the hydroarylation of internal alkynes were mixtures reported, but still the *anti*-addition product dominated (d.r. values between 100:0 and 70:30).[17a]

The crucial experiment, which excludes such a subsequent thermodynamic equilibration, is the use of a deuterium-labeled terminal alkyne—the deuterium allows a *syn* from an *anti* addition to be distinguished, but there is no siginificant difference in the thermodynamic stability of the two conceivable diastereomers. In the studies of oxazole synthesis, this case could be investigated for both gold(III) [**26**, Eq. (4)] and gold(I) intermediates [**28**, Eq. (5)], and clear proof for an exclusive *anti* addition was obtained for this reaction—an *anti* oxyauration.[29]



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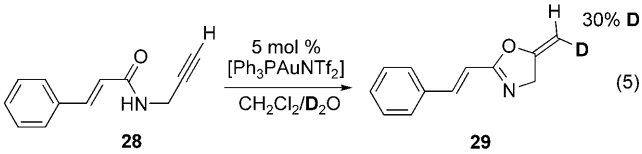

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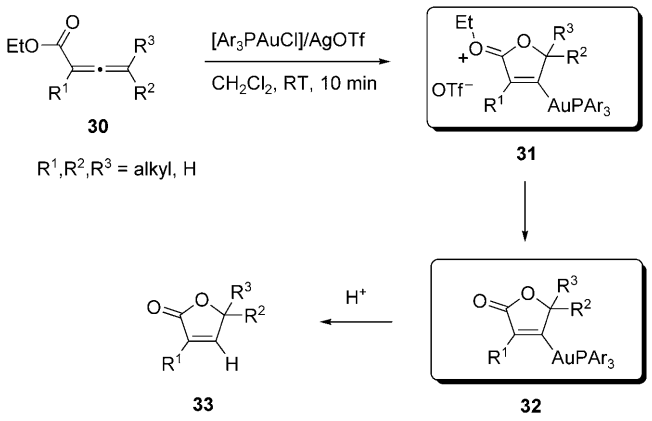
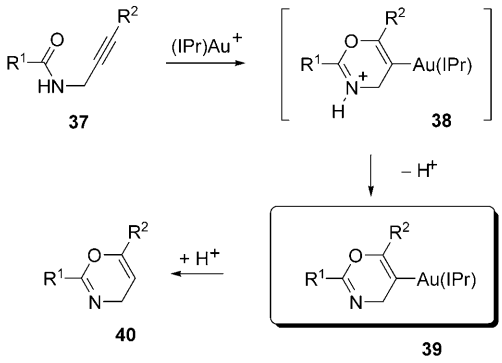
Many more similar observations have been reported for gold(I): deuterium labeling in the conia-ene reaction,[30] the cyclization of substituted acetylenic acids to unsaturated lactones,[31] the intramolecular hydroamination of allenes (the relative configuration of the newly formed stereocenter and double-bond geometry suggest an *anti* addition),[32] the cyclization of propargylic carbonates (double-bond geometry of the product when starting from a propargylic carbonate with deuterium or an iodo substitutent on the alkyne),[33] and the intermolecular addition of alcohols to allenes (again by the relative configuration of the newly formed stereocenter and the double-bond geometry).[34]

The isolation and characterization of vinylgold intermediates formed in the nucleophilic addition step has been reported since the end of 2008. The first contribution was based on the reaction of allenic esters **30**, which were found not to convert well with gold complexes in a catalytic manner (Scheme 5). This is due to a simple reason—the corresponding vinylgold species **32** is so stable to the subsequent protodeauration step that catalysis becomes inefficient. This allowed the isolation of **32** from stoichiometric reactions on a preparative scale and its characterization even by X-ray



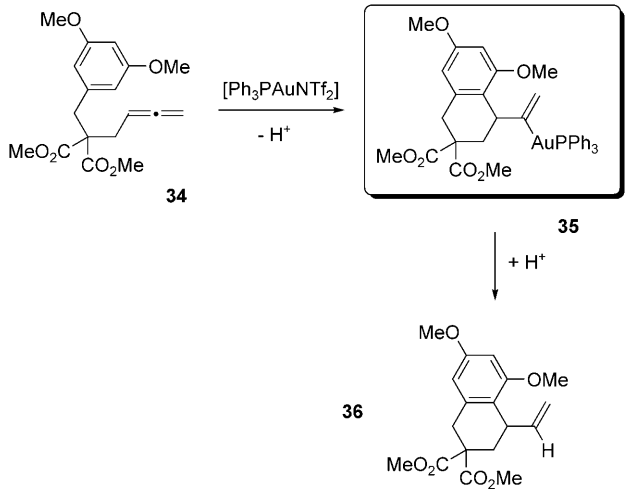
Scheme 5. The vinylgold(I) complexes **32** derived from allenic esters **30** are stable. Tf = trifluoromethanesulfonyl.



Scheme 7. Stable vinylgold(I) complexes **39** could be isolated from propargylamides **37**. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

crystal-structure analysis.[35] In a subsequent publication, even the identification of the oxonium intermediate **31** by ^{1}H NMR and ^{31}P NMR spectroscopy was described.[36]

The second report on these organogold intermediates is also based on allenes: intermediate **35** could be isolated in the intramolecular hydroarylation of allenes **34** (Scheme 6). Once



Scheme 6. The vinylgold(I) complex **35** was isolated from intramolecular hydroarylations of allenes.

more, a crystal-structure analysis confirmed the structure of **35** unambiguously. This investigation is remarkable, as experimental evidence for intermediates with two gold atoms as potential (previously unrecognized) resting states was also obtained. Proof of the involvement of this species in the catalysis still has to be delivered.[37]

Subsequent to these two reactions, which are based on phosphanegold(I) complexes and allenes, a general route to vinylgold complexes based on NHC-gold(I) complexes and alkynes was reported: Several vinylgold(I) compounds **39** were isolated on a preparative scale (Scheme 7), in one case an X-ray crystal-structure analysis was carried out. The two sp^2-hybridized carbon atoms attached to the gold center are at almost identical distances from the gold.[38] The key to success is the use of triethylamine as an external base, which traps the proton that would otherwise protodeaurate this intermediate to deliver the catalysis products **40**. Complexes **39** were catalytically active again when re-subjected to the substrate in the presence of protons.

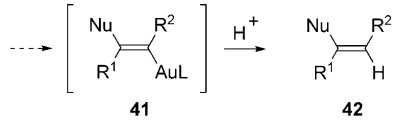
This isolation is dependent on the NHC ligand (the intermediates could be characterized by in situ spectroscopy but not isolated with phosphane ligands), and is also dependent on the use of internal alkynes **37** ($R^2 \neq H$); in the presence of the base, the corresponding terminal alkynes (such as **26** and **28**) always give the known gold(I) acetylide complexes (without base, the five-membered oxazole ring is formed).[39]

Overall, an outer-sphere mechanism (*anti* addition) has been proven experimentally for weakly coordinating nucleophiles and for cyclization reactions; an inner-sphere mechanism (*syn* addition) can be assumed in some cases only when there are strongly coordinating nucleophiles.

2.5. Protodeauration

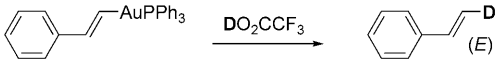
The next step after the addition of the nucleophile is typically protodeauration. The results described above for the nucleophilic addition simultaneously suggest that the protodeauration proceeds stereoselectively and without change of the steric arrangement of the subsitutents at the double bond—the proton in **42** is at the position where the gold was in **41** (Scheme 8).

A *syn* addition and a subsequent inversion of the double-bond configuration in the protodeauration can be ruled out by the following experiment: The stereoselective deauration was



Scheme 8. Stereospecific protodeauration is observed with substrates **41**.

proven experimentally in the reaction of the (*E*)-styrylgold(I) compound **43**, where the (*E*)-deuterostyrene **44** was formed [Eq. (6)].[40] Since, once more, a deuterium and a hydrogen atom occupy the end of the double bond, a subsequent thermodynamic equilibration can also be excluded in this example.



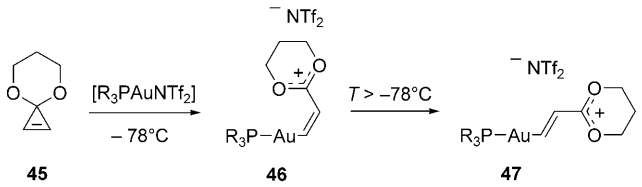
43 **44** (6)

Other examples of trapping the intermediate with retention of the arrangement of the substituents at the double bond were reported with *N*-iodosuccinimide (NIS)[41] (no direct reaction of the substrate occurs with NIS[41a]) and I_2[36] as the electrophiles.

2.6. Gold Carbenoids

For many reactions in the field of homogeneous gold catalysis, gold carbenoids have been assumed to be intermediates, for example, in cyclopropanation reactions.[1] There is evidence that the electronic structure of certain intermediates is that of a stabilized carbocation rather than a carbene.[42]

Related gold carbenoids **46**/**47** could now be prepared starting from cyclopropenone acetals such as **45** (Scheme 9). They are stable in solution and they could be studied by in situ

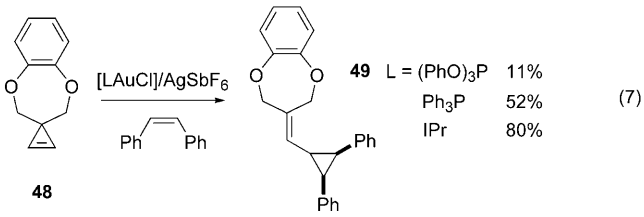


45 **46** **47**

Scheme 9. The organogold(I) complexes **46**/**47**, as analogues of intermediates of gold-catalyzed reactions, are accessible from cyclopropenes **45**.

NMR spectroscopy. The data would best be explained by the depicted oxocarbenium cation.[43] However, we have to keep in mind that **46**/**47** are just organometallic complexes, they have not been shown to undergo any of the reactions known from gold catalysis, and no substrate used in gold catalysis has two such oxygen atoms as donors.

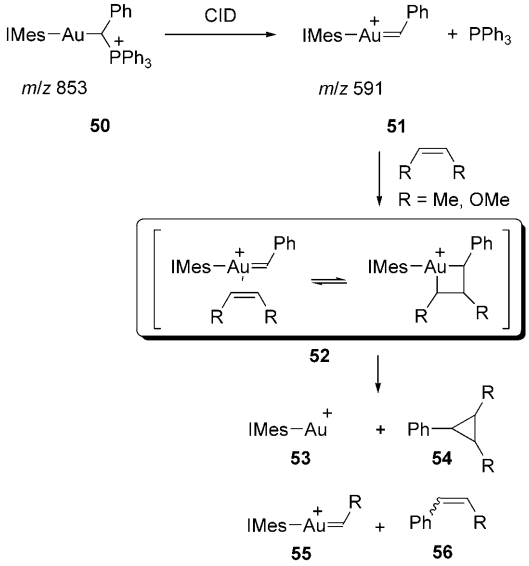
Exactly this issue was addressed in another recent investigation.[44] The authors could show that if there are weaker donating groups on the carbenoid, as in the case of the starting material **48** [Eq. (7)], the cyclopropanating properties return, and the efficiency of the cyclopropanation reaction is also directed by the donor strength of the ligand on the gold catalyst (with increasing diastereoselectivity for the depicted *cis* diastereomer of **49**). The experimental findings were in good agreement with calculations.



48 **49** L = $(PhO)_3P$ 11%, Ph_3P 52%, IPr 80% (7)

Thus, depending on the substrate and the ligand, as with the other transition metals, a continuum of intermediates ranging from gold-stabilized carbenes to gold-coordinated carbocations can be involved.

All this was determined by a gas-phase study. Starting from the precursor **50**, the gold carbenoid **51** was generated in a mass spectrometer (Scheme 10).[45] The signal at *m*/*z* 591 gives only the elemental composition, not the structure or even electronic structure of the species; the latter was addressed by reactions in the mass spectrometer: cyclopropanation (detection of **53**) and cross-metathesis (detection of **55**) was observed with both (*Z*)-2-butene and (*Z*)-1,2-dimethoxyethene.



Scheme 10. The gold(I)–carbene complex **51** undergoes both cyclopropanation and cross-metathesis with olefins. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

The authors also detected the intermediate signal of the adduct of **51** with the substrate (**52**, structurally a tricoordinated complex and/or an auracyclobutane). These reactions are the first reports on the metathesis activity of gold carbenoids.

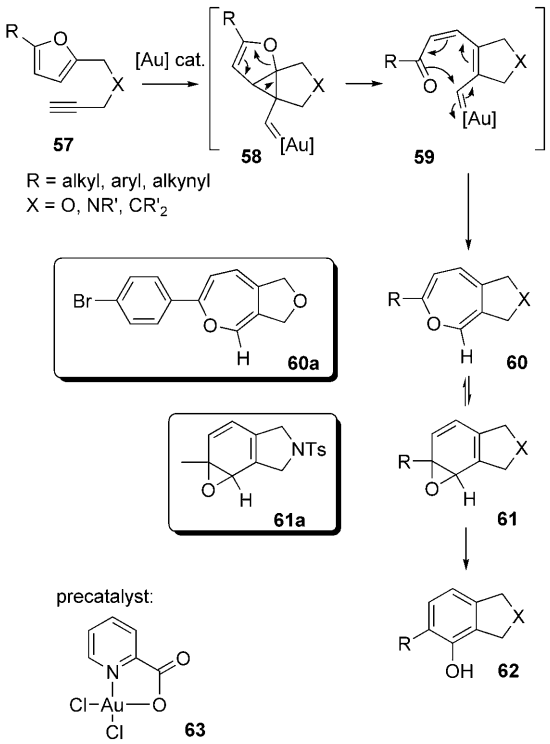
3. Organic Intermediates in Gold-Catalyzed Reactions

The first intermediates observed in gold catalysis were not complexes or organometallic compounds as described in the

previous section. In the early studies, researchers were glad if they could observe any intermediate of the reaction experimentally, even if no gold was contained in that intermediate.

3.1. Arene Oxides and Oxepines

One of the first new reactions described in gold catalysis was the gold-catalyzed synthesis of phenol.[46] The reaction has a complex mechanism, with four bonds of the substrate **57** broken and four new bonds formed in the product **62** (Scheme 11). In a subsequent investigation of the mechanism,

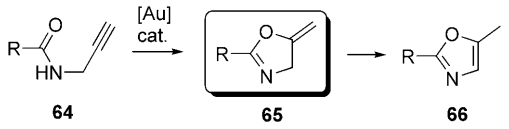


Scheme 11. Oxepines **60** and arene oxides **61** as detectable intermediates in the gold-catalyzed synthesis of phenol. Ts = toluene-4-sulfonyl.

two different intermediates could be characterized by in situ NMR spectroscopy when using a special ligand on the gold catalyst (precatalyst **63**): the arene oxide **61a**[47] (which could also be trapped by a Diels–Alder reaction, an X-ray crystal-structure analysis of the adduct was obtained), and the oxepine **60a** (even deuterium-labeling experiments could be carried out).[48] The whole arsenal of one- and two-dimensional NMR spectroscopy was available for the structural assignment since these intermediates could be accumulated in up to 80% in the reaction mixtures and the solutions were stable for weeks when cooled to −20 °C.

3.2. Alkylidene Oxazolines

The gold-catalyzed conversion of *N*-propargylcarboxamides **64** is a mild route to oxazoles **66** (Scheme 12). Initially,



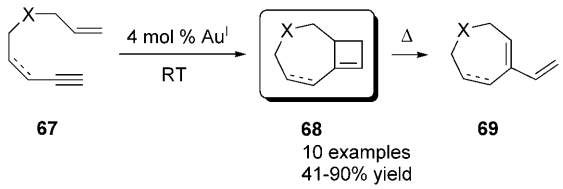
Scheme 12. Alkylideneoxazolines **65** as detectable intermediates in the gold-catalyzed synthesis of oxazoles.

gold(III) catalysts were used, and in situ NMR spectroscopic studies showed the alkylidene oxazolines **65** to be intermediates in the conversion.[29] The intermediates become enriched up to 95%. Similar observations were made recently when gold(III) iminophosphorane complexes were used as catalysts.[49]

It was recognized that the reaction conditions used with gold(I) catalysts are mild enough to selectively stop the conversion at the stage of **65**.[50] The suggestion of allenic intermediates (generated by an initial isomerization) as precursors to **65** was made,[51] but was disproved by in situ ^{1}H and ^{13}C NMR investigations.[52]

3.3. Cyclobutenes

The formation of cyclobutene intermediates is one possible pathway in the reaction of enynes. These usually quickly open by an electrocyclic ring opening to deliver 1,3-dienes, the products of an enyne metathesis, but they can be isolated when they are annelated to medium-sized rings as in **68** (Scheme 13).[53]

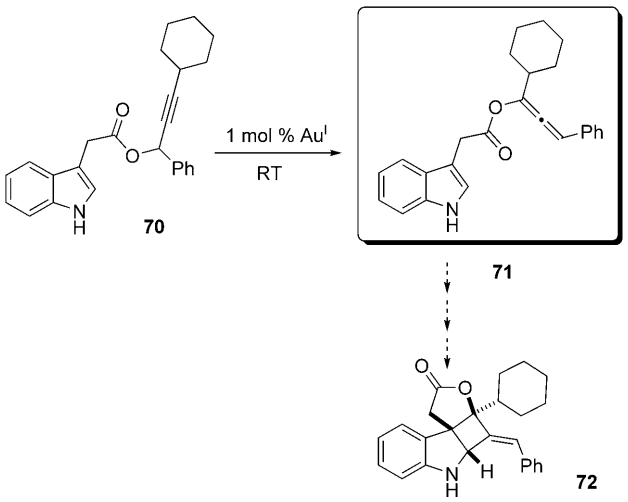


Scheme 13. Cyclobutene intermediates **68** in enyne-metathesis reactions can be stable.

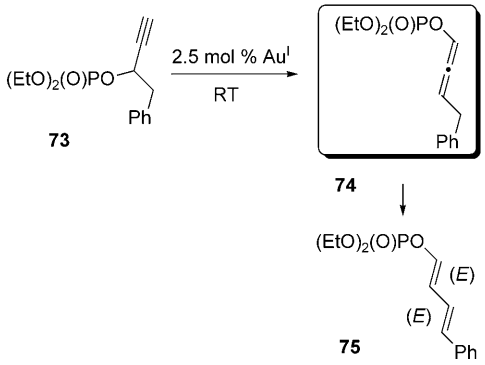
3.4. Allenic Esters

The isomerization of propargylic esters is a field with many reaction options. In one example, the [3,3] rearrangement to give the allene ester could be proven by the direct observation of the allenic ester intermediate **71** (Scheme 14) in the ^{1}H NMR spectrum.[54]

Careful monitoring of the related gold-mediated rearrangements of propargylic phosphate **73** by ^{1}H NMR spectroscopy and GC-MS at low conversions showed that allene **74** was formed as the intermediate, which was then isomerized to the (1*E*,3*E*)-diene **75** (Scheme 15). In addition, independently prepared **74** was also quantitatively transformed to the product by the catalyst.[55]



Scheme 14. Detectable allenic ester intermediates **71** in the conversion of propargyl esters **70** into the polycyclic **72**.



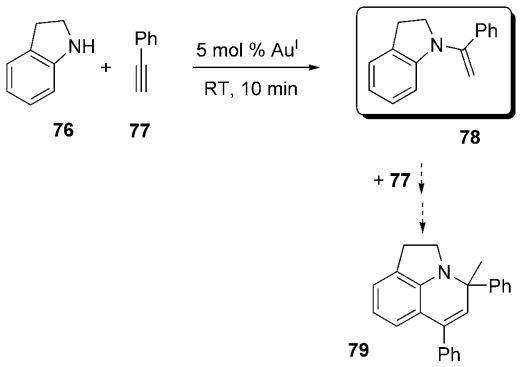
Scheme 15. The allenic phosphate **74** could be detected in the isomerization of the propargylic substrate **73** to the 1,3-diene **75**.

3.5. Enamines

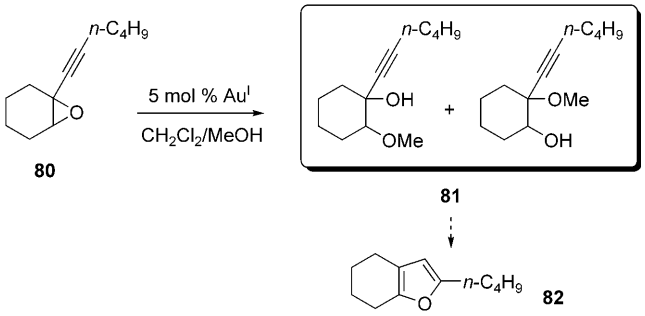
The formation of the enamine intermediate **78** was detected after 10 minutes at room temperature by ^{1}H NMR spectroscopy in a gold-catalyzed tandem hydroamination/hydroarylation reaction of **76** with two equivalents of **77**. The intermediate was completely converted into the annelated product **79** after 17 h (Scheme 16).[56]

3.6. Isomerization of Alkynylepoxides

The isomerization of alkynyl epoxide **80** to the furan **82** was assumed to proceed by the direct nucleophilic attack of the epoxide oxygen atom on the activated alkyne (Scheme 17).[57] However, a mechanistic investigation revealed that a cascade involving a nucleophilic opening of the oxirane ring and a subsequent ring closure occur (in the absence of the nucleophile, in this case methanol, the reaction did not occur). Signals corresponding to the addition products **81** appeared in the ^{1}H NMR spectra recorded at −60 °C, while the formation of the furan product was detected at −20 °C.[58]



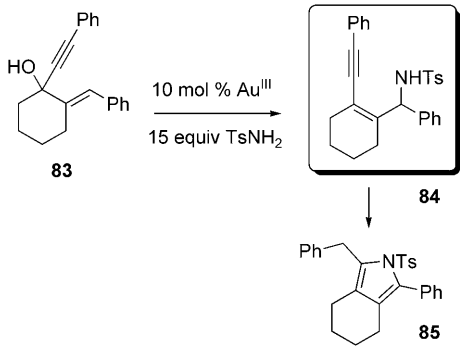
Scheme 16. Detection of the hydroamination intermediate **78** in the formation of the mixed trimer **79**.



Scheme 17. Low-temperature studies reveal the intermediacy of **81** in the isomerization of **80** to the aromatic furan **82**.

3.7. Yne-Allylamines

A new route to pyrroles is the gold-catalyzed tandem amination/hydroamination. The intermediate yne-allylamine **84** could be isolated in 73% yield (and already 18% of the final product) after only one hour from the reaction of **83**; after another six hours, **84** was completely converted into the pyrrole **85** (Scheme 18).[59]



Scheme 18. The intermediate allylamine **84** could be isolated from the conversion of **83** into pyrrole **85** after a short reaction time.

4. Summary and Outlook

While *indirect* evidence and computational chemistry tried to provide detailed insight into the mechanism during

the initial mechanistic investigations, *direct* evidence—the isolation or in situ detection of the intermediate itself (rather than a stable compound derived from it)—has become increasingly successful in the recent past. The unproblematic spectroscopic properties of the gold complexes involved will probably lead to a sharp increase in the application of all the possible spectroscopic methods for the in situ study of gold-catalyzed reactions. Furthermore, the more sophisticated ligands that are now available will allow the selective stabilization of intermediates, which will allow their electronic structure to be studied in detail, and which ultimately will lead to a more accurate insight into substrate scope, selectivity, and reactivity.

A.S.K.H. is greatful to the DFG (SFB 623) and Umicore AG & Co. KG for their continuous support in the field of homogeneous gold catalysis.

Received: December 15, 2009
Published online: June 22, 2010

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