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The golden gate to catalysis

Anja Hoffmann-Röder[a] **and Norbert Krause***[b]
[a] *ETH Zürich, Laboratorium für Organische Chemie, ETH-Hönggerberg, CH-8093, Zürich, Switzerland*
[b] *University of Dortmund, Organic Chemistry II, D-44221, Dortmund, Germany. E-mail: norbert.krause@uni-dortmund.de; Fax: +49-231-755-3884*

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The use of gold in homogeneous catalysis is a relatively new field of transition metal catalysis, but has already witnessed spectacular achievements. By virtue of their unique ability to activate carbon–carbon double and triple bonds as soft, carbophilic Lewis acids, gold salts are highly efficient catalysts for the formation of C–C, C–O, C–N, and C–S bonds. Moreover, they are capable of activating C–H bonds of aromatic and other substrates, opening unprecedented pathways for their functionalisation. By using chiral allenes as substrates, gold catalysts can even be applied in stereoselective target-oriented synthesis.

Introduction

Gold belongs to the metals that have been known since ancient times, its discovery dating back at least to 5000 BC. It is also the object of many misconceptions. For example, gold is certainly a rare element, but it is more abundant than palladium, platinum, rhodium and many other precious metals. Besides, gold is certainly inert, but is far from being chemically useless. Applications of gold and gold salts in heterogeneous catalysis evolved at the beginning of the last century, and nowadays they belong to the most active catalysts for such diverse reactions as the low temperature oxidation of carbon monoxide and the hydrochlorination of ethyne.[1] Moreover, in the last five years, the benefits of gold as a homogeneous catalyst for the synthesis of fine chemicals have emerged in a spectacular fashion.[2] The major virtue of gold salts in homogeneous catalysis is their unique ability to active C–C multiple bonds as soft, carbophilic Lewis acids, allowing for the formation of new C–C, C–O, C–N, and C–S bonds by nucleophilic attack at these activated substrates. Furthermore, gold is an excellent catalyst for the activation of C–H bonds, *e.g.*, of aromatic compounds, thereby again opening an unprecedented pathway for carbon–carbon bond formation. Occasionally, gold salts of both stable oxidation states – Au(I) and Au(III) – are capable of catalysing the same transformation, and very often it is not clear what the oxidation state of the catalytically active species might be. Also, gold compounds are easily reduced, but hard to oxidise, and do not tend to undergo β-hydride eliminations, which nicely complements the classical metals used for transition metal catalysis (palladium, platinum, *etc.*).

In this account, we present our personal selection among recent examples[2] on the use of gold in homogeneous catalysis, emphasising applications in target-oriented and stereoselective synthesis, as well as possible reaction mechanisms.

C–H bond activation

Gold(I) and gold(III) salts are able to activate C–H bonds of terminal alkynes, arenes, and β-dicarbonyl compounds, thus forming nucleophiles which can react with various electrophiles. The latter can also be activated by the Lewis-acidic gold catalyst which therefore might play a dual role in these transformations.[2] A typical example is the hydroarylation of alkynes reported by

Anja Hoffmann-Röder obtained her PhD degree in 2003 at Dortmund University on stereoselective syntheses with copper, silver, and gold. She is currently an Emmy-Noether fellow (sponsored by the Deutsche Forschungsgemeinschaft) in the group of F. Diederich (ETH Zürich, Switzerland). Her studies and research activities were recognised through stipends of the Studienstiftung des Deutschen Volkes, the Fritz-ter-Meer foundation, and the Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie, as well as through the "Heinrich-Hörlein-Gedächtnispreis" and a "DSM Award for Chemistry and Technology 2003".

Anja Hoffmann-Röder

Norbert Krause

Norbert Krause obtained his PhD degree in 1986 at the Technical University of Braunschweig and was postdoctoral fellow at the ETH Zürich (Switzerland) and Yale University (New Haven, USA). He obtained his habilitation for organic chemistry at the Technical University of Darmstadt in 1993, became Associate Professor at Bonn University in 1994 and Full Professor at Dortmund University in 1998. His research on organometallic and allene chemistry has been recognised through the award of the "Heinz-Maier-Leibnitz-Preis" (1991), a Heisenberg scholarship (1994), and a "Japan Society for the Promotion of Science (JSPS) Fellowship" (2003).

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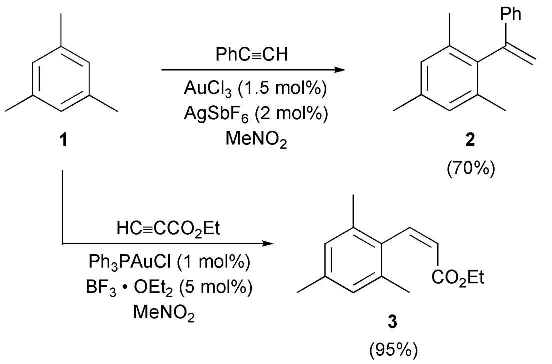
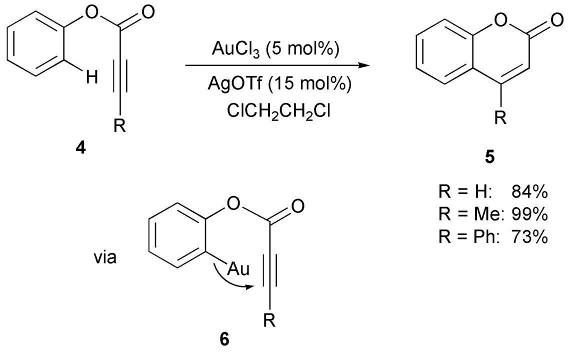
Reetz and Sommer[3] (Scheme 1); whereas gold(III) chloride is the most active precatalyst for the reaction of mesitylene (**1**) and other benzene derivatives with electron-rich acetylenes, the gold(I) complex Ph_3PAuCl is preferable for the hydroarylation of electron-poor alkynes. In both cases, the presence of silver salts or boron trifluoride etherate as a co-catalyst is required in order to achieve good yields, probably by inducing cationisation of the gold precatalyst.



Scheme 1

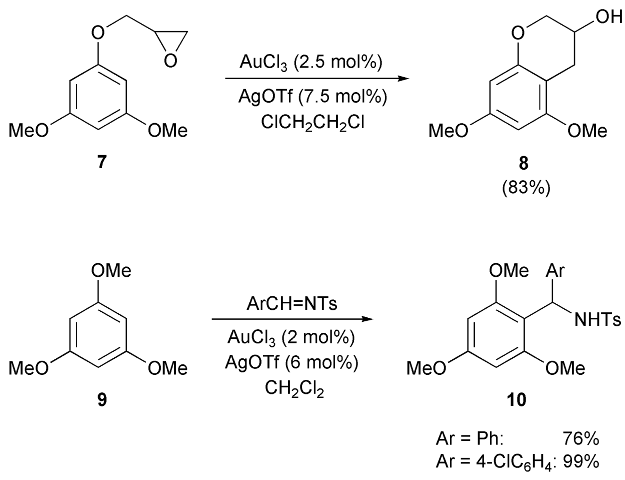
Interestingly, phenylacetylene and other terminal, electron-rich alkynes provide 1,1-disubstituted olefins of the type **2** exclusively, whereas the inverse regioselectivity in favour of product **3** is observed for ethyl propiolate. Although these authors doubt the involvement of arene auration as part of the hydroarylation process, spectroscopic and isotope labelling experiments carried out by Shi and He[4] indicate the presence of an arenegold intermediate of the type **6**, and the addition to the alkyne could be aided by Lewis acid-activation of the triple bond (*cf.* following Section). In addition, intramolecular hydroarylations of substrates of the type **4**, catalysed by $AuCl_3$ and AgOTf, leading to coumarins **5** have been reported (Scheme 2).



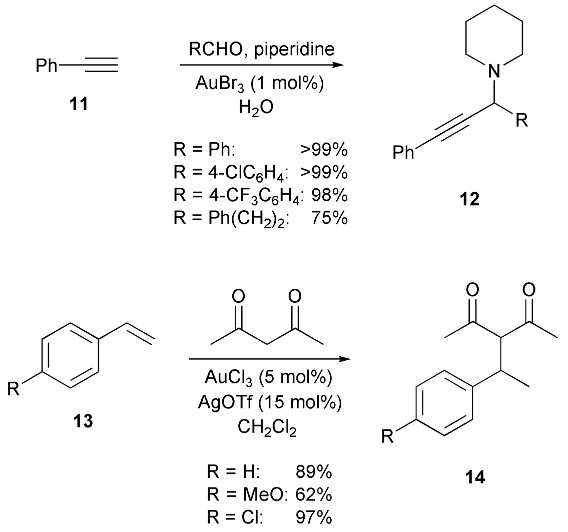
Scheme 2

Besides substituted benzenes, indoles also undergo gold-catalysed C–H bond activation with subsequent addition of the aurated heterocycles to enones.[5] Moreover, imines and oxiranes can be used instead of alkenes and alkynes as reaction partners for the arenegold intermediates (Scheme 3). Thus, treatment of (phenoxymethyl)oxiranes (*e.g.*, **7**) with gold(III) chloride and silver triflate induced a cycloalkylation to give 3-chromanols of the type **8**,[6] whereas benzylamines **10** are formed under the same conditions by addition of arenes **9** to imines.[7] Again, the gold catalyst might also act as a Lewis-acidic activator of the electrophile.

Further examples involving the C–H bond activation of substrates other than arenes were recently reported by Li and coworkers[8] (Scheme 4). Thus, the three-component coupling of an aldehyde, a secondary amine and a terminal alkyne **11** to furnish propargylamines **12** proved to be equally well catalysed by gold(I) and gold(III) halides in water, indicating that Au(I) is the catalytically active species even if a gold(III) salt is used as the precatalyst. In contrast to this, the well-established bimetallic system $AuCl_3/AgOTf$ was found to efficiently promote the regioselective addition of various β-diketones to styrenes **13**, leading to 1,1-disubstituted ethanes of the type **14** in good to excellent yield.[9]



Scheme 3

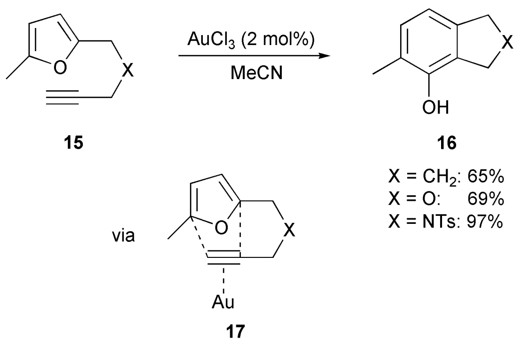


Scheme 4

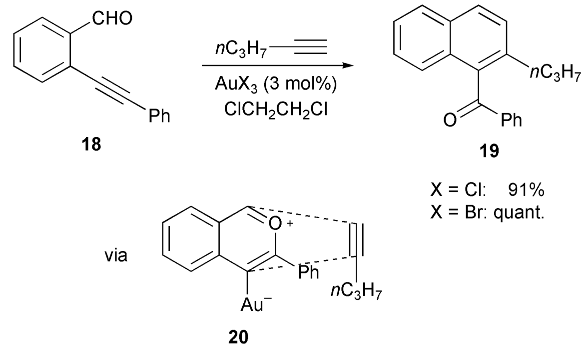
Activation of alkynes

The activation of alkynes with carbophilic, Lewis-acidic gold salts is the most widespread application of homogeneous gold catalysis, and it is very often utilised for the preparation of aromatic, as well as heterocyclic, target molecules. For example, Hashmi *et al.*[10] have shown that various furans **15** can be isomerised to phenols **16** in the presence of catalytic amounts of gold(III) chloride in acetonitrile (Scheme 5). The reaction is probably initiated by coordination of the gold catalyst to the triple bond to give intermediate **17**, thus providing by electrophilic activation the driving force required for an intramolecular Diels–Alder reaction and subsequent C–O bond cleavage.[10,11] Among several applications of this method,[11] the synthesis of the sesquiterpenes junganiol and *epi*-junganiol should be noted.

A related benzannulation process was recently reported by Asao, Yamamoto and coworkers[12] who transformed 2-alkynylbenzaldehydes **18** into naphthalene derivatives **19** by gold-catalysed intermolecular [4 + 2]-cycloaddition with an alkyne (Scheme 6). Again, activation of the triple bond of the substrate **18** by the gold catalyst is believed to be essential for the subsequent intramolecular attack of the aldehyde oxygen



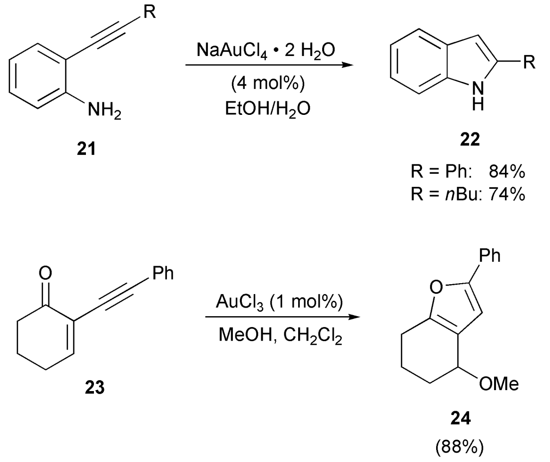
Scheme 5



Scheme 6

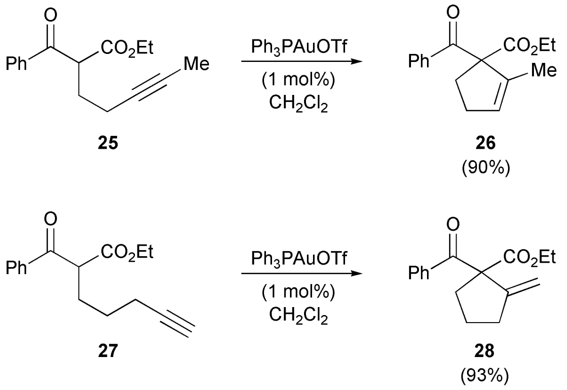
atom; the zwitterionic intermediate **20** thus formed may then act as the diene component in a Diels–Alder reaction with the external alkyne. Interestingly, $AuBr_3$ is slightly more efficient than $AuCl_3$ in this transformation. The authors also reported several variations of the method, including the use of enols as the dienophile in the cycloaddition.[13]

The gold-mediated activation of alkynes is also very prolific for the synthesis of heterocycles (Scheme 7). For example, Arcadi *et al.*[14] have reported several examples for the gold-catalysed preparation of *N*-heterocycles, including the cycloisomerisation of 2-alkynylanilines **21** to indoles **22**. Here, sodium tetrachloroaurate and gold(I) chloride are much more effective than palladium, platinum, and copper precatalysts. A gold-catalysed nucleophilic addition/cyclisation sequence of 2-alkynyl-2-enones (*e.g.*, **23**) to furans of the type **24** was recently reported by Larock and coworkers.[15,16] Although it is not yet clear whether this transformation proceeds *via* a Michael addition and subsequent cyclisation or *vice versa*, the electrophilic activation of the triple bond by the carbophilic gold catalyst seems to be the crucial step, once again. Gratifyingly, many different, highly functionalised enones and nucleophiles can be employed in this process, including carbon nucleophiles like *N*,*N*-dimethylaniline or indole.



Scheme 7

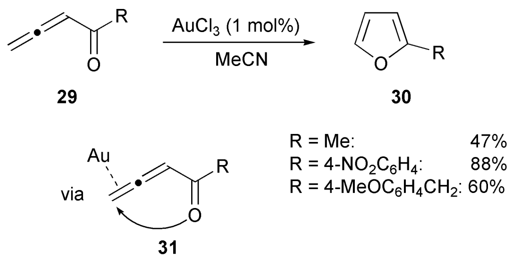
Gold(I) complexes are also the catalysts of choice for carbocyclisation reactions of alkynes (Scheme 8). Thus, treatment of the acetylenic β-ketoester **25** with catalytic amounts of Ph_3PAuCl induced a 5-*endo-dig* cyclisation to the cyclopentene derivative **26**, whereas the isomeric substrate **27** furnished the 5-*exo-dig* cyclisation product **28**.[17] Isotopic labelling experiments again favour a mechanistic model involving activation of the triple bond by the Lewis-acidic gold catalyst. In a similar fashion, gold(I) salts catalyse the carbocyclisation of enynes to cyclopentenes or bicyclo[3.1.0]hexanes.[18]



Scheme 8

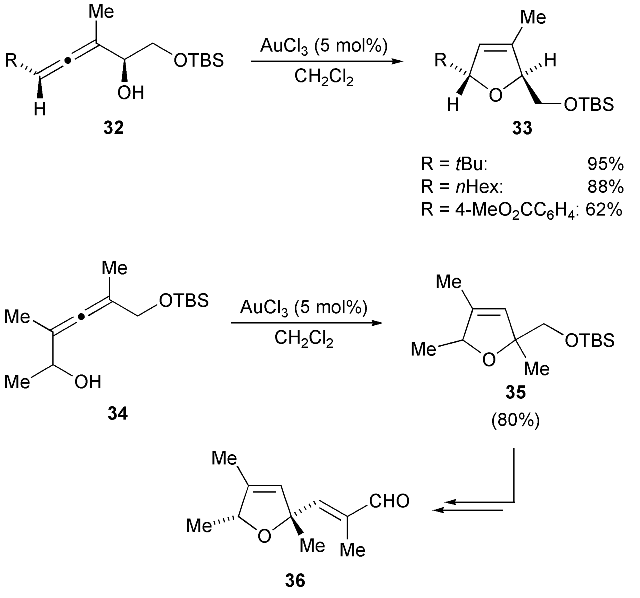
Activation of allenes

The activation of allenes is a rather new, but particularly promising area of gold catalysis. The first example for such a transformation is the cycloisomerisation of allenic ketones **29** to furans **30** which probably occurs *via* intermediate **31** (Scheme 9). Hashmi *et al.*[19] could show that this reaction proceeds much faster when gold(III) chloride in acetonitrile is employed as the precatalyst instead of the traditionally used silver salts. The products are usually contaminated by substituted furans originating from a Michael addition of aurated **30** to the substrates **29**, thereby indicating that gold(III) chloride is also capable of activating C–H bonds of furans (see above).



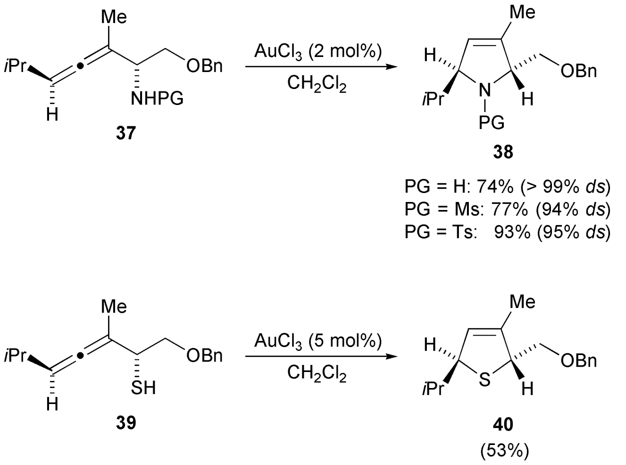
Scheme 9

As for most applications of homogeneous gold catalysis described so far, this reaction provides achiral products and therefore does not take advantage of the inherent chirality of the substrate. However, the use of chiral allenes has recently opened a third dimension to gold catalysis, *e.g.*, by employing α-hydroxyallenes **32** as substrates for the gold-catalysed cycloisomerisation to 2,5-dihydrofurans **33** (Scheme 10).[20] Similar to the corresponding cyclisation of allenic ketones **29**, the use of the gold catalyst results in much higher reaction rates than those achievable with silver salts. Since this transformation takes place with complete axis-to-center chirality transfer, it is ideally suited for application in target-oriented stereoselective synthesis. For example, the gold chloride-catalysed cycloisomerisation of the α-hydroxyallene **34** readily provides the dihydrofuran **35** which can be converted into citreoviral (**36**), a metabolite and synthetic precursor of the mycotoxin citreoviridin.[20]



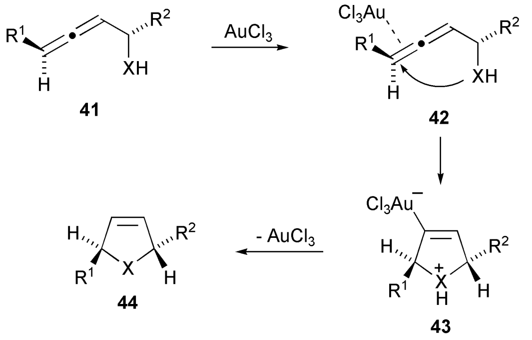
Scheme 10

Gratifyingly, the method is not limited to α-hydroxyallenes, since the corresponding α-aminoallenes **37** can also be cyclised smoothly to 3-pyrrolines **38** in the presence of catalytic amounts of $AuCl_3$ (Scheme 11).[21] In this case, however, the reactivity and degree of chirality transfer strongly depend upon the *N*-protecting group, and only the unprotected aminoallene afforded the diastereomerically pure 3-pyrroline. Since this structural element is frequently found in natural products of various biological activities, new avenues in natural product chemistry are opened with the gold-catalysed cycloisomerisation. More recently, the first example of a gold-catalysed C–S bond formation could be realised by formation of the 2,5-dihydrothiophene **40** from the thiol-substituted allene **39**.[22]



Scheme 11

What is the mechanistic origin of the high reactivity and stereoselectivity observed in these transformations? As indicated by *ab initio* calculations,[23] the key is once again the ability of gold salts to act as soft, carbophilic Lewis acids which enables them to coordinate to an allenic double bond of the substrate **41** and to form a π-complex **42** (Scheme 12). As a consequence of the increased electrophilicity, cyclisation *via* an S_N2 type transition state and subsequent protodemetallation of the intermediate **43** produces the heterocyclic product **44** with complete axis-to-center chirality transfer, releasing the gold catalyst into the catalytic cycle.



Scheme 12

Conclusion

Although homogeneous gold catalysis is still in its infancy, spectacular achievements have been reported in recent years. By virtue of their unique ability to activate carbon–carbon double and triple bonds as soft, carbophilic Lewis acids, gold complexes have been utilised as highly efficient catalysts for the formation of C–C, C–O, C–N, and C–S bonds, often in cyclisation reactions. Moreover, the ability of gold salts to activate C–H bonds of aromatic and other substrates opens unprecedented pathways for their functionalisation. The application of gold catalysis in stereoselective synthesis has been made possible by the use of chiral allenes as substrates and exciting developments in this field in the near future seem certain.

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