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Golden opportunities in catalysis*

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Abstract: The gold-catalyzed *endo*-cycloisomerization of allenes bearing nucleophilic substituents in the α- or β-position opens up a versatile access to various five- and six-membered heterocycles. Key features of these transformations are the high reactivity of the allene in the presence of Lewis-acidic, carbophilic gold(I) or gold(III) catalysts, and the chirality transfer from the allenic axis of chirality to the new stereogenic center in the cyclization product. Recent contributions of our group include the optimization of chirality transfer by using σ-donor ligands to gold, and applications in the total synthesis of natural products, e.g., of the β-carboline alkaloids (–)-isocyclocapitelline and (–)-isochrysotricine.

Keywords: allenes; chirality transfer; cycloisomerization; gold catalysis; heterocycles.

Homogeneous gold catalysis is an emerging area of transition-metal catalysis with tremendous potential for organic synthesis [1]. Both gold(I) and gold (III) salts are soft carbophilic Lewis acids and can activate C–C double and triple bonds for an inter- or intramolecular attack of a nucleophile to form new C–C or C–heteroatom bonds. Among various substrates amenable to activation, alkynes play a dominant role, whereas gold-catalyzed reactions of alkenes or allenes have been studied less frequently. From our point of view, allenes are particularly attractive starting materials since they combine high reactivity with axial chirality and therefore offer the opportunity to obtain new products in a stereoselective fashion by chirality transfer.

Based on our continued interest in the stereoselective synthesis and transformation of functionalized allenes [2], we have started a program dedicated to the development of new synthetic applications of allenes using homogeneous gold catalysis. In contrast to other research groups who have studied gold-catalyzed intermolecular additions to allenes [3] or *exo*-selective cyclizations [4], we have concentrated our efforts on *endo*-cycloisomerizations of chiral allenes bearing a nucleophilic substituent in the allylic) (α) or homoallylic (β) position (Scheme 1). These transformations take place with perfect atom economy [5].

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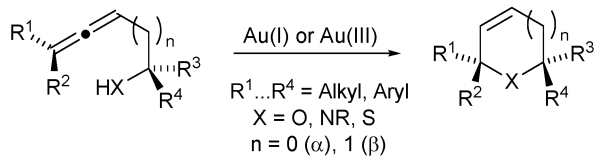
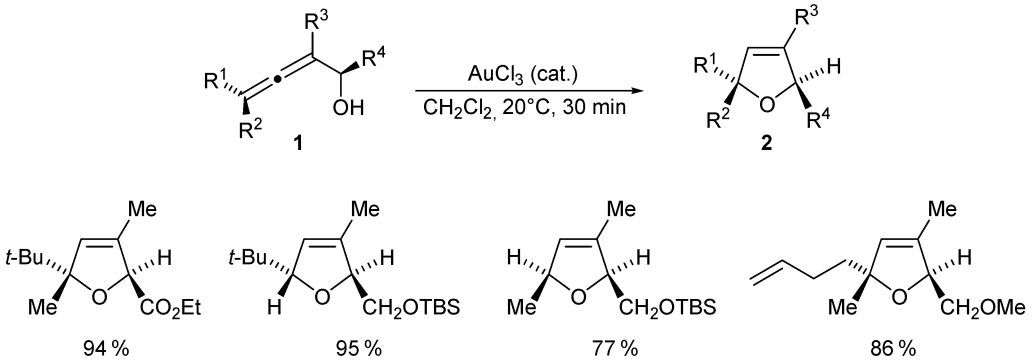


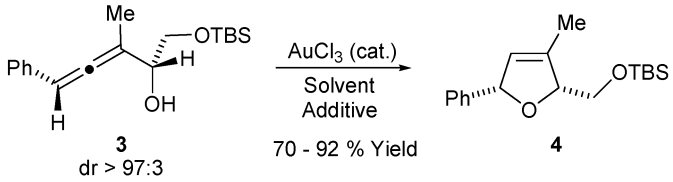
Scheme 1 Gold-catalyzed *endo*-cycloisomerization of α- or β-hetero-functionalized allenes.

The prototype of the gold-catalyzed allene cycloisomerizations established by our group is the conversion of α-hydroxyallenes **1** to 2,5-dihydrofurans **2**. This transformation has traditionally been performed by treating the allene with a silver salt; under these conditions, however, the reactivity is so low that often stoichiometric amounts of silver are required to achieve an acceptable reaction rate. In contrast to this, we have found that catalytic amounts of gold(I) or gold(III) salts induce a rapid conversion of various α-hydroxyallenes to the corresponding 2,5-dihydrofurans in unpolar solvents (Scheme 2) [6]. Many functionalities (e.g., carbonyl groups, free alcohols, acid-sensitive protecting groups) are tolerated under these conditions [6,7]. The cyclization probably proceeds via coordination of the Lewis-acidic, carbophilic gold catalyst to the "distal" allenic double bond, followed by intramolecular attack of the hydroxy group (via an S_N2-type transition state) to form a zwitterionic species which upon protodemetallation is transformed into the heterocyclic product.



Scheme 2 Gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans.

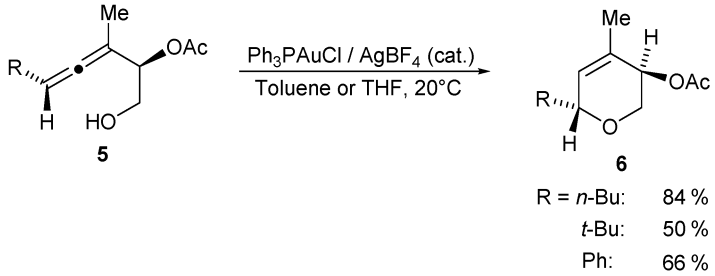
Whereas gold-catalyzed cyclizations of alkyl-substituted allenes take place with complete axis-to-center chirality transfer, α-hydroxyallenes bearing phenyl or electron-rich aryl substituents (e.g., **3**) undergo epimerization when treated with gold precatalysts (Scheme 3). Whereas $AuCl_3$ in CH_2Cl_2 epimerizes both the allene **3** and the dihydrofuran **4**, only the allene but not the dihydrofuran is epimerized in the presence of gold(I) chloride in dichloromethane [8]. Based on the assumption that the epimerization proceeds via zwitterionic intermediates comprising a benzyl cation substructure and an anionic aurate moiety, we reasoned that the stereochemical integrity of substrate and product should be preserved if the Lewis acidity of the gold catalyst is decreased. Accordingly, high levels of chirality transfer were observed when the cycloisomerization was carried out in the presence of σ-donor ligands to gold, e.g., 2,2'-bipyridine; alternatively, a weakly coordinating solvent like tetrahydrofuran (THF) can be used as well (Scheme 3). A third possibility is to conduct the reaction with the original $AuCl_3/CH_2Cl_2$ system at –30 °C instead of room temperature, giving **4** with excellent diastereoselectivity.



Solvent	Temperature	Additive	*cis:trans*
CH_2Cl_2	20°C	–	66 : 34
CH_2Cl_2	20°C	2,2'-Bipyridine	>97 : 3
THF	20°C	–	97 : 3
CH_2Cl_2	-30°C	–	97 : 3

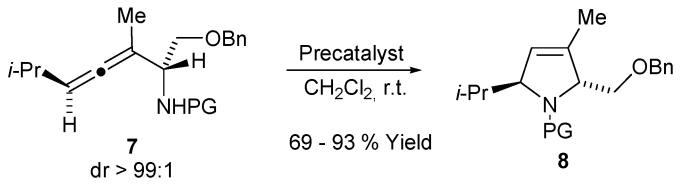
Scheme 3 Improvement of the chirality transfer in the gold-catalyzed cycloisomerization of α-hydroxyallene **3**.

The improved stability and selectivity of gold catalysts in the presence of additives and/or THF as the solvent allows a strong decrease of the catalyst loading. For example, reaction of **3** with just 0.1 mol % of $AuCl_3$ and 0.2 mol % of 2,2'-bipyridine in THF for 12 h at room temperature afforded **4** with 92 % yield (920 turnovers). Substrates which are different to cyclize (e.g., exocyclic α-hydroxyallenes, α,α'-dihydroxyallenes) can also be converted into the desired 2,5-dihydrofurans under these conditions [8]. Interestingly, the corresponding *endo*-cycloisomerization of β-hydroxyallenes **5** to 5,6-dihydro-2*H*-pyrans **6** is also influenced strongly by solvent and additives [9]. Generally, these substrates are less reactive than the α-hydroxyallenes **1**, and gold(I) chloride or the cationic gold catalyst Ph_3PAuBF_4 (generated in situ from Ph_3PAuCl and $AgBF_4$) gave the best results (Scheme 4). Interestingly, the reaction is not promoted by silver salts alone. The transformation is complete within 1 h at room temperature in toluene or dichloromethane, whereas the use of additives or THF as solvent leads to a slower, but often more selective reaction. Fortunately, the tendency of aryl-substituted β-hydroxyallenes to epimerize during the cyclization can be prevented by addition of pyridine to the reaction mixture [8].



Scheme 4 Gold-catalyzed cycloisomerization of β-hydroxyallenes **5** to 5,6-dihydro-2*H*-pyrans **6**.

The extension of the method to aminoallenes revealed some distinct differences [10]. Whereas the reactivity of various protected α-aminoallenes **7** toward gold(III) chloride in dichloromethane is very similar to that of the corresponding α-hydroxyallenes (full conversion after 30 min at room temperature), unprotected aminoallenes are rather unreactive and require several days at 20 °C for a complete conversion to the 3-pyrroline **8** (Scheme 5). This reactivity issue can be solved by using gold(I) chloride as the precatalyst, which affords the desired cyclization products with good yield after 6 h at room temperature.

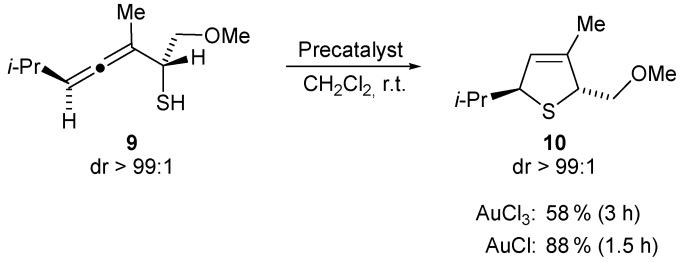


Precatalyst	PG	Time	*trans:cis*
$AuCl_3$	Ms	30 min	94 : 6
$AuCl_3$	Ts	30 min	95 : 5
$AuCl_3$	Ac	30 min	70 : 30
$AuCl_3$	Boc	30 min	46 : 54
$AuCl_3$	H	5 d	>99 : 1
AuCl	H	6 h	99 : 1

Scheme 5 Gold-catalyzed cycloisomerization of α-aminoallenes 7 to 3-pyrrolines **8**.

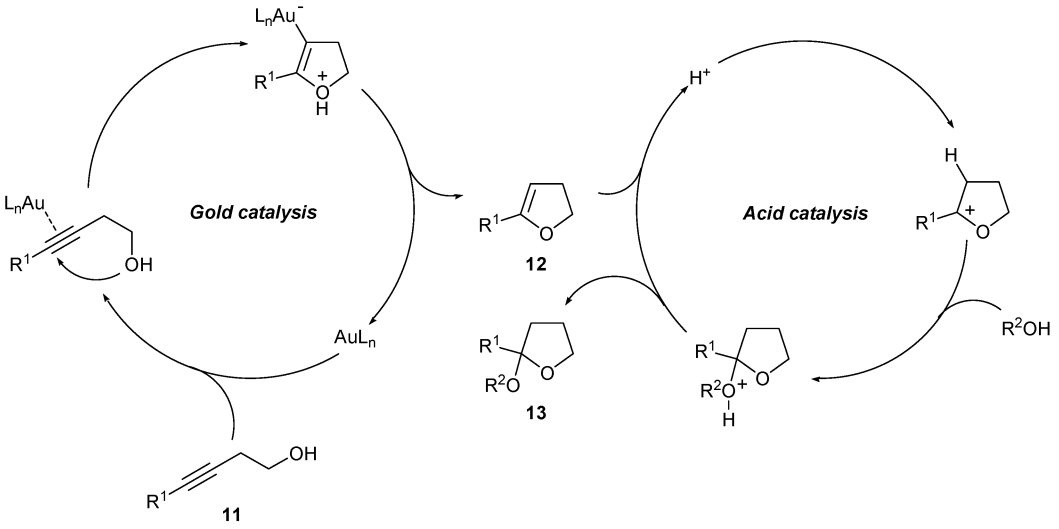
Interestingly, the protected pyrrolines are obtained as a mixture of *cis*/*trans*-isomers. In contrast to the analogous behavior of aryl-substituted α-hydroxyallenes (Scheme 3), this is not caused by gold-catalyzed epimerization of substrate or product; rather, it may be a consequence of configurational instability (possibly due to ring-chain tautomerism) of 3-pyrrolines comprising an amide substructure. The corresponding *endo*-cycloisomerization of β-aminoallenes to tetrahydropyridins can also be achieved with gold(I) chloride as precatalyst [9].

The application of gold catalysis to the cyclization of α-thioallenes to 2,5-dihydrothiophenes seemed not to be very promising since sulfur nucleophiles are well known to coordinate strongly to transition metals (especially to gold); in other words, they are excellent catalyst poisons. Nevertheless, the high reactivity of the allenic π-system enabled us to overcome this obstacle and to establish the first gold-catalyzed C–S bond formation [11]. For example, reaction of the α-thioallene **9** with AuCl or $AuCl_3$ in CH_2Cl_2 smoothly afforded the desired 2,5-dihydrothiophene **10** within a few hours at room temperature (Scheme 6). The yield of **10** is considerably higher when gold(I) chloride is used; in the case of gold(III) chloride, the disulfide formed by oxidation of the allene **9** is isolated as side product.



Scheme 6 Gold-catalyzed cycloisomerization of α-thioallene **9** to 2,5-dihydrothiophene **10**.

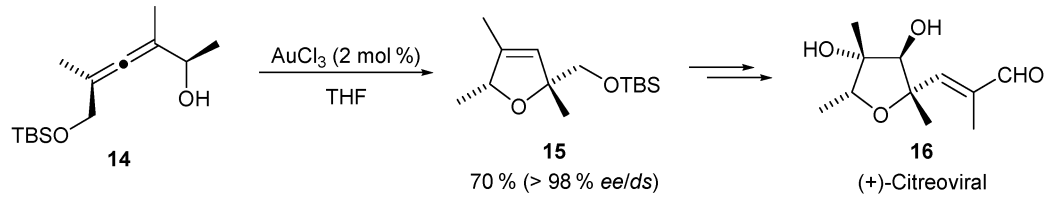
In a related study, we have also examined the gold-catalyzed cyclization of homopropargylic alcohols [12]. Initially, we intended to explore the possibility that homopropargylic alcohols **11** might undergo a gold-catalyzed isomerization to α-hydroxyallenes **1**, which would then be converted into 2,5-dihydrofurans **2**. Actually, treatment of **11** with various gold(I) or gold(III) salts did not induce an isomerization, but rather a cyclization to (unstable) 2,3-dihydrofurans **12** which were converted into cyclic acetals **13** by acid-catalyzed alcohol addition in a one-pot procedure (Scheme 7). Thus, a tandem



Scheme 7 Proposed mechanism of the tandem gold/acid-catalyzed cycloisomerization–hydroalkoxylation of homopropargylic alcohols.

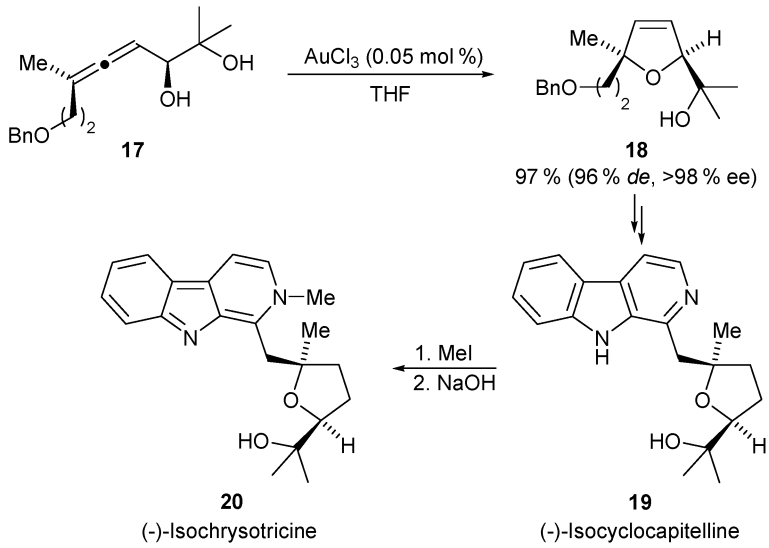
gold/acid-catalyzed cycloisomerization–hydroalkoxylation of homopropargylic alcohols was established which is reminiscent of the famous gold-catalyzed addition of alcohols to alkynes reported by Teles et al. [13] in 1998.

The true test for the usefulness of a preparative method is its application in target-oriented synthesis. Interestingly, homogeneous gold catalysis has rarely been used in (stereoselective) natural product synthesis so far. We have applied the gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans for the synthesis of several target molecules bearing a chiral dihydrofuran or THF moiety. For example, treatment of the diastereo- and enantiomerically pure hydroxyallene **14** with 2 mol % gold(III) chloride in THF afforded the dihydrofuran **15** with complete chirality transfer (Scheme 8) [14]. Previously, substoichiometric amounts of silver nitrate have been required for this cyclization [15]. The 2,5-dihydrofuran **15** is a precursor of the THF natural product (+)-citreoviral (**16**), as well as, the mycotoxins citreoviridin and verrucosidin, using the dihydrofuran double bond for oxidative functionalization.



Scheme 8 Application of the gold-catalyzed cycloisomerization of the α-hydroxyallene **14** to the synthesis of (+)-citreoviral (**16**).

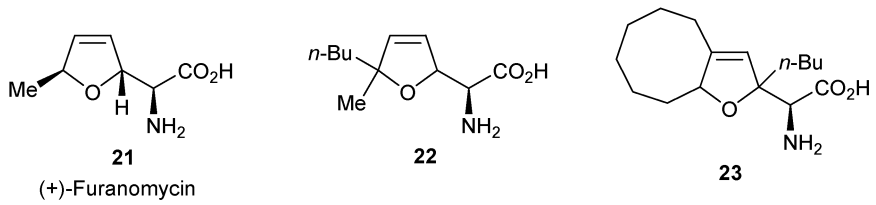
Recently, we have also described the first total synthesis of the β-carboline alkaloids (–)-isocyclocapitelline (**19**) and (–)-isochrysotricine (**20**) using the gold-catalyzed cycloisomerization of allenic diol **17** as the key step (Scheme 9) [16]. As expected from previous studies with α- and β-hydroxyallenes (Schemes 2–4), only the hydroxy group in α-position participates in the cyclization. With a catalyst loading of 0.05 mol %, this reaction belongs to the most efficient transformations reported so



Scheme 9 Application of the gold-catalyzed cycloisomerization of the α-hydroxyallene **17** to the synthesis of the β-carboline alkaloids (–)-isocyclocapitelline (**19**) and (–)-isochrysotricine (**20**).

far in homogeneous gold catalysis. The dihydrofuran **18** was converted into the diastereo- and enantiomerically pure target molecules **19** and **20** by hydrogenation of the double bond, oxidation, and Pictet–Spengler cyclization with tryptamine.

Unlike THF natural products, the number of naturally occurring target molecules comprising a 2,5-dihydrofuran ring is rather small. A prominent example is the antibiotic amino acid (+)-furanomycin (**21**) (Scheme 10). Several syntheses of **21** are known, also by cycloisomerization of an α-hydroxyallene with stoichiometric amounts of silver nitrate [17]. We have recently prepared the novel furanomycin analogs **22** and **23** by cyclization of α-hydroxyallenes with just 1 mol % $AuCl_3$ in THF [18]. These examples demonstrate the utility of gold catalysis for the synthesis of highly functionalized heterocycles.



Scheme 10 (+)-Furanomycin and analogs **22** and **23** available by gold-catalyzed cycloisomerization of α-hydroxyallenes.

In conclusion, we have shown that the gold-catalyzed cycloisomerization of allenes bearing nucleophilic substituents in the α- or β-position opens up a versatile access to various five- and six-membered heterocycles. Key features of these transformations are the high reactivity of the allene in the presence of Lewis-acidic, carbophilic gold(I) or gold(III) catalysts which even allows the formation of carbon–sulfur bonds, as well as the chirality transfer from the allenic axis of chirality to the new stereogenic center in the cyclization product. A fine-tuning of the reactivity, catalyst stability, and stereoselectivity are possible by using σ-donors ligands to gold (e.g., 2,2'-bipyridine) and/or weakly coordi-

nating solvents like THF. Several applications in target-oriented synthesis demonstrate that homogenous gold catalysis is a perfect tool for the rapid generation of molecular complexity.

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