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Review

Combined coinage metal catalysis for the synthesis of bioactive molecules

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ABSTRACT

The use of the coinage metals copper, silver, and gold enables an efficient and stereoselective assembly of bioactive heterocycles via allenic intermediates. Whereas copper is mediating or catalyzing the synthesis of functionalized allenes by S_N2'-substitution or S_N2'-reduction, silver and gold are the catalysts of choice for subsequent 5- or 6-*endo*-cyclizations. Overall, this sequence proceeds with efficient center-to-axis-to-center chirality transfer. Recent advances of this combined coinage metal catalysis include the synthesis and transformation of substrates containing two adjacent allenic π-systems or heteroatoms, the development of recyclable gold catalysts, and the combination of two catalytic processes in tandem or one-pot reactions.

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1. Introduction

The coinage metals copper, silver and gold belong to the seven metals of alchemy. They are known to mankind for thousands of years, and gold may have been the first metal ever used by humans [1]. Whereas copper enjoys a rich history in organometallic chemistry and organic synthesis, starting with contributions by Kharasch and Gilman in the 1940s and 1950s [1,2], the usage of silver and gold in transition metal catalysis commenced much more recently. In our research program, we are particularly interested in combining the (quite different) reactivities of the coinage metals for the stereoselective synthesis of bioactive target molecules [3]. Due to their high reactivity and axial chirality, functionalized allenes are ideal substrates for these transformations [4]. The challenge in using allenes in organic synthesis is twofold: the high energy of these unsaturated systems (enthalpy of formation for $H_2C{=}C{=}CH_2$: ca. 190 kJ/mol [5]) has to be provided by using suitable energy-

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rich substrates or reagents, and the relative and/or absolute configuration of these chiral molecules has to be controlled. Many classical reaction types of organic chemistry (addition, elimination, substitution, rearrangement) are applicable to the synthesis of allenes. Stereoselective variations of these transformations often take advantage of center-to-axis chirality transfer. The allenes thus formed are highly interesting in their own right, but are also converted frequently into other target molecules, e.g., by (cyclo)addition, cyclization, and rearrangement. Ideally, the chirality of allenes is utilized in these transformations for the controlled formation of stereogenic centers by axis-to-center chirality transfer.

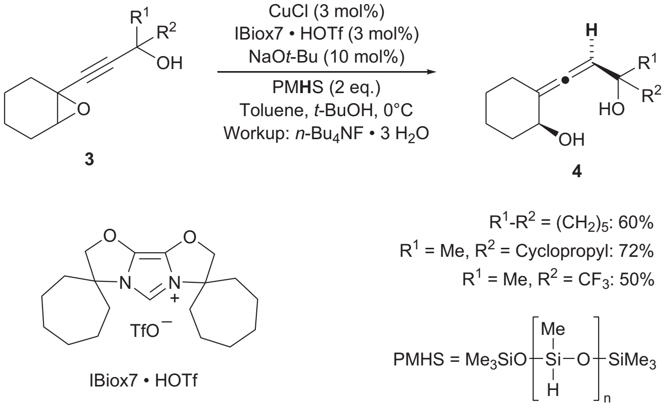
2. Copper-catalyzed synthesis of allenes

One of the most prolific methods for the synthesis of allenes is the S_N2'-substitution of propargyl electrophiles with organometallic reagents [6]. Organocopper compounds are the nucleophiles of choice for these transformations, and propargyl oxiranes **1** (or carbonates) are among the most useful electrophiles, not only because the substitution usually takes place with high S_N2'-regioselectivity and *anti*-stereoselectivity (i.e., with center-to-axis chirality transfer), but also because the α-hydroxyallenes **2** formed are highly suitable for subsequent modifications (Scheme 1). The magnesium cuprates used in these transformations are formed in situ from a Grignard reagent and a copper(I) salt, and a phosphine or phosphite added to the reaction mixture prevents the epimerization of the allene by the copper reagent. Magnesium cuprates bearing reactive functional groups can also be used [7], and variations catalytic in copper have been described as well [8].

Interestingly, the smallest nucleophile – the hydride ion – has so far only played a minor role in allene synthesis by S_N2'-substitution. Recently, we have established a copper-catalyzed S_N2'-reduction of propargyl oxiranes **3** which provides an efficient route to α-hydroxyallenes of the type **4** (Scheme 2) [9]. Key to success is the stabilization of the catalytically active copper hydride species (formed in situ from CuCl and the stoichiometric hydride source polymethylhydridosiloxane [PMHS]) by an *N*-heterocyclic carbene (e.g., IBiox7). This transformation proceeds with high *anti*-stereoselectivity by center-to-axis chirality transfer and is compatible with various functional groups (alcohols, esters, ethers, etc.). Extension to propargyl carbonates [10] has broadened the range of allenes available by the method and offers advantages with respect to stereoselectivity and substrate reactivity.

3. Silver- and gold-catalyzed cyclization of functionalized allenes

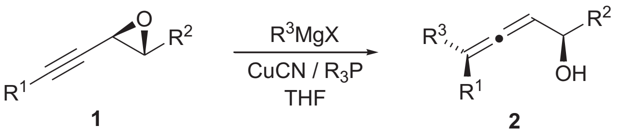
The activation of the highly reactive double system of an allene by treatment with a Brønsted or Lewis acid enables a nucleophilic attack which leads to the formation of a new C–C or C–heteroatom bond. Because of their soft and carbophilic character, silver [11] and gold catalysts [12] are particularly well suited for the selective activation of allenes in the presence of other reactive functionalities [3,13]. In the year 2000, we have started a program dedicated to gold-catalyzed *endo*-selective cycloisomerizations of chiral allenes **5** bearing a nucleophilic substituent in the allylic (α) or homoallylic (β) position to afford chiral five- or six-membered oxygen, nitrogen or sulfur heterocycles (Scheme 3). These transformations take place with perfect atom economy [14].



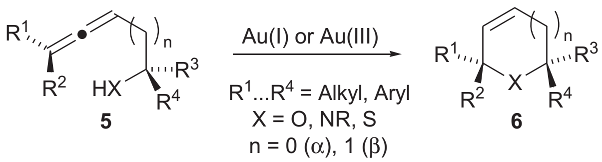
Scheme 2. Copper-catalyzed S_N2'-reduction of propargyl oxiranes **3**.

The prototype of the gold-catalyzed allene cycloisomerizations established by our group is the conversion of α-hydroxyallenes to 2,5-dihydrofurans. 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 [15]. In contrast to this, catalytic amounts of gold(I) or gold(III) salts induce a rapid conversion of various α-hydroxyallenes to the corresponding 2,5-dihydrofurans [16]. Many functionalities (e.g., carbonyl groups, free alcohols, acid-sensitive protecting groups) are tolerated under these conditions. Whereas alkyl-substituted allenes react with complete axis-to-center chirality transfer [12a,17], substrates bearing phenyl or electron-rich aryl groups are prone to epimerization when treated with gold salts. This undesired process probably occurs via zwitterionic intermediates and can be prevented by modulating the Lewis acidity of the gold catalyst [18].

The mechanistic model [19] for the gold-catalyzed cycloisomerization of α-hydroxyallenes (Scheme 4) involves coordination of the carbophilic gold catalyst to the allenic double bond distal to the hydroxy group. This affords π-complex **A** which undergoes a 5-*endo*-cyclization to the zwitterionic σ-vinylgold species **B**. Protodeauration leads to the dihydrofuran and regenerates the gold catalyst. The cyclization is accelerated in the presence of external proton donors (water, methanol); this suggests that the protodeauration of **B** is the rate-limiting step. Experimental support for this model was recently gained by Widenhoefer and coworkers [20] through the isolation of a gold π-allene complex which was characterized by X-ray crystallography and variable-temperature NMR spectroscopy. Moreover, the group of Hammond [21] has isolated



Scheme 1. *Anti*-stereoselective S_N2'-substitution of propargyl oxiranes **1** with magnesium cuprates.



Scheme 3. Gold-catalyzed *endo*-cycloisomerization of α- or β-hetero-functionalized allenes **5**.