Gold Catalysis

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Golden Opportunities in Stereoselective Catalysis**

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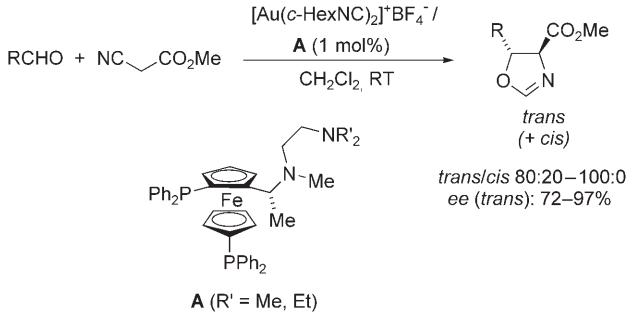
chirality transfer · cycloisomerization · enantioselectivity · gold · ion pairs

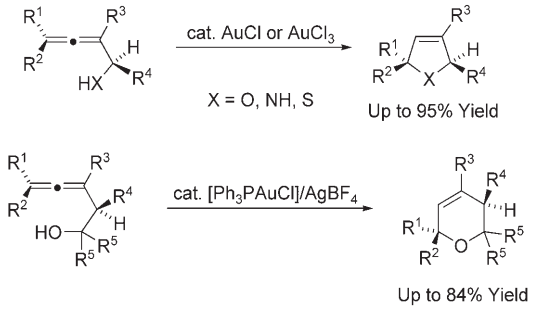
The use of gold in homogeneous catalysis has witnessed tremendous activity in recent years.[1] This is mainly due to the unique ability of gold(I) and gold(III) salts to act as soft carbophilic Lewis acids towards carbon–carbon double and triple bonds which, after this activation, undergo a variety of transformations that lead to new carbon–carbon or carbon–heteroatom bonds. Despite its utility, however, applications of homogeneous gold catalysis in stereoselective organic synthesis are still rare. This is all the more surprising since one of the first examples of the use of homogeneous gold catalysis in organic synthesis was actually a highly enantioselective reaction: In 1986, Ito et al.[2] had already published a seminal paper in which $[Au(c\text{-HexNC})_2]^+BF_4^-$ together with the chiral ferrocenylphosphane ligand **A** was used as a catalyst for the enantioselective aldol reaction of aldehydes with isocyanates to yield 5-alkyl-2-oxazoline-4-carboxylates with enantioselectivities of up to 97% *ee* and *trans/cis* ratios ranging from 80:20 to 100:0 (Scheme 1). These products are valuable precursors for β-hydroxyamino acids and related compounds.[3]



Scheme 1. Gold-catalyzed asymmetric aldol reaction of aldehydes and isocyanates in the presence of chiral ferrocenylphosphanes **A**. *c*-Hex = cyclohexyl.

Surprisingly, this potentially ground-breaking contribution was mostly ignored in later years. Only at the beginning of this century was the potential of homogenous gold catalysis in stereoselective organic synthesis again recognized. The transformations developed since rely either on the transfer of chirality from a substrate with a defined configuration to the product, or on the introduction of chirality into a prochiral substrate through the use of chiral gold catalysts.

The transfer of stereochemical information from a substrate to a product by gold-catalyzed rearrangement or cyclization has turned out to be a highly successful strategy. The reactivity and inherent axial chirality of allenes make them particularly attractive starting materials for this purpose. For example, the gold(I)- or gold(III)-catalyzed *endo*-cycloisomerization of α- and β-hydroxyallenes to the corresponding five- and six-membered heterocycles occurs with complete transfer of chirality in most cases (Scheme 2).[4] The



Scheme 2. Axis-to-center chirality transfer in the gold-catalyzed cycloisomerization of α- and β-heterosubstituted allenes.

method was recently extended to the corresponding cycloisomerization of α-aminoallenes to 3-pyrrolines, with complete transfer of chirality observed with unprotected substrates.[5] The high reactivity of the allenic π system means that even C–S bonds can be formed stereoselectively by homogeneous gold catalysis, as demonstrated by the cycloisomerization of α-thioallenes to 2,5-dihydrothiophenes.[6] In this case, the traditionally used Cu or Ag precatalysts show no or only limited reactivity.

The observation of chirality transfer in these transformations is not a trivial issue since allenes are easily racemized or epimerized in the presence of transition-metal catalysts. Indeed, both gold(I) and gold(III) salts are able to epimerize aryl-substituted hydroxyallenes, thereby causing a diminished

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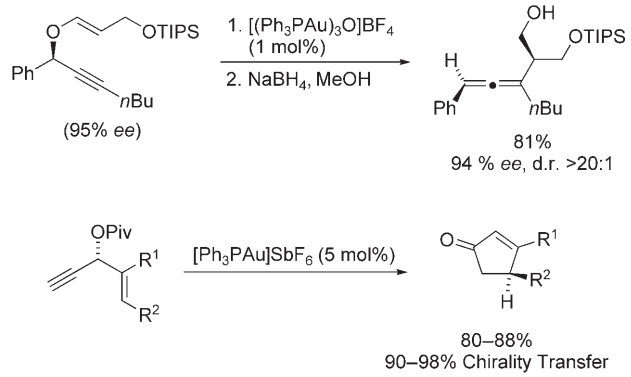
stereochemical purity of the product. This problem can be resolved by the addition of σ-donor ligands (for example, 2,2′-bipyridine) or by using weakly coordinating solvents such as THF, which leads to a decreased Lewis acidity of the gold catalyst.[7]

In contrast to these cyclization reactions, the corresponding intermolecular hydrofunctionalization of allenes has been studied less intensively. Nishina and Yamamoto[8] have recently reported on the hydroamination of allenes with aniline in the presence of gold(III) bromide to give chiral allylamines with high enantioselectivity (Scheme 3).

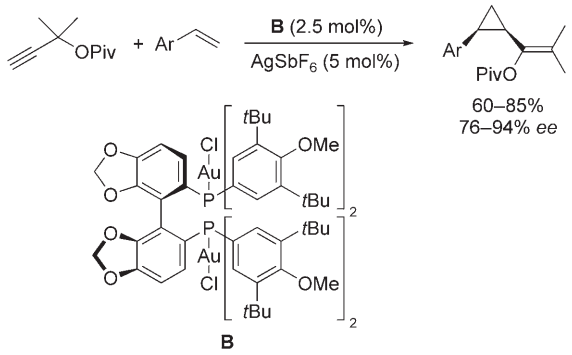
Scheme 3. Axis-to-center chirality transfer in the gold-catalyzed intermolecular hydroamination of allenes.

The simultaneous formation of a new axis of chirality and a new stereogenic center was observed by Sherry and Toste[9] in the gold-catalyzed Claisen rearrangement of enantiomerically enriched propargyl vinyl ethers, which leads to β-hydroxyallenes with high stereocontrol (Scheme 4). In contrast to this, the Rautenstrauch rearrangement of propargyl pivalates to chiral cyclopent-2-enones in the presence of a cationic gold(I) precatalyst involves a highly efficient transfer of chirality from one stereogenic center to another.[10]



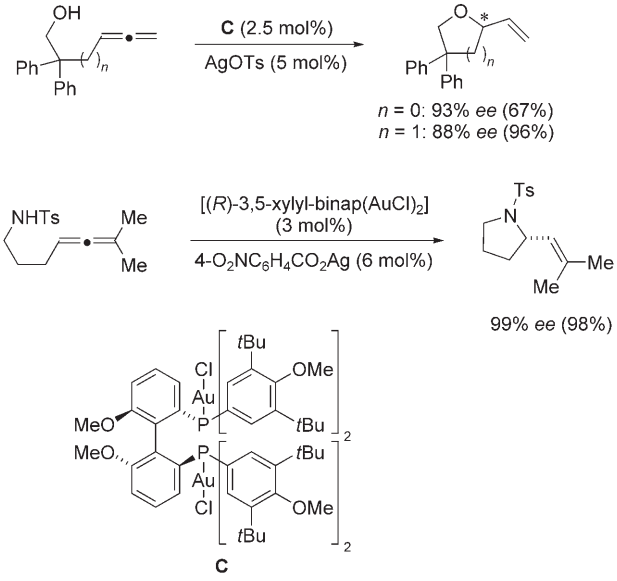
Scheme 4. Transfer of chirality in the gold-catalyzed Claisen and Rautenstrauch rearrangement. TIPS = triisopropylsilyl, Piv = pivaloyl.

The first example of an enantioselective transformation involving prochiral substrates and a chiral gold catalyst (after the aldol reaction shown in Scheme 1) was reported in 2005 by Echavarren and co-workers,[11] who achieved moderate stereoselection (up to 53% *ee*; 94% *ee* in a single case) in the alkoxycyclization of enynes in the presence of gold catalysts bearing chiral mono- or bidentate phosphane ligands. In the same year, Toste and co-workers[12] disclosed a gold(I)-catalyzed cyclopropanation of styrene derivatives, with selectivities reaching up to 94% *ee* in the presence of the (*R*)-DTBM-segphos-gold(I) complex **B** and silver hexafluoroantimonate (Scheme 5, DTBM-segphos = (4,4′-bi-1,3-benzodioxol)-5,5′-diylbis[di-(3,5-di-tert-butyl-4-methoxyphenyl)-phosphane]). Gold(I) complexes with an $Au_2(P\text{-}P)Cl_2$ stoichiometry were employed by Corma and co-workers[13] in the enantioselective hydrogenation of prochiral alkenes and imines, and afforded similar turnover frequencies, but higher selectivities (up to 95% *ee*), than the corresponding platinum and iridium catalysts.



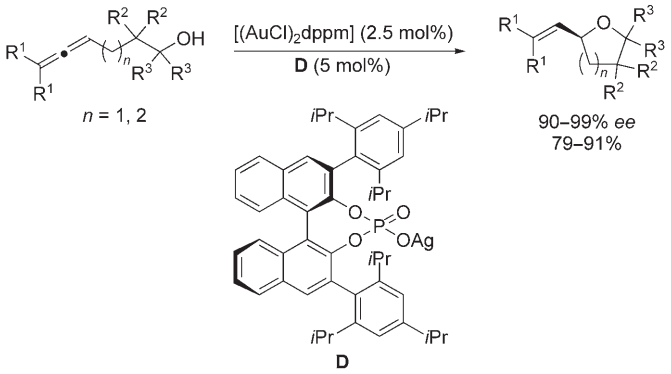
Scheme 5. Enantioselective cyclopropanation catalyzed by chiral gold(I)-phosphane complex **B**.

Once again, allenes have turned out to be particularly favorable substrates for enantioselective gold-catalyzed transformations. In a seminal contribution, Zhang and Widenhoefer[14] have shown that the *exo*-hydroalkoxylation of γ- and δ-hydroxyallenes takes place with high enantioselectivity when a cationic gold(I) catalyst generated from Au-biphep-complex **C** and silver tosylate is used (Scheme 6). The same catalyst can also be applied in the intramolecular hydroarylation of allenes with indoles to afford carbazole derivatives with up to 92% *ee*.[15]



Scheme 6. Enantioselective intramolecular hydrofunctionalization of allenes catalyzed by chiral gold(I)-phosphane complexes. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Ts = tosyl.

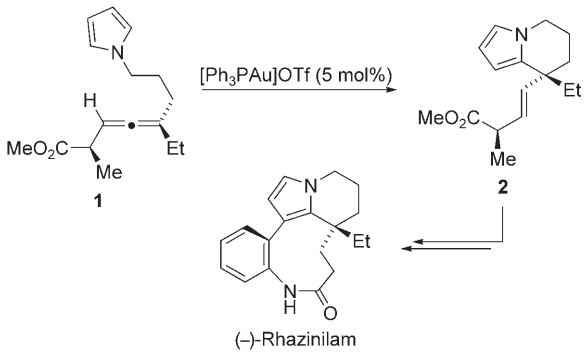
Toste and co-workers[16] have shown that a cationic 3,5-xylyl-binap-gold(I) catalyst with 4-nitrobenzoate as counterion gives the best enantioselectivities and yields for the corresponding intramolecular hydroamination of protected γ-aminoallenes (Scheme 6). Catalysts of this type can also be used for the cycloisomerization of vinylallenes,[17] whereas [(*R*)-DTBM-segphos(AuCl)$_2$] catalyzes [2+2] cycloadditions of vinylallenes with up to 97% *ee*.[18] The importance of the counterion for the stereochemical course of these transformation was demonstrated in a spectacular fashion by Toste and co-workers[19] in the cycloisomerization of various γ- and δ-hydroxyallenes (Scheme 7). Here, particularly high enantioselectivities were achieved using a mixture of the achiral gold complex [(AuCl)$_2$dppm] and the chiral silver phosphate **D**. These reagents form a catalytically active gold species in which the source of the chirality is not (as usual) a ligand tightly bound to the metal, but rather a chiral counterion. This concept of relaying stereochemical information via ion pairs may have tremendous potential for asymmetric transition-metal catalysis.



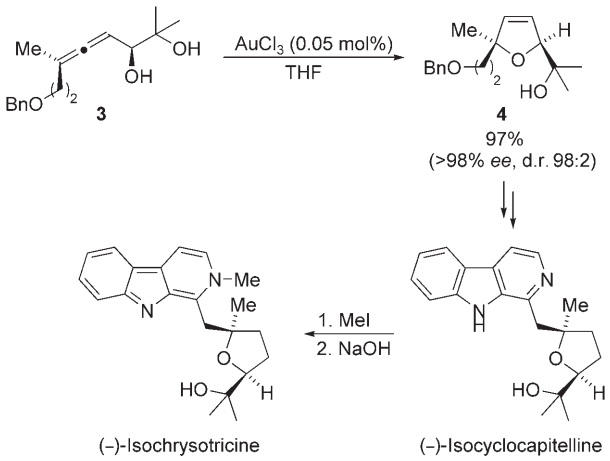
Scheme 7. Intramolecular hydroalkoxylation of allenes using a chiral counterion for the introduction of chirality. dppm = bis(diphenylphosphanyl)methane.

Since enantioselective transformations of prochiral substrates with chiral gold catalysts have only recently been developed, there are as yet no reported applications in target-oriented synthesis. In contrast to this, several examples of the total syntheses of complex target molecules were disclosed recently that take advantage of gold-catalyzed transfer of chirality. Nelson and co-workers[20] used the gold-catalyzed *exo*-cycloisomerization of the allenic ester **1** for the construction of the tetrahydroindolizine core (**2**) of the antitubulin (−)-rhazinilam (Scheme 8). The cyclization is also catalyzed by [PdCl$_2$(MeCN)$_2$], but with inferior yield and stereoselectivity.

A second application of gold-catalyzed chirality transfer from a stereogenic axis of an allene to a newly formed stereogenic center in natural product synthesis took advantage of the highly efficient chemo- and stereoselective *endo*-cycloisomerization of allenic diol **3** to the 2,5-dihydrofuran **4** in the presence of only 0.05 mol% of gold(III) chloride (Scheme 9).[21] The product was the key building block in the first enantioselective syntheses of the β-carboline alkaloids (−)-isocyclocapitelline and (−)-isochrysotricine.



Scheme 8. Axis-to-center chirality transfer in the gold-catalyzed synthesis of the tetrahydroindolizine moiety of (−)-rhazinilam.



Scheme 9. Axis-to-center chirality transfer in the gold-catalyzed synthesis of (−)-isocyclocapitelline and (−)-isochrysotricine.

Although stereoselective gold catalysis is still in its infancy, tremendous progress has been made in recent years. The transfer of chirality from the allenic axis to a new stereogenic center by gold-catalyzed cyclization or rearrangement is a powerful tool for stereoselective synthesis, as exemplified by the increasing number of applications in target-oriented synthesis. The first examples of highly enantioselective transformation using prochiral substrates and chiral gold catalysts show the remarkable potential of the method, and have even led to the new concept of relaying stereochemical information via an ion pair instead of a classical complex bearing a chiral ligand tightly bound to the transition-metal center. Further ground-breaking discoveries can be expected with certainty—A golden future lies ahead!

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