Binary Catalytic Systems

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Gold and Organocatalysis Combined

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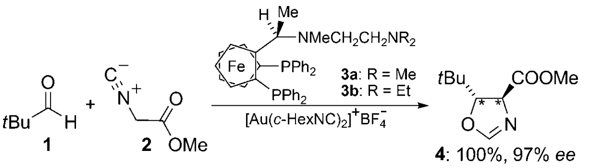
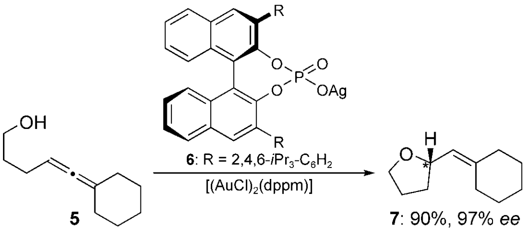
The first gold-catalyzed reaction that became significant for organic synthesis was the asymmetric aldol reaction [Eq. (1); *c*-Hex = cyclohexyl], which was reported in 1986 by Ito, Sawamura, and Hayashi,[1,2] and converted **1** and **2** into **4**. As the first efficient catalytic enantioselective aldol reaction, this reaction was not only a milestone in catalytic enantioselective synthesis, but also defined the standards in enantioselective gold catalysis for more than two decades. In a way that is considered today to be “classical”, a chiral ligand (**3a** or **3b**) coordinated to the metal catalytic center induced chirality during the conversion of the substrate.



(1)

Research in homogeneous gold catalysis focused on this particular reaction for more than a decade.[3] As expected,[4] during the exponential growth of homogeneous gold catalysis in the last years, enantioselective gold catalysis was revived, but was still based on the principle of a chiral phosphane ligand such as **3** on the metal center. This research is documented by various reactions such as the enyne cycloisomerization or hydroamination reactions.[5,6] In all of these reactions, the chiral ligand controls enantiofacial selection in the substrate.[5,6] It was only quite recently that the enantiodifferentiation of two enantiotopic groups was also described for gold catalysis.[7]

Accordingly, a second principle could be successfully applied, and again homogeneous gold catalysis was the pacemaker. Toste and co-workers succeeded in the first efficient chirality transfer from a chiral counterion of an achiral cationic gold complex [Eq. (2); dppm = bis(diphenylphosphino)methane]; the few previous efforts of other research groups had never given good *ee* values.[8]



(2)

Dixon,[9] Gong,[10] and their respective co-workers now report the latest development within enantioselective gold catalysis, namely the use of a binary catalytic system consisting of an achiral gold complex ([Au]) and a chiral Brønsted acid (B*–H). This result is a significant improvement for synthetic efficiency, as one of the major difficulties here is that the isolobal structure of a proton and a phosphane gold(I) cation, thus both could be able to catalyze the enantiodetermining step.[11,12] Therefore the key for a high enantiomeric excess is the right choice of gold catalyst, organocatalyst, and reaction conditions to assure that the proton is a significantly better catalyst for the enantiodetermining step, and that the *ee* value is not eroded by a gold-catalyzed background reaction. Both the Dixon and Gong research groups used in situ formed $[Au(PPh_3)]^+$ as the gold catalyst, BINOL phosphoric acid (BPA; BINOL = 1,1′-bi-2-naphthol) derivatives as organocatalysts, and the nonpolar toluene as solvent. The reactions could be carried out as one-pot sequential or cascade reactions.

Dixon and co-workers[9] used the binary catalytic system for a one-pot sequential reaction (Scheme 1). The reaction started with a gold catalyzed cycloisomerization of **8** to give an enol lactone **9**. Previous reports already showed that a Brønsted acid is not able to catalyze this reaction step.[13] The enol lactone **9** reacts with an amine (e.g., **10**), by nucleophilic ring opening to deliver a ketoamide intermediate. This reaction step is independent of the catalysts.[14] After proton-catalyzed recyclization, an enamide **11** is formed and BPA-catalyzed ring closure forms **12** in good yield and with a high *ee* value.[9] Both Lewis acids and Brønsted acids are able to catalyze the last two reaction steps.[15] In a preceding publication, Dixon and co-workers postulated a Lewis acid assisted Brønsted acid catalysis,[12] but the crucial control experiment with $[Au(PPh_3)]BPA$ has not been reported to date.

A hydroamination/transfer hydrogenation cascade reaction reported by Gong and co-workers involved conversion of

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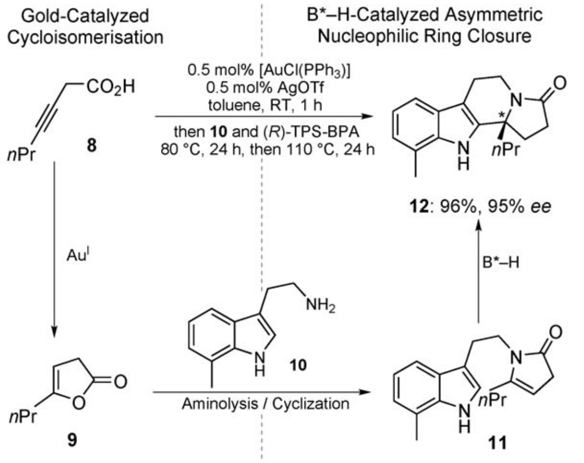
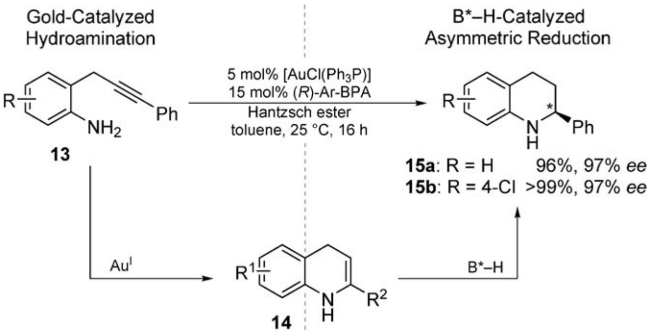


Scheme 1. Cycloisomerisation/*N*-acyliminium cyclization cascade one-pot sequential reaction. TPS = triisopropylsilyl.

2-(2-propynyl)aniline derivatives to tetrahydroquinolines (Scheme 2). The reaction is initiated by a cyclization to the dihydroquinoline **14**, which then is hydrogenated by transfer hydrogenation to give **15** in excellent yield and *ee* value.[10]



Scheme 2. Hydroamination/transfer hydrogenation one-pot cascade reaction. Ar = 9-phenanthrenyl.

A control experiment by Gong and co-workers showed that the asymmetric transfer hydrogenation catalyzed only by in situ formed [Au(PPh$_3$)]PBA gives a significantly lower yield and a lower *ee* value. It can be therefore be excluded that an in situ formed chiral gold complex is the dominant catalytic species in the hydrogenation step. A tight ion pair is most probable during the enantiodetermining step, and chirality is induced by the chiral anion.[7a,16] For an efficient acid catalysis, it is crucial that the protonated product is more acidic than the amine starting material and the imine intermediates. Furthermore, nothing is known about the influence of the chiral product as proton source during the enantiodetermining step.

In summary, the binary catalytic system is a completely new concept within gold catalysis. The system differs from previously reported binary systems because of the isolobal analogy of the proton and [LAu^{I}] cations.[17,18] Although some mechanistic details are still unexplored, synthetically this concept allows access to various efficient enantioselective one-pot cascade reactions. By now the significance of this new concept has been demonstrated by a number of follow-up publications: Another example of a hydroamination/hydrogenation cascade reaction was provided by Liu and Che.[19] Another beautiful example is the sequential reaction of a enantioselective organocatalyzed Michael addition followed by a gold catalyzed cyclization reported by Krause and coworkers.[20] This research group has also presented a binary catalytic system that consists of an enzyme and a gold complex and yields 2,5-dihydrofurans from racemic α-allenic acetates.[21] With regard to synthetic efficiency, this result is a leap forward from the previously published sequential transformations.[22]

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