

GOLD: A CATALYST WORTH ITS WEIGHT

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INTRODUCTION

Over the last five years homogeneous catalysis by gold complexes has gone from a relatively obscure sampling of reactions to a major field of research. Gold complexes have been reported to catalyze the activation of alkenes, allenes, and alkynes towards nucleophilic attack, cyclization and structural rearrangements. Furthermore, mechanistic studies suggest reactivities of gold that were previously unknown, such as carbenoid behavior,¹⁻³ and gold(III) salts have been implicated in aryl C-H bond activation.⁴

Inorganic and Organometallic Properties

Gold is most commonly found in solution in the +1 or +3 oxidation states. Gold(I) is a d^{10} cation with a preferred linear ligand binding geometry while gold(III) is d^8 and prefers to be square planar. Except in specialized binary gold systems, the +2 oxidation state is unstable and disproportionates in solution. The organometallic chemistry of gold differs significantly from that of other late transition metals. Oxidative addition and reductive elimination are very unusual, and beta-hydrogen elimination is generally slower than Au-C bond proteolysis. Also, gold ions are reluctant to participate in π -backbonding with a coordinated alkene or alkyne. The filled metal orbitals are too low in energy to access the high energy antibonding ligand orbitals. These departures from common late transition metal chemistry have been explained by relativistic effects.⁵

Relativistic Effects on Gold

Quantum mechanics alone are unable to predict some of the observed characteristics of gold. A combination of relativistic phenomena comes to a head at gold, and their effects must be included in a description of the atom. The primary effect of these phenomena is the contracting of core s electrons. This generally reduces the energy of all electrons from what quantum mechanics predict, which explains the high electrophilicity of the metal. On the other hand, the improved nuclear shielding of the core electrons leaves the outer d-orbitals more diffuse, which improves metal-ligand orbital overlap. In sum, gold forms strong σ -bonding interactions with ligands but only weak π -backbonding interactions with

high-energy antibonding orbitals. However, it has been suggested that the π -donating ability of gold can stabilize low-energy empty p-orbitals as found on carbocations, giving rise to gold carbenoid complexes.

Although homogeneous catalysis is a vast and well developed field, the use of gold was almost completely neglected during the 20th century. The first demonstration of a useful phosphine-stabilized gold catalyst was published by Teles in 1998.⁶ Since then, the number of reports of homogeneous gold catalysis has increased exponentially. Although many of the reactions involving alkynes have been accessible with Pt(II) salts, gold salts are frequently more active, are not subject to unwanted β -hydride elimination, and are stable to both air and water. In addition, whereas only a very limited number of ligands have been shown to be effective with Pt(II) salts, the reactivity of gold systems is highly dependent upon ligand and counterions. This results in tunable catalyst properties.

GOLD-CATALYZED REACTIONS OF ALLENES, ALKENES AND ALKYNES

The strong electron accepting and weak π -backbonding abilities of gold lead to activation of allene, alkene, and alkyne ligands towards nucleophilic attack. The “alkynophilicity” of gold has been well demonstrated, in that enyne-containing molecules react at the alkyne selectively. However, computations show a greater stabilizing effect for gold-alkene than gold-alkyne complexes. An explanation for the origin of the observed reactivity is that the absolute energy of the alkyne LUMO is intrinsically lower than that of the alkene, and the amount of stabilization, while decreasing the difference between the LUMOs, does not change the order of reactivity.⁵

In the case of a coordinated alkyne, the nucleophile can attack in two ways: (1) precoordination with gold, followed by insertion to form the cis-alkene; or (2) direct attack on the alkyne to form the trans-alkene. Although initial calculations by Teles et al.⁶ indicated the former mechanism for their system, most of the subsequent results have provided support for the latter mechanism (Figure 1).

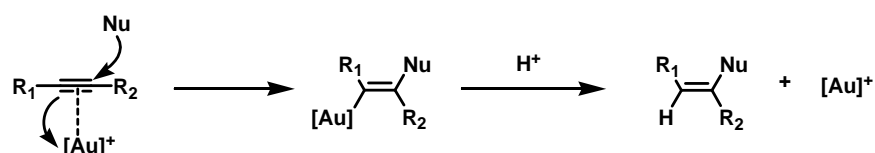


Figure 1. Anti-addition of Nucleophile to Activated Alkyne.

Direct Addition of Nucleophiles to Alkynes and Allenes.

Gold complexes can activate alkynes and allenes towards attack by oxygen,^{7-9,19} nitrogen,^{8,10,11} carbon,^{8,12,13} and sulfur^{14,15} nucleophiles. In an example of an oxygen nucleophile, Hashmi et al. used AuCl_3 to produce oxazoles from N-propargylamides (Figure 2).¹⁶ Intermediate **2**, formed from a 5-*exo*-

dig cyclization, was isolated and characterized. When deuterated substrate **4** was subjected to the reaction conditions, **6** was isolated as a single diastereomer. This finding strongly suggests a stereospecific anti-addition of the carbonyl oxygen to the activated alkyne, followed by protodeauration.

The utility of sulfur nucleophiles in gold-catalyzed reactions was unexpected, due to the high affinity of gold for sulfur ligands. However, Morita and Krause have shown this method to be a useful route to sulfur-containing heterocycles from thioallenes (Figure 3).¹⁴ While yields were moderate to good, axis-to-center chirality transfer was complete. This transfer of stereochemistry from allenes to tetrahedral carbon centers is a common feature of gold-catalyzed reactions.

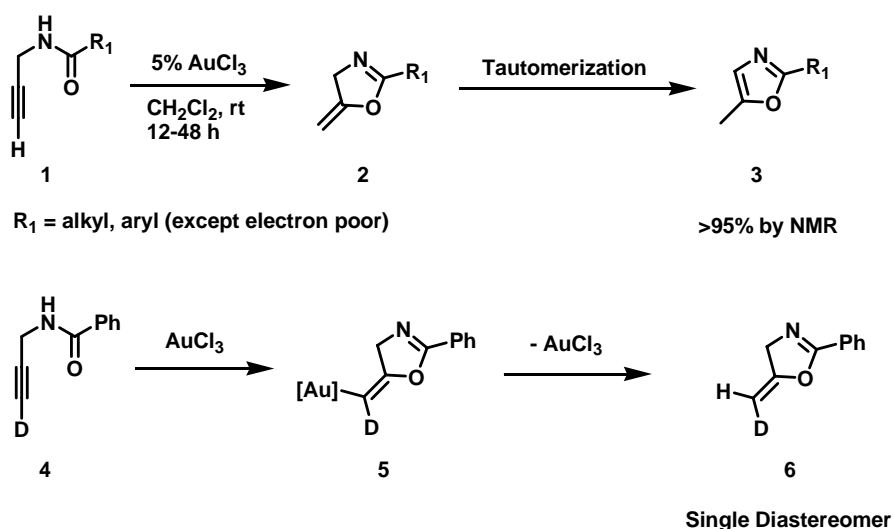


Figure 2. Formation of Oxazoles and Demonstration of Anti-addition.

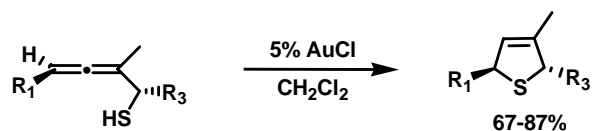


Figure 3. Intramolecular Addition of a Sulfur Nucleophile to an Allene.

Direct Addition of Nucleophiles to Alkenes and the Proton-mediated Reaction Argument

It has been suggested that some reportedly gold-catalyzed reactions are actually proton catalyzed, in particular for additions of O-H or N-H bonds across an alkene.^{17,18} Whereas metal salts and complexes containing triflate anions were reported to be active in these reactions, Hartwig and coworkers¹⁸ demonstrated that it is likely triflic acid itself which is the active catalyst. The authors also suggested useful protocols for determining if a reaction was metal or acid catalyzed.

Another criticism of gold-catalyzed reactions is the assignment of special reactivity to gold when it might in fact be simply behaving as an oxophilic Lewis acid. One case that could have been in this

category if not for proper control reactions was described by Gevorgyan and coworkers.¹⁹ Good yields were obtained for the formation of 3-bromofurans (**10**) from bromoallenones (**7**) using AuCl₃. Further investigation showed that AlCl₃ was also an effective catalyst for this transformation, demonstrating that AuCl₃ was likely functioning as an oxophilic Lewis acid (Path A, Figure 4). When various gold(I)-phosphine catalysts were used, however, a different mechanism became active, which produced 2-bromofurans (**14**) (Path B, Figure 4). In this case, the gold complex behaves as a carbophilic Lewis acid. Evidence for the carbenoid structure **13** is described below.

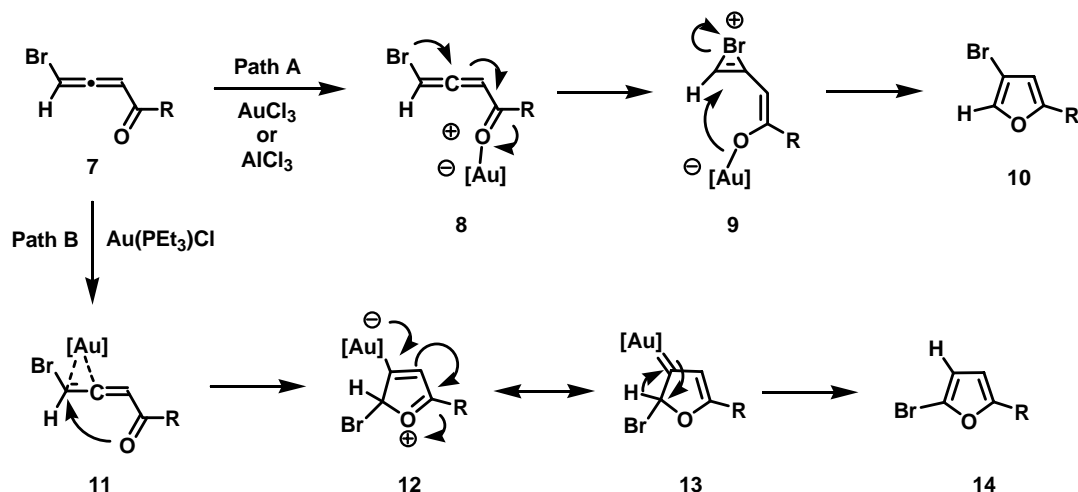


Figure 4. Gold Behaving Alternately as an Oxophilic (Path A) or Carbophilic Lewis Acid (Path B).

Gold Carbenoid Behavior

To demonstrate the ability of gold cations to stabilize an adjacent positive charge through π -backbonding, two manifolds for addition of a leaving-group-bearing nucleophile to an activated alkyne (Figure 5, Equation 1) have been reported. Toste and coworkers reported the addition of an azide followed by N₂ release, as shown in Equation 2.²⁰ After elimination of N₂, a gold-stabilized carbocation is formed (**20**). A formal 1,2-hydride shift followed by Au-C bond collapse regenerates the gold catalyst and forms 2H-pyrrole **21**. Subsequent aromatization generates the pyrrole product. In the second manifold (Equation 3), sulfoxides act as the nucleophile-leaving group pair.²¹⁻²³ In the intramolecular example shown, the benzothiepine structure **26** is formed by a Friedel-Crafts type reaction followed by protodeauration. It is proposed that these reactions would only take place if a partial gold carbene (**24**) structure were present.

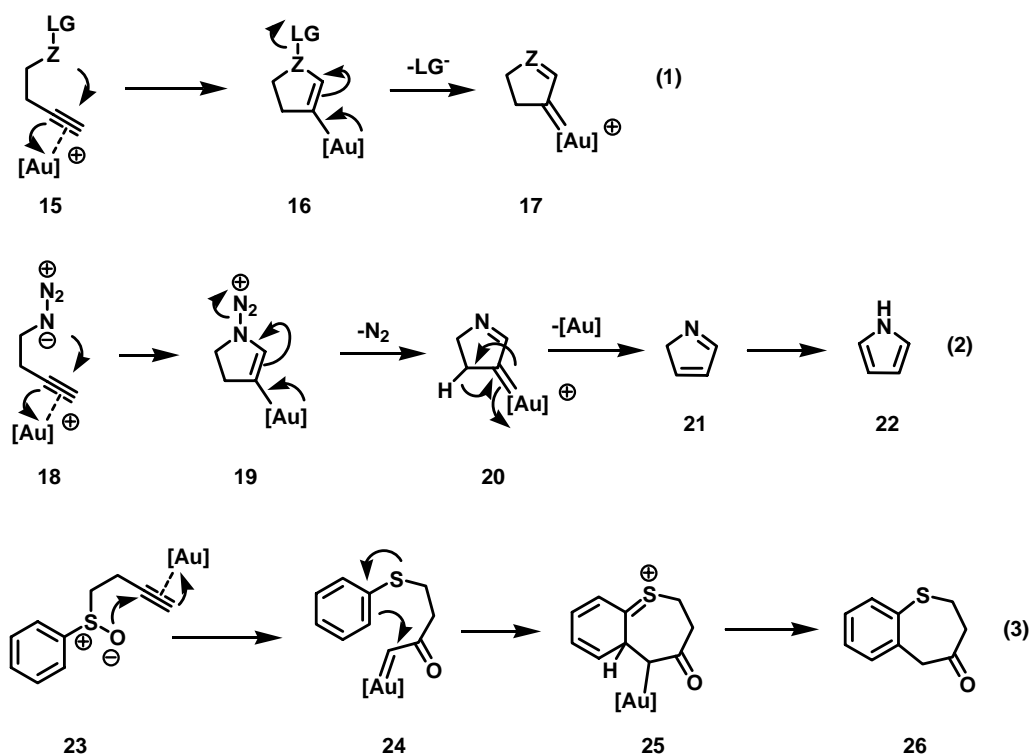


Figure 5. Evidence of Gold-Carbene Behavior.

Enyne Cyclizations

Enyne cyclizations have been amongst the most heavily studied areas of gold catalysis. The general reaction schemes for the *5-endo-dig* and *6-exo-dig* cyclizations are demonstrated in Figures 6 and 7. Coordination of the metal center activates the alkyne toward nucleophilic attack by the alkene. The generated carbocation is stabilized by the metal, forming a cyclopropane (**29** and **33**). At this point, the reaction may take several paths, depending upon the reagents present. Either the cyclopropane may be opened by a variety of nucleophiles²⁴⁻²⁸ or skeletal rearrangements may form terminal structures such as **30** for 1,5-enynes,²⁹ or **35** and **37** for 1,6-enynes.³⁰

Dozens of scaffolds have been synthesized using gold-catalyzed enyne cyclizations by varying the substituents on the enyne. Controlling the direction that cyclizations take, and where nucleophiles are introduced, is a continuing area of research.

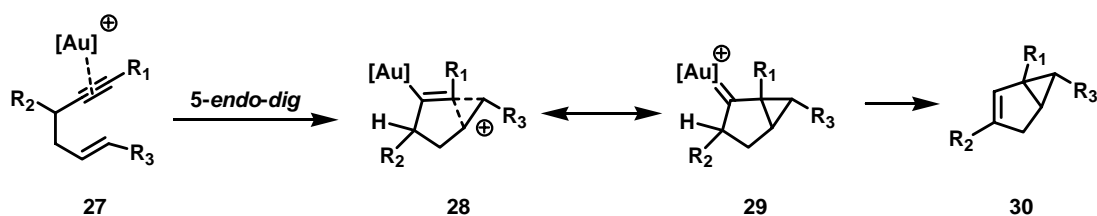


Figure 6. 5-Endo-dig Cyclization of 1,5-enynes.

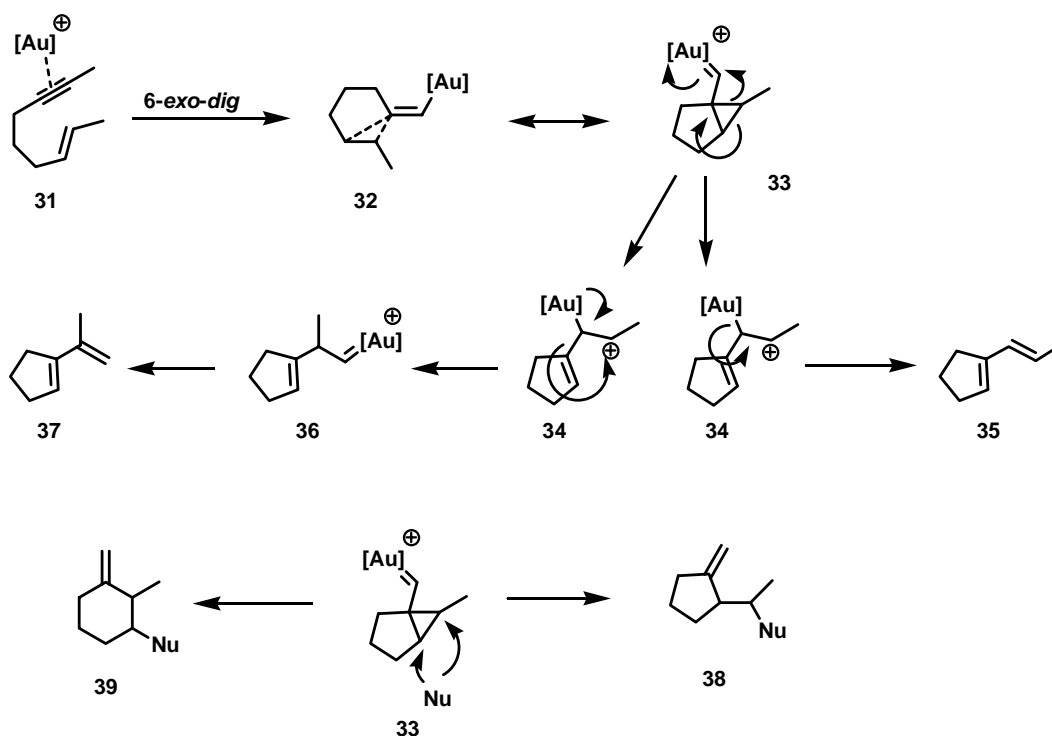


Figure 7. 6-Exo-dig Cyclization of 1,6-enynes.

PROGRESS TOWARD ASYMMETRIC INDUCTION

Counter-ion Control

Until this summer, all reports of asymmetric catalysis by gold made use of chiral amine or phosphine ligands. Toste et al. have now demonstrated a powerful method of enantioselection by a chiral *counterion*.³² Due to the linear manner that ligands bind to gold, the stereochemical information in the inner sphere is believed to be too far from the reacting species for efficient stereinduction. However, in non-coordinating and nonpolar solvents the counterion is strongly attracted to the cationic gold complex. The counterion approaches away from the bound phosphine ligand due to sterics, and hence approaches closer to the reacting species. The scope of this method is currently limited to the intramolecular addition of oxygen and nitrogen nucleophiles to allenes. In some cases combination of a chiral counterion with a matched chiral ligand on gold achieved maximal stereinduction.

ARYL C-H ACTIVATION/FUNCTIONALIZATION

In a very different form of reactivity, gold salts have been shown to activate aryl C-H bonds. In 1931, Kharasch and Isbell published the interactions of AuCl₃ with various solvents.³³ They demonstrated that auric chloride can insert into select C-H bonds forming HCl and ArAuCl₂ species.

Electron rich arenes were more reactive towards this chemistry; arenes less electron rich than benzene were not reactive. Beginning in 2003 a series of communications from the He group proposed that this C-H activation might be employed in catalysis. They demonstrated that aryl-gold species appear to attack electrophiles in an S_N2 manner. An intermolecular nucleophilic epoxide ring-opening catalyzed by $AuOTf_3$ resulted in opposing selectivity to what would be expected from a Friedel-Crafts mechanism (Figure 8, Equation 1).³⁴ Other significant support for a C-H activated aryl species being the active catalyst came from an apparent S_N2 reaction with a primary alkyl triflate.³⁵ The most electron rich arenes employed produced only a linear product, but increasing amounts of branched products were obtained upon reaction with sequentially less electron rich arenas (Figure 8, Equations 2-4). Significantly, preparation of the supposed $PhAuCl_2$ intermediate in the case of benzene produced only the linear product (Equation 5). While the actual mechanism of action in these cases is still disputed, these results indicate a potentially useful mechanism for arene functionalization by gold.

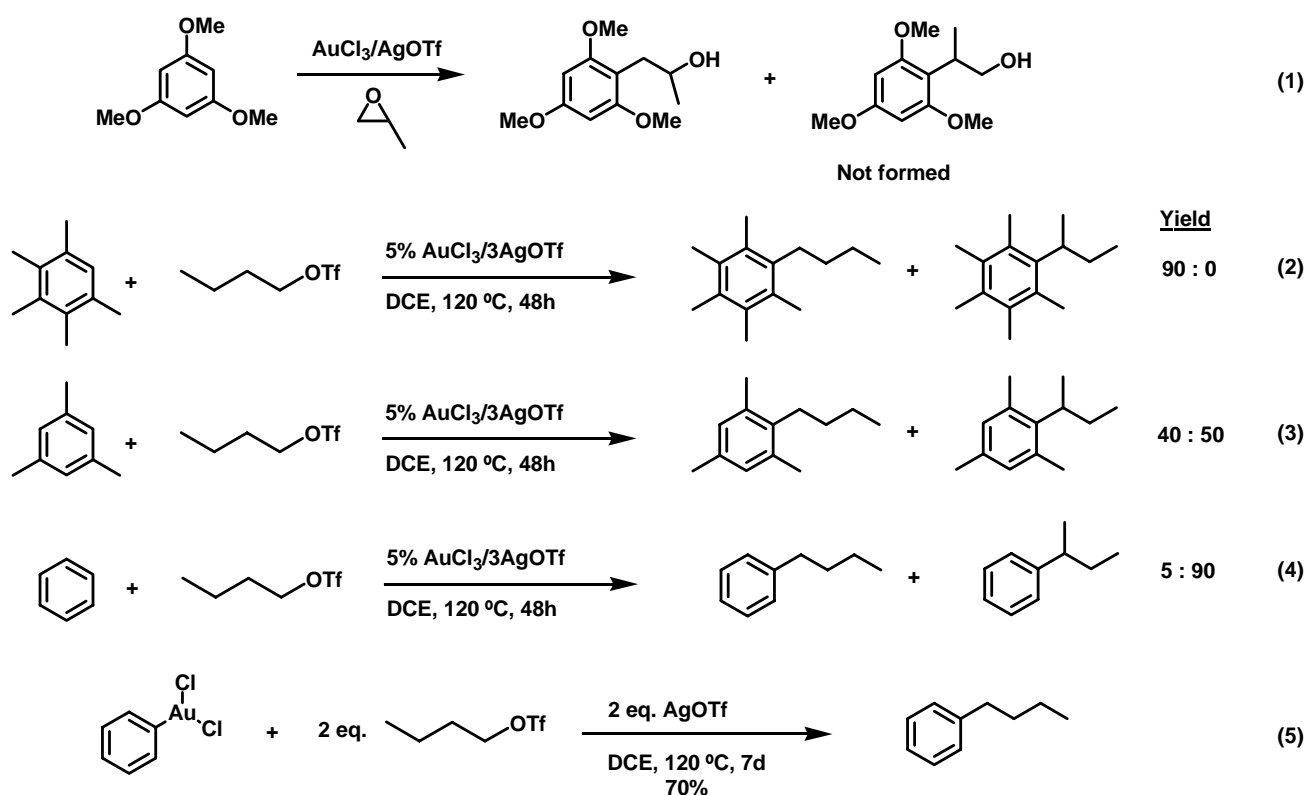


Figure 8. Evidence of Gold Catalyzed Aryl C-H Functionalization.

CONCLUSION

Homogeneous catalysis by gold complexes is a rapidly growing field of research. Gold complexes are carbophilic Lewis acids capable of stabilizing adjacent positive charge through carbene-

like behavior. Gold salts have also been implicated in catalytic aryl C-H functionalization. Although much work remains to be done to clarify the mechanisms involved, the utility of these catalysts has been recognized and their application is becoming frequent.

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