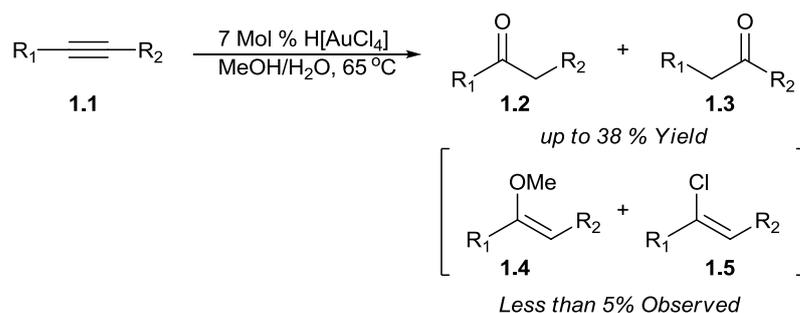


Chapter 1 – Introduction to Gold Catalysis

1.1 History

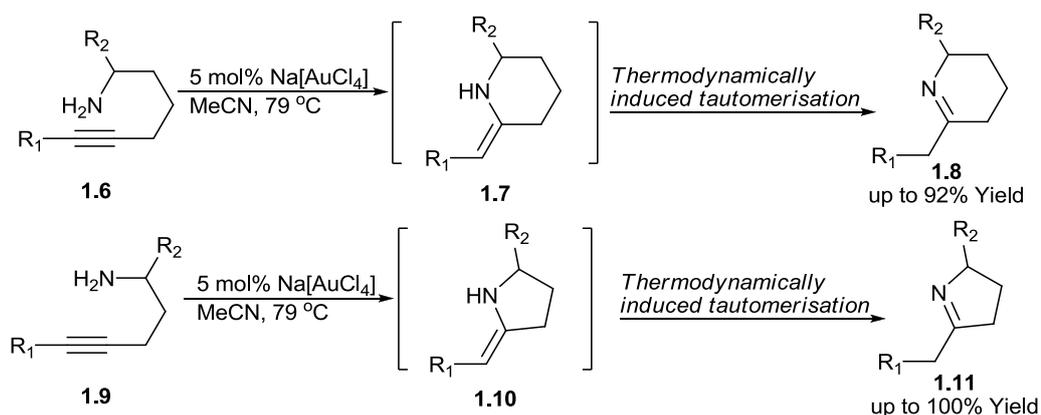
Gold has been seen as the most precious metal for thousands of years and is the basis of most monetary systems throughout the world. Gold occurs naturally in its elemental form and owing to its low reactivity, can be mined directly from the earth, leading to prospecting and the “gold-rush” observed in the latter part of the 19th century. It was used by ancient civilisations in some of their most important artefacts as representation of wealth and gods. Today the Mayan art or Egyptian burial masks look as beautiful as when they were first cast, emphasising the resilience and inertness of metallic gold. Due to the unreactive and durable nature of metallic gold it has been used in dentistry and more recently in electronics as it is also highly conductive to electricity. One might even say that the pursuit of gold was the catalyst for modern chemistry with the early alchemists generating vast amounts of knowledge, most of which is still relevant today.

Ironically gold was ignored in favour of other transition metals during the last century when chemists really began to explore homogeneous catalysis. This was somewhat of an oversight with the successes of its neighbouring metals, mercury and platinum in homogeneous catalysis and early work into organo-gold halides,¹ although its perceived inertness and value goes some way in explaining the attitude at that time. The first homogeneous gold catalysed reaction was not reported until 1976 when Thomas, working with stoichiometric tetrachloroauric acid and alkynes in aqueous methanol, observed ketones **1.2** and **1.3**, as the major products (Scheme 1). At the time it was believed to be some sort of gold(III) oxidation,² however it is indeed catalytic with the reaction of ethynylbenzene reaching almost six turnovers. The minor products (**1.4** and **1.5**) observed provide a glimpse into the future where gold is now routinely used to perform direct nucleophilic additions.

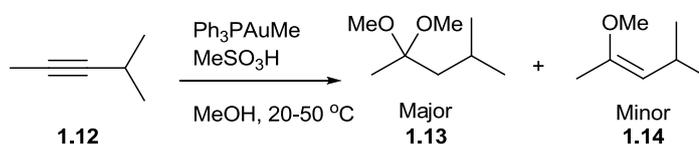


Scheme 1 Thomas Gold(III)-Catalysed Reaction

Little work followed on homogeneous gold catalysis through the 1980s and 1990s although reports from Utimoto (Scheme 2)^{3, 4} and Teles (Scheme 3)⁵ describe exciting developments, a review in 2000 by Dyker⁶ only reports as few as 13 reactions.



Scheme 2 Utimoto's Hydroamination of Alkynes



Scheme 3 Teles' Gold(I)-Catalysed Reaction

This was all to change in the following decade with the price of gold initially dropping, it being less toxic than mercury and the catalytic reactivity finally being (re)discovered.

By 2012 there have now been thousands of reactions published with hundreds of research groups dedicated to the amazing catalytic power shown by gold catalysts.⁷⁻¹³

More recently, stable cationic gold(I) complexes have been developed, the advantage of these catalysts over the generation of the cationic gold *in situ* is that it removes the requirement for hygroscopic silver salts which often produce traces of Brønsted acid. The two most commonly used are air and moisture stable and were developed by Gagosz (Cat B)¹⁵ and Echavarren (Cat C),¹⁶ which are both now commercially available (Figure 3).

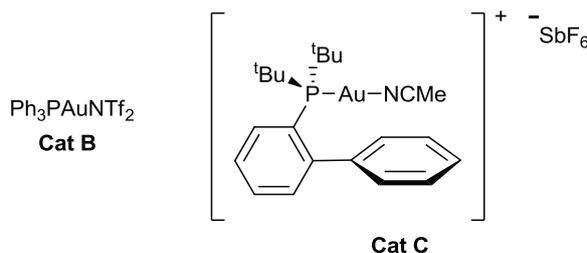
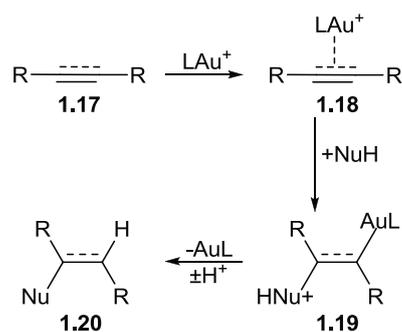


Figure 3 Air Stable Cationic Gold(I) Catalysts

The gold(I)⁺ cation is isolobal with H⁺ having an empty 6s orbital and since it is a large, diffuse cation that shares its positive charge across its ligands, one would expect orbital interactions to dominate over charge interactions in the binding of a second ligand. Gold(I) may therefore be considered a ‘soft’ Lewis acid, preferring ‘soft’ electrophiles such as C-C π systems. Calculated enthalpies of formation between alkynes and electrophiles (such as Brønsted acids, iodine, iodonium compounds, gold and silver complexes) show that bond energies associated with gold are the strongest ones.¹³ Gold(I) is therefore a strong carbophilic Lewis π -acid and its low oxophilicity means it is very effective and selective in coordinating to unsaturated carbon bonds. The coordination and the cationic nature of the gold species elicits a pull of electron density towards it, essentially activating the unsaturated carbon towards nucleophilic attack (Scheme 4).



Scheme 4 Gold(I) Activated π -Bond Towards Nucleophilic Attack

The bonding in transition metal complexes with alkenes or alkynes as π ligands occurs as a σ bond is formed by overlap of the π system of the ligand with an empty metal orbital of suitable symmetry. A π interaction then occurs through back-bonding of electron density from a filled metal d orbital into an antibonding π^* orbital of the alkene or alkyne. Complex formation alters the structures of the metal fragment and the ligand, elongation of the double or triple bond is a consequence of the net shift of electron density from the bonding π orbital into the antibonding π^* orbital. A partial pyramidalisation (of alkenes) or bending (of alkynes) then occurs as a result of the ensuing rehybridization. However the bonding with gold and the same π system cannot be considered to participate in the same way with calculations on gold(I)-ethylene complexes indicate that back bonding accounts for a small fraction of the bonding energies.¹⁷

This can be explained by the apparently high energy antibonding orbitals being unable to participate in back bonding, whereas the non-bonding orbitals are sufficiently low enough and more suited to overlap with the filled gold 5d orbitals. The lack of back bonding into the π ligands leave them more electron deficient and the strongly Lewis acidic nature of the complex contributes to the ease of nucleophilic addition. The Lewis acidic strength of a species often correlates with its electronegativity and in the case of gold (2.4, compared with 1.9 for Ag) it is crucial to realise that the electronegativity arises from the relativistic contraction of the valence 6s and 6p orbitals. Relativistic effects really only become influential with larger elements, when the 4f and 5d orbitals are filled, such as with mercury, platinum and gold (Figure 4).

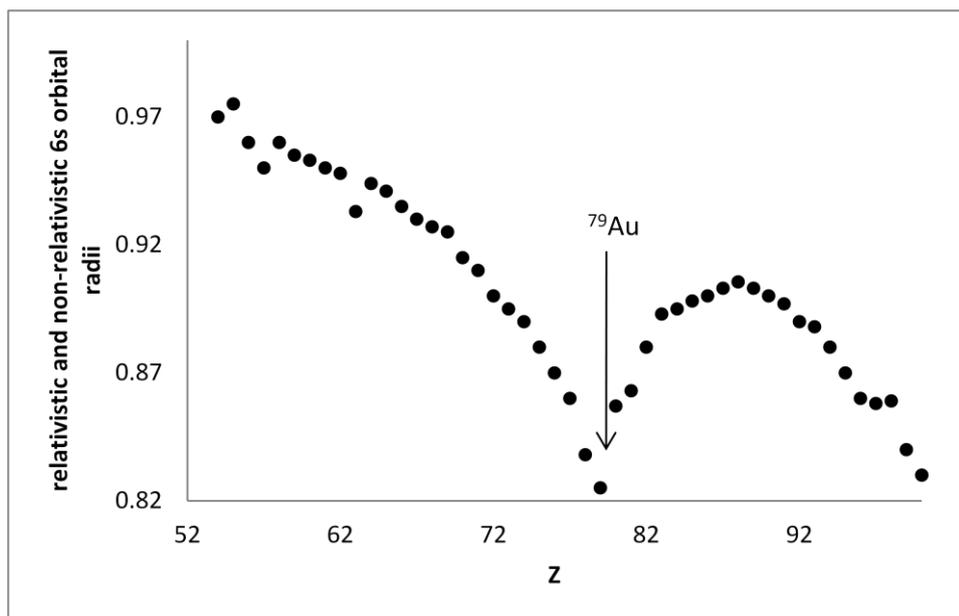
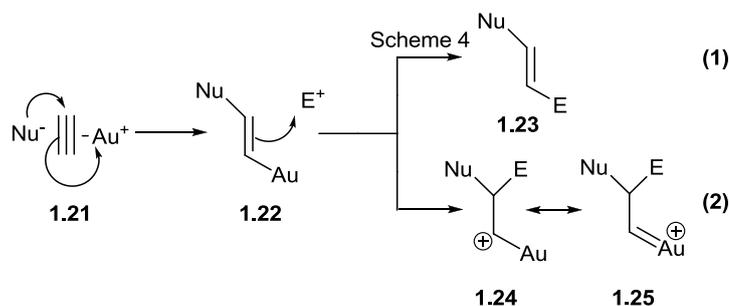


Figure 4 Calculated Relativistic Contraction of The 6s Orbital¹⁷

As the mass of the atoms rise, the radial velocity of the electrons travelling around the nucleus increase, resulting in increasing the mass of the electrons in accordance to special relativity (mass increases towards infinity as a body's velocity approaches the speed of light). This increase in mass of the electron causes the Bohr radius of the electron to decrease (Bohr radius is inversely proportional to mass of the electron) in effect contracting the s, and to a lesser extent, the p orbitals. The contraction of s and p orbitals causes the expansion of the 5d orbitals due to the greater shielding of the nucleus, and therefore creating a weaker nuclear attraction between the 5d and the nucleus. This means that the overlap with the enlarged and diffuse gold 5d orbitals with the non-bonding orbitals in the gold π -ligand complex is even greater.

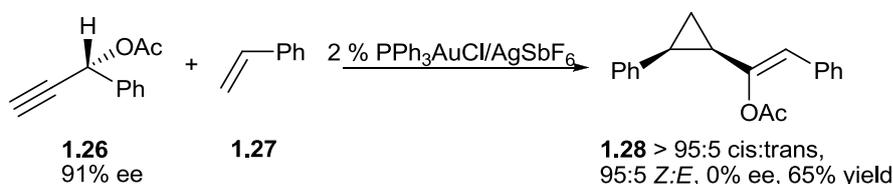
However further calculations suggested that the coordination mode is other than a simple Lewis acid-base interaction.¹⁷ It was determined that the Au-CH₂⁺ fragment should feature multiple bond character through σ bonding to the CH₂ and back bonding from the relativistically expanded 5d electrons in Au. These studies could lead to an alternate pathway to that shown in Scheme 5 (1), where the Au could facilitate the trapping of a stabilised “carbene” (2) by relativistically enhanced back bonding into the developing conjugate cation (Scheme 5).



Scheme 5 Carbocation/Carbene Intermediate

The formulation of Au=C is however purely illustrative as the calculated bond lengths (2.067(4) Å) are shorter than that of some prototypical C(sp²)-Au bonds hence, considerable partial positive charge will reside on the “carbene” C atom. Whether the entity was referred to as a “gold carbene” or “gold-stabilised carbocation” is seen therefore largely a matter of semantics.

In an attempt to determine the true nature of the intermediate, experimental evidence was needed, so research into the mechanism of nucleophilic attack on gold activated alkynes was carried out by the Toste group. At the time the reactive intermediate was a theoretical model, with Toste believing it to be carbene in nature. To enable the examination of the intermediate, a mechanistic study into the reaction of the stereoselective gold(I) catalysed olefin cyclopropanation was carried out (Scheme 6).¹⁸



Scheme 6 Stereoselective Cyclopropanation

The reaction produced the cyclopropane **1.28** with excellent cyclopropane and olefin diastereoselectivity with complete loss of enantiomeric excess, consistent with an intermediate containing a vinyl gold(I)-carbene species **1.29**. A mechanistic hypothesis

was proposed with concerted carbene transfer from gold(I)-carbenoid intermediate (Figure 5).

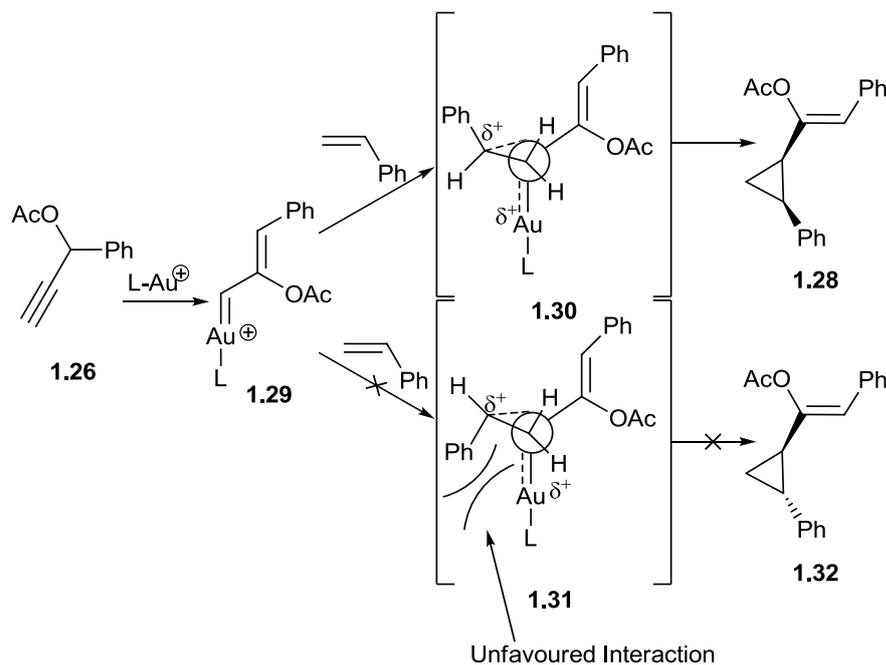
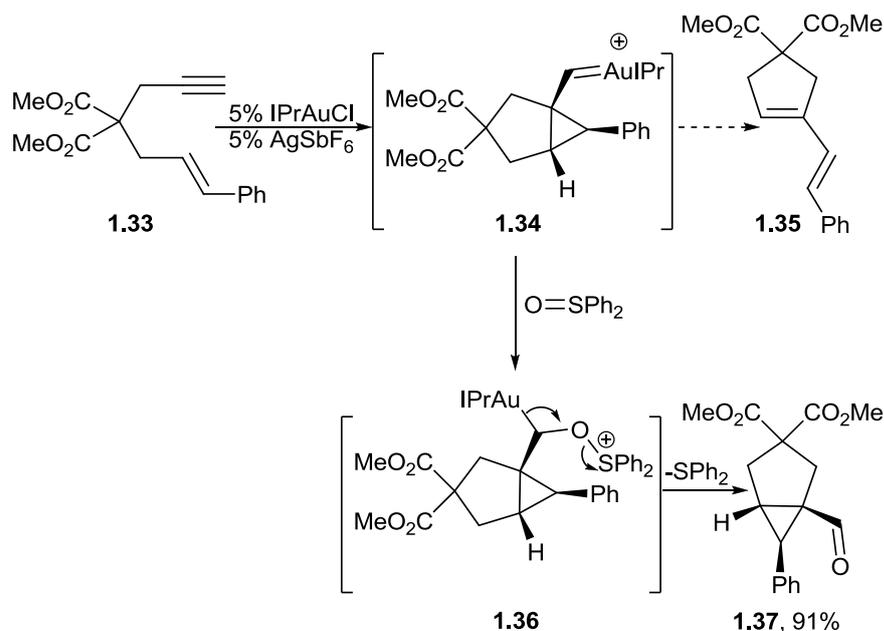


Figure 5 Stereoselective Pathway

The gold-carbene intermediate **1.29** is formed and then a concerted cyclopropanation ensues with the more sterically favoured pathway **1.30** to produce the cis product, **1.28**.

Trapping the gold-carbene by intercepting an initial reaction with a species which is known to be reactive towards metal-carbenes would provide further evidence towards the gold-carbene intermediate. This was observed by using a nucleophilic oxidant which caused oxygen transfer to the electrophilic gold-carbene intermediate **1.34** (Scheme 7).¹⁹

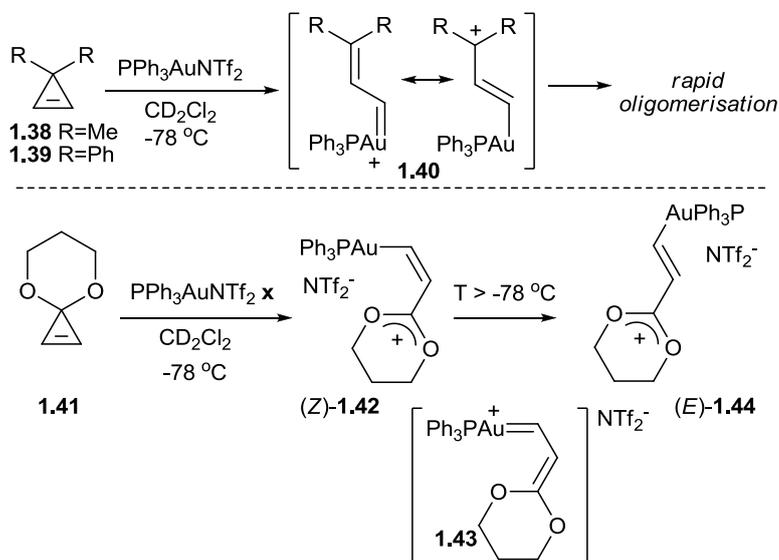


Scheme 7 Trapping the Carbenoid as an Aldehyde

Without the presence of the highly reactive (towards metal-carbenes) sulfoxide the reaction would have proceeded towards **1.35**, however, when the gold-carbene is formed (**1.34**) the reaction gets intercepted by the nucleophilic oxidant which then traps the carbene as an aldehyde **1.37**.

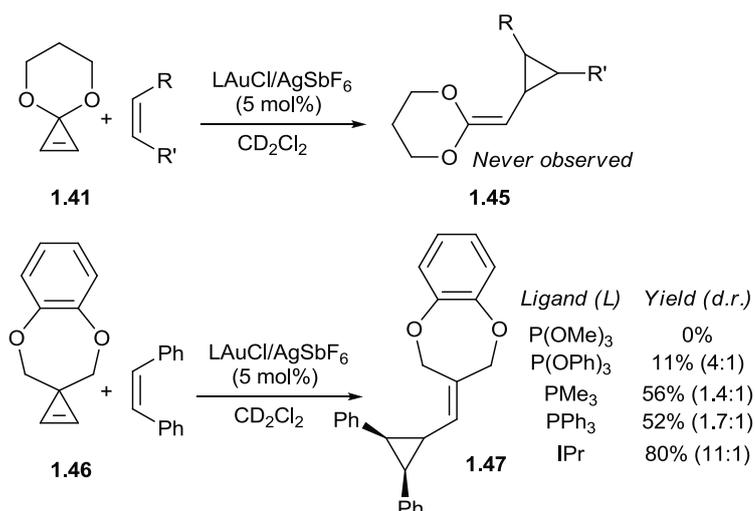
The work described above (Scheme 6 and Scheme 7) provides evidence for the gold-carbene intermediate. This was definitively followed up in 2009 (midway through the body of this PhD work) by the groups of Fürstner and Toste who carried out gold-catalysed experiments with cyclopropenes to try and determine the extent of cationic vs. carbene nature of these intermediates. Consequently, Fürstner and co-workers set out to generate a “gold carbene” *via* an independent route to investigate the bonding situation.²⁰ They chose to react cyclopropenes **1.38-1.39** with the gold catalyst [(Ph₃P)Au][NTf₂] in order to investigate the organogold intermediate **1.40** which should be formed (Scheme 8). Since treatment of **1.38** and **1.39** with the gold catalyst resulted only in rapid oligomerisation, they utilised *O*-substituted **1.41** instead, successfully observing the *O*-stabilised organogold intermediate **1.42-1.44**. ¹H-NMR studies proved that the species formed at -78 °C, is the oxocarbenium cation species (*Z*)-**1.42**, which isomerises to (*E*)-**1.44** upon warming. Using the magnitude of rotational barriers to estimate the strength of π -bonds, the researchers thus conclude that the organogold intermediates must be very close to the cationic resonance extreme **1.42** & **1.44** rather

than the carbene form **1.43**, though one could still argue that the *O*-substituents in the investigated intermediate could be biasing the system towards the cationic form.



Scheme 8 Füstner's Investigations into the Nature of Gold Catalysed Reaction Intermediates

Indeed, Toste and co-workers followed up these investigations by carrying out theoretical and experimental investigations into the gold(I)-catalysed cyclopropanation of cyclopropene substrates (Scheme 9).²¹ Based on both calculations and experimental evidence, they argue that earlier conclusions regarding the intermediate lying towards the cationic extreme is valid only in the presence of highly carbocation stabilising oxygen atoms. In the absence of these *O*-atoms, stabilisation from the gold moiety grows, its magnitude dependent on increasing electrophilicity of the allyl cation. Thus, the intermediate from **1.41** is expected to react as a gold-stabilised carbocation, while the intermediate from **1.46** is expected to react more as a gold-stabilised carbene. Indeed, cyclopropene **1.41** produces no cyclopropanation product **1.45** in the presence of gold(I) catalysts, whereas cyclopropene **1.46** produces stereospecific olefin cyclopropanation **1.47**. The researchers also observe that the yield is highly dependent on the ancillary ligand, with strongly π -acidic ligands [e.g. $\text{P}(\text{OMe})_3$] increasing the carbocation-like reactivity and thus producing no or little product **1.47**, while good σ -donor and poor π -acceptor ligands (e.g. NHC ligand IPr) increase the carbene-like reactivity, thus producing product **1.47** in high yield and d.r.



Scheme 9 Toste's Investigations into the Nature of Gold Catalyzed Reaction Intermediates

Toste and co-workers therefore conclude that the reactivity of the gold-stabilised intermediates can be accounted for by a continuum ranging from a gold-stabilised carbene extreme to a metal coordinated carbocation, with the position of a given gold species on this continuum being determined by both the carbene substituents as well as the ancillary ligand.

It is beyond the scope of this introduction to cover the wide and diverse reactions catalysed by gold, which has been the subject of numerous reviews^{7-13, 22, 23}. The main focus of this PhD has been the exploration of gold-catalysed reactions with cyclopropenes and a brief review of this area will be discussed in the following chapter.

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