Article

A golden era in modern chemistry

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Introduction

Gold (Au), the 79th element of the periodic table, has been valued since the beginning of recorded history. The initial usage of gold was probably ornamental, owing to its superior malleability, and evidence of its use can be traced as far back as the Bronze Age (ca. 5000 BC).[1] One of the most famous historical examples is the mask and sarcophagus of the young Egyptian pharaoh Tutankhamen (Fig. 1a), dated 1323 BC, which was made almost entirely of gold.

This fondness for gold is attributed to its resistance to oxidation, and its malleability. Gold is often found in its pure form, and historically this was mainly in rivers and streams. Its desirable characteristic colour inspired the element's name – 'Aurum' which when translated from Latin means 'shining dawn'. Other civilisations have similar references to gold as well. For example, the Incas referred to gold as 'the tears of the sun', and the Greeks thought of gold as a dense combination of water and sunlight.

The first valuation of gold can be dated back as far back as 3100 BC, in the first Egyptian dynasty, where its founder Menes equated one part of gold to two and a half parts silver. However, the use of gold as a universal form of currency didn't eventuate until *ca*. 600 BC when Lydian merchants produced the first gold coins (Fig. 1b).[2] This preceded Greek coinage, which was eventually adopted by the Roman Empire and the rest is history. Gold's resilience to oxidation made it ideal for this purpose.

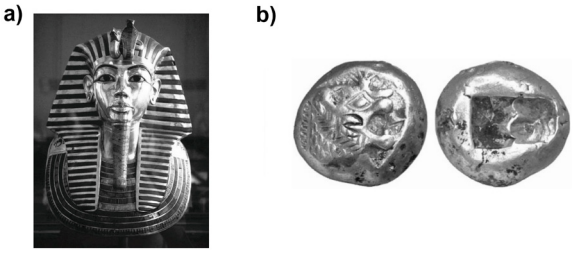


Fig. 1. a) The mask of the Pharoah Tutankhamen, b) examples of early coins created by Lydian merchants from the 6th Century B.C.

Gold was sought after throughout early history not only for the purposes listed above, but also for religious reasons. Gold is mentioned throughout the Christian Bible (e.g., Genesis 2:10-12) and even further back to mythological times. For example, in Greek mythology the god Zeus presented himself to a woman in the form of a shower of gold. This resulted in the birth of the hero Perseus who goes on to kill the evil Medusa.[3] The association of gold with the gods gave gold a divine status in ancient times: a way of communicating with the gods. It was even considered to be a link to immortality.

In the Middle Ages, this quest for immortality was at the core of western alchemy. The biggest and probably best known goal of alchemy was to produce the Philosopher's stone – a substance believed to be an elixir of life for achieving immortality, with the ability to turn any base metal into pure gold. Eventually, in the 17th and 18th centuries, alchemy declined. Robert Boyle's scientific method, led famous chemists Antoine Lavoisier and John Dalton to disprove the alchemical notion of the five fundamental elements. This was the birth of modern day chemistry.

The current use of gold in synthetic chemistry most often involves the use of its oxidised species Au(I) and Au(III), synthetically prepared from the strong acid aqua regia.[4] Access to these species has enabled a paradigm shift of the metal's once perceived inertness. As a result, the understanding of the metal's properties and applications has been a rapidly growing topic in recent times.

The rest of this article describes and explains two main paths gold is now taking in chemistry: the development of chemotherapeutic agents, and the very recent and once thought improbable application to homogeneous catalysis.

Gold Chemotherapeutics

Although alchemists used gold in the treatment of a variety of illnesses, there was no scientific evidence for such activity until the late 1800s,[5] when Robert Koch showed that the gold salt $K[Au(CN)_2]$ prevented the growth of bacteria (bacteriostasis). Since then gold has been included in realms of heavy metal therapy.

Rheumatoid Arthritis

In the 1930s Forestier showed that gold salts could be effective in the treatment of rheumatoid arthritis. Some of the drugs used in this trial, namely gold sodium thiomalate (Myochrysine, Fig. 2a) and gold thioglucose (Solganal) in the US and sodium bis(thiosulfato)gold(I) and sodium thiopropanolsulfate-*S*-gold(I) in Europe are still in clinical use today. The introduction of auranofin (Fig. 2b) in 1985 provided an oral alternative; however, the effectiveness is far less than the above intramuscularly administered drugs. The mechanism of action was not very well understood for a long time, but Stephen L. De Wall and co-workers have carried out experiments to suggest that square planar heavy metals [including Au(III)] can facilitate peptide release from MHC (II) proteins – proteins essential for normal immune function, and prevent an autoimmune response that causes the symptoms of rheumatoid arthritis.[6,7] They also postulated that the Au(I) compounds used for rheumatoid arthritis are prodrugs and provide *in vitro* evidence for its intracellular oxidation via

hypochlorite release (OCl^-) from macrophages in the synovial fluid of joints.

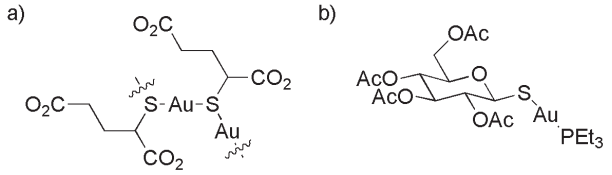


Fig. 2. The chemical structures of a) the polymeric aurathiomalate and b) auranofin.

With administration of many heavy metal compounds, there are side effects. Side-effects which result in discontinuation are experienced by 35% of patients. Along with rashes that can develop into severe dermatitis, mouth, tongue and laryngeal ulcers can also appear, as well as mild-to-severe kidney damage. Long term use of gold drugs can also cause chrysiasis – a dermatological condition that results in an irreversible discolouration of the skin to a gray-purple or gray-blue colour. In conjuction with these side effects, and the drug's latent effectiveness of 4-6 months, this class of drugs has been superseded in the treatment of rheumatoid arthritis.

Cancer

Investigations into the antitumour properties of gold compounds began in the mid-1970s.[8] Reasons for this included the fact that gold(III) compounds have a d^8 electron configuration, and are isoelectronic to platinum, adopting a square planar geometry that could possibly mimic the coordination mode of cisplatin – the most widely used heavy metal-based drug for the treatment of cancer. Other reasons for investigation were the fact that these drugs (from rheumatoid arthritis research) suppress the immune response and are therefore anti-inflammatory, and that studies showed that there was no increased risk of other diseases using gold compounds.

One of the first to be investigated was auranofin (*vide supra*) and results from studies on mouse tumour models showed *in vitro* inhibition of DNA and RNA replication, and therefore protein synthesis.[9] The P-Au(I)-S arrangement was considered essential for activity, and so development was concentrated on making modifications to the phosphine groups to impart solublility and also to modify the thiolates to incorporate biologically active thiols. These have proven successful against human leukaemia, with greater *in vitro* activity than cisplatin.

Unfortunately, although promising *in vitro*, *in vivo* they were practically inactive owing to cysteine thiols on the surface of proteins readily displacing the thioglucopyranoside moiety, deactivating the complex. Au(III) compounds at this time were also promising *in vitro*, but were not stable because of to the reducing environment of cells. It is safe to say that initial studies were discouraging.

In the late 1980s, the beginnings of a new class of thiol-free compounds emerged with the synthesis of the mononuclear bis-diphenylphosphinoethane (dppe) Au(I) complex by Sadler's group (Fig. 3a).[10] This compound was not only active *in vivo*, but the *in vitro* results showed that this class of compounds worked by a mechanism different from both auranofin and cisplatin, possibly owing to stability in vivo against ubiquitous thiols. Unfortunately, the solubility of this compound was very low in water ($<1\mu g\ mL^{-1}$) and the activity was less than that of cisplatin. Berners-Price and coworkers have since developed a more water-soluble version of this compound that is selective for cancer breast cells over healthy cells (Fig. 3b).[11]

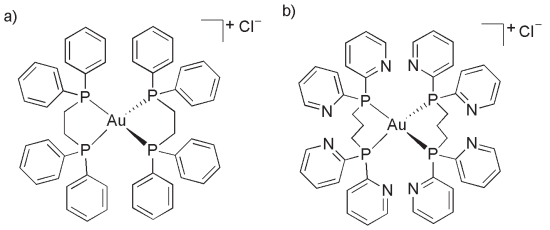


Fig. 3. Tetrahedral Au(I) complexes showing a) $[Au(dppe)_2]Cl$ and b) the cancer cell-selective $[Au(d2pypp)_2]Cl$ complex.

Hard donor polydentate ligands in gold(III) complexes were used to combat the instability *in vivo* (Fig. 4). In general, these compounds were highly cytotoxic with IC_{50} values in the low μM/nM range. Of interest was that these complexes could kill cells that cisplatin could not; thus, like the Au(I) compounds, this suggested a different mode of action.

The Berners-Price group were able to provide insight into this unknown mode of action by using *N*-heterocyclic carbenes (*N*HCs, Fig. 5).[12] These ligands have similar properties to phosphines, they are easier to modify with different substituents (allowing tunability), but, more importantly, they form more stable complexes. The group synthesised a variety of lipophilic cationic dinuclear bisbidentate *N*HC complexes (e.g., Fig. 5a), with the rationale of exploiting the negative membrane potential of the mitochondrial membrane (which is elevated in cancer cells) for entry into the mitochondria. The results of *in vitro* testing showed that they induced mitochondrial membrane permeabilisation (MMP), which plays a key

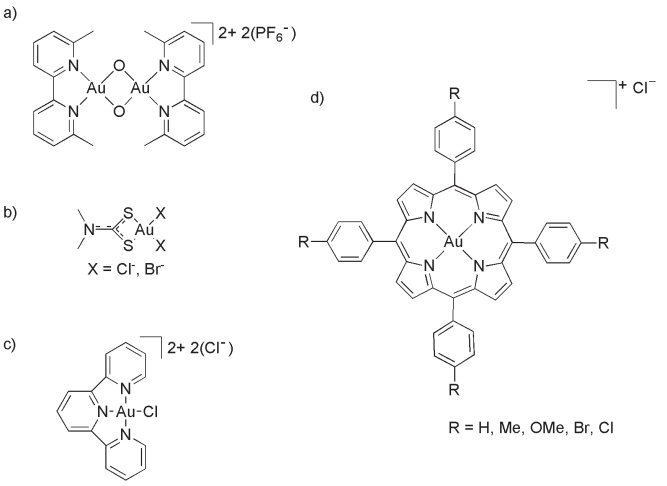


Fig. 4. Examples of gold(III) complexes with antitumour activity: a) an oxo-bridged dinuclear bis(bipyridine) complex, b) dithiocarbamate complexes, c) a gold(III) terpyridine complex and d) porphyrin complexes.

role in apoptosis, whilst also providing evidence for enzyme inhibition.

Another example is a mononuclear (amino-*N*HC)AuCl complex (Fig. 5b), which was shown to have a greater antiproliferative effect than cisplatin, with cellular selectivity for a particular glioblastoma line (U-87 MG).[13] Also interesting was that the activity of the complex was based on a DNA-dependent mechanism, in contrast to evidence gathered on many other Au compounds that involved accumulation in mitochondria followed by enzyme inhibition (DNA-independent).

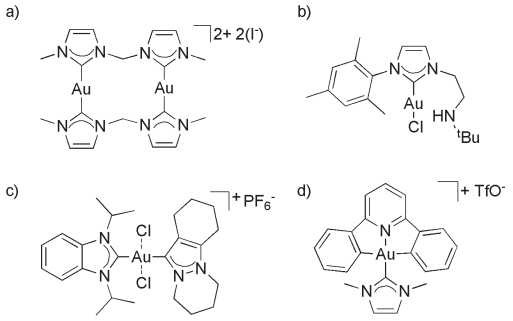


Fig. 5. Examples of successful *N*HC-based Au complexes tested for anticancer activity: a) a bis(di*N*HC) dinuclear cationic species, b) a amino-*N*HC neutral gold chloride complex, c) a heteroleptic Au(I or III) cationic complex, and d) a *N*HC gold(III) C^N^C tridentate cationic complex.

There are also examples of Au(III) *N*HC drugs based on cyclometallated C^N^C tridentate ligands, whereby the *N*HC ligand is auxiliary in the remaining coordination site (Fig. 5d).[14] These compounds were tested in a variety of cell lines, and over 80% of them possessed a higher activity than cisplatin. The mechanism by which these compounds act is proposed to be caused by binding to topoisomerase-linked DNA, which leads to DNA cleavage and eventually apoptosis.

There are now a variety of NHC-based Au complexes that have been studied for their antitumour properties. Activities for these complexes vary significantly, but most are comparable to cisplatin,[15,16] if not better.[13,14,17-19]

One of the main modes of action for gold(I) compounds, and one of the main targets when testing gold compounds, is inhibition of the selenoenzyme thioredoxin reductase (TrxR). Normally this enzyme is involved in regulating cellular redox; however, in malignant cells it is involved in apoptosis, cell proliferation and metastasis, and is upregulated in some cancers. For the lipophilic cationic gold complexes, they rapidly accumulate into the mitochondria, and selectively inhibit the enzyme (Fig. 6). This in turn causes an increase in oxidised thioredoxin (Trx2) and peroxide levels which stimulates MMP, allowing these species to diffuse into the cytosol where the hydrogen peroxide oxidises cytosolic thioredoxin (Trx1). Oxidised thioredoxin then activates apoptotic pathways leading to cell death.

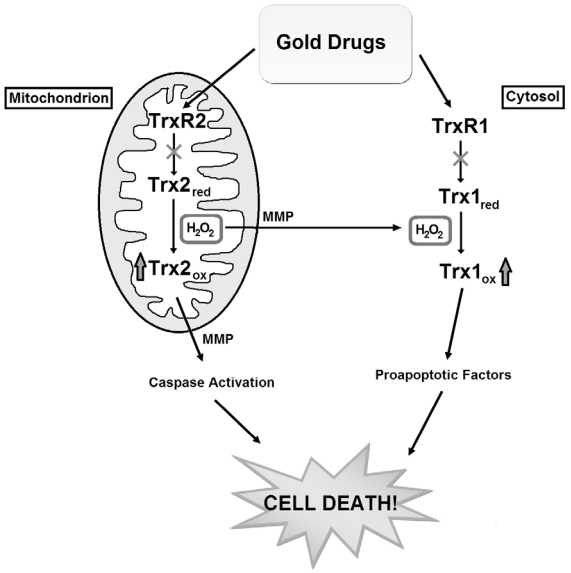


Fig. 6. A simplified mechanism of action of gold(I) antitumour agents via inhibition of thioredoxin reductase (adapted from ref. 20).

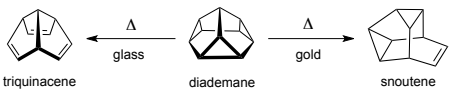
Gold(I) Catalysis

The Rise of Homogeneous Gold Catalysis

The idea of gold having chemical activity was long thought improbable owing to its well-established inert nature and its resistance to oxidation – properties which had led to gold's application in dentistry, jewellery and currency. Therefore, any use in catalysis was also considered improbable: a quote by Hubert Schmidbaur in the mid-1990s (translated by Nugent)[21] reflects this:

The general doctrine appears to have been that gold, in contrast to its neighbor element on the periodic table, platinum, in neither the homogeneous nor the heterogeneous phase, exhibits activity that is in any way satisfactory. Gold was considered to be 'catalytically dead'

Nugent mentions that this misconception of inertness provided the first hints towards gold activity. In the 1970s de Meijere and co-workers were interested in the thermal conversion of diademane to triquinacene (Scheme 1).[22] The investigation involved making a heat flow reactor, which was lined with metallic gold for its heat conductivity. However, when the reaction was carried out, instead of synthesizing the desired product, they produced snoutene. Further investigations led to the synthesis of a gold(I) complex (dicyclopentadiene gold chloride), which performed the conversion to snoutene at room temperature, strongly supporting the notion that the lining of the reactor was acting non-innocently.



Scheme 1. The initial discovery of gold's catalytic ability. Using a glass reactor, the expected retrocyclisation product triquinacene was isolated; with a gold lined reactor, the unprecedented product snoutene was produced.

The first reports of homogeneous catalysis emerged in the 1980s by the Utimoto group, employing a chiral ferrocenylphosphine gold(I) complex to catalyse the aldol reaction between aldehydes and enolates. Although they achieved high yields for this reaction, the reaction lacked selectivity (between *cis* and *trans* isomers) and the *cis* isomer had poor enantiomeric purity.

Although there have been several reports of gold(III) catalysis in the 1990s,[23-25] these catalysts had low turnover numbers owing to the propensity to reduce to Au(0), and were performed at high temperatures. There was also evidence of Au(I) being more catalytically active than the trivalent analogue Au(III), but all the reactions involved the presence of acid.

A seminal report of Teles and co-workers showed an example of LAu(I)Cl catalysts (where L = arsenes, phosphines and phosphites) in the alcohol addition to alkynes, where the turnover numbers achieved were greatly improved (5000 for L = PPh_3).[26] Teles also noted that although electron-withdrawing ligands improved the catalytic activity, the stability of the catalyst suffered. This publication was the first that gained consensus for the idea that gold was chemically active. Since this report, the rate of publication has increased exponentially, with over 200 publications submitted solely on homogeneous gold catalysis in 2010.[21] As significantly more work has been conducted with gold(I) catalysts, this will be the focus of the next section.

Reactivity of Gold(I) Catalysis

Gold catalysts act as carbophilic π-Lewis acids – i.e., they are particularly selective in coordinating to carbon-carbon π-bonds, namely alkynes, alkenes and allenes (Fig. 7).

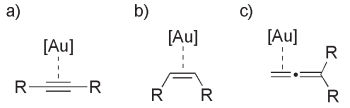


Fig. 7. Gold catalysts, [Au], activate alkynes (a), alkenes (b) and allenes (c).

The catalysts must be activated to cationic gold(I) species (Fig. 8), which traditionally involves abstraction of a halide *via* silver metathesis. Once activated, the catalyst coordinates in an η^2 fashion, activating the unsaturated bond to attack by nucleophiles such as oxygen, nitrogen, sulphur, and even carbon. Once the nucleophile attacks, the catalyst is now more strongly σ-bound to allow any further transformation of the substrate to occur. The final step, protodeauration, is the recycling step, whereby the catalyst is substituted by a proton, allowing reaction of other substrate molecules.

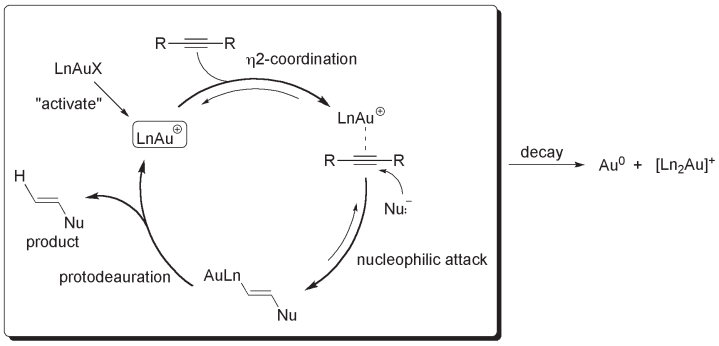


Fig. 8. The general gold(I) catalytic cycle.

This unique mode of reactivity of gold(I) has opened access to a variety of reactions that can be carried out under much milder conditions than previously reported. Unlike other heavy metals, gold(1) does not cycle between oxidation states during the catalytic cycle, and so it remains a soft Lewis acid for the entire reaction, allowing reactions that previously had to be carried out under harsh conditions to be carried out under much milder conditions, often in higher yields.

The Development of Gold(I) Catalysts

Initially, the gold(I) compounds tested consisted of phosphine ligated compounds of the formula $(PR_3)AuCl$. Phosphine ligands were already ubiquitous at the time gold(I) catalysis came about and were already successful as ligands in other heavy metal catalysis owing to their high σ-donor strength and poor π-back donation. This made the catalysts more stable than with related Werner-type complexes (*N*, *O* donors), allowing higher turnover numbers. There are now a variety of commercially available phosphine ligated Au(I) catalysts available (Fig. 9).

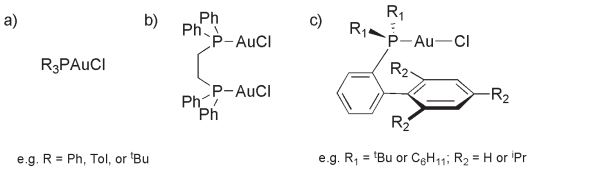


Fig. 9. Common commercially available phosphine-based gold(I) catalysts. One type of phosphine-based Au(I) catalyst to note is the range of biphenyl phosphine complexes (c) developed by Antonio Echavarren (see reference 27). The active catalyst is supposedly, in part, stabilised by a metal-arene interaction between the metal center and the phenyl ring. It is now widely used as a catalyst.

At the time this class of catalysts were developed, *N*HCs were well established in the literature. These ligands have a greater σ-donor strength than phosphines, are relatively easily synthesised, and their complexes were more stable. The most common of the *N*HCs are the 'Arduengo' imidazol-2-ylidenes (Fig. 10a) which vary with different *N*-substituents.[28] The catalysts with the most practical *N*HCs are those with sterically-hindering groups at these sites, which not only stabilize the free carbenes during synthesis, but also help shield the gold by any incoming destabilizing species in solution.

In practice, NHCs are usually synthesised with identical substituents, as the symmetric species are more trivial to synthesise than the non-symmetric analogues. Additionally, the extent of σ-donation is limited by the proximity of the two heteroatoms to the donor centre. Because of this, efforts have been made to move the heteroatoms to more remote locations of the heterocycles. Example of these so-called abnormal/mesoionic carbenes (MICs) are the isomeric imidazol-4-ylidenes (Fig. 10b)[29] and the 1,2,3-triazol-5-ylidenes (Fig. 10c).[30] The advantage of

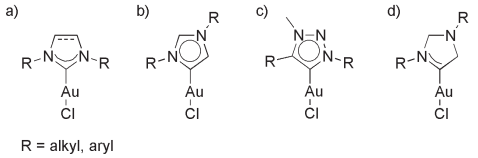


Fig. 10. a) The Arduengo-type imidazole-2-ylidene *N*HC complex, b) the isostructural mesoionic imidazol-4-ylidene complex, c) the 1,2,3-triazolylidene complex and d) the saturated imidazol-4-ylidene complex.

triazolylidenes, aside from the strong σ-donation is that they are more synthetically trivial owing to the copper-catalysed azide-alkyne cycloaddition reaction (CuAAC), and so have a more accessible range of tunability. To push the σ-donation even further, research has been undertaken into making saturated analogues of these complexes (Fig. 10d).[31]

As mentioned in the previous section, the activation of gold catalysts usually requires adding a silver salt to abstract the halide co-ligand. Recent studies have shown that in some cases the silver species (also a group 11 metal) can act non-innocently and partake in the reaction. Determining whether these reactions are completely gold catalysed is not necessarily trivial. To avoid the use of silver altogether, the idea of using labile ligands was adopted. The best example of this is work by Gagosz and coworkers, who synthesised the triphenylphoshinegold(I) triflimidate catalyst.[32] The triflimidate coligand (NTf_2^-) is labile enough to create the active species in solution, owing to its weakly coordinating nature. A variety of triflimidate analogues of the gold phosphines are now commercially available (Fig. 11).

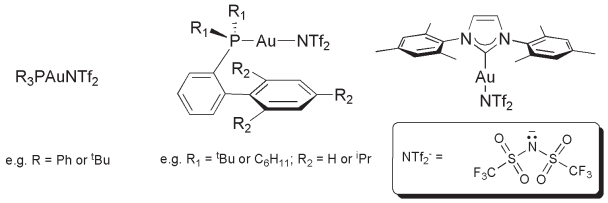


Fig. 11. A selection of new 'silver-free' triflimidate gold complexes now available.

There has been interest in the synthesis of multinuclear gold(I) catalysts for two reasons. The first reason is because of the higher gold content per mole of compound and increasing potency. The second reason is recent evidence of dinuclear participation or "dual activity" of gold species, owing to the isolation of dinuclear gold-substrate intermediates, supported by theoretical calculations. The Nolan and Toste groups have studied these in some detail (Fig. 12).[33-35]

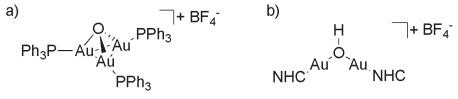
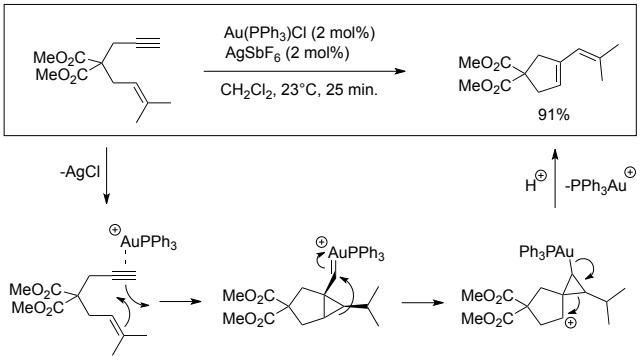


Fig. 12. Multinuclear complexes created by (a) Toste and (b) Nolan.

These catalysts function by the dissociation of an LAu^+ fragment in an equilibrium process, generating the active species. Nolan's catalyst when dissociated can impart Lewis acidity (LAu^+) and Brønsted acidity (LAu-OH) concertedly.

Along with the development of gold catalysts, gold-catalysed reactions are constantly being developed. There is now a plethora of gold-catalysed reactions that exist, with a few benchmark reactions to which these novel catalysts are subjected. One common example is the intramolecular enyne cycloisomerisation which typically rearranges 1,6-enynes via 5-*exo*-dig or 6-*endo*-dig pathways (Scheme 2).[36]



Scheme 2. Proposed mechanism for the gold(I)-catalysed cycloisomerisation of 1,6-enynes (see reference 36).

Conclusion

Gold has had a huge influence on the development of human civilization. Its physical properties prompted its use in currency as a universal form of exchange, and aesthetically we have long appreciated gold. Its inferred divine status stimulated alchemical quests that led to the development of chemistry. Even within this field, gold has emerged as a unique transition metal at the forefront of antitumor therapy, and has recently given rise to a new mode of homogeneous catalysis. Gold catalysts not only act differently from other late transition metals, but offer access to new and unique chemical transformations. The extent of catalyst development in such a short period of time indicates a desire to explore gold's full potential. The fact that research into gold chemistry is still being carried out shows us that, even after five millennia, gold still has more to offer.

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References

1. Gopher, A.; Tsuk, T.; Shalev, S.; Gophna, R. *Curr. Anthropol.* **1990,** *31*, 436-443.
2. Goldsborough, R. A Case for the World's Oldest Coin: Lydian Lion. *http://rg.ancients.info/lion/article.html* (accessed 3 August 2013).
3. Wogan, J. Gold and Religion. *http://ezinearticles.com/?Gold-and-Religion&id=4440456* (accessed 3 August 2013).
4. Schwartz, A. T.; Kauffman, G. B. *J. Chem. Ed.* **1976,** *53*, 235.
5. Shaw, C. F. *Chem. Rev.* **1999,** *99*, 2589-2600.
6. De Wall, S. L.; Painter, C.; Stone, J. D.; Bandaranayake, R.; Wiley, D. C.; Mitchison, T. J.; Stern, L. J.; DeDecker, B. S. *Nat. Chem. Biol.* **2006,** *2*, 197-201.
7. Roche, P. A. *Nat. Chem. Biol.* **2006,** *2*, 178-179.

8. Tiekink, E. R. T. *Crit. Rev. Oncol. Hemat.* **2002,** *42*, 225-248.
9. Mirabelli, C. K.; Johnson, R. K.; Sung, C. M.; Faucette, L.; Muirhead, K.; Crooke, S. T. *Cancer Res.* **1985,** *45*, 32-39.
10. Berners-Price, S. J.; Mirabelli, C. K.; Johnson, R. K.; Mattern, M. R.; McCabe, F. L.; Faucette, L. F.; Sung, C.-M.; Mong, S.-M.; Sadler, P. J.; Crooke, S. T. *Cancer Res.* **1986,** *46*, 5486-5493.
11. Humphreys, A. S.; Filipovska, A.; Berners-Price, S. J.; Koutsantonis, G. A.; Skelton, B. W.; White, A. H. *Dalton Trans.* **2007**, 4943-4950.
12. Barnard, P. J.; Baker, M. V.; Berners-Price, S. J.; Day, D. A. *J. Inorg. Bioc.* **2004,** *98*, 1642-1647.
13. Wang, C.-H.; Shih, W.-C.; Chang, H. C.; Kuo, Y.-Y.; Hung, W.-C.; Ong, T.-G.; Li, W.-S. *J. Med. Chem.* **2011,** *54*, 5245-5249.
14. Yan, J. J.; Chow, A. L.-F.; Leung, C.-H.; Sun, R. W.-Y.; Ma, D.-L.; Che, C.-M. *Chem. Commun.* **2010,** *46*, 3893-3895.
15. Siciliano, T. J.; Deblock, M. C.; Hindi, K. M.; Durmus, S.; Panzner, M. J.; Tessier, C. A.; Youngs, W. J. *J. Organomet. Chem.* **2011,** *696*, 1066-1071.
16. Patil, S.; Deally, A.; Hackenberg, F.; Kaps, L.; Müller-Bunz, H.; Schobert, R.; Tacke, M. *Helv. Chim. Acta* **2011,** *94*, 1551-1562.
17. Horvath, U. E. I.; Bentivoglio, G.; Hummel, M.; Schottenberger, H.; Wurst, K.; Nell, M. J.; van Rensburg, C. E. J.; Cronje, S.; Raubenheimer, H. G. *New J. Chem.* **2008,** *32*, 533-539.
18. Weaver, J.; Gaillard, S.; Toye, C.; Macpherson, S.; Nolan, S. P.; Riches, A. *Chem. Eur. J.* **2011,** *17*, 6620-6624.
19. Sivaram, H.; Tan, J.; Huynh, H. V. *Organometallics* **2012,** *31*, 5875-5883.
20. Bindoli, A.; Rigobello, M. P.; Scutari, G.; Gabbiani, C.; Casini, A.; Messori, L. *Coord. Chem. Rev.* **2009,** *253*, 1692-1707.
21. Nugent, W. A. *Angew. Chem. Int. Ed.* **2012,** *51*, 8936-8949.
22. Meyer, L.-U.; de Meijere, A. *Tetrahedron Lett.* **1976,** *17*, 497-500.
23. Komiya, S.; Sone, T.; Usui, Y.; Hirano, M.; Fukuoka, A. *Gold Bull.* **1996,** *29*, 131-136.
24. Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991,** *56*, 3729-3731.
25. Xu, Q.; Imamura, Y.; Fujiwara, M.; Souma, Y. *J. Org. Chem.* **1997,** *62*, 1594-1598.
26. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998,** *37*, 1415-1418.
27. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005,** *127*, 6178-6179.
28. Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991,** *113*, 361-363.
29. Xu, X.; Kim, S. H.; Zhang, X.; Das, A. K.; Hirao, H.; Hong, S. H. *Organometallics* **2012,** *32*, 164-171.
30. Kilpin, K. J.; Paul, U. S. D.; Lee, A.-L.; Crowley, J. D. *Chem. Commun.* **2011,** *47*, 328-330.
31. Manzano, R.; Rominger, F.; Hashmi, A. S. K. *Organometallics* **2013,** *32*, 2199-2203.
32. Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005,** *7*, 4133-4136.
33. Ramón, R. S.; Gaillard, S.; Poater, A.; Cavallo, L.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Eur. J.* **2011,** *17*, 1238-1246.
34. Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008,** *130*, 4517-4526.
35. Gómez-Suárez, A.; Oonishi, Y.; Meiries, S.; Nolan, S. P. *Organometallics* **2013,** *32*, 1106-1111.
36. Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004,** *43*, 2402-2406.