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TUTORIAL REVIEW

Au-Catalysed Oxidative Cyclisation

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The two main strategies of gold-catalysed oxidative cyclization are discussed in this tutorial. The first one employs nucleophilic oxidants as either internal or external nucleophiles. The inherently weak O-heteroatom bond in the oxidant enables the versatile reactivities of the initial gold-promoted adduct of oxidant to alkyne, including its fragmentation into a highly reactive α-oxo gold carbene intermediate. The second features external oxidant-powered Au(I)/Au(III) catalysis, where the metal oxidation state changes during the catalytic cycle. These strategies have been applied toward the development of a variety of valuable synthetic transformations.

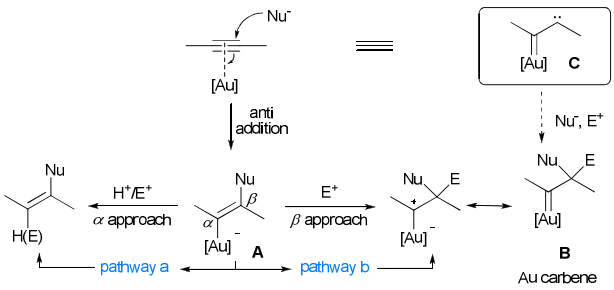
Key Learning points:

1. The two main strategies of oxidative gold catalysis
2. The reactivity manifold of the initial gold-containing adducts of nucleophilic oxidants to alkynes in the non-carbene pathway
3. The reactivities of oxidatively generated α-oxo gold carbenes
4. The oxidants capable of promoting Au(I)/Au(III) catalysis
5. The reactivities of Au(I)/Au(III) catalysis

1. Introduction

Homogeneous gold catalysis is one of a few intensely studied topics in contemporary organic synthesis and has experienced explosive development since the beginning of this millennium. Two type of gold catalysts, i.e., Au(III) salts/complexes and cationic Au(I) complexes in the form of $LAu^+ X^-$ (L: ligand; X^-: weakly coordinating or non-coordinating counter anion), have been employed, with the latter type much more versatile and predominantly studied. Early work in this area by Teles[1] and Hashmi[2] reveals the potent soft Lewis acidities of cationic gold(I) complexes. As such, they can effectively activate alkynes and allenes toward attack by a variety of nucleophiles, affording alkenylgold intermediates of type **A** (Scheme 1 using alkyne as example). With protic nucleophiles, the protodeauration of **A**, i.e., *pathway a*, renders an overall *anti* addition of H-Nu across a C-C triple bond. While this process could be promoted in theory by other metals such as Ag, Hg, Pt and Pd, Au complexes and especially $LAu^+ X^-$ is by far the most versatile and can accommodate a large array of nucleophiles, enabling facile catalytic processes under mild reaction conditions. While *pathway a* is also operative with non-protic E-Nu, an alternative, i.e., *pathway b*, for the transformation of **A** could compete. In this scenario, the E^+ generated/released can approach the alkene end of alkenylgold distal to the noble metal, as such putting a positive charge α to gold and mesomerically generating a gold carbene species (i.e., **B**). This facile access to gold carbenes is revealed in the seminal work by Echavarren,[3] where these intermediates are responsible for the rich enyne isomerization chemistry. Despite the fact that Ru, Rh and Pt complexes can also accommodate processes similar to that from **A** to **B** and, due to their less electronegative nature than Au, are generally more facile, gold complexes appear to be most versatile in catalysing the overall process, i.e., the combination of nucleophilic attack of alkynes/allenes and the gold carbene formation due to their superior activity in promoting the initial nucleophilic attack. As such, gold catalysis offers a uniquely facile access to gold carbenes from alkyne substrates. Interestingly, the overall process of forming the carbene **B** makes the gold activated C-C triple bond formally equivalent to a hypothetical α-carbene gold carbene species **C**, as sequential nucleophilic and electrophilic attacks at the free carbene centre of this provocative structure would also afford **B**. This formalism is useful as a model for understanding many gold-catalysed cycloisomerizations and the gold carbene chemistry discussed

Scheme 1 Basic reactivities of homogeneous gold catalysis



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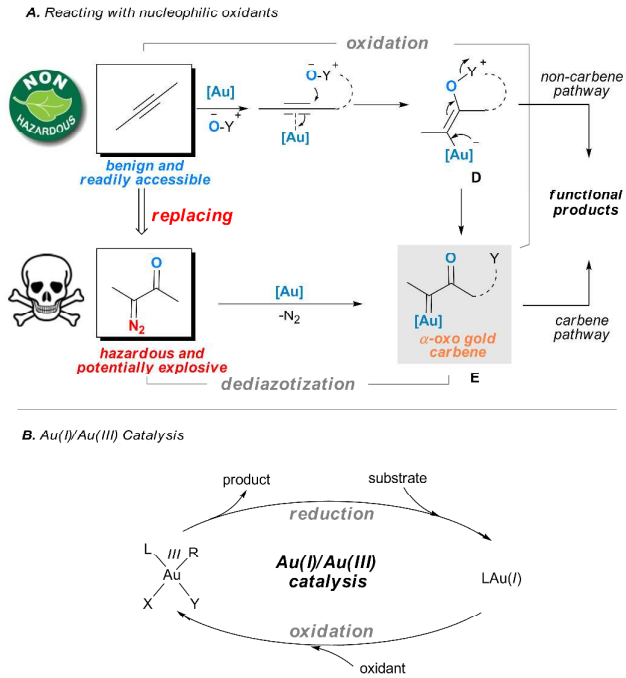
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

represented by the reactions of predominantly employed C-C triple bond.

in this tutorial and for envisioning new transformations.

In the early years, homogeneous gold catalysis was extensively explored in cyclization and cycloisomerizations based on these two types of reactivities, and the reactions are driven thermodynamically by the conversion of π bonds into stronger σ bonds. A common strategy of further improving the driving force of a reaction is oxidation by internal or external oxidants. As a result, intermediates of higher energies can be generated, which in turn enable access to novel and more potent reactivities and facilitate the development of synthetic methods otherwise not plausible. Since 2007, the incorporation of oxidation in gold catalysis has substantially invigorated this vibrant research field.



Scheme 2 Two main types of oxidative gold catalysis.

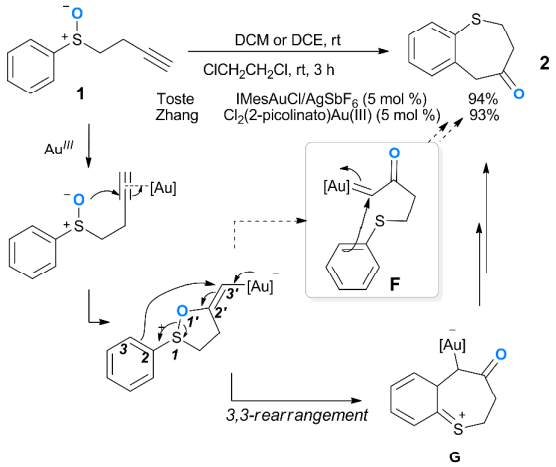
Two oxidative strategies have been emerged in the past several years and are intensely applied. As shown in Scheme 2A, the first employs an *O*-nucleophilic oxidant as nucleophile. Its gold-promoted addition to an alkyne renders an alkenylgold intermediate **D** featuring a weak O-Y bond, the heterolytic fragmentation of which, a substrate oxidation process, is the driving force for a myriad of versatile oxidative gold catalysis. A main consequence is the formation of highly electrophilic α-oxo gold carbene **E**, which can be viewed as the result of oxidizing the free carbene center of **C**. While diazo carbonyl compounds can be employed to access the same carbenes of type **E**,[4,5] this oxidation strategy, when external oxidants are used, enables the substitution of hazardous, potentially explosive and often tedious/difficult-to-access α-diazo carbonyl compounds with benign and readily available alkynes. As such, the oxidative gold catalysis would offer much improved operational safety and synthetic efficiency, in comparison to the diazo approach. Alternatively, the initial adduct **D** might bypass the intermediacy of **E**, if an alternative lower energy pathway becomes available, and directly undergo transformations to functional products.

The second strategy, as shown in Scheme 2B, is the Au(I)/Au(III) catalysis. While many gold-catalysed cross-coupling reactions such as Sonogashira and Suzuki couplings may instead be attributed to trace amounts of contaminating Pd,[6] gold does have two oxidation states, Au(I) and Au(III), that could potentially undergo redox cycles similar to Pd(II) and Pd(IV) catalysis.[7] Hence, with external oxidants, the metal centre of gold-containing intermediates generated in homogeneous gold catalysis can be oxidized, manifested as the change of its oxidation state from Au(I) to Au(III); subsequent reduction [8,9] of the thus-formed higher valent gold species would deliver oxidized products. This sequence constitutes a Au(I)/Au(III) catalytic cycle and is distinctively different from the first strategy, where the oxidation state of gold remains unchanged throughout the catalysis.

The applications of these two strategies in kinetically facile cyclization reactions have revealed many interesting and novel reactivities and resulted in the development of valuable synthetic methods. In this tutorial, these developments will be the focus of discussion, with particular emphasis on reports of original design, of novel reactivity and of exceptional synthetic value.

2. Gold-catalysed oxidative cyclization by using nucleophilic oxidants

2.1 With tethered (intramolecular) oxidants

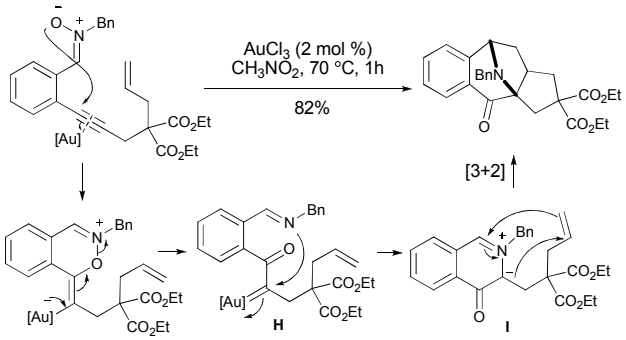


Scheme 3 With tethered sulfoxide as oxidant.

Toste[10] and Zhang[11] independently reported in early 2007 that an appropriately tethered sulfinyl group could serve as intramolecular nucleophilic oxidant, despite its mild oxidative power. As such, phenyl homopropargyl sulfoxide **1** is transformed into the tetrahydrobenzothiepinone **2** (Scheme 3). The initially proposed reaction mechanism largely follows

that the carbene pathway outlined in Scheme 2A, where the α-oxo gold carbene **F** is generated upon an initial gold-catalysed nucleophilic attack at the C-C triple bond by the sulfoxide oxygen followed by a gold-promoted heterolytic fragmentation of the S-O bond, and this intermediate would then undergo Friedel-Crafts-type cyclization by the electron-deficient carbene moiety to afford the product. However, the highly efficient formations of the 7-membered thiepinone ring in both cases appear to be surprising, especially considering the possibility of forming 5-membered sulphur ylide. Instead, detailed mechanistic studies via a combination of experiments and DFT calculations by Li and Zhang in 2012 ruled out the intermediacy of the **F** en route to **2**.[12] Instead, the initial cyclized intermediate undergoes preferably a facile 3,3-sigmatropic rearrangement to construct the 7-membered ring directly.

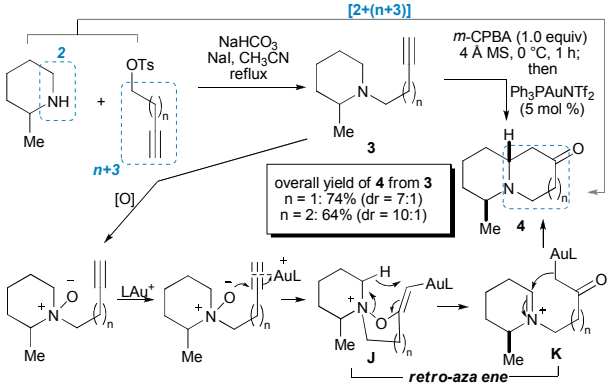
This mechanistic twist, while highlighting the versatility of the initial adduct of type **D** and the potentially competing nature of its non-carbene pathway, does not necessarily invalidate the carbene pathway. In fact, with a methyl group substituted at the alkyne terminus of **1**, the carbene intermediacy is both supported by experiments and DFT calculations.[12] Studies by Davies and co-workers of allyl alkynyl sulfoxides are also consistent with the generation of α-oxo gold carbenes.[13]



Scheme 4 Using tethered nitrone as oxidant.

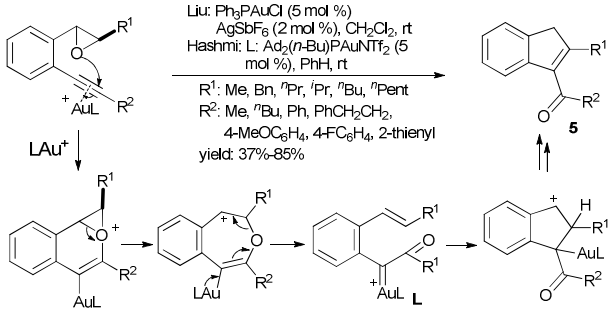
Instead of sulfoxides, Shin and co-workers reported in 2008 that nitrones[14,15] could serve as the internal nucleophilic oxidants. As shown in Scheme 4, the α-oxo gold carbene **H** is generated upon intramolecular delivery of oxygen from the nitrone moiety to the C-C triple bond. The carbene moiety of **H** reacts with the nascent imine to form an azomethine ylide (e.g., **I**), which then undergoes [3+2] cycloaddition to form the polycyclic product. Notably, Au(III) works the best in this reaction.

By extension of his original sulfoxide chemistry (Scheme 3),[11] Zhang and co-workers reported that tertiary amine *N*-oxides can be suitable intramolecular oxidants.[16-18] To avoid the decomposition of these *N*-oxides via the Cope elimination, the crude substrates, generated upon *m*-CPBA oxidation of the corresponding tertiary amines, are used without purification. As exemplified in Scheme 5, the two-step sequence, i.e., oxidation and gold catalysis, readily converts the alkynylpiperidine **3** into bicyclic piperidine-4-ones[16] or azepan-4-ones[18] in good overall yield and with synthetically useful diastereoselectivities. Since **3** can be readily prepared via a simple S_N2 reaction between a tosylated terminal alkyne and a secondary amine, this construction of the 6-/7-membered *N*-hetereocyclic ketone is realized in a conceptually simple two-pot, [2+4] or [2+5] annulation. DFT calculations do not support the intermediacy of gold carbenes but rather indicate a retro-aza ene reaction that converts the initial cyclized intermediate **J** to the iminium gold enolate **K**.[19] These reactions display good scopes and synthetically useful regio- and diastereoselectivities. Due to the prevalence of these *N*-heterocycles and especially piperidines, these reactions are of general utility and have been featured as key steps in natural product synthesis.[20,21]



Scheme 5 Using tethered in-situ generated tertiary amine *N*-oxides as oxidant in a [4+2] annulative construction of piperidin-4-ones.

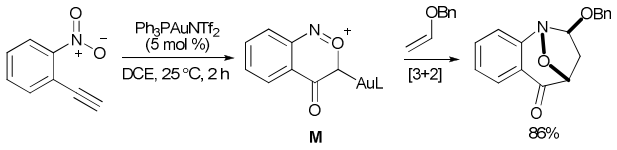
It is well established that cationic Au(I) catalysts are acidic and can be readily deactivated under basic conditions. The apparent compatibility of acidic $Ph_3PAuNTf_2$ with tertiary amine products, however, can be understood as these basic nitrogens should be protonated by the *m*-chlorobenzoic acid, an acidic byproduct of the oxidation step. To this end, the one pot approach is a necessity for the success of these reactions.



Scheme 6 Using tethered epoxide as oxidant.

Surprisingly, Liu[22] and Hashmi[23] independently reported that even disubstituted epoxides, when spaced by a double bond from and *cis* to the C-C triple bond, can react as an internal oxidant to oxidize alkynes into α-oxo gold carbenes

L, which would then be attacked by the nascent C-C double bond generated upon deoxygenation of the epoxide moiety in likely a Nazarov-like process (Scheme 6). The isolated products are synthetically useful indenyl ketones **5**. Interestingly, Liu substantiated the intermediacy of the gold carbene **L** by the observation of its oxidation by diphenyl sulfoxides to 1,2-diketones.



Scheme 7 Using *ortho*-nitro group as oxidant.

The latest variation on types of internal oxidants was reported by Liu, where an *ortho* nitro substitution in an arylacetylene is employed (Scheme 7). Different from the nitrone case,[14] a nitroso ylide (e.g., **M**) is formed as the intermediate, which readily undergoes [3+2] cycloadditions with electron-rich alkenes such as benzyl vinyl ether to furnish bridged products with excellent diastereoselectivity.[24]

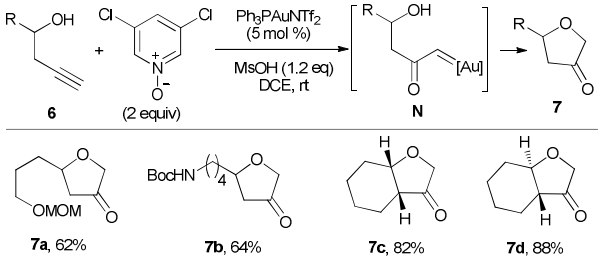
2.2 With external oxidants

While gold-promoted nucleophilic attacks at the C-C triple bond by appropriately tethered oxidants are kinetically facile and hence can serve as versatile entries into oxidative gold catalysis, the physical linkage between the two reacting partners significantly limits the reaction scope as a) a suitable functional group, being that a sulfur or nitrogen atom or an alkene needs to be present in order to deliver the nucleophilic oxygen, b) such a functional group has to be optimally positioned so that the initial cyclization forms a 5- or 6-membered cyclic intermediate, and c) unless the oxygen-delivering group is an integral part of the final target, its installation and later removal would significantly diminish the overall efficiency of any synthetic endeavor.

These problems, however, could be readily overcome if effective external oxidants could be discovered. Importantly, this intermolecular approach would make a C-C triple bond as a true surrogate of the hazardous α-diazo carbonyl moiety in gold catalysis involving gold carbene intermediates (see Scheme 2A).

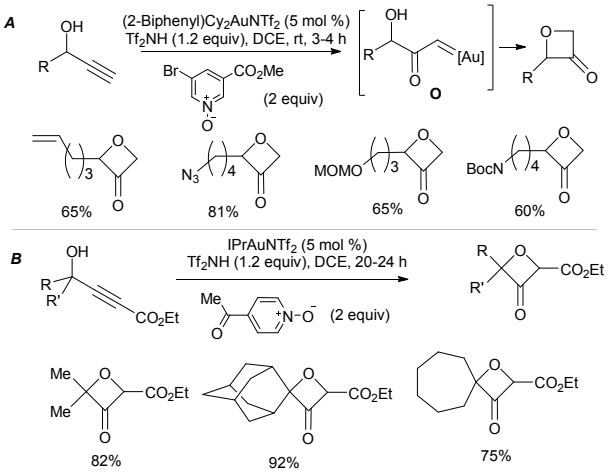
2.2.1 Trapping by heteronucleophiles

The first implementation of the intramolecular trapping approach was realized by Zhang and co-workers in 2010 using 3,5-dichloropyridine *N*-oxide as the optimized oxidant.[25] As shown in Scheme 8, the homopropargyl alcohol **6** can be easily transformed into the dihydrofuranone **7** in the presence of the Gagosz's catalyst and the oxidant. Mechanistically, the terminal C-C triple bond of **6** is likely oxidized into the α-oxo gold carbene moiety in **N**, which then is attacked by the intramolecular OH group to afford the product. Notably in the reaction conditions MsOH (1.2 equiv) is added in order to prevent the pyridine byproduct generated during the reaction from coordinating to the cationic gold catalyst and hence deactivating it. Despite the acidic conditions, the reaction can tolerate acid sensitive functional groups such as MOM in **7a** and NBoc in **7b**, which can be attributed to the buffering effect of the oxidant and the pyridine byproduct. Also shown are some additional examples of the reaction scope including the somewhat strained 5,6-trans-fused bicycle.



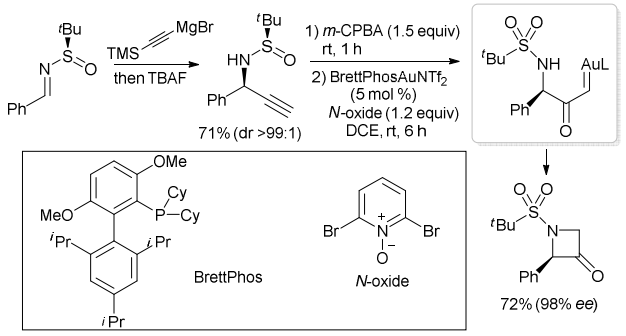
Scheme 8 Gold-catalysed cyclizations of homopropargylic alcohol using pyridine *N*-oxides as external oxidants

This facile intermolecular access to reactive α-oxo gold carbene from a C-C triple bond opens an array of other opportunities to intramolecular trapping by heteronucleophiles. For example, the same group later reported the synthesis of strained oxetan-3-ones in one step from readily available terminal secondary propargyl alcohols (Scheme 9A).[26] While the optimized oxidant appears to be somewhat intricate, other pyridine *N*-oxides are also suitable, albeit with lower yields. In addition, a stronger acid Tf_2NH performed better than MsOH. With tertiary propargyl alcohols, however, their alkyne terminus needs to be functionalized with an electron-withdrawing group in order to prevent ionization at the propargylic position under the acidic reaction conditions (Scheme. 9B). With this type of electronically deactivated alkyne substrates, a stronger oxidant, i.e., 4-acetylpyridine *N*-oxide is optimal. The formations of these strained small rings are strongly indicative of the intermediacy of the highly electrophilic α-oxo gold carbene **O**.



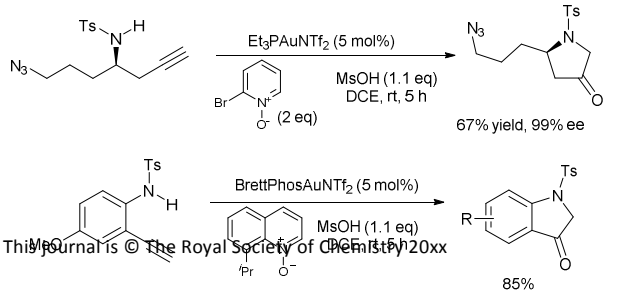
Scheme 9 Gold-catalysed cyclizations of propargylic alcohols into oxetan-3-ones

The nitrogen variant of the above reaction has also been realized by the Zhang group. Hence, strained azetidine-3-ones can be efficiently prepared from propargylic amides, as exemplified in Scheme 10. Importantly, with the sterically demanding 2,6-dibromopyridine *N*-oxide as oxidant and a bulky BrettPhos ligand, the detrimental interaction between LAu^+ and the reduced pyridine appears minimal due to steric congestion. Consequently, no acid additive is required in this reaction; as a result, a range of sensitive functional groups can be tolerated. This advance substantially broadens the potential scope and synthetic appeal of this oxidative gold catalysis strategy. Since chiral *N*-propargylsulfinamides can be prepared in excellent diastereoselectivities using chiral sulfinyl imine chemistry,[27-29] their oxidations by *m*-CPBA provide chiral sulfonamides for the gold catalysis without additional manipulation of the nitrogen protection group. With no racemization during the gold catalysis, azetidine-3-ones can be prepared readily with high *ee.*



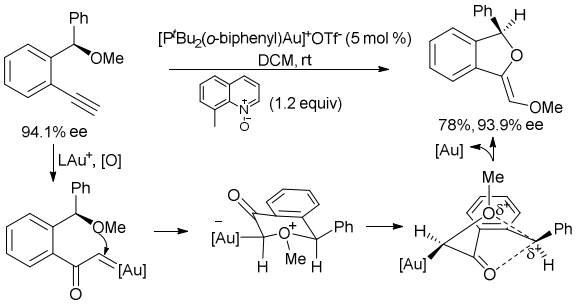
Scheme 10 Gold-catalysed cyclizations of *N*-propargylsulfonamides into strained azetidin-3-ones.

Ye and co-workers have also employed this oxidative strategy toward the facile construction of pyrrolidin-3-ones[30] and indoxyls using tethered sulphonamides as nucleophiles (Scheme 11).[31] In the former case, chiral products were obtained from readily available chiral *N*-homopropargylic amides, and one of them was converted into (-)-irniine. In the latter case, the typically observed non-oxidative 5-*endo*-dig cyclization en route to indole is outcompeted by the oxidative catalysis, highlighting its facile nature; however, with internal alkyne substrates, the indole formation was exclusively observed. It remains to be pointed out that the oxidant used in this case is 8-isopropylquinoline *N*-oxide instead of pyridine *N*-oxides. An earlier study by Zhang and co-workers[32] has established that 8-alkylated quinoline *N*-oxides are particular versatile oxidants for the oxidative gold catalysis due to a) their steric bulk so that in general no acid additive is needed and b) their generally good nucleophilicity.



Scheme 11 Formations of pyrrolidin-3-ones and benzene-fused ones via Gold-catalysed oxidative cyclizations.

Instead of protic nucleophiles, Liu reported that a closely positioned MeO group could attack an in-situ generated α-oxo gold carbene to initiate a stereospecific rearrangement. As outlined in Scheme 12, the treatment of an enantiomerically enriched 2-ethynylbenzyl ether with 5 mol % of $[(P^tBu_2(o\text{-biphenyl}))Au]^+ OTf^-$ and 1.2 equiv. of 8-methylquinoline *N*-oxide affords the cyclic product in 78% yield and with nearly perfect stereofidelity and exclusive Z-selectivity.[33] Notably, no acid additive is needed due to the combination of bulky 8-methylquinoline *N*-oxide and JohnPhos. In addition, the competitive nonoxidative carboalkoxylation reaction[34] is completely suppressed in all cases, confirming again that the oxidative gold catalysis can be facile. The fact that alternative mechanisms are not readily available to rationalize the reaction outcome offers additional support for the intermediacy of gold carbene.



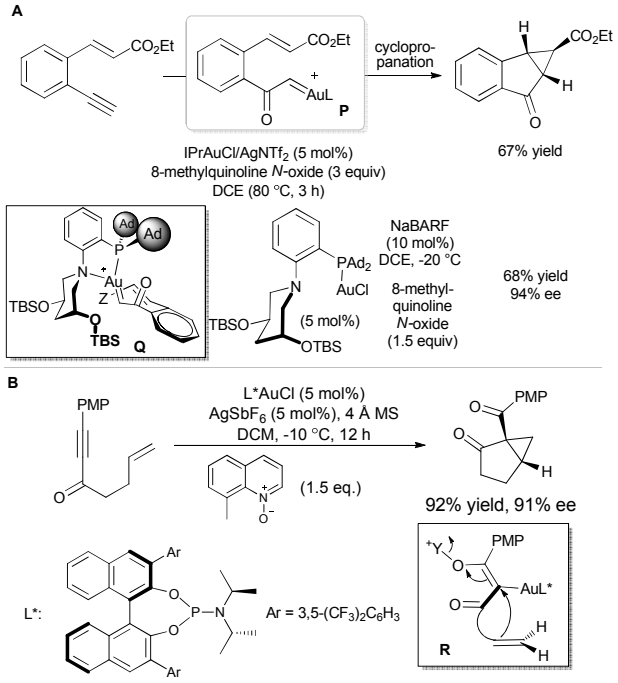
Scheme 12 Gold-catalysed oxidative cycloisomerizations of 2-ethynylbenzyl ethers.

2.2.2 Trapping by carbon-based nucleophiles

Besides trapping with tethered heteronucleophiles, intramolecular cyclopropanations of alkenes, one of the typical reactions of metal carbenes/carbenoids, was initially realized with these putative gold carbene intermediates by both Liu [35] and J. Zhang[36]. In this type of reaction, C-C double bonds act as nucleophiles. In the former case, as exemplified in Scheme 13A, electron-deficient alkenes are used, which is rare and reflects the strong electrophilicity of the gold carbene moiety in **P**. Zhang later reported that this reaction can be made enantioselective in the presence of a designed chiral *P,N*-bidentate ligand (Scheme 13A).[37] The stereochemical outcome is rationalized by the preferred organization of the tris-coordinated gold complex **Q** prior to the cyclopropanation.

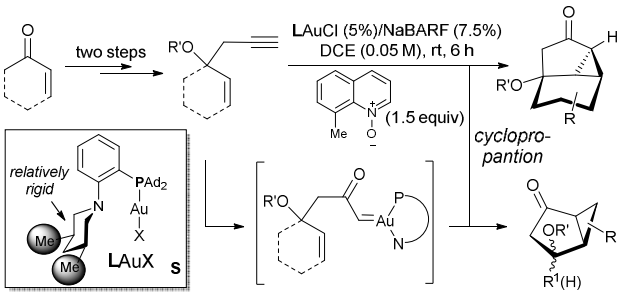
In the latter work by J. Zhang, as exemplified in Scheme 13B, an enyne with electron-deficient C-C triple bond is oxidized to the bicyclo[3.1.0]hexanone product with good enantioselectivity. In this case, a chiral phosphoramidite ligand is optimal, and mechanistic studies suggest that the reaction might form the obtained product directly from the initial adduct **R** instead of a gold carbene intermediate, which would

be more electron-deficient and hence more difficult to be generated as it is flanked by two acyl groups.



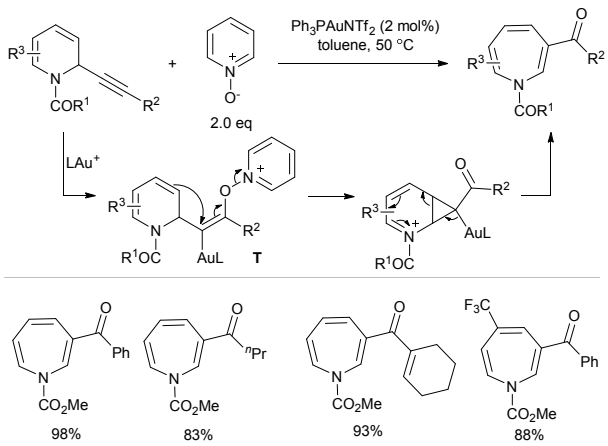
Scheme 13 Gold-catalysed oxidative intramolecular cyclopropanation reactions and their enantioselective versions.

Zhang and co-worker reported in 2014 a highly efficient intramolecular cyclopropanation reactions of flexible and electronically neutral enyne substrates (Scheme 14).[38] The key is a *P,N*-bidentate ligand possessing a conformationally relatively rigid 3,5-dimethylpiperidine, which not only enables the formation of the tris-coordinated gold carbene in **S** but also have the carbene centre more shielded. As such, side reactions are minimized. Bicyclic/tricyclic functionalized cyclopropyl ketones are formed in mostly good yields in three steps from readily available enones/enals, which compares favourably with related strategies based on the diazo approach in terms of step economy and operational safety.



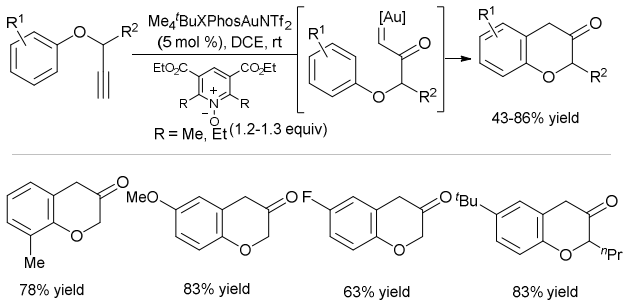
Scheme 14 Gold-catalysed cyclopropanation reactions with electronically unperturbed enynes.

A synthetically valuable application of this oxidative gold catalysis was reported by Y. Liu and co-workers, where 2-alkynyl-1,2-dihydropyridines or quinolines undergo ring expansion to afford functionalized azepines or benzazepines (Scheme 15).[39] DFT calculations support a mechanism where no gold carbene is formed and the initial adduct **T** is directly attacked by the vicinal dihydropyridine π electrons.



Scheme 15 Gold-catalysed oxidative construction of functionalized azepine or benzazepine scaffolds

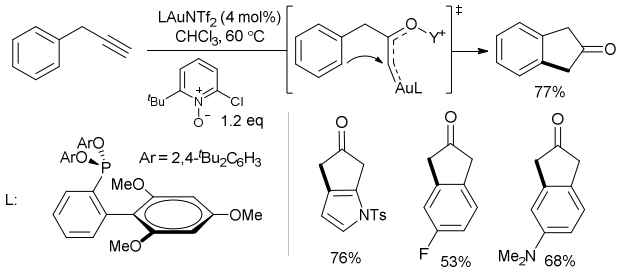
Besides alkenes, arenes can be the nucleophiles. Zhang and co-workers reported that the electron-rich phenolic benzene ring can cyclize to a presumed α-oxo gold carbene centre in the oxidative transformation of aryl propargyl ethers into synthetically useful chroman-3-ones (Scheme 16). This reaction is best performed with sterically hindered ligands, and the bulkiest commercial biaryl-2-ylphosphine $Me_4{}^tBuXPhos$ ligand is optimal.



Scheme 16 Gold-catalysed synthesis of chroman-3-ones from aryl propargyl ethers

The Gagosz group later reported an oxidative cyclization of prop-2-yn-1-yl arenes. As shown in Scheme 17, by using a designed phosphonite ligand, the reaction offers a straightforward access to 2-indanones of various substitution patterns. As the designed ligand is less σ-donating than the electron-rich NHC IPr but more effective in the catalysis, the proposed reaction mechanism favours the direct cyclization of the initial adduct instead of an α-oxo gold carbene

intermediate, as the formation of which should prefer more σ-donating ligands.

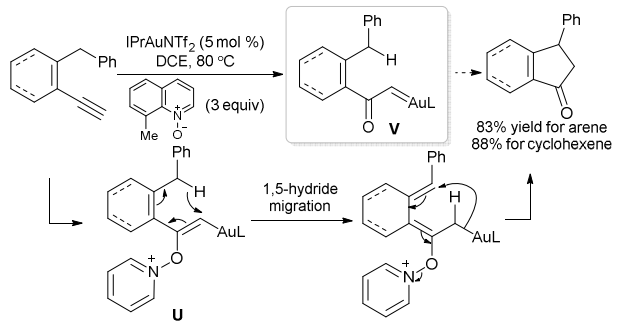


Scheme 17 Gold-catalysed synthesis of 2-indanones from prop-2-yn-1-ylarenes

2.2.3 Trapping via (formal) carbene C-H insertions

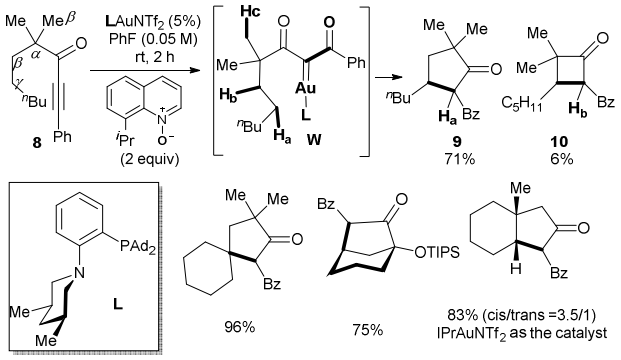
C-H insertion is one of the hallmark transformations of metal carbenes and serves as a powerful synthetic strategy in the constructions of complex functional structures. However, oxidatively generated α-oxo gold carbenes appear to be too electrophilic to be suitable for insertions into C-H bonds and in particular unactivated bonds. As a result, successful applications of this oxidative gold catalysis in this area have been scarce.

The Liu group reported in 2012 a formal gold carbene C(sp^3)-H insertion reaction (Scheme 18).[40] In this oxidative gold catalysis, arylacetylenes and enynes are converted into synthetically useful 1-indanones and cyclopentenones, respectively. Mechanistic studies including comparisons with the reactions using the corresponding diazo ketone substrates indicate that the initial adduct **U** may not undergo fragmentation to yield the gold carbene intermediate **V**. Instead, it proceeds via a 1,5-hydride migration and a subsequent cyclization to afford the cyclic ketone product. Of note is that the C-H bond is benzylic or allylic and hence activated, and overall the reaction outcome can be formally considered as a carbene C-H insertion.



Scheme 18 Gold-catalysed synthesis of 1-indanones and cyclopentanones from arylacetylenes and enynes

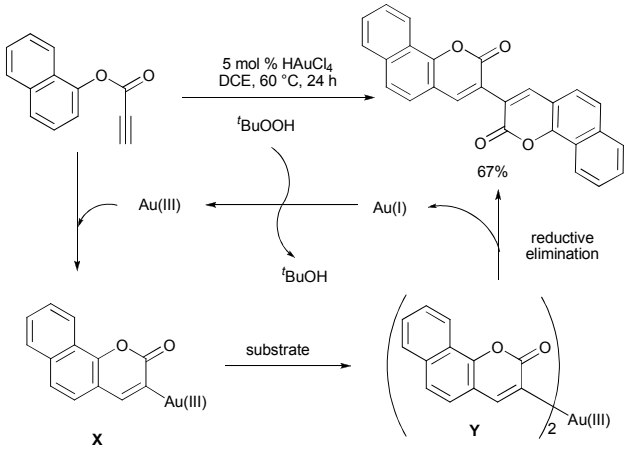
A notable advance in the C-H insertion chemistry was recently reported by the Zhang group.[41] As shown in Scheme 19, under the oxidative gold catalysis conditions, an ynone substrate such as **8** can be converted efficiently into a cyclopentanone (e.g. **9**) as the major product along with a minor cyclobutanone (e.g., **10**). These products are apparently the results of insertion into unactivated β-C-H and γ-C-H bonds, respectively, by a carbene species of type **W**. This putative β-diketone-α-gold carbene should be highly electrophilic due to the dual acceptor substituents but appears to react with synthetically useful selectivity over other side reactions, which have likely doomed earlier attempts to implement C-H insertions by using their mono-acyl substituted counterparts. It is suggested that the additional acyl group might provide extra steric hindrance to hinder intermolecular side reactions. In addition, substrate conformation control via the Thorpe-Ingold effect is a key design feature for achieving good to excellent efficiencies. Notably, the shown *P*,*N*-bidentate ligand and NHC carbene-based ligands such as IMes, both tempering the strong electrophilicity of the carbene centre, leads to good yields and excellent regioselectivities. This novel reactivity offers efficient access to synthetically versatile cyclopentanones including spiro-, bridged, and fused bicyclic systems from readily available ynone substrates. This study represents a remarkable advance in replacing toxic and potentially explosive diazo ketones with benign and easily available alkynes.



Scheme 19 Gold-catalysed synthesis of cyclopentanones via insertion into unactivated C-H bonds.

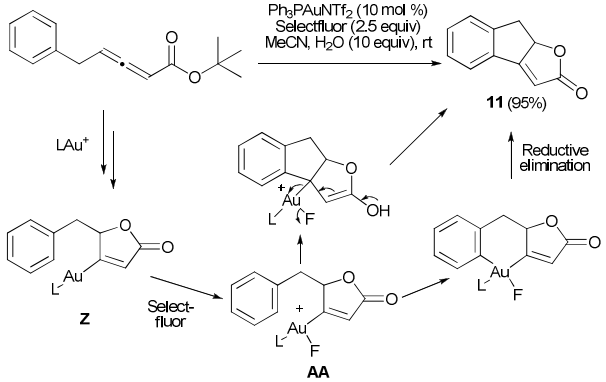
3. Gold-catalysed oxidative cyclization involving Au(I)/Au(III) catalysis

In 2008, Wegner and co-workers reported an oxidative homodimerization and proposed a Au(I)/Au(III) catalysis mechanism (Scheme 20).[42] In this reaction, the Au(III) salt first promoted an electrophilic cyclization by the alkyne, generating alkenylgold(III) species **X**. This intermediate could promote another alkyne cyclization or alternatively undergo ligand exchange with a second substrate molecule, thereby affording the Au(III) **Y** with two identical ligands attached to the metal center. Subsequent reductive elimination yields the dimeric chromen-2-ones and a Au(I) species, which is oxidized by ^{t}BuOOH to regenerate the Au(III) species. Notably, the oxidant used in this chemistry is mild and moreover, the C(sp^2)-Au bond in **X** is more stable under acidic conditions due to the electron-withdrawing α-acyl group, as such the formation of **Y** can outcompete the unwanted protodeauration step. The latter phenomenon appears to be necessary for productive Au(I)/Au(III) catalysis.



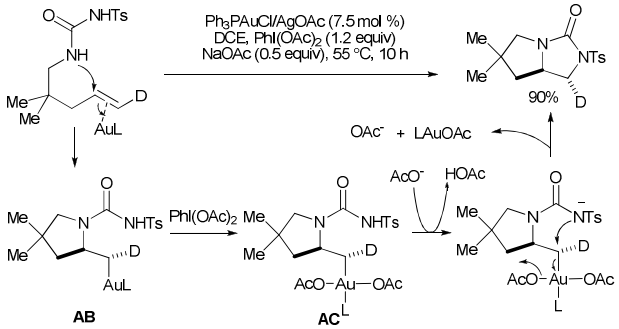
Scheme 20 Gold-catalysed cyclative dimerization of naphthyl propiolates

An alternative approach to accessing relatively stable alkenylgold species is the cyclization of allenoates. As shown in Scheme 21, the cyclized β-aurobutenolide **Z** has a relatively stable Au-C(sp^2) bond toward protonation due to the electron-withdrawing β-carbonyl group. As such, instead of protodeauration, Selectfluor can oxidize it selectively to likely afford the Au(III) intermediate **AA**, which could then undergo Friedel-Crafts type reaction at the Au(III) center or the α-carbon to eventually afford the tricyclic butenolide **11** while regenerating the Au(I) catalytic species. This Au(I)/Au(III) catalysis is realized by Gouverneur [43] and achieves an oxidative cross coupling between an in-situ generated alkenylgold and an aromatic C-H bond. Comparing to other oxidants such as $PhI(OAc)_2$, ^tBuOOH, and even NFSI (*N*-fluorobenzenesulfonylimide), Selectfluor is superior and appears to be the optimal oxidant for Au(I)/Au(III) catalysis, as previously demonstrated.[44]



Scheme 21 Gold-catalysed oxidative double cyclization of allenoates

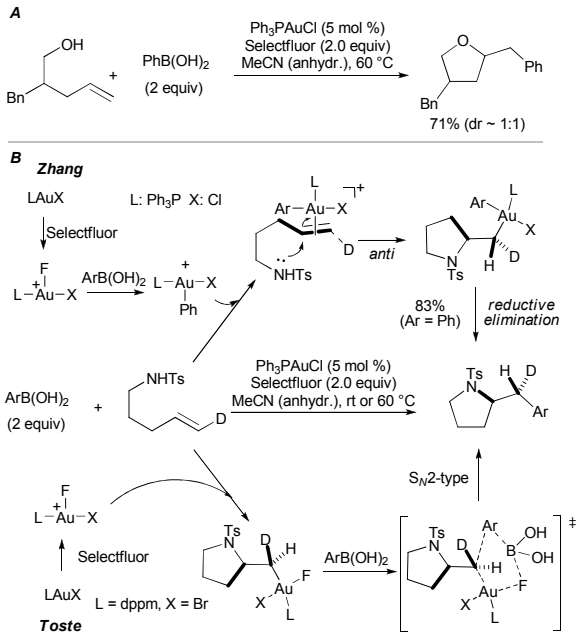
While the alkene is a ubiquitous functional group in organic synthesis, homogeneous gold catalysis typically prefers alkynes and allenes as substrates. One major reason is that the alkylgold species generated upon nucleophilic attack of gold-activated C-C double bonds cannot be readily protonated due to its covalent nature and hence the intermediate often reverts back to reactants. The inclusion of oxidants in this type of reaction enable the incorporation of Au(I) and Au(III) catalysis, which can employ the in-situ generated alkylgolds as organometallic reactants in oxidative coupling reactions. For example, Muñiz reported in 2009 a gold catalysed intramolecular oxidative diamination of alkenes (Scheme 22).[45] In this reaction, which is stereospecific with regard to the deuterium label, the putative alkylgold intermediate **AB**, generated upon the initial Au(I)-catalysed cyclization, can be oxidized by a mild $PhI(OAc)_2$ to the Au(III) species **AC** and subsequently undergo C-N



bond formation via an S_N2 process. Notably, an inner sphere reductive elimination for the collapse of Au(III) is not invoked based on the stereochemical outcome of a deuterium-labeling study.

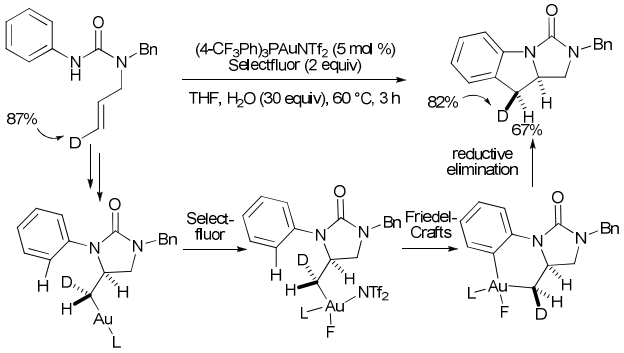
Scheme 22 Gold-catalysed intramolecular diamination of C-C double bonds.

Zhang and co-workers reported in 2010 intramolecular carboalkoxylations (Scheme 23A), carboaminations (Scheme 23B), and carbocarboxylations of alkenes by employing Au(I)/Au(III) catalysis.[46] As shown in the Scheme, these reactions accomplish oxidative cross-coupling between an in-situ generated alkylgold and an arylboronic acid. Deuterium labeling studies with the amide case (Scheme 23B) establish that the reaction was highly stereoselective, and an initial *anti* addition followed by inner sphere reductive elimination was proposed to account for the stereochemical outcome. Later, Toste and co-workers reported a similar carboamination chemistry using [dppm($AuBr)_2$] as the catalyst, and a *syn* cyclization followed by an unconventional S_N2-type of delivery of the aryl group was proposed as a part of the reaction pathway.[47] The binuclear gold catalyst allowed milder reaction conditions (rt vs. 60 °C) albeit with longer reaction times.



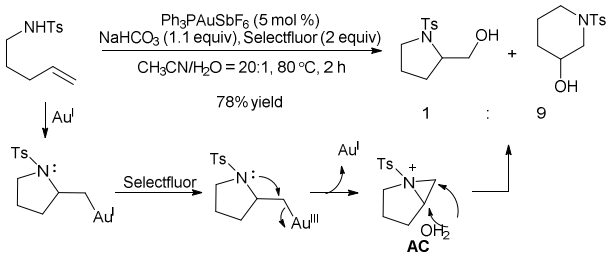
Scheme 23 Gold-catalysed oxidative cross coupling of an in-situ generated alkylgold and arylboronic acid.

In 2011, Zhang and co-workers reported that intramolecular aryl C-H bonds can replace arylboronic acids in oxidative coupling with in-situ generated alkylgold intermediates,[48] therefore combining Au(I)/Au(III) catalysis with C-H functionalization in a manner similar to that shown in Scheme 21 (Scheme 24). Deuterium labeling studies of this cascade cyclization reaction establish that the C(sp^2)-H activation proceeds via a Friedel-Crafts auration and the C(sp^2) – C(sp^3) bond formation occurs via concerted reductive elimination.



Scheme 24 Gold-catalysed oxidative cascade cyclization

Using the same kind of alkene substrates as in Scheme 23, Nevado reported a different reaction outcome in the presence of H_2O and $NaHCO_3$ instead of arylboronic acid. As shown in Scheme 25, the major product is derived from a surprising formal 6-*endo-trig* cyclization by the amide moiety.[49] Since previous studies[46] have failed to support the existence of a secondary alkyl gold intermediate in this type of reaction, this reaction likely undergo the formation of aziridinium **AC**, followed by regioselective ring opening by H_2O.



Scheme 25 Gold-catalysed oxidative cyclization of alkenyl tosylamides

Conclusions

The incorporation of oxidation into homogeneous gold catalysis has in the past several years fuelled the further explosive development of gold chemistry. In the context of kinetically favourable cyclization reactions, a variety of highly valuable synthetic methods have been developed based mainly on two outstanding strategies. One is the employment of nucleophilic oxidants as either internal nucleophiles or external nucleophiles. The initial gold-catalysed nucleophilic addition to alkynes provides access to versatile adducts possessing weak O-heteroatom bonds, which can either fragment to yield reactive α-oxo gold carbenes or undergo non-carbene pathways to functional products. The other strategy entails Au(I) and Au(III) catalysis, where the metal centre undergoes oxidation state changes during the catalytic cycle. External oxidants are required to oxidize Au(I) to Au(III). This approach permits the generation of products of higher oxidation state and hence increased functionalization.

Despite the various reactions discussed in the tutorial, many new applications of these two strategies remain to be developed. Moreover, the drawbacks associated with the current implementations of these strategies, e.g., low atom-economy with regard to the nucleophilic oxidants in intermolecular cases, and the strongly oxidative and harsh nature of the preferred oxidant Selectfluor in Au(I)/Au(III) catalysis, need to be addressed.

Acknowledgments

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