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TUTORIAL REVIEW

Gold-catalyzed C(sp^3)-H bond functionalization

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The C-H bonds are ubiquitous in organic molecules. Homogenous gold-catalyzed direct functionalization of unsaturated C-H bonds has emerged as a powerful method in our synthetic toolbox. However, C_{sp^3}-H bonds have larger dissociation energy and lower proton acidity, and thus the efficient and exquisitely selective cleavage of this kind of chemical bonds for the formation of new carbon-carbon and carbon-heteroatom bonds is still a great challenge. In this tutorial review, we will highlight the recent achievements of gold-catalyzed oxidative and redox-neutral C_{sp^3}-H bond functionalization, which opens new avenues for economical and sustainable construction of fine chemicals.

Key learning points:

1. This tutorial review highlights the significant advancements of gold-catalyzed functionalization of unreactive C_{sp^3}-H bonds.

2. Gold-catalyzed oxidative coupling reactions.

3. The C_{sp^3}-H bonds could be selectively functionalized *via* gold-mediated 1,5-hydride-shift fashion.

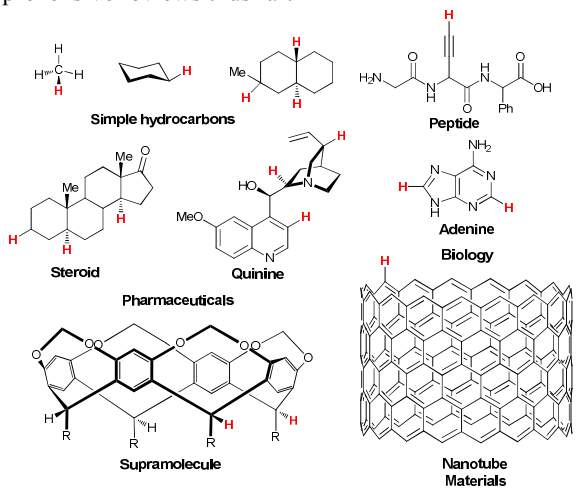
4. Gold-carbene and gold-vinylidene generated from diazo compounds and alkynes are reactive intermediates to undergo C_{sp^3}-H insertion.

5. Cationic gold-catalyzed σ,π-dual activation of 1,2-diynes represents a new chemistry for C_{sp^3}-H bond functionalization.

1. Introduction

Hydrocarbons are the main feedstocks for the chemical industry from oil and natural gas. In most organic molecules, there always have at least one of the three standard C-H bonds: sp, sp^2 and sp^3 C-H bonds (Scheme 1).[1] Generally, C-H bonds have not been seemed as the operative functional group due to their low relativities and high thermodynamic stabilities, and thus the prefunctionalization of substrates is usually required for traditional coupling reactions, such as the typical Heck, Sonogashira, Suzuki and Negishi reaction. In the past decade, we have witnessed a rapid development of transition-metal-catalyzed (Pd[2], Ru[3], Rh[4]) direct C-H bond functionalization for the formation of C-C and C-X (X= heteroatom) bonds. Undoubtedly, the C-H bond functionalization strategy offers a new, efficient and economical platform to construct target molecules.

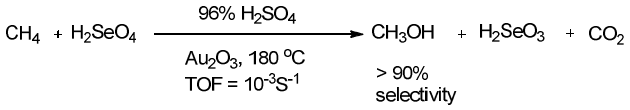
In recent years, homogeneous gold catalysis has become a hot topic in organic synthesis, since gold has its special catalytic character.[5, 6] As a consequence, great efforts were paid to develop gold-mediated organic reactions for the synthesis of intricate scaffolds.[7] Very lately, the direct functionalization of C-H bonds by means of gold catalysis has attracted a great deal of interest to both academia and industry. The main achievements of gold-catalyzed sp and sp^2 C-H bond functionalization have been summarized in several comprehensive reviews thus far.[8-11]



Scheme 1 The ubiquitous nature of C-H bonds in organic molecules.

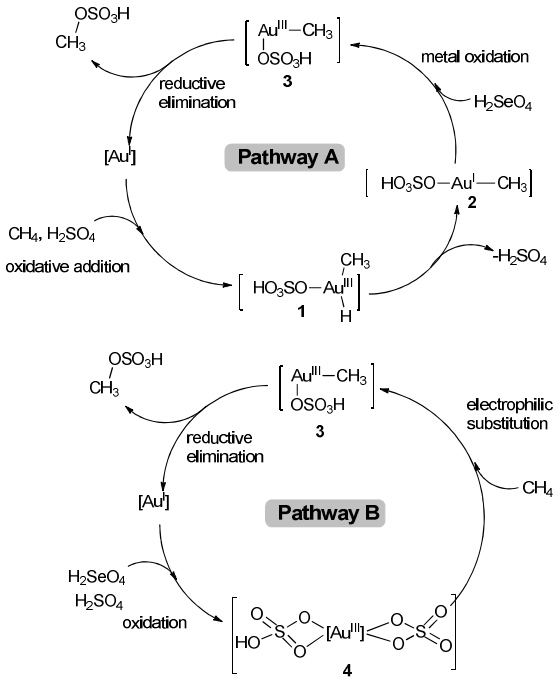
Compared with the unsaturated C-H bond, C_{sp^3}-H bond relatively has a smaller s-orbital contribution, larger dissociation energy and lower proton acidity. Therefore, gold-catalyzed functionalization of C_{sp^3}-H bond is much more challenging and has not been heavily addressed before for little successful examples. With the recent efforts of synthetic chemists, gold-catalyzed C_{sp^3}-H bond functionalization has become an intriguing opportunity for the rapid and efficient build-up of complex molecules. In this tutorial review, we will mainly focus on the recent progress of gold-catalyzed oxidative and redox-neutral C_{sp^3}-H bond functionalization.

2. Gold-catalyzed oxidative C(sp^3)-H bond functionalization



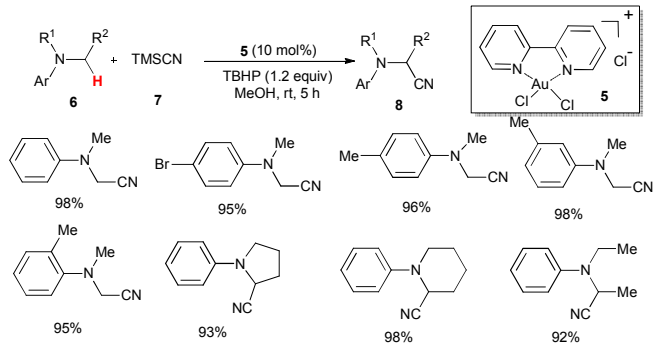
Scheme 2 Cationic gold-catalyzed conversion of methane into methanol.

In 2004, Periana and co-workers reported the first successful example of gold-catalyzed oxidative functionalization of methane (Scheme 2).[12] It afforded an efficient route to convert the richly abundant methane into chemically important methanol. They demonstrated that cationic gold-complex could effectively activate the inert C_{sp^3}-H bond of methane in the presence of concentrated H_2SO_4 with H_2SeO_4 as a sacrificial external oxidant. Methanol could be obtained in high yield with good selectivity (>90%). A little amount of CH_3D was observed when the reaction was performed in D_2O, strongly suggesting the formation of Au-CH_3 active intermediate.



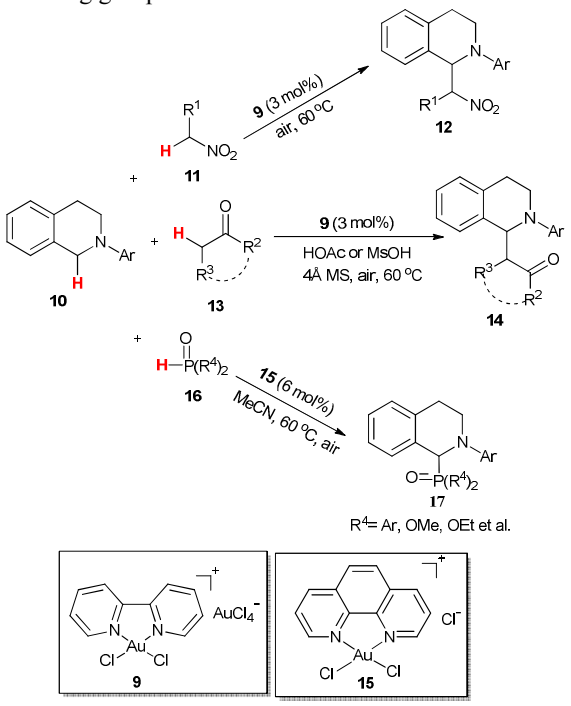
Scheme 3 The possible mechanism of gold-catalyzed methane oxidation to methanol.

Based on their experimental results and density functional theory (DFT) calculations, two possible mechanisms are given in Scheme 3. In pathway **A**, firstly, electrophilic auration of methane formed Au^{III} intermediate **1**, which was subsequently undergone reductive elimination to give Au^{I} species **2**. Oxidation of **2** with H_2SeO_4 generated intermediate **3**, which gave the product *via* further reductive elimination. In pathway **B**, a metal oxidation and subsequent electrophilic substitution process was occurred. Although most cationic gold species may be existed as Au^{III} species under the strong oxidative conditions, the DFT calculations suggested that the oxidative addition of methane to Au^{I} was relatively energetically favoured and thus pathway **A** could not be ruled out.



Scheme 4 Gold-catalyzed α-cyanation of tertiary amines.

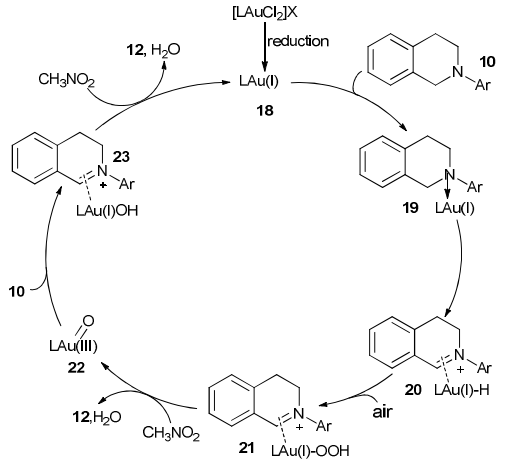
α-aminonitriles are extremely useful synthetic intermediates for the construction of many biologically active compounds. In 2011, Zhu et al. developed an elegant gold-catalyzed oxidative α-cyanation of tertiary amines **6** with trimethylsilyl cyanide using *tert*-butyl hydroperoxide (TBHP) as the stoichiometric oxidant (Scheme 4).[13] The reaction was carried out under acid-free conditions at room temperature, and the desired α-aminonitriles **8** could be got in good to excellent yields. The protocol has a broad reaction scope. Various *N*-aryl substituted cyclic and acyclic tertiary amines bearing electron-donating and -withdrawing groups are tolerated well the reaction conditions.



Scheme 5 Gold-catalyzed aerobic oxidative coupling reactions.

As the continual efforts of Zhu and co-workers, they successively developed a highly efficient aerobic oxidative C-C and C-P coupling reaction from two different C_{sp^3}-H bonds by gold catalysis (Scheme 5).[14] To the best of our knowledge, this

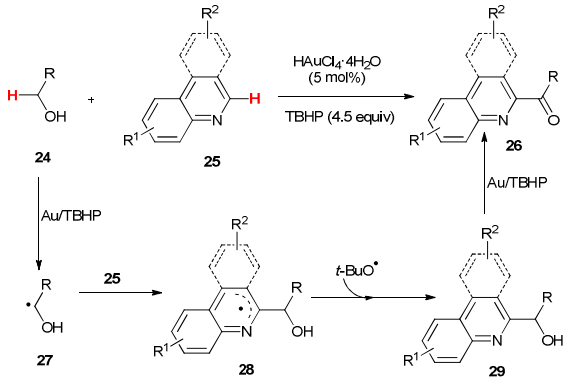
is the first example of gold-catalyzed oxidative coupling reactions by using air as the sole oxidant. When *N*-aryl 1,2,3,4-tetrahydroisoquinoline derivatives **10** with nitroalkanes or ketones were mixed together in the presence of low loading of gold-complex **9** under air, the reaction ran smoothly to afford the desired products **12** or **14** in satisfying yields in short reaction time. Taking the advantage of gold redox catalysis, they continued to report α-phosphonation of tertiary amines with diaryl phosphine oxides and dialkyl phosphites **16**.[15] The gold-catalyzed C-P coupling strategy overcomes the limitations of previous reports.[16] It disclosed that diaryl phosphine oxides were also very efficient coupling partners in the oxidative coupling reactions. Remarkably, the aerobic C-C and C-P coupling protocol can be scaled-up to the gram scale.



Scheme 6 Plausible mechanism for gold-catalyzed oxidative C-C coupling.

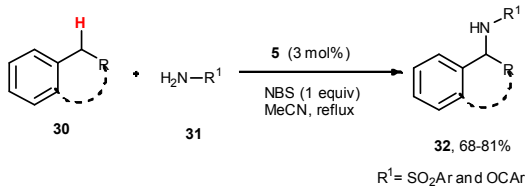
At last, the authors proposed a plausible mechanism for the gold-catalyzed oxidative coupling process (Scheme 6). They envisaged that Au(I) species **18** was generated by *in situ* reduction of Au(III)-complex in the presence of solvent and tertiary amine substrate. The reactive intermediate iminium ion was also observed by MS-ESI spectroscopy. In the pathway, an electron transfer followed by a hydrogen transfer from amine to gold species can form the iminium ions **21** and **23**, which are able to rapidly react with nucleophiles.

In 2012, Zhu and co-workers reported a gold-catalyzed oxidative C-C coupling reaction of aliphatic alcohols **24** and *N*-heterocycles **25** with TBHP as external oxidant (Scheme 7).[17] Interestingly, using simple gold salts instead of palladium catalyst, ketone **26** was obtained rather than the reported tertiary alcohol.[18] The control experiments suggested the reaction pathway involved a radical process. On the basis of MS-ESI tracing results, a possible mechanism was proposed. Initially, the homolytic cleavage of TBHP followed by hydrogen atom abstraction from alcohol **24**, the free radical intermediate **27** was generated. Subsequently, *N*-heterocycles **25** reacted with the reactive radical **27** to form radical species **28**, which would like to rearomatize by *t*-BuO· radical, forming the alcohol intermediate **29** that was detected by MS-ESI during the reaction process. Finally, oxidation of the alcohol intermediate **29** led to the acylation product **26**.

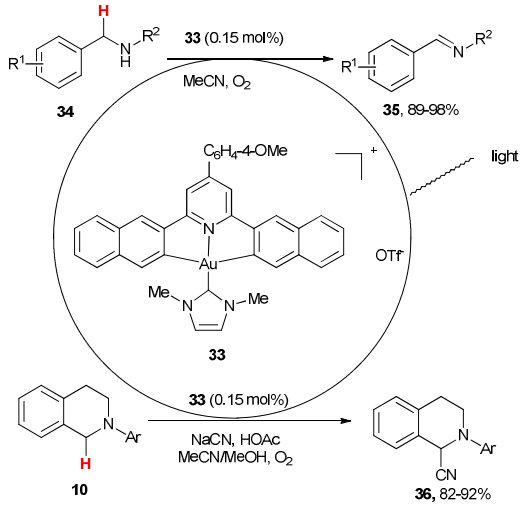


Scheme 7 Gold-catalyzed acylation of *N*-heterocycles with alcohols.

The development of efficient methods to construct C-N bonds is a major topic of recent research.[19] Zhang's group developed a gold-catalyzed selective functionalization of benzylic C-H bond for the formation of new C-N bonds with *N*-bromosuccinide (NBS) as oxidant (Scheme 8).[20] Various acidic sulfonamides and carboxamides **31** are able to perform C-N coupling reaction under the standard reaction conditions, and substrates **30** bearing secondary and tertiary benzylic C-H bonds are well tolerated. Zhang et al. proposed a mechanism concerning insertion of C_{sp^3}-H bond into the gold-nitrene, which was similar to Cu-mediated this transformation.[21]



Scheme 8 Gold-catalyzed amination of benzylic C-H bonds.



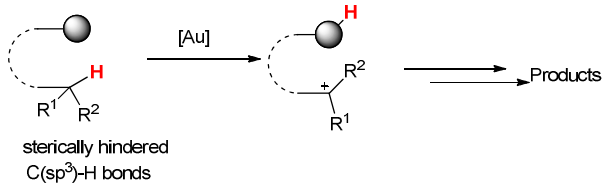
Scheme 9 Gold-catalyzed aerobic C(sp^3)-H bond functionalization by visible-light.

Photoredox catalysis is a relatively young and emerging field in organic chemistry with significant advances in energy-saving and environmentally benign features.[22] To study the photochemical characteristic of gold-complex, Che and co-workers rationally designed an organogold(III)-complex **33** with a long-lived triplet excited states by incorporation of a strong σ–donating ligand, *N*-heterocyclic carbene (NHC) (Scheme 9).[23] In addition, they found that complex **33** was also a good photosentizer for aerobic oxidative C-H bond functionalization. Secondary amines **34** were converted to imines **35** in the presence of oxygen atmosphere under light irradiation (300 W xenon lamp) at room temperature. Furthermore, Che et al. found it could catalyse the oxidative α-cyanation of *N*-aryl-1,2,3,4-tetrahydroisoquinolines **10** under mild reaction conditions. They envisioned that the mechanism should involve C_{sp^3}-H oxidation of amines with singlet oxygen to form the reactive iminium ions, which subsequently were trapped by CN^-. In the light of Che's work, Zhu and co-workers also developed a highly efficient visible-light-induced aerobic oxidative C-C and C-P coupling reaction by gold(III)-complex.[24] Interestingly, the similar C-C and C-P coupling transformation could also be finished by heterogeneous gold nanoparticles under molecular oxygen.[25]

3. Gold-catalyzed redox–neutral C(sp^3)-H bond functionalization

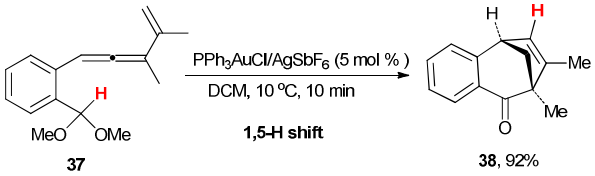
Although transition-metal-mediated C-H bond functionalization is a promising strategy for the construction new chemical bonds, the using external redox reagents usually decreases the total atom economy of the chemical processes. In contrast, neutral redox reactions can fully address this problem owing to the absence of stoichiometric redox reagents. In this section, we will introduce the recent achievements of homogeneous gold-catalyzed redox-neutral C_{sp^3}-H bond functionalization.

3.1 H-shift-induced C(sp^3)-H bond functionalization



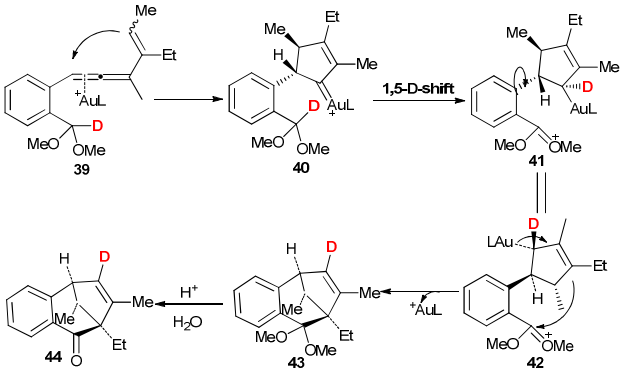
Scheme 10 Gold-catalyzed hydride-shift strategy for C(sp^3)-H bond functionalization.

Generally, selective functionalization of C-H bonds is achieved by the assistance of directing groups. However, the directing-group strategy do not only requires additional operations for first introduction and subsequent removal of directing groups, but it also functionalizes the less hindered C_{sp^3}-H bonds.[2] Thus, the development of new methods to selectively cleave sterically hindered C_{sp^3}-H bonds is a great challenge. With the proper choice of electrophilic gold complex, it is able to initially activate an unsaturated moiety followed by a hydride shift process, generating a carbocation for further functionalization (Scheme 10). Remarkably, gold-catalyzed hydride-shift C-H bond functionalization mode usually requires the substrates possesses a migrating hydrogen with a relatively high hydridic character, such as benzylic hydrogen, hydrogen adjacent to heteroatom.

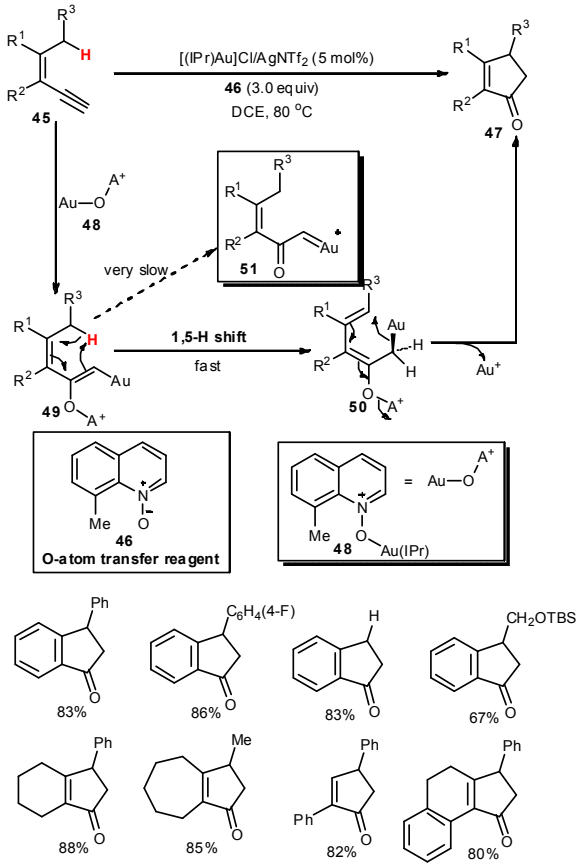


Scheme 11 Gold-catalyzed cycloisomerization/1,5-H shift.

In 2008, Liu et al. disclosed a cationic gold-catalyzed stereoselective cycloisomerization reaction of allenene-acetal **37**,[26] providing a powerful protocol for the synthesis of bicyclo[3.2.1]oct-6-en-2-one **38** that was key intermediate for construction of bioactive (-)-cytisine (Scheme 11). In the proposed mechanism, an unprecedented 1,5-addition of C(sp^3)-H bond to vinylcarbene intermediate **40** was speculated (Scheme 12). And the results of deuterium-labeling study and cross-over experiments supported their speculation. First, the carbon of Au=C induced an intramolecular 1,5-hydride shift to form Au(I)-η^1-allyl species **41** containing a dimethoxymethyl cation. A subsequent S_E2' addition of Au(I)-η^1-allyl functionality at this carbocation terminus, opposite the neighboring methyl group, formed tricyclic species **43** with its methyl group on the same side as the adjacent hydrogen and ethyl group. Alternatively, a possibility that the methoxy group in intermediate **40** facilitated the 1,5-hydride shift through its coordination to the carbenoid carbon could not be ruled out.



Scheme 12 The proposed mechanism of gold-catalyzed 1,5-H shift.

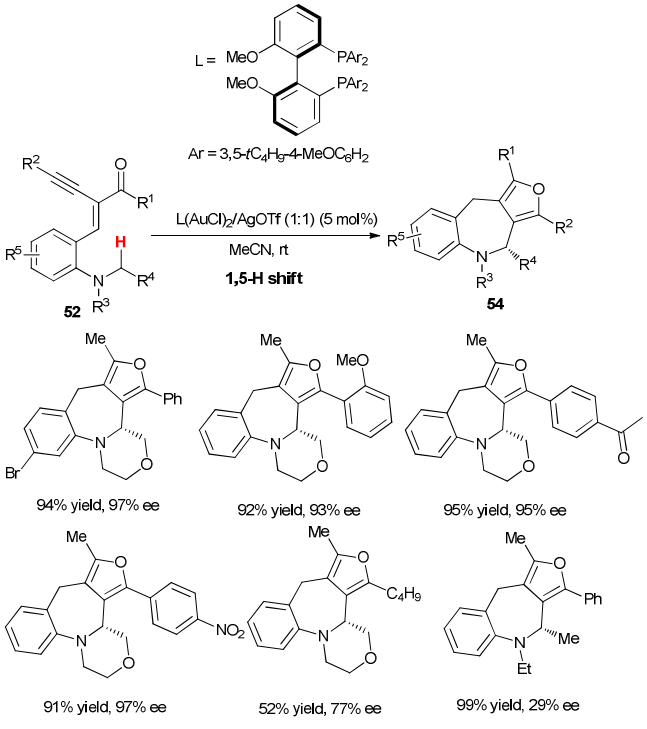


Scheme 13 Gold-catalyzed O-atom transfer/1,5-H shift of *cis*-substituted 3-en-1-ynes.

Later, Liu et al. reported a gold-catalyzed O-atom transfer/1,5-H shift of *cis*-substituted 3-en-1-ynes **45** in the presence of *N*-oxides **46** (Scheme 13).[27] The combination of IPrAuCl and $AgNTf_2$ resulted in complete conversion of substrates **45** in 1,2-dichloroethane (DCE) under practical conditions. A wide range of benzene and non-benzene-derived 3-en-1-ynes could be employed to produce various indanone and cyclopentenone derivatives **47**. Interestingly, generation of gold-carbenoid **51** *in situ* from the corresponding diazocarbonyl compound did not efficiently proceed the cyclization reaction. To gain insight into the mechanism and chemoselectivity, deuterium-labeling study was carried out, and a three-centered concerted C-H insertion pathway of gold-carbenoid **51** was ruled out. Consequently, the 1,5-hydride shift of the electron-rich gold-containing enol ether **49** was proposed as the key step, which was in agreement with their observations that the acidic C-H bonds could accelerate the 1,5-H shift. In fact, despite of using an external oxidant, the final result was transferring an oxygen atom from *N*-oxide **46** to the terminal alkyne moiety and subsequent 1,5-H shift for cyclization. The valence state of gold-complex was not changed in the catalytic cycle and there was no oxidative cleavage of C_{sp^3}-H bond. Therefore, we prefer to put this work in this section rather than the oxidative C-H bond functionalization. Interestingly, a similar intramolecular cyclization reaction was also reported by Zhang and co-workers using amine *N*-oxides bearing an *N*-methylene group and a terminal alkyne moiety.[28]

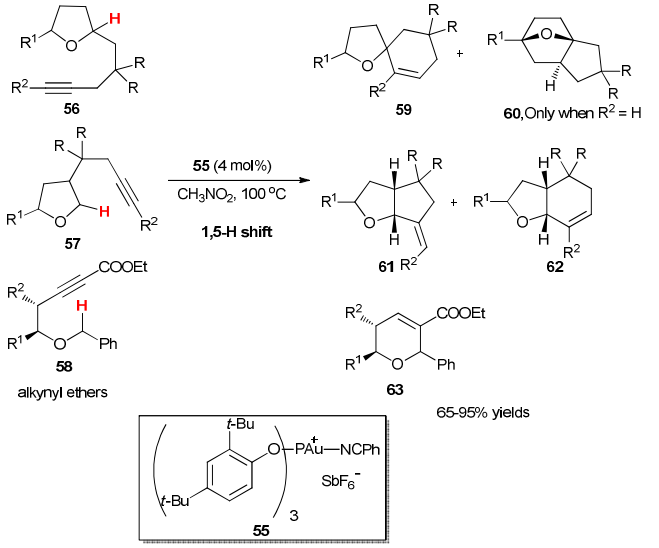
In 2010, Zhang et al. documented a gold-catalyzed redox-neutral C_{sp^3}-H bond functionalization for tandem construction of furan-fused azepines **53** in good yields (Scheme 14).[29] Additionally, it was found that ring-fused tetrahydroquinolines was achieved by using oxophilic $Sc(OTf)_3$ instead of the carbophilic IPrAuOTf catalyst.[30] Later, an enantioselective version of this useful protocol was developed by this group.[30] By using a chiral phosphine ligand, the resulting furan-fused azepines **54** could be obtained in good to excellent yields with satisfying enantioselectivity for most substrates (Scheme 15). A fly in the ointment is that when the substrates bearing simple tertiary amine moiety except rigid cyclic tertiary amines are not very effective, and low enantioselectivity is observed. The possible mechanism includes the initial generation of a carbocation by chiral gold-complex-catalyzed heterocyclization of 2-(1-alkynyl)-2-alken-1-one **52**, which results in a further 1,5-hydride shift and subsequent cyclization to produce the enantioenriched furan-fused azepines **54**.

Scheme 14 Gold-catalyzed cycloisomirization/1,5-H shift for furan-fused azepines.



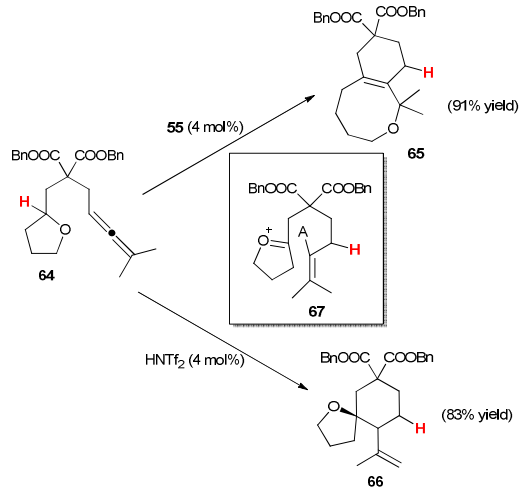
Scheme 15 Gold-catalyzed cycloisomerization/1,5-H shift for enantioselective construction of azepines.

Gagosz et al. reported a homogeneous gold-catalyzed cycloisomerization reaction through hydroalkylation of alkynyl ethers **56-58** (Scheme 16).[31] A wide range of structurally important spiro or fused dihydrofurans and dihydropyrans **59-63** were dexterously constructed. The terminal and ester-substituted alkynes ethers tolerated the reaction conditions well, and the complex products could be isolated in 65-95% yields with satisfactory diastereoselectivity. The authors proposed that 6-*exo* activation of alkynyl ethers by gold(I) catalyst **55**, promoted a 1,5-hydride shift from the C_{sp^3}-H bond (adjacent to oxygen atom) to the alkyne. On the basis of deuterium-labeling study, the 1,6-hydride shift mechanism for the formation of six-membered cyclic products was excluded. Significantly, this protocol allows the direct functionalization of the unreactive secondary or tertiary C_{sp^3}-H bonds to forge new C-C bonds. The stereoselectivity of the cycloisomerization process toward the formation of a five- or six-membered cycle is mainly dependent on the steric factors and alkyne substitution.

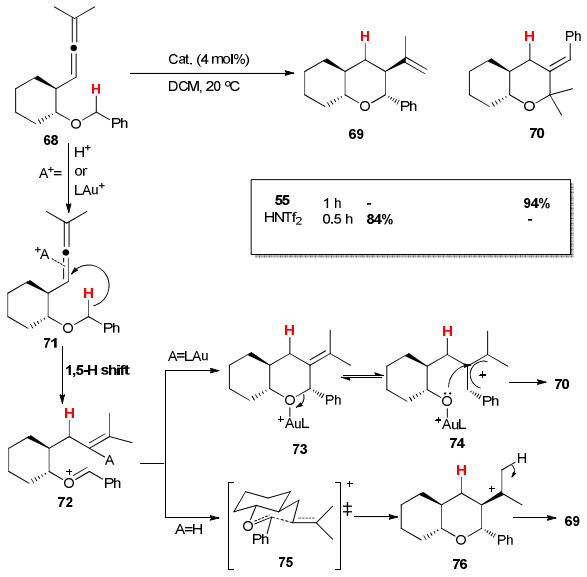


Scheme 16 Gold-catalyzed 1,5-H shift/cycloisomerization of alkynyl ethers.

With their on-going interests in gold-catalyzed tandem cyclization with 1,5-hydride shift, Gagosz and co-workers developed gold-catalyzed hydride shift model to allenes and subsequent cyclization sequence (Scheme 17).[32] The reaction proceeded with a 1,5-hydride shift that underwent a six-membered transition state and generated an oxonium ions **67**, which could be rapidly trapped by nucleophilic species (vinyl-gold species). Interestingly, they found that both electrophilic gold-complex and Brønsted acid were effective catalysts for the 1,5-hydride shift process, but the product selectivity was sharply different. For example, when the cyclic ether substrate **64** was employed in the catalysis of gold-complex **55** and $HNTf_2$, they could lead to formation of different products **65** and **66** in high yields, respectively.

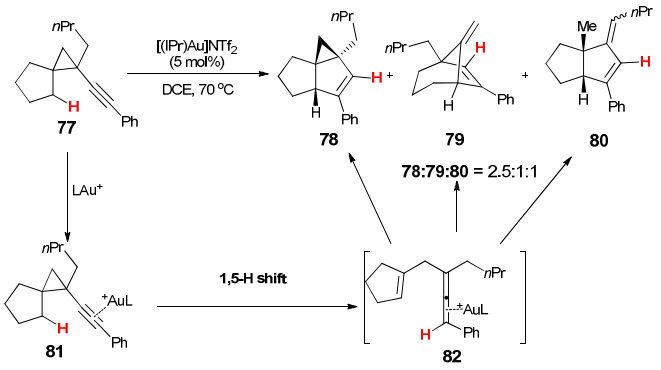


Scheme 17 Gold-catalyzed 1,5-H shift/cycloisomerization of allenyl cyclic ethers.



Scheme 18 Gold-catalyzed 1,5-H shift/cycloisomerization of allenyl benzylethers.

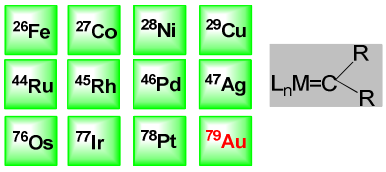
In addition, Gagosz et al. found that the hydroalkylation of allenes could occur when the substrates involving a benzylether moiety (Scheme 18). The same guideline was observed with cyclic ether **64**. Gold-complex **55** and $HNTf_2$ resulted in different selectivity. To have a better understanding of the mechanism and stereoselectivity, a possible mechanism was proposed (Scheme 21). Activation of the allene moiety with electrophilic gold-complex or proton acid, the 1,5-hydride shift process was initiated to form an oxonium intermediate **72**. The authors accounted for the selective production of tetrahydropyrans **69** and **70**. They thought the highly ordered chair-like transition state **75** leading to carbocation **76** was the key point for the stereoselectivity by Brønsted acid. This piece of work fully demonstrated that cationic gold-complexes were not the same with proton acids.



Scheme 19 Gold-catalyzed 1,5-H shift/cycloisomerization facilitated by alkylspirocyclopropanes.

In 2012, Ballesteros et al. discovered an unprecedented gold-catalyzed 1,5-hydride shift process from an unreactive methylene C-H bonds to the alkyne, leading to the subsequent selective cyclization (Scheme 19).[33] The restricted geometry in **81** may facilitate the 1,5-hydride shift to the gold-activated alkyne. From the screening of reaction conditions, it was found that the products could be controlled under microwave irradiation by simply changing the gold-complex or reaction temperature. Using [(IPr)Au(NTf$_2$)]) as catalyst, low temperature (90 °C) and high temperature (150 °C) can exclusively lead to the formation of product **78** and **80,** respectively. Product **79** could be obtained when the reaction was carried out at 150 °C in the catalysis of 5 mol% [(JohnPhos)Au(MeCN)][SbF$_6$]. This 1,5-hydride shift strategy would give a nice addition to gold-catalyzed cycloisomerization reactions and open a new mode to study other hydride acceptor groups.

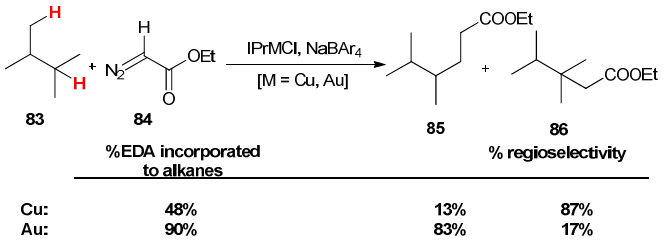
3.2 Gold–carbene and gold-vinylidene induced C(sp^3)–H bond functionalization



Scheme 20 Metals of groups 8-11 in Elements Periodic Table.

Metal-carbenoids are very reactive and important organometallic species. Functionalization of a C-H bond by insertion into a metal-carbenoid represents a green and powerful tool to construct new C-C bonds.[34] Among the 12 elements of groups 8-11, gold was the last explored metal to induce carbene transfer (Scheme 20).[35] The common method to produce gold-carbenoid is generated *in situ* from diazo compounds, and the recent advent is the generation of it from an alkyne. In this part, we will highlight the richness of gold-carbenoid-induced unreactive C$_{sp^3}$-H bonds functionalization.

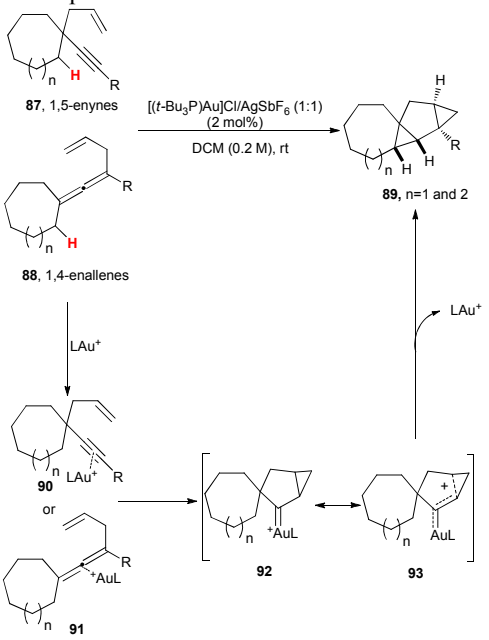
In 2005, Nolan and co-workers developed the first gold-catalyzed carbene-transfer reactions from ethyl diazoacetate (EDA). Cyclopropanation of olefins and insertion of the carbene units into N-H, O-H and sp^2 C-H bonds were achieved.[35] The next year, Nolan and Pérez disclosed the first gold-catalyzed insertion of a carbene into C$_{sp^3}$-H bonds. Using (IPr)AuCl as the Au(I) source with halide abstractor NaBAr$_4$, the transfer of a carbene unit from EDA to primary and tertiary C$_{sp^3}$-H bonds was highly favoured (Scheme 21).[36] Interestingly, (IPr)CuCl and (IPr)AuCl could result in different regioselectivity owing to the electronic effects of metal centres. A high selectivity towards the primary C$_{sp^3}$-H product **85** was obtained when (IPr)AuCl and NaBAr$_4$ were employed. Under the same reaction conditions, an opposite regioselectivity (product **86**) was observed in the catalysis of (IPr)CuCl. The authors also found that the reaction proceeded sluggishly in the absence of halide scavenger NaBAr$_4$. They proposed that the active catalyst was a cationic gold species which mediated the carbene transfer from diazoacetate **84** and C$_{sp^3}$-H bond insertion. Significantly, the observed regioselectivity with gold-based system is higher than that reported with rhodium or silver. Later, Pérez and co-workers finished gold-catalyzed selective insertion of a carbene unit into aromatic C(sp^2)-H bonds with other C(sp^3)-H bonds remaining unreacted.[37]



Scheme 21 Gold–carbene-induced C(sp^3)–H bond functionalization.

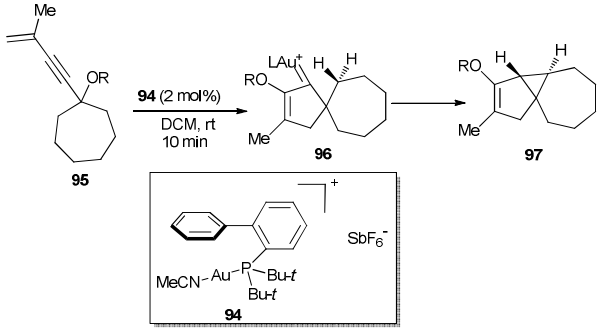
The electrophilic Au(I)-complexes are powerful π acids to promote cycloisomerization of 1,5-enynes terminated by C$_{sp^3}$-H bond insertion into the gold-carbene intermediate. In 2008, Toste et al. reported an elegant gold-catalyzed cycloisomerization of a diverse range of 1,5-enynes **87** and 1,4-enallenes **88** for tandem construction of tetracyclododecane and tetracyclotridecane derivatives **89** in high yields (Scheme 22).[38] A possible mechanism was proposed based on the deuterium-labeling experiments. Initially, the cationic Au(I)-complex activates the alkyne (allene) moiety towards an intramolecular nucleophilic addition of the alkene, generating intermediate **90** (**91**). Then, the formed Au(I) carbenoid **92** invokes an insertion of the carbene unit into unreactive C$_{sp^3}$-H bond. Subsequently, to further determine the pathway of gold-catalyzed cycloisomerization of 1,5-enynes, Zhang et al. carried out the DFT calculations.[39] It was found that the formation of intermediate **92** was the rate-determining step of the reaction pathway. In addition, the theoretical calculations also demonstrated that the size of the cycloalkyl substitutions was crucial for the success of cycloisomerization/C$_{sp^3}$-H insertion tandem sequence. When seven- or eight-membered cycloalkyl

substituted substrates were employed, insertion of gold-carbenoid into C_{sp^3}-H bonds was favored. If the ring size of cycloallkyl was less than seven, intermediate **92** could undergo a ring expansion process. Zhang's work gave mechanistic insight into the gold-catalyzed cycloisomerization and consisted with Toste's experimental observations.

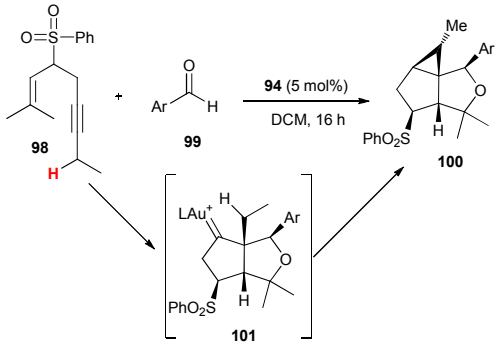


Scheme 22 Gold-catalyzed cycloisomerization/C-H insertion reaction of 1,5-enynes and 1,4-enallenes.

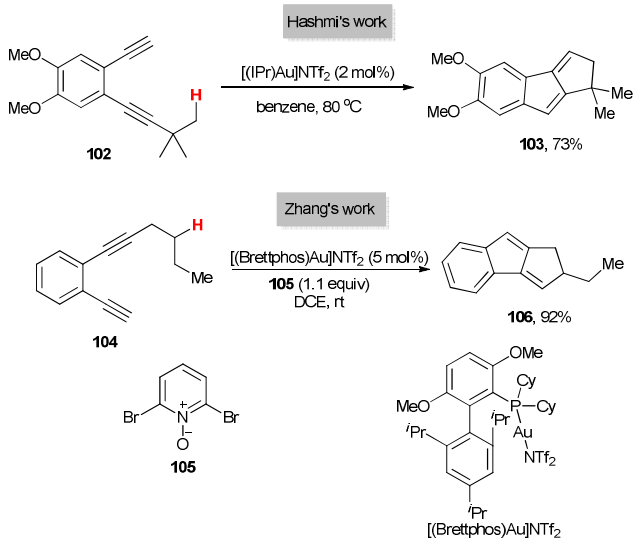
In the same year, Malacria et al. also reported a gold-catalyzed cycloisomerization of 1,5-enynes under room temperature (Scheme 23).[40] The tricyclic product **97** was isolated nearly quantitatively as a single diastereomer in only 10 minutes. The ring size of cycloalkyl substitutions was also important for C_{sp^3}-H insertion process, and the smaller (less than seven-membered) ring would result in a ring expansion. In 2009, another interesting cycloisomerization/C_{sp^3}-H insertion tandem reaction was found by Echavarren[41] and co-workers when they studied the gold-catalyzed cycloaddition reactions of 1,5- and 1,6-enynes with carbonyl compounds (Scheme 24). Unlike the above C_{sp^3}-H insertion reactions, the cycloalkyl moiety was not necessary.



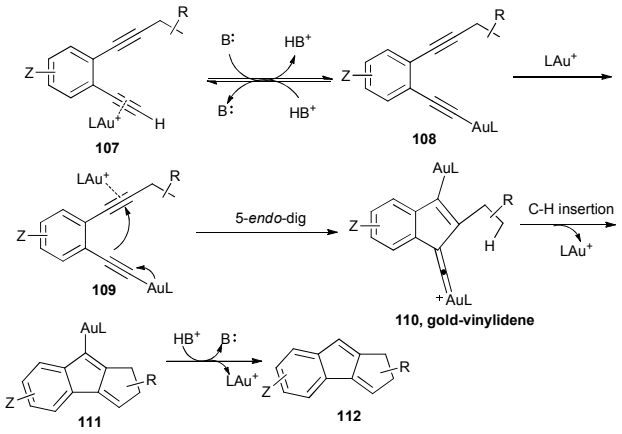
Scheme 23 Gold-catalyzed cycloisomerization/C-H insertion reaction of 1,5-enynes.



Scheme 24 Gold-catalyzed cycloisomerization/C-H insertion reaction of 1,5-enynes with aldehydes.



Scheme 25 Gold-vinylidene-induced intramolecular C(sp^3)-H insertion reactions.

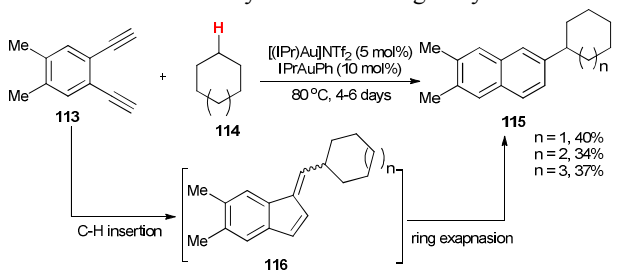


Scheme 26 The mechanism of dual activation by gold catalysis.

In the above mentioned gold-cycloisomerization reactions, only one gold centre was interacted to activate the substrates. What's the result about two gold centres for activating the substrates? Two metals are usually better than one![42] In 2012,

Hashmi's[43] and Zhang's[44] group independently reported a new activation mode which comprised a dual role of the gold catalyst (Scheme 25). The two protocols involved C_{sp^3}-H bond functionalization leading to the synthesis of a tricyclic structural motif that was found in natural products such as pallidol and sporolides. Notably, *N*-oxide compound **105** was used as a weak base to improve the reaction efficiency. These works represent a novel mode for reactions involving σ,π-type dual activation of the substrates.

To gain insight into the synergistic dual activation mode, DFT calculations were carried out by Zhang and co-workers. Based on the results of mechanistic studies and theoretical calculations, they hypothesized that the relatively stable gold-vinylidene species **110** were still sufficiently reactive to undergo the C_{sp^3}-H bond insertion reaction readily. The later work of Hashmi' group also indicated it might undergo a concerted C-H insertion to the gold-vinylidene rather than a stepwise process initiated by a 1,5-H shift.[45] The detailed mechanism of the dual activation is described in Scheme 26. First, the gold-complex activates the terminal alkyne with the help of a weak base. Once the gold acetylide **108** is formed, subsequent 5-*endo*-dig cyclization is taken place, resulting in the rapid formation of a reactive gold-vinylidene **110**, which is apparently reactive to proceed facile C_{sp^3}-H bond insertion to produce intermediate **111**. Finally, protodeauration of **111** could afford the desired tricyclic indenes in good yields.

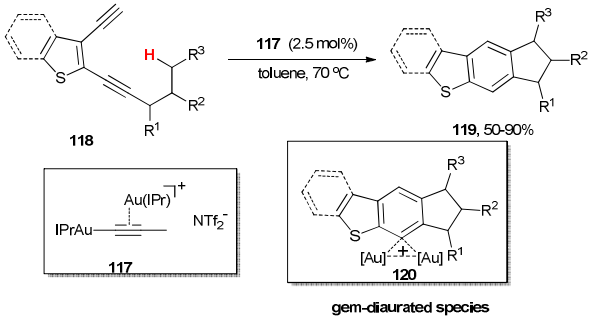


Scheme 27 Gold-vinylidene-induced intermolecular C(sp^3)-H insertion reactions.

In the same year, to demonstrate the immense reactivity of gold-vinylidene intermediate, Hashmi et al. continued to apply it for intermolecular C_{sp^3}-H bond insertion process (Scheme 27).[45] To avoid the regioselectivity of alkanes, cycloalkanes were selected for intermolecular C-H insertion reactions. When benzene-1,2-dialkynes **113** was employed in the catalysis of $IPrAuNTf_2$ with IPrAuPh as additives, the gold-vinylidene species could be formed as speculated, but the intermolecular C_{sp^3}-H insertion rates turned out to be very slow. Surprisingly, unlike the intramolecular C-H insertion reactions, a ring expansion step was taken place to afford the naphthalene skeleton **115** instead of the benzofulvene product **116**. Very lately, Hashmi's group reported a gold-catalyzed 1,6-carbene transfer followed by C_{sp^3}-H insertion strategy for desymetrization of 1,2-bis(3,3-dimethylbut-1-yn-1-yl)-4,5-dimethylbenzene.[46]

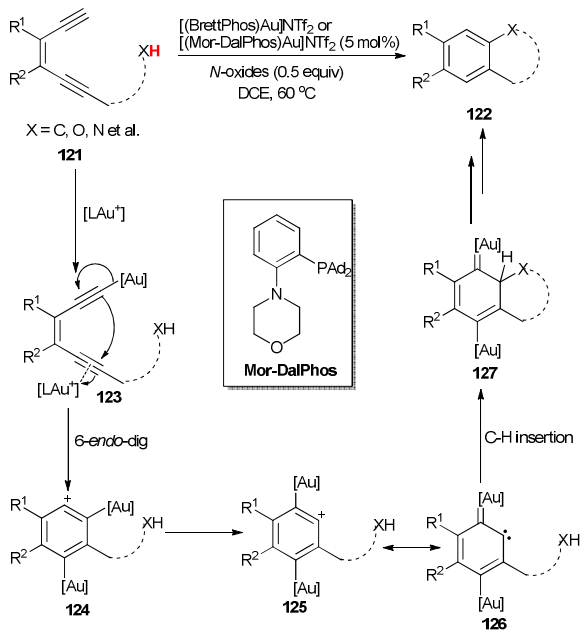
3.3 Miscellaneous reactions

Encouraged by the ring expansion, Hashmi and co-workers examined the pathway of the dual activation by gold catalysis from the above 5-*endo*-dig to 6-*endo*-dig pathway. They rationally developed an alternative and efficient method for the synthesis of six-membered aromatic ring skeletons through the bifurcation mechanism. When the benzene ring of substrate **102** was switched to a thiophene moiety, the six-membered thiophene-fused benzene **118** could be obtained (Scheme 28).[47] A variety of substrates bearing primary, secondary and tertiary C_{sp^3}-H bonds could be employed to give the indanothiophenes **119** in high yields under the optimal reaction conditions.



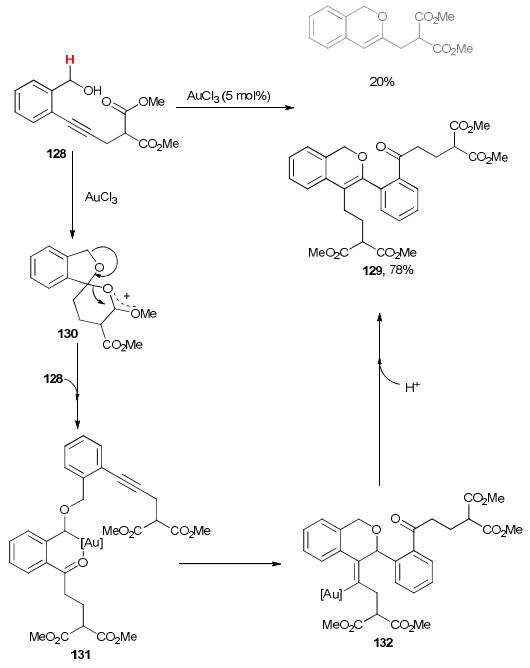
Scheme 28 Gold-catalyzed dual activation for intramolecular C-H insertion through bifurcation mechanism.

Almost simultaneously, Zhang et al. reported a similar transformation (Scheme 29).[48] Without a thiophene directing-group, the general *cis*-enediynes could be used to promote the 6-*endo*-dig cyclization *via* bifurcation mechanism. Besides the sp^3 C-H bonds, O-H and N-H bonds could also undergo the insertion process, affording an excellent approach to construct indanes- and heterocycles-fused benzene derivatives. Notably, both Hashmi and Zhang have mechanistic insights on the interaction of cationic gold-complex to the alkynes. A highly similar mechanism about the 6-*endo*-dig cyclization reaction was proposed, respectively. The initial σ,π dual activation of *cis*-enediynes **121** followed by 6-*endo*-dig cyclization results in the formation an unstable intermediate **124**, which can readily proceed the 1,2-metal shift to generate intermediate **125**. The DFT calculations indicate that intermediate **125** has a much lower energy than **124**. Then, facile intramolecular C-H insertion through α-carbene gold carbene **126** could lead to the formation of desired products **122**. Differently, Hashmi et al. found the gem-diaurated gold-intermediate **120** was a potential resting state in the catalytic cycle based on their deuterium-labeling studies together with the capture experiments. Alternatively, the 5-*endo*-dig cyclization followed by ring expansion pathway could not be ruled out at present although it is energetically disfavoured on the basis of computational results.[47] The two works expand the scope of the gold-catalyzed σ,π dual-activation chemistry.



Scheme 29 Gold-catalyzed dual activation for *cis*-enediynes through bifurcation mechanism.

In 2007, when Hashmi and co-workers examined the gold-catalyzed ring closure of alkynylbenzylic alcohol **128**, they observed an unexpected tandem reaction. (Scheme 30).[49] The direct functionalization of benzylic C_{sp^3}-H bonds can take place under neutral conditions at room temperature. Remarkably, eight new chemical bonds were forged in the reaction process at once.



Scheme 30 Gold-catalyzed benzylic C-H bond functionalization.

The tandem reaction may be initiated by the nucleophilic addition of the carbonyl ester group and subsequent the hydroxyl group onto the gold-activated alkyne, generating the activated tricyclic benzyl alcohol intermediate **130**. Then, the hydroxyl group of a second molecule of the starting material **128** quickly reacted with **130** to generate the dibenzyl ether **131**. Importantly, an electrophilic C_{sp^3}-H bond functionalization was taken place during this step to form a C-Au bond, which was stabilized by coordination/chelation with the adjacent carbonyl group. Finally, insertion of the alkyne into the C-Au bond followed by protonolysis and migration of the double bond in **132** resulted in the corresponding dimer product **129**.

4 Conclusion

The direct functionalization of C_{sp^3}-H bonds is a very promising but greatly challenging subject, which providing a new platform to develop new reactions and construct complex organic frameworks. In this tutorial review, we gave an overview of the recent developments of gold-catalyzed oxidative and redox-neutral C_{sp^3}-H bond functionalization. The unreactive C_{sp^3}-H bonds could be directly converted into carbon-carbon and carbon-heteroatom bonds through gold-mediated oxidative cleavage of C-H bonds, hydride shift and C-H insertion. Some of these transformations are unique to gold catalysts, and thus highlight the good potential of gold chemistry. In future, much attention will be paid to study and understand the reactivity modes of gold centres. The exploration of chiral gold-complex-catalyzed enantioselective C_{sp^3}-H bond functionalization will be actively pursued.

Acknowledgements

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Notes and references

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DFT	density functional theory
rt	room temperature
DCM	dichloromethane
MsOH	methanesulfonic acid
TBS	*tert*-butyldimethylsilyl
NMP	1-methylpyrrolidin-2-one
Tf	(trifluoromethyl)sulfonyl
TBHP	*tert*-butyl hydroperoxide
4Å MS	molecular sieves (4Å)
DCE	1,2-dichloroethane
NBS	*N*-bromosuccinide
NHC	*N*-heterocyclic carbene
LEDs	light-emitting diode strips
EDA	ethyl diazoacetate
IPr	1,3-bis(d iisopropylphenyl)imidazol-2-ylidene
JohnPhos	2-(di-*t*-butylphosphino)biphenyl
Ad	Adamantanyl

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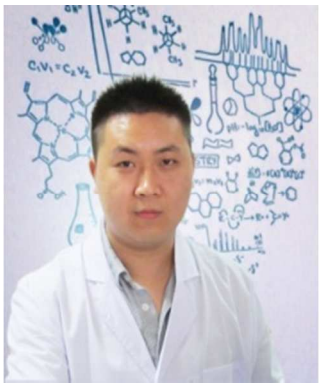
AUTHOR CV



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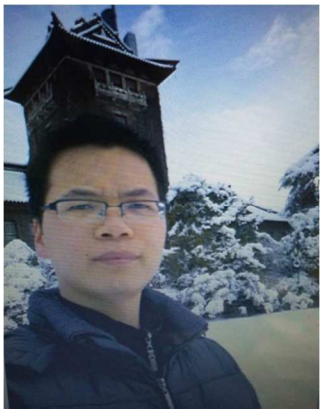

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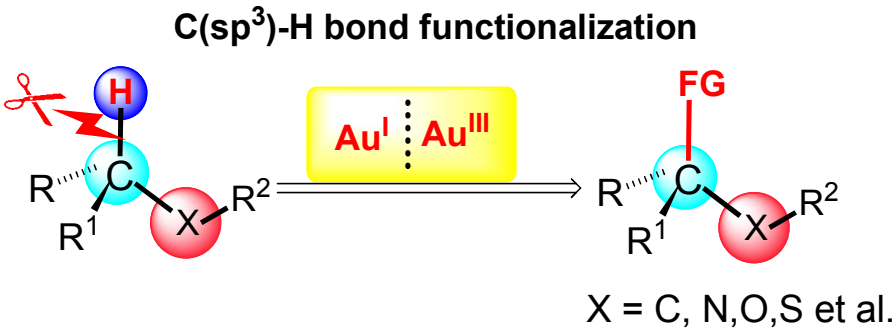
Prof. Chengjian Zhu was born in Henan, China, in 1966. He obtained his Ph. D. from Shanghai Institute of Organic Chemistry (CAS) in 1996 under the supervision of Professor QIAN. Then he worked as a postdoctoral fellow successively in Universite de Bourgogne, University of Oklahoma, and then University of Houston from 1997 to 2000. He joined Nanjing University as an associate professor in 2000. Since 2003, he has been a professor at Nanjing University. His present research interests lie in organometallic chemistry and asymmetric catalysis.

Graphic abstract



Homogeneous gold-catalyzed sp^3 C-H bond functionalization strategy opens a new avenue for economical and sustainable construction of fine chemicals.