Chem Soc Rev

Gold-catalyzed transformations of α-diazocarbonyl compounds: selectivity and diversity

Key Learning points

In recent years, the research area of gold catalysis has attracted many attentions and brought a new "gold rush" for discovery of novel organic transformations and gold-carbenoids have been regarded as the key species. The decomposition of diazo compounds via gold catalysts is the most direct method to generate gold-carbenoids. Compared to other transition metals (*e.g.*, Rh), gold complexes display their unique catalytic activity in diazo transformations. We summarized all the examples in this field by highlighting the specificity and provided the mechanistic rationale to understand these reactions.

In this review, a critical overview is presented to the readers, providing fundamental knowledge about homogenous gold-catalyzed transformations of α-diazocarbonyl compounds.

(1) Gold-catalyzed X-H insertion and cascade reaction.

Recent advances in gold-catalyzed X-H (X = N, O) are described. In this transformation, the ligands and counteranions have huge effects on the catalytic activities of gold complexes. Moreover, the alkynes-involved tandem reactions are realized via gold catalyst.

(2) Gold-catalyzed site-selective C-H functionalization.

The selective functionalization of C−H bonds is one of the most encompassing transformations in organic chemistry. Gold complexes showed highly chemo- and site-selective direct C−H bond functionalization of unprotected phenols with diazo compounds under mild conditions and the chemoselectivity is heavily dependent on the nature of ligands of gold catalysts. The gold catalysts also show high efficiency and selectivity on $C(sp^2)$-H functionalization of electron-rich aromatic rings and alkenes. For $C(sp^3)$-H functionalization, ligands can control the selectivity on primary or tertinary C-H bond.

(3) Gold-catalyzed selective cross coupling of two different diazo compounds.

The carbenoid-induced coupling of diazo compounds affords an efficient approach to construct C=C bonds. Gold catalysts are utilized not only in

intramolecular diazo coupling but also in intermolecular diazo coupling to construct tetrasubstituted alkenes highly *E/Z* selectively.

(4) Gold-catalyzed cyclopropnations and cycloadditions.

In this section, gold complexes provide excellent catalytic activities in cyclopropnation, [3+2] cycloaddition, [3+3] cycloaddition, [4+2] cycloaddition and so on. In cyclopropnation, chiral gold complex provide highest level of enantiselectivity especially for the 1,2-disubstituted alkenes. In [4+2] cycloaddition, vinyldiazo acetates can be served as nucleophilic C2 synthons under the catalysis of gold-complexes.

(5) Gold-catalyzed tandem rearrangement reactions.

Some specific tandem rearrangement reaction involving diazo compounds are developed. In those reactions, the cleavages of C-C bond occurred. More examples of tandem reactions consisting of rearrangement are expecting.

Journal Name

REVIEW ARTICLE

Gold-catalyzed transformations of α-diazocarbonyl compounds: selectivity and diversity

Lu Liu,*[a] and Junliang Zhang*[ab]

Metal carbenes, generated from the decomposition of diazo compounds by transition-metal, have broad applications in organic synthesis. The progress of organic transformation via transition metal (such as Rh, Cu, Fe, Ag) carbenes has been well summarized in a few nice reviews. This review will summarize gold-catalyzed transformations of α-diazocarbonyl compounds by highlighting the specificity and applicability of these diverse transformations such as X-H insertion, C-H functionalization, cyclopropanation, cycloaddition, and coupling reactions. In order to understand these reactions, the mechanistic rationale for selected examples is also provided.

1. Introduction

In the past decade, gold catalysis has attracted much attention and brought a new "gold rush" for discovery of novel organic transformations, due to the specific carbophilic π-acidic and catalytic activities of gold complexes which are air and moisture stability.[1-3] In many transformations, gold-carbenes (scheme 1, in this review, we used carbenes to indicate all the resonant structures **A** and **B**), have been proposed as the key intermediates,[4,5] which can undergo various challenging yet valuable transformations to construct acyclic and cyclic scaffolds. Above all, these transformations afford diverse and complex molecules from simple starting materials accompanied by high degrees of chemo-, regio-, diastereo-, enantioselectivity.

Meanwhile, diazo compounds are of high importance in organic synthesis due to their high and versatile reactivity.[6] Metal carbenes, generated from diazo compounds, especially easily prepared and handled α-diazocarbonyl compounds under the catalysis of transition metals, has broad applications in organic synthesis. A few classic bench-marked reactions such as X-H (X = O, N, S, etc.) insertion, C-H insertion and cyclopropanation catalyzed by the common-used transition metals such as rhodium, copper, silver, palladium, ruthenium, cobalt, have been well established.[7-10] Over the past decade, and especially since 2010, much effort has been devoted in developing gold-catalyzed diazo transformations and a series of novel and interesting transformations have been developed. More importantly, these transformations offer very unique
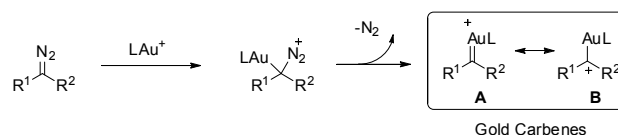
Scheme 1. Formation of gold carbenes from diazo compounds.

reactivity and selectivity compared to other noble metals-catalyzed reactions. This review will cover homogeneous gold-catalyzed reactions of α-diazocarbonyl compounds, highlighting their specificity compared with other transition-metal complexes. It is our hope that this review will guide the development of new transformations in gold-catalyzed carbene transfer and the design of new gold based catalysts.

2. X-H insertion

Transition-metal-catalyzed X–H insertions into carbene from diazo compounds (where X is any heteroatom) are the straightforward way to construct the carbon–heteroatom bond, which is a ubiquitous motif in both natural and man-made molecules. However, homogeneous gold-catalyzed X-H insertion reactions with diazo compounds were unknown untill 2005. Nolan, Díaz-Requejo, and Pérez reported a first gold-catalyzed X-H (X = O, N) insertion reaction with the aid of *N*-heterocyclic carbene ligands (IPr). They found that the reaction of ethyl diazoacetate (EDA) **1** with anilines, amines and alcohols catalyzed by IPrAuCl/NaBAr$^F_4$ [Ar^F = 3,5-(CF$_3$)$_2$Ph] afforded N-H insertion products **2** and O-H insertion products **3** in >99% GC yield. The authors assumed that the acceptor-gold carbene **4** was the catalytic species (Scheme 2).[11] Later, Gagosz introduced another air-stable gold complex IPrAuNTf$_2$
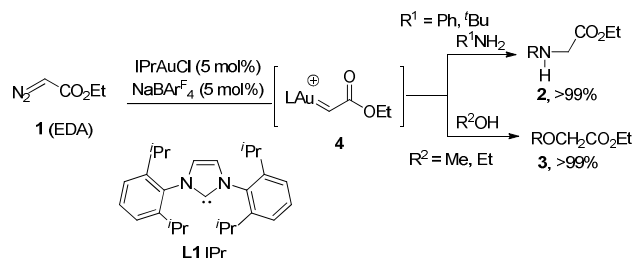
as the catalyst for the reaction of EDA and alcohol, which can lead to the O-H insertion products in excellent isolated yields.[12] The EDA homo-coupling was completely suppressed under this catalyst, even though the diazo compound was added in one portion. However, it is noteworthy that the N-H insertion was failed with the use of IPrAuNTf$_2$ catalyst.

Scheme 2. X-H (X = N, O) insertion reactions of EDA.

In 2011, Wang *et al.* developed a novel IPrAuCl-catalyzed cascade reaction O-H insertion/cyclization of water with *o*-acetylenyl phenyl diazoacetates. This methods affords the corresponding isochromene derivatives **6** in good yields along with dihydroisobenzofuran **6'** as by-product (Scheme 3).[13] A mechanistic rationale for this transformation is proposed by Wang in Scheme 3. Gold carbene species **7**, generated from the gold-catalyzed decomposition of aryldiazoacetate **5**, inserts into the O–H bond of H$_2$O to form the intermediate **8**. Subsequently, 6-*endo-dig* or 5-*exo-dig* cyclization was occurred via the Au(I)-activated triple bond to afford the vinylgold intermediate **9** or **9'**. After protonation, the final product **6** or **6'** was afforded and the gold catalyst was regenerated. In this transformation, the single gold catalyst mediates two different reactions including O-H insertion and alcohol–alkyne cyclization in a selective manner. In the tamdem reaction, the alkynylphilicity of gold catalyst played the vital role. And other
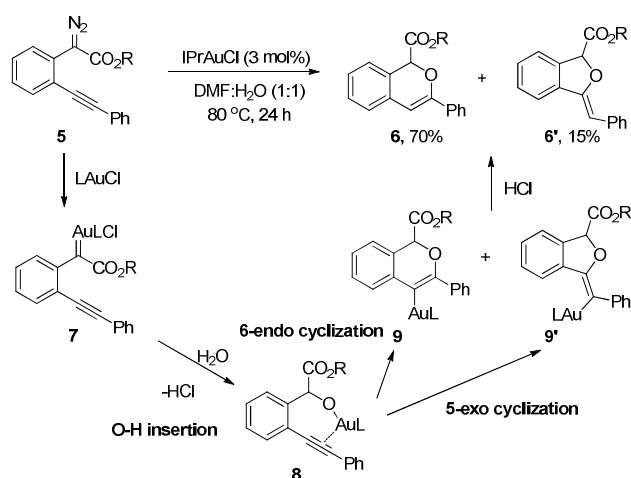
**Scheme 3.** O-H insertion/cyclization sequential reaction.

transition-metal complexes, such as copper-, silver-, even gold-complexes without or with phosphine ligands can not promote this transformation effeciently.

3. C-H Functionalization

Carbon-hydrogen bond is widely existed in organic compounds. In the past two decades, the selective functionalization of C–H bonds is one of the most encompassing transformations in organic chemistry.[14] However, it is still challenging because of the inert and stable property of C–H bonds. In this context, transition-metal-catalyzed carbene transfer reactions of diazo compounds are one of the most efficient methods for C-H bond functionalization.
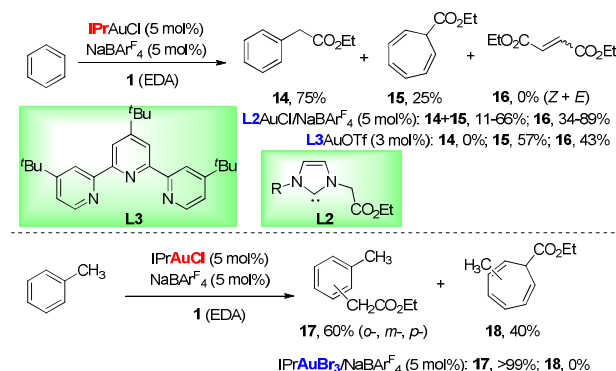
3.1. C(sp^2)-H Functionalization

Nolan, Díaz-Requejo, and Pérez disclosed that the reaction of ethyl diazoacetate (EDA) **1** and styrene catalyzed by IPrAuCl/NaBAr$^F_4$ afforded the major C-H insertion product **10** as well as the cyclopropane **11** as the minor product.[11] Other metals, even the copper complex with the same ligand IPr would favor the cyclopropanation to afford the cyclopropane **11** as the single product (Scheme 4, top).[15] It is quite interesting to find that the reaction of naphthalene with EDA **1** would lead the mixture of the C-H functionalization product **12** and cyclopropanation product **13** under the gold-catalysis. In contrast, the copper complex favor the chemoselective formation of cyclopropanation product **13** (>99% yield, Scheme 4, bottom).[16]
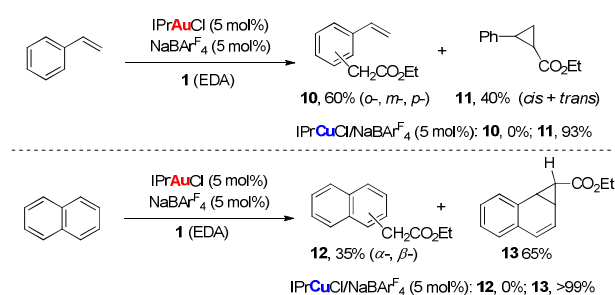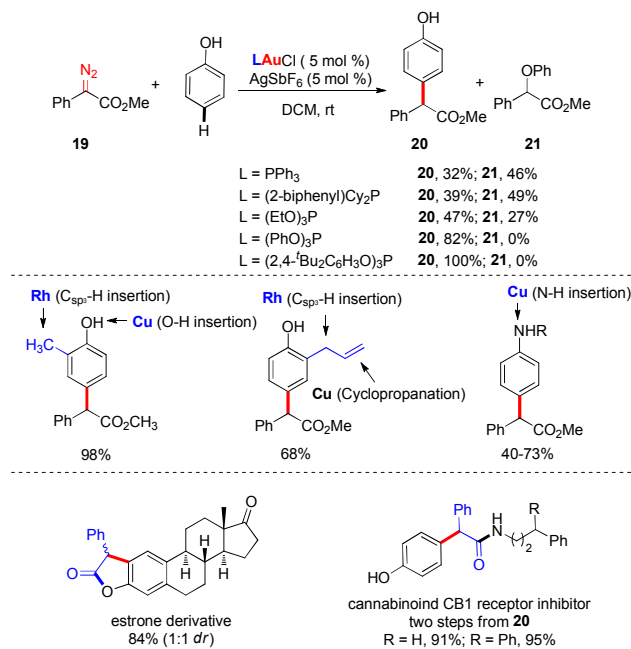

Scheme 4. Aromatic C(sp^2)-H functionalization versus cyclopropanation.

Under the catalysis of IPrAuCl/NaBAr$^F_4$, the reaction of benzene with EDA **1** afforded the C-H insertion product **14** as the major product as well as Buchner reaction product **15** as the minor one (3:1 ratio).[11] Later, the new NHC ligand **L2**, developed by Pérez, Echavarren and coworkers, failed to improve this chemoselectivity.[17] Notably, terpyridine **L3** coordinating Au(I) catalyst was unable to promote the C-H functionalization of benzene with EDA **1** (Scheme 5, top).[18] Similarly, in the IPrAuCl/NaBAr$^F_4$ catalyzed reaction of toluene and EDA **1**, a 3:2 mixture of products **17** and **18** was also

produced.[11] Another gold-based precatalysts IPrAuBr₃, which was developed by Pérez *et al.* in 2011, has been found to favor the aromatic C-H bond functionalization (Scheme 5, bottom).[19] Unfortunately, the issue of regioselectivity was still not addressed in this case.


Scheme 5. Aromatic C(sp²)-H functionalization versus Buchner reaction.

Scheme 6. Aromatic C(sp²)-H functionalization of phenols and anilines with α-aryl-α-diazoacetates.

Very recently, Liu, Zhang and co-workers have developed the first example of gold-catalyzed highly chemo- and site-selective direct C–H bond functionalization of unprotected phenols and *N*-acylanilines with aryl diazoacetates and diazooxindoles under mild conditions.[20] Most notably, the chemoselectivity is heavily dependent on the nature of ligand of gold catalyst. The gold complexes with phosphine ligands showed the chemoselectivity like the commonly used metal complexes such as copper, rhodium, to prefer the O-H insertion, while the gold complexes with phenyl phosphite ligands

exhibited the opposite chemoselectivity to prefer C-H functionalization (Scheme 6, top). Meanwhile, the benzylic C-H insertion, cyclopropanation and N-H insertion were not observed when the substrates was attached with methyl, allyl or amine on the phenyl ring (Scheme 6). This methodology represents an exciting opportunities for the functionalization of C-H bonds and promising synthetic tool for natural products and pharmaceuticals, especially in late-stage modification (Scheme 6, bottom).
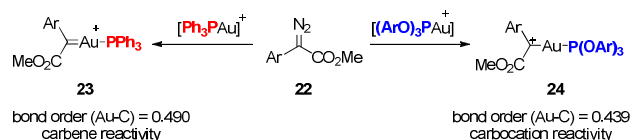
Scheme 7. The bond order for gold-carbene bond with the phosphite and phosphine ligand respectively by DFT calculation.

Later, Lan and Shi *et al.* reported the similar work independently and proposed the mechanistic study on the aromatic C-H functionalization of electon-rich aromatic compounds with diazoacetates and diazooxindoles.[21] They suggested that "carbophilic carbocation" is the key intermediate in this transformation. Based on their DFT calculations, the bond order of Au-C is 0.49 with the phosphine ligand PPh₃, which carbene reactivity is revealed (Scheme 7, **23**). While the electon-deficient phosphite (2,4-*t*Bu₂C₆H₃O)₃P is used as ligand, the bond order of Au-C is 0.439 and the gold carbene acts as a "carbophilic carbocation", leading to a chemoselective nucleophilic addition on carbon instead of addition at typical carbene receptors (Scheme 7, **24**).
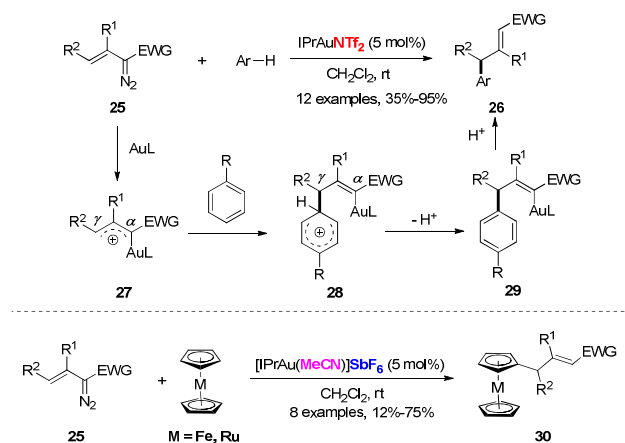

Scheme 8. C-H functionalization with alkenyl diazoacetates.

In 2012, Barluenga and López *et al.* reported another kind of IPrAuNTf₂-catalyzed aromatic C(sp²)-H fuctionalization with alkenyl diazoacetates **25**, which gave allyl substituted arenes **26**.[22] This transformation is initiated by gold-catalyzed decomposition of alkenyl diazo compounds **25** to afford the gold alkenylcarbenes, which can be described as an allyl gold cation **27**. The nucleophilic addition then occurred at the *γ*-

position of allylic cation **27** with electron-rich arenes to form the cation intermediate **28**, which could be converted to the product **26** by following deprotonation/deauration (Scheme 8, top). Later, López *et al.* also utilize this strategy in the C-H functionalization of metallocens including ferrocenes and ruthenocenes, which enabled the preparation of metallocene derivatives with difficult-to-access substitution pattern (Scheme 8, bottom).[23] These results also indicated the "carbophilic carbocation" proposed by Shi may be responsible for as a key intermediate in this reaction.
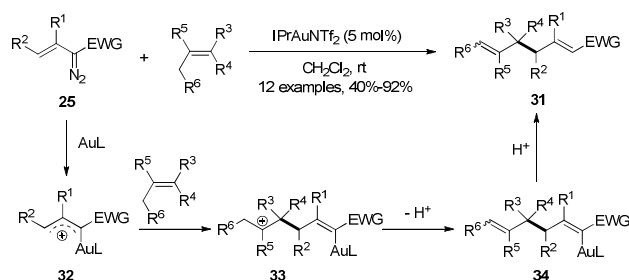
**Scheme 9.** C-C bond formation and double bond migration.
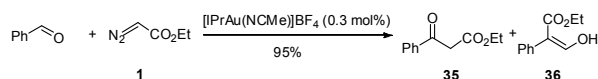
Scheme 10. Gold-catalysed reaction of benzaldehyde with EDA.

A tandem addition and elimination reaction of alkenes with alkenyl diazoacetates **25** was realized by the same group under the gold catalysis. The formed allyl gold cation **32** from **25** reacted with alkene to generate carbocation intermediate **33**, followed by elimination and protodemetalation to give the product 1,5-dienes **31** (Scheme 9).[22]

In 2009, Díaz-Requejo and Pérez *et al.* developed a gold-catalyzed C-H insertion reaction of benzaldehyde with EDA **1** leading to β-keto ester **35** via H-shift and the isomer **36** via Ph-shift (Scheme 10).[24] It should be noted that the gold catalyst is remarkably active and the TOF is 2500 times faster than the previously reported iron-based catalysts. In this case, gold catalyst served as Lewis acid activating the aldehyde by coordination at the oxygen.
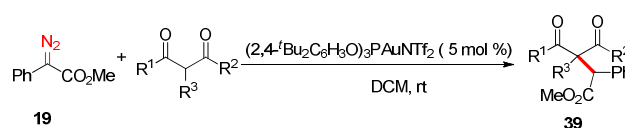
3.2. C(sp³)-H Functionalization
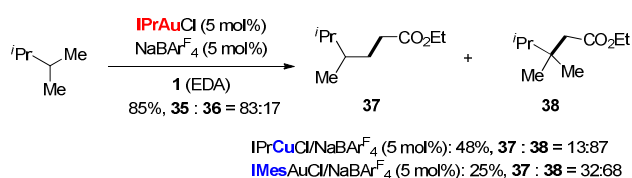
Scheme 11. Alkane C-H insertion with EDA.

In 2006, Nolan, Díaz-Requejo, and Pérez *et al.* examined the reaction of 2,3-dimethylbutane and EDA **1** under the catalysis of Au- or Cu-based complexes, respectively.[25] The effect of

metal is outstanding: the ratio of **37** (1° C-H insertion) and **38** (3° C-H insertion) reverses from IPrAuCl/NaBArF4 to IPrCuCl/NaBArF4 (83:17 vs 13:87). Meanwhile, the regioselectivity of the C-H insetion could be tuned by simple modification of NHC. For example, the reaction catalyzed by IMesAuCl/NaBArF4 afforded **37** and **38** in 32:68 ratio (Scheme 11). The selectivity on primary carbon might be attributed to the steric hindrance between tertiary carbon and IPrAu.

In 2014, Shi *et al.* found that the reaction 1,3-dicarbonyl compounds and phenyldiazoacetates **19** could furnish tricarbonyl compounds **39** under the catalysis of gold complexes with phosphite ligand (Scheme 12).[21] This transformation is rarely found before and give the exclusively product of C-H functionalization over *O*-nucleophilic addition, which is consistent with the specificity of the gold catalysts with phosphite ligand as mentioned in Scheme 7.

Scheme 12. C-H Fuctionalization of 1,3-dicarbonyl compounds with α-aryl-α-diazoacetates.
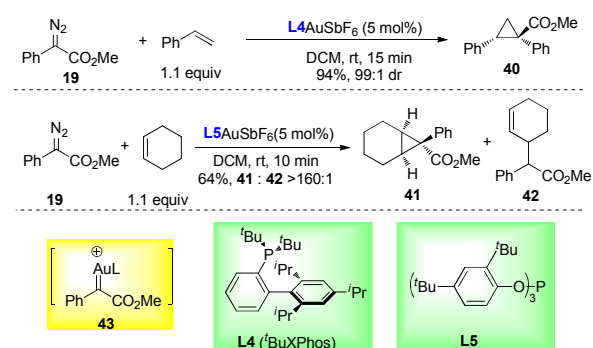
4. Cyclopropanation and Cyclopropenation

Cyclopropane motifs are widely found in bioactive natural products and pharmaceuticals, using as a conformationally restricted biological probe, as well as versatile synthons in organic synthesis. Among those various methods to access these structures, the most efficient way is transition-metal catalyzed cyclopropanation of olefins with diazo compounds.[26] Although the cyclopropanation product **11** of EDA and styrene was formed under the catalytic system of IPrAuCl/NaBArF4 introduced by Nolan and Pérez *et al.*, the yield and the chemoselectivity was unsatisfactory.[11,16] This issue was later addressed by Nolan, Pérez *et al.* and Dias *et al.*. By the application of a novel gold complex [N{(C₃F₇)C(2,6-Cl₂C₆H₃)N}₂]Au(C₂H₄), the cyclopropane **11** was isolated in good yield (69%) as well as a trace amount of C-H functionalization by product,[27] whilst excellent yield and selectivity were observed with the use of gold catalyst IPrAu(NCMe)PF₆ (>99% GC yield, Scheme 13).[28] The authors suggested that the counterion plays an vital role in this catalytic transformation.
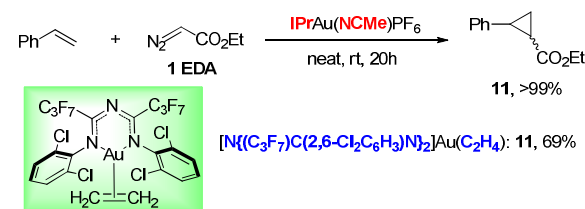

Scheme 13. Cyclopropanation of styrene with EDA.

In 2009, Pérez and Echavarren found that cationic gold complexes with different ligands such as phosphine or phosphite or N-heterocyclic carbene (NHC) ligands showed different catalytic activity.[29] Gold complexes with phosphine ligand **L4** and phosphite ligand **L5** have no catalytic activity on the reaction of styrene and EDA. Nevertheless, these two gold catalysts performed very well for the cyclopropanation of α-phenyl-α-diazoacetates **19** with styrene via donor/acceptor-gold carbene **43**, leading to very high conversions and complete chemoselectivity and diastereoselectivity (Scheme 14, top). These results have also been achieved by the copper-based catalysts. The phosphite derived gold catalyst can promote the cyclopropanation of phenyldiazoacetates **19** and cyclohexene efficiently and chemoselectively. Only a trace amount of C-H insertion product **42** was formed, which is the major product in most cases under the catalysis of Rh (Scheme 14).


Scheme 14. Cyclopropanation of styrene and cyclohexene with α-aryl-α-diazoacetates.

Zhou *et al.* presented the first example of highly enantioselective gold-catalyzed cyclopropanation reaction of olefins with diazooxindoles (Scheme 15).[30] Importantly, they demonstrated that the chiral spiroketal bisphosphine **L6**, developed by the group of Ding, was the most efficient ligand for this transformation. The resulting spirocyclopropyl oxindoles **45** are obtained generally in good to excellent yields with high enantioselectivities. Most notably, other chiral catalysts, such as Rh$_2$(S-PTTL)$_4$ and the (R)-difluorphos/Hg(II) complex, can't provide similar level of enantioselectivity especially for the 1,2-disubstituted alkenes.
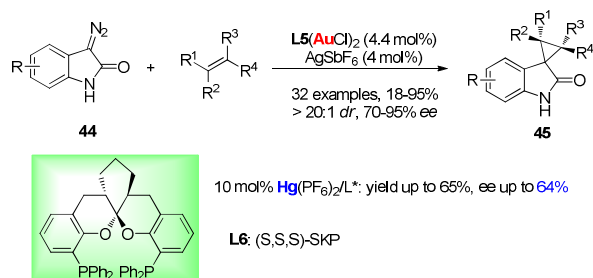
Scheme 15. Asymmetric cyclopropanation of olefins with diazooxindoles.

In 2012, Davies and co-workers reported a highly enantioselective cyclopropenation of internal alkynes with aryldiazoacetates **22** (Scheme 16).[31] A cationic Au(I)-catalyst with chiral binaphthalene-based phosphine ligand **L7** was found to efficiently induce high enantioselectivity and the desired cyclopropenes **46** were obtained in good yields. The substrate scope encompasses various aryl or alkyl disubstituted alkynes and several aryldiazoacetates **22**. Silver catalysts showed the similar reactivity but less enantioselectivity compared with gold catalyst. Moreover, the gold carbenes have a very different reactivity profile compared to the corresponding rhodium carbenes, and are much less susceptible to steric interference.[32,33]
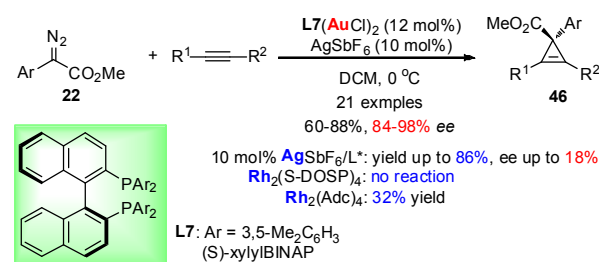

Scheme 16. Asymmetric cyclopropanation of internal alkynes with α-aryl-α-diazoacetates.

5. Coupling of Two Diazo compounds

The carbene-induced coupling of diazo compounds affords an alternative approach to construct C=C bonds besides Wittig-type reactions and olefin metathesis. Although the intramolecular coupling of bis(diazocarbonyl) compounds was developed, the intermolecular version might be more challenging due to the inevitable competition between homo- and cross-coupling as well as difficult stereoselectivity control. Very recently, Sun and co-workers explored the first successful gold(I)-catalyzed cross-coupling of aryldiazoacetates **22** and vinyldiazoacetates **47** to afford Z-configured tetra-substituted alkenes **48** (Scheme 17, top).[34] In this case, a NHC-derived gold complex IPrAuNTf$_2$/NaBArF$_4$ is the most efficient catalyst. Based on this transformation, the homo- and cross-coupling of vinyldiazoacetates **47** and **47'** were realized, which produced the trienes **53** in good isolated yield (86%) with Z/E = 9:1 ratio. Furthermore, polysubstituted benzenes **49** could be easily synthesized as major products via gold-initiated benzannulation involving a diazo cross-coupling, 6π electrocyclization and oxidative aromatization (Scheme 17, bottom). In contrast, the reaction of **47** catalyzed by [Rh$_2$(OPiv)$_4$] afforded pyrazole as the sole product instead of trienes. Of course, the intramolecular diazo coupling could also

be realized via gold catalyst to construct a series of membered cyclic olefins.[35,36]
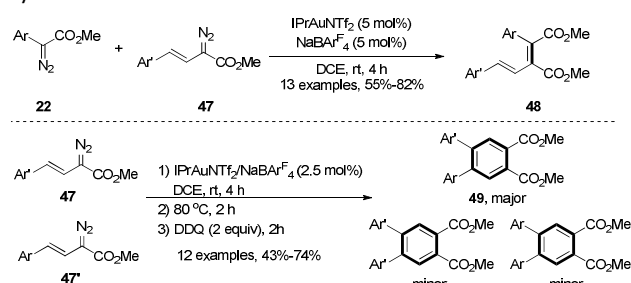
Scheme 17. Intermolecular diazo cross-coupling and benzenes synthesis.
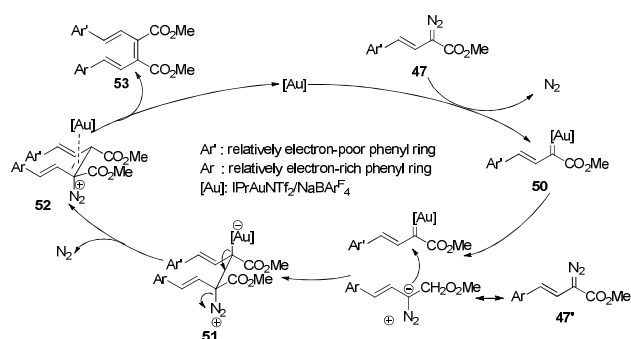
Scheme 18. Propose mechanism for the intermolecular diazo cross-coupling.

A plausible mechanistic rationale for the gold(I)-mediated cross-coupling of vinyldiazoacetates is proposed (Scheme 18). Firstly, the preferential reaction of the relatively electron-poor vinyldiazoacetate **47** and the gold catalyst generates the gold-carbene **50**, which would quickly undergo C-nucleophilic addition by the relatively electron-rich vinyldiazoacetate **47'**, thus giving rise to the intermediate **51**. Then, the emission of one molecule of nitrogen and subsequent migration of the C-Au bond resulting in C=C bond formation would give the triene **53**. It is clear that the trivial electronic difference between **47** and **47'** plays the vital role during the reaction process.
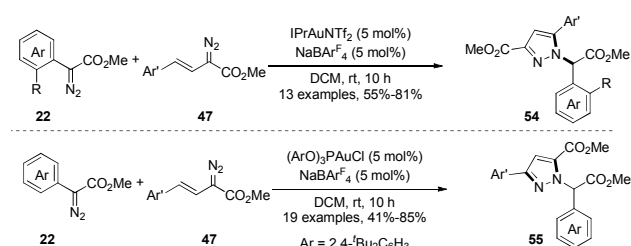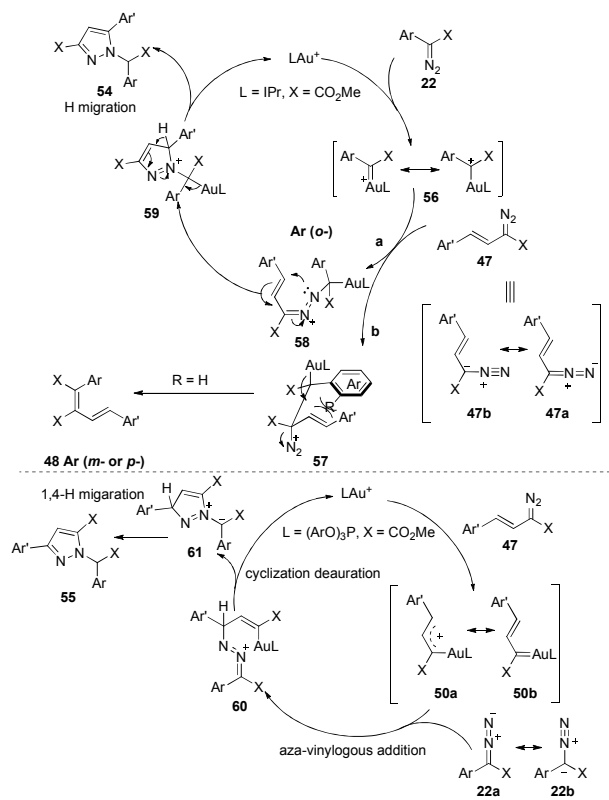

Scheme 19. Divergent diazo cross-coupling.

Later, Sun *et al.* demonstrated an unprecedented gold(I)-catalyzed ligand-controlled cross-coupling of aryldiazoacetates **22** and vinyldiazoacetates **47** by sequential selective

denitrogenation and cyclization affords *N*-substituted pyrazoles **54** or **55** in a position-switchable mode (Scheme 19).[37] Based on the experimental observations, aryldiazoacetates exhibited higher reactivity than vinyldiazoacetates in the IPrAuNTf$_2$/NaBAr$^F_4$-catalyzed cross-coupling reactions. However, vinyldiazoacetates are more reactive, when (ArO)$_3$PAuCl/NaBAr$^F_4$ (Ar = 2,4-^{t}Bu$_2$C$_6$H$_3$) was employed as catalyst.

Two proposed divergent mechanistic pathways were depicted in Scheme 20. When IPrAuNTf$_2$ was used as catalyst, the preferential formation of the gold carbene **56** from the aryldiazoacetate **22** would undergo C- or N-nucleophilic addition by the vinyldiazoacetate **47** to yield the active intermediate (**57** or **58**). The steric effect of aryldiazoacetates is crucial to the reaction mode. The reaction of **56** via C-nucleophilic addition by **47b** would produce diene **48** as the single isomer for the *m*- of *p*-substituted aryldiazoacetates (Scheme 20, top, step b). The *o*-substituted aryldiazoacetates could not deliver dienes due to the steric effect, but deliver **58** through nitrogen attack by **47a** (Scheme 20, top, step a). Pyrazoles **54** was finally produced after sequential cyclization and hydrogen migration. In contrast, the vinylcarbene **50** was trapped by aryldiazoacetate **22** under the catalysis of gold-phophite complex (Scheme 20, bottom). Then the cyclization deauration generates the zwitterionic intermediate **61**, followed by 1,4-H shift to afford the product **55**.


Scheme 20. Propose mechanism for the divergent diazo cross-coupling.

6. Cycloaddition

Carbo- and heterocycles are widely found in natural products and pharmaceutics. The rapid creation of diverse and complex cyclic skeletons from acyclic starting materials is one of the most fundamental goals of synthetic chemists.[38] And catalytic cycloaddition reaction is one of the most efficient strategies for the construction of cyclic compounds. In this field, vinyldiazo compounds are commonly used as C3 synthons in transition-metal-catalyzed [3+n] cycloadditions.[39]
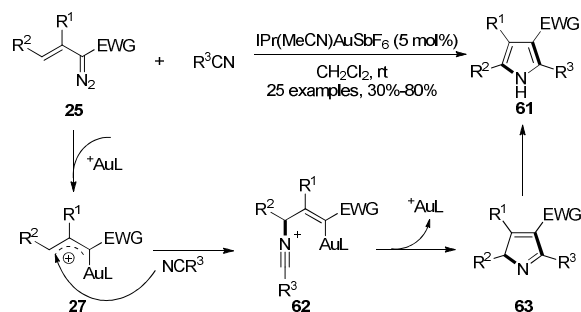
6.1. [3+2] cycloaddition

In 2013, Davies *et al.* presented a gold-catalyzed enantioselective formal [3+2] cycloaddition reactions of vinyldiazoacetates **56** and enol ethers, efficiently affording enantioenriched cyclopentenes **57** (Scheme 21, top).[39] However, rhodium catalyst leads to a cascade C-C bond formation/double bond migration. Importantly, a novel dynamic kinetic resolution was also observed under the same conditions with highly diastereo- and enantioselective when 4-substituted 1-(methoxymethylene)cyclohexanes were used as substrates (Scheme 21, bottom).
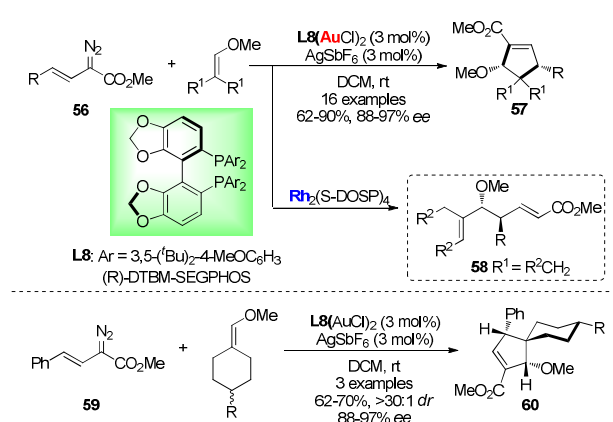
Scheme 21. Asymmetric [3+2] cycloaddition of vinyldiazoacetates and enol ethers and dynamic kinetic resolution.

In 2013, López *et al.* developed a gold(I)-catalyzed formal [3+2] cycloaddition reaction of nitriles with alkenyl diazoacetates **25**, affording functionalized pyrroles **61** in moderate to high yields with complete regioselectivity (Scheme 22).[40] Notable, other transition metals, such as copper, rhodium, silver etc. as well as those phosphine or phosphite derived gold complexes cannot promote this transformation. The authors assume that the initial reaction of the alkenyl diazo compound **25** with the gold complex would afford an allyl gold cation **27**. Next, regioselective *N*-nucleophilic addition of the nitrile to the *γ* position would generate the species **62**, which would produce intermediate **63** by cyclization. Final tautomerization would lead to the pyrrole derivatives **61**.


Scheme 22. [3+2] cycloaddition of nitriles with alkenyl diazo compounds.

6.2. [3+3] cycloaddition

In 2011, Liu *et al.* reported a gold-catalyzed formal [3+3] cycloaddition reaction of nitrosobenzenes with alkenyl diazoacetates **64** with the use of ClAuP^{t}Bu$_2$(*o*-biphenyl)/AgNTf$_2$, in which quinoline *N*-oxides **65** were obtained in good isolate yield (Scheme 23).[41] Rh catalyst could promote the same transformation but give lower yield.
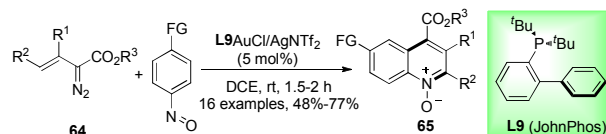
**Scheme 23.** [3+3] cycloaddition of nitrosobenzenes with alkenyl diazoacetates.
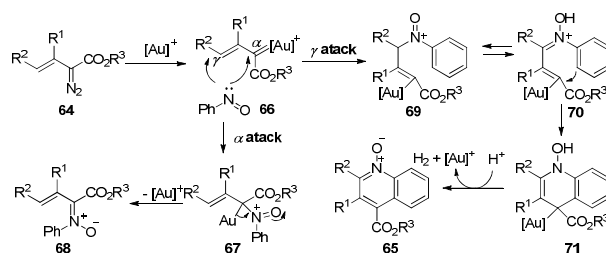
**Scheme 24.** Proposed mechanism for the [3+3] cycloaddition.

A plausible mechanism for this formal [3+3] cycloaddition was proposed in Scheme 24. The success of this formal cycloaddition relies on the vinylogous aza-addition by nitrosobenzene at the *γ* position of carbenes **66** rather than the aza-addition at the *α* position which would be expected to give nitrone product **68**. The resulting species **69** could be converted to gold-containing alkenyl iminium **70** via oxime/nitroso tautomeric equilibrium, which undergoes sequential 6-*π* electrocyclization/deprotonation to generate *N*-hydroxy dihydroquinoline **71**. The product **65** will be obtained after an oxidative aromatization or dehydrogenation.

6.3. [4+2] cycloaddition

Besides C3 synthons, vinyldiazo acetates can be served as nucleophilic C2 synthons under the catalysis of gold-complexes. In 2012, Liu *et al.* discovered an unprecedented gold-catalyzed formal [4+2] cycloaddition (Povarov reaction) between *N*-phenyl imines and alkenyl diazoacetates **72** catalyzed by IPrAuCl/AgNTf$_2$ at room temperature. Diazo-containing tetrahydroquinoline **73** was isolated in 82% yield (Scheme 25).[42] The reaction catalyzed by other noble metals, such as rhodium, silver etc. gave a complex mixtures. The resulting **73** would undergo the formation of gold carbene/1,2 H-shift to afford the product **74** under the catalysis of **L9**AuNTf$_2$. A one-pot reaction for synthesis **74** from the starting diazo acetates **72** and imines was realized by running the reaction at 60 ^{o}C.
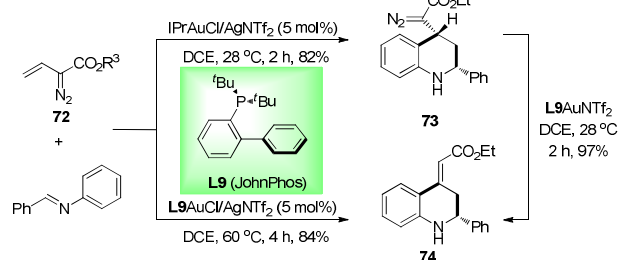
Scheme 25. Gold-catalyzed Pavarov reaction of alkenyl diazoacetates.
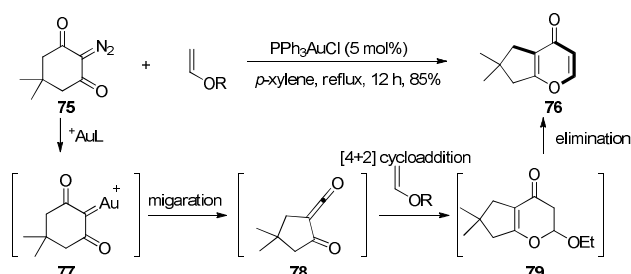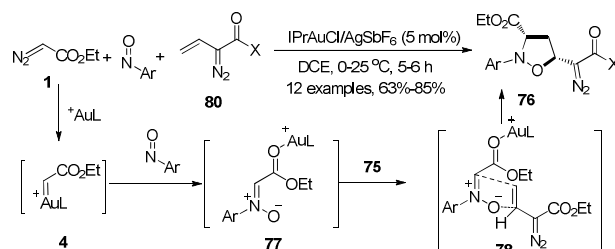

Scheme 26. Gold-catalyzed [4+2]-cycloaddition-involved tandem reaction.

A gold-catalyzed tandem reaction including [4+2] cycloaddition was reported by Lee *et al.* (Scheme 26).[43] The 1,2-shift of alkyl group on gold carbene species **77** from diazo **75** via Wolff rearrangement led to the α-oxoketene **78**, which reacted with vinyl ether via [4+2] cycloaddition and subsequent elimination to afford the multi-substituted 4-pyrones **76**.

6.4. [2+2+1] cycloaddition

In 2015, a novel gold(I)-catalyzed three component cycloaddition of EDA, nitrosobenzenes and alkenyl diazoacetates was developed by Liu and co-workers.[44] As shown in Scheme 27, IPrAuSbF$_6$ decomposes EDA **1** selectively to generate the gold carbene **4**, whereas alkenyl diazoacetates **80** remains intact. A subsequent reaction of the gold carbene **4**

with nitrosobenzenes affords the nitrone species **82**. The concerted [3+2] cycloaddition of **82** with **80** in an exo-cycloaddition as depicted in **83** affords the diazo-containing isoxazolidines **81**. Unlike classic rhodium-catalyzed cyclization of nitrones and alkenyl diazo esters, the in-situ generated nitrone serves as electophile in this case. Commonly used rhodium catalyst in this reaction led to a complete consumption of EDA and **80**, but giving a complex mixtures. The key issue for this cycloaddition is the selective diazo decomposition between two diazo esters.

**Scheme 27.** Gold-catalyzed three component cycloadditions.
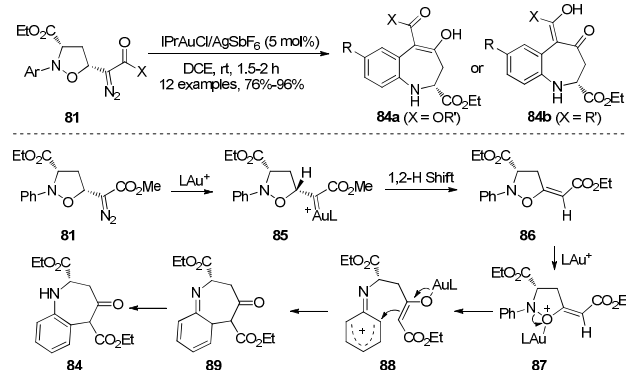
Scheme 28. Synthesis of benzoazepines.

The diazo product **81** can be further converted to seven-membered benzoazepine **84a** or **84b** under the gold-catalysis. The proposed mechanism involves an initial diazo decomposition of **81** to form the gold carbene species **85**, which undergoes a 1,2-H shift to generate the isoxazolidine intermediate **86**. The N-O bond cleavage of isoxazolidine ring generates the gold-enolate-containing anilinium species **88** in the presence of gold complex. The final product **84** is obtained after sequential intramolecular cyclization and aromatization of this species (Scheme 28). This reaction pathway is proved by the deuterium-labeling control experiments.

7. Miscellaneous reactions

In 2007, Toste *et al.* developed an unprecedented gold(I)-catalyzed oxidative rearrangements of diazo compounds.[45] The reaction of α-diazoketone **90** catalyzed by PPh$_3$AuSbF$_6$ with diphenylsulfoxide as the oxidant afforded 1,2-diketone **92** in 88% yield via gold-carbene intermediate **91** (Scheme 29, top). Then the oxidative rearrangements of diazoacetylenes **93** were

realized under the same conditions (Scheme 29, bottom). The authors hypothesized that the cascade process involving gold-induced the intramolecular 5-*exo*-dig nucleophilic addition of diazo onto the alkyne and loss dinitrogen generated the gold-carbenes **94**, which underwent the following oxygen atom transfer from diphenylsulfoxide to afforded 1,4-endiones **95**. In this transformation, gold catalyst exhibited more efficiency and selectivity than rhodium catalyst.
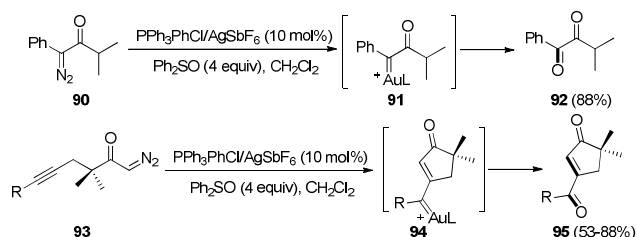
**Scheme 29.** Gold-catalyzed oxidative rearrangements.

In 2013, Liu *et al.* developed an IPrAuSbF$_6$-catalyzed interesting reaction between vinyldiazo carbonyl compounds **80** and acetals to afford the *E*-configured products **96** (Scheme 30, top).[46] Other gold catalysts derived from phosphine ligands (PPh$_3$ and **L9**) and silver salts show lower catalytic activity. Other commonly used transition metal catalysts, such as Rh$_2$(OAc)$_4$, Cu(OTf)$_2$ etc., gave a complicated mixture. As shown in Scheme 29, the oxonium species **97** undergo the Prins-type reaction with vinyldiazo compounds **80** to generate diazo-containing cation **98**, which was attacked by IPrAuOR to form diazo compound **99**. Subsequent decomposition of diazo **99**, followed by 1,2-H shift, would produce the final product **96**. It is noteworthy that the observed *E*-stereoselectivity in this reaction is different with that catalysed by rhodium.
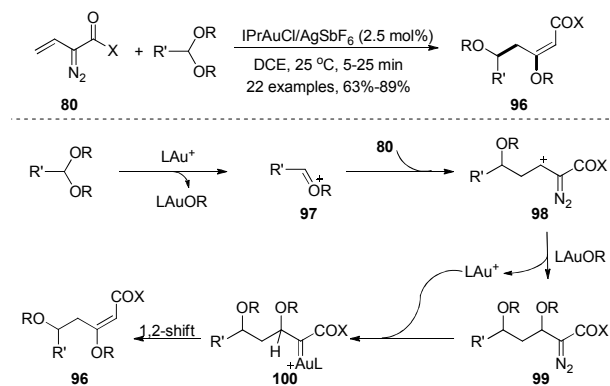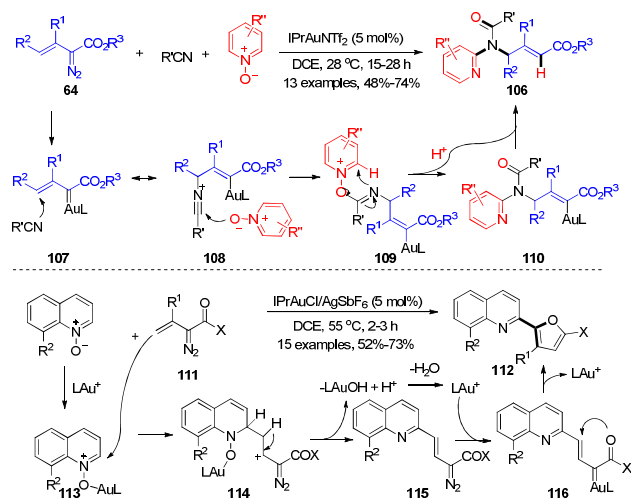

Scheme 30. Gold-catalyzed reactions between alkenyldiazo carbonyl compounds and acetals.

A benzannulation of 2-ethynylbenzyl acetals with EDA **1** was realized by the group of Liu. In this transformation, ClAuP^{t}Bu$_2$(*o*-biphenyl)/AgSbF$_6$ was found to be efficient catalyst resulting the benzenes and naphthalenes **101** (Scheme 31, top).[47] The authors suggest that the EDA serving as C-

nucleophile attacks the oxonium species **102** to form species **103**, which is followed by a Roskamp-type rearrangement involving a 1,2-phenyl shift to afford another oxonium intermediate **104**. After sequential ring closure and the loss of methanol of species **104**, the observed naphthalene product **101** was finally produced. The gold catalyst activated the alkynyl group instead of decomposition EDA was vital in this transformation.
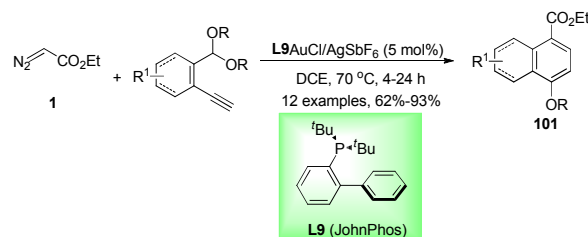
Scheme 31. Gold –catalyzed benzannulation and the proposed mechanism.

Scheme 32. Gold-catalyzed reactions involving alkenyldiazo carbonyl compounds and pyridine-derived oxides.

Recently, another interesting three-component reaction of alkenyldiazo esters, pyridine-derived oxides and nitriles was developed by Liu *et al.* (Scheme 32, top).[48] The carbene species **107** was attacked at *γ*-position by nitrile to form nitrilium intermediates **108**, which might undergo not the cyclization

(Scheme 22) but instead of reaction with N-oxides to afford the species **109**. The products **110** were finally obtained after sequential cyclization, N-O bond cleavage and protonation. This reaction represents the first example in gold-catalyzed oxoarylations of nitriles. Later, the authors also developed gold-catalyzed two-componet reaction between alkenyldiazo compounds and quinoline oxides to construct *α*-furanyl quinolines **112** (Scheme 32, bottom).[49] In this transformation, alkenyldiazo compounds **111** attacked *α*-position of gold activated quinoline *N*-oxides **113** to generate the addition products **114**, which underwent elimination to form species **115**. Then gold complexes decomposed the diazo species **115** to give gold carbene **116**, which afforded the products **112** via tandem oxa-Nazarov cyclization/protodeauration.

8. Summary and outlook

In this Review, we described various transformations of *α*-diazocarbonyl compounds catalyzed by gold complexes. Although the transformation of *α*-diazocarbonyl compounds have been studied for many years, gold-catalyzed carbene transfer reactions remain relatively less developed. Moreover, compared with other noble metals, such as rhodium, copper, silver etc., gold catalysts often showed unique catalytic activity and selectivity, especially in C-H functionalization, diazo coupling and cycloadditions. These unique properties of gold may stimulate organic chemists to develop more novel carbene transfer reactions.

In the future, the following breakthroughs in several fronts are desirable: (1) more mechanistic study. Although there exist a few preliminary mechanistic studies of the reactivity modes of gold carbenes, more extensive mechanistic investigations involving DFT calculations must be carried on to understand further the unique reactivity and selectivities of gold carbenes. Despite that gold-carbenes are commonly proposed as intermediates in these gold-catalyzed transformations of α-diazocarbonyl compounds, the gold-complexes simply functionalize as Lewis acid to activate the diazo compoud by coordination at the terminal nitrogen of diazo group might be a viable alternative to the reported mechanism. This interpretation can also explain all of the ylide-forming reactions and the aromatic substitution (addition/elimination) reactions (2) asymmetric catalysis. Only few examples of asymmetric reactions have been developed to date, the development of more enantioselective gold-catalyzed carbene transfer reactions are highly desirable. In this context, much efforts should be made to design of novel chiral ligands and multi-catalysis strategy; (3) tandem reactions and multi-component reactions. As the rhodium-catalyzed multiple components reactions, more novel tandem reactions based on trapping of the resulting C-Au bond via the addition of gold carbenoinds will be developed; and (4) synthetic applications. More examples of synthetic applications to the synthesis or late-stage modification of natural and biologically active compounds will be one of the major topics in this field. In summary, the coupling of the unique catalytic activity gold

complex with diverse reactivity of α-diazocarbonyl compounds should offer ample opportunities for the design of new reactions.

Acknowledgements

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Journal Name

REVIEW ARTICLE

Lu Liu obtained his BS (2001) and PhD (2010, supervisor: Prof. Junliang Zhang) degrees from East China Normal University (ECNU). After conducting postdoctoral reasearch with Prof. Hong Wang in Miami University, he joined in Prof. Zhang's group as an associate professor in 2013. His research interests are selective metal-catalyzed C-H functionalization and asymmetric catalysis.
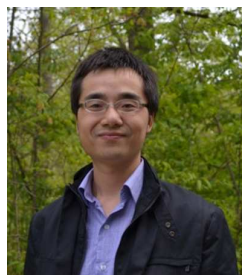
Junliang Zhang obtained his PhD from Shanghai Institute of Organic Chemistry under the supervision of professor Shengming Ma in 2002. He then conducted his postdoctoral research at University of Cologne (Humboldt Fellowship) and University of Chicago. He started his independent career as a full professor at ECNU since the end of 2006. His research interests include developing novel synthetic methodology, asymmetric catalysis and gold chemistry.

Graphical abstract
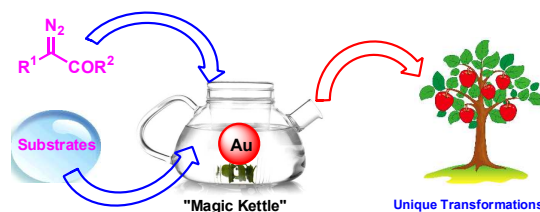
Gold-catalyzed diazo transformations display very unique reactivity and selectivity compared to other noble metals. This review will summarize gold-catalyzed transformations of α-diazocarbonyl compounds.