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Gold-Catalyzed Carbene Transfer Reactions

Seunghoon Shin

Abstract In homogeneous gold catalysis, generations and reactions of metal carbenes have been one of the most rapidly developing areas because of their diverse reactivity under mild conditions. This review covers recent advances in the gold-catalyzed oxygen atom transfer and carbene transfer reactions to alkynes. Atom transfer to an alkyne enables alkynes to function as metal carbene synthons. Many such reactions fulfill redox neutrality starting from safe and easily handled precursors.

Keywords Carbene transfer, Gold carbene, Gold catalysis, Oxygen atom transfer

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Abbreviations

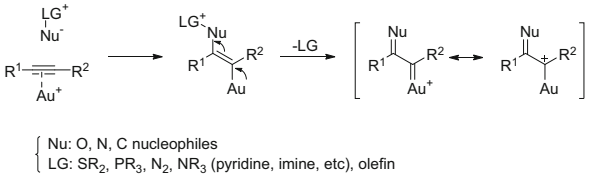
Ad	1-Adamantyl
cat.	Catalyst
DCE	1,2-Dichloroethane
Dipp	2,6-Diisopropylphenyl
dppm	1,1-Bis(diphenylphosphino)methane
equiv.	Equivalent
IAd	1,3-Bis(1-adamantyl)imidazole-2-ylidene
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene
L	Ligand
LG	Leaving group
mCPBA	*m*-Chloroperbenzoic acid
Ms	Methanesulfonyl
OAT	Oxygen atom transfer
pyr	Pyridine
rt	Room temperature
Tf	Trifluromethanesulfonyl

1 Introduction

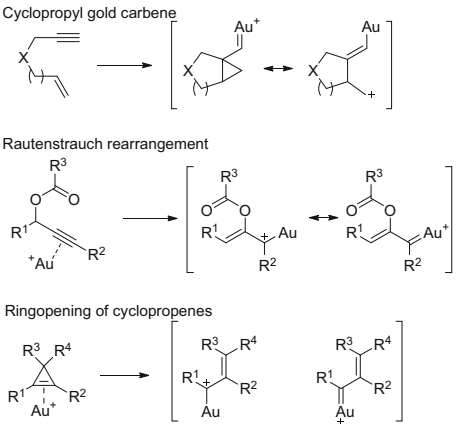
Among the rapid developments in homogeneous gold catalysis in the past decade, those involving gold carbenes have received increasing attention from the synthetic community. This is because diverse reactivity is displayed under mild reaction conditions and these protocols do not need traditional diazo compounds as precursors to the metal carbenes [1, 2]. Although stabilized diazo compounds with electron-accepting substituents are stable under most reaction conditions, synthesis of functionalized diazo compounds often requires diazo transfer reactions which can involve potential hazards [3] and/or the use of toxic and explosive diazomethane [4]. The ability to utilize stable, readily available and easily handled precursors to gold carbenes should open up new paths to metal carbene chemistry.

This review focuses on the reactions in which oxygen (and other) atoms are transferred to alkynes to form what can be envisioned synthetically as gold carbenes (Scheme 1). Although the nature of such gold carbenes can best be described as Au (I)-coordinated carbocations, the representation of gold carbene with a double bond between Au and carbon is used in this review.

Scheme 1 General reactivity pattern



Scheme 2 Other methods of carbene generation not covered in this review



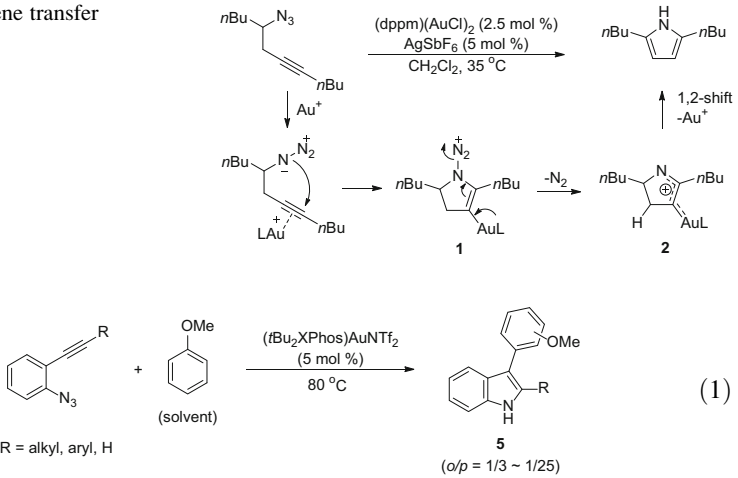
Impressive developments have been made in developing new methods of generating Au-carbenes which are covered according to the type of atom (or carbene) transfer reagents in approximately chronological order. Some of these aspects have been the topic of other recent reviews [5–8]. However, some other important methods of the generation of gold carbenes (Scheme 2) that do not fall into this category (Scheme 1) are not covered in this review [9–11].

2 General Reactivity Pattern

2.1 Nitrene Transfer by Azides and N–N Bond Reagents

A formal nitrene transfer using azides was demonstrated by Toste and coworkers in 2005 [12]. As delineated in Scheme 3, liberation of N_2 gas from the adduct **1** would lead to nitrene transfer forming α-imino Au-carbene **2**. The reactivity pattern between azides and alkynes demonstrated here was the first case of addition of a leaving group (in this case, N_2) bearing a nucleophile onto alkyne, and formed a paradigm for subsequent alkyne oxidation chemistry. Various combinations of nucleophilic atoms and leaving groups (LG) later resulted in a variety of synthetic methods for generation of Au-carbenes via alkyne oxidation. In this particular case, the Au-carbene may evolve via 1,2-H shift into pyrroles or ring expansion via a Wagner–Meerwein shift.

Scheme 3 Nitrene transfer from azide

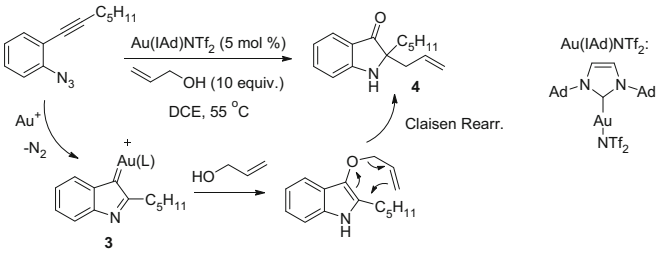


(1)

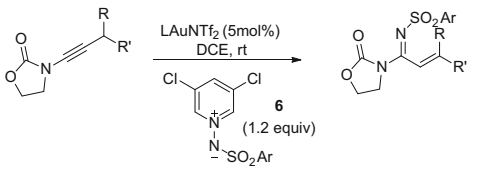
Later, in 2011, Gagosz and coworkers further developed the azide chemistry for oxindole synthesis (Scheme 4) [13]. The Au-carbene **3** could be intermolecularly trapped by an alcohol (10 equiv.), and the following Claisen rearrangement occurred under relatively mild conditions (50–60°C), providing oxindoles **4** with an α-quaternary center. In the same paper, trapping Au-carbenes with Ar–H was also reported, leading to 3-aryl indoles **5** (Eq. 1). Shortly afterwards, Zhang and coworkers reported similar reactions employing arenes, heteroarenes, and alcohols as nucleophiles [14].

Sulfilimines were shown to be viable intramolecular nitrene donors which can generate α-imino Au-carbene synthons [15]. In 2011, Zhang and coworkers introduced a new nitrene transfer reagent, namely *N*-tosyliminopyridinium ylides **6** which allowed for intermolecular nitrene transfer with activated alkynes, such as ynamides (Scheme 5) [16]. An outer-sphere attack of ylides onto Au-activated alkynes was proposed as the mechanism, similar to that for the reactions of N–O oxidants. The geometry of the imine C=N bond was determined to be (E) based on X-ray crystallographic as well as stereochemical analysis. However, unlike related *N*-oxide oxidations of alkynes ending with 1,2-H (or alkyl) shift, the geometry of the C=C bond was obtained as a mixture.

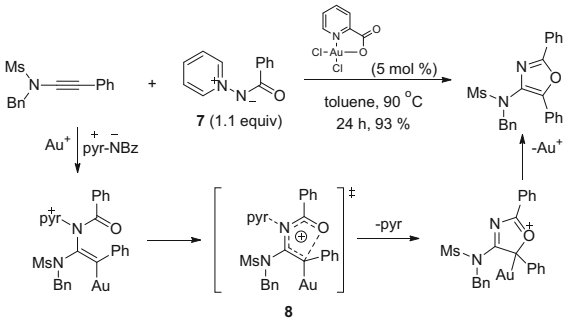
Shortly afterwards, Davies and coworkers reported a related transfer reagent, pyridine-*N*-aminides **7** (Scheme 6) [17]. In the presence of an N-acyl group which can act as an intramolecular nucleophile, the α-imino Au-carbene **8** can be transformed into oxazoles, which can be envisioned as a formal (3 + 2) cycloaddition between 1,3-N,O dipoles and alkynes. Thus, the reaction of pyridine-*N*-aminides with ynamides occurred intermolecularly in the presence of dichloro (pyridine-2-carboxylato)Au(III) complex, leading to various oxazoles. Chemoselectivity was excellent in favor of the desired oxazole formation in the presence of competing functional groups, such as alkynes and alkenes which are potentially apt for cyclization and cyclopropanation, respectively, or cyclopropyl or alkyl groups at R which can participate in a competitive ring expansion and a



Scheme 4 Cascade nitrene transfer and Claisen rearrangement



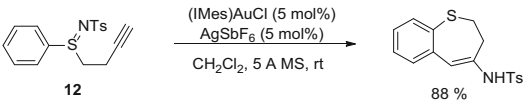
Scheme 5 *N*-Tosyliminopyridinium ylides as nitrene transfer reagents



Scheme 6 Pyridine-*N*-aminides as OAT reagents

1,2-insertion, respectively. A gold-carbene route was not favored because of the mechanism based on the absence of 1,2-shift. Instead, a cationic electrocyclization of **8** in concert with N–N cleavage was suggested as a preferred mechanism.

2.2 Oxygen Atom Transfer from Sulfoxides



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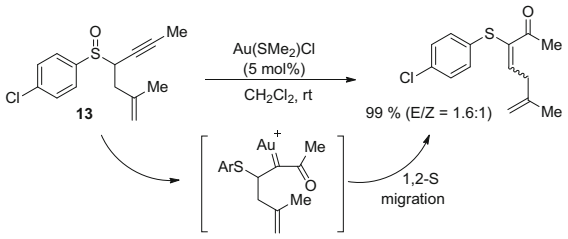
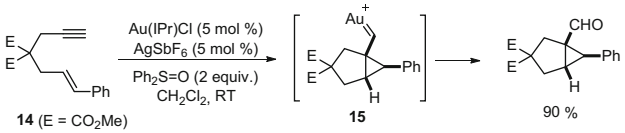
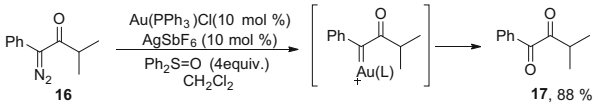


(3)

In 2007, Toste and coworkers reported a pioneering oxygen atom transfer (OAT) chemistry introducing sulfoxides (Scheme 7) [15]. Homopropargyl sulfoxide **9** underwent initial 5-exo-dig O-attack on alkynes and delivered benzothiophenones **10**. The initial addition mode (5-exo-dig vs 6-endo-dig) dictated the outcome of regioselectivity in the alkyne oxidation and the alkyne substituents had a strong influence on the products obtained (**10** or **11**). In addition to this O-transfer chemistry, sulfimine substrates **12** were shown to transfer nitrene equivalent (Eq. 2). For the propargyl sulfoxide substrates **13**, on the other hand, the posited carbene underwent a 1,2-sulfide shift as the major pathway (Eq. 3). Also notable in the last example is that a possible cycloisomerization of 1,5-enynes did not occur, indicating the chemoselectivity of this OAT protocol.



(4)



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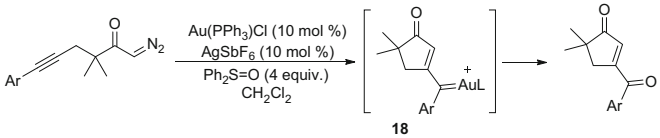
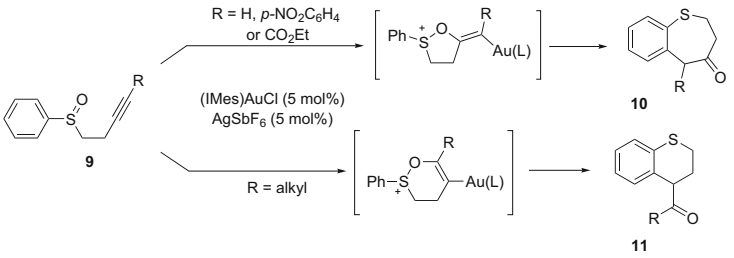


(6)

Diphenyl sulfoxide can also be an Au-carbene trap, transforming metal carbenes into the corresponding carbonyl compounds (Eqs. 4–6) [18]. The 1,6-enyne **14** transformed into carboxaldehyde derivatives in the presence of Au-catalyst and $Ph_2S{=}O$, which can best be explained by initial cycloisomerization into cyclopropyl gold carbenes **15**, followed by the oxidation with $Ph_2S{=}O$. Whether the OAT occurred first and then cyclopropanation occurred, or the initial formation of cyclopropyl carbenes followed by their oxygenation, can be inferred from the regioselectivity of the oxygen delivery, suggesting the latter scenario is in effect (Eq. 4). Further evidence of OAT to Au-carbene centers can be gleaned from the oxidation of gold carbenes generated from the α-diazoketone **16** into 1,2-diketone



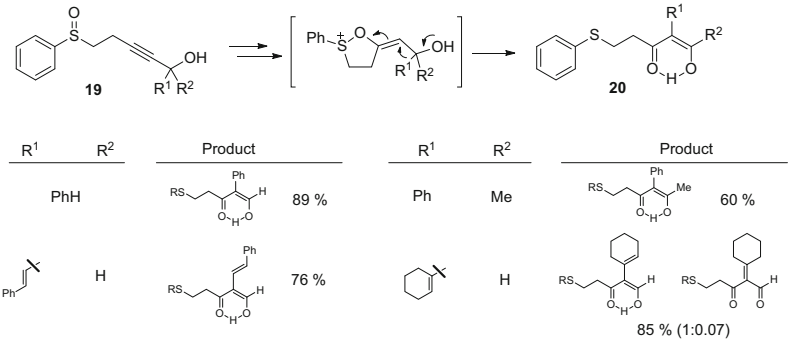
Scheme 7 Sulfoxides as OAT reagents

17 (Eq. 5). Similarly generated gold carbenes can also undergo intramolecular carbene transfer to alkynes leading to **18**, followed by oxidation (Eq. 6).

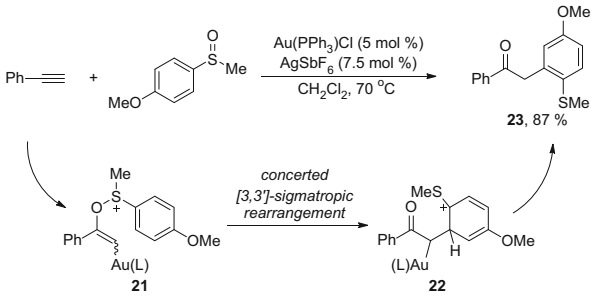
Shortly afterwards, Zhang and coworkers reported OAT from homopropargyl sulfoxides **19** leading to α,β-unsaturated enones **20** via pinacol shift (Scheme 8) [19]. The migratory aptitude among Ar, alkenyl, H and alkyl groups to the carbene center was investigated. In acyclic cases, Ar and alkenyl groups preferentially migrated over H and alkyl groups into the α-position of enones. This migratory aptitude is distinct from those observed in the Rh-catalyzed decomposition of α-diazo-β-hydroxyesters, where H migration is preferred [20].

Whether distinct Au-carbene is involved in the OAT of sulfoxides is an intriguing issue. While extending the above sulfoxide redox chemistry to an intermolecular setting, Ujaque and coworkers reported a synthetic pathway to α-aryl ketones **23** via intermolecular alkyne oxidations with sulfoxides (Scheme 9) [21]. Interestingly, the regioselectivity at the aryl ring did not follow the expected trend in the intermolecular electrophilic aromatic substitution of the purported Au-carbenes and, instead, the alkyl group ended up at the position ortho to the alkylthio group. Moreover, no cross-over products were identified [22]. Furthermore, computational study failed to identify a discreet minimum for the Au-carbene and the sulfide, and instead suggested that a concerted [3,3]-sigmatropic rearrangement of **21** into **22** was operative for the process [23].

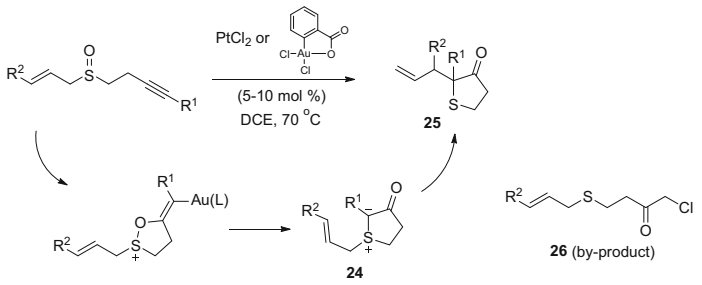
In 2009, Davies demonstrated that gold-carbene generated from the OAT of sulfoxides can be trapped by the liberated sulfides to form sulfonium ylides **24** which were shown to undergo 2,3-sigmatropic rearrangement of the S-bound allyl unit into **25** (Scheme 10) [24]. The mechanism seems to involve a concerted sigmatropic shift of the allyl group, as can be seen in the 1,3-transposition of the substituted allyl unit. The optimized catalytic system turned out to be $PtCl_2$ (5 mol %) in DCE for terminal alkynes, and dichloro(pyridine-2-carboxylato)Au(III) for internal alkynes. Notably, in the latter case, a quaternary α-center can be formed. An interesting by-product, namely **26**, was observed in a small amount in the reaction of terminal alkynes which presumably arose from α-chlorination (from solvent DCE) of Pt-carbene species [25].



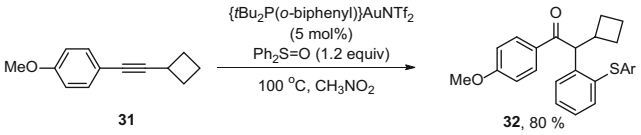
Scheme 8 Sulfoxide-mediated OAT and 1,2-alkyl shift



Scheme 9 Intermolecular OAT from sulfoxides via [3,3]-sigmatropic rearrangement

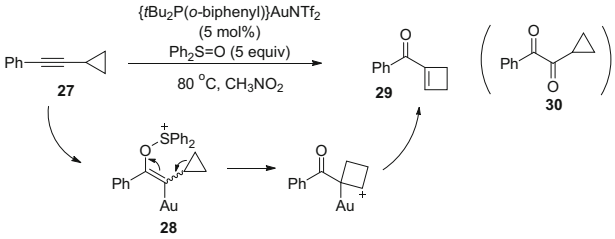


Scheme 10 Sulfoxide-mediated OAT and 2,3-Wittig rearrangement



(7)

Ring expansion can be induced by the generation of a carbene center next to cyclopropyl rings [26]. Liu and coworkers examined the ability of a carbene generated from the sulfoxide redox of **27** to incur cyclopropane ring expansion to



Scheme 11 Sulfoxide-mediated OAT and ring expansions of cyclopropanes

29 (Scheme 11) [22]. In the screening of appropriate OAT reagents, N–O oxidants such as amine-*N*-oxides, pyridine-*N*-oxides, and nitrones were not effective. Using 5 equiv. of $Ph_2S{=}O$, the desired acylcyclobutenes were obtained in CH_3NO_2 as solvent without competitive formation of 1,2-diketo compounds **30** [27]. Here, the ring expansion of the cyclopropane ring was faster than the competing 3,3-sigmatripic rearrangement of **28** (Scheme 8) [21]. However, the ring expansion reaction could not be extended to homologous cyclobutyl alkyne substrates **31** as these substrates followed a competitive formation of [3,3]-sigmatropic rearrangements to **32** (Eq. 7).

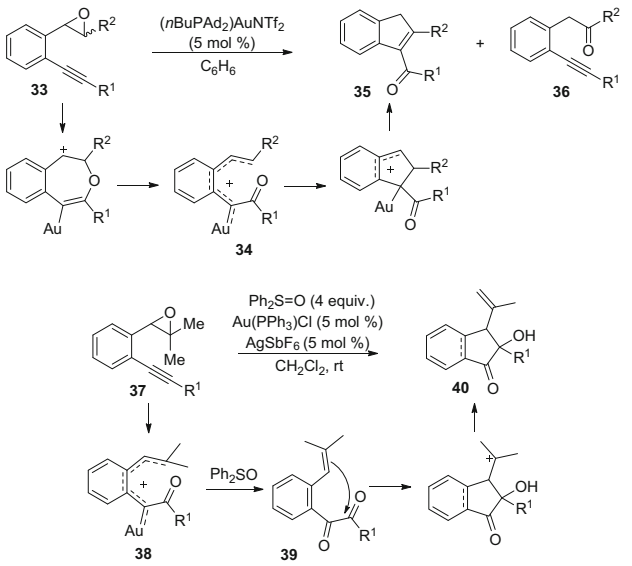
2.3 OAT from Epoxides

OAT from epoxides to alkynes was first reported by Hashmi and coworkers in 2008 [28]. Epoxyalkynes **33** prepared by mCPBA oxidation of the corresponding 1,5-enynes underwent a rearrangement, leading to 1-acylindenes **35** (Scheme 12). The mechanism is consistent with the formation of gold carbene **34** via attack of epoxide oxygen on the Au-activated alkynes. A small amount of by-product **36** was also observed, which results from the coordination of Au^+ on epoxide, followed by 1,2-shift. The presence of Au-carbene in this reaction was supported by the trapping of **34** with styrene or ethyl vinyl ether [29]. In the presence of $Ph_2S{=}O$ as oxidants, similar substrates **37** underwent further oxidation into 1,2-diketones **39**, which isomerize into 2-hydroxyindanones **40** with a quaternary center [30].

3 N–O Bond-Based Oxidants

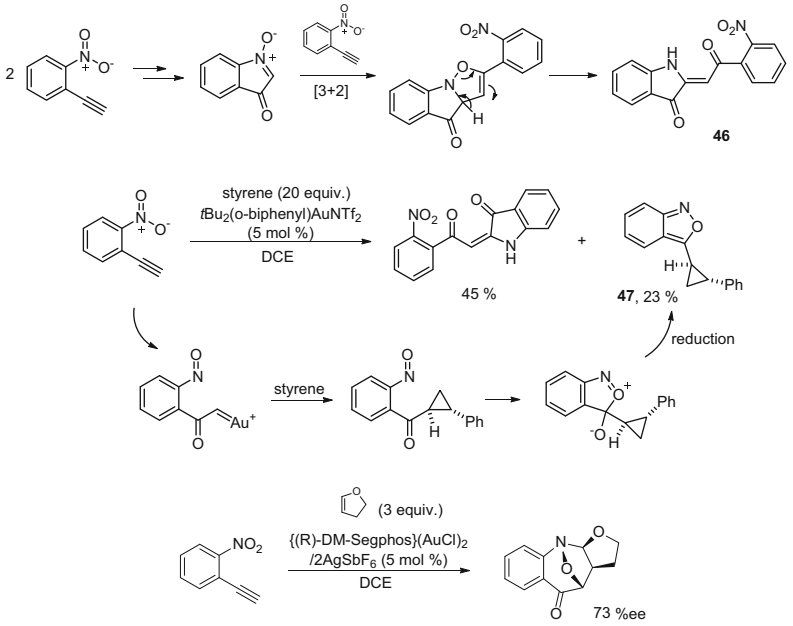
3.1 Nitro Compounds

The first OAT onto alkynes in gold catalysis was reported by Asao and coworkers in 2003 (Scheme 13). They reported *o*-alkynyl nitroarenes were converted into a mixture of isatogens **41** and anthranils **42** upon treatment with $AuBr_3$ in DCE



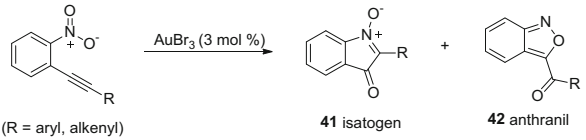
Scheme 12 OAT from epoxides

[31]. Afterwards, a similar transformation was also reported with Ir(III)-catalyst by Crabtree and coworkers [32].



In 2011, Liu and coworkers made use of this reactivity to develop an elegant (2 + 2 + 1) formal cycloaddition involving nitroso groups, alkenes, and carbenyl carbons

Scheme 13 The first intramolecular OAT from alkynes



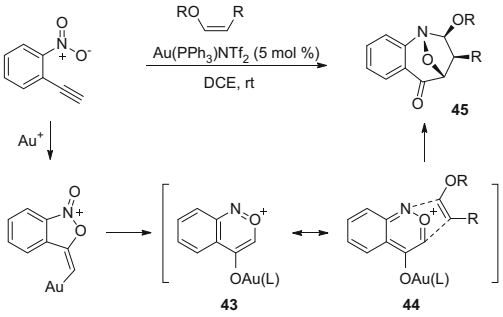
(Scheme 14) [33]. To minimize the dimerized by-product **46** resulting from [3 + 2] cycloaddition of isatogens with starting nitroalkynes (Eq. 8), slow addition of *o*-nitroethynylbenzene was required in the presence of excess dipolarophile. High regio- and diastereoselectivity was observed with a range of vinyl ethers and vinyl sulfides. The authors proposed that the mechanism of this cascade transformation involved generation of dipolar species **43**/**44** and the subsequent [3 + 2] cycloaddition with electron-rich olefin to form **45**. The high diastereoselectivity observed as well as the trapping of the gold carbene intermediate by styrene to form cyclopropyl anthranils **47** (Eq. 9) were taken as evidences for their proposal. Conspicuously, the cycloaddition could be rendered enantioselective, in the presence of (R)-DM-Segphos ligand, delivering the cycloadduct in 73% *ee* (Eq. 10).

3.2 Oximes

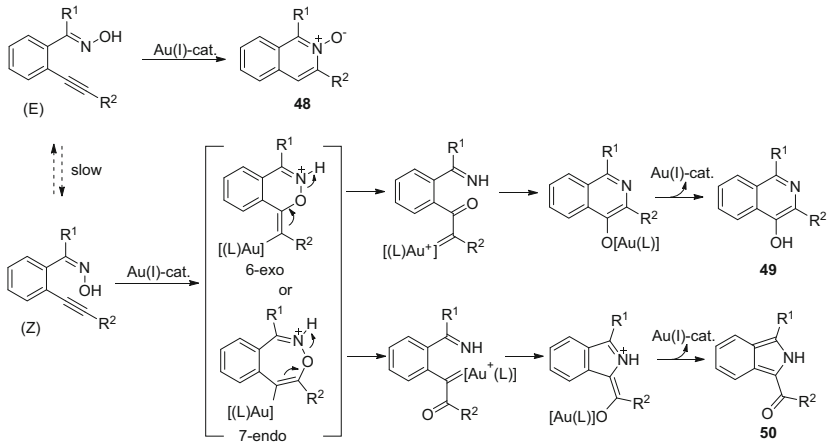
The ability of oximes to function as O-atom donors onto alkynes was found by Shin and coworkers in 2009 (Scheme 15) [34]. In the reaction of *o*-alkynylbenzaldoxime derivatives catalyzed by cationic of Au(I) complexes, (E)-oximes led to isoquinoline-*N*-oxides **48** [35] and (Z)-oximes formed isoindoles **50** in a mutually exclusive fashion. They proposed that the two pathways diverged at the point of the initial 6-endo-dig *N*-attack or 6-exo-dig *O*-attack. This mechanistic picture could explain the N–O cleaving steps in nitronyl alkynes by Yamamoto and coworkers [31] and laid a background for developing further N–O bond cleaving redox chemistry.

3.3 Nitrones

In 2008, Shin and coworkers reported that nitrones can function as OAT agents onto alkynes under electrophilic metal catalysis (Scheme 16) [36]. Nitrones can be easily assembled from the condensation of hydroxylamine derivatives and the corresponding aldehydes. Yet, in the presence of electrophilic metal salts, intramolecular transfer of an oxygen atom from nitrones onto alkynes occurs smoothly, leading to azomethine ylides **51**. The pendent alkenes would undergo stereospecific [3 + 2] dipolar cycloaddition with these in situ formed azomethine ylides, leading to 8-aza[3.2.1]bicyclooctanes **52**. Pt(II), Au(III), Au(I), and Ag(I) complexes were able to catalyze this process, and among them, $AuCl_3$ in CH_3NO_2 gave the best rates



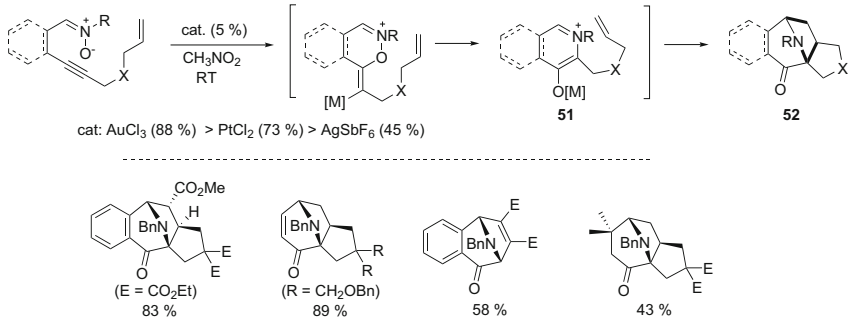
Scheme 14 Nitro group-mediated OAT and [3 + 2] cycloaddition



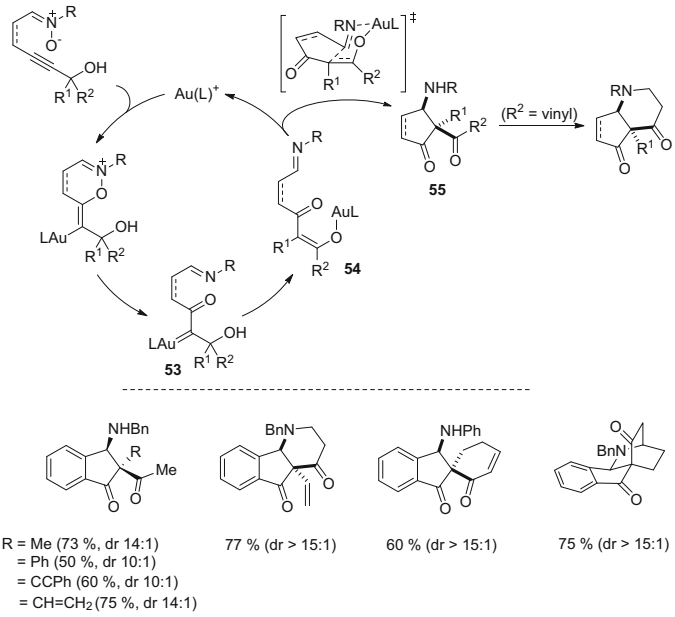
Scheme 15 OAT transfer from (Z)-oximes

and selectivity between [3 + 2] cycloaddition and isoindole products. For the mechanism of N–O bond cleavage, an alkynylnitrone substrate with alkyl tether between nitrone and alkyne groups was shown to form the desired [3 + 2] adduct, which suggested that the oxygen transfer occurs through the N–O–C=C–Au bond and not through a retro-electrocyclization mechanism. In 2011, Li and coworkers have found that the similar N–O redox reactivity of nitronyl alkyne substrates can be manifested by Ir(III), Rh(III), and Ru(II) complexes in both catalytic and stoichiometric reactions [37]. They reported the X-ray crystallographic structure of Ir(III)-bound azomethine ylides and the solid state structure had *O*-bound tautomeric form. Development of an asymmetric version of this [3 + 2] cycloaddition of azomethine ylides were examined by Shin and coworkers, resorting to the auxiliary controlled approach [38].

In 2010, Shin and coworkers further expanded the scope of nitrone redox chemistry by converting electrophilic carbenes **53** into nucleophilic enolates **54** via 1,2-pinacol shift (Scheme 17) [39]. The reaction of nitronylalkynes having tertiary alcohols at the alkynyl terminus led to cascade transformations comprising



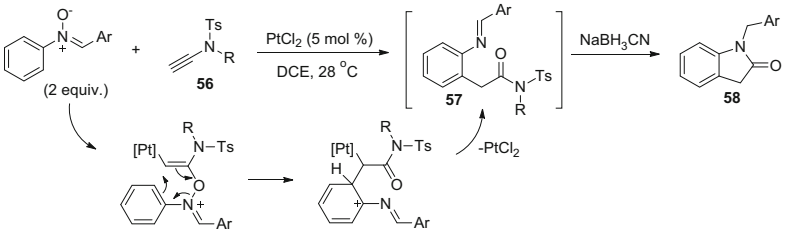
Scheme 16 Nitrone-mediated OAT and [3 + 2] dipolar cycloaddition



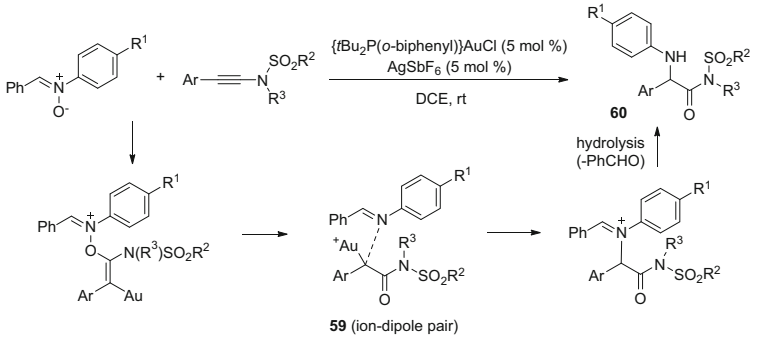
Scheme 17 Nitrone-mediated OAT, pinacol shift and Mannich (and Michael) addition sequence

OAT, pinacol, and Mannich (and Michael) addition. The migrating groups in the pinacol shift ended up at the quaternary position of the resulting 3-amino-cyclopentanones, and therefore the selectivity of various migrating groups was investigated. Among alkyl groups at R^1 and R^2, the smaller alkyl groups preferentially migrated (Me > Et > *i*Pr). π-Functional groups, such as aryl, vinyl, and alkynyl groups preferentially migrated over a methyl group. These migrating groups ended up at the quaternary position of **55** in a stereoselective fashion after Mannich addition through a cyclic transition state.

Intermolecular OAT from nitrones to alkynes was examined for the synthesis of indolin-2-ones **58** by Liu and coworkers (Scheme 18) [40]. To induce



Scheme 18 Intermolecular OAT from nitrones-[3,3] sigmatropic rearrangement: oxyarylation of alkynes)



Scheme 19 Oxyamination of alkynes

intermolecular reactivity and regioselective OAT, donor-activated ynamides were selected. Notably, commonly employed cationic Au(I) complexes led to an extensive decomposition of starting materials and less acidic AuCl or $PtCl_2$ were found to be efficient catalysts. The intermediate carbonylimines **57** were isolated in good yields or they can be reduced with $NaBH_3CN$ in THF to afford indolin-2-ones **58**. Absence of cross-over indicated an intramolecular sigmatropic rearrangement mechanism.

With aryl substituted ynamides, oxyamination was followed instead of the above oxyarylation (Scheme 19) [41]. Using sterically bulky 8-methylquinoline-*N*-oxide as oxidants and tBu$_2$P(*o*-biphenyl)AuCl/$AgSbF_6$ as the catalyst, the desired oxyamination product **60** was obtained smoothly at room temperature. Use of nitrones here functioned both as aniline and oxygen donor. The authors proposed α-oxo gold carbene intermediates **59** that form a tight ion-dipole pair to explain the absence of cross-over.

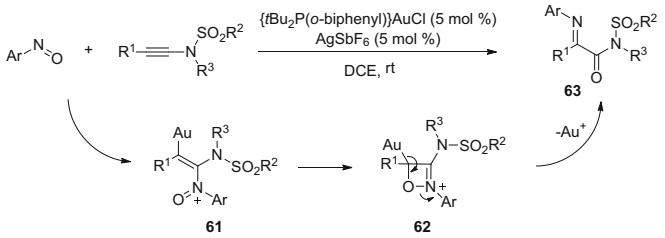
With the same aryl substituted ynamides, a change of reaction partner from nitrones to nitroso arenes led instead to oxyimination instead of oxyamination (Scheme 20) [41]. This transformation is equivalent to a nitroso/alkyne metathesis and was proposed to proceed through the N-attack of nitroso compounds onto ynamides to **61**, cyclization into 4*H*-oxazet-2-ium species **62**, followed by its

fragmentation to **63**. The oxyimination products could be converted with $NaBH_4$ into synthetically useful α-amino alcohols.

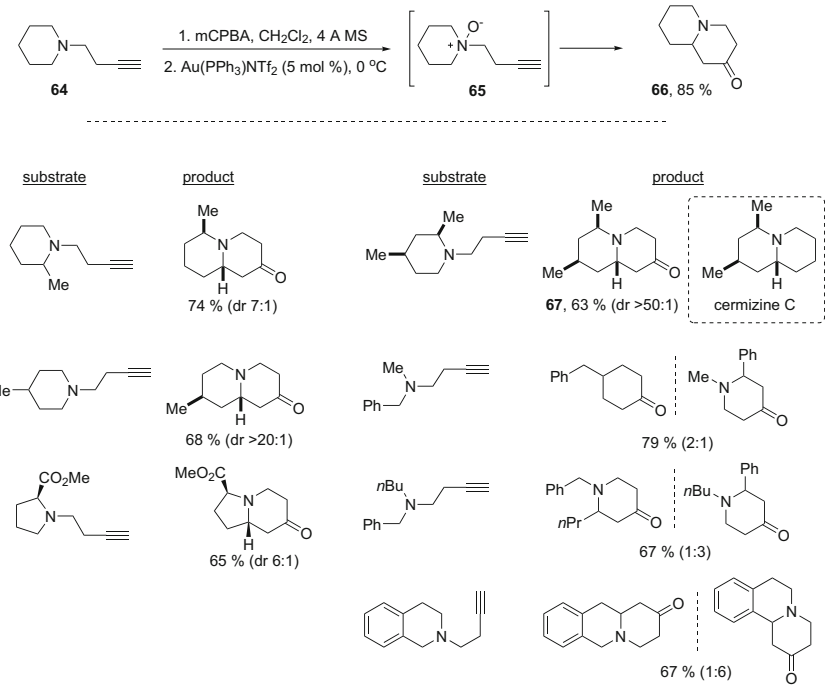
*3.4 Amine-*N*-Oxides*

In 2009, Zhang and coworkers reported that 3-butynylpiperidine-*N*-oxides **65**, prepared in situ from mCPBA oxidation of the corresponding amines **64**, undergo OAT to alkynes (Scheme 21) [42]. In the presence of $(PPh_3)AuNTf_2$ (5 mol%) in dichloromethane, the substrates **65** smoothly transformed into piperidin-4-ones **66** at 0°C for 1 h via an apparent C–H activation. With substituted piperidine, pyrrolidine, and acyclic tertiary amines as substrates, high diastereoselectivity was observed, ranging from 6:1 to >20:1, depending on the substitution pattern. Interesting selectivity issues arise when the starting amines substituted with two different alkyl groups were used. Representative reactivity profile revealed that the hydride is transferred from the least hindered alkyl group and that the hydride transfer is favored in the case where the corresponding carbenium ion can be stabilized by resonance. The efficiency of the two-step piperidin-4-ones synthesis was demonstrated in the total synthesis of cermizine C from **67** (Scheme 21). The involvement of gold carbene in this transformation became even more intriguing issue because the reaction of substrates with EWG at the alkynes proceeded smoothly even in the *absence* of Au-catalyst at mild temperatures (0°C and below) [43].

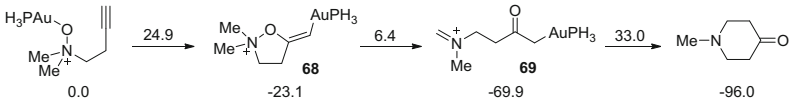
Given these experimental results, the mechanism of this amine-*N*-oxide-mediated OAT was computationally studied (Scheme 22) [44]. Density functional calculation suggested that a formal 1,5-hydride shift occurred through a single concerted transition state by a hetero-retroene mechanism (from **68** to **69**), thus disfavoring the Au-carbene mechanism. Experimental evidence for disfavoring the gold carbene intermediate was based on the observation in which a related gold carbene generated from the α-diazo-precursor did not undergo this 1,5-hydride shift, but instead produced a Wolff rearrangement. The computational results also successfully accounted for the product ratio when two alkyl substituents on N are different.



Scheme 20 Oxyimination of alkynes



Scheme 21 Tertiary amine-*N*-oxides as OAT reagents

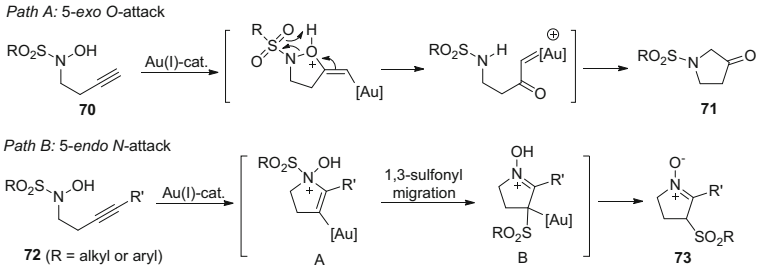


* Relative free energies and activation energies (in kcal/mol) are shown below the structure and above the reaction arrows, respectively (B3LYP-D3)

Scheme 22 DFT computational study of OAT process from 3° amine-*N*-oxides

3.5 Hydroxylamines and Nitroso Compounds

N-Hydroxylamines are appealing OAT agents because of their availability [45, 46] and their potential reactivity involving N–O cleavage. Conceptually, formal addition of N- and O-atoms in the *N*-hydroxylamines onto alkynes would provide a direct route to synthetically useful α-amino carbonyl compounds. In 2011, Shin and coworkers reported the first gold-catalyzed intramolecular reactions of *N*-hydroxyl homopropargylamines (Scheme 23) [47]. *N*-Sulfonyl hydroxylamine derivatives reacted in the presence of (IPr)AuCl and $AgBF_4$ (5 mol% each) to provided 3-pyrrolidinones **71**. Being an ambident nucleophile, the reaction of *N*-hydroxylamines with internal alkynes **72** led to initial 5-endo-dig N-addition, giving nitrones

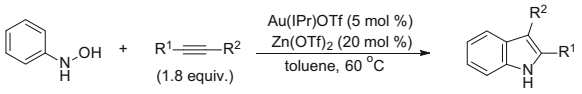


Scheme 23 *N*-Hydroxylamines as OAT reagents

73 instead. In the formation of pyrrolidinones **71**, the presence of the N-sulfonyl protecting group was essential for the N–O cleavage.

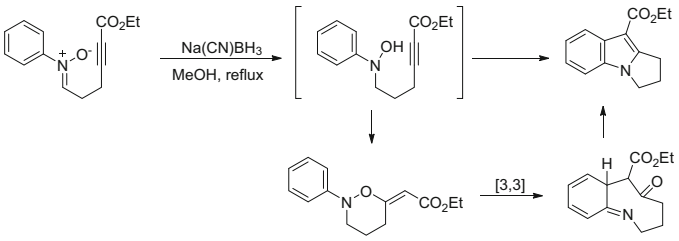
Metal-free rearrangement of *O*-vinyl-*N*-arylhydroxylamines has long been known to undergo thermal [3,3]-sigmatropic rearrangement by Coates and coworkers (Scheme 24) [48]. Utilizing efficient gold-catalyzed alkoxylation of alkynes, this [3,3]-sigmatropic rearrangement have received renewed interest in indole and pyrrole synthesis as follows.

Thermal rearrangement of *O*-vinyl-*N*-arylhydroxylamine derivatives and subsequent dehydration can lead to indoles [49]. In common with Fisher indole synthesis, a key issue in terms of selectivity lies in the preparation of *O*-vinyl-*N*-arylhydroxylamine in a regioselective manner. In 2011, Zhang and coworkers addressed this issue utilizing gold-catalyzed Markovnikov O-addition of *N*-aryl-*N*-hydroxylamines onto terminal alkynes (Scheme 25) [50]. The intermolecular addition involving addition of hydroxylamines, [3,3]-sigmatropic rearrangement, and dehydrative cyclization occurred efficiently at room temperature in the presence of $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*t*Bu-C_6H_3) complex in DCE, providing various 2-aryl and 2-alkyl indole derivatives. This protocol has advantages over conventional Fisher indole synthesis in that the reaction conditions are neutral and acid-labile-protecting groups (THP ethers) can survive. However, in some cases, disproportionation of *N*-aryl-*N*-hydroxylamines into nitrosobenzenes and anilines was noted, resulting in azoxybenzenes as by-products.

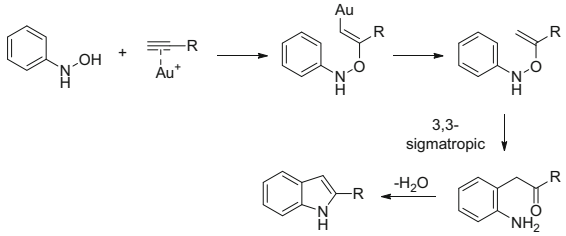


(11)

The reaction with internal alkynes required a modification of reaction conditions because of the attenuated reactivity. Zhang and coworkers found that the use of Zn (II) as a co-catalyst along with an Au(I) catalyst provided an effective solution for internal alkynes (Eq. 11) [51]. The chelation of Zn(II) ion with N-Boc-protected hydroxylamine was proposed to enhance the nucleophilicity of the O-nucleophile. The regio-selectivity in the reactions of internal alkynes ranged from 2:1 to >20:1 providing 2,3-disubstituted indoles. This regio-selectivity follows from steric and electronic effect and can be controlled by judicious choice of substituents.



Scheme 24 Metal-free redox isomerization by Coates [48]



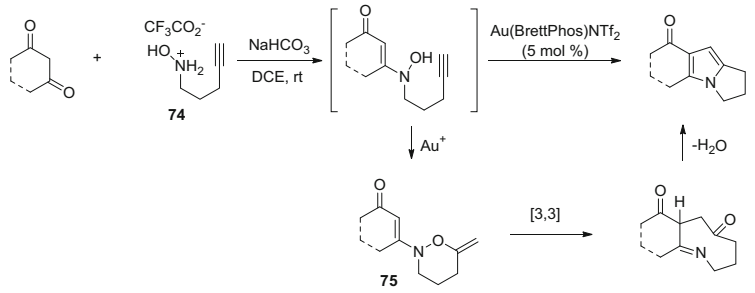
Scheme 25 Gold-catalyzed formation of *O*-vinyl hydroxylamines and [3,3]-sigmatropic rearrangement

O-Vinyl hydroxylamines can be prepared from the condensation of hydroxylamines with 1,3-dicarbonyl compounds (Scheme 26) [52]. Salt forms of hydroxylamines **74** were used as starting materials along with mild bases because salt-free forms were prone to oxidation under aerobic environments. In situ condensation and gold-catalyzed 6-exo-dig addition to alkynes led to *N*,*O*-divinyl hydroxylamines **75** which thermally underwent a known [3,3]-sigmatropic rearrangement, leading to fused pyrroles [48].

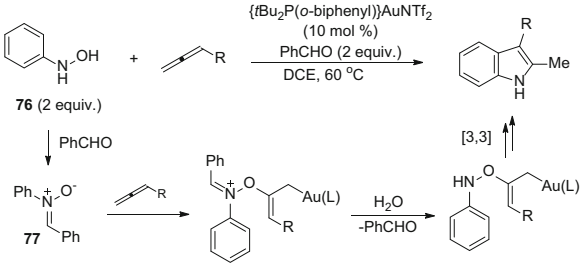
Liu and coworkers employed allenes as substrates for the indole synthesis (Scheme 27) [53]. The reaction of hydroxylamines with allenes under the gold (I) catalysis gave a complicated mixture, indicating possible instability of hydroxylamines. Addition of 2 equiv. of benzaldehyde as an additive was necessary initially to convert the hydroxylamines **76** into nitrones **77** and the resulting nitrones underwent regioselective indole formation, and the benzaldehyde was liberated by hydrolysis. The scope of allenes in this case remained terminal ones.

The intermolecular reaction of nitrosoarenes with alkynes can also lead to (*N*-hydroxy)indoles. Srivastava and coworkers reported an in situ cyclization in the presence of AuCl as a catalyst and reduction of the resulting *N*-hydroxyindoles with $NaBH_4$ (Scheme 28) [54].

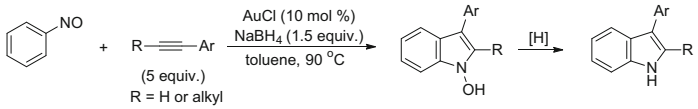
In 2012, Liu and coworkers explored the gold-catalyzed generation of vinyl gold carbene intermediates from vinyl diazo compounds **78** and developed new cycloannulation pathways using nitrosoarenes as reagents (Scheme 29) [55]. Vinyl metal carbenes generated via Rh- or Cu-catalyzed decomposition of vinyl diazo compounds displays diverse cycloaddition reactivity. While other metal-catalyzed decomposition of vinyl diazo compounds led to isolation of nitrones **79** (path A), gold catalysts provided two new intermolecular



Scheme 26 Formation of *O*-vinylhydroxylamine from 1,3-dicarbonyl compounds



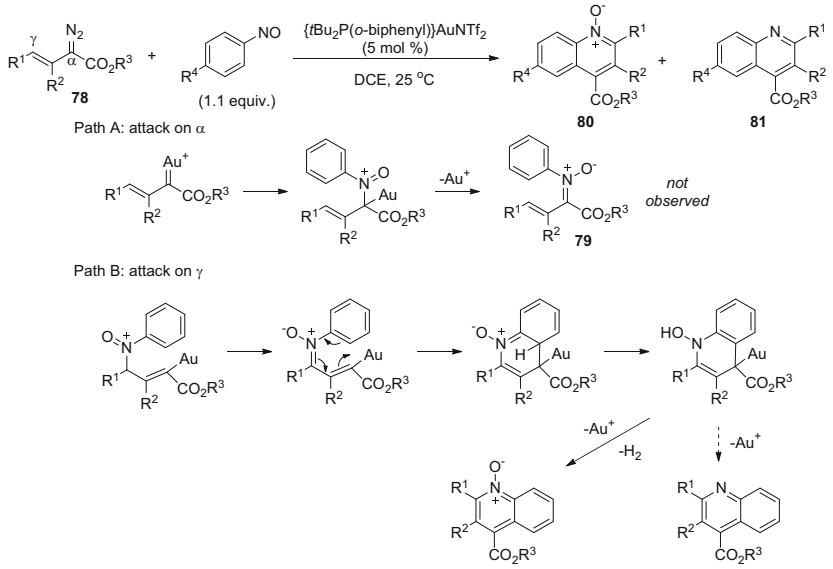
Scheme 27 Addition of hydroxylamines to allenes



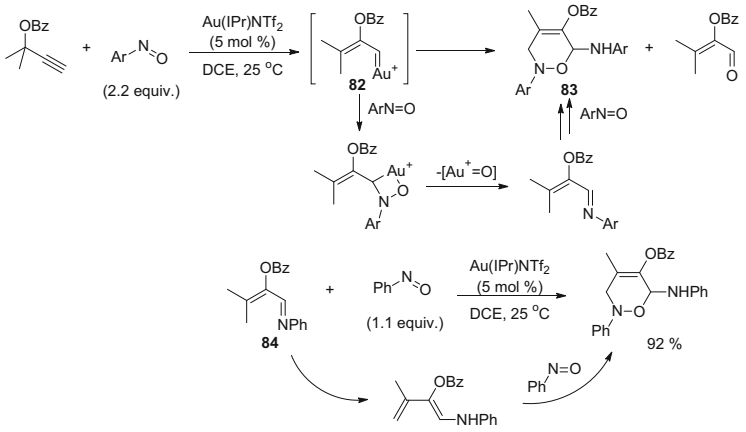
Scheme 28 Intermolecular reactions of nitrosoarenes with alkynes leading to indoles

cycloannulation products **80** and **81** [56]. From vinyl diazo precursors **78**, use of {*t*Bu$_2$P(*o*-biphenyl)}AuNTf$_2$ provided quinoline-*N*-oxides **80**, with a small amount of quinolones **81**. The mechanism involves the N-addition of nitrosoarenes at the γ-position (path B), followed by [3,3]-sigmatropic rearrangement. Liberation of Au$^+$ catalyst would provide quinolones or an oxidative aromatization would provide quinolone-*N*-oxides.

Vinyl gold carbenes **82** generated from Rautenstrauch rearrangement of propargyl carboxylates returned a different outcome, providing cycloadducts **83** (Scheme 30) [55]. With Au(IPr)NTf$_2$ as a catalyst, the mixture of propargyl pivalates and nitrosoarenes smoothly converted into 3,6-dihydro-2*H*-[1, 2]-oxazines **83**. To elucidate this intriguing reaction mechanism, vinylimine **84** was prepared and was treated under the above conditions to give the identical product, showing that the vinylimines **84** are involved as actual intermediates for the formation of **83**. The formation of the vinylimines from propargyl pivalates was rationalized by the loss of Au$^+$=O fragments which returned to Au$^+$ with the liberation of O_2.



Scheme 29 Reactions of vinyl gold carbenes with nitroso compounds



Scheme 30 Reactions of vinyl gold carbenes from propargylic esters

3.6 Pyridine-N-*Oxides*

Intermolecular OAT reaction onto alkynes was first demonstrated by Zhang and coworkers employing pyridine- *N*-oxides. Pyridine-*N*-oxide derivatives have unique features as oxygen transfer agents and this chemistry has been demonstrated in the oxyarylation of benzynes in the early literature [57]. These compounds can be readily prepared by a variety of methods, including mCPBA oxidation, metal- or

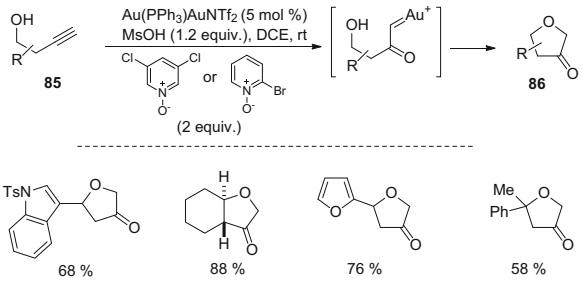
organocatalyzed oxidation by H_2O_2 or other peroxy reagents [58, 59]. In comparison, other heteroaromatic-*N*-oxides, such as those from oxazoles and imidazoles, are hydrolytically unstable and/or undergoes competitive [3 + 2] dipolar cycloaddition [60, 61]. In contrast, pyridine-*N*-oxides can often be prepared in crystalline form. Synthetically, the use of pyridine-*N*-oxides as intermolecular OAT reagents are advantageous because residual atoms from OAT reagents do not remain in the product. This results in an increased scope of applications and less efforts in the preparation of substrates. Au-carbene synthons generated thus have significantly expanded applications, now including X–H (X=O, N) insertion, cyclopropanation, cyclization, and rearrangements, covering most areas of traditional diazotransfer chemistry [1, 2]. Importantly, being able to trap the α-oxo gold carbenes by intermolecular nucleophiles requires an additional dimension of chemoselectivity. However, in recent years, increasingly elegant examples of intermolecular trapping have been reported, adding to the diversity of accessible structures.

3.6.1 Intramolecular Trapping of α-Oxo Gold Carbenes

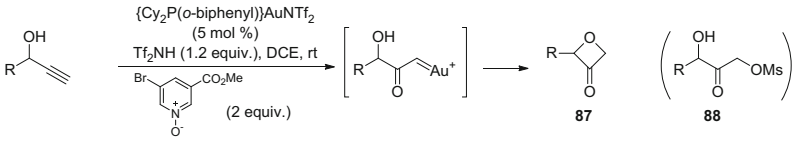
In 2010, Zhang and coworkers reported the first intermolecular OAT of N–O bond oxidants (Scheme 31) [62]. Treating the starting homopropargyl alcohols **85** and pyridine-*N*-oxides (2 equiv.) with Au(I) catalysts in DCE provided dihydrofuran-3-ones **86** and the use of strong acid (MsOH) increased the rate and yield of the product, leading to the reaction occurring at room temperature. The reaction conditions were mildly acidic because of the buffering effect of excess pyridine-*N*-oxides, where MOM-protected alcohols and Boc-protected amines could survive. Potential side reaction, i.e., 5-exo-dig or 6-endo-dig cyclization of tethered electron-rich aromatic or heteroaromatic rings onto alkynes, did not compete, illustrating efficiency and chemoselectivity of this intermolecular OAT. However, the efficiency of the reaction dropped when extended to the bis-homopropargylic alcohols, because of a competing and very facile 5-exo-dig cyclization.

Shortly afterwards, the same group extended this intramolecular O–H insertion into propargyl alcohols delivering a facile route to oxetan-3-one **87** (Scheme 32) [63]. Optimal conditions for this transformation involve the use of Au(*o*-biphenylPCy_2)NTf_2 as catalyst, 3-methoxycarbonyl-5-bromopyridine-*N*-oxide (2 equiv.) and 1.2 equiv. of HNTf_2. The latter acid additive minimized the reaction of Au-carbene with MsOH to form α-MsO-methylketones **88** when MsOH was used. For tertiary propargyl alcohol substrates, oxetanone formation required the presence of a CO_2R group at the alkyne terminus and switching to 4-acetylpyridine-*N*-oxide (2 equiv.) and IPrAuNTf_2 (5 mol%).

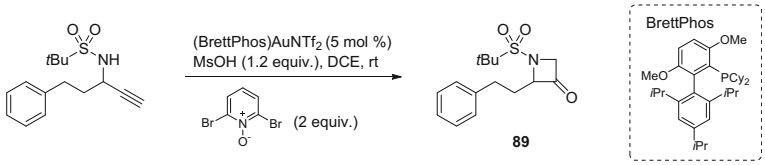
Azetidin-3-ones **89** can also be synthesized from *N*-sulfonyl protected propargyl amines (Scheme 33) [64]. To alleviate the difficulty of removing the *N*-sulfonyl group, the N-Bus (*tert*-butylsulfonyl) group was installed by oxidation of the corresponding sulfoxide and, moreover, these substrates could be easily prepared in enantiopure forms via Ellman's protocol [65].



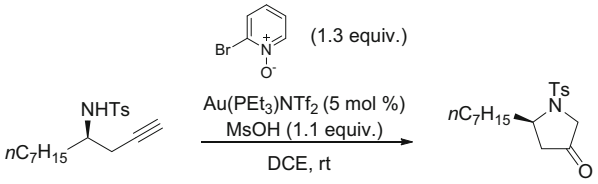
Scheme 31 OAT and formation of furan-3-ones



Scheme 32 OAT and formation of oxetan-3-ones



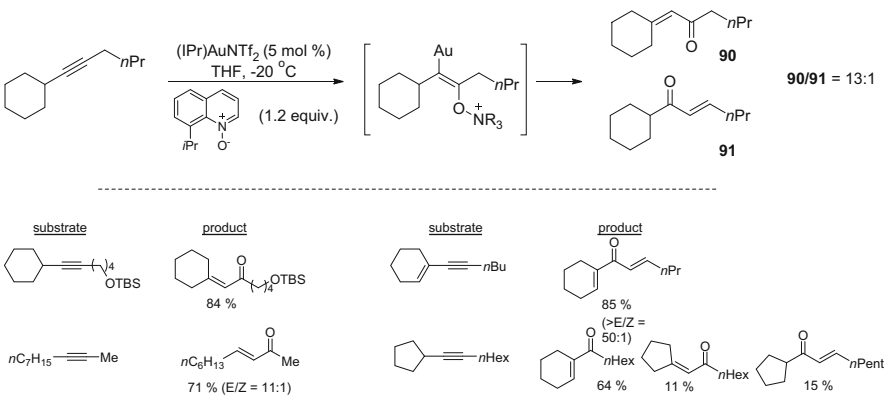
Scheme 33 OAT and formation of azetidin-3-ones



Scheme 34 OAT and formation of pyrrolidin-3-ones

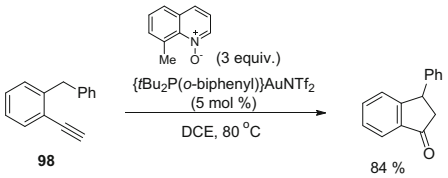
A similar strategy was explored in the synthesis of pyrrolidin3-ones by Ye and coworkers (Scheme 34) [66]. Switching substrates to homopropargyl amines led to an efficient synthesis of pyrrolidin-3-ones using $Au(PEt_3)NTf_2$ as a catalyst, 2-bromopyridine-*N*-oxide as an oxidant, and MsOH as an additive. *tert*-Butyl sulfinimine chemistry allowed access to enantiopure *N*–Ts sulfonamides which, in turn, led to the optically pure pyrrolidin-3-ones.

Generally, oxidation of triple bonds has had limited synthetic applications so far compared to that of alkenes, because of the low chemoselectivity. In comparison, alkyne oxidations mediated by the OAT from pyridine-*N*-oxides to alkynes



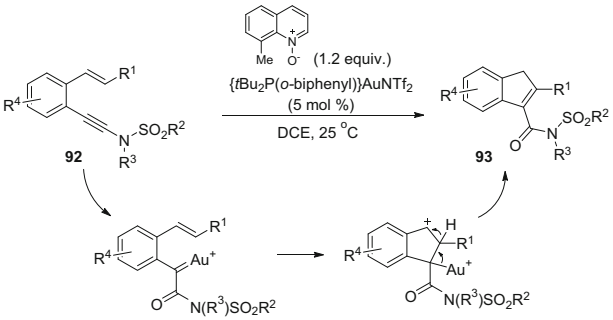
Scheme 35 OAT and 1,2-H shift

provides α-oxo gold carbenes synthons. Such an example employing internal alkynes has been demonstrated, providing α,β-unsaturated enones via 1,2-H-shift (Scheme 35) [67]. Transformation of internal alkynes into the α,β-unsaturated enones requires a regioselective OAT from pyridine-*N*-oxides. With a small bias in the alkyne substituents (i.e., primary vs secondary alkyl), gold-catalyzed OAT allowed the oxygen atom to add onto the less hindered alkyne carbon, where the selectivity increased as the steric bulk *N*-oxides increased. Also, by using hindered 8-isopropylquinoline-*N*-oxide, the addition of buffering acid was not needed. In the case when one of alkyne substituents is a cyclopentyl group, ring expansion via 1,2-shift onto carbene center is observed, leading to cyclohexenyl ketones.

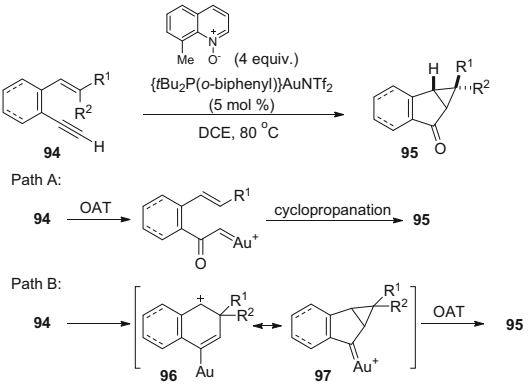


(12)

In 2011, Liu and coworkers reported formal *sp2* C–H insertion and intramolecular cyclopropanations of α-oxo gold carbenes generated from ynamides and terminal alkynes, respectively (Schemes 36 and 37) [68]. The former transformation can be explained by a sequence consisting of the ynamide-controlled regioselective OAT of **92** from 8-methylquinoline-*N*-oxide, intramolecular cyclization to form benzyl cation, and a concerted 1,2-hydride migration with the turnover of Au-catalyst to form **93**. The reaction of terminal acetylene substrates **94** required higher temperature (80°C) and 4 equiv. of 8-methylquinoline-*N*-oxide and led instead to cyclopropanation product **95**. This transformation can be explained by the initial OAT followed by intramolecular cyclopropanation to **95** or by the formation cyclopropyl gold carbenes **96**/**97** first, which are then trapped via OAT to form **95**. Initially, the authors proposed the former pathway is operative based on the analysis that the benzylic cation such as **96** would be highly prone to aromatization to afford naphthalene derivatives, and on the experimental



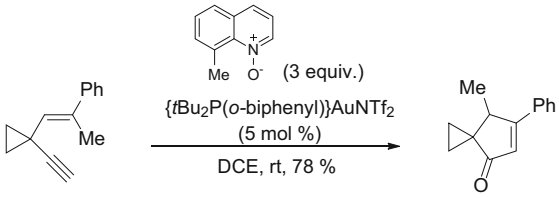
Scheme 36 OAT and synthesis of indenes



Scheme 37 OAT and intramolecular cyclopropanation

observation where an apparent benzylic C–H activation occurred in the reaction of **98** (Eq. 12). However, the apparent C–H activation product was later found to form via 1,5-H-shift, not through α-oxo gold carbenes by the same group [69].

In 2012, Liu and coworkers reported benzylic C–H functionalization/cyclization in the gold-catalyzed reaction of *o*-alkynylbenzenes (Scheme 38) [69]. As benzylic substituents (R), various groups including relatively electron-deficient aromatic and heteroaromatic groups, functionalized alkyl groups and hydrogen can be accommodated. Deuterium labeling experiments and other control experiments suggested that the α-oxo gold carbene route was not likely. Instead, a fast 1,5-hydrogen shift, following by aromatization with the N–O bond cleavage, was proposed to explain the outcome.



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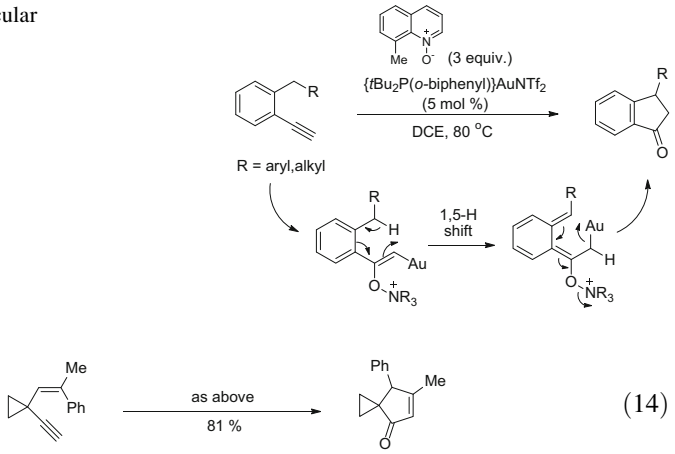
Scheme 38 Intramolecular C–H functionalization/ cyclization

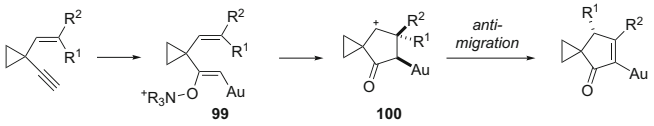


(14)

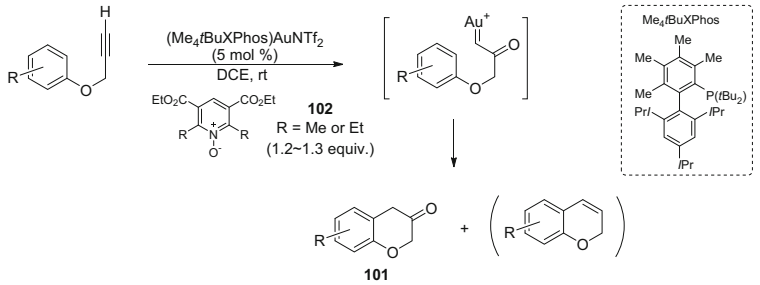
More recently, Liu and coworkers reported an interesting observation in the oxidative cyclization of 1,4-enynes for the formation of cyclopentenones (Eqs. 13 and 14) [70]. Interestingly, the carbocationic intermediate **100** (Scheme 39) underwent a stereospecific migration of an alkyl group positioned at the *cis*-position (R^1) in the substrate and a surprisingly high level of stereospecificity was demonstrated. Electron-rich ligands on gold – such as Me_3P – showed higher stereospecificity than electron-deficient phosphite ligands and, finally, *t*Bu2P(*o*-biphenyl) ligand gave almost complete stereospecificity. The dependence of migratory aptitude on the stereochemistry at the γ-carbon to the cationic center is very rare. The authors proposed that the observed stereospecificity can be explained by a *disrotatory* closure of the α-oxo gold carbene with pendent olefins to form **100**, followed by *anti*-selective migration onto the cationic center. The formation of the cationic intermediate **100** can also be rationalized by a concerted N–O cleavage with the formation of the new C–C bond from the **99**.

In 2012, Zhang and coworkers developed synthesis of chroman-3-ones **101** via intramolecular oxyarylation using pyridine-*N*-oxides (Scheme 40) [71]. In this transformation, Buchwald-type ligands with increasingly bulky biphenyl moieties turned out to be more effective and Me_4*t*BuXPhos was chosen as the optimal ligands. Competitive formation of benzopyran via 6-endo-dig cyclization slowed down in the presence of pyridine-*N*-oxides, possibly because of coordination of the gold complex onto pyridine-*N*-oxides. Among the oxidants tried, electron-deficient and sterically bulky oxidants such as **102** returned the best results. As a note, a high degree of *o*-/*p*-selectivity was observed in the case of *m*-substituted substrates.

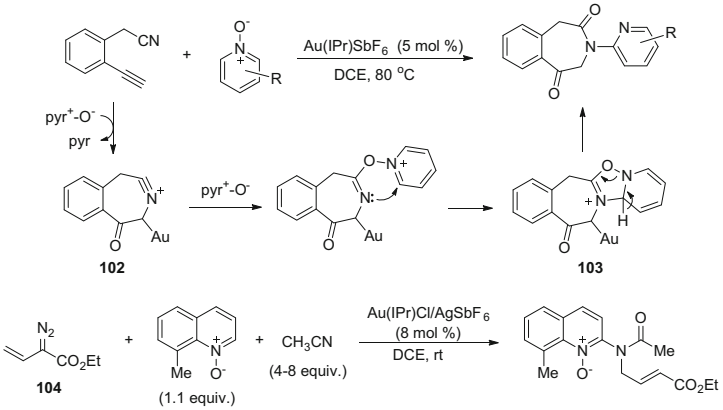
Liu and coworkers reported intramolecular reactions of nitriles onto the electrophilic α-oxo gold carbenes (Scheme 41) [72]. Interestingly, two theoretical equivalents of pyridine-*N*-oxides were utilized, one for OAT to alkynes to form α-oxo gold carbenes and the other for oxyarylation of the strained nitrilium ion **102**. Thus, the initially formed nitrilium species undergo addition of pyridine-*N*-oxides, followed by five-membered ring closure to **103** and fragmentation with the N–O



Scheme 39 Possible mechanism of selective migration of *cis*-substituent



Scheme 40 Intramolecular trapping with arenes

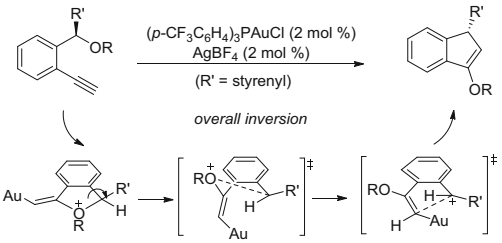


Scheme 41 Trapping of α-oxo gold carbenes with nitriles

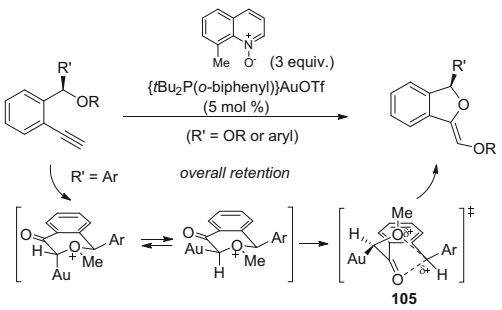
bond cleavage. The oxyarylation of the nitrilium species can also occur intermolecularly, starting from vinyl diazoesters **104** with 1.1 equiv. of 8-methylquinonine-*N*-oxide.

In 2006, Toste and coworkers reported that *o*-ethynylbenzyl ethers undergo intramolecular carboalkoxylation to afford indenyl ethers catalyzed by gold (Scheme 42) [73]. During this process, the benzylic center underwent an overall inversion of configuration at the benzylic center via an axially chiral transition state. In 2013, Liu and coworkers employed similar substrates in the oxidative gold-catalyzed cyclization (Scheme 43) [74]. The α-oxo gold carbenes formed would be intramolecularly trapped by ether oxygen, which is followed by a new C–O bond

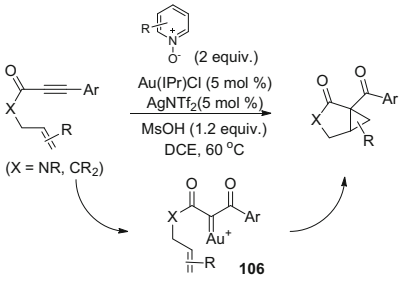
Scheme 42 Chirality transfer in the carboalkoxylation: *overall inversion*



Scheme 43 Chirality transfer in the oxidative dialkoxylation: *overall retention*



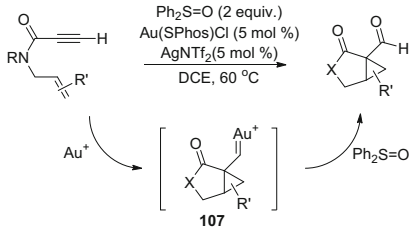
Scheme 44 Intramolecular oxidative cyclopropanation by pyridine-*N*-oxides



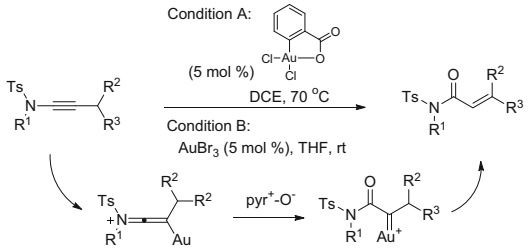
formation, leading to cyclic enol ethers or acetals (R′=OR) with (Z) geometry. A notable feature during this transformation is the complete transfer of chirality at the benzylic center, in this case, with overall retention of configuration. This process was explained by a 'front-on' substitution transition state **105** where the developing cationic charge is compensated for by the incoming ketone oxygen.

In 2011, Zhang and coworkers reported intramolecular oxidative cyclopropanation starting with 1,6-enynes derived from propiolamides (Scheme 44) [75]. In their screening of oxidants, $Ph_2S{=}O$ did not effectively provide the desired products and pyridine-*N*-oxides or quinoline-*N*-oxides were optimal oxidants, depending on substrates. The reaction could be rationalized by the initial formation of gold carbenes **106**, followed by intramolecular cyclopropanation. Subsequently, related substrates with terminal alkynes were investigated by Shin and coworkers (Scheme 45) [76]. Interestingly, in this case, 2-bromopyridine-*N*-oxide was ineffective, forming a conjugate addition adduct instead. Formation of cyclopropyl gold

Scheme 45 Intramolecular oxidative cyclopropanation by sulfoxides



Scheme 46 Formation of enones



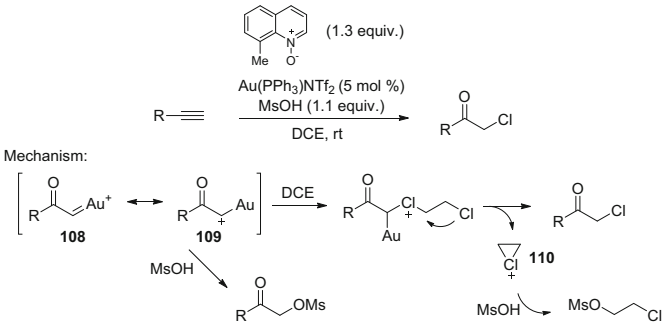
carbene **107** formed from the cyclization of 1,6-enynes, followed by trapping the carbenes with $Ph_2S{=}O$, was the most reasonable explanation.

Davis and coworkers introduced ynamides for intermolecular reaction of pyridine-*N*-oxides, providing α,β-unsaturated imides via 1,2-H shift (Scheme 46) [77]. The polarized nature of ynamide electrophiles were utilized for inducing intermolecular reactivity as well as controlling regioselectivity in the addition to alkynes. A potentially competing process is the reaction of Au-carbene with another equivalent of pyridine-*N*-oxide, producing 1,2-dicarbonyl compounds. Apparently, intramolecular 1,2-shift turned out to be faster than the over-oxidation of the α-oxo gold carbenes by pyridine-*N*-oxides. The double bond geometry ranged from 1.9:1 to 7.7:1 in favor of the E-isomer, unless the β-alkoxy group is present.

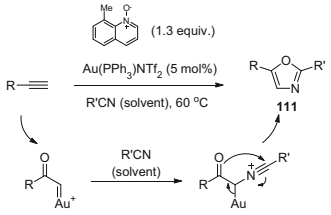
3.6.2 Intermolecular Trapping of α-Oxo Gold Carbenes

During the oxidation of alkyne by OAT from pyridine-*N*-oxides, chloride abstraction from solvents, such as DCE, are often observed as a side reaction. Xiang and coworkers have examined the generality of this reaction (Scheme 47) [78]. The viability of chloride abstraction indicates the highly electrophilic nature of the α-oxo gold carbene **108**/**109** and the mechanism was proposed to involve the formation of the cyclic chloronium intermediate **110**, which reacts with MsOH to form the experimentally observed 2-chloroethyl mesylate. Alternatively, switching solvent to chlorobenzene led to selective formation of α-mesyloxymethyl ketones [79].

Nitriles can trap the α-oxo Au-carbene generated from OAT of pyridine-*N*-oxides intermolecularly (Scheme 48) [80]. This required use of nitriles as reaction solvents and the resulting nitrilium species undergo 5-endo-dig cyclization leading



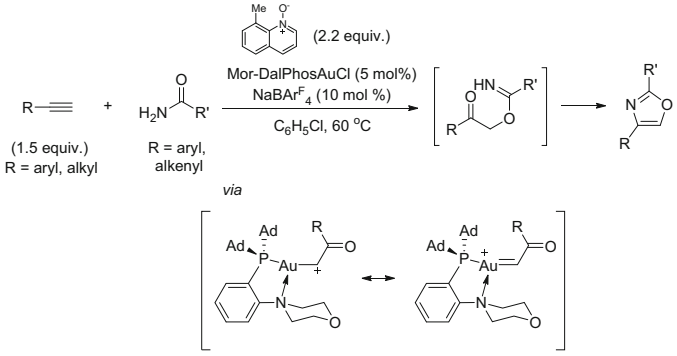
Scheme 47 Intermolecular trapping by DCE solvent



Scheme 48 Intermolecular trapping by nitrile solvents

to 2,5-disubstituted oxazoles. For example, using 8-methylquinoline-*N*-oxide as an oxidant in acetonitrile, terminal alkynes were efficiently converted into 2,5-dialkyl oxazoles **111**. It should be noted that this report constitutes the first intermolecular trapping of gold carbenes generated via gold-catalyzed OAT although the nucleophile came from solvent.

Variation of structures of ligands in terms of steric and electronic environment and/or coordinating atoms may play a vital part in the reaction outcome of transition metal catalysis. Previously, Zhang and coworkers developed 2,5-disubstituted oxazole synthesis involving trapping of α-oxo gold carbenes with a large excess of nitrile compounds as solvents [80]. In contrast, using the P,N ligand system, they were able to access 2,4-disubstituted oxazoles without using a large excess of reactants (Scheme 49) [81]. In this effort, Zhang and coworkers applied Mor-DalPhos [82] ligand having bulky adamantyl groups at the P atom and an *o*-morpholine. While typical ligands on cationic gold, such as Cy-JohnPhos, led to no desired product, a combination of Mor-DalPhos and $NaBAr^F{}_4$ as a counter-anion source provided respectable yields of the desired product. Although the mainstay of Au(I) catalysis is represented by di-coordinated Au(I) species, they proposed that trivalent P,N-coordinated Au(I) complexes would be less electron-deficient and thus allow more back-donation from Au to the cationic center, resulting in a more chemo-selective functionalization. DFT computational results were also provided, indicating a shortened Au–C bond caused by the increased backbonding and shorter Au–N distance (2.930 Å).

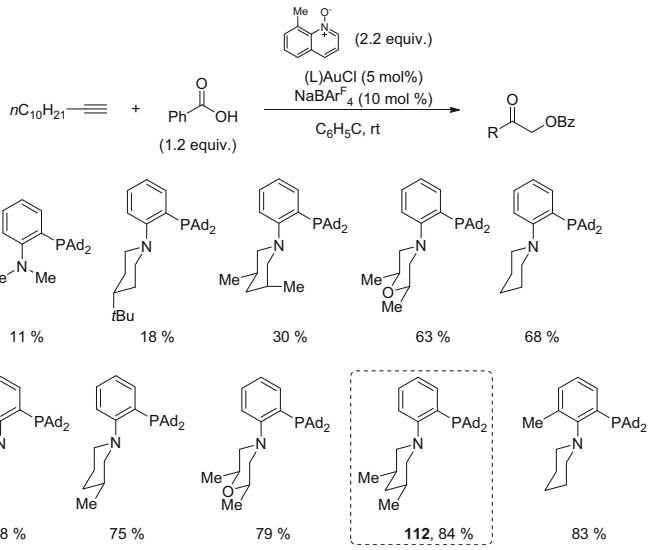


Scheme 49 P,N ligand strategy: oxazoles formation

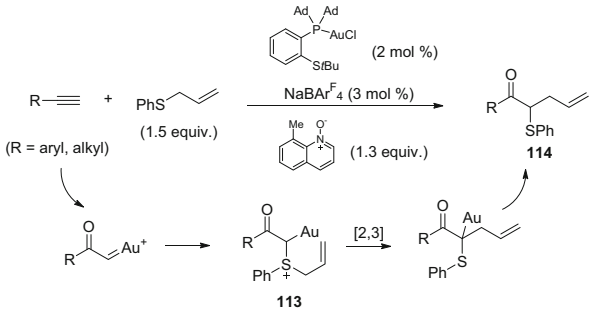
In a subsequent study, Zhang and coworkers expanded upon their P,N-bidentate ligands-based strategy (Scheme 50) [83]. As external nucleophiles, carboxylic acids were employed, producing α-benzoxymethyl ketones. A systematic variation of N-substituents of the P,N-bidentate ligands was tried, aimed at exploring requisite steric environment around the Au-carbenic center. Among them, **112** provided a significant improvement over Mor-DalPhos. Carboxylic acid, being less nucleophilic than carboxamide above, requires more steric protection of α-oxo gold carbene intermediate from competing side pathways. With the help of X-ray crystallography, the two equatorial methyl groups in **112** were reasoned to provide a conformational lock to provide an effective shielding of the cationic gold and thus the gold carbene can be protected from decomposition by bigger nucleophiles, including oxidants, and is selectively allowed to react with smaller nucleophiles, such as carboxylic acids. The generality of Mor-DalPhos in the trapping with MsOH was also explored in the synthesis of α-mesyloxymethyl ketones [84].

Intermolecular trapping of α-oxo gold carbenes by nucleophiles adds to the complexity of chemoselectivity because of the highly electrophilic nature of such intermediate and competing intramolecular side reactions. The scope of stoichiometric nucleophiles has remained rather limited, including carboxylic acids, sulfonic acids, and carboxamides. Recently, Zhang and coworkers addressed this deficiency in the reaction of allyl sulfides with the α-oxo gold carbenes (Scheme 51) [85]. The intermolecular trapping with allyl sulfides and the thio-Wittig [2, 3] rearrangement of **112** as described by Davies in the intramolecular setting [24] led to a new C–C bond with allylic transposition, leading to **113**. In order to reduce further the amount of the allyl sulfides and the *N*-oxides, P,S-ligand was introduced. The resulting γ,δ-unsaturated ketones could be converted to conjugated dienones in subsequent transformations.

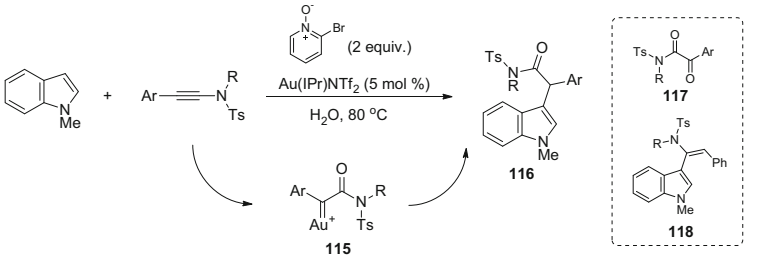
In 2014, Ye and coworkers reported indole-3-functionalization through pyridine-*N*-oxide-based alkyne oxidation (Scheme 52) [86]. They demonstrated that the use of water as solvent alleviated the above-mentioned over-oxidation of alkynes into 1,2-diketones **117** in comparison with organic solvent such as 1,2-DCE. Direct addition of indoles to the activated ynamides to form **118** could also be minimized.



Scheme 50 Investigation of P,N bidentate ligands



Scheme 51 Intermolecular trapping with allyl sulfides



Scheme 52 Intermolecular trapping with indoles

This protocol allows efficient access to a pharmaceutical agent UK-350,926, by C–C bond formation between indoles and α-oxo gold carbenes, leading to **116**.

In using water as a medium, potentially competing side-pathways can be considered, namely an insertion of the O–H bond of water into the highly electrophilic Au-carbene **115** and a hydration of ynamides. The former O–H insertion has not been observed, unlike in the case of other transition metals, and the latter hydration could be minimized by increasing the concentration of electron-rich arenes, without complication resulting from the direct addition into ynamides to form **118**. To track down the origin of the beneficial effect of water, water-insoluble *N*-oxides have been prepared and tested. Their reaction gave a significant amount of over-oxidation by-product, just as in organic solvents. These results suggested water-soluble 2-bromo-pyridine-*N*-oxides mostly reside in the aqueous phase so that a low concentration of this oxidant is maintained in the organic phase during the reaction. This simulates a situation in which a slow addition of pyridine-*N*-oxides is adopted.

4 Other Carbene Transfer Agents

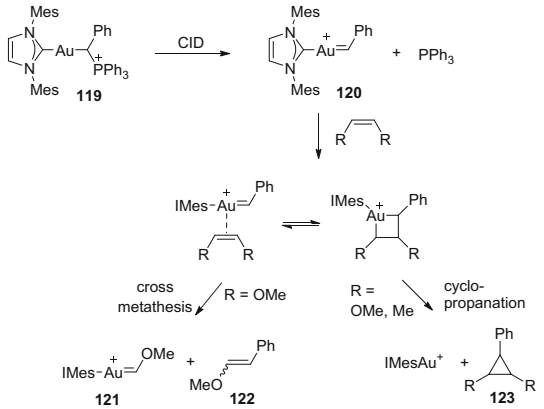
Ylides can be appropriate carbene transfer agents which can generate gold carbenoids or can be added to alkynes to generate metal carbenes. Initial studies in this category include those using diazo compounds [18, 55, 72]. More diverse ylidic species have been reported in recent years, including sulfonium and phosphonium ylides. These reagents are often stable in storage and, importantly, are safer to handle than classical diazo compounds.

4.1 Gold-Carbenes from Phosphonium Ylides

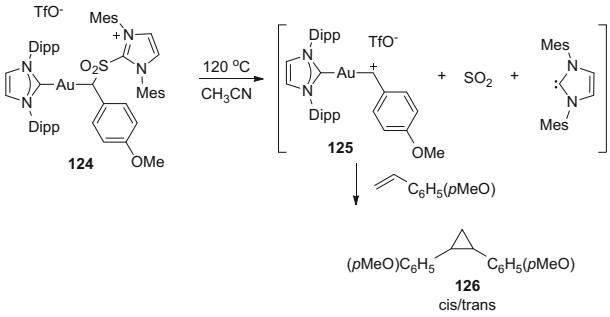
In 2008, Chen and coworkers reported observation of the first non-Fischer type gold-carbene complex of general formula (L)Au=CHR by mass spectroscopy (ESI-MS/MS) in the gas phase (Scheme 53). The precursor **119**, a gold ylide complex, was synthesized by substitution of acetoacetyl Au(I) complex with phosphorus ylide and it underwent a collision-induced dissociation (CID) by Xe atoms to generate a cationic species whose mass corresponds to **120**. Its reactivity was examined with various olefins. With *cis*-1,2-dimethoxyethene, cross metathesis reactivity to Fischer carbene **121** and β-methoxystyrene **122** dominated, while with 1,2-alkylethene, cyclopropanation to **123** prevailed, suggesting its carbene character.

4.2 Gold-Carbenes from α-Sulfonium Salts

Ingenious approaches toward new carbene precursors are continuously being developed, most notably by Chen and coworkers, from sulfonium salts (Scheme 54)



Scheme 53 Gas-phase reactivity of non-Fisher-type gold carbenes



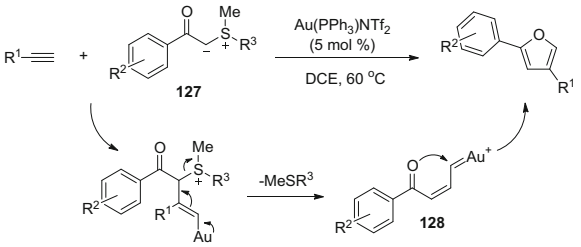
Scheme 54 Solution cyclopropanation of non-Fisher-type gold carbenes

[87]. The isolable gold complex **124** was generated by the reaction of a lithium anion of the corresponding sulfonium salt with cationic (NHC)Au^+. Upon heating, this gold alkyl complex fragmented into SO_2 gas, free NHC carbene, and gold carbene complex **125** which was identified in the gas phase. Notably, cyclopropanation of **125** with styrene derivatives has been demonstrated in a solution phase, providing the cyclopropane as a mixture of isomers.

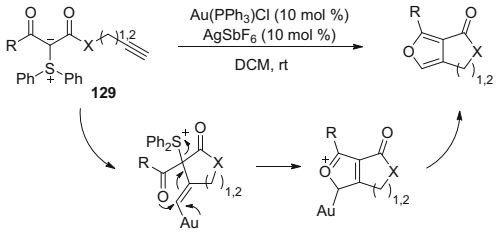
4.3 Gold-Carbenes from Sulfonium Ylides

In 2012, Skrydstrup and coworkers reported that sulfonyl ylides can react intermolecularly with terminal alkynes, leading to formation of 2,4-disubstituted furans (Scheme 55) [88]. They envisioned the addition of sulfonium ylides **127** onto the alkynes followed by liberation of the alkyl aryl sulfide, forming a vinyl Au-carbene intermediate **128**. This, in turn, can be intramolecularly trapped by

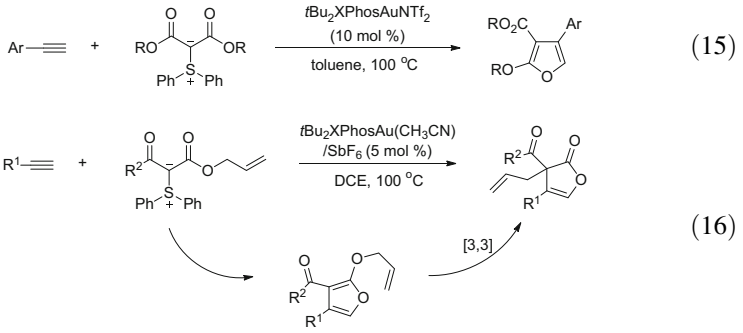
Scheme 55 Synthesis of furans



Scheme 56 Synthesis of fused furans



the ketone, delivering furans. The accessibility of stable zwitter-ionic sulfonium ylides that can be isolated by column chromatography was key to the successful implementation of this strategy. The scope of the alkynes is limited to aliphatic terminal alkynes. They supported a mechanism involving vinyl Au-carbene **128**, because alternative concerted nucleophilic 5-endo-dig addition of carbonyl onto the vinyl gold should be disfavored according to Baldwin's rule.

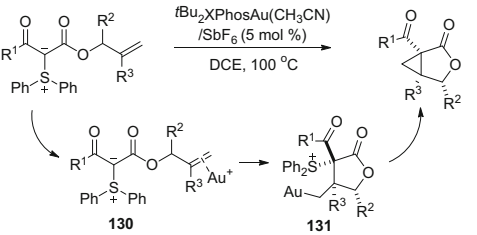


Shortly after this report, Maulide and coworkers reported a related strategy involving diphenyl sulfonium ylides **129** [89] which were, in turn, prepared by a ylide transfer protocol developed by themselves (Scheme 56) [90]. The reaction between sulfonium ylides and alkynes occurred intramolecularly, and trapping the formal Au-carbene by keto- or ester-carbonyl led to fused furans. The coupling of diphenylsulfonium ylides with alkynes can also occur intermolecularly with aryl alkynes, delivering 2,3,4-trisubstituted furans (Eq. 15). For allyl β-ketoesters, the

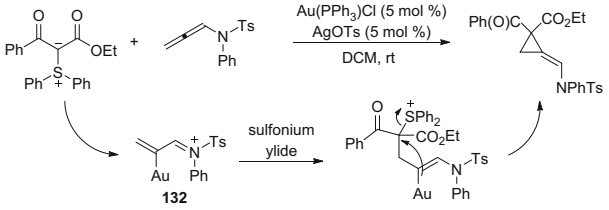
intermediate furan underwent a [3,3] sigmatropic rearrangement at 100°C, leading to δ-lactones with a quaternary α-center (Eq. 16). According to their DFT study, the Au-carbene could not be located as an intermediate. However, the cleavage of the S–C bond was suggested to be the rate-determining step.

Afterwards, Maulide and coworkers found that the same substrate in the absence of alkyne components underwent intramolecular cyclopropanation in highly diastereoselective fashion (Scheme 57) [91]. It is conceivable that this process is occurring through initial carbene transfer to gold, followed by intramolecular cyclopropanation. However, control experiments and DFT computation indicated that the anionic carbon of the sulfonium ylides attacks the Au-activated alkene **130** first, and the following substitution of Ph_2S in **131** closes the cyclopropane rings. In accord with this, β-ketoesters underwent slower reactions than malonate-derived substrates (R^1=O-alkyl) because of their more stabilized and lower carbon nucleophilicity. It should be noted that the present reaction by gold catalysis outperformed diazo-mediated Rh(I)-catalyzed cyclopropanation, where C–H activation products are accompanied as by-products [92].

Sulfonium ylides can also be transferred to allenes to form vinyl cyclopropanes (VCPs) [93]. As in the reaction with alkenes, the reaction with allenylamides occurs with the initial addition of sulfonium ylidic carbon at the γ-carbon of allene **132**, followed by intramolecular substitution of the sulfonium moiety (Scheme 58).



Scheme 57 Intramolecular cyclopropanation



Scheme 58 Synthesis of vinylcyclopropanes

5 Conclusion

The ability of gold metal to stabilize an α-carbocation has spurred interest in the methods of generation and reactions of gold carbenes. In this field, one of the most prominent approaches has been the reactions of leaving group-bearing nucleophiles with alkynes which have been discussed in this review. Novel catalytic methodologies have been developed at a rapid pace, employing various combinations of nucleophilic atoms and leaving groups, which resulted in a large repertoire of useful reactions. The prospects are that new carbene precursors or OAT transfer reagents should continue to be developed in the future.

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