Coinage Metal Carbenes in Heterocyclic Synthesis *via* Formation of new Carbon-Heteroatom Bonds

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Abstract

The review describes the most recently reported and efficient methods for the synthesis of heterocyclic compounds involving metal carbenes. In particular, copper, silver and gold carbenes, generated from suitable precursors, are involved in the synthesis of heterocyclic compounds through the formation of new carbon-heteroatom bonds.

Keywords
Metal carbenes
Heterocyclic synthesis
Copper catalysis
Silver catalysis
Gold catalysis

Contents

1. Introduction

In the last 15 years, coinage-carbene complexes that can be assimilated to the class of electrophilic Fischer carbenes,[1] emerged as a valuable tool for the synthesis of linear or cyclic frameworks.[2] Their use resulted in the assessment of chemo-, regio- and enantioselective processes, often fulfilling the requirements of developing safe and environmentally sustainable procedure. The success of these reactive intermediates is also related to the setup of new simple and efficient methods for their generation. In the field of heterocyclic chemistry, these methodologies are applied mainly in reactions involving the carbene carbon atom in the formation of new carbon-carbon bonds and in which the heteroatom is embedded as an outsider in side chain. Examples involving the formation of carbon-heteroatom bonds by interaction of a carbene with a heteroatom nucleophile are rare. However, in our opinion, this kind of reactions, if properly developed, could furnish an elegant alternative to conventional syntheses of heterocycles. For these reasons, we decided to report in this review the state of the art of the reaction of coinage metal carbenes for the synthesis of heterocycles via formation of new carbon-heteroatom bonds, scheme 1.

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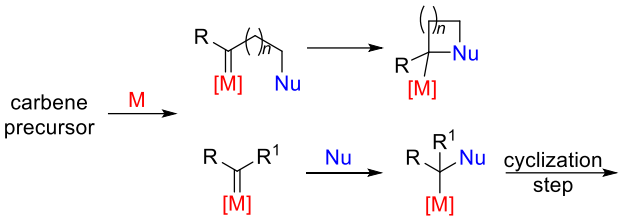


Scheme 1. Metal carbenes for the synthesis of heterocycles *via* formation of new carbon-heteroatom bonds.

The general mechanism for the reactions described in this review involves the generation of the metal carbene complex from suitable precursors followed by the addition of a nucleophilic heteroatom to the electrophilic carbon atom of the carbene. If this step proceeds in an intramolecular fashion it matches with the cyclization step. On the other hands, the cyclisation can occur in a second step involving distinct reaction mechanisms or in a concerted way like in cycloaddition reactions.

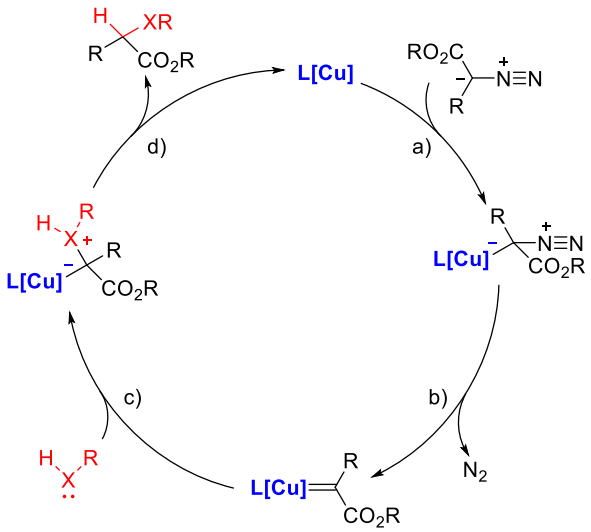
The review is organized in 5 parts. After the introduction, copper, silver and gold species are treated in separated chapters and each chapter contains an introduction on the structural and electronic properties of the metal-carbene, an overview on the methods developed for the synthesis and finally the application in the targeted reactions. A final chapter contains a comparative evaluation of the obtained results and the plausible evolution and implementation of these reactions.

Covered literature from 2005 to 2021.

2. Copper carbenes in heterocyclic synthesis

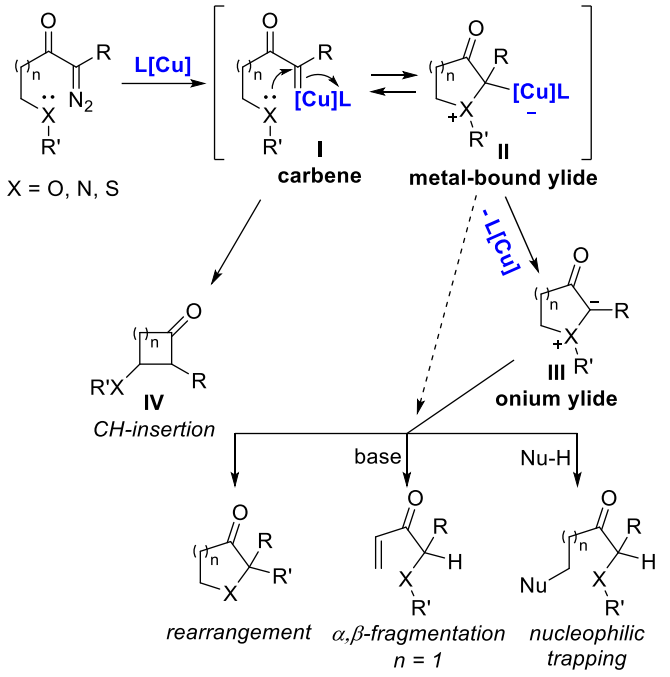
A major goal in organic chemistry is represented by the ability of controlling the selectivity of highly reactive intermediates. Carbenes generated either thermally or photochemically from diazo compounds by nitrogen extrusion generally lack of control and normally lead to complex mixtures of products. On the other hand, the metal catalyzed decomposition of diazo compounds yields to highly selective “carbenoids” capable of giving reactions with high selectivities.[3,4] Copper salts[5,6] and complexes[7–11] play a prominent role in the field of diazo compounds activation and structural evidences for the transient “carbene” formation have become evident through experiment and computation. Both Cu^{I} and Cu^{II} species can be catalytically active,[12] although for mechanistic studies, well-defined Cu^{I} complexes are surely more suited. Both anionic ligands to form neutral complexes[13–20] and neutral ligands to obtain cationic complexes[21–32] have been used and showed to be useful in controlling the selectivity of the transfer of the carbene. In the case of cationic complexes, the reactivity is strongly influenced by the counteranion and triflates were found to be the most effective.[33–35]

The mechanism of the copper(I) promoted activation of diazo compounds has been studied by DFT (Scheme 2).[36–38] The rate-determining step has been often proposed to be the complexation of the diazo compound (step a), which occurs by coordination of the negatively polarized carbon of the diazo substrate to the Lewis acidic free copper and can be in competition with other Lewis bases that can potentially slow or even halt copper catalysis by blocking the crucial substrate binding. Kinetic data reported fit with a dissociative ligand exchange mechanism.[39,40] All theoretical studies so far agree in attributing a pivotal role to the carbene complex, which is formed upon loss of nitrogen (step b), as the active catalyst in the transfer of the carbene moiety. In the presence of a carbene acceptor, the carbene transfer leads to fast and selective reaction, whilst in its absence, the carbene intermediate decomposes slowly to give a carbene dimer, $(RO_2C)R'C{=}CR'(CO_2R)$.



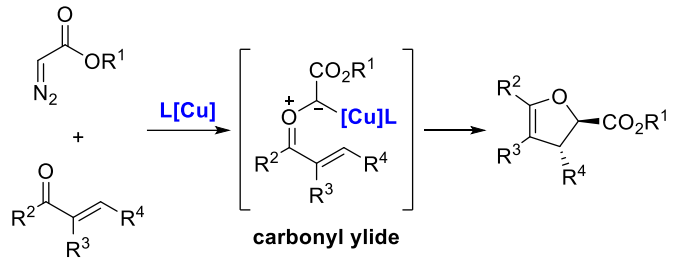
Scheme 2. General accepted mechanism for copper catalyzed decomposition of diazo compounds.

When the carbene acceptor is represented by an alkene, cyclopropanes are formed in good to excellent yields and two new C-C bonds are formed with extremely controlled stereoselectivities, depending on the choice of the ligand. When the carbenoid source and the C=C acceptor are present on the same molecule, the intramolecular reaction observed is of relevance, especially when starting from poly-functionalized compounds.[41] In general, a concerted mechanism is accepted for reactions of copper carbenes with non polar bonds. However, when the nucleophile is represented by a heteroatom donor a fast reaction leads to the formation of highly reactive metal-ylide (step c). Normally, when the reacting partner contains an α hydrogen atom, the insertion into the X-H bond is observed (step d), yielding to the product and restoring the metal catalyst.[42] Copper catalyzed X–H insertion reactions into diazo compounds (where X is any heteroatom) are a powerful yet underutilized synthetic tool for generating high molecular complexity with high selectivity. In the absence of a hydrogen atom, upon dissociation of the metal, onium ylides are formed. When the heteroatom is nitrogen or sulfur, quite stable ylides are formed that can be isolated, whilst in the case of oxygen, oxonium ylides obtained are highly reactive intermediates that cannot be isolated, but whose existence has been suggested from spectroscopic evidence.[43] Further rearrangements of the onium ylide can then lead to the products *via*: 1) rearrangement (by either [2,3]-sigmatropic shift or [1,2]-shift), 2) α,β-fragmentation; 3) protonation and nucleophilic trapping; and 4) C-H insertion into α-bonds (Scheme 3). Those reactions are normally much more easily controlled when the two reacting partners are on the same scaffold and the reaction occurs in an intramolecular fashion.



Scheme 3. Possible reactive pathways upon formation of an onium ylide.

On the other hand, when a carbonyl oxygen intercepts the copper-carbene, carbonyl ylides are formed, which are prevalent in chemical synthesis and particularly in the area of cycloadditions (Scheme 4). Namely, the catalytic [4+1]-cycloaddition of diazo compounds with α,β-unsaturated carbonyl reagents yields to 2,3-dihydrofuran with high stereoselectivities in an intermolecular fashion.[44]



Scheme 4. Cu-catalyzed [4+1]-cycloaddition *via* carbonyl ylide intermediate.

Coinage metal catalyzed transformations of vinyldiazo compounds as a versatile tool in organic synthesis have been the object of a quite recent excellent review by López and coworkers and will be here only marginally treated.[45]

Tandem N-H insertion reaction followed by intramolecular Diels-Alder or hydroamination of alkynes to afford heterocyclic products will not be covered.

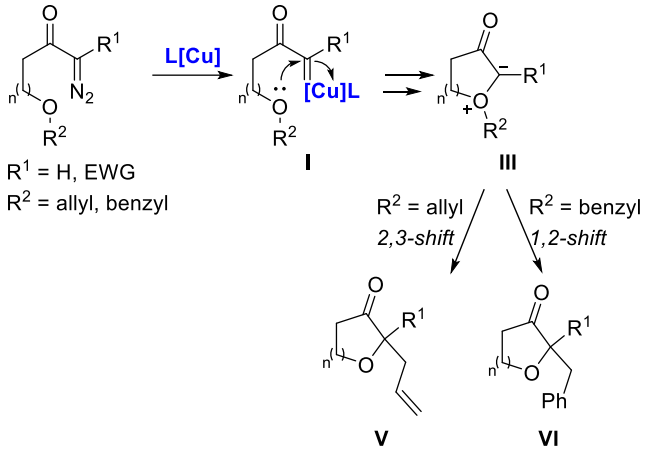
2.1. Intramolecular Cu-catalyzed ylide formation and subsequent rearrangements

The intramolecular Cu-carbenoid cyclization/cycloaddition reaction offers a very powerful catalytic approach to the stereoselective construction of heterocycles, given the rapid introduction of molecular complexity within a single chemical process.[46,47]

In fact, when in the nuclear scaffold a heteroatom is present, the electrophilic metal carbene **I**, undergoes nucleophilic attack by the heteroatom lone pair to give a transient metal-bound intermediate **II**. Dissociation of the metal delivers a very reactive ylide **III** that undergoes further rearrangements (where R' is a suitable group to permit rearrangement) to give new heterocyclic scaffolds with high selectivity. Other mechanism, as we will discuss

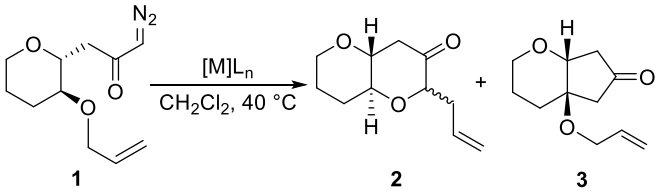
later, involving the direct rearrangement of the metal-bound ylide **II** are also possible, as well as the C-H insertion pathway to give cyclic compounds, **IV** (Scheme 3).

In the case of oxonium ylides, intermediates cannot be isolated and, especially for *O*-allyl or benzyl compounds, [2,3]- or [1,2]-rearrangement are often observed to yield the heterocyclic products. In particular, the formation of a copper-carbene **I** in the presence of an allylic ether moiety, and the following [2,3]-sigmatropic rearrangement has been used for the stereoselective construction of cyclic ethers **V**.[48,49] On the other hand, cyclic ethers **VI** can be obtained *via* a [1,2]-shift of a benzyl ether moiety of the oxonium ylide intermediate (Scheme 5).[50]

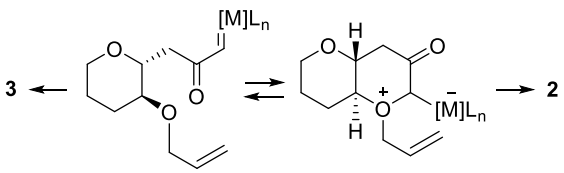


Scheme 5. Intramolecular reaction of the electrophilic copper-–carbene with oxygen nucleophiles and subsequent [2,3]- or [1,2]-rearrangement of reactive oxonium ylides.

In the early '90, both Clark[51] and West[52] showed that generally copper(II) catalysts lead to ylide rearrangement to provide heterocyclic products whenever this is possible, whilst with other metals such as rhodium(II) the C-H insertion product **IV** become more favorable (Scheme 3). West and coworkers showed for example that allyl ethers **1** may undergo efficient conversion to bis-pyran products **2** when soluble Cu(II) trifluoroacetylacetonate is used as catalyst (Scheme 6).[53,54] On the other hand, employment of Rh(II) catalyst led to the formation of both the heterocyclic and the C-H insertion products **2** and **3** in almost equal yield.



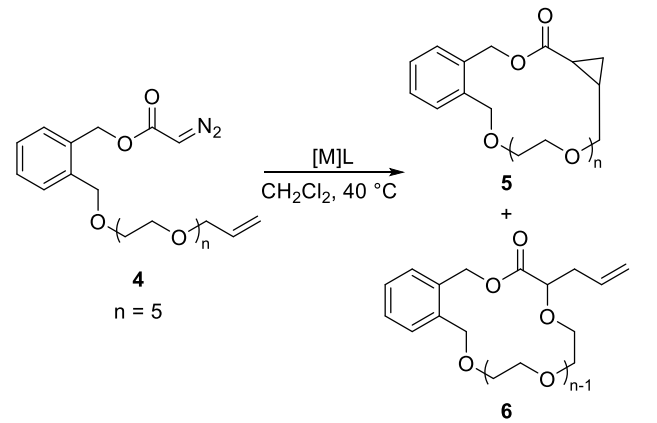
$Cu(tfacac)_2$, 5 mol%: **2** = 80%, *dr*(α/β) = 1:30; **3** = traces
$Rh_2(OAc)_4$, 3 mol%: **2** = 27%, *dr*(α/β) = 4:1; **3** = 31%

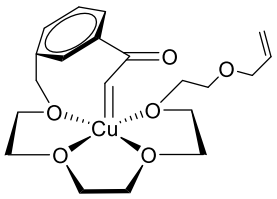


Scheme 6. Concerted [2,3]-shift of *O*-allyl oxonium ylides yielding to bis-pyran products **2**.

Some years later, in an elegant work toward the synthesis of polyether macrocycles **5** and **6** from **4** by intramolecular cyclopropanation and/or ylide formation followed by [2,3]-sigmatropic rearrangement, Doyle and coworkers demonstrated that, contrary to dirhodium(II) catalyst that yielded to quantitative cyclopropanation, copper(I) complexes, in competition with cyclopropanation, gave also intramolecular oxonium ylide formation, favoring the [2,3]-sigmatropic rearrangement of the pendant allyl group (Scheme 7).[55] However, when sodium tetraphenyl borate was added, coordination of Na^+ ions to the polyether chain completely inhibited the oxonium

ylide formation in the copper-catalyzed diazo decomposition. Thus, the authors proposed that copper may act as a template for the substrate yielding to a carbene complex **I** that can facilitate the subsequent reaction. Interestingly, the authors found that both chemo- and diastereoselectivity of the reaction outcome are very close either employing copper(I) hexafluorophosphate or copper(II) hexafluoroacetylacetonate (hfacac), suggesting that this ligand is not bound to the metal ion during the product-forming step.

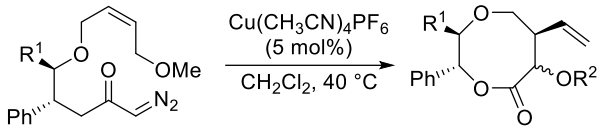




I

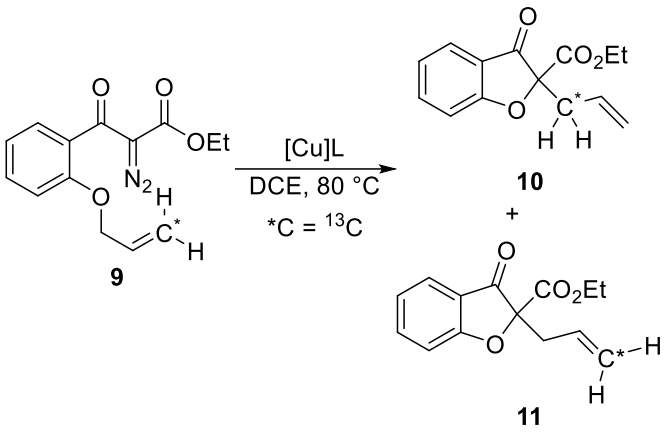
Scheme 7. Cu(I) versus Rh(II) catalyzed polyether macrocycle synthesis.

Examples of heterocycle synthesis *via* the oxonium ylide/[2,3]-sigmatropic rearrangements include also the highly diastereoselective preparation of eight-membered ring **8** from diazo compound **7** reported by Kumaraswamy (Scheme 8).[56]



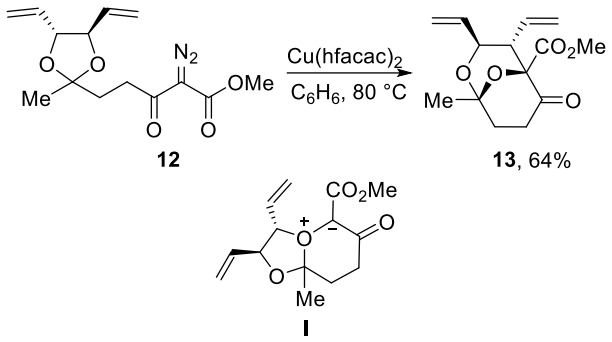
Scheme 8. Diastereoselective eight-membered oxacycle **8** formation reported by Kumaraswamy.

The intermediacy of a free oxonium ylide (**III**, Scheme 3) or of a metal bound ylide (**II**, Scheme 3) in the key [2,3]-sigmatropic rearrangement has been the object of investigation by using simple diazo substrates to give benzofuranones.[57] The use of substrates **9** with ^{13}C-labelled allyl moiety at the terminal position allowed to determine the relative amount of the apparent [2,3]- and/or [1,2]-rearrangement depending on the employed catalyst (Scheme 9). When using copper(I) and copper(II) catalysts, analysis of the product distribution allowed to determine that along with the expected formal [2,3]-rearrangement product **10**, in which the label is found at the internal allylic position, significant amounts of **11** (14-16%) were also obtained. These results indicate that these reactions do not necessarily proceed by a free oxonium ylide but can follow instead a competing path involving the metal center in the rearrangement reaction.



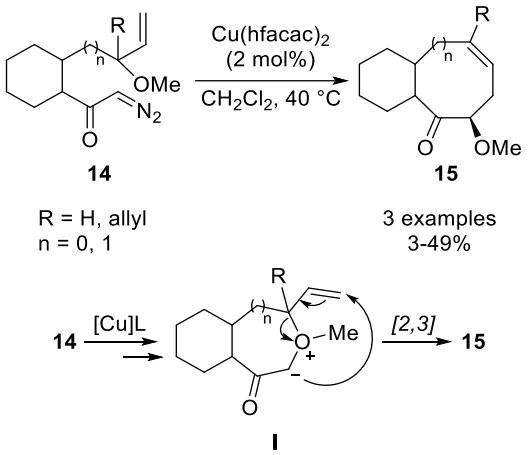
Scheme 9. Use of substrate **9** with ^{13}C-labelled allyl moiety to determine the relative amount of apparent [2,3]- and/or [1,2]-rearrangement depending on the employed catalyst.

Preferred [1,2]-rearrangement product **13** has been described for reactions of cyclic allylic oxonium ylides **I** arising from **12**, both in the presence of rhodium and copper catalysts (Scheme 10).[58]



Scheme 10. [1,2]-rearrangement of ylide **I**.

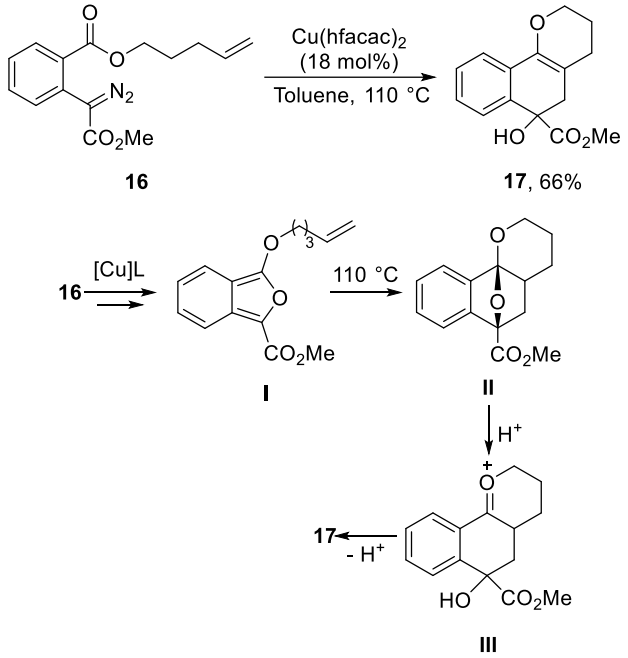
The Clark group has also taken advantage of a different type [2,3]-rearrangement of the oxonium ylide **I** formed upon copper-catalyzed carbene reaction of **14** to give fused carbocyclic systems **15**. The oxonium ylide intermediate **I** in fact, may lead to a ring-expanding [2,3]-rearrangement to construct a carbocycle (Scheme 11).[59–64]



Scheme 11. Ring-expanding [2,3]-rearrangement of intermediate oxonium ylides **I**.

The copper(II) acetoacetate catalyzed rearrangement of *o*-acylphenyldiazometane to yield 1-alkoxy-benzofurane by intramolecular copper-carbene reaction has been initially reported by Hamaguchi and Ibata in 1976.[65] Trapping experiments with dienophiles confirmed that isobenzofurans were generated as transient intermediates. Since then, quite a number of this versatile kind of rearrangements have been reported, mainly employing copper or

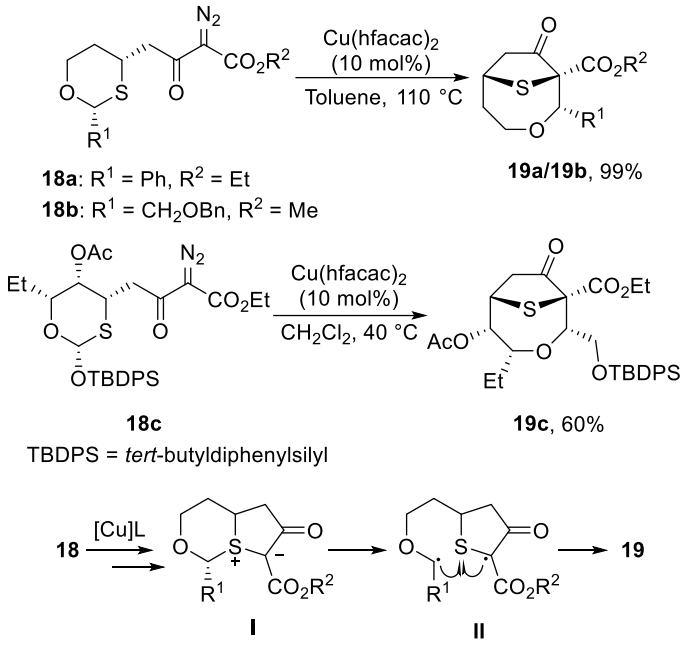
rhodium based catalysts.[66–69] More recently, Padwa and coworkers have reported the metallo-catalyzed reaction of α-diazo diester **16**, that contains a tethered oxapentyl side chain, by screening several different Rh(II) and Cu(II) catalysts. Interestingly, while when using rhodium catalyst they could not isolate any product (probably due to competing C-H insertion reaction), with $Cu(hfacac)_2$ tetrahydrochromene **17** was obtained as the only product in 66% yield (Scheme 12).[70]



Scheme 12. Cu(II)-catalyzed synthesis of tetrahydrochromene **17**.

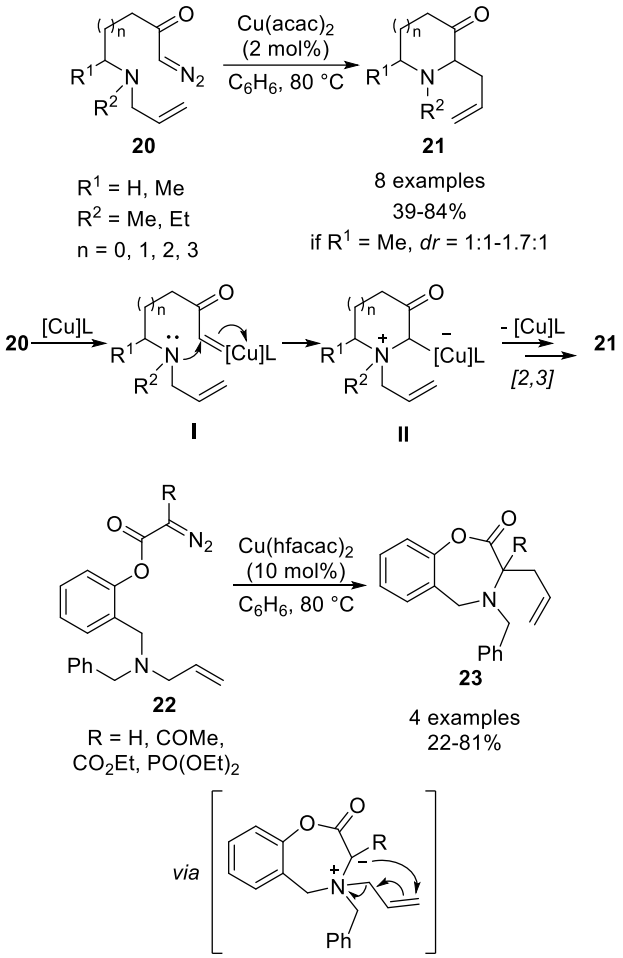
Mechanistic investigations revealed that the first reaction step involves generation of the expected copper-carbene intermediate that after intramolecular cyclization with the adjacent carbonyl group yields the reactive benzo[*c*]furan **I** which is subsequently trapped by an intramolecular [4+2] cycloaddition with the tethered alkenyl π-bond to give **II**. The authors proposed that the increased reactivity of the generated metallo-carbenoid could influence the reaction in different ways: more reactive Rh(II) catalysts would favor the ylide formation but also the competitive C-H insertion reaction, whilst the higher yields of the cyclized product in the Cu(II) catalyzed reactions results from stabilization of the metal-ylide intermediate.

Contrary to oxonium ylides, sulfonium ylides are less prone to undergo further rearrangements and have been isolated, especially when the ylide carbon bears electron-withdrawing substituents.[71] Copper-catalyzed sulfonium-ylide [2,3]-sigmatropic rearrangement have been reported in the early literature,[72,73] but, to the best of our knowledge such reactions have not been applied to the one-pot synthesis of sulphur-heterocycles. However, intramolecular thia-Stevens rearrangements of diazo esters **18** have been used for the synthesis of sulfur-containing heterocycles **19a-c** through ring-expanding 1,2-shifts. In particular, West and coworkers reported the formation of medium-sized cyclic thioether **19c** in 60% yield from the copper-catalyzed thia-Stevens rearrangement of a monothioacetal-derived ylide **I** as a key step in their synthesis of (+)-laureomicin (Scheme 13).[74] Worth to note, the α-stereogenic center was retained during the 1,2-migration with stereo-chemical fidelity comparable to the ammonium ylide variants.



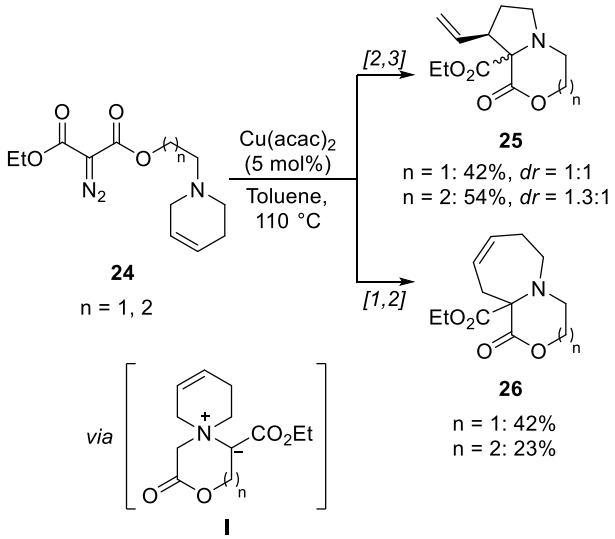
Scheme 13. Stevens [1,2]-shift of ylide **I** derived from mixed monothioacetal.

The strong Lewis base nature of nitrogen donor atom of the amine precursor that form stable complexes with transition metals renders the use of ammonium ylides generated from metal-carbene a more challenging task if compared to the oxygen and sulphur counterparts. However, intramolecular addition of tertiary amines to copper carbene, followed by [2,3]-sigmatropic rearrangement has been proven to be a quite effective method for the synthesis of cyclic amino ketones **21** from **20** (Scheme 14). Clark and coworkers reported that Cu(II) acetylacetonate is a superior catalyst with respect to Rh(II) acetate for those transformations, although elevated temperatures are needed to obtain reasonable yields.[75] When the amine forms part of a pre-existing ring, bicyclic amines could be obtained in a stereoselective manner.[76] Using appropriate precursor **22**, reactions of this type can be used to construct azalactones **23**, which upon lactone cleavage and hydrogenolysis provide highly functionalized non-natural α-substituted and α,α-disubstituted amino acids.[77]



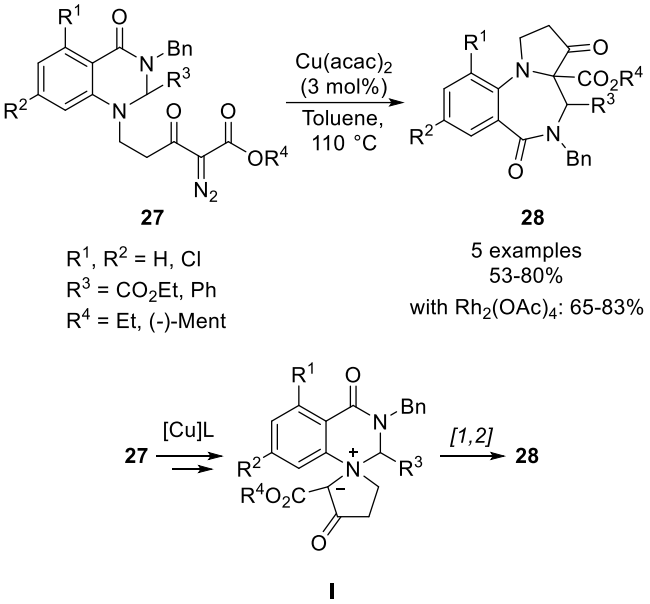
Scheme 14. Cu(II)-catalyzed [2,3]-sigmatropic rearrangement to yield cyclic amino ketones **21** and **23**.

More recently, Sweeney and coworkers introduced the [2,3]-sigmatropic rearrangements of spirocyclic ammonium ylides **I** in which the alkene component is endocyclic in the starting diazo ester **24**, allowing a rapid entry to pyrroloazaepines **25** (Scheme 15).[78] Along with the major product derived from the desired [2,3]-rearrangement of the *endo*-spiro ammonium ylide, obtained as mixture of diastereoisomers, minor amounts of the product of [1,2]-rearrangement **26** were also isolated. However, nearly equal amounts of the Stevens-type [1,2]-rearrangement product and [2,3]-rearrangement product were obtained when lower homologues of the spiro-ylide were used, indicating that the extra rigidity imposed by a smaller cycle imposes higher geometric constraints upon the [2,3] reaction.



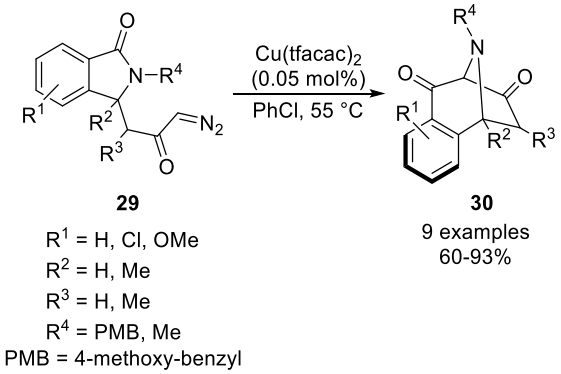
Scheme 15. Cu(II)-catalyzed [2,3]-sigmatropic rearrangement of ene-endo-spirocyclic ylides **I**.

Early examples reported in the literature by West, demonstrated that piperidinones[79] and morpholinones[80] can be obtained by copper(II) acetylacetonate catalyzed ammonium ylide formation followed by [1,2]-Stevens rearrangement. This approach has been used to synthesize novel pyrrolo-benzodiazepinone alkaloids **28** starting from dihydroquinazolin-4(*1H*)-ones **27**. Contrary to other cases previously reported, the authors found that rhodium(II) catalyst gave better yields than $Cu(acac)_2$ (Scheme 16).[81]



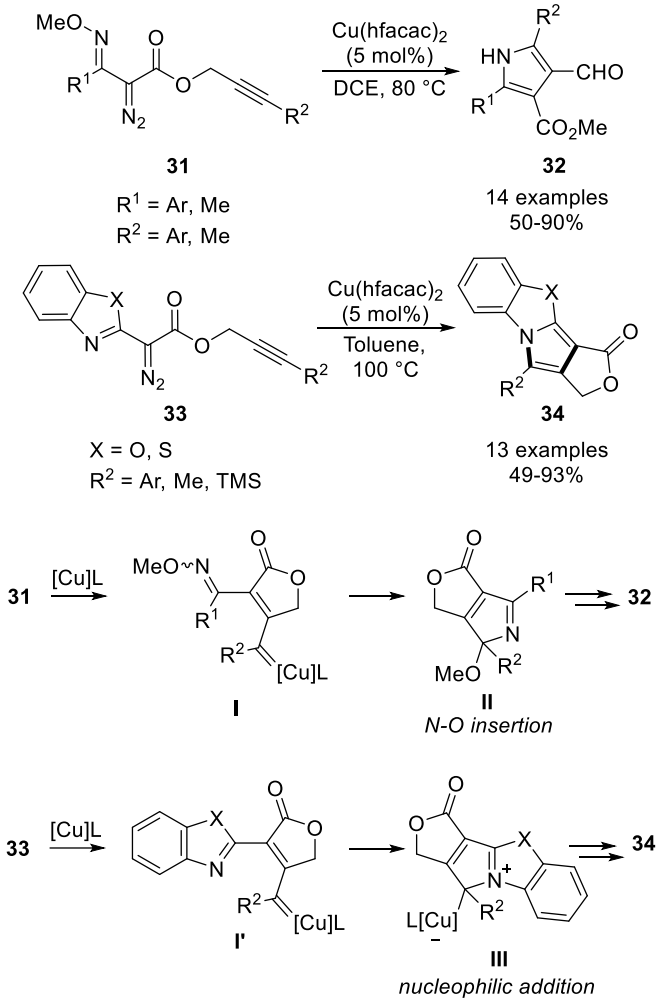
Scheme 16. Cu(II)-catalyzed [1,2]-Stevens rearrangement of ammonium ylides **I** to give pyrrolo-benzodiazepinones **28**.

The formal intramolecular amide insertion of the ammonium ylide intermediate generated in the reaction of isoindolinones **29** bearing a pendant diazocarbonyl group, for the construction of functionalized azapolycyclic ring systems **30** recently reported by Harada and Nemoto, takes advantage of the use of low catalytic loading of copper(II) complexes and mild reaction conditions (Scheme 17).[82] Best yields have been obtained with copper(II) trifluoroacetylacetonate (0.05 mol%).



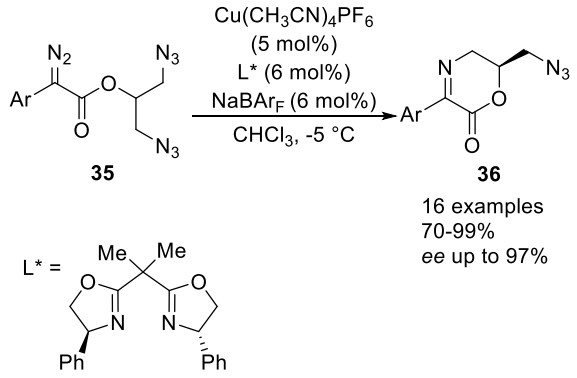
Scheme 17. Synthesis of azabicyclo derivatives **30** catalyzed by $Cu(tfacac)_2$ *via* formal amide insertion**.**

The □-imino copper carbene **I/I'** generated by copper(II) acetylacetonate catalyzed carbene/alkyne metathesis of alkynyl-tethered diazo compounds **31** and **33** can evolve toward the synthesis of multisubstituted pyrroles **32** or fused pyrroles **34** depending upon the substitution pattern round the starting compounds. Multisubstituted pyrroles were obtained from the □-imino copper carbene **I** *via* cascade N-O insertion (**II**)/alkoxy migration/alcoholysis sequence. In a divergent approach, from **I'** intramolecular nucleophilic attack generating a reactive iminium ylide **III** allowed the straightforward synthesis of fused pyrroles **34** in high yields. (Scheme 18).[83]



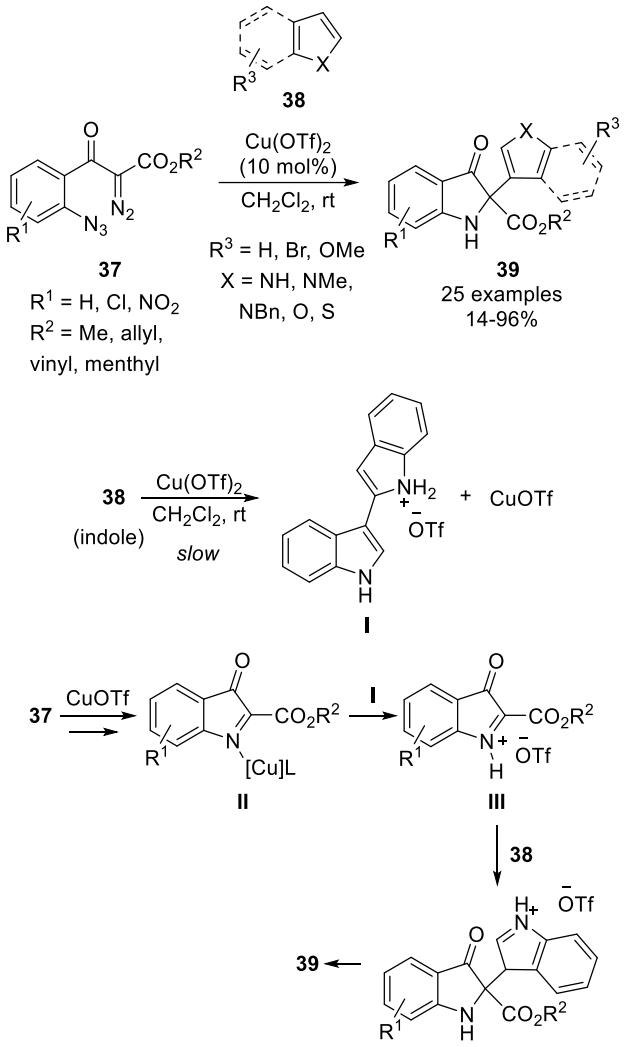
Scheme 18. Chemodivergent synthesis of multi-substituted/fused pyrroles **32** and **34** *via* Cu(II)-catalyzed carbene cascade reaction.

It is known that intramolecular interception of metallo-carbenes with alkyl azides leads to the direct formation of nitrogen heterocyclic compounds.[84] Gu and coworkers reported the first copper catalyzed enantioselective desymmetrization of 1,3-diazido-2-propanol derivatives **35** *via* the intramolecular interception of alkyl azides with diazoacetates to yield asymmetric morpholinones **36**.[85] To the purpose, several metal complexes and chiral ligands were tested, but the best results in terms of yield and selectivity were obtained by using $Cu(CH_3CN)_4PF_6$ in combination with (*S*,*S*)-Ph-bisoxazoline in chloroform at low temperatures (Scheme 19). Enantioenriched α-imino esters with three contiguous stereocenters have been obtained by the asymmetric intramolecular desymmetrization of meso-1,3-diazido-2-propanol derivatives.[86]



Scheme 19. Asymmetric synthesis of 1,3-diazidoisopropyl diazo(aryl)acetates **36**.

Intramolecular azide trapping of copper-carbene intermediates has been more recently used also for the one-step synthesis of Isatine A analogues **39** from diazo ester **37** (Scheme 20).[87] In this case, copper(II) triflate was found to be a superior catalyst with respect to copper(I) sources. It is commonly accepted that, when copper(II) salts are employed for the generation of copper-carbenes an in situ reduction of Cu(II) to Cu(I) by a sacrificial amount of the diazo compound may occur.[6] The induction period observed by West and coworkers in this case is fully consistent with such a preactivation step of the copper source, but the higher yield observed when $Cu(OTf)_2$ was used instead of $[Cu(OTf)]_2$·tol strongly suggested that excess indole **38** is involved in the initial reduction. Also, the generation of triflic acid and subsequently of indolylindoline triflate salt **I** in this step plays an important role in the clean trapping of the indole **38** to yield the final 2-indolylindolin-3-one **39**.

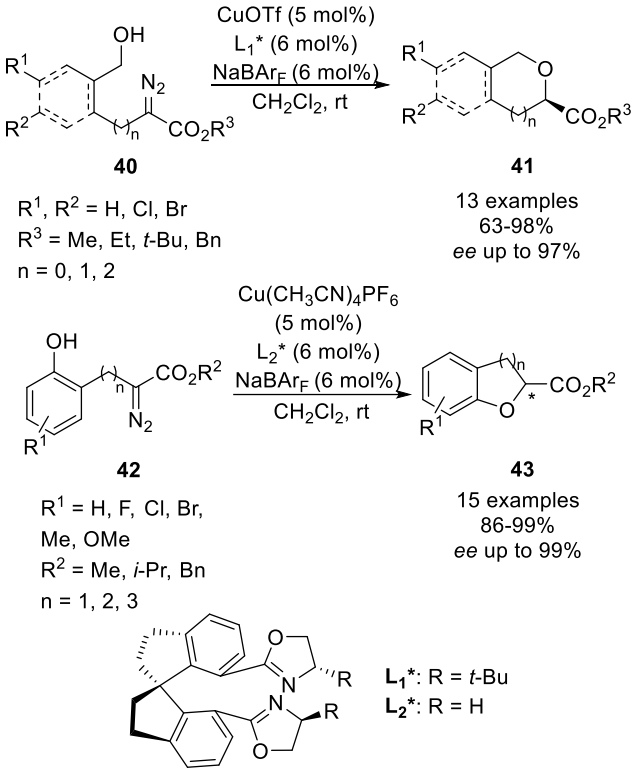


Scheme 20. One-step synthesis of Isatine A analogues **39**.

2.2. Intramolecular Cu-catalyzed X-H insertion reactions

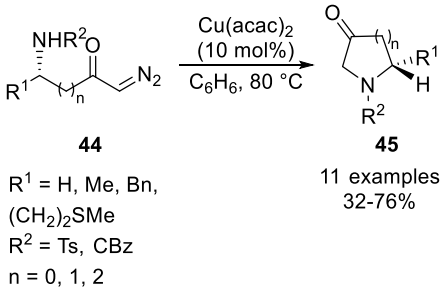
As discussed in the introduction of this section, when the reacting partner contains a α hydrogen atom, ylide formation by nucleophilic attack of the heteroatom to the metal carbene is followed by formal insertion into the X-H bond leading to the products (see Scheme 2). Intramolecular insertion into X-H bond leads to the formation of heterocycles that has been exploited especially when X = O or N, for the synthesis of five and six membered rings. Zhou reported a copper-catalyzed asymmetric intramolecular O-H bond insertion reaction of ω-hydroxy-α-diazo esters **40** (Scheme 21).[88] The use of chiral spiro bisoxazoline ligands **L_1*** in combination with copper(I) triflate and in the presence of $NaBAr_F$ (BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) allowed for the isolation of a variety

of enantiopure 2-carboxy-substituted cyclic ethers **41**. High yields (63-98%) were obtained for five and six membered rings, while in the case of seven ring products, the competitive β-H elimination of the carbene intermediate was observed, preventing the isolation of the cyclic ether in satisfactory yield. Interestingly, however, if a less bulky ligand was used, the desired seven-membered cyclic ether resulting from the carbene O-H bond insertion reaction was isolated in acceptable yield (70%) albeit at cost of a lower enantioselectivity. The group has then extended the use of the same catalytic system to diazo esters **42**, but changing the copper source from copper(I) triflate to copper(I) hexafluorophosphate, that promoted the reaction with better enantioselectivities, to obtain chiral tetrahydrobenzo[*b*]oxepines **41** and 2-carboxy dihydrobenzofurans **43** in good yields and high enantiomeric excesses (Scheme 21).[89]



Scheme 21. Cu(I)-catalyzed asymmetric intramolecular O-H insertion.

The $Cu(acac)_2$ intramolecular N-H insertion of α-diazo carbonyls **44** to furnish 3-oxo-azetidines, -pyrrolidines and -piperidines **45** was firstly reported by Wang and coworkers in 1999.[90] The use of the copper(II) catalyst allowed for the isolation of the desired heterocycles in good yield, avoiding the competitive C-H bond insertion even when the substrates possess quite reactive C-H bond adjacent to the methylthio group were employed (Scheme 22). However, when the same synthesis was attempted to build seven-membered rings, only complex mixtures of product were observed. When the reaction was performed in the presence of an excess of styrene, the competing reaction with intermolecular cyclopropanation was not observed, and only the product of N-H insertion was obtained, as expected for a polar addition of a strong nucleophile to the metal-carbenoid. Unexpectedly, however, the presence of styrene markedly improved the yield of the N-H insertion products.

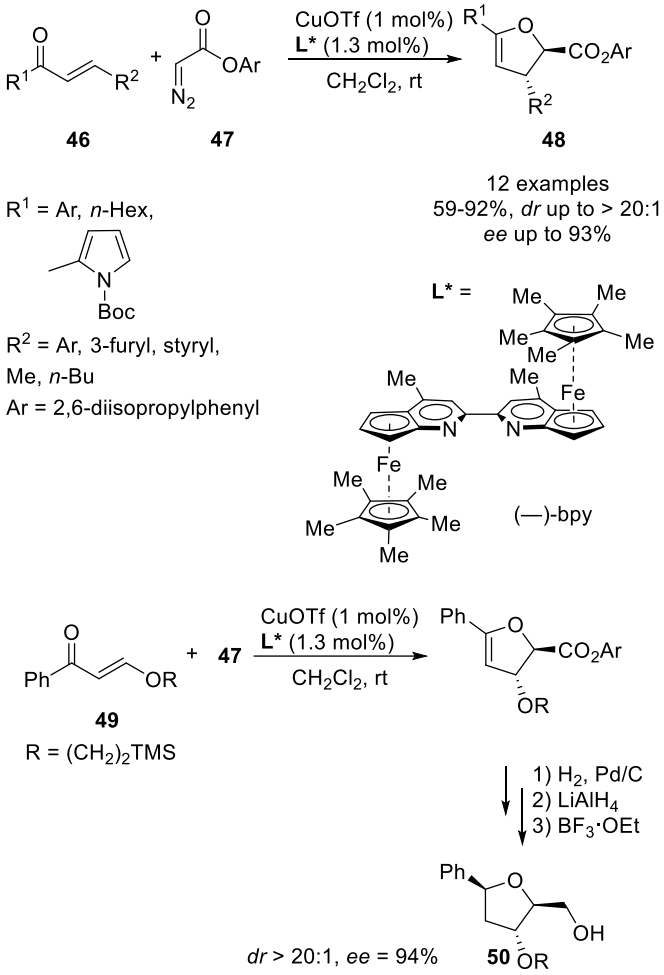


Scheme 22. Cu(II)-catalyzed intramolecular N-H insertion.

2.3. Intermolecular Cu-catalyzed carbenoid cyclization reactions

As for intramolecular reactions, intermolecular onium ylide formation from the reaction of a metal carbene with a heteronucleophile, followed by a rearrangement to yield the desired cyclization product, represents a useful synthetic strategy for the direct construction of highly functionalized heterocyclic compounds.

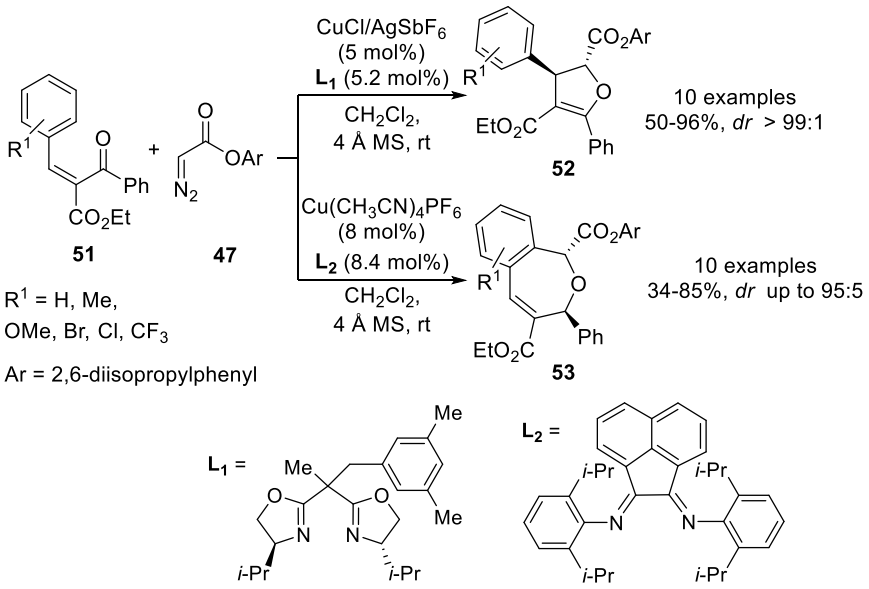
Since the first report by Spencer in 1967 on the $CuSO_4$ catalyzed furan synthesis by 1,4 addition of carbethoxycarbene to α-methoxymethylene ketones,[91] the most common approach for the synthesis of five-membered heterocyclic compounds *via* corresponding copper-carbene complexes is represented by a [4+1] annulation process.[44] The first diastereo- and enantioselective examples of the copper-carbene catalyzed [4+1] cycloadditions of enones **46** with diazo compounds **47** to give highly substituted 2,3-dihydrofuran derivatives **48** were reported by Son and Fu (Scheme 23).[92] Whereas simple α,β-unsaturated esters failed to react, vinylogous ester **49** provided 2,3-dihydrofuranes that were not isolated but, after hydrogenation of the double bond followed by reduction of the ester provided tetrahydrofuran **50** in good *ee*, paving the way for the synthesis of deoxy-C-nucleosides.



Scheme 23. Cu(I)-catalyzed asymmetric [4+1] cycloadditions *via* carbonyl ylide.

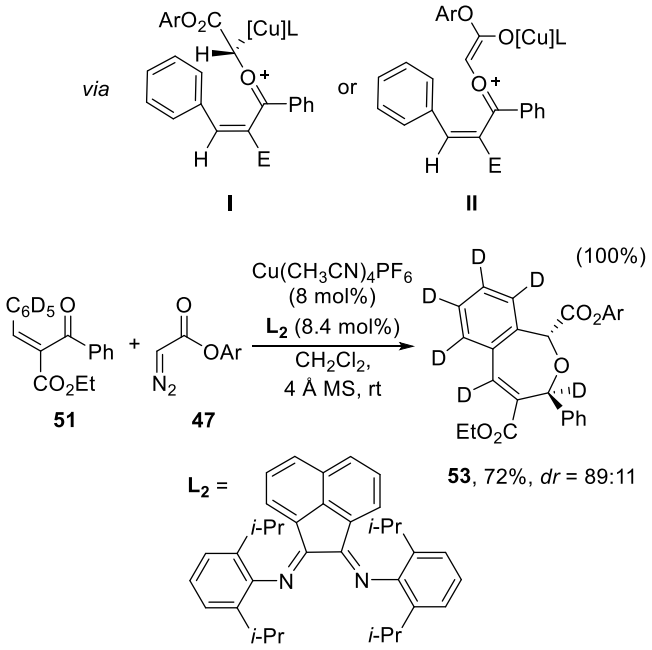
Few years later, Tang and coworkers extended this reaction to the diastereoselective synthesis of dihydrofurane **52** or dihydrobenzo[*b*]oxepines **53** by reacting α-benzylidene-β-ketoesters **51** with diazo compound **47**. The chemoselectivity depended on the nature of the copper(I) ligands employed. Thus, formation of tetrasubstituted 2,3-dihydrofurans **52** took advantage of chiral copper(I) complexes formed in situ by reaction of CuCl and side-

armed BOX ligands (BOX = bisoxazoline) in the presence of $AgSbF_6$.[93] Moreover, the reaction outcome was found to be strongly dependent on the ligand used, so by using bulkier aryl substituted 1,2-diimine ligands **L_2**, the reaction yielded preferentially the seven membered products **53** (Scheme 24).[94]



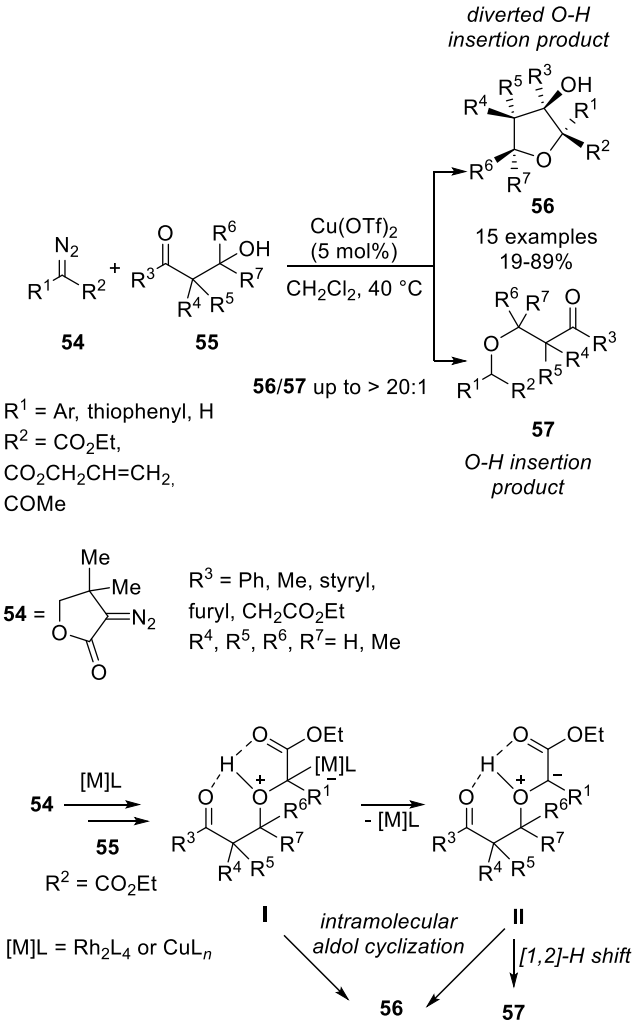
Scheme 24. Cu(I)-catalyzed asymmetric ylide cycloadditions to yield dihydrofurans **52** or dihyrdrobenzo[*b*]oxepines **53**.

DFT calculations allowed to shed light on the observed experimental results. In addition to the commonly accepted ylide **I**, the cyclization reaction can proceed *via* the ylide **II**, in which the carbonyl oxygen atom of the ester group is coordinated to the copper center (Scheme 25). Contrary to ylide **I** that can give only the 2,3-dihydrofuran derivatives **52**, ylide **II** can give either a 1,5-cyclization mode to furnish the formal [4+1] cycloaddition product or the observed dihydrobenzo[*b*]oxepine **53** through a process that involves a 1,7-cyclization and a [1,5] H-shift. The occurrence of such a [1,5] H-shift has been demonstrated experimentally by the use of a deuterium labeled substrate (Scheme 25). When bulkier ligands are used, the reaction most probably occurs through the ylide **II** to give the seven-membered ring, since the 1,5-cyclization becomes energetically disfavored. On the other hand, with less bulky ligands the reaction follows the ylide **I** pathway to afford the five-membered dihydrofurans **52**.



Scheme 25. Possible ylide intermediates **I** and **II** involved in the reaction of α-benzylidene-β-ketoesters **51** with diazo compounds **47** and experimental observation of the [1,5] H-shift involved.

The copper-catalyzed reaction of β-hydroxyketones **55** with diazo carbonyl compounds **54** to yield directly substituted tetrahydrofurans **56** through a process that the authors defined as "diverted O-H carbene insertion" has been reported by Moody and coworkers (Scheme 26).[95] The intramolecular aldol cyclization of the O-H insertion product **57** to give the tetrahydrofuran **56** has been ruled out even in the presence of bases, clearly showing that the transient oxonium-ylide formed in the first step of the insertion process can be trapped by the carbonylic carbon electrophile in a [4+1] cyclization process. It has been proposed that the main difference between copper and rhodium catalyzed O-H insertion reaction is the fact that the former favors a metal-associated ylide **I** pathway.[96] Thus, the free onium ylide intermediate **II** formed in the case of the rhodium catalyzed reaction favor the observed [1,2] H-shift process, while the copper-bound ylide **I** give preferentially the intramolecular aldol cyclization.

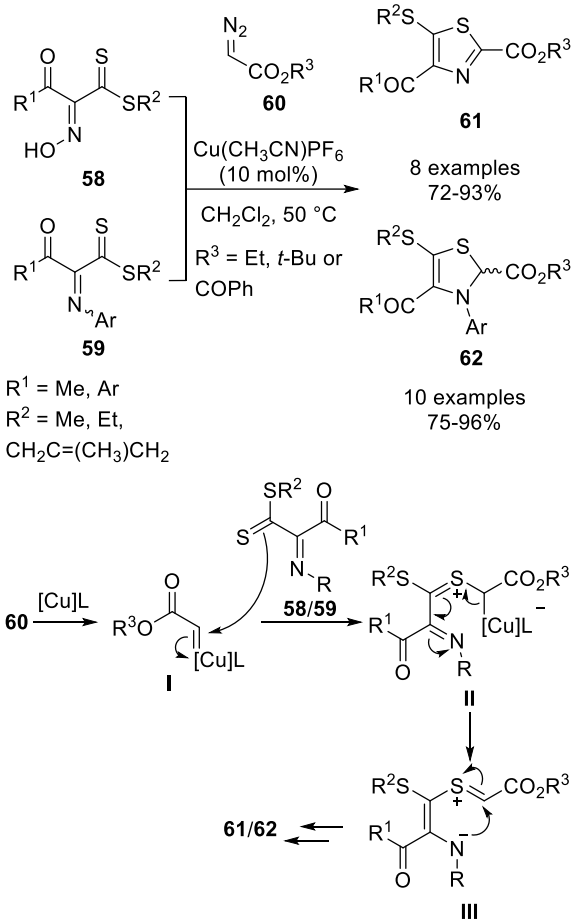


Scheme 26. Synthesis of tetrahydrofurans **56** and/or O-H insertion products **57** *via* Cu(II)-catalyzed reaction of β-hydroxyketones **55** with diazo carbonyl compounds **54**.

Alkynes can also trap oxonium ylides to yield 2,5-dihydrofuran derivatives, as demonstrated in the metal-catalyzed formal [4+1] cycloaddition of aryl diazoacetates and aryl-propargyl alcohols.[97] Also in this case, contrary to rhodium catalysts, which gave only the O-H insertion products, copper salts furnished the [4+1] cycloadducts in modest yield, along with products derived from [2,3]-sigmatropic rearrangement. However, higher yields of dihydrofurans were obtained using Pd(II) complexes.

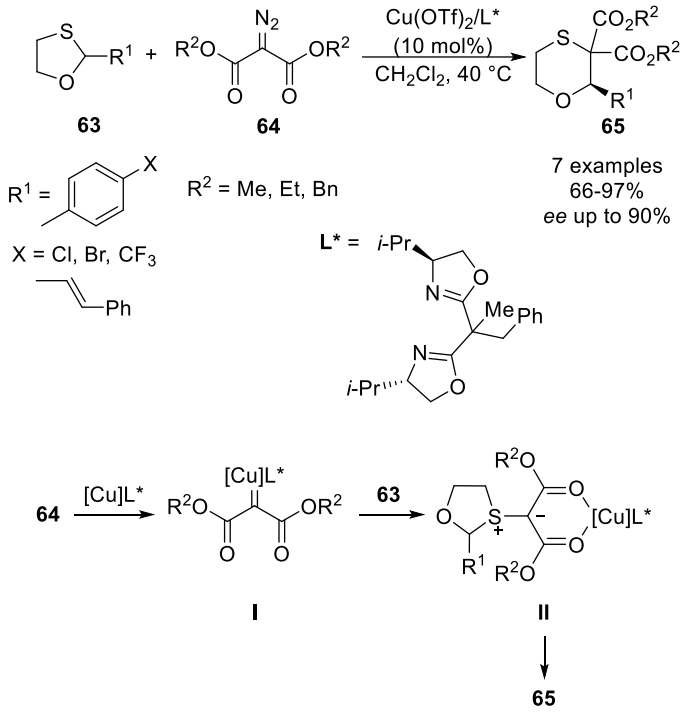
Sulfur containing heterocycles can also be obtained by taking advantage of a copper catalyzed sulfonium ylide formation, followed by a [4+1] cyclization process (Scheme 27). For instance, the synthesis of fully substituted

thiazoles **61** and 2,3-dihydrothiazoles **62** by [4+1] heterocyclization of α-(*N*-hydroxy/aryl)imino-β-oxodithioesters **58** and **59**, with in situ generated Cu-carbenoids of diazo carbonyls **60** has been reported by Singh *et al*.[98] α-(N-hydroxy/aryl)imino-β-oxodithioesters **58** and **59**, that are accessible by the reaction of β-oxodithioesters with nitrous acid/nitrosoarenes, can be either isolated or reacted in situ by a based promoted coupling and reacted in one-pot with the copper carbenoid generated by reaction of the diazoacetate with the metal salt. Mechanistically, the reaction is initiated by the nucleophilic attack of the thiocarbonyl sulfur to the metal carbene **I** to generate the sulfur ylide **II**. Worth to note that this attack is preferred with respect to the oxygen carbonyl acting as the nucleophile. Demetallation of intermediate **II** would lead to the free ylide **III** that undergoes the [1,4] heterocyclization to yield the 2,3-dihydrothiazoles **62**. When R' = OH, moderate heating favors the dehydration leading to the aromatic thiazoles **61** (Scheme 27). Interestingly, again for such a chemoselective heterocyclization, copper catalysts resulted in better yields with respect to rhodium ones. Worth to note the fact that silver(I) salts were also very effective in triggering the reaction, giving comparable yields.



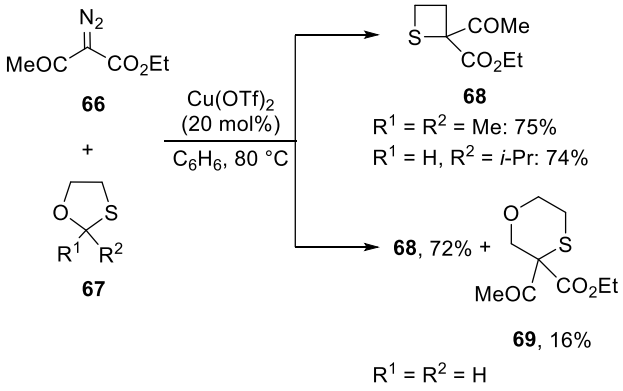
Scheme 27. Synthesis of thiazoles **61** and 2,3-dihydrothiazoles **62** *via* Cu(I)-catalyzed [4+1] heterocyclization.

Tang and coworkers reported the catalytic asymmetric formation of sulfonium ylide **II** and subsequent intramolecular [1,2]-Stevens rearrangement to yield 1,4-oxathianes **65** in high yield and with excellent enantioselectivities (Scheme 28).[99] The best results were obtained in the reaction of 2-(Ar)-1,3-oxathiolanes **63** bearing EWG-substituted benzene ring with benzyl diazomalonate **64** in the presence of copper catalysts generated in situ from $Cu(OTf)_2$ and chiral *bis*-oxazoline ligands.



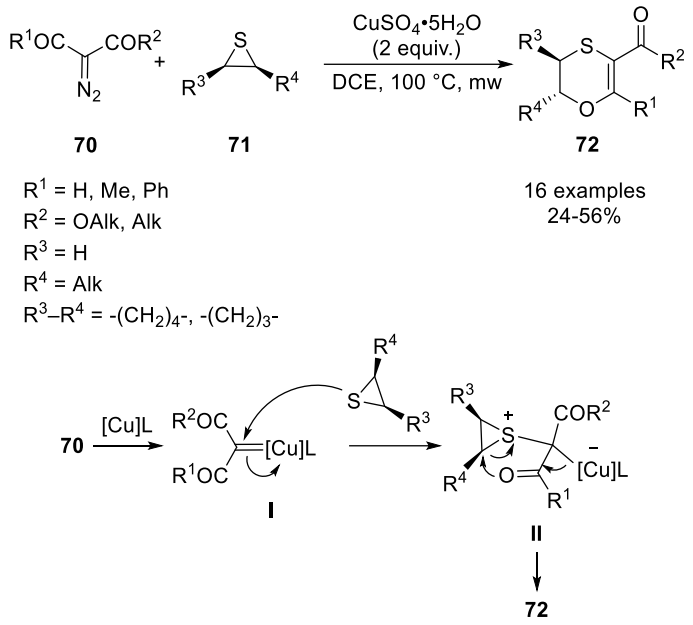
Scheme 28. Cu(II)-catalyzed asymmetric [1,2]-Stevens rearrangement and proposed mechanism.

The reaction of 2-alkyl or 2-aryl substituted oxathiolanes with metal-carbenes generated by reaction of diazo carbonyl compounds with rhodium or copper catalysts has been the subject of a following study by Sultanova.[100] In particular, the reaction of substituted 1,3-oxathiolanes **67** and dicarbonyl diazo compound **66** in the presence of $Cu(OTf)_2$ as catalyst resulted in the selective ring contraction to give 2-acetylthietane-2-carboxylate **68** derived from the cleavage of the carbonyl compound from **67** and subsequent ring closure. On the other hand, when $R^1 = R^2 = H$ thietane **68** was isolated along with the 1,4-oxathane **69** derived from the [1,2]-Stevens rearrangement (Scheme 29).



Scheme 29. Catalytic reaction of substituted 1,3-oxathiolanes **67** with diazo carbonyl compound **66**.

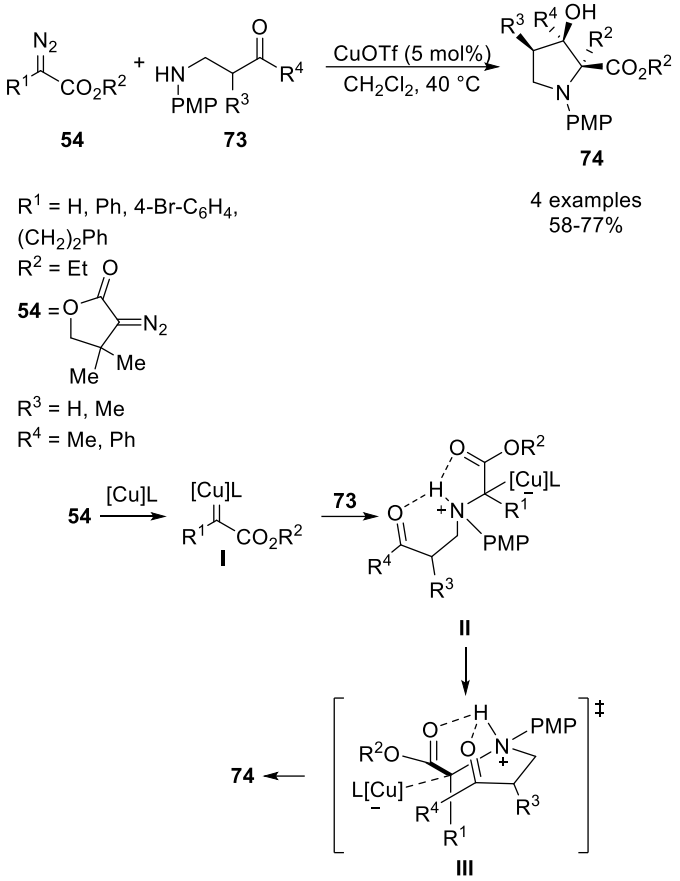
Finally, 3-acyl-5,6-dihydro-1,4-oxathiines **72** have been obtained by reaction of thiiranes **71** and diazoacetates **70** under microwave heating and in the presence of copper sulfate as additive (Scheme 30).[101] It was found in this case that the presence of water (from the hydrated copper sulfate salt) had a crucial role in the reaction outcome, since under strict anhydrous conditions no reaction was observed. Again, the mechanism proposed involves the initial formation of a sulfonium ylide **II** by reaction of the nucleophilic sulfur atom with the copper carbene **I**, followed by an attack of the enolate formed upon loss of metal (assisted by water) on the thiirane ring, causing the cleavage of the C-S bond and generating the ring expansion product **72**. The work was extended also to the synthesis of 2-acyl-5,6-dihydro-1,4-dioxines.[102]



Scheme 30. Cu(II)-catalyzed synthesis of 3-acyl-5,6-dihydro-1,4-oxathiines **72** and proposed mechanism.

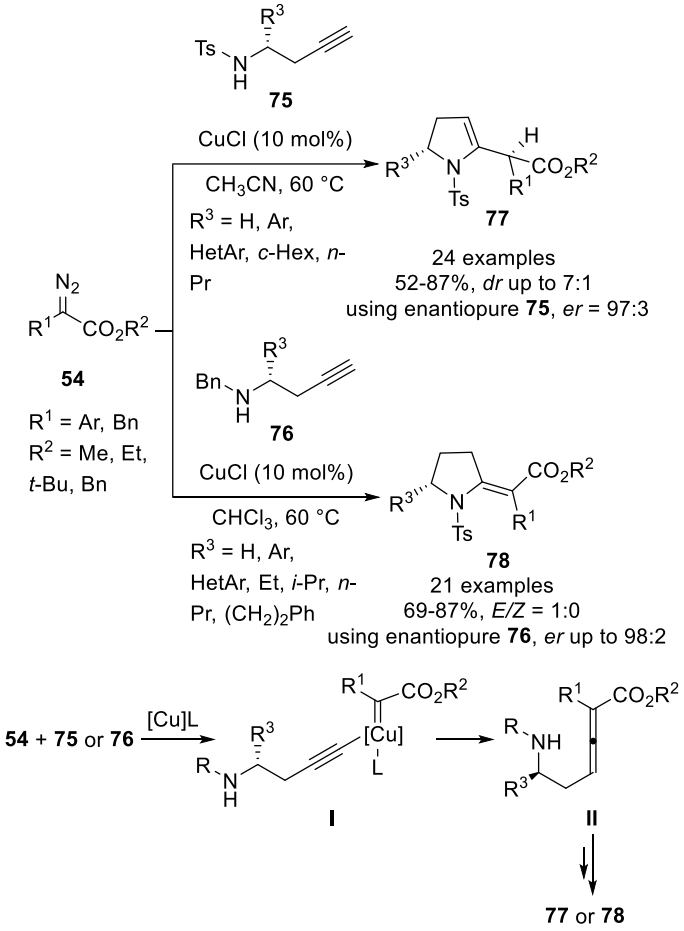
Amongst the different strategies used to build new N-heterocycles, the intermolecular reaction between a copper-carbene and a nitrogen nucleophile followed by cyclization surely represent one of the most commonly followed pathways.

Moody reported that if *N*-p-methoxyphenyl (*N*-PMP) protected β–aminoketones **73** are used instead of β-hydroxyketones (see Scheme 26) in the copper-catalyzed reaction with diazo carbonyl compounds **54**, highly functionalized pyrrolidines **74** are obtained in good yields through a "diverted N-H carbene insertion" reaction (Scheme 31).[103] Also in this case, the transient ammonium-ylide **II** formed in the first step of the insertion process can be trapped by the carbonylic carbon electrophile in a [4+1] cyclization process. However, in order that this reaction occurs, at least in the presence of copper catalysts, the nucleophilic character of the attacking N-H aniline should be conserved; in fact, the deactivated N-H of corresponding carbamates failed to give the reaction. It should be noted that in this case, the N-H insertion product was not observed neither with rhodium catalysts nor with simple copper salts. The high *cis* stereoselectivity obtained in favor of the *cis* product obtained was explained invoking the highly ordered transition state **III**, which involves a proton transfer from the aniline nitrogen atom to the ketone carbonyl group that is assisted by the ester carbonyl group.



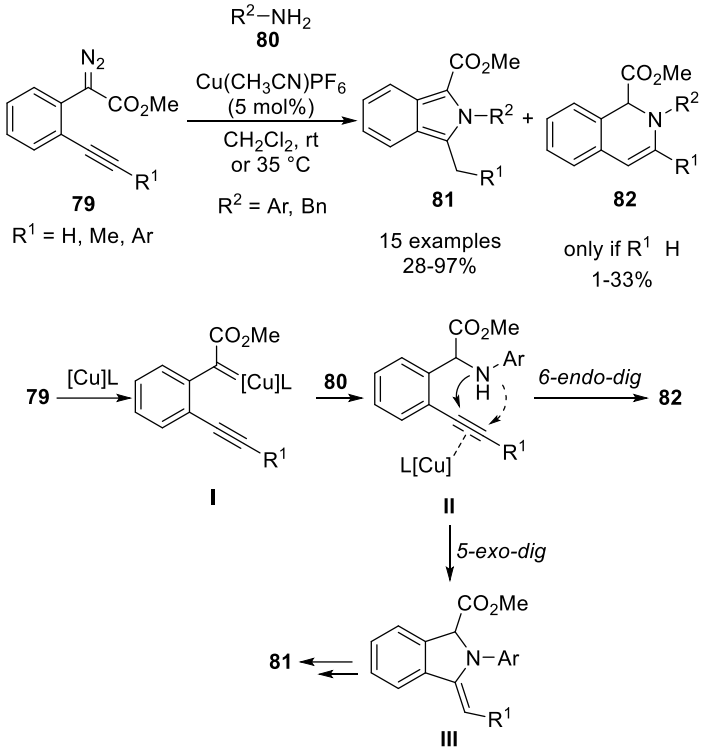
Scheme 31. Synthesis of functionalized pyrrolidines **74** by the Cu(I)-catalyzed reaction of ethyl phenyl diazoacetate and *N*-PMP protected β-aminoketones.

The stereo-divergent synthesis of pyrrolidines **77** and **78** *via* tandem annulation of diazo compounds **54** with amino-alkynes **75** and **76** was reported by Sun and coworkers in 2015.[104] Mechanistic investigations indicate that in this case, the copper-catalyzed formation of pyrrolidines **77** and **78** does not proceed by tandem N-H insertion/cyclization, but by the prioritized coupling of alkyne with the diazo compound to give the allenoate intermediate (**II**) and subsequent intramolecular hydroamination (Scheme 32).



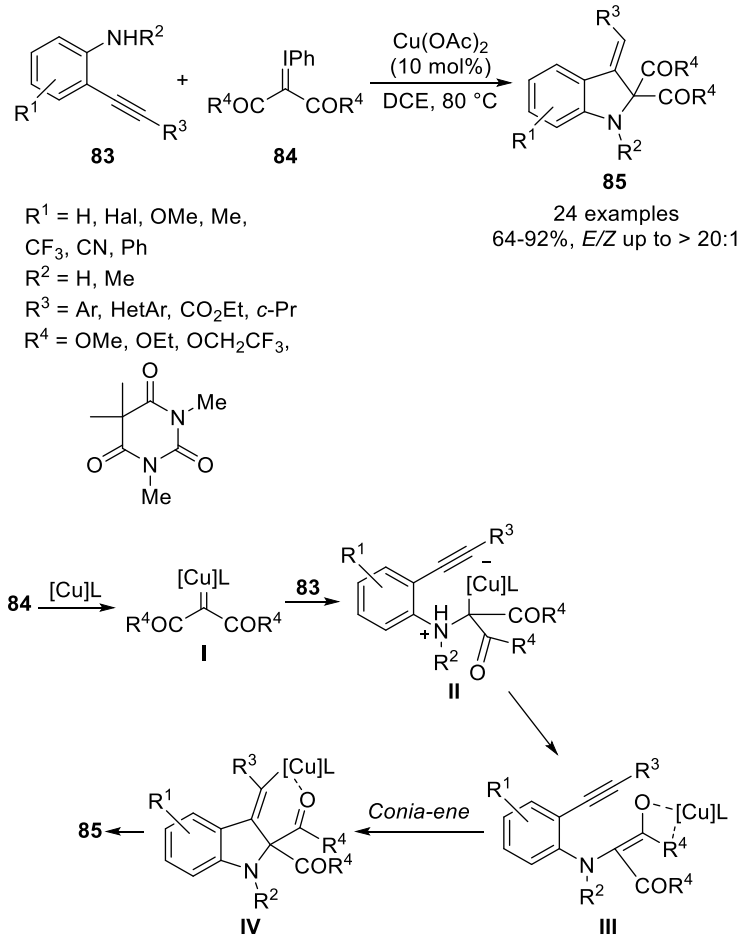
Scheme 32. Tandem annulation of diazo compounds **54** with aminoalkynes **75** and **76**.

A combined formal N-H insertion followed by alkyne hydroammination which leads to sequential formation of two C-N bonds to give isoindole derivatives **81** was reported by the group of Wang.[105] A remarkable effect of amine in directing the regioselectivity of Cu(I)-catalyzed intramolecular hydroamination of alkynes was observed. The authors proposed that Cu(I) carbene **I** is generated upon treatment of **79** with Cu $(CH_3CN)_4PF_6$. Intermolecular N-H insertion with aniline **80** leads to amine **II**. Subsequently, the amino nitrogen attacks the activated triple bond, which is coordinated with Cu(I) complex, in a *5-exo-dig* manner, to give intermediate **III**. Compound **III** quickly isomerizes to isoindole **81**. If *6-endo-dig* cyclization from **II** occurs, dihydroisoquinoline **82** is generated (Scheme 33).



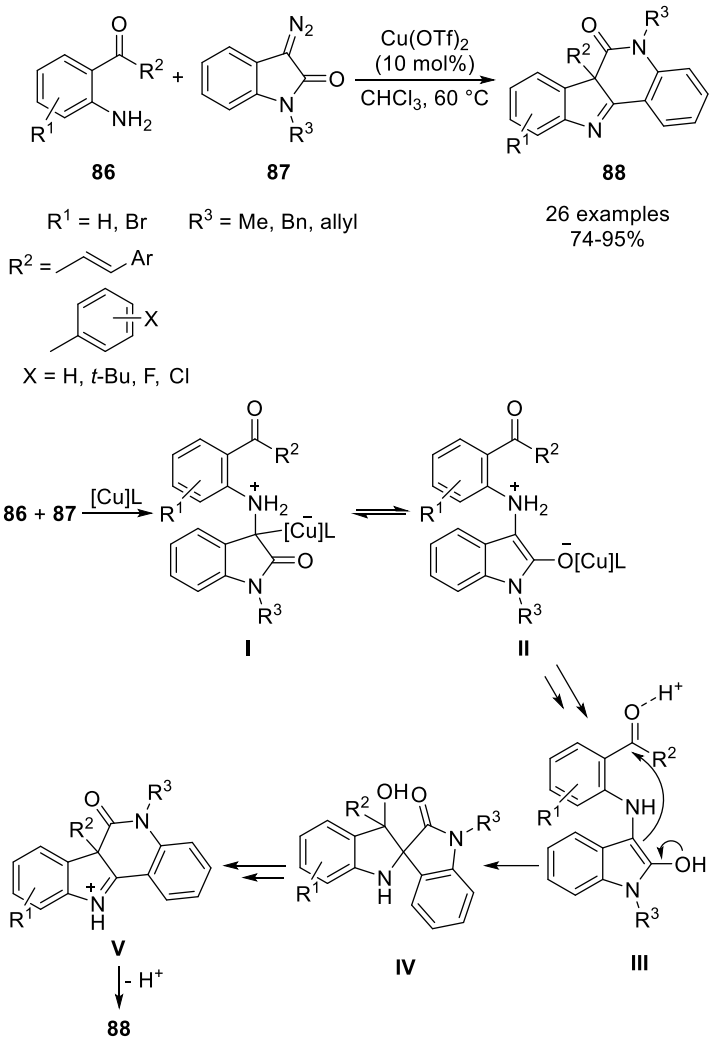
Scheme 33. N-H insertion followed by hydroalkyne hydroammination which leads to isoindoles **81**.

A complementary approach for synthesis of highly functionalized indoline cores **85** has been recently proposed by Qui and coworkers.[106] Instead of traditional diazo compounds, their approach is based on the use of iodonium ylides **84** to generate in situ the transient copper carbene complex **I** (Scheme 34). Subsequent reaction with nucleophilic 2-(phenylethynyl) aniline **83** leads to the ammonium ylide intermediate **II** that upon [1,2] H-shift gives the insertion product **III**. The indoline core is obtained by a copper-catalyzed Conia-ene reaction to give **IV**, followed by protodemetallation. The observed *5-exo-dig* carbocyclization is favored by steric hindrance effect, yielding to the final *E*-configuration observed. It is worth to note that, iodonium ylide, at least in this kind of cyclization and when using copper(II) salts, provided higher yields with respect to dimethyl 2-diazomalonate, but failed to react in the presence of copper(I) salts.



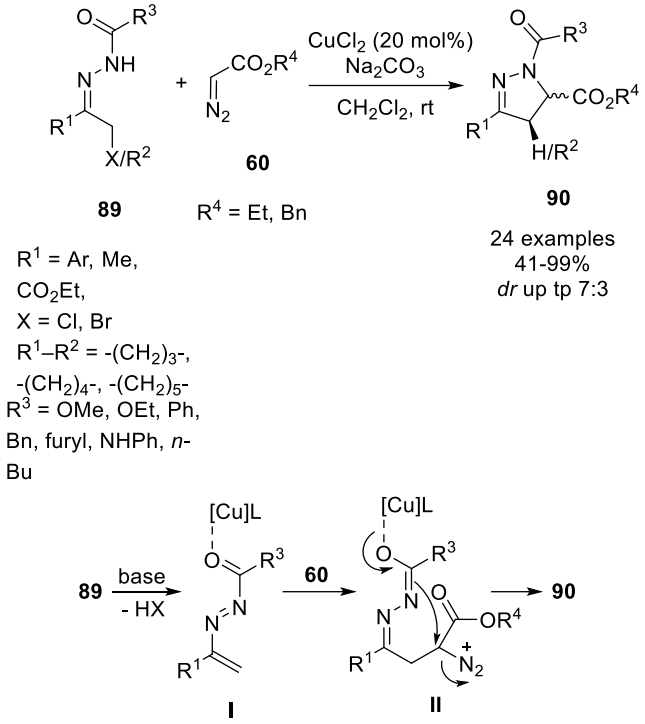
Scheme 34. Cu(II)-catalyzed [4+1] cyclization of iodonium ylides **84** with alkynes **83**.

A copper(II) catalyzed domino process involving a carbene N-H insertion followed by aldol trapping and ring expansion for the synthesis of indolo[3,2-*c*]quinolinones **88** has been proposed by Arunprasath and Sekar (Scheme 35).[107] Again, the reactive zwitterionic ylide intermediates **I** and **II** are formed by nucleophilic attack of the aniline nitrogen atom of **86** to the copper-carbene arising from diazo compound **87**. Copper(II) triflate gave the best results if compared with rhodium catalysts. It was shown that the TfOH formed in situ acts as hidden Brønsted acid catalyst to promote both the aldol-type trapping to provide the indole nucleus **IV**, and the subsequent unexpected carbonyl migration step with consequent ring expansion to give the quinolone core **V**.



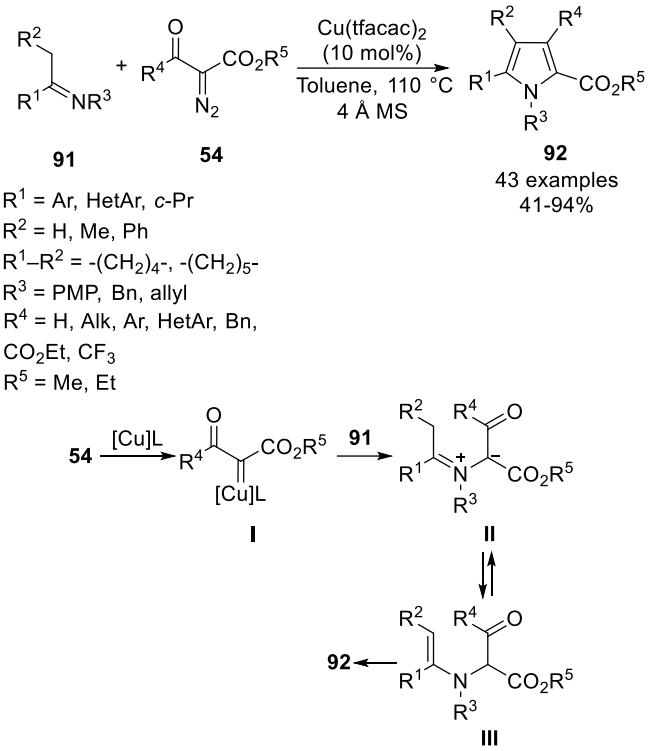
Scheme 35. N-H insertion/aldol trapping/selective carbonyl migration sequence to give indolo[3,2-*c*]quinolinones **88**.

It has been proposed that not necessarily copper-carbenes are involved in the reaction of diazo compounds in the presence of copper(II) catalyst. Favi and coworkers reported the selective direct synthesis of different 4,5-dihydropyrazole-5-carboxylic acid derivatives **90** *via* the $CuCl_2$ catalyzed [4+1] annulation of diazo esters **60** with electron-deficient acyclic or cyclic 1,2-diaza-1,3-dienes **89**.[108] These last were easily generated in situ from the corresponding α-halo *N*-acyl hydrazones. The authors propose that, at least in their reaction conditions, the carbon of the diazo compound would act as a soft nucleophile and react with the diazodiene species **I**, formed by reaction of the starting α-halo *N*-acyl hydrazone in the presence of a base, to generate intermediate **II** (Scheme 36). Nitrogen loss would be favored only in the cyclization step to yield the dihydropyrazole nucleus. However, the authors noted that the reaction catalyzed by $CuCl_2$ was accompanied by visible evolution of N_2 gas and the formation of the electrophilic copper-carbene, in the absence of any other mechanistic investigation, cannot be ruled out. One major synthetic advantage of this kind of transformation, a part from the use of inexpensive $CuCl_2$, is that strictly anhydrous conditions are not needed.



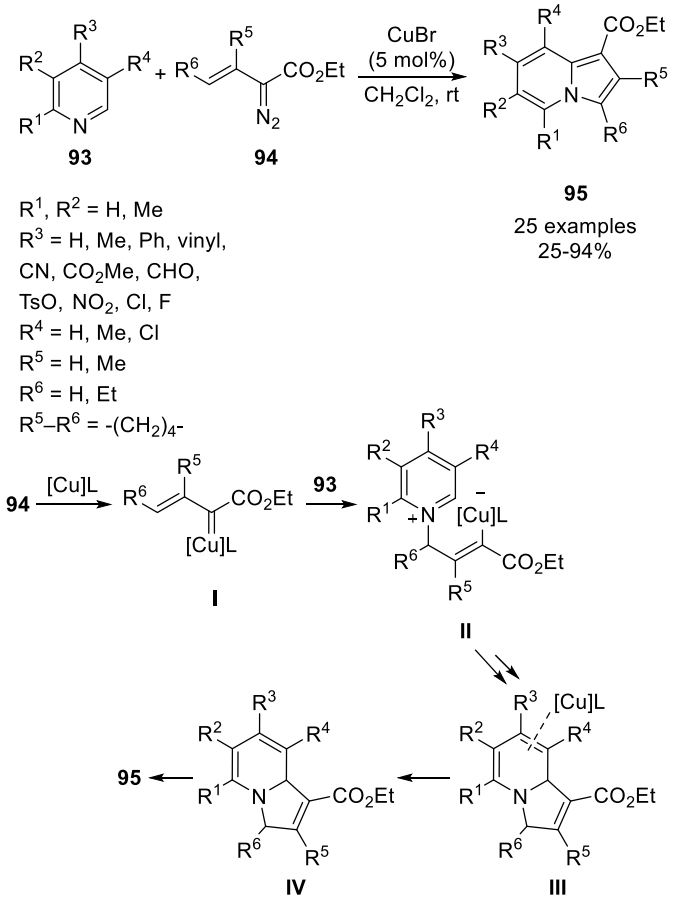
Scheme 36. Formal [4+1] annulation reaction of diazo esters **60** with 1,2-diaza-1,3-dienes **89**.

On the other hand, it has been reported that copper(II) complexes may promote the condensation of enolizable imines **91** bearing various *N*-substituents with α-diazo-β-ketoesters **54** to afford highly substituted pyrroles **92** with high regioselectivity (Scheme 37).[109] The best results were obtained using classical copper(II) triflouro- or hexafluoro-acetylacetonate complexes, while other copper(II) salts were less effective. The absence of molecular sieves was detrimental for the yield, proving that moisture in this case affect the reaction outcome. Also in this case, the reaction is triggered by nucleophilic attack of the imine nitrogen to the copper carbene **I**. Then, tautomerization of the resulting azomethine ylide **II** *via* proton transfer gives a α-enaminoketone **III** which is followed by cyclocondensation to finally furnish the pyrrole products **92**. The synthetic utility is clearly demonstrated by the rather broad scope with easily available starting materials. Both aryl and alkyl imines could be reacted with various α-diazo-β-ketoesters and the synthetic strategy has been applied to the synthesis of polyarylated pyrrole structure of lamellarins. When α-diazo-β-diketones were employed, it was found that the addition of a Lewis acid, as a co-catalyst was helpful. The authors tentatively proposed that $Y(OTf)_3$ might serve coordinate to the diketo moiety, enhancing the electrophilic character of the copper-carbene.



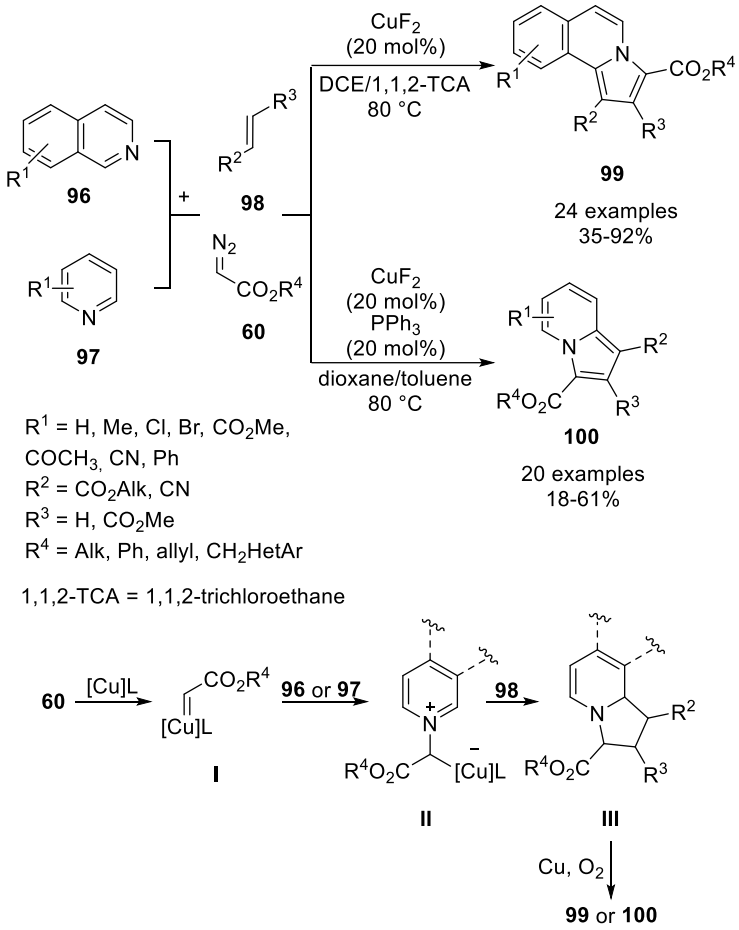
Scheme 37. Cu(II)-catalyzed condensation of imines **91** and diazocarbonyl compounds **54.**

In addition to ammonium ylides, pyridinium or quinolinium ylides generated by reaction with copper-carbene have been used as building blocks for the synthesis of different heterocyclic scaffolds. A pioneering contribution in the field is due to the work of Barluenga and Tómas, who reported the synthesis of indolizines **95** through copper(I)-catalyzed [3+2] cyclization of activated pyridines **93** with alkenyldiazoacetates **94**.[110] Again, in this case, a broad reaction scope with high regioselectivities was observed and several pyridines, as well as quinolines and isoquinolines were found to be tolerated in this cyclization reaction (Scheme 38). In this case, it has been proposed that the pyridine would give a Michael-type addition to the copper(I) alkenyl carbene **I** to yield the cuprate **II**, probably directed by the previous coordination of copper to the nitrogen atom. A carbocupration reaction of the pyridine ring would give the intermediate **III** that upon demetallation would afford the dihydroindolizine **IV** and a final oxidative aromatization would result in the observed indolizidine (Scheme 38). A complete computational study conducted more recently supported this mechanism, highlighting the attack of the pyridine derivative at the vinylogous position of the copper carbene.[111]



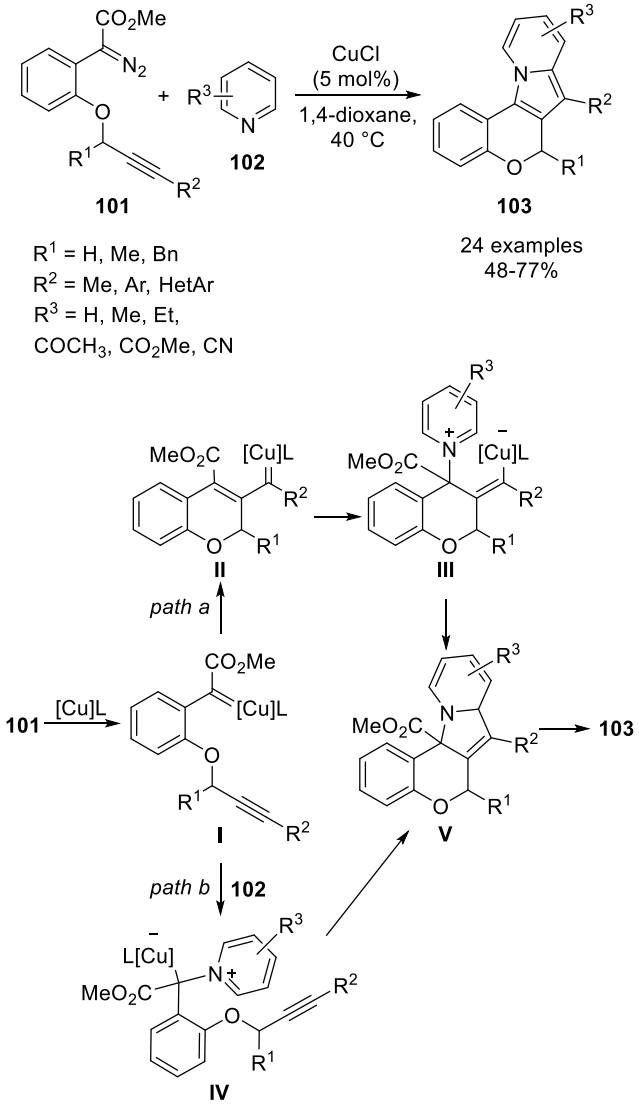
Scheme 38. Cu-catalyzed synthesis of indolizine derivatives **95** from pyridines **93** and proposed mechanism.

Several years later, a related approach toward the synthesis of the indolizine nucleus was employed by Wan and coworkers, who reported the copper(II) catalyzed three components reaction between quinolines **96** or pyridines **97**, diazo compounds **60** and alkenes **98** for the synthesis of indolizines **99** and **100**, respectively (Scheme 39).[112] In this case, although other copper catalysts showed the desired activity, better results were obtained with CuF_2, while other metals were completely inactive. Based on control experiments, the authors proposed that the pyridine nitrogen would give a nucleophilic attack to the copper-carbene **I** to give the quinolinium ylide intermediate **II** which, upon previous demetallation (**III**), would undergo a 1,3-dipolar cycloaddition reaction with the olefin to yield the tetrahydroindolizine intermediate. Finally, a copper catalyzed oxidation by O_2 would provide the indolizine. To the best of our knowledge, a detailed DFT calculation on those system, that would help in defining the transition states, has not been reported, but would shed light if a common intermediate is formed in the aforementioned reactions.



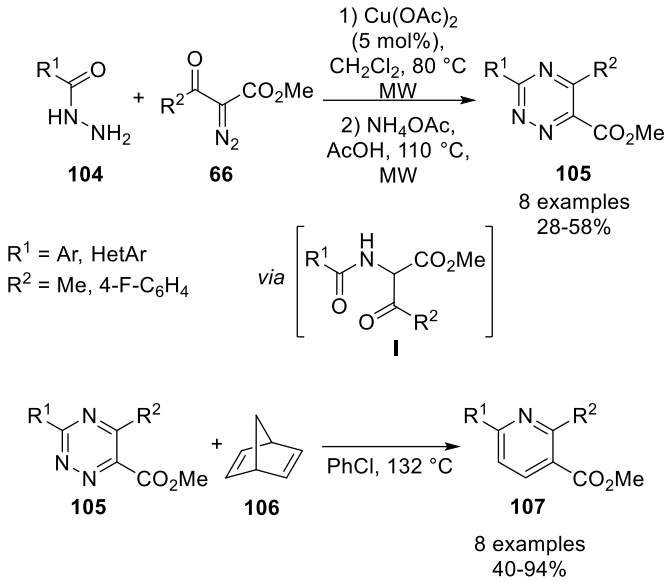
Scheme 39. Scope of the Cu(II)-catalyzed three component reaction between quinolines **96** or pyridines **97**, diazo compounds **60** and alkenes **98**.

A copper-catalyzed approach to the synthesis of polycyclic fused indolizine derivatives **103** *via* formal [1+2+2] cascade reaction of alkyne-tethered diazo compounds **101** with pyridines **102** has been recently proposed by Xu *et al*. (Scheme 40).[113] Quite surprisingly, in this case, copper(I) salts performed better than copper(II) catalysts and amongst the different used compounds, CuCl in dioxane gave the most promising results. The scope of the reaction was demonstrated by the use of a variety of diazo compounds bearing electron-rich, electron-poor or electron-neutral substituents at the terminus of the acetylene moiety. Different substituents, ranging from acyl to alkyl groups on the pyridine partner were also tolerated. Interestingly, the authors proposed two possible pathways for this cyclization, both involving the copper-carbene intermediate **I**. A carbene/alkyne metastasis process would give the vinyl carbene intermediate **II** that undergoes an intramolecular [3+2] cycloaddition (**III**) followed by decarboxylative aromatization to deliver the observed polycyclic fused indolizine **103** (path a, Scheme 40). Alternatively, as previously seen, the direct formation of pyridinium ylide **VI** followed by a [3+2]-cycloaddition with the tethered alkyne species would also give rise to the common intermediate **V** (path b, Scheme 40). Some control experiments demonstrated that results are consistent with both possible mechanistic proposals, although path b seems to be favorable.



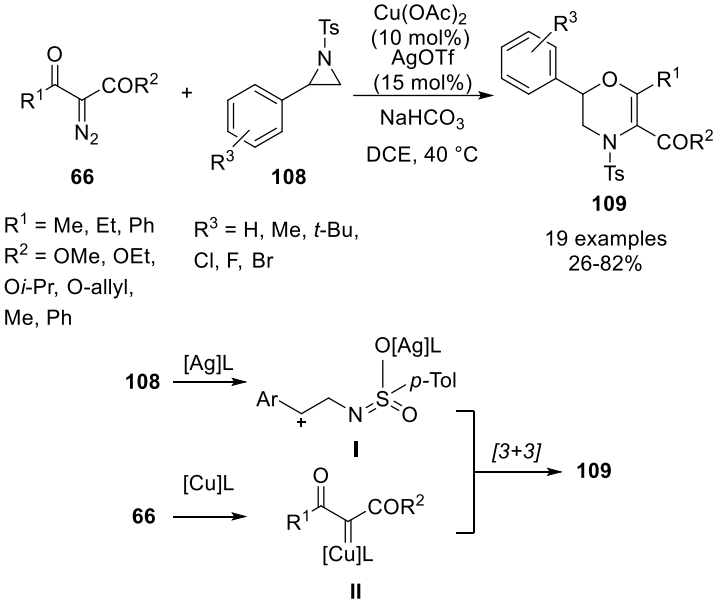
Scheme 40. Formal Cu(I)-catalyzed [1+2+2] cycloaddition of alkyne-tethered diazo compounds **101** with pyridines **102** and proposed mechanism.

Microwave heating has been used to promote the copper catalyzed insertion reaction (diazo compound **66**) into the N-H bond of hydrazide **104**, followed by in situ reaction of the intermediate **I** with ammonia and aromatization to yield 1,2,4-triazines **105** (Scheme 41).[114] Although yields of this cascade reaction are modest (28-58%), triazines **105**, could be directly transformed into pyridines **107** in high yield by subsequent Diels-Alder reaction with norbornadiene (**106**), thus providing a three-step direct transformation of readily available hydrazines into functionalized pyridines. In 2012, Moody reported the extension of this work to the synthesis of 2-triflouromethylnicotinates by using ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate.[115]



Scheme 41. Cu(I)-catalyzed, microwave assisted, carbene N-H insertion route to 1,2,4-triazines **105**.

Finally, more recently, Wan and coworkers have reported a new [3+3] cycloaddition of α-diazo carbonyl compounds **66** with *N*-tosylaziridines **108** through the synergetic catalysis with silver(I) triflate and copper(II) acetate to furnish highly substituted 2*H*-1,4-oxazine derivatives **109** (Scheme 42).[116] Compared to traditional methods for the synthesis of the 1,4-oxazoline skeleton, such process is characterized by very mild reaction conditions and a wide reaction scope. Ag(OTf) was used as Lewis acid catalyst for the activation of *N*-tosylaziridines, while $Cu(OAc)_2$ was found to be the optimal catalyst for the carbene formation at a convenient rate in order to obtain good yield of the cyclization product. Interestingly, in the optimization process it was found that $NaHCO_3$ as a base was beneficial to the yield, while other bases tested completely inhibited the reaction. Different α-diazo esters **66** and various *N*-tosylaziridines **108** were tolerated, showing that electronic effects seem to be more relevant than steric hindrance. In fact, while the reaction outcome seems to be only slightly influenced by bulky substituents on the aryl moiety of the starting aziridine, alkyl substituted 2-arly-*N*-tosylaziridines were less efficient. The authors propose that the aziridine **108** would react with silver triflate, to afford a ring opened zwitterionic intermediate **I**, while at the same time, diazo compound **66** in the presence of $Cu(OAc)_2$ will form the copper-carbene **II**. Subsequent [3+3] cycloaddition would generate the observed 2*H*-1,4-oxazine product **109**. As correctly pointed out in the manuscript, and in agreement with most of the mechanisms reported so far, it is reasonable to assume that, after the formation of an ammonium ylide intermediate, the Lewis acid might facilitate the attack of the enolate on the aziridine ring, causing the cleavage of the C-N bond and generating the ring expansion product (see for example scheme 30).

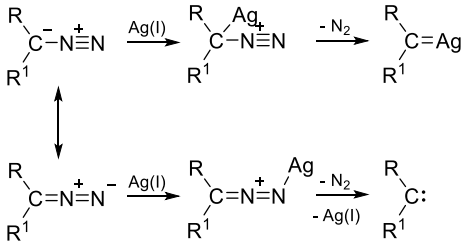


Scheme 42. [3+3]-cycloaddition of □-dicarbonyl compounds **66** and *N*-tosylaziridines **108** to give 2*H*-1,4-oxazines **109**.

3. Silver carbenes in heterocyclic synthesis

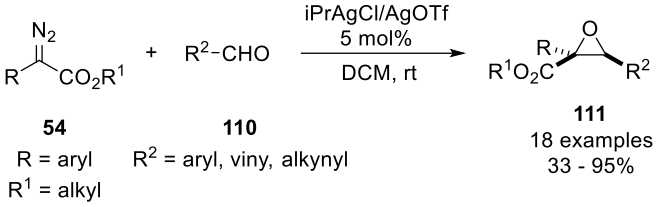
Silver(I) salts and complexes are widely employed in catalytic homogeneous organic transformations both as co-catalysts and Lewis acidic σ- or π-activators.[117-124] Intramolecular and seldom intermolecular nucleophilic addition of nucleophiles to silver-activated carbon-carbon multiple bonds allow for the straightforward synthesis of carbo- and heterocycles and are the most representative application of silver(I) salts and complexes in organic synthesis.[125-131] However, silver compounds can catalyze also the formation of reactive silver carbene intermediates as typical Fischer-type complexes able to react with suitable nucleophiles.[132-134]

Diazo compounds are the most common precursors in silver carbenes generation following two plausible main reaction mechanisms (Scheme 43). However, the electronic properties of diversely substituted diazo precursors influence the reaction pathways leading to the formation of silver carbenes through different mechanisms as demonstrated by several recently published theoretical investigations.[132]



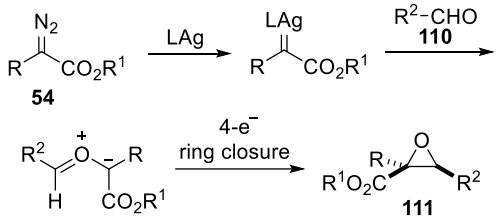
Scheme 43. Silver mediated formation of carbenic species from diazo compounds.

Moreover, nucleophiles involved in the silver carbene transfer reactions mainly are halogens, carbonyl groups as well as alkanes and arenes. However, reactions giving rise to heterocyclic compounds *via* formation of new carbon-heteroatom bonds have been rarely reported in literature. To the best of our knowledge only two recent examples fulfill with the topic of this review. Thus, in 2014 Chen and coworkers reported the first example of this kind of transformation. They described the straightforward synthesis of oxiranes from diazo carbonyl compounds and aryl/vinyl aldehydes in the presence of an in situ generated cationic Ag(I) N-heterocyclic carbene complex as the catalyst (Scheme 44).[132-133]



Scheme 44. Oxirane synthesis from diazo carbonyl compounds and aldehydes *via* NHC-Ag$^+$ catalysis.

As reported by the authors, the reaction works also in the presence of rhodium and copper catalysts and proceeds by the intermediacy of a carbonyl ylide intermediate that undergoes an intramolecular 4-electrons ring closure (Scheme 45).

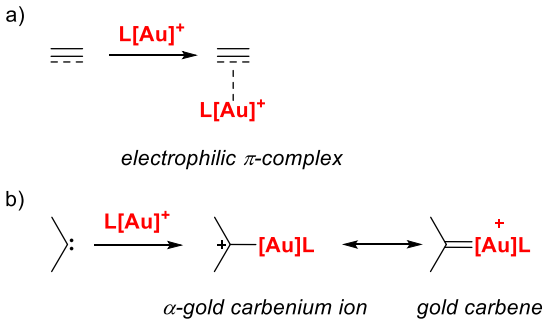


Scheme 45. Mechanism for the formation of oxirane derivatives **111**.

Moreover, as reported in Scheme 27,[98] silver salts as well as copper salts are able to catalyze the synthesis of thiazole derivatives through a mechanism similar to that reported in scheme 45, a silver catalyzed sulfonium ylide formation, followed by a [4+1] cyclization process.

4. Gold carbenes in heterocyclic synthesis

Gold catalyzed transformations are nowadays a well-established component of the synthetic chemist's toolbox. We are talking about reactions in which a π-acid activator,[135,136] the gold(I) catalyst, and a π-system interact to generate an electrophilic cationic π-complex intermediate (Scheme 46a).[137-144] Beside, further gold catalyzed reactions are supposed to proceed through the intermediacy of electrophilic species in which the gold(I) center is bonded to a divalent carbon atom. These intermediates can be described as gold carbenes or α-gold carbenium ions (Scheme 46b).



Scheme 46. Gold activated species.

A bonding model between cationic gold species and divalent carbon atoms has been developed by Toste and Goddard[144] and more recently discussed by Echavarren[146] and Widenhoefer,[147] (Figure 1).

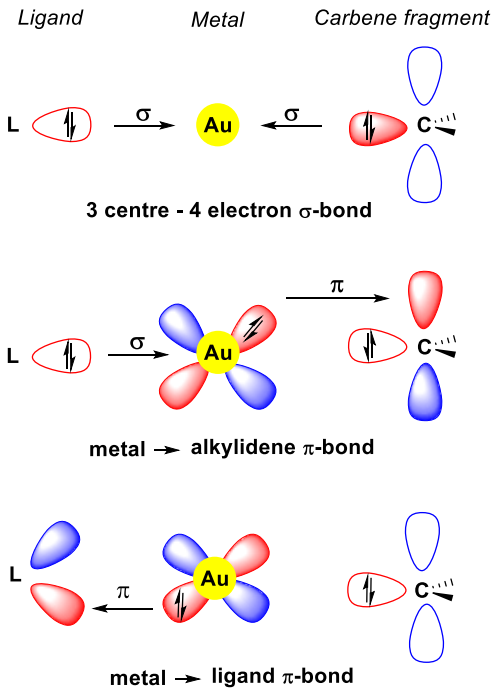
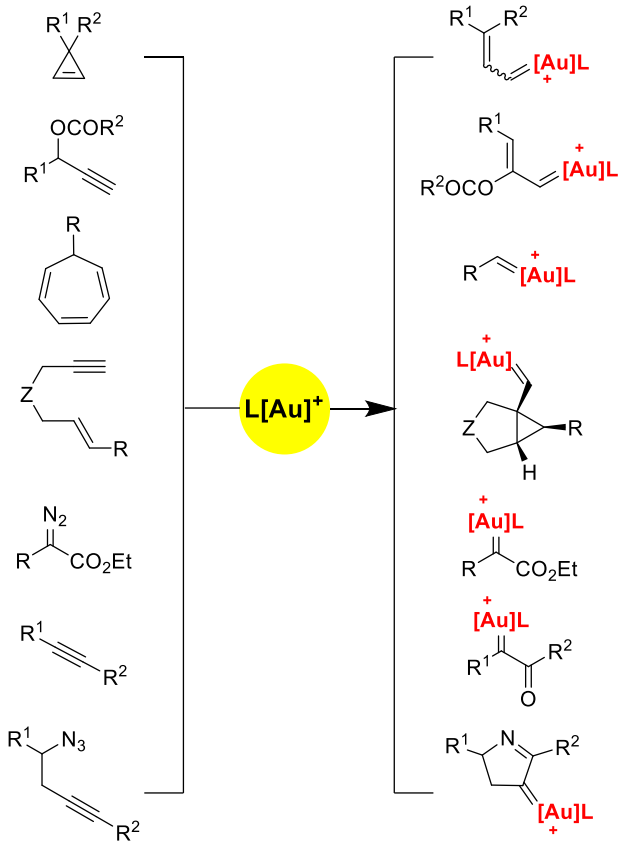


Figure 1. Ligand metal carbene bond.

Bearing in mind the linear two-coordination mode of gold(I) complexes, the ligand L and carbene can both contribute with their paired electrons to the formation of a three-centers four-electrons σ-hyperbond. Besides, two π-bonds can be built by backdonation from two filled 5d orbitals of the gold atom to empty π-acceptors on the ligand and carbene. It is obvious that the real nature of the gold carbene bond is dictated by the electronic features of both the gold ligand and C1 of the carbene and it must be evaluated on a case-by-case basis. The main "rules" we could underline are inspired by the analysis of the cited literature. Therefore, as the electron-donor properties of the ligand increase, the strength of the gold-ligand σ-bond increases and that of the gold-C1 bond decreases. The same reasoning applies to the π-back-donation from ligand to the metal center. Increasing of the π-acidic properties of the ligand determines a weakening of the π-back-donation from gold to C1. At the same time, the strength of the gold-C1 bond decreases and that of the π-back donation increases as the electrophilicity of the carbene reduces. As a consequence, the electronic arrangements of both the ligand L and the carbene carbon atom C1 compete in determining the reactivity in gold(I)-coordinated carbenes ranging from that of a metal-stabilized singlet carbene to a metal-coordinated carbocation. As suggested by Goddard and Toste, "the reactivity in gold(I)-coordinated carbenes is best accounted for by a continuum ranging from a metal-stabilized singlet carbene to a metal-coordinated carbocation".[144] The prevalence of one structure over the other determines the formation of reaction products that derive from the cyclopropanation reactions (carbene-like structure) or from stepwise processes (carbocation-like structure). A clear and thorough discussion on the topic can be found in the above-mentioned papers.

For synthetic purposes, gold carbene/carbenium ion complexes can be generated in situ from different precursors and these latter obviously determine the substituents arrangement around the reacting carbene moiety and in turn the achievable reaction products (Scheme 47).



Scheme 47. Generation of gold carbenes from various precursors.

For example, formally conjugated vinyl and aryl substituted gold carbene complexes can be prepared from cyclopropenes,[148-150] cycloheptatrienes[151] and propargyl esters.[152] Moreover, carbenes directly bonding to the carbene carbon atom, a Csp^3 carbon of a cyclopropane ring are the classical product of ene-yno cycloisomerization reactions.[153,154] Whereas □-carbonylsubstituted carbenes are the products of the decomposition of diazo compounds[155-157] or of the oxidative addition to triple bonds.[158,159] Similarly, □-imino gold carbene intermediates have been reported as the products of inter- or intramolecular addition/elimination reactions of nitrogen nucleophiles to alkynes.[160,161]

Among all gold carbene intermediates reported in scheme 47, those arising from propargyl esters, diazo compounds and from the addition of oxygen or nitrogen nucleophiles to alkynes found application in the synthesis of heterocyclic compounds by formation of a new bond between the carbene carbon atom and a heteroatom. In order to achieve these transformations several gold(I) complexes have been employed and, for a better comprehension, a list of the ligands reported in the following paragraphs is summarized in Figure 2.

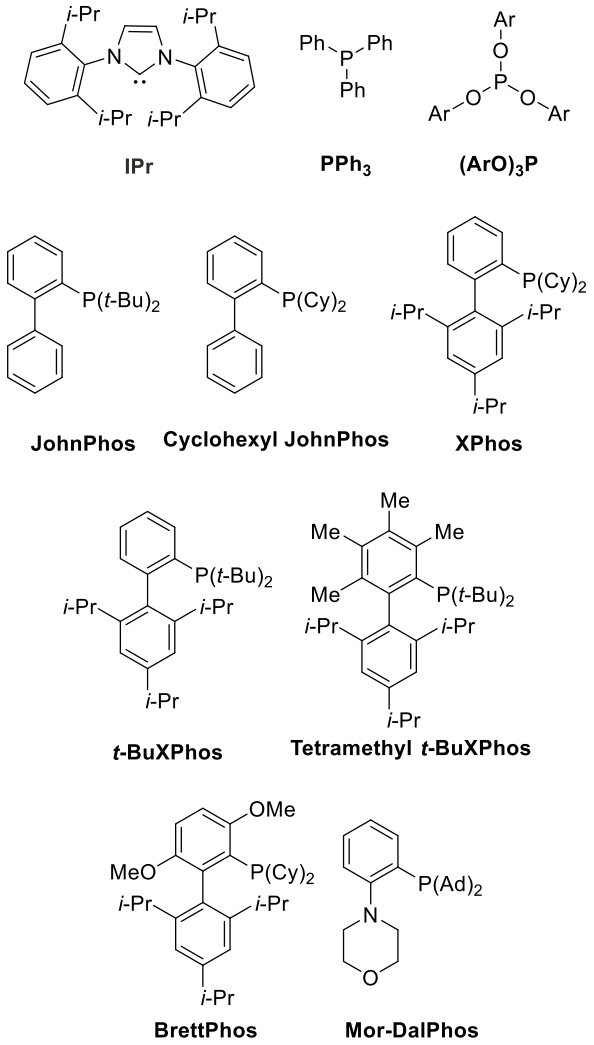
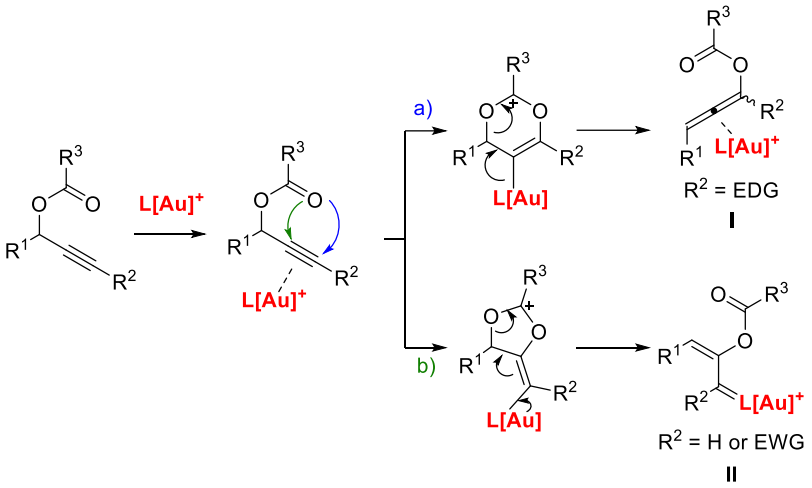


Figure 2. Ligands for gold(I) complexes.

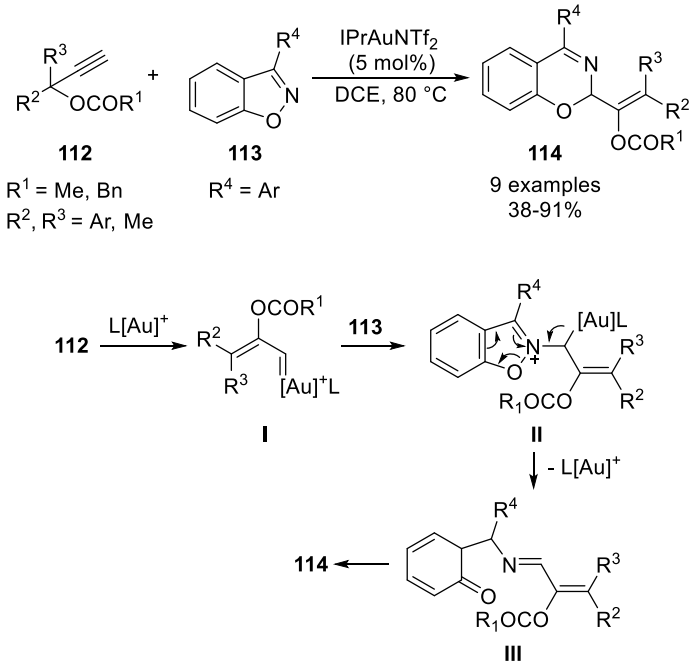
4.1. Carbenes generated from propargyl esters

Propargyl esters pertain to an interesting class of compounds employed in the presence of suitable metal catalysts in cycloisomerization, cycloaddition and cyclization reactions generating compounds with high molecular complexity.[137] These alkynes can be activated by a π acidic gold catalyst through interaction with the triple bond.[139] After coordination, the triple bond undergoes an intramolecular nucleophilic attack by the carbonyl oxygen of the ester.[162] Depending on the characteristics of propargylic ester and the reaction conditions, the cyclization can generate two different intermediates leading to distinct reactivity.[163] In one case, the result is a 1,3 acyloxy migration or a [3,3]-rearrangement of the ester moiety (*6-endo-dig* cyclization, Scheme 48a) to give Au-coordinated allene **I**. The type of substituents on the allene determine the η1 or η2 allene character of the complex, influencing the reactivity. The second mechanism involves 1,2 acyloxy migration with formation of a 5-member cyclic intermediate that evolves into gold carbene species **II** (*5-endo-dig* cyclization, Scheme 48b). The reactivity can be modulated by the electrophilicity of the two carbon atoms of the triple bond. In fact, an internal and neutral propargyl ester leads to the 1,3 migration, while [2,3]-rearrangement is involved with terminal alkynes and internal alkynes bearing EW groups.[164]



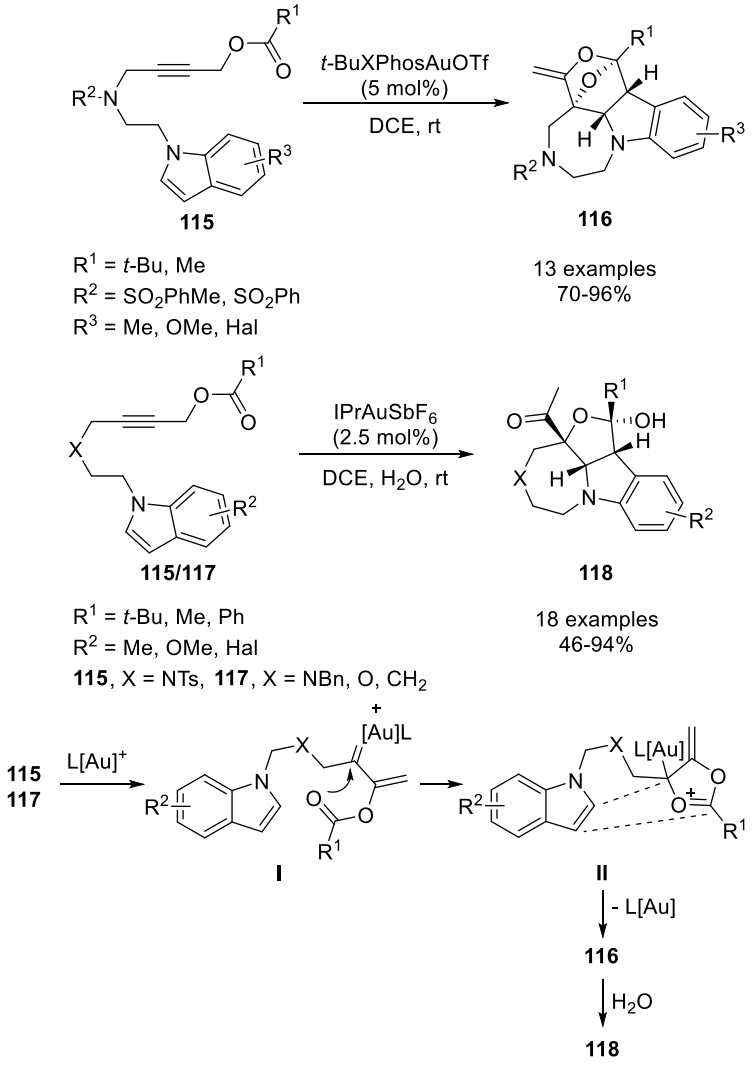
Scheme 48. Generation of Au-coordinated allenes and gold carbenes from propargyl esters.

Thus, following the reaction path shown in Scheme 48b it is possible to use properly substituted propargyl esters for the in-situ generation of gold carbene that in turn can be involved in the synthesis of new heterocyclic scaffolds. The usefulness of these transformations has been rarely explored in reactions involving formation of a new bond between the carbene carbon atom and a heteroatom. However, in our opinion, more detailed searches of new nucleophilic reagents could expand the scope of these methodologies. Among the few existing examples, in 2018, Liu and coworkers reported the synthesis of benzo[*e*][1,3]oxazine derivatives **114** from the reaction between benzo[*d*]isoxazoles **113** and terminal unsubstituted propargyl esters **112** under IPrAuNTf$_2$ catalysis (Scheme 49).[165] The authors proposed the initial formation of the gold(I) carbene intermediate **I** from propargyl ester **112**, followed by nucleophilic attack on the carbene carbon by the nitrogen of benzo[*d*]isoxazole **113** to form iminium intermediate **II**. Its rearrangement and the elimination of gold(I) catalyst led to the formation of imine intermediate **III** able to undergo a 6π electrocyclization yielding the final products **114**. The transformation tolerated modification on both starting materials. Better results were obtained with monosubstituted propargyl esters and in the presence of electron withdrawing groups on the benzo[*d*]isoxazoles **113** (Scheme 49).



Scheme 49. Synthesis of benzo[*e*][1,3]oxazines **114** from benzo[*d*]isoxazoles **113** and propargyl esters **112**.

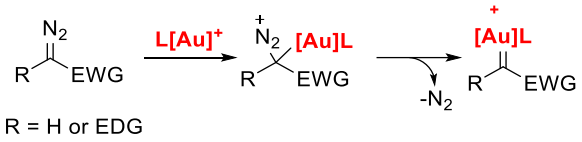
A quite different approach, involving propargyl esters bearing an electron withdrawing group at the terminal carbon atom of the triple bond, was reported in 2016 by Shi and coworkers (Scheme 50). They proposed a gold(I) catalyzed cascade intramolecular cyclization of indolyl propargylic esters **115** and **117** for the synthesis of polycyclic indoline derivatives **116** and **118** bearing four contiguous stereocenters.[166] During the screening for the best reaction conditions, the authors were able to establish the best reaction conditions for the synthesis of **116** and **118**. In particular, 5 mol% of *t*-BuXPhosAuOTf in dry dichloroethane for the synthesis of **116** and 2.5 mol% of $IPrAuSbF_6$ in wet dichloroethane for the synthesis of **118**. Furthermore, the authors demonstrated that the hydrolysis reaction occurred only in the presence of the gold catalyst. The proposed mechanism involved activation of propargyl ester leading to the formation of gold carbene intermediate **I** through 1,2-acyloxy migration. Successively, intramolecular nucleophilic attack of the carbonyl group generated the 1,3- dipolar intermediate **II** able to undergo a [3+2] cycloaddition with the C2-C3 carbons of the indole moiety forming **116** and finally **118** after addition of one equivalent of H_2O (Scheme 50). In both cases, products **116** and **118** well tolerated the presence of different electron-withdrawing and donating substituents on the indole core and the presence of pivaloyl or methyl esters at the propargyl terminus. Furthermore, in the same work, the research group of Shi proposed the enantioselective version of this transformation showing the possibility of obtaining products **118** in moderate yield and moderate to good enantiomeric excesses using a chiral phosphoroamidite gold(I) catalyst.



Scheme 50. Synthesis of polycyclic indolines **116**/**118** from indolyl propargylic esters **115**/**117**.

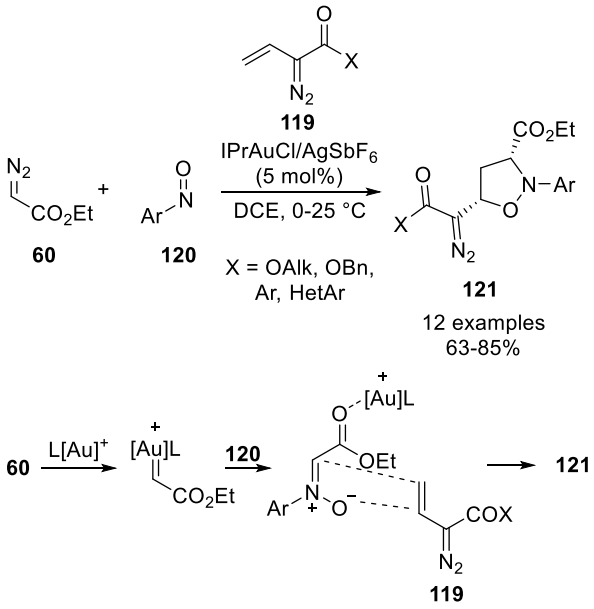
4.2. Carbenes generated from diazo carbonyl compounds

Metal-catalyzed decomposition of α-diazo carbonyl compounds represents one of the most exploited method to generate a metal carbene able to participate in the formation of new C-C and C-X bonds *via* cyclopropanation, C-H or X-H insertion, ylide formation, cycloaddition and cascade reactions.[167,3] Among the metal catalysts employed to generate reactive carbene intermediates, gold has recently emerged as an attractive alternative to the more studied rhodium and copper, showing a unique reactivity and selectivity.[157,168] In particular, gold carbenes generated from (donor)/acceptor diazo compounds (Scheme 51), have been employed for the preparation of highly substituted five- and six-membered heterocyclic derivatives.



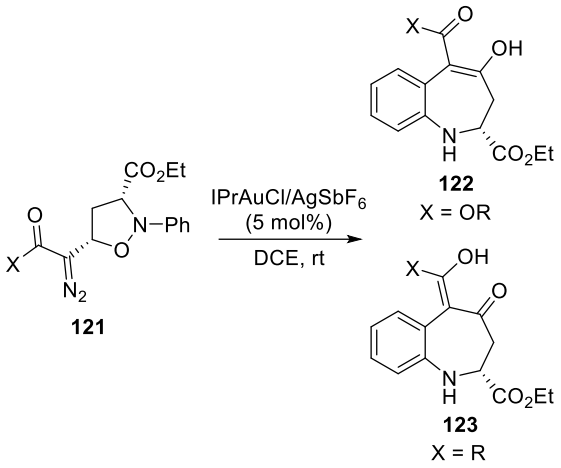
Scheme 51. Generation of gold carbenes by decomposition of properly substituted diazo compounds.

One of the most intriguing examples of this chemistry was reported by Liu and coworkers in 2015.[169] Simple diazo ester **60** was selectively decomposed by gold catalyst to form gold carbene in the presence of vinyl diazo ester **119**. These two reactants and nitrosoarenes **120** participated in a three-component cycloaddition for the synthesis of diazo isoxazolidine derivatives **121**. According to the proposed reaction mechanism the gold carbene intermediate reacted with the nitrogen atom of **120** to give a highly electrophilic nitrone intermediate. Further concerted [3+2] cycloaddition of this intermediate with **119** led to final product as single *cis*-isomer (Scheme 52).



Scheme 52. Three-component cycloaddition for the synthesis of isoxazolines **121**.

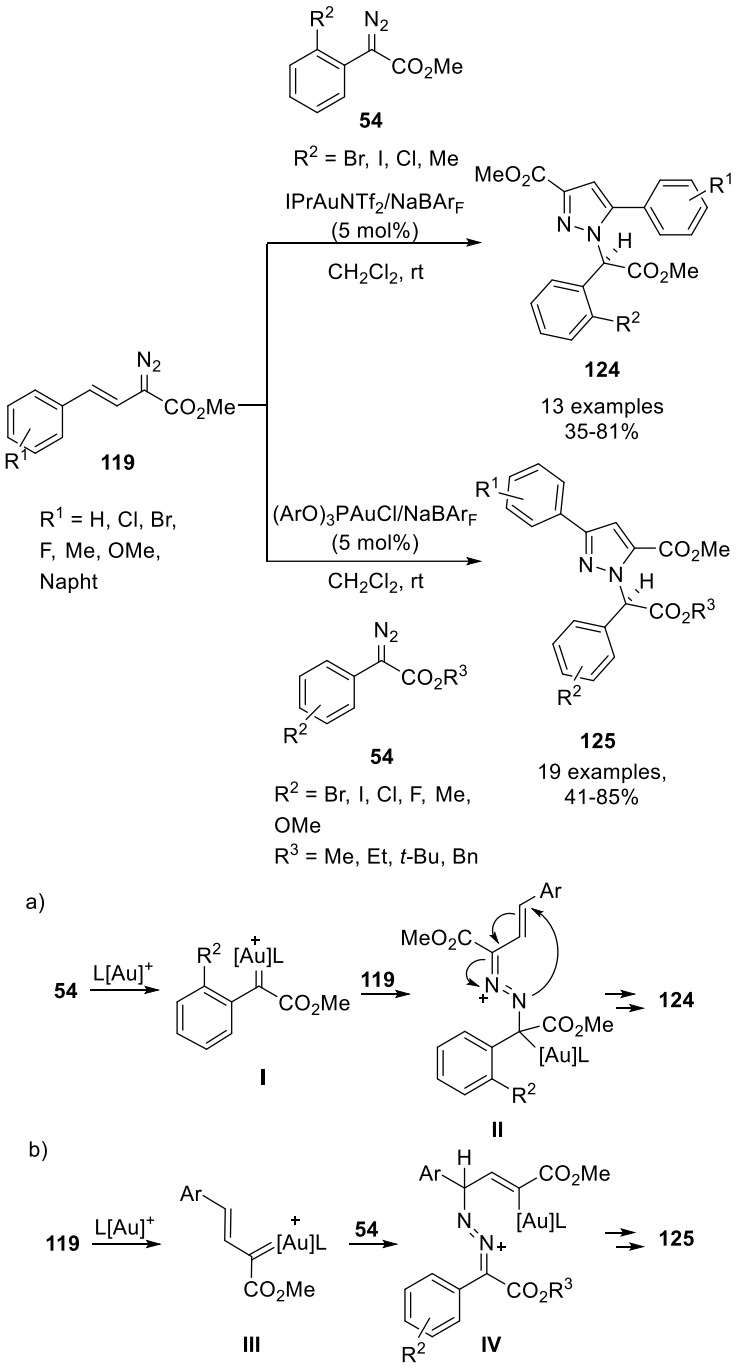
Interestingly, isolated diazo isoxazolidines **121** could be further reacted in the presence of 5 mol% IPrAuCl/$AgSbF_6$ to afford benzoazepines **122** and **123** (Scheme 53).



Scheme 53. Transformation of diazo isooxazolines **121** into benzoazepines under gold(I) catalysis.

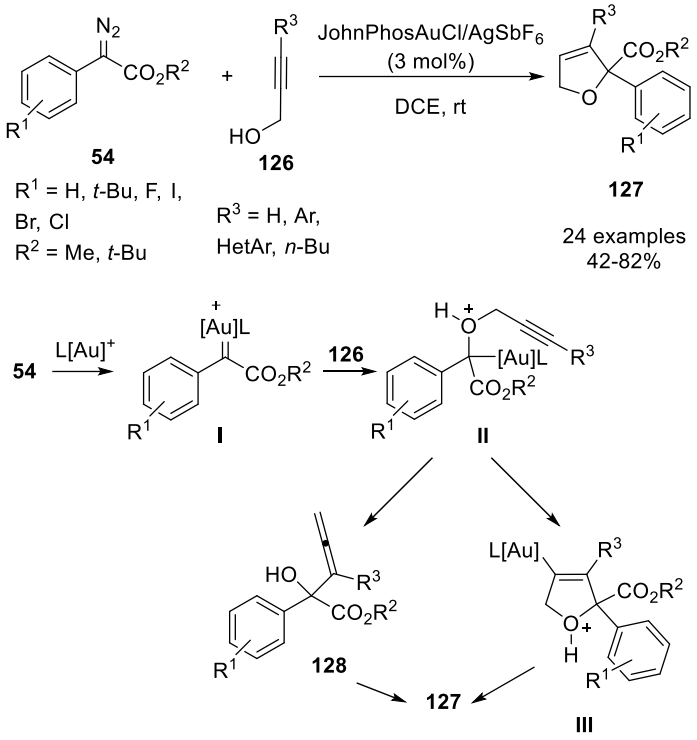
The reaction proceeded through the formation of a new gold carbene intermediate that underwent a ring opening/ring closing event involving the phenyl ring and affording the final compounds.

Another example of selective decomposition of different diazo esters was reported by Sun and coworkers in 2015. They studied the gold(I) catalyzed denitrogenative cross-coupling between vinyl diazo esters **119** and aryl diazo acetates **54** to give *N*-substituted pyrazoles.[170] Noteworthy, the accurate choice of gold(I) ligand and the use of properly substituted aryl diazo acetates **54**, allowed for the synthesis of two isomeric pyrazoles **124** and **125** in high yields. In particular, the use of IPrAuCl/$NaBAr_F$ as catalyst and of sterically hindered *ortho*-substituted aryl diazo acetates led to pyrazoles **124**. Conversely, the reaction between variously substituted vinyl diazo esters and aryl diazo acetates led to pyrazoles **125** when a more electrophilic gold(I) species, such as $(ArO)_3PAuCl$/ $NaBAr_F$ (Ar = 2,4-*t*-$Bu_2C_6H_3$), was employed. In order to explain this reactivity difference, the authors supposed that the establishment of **124** is due to a preferential formation of gold carbene **I** from aryl diazo acetate **54**. Then, because of the steric hindrance of *ortho*-substituted **54**, vinyl diazo acetate cannot give a carbanion nucleophilic attack,[171] but led to intermediate **II** *via* nitrogen attack. Sequential cyclization and hydrogen migration afforded **124** as final product (Scheme 54 a). Nevertheless, in the presence of gold phosphite, the formation of vinyl carbene **III** is preferred. Thus, vinylogous addition of aryl diazo ester gave **IV** and is followed by a cyclization deauration cascade leading to **125** as final product (Scheme 54 b).



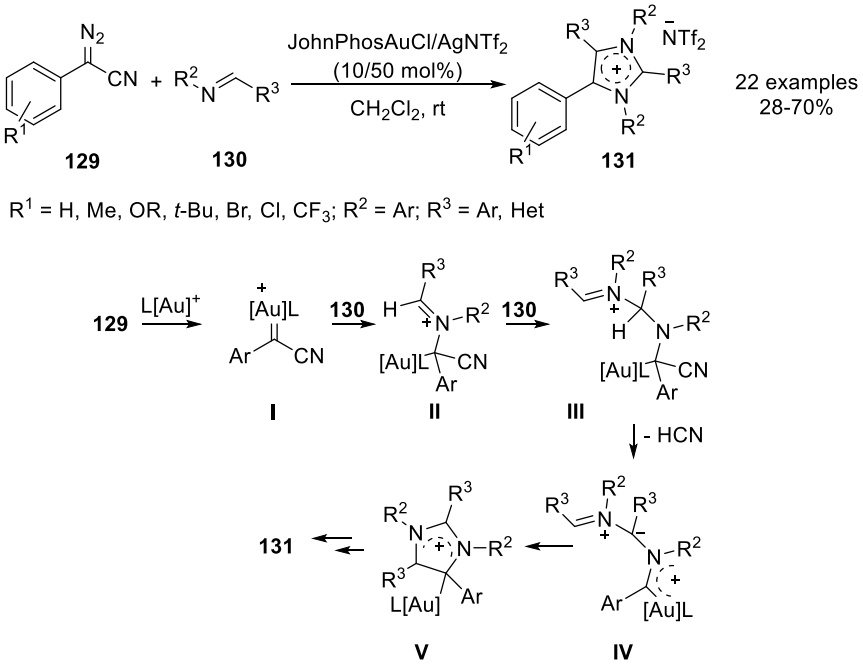
Scheme 54. Synthesis of *N*-pyrazoles **124** and **125** by gold catalyzed denitrogenative cross-coupling.

Besides, donor-acceptor diazo compounds such as α-aryl diazo esters were frequently employed to synthetize five-membered heterocyclic rings in the presence of nitrogen or oxygen nucleophiles. In 2015 Wang and Zhang, described for example the synthesis of 2,5-dihydrofurans **127** by a gold catalyzed formal [4+1] cycloaddition between aryl diazo esters **54** and propargyl alcohols **126**.[172] Mechanistically, the formation of **127** could be explained by generation of an oxonium ylide **II** from gold carbene **I** and propargylic alcohol. Then, two different pathways are possible: a [2,3]-σ-rearrangement of **II** would give α-hydroxyallene **128**, which could further react with gold to produce the final product by *5-endo-dig* cyclization. Alternatively, direct insertion of propargyl alcohol triple bond into Au-C bond would lead to the formation of intermediate **III** that, after protodeauration would afford **127** (Scheme 55).



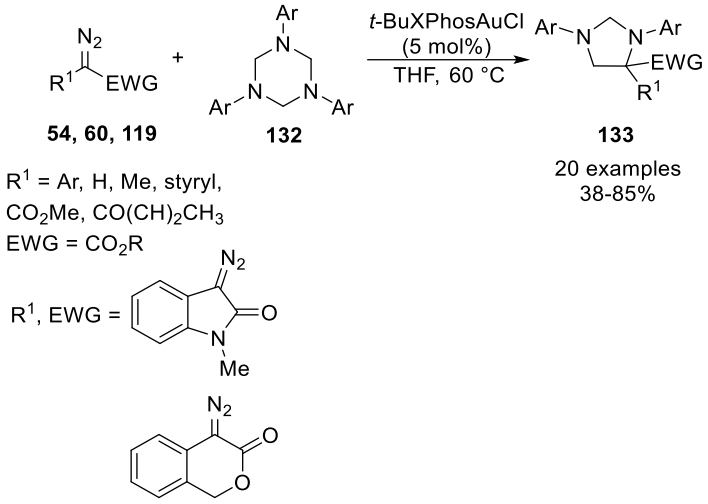
Scheme 55. Formal [4+1] cycloaddition between aryl diazo esters **54** and propargyl alcohols **126**.

Finally, aryl diazo nitriles **129** were used as arylmethine precursor in an oxidative [2+2+1] cycloaddition with 2 equivalent of imines **130** in a work of Liu and Su published in 2017.[173] The reaction was catalyzed by JohnPhosAuCl/$AgNTf_2$ (10/50 mol%) and led to the synthesis of a series of imidazolium salts **131** in moderate to good yields. The authors proposed, and supported with DFT calculations, a mechanism in which *cis*-configured imine attacked gold carbene **I** to give iminium species **II**. A second nucleophilic attack by an imine generated new iminium intermediate **III**, which lost HCN to give **IV**. 6π-Electro-cyclization of **IV** formed **V**, which after release of gold(I) and oxidation afforded the final product. A concerted-type 1,3-dipolar cycloaddition between **II** and **130** was excluded by control experiments with benzaldehyde or 1,3-acetylenedicarboxylate which fail to trap any possible 1,3-dipole intermediate (Scheme 56).



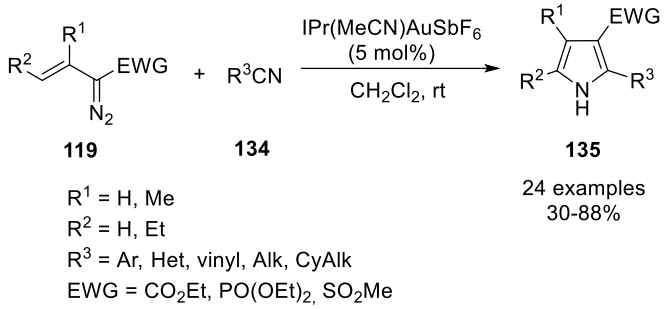
Scheme 56. Synthesis of imidazolium salts **131** by [2+2+1] cycloaddition.

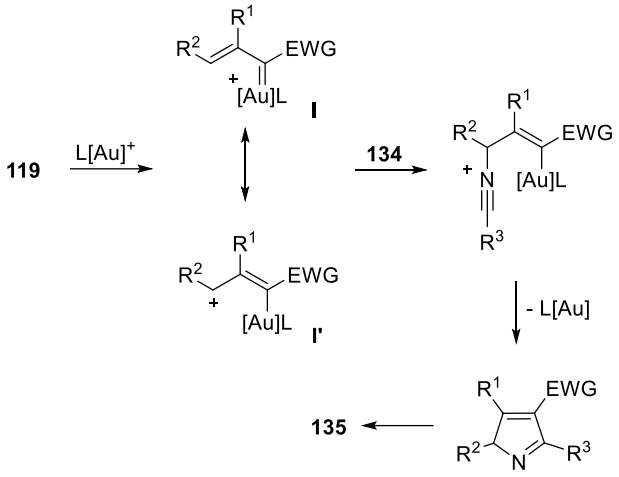
A more general approach was reported in 2016 by Sun and coworkers, which used unsubstituted, aryl and vinyl diazo carbonyl compounds **54**, **60** and **119** to synthetize imidazolines derivatives **133** by formal [4+1] cycloaddition with triazines **132**.[174] The reaction was performed with 5 mol% of *t*-BuXPhosAuCl as catalyst and efficiently proceed with all range of diazo compounds including, not only aryl diazo esters, but also alkyl diazo acetates, cyclic diazo compounds and acceptor/acceptor diazo esters. In addition, when enol diazo compounds were employed under optimized conditions with triazine **132**, it was possible to isolated seven-membered heterocycles arising by a formal [4+3] cycloaddition (Scheme 57).



Scheme 57. Formal [4+1] cycloaddition between diazo carbonyl compounds and triazines **132**.

Finally, we are pleased to report two examples of formal [3+2] cycloadditions for the synthesis of pyrroles and oxazoles starting from vinyl and oxime diazo esters in the presence of nitriles or vinyl ethers.[175,176] These reactions did not involve the formation of a new bond between the carbene carbon and a heteroatom. However, they both represent a straightforward example of transition metal catalyzed formal [3+2] cycloaddition involving simple nitriles or electronrich carbon-carbon double bond as cyclization partners. In particular, in 2013, López and coworkers described the synthesis of polysubstituted *NH*-pyrroles **135** from vinyl diazo esters **119** and nitriles **134**.[175] The regioselective reaction occurred in the presence of 5 mol% of IPr(MeCN)AuSbF$_6$ *via* formal [3+2] cycloaddition between in situ generated gold(I) vinyl carbene species **I** and nitriles **134** (Scheme 58).

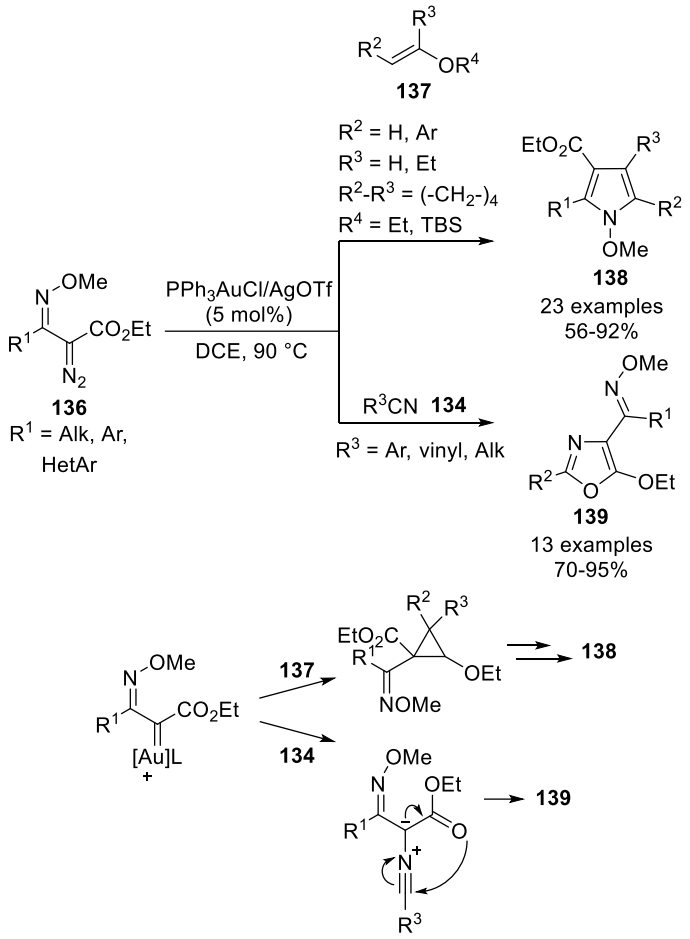




Scheme 58. Formal [3+2] cycloaddition between vinyl diazo carbonyl compounds **119** and nitriles **134**.

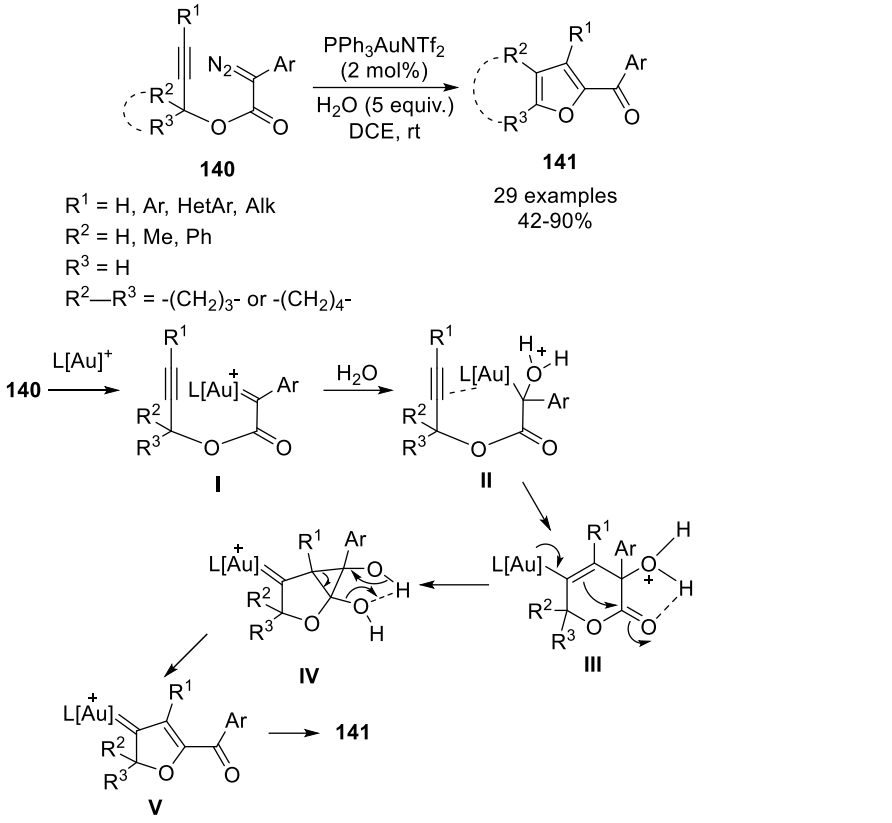
The observed regioselectivity is related to the formation of the gold vinyl carbenoid specie **I'** in which the distal vinyl carbon atom holds a positive charge and reacts with the nucleophilic nitrile nitrogen atom. Substituted aryl, heteroaryl, vinyl, alkyl and cycloalkyl nitriles are well tolerated furnishing the desired compounds in good yields.

Moreover, the group of Park studied the reaction between α-diazo oxime ethers **136** and vinyl ethers **137** or nitriles **134** in the presence of PPh_3AuOTf, generated in situ by silver abstraction from PPh_3AuCl (Scheme 59).[176] In the reaction with **137**, the gold carbene intermediate furnishes the three atoms unit and the double bond of **137** the two atoms one. The authors proposed a mechanism involving cyclopropanation followed by spontaneous ring expansion and aromatization. The reaction tolerated a broad substitution pattern both on α-diazo oxime ethers and enol ethers, affording the corresponding *N*-methoxy pyrroles **138** in high yields. On the other hands, by reacting **136**, under the same reaction conditions, with nitriles **134** instead of vinyl ethers, led to the efficient formation of a series of oxazoles **139**. The formation of oxazoles could be explained by the intermediacy of a zwitterionic species, generated by nucleophilic addition of nitrogen atom of **134** to the carbene carbon atom, which subsequently reacted with the carbonyl group of the ester to give **139** (Scheme 59).



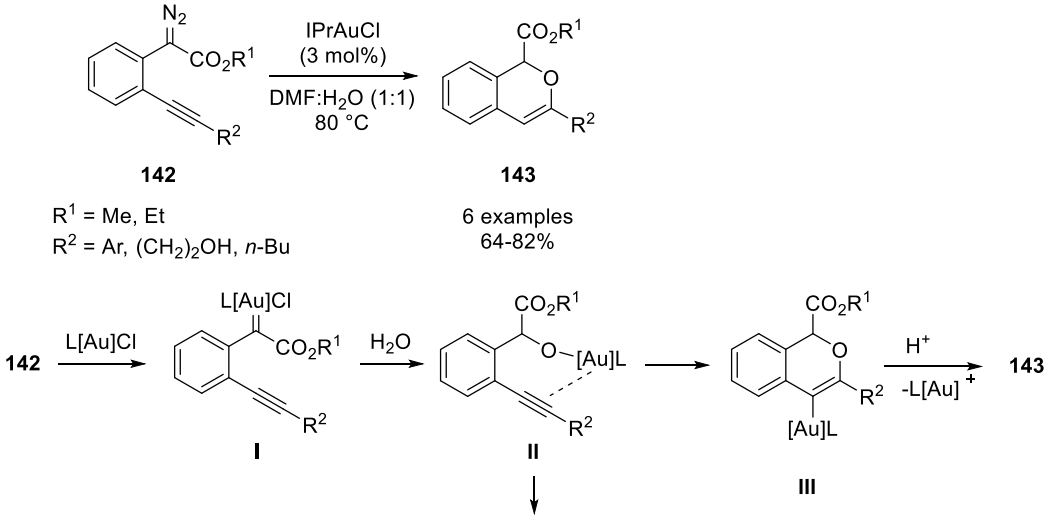
Scheme 59. Synthesis of pyrroles **138** and oxazoles **139** from α-diazo oxime ethers.

Besides intermolecular reactions also intramolecular variants for the synthesis of five-membered heterocycles were realized, as for examples in the work published in 2018 by Xu and Hu. In this case propargyl diazo acetates **140** reacted in a gold-catalyzed water-mediated carbene cascade reaction to give substituted furans **141** as products.[177] According to the proposed mechanism, carbene **I** reacted with water to form oxonium intermediate **II**, which underwent a *6-endo-dig* carbocyclization leading to **III**. Ring contraction and simultaneous H-shift delivered a second carbene intermediate (**IV**) that was converted to **V** through pinacol rearrangement. Final β-hydrogen elimination and protodeauration generated products **141** (Scheme 60).



Scheme 60. Water mediated carbene cascade reaction of propargyl diazo acetates **140** to give furans **141**.

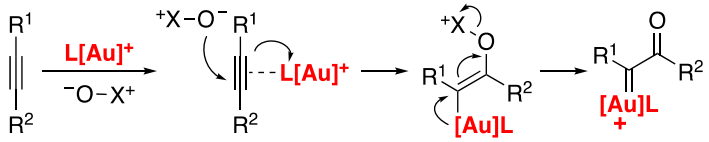
Gold carbenes generated from diazo compounds, have infrequently found application in the synthesis of 6-membered heterocyclic scaffolds. Syntheses of oxygenated species were reported, as for example in the work of Wang of 2011 on gold-catalyzed reaction of *ortho*-alkynyl phenyl diazo acetates **142** with water to afford 1-*H*-isochromenes **143**.[178] The reaction was promoted by NHC-gold(I) chloride catalyst and proceeded through generation of gold carbene **I** by diazo decomposition, followed by its insertion into the OH bond of water to give chelated intermediate **II**. 6-*endo-dig* cyclization formed **III**, which after protodeauration led to final products **143** (Scheme 61).



Scheme 61. Synthesis of 1-*H*-isochromenes **143** from ortho-alkynyl-phenyldiazo acetates **142**.

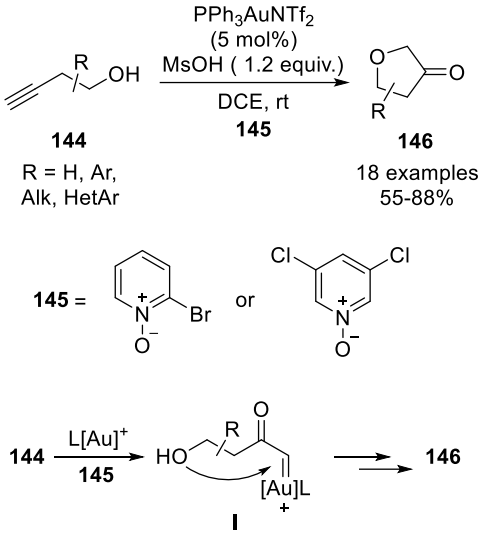
4.3. Carbenes generated from alkynes and N-oxides

The generation of α-oxo gold(I) carbene certainly represents a powerful strategy for the formation of new bonds and for cyclization reactions as demonstrated by the large number of works in which these intermediates are generated by decomposition of a diazo carbonyl species. However, this class of compounds present hazardous and potential explosivity features and the development of new safer strategies to obtain gold carbene derivatives has therefore become necessary. Among several alternatives, the employment of alkynes and stoichiometric amounts of external oxidant under gold catalysis has showed a great potential.[158,179,180] Thanks to gold(I) activation, alkyne triple bond can undergo a nucleophilic attack by the negative oxygen atom of a pyridine or quinoline *N*-oxide forming an alkenyl gold intermediate. After fragmentation of the weak O-X^+ bond, the α-oxo gold carbene is formed and can take part in different cyclization reactions with various nucleophiles (Scheme 62).



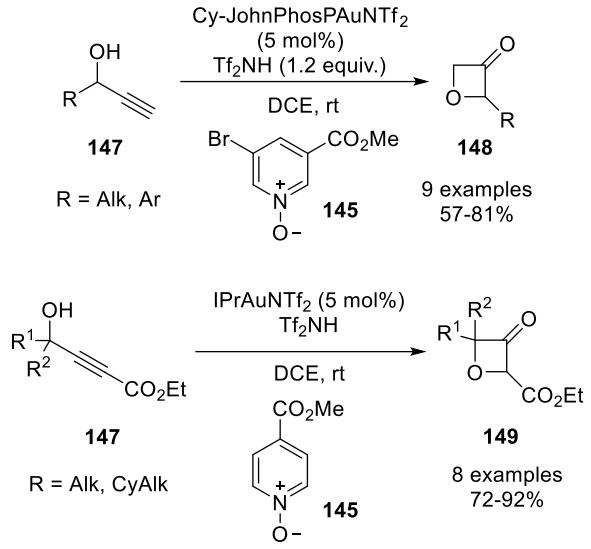
Scheme 62. Generation of a gold carbene by alkyne oxidation.

The first example of α-oxo gold carbene formation was made by Zhang and coworkers in 2010.[181] The reaction involved homopropargylic alcohol **144** and pyridine *N*-oxide **145** under PPh_3AuNTf_2 catalysis for the synthesis of dihydrofuran-3-one derivatives **146**. After the activation of the triple bond by gold(I) catalyst, the oxidation of the C2 carbon led to the formation of the gold carbene **I** that by intramolecular nucleophilic attack followed by protodeauration gave the corresponding 5-membered ring products **146** (Scheme 63).



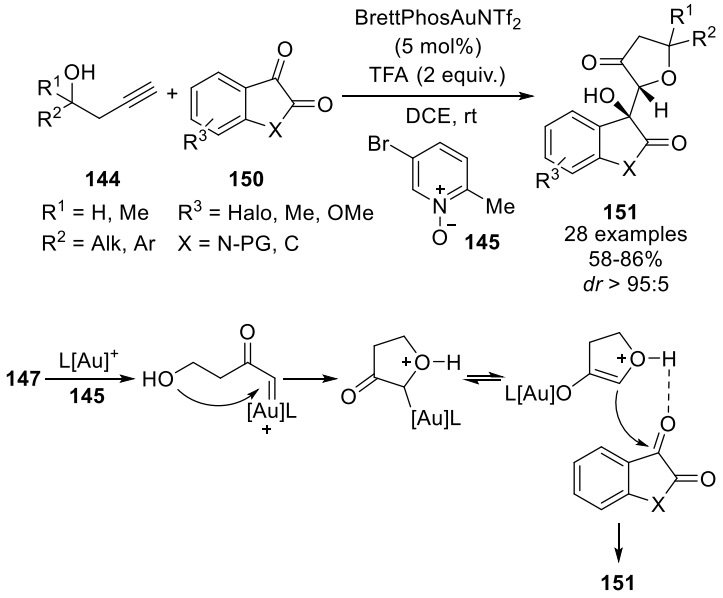
Scheme 63. Synthesis of dihydrofuran-3-ones **146** from homopropargylic alcohols **144**.

Few months later, the same group developed the synthesis of mono and poly-substituted oxetan-3-ones **148** and **149** starting from terminal or substituted propargylic alcohols **147** (Scheme 64).[182]



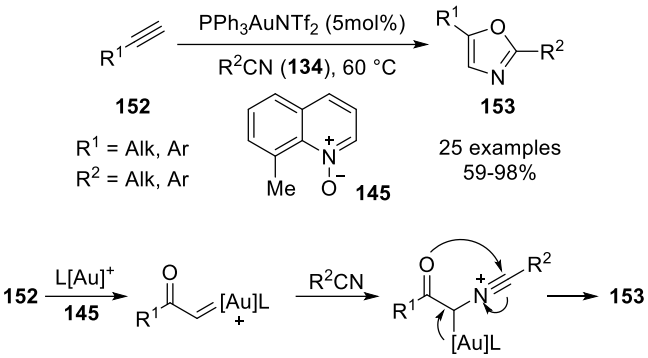
Scheme 64. Synthesis of oxetan-3-ones from propargylic alcohols.

In 2019, analogous intramolecular trapping performed on homopropargylic alcohols was employed by Xu and coworkers to prepare 3-hydroxyindoles **151** in a domino reaction involving intramolecular cyclization of the homopropargylic alcohols in the presence of isatin derivatives **150**.[183] In particular, oxonium ylide, or its enolate, generated from α-oxo gold carbene, were trapped by electrophilic isatin instead of undergoing direct proton shift thus providing products **151**. The reaction showed a broad functional group tolerance and a high diastereoselectivity probably because of the formation of a hydrogen bond between the oxygen ylide and the carbonyl group of isatin in the aldol-type addition step (Scheme 65).



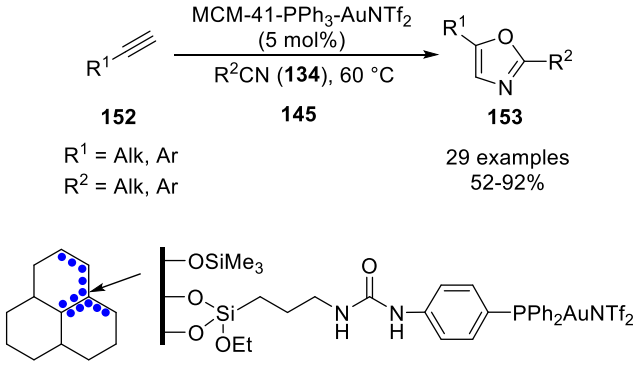
Scheme 65. Synthesis of 3-hydroxyoxindolinones **151** from homopropargylic alcohols **144** and isatins **150**.

Besides intramolecular trapping by hydroxy group of propargylic alcohols, these gold carbenes could also react with other nucleophiles such as nitriles in an intermolecular fashion. For example, in 2011, Zhang and coworkers described the first intermolecular synthesis of 2,5-disubstituted oxazoles **153** through a [2+2+1] annulation between gold carbene intermediate, generated from gold-catalyzed oxidation of terminal alkynes **152**, and a nitrile **134** (Scheme 66).[184]



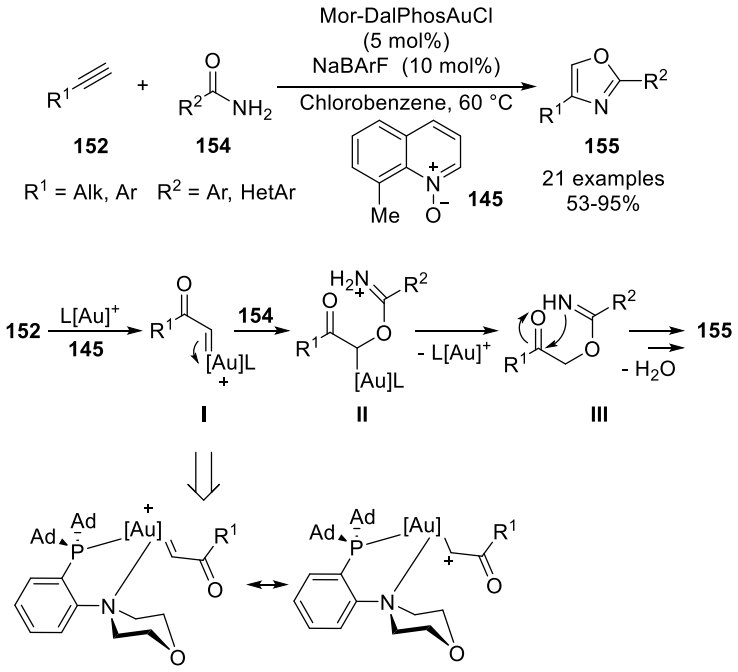
Scheme 66. Synthesis of 2,5-disubstituted oxazoles **153** from terminal alkynes **152** and nitriles **134**.

Starting from these results, in 2013, Xiang and coworkers developed the synthesis of a series of 2,5-disubstituted oxazoles with antiproliferative activities against cancer cell lines.[185] In addition, in 2017, the group of Cai expanded the scope of this transformation synthetizing 2,5-disubstituted oxazoles **153** from alkynes **152** and nitriles **134** under heterogeneous gold(I) catalysis.[186] As catalyst they employed an immobilized phosphine gold(I) complex on mesoporous MCM-41 material that showed high activity under mild reaction conditions and that could be easily remove by filtration at the end of the reaction. The reaction tolerated a wide range of functional groups, from alkyl to aryl moieties with different steric and electronic features. In addition, the authors reported that the catalyst was stable and could be recycled until eight times (Scheme 67).



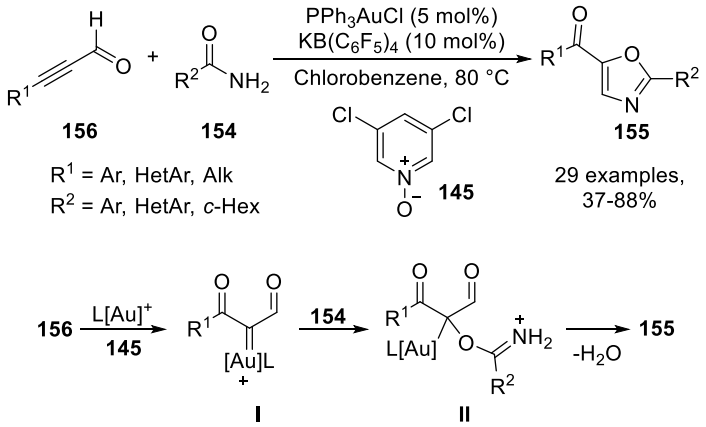
Scheme 67. Synthesis of 2,5-disubstituted oxazoles **153** from terminal alkynes **152** and nitriles **134** under heterogeneous gold(I) catalysis.

Another interesting approach for the synthesis of 2,4-disubstituted oxazoles **155** was realized by oxidative [3+2] annulation between terminal alkynes **152** and carboxamides **154** catalyzed by Mor-DalPhosAuCl/$NaBArF_4$ and developed by Zhang in 2012.[187] In this case, the α-oxo gold(I) carbene **I** underwent a nucleophilic attack by the oxygen atom of the amide forming imidate **III**, after protodeauration. Subsequently, the cyclization of intermediate **III** took place generating an oxazinol that dehydrated affording the 2,4-disubstituted oxazole. In order to explain the effectiveness of bidentate Mor-DalPhos as gold(I) ligand, the authors suggested the formation of a tri-coordinated gold center in intermediate **I**. This species should be more capable of back-donating electrons to the carbene center, rendering it less cationic and allowing the chemoselective trapping by carboxamides with high efficiency (Scheme 68).



Scheme 68. Synthesis of 2,4-disubstituted oxazoles **155** from terminal alkynes **152** and carboxamides **154**.

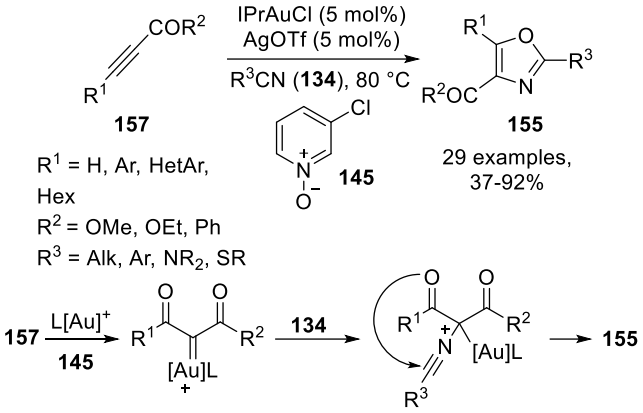
Switching from simple alkynes and alkynols to propynal, a different strategy for the synthesis of 2,5-disubstituted oxazoles **155** bearing a carbonyl substituent was studied in 2019 by Hashmi and coworkers. Thus, they employed propynal derivatives **156** and carboxamide **154** under PPh_3AuCl catalysis.[188] After the formation of intermediate **I**, the nucleophilic oxygen of the amide attacked the carbene carbon atom generating intermediate **II**. Subsequently, regioselective nitrogen nucleophilic attack on electrophilic aldehyde carbon led to 2,5 disubstituted oxazole **155** after dehydration. (Scheme 69).



Scheme 69. Synthesis of 2,5-disubstituted oxazoles **155** from propynals **156** and carboxamides **154**.

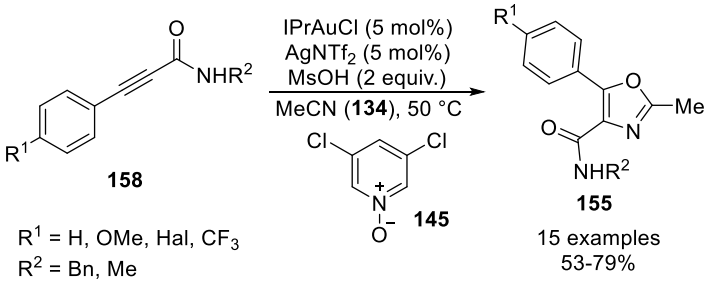
More recently several research groups developed the synthesis of trisubstituted oxazole derivatives **155**. The first example, reported in 2019 by Kukushkin and coworkers, involved the use of alkynyl ester or ketones **157**, nitrile derivatives **134** and IPrAuCl/AgOTf as catalyst.[189] It was observed that the presence of the electron withdrawing ester or keto group on the alkyne was essential to increase the electrophilicity of the α-oxo gold(I) carbene and, because of this electron-deficiency, they decided to stabilize these intermediates employing σ-donating NHC ligands instead of the most used phosphines. The reaction scope well tolerated different unsaturated, aromatic and aliphatic nitriles, but also cyanamides and thiocyanates. However, the presence of less reactive electron-deficient nitrile reduced the formation of oxazoles promoting the formation of over-oxidation by-products arising from the alkyne. On the other hand, taking into consideration the variation on the alkyne substrate, electron-withdrawing

groups presented higher yields than electron-donating ones. Moreover, heteroaryl and alkyl 3-substituted propiolates or unsubstituted methyl propiolate gave good to moderated yield (Scheme 70).



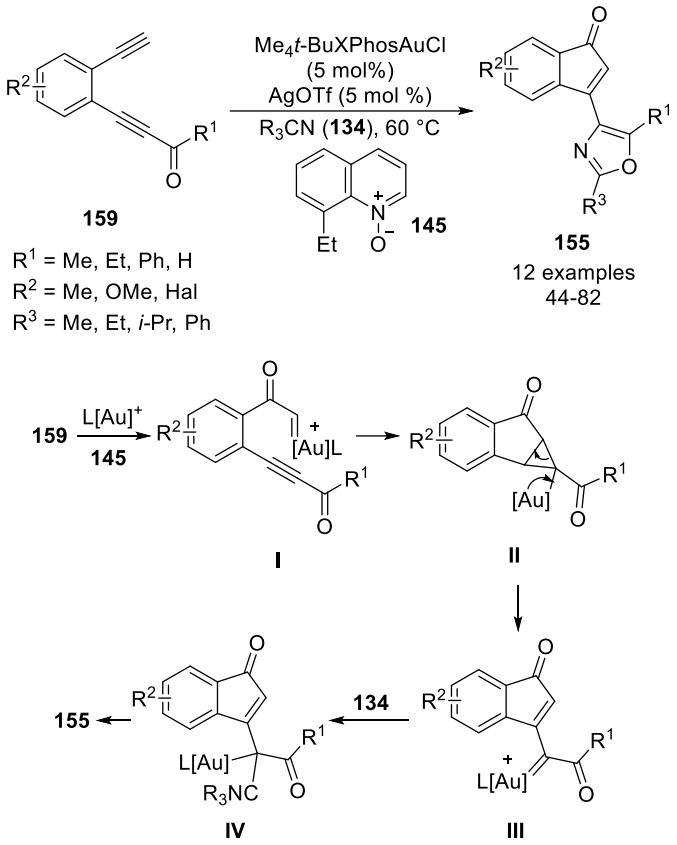
Scheme 70. Synthesis of 2,4,5-trisubstituted oxazoles **155** from alkynyl ester or ketones **157** and nitriles **134**.

Following the same strategy, in 2020 Hashmi and coworkers expanded the scope of this transformation employing alkynamides **158** instead of alkynoates **157** (Scheme 71).[190]



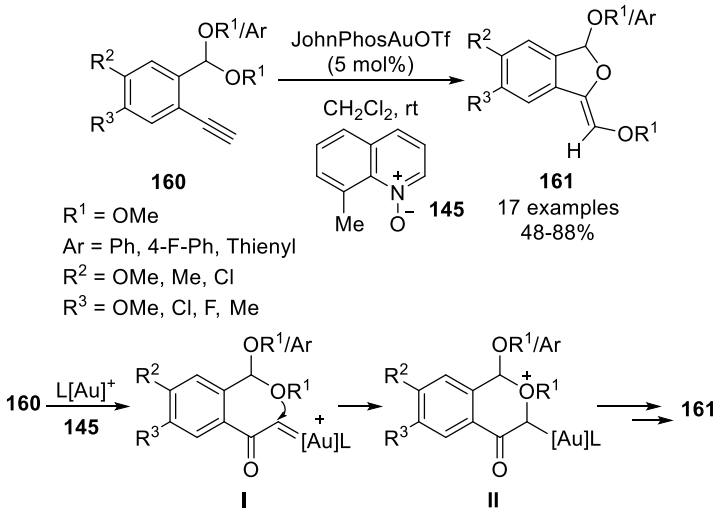
Scheme 71. Synthesis of 2,4,5-trisubstituted oxazoles **155** from alkynamides **158** and acetonitrile.

In addition, the same group developed the synthesis of 3-(oxazol-4-yl)-1*H*-inden-1-one **155**, through an intermolecular oxidative cyclization via 1,6-carbene shift, starting from diynes **159** and nitriles **134**. As mechanism the authors proposed a first formation of the α-oxo gold carbene intermediate **I** on the terminal alkyne. Subsequently an intramolecular cyclopropanation gave rise to the intermediate **II** that underwent a gold-mediated ring opening forming the second gold carbene **III**. Finally, nitrile took part in the reaction trapping the gold-carbene to obtain intermediate **IV** that after cyclization formed the desired products (Scheme 72).[191]



Scheme 72. Synthesis of 3-(oxazol-4-yl)-1*H*-inden-1-ones **155** from diynes **159** and nitriles **134**.

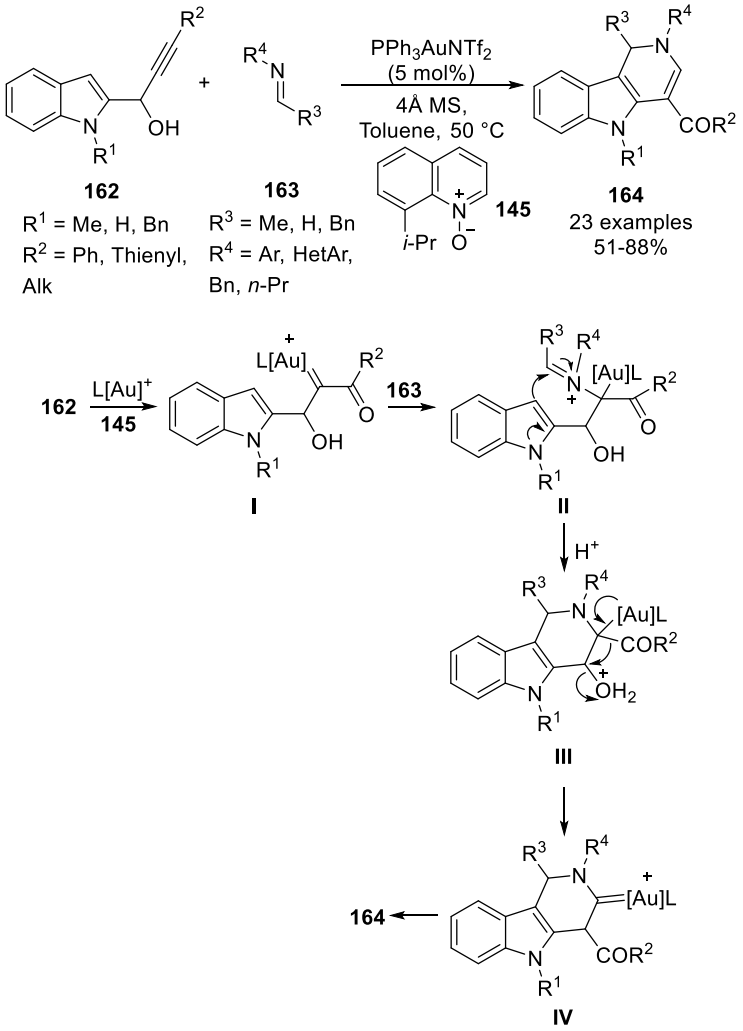
A gold-catalyzed oxidative cycloaddition reaction was used for the synthesis of 1,3-dihydroisobenzofuran derivatives **161** as described by Liu and coworkers in 2013.[192] In this work the synthesis of this class of compounds was obtained starting from alkynyl acetals or benzyl esters **160** employing JohnPhosAuOTf as catalyst under mild reaction conditions. As mechanisms, the authors suggested that after gold-mediated formation of intermediate **I**, nucleophilic attack of the alkoxy group on carbene generated intermediate **II** that evolved to give a gold enolate and then the final products **161** (Scheme 73).



Scheme 73. Synthesis of 1,3-dihydroisobenzofurans **161** from alkynyl acetals **160**.

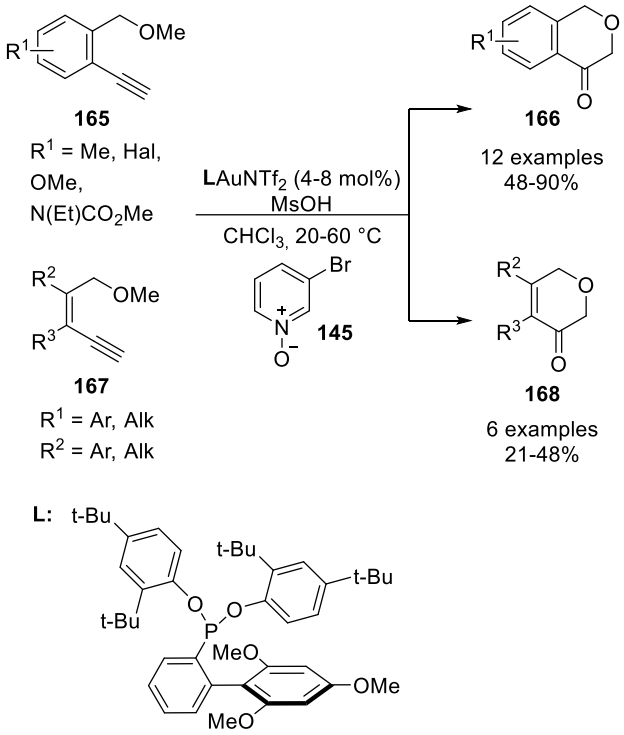
Even if less explored, also 6-membered scaffolds could be obtained applying α-oxo gold(I) carbene cyclization strategy. One of the first examples was reported by Liu and co-worker, that described the synthesis of functionalized dihydro-γ-carbolines **164** from α-(2-indolyl) propargylic alcohols **162** and imines **163** employing

PPh_3AuNTf_2 as catalyst.[193] The proposed mechanism included the formation of α-oxo gold(I) carbene **I** that underwent a nucleophilic imine nitrogen attack generating the iminium intermediate **II**. Subsequent C3 indole nucleophilic attack led to the cyclic intermediate **III**, that after gold-assisted 1,2-acyl migration (intermediate **IV**) and 1,2-H shift afforded dihydro-γ-carbolines **164** (Scheme 74).



Scheme 74. Synthesis of dihydro-γ-carbolines **164** from α-(2-indolyl) propargylic alcohols **162** and imines **163**.

Finally, in 2019 Gagosz and coworkers studied the synthesis of isochroman-4-ones **166** and 2*H*-pyran-3(6*H*)-ones **168** from *o*-alkynylbenzylethers **165** and 5-methoxypent-3-en-1-yne derivatives **167** employing a gold(I) triflimidate coordinated by a phosphonite ligand as catalyst.[194] The proposed mechanism was similar to the one reported by Zhang (Scheme 63): in fact, after the formation of α-oxo gold(I) carbene, the nucleophilic methoxy group attacked the carbene carbon atom, forming in this case a 6-member oxonium intermediate. The mesylate anion present in the reaction induced the demethylation, forming the corresponding products in moderate to high yields (Scheme 75).

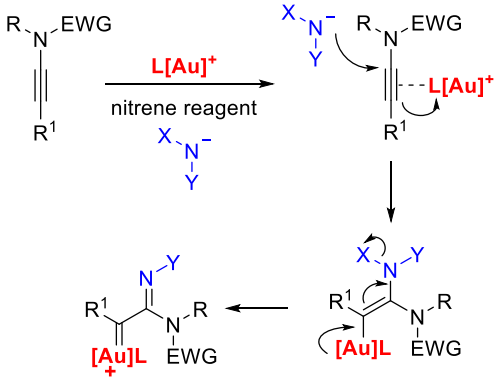


Scheme 75. Synthesis of isochroman-4-ones **166** and 2*H*-pyran-3(6*H*)-ones **168** from *o*-alkynylbenzylethers **165** and 5-methoxypent-3-en-1-ynes **167**.

4.4. Carbenes generated from ynamides and nitrogen nucleophiles

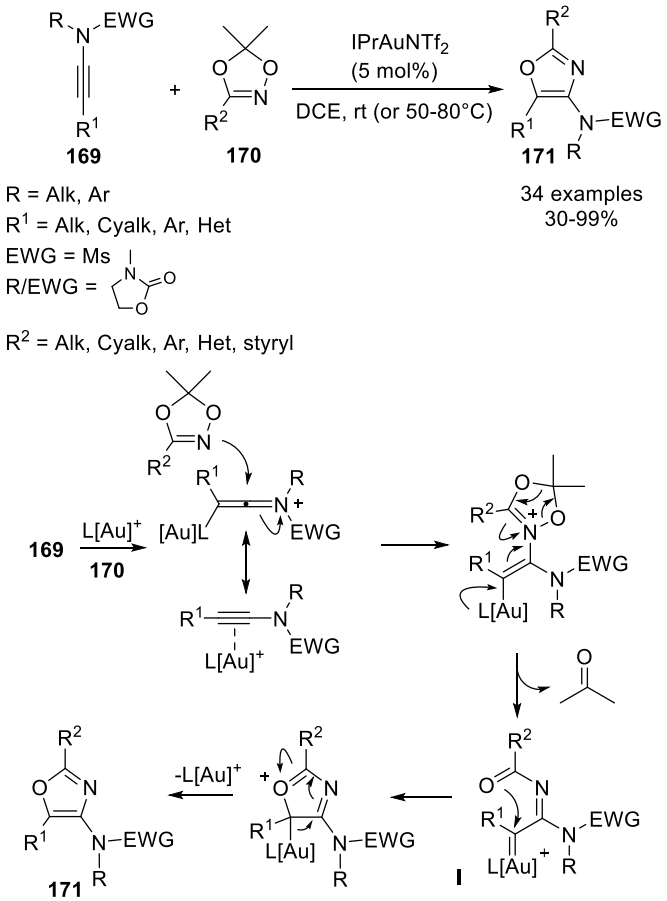
Beside α-oxo gold carbene, highly reactive α-imino gold carbenes can be generated in situ and take part in a huge array of transformation for the synthesis of aza-heterocycles.[160,161,195-197]

The generation of these intermediates can be achieved using ynamides as stable and reactive substrates and suitable nitrogen-transfer reagents even containing quite poor nucleophiles (Scheme 76).



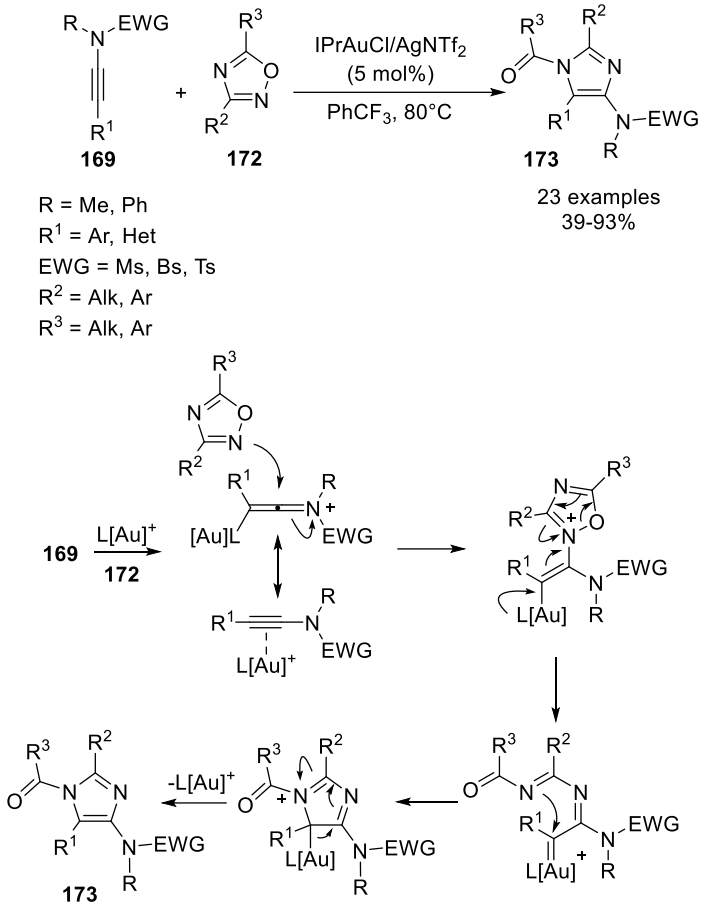
Scheme 76. Generation of α-imino gold carbenes from ynamides and nitrogen nucleophiles.

In several cases the α-imino gold carbenes generated from these precursors served as intermediates for the synthesis of heterocycles through the formation of new carbon-heteroatom bond between the carbene carbon atom and a suitable nucleophile. For example, nitrogen containing five membered heterocycles and ynamides has been involved in [3+2] annulation reactions for the synthesis of five membered azacycles. One of the first reported example disclosed the use of 1,4,2-dioxazoles **170** as nitrogen transfer reagents and ynamides **169** for the synthesis of oxazoles **171** (Scheme 77) and was reported by Liu and coworkers in 2016.[198]



Scheme 77. Synthesis of oxazoles **171** *via* α-imino gold carbene intermediacy.

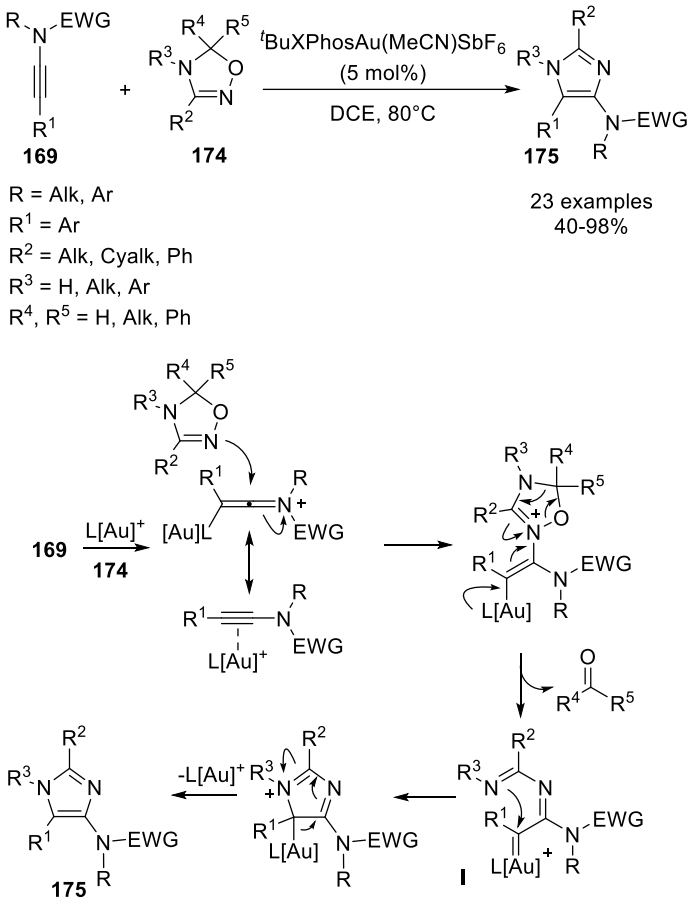
As observed by the authors, the nucleophilicity of the 1,4,2-dioxazole played a crucial role for the success of the transformation. Accordingly, dioxazole **170**, with good nucleophilic character, was essential in order to avoid the gold catalyzed self-condensation of ynamides **169**. It is worth to note that simple cationic gold(I) complexes such as JohnPhos and IPr based catalysts resulted in the isolation of the desired compounds in 72-95% yields in the model reaction using different solvents/temperatures combinations. Best results were achieved using $IPrAuNTf_2$ as catalyst in DCE at room temperature or at temperatures ranging from 50 to 80°C. The reaction sequence started with the activation of the ynamide moiety by the gold(I) catalyst with formation of a ketene iminium specie able to undergo the nucleophilic attack by the nitrogen atom of **170**. A concerted ring opening step resulted in the α-iminium gold carbene **I** with elimination of acetone. Finally, intermediate **I** gave the final product **171** by intramolecular ring closure. Almost at the same time, a conceptually equivalent work was published by Hashmi and coworkers. They developed the synthesis of *N*-acylimidazoles **173** from ynamides **169** and 1,2,4-oxadiazoles **172** (Scheme 78).[199]



Scheme 78. Synthesis of *N*-acylimidazoles **173** *via* α-imino gold carbene intermediacy.

After the nucleophilic attack of the nitrogen atom of the 1,2,4-oxadiazole **172** on the activated ynamide **169**, a ring opening- ring closing sequence resulted in the isolation of *N*-acylimidazoles **173** with 100% atom economy. As in the previous work, complete regioselectivity was observed and lower yields were detected using less nucleophilic nitrogen transfer partners such as 2-methyl or 2-(4-methoxyphenyl) oxadiazole derivatives.

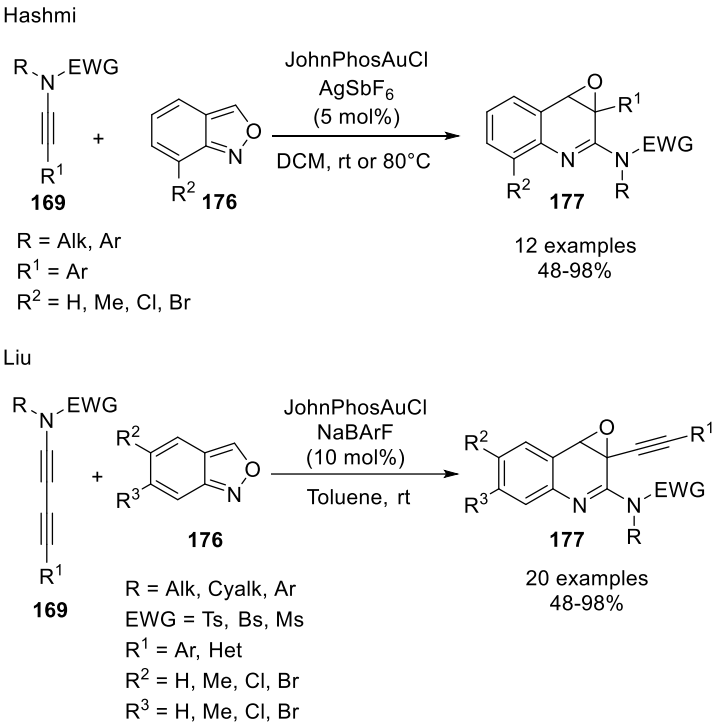
As a corollary of these two applications, which respectively used a non-aromatic heterocycle (Liu, 1,4,2-dioxazole, Scheme 77) and an aromatic heterocycle (Hashmi, 1,2,4-oxadiazole, Scheme 78), a further application reported in the same period by Liu's group, involved the use of non-aromatic 4,5-dihydro1,2,4-oxadiazoles **174** as nucleophilic partners (Scheme 79).[200] They used ynamides **169** as substrates and *t*-BuXPhosAuSbF$_6$ as catalyst for the synthesis of *N*-unsubstituted, *N*-aryl and *N*-alkylimidazoles **175**.



Scheme 79. Synthesis of *N*H, *N*-alkyl, *N*-arylimidazoles **175** via α-imino gold carbene intermediacy.

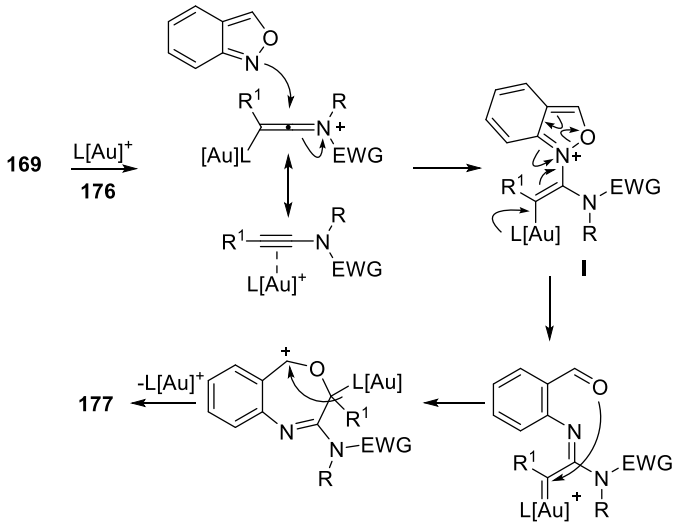
The non-aromaticity of the nucleophilic partner triggered the elimination of the O-C(R^4R^5) fragment in the dihydrooxadiazole as carbonyl derivative. The same behavior was reported in scheme 77 for the reactions with dioxazole derivatives (elimination of acetone).

Beside nitrogen containing five membered heterocycles, very inspiring papers has been recently published by Hashmi[201] and Liu[202] dealing with the use anthranils (2,1-benzisoazoles) as nitrogen transfer reagents towards ynamides. In these works, gold carbene intermediates underwent intramolecular nucleophilic attack by oxygen containing functionalities generated in situ (Scheme 80).



Scheme 80. Synthesis of quinoline derivatives **177**.

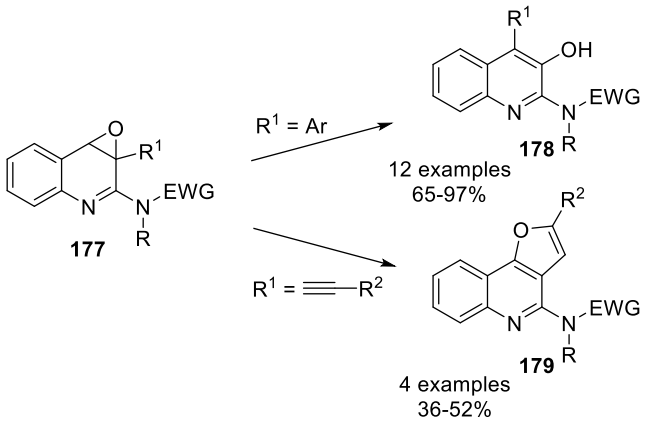
Both these reactions occur through the intermediacy of gold carbene **I** generated upon addition of the anthranil over the activated ketene iminium anion (Scheme 81).



Scheme 81. Proposed reaction mechanism for the synthesis of quinazolines **177**.

Intermediate **I** then evolved by a ring opening/ring closing event whereas final releasing of cationic gold(I) species delivered the quinoline oxides **177**.

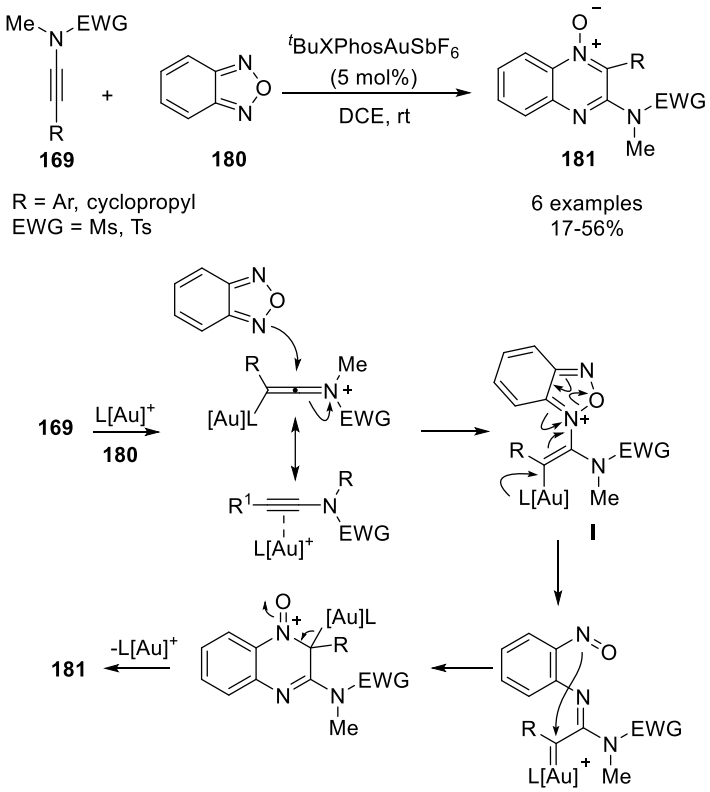
Some of these quinoline oxides underwent rearrangements under the reported reaction conditions to 3-hydroxylquinolines **178** and furoquinoline derivatives **179** depending on the substituents at the alkyne moiety (Scheme 82).



Scheme 82. Rearrangements of quinoline oxide **177**.

It is worth to underline that both works from Hashmi and Liu belong to a series of papers reporting the straightforward results of both research groups on the chemistry of gold-activated ynamides in nitrogen transfer reactions with heterocycles.[203]

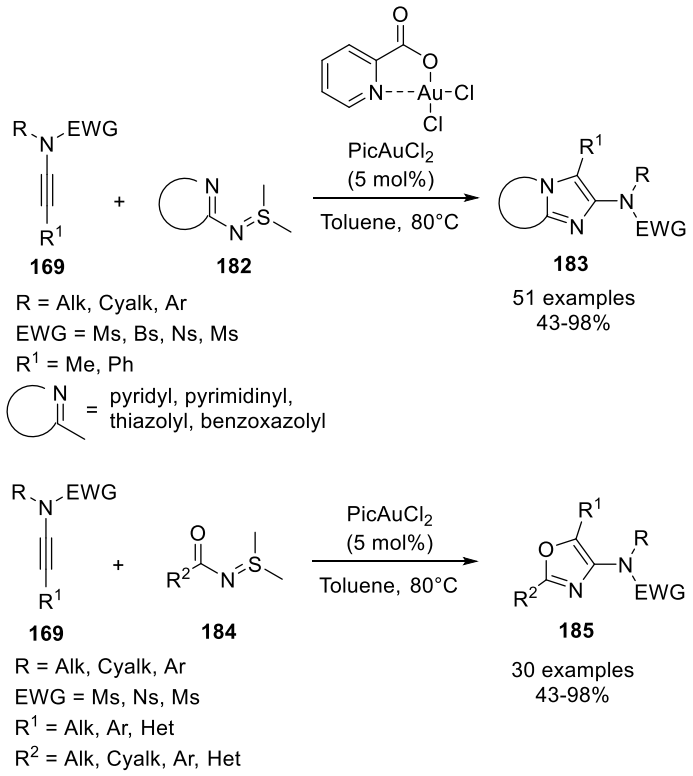
Finally, beside anthranils, benzofurazans **180** (2,1,3-benzoxadiazoles) have been reported as useful nitrogen transfer reagents for the synthesis of quinoxaline-*N*-oxides **181** in the presence of gold(I) activated ynamides (Scheme 83).[204]



Scheme 83. Synthesis and proposed reaction mechanism for the synthesis of **181**.

The reactions encompassed a [4+2] annulation pathway occurring on a gold carbene intermediate formed following the usual reaction path from activated ynamide **169** and benzofurazan **180**.

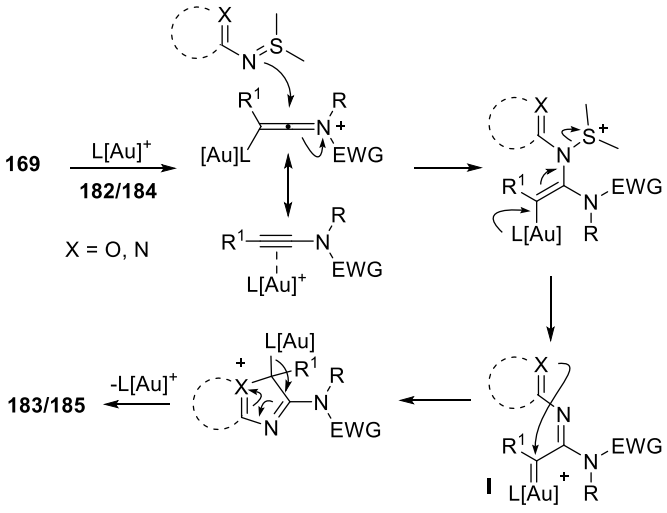
Different sources of nitrogen for the gold catalyzed reactions with ynamides have been recently reported by Hashmi and coworkers. They involved *N*-pyridinyl and *N*-acyl sulfimines **182** and **184** in gold-catalyzed formal [3+2] dipolar annulation reactions with ynamides **169** for the synthesis of 2-amino-*N*-fused imidazoles **183** and 4-aminooxazoles **185**, respectively (Scheme 84).[205,206]



Scheme 84. Sulfimines **182** and **184** as nitrogen transfer reagents in the reactions with ynamides **169**.

For both processes dimethyl sulfide is the sole and easily removable by-product. Moreover, starting sulfimines **182** and **184** are easily prepared from cheap and commercially available heteroaryl amines and amides, respectively.

The driving force triggering the formation of the imino gold carbene intermediate **I** is the elimination of a neutral molecule such as dimethyl sulphide (Scheme 85). From intermediate **I**, intramolecular ring closure followed by gold(I) elimination gave rise to 2-amino-substituted *N*-fused imidazoles **183** and 4-aminooxazoles **185**.



Scheme 85. Proposed reaction mechanism for the synthesis of **183/185**.

5. Conclusion and outlook

The review highlights the catalytic reactivity of coinage-metal carbenes involved in the synthesis of heterocyclic carbenes through the formation of new carbon-heteroatom bonds. As exemplified by the numerous examples

reported, the success of such transformation to give high molecular complexity in a single reaction relies on the peculiar chemo-, regio- and in some cases enantio-selectivity obtained fulfilling the requirements of safe and sustainable procedures.

In the case of copper, reactive carbenes are mainly generated catalytically from diazo compounds by nitrogen extrusion, and subsequent intra- or inter-molecular attack of a heteroatom nucleophile. When such process occurs in an intramolecular fashion, onium ylides are often generated and there is a commonly observed kinetic preference for the formation of five-membered cycles. Several are the pathways in which these onium ylides decompose to yield the final heterocyclic compounds, and [1,2]- or [2,3]-rearrangements are often observed, strongly dependents on the substitution pattern. If in the case of oxygen nucleophiles, the oxonium intermediates formed are very reactive and cannot be isolated, sulfonium ylides are less prone to undergo further rearrangements and can be easily handled, especially in the presence of electron-withdrawing groups on the ylide carbon. On the other hand, the stronger basic nature of nitrogen donor atoms, yielding to stable complexes with transition metals, render the use of ammonium ylides a more challenging task, but again several examples of successful intramolecular addition of especially tertiary amines to copper carbenes followed by [2,3] and in some cases Stevens type [1,2]-rearrangements have been reported.

Other examples instead include the Cu-catalyzed intramolecular insertion of the carbenoid into the X-H bond, especially in the case of X =O or N and in this case five and six membered heterocycles are formed.

Intermolecular rearrangements of onium ylides following the reaction of a copper carbenoid with a heteronucleophile represents a powerful synthetic method for the direct construction of highly functionalized heterocyclic scaffolds. In this case, the most common approach is represented by a [4+1] annulation process to give five membered rings.

However, it is quite surprising to note that examples involving the formation of copper-carbenoid *via* other methods than the diazo compounds are scarce. Since this class of compounds might present hazardous risk related to their potential explosivity features, the development of new safer alternatives might represent a future challenge that has been already implemented in the formation of gold-carbenoids.

In this latter case, the high electrophilicity of the gold-π system complexes permitted the development of methodology for the synthesis of gold carbene complexes by simple addition of oxygen and nitrogen nucleophiles to carbon-carbon triple bonds. In particular, the chemistry of the *N*-oxides addition to triple bonds and the nitrogen transfer reactions to ynamides triggered the application of gold carbenes to the synthesis of heterocycles in inter and intramolecular reactions. These reactions occur under mild reaction conditions, often at room temperature, and don't require strictly anaerobic or dry conditions. Instead, the formation of gold carbenes from less stable α-diazo carbonyl compounds is more challenging and side reactions such as dimerization and decomposition of these substrates can often occur also under mild and controlled reaction conditions. Thus, the use of these substrates requires the use of reactive reaction partners in order to drive the reactions toward the formation of addition/cyclization compounds. When these requirements are fulfilled the intermolecular reactions with suitable nitrogen or oxygen nucleophiles give rise to the almost exclusive synthesis of five membered rings. Instead, the formation of six membered cycles and intramolecular transformations are seldom been explored.

As exemplified by the examples reported, and in general looking at the chemistry of gold complexes, the development of all these reactions takes advantage also by the facile modulation of the gold center by the use of appropriate ligands.

Finally, it is our opinion that the scarcity of examples involving the use of silver carbenes is related to the few studies dedicated to the preparation of these intermediates more than to their poor reactivity. Further investigations would therefore be desirable to evaluate the complementarity and differences between the different carbenes generated in the presence of different coinage metals.

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