Organic Chemistry Frontiers

REVIEW

Gold-catalyzed heterocyclic synthesis through α-imino gold carbene complexes as intermediates

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Gold carbene complexes have been recognized as common intermediates in gold catalyzed organic synthesis. In this field, α-imino gold carbene complexes have emerged in the last years as valuable intermediates towards the synthesis of *N*-heterocycles. This review is dedicated to a comprehensive compilation of the different methodologies, arised in heterocyclic synthesis, postulating the participation of α-imino gold carbene complexes as intermediates. In addition to the scarce examples involving a direct formation from gold decomposition of α-imino diazo compounds, the use of nitrogenated nucleophiles, through an initial attack to gold activated alkynes followed by gold retrodonation and expulsion of a leaving group, constitutes the most commonly employed strategy for this target. This revision has been divided into different sections according to the type of *N*-nucleophile used, as follows: azides, aza-ylides, 2*H*-azirines, isoxazoles and derivatives, indazoles, and triazapentalenes. A large number of heterocycles, ranging from five to seven membered ring have been eficiently synthesized following this methodology.

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†Dedicated to Professor Dr. Julius Rebek, Jr. on the occasion of his 75th birthday.

Introduction

The activation of C-C multiple bonds by transition metal complexes to enhance and control their reactivity has been a long-standing strategy in organic chemistry.[1] Besides the paramount role of palladium, both late and early transitions metals have been used in either stoichiometric or catalytic conditions to promote relevant synthetic transformations involving different types of C-C multiple bonds. The usually accepted Dewar, Chatt, and Duncanson model for π-bonding in organotransition metal complexes, involving both σ and π interactions, discusses the relationship between the metal and the C-C multiple bond in donor-acceptor terms,[2,3] and has served as an inspirational source for the development of novel reactive species and synthetic strategies. More recently, in a seminal review, Fürstner and Davies defined the concept of π-acid as "any metal fragment that binds to a carbon-carbon multiple bond, and thereby deprives it of part of its electron density".[4] Therefore, by employing π-acids the corresponding C-C multiple bond is rendered more electrophilic due to net loss of electron density in the donation-retrodonation balance. In this regard, metals of several groups of the periodic table[5] and, among them, gold and other coinage metals,[6] have already shown this mode of action.

The behaviour as π-acid is extremely linked to the concept of carbophilicity, which defines the strong preference of the gold catalyst moiety for C-C multiple bonds over other functional groups present in the reactants. In the last two decades gold has been by far the most active metal in this sense, showing a special π-acid behaviour attributed to relativistic effects, because of the contraction of the 6s orbital and the expansion of the 5d orbitals.[7,8]

All species bearing C-C multiple bonds (alkenes, allenes or alkynes) may be activated by gold coordination in the initial step of the catalysis, but a higher affinity towards alkyne activation has been clearly established, so the concept alkynophilicity has also been coined to describe such behaviour.[8] Thus, when both double or triple C-C bonds are present, the reaction is usually initiated by coordination to the triple bond.

After coordination, a nucleophilic attack could take place, and crucial issues, such as regioselectivity (in all cases) and chemoselectivity (for allenes), should be addressed to achieve an effective control of the reaction (Fig. 1; *top*). Slippage of the metal moiety along the axis of the bound double or triple bond accompanies activation and results in a redistribution of the internuclear electron density upon nucleophilic attack onto the C-C multiple bond (Fig. 1; *bottom*).

Among them, alkynes have been by far the most prolific substrates for gold-catalyzed electrophilic additions, and there has been some controversy about the carbocation or

carbene nature of the intermediates partaking in such reactions.[9] Indeed, such dual character can be illustrated by the two resonant structures shown in Fig. 2, which depicts gold bound to a divalent carbon atom. Along this review the notation [Au] will be used to denote the combination of the gold atom {either Au(I) or Au(III)} and the ligand (L) employed in each case to modulate its reactivity {[Au] = Au(L)}.
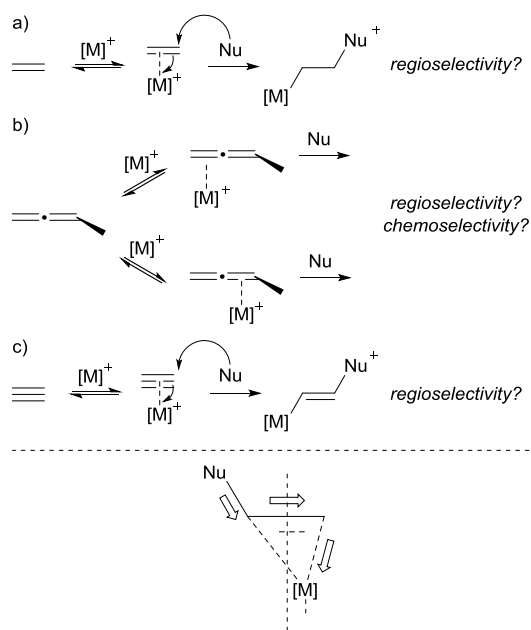

Fig. 1 Metal activation and nucleophilic addition to different C-C multiple bonds (top) and "slippage" (bottom).

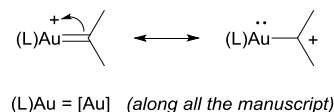(L)Au = [Au]   *(along all the manuscript)*

Fig. 2 Resonance structures which illustrate the dual carbene and carbocation character of gold bound to a divalent carbon atom.

Fürstner and Davies compared the interaction and bonding in gold(I) carbene complexes with that of group 6 Fischer carbene complexes.[4] For this type of compounds the [M]-C bond is explained by an interaction between a carbene carbon in a singlet state with σ-donation from the carbene ligand to the metal, together with a π-back donation from the metal to the ligand (Fig. 3); therefore, the pair of electrons in the π-bonding MO resides mainly on the metal, conferring electrophilic behaviour to this type of carbene complexes. Gold(I) carbene complexes are indeed electrophilic, and also thermodynamically highly stable, as they can be prepared from group 6 Fischer carbene complexes by carbene transfer.[10]
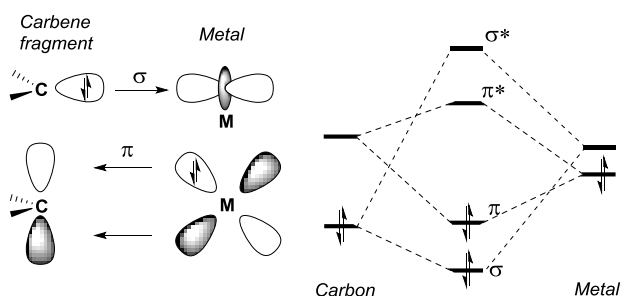
Fig. 3 Dominant orbital interactions and bonding, in Fischer carbene complexes.

More recently, based on theoretical calculations and experimental results, Goddard and Toste presented a model for the chemical bond in gold(I) carbene complexes. They concluded that three sets of orbital interactions partake in such bonding: a three-centre four-electron σ-bond, due to donation to the empty $6s$ orbital of gold from occupied orbitals at the ligand and the carbene carbon atom, and two orthogonal π-electron density back donations from filled gold $5d$ orbitals to π-acceptor orbitals in the carbene carbon atom and on the ligand (Fig. 4). As a result, they suggested "that 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".[11] The nature of the ligand and of the carbene substituents is crucial to determine the position of a given gold species in such continuum. Additionally, it should be pointed out that the bond order in gold(I) carbene complexes is typically close to one (or even less), and therefore, the [Au]=C representation is not accurate although it may be convenient mainly for mechanistic purposes.
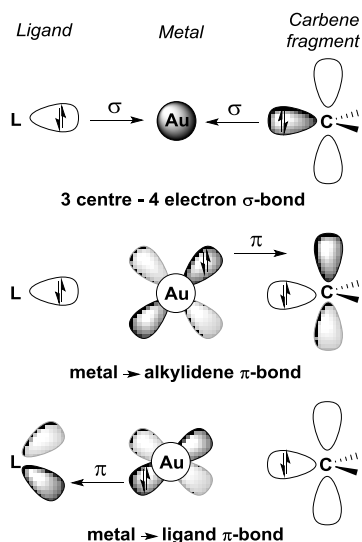

Fig. 4 Goddard-Toste bonding model for gold(I) carbene complexes.

Regarding the intermediates partaking in gold(III) catalysis the available information is more limited. Although the

reactions are initiated by alkyne coordination, only a few alkyne adducts of gold(III) have been characterized, because of their lability. Then, alkyne slippage occurs facilitating C-C triple bond polarization,[12] concomitantly to the regioselective attack of the nucleophile and formation of the gold carbene complex. Remarkably, the only example of a gold(III) carbene complex which has been isolated and characterized from a reaction of a gold(III) salt with an alkyne corresponds to a non-nitrogen-containing six-membered mesoionic species, reported by Bertrand *et al*.[13]

As stated above, both the nature of the ligand and the substituents of the divalent carbon atom will have a decisive role to determine the predominant carbocation or carbene nature of the reaction intermediates. Therefore, on the one hand, the behaviour of the gold catalyst can be sterically or electronically modulated for a specific chemical transformation by changing the ligand (employing more or less bulky ligands o switching from more electron-rich *N*-heterocyclic carbenes to less electron-rich phosphites).[14]

On the other hand, from the point of view of the reactivity, the substitution at the carbene complexes will also exert huge influence in their chemical behaviour. Thus, the presence of an electron-withdrawing group in α-position renders α-oxo and α-imino gold carbene complexes even more electrophilic (Fig. 5). In this regard, α-oxo carbene complexes can be prepared from π-alkyne gold complexes with *N*-oxides or sulfoxides, or alternatively from α-diazo carbonyl compounds with gold(I) precursors in a very efficient and general route.[15] In fact, using this strategy, a reactive tricoordinate α-oxo gold carbene complex has been isolated for the first time by Bourissou and co-workers.[16]
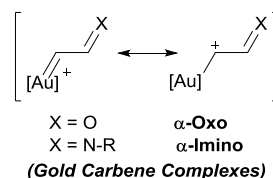

X = O   α-**Oxo**
X = N-R   α-**Imino**
(Gold Carbene Complexes)

Fig. 5 Gold Carbene Complexes bearing oxo or imino substituents at α-position.

α-Imino gold carbene complexes (αIGCCs) are less common than their oxygenated analogues, even though they display an increasingly versatile chemistry, as it will be outlined in this review. In general, the synthesis of αIGCCs involves the addition, to a gold activated alkyne, of a *N*-nucleophile where the nitrogen atom is also linked to a good leaving group (LG) by a readily labile bond. Therefore, after the addition, and under the reaction conditions, such bond undergoes breaking leading to the αIGCC species, which may evolve by different manners depending on its chemical environment to produce the final *N*-heterocycles (Fig. 6).

In a similar manner to what happens for α-oxo gold carbene complexes, an alternative route to αIGCCs has

been developed from α-diazo imino compounds with gold(I) precursors, although so far it has a more limited scope.
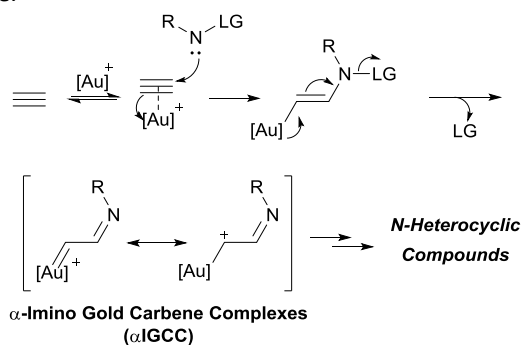
Fig. 6 General strategy for the gold catalyzed synthesis of *N*-heterocyclic compounds through the intermediacy of αIGCCs.

When comparing α-oxo and α-imino gold carbene complexes two major differences are easily perceived. First, because of structural reasons, α-oxo GCCs will produce *O*-heterocycles while α-IGCCs will form *N*-heterocycles. The second one concerns to their chemical behaviour as, because of the higher electronegativity of oxygen *vs* nitrogen, α-IGCCs are less electrophilic than their oxygenated analogs. A third but also relevant difference, that would involve both chemical behaviour and structural features, is the possibility of placing a substituent at the imino group, which would help to control and modulate the reactivity in terms of sterics and/or electronics and offer an additional point of diversity (and even of reactivity).

However, even though αIGCCs have been proposed as reactive key intermediates in many transformations and their involvement has been predicted by DFT calculations, as far as we are aware, their isolation and/or spectroscopic characterization remains elusive. This difference between α-oxo and α-imino gold carbene complexes, should be override along next years.

On the other hand, despite of the increasing attention that gold catalyzed synthesis involving αIGCCs as intermediates has received in the last years, only a thematic review focused on isoxazoles as nucleophiles[17] and a more general revision, although with scarce diffusion,[18] (both published in 2017) accompany the excellent 2015 manuscript by Davies and Garzón on this field.[19] Our intention is to fill such existing gap with a comprehensive review on this topic.

When describing the postulated mechanisms for each transformation, our attention has been focused in the proposed αIGCCs intermediates, and they have been depicted as suggested by the authors regardless of the gold(I) or gold(III) nature of the catalyst.

Our revision is completely devoted to heterocyclic chemistry, and therefore, those reactions proposed to occur through α-imino gold carbene complexes but leading to non-heterocyclic compounds are out of the scope and have not been included. Nevertheless, they may be eventually mentioned when they provide support to processes which generate heterocycles.

We have organized our manuscript attending to the type of nucleophile that reacts to the π-acid-coordinated alkyne to generate the αIGCC. A comprehensive representation of all the current approaches to αIGCCs is shown in Fig. 7, with indication of the section of this review where the reactivity of each one of those systems is described.

For the sake of simplicity and to facilitate the lecture of the manuscript, we have decided to include in Fig. 8 all catalysts and ligands that appear in the schemes, according to the order they are mentioned in text and schemes.
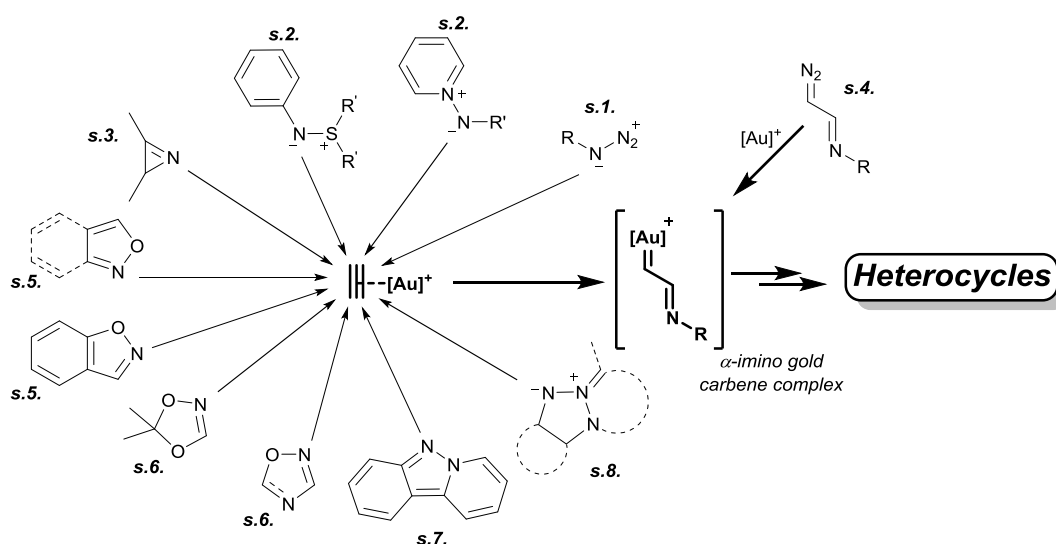
Fig. 7 General overview of nucleophiles, and α-imino diazo compounds, employed in the generation of αIGCCs, with counterclockwise indication of the section where their chemistry is covered.
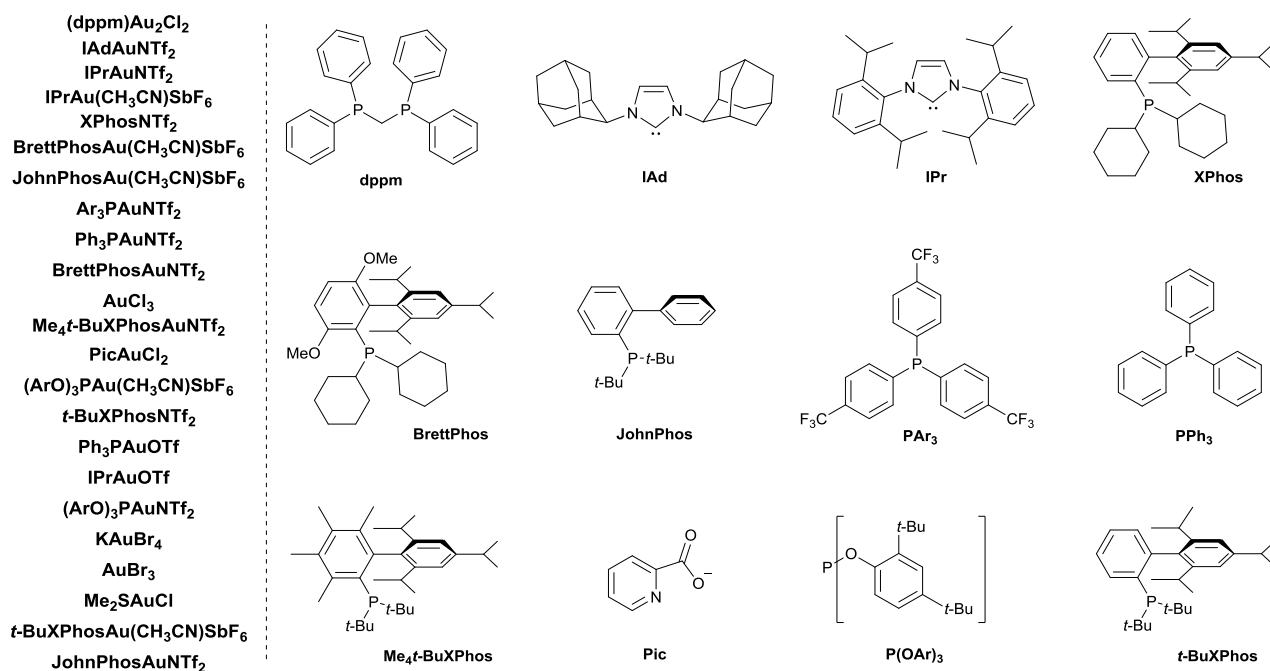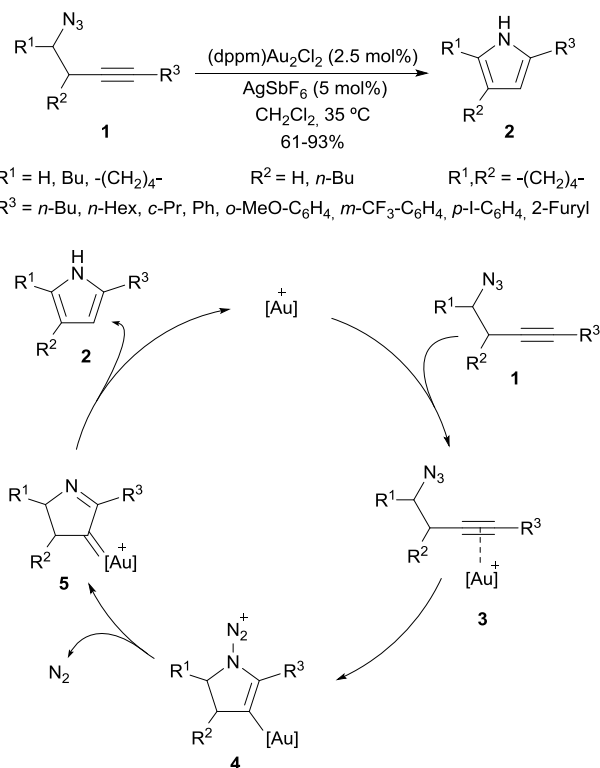
Fig. 8 Gold catalysts and ligands mentioned along the manuscript.

Results and discussion

The discussion has been divided in eight sections according to the compounds employed as α-imino gold carbene precursors.

1. From azides. Pioneering work and other contributions

The first reported example of a gold catalyzed heterocyclic synthesis, invoking the participation of α-imino gold carbene complexes, was due to Toste and co-workers in 2005.[20] In this pioneering work, the authors reported the use of homopropargyl azides **1** acting as nitrene transfer reagents (Scheme 1). Thus, the intramolecular attack of the nitrogen atom to the gold π-activated alkyne **3** would generate an alkenyl gold intermediate **4** through a *5-endo-dig* cyclization. Next, this intermediate could evolve towards the participation of an α-imino gold carbene complex **5**, as retrodonation from gold is facilitated by the expulsion of the nitrogen molecule. Finally, a 1,2-hydrogen shift, followed by a tautomerization step, could explain the formation of pyrroles **2**. This seminal result opened the door to a new catalytic field in the synthesis of nitrogenated heterocycles. However, for several years it remained as the sole example of gold catalysis following this methodology.

R^1 = H, Bu, -(CH$_2$)$_4$- R^2 = H, *n*-Bu R^1,R^2 = -(CH$_2$)$_4$-
R^3 = *n*-Bu, *n*-Hex, *c*-Pr, Ph, *o*-MeO-C$_6$H$_4$, *m*-CF$_3$-C$_6$H$_4$, *p*-I-C$_6$H$_4$, 2-Furyl

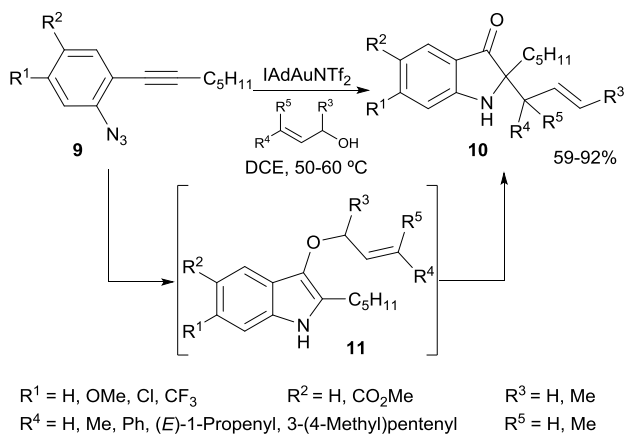**Scheme 1** First reported example and mechanistic proposal.

Later on, several examples have been reported, employing this strategy, for the use of azides in the synthesis of different families of heterocycles. Thus, Gagosz[21] and L.

Zhang[22] independently published the synthesis of indole derivatives **7** from *ortho*-alkynylphenyl azides **6** (Scheme 2). In those examples, after the formation of the proposed α-imino gold carbene complexes **8** from an intramolecular azide attack and nitrogen removal, these intermediates **8** could be captured by an external nucleophile leading to indole derivatives **7**.
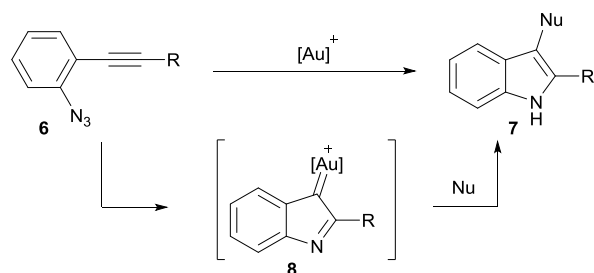

Scheme 2 General overview for the synthesis of indoles.

In this sense, Gagosz group focused its work on the addition of allylic alcohols to form indolin-3-ones **10**. Thus, the reaction could evolve, after the nucleophilic attack of the alcohol to the α-imino carbene **8**, through a gold catalyzed Claisen rearrangement from intermediate **11** (Scheme 3).

R^1 = H, OMe, Cl, CF$_3$ R^2 = H, CO$_2$Me R^3 = H, Me
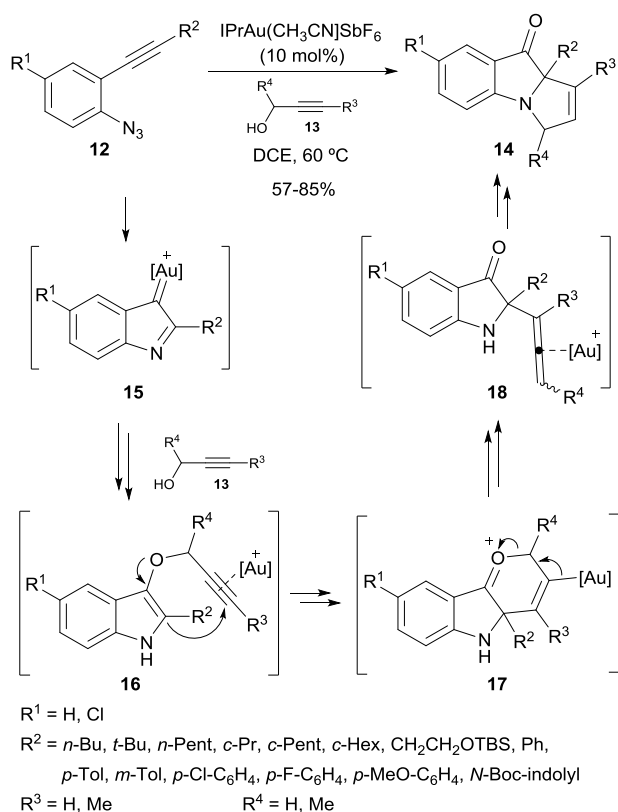R^4 = H, Me, Ph, (*E*)-1-Propenyl, 3-(4-Methyl)pentenyl R^5 = H, Me

Scheme 3 Gold catalyzed formation of indolinones **10** from alkynylphenyl azides **9**.

On the other hand, L. Zhang and co-workers employed electron-rich arenes or heteroarenes, such as xylenes, naphthalenes, anisoles, pyrroles or indoles, as carbon-nucleophiles (Scheme 4).

R = H, *n*-Bu, *t*-Bu, *c*-Pr, *c*-Pent, *c*-Hex, CH$_2$Bn, CH$_2$OBn, *p*-MeO-C$_6$H$_4$, *p*-MeO$_2$C-C$_6$H$_4$
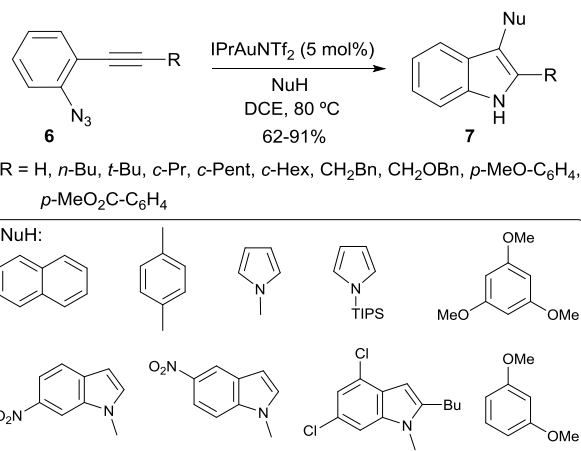
Scheme 4 Nucleophile scope for the capture of carbene intermediates.

Several other examples have been reported using 2-alkynyl aryl azides, presumably involving the participation of α-imino gold carbene intermediates, followed by their capture with diverse types of nucleophiles. In this sense, the use of propargyl alcohols **13** as nucleophiles, reported by Gong, L. Zhang and co-workers,[23] yielded a family of pyrroloindolone derivatives **14** (Scheme 5). Thus, after the intramolecular azide addition and formation of carbene intermediate **15**, this species could undergo a nucleophilic attack by propargylic alcohol **13**. Next, gold activation of the alkyne moiety could facilitate a Saucy-Marbet rearrangement on intermediate **16**,[24] followed by a gold catalyzed intramolecular hydroamination of allenyl intermediate **18**, leading to pyrroloindolones **14**.

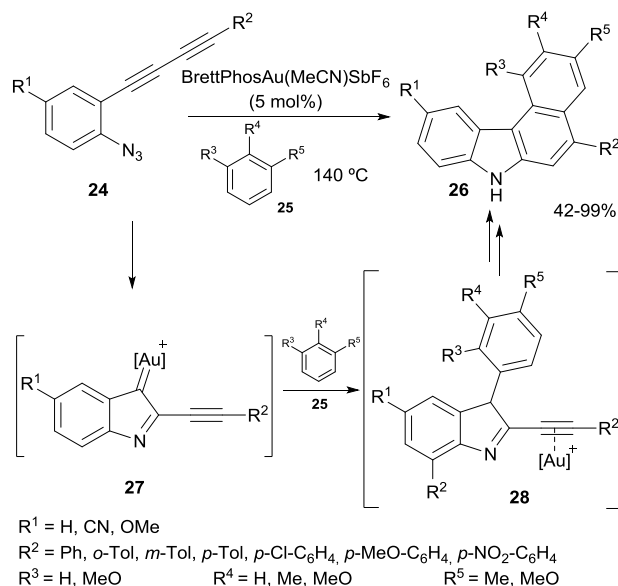**Scheme 5** Synthesis of pyrroloindolones **14**.

R^1 = H, Cl
R^2 = n-Bu, t-Bu, n-Pent, c-Pr, c-Pent, c-Hex, CH$_2$CH$_2$OTBS, Ph,
p-Tol, m-Tol, p-Cl-C$_6$H$_4$, p-F-C$_6$H$_4$, p-MeO-C$_6$H$_4$, N-Boc-indolyl
R^3 = H, Me   R^4 = H, Me

Following this methodology, the use of enantiopure (S)-3-butyn-2-ol allowed the synthesis of optically active pyrroloindolones with high enantiomeric excesses (up to >99% ee). These results indicate a high degree of chirality transfer from the propargylic alcohol to the pyrroloindolones, although low diastereoselectivity was observed.

In a similar approach, X. Zhang and Rao described the synthesis of [1,3]dioxino[5,4-b]indoles **21** invoking a formal [4+2] cycloaddition of the 3-indolylidene gold carbene intermediate **22** with an aldehyde **20** (Scheme 6).[25] The reaction presumably takes place due to the presence of an hydroxyl group in the 3-(2-azidophenyl)prop-2-yn-1-ols **19**, used as starting materials. On the other hand, the presence of electron-withdrawing groups, such as 3,5-dichloro or 3-cyano, in the phenyl ring, facilitates the reaction avoiding a competitive initial aldehyde attack to the gold activated alkyne.


R^1 = Cl, CN   R^2 = H, Cl   R^3 = H, Me
R^4 = Me, Et, n-Pr, n-C$_6$H$_{13}$, s-Bu, n-Pent-3-yl, c-C$_6$H$_{13}$,
     Cyclohex-3-en-1-yl, Ph
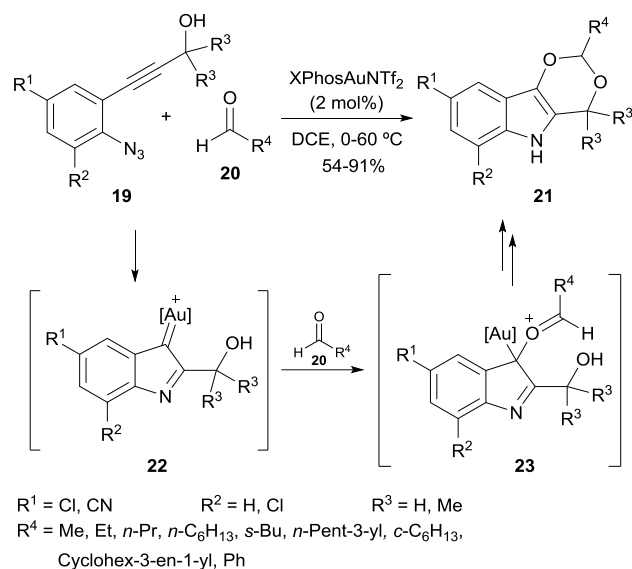
**Scheme 6** Preparation of [1,3]dioxino[5,4-b]indole derivatives **21**.

The presence of an additional triple bond in the starting materials allowed the formation of more complex heterocycles. Thus, Uchiyama, Ohno and co-workers recently reported the synthesis of annulated carbazoles using pyrroles, indoles or electron-rich arene derivatives as nucleophiles.[26] Thus, after the attack of the nucleophile to the α-imino gold carbene intermediate **27**, the reaction could evolve through a second nucleophilic attack over the gold activated alkyne **28**, yielding several types of aryl-annulated[c]carbazoles. Scheme 7 shows the reaction conditions and mechanistic proposal for the synthesis of benzene-fused carbazoles **26**. The use of other nucleophiles, such as pyrroles or indoles, also yielded good results.

R^1 = H, CN, OMe
R^2 = Ph, o-Tol, m-Tol, p-Tol, p-Cl-C$_6$H$_4$, p-MeO-C$_6$H$_4$, p-NO$_2$-C$_6$H$_4$
R^3 = H, MeO   R^4 = H, Me, MeO   R^5 = Me, MeO

**Scheme 7** Gold catalyzed access to benzofusedcarbazoles **26**

This approach has also been employed in cascades involving two consecutive intramolecular reactions of 2-alkynylphenyl azides with a nucleophile pending at the end of the alkyne functionality. In this sense, Qiu, Xu and co-workers recently reported the synthesis of a family of indole-fused derivatives **30**[27] from 2-alkynylphenyl azides **29** bearing a benzyl alcohol attached to the alkyne (Scheme 8). As a mechanistic proposal, after the initial formation of the imino gold carbene **31**, the reaction could evolve through an insertion of the carbene functionality in the O-H bond yielding tetracyclic indole derivatives **30**. In addition, this methodology has also worked satisfactorily for nitrogen or aryl nucleophiles.

R^1 = H, Me, MeO, F, Cl, Br, p-MeO-C$_6$H$_4$, Phenylethynyl
R^2 = H, Me   R^3 = H, Me, n-Bu
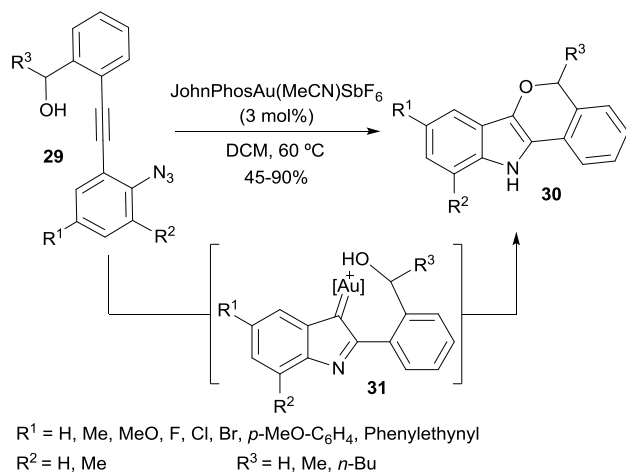
Scheme 8 O-H Insertion on carbene intermediate **31**.

Same approach was followed by Li, Ye *et al.* in the synthesis of oxazino and pyrazino indoles **33**.[28] For this purpose, phenylazides **32**, with an ynamide group at the *ortho*-position, were selected (Scheme 9). The imino carbene intermediate was captured by an heteroatom attached to the ynamide moiety, to form a new ring.
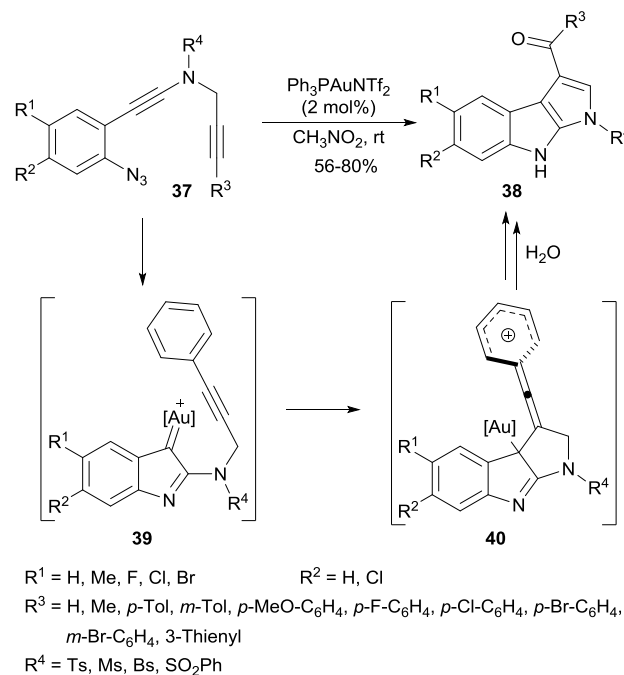

X = O, NTs   R^1 = H, Cl, Br, Me   R^2 = H, Cl, MeO
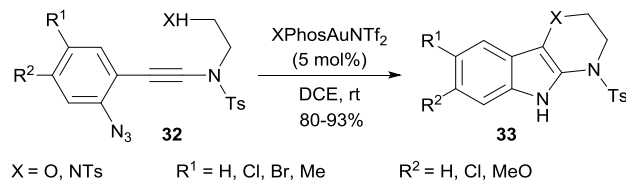
Scheme 9 Synthesis of oxazino and pyrazino indoles **33**.

Similarly, Fujui, Ohno and co-workers prepared several types of indoloquinolines[29] taking advance of the presence of different groups in the molecule, such as olefins, allylsilanes or arenes, acting as nucleophiles. Among then, it is worth to mention the intramolecular cyclopropanation, by α-imino carbenes **36**, to form polycyclic compounds **35** (Scheme 10).

Ar = p-CF$_3$-C$_6$H$_4$
R^1 = H, n-Bu, Ph
R^2 = H, n-Bu, Ph
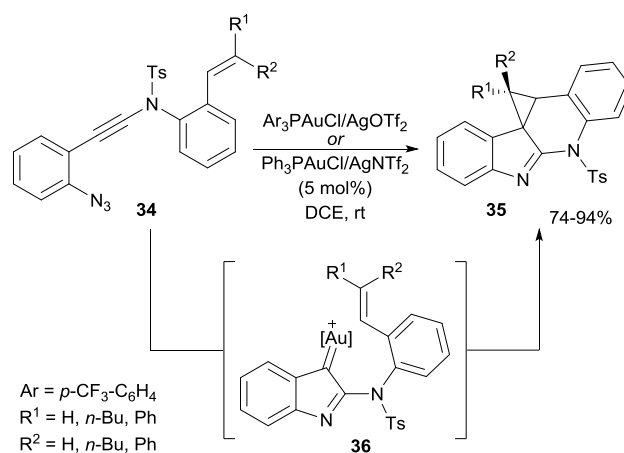
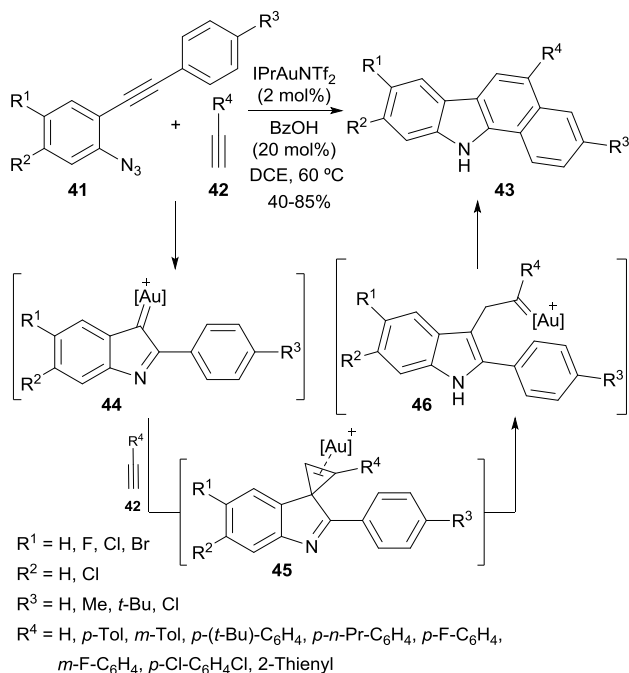**Scheme 10** Intramolecular cyclopropanation.

The use of alkynyl propargyl ynamides **37** rose in the formation of pyrrolo[2,3-*b*]indoles **38**, as it has been described by Ye *et al.*[30] (Scheme 11). The authors invoked a mechanistic proposal involving an alkyne attack to the carbene complex **39**. This evolution, which could be facilitated by the presence of an arene ring, resulted in the formation of allenyl intermediate **40**. Next, allenyl **40** would undergo a nucleophilic addition of water, yielding the pyrrolo[2,3-*b*]indole **38**.

R^1 = H, Me, F, Cl, Br   R^2 = H, Cl
R^3 = H, Me, p-Tol, m-Tol, p-MeO-C$_6$H$_4$, p-F-C$_6$H$_4$, p-Cl-C$_6$H$_4$, p-Br-C$_6$H$_4$,
          m-Br-C$_6$H$_4$, 3-Thienyl
R^4 = Ts, Ms, Bs, SO$_2$Ph

Scheme 11 Synthesis of pyrrolo[2,3-*b*]indoles **38**.

Finally, to close this part of intramolecular additions of azides to gold activated alkynes and formation of gold indolylidene intermediates, in Scheme 12 is described a result by Zhang *et al.*[31] For this reaction, the mechanistic

proposal could involve an intermolecular gold catalyzed cyclopropenation reaction. Next, gold catalyzed regioselective opening of cyclopropene intermediate **45** would result in the formation of a new gold carbene complex **46**. Finally, C-H insertion of the carbene **46** over an arene ring followed by oxidation raises in the formation of arene-fused carbazole derivatives **43**.

R^1 = H, F, Cl, Br
R^2 = H, Cl
R^3 = H, Me, *t*-Bu, Cl
R^4 = H, *p*-Tol, *m*-Tol, *p*-(*t*-Bu)-C$_6$H$_4$, *p*-*n*-Pr-C$_6$H$_4$, *p*-F-C$_6$H$_4$,
   m-F-C$_6$H$_4$, *p*-Cl-C$_6$H$_4$Cl, 2-Thienyl
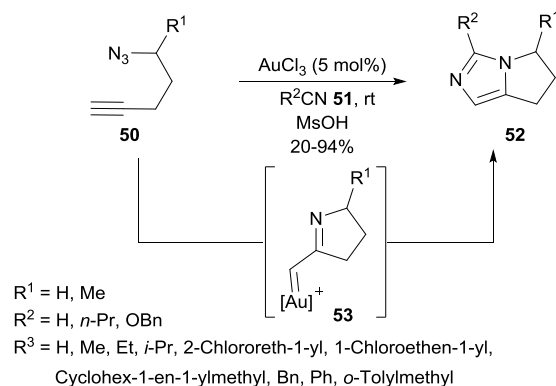
Scheme 12 Intermolecular cyclopropenation.

This methodology was also extended to the synthesis of benzofuran-fused carbazoles or 13*H*-dibenzo[*a,h*]carbazoles, in moderated yields, by the correct choice of the corresponding azides.

L. Zhang *et al.* reported in 2012 the synthesis of five membered ring heterocycles invoking a different reactive pattern in the formation of the α-imino carbene complex. Thus, the use of alkynyl azides **47**, with an additional carbon atom, resulted in the generation of dihydropyrrolizines **48** (Scheme 13).[32] The reaction would involve a gold catalyzed 5-*exo-dig* cyclization for the formation of the corresponding α-imino gold carbene intermediate **49**. Next, an intramolecular conjugated nucleophilic attack to the carbene complex would drive the reaction towards the corresponding 2,3-dihydropyrrolizines **48**.

R^1 = H, *n*-Pr R^2 = H, OBn R^3 = H, Me
R^4 = H, Me, *n*-Bu, Ph R^5 = COMe, COPh, CO$_2$Me, CO$_2$Et, SO$_2$Ph
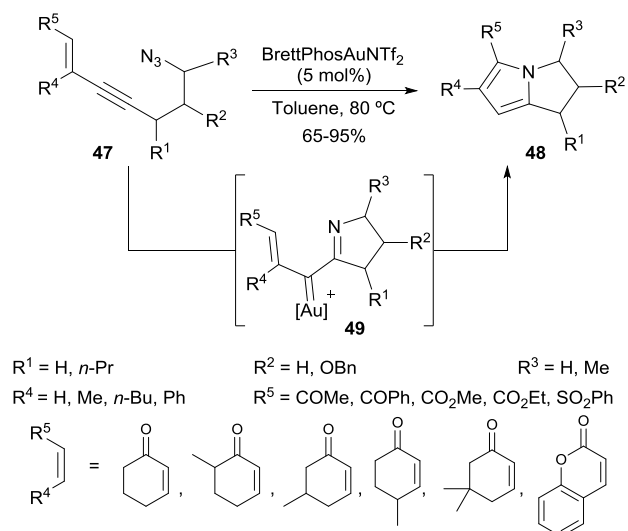
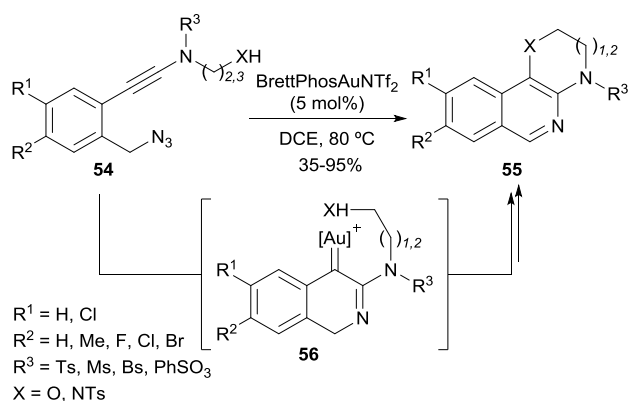Scheme 13 α-Imino gold carbene complexes from a 5-*exo-dig* cyclization.

On the other hand, the gold dihydropyrrolyl methylidene intermediate could also react in an intermolecular fashion.[33] Thus, when the gold catalyzed reaction is performed using a nitrile **51** as solvent, the α-imino gold carbene intermediate **53** could be captured by the solvent (Scheme 14). As result of the nucleophilic attack of the nitrogen atom of the nitrile, followed by a closure of the five membered ring, several pyrroloimidazoles **52** were synthesized.

R^1 = H, Me
R^2 = H, *n*-Pr, OBn
R^3 = H, Me, Et, *i*-Pr, 2-Chlororeth-1-yl, 1-Chloroethen-1-yl,
   Cyclohex-1-en-1-ylmethyl, Bn, Ph, *o*-Tolylmethyl

Scheme 14 Nitrile capture of carbene intermediate **53**.

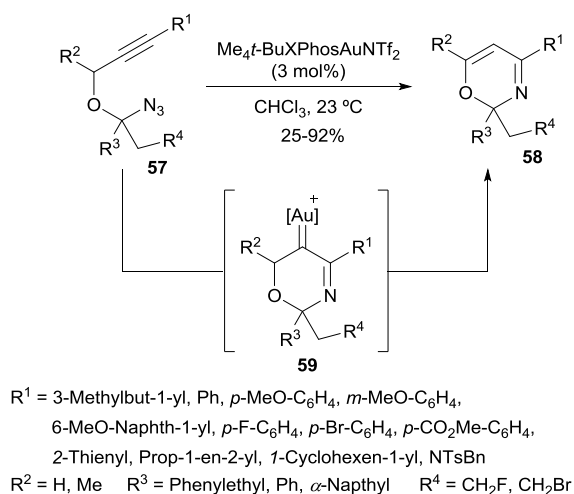In addition to α-imino gold carbene complexes supporting an indole skeleton in their structure, other heterocyclic carbene intermediates have also been described. Thus, in Scheme 15 is outlined the gold catalyzed intramolecular reaction of 2-alkynyl benzyl azides **54** to form isoquinoline derivatives **55**. In this work, reported by He, Ye *et al.*,[34] the mechanistic proposal postulates the participation of a 4-isoquinolidinylidene gold complex **56** formed through an 6-*endo-dig* cyclization. Finally, intramolecular nucleophilic attack of the alcohol or sulfonylamide moiety would drive

the reaction to the formation of the corresponding tricyclic compounds **55**.

Scheme 15 α-Imino gold carbene complexes from a 6-*endo-dig* cyclization.

In a similar approach, the group of Chiba and Gagosz reported the synthesis of oxazine derivatives **58**, presumably involving the intramolecular formation of an oxazinylidene gold complex **59** (Scheme 16).[35] Intermediate **59** would evolve towards the corresponding 2*H*-1,3-oxazine **58** by [1,2]-hydrogen migration.

R[1] = 3-Methylbut-1-yl, Ph, *p*-MeO-C₆H₄, *m*-MeO-C₆H₄,
   6-MeO-Naphth-1-yl, *p*-F-C₆H₄, *p*-Br-C₆H₄, *p*-CO₂Me-C₆H₄,
   2-Thienyl, Prop-1-en-2-yl, *1*-Cyclohexen-1-yl, NTsBn
R[2] = H, Me   R[3] = Phenylethyl, Ph, α-Napthyl   R[4] = CH₂F, CH₂Br
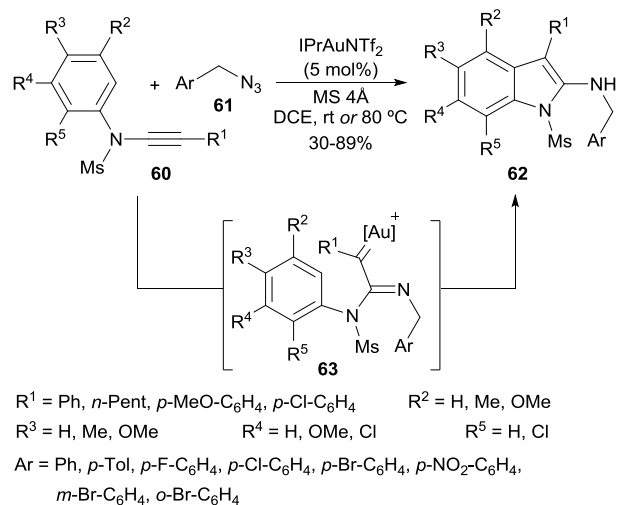
Scheme 16 Synthesis of 2*H*-1,3-oxazines **58**.

In addition to the intramolecular reactions, scarce examples have been reported to date related to the intermolecular generation of α-imino gold carbene intermediates.[36] Additionally, to the best of our knowledge, in all the examples the reaction requires the presence of highly polarized alkynes as ynamides.
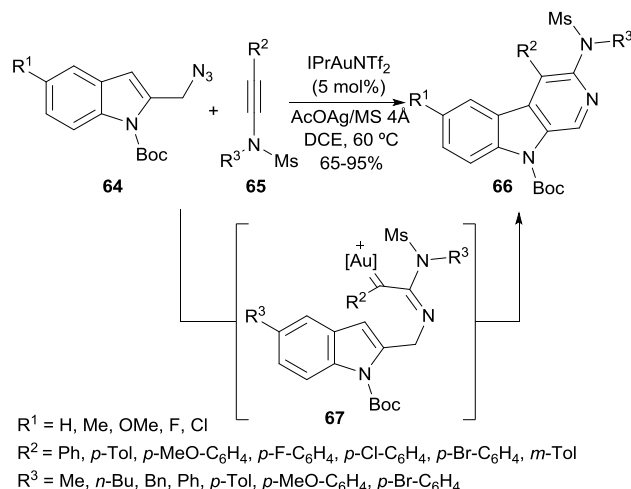
In this sense, the first reported example in this field was due to Lu, Ye *et al.* describing the synthesis of valuable heterocycles, such as indoles, from benzyl azides and *N*-phenyl ynamides.[37] As it is outlined in Scheme 17, the gold carbene intermediate **63**, which could be formed by the nucleophilic addition of benzyl azides **60** to the activated

ynamides, would react in an intramolecular fashion with the aromatic ring of the ynamides. Finally, after the corresponding C-H insertion and tautomerization steps, indoles **62** were obtained.

R[1] = Ph, *n*-Pent, *p*-MeO-C₆H₄, *p*-Cl-C₆H₄   R[2] = H, Me, OMe
R[3] = H, Me, OMe   R[4] = H, OMe, Cl   R[5] = H, Cl
Ar = Ph, *p*-Tol, *p*-F-C₆H₄, *p*-Cl-C₆H₄, *p*-Br-C₆H₄, *p*-NO₂-C₆H₄,
   m-Br-C₆H₄, *o*-Br-C₆H₄

Scheme 17 Synthesis of indoles **62** from intermolecular access to imino carbenes.
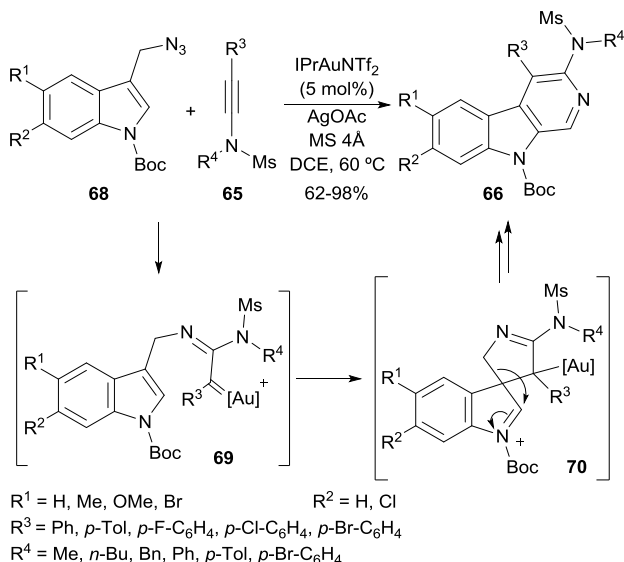
The use of indolomethyl azides **64** in their gold catalyzed reaction with ynamides **65** follows a similar behaviour and gave rise to the formation of 3-amino-β-carbolines **66**. Thus, due to the high nucleophilicity of the indole ring, the reaction would progress through the heterocyclic attack to the carbene intermediate **67**. As the result of this evolution, 3-amino-β-carboline derivatives **66** were obtained by a pathway that would imply consecutive C-H insertion and oxidation steps (Scheme 18).

R[1] = H, Me, OMe, F, Cl
R[2] = Ph, *p*-Tol, *p*-MeO-C₆H₄, *p*-F-C₆H₄, *p*-Cl-C₆H₄, *p*-Br-C₆H₄, *m*-Tol
R[3] = Me, *n*-Bu, Bn, Ph, *p*-Tol, *p*-MeO-C₆H₄, *p*-Br-C₆H₄

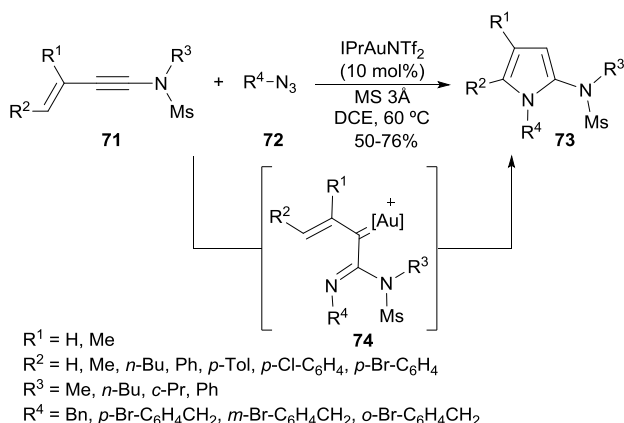**Scheme 18** β-Carboline synthesis from indolomethyl azides **64**.

Surprisingly, when the reaction was performed starting from 3-indolomethyl -instead of 2-indolomethyl- azides, 3-amino-β-carbolines **66** were also obtained (Scheme 19).[38]

To explain this result, the corresponding carbene intermediate **69** could react intramolecularly with the indole ring to form intermediate **70**. Next, a 1,2-alkyl migration from C3 to C2 of the indole skeleton of **70** should occur. Final protodeauration and aromatization steps could drive to the formation of the same β-carboline derivatives **66** as starting from the regioisomeric indoles **64**.

R^1 = H, Me, OMe, Br   R^2 = H, Cl
R^3 = Ph, p-Tol, p-F-C$_6$H$_4$, p-Cl-C$_6$H$_4$, p-Br-C$_6$H$_4$
R^4 = Me, n-Bu, Bn, Ph, p-Tol, p-Br-C$_6$H$_4$

Scheme 19 β-Carboline synthesis from regioisomeric indolomethyl azides **68**.

Finally, it is worth to mention the formation of pyrrole derivatives **73** from enynamides **71**. This research, by Lu, Ye et al.,[39] is closely related to the intramolecular version reported by other authors in 2012.[32] The proposed gold carbene intermediate **74**, similarly to complex **49** (*see Scheme 13*), could evolve through an aza-Nazarov-type reaction to the synthesis of pyrroles **73** (Scheme 20).

R^1 = H, Me
R^2 = H, Me, n-Bu, Ph, p-Tol, p-Cl-C$_6$H$_4$, p-Br-C$_6$H$_4$
R^3 = Me, n-Bu, c-Pr, Ph
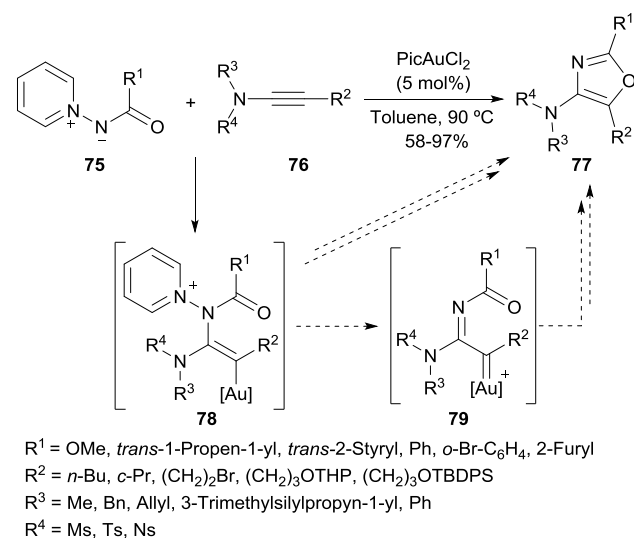R^4 = Bn, p-Br-C$_6$H$_4$CH$_2$, m-Br-C$_6$H$_4$CH$_2$, o-Br-C$_6$H$_4$CH$_2$

Scheme 20 Formal [4+1] heterocycloaddition.

2. From aza-ylides (Aminides and sulfilimines)

Azides are not the only nucleophilic compounds that can act as nitrene transfer reagents, as other nitrogenated systems have also been employed. Among then, aminides (pyridine aza-ylides) can be considered as nitrogenated analogues to pyridine oxides, widely used in reactions that postulate the participation of α-oxo gold carbene complexes.[15b,e,g-i]

The first reported example for the use of these compounds in reactions invoking the participation of α-imino gold carbene complexes was due to L. Zhang et al.,[40] although acyclic products were obtained. However, the application of this methodology in the field of the heterocyclic synthesis has been mainly developed by Davies and co-workers. In this sense, in 2011 these authors reported a gold catalyzed synthesis of oxazoles, in a formal [3+2] dipolar heterocycloaddition, from aminides and ynamides.[41] As an analogy to the proposed mechanism for the formation of α-oxo gold carbene complexes, after the nucleophilic attack of the aminide **75** to the gold activated ynamide, an α-imino gold carbene **79** could participate as intermediate (Scheme 21). Finally, an intramolecular attack from the carbonyl oxygen to the carbenic centre, could explain the formation of oxazole derivatives **77**. However, a direct 4-π ring closing electrocyclization through a synchronic mechanism, with elongation of the pyridine N-N bond before the total pyridine elimination, could not be ruled out by the authors. The reaction has also been extended to the use of ynol ethers.

R^1 = OMe, trans-1-Propen-1-yl, trans-2-Styryl, Ph, o-Br-C$_6$H$_4$, 2-Furyl
R^2 = n-Bu, c-Pr, (CH$_2$)$_2$Br, (CH$_2$)$_3$OTHP, (CH$_2$)$_3$OTBDPS
R^3 = Me, Bn, Allyl, 3-Trimethylsilylpropyn-1-yl, Ph
R^4 = Ms, Ts, Ns

Scheme 21 Synthesis of oxazoles **77** from aminides **75** and ynamides **76**.

Two years later, the same authors[42] were able to perform the reaction using electron-rich alkynes instead of ynamides. Thus, the reaction of formation of oxazole derivatives **82** could also be achieved using 3-indolyl, 4-anisolyl or 4-anilinylalkynes, species that can be able to

conjugate the heteroatom lone electron pair to the gold activated alkyne. The procedure required a bulkier gold(I) catalyst and harsh reaction conditions. As a representative example, in Scheme 22 is outlined the high yielding synthesis of 4-(3-indolyl)oxazole **82**.
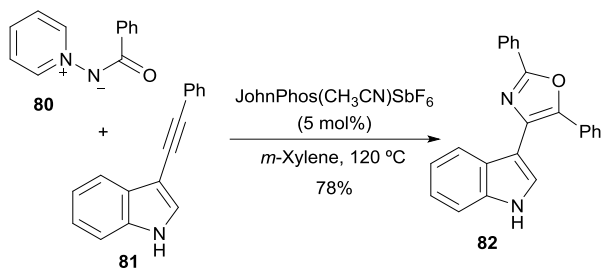

Scheme 22 3-Alkynyl indoles **81** as highly polarized alkynes in gold catalysis.

This methodology, employing *N*-nucleophilic 1,3-*N,O* dipole equivalents as acyl nitrene transfers, has been widely expanded by the authors with the publication of the synthesis of a plethora of different 4-aminooxazoles.[43] In this work, in addition to the preparation of a large number of aminides to extend the study, the influence of the ynamide substitution pattern and the aminide nature have been extensively studied. This methodology demonstrated to be tolerant with a wide number of functional groups, allowing the access to a large family of 4-aminooxazoles.

Following this strategy, alkynyl thioethers **83** also react with aminides **75** to form the corresponding 4-thiooxazoles[44] (Scheme 23). As a relevant behaviour, the reaction products were synthesized as a mixture of regioisomers, being the major oxazole **84** the regioisomer opposite to that expected and obtained in the reaction with ynamides. The formation of the major isomer could be explained, after the nucleophilic attack to the gold activated alkyne, through a stabilizing interaction between sulphur and gold atoms in intermediate **86** (Scheme 23; *bottom*).
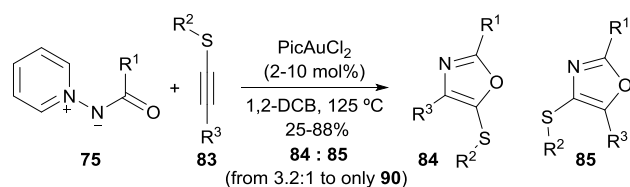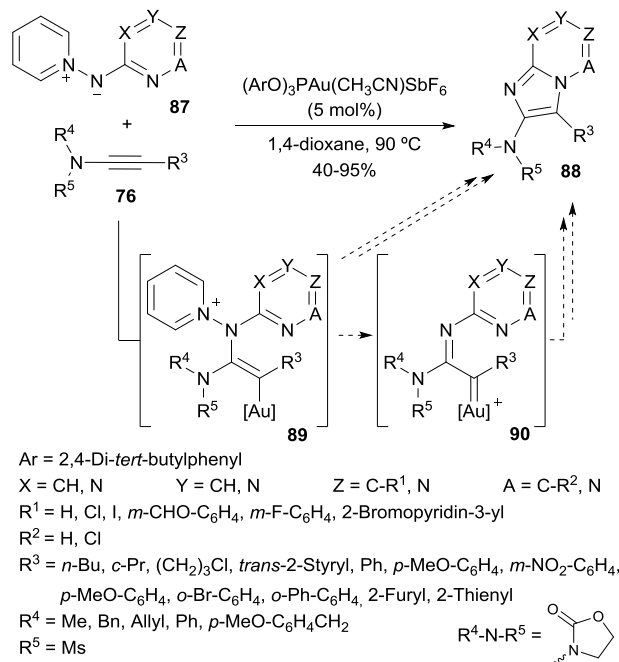

R^1 = CH(OMe)$_2$, 2-Methylethanol-2-yl, CH$_2$CO$_2$Me, Ph, *o*-Br-C$_6$H$_4$, *o*-CO$_2$Me-C$_6$H$_4$, α-Naphthyl, β-Naphthyl, 2-Furyl, NHBoc, (*S*)-1-NHBoc-2-phenyleth-1-yl, Boc,

R^2 = Me, Et, *i*-Pr, Ph, Bn

R^3 = *n*-Bu, Ph, *p*-Tol, *p*-MeO-C$_6$H$_4$, *p*-Et$_2$N-C$_6$H$_4$, 3,4-(MeO)$_2$-C$_6$H$_3$, 2,4,6-Me$_3$-C$_6$H$_2$, *N*-Tosylindol-3-yl
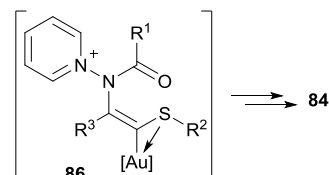
Scheme 23 Regioselective cycloaddition with alkynyl thioethers **83**.

The use aminides as nitrene transfer reagents in gold catalysis was also applied for the synthesis of other heterocycles. In this sense, the employment of pyridinium *N*-(pyridinyl or diazyl)aminides **87** as *N*-nucleophilic 1,3-*N,N* dipole equivalents, in their reaction with ynamides **76**, resulted in the formation of a family of fused imidazolopyridines and imidazolodiazines **88**.[45] The mechanistic proposal, which is outlined in Scheme 24, resembles the one previously reported for the formation of 4-aminooxazoles (*see Scheme 21*).

Ar = 2,4-Di-*tert*-butylphenyl
X = CH, N   Y = CH, N   Z = C-R^1, N   A = C-R^2, N
R^1 = H, Cl, I, *m*-CHO-C$_6$H$_4$, *m*-F-C$_6$H$_4$, 2-Bromopyridin-3-yl
R^2 = H, Cl
R^3 = *n*-Bu, *c*-Pr, (CH$_2$)$_3$Cl, *trans*-2-Styryl, Ph, *p*-MeO-C$_6$H$_4$, *m*-NO$_2$-C$_6$H$_4$, *p*-MeO-C$_6$H$_4$, *o*-Br-C$_6$H$_4$, *o*-Ph-C$_6$H$_4$, 2-Furyl, 2-Thienyl
R^4 = Me, Bn, Allyl, Ph, *p*-MeO-C$_6$H$_4$CH$_2$
R^5 = Ms

Scheme 24 Synthesis of imidazolopyridines and imidazolodiazines.

After the nucleophilic attack from the aminide **87**, intermediate **89** could evolve either through a direct ring closure in a 4π synchronic electrocyclization or be transformed into an α-imino gold carbene complex **90**, that undergoes a nucleophilic attack from the nitrogen of the pyridine or the diazine ring. A DFT study, by X. Zhang *et al.*, for the mechanism of this reaction[46] points out to a near-synchronous 4π-electrocyclization with the elimination of the pyridine ring although the carbene intermediate **96** has not been considered in the study.

The use of 3-indolyl alkynes also drives the reaction to the formation of the corresponding imidazolo-fused heterocycles.

More recently, this methodology was extended to the preparation of more complex polyfused heterocycles, such as fused imidazolo[2,1-*b*]-benzoxazoles and benzothiazoles, among others (Scheme 25).[47] These results, emerging from a careful selection of the appropriated aminides **91**, allowed the preparation of a wide variety of valuable compounds closely related structurally to biomedical active compounds. A formal [3+2] dipolar heterocycloaddition through a nitrene transfer has been again invoked by the authors.
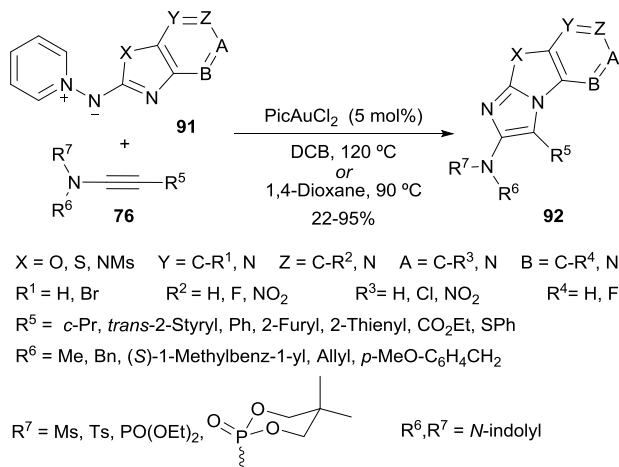
Scheme 25 Generalization of the reaction to other polyheterocycles.
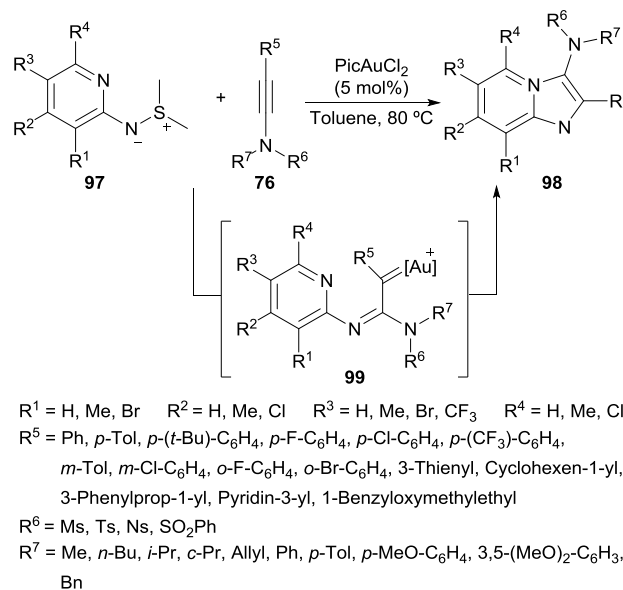
In addition to the use of pyridine aza-ylides, very recently Hashmi *et al.* reported the use of sulfur aza-ylides, such as sulfilimines **93**, as a new type of nitrene transfer reagents.[48] This work resembles the reported use of sulfonium ylides as carbene transfer reagents.[49] Following this methodology, several heterocycles could be efficiently synthesized, such as indoles **95** or bicyclic compounds **96** (Scheme 26). The mechanistic proposal implies a nucleophilic attack from the nitrogen atom of the sulfonylimide **93** to the gold activated ynamide, followed by the formation of the α-imino carbene intermediate **94** triggered by the cleavage of the dialkyl sulphide moiety. Next, carbene complex **94** could evolve

towards either the formation of indoles **95** through a C-H insertion, or the cyclopropanation of an allylic group attached to the imide.
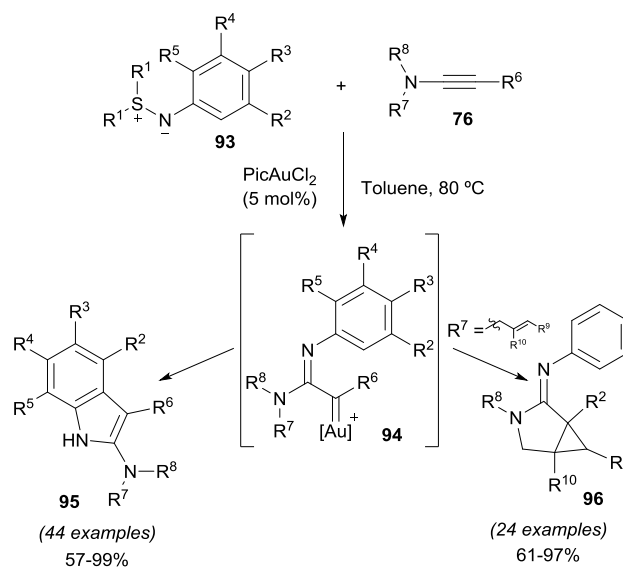
Scheme 26 α-Imino gold carbene complexes **94** from sulfilimines **93**.
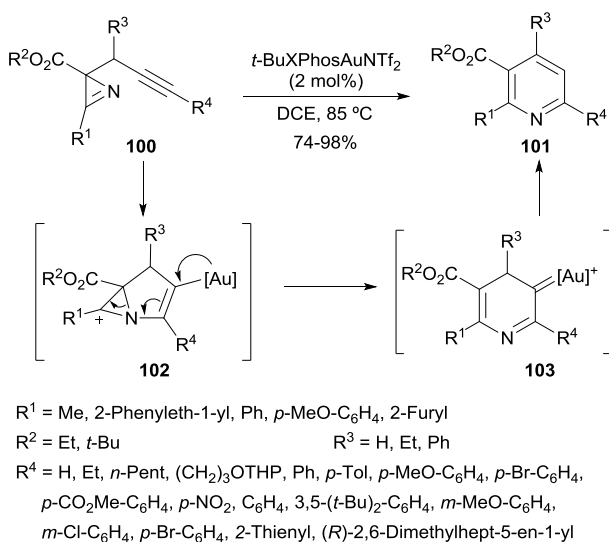
The use of pyridinyl sulfilimines, among others, allowed the same group to extend this methodology to the synthesis of imidazole fused heterocycles.[50] In this sense, in Scheme 27 it is shown the synthesis of a large family of pyridine[1,2-*a*]imidazoles **98** through the gold catalysed reaction of sulfinimines **97** and ynamides **76**. Thus, after the presumable formation of the α-imino carbene complex **99**, this intermediate could undergo a cyclization through the nucleophilic attack of the nitrogen atom of the pyridine ring to the carbene moiety, to form pyridine imidazoles **98**.

R¹ = H, Me, Br   R² = H, Me, Cl   R³ = H, Me, Br, CF₃   R⁴ = H, Me, Cl
R⁵ = Ph, *p*-Tol, *p*-(*t*-Bu)-C₆H₄, *p*-F-C₆H₄, *p*-Cl-C₆H₄, *p*-(CF₃)-C₆H₄,
    m-Tol, *m*-Cl-C₆H₄, *o*-F-C₆H₄, *o*-Br-C₆H₄, 3-Thienyl, Cyclohexen-1-yl,
    3-Phenylprop-1-yl, Pyridin-3-yl, 1-Benzyloxymethylethyl
R⁶ = Ms, Ts, Ns, SO₂Ph
R⁷ = Me, *n*-Bu, *i*-Pr, *c*-Pr, Allyl, Ph, *p*-Tol, *p*-MeO-C₆H₄, 3,5-(MeO)₂-C₆H₃,
    Bn

Scheme 27 Synthesis of imidazo[1,2-*a*]pyridines **98** from sulfilmines **97**.

3. From 2H-azirines

2H-Azirines emerged in 2014 as efficient counterparts for the synthesis of heterocycles in their reaction with gold activated alkynes. This type of reactions is invoked to involve azirines acting as nitrene transfers and α-imino gold carbene complexes as intermediates. The first reported example of this methodology was due to Gagosz et al. who described the synthesis of pyridines **101** from 2-propargyl 2H-azirines **100** (Scheme 28).[51] The mechanistic proposal for the formation of the pyridines **101** implies an initial step of intramolecular nucleophilic attack of the azirine nitrogen atom to the gold activated alkyne, to perform a 5-endo-dig cyclization leading to **102**. Next, opening of the cyclopropane ring favoured by the electron retrodonation from the gold moiety could rise to the α-imino gold carbene intermediate **103**. Finally, [1,2]-hydrogen shift and aromatization would drive the reaction to the pyridine derivatives **101**.

R^1 = Me, 2-Phenyleth-1-yl, Ph, p-MeO-C$_6$H$_4$, 2-Furyl
R^2 = Et, t-Bu   R^3 = H, Et, Ph
R^4 = H, Et, n-Pent, (CH$_2$)$_3$OTHP, Ph, p-Tol, p-MeO-C$_6$H$_4$, p-Br-C$_6$H$_4$,
    p-CO$_2$Me-C$_6$H$_4$, p-NO$_2$, C$_6$H$_4$, 3,5-(t-Bu)$_2$-C$_6$H$_4$, m-MeO-C$_6$H$_4$,
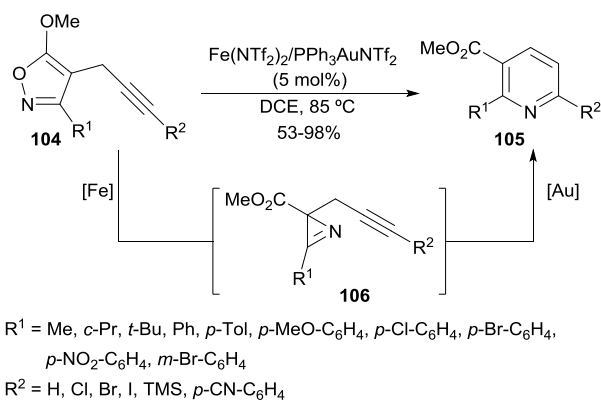   m-Cl-C$_6$H$_4$, p-Br-C$_6$H$_4$, 2-Thienyl, (R)-2,6-Dimethylhept-5-en-1-yl

Scheme 28 Intramolecular pyridine synthesis from propargyl azirines **100**.

Other mechanistic proposals, without participation of the carbene complex **103**, could be envisaged. In this sense, an almost concerted three membered ring fragmentation and [1,2]-hydrogen migration has also been considered by the authors. The reaction mechanism for this synthesis was explored by a DFT study by Wu, Zhao et al.[52] These authors analyzed the two mentioned reaction pathways together with other alternatives. As the result of the computational study, the sequential pathway involving the α-imino gold carbene intermediate **103** seemed to be the energetically more favoured one.
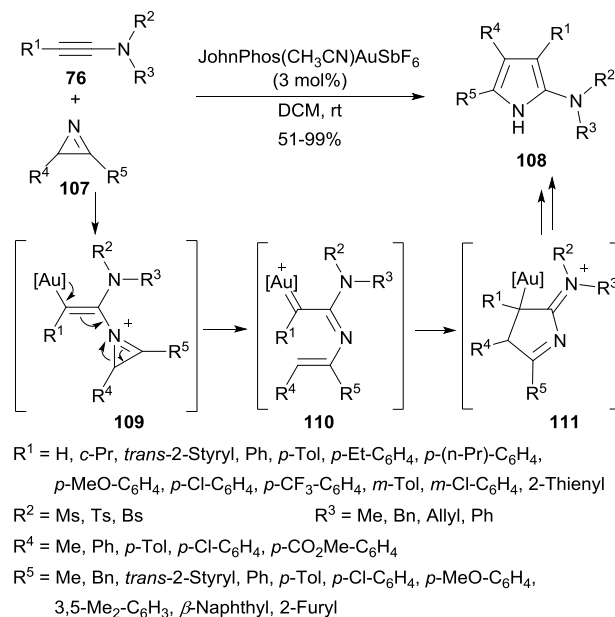
A similar reaction of formation of pyridine derivatives **105**, initiated by an intramolecular reaction of homopropargyl azirines, was reported by Khlebnikov et al.[53] (Scheme 29). In this work, the procedure involves a double iron and gold

catalysis as the propargyl azirine **106** was in situ synthesized from propargyl isoxazoles **104** in an iron catalyzed process.
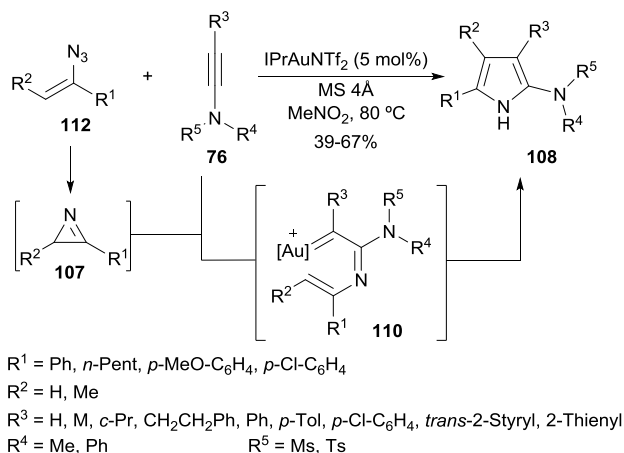

R^1 = Me, c-Pr, t-Bu, Ph, p-Tol, p-MeO-C$_6$H$_4$, p-Cl-C$_6$H$_4$, p-Br-C$_6$H$_4$,
    p-NO$_2$-C$_6$H$_4$, m-Br-C$_6$H$_4$
R^2 = H, Cl, Br, I, TMS, p-CN-C$_6$H$_4$

Scheme 29 Double iron-gold catalysis.

Huang and co-workers published the first intermolecular version of this reaction[54] using highly polarized alkynes, such as ynamides, as counterparts. Thus, the reaction of 2H-azirines **107** with ynamides **76** resulted in the formation, under mild conditions, of 2-aminopyrroles **108** in a formal [3+2] gold catalyzed cycloaddition. The mechanistic proposal is outlined in Scheme 30 and it is initiated by an attack from azirine **107** to the gold activated ynamide, to form alkenyl gold intermediate **109**. Next, intermediate **109** could evolve through the formation of the α-imino gold carbene complex **110**, favoured by the electronic back donation from the gold complex and the opening of the three membered ring. Finally, cyclization, protodeauration and aromatization steps would give rise to 2-amino pyrroles **108**.

R^1 = H, c-Pr, trans-2-Styryl, Ph, p-Tol, p-Et-C$_6$H$_4$, p-(n-Pr)-C$_6$H$_4$,
    p-MeO-C$_6$H$_4$, p-Cl-C$_6$H$_4$, p-CF$_3$-C$_6$H$_4$, m-Tol, m-Cl-C$_6$H$_4$, 2-Thienyl
R^2 = Ms, Ts, Bs   R^3 = Me, Bn, Allyl, Ph
R^4 = Me, Ph, p-Tol, p-Cl-C$_6$H$_4$, p-CO$_2$Me-C$_6$H$_4$
R^5 = Me, Bn, trans-2-Styryl, Ph, p-Tol, p-Cl-C$_6$H$_4$, p-MeO-C$_6$H$_4$,
    3,5-Me$_2$-C$_6$H$_3$, β-Naphthyl, 2-Furyl

Scheme 30 Intermolecular reaction between 2H-azirines **107** and ynamides **76**.

A few months later, R.-S. Liu and co-workers[55] described the use of vinyl azides **112**, in their gold catalyzed reaction with ynamides **76**, for the synthesis of pyrrole derivatives **108** (Scheme 31). Although, an azide derivative was used as starting material, the presumable formation of the α-imino carbene intermediate **110**, would occur through a previous transformation of the vinyl azide **112** into 2*H*-azirine **107**, which would attack to the gold activated ynamide. Finally, evolution from the carbene intermediate would explain the formation of the 2-aminopyrroles **108**. Similar results were also published afterwards by Huang *et al.*[56]

R[1] = Ph, *n*-Pent, *p*-MeO-C₆H₄, *p*-Cl-C₆H₄

R^1 = Ph, *n*-Pent, *p*-MeO-C₆H₄, *p*-Cl-C₆H₄

R[2] = H, Me
R[3] = H, M, *c*-Pr, CH₂CH₂Ph, Ph, *p*-Tol, *p*-Cl-C₆H₄, *trans*-2-Styryl, 2-Thienyl
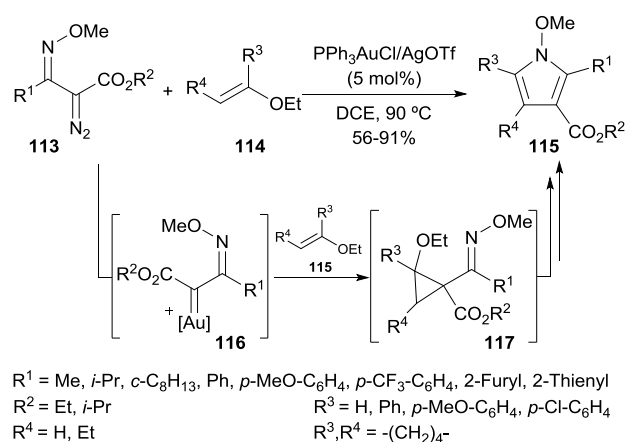R[4] = Me, Ph   R[5] = Ms, Ts

Scheme 31 Synthesis of pyrroles **108** from alkenyl azides **112**, via 2*H*-azirine **107**.

Interestingly, the presence of electron-donating groups, such as methyl or methoxy, in the aromatic ring of the ynamides, allows the formation of benzoazepine derivatives, in a formal [4+3] heterocyclization, although a carbene intermediate is not postulated.[55]
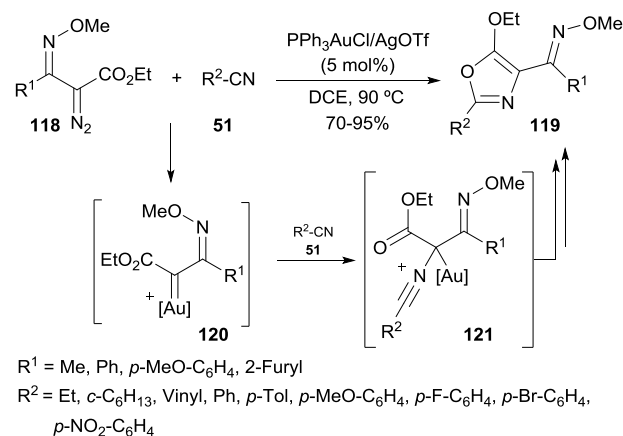
4. From decomposition of diazo compounds

The decomposition of diazo compounds in synthetic procedures involving the participation of α-oxo gold carbene complexes has been widely extended.[15c,d,f] However, in this field, to the best of our knowledge, a single result by Park *et al.*[57] has described their nitrogenated analogues, the α-imino gold carbenes, as intermediates. Taking advantage of this methodology two families of five membered ring heterocycles have been synthesized, through formal [3+2] gold catalyzed cycloadditions, and invoking the participation of the same type of carbene intermediate. Thus, in Scheme 32 the synthesis of pyrroles **115**, from α-diazo oxime ethers **113** and enol ethers **114**, is described. The mechanistic proposal could involve, in addition to the gold decomposition of the diazo compound, a cyclopropanation reaction followed by the ring expansion of the cyclopropyloxime intermediate **117** and aromatization.

R^1 = Me, *i*-Pr, *c*-C₈H₁₃, Ph, *p*-MeO-C₆H₄, *p*-CF₃-C₆H₄, 2-Furyl, 2-Thienyl
R^2 = Et, *i*-Pr R^3 = H, Ph, *p*-MeO-C₆H₄, *p*-Cl-C₆H₄
R^4 = H, Et R^3,R^4 = -(CH₂)₄-

Scheme 32 α-Imino gold carbene complexes from α-imino diazo compounds **113**.

On the other hand, when the reaction is performed in the presence of nitriles instead of enol ethers (Scheme 33), the carbene complex **120** could undergo a nucleophilic attack by the nitrile **51**, to form intermediate **121**. Next, the oxygen atom of the carbonyl group would add to the triple bond, closing the ring. A final aromatization step would give rise to the formation of isoxazoles **119**.

R^1 = Me, Ph, *p*-MeO-C₆H₄, 2-Furyl
R^2 = Et, *c*-C₆H₁₃, Vinyl, Ph, *p*-Tol, *p*-MeO-C₆H₄, *p*-F-C₆H₄, *p*-Br-C₆H₄, *p*-NO₂-C₆H₄

Scheme 33 Intermolecular capture of carbene intermediate **120** by nitriles **51**.

5. From isoxazoles, anthranils and 1,2-benzoisoxazoles

Taking advantage of the lability of the N-O bond, isoxazoles, 2,1-benzoisoxazoles (anthanils, benzo[*c*]isoxazoles), and 1,2-benzoisoxazoles (benzo[*d*]isoxazoles) have also served as nucleophiles in gold-catalyzed electrophilic cyclizations, leading to different heterocyclic skeletons. Although the mode of reactivity of all these substrates is similar, it is worth to mention that the aromatic properties of isoxazoles are completely lost along the reaction, while the aromaticity is retained in the benzene ring for benzoisoxazoles. In most of these reactions highly polarized electron-rich alkynes, such as ynamides, have been

employed as electrophilic counterparts. Additionally, it should be pointed out that a partial revision of this type of reactions from a different perspective has been recently published.[17]

Ye and co-workers pioneeringly reported the employment of isoxazoles unsubstituted at position 4 **122** as nucleophiles in gold phosphite catalyzed reactions with ynamides **76**, to produce 2-amino-4-acylpyrroles **123** (Scheme 34). After the initial gold complexation of the ynamide **76** a nucleophilic attack by the isoxazole **122** takes place leading to alkenylgold species **124**, which could evolve by a breakage of the labile N-O bond to form the α-imino gold carbene complex **125**. Then, a sequence involving cyclization and deauration accounts for the formation of the reaction products.[58] Overall, this is an atom-economic formal [3+2] cycloaddition for the preparation of a wide scope of synthetically useful tetrasubstituted pyrroles.
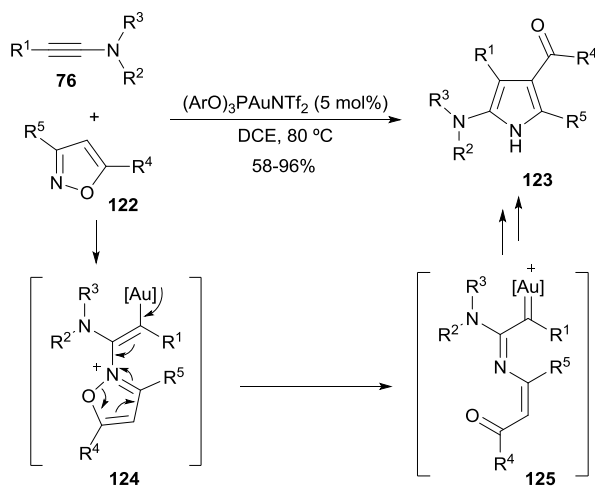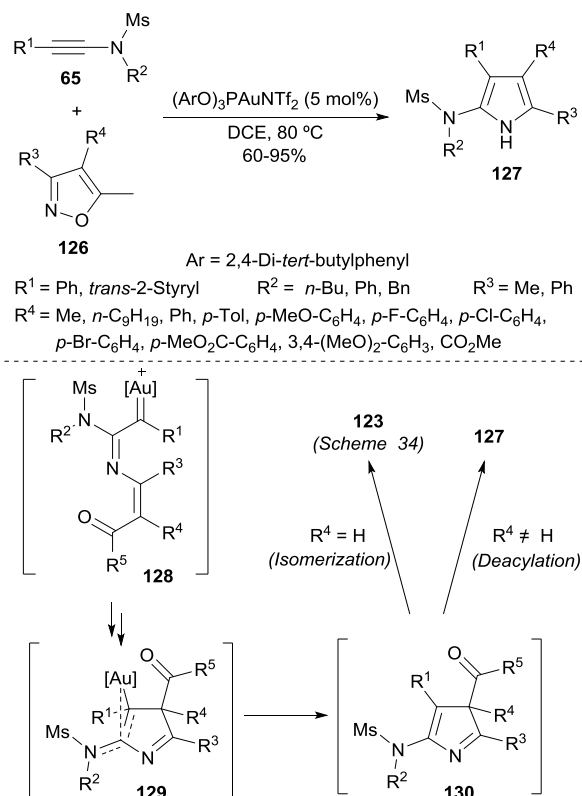

Ar = 2,4-Di-*tert*-butylphenyl

R^1 = *c*-Pr, Ph, *p*-F-C$_6$H$_4$, *p*-Tol, *trans*-2-Styryl

R^2 = Me, *n*-Bu, Allyl, 2-Bromoethyl, Ph, Bn, *p*-MeO-C$_6$H$_4$CH$_2$

R^3 = Ms, Ts, Bs, Ns

R^4 = H, Me, *n*-Bu, Ph, MeO

R^5 = H, Me, *n*-Pent, Ph, *p*-F-C$_6$H$_4$, *p*-Br-C$_6$H$_4$, *p*-Tol, *p*-MeO-C$_6$H$_4$, *trans*-2-Styryl

R^2-N-R^3 =

Scheme 34 4-Acylpyrroles **123** from isoxazoles **122**.

A highly related transformation occurs when the starting isoxazoles **126** are fully substituted; in this case 2-aminopyrroles **127**, non-acylated at position 4, are formed as unique reaction products in moderate to excellent yields[58] (Scheme 35; *top*). According to DFT calculations, both transformations (Scheme 34 and Scheme 35; *top*) follow a common mechanism (Scheme 35; *bottom*) through imino carbene complex **128**, which undergoes a 1,5-cyclization to generate Au(I)-ligated 3*H*-pyrrole **129**. Then, intermediate **129** is released by ligand exchange with another unit of ynamide, being the nature of the

substituent at position 4 of the pyrrole the factor which determines the evolution of this intermediate. Thus, an isomerization takes place when position 4 is unsubstituted (R^4 = H) leading to 4-acyl-2-aminopyrroles **123** while a deacylation occurs for R^4 ≠ H to produce 2-aminopyrroles **127**.

Ar = 2,4-Di-*tert*-butylphenyl

R^1 = Ph, *trans*-2-Styryl   R^2 = *n*-Bu, Ph, Bn   R^3 = Me, Ph

R^4 = Me, *n*-C$_9$H$_{19}$, Ph, *p*-Tol, *p*-MeO-C$_6$H$_4$, *p*-F-C$_6$H$_4$, *p*-Cl-C$_6$H$_4$, *p*-Br-C$_6$H$_4$, *p*-MeO$_2$C-C$_6$H$_4$, 3,4-(MeO)$_2$-C$_6$H$_3$, CO$_2$Me

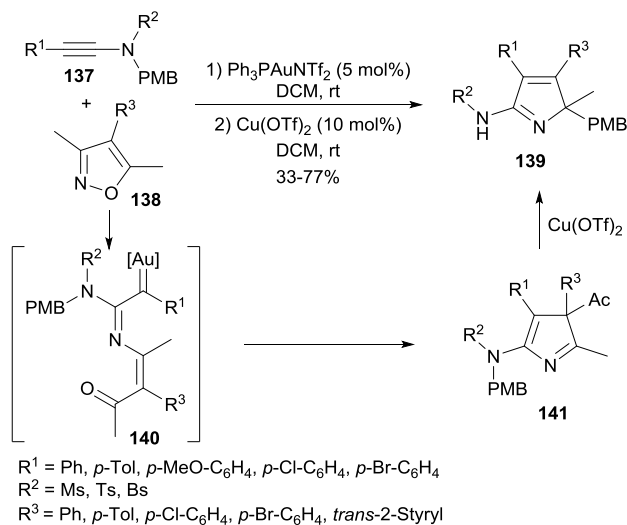**Scheme 35** Synthesis of pyrroles and divergent evolution from intermediate **130**.

An additional outcome has been observed for the gold-catalyzed reaction between oxazolidinone derived ynamides **131** and fully substituted isoxazoles **132**: *N*-acyl fully substituted pyrroles **133** are formed as major products besides tetrasubstituted pyrroles **134**, analogous to the ones mentioned in the previous scheme, which are the minor components[59] (Scheme 36). In this case, the evolution of 3*H*-pyrrole intermediate **136**, formed from α-imino gold carbene complex intermediate **135** by a 1,5-cyclization, generates tetrasubstituted pyrroles **134** and *N*-acyl fully substituted pyrroles **133** (the authors suggest an intermolecular migration of the acyl group for this compound). The relatively weak electron-withdrawing character of the oxazolidinone group, compared to the sulfonyl groups present in other ynamides, would explain the different evolution of this type of 3*H*-pyrroles **136**.
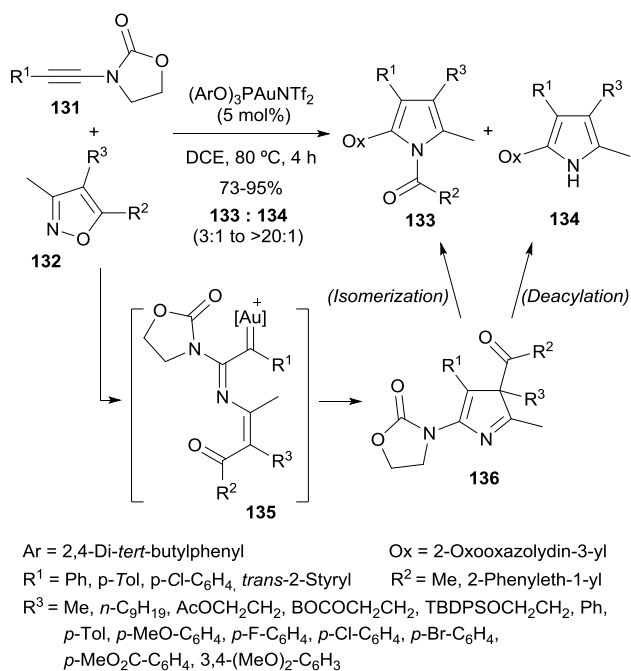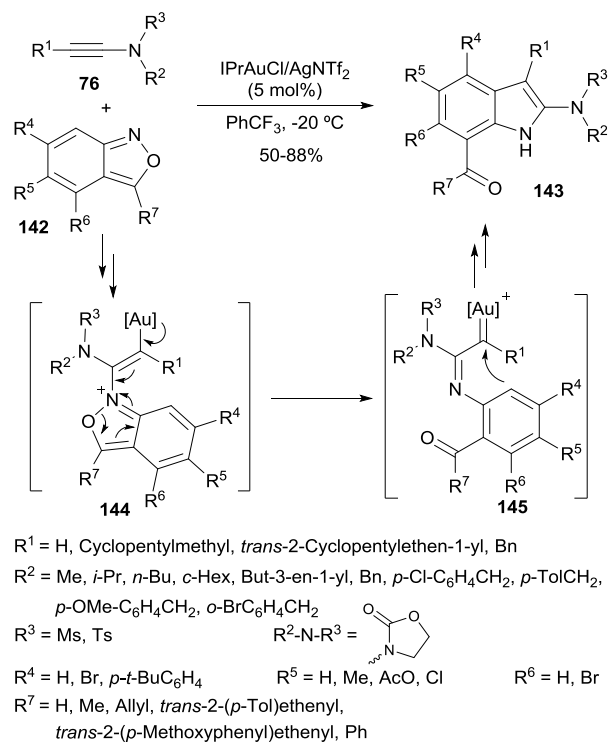
Scheme 36 Synthesis of pyrroles from ynamides **131** derived from 2-oxazolidinone.

A combination of π-acid (gold) and Lewis acid (copper) catalysis allowed the synthesis of 5-amino 2*H*-pyrroles **139** from isoxazoles **138** and ynamides **137** under mild conditions (Scheme 37). The two-step reaction sequence is proposed to involve α-imino gold carbene intermediates **140**, which should lead to isolable 5-amino 3*H*-pyrroles **141**. Treatment with the copper salt results in deacylation and migration of the PMB group. Scalability, moderate to good chemical yields, as well as limited functional group tolerance are the main features of this transformation which appears to be influenced by the nature of the substituents.[60]

R^1 = Ph, *p*-Tol, *p*-MeO-C$_6$H$_4$, *p*-Cl-C$_6$H$_4$, *p*-Br-C$_6$H$_4$
R^2 = Ms, Ts, Bs
R^3 = Ph, *p*-Tol, *p*-Cl-C$_6$H$_4$, *p*-Br-C$_6$H$_4$, *trans*-2-Styryl

**Scheme 37** Synthesis of 2*H* pyrroles **139**.

In a similar manner to previously discussed reactions, 7-acyl indoles **143** have been efficiently synthesized by Hashmi and co-workers by a gold catalyzed reaction between ynamides **76** and anthranils **142** (Scheme 38).[61] Soft reaction conditions, flexibility due to several points of diversity, and atom-economy are the main features of this formal [3+2]-approach. In the proposed mechanism, the intermediate **144** formed by anthranil addition to the gold-activated alkyne should evolve by benzoisoxazole ring-opening to α-imino gold carbene complex **145**. An intramolecular *ortho*-aryl C-H insertion, due to the high electrophilicity of the gold carbene, should lead to the reaction products (Scheme 38).

R^1 = H, Cyclopentylmethyl, *trans*-2-Cyclopentylethen-1-yl, Bn
R^2 = Me, *i*-Pr, *n*-Bu, *c*-Hex, But-3-en-1-yl, Bn, *p*-Cl-C$_6$H$_4$CH$_2$, *p*-TolCH$_2$, *p*-OMe-C$_6$H$_4$CH$_2$, *o*-BrC$_6$H$_4$CH$_2$
R^3 = Ms, Ts R^2-N-R^3 =
R^4 = H, Br, *p-t*-BuC$_6$H$_4$ R^5 = H, Me, AcO, Cl R^6 = H, Br
R^7 = H, Me, Allyl, *trans*-2-(*p*-Tol)ethenyl, *trans*-2-(*p*-Methoxyphenyl)ethenyl, Ph

Scheme 38 Synthesis of 7-acylindoles **143**.

Aryl ynol ether **146** has also shown to be reactive towards unsubstituted anthranil **147** under the standard conditions to produce 7-formyl-2-aryloxyindol **148** in fairly good yield (Scheme 39; *top*). On the other hand, non-polarized or low polarized alkynes **149** require the addition of 10 mol % of MsOH (presumably to facilitate the deauration process), higher temperatures, longer reaction times and higher excesses of alkynes. In this manner, the corresponding 2-substituted indoles **151** (R^2 = H) are regioselectively formed from terminal alkynes, and 2,3-disubstituted indoles **151** ($R^2 \neq$ H) from symmetrical internal alkynes, both with reasonable yields (Scheme 39; *middle*). An example of an unsymmetrically alkyl/aryl-substituted alkyne leads to the 2-alkyl-3-aryl indole **152** as the only regioisomer (Scheme 39; *bottom*). Besides been pioneer in employing anthranils

as nucleophiles, this research represents the first example[62] that postulates an intermolecular formation of an α-imino gold carbene complexes using non-polarized or low polarized alkynes.
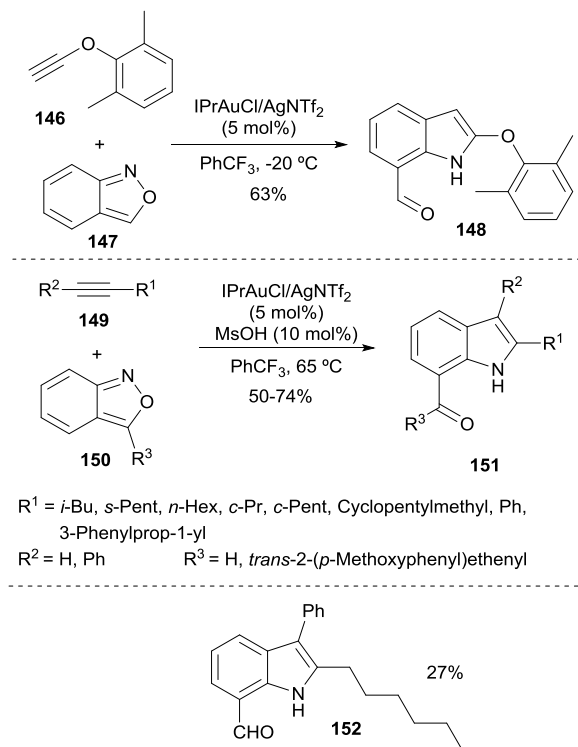
Scheme 39 Reactivity of anthranils with ynol ethers and non-polarized alkynes.

R.-S. Liu and co-workers have shown that, besides alkynamides, isoxazoles react under gold-catalyzed conditions with other types of alkynes such as 1,4-diyn-3-ols 153. Thus, a gold-catalyzed [4+1]-annulation takes place between isoxazoles 154 and bispropargyl alcohols 153, leading to tetrasubstituted pyrroles 155 (Scheme 40).[63] The reaction is highly: (i) regioselective (the nucleophilic attack of the isoxazole takes place at the C_{sp} linked to the substituent); (ii) chemoselective (in most cases, there is a preference for the attack to the more accessible triple bond over the other; for instance, initial attack occurs at the cyclopropyl substituted triple bond instead of at the phenyl substituted triple bond), and (iii) stereoselective (see below). Only the nitrogen atom from the isoxazole unit is incorporated into the pyrrole skeleton and bears, as substituents, an enal or enone moiety depending on the substitution of the starting isoxazole. The diastereoselectivity of the new double bond of the enal or enone goes from >4/1 up to >20/1 for the Z-isomer for $R^1 \neq$ H, while only the E-isomer is formed for terminal alkynes (Scheme 40; top). Substituted isoxazoles also partake in this reaction (Scheme 40; middle). The reaction is proposed to occur via an α'-hydroxy α-imino gold carbene complex 158, which undergoes a 1,2-alkyne migration to form propargyl

gold species 159, which should evolve to the final products (Scheme 40; bottom).
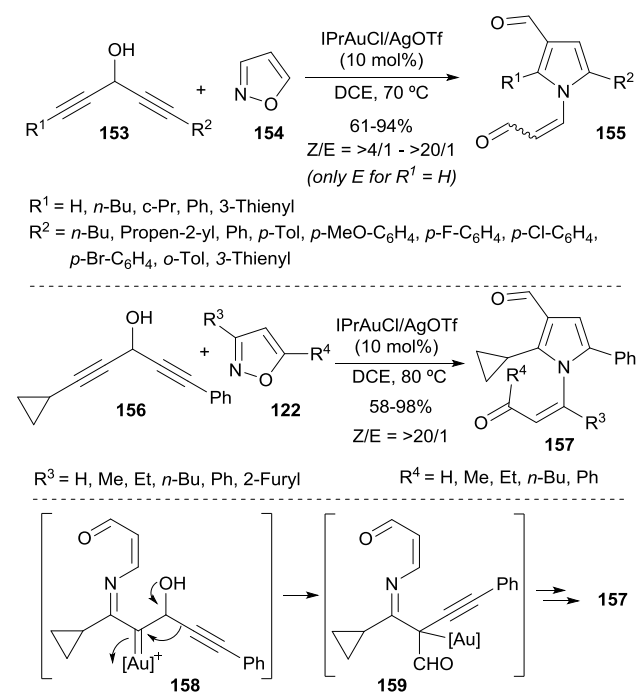
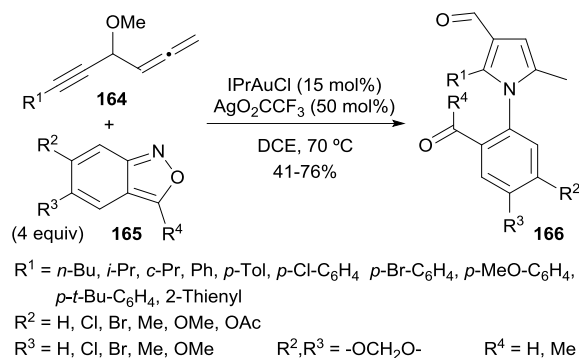Scheme 40 Gold catalyzed synthesis of pyrroles through 1,2-migration of alkynes.

The reaction has been extended to the employment of anthranils 160 as source of the nitrogen atom and produces N-aryl pyrroles 161 (Scheme 41; top). Additionally, 1,4-diyn-3-ol 162 bearing a tertiary alcohol has demonstrated to be a suitable partner leading to N-aryl pyrrole 163, with an acetyl group at position 3 of the pyrrole ring (Scheme 41; bottom).
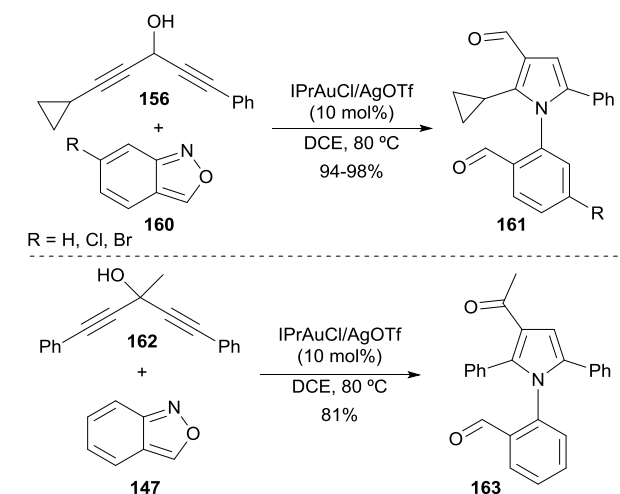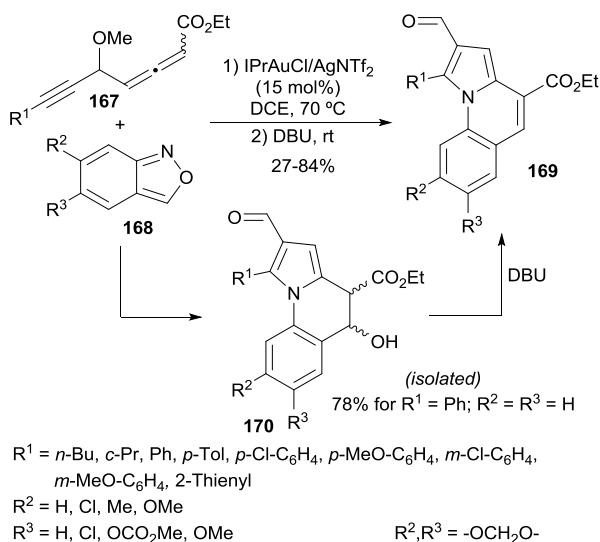

Scheme 41 Synthesis of N-aryl pyrroles.

A similar reaction takes place satisfactorily between anthranils 165 and 4-methoxy-1,2-dienyl-5-ynes 164, where

a terminal allene unit has replaced one of the triple bonds. Although a large excess (4 equiv) of the anthranil component **165** and semi-stoichiometric amounts of silver trifluoracetate are required, 3-acyl-1-aryl-2,5-disubstituted pyrroles **166** are thus obtained in moderate to good yields (Scheme 42). The reaction is inhibited if the terminal allene unit is disubstituted.[64]

R^1 = n-Bu, i-Pr, c-Pr, Ph, p-Tol, p-Cl-C$_6$H$_4$ p-Br-C$_6$H$_4$, p-MeO-C$_6$H$_4$,
    p-t-Bu-C$_6$H$_4$, 2-Thienyl
R^2 = H, Cl, Br, Me, OMe, OAc
R^3 = H, Cl, Br, Me, OMe R^2,R^3 = -OCH$_2$O- R^4 = H, Me

**Scheme 42** Gold catalyzed synthesis of aryl pyrroles **166** from allenyl alkynes **164**.

Following this strategy, pyrrolo[1,2-a]quinolines **169** can be prepared in moderate to good yields, when ethyl 5-methoxy-2,3-dienyl-6-ynecarboxylates **167** (that is, internal allene units bearing a terminal ester group) are employed (Scheme 43). The optimized conditions consisted on a one-pot two-step protocol, being dehydration of aldol adduct **170**, which was isolated in one case, readily performed by DBU at room temperature in the last stage.

R^1 = n-Bu, c-Pr, Ph, p-Tol, p-Cl-C$_6$H$_4$, p-MeO-C$_6$H$_4$, m-Cl-C$_6$H$_4$,
    m-MeO-C$_6$H$_4$, 2-Thienyl
R^2 = H, Cl, Me, OMe
R^3 = H, Cl, OCO$_2$Me, OMe R^2,R^3 = -OCH$_2$O-

Scheme 43 Preparation of pyrrolo[1,2-a]quinolines **169**.

In these gold-catalyzed transformations of 1,2-diene-5-yne moieties, a 1,2-migration of the allenyl fragment (analogous to the 1,2-alkyne migration described previously, *see Scheme 40*) is proposed to take place on α-imino carbene intermediate **171** leading to alkylgold

species **172**. This intermediate **172** would evolve by a sequence involving migration of Au, activation of the allene (Au-π-allene species) to undergo intramolecular electrophilic addition, and cyclization to form gold-containing intermediate **173**. The preferred evolution of this type of intermediates **173** would depend on the nature of R: (i) for terminal allenes (R = H) protodeauration should take place to pyrroles **166**, while (ii) for internal allenes (R = CO$_2$Et), the more stable enolate should partake in an aldol reaction to generate intermediate **174**, and finally pyrrolo[1,2-a]quinolines **169** (Scheme 44).
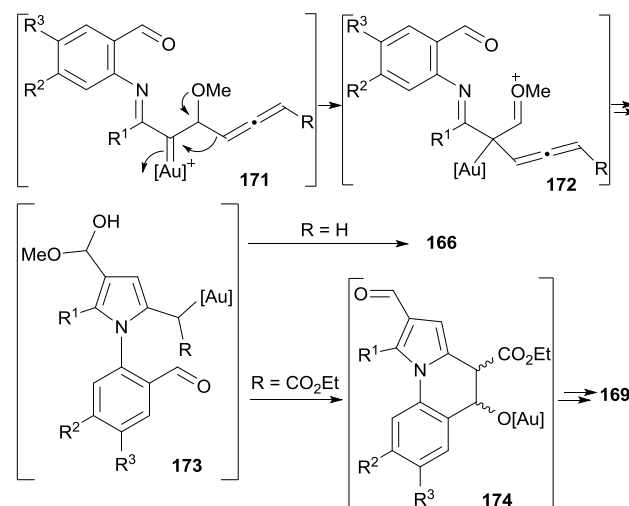

Scheme 44 Mechanistic proposal involving a 1,2-migration of allenes.

Additionally, unsubstituted isoxazole **154** affords 3,8-dicarbonylimidazo[1,2-a]pyridines **176** in a trimolecular reaction which includes two units of isoxazole and one unit of propiolate ester (Scheme 45; *top*).[65] Pyrroles **177** are always obtained as byproducts. Four equivalents of isoxazole **156** are required for this transformation, which involves, in the proposed mechanism, two α-imino gold carbene complex species as intermediates. After the addition and ring-opening of the oxazole, carbene complex **178** is formed and undergoes a ring-closure to intermediate **179**. Then a [4+2]-cycloaddition with another unit of oxazole **156**, followed by opening of the seven-membered ring of **180** and elimination of H$_2$O should lead to a new α-imino gold carbene complex **181**, which bears a pyridine moiety in its structure. Nucleophilic attack by the pyridine nitrogen atom to the carbene would explain the formation of the reaction products (Scheme 45; *bottom*). Overall, the cascade sequence can be labelled as a formal [2+2+1]/[4+2] cycloaddition.

It also should be noted that the title heterocycles have a dual nucleophilic character; therefore, they may behave either as *O-* or as *N-*nucleophiles depending on both their counterpart and the reaction conditions. In the presence of gold catalysts, 3,5-disubstituted oxazoles react with

propiolate derivatives to produce a regioisomeric type of pyrroles whose formation may be explained considering a nucleophilic *O*-attack and the subsequent participation of an α-oxonium gold carbene.[65]
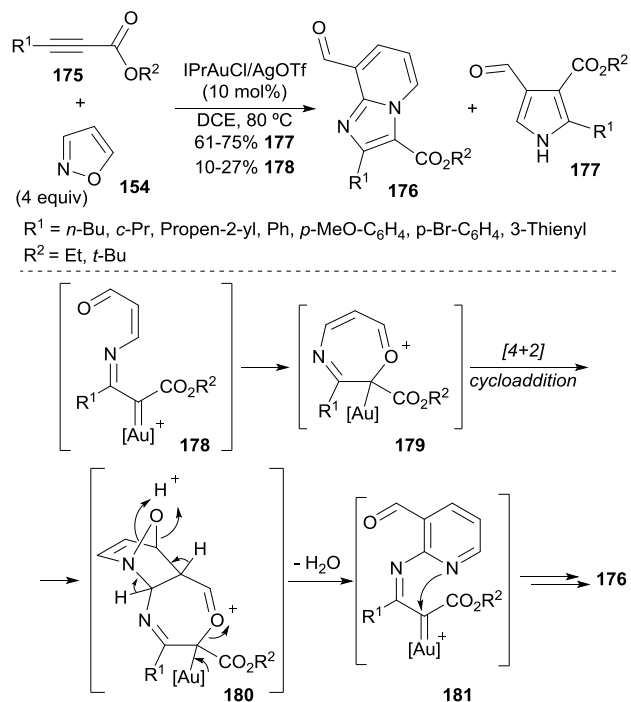
**Scheme 45** Gold catalyzed reaction of isoxazol **154** and propiolates **175**.

When 3-en-1-ynamides **182** are employed as starting materials moderate to good yields of azepine derivatives **183** can be obtained, in a formal [4+3]-cycloaddition, as pointed out by Liu *et al.*[66] (Scheme 46; *top*). The combination of IPrAuCl with silver triflimide proved to be the best catalyst for this transformation, providing clean reactions. The nature of the substituents of the enynamides appears to be crucial for the reaction outcome, as 3-aza-bicyclo[4.1.0]hepta-2,4-diene derivatives **184** or 2-amino-4-acylpyrroles **185** have been obtained occasionally (Scheme 46; *middle*). Thus, while the formation of the 2-amino-4-acylpyrroles **185** has been explained before, the bicyclic derivatives **184** probably arise from a rearrangement on the azepine skeleton under the reaction conditions. As observed, formation of seven-membered ring is indeed preferred for small R^4 groups and for substitution at R^3. The chemoselectivity of the reaction seems to depend on the conformational equilibrium between two gold α-imino carbene complex species **186** and **187**, which can be considered as gold-stabilized heptatrienyl cations. On the one hand, conformation **187** should be favoured for R^3 = H, and would evolve by aza-Nazarov reactions to form pyrroles **185**. Additionally, bulky R^4 groups also favour the formation of conformer **187**, thus yielding pyrrole **185** as byproducts. On the other hand, all *s*-

cis configured species **186** should be the preferred geometry for R^3 = alkyl and aryl, and undergo 6π electrocyclizations to form azepine products **183**.
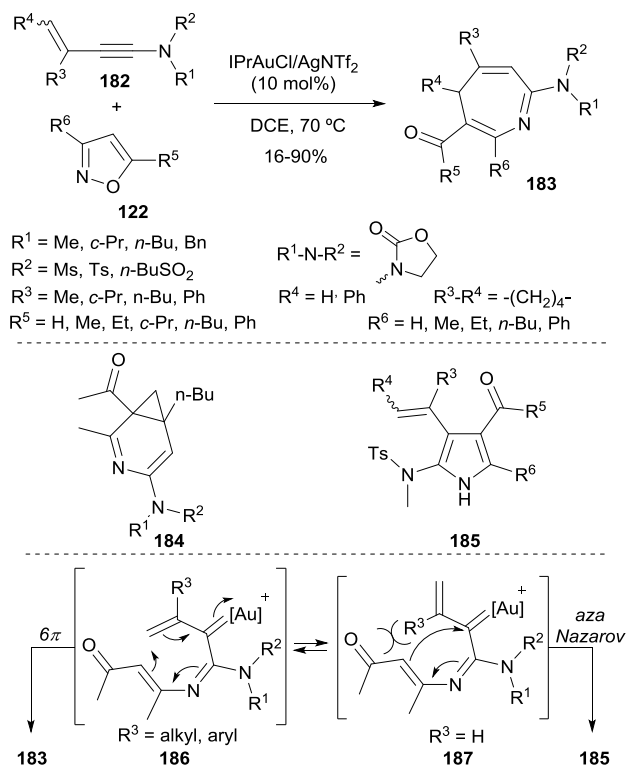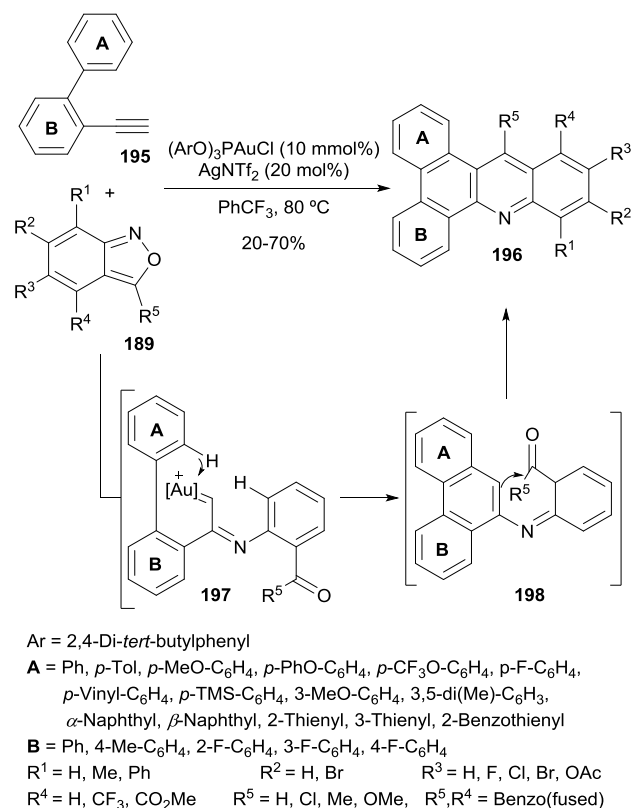

Scheme 46 Formal [5+2] cycloaddition of ynamides **182** and isoxazoles **122**.

Anthranils **189** are also able to react with ynamide propargyl silyls ethers **188** under gold-catalyzed reaction conditions leading to the formation of 2-aminoquinolines **190**, as pointed out by Hashmi and co-workers.[67] This is a formal [3+3]-cycloaddition where the evolution of the postulated α-imino gold carbene complex intermediate **191** is completely different from what has been described in previous examples; thus, a 1,2-hydrogen shift should take place with deauration leading to *N*-aryl-α,β-unsaturated imine **192**. Then, further evolution involving intramolecular Mukaiama-type nucleophilic attack from the silyl enol ether to the carbonyl functional group should lead to the obtained 2-aminoquinolines **190** (Scheme 47; *top*). The umpolung behaviour of the carbene carbon which acts as a nucleophile rather than as an electrophile in the proposed mechanism must be highlighted. The presence of the ynamide moiety is not a requisite for the reaction to occur as less polarized simple propargyl silyl ethers also undergo this type of transformation, although a different catalyst (a phosphite gold chloride), a more polar solvent combination (trifluroethanol:dichloroethane) and longer reaction times are needed. Quinolines **194** bearing alkyl, alkenyl or aryl substituents at position 2 have thus been prepared (Scheme 47; *bottom*).
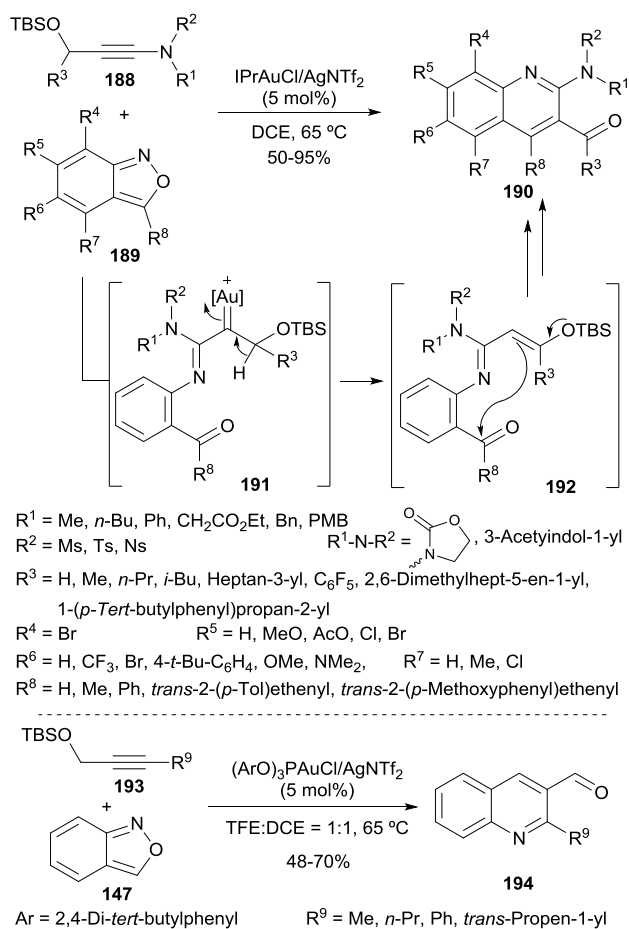
Scheme 47 Gold catalyzed synthesis of quinolines from antranils and alkynes. (Substituents omitted in intermediates, for simplicity).

Scheme 48 Synthesis of polyaromatic hydrocarbons (PAHs). (Substituents omitted in intermediates, for simplicity).

Depending on the functional groups surrounding it, the α-imino gold carbene complex intermediate may evolve by different routes leading to complex structures difficult to access by other strategies. For instance, the reaction of anthranils **189** with o-ethynylbiaryls **195** in the presence of a phosphite gold catalyst produces diverse N-doped polycyclic aromatic hydrocarbons (PAH) **196** in moderate to good yields (Scheme 48).[68] In this particular case, the carbene complex **197** should undergo a regioselective C-H insertion to generate iminophenanthrene intermediate **198**; then, a Friedel-Crafts-type cyclization under the reaction conditions should allow evolution towards the final products. Several points of diversity have been explored, in each one of the starting materials, to provide a wide variety of N-doped PAHs; some of them have shown to emit violet-blue fluorescence and display potential application in material science.

A similar cascade annulation takes place when an aryl group is placed as substituent at the ynamide nitrogen atom. R.-S. Liu et al. showed that, in the case of terminal ynamides **199** with anthranils **165**, and employing a JohnPhos gold catalyst, it leads to 6H-indolo[2,3-b]quinolines **200** in a fast reaction.[69] As stated before, the α-imino gold carbene intermediate **201** evolves by a regioselective C-H insertion to generate indol **202**; again, a Friedel-Crafts type cyclization and further evolution should produce 6H-indolo[2,3-b]quinolines **200** (Scheme 49).
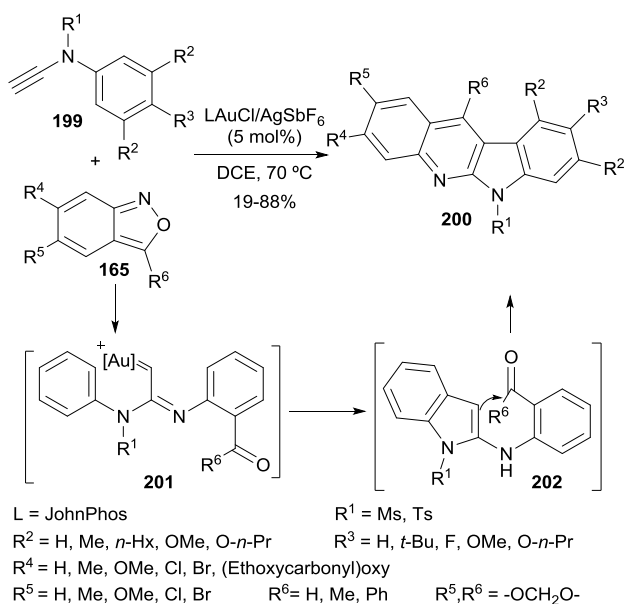
Scheme 49 Synthesis of 6H-indolo[2,3-b]quinolines 200. (Substituents omitted in intermediates, for simplicity).

An internal ynamide, tested as substrate when developing the reaction scope, did not lead to the expected 6H-indolo[2,3-b]quinoline; however, the isolation of a 2-amido-1-azadiene supports the participation of α-imino gold carbene complexes as reaction intermediates in this transformation.[69]

Besides terminal ynamides, highly polarized dimethylphenoxyacetylene 203 proved to be active against anthranil 147, under smooth reaction conditions, leading to 1,3-dimethylbenzofuro[2,3-b]quinoline 204 in 42% yield (Scheme 50).
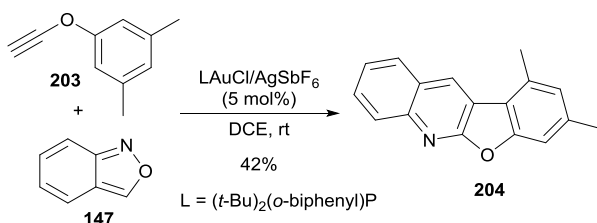

Scheme 50 Reactivity of anthranil 147 with ynol ether 203.

The gold-catalyzed reaction between anthranils 165 and N-benzyl ynamides 205 follows a similar reaction sequence to generate quinoline-fused polyazaheterocycles 206, as pointed out by Hashmi and co-workers.[70] A gold(III) catalyst (KAuBr₄) turned out to be the most efficient for this transformation, which requires further heating in a second step. The proposed α-imino gold carbene complex intermediate 207 should undergo again a regioselective C-H insertion, which in this occasion must be followed by nucleophilic addition of the enamine to the carbonyl group

and a subsequent elimination, to account for the final products 206.
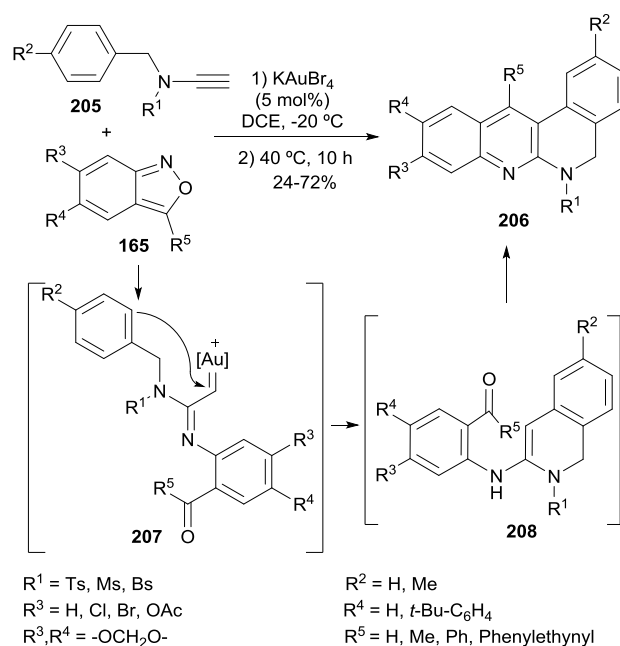
Scheme 51 Synthesis of quinoline-fused polyazaheterocycles 206.

2-Aminopyrrols 211 bearing a propenal side chain at C4 position can be obtained when N-furylmethyl ynamides 209 are employed as the antagonists of anthranils 165. Moreover, for terminal ynamides (R² = H), pyrrolo[2,3-b]quinolines 210 become the final products if slightly higher temperatures are used (Scheme 52).[70] In the proposed mechanism, the evolution of the α-imino gold carbene complex intermediate 212 follows a sequence involving (i) an intramolecular nucleophilic attack by the furan moiety to form intermediate 213, (ii) a C-O cleavage with (iii) subsequent aromatization, and (iv) double bond cis-trans isomerization to produce 2-aminopyrrols 211.
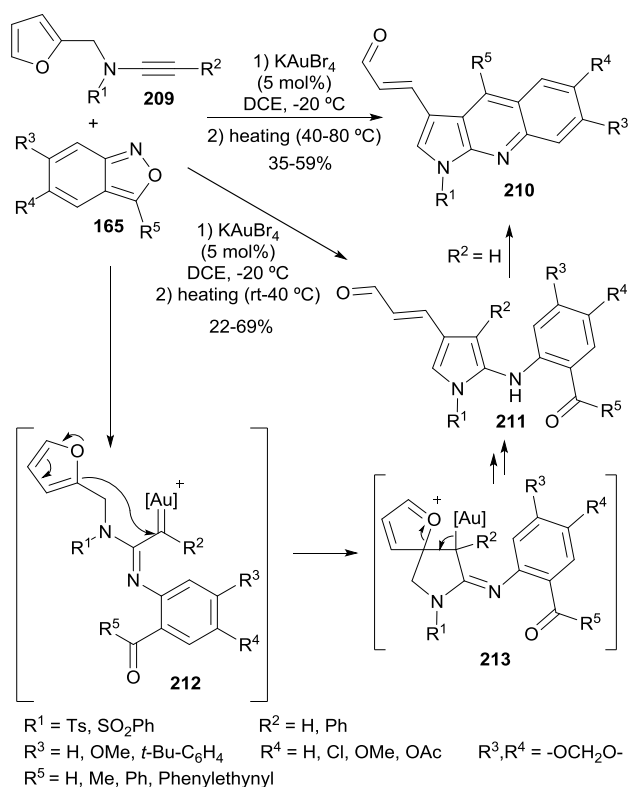
Scheme 52 Furan-ring opening in the synthesis of pyrroloquinolines **210**.

R.-S. Liu and co-workers have described the synthesis of pyrrolo[2,3-*b*]quinolines **215** from terminal *N*-propargyl ynamides **214** and anthranils by a two-step reaction procedure employing gold(III) and Brønsted acid catalysis sequentially[71] (Scheme 53). As usual, the mechanistic proposal should involve formation of α-imino gold carbene complex **216**, which now is ready to undergo a nucleophilic attack by the tethered internal alkyne to generate alkenyl cation **217**. Then, hydration should take place to produce dihydropyrrole **218**, which by in situ oxidation would lead to isolable 4-aminopyrroles **219**. A final treatment with TsOH allows the cyclization of pyrrole adducts **219** into pyrrolo[2,3-*b*]quinolines **215**. Some limitations in the scope of the reaction include: (i) only aryl groups may act as substituents in the triple bond of the alkyne (R^2 = aryl), and (ii) substitution is not allowed at position 5 of the anthranil (R^5 = H), as otherwise the final cyclization does not occur.
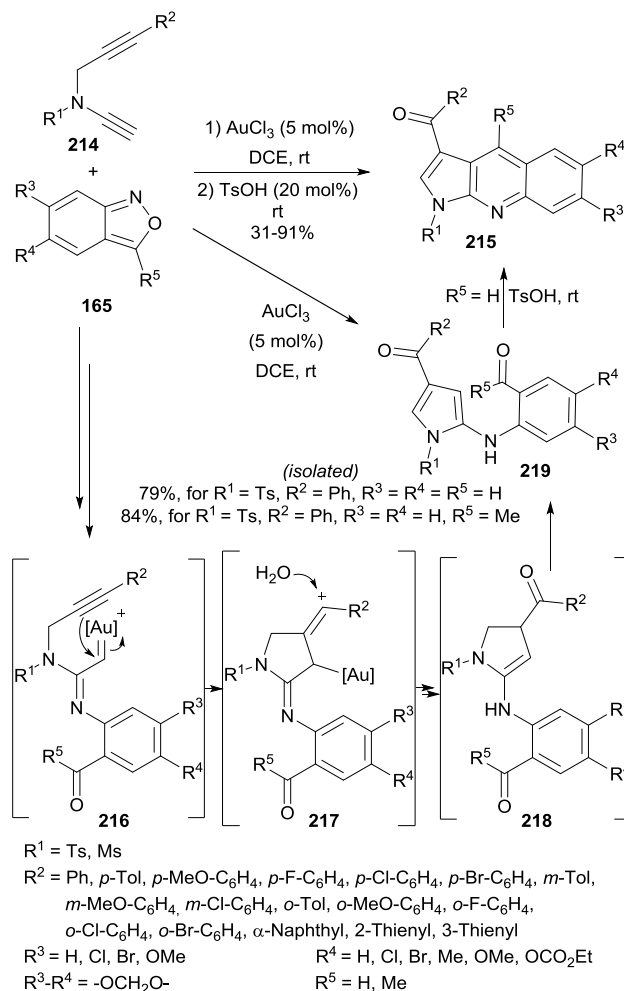
Scheme 53 Synthesis of pyrrolo[2,3-b]quinolines **215**.

Internal *N*-propargyl ynamides **220** do not undergo cyclization to pyrrolo[2,3-*b*]quinolines either; on the contrary, after the gold catalyzed step, a further treatment with aqueous HCl produces 4-acylpyrroles **221** in synthetically useful yields (Scheme 54).
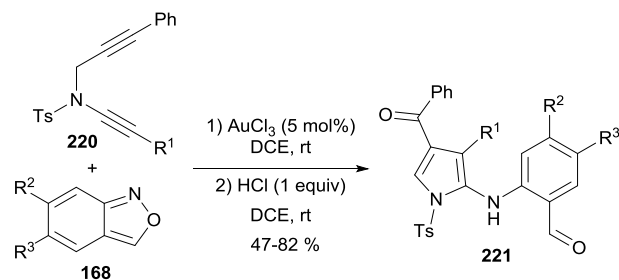
Scheme 54 Synthesis of pyrroles **221** from internal *N*-propargyl ynamides **220**.

R.-S. Liu and co-workers have also proved that, although weak nucleophiles, 1,2-benzoisoxazoles (benzo[*d*]isoxazoles) **222** are also reactive to ynamides **76**, leading selectively to benzo[*f*][1,4]oxazepine derivatives

223 under gold-catalysis and mild reaction conditions (Scheme 55; *top*).[72] A 5 mol% loading of a combination of IPrAuCl and AgNTf$_2$ was the best catalyst found (Scheme 55; *top, conditions 1*). Four points of diversity were studied to illustrate the scope of the reaction. Almost simultaneously, the group of Y. Liu reported very similar results, but employing AuBr$_3$ as catalyst (Scheme 55; *top, conditions 2*); shorter reaction times and the inclusion of an additional point of diversity were the main contributions of this research.[73] Moreover, Me$_2$SAuCl was shown as the catalyst of choice for the preparation of two specific benzo[*f*][1,4]oxazepines **223** bearing R^2 = Ph (Scheme 55; *top, conditions 4*).

In this reaction, after the usual opening of the benzoisoxazole moiety, α-imino gold carbene complex **224** is proposed as reaction intermediate. Then, a 6-π-electrocyclization should occur, leading to benzoxazepinyl gold species **225**, which should evolve to the final products (Scheme 55; *top*).
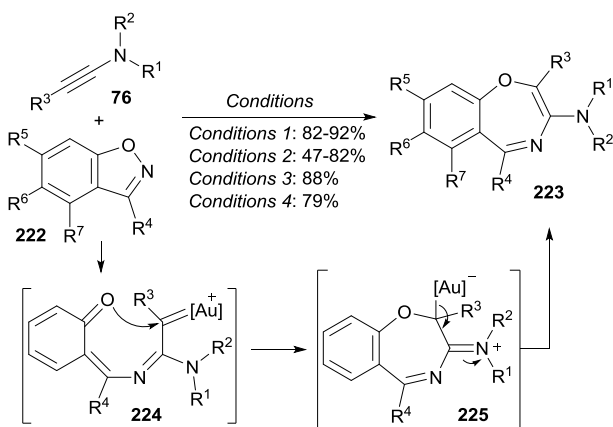
Conditions 1: IPrAuCl/AgNTf$_2$ (5 mol%), DCE, rt
Conditions 2: AuBr$_3$ (5 mol%), DCE, rt
Conditions 3: JohnPhosAuCl/AgNTf$_2$ (5 mol%), DCE, rt
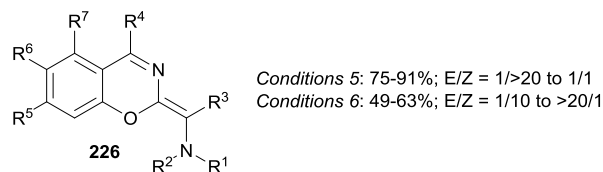**Conditions 4**: Me$_2$SAuCl (5 mol%), DCE, rt

R^1 = Me, *n*-Bu   R^2 = Ms, Ts, SO$_2$-*n*-Bu
R^3 = Ph, *p*-Tol, *p*-MeO-C$_6$H$_4$, *p*-F-C$_6$H$_4$, *p*-Cl-C$_6$H$_4$, *p*-Br-C$_6$H$_4$,
     p-CO$_2$Me-C$_6$H$_4$, α-Naphthyl, 2-Thienyl, Formononetin moeity,
     1,3,5(10)-Estradien-3-ol-17-one derivative
R^4 = H, Me, 2-Phenyleth-1-yl, Ph, *o*-MeO-C$_6$H$_4$, *p*-OMe-C$_6$H$_4$, *p*-Cl-C$_6$H$_4$
R^5 = H, Me, Cl, Br   R^6 = H, Me, Cl, Br   R^7 = H, Me

Conditions 5: 75-91%; E/Z = 1/>20 to 1/1
Conditions 6: 49-63%; E/Z = 1/10 to >20/1

Conditions 5: JohnPhosAuCl/AgNTf$_2$ (5 mol%), DCE, rt
Conditions 6: JohnPhosAu(MeCN)SbF$_6$, rt

Scheme 55 Gold catalyzed reactivity of 1,2-benzoisoxazoles **222** with ynamides **76**. (Substituents omitted in intermediates, for simplicity).

In a general manner, the outcome of the gold-catalyzed reaction of ynamides **76** and 1,2-benzoisoxazoles **222** is controlled by the catalyst species. Thus, usually, formal

[5+1] adducts (benzoxazine derivatives **226**) are instead synthesized when JohnPhosAuCl/AgNTf$_2$ or JohnPhosAu(MeCN)SbF$_6$ are employed (Scheme 55; *bottom*). Nevertheless, some exception occurs. For instance, formal [5+2]-cycloaddition takes place under both reaction conditions (Scheme 55; *top, conditions 1 and 3*) in the only example studied for R^3 = α-naphthyl. In the same manner, some other combinations of 1,2-benzoisoxazoles **222** and ynamides **76** lead exclusively to the benzoxazine derivatives **226** regardless of the catalyst employed. Its formation is proposed to involve a 1,2-shift of the amide group but not an α-imino gold carbene complex as intermediate.

Therefore, although the ligand controls the reaction outcome some exceptions occur depending on the nature of both starting materials.

## 6. From dioxazoles and oxadiazoles

Other oxazole derivatives, such as dioxazoles and oxadiazoles, have proven their wellness as nitrene transfer reagents to gold activated alkynes. In this sense, Y. Liu and co-workers described a simple synthesis of oxazoles by the gold catalyzed reaction of dihydro-1,2,4-dioxazoles **227** and ynamides **76**.[74] The procedure involves a retro [3+2] and a formal [3+2] cycloadditions (Scheme 56). Thus, after the presumable nitrogen attack of the dioxazole **227** to the gold activated ynamide, to form the alkenyl gold intermediate **229**, retrodonation from the gold atom to produce the α-imino gold carbene complex **230** could occur. Formation of intermediate **230** is also triggered by the elimination of a molecule of acetone. Finally, consecutive intramolecular closure and aromatization steps could explain the synthesis of the oxazole derivatives **228**. The same reactivity pattern could also be proposed for other activated alkynes, such as alkynyl esters or alkynyl ketones.
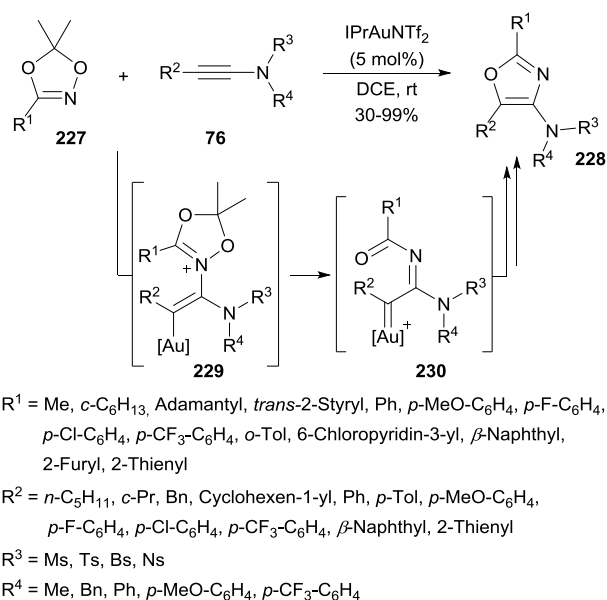
Scheme 56 Gold catalyzed transformation from dioxazoles **227** to oxazoles **228**.

The same authors also published a nitrogenous version of this reaction, using dihydrooxadiazoles as the reagents for the nitrene transfer[75] (Scheme 57). Thus, the use oxadiazoles **231**, in their gold catalyzed reaction against ynamides **76**, resulted in the formation of imidazoles **232**. The reaction seems to proceed through intermediates **233** and **234** in a similar way as for their oxygenated analogues.
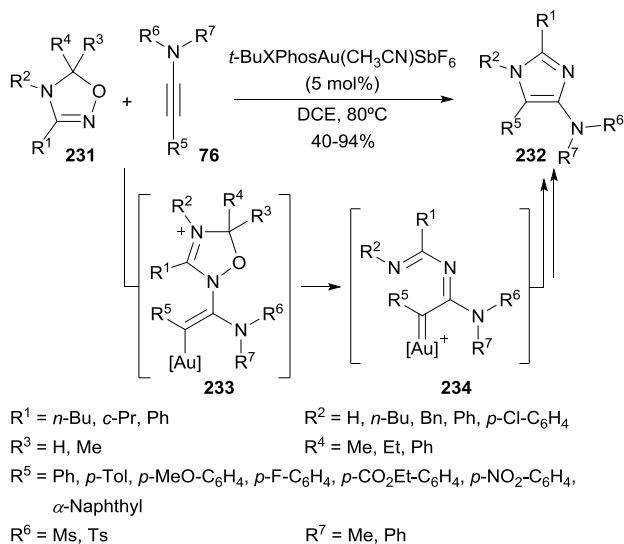
Scheme 57 Oxadiazoles **231** as precursors of α-imino gold carbenes **234**.

On the other hand, the use of aromatic oxadiazoles **235** in this field was described by Hashmi and co-workers for the synthesis of *N*-acylimidazoles **236**.[76] This reaction occurs with a total atom-economy as the acyl group remains as a part of the oxadiazole **235**. As it is outlined in Scheme 58, the mechanistic proposal for this reaction differs from the

one invoked in the two previous examples, as the formation of the carbene complex **238** does not require a retro [3+2] reaction with the expulsion of a carbonyl moiety (*See Schemes 56 and 57*). Next, intramolecular closure of intermediate **238** and aromatization would form *N*-acylimidazoles **236**.
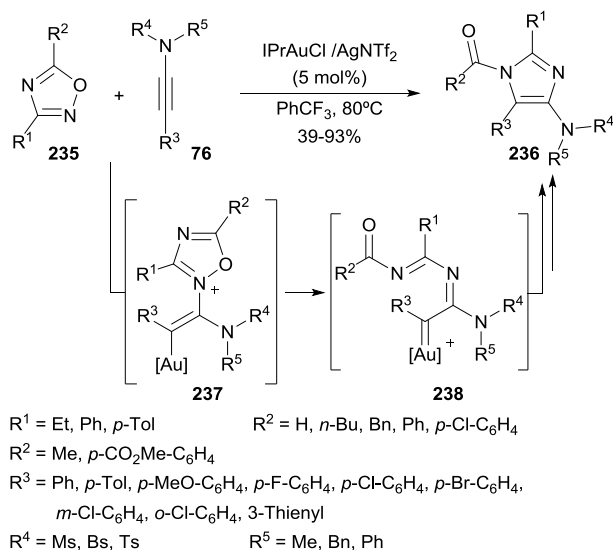

Scheme 58 Gold catalyzed transformation of oxadiazoles **235** into imidazoles **236**.

Finally, it is worth to mention the preliminary results by Davies *et al.*[44] using alkynyl thioethers in their reaction with dioxazoles **227**. As it has been previously described for the use of aminides (Scheme 23) the presence of a sulfur group allows the formation of isoxazole derivatives with a novel regioselectivity.

7. From indazoles

Indazoles are also suitable substrates for heterocyclic synthesis through α-imino gold carbene complexes. Thus, Huang *et al.* reported a remarkable gold catalyzed synthesis of 7-pyridinylindoles **240** from indazoles **239** and ynamides **131** derived from oxazolidine carbamates.[77] The mechanistic proposal seems to be very similar to the one reported for the use of other heterocycles, such as isoxazoles, dioxazoles or oxadiazoles, in terms of the carbene formation (*vide supra*). However, from the regiochemistry of the final compound, a special behaviour can be inferred, as the expected regioisomer was not obtained (Scheme 59). Thus, the nucleophilic attack could occur, for the first time, over the β-carbon instead of the α-carbon of the ynamide **131**. This reactivity could be explained through an initial intramolecular gold catalyzed reaction of the ynamide **131** with formation of intermediate **243** (Scheme 59; *bottom*), which could be isolated and characterized. Compound **243** could undergo a

nucleophilic attack from the indazole heterocycle to form intermediate **241**, which would evolve to the α-imino gold carbene complex **242** first and the final indole **240** later.
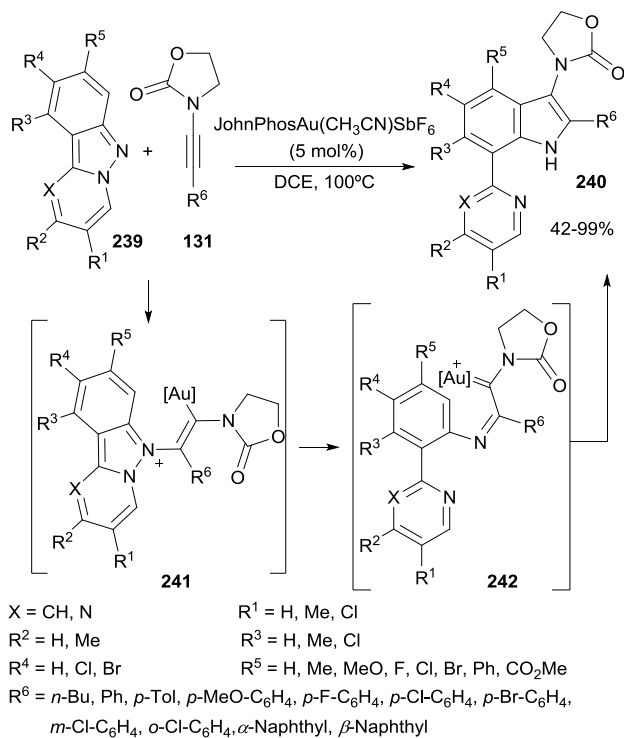
Scheme 59 Gold catalyzed reaction of indazoles **239** with ynamides **131**.

8. From triazapentalenes

Finally, in the last section, the use of 1,2,3-triazapentalenes, or their benzotriazole precursors, in the gold catalyzed heterocyclic synthesis, is described. This methodology has been developed in our research group and implies an initial gold catalyzed intramolecular 5-*endo-dig* cyclization of 1*H*-propargyl benzotriazoles **244**, giving rise to the formation of dipolar 1,2,3-triazapentalenes **245** (Scheme 60).[78]
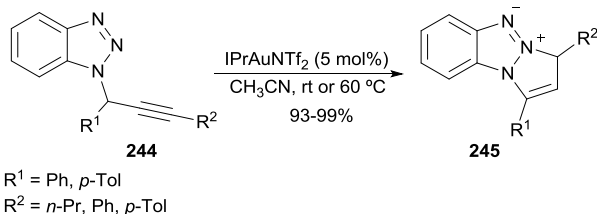
Scheme 60 5-*Endo-dig* cyclization of 1*H*-propargyl benzotriazoles **244**.

These species **245**, which can be isolated and handled, are suitable to participate in a new catalytic cycle attacking gold activated alkynes. In this sense, as it is outlined in Scheme 61, an atom-economical gold catalyzed three-component synthesis of *ortho*-imidazolylpyrazolylbenzenes **246** could be achieved directly from triazapentalenes **245** or their 1*H*-propargylbenzotriazole precursors **244**. Thus, triazapentalene **245**, could enter, after its formation, in a second catalytic cycle to form intermediate **247**. Compound **247** could evolve towards the carbene intermediate **248**, triggered by the breakage of the triazole ring and formation of the pyrazole ring. Next, capture of the carbene complex **248** by nitrile **51** and closure of the ring, could explain the formation of the imidazolyl pyrazolyl arenes **246**.
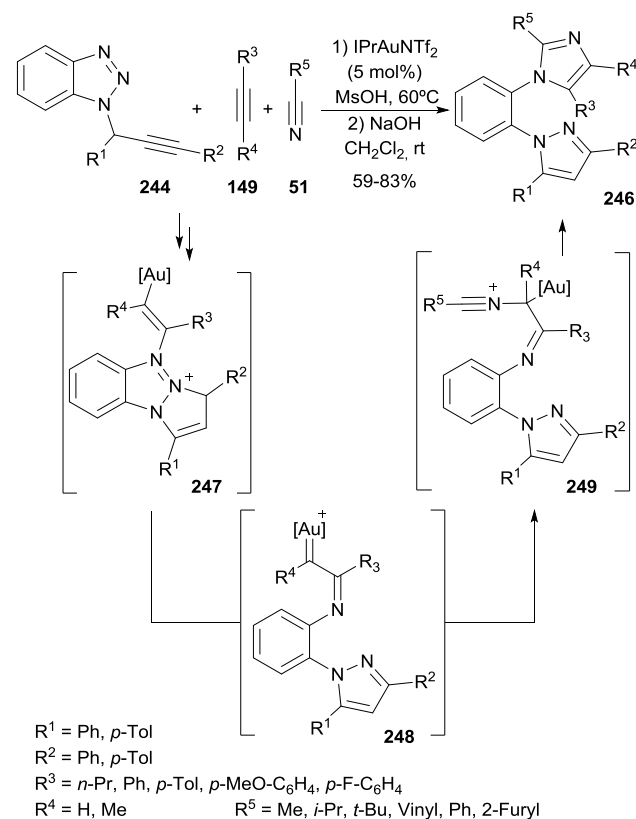
Scheme 61 Synthesis of *ortho*-imidazolylpyrazolylbenzenes **246**.

This reaction, in addition to the examples reported by Hashmi *et al.*[61,67,68] and R.-S. Liu *et al.*[63,64] using anthranils and isoxazoles, respectively, remains, to the best of our knowledge, as the sole intermolecular examples of this type of processes that do not require the participation of highly polarized alkynes.

In a very recent work,[79] triazapentalenes **245**, or their benzotriazole precursors **244**, also reacted with ynamides **76** to form the corresponding indoles **250**, upon gold catalysis with IPrAuNTf₂ (Scheme 62). The formation of

compounds **250** could be explained through the same reactive pattern described for the formation of the α-imino gold carbene intermediate **251**, followed by intramolecular C-H insertion.

R[1] = Ph, *p*-Tol
R[2] = Ph, *p*-Tol
R[3] = Ph, *p*-Tol, *p*-MeO-C$_6$H$_4$, *p*-Br-C$_6$H$_4$, 3,4,5-(MeO)$_3$-C$_6$H$_2$
R[4] = Me
R[5] = Ts
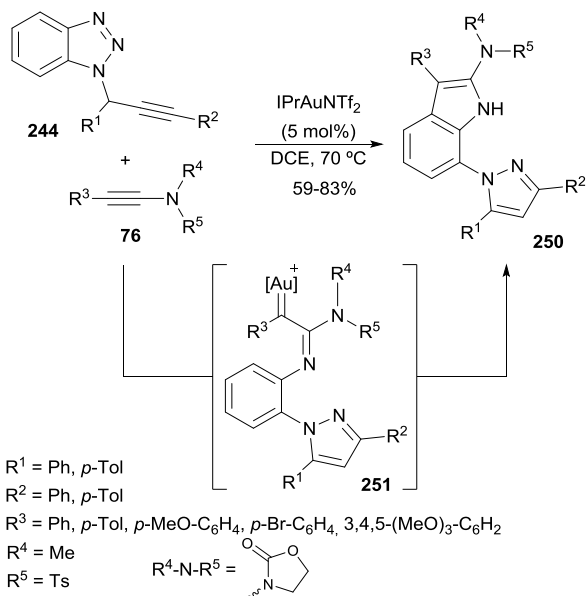
Scheme 62 Synthesis of 7-pyrazolylindoles **250**.

However, when this reaction was performed using JohnPhosAuNTf$_2$ as the gold catalyst and arylynamides **253** derived from oxazo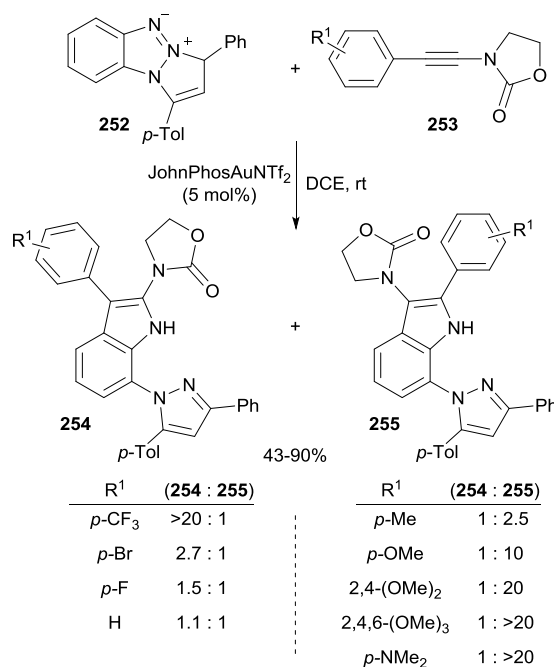lidinone carbamates, the regioselectivity of the reaction could be controlled or even reversed.[79] In this sense, as it is shown in Scheme 63 for triazapentalene **252**, in addition to the gold ligand nature the electron-donating or withdrawing capability of the aromatic ring of the ynamide **253** plays an important role in the regioselectivity of the reaction.

Scheme 63 Regiodivergent synthesis of indoles.

R[1]	(254 : 255)		R[1]	(254 : 255)
p-CF$_3$	>20 : 1		*p*-Me	1 : 2.5
p-Br	2.7 : 1		*p*-OMe	1 : 10
p-F	1.5 : 1		2,4-(OMe)$_2$	1 : 20
H	1.1 : 1		2,4,6-(OMe)$_3$	1 : >20
			p-NMe$_2$	1 : >20

As it can be inferred from Scheme 63, electron-withdrawing groups favour the formation of indoles **254**, emerging from the attack of the triazapentalene **252** to the α-carbon of the ynamide **253**. On the other hand, electron-donating groups direct the reaction mainly through the β-carbon of the gold activated ynamide. This effect was also observed using propargyl-1*H*-benzotriazoles as starting materials. Moreover, both regioisomers could be isolated and characterized. The mechanistic proposal for the formation of regioisomer **255** could be explained in a similar way to the one invoked for the reaction performed with indazoles (*see Scheme 59*). Thus, the alkenyl gold intermediate **243**, obtained from the intramolecular cyclization of ynamides **253**, could also be isolated and characterized. Following this methodology, several indoles **257** could be synthesized with high or total regioselectivity (Scheme 64).

R[1] = Ph, *p*-Tol   R[2] = Ph, *p*-Tol   R[3] = H, MeO   R[4] = MeO, NMe$_2$
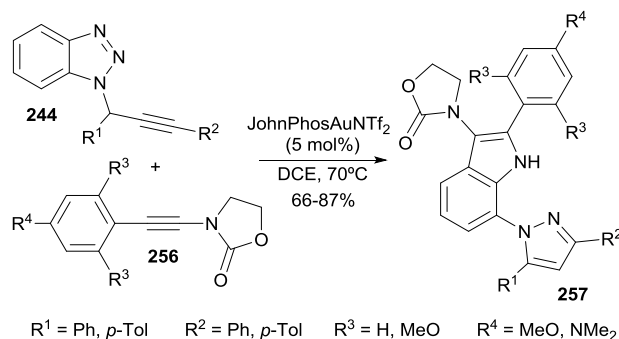
Scheme 64 Indole synthesis from nucleophilic attack to β-position of ynamides.

Conclusions

Along this review we have shown that a lot of differently functionalized *N*-heterocycles can be readily accessed by gold catalyzed electrophilic additions of *N*-nucleophiles to activated alkynes. Thus, five to seven membered ring heterocycles constitute the current plethora of structural diversity available so far employing this strategy. A common feature to all these transformations is the participation of α-imino gold carbene complexes as proposed reaction intermediates. For their formation, the *N*-nucleophiles should present a labile bond between the nucleophilic nitrogen atom and a good leaving group. In this approach a formal nitrene transfer is postulated, with concomitant formation of both the metal stabilized carbene and the imino functional group. Alternatively, α-diazo imino compounds have also been shown to produce α-imino gold carbene complexes under gold-catalyzed conditions; thus, in this second strategy, a preformed imino group is installed prior to carbene generation. In this comprehensive revision we have shown that, far for being like a painter's palette crammed with all kinds of colours, the organic chemist's toolbox continues its expansion in terms of new and more diverse and efficient methodologies.

However, there is still plenty of room for growing in the field. For instance, most of the reactions here described involve highly polarized alkynes such as ynamides, ynol ethers or ynol thioethers as starting materials, and the examples with non-polarized alkynes are still scarce. On the other hand, the option of employing allenes as electrophilic substrates in this type of chemistry remains unexplored. Moreover, most of the chemistry covered in this review leads to flat heteroaromatic reaction products and only one example of an enantioselective synthesis has been reported; therefore, the option of performing enantioselective (or even just stereoselective) transformations, always challenging in gold chemistry, has received low attention and should be subject of further development. Finally, there is no direct structural evidence of the existence of such α-imino gold carbene complexes, since they neither have been isolated nor spectroscopically detected or characterized, and efforts should also be undertaken in this direction.

Therefore, far from being a fully mature topic, the chemistry of α-imino gold carbene complexes is still waiting for courageous and enthusiastic chemists to contribute to the development of this area.

Conflicts of interest

"There are no conflicts to declare".

Notes and references

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