Gold-catalyzed functionalization reactions of indole

Valentina Pirovano*[a]

Dedicated to the memory of Dr. Laura Toffetti

Abstract: This review summarized the progresses achieved in the last fifteen years by application of homogeneous gold catalysis in the field of indole functionalization. Several electrophilic species, obtained *via* gold-catalyzed π-activation, in fact, have been reacted with the nucleophilic positions of indole, thus allowing its efficient manipulation. In order to furnish a complete and clear overview on the role of the catalyst, the review is organized from the perspective of the gold-activated substrate, which is reacting with indole. In addition, considering the ability of gold to catalyze tandem and cascade reactions, a separate section describes tandem/cascade protocols useful for the synthesis of complex polycyclic indole derivatives. Finally, gold catalysis has also been employed for the synthesis of indole-based natural products. For this reason, a dedicate section collects all the work in which the key step to obtain these complex indoles is represented by a gold-catalyzed reaction.

1. Introduction

The concepts of indole functionalization and gold catalysis can be certainly both considered as "hot topics" in synthetic organic chemistry. Indole is probably one of the most important and studied heterocyclic system in different research areas including pharmaceutical, agrochemical and material sciences.[1–4] Therefore, since its discovery and characterization in 1866,[5] enormous efforts have been dedicated to the development of efficient methods of preparation[6–12] and functionalization.[13–16] On the other side, homogeneous gold catalysis has emerged in the last decades as a powerful tool for the formation of C-C and/or C-X (X = O, N, S) bonds under mild reaction conditions.[17–19] Consequently, indole derivatives have immediately become object of intensive studies in gold-catalyzed reactions aimed to create new reactivity patterns. Progresses in indole functionalization by means of catalytic methodologies have been highlighted by excellent reviews by Bandini[13] and Jia.[15] However, over the last years, several research groups have reported important improvements in this field by application of homogeneous gold catalysis. Indole is a π-excessive aromatic heterocycle able to undergo electrophilic substitution preferentially at the nucleophilic C-3 position. In addition, also N-1 and C-2 are potential reaction sites, especially when C-3-substituted indoles are employed (Figure 1).

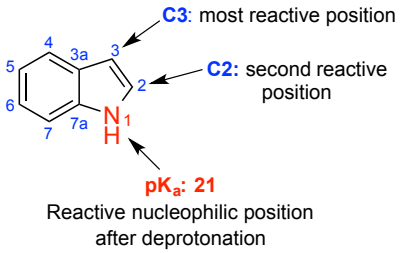

Figure 1: Nucleophilic reactive sites in indole.

Considering this kind of reactivity, it is easy to understand that, electrophilic species, obtained *via* π-activation by gold, can react with the nucleophilic positions of indole and therefore be employed for its manipulation. In particular, this review will focus on the collection and analysis of gold-catalyzed functionalization reactions of indole, covering the literature of the last 15 years. The aim is to give a complete overview on how these two important research fields, indole chemistry and gold catalysis, can be efficiently merged together in order to obtain not only effective but also useful synthetic protocols. This review is organized from the perspective of the gold-activated substrate, which is reacting with the indole derivative. In addition, a great number of reports, dealing with cascade/tandem processes for the construction of polycyclic indoles, have been described in literature. Thus, a separate section will be dedicated to this topic with particular attention to the first gold-catalyzed process, which is initiating the catalytic cycle. Finally, considering the importance of indole-based natural products syntheses, a section will collect all the works in which the key step in the preparation of these complex molecules is represented by reaction on a gold-activated indole derivative.

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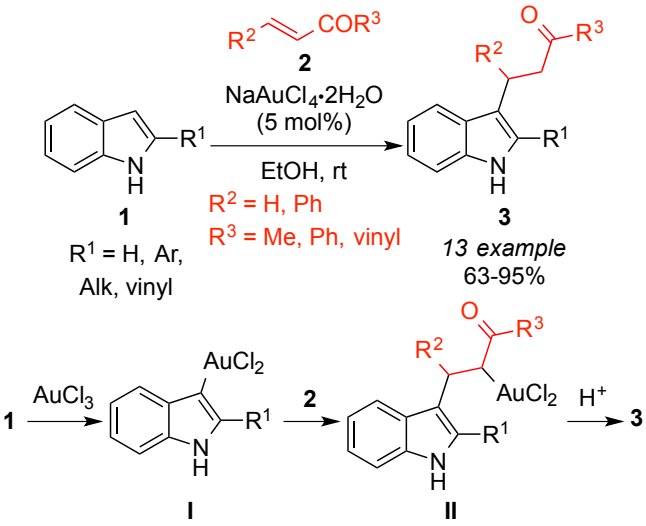
Valentina Pirovano was born in Bergamo (Italy) in 1986. In 2010, after a six-month stay in the research group of Prof. Lutz Ackerman (University of Göttingen), she obtained her master degree in Chemistry and Pharmaceutical Technology at University of Milan (Italy). From 2011 to 2014, she pursued a co-tutored Ph.D. under the supervision of Prof. Elisabetta Rossi (University of Milan) and Dr. Rubén Vicente (University of Oviedo, Spain). From 2014, she is working as Post-doctoral researcher in the group of Prof. Elisabetta Rossi, focusing her studies on transition-metal catalysis applied to the synthesis and the functionalization of heterocyclic moieties.

2. Reaction with carbon-carbon multiple bonds

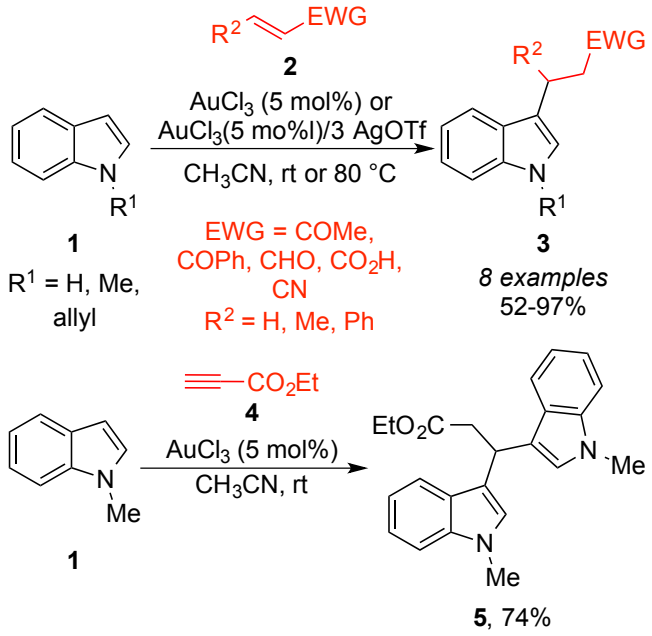
2.1. Activated π-systems

The conjugated addition to α,β-carbonyl compounds represents one of the most exploited methods for the formation of a new C–C bond at C-3 position of indole through a Friedel-Craft alkylation that is usually Brønsted- or Lewis-acid catalyzed.[20] Prompted by the seminal work of Hashmi of 2000, which demonstrated the ability of gold(III) chloride to promote the reaction between methylvinylketone and 2-methylfuran,[21] several groups reported the use of gold catalysis in similar reactions with indole. In a first work of 2004, Arcadi and coworkers described the use of $NaAuCl_4 \cdot H_2O$ for the regioselective alkylation at C-3 position of 3-unsubstituted indoles **1** through conjugated addition with α,β-unsaturated ketones **2** (Scheme 1).[22] Similarly, 3-substituted indoles underwent C-2 alkylation. According to the authors, and as described also by Hashmi[21] and Reetz,[23] the proposed reaction mechanism involved an initial auration of the indole by gold(III) to form an indolyl-gold species **I**, which gave 1,4-addition to the Michael acceptor leading to intermediate **II**. Subsequent protonolysis of **II** afforded final alkylated indole **3** and regenerated the catalyst. An alternative mechanism that cannot be ruled out, could involve the activation of the carbonyl group of **2** by gold(III), which would act as a Lewis acid. Thus, in order to support their hypothesis, the authors submitted a stoichiometric solution of **1** and $NaAuCl_4 \cdot 2H_2O$ in CH_3CN to electrospray mass analysis (ESI-MS). The positive ion mass spectra showed ion peaks at *m/z* = 348 and 350 with isotope distribution matching calculated patterns for $[indolyl\text{-}AuCl]^+$.



Scheme 1: Regioselective indole alkylation using $NaAuCl_4$ as catalyst.

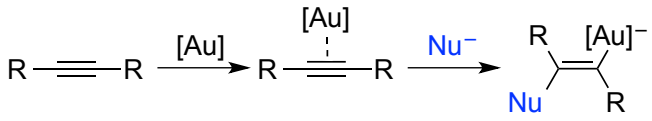
One year later, He and coworkers, expanded the scope of the process to different α,β-carbonyl compounds, employing not only ketones but also aldehydes, carboxylic acid and nitriles in a gold(III)-catalyzed reaction (Scheme 2).[24] In general this method afforded high yields of functionalized products **3**, at room temperature and with the sole $AuCl_3$ as catalyst, when α,β-unsaturated ketones or aldehydes were used. On the other hand, acrylic acid and acrylonitrile required harsher conditions, in particular higher temperature and the use of AgOTf as co-catalyst. In fact, through chloride abstraction, a more electrophilic cationic gold(III) species is generated in the reaction medium. Apart from activated alkenes, also an alkyne such as ethyl propiolate (**4**), was tested under optimized conditions. In this case, the only isolated product was **5**, arising from a double addition of *N*-methylindole on the alkyne. This result could be probably due to a first addition of the indole to **4** to give an activated alkene, followed by its fast reaction with a second equivalent of the heteroarene.



Scheme 2: Gold(III)-catalyzed reaction between indoles, α,β-unsaturated compounds and ethyl propiolate.

2.2. Non-activated π-systems

The coordination of gold to C-C multiple bonds of alkenes, alkynes and allenes is by far the most common reactivity pattern in gold-catalyzed organic reactions with activation of these systems to nucleophilic attack, as exemplified for alkynes in Scheme 3.[25]

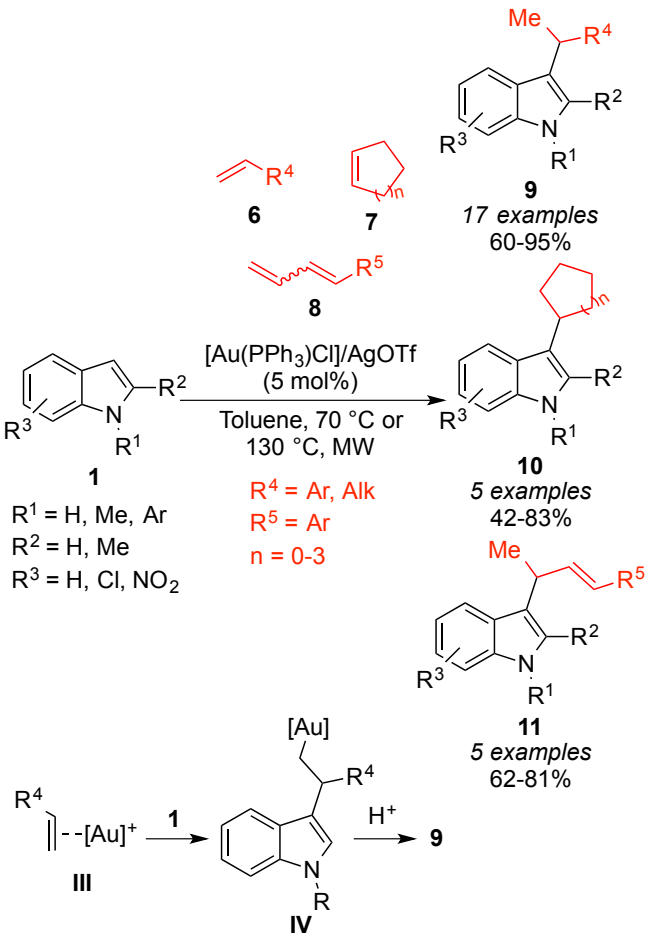


Scheme 3: Activation by gold of multiple C-C bonds.

Hydroarylation reactions involving indole as nucleophile, represent an efficient and atom-economical way to functionalize this nucleus. For this reason, they have been widely exploited in both intermolecular and intramolecular processes for the synthesis of indolyl-alkanes or -alkenes and for the construction of polycyclic derivatives.

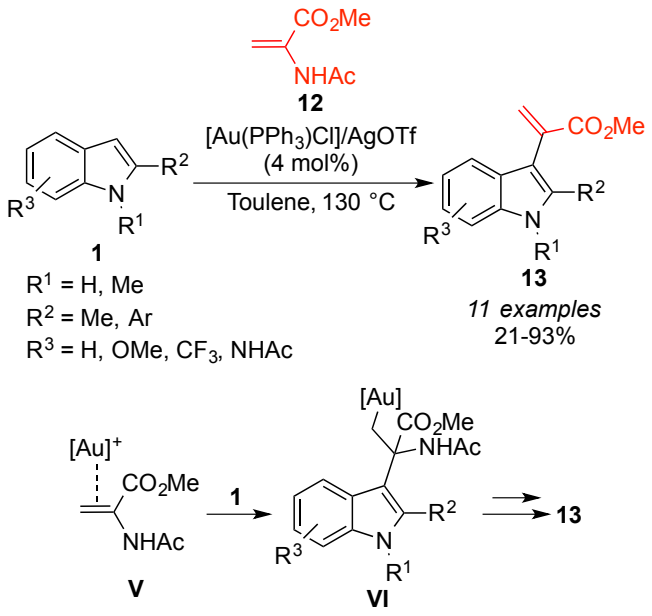
2.2.1. Intermolecular hydroarylation of alkenes

In an extended work of 2008, Wong and Che reported the first gold-catalyzed intermolecular hydroarylation of alkenes **6**, cycloalkenes **7** and conjugated dienes **8** with indoles under conventional or microwave heating (Scheme 4).[26] The reaction afforded different alkylated indoles **9**-**11** with general high yields. Noteworthy, starting from *E/Z* mixture of conjugated dienes **8**, the reaction led to alkenes **11** as single *E* isomer, probably because of precedent gold-catalyzed isomerization of the diene mixture. The mechanism proposed for the hydroarylation reaction of **6** involved a first coordination of the alkene double bond by the cationic gold(I) catalyst to give complex **III**, followed by nucleophilic attack of indole to form **IV.** Finally, the protonolysis of C-Au bond produced alkylated indoles **9.**



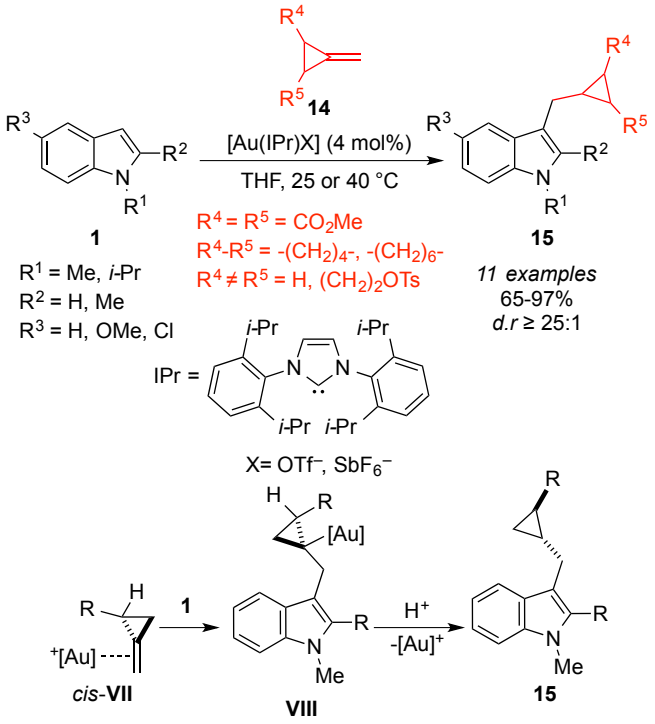
Scheme 4: Hydroarylation of non-activated alkenes and dienes.

In my research group, we also envisioned a similar gold π-activation of C-C double bond to explain the reaction between various indoles and acetamido acrylate (**12**) for the synthesis of indolyl-acrylates **13** (Scheme 5).[27] Importantly, our approach gave easy access to these interesting derivatives, which are usually obtained by addition/elimination sequences.[28–30] According to our proposed mechanism, after π-activation by gold(I), nucleophilic addition of indole to intermediate **V** led to gold-indolyl species **VI**. Then, after thermal and proton assisted elimination of acetamide and rearomatization, indolyl-acrylates **13** are formed and the catalyst is regenerated.



Scheme 5: Gold-catalyzed synthesis of indolyl-acrylates **13**.

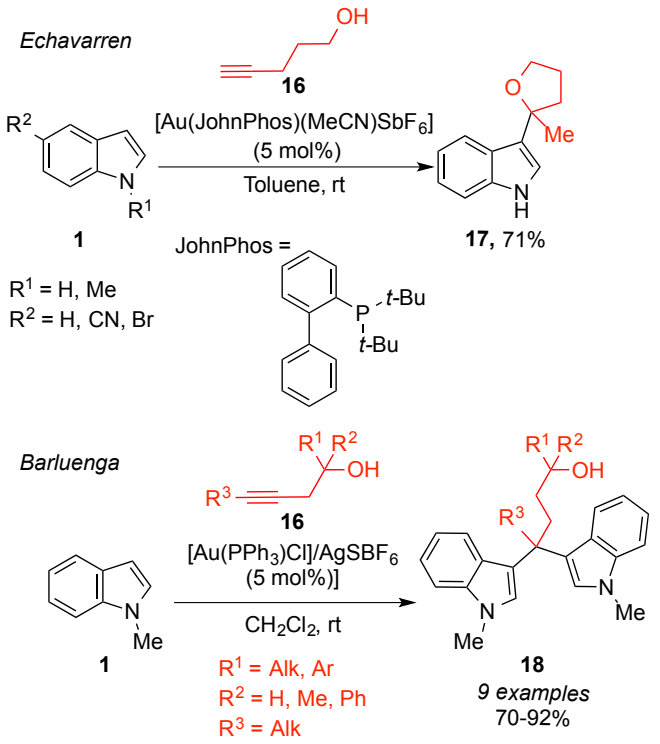
Cyclopropyl-derived alkenes represent attractive substrates for indole functionalization. However, their use require strictly controlled reaction conditions, as reported for example by Lee for gold-catalyzed addition of indoles to 3,3-disubstituted cyclopropenes.[31] In 2016 Widenhöfer and coworkers realized a gold-catalyzed anti-Markovnikov intermolecular hydroarylation of methylene cyclopropanes **14**, providing an interesting methodology for the preparation of (cyclopropylmethyl)indoles **15** (Scheme 6).[32] The high *trans*-selectivity, observed when *cis*-substituted methylenecyclopropane are used, is consistent with a mechanism in which indole is added to the *cis* π-gold complex **VII**, to give **VIII**, followed by protodeauration.



Scheme 6: Synthesis of (cyclopropylmethyl)indoles **15** by reaction with methylene cyclopropenes **14**.

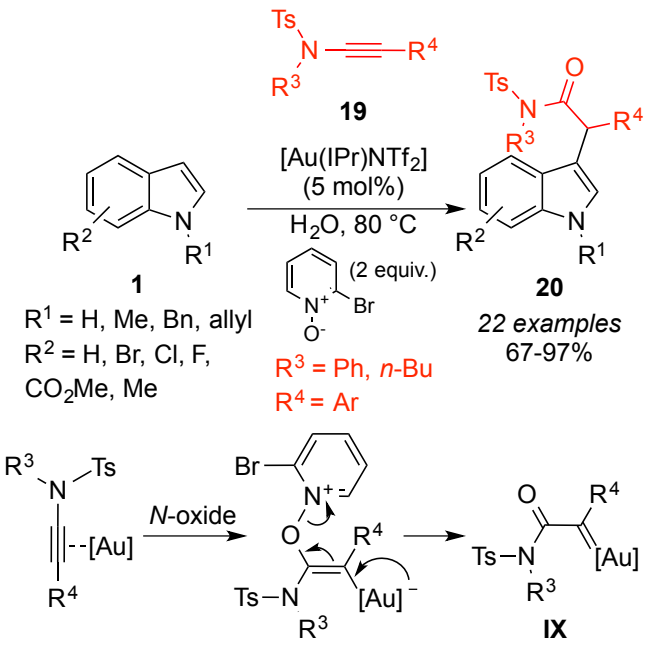
2.2.2. Intermolecular hydroarylation of alkynes

Intermolecular gold-catalyzed hydroarylation of alkynes has been studied in the last years as innovative approach for the synthesis of bis(indolyl)alkanes. Besides the work of He that made use of ethyl propiolate (see scheme 2),[24] also other research groups developed methodologies which enabled the use of unactivated terminal triple bonds for synthetizing these molecules. Remarkably, the groups of Echavarren[33] and of Barluenga[34] proposed two complementary syntheses of bis(indolyl)alkanes characterized by a diverse regioselectivity, with the addition of indole **1** at the internal or at the terminal carbon of substituted/unsubstituted alkynes, respectively. This different behavior became particularly relevant when alkynol **16** was employed (Scheme 7). Thus, when the reaction was conducted under the conditions optimized by Echavarren, the formation of bis(indolyl)alkanes was inhibited and the tetrahydrofuranyl indole **17** was isolated in high yield. On the other side, in the work of Barluenga, the use of another gold(I) species allowed for the use of 3-butyn-1-ol derivatives for synthetizing bis(indolyl)alkanes **18** as unique reaction products.



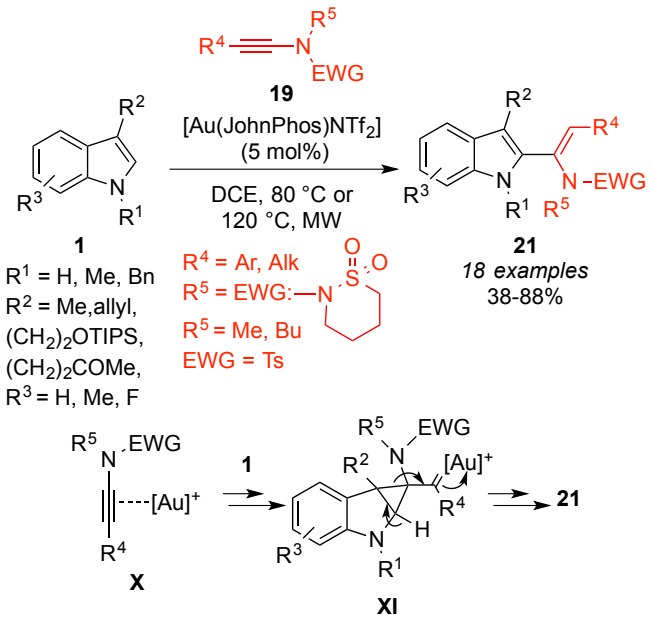
Scheme 7: Stereodivergent reaction between **1** and alkynols **16**.

Among alkynes, ynamides have emerged in the last years as versatile building blocks[35–37] and, for this reason they have been employed in gold-catalyzed reactions having indoles as nucleophiles. In 2014, Ye and collaborators, described, for example, the formation of an α-oxo gold carbene **IX** by gold-catalyzed oxidation of gold-activated ynamide **19** with a pyridine *N*-oxide and its subsequent reaction with an indole to form a 3-indolyl-amide derivatives **20** (Scheme 8).[38] The reaction had a broad scope and interestingly it could be applied to the synthesis of Pfizer endothelin antagonist UK-350,926.



Scheme 8: Gold-catalyzed synthesis of α-oxo carbenes **IX** from ynamides **19** and their reaction with indoles **1**.

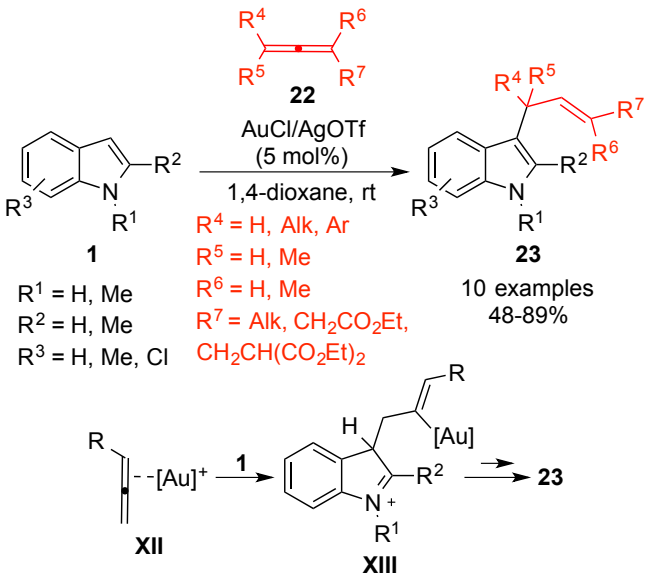
Recently, we tested the reactivity of C-3 substituted indoles in gold catalyzed intermolecular reaction with ynamides under non-oxidative conditions. In particular, nucleophilic addition of **1** to gold-activated ynamides **19** afforded 3-methyl-2-α-amidovinylindoles **21** as single isomers in high yields (Scheme 9).[39] We hypothesize that the reaction proceeded through the formation of a cyclopropyl gold carbenoid **XI** from intermediate **X**, which after ring opening and protodeauration gave rise to final products **21.**



Scheme 9: Reaction between indoles **1** and **19** under non-oxidative conditions.

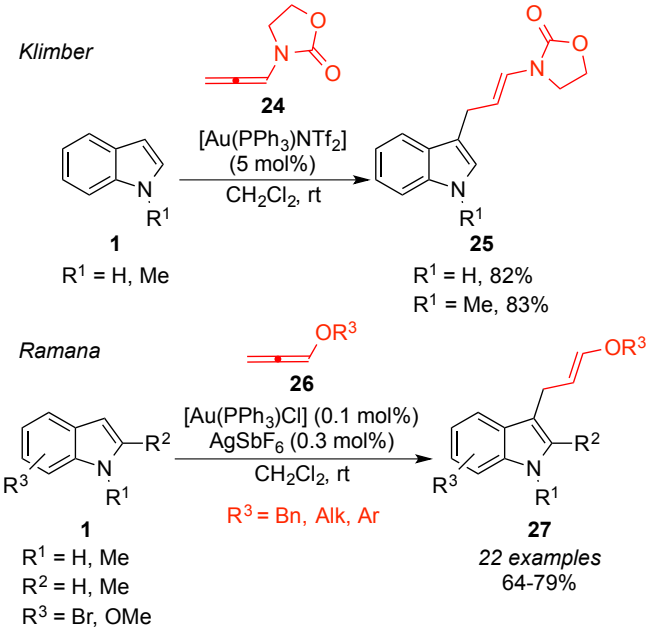
2.2.3. Intermolecular hydroarylation of allenes

Intermolecular hydroarylation of allenes certainly represents an attractive and atom-economical way to synthetize alkenylindole derivatives bearing different substituents. The first example on this topic was proposed in 2009 by Widenhöfer, who studied the reaction between non-activated allenes **22** and indoles **1** using simple AuCl/AgOTf as catalyst and affording *E*-allylic indoles **23** (Scheme 10).[40] According to the authors the formation of alkylated indoles **23** could be ascribed to a first activation of allene by cationic gold(I) to generate π-allene complex **XII**, followed by nucleohplic attack of indole yielding **XIII**. Rearomatization and protodemetallation of this intermediate finally led to functionalized indoles **23**.



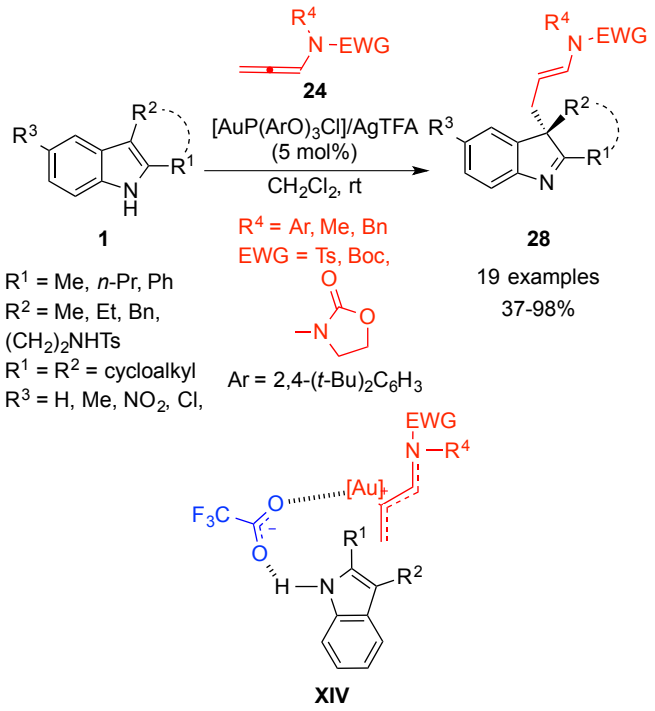
Scheme 10: Reaction between indoles **1** and non-activated allenes **22**.

Through a similar approach, Che and coworkers proposed an enantioselective intermolecular hydroarylation of allenes using a chiral gold(I) catalyst.[41] In addition, Klimber developed a mild synthesis of indolyl-enamides **25** by nucleophilic addition of indoles on gold activated *N*-allenamides **24**,[42] while Ramana and coworkers used allenylethers **26** for preparing indole allylethers **27**[43] (Scheme 11).



Scheme 11: Other intermolecular reactions between indoles **1** and allenes.

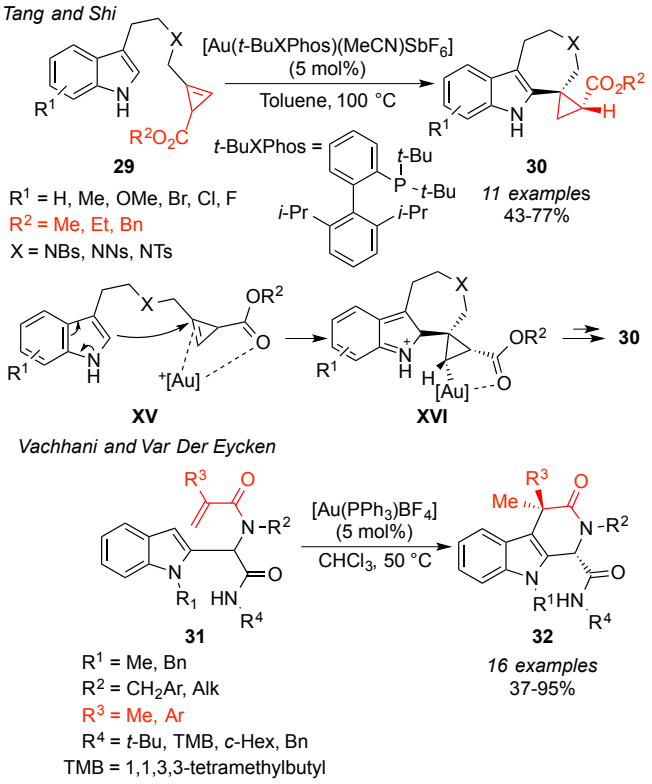
Recently, the research group of Bandini proposed an alternative application of *N*-allenamides **24**, by reacting them with 2,3-disubstituted indoles in the presence of a gold(I) phosphite catalyst. Noteworthy, the reaction afforded de-aromatized indoles **28** as single products, thus avoiding the competitive formation of *N*-alkylated compounds, only when trifluoroacetate group is used as counterion of the cationic gold(I) catalyst. This C-3 regioselectivity is explained assuming activation of the indole through hydrogen bonding interactions, forming intermediate **XIV**, which takes places only when a suitably basic counterion is employed (Scheme 12).[44]



Scheme 12: Synthesis of de-aromatized indoles **28**.

2.2.4. Intramolecular hydroarylation of alkenes

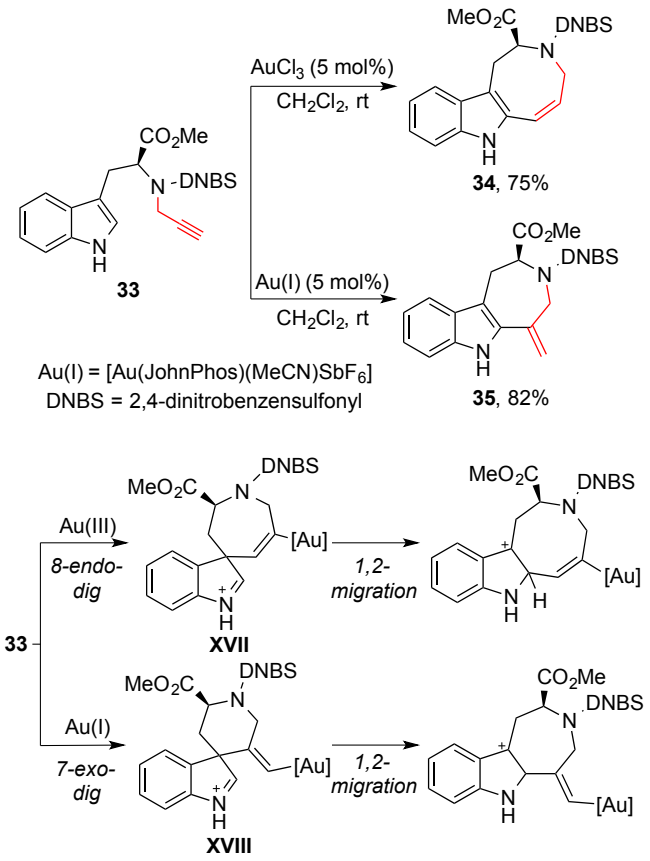
There are few examples of intramolecular hydroarylation of alkenylindoles. In 2015 Tang and Shi described the synthesis of azepinoindoles **30** by gold-catalyzed cyclization of indolylcyclopropenes **29**. After coordination of both the ester group and the double bond (intermediate **XV**), a Friedel-Craft reaction at the C-2 position of indole is responsible for the formation of intermediate **XVI**, which after re-aromatization and protodeauration afforded **30** (Scheme 13).[45] Besides, in the same year Vachhani and Van Der Eycken reported the stereoselective hydroarylation of indole **31**, synthetized through a Ugi 4-component reaction, to give pyrido[3,4-*b*]indoles **32**. The formation of **32** is explained by initial by coordination of acrylamide double bond, followed by nucleophilic addition of C-3 position, rearomatization and protodeauration (Scheme 13).[46]



Scheme 13: Intramolecular hydroarylation of indolylalkenes **29** amd **31**.

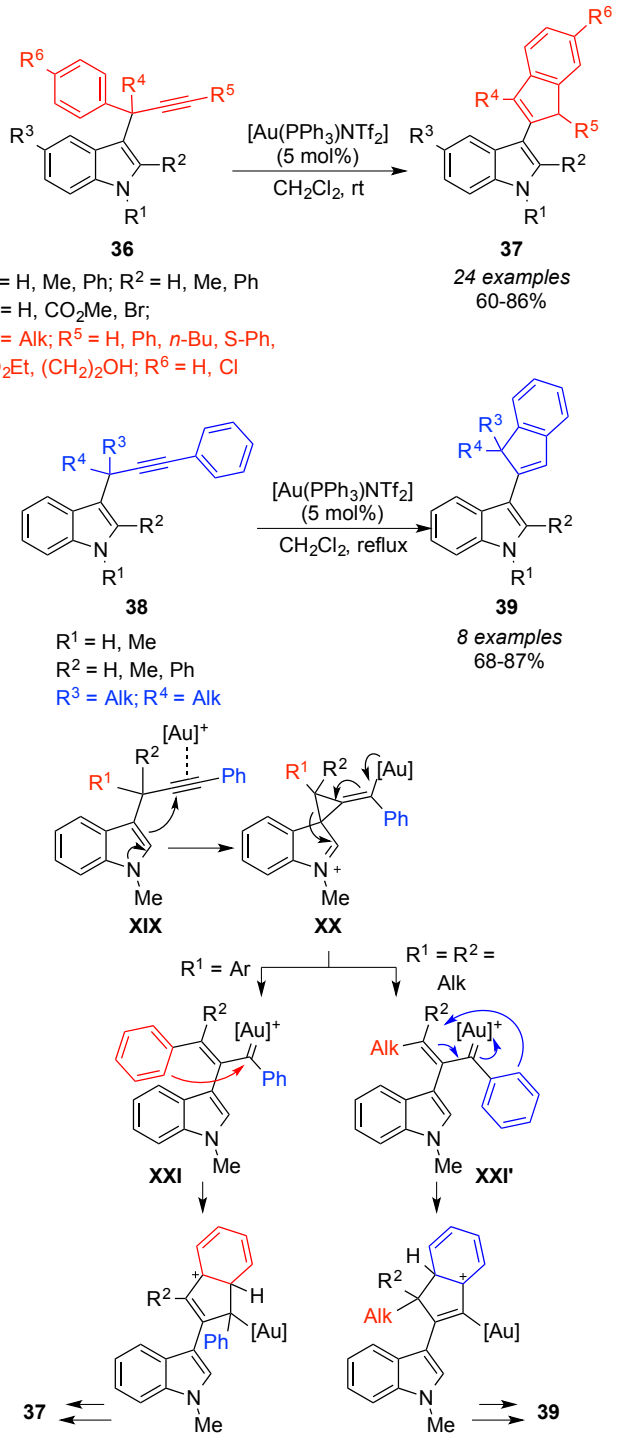
2.2.5. Intramolecular hydroarylation of alkynes

The intramolecular hydroarylation of alkyne-tethered indoles is probably one of the most exploited methodologies for synthetizing selectively polycyclic indoles as demonstrated by the great number of publications on this topic. Starting from the pioneeristic findings of Echavarren,[33,47] several research groups studied the synthesis of six-, seven- or eight-membered ring derivatives through carbocyclization of different alkynylindoles. In their early works, Echavarren and coworkers reported that C-3 alkynylindole **33** could be transformed in indoloazocine **34** or in azepino[4,5-*b*]indole **35** depending on the nature of the employed gold catalyst. Thus, gold(III) afforded **34** through an unprecedented *8-endo-dig* process, while cationic gold(I) catalyst led to **35** through a *7-exo-dig* cyclization. In both cases, the first reaction step is represented by an intramolecular cyclization, leading to spirocyclic intermediates **XVII** and **XVIII**, which further evolve to final products after 1,2-migration of the vinyl group (Scheme 14).[47]



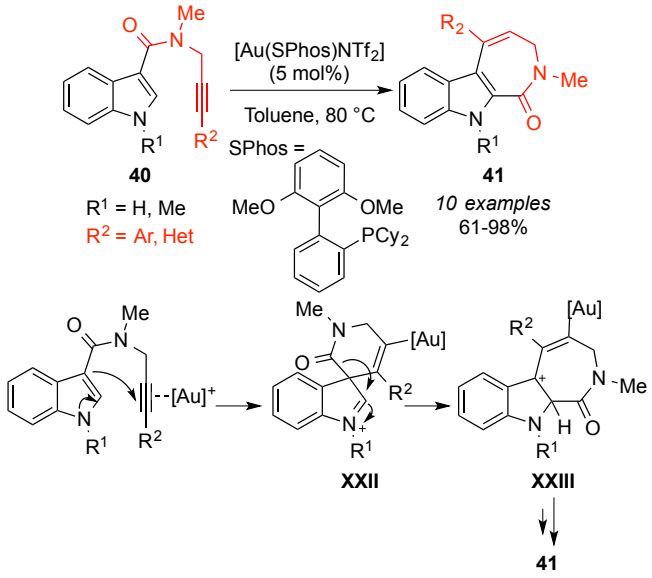
Scheme 14: Gold-catalyzed 8-*endo*-dig and 7-*exo-dig* cyclization of **33**.

A similar mechanism, involving gold activation of alkyne, nucleophilic addition of C-3 position of indole forming a spirocyclic compound and vinyl 1,2-migration, prior to rearomatization and protodeauration, has also be invoked by Enders[48] and Van Der Eycken,[49,50] among others,[51–53] to justify the cyclization of alkynylindoles to different polycycles. On the other side, different research groups concentrated their attention in the study of alternative mechanistic pathways, including other types of 1,2-migrations of spirocyclic intermediates, starting from indoles bearing alkynes on their C-3 position. For example, from 2008, Sanz and coworkers published a series of works on gold-catalyzed cyclization of C-3 propargylated indoles **36**/**38** for the synthesis of 3-(inden-2-yl)indoles **37** and **39** (Scheme 15).[54–57] Interestingly, for both products, the reaction took place through a first coordination of triple bond of starting indole (intermediate **XIX**), followed by Intramolecular attack of indole C-3 on **XIX** to give vinyl gold complex **XX.** Subsequently, 1,2-migration of the indole nucleus led to gold-carbene **XXI** or **XXI'**, depending on the substitution pattern of the starting indoles **36**/**38**. Finally, from these intermediate an iso-Nazarov or a Nazarov type mechanism could operate leading to **37** or **39**, respectively. More recently, the same group proposed also the preparation of 1-(indol-3-yl)carbazoles from 3,3-bis(indolyl)methane derivative through preferential migration of an indol-3-ylmethyl group.[58]



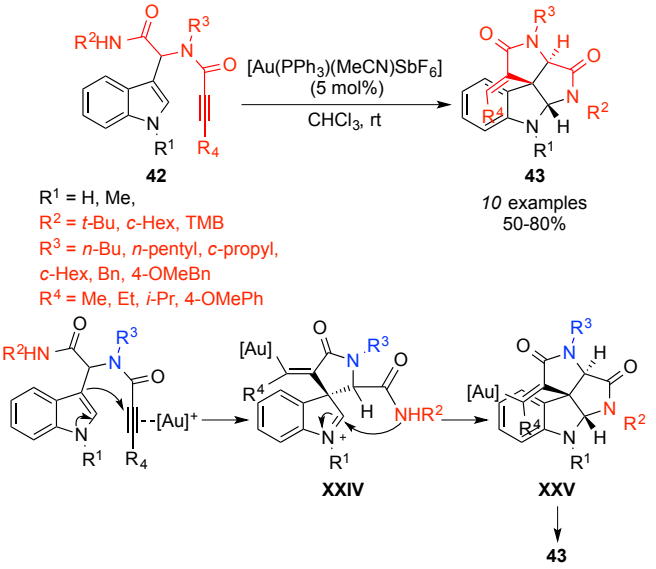
Scheme 15: Cyclizations of propargylated indoles **36** and **38** to 3-(inden-2-yl)indoles **37** and **39**.

In 2012, the group of Hashmi investigated the gold-catalyzed cyclization of alkene-substituted indole carboxamides **40**, which led to indoloazepinones **41** through a selective gold-promoted 1,2-acyloamino migration (Scheme 16).[59] Thus, after an initial π-coordination of the alkyne, spirocyclic cationic intermediate **XXII** is formed by *6-endo-dig* cyclization. Then, the migration of the acylamino group from the C-3 to C-2 position of indole led to **XXIII**, which evolved to final products **41**.



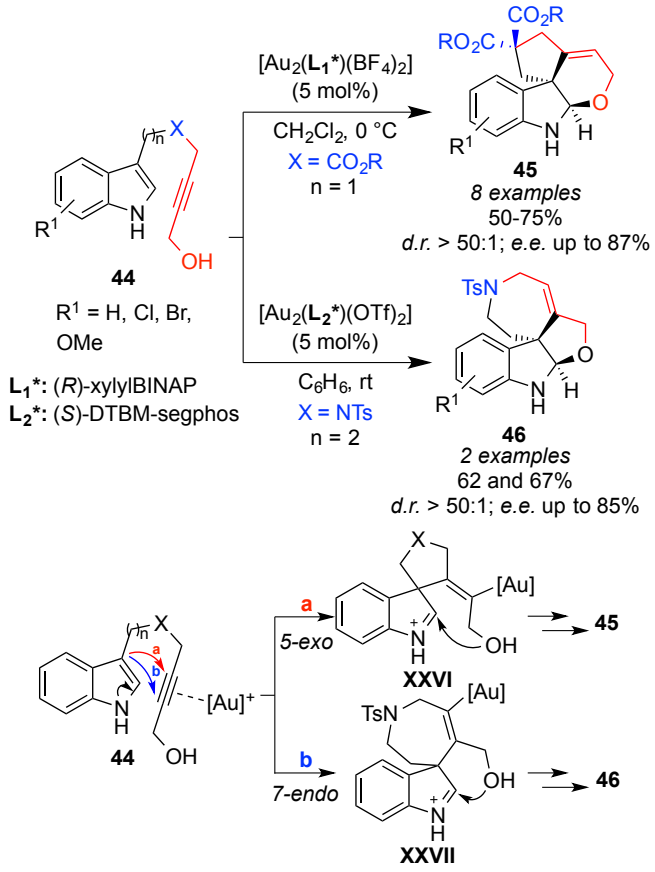
Scheme 16: Synthesis of indoloazepinones **41**.

In 2012, Van Der Eycken, proposed the synthesis of spirocyclic indolines **43**, by an interesting alternative evolution of a spirocyclic intermediate arisen from *exo-dig* cyclization of Ugi-adduct **42** (Scheme 17).[60] According to the proposed reaction mechanism, *5-exo-dig* cyclization of activated **42** afforded iminium cation **XXIV**, which is trapped by the secondary amide to give intermediate **XXV** and finally product **43**. The observed diasteroselectivity is explained through the nucleophilic attack of the amide nitrogen on iminium cation by the back side, which is the only one approachable for sterical reasons.



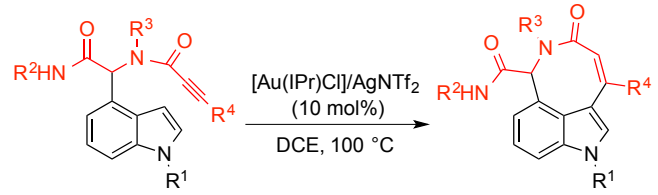
Scheme 17: Synthesis of spirocyclic indolines **43** from Ugi-adduct **42**.

A similar approach, based on the strategic trapping of indolenyl iminium ions **XXVI** and **XXVII**, obtained *via* C-3 hydroarylation of propargylic alcohol derivatives **44**, was proposed by Bandini for the enantioselective synthesis of tetracyclic fused indolines **45** and **46** (Scheme 18).[61][62] Interestingly, the preferential formation of indolines **45** or **46** could be modulated by an accurate substitution of starting propargylic alcohols **44**. By reacting malonate ester derivatives (X = CO_2R and n = 1), in fact, the reaction proceeded through *5-exo-dig* cyclization to give iminium ion **XXVI**. Instead, tryptamine derivatives (X = NTs and n = 2) underwent cyclization via *7-endo-dig* pathway forming **XXVII**. Finally, trapping of the iminium ion by the hydroxyl group was responsible for the formation of tetracyclic indolines in both cases.



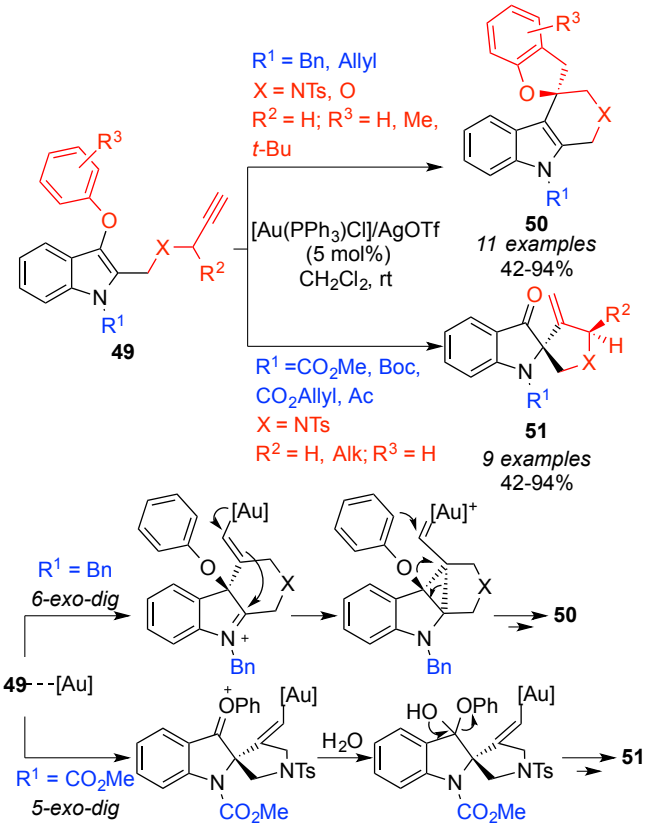
Scheme 18: Enantioselective synthesis of indolines **45** and **46** from propargylic alcohol derivatives **44**.

Besides C-3 alkynylated derivatives, other indoles prepared through an Ugi condensation and having a triple bond in other positions of their skeleton, have been tested in gold-catalyzed cyclizations by the Van Der Eycken research group.[63] For example, C-4 functionalized indoles **47** were employed to synthetize azocinoindolones **48** through direct C-3 nucleophilic attack of indole on gold-activated alkyne (Scheme 19).[64]



Scheme 19: Synthesis of azocinoindolones **48** from Ugi adduct **47**.

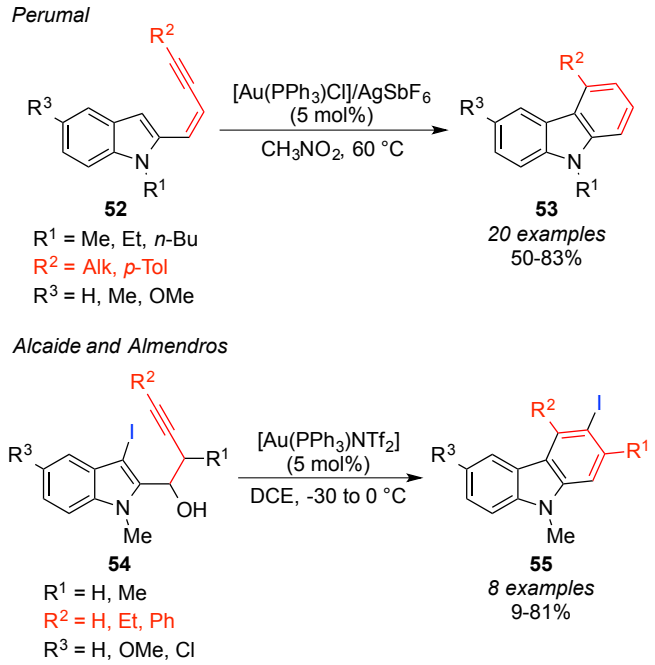
Intramolecular hydroarylation reactions have also been described for C-2 alkynylindole derivatives. For example, Padwa and collaborators reported the gold-promoted cycloisomerization of *N*-propargylindole-2-carboxamides to yield ß-carbolinones, further functionalized to prepare natural product analogues,[65,66] while the group of Liu proposed the synthesis of highly functionalized tetrahydrocarbazoles through gold-catalyzed deacylative cycloisomerization of 3-acylindole-2-ynes.[67] Besides, *N*- and *O*-propargylated indole derivatives **49**, bearing a 3-phenoxy substituent, were prepared by the group of Tu and employed in regiodivergent gold-catalyzed annulations controlled by the electronic properties of the indole protecting group R^1 (Scheme 20).[68] Having an electrodonating group, C-3 selective cyclization afforded spiro-derivatives **50** through an unusual phenoxy migration. In contrast, having an electrowithdrawing R^1, the cyclization took place at C-2 position, affording 3-oxospiroindole products **51** after water-assisted elimination of phenol.



Scheme 20: Stereodivergent synthesis of **50** and **51** from **49**.

Another interesting substrate for gold-catalyzed hydroarylation reactions is represented by 2-(enynyl)indoles, and related compounds, which cyclize to carbazole derivatives. In a work published in 2011, Perumal investigated the reaction of **52** with cationic gold(I) to yield carbazoles **53** (Scheme 21).[69] More recently, Alcaide and Almendros employed (3-iodoindol-2-

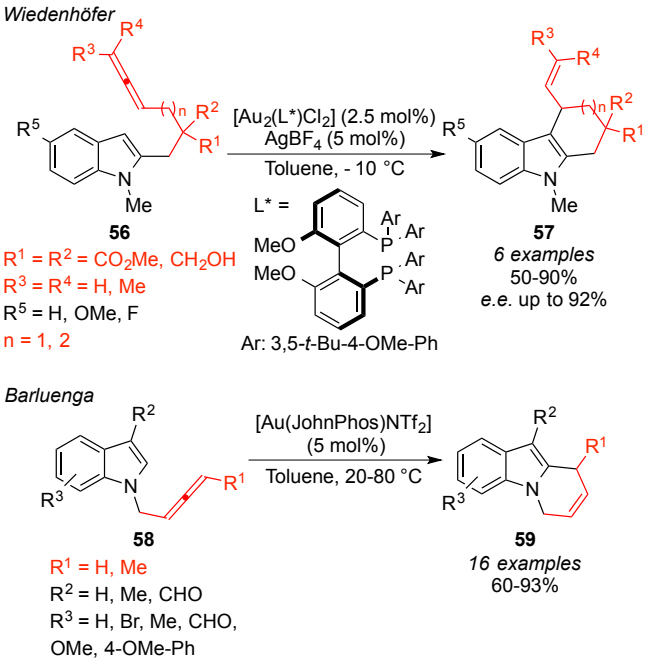
yl)butynols **54** for the synthesis of 3-iodocarbazoles **55**. In this latter case, gold-catalyzed *6-endo-dig* cyclization was followed by 1,3-iodine shift with regeneration of the catalyst and formation of the product after elimination of water (Scheme 21).[70]



Scheme 21: Synthesis of carbazoles **53** and **55** by gold-catalyzed cyclizations.

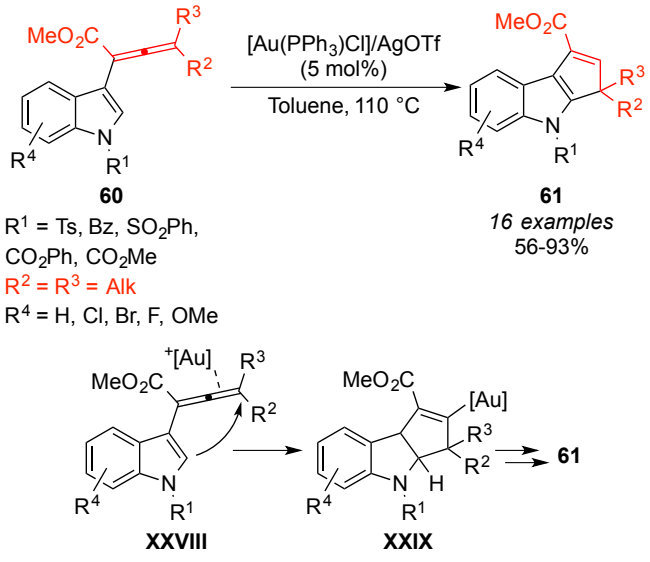
2.2.6. Intramolecular hydroarylation of allenes

Allenyl-tethered indoles represent another well-studied class of substrates for gold-catalyzed intermolecular hydroarylation and, as for alkyne derivatives, the π-bond can be installed in different position of the indole ring allowing the synthesis of a wide range of functionalized polycyclic products. Early reports on this topic were described by Wiedenhöfer and by Barluenga, which studied the reactivity of 2- and *N*-allenylindoles, respectively (Scheme 22).[71,72] Thus, according to the method reported in the first of these works, hydroarylation of 2-allenylindoles **56**, conducted in the presence of a chiral gold(I) catalyst, led to the synthesis of tetrahydrocarbazoles **57** with high enantiomeric control. On the other hand, *N*-(buta-2,3-dienyl)indoles **58** underwent a *6-endo-dig* cyclization to produce dihydropyridoindoles **59**.



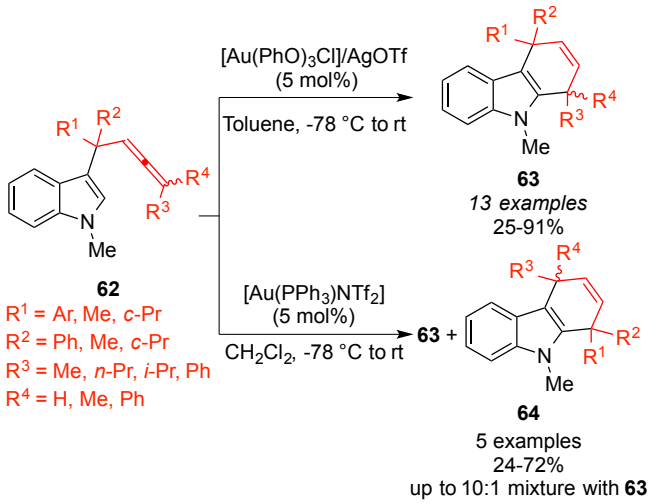
Scheme 22: Intermolecular hydroarylation of allenylindoles **56** and **58**.

In 2012, the group of Ma proposed the cyclization of indoles functionalized at C-3 position with an electronpoor allene (**60**) to give dihydrocyclopenta[*b*]indoles **61**.[73] In this case, the gold-activated π-bond of **XXVIII** is directly attacked by indole C-2 to form vinylgold intermediate **XIX**. Subsequent deprotonative re-aromatization and demetalation afforded final products **61** (Scheme 23).



Scheme 23: Intermolecular hydroarylation of C-3 allenylindoles **60**.

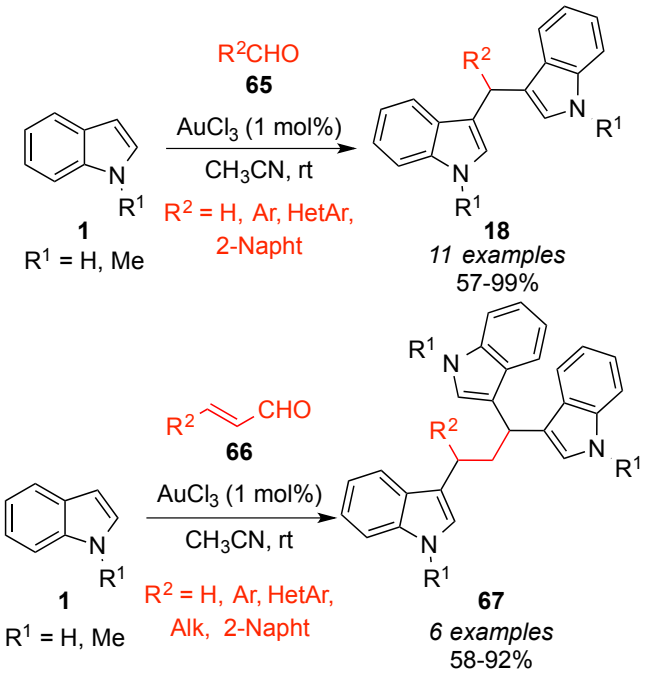
Another interesting class of C-3 allene-containing indoles, employed for intramolecular hydroarylation, is represented by 3-allenylmethylindoles **62**, prepared by Sanz and coworkers.[74] These substrates underwent gold-catalyzed cyclizations affording 4,9-dihydro-1*H*-carbazoles **63** and **64** with variable regioselectivity according to the substitution pattern of starting material and to the employed gold(I) catalyst (Scheme 24).



Scheme 24: Synthesis of 4,9-dihydro-1*H*-catbazoles **63** and **64.**

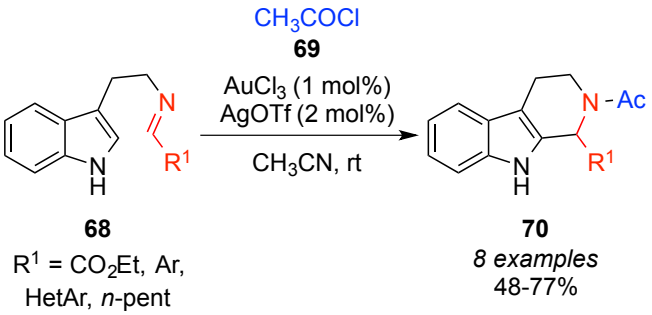
3. Reactions with carbon-heteroatom multiple bonds

Gold-catalyzed condensations between indoles and aldehydes have been investigated by the group of Nair with the scope to develop a mild protocol for the synthesis of bis- and tris(indolyl)alkanes (Scheme 25).[75–77] These products, in fact, have gained increasing attention because of their pharmaceutical properties.[78–81] In a first study, the reaction between indoles **1** and a variety of aromatic aldehydes **65** was conducted using gold(III) chloride as catalyst and yielded efficiently bis(indolyl)methane derivatives **18**. In addition, using 3-methylindole the reaction proceeded smoothly at C-2 position. As continuation to this work, the authors explored also the reactivity of α,β-unsaturated aldehyes **66** under the same catalytic conditions, obtaining products **67** arising from addition of indole to both double bond and carbonyl moieties.



Scheme 25: Gold(III)-based protocol for preparing bis- and tris-(indolyl)alkanes **18** and **67**.

Gold-catalysis has found also an application in acyl-Pictet-Spengler reaction for the synthesis of tetrahydro-β-carbolines, as reported by Youn, who studied a mild protocol for converting indole derivatives **68** into carbolines **70** (Scheme 26).[82] The reaction proceeded in the presence of cationic gold(III) and required the use of acetyl chloride (**69**) to enhance the reactivity of the imine by formation of the corresponding *N*-acyliminium ion .

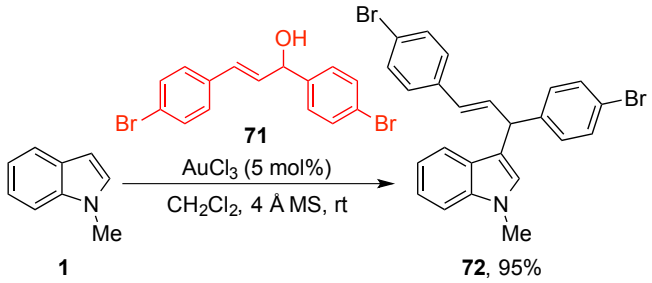


Scheme 26: Acyl-Pictet-Spengler reaction of **68** to give **70**.

4. Reactions with Csp_3 alkylating agents

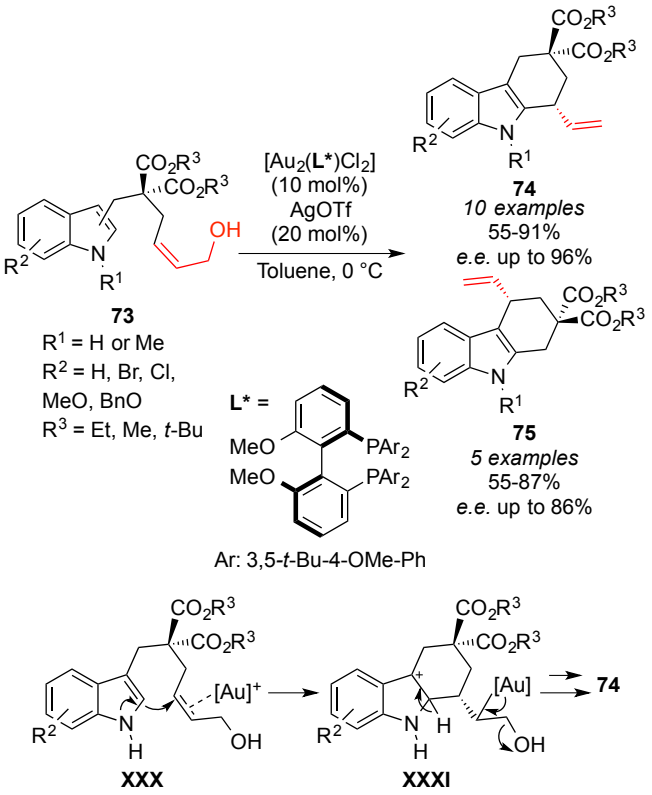
Friedel-Crafts reaction represents one of the most important C-C bond forming processes and remains the method of choice for the alkylation of arenes and heteroarenes, including indoles. However, the requirement of more environmentally and

economically benign processes, has strongly limited the use of classic alkylating agents, such as alkyl halides, in favor to more sustainable alternatives.[13] Among them, π-activated alcohols and aziridines have been employed as electrophilic Csp_3 agents to functionalize indoles under gold catalysis. A first example of this reactivity was given in 2008 by Chan and coworkers. In an extended work on gold-catalyzed allylic alkylation of aromatic and heteroaromatic compounds, they reported that *N*-methylindole **1** could be efficiently alkylated to give **72** using allylic alcohol **71** and gold(III) chloride (Scheme 27).[83]



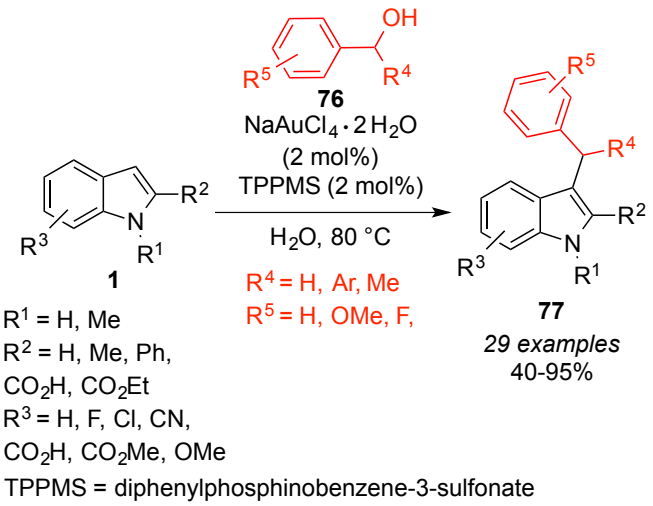
Scheme 27: Allylic alkylation of *N*-methylindole with allylic alcohol **71**.

One year later, the group of Bandini demonstrated the powerfulness of this approach with a study on gold-catalyzed intramolecular enantioselective Friedel-Crafts allylic alkylation of (*Z*)-indolyl alcohols **73** to form 1-vinyl-tetrahydrocarbazoles **74** and 4-vinyl-tetrahydrocarbazoles **75** (Scheme 28).[84–86] According to this methodology valuable alkaloids precursors could be obtained in high yield and enantiomeric excess by conducting the reaction in the presence of a chiral binuclear gold(I) catalyst. Remarkably, the (*Z*) configuration of the starting alkene, as well as the presence of hydroxyl group and the nature of the gold(I) counterion, played a crucial role in the formation of the products. (*E*)-indolyl alcohols were in fact totally unreactive while O-substituted substrates afforded significantly lower conversion and enantiomeric excess. A similar decrease in the reaction performance was observed also using a counterion different from triflate. Thus, to get an insight in the reaction mechanism, the authors performed detailed experimental and computational studies proposing a SN_2' type mechanism taking place from gold-coordinated intermediate **XXX**. Subsequent re-aromatization of **XXXI** and β-elimination of gold(I) and water led to the final products and to regeneration of the catalytic species.



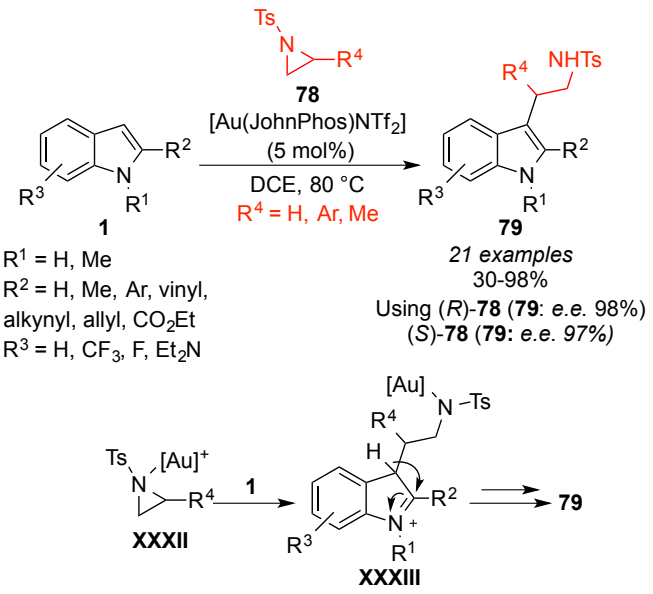
Scheme 28: Enantioselective allylic alkylation of (*Z*)-indolyl alcohols **73**.

The benzylation of indole with benzylic alcohols was later object of investigation by Hikawa and Azumaya, who developed a gold(III) promoted protocol in water (Scheme 29).[87] The reaction was catalyzed by [Au(TPPMS)Cl_2] complex, generated *in situ* (TPPMS = diphenylphosphinobenzene-3-sulfonate), and had a general broad scope considering both indoles **1** and benzylic alcohols **76**. Notably, also simple benzyl alcohols could be employed (R^4 = H), but only when the benzene ring was substituted with an electron-donating group.



Scheme 29: Benzylation of indoles using benzylic alcohols **76**.

Aziridine nucleophilic ring opening is considered one of the most reliable tool for introducing a C–C–N sequence[88–90] and, in the specific case of indole, it led to the synthesis of biologically-relevant tryptamine derivatives. For this reason, in 2016, we proposed a gold(I)-catalyzed procedure to achieve tryptamines **79** by ring-opening of *N*-tosylaziridines **78** (Scheme 30).[91] The regioselectivity of the reaction was complete in case of aryl-substituted aziridines, while alkyl substituent led to a reduced regiochemical control. We proposed that products **79** were formed through an SN_2 type nucleophilic addition of indole on gold-activated aziridine **XXXII**, followed by re-aromatization and protodeauration of corresponding intermediate **XXXIII**. Moreover, SN_2 type mechanism was supported by experimental evidences. When we employed enantiomerically pure (*R*)-**78**, in fact, the corresponding tryptamine was obtained in a stereospecific fashion.

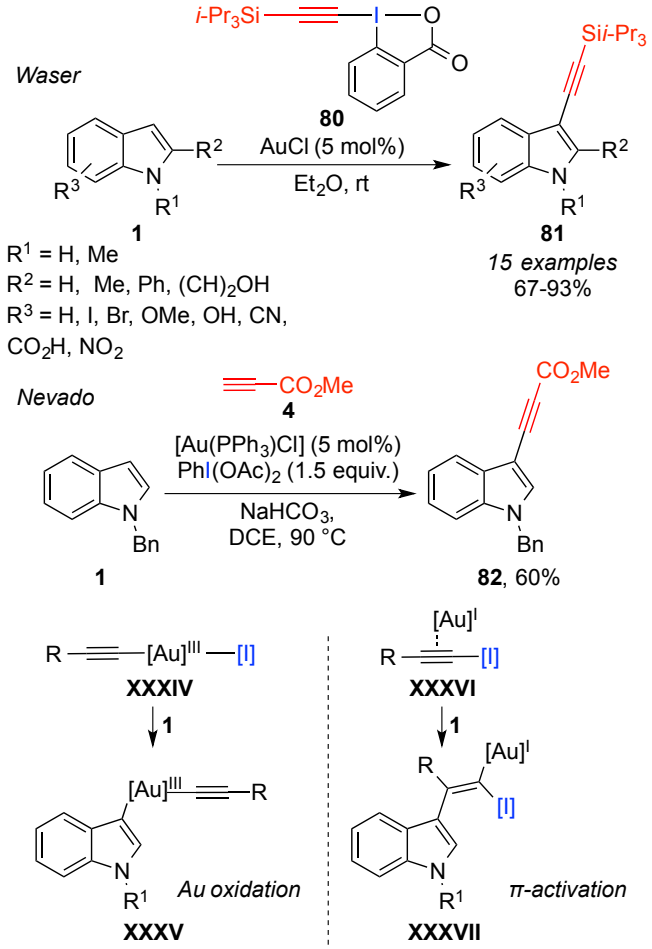


Scheme 30: Synthesis of tryptamines **79** *via* gold-catalyzed aziridine ring-opening.

5. Direct alkynylation and arylation reactions

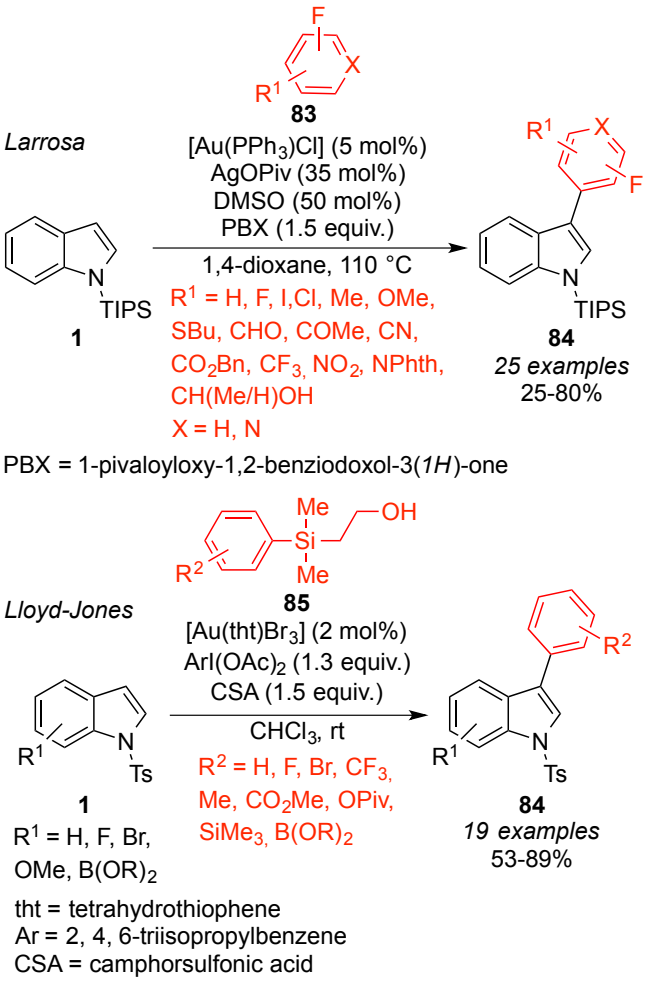
Metal-catalyzed cross-coupling reactions are a widespread and powerful method for introducing an aryl, vinyl or acetylene group on indole.[92][93] Nevertheless, this approach requires pre-modification of the heterocyclic scaffold and, for this reason, the search for direct C–H functionalization alternatives has become particularly attractive. The use of gold catalysis in direct alkynylation of indoles was reported by the groups of Waser and of Nevado in 2009 and 2010, respectively (Scheme 31).[94,95] In the first case, alkynylation of various indoles **1** was obtained by the use of a benziodoxolone-based hypervalent iodine reagent **80** under gold(I) chloride catalysis. The method was characterized by a wide functional group tolerance that allowed for the preparation of easily deprotectable silylacetylene derivatives **81**. On the other hand, in an extended study on gold-catalyzed ethynylation of electron-rich arenes, Nevado reported an example of coupling between indole **1** and methylpropiolate (**4**) in the presence of (diacetoxy)iodobeneze. Importantly, in both these works, the authors hypothesize two plausible mechanistic pathways, which account for the formation of products. Gold(I) could be in fact oxidized to a gold(III) alkynyl intermediate **XXXIV** by hypervalent iodine-based reagent and, then, indole metalation to form **XXXV** followed by reductive elimination, would led to the formation of functionalized products **81** and **82** with regeneration of gold(I) species. Alternatively, the reaction of gold-activated alkyne with hypervalent iodine compound could afford alkynyl-iodonium complex **XXXVI**. Nucleophilic attack of indole, would led to vinyl

gold intermediate **XXXVII**, which after β-elimination would provide alkynylated indoles.



Scheme 31: Gold-catalyzed direct alkynylation of indoles.

A mechanism involving an Au(I)/Au(III) process has been invoked also by Larrosa for the gold-catalyzed oxidative cross-coupling of electronpoor arenes with indoles.[96] According to this protocol, the reaction between *N*-TIPS indole **1** and fluorinated arenes **83** afforded arylated indoles **84** through double C-H activation and without the requirement of prefunctionalization or of directing groups. Lloyd-Jones and coworkers also investigated the direct arylation of indoles using 3-hydroxypropyldimethylsilyl derivatives **85** as arylating agents.[97] The reaction occurred in the presence of a gold(III) catalyst and of iodine(III) oxidant, under mild and non-inert conditions affording arylated indoles **84** efficiently (Scheme 32).

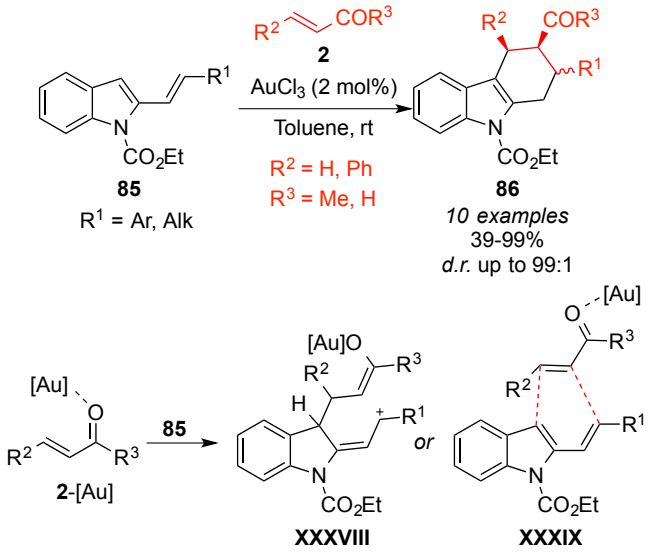


Scheme 32: Gold-catalyzed direct arylation of indoles.

6. Formal cycloaddition reactions

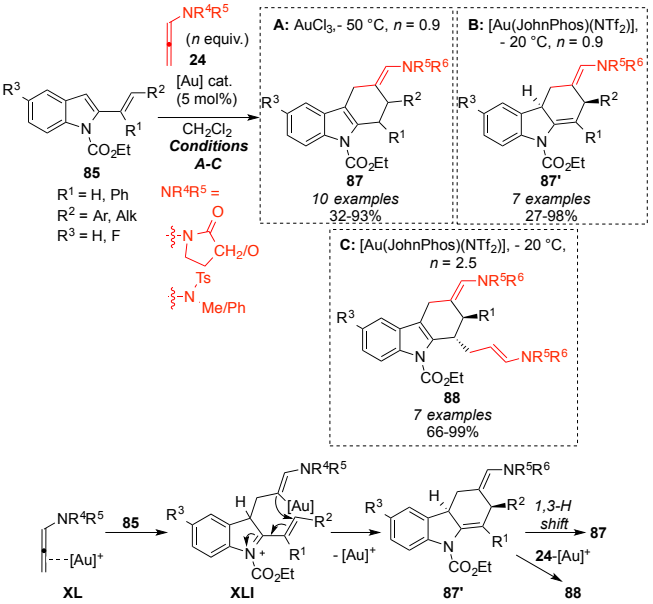
Because of the peculiar π- and carbophilicity and of the low tendency to participate in redox processes, gold has become the catalyst of choice in various cycloaddition reactions, with the formation of at least two new bonds in high chemoselective manner.[98] In 2013, we started a series of studies on the application of gold-catalysis in formal intermolecular [4+2] cycloadditions of 2-vinylindoles, an interesting class of internal-external ring dienes, with different dienophiles for the synthesis of tetrahydrocarbazoles.[99] Firstly, we concentrated our attention on the use of activated dienophiles, in particular α,β-unsaturated ketones and aldehydes **2** (Scheme 33).[100] Thus, the use of gold(III) chloride in the reaction between 2-vinylindoles **85** and **2** afforded tetrahydrocarbazoles **86** with better yield and diasteroselectivity compared to other Lewis acids such as magnesium perchlorate, scandium triflate and copper(II) triflate,

among others. We supposed that the reaction involved a first gold σ-activation of the carbonyl compound and then proceeded through a fast stepwise or a pseudoconcerted mechanism *via* intermediates **XXXVIII** or **XXXIX**. In both cases, after cyclization, 1,3-proton shift and protodeauration led to final carbazole derivatives, with general high degree of stereocontrol in favor of the *endo* adduct.



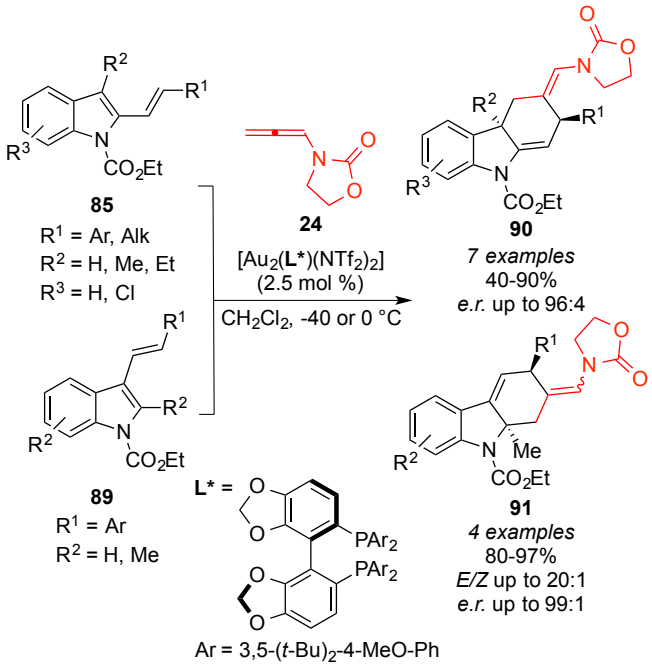
Scheme 33: [4+2] Cycloaddition of 2-vinylindoles **85** with α,β-unsaturated compounds **2**.

Prompted by this result, we next continued our investigations by using non-activated unsaturated compounds as alternative dienophiles. In particular, we thought that allenes would have been an attractive substrate, able to participate in [4+2] cycloaddition with 2-vinylindoles **85** after π-activation by gold. According to our proposal, the gold-catalyzed reaction between *N*-allenamides **24** and **85** resulted to be an effective approach to synthetize highly functionalized tetrahydrocarbazoles **87/87'-88** (Scheme 34).[101] Notably, an appropriate choice of the reaction conditions (gold catalyst and temperature) enabled the selective preparation of isomeric tetrahydrocarbazoles **87** and **87'**. In this last product, in fact, the [4+2] cycloaddition process is not followed by 1,3-shift, with the isolation of a non-aromatic carbazole derivative in high yield and with complete diasteroselectivity. Moreover, when the reaction was conducted in the presence of cationic gold(I) and of an excess of *N*-allenamide, we were able to isolate tetrahydrocarbazoles **88** as single diasteroisomer. The formation of products **87/87'** and **88** could be explained by a first nucleophilic attack on gold-activated complex **XL** to give intermediate **XLI**, which cyclize to **87'**. Then, according to the reaction conditions **87'** could aromatize or react with a second equivalent of allene. We demonstrated that the cyclization of **XLI** was possible only if the indole nitrogen was protected with an electrowithdrawing group, which enhanced the electrophilicity of β-vinyl carbon. Having electrondonating substituents, in fact, protodeauration of **XLI** was favored and the corresponding hydroarylation product was isolated.



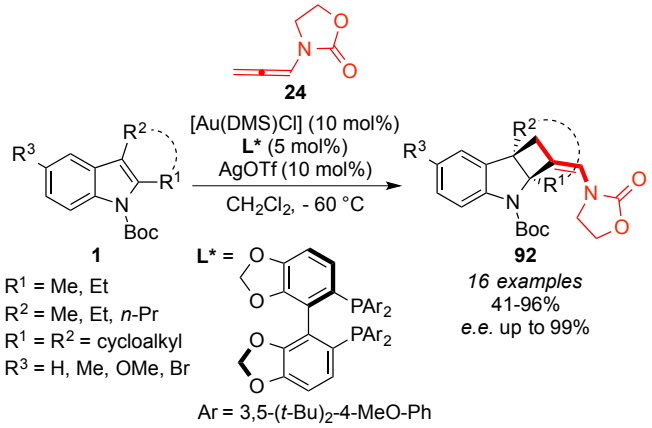
Scheme 34: Gold-catalyzed reactions of 2-vinyindoles **99** with *N*-allenamides **24**.

Very recently, we expanded our studies to 3/2- and 2/3-substitued vinylindoles **85** and **89**, which reacted with *N*-allenamides **24** in the presence of a chiral binuclear gold catalyst to furnish efficiently dearomatized tetrahydrocarbazoles **90** and **91** bearing a quaternary C-4a/C-9a sterocenter (Scheme 35).[102]



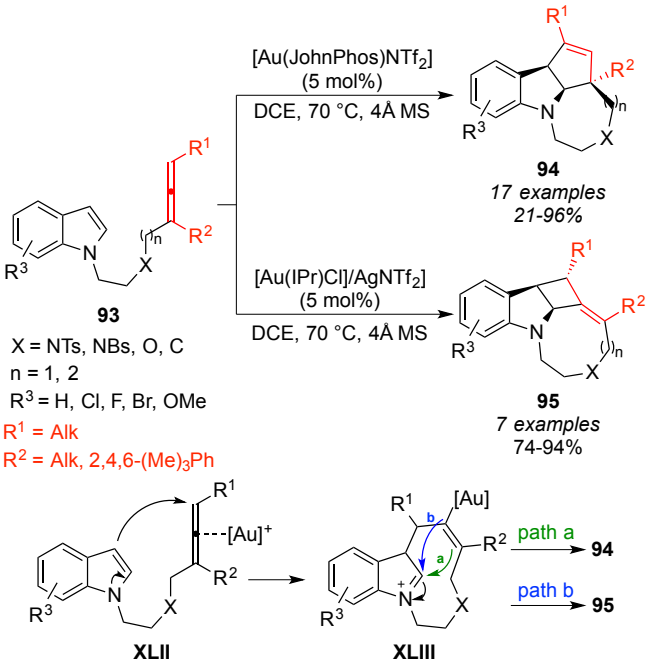
Scheme 35: Enantioselective synthesis of dearomatized **90** and **91**.

N-Allenamides served as useful building block also in [2+2] intermolecular cycloaddition reactions with 2,3-disubstituted indoles, as reported by Bandini and coworkers. Indeed, the chiral gold-promoted reaction between *N*-Boc-2,3-dimethylindole **1** and *N*-allenamides **24** yielded 2,3-indoline-cyclobutanes **92** in high yield and enantiomeric excess (Scheme 36).[103,104] Also in this case, the presence of an electrowithdrawing group at indole nitrogen was fundamental for the formation of the products.



Scheme 36: Enantioselective [2+2] cycloaddition between **1** and *N*-allenamides **24**.

In 2015 the group of Tang and Shi studied intramolecular cycloaddition reactions of allenyl-tethered indole **93**. These molecules showed interesting regiodivergent reactivity when treated with two different gold(I) catalysts or with platinum(II) chloride (Scheme 37).[105] In particular, in the case of gold, **93** could be transformed selectively into [3+2] or [2+2] cycloadducts **94** and **95** depending on the employment of JohnPhos- or IPr-based cationic catalysts. In both cases the authors assumed the formation of common alkenyl gold intermediate **XLIII** from **XLII**, which then diverged into two different products.



Scheme 37: Gold-catalyzed divergent [3+2] o [2+2] cycloaddition of allenyl-indole **93**.

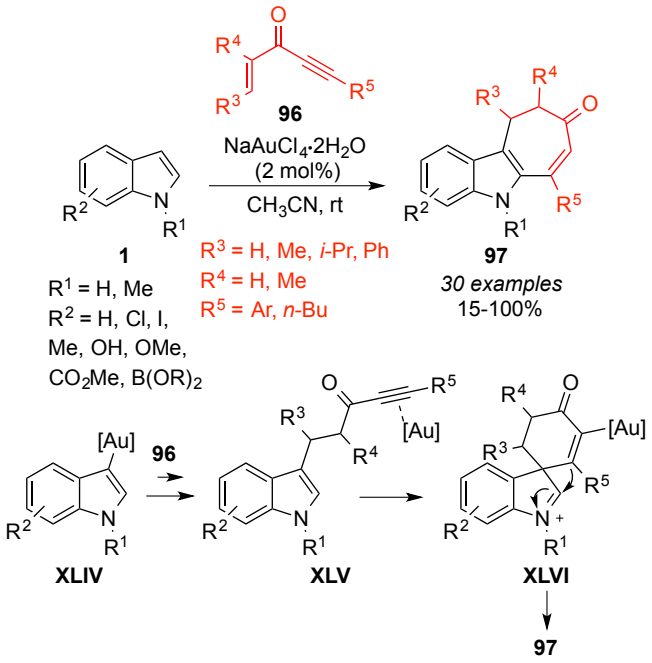
7. Tandem and cascade reactions

The development of tandem and/or cascade reactions is a highly attractive target in organic synthesis because of the possibility to increase molecular complexity in a single step. Because of their peculiar π- or -σ-selectivity and functional group tolerance, gold catalysts have been often selected as promoter of intra- and intermolecular cascade processes[106,107] also involving indole nucleus.

7.1. Initiated by the addition of activated C=C bond

In 2013 Carbery and coworkers described an intermolecular gold-catalyzed cascade reaction between indoles **1** and enynones **96** to yield [6,5,7]-tricyclic indoles **97** (Scheme 37).[108] The mechanism, supported by a series of experimental tests, involved first the indole C-3 auration[22] (**XLIV**) followed by reaction with enynone **96**. Subsequently, the π-bond of the resulting product is further activated by gold catalyst (**XLV**) and spirocyclic derivative

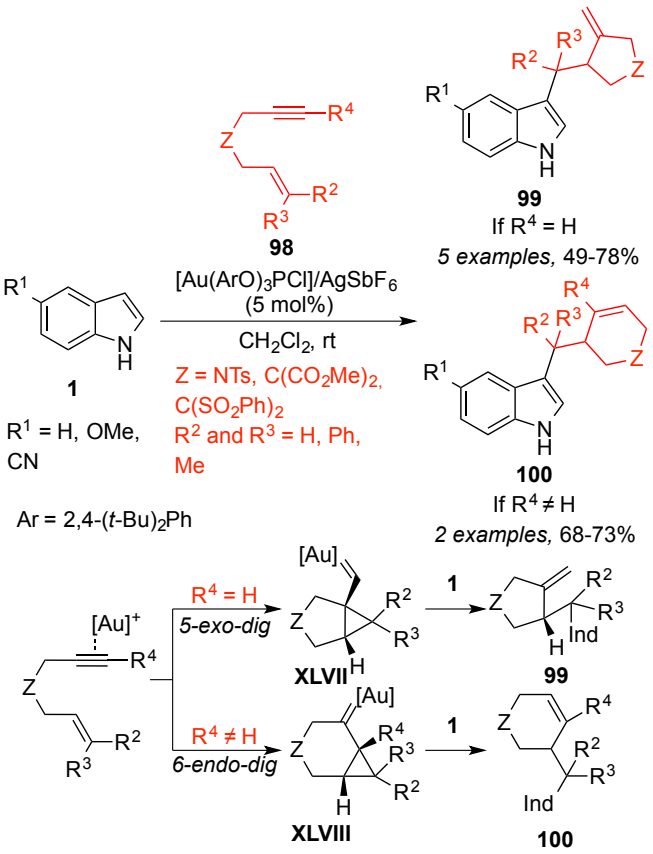
XLVI is formed. Finally, 1,2-migration and protodeauration led to **97**. A similar cascade sequence was also described by Xu and Liu for the synthesis of tetracyclic indole derivatives from indoles and 2-phenylethynyl substituted nitrostirenes.[109]



Scheme 38: Micheal addition/carbocyclization cascade reaction to yield **97**.

7.2. Initiated by a carbo- or heterocyclization

In a series of works from the research group of Echavarren, indoles **1** were employed as carbon nucleophiles in the reaction with cyclopropyl gold carbenic intermediates, generated from 1,6-enynes **98**. In this way, a series of functionalized indoles derivatives **99** and **100** were obtained through a cycloisomerization/hydroarylation sequence (Scheme 39).[110,111] The formation of these two different classes of products was explained by a *5-exo-dig* or *6-endo-dig* cyclization of π-activated **98** to give metal-carbenes **XLVII** and **XLVIII**. The preferential formation of one of these two intermediates was strictly dependent by the presence of a terminal or internal alkyne moiety on enyne **98**. In both cases, final nucleophilic attack of indoles **1** to cyclopropane ring of intermediates **XLVII**/**XLVIII** afforded efficiently five- or six-membered ring products **99** and **100**. An enantioselective version of this transformation was later proposed by Michelet yielding indoles **100** with high enantiocontrol using a chiral binuclear gold(II) catalyst.[112]

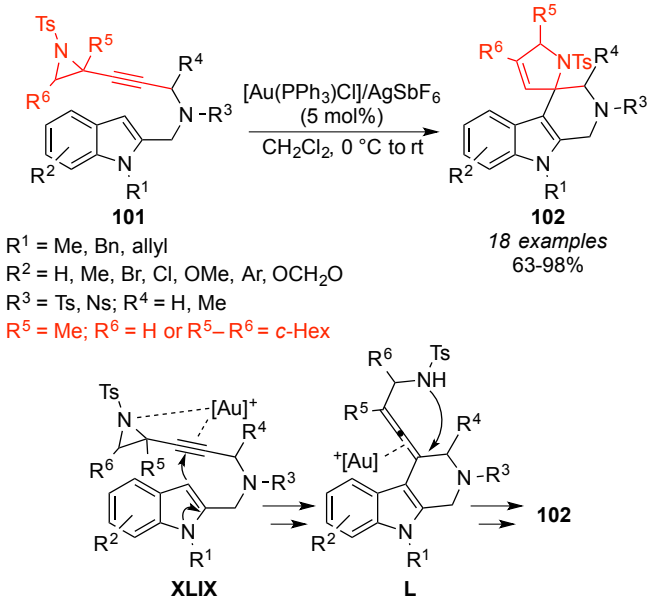


Scheme 39: Cycloisomerization/hydroarylation reaction between **1** and enynes **98**.

A similar approach, involving the formation of a cyclopropyl carbenoid species, was also applied by Waldmann and Kumar, who reported the synthesis of tetracyclic indole derivatives starting from 1,6-indolyl-enyne and aldehydes,[113] while other enyne-tethered indole sulfides were prepared and tested by Jha in the tandem gold-catalyzed synthesis of thiopyrano[2,3-*b*]indoles.[114] Another cascade processes involving alkyne hydroarylation reactions was proposed by Kundo, who reported the synthesis of various carbazoles through a gold-catalyzed sequential activation of alkynyl indoles and arylacetilyenes.[115] In addition, Nevado and coworkers reported the preparation of highly substituted tetrahydrocarbazoles by reaction between 1-ethynlcyclopropyl derivatives and indoles under gold-catalysis through a complex gold-mediate cascade sequence.[116]

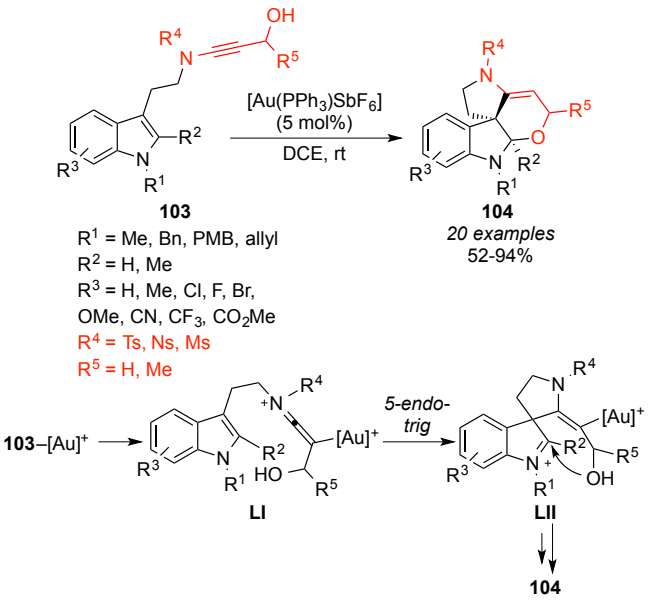
In 2014, Liang and coworkers studied the synthesis of functionalized spiro-tetrahydro-β-carbolines **102** by intramolecular gold-catalyzed carbocyclization/hydroamination of alkynylaziridine indoles **101** (Scheme 40).[117] In this case, an initial indole C-3 nucleophilic addition on dually coordinated intermediate **XLIX** led to formation of the six-membered ring with concomitant opening of the aziridine to give intermediate **L**. Then,

gold-activation of the allene moiety of **L** triggered hydroamination/cyclization and formation of final products **102**.



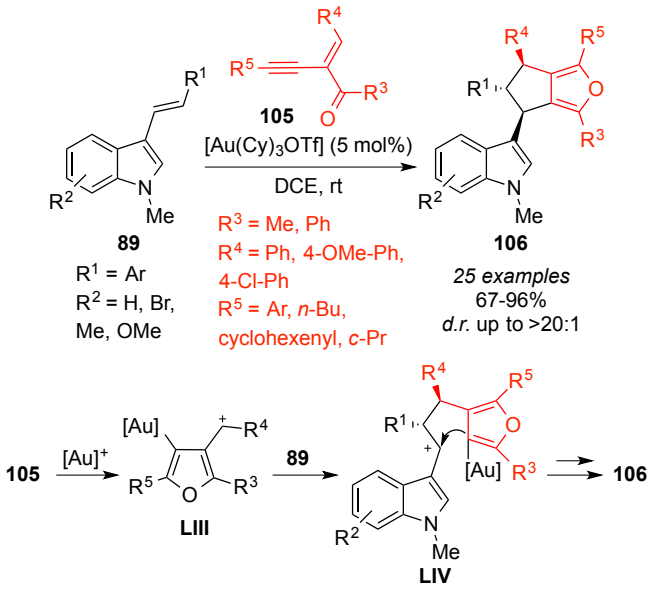
Scheme 40: Synthesis of spiro-tetrahydro-β-carbolines **102** from **101**.

Related spirocyclic indole derivatives **104** were also synthetized by the group of Yang through a gold-catalyzed tandem cyclization of indolyl ynamides **103** (Scheme 41).[118] In this case, formation of pyrrolidino indolines **104** was explained by gold-promoted generation of ketiminium species **LI**, followed by cascade double annulations to give spirocyclic iminium ion **LII** and finally formation of products **104**.

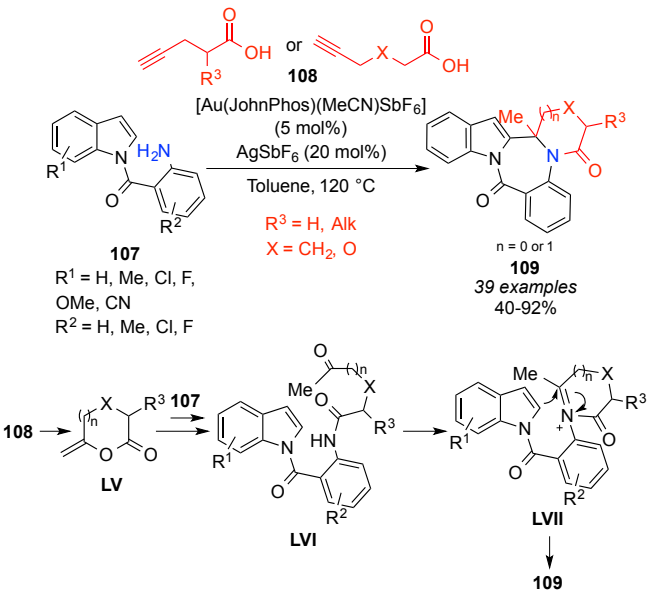


Scheme 41: Synthesis of pyrrolidino indolines **104** through ketimiun formation/annulation sequences.

Besides carbocyclization, other gold-cascade transformations took place from an initial intra- or intermolecular heterocyclization of an alkynyl derivative, to form an active intermediate, which further reacted with a nucleophilic indole species. A seminal example of this reactivity was reported by Schmalz in 2006 with his study on gold(I) catalyzed reaction of 1-(1-alkynyl)-cyclopropyl ketones with different carbon nucleophiles, including indole.[119] Similarly, in 2009, the group of Liang investigated the synthesis of furan derivatives through gold-catalyzed tandem cyclization/Friedel-Crafts reactions of 1-oxiranyl-2-alkynyl esters with various nucleophiles, comprising indole,[120] while furanyl-tethered indoles such as cyclopenta[*c*]-furans **106**, were prepared according to the methodology proposed in 2011 by Zhang (Scheme 42).[121] In this study 2-(1-alkynyl)-2-alken-1-ones **105** and 3-vinylindoles **89** underwent cascade heterocyclization/formal [3+2] cycloaddition reaction to give indoles **106** with high diasteroselectivity. The authors proposed as mechanism a first heterocyclization of **105** producing intermediate **LIII**, followed by nucleophilic attack of **89**. Subsequently, the resulting intermediate **LIV** cyclized to afford final formal [3+2] cycloaddition products **106** with regeneration of the gold species.



Scheme 42: Heterocyclization/formal [3+2] cycloaddition between **89** and **105**.

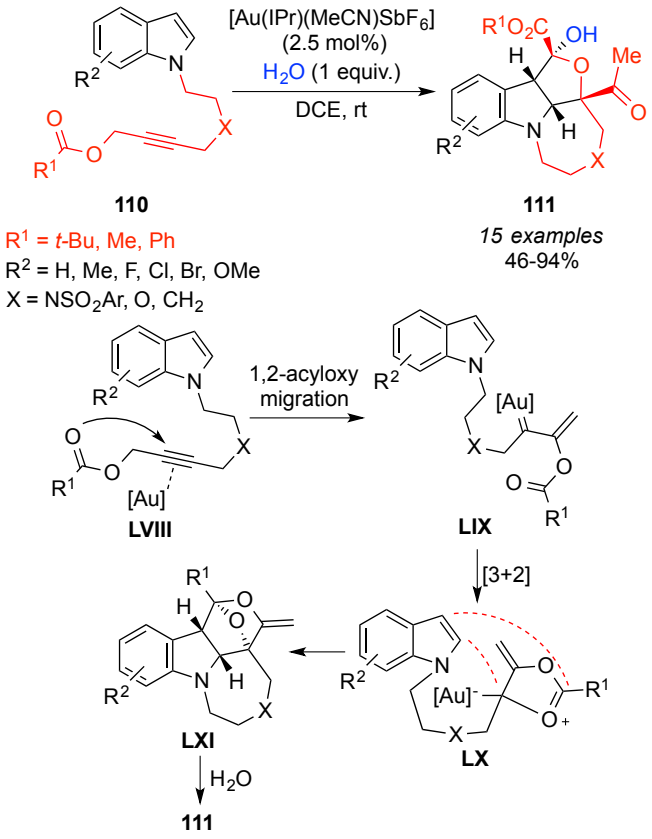


Scheme 43: Synthesis of indole-diazepinediones **109**.

Bis(alkynyl)-2-en-1-ones related to **105** were also employed by Liu in a gold-catalyzed reaction with indoles for the synthesis of furan-indole fused scaffolds.[122] In addition to these results, other intriguing polycyclic indoles were prepared starting from alkynoic acids through tandem reactions with *N*-functionalized indoles.[123,124] For example, the gold- and silver-promoted reaction between pentynoic or hexynoic acid derivatives **108** and *N*-2-aminophenyl functionalized indoles **107** afforded a series diazepinediones **109** efficiently (Scheme 43).[123] The authors demonstrated the formation of an activated enol-lactone **LV**, which then reacted with the aromatic primary amine of **107** to give **LVI**. Subsequent formation of acyl iminium intermediate **LVII** and nucleophilic addition of C-2 of indole are responsible for the final formation of products **109**. Nevertheless, the exact role of silver or gold species in the catalytic cycle was not further clarified.

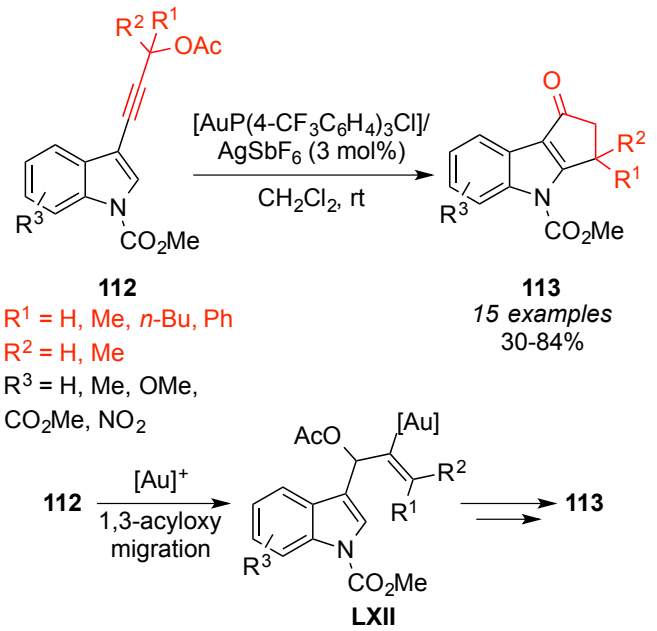
7.3. Initiated by the rearrangement of a propargylic ester

The well-known ability of gold catalysts to induce propargylic ester rearrangements, such as Rautenstrauch or [3,3]-rearrangements, has been exploited in various cascade reactions initiated by 1,2- or 1,3- acyloxy migrations.[125–128] Starting from the first work of Zhang of 2005,[129] other research groups have studied the reactivity of indoles and propargylic esters under gold catalysis in both intra- and intermolecular processes. Very recently, Shi and coworkers prepared a series of indoles **110**, *N*-substituted with propargylic esters, able to undergo tandem gold-catalyzed 1,2-acyloxy migration/[3+2] cycloaddition reaction and to afford a series of polycyclic indolines **111** bearing four contiguous stereocenters (Scheme 44).[130] According to the proposed reaction mechanism gold-activated indole **LVIII** was firstly transformed into gold carbene intermediate **LIX** *via* 1,2-acyloxy migration. Then, the nucleophilic attack of the carbonyl group on gold-carbene formed 1,3-dipolar intermediate **LX**, which underwent a [3+2] cycloaddition with C-2 and C-3 of the indole nucleus with the synthesis of vinyl ketal **LXI**. Final hydrolysis of this substrate furnished indolines **111**. In addition to these results, the authors demonstrated the possibility of conducting an asymmetric synthesis of **111** by using a chiral gold(I) phosporamidite catalyst.



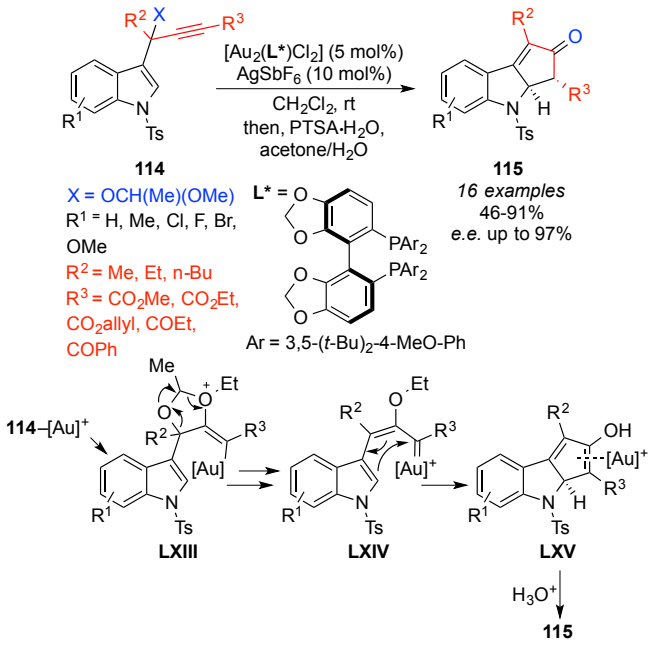
Scheme 44: Intramolecular tandem 1,2-acyloxy migration/[3+2] cycloaddition of **110**.

The strategic functionalization of an indole with a propargylic ester and its subsequent intramolecular reaction under gold catalysis was also investigated by Occhiato and coworkers.[131] In particular, 3-indolylpropynyl acetates **112** reacted in the presence of cationic gold(I) catalyst to give cyclopenta[*b*]indoles **113** through a tandem 1,3-acyloxy migration, yielding intermediate **LXII**, followed by a Nazarov cyclization (Scheme 45).



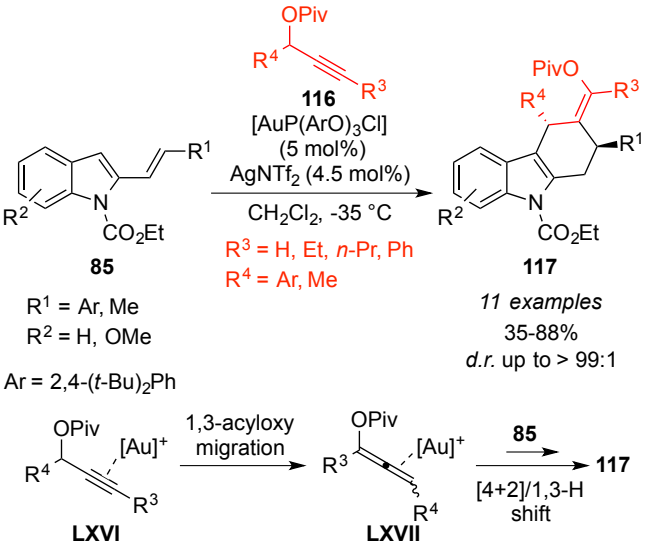
Scheme 45: Intramolecular tandem 1,3-acyloxy migration/Nazarov cyclization of **112**.

In a challenging study of 2015, Toste and collaborators investigated the asymmetric synthesis of cyclopenta[*b*]indoles **115** initiated by gold-catalyzed Rautenstrauch rearrangement of indolyl propargyl acetates.[132] At the outset, despite of the high yield, the desired product was obtained with low enantioselectivity even when using very bulky chiral ligands. To overcome this issue, propargyl ketals **114** were used instead of the corresponding acetates, affording **115** with both high yields and enantiomeric excesses (Scheme 46). The success of this approach is attributed to the formation, from oxonium species **LXIII**, of a fully planar intermediate **LXIV** that could cyclize to yield **LXV** in a ligand controlled fashion.



Scheme 46: Enantioselective synthesis of **115** initiated by Rautenstrauch rearrangement of **114**.

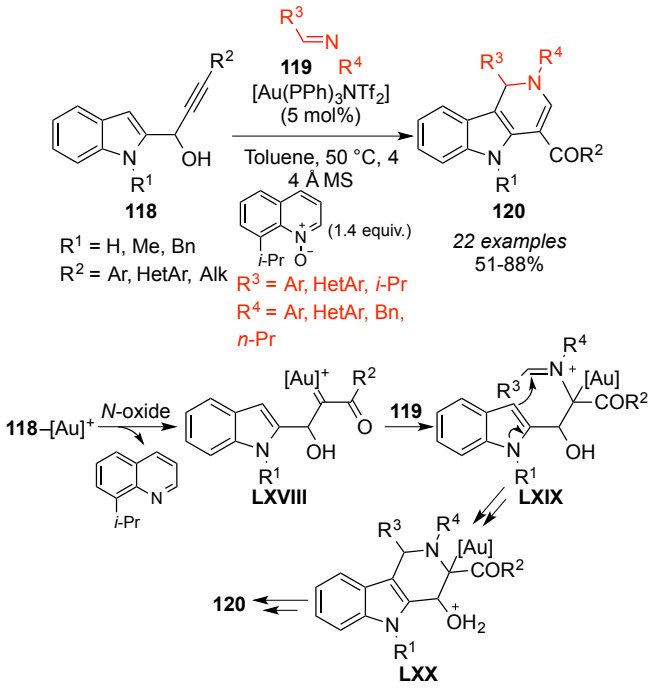
Intermolecular gold-catalyzed reactions between propargyl carboxylates and simple indoles were also described. In 2007, Echavarren reported that gold-carbenes, generated from 1,2-acyloxy migration of terminal alkynyl acetates, could be trapped by different carbon nucleophiles including indoles to provide enol carboxylates as products.[133] Furthermore, the group of Carbery proposed the stereoselective synthesis of indolyl α-acyloxyenamides by reaction of indoles with α-vinyl gold oxocarbenium complexes generated from 1,3-migration of ynamide propargyl esters.[134] As continuation of our studies on the reactivity of vinylindoles with gold-activated π-systems, in 2016 we proposed a cascade [3,3]-propargylic ester rearrangement/[4+2] cycloaddition reaction for the synthesis of tetrahydrocarbazoles **117** (Scheme 47).[135] We found that, the activation of propargylic esters **116** by means of an electrophilic gold(I) catalyst (intermediate **LXVI**), triggered the 1,3-migration leading to gold-activated allenes **LXVII**. Subsequent [4+2] cycloaddition with 2-vinylindoles **85** followed by 1,3-proton shift led to carbazoles **117** mostly with complete *trans* diasteroselectivity. A preliminary screening of chiral gold(I) phosporamidite revealed also the possibility to synthetize **117** with good enantioselectivity.



Scheme 47: Gold-catalyzed 1,3-acyloxy migration/[4+2] cycloaddition reaction of **85** and **116**.

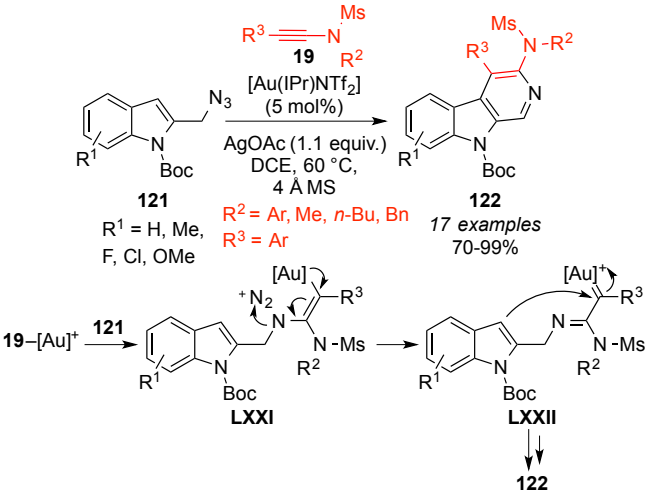
7.4. Initiated by the formation of an α-oxo or α-imino carbene from an alkyne

Gold-catalyzed oxidative reactions on alkynes represent an interesting methodology for the generation of highly reactive α-oxo or α-imino carbenes species able to participate to further transformations with various nucleophiles.[19,136] For this reason, in 2013, Liu explored the formation of indolyl-α-carbonyl gold carbenoids **LXVIII** by reaction of alkynylindoles **118** with an external oxidant, and the sequential nucleophilic addition/cyclization with imines **119** to finally yield dihydro-γ-carbolines **120** (Scheme 48).[137] According to the proposed reaction mechanism, after initial gold-promoted formation of intermediates **LXVIII** and **LXIX**, the formation of carbolines **120** could be ascribed to nucleophilic attack of indole C-3 on iminium ion **LXIX** to give **LXX**, followed by unusual 1,2-acyl migration and 1,2-proton shift.



Scheme 48: Gold-catalyzed synthesis of **120** from α-oxo carbenoid **LXVIII** and imines **119**.

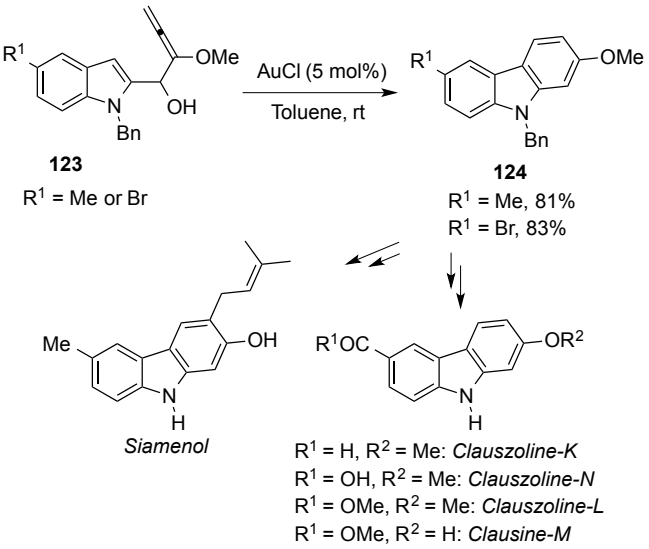
In the context of their investigation on gold-catalyzed intermolecular reaction of ynamides **19** with arylazides for the synthesis of 2-aminoindoles, Lu and Ye extended this methodology to indolyl azides **121** with the scope to obtain a tandem protocol initiated by formation of a α-imino gold carbene (Scheme 49).[138] Therefore, gold-catalzyed reaction between **121** and **19** generated intermediate **LXXI**, which evolved to α-imino carbene **LXXII**. Then, nucleophilic trapping by indole and dehydrogenative oxidation promoted by silver acetate led to 3-amino-β-carbolines **122**.



Scheme 49: Synthesis of **122** from α-imino gold carbene intermediate.

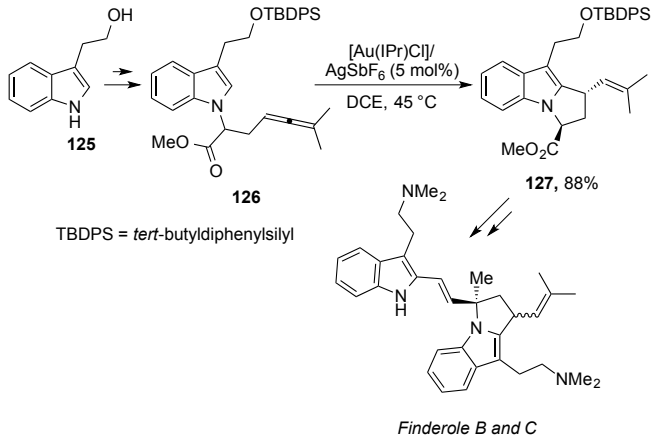
8. Application of gold-catalysis to the synthesis of indole-based natural products

In the last decade, gold catalysis has gained a remarkable position in the synthesis of bioactive complex products as summarized in the recent reviews by Hashmi[139,140] and by Yang.[141] Taking into account indole alkaloids, Ma and coworkers reported in 2011 the gold(I) chloride catalyzed carbocyclization of 2,3-allenols **123** to carbazoles **124** as key step in the total synthesis of *Siamenol* and *Clauszoline-K,L* or *Clausine-M* derivatives (Scheme 50).[142]



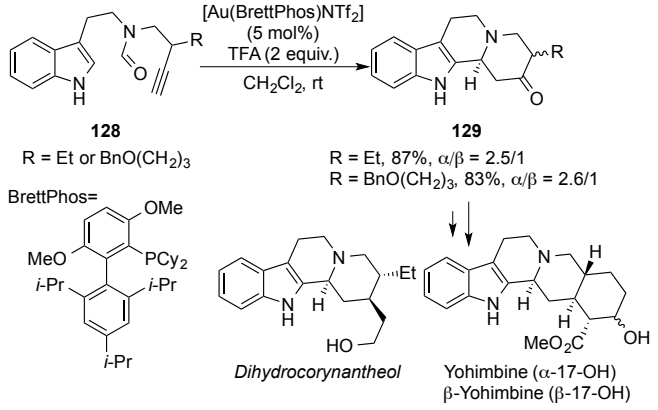
Scheme 50: Gold-catalyzed carbocyclization of **123** as key step in the synthesis of *Siamenol* and *Clauszoline-K,L* or *Clausine-M* derivatives.

In the same year, the group of Toste applied a gold-based protocol to the synthesis of antimalarian bisindole diasteromeric alkaloids *Finderole B and C* (Scheme 51).[143] Starting from commercially available tryptophol (**125**), key *N*-allenyl intermediate **126** was prepared in five steps and then subject to a gold(I)-catalyzed hydroarylation to give **127**.



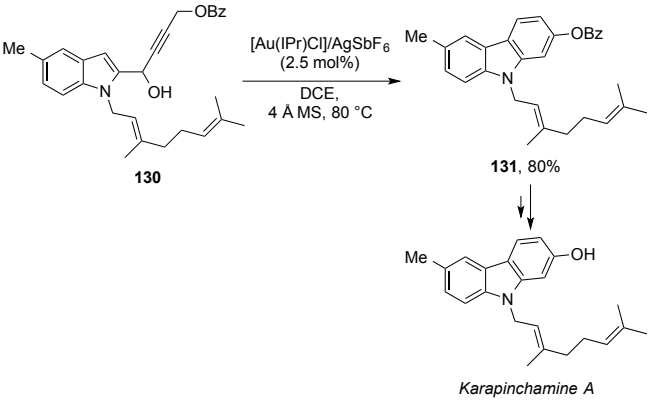
Scheme 51: Gold-catalyzed hydroarylation of **126** to **127** in the total synthesis of *Finderole B* and *C*.

In 2012, Zhang proposed an elegant approach to indole alkaloids having a hexahydroindolo[2,3-*a*]quinolizine skeleton, such as *Dihydrocorynantheol*, *Yohimbine* and *β-Yohimbine* (Scheme 52).[144] The key step in their synthesis was represented by a cascade gold-catalyzed amide cyclization of **128**, followed by Friedel-Crafts cyclization and Ferrier rearrangement to give indole-fused hexahydroquinolizinones **129**, subsequently transformed into final alkaloids.



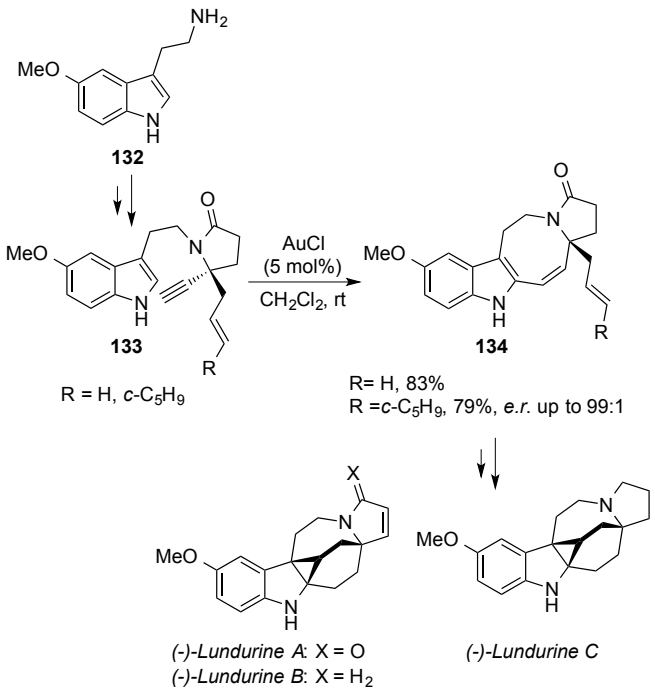
Scheme 52: Gold-catalyzed cascade cyclization of **128** for the synthesis of hexahydroindolo[2,3-a]quinolizine-based alkaloids.

In the context of their studies on the synthesis of carbazoles by cyclization of 4-benzoxyl-1-(indol2-yl)-2-alkynols, Ma and coworkers demonstrated the utility of their methodology by its application to the total synthesis of *Karapinchamine A* (Scheme 53).[145] Key propargylic alcohol derivative **130** was prepared from commercially available 5-methyl-1*H*-indole-2-carboxylate, and then cyclized in the presence of cationic gold(I) catalyst to give **131**. Subsequent deprotection led to *Karapinchamine A*. Remarkably the total synthesis was conducted on a multi-gram scale, thus allowing the isolation of more than five grams of the final product.



Scheme 53: Gold-catalyzed cyclization of **130** as key step in the total synthesis of *Karapinchamine A*.

Finally, in 2016, the group of Echavarren proposed an outstanding protocol for the synthesis of *Lundurines A*, *B* and *C,* having as key step, for the construction of polyhydroazocine ring, a gold(I)-catalyzed *8-endo-dig* alkyne hydroarylation reaction (Scheme 54).[146] Starting from 5-methoxy-tryptamine (**132**), alkynyl intermediate **133** was obtained through a condensation/lactamization/Claisen rearrangement cascade, followed by Ohira-Bestmann homologation. Subsequently, it was subjected to gold(I) chloride catalyzed cyclization to afford efficiently cyclic intermediates **134**, further transformed into final *Lundurines A-C*.



Scheme 54: Total synthesis of *Lundurine A-C*, based on gold(I)-catalyzed *8-endo-dig* cyclization of alkynylindole **133**.

9. Final remarks

After more than 150 years from its discovery, indole still dominates the scene of heterocyclic compounds and, consequently, the discovery of new approaches for its functionalization represents a stimulating challenge for synthetic organic chemists. For this reason, the objective of this review is to give to the readers an overview on how gold catalysis, in the last fifteen years, has been influencing indole chemistry, opening new synthetic possibilities. The peculiar ability of gold species to activate multiple bonds, in fact, has allowed the development of selective and efficient protocols for indole functionalization, exploiting its intrinsic nucleophilicity. In this way, through an accurate choice of gold catalysts and of reaction conditions, it has been possible to synthetize a plethora of indole derivatives, including complex polycyclic compounds, usually by means of extraordinarily selective and mild protocols.

Certainly, the application of homogeneous gold catalysis in indole chemistry has become a well-explored research field and, at glance, several challenging goals have already been reached. However, the continuous need for effective and regio- and stereoselective methods, both in the synthesis of simple indoles or alkaloid derivatives, opens new possibilities in particular by the use of chiral gold species. Some asymmetric indole functionalizations have been also described in this review, although their number is very limited compared to the racemic protocols. Moreover, considering the excellent capability of gold catalysts to promote tandem and cascade processes, some efforts still deserve to be devoted to the study of new strategies for the synthesis of complex polycyclic indoles. For these reasons, in the future, gold catalysis will probably continue to play a privileged role in indole chemistry, confirming the potential gained in these last years and creating stimulating alternatives for the synthesis of useful indole derivatives.

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Keywords indole • gold • homogeneous catalysis• synthetic methods • nitrogen heterocycles

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