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Spiroindoles as Intermediates/Products in Transition Metal Catalyzed Dearomatization of Indoles

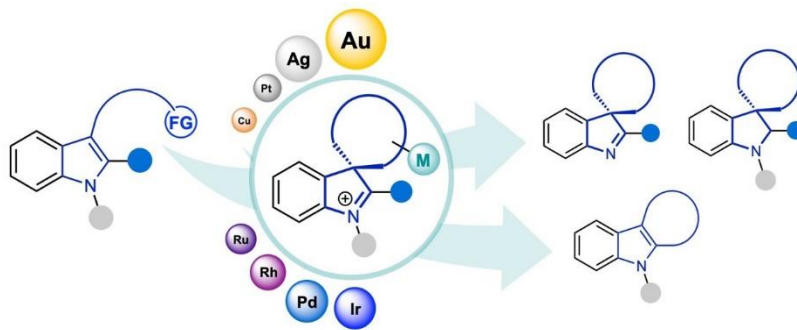
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Spirocyclic indole derivatives are fascinating tridimensional molecular scaffolds, from both a synthetic and biological point of view. Among the diversity of strategies developed to access this kind of structures, transition-metal catalysis recently led to impressive advances, especially in order to tame the unique reactivity of the dearomatized spirocyclic intermediates. These species can indeed evolve towards both spirocyclic or non-spirocyclic products through re-aromatization-driven processes which are at the same time highly challenging to control but also source of a large structural diversity. This review highlights the most prominent methods of the last decade allowing to trigger a spirocyclization on indole derivatives tethered with a transition metal-activable functional group, leading to both spirocyclic and rearomatized products. The discussion is particularly focused on the reactivity and the complex mechanistic features regarding the evolution of the spiroindolenium intermediate, highly dependent on the catalytic system.



1. Introduction

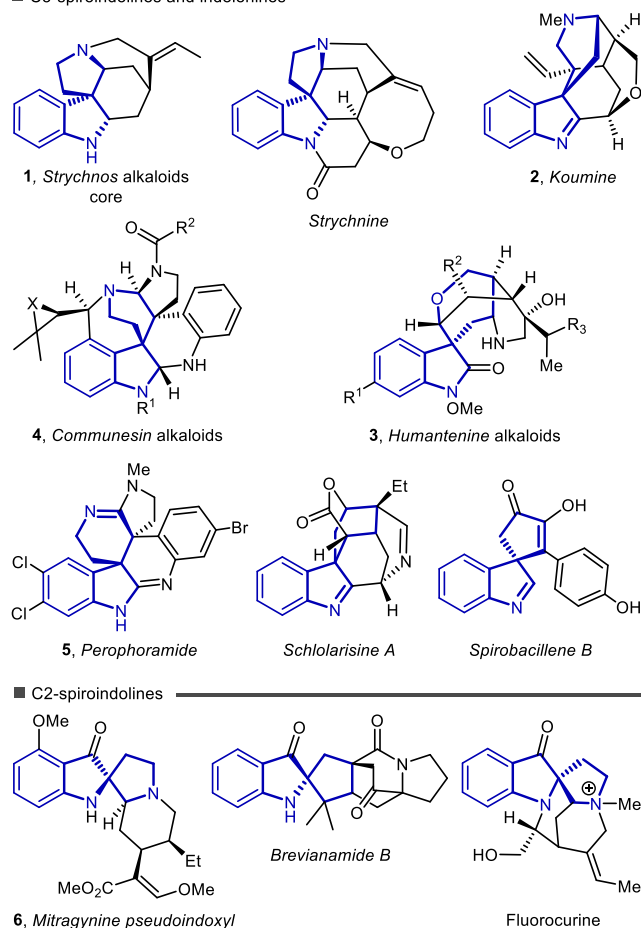
As tridimensional objects, spirocyclic¹ compounds are highly valuable scaffolds in medicinal chemistry and for the diversity-driven exploration of new hits for biological activities.² Besides their ability to project functionalities in the three dimensions, they present an ideal balance between conformational rigidity and flexibility, allowing for potential adaptation of their geometry to interact with biological targets, with a reduced entropy penalty compared with linear scaffolds.³ Spirocyclic indole derivatives, on which the indole core shares one single carbon atom with an adjacent cycle, have emerged as privileged motifs in drug discovery, and consequently as target products in the development of new synthetic methods. They are ubiquitously present in numerous natural alkaloids (Scheme 1), exhibiting for most of them proven biological activities, such as cytotoxic (**1**,⁴ **2** and **3**,⁵ **4**⁶ and **5**⁷), antimalarial⁸, and opioid agonistic (**6**⁹) activities, along with the well-known strychnine as a neurotoxic.^{4a,10} As a consequence, a rising interest in these highly biologically relevant structures has been witnessed over the last three decades and many efforts were devoted to the development of new synthetic approaches towards spirocyclic indole derivatives.

One of the most efficient approach for the formation of spirocyclic compounds relies on catalyzed dearomatization reactions¹¹ that

have largely been applied to indole nucleus, by intramolecular nucleophilic addition of the indole onto an electrophilic moiety tethered to the reacting position.¹² These transformations have harvest the curiosity of synthetic chemists and ignited their creativity in order to tame this chemistry for the construction of complex polycyclic scaffolds.

In this very active and topical field, transition metal catalysis plays an unwavering role,^{11a,11d} by allowing the selective activation of various functional groups into potent electrophiles and has led to the development of numerous highly efficient reactions towards spiroindolenines and spiroindolines (Scheme 2.A). Indeed, it is truly fascinating that each transition metal (Pd, Rh, Ru, Cu, Ir, Pt, Ag, and Au mainly) are specific to certain electrophilic chemical functions, which results in a very large structural diversity and myriads of different methods to access spiroindoles from a vast reservoir of possible starting materials.

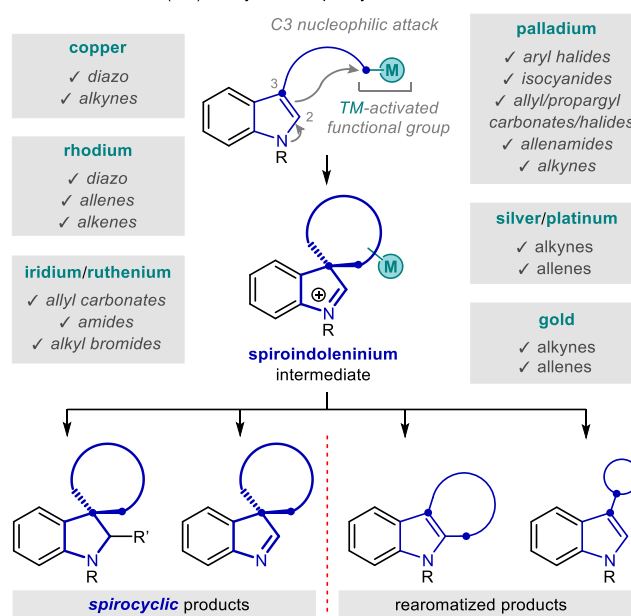
■ C3-spiroindolines and indolenines



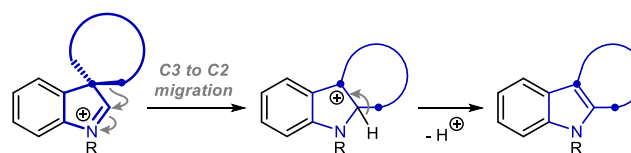
Scheme 1. Selected examples of biologically active spiroindole-containing natural compounds.

However, these reactions have more to offer than just the isolation of spirindoles. Indeed, the dearomative C3-spirocyclization on indole substrates leads to the formation of a spiroindoleninium intermediate, with a C2-position being highly electrophilic. A common reactivity feature in these transformations is the Wagner-Meerwein-like 1,2-migration¹³ occurring through the C3-to-C2 shift of one of the spirocyclic bond, driven by the rearomatization of the indole ring (Scheme 2.B). This results in the loss of the stereogenic center at C3 and this reactivity is often highly challenging to prevent when the spirocyclic products are targeted. However, the formation of the transient spiroindole intermediate followed by the migration may also be a way to access complex fused polycyclic scaffolds and these methods should not be neglected.

A. Transition metal (TM)-catalyzed C3-spirocyclizations on indoles



B. 1,2-migration: a common rearomatization pathway of spiroindoleniniums



Scheme 2. General features in the transition metal (TM)-catalyzed C3-spirocyclizations on indoles.

In this review, we aim at giving a comprehensive picture of the spirocyclization of indoles catalyzed by transition metal catalysis and the associated mechanisms, with a large focus on the evolution of the spiroindoleninium. The strategies developed to prevent or to trigger the rearomatization events – and hence to obtain either a spiro or rearomatized product – are discussed. The review is organized according to the metal used as catalyst for the C3-spirocyclization, overwhelmingly predominant in the literature, and the C2-spirocyclizations reported will be discussed in a last section. Each section may be sub-divided according to the different reactivities observed and/or intermediates involved. Due to an abundant bibliography, the focus of this Review is given on the last decade period and does not aim at being exhaustive. A large part is devoted to Au(I) catalysis, since this is the most predominantly used metal in these approaches. Finally, the synthesis of spirooxindole compounds, largely based upon the chemistry of isatin derivatives and methyleneindolinones, is a very fruitful field of research that has been extensively reviewed over the past years,¹⁴ but however differs deeply from the spirocyclization reactions on the aromatic indole core. It is consequently not treated in the course of this Review.

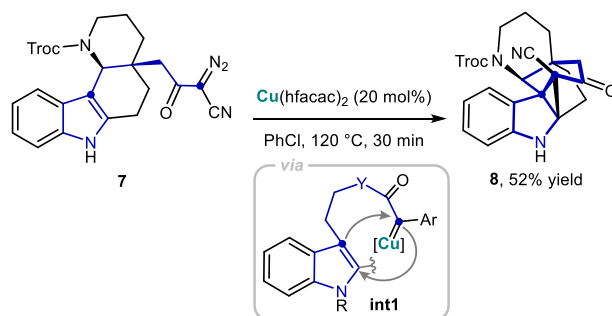
2. Copper catalysis

Most of the copper-catalyzed approaches towards spirocyclic indole derivatives rely on the generation of electrophilic Cu(I)-carbene intermediates from α -carbonyl diazo compounds. The cyclopropanation of these species into the indole C2-C3 double bond allows for the formation of C3-spirocyclic products fused with the cyclopropyl ring when the diazo precursor is tethered on this position.

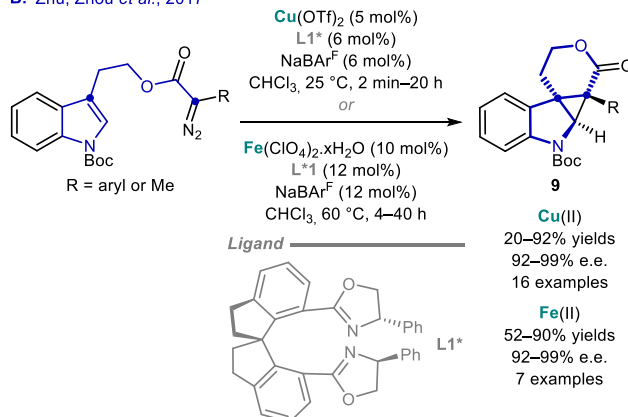
This approach was first used by Qin and co-workers for the development of the total synthesis of perophoramidine and communesin natural products.¹⁵ In the presence of a catalytic loading of Cu(hfacac)₂, the diazo compounds **7** was converted into the polycyclic indoline product **8** through the intramolecular cyclopropanation of copper-carbenoid **int1** (Scheme 3A). Later on, an enantioselective version of this transformation has been developed by the group of Zhu and Zhou using a copper(II) and iron(II)-based catalytic system in the presence of the spirocyclic bis-oxazoline ligand **L1*** (Scheme 3B).¹⁶ Indolines **9** are obtained with very good yields (most of them above 80%) and excellent 92 to 99% enantiomeric excesses.

While the two precedent approaches afforded spirocyclic products through a cyclopropanation between the copper carbenoid and the indole C2-C3 bond, Unsworth *et al.* reported the synthesis of the carbazoles **10** from the α -diazocarbonyl-tethered indoles **11** (Scheme 3C).¹⁷ In this case, the mechanism of the reaction involves the nucleophilic addition of the indole from its C3-position onto the carbon atom of the copper carbenoid, to afford indolenine **int2**. The authors showed that the isolated indolenine undergoes a 1,2-migration event in the presence of copper(II) triflate towards tetrahydrocarbazole **int3**, which is further oxidized in the presence of oxygen to deliver the fully aromatic carbazole **10**. The products are isolated with average 70% yields, except when an electron-donating group is present on the indole 5-position (5-OMe), affording a much lower 35% yield.

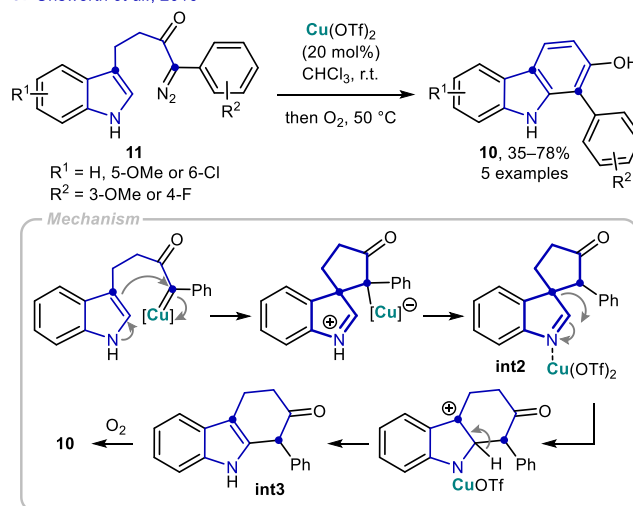
A. Qin *et al.*, 2017



B. Zhu, Zhou *et al.*, 2017



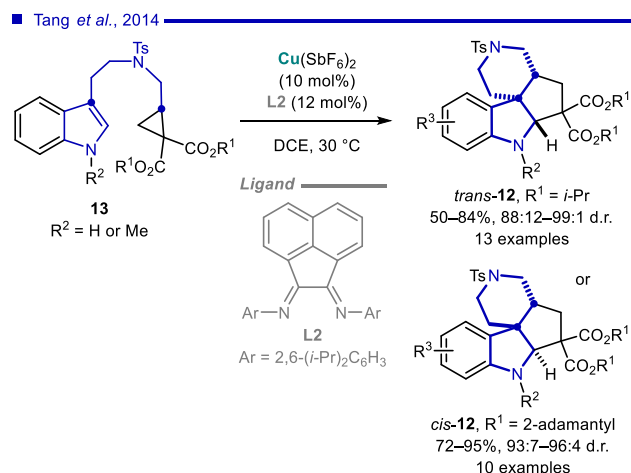
C. Unsworth *et al.*, 2016



Scheme 3. Diazo-compounds cyclopropanation (hfacac stands for hexafluoroacetylacetone)

When used as Lewis acid, copper(II) complexes are able to activate 1,1-dicarboxylate cyclopropane moieties, which can undergo nucleophilic attack from the indole C3 via ring opening. Tang's group thereby synthesized the (3+2)-annulated indoline **12** from substrates **13** in the presence of Cu(SbF₆)₂ (Scheme 4).¹⁸ The coordination of the Lewis acidic Cu(II) complex on the ester moieties triggers the addition of the indole, with a stereoselectivity for the tetracyclic indoline (*trans*-**12** vs. *cis*-**12**) that can be tuned by the R¹ groups on the geminal esters (>88:12 d.r.): if isopropyl esters give preferentially the *trans* isomers, the *cis* products are obtained when compounds with 2-adamantyl groups are used, as the bulky

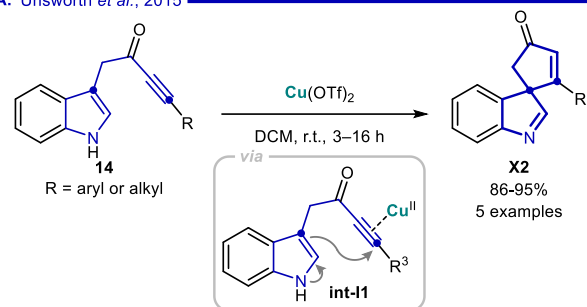
group induces important steric hindrance with the indole ring in the otherwise favored *trans*-leading transition structure.



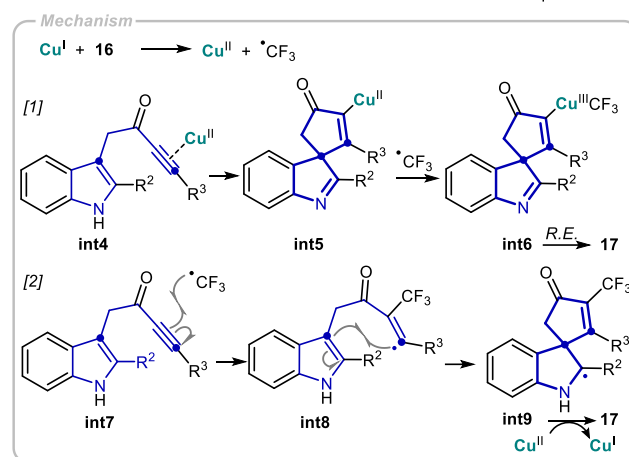
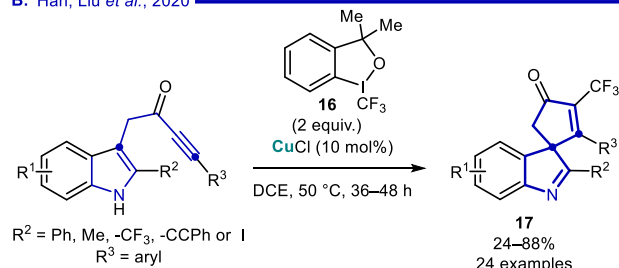
Scheme 4. (3+2)-annulation on cyclopropanes

Copper(II) complexes have also been shown to be efficient catalysts for the electrophilic activation of carbon–carbon triple bonds,¹⁹ affording spirocyclic products when tethered on the C3-position of indoles derivatives. The group of Unsworth developed the spirocyclization of ynone-tethered indoles **14** in the presence of copper(II) triflate, forming the corresponding spiroindolenines **15** with yields ranging from 86 to 95% (Scheme 5.A).²⁰ The same products can be synthesized in the presence of a silver(I) catalyst, giving the opportunity of an enantioselective transformation by using chiral silver phosphate (see Silver and platinum catalysis section, Scheme 22). Han and co-workers used similar substrates in the presence of Togni's reagent **16** to access trifluoromethylated products **17** (Scheme 5.B).²¹ The authors proposed two different pathways the transformation could occur through: [1] the electrophilic activation of the triple bond by Cu(II) triggering the spirocyclization (**int4** → **int5**) and subsequent reaction with the [•]CF₃ radical which furnishes product **17** after reductive elimination (*R.E.*) from intermediate **int6**. [2] the addition of [•]CF₃ on the ynone α-position, spirocyclization and subsequent oxidation of the intermediate by Cu(II) into the indoleninium (**int7** → **int8** → **int9**).

A. Unsworth *et al.*, 2015

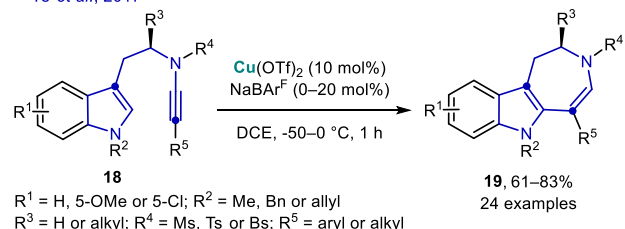


B. Han, Liu *et al.*, 2020



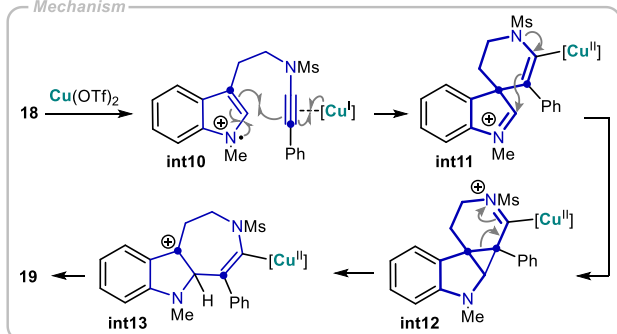
Scheme 5. Spirocyclization of ynone-tethered indoles

Ye, Lu and co-workers showed the cyclization of ynamides **18** towards carbolines **19** occurred with a reversed regioselectivity compared with the usual ynamide reactivity (Scheme 6).²² Indeed, previously reported Brønsted acid and π-acidic transition metals-catalyzed cyclizations on ynamides are exclusively observed on the α-position, while carbolines **19** are formed from the addition of the indole on the β-carbon of the ynamide.²³ Based upon control experiments and DFT calculations, the authors proposed a mechanism involving at first an intramolecular electron transfer triggered by the coordination of the Cu(II) complex on the ynamide triple bond to form intermediate **int10**. The Cu(I) species then undergoes the nucleophilic attack from the indole C3 position onto the α-carbon (favored over the attack on the β-position) towards indoleninium **int11**, followed by a stepwise 1,2-migration through a cyclopropane species **int12** and eventually to the ring-extended intermediate **int13**. Rearomatization and demetalation finally afford the carboline **19**. The reaction tolerates both aryl and alkyl groups on the ynamide triple bond (R³), as well as chiral indolyl ynamides (R³ ≠ H) in the presence of NaBAR^F (BAR^F = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate)).



$\text{R}^1 = \text{H}$, 5-OMe or 5-Cl; $\text{R}^2 = \text{Me}$, Bn or allyl
 $\text{R}^3 = \text{H}$ or alkyl; $\text{R}^4 = \text{Ms}$, Ts or Bs; $\text{R}^5 = \text{aryl}$ or alkyl

Mechanism



Scheme 6. Reversed regioselectivity in ynamide cycloadditions. BARF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate).

3. Palladium catalysis

3.1 Coupling reactions with halide partners

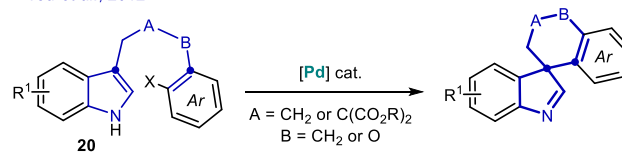
Quite recently, by comparison with the extensive use of palladium catalysis in organic synthesis, coupling reactions between the nucleophilic indole core and aryl halides partners have also been developed to form spirocyclic products. Most of these reactions are based on the addition of the indole on the palladium center generated from oxidative addition of the catalyst on the aryl halide partner, furnishing a spirocyclic palladacycle intermediate which evolves towards the spiroindolenines product through reductive elimination.

You's group pioneered the access to spirocyclic indolic products through the dearomative arylation of C3-tethered arylbromides **20** (Scheme 7.A). Early development of an enantioselective version were however tedious.²⁴ More recently, a similar intramolecular asymmetric arylation on indole C3 position has been described by desymmetrization of compounds **21**,²⁵ that can be efficiently transformed into spiroindolenines **22** with excellent ees in the presence of phosphoramidite **L3a***, with a total diastereoselectivity in most cases (Scheme 7.B). The authors observed an important influence of the electronic properties of the aromatic ring substituents. While electron-donating groups and aryl halides on the indole (R^1) allow for smooth reactions, electron-withdrawing groups are tolerated but make the substrates less reactive and require higher catalytic loadings and temperature to reach acceptable yields.

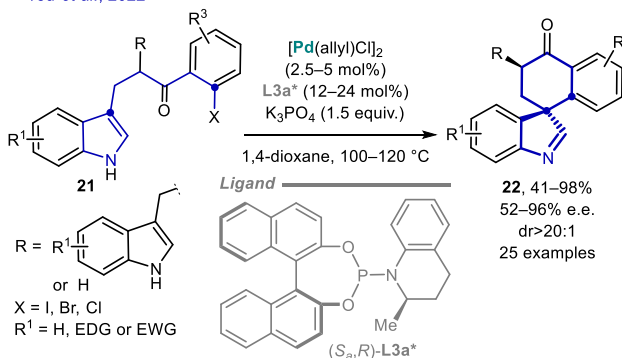
In their development of the first total synthesis of (+)-spiroindimicin A, Smith and co-workers designed an enantioselective palladium-catalyzed spirocyclization from polyaromatic aryl iodide substrate **23** (Scheme 7.C).²⁶ With a high catalytic loading in the presence of spirocyclic phosphoramidite ligand **L3b***, the complex spiroindimicin precursor **24** is obtained in the reaction conditions with a low yield, but an excellent enantioselectivity (98% e.e.). The major product of the reactions however, observed in all the conditions tested, is the C2-linked product formed either by a

direct C2-coupling with the iodide, as proposed by the authors, or by a 1,2-migration event from the spiroindoleninium intermediate.

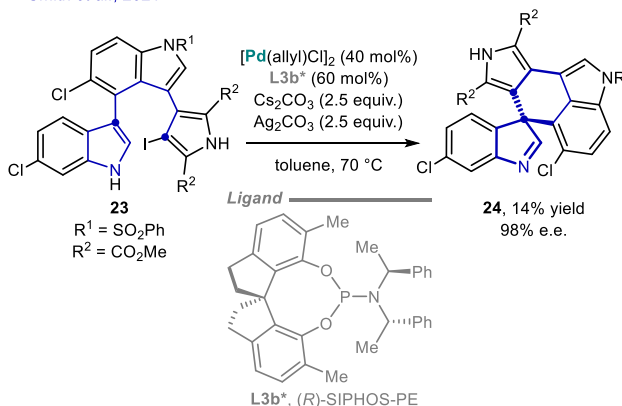
A. You et al., 2012



B. You et al., 2022



C. Smith et al., 2021



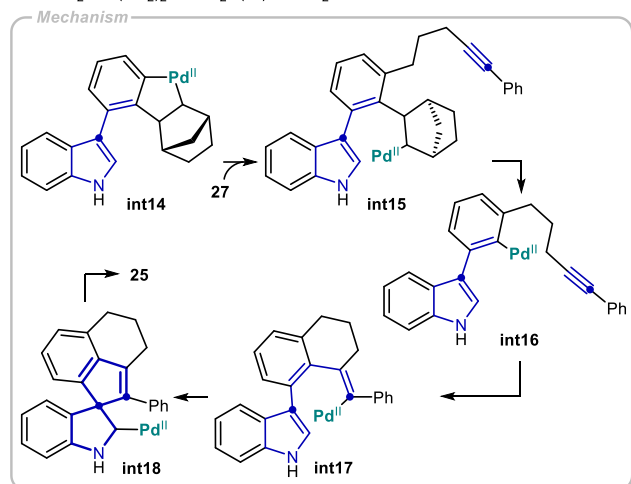
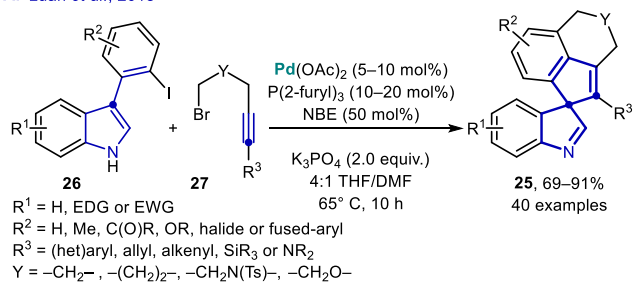
Scheme 7. Palladium-catalyzed spirocyclization on aryl bromides.

Another elegant approach relying on the use of palladium(0) catalysis and aryl halides is based upon the migratory insertion of alkynes onto a Pd(II) species which is formed from a first oxidative addition. The vinyl-palladium intermediate subsequently undergoes a Heck-type annulation with the indole to afford a spiroindolenine product.

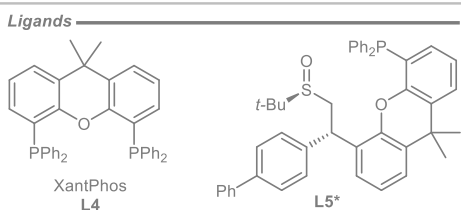
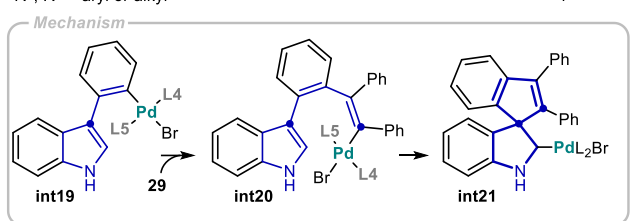
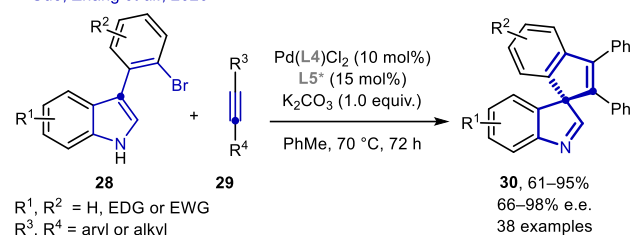
Luan and co-workers developed the synthesis of spiroindolenines **25** involving a Catellani-type reaction between aryl iodide-substituted indole derivatives **26** and bromoalkyne **27** in the presence of Pd(0) and norbornene (NBE, Scheme 8.A).²⁷ The reaction of the bromide partner **27** and the palladacycle **int14**, formed via the carbopalladation of norbornene by the first oxidative addition intermediate and the subsequent *ortho*-C-H activation, affords the Pd(II) species **int15**. The following extrusion of norbornene is favored over a cyclization on the triple bond and furnishes **int16**, which undergoes the migrative insertion of the alkyne moiety to form the alkenyl-Pd(II) species **int17**. Finally, the author's mechanistic investigations suggest the spirocyclic scaffold is most likely formed through a Heck-like annulation on the C2-C3 indole bond,

leading to **int18** and the spiroindolenine **25** after β -hydride elimination. Various functional groups are well tolerated on the iodoaryl moiety (R^2) such as aldehydes, ketones, nitriles and nitro groups, and furnish the spirocyclic products with good yields after the successive formation of three new carbon-carbon bonds.

A. Luan *et al.*, 2018



B. Guo, Zhang *et al.*, 2020



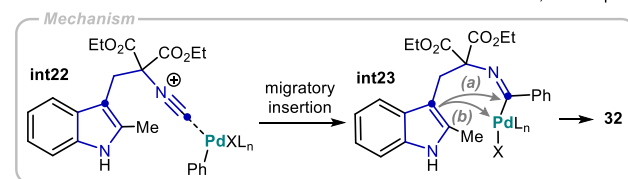
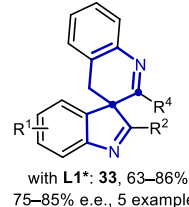
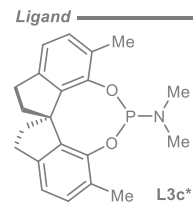
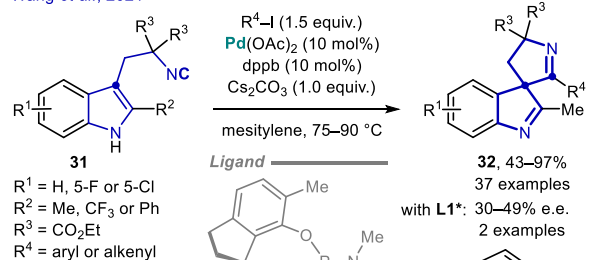
Scheme 8. Migratory insertion and subsequent Heck annulation towards spiroindolenines.

Guo and Zhang described the intermolecular enantioselective dearomatization of 3-aryloxyindoles **28** with internal alkynes **29**

(Scheme 8.B).²⁸ The use of achiral XantPhos (**L4**) and chiral sulfonamide phosphine **L5*** as co-ligands allows for the formation of various spiroindolenines **30** with excellent enantioselectivities in most cases. In the presence of the ligand **L5***, the pre-catalyst Pd(XantPhos)Cl₂ allows for the formation of the palladium(0) Pd(XantPhos)(**L5***) complex, critical for a high enantioselectivity, which undergoes oxidative addition on the aryl bromide to afford intermediate **int19**. The successive migratory insertions of the alkyne and the indole C2-C3 bond, respectively forming Pd(II) species **int20** and **int21**, lead to the formation of the dearomatized products **30** after β -hydride elimination. In most examples, symmetrical internal alkynes substituted with aryl or functionalized alkyl groups are used ($R^3 = R^4$). Nevertheless, unsymmetrical alkynes have been described as well and furnish mixtures of regioisomers.

Wang and co-workers reported the spirocyclization of isocyanatoethyl indoles **31** in the presence of aryl or alkenyl iodides (R^4), affording spiro dihydropyrroloindolenines **32** (Scheme 9).²⁹ In the presence of the chiral phosphoramidite ligand **L3c*** (instead of 1,4-bis(diphenylphosphino)butane), the products are obtained with moderate enantioselectivity. However, 6-membered ring products **33** are also accessible from the corresponding aryl isocyanide, with much better chiral induction (75 to 85% e.e.). The suggested mechanism involves the coordination of the isocyanide on the Pd(II) species resulting from the oxidative addition of the aryl iodide on Pd(0) catalyst forming intermediate **int22** which undergoes migratory insertion towards intermediate **int23**. The spirocyclization then takes place *via* the nucleophilic attack of the indole C3 either on the electrophilic imino carbon atom with concomitant elimination of a Pd(0) complex (pathway (a)) or on the palladium center and subsequent R.E. to furnish product **32** (pathway (b))

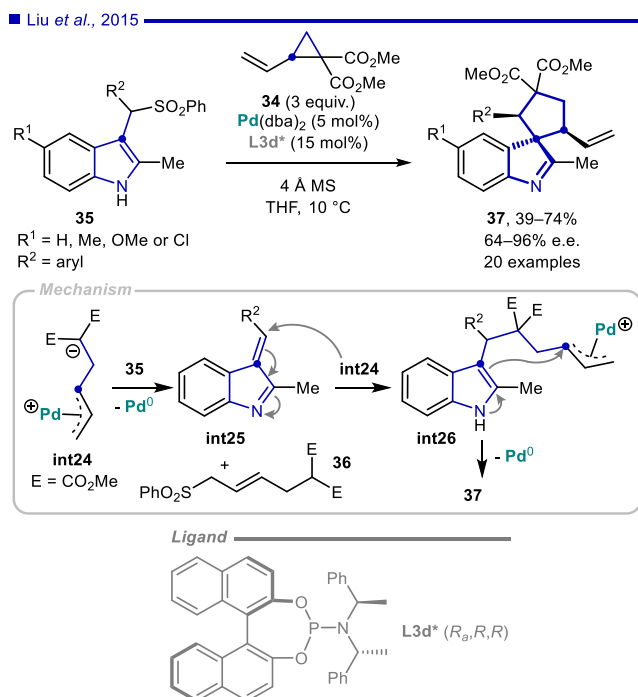
■ Wang *et al.*, 2021



Scheme 9. Palladium-catalysed imidoxylic spirocyclization. ddpb = 1,4-bis(diphenylphosphino)butane.

3.2 π -allyl-Pd intermediates

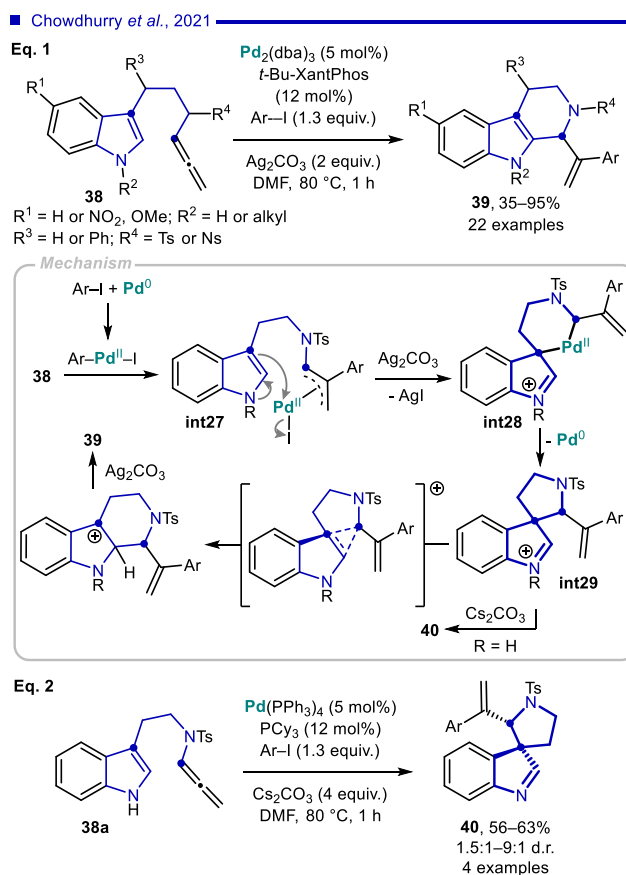
Much earlier than the above-discussed coupling with aryl halides, the group of Sakai reported in 1986 the first example of an intramolecular addition of an indole moiety onto a π -allyl-palladium intermediate during their effort to develop the synthesis of a koumine derivative, forming the corresponding spirocyclic indole in moderate yield.³⁰ Since these first developments, numerous works were then devoted to access various complex indole-based compounds from C3-spirocyclizations on electrophilic π -allyl-palladium intermediates. Liu *et al.* used vinylcyclopropanes **34**, which are converted into the ring-opened zwitterionic π -allyl-palladium intermediates **int24** upon oxidative addition on the catalyst (Scheme 10).³¹ The subsequent deprotonation of the indole substrate **35** triggers the elimination of the benzenesulfinate moiety which subsequently adds on a sacrificial intermediate **int24** to form by-product **36** and the conjugated imine **int25**. The conjugate addition of a second equivalent of malonate nucleophile **int24** furnishes the indole intermediate **int26** tethered with the π -allyl-palladium moiety, and the final nucleophilic attack from the C3-position affords product **37**. These spiroindolenines are obtained in good yields as single diastereomers and with excellent enantioselectivities in the presence of the BINOL-based phosphoramidite ligand **L3d*** (up to 97%). C2-unsubstituted substrates furnish the expected aldimine products, however with no diastereoselectivity (1.2:1 d.r.).



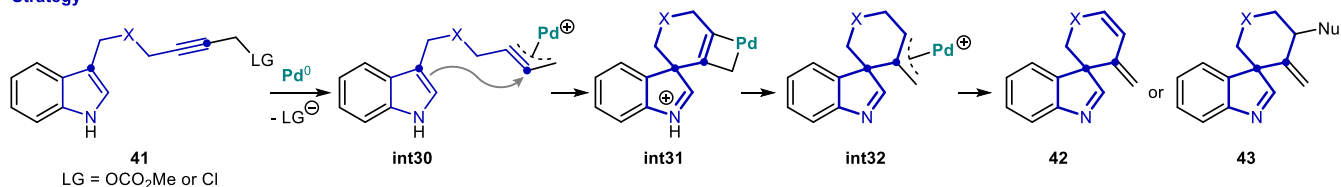
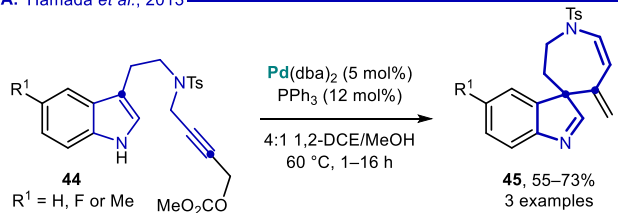
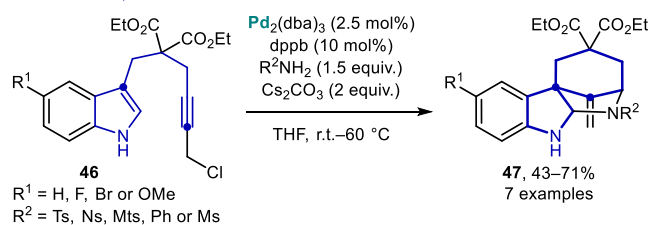
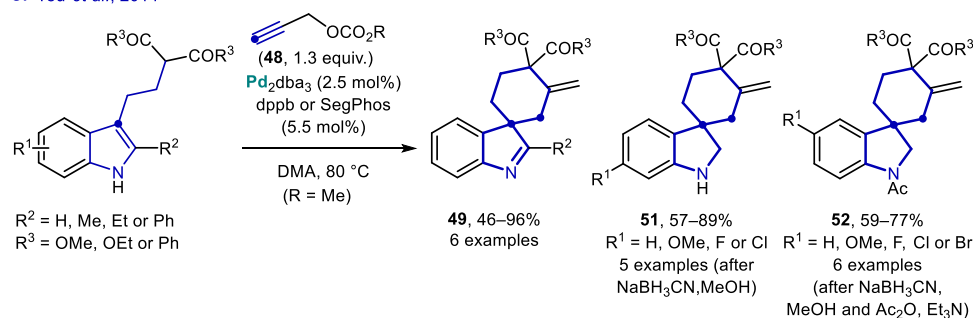
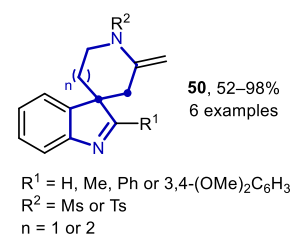
Scheme 10. Addition and cyclization of zwitterionic π -allyl-palladium intermediates

In some cases, the neat result of these reactions is not a spirocyclic indole derivative, but instead a tetrahydro- β -carboline, resulting from the C3-to-C2 migration of spirocyclic intermediates. Remarkably, the chiral center generated by the spirocyclization step retains its chiral information. In 2006, Bandini and co-workers developed the first enantioselective metallo-catalyzed synthesis of and

tetrahydro- β -carbolines from indoles tethered with an allylcarbonate moiety.³² The strategy to generate the key π -allyl intermediate however varies. Chowdhury *et al.* reported the palladium-catalyzed formation of 1-vinyltetrahydro- β -carbolines and spiroindolenines from allenyl tryptamines **38** and aryl iodides (Scheme 11).³³ In the presence of Pd₂(dba)₃, the sterically bulky *t*-BuXantPhos ligand and silver carbonate, compounds **38** are readily converted into tetrahydro- β -carbolines **39** within 1 hour. Mechanistically, the addition on the allenyl moiety of the Ar-Pd(II)-I intermediate, formed by the oxidative addition of the aryl iodide on the palladium catalyst, leads to the Pd(II)- π -allyl complex **int27**. Indole C3-attack on the Pd center affords the six-membered spirocyclic palladium(II) intermediate **int28** which undergoes reductive elimination **int29**. Subsequent 1,2-migration of the allyl group, which is known to exhibit better migratory aptitude than the alternative alkyl group, furnishes the rearomatized indolyl products **39** after deprotonation. N1-H indole substrates (R² = H) are reactive as well in these conditions, although affording the products with moderate yields (35-45%). Nevertheless, with a slight modification of the reaction conditions (Pd(PPh₃)₄, PCy₃, Cs₂CO₃), spiroindolenines **40** are obtained from compound **38a** as mixtures of diastereoisomers (Scheme 11, Eq. 2).



Scheme 11. Spirocyclization on π -allyl Pd(II) complexes from allenyl tryptamine derivatives.

A. Hamada *et al.*, 2013B. Ohno *et al.*, 2014C. You *et al.*, 2014D. Rawal *et al.*, 2014Scheme 12. Spirocyclizations via π -propargyl-palladium complexes. dppb: 1,4-bis(diphenylphosphino)butane.3.3 π -Propargyl-Pd intermediates

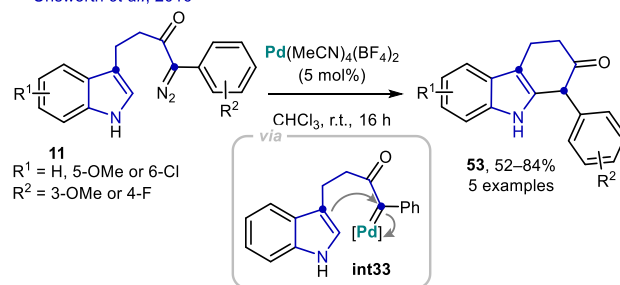
The activation of propargyl carbonates (or chlorides) as π -propargyl-palladium intermediates as also been successfully used to trigger spirocyclization on suitably functionalized indole derivatives. Previous chemistry on π -propargyl-palladium complexes³⁴ established that oxidative addition of propargyl carbonates/halides **41** on the palladium catalyst affords intermediates **int30**, which undergo nucleophilic attack from the indole C3-position onto its central carbon atom towards the palladacyclobutenes **int31**. Protonation of this intermediate leads to the corresponding π -allyl-Pd complex **int32**, which undergoes β -hydride elimination to form the spirocyclic conjugate diene **42**. These intermediates can also be trapped by nucleophiles to deliver products **43**.

During the development of an intramolecular nucleophilic dearomatization of phenols strategy, Hamada and co-workers applied their approach to tryptamine derivatives **44** which are converted into the spiroindolenines **45** (Scheme 12.A).³⁵ The group of Ohno used a similar approach with propargyl chlorides **46** for the construction of the tetracyclic spiroindoles **47** obtained in the presence of a sulfonamide (R^2-NH_2) as external nucleophile, which adds on C2 of the spiroindolenines intermediate **int31** (Scheme 12.B).³⁶ Subsequent intramolecular addition on π -allyl-Pd intermediate **int-32**-like affords the tetracyclic product in moderate to good yields. As π -propargyl-palladium species can be seen as bis-electrophiles, able to successively undergo nucleophilic attack on the central atom of the complex and subsequently a second addition on the π -allyl intermediate, the groups of You and Rawal used propargyl carbonates **48** to functionalize indoles derivatives with

an activated electrophilic pendant which then undergoes C3-spirocyclization (Scheme Pd12.C and D).³⁷ Indolenines **49** and **50** were isolated with overall good yields, and the scope of *gem*-dicarbonyl compounds described by You *et al.* can be broadened with more C2-unsubstituted substrates ($R^2 \neq H$) by the one-pot reduction and *N*-acetalization of the corresponding unstable spirocyclic aldimines, allowing to isolate indolines **51** and **52**.

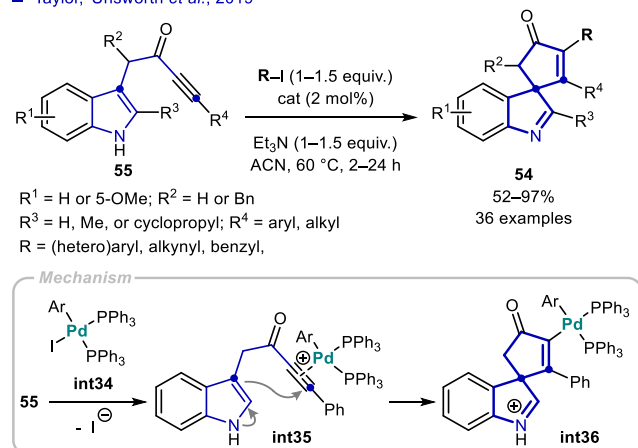
3.4 Other reactivities: Pd-carbenoids and triple bonds activation

Similarly as the formation of copper carbenoid from substrate **11** (cf. Scheme 3), Unsworth *et al.* demonstrated that a palladium(II) catalyst allowed the formation of the corresponding palladium species **int33**, which most likely undergoes spirocyclization on the C3-position followed by a 1,2-migration towards the rearomatized tetrahydrocarbazole compound **53** (Scheme 13).¹⁷

■ Unsworth *et al.*, 2016Scheme 13. Access to tetrahydrocarbazole derivatives *via* spirocyclization on palladium-carbenoid and subsequent 1,2-migration.

Taking advantage of the ability of palladium(II) complexes to activate triple bonds in cycloisomerization reactions³⁸ Toste's group developed an enantioselective cyclization of alkyne-tethered cyclic enamines leading to spirocyclic spiroindolenine scaffold with moderate enantioselectivity (71% ee) using DTBM-SEGPHOS ligand.³⁹ In an elegant approach towards highly substituted spiroindolenines **54**, Taylor and Unsworth merged the π -acidic (Pd(II)) and the cross-coupling (Pd(0)) catalytic activities of palladium.⁴⁰ The use of the aryl iodide oxidative addition product **int34** as π -acid for the electrophilic activation of the triple bond of ynone **55** allows to trigger the C3-spirocyclization on **int35** (Scheme 14). The resulting vinyl palladium intermediate **int36** subsequently undergoes reductive elimination towards spiroindolenine **54** faster than the protodemetalation. The products are obtained with very good yields in most cases, either from C2-H or C2-substituted indoles.

■ Taylor, Unsworth *et al.*, 2019



Scheme 14. Pd(II)-catalyzed activation of alkynes. cat = *trans*-PdBr(*N*-succinimide)(PPh₃)₂.

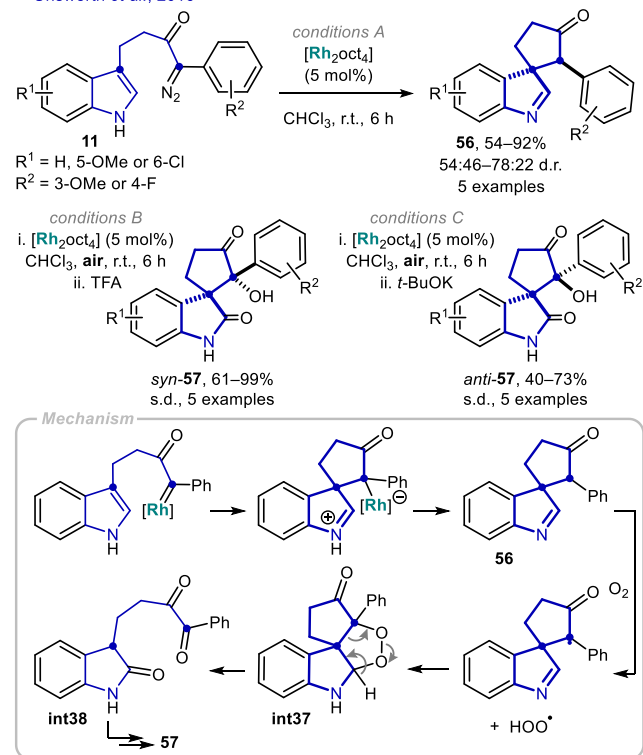
4 Rhodium catalysis

4.1 Rhodium-carbenoids intermediates (Rh(II) catalysis)

Similarly with the above-mentioned Cu(II) and Pd(II)-catalyzed approaches (see Scheme 3 and Scheme 13), the formation of electrophilic rhodium-carbene intermediates, from the decomposition of α -carbonyl diazo compounds or sulfonyl-1,2,3-triazoles, can trigger the C3-spirocyclization. However, in opposition with the copper and palladium species formed from the same indolyl α -diazo carbonyl substrates **11**, the group of Unsworth showed that the rhodium-catalyzed reaction allows for the isolation of the spiroindolenine products **56**, without 1,2-migration towards tetrahydrocarbazoles (see Scheme 3 and Scheme 15).¹⁷ The products were obtained in good yields in strictly inert conditions, but in the presence of air, indolenines can be oxidized by dioxygen into intermediate **int37**, delivering a ring-opened product **int38**. Although this intermediate appeared relatively short-lived and unstable over silica gel chromatography, it can be engaged in a one-pot diastereoselective aldol-type reactions either in acidic (conditions B) or basic (conditions C) conditions, affording *syn*-**57** and *anti*-**57** spirooxindoles respectively. The generation of a rhodium carbenoid on the C3-indole pendant has also been used to generate an oxonium electrophile, which then undergoes the spirocyclization.

This strategy was extensively used by Padwa and Hashimoto in total synthesis.⁴¹

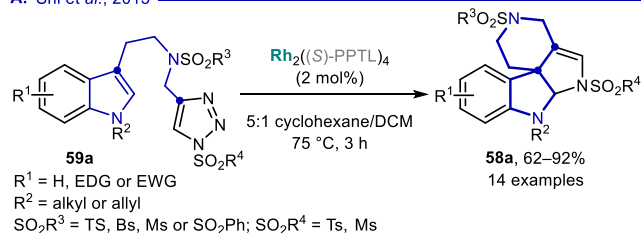
■ Unsworth *et al.*, 2016



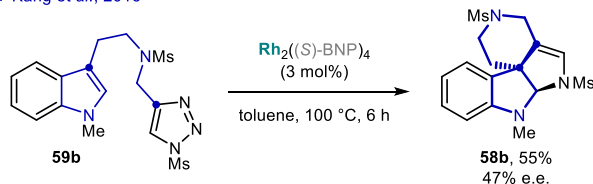
Scheme 15. Spiroindolenine formation from indolyl Rh-carbenoid.

At the same period, three groups independently reported the formation of spiroindolines **58** from 1-sulfonyl-1,2,3-triazole-tethered indoles **59** (Scheme XX).⁴² Shi and co-workers reported the synthesis of spirocyclic products **58a** in the presence of the chiral bisrhodium complex Rh₂((*S*)-PPT)₄, which was shown to be the most efficient in catalyzing the reaction (75% yield vs. 25-35% with Rh₂(Piv)₄ or Rh₂(O₂C-*n*-hept)₄, Scheme 16.A).^{42a} However, no mention of any stereoselection was made in the report, presumably because racemates are obtained in these conditions. The team of Kang later reported a similar approach using Rh₂(O₂C-*n*-hept) as catalyst (10 examples, 36-92% yields).^{42b} In the presence of the binaphthyl-based chiral dirhodium complex Rh₂((*S*)-BNP)₄, the formation of product **58b** was reported with a 55% yield and a 47% e.e. (Scheme 16.B). In their study of this kind of systems, Davies and co-workers proved the scope of the transformation was even broader, tolerating different kind of tethers between the indole and the triazole, with carbonate- or ether-containing chains (the later with a lower 31% yield) in addition to sulfonamide-protected tryptamine derivatives.^{42c} 7-membered ring spirocyclic products are also accessible, although with a moderate yield (35%). The proposed mechanism of the reaction, based on Davies' group previous report on the synthesis of pyrrolindolines,⁴³ involves two potential reaction pathways. The thermal decomposition of the

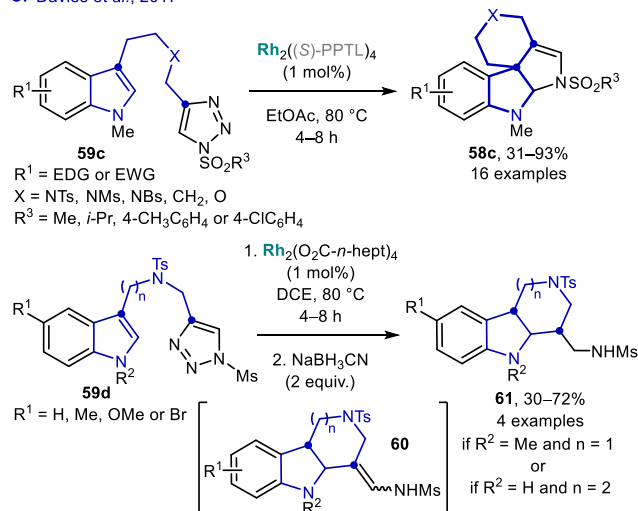
A. Shi et al., 2015



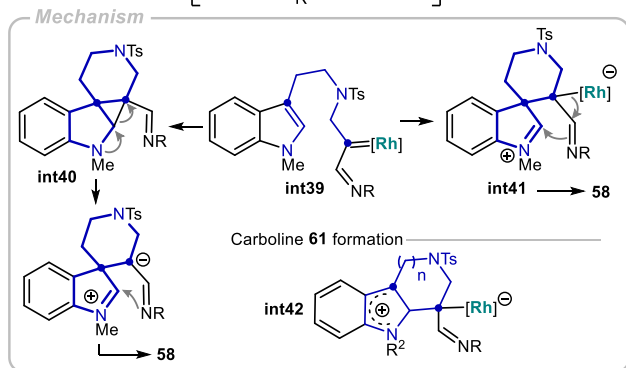
B. Kang et al., 2016



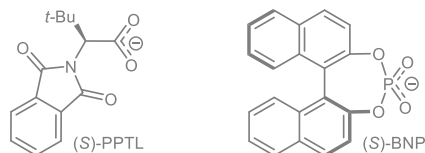
C. Davies et al., 2017



Mechanism



Ligands



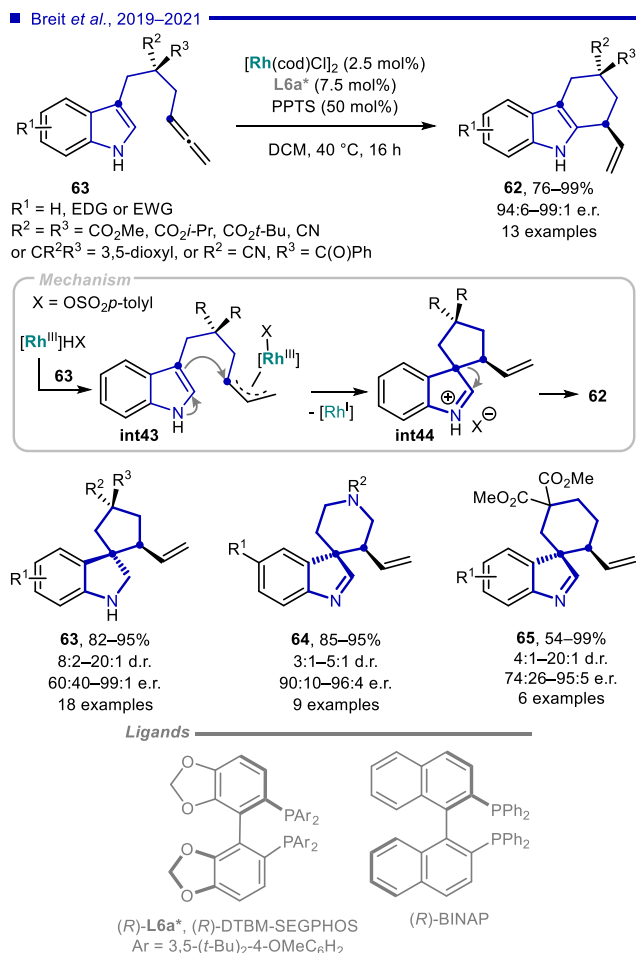
Scheme 16: α -imino rhodium carbenoid-mediated formal (3+2)-cycloadditions

triazole derivative in the presence of the rhodium complex leads to α -imino carbenoid **int39**, which may undergo cyclopropanation onto the C2-C3 indole bond (**int40**), the subsequent ring opening

and addition on the electrophilic C2 carbon furnishing the product **58**. Alternatively, C3 attack on the rhodium carbenoid may form the zwitterionic intermediate **int41** which would undergo cyclization onto the indoleninium. Both Shi's and Davies' group observed the formation of carboline **60** (or **61** after reduction) in the cases of N1-unsubstituted indoles ($R^2 = \text{H}$) or shorter tether between the indole C3 and the triazole ($n = 1$). This product may arise either from a direct C2-addition onto the rhodium carbenoid on **int39**, or from a 1,2-migration event from an intermediate like **int41**, leading to **int42** in both cases. The preferred formation of the carboline in these cases likely arises from a more stable cycle formation (5 to 6 for $n = 1$) or an intramolecular H-bonding between the sulfonamide and the N1-H on non-alkylated indoles (as proposed by Shi).

4.2 π -allyl-Rhodium intermediates (Rh(I) catalysis)

The group of Breit developed an enantioselective spirocyclization towards vinyl-substituted tetrahydrocarbazoles **62** through the rhodium(III)-mediated activation of allenyl-tethered indoles **63** (Scheme 17).^{44a} The products are obtained with excellent yields and outstanding enantioselectivities in the presence of a Rh(I) catalyst, pyridinium *p*-toluenesulfonate and the sterically bulky DTBM-SegPhos ligand (**L6a***). The formation of a rhodium(III) hydride complex from $[\text{Rh}(\text{cod})\text{Cl}]_2$ and the pyridinium furnishes the allyl rhodium complex **int43** upon hydrometallation of **63**, triggering the C3 nucleophilic attack towards spiroindoleninium **int44** and concomitant regeneration of the Rh(I) catalytic species. The five-membered ring spirocycle **int44** subsequently undergoes 1,2-migration of the allyl group (presenting a higher lying HOMO compared with the alternative alkyl group) to form tetrahydrocarbazole **62** after rearomatization. However, the spiroindolenine intermediate can be isolated with a 44% yield (9:1 dr, 99:1 er, $R^1 = \text{H}$, $R^2 = R^3 = \text{CO}_2\text{Me}$) by stopping the reaction in these conditions after 15 min. Alternatively, the authors have shown the spirocyclic products can also be trapped *in situ* via reduction by the Hantzsch ester, furnishing the corresponding spiroindolines **63** in good yields (Scheme 17, bottom). This reactivity has then been extended to tryptamine derivatives and malonates starting materials presenting a longer linker between the indole C3 position and the allenyl group compared with the previous systems to deliver spiroindolenines **64** and **65** with excellent yields and high enantioselectivities in the presence of a BINAP ligand.^{44b}



Scheme 17. Rhodium-catalyzed spirocyclization of allenyl indoles. cod = 1,5-cyclooctadiene.

Other approaches to spiroindoles have been reported by Gong⁴⁵ and Shi,⁴⁶ leading to spiroindolenines and tetrahydro- β -carboline, respectively, using amidine and vinylcyclopropane as reacting electrophilic functions.

5. Iridium and Ruthenium catalysis

5.1 Iridium-catalyzed allylic substitutions

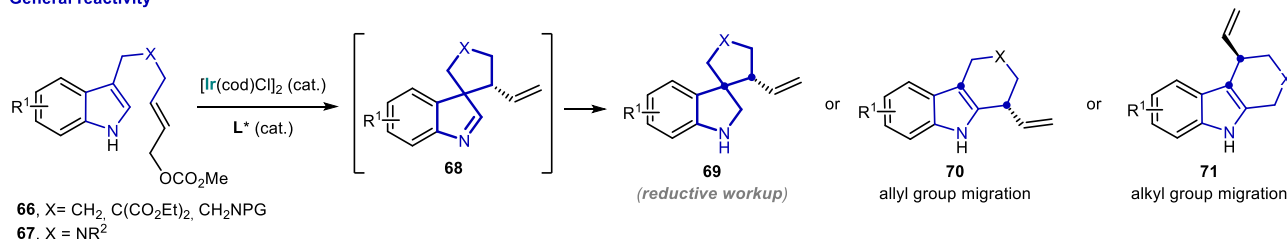
You and co-workers have studied in-depth iridium-catalyzed allylic substitution strategies to form a number of chiral spiroindolenines, spiroindolines or rearranged products from the corresponding carbonates-tethered to indole rings (Scheme 18, top).⁴⁷ From allyl carbonate **66**, the reactions evolve through the formation of an Ir(III)- π -allyl complex that undergoes nucleophilic addition of the indole ring, affording vinyl spiroindoles **68**. The fate of this compound strongly depends on the nature of the linker X and the workup. While some compounds **68** can be inherently stable and hence isolated, a reductive workup allows a conversion into the corresponding spiroindolines **69**. Unstable products **68** can undergo 1,2-migration either on the allyl side or alkyl side to deliver carbolines **70** and **71**, respectively.

Allylic substitutions using the phosphoramidite ligand **L3e*** led to the dearomatized 6-membered ring spiroindolenine **72** in excellent *e.e.s*, tolerating C2-unsubstituted or substituted ($R^2 = \text{Me, Ph}$) substrates (Scheme 18.A).^{47a} However, the scope is limited to *N*-tethers bearing an electron-donating group on the nitrogen (alkyl, allyl), with no reaction occurring with protecting groups such as Boc or Ts. C-linker indole derivatives smoothly undergo the allylic substitution as well towards 5-membered ring spiroindolenine **68** in similar conditions, although a reduction into indoline **73** is required to isolate the products by chromatography.^{47b} The authors also demonstrated that the isomerization by 1,2-migration of **68** into tetrahydro-1*H*-carbazoles **74** could be triggered by a Brønsted acid catalysis (30 mol% of *para*-toluene sulfonic acid) with conservation of the chiral information on the allylic position. As observed in other analogous systems, such as Breit's rhodium-catalyzed spirocyclizations (*vide supra*), 5-membered ring spiroindoleninium intermediates are indeed prone to 1,2-rearrangements furnishing more favorable 6-membered ring aromatic tetrahydrocarbolines. DFT calculations confirmed the rearomatizing migration event is highly favored thermodynamically, regardless of the nature of the migrating group.^{47c}

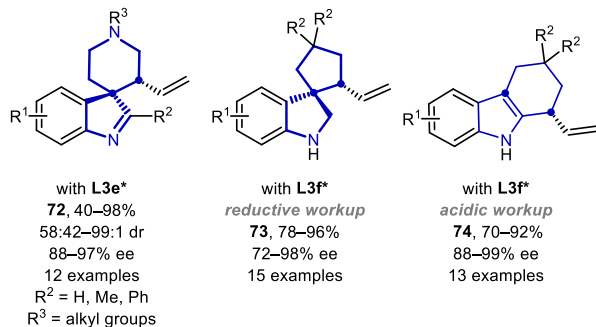
As it has been observed for several systems previously described the electronic properties of the two potential migrating moieties on the spiroindolenine intermediates play a critical role in the migration event. When compounds **67** ($X = \text{NR}^2$) undergo the iridium-catalyzed cyclizing allylic substitution towards indolenine **68** (highly reactive, but observed *in situ* by IR spectroscopy), this intermediate evolves towards tetrahydro- β -carboline **75**, which results from the migration of the methane amine moiety, originally linked to the indole C3 on **67** (Scheme 18.B).^{47d} In contrast with the migration of the allyl group, thought to be concerted, the mechanism of the methane amine migration is thought to be a stepwise process involving the formation of an iminium intermediate which subsequently undergoes direct C2-attack from the indole ring, somewhat analogous with a Pictet-Spengler reaction.^{12f, 47c, 48} The substitution of the linker nitrogen atom with an electron withdrawing group, by reducing the ability of the methane amine moiety to undergo migration, allows for stable 5-membered ring spiroindolenines **76** to be formed and isolated from C2-unsubstituted substrates in similar conditions.^{47e} The products are obtained as a mixture of three diastereoisomers, each of them exhibiting different reactivity towards the acid-catalyzed 1,2-migration. The migration event can also be prevented by substituting the C2-position of the indole. Using similar conditions, spiroindolines **77** can be isolated with good yields and excellent enantioselectivity, after reduction of the corresponding spiroindolenine.^{47f}

Taking advantage of the strong electron donating nature of the indole ring, You's team extended their strategy to symmetrical bis-indole compounds **78**, which, after formation of the spiroindolenines **79** as a single diastereoisomer, allows for a 6 to 7 ring extension towards products **80** in acidic conditions (Scheme 18.C).^{47g} The configuration of the migrating group in these products is inverted in the course of the migration event, showcasing that the mechanism involves a pro-chiral allyl iminium intermediate **int45**, with the stereochemistry of the cyclization step controlled by the stereogenic center on the allylic position.

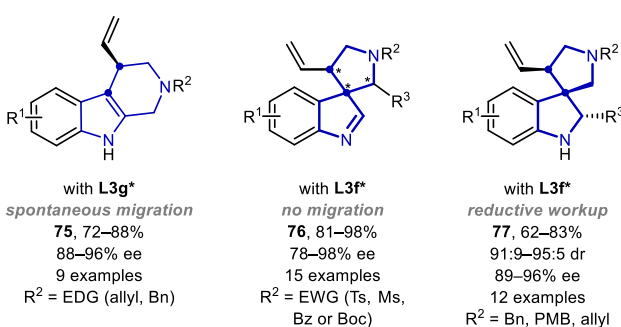
General reactivity



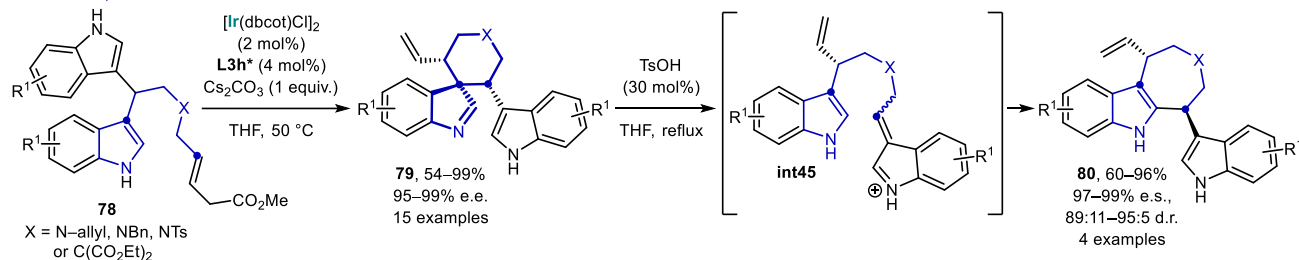
A. You *et al.*, 2010–2013



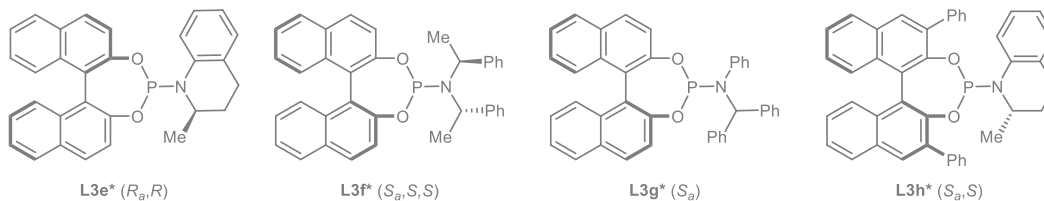
B. You *et al.*, 2013–2016



C. You *et al.*, 2017



Ligands



Scheme 18. Ir-catalyzed allylic substitution.

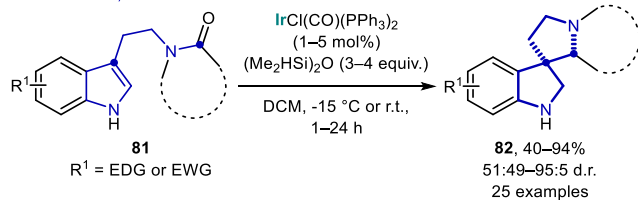
5.2 Other types of iridium-catalyzed reactions

Based on their previous reports on iridium-catalyzed cyclization *via* reductive lactam activation,⁴⁹ Dixon's group described the spirocyclization of lactams or amides **81** into the indolenines **82** in the presence of Vaska's catalyst (Ir(CO)Cl(PPh₃)₂) and tetramethyldisiloxane (TMDS) (Scheme 19).⁵⁰ The reaction is selective for the *syn* diastereoisomer (most d.r. are above 90:10) and tolerates electron-donating and withdrawing on the indole, as well as substituted lactams and acyclic amides. The partial reduction of the lactam produces the siloxy intermediate **int46** via C–O insertion into the Ir–Si bond of hydrido(silyl) Ir^{III} species **int47**, formed by the oxidative addition of the silane to the Ir^I complex, and subsequent reductive elimination. Elimination of the oxasilane furnishes the Pictet–Spengler iminium **int48**, which undergoes the 5-endo-trig spirocyclization into the corresponding spiroindoleninium. The reduction of this intermediate into the indolenine **82** occurs before

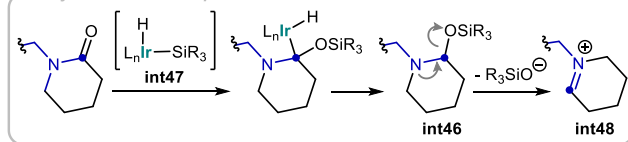
any migration event, as no trace of aromatized product was detected.

The group of Zhang used the well-known photoactive iridium complex *fac*-Ir(ppy)₃ to catalyze the formation of spiroindolenines **83** *via* radical mechanisms from bromide-tethered indoles derivatives **84** and aromatic alkynes under blue light irradiation (Scheme 20).⁵¹ The transformation tolerates a wide variety of aromatic moieties on the alkyne, but internal or aliphatic alkynes were shown to be unreactive in these conditions.

■ Dixon *et al.*, 2019

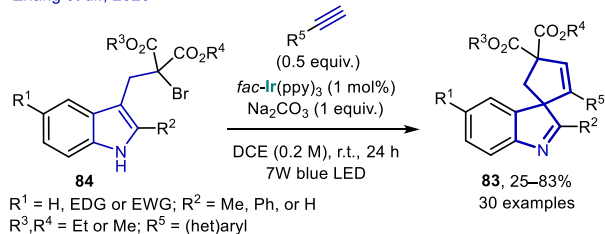


Key mechanistic steps



Scheme 19. Ir-catalyzed reductive activation of amides.

■ Zhang *et al.*, 2020



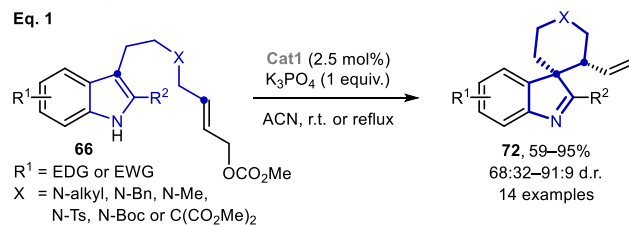
Scheme 20. Photoredox-catalyzed synthesis of spiroindolenines.

5.3 Ruthenium catalysis

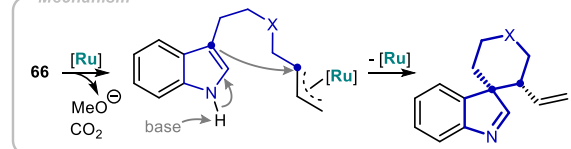
The group of You extended their allylic substitution approach from iridium to a ruthenium catalytic system, which allows extending the scope of the 6-membered ring spiroindolenines **72** available (Scheme 21, Eq. 1).⁵² While the iridium-catalyzed approach was limited to *N*-linker bearing an electron-donating group on the nitrogen atom (*cf.* Scheme 18), various indole derivatives **66** with carbonate linker or bearing electron-withdrawing groups are readily transformed into the corresponding indolenines **72** in the presence of the ruthenium(IV) complex **Cat1** (Ru(II) complexes are also active in the reaction, but less effective). The products are obtained with good yields. However, the ruthenium catalytic system tend to furnish satisfactory but yet lower diastereoselectivity in the transformation compared with the iridium approach, with most of the diastereoisomeric ratios below 90:10. In addition, no enantioselective version of this reaction is reported. The authors then extended their strategy to substrates **67**, one carbon shorter between the indole and the allyl carbonate, furnishing products **75** (Scheme 21, Eq. 2).⁵³ The *in situ* spectroscopic observation of the intermediate spiroindolenine **84** and its reduction towards the corresponding indoline in the presence of sodium borohydride confirmed these products arise from a migration event of the methylamine moiety, common on this kind of 5-membered ring spirocyclic compounds (*vide supra*).

■ You *et al.*, 2013 and 2014

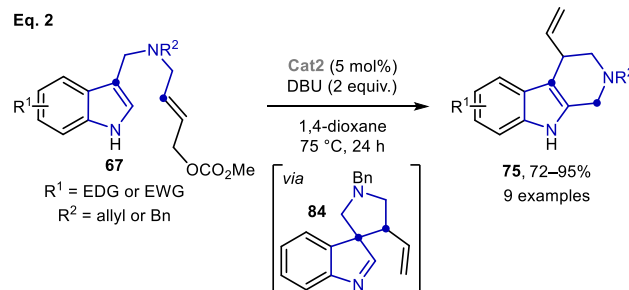
Eq. 1



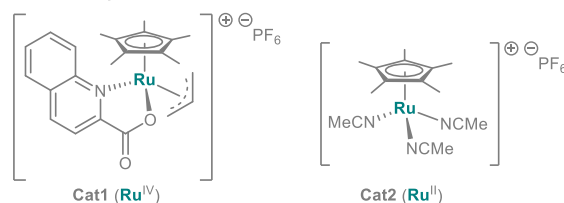
Mechanism



Eq. 2



Ruthenium complexes



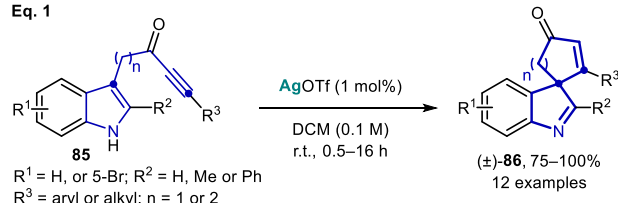
Scheme 21. Ruthenium-catalyzed allylic substitutions.

6. Silver and platinum catalysis

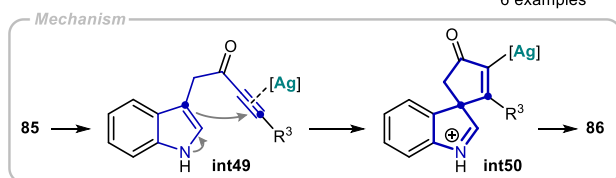
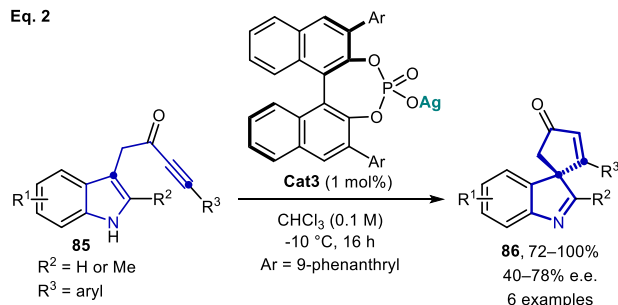
6.1 Silver-catalyzed spirocyclizations on ynones derivatives

The group of Unsworth reported the silver-catalyzed spirocyclization of ynone-substituted indoles **85** allowing to form the corresponding spiroindolenines **86** without formation of the migration product (Scheme 22, Eq. 1).²⁰ The carbonyl group on the tether indeed reduces the ability of the adjacent alkene intermediate to undergo the 1,2-shift towards the rearomatized product. In the presence of silver triflate, a wide variety of spiroindolenines **86** are obtained from C2-substituted or unsubstituted indoles, but the transformation requires a substituted alkyne (R³ ≠ H). Nevertheless, unsubstituted spiroindolenines (R³ = H) can be formed with an excellent yield (93%) from the TMS-substituted ynone (R³ = TMS) in slightly different conditions (20 mol% of AgNO₃ in acetone) through a desilylation/spirocyclization process. The authors investigated as well the asymmetric version of the transformation with the use of BINOL-based chiral phosphate silver salts (**Cat3**), allowing to synthesize the enantioenriched spiroindolenines **86**

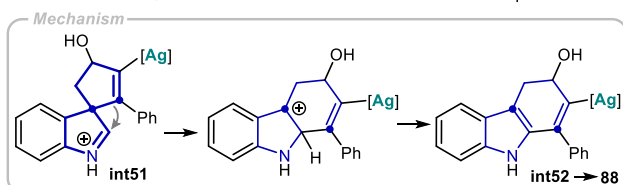
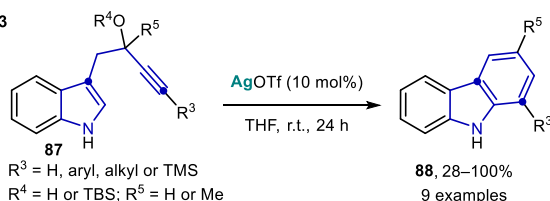
Eq. 1



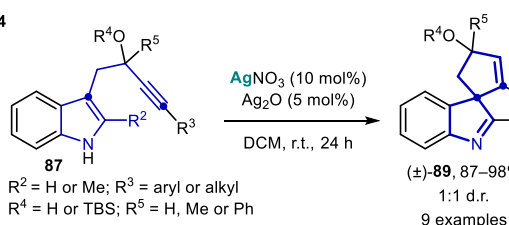
Eq. 2



Eq. 3



Eq. 4



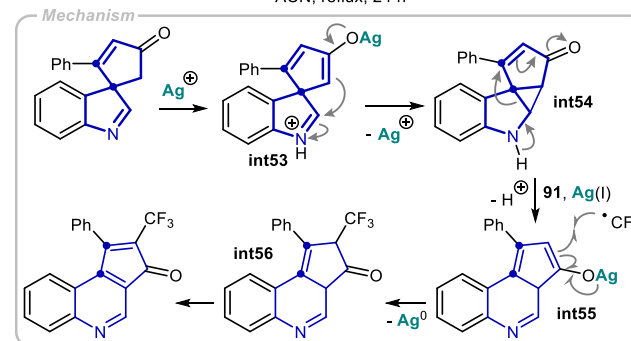
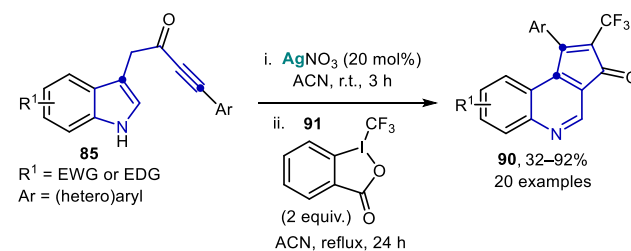
Scheme 22. Silver-catalyzed deraromatic cyclization of ynone and propargyl alcohols.

with up to 78% ee (Scheme 22, Eq. 2). The mechanism of the reaction involves the classical C3 attack of the indole on the π -activated alkyne (**int49**) and the subsequent protodemetalation of **int50** towards the indolenine product.

In similar conditions (in the presence of 10 mol% of AgOTf instead of 1%), propargyl alcohols (or silyl ethers) **87** are converted into carbazoles **88**.⁵⁴ These products are likely formed from a silver indoleninium intermediate such as **int51**, which undergoes 1,2-migration towards **int52** and subsequent aromatizing elimination.

Switching the silver salt anion from TfO^- to NO_3^- allows in the presence of silver oxide for the exclusive formation of the spirocyclic allylic alcohol products **89** with high yields in the form of an equimolar mixture of diastereoisomers. The authors hypothesized that the 1,2-migration event in the silver triflate conditions was triggered by the presence of an adventurous Brønsted acid, as the addition of a base in the reaction mixture prevents the formation of the carbazole. The 1,2-shift has been shown to only occur on the vinyl silver intermediate **int51**, as the reaction conditions of Eq. 3 on spirocyclic compounds **89** do not afford any migration product. The synthesis of products **86** and **88** can also be achieved very effectively in the presence of silica-supported silver nitrate, which appears much more active than the unsupported catalyst, presumably due to synergistic effect between the silica support and the silver nanoparticles.⁵⁵

Liu, Song and co-workers, expecting to form CF_3 substituted spiroindolenines, showed that indolyl-ynones **85** are converted into cyclopentaquinolinones **90** in the presence of Togni's reagent **91** after the first silver-catalyzed dearomative cyclization (Scheme 23).^{56a} The transformation is proposed to occur through a radical-mediated ring extension mechanism. The Lewis-acidic silver cation promotes the formation of the enolate **int53**, which undergoes cyclopropanation, ring extension, and reaction with the trifluoromethyl radical (**int54** \rightarrow **int55** \rightarrow **int56**), eventually furnishing the oxidized product **90**. A wide panel of products are accessible, with no noticeable effect of the electronic properties of the indole substituents (R^1) or the nature of the triple bond aryl group (Ar) on the reaction yields.

Liu, Song *et al.*, 2019

Scheme 23. Formation of cyclopentaquinolinones in the presence of Togni's reagent.

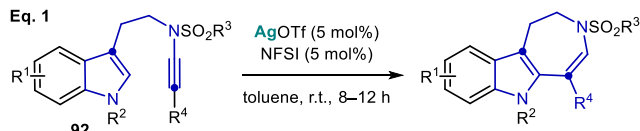
6.2 Silver-catalyzed spirocyclizations on ynamides derivatives

Lin and Liu reported several approaches to perform the silver-catalyzed spirocyclization of tryptamine-ynesulfonamides (**92**).

A. 1,2-migration

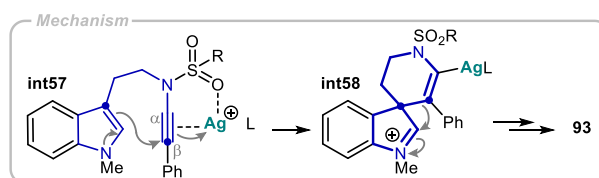
■ Liu, Lin *et al.*, 2019

Eq. 1



$R^1 = \text{H, EDG or EWG}; R^2 = \text{H, Me or Bn}$
 $\text{SO}_2\text{R}^3 = \text{Ts, Ns or Ms}; R^4 = \text{aryl or alkyl}$

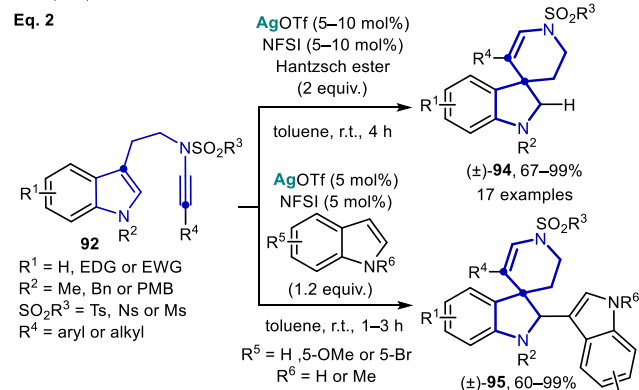
93, 26–95%
22 examples



B. Indoleninium trapping

■ Liu, Lin, Liu *et al.* 2020

Eq. 2

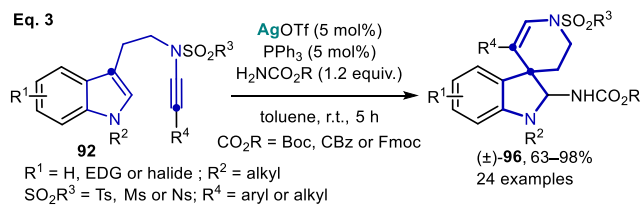


$R^1 = \text{H, EDG or EWG}$
 $R^2 = \text{Me, Bn or PMB}$
 $\text{SO}_2\text{R}^3 = \text{Ts, Ns or Ms}$
 $R^4 = \text{aryl or alkyl}$

(\pm) -**94**, 67–99%
17 examples

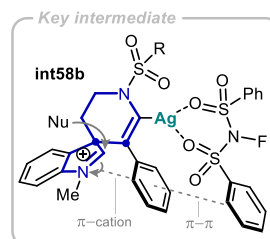
(\pm) -**95**, 60–99%
17 examples

Eq. 3



$R^1 = \text{H, EDG or halide}; R^2 = \text{alkyl}$
 $\text{SO}_2\text{R}^3 = \text{Ts, Ms or Ns}; R^4 = \text{aryl or alkyl}$

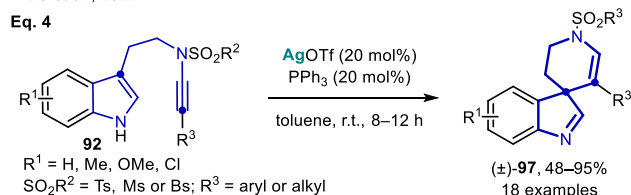
(\pm) -**96**, 63–98%
24 examples



C. Stable spiroindolenine

■ Liu *et al.*, 2022

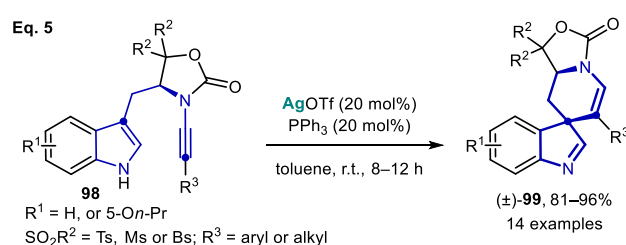
Eq. 4



$R^1 = \text{H, Me, OMe, Cl}$
 $\text{SO}_2\text{R}^2 = \text{Ts, Ms or Bs}; R^3 = \text{aryl or alkyl}$

(\pm) -**97**, 48–95%
18 examples

Eq. 5



$R^1 = \text{H, or 5-On-Pr}$
 $\text{SO}_2\text{R}^2 = \text{Ts, Ms or Bs}; R^3 = \text{aryl or alkyl}$

(\pm) -**99**, 81–96%
14 examples

Scheme 24. Cycloisomerization of tryptamine ynamides.

(Scheme 24). While these substrates tend to easily decompose under gold or silver catalysis conditions, they demonstrated that the use of NFSI (*N*-FluorobenzeneSulfonyl-imide) as ligand could moderate the activity of the silver complex and allow the formation of 1,2,3,6-tetrahydroazepino[4,5-*b*]indole **93** with satisfactory yields (Scheme 24A, Eq. 1).^{56b} The reaction occurs *via* the dearomative cyclization on **int57**, with attack of the indole on the β -position of the ynamide, through an Umpolung effect triggered by the coordination of the silver complex with the adjacent sulfonyl group (the electron donating character of nitrogen usually induces the regioselective addition of nucleophiles on α -position). The spirocyclic intermediate **int58** then undergoes 1,2-migration and subsequent rearomatization towards the product (**93**). The yields increase with the electron-donating character of the indole nitrogen substituent (R^2 , 74 to 90% from Bn to PMB). The reaction tolerates a large variety of aryl substituents on the triple bond (R^4), but its efficiency declines importantly with alkyl groups (26–28%). Tryptamine ynesulfonamides **92** can also be successfully converted into spiroindolines by intercepting the indoleninium intermediate with suitable nucleophiles before the 1,2-migration (Scheme 24.B).^{56c} In the presence of Hantzsch's ester as a hydride donor, indolines **94** are smoothly obtained with excellent yields (Eq. 2

Indoles are potential partners as well, furnishing compounds **95** as single diastereoisomers with yields ranging from 68 to 94%. Interestingly, the authors showed that NFSI greatly increases the reaction kinetics, although the products are still obtained with similar yields over longer reaction times in its absence. Based on DFT calculations, the authors rationalized the impact of the NFSI ligand by proposing a π -stacking stabilization of the intermediate **int58b**.

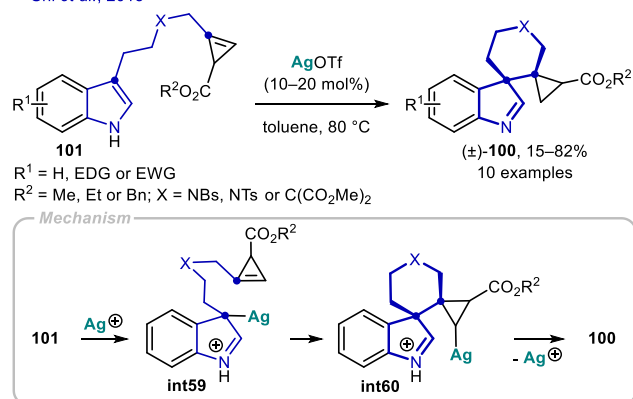
The same group reported the synthesis of indoline carbamate **96** from ynesulfonamide tryptamines **92** in the presence of silver triflate, triphenyl phosphine as ligand and various carbamates as nucleophiles to trap the silver indoleninium intermediate (Eq. 3).^{56d} The products are obtained with excellent yields (63 to 98%) with electron donating groups and halides on the indoles, but stronger electron withdrawing groups hindered the reactivity. Interestingly, their previously reported AgOTf -NFSI catalytic system failed to provide the intercepted indoline, with the exclusive formation of the migration product **93** in the otherwise same reaction conditions.

With higher catalytic charges (20 mol% of AgOTf and PPh₃) and in the absence of a nucleophile to trap the silver indoleninium intermediates, the later evolves through protodemetalation towards the spiroindolenines **97**, which are isolated with good yields (48 to 95%) without degradation or 1,2-migration events towards re-aromatized products (Scheme 24.C, Eq. 4).^{56e} Chiral oxazolidinone ynamides **98** are smoothly converted in these conditions into the corresponding indolenines **99** as single diastereoisomers (Eq. 5).

6.3 Other silver-catalyzed reactions

Shi, Tang and co-workers developed the synthesis of spiro[indoline-3,4'-piperidine] **100** using silver and gold catalysis on indolylcyclopropenes **101** (Scheme 25).⁵⁷ The major pathway for the silver-catalyzed transformation is thought to involve a first addition from the C3 position of the indole onto the silver catalyst to form the C(sp³)-Ag intermediate **int59**. A subsequent *syn*-addition on the cyclopropane, leads to intermediate **int60**, which furnishes the spiroindolenines **100** with overall good yields (over 60% in most cases), with electron-donating and withdrawing groups tolerated on the indole moiety. Surprisingly, nosyl-sulfonamides reacted sluggishly and furnished the expected products in low yield.

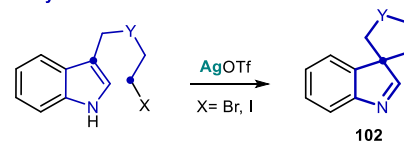
■ Shi *et al.*, 2015



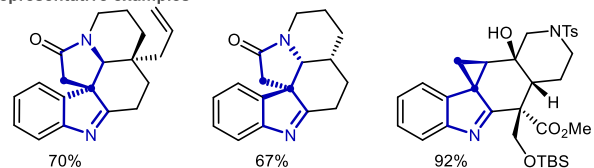
Scheme 25. C3-Ag indoleninium addition on cyclopropane

The formation of spiroindolenines **102** was also reported from tethered alkyl halides by silver-mediated cyclizations. This strategy was demonstrated using alkyl bromides or iodides and were mostly performed using stoichiometric amounts of silver triflate (Scheme 26).⁵⁸

General reactivity



Representative examples

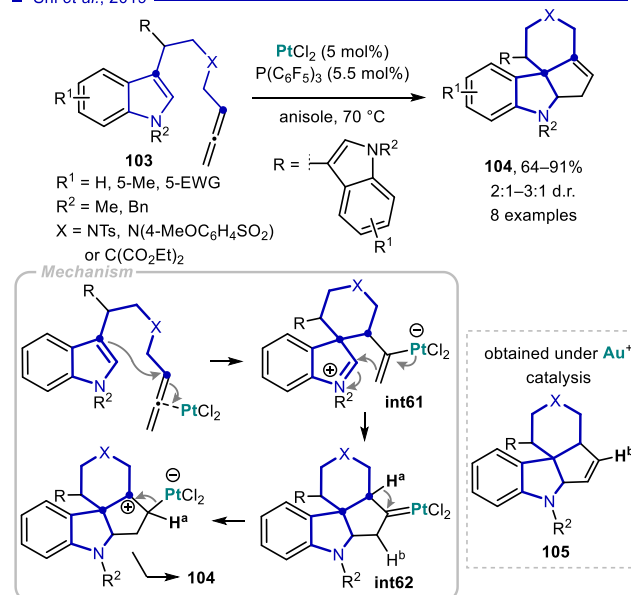


Scheme 26. Formation of spiroindolenines by alkylation with alkyl iodides.

6.4 Platinum catalysis

Shi and co-workers demonstrated that platinum catalysis could allow for the formation of different products compared with gold catalysis on the same substrates. Bis(indol-3-yl)-allenes **103** can indeed be converted into two different fused spiroindoline products **104** and **105** depending on the metallic complex used to catalyze the reaction (Scheme 27).⁵⁹ In the presence of platinum dichloride and tri(pentafluorophenyl)phosphine at 70 °C, indolines **104** are obtained as a mixture of diastereoisomers with yields ranging from 64 to 91%. Dearomative indole addition on the activated allenyl moiety affords the vinyl platinum intermediate **int61**, which undergoes addition onto the indoleninium to furnish carbenoid **int62**. The formation of the final product **104** occurs through the preferred 1,2-migration of H^a from the tertiary carbon. In the case of gold catalysis, the analogous gold carbenoid species undergoes a deprotonation of the secondary carbon (H^b) by the ditriflimide counterion (cf gold catalysis section, Scheme 41 for the asymmetric version with a chiral gold complex) towards regioisomer **105**.

■ Shi *et al.*, 2019

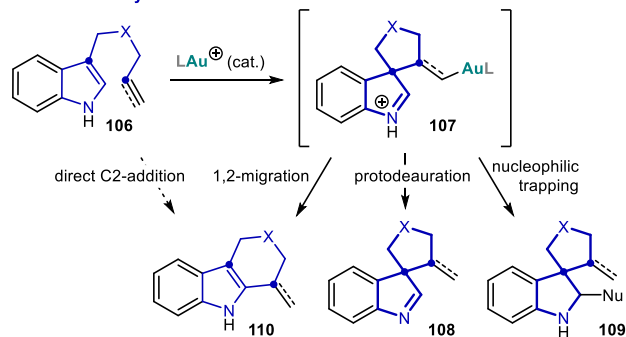


Scheme 27. Platinum-catalyzed formation of fused spiroindoline from(indol-3-yl)-allenes

7 Gold catalysis

Gold catalysis is undoubtedly the most fruitful approach reported for dearomative spirocyclizations on indole derivatives, mainly due to the high affinity of gold cations for insaturations that allows for efficient activations with outstanding selectivity.⁶⁰ As a consequence, all the approaches described below are based on the π -activation of unsaturated moieties tethered on the indole C3-position of general compounds **106**, leading to spiroindolenium intermediates **107** which eventually lead to the target spiroindolenine **108** (Scheme 28). Alternatively, the spiroindolenium **107** may be trapped by a nucleophile to deliver stable spiroindolines **109** (that can also result from the nucleophilic addition on indolenines **108**). These systems however share many of the mechanistic features encountered with the above-discussed transition metal catalytic systems, including the high propensity of the dearomatized spiroindolenium intermediate to undergo 1,2-migration towards a rearomatized indole product **110**. However, it cannot be ruled out that the formation of this aromatic compound may result from a direct C2 addition of the indole ring. These labyrinthine pathways have been studied and exploited to trigger the formation of a number of achiral and chiral derivatives, the aim being most of the time to understand and control the mechanistic route. Accordingly, the works reported in this section are sorted regarding the evolution of the spiroindolenium intermediate **107**. The timespan of the results summarized below has been extended in order to provide a more comprehensive overview of the challenges and opportunities in this field.

General reactivity



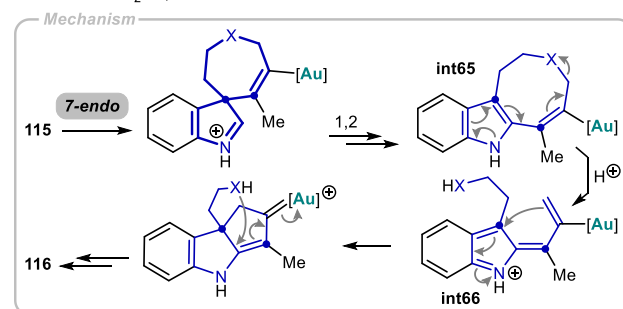
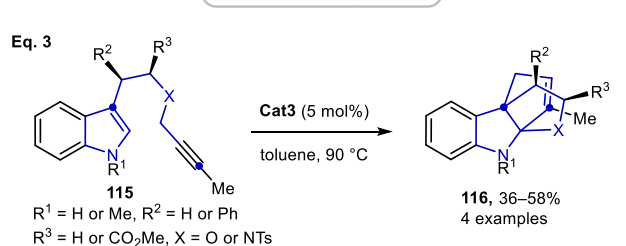
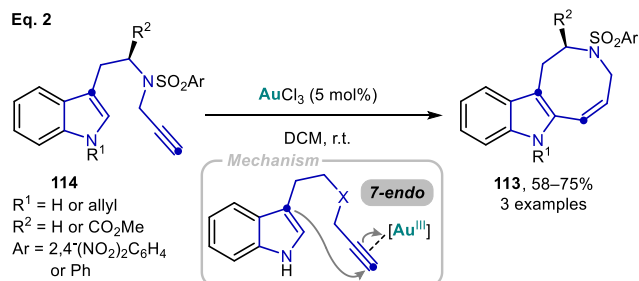
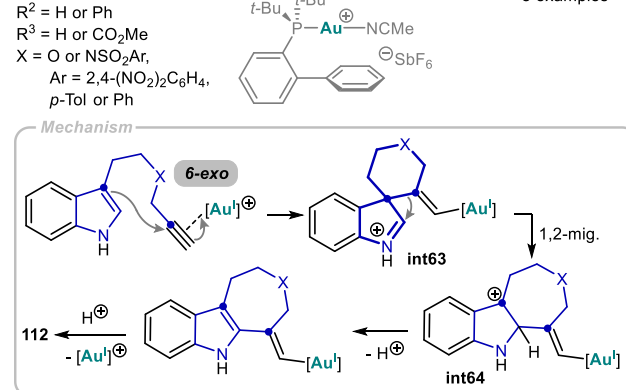
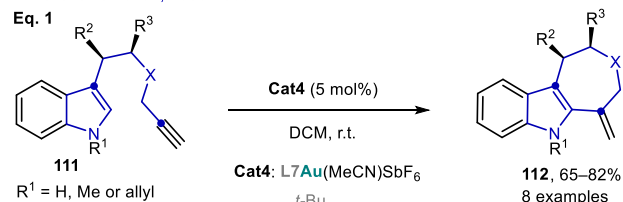
Scheme 28. Gold-catalyzed formation of polycyclic indole derivatives.

7.1 Spirocyclization and subsequent 1,2-migration

7.1.1 Migration of the vinyl-gold moiety

As carbon-carbon triple bonds are the most used unsaturated moiety in gold-catalyzed reactions,⁶¹ it is not surprising that the majority of the spirocyclizations discussed herein occur on alkyne-tethered indole derivatives. In pioneering developments, the group of Echavarren studied the gold-catalyzed activation of

■ Echavarren *et al.*, 2006-2009



Scheme 29. Early results in gold-catalyzed reactions of indoles with alkynes

propargyl-tethered indoles derivatives for the construction of polycyclic scaffolds, and furnished along the way valuable insights on the reactivity of these systems.⁶² In the presence of gold catalyst **Cat4**, propargylic tryptophane and tryptophol derivatives **111** are readily transformed into indolic compounds **112** containing a 7-

membered ring (Scheme 29, Eq. 1). The reaction has been proposed to occur through a first dearomative *6-exo-dig* spirocyclization by addition of the indole C3 position onto the proximal position of the gold-activated triple bond. The resulting spiroindoleninium intermediate **int63** then undergoes 1,2-migration of the vinyl-gold moiety towards ring-extended **int64**. Rearomatization of the indole ring and subsequent protodeauration furnish the final product **112**. It is however impossible at this stage to preclude totally a 7-*exo* addition of the nucleophilic C2 position of the indole ring.

However, when AuCl₃ was used as catalyst in otherwise identical conditions, 8-membered ring products **113** are obtained from the tryptamine derivatives **114**, which undergo in this case a 7-*endo-dig* spirocyclization (Eq. 2) followed by a 1,2-migration. In this study, Echavarren pinpointed the critical influence of the protecting group on the tether nitrogen (SO₂Ar), as benzylamine derivatives were shown to be unreactive in identical conditions.

With gold(I) catalyst **Cat4**, substrates **115** substituted by a methyl group on the alkyne exhibited an unexpected reactivity (Eq. 3). At 90 °C in toluene, tetracyclic products **116** are obtained with moderate yields. Their formation is proposed to arise from the usual successive 7-*endo-dig* spirocyclization and 1,2-migration towards **int65**, which undergoes ring opening faster than protodeauration to form **int66**. Cyclization onto the electrophilic C3-position and subsequent addition of the alcohol (X = O) or sulfonamide (X = NSO₂Ar) furnishes the tetracyclic indolines **116**. Noteworthy, the treatment of the above-mentioned substrates with a Brønsted acid fails to provide any cyclization product, as the starting material remain inert in these conditions.

The use of indole substrates bearing an alkyne group as a gold-activable function to trigger the dearomative spirocyclization has since been a very fertile approach to access various polycyclic indole derivatives after 1,2-migration.

Enders and co-workers designed an enantioselective synthesis of chiral tetracyclic compounds **117** containing a seven-membered ring from indole derivatives **118** and *ortho*-alkyne-substituted nitrostyrenes **119**, using successively H-bonding and gold catalysis in a one pot process (Scheme 30.A).⁶³ The thiourea-based organocatalyst **Cat5** allows for the highly enantioselective Friedel-Craft addition of the indole on the nitroalkene. In the presence of the cationic gold catalyst AuPPh₃NTf₂,⁶⁴ the alkyne-activated intermediate **int67** undergoes dearomative spirocyclization towards **int68**, which evolves towards the seven-membered ring indole product **117**. The acidic additive required for the cyclization step is thought to assist the regeneration of the gold catalyst, likely at the protodeauration step. In a later report, the group of Liu demonstrated the racemic products **117** could be obtained in very short reaction times (20 minutes vs. 40 to 80 hours for Enders' system) using Echavarren's catalyst **Cat4** in the presence of a catalytic amount of trifluoroacetic acid, in water, under microwave irradiation at 120 °C (59–91% yields).⁶⁵

Kundu and co-workers developed the synthesis of indoloazepino-benzimidazole products **120** from 3-formylindole derivatives **121** and aromatic *N*-alkyne diamine **122**, in the presence of PPh₃AuSbF₆ (Scheme 30.B).⁶⁶ Reaction of the amine with the aldehyde forms the bezimidazole-tethered indole substrate **int69** which contains the internal alkyne to be activated by the gold catalyst for the intramolecular indole addition towards **int70**. The

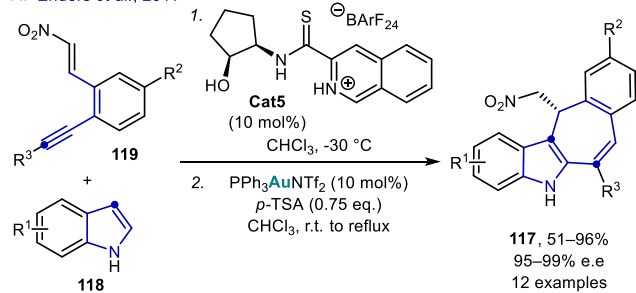
pentacyclic products are obtained in good yields without significant effect of the substitution of the indole ring (R¹) or the alkyne aryl moiety (Ar), although electron-withdrawing groups on the aromatic diamine **122** (R²) induce a slight decrease of the yields (below 70%).

8-Membered ring-containing compounds can be smoothly accessed from the tryptamine-derived alkyne amides **121** in the presence of the *in situ*-generated cationic AuPPh₃OTf, as reported by the group of Van der Eycken (Scheme 30.C, Eq. 1).^{67a} A wide variety of substrates **121** are accessible *via* a multicomponent Ugi reaction (R³ = CHRC(O)NHR'), elegantly used by the authors to extend the scope of the transformation.^{67b} Their approach generally provides products **122** in high yields but is limited on the substitution of the triple bond (R⁴), with a lower reactivity with bulky groups. In line with precedent reports, unsubstituted alkynes (R⁴ = H) furnish the *6-exo-dig* cyclization product **123**. A similar post-Ugi spirocyclization approach also allows to access 7-membered ring-containing products **124** (one carbon shorter) from indole-methylamine-derived substrates **125** (Scheme 30.C, Eq. 2).^{67c} This system appears slightly more tolerant regarding the substitution of the triple bond (R¹), but substrates with very bulky substituents such as *tert*-butyl remain unreactive.

Unsworth's group demonstrated that the reactivity of ynone-tethered indole derivatives **126** in the presence of a cationic gold catalyst differs from the silver-catalyzed reaction discussed above (Scheme 30.D and Scheme 22).⁶⁸ In the presence of AgOTf, the substrates underwent 5-*endo-dig* cyclization, and the spiroindolenines were isolated after protodemetalation without 1,2-migration event. Vinylgold spiroindoleninium intermediates **int71** appear more prone to the rearomatization than their silver equivalents **int50** (Scheme 22), and the authors highlighted the importance of the vinylmetal intermediate in the 1,2-migration process, as no reaction occurred when the isolated spiroindolenine **86** was subjected to the same catalytic systems (AgOTf or AuPPh₃NTf₂). From the migration intermediate **int72**, the aromatic phenol products **127** were obtained after deauration in good yields.

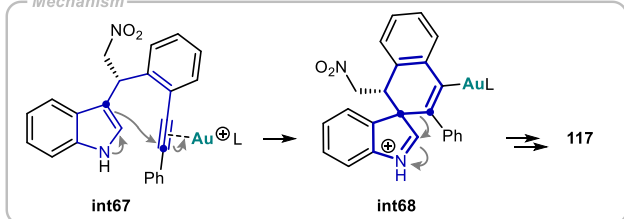
Xei, Wei, He and co-workers reported the synthesis of indole-fused azabicyclo[3.3.1]nonanes **128** *via* a domino cyclization of 1,6 diynes **129** (Scheme 30.E).⁶⁹ Between two potential triple bonds for dearomative indole addition, the 5-*endo-dig* cyclization on the gold-activated proximal alkyne is preferred over a 6-*exo* process on the distal alkyne (backed up by DFT calculations), furnishing spiroindoleninium **int73**. Subsequent 1,2-shift, indole rearomatization and protodeauration lead to an alkyne-tethered dihydro-carbazole **int74** which undergoes a second dearomative addition from the indole C-3 position in a *6-exo-dig* spirocyclization towards **int75**, affording final product **128** after protodeauration. The reaction provides satisfactory yields with both sulfonamides and carbamate tryptamine derivatives (R²), however with a slight decrease in efficiency with substrates substituted by electron-withdrawing groups on the indole ring (R¹).

A. Enders *et al.*, 2011

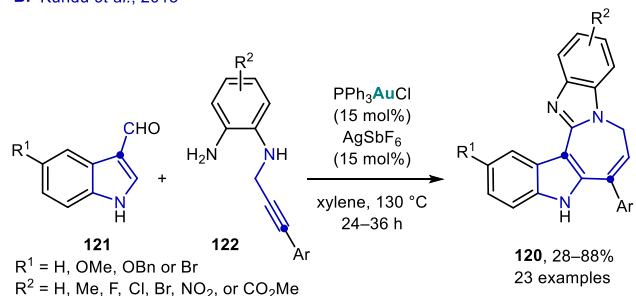


$\text{R}^1 = \text{H}$ or EDG
 $\text{R}^2 = \text{H}$ or F
 $\text{R}^3 = \text{Ph}$ or 3-tolyl

Mechanism

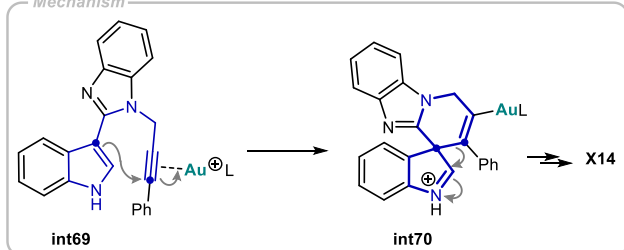


B. Kundu *et al.*, 2015

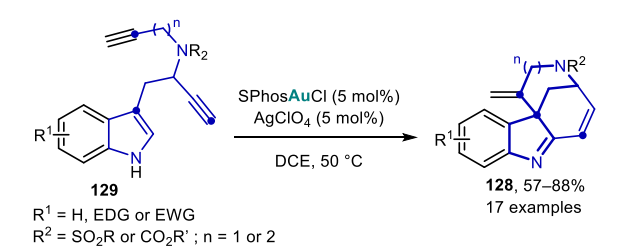


$\text{R}^1 = \text{H}$, OMe, OBn or Br
 $\text{R}^2 = \text{H}$, Me, F, Cl, Br, NO_2 , or CO_2Me

Mechanism

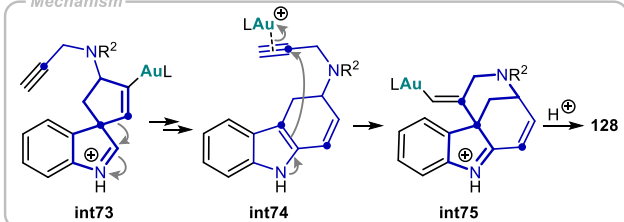


E. Xei, Wei, He *et al.*, 2021

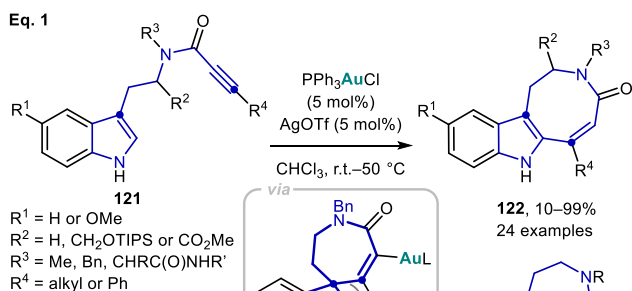


$\text{R}^1 = \text{H}$, EDG or EWG
 $\text{R}^2 = \text{SO}_2\text{R}$ or CO_2R^1 ; $n = 1$ or 2

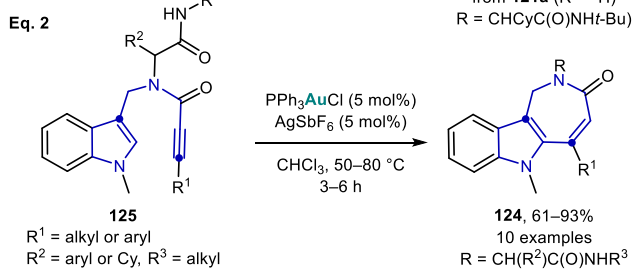
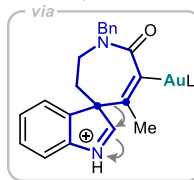
Mechanism



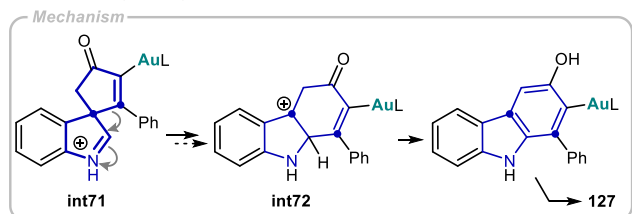
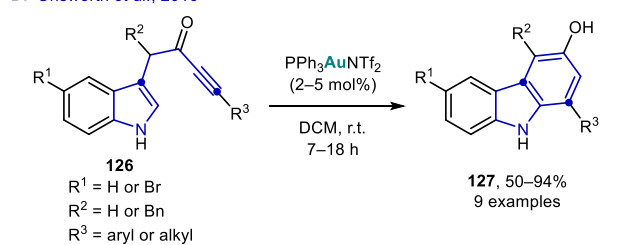
C. Van der Eycken *et al.*, 2012 and 2015



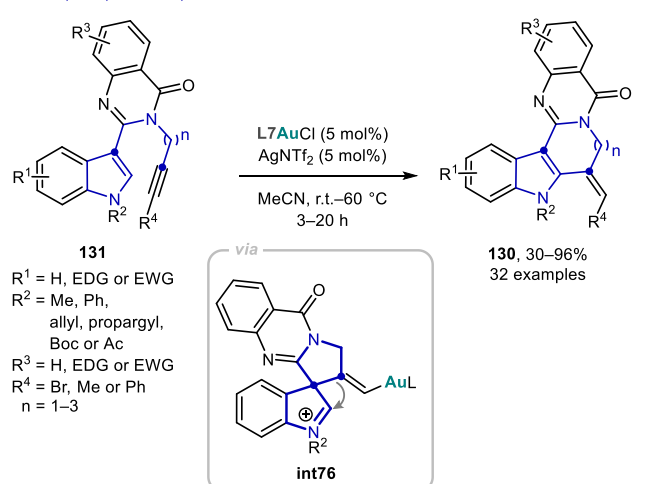
$\text{R}^1 = \text{H}$ or OMe
 $\text{R}^2 = \text{H}$, CH_2OTIPS or CO_2Me
 $\text{R}^3 = \text{Me}$, Bn, $\text{CHRC}(\text{O})\text{NHR}'$
 $\text{R}^4 = \text{alkyl}$ or Ph



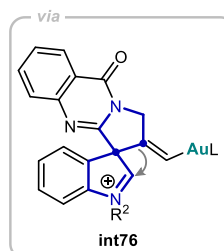
D. Unsworth *et al.*, 2016



F. Su, Pan, Mo *et al.*, 2022



$\text{R}^1 = \text{H}$, EDG or EWG
 $\text{R}^2 = \text{Me}$, Ph, allyl, propargyl, Boc or Ac
 $\text{R}^3 = \text{H}$, EDG or EWG
 $\text{R}^4 = \text{Br}$, Me or Ph
 $n = 1\text{--}3$

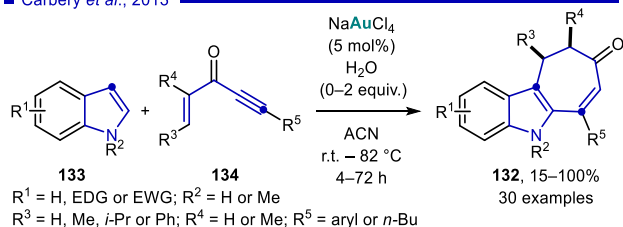


Scheme 30. Gold(I) activation of alkyne-tethered indoles and subsequent 1,2-migration of the vinyl-Au moiety

Su, Pan, Mo *et al.* designed the synthesis of pseudorutaecarpine derivatives **130** from *N*-alkynyl quinazolinone-tethered indoles **131** in the presence of 5 mol% of cationic gold catalyst. The reaction occurs through the formation of the spirocyclic indoleninium **int76** and the subsequent 1,2-migration of the vinyl-gold moiety (Scheme 30.F).⁷⁰ The reaction tolerates a wide substitution pattern on the quinazolinone (R^3) and the indole (R^1 and R^2) moieties, as well as substituted alkynes ($R^4 \neq H$) and extended ring sizes in the products ($n = 2$ or 3), although requiring longer reaction times and higher temperatures.

The group of Carbery designed a procedure to access the tricyclic indolic compounds **132** from indoles **133** and enynones **134** via a gold(III)-catalyzed cascade conjugate addition and cyclization (Scheme 31).⁷¹ A wide selection of products is described with most yields over 75%, but the scope is limited to substituted alkynes ($R^5 \neq H$). The reaction is proposed to be initiated by 6-*endo*-dig spirocyclization followed by 1,2-migration, furnishing the rearomatized product **132** after protodeauration.

■ Carbery *et al.*, 2013



Scheme 31. Gold(III)-catalyzed indole conjugate addition and spirocyclization.

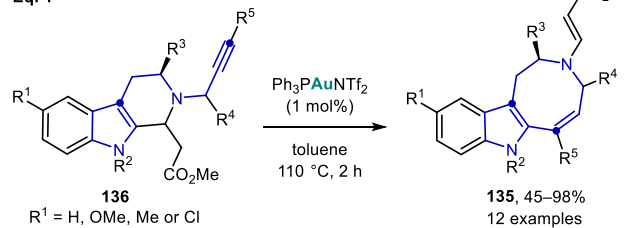
7.1.2 Reaction of alkyne-substituted tetrahydro- β -carbolines

Wang *et al.* reported the construction of 1*H*-azocino[5,4-*b*]indole products **135** from 2-propargyl tetrahydro- β -carbolines **136**, with the indole rearomatization event differing from the usual mechanism (Scheme 32, Eq. 1).⁷² After the gold-triggered 7-*endo* spirocyclization (affording **int77**) and 1,2-migration, **int78** undergoes a rearomatization-driven Grob-like fragmentation, resulting in a ring opening to form iminium **int79**, which then evolves towards **135** after successive deprotonation and protodeauration. The reaction is overall high yielding, with no significant influence of the electronic properties of the substitution of the indole ring (R^1) observed. Nevertheless, the methoxycarbonylmethyl group at the tetrahydro- β -carboline C1-position is crucial for the ring extension to happen. In order to extend the synthetic applicability of their system, the authors developed modified conditions on substrates **136** bearing alkyl or aryl groups on the C1 position (R^2 , Scheme 32, Eq. 2), the addition of acidic additives being able to promote the ring extension, furnishing secondary amine products **137** after hydrolysis.⁷³ However, the substitution of the triple bond on **136** (R^4) has a critical impact on the outcome of the reaction. When azocino[5,4-*b*]indoles **137** are obtained with alkyl or aryl substituents, terminal alkynes furnish spirocyclic products **138** in similar conditions, with the concomitant formation of ring extended compounds like **137** as minor products (Eq. 3). To unveil the reactions mechanisms, Wang and Yu conducted a thorough DFT study and highlighted a peculiar bifurcating potential energy surface (PES)

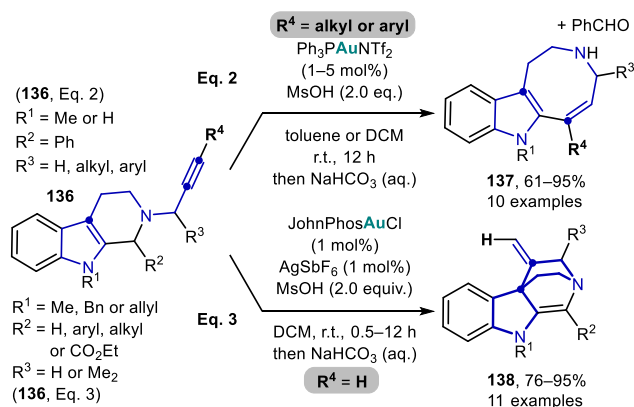
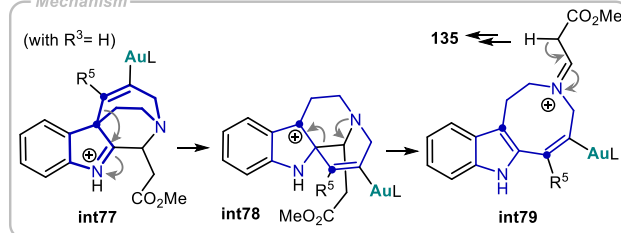
phenomenon, where several products can be obtained from the same transition structure.⁷⁴ According to their calculations, the indole nucleophilic attack on the gold-activated alkyne occurs through one single TS, furnishing both C3- and C2-addition products.

■ Wang, Yu *et al.*, 2014–2015

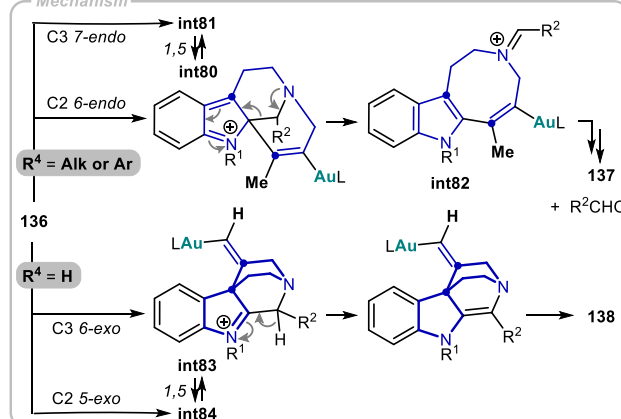
Eq. 1



Mechanism



Mechanism



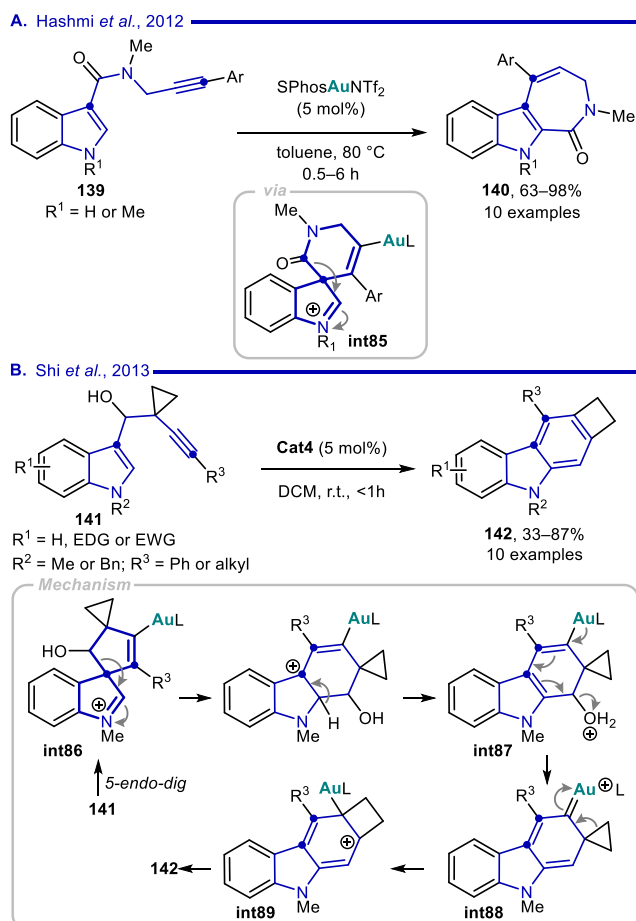
Scheme 32. Gold activation of N2-propargyl tetrahydro- β -carbolines.

For substituted alkynes ($R^4 = \text{alkyl or aryl}$), **int80** and **int81** may be formed and interconvert *via* a 1,5-alkenyl shift, although the ring

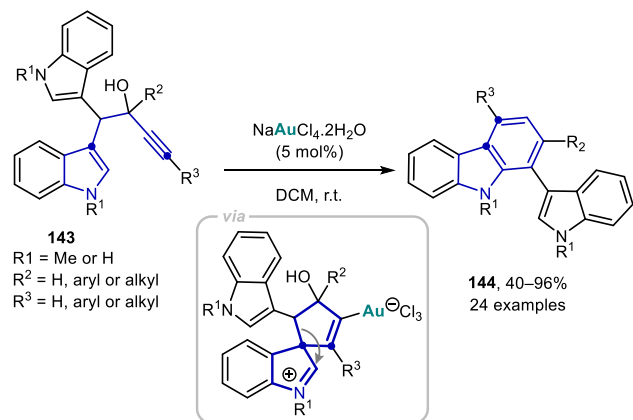
extension pathway leading to **137** involves the fragmentation of the former towards **int82**, furnishing the product after proto-deauration and iminium hydrolysis. For unsubstituted alkynes ($R^4 = H$), indole attack on the activated alkyne furnishes **int83** and **int84** in an *exo*-cyclization process, with the spirocyclic intermediate **int83** undergoing deprotonation and subsequent proto-deauration to form product **138**. The authors hypothesized the acidic additive (MsOH) in this system can promote the ring extension pathway by protonation of the amine, and prevent the formation of unreactive σ,π -digold species which can be formed from the gold catalyst and the terminal alkynes.⁷⁵

7.1.3 Other migrating groups on the spiroindolenium

In opposition with the above-mentioned systems for which the re-aromatization event is initiated by the migration of the vinyl-gold moiety, Shi's and Hashmi's groups reported examples involving the migration of the alternative group on the spiroindolenium intermediate. In the presence of a cationic gold catalyst, alkyne-substituted 3-indole amides **139** are converted into azepino[3,4-*b*]indol-1-one **140** via a 6-*endo*-dig spirocyclization towards **int85** and the subsequent migration of the acyl group onto the indole C2-position (Scheme 33.A).⁷⁶ Similarly, from substrates **141**, spiroindolenium **int86** undergoes 1,2-migration of the C-OH group towards **int87** (Scheme 33.B).⁷⁷ Water elimination (forming cyclovinyl gold carbene **int88**) and 1,2-shift to the adjacent gold-carbenoid leads to the ring-expanded intermediate **int89**, which undergoes elimination of the cationic gold catalyst to form the all-aromatic carbazole derivative **142**. Besides this transformation, the authors were able to access a significant molecular diversity by tuning the reaction conditions, allowing for instance the opening of the cyclopropane intermediate **int88** by an external nucleophile. An analogous migration of C-O group on silylether indolenium intermediates has been reported by Hashmi for the synthesis of carbazole products (2 examples).⁷⁸ The higher propensity of the C-O moiety to undergo the 1,2-shift likely arises from a more important electronic density on the migrating carbon, while the preferred migration of the carbonyl group in Shi's system can be explained by the stabilization of the migration transition structure as a keteniminium species.



In the presence of a gold(III) catalyst, 3,3-bis(indolyl)methane derivatives **143** are readily converted into 1-indolylcarbazoles **144** through the preferred migration of the alkyl moiety on the spiroindolenium intermediate and subsequent aromatization of the carbazole (Scheme 34).⁷⁹ The DFT investigation performed by the authors suggests the bis-indolyl structure is critical to favor the migration of the alkyl group over the vinyl-gold moiety. While the substrates with a phenyl substituent in place of the second indole would undergo the alkenyl migration, the indole allows for a step-wise migration process involving the cleavage of the C3-C(sp³) spirocyclic bond and the formation of a carbocation intermediate, stabilized by the indole moiety, and a subsequent C2-nucleophilic attack would afford the dihydrocarbazole intermediate.

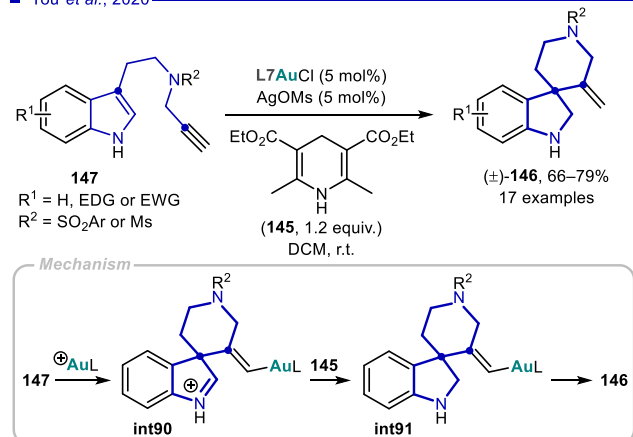


Scheme 34. Gold(III)-catalyzed spirocyclization and subsequent migration of the alkyl group.

7.2 Spirocyclization followed by indolenium trapping

7.2.1 Spiroindolenium trapped by a hydride

The trapping of spiroindolenium intermediates is a suitable strategy to ensure the isolation of a spirocyclic product over a rearranged product. Zhang and You showed that metastable indolenium intermediates **int90** could be reduced *in situ* in the presence of Hantzsch ester **145** as a hydride donor to form indolines **int91** before any 1,2-migration event (Scheme 35).⁸⁰ Products **146** are formed upon protodeauration and isolated with yields ranging from 66 to 79%. This approach represents a first solution for the isolation of spiro[indole-3,4'-piperidines] that were hitherto non-accessible by Echavarren's method because of the inevitable rearrangement.^{62b}

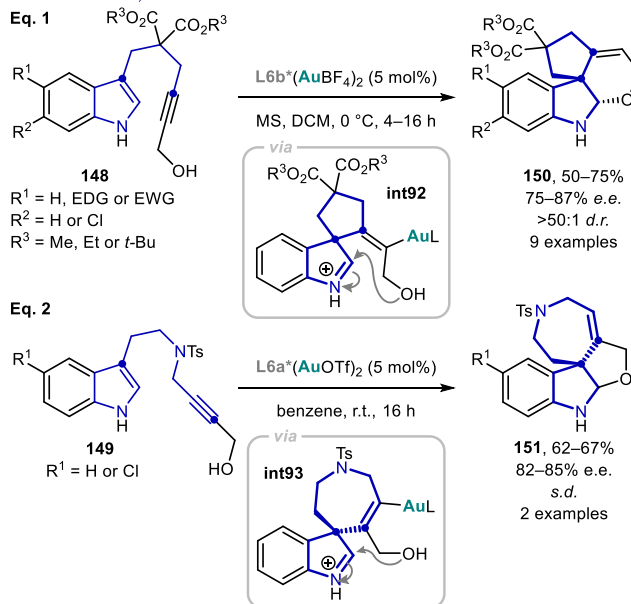


Scheme 35. *In situ* reduction of the spiroindolenium intermediate

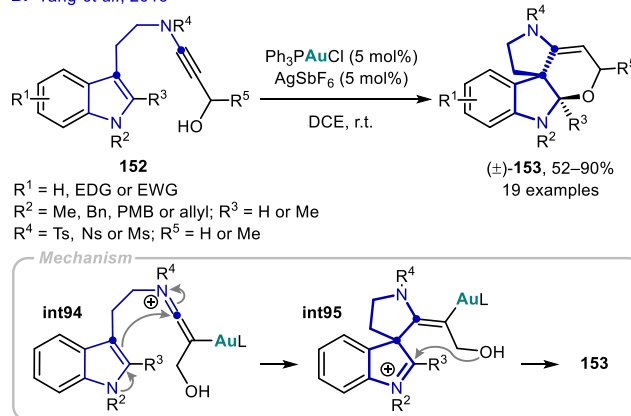
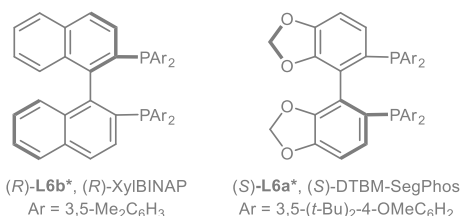
7.2.2 Spiroindolenium trapped by internal nucleophile.

Beyond the reduction of the intermediate spiroindolenium, the most common strategy is to trap it by an intramolecular addition of a nucleophile. This strategy offers the additional interest to trap intermediates that may be kinetically favored but not necessarily productive in the absence of the trapping nucleophile.

The group of Bandini used propargylic alcohols-tethered NH-indoles **148** and **149** to obtain tetracyclic fused indoline products **150** and **151** after trapping by the hydroxyl pendant of the spiroindolenium intermediates **int92** and **int93**, Scheme 36.A) formed by the initial gold-triggered spirocyclization.⁸¹



Ligands

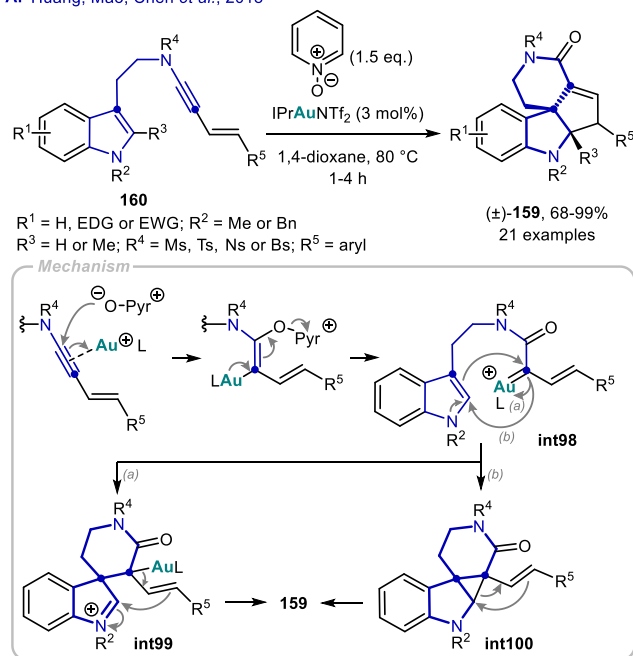


Scheme 36. Synthesis of tetracyclic spiroindolines via the trapping by a hydroxyl pendant.

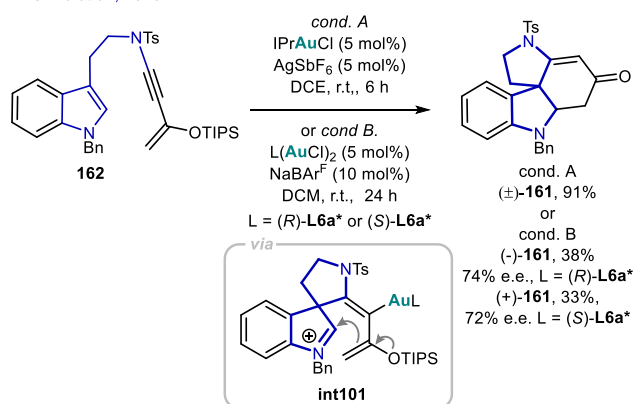
In the presence of achiral catalyst **Cat4** (not shown), substrates **148** containing a 3-carbon atoms linker between the indole and the alkyne deliver 5-*exo*-dig cyclization products **150** with yields ranging from 59 to 86%. Electron-withdrawing groups on the indole ring are well-tolerated, but interestingly, substrates with

ether-substituted ynamide **162**. (Scheme 39.B).⁸⁹ Upon activation of the triple bond by the NHC-based cationic gold catalyst, the substrate undergoes 5-*exo*-dig spirocyclization, and the obtained indolenium intermediate **int101** is trapped by addition of the silyl enol ether, affording the cyclohexenone **161** with an excellent 91% yield. In the presence of chiral gold complexes, using C2-symmetrical DTBM-SegPhos ligands **L6a*** (*R*) and **L6c*** (*S*), a BAR^F counterion, each enantiomer of **161** can be formed with enantiomeric excesses up of 74%.

A. Huang, Mao, Chen *et al.*, 2018



B. Ohno *et al.*, 2019



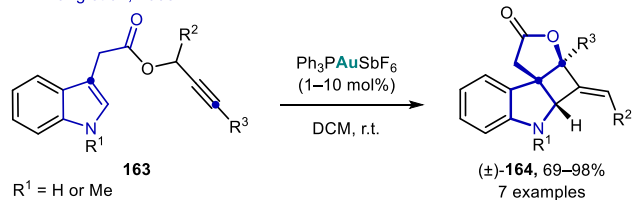
Scheme 39. Cascade reactions from ene-ynamides.

As the reaction of the gold-activated unsaturated moiety forms a nucleophilic vinylgold intermediate, spirocyclization reactions with indoles sometimes involve the intramolecular trapping of the spiroindolenium intermediate and the formation of a fourth cycle. Zhang has shown that propargylic esters **163** could be used to access spirocyclic 2,3-indoline-fused cyclobutanes **164** (Scheme 40.A).^{90a} The transformation involves a first 3,3-rearrangement triggered by the gold activation of the triple bond *via* the cyclic vinyl-gold species **int101** furnishing the allenyl intermediate

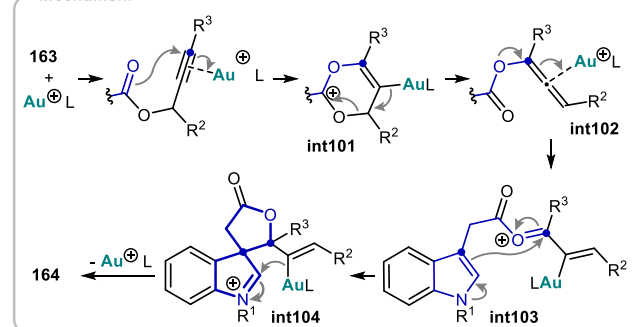
int102. The allene moiety is subsequently activated by the catalyst, allowing for the formation of the oxonium intermediate **int103** which undergoes the 5-*endo*-*trig* spirocyclization. The indolenium intermediate **int104** is finally trapped by the vinyl-gold pendant to form product **164**. The reaction is generally high yielding, although requiring a substituted propargyl group, as no reaction occurs on unsubstituted substrates (R² = R³ = H). The groups of Toste and Sigman later developed an highly enantioselective version of this transformation, by designing a chiral acyclic diaminocarbene ligand from computational investigations, modelling various compounds with different aryl groups (Ar¹ and Ar², Scheme 40.B).^{90b} They identified **L8*** as the most promising ligand and used the corresponding bis-gold complex in the presence of propargyl esters **165**. The spirocyclic indolines **166** are obtained with very good enantiomeric excesses (above 80%), except in the case of a 4-bromo-substituted substrates which furnishes a nearly racemic mixture.

From substituted *N*-homoallenyl tryptamine derivatives **167**, Guinchard, Voituriez and co-workers developed the analogous asymmetric [2+2] cycloaddition towards cyclobutene-fused spiroindolenines from *N*-homoallenyl tryptamines via similar mechanism (Scheme 40.C).^{90c} Their newly designed chiral phosphathialicene scaffolds **L9a*** and **L9b***,^{90d} used as gold complexes, allow for the highly enantioselective spirocyclization of substrates **167**, and the subsequent trapping of the indolenium intermediate furnishes the cyclobutane derivatives **168** with enantiomeric excesses up to 93%.

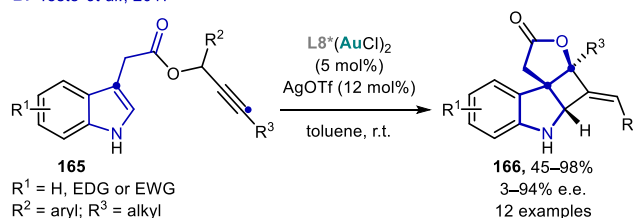
A. Zhang *et al.*, 2005



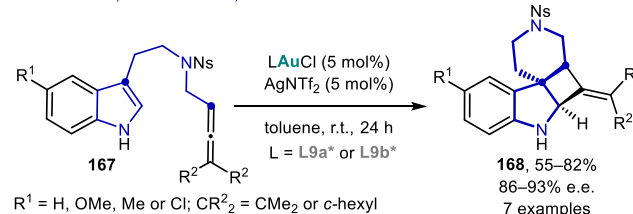
Mechanism



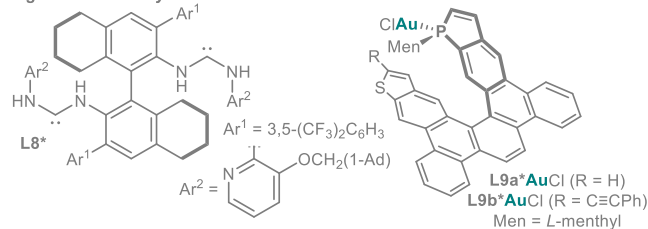
B. Toste *et al.*, 2017



C. Guinchard, Voituriez *et al.*, 2020



Ligands and catalysts



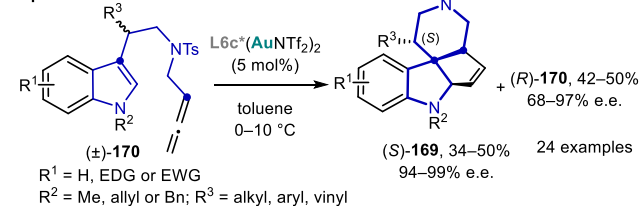
Scheme 40. Domino 3,3-rearrangement/[2+2]-cycloaddition on propargyl esters-tethered indoles.

Shi and co-workers developed a kinetic resolution strategy to access enantio-enriched spiroindolines **169** from racemic indoles **170**, involving a similar trapping of the indoleninium by a vinyl-gold intermediate (Scheme 41, Eq. 1).⁹¹ In the presence of (*R*)-DTBM-Segphos-based (*R*)-**L6c*** gold complex, the (*S*)-enantiomer of **170** readily undergoes the spirocyclization on the activated allenyl moiety towards **int105**, furnishing the polycyclic product **169** after deprotonation and prodeauration with excellent enantiomeric excesses (>94%). The same chiral gold complex catalyzes the asymmetric desymmetrization of similarly substituted bis-indoles **171** towards spiroindolenines **172** (Scheme 41, Eq.

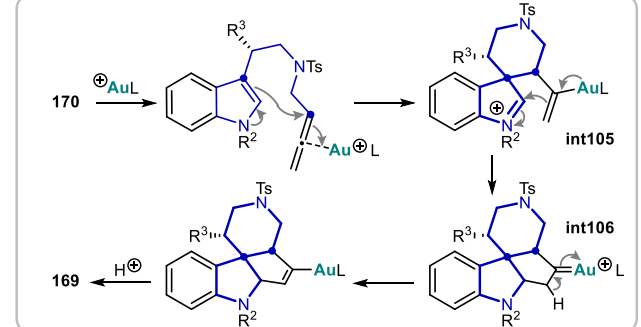
2).⁵⁹ The authors also exemplified the racemic version of the reaction in the presence of gold (18 examples) and platinum (8 examples) complexes, which interestingly afford different regioisomers from the metal carbenoid intermediate like **int106** (cf. Scheme 27). The polycyclic products are obtained with excellent stereoselectivities (>86% e.e.), except for carbonated linkers with $X = \text{C}(\text{CO}_2\text{Et})_2$.

■ Shi *et al.*, 2019

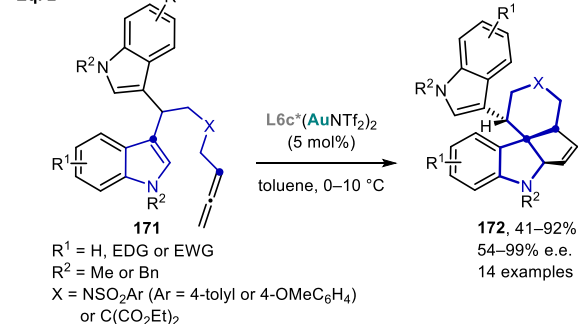
Eq. 1



Mechanism



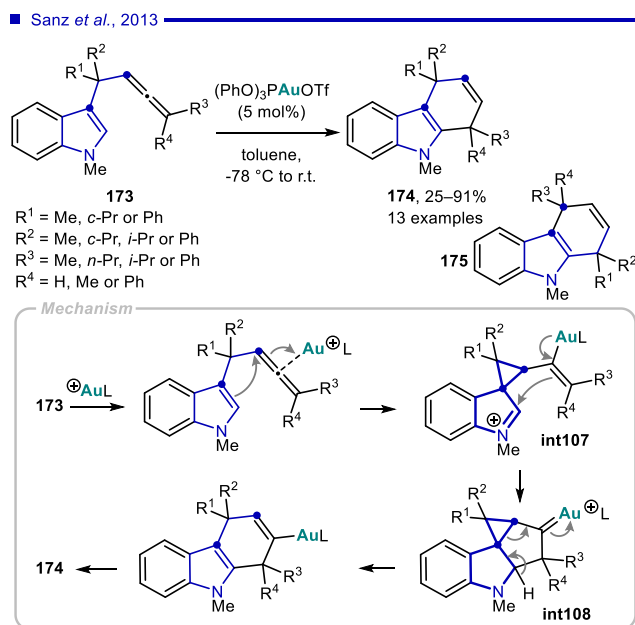
Eq. 2



Scheme 41. Cycloadditions on unsubstituted *N*-homoallenyl tryptamine derivatives

Sanz and co-workers explored the reactivity of 3-allenylmethylindoles **173** in the presence of gold complexes (Scheme 42).⁹² Mixtures of the two regioisomers **174** and **175** are often obtained, with proportions highly dependent upon the nature of the solvent used for the reaction. **175** is obtained as a major product in halogenated solvent (such as dichloromethane, dichloroethane or trifluorotoluene), while **174** is mostly formed in dimethoxyethane, THF, or methanol. By tuning the reaction conditions, in the presence of the phosphite gold complex (PhO)₃PAuOTf in toluene, dihydrocarbazole **174** can be obtained exclusively with most yields above 70%. The reaction to form this product first proceeds through the 3-*exo-trig* spirocyclization towards **int107**, which undergoes nucleophilic attack of the vinyl gold moiety onto the electrophilic C2-position of the indoleninium to form **int108**. A re-aromatization of the indole ring can subsequently occur through

the opening of the cyclopropane, furnishing the final dihydrocarbazole **174** after protodeauration. On another hand, the formation of **175** in the unoptimized conditions can be explained by a first 5-*endo-trig* spirocyclization, followed by either 1,2-migration or a ring opening / cyclization cascade.



Scheme 42. Trapping of the indoleninium intermediate by the vinylgold moiety en route to dihydrocarbazoles.

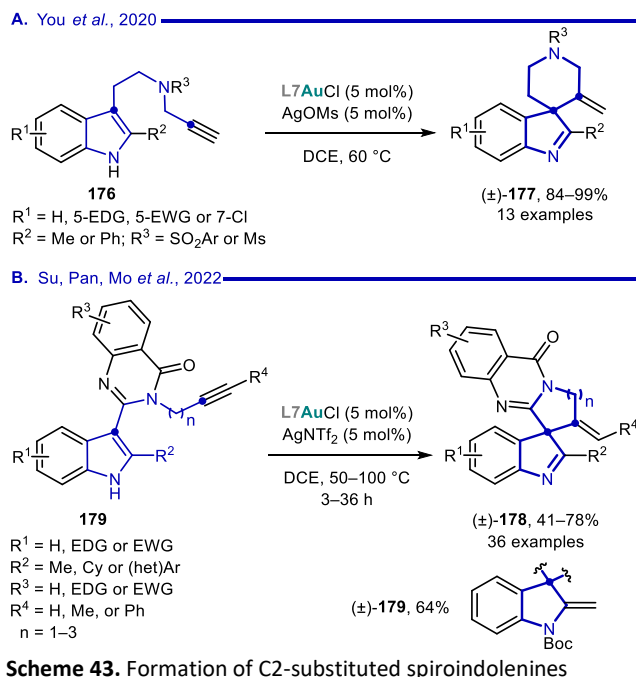
7.3 Reactions delivering spiroindolenines

7.3.1 C2-substituted spiroindolenines

In their early work, Echavarren *et al.* demonstrated that a stable spiroindolenine product could be isolated by deprotonation of a C2-methyl substituent on the indoleninium intermediate, affording an enamine product.^{62b} Later, the group of Bandini isolated a spiroindolenine (1 example) from a C2-methylated indole substrate tethered with an allenamide moiety in the presence of a gold catalyst.⁹³ Since these first results, several approaches have been developed to access indolenine derivatives from C2-substituted substrates.

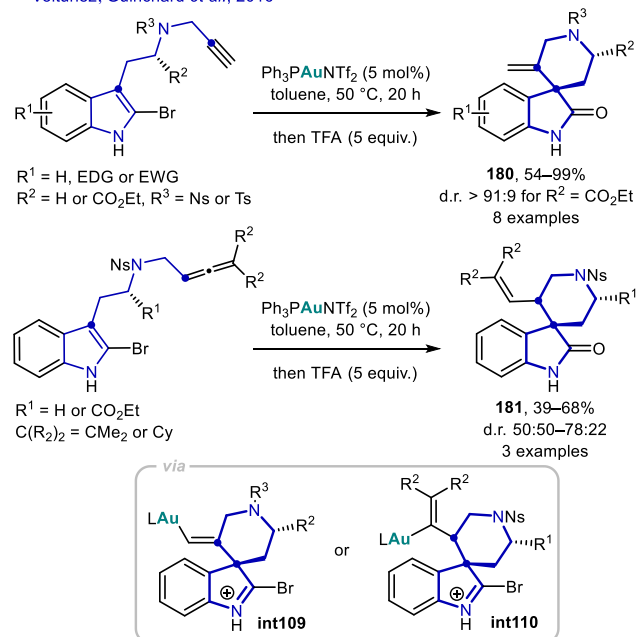
You and co-workers reported that C2-substituted propargyl tryptamine derivatives **176** could be readily converted into spiroindolenines **177** in the presence a JohnPhos (**L7**) gold complex, and isolated with high yields, regardless of the electronic properties of the indole substituents or the sulfonamide protecting group (Scheme 43.A).⁸⁰ Similarly, the group of Su, Pan and Mo accessed spiroindolenine-3,3'-pyrrolo[2,1-*b*]-quinazolinones **178** from C2-substituted indoles **179**, prohibiting the rearomatizing 1,2-migration that they previously used on these substrates for the synthesis of *pseudorutaecarpine* derivatives (Scheme 43.B).^{70, 94} The authors report a wide scope of spiroindolenines accessible, with no obvious influence of the electronic properties of the substituents on the indole (R^1) or the quinazolinone (R^3). The products obtained from substituted triple bonds (R^5) or with a longer chain between the quinazolinone and the alkyne can be accessed as well but require higher temperatures to form the product in satisfactory yields (up to 100 °C). Interestingly, Boc-protected indoles bearing

a methyl group on the C2 position can be used as well, affording the indoline **179** with a 64% yield *via* the deprotonation of the methyl group, similarly with the example reported by Bandini.⁹³



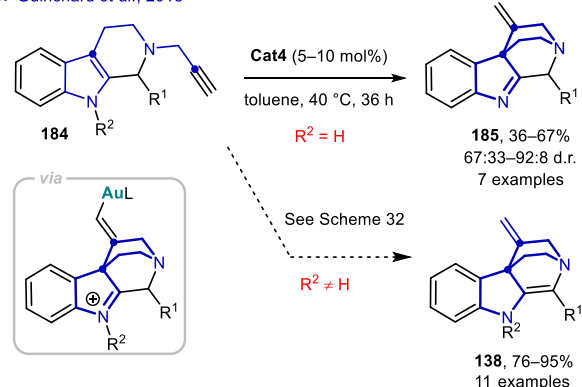
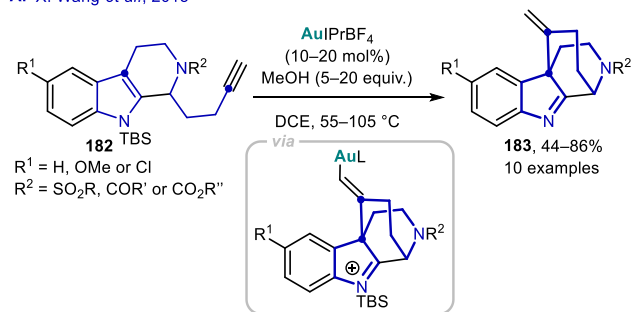
Scheme 43. Formation of C2-substituted spiroindolenines

Taking advantage of the known reactivity of 2-halotryptamine derivatives,⁹⁵ the group of Guinchard designed the synthesis of spirooxindoles **180** and **181** from 2-bromo-*N*-propargyl and *N*-homoallenyl tryptamine derivatives in the presence of $\text{Ph}_3\text{PAuNTf}_2$ (Scheme 44).⁹⁶ The substitution of the indole ring with the bromine prevents the 1,2-migration event on **int109** and **int110**, which can subsequently be hydrolyzed by wet TFA to form the expected oxindoles, although the bromoindolenine can also be isolated by silica gel chromatography. The reaction tolerates various substitution patterns on the substrates, however with lower yields for tosyl protecting group (R^3) or when the bromine is replaced by a chlorine atom. Other substrates bearing a sulfide function at C2 position furnished stable 2-sulfonylspiroindolenines.⁹⁷



Scheme 44. Synthesis of spirooxindoles from 2-bromo-*N*-propargyl and *N*-homoallenyl tryptamine derivatives

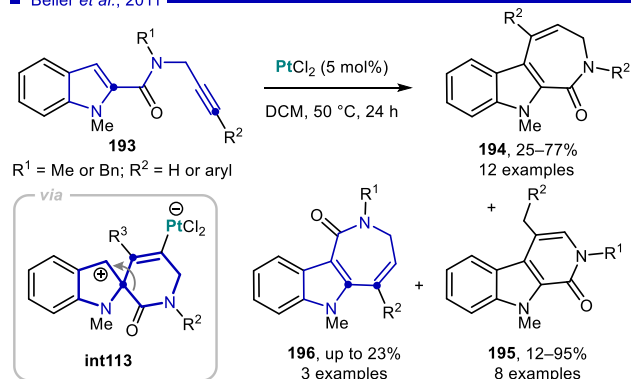
Using *N*-silylated tetrahydro- β -carboline **182** bearing an alkyne pendant on the C1 position, Wang and co-workers accessed fused-spirocyclic products **183** *via* a desilylative *exo*-cyclization in the presence of the carbene gold complex $\text{AuI}^+\text{PrBF}_4^-$ and methanol as silyl scavenger and protic source (Scheme 45.A).⁹⁸ Starting from tetrahydro- β -carbolines **184** as substrates (prepared by acid-catalyzed Pictet-Spengler reaction), Guinchard *et al.* developed the synthesis of indoloquinuclidines **185** in the presence of $\text{JohnPhosAuSbF}_6 \cdot \text{MeCN}$ catalyst **Cat4** (Scheme 45.B).⁹⁹ The products are obtained with satisfactory yields, ranging from 36 to 67% as mixtures of diastereoisomers (up to 92:8 dr for $R^1 = i\text{-Pr}$). The team also explored the combination of asymmetric CPA-catalyzed Pictet-Spengler reaction (in the presence of a chiral phosphoric acid catalyst) with the gold-catalyzed cyclization in a one-pot sequence, delivering enantioenriched quinuclidines with very good enantiomeric excesses, ranging from 77 to 90 %, however with limited conversion after 36 h. As a reminder, similar starting materials were used by Wang and Yu (see Scheme 32) but with *N*-substituted indoles ($R^2 \neq \text{H}$), which promoted the loss of the stereogenic center. The two approaches are hence complementary. It should be noted that zinc-promoted reactions have also been reported from closely related starting materials by Oguri, delivering targets similar to **185**.¹⁰⁰



Scheme 45. Polycyclic spiroindolenines synthesis from tetrahydro- β -carbolines.

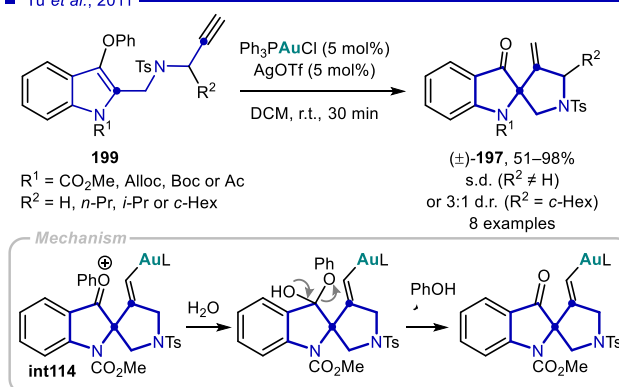
7.3.2 C2-unsubstituted spiroindolenines.

As seen in numerous examples discussed above, spiro vinylgold intermediates formed in the reaction conditions from C2-unsubstituted indoles tend to undergo uncontrolled migration to C2, rendering these substrates highly challenging. Guinchard *et al.* discovered that C2-unsubstituted *N*-alkyl propargyl tryptamines **186** afford the dearomatized spiroindolenine products **187** in the presence of **Cat4**, however in mixture with the 1,2-shift product **188** (Scheme 46.A).¹⁰¹ The addition of a stoichiometric amount of Brønsted acid (acetic acid) was found to improve both conversion and selectivity in favor of indolenine **187**, formed with yields ranging from 45 to 86%, the lowest with electron-withdrawing groups on the indole (R^1), and with **187/188** selectivities up to 99:1. The screening of various chiral gold complexes allowed to synthesize compound **187a** with a moderate enantiomeric excess of 68% in the presence of the helical gold precatalyst **L9c*** AuCl and silver ditriflimide. DFT investigations performed of the system revealed the acidic additive facilitates the spirocyclization, with a lower activation barrier calculated for the protonated tryptamine, and favors the protodeauration towards the indolenine over the 1,2-migration event that leads to the rearomatized product **188**. Besides, their calculations show that the sp^3 hybridization of the tryptamine nitrogen (compared with the more sp^2 -character of a sulfonamide) allows to ideally position the gold-activated alkyne over the C3-position of the indole, while a sulfonyl protecting groups tends to push the triple bond near the C2-position, possibly triggering a direct C2-addition of the indole ring.

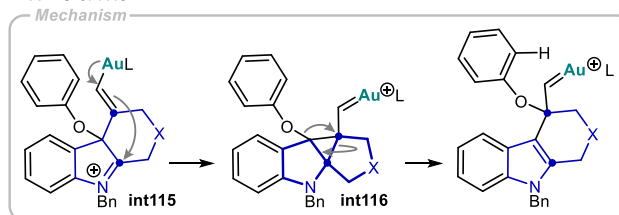
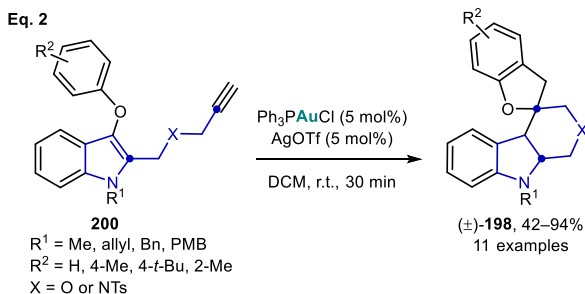


Scheme 48. Platinum-catalyzed C2-spirocyclization and rearomatization.

Tu and co-workers reported the formation of C2-spiroindolines **197** and tetrahydrocarbolines **198** from 3-phenoxy alkynyl indole derivatives **199** and **200** in the presence of a cationic gold catalyst (Scheme 49).¹⁰⁶ The outcome of the reaction is dependent on the protecting group born on the indole N1-position (R¹): with electron-withdrawing groups, substrates **199** undergo 5-*exo*-dig C2-spirocyclization upon activation of the triple bond, to form oxacarbenium intermediate **int114**. Water addition, phenol elimination and final protodeauration furnish products **197** in good yields and as single diastereoisomers in most instances. On another hand, when the indole is substituted with an electron-donating group, the more nucleophilic C3-position of the indole adds on the gold-activated alkyne via a 6-*exo*-dig cyclization towards vinylgold intermediate **int115**. Nucleophilic attack on the iminium affords gold cyclopropyl carbene **int116**. Rearomatization through 1,2-migration of the phenoxy group and ring opening affords the spirocyclic tetrahydrocarboline **198**.

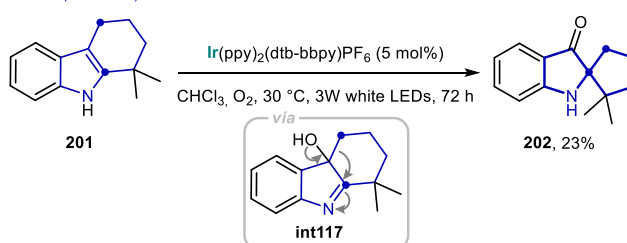


Eq. 2



Scheme 49. Gold-catalyzed C2-spirocyclizations.

Xiao and Lu designed a photocatalytic C3-oxidation of 2,3-disubstituted indole derivatives generating 3-hydroxyl indolenines intermediates such as **int117** prone to semipinacol rearrangement (Scheme 50).¹⁰⁷ When applied to a tetrahydrocarboline substrate **201**, the rearrangement furnishes a C2-spirocyclic product **202**, however obtained in much lower yield (23%) compared with substrates bearing an aromatic substituent on C2.

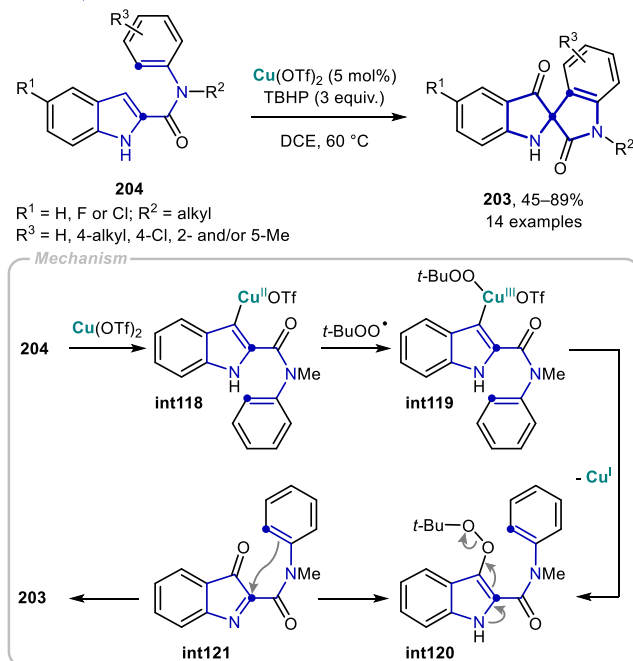


Scheme 50. Ring-contraction via semipinacol rearrangement on photoredox-oxidized intermediates

The group of Li designed a dearomative oxidation/spirocyclization sequence in the presence of *tert*-butyl hydroperoxide (TBHP) and copper(II) triflate allowing to access a variety of C2-spiropseudoindoxyls derivatives **203** from indole-2-carboxamides **204** (Scheme 51).¹⁰⁸ The procedure provides the products with overall satisfactory yields, although its efficiency is slightly decreased when electron-withdrawing substituents are present on the indole

ring (R^1) or on the N-aryl ring (R^3). A plausible mechanism proposed by the authors involves the formation of an indolyl copper(II) intermediate **int118**, which subsequently reacts with the *tert*-butoxy radical ($t\text{-BuOO}^\bullet$, formed from TBHP and the copper(II) catalyst) to form the Cu^{III} species **int119**. Reductive elimination towards **int120** and elimination of *tert*-butanol would deliver intermediate **int121** and spirocyclic product **203** through the Friedel-Crafts addition of the N-aryl ring on the electrophilic indolenine.

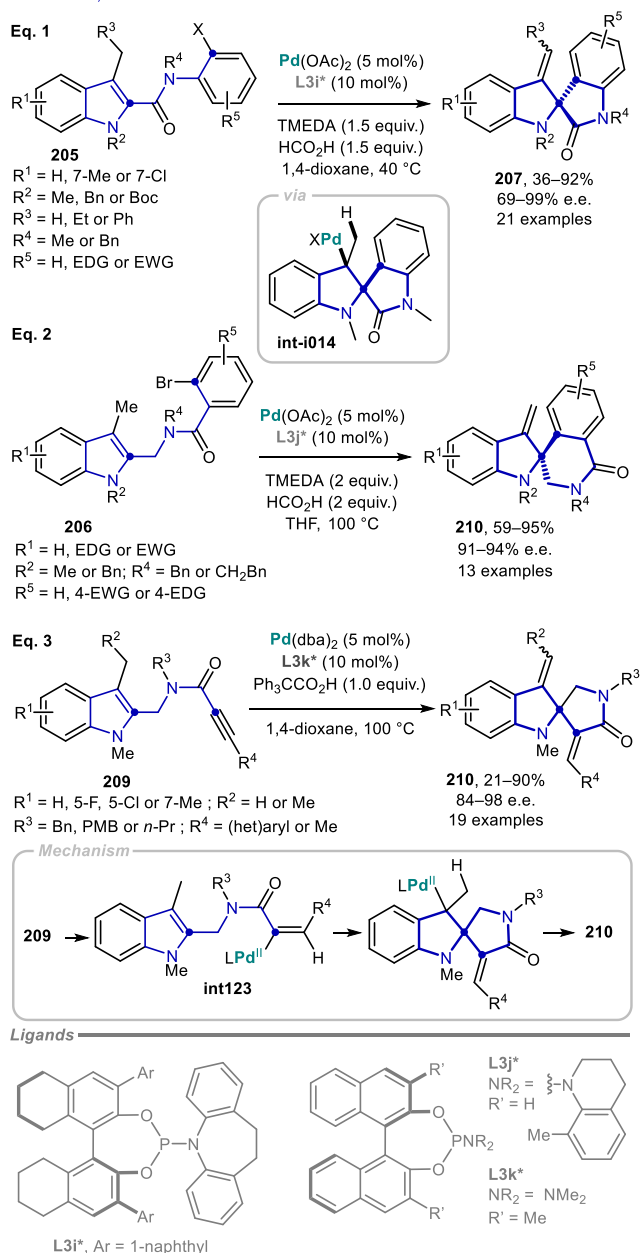
■ Li *et al.*, 2016



Scheme 51. Oxidation/spirocyclization sequence.

Jia and co-workers developed an enantioselective dearomative Heck coupling on indole derivatives **205** and **206** between the C=C double bond and a tethered aryl halide (Scheme 52, Eq. 1 and Eq. 2).¹⁰⁹ The method is generally high yielding over the large panel of substrates exemplified and delivers the C2-spirocyclic products **207** and **208** with outstanding enantioselectivities. After oxidative addition of the palladium catalyst, the regioselective dearomative migratory insertion of the C–Pd(II) bond affords the C3-Pd intermediate **int122**, which undergoes β -hydride elimination from the adjacent methylene. This elegant approach has later been used by the same group on amine-tethered substrates, allowing to access complex polycyclic scaffolds upon aza-semipinacol rearrangement.¹¹⁰ In 2021, they reported the ene-type cycloisomerization on indoles **209** tethered with an ynamide on the C2-position (Scheme 52, Eq. 3).¹¹¹ A first hydropalladation of the triple bond by a palladium hydride species formed from $\text{Pd}(\text{dba})_2$ and triphenylacetic acid leads to intermediate **int123**, which undergoes a Heck-type cyclization to form the C2-spiroindolines **210** after β -hydride elimination. In the presence of the chiral phosphoramidite **L3k***, the products are obtained with overall good yields and high enantioselectivities. Nevertheless, without an aryl group on the ynamide, the products are obtained with low yields (21% with $R^4 = \text{Me}$), albeit an excellent 92% enantiomeric excess.

■ Jia *et al.*, 2018 and 2021



Scheme 52. Dearomative Heck couplings.

Conclusion

The intramolecular catalytic dearomatization of indoles by transition metal is the source of an inextinguishable structural diversity. As such, this method is established as a key player for the synthesis of libraries to explore the three-dimensional space in medicinal chemistry. As shown in this Review, the mechanisms associated to these reactions are complex. The first step mostly leads to a spiroindolenine (or indoleninium) intermediate. The fate of this intermediate mostly depends on the reaction conditions and skeleton of the intermediate and the nature of the transition metal used. In a significant number of cases (particularly in Au(I) catalysis), a 1,2-migration occurs, delivering a rearomatized compound without neo-formed stereogenic center. These methods, at first

sight of lesser interest, should however not be neglected and are also stemming in a large structural diversity that could not be possible without this inherent dearomatizing reactivity of indoles.

In other situations, the intermediate spiroindolenine can undergo nucleophilic inter- or intramolecular additions or reductions if a reducing agent (such as a Hantzsch ester) is present in the reaction mixture. This will deliver chiral spiroindolines that are of major interest in total synthesis and medicinal chemistry. Trapping the spiroindolenine intermediate is also a clever way to avoid a C3-to-C2 migration.

In all other cases, a spiroindolenine is obtained. The challenge of these reactions clearly relates on the nature of the transition metal used and the substituting pattern of the indole ring. C2-substituted indoles will easily deliver stable spiroindolenines regardless the metal. However, C2-unsubstituted indoles may be very challenging substrates, especially in silver and gold catalysis, while palladium, copper or iridium catalysis will easily deliver the chiral spiro products. This mainly relates on the nature of the organometallic intermediate involved and its tendency to undergo the C3-to-C2 migration. This process is for instance extremely challenging in Au(I) catalysis, where the vinylgold intermediate species are largely prone to migration. It should be noted however that the obtention of a rearranged aromatic product does not necessarily implies a spirocyclization/migration process but could also be the result of a direct C2-addition of the indole ring. This debate is not an easy one to decide and DFT calculations are often helpful to support experimental data and mechanistic hypotheses.

Finally, one of the great features of these methods is that they lead mostly to chiral spiro compounds. The use of chiral ligands with the transition metal catalysts is an efficient method for the control of the absolute stereochemistry of the neoformented stereogenic center. However, a close look reveals severe discrepancies between the different methods. While palladium or iridium are very well-established for enantioselective catalysis, silver and gold catalysis are far from being reliable routine methods for enantioselective processes, in particular when alkynes are used as electrophilic partners. The development of chiral ligands, a better understanding of the mechanisms associated and control of the migrating processes are necessary to achieve these challenges.

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