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, spirocyclic\textsuperscript{1} compounds are highly valuable scaffolds in medicinal chemistry and for the diversity-driven exploration of new hits for biological activities.\textsuperscript{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.\textsuperscript{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,\textsuperscript{4} 2 and 3,\textsuperscript{5} 4\textsuperscript{6} and 5\textsuperscript{7}), antimalarial\textsuperscript{8}, and opioid agonistic (6\textsuperscript{8}) activities, along with the well-known strychnine as a neurotoxic.\textsuperscript{4b, 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 reactions\textsuperscript{11} that have largely been applied to indole nucleus, by intramolecular nucleophilic addition of the indole onto an electrophilic moiety tethered to the reacting position.\textsuperscript{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,\textsuperscript{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 spiroindolines 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.


However, these reactions have more to offer than just the isolation of spiroindoles. 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-migration 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.

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, 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. 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). 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 carbend 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). 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-OH), affording a much lower 35% yield.

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(SbF$_5$)$_2$ (Scheme 4). The coordination of the Lewis acidic Cu(II) complex on the ester moieties triggers the addition of the indole, with a stereoselectivity for the tricyclic indoline (trans-12 vs. cis-12) that can be tuned by the R$^2$ 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,\textsuperscript{19} affording spirocyclic products when tethered on the C3-position of indoles derivatives. The group of Unsworth developed the spirocyclization of ynone-tethered indoles \textit{14} in the presence of copper(II) triflate, forming the corresponding spiroindolenines \textit{15} with yields ranging from 86 to 95% (Scheme 5.A).\textsuperscript{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 \textit{16} to access trifluoromethylated products \textit{17} (Scheme 5.B).\textsuperscript{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 (\textit{int4} \rightarrow \textit{int5}) and subsequent reaction with the \textsuperscript{13}CF\textsubscript{3} radical which furnishes product \textit{17} after reductive elimination (R.E.) from intermediate \textit{int6}. [2] the addition of \textsuperscript{13}CF\textsubscript{3} on the ynone α-position, spirocyclization and subsequent oxidation of the intermediate by Cu(II) into the indoleninium (\textit{int7} \rightarrow \textit{int8} \rightarrow \textit{int9}).

Scheme 5. Spirocyclization of yrones-tethered indoles

Ye, Lu and co-workers showed the cyclization of ynamides \textit{18} towards carbolines \textit{19} occurred with a reversed regioselectivity compared with the usual ynamide reactivity (Scheme 6).\textsuperscript{22} Indeed, previously reported Brønsted acid and π-acidic transition metals-catalyzed cyclizations on ynamides are exclusively observed on the α-position, while carbolines \textit{19} are formed from the addition of the indole on the β-carbon of the ynamide.\textsuperscript{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 \textit{int10}. The Cu(II) 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 \textit{int11}, followed by a stepwise 1,2-migration through a cyclopropane species \textit{int12} and eventually to the ring-extended intermediate \textit{int13}. Rearomatization and demetalation finally afford the carboline \textit{19}. The reaction tolerates both aryl and alkyl groups on the ynamide triple bond (R\textsubscript{3}), as well as chiral indolyl ynamides (R\textsubscript{3} ≠ H) in the presence of NaBAR\textsuperscript{+} (BAR\textsuperscript{+}= tetraakis(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.

Your group pioneered the access to spirocyclic indolic products through the dearomatative arylation of C3-tethered arylbromides 20 (Scheme 7.A). Early development of an enantioselective version were however tedious. 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 (R1) 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). 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.

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). 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 (R²) 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., 2016

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

Wang and co-workers reported the spirocyclization of isocyanate-ethyl indoles 31 in the presence of aryl or alkenyl iodoses (R'ᴵ), affording spiro dihydropyrroloindolenines 32 (Scheme 9). 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)).
3.2 π-allyl-Pd intermediates

Much earlier than the above-discussed coupling with aryl halides, the group of Sakal 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. 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, which are converted into the ring-opened zwitterionic π-allyl-palladium intermediates int24 upon oxidative addition on the catalyst (Scheme 10). The subsequent deprotonation of the indole substrate triggers the elimination of the benzenesulfinate moiety which subsequently adds on a sacrificial intermediate int24 to form by-product and the conjugated imine int25. The conjugate addition of a second equivalent of manolate nucleophile int24 furnishes the indole intermediate tethered with the π-allyl-palladium moiety, and the final nucleophilic attack from the C3-position affords product. 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 amidine 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 allylicarbanate moiety. 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 and aryl iodides (Scheme 11).11 In the presence of Pd2(dba)3, the sterically bulky t-BuXantPhos ligand and silver carbonate, compounds are readily converted into tetrahydro-β-carbolines 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 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 are obtained from compound 38a as mixtures of diastereoisomers (Scheme 11, Eq. 2).
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 complexes established that oxidative addition of propargyl carbonates/halides on the palladium catalyst affords intermediates int30, which undergo nucleophilic attack from the indole C3-position onto its central carbon atom towards the palladacyclobutene 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 int32-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 to functionalize indoles derivatives with an activated electrophilic pendant which then undergoes C3-spirocyclization (Scheme Pd12.C and D). 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 (R2 ≠ H) by the one-pot reduction and N-acetylation 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).
Taking advantage of the ability of palladium(II) complexes to activate triple bonds in cycloisomerization reactions, Toste's group developed an enantioselective cyclization of alkyne-tethered cyclic enamines leading to spirocyclic spirolindolenolene scaffold with moderate enantioselectivity (71% ee) using DTBM-SEGPHOS ligand. In an elegant approach towards highly substituted spirolindolenes, Taylor and Unsworth merged the π-acidic (Pd(III)) and the cross-coupling (Pd(0)) catalytic activities of palladium. The use of the aryl iodide oxidative addition product as π-acid for the electrophilic activation of the triple bond of ynone allows to trigger the C3-spirocyclization on (Scheme 14). The resulting vinyl palladium intermediate subsequently undergoes reductive elimination towards spirolindolene faster than the protodemetalation. The products are obtained with very good yields in most cases, either from C2-H or C2-substituted indoles.

\[ R^1 = H \text{ or } 5-\text{OME}; R^2 = H \text{ or } 8n \]
\[ R^3 = \text{Me, or cyclopropyl}; \]
\[ R^4 = \text{aryl, alkyl} \]
\[ R = \text{heteroaryl, alkylnyl, benzyl,} \]

\[ \text{Scheme 14. Pd(II)-catalyzed activation of alkynes. cat} \rightarrow \text{trans-PdBr(N-succinimide)(PPh}_3)_2. \]

\[ \text{4 Rhodium catalysis} \]

\[ \text{4.1 Rhodium-carbenoids intermediates (Rh(II) catalysis)} \]

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 sulfoniy-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, the group of Unsworth showed that the rhodium-catalyzed reaction allows for the isolation of the spiroindolene products, without 1,2-migration towards tetrahydrocarbazoles (see Scheme 3 and Scheme 15). The products were obtained in good yields in strictly inert conditions, but in the presence of air, indolines can be oxidized by dioxygen into intermediate, delivering a ring-opened product. Although this intermediate appeared relatively short-lived and unstable under 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- and anti-spiroindolines specifically. 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.

\[ \text{Scheme 15. Spiroindolene formation from indolyl Rh-carbenoid.} \]

At the same period, three groups independently reported the formation of spiroindolines from 1-sulfoniy-1,2,3-triazole-tethered indoles in the presence of the chiral bishorodium complex Rh\textsubscript{2}(S)-PPT\textsubscript{4}, which was shown to be the most efficient in catalyzing the reaction (75% yield vs. 25-35% with Rh\textsubscript{2}(Pvp) or Rh\textsubscript{2}(O\textsubscript{2}C-n-hept)\textsubscript{4}, Scheme 16.A). However, no mention of any stereoinduction was made in the report, presumably because racemates are obtained in these conditions. The team of Kang later reported a similar approach using Rh\textsubscript{2}(O\textsubscript{2}C-n-hept)\textsubscript{4} as catalyst (10 examples, 36-92% yields). In the presence of the bispinaryl-based chiral dirhodium complex Rh\textsubscript{2}(S)-BNP\textsubscript{4}, the formation of product was reported with a 55% yield and a 47% ee. (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 latter with a lower 31% yield) in addition to sulfonamide-protected tryptamine derivatives. 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 pyroloindolines, involves two potential reaction pathways. The thermal decomposition of the
Sche: α-imino rhodium carbenoid-mediated formal (3+2)-cycloadditions

The 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 carbene may form the zwitterionic intermediate int41 which would undergo cyclization onto the indolenium. Both Shi’s and Davies’ group observed the formation of carboline 60 (or 61 after reduction) in the cases of N1-unsubstituted indoles (R² = 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). 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 [Rh(cod)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 rearomization. However, the spiroindole intermediate can be isolated with a 44% yield (9:1 dr, 99:1 er, R¹ = H, R² = R³ = CO₂Me) 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 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 carbene may form the zwitterionic intermediate int41 which would undergo cyclization onto the indolenium. Both Shi’s and Davies’ group observed the formation of carboline 60 (or 61 after reduction) in the cases of N1-unsubstituted indoles (R² = 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).
Allylic substitutions using the phosphoramidite ligand \( \text{L}^3 \) led to the dearomatized 6-membered ring spiroindolenine \( \text{L}^4 \) in excellent e.e.s., tolerating C2-unsubstituted or substituted \( (R^2 = \text{Me, Ph}) \) substrates (Scheme 18.A).\(^{37a}\) 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 \( \text{L}^5 \) in similar conditions, although a reduction into indoline \( \text{L}^3 \) is required to isolate the products by chromatography.\(^{37b}\) The authors also demonstrated that the isomerization by 1,2-migration of \( \text{L}^6 \) into tetrahydro-1H-carbazoles \( \text{L}^7 \) could be triggered by a Bransted acid catalysis (30 mol% of para-toluenesulfonic 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 desirable 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 \( \text{L}^6 \) (X = \( \text{NR}^2 \)) undergo the iridium-catalyzed cyclizing allylic substitution towards indolene \( \text{L}^8 \) (highly reactive, but observed in situ by IR spectroscopy), this intermediate evolves towards tetrahydro-β-carboline \( \text{L}^7 \), which results from the migration of the methane amine moiety, originally linked to the indole C3 on \( \text{L}^6 \) (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.\(^{12f, 47e, 48}\) 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 \( \text{L}^6 \) to be formed and isolated from C2-unsubstituted substrates in similar conditions.\(^{47f}\) 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, spirodolines \( \text{L}^7 \) can be isolated with good yields and excellent enantioselectivity, after reduction of the corresponding spiroindolenine.\(^{47g}\)

Taking advantage of the strong electron donating nature of the indole ring, You’s team extended their strategy to symmetrical bis-Indole compounds \( \text{L}^8 \), which, after formation of the spiroindolenines \( \text{L}^7 \) as a single diastereoisomer, allows for a 6 to 7 ring extension towards products \( \text{L}^9 \) in acidic conditions (Scheme 18.C).\(^{47h}\) 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 \( \text{int}\) with the stereochemistry of the cyclization step controlled by the stereogenic center on the allylic position.

**Scheme 17.** Rhodium-catalyzed spirocyclization of allenyl indoles.

\text{Cod} = 1,5-cyclooctadiene.

Other approaches to spiroindoles have been reported by Gong\(^{45}\) and Shi,\(^{46}\) leading to spiroindolenines and tetrahydro-β-carbolines, 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 \( \text{L}^6 \), the reactions evolve through the formation of an Ir(III)-Ir-allyl complex that undergoes nucleophilic addition of the indole ring, affording vinyl spiroindoles \( \text{L}^8 \). The fate of this compound strongly depends on the nature of the linker X and the workup. While some compounds \( \text{L}^6 \) can be inherently stable and hence isolated, a reductive workup allows a conversion into the corresponding spiroindolines \( \text{L}^9 \). Unstable products \( \text{L}^6 \) can undergo 1,2-migration either on the allyl side or allyl side to deliver carbolines \( \text{L}^{10} \) and \( \text{L}^{11} \), respectively.
5.2 Other types of iridium-catalyzed reactions

Based on their previous reports on iridium-catalyzed cyclization via reductive lactam activation, 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(PPh$_3$)$_2$) and tetramethyldisiloxane (TMDS) (Scheme 19). 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 int$_{46}$ via C-O insertion into the Ir-Si bond of hydrido(silyl) Ir$^{III}$ species int$_{47}$, formed by the oxidative addition of the silane to the Ir$^{I}$ complex, and subsequent reductive elimination. Elimination of the oxisilane furnishes the Pictet-Spengler iminium int$_{48}$, 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). 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.

Scheme 18. Ir-catalyzed allylic substitution.
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). 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). 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 acetonitrile) 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.
Scheme 22. Silver-catalyzed deraromative cyclization of ynones 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 n-activated alkyne (int49) and the subsequent protodemetalation of int50 towards the indolene 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. These products are likely formed from a silver indoleninium intermediate such as int51, which undergoes 1,2-shift towards int52 and subsequent aromatizing elimination.

Switching the silver salt anion from TfO− to NO3− 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.

Liu, Song and co-workers, expecting to form CF3 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). 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 → int55 → 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 (R1) or the nature of the triple bond aryl group (Ar) on the reaction yields.

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 ynamide-ynesulfonamides 92).
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-FluorobenzeneSulfonImide) as ligand could moderate the activity of the silver complex and allow the formation of 1,2,3,6-tetrahydroazepino[4,5-b]indole \( \mathbf{93} \) with satisfactory yields (Scheme 24A, Eq. 1).\(^{56b}\) The reaction occurs via the dearomative cyclization on \( \mathrm{int57} \), with attack of the indole on the \( \beta \)-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 \( \alpha \)-position). The spirocyclic intermediate \( \mathrm{int58} \) then undergoes 1,2-migration and subsequent rearomatization towards the product (\( \mathbf{93} \)). 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\(^3\)), but its efficiency declines importantly with alkyl groups (26-28%). Tryptamine ynesulfonamides \( \mathbf{92} \) can also be successfully converted into spiroindolines by intercepting the indoleninium intermediate with suitable nucleophiles before the 1,2-migration (Scheme 24A).\(^{56c}\) In the presence of Hantzsch’s ester as a hydride donor, indolines \( \mathbf{94} \) are smoothly obtained with excellent yields (Eq. 2).

Indoles are potential partners as well, furnishing compounds \( \mathbf{95} \) 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 \( \pi \)-stacking stabilization of the intermediate \( \mathrm{int58b} \).

The same group reported the synthesis of indoline carbamates \( \mathbf{96} \) from ynesulfonamide tryptamines \( \mathbf{92} \) in the presence of silver triflate, triphenyl phosphate 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 \( \mathbf{93} \) 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). Chiral oxazolidin-2-one 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 indolycyclopropenes 101 (Scheme 25). 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 final product after protodemetalation. The reaction delivers 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.

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).

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). 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 H₂ from the tertiary carbon. In the case of gold catalysis, the analogous gold carbenoid species undergoes a deprotonation of the secondary carbon (Hb) by the ditriflimide counterion (cf gold catalysis section, Scheme 41 for the asymmetric version with a chiral gold complex) towards regioisomer 105.
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.\textsuperscript{60} As a consequence, all the approaches described below are based on the \(\pi\)-activation of unsaturated moieties tethered on the indole C3-position of general compounds \textbf{106}, leading to spiroindoleninium intermediates \textbf{107} which eventually lead to the target spiroindolene \textbf{108} (Scheme 28). Alternatively, the spiroindolenium \textbf{107} may be trapped by a nucleophile to deliver stable spiroindolines \textbf{109} (that can also result from the nucleophilic addition on indolenines \textbf{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 spiroindoleninium intermediate to undergo 1,2-migration towards a rearomatized indole product \textbf{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 spiroindoleninium intermediate \textbf{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.

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,\textsuperscript{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 propargyl-tethered indoles derivatives for the construction of polycyclic scaffolds, and furnished along the way valuable insights on the reactivity of these systems.\textsuperscript{62} In the presence of gold catalyst \textbf{Cat4}, propargylic tryptophane and tryptophol derivatives \textbf{111} are readily transformed into indolic compounds \textbf{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 alkynyl 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 alkynyl group as a gold-activatable function to trigger the dearomatative 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 AuPPh3OTf,64 the alkynyl-activated intermediate int67 undergoes dearomatative 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 indolazepino-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 benzimidazole-tethered indole substrate int69 which contains the internal alkynyl 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 alkynyl aryl moiety (Ar), although electron-withdrawing groups on the aromatic diamine 122 (R3) induce a slight decrease of the yields (below 70%).

8-Membered ring-containing compounds can be smoothly accessed from the tryptamine-derived alkynyl 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).652 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.670 Their approach generally provides products 122 in high yields but is limited on the substitution of the triple bond (R3;), 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-methylene-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 ynones-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 vinylnmetal 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 alkynyl is preferred over a 6-exo process on the distal alkynyl (backed up by DFT calculations), furnishing spiroindoleninium int73. Subsequent 1,2-shift, indole rearomatization and protodeauration lead to an alkynyl-tethered dihydro-carbazole int74 which undergoes a second dearomative addition from the indole C3 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 (R3;), however with a slight decrease in efficiency with substrates substituted by electron-withdrawing groups on the indole ring (R1;).
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 133 in the presence of 5 mol% of cationic gold catalyst. The reaction occurs through the formation of the spirocyclic indoleninium ion76 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 (R3) and the indole (R1 and R2) moieties, as well as substituted alkyynes (R4 ≠ 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 (R5 ≠ 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.

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 1H-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 (R1) 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 (R2, 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 (R4) 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 alkyynes 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.

Scheme 32. Gold activation of N2-propargyl tetrahydro-β-carbolines.
extension pathway leading to 137 involves the fragmentation of the former towards int82, furnishing the product after protodeauration and iminium hydrolysis. For unsubstituted alkynes (R² = 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 protodeauration 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 spiroindoleninium

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 spiroindoleninium 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, spiroindoleninium int86 undergoes 1,2-migration of the C-OH group towards int87 (Scheme 33.B).77 Water elimination (forming cyclovinylc 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 indoleninium 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 spiroindoleninium 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 carboxation intermediate, stabilized by the indole moiety, and a subsequent C2-nucleophilic attack would afford the dihydrocarbazole intermediate.

Scheme 33. Migration of acyl and alkyl groups.

A. Hashmi et al., 2012

B. Shi et al., 2013

Scheme 34. Migration process.
Sanz et al., 2017

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\begin{align*}
\text{Scheme 34. Gold(III)-catalyzed spirocyclization and subsequent migration of the alkyl group.}
\end{align*}
\]

7.2 Spirocyclization followed by indoleninium trapping

7.2.1 Spiroindoleninium trapped by a hydride

The trapping of spiroindoleninium intermediates is a suitable strategy to ensure the isolation of a spirocyclic product over a rearranged product. Zhang and You showed that metastable indoleninium 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). 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.52b

You et al., 2020

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\begin{align*}
\text{Scheme 35. In situ reduction of the spiroindoleninium intermediate}
\end{align*}
\]

7.2.2 Spiroindoleninium trapped by internal nucleophile.

Beyond the reduction of the intermediate spiroindoleninium, 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 spiroindoleninium intermediates int92 and int93, Scheme 36.A) formed by the initial gold-triggered spirocyclization.81

\[
\begin{align*}
\text{Scheme 36. Synthesis of tetracyclic spiroindolines via the trapping by a hydroxyl pendant.}
\end{align*}
\]

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
electron-donating groups on the 5-position exhibit lower reactivity in the cyclization/trapping sequence and require a higher catalytic loading (10 mol%) to afford similar conversions. When tryptamine derivatives 149 are submitted to similar reaction conditions, 7-endo-dig spirocyclization occurs, furnishing tetrahydrofuranyl-fused products 151 as single diastereoisomers. The application of this strategy to chiral gold complexes containing C2-symmetrical bis-phosphate ligands (L6b* and L6a*) as catalysts allowed to form the enantioenriched products 150 and 151 with enantiomeric excesses up to 87% (reactions shown in Scheme 36.A). Propargyl alcohols ynamides 152 have similarly been used by Yang et al. to access 2,3-fused dihydropyranes 153 (Scheme 36.B). Upon coordination of the cationic gold complex on the ynamide, the resulting keteniminium int94 undergoes 5-endo-dig spirocyclization towards int95, and the subsequent addition of the hydroxyl pendant furnishes the tetracyclic product 153 with high yields (above 75% for most examples). In the presence of a chiral gold complex (with a bisphosphine BIPHEP ligand), the tetracyclic product was obtained with a moderate 60% ee.

Volturiez and co-workers achieved the asymmetric synthesis of the complex polycyclic scaffolds 154 from indoles tethered with a triple bond bearing an electron ring aryl (155, Scheme 37). After the gold-triggered 6-endo-dig spirocyclization towards int96, the Friedel-Craft addition of the furan ring onto the electrophilic indolium affords the pentacyclic indoline after aromatisation and protodeauration. The reaction is generally high-yielding, providing the products with most yields above 70% in the presence of catalyst Cat4 and enantioenriched products with enantiomeric excesses up to 93% can be formed when BIPHEP or SegPhos-based (L6c* or L6a*) complexes are used.

![Scheme 37](image_url)

**Scheme 37.** Trapping of the intermediate by a furyl group

In line with their previously discussed reports on the use of multicomponent Ugi reactions products in deraomatve cyclizations, Van der Eycken’s group developed a diastereoselective domino spirocyclization/indolinium trapping transformation en route to tetracyclic spirocyclic products 156 (Scheme 38, Eq. 1). In contrast with their previous reports (Scheme 30.C), the free amidic N-H moiety is in this case suitably positioned to add on the electrophilic indolinium C2-position on int97 towards the formation of indolines 156. The diastereoselectivity is directed by the chiral center already present on the Ugi product, as the nucleophile needs to be properly oriented to undergo the second cyclization. The authors then extended their strategy to substrates 157 bearing an unsubstituted triple bond, obtained by switching the alkyne source from the carbocyclic acid (2-butyric acid) to the amine component (propargylamine) (Scheme 38, Eq. 2). Products 158 are obtained with similar yields in the presence of a stoichiometric amount of trifluoroacetic acid, which is likely to facilitate the reaction by assisting the protodeauration step and behaving as a co-ligand for the gold catalyst.

![Scheme 38](image_url)

**Scheme 38.** Diastereoselective synthesis of tetracyclic indolines from Ugi products via the trapping by an amide pendant

The team of Huang, Mao and Chen described the formation of spirocyclic indolines 159 from e-ne-ynamides substrates 160, in the presence of the IPrAuNTf2 cationic gold complex bearing a NHC ligand (Scheme 39.A). The transformation involves the formation of an α,ω-oxo-carbene species int98, generated from the ynamide moiety and pyridine N-oxide which is subsequent trapped by the indole ring, as reported by Ye and co-workers. The spirocyclization can either occur through the nucleophilic attack of the C3-position onto the carbene carbon center, followed by the trapping of the indolinium intermediate (pathway a, int99) or via cyclopropanation and subsequent ring expansion (pathway b, int100). Ohno and co-workers reported the construction of pyrrolo[2,3-d]carbazole 161 en route to the synthesis of a terpene indole alkaloid precursor, using a similar strategy from silyl enol...
ether-substituted ynamide 162. (Scheme 39.B). Upon activation of the triple bond by the NHC-based cationic gold catalyst, the substrate undergoes S-exo-dig spirocyclization, and the obtained indolenium intermediate int103 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* counterion, each enantiomer of 161 can be formed with enantiomeric excesses up to 74%.

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 spiroindoleninium intermediate and the formation of a fourth cycle. Zhang has shown that propargylic esters 163 could be used to access spiroyclic 2,3-indoline-fused cyclobutanes 164 (Scheme 40A). 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 40C). Their newly designed chiral phosphathi-helicene scaffolds L9a* and L9b* used as gold complexes, allow for the highly enantioselective spirocyclization of substrates 167, and the subsequent trapping of the indoleninium intermediate furnishes the cyclobutane derivatives 168 with enantiomeric excesses up to 93%.
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). 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 enantio-meric excesses (>94%). The same chiral gold complex catalyzes the asymmetric desymmetrization of similarly substituted bis-indoles derivatives 171 towards spiroindolenenes 172 (Scheme 41, Eq. 2). 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 carbeneoid intermediate like int106 (cf. Scheme 27). The polycyclic products are obtained with excellent stereoselectivities (>86% e.e.), except for carbonated linkers with $X = \text{C(CO}_2\text{Et)}_2$.}

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

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Sanz and co-workers explored the reactivity of 3-allenylmethylindoles 173 in the presence of gold complexes (Scheme 42). 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 ($\text{PhO}_3\text{PAuOTf}$ 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 spiroindoline 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 spiroindoline (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 pseudorutacarpine derivatives (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 (R3) or when the bromine is replaced by a chlorine atom. Other substrates bearing a sulfide function at C2 position furnished stable 2-sulfenylspiroindolenines.97

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 Ph3PAuNTf2 (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 (R3) or when the bromine is replaced by a chlorine atom. Other substrates bearing a sulfide function at C2 position furnished stable 2-sulfenylspiroindolenines.97

- **A. You et al., 2020**
  - ![Scheme 43.A](image_url)
  - R1 = H, 5-EDG, 5-EWG or 7-Cl
  - R2 = Me or Ph; R3 = SO2Ar or Ms
  - DCE, 60 °C
  - (a)-177, 84–99% 13 examples

- **B. Su, Pan, Mo et al., 2022**
  - ![Scheme 43.B](image_url)
  - R1 = H, EDG or EWG
  - R2 = Me, Cy or (het)Ar
  - R3 = H, EDG or EWG
  - DCE, 59–100 °C 3–38 h
  - (a)-179, 41–78% 36 examples
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 AuIPrBF₄ and methanol as silyl scavenger and protic source (Scheme 45.A).³⁹ Starting from tetrahydro-β-carboline 184 as substrates (prepared by acid-catalyzed Pictet-Spengler reaction), Guinchard et al. developed the synthesis of indoloquinuclidines 185 in the presence of JohnPhosAuSbF₆·MeCN catalyst Cat₄ (Scheme 45.B).³⁹ The products are obtained with satisfactory yields, ranging from 36 to 67% as mixtures of diastereoisomers (up to 92:8 dr for R₁ = i-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 enantiomeric-rich 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 (R²≠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

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 spiroindoline 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 indoline 187, formed with yields ranging from 45 to 86%, the lowest with electron-withdrawing groups on the indole (R₁), 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 indoline over the 1,2-migration event that leads to the rearomatized product 188. Besides, their calculations show that the sp³ hybridization of the tryptamine nitrogen (compared with the more sp²-character of a sulfonamide) allows to ideally position the gold-activated alkyne over the C3-position of the indole, while a sulfonamide protecting groups tends to push the triple bond near the C2-position, possibly triggering a direct C2-addition of the indole ring.
While this approach allows for the successful synthesis of C2-unsubstituted spiroindolenines, it remains limited to N-alkyl products. Propargyl tryptamine derivatives protected as sulfonamides remain a challenge, as the gold-catalyzed spirocyclization is followed by the 1,2-migration from the C3 to the electrophilic C2-position, as reported by Echavarren. This challenge was indirectly addressed by You and Zhang by the in situ reduction of the spiroindolenine vinylgold(I) intermediates to ensure the isolation of the spiroindoleninium intermediate.

### 7.4 Other evolutions of the spiroindoleninium intermediate

Shi et al. described the cycloisomerization of 1,1-bis(indolyl)-5-alkynes 190 into cycloadducts 191, involving the spirocyclic intermediate int111, formed through the nucleophilic attack of the indole on the gold-activated triple bond (Scheme 47). The fragmentation of the intermediate towards a pseudo-1,5-indolyl migration product int112 occurs preferentially over the classical 1,2-migration which furnishes an indole-fused minor product 192 (not shown). The subsequent intramolecular nucleophilic attack of the alkynyl-gold complex int112 on the β-position of the conjugated iminium affords the 6-membered ring bis-indolyl product 191. The reaction tolerates various substitution partners on the indole ring, although N2-substituted substrates (with Bn or allyl groups) give better yields and regioselectivity, and internal alkynes undergo cycloisomerization smoothly as well. In the presence of DM-SegPhos L6d*-based gold complexes with benzoate counter-ions, the products are obtained with good enantiomeric excesses, above 80% in most cases.

### 8. C2-spirocyclizations

Spirocyclizations proceeding at the C2 atom of the indole ring are by far less frequent. Like their C3 counterparts, they can lead to a C2 spiroindoline or a rearranged product. When C2 alkynyl-tethered substrates 193 are put in the presence of platinum dichloride, Beller et al. observed that three different products may be formed upon activation of the triple bond by the catalyst (Scheme 48). The major product of the reaction is, in most cases, the 7-endo-dig cyclization product 194 resulting from the nucleophilic attack of the indole C3-position onto the triple bond. Depending on the electronic properties of the aryl group on the alkyne (R2), the 6-exo-dig product 195 can be formed as well, and as the only product of the reaction for terminal alkynes (R2 = H). Additionally, in some instances (R2 = Bn or R3 = 2-OMe-S-CO2Me-C6H5 or high temperature reaction), the formation in small quantity of compound 196 is observed, with yields up to 23%, which results from a spirocyclization on the C2-position to form intermediate int113 and subsequent 1,2-migration of the acyl moiety.
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). 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.

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). When applied to a tetrahydrocarboline substrate 201, the rearrangement furnishes a C2-spiroycyclic product 202, however obtained in much lower yield (23%) compared with substrates bearing an aromatic substituent on C2.

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). 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 ($t$-BuOO•, 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.

**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).

**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 spiroindolene (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 dearmatizing reactivity of indoles. In other situations, the intermediate spiroidolindene can undergo nucelophilic 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 spiroidolindenes that are of major interest in total synthesis and medicinal chemistry. Trapping the spiranic intermediate is also a clever way to avoid a C3-to-C2 migration.

In all other cases, a spiroidolindene 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 spiroidolindenes regardless the metal. However, C2-unsubstituted indoles may be very challenging substrates, especially in silver and gold catalysis, while palladium, copper or iodium 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(III) catalysis, where the vinyldiol intermediate species are largely prone to migration. It should be noted however that the obtaining of a rearranged aromatic product does not necessarily imply a spirocyclication/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 neoformed stereogenic center. However, a close look reveals severe discrepancies between the different methods. While palladium or iodium are very well-established for enantioselective catalysis, silver and gold catalysis are far from being reliable routine methods for enantioselective processes, in particular when alkenes 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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References


