

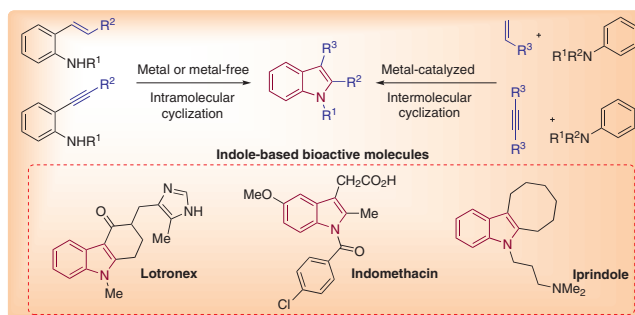
Recent Advances in the Regioselective Synthesis of Indoles via C–H Activation/Functionalization

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Abstract Indole is an important heterocyclic motif that occurs ubiquitously in bioactive natural products and pharmaceuticals. Immense efforts have been devoted to the synthesis of indoles starting from the Fischer indole synthesis to the recently developed C–H activation/functionalization-based methods. Herein, we have reviewed the progress made on the regioselective synthesis of functionalized indoles, including 2-substituted, 3-substituted and 2,3-disubstituted indoles, since the year 2010.

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Key words indoles, C–H activation, catalytic, metal-free, natural products

1 Introduction

The indole moiety is one of the key heterocyclic motifs that occur ubiquitously in bioactive natural products, pharmaceuticals, agrochemicals, fragrances, pigments and in optoelectronic functional materials.¹ Examples of indole-containing biologically active compounds include arbidol (**1**), indomethacin (**2**), PD-0298029 (**3**), reserpine (**4**), iprindole (**5**) and dimebon (**6**) (Figure 1).² The synthesis of indole

and its derivatives has been the topic of research for over 130 years, and a variety of classical methods have been discovered during this time including: Fischer, Bischler, Gassmann and Batcho–Leimgruber syntheses of indoles.³ However, these methods have several limitations, for example, in the case of the Fischer indole synthesis, toxic hydrazine hydrate is required along with highly acidic conditions and overall, the functional group tolerance is moderate. Over the last two decades, various methodologies have been developed to overcome the existing limitations of the synthesis of indole derivatives. Several metal-catalyzed and metal-free approaches have been reported for the synthesis of indole derivatives. Different research groups have compiled the literature on the synthesis of indoles with focus on diverse aspects.⁴

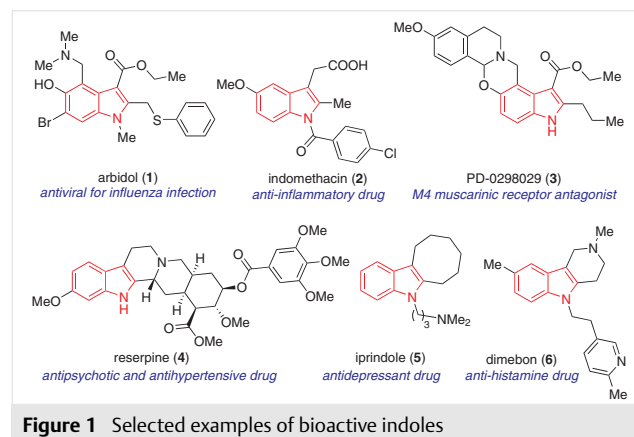


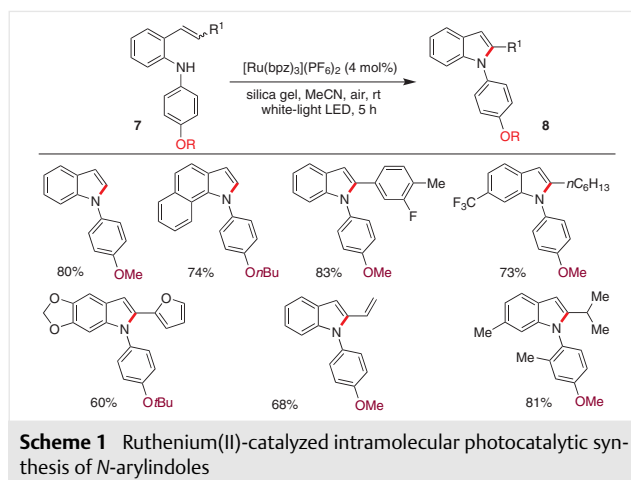
Figure 1 Selected examples of bioactive indoles

The present review focuses on the recent advancements in the regioselective synthesis of substituted indole derivatives, covering the literature from 2011 to present.

2 Metal-Catalyzed Synthesis of 2-Substituted Indoles

For many alkaloids and pharmacologically significant compounds, 2-substituted indoles are important intermediates. Many research groups have focused their work on the synthesis of 2-functionalized indoles, mainly through transition-metal-catalyzed C–H bond activation strategies. Furthermore, photocatalytic approaches have also been used for their synthesis.

In 2012, Maity et al. reported on the ruthenium(II)-catalyzed photocatalytic synthesis of *N*-arylindoles **8** using an 18 W white-light LED (Scheme 1).⁵ An appealing methodology involving oxidative C–N bond formation leads to the synthesis of indoles under aerobic oxidation conditions. However, the role of the *p*-alkoxyphenyl group and the silica gel used in the reaction was not clear, the *p*-alkoxyphenyl group on the nitrogen atom being essential for the reaction. This methodology is applicable to a broad range of substrates giving the desired indoles in moderate to good yields. Electron-donating and electron-withdrawing groups on the aryl ring were well tolerated. Alkenes with different substituents such as alkanes, alkenes, arenes and furans gave the desired products in good yields and the method was also applicable for the synthesis of 2,3-disubstituted indoles.



The proposed catalytic cycle for this transformation involves conversion of the amine into a nitrogen-centered radical cation using photoexcited $[\text{Ru}(\text{bpz})_3](\text{PF}_6)_2$, followed by the generation of benzylic radical **I**. Oxidation of the benzylic radical resulted in benzylic cation **II**, which finally undergoes aromatization to form the indole ring (Scheme 2).

Biographical Sketches



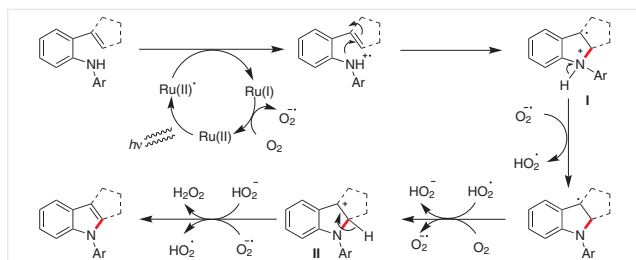
Inder Kumar (right) graduated in Science from Himachal Pradesh University, Shimla, in 2011. He obtained his M.Sc. (2013) and M.Phil. (2014) in Chemistry from HPU, Shimla, and then joined the group of Dr. Sharma in 2015 to undertake doctoral studies. Currently, he is working on first row transition-metal-catalyzed C–H activation/functionalization.

Rakesh Kumar (left) graduated in Science from Himachal Pradesh University, Shimla, in

2011. He completed his M.Sc. in organic chemistry at HPU, Shimla, in 2013, before joining Dr. Sharma's group in 2015 for his doctoral studies. Currently, he is working on transition-metal-catalyzed C–H activation/functionalization.

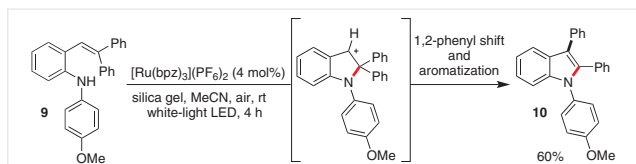
Upendra Sharma (center) is currently a scientist and assistant professor at CSIR-IHBT, Palampur. He completed his Ph.D. on natural product chemistry and metal-phthalocyanine-catalyzed reactions in the fall of

2012, under the supervision of Dr. Bikram Singh. He then joined Prof. Debabrata Maity's group at IIT Bombay, India as a postdoctoral researcher. In March 2014, Dr. Sharma continued his postdoctoral studies with Prof. Sukbok Chang at KAIST, Daejeon, Korea. In September 2014, he started his independent research as a Scientist at NPC&PD Division, CSIR-IHBT, Palampur, India. His research is focused on transition-metal-catalyzed C–H activation/functionalization and natural product chemistry.



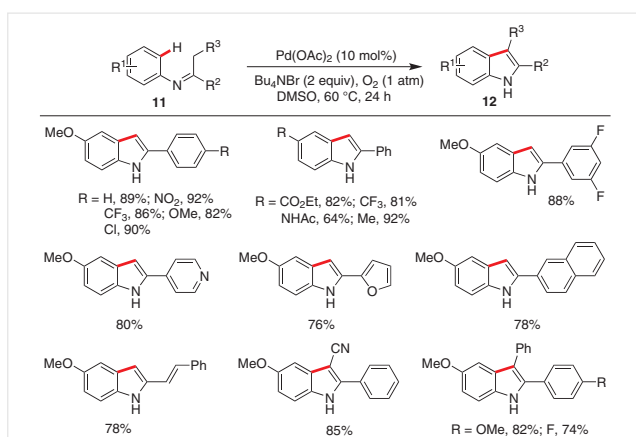
Scheme 2 Proposed mechanism for the photocatalytic synthesis of *N*-arylindoles

The involvement of benzylic carbocation **II** in the visible-light-mediated reaction was further supported by the formation of 2,3-disubstituted indole **10** from *gem*-styrylaniline **9** through a 1,2-carbon shift under the optimized reaction conditions (Scheme 3).



Scheme 3 Proof for the involvement of a benzylic carbocation in visible-light-mediated reaction

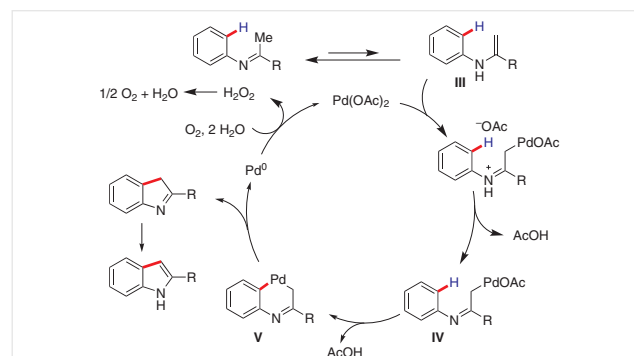
In 2012, Yoshikai et al. reported the palladium-catalyzed cyclization reaction of *N*-arylamines **11** forming C-2 substituted indoles **12** via the oxidative linkage of two C–H bonds (Scheme 4).⁶ The methodology gave rapid, atom-economic and regioselective access to various indole derivatives under mild reaction conditions using molecular oxygen as the solitary oxidant. Inexpensive and readily available anilines and ketones were used to prepare imines, which were cyclized to form indole moieties; the reaction was also successfully carried out on gram scale. Indole derivatives with heterocyclic substituents such as pyridine and furan at the C-2 position were obtained in excellent



Scheme 4 Palladium(II)-catalyzed intramolecular synthesis of indoles

yields. This mode of cyclization was also applicable for the synthesis of 2,3-diarylindoles, overcoming the difficulties of the Larock- and Fagnou-type annulation reactions.

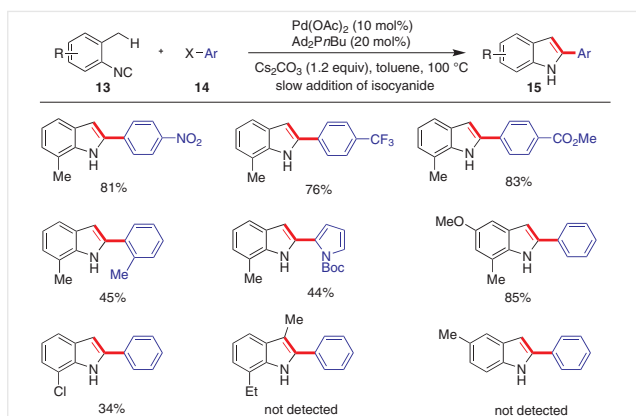
The authors observed a KIE value of 5.2 indicating a concerted metalation–deprotonation mechanism. The plausible mechanism for this transformation involves a Pd(II)/Pd(0) redox process proceeding via electrophilic attack of Pd(OAc)₂ on enamine **III** generated via tautomerization (Scheme 5).



Scheme 5 Proposed mechanism for the palladium(II)-catalyzed intramolecular synthesis of indoles

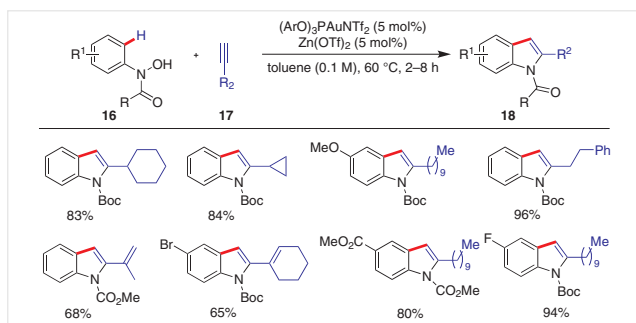
This is followed by elimination of AcOH to give α -palladated imine intermediate **IV**, which after intramolecular aromatic C–H palladation gave palladacycle **V**, thus forming a 3*H*-indole and Pd(0) after reductive elimination. The 3*H*-indole undergoes tautomerization rapidly to give the indole, while combination of molecular oxygen and AcOH oxidizes Pd(0) back to Pd(II), thus completing the catalytic cycle.

In 2012, Yoshiji Takemoto and co-workers synthesized the indole skeleton **15** using a palladium-catalyzed cascade process involving isocyanide **13** insertion and benzylic C(sp³)–H activation (Scheme 6).⁷ This represents the first report on the use of a combination of palladium-catalyzed isocyanide insertion and C(sp³)–H activation for the synthesis of heterocycles. The synthesis of different 2-arylindoles can be achieved by changing the coupling partners and represents a unique palladium-catalyzed strategy for C–C bond formation between the 2- and 3-position of indole. The slow addition of the isocyanide was adopted to avoid catalyst deactivation. Using different aryl halides **14** as coupling partners resulted in the synthesis of a range of indoles with different substituents. Electron-donating and electron-withdrawing groups at the *para* position of aryl iodides were well tolerated, whereas the introduction of a methyl group at the *ortho* position led to a lower yield of the final product. Bromobenzene gave the desired product in good yield, but chlorobenzene did not react under these conditions. Diethylphenyl isocyanide and 2,4-dimethylphenyl isocyanide were also found to be unsuitable under the developed conditions.



Scheme 6 A palladium(II)-catalyzed cascade process for the synthesis of 2-substituted indoles

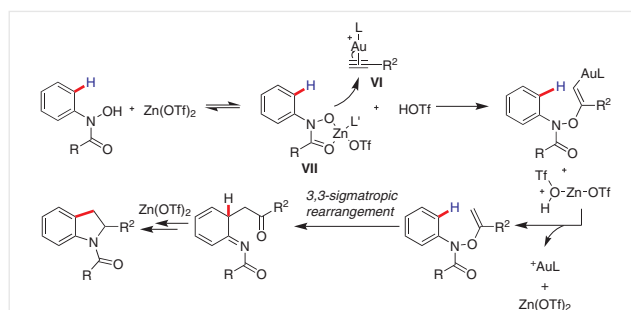
In 2013, Zhang's group delineated the synthesis *N*-protected C-2 functionalized indoles **18** through combined gold/zinc catalysis using *N*-arylhydroxamic acids/*N*-hydroxycarbamates **16** and alkynes **17** (Scheme 7).⁸



Scheme 7 Gold-catalyzed synthesis of 2-substituted indoles

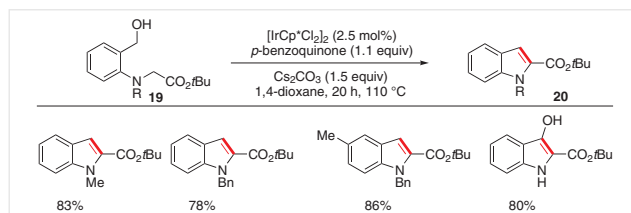
The limitations associated with the well-known Fischer indole synthesis and Bartoli reaction, such as strong acidic conditions, regioselectivity, tolerance to sensitive moieties like the Boc protecting group and limited substrate scope, were overcome by employing this synthetic strategy. Indoles with different functional groups, such as aliphatic alkanes, cyclohexane, and cyclopropane, were easily prepared.

Indoles with a methyl group at the C-2 position were favored with high regioselectivity, possibly because of less steric hindrance. The authors proposed that the pathway involves activation of the hydroxamic acid or a related substrate via zinc chelate formation (Scheme 8). Gold-activated alkyne **VI** was then effectively attacked by the more O-nucleophilic zinc chelate **VII**, which upon subsequent protodeauration formed a precursor for 3,3-sigmatropic rearrangement. Finally, the Lewis acid Zn(OTf)₂-assisted cyclodehydration leads to the desired indole product.



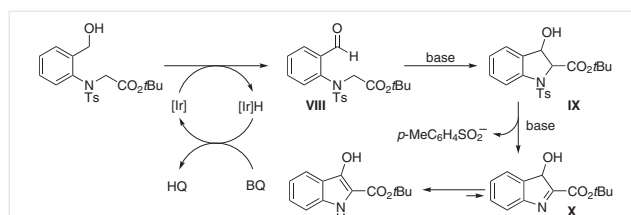
Scheme 8 Proposed mechanism for the gold-catalyzed synthesis of indoles

In 2013, Cossy's group carried out the synthesis of 1,2-disubstituted indoles from benzyl alcohols through an iridium-catalyzed hydrogen atom transfer process (Scheme 9).⁹ *p*-Benzoquinone was used as the co-oxidant in the reaction.



Scheme 9 Iridium-catalyzed synthesis of 2-substituted indoles

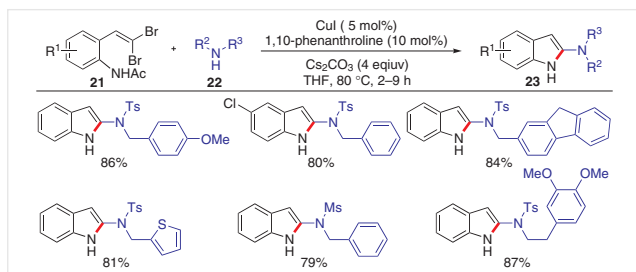
The proposed mechanism of the reaction involves the conversion of the alcohol into an aldehyde **VIII** through hydrogen atom transfer involving the iridium catalyst. *p*-Benzoquinone regenerates the catalyst through oxidation. The intermediate **VIII** then undergoes intramolecular cyclization in the presence of a base to give **IX**, which may aromatize with removal of water to give the 1,2-disubstituted indole. Removal of the tosyl protecting group from **IX** in the presence of the base generates **X**, which upon further rearrangement gives the expected indole (Scheme 10).



Scheme 10 Predicted mechanism for the synthesis of 2-substituted indoles

In 2013, Kiruthika and Perumal disclosed an efficient strategy for the synthesis of 2-amidoindoles **23** through in situ generated ynamides followed by hydroamidation

(Scheme 11).¹⁰ The method involves the intermolecular coupling of *gem*-dibromovinylanilide **21** and sulfonamides **22** using Cu(I) iodide as the catalyst.

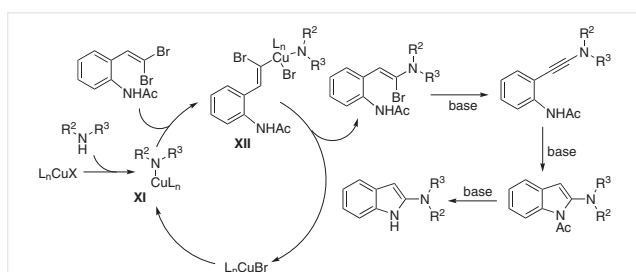


Scheme 11 Cu(I)-catalyzed synthesis of 2-substituted indoles

Acetamide derivatives **21** were used as the product yield was low in the case of an aniline derivative. The presence of an electron-withdrawing group such as tosyl or mesitylsulfonyl was essential on the nitrogen of **22** for the reaction to progress.

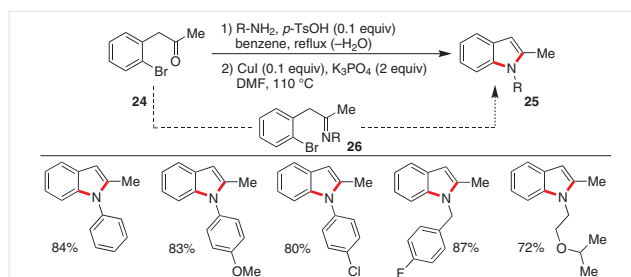
The plausible mechanism for the reaction involves the oxidative insertion of the more reactive *trans* C–Br bond of **21** into **XI** to furnish intermediate **XII** (Scheme 12). Reductive elimination followed by dehydrobromination in the presence of a base provides the ynamide. Further base-promoted intramolecular hydroamidation and deacetylation results in the formation of the desired 2-substituted indole.

May and co-workers reported the copper-catalyzed synthesis of *N*-substituted indoles **25** from the corresponding primary amines and carbonyl compounds **24** through a two-step, one-pot approach (Scheme 13).¹¹ The authors optimized the reaction conditions separately for imine **26** formation and cyclization.



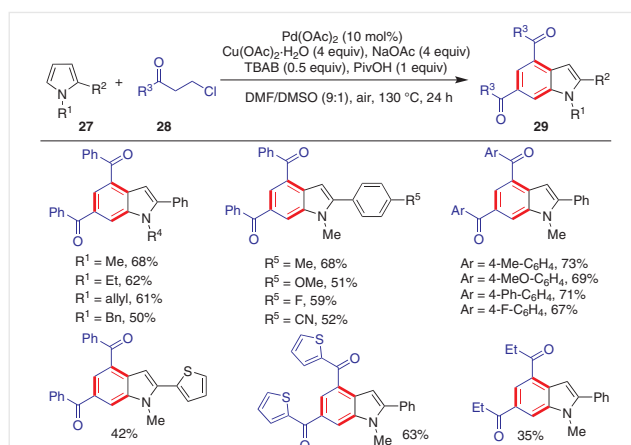
Scheme 12 Plausible catalytic cycle

Imine formation was efficient in benzene whereas for cyclization DMF was used as the reaction medium. The method was applicable for anilines, benzylamines, and aliphatic amines providing the desired indoles in good yields. Further, diversified 3- or 2,3-substituted indoles could also be synthesized through this method by using α -aryl or cyclic ketones, respectively.



Scheme 13 Cu(I)-catalyzed synthesis of indoles from primary amines

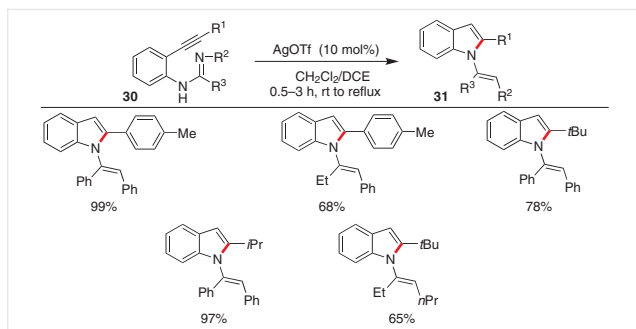
Yu et al. reported the synthesis of functionalized indoles **29** through palladium-catalyzed, copper-mediated oxidative annulations of in situ generated enones with *N*-substituted pyrroles **27** (Scheme 14).¹² Various 3-chloroalkyl ketones and pyrrole derivatives were well tolerated under the reported reaction conditions providing the corresponding indole products in moderate to good yields. Although the method was applicable for the synthesis of multi-substituted indoles, the reaction conditions were very harsh which limits the scope of the reaction on industrial scale. The authors proposed that the reaction proceeds through a sequence of dehydrochlorination, C–H activation, Diels–Alder cycloaddition and dehydrogenative aromatization.



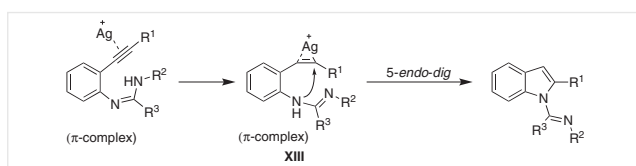
Scheme 14 Pd(II)-catalyzed, Cu(II)-mediated synthesis of indoles through annulations of enones with *N*-substituted pyrroles

Otani and co-workers examined the Lewis acid promoted cycloisomerization of *N*-imidoyl-2-alkynylanilines **30** with substituents such as alkyl or aryl (Scheme 15).¹³ They showed the formation of indole derivatives via a 5-*endo-dig* cyclization mode.

The electronic effects of the R^1 substituent affect the cyclization selectivity; the plausible mechanism for the cyclization involves the Ag–alkyne complex species **XIII** in the stereoelectronically favorable 5-*endo-dig* mode of cyclization (Scheme 16).

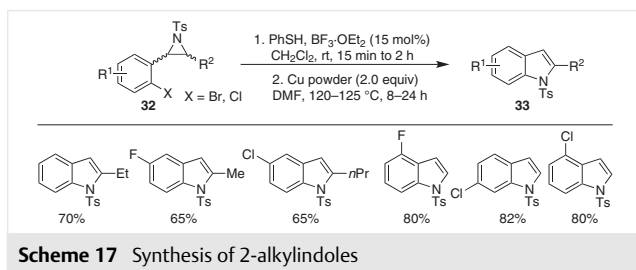


Scheme 15 Silver(I)-promoted intramolecular synthesis of indoles



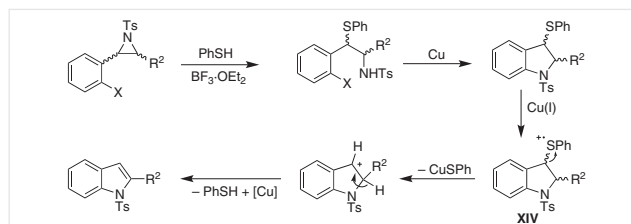
Scheme 16 Proposed pathway for the silver(I)-promoted intramolecular synthesis of indoles

In 2015, Ghorai's group developed a two-step, one-pot strategy to synthesize 2-alkylindoles **33** via thiophenol-mediated regioselective ring-opening of 2-(2-haloaryl)-3-alkyl-*N*-tosylaziridines **32**, followed by copper-mediated intramolecular C–N cyclization with subsequent aromatization by thiophenol elimination (Scheme 17).¹⁴ This method overcomes the limitation of the synthesis of halogenated 2-alkylindoles, which otherwise were impossible to synthesize by alpha-lithiation of indoles.¹⁵ Various halogenated indoles were prepared in good to excellent yields using either a *cis/trans* mixture or mono-substituted aziridines, though *trans* disubstituted aziridines were found to be more reactive than the *cis* isomer due to steric reasons.



Scheme 17 Synthesis of 2-alkylindoles

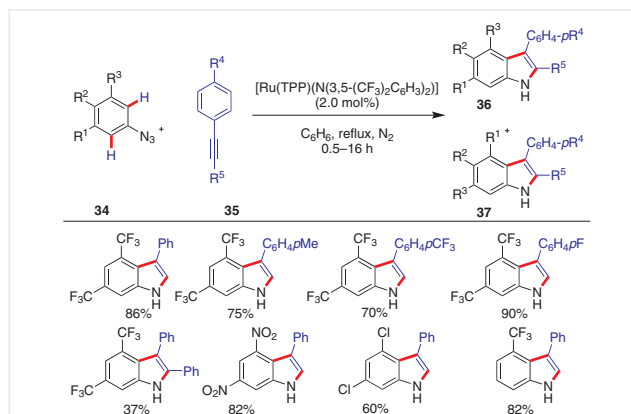
The mechanism of the reaction possibly follows the copper-powder-mediated C–N cyclization as described in Ghorai's earlier report,¹⁶ with the final aromatization step involving Cu(I)-mediated desulfonation via the formation of cationic thioether intermediate **XIV** (Scheme 18).



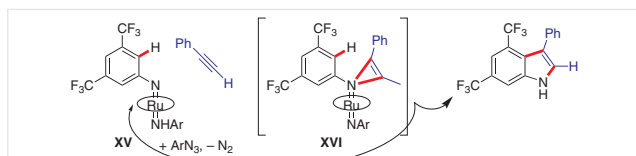
Scheme 18 Reaction pathway for the Cu-mediated C–N cyclization

3 Metal-Catalyzed Synthesis of 3-Substituted Indoles

The regioselective synthesis of C-3 functionalized indoles **36** and **37** from the aryl azides **34** having exceptional reactivity toward alkynes **35** was reported by Gallo's group in 2014 (Scheme 19).¹⁷ This ruthenium–porphyrin-complex-catalyzed methodology furnished indoles instead of triazoles and is attractive for the synthesis of C-3 functionalized indoles having electron-withdrawing substituents on the azide fragment. Only C-3 functionalized indoles were obtained in high yield with aromatic terminal alkynes. The steric hindrance caused by the alkynes was responsible for the low reaction yield observed for C-2 functionalized indoles when using internal alkynes as coupling partners. Also, aliphatic alkynes were not suitable for indole synthesis under the reported conditions. It was observed that when $R^1 = R^3$, the reaction yield was high, while with different substituents the product was obtained in a lower yield, and when only one substituent was present on the benzene ring of the azide, the indole yield was lower. The proposed mechanism for this reaction involves initially the formation of N-substituted-1*H*-azirine intermediate **XV**. The polarization of a sp^2 C–H aromatic bond *ortho* to the electron-withdrawing group assists a hydrogen transfer reaction, which is responsible for the indole cyclization (Scheme 20).

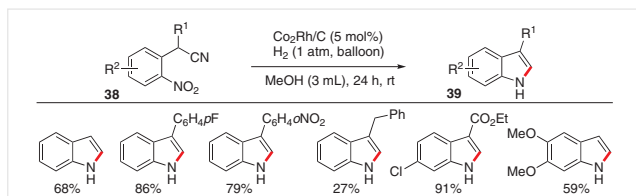


Scheme 19 Ruthenium-catalyzed regioselective synthesis of indoles



Scheme 20 Proposed mechanism for the synthesis of C-3 functionalized indoles

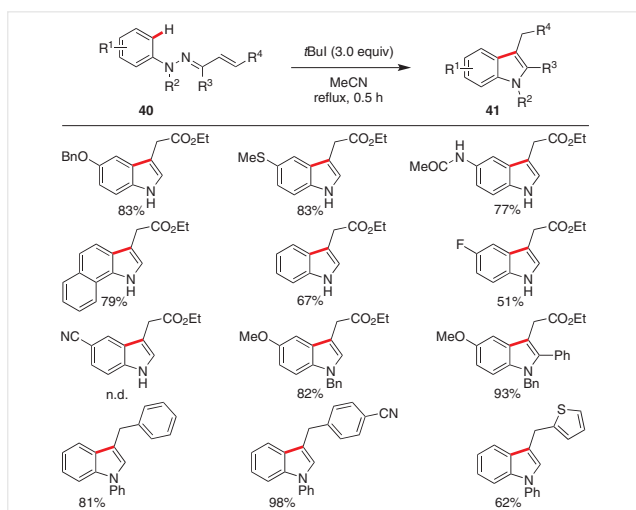
Choi et al. reported the Co–Rh heterobimetallic nanoparticle-charcoal-catalyzed reductive cyclization of 2-(2-nitroaryl)-acetonitriles **38** to give indole motifs **39** (Scheme 21).¹⁸ The catalyst can be reused more than ten times without any loss of activity and the developed strategy was also applicable for gram-scale reactions. Under the optimized conditions, several functional groups were tolerated affording high product yields.



Scheme 21 Heterobimetallic nanoparticle-charcoal-catalyzed synthesis of 3-substituted indoles

4 Metal-Free Synthesis of 3-Substituted Indoles

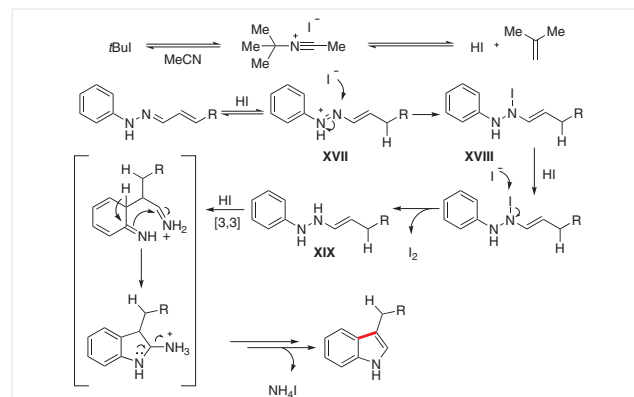
Recently, Ito et al. developed a novel transition-metal-free reductive Fischer indole synthesis by reacting easily available *N*-aryl hydrazones **40** with *tert*-butyl iodide as a source of anhydrous HI, which acts as Bronsted acid as well as a reducing agent (Scheme 22).¹⁹ The developed method



Scheme 22 Fischer indole synthesis of C-3 substituted indoles

represents the first ever report on a 1,4-reduction of a conjugated hydrazone with a sequential Fischer indolization reaction of an in situ generated enamine, and can be applied to the synthesis of biologically active C-3 substituted indole derivatives. The role of the solvent was crucial for the transformation as only polar solvents were able to give the desired product.

Various substituted *N*-aryl hydrazones were selectively converted into the corresponding indoles **41**, including substrates with an electron-donating methoxy group at the *para* position of the benzene ring, amide, halogen atoms, etc., or substrates without substituents. As electron-withdrawing groups were not suitable for the 3,3-sigmatropic rearrangement step, an indole with a cyano group at the C-5 position was not observed under these conditions. Heterocyclic, electron-donating and electron-withdrawing groups at the R⁴ position were well tolerated.



Scheme 23 Proposed mechanism for the metal-free synthesis of 3-substituted indoles

A plausible mechanism for this transformation involves the initial attack of *tert*-butyl iodide at MeCN to give HI, which then regioselectively protonates the *N*-aryl hydrazone to give azonium ion **XVII**. The addition of an iodide anion to the azonium ion converts it into another intermediate **XVIII**, which was further reduced by HI to give enamine **XIX**. After the 3,3-sigmatropic rearrangement of the enamine, subsequent cyclization and aromatization with the loss of ammonium iodide gives the desired indole (Scheme 23).

5 Metal-Catalyzed 2,3-Disubstituted Indole Synthesis

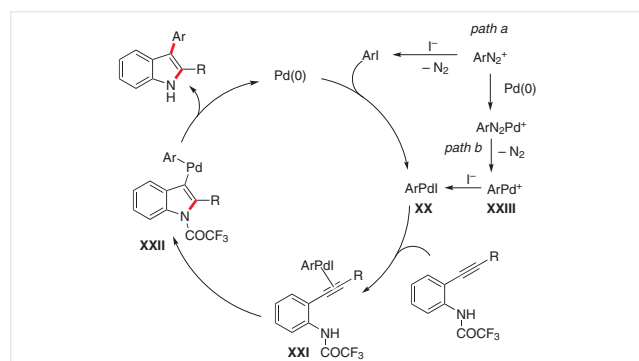
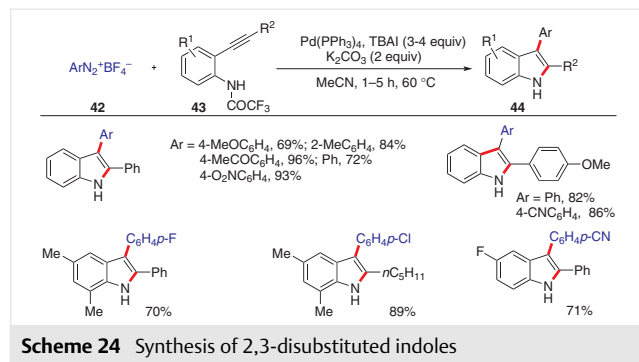
Over the last two decades, many new methodologies have been reported for the synthesis of indole derivatives to overcome the existing limitations. Various metal-catalyzed as well as metal-free approaches have been developed for the synthesis of 2,3-disubstituted indole derivatives.²⁰

5.1 Metal-Catalyzed Intramolecular 2,3-Disubstituted Indole Synthesis

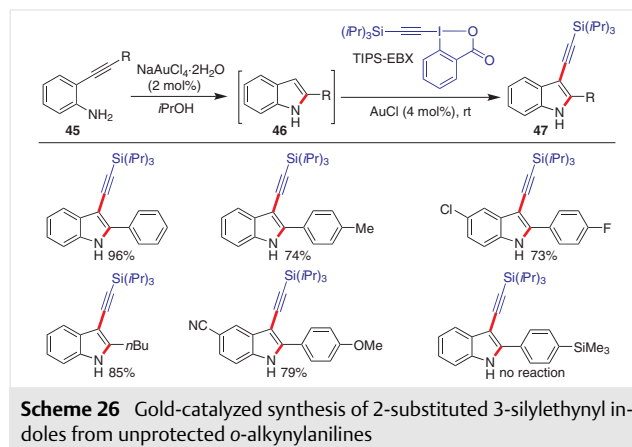
Considering the high importance of the 2,3-disubstituted indole structural motif in the pharmaceutical industry and in medicinal chemistry, a large number of efforts have been made in the last few years to develop simple and cost-effective methods for their synthesis.

In 2010, Cacchi's group disclosed the synthesis of 2,3-disubstituted indoles **44** from arenediazonium tetrafluoroborates **42** and 2-alkynyltrifluoroacetanilides **43** using a palladium catalyst. The method showed excellent functional group tolerance both in the alkyne and the arenediazonium component, including halo substituents. Arenediazonium salts containing *ortho* substituents gave the corresponding products in good to high yields (Scheme 24).²¹

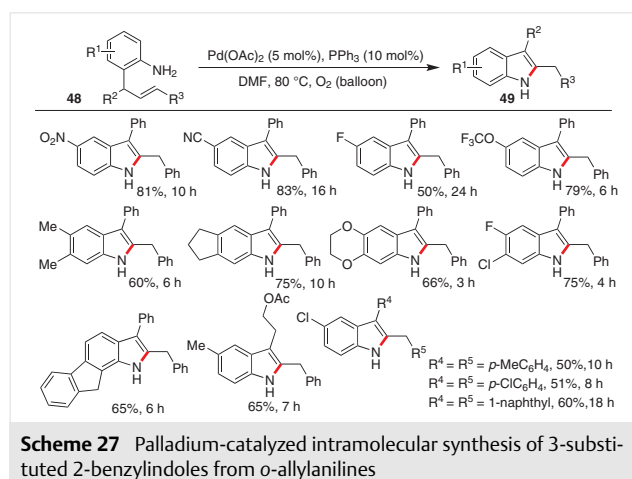
This reaction proceeds through an iododediazonization step (Scheme 25, path a) followed by oxidative addition to Pd(0) to afford the arylpalladium iodide **XX** that coordinates with the alkyne to give palladium complex **XXI**. A subsequent intramolecular aminopalladation generates σ -intermediate **XXII**, which via reductive elimination and hydrolysis gives the desired product.²¹ Alternative mechanisms, which appear less likely, involve the formation of arylpalladium iodides through the reaction of σ -aryl palladium cation **XXIII** with iodide anions (Scheme 25, path b).



In 2011, the Waser group reported the one-pot synthesis of 3-silylethynyl indoles **47** via the cyclization of 2-alkynylanilines **45** using NaAuCl₄ as the catalyst. The intermediate indoles **46** underwent C3-alkynylation with AuCl and TIPS-EBX to afford the products **47**. This reaction was also applicable for unprotected anilines, demonstrated good functional group tolerance and was very easy to carry out (Scheme 26).²²

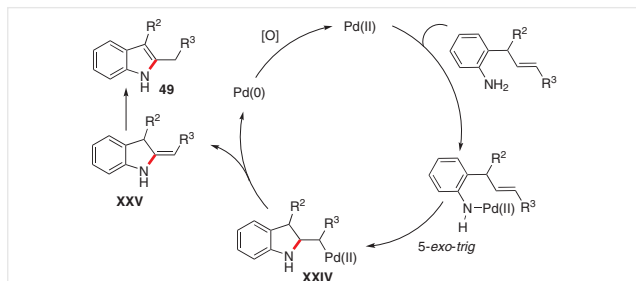


Ghorai and co-workers reported the palladium-catalyzed synthesis of 3-substituted 2-benzylindoles **49** through oxidative annulations of *o*-allylanilines **48** with O₂ as the oxidant (Scheme 27).²³ The same authors also reported the one-pot synthesis of indoles from **48**, which are prepared from aniline and substituted allyl alcohols using an oxorhenium catalytic system.²³ The reported catalytic system provided good regioselectivity and was amenable to a broad substrate scope with high functional group tolerance.



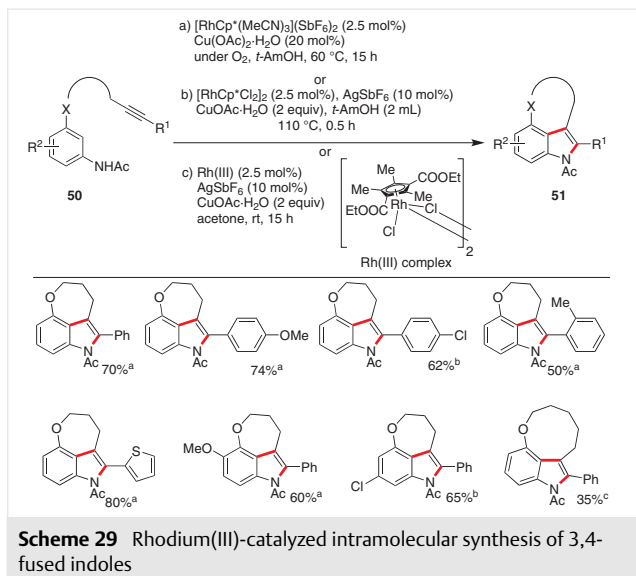
The catalytic cycle of this reaction was initiated by palladium-catalyzed aminopalladation of the 2-allylaniline via an intramolecular 5-*exo-trig* cyclization to generate intermediate **XXIV**, followed by β -hydride elimination to form

intermediate **XXV**. Isomerization of this intermediate gives the final product **49** and O₂ oxidizes Pd(0) to regenerate the active catalytic cycle (Scheme 28).



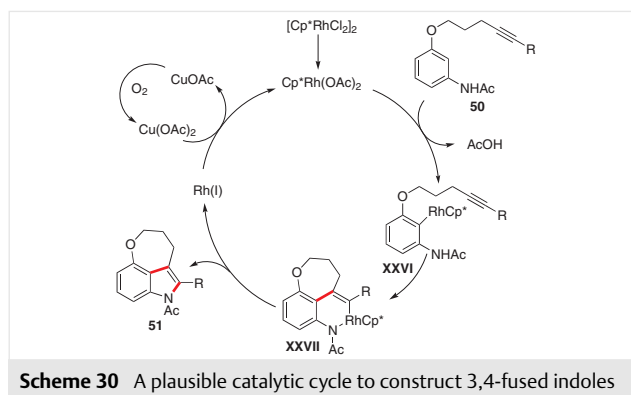
Scheme 28 A plausible catalytic cycle for the synthesis of 3-substituted 2-benzylindoles from *o*-allylanilines

In 2014, Li's group reported the Rh(III)-catalyzed intramolecular annulations of alkynes **50** via C–H activation for the synthesis of 3,4-fused indoles **51**.²⁴ The indoles were synthesized in moderate to good yields with excellent regioselectivity and broad substrate scope. Substrates containing both electron-donating and electron-withdrawing groups at *ortho*, *para* and *meta* positions of the aryl ring of the alkynes were well tolerated. 3,4-Fused indoles with six- to nine-membered rings were generated in relatively low yields (Scheme 29).²⁴



Scheme 29 Rhodium(III)-catalyzed intramolecular synthesis of 3,4-fused indoles

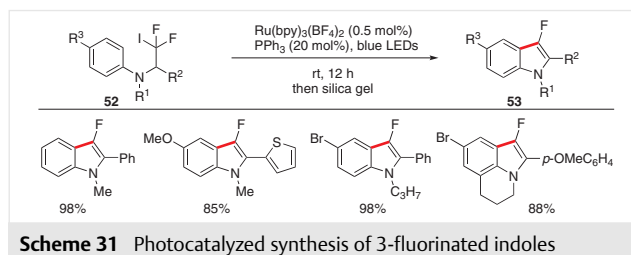
The reaction was initiated by *ortho* C–H bond activation of **50** to form intermediate **XXVI**. Alkyne insertion to **XXVI** gives rhodacycle **XXVII**, which on reductive elimination provides the desired product **51** and Rh(I). Finally, the active catalytic species was regenerated by Cu(II) (Scheme 30).



Scheme 30 A plausible catalytic cycle to construct 3,4-fused indoles

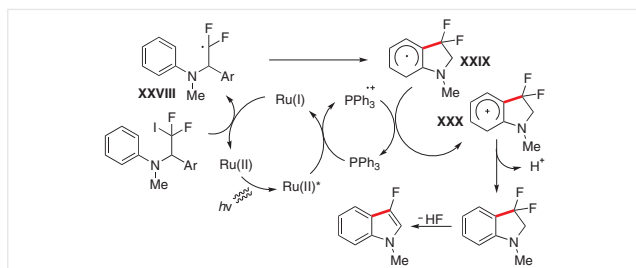
In 2016, Dilman et al. described the photocatalyzed conversion of CF₂I-substituted *N*-arylamines **52** into the corresponding 3-fluoroindoles **53**.²⁵ The starting materials were obtained by nucleophilic iododifluoromethylation of iminium ions. The developed strategy utilized blue LEDs for irradiation of the reaction mixture for 12 hours. A series of 3-fluoroindoles was synthesized effectively with excellent yields using the developed photocatalytic methodology (Scheme 31).

Mechanistic studies involved measurements of the redox potentials of the catalyst, the starting material and triphenylphosphine to check the feasibility of the electron-transfer step. The reduction potential studies suggested the initial conversion of photoexcited Rh(II)* into Rh(I) [$E_{\text{Rh(II)*}/\text{Rh(I)}} = +0.84 \text{ V}$] by triphenylphosphine [$E_{\text{PPh}_3^+/\text{PPh}_3} = +0.77 \text{ V}$]. Rh(I) then generates the difluorinated radical **XXVIII** via a single electron transfer and the catalyst is regenerated. Intramolecular attack of the radical onto the aromatic ring furnished **XXIX**, oxidation of which by the triphenylphosphine radical cation produced aromatic cation **XXX**. Elimination of a proton from **XXX** followed by removal of HF provided the expected indole product (Scheme 32).



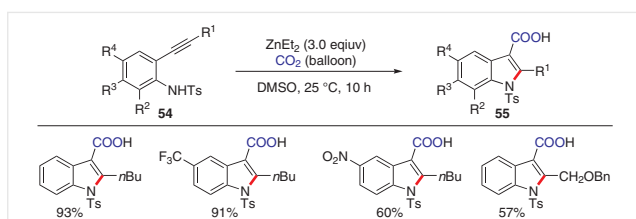
Scheme 31 Photocatalyzed synthesis of 3-fluorinated indoles

In 2016, Miao et al. reported the ZnEt₂-mediated *anti*-azacarboxylation of 2-alkynylanilines **54** with CO₂ for the synthesis of 2,3-disubstituted indoles **55** (Scheme 33).²⁶ The method represents an easy access to indole moieties as it involves the use of readily available starting materials and various functional groups are tolerated. Trifluoromethyl- and nitro-substituted reactants provided indoles in good to



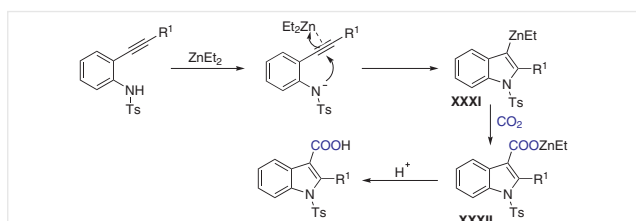
Scheme 32 Mechanistic cycle for the ruthenium-photocatalyzed reaction

excellent yields. The utility of this method involves the synthesis of the drug Lotronex, which is used for the treatment of irritable bowel syndrome.



Scheme 33 Diethylzinc-mediated intramolecular cyclization for the synthesis of indoles

The reaction was proposed to proceed through initial activation of the alkyne by diethylzinc making it susceptible to intramolecular nucleophilic attack by nitrogen to generate intermediate **XXXI** (Scheme 34). The insertion of carbon dioxide into the C–Zn bond leads to the formation of **XXXII**, which on demetalation in the presence of an acid gives the indole.



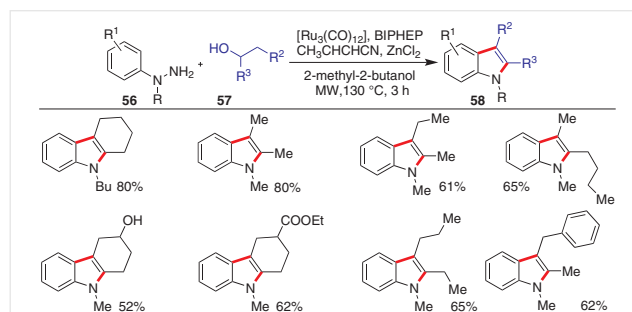
Scheme 34 A plausible reaction mechanism for the synthesis of 2,3-disubstituted indoles

5.2 Metal-Catalyzed Intermolecular 2,3-Disubstituted Indole Synthesis

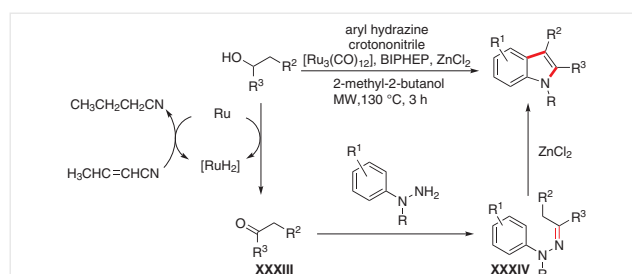
Beyond intramolecular indole synthesis, Maurizio Taddei and co-workers reported the Ru-catalyzed H-transfer Fischer indole synthesis of **58**, from primary and secondary alcohols **57** and aryl hydrazines **56** (Scheme 35).²⁷ The use of alcohols in place of aldehydes or ketones makes this sys-

tem more advantageous compared to the classical Fischer indole synthesis.²⁷

This reaction may proceed through oxidation of the alcohol into a carbonyl compound **XXXIII** by transfer of a H₂ molecule to the crotononitrile. Compound **XXXIII** is immediately converted into hydrazone **XXXIV** by reaction with aryl hydrazine **56** and finally, an acid-catalyzed aromatic [3+3] sigmatropic rearrangement gives the desired indole ring (Scheme 36).



Scheme 35 Ruthenium-catalyzed hydrogen transfer Fischer indole synthesis

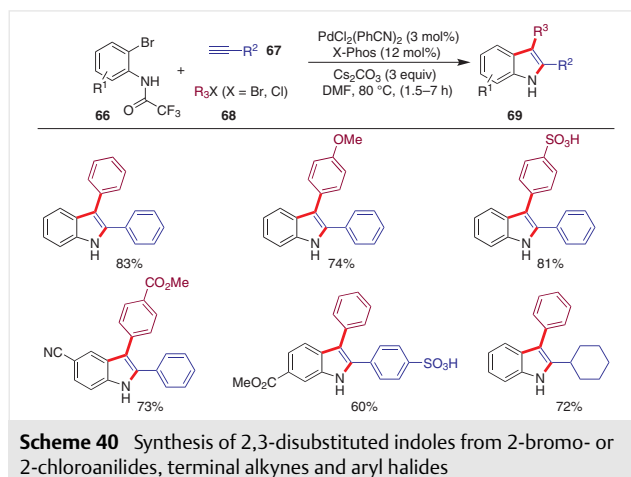
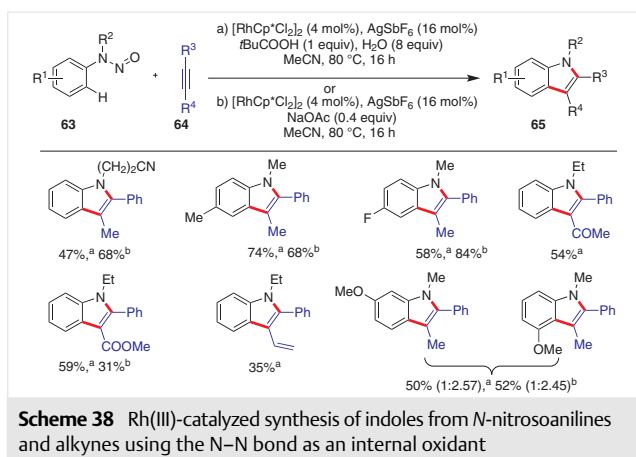
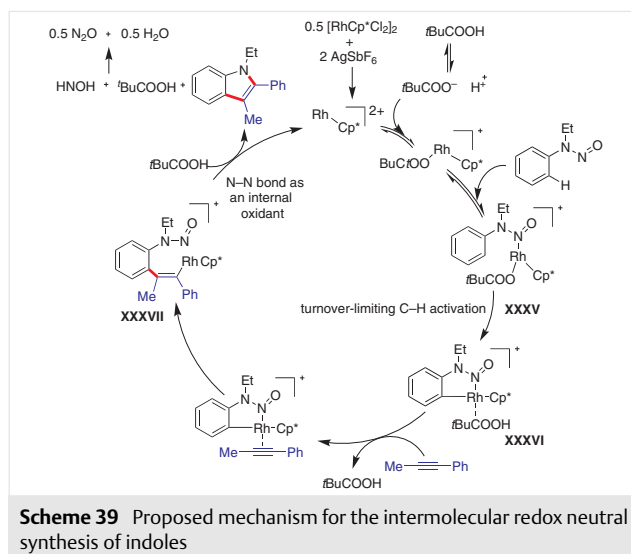
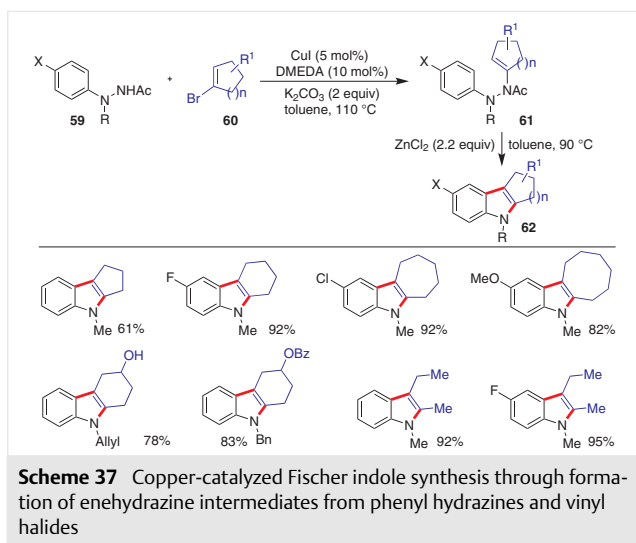


Scheme 36 A plausible catalytic cycle for the synthesis of substituted indoles from aryl hydrazines and alcohols

In 2013, Liang and Zhan reported the copper-catalyzed formation of enehydrazine intermediates **61** through the coupling of phenyl hydrazines **59** with vinyl halides **60**, and its synthetic application for the synthesis of indoles **62**.²⁸

This catalytic system tolerates ester, hydroxy and amine functional groups leading to the selective synthesis of isomeric indoles and has been employed for the interrupted indolization to synthesize the pyrrolidinoindoline **62** (Scheme 37). This catalytic system opens a new way for the asymmetric synthesis of indoles.²⁹

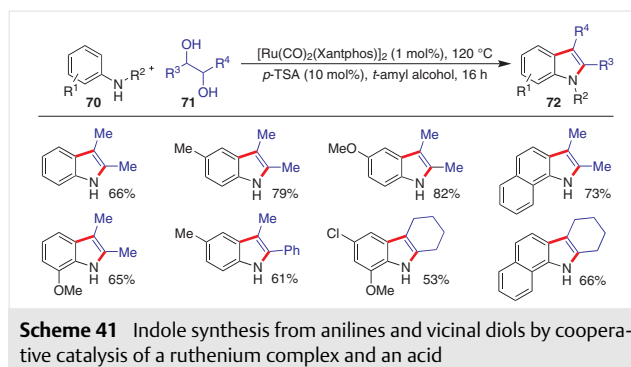
Zhu and co-workers reported a Rh(III)-catalyzed, C–H activation based intermolecular redox neutral strategy for the synthesis of indoles **65** by cyclization of *N*-nitrosoanilines **63** with alkynes **64** using the N–N bond as an internal oxidant. This catalytic procedure showed good functional group tolerance and the compatibility of seemingly dichotomous acidic and basic conditions makes it a versatile method (Scheme 38).³⁰



A detailed mechanistic study proved that the generation of $[\text{RhCp}^*]^{2+}$ leads to reversible coordination of $t\text{BuCOO}^-$ and *N*-nitrosophenylhydrazine derivative to give **XXXV**, and the turnover-limiting C–H activation then forms rhodium intermediate **XXXVI** via a $t\text{BuCOO}^-$ -assisted CMD (concerted metallation deprotonation) pathway. Interaction of the alkyne with **XXXVI** followed by migratory insertion leads to the formation of intermediate **XXXVII**. Concerted N–N bond cleavage and C–N bond formation leads to formation of the final product with the abstraction of NO^+ by H^+ and regeneration of the active $[\text{RhCp}^*]^{2+}$ species (Scheme 39).³⁰

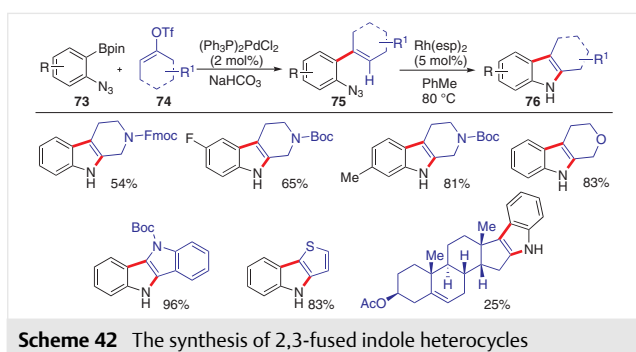
In 2013, Senanayake and co-workers disclosed the one-pot synthesis of indoles **69** by reacting 2-bromoanilides **66**, terminal alkynes **67**, and aryl halides **68** via a palladium-catalyzed reaction sequence involving Sonogashira coupling, aminopalladation and reductive elimination (Scheme 40).³¹ All the reactions were carried under normal conditions without the use of $n\text{Bu}_4\text{NBr}$ and good to excellent yields were achieved.

In 2013, Ding et al. reported the Ru complex and *p*-TSA catalyzed synthesis of indole derivatives **72** from anilines **70** and vicinal diols **71**. Electron-donating substituents on the aryl ring of the aniline gave the products in higher

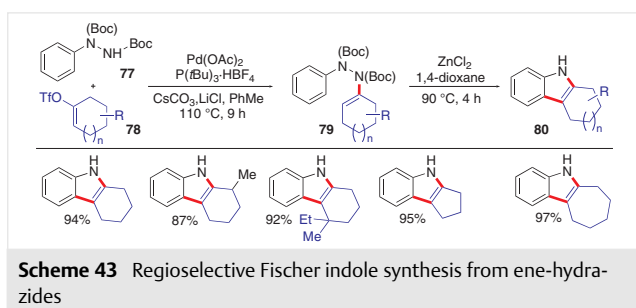


yields, while strong electron-withdrawing groups (i.e., NO₂ or CF₃) failed to give the expected products. An *ortho*-substituted aniline gave a lower yield because of steric hindrance (Scheme 41).³²

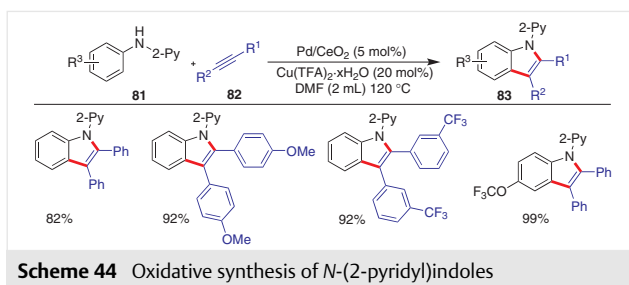
A year later, Driver and co-workers reported a Suzuki cross-coupling reaction for the regioselective synthesis of 2,3-fused indole heterocycles **76** from 2-azidoarylboronic esters **73** and vinyl triflates **74**.³³ The 5-substituted aryl azides smoothly gave the indole products; these products cannot be accessed as single regioisomers using the Fisher indole reaction. The conversion of androsterone into an indole proved that this method is applicable for complex molecules, albeit a reduced yield was obtained (Scheme 42).³³



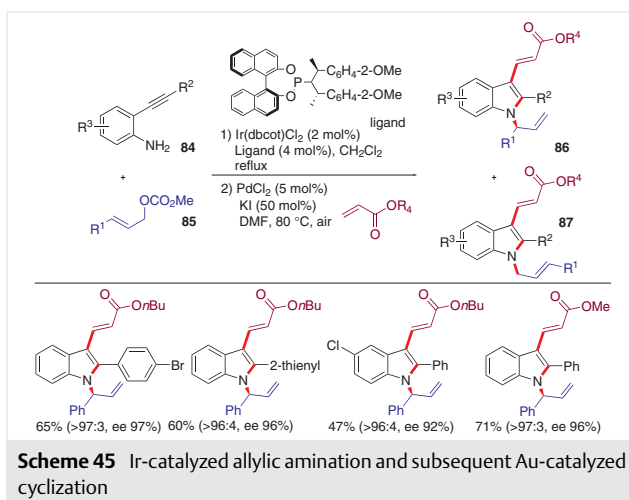
In the same year (2104), Cho and co-workers reported the synthesis of ene-hydrazides **79** from bis-Boc-hydrazide **77** and enol triflates **78**, and their subsequent enolization reaction to give the regioselective Fischer indole products **80**. The catalytic system showed broad substrate scope and enabled the synthesis of indole natural products with excellent regioselectivities (Scheme 43).³⁴



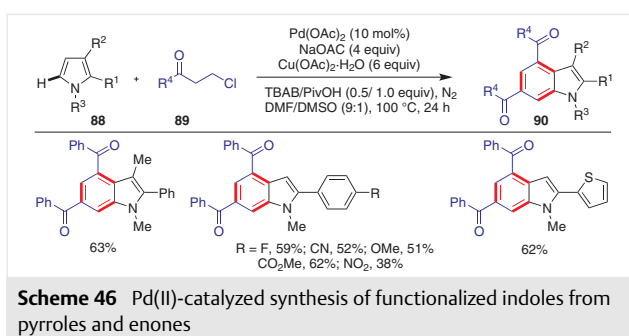
In 2014, Wu's group reported the synthesis of *N*-(2-pyridyl)indoles **83** from internal alkynes **82** and *N*-phenylpyridin-2-amines **81** catalyzed by palladium@cerium(IV) oxide. This method affords better yields compared to other heterogeneous catalytic methods and demonstrates good functional group tolerance; however, the nitro functional group was not tolerated (Scheme 44).³⁵



The regio- and enantioselective synthesis of *N*-allyl indoles **86** and **87** was reported by You's group in 2014.³⁶ This reaction proceeds through an Ir-catalyzed asymmetric allylic amination with 2-alkynylanilines **84** and subsequent Au-catalyzed cyclization. The catalytic system proved was applicable to a broad substrate scope, affording high yields and good enantiomeric excess. The reaction was also compatible with a one-pot procedure and cascade reaction (Scheme 45).³⁶

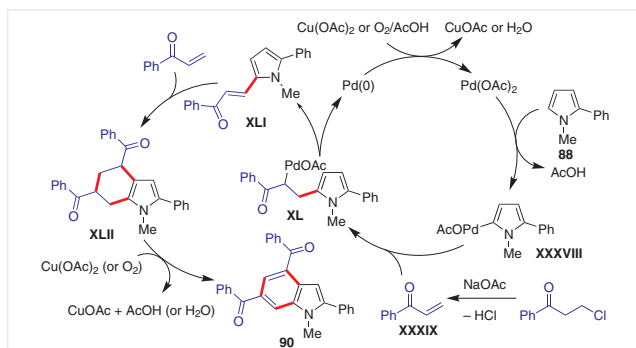


The Yu group reported, in 2015, the Pd(II)-catalyzed synthesis of functionalized indoles **90** from simple *N*-substituted pyrroles **88** and 3-chloropropiophenones **89** and



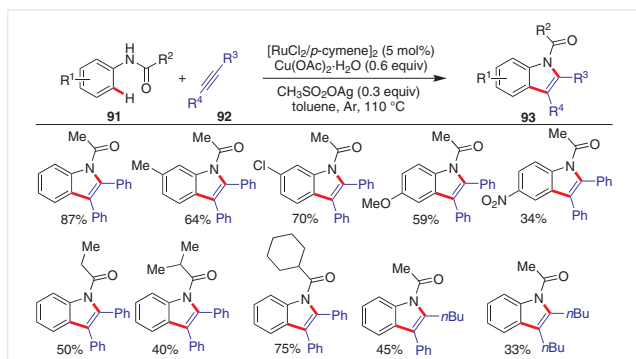
their analogues. This reaction proceeds through the construction of a benzene ring onto a pyrrole backbone using enones **89** (Scheme 46).¹²

The proposed catalytic cycle started with palladation at the C-5 position of pyrrole **88** giving intermediate **XXXVIII** with simultaneous removal of acetic acid. Intermediate **XXXVIII** then reacts with the enone **XXXIX**, generated from 3-chloropropiophenone **89**, to form palladium intermediate **XL**. Reductive elimination leads to the formation of pyrrole derivative **XLI**, which undergoes a Diels–Alder cycloaddition with another molecule of the enone to form tetrahydroindole **XLII**. Finally, the tetrahydroindole is oxidized to indole **90** and catalytic system is regenerated by Cu(II) oxidant or air (Scheme 47).



Scheme 47 Proposed mechanism for the synthesis of functionalized indoles from pyrroles and 3-chloropropiophenones

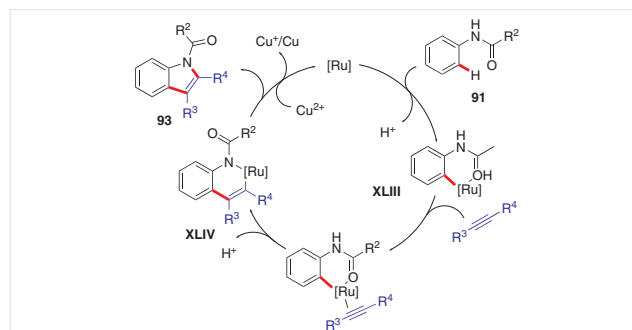
In 2015, Dong and co-workers reported the Ru(II)-catalyzed oxidative coupling via C–H activation of NH protic amides **91** with alkynes **92** for the synthesis of *N*-acylindole derivatives **93**. This catalytic method shows good functional group tolerance and affords moderate yields of the products (Scheme 48).³⁷



Scheme 48 Synthesis of indoles via ruthenium(II)-catalyzed C–H activation and annulations

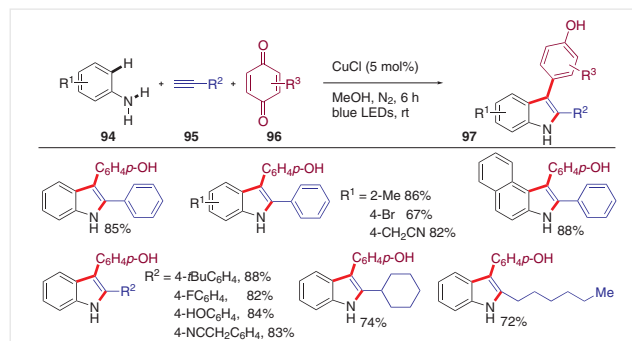
A plausible mechanism was proposed in which the insertion of Ru(II) metal activates the *ortho* C–H bond of amide **91** to form the six-membered ruthenacycle **XLII**. Alkyne

interaction with **XLIII** followed by migratory insertion leads to the formation of another ruthenacycle (**XLIV**). Finally, reductive elimination provides the product **93** (Scheme 49).³⁷



Scheme 49 Proposed catalytic cycle for the synthesis of *N*-acylindoles from NH protic amides and alkynes

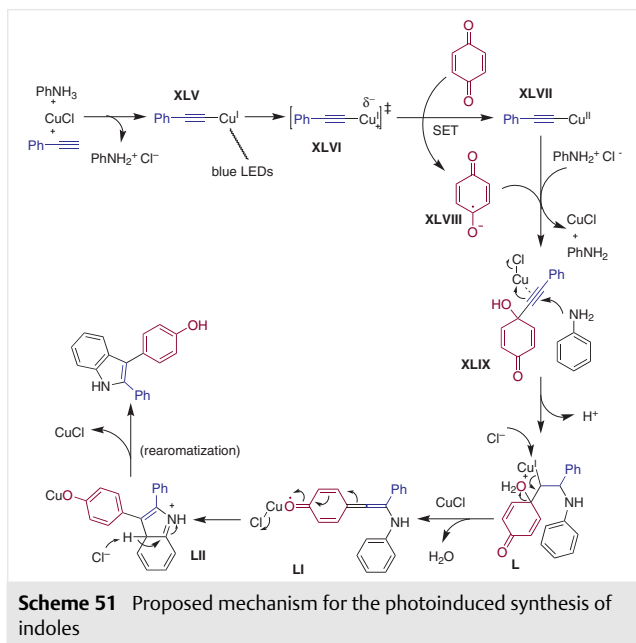
In 2015, Hwang's group reported the visible-light-mediated CuCl-catalyzed regioselective synthesis of indoles **97** via coupling of arylamines **94**, terminal alkynes **95** and quinines **96** at room temperature (Scheme 50). This photoinduced method showed broad substrate scope with good to excellent selectivities. However, the use of *meta*-substituted anilines resulted in the formation of a mixture of regioisomers.³⁸



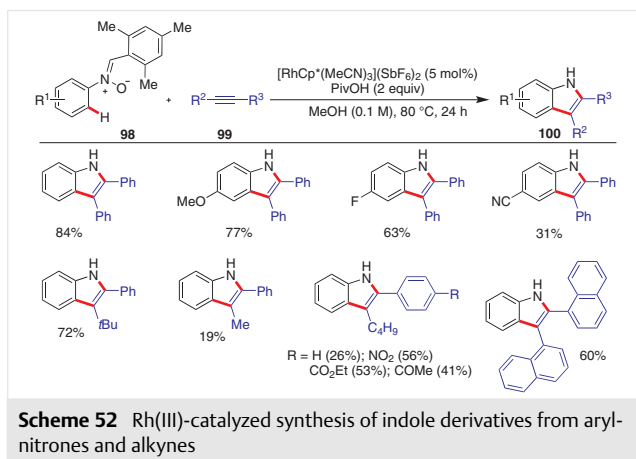
Scheme 50 Photoinduced copper-catalyzed synthesis of indoles from arylamines, terminal alkynes and quinines

This reaction was proposed to commence by photoirradiation of in situ generated **XLV** by blue LEDs. This produces the photoexcited triplet state **XLVI** ($\tau = 15.95 \mu\text{s}$) by ligand-to-metal charge transfer (LMCT).³⁹ This is followed by intersystem crossing of the singlet excited state of copper(I) phenylacetylide to the triplet excited state.⁴⁰ Next, a SET process with benzoquinone gives the copper(II) phenylacetylide **XLVII** and benzoquinone radical **XLVIII**, which has the tendency to attack **XLVII** to regenerate the copper(I) catalyst and form copper(I)-coordinated alkyne complex **XLIX**. The electrophilicity of the triple bond in the disubstituted alkyne moiety must be enhanced through coordination with CuCl,⁴¹ facilitating nucleophilic attack by aniline to provide complex **L**, thus leading to the formation of com-

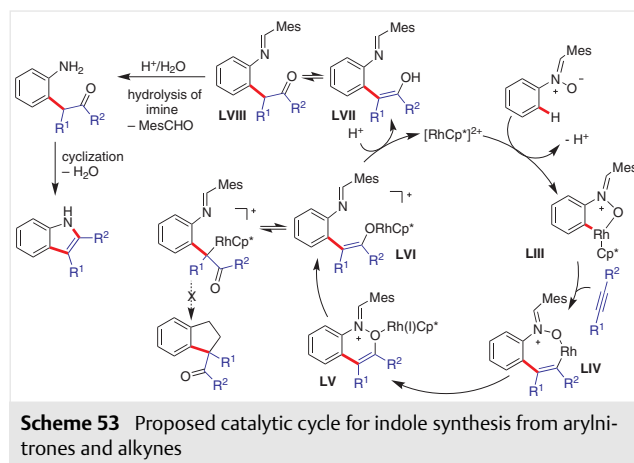
plex **LI**. Friedel–Crafts-type cyclization then generates the intermediate **LII**⁴² and finally, a rearomatization process provides the indole product (Scheme 51).



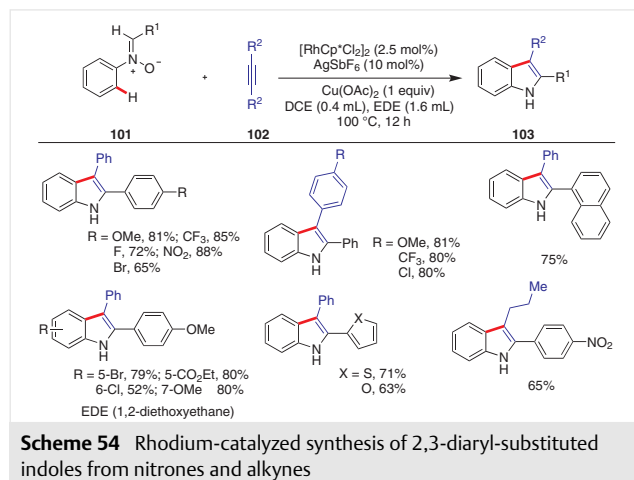
Lu's group reported the Rh(III)-catalyzed synthesis of indoles **100** by annulation of arylnitrones **98** and alkynes **99** without using any external oxidant. Symmetric diarylacetylenes bearing various substituents at the *para* and *meta* positions gave the best results.⁴³ While *ortho*-methyl-substituted diarylacetylene gave a low yield, an unsymmetrical diarylacetylene afforded a mixture of two regioisomers. *para*-Cyano-substituted *N*-phenyl-*C*-mesitylnitronone appeared to be a less effective substrate, affording the desired product in a low yield with a higher catalyst loading at 100 °C (Scheme 52).⁴³

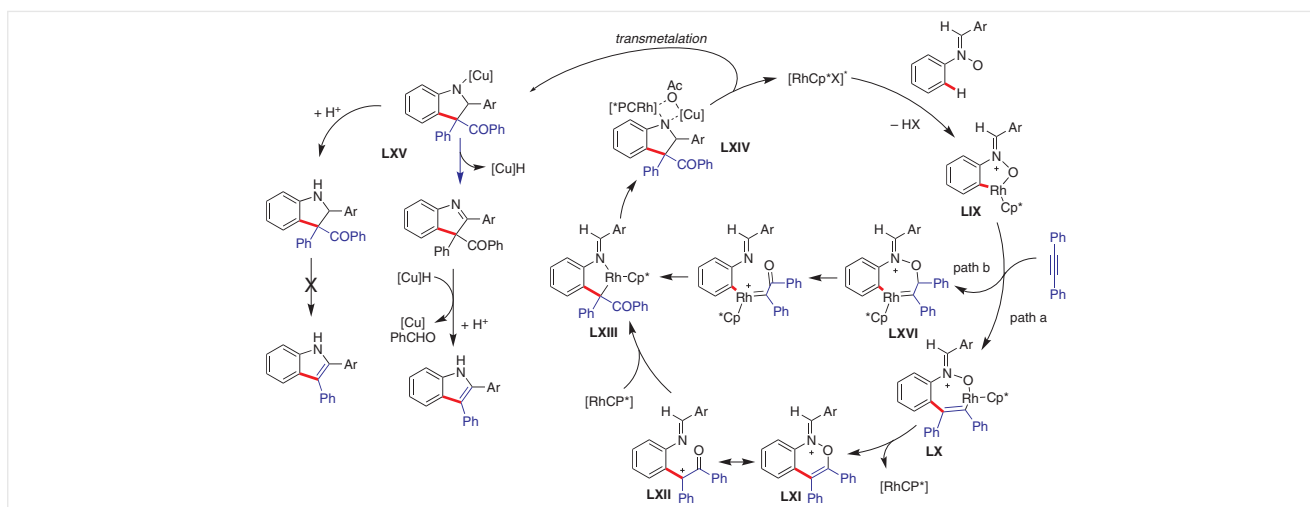


The catalytic cycle was initiated with the formation of rhodacycle **LIII** followed by insertion of the alkyne to give the seven-membered intermediate **LIV**. Reductive elimination leads to the formation of intermediate **LV**. This resulting Rh(I) intermediate could be oxidized by the *N*-O bond via oxidative addition to provide enolate **LVI**, which upon protonolysis provides intermediate **LVII** and regenerates Rh(III) to complete the cycle. Enolate intermediate **LVII** is in equilibrium with keto intermediate **LVIII**, which gives the indole by imine hydrolysis and intramolecular cyclization (Scheme 53).



In 2015, Wan and co-workers reported the synthesis of unsymmetrical 2,3-diaryl-substituted *N*-unprotected indoles **103** via rhodium-catalyzed C–H annulations of nitrones **101** with symmetrical alkynes **102** (Scheme 54).⁴⁴ The catalytic system showed tolerance of various functional groups on the aryl rings of the nitrones and the symmetrical alkynes for the regioselective preparation of the 2,3-disubstituted indoles **103**.

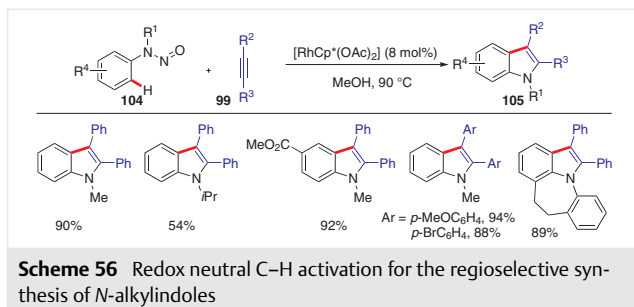




Scheme 55 A plausible catalytic cycle for the synthesis of unsymmetrical 2,3-disubstituted indoles

The catalytic cycle of this reaction also involves the formation of a rhodacyclic intermediate **LIX**, which undergoes insertion with the alkyne to give the seven-membered intermediate **LX** (Scheme 55, path a). Reductive elimination then provides the intermediate **LXI**. Intramolecular oxygen atom transfer and subsequent oxidative addition of **LXII** and electrophilic cyclization generates intermediate **LXIII**. Intermediate **LXV** is formed by transmetalation and subsequent β -hydride elimination,⁴⁵ finally leading to the formation of product **103** by elimination of PhCHO.⁴⁶ Alternatively, the reaction can proceed through **LIX** and intermediate **LXVI** (Scheme 55, path b).

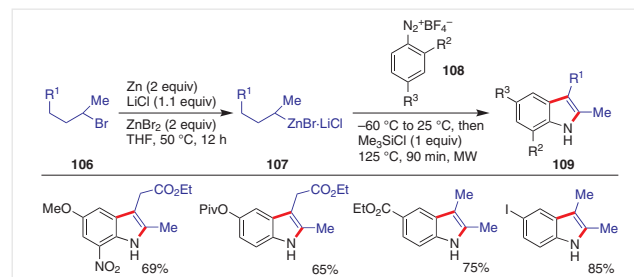
Wang and Huang, in 2015, developed a general protocol for the synthesis of *N*-alkylindoles **105** using a traceless nitroso directing group via redox neutral C–H activation (Scheme 56).⁴⁷ This rhodium-based catalytic system provided *N*-alkylindoles regioselectively, with a broad scope of substituents, in good to excellent yields and without the use of any oxidant or other additive.



Scheme 56 Redox neutral C–H activation for the regioselective synthesis of *N*-alkylindoles

Though the full catalytic cycle of the reaction remains elusive, the C–H activation step may proceed via a concerted metalation–deprotonation (CMD) mechanism.

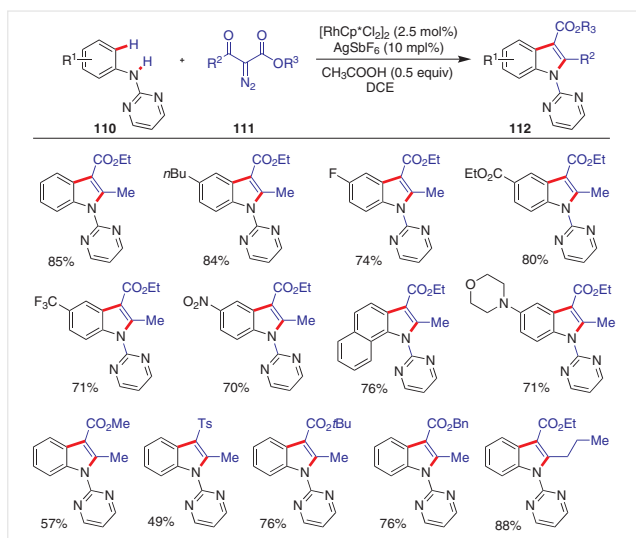
In 2010, the Knochel group reported a microwave-assisted Fischer indole synthesis for the preparation of polyfunctional indoles **109** from aryldiazonium tetrafluoroborates **108** and functionalized alkylzinc halides **107**, which were generated from substituted bromobutanes **106** (Scheme 57).⁴⁸ The catalytic system showed a broad substrate scope with excellent regioselectivity, and with many functional groups such as nitro, ester, keto, cyano and iodo being tolerated. This catalytic method was successfully used for the synthesis of indole-containing drug molecules.



Scheme 57 Preparation of polyfunctional indoles by the addition of alkylzinc reagents to aryldiazonium tetrafluoroborates

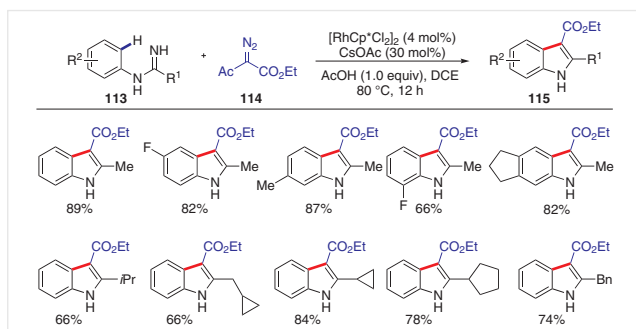
Hui Jiang and co-workers reported the rhodium(III)-catalyzed regioselective synthesis of indole-3-carboxylic acid esters **112** using a pyrimidyl directing group.⁴⁹ *N*-Substituted anilines **110** and diazo compounds **111** were used as the starting materials and the reactions proceeded via aromatic C–H bond activation followed by C–N bond formation to give 2,3-difunctionalized indoles (Scheme 58). The presence of the pyrimidyl directing group was essential for the synthesis of the desired indoles under the specified conditions, and it can be reutilized for further functionalization of the synthesized indoles, or can be easily removed to provide different free *N*–H indoles. The limitations of preactivated substrates, the requirement for excess oxidant and

the substrate scope associated with the previous reports of Glorius,⁵⁰ Jiao⁵¹ and Cacchi²¹ for the synthesis of indole-3-carboxylic acid esters were overcome by using this method. Various alkyl, halogen and ester substituents on the phenyl ring were well tolerated under the reported conditions. Substituents with strong-electron withdrawing effects such as CF₃ and NO₂ and electron-donating methoxy substituents afforded the expected products, exclusively. The desired indole was obtained with a morpholinyl substituent at the *para* position of the phenyl ring. Also, the reaction was successful on gram scale.



Scheme 58 Regioselective synthesis of indole-3-carboxylic acid esters

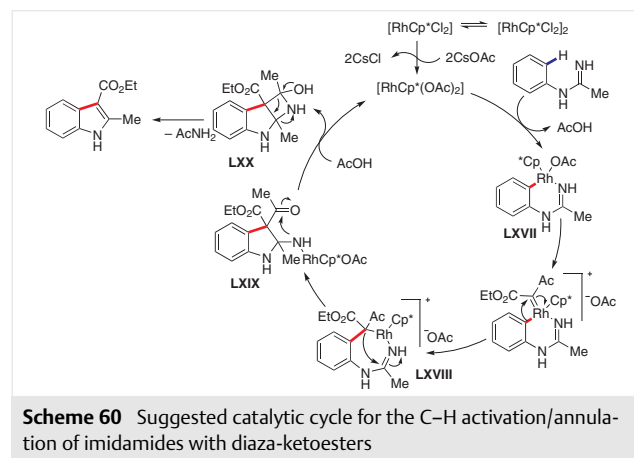
In 2016, Li's group described the synthesis of 2,3-disubstituted indoles **115** via C–H activation/annulation of imidamides **113** with diaza-ketoesters **114** using a Rh(III) catalyst (Scheme 59).⁵² This redox-neutral strategy proceeded under mild conditions with a variety of substrates.



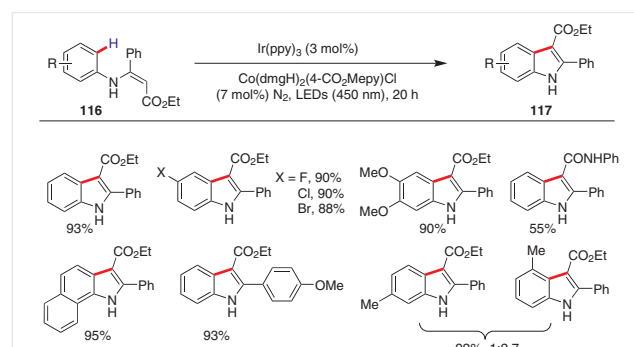
Scheme 59 Rhodium-catalyzed synthesis of 2,3-disubstituted indoles

The mechanistic studies of the reaction revealed the kinetic isotope effect (KIE) value to be 3.3, which indicates C–H bond cleavage may be involved in the rate-determining step. The proposed mechanism of the reaction includes the

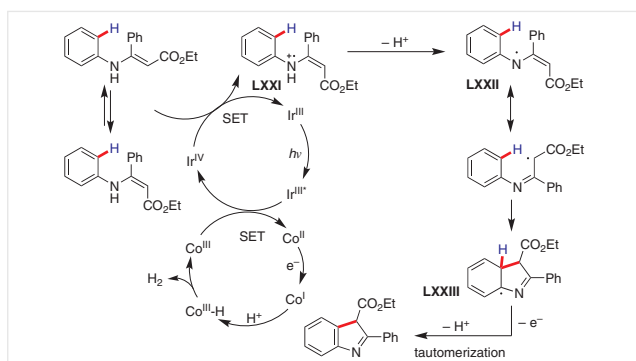
initial generation of an active catalyst through anion exchange. Insertion of the active catalyst into the *ortho* C–H bond followed by cyclization gives the six-membered rhodacycle **LXVII**. Elimination of nitrogen with subsequent insertion of the diazo substrate generates **LXVIII** and migratory insertion of the Rh–C bond into the C=N bond provides **LXIX**. Protonolysis of **LXIX** generates **LXX** and the active catalyst. The elimination of acetamide from **LXX** gives the final product (Scheme 60).



Recently, in 2016, Wu et al. developed an oxidant-free intramolecular C–C bond-formation strategy for the regioselective synthesis of indoles **117** using an iridium(II) photosensitizer and a cobaloxime catalyst under visible light irradiation (LEDs, 450 nm). This procedure successfully converted *N*-arylenamines **116** into indoles in good to excellent yields, while producing H₂ as the only side product (Scheme 61).⁵³ The reported method overcomes the limitations of Glorius and co-worker's⁵⁰ procedure using a stoichiometric amount of oxidant, which can lead to the formation of side products. Under the optimized reaction conditions, various electron-withdrawing as well as electron-donating substituents were well tolerated, affording the corresponding indoles in high yields. When *meta*-substituted enamines were



Scheme 61 Photocatalyzed regioselective synthesis of indoles



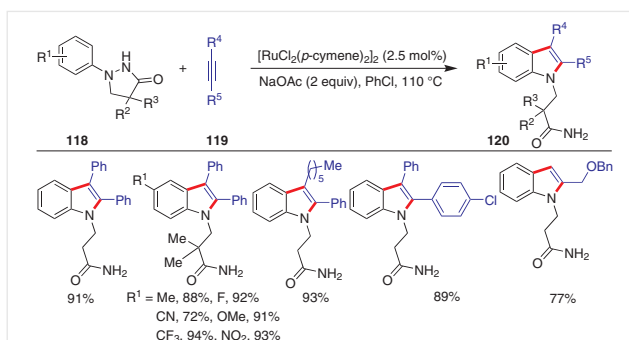
Scheme 62 A plausible mechanism for the photocatalytic synthesis of indole derivatives

used as the starting materials, more than one product could be obtained. The desired indole product could also be obtained on gram scale in 82% yield.

A plausible mechanism for the reaction involves initial photoirradiation of the $\text{Ir}(\text{ppy})_3$ photosensitizer to produce $\text{Ir}(\text{ppy})_3^*$, which transfers an electron to the cobaloxime complex, thus forming $\text{Ir}(\text{IV})$ and $\text{Co}(\text{II})$. The $\text{Ir}(\text{IV})$ so formed abstracts an electron from **116** to produce **LXXI** and regenerate the photosensitizer $\text{Ir}(\text{ppy})_3$. Intermediate **LXXI** loses a proton to give **LXXII** that undergoes intramolecular radical cyclization to produce **LXXIII**. Finally, oxidation and deprotonation followed by tautomerization of **LXXIII** afforded the desired indole product (Scheme 62).

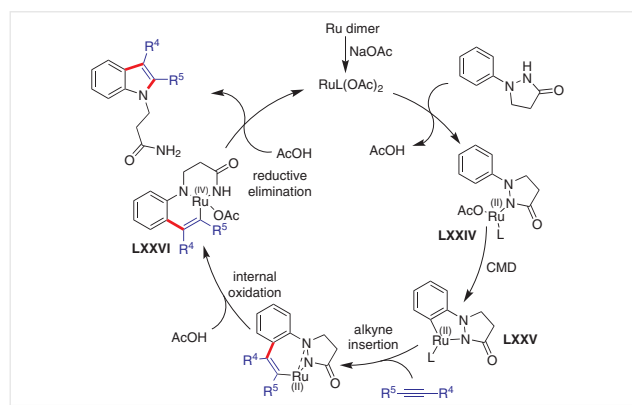
In 2014, Zhang et al. developed a regioselective synthesis of polysubstituted indoles **120** via an Ru-catalyzed redox-neutral C–H activation reaction involving N–N bond cleavage.⁵⁴ The C–H annulation reaction of alkynes **119** was carried out using pyrazolidin-3-one **118** as the internal oxidant as well as the directing group (Scheme 63). The use of ruthenium metal avoided homocoupling of the terminal alkynes, which was a major side reaction when using $\text{Rh}(\text{III})$. Also, the oxidative potential of the N–N bond of the aliphatic hydrazine was not enough to regenerate the $\text{Ru}(\text{II})$ catalyst. So, the authors used cyclic hydrazides with increased ring strain to activate the N–N bond. The designed protocol was effective for a broad range of functional groups on the arene moiety: electron-withdrawing as well as electron-donating substituents were well tolerated. Symmetrical, unsymmetrical and 1-substituted alkynes gave single regioisomers, exclusively. The utility of the developed method was demonstrated by the synthesis of a P2 inhibitor,⁵⁵ a SIRT1 activator⁵⁶ and an NS5B inhibitor.⁵⁷

A plausible $\text{Ru}(\text{II})$ – $\text{Ru}(\text{IV})$ – $\text{Ru}(\text{II})$ catalytic mechanism for the reaction was proposed on the basis of redox-neutral Rh catalysis reported in the literature.⁵⁸ $\text{Ru}(\text{II})$ amido complex **LXXIV** is obtained by initial insertion of the active $\text{Ru}(\text{II})$ acetate into the N–H bond of pyrazolidin-3-one, which undergoes metalation–deprotonation to give **LXXV**. Subsequent alkyne insertion followed by oxidation to $\text{Ru}(\text{IV})$ by the N–N



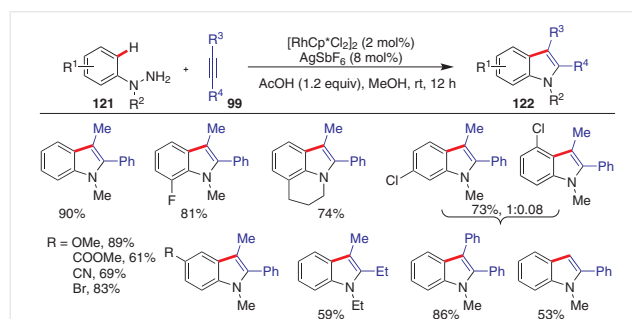
Scheme 63 Ruthenium-catalyzed redox-neutral C–H activation, regioselective synthesis of N-substituted indoles

bond gives **LXXVI**, which upon reductive elimination gives the final product and regenerates the active $\text{Ru}(\text{II})$ catalyst (Scheme 64).



Scheme 64 Proposed catalytic cycle for the synthesis of polysubstituted indole derivatives

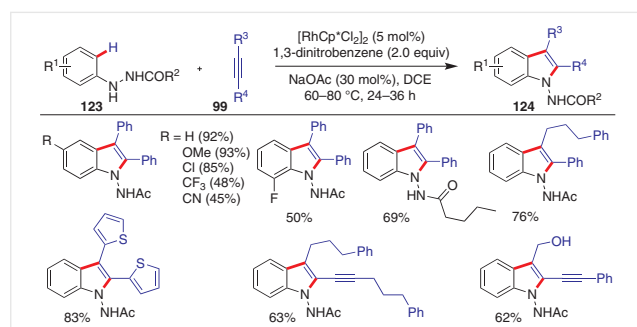
In 2016, Zhou et al. developed a versatile, traceless, $\text{Rh}(\text{III})$ -catalyzed annulation of arylhydrazines **121** and alkynes **99** for the synthesis of indoles **122**, with a very low catalyst loading (0.1 mol%) on gram-scale reactions (Scheme 65).⁵⁹ The *N*-amino-directed C–H alkenylation generated indoles in a step- and atom-economic manner at



Scheme 65 Traceless synthesis of indoles at room temperature

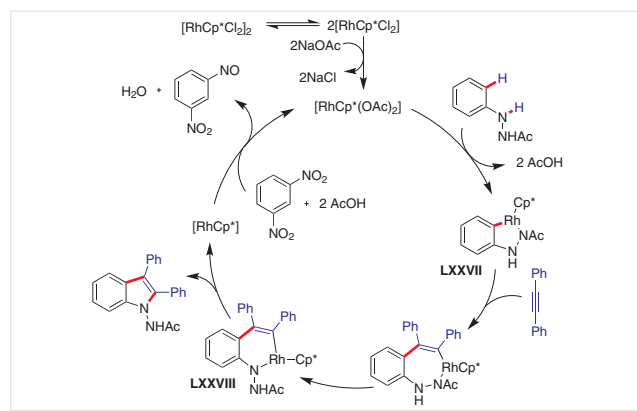
room temperature and showed tolerance toward a broad range of functional groups on the arylhydrazines and alkynes. The room-temperature conditions for the traceless indole synthesis are unexcelled via C–H activation strategy.

In 2014, Liu's group reported the Rh-catalyzed synthesis of 1-aminoindole derivatives **124** via oxidative annulation of hydrazines **123** with alkynes **99** (Scheme 66).⁶⁰ The authors described the use of 1,3-dinitrobenzene as an oxidant in transition-metal-catalyzed C–H activation for the first time.^{58a}



Scheme 66 Oxidative annulations of hydrazines and alkynes to give indoles

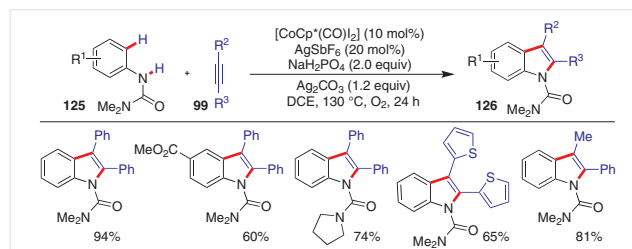
The course of the reaction includes formation of rhodacycle **LXXVII** by insertion of the active metal catalyst into the hydrazine. Alkyne coordination and insertion gives a more stable six-membered intermediate **LXXVIII**, which undergoes internal oxidation to release the indole in the presence of AcOH. The active catalyst is regenerated by the external oxidant, 1,3-dinitrobenzene (Scheme 67).



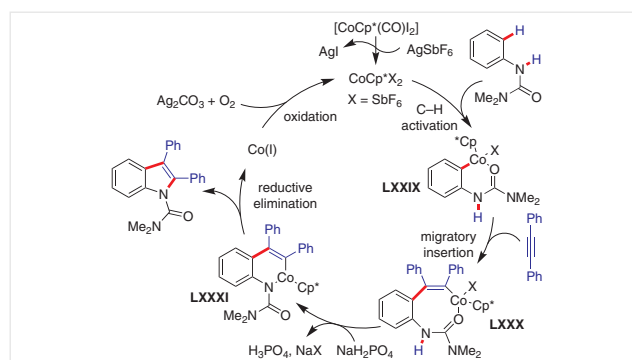
Scheme 67 A plausible reaction mechanism

In 2016, Zhang and co-workers developed a new strategy for the synthesis of indoles **126** via Co(III)-catalyzed oxidative annulations of *N*-arylhyaides **125** and alkynes **99** possessing a broad range of synthetically useful substituents (Scheme 68).⁶¹ However, the strategy is limited to the use of

less electrophilic ureas other than acetamide as the directing groups, and gave the products in good to excellent yields.



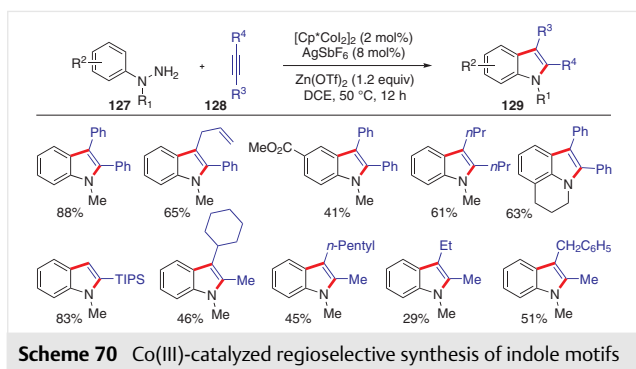
Scheme 68 Co(III)-catalyzed oxidative coupling of *N*-arylhyaides and internal alkynes



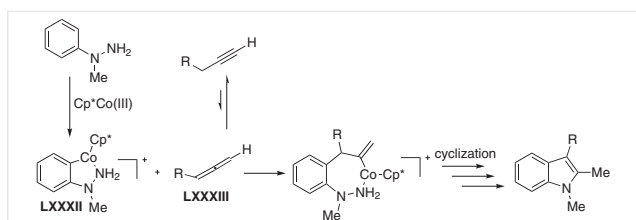
Scheme 69 The catalytic cycle for coupling of *N*-arylhyaides with internal alkynes

A plausible mechanism for the reaction involves the generation of an active cationic Co(III) catalyst followed by irreversible C–H bond activation affording six-membered metallacycle **LXXIX**. Coordination and migratory insertion of the alkyne generates the species **LXXX**, which upon elimination of HX yields intermediate **LXXXI**. Reductive elimination of the C–N bond generates the desired indole along with Co(I), which is further oxidized by silver and oxygen to regenerate the active catalyst (Scheme 69).

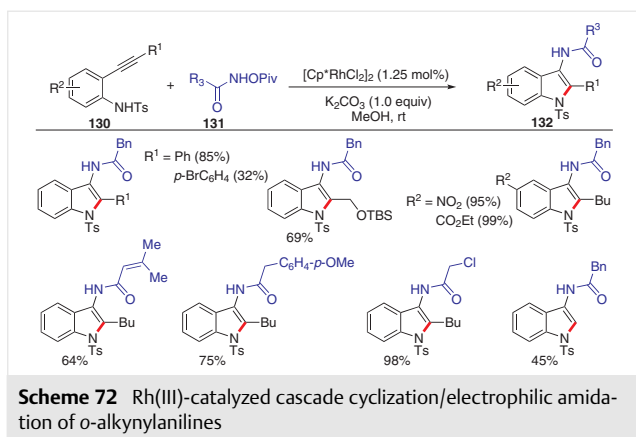
A Co(III)-catalyzed regioselective synthesis of indole motifs **129** was reported by Zhu's group (Scheme 70).⁶² Internal and terminal alkynes **128** were compatible with *N*-aminoaniline derivatives **127** for cyclization. This strategy overcomes the drawbacks of earlier Co(III)-catalyzed redox-neutral methods for indole synthesis including high reaction temperatures, retention of bulky groups in the products and the generation of side products from external oxidants. The method provided the indole skeleton with diverse functional groups in moderate to excellent yields. Both electron-rich and electron-deficient substituents were tolerated, but steric effects played a dictating role in the reaction yield.



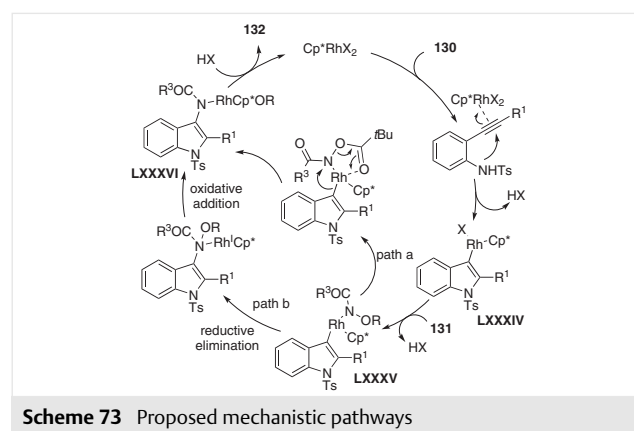
The mechanism of the reaction involves the initial cobaltation of **127** and Co(II)-promoted alkyne–allene isomerization. The insertion of allene **LXXXIII** via the internal C=C bond into five-membered cobaltacycle **LXXXII** followed by cyclization provided the desired product (Scheme 71).



In 2016, Liu reported the synthesis of 3-amidindoles **132** via Rh(III)-catalyzed cascade cyclization/electrophilic amidation of *o*-alkynylanilines **130** (Scheme 72).⁶³ The authors used *N*-pivaloyloxamides **131** as the electrophilic nitrogen source. The developed strategy provided 3-amidindoles under mild conditions with good to excellent yields. Different functional groups present on both reactants were tolerated.



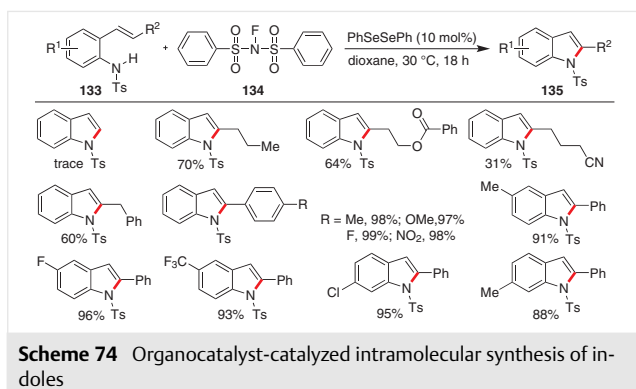
The proposed mechanism of the reaction involves the initial coordination of rhodium with **130**. This makes the triple bond more susceptible to intramolecular nucleophilic attack by nitrogen and generates intermediate **LXXXIV**. The intermediate **LXXXIV** then reacts with **131** to furnish **LXXXV** through deprotonation of **131** and ligand exchange on **LXXXIV**. The expected product can be obtained from **LXXXVI** via two pathways (paths a and b). Path a, involves concerted N–O bond cleavage with C–N bond formation and regeneration of the catalyst. In path b, reductive elimination followed by oxidative addition through pivaloyl group migration generates intermediate **LXXXVI**, which on protonolysis furnishes the indole product (Scheme 73).



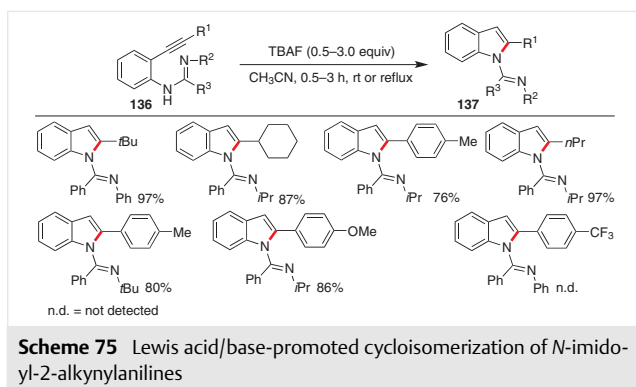
6 Metal-Free 2,3-Disubstituted Indole Synthesis

6.1 *N*-Protected 2,3-Disubstituted Indole Synthesis

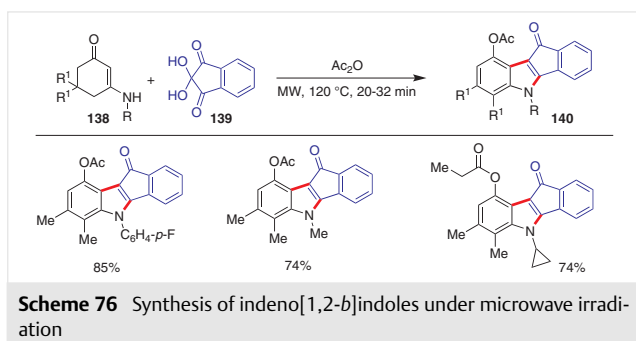
Zhao et al. reported the synthesis of indoles **135** via intramolecular amination (Scheme 74).⁶⁴ They used an organoselenium catalyst under mild conditions and obtained product yields of up to 99%. Polar solvents were ineffective in this transformation and an electron-donating protecting group on the nitrogen disfavored the transformation, probably because the nitrogen of the substrate becomes less nucleophilic, hence preventing attack by the intermediate seleniranium ion. Only a trace amount of the product was obtained when using unsubstituted terminal alkenes. Different substituents on the aromatic ring of the substrate only slightly influenced the nitrogen nucleophilicity and hence the C–H bond amination. Electron-donating Me and electron-withdrawing CF₃ groups at the same position of the benzene ring gave the desired products in high yields (91% and 93%).



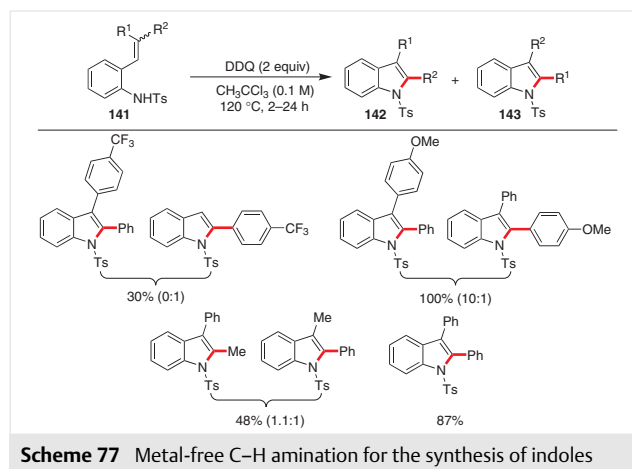
Otani and co-workers examined the Lewis acid- or base-promoted cycloisomerization of *N*-imidoyl-2-alkynylanilines **136** with substituents such as alkyl or aryl.¹³ They described the formation of indole derivatives **137** via a 5-*endo-dig* cyclization mode (Scheme 75).



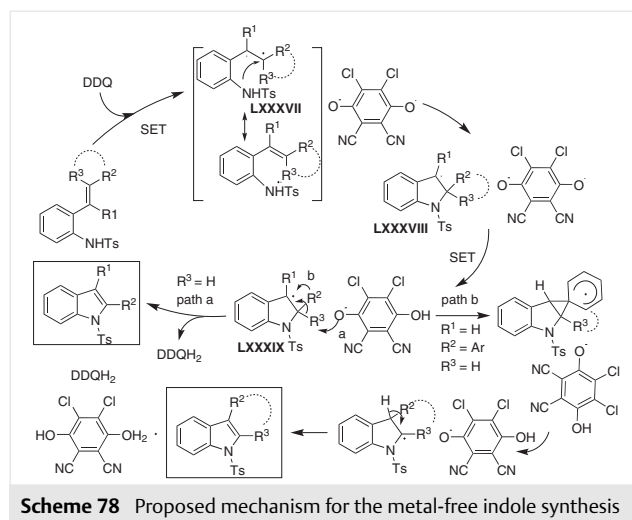
In 2012, Li's group reported the reaction of enaminones **138** with 2,2-dihydroxyindene-1,3-dione (**139**) on heating in acetic anhydride at 120 °C under microwave irradiation conditions. Polyfunctionalized tetracyclic indeno[1,2-*b*]indoles **140** were obtained with different substitution patterns.⁶⁵ This catalytic system showed excellent regioselectivity, short reaction times, mild conditions and good functional group tolerance at the *N*-protected aryl ring of the enaminones **138** (Scheme 76).



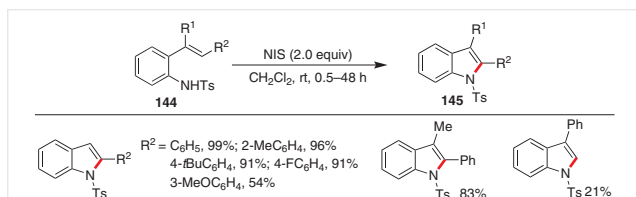
In 2014, Youn's group reported a metal-free synthesis of substituted indoles **142** and **143** via C–H amination of *N*-Ts-2-alkenylanilines **141**.⁶⁶ This method showed broad substrate scope, good functional group tolerance and afforded good to excellent yields of the products. In the case of electron-withdrawing groups [CO₂*n*Bu, CONMe₂, CN, PO(OEt)₂] on the alkene moiety, no product was formed and mostly starting material was recovered. The reactions of β,β-disubstituted 2-alkenylanilines proceeded as expected to generate 2,3-disubstituted indoles, which showed that electron-rich aryl groups migrated preferentially (Scheme 77).



The mechanism of the reaction was proposed after conducting a series of experiments. It was suggested that intramolecular nucleophilic attack by the *N*-tosyl group of **LXXXVII** towards an olefin radical cation generates intermediate **LXXXVIII**. Oxidation of carbon radical of **LXXXVIII** gives the corresponding benzylic carbocation intermediate **LXXXIX**. This was followed by deprotonation to form the product via path a, which is much faster than alternative path b (Scheme 78).

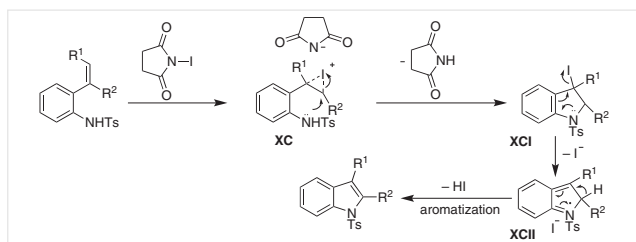


In 2015, Deng's group reported the metal-free synthesis of indoles **145** from *N*-Ts-2-alkenylanilines **144** via a NIS-mediated cascade C–N bond formation/aromatization.⁶⁷ This reaction showed broad substrate scope and provided good to excellent yields under mild reaction conditions (Scheme 79).



Scheme 79 NIS-mediated metal-free indole synthesis

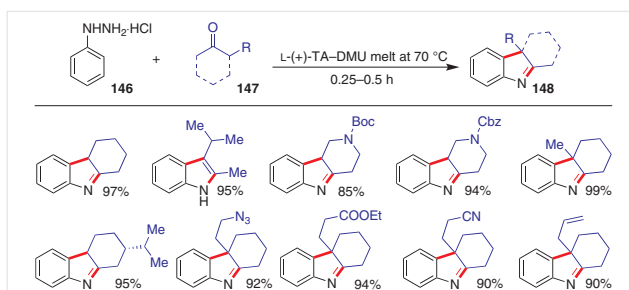
Primarily, the iodonium ion intermediate **XC** is formed as NIS reacts with the substrate alkene, which undergoes intramolecular amination by the amino group to form indoline **XCI**. This is followed by aromatization to form the indole product or 1,2-arylation occurs to form intermediate **XCII**, which after aromatization gives the final product (Scheme 80).



Scheme 80 Proposed mechanistic pathway for the metal-free indole synthesis

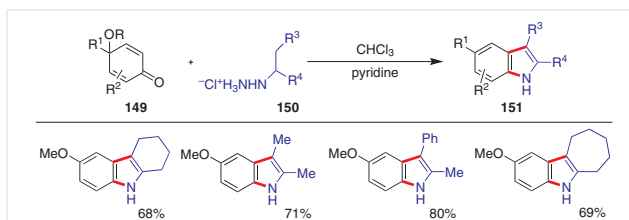
6.2 *N*-Unprotected 2,3-Disubstituted Indole Synthesis

König and co-workers reported the synthesis of functionalized indoles **148** in a tartaric acid–dimethylurea [L-(+)-TA–DMU] melt under solvent- and catalyst-free conditions, starting from phenylhydrazine (**146**) and aldehydes/ketones **147**.⁶⁸ Examination of substrate scope showed that it tolerated sensitive functional groups such as *N*-Boc, *N*-Cbz and azides with excellent yields of products regioselectively. In addition, the method is environmentally benign and applicable for the synthesis of bioactive indoles (Scheme 81).



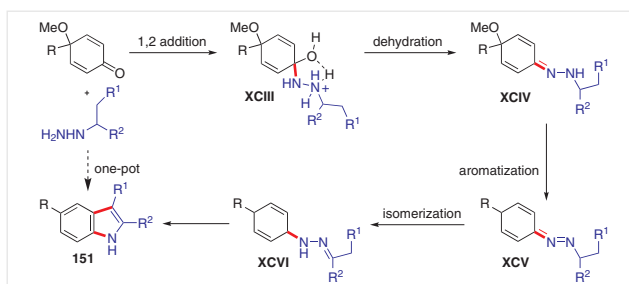
Scheme 81 Fischer indole synthesis in low melting mixtures

Zheng's group reported a one-pot procedure for the Fischer indole synthesis of compounds **151** from quinone monoketals **149** and aliphatic hydrazines **150** in chloroform with two equivalents of pyridine or under microwave conditions.⁶⁹ The method showed good functional group tolerance, broad substrate scope and gave good to excellent yields of the indole products. An unsymmetrical hydrazine gave the cyclization product regioselectively (Scheme 82).



Scheme 82 Synthesis of indoles by condensation of quinone monoketals and aliphatic hydrazines

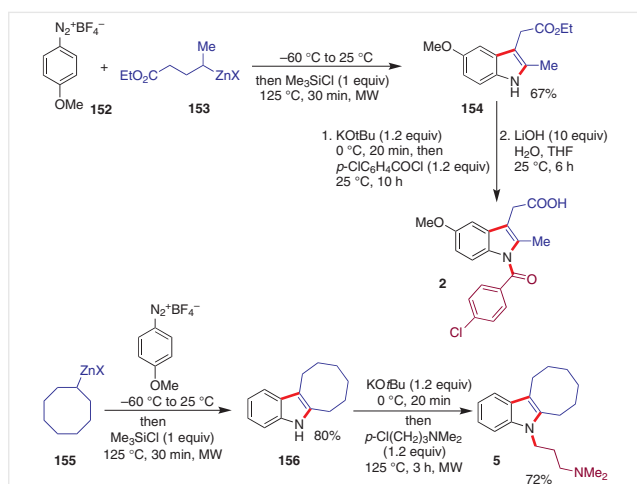
The condensation of quinone monoketals **149** with hydrazines **150** through 1,2-addition gave intermediate **XCIII**, which on dehydration gave intermediate **XCIV**. Subsequent aromatization gave the alkylaryldiazene **XCVI**, which underwent isomerization to afford intermediate **XCVI**. The indole product was obtained after elimination/cyclization process (Scheme 83).



Scheme 83 Proposed mechanism for the Fischer indole synthesis of compounds **151**

7 Applications

Knochel and co-workers successfully synthesized indomethacin (**2**) and iprindole (**5**). Organozinc reagent **153** reacts with aryldiazonium salt **152** to produce the indole **154**, which is further converted into indomethacin (**2**).⁴⁸ Similarly, the reaction of cyclooctylzinc **155** with aryldiazonium salt **152** under standard reaction conditions provides indole **156**, which was *N*-alkylated to generate iprindole (**5**) (Scheme 84).⁴⁸



Scheme 84 The synthesis of indomethacin (**2**) and iprindole (**5**)

8 Summary and Outlook

In this review, we have described the recent progress in the field of the regioselective synthesis of indoles. We have discussed transition-metal-catalyzed methodologies via C–H activation and have also described metal-free approaches for the synthesis of 2,3-disubstituted indoles with mechanisms. Some limitations of the classical Fisher indole synthesis were overcome by applying these new procedures. There is scope for the further development of new methodologies and for improvement of the reaction conditions. Future studies will provide new applications for the synthesis of complex bioactive molecules.

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