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Metal-catalyzed privileged 2- and 3-functionalized indole synthesis*

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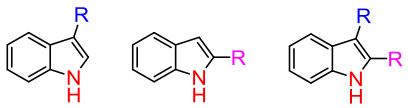


This review summarizes the metal-catalyzed approaches for the synthesis of privileged 2- and 3-functionalized indoles *via* the Fischer indole synthesis, cycloaddition reaction, C–H activation reaction, and coupling reactions. Polycyclic derivatives of indole are also listed including triptamine-based pharmaceutical 5-HT1D agonist L 775,606. Some important mechanism studies are described in details in this review. The review covers literature for the last 20 years.

Keywords: bioactive indole scaffolds, functionalized indole, heterocycles, indole, C–H activation, metal catalysis.

Indole (also called benzopyrrole) is a planar bicyclic molecule in which the benzene ring is fused to the pyrrole ring through C-2 and C-3 atoms. Indole with 10 π-electrons (8 from double bonds and 2 from lone pair of electrons on nitrogen) has aromatic nature according to Huckel's rule. Due to delocalization of excessive π-electrons, indole readily undergoes electrophilic substitution reactions similar to benzene ring. Indoles, like pyrroles, are very reactive with strong acids due to the weak basicity.[1] Indole scaffold has been found in many synthetic drug molecules and exhibit numerous biological activities.[2] Over 10000 biologically active indole derivatives have been identified to date, in which over 200 are currently marketed as drugs or undergoing clinical trials.[3] Among the indole core-containing compounds, 2- and 3-arylindoles appear to be among the most promising lead candidates for drug development. Although numerous examples of 2,3-substituted indole analogs are cited in the literature, there is no comprehensive review focusing on reactions pertaining to privileged positions 2 and 3. They exhibit several potential therapeutic uses[2] as antibacterial, anticancer, antioxidant, anti-inflammatory, antidiabetic, antiviral, antiproliferative, antituberculosis, etc. (Fig. 1).

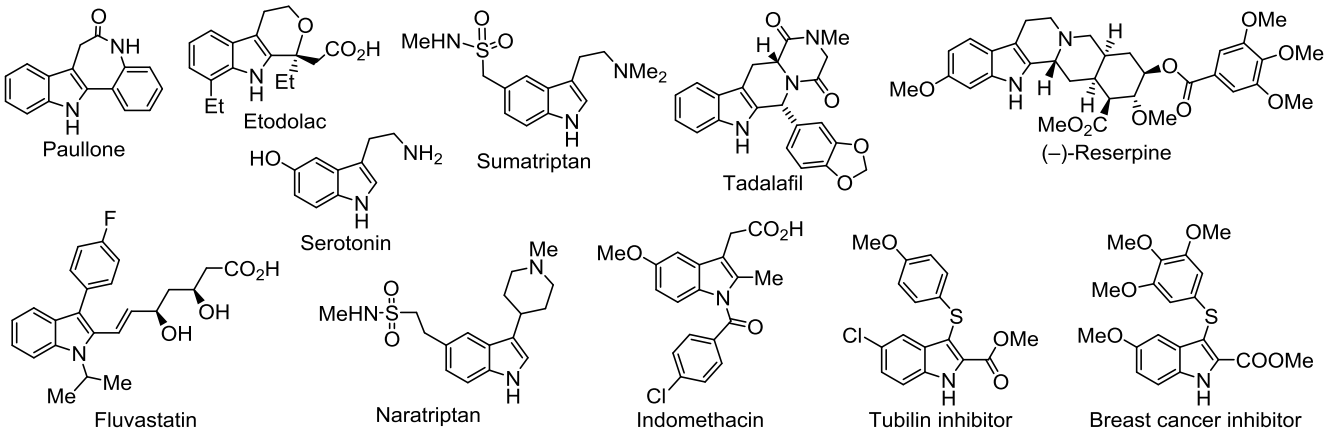


Figure 1. Indole-based drugs and biologically active molecules.

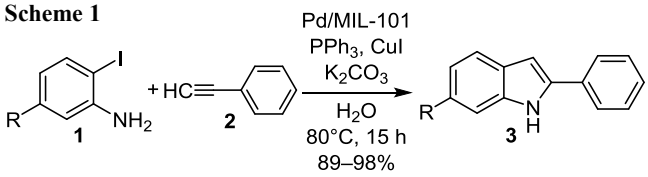
* CDRI Communication No. 9650.

Indole core is important not only in biological and pharmaceutical research, but is also a structural unit of compounds studied by materials science,[4] henceforth referred to as "privileged structure". Due to its vast importance, synthesis of indoles and indole-based heterocycles has attracted great attention of synthetic organic chemists, which has turned into a large number of different synthetic approaches including C–H activation. Thus, while traditional approaches are based on condensation and cyclization sequences,[5] transition metal-catalyzed C–C and C–N bond formation reactions have recently enabled the development of alternative methodologies toward modular indole syntheses. Despite the plentiful collection of available protocols to prepare indoles, the enormous interest in the indole structure results in this research area being continuously active. This review summarizes the metal-catalyzed synthesis of substituted indoles and indole-based fused heterocycles. Due to the biological importance of 2- and 3-substituted indoles, this review offers discussion on synthesis of privileged 2- and 3-substituted indole.

Synthesis of 2-substituted indoles

Li et al. used a hydrothermally stable metal-organic framework, MIL-101-supported metallic Pd nanoparticle catalyst for the synthesis of 2-phenylindoles **3** using substituted 2-iodoanilines **1** and phenylacetylene (**2**) in water (Scheme 1).[6]

Scheme 1



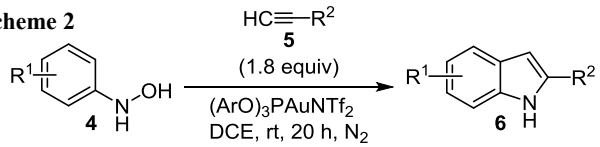
R = H, Me, CN, NO_2, CO_2Me

MIL-101 = $Cr_3F(H_2O)_2O$(benzene-1,4-dicarboxylate terephthalate)$_3$

In this method, authors also showed that Pd/MIL-101 catalyst possesses high stability and can be used repetitively for at least 10 times, showing a good potential for practical application.

Zhang et al. for the first time reported 2-substituted indole synthesis by gold catalysis *via* the addition of *N*-arylhydroxylamines **4** to aliphatic terminal alkynes **5** (Scheme 2).[7] This mild gold catalysis occurs *in situ* followed by sequential facile 3,3-rearrangement and cyclodehydration, affording 2-alkylindoles **6** regiospecifically with typically good yields and under exceptionally mild reaction conditions.

Scheme 2

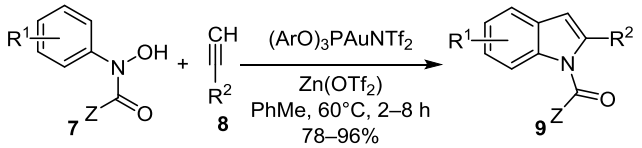


R^1 = H, Me, Br, F, Cl, CO_2Me; R^2 = Cy, cyclopentyl, $(CH_2)_2Ph$, $(CH_2)_2OBn$, $(CH_2)_2OTHP$, $(CH_2)_4Cl$, $(CH_2)_4CO_2H$, $(CH_2)_9Me$

Proposed mechanism of the reaction is depicted in Scheme 3. Nucleophilic attack of hydroxylamine on alkyne is followed by 3,3-rearrangement and cyclodehydration, affording 2-alkylindoles regiospecifically.

In 2013, Zhang et al. disclosed a mild and an efficient synthesis of *N*-protected 2-substituted indoles from *N*-arylhydroxamic acids or *N*-aryl-*N*-hydroxycarbamates **7** and a variety of alkynes **8** *via* cooperative gold and zinc catalysis (Scheme 4).[8] The Zn catalysis is similar to the related zinc ion catalysis in metalloenzymes such as human carbonic anhydrase II and substantially enhances the nucleophilicity of *N*-acylated hydroxylamine by forming the corresponding Zn chelates. The Zn chelates can attack Au-activated alkynes to form *O*-alkenyl-*N*-arylhydroxamates, which can undergo facile 3,3-sigmatropic rearrangement and subsequent cyclodehydration to yield indole products **9**. This reaction is regiospecific, it offers 2-substituted indoles and tolerates a range of functional groups. This reaction also works with internal alkynes of moderate steric demand, and the regioselectivity can be controlled both by steric and/or by electronic effects: the small substituent on the C–C triple bond ends up selectively at the indole C-2 position, and the electron-withdrawing groups direct the substituents to the indole C-3 position *via* either induction or conjugation.

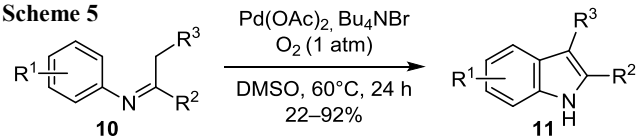
Scheme 4



Z = O*t*-Bu, OMe, Me; R^1 = H, Me, OMe, Cl, F, Br, CO_2Me; R^2 = Cy, cyclopentyl, cyclopropyl, $(CH_2)_2Ph$, $(CH_2)_2OBn$, $(CH_2)_3Cl$, $(CH_2)_4OTIPS$, $(CH_2)_4CO_2Me$, $(CH_2)_9Me$

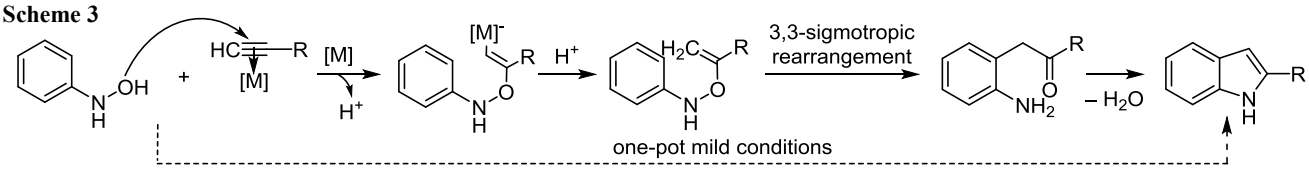
Yoshikai et al. report an operationally simple, mild, and scalable Pd-catalyzed aerobic oxidative cyclization reaction of *N*-arylimines **10**, affording indoles **11** *via* the oxidative linkage of two C–H bonds under mild conditions using molecular oxygen as the sole oxidant (Scheme 5).[9] This process allows quick and atom economical assembly of

Scheme 5



R^1 = H, MeO, CF_3, CN; R^2 = *t*-Bu, Ph, 4-Py, 2-BrC_6H_4, 3-CNC_6H_4, 4-CNC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, CH=CHPh, cyclopropyl, 2-furanyl; R^3 = H, Me

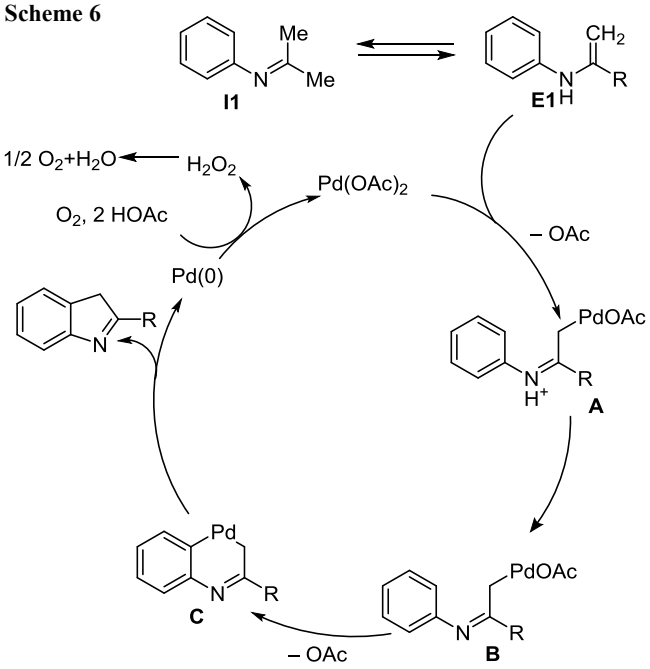
Scheme 3



indole rings from inexpensive and readily available anilines and ketones and tolerates a broad range of functional groups.

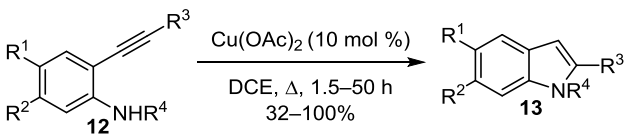
Reaction mechanism can be represented as follows (Scheme 6): enamine **E1** generated *via* tautomerization of imine **I1** would be electrophilically attacked by $Pd(OAc)_2$ forming intermediate **A**, followed by elimination of HOAc to give a palladated imine intermediate **B**. Intermediate **B** would then undergo intramolecular aromatic C–H palladation to give a six-membered palladacycle **C**. Subsequent reductive elimination affords indole and Pd(0).

Scheme 6



In 2004, Hiroya et al. developed an efficient method for the synthesis of indoles **13** form alkynes **12** catalyzed by Cu(II) salts (Scheme 7).[10] This method is suitable for both electron-withdrawing and position 2 of indoles. In this method, $Cu(OCOCF_3)_2$ showed good activity for primary aniline derivatives, while $Cu(OAc)_2$ was a good catalyst for the cyclization of secondary anilines.

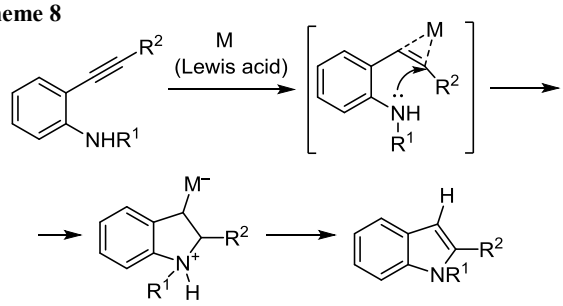
Scheme 7



R^1= H, Me, Br, CN; R^2= H, OMe
R^3= H, Bu, *t*-Bu, Ph, CH_2OH, CO_2Me, TMS; R^4= Ms, Ts

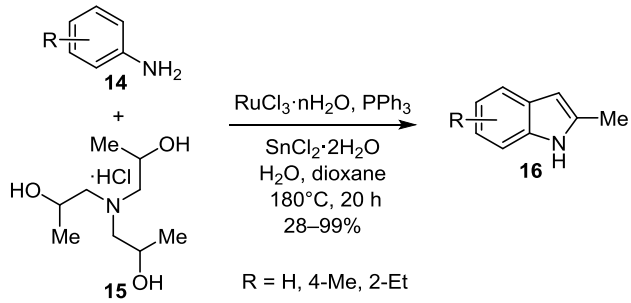
Proposed mechanism of this reaction is on Scheme 8. First, the triple bond is activated by Lewis acid which should not form a strong complex with the nitrogen atom, afterwards the nucleophilic attack of nitrogen on activated triple bond, followed by oxidative indole formation, takes place.

Scheme 8



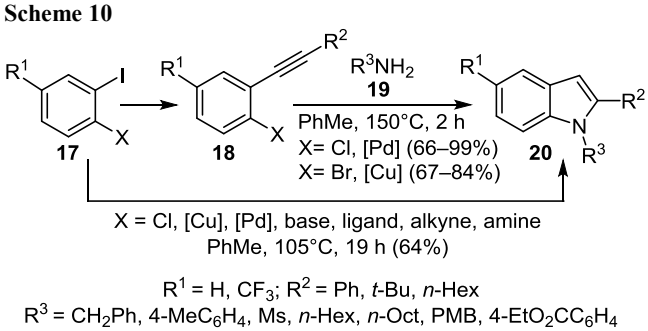
Shim et al. reported a method, in which anilines **14** react with trialkanolammonium chlorides **15** in aqueous media (H_2O, dioxane) at 180°C in the presence of a catalytic amount of ruthenium(III) chloride hydrate and triphenylphosphine together with tin(II) chloride dihydrate to afford the corresponding indoles **16** in good to exellent yields (Scheme 9). [11]

Scheme 9



In 2004, Ackermann reported a highly flexible and efficient synthesis of indole backbone **20** starting from *o*-alkynylhaloarenes **18**, synthesized from the corresponding iodides **17**, and amines **19** (Scheme 10).[12] These transformations proceed *via* a palladium- or a copper-catalyzed amination reaction and a subsequent cyclization in good to excellent yields. Furthermore, a multicatalytic one-pot indole synthesis starting from *o*-chloroiodobenzene is viable using a single catalyst consisting of an *N*-heterocyclic carbene palladium complex and CuI.

Scheme 10

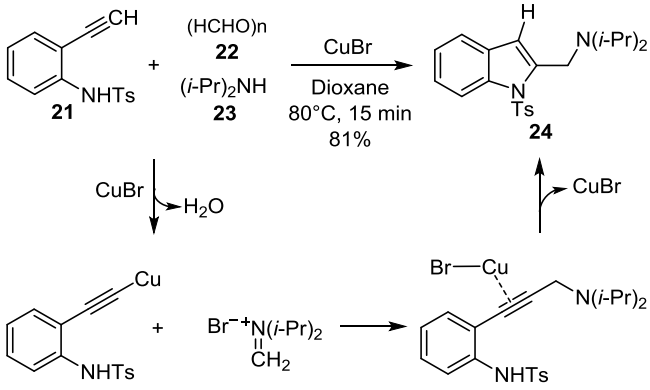


R^1 = H, CF_3; R^2 = Ph, *t*-Bu, *n*-Hex
R^3 = CH_2Ph, 4-MeC_6H_4, Ms, *n*-Hex, *n*-Oct, PMB, 4-$EtO_2CC_6H_4$

Fujii et al. have reported a novel domino three-component coupling reaction for the synthesis of 2-aminomethylindoles **24** and polycyclic indole derivatives starting from acetylene **21**, paraformaldehyde (**22**), and diisopropylamine (**23**) (Scheme 11).[13] This reaction is catalytic

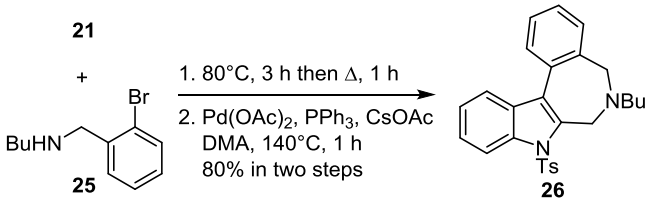
multicomponent construction of an indole ring that produces water as the only by-product. This domino reaction goes *via* two C–N and one C–C bonds formation.

Scheme 11



This method is applicable for the synthesis of functionalized 2-aminomethylindoles and, for example, polycyclic derivative **26** directly from readily available *N*-protected ethynylaniline **25** and acetylenes **21** (Scheme 12).

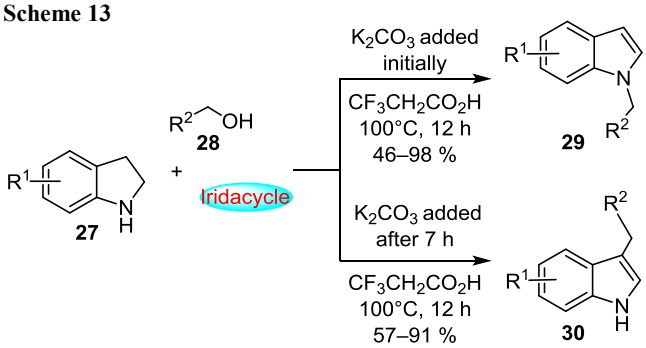
Scheme 12



Synthesis of 3-substituted indoles

Wang et al. reported iridium-catalyzed protocol for synthesis of both *N*-alkylated **29** and 3-alkylated **30** indoles selectively *via* dehydrogenative coupling of indolines **27** with alcohols **28**,[14] by simple changing the addition time of a base (Scheme 13). The iridacycle catalyst plays multiple roles in these reactions, namely, dehydrogenates both amines and alcohols and catalyzes the coupling reactions.

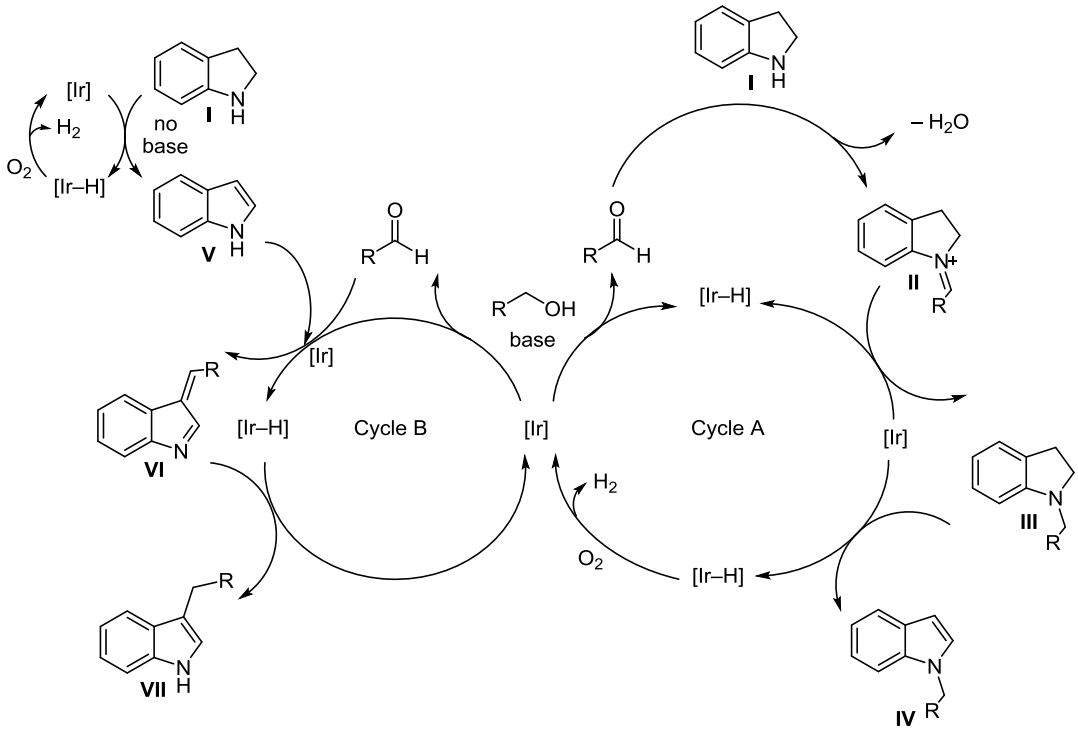
Scheme 13



R^1 = H, Cl, Me, OMe; R^2 = Me, Et, *i*-Pr, $(CH_2)_2Me$, $(CH_2)_3Me$, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-$CF_3C_6H_4$, $(CH_2)_2Ph$, *i*-Pr, CH_2*i*-Pr, $(CH_2)_3OH$, $(CH_2)_4OH$

Mechanism of both catalytic cycles – *N*-alkylation (cycle A) and 3-alkylation (cycle B) have been proposed by the authors (Scheme 14).[14] Cycle A describes the formation of *N*-substituted indole **IV** from indoline **I** and alcohol *via* aldehyde and iminium intermediate **II**. In this cycle, the iridium hydride, which is formed from the dehydrogenation of an alcohol in the presence of a base, reduces the iminium intermediate **III**, which is then dehydrogenated by the

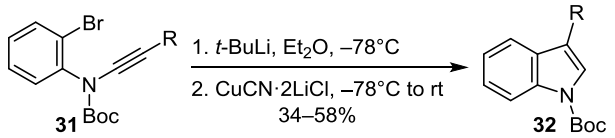
Scheme 14



iridium catalyst to give *N*-substituted indole **IV**. Cycle B explains the formation of 3-substituted indole **VII** *via* the intermediacy of indole **V** and an aldehyde. In the absence of a base, indoline **I** is dehydrogenated to unsubstituted indole **V**, which then reacts with the aldehyde under iridium catalysis to afford intermediate **VI**, which is then transformed into 3-substituted indole **VII** by the iridium hydride.

A modular indole synthesis *via* an intramolecular 5-*endo-dig* carbocupration starting from readily available *N*-arylynamides **31** is reported by Evano et al. (Scheme 15).[15] A variety of ynamides are converted to indoles **32** in moderate to good yields and with varying substitution pattern on the indole ring. This further extends the synthetic utility of ynamides in organic synthesis and provides additional insights in the use of intramolecular carbometalation reactions.

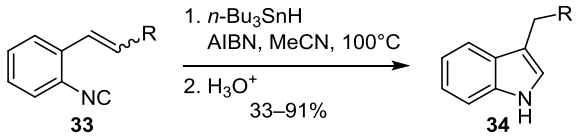
Scheme 15



R = Ph, 4-MeC_6H_4, 2-MeC_6H_4, $CF_3OC_6H_4$, 2-Me, 4-FC_6H_3, 3,4-$Cl_2C_6H_3$, 2-$CF_3C_6H_4$, 4-FC_6H_4, CH=CHPh, *t*-Bu, *n*-Pr, TIPS

Peng et al. reported a method for the synthesis of 3-substituted indoles **34** by treatment of isonitriles **33** with tributyltin hydride and catalytic amount of AIBN in high yields (Scheme 16).[16]

Scheme 16

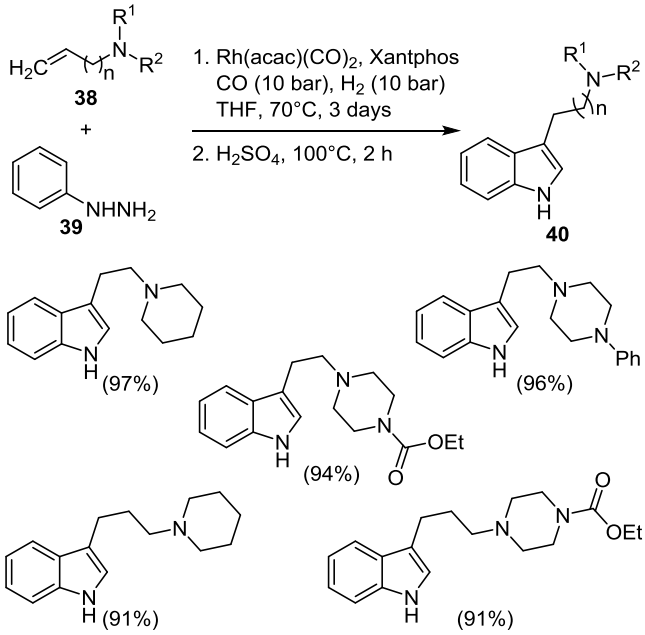


R = *n*-Bu, CO_2Me, CH_2OTHP, CH_2OBn, Ph

A new approach for regioselective synthesis of 3-substituted indoles **37** employing the air- and moisture-stable reagent Cp_2TiCl_2 is described by Buchwald et al. (Scheme 17).[17] This reaction proceeds *via* first intermolecular insertion reactions of an olefin and a titanocene-stabilized benzyne complex and then Pd-catalyzed arylamination reaction of aryl bromide **35**, through *N*-substutited indole **36**. The simplicity and availability of the requisite starting materials gives this method a broad scope for the preparation of polysubstituted indoles.

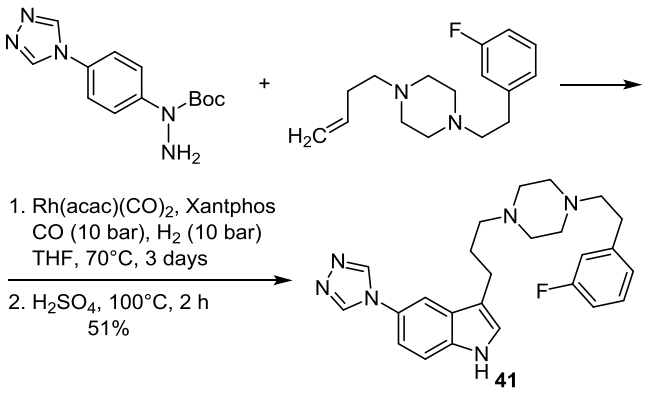
Eilbracht et al. reported a tandem hydroformylation/Fischer indole synthesis with high selectivity starting from aminoolefins **38** and phenylhydrazine (**39**) (Scheme 18).[18] In many cases the obtained products **40** did not require further purification.

Scheme 18

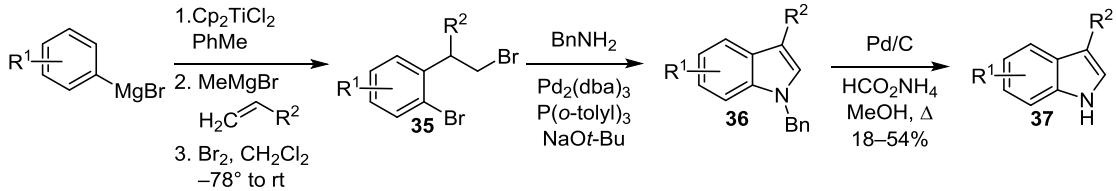


This new modular, simpler, and diversity-oriented approach allowed synthesis of branched and nonbranched tryptamines, as well as tryptamine-based pharmaceuticals such as the 5-HT1D agonist L 775,606 **41** (Scheme 19).[18] With this methodology drug candidates can be synthesized more conveniently than with previously reported methodologies.

Scheme 19



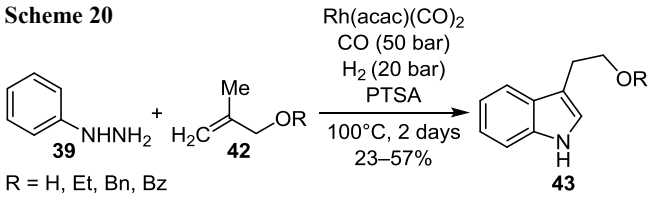
Scheme 17



R^1 = Me, OMe, Ph; R^2 = H, Bu, $(CH_2)_3OTIPS$, $CH_2CH(Ph)OTIPS$

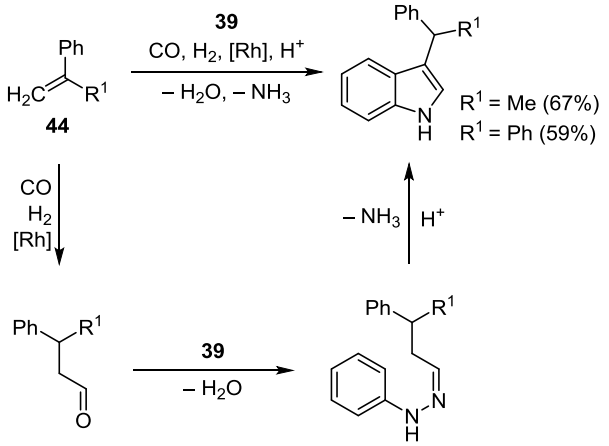
A novel one-pot synthesis of indole systems *via* tandem hydroformylation/Fischer indole synthesis starting from olefins **42** and phenylhydrazine (**39**) is reported by Eilbracht et al. (Scheme 20).[19] This tandem procedure leads directly to 3-substituted indoles **43**.

Scheme 20



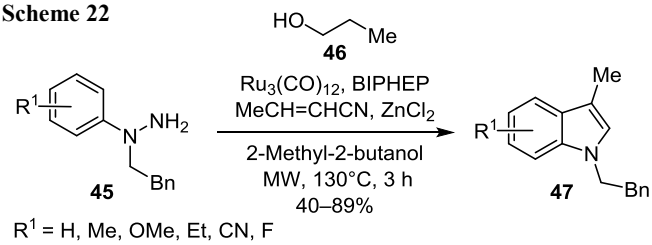
Mechanism of the reaction is as follows (Scheme 21). First, *in situ* generation of aldehyde from compound **44**. Then aldehyde forms arylhydrazones after reaction with phenylhydrazine, and following [3,3]-sigmatropic rearrangement gives the final products.

Scheme 21



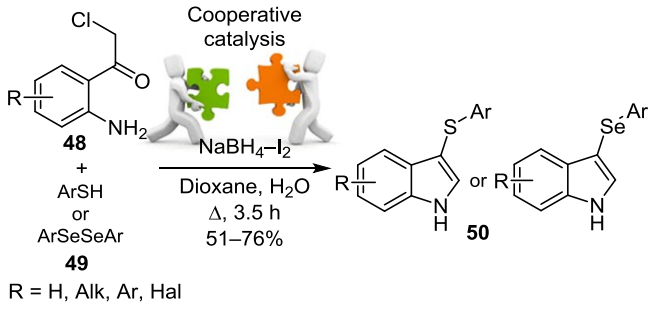
Taddei and coworkers reported a simple, convenient, and efficient new version of the Fischer indole synthesis (Scheme 22).[20] In this reaction, primary (compound **46**) or secondary alcohols have been catalytically oxidized in the presence of phenylhydrazines **45** to give the corresponding indoles **47**. The overall reaction can be accomplished in one step. The most remarkable advantage of this reaction is the use of alcohols instead of aldehydes or ketones as starting materials, which are easy in handling, lower in toxicity, more stable, and the large selection of commercially available alcohols can be employed. The ability to easily incorporate in the indole ring a further element of molecular diversity, which is subsequently modified, makes this synthetic protocol particularly attractive for increasing the molecular complexity. In addition, microwave irradiation significantly increases the reaction rate and enhances the indole yields.

Scheme 22



Recently, Sinha et al. reported a new strategy to synthesize 3-sulfenyl(selenyl)indoles **50**.[21] In this work, $NaBH_4$–I_2 works as a cooperative catalyst which allows cascade C–N and C–S/C–Se bond formations *via* reduction–nucleophilic cyclization–chalcogenylation, i.e., three steps in one pot. This is regioselective synthesis of diverse 3-chalcogenylindoles, including 5-bromo-3-[(3,4,5-trimetoxyphenyl)sulfanyl]-1*H*-indole, a known lead anticancer compound, directly from 2-aminophenacyl chlorides **48** and thiophenols or disulfides(diselenides) **49** in aqueous dioxane under metal-free conditions (Scheme 23).

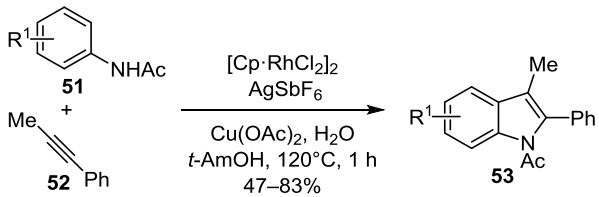
Scheme 23



Synthesis of 2,3-substituted indoles

Fagnou et al. reported a method for indole synthesis *via* Rh-catalyzed oxidative coupling of acetanilide **51** and internal alkyne **52** leading to 2,3-substituted indoles **53** (Scheme 24) and described the preliminary mechanistic studies based on the known ability of *N*-acetylanilines to undergo *ortho* metalation.[22]

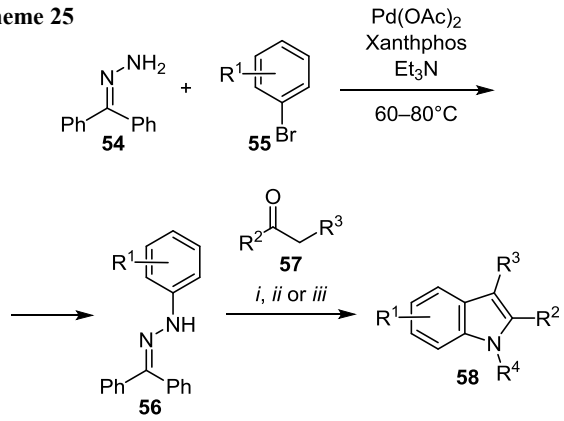
Scheme 24



Buchwald et al. reported a Pd-catalyzed method for the preparation of *N*-arylbenzophenone hydrazones **56** which were converted to substituted indole products in good yield *via* an *in situ* hydrolysis/Fischer cyclization protocol (Scheme 25).[23] This methodology provides an opportunity for the preparation of a structurally diverse set of indoles **58** from simple, commercially available precursors **54**, **55**, and **57**.

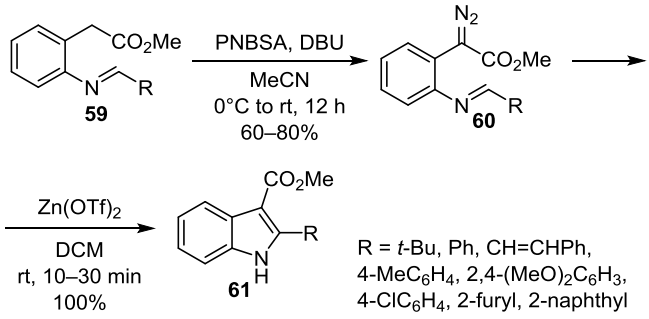
Doyle et al. reported a Lewis acid-catalyzed cyclization of methyl phenyl diazoacetates **60** with an *ortho*-imino group, prepared from *o*-aminophenylacetic acid esters **59**, to give 2,3-substituted indoles **61** in quantitative yields (Scheme 26).[24] This reaction conditions are mild, and

Scheme 25



R^1 = H, Me, OMe, Cl, Br
R^2 = H, Me, Ph, CN, Cl
R^3 = Me, Et, *n*-Pr, *n*-Pent, CH_2CO_2Et
for R^4 = Ar *i*: 1. [Pd], R^4X; 2. H^+, H_2O (68–90%)
for R^4 = Alk *ii*: 1. LDA; 2. R^4X; 3. H^+, H_2O (10–86%)
for R^4 = H *iii*: TsOH·H_2O, EtOH, Δ (5–95%)

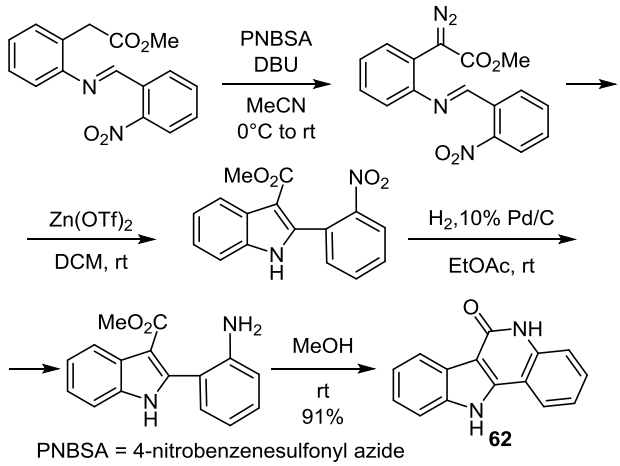
Scheme 26



product yields are good under low catalyst loading with inexpensive, commercially available Lewis acids.

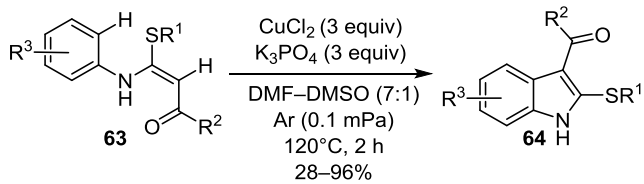
The method is very useful for the synthesis of biologically active and naturally occurring indole derivatives like indoloquinolin-2(1*H*)-one **62** (Scheme 27).

Scheme 27



Yu et al. reported a $CuCl_2$-mediated synthesis of 3-acyl-2-alkylsulfanylindoles[25] **64** using oxoketene *N*,*S*-acetals **63** *via* intramolecular C−H/C−H cross-dehydrogenative coupling (CDC) (Scheme 28). Tunable C−S bond transformations of the resultant indoles led to highly functionalized *N*-heterocyclic compounds. A β-alkylsulfanyl group is necessary to activate the *N*,*S*-acetal substrate and enable the CDC reaction to occur, and the relevant mechanism studies revealed that the CDC reaction follows a radical pathway.

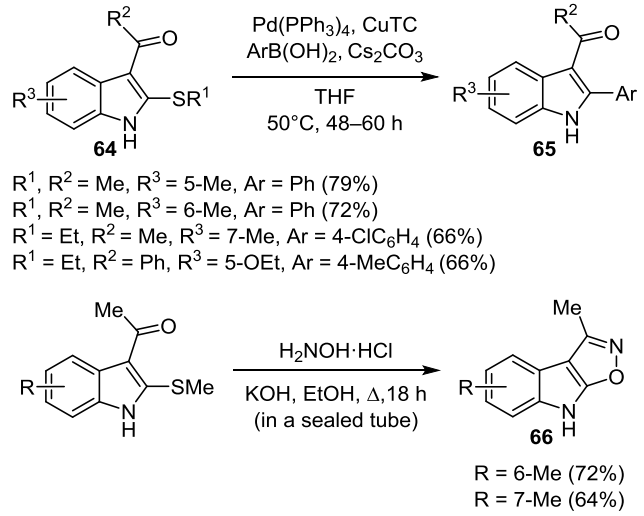
Scheme 28



R^1 = Me, Et; R^2 = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 3-ClC_6H_4, 3-BrC_6H_4; R^3 = H, F, Cl, Me, OMe, OEt

In this paper, authors also reported a method for functionalization of 3-acyl-2-alkylsulfanylindoles **64** in the presence of a base and Pd catalyst *via* Suzuki reaction to give 3-acyl-2-alkylsulfanylindoles **65** in good yields. In order to show the potential of further functionalization, 3-acyl-2-alkylsulfanylindoles were converted to cyclized products **66** (Scheme 29).[25]

Scheme 29

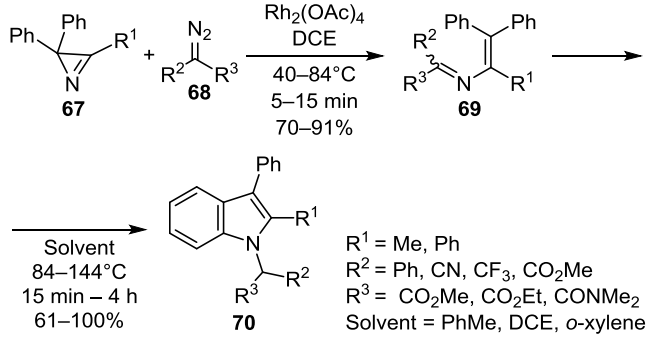


R^1, R^2 = Me, R^3 = 5-Me, Ar = Ph (79%)
R^1, R^2 = Me, R^3 = 6-Me, Ar = Ph (72%)
R^1 = Et, R^2 = Me, R^3 = 7-Me, Ar = 4-ClC_6H_4 (66%)
R^1 = Et, R^2 = Ph, R^3 = 5-OEt, Ar = 4-MeC_6H_4 (66%)

R = 6-Me (72%)
R = 7-Me (64%)

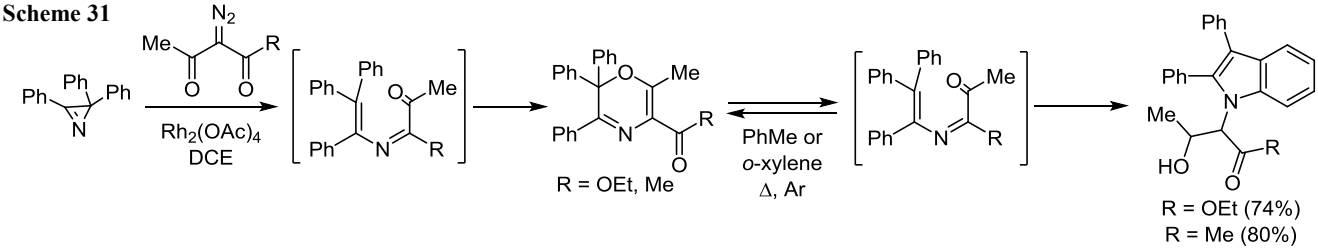
A $Rh_2(OAc)_4$-catalyzed reactions of diazocarbonyl compounds **68** with 2*H*-azirines **67** *via* 2-azabuta-1,3-diene intermediates **69** giving substituted indoles **70** are reported by Yufit et al. (Scheme 30).[26]

Scheme 30



R^1 = Me, Ph
R^2 = Ph, CN, CF_3, CO_2Me
R^3 = CO_2Me, CO_2Et, $CONMe_2$
Solvent = PhMe, DCE, *o*-xylene

Scheme 31

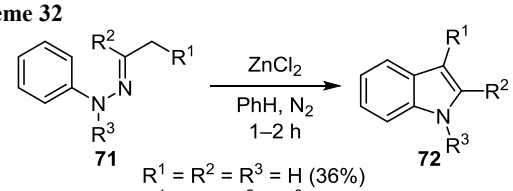


This reaction is dependent on the nature of substituents. 4,4-Diphenyl-2-azabuta-1,3-dienes with two electron-acceptor substituents at position 1 undergo thermal 1,5-cyclization to give indoles in good yields. The increase in electron-withdrawing ability of these substituents facilitates the reaction that proceeds *via* pseudopericyclic 1,5-electrocyclization of 2-azabutadiene into indolium ylide followed by prototropic shift.

The reaction of 2,3-diphenyl-2*H*-azirine and diazo compounds gives 3,4-diphenyl-2-azabuta-1,3-dienes, followed by 2*H*-1,4-oxazine formation in place of indoles *via* rapid 1,6-cyclization due to the *trans* configuration of the 4-phenyl group and the nitrogen (Scheme 31). Authors proved that at elevated temperatures 2*H*-1,4-oxazines can reversibly produce azadiene tautomer, which, in turn, can undergo 1,5-cyclization to indole derivative. Authors have done mechanistic studies and DFT calculations.

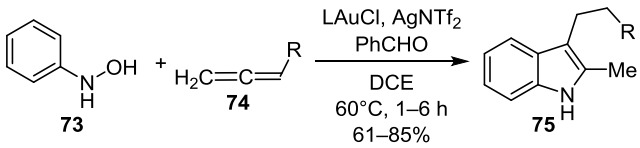
Yamamoto et al. reported direct synthesis of substituted indoles **72** from aryl hydrazones **71** by the Fischer indole synthesis (Scheme 32).[27] The Fischer indole syntheses have been regarded as the most versatile methods for the preparation of indoles.

Scheme 32



A Au-catalyzed syntheses of 2,3-disubstituted indole derivatives **75** from *N*-hydroxyaniline (**73**) and allenes **74** are described by Liu et al. (Scheme 33),[28] this reaction requires benzaldehyde as an additive to generate nitrones and water *in situ*. The control experiments indicate that

Scheme 33



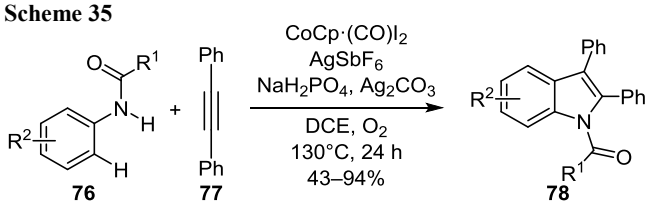
L = P(*t*-Bu)$_2$(*o*-biphenyl)
R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-thienyl, 3-thienyl, OBn, OTHP, NO$_2$, OCOPh

nitrones and water were indispensable in the reactions whereas *N*-hydroxyaniline alone was inactive nucleophile.

Plausible reaction mechanism of Au-catalyzed synthesis of 2,3-disubstituted indoles **75** is depicted in Scheme 34. First, *N*-hydroxyaniline reacts with benzaldehyde to give nitrone that attacks the Au-π-allene to form an allylgold species. This allylgold species is inactive toward [3+2] nitrone/allene cycloaddition because of the lack of an activation group on allene or nitrone, instead the newly generated water hydrolyzes the iminium group, further giving enol ether accompanied by a loss of LAu$^+$ and benzaldehyde. This enol ether species is expected to undergo a 3,3-sigmatropic rearrangement to form an aniline intermediate bearing a tethered ketone, which ultimately forms indole through an intramolecular cyclization.

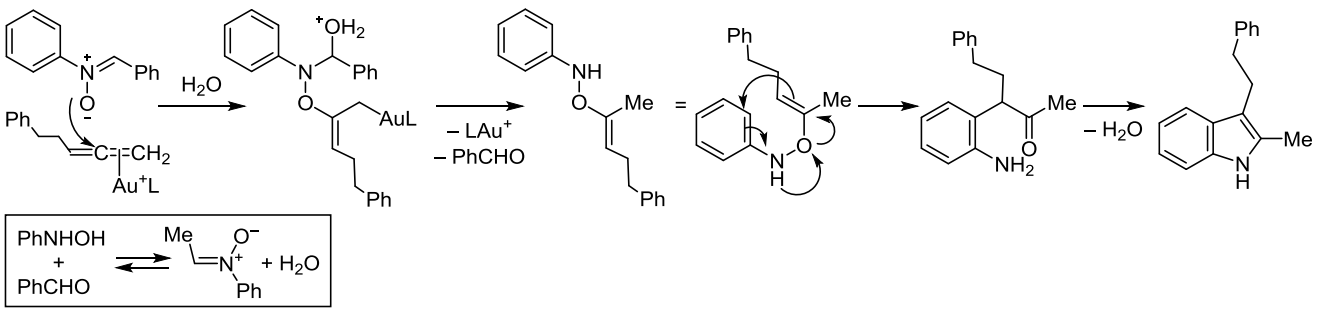
Shi et al. reported a mild Co(III)-catalyzed oxidative annulation of *N*-arylureas **76** and internal alkyne **77** for the synthesis of diverse indoles **78** (Scheme 35).[29] The use of less electrophilic ureas rather than acetamides as directing

Scheme 35



R^1 = NMe$_2$, tetrahydropyrrole; R^2 = H, Me, F, Br, Cl, OMe, CO$_2$Me

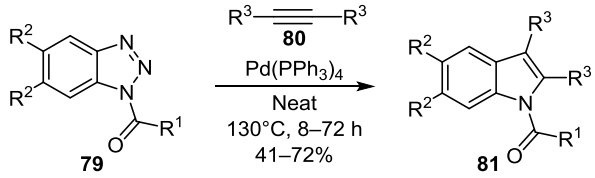
Scheme 34



groups is crucial for the reaction. A broad range of synthetically useful functional groups are compatible with this reaction. This reaction proceeds under mild conditions providing a straightforward access to diverse indoles. In addition, when unsymmetrical internal alkynes were employed, the annulation adducts obtained with high regioselectivity.

Terada et al. reported Pd-catalyzed denitrogenative [3+2] cycloaddition of *N*-aroylbenzotriazoles **79** and internal alkynes **80** producing the corresponding polysubstituted indoles **81** in good to high yields (Scheme 36).[30] The present results suggest that benzotriazoles can be synthetic equivalents of 2-haloanilides in Pd-catalyzed reactions. This reaction is free from the use of bases and formation of nitrogen as by-product, the present methodology gives an opportunity to synthesize polysubstituted indoles **81** in an efficient and atom economic manner.

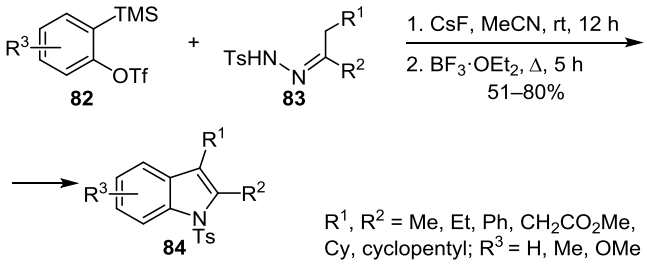
Scheme 36



R^1 = Me, OEt, Ph, 4-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 3-FC_6H_4, 4-$MeOC_6H_4$, 4-AcC_6H_4; R^2 = H, Me, OMe, CN; R^3 = H, Me, *n*-Pr, *n*-Bu, Ph, $(CH_2)_3OAc$, $(CH_2)_3OMOM$, $(CH_2)_3OTBS$

A new approach to the classic Fischer indole synthesis is reported by Greaney et al. (Scheme 37).[31] The addition of *N*-tosylhydrazones **83** to arynes, generated through fluoride activation of precursors **82**, in presence of Lewis acid affords *N*-tosylindole products **84** *via* Fischer cyclization. The procedure requires no transition metal catalysis and compliments the existing syntheses that form the aniline C–N bond of the indole heterocycle.

Scheme 37

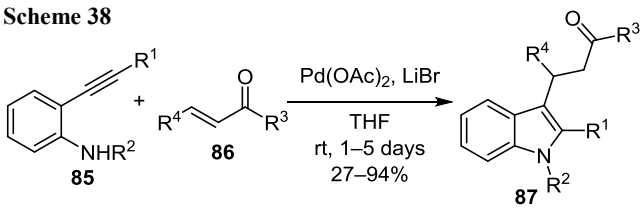


R^1, R^2 = Me, Et, Ph, CH_2CO_2Me, Cy, cyclopentyl; R^3 = H, Me, OMe

Lu et al. reported an efficient method for the synthesis of 2,3-disubstituted indoles **87** with high selectivity from 2-ethynylaniline derivatives **85** and unsaturated carbonyl compounds **86** (Scheme 38).[32] This Pd(II)-catalyzed reaction proceeds through tandem intermolecular aminopalladation, olefin insertion, and protonolysis of the C–Pd bond with the regeneration of Pd(II) species in the presence of halide ions.

A Rh(III)-catalyzed cyclization of *N*-nitrosoanilines **88** with alkynes **89** *via* C–H activation-based intermolecular redox-neutral strategy for streamlined synthesis of indoles

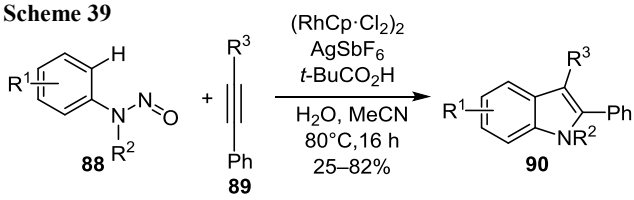
Scheme 38



R^1 = H, n-Bu, CH_2OMe, TMS, Ph; R^2 = H, Ts, Ms, Ac, $COCF_3$
R^3, R^4 = H, Me

90 is reported by Zhu et al. (Scheme 39).[33] The synthetic protocol features a distinct internal oxidant, N–N bond, as a reactive handle for catalyst turnover, as well as a hitherto tantalizingly elusive intermolecular redox-neutral manifold, predicated upon C–H activation, for the formation of a five-membered aza heterocycle.

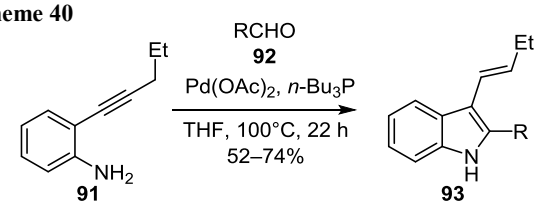
Scheme 39



R^1 = H, Me, OMe, Cl, F, Br; R^2 = Me, Et, $(CH_2)_2CN$
R^3 = Et, Ph, allyl, COMe, CO_2Me

Yamamoto et al. reported a method for the synthesis of substituted indoles **93** *via* Pd-catalyzed intramolecular cyclization of alkyne and *in situ* formed imine functional groups of compound **91** and aliphatic secondary aldehydes **92** (Scheme 40).[34]

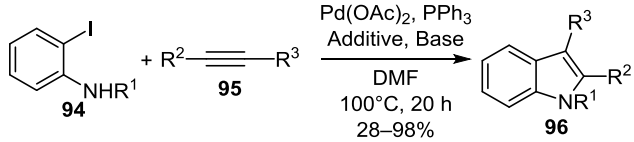
Scheme 40



R = Cy, CH(Me)Ph, $CHMe_2$, $CHPh_2$

Pd-catalyzed coupling of 2-iodoaniline or the corresponding *N*-methyl, acetyl, and tosyl derivatives **94** with a wide variety of internal alkynes **95** for the regioselective synthesis of 2,3-disubstituted indoles **96** in good to excellent yield is reported by Refvik et al. (Scheme 41).[35] This process is quite general and applicable for the synthesis of different types of substituents which can be

Scheme 41



R^1 = H, Me, Ac, Ts; R^2 = Et, *n*-Pr, *i*-Pr, t-Bu, TMS, Cy, CMe_2OH, CH_2OH, $(CH_2)_2OH$, Ph, $CH_2CH(OH)Me$, $CH(OEt)_2$;
R^3 = Me, Et, Ph, CH_2OH, CMe_2OH, $C(Me)=CH_2$, *n*-Pr, *n*-Bu;
Additive = LiCl, *n*-Bu_4NCl; Base = K_2CO_3, Na_2CO_3, KOAc, NaOAc

accommodated on the aniline nitrogen and the two ends of the alkyne. This methodology readily affords 2-silyl-indoles, which can be easily protodesilylated, halogenated, or reacted with alkenes and $Pd(OAc)_2$ to produce 3-substituted indoles, 2-haloindoles, or 2-(1-alkenyl)indoles, respectively. The presence of an alcohol group in the alkyne seems to have a particularly strong directing effect, due to coordination with palladium.

The present review has provided a comprehensive overview for the synthesis of privileged 2,3-substituted indoles under various metal-catalyzed conditions. A large number of methods including Fischer indole synthesis, C–H activation, cycloaddition, and coupling reactions are described in details.

References

1. Sundberg, R. J. *The Chemistry of Indoles*; Bloquist, A. T., Eds.; Academic Press: New York, 1970, p 1.
2. (a) Patil, S. A; Patil, R.; Miller, D. D. *Future Med. Chem.* **2012**, *4*, 2085. (b) Zhang, M.-Z; Mulholland, N; Beattie, D; Irwin, D; Gu, Y.-C; Chen, Q; Yang, G.-F; Clough, J. *Eur. J. Med. Chem.* **2013**, *63*, 22. (c). Funk, C. D. *Nat. Rev. Drug Discovery* **2005**, *4*, 664. (d) Giansanti, V; Piscitelli, F; Camboni, T; Prosperi, E; Regina, G. L; Parks, M; Silvestri, R; Scovassi, A. I. *Oncol. Lett.* **2010**, *1*, 109. (e) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (f) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620. (g) Singh, T. P.; Singh, O. M. *Mini-Rev. Med. Chem*. **2018**, *18*, 9.
3. (a) Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH Verlag GmbH & Co, 2011, p. 221. (b) Sravanthi, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, *91*, 1.
4. (a) Owczarczyk, Z. R.; Braunecker, W. A.; Garcia, A.; Larsen, R.; Nardes, A. M.; Kopidakis, N.; Ginley, D. S.; Olson, D. C. *Macromolecules* **2013**, *46*, 1350. (b) Nie, G.; Bai, Z.; Yu, W.; Zhang, L. *J. Polym. Sci*., *Part A: Polym. Chem.* **2013**, *51*, 2385. (c) Manickam, M.; Iqbal, P.; Belloni, M.; Kumar, S.; Preece, J. A. *Isr. J. Chem*. **2012**, *52*, 917.
5. Joule, J. A. *Indole and its Derivatives* in *Science of Synthesis. Houben–Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000, vol. 10, p. 361.
6. Li, H.; Zhu, Z.; Zhang, F.; Xie, S.; Li, H.; Li, P.; Zhou, X. *ACS Catal*. **2011**, *1*, 1604.
7. Wang, Y.; Ye, L.; Zhang, L. *Chem. Commun.* **2011**, *47*, 7815.
8. Wang, Y.; Liu, L.; Zhang, L. *Chem. Sci*. **2013**, *4*, 739.
9. Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098.
10. Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem*. **2004**, *69*, 1126.
11. Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett*. **2000**, *41*, 1811.
12. Ackermann, L. *Org. Lett*. **2005**, *7*, 439.
13. Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem*., *Int. Ed*. **2007**, *46*, 2295.
14. Jiang, X.; Tang, W.; Xue, D.; Xiao, J.; Wang, C. *ACS Catal*. **2017**, *7*, 1831.
15. Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett*. **2013**, *15*, 3122.
16. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc*. **1994**, *116*, 3127.
17. Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 3068.
18. Schmidt, A. M.; Eilbracht, P. *J. Org. Chem*. **2005**, *70*, 5528.
19 Kolhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett*. **2003**, *5*, 3213.
20. Porcheddu, A.; Mura, M. G.; Luca, L. D.; Pizzetti, M.; Taddei, M. *Org. Lett*. **2012**, *14*, 6112.
21. Lavekar, A. G.; Equbal, D.; Saima; Sinha, A. K. *Adv. Synth. Catal*. **2018**, *360*, 180.
22. Stuart, D. R.; Laperle, Megan, B.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.
23. Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 10251.
24. Zhou, L.; Doyle, M. P. *J. Org. Chem*. **2009**, *74*, 9222.
25. Huang, F.; Wu, P.; Wang, L.; Chen, J.; Sun, C.; Yu, Z. *J. Org. Chem*. **2014**, *79*, 10553.
26. Novikov, M. S.; Khlebnikov, A. F.; Rostovskii, N. V.; Tcyrulnikov, S.; Suhanova, A. A.; Zavyalov, K. V.; Yufit, D. S. *J. Org. Chem*. **2015**, *80*, 18.
27. Nakazaki, M.; Yamamoto, K. *J. Org. Chem*. **1976**, *41*, 1877.
28. Kawade, R. K.; Huang, P.-H.; Karad, S. N.; Liu, R.-S. *Org. Biomol. Chem*. **2014**, *12*, 737.
29. Zhang, Z.-Z.; Liu, B.; Xu, J.-W.; Yan, S.-Y.; Shi, B.-F. *Org. Lett*. **2016**, *18*, 1776.
30. Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. *Org. Lett.* **2009**, *11*, 1055.
31. McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett*. **2011**, *13*, 3667.
32. Shen, Z.; Lu, X. *Tetrahedron* **2006**, *62*, 10896.
33. Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625.
34. Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662.
35. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.