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Recent metal-catalysed approaches for the synthesis of cyclopenta[*b*]indoles

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The cyclopenta[*b*]indole scaffold is ubiquitously present in several bioactive natural products and pharmaceutically interesting compounds. Of the numerous methods known for the synthesis of cyclopenta-fused indoles, this review highlights only the metal-catalysed approaches reported from the year 2015 onwards. This review encompasses our own efforts leading to the synthesis of cyclopentannulated indoles, in addition to the seminal contributions of several other researchers.

1. Introduction

The majority of natural products, synthetic drugs, agrochemicals and other biologically significant molecules are heterocyclic compounds, predominantly nitrogen-containing heterocycles.[1] Consequently, synthesis of N-heterocycles became one of the main branches of synthetic chemistry.[2] Among N-heterocycles, indole and indoline scaffolds are privileged substructures owing to their occurrence in a large number of natural products, bioactive compounds and materials of industrial relevance.[3,4]

Among indole derivatives, cyclopenta[*b*]indoles are of great significance because of their prevalence in a large number of alkaloids possessing wide-ranging biological activities.[5] For example, fischerindole L shows cytotoxicity against HCl-H460 cell lines,[6] terpendole E is an important mitotic kinesin Eg5 inhibitor,[7] yuehchukene possesses anti-fertility and estrogenic activities,[8] bruceollines are traditionally used for treating malaria and other parasitic diseases,[9] paspaline exhibits antibacterial and insecticidal activity,[10] and drugs such as laropiprant, which is believed to have a cholesterol lowering effect,[11] possess a cyclopenta[*b*]indole core, while polyveoline[12] represents an example of natural products having a cyclopenta[*b*]indoline scaffold (Fig. 1).

Due to their significant biological properties, various synthetic protocols have therefore been described to prepare cyclopenta[*b*]indoles. Some of the prominent approaches include, [3 + 2]-cycloaddition,[13] Yonemitsu condensation,[14] gold(I) catalysed Rautenstrauch rearrangement,[15] bismuth(III) catalysed condensation,[16] Nazarov cyclisation,[17] Heck–Suzuki cascade,[18] Fischer indole synthesis,[19] indole electrophilic substitution reactions,[20] [3,3]-sigmatropic rearrangement,[21] Dieckmann condensation,[22] vinylogous Michael addition/Friedel–Crafts reaction,[23] enzymatic synthesis,[24] *etc.*

In the past few decades, chemists have extensively explored various routes for the synthesis of cyclopenta[*b*]indoles *via* metal catalysis and these efforts have been reviewed recently.[25] The scope of the present review is to provide a detailed account of various metal-catalysed approaches reported for cyclopenta[*b*]indoles from the year 2015 onwards. The works highlighted herein have been categorised based on the metal catalyst employed.

2. Palladium-catalysed approaches

In 2017, Lu and Han reported a Pd(II)-catalysed tandem cyclisation of alkynones **1** to synthesise pentaleno[2,1-*b*]indoles **2** (Scheme 1).[26] Tetracyclic indoles bearing two neighbouring stereogenic centres, one being all-carbon quaternary, were constructed in a single operation in an excellent diastereoselectivity. The tandem cyclisation is initiated by the *trans*-amino palladation of the alkyne moiety to generate **3**. A subsequent nucleophilic addition of the C–Pd bond to the intramolecular carbonyl group followed by the protonolysis of **4** results in the formation of product **2**. Thereby, this reaction offers an efficient and atom-economic alternative for the synthesis of pentaleno[2,1-*b*]indoles **2**.

In 2018, Cheng and Zhai demonstrated a novel Pd-catalysed decarboxylative coupling reaction of vinyl benzoxazinanones **6** with aryne precursors **5** to achieve the synthesis of *cis*-tetrahydroindeno[2,1-*b*]indoles **7** in good yields (Scheme 2).[27] The authors propose that the mechanism involves a nucleophilic attack at the central carbon of vinyl benzoxazinanone-derived π-allyl palladium species **8** that gives a palladacyclobutane intermediate **9**, which then reacts with arynes to afford the polycyclic heterocycles such as **7**.

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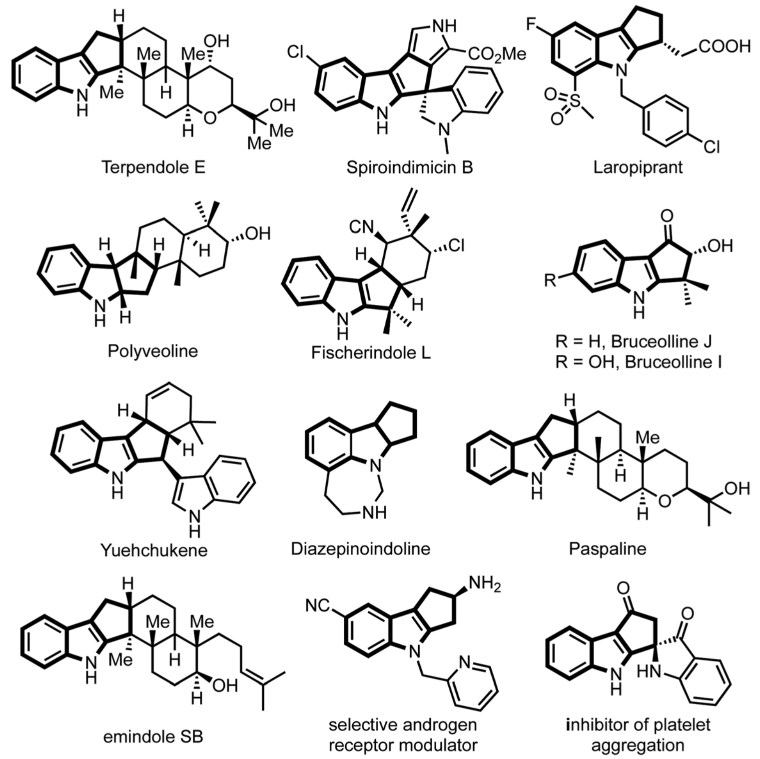
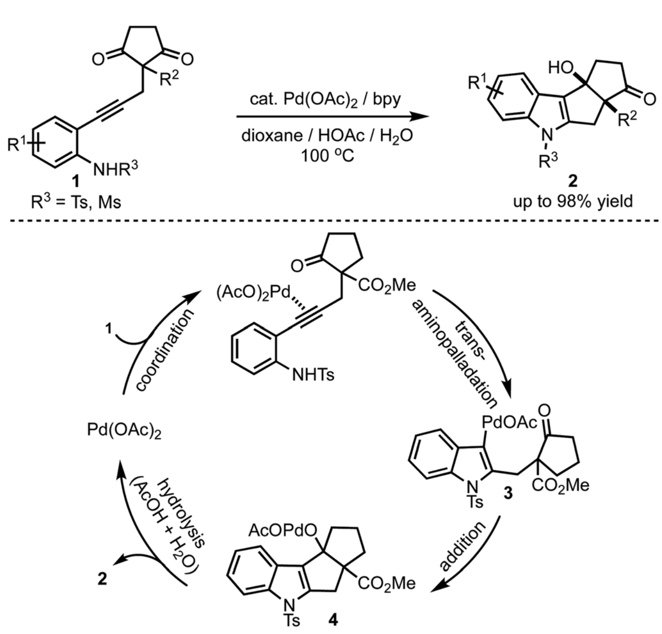
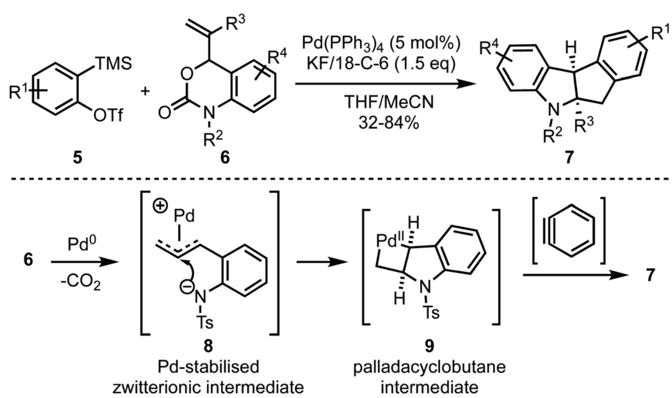


Fig. 1 Representative natural products and medicinally significant compounds possessing cyclopenta[*b*]indole core.

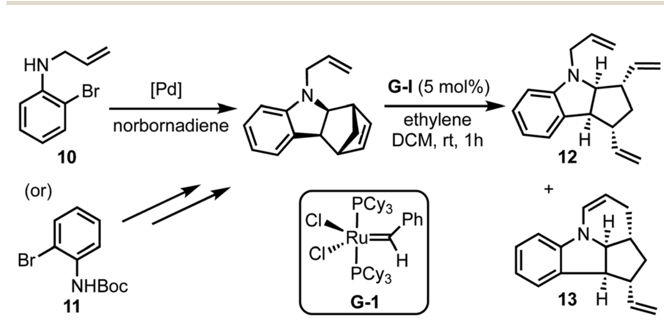
Kotha and Gunta reported an interesting approach for the synthesis of fused N-heterocycles (for example, **12** and **13**) *via* C–H activation and ring-rearrangement metathesis (RRM) of 2-bromo-*N*-protected anilines **10** (or **11**) with norbornadiene (Scheme 3).[28] Through this method, various structurally intricate polycyclic amides were prepared, and some of the products obtained herein represent the core structures of the bioactive



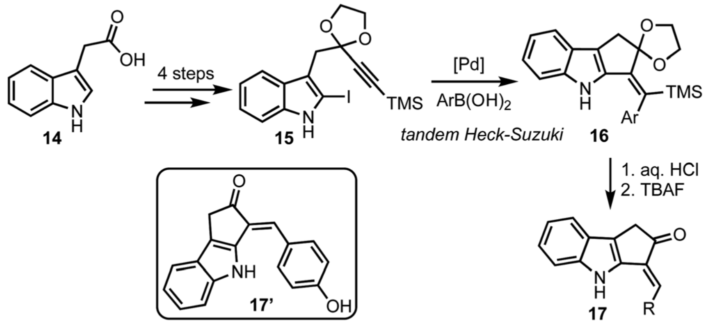
Scheme 1 Palladium-catalysed tandem cyclisation leading to the formation of pentaleno[2,1-*b*]indoles.



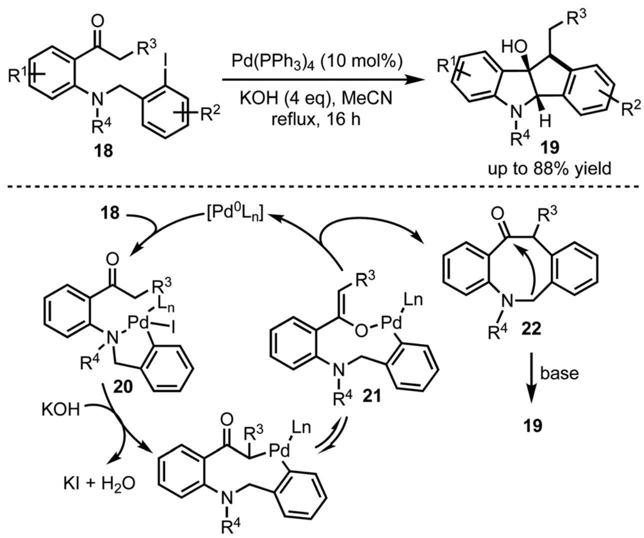
Scheme 2 A Pd-catalysed synthesis of tetrahydroindeno[2,1-*b*]indoles.



Scheme 3 Kotha's synthesis of fused-indolines *via* C–H activation and ring-rearrangement metathesis.



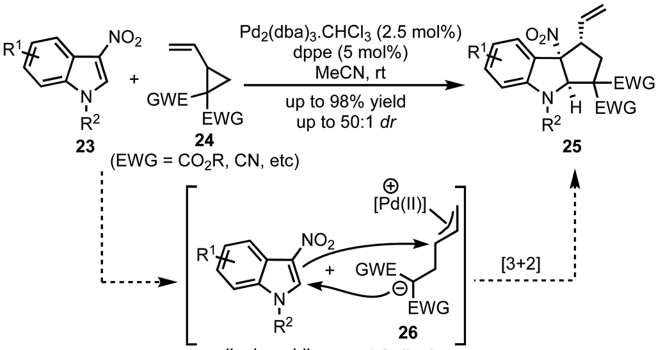
Scheme 4 Mårtensson's synthesis of bioactive cyclopenta[*b*]indoles.



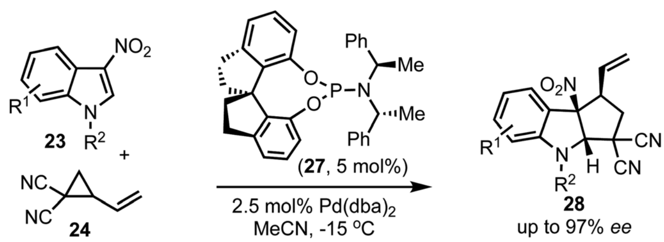
Scheme 5 Wang's approach for cyclopenta-fused indolines.

alkaloids epimeloscine, deoxycalyciphylline B, daphlongamine H and isodaphlongamine H. Key advantages of the C–H activation/RRM strategy are: (i) it is atom-economical, and (ii) provides access to intricate molecular scaffolds amenable for further synthetic transformations.

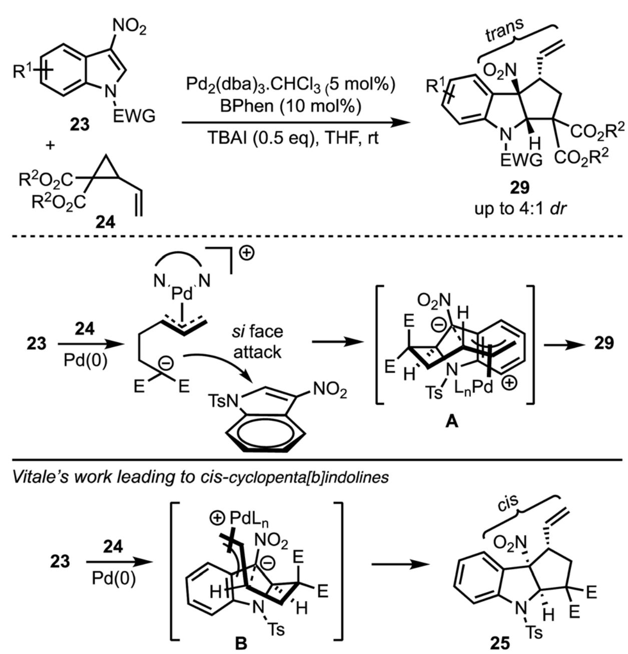
In 2015, Mårtensson and co-workers developed a diversity oriented synthesis of 3-arylidine-cyclopenta[*b*]indol-2-ones **17** *via* Pd-catalysed Heck–Suzuki reaction cascade (Scheme 4).[29] Indole-3-acetic acids **14** were converted to iodoindoles **15** in four steps. A tandem Heck–Suzuki reaction of **15** provided access to cyclopenta-fused indoles **16**, which were converted to enones **17** in two straight forward steps. Among several analogs of **17** prepared, **17′** particularly displayed impressive anti-melanoma



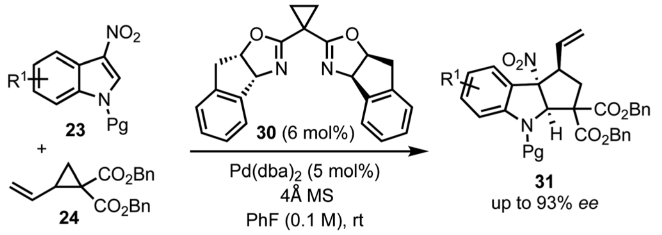
Scheme 6 Vitale's synthesis of fused cyclopentannulated indolines.



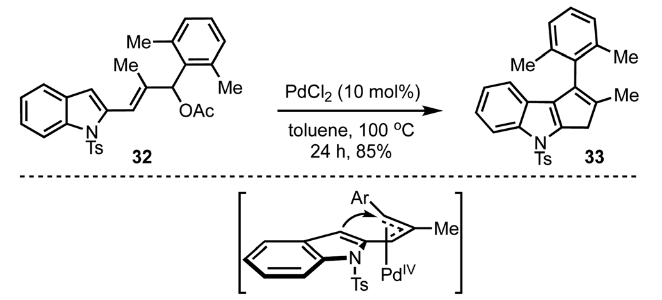
Scheme 7 Shi's catalytic synthesis of chiral cyclopenta-fused indolines.



Scheme 8 Hyland's diastereoselelctive synthesis of cyclopenta[*b*]indolines.



Scheme 9 Wang's synthesis of cyclopenta[*b*]indolines *via* Pd-catalysed asymmetric dearomative cycloaddition.



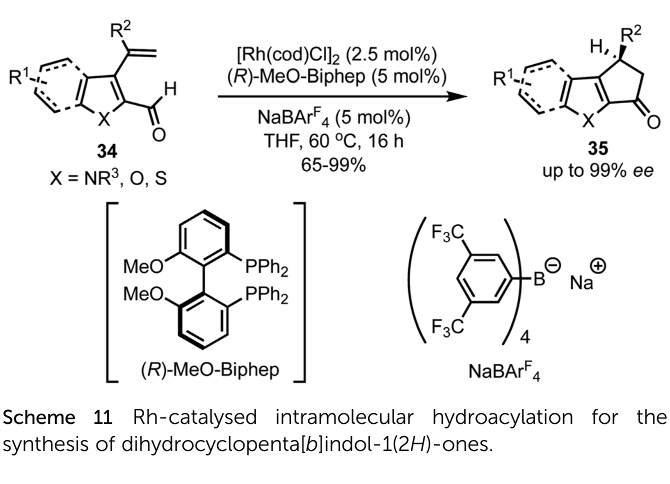
Scheme 10 Pd-catalysed iso-Nazarov-type cyclisation.

properties by inhibiting Aurora A, Aurora B, BRAF V600E, IRAK4 and also inhibiting cell proliferating PBMC. In addition, **17′** also displayed interesting fluorescent properties, enabling its intracellular accumulation to be visualised.

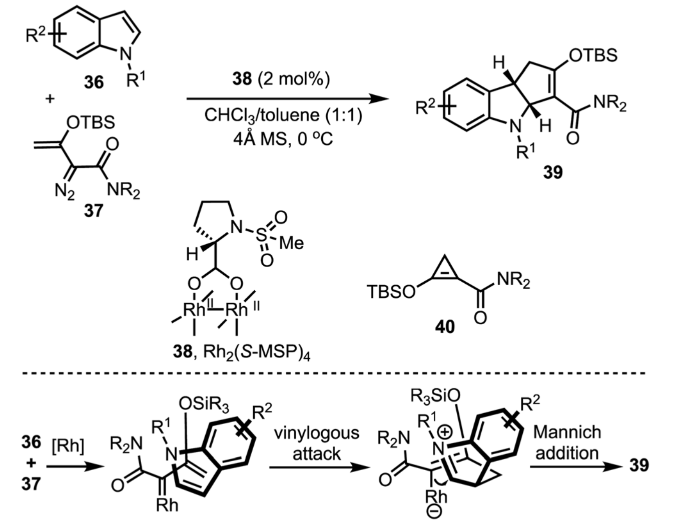
Synthesis of dihydro[1,2-*b*]indenoindole-9-ols **19** through a Pd-catalysed cascade process was developed by Wang and co-workers (Scheme 5).[30] The mechanism involves an oxidative addition of Pd(0) with an aryl iodide **18** leading to the formation of a chelation stabilised intermediate **20**. Subsequently, base-mediated generation of nine-membered palladacycle **21** undergoes reductive elimination to form 8-membered β-arylated compound **22**. Further base-mediated intramolecular cyclisation furnished **19** in good yields. The control experiments and the isolation of 8-membered β-arylated intermediate **22** further ascertain the proposed palladium cycle.

In 2017, Vitale and co-workers disclosed a highly efficient and atom-economical Pd(0)-catalysed dearomative [3 + 2]-cycloaddition of 3-nitroindoles **23** with vinylcyclopropanes **24** to obtain cyclopentannulated indolines **25** possessing three stereogenic centers in high diastereoselectivity (Scheme 6).[31] The zwitterionic 1,3-dipole **26** undergoes Michael addition with the electrophilic 3-nitroindoles. This follows an irreversible intramolecular attack of the nitronate anion onto the π-allyl palladium(II) moiety to afford 2,3-fused cyclopenta[*b*]indolines **25** in a stereo-defined fashion.

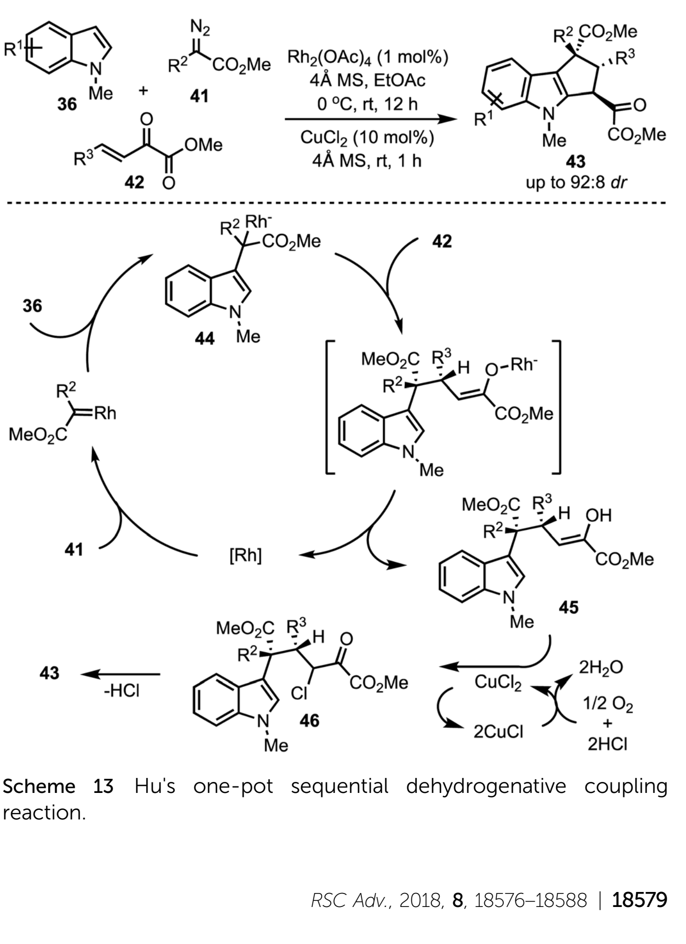
In 2018, Shi and co-workers demonstrated the catalytic asymmetric dearomative [3 + 2]-cycloaddition of electron-



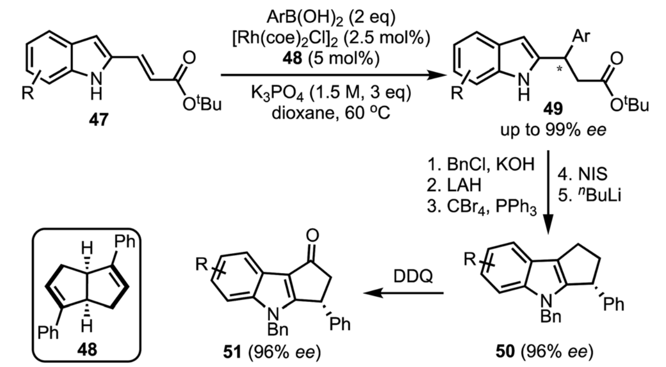
Scheme 11 Rh-catalysed intramolecular hydroacylation for the synthesis of dihydrocyclopenta[*b*]indol-1(2*H*)-ones.



Scheme 12 Rh-catalysed approach for cyclopenta-fused indolines.



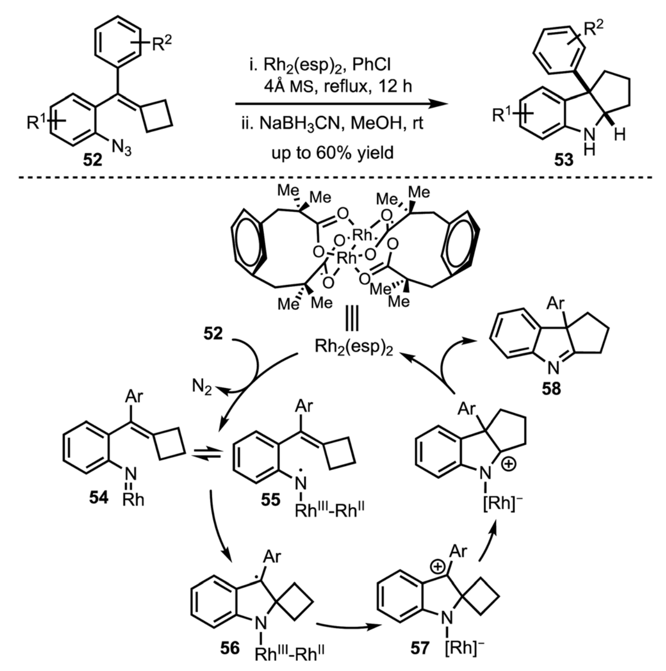
Scheme 13 Hu's one-pot sequential dehydrogenative coupling reaction.



Scheme 14 Xu's synthesis of cyclopenta[*b*]indoles.

deficient indoles with 1,3-dipoles (Scheme 7).[32] For example, phosphoramidite **27** catalysed reaction of 3-nitroindoles **23** with vinyl cyclopropanes **24** provided chiral cyclopenta[*b*]indolines **28** in high enantioselectivities (up to 97% ee). This also presents a case for catalytic asymmetric dearomatisation (CADA) reactions, which are well-known for electron-rich indoles, but in this case, the authors have demonstrated the CADA concept on electron-poor indoles to obtain chiral cyclopenta[*b*]indolines of the type **28**.

In 2017, Hyland and co-workers reported a Pd-catalysed diastereoselective synthesis of cyclopenta[*b*]indolines **29** from 3-nitro indoles **23** and vinylcyclopropane dicarboxylates **24** by Pd-catalysed dearomative [3 + 2]-cycloaddition process (Scheme 8).[33] The authors have identified that the halide addition [in the form of tetrabutylammonium iodide (TBAI)] is critical for the diastereo induction in products. It was hypothesised that the halide allows a Curtin–Hammett control of the reaction there by introducing diastereoselectivity. Unlike Vitale's work,[31] a switch in the diastereoselectivity was observed with the vinyl and nitro groups being *trans* to each other. The difference between the transition states involved in Hyland's work (**A**) and Vitale's work (**B**) is presented in Scheme 8.



Scheme 15 Rh-catalysed synthesis of pentannulated indoles.

In 2018, Wang's group reported a Pd-catalysed asymmetric dearomative [3 + 2]-cycloaddition strategy for the construction of optically active cyclopenta-fused indolines **31** (Scheme 9).[34] For example, the reaction of 3-nitroindoles **23** with vinyl cyclopropanes **24** in the presence of a chiral box (**30**)/Pd(0) complex delivered 8*b*-nitro hexahydrocyclopenta[*b*]indoles **31** containing up to three contiguous chiral centres in high yields and good regio-, chemo-, and enantioselectivities. The synthetic utility of this method was demonstrated through direct functionalisation of the carbon–carbon double bond of **31**. The salient features of this transformation include good functional group tolerance, stereospecificity, atom-economy, and scalability.

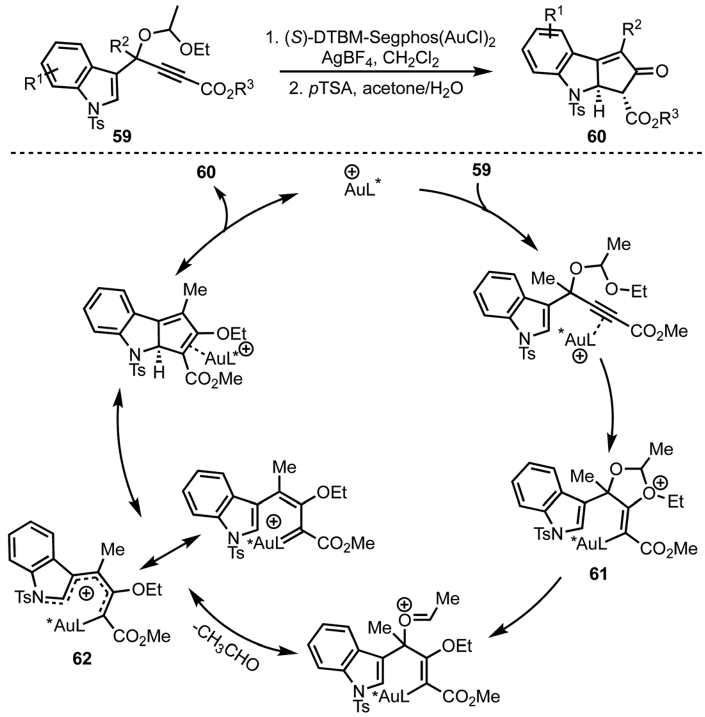
Recently, our group demonstrated a Pd-catalysed Trost–Oppolzer type Alder-ene reaction of 2,4-pentadienyl acetates for the synthesis of cyclopentadienes and cyclopentene-fused arenes and heteroarenes. For example, in the presence of a catalytic amount of palladium chloride, the allyl acetate **32** afforded the cyclopenta[*b*]indole **33** in good yield (Scheme 10).[35] The reaction is believed to involve the formation of a π-allyl palladium complex and an intramolecular Alder-ene reaction as in the model depicted in Scheme 10. The overall reaction also represents an unprecedented acid-free iso-Nazarov-type cyclization.

3. Rhodium-catalysed approaches

In 2017, Vickerman and Stanley reported an enantioselective approach for the synthesis of N/O/S-heterocycles **35** by the intramolecular Rh-catalysed hydroacylation of olefins **34** (Scheme 11).[36] Employing this strategy, 1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-ones and 3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-ones are accessible in high yields and in excellent enantioselectivities. This protocol allowed the alkene hydroacylation of 3-vinylfuran-, 3-vinyl benzothiophene-, and 3-vinyl thiophene-2-carboxaldehydes to generate the corresponding oxygen, and sulphur-containing heterocycles in chiral fashion.

Doyle and co-workers developed a highly regio-and enantiocontrolled formal [3 + 2]-annulation of indoles and electrophilic enol carbenes for the synthesis of chiral cyclopenta-fused indolines **39** (Scheme 12).[37] An enantioselective vinylogous addition of enoldiazoacetamides **37** to *N*-substituted indoles **36** (without 2- or 3-substituents) was facilitated by the prolinate-ligated dirhodium(II) catalyst **38**. Interestingly, the donor–acceptor cyclopropane **40** was realised to be the carbene precursor in this transformation. It is interesting to note that prior to this study, dearomatising [3 + 2]-annulation of 2- or 3-unsubstituted indoles that occurs with good chemo-, regio-, and enantiocontrol was not achieved.

In 2016, Hu and co-workers reported a Rh-catalysed highly diastereoselective three-component reaction for the generation of polyfunctionalised cyclopenta[*b*]indoles **43** (Scheme 13).[38] $Rh_2(OAc)_4$ catalysed dehydrogenative coupling between indoles **36** and diazoacetates **41** generates intermediate **44**. A subsequent trapping of **44** with α,β-unsaturated-α-keto esters **42**



Scheme 16 Toste's Au-catalysed dearomative Rautenstrauch rearrangement for the synthesis of cyclopenta[*b*]indoles.

through Michael addition results in the formation of the enol **45**. An aerobic intramolecular direct Csp^2–Csp^2 cross-coupling of indole–enol is promoted by $CuCl_2$. Further, XPS and control experiments revealed the role of Cu(II) in the single electron transfer oxidation [a catalytic cycle of Cu(II) to Cu(I)] of the enol **45** to α-chloro carbonyl intermediate **46**. An intramolecular Friedel–Crafts-type alkylation of **46** delivers the cyclopenta[*b*]indoles **43**.

In 2017, Xu and co-workers developed a Rh-catalysed asymmetric β-arylation of indole-derived α,β-unsaturated esters and aryl boronic acids for the synthesis of 3-(1*H*-indol-2-yl)-3-arylpropanoates **49** in good yields and excellent enantioselectivities (Scheme 14).[39] The method is applicable to α,β-unsaturated benzofuran- and benzothiophene-derived acrylates as well. The β-arylated products obtained herein were transformed to cyclopenta[*b*]indoles **50** *via* a multistep sequence. A 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-mediated oxidation of **50** further provided functionalised cyclopenta-fused indoles of the type **51**.

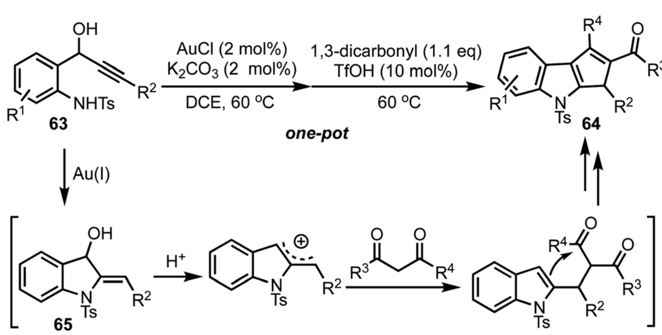
In 2016, Tang and Shi demonstrated a ring expansion of styrylazides **52** *via* Rh(II)-catalysed single electron transfer mechanism (Scheme 15).[40] The reaction path follows an initial Rh–nitrene **54** formation *via* nitrogen elimination and subsequent single electron transfer to generate the radical **55**. The radical addition to the olefin generates the spirocyclic radical **56** which undergoes another SET to form **57**. Further, 1,2-alkyl migration of **57** and elimination affords the imine **58**. *In situ* borohydride reduction of the imine **58** delivers pentannulated indoles **53** in a highly diastereoselective manner. The authors also provided an evidence in favor of the generation of Rh^{III}–Rh^{II}–nitrene with DFT studies.

4. Gold-catalysed approaches

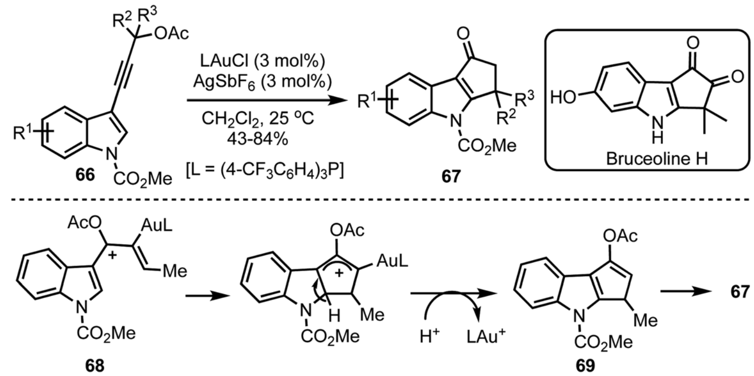
In 2015, Toste and co-workers reported a highly enantioselective dearomative Rautenstrauch rearrangement of propargyl acetals **59** catalysed by cationic (*S*)-DTBM-Segphos gold(I) (Scheme 16).[15] This reaction provides a straightforward method for the preparation of enantioenriched cyclopenta[*b*]indoles **60**.

The proposed mechanism involves an anti-attack of ethoxy ether of the acetal on to the Au-coordinated alkyne leading to the formation of oxonium species **61**. An eventual extrusion of acetaldehyde generates gold-substituted 1-amino pentadienyl intermediate **62**. An enantio-determining imino-Nazarov cyclisation of **62** followed by protodeauration affords product **60**.

Recently, our group reported the synthesis of 1,2,3-trisubstituted cyclopenta[*b*]indoles **64** from 1-(2-aminophenyl)prop-2-ynols **63** *via* one-pot relay Au(I)/BrØnsted acid catalysis (Scheme 17).[41]



Scheme 17 A sequential Au(I)/BrØnsted acid catalysis.

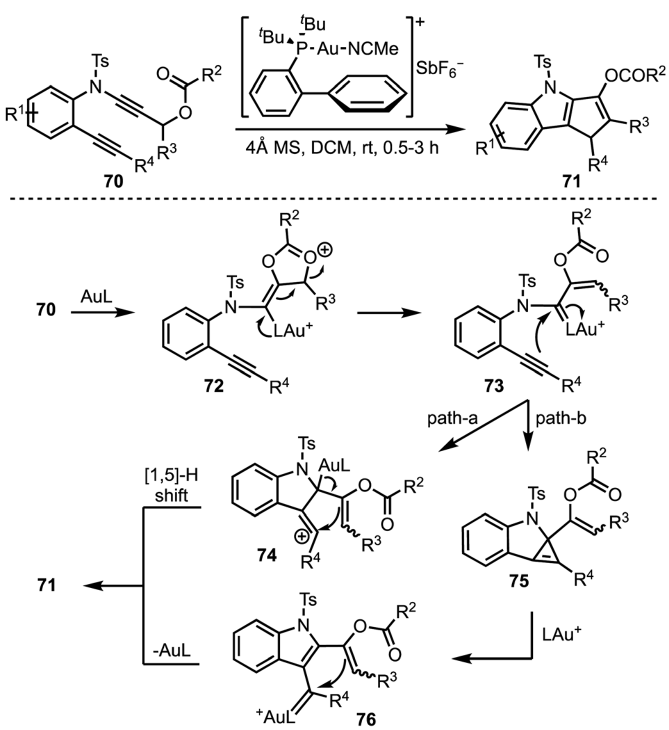


Scheme 18 Occhiato's tandem Au(I)-catalysed rearrangement/Nazarov cyclisation.

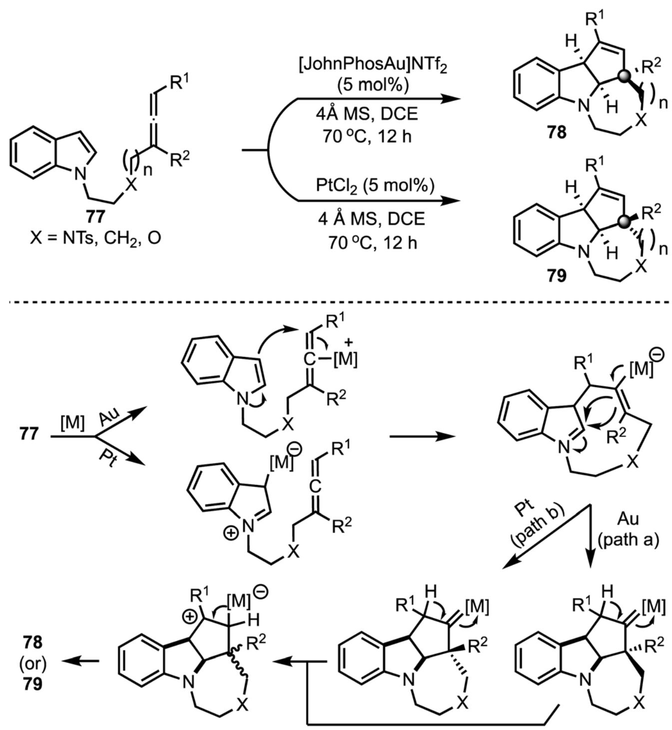
The reaction of ynols **63** under Au(I) catalysis generates indolines **65**, which undergoes an acid mediated cation–ene reaction with 1,3-dicarbonyls and a subsequent intramolecular Friedel–Crafts-type reaction to provide **64**. It is noteworthy to mention that Au(I) or Ag(I) alone or a combination of Au(I) and silver based Lewis acids failed to deliver the indoline **65**, whereas Au(I) with a combination of a base (such as K_2CO_3) was found to be effective. The reaction tolerates a wide range of ynols possessing electron donating as well as withdrawing groups. A variety of 1,3-dicarbonyls, 1,2,3-tricarbonyls, β-ketoesters and β-ketoamides are also tolerated under the reaction conditions.

Occhiato and co-workers developed a tandem gold(I)-catalysed rearrangement/Nazarov cyclisation of enynyl acetates **66** to obtain cyclopenta[*b*]indol-1-ones **67** in good yields (Scheme 18).[42] The process entails the gold(I)-catalysed [3,3]-sigmatropic rearrangement of the propargylic acetates **66** to generate requisite pentadienyl cation **68**. The Nazarov cyclisation followed by hydrolysis of the enol acetate **69** generates cyclopenta[*b*]indol-1-ones **67**. The potential of this synthetic methodology was demonstrated in the total synthesis of Bruceolline H.

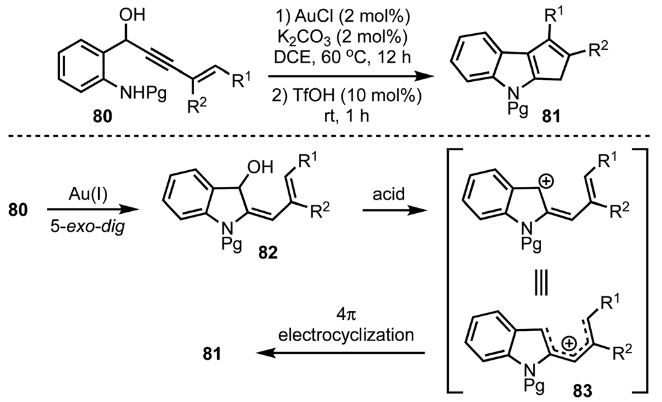
Liu and co-workers presented a gold-catalysed cycloisomerisation of 1,6-diynes **70** containing a ynamide propargyl ester functionality, leading to the synthesis of densely functionalised 1,4-dihydro cyclopenta[*b*]indoles **71** (Scheme 19).[43] The reaction proceeds through a selective activation of ynamide propargyl ester by Au(I) to afford α-vinyl gold carbenoid **72**. Intramolecular attack of the alkyne moiety on to the gold carbenoid (in **73**) affords vinyl cationic species **74**, which undergoes [1,5]-*H* shift to furnish the product **71** (path a). On the other hand, transfer of the gold carbenoid moiety across the alkyne in **73** generates **76**, *via* the cyclopropene intermediate **75**. Intramolecular cyclisation of the enol acetate on to the gold



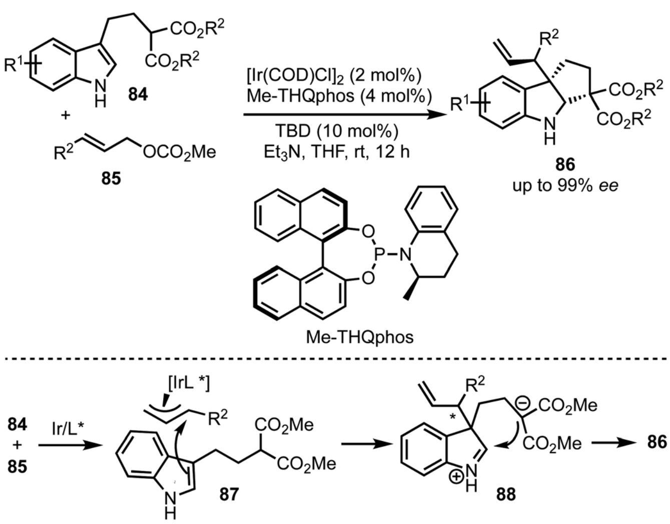
Scheme 19 Liu's synthesis of dihydrocyclopenta[*b*]indoles.



Scheme 20 Shi's Au- and Pt-catalysed cycloaddition of indolyl–allenes.



Scheme 21 One-pot synthesis of cyclopentannulated indoles by using sequential gold(I) and Brønsted acid catalysis.

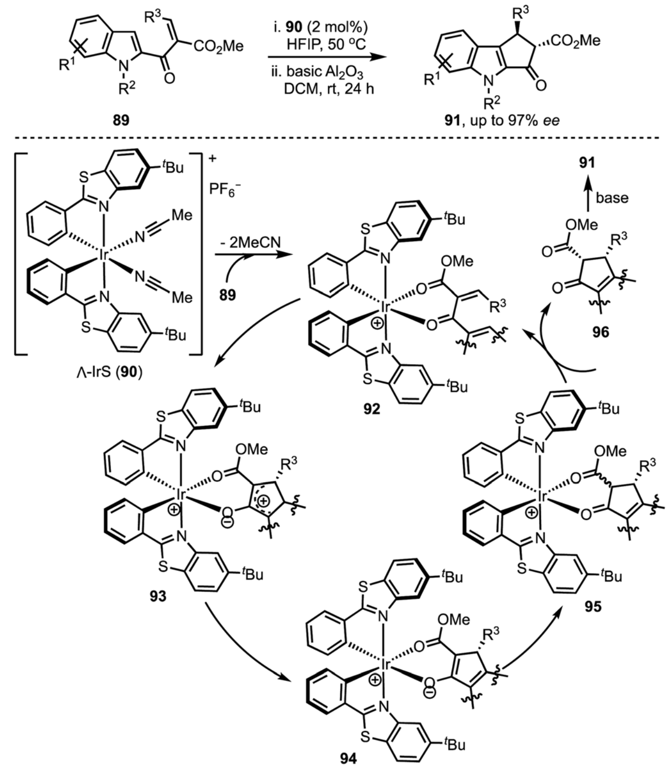


Scheme 22 You's Ir-catalysed intermolecular allylic alkylation reaction of 3-substituted indoles.

carbenoid in **76** followed by deprotonation and protodeauration provides **71** (path b).

In 2015, Shi and co-workers reported a catalyst-dependent stereodivergent and regioselective construction of indole-fused heterocycles **78** and **79** from indolyl–allenes **77** (Scheme 20).[44] This is an atom-economical method to access indole-fused tricyclic systems under mild conditions. Interestingly, reversion in the stereochemistry of an all-carbon quaternary stereocentre in **78** and **79** was observed depending on whether gold or platinum complexes were employed during the [3 + 2]-cycloaddition of allenes with indoles. The authors have proposed mechanisms for these transformations based on deuterium labeling studies and control experiments.

Recently, we have disclosed a one-pot indole cyclopentannulation of 1-(2-aminophenyl)pent-4-en-2-ynols **80** which involves a tandem gold(I)-catalysed intramolecular hydroamination of alkynes followed by Brønsted acid catalysed 4π-electrocyclisation sequence (Scheme 21).[45] The proposed mechanism involves an initial Au(I)-catalysed 5-*exo*-dig cyclisation to form 2-allylidene indolinols **82**. Subsequently, under

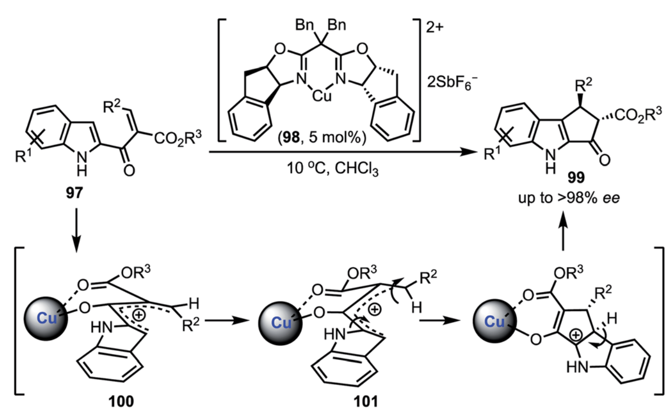


Scheme 23 Meggers' asymmetric Nazarov cyclisation catalysed by chiral-at-metal Ir-complex.

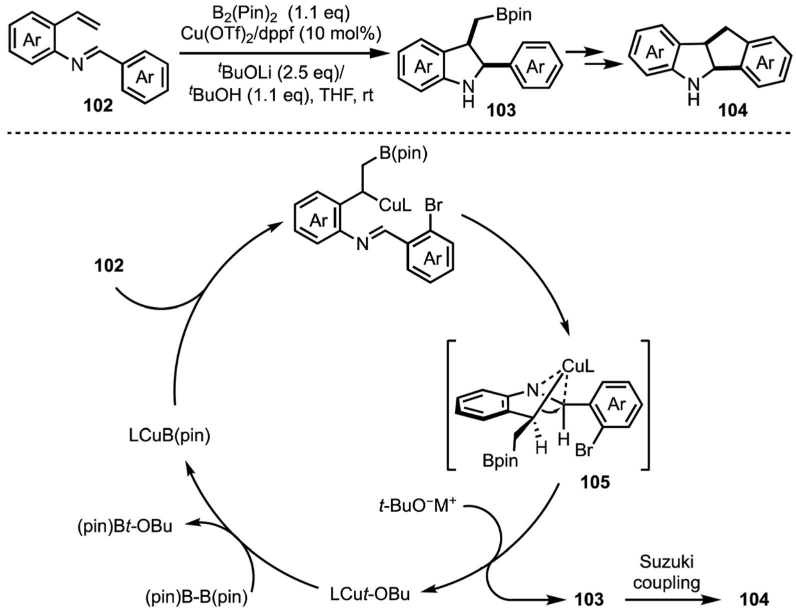
acidic conditions, intermediate **82** generates a pentadienyl cationic system **83**, which undergoes Nazarov cyclisation to give **81**. This strategy was successfully applied to the synthesis of core carbon structure of the natural product polyveoline, in addition to synthesising several other complex molecular architectures.

5. Iridium-catalysed approaches

In 2015, You and co-workers reported an Ir-catalysed asymmetric allylic alkylation of 3-substituted indoles **84** to access



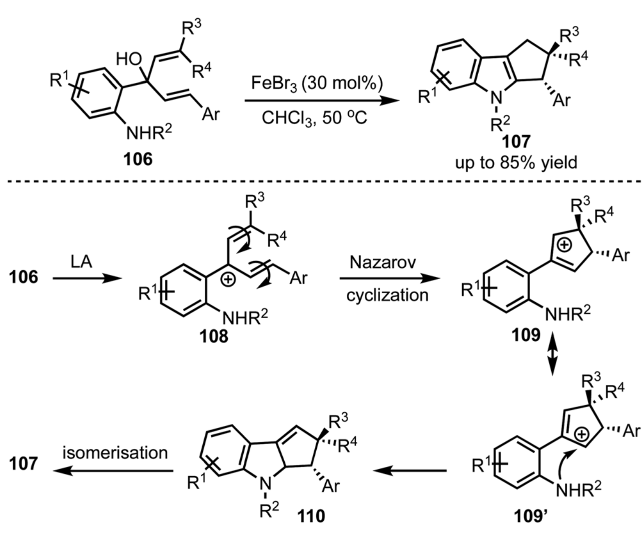
Scheme 24 Rueping's asymmetric Nazarov cyclisation.



Scheme 25 Cu(I)-catalysed borylative cyclisation.

structurally complex cyclopentannulated indolines **86** (Scheme 22).[46] The transformation is initiated by a Tsuji–Trost reaction between π-allyl iridium complex and indoles (as in **87**) leading to the formation of indolines **88**. Intramolecular attack of the malonate anion on to the iminium ion (in **88**) generates product **86**. Versatility of this method was demonstrated *via* the synthesis of a diverse set of furoindolines, pyrroloindolines and cyclopentaindolines in high regio-, diastereo- and enantioselective manner. Other salient features of this method are: easily accessible starting compounds and inception of three contiguous stereocentres in products.

In 2018, Meggers and co-workers have come up with the synthesis of cyclopenta[*b*]indoles **91** *via* asymmetric Nazarov cyclisation by employing chiral-at-metal Ir-complex **90** (Scheme 23).[47] The mechanism involves an initial *O*,*O*-bidentate coordination of the unsaturated β-ketoester **89** to the iridium complex (**92**). A conrotatory electrocylisation leads to the formation of the cationic intermediate **93**, and the asymmetric induction is provided by the helical chirality of the C_2-symmetric iridium complex **90**. Subsequent deprotonation and reprotonation of **94** furnished the catalyst-bound Nazarov product **95**. Base-mediated epimerisation of the 2,3-*cis*-Nazarov product leads to the thermodynamically stable 2,3-*trans* product **96**. The role of the solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was found to be crucial in releasing the catalyst bound product **95**, which was attributed to its weak acidity. Thereby, functionalised pentannulated indoles **91** were obtained in good yields and excellent enantiopurities. Some of the advantages of this work are: low catalyst loading of Λ-IrS (**90**, 2 mol%), avoiding dry solvents and inert atmosphere, *etc.*

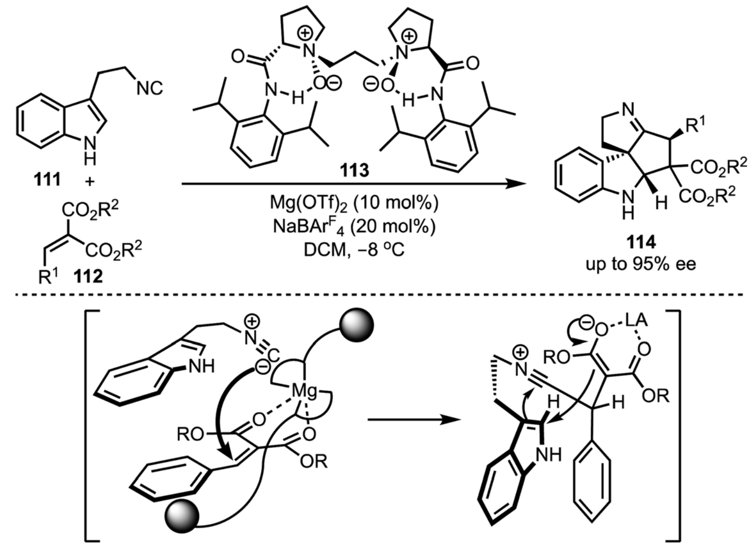


Scheme 26 Kwon's Nazarov cyclisation.

6. Copper-catalysed approaches

A Cu-catalysed asymmetric Nazarov cyclisation of indoles was demonstrated by Rueping and co-workers (Scheme 24).[48] Through this approach, highly enantioenriched cyclopenta[*b*] indoles **99** were synthesised in the presence of a chiral [Cu^{II}(box)] complex **98** in good yields. The proposed mechanism involves a six-membered boat conformation **100**, formed between Cu(II) and β-keto ester **97** by coordinating with two carbonyl groups. Subsequent isomerisation to **101** and a 4π-electrocylisation afforded desired products **99** in excellent enantioselectivities. The authors have further explained the origin of the enantioselectivity with the aid of DFT studies.

In 2018, Shen and Xu described a borometalation–imine addition cascade reaction for the synthesis of 2,3-*cis*-disubstituted indolines **103** by using $Cu(OTf)_2$ as precatalyst (Scheme 25).[49] The indolines preinstalled with *ortho*-bromo aryl groups (at indoline C-2 position) were further elaborated to varieties of

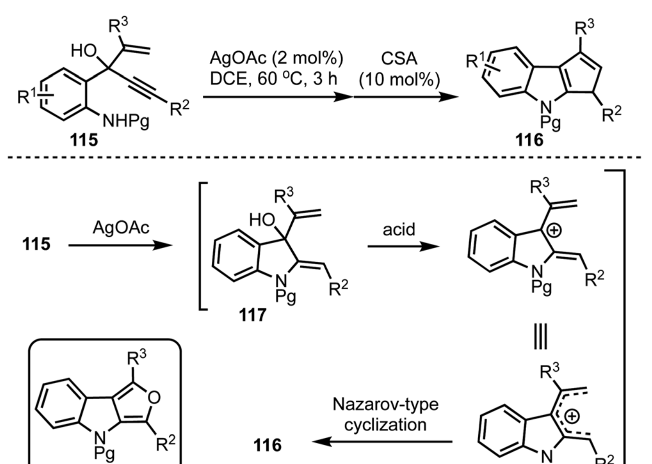


Scheme 27 Liu and Feng's cascade process leading to the synthesis of polycyclic spiroindolines.

cis-tetrahydroindenoindoles **104** in excellent yields through an intramolecular Suzuki coupling. The exclusive diastereoselective formation of *cis*-2,3-disubstituted indolines is partly attributed to the hypothetical imine–copper coordination complex **105**.

7. Other metal-catalysed approaches

In 2016, Kwon and co-workers demonstrated an interesting Lewis acid mediated Nazarov cyclisation of 1,4-pentadien-3-ols **106** (Scheme 26).[50] An inexpensive and environmental friendly $FeBr_3$ was used as a catalyst for the transformation. A diverse range of cyclopenta[*b*]indoles **107** were synthesised in a highly regio- and stereoselective manner under mild Lewis acidic conditions. Regarding mechanism, in presence of $FeBr_3$, **108** undergoes Nazarov cyclisation to generate the cationic intermediate **109**. A subsequent stereoselective intramolecular nucleophilic amination on to **109′** forms **110**, which isomerises to cyclopenta[*b*]indoles **107**.

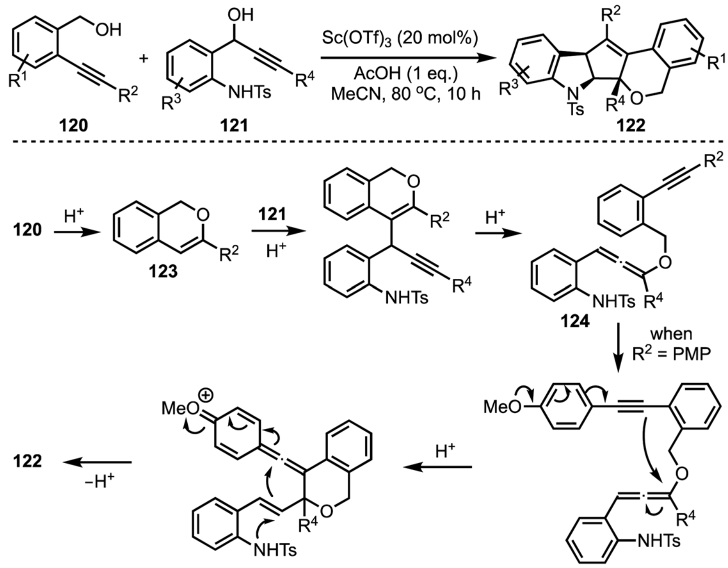


Scheme 28 Ag(I)-catalysed approach for cyclopenta[*b*]indoles.

In 2015, Liu and Feng have reported an asymmetric dearomatisation of indoles through a cascade Michael/Friedel–Crafts-type reaction sequence to construct polycyclic spiroindolines **114** (Scheme 27).[51] The reaction of 2-isocyanoethyl indoles **111** and alkylidene malonates **112**, catalysed by a chiral *N*,*N′*-dioxide/Mg^{II} complex **113**, furnished highly functionalised polycyclic indolines **114** possessing up to three stereocentres in good yields, and excellent diastereo- and enantioselectivities. The reaction proceeds *via* an initial Michael addition of isocyanides to alkylidene malonates which subsequently undergo Friedel–Crafts/Mannich-type reaction to generate complex structures.

Recently, we have developed an efficient synthetic protocol for the synthesis of 1,3-disubstituted cyclopenta[*b*]indoles **116** *via* a sequential Ag(I)/Brønsted acid catalysis from easily accessible 3-(2-aminophenyl)-4-pentenyn-3-ols **115** (Scheme 28).[52] The reaction is initiated by a Ag(I)-catalysed 5-*exo*-dig cyclisation (**117**) followed by a Brønsted acid catalysed Nazarov-type cyclisation of pentadienyl cationic system **118** to obtain cyclopenta[*b*]indoles **116**. This divergent strategy also provides access to furo[3,4-*b*]indoles **119** *via* a sequential one-pot Ag(I)/Bi(III)/Pd(II) catalysis.

In 2017, Liu reported an interesting triflic acid-catalysed cascade reaction involving 2-alkylnylbenzyl alcohols **120** and 1-(2-aminophenyl)prop-2-ynols **121** to access an unusual set of *N*,*O*-containing pentacyclic cyclopenta[*b*]indole scaffolds **122** (Scheme 29).[53] The transformation involves an *in situ* generation of triflic acid [by combining acetic acid and $Sc(OTf)_3$], which promotes cycloisomerisation of alkynol **120** to **123** followed by intermolecular substitution to afford an allene intermediate **124**. A sequence of conjugate additions and cyclisation events provide the final product **122**. Several control experiments were performed to get insights about the mechanism. The efficiency of this method lies in its ability to construct pentacyclic cyclopentannulated indoles in a single operation, in which two C–C bonds, one C–O bond and one C–N bond form.



Scheme 29 Liu's cascade approach for the synthesis of pentacyclic cyclopenta[*b*]indoles.

8. Conclusion

Among indole derivatives, cyclopenta[*b*]indole scaffold is an important structural motif which is widely found in bioactive natural products and pharmaceutically important compounds. Consequently, an array of synthetic protocols have been developed to prepare this heterocyclic core.[54] Among which, metal-catalysed approaches are popular due to their versatility, broad substrate scope, scalability, wide functional group tolerance, *etc.* Through this review, a summary of metal-catalysed transformations leading to the synthesis of cyclopenta[*b*]indoles is presented. In addition to the inspirational contributions from various research groups, our own efforts pertaining to the one-pot synthesis of cyclopentannulated indoles have also been discussed herein. From these deliberations, it is evident that there exist potential opportunities to devise efficient and straightforward enantioselective approaches, especially promoted by non-precious metals. Towards this, the development of one-pot multiple bond-forming multicomponent strategies can offer a potential solution.

Another important aspect that deserves attention at this stage is the development of biomimetic approaches for the synthesis of cyclopenta[*b*]indoles.[55] For example, Nature prepares majority of these heterocycles starting from the amino acid tryptophan. So, the evolution of novel chemical transformations leading to the construction of complex molecular architectures by employing readily available materials is desired. We anticipate that more progress would be realised in this direction.

Conflicts of interest

The authors declare no conflict of interest.

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