SYNTHETIC APPROACHES TOWARDS CYCLOPENTA[*b*]INDOLE SCAFFOLD

DOI: http://dx.medra.org/10.17374/targets.2019.22.224

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Abstract. *Cyclopenta[b]indoles comprise a class of heterocyclic compounds present in several molecules that exhibit significant biological activities. They have thus found wide application in synthetic and medicinal chemistry. Due to their importance, this present chapter is intended to survey several synthetic approaches to furnish cyclopenta[b]indolic compounds. Most of these approaches require catalysts or promoters in order to achieve these products. This review is organized according to which type of catalyst or promoter is used in the synthesis of this scaffold, namely metallic compounds, Brønsted acids or Lewis acids.*

Contents

1. Introduction

Heterocyclic compounds display an important role in several activities closely related to the human life on the planet.[1] Representatives of this class of compounds mediate several biological processes that are crucial for maintenance of life. For instance, heterocycles are present in the structure of aminoacids and nitrogenated bases that regulated DNA synthesis or proteins. Besides, heterocycles are widespread in several branches of chemistry,[2] agrochemicals,[3] biology, material sciences, polymers and electronic devices.[4]

Among the heterocyclic systems, cyclopenta[*b*]indoles play a fundamental role. This motif is present in several compounds which exhibits a wide range of biological activities, and in most of the cases, this activity is directly related to its presence. Structurally, this heterocyclic motif is composed by a tricyclic system formed by the junction of an indole and a 5-membered carbocyclic ring attached by the *b* side of the former. Several structural arrangements are possible, according to that depicted in Figure 1.

Several compounds classified as indole alkaloids have in fact a cyclopenta[*b*]indole scaffold in their structure. Fischerindole L **1**, isolated from blue-green algae (cyanobacteria) *Fischerella muscicola* by Moore and Patterson in 1992, is one of the first examples of natural products exhibiting an isonitrile in its structure. This alkaloid, a cyclopenta[*b*]indole, exhibits antifungal and cytotoxic activity against HCl-H460, lung human carcinoma cell lines (Figure 2).[5] Terpendole E **2**, a secondary metabolite isolated from the fungus *Albophoma yamanashiensis*, is the first natural inhibitor of kinesin Eg5.[6] This enzyme is deeply involved in the separation of centrosomes during the mitosis process. Selective inhibitors of this enzyme can induce cell cycle arrest at the M phase, being considered thus potential anticancer agents. Moreover, compounds acting by this inhibition mechanism present fewer side effects when compared with the conventional tubulin inhibitors.[2c] Yuehchukene **3** is another example of biologically active natural product exhibiting the

cyclopenta[*b*]indole scaffold.[7] This alkaloid, isolated from *Murraya paniculata*, showed anti-implantation activities, and could be used as an antifertility agent. Besides the products from natural sources, there are some examples of synthetic compounds in which this heterocyclic motif was incorporated searching to design new biologically active substances. Laropiprant **4** is an example of synthetic cyclopenta[*b*]indole that presents a cholesterol-lowering effect,[8] while **5** was designed to act as selective androgen receptor modulator.[9] Most recently, we demonstrated that compound **6** and derivatives are selective inhibitors of tubulin in colchicine binding site, acting as a promising antitumoral compounds.[10]

All effects associated to the presence of a cyclopenta[*b*]indole scaffold in a given molecule have stimulated efforts towards the development of a collection of protocols to their synthesis. Specifically, metal-catalyzed approaches to this nucleus have been recently reviewed.[11] In this chapter, we intend to cover comprehensively all synthetic methods to prepare cyclopenta[*b*]indolic compounds, focusing our attention on the 1*H*,2*H*,3*H*,4*H*-cyclopenta[*b*]indole skeleton **A** as well as on derivatives containing an endocyclic double bond at the 5-membered carbocycle **B** and **C**. It worth mentioning that no comments referring to others isomers or related structures were addressed in this chapter (see Figure 1).

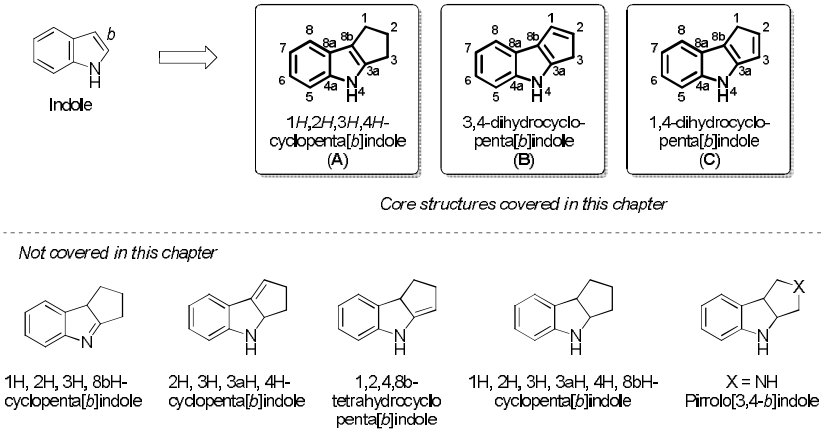


Figure 1. Structure of cyclopenta[*b*]indole and derivatives.

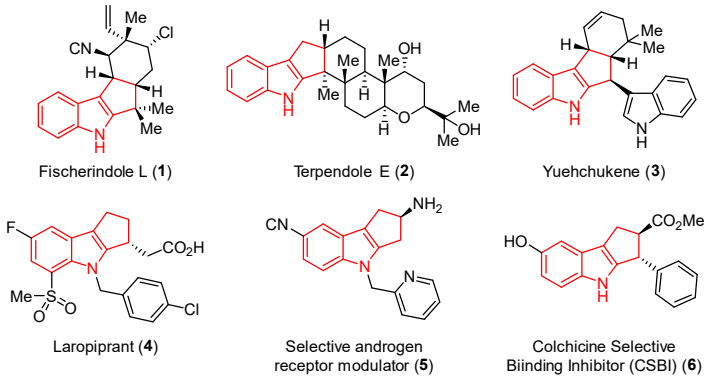


Figure 2. Some representative examples of biologically active compounds from natural or synthetic sources having the cyclopenta[*b*]indole scaffold in their structures.

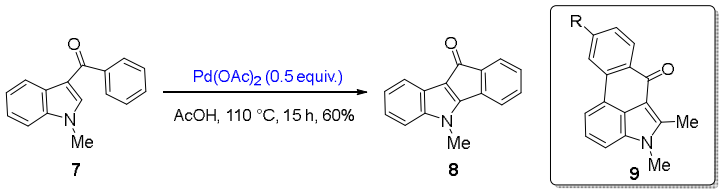
2. Metal-catalyzed approaches

The main methodologies for construction of cyclopenta[*b*]indole framework by means of transition-metals catalysis rely on functionalization of indole nucleus either through pre-halogenation and cross-

coupling reaction or direct C–H activation to form one C–C bond. Palladium-catalyzed transformations was firstly developed and corresponds to the highest number of reports. However, in the last few years, rhodium-catalysis has emerged as a powerful strategy to direct C–H functionalization, including an asymmetric approach. Some methodologies employing functionalized anilines have also been successfully developed to access cyclopenta[*b*]indoles through tandem C–N and C–C bonds formation. These processes are predominantly based on Au(I)-activation of triple C≡C bonds towards nucleophilic attacks.

2.1. Palladium-catalyzed approaches

In 1978, in attempt to develop a novel route to prepare polycyclic indole scaffolds, Itahara and Sakakibara reported one of the first examples of palladium-catalyzed indole annulation through direct C–H activation.[12] In the presence of acetic acid and palladium(II) acetate, 3-indolylphenylketone **7** afforded cyclopenta[*b*]indol-1-one **8** in 60% yield (Scheme 1). C2 substituted substrates led to 1-methyl-4,6-dihydronaphth[3,2,1-*c*,*d*]indol-6-ones **9** in poor yields. It is worth pointing out that, in this work, only one example of cyclopenta[*b*]indole was obtained and 50 mol% of $Pd(OAc)_2$ was required.



Scheme 1. Synthesis of cyclopenta[*b*]indol-1-one **8** through Pd-catalyzed C–H activation.

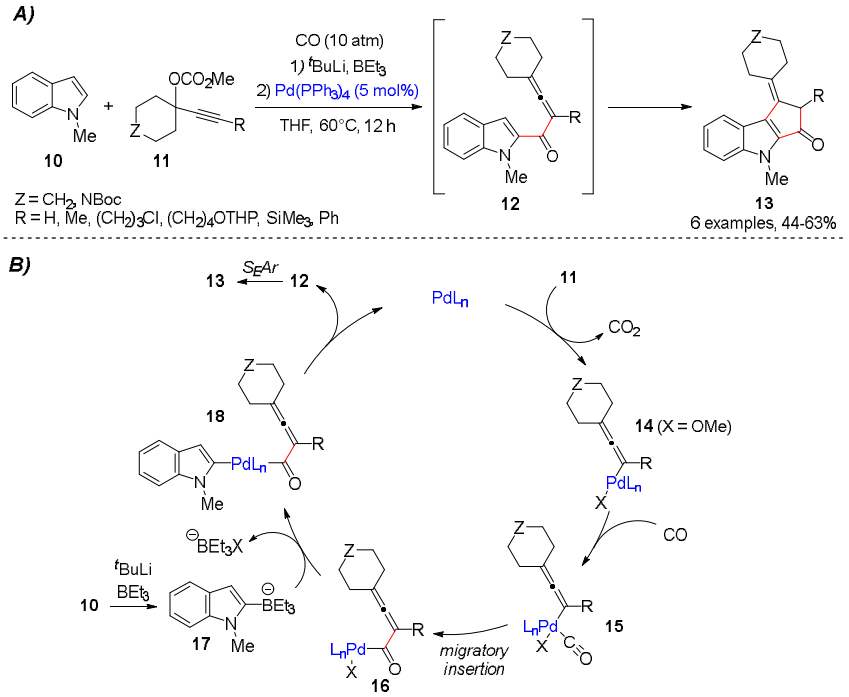
In 1996, Ishikura and coworkers reported a palladium-catalyzed carbonylative cross-coupling reaction of indolylborate generated *in situ* from **10** with prop-2-ynyl carbonates **11** to afford cyclopenta[*b*]indol-3-ones **13** (Scheme 2A).[13] These products were synthesized in moderate yields when alkyne moiety of **11** bears a substituent such as phenyl and alkyl. On the other hand, the product was not detected in reactions carried out with **11** bearing either trimethylsilyl group or hydrogen on the acetylenic carbon. Additionally, the presence of a Z=NBoc group instead of CH_2 has not been shown to influence the yield of the carbonylative cross-coupling reaction. The proposed mechanism involves the palladium-catalyzed formation of intermediate allenyl ketone **12**, and consecutive nucleophilic addition of the C3 carbon of indole to the internal allenic carbon to yield **13** (Scheme 2B).

Chen and coworkers developed an intramolecular Heck arylation to synthesize a diversity of indole frameworks from *o*-iodoanilines and ketones. Reaction of iodoaniline **19** with cyclopentanone **20** affords intermediate arylenamine **21** which undergoes Heck arylation to furnish cyclopenta[*b*]indole **22** (Scheme 3).[14]

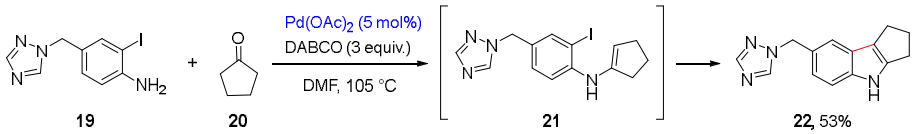
Chen's methodology was applied, with modifications, in several other works,[15] including the synthesis of biologically actives cyclopenta[*b*]indoles **25** from *o*-iodoanilines **23** and ethyl 2-(2-oxocyclopentyl)acetates **24**, by Sturino and O'Neill[16] and by Buzard and coworkers[17] (Scheme 4).

Stoltz and coworkers developed an indole C–H bond functionalization under mild and direct palladium catalysis, employing inexpensive and abundant molecular oxygen as oxidant.[18] Several C3-substituted indoles **30**, typically used as a mixture of olefin isomers, provided the correspondent cyclopenta[*b*]indoles **31** in good yields (Scheme 5). Cyclization could proceed either from C3 to C2 positions (Scheme 5A, 5D and 5E) or from C2 to C3 positions (Scheme 5B and 5C). Substrate **36**, a *Z*-alkene, afforded cyclopenta[*b*]indole **37** in a 6:1 mixture of diastereoisomers. Cyclization of **38** led to product **39** as a single diastereoisomer.

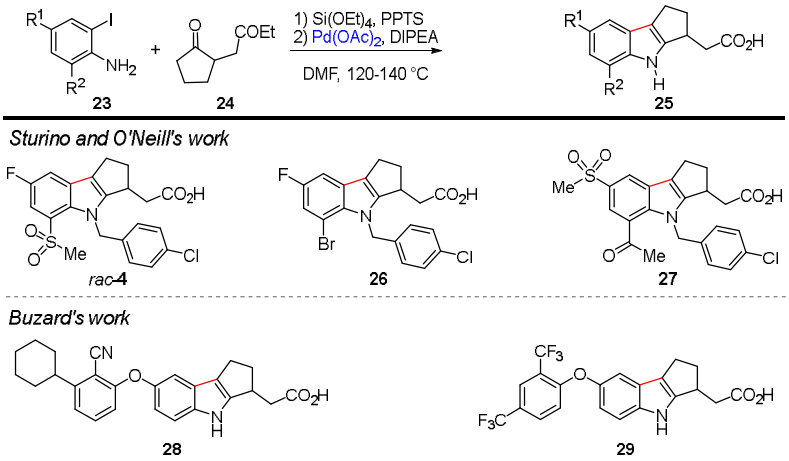
Inspired by Stoltz's work, Oestreich and coworkers have published initial efforts in the development of an enantioselective version of this reaction, although the observed enantioselectivity was poor.[19] In 2017, Fujita and Sasai succeeded in performing this transformation, obtaining products **41** in mostly good to excellent yields and with up to 99% enantiomeric excess employing their previously developed SPRIX ligand and benzoquinone as oxidant (Scheme 6).[20] The presence of a *N*-allyl group is crucial for the high enantioselectivity of the process, since the use of other groups attached to nitrogen led to lower ee's.



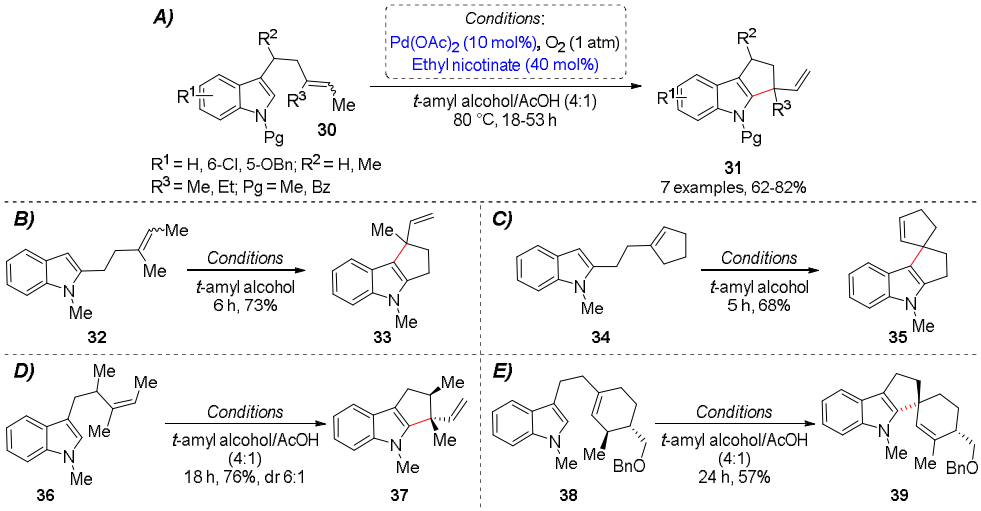
Scheme 2. A) Palladium-catalyzed carbonylative cross-coupling reaction leading to cyclopenta[*b*]indol-3-ones **13** and B) proposed mechanism.



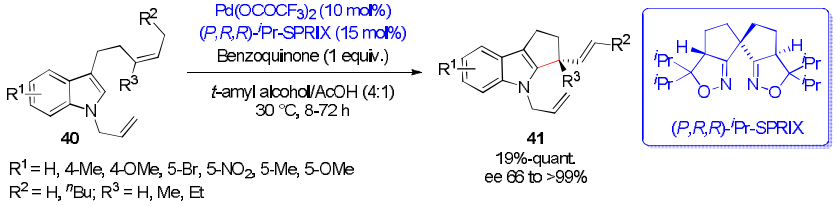
Scheme 3. Intramolecular Heck arylation approach to cyclopenta[*b*]indole.



Scheme 4. Representative examples of biologically actives cyclopenta[*b*]indoles prepared according to the approach developed by Chen.



Scheme 5. Scope of cyclopenta[*b*]indoles synthesized by Stoltz and Ferreira's approach.



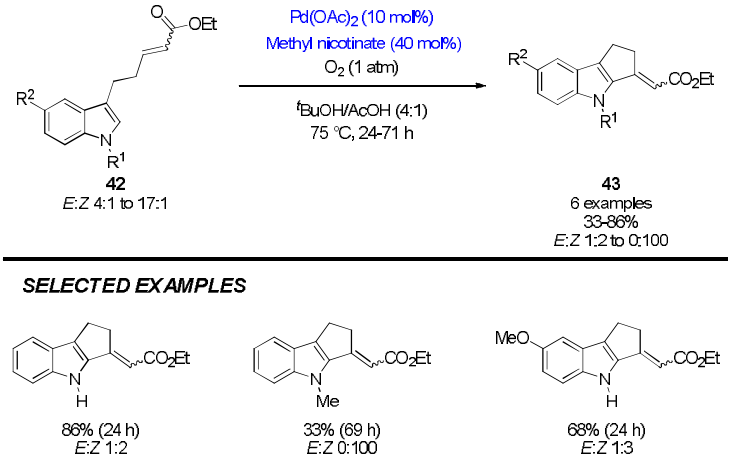
Scheme 6. Pd(II)-SPRIX-catalyzed C–H activation for the synthesis of cyclopenta[*b*]-indole **41**.

Recently, our group developed a breakthrough contribution in the oxidative Heck reaction employing electron deficient alkenes **42** to afford cyclopenta[*b*]indoles **43** (Scheme 7).[21] A *E*/*Z* mixture of substrates **42** containing an α,β-unsaturated ester moiety, prepared from substituted indole, reacts smoothly under palladium(II) catalysis to afford diastereoisomeric cyclopenta[*b*]indoles in mostly moderate yields. Low diastereoselectivities, favoring the *Z*-isomer, were observed, except when the nitrogen atom was attached to a methyl group. In this case, only the *E*-isomer was isolated, albeit in poor yield and longer reaction time.

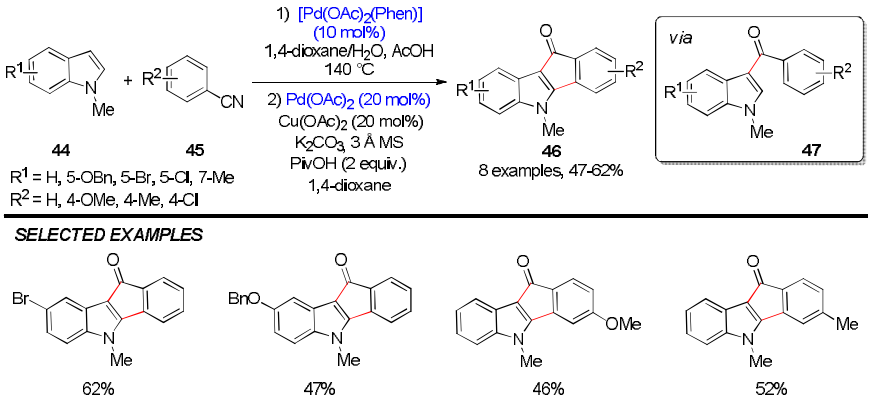
A one-pot approach to cyclopenta[*b*]indol-1-ones **46**, using *N*-methylindoles **44** and benzonitriles **45** as starting materials, was reported by You and coworkers (Scheme 8).[22] A general and selective Pd(II)-catalyzed addition of indoles to nitriles forms the intermediates 3-indolylarylketones **47**. This transformation followed by a palladium-catalyzed intramolecular oxidative C–H/C–H coupling leads to cyclopenta[*b*]indol-1-ones in mostly moderate yields.

Pal and coworkers have developed an unprecedented Pd-catalyzed cascade involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring from *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(2-iodoaryl)thiophene-2-sulfonamides **48** to synthesize novel cyclopenta[*b*]indoles **49** containing a thiophenesulfonamide group (Scheme 9).[23] The use of $Cu(OAc)_2$ instead of $Pd_2(dba)_3$ was found to be ineffective. The protocol afforded 23 examples of the desired product in moderate to good yields. Halogens, electron rich methoxy group or electron withdrawing substituents (such as NO_2 and CN) were all well tolerated. The proposal for the mechanism involves an intramolecular Heck arylation of allyl moiety to afford intermediate **50**, which could be isolated. This intermediate, after protonation, undergoes a C–N bond cleavage to give **52**. Attack of indolic carbon C3 towards terminal double C=C bond leads to **53**. Activation of C=N of **53** in presence of proton source and Pd(0), aided by sulfonamide moiety, promotes an transannular attack of indolic carbon C2 to form polycyclic intermediate

55. Although this intermediate could not be isolated, a similar tetracyclic species was identified. The six-membered Pd-containing ring of **55** undergoes another C–N bond cleavage to form **56**. Reductive elimination of Pd(0), regeneration of sulfonamide group and protonation of indolic nitrogen afford product.



Scheme 7. Synthesis of cyclopenta[*b*]indoles 43 *via* oxidative Heck reactions of α,β-unsaturated esters **42**.



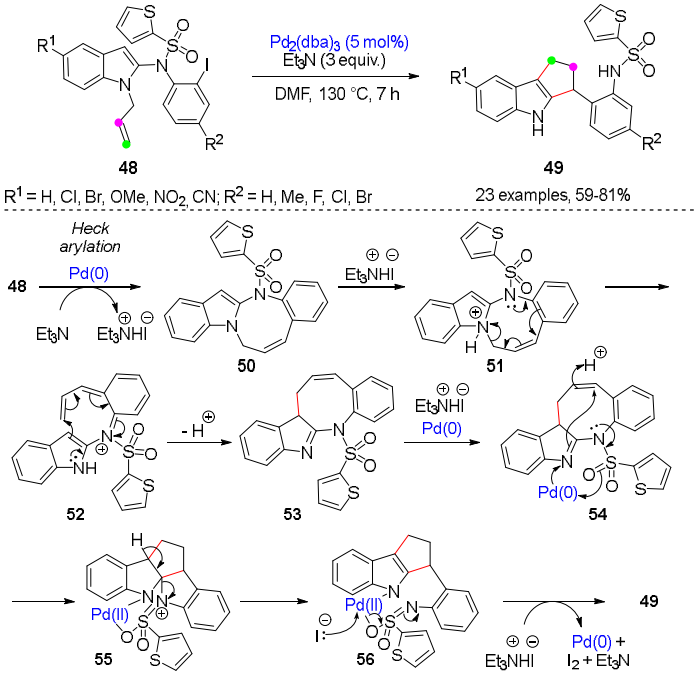
Scheme 8. Synthesis of cyclopenta[*b*]indol-1-ones **46** via Pd(II)-catalyzed oxidative C–H/C–H coupling.

In 2011, Mårtensson and coworkers described the first total synthesis of the dimeric alkaloid pigment scytonemin **60** through a stereoselective tandem Heck carbocyclization/Suzuki-Miyaura cross-coupling reaction (Scheme 10).[24] The starting material, 3-indole acetic acid **57**, was converted to iodoindole **58** in four steps. Then, a diastereoselective Heck-Suzuki sequence led to spiro cyclopenta[*b*]indole **59**, which was applied in the synthesis of natural product Scytonemin **60** through deprotections, dimerization and, lastly, oxidation steps.

An improved protocol has also been applied in the synthesis of 3-alkenyl substituted cyclopenta[*b*]indol-2-ones (Scheme 11).[25] In this work, 13 analogs were obtained in moderate to good overall yields and, in most cases, with high stereoselectivity. The ketals **67** were converted to enones **68** in two straightforward steps.

Mårtensson and coworkers have developed an intramolecular reductive Heck cyclization, used as the key step for the synthesis of alkaloid Nostodione A **71** from 3-indole acetic acid **57** (Scheme 12).[26] Heck cyclization yielded cyclopenta[*b*]indoles **70a** and **70b** in 78% combined yield of major *Z*-isomers. Although

both protected and unprotected products were obtained, the mixture of these compounds could be directly used in the following steps of the proposed synthetic route. The synthesis of **71** was accomplished with oxidations and protection/deprotection steps, affording the desired natural product in excellent *E*-selectivity.

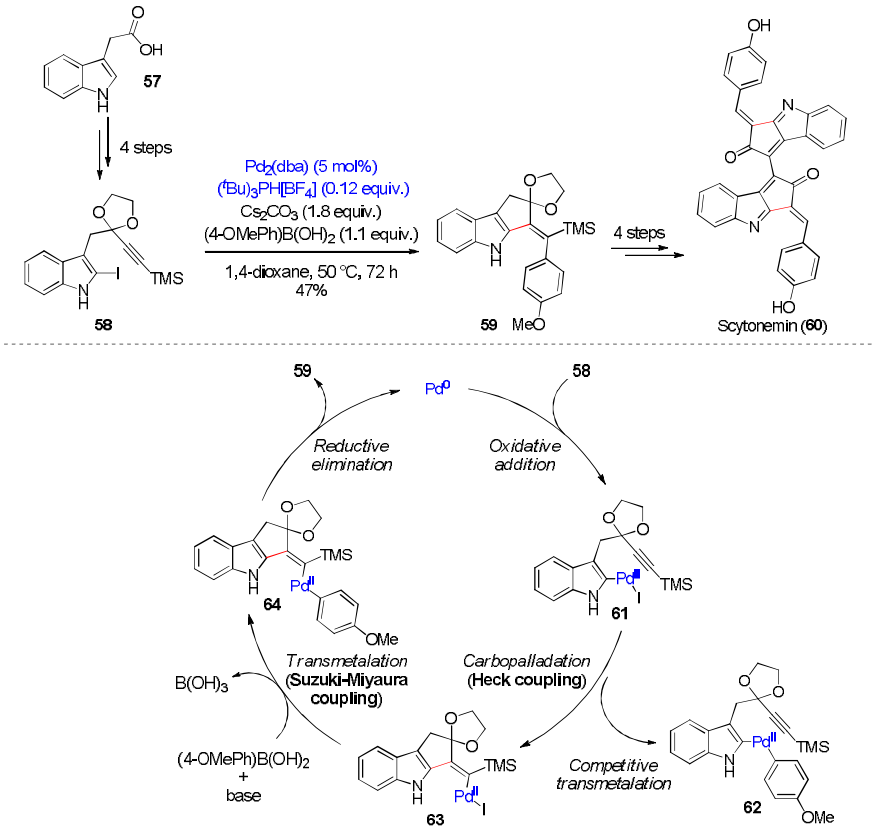


Scheme 9. Pal's approach to cyclopenta[*b*]indoles **49**.

A tandem cyclization of alkynones **72** to prepare pentaleno[2,1-*b*]indoles **73** was reported by Han and Lu (Scheme 13).[27] In a single operation, the polycyclic compounds, containing two adjacent stereocenters, were assembled with excellent diasteroselectivity. The transformation is initiated by *trans*-aminopalladation of alkyne moiety leading to intermediate **74**. Then, intramolecular nucleophilic addition of the C−Pd bond to the carbonyl group followed by protonolysis results in the formation of product **73**.

This protocol provided the products in typically good yields. When the benzene ring was substituted with an electron withdrawing group, the product was obtained in lower yields, as exemplified by **73b**. On the other hand, when the cyclopentanone moiety was substituted with an additional benzene ring, pentacyclic compound **73e** was obtained in excellent yield. Preliminary results of an asymmetric version were also reported: **73e** was obtained in 89% yield but with poor enantiomeric excess (64%) using chiral pyridine-oxazoline ligand **75** (Scheme 14).

In 2018, a new and general approach to prepare highly substituted cyclopentadiene frameworks through palladium catalysis was developed by Ramasastry and coworkers.[28] A Trost-Oppolzer type Alder-ene reaction of 2,4-pentadienyl acetates was efficiently applied to synthetize mostly indenes, including natural products. Few benzothiophenes were also obtained in good yields. Remarkably, the methodology could afford cyclopentapenta[*b*]indole **77** in 85% yield from corresponding indole **76** (Scheme 15). This strategy brings together electrophilic features of Tsuji-Trost reaction and nucleophilic features of Alder-ene reaction to afford cyclopentenyl cation **79** *via* π-allylpalladium **78**. Species **79**, upon proton loss and isomerization, leads to the more stable cyclopentadiene product **77**.



Scheme 10. Stereoselective tandem Heck-Suzuki sequence for the preparation of an advanced intermediate for the synthesis of natural product Scytonemin **60**.

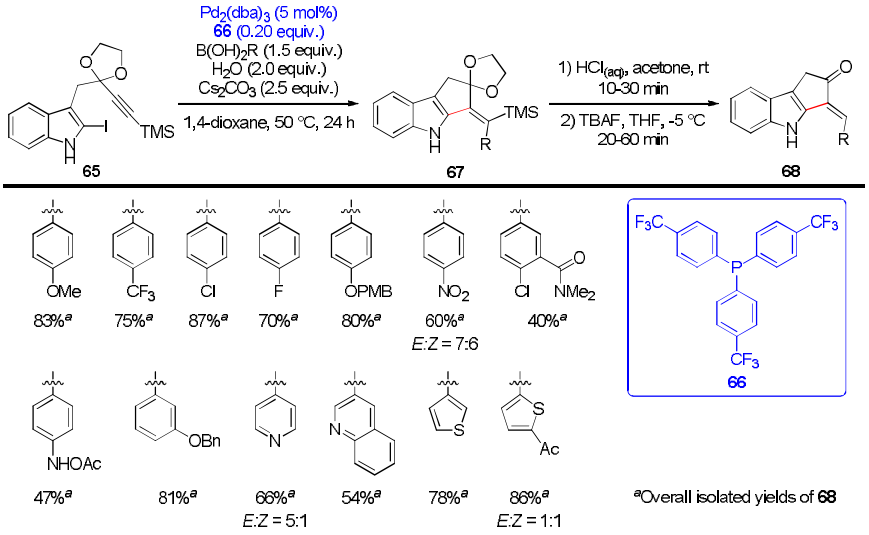
Despite only a single example of cyclopentapenta[*b*]indole prepared, the unprecedent transformation showed robusteness to introduce several groups across the diene skeleton. Therefore, further developments may expand its application in cyclopenta[*b*]indole synthesis, for example by means of substrate design.

2.2. Gold-catalyzed approaches

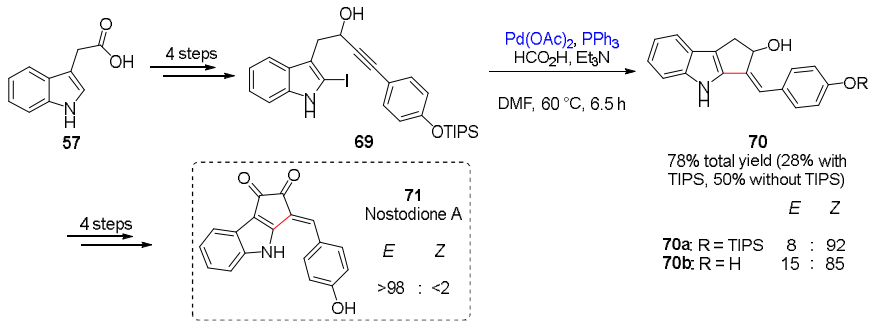
Gold-catalysis has emerged as an important area in organic synthesis due to its exceptional ability to activate triple bonds, such as alkynes, towards nucleophilic attack. In recent years, this alkyne-gold affinity has been efficiently applied as a strategy for cyclopenta[*b*]indole synthesis through activation of triple C≡C bonds towards attack of nitrogen- and carbon-based nucleophiles.

Ma and coworkers employed indoles with an electron-deficient allene at the C3-position **81** to form dihydrocyclopenta[*b*]indoles **82** in moderate to excellent yields via C2–H bond functionalization of the indole nucleus (Scheme 16).[29] It was verified that the presence of an electron withdrawing group, such as alkoxycarbonyl, dialkoxyphosphono or phenyl, attached on allene moiety is required for this transformation. In a mechanistic point of view, this transformation involves a selective coordination of cationic gold complex at the relatively electron-rich C=C bond in the allene moiety, followed by nucleophilic attacked of indolic carbon C2, in a 5-*endo*-*trig* cyclization, to form vinyl gold intermediate **84**. Subsequent deprotonative rearomatization and deauration steps lead to the product.

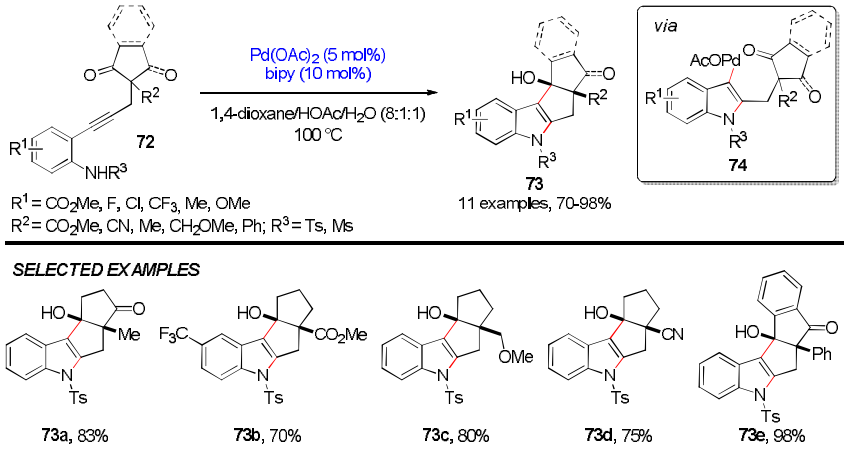
A similar strategy to synthesize cyclopenta[*b*]indole-1-ones **87** and 3-(furan-2-yl)-indoles **88** from *N*-SO_2py-protected allenones **86** was employed by Alcaide and coworkers (Scheme 17).[30]



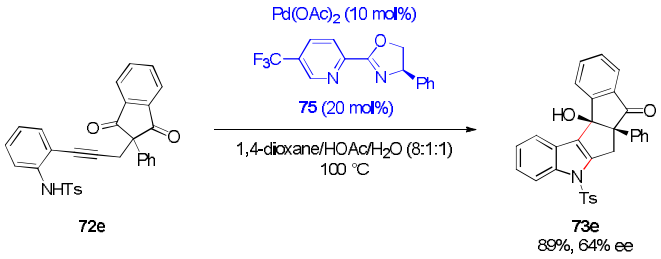
Scheme 11. Synthesis of 3-alkenyl substituted cyclopenta[*b*]indole compounds *via* stereoselective tandem Heck-Suzuki sequence.



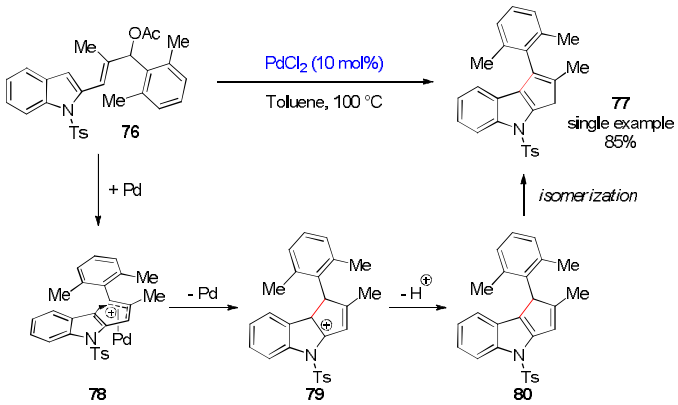
Scheme 12. Synthesis of Nostodione A *via* intramolecular reductive Heck cyclization.



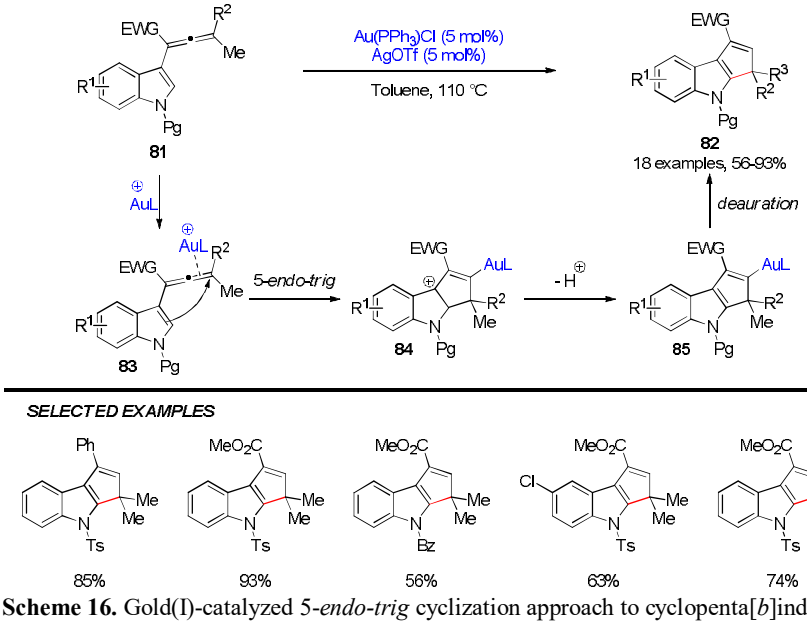
Scheme 13. Synthesis of pentaleno[2,1-*b*]indoles *via* tandem Pd(II)-catalyzed cyclization of alkynones **72**.



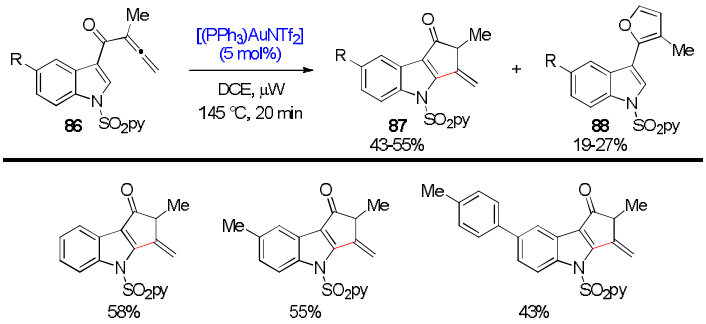
Scheme 14. Asymmetric synthesis of pentaleno[2,1-*b*]indole **73e**.



Scheme 15. Synthesis of cyclopenta[*b*]indole **77** from indole derivative **76**.



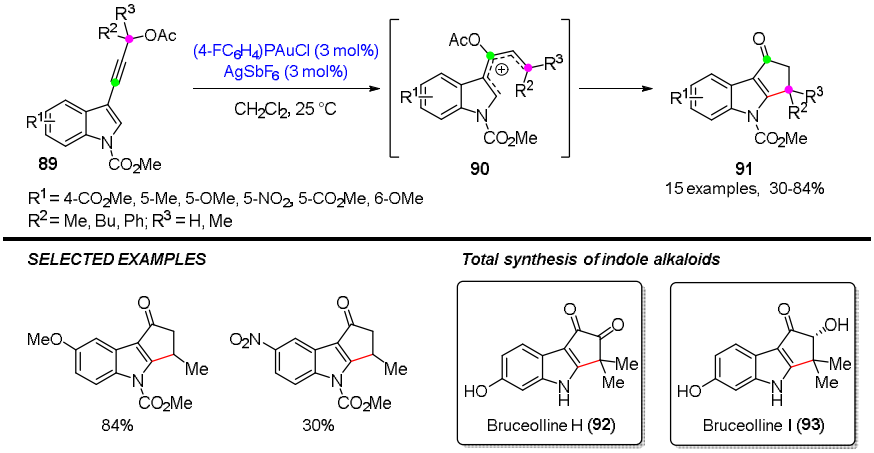
Scheme 16. Gold(I)-catalyzed 5-*endo-trig* cyclization approach to cyclopenta[*b*]indole **82**.



Scheme 17. Non-selective synthesis of *N*-protected cyclopenta[*b*]-indol-1-ones **85**.

Furan derivatives could be selectively obtained from both *N*-protected and *N*-unprotected allenones in good yields using dichloromethane as solvent at room temperature. On the other hand, the optimized conditions to prepare cyclopenta[*b*]indoles through gold-catalysis (1,2-dichloroethane as solvent, microwave-assisted) furnished only three examples in moderate yields, exclusively from *N*-protected substrates. Mechanistic studies indicate that after distal coordination of cationic gold at allene moiety, 5-*endo-dig* oxycyclization, affording **88**, is the preferred reaction pathway from both kinetic and thermodynamic perspectives.

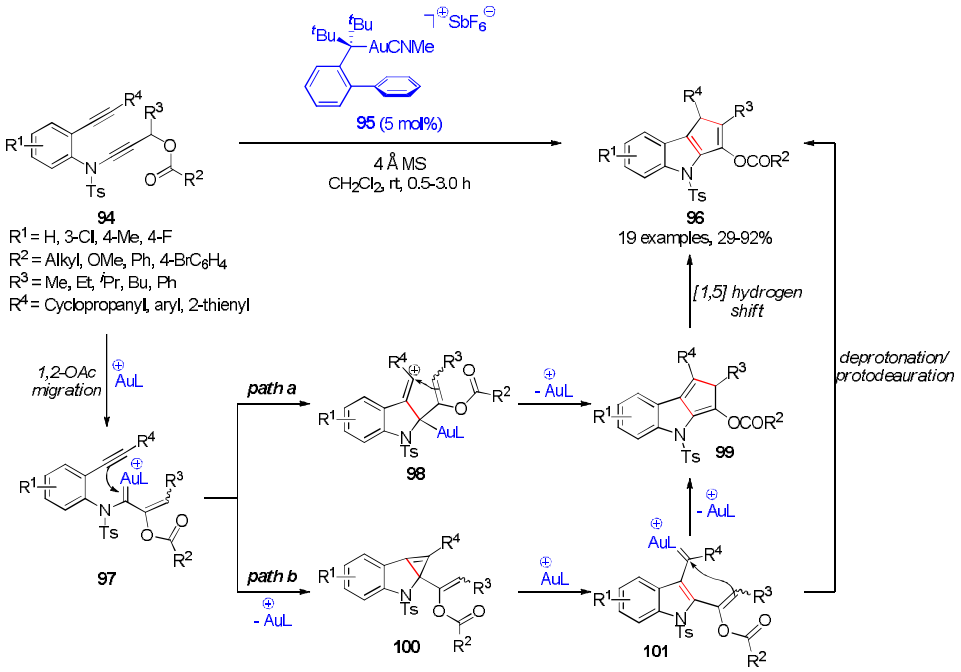
An efficient synthesis of cyclopenta[*b*]indol-1-ones **91** through a tandem gold(I)-catalyzed rearrangement/Nazarov reaction of propargylacetate indoles **89** was described by Occhiato and coworkers (Scheme 18).[31] The synthetic usefulness of the protocol was demonstrated by the total synthesis of Bruceolline H (**92**) and Bruceolline I **93**.[32] The transformation begins with gold(I)-catalyzed [3,3]-sigmatropic rearrangement of propargylacetate indoles to generate pentadienyl cation **90** which undergoes Nazarov cyclization to furnish desired product in mostly good yields.



Scheme 18. Cyclopenta[*b*]indol-1-ones **91** synthesized from propargylacetate indoles **89**.

In 2015, Liu and coworkers presented the first gold-catalyzed cycloisomerization of 1,6-diynes **94** with an ynamide propargyl ester moiety to access cyclopenta[*b*]indoles **96** (Scheme 19).[33] This methodology has broad substrate scope and furnishes the desired products in typically good yields. Mechanistic studies indicate that the reaction proceeds through a selective activation of ynamide propargyl ester by Au(I) followed by a 1,2-OAc migration to provide a vinyl gold carbenoid **97**. From this point, two reaction paths can supposedly lead to the same product. In *path a*, attack of the remaining alkyne moiety to the gold

carbenoid affords vinylic cation **98**. Subsequent nucleophilic attack of the alkene moiety to the vinyl cation followed by deauration leads to intermediate **99**, which undergoes a [1,5] hydrogen shift to provide the cyclopenta[*b*]indole **96**. In *path b*, a cyclopropene intermediate **100** leads to formation of gold-carbenoid **101**, which then cyclizes and can either form intermediate **99** via direct deauration or undergo deprotonation/protodeauration steps to furnish cyclopenta[*b*]indolic compound.



Scheme 19. Liu's approach to cyclopenta[*b*]indoles **96**.

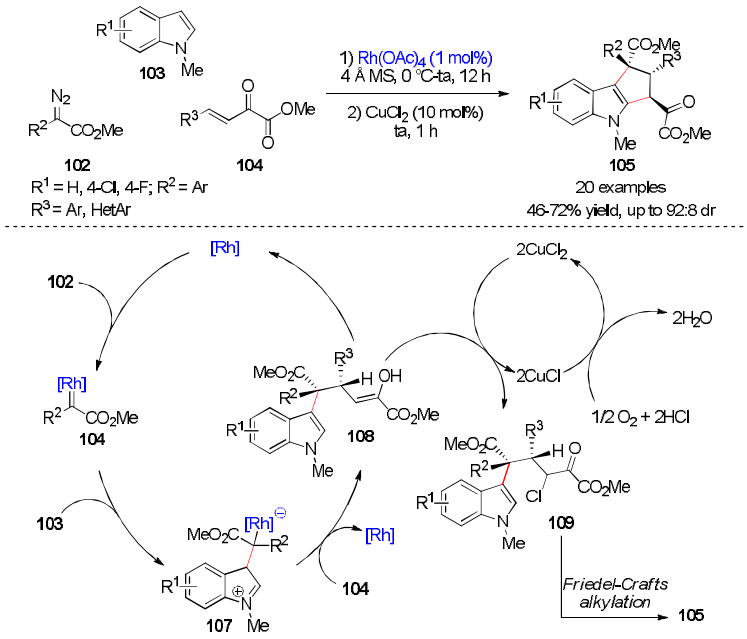
2.3. Rhodium-catalyzed approaches

In 2016, Hu and coworkers reported a Rh- and $CuCl_2$-catalyzed, highly diastereoselective three-component reaction for the synthesis of polyfunctionalized cyclopenta[*b*]indoles **105** in an atom- and step-economic fashion (Scheme 20).[34] Rhodium carbenoid generated *in situ* from diazoacetates **102** reacts with indoles **103** to give intermediate **107**. A subsequent trapping of **107** with α,β-unsaturated α-keto esters **104** through conjugate addition results in the formation of the three-component enol **108**. Attempts to achieve postcyclization product **105** with several oxidants have failed. However, addition of $CuCl_2$ led to the formation of α-chloro carbonyl key intermediate **109**, which undergoes intramolecular Friedel-Crafts alkylation to furnish the cyclopenta[*b*]indole product **105**. Mechanistic studies suggest that the catalytic cycle involves Cu(II) and Cu(I) species. In the presence of HCl, copper(I) chloride is oxidized to regenerate catalyst under aerobic conditions. This coupling reaction represents a unique example of aerobic Cu-catalyzed direct coupling of indoles with enols under mild conditions.

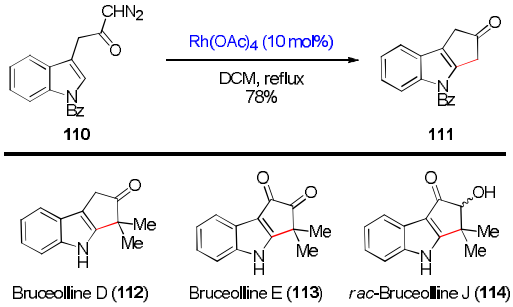
An intramolecular rhodium carbenoid C–H insertion was employed by Dethe and Kumar as key step in the divergent synthesis of natural products Bruceollines D, E and J **112-114** (Scheme 21).[35] The diazoketone **110**, prepared in two steps from 3-indole acetic acid **57**, was submitted to reflux of CH_2Cl_2 in presence of catalytic amount of $Rh(OAc)_4$ to afford cyclopenta[*b*]indol-2-one **111** in 78% yield, which after a high regioselective *gem*-dimethylation and deprotection provides Bruceolline D **112**. The other two Bruceollines **113** and **114** were obtained upon redox and deprotection steps.

In 2017, Stanley and Vickerman reported an enantioselective intramolecular Rh-catalyzed hydroacylation of alkene moiety of oxygen-, sulfur- and nitrogen-heterocycles to synthesize complex

polycyclic structures. The developed protocol allowed the access of cyclopenta[*b*]indol-3-ones **117** from 3-vinylindole-2-carboxaldehydes **115** in yields ranging from good to excellent and with good to excellent enantioselectivities (Scheme 22).[36] While investigating the substrate scope, the authors verified that arenes containing either electron-rich or electron-poor groups are suitable substituents at the internal carbon of the olefin (R^2). Substrates containing arenes with larger *ortho*-substituents require a higher temperature (100 °C) and 1,4-dioxane as solvent to generate the corresponding cyclopenta[*b*]indole in high yields, although with loss of enantioselectivity. Substrates containing heteroarenes and the electron withdrawing methyl ester group at the internal carbon of the vinyl moiety could afford the desired product in good yield and ee higher than 98%. Indoles with different substituents at the nitrogen are also well tolerated.



Scheme 20. Rh- and $CuCl_2$-catalyzed three-component reaction for the synthesis of polyfunctionalized cyclopenta[*b*]indoles **105**.

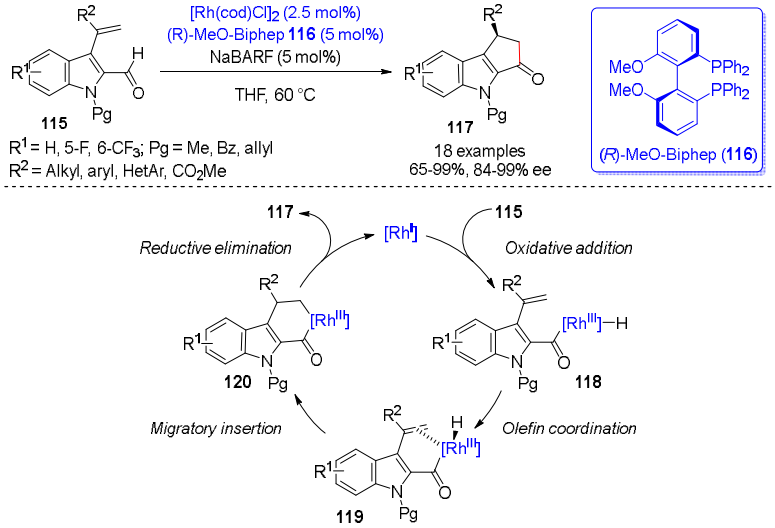


Scheme 21. Rh-catalyzed synthesis of a cyclopenta[*b*]indol-2-one for the divergent synthesis of Buceollines D, E and J.

3. Brønsted acid catalyzed or promoted approaches

Among the methodologies to access cyclopenta[*b*]indolic compounds catalyzed by Brønsted acids, the Fisher indole synthesis can be highlighted as a classical one. This reaction was applied in several

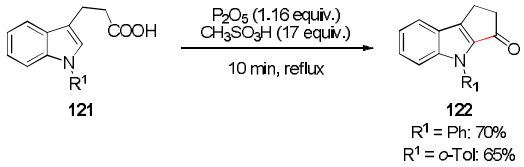
descriptions in the chemical literature, reporting the construction of cyclopenta[*b*]indoles and investigation of their bioactive properties.



Scheme 22. Synthesis of cyclopenta[*b*]indol-3-ones **117** via Rh-catalyzed intramolecular hydroacylation.

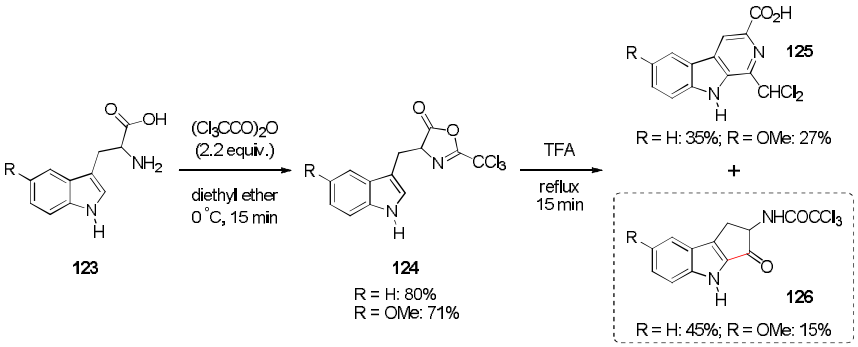
For example, Fischer indole synthesis was used by Ratni and coworkers,[37] who prepared tetrahydrocyclopenta[*b*]indoles found to be selective modulators of LXRs hormones, and by Montalban and coworkers in the synthesis of tetrahydrocyclopenta[*b*]indoles by reacting disubstituted cyclopentanones and phenyl hydrazines.[38] Another classical approach for the synthesis of this tricyclic scaffold is the Nazarov cyclization. It was explored in the synthesis of natural product Bruceolline E **113** by Badenock and coworkers, who achieved a cyclization of *in situ* generated 3-indolyl vinyl ketones in presence of trifluoroacetic anhydride.[39] More recently, an asymmetric version was developed by Chan and coworkers to access indanes and polysubstituted cyclopenta[*b*]indoles from aryl-vinyl alcohols.[40]

Friedel-Crafts reactions have also been employed in the synthesis of cyclopenta[*b*]indole. In 2003, Horton and coworkers[41] described the synthesis of ansa-zirconocenes cyclopenta[*b*]indolic compounds, which were further applied as catalysts in propylene polymerization. The key step in the synthesis of the cyclopenta[*b*]indolic nucleus was a Brønsted acid-mediated, intramolecular Friedel-Crafts reaction. Cyclization of propionic acids **121** to cyclic ketones **122** occurred under the action of polyphosphoric acid (PPA) or a solution of P_2O_5 in methanesulfonic acid (Scheme 23).



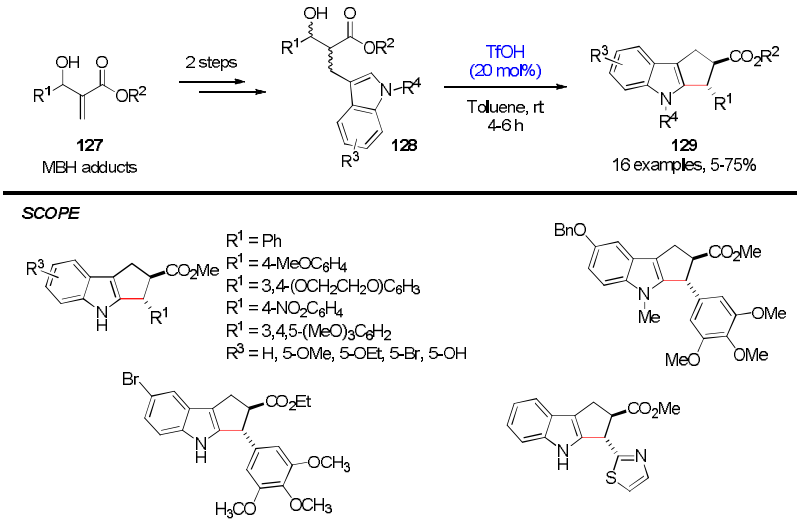
Scheme 23. Cyclization step catalyzed by methanesulfonic acid to access cyclopenta[*b*]indoles **122**.

In a similar approach, Bergman and coworkers have prepared cyclopenta[*b*]indolic compounds using an intramolecular cyclization of 5-(4*H*)-oxazolones **124**, readily obtained from tryptophan derivatives **123** (Scheme 24).[42] Use of trifluoroacetic acid as catalyst in the intramolecular cyclization furnishes cyclopenta[*b*]indoles **126** as byproducts in low yields. The observed product distribution was dependent of the reaction temperature, with lower temperatures favoring the formation of β-carbolines **125**.



Scheme 24. Access to cyclopenta[*b*]indoles **126** *via* intramolecular cyclization of oxazolones catalyzed by trifluoroacetic acid.

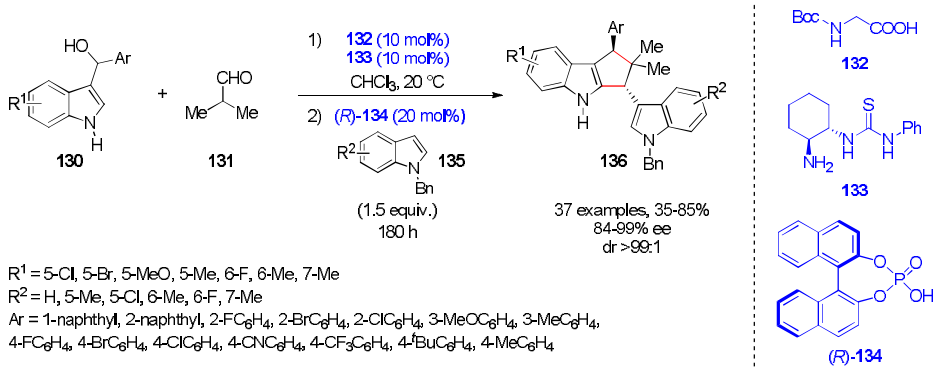
In 2016, our research group reported a new, highly diastereoselective methodology to access cyclopenta[*b*]indolic compounds from Morita-Baylis-Hillman (MBH) adducts with high atom economy.[10] In this approach, the MBH adducts **127** are converted to β-hydroxyesters **128**, which were treated with catalytic triflic acid to furnish cyclopenta[*b*]indoles **129** *via* an intramolecular Friedel-Crafts cyclization. The authors obtained 16 examples of polysubstituted cyclopenta[*b*]indolic compounds with excellent diastereoselectivity in mostly moderate to good yields (Scheme 25).



Scheme 25. Diastereoselective synthesis of cyclopenta[*b*]indoles **129** through triflic acid-catalyzed Friedel-Crafts alkylation.

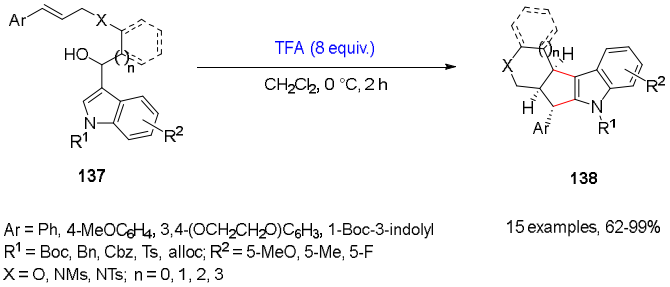
In 2012, Guo and coworkers established an asymmetric methodology to access cyclopenta[*b*]indolic compounds.[43] In this approach, the authors described diastereo- and enantioselective one-pot reactions to obtain polysubstituted cyclopenta[*b*]indoles **136** (Scheme 26). The reaction sequence begins with an α-alkylation of isobutyraldehyde **131** with the indolylmethyl cation generated by dehydration of substrate **130**. This process is catalyzed by a combination of aminoacid derivative **132** and chiral thiourea **133**. Then, under the action of chiral phosphoric acid (*R*)-**134**, the resulting aldehyde undergoes an intermolecular Friedel-Crafts alkylation with *N*-benzylindoles **135** to afford a 3-indolylmethanol moiety, which in turn

cyclizes through another Friedel-Crafts step to furnish polysubstituted products **136** in poor to good yields and with good stereoselectivity.



Scheme 26. Enantioselective one-pot synthesis of polysubstituted cyclopenta[*b*]indoles **136** *via* Brønsted acid catalysis.

In 2013, Hamada and coworkers developed a protocol to obtain cyclopenta[*b*]indoles based in a three step sequential approach.[44] Substrates **137** undergo dehydration in acidic medium, followed by an intramolecular ene-type reaction and finally Friedel-Crafts alkylation to generate polycyclic cyclopenta[*b*]indolic derivatives **138** with yields ranging from moderate to excellent (Scheme 27). Nevertheless, some limitations of this protocol are the need to employ high amounts of trifluoroacetic acid and substrate dependency, since electron rich aryl (Ar) groups are required to stabilize the cationic intermediate generated in the ene-type cyclization step.

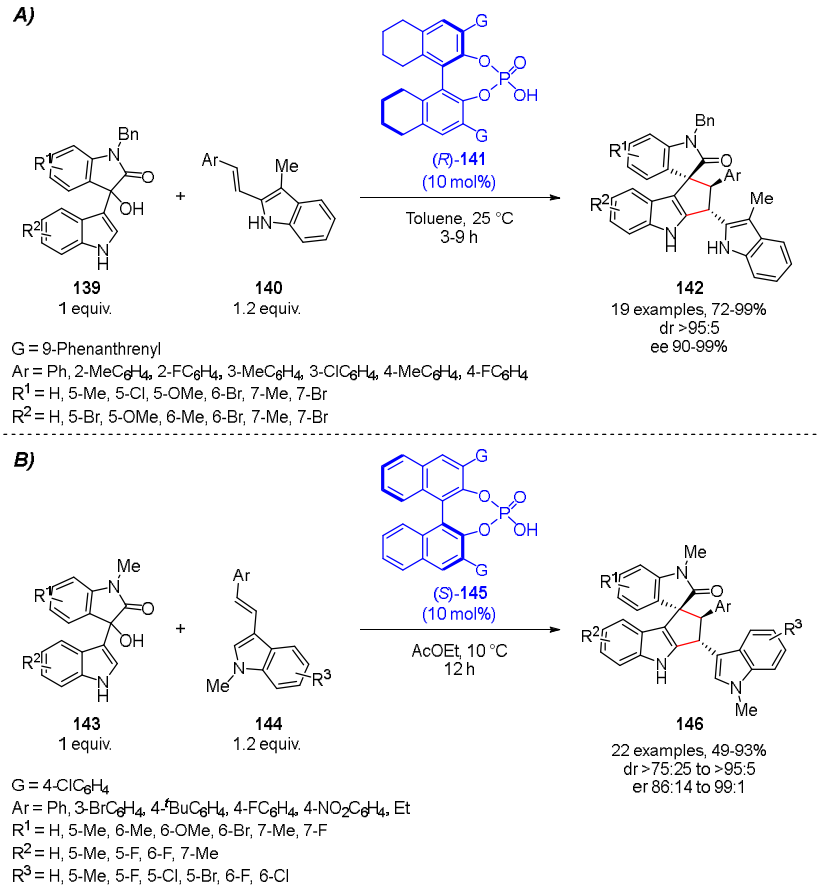


Scheme 27. Synthesis of polycyclic cyclopenta[*b*]indoles **138**.

In 2014, Shi and coworkers developed an asymmetric organocatalytic strategy to synthesize spirocyclopenta[*b*]indoles.[45] 3-hydroxy-3-(indol-3-yl)-oxindoles **139** and 3-methyl-2-styrylindoles **140** were employed as starting materials, generating spiro cyclopenta[*b*]indole-1,3-oxindoles **142** (Scheme 28A). The reaction is catalyzed by chiral phosphoric acid (*R*)-**141**, leading to three contiguous stereogenic centers with yields ranging from good to excellent and good diastereo- and enantioselectivities. From a mechanistic point of view, compounds **139**, under acid catalysis, afford stable indolylmethyl cations, which undergo a stepwise [3+2]-cycloaddition with styrenes **140** to form the products in an enantioselective fashion. Guo and coworkers have employed 3-styrylindoles and 3-indolylmethanols as substrates in a similar approach.[46] Later in 2016, Shi and coworkers expanded the scope of this transformation by using 3-hydroxy-3-(indol-3-yl)-oxindoles **143** and *N*-methyl-3-styrylindoles **144** as starting materials and chiral phosphoric acid (*S*)-**145** as catalyst (Scheme 28B).[47]

Shi's group have continued to give contributions on cyclopenta[*b*]indole synthesis through (3+2)-annulations of stable indolylmethyl cations and relatively electron rich alkenes. In 2017, they described

another enantioselective methodology to access indolic derivatives now employing substituted indoles **147** and 4-hydroxystyrenes **148** as starting materials, with chiral phosphoramide (*S*)-**149** as catalyst (Scheme 29A).[48] This approach allowed the authors to access novel cyclopenta[*b*]indolic derivatives **150** in good yields and with moderate to good enantiomeric excesses. Shi and coworkers have expanded the scope of this reaction with structurally modified substrates. 3-Styrylindoles **151** reacted with indoles **152** or naftols **153** under catalysis of chiral phosphoric acid (*S*)-**141**. The methodology furnished polysubstituted compounds **154** or **155**, which possess a completely substituted saturated ring, in poor to good yields and with moderate to excellent enantiomeric excesses (Scheme 29B).[49] It is believed that, once substrates **151** dehydrate by action of acid, the resulting carbocations are attacked by the 3-stytyl moiety in an intramolecular fashion, forming the 5-membered carbocyclic units. Final nucleophilic attack by **152** or **153** completes the mechanism. The use of enaminones as nucleophilic partners in this reaction has also been reported.[50]

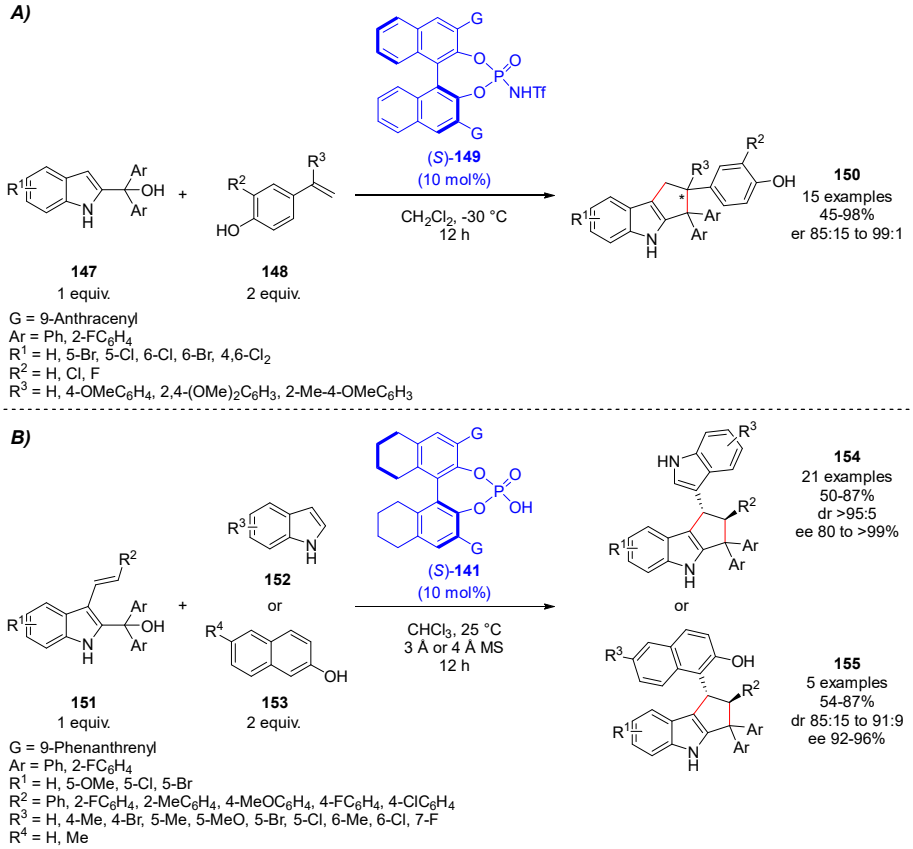


Scheme 28. Enantioselective synthesis of spiro cyclopenta[*b*]indoles **142** and **146** *via* chiral phosphoric acid-catalyzed [3+2]-cycloaddition.

In 2015, Masson and coworkers described an asymmetric synthesis of 3-aminocyclopenta[*b*]indoles **159** through an organocatalyzed [3+2]-cycloaddition reaction between ene-carbamates **156** and 3-indolylmethanol **157** (Scheme 30).[51]

Also in 2015, in a novel approach, Rodríguez and coworkers performed the synthesis of a series of cyclopenta[*b*]indolic derivatives *via* Brønsted acid catalyzed (3+2)-carbocyclization reactions of imines **163**,

generated *in situ* from indole-2-carboxaldehydes **160** and anilines **161**, with electron rich alkenes **162**.[52] The methodology afforded a broad scope of cyclopenta[*b*]indoles **164** easily accessed employing diphenyl phosphate acid (DPP) as catalyst with yields ranging from moderate to excellent (Scheme 31A). Computational studies supported the mechanistic proposal of a Mannich/Friedel-Crafts cascade *via* an oxocarbenium ion intermediate. The asymmetric version, nevertheless, was poorly explored by the authors who reported only one example. Reaction between **160a**, **161a** and **162a** using catalytic amounts of (*R*)-VAPOL phosphoric acid (*R*)-**165** gave the desired product **164a** in 94% yield and excellent diastereoselectivity, but only moderate enantioselectivity (Scheme 31B).



Scheme 29. Enantioselective synthesis of polysubstituted cyclopenta[*b*]indoles *via* [3+2]-cycloaddition reactions catalyzed by chiral A) phosphoramide and B) phosphoric acid.

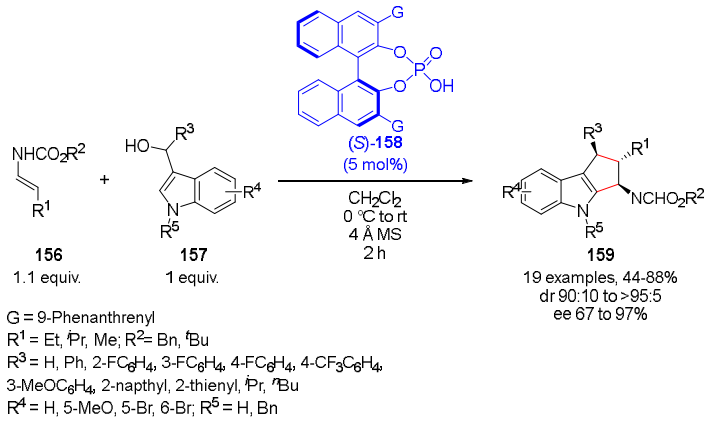
4. Lewis acid catalyzed or promoted approaches

The synthesis of cyclopenta[*b*]indoles through use of Lewis catalysts (or promoters) has been explored in the chemical literature. It is possible to identify two main strategies envolving the construction of the cyclopenta ring: an approach based on electrophilic aromatic substitution (S_EAr) at C2 or C3 position of the indole ring, and other based on the concerted Nazarov approaches (Scheme 32). Examples of these two approaches will be discussed in this section.

4.1. Cyclization based on electrophilic aromatic substitutions (S_EAr)

An early example of Lewis acid as a promoter of electrophilic aromatic substitution in order to synthesize cyclopenta[*b*]indoles comes from the Moody group, which reported the synthesis of compounds

168 from indole-3-methanols **166** (Scheme 33).[53] Treatment of these reagents with styrenes **167** and 4 equivalents of titanium(IV) chloride as a promoter in low temperatures leads to the cycloadducts **168** in low to moderate yields and retention of relative stereochemistry of the alkene. Except for one example, products were obtained as only one diastereoisomer. Indole-2-methanols also proved to be suitable substrates for this transformation, but electron-rich alkenes, such as dihydropyran and 1-diethylaminocyclohexene, could not afford the desired products. The proposed mechanism involves a dehydration promoted by the Lewis acid and formation of indolylmethyl cation **169**. This stable specie reacts promptly with styrene **167** in a C–C bond forming step to give cation **170**, which undergoes Friedel-Crafts alkylation at position 2 in three steps: nucleophilic attack *via* C3, forming spirocyclic intermediate **171**, and then a migration step followed by rearomatization of indole system to provide **168**.

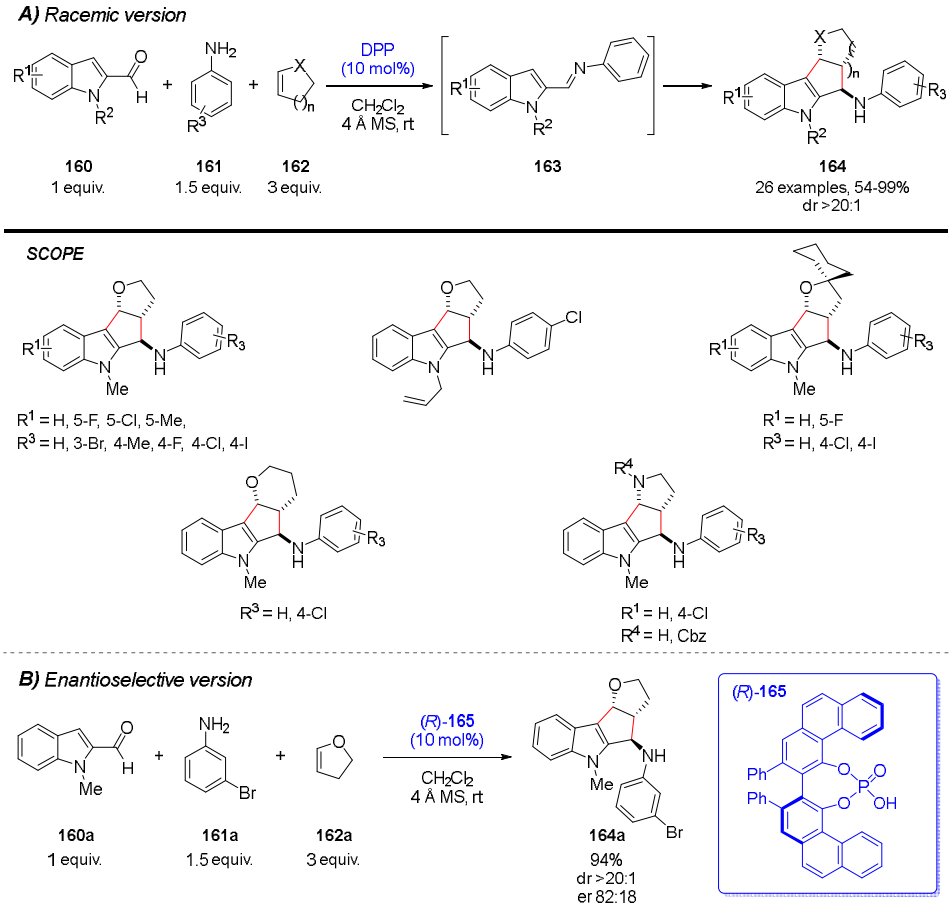


Scheme 30. Enantioselective synthesis of 3-aminocyclopenta[*b*]indoles **159** *via* chiral phosphoric acid-catalyzed [3+2]-cycloaddition.

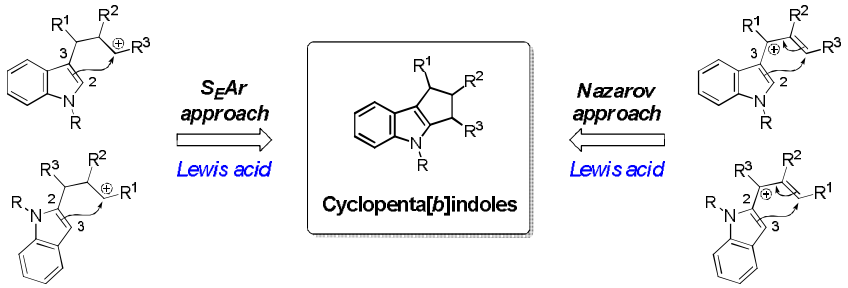
When a styryl group is conveniently placed in indole-3-methanols, like in compounds **137**, acid-catalyzed intramolecular cyclization occurs to form polycyclic cyclopenta[*b*]indoles **138** (Schemes 27 and 34). In a report from 2013, Hamada and coworkers reported three different acidic conditions that promote cyclization to the desired compounds, two of which being Lewis acids (boron(III) and scandium(III) compounds)in catalytic amounts.[44] Products **138** were obtained in moderate to excellent yields and as only one isomer (with one exception), the methodology using scandium(III) triflate being specially successful for the formation of 8-membered rings. The sequence of reactions is analogous to that described in Scheme 33, with substrate **137** undergoing acid-catalyzed dehydration, intramolecular ene-type addition of the styryl moiety and intramolecular Friedel-Crafts reaction to afford polycyclic compounds **138**. It is worth mentioning that although TFA was used efficiently as Brønsted acid promoter, high quantities (8 equiv.) were necessary to complete the reaction. Also, when an analogous indole-2-methanol was used as substrate, the corresponding isomeric cyclopenta[*b*]indole was obtained in good yield. A rationalization of the diastereoselectivity of this transformation was presented, in which avoidance of allylic strain could explain the observed relative stereochemistry of the products.

In 2011, McNulty and coworkers used a similar strategy by developing a cyclodimerization of 2'-aryl-substituted 3-vinylindoles **172**, forming [3+2] cycloadducts **173** (Scheme 35).[54] In an attempt to obtain the corresponding (4+2) products, the authors reported that Lewis acids such as $ZnBr_2$ catalyze the dimerization of **172** in toluene at 80 °C, affording cycloadduct **173** as the only isolated diastereoisomer. Although few examples are presented, aryl derivatives containing electron withdrawing and electron donating groups reacted equally well and yields were good to excellent. A derivative containing heteroaryl moieties was also synthesized. The suggested mechanism is based on formation of indolylmethyl cation **174,** by protonation of the alkene or its coordination with the Lewis acid (Scheme 34), which is then trapped by the starting alkene, leading to intermediate **175**, and final Friedel-Crafts alkylation step completes the

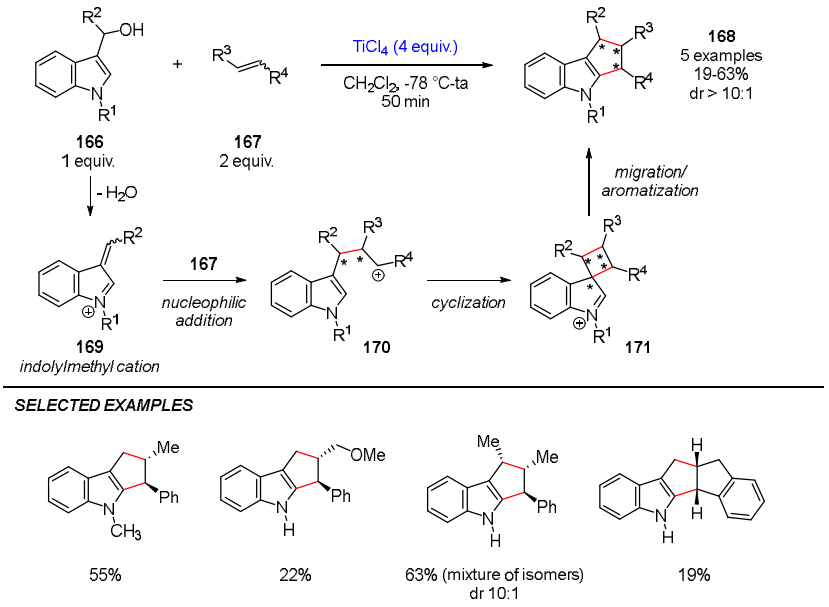
mechanism. It was speculated that π-stacking interactions are involved in the late transition state forming product **173** and could account for the observed diastereoselectivity.



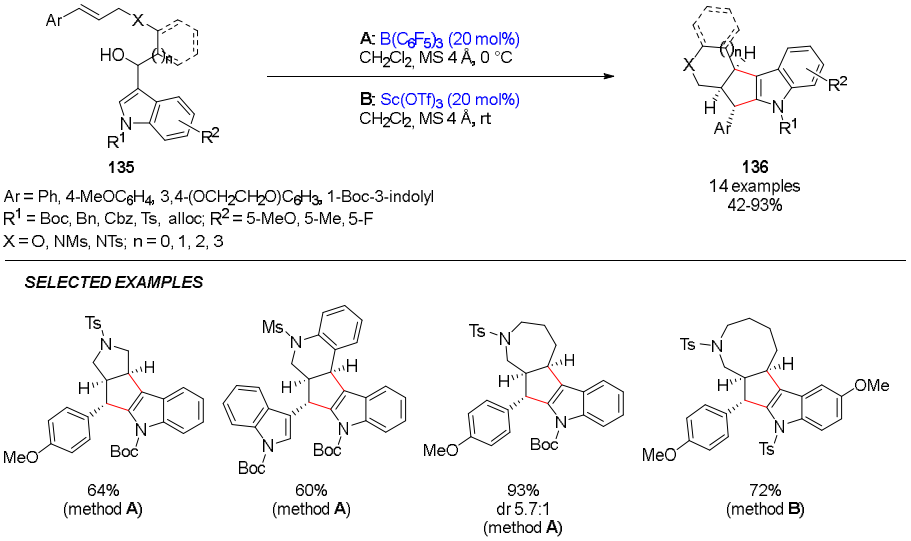
Scheme 31. Multicomponent synthesis of cyclopenta[*b*]indoles **164** catalyzed by phosphoric acids: A) racemic version and B) enantioselective version.



Scheme 32. Two main strategies for assembling the cyclopenta[*b*]indole motif using Lewis acid catalysis.



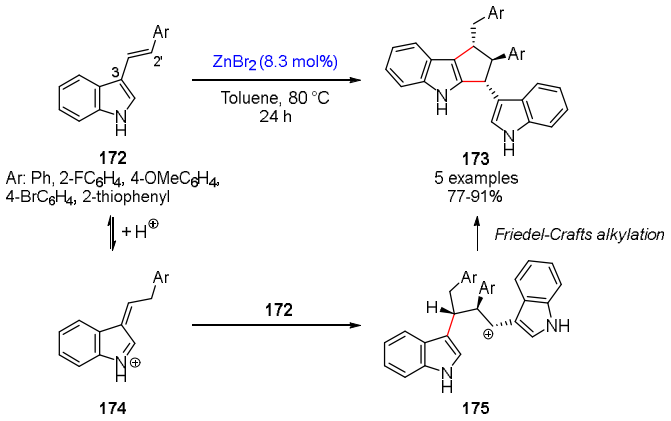
Scheme 33. Synthesis of cyclopenta[*b*]indoles from indole-3-methanols **166**.



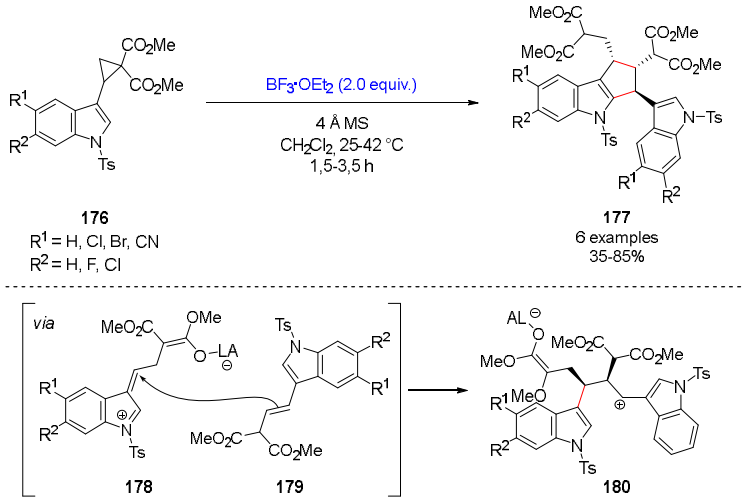
Scheme 34. Synthesis of polycyclic cyclopenta[*b*]indoles **138** *via* acid-catalyzed intramolecular annelation.

Another cyclodimerization approach was latter introduced by Budynina and coworkers by using dimethyl 2-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1,1-dicarboxylates **176** as substrate (Scheme 36).[55] Combination of $BF_3{\cdot}OEt_2$ as mediator and dichloromethane as solvent proved to be a more successful catalyst system over other Lewis or Brønsted acids. In fact, under these conditions, cyclopenta[*b*]indoles **177** were obtained as only one diastereoisomer and in mostly good yields. They propose that Lewis acid complexation to the starting material induces formation of stable *zwitterion* **178**, which then reacts with **179**

(formed by proton migration of **178**) to afford **180**. An intramolecular Friedel-Crafts alkylation of **180** completes the mechanism.

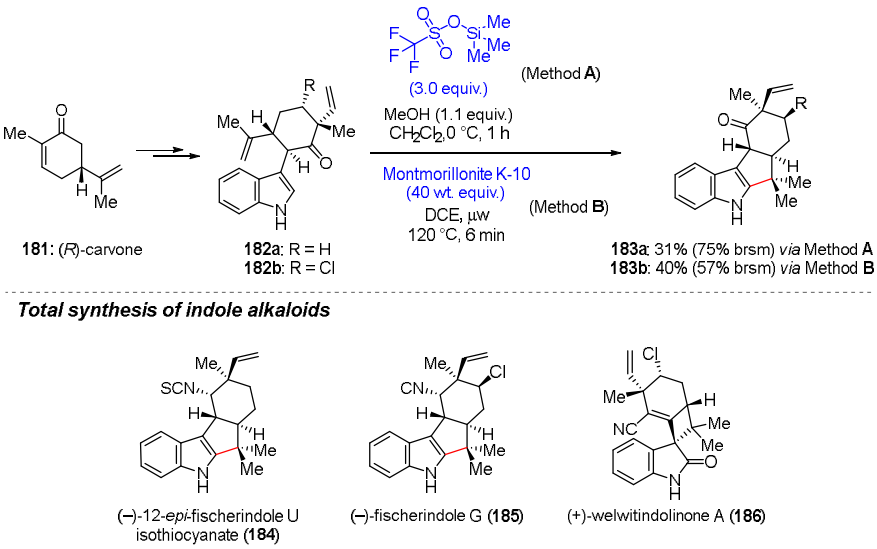


Scheme 35. Cyclodimerization of of 2'-aryl-substituted 3-vinylindoles **173**.



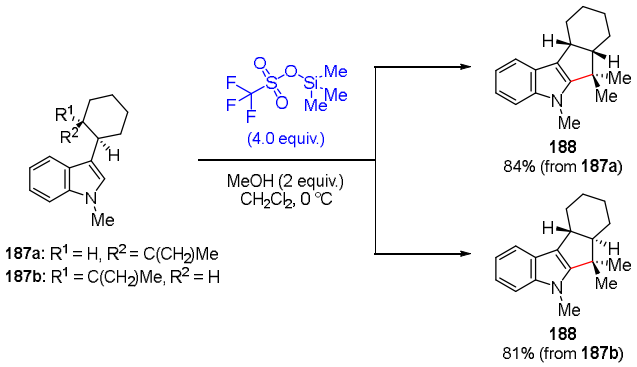
Scheme 36. Cyclodimerization of dimethyl 2-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1,1-dicarboxylates **176**.

In their elegant work describing the synthesis of several indole alkaloids **184-186**, Baran and Richter envisaged the preparation of advanced intermediates **183** through biomimetic intramolecular Friedel-Crafts reaction of C3-substituted indole substrates **182** (Scheme 37).[56] The authors based their conditions on a previous report describing this acid-promoted cyclization as an undesired parallel reaction.[57] Thus, ketone **183a** was obtained as only isomer by treatment of (*R*)-carvone derivative **182a** with 3.0 equivalents of TMSOTf as Lewis acid and methanol in dichloromethane at 0 °C. After one hour, compound **183a** was obtained in 31% yield, with recovery of 59% of unreacted **182a**. For the chlorinated structural analogous **182b**, however, numerous acid catalysts were tested, high loadings of solid Lewis acid Montmorillonite K-10 clay (40-fold weight excess to **182b**) being the choice to furnish cyclopenta[*b*]indole in acceptable yield with recovery of unreacted starting material. Even though this transformation had poor yields, it allowed the construction of the carbon skeletons of natural products **184** and **185** with the correct absolute and relative stereochemistry.



Scheme 37. Synthesis of cyclopenta[*b*]indoles as intermediates for the asymmetric total synthesis of indole alkaloids.

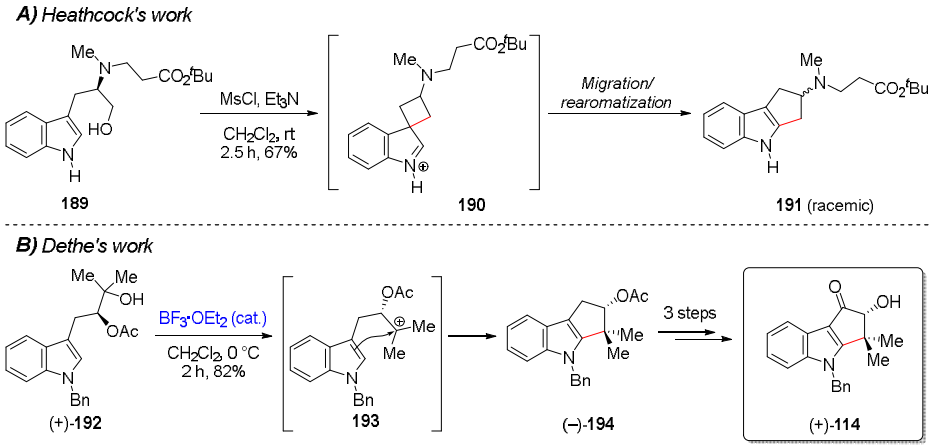
A few years later, Banwell and coworkers also synthesized cyclopenta[*b*]indoles via intramolecular Friedel-Crafts reaction of indoles (Scheme 38).[58] Unfunctionalized compounds **188**, which embody the framework associated with fischerindoles (*e.g.* compounds **184** and **185**), were formed in good yields upon treatment of C3-substituted indoles **187** with TMSOTf as Lewis acid promoter. This transformation has also proved to be highly stereoselective, since distinct diastereoisomers **187a** and **187b** afford different products **188a** (*cis*-fused ring) and **188b** (*trans*-fused ring), respectively.



Scheme 38. Synthesis of analogues of the fischerindole class of indole alkaloids.

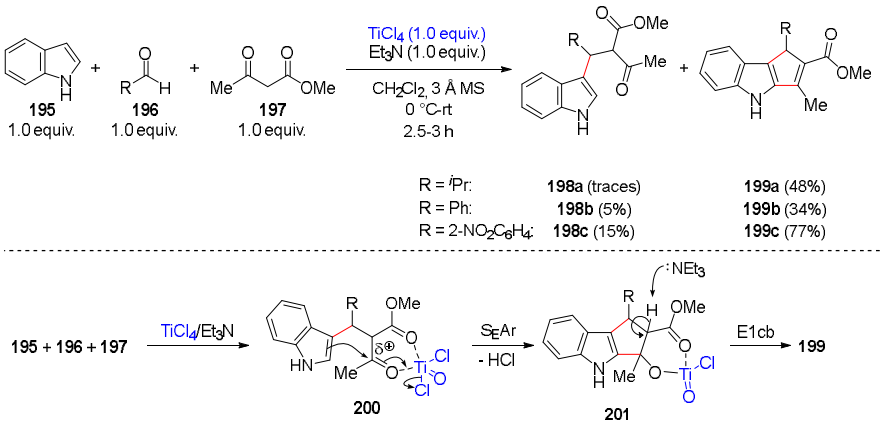
Alcohols can be suitable substrates for the construction of cyclopenta[*b*]indoles. In 1993, Ganesan and Heathcock reported the synthesis of a cyclopenta[*b*]indole structure derived from D-tryptophan.[59] Their protocol was not a catalyzed process, as the primary alcohol **189** was converted in situ to the corresponding mesylate, which then reacts *via* electrophilic aromatic substitution (Scheme 39A). Despite the starting material being enantiopure, product **191** was obtained as a racemic mixture, suggesting that achiral 3,3-disubstituted indolenine **190** might be a suitable intermediate for this reaction. Recently, a biomimetic cyclopentannulation of quiral tertiary alcohol (+)**-192** using a boron(III) catalyst was described (Scheme

39B).[35] In this prototypical Friedel-Crafts reaction, only one example was reported and the authors used product (–)-**194** to accomplish the asymmetric synthesis of natural product (+)-Bruceolline J, (+)-**114**.



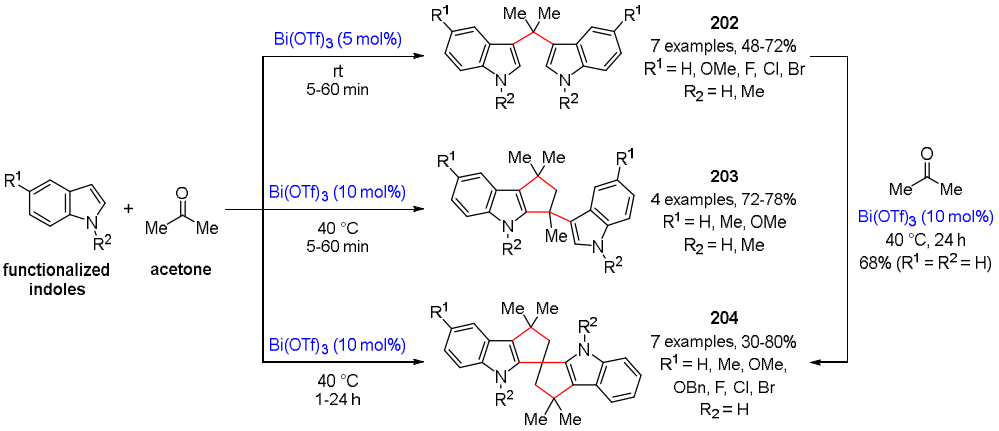
Scheme 39. Cyclopentannulation reactions of alcohols: A) Heathcock's work; B) Dethe's work.

A multicomponent protocol for the synthesis of cyclopenta[*b*]indoles has been published. Gérard and Sapi have developed a Ti(IV)-promoted reaction of indole **195**, aldehydes **196** and an activated methylene compound **197** (Yonemitsu condensation) to form selectively trimolecular adducts **198** and/or tricyclic compounds **199** depending on the reaction conditions (Scheme 40).[60] Although only three examples were reported by the authors, the cyclopenta[*b*]indoles **199** were obtained in a unique step from simple starting materials in low to good yields. From a mechanistic point of view, compound **198** likely arises from enolate formation and Knoevenagel condensation with the aldehyde, followed by Michael addition of indole. Evidence from ^{1}H and ^{13}C NMR corroborates the formation of titanium enolates. Complexation of **198** with Ti(IV) species generates **200**, and then an intramolecular electrophilic aromatic substitution followed by an E1cb step could account for the formation of the desired product **199**. There is evidence that complex **199** is not a $TiCl_4$ complex: treatment of isolated **197** with $TiCl_4$ in CH_2Cl_2 does not afford the tricyclic compound even after 24 hours. *In situ* conversion of $TiCl_4$ to $TiOCl_2$ is assumed to take place.



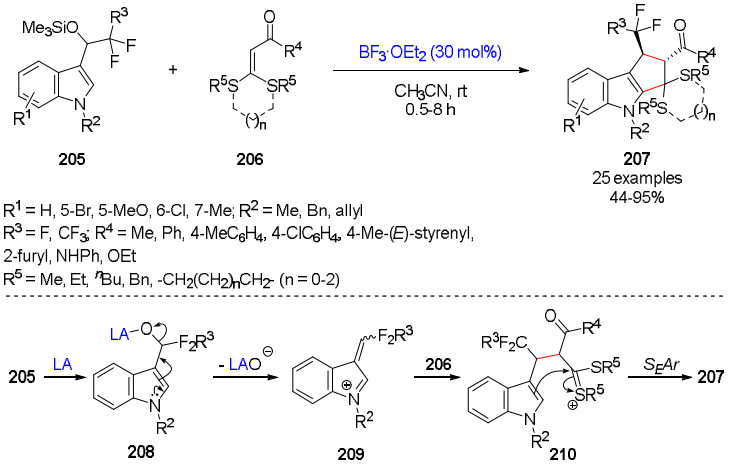
Scheme 40. $TiCl_4/Et_3N$-promoted multicomponent condensation of indole with aldehydes and methyl acetoacetate.

By reacting indoles and acetone in specific conditions under bismuth(III) triflate catalysis, Kumar and coworkers synthezized condensation derivatives **202-204** appropriately in mostly good yields and low reaction times (Scheme 41).[61] In general, cyclopenta[*b*]indoles **203** were obtained from *N*-methylindoles containing electron donating groups in a few minutes, while spirocyclic compounds **204** were synthesized from *N*-unsubstituted indoles bearing both electron donating and electron withdrawing in up to 24 hours. It has been suggested that products distribution depends directly on the electronics of the indole ring. A protocol to prepare bis(indolyl)-propanes **202** has also been developed. These compounds upon treatment with acetone and $Bi(OTf)_3$ at 40 °C also give spirocycle **204**, which suggests they might be suitable intermediates for the reaction from indoles.



Scheme 41. Condensation of indoles with acetone catalyzed by $Bi(OTf)_3$.

Recognizing the reactivity of indolylmethyl cations, Pan and Liu investigated the formal [3+2]-cycloaddition of α-trifluoromethyl-3-indolylmethanol silyl ethers **205** and ketene dithioacetals **206** catalyzed by Lewis acids (Scheme 42).[62] They found that, under catalysis of $BF_3{\cdot}OEt_2$ in acetonitrile at room temperature, the starting materials were smoothly converted to cyclopenta[*b*]indoles **207** as a sole *trans*-diastereoisomer in up to 8 hours and in high to excellent yields in most of the cases.



Scheme 42. Formal [3+2]-cycloaddition between α-trifluoromethyl-3-indolylmethanol silyl ethers and ketene dithioacetals.

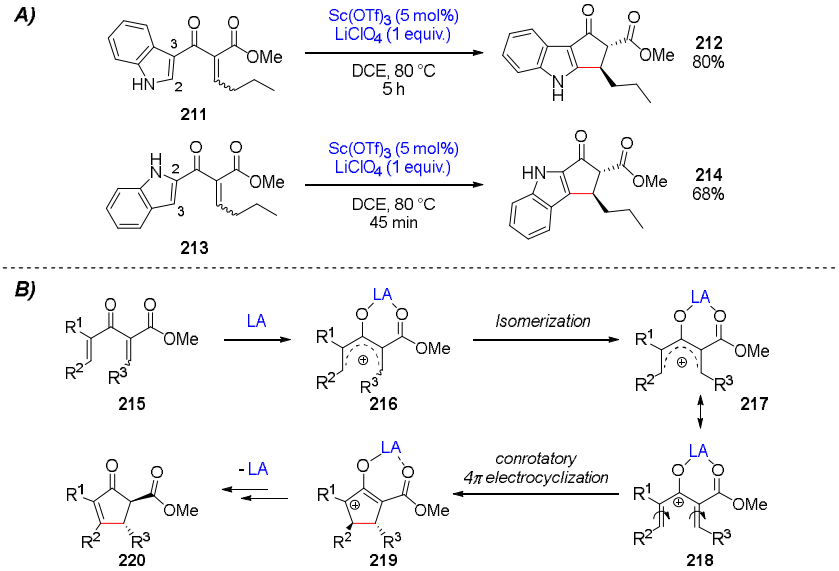
The reaction works well with both electron donating and electron withdrawing groups attached to the indole ring and has a broad scope in terms of substrate **206**. Indeed, ketene dithioacetals bearing aromatic or aliphatic ketone, ester and even amide moieties were tolerated in this transformation. Cyclic ketene dithioacetals also provide the desired product in high yields. It is believed that compound **205** interacts with Lewis acids, leading to indolylmethyl cation **209** *via* a dehydration step. This reactive species is attacked by a molecule of ketene dithioacetal to give intermediate **210**, which undergoes intramolecular cyclization followed by rearomatization to furnish the cyclopenta[*b*]indole scaffold. The authors also propose that the observed *trans* stereochemistry might be due to thermodynamic equilibration since the CH at position 1 has a relatively enhanced acidity.

4.2. Cyclization based on Nazarov and Nazarov-type reactions

The synthesis of cyclopentenones from cross-conjugated dienones as starting materials is known as Nazarov cyclization. One of the few eletrocyclic that are prone to catalysis, it allows quick synthesis of either cyclopenta[*b*]indol-1-one or cyclopenta[*b*]indol-3-one structure depending on the substrate used. Indolyl vinyl ketones are suitable substrates for this reaction, because the 4π electrocyclization benefits from having an electron-rich π-system (vinyl nucleophile) and an electron-poor one (vinyl electrophile).

4.2.1. Racemic approaches

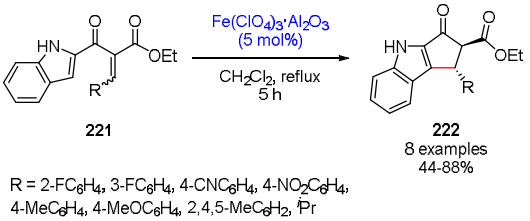
Until the earlies 2000s only isolated examples[63] of Nazarov cyclizations could be found in the chemical literature, all of them using high loadings of Brønsted or Lewis acids. In 2006, the Frontier group reported the first general, catalytic protocol for the Nazarov cyclization of systems containing heteroaromatic groups.[64] By using scandium(III) triflate in catalytic amounts and lithium perchlorate as additive, they were able to perform these cyclizations with several heterocyclic compounds. Among these substrates, 3-indolyl vinyl ketone **210** and 2-indolyl vinyl ketone **212** were smoothly converted to cyclopenta[*b*]indolones **211** and **213** in good yields (80% and 68% respectively) of a sole isomer in each case (Scheme 43A).



Scheme 43. A) Nazarov reaction of 2- and 3-indolyl vinyl ketones catalyzed by $Sc(OTf)_3$; B) proposed mechanism of the Lewis-catalyzed Nazarov cyclization.

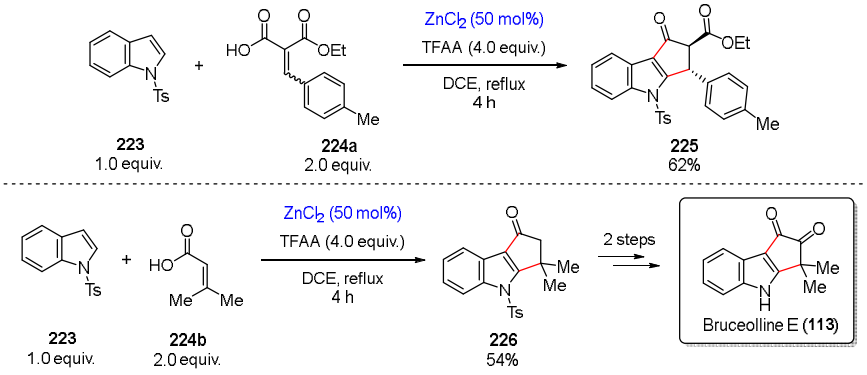
As expected in terms of reactivity, ketone **212** cyclizes in shorter reaction time than ketone **210** due to the more electron rich and nucleophilic position 3 of the indole ring. It is worth noting that the absence of $Sc(OTf)_3$ or $LiClO_4$ led to low yields, which prompted the authors to propose that actually $Sc(OCl_4)_3$ is the active catalyst. However, stoichiometric quantities of lithium perchlorate were necessary. In a mechanistic point of view (Scheme 43B), coordination of the catalyst with the Lewis acid and an isomerization step forms pentadienyl cation **216**. This intermediate undergoes concerted, conrotatory electrocyclization, furnishing cyclic intermediate **218**. Further aromatization and protonation of enolate lead to the desired product.

Itoh and coworkers have developed an iron(III)-catalyzed cyclopentannulation of indoles, benzofurans and benzo[*b*]thiophenes in their search to expand the scope of Nazarov cyclization with heteroaromatic moieties. When treated with catalytic amounts of cheap alumina-supported iron(III) perchlorate in dichloromethane in reflux conditions, 2-indolyl vinyl ketones **221** were converted in the corresponding cyclopenta[*b*]indolones **222** with *trans* relative stereochemistry and in moderate to good yields (Scheme 44).[65] The authors also demonstrated that the catalyst can be recovered by using an ionic liquid as solvent, forming the desired product in good yields even after 5 consecutive runs.



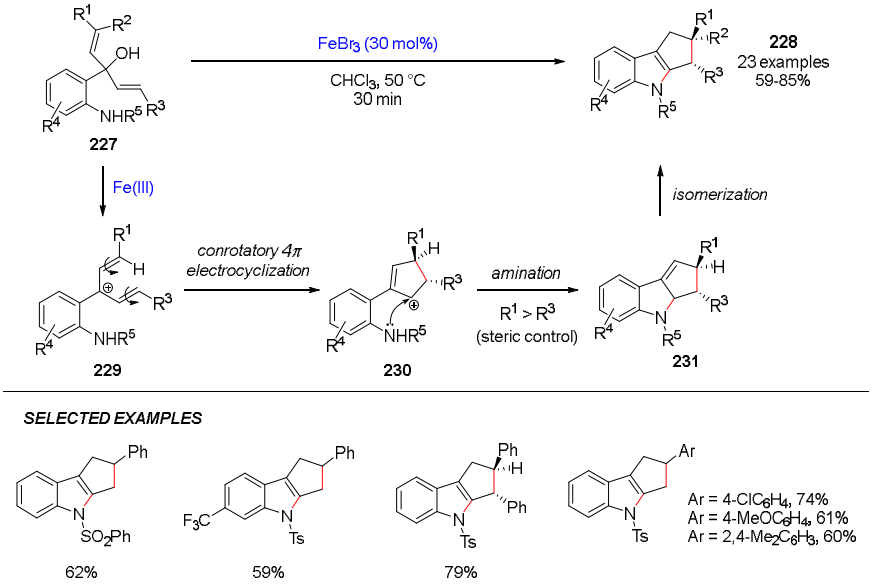
Scheme 44. Nazarov cyclization catalyzed by alumina-supported iron(III) perchlorate.

In order to circumvent the need to prepare suitable substrates for the Nazarov cyclization, Song and Chang have developed a Lewis acid-catalyzed tandem acylation/Nazarov cyclization for the synthesis of cyclopentenones directly from the correspondent *N*-tosylpyrroles and *N*-tosylindoles.[66] For the latter, the authors reacted *N*-tosylindole **223** with α,β-unsaturated carboxylic acids **224** in presence of 50 mol% of zinc chloride, excess trifluoroacetic anhydride and 1,2-dichloroethane as solvent, obtaining cyclopenta[*b*]indolones **225** and **226** in moderate yields (Scheme 45). Either no reaction or only the acylated product formation occurred in the absence of the catalyst, indicating it might be activation both the acylation and the subsequent cyclopentannulation. Additionally, the synthesis of natural product Buceolline E (**113**) was accomplished in an oxidation/deprotection sequence from tricyclic compound **225**.



Scheme 45. Tandem acylation/Nazarov cyclization reaction of *N*-tosylindoles.

A method for construction both pyrrole and cyclopentane rings of the cyclopenta[*b*]indole scaffold through intramolecular interrupted Nazarov reaction has been published. In a recent, clever report that first described this process, regio- and diastereoselective $FeCl_3$-catalyzed cyclization of 1,4-pentadien-3-ols **227** provided tricyclic compounds **228** in good yields (Scheme 46).[67] Several substitution patterns of the substrate were tested, giving both 2-substituted and *trans*-2,3-disubstituted cyclopenta[*b*]indoles under the optimized reaction conditions. This cascade reaction tolerates either electron donating or electron withdrawing substituents on the 2-aminophenyl ring or on the phenyl ring of the 1-phenyl-1,4-pentadien-3-ols. This method also benefits from short reaction times (30 minutes) and use of an inexpensive catalyst. Based on control experiments in which key intermediates were either isolated or trapped, the authors proposed that the acidic catalyst induces dehydration of substrate **227** and generates pentadienyl cation **229**. This species undergoes conrotatory electrocyclization, forming the cyclopentene ring with R^1 and R^3 substituents in a *trans* relationship (**230**). The regioselectivity arises from the amination step, in which intramolecular trapping of the allylic cation by the adjacent aniline occurs at the less hindered portion of the cation. Further isomerization and consequently rearomatization of the indole ring yield desired product **228**.



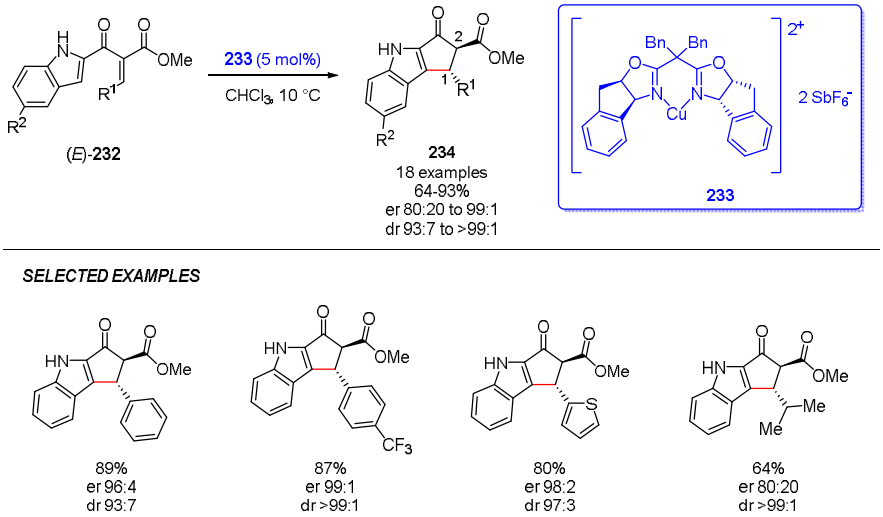
Scheme 46. Iron(III) bromide catalyzed interrupted Nazarov cyclization of 1,4-pentadien-3-ols **227**.

4.2.2. Enantioselective approaches

Due to the importance of the cyclopenta[*b*]indolone motif, an asymmetric version allowing the synthesis of enantioenriched products is highly desirable. Despite the difficulties of this transformation using heterocyclic substrates, a few reports have been recently published. These works rely basically on using chiral complexes which activate the substrate and induce chirality in the product by affecting either the torquoselectivity (*i.e.* the preference for 'inward' or 'outward' rotation of substituents) of the conrotatory electrocyclization step, or the reprotonation step.

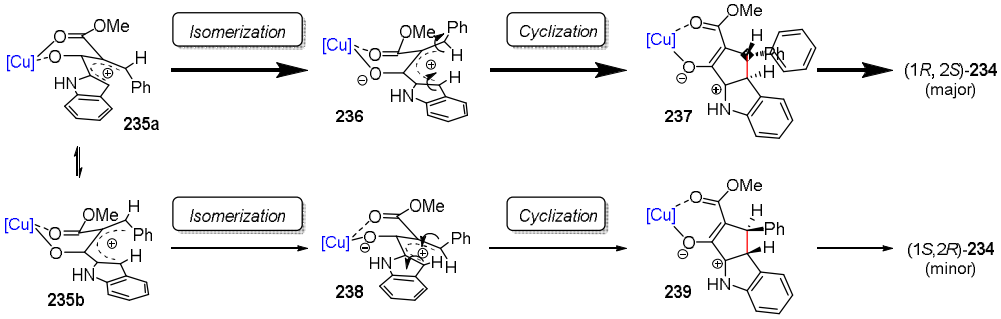
The first Lewis acid-catalyzed Nazarov cyclization of indole derivatives was reported by the Rueping group in 2015.[68] Using 2-indolyl vinyl ketones **232** (*E* isomers) as starting materials, the authors found that copper(II) complexes containing a chiral C_2-symmetric bisoxazoline ligand (a BOX ligand) did catalyze the enantioselective conversion to the desired cyclopenta[*b*]indol-3-ones **234** (Scheme 47). After optimization experiments, they identified complex **233** in 5 mol% in chloroform as solvent at 10 °C to be optimal, mild conditions. The scope of this transformation was evaluated, with substrates containing either aromatic

groups with electron withdrawing or electron donating substituents or even a heteroaromatic moiety being suitable reagents. The observed yields of **234** were higher than 85% in most of the cases, with enantiomeric and diastereoisomeric ratios equal or higher than 95:5. When R^1 is a aliphatic group however the yield and enantioselectivity is greatly decreased, in spite of the excellent diastereoselectivity. The absolute configuration of the tricyclic compounds **234** was determined as (1*R*,2*S*) by X-ray diffraction analysis.



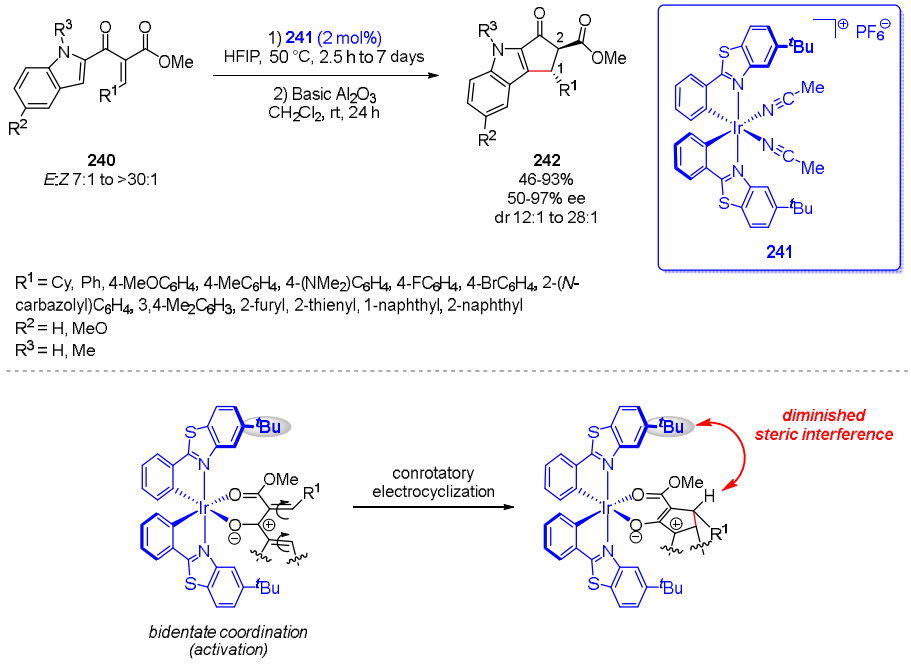
Scheme 47. Enantioselective Nazarov cyclization of 2-indolyl vinyl ketones using a copper(II) bisoxazoline ligand complex as catalyst.

In order to gain insights about the origins of the observed enantioselectivity, DFT calculations of the reaction profile were conducted (Scheme 48). Upon coordination with **233**, β-keto ester **232** can generate two diastereoisomeric complexes in six-membered boat conformations **235a** and **235b**. Isomerization of these species into reactive species **236** and **238**, subsequent cyclization to give chelates **237** and **239**, and final deprotonation/protonation steps lead to enantiomeric compounds (1*R*,2*S*)-**234** and (1*S*,2*R*)-**234**, respectively. It is worth noting that, in the cyclization of **236**, whose sp^2-carbon bonded to the phenyl moiety is located above the plane of the indole ring, clockwise conrotatory reaction is favored, while the inverse occurs with **238**. The calculations also corroborated the observation of (1*R*,2*S*)-**234** as major enantiomer, since the reaction path leading to it involves lower energy transition states.



Scheme 48. Mechanistic proposal of copper(II)-catalyzed asymmetric Nazarov reaction based on DFT calculations.

A recent breakthrough contribution to the field came to light in 2018, when Meggers and coworkers applied hexacoordinated, octahedral iridium(III) complex **241** in the asymmetric Narazov cyclization of 2-indolyl vinyl ketones **240** (Scheme 49).[69] Despite being achiral, the ligands are asymmetrically arranged around the iridium(III) stereogenic center, thus inducing chirality. Under their optimized conditions (2 mol% of catalyst **241**, hexafluoroisopropanol as solvent, 50 °C), the authors were capable of isolating products **240** in good yields (>70%) and enantioselectivities (ee>90%) and satisfactory *trans*/*cis* ratios (>12:1) in most of the cases. Because the diastereoselectivity right after isolation of the cyclopenta[*b*]indol-3-ones was found to be relatively low, a second one-pot step with basic alumina treatment for 24 h was necessary to ensure enhanced diastereoselectivity through *cis* (kinetic product) to *trans* (thermodynamic product) isomerization. This protocol features some significant advantages, such as the use of achiral ligants to the metal, low catalyst loadings (2 mol%) and no need for dry solvents or inert atmosphere. Remarkably, substrates bearing an aliphatic (R^1=cyclohexyl) or a voluminous (R^1=*o*-(*N*-carbazolyl)-Ph) substituent were also successfully converted to the respective tricyclic compounds, although the former being isolated in moderate enantioselectivity (58% ee). Analogous chiral complex of rhodium(III) has also shown to be active catalyst for this stereoselective transformation. In a mechanistic point of view, it is proposed that, after ligands exchange and activation of the substrate by the chiral complex, the conrotatory electrocyclization step leads to stereoselective formation of stereogenic center at indolic carbon 2 *via* avoidance of sterically unfavorable interactions between R^1 and the *tert*-butyl group in the catalyst.

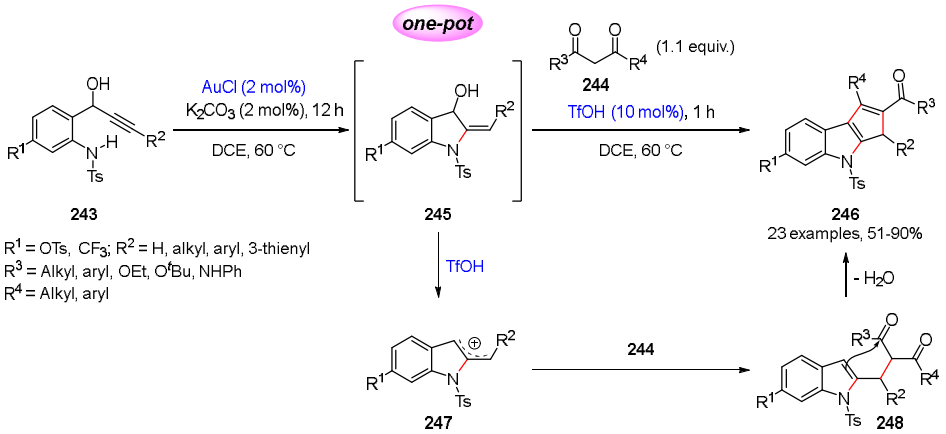


Scheme 49. Enantioselective Nazarov cyclization of indolefunctionalized α-unsaturated β-ketoesters *via* iridium(III) catalysis.

5. Miscellaneous approaches

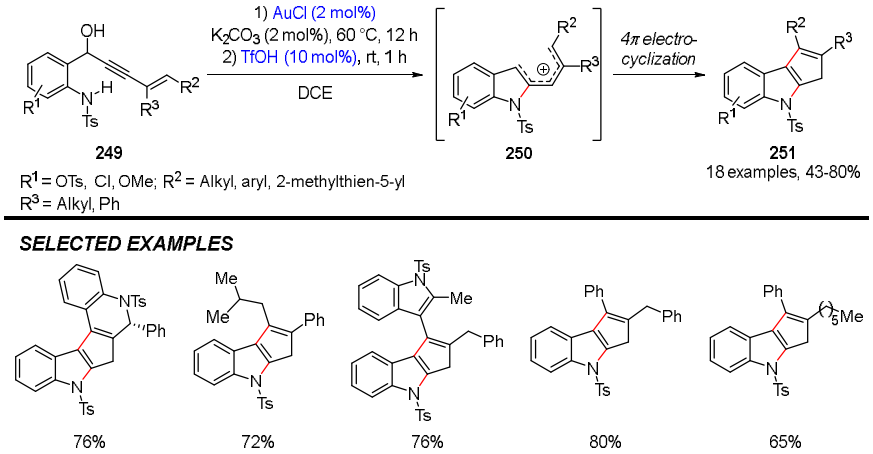
A one-pot tandem gold(I)- and triflic acid-catalyzed reaction of 1-(2-aminophenyl)prop-2-ynols **243** and 1,3-dicarbonyl compounds **244** to synthesize polyfunctionalized cyclopenta[*b*]indoles **246** has been described by Ramasastry and coworkers (Scheme 50).[70] Substrates **243**, readily prepared in few steps from 2-nitrobenzaldehydes, were submitted to Au(I) catalysis in presence of catalytic amount of potassium carbonate to form hydroamination intermediate **245**. This step occurs with gold activation of triple bond and

subsequent nitrogen attack in a 5-*exo*-*dig* cyclization. Subsequent addition of TfOH leads to allylic cation **247**, which is trapped by 1,3-dicarbonyl compound **244** yielding indolic intermediate **248**. A highly selective cyclization of **248** *via* S_EAr followed by a dehydration step affords the product in typically good yields.



Scheme 50. Synthesis of cyclopenta[*b*]indoles **246** via one-pot tandem gold(I)- and triflic acid-catalyzed hydroamination/Friedel-Crafts type cyclization.

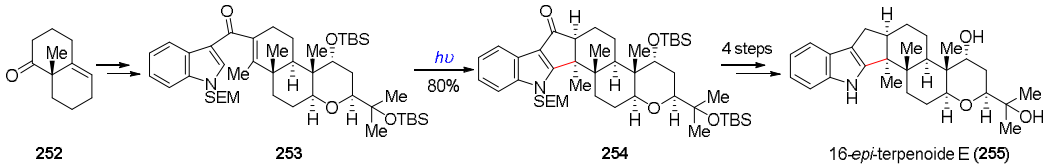
The efficient methodology developed by Ramasastry and coworkers has also been reported in an intramolecular fashion, in which cyclopenta[*b*]indoles with different substitution patterns are obtained. Through Au(I)- and triflic acid-catalysis in a hydroamination/Nazarov-type cyclization sequence of 1-(2-aminophenyl)pent-4-en-2-ynols **249**, the synthesis of 18 examples of cyclopenta[*b*]indoles **251** has been achieved in moderate to good yields (Scheme 51).[71]



Scheme 51. Synthesis of cyclopenta[*b*]indoles **251** *via* gold(I)- and Brønsted acid-catalyzed tandem hydroamination/Nazarov-type cyclization.

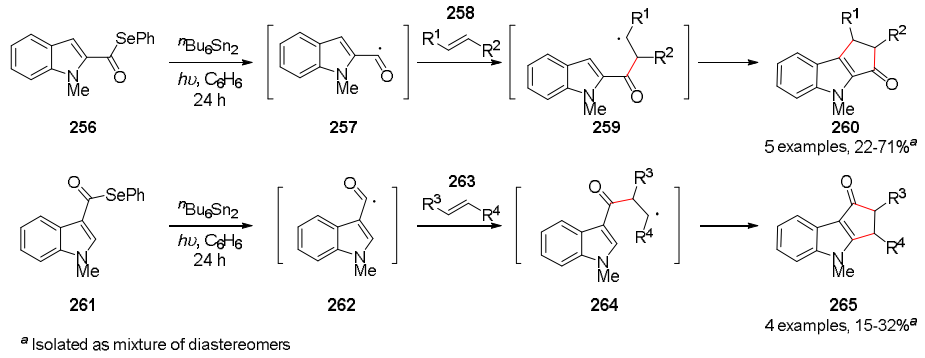
Besides gold and triflic acid, Ramasastry and coworkers have also employed silver and camphorsulfonic acid to perform a similar transformation from 3-(2-aminophenyl)-4-pentenyn-3-ols, the corresponding 1,3-disubstituted cyclopenta[*b*]indoles being isolated in good yields.[72]

In 1989, Gardette and coworkers reported a photocyclization of *N*-aryl-enaminones to afford several examples of cyclohexa[*b*]- and cyclopenta[*b*]indolines in mostly good yields besides two examples of cyclopenta[*b*]indoles in poor yields.[73] An analogous approach has been applied by Giannis and coworkers in the synthesis of a novel indoloditerpenoid (Scheme 52).[74] Indolylenone **253**, prepared from (+)-Wieland-Miescher ketone **252**, was irradiated at 350 nm to furnish cyclopenta[*b*]indol-1-one **254** in good yield as a single diastereoisomer, through a photoinduced Nazarov cyclization. Lewis or Brønsted acid catalysis was found to be ineffective in this transformation, leading either to recovery or decomposition of the starting material. In order to finish the synthetic route, deprotection and reduction steps were performed to provide the product 16-*epi*-terpenoide E **255**.



Scheme 52. Nazarov photocyclization in the synthesis of cyclopenta[*b*]indole 16-*epi*-terpenoide E **255**.

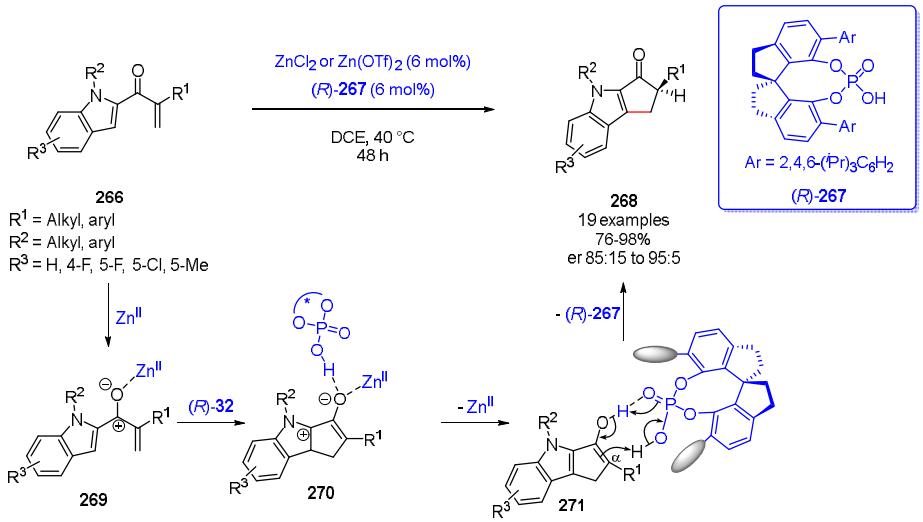
A photolytic radical reaction with phenyl indolylselenoesters **256** or **261** and electrodeficient alkenes **258** or **263**, affording cyclopenta[*b*]indol-3-ones **260** and cyclopenta[*b*]indol-1-ones **265**, respectively, has been reported by Bennasar and coworkers (Scheme 53).[75] Under nonreductive conditions (*hv*, $^{n}Bu_6Sn_2$), the indolylacyl radical generated in the sequence of radical reactions initiated by homolytic cleavage of $^{n}Bu_6Sn_2$, can undergo an addition-cyclization-oxidation cascade to afford cyclopenta[*b*]indole products with several alkenes in poor to good yields. Selenoester **261** appears to be less reactive than **256**. Indeed, under the same reaction conditions, indolylselenoester **256** reacted with dimethyl fumarate to afford the correspondent tricyclic product in 45% yield, while indolylselenoesters **261** reacted with dimethyl fumarate to provide the product in 32% yield.



Scheme 53. Radical synthesis of cyclopenta[*b*]indol-3-ones **260** and cyclopenta[*b*]indol-1-ones **265**.

Recently, an enantioselective Nazarov protocol cooperatively catalyzed by a zinc(II) salt and chiral spiro phosphoric Brønsted acid (*R*)-**267** was developed by Zhu and Zhou (Scheme 54). Using indole enones **266** as starting materials, (*R*)-**267** and $ZnCl_2$ (when R^1=alkyl) or $Zn(OTf)_2$ (when R^1=aryl) as catalysts, the synthesis of various 2-substituted cyclopenta[*b*]indol-3-ones **268** was accomplished in good to excellent yields and with good enantioselectivities. The authors have also demonstrated that this reaction can be carried out on a gram scale (one example). Experimental results confirmed the hypothesis of both Brønsted and Lewis acids acting cooperatively, as the absence of one of these compounds leads to either lowered reaction rates and racemic products or no product formation at all, respectively. Theoretical calculations suggest that the electrocyclization/aromatization steps to furnish enol **271** are both catalyzed by Zn(II) and

Brønsted acid (*R*)-**262**. Further investigation revealed that enantiocontrol is exerted only by (*R*)-**267**, which acts as a chiral proton transfer shuttle and leads to enantioselective protonation of enol **271** *via* the C-α *Si* face.[76]



Scheme 54. Enantioselective Nazarov cyclization of indole enones.

6. Conclusions

Within the heterocyclic systems, cyclopenta[*b*]indoles are an important motif present in many natural products and bioactive synthetic compounds. The numerous effects associated with this heterocyclic has stimulated the conception of several innovative and creative chemical processes to their preparation. This chapter covers several 1) metal-catalyzed, 2) Brønsted acid- and 3) Lewis acid-catalyzed or promoted methodologies allowing the synthesis of pentacyclopenta[*b*]indole unity with different substitution patterns, most of them in a highly stereoselective fashion. We intend to give an updated summary of the chemical literature regarding the preparation of cyclopenta[*b*]indoles and we hope that it will support and stimulate the development of novel synthetic methodologies to access these compounds.

Acknowledgements

We thank Prof. Orazio Antonio Attanasi for his kind invitation to write this chapter. We are very grateful to São Paulo Foundation for Science (FAPESP) for financial support (process number 2018/02611-3 and 2013/07600-3). FC thanks Brazilian National Council for Science and Development (CNPq) for research fellowship (process number 307840/2014-0). HS thanks FAPESP for a doctorate scholarship (process number 2015/09205-0), SRL and RCG thank CNPq for doctorate scholarships, and MTRJr thanks Coordination for the Improvement of Higher Education Personnel (CAPES) for a fellowship (Finance Code 001).

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