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New Perspectives in the Indole Ring Functionalization Using 2-Indolylmethanols

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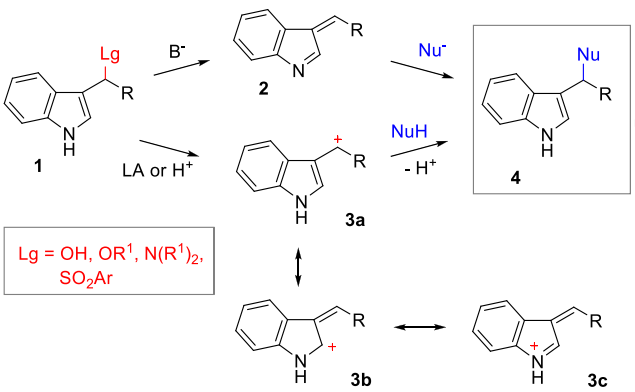
Abstract. 2-Indolylmethanols have been recently involved in several processes dealing with indole functionalization. These compounds, upon activation by Brønsted or Lewis acids, generate a bidentate electrophilic system amenable to react at 3-position or at the benzylic site with a wide range of nucleophilic reagents. The functionalization pattern is affected by the nature of the substituents at the carbinol unit and also depends on the nature of the nucleophile used. Nucleophilic reactants bearing a remote electrophilic site in their structure can be involved in a further ring closure ultimately leading to polycyclic derivatives. This review article summarizes some fundamental aspects of the chemistry of 2-indolylmethanols with particular attention to those related to asymmetric synthesis.

Keywords: asymmetric synthesis; cyclization; indoles; imines; nucleophilic addition.

1 Introduction

Synthetic procedures to access functionalized indole derivatives are of widespread interest for the preparation of bioactive compounds, pharmaceuticals and advanced materials.[1] Versatile approaches are currently available to insert, in a regio and stereoselective fashion, various functional groups in the indole nucleus.[2] The intrinsic preference displayed by the indole ring toward the C-3 functionalization makes the preparation of 3-substituted indoles quite straightforward using direct procedures mostly based on the classical Friedel–Crafts reaction. Conversely, the introduction of a C-2 functional group requires the presence of a regiodirecting substituent at the nitrogen atom showing coordinating properties.[3] Structural implementation of 3-substituted indoles **1** bearing a suitable leaving group at 'benzylic' position can be readily made exploiting the formation of alkylideneindolenine species **2** and **3** (Scheme 1).[4] Removal of the leaving group from these substrates can be realized under acidic or basic conditions leading to neutral alkylideneindolenine **2** or the more reactive cationic analogue **3**.[5] These intermediates act as vinylogous imino derivatives allowing the subsequent nucleophilic addition leading to the target functionalized indole. Despite of the presence of two electrophilic sites in intermediate **3**, attack by the nucleophilic reagent occurs exclusively at the exocyclic carbon thus enabling the immediate restoring of the ring aromaticity.



Scheme 1. General reactivity of 3-substituted indoles **1**.

Along the years, several indole derivatives embedding different leaving groups such as gramines (**1**, Lg = NR^1R^2),[6] 3-(1-arylsulfonylalkyl) indoles (**1**, Lg = SO_2Ar),[7] and 3-indolylmethanols (**1**, Lg = OH),[8] have been devised for such purpose. Straightforward access to these substrates is achievable by simple processes involving Mannich-like reactions and Friedel–Crafts addition to carbonyls. A similar approach could be in principle envisaged for the C-2

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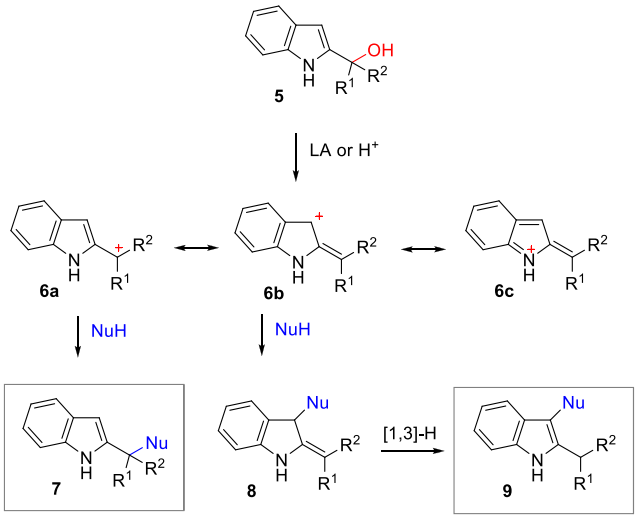
functionalization of indoles using substrates bearing the same leaving groups. However, installation of nitrogen and sulfur-based substituents in that position is not as trivial as in the C-3 regioisomeric counterpart. Conversely, 2-indolylmethanols are easily obtainable by usual chemical processes involving carbonyl reductions and regioselective Friedel–Crafts reactions. The observed reactivity pattern using 2-indolylmethanols follows the general trend depicted in Scheme 2.



Scheme 2. General reactivity of 2-indolylmethanols **5**.

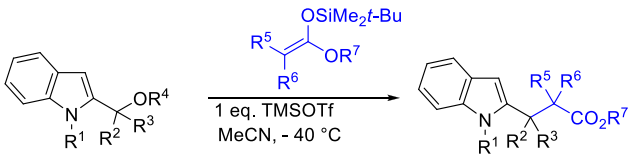
Dehydration of 2-indolylmethanols **5** occurs under acidic conditions leading to a stabilized carbocation which according to its resonance structures **6a-c** shows two main electrophilic sites (**6a** and **6b**). Nucleophilic attack to both these positions is normally observed leading to the substituted indole derivative **7** or the C-3 adduct **8** which after the hydrogen shift affords stable indole derivative **9.**

Marino Petrini obtained the Laurea degree in Chemistry in 1980 (University of Camerino). In 1983 he became Research Associate at the University of Camerino and during the period 1987-88 he has been visiting scientist at the University of Montreal (Prof. S. Hanessian). In 1992 he was appointed Associate Professor and then Full Professor in Organic Chemistry at the University of Camerino. His research interests mainly deal with the following topics: synthesis and reactivity of aliphatic and aromatic nitro compounds; synthesis of natural products featured by enhanced biological activity; synthesis and reactivity of imino derivatives.

This review article aims to report on the utilization of 2-indolylmethanols as valuable substrates for indole functionalization using a wide array of nucleophilic reagents under different reaction conditions. The activation mode of 2-indolylmethanols prevents from the utilization of strong nucleophilic reagents or metal enolates but alkenes, aromatics and heteronucleophiles can be commonly used in these processes.

2 Enol ethers and azaenols

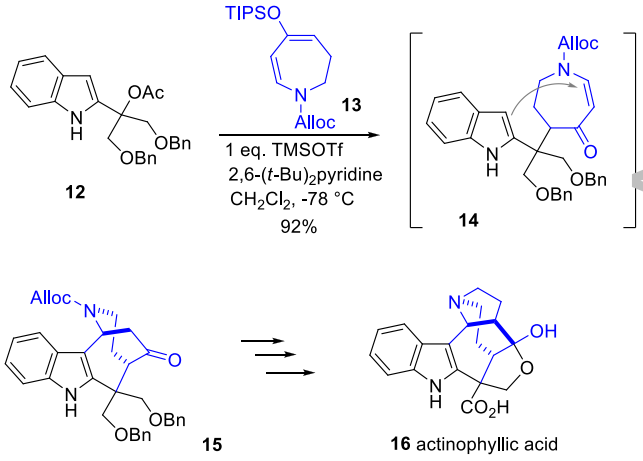
Silyl ketene acetals were among the first enol derivatives tested in the reaction with 2-indolylmethanols. The reactivity of 2-indolylmethanols **10** toward silyl ketene acetals in the presence of trimethylsilyl triflate is strongly affected by the nature of the alcohol used (Scheme 3).[9] Tertiary derivatives **10** (R^2= R^3= Me) give satisfactory results in this process but secondary substrates are converted into adducts **11** only upon acetylation of the hydroxy group.[10] Primary 2-indolylmethanols are unreactive even when converted into ester or carbamate derivatives.



R^1= R^2= R^3= R^4= H, R^5= R^6= R^7= Me, 93%
R^1= H, R^2= R^3= Me, R^4= H, R^5= R^6= R^7= Me, 77%
R^1= R^2= Me, R^3= H, R^4= Ac, R^5= R^6= H, R^7= Et, 68%

Scheme 3. Reaction of 2-indolylmethanols with silyl ketene acetals.

These findings have been used in a crucial step toward the racemic synthesis of actinophyllic acid **16** a carboxypeptidase U inhibitor useful for the treatment of thrombotic diseases (Scheme 4).[11]



Scheme 4. Reaction of 2-indolylmethanols **12** with dihydroazepine **13.**

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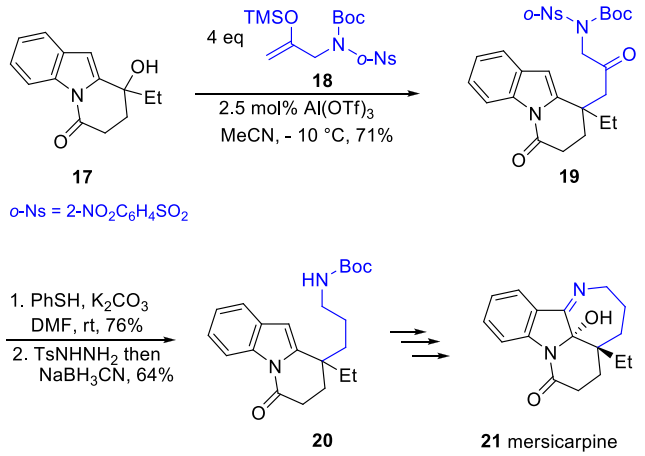
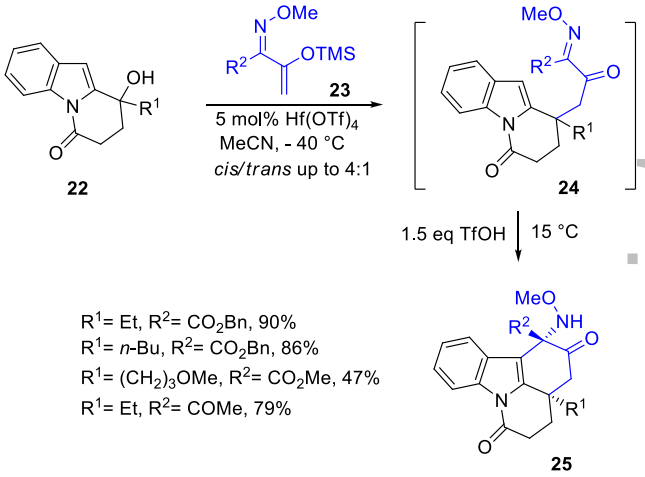
The reaction entails a tandem process starting with the acid promoted reaction between acetate **12** and dihydroazepine **13** leading to intermediate azepinone **14** which undergoes a further ring closure involving the indole and the enone system. The obtained derivative **15** bearing the core structure of the target alkaloid has been then converted into actinophyllic acid **16** in few synthetic steps. The formal racemic total synthesis of the alkaloid mersicarpine **21** has been realized starting from the reaction of tetrahydropyridoindolone **17** with silyl enol ether **18** in the presence of aluminium(III) triflate (Scheme 5).[12] The obtained amino ketone **19** was then partially cleaved at the nitrogen atom and totally reduced at the carbonyl group leading to compound **20** which was converted into mersicarpine **21** in few steps following a previously released procedure. Under similar reaction conditions, various heteroaromatic reagents including indoles, pyrroles and furan derivatives can be added to tetrahydropyridoindolone **17** with satisfactory results.

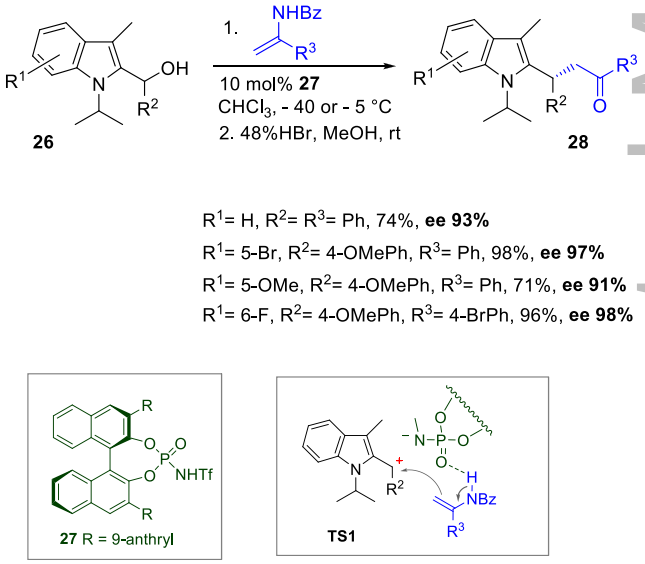


Scheme 5. Synthesis of a key intermediate **20** for the preparation of mersicarpine.

In a related process, azadienes **23** have been used as reagents in the reaction with differently substituted tetrahydropyridoindolones **22** (Scheme 6).[13] The reaction is catalyzed by hafnium(IV) triflate and leads to the formation of adducts **24** together with a minor amount (<10%) of the C-3 regioisomeric product. The one-pot addition of triflic acid ensures the subsequent ring closure leading to tetracyclic derivative **25** in satisfactory yields and moderate *cis* stereoselectivity. Compounds **25** have been used in some studies toward the total synthesis of the natural alkaloid thronoarine. Enamides can be successfully used as nucleophiles in asymmetric processes involving 2-indolylmethanols **26** catalyzed by chiral phosphoramide **27** (Scheme 7).[14] The catalyst probably acts through a bifunctional activation mode stabilizing the carbocationic center of the substrate with the negatively charged nitrogen atom and upon hydrogen bonding of the phosphate oxygen and the enamide NH according to **TS1**.The latter interaction seems of fundamental importance for a viable process since *N*-disubstituted enamides and silyl enol ethers, although more nucleophilic than enamides, are both ineffective in this reaction.[15] The final acidic quenching of the reaction mixture using HBr in methanol is required in order to hydrolyze the resulting *N*-acylimine leading to compounds **28** in good yield and generally excellent enantioselectivities.



Scheme 6. Synthetic approach to tetracyclic indole derivatives **25**.



Scheme 7. Enantioselective addition of enamides to 2-indolylmethanols.

The utilization of cyclic enamides derived from tetrahydro naphthalenones **30** is also effective in the reaction with 2-indolylmethanols **29** in the presence of chiral phosphoric acid **31** (Scheme 8).[16] The activation mode of the reactants by the catalyst is supposed to be identical to that observed with linear enamides but the intermediate *N*-acylimine formed

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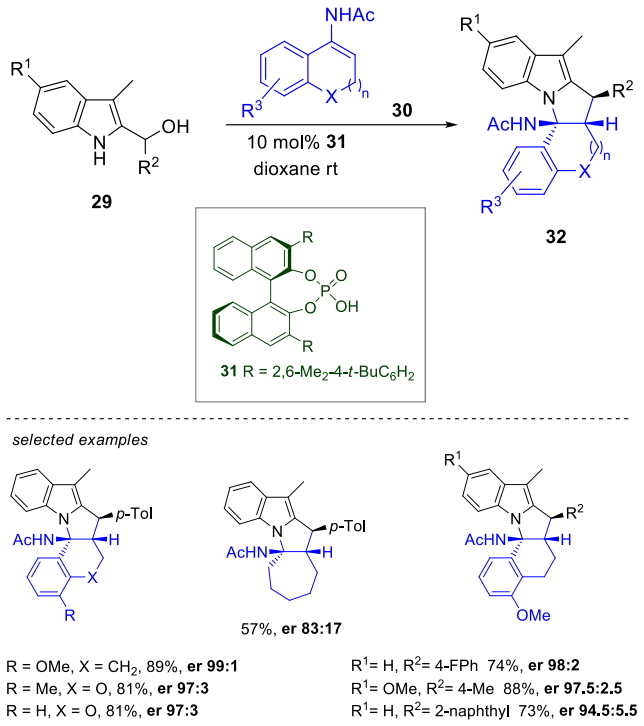
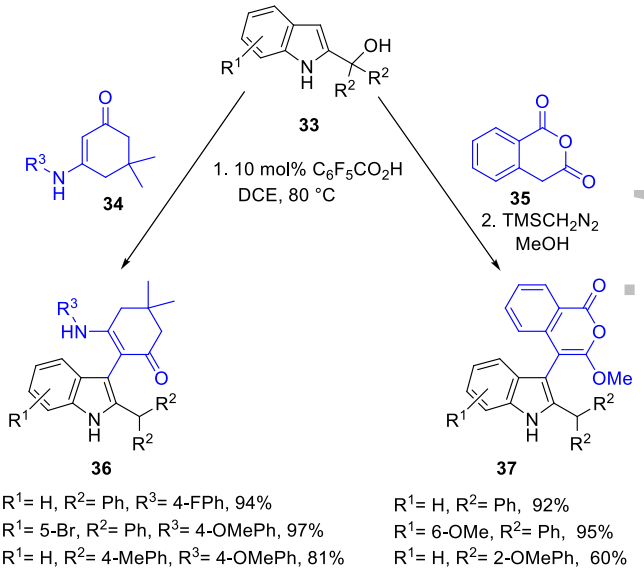
upon addition reacts with the indole nitrogen atom leading to pentacyclic derivatives **32** as single diastereoisomers in high enantioselectivity. The enamide obtained from cycloheptanone gives the corresponding adduct albeit in lower yield and enantioselectivity while the enamide of indanone leads to a simple adduct with totally unsatisfactory ee (3:2).



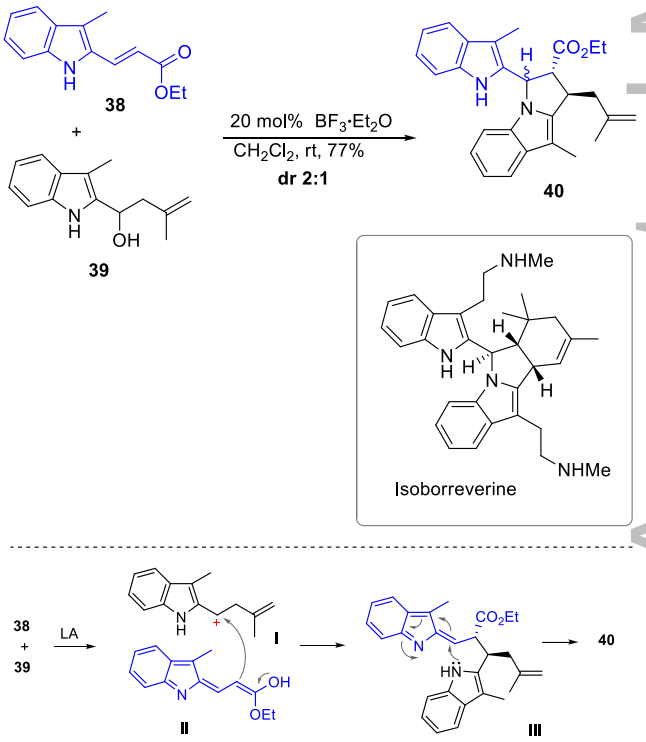
Scheme 8. Enantioselective synthesis of polycyclic derivatives embedding the indole ring.

Tertiary 2-indolylmethanols **33** react with cyclic enaminones **34** in the presence of pentafluorobenzoic acid leading to compounds **36** showing a marked preference for the the C-3 ring addition (Scheme 9).[17] The steric hindrance around the exocyclic electrophilic site is probably responsible for the observed regioselectivity in these reactions. Activation of the nucleophile **34** is probably provided by hydrogen bonding of the NH with the acyl oxygen of the catalyst. This assumption seems confirmed by the reduced yield obtained in this reaction using *N,N*-disubstituted enaminones **34**. In the same reaction conditions, homophthalic anhydrides **35** afford the corresponding C-3 substituted indole adducts which are better isolated as stable isochromenone derivatives **37** upon methylation with trimethylsilyl diazomethane. The reaction of 2,3-indolyldimethanols with enaminones **34** using a chiral phosphoric acid as activator shows the exclusive preference of these substrates for the addition on the C-3 arylmethyl framework.[18] In a study directed toward the synthesis of the alkaloid isoborreverine, 2-indolylmethanol **39** has been made to react with ethyl 3-indolylacrylate **38** in the presence of a catalytic amount of boron trifluoride etherate (Scheme 10).[19]

The Lewis acid is able to promote the formation of carbocation **I** and the enol of the acrylate ester **II** which react together leading to adduct **III** with high diastereoselectivity. The subsequent ring closure involving the indole nitrogen atom is a less diastereoselective process but the target product **40** representing the core structure of isoborreverine is obtained in satisfactory yield.



Scheme 9. Regioselective reaction of 2-indolylmethanols with enaminones **34** and anhydrides **35**.



Scheme 10. Synthetic study toward the preparation of isoborreverine analogues.

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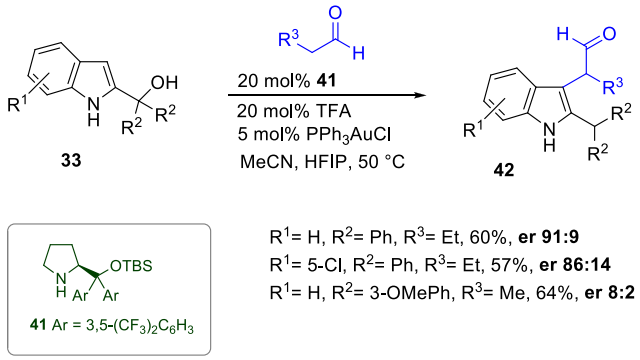
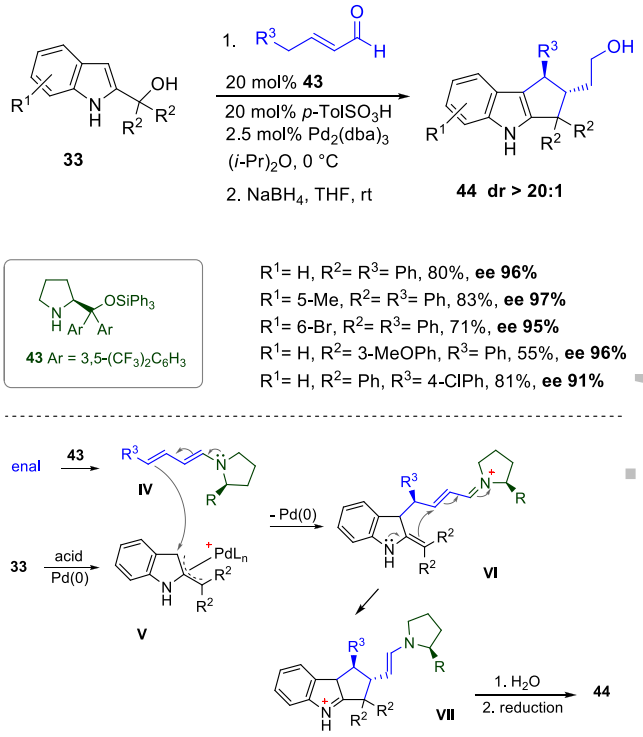
Reaction of alkanals with 2-indolylmethanols **33** in the presence of Jørgensen organocatalyst **41** is particularly effective in leading to α-indolylaldehydes **42** (Scheme 11).[20] This process occurs *via* enamine catalysis and the yield of the corresponding adducts can be substantially improved adding PPh_3AuCl exploiting an asymmetric cooperative catalysis. Generation of the required cationic intermediate from **33** is jointly provided by the gold complex and trifluoroacetic acid (TFA). Similarly to what was observed for the reaction with enamides, the intermediate chiral enamine reacts regioselectively at C-3 thus generating the target compounds **42**. The coordinating effect exerted by the indole NH group toward TFA is crucial for a positive outcome of this process as evidenced by the failure observed in the utilization of *N*-methylated substrates **33**.

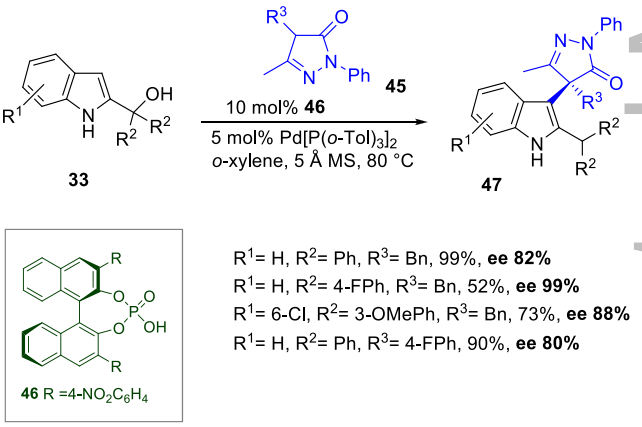


Scheme 11. Enantioselective addition of aldehydes to 2-indolylmethanols.

This process has been recently implemented using enals as reagents in the reaction with indolylmethanols **33** jointly catalyzed by chiral pyrrolidine **43** and $Pd_2(dba)_3$ (Scheme 12).[21] The target hydroxyethylcyclopenta[*b*]indoles **44** are obtained in high *anti* diastereoselectivity and excellent enantioselectivity in a two-step process involving the final reduction of the intermediate aldehyde with sodium borohydride. Reaction of the enal with chiral pyrrolidine **43** generates dienamine **IV** which reacts with Pd-stabilized cation **V** formed by acid promoted dehydration of indolylmethanol **33**. The obtained intermediate **VI** undergoes an intramolecular conjugate addition between the enamino-like framework and the vinylogous imino appendage affording the cyclopenta[*b*]indole system **VII** which upon hydrolysis and subsequent reduction gives the final product **44**. Another example of asymmetric cooperative catalysis has been observed in the reaction of 2-indolylmethanes **33** with pyrazolones **45** which is assisted by chiral phosphoric acid **46** and a palladium(0) complex (Scheme 13).[22] Palladium is supposed to stabilize the delocalized cation formed upon dehydration of substrate **33** while the chiral catalyst **46** favors the enolization of the pyrazolone by a suitable hydrogen bonding. At any event, although the chemical yields observed in this reaction are good, the enantioselectivity level of the obtained products is excellent only for a couple of reported examples.



Scheme 12. Enantioselective addition of α,β-unsaturated aldehydes to 2-indolylmethanols.



Scheme 13. Asymmetric cooperative catalysis in the reaction of pyrazolones with 2-indolylmethanols.

Simple acidic catalysis is applied to the reaction of 2-indolylmethanols **48** with azlactones **49** (Scheme 14).[23] The observed diastereoselectivity is generally more than satisfactory but any attempt to realize an asymmetric version of this reaction using chiral phosphoric acids only led to disappointing results. Azlactones **49** involved in a related reaction with 2-indolylmethanols **33** afford the corresponding 3-substituted derivatives of type **47** in usually very good yield.[24]

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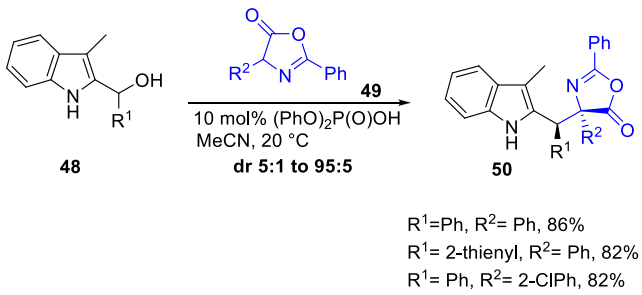
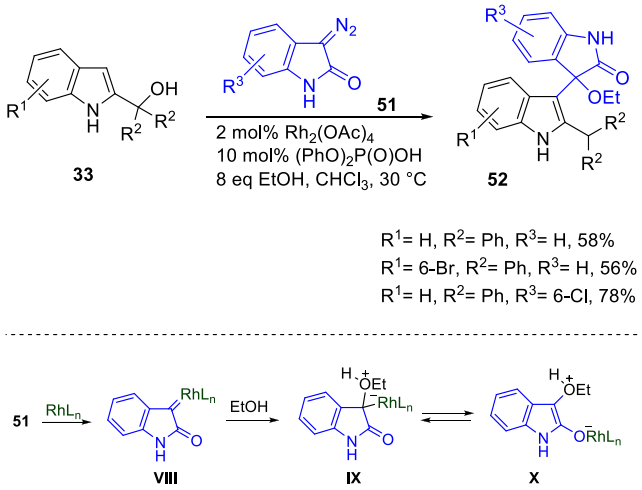


Scheme 14. Diastereoselective reaction of azlactones with 2-indolylmethanols

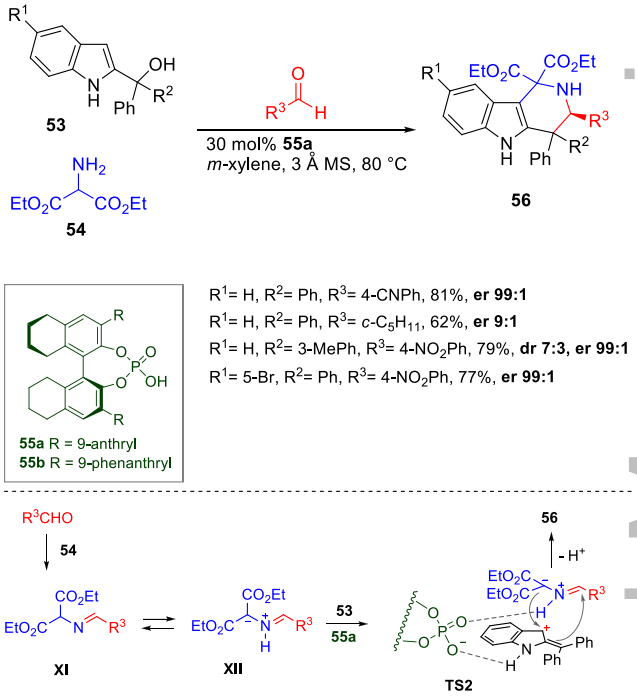
The rhodium-catalyzed reaction of 3-diazooxindoles **51** with 2-indolylmethanols **33** affords 3-indolyl-3-ethoxyoxindoles **52** (Scheme 15).[25] This approach is complementary to the direct aldol-type reaction of indoles with isatins for the synthesis of these target compounds. It should be observed that the yields of the obtained adducts **52** are generally moderate and that attempts to use chiral phosphoric acids in order to develop an asymmetric process only gave negligible results. Following the well-known chemistry of diazo compounds, reagent **51** is converted into rhodium carbene **VIII** by interaction with the metal catalyst and upon reaction with ethanol this intermediate is transformed into **IX**. The internal rearrangement of **IX** into **X** generates an enolate-type intermediate which acts as an effective nucleophile with the carbocationic species obtained by acid catalyzed dehydration of **33**.



Scheme 15. Reaction of 3-diazooxindoles **51** with 2-indolylmethanols.

3 Malonate ester derivatives

Functionalized malonic acid esters are broadly used as highly stabilized carbanionic systems in several carbon-carbon bond forming processes. Particularly, the one-pot reaction of 2-indolylmethanol **53** with ethyl 2-aminomalonate **54** and arylaldehydes in the presence of chiral phosphoric acid **55a** affords tetrahydro-γ-carboline derivatives **56** in good yield and high enantioselectivity (Scheme 16).[26] The reaction is based on the preliminary formation of imine **XI** which is in equilibrium with zwitterion **XII** due to the high mobility of the methylene active hydrogen atom. As portrayed in **TS2**, attack of the anionic moiety in **XII** occurs regioselectively at C-3 of the intermediate carbocationic system generated from **53** and is followed by nucleophilic addition of the exocyclic double bond to the azomethine carbon. The whole process is efficiently assisted by chiral catalyst **55a** which ensures the correct enantiofacial approach of the reactants through an appropriate hydrogen bonding.



Scheme 16. Asymmetric synthesis of tetrahydro-γ-carbolines.

The same reaction carried out on substrates **57** bearing C-3 substituents follows a different pattern since the indole nitrogen atom is involved in the final ring closure leading to tetrahydropyrimido indoles **58** (Scheme 17).[27] Although the chemical yields are not particularly high, the diastereo and enantioselectivities of the process are generally good when 3-methyl substituted indoles **57** are used as substrates in the presence of chiral catalyst **55b**. Other C-3 substituents present in compounds **57** give moderate results in term of diastereoselectivity albeit the enantioselectivity still remains high. This procedure has been also applied to isatin derivatives as carbonyl reactants leading to spirooxindoles compounds.[28] The observed diastereoselectivity is high (dr>95:5) but the recorded enantioselectivity is slightly lower compared to the use of simple aldehydes.

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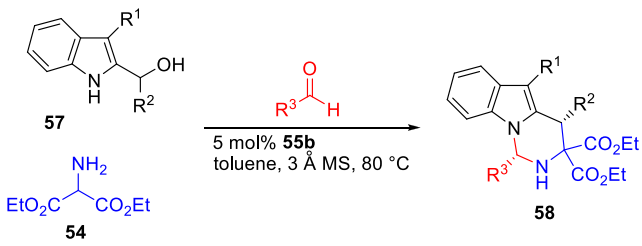
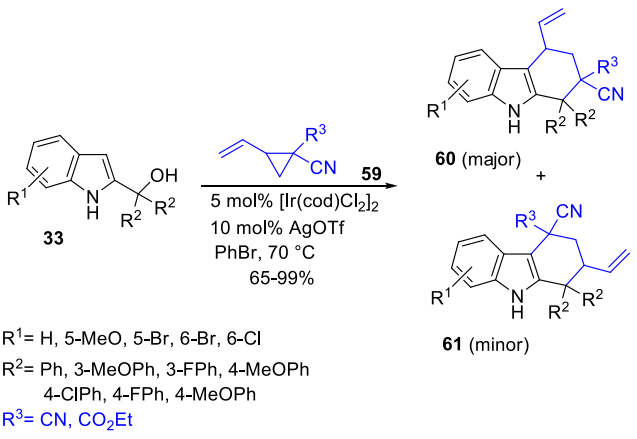
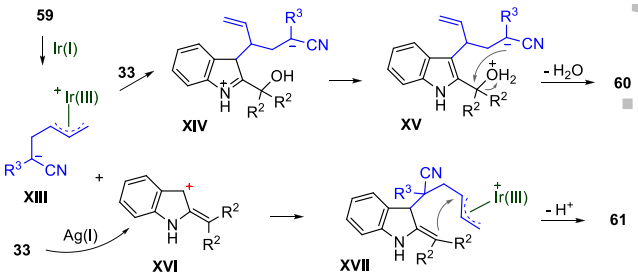


Scheme 17. Asymmetric synthesis of tetrahydropyrimido indoles.

Vinylcyclopropanes **59** bearing geminal electron-withdrawing groups react with 2-indolylmethanols **33** under Ir(I)/Ag(I) catalysis following two different reaction pathways leading to regioisomeric tetrahydrocarbazole systems **60** and **61** (Scheme 18).[29] Compound **60** largely predominates over **61** and this process can be also successfully extended to vinyloxirane although a single example of this reaction is reported. The iridium complex is responsible for the cleavage of the cyclopropyl ring in reagent **59** leading to intermediate zwitterion **XIII** which in the main process reacts with substrate **33** giving adduct **XIV**. Proton shift from **XIV** generates intermediate **XV** which undergoes a nucleophilic substitution that affords tetrahydrocarbazole **60**. In the alternative pattern stabilized carbocation **XVI** is formed by action of the silver salt on substrate **33** and then regioselectively reacts at C-3 with the stabilized nucleophilic site of **XIII**. The obtained intermediate **XVII** by further ring closure leads to the other regioisomer **61**.

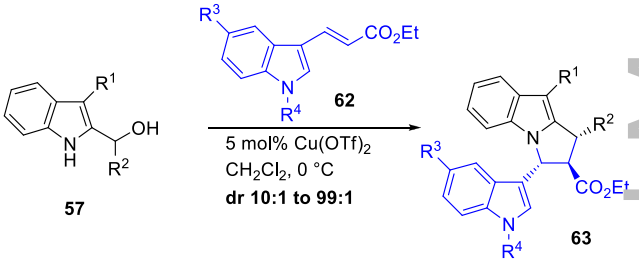


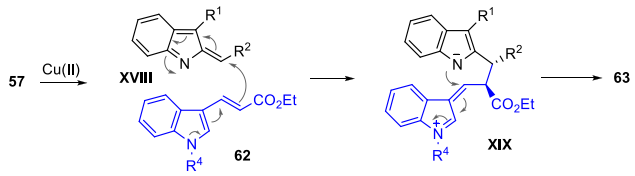


Scheme 18. Metal catalyzed reaction of vinylcyclopropanes to 2-indolylmethanols.

4 Alkenyl derivatives

Functionalized alkenes have been used in the reaction of 2-indolylmethanols mainly to obtain pyrroloindole derivatives exploiting different cycloaddition processes. In some preliminary studies aimed at the synthesis of analogs of the hallucinogenic drug yuremamine, 2-indolylmethanols **57** have been made to react with 3-indolylacrylates **62** (Scheme 19).[30] This process is catalyzed by $Cu(OTf)_2$ and the target compounds **63** are obtained in very high yields and generally excellent diastereoselectivities. The hypothesized mechanism involves the diastereoselective reaction between the indolenine intermediate **XVIII**, formed upon dehydration of **57**, and acrylate **62**. The formed intermediate **XIX** undergoes a ring closure by reaction of the nucleophilic nitrogen atom with the vinylogous iminium ion moiety.





Scheme 19. Coupling of 3-indolylacrylates with 2-indolylmethanols.

Later on, the asymmetric version of this process has been proposed using 2-alkenylindoles **65** in the reaction with 2-indolylmethanols **64** (Scheme 20).[31] Similarly to other related approaches the cycloaddition is catalyzed by chiral phosphoric acid **66** and the obtained adducts **67** are obtained as single diastereoisomers and with elevated ee values.

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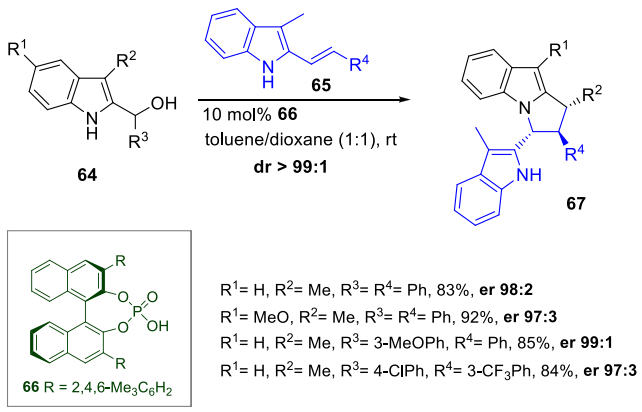
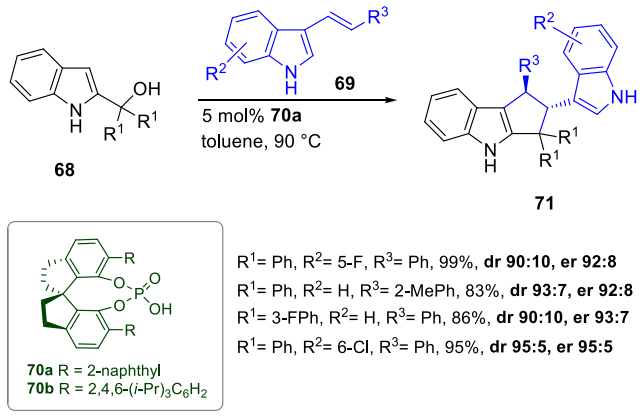


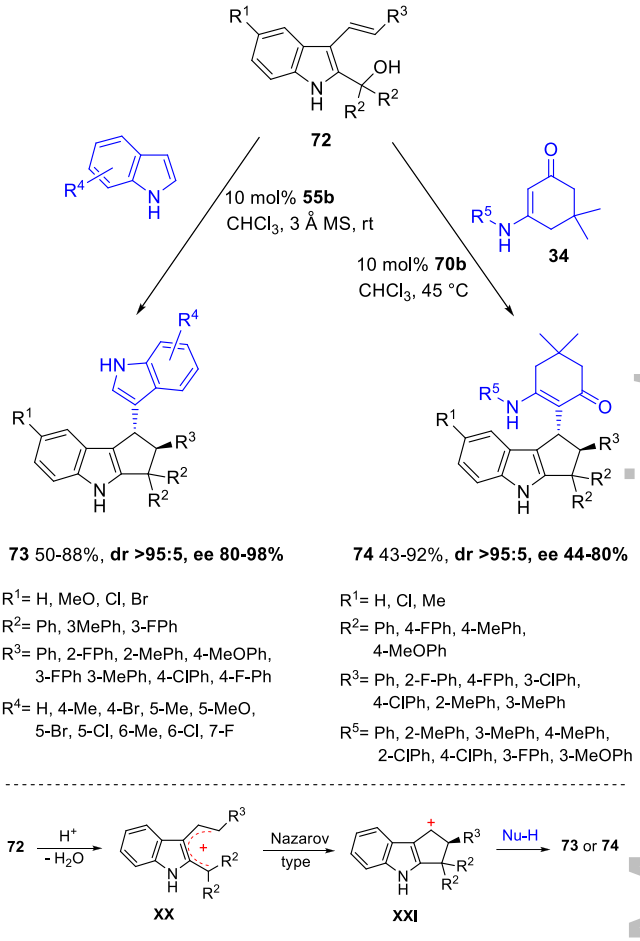
Scheme 20. Enantioselective addition of 2-alkenylindoles to 2-indolylmethanols.

A complementary reaction leading to regioisomeric pyrroloindoles **71** can be obtained by reaction of C-3 unsubstituted 2-indolylmethanols **68** with 3-alkenylindoles **69** in the presence of SPINOL-derived chiral phosphoric acid **70a** (Scheme 21).[32] As previously observed in similar reactions, the intermediate carbocation generated upon dehydration of **68** undergoes a selective nucleophilic attack at C-3 with subsequent ring closure of the resulting indoleninium ion intermediate.



Scheme 21. Enantioselective addition of 3-alkenylindoles to 2-indolylmethanols.

Carbocations with extended stability can be generated by dehydration of 3-alkenyl-2-indolylmethanols **72** (Scheme 22).[33,34] Upon reaction with chiral phosphoric acids already proved effective in related processes, the highly stabilized carbocationic intermediate **XX** undergoes a Nazarov-type reaction leading to a new carbocation **XXI** featured by the pyrroloindole system. Carbocation **XXI** can intercept indole reagents leading to derivatives **73** or β-enaminoketones **34** giving adducts **74**. The reaction with indoles is featured by a high level of diastereo and enantioselectivity while the same process using β-emaminoketones **34**, although still excellent in term of diastereoselectivity, affords adducts **74** with moderate enantioselectivity. Among other aromatic derivatives tested in this reaction, β-naphthols can be used with satisfactory results.

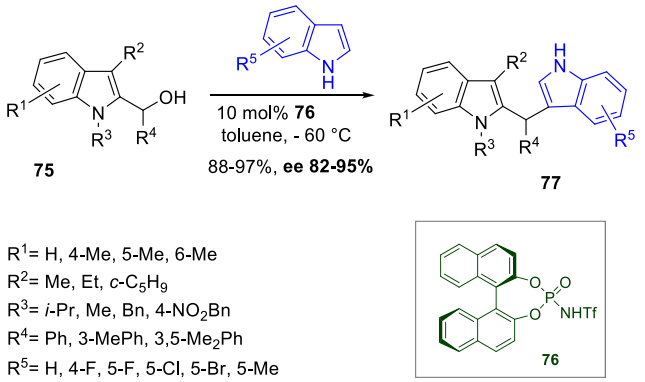


Scheme 22. Enantioselective addition of indoles and enaminoketones to 2-indolylmethanols.

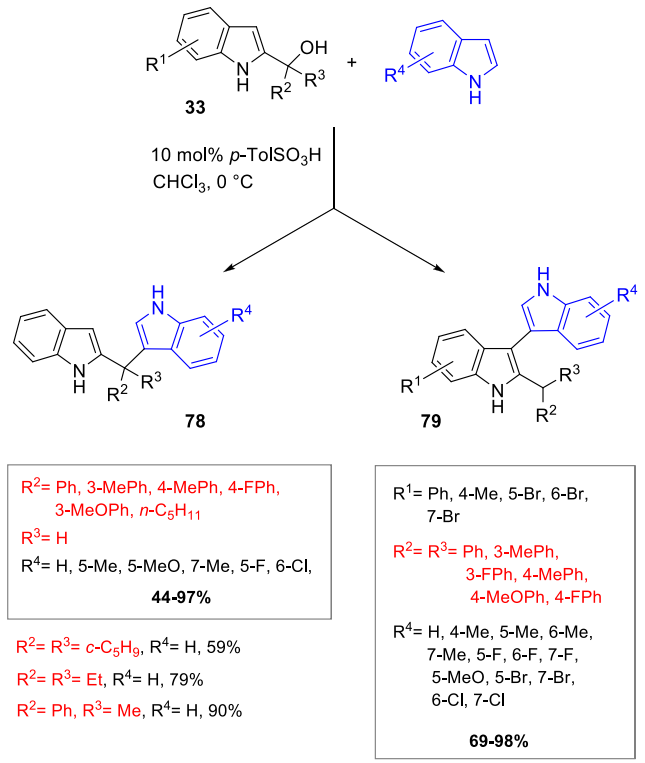
5 Aromatic and heteroaromatic compounds

The reaction of 2-indolylmethanes with aromatic derivatives has been mainly studied in the search of new procedures to access unsymmetrical bisindolylmethanes,[35] and more generally triarylmethanes embedding the indole moiety.[36] The first asymmetric synthesis of 2,3'-bisindolylmethanes **77** has been carried out by reaction of 2-indolylmethanols **75** with indoles in the presence of chiral phosphoramide **76** (Scheme 23).[37] The chemical yields of the resulting adducts **77** are very good and the level of enantioselectivity recorded rather satisfactory. As observed in related processes using chiral phosphoramides (*cf* Scheme 7), the presence of the acidic NH group in the reacting indole is instrumental in ensuring high ee values through a suitable hydrogen bonding with the catalyst. A related procedure has been devised for the preparation of optically active 2,2'-bisindolylmethanes using 3-substituted indoles as reactants in the reaction with 2-indolylmethanols.[38] This process is catalyzed by chiral phosphoric acid **31** [R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$] but

although the chemical yields are satisfactory, moderate levels of enantioselectivity are recorded. As already discussed in previous sections, a regiodivergent addition of indoles to 2-indolylmethanols **33** can be achieved depending on the nature and number of substituents R^2 and R^3 present at the carbinol system (Scheme 24).[39] In the acid catalyzed reaction, attack of the indole at the exocyclic carbon leading to 2,3'-bisindolylmethane **78** occurs when secondary diarylalkanols **33** (R^3= H) are employed.



Scheme 23. Enantioselective synthesis of 2,3'-bisindolylmethanes.



Scheme 24. Regiodivergent synthesis of 2,3'-bisindolylmethanes and 3,3'-bisindoles.

However the same regiochemical preference for compounds **78** is observed when tertiary 2-indolylmethanols **33** bearing two alkyl groups (R^2= R^3= alkyl) or mixed substituents (R^2= aryl, R^3= alkyl) are used as substrates. As expected, diaryl substituted 2-indolylmethanols **33** (R^2= R^3= aryl) afford 3,3'-bisindolyl derivatives **79** arising from attack of the indole reactant to the electrophilic C-3 position of the intermediate carbocationic system. Recently, this approach has been used for the synthesis of 3,2'-bisindolyl derivatives **80** and **81** prepared by acid catalyzed reaction of compounds **33** with tryptophols and *N*-protected tryptamines respectively (Figure 1).[40]

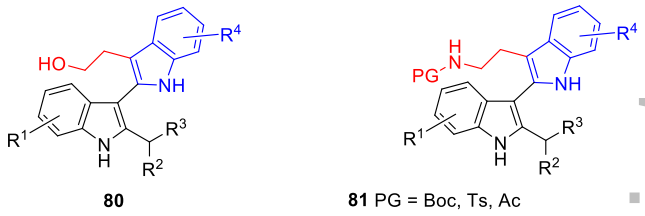
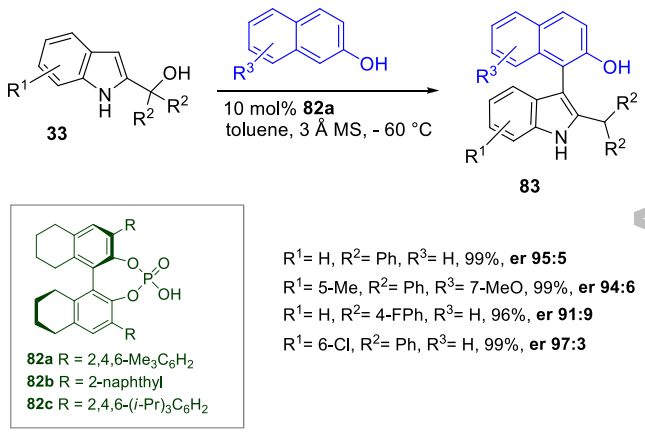


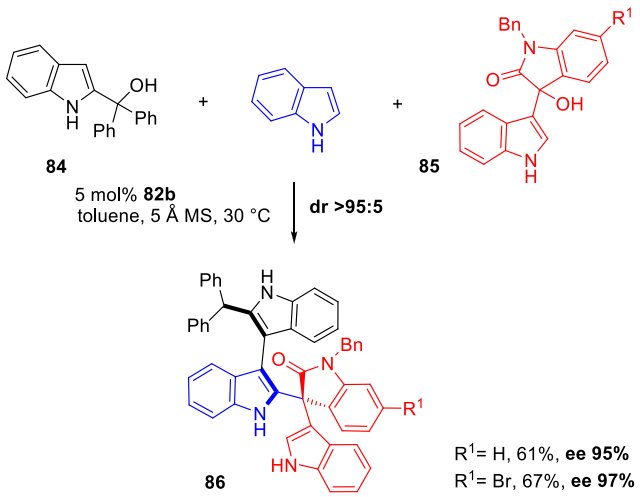
Figure 1. Examples of 3,3'-bisindoles embedding the tryptophol and tryptamine moieties.

The asymmetric version of this process has been devised for the assembling of optically active axially constrained 3,1'-naphthylindole systems as portrayed in Scheme 25.[41] In the presence of chiral phosphoric acid **82a**, 2-indolylmethanols **33** react with 2-naphthol derivatives leading to diaryl derivatives **83** in excellent yield and satisfactory enantioselectivity. The configurational stability of the obtained compounds **83** is ensured by the joint steric effect brought by the C-2 diarylmethane substituent and the hydroxy group. As a matter of fact, hydrogen substitution of the hydroxy group entails a notable drop in the er value from 95:5 to 73:27 in one of the compounds prepared with this procedure. It should be also observed that the utilization of 2-styrylindole instead of 2-naphthol in this reaction readily affords the expected 3,3'-bisindolyl derivative in good yield (99%) but low er (77:23).



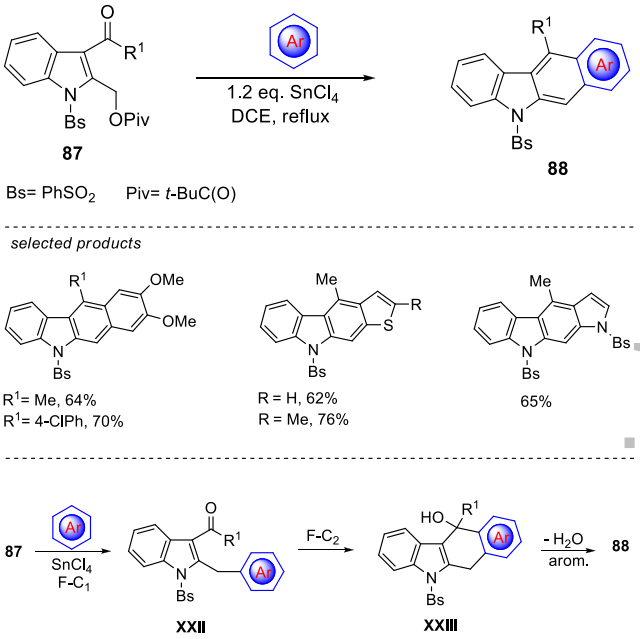
Scheme 25. Enantioselective synthesis of axially constrained naphthyl derivatives **83**.

Following a similar procedure, more complex and structurally rigid derivatives embedding four indole structures can be obtained by a three component reaction involving 2-indolylmethanol **84**, indole and bisindoles **85** (Scheme 26).[42] The 3,3'-bisindolyl derivative preliminarily formed reacts with the alkylideneindolenine intermediate generated upon dehydration of **85** (*cf* **3**, Scheme 1) finally leading to compound **86**. The sterical constraint of the resulting derivatives **86** allows their formation with a good level of enantioselectivity and configurational stability.

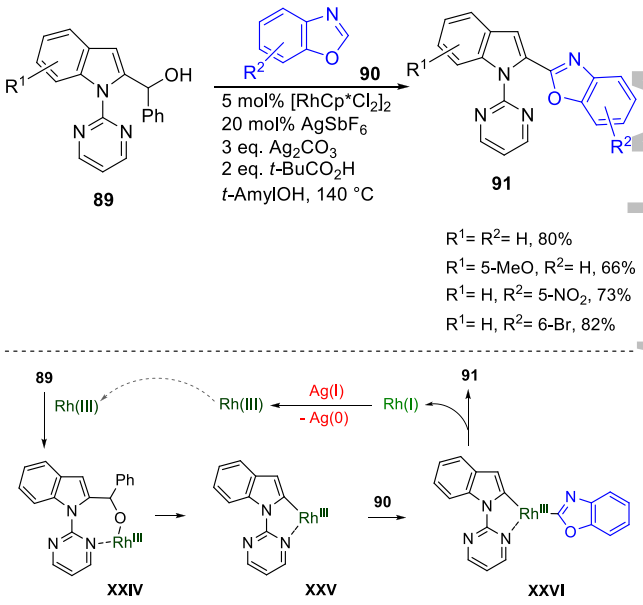


Scheme 26. Enantioselective synthesis of tetraindole derivatives **86**.

Primary 2-indolylmethanols **87** are involved in the Lewis acid promoted reaction with aryl and heteroaryl reagents giving aryl and heteroaryl [*b*]carbazole derivatives **88** (Scheme 27).[43] Compounds **88** are the result of a tandem process involving a preliminary Friedel–Crafts reaction promoted by the Lewis acid leading to intermediate arylated compound **XXII**. The ring closure is realized through a second Friedel–Crafts reaction generating the hydroxy compound **XXIII** which upon aromatization by dehydration affords the target compounds **88**. This methodology is rather versatile since various electron-rich benzene derivatives and five-member ring heterocycles can be successfully used. Functionalization of indoles at C-2 exploiting metal-catalyzed processes is a viable procedure providing that a suitable directing group is linked at the nitrogen atom.[3] Heteroarylation of *N*-(2-pyrimidyl)-2-indolylmethanols **89** by benzoxazoles **90** can be achieved with concomitant carbon-carbon bond cleavage of the carbinol system in a rhodium-catalyzed process leading to derivatives **91** in satisfactory yields (Scheme 28).[44] The mechanism involves the initial formation of intermediate rhodium complex **XXIV** stabilized by the interaction of the metal with the pyrimidine nitrogen atom. Upon β-elimination the obtained rhodacycle **XXV** reacts with benzoxazole **90** giving intermediate **XXVI** which upon reductive elimination affords the target compound **91**. The catalytic cycle is ensured by a rapid oxidation of the released Rh(I) species by silver carbonate.



Scheme 27. Synthesis of aryl and heteroaryl [*b*]carbazoles.



Scheme 28. Debenzylative coupling of 2-indolylmethanols with benzoxazoles.

6 Intramolecular reactions

The metal-catalyzed ring closure of 1-(indol-2-yl)-2,3-allenols **92** has been mainly studied in connection with the synthesis of carbazole derivatives **93** (Scheme 29).[45] The reaction is catalyzed by $PtCl_2$ and is effective on various substituted allenols **92** providing the target carbazoles **93** in usually good yields. Coordination of the Pt(II) species to the allenyl

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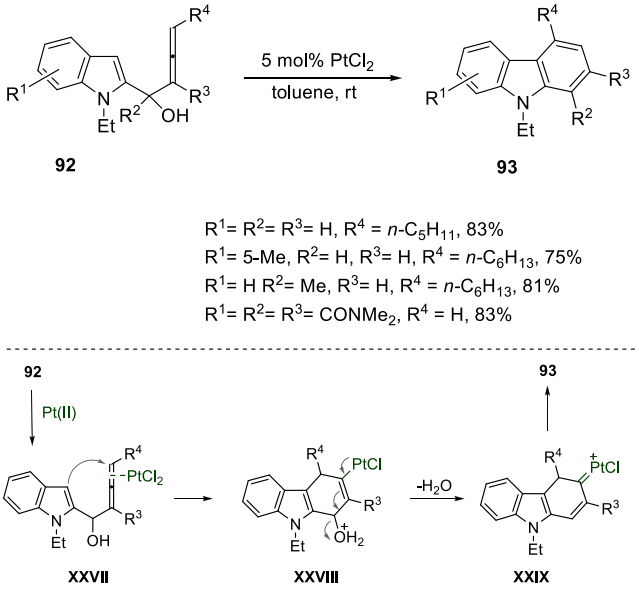
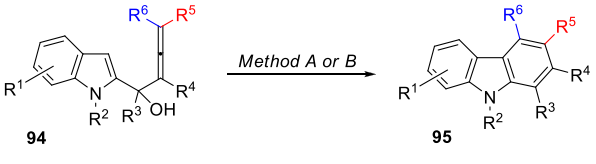
group provides the required electrophile **XXVII** which undergoes to an intramolecular Friedel–Crafts reaction. The resulting intermediate **XXVIII**, after protonation of the hydroxy group, eliminates a water molecule leading to a metal carbene **XXIX** which upon a 1,2-hydrogen shift and demetalation affords the final carbazole compound **93**.



Scheme 29. Ring closure of 1-(indol-2-yl)-2,3-allenols to carbazole systems.

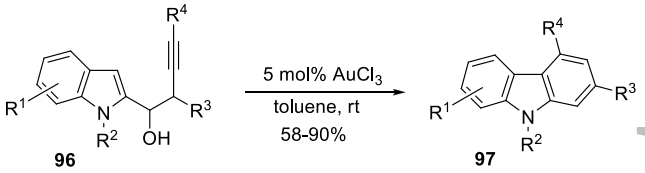
The utilization of terminally disubstituted allenols **94** results in the selective 1,2-migration of the aryl groups over the methyl one using $PtCl_2$ as catalyst (Method A, Scheme 30).[46] A better level of selectivity in the final migration step can be achieved in reactions catalyzed by AuCl (Method B, Scheme 30).[47] In this case, even reactions proved ineffective with $PtCl_2$ were successful and selectivity between various alkyl groups and the methyl one was observed.



R1= H, 5-Me, 7-Me, 5-OMe
R2= Et, Bn
R3= H, Me
R4= H, Me
R5= Ph, 3-MeOPh, 4-MeOPh, 4-ClPh 4-F-Ph, 2-furyl, 2-thienyl, Et, *i*-Pr, *n*-Pr, *c*-C_3H_5,
R6= H, Me, Et, *c*-C_3H_5, *i*-Pr.

Scheme 30. Synthesis of carbazoles by ring closure of indolylallenols.

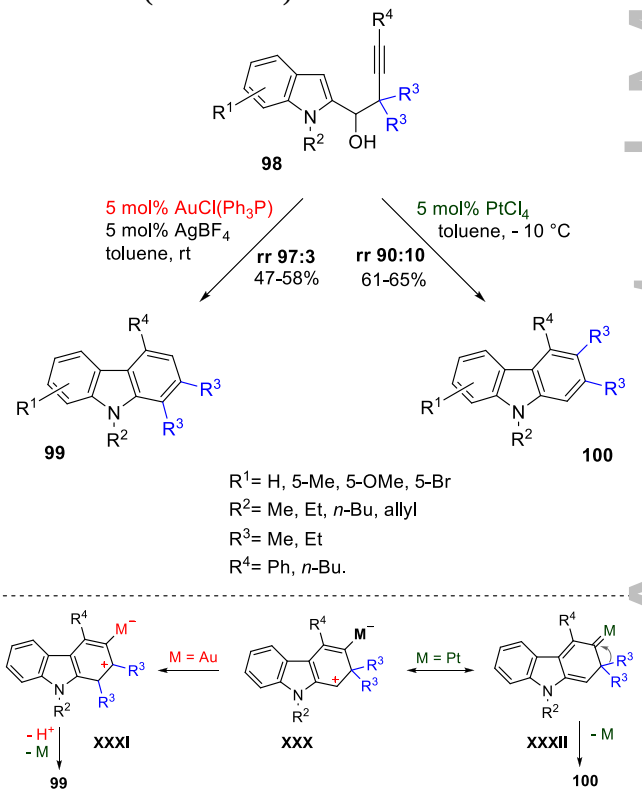
The metal-catalyzed intramolecular reaction described on allenols can be easily extended to the parent indolylalkynols using the same metals although in a different oxidation state. Indolylalkynols **96** afford the expected 2,4-disubstituted carbazoles **97** in a ring closure process catalyzed by $AuCl_3$ following the classical activation of alkynes provided by gold(III) salts (Scheme 31).[48] Similarly to the carbazole synthesis using allenols, the final aromatization step is caused by dehydration.



R1= H, 4-Me, 5-Me, 7-Me, 5-OMe, 5-Br
R2= Et, Bn, 4-MeOBn
R3= Me, Et, Bn, Ph
R4= Et, Ph, *n*-Bu.

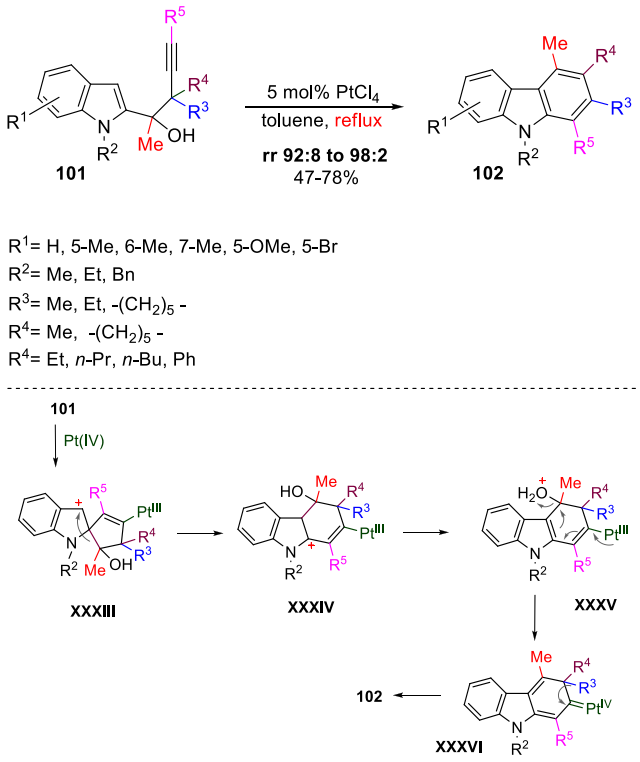
Scheme 31. Ring closure of indolylalkynols to carbazoles.

A more intriguing behavior is displayed by *gem*-disubstituted indolylalkynols **98** which undergo to a regiodivergent ring closure to carbazole systems depending on the nature of the metal catalyst used in the reaction (Scheme 32).[49]



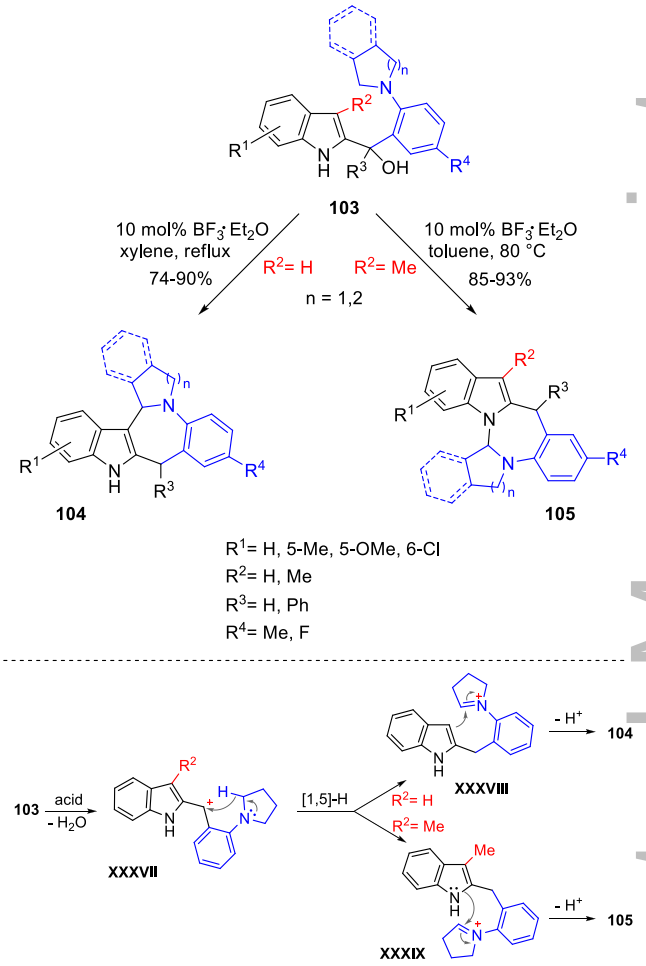
Scheme 32. Ring closure of *gem*-disubstituted indolylalkynols to rearranged carbazoles.

In the presence of the AuCl(Ph_3P) complex the major product formed is 1,2,4-trisubstituted carbazole **99** while platinum tetrachloride mostly affords the 2,3,4-trisubstituted regioisomer **100**. In gold(I) catalyzed reactions, the carbocationic intermediate **XXX** directly undergoes to a 1,2-alkyl shift leading to rearranged carobocation **XXXI** which after proton elimination and deauration affords carbazole **99**. The presence of platinum in intermediate **XXX** makes the resonance structure **XXXII** with metal-carbene character more significant and therefore the carbon shift involves alkyl migration at C-4 leading, after demetalation, to carbazole **100**. The crucial importance of the reaction conditions in these processes is further demonstrated by the different regioselectivity observed using platinum tetrachloride under reflux instead that at low temperature in the reaction of indolylalkynols **101** (Scheme 33).[50] Carbazoles **102** are formed through a cascade process starting from the electrophilic metal activation of the triple bond in **101** and the subsequent unusual *endo* ring closure at C-2 leading to spiro carbocation **XXXIII**. Ring expansion of this intermediate generates carbocation **XXXIV** which upon proton transfer is then converted into **XXXV**. Elimination of water from this intermediate affords vinylic platinum carbene **XXXVI** which after the usual 1,2-carbon shift and demetalation gives the final carbazole **102**.



Scheme 33. Ring closure of indolylalkynols to carbazoles.

Indolylmethanols **103** bearing a saturated heterocyclic group in the aryl moiety can be involved in the acid catalyzed synthesis of indoloazepines **104** or indolodiazepine **105** (Scheme 34).[51] The reaction is catalyzed by boron trifluoride etherate and as in other related reactions involves a preliminary dehydration leading to stabilized carbocation **XXXVII**. In the devised reaction conditions, a 1,5-hydrogen shift generates an iminium ion intermediate **XXXVIII** which undergoes to a Friedel–Crafts reaction leading to indoleazepine **104**. The iminium ions **XXXIX** obtained from 2-indolylmethanols **103** bearing a C-3 methyl substituent are prevented to react at this position and therefore a regiocomplementary cyclization involving the indole nitrogen atom leads to indolodiazepines **105**.



Scheme 34. Synthesis of indoloazepines **104** and indolodiazepine **105**.

7 Heteronucleophiles

Common reagents based of different nucleophilic heteroatoms can be used in the reaction with 2-indolylmethanols. These processes have been rather underdeveloped with respect to other reactions leading to carbon-carbon bond formation and could represent a major advance for future studies on these substrates.

7.1 Diarylphosphine oxides

The metal catalyzed addition of diarylphosphine oxide to 2-indolylmethanols evidences the same

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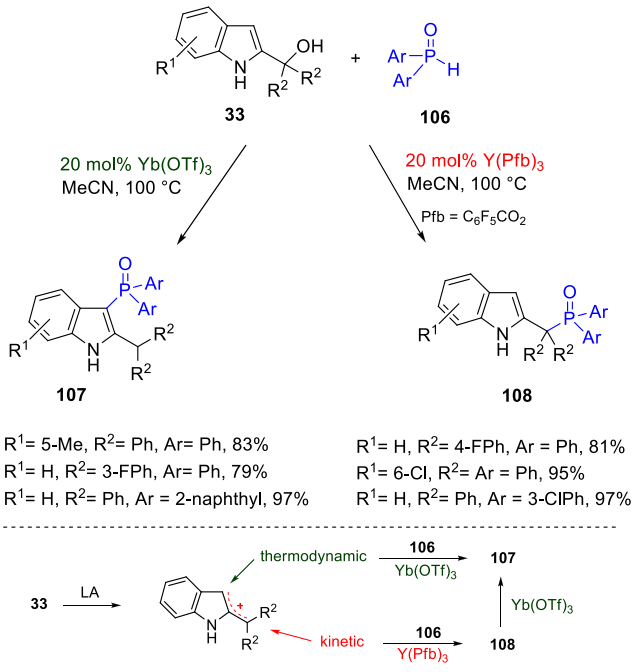
regioselectivity pattern already observed in similar reactions using carbon nucleophiles. This aspect has been successfully faced using two different metal complexes which are able to drive the addition of diarylphosphine oxides **106** to 2-indolylmethanols **33** at the selected carbon atom as portrayed in Scheme 35.[52] The utilization of $Yb(OTf)_3$, which is featured by a very stable anion, forms a weak ion pair with the intermediate carbocation allowing a reversible reaction which favors the thermodynamic C-3 substituted product **107**. Conversely, the pentafluorobenzoate anion of $Y(Pfb)_3$ forms a stronger ion pair with the carbocation addressing the nucleophilic attack at the benzylic position endowed of a greater LUMO coefficient leading to the preferential formation of the kinetic regioisomer **108**. The reversibility of this phosphorylation process is nicely demonstrated by the conversion of the kinetic product **108** into the thermodynamic isomer **107** by treatment with $Yb(OTf)_3$ in the same reaction conditions.

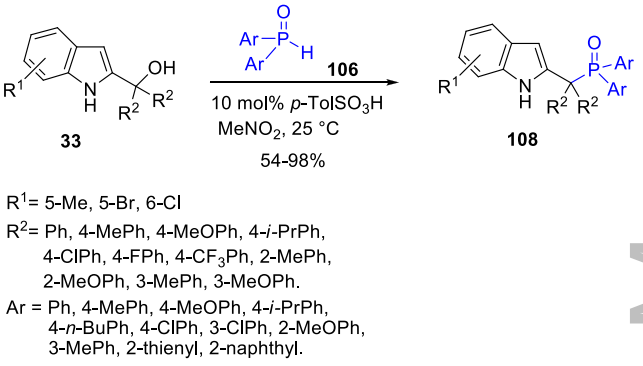


Scheme 35. Regiodivergent addition of diarylphosphine oxides to 2-indolylmethanols.

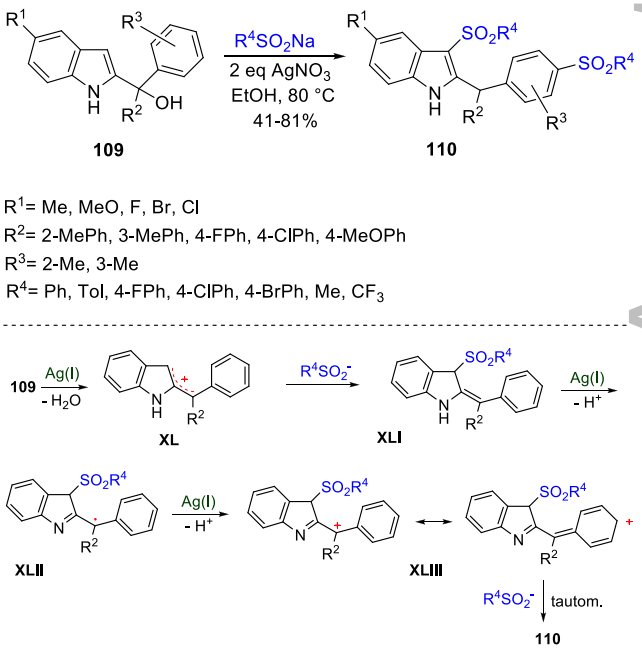
This behavior seems confirmed for a related process in which the same reactants are made to react in the presence of a catalytic amount of *p*-$TolSO_3H$ (Scheme 36).[53] At 25 °C the kinetic products **108** are formed in usually high yield for a large variety of reactants combinations. The same reaction carried out at higher temperature (80 °C) using 20 mol% of triflic acid affords the thermodynamic product **107** albeit in general lower yields (36-80%).

7.2 Aryl and alkylsulfinates

Organic derivatives of sulfinic acids are widely employed as nucleophilic reagents in many synthetic processes aimed at the preparation of sulfones.[54] A recent procedure has been employed to convert 2-indolylmethanols **109** into bissulfonylated derivatives **110** using sodium aryl and alkylsulfinates in the presence of an excess of silver nitrate (Scheme 37).[55] The double sulfonylation process starts by a silver(I)-promoted dehydration of the 2-indolylmethanol giving the carbocation intermediate **XL** which expectedly adds the arylsulfinate anion at C-3 leading to monosulfonylated intermediate **XLI**. The latter compound undergoes to a monoelectronic oxidation by the silver cation giving a radical cation that after deprotonation affords the radical **XLII**. A further oxidation by the same metallic ion generates a largely delocalized carbocation **XLIII** which selectively reacts with the sulfinate anion at C-4 of the benzene ring leading after a suitable tautomerism to the target bissulfonylated indole compound **110**. The proposed mechanism involving a SET oxidation of the azafulvene-type intermediate **XLI** seems corroborated by the observation that 3-benzenesulfonyl-2-indolylmethanols are totally unreactive under the devised reaction conditions.



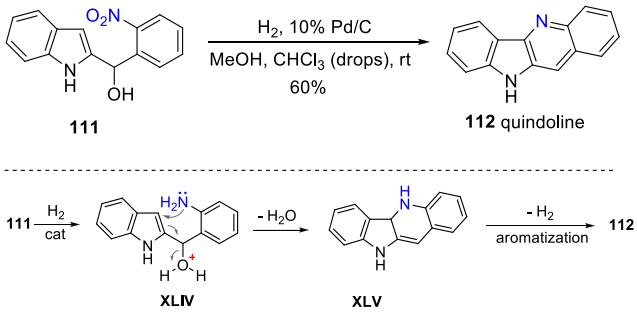
Scheme 36. Brønsted acid catalyzed addition of diarylphosphine oxides to 2-indolylmethanols.



Scheme 37. Bissulfonylation of 2-indolylmethanols.

7.3 Nitrogen derivatives

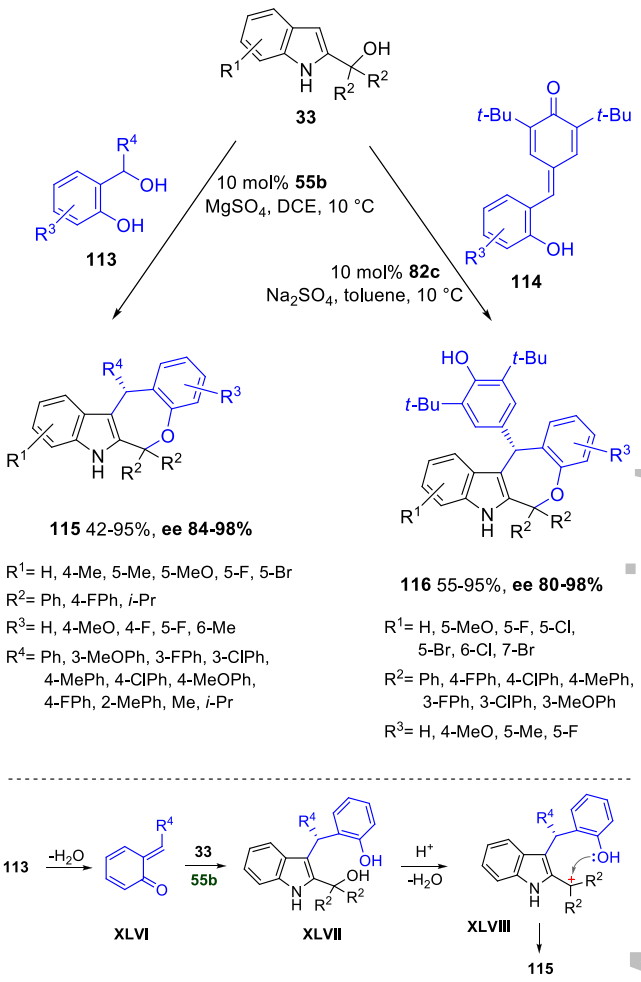
Reactants containing nucleophilic nitrogen atoms have been scarcely employed in reactions with 2-indolylmethanols.[56] The only valuable example available refers to the synthesis of the antimalarial alkaloid quindoline **112** obtained in a single step by reduction of the nitroaryl-2-indolylmethanol **111** (Scheme 38).[57] Catalytic hydrogenation of substrate **111**, in the presence of chloroform which is supposed to provide a mild acidic environment, initially affords aniline derivative **XLIV** that upon ring closure with water elimination leads to dihydroquinoline **XLV**. The final aromatization step by dehydrogenation gives quindoline **112** in satisfactory yield.



Scheme 38. Synthesis of quindoline by reductive cyclization.

7.4 Oxygen derivatives

The utilization of hydroxylated derivatives such as alcohols and phenols as nucleophilic reagents in the reaction with 2-indolylmethanols is seldom observed and is currently of very limited practical interest. In a very recent paper, the substitution of the hydroxy group in 2-indolylmethanols **33** by a phenolic system is the last step of a catalytic asymmetric cyclization leading to optically active benzoxepine derivatives **115** and **116** in good yields and satisfactory enantioselectivities (Scheme 39).[58] Reactions with 2-hydroxybenzyl alcohols **113** involve the initial formation of *o*-quinone methides **XLVI** which in the presence of a chiral phosphoric acid **45b** lead to the corresponding Friedel–Crafts adducts **XLVII**. The acid catalyst also promotes the formation of carbocations **XLVIII** which promptly react with the nucleophilic oxygen atom leading to the benzoxepine products **115**. A related process is possible using stable *p*-quinone methides **114** which react in a similar fashion leading to benzoxepines **116** featured by a phenolic substituent.

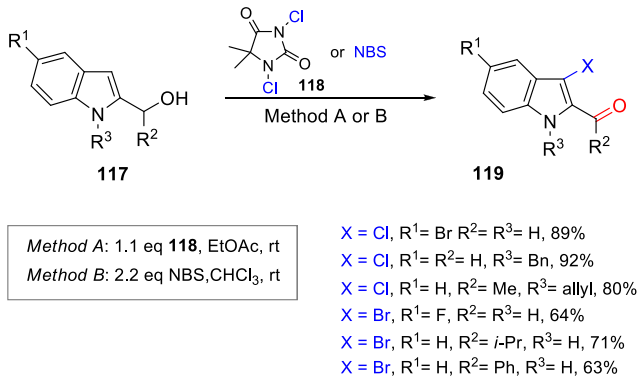


Scheme 39. Synthesis of benzoxepine derivatives.

8 Redox reactions

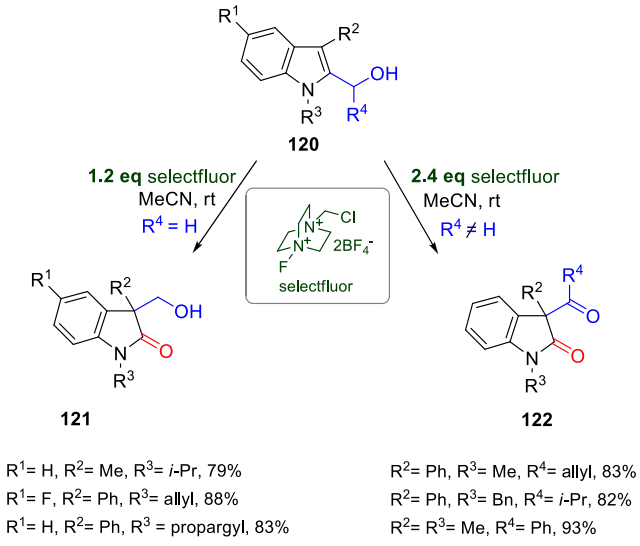
Reductive processes replacing the hydroxy group in 2-indolylmethanols with an hydrogen atom have found limited application in synthesis. Catalytic hydrogenation carried out under acidic condition has been used on a single example of secondary 2-indolylmetanol with rather modest results (25% yield).[59] A mixture of trifluoroacetic acid/sodium borohydride has been used for a similar process evidencing better performances on four different substrates.[60] Oxidation of secondary 2-indolylmethanols to the corresponding ketones is more common but this process does not present any synthetic peculiarity. Organic reagents working as halonium ion sources provide more interesting results in the reaction with 2-indolylmethanols **117** (Scheme 40).[61] These substrates are converted into 3-haloindolyl aldehydes or ketones **119** upon reaction with 1,3-dichloro-5,5-dimethylhydantoin **118** or NBS. Hydantoin **118** is more effective than NBS in providing the expected products since chloro derivatives **119** (X = Cl) are obtained in higher yields than the corresponding brominated products. The halogenation and the oxidation processes seem to occur in two separate steps which are not related each

other. A possible alternative mechanism involving a spiroacetal intermediate formed by anchimeric assistance of the hydroxy group can be ruled out by the observed formation of 3-chloro-2-indolylmethanols using a substoichiometric amount of the halogenating reagent.



Scheme 40. Halogenative oxidation of 2-indolylmethanols.

Selectfluor is a fluorinating agent which has been frequently used as oxidizing agent on various indole derivatives.[62] The utilization of selectfluor in the reaction with 2-indolylmethanols **120** allows their conversion into 3-hydroxymethyloxindoles **121** or their parent 3-acyl derivatives **122** according to the amount of the reagent used (Scheme 41).[63]



Scheme 41. Synthesis of oxindoles from 2-indolylmethanols.

Formation of the target rearranged oxindoles probably occurs by preliminary fluorination at the indole nitrogen atom leading to a cationic intermediate which promotes the 1,2-rearrangement of the alkanol group. In the presence of an excess of selectfluor, the hydroxy group of **121** is further oxidized to generate the dicarbonyl compound **122**.

9 Conclusion and outlook

Indolylmethanols are pivotal substrates for the preparation of architecturally complex molecules embedding the indole ring. Although less exploited than their C-3 regioisomers, 2-indolylmethanols are gaining increasing interest for their peculiar reactivity associated to the generation of two reactive electrophilic sites upon their dehydration under acidic or metal catalysis. The subsequent nucleophilic addition can be regiodirected according to the nature of the 2-indolylmethanol employed. Tertiary 2-indolylmethanols bearing two aryl groups generally address the nucleophilic attack at C-3 when that position is not substituted. Conversely, secondary or dialkyl substituted 2-indolylmethanols preferentially react at the exocyclic benzylic position. A notable number of transformations entail tandem or cascade processes leading to the synthesis of polycyclic derivatives in which is often possible to achieve a remarkable control of the stereoselectivity of the obtained products. The activation of 2-indolylmethanols achieved using chiral Brønsted acids is particularly effective for the catalytic enantioselective synthesis of various indole derivatives using weak nucleophilic reagents such as enols, enecarbamates, alkenes, electron-rich aromatic and heteroaromatic derivatives. An inherent limitation in the use of 2-indolylmethanols is related to the hydrogen mobility of the hydroxy group which prevents from the utilization of strong nucleophilic reagents or activation of the substrate under basic conditions. This drawback could be in principle overcome by a derivatization of the hydroxy group (organic or inorganic esters formation) or by a suitable conversion into other leaving groups featured by a carbon-heteroatom bond as experienced for related 3-indolyl derivatives. This complementary reactivity is still rather underdeveloped and may represent a future field of study in order to enlarge the synthetic significance of 2-indolylmethanols.

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