Synthesis of 3-substituted indoles *via* reactive alkylideneindolenine intermediates

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Elimination of suitable leaving groups from 3-substituted indoles under basic or acidic conditions readily provides alkylideneindolenine intermediates that may react with a large variety of nucleophilic reagents. This article highlights some recent developments of this synthetic approach for the preparation of functionalized indole derivatives.

Introduction

The indole ring is included in a plethora of biologically active compounds, and this feature fully justifies the deep interest addressed to all synthetic processes concerning this heterocyclic system.[1] The assembly of the indole core starting from benzene derivatives represents a viable procedure to obtain regiodefined compounds, hardly achievable by direct electrophilic substitution.[2] Regioselective functionalization of the indole ring at the 3-position can be carried out exploiting a Friedel–Crafts process using electron-poor alkenes, which may require a tunable activation by Lewis or Brønsted acids, depending on the electrophilic aptitude of the olefin used.[3] Although a large variety of electrophilic systems are available for such purpose, some notable exceptions can be pointed out such as β-substituted α,β-unsaturated esters that are poorly reactive with indoles in whatever condition.[4] Since halogenation of indoles occurs regioselectively at C-3, the corresponding haloindoles can be profitably involved in a Suzuki or Heck cross-coupling using aryl or alkenyl reagents.[5] An iodine–copper exchange reaction readily provides 3-metalated indoles that can be used as reagents in nucleophilic substitutions.[6] A complementary approach involves functionalization of the indole ring by electrophilic substitution, inserting a good leaving group at benzylic position. This process is usually carried out by a three component coupling of the indole with an aldehyde and the protonated leaving group HL. A preliminary Friedel–Crafts reaction of the indole **1** with an aldehyde leads to the corresponding alcohol **2**, which upon dehydration, gives a vinylogous iminium ion **3**. This highly electrophilic species is trapped by HL giving indole **4** (Scheme 1). Starting from indoles **4**, it is possible to generate, under basic conditions, an alkylideneindolenine intermediate **5**, which is able to add nucleophiles in a conjugate fashion leading to substituted indoles **6**. The success of this strategy is strongly affected by a series of factors such as the ease of formation of indolenine precursor **4**, its stability, and the aptitude of the leaving group L to be eliminated under mild and controlled conditions. Removal of leaving group L from **4** can be also pursued under acidic conditions, thus regenerating the iminium ion **3**, which

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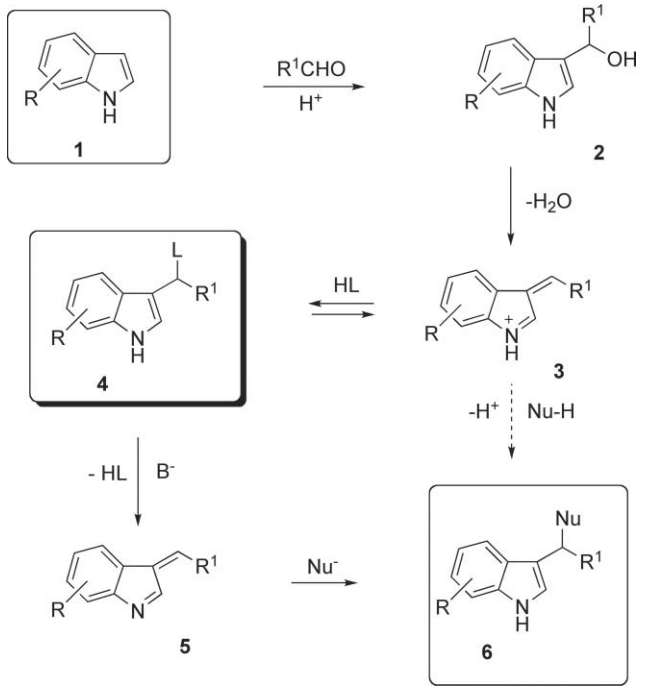
adds weak nucleophiles equally, leading to substituted indoles **6**. Finally, in a sparing number of processes it is possible to bypass derivative **4** directly starting from alcohol **2** for the preparation of compound **6**. In this article, some important aspects of the alkylideneindolenine chemistry will be highlighted. The aim is to outline advantages and limits of this synthetic approach, thus offering the reader a different perspective with which to face indole functionalization.



Scheme 1 General strategy for the synthesis and utilization of alkylideneindolenines and alkylideneindoleninium ions.

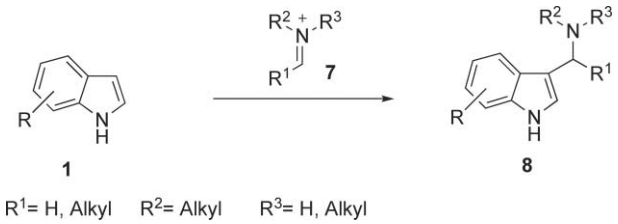
Rafik Rajjak Shaikh

Rafik Rajjak Shaikh was born in Nanded (Maharashtra), India. He obtained his Bachelor and Master degree (organic chemistry) from Yeshwant College, SRTM University, Nanded, India. In 2007, he started his research career as a PhD fellow under the supervision of Prof. M. Petrini at the University of Camerino, Italy. In 2009, he was a visiting PhD student in the research laboratory of Prof. L. F. Tietze at IOBC, University of Göttingen, Germany. His research interests mainly include: development of efficient synthetic methods, synthesis of indole derivatives, study of reactivity of vinylogous imino derivatives, heterogeneous catalysis and organocatalysis.

Synthesis of alkylideneindolenine precursors

Gramines and related amino derivatives

Although in principle gramines **8** could be obtained using the strategy depicted in Scheme 1, these compounds are more conveniently prepared by dialkylaminomethylation of indoles **1** by a Mannich reaction using imino derivatives **7** (Scheme 2).[7] Formaldehyde as well as other aldehydes can be used in this process, showing a comparable degree of efficiency. An acid catalysis is usually required and the reaction is carried out in a range from 0 °C to room temperature.



Scheme 2 Synthesis of gramine derivatives.

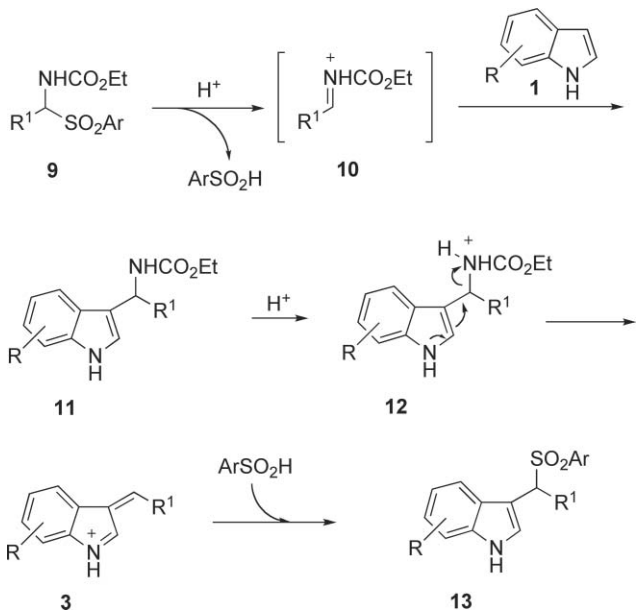
A different procedure for preparation of iminium salts, other than condensation of carbonyls with secondary amines, can be found in the oxidation of silyl ketene acetal derived from ethyl 2-(dibenzylamino)acetate by DDQ.[8] The *in situ*-generated iminium salt reacts with different indoles leading to the corresponding indolyl α-amino ester derivatives. Utilization of alkylimines *in lieu* of the corresponding iminium salts can also be pursued, although the yield of the substituted gramine is often lower compared to the classical method (*vide infra*).[9]

Recently, amidoalkylation of indoles has been proposed as an alternative to the formation of gramines. However, it should be pointed out that this practice is mainly devoted to the preparation of amido derivatives in enantiomerically pure form to be used as pivotal intermediates in the synthesis of biologically active compounds. The reactive imino derivatives used for the Mannich reaction are *N*-acylarylimines or *N*-*p*-tosylimines in the presence of different chiral catalysts. Particularly effective for these purposes are chiral phosphoric acids obtained from optically active binaphthol.[10] Activation of the imine by the acid probably involves protonation of the nitrogen lone pair, albeit its basicity is rather scanty. The intimate ionic couple formed provides the necessary stereochemical bias in the subsequent electrophilic substitution. The utilization of *N*-acylalkylimines in these reactions usually produces poor results both in terms of chemical yield and enantioselectivity. A clever solution to this failure can be found in the utilization of *N*-Boc-enamides as iminium ion precursors. Regioselective protonation of the alkene by chiral phosphoric acid results in the formation of the corresponding *N*-acyliminium ion that reacts with the indole in the usual manner.[11] Optically active β-indolyl-α-amino acid derivatives are readily available by means of a related strategy using the *N*-tosylimino ester of ethyl glyoxylate. As a chiral promoter for this reaction, a copper(I)-TolBINAP catalyst is successfully employed.[12] A conceptually different approach to gramines consists of the reduction of indole-3-carboxamides using diisobutylaluminium hydride (DIBALH). Protection of the indole nitrogen as phenylsulfonylamide is not mandatory for a successful

reduction, but with unsubstituted indoles, lower yields of gramines are recorded.[13]

Arylsulfonyl indoles

The well-known aptitude of the arylsulfonyl moiety to act as a good leaving group makes the corresponding indolyl derivatives excellent precursors of alkylideneindolenines. Curiously, this class of derivatives was practically unknown until their serendipitous synthesis was disclosed three years ago.[14] During an attempt to prepare *N*-ethoxycarbonylaminoalkylindoles **11** by reaction of α-amidoalkylarylsulfones **9** with indoles **1**, formation of a totally different compound was observed (Scheme 3).



Scheme 3 Synthesis of arylsulfonyl indoles from α-amido sulfones.

Although compound **11** is recognized as an intermediate in this reaction, protonation of the carbamoyl group assists an elimination reaction that produces an iminium ion **3**. This reactive electrophile intercepts the arylsulfinic acid released by the amido sulfone **9** in the first step, thus providing sulfonyl indole **13**. Various acidic promoters have been tested for this reaction and montmorillonite K-10 under solventless conditions proved to be the most effective one. An improved preparation of compounds **15** can be devised by directly using indoles **14** and aldehydes in the presence of *p*-toluenesulfinic acid.[15] The latter procedure is more viable and allows propanone to be used for the preparation of sulfonyl indoles (Scheme 4).

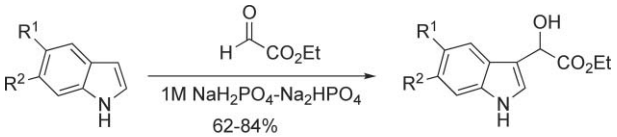
Hydroxy indoles

The introduction of oxygenated groups at the benzylic position of 3-substituted indoles can be easily achieved by reaction of the corresponding aldehyde with carbon nucleophiles.[16] Direct functionalization of indoles at the 3-position is obviously a more appealing process since it entails the utilization of simple indole derivatives in the carbon–carbon bond formation. Curiously, a straightforward Friedel–Crafts reaction involving indoles and aldehydes has been seldom exploited in order to synthesize indolyl alcohols. Under acidic conditions, which are normally required

R = H, MeO R^1= H, Me, Ph, CO_2Et
R^2= Et, *n*-C_5H_{11}, Ph, $Ph(CH_2)_2$, *c*-C_6H_{11}
R^3 = H, Me Ar = Ph, 4-MeC_6H_4

Scheme 4 Synthesis of sulfonyl indoles by three-component coupling.

for the reaction, the formation of bisindoles as main products is evidenced, as will be discussed later in this article.[17] However, under mildly basic conditions (NaH_2PO_4–Na_2HPO_4, pH = 7.5) it is possible to obtain hydroxy indoles **17** using ethyl glyoxylate and different indole derivatives **16** in water as solvent (Scheme 5).[18]



R^1= H, Me R^2= H, Me, Cl

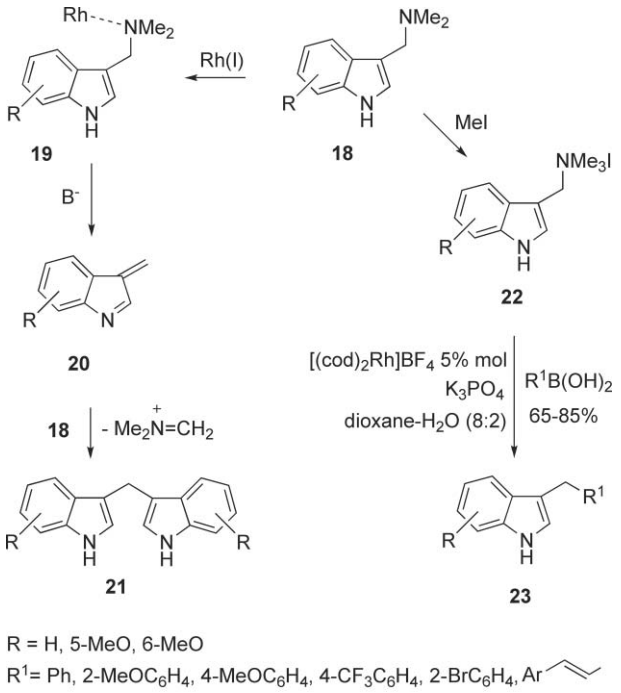
Scheme 5 Reaction of indoles with ethyl glyoxylate.

The impressive development of organocatalytic methods for enantioselective synthesis also has a major impact in solving several reactivity problems commonly found in traditional processes. Bifunctional *Cinchona* alkaloids are able to promote the Friedel–Crafts addition of different indoles to simple aldehydes and α-ketoesters leading to the corresponding hydroxy derivatives in good yield and high enantiomeric excesses.[19] Lithiation of indoles at the 3-position only occurs on selected substrates bearing a substituent on nitrogen and a stabilizing group at the 2-position. So, *N*-methylindole 2-hydrazide can be lithiated using *t*-BuLi/TMEDA and then made to react with several electrophiles including aldehydes and ketones.[20] The obtained derivatives can be further cyclized leading to tricyclic lactones.

Synthetic applications of alkylideneindolenine precursors

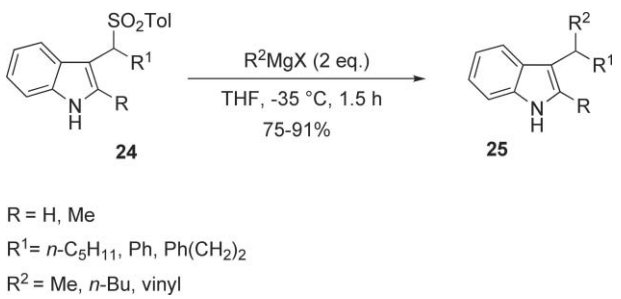
Reaction with organometallic reagents

Reaction of gramines with organometallic reagents is rather uncommon and only sparing examples can be found in the literature. Boronic acids under rhodium or iridium catalysis are ineffective in producing the corresponding adducts with gramines **18**, since coordination of rhodium with the nitrogen lone pair prevents the necessary transmetalation with boronic acids (Scheme 6).[21] The alkylideneindolenine **20** thus formed reacts with gramine **18**, leading to bisindole derivative **21**. Methylation of the gramine produces the corresponding ammonium salt **22**, which is now able to react in a suitable manner giving adduct **23**. Furthermore, the utilization of ammonium salt brings about a reactivity enhancement being a better leaving group compared to dimethylamine.



Scheme 6 Reactivity of gramines with boronic acids under Rh(I) catalysis.

A three component reaction involving indoles, glyoxylic acid and organoboronic acids under standard Petasis conditions provides a useful procedure for the preparation of indolylaryl acetic acids. The intermediate indolyl hydroxy acid of type **17** formed by reaction of the indole with glyoxylic acid is protonated and upon elimination of water generates an iminium ion, which is attacked by the boronic acid.[22] The formation of alkylideneindolenines from their precursors requires an unsubstituted nitrogen atom to properly effect the elimination. However, *N*-silylated trialkylammonium salts of gramines are reactive toward vinyl and ethynyl Grignard reagents, providing the corresponding substitution products.[23] This reactivity could be ascribed to a direct nucleophilic substitution of the organomagnesium reagent on the benzylic position of the indole system. Arylsulfonyl indoles **24** are more effective than gramines in the reaction with Grignard reagents.[14] Simple alkyl and vinylmagnesium halides afford the corresponding substitution products **25** when reacting with sulfonyl indoles (Scheme 7). A two equivalent excess of the reagent is usually required since generation of the alylideneindolenine is brought by the reagent itself acting as a base. Following the same principle, reductive removal of the arenesulfonyl group can be



Scheme 7 Reaction of sulfonyl indoles with Grignard reagents.

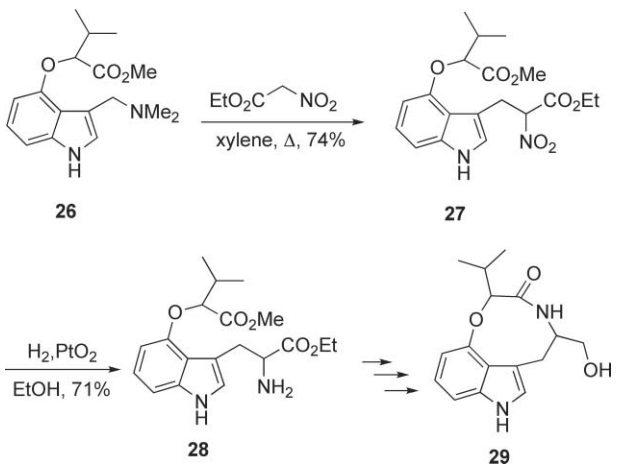
pursued from sulfonyl indoles **24** using $LiAlH_4$ or other desulfonylating agents acting under radical conditions (*e.g.* Bu_3SnH or Na–Hg amalgam).

Reaction with enolates and other stabilized carbanions

Most of the synthetic processes involving alkylideneindolenine intermediates concern the reaction of their precursors with stabilized carbanions. Enolates and related derivatives are generally prepared under basic conditions that are also suitable for promoting the elimination step required for the alkylideneindolenine formation.

Nitroalkanes

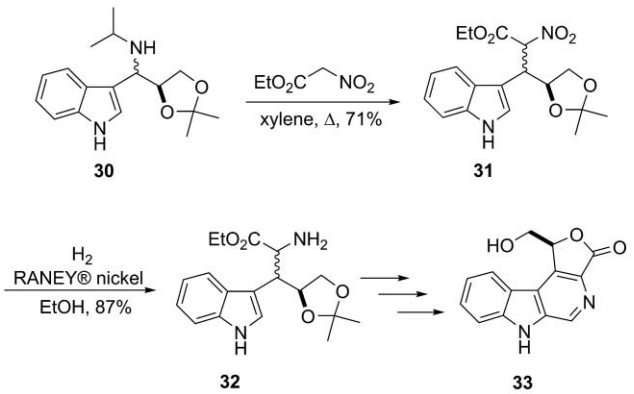
The high electron-withdrawing power of the nitro group provides a remarkable enhancement of the hydrogen acidity at the α-position of nitroalkanes.[24] Thus, nitronate anions can be easily generated under homogeneous as well as heterogeneous conditions using mild basic promoters, and then used as effective carbon nucleophiles in conjugate additions and nitroaldol reactions.[25] Elimination of the dialkylamino group from gramines is usually carried out under thermal conditions in boiling toluene or xylenes. Dimethylamine delivered from gramine **26** is able to deprotonate ethyl nitroacetate leading to the corresponding adduct **27** (Scheme 8).[26]



Scheme 8 Synthesis of tryptophan derivative **28** by reaction of gramine **26** with ethyl nitroacetate.

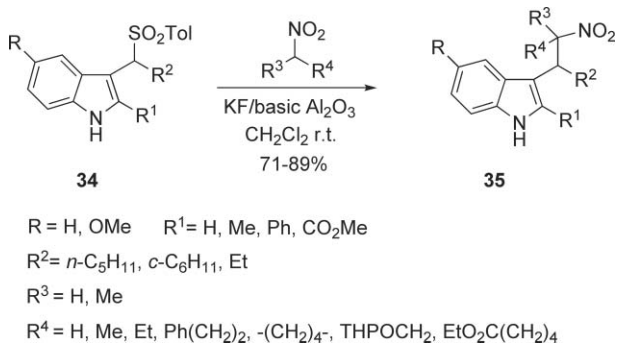
Once introduced in a molecular framework, the nitro group is amenable to several synthetic transformations including conversion into carbonyls, reductive removal and reduction at the nitrogen atom. Reduction of the nitro group in compound **27** ensures an efficient entry to functionalized tryptophan derivative **28**, which is a pivotal intermediate in the synthesis of desmethylindolactam **29**. Similarly, gramine **30**, obtained by reaction of indole with a chiral imine derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde, reacts with ethyl nitroacetate leading to adduct **31** as a mixture of diastereomers (Scheme 9).[27] Reduction of the nitro group and further synthetic manipulations affords enantiopure β-carboline **33**.

Simple nitroalkanes such as nitromethane seem poorly reactive with gramine derivatives so that methylation of the amino group is mandatory in order to have a better leaving group for the



Scheme 9 Synthesis of functionalized β-carbolines.

elimination step.[28,29] This drawback can be easily circumvented using sulfonyl indoles as substrates. Potassium fluoride supported on basic alumina is able to promote the addition of different nitroalkanes to sulfonyl indoles **34** under heterogeneous conditions at room temperature (Scheme 10).[30] The remarkable efficiency of this procedure is evidenced by the good reactivity of secondary nitroalkanes and sterically hindered sulfonyl indoles (R^2 = cyclohexyl).

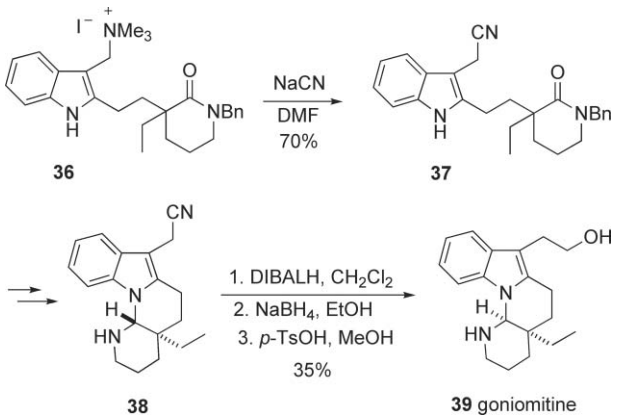


Scheme 10 Reaction of sulfonyl indoles with nitroalkanes under heterogeneous conditions.

All these procedures allowing the introduction of the nitro group in indole containing frameworks find their counterpart in the Friedel–Crafts reaction of indoles with nitroalkenes. Although these complementary approaches convey to the same final products, the alkylideneindolenine system presents some evident advantage over the nitroalkene usage. It should be observed that nitroalkenes are rather toxic and are lachrymatory compounds, so direct manipulation of these reactive alkenes is often not advisable. Furthermore, the synthesis of tertiary indolyl nitroalkanes, which is prevented using the Friedel–Crafts procedure, is, on the contrary, possible using sulfonyl indoles **34**.

Cyanide ions

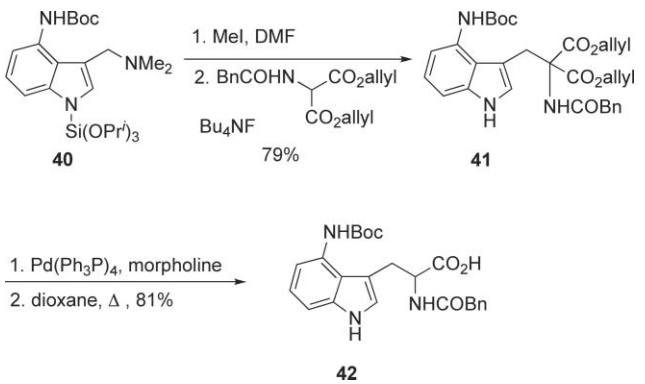
Reaction of alkaline salts of hydrogen cyanide with alkylideneindolenine precursors produces a chain homologation in the final product. Synthetic manipulation of the cyano group allows the insertion of primary amino or hydroxy groups in the side chain of the substituted indole.[31] The introduction of the hydroxyethyl group in the indole ring of the aspidosperma alkaloid goniomitine is carried out on ammonium salt **36** using sodium cyanide (Scheme 11).[32] The obtained cyanomethyl derivative **37** after some synthetic manipulations is converted into tetracyclic derivative **38** which through a reductive transformation is finally converted into goniomitine **39**. Reduction of the triple bond in the cyano group provides a prompt entry to tryptamine derivatives and represents a valid option to the Friedel–Crafts reaction of indoles with nitroalkenes, and the subsequent reduction of the nitro group.[33]



Scheme 11 Cyanation of gramine salt **36** as key step for the synthesis of goniomitine.

Methylene active compounds

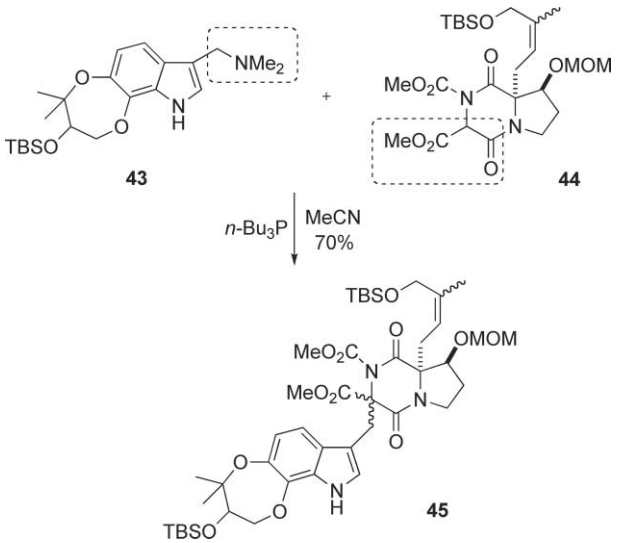
Easily enolisable reagents such as malonic acid derivatives and β-keto esters are a formidable source of stabilized carbanions. Under a large variety of reaction condition these enolates may react with gramines and sulfonyl indoles, leading to the corresponding adducts. Of particular interest is the utilization of 2-amidomalonic esters that provide an efficient access to functionalized tryptophan derivatives. *N*-Silylated gramine **40** is preliminarily converted into the corresponding ammonium salt and then made to react with phenylacetamidomalonic acid bisallyl ester in the presence of Bu_4NF (Scheme 12).[34]



Scheme 12 Synthesis of tryptophan derivative **42** from gramine **40**.

This mild basic reagent also carries out the indole nitrogen deprotection leading to adduct **41**, which under Pd(0) catalysis, suffers ester cleavage and subsequent thermal decarboxylation to tryptophan derivative **42**. The choice for the *N*-phenylacetamido group in the reagent is due to the subsequent enantioselective hydrolysis by penicillin G acylase, which produces enzymatic

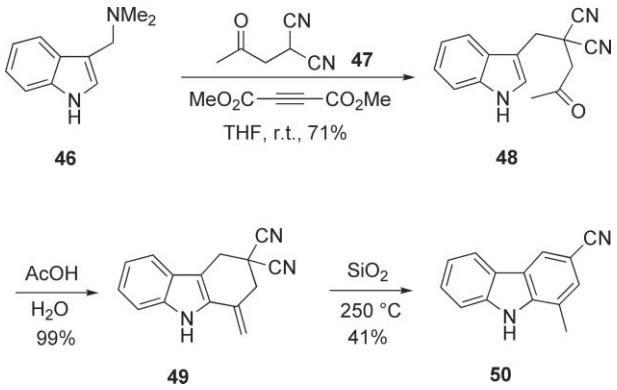
resolution of racemic **42**. The need to convert gramines into the corresponding ammonium salts in order to get a better leaving group can be circumvented using *n*-Bu_3P, which probably produces a reactive phosphonium salt intermediate, or by addition of activated acetylenes, which facilitate removal of the amino group through the formation of enamino derivatives.[35] The formation of phosphonium salts when trialkylphosphines are used seems to be confirmed by the observation that the reaction of gramines with aldehydes in the presence of *n*-Bu_3P affords 3-vinylindoles, probably arising from a Wittig-like reaction.[36] Alternatively, sulfonyl indoles **34** can be made to react with malonate esters, malononitrile, β-keto esters and even with *p*-toluenesulfonyl isocyanide in the presence of KF/basic alumina at room temperature.[30] A certain number of structurally complex biologically active compounds have been prepared exploiting the utilization of alkylideneindolenines, as illustrated for the total synthesis of the anthelmintic agent paraherquamide A (Scheme 13).[37] A crucial step of the convergent synthesis of this compound involves a coupling of gramine **43** with cyclic amidodiester **44**, which is realized using *n*-Bu_3P in acetonitrile at reflux.



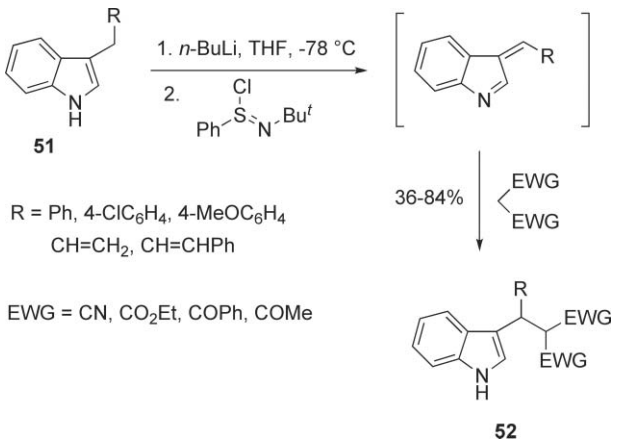
Scheme 13 Synthesis of an advanced precursor of parahequamide A.

The stereocontrol of the newly formed stereocenter in adduct **45** is not particularly efficient (dr = 3 : 1), but this feature lacks interest since in the subsequent transformations, decarboxylation and enolate formation destroy its chirality. The reaction of gramines with functionalized methylene active compounds can be adopted for the introduction of a further aromatic ring into the indole system. Activation of gramine **46** by dimethyl acetylenedicarboxylate allows its reaction with 2-(2-oxopropyl)malononitrile **47** (Scheme 14).[38]

The resulting adduct **48** is cyclized under acidic conditions, leading regioselectively to exocylic compound **49**, which upon heating in the presence of silica, is aromatized to tricyclic **50**. The obtained compound is easily converted into a fully aromatic pyridocarbazole olivacine. An original procedure for alkylideneindolenine formation consists of oxidation of the benzylic position in 3-substituted indoles **51** (Scheme 15).[39] The oxidation is carried out using *N*-*t*-butylbenzenesulfinimidoyl chloride and is effective



Scheme 14 Acetylenedicarboxylate ester as an activator in the reaction of gramine **46** with malononitrile derivative **47**.



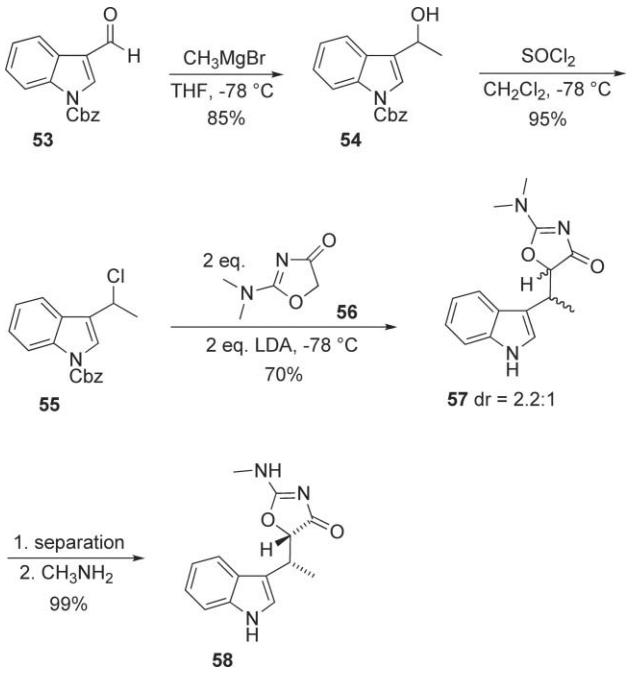
Scheme 15 Formation of alkylideneindolenine intermediates by benzylic oxidation of 3-substituted indoles.

only for 3-benzyl or allyl indoles. The subsequent addition of methylene active compounds to the intermediate imine produces substituted indoles **52** in satisfactory yield. Interestingly, various high-order lithium cuprates are also effective as nucleophiles for this process.

Enolates and enol ethers

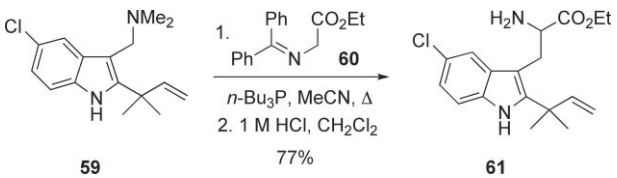
Simple carbonyl and ester derivatives usually require strong bases in order to be converted into the corresponding enolate anions. In a convergent synthetic approach to the preparation of racemic indolmycin **58**, an antibiotic of natural origin, the alkylideneindolenine precursor is represented by chloro indole **55**, which is made to react with lithium enolate of oxazolone **56** (Scheme 16).[40]

The utilization of chloro indoles for these purposes is rather uncommon, since they are unstable and therefore difficult to purify. Preparation of indole **55** is realized starting from aldehyde **53** that upon reaction with methylmagnesium bromide affords alcohol **54**, which in turn is chlorinated using thionyl chloride. Reaction of chloro indole **55** with the lithium enolate of oxazolone **56** at low temperature leads to adduct **57** as a mixture of diastereomers. The mechanism seems to involve a preliminary removal of the Cbz group by the metal enolate that favors the elimination step leading to the alkylideneindolenine intermediate. This intermediate is then attacked by a second equivalent of



Scheme 16 Synthesis of racemic indolmycin.

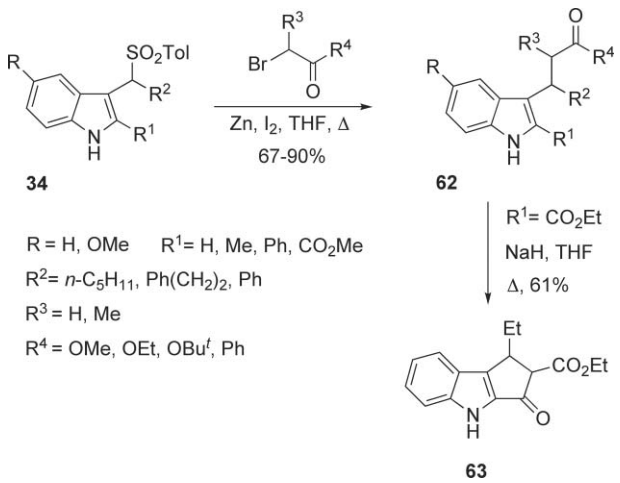
the lithium enolate of **56**, leading to the adduct **57**. After separation of the diastereomeric mixture, the appropriate isomer is made to react with methylamine leading to racemic indolmycin **58**. Mild reaction conditions can often be pursued providing that activation of the indolenine precursor is accomplished. An alternative method to introduce a 'glycine' synthon into indole frameworks other than 2-amidomalonates consists of the reaction of ethyl 2-[(diphenylmethylene)amino]acetate **60** to gramine **59** (Scheme 17).[41] Hydrolysis of the imino group leads to tryptophan derivative **61**, a key intermediate to the synthesis of prenylated indole alkaloid malbrancheamide B.



Scheme 17 Reaction of gramine **59** with glycine derivative **60**.

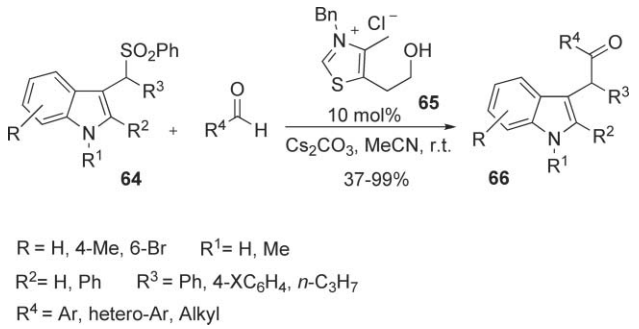
Lithium enolates are seldom used in the reaction with gramines or other related derivatives. Reformatsky reagents are a popular form of zinc enolates that can be formed *in situ* by reaction of α-haloesters and α-haloketones with activated zinc. Sulfonyl indoles **34** are particularly reactive toward these reagents leading to 3-(3-indolyl) alkanoates **62** (Scheme 18).[15]

An excess of zinc enolate is required in this process since one equivalent of the reagent is expected to act as a base, providing formation of the indolenine intermediate. One of the prepared esters **62** bearing a carboxylate group at the 2-position in the indole ring has been cyclized under Dieckmann conditions giving a tricyclic β-keto ester **63**, which belongs to a class of intermediates involved in the synthesis of lactam derivatives with potential activity as neurotransmitters. Acyl anion equivalents can be generated under different conditions allowing a formal linkage



Scheme 18 Reaction of sulfonyl indoles with Reformatsky reagents.

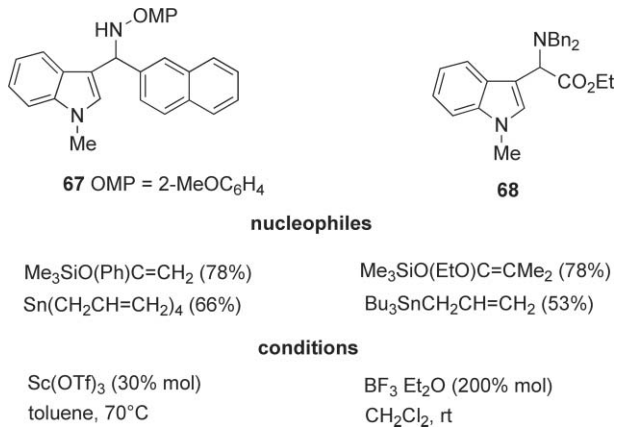
between electrophilic systems. Among such procedures, umpolung reaction of aldehydes catalyzed by *N*-heterocyclic carbenes, also known as the Stetter reaction, occupies a prominent position for its simplicity and suitability to be used in enantioselective processes.[42] Reaction of sulfonyl indoles **64** with aldehydes in the presence of catalytic amount of commercially available thiazolium salt **65** provides a straightforward entry to 2-(3-indolyl) ketones **66** (Scheme 19).[43] Preliminary results on the utilization of a chiral triazolium salt for the same purpose are encouraging in terms of enantioselection, but low conversions of the starting material are still experienced.



Scheme 19 Reaction of sulfonyl indoles with aldehydes under Stetter conditions.

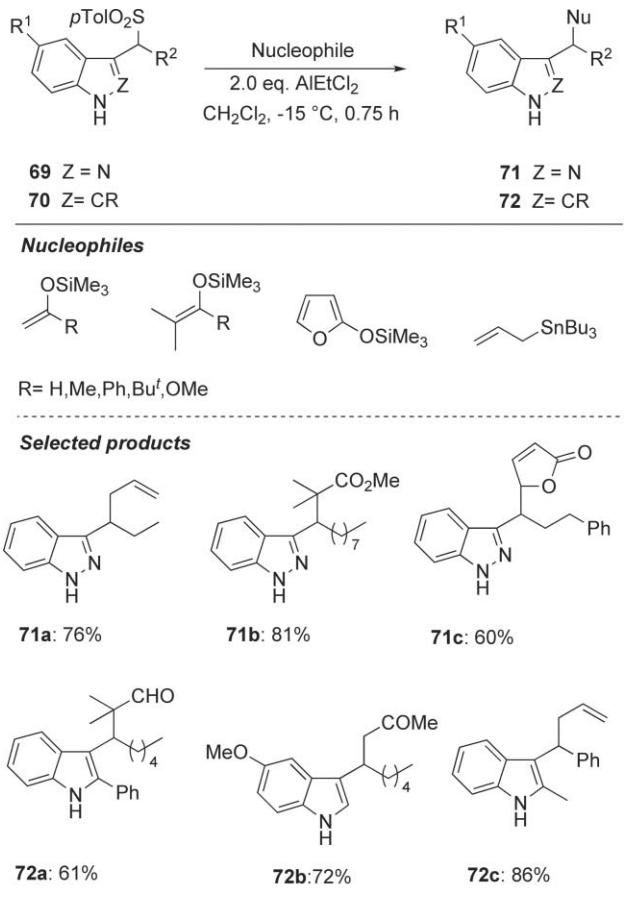
From a synthetic standpoint, a complementary approach to the above described basic activation of precursors **4**, lies in the elimination of the leaving group L under acidic conditions. The promoters involved in this process are mostly Lewis acids that can be used either in catalytic or stoichiometric amounts. Since a stabilized iminium ion with a carbocationic character is presumably formed in these reactions, the presence of benzyl substituents at the 3-position of indoles greatly assists the whole elimination-addition process. Until recently, the viability of this strategy using weak nucleophiles such as silyl enol ethers, silyl ketene acetals and allyltin reagents has been demonstrated only on single 1-methyl gramines **67** and **68** using scandium(III) triflate[44] and boron trifluoride etherate (Scheme 20).[8]

A more general procedure can be found in the utilization of sulfonyl indoles and even sulfonyl indazoles for the same



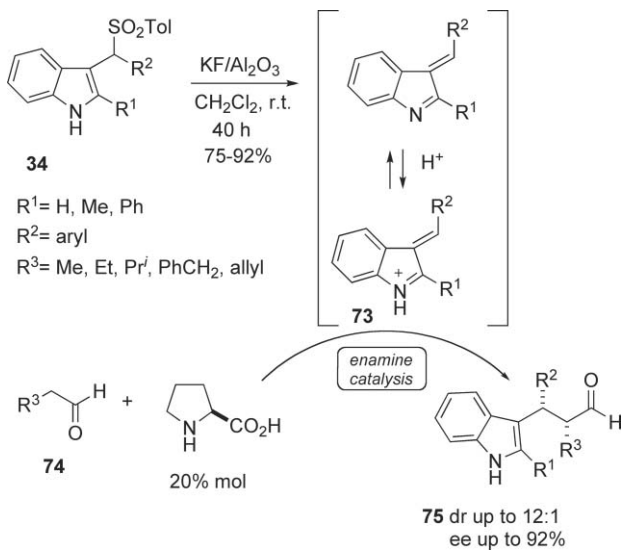
Scheme 20 Lewis acid-promoted deamination of gramine precursors.

purpose. Functionalization of indazoles at the 3-position by a Friedel–Crafts process is strongly inhibited by the reduced electronic density of the pyrazole ring. However, it is possible to convert indazoles into the corresponding sulfonyl derivatives using the same procedure proved to be effective with indoles (*cf.* Scheme 4).[45] Sulfonyl indazoles **69** are rather reluctant in giving alkylideneindazolenine intermediates under basic conditions, but can be forced to eliminate the arenesulfonyl group in the presence of $AlEtCl_2$ at moderately low temperature (Scheme 21).[46] The



Scheme 21 Reaction of sulfonyl indoles and indazoles with ethylaluminium dichloride in the presence of weak nucleophiles.

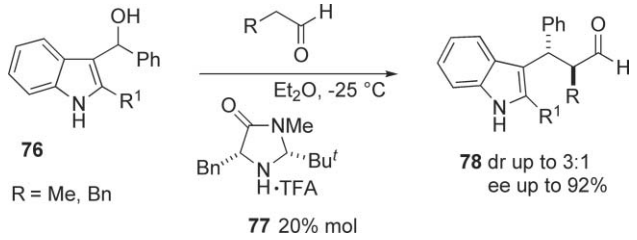
obtained iminium ion intermediate reacts with allyltributyltin, silyl enol ethers and silyl ketene acetals, leading to the corresponding adducts **71**. The same process is also available for sulfonyl indoles **70**, which are promptly converted into carbonyl and allylated derivatives **72**. It is interesting to observe that for some products **71** and **72** this reaction represents the only profitable key for their preparation, since the utilization of the Friedel–Crafts reaction is precluded when carbonyl derivatives bearing quaternary carbon atoms at the 2-position are to be obtained. A slow release of reactive intermediates from their stable precursors can be fruitfully exploited in enantioselective organocatalyzed reactions. Enamine catalysis brought by chiral pyrrolidines allows the reaction of carbonyl derivatives with a consistent number of electrophiles. The reaction of aldehydes **74** with sulfonyl indoles **34** occurs in the presence of potassium fluoride on alumina (Scheme 22).[47] Rather surprisingly, L-proline proved to be the best catalyst for this process, leading to the corresponding adducts **75** in good yield and with a high level of stereoselectivity. The presence of a free carboxylic group in the catalyst is mandatory for a successful reaction since L-proline methyl ester is almost completely ineffective, both in terms of the reactivity and selectivity of the process. A possible explanation of this observation clearly calls for a direct involvement of the carboxylic group as a proton source that would provide protonation of the neutral alkylideneindolenine, thus generating a corresponding iminium ion **73** endowed with superior electrophilic character.



Scheme 22 Alkylation of aldehydes with sulfonyl indoles under enantioselective organocatalysis.

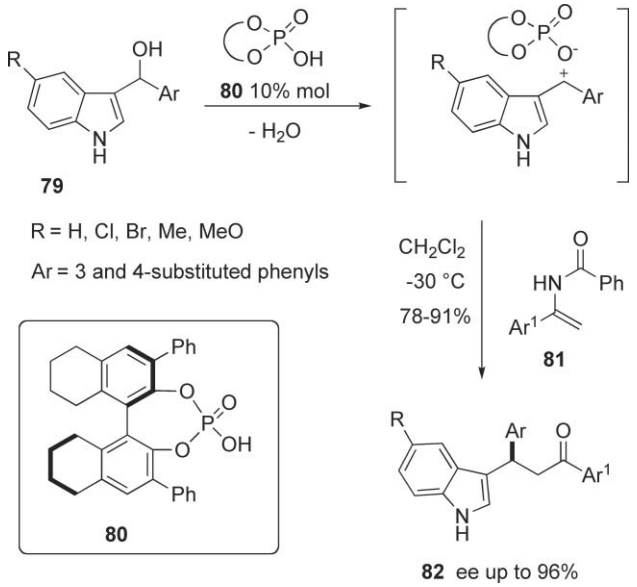
The high stabilization pertaining to iminium ions of type **73** allows their formation starting from the corresponding hydroxy derivatives. Thus, alcohol **76** reacts with aldehydes in the presence of trifluoroacetate salt of chiral imidazolidinone **77** leading predominantly to the *anti* adducts **78** with good enantioselectivity (Scheme 23).[48]

The overall process occurs under enamine catalysis while the intermediate carbocation is believed to be formed by action of trifluoroacetic acid delivered by the catalyst. Chiral phosphoric acids are deeply involved as organocatalysts in enantioselective processes.[49] As Brønsted acids these compounds can provide



Scheme 23 Alkylation of aldehydes with hydroxy indoles under enantioselective organocatalysis.

generation and stabilization, through ion pair formation, of carbocations and iminium ions. Thus protonation of indolylarylmethanols **79** by chiral phosphoric acid **80**, produces a stabilized carbocation tightly bound to the phosphate anion (Scheme 24).[50] The oxygen atom on phosphor is also able to activate enamides **81** in the subsequent nucleophilic addition leading to indolyl ketones **82** *via* the corresponding acylimino intermediate.

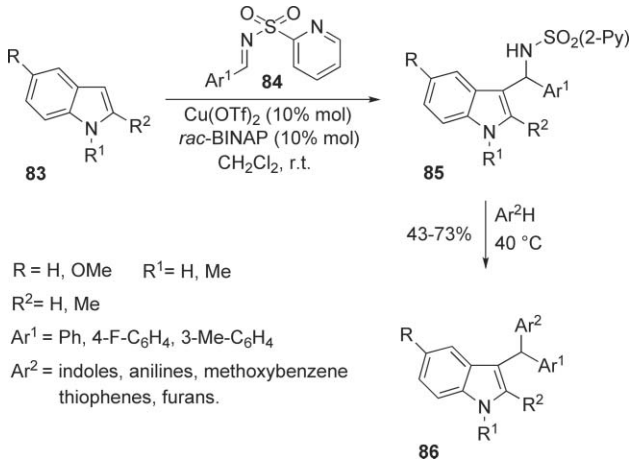


Scheme 24 Alkylation of enamides with indolylarylmethanols by asymmetric counteranion-directed catalysis.

In a synthetic approach to the welwitindolinone skeleton, a 2-(3-indolyl)-2-propanol derivative is made to react with the trimethylsilyl enol ether of cyclohexanone in the presence of $TiCl_4$, generating the corresponding adduct in respectable yield.[51]

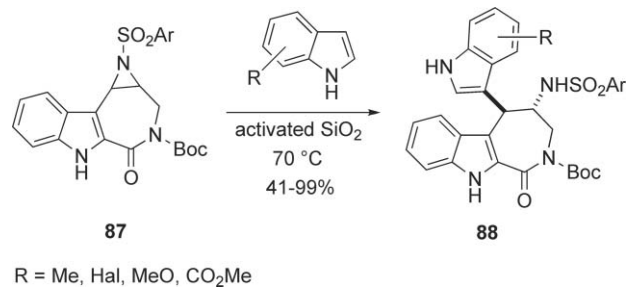
Electron-rich aromatic compounds

Formation of alkylideneindoleninium ions **73** also constitutes the crucial step in the synthesis of bisindoles exploiting an acid-promoted condensation between indoles and aldehydes. This simple procedure is catalyzed by Brønsted as well as Lewis acids, but in this version only allows the preparation of symmetrical bisindoles.[52] The previously described procedures involving iminium ions **73** can be also used with electron-rich aromatics as nucleophiles, leading to the corresponding adducts in satisfactory yield. Amidoarylation of indoles by a Friedel–Crafts reaction with *N*-*p*-tosylarylimines generates the corresponding 3-substituted derivatives in which the amido moiety, being a good leaving group, can be readily eliminated under a large variety of conditions. In the presence of (hetero)aromatic reagents, a further Friedel–Crafts reaction occurs leading to triarylmethane derivatives.[53] These two synthetic operations can be joined together in a one pot process in which a preliminary aza-Friedel–Crafts reaction occurs between indole **83** and *N*-(2-pyridyl)sulfonylimide **84** (Scheme 25).[54]



Scheme 25 Synthesis of triarylmethane derivatives by one pot reaction of indoles with arylimines and electron-rich aromatics.

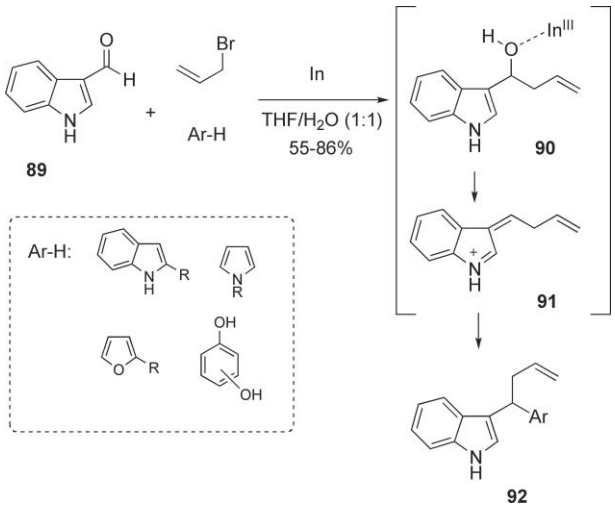
This reaction is catalyzed by copper(II) triflate, while the presence of BINAP provides a consistent acceleration of the process. Among various sulfonylimides tested for this transformation, the 2-pyridyl derivative **84** is the only one that avoids formation of the bisindole as the main product. Once adduct **85** is formed, a subsequent addition of another aromatic reagent at reflux readily provides the final indolyldiarylmethane **86**. Regioselective ring-opening of aziridines **87** is favored by the presence of the indole ring that strongly stabilizes the probable iminium ion intermediate (Scheme 26).[55]



Scheme 26 Ring opening of aziridine **87** for the preparation of *trans*-bisindolyl derivatives **88**.

Indoles, as well as other nucleophiles, react with this electrophilic species generated in the presence of activated silica gel under solventless conditions in a stereoselective fashion leading to *trans*-bisindolyl derivatives **88**. Although nitrones are well known 1,3-dipoles involved in cycloaddition reactions aimed at the preparation of heterocyclic compounds, they can be actually used as imine surrogates in the reaction with nucleophiles.[56] The reaction of nitrones with indoles generates the corresponding hydroxylamines that can be isolated, and upon reaction with a second molecule of indole in the presence of trimethylchlorosilane,

affords unsymmetrical bisindoles.[57] The utilization of 1-(3-indolyl)-1-alkanols can be also envisaged for this purpose exploiting an acid promoted elimination of a water molecule that generates the reactive iminium ion intermediate.[58] Depending on the reaction conditions, it is possible to conceive a three component synthesis of allylaryl indoles starting from indole 3-carbaldehyde **89** allylbromide and aromatic derivatives in the presence of indium metal (Scheme 27).[59]



Scheme 27 Alkylideneindolium ions formation in the reaction of indole 3-carbaldehyde with allylindium reagents.

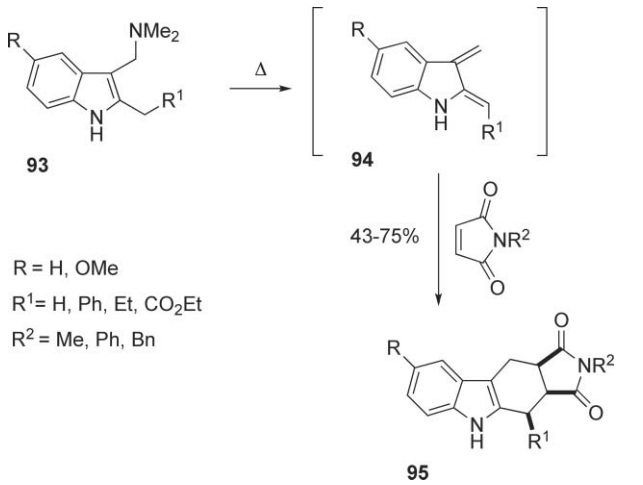
A preliminary allylation of the aldehyde affords the corresponding alcohol **90** from which elimination to the iminium ion **91** is favored by the presence of indium salts. A selective reaction with electron-rich aromatic compounds follows leading to the final indole derivative **92**. Using the same procedure it is also possible to achieve the addition of easily enolizable compounds and heteronucleophiles to the intermediate iminium ion **91**.

Cycloadditions

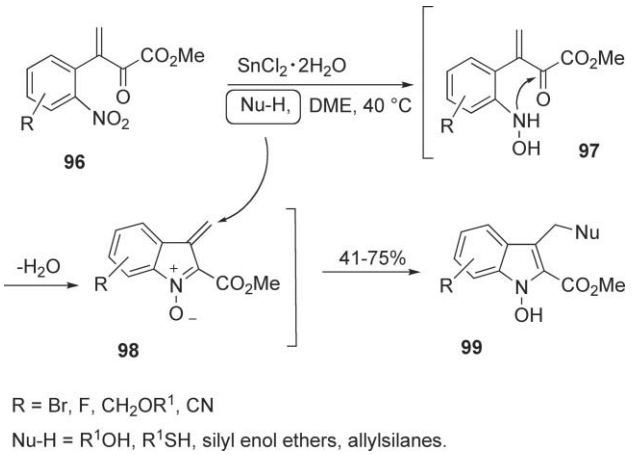
Alkylideneindolenines, although featured by a couple of conjugated double bonds, are not suitable as dienyl derivatives for hetero-Diels–Alder processes. The presence of mobile hydrogen atoms in substituents at C-2 of the indole **93** may cause a rearrangement in the initially formed alkylideneindolenine (Scheme 28).[60] This provides the formation of a diene system **94** endowed of the appropriate stereochemistry to readily undergo a cycloaddition reaction with different maleimides leading to tetracyclic derivative **95**.

Miscellaneous methods

A clever strategy for the construction of 1-hydroxyindole ring systems combines in a tandem process indole ring build-up and formation of alkylideneindolenine-like intermediates.[61] Nitro keto ester **96** is partially reduced to the parent hydroxylamine **97** that undergoes a regioselective nucleophilic addition to the carbonyl group (Scheme 29).[62] This synthetic operation results in the formation of an alkylideneindolenine *N*-oxide **98** that promptly adds a large variety of hetero and carbon nucleophiles giving 1-hydroxyindoles **99**. The intermediate **98**, which can be



Scheme 28 Cycloaddition on diene intermediates formed by elimination from 2-substituted gramines.



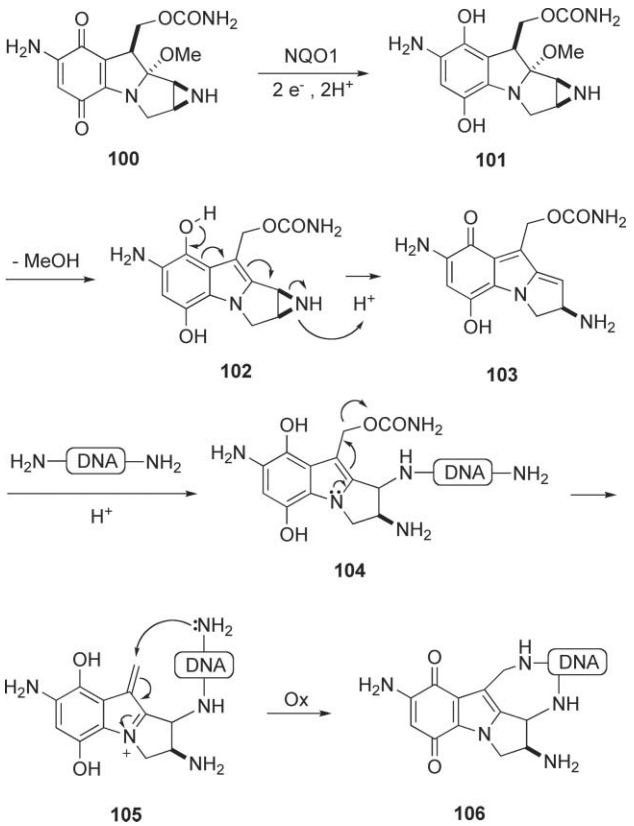
Scheme 29 Regioselective intramolecular addition of hydroxylamines in the formation of alkylideneindolenine *N*-oxides.

also regarded as a vinylogous nitrone, shows a reactivity closely related to that of alkylideneindolium ion **3**. As a matter of fact, nucleophiles such as alcohols, thiols, silyl enol ethers and allylsilanes easily react with derivatives **96** without the need for any further activating system.

Biological significance of alkylideneindolenine intermediates

Alkylideneindoleninium ions are deeply involved in the mechanism of action of some naturally occurring quinones with anticancer properties. The pharmacological profile of these derivatives seems related to their DNA cross-linking ability, as demonstrated by the naturally occurring quinone mitomycin C **100** (Scheme 30).[63]

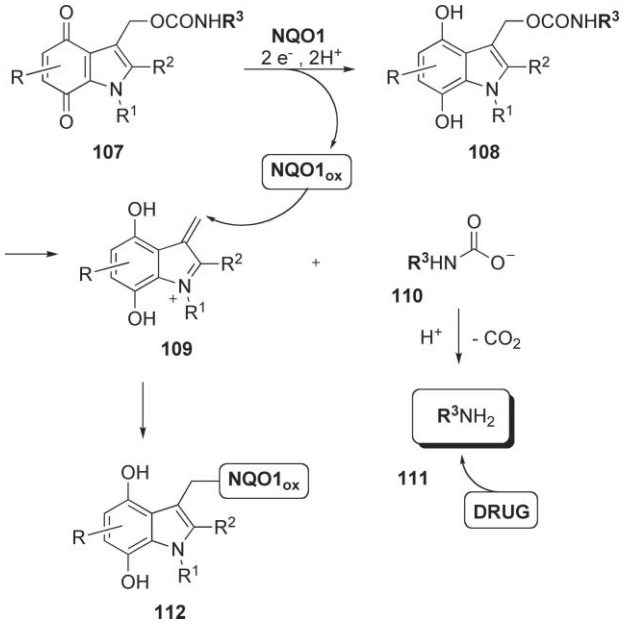
Activation of mitomycin C by the quinone reductase enzyme NQO1 involves a two-electron delivery, which converts the quinone ring into the hydroquinone **101**. This step is mandatory in order to facilitate a subsequent loss of methanol that generates indole **102**, which suffers aziridine ring opening to intermediate



Scheme 30 Mechanism of action of mitomycin C as a DNA cross-linking agent involving alkylideneindoleninium ion.[63]

103. This compound is featured by a dienone moiety that can intercept DNA by linking one of its manifold free amino groups. The obtained derivative **104** undergoes an irreversible elimination of the carbamate, leaving the alkylideneindoleninium ion **105**. The latter intermediate acts as a strong alkylating agent towards a second amino residue of the DNA molecule, thus providing a linkage that is made definitive by oxidation of the hydroquinone ring to quinone **106**. The quinone–hydroquinone redox couple therefore acts as a 'switch' blocking or restoring the indole reactivity that allows the biological response. The mechanism of action of mitomycin C has suggested the opportunity of using indolequinones as prodrugs and inhibitors of the quinone reductase enzyme NQO1. Activation of indolequinone **107** by two-electron transfer carried out by the enzyme NQO1 generates the hydroquinone system **108**, which undergoes elimination of the carbamate group (Scheme 31). Since the iminium ion **109** is formed in the active site of the enzyme, providing that a fast fragmentation occurs, it can reacts with the oxidized form of NQO1 leading to the alkylated system **112**.[64] On the other hand, the released carbamate unit **110** could be profitably employed as a drug delivery system since it rapidly decomposes providing amino derivative **111**.[65]

Recently, indolequinones of type **107**, bearing a phenoxide group instead of a carbamate group, have been recognized as potent antitumor agents against pancreatic cancer.[66] These derivatives act as inhibitors of thioredoxin reductase both in pancreatic cancer cells and in cell-free systems.



Scheme 31 Indolequinones **107** as drug carriers and/or inhibitors of the quinone reductase enzyme NQO1.

Conclusion

Functionalization of the indole ring at the 3-position is a pivotal synthetic operation in the preparation of biologically active molecules embedding the indole nucleus. Besides the classical Friedel–Crafts reaction, a procedure involving generation of reactive alkylideneindolenines can be devised. These unstable intermediates behave as vinylogous imino derivatives that may add, in a regioselective fashion, a large variety of nucleophilic reagents. Formation of alkylideneindolenines can be properly realized from precursors that have a suitable leaving group at the benzylic position of 3-substituted indoles. Nowadays, this synthetic approach is gaining increased attention because of the widening of alkylideneindolenine precursors, other than gramines, of which preparation is easy, efficient and affordable starting from cheap materials. The alkylideneindolenine route to functionalized indoles does not merely represent another way to prepare the same compounds obtainable using the Friedel–Crafts reaction. It actually provides a different strategy that warrants access to indole derivatives hardly achievable using more traditional procedures.

Acknowledgements

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