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ARTICLE TYPE

# Application of Bartoli Indole Synthesis

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In 1989, the reaction of vinyl magnesium halides with ortho-substituted nitroarenes to lead to indoles was discovered. This reaction is now frequently reported as the "Bartoli reaction" or the "Bartoli indole synthesis" (BIS). It has rapidly become the shortest and most flexible route to 7-substituted indoles, because the classical indole syntheses generally fail in their preparation. The flexibility of Bartoli reaction is great as it can be extended to heteroaromatic nitro derivatives and can be run on solid support. This review will focus on the use of the Bartoli indole synthesis as key step in preparations of complex indoles, which appeared in the literature in the last years.

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## 1. Introduction

Heterocycles are among the most important structural classes of chemical substances,[1, 2] which are particularly well represented among agrochemicals, herbicides, natural products, biological electrical sensors and pharmaceuticals. It is estimated that more than 50 % of the published chemical literature contains heterocyclic structures and 70 % of all pharmaceutical products possess heterocyclic structural subunits, because of a favourable combination of drug-like properties. Bicyclic aromatic heterocycles containing nitrogen atoms, such as quinolines, isoquinolines, and indoles are present in all classes of organic compounds in the biological and medicinal arena.[3-11] In particular, over ten thousand biologically active indole derivatives have been identified to date. Of those, over 200 are currently marked as drugs or undergoing clinical trials.[12] Furthermore, the indole nucleus is not only important in biological systems and in pharmaceutical research, but also it is a common moiety in material science,[13, 14, 15] so it is referred to as "privileged structure". Therefore, the search for an efficient synthesis of the indole ring system is a longstanding goal, and effective methodologies for the synthesis of functionalized indoles bearing a number of useful properties are of great interest.

In the midst of many indole syntheses and functionalization,[1, 2, 10, 11, 16-46] one has to choose two principal synthetic strategies: starting with an indole core and adding the missing structural part, or starting from acyclic precursors. The choice between the two strategies is suggested by what has to be constructed. In fact, indole is an electron rich aromatic system which undergoes electrophilic substitutions in the 3-position (*i.e.* in the heterocyclic ring). Deprotonation of *N*-substituted indoles takes place readily at the 2-position and a plethora of removable *N*-blocking groups are available, which allows the preparation of *N*-unsubstituted 2-substituted indoles. On the other hand, substitution on the benzene ring only occurs in special cases, thus one prefers to start from suitable precursors through pyrrole or benzene ring assembly, when a substituent is needed on the carbocycle moiety.[11] Although all methods certainly provide rapid assembly of the indole nucleus, the reaction conditions are generally relatively harsh. This is less important when the starting materials are readily available, but, when the starting materials arise from multi-step sequences, the conditions may not be amenable.

However, the construction of 7-substituted derivatives was very difficult until the introduction of the Bartoli Indole Synthesis (BIS),[47] notwithstanding in many naturally occurring or pharmaceutically important indoles, 7-substitution is often needed (Figure 1).

BIS represents a general and efficient method for producing indoles substituted on both the carbocycle and the pyrrole ring. It starts from nitroarenes of easy disposability with many different substitutions onto all the five aromatic positions and vinyl Grignard reagents also easy available or synthesizable. Reaction conditions are very mild and this feature allows the survival of many sensitive organic functions. Thus, BIS has had an intensive development to prepare indoles bearing a large variety of substituents on the two rings and, consequently, the merits, drawbacks, and applicability are well established.[48-50]

The wide applicability outside academic research laboratories fuelled the increasing popularity of the BIS, particularly in the pharmaceutical industry, providing new avenues for the key steps

of the synthetic sequences of drugs and natural products, and this review aims to present the most recent application in this field.

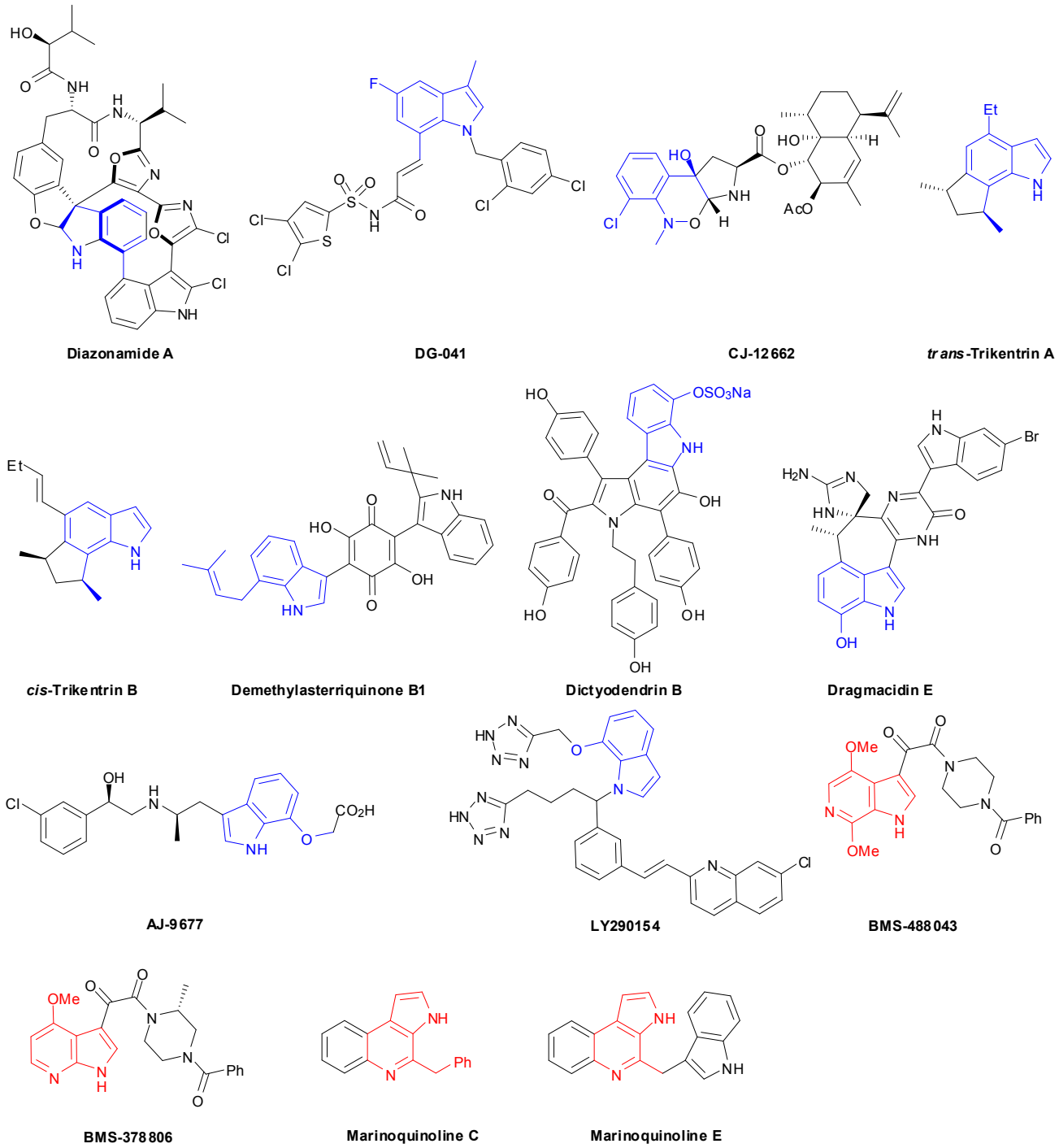



**Fig. 1** Some natural occurring products or drugs containing 7-substituted-indole (blue) or azaindole (red) moiety

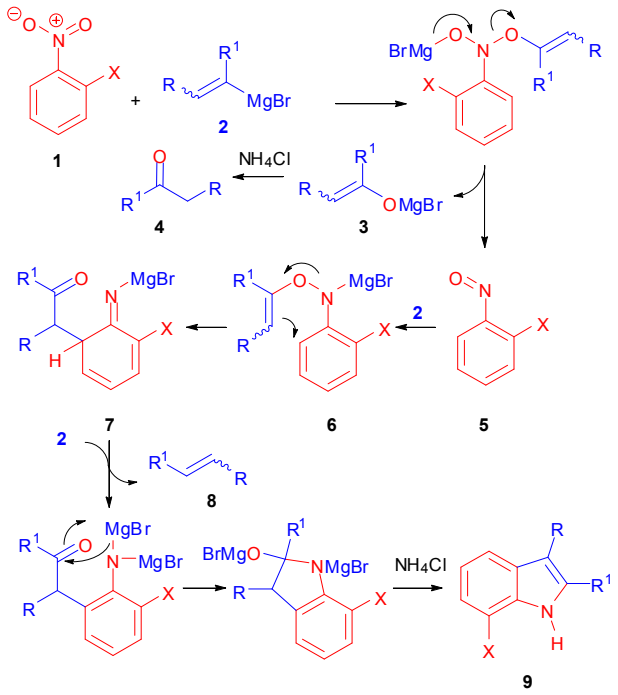
## 1. From Mechanism to Scope and Limitation

Although accurate and classical kinetic investigations have never been made, the mechanism of the BIS proposed by us is now accepted and further reactions all confirmed our initial hypothesis. [51]

The first observation was that the stoichiometry of the reaction (3:1 Grignard *vs.* nitroarene ratio) and the products arising from the excess Grignard reagent suggest that the indole nucleus incorporated one molecule of Grignard reagent, another reduces the nitro group, and the last serves as in an acid-base function, thus the mechanism depicted in Scheme 1 was proposed. [52]

This mechanism was rationalized into our proposed SET mechanism for the reaction of Grignard reagents and nitroarenes, in which the first interaction is an in-cage electron transfer from Grignard reagent to nitroarene.[53] The shape of the alkyl radical influences the attack to the radical centres of the radical anion. In

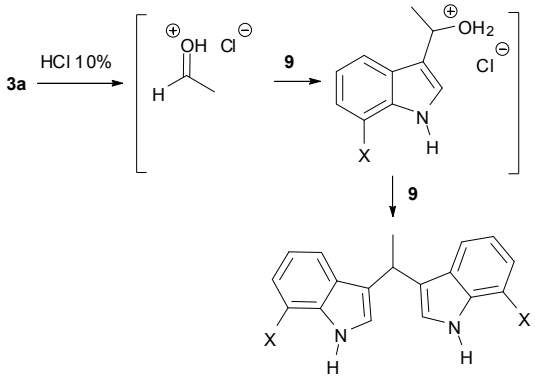
particular, bent $sp^2$-vinyl radicals [54] attack onto the oxygen atom of the nitro group and this attack is favoured by bending (π- or 1-trimethylsilyl-substituted linear radicals gave lower yields) and by crowding at the nitro position because a collapse of radical species is much more sensitive to steric hindrance that polar reactions.[55]




**Scheme 1** Proposed mechanism[52]

In a fashion of such a mechanism the first step consists in the nitro group reduction to nitroso derivative and this step is the only with clear experimental evidences. In fact, indolization was observed starting from nitrosoarenes (**5**).[51] Moreover, the elimination of an enolate molecule (**3**) has to lead ultimately to an aldehyde or a ketone (**4**). Actually, in our experiments, aldehyde was detected among the reaction products, but in very low amounts, when water-soluble and volatile. However, one mole of non-volatile aldehydes was recovered per mole of nitroarene.[51] Recently, Ishikura and co-workers recovered bisindolylmethane on quenching the reaction with 10 % HCl instead of $NH_4Cl$.[56] Authors explained the presence of bisindolylmethane by the rapid hydrolysis of vinyloxymagnesium bromide under strongly acidic conditions, and then the acetaldehyde can add in a Friedel-Crafts fashion (Scheme 2).

The second step involves a very fast further attack of Grignard reagent at the nitroso group. In a single electron transfer triggered reaction, the vinyl carbanion is turned into a vinyl radical and its coupling to both termini of the N=O double bond is reported.[51] In our speculation, the attack at the nitrogen terminus leads ultimately to aniline, which is actually recovered among the reaction product, at the same manner of the reaction reported by Knochel with aryl Grignard reagents,[57] whereas attack at the oxygen terminus leads to indole. Although attack at the oxygen atom of the nitrosoarene radical anion appears most probably,[55] nevertheless, steric hindrance emanating from the *ortho* position could aid reorientation of the attack of the vinylmagnesium bromide from the nitrogen to the oxygen atom of the transient nitroso substrate.[51] Noteworthy, yield declines when a small fluorine atom instead of a voluminous bromine atom occupies the position adjacent to the nitro group. [55] In the solid-supported BIS, an *ortho* substituent is not necessary, because, very likely, the entire solid support causes enough steric hindrance to address the vinyl radical on the oxygen atom.[58]

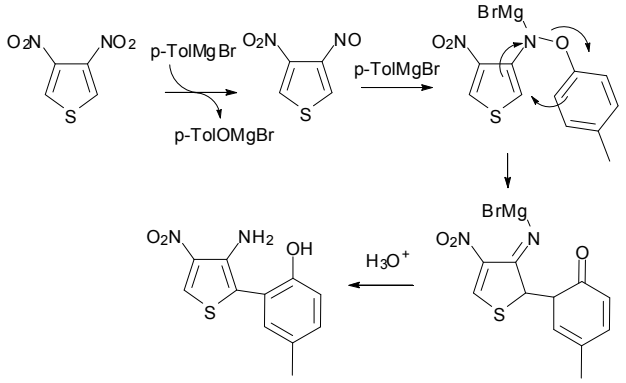



**Scheme 2** Bisindolylmethane formation in strong acidic media [56]

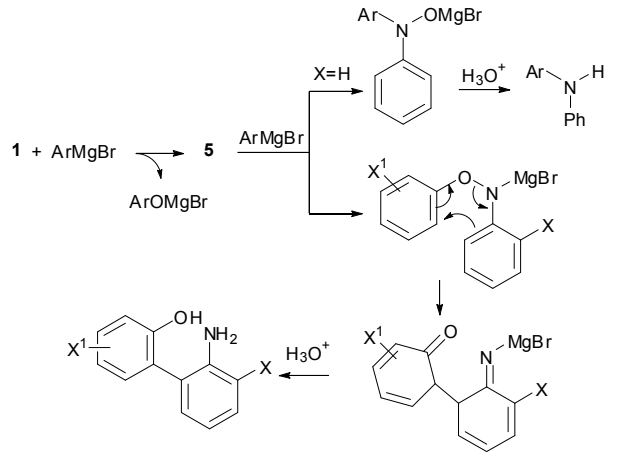
The third key step is the 1-aza-1'-oxa-[3,3]-sigmatropic rearrangement of the *N*-aryl-*O*-vinylhydroxylamino magnesium salt **6** (Scheme 1) in order to justify the substitution pattern in the final indole nucleus.[51] After publication of our hypothetical mechanism, other reactions of aryl Grignard reagents with nitroarenes were justified surmising a mechanism superimposable with our speculation. For instance, the treatment of 3,4-dinitrothiophene with an aryl Grignard reagent (but not aryllithium reagents) was found to result in the reduction of one nitro group to the nitroso intermediate accompanied by binding of the aryl to the oxygen atom of the N-O double bond and by Claisen-like rearrangement to 2-(3-aminothiophen-2-yl)phenols (Scheme 3).[59]

More recently, Kurti and co-workers succeeded in the synthesis of biaryls from *ortho*-substituted nitrobenzenes and aryl Grignard reagents.[60] They found that *ortho*-halonitrobenzenes undergo reduction to *ortho*-halonitrosoarenes, followed by *O*-arylation and sigmatropic rearrangement to 2-amino-2′-hydroxy-1,1′-biaryls and supported the mechanism with DFT calculations at the M06-2X/6-31G-(d,p) level (Scheme 4). Thus, they stated that the *ortho*-halogen substituent changes the regioselectivity of the aryl addition across the N-O bond, leading to 1,1′-linked biaryl products that were not observed by Knochel, who used *ortho* unsubstituted nitroarenes.[57]

Deprotonation of the intermediate **7** by means of a third vinylmagnesium halide allows re-aromatization of the six-member ring. This step takes the alkene molecule (**8**) found among the reaction products into account. The reaction with ω–styrylmagnesium bromide (**2b**) with 2-chloronitrobenzene (X=Cl) demonstrates that one mole of styrene per mole of indole is formed and deuterium-labelling experiments on the same reaction show that the alkene is formed during the reaction course, and not by aqueous quenching of the excess reagent.[51]



**Scheme 3** [3,3]-Sigmatropic rearrangement of nitroarenes of dinitrothiophene[59]



**Scheme 4** Reaction of nitroarenes with aryl Grignard reagents; top from ref 57, bottom from ref 60

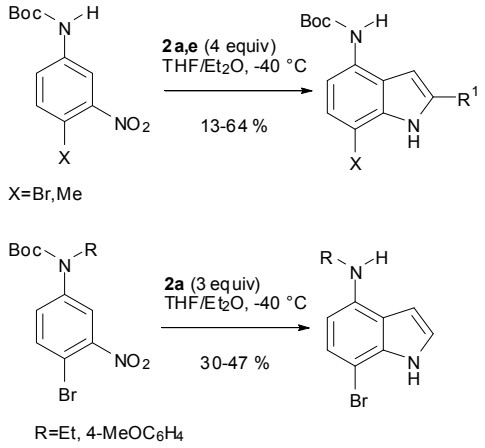
At the end of the reaction, acid quenching adds hydrogen atoms to all the metallated positions and allows the aromatization step of the five-membered ring by dehydration.

In conclusion, the Bartoli indolization follows a very complex mechanism, but its comprehension makes predictable drawbacks, limitations, and advantages to allow chemists to use the reaction appropriately during retrosynthetic analysis. [52]

The greatest advantage of the BIS undoubtedly is the ready availability of the starting materials.[61] Many nitroarenes are available from chemical product suppliers or nitro group can be directly introduced onto an aromatic ring by simple electrophilic substitution through several methods.[61] Moreover, the BIS is complete in few minutes at low temperatures (-40 °C and lower), thus saving many labile substituents or protecting groups. The reaction can be easy scaled-up and many examples are reported in the literature.[62-65]

It is worth noting that the reactivity of Grignard reagents towards nitro and nitrosoarenes is much higher than that of many carbonyl functions, such that the reagent is completely consumed in the indole formation before having a chance to attack any other reactive moiety.[58, 66, 67] Thus, only few very highly reactive electrophilic functions on the starting nitroarene need protection, in particular aldehyde and hydroxyl moieties. Actually, Dobson was interested in these protections and set up the optimum protecting groups for both hydroxyl and formyl moieties.[62, 63]

The amino group is another function needing protection. Helder and co-workers developed the BIS for the synthesis of substituted 4-aminoindoles, with yields comparable to those of other substitution patterns.[68] The Boc group is the most effective *N*-protecting group (Scheme 5). Obviously, a further equivalent of vinyl Grignard reagent is necessary, because of the presence of an acidic NH framework. Alternatively, a combination of two protecting groups can also be employed to produce protected 4-aminoindoles in useful yields. In these cases, the Boc group is removed from the final product. Moving the amino group round the benzene ring and the use of substituted vinyl reagents often did not yield indole. The reason of these failures is to-date unclear.



**Scheme 5** Synthesis of substituted 4-aminoindoles.[68]

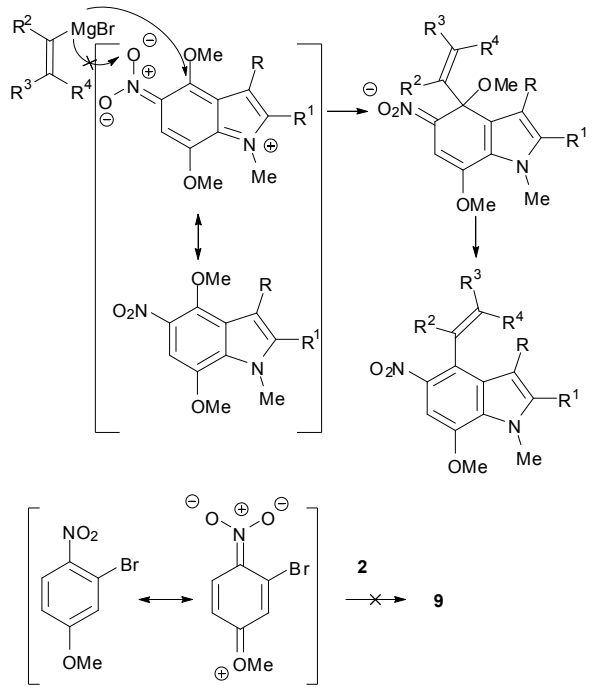
Conversely from the reaction of alkyl Grignard reagents,[69] BIS occurs at -78 °C also on dinitrobenzene derivatives.[70,71] Considering the high stabilization of dinitrobenzene radical anions,[72] the occurrence of the reaction is quite surprising.

BIS can be carried out on solid support, thus avoiding the tedious separation procedures.[58] More recently, Braese's group presented scope and limitation of this procedure, finding the best yields and purities at −40 °C.[73] However, they observed the failure of the reaction with 2-hydroxynitrobenzenes and 2-methoxynitrobenzenes that led to very complex mixtures.

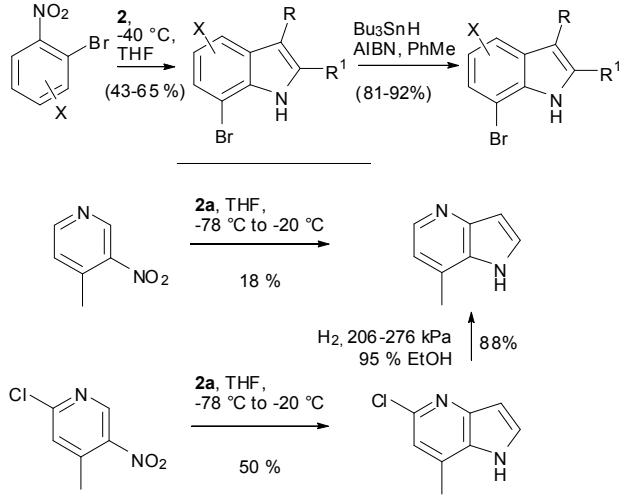
Also Menendez' group did not observed BIS with 5- (or 6-) nitroindoles,[70] but products from vinylation through an addition–elimination mechanism from *ipso*-attack to a substituted ring position were recovered (Scheme 6). They attributed this preference to the fact that direct conjugation with the indole nitrogen renders the N-O double bond of the nitro group insufficiently electrophilic to be attacked by the Grignard reagent. They supported this assumption, studying the product distribution of other reaction of vinylmagnesium bromides with some aromatic compounds containing electron-releasing substituents conjugated with the nitro group.[70] Related 5,8-dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one undergo both vinylation and Bartoli indolization depending from substitution of the Grignard reagent.[70, 74] Moreover, methoxy substituted 4-nitroanilides undergo vinylation,[70] whilst methyl substituted ones undergo only Bartoli indole synthesis.[75]

The main consequence of the mechanism described above is that *ortho*-substitution in the nitroarene is crucial for the reaction to proceed in good yields. In fact, the addition of vinyl Grignard

reagents to *meta*- or *para*-substituted nitrobenzenes for the preparation of 4(6)- or 5-substituted indoles, respectively, always furnished unsatisfactory results (yields not exceeding 15 %). However, Dobbs found that bromine can work as a transient group.[76] Actually, the Bartoli indolization of *meta*- or *para*-substituted 2-bromonitrobenzenes followed by removal of the bromine atom by reduction with tributyltin hydride led to 4(6)- or 5-substituted indoles in satisfactory overall yield (Scheme 7, top). This modification can give a significant reduction of the steps required for the preparation of many complex 7-unsubstituted indoles, whose functions are tolerant to the reaction conditions, but not to classical indole syntheses.



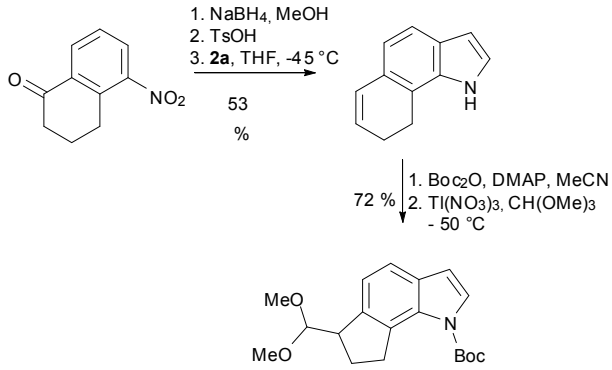

**Scheme 6** Limits of BIS with aromatic compounds containing electron-releasing substituents conjugated with the nitro group: top from ref [70], bottom from ref [77]



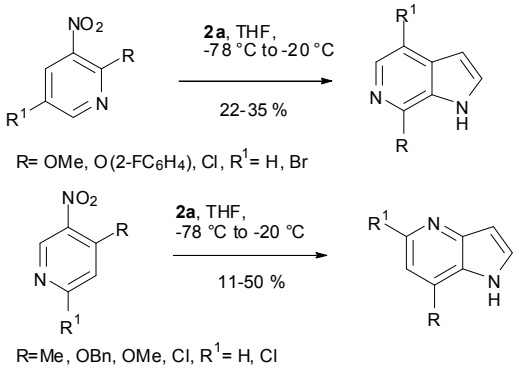

**Scheme 7** Bromine (top) and chlorine atom (bottom) as promoters

BIS is extendible to more complex systems than nitrobenzenes, with crowding near the nitro group. For instance, bicyclo aromatic nitro compounds, which possess *peri* steric hindrance, give benzindoles. The steric hindrance emanated by the H-8 addresses vinylmagnesium halides towards oxygen atoms of 1-nitronaphthalene, 5-nitroquinoline[47, 78] or 5-nitroisoquinoline,[79] leading to benzo- or pyridoindoles respectively.

Silva and co-workers proposed the synthesis of cyclopenta[g]indole derivatives taking advantage from the steric hindrance of the nitrodihydronaphthalene (Scheme 8).[80] The key steps in the sequence are the BIS to build the indole nucleus and a thallium(III)-mediated ring-contraction reaction to transform the cyclohexenone moiety into a functionalized cyclopentyl unit.




**Scheme 8** Synthesis of cyclopenta[g]indole[80]




**Scheme 9** Synthesis of 4- and 6-azaindoles[81]

Wang and co-workers successfully undertook a systematic study of Bartoli indolization on nitropyridines with the aim to develop a general and efficient method for preparing azaindoles (Scheme 9).[81] Yields (11–50 %) are comparable with most other indoles obtained by BIS, and mainly, comparable or higher than the previous multi-step syntheses of these compounds. 4- And 6-azaindoles were prepared, but not 5-azaindole, although the authors reported the probable application by the use of an appropriate nitropyridine. The presence of a chlorine atom in a conjugated position to the nitro group increases the yields. Therefore, chlorine is sometimes used as a promoter similar to bromine in the indole series (Scheme 7, bottom). Interestingly, the effect of the chlorine atom on nitropyridine is not observed in the strictly related quinoline system.[82] In fact, Mansell and co-workers found that 5-chloro-*1H*-pyrrolo[2,3-f]quinolines can be prepared in a more efficient manner using the Batcho-Leimgruber[83] than the Bartoli reaction, but they observed the opposite in the synthesis of *1H*-pyrrolo[2,3-f]quinolines. A reasonable explanation of the two different behaviours is not yet

reported.

The substitution on 2- and 3-positions of the indole nucleus is unfortunately limited both by the availability of the corresponding Grignard reagents and by the shape of the vinyl radical intermediate. In the latter case, nitrosoarenes could be a solution for instance in the preparation of 2-phenyl and 2-(trimethylsilyl)indoles.[52] Moreover, the use of nitrosoarenes saves one mole of the Grignard reagent, but they are less available, less stable, and, often, their dimeric forms lead to byproducts lowering indole yield, if particular reaction conditions are not adopted. Luckily, indole chemistry has developed many strategies for functionalization of 2- and 3-positions after the creation of the indole core, thus these drawbacks can be easy overcome.[46]

Notwithstanding the low atom economy of the reaction, BIS should be considered a "green reaction" because magnesium ion is practically non-toxic, so low concentrations into the recovered indole do not represent a problem when indole itself is used as a drug. Conversely, palladium salts,[40, 43] used as the catalysts in some indole syntheses, must be completely removed, owing to their human high toxicity.

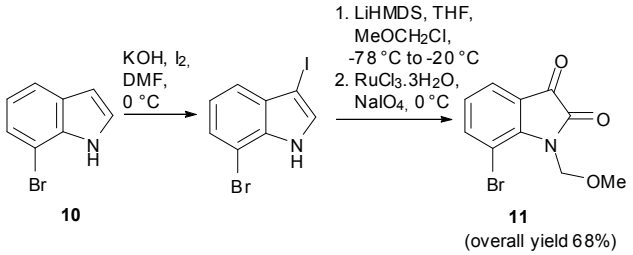
In conclusion, since its appearance in the literature, the Bartoli indole synthesis has provided a useful way to key intermediates for the synthesis of complex indoles. The core of this review is dedicated to synthetic applications of BIS appeared in literature since 2005, being the more ancient literature covered by our previous review.[48] Syntheses will be itemized based on starting 7-substituted indole.

## 2. Syntheses from 7-Haloindoles

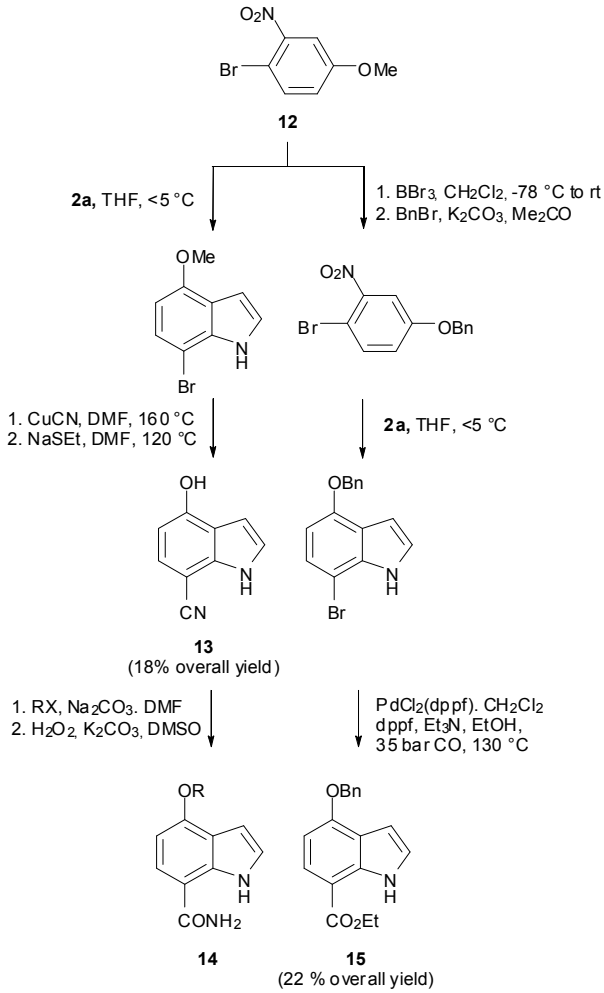
7-Haloindoles, and in particular 7-bromoindole (**10**), are useful intermediates in the synthesis of many interesting indole derivatives. For instance, **10** is the starting material for the synthesis of MOM-protected isatin **11** (Scheme 10). Compound **11** is then employed as useful building block for the ring F and E of the complex cytotoxic peptide diazonamide A (Figure 1, blue coloured), isolated from the marine ascidian *Diazona* species.[84, 85]

Grant and co-workers proposed BIS for the preparation the medicinal interesting 3-substituted-4-alkoxyindole-7-carboxamides. [86] After construction of the indole ring by reaction of 5-methoxy-2-bromonitrobenzene (**12**) with vinylmagnesium bromide, cyanation was performed using copper(I) cyanide followed by demethylation with sodium ethanethiolate to afford the 4-hydroxyindole **13** and, finally, hydration of nitrile to amide **14** (Scheme 11). This synthesis was not very efficient (18 % overall yield for the three steps from **12** to **13**). However, benzyl protection of starting nitrophenol **12** and replacing the cyanation with a carbonylation reaction resulted in improved yields (22 % overall with four reaction steps). Moreover, the reaction was more scalable, providing more than 10 g of ester **15**.

Sugden and co-workers prepared a series of 7-substituted melatonin and 1-methylmelatonin analogues and tested them against human and amphibian melatonin receptors. 7-Substituents reduced the agonist potency of all the analogues with respect to melatonin in the *Xenopus laevis* melanophore, but 7-bromomelatonin was among the less reducing compounds. 7-Bromomelatonin was prepared from 2-bromo-4-methoxynitrobenzene (see also section 2). [87]



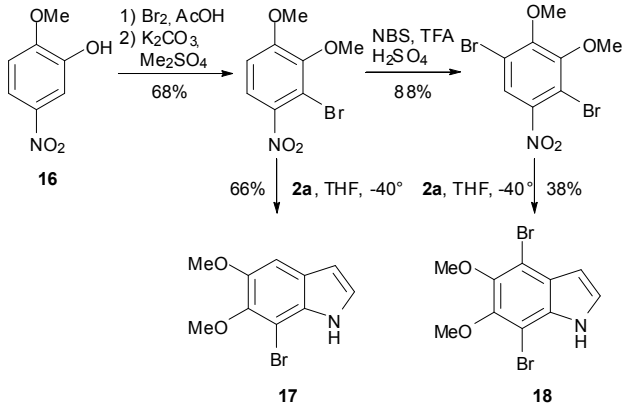

**Scheme 10** Synthesis of MOM-protected 7-bromoisatin [84]



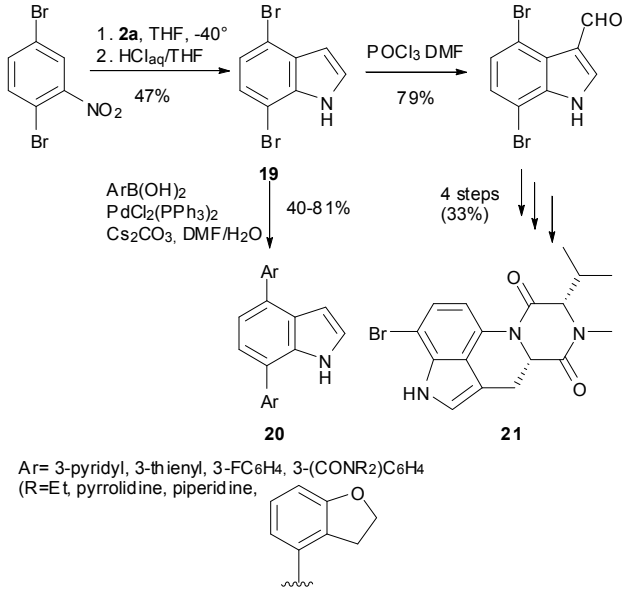

**Scheme 11** Synthesis of 3-substituted-4-alkoxyindole-7-carboxylic acid derivatives [86]

It is interesting to note that 7-bromo- (**17**) and 4,7-dibromo-5,6-dimethoxyindole (**18**) are also obtained by treatment of the corresponding nitroarenes with 4 equiv. of vinylmagnesium bromide. [88] The nitroarenes, in turn, can be easily prepared by bromination of the commercially available 5-nitroguaiacol (**16**) (Scheme 12).

4,7-Dibromoindole (**19**) was the starting material for the preparation of a series of 4,7-diarylindole derivatives (**20**), which show significant changes in UV-Vis and fluorescent intensity with addition of iodides, thus behaving as selective iodide chemosensors (Scheme 13).[89] Moreover, compound **19** was used also in the synthesis of an indolyldipeptide, starting material for the synthesis 2,5-diketopiperazines (**21**) promising compounds for the treatment of some human diseases.[90]



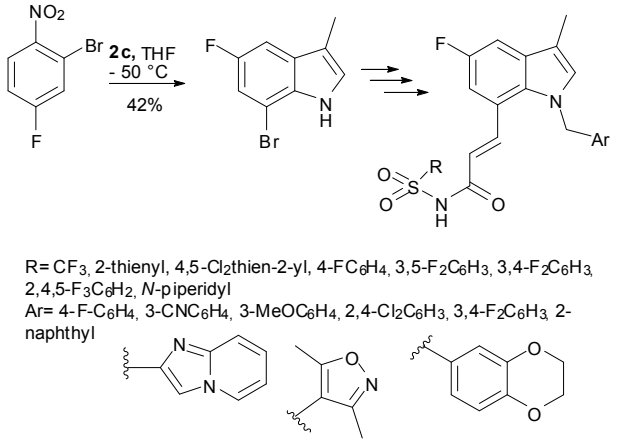

**Scheme 12** Synthesis of 7-bromo-5,6-dimethoxyindole (**17**) and 4,7-dibromo-5,6-dimethoxyindole (**18**) [88]



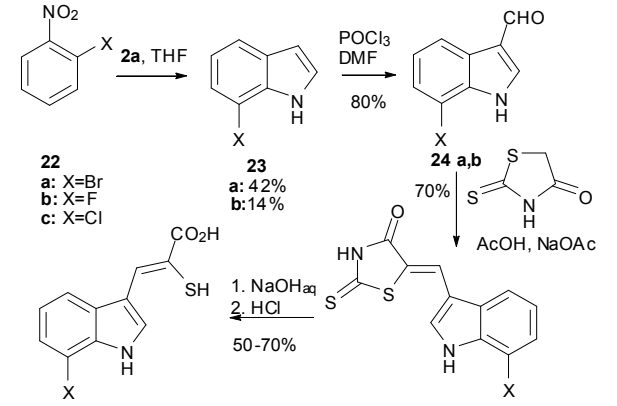

**Scheme 13** Synthesis of iodide chemosensors (**20**), [89] and 2,5-diketopiperazines (**21**) [90]

Singh and co-workers prepare some indole derivatives analogues to human $EP_3$ receptor antagonists with good activity.[91] The $EP_3$ receptor is one of eight G-protein-coupled receptors that belong to the prostanoid receptor family. Prostanoids are ubiquitous autocrine mediators involved in numerous physiological and pathological processes including inflammation. For the synthesis of 1,7-disubstituted analogues derived from 5-fluoro-3-methylindole core, BIS revealed the reaction of choice for laboratory scale (Scheme 14). However, scale up of the reaction for the preparation of **DG-041** (Figure 1) revealed difficult.[92]

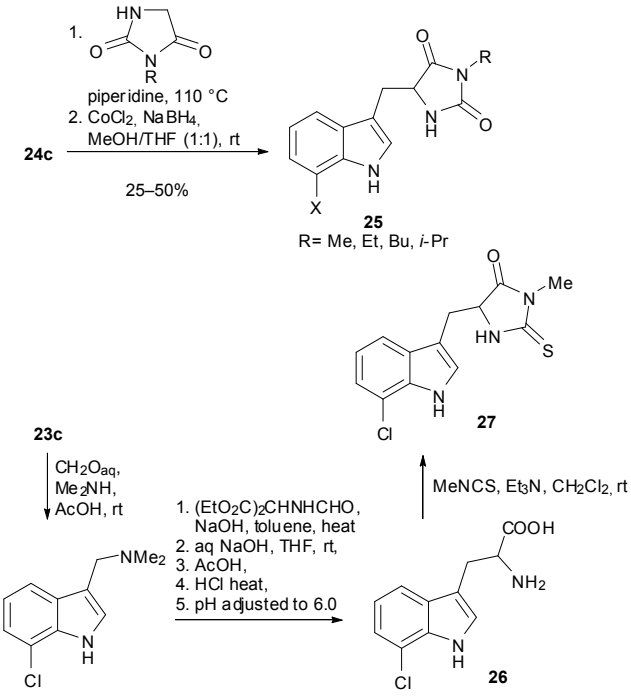
7-Halo-3-indolecarbaldehyde (**23**) prepared by the BIS and Vilsmeier-Haack sequence is also the starting material for many biological interesting products. For instance, it served as key building block for the synthesis of a series of monohalide mercaptoacrylic acid derivatives, which were employed in a study of SAR on the efficacy of these molecules for inhibition of $Ca^{2+}$-activation of calpain-1 (Scheme 15).[93] Yields reported in this work confirmed the decline from voluminous bromine to small fluorine atom. [55]




**Scheme 14** Synthesis of some indole derivatives analogues to human $EP_3$ receptor antagonists [91]



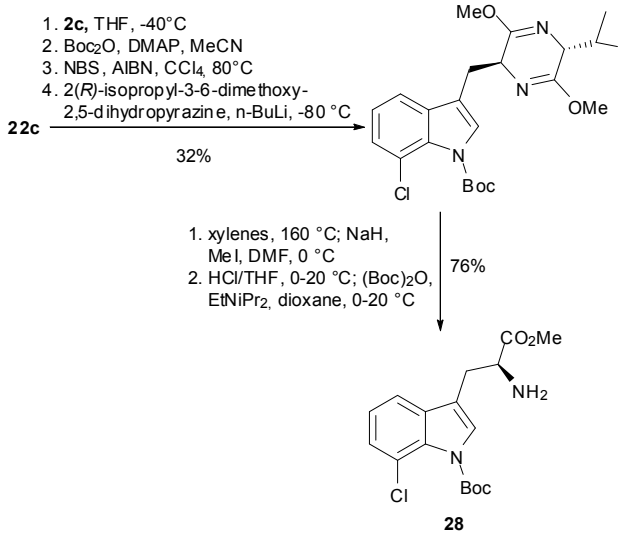

**Scheme 15** Synthesis of 7-haloindolylmercaptoacrylic acid derivatives [93]



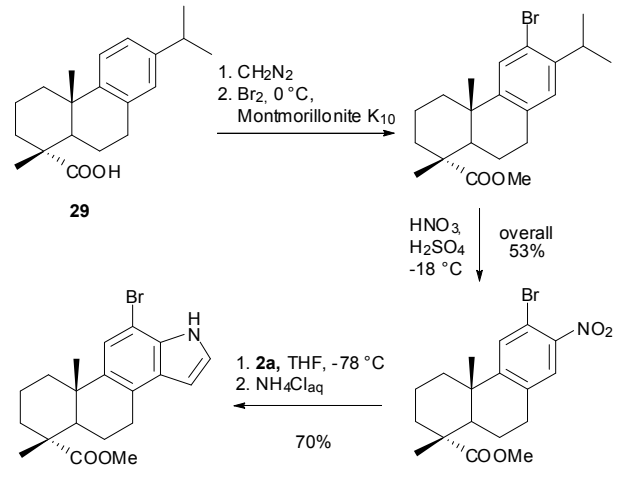

**Scheme 16** Synthesis of 5-(1H-indol-3-ylmethyl)hydantoins (**25**) and 5-(*1H*-Indol-3-ylmethyl)-2-thiohydantoins (**27**) [94]

Moreover, compound **23c** allowed the synthesis of 5-(7-chloro-*1H*-indol-3-ylmethyl)hydantoin (**25**) (Scheme 16), while 5-(7-chloro-*1H*-indol-3-ylmethyl)-2-thiohydantoin (**27**) was prepared from the corresponding tryptophan **26**, but always starting from 7-chloriondole (**23c**).[94] These hydantoins are also called necrostatins, since they are found to be involved in necroptosis inhibition and can provide lead compounds for therapeutic development. A SAR study revealed that 7-substituted derivatives such as **25** and **27** resulted in increased activity with respect unsubstituted ones.

Barret and co-workers enantioselectively prepared 7-chloro-1-methyltryptophan derivative **28** from 1-chloro-2-nitrobenzene by BIS (Scheme 17),[95] and used **26** as the key intermediate in a four-steps synthesis of CJ-12662, (Figure 1) a potent anthelmintic natural product from the fermentation broth of *Aspergillus fischeri* var. *thermomutatus*.




**Scheme 17** Synthesis of 7-chloro-1-methyltryptophan [95]

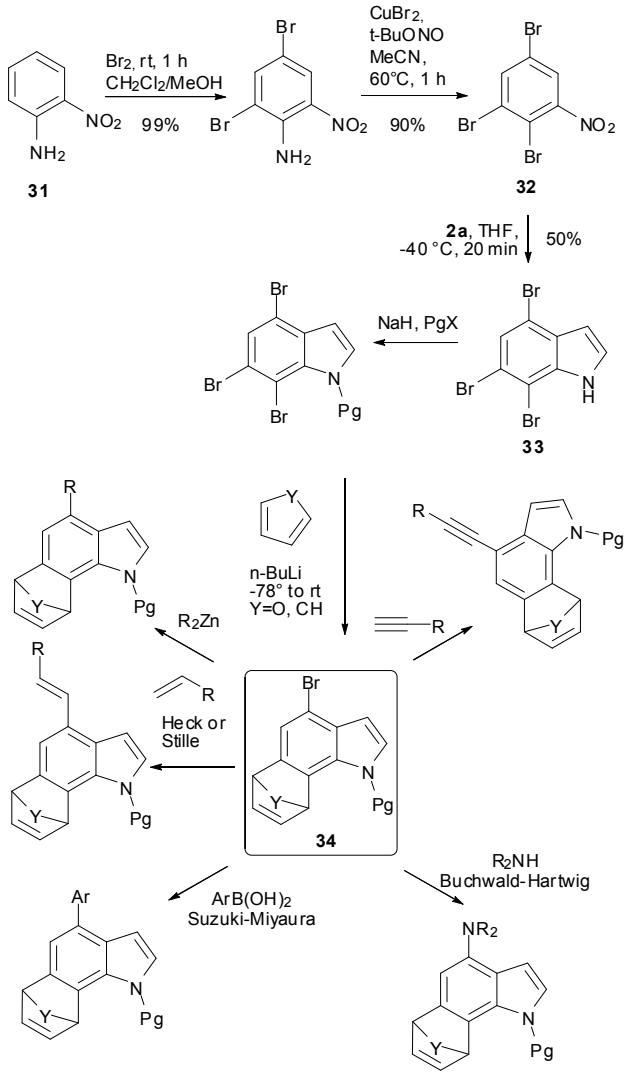



**Scheme 18** Synthesis of 7-Bromo substituted indole from dehydroabietic acid[67]

In section 2, the synthesis of bisindolylmethane derivatives was already mentioned as a support of the reaction mechanism (Scheme 2). However, many bisindolylmethane alkaloids show biological activities, such as potent carcinogenicity or antibacterial activity, thus Ishikura and co-workers prepared various derivatives combining BIS and Friedel-Crafts reaction in the presence of an additional aldehyde or isatin in a one-pot manner.[56]

7-Bromo substituted indole derivative (**30**) showed activity against human cytomegalovirus and varicella-zoster virus comparable to that of classical acyclovir. It was obtained in four steps from naturally occurring dehydroabietic acid (**29**), a natural occurring diterpenic compound (Scheme 18). [67]

However, the most important application of haloindoles prepared by BIS is the synthesis of *cis* and *trans*-trikentrins (Figure 1). Trikentrins are cytotoxic indole alkaloids isolated from marine sponges of the *Trikentrion* genus. They are constituted by a cyclopentane ring annulated to the 6-7 carbon-carbon bond of the benzene ring portion of the indole. [96]

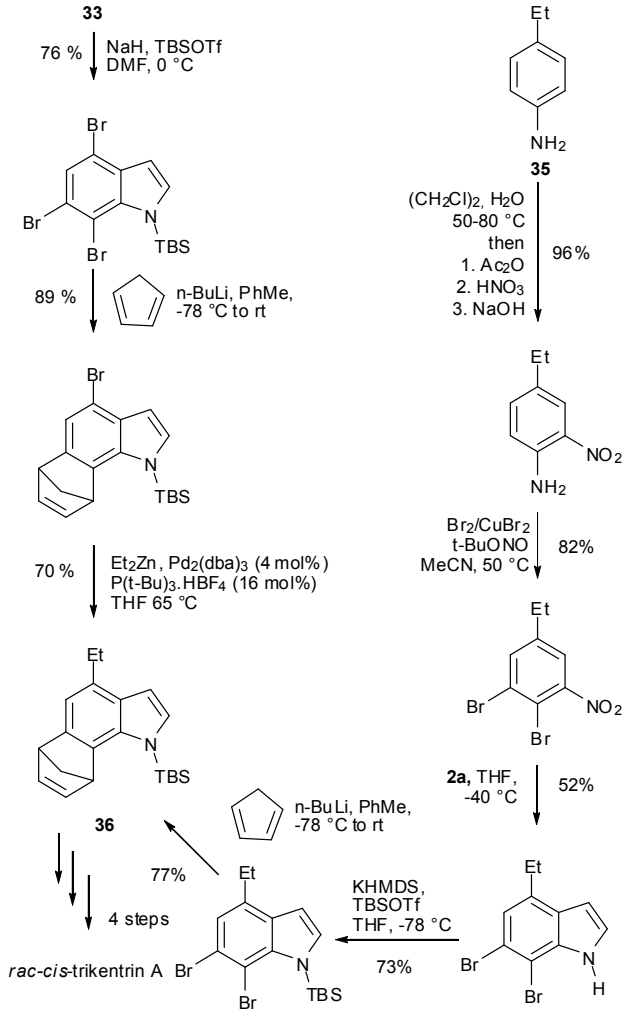



**Scheme 19** Synthesis of 4,6,7-tribromoindole [97]

Buszek and co-workers prepared the very versatile 4,6,7-tribromoindole (**33**) by BIS. This synthesis is an example of the easy availability of the starting materials for BIS, since the starting nitroarene is prepared in two easy steps from the commercial 2-nitroaniline (**31**, Scheme 19).[97] Starting from **33,**

they prepared two libraries (93 members[98] and 66 members,[99] respectively) of annulated indoles, combining indole aryne cycloadditions at the 6,7-positions and both the Suzuki-Miyaura and Buchwald-Hartwig condensation at the 4-position. These structural entities could have unique chemical property and should be reasonably amenable to both biochemical and cell based assays. In particular, members of the 66-library were tested *in vitro* in L1210 leukemic cells with promising results. [99]

Buszek's group also studied the effects of pyrrole and benzene ring substitution patterns on the regioselectivity of 6,7-indole aryne cycloadditions with 2-*tert*-butylfuran. The results of this investigation revealed a remarkable regiocontrol by substitution at the 3-position, whereas most of 4- or 5-substituents generally markedly reduced selectivity except for 4-ethyl and 4-iodo cases.[100] Moreover, they prepared intermediate **36**, a key intermediate for the preparation of (±)-*cis*-trikentrin A.




**Scheme 20** Syntheses of (±)-*cis*- trikentrin A proposed by Buszek: left ([97]) right ([101])

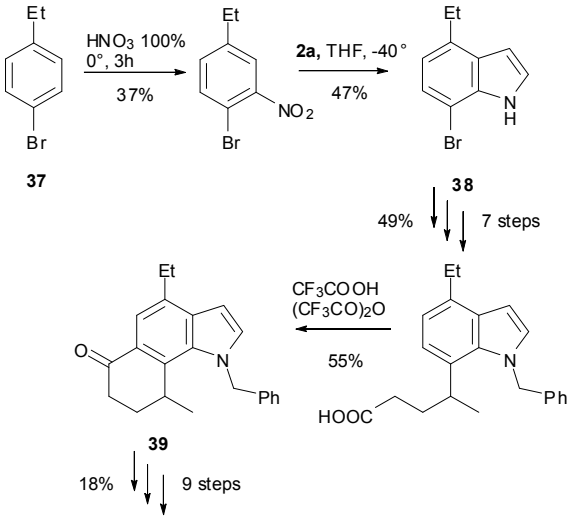
The same research group published a second synthesis of (±)-*cis*-trikentrin A from 4-ethyl aniline (**35**) by a very similar reaction sequence (Scheme 20). [101] The two reactions have similar yields (21 % overall from **31** to **36** with respect to 23 % overall from **35** to **36**).

Prompted by these achievements, Buszek's group attempted also the synthesis of (±)-*cis*-trikentrin B (Figure 1), but application of the Bartoli indole synthesis to 2,3,4-tribromonitrobenzene afforded the desired 5,6,7-tribromoindole only in 32 % yield. They then succeeded in the synthesis of desired indole in 61 % yield by Leimgruber–Batcho route. [102]

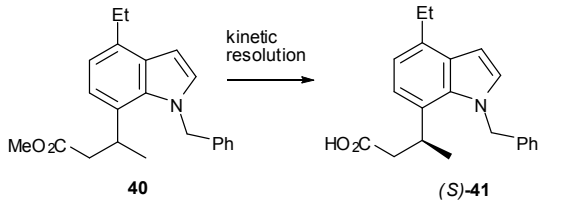
An alternative route to trikentrins contemplates a Friedel-Crafts acylation of 7-alkylindole and it was especially employed in the preparation of the more challenging *trans*-trikentrins, the synthesis of which have serious problems associated with the formation of the *trans*-1,3-dimethylcyclopentyl unit.

Silva and Craveiro synthesized *trans*-trikentrin A preparing the indole nucleus by BIS, from 4-bromoethylbenzene (**37**), followed by Heck coupling to add the carbon atoms that will originate the nonaromatic cycle. Friedel-Crafts acylation allowed the second ring closure to **39**. Finally, the thallium(III)-mediated ring contraction reaction[80] allowed to obtain the *trans*-1,3-disubstituted five-membered ring in a diastereoselective manner (Scheme 21).[103]

They were also successful in the first total synthesis of (+)-*trans*-trikentrin A by using a kinetic resolution of ester **40** performed by using the enzyme Amano PSCII, which is a formulation of *Pseudomonas cepacia* lipase immobilized on a ceramic substrate, which achieved acid (*S*)-**41** (Scheme 22). [104] This step is one of the eight necessary to transform **38** in **39** (Scheme 21).



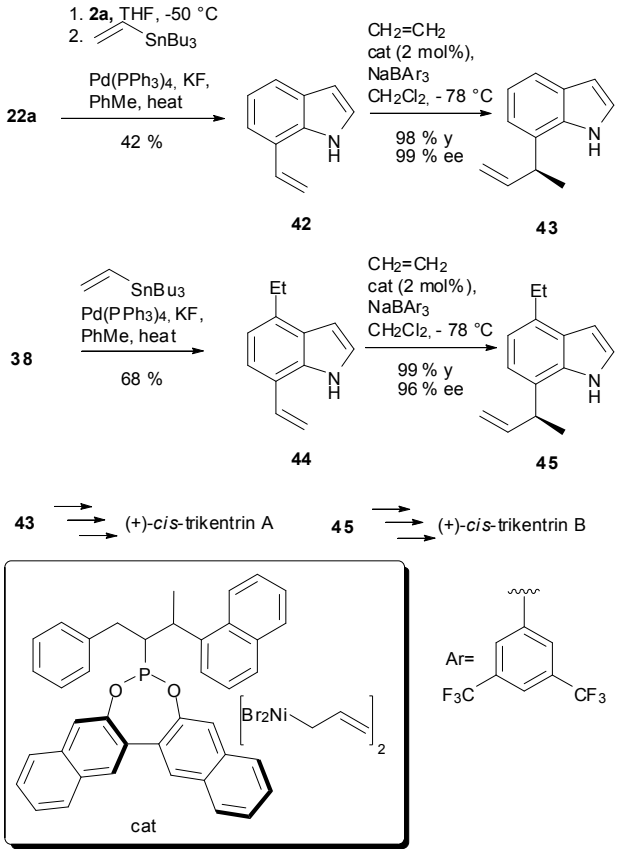

**Scheme 21** Syntheses of (±)-*trans*-trikentrin A proposed by Silva [103]



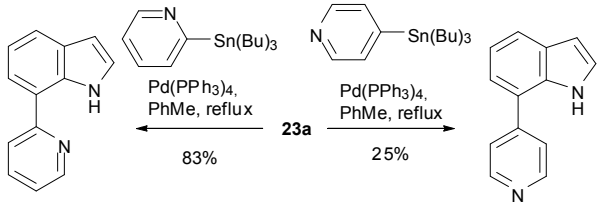

**Scheme 22** Kinetic resolution for asymmetric preparation of *trans*-trikentrin A [104]

Finally, enantiomerically enriched *cis*-trikentrins A and B were prepared by asymmetric hydrovinylation of vinylindoles at −78 °C under 1 atm of ethylene. Starting 7-vinylindoles (**42** and **44**) are achieved from BIS of the corresponding bromonitrobenzenes,

followed by vinylation with vinylstannane (Scheme 23).[105] Enantioenriched compounds **43** and **45** were converted into (+)-*cis*-trikentrins A and B in 8 and 11 steps, respectively.




**Scheme 23** Asymmetric synthesis of key intermediate for trikentrins[105]




**Scheme 24** Synthesis of 2'- and 4'-pyridyl 7-substituted indoles by Stille reaction [106]

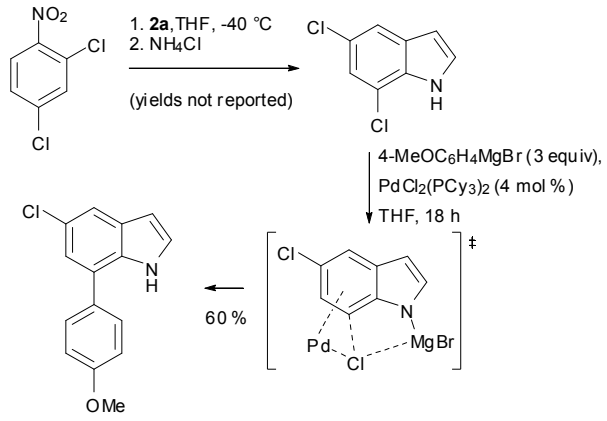
Differently from Buszek's approach (see above), in this reaction the 6-substitution performed after indole nucleus formation should be noted.

7-Alkyl- and 7-arylindoles are another very important class of compounds widely used in the synthesis of naturally occurring indoles. Both compounds have been synthesized by means of a two-step protocol involving Bartoli indolization that precedes or follows classical couplings of aryl bromides. In this section, we report reactions in which Bartoli indolization precedes the coupling.

For instance, Suzuki couplings of indole bromides and commercially available substituted phenyl boronic acids all occur in high to excellent yields. Another typical reaction of aryl halides is the Stille coupling with arylstannanes, which is performed under anhydrous conditions in aprotic solvents. Toluene or xylene is used as solvent to allow increased reaction temperature and improve the solubility. Examples of these reactions were already described in schemes 19, 21, 23.

Moreover, an interesting Stille reaction is reported to give the fluorescent 2'- and 4'-pyridyl 7-substituted indoles in good yield from coupling between the corresponding pyridyl tri-*n*-butylstannane and 7-bromoindole (Scheme 24).[106] It is worth of note that the position of the nitrogen atom on the pyridylstannane strongly influences the reaction yields, but no explanation is given. The *ortho* and *para* derivatives are obtained in 83 % and 25 % yields, respectively.

Manabe and co-workers found that dichlorinated benzo-fused nitrogen-heterocycles, such as 5,7-dichlorindole, undergo site-selective cross-coupling with Grignard reagents in the presence of $PdCl_2(PCy_3)_2$ at the *ortho* positions to the nitrogen. Authors envisaged that an interaction between Lewis acidic Mg and Cl of the *ortho* position facilitates C–Cl bond cleavage (Scheme 25).[107] This procedure allowed the preparation of 7-alkyl-5-chloroindole starting from 2,4-dichloronitrobenzene, arranging BIS and site-selective cross-coupling. In addition, Suzuki coupling can attach a 6-tetrahydroquinolinyl substituent to 7-bromoindoles. [108]




**Scheme 25** Preparation of 7-alkyl-5-chloroindole [107]

Finally, 7-bromoindole is the starting material of many interesting key intermediates such as 7-formyl-,[63] 7-carbomethoxy-,[109, 110] and 7-amino-indole,[111] since these procedures are more convenient than directed-metallation of the 7-unsubstituted indole.

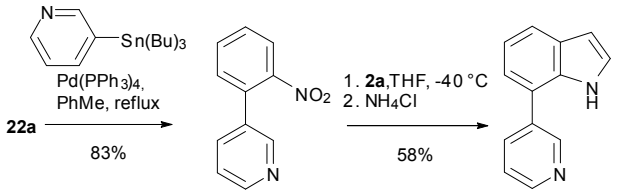
## 3- Syntheses from 7-Alkylindoles

This section will be devoted to reactions, which employ alkylnitrobenzenes for the preparation of 7-alkyl- and 7-arylindoles.

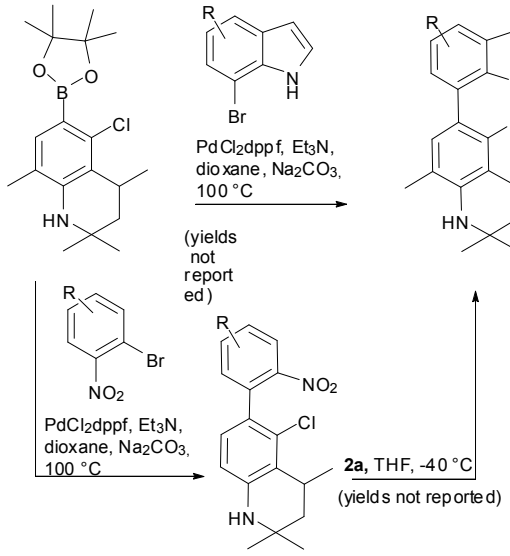
Conversely from the 2'- and 4'-pyridyl derivatives (Scheme 24), the 7-(3'-pyridyl)indole synthesis is unsuccessful either by Stille (with 3'-pyridyl tri-*n*-butylstannane) or Suzuki (with 3'-pyridylboronic acid) couplings on 7-bromoindole. The synthesis can be, however, accomplished by preceding Stille coupling to Bartoli indolization (Scheme 26).[106]

Moreover, when the appropriate 7-bromoindole is not available (see previous section), *ortho*-(6-tetrahydroquinolinyl)-nitrobenzenes can be cyclised by BIS with comparable yields, (Scheme 27).[108] By this way a series of nonsteroidal glucocorticoid receptor ligands based on a 6-indole-1,2,3,4-

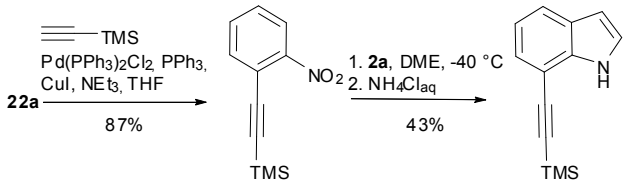
tetrahydroquinoline scaffold was prepared.




**Scheme 26** Synthesis of 3'-pyridyl 7-substituted indoles [106]




**Scheme 27** Synthesis of 6-indole-1,2,3,4-tetrahydroquinoline derivatives [108]



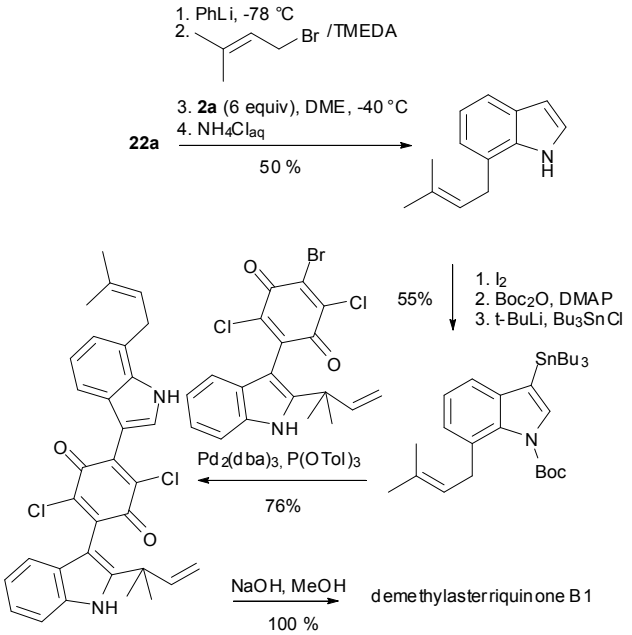

**Scheme 28** Synthesis of 7-alkynylindoles [112]

The reaction of choice for the synthesis of 7-alkynylindole is the alkylation of nitrobenzenes by Sonogashira coupling,[113] followed by Bartoli reaction (Scheme 28).[112] 7-Alkynylindole has been then used for Diels-Alder reactions with cyclopentadienones, to afford substituted biaryls of biological interest.

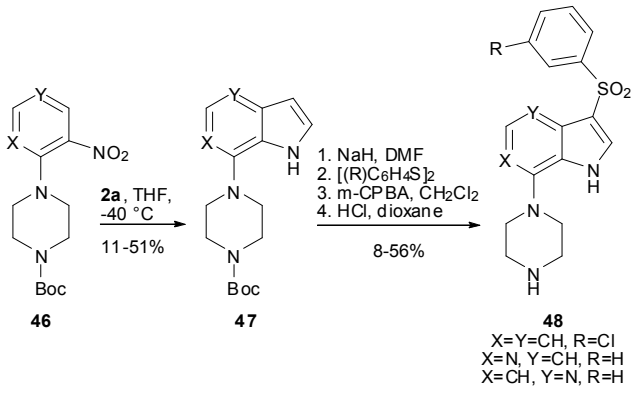
Furthermore, allyl bromides are found to react easily with 2-lithionitrobenzene, carefully prepared from 2-bromonitrobenzene, to avoid biphenyls or by-products arising from reduction of the nitro group.[114] These compounds undergo BIS, if some modifications to the original procedure are made. In particular, DME is used as the solvent to increase the solubility; otherwise, heterogeneous mixtures occur in other ethereal solvents. Moreover, higher yield is obtained, if the Grignard reagent is always in excess throughout the reaction. Therefore, the nitroarene is added to a six-fold excess of Grignard solution.[115]

7-Prenylindole, prepared by this method, was transformed into the Boc-protected 3-tributylstannane derivative, followed by Stille-coupling with the appropriate indolylquinone and hydrolysis with methanolic NaOH targeting demethylasterriquinone B1 (DAQ B1), a small-molecule mimetic of insulin (Scheme 29). This synthesis is extended to a series of methyl derivatives of DAQ B1 starting from the appropriate bromonitrotoluenes, some commercially available, other easily prepared from the corresponding aniline by m-CPBA oxidation.[116]

7-Piperazinylindoles (**47**) are also obtained starting from 2-fluoronitrobenzene or fluoronitropyridines treated with *N*-Boc-piperazine and cyclised with vinylmagnesium bromide (Scheme 30). Then, an aryl sulfonyl group is introduced onto the 3-position of the indole nucleus by reaction with the appropriate disulphide. Oxidation with m-CPBA and acid deprotection, complete the steps for the preparation of a series of indole sulfones (**48**) with high 5-$HT_6$ receptor affinity.[117]




**Scheme 29** Synthesis of demethylasterriquinone B1[116]

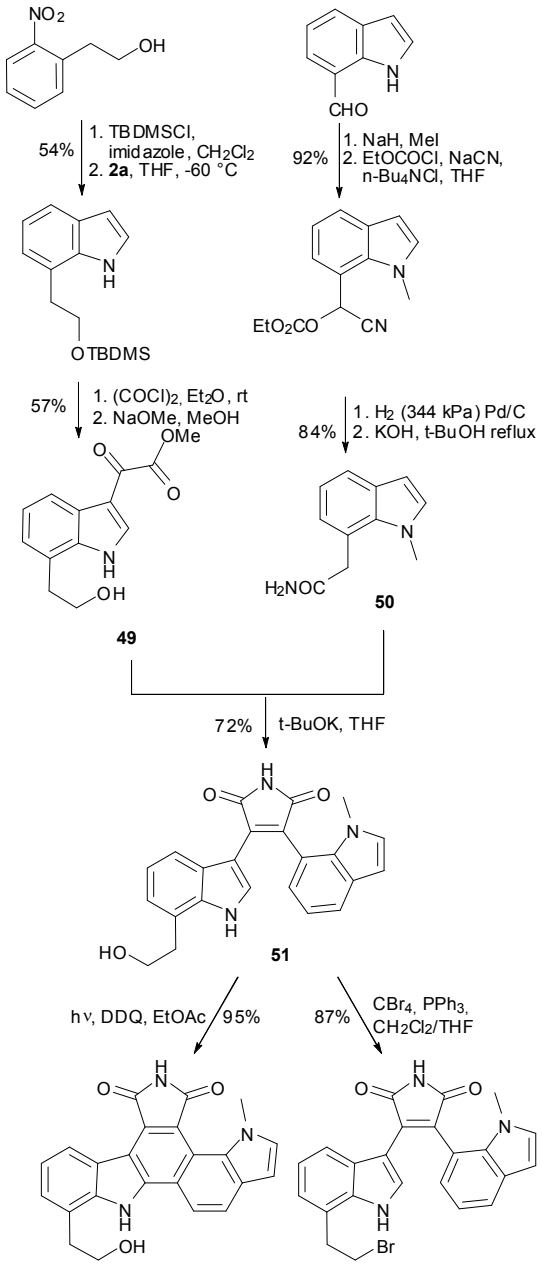



**Scheme 30** Synthesis of 7-piperazinylindoles [117]

Indolocarbazoles, namely indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles, are potent inhibitors of cyclin D1/CDK4. Cyclin D1/CDK4 and related molecules play an essential role in the transition of cells from G1 to S phase. Several tumours are found to have major alterations in this pathway. Numerous efforts are undertaken to modify the polycyclic structure to obtain analogues with improved pharmacological profiles. Many syntheses start from 7-substituted indoles and often represent an elegant application of

BIS and its modifications.

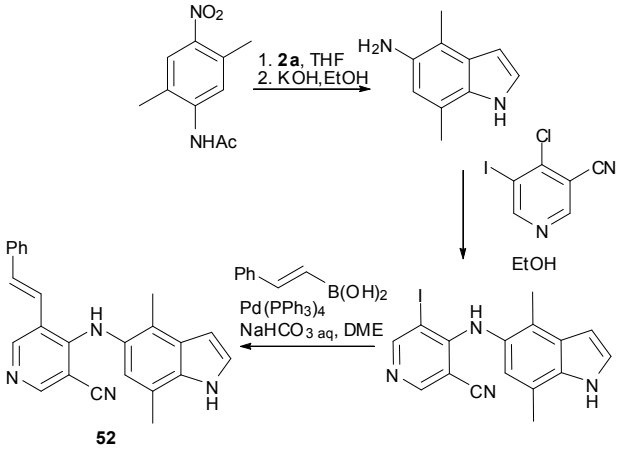
In particular in the range of years covered by this review, the synthesis of indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles has been published in two phases.[118, 119] Silyl protection of 2-(2-nitrophenyl)ethanol followed by BIS produces the protected 7-(2-hydroxyethyl)indole (Scheme 31). Glyoxylation with oxalyl chloride, followed by *in situ* quenching with MeOH/NaOMe, affords, after spontaneous desilylation, compound **49**.



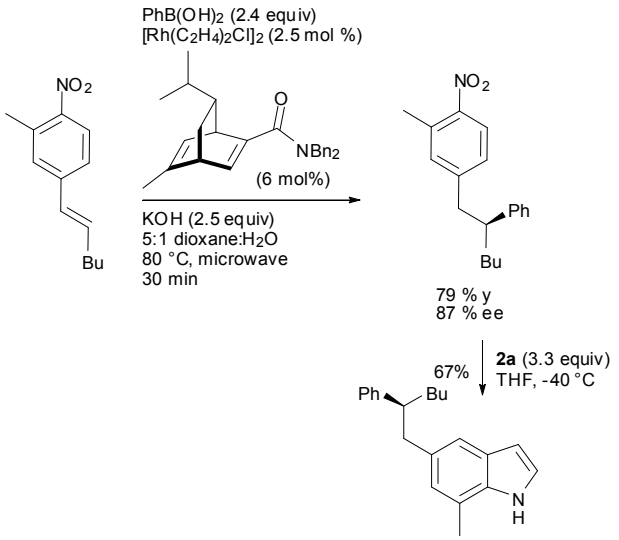

**Scheme 31** Synthesis of the key intermediates for indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazole derivatives.

7-Formylindole, readily available from BIS,[63] reacts with ethyl chloroformate to lead to cyanocarbonate. Hydrogenation and hydrolysis using KOH/*t*-BuOH at reflux afford an efficient practical synthesis of *N*-methylindole-7-acetamide (**50**). The two indolic building blocks are coupled with *t*-BuOK to form the bis-indolylmaleimide **51**. For the carbazole formation, the preferred strategy is to perform a photo-oxidation reaction.

During the preparation of a library of 5-vinyl-3-pyridinecarbonitriles to be evaluated as PKCθ inhibitors, derivative **52** was prepared from 2,5-dimethyl-4-nitroaniline using vinyl Grignard reagent.[75] Removal of the acetyl protecting group produced the desired 5-amino-4,7-dimethylindole, which was then converted into **52** in two reaction steps (Scheme 32). It was found to be the most potent and selective compound with an $IC_{50}$ value of 34 nM for the inhibition of PKCθ and 41-fold selectivity over PKCδ. Unfortunately, the yield of this synthesis is not reported.




**Scheme 32** Synthesis of 5-vinyl-4-indolyl-3-pyridinecarbonitriles as PKCθ inhibitors [75]




**Scheme 33** Enantioselective synthesis of indole [120]

Finally, a highly enantioselective rhodium-catalysed additions of arylboronic acids to alkenyl-*p*-nitroarenes appeared recently in the literature.[120] Authors reported the conversion of one product into indole by BIS, as an example of the synthetic utility of the arylation products (Scheme 33).

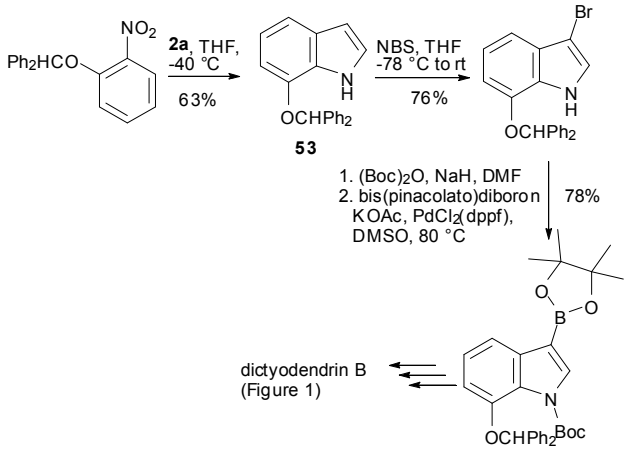
## 4. Syntheses from 7-Hydroxyindoles

As reported above, the hydroxyl function cannot survive under BIS reaction conditions; therefore, Dobson studied 2-nitrophenol

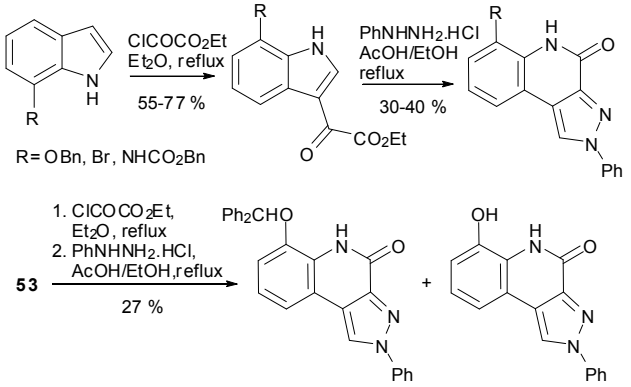
protections in order to reach the optimum cyclisation yields. [62] Benzhydryl protecting group is demonstrated to be more efficient than both the originally suggested TMS-group,[47] and many others. [62] Its efficiency is related both to the yields and to the ease of removal.

7-Benzhydryloxindole obtained by this methodology was employed for the preparation of many biologically-interesting indole derivatives. For instance, 3-bromo-7-benzhydryloxyindole is an intermediate used for the construction of the core structure of the telomerase inhibitor dictyodendrin (Scheme 34).[121] Starting from indole **53**, strategies for different and orthogonal protections of both the 7-hydroxy and the NH moieties are also described.

2-Phenylpyrazolo[3,4-c]quinolin-4-ones, which are adenosine receptor antagonists, were prepared in fair yields from 7-substituted indoles derived by BIS from the appropriate nitroarene. It should be noted that **53**, under these reaction conditions, yielded a mixture (about 1:1) of the corresponding 6-benzhydryloxy-pyrazoloquinoline and of the 6-hydroxy derivative (Scheme 35). [122]



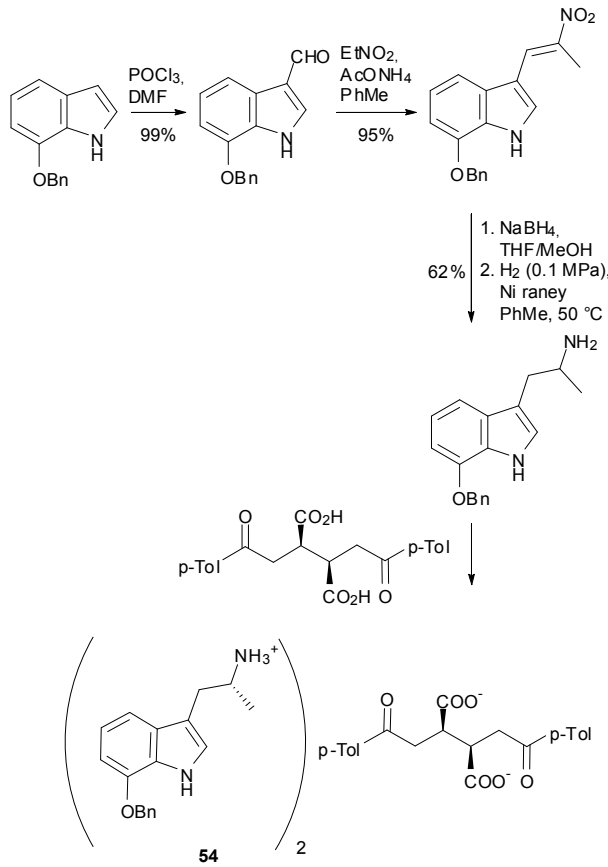

**Scheme 34** Synthesis of the key intermediate for the preparation of dictyodendrin[121]



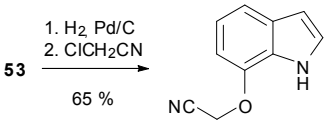

**Scheme 35** Synthesis of 2-phenylpyrazolo[3,4-c]quinolin-4-ones[122]

The bisindole alkaloid dragmacidin E (Figure 1) was isolated from a *Spongosortes* sp. collected in Australian waters. It is described as exhibiting potent serine-threonine protein phosphatase inhibitory activity. The synthesis plan proposed by Feldman and Ngernmeesri commenced from **53,** available via BIS. The synthesis led to the racemic form of dragmacidin E in over 25 steps.[123]

The synthesis of *(R)*-3-(2-aminopropyl)-7-benzyloxyindole has been accomplished starting from 7-benzyloxindole prepared by BIS.[124] After formylation at C-3, nitroaldol reaction provided the nitro olefin, which undergoes two reduction steps firstly with $NaBH_4$ and then with Ni-raney (Scheme 36). The racemic product is resolved with a tartrate salt. The *(R)*-isomer (94 % ee) is recovered as a solid, while the *(S)*-isomer remained in solution. The *(S)*-isomer can be then racemized and further resolved. Compound **54** is the key chiral intermediate for the synthesis of AJ-9677 (Figure 1) a potent and selective adrenaline $\beta_3$-agonist used in the treatment of obesity in diabetics.




**Scheme 36** Synthesis of *(R)*-3-(2-Aminopropyl)-7-benzyloxyindole[124]




**Scheme 37** Synthesis of 7-cyanomethoxyindole [125]

Merschaert group reported the synthesis in racemic and enantioenriched form of compound LY290154 (Figure 1) in a gram-scale starting from 7-cyanomethoxyindole prepared from **53** (Scheme 37).[125] LY290154 is a drug candidate to be an antagonist of leukotriene D4, the major slow reacting substance in human lung. Actually, asthma attacks are caused by production of slow reacting substances, triggered by pollen or other allergens.

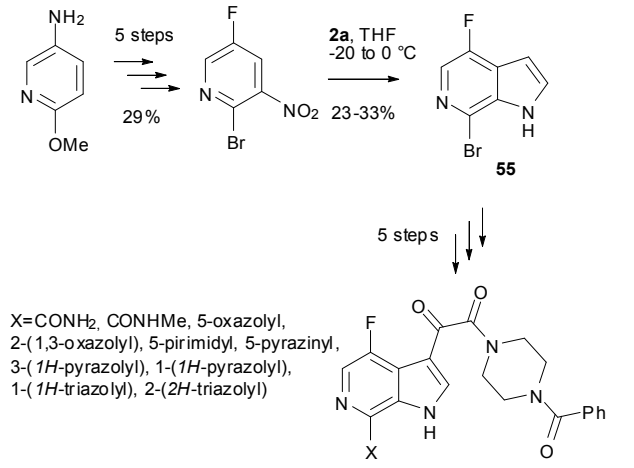
## 5. Syntheses from Azaindoles

Azaindoles, originated replacing one of the carbon atoms at positions 4–7 in the indole template with a nitrogen atom, have medicinal relevance and they are frequently exploited as indole bioisosteres in the design of biologically interesting molecules. In addition, azaindoles have also found applications in material synthesis and coordination chemistry.[126-128]

Some applications of azaindoles prepared by Wang's BIS modification[81] are reported recently in the literature and are collected in this section. For instance, nitropyridines obtained from reaction of the appropriate fluoro compound with N-Boc-piperazine were successfully treated with vinylmagnesium bromide, as described above (Scheme 30),[117] to afford the desired azaindoles. This experimental procedure was applied recently in patents relating to the design of 4- and 6-azaindolyloxoacetylpiperazines as anti-HIV drugs.[129-131]

Moreover, in an effort to identify HIV-1 attachment inhibitors with the potential to improve the clinical profiles of BMS-488043 and BMS-378806 (Figure 1), the same research group prepared a series of 6-azaindole,[132] and of 4-azaindole oxoacetic acid piperazine benzamides by their modified BIS.[133]

Regueiro-Ren and co-workers prepared and tested another series of HIV-1 attachment inhibitors with 4-fluoro-6-azaindole core, with the aim to target the viral envelope protein gp120. Substitution of the bromine atom in the 7-position of **55** with amides, C-, and N-linked heterocycles provided compounds with good pharmacokinetic profiles *in vivo*. The synthesis of these compounds used BIS modification as the key step for the formation of indole nucleus (Scheme 38). [134]

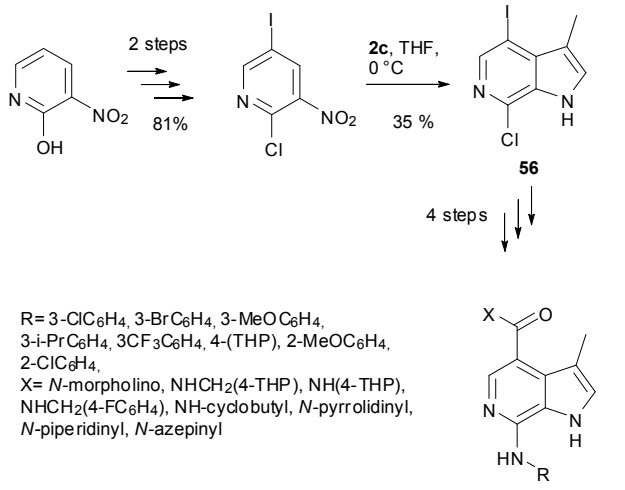



**Scheme 38** Synthesis of the 4-fluoro-6-azaindole core, key intermediate for preparation of HIV-1 attachment inhibitors[134]

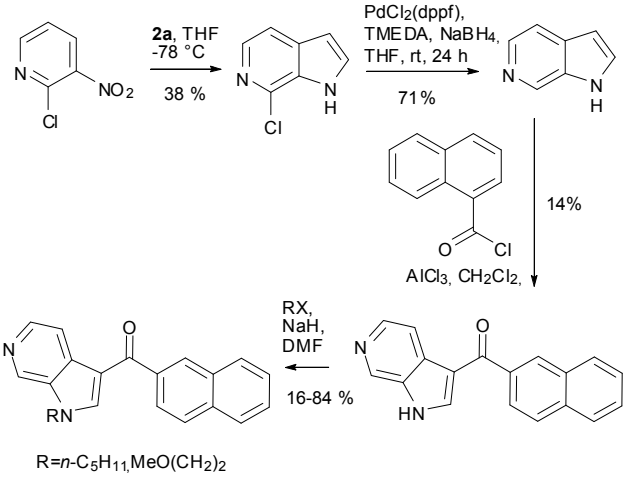
Giblin's[135] and Blaazer's[136] groups independently proposed 6-azaindole derivatives as interesting candidates for structure-activity relationships of cannabinoid receptor agonists. Both groups prepared the azaindole nucleus by BIS-type cyclization from the appropriate chloronitropyridine with excess vinylmagnesium bromide.

Giblin[135] then used chlorine as well as Regueiro-Ren[134] used bromine, that is as a way for functionalization of the 7-position (cfr compounds **55** and **56**, Schemes 38 and 39, respectively). On the other hand, Blaazer's group[136] used chlorine as promoter of the cyclization partially modifying the procedure of Wang[81] (cfr Schemes 7 and 40).

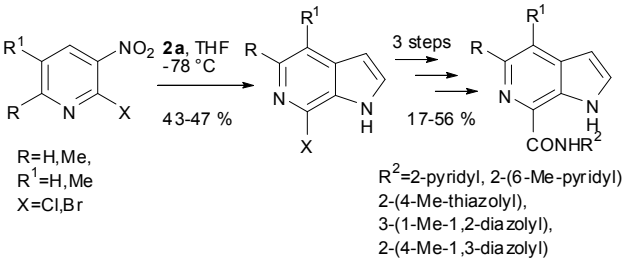
In section 4, we mentioned indolocarbazoles as possible anticancer drugs (see for instance scheme 31), thus 3-(azaindolyl)-4-arylmaleimides were prepared with the aim of testing them for treatment of certain tumours. In particular 6-azaindole derivatives were proepared from BIS-like reaction through a reaction pathway surmising the synthesis of 6-azaindole reported in Scheme 40.[137] The only significant difference is the removal of chlorine atom with palladium on charcoal in a basic medium.




**Scheme 39** Synthesis of azaindole derivatives for SAR of cannabinoid receptor agonist[135]



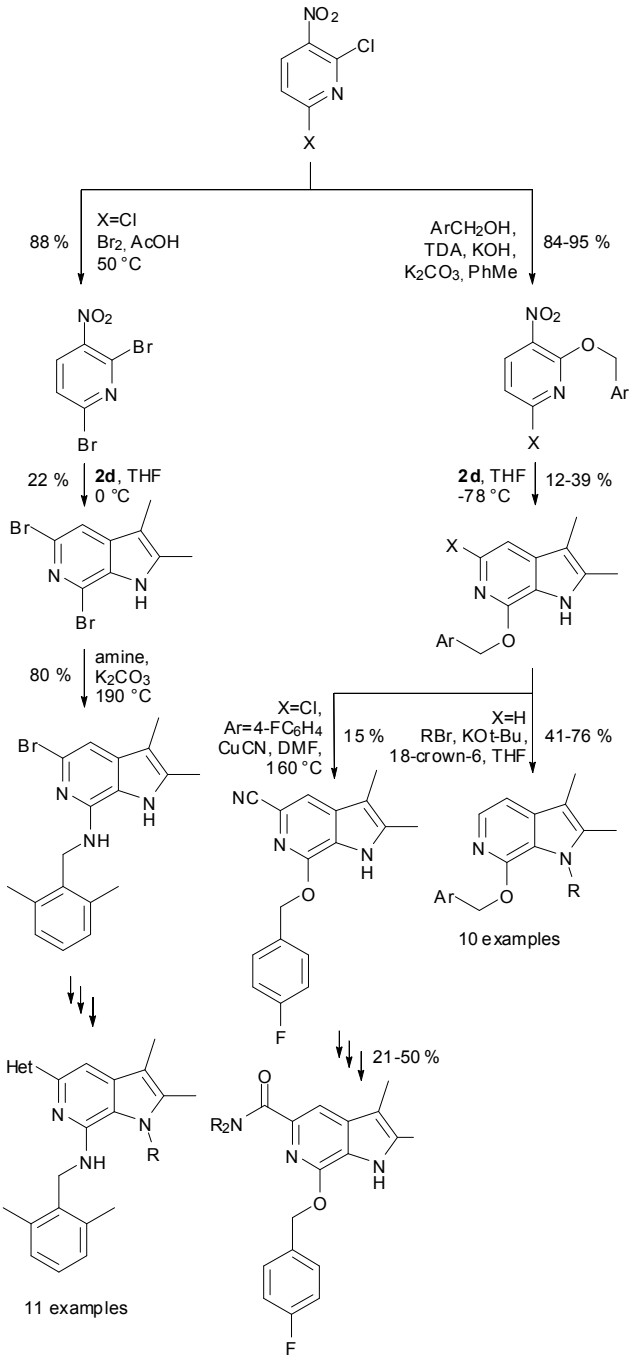

**Scheme 40** Synthesis of azaindole derivatives for SAR of cannabinoid receptor agonist[136]




**Scheme 41** Synthesis of 6-azaindole-7-carboxamides[138]

6-Azaindole-7-carboxamides constitute allosteric metabotropic glutamate receptor (mGluR5) antagonists. [138] The different 7-

substitutents modify the physico-chemical parameters for optimization of the aqueous solubility, without affecting high *in vitro* potency. The complete series of 2,3-unsubstituted azaindoles were obtained by BIS-type reaction (Scheme 41), whereas 2-substituted azaindoles were obtained by copper catalysed cyclization of alkynylaminopyridines.

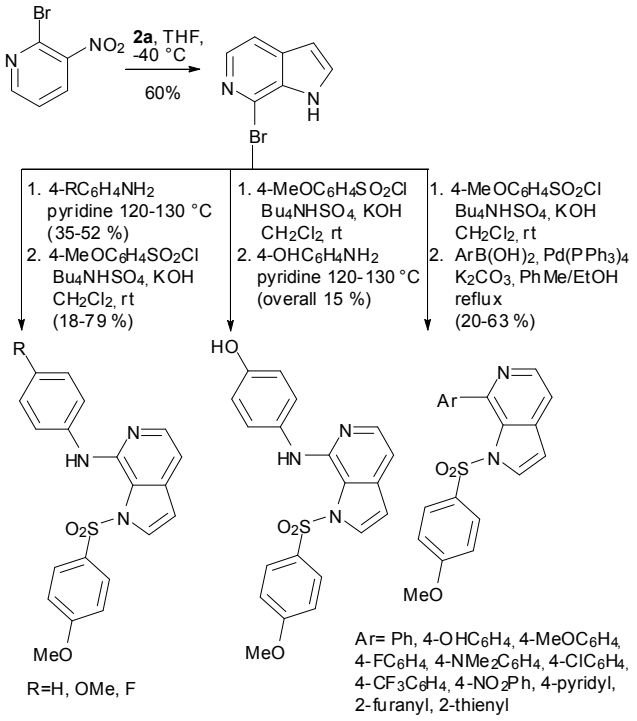



**Scheme 42** Synthesis of 6-azaindoles as APAs Panchal's procedure on the left;[139] Kim's on the right [140]

7-Amino- and 7-alkoxy-6-azaindole are candidates for clinical use as acid pump antagonists (APAs) also known as potassium-competitive acid blockers (pCABs). Recently, two different SAR evaluation of these compounds appeared in the literature (Scheme 42).[139, 140] In particular, Panchal and co-workers transformed 2,6-dichloro- into 2,6-dibromo-3-nitropyridine, then built the indole-like nucleus by BIS and finally substituted the halogens with formation of 7-amino derivatives.[139] On the other hand, Kim and co-workers introduced the alkoxy substituent before cyclization and uses dichloropyridine without any halogen exchange and finally synthesized 7-alkoxy-6-azaindoles.[140]

Both reactions employed 1-methyl-1-propenylmagnesium bromide (**2d**) as the Grignard reagents and, remarkably, they represent two of the few examples of preparation of 2,3-disubstituted indole-like nuclei. The selective removal of the halogen atoms in the 2- and 6-positions in both reactions is also worth of note (Scheme 42).

Very recently, 7-anilino- and 7-aryl-6-azaindole-1-benzene-sulfonamides were found to exhibit potent anticancer activity against some cancer cell lines. The synthetic route to these compounds starts from 2-bromo-3-nitropyridine under BIS conditions (Scheme 43).[141]




**Scheme 43** Synthesis of azaindoles with anticancer properties[141]

Then reaction with various anilines in the presence of pyridine gave 7-anilino-6-azaindoles, whereas treatment with various phenylboronic acids under conditions of the Suzuki reaction yielded 7-aryl-6-azaindoles.

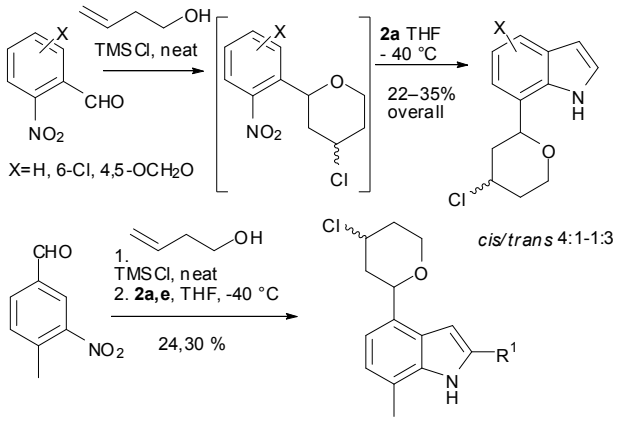
Finally, Sperry and Lindsay prepared marinoquinolines C and E (figure 1), from 2-chloro-3-nitroquinoline by Bartoli indolization and Suzuki coupling between 2-chloropyrroloquinoline and two different boronates.[142] Authors claimed their reaction as the first example of BIS on nitroquinoline, but other examples were reported as mentioned in section 2.[47, 78]

## 6. Miscellaneous

At the end of section 3, we affirmed that 7-bromoindole is the

starting material of 7-formyl-,[63] and 7-amino-indole.[111] All these indole derivatives are in turn starting materials for interesting and more complex molecules. Moreover, in section 2, we already reported that 7-formyl indole can also be obtained from protected 2-nitrobenzaldehyde.[63]

Recently, Fache and co-workers utilized 2-nitrobenzaldehyde in an alternative manner. In fact, they prepared new indole derivatives, combining Prins cyclization and Bartoli indolization in one-step procedure (Scheme 44).[143] Actually, Prins cyclization, modifying the aldehyde moiety, allows BIS reaction. The THP-indoles, thus obtained, are free from heavy metal and therefore suitable for drug preparation.

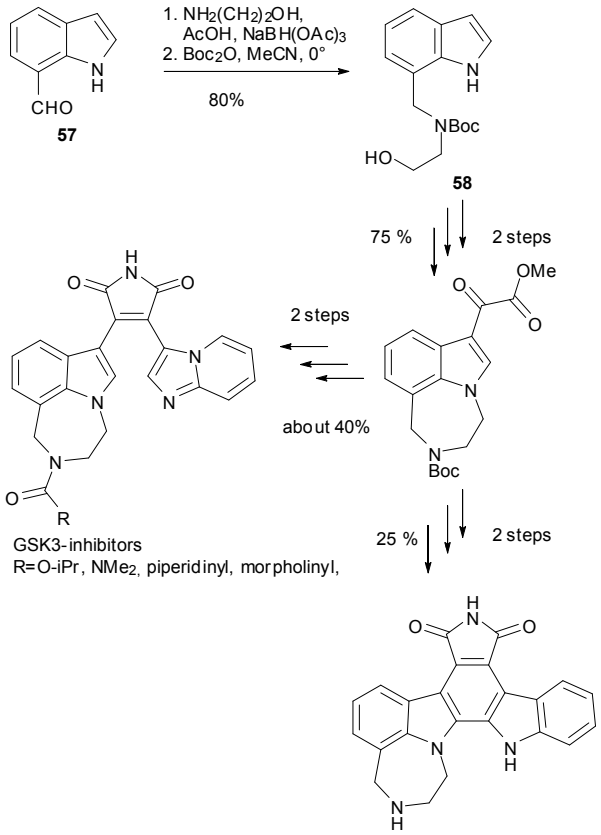



**Scheme 44** Prins cyclization-BIS sequence[143]

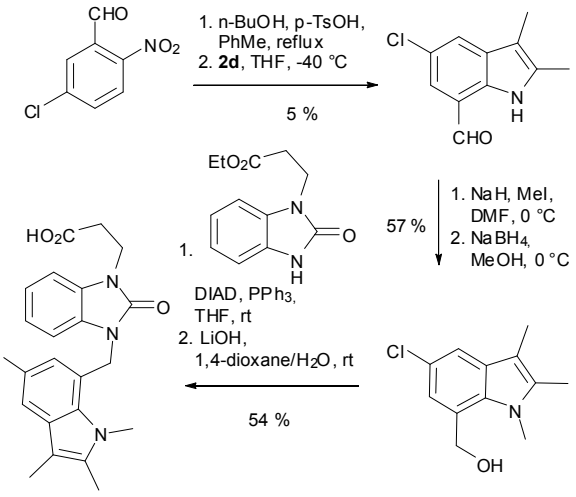
Aza-1,7-annulated indoles are the key structure of a class of orally available and efficacious glycogen synthase kinase-3 (GSK3) inhibitors.[144] They would be expected to have some of the same effects as insulin, such as ability to activate glycogen synthase and to stimulate the conversion of glucose to glycogen, thereby lowering plasma glucose. In other words, they are very attractive targets for the potential treatment of non-insulin-dependent diabetes mellitus. The synthesis of GSK3 inhibitors starts from 7-formylindole prepared by BIS.[144] The treatment of 7-formyl indoles with ethanolamine under reductive amination conditions followed by protection of the resulting secondary amine with Boc gives alcohol **58** (Scheme 45). Further steps for the synthesis of the maleidoimide derivative are very close to those reported in Scheme 31. GSK3 inhibitors are then prepared by incorporation of a variety of acyl groups on the diazepino nitrogen atom.[144] The synthesis of 5-fluoro-7-formylindole from the corresponding protected nitrobenzaldehyde has also been reported in 52% yield in this paper.

The same synthetic route is also applied to the synthesis of 1,7-annulated indolocarbazoles by reaction of 3-indolylacetamide followed by cyclization with palladium acetate (Scheme 45). Always starting from 7-formylindole, other indolocarbazoles with different 1,7-ring size were prepared.[145]

Lo's group recently reported a new class of chymase (a chymotrypsin-like serine protease) inhibitors featuring a benzimidazolone core with an acid side chain and a hydrophobic moiety. In particular, the hydrophobic moiety could be represented by an indole framework.[146] The general synthesis of this indole starts from 3-chloro-5-nitrobenzaldehyde, followed by acetal formation with n-butanol and BIS with 1-methyl-1-propenylmagnesium bromide (another example of 2,3-disubstituted indole). Methylation of the indole followed by reduction of the aldehyde provided 1,2,3-trimethylindole, which in turn was coupled to the benzimidazolone core (Scheme 46). Other indoles (8 examples) were prepared similarly, starting from the appropriate nitrobenzaldehyde, but yields are not reported.



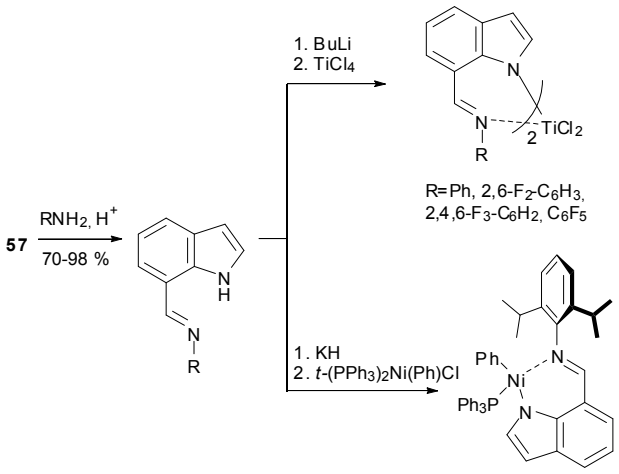

**Scheme 45** synthesis of GSK3 inhibitors[144] and indolocarbazoles[145]



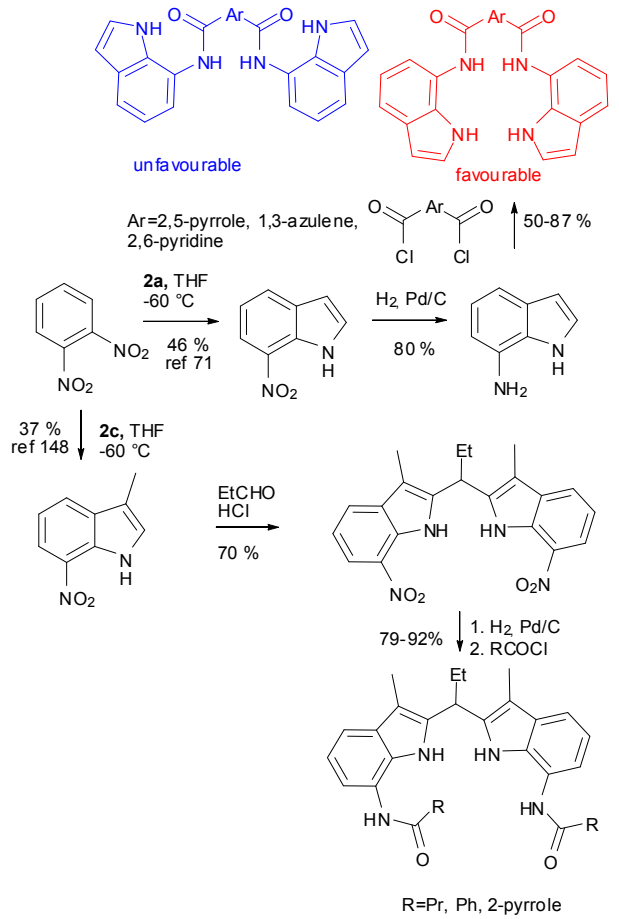

**Scheme 46** Synthesis of chymase inhibitors with indole as the hydrophobic moiety[146]

7-Formylindole is also the staring material for the synthesis of indolide-imine chelate ligands for living ethylene polymerization (Scheme 47). Both nickel [147] and titanium [148, 149] are used as the

chelate metal.



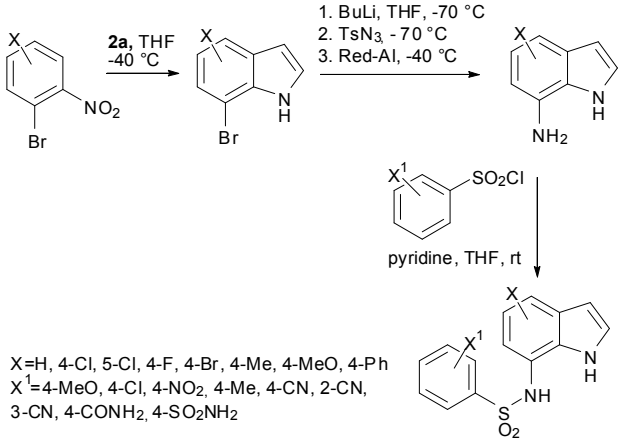

**Scheme 47** Synthesis of indolide-imine nickel[147] and titanium[148, 149] chelate ligands




**Scheme 48** 7-Aminoindole derivatives as anion receptors[71,150]

Differently from Schiff base indole derivatives described in scheme 47 that are cation receptors, 7-aminoindole derivatives are interesting alternative to aniline for the construction of anion receptors.[71] Introduction of indole NH as an additional binding site can improve anion binding in the presence of favourable ligand preorganization and in the absence of strong intramolecular hydrogen bonds. The synthesis of 7-aminoindole was carried out from 1,2-dinitrobenzene (Scheme 48). The occurrence of BIS on dinitroarenes has to be underlined (see also section 2). The same research group also provided anion receptors based on 7,7′-diamido-2,2′-diindolylmethane by using the same reaction to prepare 7-amino-3-methylindole.[150, 151]

This procedure represents a valuable alternative synthesis of 7-amino indole with respect to that proposed by Owa,[111] which starts from already prepared 7-bromoindole, via metallation, azide substitution and finally reduction. In fact, from nitrobenzene to 7-aminoindole, Jurczak's method is a two-steps procedure,[148] while Owa's reaction is a four-steps one.[111] Unfortunately, we cannot compare the efficiency of the two methods, because Owa did not report the yield of his procedure. We can only surmise a higher efficiency of the shortest method. Owa used its procedure for the synthesis of a series of antitumor sulphonamides by coupling 7-aminoindoles with a variety of substituted benzenesulfonyl chlorides (Scheme 49).[152]




**Scheme 49** Synthesis of antitumor sulfonamides[152]

## 7. Conclusions

In conclusion, the difficulty of classical indolization in preparing 7-substituted indoles and the easy scaling-up make BIS the reaction of choice for the synthesis of 7-substituted indoles.

Moreover, the conciseness of this reaction, the high chemoselectivity of the Grignard reagents towards the nitroarene moiety, the tolerance to most electrophilic functions on the benzene ring, the generality towards different nitro aromatic compounds, the synthesis of indoles on solid support outweigh the moderate yields, the substrate dependency and the often no clear reactivity trend.

The reaction usefulness is also demonstrated by the interest showed by the pharmaceutical industry.[129-131, 153]

Generally, simple vinylmagnesium bromide is used, but substituted alkenyl Grignard reagents can also be applied, and afford the corresponding indoles with substituents at the C-2 and C-3 positions. The combination of these results with the possibility of using the bromine or chlorine atoms as labile protecting groups makes the BIS a very easy strategy for the construction of the indole backbone featuring substituents in all positions.

Other efficient preparation of 7-substituted indoles such as Larock[154] and Leimgruber–Batcho indole syntheses[83] suffer from the use of transition metal catalyst. The purification of indoles for

drug use from these reactions needs microfiltration procedures to eliminate traces of the potentially toxic metal catalyst. Moreover, starting materials of these reaction are often less easily available than *ortho*-substituted nitrobenzenes.

Finally, in the recent years the commercial availability of many 7-substituted indoles has reduced but not eliminated papers that mention BIS as the reaction of choice for preparation of these compounds.

## 8. Abbreviations

| | |
|---|---|
| AIBN | azobisisobutyronitrile |
| Bn | benzyl |
| Boc | t-butoxycarbonyl |
| dba | benzylideneacetone |
| Cy | cyclohexyl |
| DIAD | Diisopropyl azodicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| HMDS | hexamethyldisilazane |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| MOM | methoxymethyl |
| NBS | *N*-bromosuccinimide |
| Pg | Protecting group |
| rt | room temperature |
| SAR | structure activity relationship |
| TBS | *t*-butyldimethylsilyl |
| TDA | 4-methylbenzene-1,3-diamine |
| Tf | trifluoromethanesulphonyl |
| THP | tetrahydropyranyl |

## 9. Notes and References

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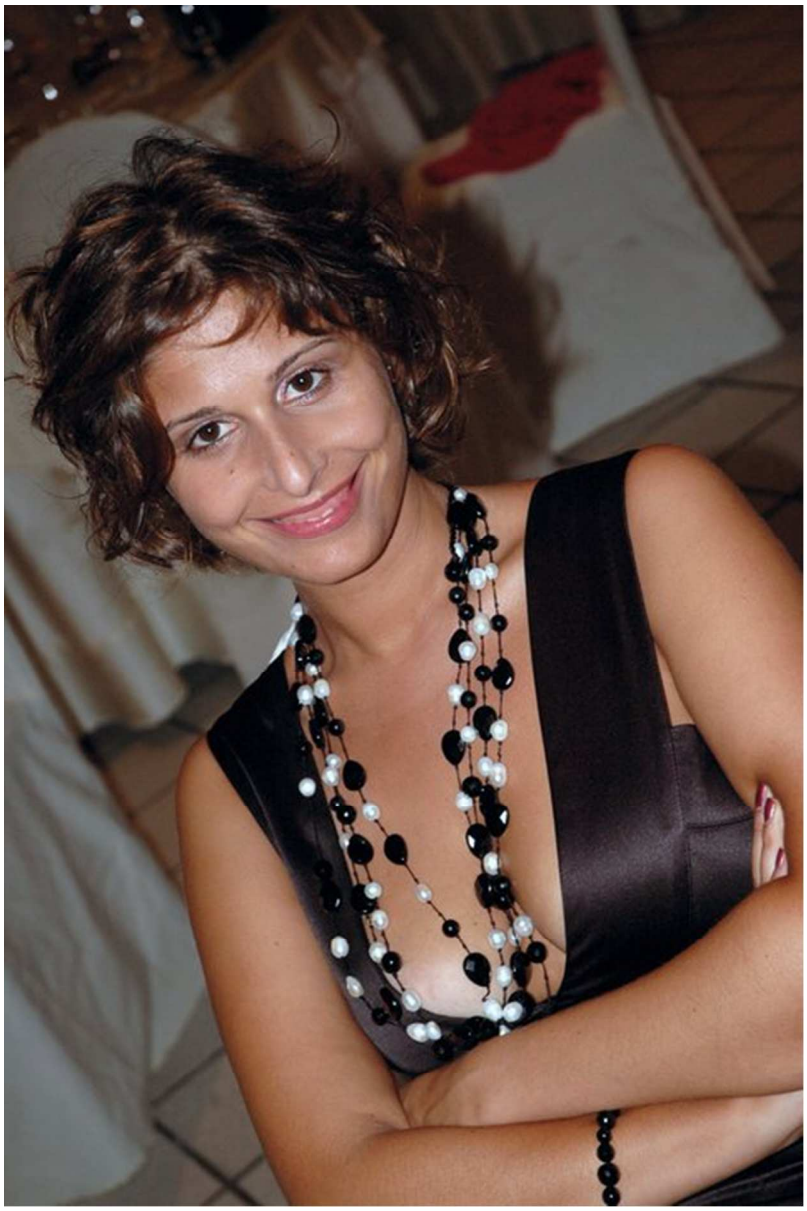

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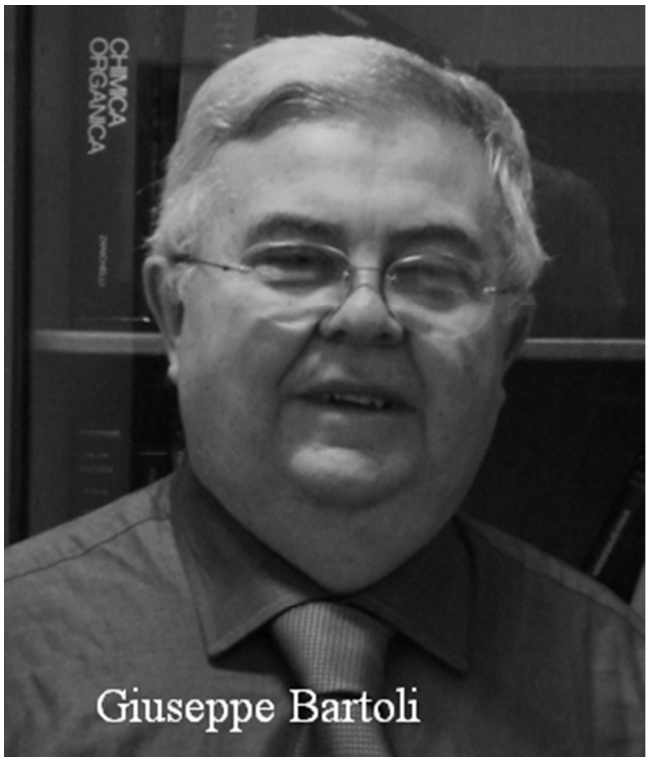


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**Renato Dalpozzo** was born in 1957. He graduated from the University of Bologna in 1981, with a Laurea in Industrial Chemistry under the supervision of professor Bartoli. He was Researcher of Organic Chemistry at University of Bologna since 1983. In 1992, he moved to the University of Calabria as Associate Professor and then as Full Professor of Environmental and Cultural Heritage Chemistry and now of Organic Chemistry. His research interests include studies on the reactivity of organometallic compounds with aromatic systems, the use of dianions derived from enamino carbonyl compounds, the stereoselective reduction of various classes of ketones, the development of new Lewis acid systems, the chemistry of mimicry of social insects, and the enantioselective organocatalysis.

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# Application of Bartoli Indole Synthesis

**Giuseppe Bartoli,[a] Renato Dalpozzo*[b] and Monica Nardi[b]**

Bartoli Indole Synthesis is the reaction of choice for the synthesis of many biologically interesting 7-substituted indoles.


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