Bartoli Indole Synthesis

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Abstract: Due to the potent biological activity exhibited by various indole derivatives, there is a continuous demand for novel synthetic procedures in this area. In 1989, the reaction of vinyl magnesium halides with *ortho*-substituted nitroarenes was discovered to lead to indoles. In the 1990s, it has attracted much attention, as it employs simple and readily available starting materials. This reaction is now frequently reported as the "Bartoli reaction" or the "Bartoli indole synthesis" and has rapidly become the shortest and most flexible route to 7-substituted indoles, as 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.

The necessity of an *ortho*-substituent on the aromatic ring is the limit of the Bartoli indole synthesis, because *o,o'*-unsubstituted nitroarenes follow a completely different pathway when reacting with vinyl Grignard reagents. Bromine, however, should be a transient group, which can enforce the sigmatropic rearrangement, as requested by the mechanism, and is easily removed. A combination of the two methodologies can give a significant reduction of 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.

This review will focus both the use of the Bartoli indole synthesis as key step in many preparation of complex indoles and the improvements of the reaction.

1. INTRODUCTION

Indoles [1] are a pervasive class of compounds found in abundance in biologically active compounds such as pharmaceuticals, agrochemicals and alkaloids. Indole myriad derivatives have, therefore, captured the attention of organic synthetic chemists. Medicine and biochemistry are also interested in many aspects of the indole chemistry.

Since the first synthesis of indole in 1866 [2], a number of synthetic methods for the construction of the indole nucleus have been devised: still today, the most famous are the Fischer [3], Bischler [4], Hinsberg [5], Reissert [6], Nenitzescu [7] and Madelung ones [8], which date from the late 19th to the beginning of 20th centuries and all employ drastic conditions.

The substituted indole nucleus is prevalent in natural products: the availability of the starting materials and the compatibility with the reaction conditions dictate the choice of the appropriate synthesis for a target molecule [9]. Several factors account for the current interest in new original syntheses of the indole ring. Therefore, a large number of new original syntheses or modifications and applications of known methods continue to be reported [10]. The functionalization of the indole ring could be considered an alternative to the *de novo* construction, although regioselectivity remains a challenging synthetic problem. [11]. Among others, 7-functionalised indoles are starting materials for biologically important compounds and drugs and few methods are reported to obtain them, both by *de novo* construction and by functionalization of the indole ring [12].

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2. THE REACTION OF CARBANIONS AND NITROARENES

2.1 Reaction Survey

Due to its electron withdrawing effect, in nitroarenes, the nitro group activates *ortho* and *para* positions for the addition of nucleophilic reagents. The first step of the reaction is the formation of an σ−adduct in these positions and, when a leaving group is located there, the well-known process of nucleophilic aromatic substitution (S_NAr) can occur [13]. This reaction is generally limited to non-carbon nucleophiles, whereas carbanions give unstable intermediates.

The seventies and eighties of the 20th century were the years when the longstanding problem of the reaction of nitroarenes and organometallic reagents was finally understood. The course of the reaction, in fact, depends strongly upon the nature of the carbanionic moiety in the organometallic species.

For example, Makosza introduced and rationalized the vicarious nucleophilic substitution (VNS) of hydrogen in electrophilic arenes by stabilized carbanions (Scheme **1**) [14].

The process is of general character, practically any carbanion (**2**) containing a leaving group X and a carbanion-stabilizing group Y can undergo VNS. The reaction is not limited to nitrobenzene, but can be also applied to substituted benzenes, aromatic heterocycles, naphthalenes etc.

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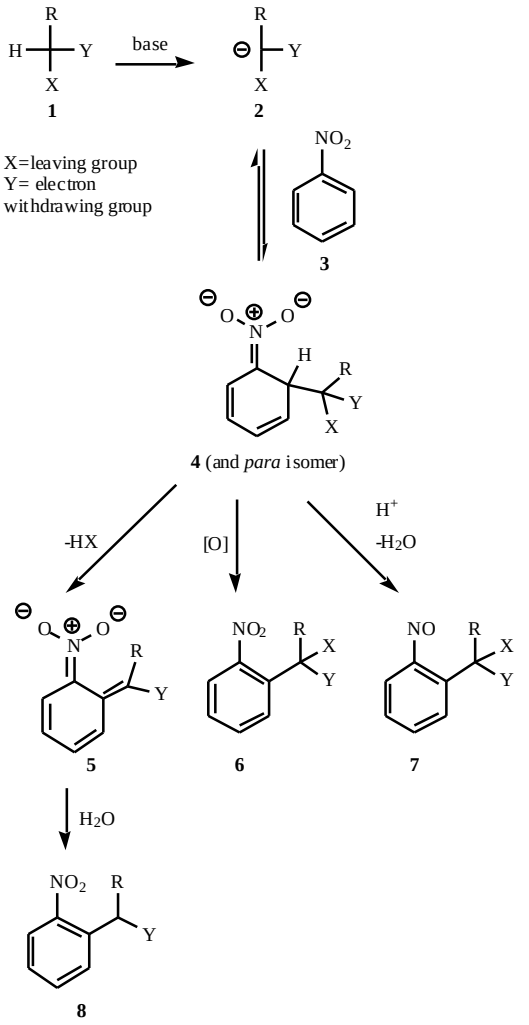


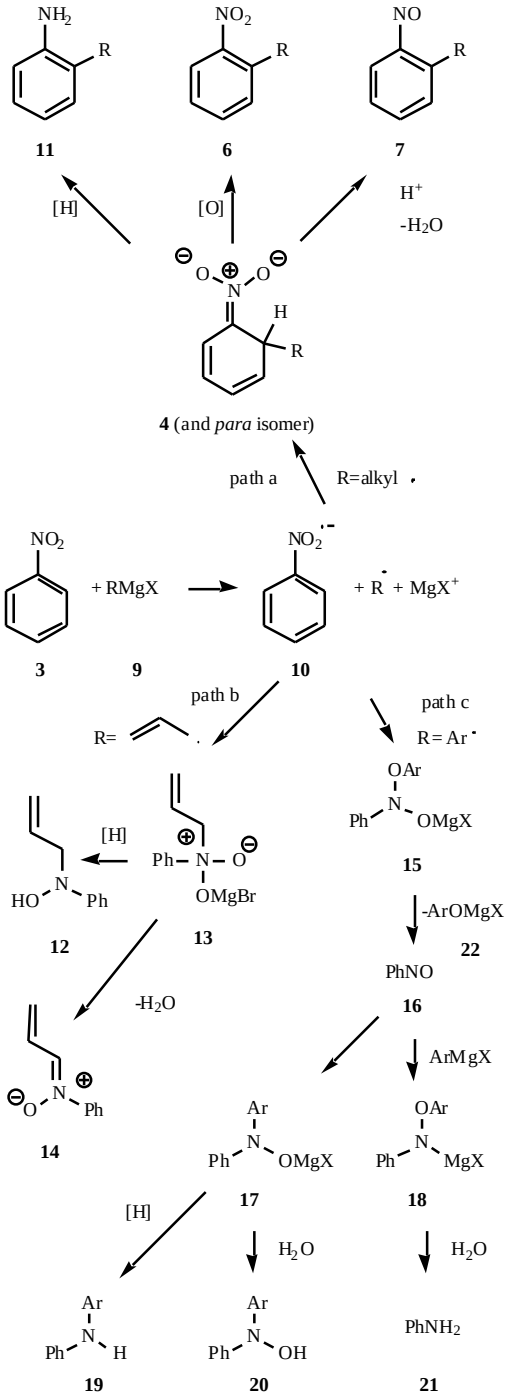
Scheme 1.

Also non-benzenoid aromatics, which exhibit electrophilic character *per se*, can undergo VNS. Usually VNS proceeds faster at the unsubstituted position than the conventional S_NAr of halogen located at reactive positions, so they survive the reaction conditions and prevent attack at the substituted positions. The reaction mechanism of the VNS is clearly a polar pathway that proceeds through the reversible addition of carbanions to the nitroarene, followed by the irreversible β-elimination of HX, oxidation or dehydration. Polar effects and solvation play fundamental roles in influencing orientation, as well as bulkiness of nucleophile and the steric environment of the ring reactive positions.

Independently and complementarily, we were able to transform once poorly known or misinterpreted procedures upon Grignard reagents into a series of rational pathways [15]. As VNS, also this reaction can be applied to all nitroaromatics [16].

Functionalities, reactive towards Grignard reagents such as esters, ketones and nitriles, are unaffected and when, located at reactive positions, prevent attack at these positions [17].

We discovered, however, an important different feature from VNS: the first interaction between nitroarene and Grignard reagents is a single electron transfer (SET) [18], leading to nitroarene radical anions and alkyl radicals. The shape of the alkyl radical [19] influences the attack to the radical centers of the radical anion (Scheme **2**): simple alkyl radicals, which are pyramidal, [19] bind to the reactive ring positions, leading to an adduct very similar to that of VNS, which can undergo reduction to alkylanilines (**11**), [20]



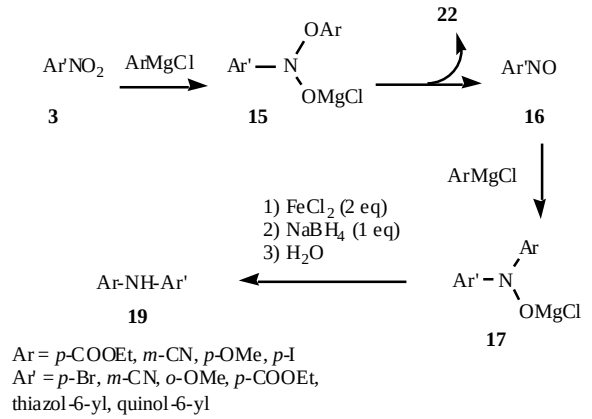
Scheme 2.

oxidation to alkylnitroarenes (**6**), [15] or dehydration to alkylnitrosoarenes (**7**) (path a) [15]. Allyl radicals, which are planar [19], exclusively link to the nitrogen atom giving tetrahedral intermediates which can then be reduced to allylhydroxylamines (**12**) or dehydrated to nitrones (**14**) (path b) [21]. Since the attack occurs at the nitrogen atom, this reaction can be extended to every nitro compound [22]. The same pathway is followed by a planar alkyl radical such as the *t*-butyl radical.

In fact, the reaction of *t*-butylmagnesium chloride with 1,4-dinitrobenzene led to exclusive 1,2-attack with C-N bond formation [23].

No firm mechanistic conclusions were made for aryl derivatives. In fact, we were unable to set up the best conditions for isolation of the final products. Literature data reported formation of a complex mixture of anilines, hydroxylamines and diarylamines [24]. In a fashion of a SET mechanism, aryl radicals, whose shape is different from both alkyl and allyl radicals, can be supposed to attack at the oxygen atom of the nitro group, leading to a nitroso derivative **16**, which, in turn, undergoes 1,2-attack on the nitrogen atom (path c).

Recently Knochel succeeded to prepare highly functionalized diarylamines from many functionalized aryl Grignards and nitroarenes (Scheme **3**), by reduction of the unstable intermediate **17** with $FeCl_2/NaBH_4$ [25].



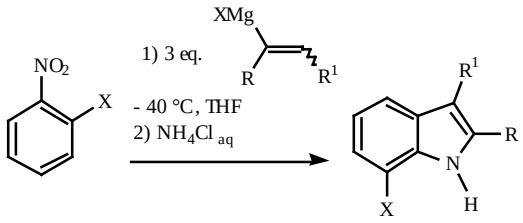
Scheme 3.

From these studies, the first equivalent of Grignard reagent was confirmed to add at the oxygen atom, producing an arylnitroso derivative **16**. The second equivalent of Grignard reagent leads to the air-sensitive diarylhydroxylamine **17**, which is converted into a stable diarylamine **19** by reduction. This hypothesis is supported by Knochel's observation that ArNHAr derivatives were never found. Such products should appear if C-N bond formation takes place in the 1,2-addition to the nitroarene **3**. Finally, arylnitroso derivatives **16** furnish the expected diarylamines **19;** the reaction needs two equivalents of aryl Grignard reagent and the phenoxide derivative **22** is always recovered.

2.2 Synthesis of Indoles

The reactions described in the previous paragraph could be all applied, in principle, to the synthesis of indoles. Actually, the indole nucleus can be built by VNS from derivatives of *m*-nitroaniline, from reductive cyclization of *o*-nitrobenzylic compounds *via* interaction of the nitro group with *o*-carbon substituents and it has already been reviewed [26].

Table 1. Reaction of vinyl Grignard reagents with *o*-substituted nitrobenzenes.



R	R^1	X in nitroarene	Indole Yield (%)
H	H	2-Me	67[a]
H	H	2-Me	71[b]
H	H	2-Me	58[b,c]
H	H	2-Br	62[a]
H	H	2-F	42[a]
H	H	2-Cl	63[a]
H	H	2-TMSO	41[a]
H	H	2-BnO	13[d]
H	H	2-Ph_2CHO	57[d]
H	H	2-(9-anthracenemethoxy)	53[d]
H	H	2-trityloxy	62[d]
H	H	2-BnO, 4-Cl	31[d]
H	H	2-Ph_2CHO, 4-Cl	50[d]
H	H	2-BnO, 4-CF_3	40[d]
H	H	2-Ph_2CHO, 4-CF_3	54[d]
H	H	2,4-BnO	10[d]
H	H	2-BnO, 4-CO_2Me	20[d]
H	H	2-CF_3	56[b]
H	H	2,5-dibromo	69[b]
H	Ph	2-Cl	47[e]
H	Me	2-Me	35[e]
H	Me	2-Cl	38[e]
Me	H	2-Me	76[e]
Me	Me	2-Me	73[b]
$(CH_2)_3$		2-Me	49[b]
$(CH_2)_4$		2-Me	47[b]
$(CH_2)_5$		2-Me	41[b]

[a] See ref. 27. [b] See ref. 33. [c] Using vinylmagnesium chloride instead of bromide. [c] See ref. 34. [d] See ref. 29.

In 1989, [27], we discovered that the reaction of vinyl magnesium halides with *ortho*-substituted nitroarenes leads to indoles (Table **1**).

The reaction can be applied to nitronaphthalenes and nitroheterocycles, as well (Table **2**) [27].

Table 2. Reaction of 3 equivalents of vinylmagnesium bromide with nitronaphthalenes and nitroheterocycles in THF at – 40 °C.

Nitroarene	Indole Yield (%)
1-nitronaphthalene	53[a]
5-nitroacenaphthene	59[a]
5-nitroquinoline	42[a]
5-nitroisoquinoline	35[b]

[a]See ref. 27[a] See ref. 28a

Table 3. Reaction of 3 equivalents of vinyl Grignard reagents with nitroarenes having unsubstituted *ortho* positions in THF at – 40 °C.

R	R^1	Nitroarene	Indole Yield (%)
H	H	3-chloronitrobenzene	19[a]
H	H	4-nitrotoluene	15[b]
H	H	4-chloronitrobenzene	17[a]
H	Me	4-chloronitrobenzene	11[b]
H	H	4-bromonitrobenzene	12[a]
H	H	2-nitronaphthalene	17[a]
H	H	6-nitroquinoline	Low[c]
H	H	8-nitroquinoline	0[c]
H	H	3-(trifluoromethyl)-nitrobenzene	0[d]
H	H	4-(trifluoromethyl)-nitrobenzene	0[d]
H	H	3-(trifluoromethyl)-4-methylnitrobenzene	36[d]
H	H	3-bromo-4-methylnitrobenzene	34[d]

[a] See ref. 27. [b] See ref. 29. [c] See ref. 28b. [d] See ref. 33.

Meta- and *para*-substituted nitroarenes as well as nitronaphthalenes and nitroheterocycles without *peri* hindrance give poor yields of indole and often anilines are the main product (Table **3**) [28].

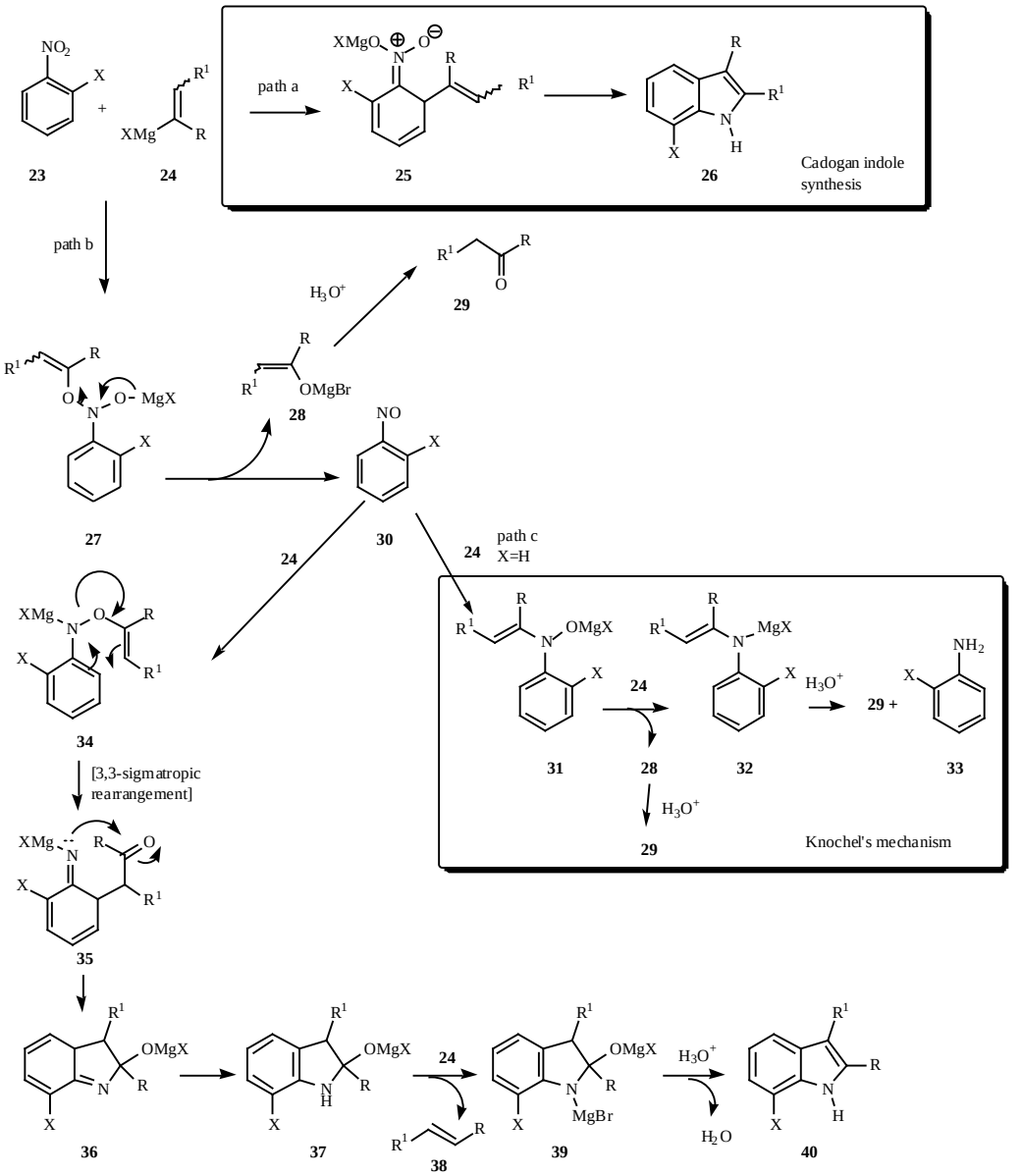
In the 1990s, much attention has been paid to this indole synthesis, as it employs simple and readily available starting materials.

This reaction is now frequently reported as the "Bartoli reaction" or the "Bartoli indole synthesis" and has rapidly become the shortest and most flexible way to 7-functionalised indoles.

This review aims to give an overview both of the use of the Bartoli indole synthesis as key step in many preparations of complex indoles and of the improvements of the reaction.

2.3 Mechanism of the Reaction

Reaction mechanism was studied in detail to clearly rationalize the observed results (Scheme **4**) [29]. Firstly the



Scheme 4.

stoichiometry of the reaction was investigated: a 3-fold excess is always required to obtain satisfactory yield and, together with indole (**40**), a carbonyl derivative (**29**) and an alkene (**38**) were always recovered. The presence of **29** clearly comes from an enolate derivative **28,** which arises from a reduction of the nitro derivative. Deuterium labeling experiments show only trace amounts of deuterium incorporation on **38**, demonstrating that it must be formed during the reaction course and does not arise from quenching. The fate of the Grignard reagent is now clear: the first equivalent is incorporated in the indole nucleus, a second reduces the nitro group somewhere in the reaction pathway, and the third reacts in an acid-base fashion elsewhere. The second oxygen atom of the nitro group must be lost as water, since it is not detected among the reaction products. Finally, carrying out the reaction in defect of Grignard reagent, trace amounts of nitrosoarenes (**30**) were detected.

These evidences can be easily rationalized into our proposed SET mechanism for the reaction of Grignard reagents and nitroarenes. The first interaction is an in-cage electron transfer from Grignard reagent to nitroarene. Vinyl radicals could behave like alkyl or aryl radicals, in other words, they can attack the ring or the oxygen atom. If the vinyl radical and the nitroarene radical anion collapse at the *ortho* position of the nitroarene ring (**25**) [18], the anionic carbon should occupy the 3-position of the indole nucleus. This pathway leads to a synthesis known as the Cadogan-Sundberg indole synthesis (Scheme **4**, path a) [30]. It was, however, ruled out by the experimental evidence that the anionic carbon is linked in the 2-position (see disposition of alkyl chains R and R^1 in Cadogan indole **26** and our indole **40**).

A vinyl radical is found by theory and experiment to be bent [19]. Its shape is very similar to aryl radicals, since the bond angle (137°) is compatible with an sp^2 geometry. Therefore, a 1,2-addition has to occur to give intermediates **27** (Scheme **4**, path b), according to aryl radical reactivity [25]. Intermediate **27** is then reduced by organomagnesium to nitrosoarenes (**30**). This reduction step accounts for enolate **28** formation.

The reaction of nitrosoarene **30** with two equivalents of **24** led to the expected indole, confirming that product **30** lies on the main reaction pathway [29,31].

It is reasonable to think that nitrosoarene is a better substrate than nitroarene to undergo SET. A second 1,2-addition of **24** to **30** should occur to give the *N*,*O*-disubstituted (**34**) and the *N*,*N*-disubstituted (**31**) hydroxylamino derivatives with a second SET step. The former attack resembles the early one, the latter follows the aryl pathway [24,25]. We think that, conversely from aryl derivatives, where the C-N bond formation is always favored, the bulkiness of the *ortho*-substituent influences this attack. Bulky substituents crowd the nitrogen atom addressing the Grignard reagent on the oxygen atom, favoring **34** which leads to indole. This hypothesis is supported by the observation that, in a SET mechanism, a collapse of a radical species is much more sensitive to steric hindrance that polar reactions [18]. Little or no substituents allow addition to the nitrogen atom leading to **31,** as aryl derivatives prevalently do [18,24,25]. Intermediate **31** can easily be reduced by a further equivalent of Grignard to the enamine salt (**32**), and finally hydrolyzed to aniline (**33**) and a carbonyl derivative (**29**). Finally, further evidence, which supports our hypothesis, is that indole and aniline yields are comparable for all the *para*-substituted nitroarenes, with preponderance of aniline, whereas indole yields increase with steric hindrance of the substituent in *ortho*-substituted nitroarenes (Table **1**) [29,32].

To yield indole, **34** must undergo [3,3]-sigmatropic rearrangement to **35,** followed by immediate cyclization to **36**, where the indole nucleus is now built. The addition of a third equivalent of Grignard reagent, in a acid-base reaction for removing the acidic proton bound to the nitrogen atom in the tautomer **37**, accounts for the equivalent of alkene found among the reaction products.

The proposed mechanism is in agreement with experimental evidences and reaction stoichiometry. It has not been rebutted by subsequent studies. For example, the observed lower yields with vinylmagnesium chloride instead of bromide (see Table **1**, entries 1-3) [33] although not rationalized, are not in contrast with the proposed mechanism.

3. IMPROVEMENTS

Since our discovery, Bartoli indole synthesis has attracted the attention of many organic and biological chemists, who have worked to improve the original reaction. This section collects these improvements.

3.1 Synthesis of Indole-7-Carbaldehyde and 7-Carbomethoxyindole (Gilmore's Modification)

7-Bromoindole (**42aa**) provides a convenient precursor to 7-formylindole and 7-carbomethoxyindole (Scheme **5**).

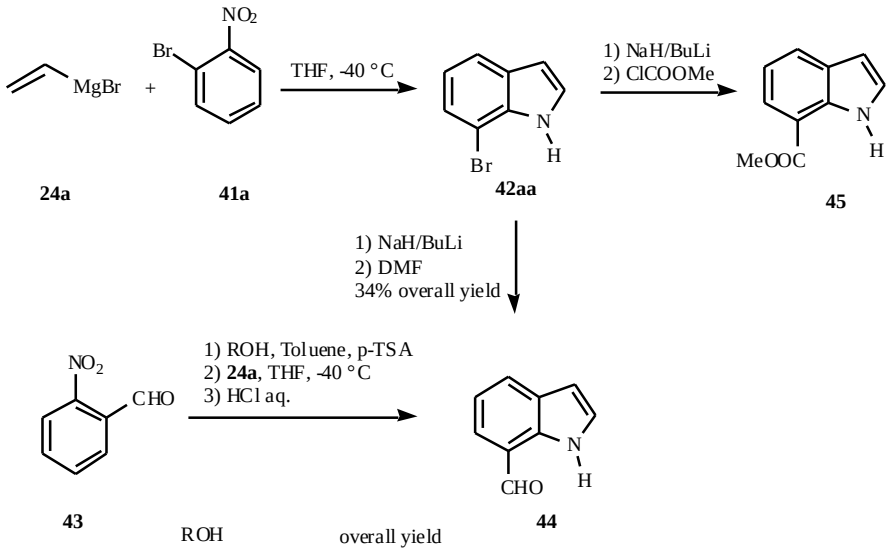
It can be metalated with sodium hydride / butyllithium and allowed to react either with DMF, as a formylating agent [34], or with methylchloroformate [35].

Although the two 2-step process is facile on a small scale, it is unsuitable for scale-up, due to need for purification of 7-bromoindole.

Owing to the high interest in the synthesis of 7-formylindole as a key intermediate for more complex structures, direct Bartoli synthesis on easily available 2-nitrobenzaldehyde was studied to give a solution to the problem [34]. A suitable protection of the aldehyde moiety is necessary, since it is the only electrophilic group which interferes with nitroarene moiety [17]. In order to improve yields, bulky protecting groups are needed (see section 2.3). Unsubstituted cyclic acetals are not sterically demanding enough, while 4-phenyl-2-(2-nitrophenyl)-1,3-dioxolane is difficult to form and problematic to deprotect. The best results were obtained with dibutyl acetal. The 3-step procedure can be performed without need for purification of the intermediates and provides 7-formylindole in 68% overall yield on a 70g-scale.

3.2 Synthesis of 7-Alkylindoles

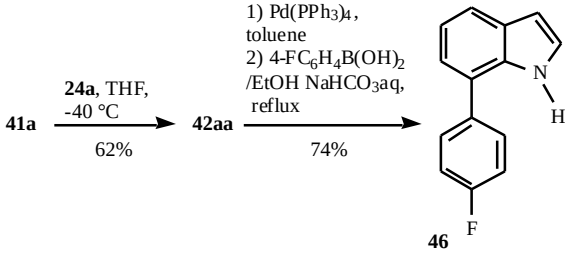
7-Alkylindoles are important as intermediates for natural products synthesis. Both the Heck and Suzuki reactions are the most commonly performed alkylation reactions on 7-bromoindole (**42aa**), pre-formed by Bartoli indole synthesis (see section 4).



ROH	overall yield
1,2-ethandiol	23%
1-phenyl-1,2-ethandiol	35%
methanol	44%
n-butanol	68%
n-pentanol	39%

Scheme 5.

For example, Suzuki cross-coupling on **42aa** is reported to be accomplished in 46% overall yields from 2-bromonitrobenzene to give 7-(4-fluorophenyl)indole (**46**) in a 10-20 grams scale (Scheme **6**) [36].

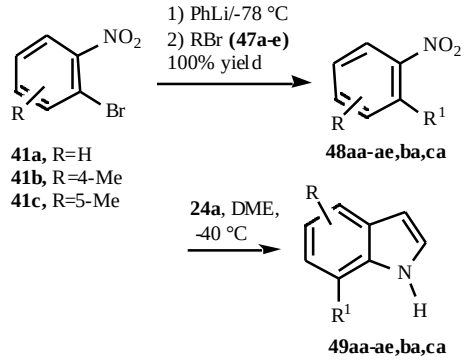


Scheme 6.

Recently, these procedures have been re-visited and it has been found that the Bartoli reaction carried out on 2-alkylnitrobenzenes leads to the target molecules with quite good efficiency.

With respect to the Heck and Suzuki procedures, this two-steps reaction starts from easily available alkylhalides and 2-bromonitrobenzene and it is more facilely performed (Scheme **7**, Table **4**) [37].

Improvements to our procedure was made to overcome heterogeneous mixtures at -40 °C, by using dimethoxyethane (DME) as solvent. Moreover, nitrobenzene was added to Grignard reagent to maintain the Grignard in excess throughout the reaction; [38] the excess was increased to 6-fold.



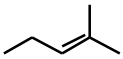
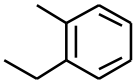
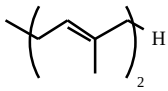
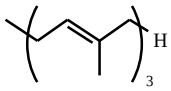
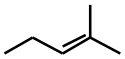
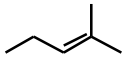
Scheme 7.

This fascinating procedure was then applied to a key intermediate in the total synthesis of demethylasterriquinone B1 (Figure **1**), a bis-indolylquinone isolated from a Congo fungus [39]. It was proved to be a specific agonist for the insulin receptor tyrosine kinase.

3.3 Synthesis of 7-Aminoindole [40]

Starting from 7-bromoindoles (**42**), an interesting three-step synthesis of 7-aminoindoles has been accomplished. It requires metallation of the 7-position with butyllithium, coupling with tosylazide *o*-diphenylphosphorazidate (DPPA) to give 7-azidoindole and finally reduction to 7-aminoindole with Red-Al (Scheme **8**). The procedure is selective for the 7-position and other halogen atoms are unaffected by metallation. Unfortunately, authors do not report yields of their interesting modification. Selective metallation at the 7-

Table 4. Synthesis of 7-Alkylindoles.

	R	R^1	Indole Yield (%)
49aa	H		50
49ab	H	$PhCH_2$	53
49ac	H		57
49ad	H		37
49ae	H		41
49ba	5-Me[a]		43
49ca	4-Me[a]		49

[a]It should be noted that a 4-substituent in the benzene ring assumes the 5-position in the indole nucleus and *vice versa*, owing to the nomenclature rules of the two compounds.

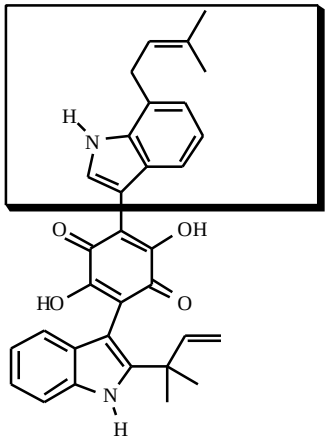
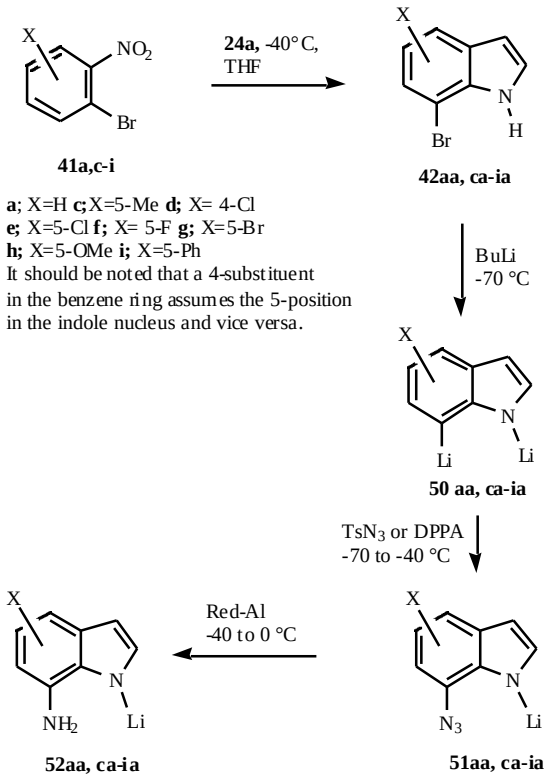


Fig. (1). Demetylasterriquinone B1 or l-783,281 or DAQ B1. Building block created with Bartoli indole synthesis is highlightened.

position was also confirmed by a further study on 4,7-dibromoindoles [41].

3.4 Synthesis of Azaindoles

In Table **2** some examples of construction of the indole nucleus on compound different from nitrobenzenes are summarized. Recently, these poor examples have been improved with a systematic study on nitropyridines (Table **5**), which provides a useful method for the synthesis of 4- and 5-azaheterocycles, offering simplicity and efficiency, if compared with other multi-step procedures for the same compounds [42].



Scheme 8.

Some peculiarities of this reaction should be underlined. Nitropyridines need lower temperatures than nitrobenzenes.

As well as indoles, azaindoles are the only recoverable products from the crude reaction and yields are comparable.

Consistent with previous observations, [27, 33,32] *ortho* bulky substituents increases the yields of cognate indole.

It should be noted, that the presence of a chlorine atom in a conjugated position with the nitro group increases the yields. A possible explanation may be an increased electrophilicity of the substrate toward the nucleophilic vinyl radical. This effect, however, should be exerted on the nitro group of every nitroarene, but the same pattern is not followed by simple nitroarenes (Table **1**). Therefore, to completely understand the influence of the chlorine atom in these substrates, an *ab initio* charge distribution map of the radical anion, including the ring nitrogen atom, should be calculated.

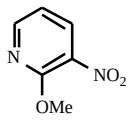
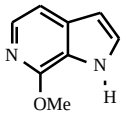
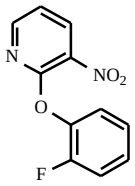
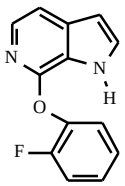
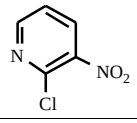
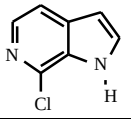
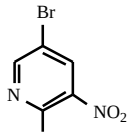
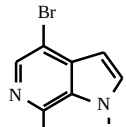
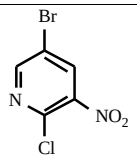
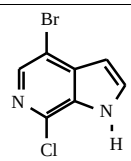
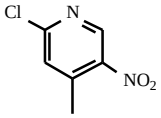
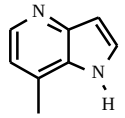
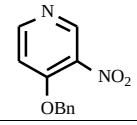
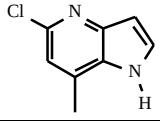
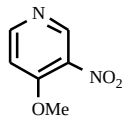
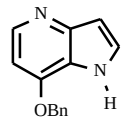
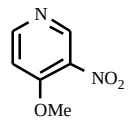
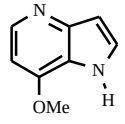
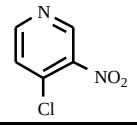
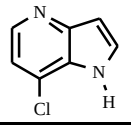
Nevertheless, the halogen atom has a fundamental synthetic value. In fact, it may be exploited as a promoting element, which can then be removed by raised-pressure hydrogenolysis (Scheme **9**).

The two-step procedure afforded azaindoles in better overall yields than the simple one-step procedure without a chlorine atom.

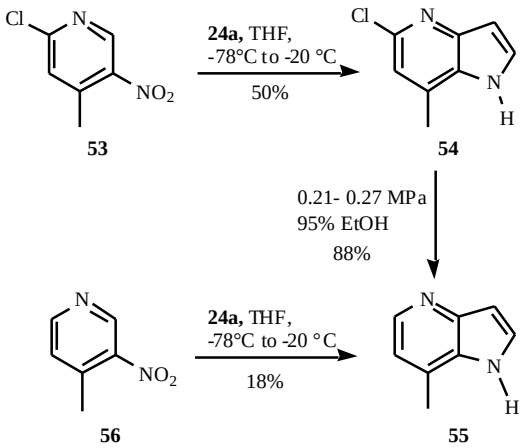
3.5 Indoles from Nitrosoarenes [31]

2-(Trimethylsilyl)-7-substituted indoles are a very interesting class of compounds. In fact, they are intermediates for indol-2-yl ketones, classical building blocks in the synthesis of indole alkaloids and can be used as masked indol-2-yl carbanions. However, the use of a three-

Table 5. Preparation of azaindoles from nitropyridines.

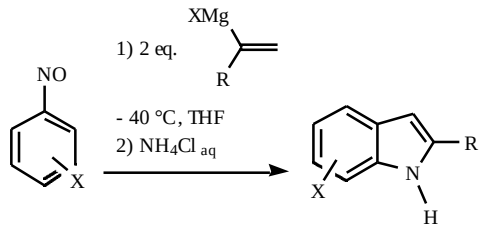
Pyridine	Azaindole	Yield (%)
		20
		35
		33
		22
		35
		18
		50
		25
		11
		30

fold excess of the expensive 1-(trimethylsilyl)-vinylmagnesium bromide should be reasonably avoided. Nitrosoarenes can overcome this drawback, since one equivalent of reagent is not destroyed to reduce the nitro to nitroso-derivative and only a two-fold excess of Grignard is needed. The same procedure can be extended to other expensive Grignard reagents to functionalize positions 2 and 3 of the indole nucleus. In this reaction, as in the synthesis of 7-alkylindoles, the best results are obtained when adding nitrosoarenes to the Grignard reagent solution, rather than the opposite way around (Table **6**).



Scheme 9.

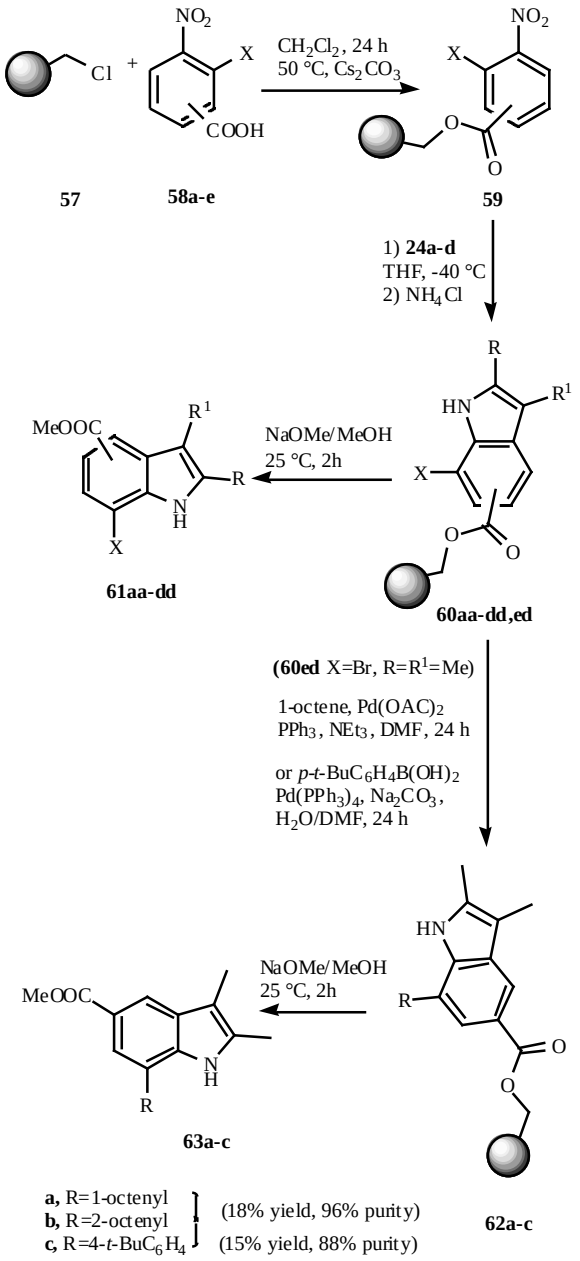
Table 6. Reaction of vinyl Grignard reagents with nitrosoarenes.



R	X	Solvent	Indole Yield (%)
Me	7-Cl	THF	32[a]
Me	7-Me	Et_2O	56[a]
Ph	7-Me	Bu_2O	48[b]
TMS	7-Me	Bu_2O	46[b]
TMS	7-Br	Bu_2O	42[b]
TMS	7-Cl	Bu_2O	50[b]
TMS	7-Et	Bu_2O	39[b]
TMS	5,7-dichloro	Bu_2O	42[b]
TMS	7-Me-5-PhO	Bu_2O	28[b]

[a] See ref. 29. [b] See ref. 31

Reactions were run out in dibutyl ether. Nitrosoarenes are highly reactive in an SET mechanism, therefore they need weakly polar solvents, which have high diffusion coefficients. They disfavor the escape of radical anions from the solvent cage, favoring indole formation over "out-of-cage" recombination, which lead to azoxy derivatives rather than 1,2-addition of the vinyl radical. It is well-known, in fact, that azoxy derivatives can arise from the coupling of two nitrosoarene radical anions [43] and azobenzenes from the reduction of the former compound by Grignard reagents [18].



Scheme 10.

3.6 Synthesis on Solid Support [44]

Bartoli indole synthesis was carried out on Merrifield resin. Nitrobenzenes were linked through an ester linkage; however, ester group cannot act both as linkage to the resin and crowding the nitro group, since unfortunately o*rtho*-nitrobenzoic acids give a premature cleavage from resin. Indoles were then cleaved from the resin as the methyl ester with 30% sodium methylate in methanol (Scheme **10**).

Indoles were obtained in high purity and moderate overall yields (Table **7**).

Some observations must be made on this useful modification of the Bartoli indole synthesis. The chemoselectivity of the attack at the nitro function in the presence of other reactive functions is confirmed [17]. The failure of the *ortho*-linkage is very likely due to the very close position of the two functionalities, so a subtle interplay between the two functions is very probable.

Table 7. Bartoli reaction on solid support.

Indole	X	Position of COOMe	R	R^1	Yield (%)	Purity (%)
61aa	H	5	H	H	15	82
61ab	H	5	Me	H	28[a]	14[b]
61ac	H	5	H	Me	32[a]	16[b]
61ad	H	5	Me	Me	13	88
61ba	Cl	4	H	H	15	94
61bb	Cl	4	Me	H	19	84
61bc	Cl	4	H	Me	11	98
61bd	Cl	4	Me	Me	37	96
61ca	Me	5	H	H	17	79
61cb	Me	5	Me	H	12	85
61cc	Me	5	H	Me	12	81
61cd	Me	5	Me	Me	13	90
61da	F	4	H	H	18	80
61db	F	4	Me	H	19	71
61dc	F	4	H	Me	20	81
61dd	F	4	Me	Me	14	97

[a] Combined yields [b] The main products were anilines

A nitro group in a position far from the resin is much more easily attainable and the Grignard reagent prefers to attack here, due to its higher reactivity.

Reduced products such azo and azoxy derivatives are suppressed, [44] however, in our opinion, the mechanism remains unchanged. Azo and azoxy derivatives arise from the coupling of two nitrosoarene radical anions (see section 3.5) [31]. Their coupling is very unlikely when they are linked to the resin and very probably far away from each other. The mechanism is indirectly confirmed by the failure of the reaction of allylmagnesium bromide [44]. This Grignard reagent give unstable tetrahedral intermediates (**13,** Scheme **2**, path b) [21] which dehydrate only when very stable nitrones are formed; otherwise, a reductive workup is needed.

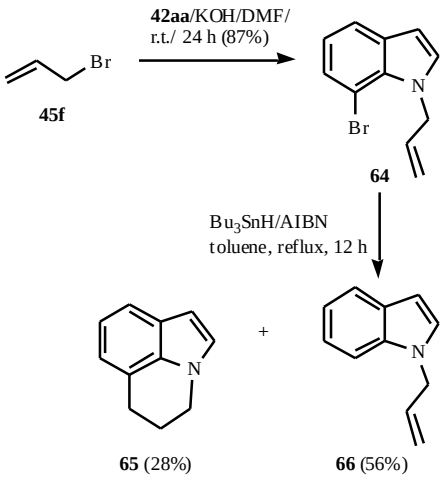
The most significant feature of this modification is that *o,o'*-unsubstituted nitroarenes are good substrates for certain Bartoli reactions. The reduction to the corresponding aniline was observed as a minor product when using 1-methylpropen-1-ylmagnesium bromide (**24d**), while it was the main product with propenyl Grignard (**24b**).

Finally both the Heck and Suzuki reactions can be performed on indole **60ed** still linked to the resin (Scheme **10**). These examples are very important, since they are often the cornerstone steps in many syntheses of naturally occurring indoles (see section 4).

3.7 Dobbs' Modification

To obtain 7-unsubstituted indoles by means of a Bartoli indole synthesis, the most important improvement is undoubtedly the modification proposed by Dobbs [45]. He worked for four years to realize this goal.

Working on radical reactions on the indole nucleus, interesting tricycloindolyl derivatives are generated by radical cyclization of *N*-alkylated or acylated indoles

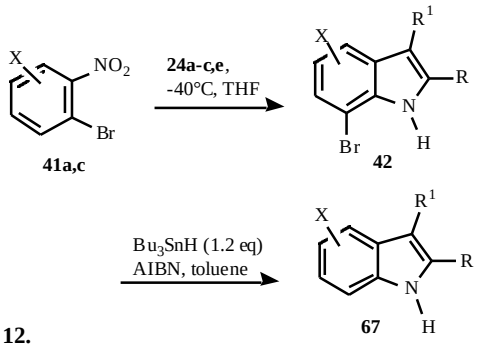


Scheme 11.

(Scheme **11**) [46]. However, rather than cyclization, considerable amounts of reduction of the indolyl radical are observed. For example *N*-allyl-7-bromoindole (**64**) gave debromination to **66** in larger amounts (56%) than the expected cyclization to **65** (28%).

Furthermore, *N*-propargyl and *N*-benzoyl-7-bromoindoles failed to cyclize and only debrominated derivatives were recovered in 18% and 53% yields respectively.

Dobbs described further examples of Bartoli synthesis, which are already summarized in Table **1** and **3**, [33] in order to improve yields of 7-unsubstituted indoles. Attempts to increase yields were unsuccessful, notwithstanding many modifications of the reaction conditions: *i.e.* reaction temperature, solvent, reaction times and electronic factors on the nitroarene ring, so these results cannot be considered a real improvement of the reaction but a simple extension. Moreover, heteroaryl Grignard reagents, such as thien-2yl and *N*-methylpyrrolidin-2-yl, are demonstrated to fail to give any fused indole, showing that these border-line Grignard reagents behave more similarly to aryl than vinyl reagents.

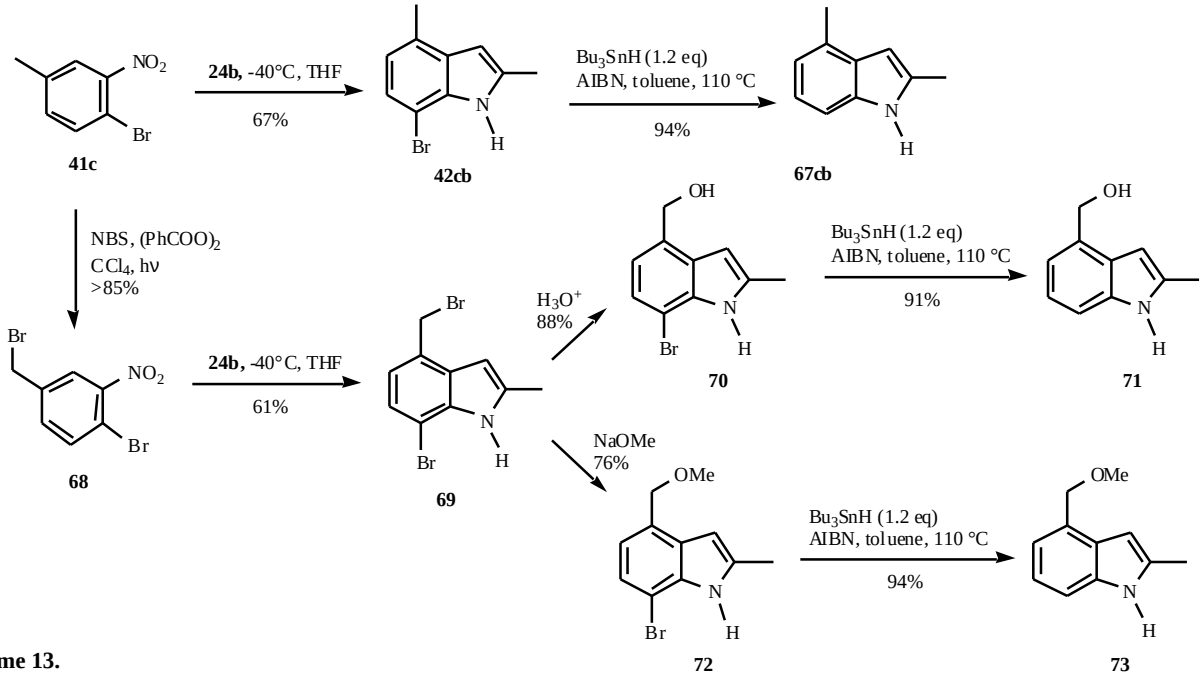


Scheme 12.

Table 8. Examples of Bartoli reaction followed by radical reduction.

X	R	R^1	Yield (%)	
			7-bromoindole	Indole
H	H	H	65 (**42aa**)	92 (**67aa**)
H	Me	H	62 (**42ab**)	89 (**67ab**)
H	H	Me	63 (**42ac**)	86 (**67ac**)
H	$(CH_2)_4$		43 (**42ae**)	81 (**67ae**)
5-Me	H	H	59 (**42ca**)	89 (**67ca**)

These, apparently unlucky, results were cleverly interpreted [45]. Often during this review, we underlined that *ortho*-substitution of the nitroarene is the biggest drawback of Bartoli indole synthesis, since only such a substitution allows high yields to be obtained. The radical debromination by means of tributyltin hydride promoted by azobisisobutyronitrile (AIBN) opened a new and very interesting scenario: the use of bromine atom as a labile directing group (Scheme **12**).



Scheme 13.

The *ortho*-substituent can now enforce selectivity in attack to the nitrosoarene intermediate according to the pathway depicted in Scheme **4**, but can be easily removed by radical reduction. The combination of these two methodologies allows the synthesis of many indoles, where the Bartoli approach is advantageous, but *ortho*-substitution undesirable. Some examples are summarized in Table **8**.

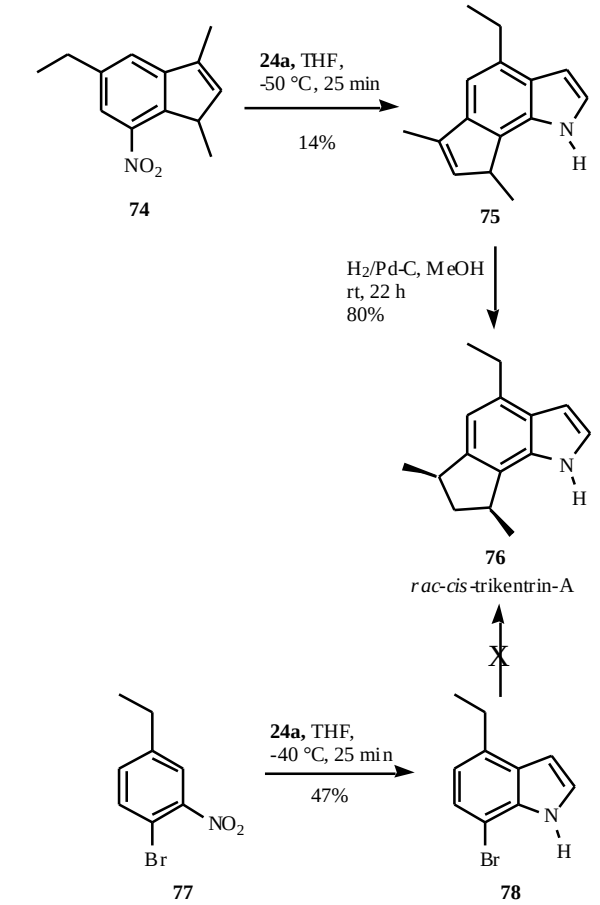
This method may reduce the number of steps required for the synthesis of some complex indoles and also offers the advantage that many functionalities are tolerant to both the Bartoli synthesis and the radical-generating conditions, without the need for their protection as demonstrated by the synthesis of three indole alkaloids (**67, 71, 73**) from European *Tricholoma* species (Scheme **13**) [45].

4. USE IN SYNTHESIS OF NATURAL PRODUCTS

Since its appearance in the literature, the Bartoli indole synthesis has provided a useful way to key intermediates for the synthesis of complex indoles. Two examples are already reported in the previous section [39,45]. This section is dedicated to other examples of synthetic applications.

4.1 7-Haloindoles

7-Haloindoles are certainly the most important building block prepared *via* vinyl Grignard addition to nitroarenes, owing to the high versatility of the halogenated function to further transformations. As reported above, both Heck and Suzuki couplings are very often used to attach a suitable side chain to the 7-position of the indole.

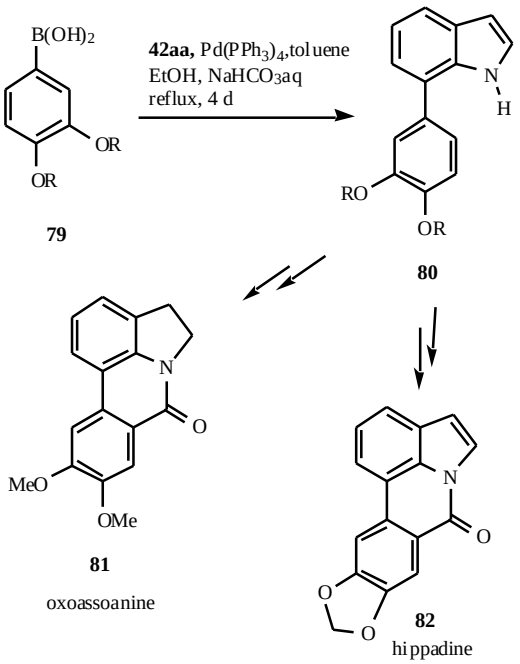


Scheme 14.

The first reported example was the total synthesis of (+/-)-*cis*-trikentrin-A (**76**), a cytotoxic indole alkaloid isolated from the marine sponge *Trikentrion flabelliforme* [47].

5-Ethyl-1,3-dimethyl-7-nitro-*1H*-indene (**74**) and 2-bromo-5-ethylnitrobenzene (**77**) were the substrates for indole synthesis (Scheme **14**). The latter failed to give the target molecule, owing to a rearrangement during a subsequent Friedel-Crafts construction of the cyclopentane ring fused to indole.

The key intermediate **80** for the synthesis of two pyrrolophenanthridinone alkaloids extracted from *Amaryllidaceae* (oxoassoanine, **81** and hippadine **82**, Scheme **15**) was accomplished by a Suzuki coupling on **42aa** [48].

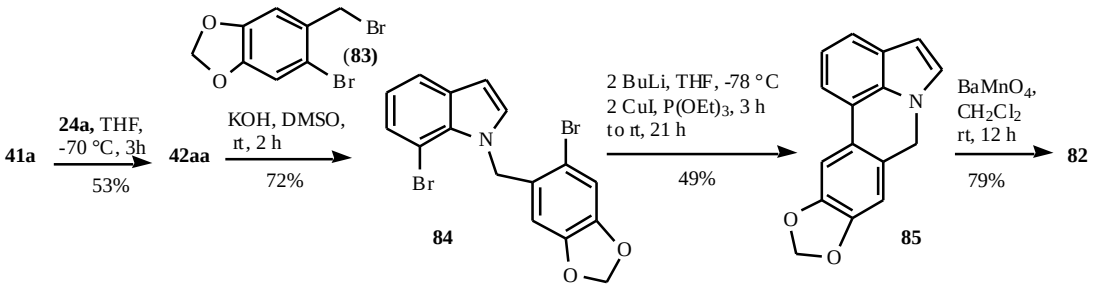


Scheme 15.

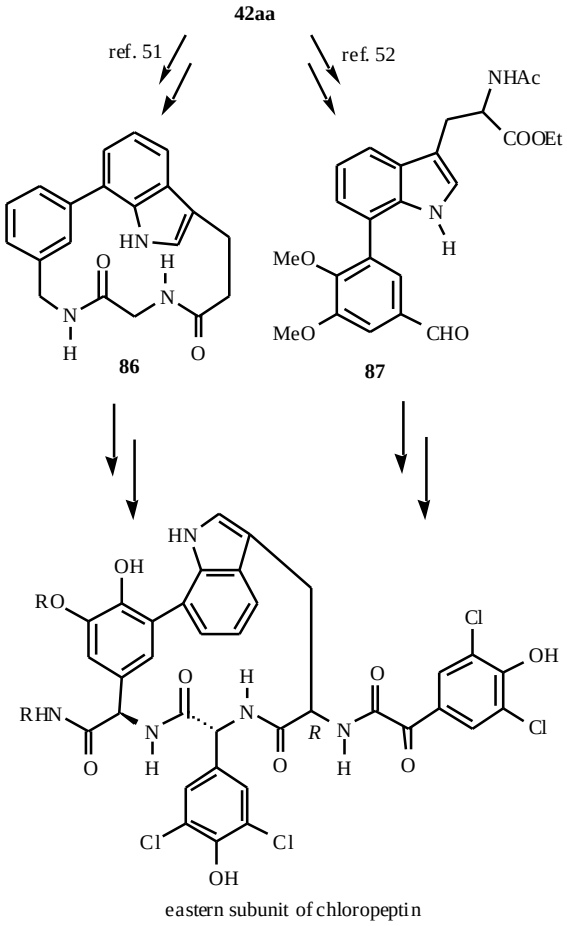
Hippadine was also prepared *via* a four-step synthesis; using a copper(I) promoted aryl to aryl coupling from **42aa** as a precursor (Scheme **16**) [49]. Interestingly, **42aa** was prepared in a 53% yield at -70 °C, starting from vinylmagnesium chloride, in sharp contrast with Dobbs' assertions that decreasing the temperature and using chloride instead of bromide lowers yields [33,50].

The synthesis of the eastern subunit of chloropeptine (Scheme **17**), a glycopeptide antibiotic produced by *Streptomices* species, was also accomplished starting from **42aa.** Two strategies are reported. The first prepares, in 1% yield, the macrocyclic derivative **86** [51]. The second builds the biaryl derivative, ethyl 2-acetamido-3-[7-(5-formyl-2,3-dimethoxyphenyl)-1H-indol-3-yl]propanoate (**87**) in a 30% yield [51].

Synthesis of **87** requires the preparation of 7-bromotryptophan. It can be achieved from **42aa**, by coupling either with dehydroserine in the presence of $PdCl_2$-NaOAc [52] or with serine in Ac_2O-AcOH [53]. A third route to 7-bromotriptophan was suggested in the synthesis of macrocyclic peptide analogues of proteasome inhibitor



Scheme 16.

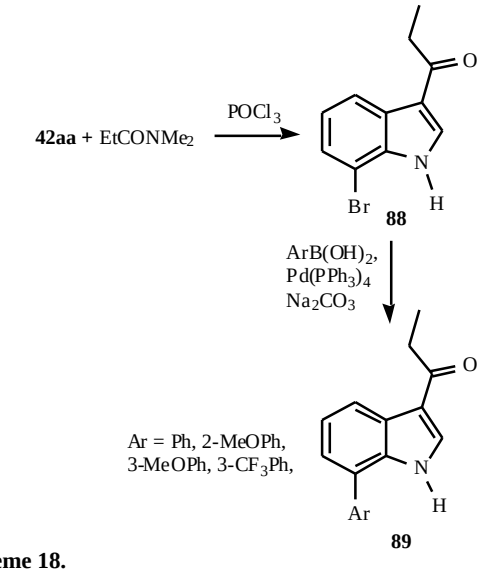


Scheme 17.

TMC-95A [54]. It is quite complex, but the starting step is always the synthesis of **42aa.**

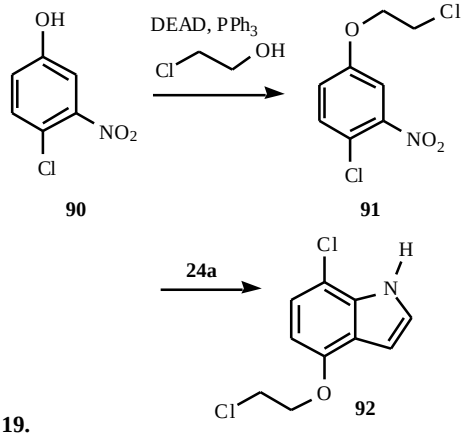
7-Bromoindole can be acylated in a 65% yield by a modified Friedel-Crafts reaction and submitted to a further Suzuki cross-coupling reaction to give the indole ketone **89**, used for a structure-activity relationship study on Brequinar analogues (Scheme **18**) [55].

7-Chlorindole itself was also used in the synthesis of pharmacologically important compounds. An example is represented by the synthesis of 4-(aminoethoxy)indoles, potential agonists of the dopamine receptor D_2 [56].The synthesis starts from the easily available 3-nitro-4-



Scheme 18.

chlorophenol and the indole ring is built by Bartoli indole synthesis (Scheme **19**).



Scheme 19.

7-Chloroindole is also the key intermediate for a synthesis of rebeccamycin (Figure **2**) an indolocarbazole derivative, isolated from an actinomycete, which demonstrates potent antitumor activity [57].

4.2 Indoles from Gilmore's Modifications of the Bartoli Reaction.

7-Formylindole (**44**), prepared according to Gilmore's procedure described in section 3.1,[34] has been used as

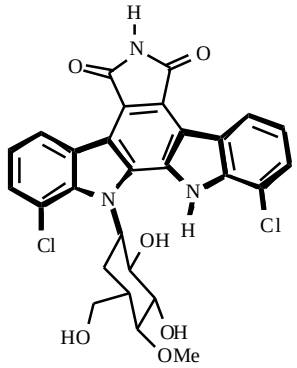


Fig. (2). Structure of rebeccamycin. Both indole nuclei highlightned in figure are constructed by Bartoli indole synthesis [58].

precursor for N^N-chelating ligands for titanium(IV)[58] and nickel(II)[59] complexes (Figure **3**). They are subsequently employed as catalysts for ethylene polymerization. Titanium complexes can polymerize ethylene in a living fashion to form linear polyethylenes with, in same cases, extremely narrow molecular weight distributions [58]. On the other hand, the nickel complex is completely inactive in ethylene polymerization [59].

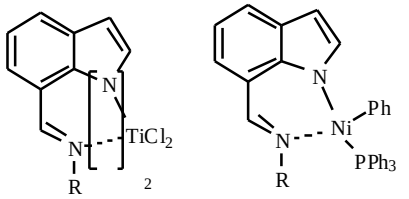


Fig. (3). Structure of complexes synthesized for ethylene polymerization. R is a fluorinated benzene or 2,6-diisopropylphenyl in titanium or nickel complex respectively.

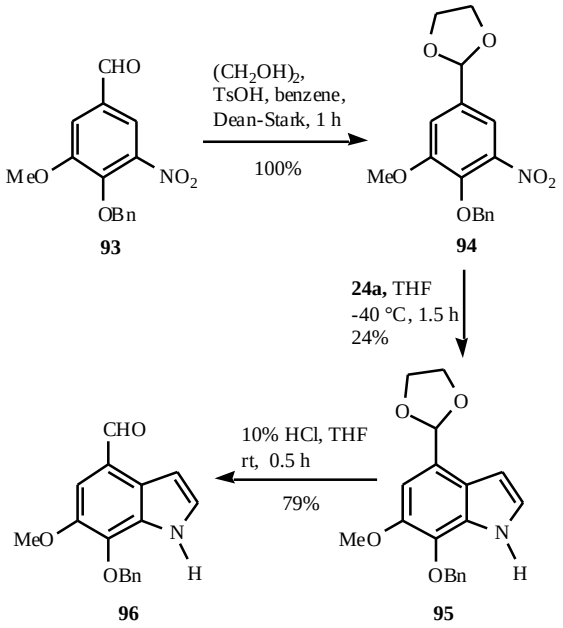
4-Benzyloxy-5-methoxy-3-nitrobenzaldehyde (**93**) is the starting material for the synthesis of 7-benzyloxy-4-formyl-6-methoxyindole (**96**), a key building block in a synthesis of CC-1065, a potent antitumor antibiotic from *Streptomices* species (Scheme **20**) [60].

Benzocarbapenems from indoles has been recently unsuccessfully proposed as antibacterial agents. Among the explored syntheses of the indole nucleus, Gilmore's modification [32] on protected phenols has been used to synthesize the benzocarbapenem **100** *via* the benzhydryl protected 7-hydroxyindole **99** (Scheme **21**) [61].

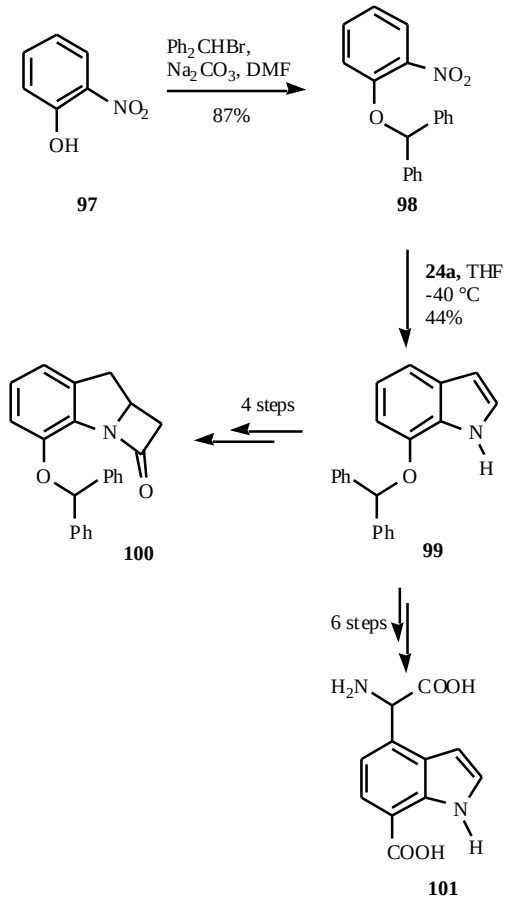
99 is also the key intermediate in the synthesis of **101** (Scheme **21**), a 7-carboxyindolylglycine derivative, proposed as a putative mGluR1 receptor antagonist [62].

7-Benzyloxyindole is the starting material for a 10-g scale synthesis of (+/-)-3-(2-aminopropyl)-7-benzyloxyindole, whose *R*-isomer is a key chiral intermediate of AJ-9677 (Figure **4**), a potent and selective adrenaline β_3-agonist and a clinical candidate for treatment of obesity in diabetes sufferers [63].

Dragmacidins are a class of marine natural products obtained from some deep water sponges. Dragmacidin D, in particular, is a potent inhibitor of serine-threonine protein phosphatases (PP), in particular it is selective of PP1 versus



Scheme 20.



Scheme 21.

PP2A, but other pharmaceutically interesting properties are now under investigation. The synthesis of the 7-hydroxyindole subunit of Dragmacidin D was attempted

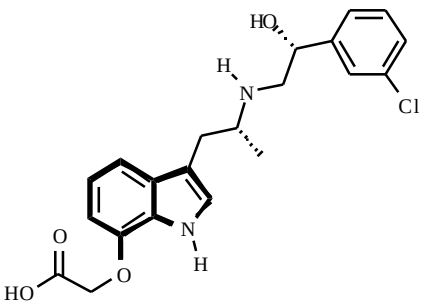


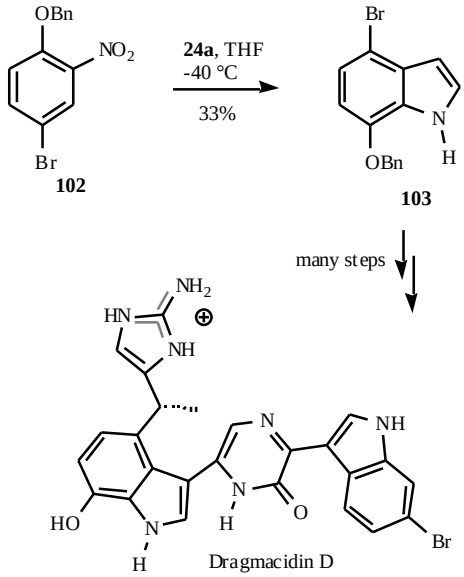
Fig. (4). Structure of AJ-9677. The building block prepared according to Bartoli indole synthesis is highlightened.

starting from 1-benzyloxy-4-bromo-2-nitrobenzene *via* Gilmore's procedure (Scheme **22**) [64].

4.3 Miscellaneous

Classes of indolocarbazole derivatives (analogues of rebeccamycin, Figure **2**), which are potent inhibitors of cyclin D1/CDK4, a protein involved in the cell division cycle, have been recently synthesized [65]. The western subunit was synthesized by Gilmore's modification and, among the eastern units, the 7-(2-hydroxyethyl) substituted indole was prepared by the Bartoli reaction (Scheme **23**).

On methyl 12-bromo-13-nitrodeisopropyl dehydroabietate **111** has been constructed an indole ring by Bartoli indole synthesis in very good yields and the ester function

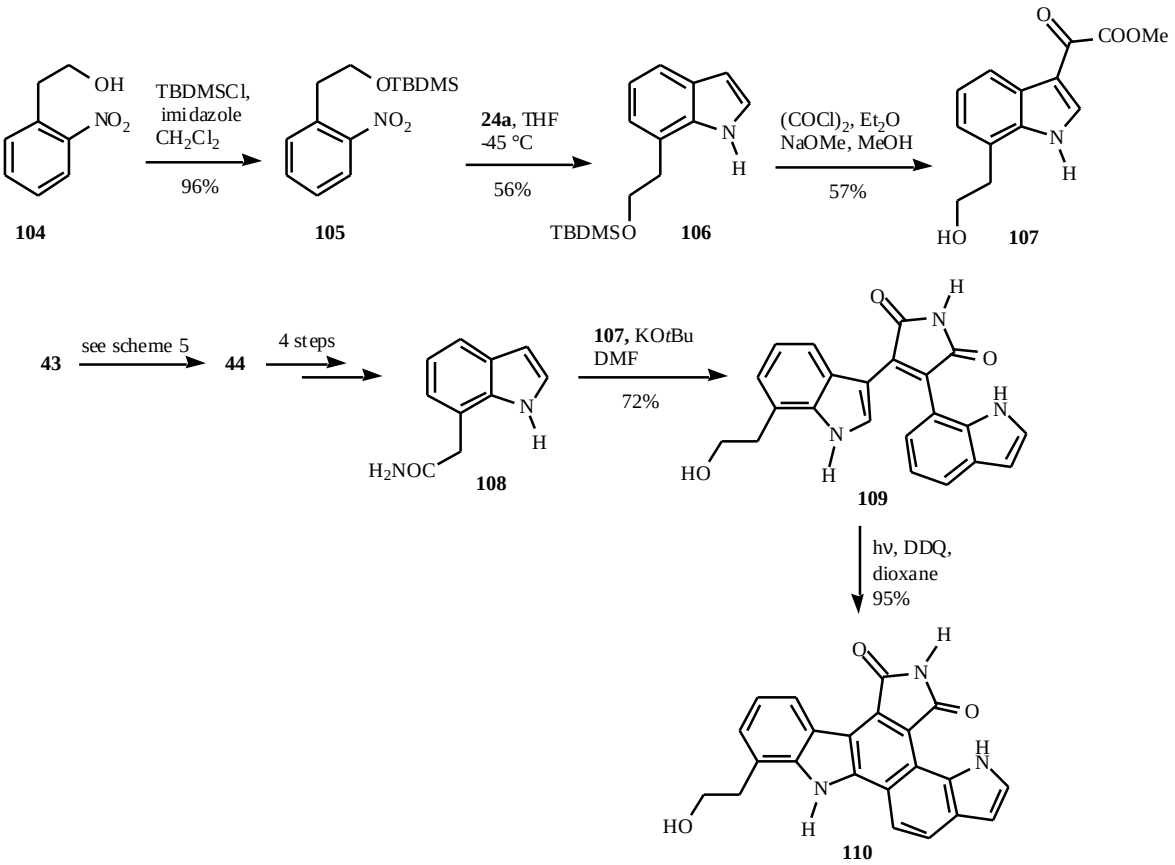


Scheme 22.

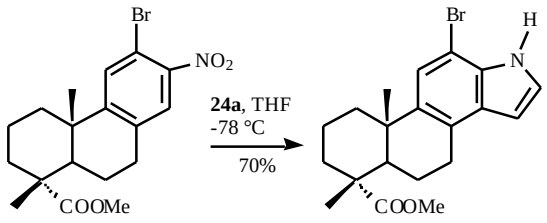
remains unaffected (Scheme **24**). The product **112** inhibits both varicella-zoster virus and cytomegalovirus and its activity is comparable with acyclovir [66].

CONCLUSIONS

The reaction of vinyl Grignard reagents with nitroarenes, owing to the peculiarity of the vinyl radical when it attacks



Scheme 23.



111 **112**

Scheme 24.

the nitroarene radical anion, opened a new and wide perspective in the synthesis of indoles. Since the attack occurs on the nitro group and does not involve the aromatic ring, the reaction can be, in principle, extended to every substrate able to give a [3,3]-sigmatropic rearrangement, as well as allyl Grignard reagents [22]. Unfortunately, the cognate nitroso derivative, which allows the synthesis of pyrroles, is a nitroso-ene, which is unstable.

The variety of functionalized substituents which can be introduced into nitroarenes is practically unlimited, since the reaction is selective at the nitroaromatic moiety of the molecule. The chance of carrying out the reaction on solid resins overcomes the tedious separation processes. The versatility of bromo substitution on the 7-position of the indole ring and its selective modification allows the synthesis of 7-formyl, 7-carboxy, 7-amino, and 7-alkyl derivatives.

Finally Dobbs' modification uses the bromine as a protecting and activating group, which can be removed from the indole when necessary. This very recent improvement of Bartoli indole synthesis opens up other possibilities of applications.

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