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Benzo[*g*]indoles

Alexander F. Pozharskii, Svetlana G. Kachalkina, Anna V. Gulevskaya, Ekaterina A. Filatova

Faculty of Chemistry, Southern Federal University
prosp. Zorge 7, 344090 Rostov-on-Don, Russian Federation

The data on the synthesis and properties of benzo[*g*]indoles accumulated mainly over a period of the past 15 – 20 years are integrated. Various variants of pyrrole ring and naphthalene nucleus closure are considered. It is demonstrated that, in addition to the expected similarity between benzo[*g*]indoles and indoles, there are noticeable differences between them as well, especially where the synthesis of the benzoindole system is concerned. Practical applications of benzo[*g*]indoles are discussed.
The bibliography includes 199 references.

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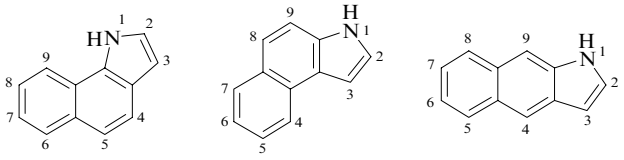
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I. Introduction

Indoles constitute one of the most widespread classes of heterocyclic systems in nature. They are part of the structure of proteins, neurotransmitters, hormones, alkaloids and natural pigments. Medicines, plant protection products, electronic materials, dyes, fluorophores, *etc*., have been created on their basis.[1,2] There are a great number of books and reviews devoted to both general and special issues of indole chemistry (see, for example,[3–9]). Unfortunately, they only occasionally mention benzoindoles, including the derivatives of the three main representatives of these systems: benzo[*g*]indole (**1**), benzo[*e*]indole (**2**) and benzo[*f*]indole (**3**). This can be explained to an extent by the considerable similarity in the methods of synthesis and reactivity of indole and benzoindoles, although in reality this is not always the case. An important distinction of benzoindoles from indoles and pyrroles lies in the more extended π-system, which favours the search for materials based on them for modern electronic equipment.

This review focuses on benzo[*g*]indoles, which is caused by both our interest in these compounds and the fact that they have been rather sparingly mentioned in modern databases (we have used Reaxys and SciFinder as of June 1, 2016). With rare exceptions, the review does not include information on benzo[*g*]indole-based polyfused systems, as well as on the reactions of functional groups bonded to the heterocycle. Obviously, integration of data concerning isomeric systems **2** and **3** requires writing a separate review.

Structures 1 – 3



1 **2** **3**

A.F.Pozharskii. Doctor of Chemical Sciences, Professor, Head of the Department of Organic Chemistry at the Faculty of Chemistry, SFedU.
E-mail: apozharskii@sfedu.ru
Current research interests: the chemistry of heterocycles and organic superbases, theoretical organic chemistry.
S.G.Kachalkina. Laboratory Assistant at the same Department.
E-mail: kachalkena@mail.ru
Current research interests: the chemistry of 'proton sponges'.
A.V.Gulevskaya. Doctor of Chemical Sciences, Professor at the same Department.
E-mail: agulevskaya@sfedu.ru
Current research interests: the chemistry of heterocyclic and acetylene compounds, homogeneous catalysis, nucleophilic substitution.
E.A.Filatova. PhD in Chemistry, Associate Professor at the same Department.
E-mail: pansha@rambler.ru
Current research interests: cross-coupling reactions, the chemistry of acetylenes and 'proton sponges'.

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II. Synthesis of benzo[*g*]indoles

All the known methods for constructing the benzo[*g*]indole system can conveniently be divided into three general groups, depending on whether they are based on the closure of the pyrrole ring on the existing naphthalene nucleus, on the construction of the naphthalene ring at the already available pyrrole moiety, or on the simultaneous assembly of both cyclic systems. As for the preparation of benzo[*g*]indoles from their partially hydrogenated precur-

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sors, the corresponding aromatization reactions are considered in the review as necessary within the three above groups of methods.

II.1. Methods based on the pyrrole ring closure

From the point of view of formation of the last bond (shown by the dashed lines in Fig. 1), the methods of pyrrole ring closure to give benzo[*g*]indoles can conveniently be divided into four types (**A** – **D**). The most common are the first three types, while the examples of type **D** are less numerous. It is evident that this classification should be based on an accurate knowledge of the reaction mechanism. Meanwhile, there are cases when information on the mechanism seems insufficient. Therefore, a special section devoted to the methods with an ambiguous mechanism is introduced into the review (the classification of pyrrole cyclization reactions has been reviewed in more detail by Taber and Tirunahari [10]). It should also be noted that, over the last 10 – 15 years, the methods of pyrrole ring closure based on the reaction of arylamines with acetylenes, especially internal ones, have come to the fore. These reactions, as a rule, require the use of transition metal complexes as catalysts. Such processes are usually characterized as proceeding with CH- or CH/NH-activation. In Fig. 1, they are shown as type **E**. Although the vast majority of such reactions can be reduced to type **A** or **B** cyclization, we found it expedient to consider them in separate Section II.1.d.

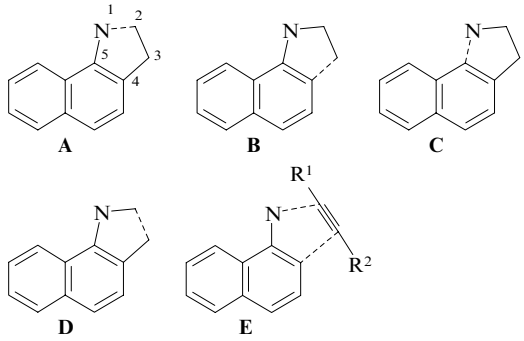


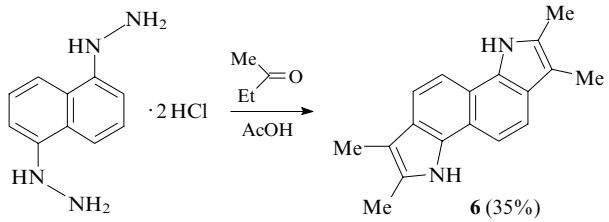
Figure 1. Types of pyrrole ring closure to form benzo[*g*]indoles.

II.1.a. Cyclization of type A

The classical and probably the most common method of synthesizing indoles, including benzo[*g*]indoles, is the Fischer reaction. It was precisely in this way that parent compound **1** was first synthesized in 1887.[11] The Fischer reaction consists of heating *N*-arylhydrazones of aldehydes and ketones in the presence of a catalyst, a Brønsted or Lewis acid. As a rule, the reaction gives the product in good yield, although in the early works it has not been always indicated. In particular, monoethyl esters of α-ketoadipic acid or α-ketoglutaric acid 1-naphthylhydrazones (**4**) have been converted into benzo[*g*]indoles **5** (Scheme 1). References to these and other old data on the synthesis of benzo[*g*]indoles by Fischer's method can be found in the reviews.[3 – 9]

Samsoniya *et al.*[12] described the synthesis of 2,3,7,8-tetramethylindolo[7,6-*g*]indole (**6**) by brief refluxing 1,5-dihydrazinonaphthalene dihydrochloride with methyl ethyl ketone in acetic acid (Scheme 2).[12] There are also other examples of synthesis of this system.[13, 14]

Scheme 2

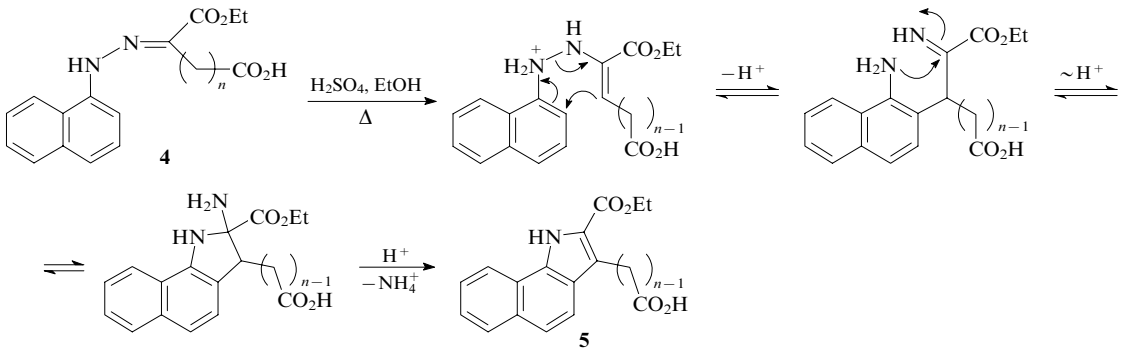


In recent years, the Fischer reaction has been improved, for example, by using microwave irradiation (MW) or modifying the usual reagents. In particular, it has been shown [15, 16] that it is very convenient to introduce benzophenone *N*-arylhydrazones (including compound **7**) into the Fischer reaction, since they are more stable, stored for weeks without significant decomposition, and can be easily obtained by the Buchwald – Hartwig method in the presence of palladium diacetate and BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] (for example, from 1-bromonaphthalene **8**, Scheme 3). During further indolization in an acidic medium, compound **7** is converted into the corresponding benzo[*g*]indoles **9a**,**b** in ~90% yield. The whole process can be carried out as one-pot reaction.

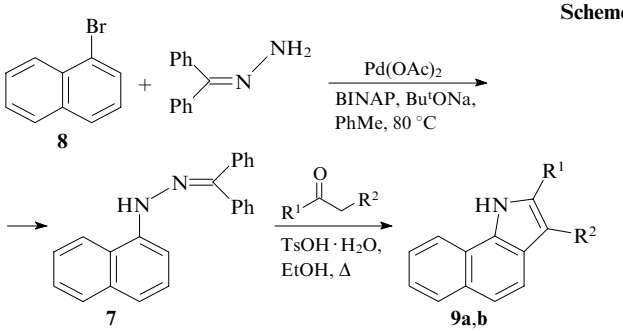
In another example (see Scheme 3), the reaction of 1-hydrazinonaphthalene hydrochloride with *N*-acetyl-3-bromo-4-piperidone hydrobromide (**10**) under microwave irradiation gave pyrido[4,3-*b*]benzo[*g*]indole (**11**), which can also be treated as a γ-carboline derivative, in an almost doubled yield (44% as compared with 25% under common conditions).[17]

A rather efficient modification of the Fischer reaction is the use of aryl halides as starting compounds, which are successively converted to an organomagnesium compound,

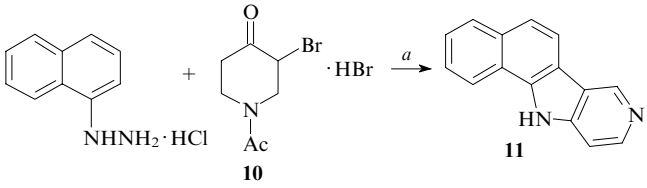
Scheme 1



Scheme 3



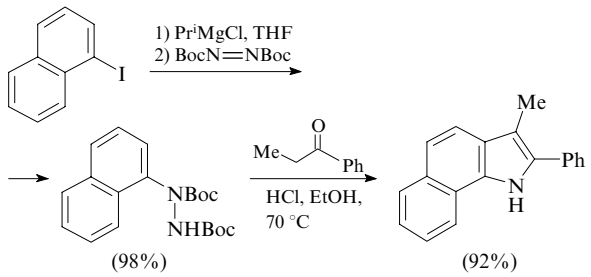
R^1 = Ph, R^2 = H (**a**, 85% yield); R^1 = Me, R^2 = CH_2CO_2Et (**b**, 90%); Ts = 4-$MeC_6H_4SO_2$



(*a*) AcOH or $BF_3 \cdot Et_2O$, Δ, 12 h or MW

Boc-protected arylhydrazine [Boc = $Bu^tOC(O)$] and then to indole after treatment with the appropriate ketone (Scheme 4).[18, 19] The attractiveness of this method lies in the ease of removing protective Boc-groups under the acidic conditions of the Fischer cyclization. For example, the yield of 3-methyl-2-phenylbenzo[*g*]indole obtained through this route from 1-iodonaphthalene was 92% (see Scheme 4).

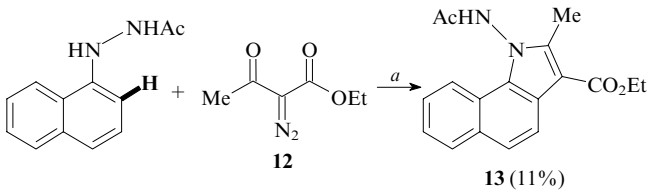
Scheme 4



Fischer synthesis of indoles and benzoindoles has also been carried out on a solid polymer substrate made of hydroxymethylated polystyrene with a carbamate linker. The latter is stable in acidic and basic media and under reductive conditions, but is cleaved under the action of a $CF_3CO_2H - Me_2S$ mixture at room temperature.[20] The possibility of continuous automatic multistage assembly of the indole and benzo[*g*]indole systems using the Fischer reaction has been exemplified by the synthesis of a large series of 3-(thiazol-2-yl)indoles.[21]

It has been recently shown that arylhydrazines can be converted to 1-aminoindoles without loss of the terminal nitrogen atom (Scheme 5).[22] In particular, the Rh^{III}-catalyzed reaction of 2-acetyl-1-(1-naphthyl)hydrazine with diazo compound **12** in aqueous acetic acid gave benzo[*g*]indole **13**, albeit in low yield. This reaction is much more efficient (76% – 91% yields) in synthesis of 1-amino derivatives of indole and benzo[*f*]indole. It is believed that the process starts with CH activation through the insertion of Rh into the C – H bond (shown in boldface type), followed by the formation of the carbene complex through the elimination of N_2 molecule from diazo compound **12**, the insertion of the carbene ligand into the C – Rh bond and the closure of the rhodacycle, catalyst regeneration and final cyclocondensation. Below, we will give numerous examples of Rh-catalyzed syntheses of other indoles.

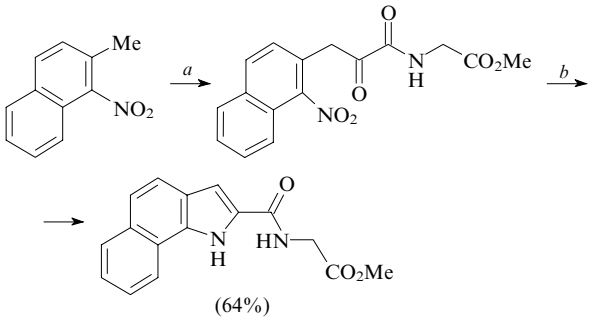
Scheme 5



(*a*) $[Cp^*RhCl_2]_2$, AcOCs, AcOH, H_2O, 100 °C, 1 h; $Cp^* = \eta^5$-C_5Me_5

Like many indoles, benzo[*g*]indoles can be synthesized by the Reissert method from *o*-nitromethylarenes (for example, 2-methyl-1-nitronaphthalene) and diethyl oxalate (Scheme 6).[23]

Scheme 6

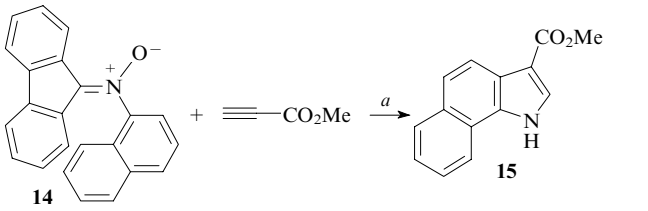


(*a*) 1) EtO_2CCO_2Et, EtONa; 2) $H_2NCH_2CO_2Me$;
(*b*) H_2, Pd (10%)/C, AcOEt

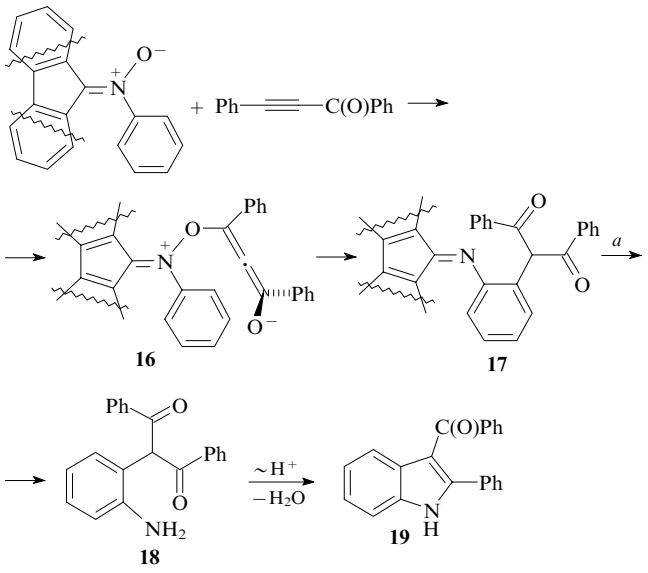
Another route to the preparation of indoles and benzo[*g*]indoles is *via* the amine – carbonyl condensation of *N*-arylfluorenoneimine nitrones with electron-deficient acetylenes.[24] For example, the reaction of nitrone **14** with methyl propiolate leads to 3-methoxycarbonylbenzo[*g*]indole (**15**) in 89% yield (Scheme 7). For simplicity, the mechanism of this reaction exemplified for the synthesis of indole is shown in the same scheme. The key stage of this reaction is the aza-Cope rearrangement of *O*-allenyl intermediate **16** to Schiff base **17**, which can be isolated from the reaction mixture. Oxalic acid-catalyzed hydrolysis of compound **17** in the presence of silica gel gives aniline **18**, which spontaneously cyclizes to the corresponding indole **19**. The fluorenone forming during hydrolysis is easily separated and can be reused ensuring the atom-economy of the process as a whole.

An original variant of amine – carbonyl condensation has been recently recommended by German chemists[25] to synthesize relatively unavailable 2-aminomethyl indole and benzo[*g*]indole derivatives, for example, compound **20** (Scheme 8). The starting material in this synthesis is *o*-nitroarylacetic acid, which is first converted by a known method to 4-methoxycarbonyloxazole derivative **21**, then the nitro group is reduced to amine **22**, and the mixture is heated with an acid. It is believed that the synthesis involves saponification of the ester group, decarboxylation and hydrolytic

Scheme 7

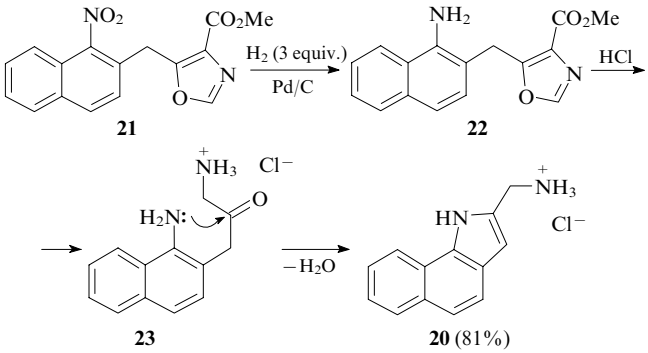


(*a*) 1) MeCN, Δ; 2) HO_2CCO_2H, SiO_2, CH_2Cl_2, rt



(*a*) $H_2C_2O_4$, SiO_2

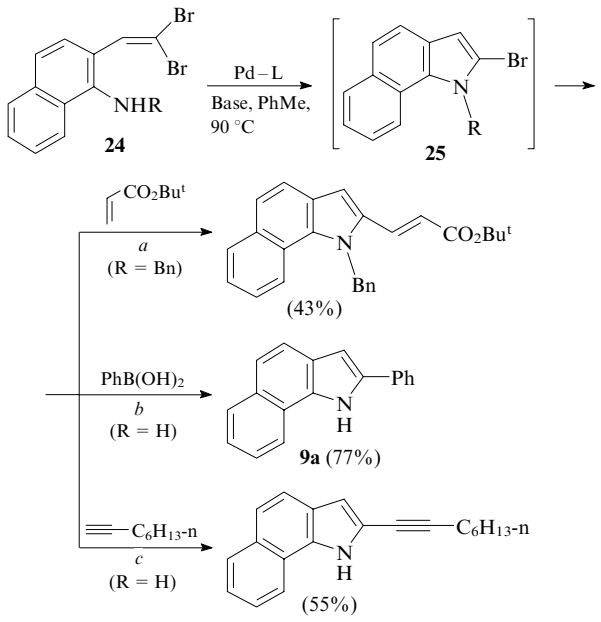
Scheme 8



cleavage of the oxazole ring to give intermediate **23**, which spontaneously cyclizes to indole.

o-(2,2-Dihalovinyl)arylamines, for example, compounds **24**, are rather widely used as synthons in synthesis of heterocyclic compounds, including indoles and benzo[*g*]indoles (Scheme 9). Since the substrate contains two geminal bromine atoms, it is convenient to carry out the corresponding reactions in tandem; both stages are catalyzed by transition metals, generally, by palladium complexes in combination with an appropriate ligand (L), copper salts and a base. The first stage proceeds as an intramolecular Buchwald – Hartwig or Ullmann reaction to give 2-bromoindole or its benzo analogue in which the bromine atom is replaced at the second stage by vinyl,[26] aryl[27] or

Scheme 9

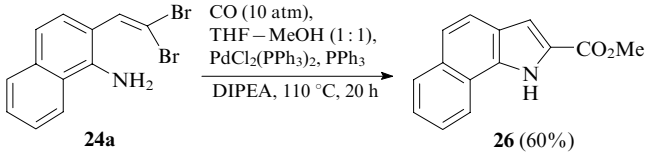


(*a*) $Pd(OAc)_2$, $P(o\text{-Tol})_3$, $K_3PO_4 \cdot H_2O$; (*b*) $Pd(OAc)_2$, S-Phos, $K_3PO_4 \cdot H_2O$; (*c*) Pd/C, CuI, $P(C_6H_4OMe\text{-}4)_3$, Pr^i_2NH; R = H, Bn; *o*-Tol = 2-MeC_6H_4, S-Phos is 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

alkynyl[28] group *via* the Heck, Suzuki or Sonogashira reaction, respectively. It has been reported that similar cyclizations are also very efficient in the presence of only CuI and K_3PO_4 as a base. In particular, this route has been used to convert 1-methylsulfonylamino-2-(2,2-dibromovinyl)naphthalene to 2-bromo-1-methylsulfonylbenzo[*g*]indole in 82% yield.[29] Recently, a method has been developed for the metal-free synthesis of compound **25** and other indoles in almost quantitative yield.[30] The success of the method is believed to be due to the use of the *N*-methylsulfonyl derivative **24** and its analogues as the starting compound and tetra-n-butylammonium fluoride (TBAF) as a base, as well as due to the application of microwave irradiation. It is assumed that the $MeSO_2$ group facilitates the acid ionization of the N – H bond required for nucleophilic cyclization with replacement of the bromine atom, while TBAF promotes its subsequent smooth elimination from the resulting indole.

The Pd-catalyzed synthesis of 2-methoxycarbonylbenzo[*g*]indole (**26**) by reacting dibromide **24a** with carbon monoxide and methanol in the presence of diisopropylethylamine (DIPEA) as the base (Scheme 10) can be considered as a variant of the above approach. It is evident that the intermediately forming organopalladium compound is carbonylated with subsequent addition of methanol.[31] Other syntheses from compounds **24**, for example, the conversion of the *N*-methylsulfonyl derivative to 2-bromo-3-phenyl-

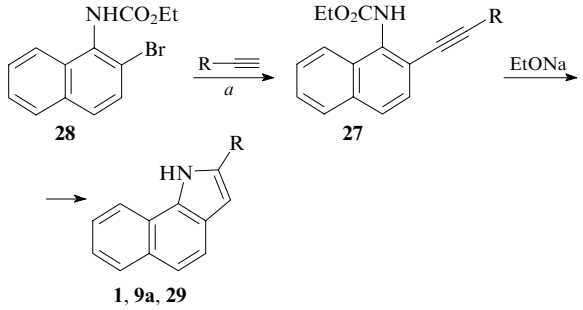
Scheme 10



sulfanyl- or 2-bromo-3-phenylselenylbenzo[*g*]indole have been reported by Liu *et al.*[32]

Synthesis of benzo[*g*]indoles through the addition of the arylamino group to *ortho*-substituents containing C≡C or C≡N bonds has been addressed in a number of studies. In particular, aminoacetylenes **27**, prepared by the Sonogashira reaction from 2-bromo-1-ethoxycarbonylaminonaphthalene (**28**), react with sodium ethoxide to give unsubstituted benzo[*g*]indole (**1**) and its 2-substituted derivatives **9a** and **29** in moderate yield (Scheme 11).[33] It is likely that the cyclization itself is promoted by basic catalysis, which leads to preliminary ionization of the NH group to give the anion more reactive towards nucleophilic addition.

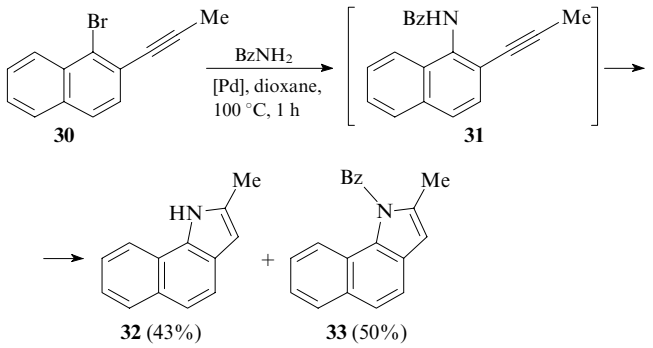
Scheme 11



(*a*) $PdCl_2(PPh_3)_2$, CuI, Et_3N; R = H (**1**, 53% yield), Ph (**9a**, 42%), Bu^n (**29**, 30%)

A more complicated process of this kind is presented in Scheme 12.[34] Its specifics is in Buchwald – Hartwig tandem benzamidation that converts compound **30** to derivative **31**, which undergoes nucleophilic cyclization to give a mixture of compounds **32** and **33** in nearly quantitative overall yield. The use of 2-allenyl-1-bromonaphthalene instead of brominated propynylnaphthalene **30** leads to similar results. Analogous reactions of 2-alkynyl-1-benzylaminonaphthalenes leading to 1-benzylbenzo[*g*]indoles have been described.[35]

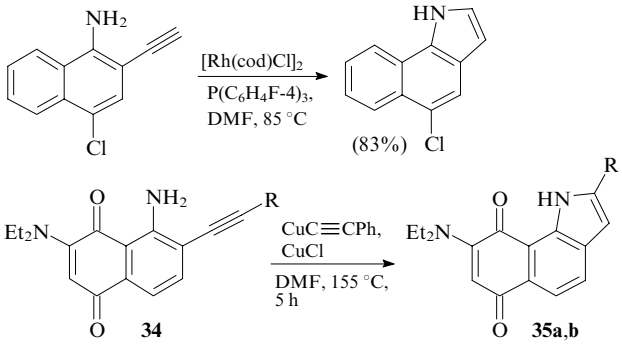
Scheme 12



[Pd] = $Pd(OAc)_2$ – Xantphos – Cs_2CO_3; Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Examples of the participation of the primary amino group in such cyclizations are also numerous.[14, 36 – 38] Two of them are shown in Scheme 13.[36, 37] The reaction is usually catalyzed by transition metal complexes, for example, palladium, copper, gold and rhodium complexes, which provides, as a rule, a good yield of the product under

Scheme 13

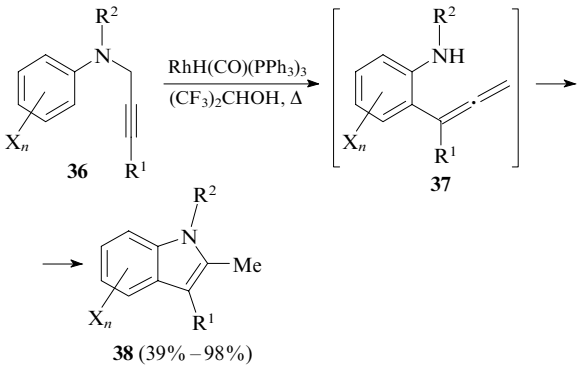


R = Ph (**a**, 83% yield), C(Me)=CH_2 (**b**, 56%); cod is 1,5-cyclooctadiene

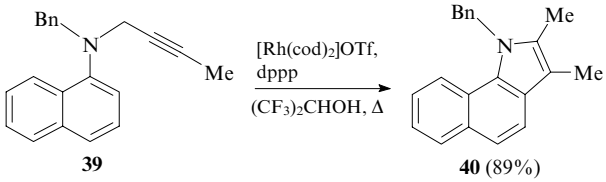
relatively mild conditions. The more severe conditions for the cyclization of naphthoquinones **34** into indole derivatives **35a**,**b** can be explained by the electron-withdrawing effect of the carbonyl groups in the starting compound, which reduces the nucleophilicity of the NH_2 group.

Japanese chemists[39, 40] have found a rather efficient route with an unexpected mechanism to the preparation of 2-substituted and 2,3-disubstituted indoles, which consists in the rhodium-catalyzed cyclization of *N*-propargylanilines in boiling hexafluoroisopropyl alcohol (Scheme 14). It has

Scheme 14



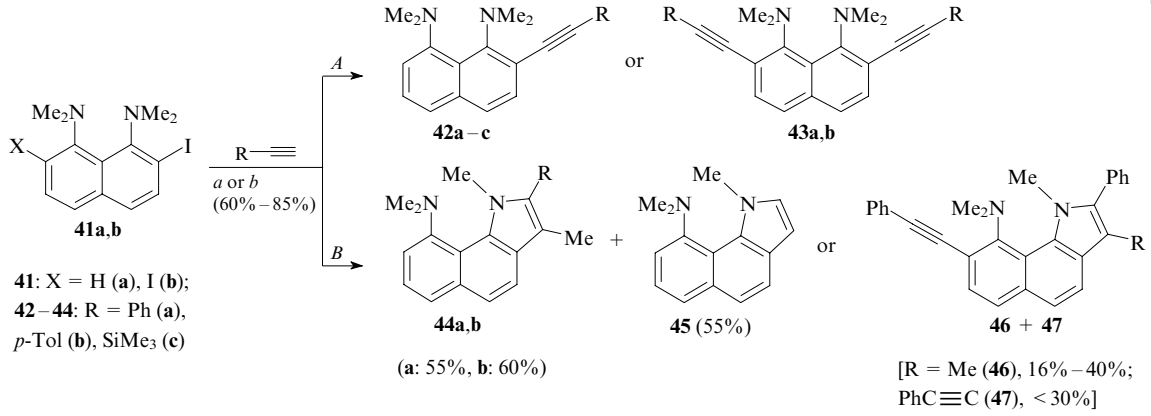
for **36**: X_n = H, 2-OMe, 3-OMe, 4-OMe, 2-Br, 4-Br, 2-F, 4-F, 3,5-F_2, 4-CF_3, 2,3-benzo; R^1 = Me, $CH_2OP(O)(OEt)_2$; R^2 = H, Et, Bn



dppp is 1,3-bis(diphenylphosphino)propane

been shown that the starting acetylene **36** is first isomerized to *o*-allenylaniline intermediate **37**, which is cyclized to indole **38**, as a rule, in good yield. It is interesting that the active catalyst in this reaction is the $[Rh(CO)(PPh_3)_2]OCH(CF_3)_2$ complex; it was isolated, and its structure was confirmed by X-ray single-crystal diffraction analysis. The method, which has something in common with the reactions described in Section II.1.d, is also

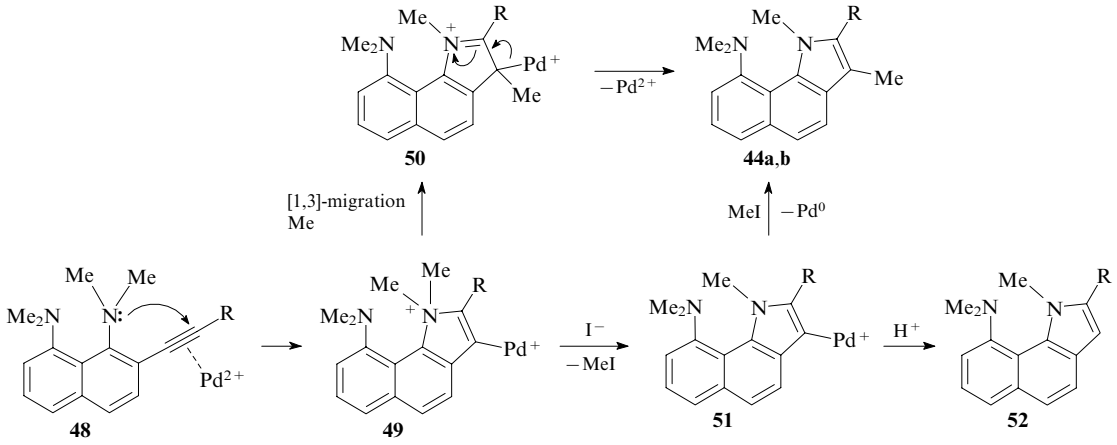
Scheme 15



41: X = H (**a**), I (**b**);
42–**44**: R = Ph (**a**), *p*-Tol (**b**), $SiMe_3$ (**c**)

(*a*) for R = Ph, *p*-Tol: $Pd_2(dba)_3$, CuI, PPh_3, K_2CO_3, DMF; (*b*) for R = $SiMe_3$: $Pd_2(dba)_3$, CuI, PPh_3, Et_3N; dba is dibenzylideneacetone; for *A* and *B*, see text

Scheme 16



R = Ph (**a**), *p*-Tol (**b**)

applicable to the synthesis of benzo[*g*]indoles: for example, alkyne **39** can be converted to benzyldimethyl derivative **40** (see Scheme 14).

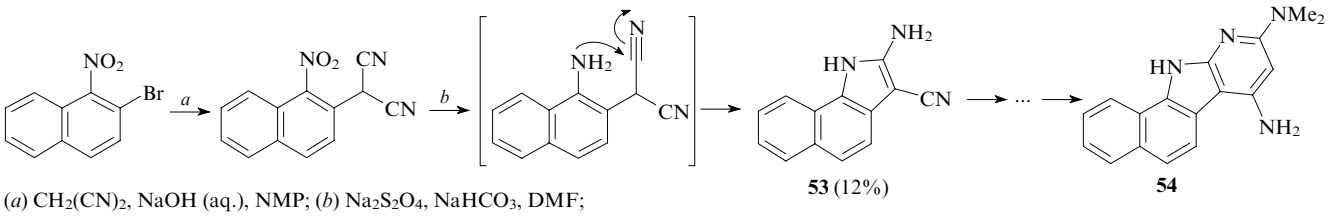
Even a tertiary dimethylamino group in *o*-alkynylanilines under certain conditions is capable of participating in cyclization to form the pyrrole ring. In particular, it has recently been shown in our laboratory[41] that 2-iodo- (**41a**) and 2,7-diiodo-1,8-bis(dimethylamino)naphthalenes (**41b**), when treated with acetylenes under Sonogashira conditions, give completely different products depending on the method of isolation and some additives (Scheme 15). If the final reaction mixture is poured into water, then the expected alkynyl derivatives **42a**–**c** or **43a**,**b** are obtained after extraction and column chromatography (separation conditions *A*). If the reaction mixture after completion of the reaction is evaporated to dryness in a porcelain dish at 90–100 °C and the residue is chromatographed (isolation conditions *B*), the reaction products are benzo[*g*]indoles **44a**,**b** and **45** (in the case of monoiodide **41a**) and **46**, **47** (in the case of diiodide **41b**).

The most interesting in these transformations, apart from cyclization itself, is the migration of the methyl group to the 3-position of the pyrrole ring and the catalysis by porcelain (actually aluminosilicate). It is assumed (Scheme 16) that, under more severe and aerobic conditions of evaporation of the reaction mixture, the $Pd^0 \rightarrow Pd^{2+}$ conversion becomes possible, which opens the way to activation of the triple bond in acetylenes **42** and **43** through coordination to Pd^{2+} and subsequent cyclization of Pd intermediate **48** to give tricyclic Pd derivative **49**. Further transition to benzo[*g*]indole **44** can proceed either intramolecularly through intermediate **50** (in tight porcelain nanopores and involving a carbonate ion as a shuttle) or through elimination of MeI and methylation of Pd intermediate **51**. In the absence of MeI in the reaction zone, intermediate **51** is subjected to protolytic demetallation to form benzo[*g*]indole **52**. The cyclizations of compounds **42** and **43** into 3-aroylbenzo[*g*]indoles and 3,3′-bis(benzo[*g*]indole)s have also been reported.[41]

The one-pot transformation of 2-bromo-1-nitronaphthalene to 2-amino-3-cyanobenzo[*g*]indole (**53**) (Scheme 17) demonstrates the possibility of pyrrole cyclizations involving the *ortho*-arranged amino and cyanomethyl groups. Compound **53** has been used to synthesize polynuclear heterosystem **54**.[42] Similar cyclization has been applied to synthesize 2-amino-3-carbamoylbenzo[*g*]indoles by reacting *N*-(1-naphthyl)hydroxamic acids with malononitrile (Scheme 18).[43]

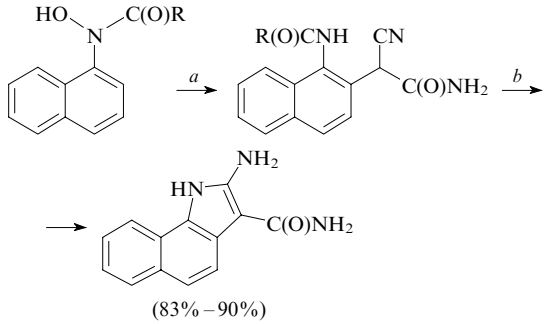
The Leimgruber–Batcho indole synthesis is also classified as benzoindole cyclization of type **A** (see Fig. 1). The starting compound in this synthesis is nitroarene, for example, methylnitronaphthalene **55**, containing a suffi-

Scheme 17



(*a*) $CH_2(CN)_2$, NaOH (aq.), NMP; (*b*) $Na_2S_2O_4$, $NaHCO_3$, DMF; NMP is *N*-methylpyrrolidone

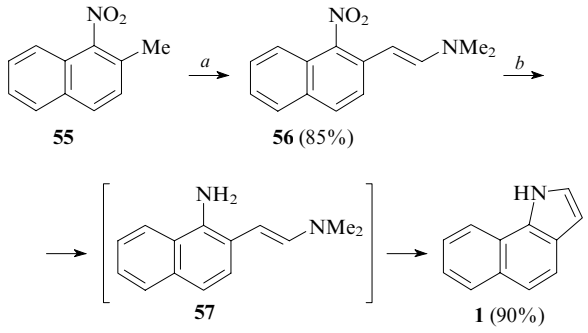
Scheme 18



(*a*) $CH_2(CN)_2$, Et_3N, $CHCl_3$; (*b*) MeONa, MeOH, Δ, 3 h; R = Me, Ph, 4-$MeOC_6H_4$

ciently acidic *ortho*-methyl group which is capable of condensation with formamide dimethylacetal to form enamine **56**. Usually, this reaction requires relatively severe conditions, which could be mitigated by using dimethylformamide, microwave irradiation, and univalent copper salts as a catalyst. The subsequent reduction of the nitro group results in amine **57**, which is cyclized *in situ* to unsubstituted benzo[*g*]indole (**1**) (Scheme 19).[44, 45]

Scheme 19

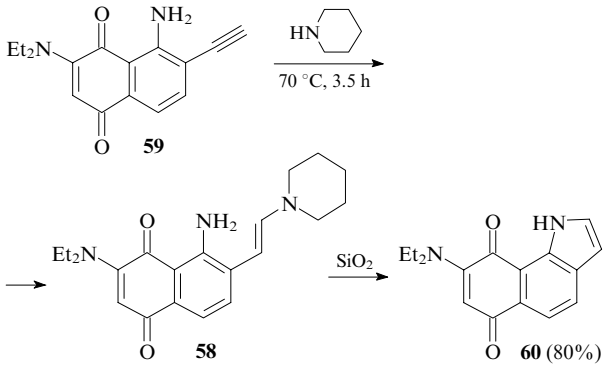


(*a*) $Me_2NCH(OMe)_2$, CuI, DMF, sealed tube, MW; (*b*) H_2, Pd/C, MeOH

A modification of the Leimgruber – Batcho method has been described in which enamine **58** is obtained by adding a secondary amine to *o*-ethynylaminoarene **59** and then is cyclized into benzoindole **60** in the presence of a mineral acid or SiO_2 (Scheme 20).[37] The method seems to be especially valuable for arylamines in which the amino group has a reduced nucleophilicity, as in the case of 1,4-naphthoquinone derivatives.

There are examples of pyrrole ring closure in benzo[*g*]indoles *via* the intramolecular addition of the amino group to the C=C double bond, although the reaction in this case proceeds not so easily and formally leads to 2,3-dihydrobenzoindoles. In particular, Alajarín *et al.*[46] have shown that the thermolysis of *N*-(propen-2-yl)-1-aminonaphthalene (**61a**) leads, in addition to the

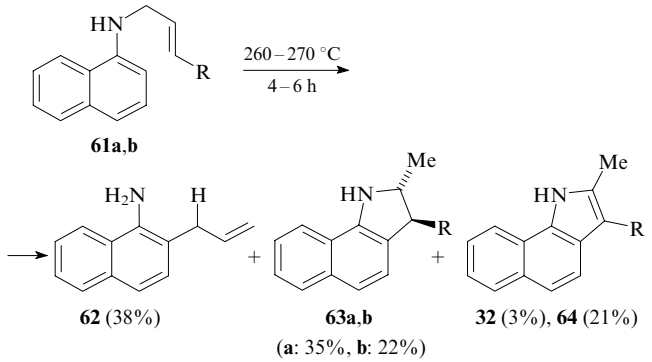
Scheme 20



expected aza-Claisen rearrangement product **62**, to some amounts of 2,3-dihydrobenzoindole **63a** and benzoindole **32** (Scheme 21).[46] Under the same conditions, *N*-(2-buten-1-yl)-1-aminonaphthalene (**61b**) gives comparable amounts of *trans*-2,3-dimethyl-2,3-dihydrobenzo[*g*]indole (**63b**) and its aromatization product **64**.

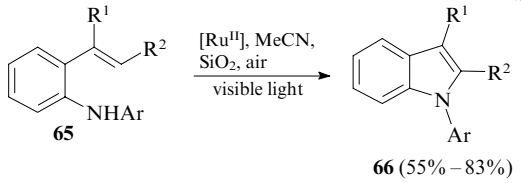
The alkene bond can be more efficiently involved in similar cyclization by the radical ion mechanism.[47] Thus, it was shown that *N*-aryl-2-vinylanilines **65** exposed to visible light in the presence of the Ru^{II} tris(bipyrazine) complex and oxygen are converted into indoles **66** in good yield (Scheme 22). For example, this protocol afforded benzoindole **67** from the corresponding amine in 74% yield. It is believed that photons transform the ruthenium atom into an excited state in which it accepts an electron from arylamine to form N-centred radical cation **68**. Further development of the reaction is shown in Scheme 23.

Scheme 21



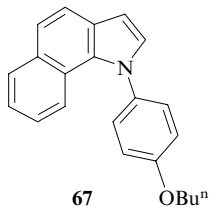
R = H (**63a**, **32**), Me (**63b**, **64**)

Scheme 22



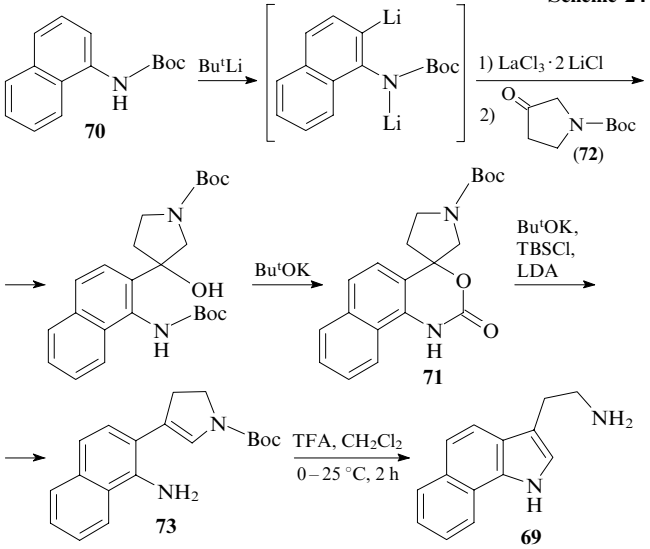
R^1 = H, Me, Ph, *etc*.; R^2 = H, Me, Pr^n, Pr^i, All, *etc*.;
Ar = 4-$MeOC_6H_4$, 4-$Bu^nOC_6H_4$, *etc*.

Structure 67



Nicolaou *et al*.[48,49] have proposed a convenient strategy for the synthesis of biologically important indole derivatives — tryptamines. It has been successfully tested on a wide range of indoles, including benzo[*g*]indole derivative **69**. The starting compounds are N-Boc-protected anilines and naphthylamine **70**. The multistage method

Scheme 24

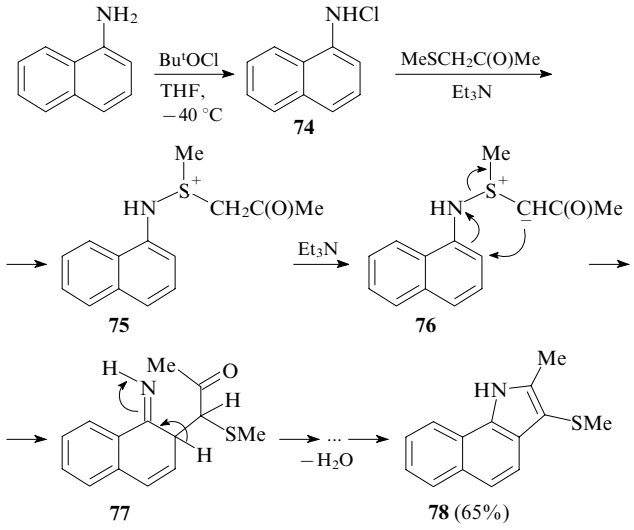


TBS = Bu^tMe_2Si; LDA is lithium diisopropylamide; TFA = CF_3CO_2H

(Scheme 24) consists of three main stages: (1) synthesis of spiro compound **71** through the lithiation of aniline **70** and the subsequent condensation of the lithium derivative with β-pyrrolidone **72**; (2) protection of the NH group and decarboxylation of tetracyclic compound **71**, which makes it possible to introduce a double bond into the five-membered ring; (3) acidic cyclization of naphthylamine **73**. This strategy afforded indoles in 65% – 84% yields, but the yield of benzo[*g*]indole **69** was noticeably lower (41%).

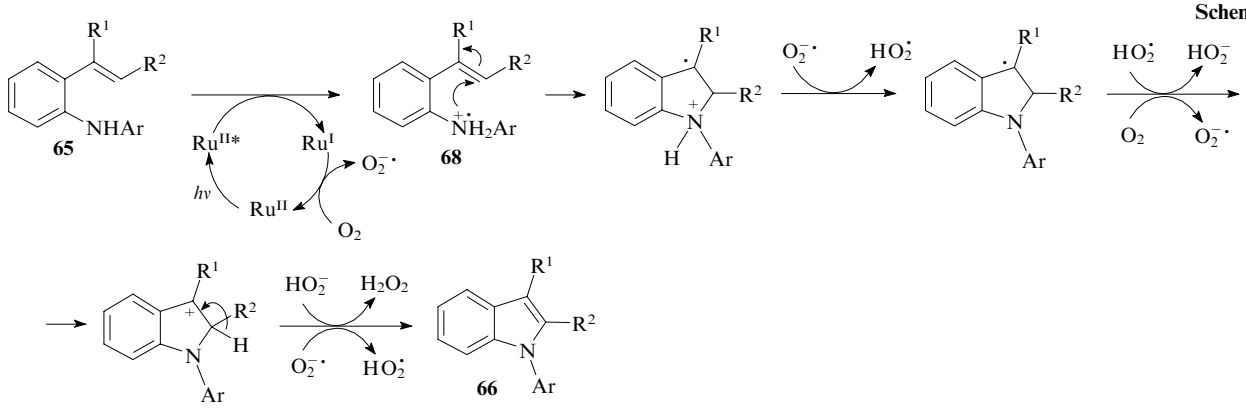
Gassman and Schenk[50] have developed a protocol for pyrrole ring closure based on the specific *ortho*-alkylation of arylamines. For 1-aminonaphthalene as the starting compound, it leads to the formation of the benzo[*g*]indole system (Scheme 25). In the one-pot process, arylamine in THF is successively treated at −40 °C with *tert*-butyl

Scheme 25



hypochlorite, dialkyl sulfide containing a carbonyl function in the β-position to the sulfur atom, for example, 1-(methylsulfanyl)propan-2-one, and a base (conventionally, aqueous alkali or triethylamine). The first steps of the process include the formation of *N*-chloramine **74**, sulfonium salt **75** and ylide **76** undergoing the [2,3]-sigmatropic rearrangement into compound **77**. Tautomerization of the latter to the amine and its cyclization through the addition of the amino group to the carbonyl complete the formation of the pyrrole ring. The method provides opportunities for the functionalization of the final product. In particular, the

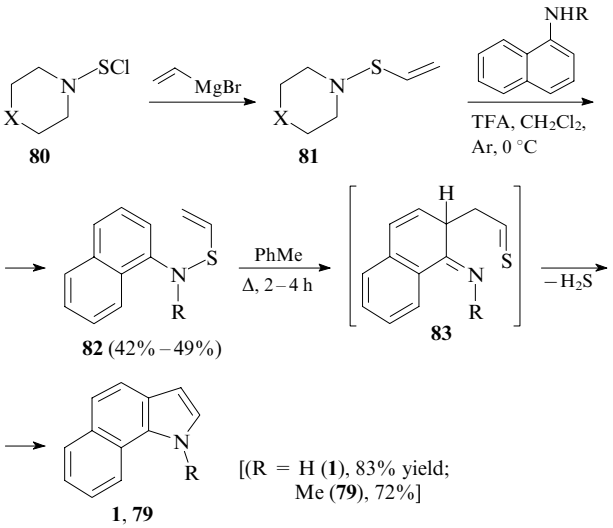
Scheme 23



methylsulfanyl group in benzoindole **78** can be removed by treatment with Raney nickel.

Another kind of cyclization is based on the [3,3]-sigmatropic rearrangement and leads to compounds **1** and **79** (Scheme 26).[51] First, morpholinyl- and piperidinylsulfenyl chlorides **80** react with vinylmagnesium bromide to produce *N*-vinylsulfanyl morpholine and piperidine derivatives **81**. Their subsequent reaction with 1-amino- or 1-methylaminonaphthalene in the presence of TFA gives sulfenamides **82**, which are converted to benzo[*g*]indoles in high yield when refluxed in toluene. It is especially interesting that the method is unsuitable for obtaining indoles themselves. It is believed that this is due to the higher aromaticity of the benzene ring as compared to the naphthalene ring, so that non-aromatic intermediate **83** is not formed in the case of benzene.

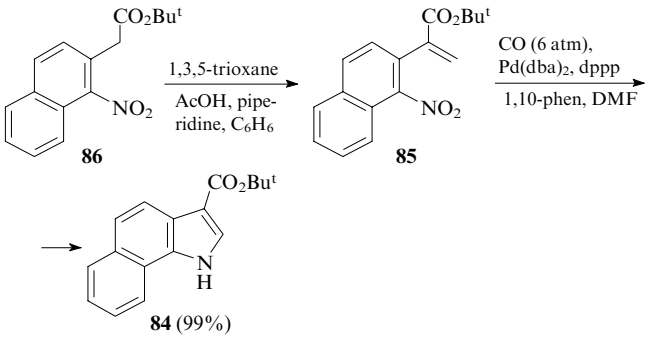
Scheme 26



X = O, CH_2

Indoles with an ester function in the 3-position, for example, compound **84**, are formed in nearly quantitative yields from 2-(1-nitronaphthalen-2-yl)acrylates under Pd catalysis and in a carbon monoxide atmosphere acting as a reducing agent (Scheme 27).[52] The reactants in the synthesis of acrylates (in particular, ester **85**) are nitro esters (for example, ester **86**), which are methylenated on treatment with trioxane.

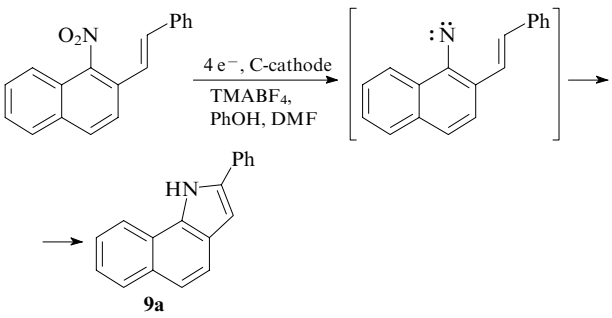
Scheme 27



1,10-phen is 1,10-phenanthroline

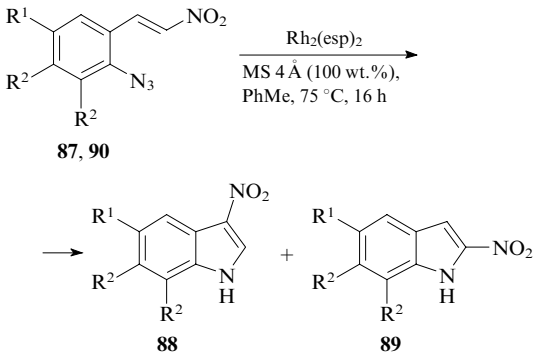
An electrochemical method for the synthesis of indoles by the reduction of *o*-nitrostyrenes on a carbon electrode has been studied.[53] The process was carried out at room temperature in DMF in the presence of tetramethylammonium tetrafluoroborate ($TMABF_4$) (supporting electrolyte) and an excess of a proton donor, for example, phenol. In the case of 1-nitro-2-styrylnaphthalene, the reaction product was 2-phenylbenzo[*g*]indole (**9a**) formd in ~65% yield (Scheme 28). Coulometric studies have shown that one molecule of the initial nitro compound requires ~4 electrons; therefore, it has been assumed that the nitrene intermediate is directly subjected to cyclization.

Scheme 28



Apparently, the nitrene intermediate plays an important role in the formation of indoles from 2-β-nitrostyryl azides under the action of rhodium(II) complexes on them, in particular, $Rh_2(esp)_2$ (esp is α,α,α′,α′-tetramethylbenzene-1,3-dipropionate) (Scheme 29).[54]

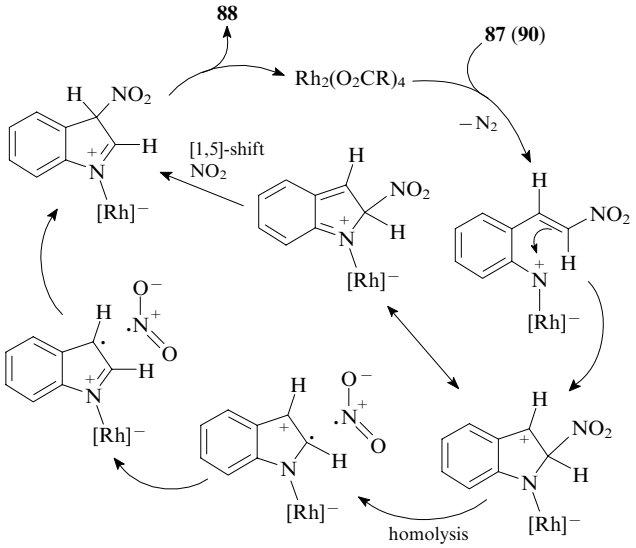
Scheme 29



R^1 = Cl, R^2 = H (**87**); R^1 = H, R^2 – R^2 is benzo (**90**);
MS are molecular sieves

However, most attractive in this transformation is the migration of the nitro group and other electron-withdrawing substituents in the expected 2-nitro product from the 2- to the 3-position. For example, in the case of styryl azide **87**, the ratio of 3- (**88**) and 2-nitro (**89**) derivatives exceeded 95 : 5 at the 90% overall yield of isomeric indoles. Interestingly, in the case of synthesis of benzo[*g*]indoles from compound **90**, this method leads to the ratio close to 1 (49 : 51) at the 94% overall yield. The tentative reaction mechanism in shown in Scheme 30 (substituents in the benzene ring are omitted for clarity). Similar cyclizations that occur upon photolysis of 1-azido-2-alkenylnaphthalenes have been reported.[55]

Scheme 30



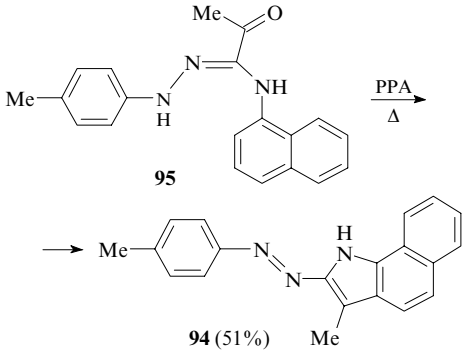
Rare examples are known when the aryl nitro group, without its preliminary reduction to the amino group, serves as the source of the pyrrole nitrogen atom. For example, *o*-nitroarylethanes which contain a methylene moiety activated for acid ionization by an acceptor and an alkene group are cyclized in the presence of bases into 1-hydroxyindoles. In particular, treatment of 1-nitro-2-cyanomethylnaphthalene (**91**) with allyl bromide in methanol in the presence of potassium carbonate gives benzo[*g*]indoles **92** and **93**.[56] The tentative reaction mechanism is shown in Scheme 31. Recently, other synthetic possibilities for the synthesis of indoles from 1-nitro-2-cyanomethylarenes have been demonstrated.[57]

II.1.b. Cyclization of type B

A simple example of such cyclization is the formation of 3-methyl-2-(*p*-tolyldiazenyl)-1*H*-benzo[*g*]indole (**94**) by heating amidrazone **95** in polyphosphoric acid (PPA) (Scheme 32).[58] As in many other reactions of nucleophilic addition to the carbonyl group, PPA plays the role of an acid catalyst and a water-removal agent.

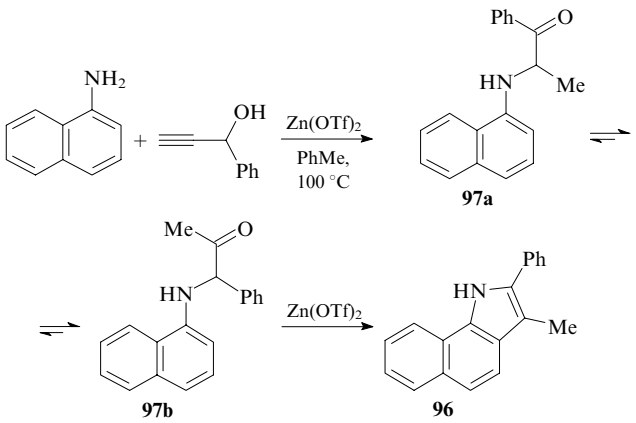
One of the known examples of pyrrole ring closure of type **B** in indoles and benzo[*g*]indoles is shown in Scheme 33. It consists in heating primary arylamines with propargyl alcohols in toluene in the presence of zinc triflate.[59] In particular, the treatment of 1-naphthylamine

Scheme 32



with 1-phenyl-2-propyn-1-ol leads to benzo[*g*]indole derivative **96** in 93% yield. The process is very difficult. First, the reaction gives two products of addition of the amino group to the triple bond (**97a** and **97b**). However, the equilibrium between them gradually shifts towards isomer **97b** due to its greater ability to transform into indole. A different version of this method has been described where $Ru_3(CO)_{12}$ is used as a catalyst.[60]

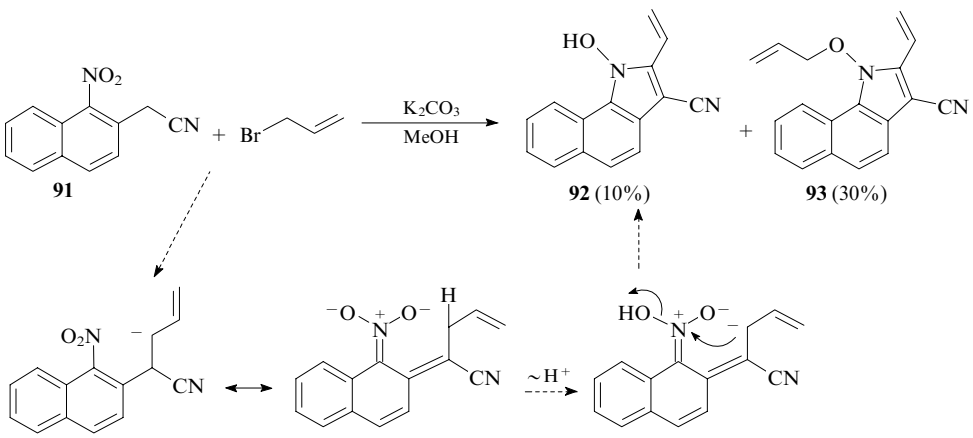
Scheme 33



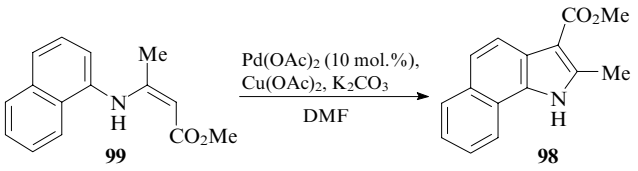
Tf = CF_3SO_2

Benzo[*g*]indole **98** has been synthesized through oxidative cyclization of methyl 3-(1-naphthylamino)crotonate (**99**) (Scheme 34).[61, 62] The process involves simultaneous activation of two $C(sp^2)-H$ bonds by catalytic amounts of $Pd(OAc)_2$. Copper acetate is used as an oxidant for regenerating Pd^{II} from Pd^0 in the course of the catalytic process.

Scheme 31



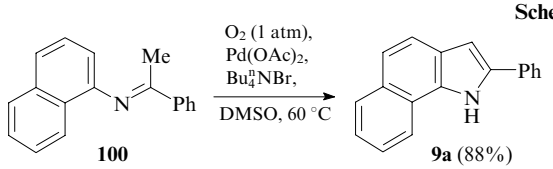
Scheme 34



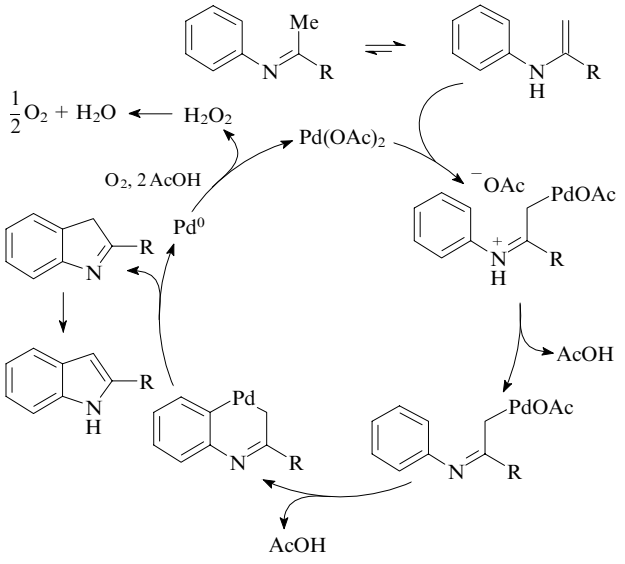
In DMF and in the presence of potassium carbonate as a base, the reaction lasts for 3 h at 80 °C and for 30 min at 140 °C; the yield of compound **98** is as high as 85%. It is possible to use in this reaction iron(III) salts in combination with copper(II) salts,[63] as well as *tert*-butyl hydroperoxide in the presence of catalytic amounts of Bu^n_4NI.[64]

The following example is the Pd-catalyzed aerobic cyclization of imines based on anilines and ketones.[65] Unlike the above reactions, in this transformation $C(sp^2)-H$ and $C(sp^3)-H$ bonds are activated. The yields of indoles are, as a rule, high. In particular, the reaction of imine **100** gave 2-phenylbenzo[*g*]indole (**9a**) in 88% yield (Scheme 35). The tentative mechanism of the process is shown in Scheme 36.

Scheme 35

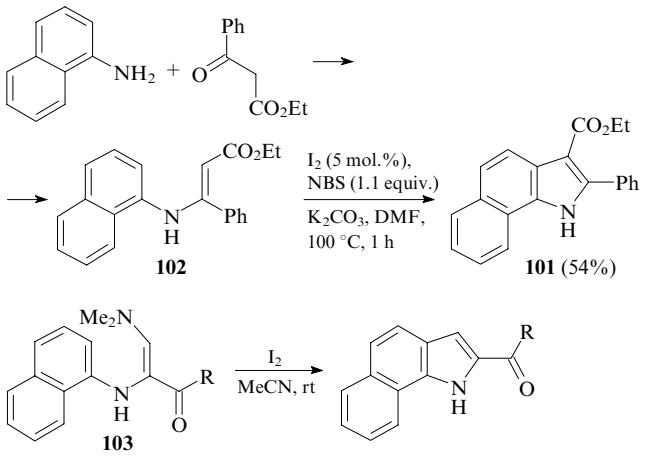


Scheme 36



An iodine-catalyzed synthesis of benzoindoles, for example, compound **101**, from readily available carboxylates **102** (Scheme 37) has been proposed.[66] It works well only when *N*-bromosuccinimide (NBS) is used as the oxidant. It is believed that first NBS oxidizes iodine to I^+, which converts enaminone **102** to the N – I derivative. The homolysis of the N – I bond leads to the closure of the pyrrole ring. As a result of further oxidation and deprotonation, product **101** is formed. At the same time, there is a non-catalytic version of this method where iodine is used in a stoichiometric amount, and enaminones **103** serve as substrates (see Scheme 37).[67] In this case, NBS is not required.

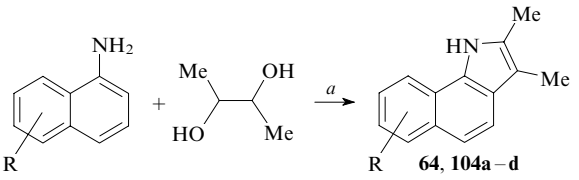
Scheme 37



R = OMe (70% yield), Me (25%)

It has been shown that 1-naphthylamines react with vicinal diols at elevated temperature in the presence of catalytic systems, such as $IrCl_3$ – BINAP,[68] $RuCl_3$ – Xantphos[69] and $[Ru(CO)_2(Xantphos)]_2$,[70] to form benzo[*g*]indole derivatives **64**, **104a** – **d** in high yield (Scheme 38). The reaction with ethylene glycol gave parent compound **1** in 43% yield,[68] and with phenylethylene glycol, the reaction led to 2-phenylbenzo[*g*]indole (**9a**) in 46% yield.[69]

Scheme 38

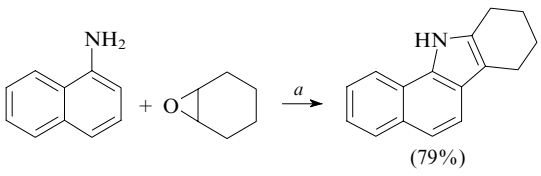


(*a*) $IrCl_3 \cdot 3H_2O$, BINAP, Na_2CO_3, mesitylene, air, Δ, 15 h

R in starting amine	Product	Yield (%)
H	**64**	96
4-Me	**104a**	88
5-OMe	**104b**	76
7-OMe	**104c**	76
5-NH_2	**104d**	52

A version of this method is direct synthesis of indoles and benzo[*g*]indoles by the reaction of anilines and their benzo analogues with epoxides in the presence of ruthenium complexes (Scheme 39).[71]

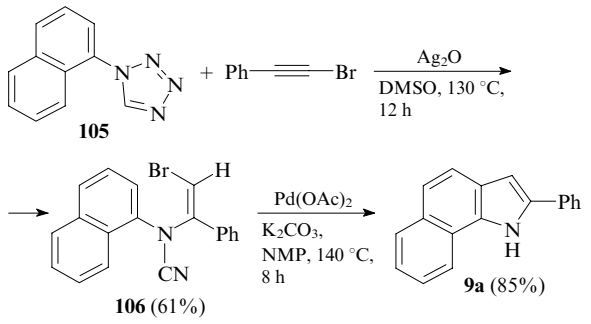
Scheme 39



(*a*) $Ru_3(CO)_{12}$, dppf, TsOH, 1,4-dioxane, 150 °C, 22 h;
dppf is 1,1′-bis(diphenylphosphino)ferrocene

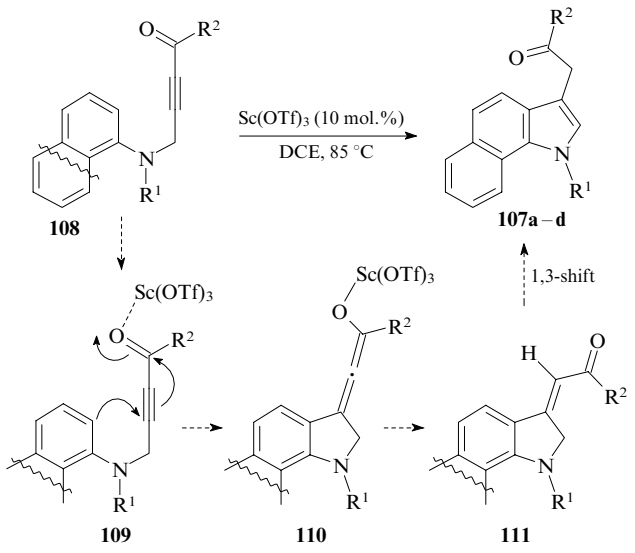
2-Arylindoles and 2-arylbenzo[*g*]indoles can be produced in two stages from 1-aryltetrazoles (Scheme 40).[72] At the first stage, the Ag-catalyzed reaction of aryltetrazole, for example, compound **105**, with 1-phenyl-2-bromoacetylene leads to (*Z*)-*N*-aryl-*N*-(2-bromovinyl)cyanamide **106**. The treatment of the latter with palladium(II) acetate in the presence of potassium carbonate in *N*-methylpyrrolidone leads to the pyrrole ring formation due to the aromatic C–H bond activation. The cyano group in the initially formed 1-cyanobenzoindole is readily removed by hydrolysis. The method ensures high yields (for example, 85% in the case of compound **9a**).

Scheme 40



3-Phenacylbenzo[*g*]indoles **107a–d** have been synthesized in moderate yield by the reaction of aryl[3-(1-naphthylamino)prop-1-ynyl]ketones **108** with scandium triflate in dichloroethane.[73] The tentative reaction mechanism involving formation of intermediates **109–111** is shown in Scheme 41.

Scheme 41

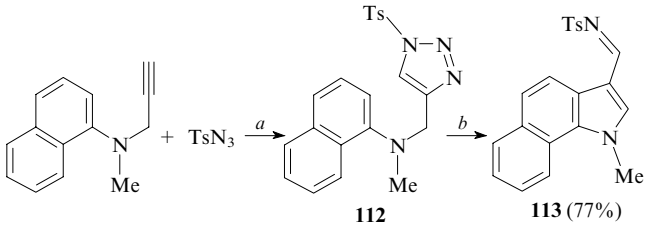


DCE is 1,2-dichloroethane

Compound **10**	R^1	R^2	Yield (%)
a	Bn	Ph	56
b	All	Ph	40
c	Me	Ph	45
d	Me	4-MeC_6H_4	42

Another option of using *N*-propargylanilines implies their Cu-catalyzed (CuTC is copper thiophene-2-carboxylate) conversion to *N*-[(1-tosyl-1,2,3-triazol-4-yl)methyl]-anilines **112** followed by the treatment with the Rh^{II} catalyst (Scheme 42).[74] The final product of the reaction proceeding with elimination of the N_2 molecule through the carbenoid intermediate is benzoindolyltosylimine **113**. Subsequent hydrolysis or reduction in the same flask leads to 3-formyl- or 3-aminomethylbenzoindole; the yields of all products are generally high.

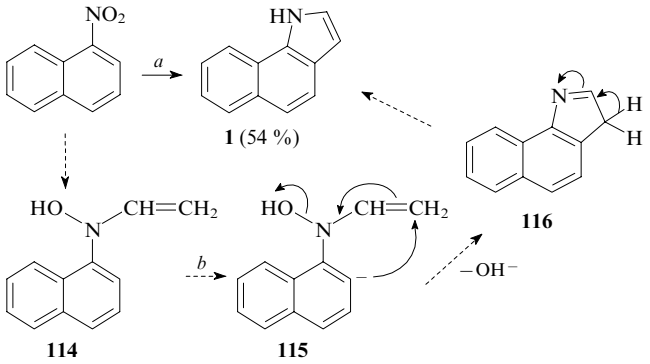
Scheme 42



(*a*) CuTC, PhMe, rt, 2 h; (*b*) $Rh_2(oct)_4$, DCE, 60 °C, 4 h; oct is octanoate

The reaction of *ortho*-substituted nitrobenzenes with vinylmagnesium bromide (3 equiv.) in THF at −40 °C followed by the treatment with water has been reported to give the corresponding 7-substituted indoles in 41%–67% yield.[75] The use of 1-nitronaphthalene as a substrate results in unsubstituted benzo[*g*]indole (**1**) (Scheme 43). Although there is no exact information on the mechanism of this reaction, it presumably includes the reductive addition of vinylmagnesium bromide to the nitro group to form arylvinylhydroxylamine **114**, metallation of the *ortho*-position with another equivalent of vinylmagnesium bromide to form carbanion **115** and its cyclization accompanied by elimination of the hydroxyl group and tautomerization of 3*H*-indole **116**.

Scheme 43

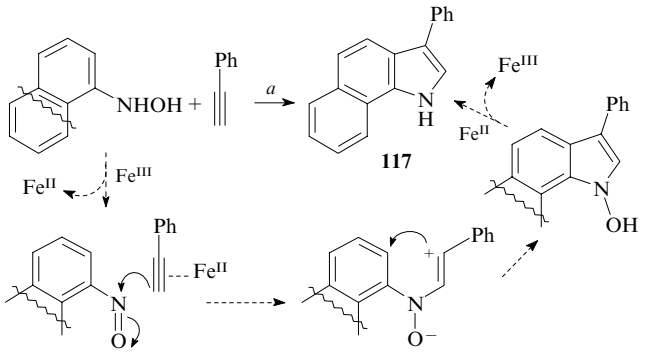


(*a*) 1) CH_2=CHMgBr (3 equiv.), THF, −40 °C; 2) NH_4Cl (aq.); (*b*) CH_2=CHMgBr

A highly regioselective method for the preparation of 3-arylindoles has been developed, consisting in the reaction of terminal arylacetylenes with arylhydroxylamines in boiling toluene.[76] The reaction is catalyzed by an iron(II) complex with phthalocyanine (Pc) and generally gives the products in good yields. The method is suitable for the production of benzo[*g*]indoles, although the yields in this case are somewhat lower, for example, 37% for 3-phenyl derivative **117**. The reaction mechanism seems to include the preliminary formation of nitrosoarene (as a result of oxidation of the substrate by Fe^{III} generated, according to the

authors, in trace amounts when hydroxylamine is reduced by Fe^{II}) and addition of the acetylene group to the latter, as shown in Scheme 44. One example of such a reaction with internal acetylene (methylphenylethyne) has been described; however, the yield of 2-methyl-3-phenylindole was no higher than 25%.

Scheme 44

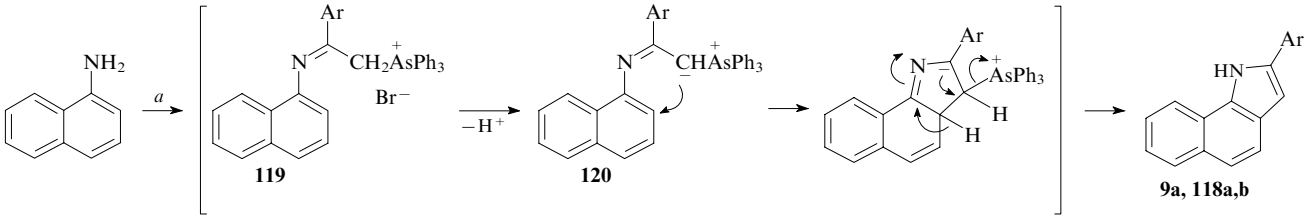


(*a*) $Fe^{II}Pc$, PhMe, Δ

The synthesis of 2-arylindoles and 2-arylbenzo[*g*]indoles **9a** and **118a**,**b** *via* the reaction of arylamines, including 1-aminonaphthalene, with phenacyltriphenylarsonium bromide has been reported (Scheme 45).[77] The reaction is carried out in *N*,*N*-dimethylaniline, which acts simultaneously as a high-boiling solvent and a soft base. There is evidence that the process begins with the formation of Schiff base **119**, converting to ylide **120**, which is subjected to cyclization in quite acceptable yields of the product. The use of ylides based on phenacylpyridinium[78] and phenacyltriethylammonium[79] salts in the reaction affords benzo[*g*]indoles in much lower yields.

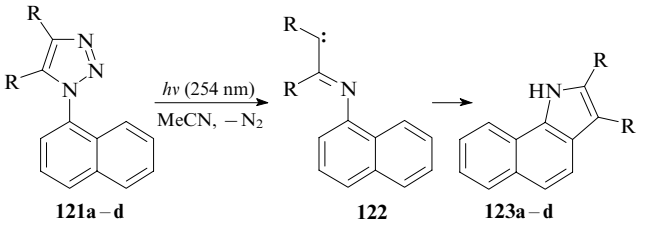
In their now classical study, Mitchell and Rees[80] have demonstrated that benzo[*g*]indoles are formed in photolysis of 1-(1-naphthyl)-1,2,3-triazoles **121** (Scheme 46). This transformation involves the photolytic extrusion of the dinitrogen molecule from the triazole ring to give carbene **122** and its subsequent insertion into the C(2)—H bond of the naphthalene system. The stability of the carbene and its activity in the insertion reaction are crucially determined by the nature of substituents in the 4- and 5-positions of the triazole ring. Carbene is more stable and the reaction is more regioselective when these substituents are identical and are electron acceptors (see Scheme 46, triazoles **121a**–**d**). In particular, the yields of benzo[*g*]indoles **123b**–**d** are 100%, 81% and 64%, respectively (the sharp

Scheme 45



(*a*) $Ph_3\overset{+}{A}sCH_2C(O)ArBr^-$, $PhNMe_2$, Δ, 4 h; Ar = Ph (**9a**, 65% yield), 3-$O_2NC_6H_4$ (**118a**, 53%), 4-MeC_6H_4 (**118b**, 58%)

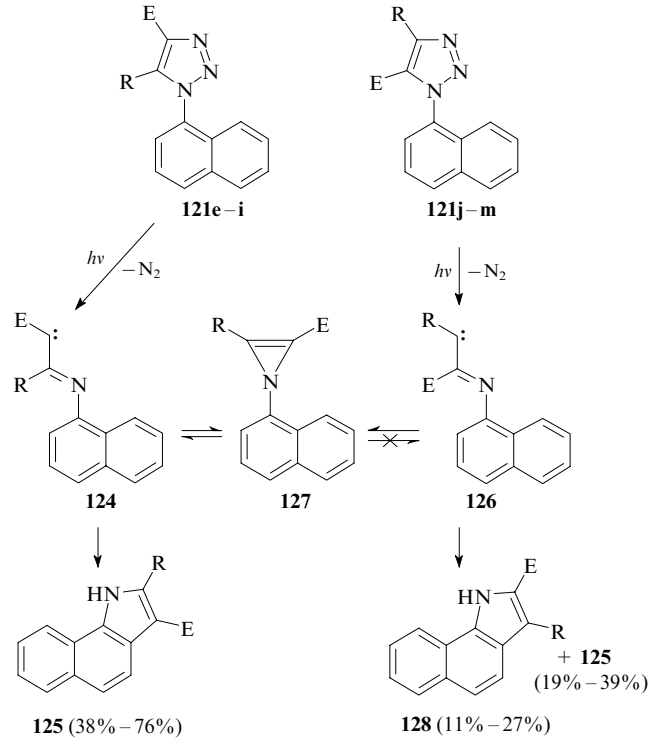
Scheme 46



121a–**d** **122** **123a**–**d**

Compounds **121**, **123**	R	Yield of **123** (%)
a	Bz	18
b	CO_2Me	100
c	$C(O)NH_2$	81
d	CN	64

Compound **121**	E	R
e	CO_2Et	H
f	CO_2Me	Me
g (4-E, 5-R)	CN	H
h (4-E, 5-R)	CN	Me
i (4-E, 5-R)	CO_2Me	H
j	CO_2Et	H
k (5-E, 4-R)	CO_2Me	Me
l (5-E, 4-R)	CN	H
m (5-E, 4-R)	CN	Me



121e–**i** **121j**–**m**

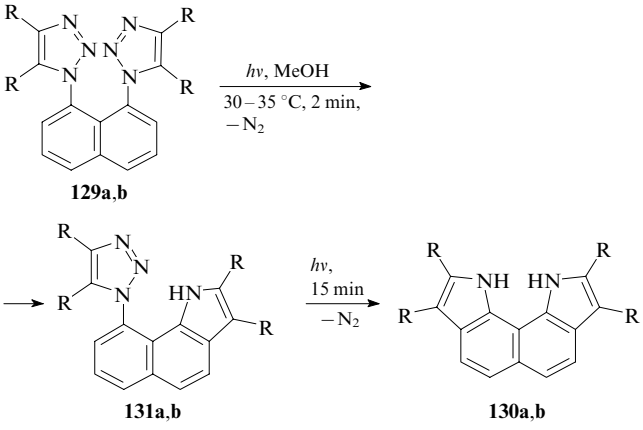
124 **127** **126**

125 (38% – 76%) **128** (11% – 27%) + **125** (19% – 39%)

decrease in the yield of **123a** was attributed to the specifics of its photoexcited state). The situation changes significantly when the substituents in the triazole ring are different (see Scheme 46, triazoles **121e**–**m**). If the more electron-withdrawing group (denoted as E in the Scheme) is in the 4-position, as in triazoles **121e**–**i**, carbenes **124** are formed, which are converted into benzoindoles **125** rather selectively and in good yield. If group E is located at the C(5) atom (compounds **121j**–**m**), the initially formed carbene **126** irreversibly isomerizes to more stable carbene **124** through their common aziridine intermediate **127**. In this case, a mixture of two isomeric benzo[*g*]indoles **125** and **128,** with some predominance of the former, is formed.

Using this approach and 1,8-bis(1,2,3-triazol-1-yl)naphthalenes **129a**,**b** as initial compounds, Japanese chemists[81,82] pioneered the synthesis of tetranuclear indolo[6,7-*g*]indoles **130a**,**b** (Scheme 47). Reducing the irradiation time from 15 to 2 min also allowed them to isolate compounds **131a**,**b**, which formed as intermediates in this reaction. The use of this method for the preparation of other benzo[*g*]indole derivatives has been described.[83] Recently, Curiel *et al.*[84] have developed another route to system **130**, preparing it in the form of carbazolo[1,2-*a*]carbazole.

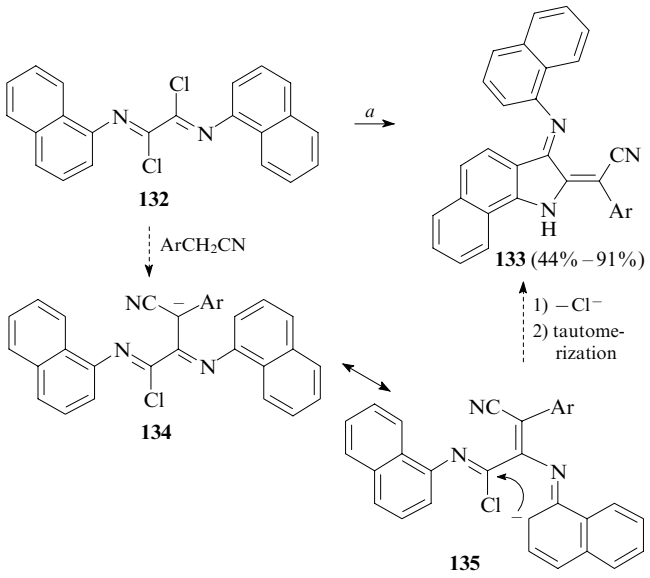
Scheme 47



Compounds **129**–**131**	R	Yield of **130** (%)	Yield of **131** (%)
a	CO_2Et	70	25
b	CO_2Pr^i	72	30

N,*N*′-Bis(1-naphthylimino) derivative of oxalyl chloride **132** reacts with benzyl cyanides in the presence of lithium diisopropylamide, forming 2-alkylidene-3-imino derivatives of benzoindole **133** in good yield.[85] The reaction is accompanied by successive nucleophilic substitution of two chlorine atoms: first, by the benzylcyano group to form resonance-stabilized anion **134**, and then as a result of the intramolecular attack of the *ortho*-C atom of the naphthalene ring in canonical structure **135**, as shown in Scheme 48.

Scheme 48



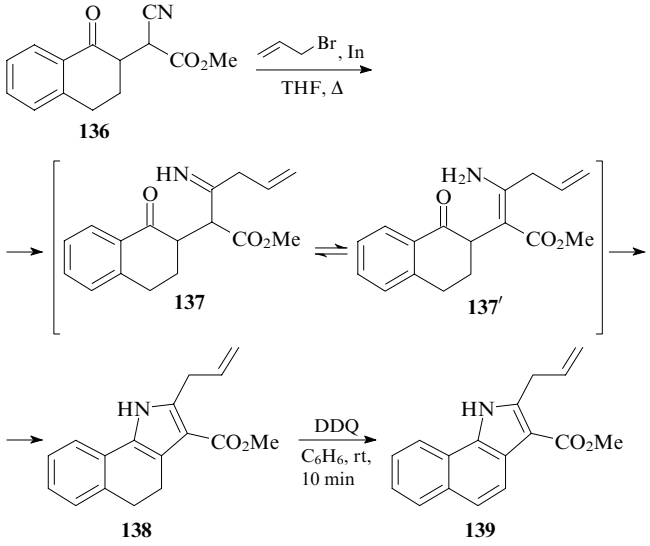
(*a*) LDA (excess), THF, from 0 to −78 °C;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-Naph; Naph is naphthyl

II.1.c. Cyclization of type C

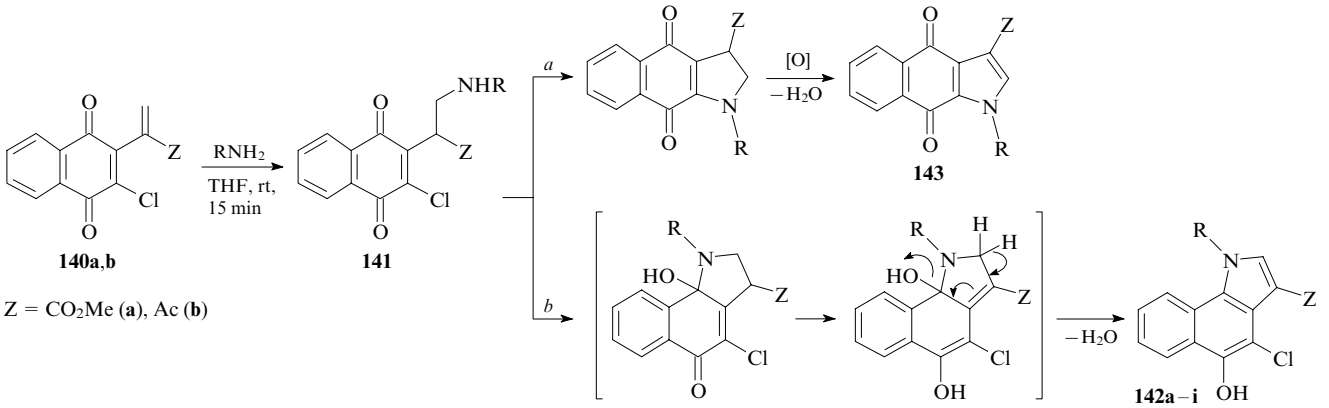
An efficient synthetic strategy for substituted pyrroles, indoles and benzo[*g*]indoles *via* an indium-mediated Barbier type allylation from γ-ketonitriles has been developed.[86] The essence of the method exemplified by tetralone **136** is shown in Scheme 49. The reaction begins with the addition of the allyl anion to the CN group to give imine **137**, which is presumably in equilibrium with enamine **137**′. The latter cyclizes to give 4, 5-dihydrobenzo[*g*]indole **138** (62% yield), which is almost quantitatively dehydrogenated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to form compound **139**.

A protocol has been suggested for the synthesis of benzo[*g*]indoles from 2-chloro-1,4-naphthoquinones **140a**,**b**, containing the methyl acrylate or methyl vinyl ketone residue in the 3-position (Scheme 50).[87] The anti-Markovnikov addition of primary amines to the C=CH_2 bond in quinone **140** leads to the formation of amines **141**, which are then cyclized *via* displacement of the chlorine atom (path *a*) or through nucleophilic addition to the quinoid carbonyl group (path *b*). Path *b* prevails to give 1*H*-benzo[*g*]indoles **142a**–**i**, as a rule, in good yield. The yield of isomeric benzo[*f*]indoles **143** is no higher than 6%–14%.

Scheme 49



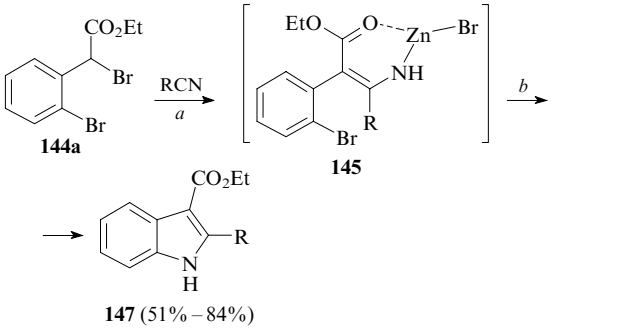
Scheme 50



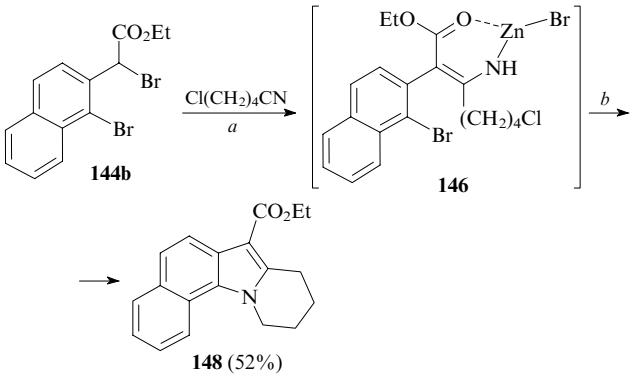
Z = CO_2Me (**a**), Ac (**b**)

Compound **142**	R	Z	Yield (%)	Compound **142**	R	Z	Yield (%)
a	H	CO_2Me	51	**e**	Pr^i	CO_2Me	79
b	H	Ac	27	**f**	Ph	CO_2Me	75
c	Me	CO_2Me	79	**g**	Bn	CO_2Me	68
d	Et	CO_2Me	75	**h**	Me	Ac	82
				i	Et	Ac	85

Scheme 51



R = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$F_3CC_6H_4$, 4-$EtO_2CC_6H_4$, 4-NCC_6H_4, 3-Py, 2-Fu, Et, Bn; Py is pyridyl, Fu is furyl

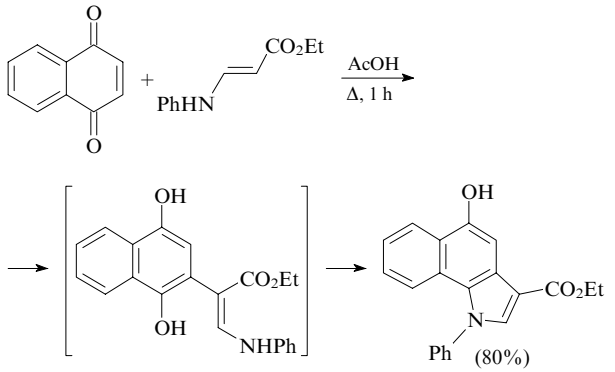


(*a*) Zn, THF, Δ, 1.5 h; (*b*) $Pd(PPh_3)_4$, Bu^tOK, THF – DMF (1 : 10), 120 °C, 15 h

Another original route, in which the pyrrole ring closure occurs through intramolecular substitution of the side amino group for the aromatic halogen atom, starts from dibromo derivatives **144a**,**b**. The latter, under the action of zinc and an appropriate nitrile, are converted to Reformatsky reagents **145** or **146**. Then, a Pd-catalyst and a base are added into the mixture, which causes the formation of 3-ethoxycarbonyl derivatives of indole **147** or benzo[*g*]indole **148** (Scheme 51).[88]

5-Hydroxybenzo[*g*]indoles, especially attractive for medicinal chemistry, are commonly synthesized by the Nenitzescu reaction — the acid-catalyzed addition of unsaturated β-amino acid esters to 1,4-quinones with subsequent intramolecular substitution of the amino group for one phenohydroxy group (Scheme 52).[89]

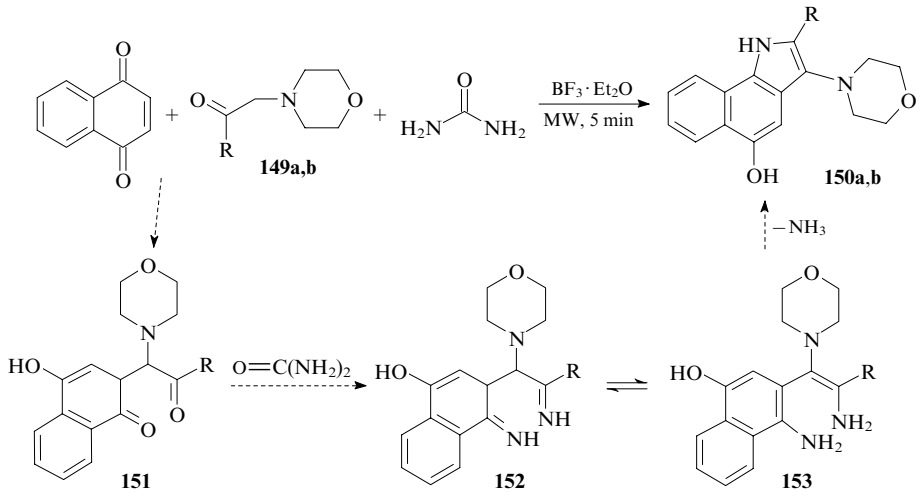
Scheme 52



A modified variant of the Nenitzescu reaction has been suggested in which 1,4-naphthoquinone reacts with morpholinoacetophenone **149** and urea in the presence of boron trifluoride etherate under microwave irradiation (Scheme 53).[90] A total of twelve benzo[*g*]indole derivatives in 52% to 88% yield have been synthesized under these conditions (for example, compound **150a**,**b**). The tentative reaction mechanism comprises 1,4-conjugate addition of ketone **149** to quinone to give diketone **151**, its transformation under the action of urea to diimine **152**, which is in tautomeric equilibrium with enamine **153**, and cyclization of the latter accompanied by elimination of ammonia molecule.

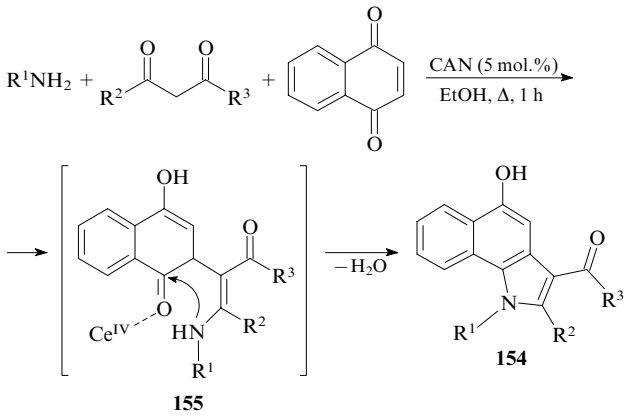
One more modification of the Nenitzescu reaction, which affords various benzo[*g*]indoles **154** in high yield

Scheme 53



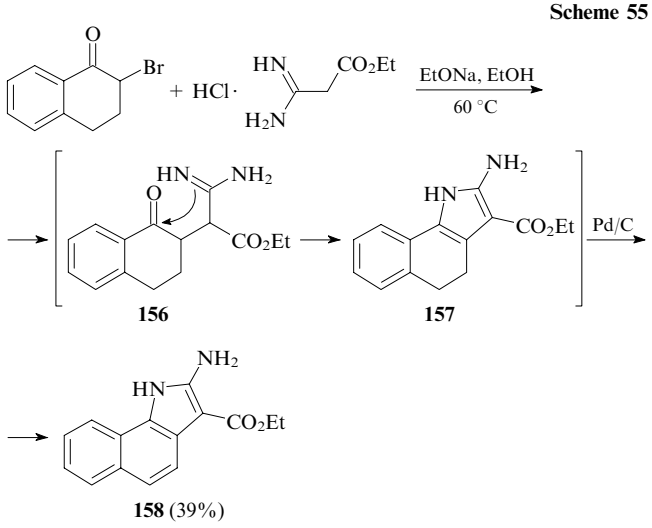
R = 4-MeC_6H_4 (**a**, 80% yield), 4-ClC_6H_4 (**b**, 75%)

Scheme 54



R^1 = Alk, All, $CH_2C{\equiv}CH$, Bn; R^2 = Alk; R^3 = OAlk, SBu^t

Scheme 55



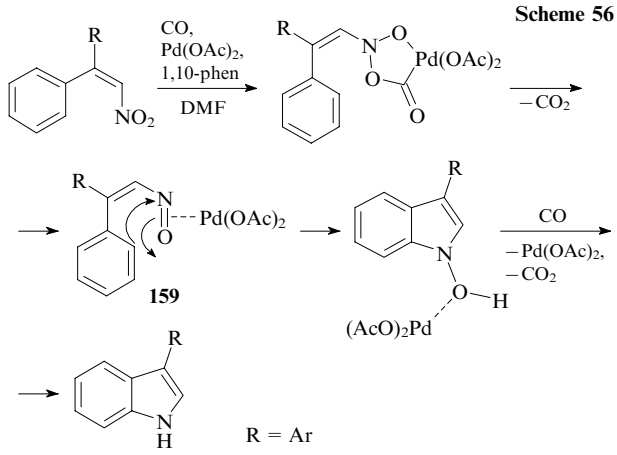
158 (39%)

(50% – 96%), is the three-component reaction of a primary amine, β-dicarbonyl compound and 1,4-naphthoquinone. The reaction is catalyzed by cerium ammonium nitrate (CAN), and the immediate precursor of benzo[*g*]indole is enamine **155** (Scheme 54).[91,92] To produce complex polysubstituted benzo[*g*]indoles, quinone-2,3-dicarboxylates[93] and other 1,4-naphthoquinone derivatives can be used.[94] The use of the known aluminosilicate montmorillonite as an acid catalyst in the Nenitzescu reaction turns out to be very efficient, including benzoindole synthesis.[95]

2-Bromotetralone, when heated with ethyl 3-amino-3-iminopropanoate in ethanol in the presence of sodium ethoxide, first undergoes alkylation to form intermediate **156**, which is cyclized to 4,5-dihydrobenzo[*g*]indole derivative **157**. The attempt to isolate the latter in the pure form failed. However, it was dehydrogenated directly in the reaction mixture to benzo[*g*]indole **158** by the action of palladium on carbon (Scheme 55).[96]

The Pd-catalyzed reduction of (*Z*)-(2-nitrovinyl)arenes with carbon monoxide is another relatively recent method for the preparation of indoles and benzoindoles

Scheme 56

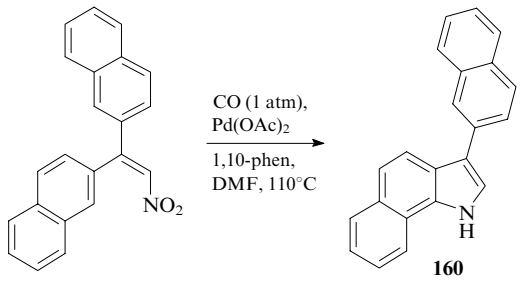


R = Ar

(Scheme 56).[97] Palladium is believed to facilitate the reduction of the nitro group to the nitroso group. The latter, being activated by the action of $Pd(OAc)_2$, already as an electrophile in intermediate **159**, intramolecularly attacks the benzene ring to form the corresponding indole in good yield (58% – 98%). The method successfully complements the traditional methods of producing nitrosoarenes from oximes and vinyl azides, which have limitations.

This protocol enabled the synthesis of 3-(2-naphthyl)-benzo[*g*]indole (**160**) in 79% yield from 2,2-bis(2-naphthyl)-nitroethene (Scheme 57).[97]

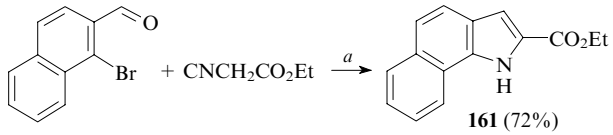
Scheme 57



160

The synthesis of benzo[*g*]indole-2-carboxylate **161** from 1-bromonaphthalene-2-carbaldehyde and ethyl isocyanoacetate turned out to be simple and efficient (Scheme 58).[98] The tandem reaction involving the Ullmann coupling is best carried out in DMSO in the presence of CuI and does not require using any ligand. The reaction is also efficient for synthesis of indoles.

Scheme 58



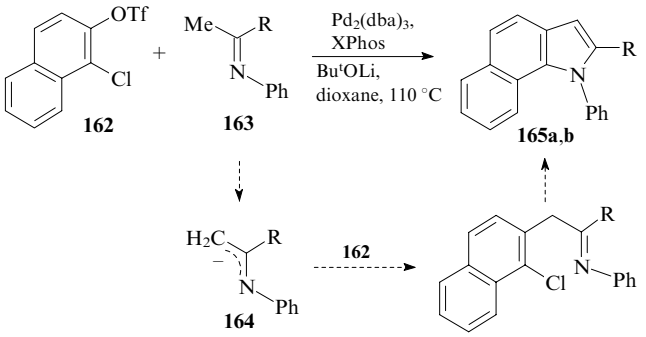
161 (72%)

(*a*) CuI, Cs_2CO_3, DMSO, N_2, 50 °C, 4 h

In 2009, Spanish chemists[99, 100] have developed a method for the synthesis of indoles and their benzo analogues based on the Pd-catalyzed reaction of *o*-dihaloarenes or *o*-chloroaryl sulfonates (for example, compound **162**) with imines **163** in the presence of a base. The reaction starts with the formation of azaallyl anion **164**, which is subjected under these conditions to selective α-arylation followed by the C—N bond formation and pyrrole core closure. Generally, the reaction affords the product in good yield and is especially important for indole synthesis in view of the wide possibilities for varying the substituents in the aryl nucleus and imine. It proceeds somewhat more difficultly for benzo[*g*]indoles, for example, compounds **165a**,**b** (Scheme 59).

It is known that indoles can be synthesized from α-azido-β-arylacrylates through intramolecular amination

Scheme 59

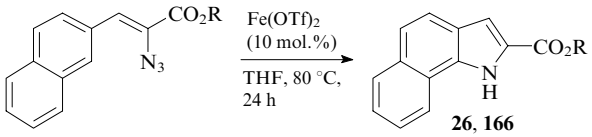


162 **163** **165a**,**b** **164**

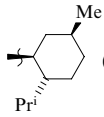
XPhos is 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl;
R = Ph (**a**, 66% yield), Me (**b**, 26%)

of the aromatic C—H bond. For a long time, reactions of this type were carried out *via* azide photolysis or thermolysis, which resulted in elimination of N_2 molecule and formation of nitrene as an active intermediate.[101] However, it has recently been shown that it is more practical to use a transition metal salt, for example, Pd^{II} (Ref. 102), Rh^{II} (Ref. 103), Zr^{IV} (Ref. 104) or Fe^{II} (Ref. 105) as a catalyst. This can be exemplified by the preparation of benzo[*g*]indoles **26** and **166** in nearly quantitative yield (Scheme 60).[105] Nitrene precursors in such transformations can also be *O*-acyloximes.[102] It is believed that the transition metal promotes both the generation and stabilization of nitrene, which is inserted into the C—H bond (*cf.* Schemes 28 and 29, 30).

Scheme 60

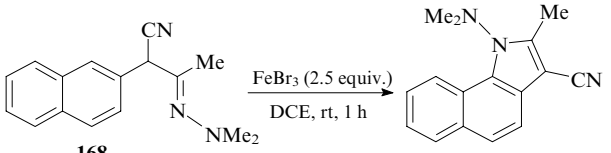


26, **166**

R = Me (**26**, 98% yield),  (**166**, 92%)

Like many other 1-aminoindoles, the 1-dimethylamino-benzo[*g*]indole derivative **167** was obtained by the oxidative C—N coupling of hydrazone **168** under the action of $FeBr_3$ (Scheme 61).[106] In a similar way, 1-methoxybenzo[*g*]indoles can be synthesized from the corresponding *O*-methyloximes under the action $FeCl_3$.[107]

Scheme 61



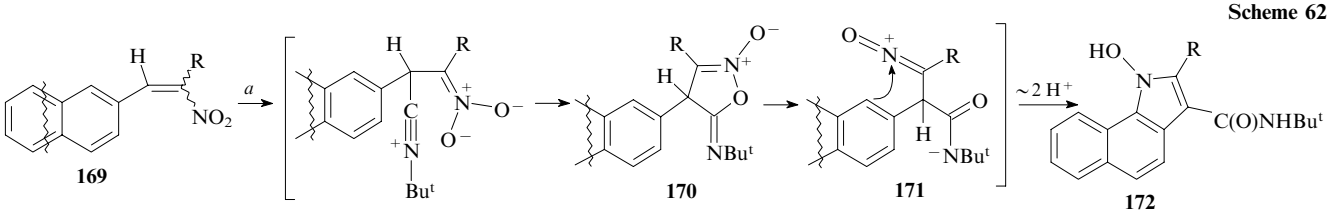
168 **167** (48%)

An original protocol for the synthesis of N-hydroxy derivatives of indoles and benzoindoles has been reported,[108] which is based on the [1 + 4]-cycloaddition of isonitriles to 1-aryl-2-nitropropenes **169** (Scheme 62). The primary products of this reaction are isoxazoline *N*-oxides **170**. They are isomerized into open chain species — cyanide oxides **171**, which electrophilically attack the arene nucleus to give benzoindoles **172**.

Because of the increased interest in superelectrophiles, bis(1-methylbenzimidazol-2-yl)(2-naphthyl)methanol (**173**) was treated with a $TfOH-SbF_5$ mixture to give trication **174**. Its further transformation unexpectedly led to fused benzo[*g*]indole derivative **175** in almost quantitative yield. The mechanism of its formation implies the nucleophilic attack of the nitrogen atom at the naphthalene nucleus in the canonical structure of dication **176**, which forms in a mixture as a result of partial deprotonation of trication **174** (Scheme 63).[109]

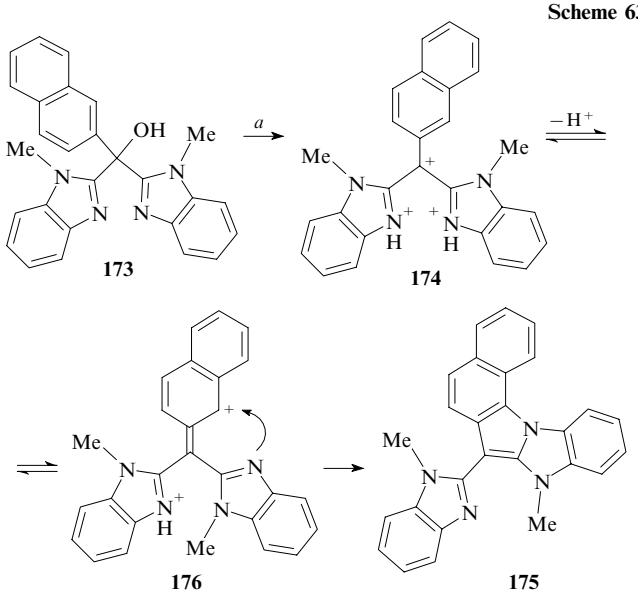
Type **C** pyrrole ring closure can be realized using acetylene building blocks.[110] In particular, a highly effective synthesis of 2,3-fused pyrroles from cyclic ketones has been achieved under relatively mild conditions. The cyclic ketones are converted in two stages into 1-ethynylcyclohex-

Scheme 62



(*a*) $Bu^t-\overset{+}{N}\equiv\overset{-}{C}$; **172**: R = Me, 30% yield; CO_2Me, 26%

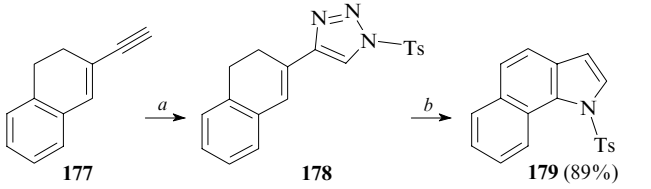
Scheme 63



enes. For example, from 2-tetralone, compound **177** is synthesized (Scheme 64).

Enyne **177** reacts with sulfonyl azides to give 4-alkenyl-1-sulfonyl-1,2,3-triazoles (for example, triazole **178**); when treated with Rh^{II} complexes, they are transformed to partially hydrogenated indoles (in the case of compound **178**, the primary reaction product is 1-tosyl-4,5-dihydrobenzo[*g*]indole). To synthesize aromatic indole **179**, a dehydrogenating agent, usually DDQ, is introduced into the flask where cyclization is carried out. The mechanism of this reaction shown in Scheme 65 for the synthesis of hydrogenated indoles implies the formation of metallocarbene **180** as a key intermediate and its 4π-electrocyclization.

Scheme 64

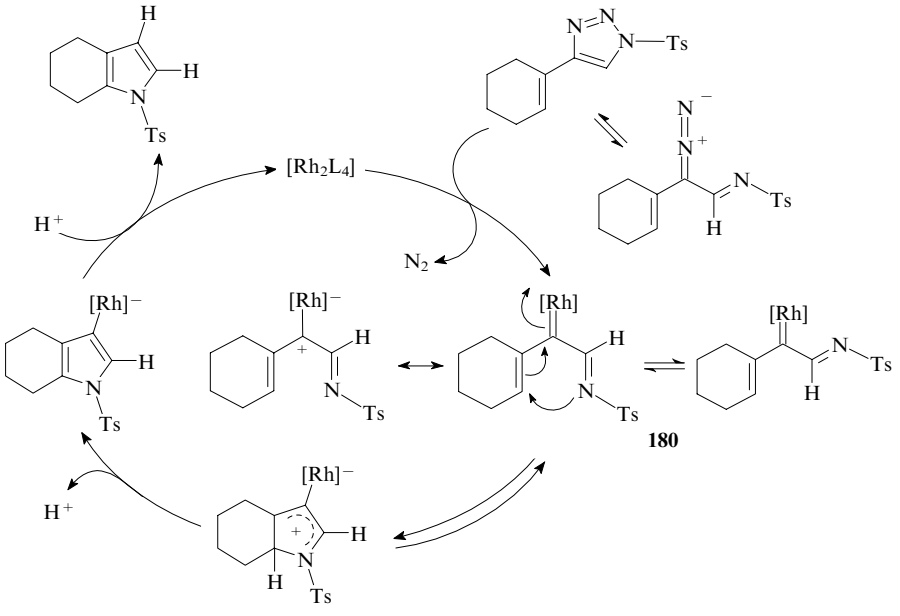


(*a*) TsN_3, CuTC, PhMe, rt, 4 h;
(*b*) 1) $Rh_2(esp)_2$, DCE, 60 °C, 4 h; 2) DDQ

II.1.d. Cyclization of type D

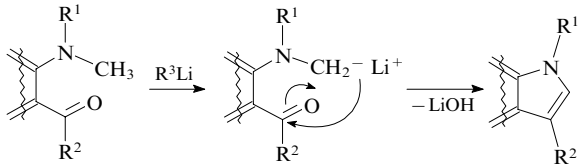
The simplest and most obvious way of closing the pyrrole ring in indoles according to type **D** would be the cyclization of the α-aminomethyl carbanions **181**, generated from 2-carbonyl or 2-cyano derivatives of *N*,*N*-dimethylanilines (Scheme 66). To the best of our knowledge, until recently there have been only two reports[111,112] on this subject, which can be explained by the following reasons. First, α-aminomethyl carbanions are strongly destabilized by repulsion of neighbouring electron pairs on nitrogen and carbon atoms. Indeed, no evidence of their formation in the reaction of, for example, n-butyllithium with dimethylaniline, has been detected.[113] Second, the strong bases required

Scheme 65



for ionization of such slightly acidic C – H bonds should be weak nucleophiles, otherwise their addition to the C=O or C≡N bonds in the *ortho*-substituent to form a tertiary alcohol or imine will prevail. However, the range of such bases is still very limited.

Scheme 66

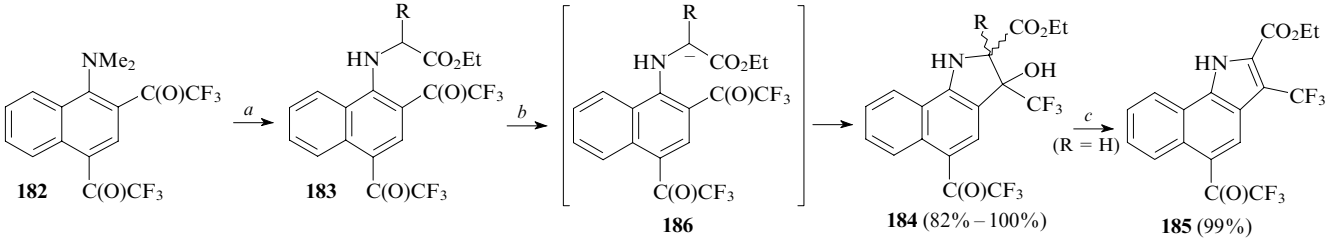


181

Hojo *et al.*[111] found that the treating 1-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene (**182**) with α-amino acid ester leads to the nucleophilic displacement of the NMe_2 group with a primary amino group to give aminodiketones **183**. Their subsequent treatment with triethylamine led to 2,3-dihydro derivatives of benzo[*g*]indole **184** (as two stereoisomers). Alcohol **184** (R = H) was quantitatively aromatized by refluxing in trifluoroacetic acid to give benzo[*g*]indole **185** (Scheme 67). It is likely that in the course of treatment of aminodiketones **183** with triethylamine, an equilibrium amount of aminomethyl carbanion **186** was generated, which was cyclized into pyrrole.

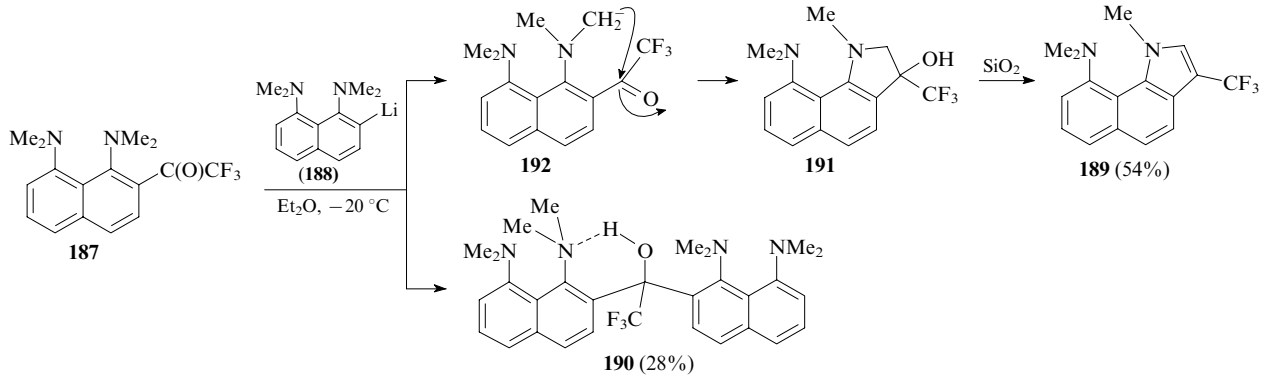
Recently, similar cyclizations involving the aniline NMe_2 group have been performed for the first time in our laboratory (Scheme 68).[112] It turned out that ketone **187** reacts with 2-lithio-1,8-bis(dimethylamino)naphthalene (**188**) in diethyl ether to give a mixture of benzo[*g*]indole **189** and bis(2-naphthyl)methanol **190** in 54% and 28% yield, respectively. The reaction proceeds through the formation of intermediate alcohol **191**, which can be isolated and easily converted into benzoindole **189** by treatment with silica gel. We believe that organolithium compound **188** has an exceptionally high basicity necessary for the acid ionization of the N-methyl group to form carbanion **192**. At the same time, its molecule is sufficiently bulky and, accordingly, its nucleophilicity is low enough to prevent the

Scheme 67

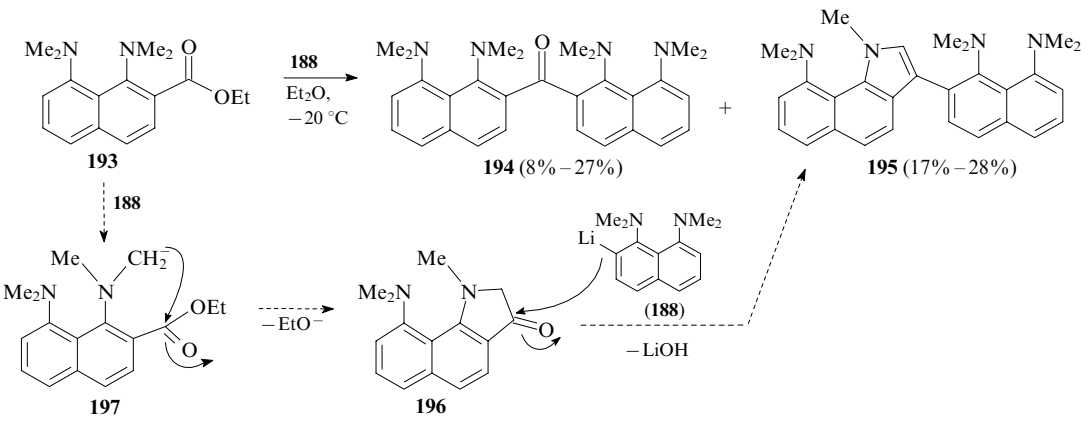


(*a*) $H_3\overset{+}{N}CH(R)CO_2Et$, AcONa, MeCN, rt, 4 h; (*b*) Et_3N, MeCN, Δ; (*c*) TFA; R = H, Me, $(CH_2)_2SMe$, Ph

Scheme 68



Scheme 69



complete attachment to the carbonyl group to form alcohol **190**. Similarly, 1,8-bis(dimethylamino)-2-ethoxycarbonylnaphthalene (**193**) reacts with base **188** to give a mixture of bis(2-naphthyl) ketone **194** and benzo[*g*]indole derivative **195** (Scheme 69). Based on control experiments, it has been shown that the reaction most likely proceeds through 3-oxopyrrole intermediate **196**, which forms upon the cyclization of aminomethyl anion **197**. Attempts to synthesize indoles in this way have not yet been successful.

II.1.e. Cyclization of type E

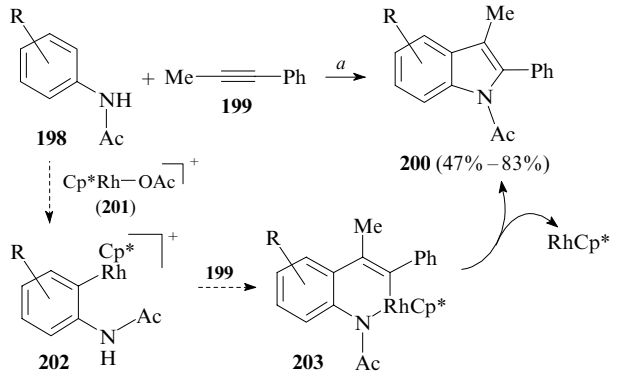
Since the 1980s, acetylenes have become increasingly frequently used as building blocks in synthesis of heterocyclic compounds in general and indoles in particular (see review [114]). In the case of indoles, *o*-haloanilines originally served as starting compounds (see, for example, Scheme 11), which were cyclized when reacting with both terminal and internal acetylenes under Pd catalysis. However, by the end of the first decade of the 21st century, the opinion has been formed that, from considerations of 'green' chemistry and atom-economic technology, it is necessary to abandon the use of halides, replacing them with non-halogenated anilines. This meant that new approaches should, if possible, be based on CH-activation methods therefore, on more efficient catalysts. In this regard, the best results have been demonstrated by rhodium complexes.

For example, in the presence of the $[Cp^*RhCl_2]_2$ catalyst and with the participation of Cu^{2+} and Ag^+ salts, which play the role of oxidants, acetanilides **198** react with acetylenes, for example, with 1-phenylpropyne (**199**), to form polysubstituted indoles **200**.[115,116] It is believed that the cationic form of catalyst **201**, which promotes the activation of the C–H bond in the *ortho*-position of the acetanilide, is generated first under the action of copper acetate. The rhodium atom in intermediate **202** is coordinated to the C≡C bond and makes it possible for six-membered metallacycle **203** to form. Subsequent reductive elimination completes the reaction leading to indole **200** (Scheme 70). The process is characterized by high yields of the products and regioselectivity. As a rule, in the case of asymmetric acetylenes, the sterically less hindered carbon atom of the triple bond is attached to the aniline carbon atom and the sterically more hindered atom is attached to the nitrogen atom. The reaction is also applicable to the synthesis of substituted benzo[*g*]indoles, for example, compound **204** (see Scheme 70). The use of another catalyst — $[Cp^*Rh(MeCN)_3](SbF_6)_2$ — in this method made it possible to greatly extend the range of acetylenes introduced into the reaction and to perform the reaction under milder conditions.[116] The Rh complex containing the cyclopentadienyl ligand with electron-withdrawing groups turned out to be rather efficient.[117]

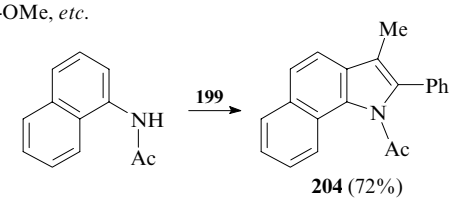
The reaction of *N*-acyl- and *N*-carbamoylanilines with internal enynes in the presence of Rh^{III} and Cu^{II} cocatalysts has been suggested as an efficient method of the preparation of 3-alkyl-2-vinylindoles or 2,3-dialkylindoles [after the reduction of the vinyl group with hydrogen on Pd (10%)/C] (Scheme 71).[118]

The direction of such reactions can be sensitive even to insignificant changes in the catalytic additives and the nature of the solvent.[119] In particular, 1-naphthylcarbamates **205** react with acetylenes in the presence of a neutral Rh^{II} catalyst in a polar medium (DMF) through *peri*-C–H bond activation to form benzoquinoline derivatives **206** in high yield (Scheme 72). At the same time, in less polar

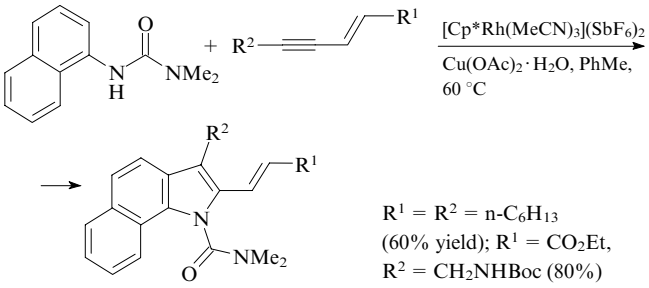
Scheme 70



(*a*) $[Cp^*RhCl_2]_2$, $AgSbF_6$, $Cu(OAc)_2 \cdot H_2O$, Am^tOH, 120 °C, 1 h; $Am^t = CMe_2Et$; for **198**: R = 4-OMe, 4-F, 4-Cl, 4-CO_2Me, 2-Me, 3-OMe, *etc.*



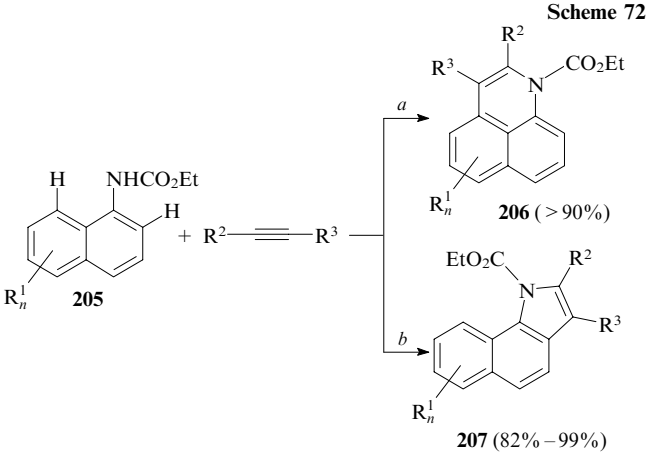
Scheme 71



$R^1 = R^2 = n\text{-}C_6H_{13}$ (60% yield); $R^1 = CO_2Et$, $R^2 = CH_2NHBoc$ (80%)

dichloroethane, the rhodium-catalyzed reaction proceeds through *ortho*-C–H bond activation to give benzo[*g*]indoles **207** also in almost quantitative yield.

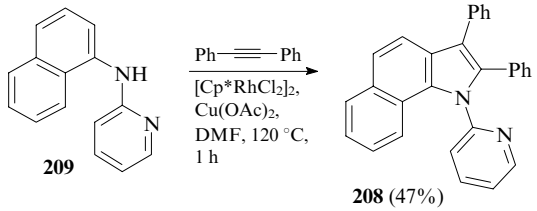
Scheme 72



(*a*) $[Cp^*RhCl_2]_2$, Ag_2CO_3, DMF, 70 °C; (*b*) $[Cp^*RhCl_2]_2$, $AgSbF_6$, $Cu(OAc)_2$, O_2 (1 atm), DCE, 100 °C; for **205**: R^1_n = 4-Br, 4-Me, 4-NO_2, 5-OMe, 6,7-benzo, *etc.*; R^2, R^3 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-Th; Th is thienyl

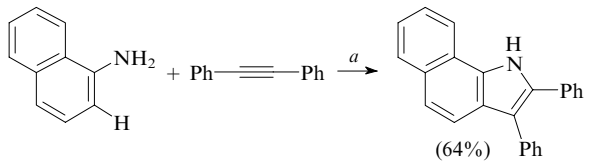
Chinese chemists [120, 121] have developed a method for the synthesis of 1-(2-pyridyl)indoles, which consists in the oxidative coupling of internal alkynes with 2-arylaminopyridines in the presence of a Rh^{III} complex and copper diacetate or a Pd^{II} complex and $CuCl_2$. In Scheme 73, this reaction is exemplified by the preparation of benzo[*g*]indole **208** from 1-naphthylamine derivative **209**. In the mechanism proposed by the authors, an important role of the coordinating and directing centre is assigned to the pyridine nitrogen atom. Subsequently, this approach with even greater efficiency has been extended to alkyne coupling with *N*-(pyrimidin-2-yl)anilines.[122] The reaction was carried out in the presence of the $[RuCl_2(p\text{-cymene})]_2 - Cu(OAc)_2 \cdot H_2O - KPF_6$ catalytic system, the solvent being water. The yield of 1-(pyrimidin-2-yl)-2,3-diphenylbenzo[*g*]indole was 84% in this case. It is also possible to use cheaper nickel complexes in this cyclization either in toluene or under solvent-free conditions.[123] It is also essential that the 2-pyrimidinyl group can be removed by heating with sodium ethoxide in DMSO, which opens the way to N-unsubstituted indoles.[122 – 124]

Scheme 73



To maintain the catalytic cycle in reactions of this type, stoichiometric amounts of oxidizing agents — $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$ or Bu^tOOH — are required. To avoid the associated contamination of the mixture and reaction products, protocols implying the use of oxygen as the oxidant have been proposed. For the first time, this protocol has been applied with $Pd(OAc)_2$ as the catalyst.[125] However, under such conditions, good results have been obtained only with electron-poor alkynes. This limitation was overcome by replacing palladium diacetate with a rhodium complex (Scheme 74).[126]

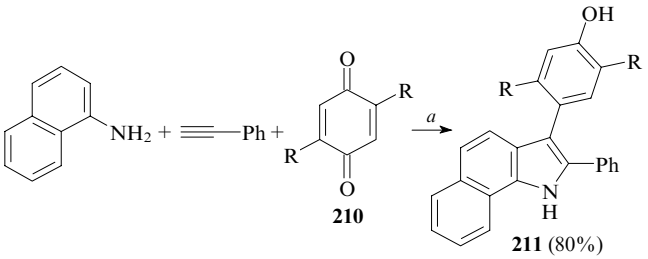
Scheme 74



(*a*) 1) $Cp^*Rh(H_2O)_3(OTf)_2$ (5 mol.%), Ac_2O (1.5 equiv.), O_2 (1 atm); 2) NaOH

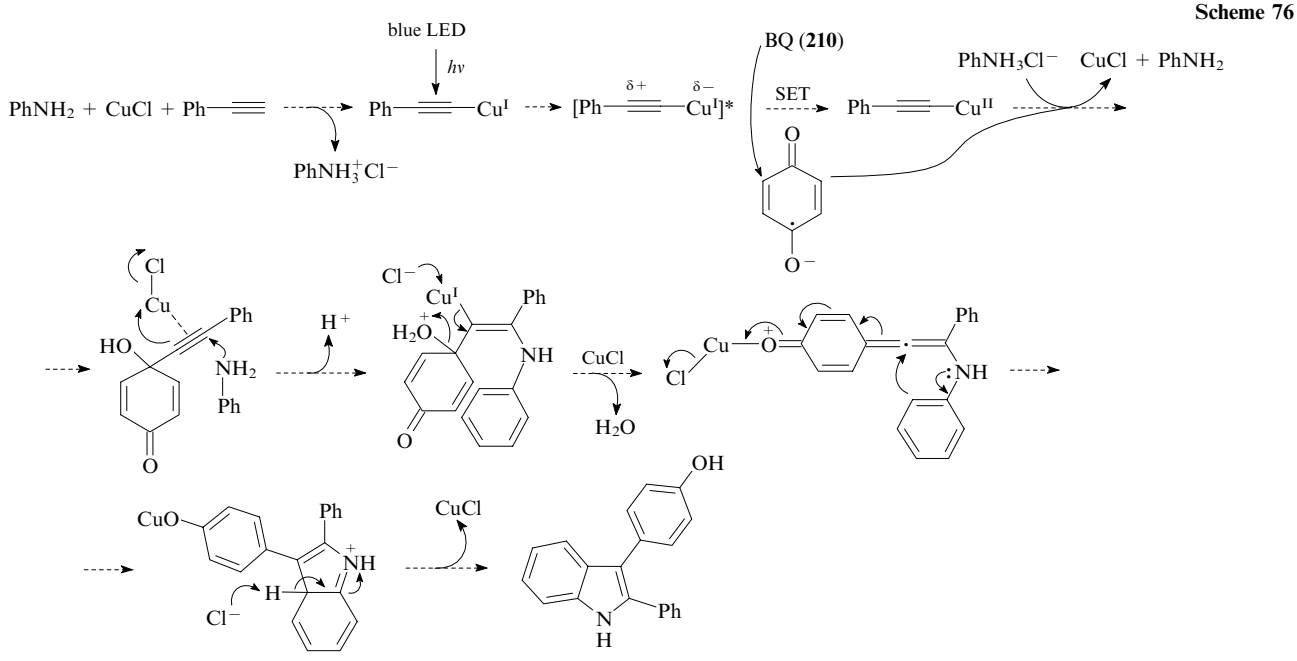
A photochemical approach to indole cyclizations with CH/NH activation, which does not require the use of expensive Rh, Ru or Pd complexes, has also been developed.[127] In particular, a three-component mixture of aniline, terminal alkyne and benzoquinone **210** in methanol exposed to blue light at room temperature undergoes a Cu^I-catalyzed cyclization to the corresponding 3-(4-hydroxyphenyl)indole. In the case of 1-aminonaphthalene, benzo[*g*]indoles **211** were obtained in 80% yield (Scheme 75). The proposed reaction mechanism implies the formation of copper(I) acetylide, its photoexcitation, one-electron transfer to benzoquinone (BQ), the addition of copper(II) acety-

Scheme 75



(*a*) CuCl, MeOH, N_2, rt, blue LED; R = H, Me

Scheme 76

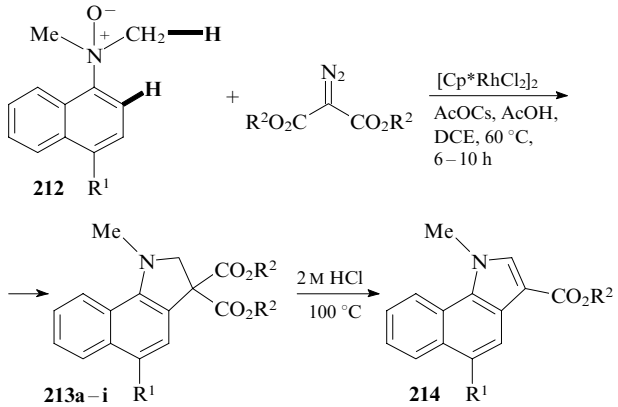


lide to the benzoquinone radical anion and a chain of subsequent reactions shown in Scheme 76.

II.1.f. Miscellaneous methods of pyrrole ring closure

In this Section, we have included mainly the methods in which the bond closure sequence in the pyrrole ring is not completely clear. Several possible mechanisms have been reported. In particular, the Rh-catalyzed reaction of 1-naphthylamine *N*-oxides **212** with diazomalonates gives benzo[g]indolines **213a – i** in 65% – 85% yield. Upon boiling in hydrochloric acid the latter are converted to benzo[*g*]indole-3-carboxylates **214** (Scheme 77).[128] The most significant here is the activation of two bonds at once — $C(sp^3)-H$ and $C(sp^2)-H$ (shown by bold lines in the diagram). However, the sequence of formation of each of the new C – C bonds remains unclear. The reaction is very sensitive to the choice of medium, the best results being obtained in a mixture of dichloroethane and acetic acid. It is noteworthy that the method in which the active intermediate is most likely the metallocarbene formed from the diazo compound is unsuitable for the synthesis of the indoles themselves: in this case, the reaction of *N*,*N*-dimethylaniline *N*-oxides proceeds in another direction.

Scheme 77

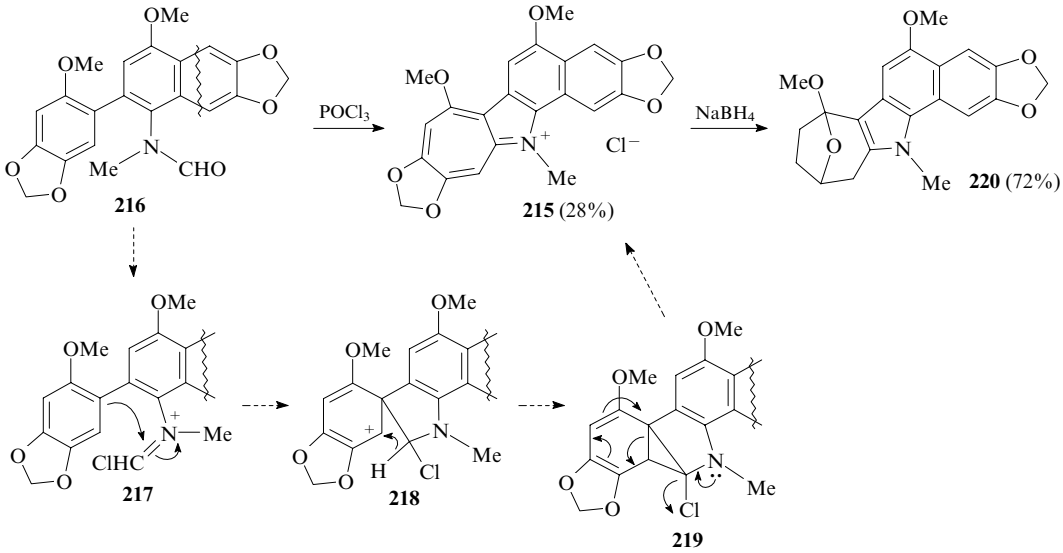


Compound **213**	R^1	R^2	Yield (%)	Compound **213**	R^1	R^2	Yield (%)
a	H	Me	78	**e**	Br	Me	73
b	Me	Me	77	**f**	CO_2Me	Me	65
c	OMe	Me	70	**g**	H	Et	80
d	F	Me	74	**h**	H	Pr^i	85
				i	H	Bn	77

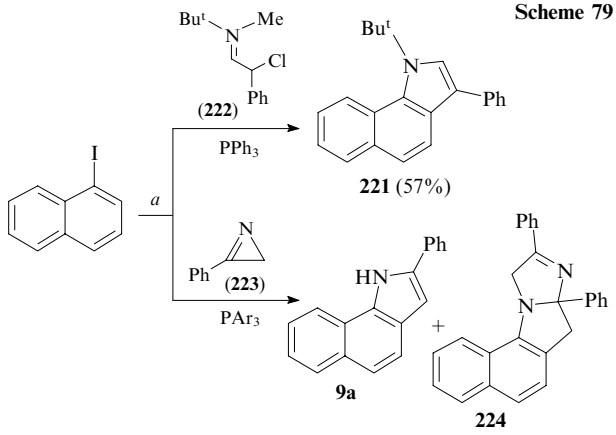
A rather complex case of the pyrrole ring closure with the formation of the benzo[*g*]indolium salt **215** was observed when *N*-(1-naphthyl)formamide **216** was treated with phosphorus oxychloride (Scheme 78).[129] The reaction resembles the first stages of Vilsmeier formylation and probably proceeds through chloromethyleneiminium intermediate **217**. The subsequent electrophilic attack of the π-excessive benzene ring gives σ-complex **218**, which is isomerized to the azaazulene system through intermediate **219**: **218** → **219** → **215**. Reduction of salt **215** with sodium borohydride yielded benzo[*g*]indole derivative **220**.

Strained bicyclic alkenes, especially norbornene (strain energy ~20 kcal mol^{-1}), favour the C – H bond activation in cross-coupling reactions and domino cyclizations, somehow discharging excess energy through a decrease in the activation energy of the process. A typical example is the formation of benzo[*g*]indole **221** in the Pd-catalyzed reaction of 1-iodonaphthalene with chloroimine **222** (Scheme 79).[130] Because of the instability of the chloroimines, 2*H*-azirines were subsequently used instead (see Scheme 79).[131] Careful optimization of the process conditions for azirine **223** and tris(3-chlorophenyl)phosphine as a ligand made it possible to increase the yield of benzo[*g*]indole **9a** to 95%. As a rule, a certain amount of hydrogenated imidazoindoles **224** is formed as a by-product in this reaction, which is also suitable for the synthesis of conventional indoles. The hypothetical mechanism of the process is shown in Scheme 80. Since the reaction does not occur in the absence of norbornene, it is assumed that carbopalladation of its double bond takes place in the first stage to form adduct **A**, after which one of the ligands at the Pd atom is replaced by azirine (complex **B**). The subsequent chain of transformations is determined by the behaviour of azirine as a latent 1,3-dipole, which leads to complex **C** and electrophilic substitution in the aromatic nucleus where the positive end of the 1,3-dipole functions as the electrophile. After reductive elimination, during which norbornene and

Scheme 78

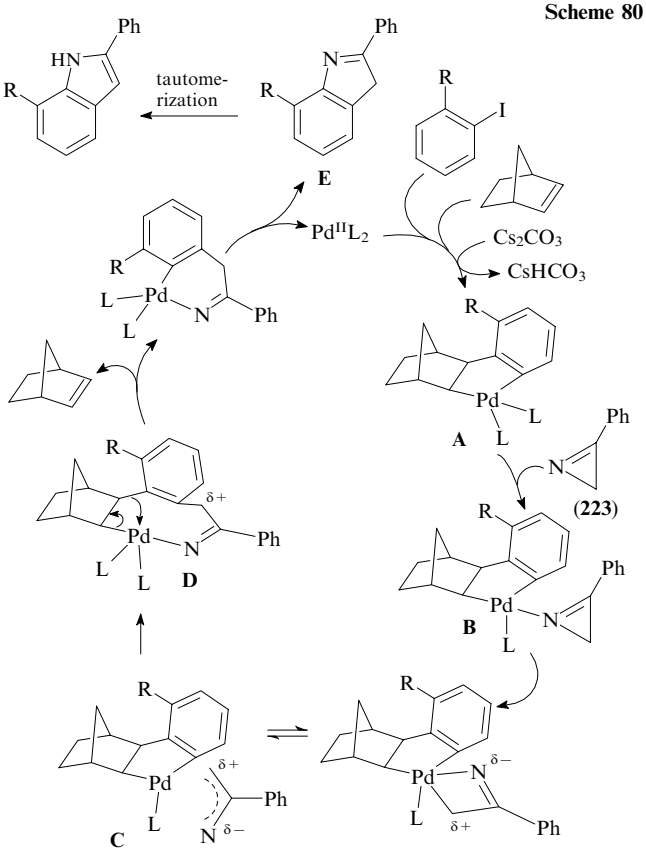


Scheme 79



(*a*) $Pd(OAc)_2$, Cs_2CO_3, norbornene (8 equiv.), MeCN, 90 °C, 16 h; Ar = 3-ClC_6H_4

Scheme 80

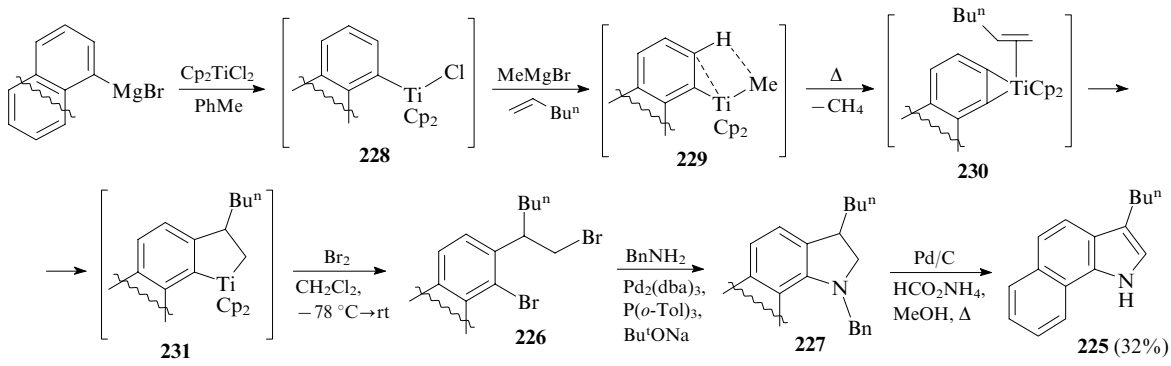


the Pd-catalyst are regenerated, intermediate **D** cyclizes to 3*H*-indole **E**. Tautomerization of the latter results in 1*H*-indole. Indirect evidence in favour of the formation of 3*H*-indole is the isolation of imidazoindole **224** as a by-product and sometimes as the major product, which is represented most reasonably as being a result of the interaction of compound **E** with the 1,3-azirine dipole.

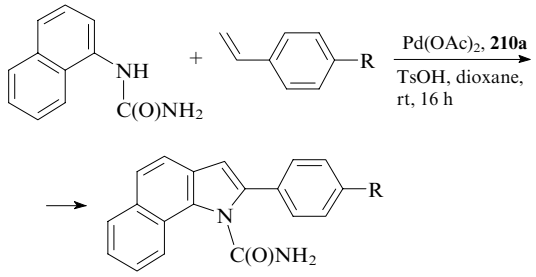
We have already mentioned a few cases of using the Buchwald – Hartwig reaction in modern indole syntheses. This reaction can be useful both directly in pyrrole ring closure and at the stage of preparation of the starting compounds. One more similar example is so-called titanocene-based method of synthesis of indoles, including benzo[*g*]indole **225** (Scheme 81).[132] The key step of this synthesis is the Pd-catalyzed cyclization of 2-bromophenethyl bromide **226** to the corresponding 1-benzylbenzoindoline **227** *via* the treatment with benzylamine in the presence of Bu^{t}ONa. Subsequent reductive debenzylation of compound **227** gives benzoindole **225** with a free NH group. The whole method is called titanocene one because of the time-consuming synthesis of dibromide **226**, employing the air- and moisture-stable reagent Cp_2TiCl_2 (Cp = η^5-C_5H_5). The first step of this route is the synthesis of aryltitanium intermediate **228** by treating initial arylmagnesium bromide with Cp_2TiCl_2. Then, the second chlorine atom is replaced by a methyl group by reacting intermediate **228** with methylmagnesium bromide in the presence of a suitable alkene, which is involved in the formation of the C(2) – C(3) bond in the target indole with a substituent at the 3-position. The resulting methyltitanium derivative **229** readily loses the methane molecule to give complex **230** of dicyclopentadienyltitanium with two ligands, 1,2-aryne and alkene. Subsequent insertion of alkene into the C – Ti bond and bromination of titanacycle **231** gives target dibromide **226**. Although the method as a whole makes it possible to obtain rather complex indole derivatives, its shortcomings are the multistage character, the lack of atom-economy and relatively low yields of products, rarely exceeding 50% (relative to Cp_2TiCl_2).

Reactions resembling aniline–acetylene cyclizations with CH/NH activation (see Section II.1.e) can also be carried out with alkenes. For example, the synthesis of 1-carbamoylindoles from *N*-arylureas and vinylarenes has recently been developed (Scheme 82).[133] Palladium diacetate is used as a catalyst, and 1,4-benzoquinone (BQ, **210a**) is used as an oxidant. The method is characterized by very mild conditions and good yields of the products, including benzo[*g*]indoles.

Scheme 81



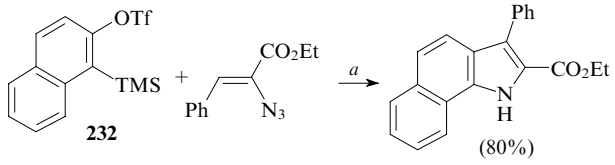
Scheme 82



R = H (82% yield), Me (73%)

Another way to synthesize substituted indoles, notable for the lack of transition metal catalysts, is through the reaction of *o*-trimethylsilylaryl triflates **232** with 2-azidoacrylates in the presence of triphenylphosphine and caesium fluoride (Scheme 83).[134] It is assumed that, first, under the action of CsF, triflate **232** is converted to the corresponding aryne, which then enters into the 1,3-dipolar cycloaddition with nitrene formed from the azide under the action of PPh_3.

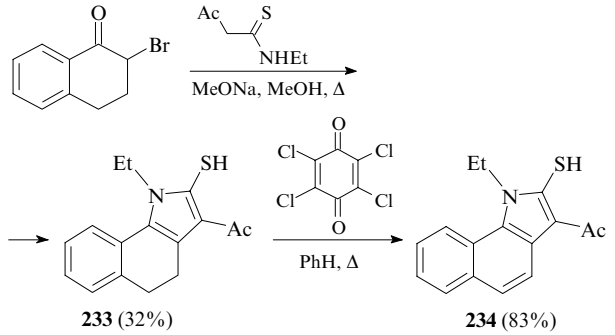
Scheme 83



(*a*) PPh_3, CsF, MeCN, PhMe, air, 50 °C; TMS = $SiMe_3$

2-Bromotetralone reacted with *N*-ethylamide of thioacetoacetic acid in a basic medium to give 4,5-dihydrobenzo[*g*]indole **233** in 32% yield. Subsequent aromatization to form benzo[*g*]indole **234** was carried out in the presence of chloranil (Scheme 84).[135]

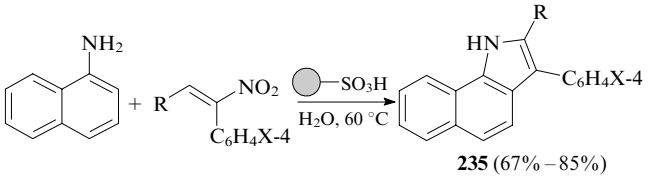
Scheme 84



233 (32%) **234** (83%)

Recently, a method has been described for the preparation of benzoindoles **235** by the reaction of 1-aminonaphthalene with nitroalkenes in water in the presence of a polymer-supported acid catalyst (Scheme 85).[136] We do not describe the cyclization mechanism proposed by the authors of the method, since it does not seem convincing enough.

Scheme 85



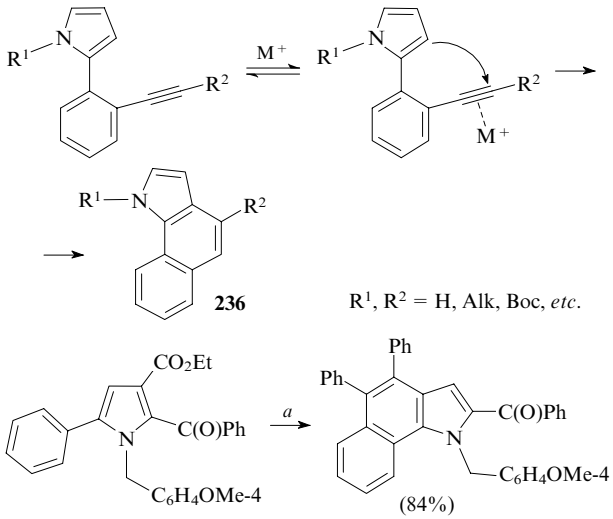
235 (67%–85%)

R = H, Me; X = H, Me, OMe, F, Cl, NO_2; ◯ is polymer

II.2. Synthesis of benzo[*g*]indoles based on construction of the naphthalene ring

A number of methods for the production of benzo[*g*]indoles have been described in which missing benzene nuclei are added to the already finished pyrrole or indole system. One of such methods is based on 2-alkynylphenylpyrroles, which are converted to substituted benzo[*g*]indoles **236** under the catalytic action of transition metal salts or complexes, such as $PtCl_2$, $AuCl_3$, $GaCl_3$, $InCl_3$, $RuCl_2$ and $[Rh(CO)_2Cl]_2$ (usually on heating in toluene or cymene) (Scheme 86).[137–140] The product yields usually reach 70%–95%. According to Lin *et al.*,[141] this method can be simplified by introducing 2-arylpyrroles and acetylenes into the Pd-catalyzed coupling reaction (see Scheme 86). The reaction is accompanied by decarboxylation of the pyrrole moiety.

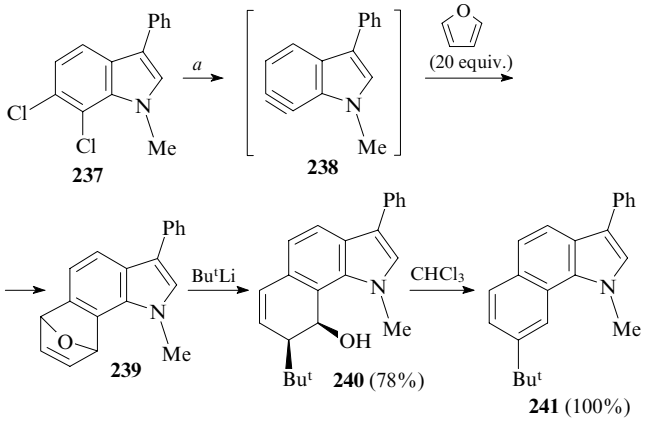
Scheme 86



(*a*) Ph—≡—Ph, $Pd(OAc)_2$, $Cu(OAc)_2 \cdot H_2O$, AcOLi, MS 4 Å, $AcNMe_2$, N_2, 120 °C, 12 h

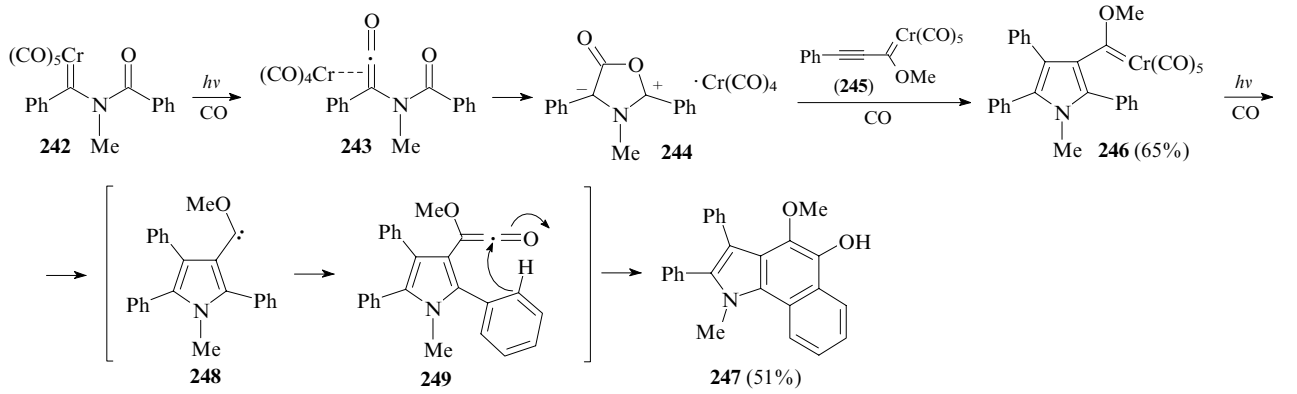
Buszek and coworkers[142, 143] have shown that the benzene nucleus can be built on to the indole system by means of aryne methodology (Scheme 87). The starting compounds in their experiments were 6,7-dihaloindoles, which were treated with metallating agents. In particular, treat-

Scheme 87



(*a*) Bu^tLi (4 equiv.), Et_2O, −78 °C → rt

Scheme 88



ment of dichloride **237** with *tert*-butyllithium in the presence of furan gave aryne **238**, which was *in situ* converted to unstable adduct **239** and then to alcohol **240**. Stirring the latter in chloroform led to dehydration and formation of benzo[*g*]indole **241** in quantitative yield.

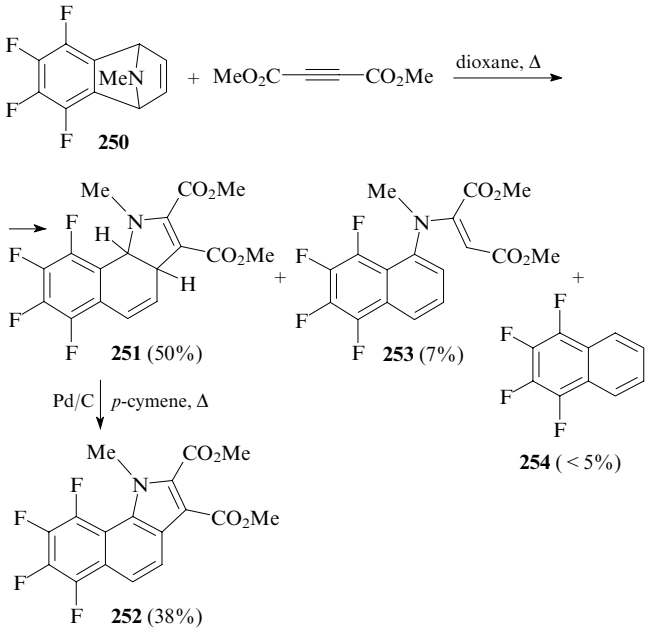
The large synthetic potential of Fischer carbene metal complexes has been used repeatedly to produce complex and unavailable heterocyclic compounds, including benzoindoles (Scheme 88).[144] For example, the photolysis of chromium complex **242** in a carbon monoxide atmosphere leads to the insertion of the CO molecule to form ketene complex **243**. The latter is easily transformed to so-called münchnone **244**, capable of entering into numerous 1,3-dipolar cycloaddition reactions. In particular, in the presence of acetylenes, it gives pyrroles with the extrusion of the CO_2 molecule. Using this circumstance, Merlic *et al.*[144] treated münchnone *in situ* with acetylene carbene metal complex **245**, which gave first pyrrole **246** and then, after photolysis in the presence of CO, benzo[*g*]indole **247**. It is logical to assume that the mechanism of this elegant transformation involves the formation of intermediates **248** and **249** and the chromium-catalyzed insertion of the ketene function into the aromatic C – H bond.

II.3. Simultaneous construction of pyrrole and naphthalene rings

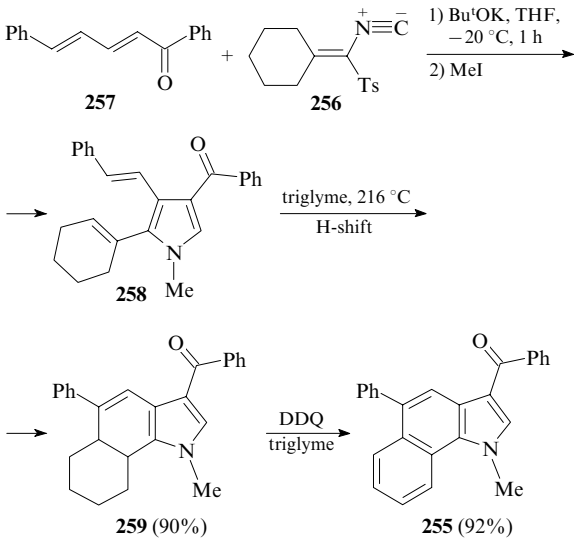
At least ten methods of synthesizing benzo[*g*]indoles of this kind have been reported. They are all multistep or cascade processes of varying complexity. Apparently, British chemists[145] were the first to observe such an assembly of the benzoindole system back in 1978. They studied the reaction of the Diels – Alder adduct **250**, obtained from tetrafluorodehydrobenzene and 1-methylpyrrole, with dimethyl acetylenedicarboxylate (DMAD) and found that the major reaction product is 3a,9b-dihydrobenzoindole **251**, which can be aromatized to benzoindole **252** on heating with palladium on carbon. In addition to dihydrobenzoindole **251**, the reaction of adduct **250** with DMAD also gives small amounts of naphthalene derivatives **253** and **254** (Scheme 89).

Somewhat later, another transformation of this kind has been discovered, which is exemplified by the synthesis of benzo[*g*]indole **255** (Scheme 90).[146, 147] In the first stage, the allylic anion generated *in situ* from 1-tosyl-1-alkenylisonitriles **256** under the action of a base is attached to suitable Michael acceptors, for example, to ketone **257**. This results in the closure of the pyrrole ring involving the isonitrile group and the elimination of TsOH. After intermediate N-methylation, 2,3-dialkenyl-4-benzoylpyrrole **258** is formed in the same pot, which is then subjected to thermal

Scheme 89



Scheme 90

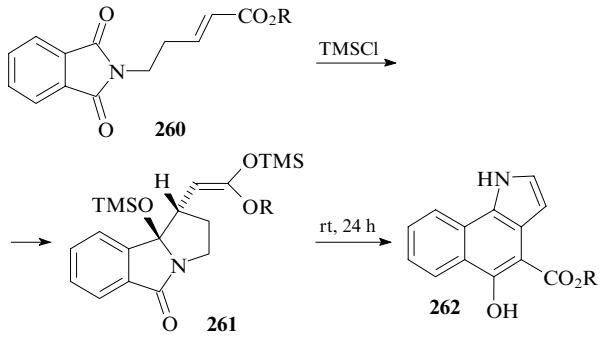


Triglyme is 1,2-bis(2-methoxyethoxy)ethane

or photochemical electrocyclization to give tetrahydrobenzoindole **259**. Dehydrogenation of the latter with DDQ completes the process, all stages of which proceed with high yield of the products. This approach is also applicable for obtaining a wide range of indoles.

In another method, N-substituted phthalimides **260** were used as starting compounds. Their treatment with trimethylchlorosilane led to acetals **261**, which, on standing in air under acid catalysis, were gradually converted to 5-hydroxy-1*H*-benzo[*g*]indole-4-carboxylates in 55%–57% yield (Scheme 91).[148] The tentative reaction mechanism is shown in Scheme 92. The driving force of this complex cascade process, involving the stages of cyclization and ring contraction and expansion (see Scheme 92, stages *a*, *b*, *e*), is the proton catalysis (stages *a*, *d*, *f*, *g*) and the associated lability of O-trimethylsilyl groups formally split off as cations (see Scheme 92, stages *c*, *e*).

Scheme 91

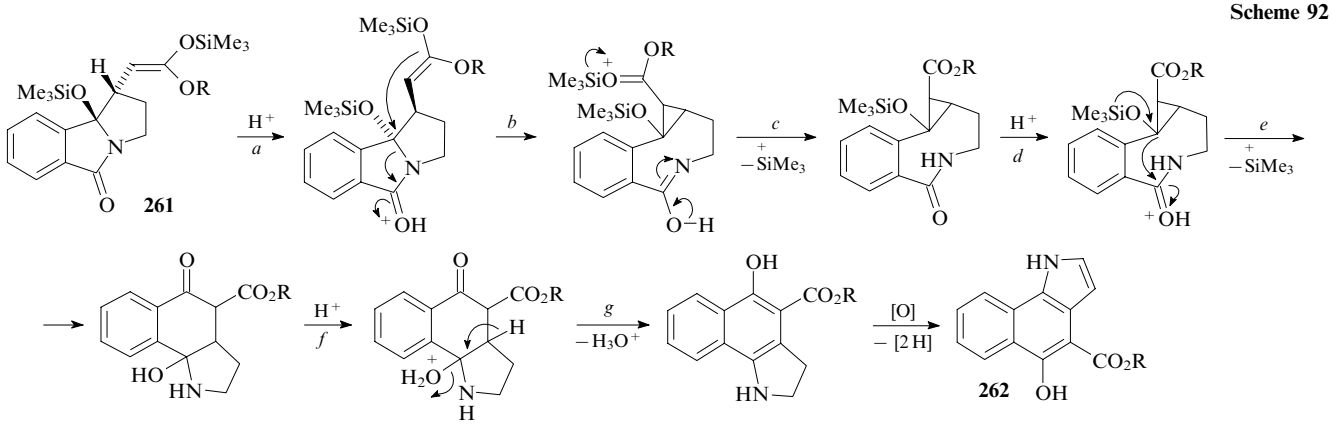


R = Me, Et

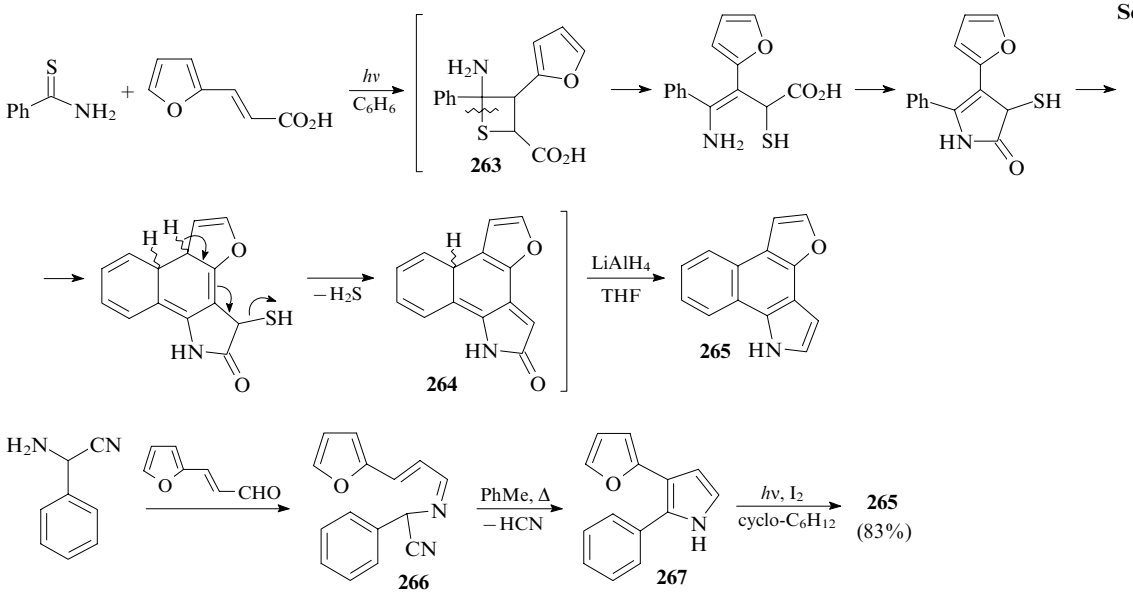
The fourth approach is based on a photochemical reaction in which a mixture of thiobenzamide and β-(2-furyl)acrylic acid is irradiated in benzene (Scheme 93).[149] This initiates [2+2]-cycloaddition leading to thiethane derivative **263**, which is further converted to compound **264**. The reduction of the latter with lithium aluminium hydride yields furo[2,3-*e*]benzo[*g*]indole (**265**). A shorter route to compound **265** is also possible. Its first stage is the reaction of α-aminophenylacetonitrile with 2-furylacrolein to give Schiff base **266**, which loses the HCN molecule when refluxed in toluene to convert to pyrrole **267**; photochemical oxidation of the latter gives tetracycle **265**.

A direct atom-economical cascade transformation of diynes of type **268** and **269** to, respectively, naphtho[1,2-*b*]indoles **270** and 2,3-dihydrobenzoindole **271** (Scheme 94)[150] seems a very elegant method and, what is especially important, it meets modern trends. These reactions are catalyzed by Au^{I} salts, which are believed to activate the triple bond for pyrrole ring closure, followed by a second cyclization, which gives the final product. The yields are 75%–87%, with the exception of compounds **270**

Scheme 92

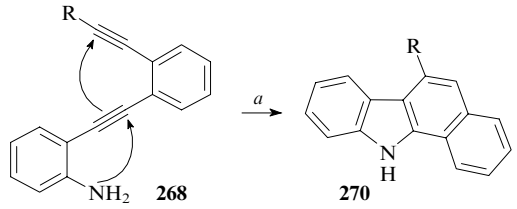


Scheme 93

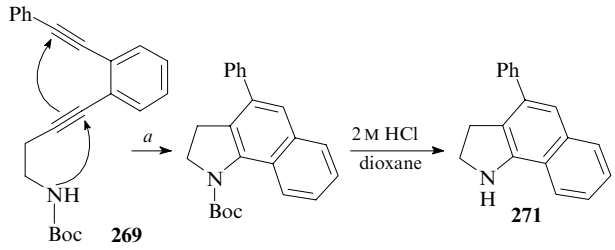


with electron-releasing groups in the substituent R, for which the yields do not exceed 30% – 65%.

Scheme 94



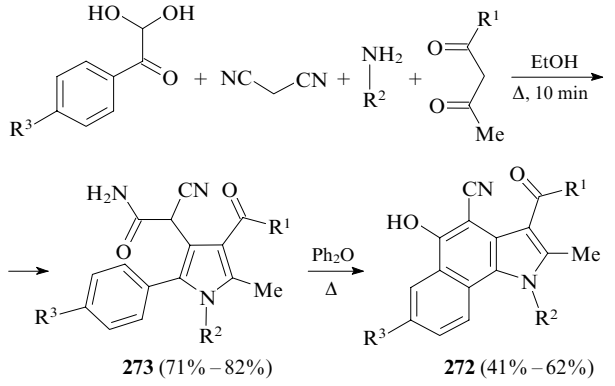
R = Pr^n, cyclo-C_6H_{11}, Ph, 4-XC_6H_4 (X = CF_3, CN, Cl, Me, OMe)



(*a*) Ph_3PAuCl, AgOTf, MeCN, 80 °C

A multicomponent domino condensation with the participation of arylglyoxal, 1,3-dicarbonyl compound, malononitrile and primary amine to give benzoindoles **272** has been suggested (Scheme 95).[151] The reaction proceeds through the intermediate formation of pyrroles **273**, which can be isolated, under definite conditions, in good yield. Their subsequent thermal cyclization during short-term boiling in diphenyl ether gives 3-acyl-5-hydroxy-4-cyanobenzo[*g*]indoles **272** in 41% – 62% yield.

Scheme 95

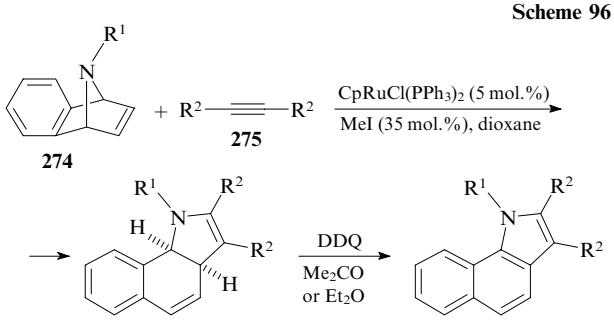


R^1 = Me, Ph, OEt; R^2 = Ar, Bn, Alk; R^3 = H, Cl, OMe

Tenanglia and Marc[152] have developed a method for synthesis of benzo[*g*]indoles in which the *in situ* generated Ru complex $CpRuI(PPh_3)_2$ catalyzes the coupling reaction of 7-azabenzonorbornadienes **274** with internal alkynes **275**, giving rise to 3a,9b-dihydrobenzo[*g*]indoles **276** in good yield (Scheme 96).

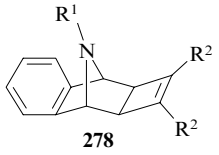
In the course of this transformation, the C – N bond in the initial bicyclic alkene is cleaved and two new bonds (C – C and C – N) are formed at the acetylene carbon atoms. Compounds **276** are readily aromatized when treated with DDQ to form benzoindoles **277**. In some cases, the first of these reactions gives, as a by-product, [2 + 2]-cycloaddition product **278**.

Scheme 96



R^1 = Boc, CO_2Me, Ts; R^2 = Et, CH_2OMe, CH_2OAc

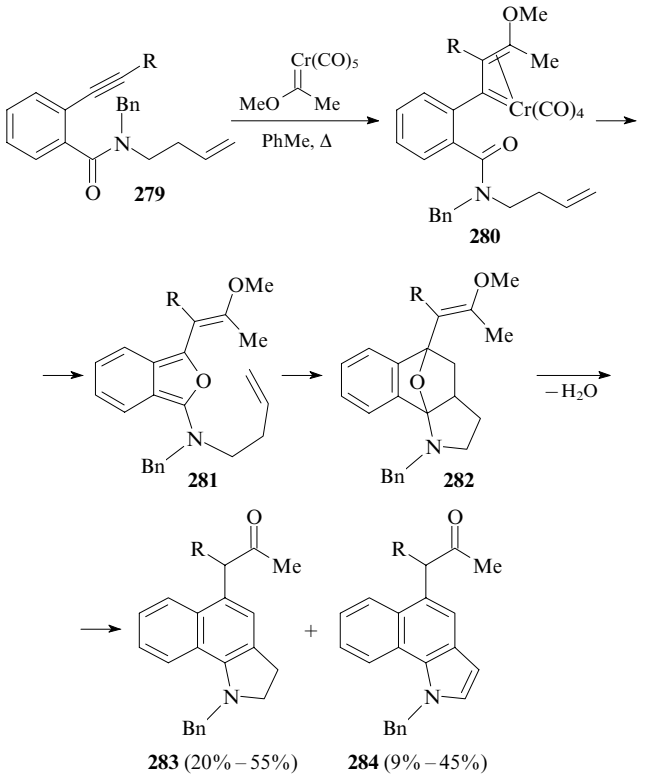
Structures 278



R^1 = Boc, CO_2Me, Ts;
R^2 = Et, CH_2OMe, CH_2OAc

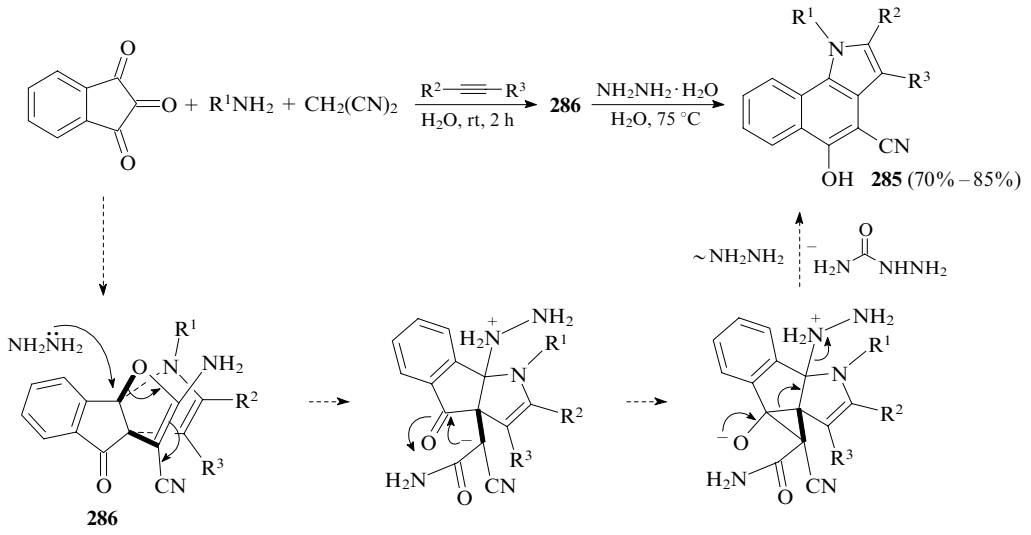
In yet another method, *o*-alkynylbenzamides **279**, containing a substituent with a terminal alkenyl group at the nitrogen atom, were reacted with Fischer metallocarbenes (Scheme 97).[153] This initiated the cascade insertion of the carbene into the triple bond to form intermediates **280**, their transformation to isobenzofurans **281**, intramolecular Diels – Alder reaction, dehydration of adducts **282** and oxidation of the forming 2,3-dihydrobenzo[*g*]indoles **283** with air oxygen to give target products **284**. It should be noted that earlier the possibility of synthesizing benzo[*g*]indoles from 2-aminoalkenyl derivatives of isobenzofuran has been demonstrated by Padwa *et al.*[154]

Scheme 97



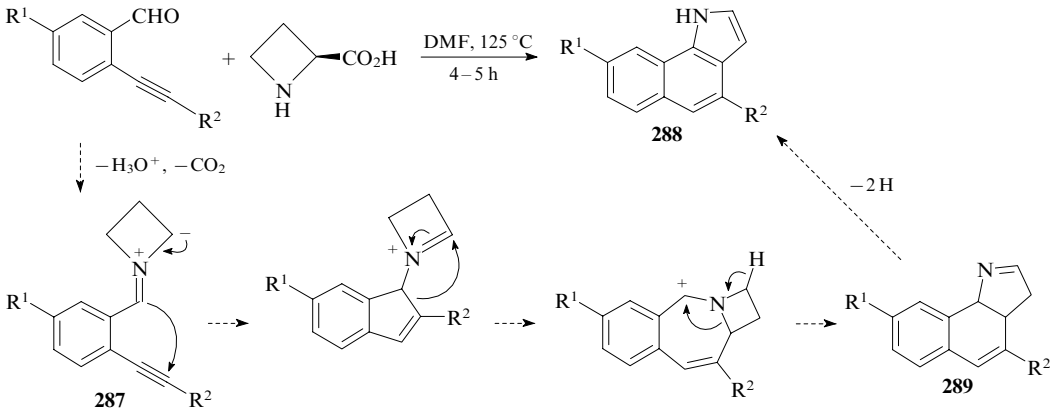
R = H, Bu^n

Scheme 98



R^1 = Pr^n, Bu^n, Bu^t; R^2 = Me, CO_2Me, CO_2Et; R^3 = CO_2Me, CO_2Et

Scheme 99



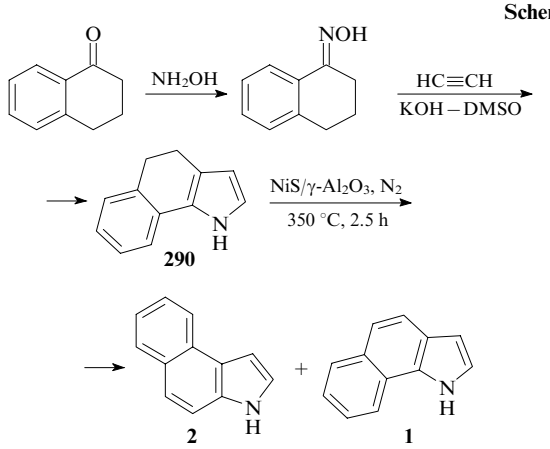
R^1 = MeO, F; R^2 = *p*-Tol, 4-$Bu^tC_6H_4$

Recently, a multicomponent process has been discovered in which the reaction of indane-1,2,3-trione, primary alkylamine, malononitrile and acetylene in the presence of nucleophile, for example, hydrazine or sodium azide, gives 5-hydroxy-4-cyanobenzo[*g*]indoles **285** in high yield.[154] It has been elucidated that the key intermediate in this complex reaction is oxaaza[3.3.3]propellane **286**, which is subjected to a nucleophile attack at the bridgehead atom. The subsequent chain of transformations is shown in Scheme 98.

No less challenging is the assembly of the benzo[*g*]indole system based on the reaction of 2-alkynylbenzaldehydes with azetidine-2-carboxylic acid (Scheme 99).[156] The reaction is a multistep one-pot process involving the formation of azomethine ylide **287** accompanied by decarboxylation, its cyclization and a chain of ring expansion and contraction steps. Disadvantages of the method are relatively low yields of compounds **288** (49% – 57%), as well as the formation of 2,3-dihydrobenzoindoles as by-products (structure **289** is actually isomeric to the latter and requires an oxidant for aromatization).

Trofimov *et al.*[157] have developed a method for synthesis of unsubstituted benzo[*g*]indole from readily available 1-tetralone by means of the Trofimov reaction (Scheme 100). First, tetralone is converted to oxime, which is treated with acetylene in the superbasic KOH – DMSO system to give 4,5-dihydrobenzo[*g*]indole **290**. Its subsequent dehydrogenation on the fresh $NiS/\gamma\text{-}Al_2O_3$ catalyst leads to benzo[*e*]indole (**2**) as a major primary product (> 70% in the crude reaction mixture); the latter is converted with time to benzo[*g*]indole (**1**). The total yield of benzoindoles after 2.5 h reached 88%: product **1** accounted for 70% and product **2**, for 18%. The selective synthesis of dihydrobenzo[*e*]indole from 2-tetralone and the Trofimov reaction mechanism have been discussed.[158]

Scheme 100



III. Properties of benzo[*g*]indoles

III.1. General characteristic, spectral and structural properties

Unsubstituted benzo[*g*]indole (**1**) is a commercially available grey-white compound with a melting point of 178 °C and moderate chromatographic mobility. When working with mixtures containing benzo[*g*]indoles, it is expedient to remember that, on thin-layer chromatograms, they are stained blue with iodine vapour. In ^{1}H NMR spectra of benzo[*g*]indoles, the pyrrole protons give rise to two characteristic doublets at 6.5 – 7.3 ppm with a small (2 – 3 Hz) *ortho* spin – spin coupling constant (see examples in Refs 41, 51 and 112). For compounds that have no substituent at the heteroatom, the signal of the free NH group is usually observed at $\delta \approx 9$ ppm;[51] however, when it is involved in intramolecular hydrogen bonding with a chelating group in the 2- or 9-positions, this shift can increase to 11 – 13 ppm.[81] The signal of the N-methyl group is observed at about 4 ppm, that is, in a noticeably lower field than in the case of aniline NHMe and NMe_2 groups.[41, 51, 112] Information on the ^{13}C NMR spectra of such compounds is presented in most of the modern works on this subject.

In the IR spectrum of parent compound **1**, the ν_{N-H} band is observed at 3428 cm^{-1} (KBr pellets);[138] however, in the spectra of solutions ($CHCl_3$), this band is 40 – 100 cm^{-1} shifted towards lower frequencies.[90] In the mass spectra of compound **1** and its numerous derivatives, the molecular ion peak is commonly the strongest one.[51, 112] The Cambridge Structural Database contains 32 structures of benzo[*g*]indole derivatives as of September 2016; however, among these data, there is no information on parent compound **1** and its simple derivatives.

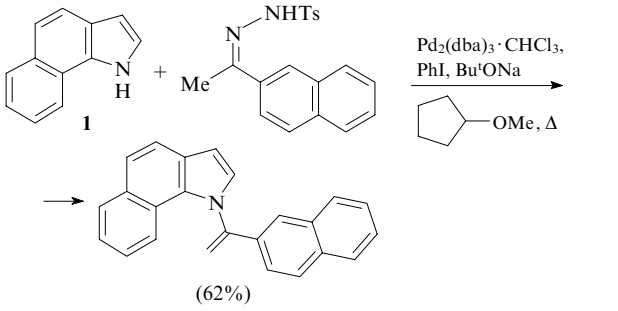
III.2. Reactions of benzo[*g*]indoles

III.2.a. Reactions involving the pyrrole ring

As in pyrrole and indole, all the atoms of the pyrrole ring in the benzo[*g*]indole molecule are electron-rich, and, therefore, they tend to react with electrophiles. The most active in this respect is the nitrogen atom in the anionic form, whereas in the neutral form, it is the C(3) atom. In general, the reactivity of atoms in the pyrrole ring of benzo[*g*]indole decreases in the following order: $N^- > C(3) > C(2) > NH$. Nevertheless, it is not unusual for an electrophile to attack the C(3) atom in a molecule with a seemingly ionized NH group, and, conversely, under seemingly neutral conditions, the reaction occurs at the nitrogen atom. The cause for these anomalies lies primarily in the reaction conditions and, first of all, in the nature of the solvent and the relative stability of the alternative products of the reaction. Let us first consider the behaviour of the anionic form.

There are no data on the NH-acidity of benzoindoles; however, judging by the acidity constants of pyrrole ($pK_a = 17.5$, H_2O) and indole ($pK_a = 17.0$),[159] it should not differ significantly from them. This means that sufficiently strong bases and ionizing solvents are required for generation of the N anion and its alkylation. Indeed, the methylation of benzo[*g*]indole[160] and 3-chlorobenzo[*g*]indole (and other derivatives)[161] with methyl iodide has been carried out in the $NaNH_2$ – liquid NH_3 and NaH – DMF systems to give the corresponding 1-methyl derivatives in, respectively, 75% and 97% yield. Benzo[*g*]indole (**1**) is readily vinylated with acetylene in a KOH – DMSO medium under atmospheric pressure (~130 °C, 7 h) to form 1-vinyl derivative in 78% yield.[157] Recently, a Pd^0-catalyzed ligand-free method of N-vinylation of NH-heterocycles, including indoles and benzoindoles, with tosylhydrazones in a basic medium has been developed (Scheme 101).[162] Its advantage is the possibility of introducing vinyl groups with a wide range of substituents at the C=C double bond.

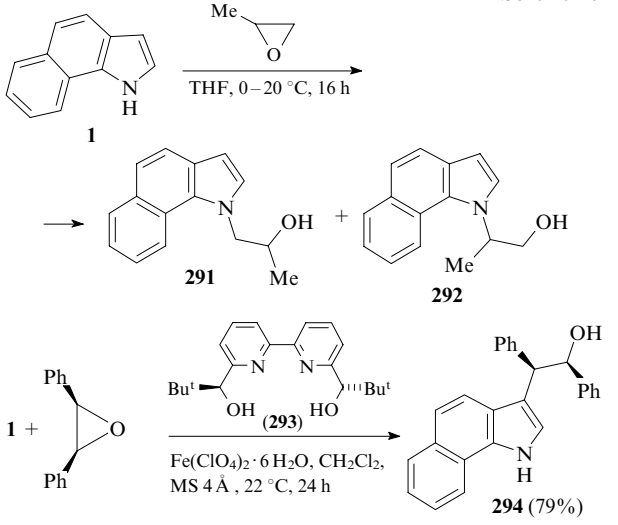
Scheme 101



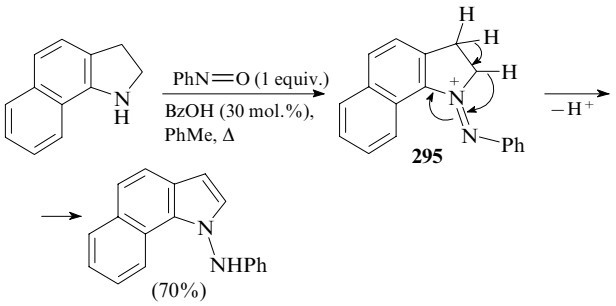
At the same time, carboxylation of benzo[*g*]indole with carbon dioxide in the presence of a large excess of Bu^tOLi (DMF, 100 °C, 24 h) gives exclusively benzo[*g*]indole-3-carboxylic acid.[163] Similarly, sequential treatment of benzo[*g*]indole with sodium ethoxide in ethanol, isoamyl nitrite and $NaHSO_3$ resulted in the formation of 3-aminobenzo[*g*]indole in 36% yield, which can be interpreted as nitrosation of its N-anion at the 3-position.[164] The reaction of 1-bromomagnesium-2,3-dimethylbenzo[*g*]indole with diethyl oxalate in ether led to ethyl 2,3-dimethylbenzo[*g*]indolyl-1-glyoxalate.[165] The introduction of protective groups, for example, Boc, into the NH group of benzo[*g*]indole and their removal have been discussed by Tanaka *et al.*[166] Interestingly, propylene oxide reacts with benzoindole **1** in THF under neutral conditions exclusively at the nitrogen atom to give isomeric alcohols **291** and **292** in the 10 : 1 ratio (the overall yield has not been specified) (Scheme 102).[167] Unlike this reaction, the transformation with stilbene oxide in the presence of chiral catalyst **293** and $Fe(ClO_4)_2$ proceeds with high enantioselectivity at the 3-position to give alcohol **294** in 79% yield (see Scheme 102).[168]

Recently, a surprisingly simple and effective method for the preparation of *N*-arylaminoindoles and their benzo analogues (Scheme 103) has been proposed.[169] It is based on the reaction of indolines with nitrosoarenes in the presence of benzoic acid as a catalyst. Apparently, cation **295** is formed as an intermediate, which is aromatized through intramolecular oxidation – reduction.

Scheme 102

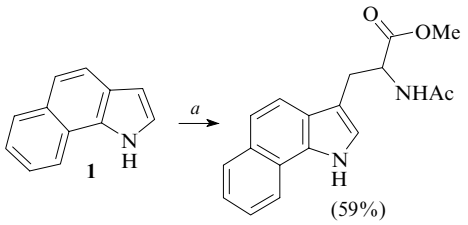


Scheme 103

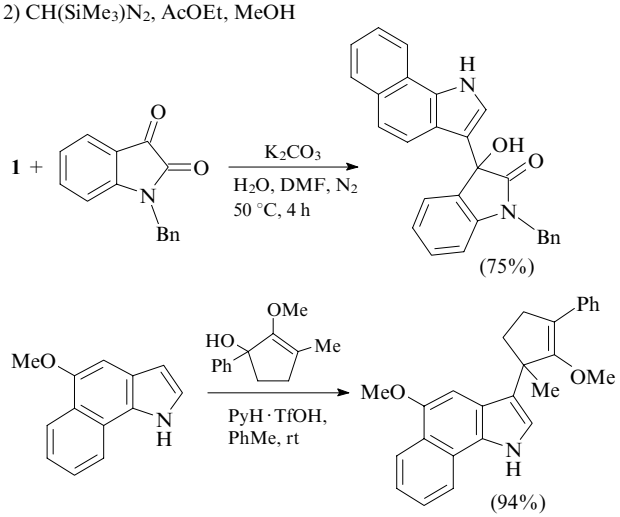


Benzo[*g*]indoles are regioselectively chlorinated at the 3-position with *N*-chlorosuccinimide (NCS),[161] formylated according to Vilsmeier,[160] and enter into the Mannich reaction (3-dimethylaminomethyl derivative is used for synthesis of the benzo[*g*]indole analogue of tryptophan).[170] Among the other reactions, note acylation with oxalyl chloride,[164] reactions with a variety of complex electrophiles, for example, with amino acid-based alcohols (serine),[166] isatin,[171] and resonance-stabilized carbocations[172] (Scheme 104) or α,β-unsaturated aldehydes (Scheme 105).[173] Reactions of this type are usually employed to obtain and screen new compounds for medicinal chemistry.

Scheme 104



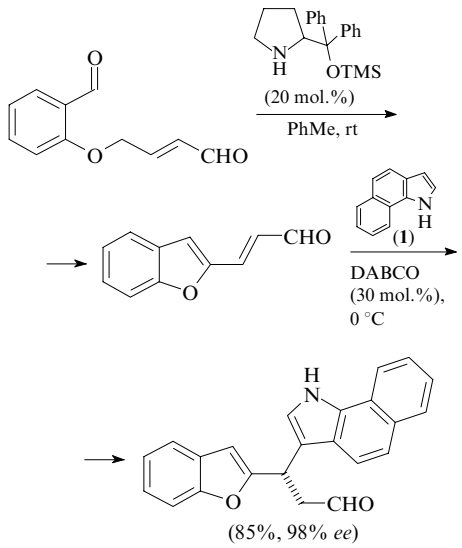
(*a*) 1) $HOCH_2CH(NHAc)CO_2H$, AcOH, Ac_2O;
2) $CH(SiMe_3)N_2$, AcOEt, MeOH



Pd-catalyst-free cross-coupling of pyrroles and indoles with haloacetylenes on active Al_2O_3 usually proceeds selectively at the α-position of pyrrole and β-position of indole; in the case of the reaction of benzo[*g*]indole (**1**) with 1-benzoyl-2-bromoacetylene, it leads to a mixture of equal amounts of isomeric acetylene derivatives of benzoindoles **296a**,**b** in overall yield of 45% (Scheme 106).[174]

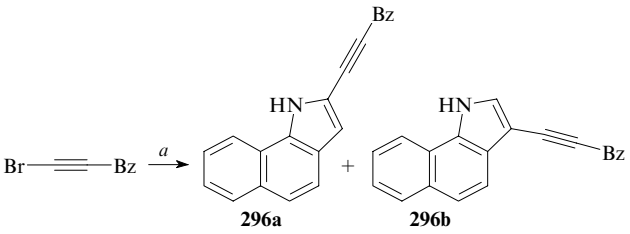
For the latter reaction, attention should be paid to the problem of carbocycle annulation on the C(2)–C(3) bond of the indole system.[175] For a long time, similar reactions have been mainly performed with bifunctional reagents containing terminal sp^2 and sp carbon atoms. Recently, these reactions have been successfully accomplished with reagents in which one of the terminal carbon atoms is

Scheme 105



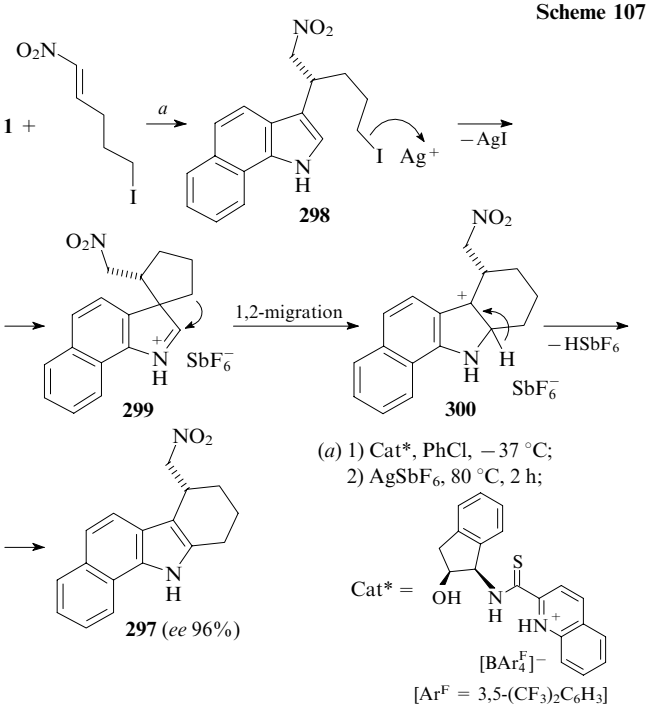
DABCO is 1,4-diazabicyclo[2.2.2]octane

Scheme 106

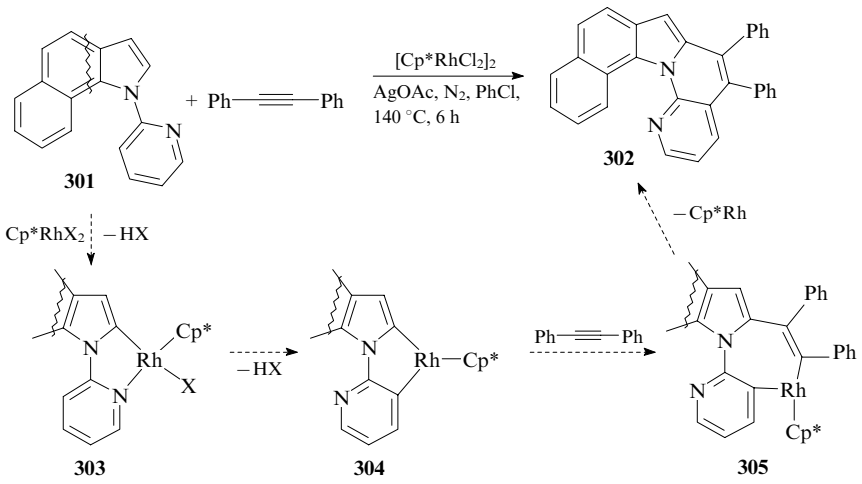


saturated (Scheme 107).[175] In particular, treatment of benzo[*g*]indole (**1**) with 5-iodo-1-nitro-1-pentene in the presence of a special chiral organocatalyst (Cat*) and $AgSbF_6$ gave

Scheme 107



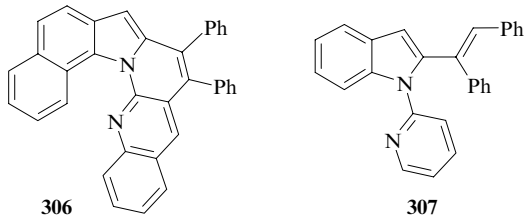
Scheme 108



benzo derivative of 1,2,3,4-tetrahydrocarbazole **297**. Although its yield (40%) is significantly lower than in the case of common indoles (50% – 90%), the reaction proceeds with nearly ideal enantioselectivity. It is believed that the process involves the double addition of the reagent electrophilic atoms to the 3-position of the pyrrole ring to form intermediates **298** and **299** and the subsequent Ciamician – Plancher rearrangement leading to intermediate **300**.

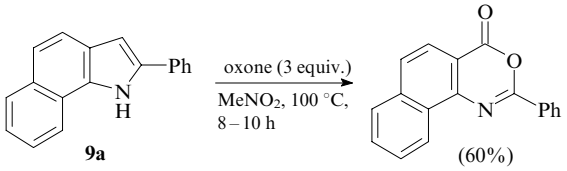
Very wide possibilities are provided by cross-coupling reactions catalyzed by transition metals and their complexes. For example, *N*-(2-azinyl) derivatives of indole and benzo[*g*]indole react with alkynes in the presence of a Rh^{III} complex and the AgOAc cocatalyst (necessary for the generation of intermediate Rh^{I}) to give a variety of polycyclic helicene-type systems in nearly quantitative yield; for example, benzo[*g*]indole **301** produces pentacycle **302** (Scheme 108).[176] The reaction presumably begins with the metallation of the pyrrole C(2) – H bond upon coordination with the pyridine heteroatom, after which the azine ring rotates, making possible its own cyclometallation (conversion of complex **303** to intermediate **304**) and insertion of an acetylene reagent. The resulting seven-membered metallacycle **305** is converted to the final product with elimination of the Rh^{I} complex. When the 2-pyridyl substituent in the starting compound is replaced by 2-quinolyl, the reaction gives the indolo[1,2-*a*][1,8]naphthyridine derivative **306** in 93% yield. It is interesting that the reaction proceeds smoothly only on heating in chlorobenzene. The use of other high-boiling solvents, for example, dichloroethane, results in the formation of alkenes like **307**.

Structures 306, 307



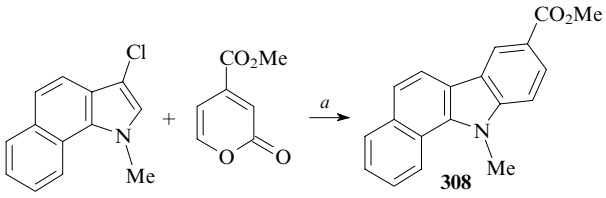
A deep, but nevertheless regioselective oxidation of 2-aryl indole and benzo[*g*]indole derivatives with oxone ($2\,KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) to 2-arylbenzoxazinones has been described (Scheme 109).[177] The reaction provides the products in high yields without affecting most of the substituents. It has been recently demonstrated that the reaction can be carried out in the presence of molecular oxygen in DMSO; in this case, the presence of a Cu catalyst (CuCl) is required.[178]

Scheme 109



Like indoles, benzo[*g*]indoles can act as dienophiles in the inverse electron demand Diels – Alder reaction. In particular, 1-methyl-3-chlorobenzo[*g*]indole reacts on heating with methyl 2-oxopyran-4-carboxylate to give carbazole derivative **308** in 67% yield (Scheme 110).[161]

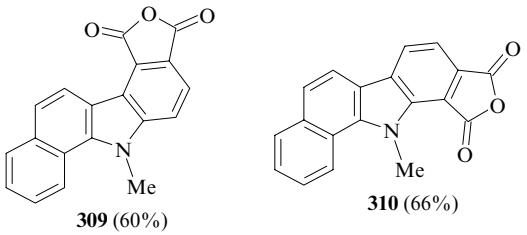
Scheme 110



(*a*) PhMe, sealed tube, 200 °C, 24 h

At the same time, 2- and 3-(2-nitrovinyl)benzo[*g*]indoles act as *endo* – *exo*-dienes and undergo the Diels – Alder reaction with, for example, maleic anhydride to give benzo[*a*]carbazole derivatives **309** and **310**.[179]

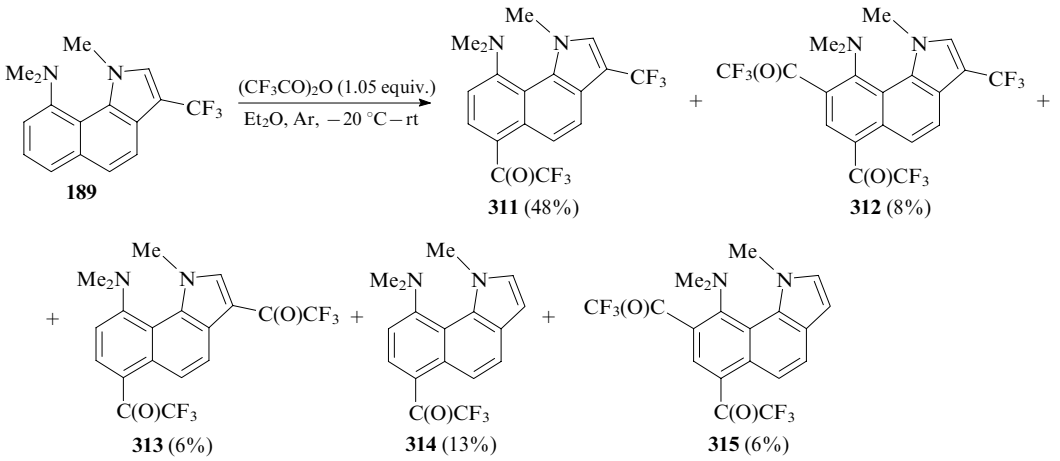
Structures 309, 310



III.2.b. Reactions involving benzene nuclei

As we saw above, the heterocycle in benzo[*g*]indole and its simple derivatives is much more sensitive to electrophile attack than the naphthalene system. It is not surprising that so far only a few works have been known where the substitution of hydrogen atoms in benzene nuclei has been

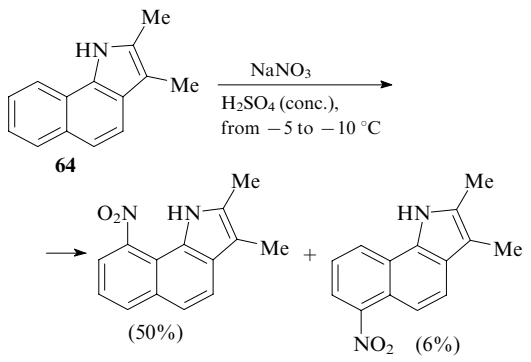
Scheme 111



reliably recorded. To accomplish this, a number of conditions should be met: the pyrrole ring should be passivated by introducing electron-withdrawing groups, the 2- and 3-positions should be blocked, while the benzene ring should be activated. A recent example of this kind is trifluoroacetylation of compound **189** with trifluoroacetic anhydride (1 equiv.) (Scheme 111).[112] In this experiment, five products, **311** – **315**, have been identified. All of them contain the $C(O)CF_3$ group in the 6-position and, in two cases (compounds **312** and **315**), an additional keto group in the 8-position in the terminal benzene ring, which is evidently much more reactive than the central nucleus and pyrrole ring in starting benzoindole **189**. Nevertheless, in this case as well, a certain competition of the pyrrole system is clearly pronounced. This is indicated by the *ipso*-substitution of $C(O)CF_3$ for the 3-CF_3 group or protodetrifluoromethylation to form compounds **313** – **315**. Since no examples of the latter reaction have been found in the literature, it is more likely that first the CF_3 group is replaced by $C(O)CF_3$, which is then subjected to protodetrifluoroacetylation.

To all appearances, the terminal benzene ring is also more reactive towards nitration of 2,3-dimethylbenzo[*g*]indole (**64**). In this reaction, the NO_2 group predominantly enters the 9-position and, to an insignificant degree, to the 6-position (Scheme 112).[180] This tendency also persists in 3-formylbenzo[*g*]indole; however, presumably because of intensive oxidation processes, the yields of two isolated reaction products — 9-nitro-3-formyl- and 5,6-dinitro-3-formylbenzo[*g*]indoles — were no higher than 4%.[181]

Scheme 112



IV. Practical applications of benzo[*g*]indoles

Despite the great significance of indole derivatives in nature, there are not many popular drugs based on them.[2] Nevertheless, indole and benzo[*g*]indole are traditionally considered the privileged 'building blocks' in the synthesis of biologically active compounds. There are numerous data on the screening of benzo[*g*]indole derivatives for their anti-inflammatory, antiallergic, carcinostatic, antibacterial, antiviral and fungicidal activity, as well as in the search for agents for the treatment of bone diseases, in particular, osteoporosis, *etc*. Recent tests of a large series of 5-hydroxybenzo[*g*]indoles have shown that an especially strong anti-inflammatory effect, superior to that of standard preparations, is exhibited by compound **316**.[182] Its mechanism of action is associated with inhibition of 5-lipoxygenase (5-LOX) enzyme, which catalyzes the synthesis, in the body, of a number of agents contributing to inflammatory and allergic disorders (see also [98, 183]).

(*S*)-3-(1*H*-Benzo[*g*]indol-3-yl)-3-(benzofuran-2-yl)propanal (see Scheme 105) exhibits the antiproliferative activity comparable with that of Cisplatin and, what is especially remarkable, superior to that of its indole analogues.[173]

Significant antitumour and cytostatic activities have been reported for bis(benzo[*g*]indol-3-ylcarboxamides) and their thio and CH_2 analogues (compounds **317**),[184] as well as for 3-(1,3,4-oxadiazol-2-yl)benzo[*g*]indoles.[185] Antiproliferative activity tests for other compounds of this group have been described.[163, 186, 187]

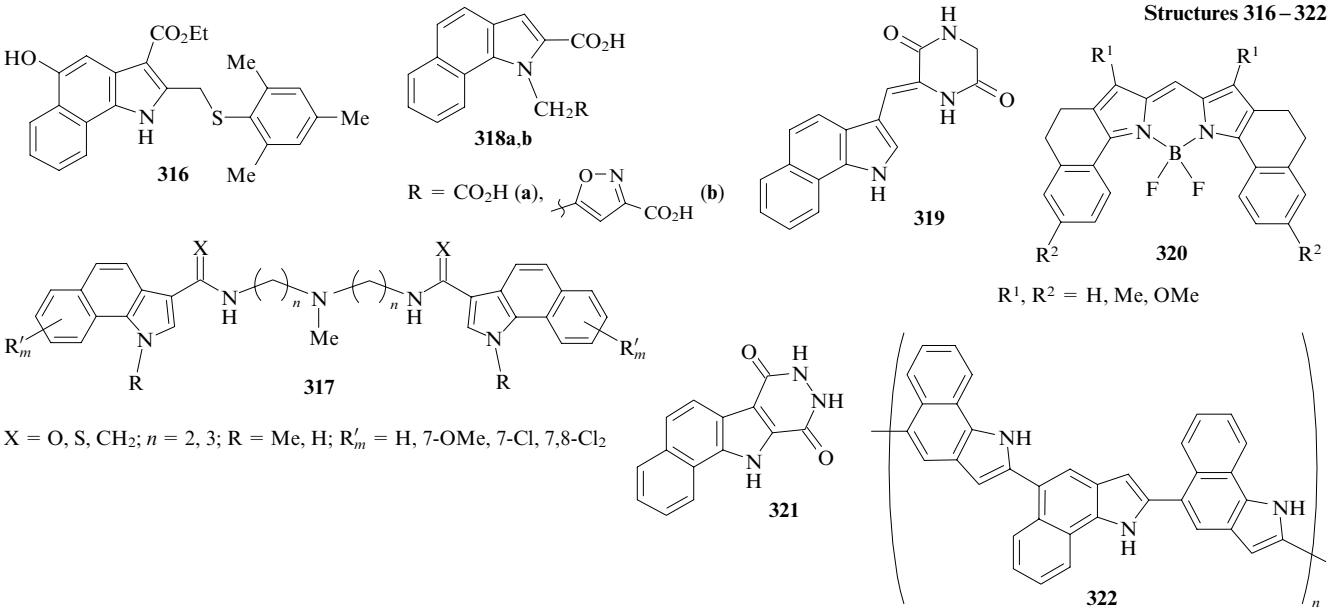
Very numerous studies of the antibacterial and antiviral activity of benzo[*g*]indoles have revealed their weak or moderate action against various strains of microorganisms.[188 – 192]

It is known that bisphosphonates are active inhibitors of farnesyl pyrophosphate synthase and are very efficient for treating bone diseases, in particular, osteoporosis. A recent search for drugs with a fundamentally different mechanism of action revealed two leading compounds **318a**,**b** based on benzo[*g*]indole-2-carboxylic acid.[193]

A biological problem of another kind, which causes significant economic damage, is the fouling of underwater surfaces of sea vessels, drilling platforms and other marine structures. A patent[44] has been granted for the use of compounds of the dipodazine type as antifouling agents, among which benzo[*g*]indole derivative **319** is particularly well proven. Its significant advantage, in addition to direct biological action, is the ability to biodegrade in the marine environment.

Since benzoindoles are distinguished from indoles by a more extended π-system, their photophysical properties are especially attractive for the creation of luminophores, photochromes, organic semiconductors and other materials

Structures 316 – 322

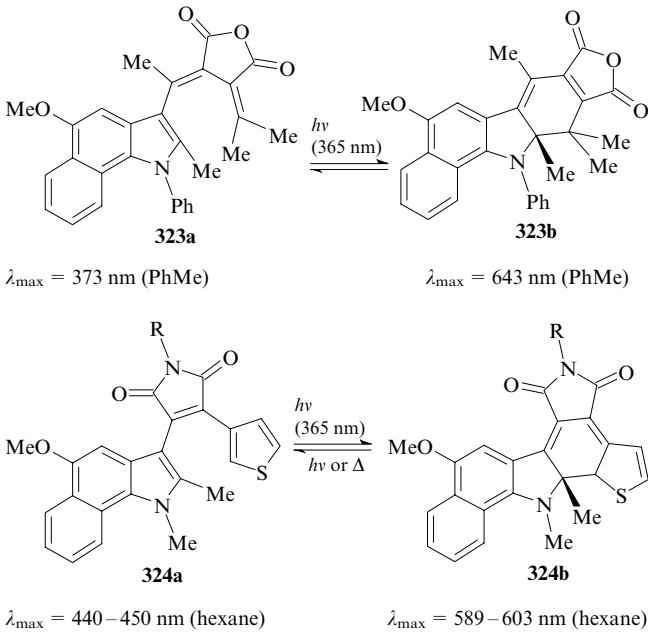


for molecular electronics.[194] Indeed, Maity *et al.*[151] found active fluorescence for 5-hydroxybenzo[*g*]indoles **272**. It has a sufficiently high quantum yield ($\Phi_F \approx 0.50$) and can be switched off in the presence of Fe^{3+} ions forming a complex with the OH group. Based on this, some compounds of this series were recommended as sensitive sensors for iron. Benzo[*g*]indole analogues **320** of the known BODIPY fluorophore (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) have been created.[195] Some of the produced dyes absorb light and fluoresce at longer wavelengths (λ_{max}^{abs} = 620 – 660 nm; λ_{max}^{fluor} = 630 – 680 nm) than their indole and pyrrole analogues, and the quantum yield of fluorescence is as high as 0.72 at a larger absorption coefficient ($>10^5$ litre · mol^{-1} cm^{-1}). Fused benzo[*g*]indole derivatives such as **321** exhibit chemiluminescence in an alkaline medium, even if they are inferior in luminescence intensity to luminol.[83]

Chinese scientists[196] have electrochemically prepared a high-quality free-standing† film based on poly(1*H*-benzo[*g*]indole) with a conductivity of 0.29 S cm^{-1} and a band gap of 1.59 eV. By its thermal stability, the film is superior to all known polyindole-based films. It is insoluble in acetone and THF and emits yellow light. It has been concluded from spectral data and quantum-chemical calculations that anodic polymerization of benzo[*g*]indole occurs at the 2- and 5-positions (structure **322**).

In the framework of studies aimed at designing optical molecular switches and three-dimensional devices for optical data storage, fulgimide **323a** and asymmetric dihetarylethenes **324a** have been synthesized on the basis of benzo[*g*]indoles (Scheme 113).[197, 198] In both cases, their deep-coloured photoexcited forms **323b** and **324b** have been identified and studied; however, due to the fluorescence of **323b** and **324a** and the overlap of the electronic transition bands of two species, the practical use of these compounds is impossible.

Scheme 113



V. Conclusion

From the material presented in the review, it follows that in the last 10 – 15 years there has been a rapid development of methods for the synthesis of indoles and benzo[*g*]indoles. First of all, it is worth noting that acetylene compounds, highly reactive reagents and intermediates like carbenes and carbenoids (especially Fischer metal complexes), nitrenes and arynes are widely used as 'building blocks'. Transformations on polymer substrates, automated synthetic lines, cross-coupling reactions, metal catalysis, various cascade processes that ensure atom economy, environment-friendly and technological methods have become widespread. It is noteworthy that, despite the fact that the methods of synthesis of indoles and benzoindoles are often identical, the presence of an additional benzene ring significantly extends the options for assembling the benzoindole system. In particular, we would like to mention the paper,[199] which appeared during the preparation of the review for publication, devoted to the mechanism of the pyrrole ring closure in 2-substituted 1,8-bis(dimethylami-

† A free-standing film is such that at least part of it does not contact with the substrate.

no)naphthalenes leading to the formation of a benzoindole nucleus. For indoles, a similar protocol have not been realized so far. In addition, having a more extended π-system and formally being polynyclear compounds, benzoindoles are more attractive for design of new fluorescent materials and structures for molecular electronics. At the same time, the poor development of methods for the functionalization of the naphthalene system of benzo[*g*]indoles, in particular, methods based on electrophilic substitution reactions, is noteworthy, especially in comparison with indole. This is all the more important because the uniqueness of the benzo[*g*]indole structure is in the stereoorientation of the pyrrole N – H bond toward the 9-position, which makes it possible to investigate *peri*-interactions with different *peri*-substituents. The latter, as well known, is very in demand for modelling and better understanding of the 'proximity effect' in the work of enzymes and self-organization of proteins. This review also demonstrates the urgent need for such an integration of the properties of the two other isomers of benzo[*g*]indole — benzo[*e*]- and benzo[*f*]indoles, which will give a more complete picture of the methods of synthesis, reactivity and physicochemical characteristics in a pyrroles – indoles – benzoindoles series. We hope that it is precisely here where the future growing points of knowledge both about the benzoindoles themselves and about pyrrole compounds in general are located.

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