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Synthesis of indoles: recent advances

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Published data of the last 10 years concerning the development of new and upgrading of known approaches to indole synthesis are integrated and analyzed. Modern versions of the classical syntheses such as the Fischer synthesis, Nenitzescu synthesis, Ullmann reaction, Leimgruber – Batcho synthesis, Reissert synthesis, Bartoli reaction, Madelung synthesis and Cadogan – Sundberg reaction are considered. The presented new approaches include transformations of heterocycles, synthesis from *o*-alkynylanilines, reductive cyclization of nitrobenzene derivatives, synthesis with the use of arynes and catalysis by N-heterocyclic carbenes. The final Section summarizes original methods for the synthesis of indoles other than those listed above; they are classified in terms of the nature of the forming bond (C – C, C – N). Rarely used methods based on benzene ring construction in pyrrole derivatives are discussed separately.
The bibliography includes 246 references.

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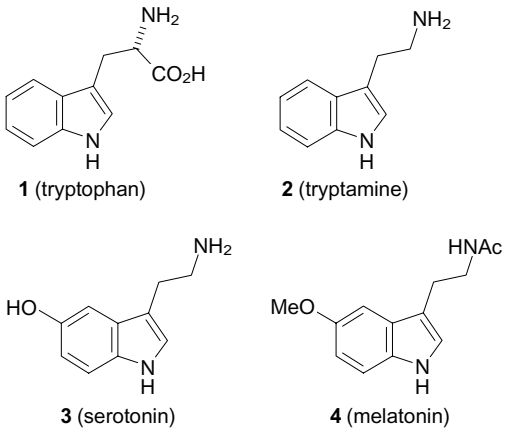
1. Introduction

Indole is one of the most abundant heterocycles occurring in natural products. Some indole derivatives are widely known to play an important role in the vital activity of humans and animals, namely, the amino acid tryptophan (**1**); the biogenic amines tryptamine (**2**) and serotonin (**3**); and the mammalian hormone melatonin responsible for psychiatric health (**4**).[1, 2]

In addition, an indole moiety is encountered in many pharmaceutical and agrochemical agents such as the antidepressant drug indopan (**5**) (currently included in the narcotics list), the nonsteroidal anti-inflammatory drug indomethacin (**6**), the hypertensive drug dimecarbin (**7**), the antihistamine agent dimebon used to treat Alzheimer's disease (**8**), the antiviral agent arbidol (**9**) and indolylacetic acid, a plant growth stimulant (**10**).

Fused indole derivatives such as carbazole (**11**), indolo[3,2-*b*]carbazole (**12**) and triindole (**13**)[3] are used as the donor components in organic electronic devices (light-emitting diodes, organic transistors, solar batteries, *etc.*).

Structures 1 – 4

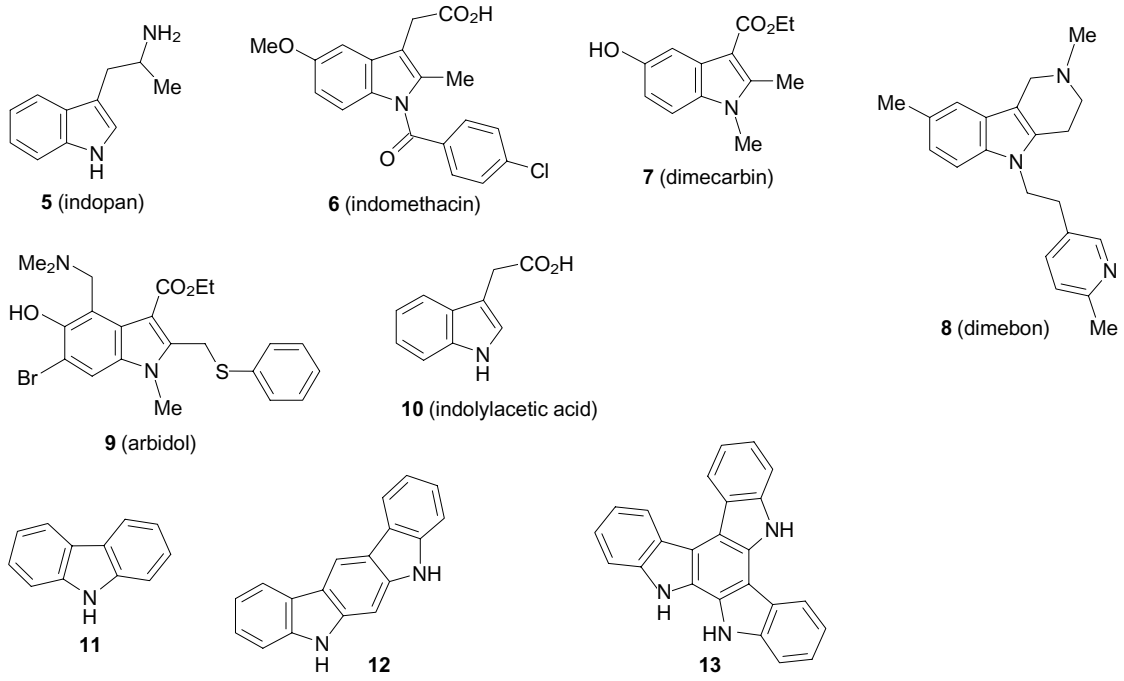


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Current research interests of the authors: chemistry of heterocyclic compounds, new synthetic methods, non-catalytic methods for C – C and C – heteroatom bond formation

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Structures 5 – 13



The diversity of useful properties of molecules containing the indole structural moiety constantly stimulates development of methods for their synthesis. In recent years, considerable efforts of chemical community have been directed not only towards the development of new synthetic routes to indole, but also towards advancement of the known classical approaches.

The interest in the problems of indole synthesis is indicated by a large number of literature reviews, both broad and specialized, that appeared in the last decade. The monograph of Gribble [4] published in 2016 addresses the synthesis and chemical properties of indoles ranging from natural compounds to pharmaceuticals and includes literature data from the mid-20th century up to recent times, but mainly up to 2014. Some general reviews cover publications up to 2011.[5–11] Most specialized reviews are devoted to the application of particular methods for indole ring formation, for example, to the use of isocyanates,[12] propargyl compounds,[13] azides [14] and isonitriles [15] or to particular indole structures. There are reviews considering the Bartoli reaction,[16] vicarious nucleophilic substitution,[17] Granberg tryptamine synthesis,[18] photochemical activation,[19] synthesis of fused indole derivatives [20] and indole dicarboxylic acids,[21] and indoles as potential medicinal agents for the treatment of neurodegenerative diseases.[22] The most recent reviews that appeared in the journal *Chemistry of Heterocyclic Compounds* in 2018 deal with modern catalytic methods for indole synthesis.[23–25]

The absence of comprehensive reviews that would cover detailed information on the methods of indole synthesis of the last ten years, including both modern versions of classical methods and new synthetic approaches based on modern achievements of organic chemistry stimulated us to write this review.

The following abbreviations are used:

ACVA — 4,4′-azobis(4-cyanovaleric acid),
BHT — 2,6-di-*tert*-butyl-4-methylphenol,
Boc — *tert*-butoxycarbonyl,
bpy — 2,2′-bipyridine,
Cbz — benzyloxycarbonyl,
CDK — cyclin-dependent kinase,
1,4-CHD — cyclohexa-1,4-diene,
Cy — cyclohexyl,
dba — dibenzylideneacetone,
DBU —1,8-diazabicyclo[5.4.0]undec-7-ene,
DCE — 1,2-dichloroethane,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DFT — density functional theory,
DMAP — 4-dimethylaminopyridine,
DME — 1,2-dimethoxyethane,
DMEDA — 1,2-dimethylethylenediamine,
dppf — 1,1′-bis(diphenylphosphino)ferrocene,
FG — functional group,
FLP — frustrated Lewis pairs,
Fu — furyl,
Hex — n-hexyl,
KHMDS — potassium bis(trimethylsilyl)amide,
LA — Lewis acid,
m-CPBA — *m*-chloroperbenzoic acid,
Mes — mesityl (2,4,6-trimethylphenyl),
Moc — methoxycarbonyl,
Ms — mesyl (methanesulfonyl),
MS — molecular sieves,
MW — microwave radiation,
Naph —naphthyl,
NFSI — *N*-fluorobenzenesulfonimide,
NHC — N-heterocyclic carbene,
NIS — *N*-iodosuccinimide,
Ns — nosyl (4-nitrobenzenesulfonyl),
PCC — pyridinium chlorochromate,
PEG — polyethylene glycol,
PG — protecting group,
PIDA — phenyliodine(III) diacetate,
PIFA — phenyliodine(III) bis(trifluoroacetate),
Pip — piperidine,
Piv — pivaloyl,

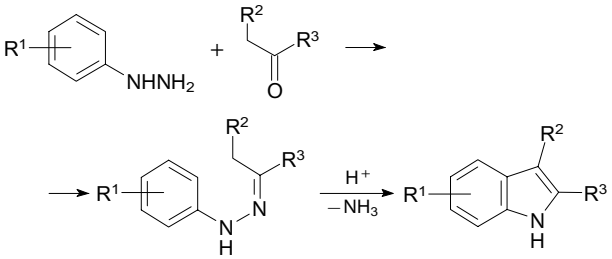
PMB — *p*-methoxybenzyl,
PNBSA — *p*-nitrobenzenesulfonyl azide,
PPA — polyphosphoric acid,
Py — pyridyl,
rt — room temperature,
SEM — [2-(trimethylsilyl)ethoxy]methyl,
SET — single-electron transfer,
TBAF — tetra-n-butylammonium fluoride,
TBAI — tetra-n-butylammonium iodide,
TBDMS — *tert*-butyldimethylsilyl,
TBHP — *tert*-butyl hydroperoxide,
TCT — 2,4,6-trichloro-1,3,5-triazine,
TEMPO — (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
Tf — triflyl (trifluoromethanesulfonyl),
TIPS — triisopropylsilyl,
TMS — trimethylsilyl,
TNT — trinitrotoluene,
Tol — tolyl (methylphenyl),
Ts — tosyl (*p*-toluenesulfonyl).

2. Modern versions of classical synthetic methods

2.1. Fischer indole synthesis

The classical Fischer indole synthesis involves cyclization of arylhydrazones of carbonyl compounds under the action of acidic agents (Scheme 1).[26]

Scheme 1



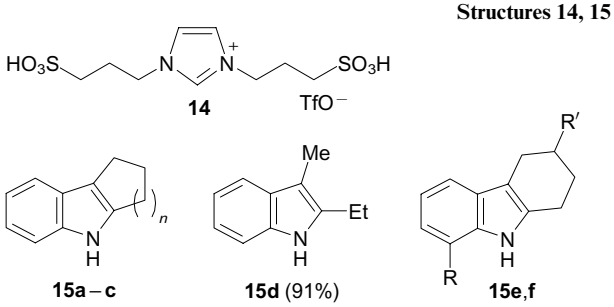
The modern modifications of the method include the change in the reaction conditions, application of new catalysts and approaches to the synthesis of starting arylhydrazines and hydrazones and the use of unusual latent forms of carbonyl compounds.

In recent years, the development of the synthetic methods has been targeted towards green chemistry requirements. For example, an easy and efficient one-pot procedure has been proposed for the Fischer synthesis of indoles in 90%–96% yields from ketones and arylhydrazine hydrochlorides in water, under sonication and in the presence of a new SO_3-functionalized ionic liquid **14** as the catalyst.[27] The benefits of this method include easy workup of the reaction mixture, the use of environmentally clean, inexpensive and non-toxic catalysts, short time of the reaction (~15 min) and excellent yields of the target products. This creates broad prospects for the practical use of the method (the synthesized indoles are represented by compounds **15a**–**f**).

The Fischer synthesis of complex δ-opioid receptor antagonists **16** from natural ketones, 4,5α-morphinans (Scheme 2), was also carried out in water with 0.1 N HCl as the catalyst.[28]

Often, ionic liquids function as both the catalysts and the reaction media.[29] The scalable synthesis of 3-methylindole from phenylhydrazine and propanal in ionic liquid (3-ethyl-1-methylimidazolium tetrafluoroborate) carried out in the presence of a stoichiometric amount of $ZnCl_2$ in a continuous-flow reactor gives a high yield of the product (>90%) (Scheme 3).[30]

Structures 14, 15



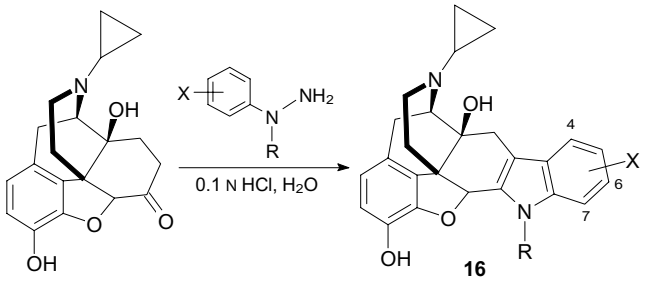
14

15a–c **15d** (91%) **15e,f**

n = 1 (**a**, 90% yield),
2 (**b**, 93%),
4 (**c**, 91%)

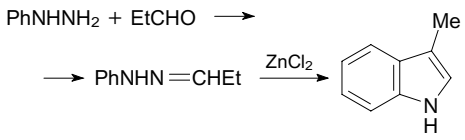
R = H,
R′ = Bu^t (**e**, 96%);
R = Cl,
R′ = H (**f**, 94%)

Scheme 2



R = X = H (96%); R = Me, X = H (73%); R = H:
X = 5-OMe (61%), 7-Cl (28%), 7-F (53%)

Scheme 3



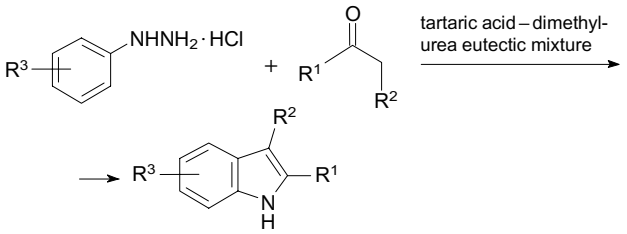
The dual role of both the reaction medium and the catalyst can also be performed by the low-melting eutectic mixture of tartaric acid with dimethylurea (Scheme 4).[31]

Zirconium hydroxide-supported niobium oxide, Nb_2O_3/$Zr(OH)_4$, was used as the catalyst in the Fischer indole synthesis (Scheme 5).[32] In this case, like in other versions of the reaction, the use of unsymmetrical ketones results in the formation of isomeric indoles **17a** and **17b**.

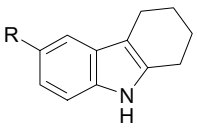
The application of a catalytic amount of bismuth nitrate for the formation of arylhydrazones followed by cyclization induced by polyphposphoric acid (PPA) in a one-pot procedure leads to the synthesis of isomeric 5(6,7)-nitroindoles in high yields (Scheme 6; here and below, the locants refer to the product unless otherwise specified); this is hardly possible under standard indolization conditions.[33]

The use of cyclic propylphosphonic acid anhydride (T3P) as the catalyst and microwave radiation (MW) for indolization considerably simplifies the preparation proce-

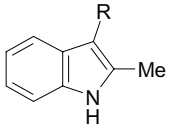
Scheme 4



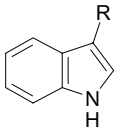
Examples of products



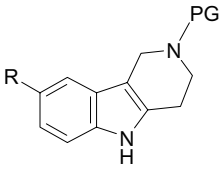
R = H (97%), Cl (97%)



R = Me (88%), Pr^i (95%)

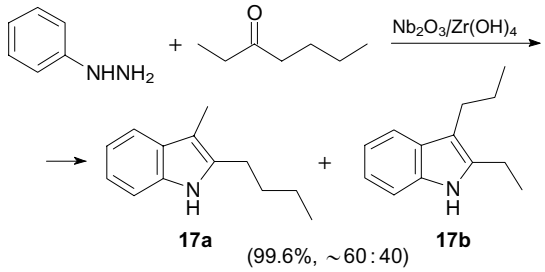


R = Ph (87%),
$(CH_2)_3OH$ (85%)

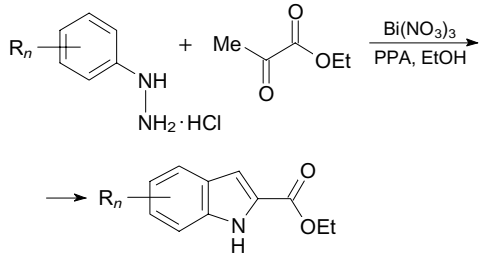


R = H, PG = Cbz (94%);
R = MeO, PG = Boc (88%)

Scheme 5



Scheme 6

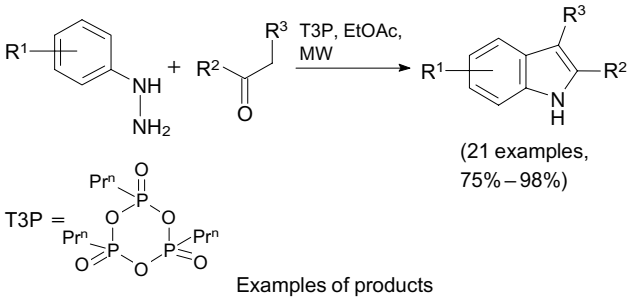


R_n = H (90%), 5-NO_2-7-F (80%), 5-NO_2 (80%), 6-Cl (85%),
6-NO_2 (80%), 7-NO_2 (80%), 6-Br (85%), 5-Br (85%), 5-F (85%),
4-Cl (80%)

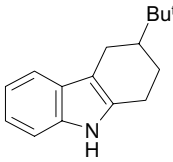
dure of the target indoles and reduces the reaction time (Scheme 7).[34]

The use of readily accessible and cheap, although relatively toxic, 2,4,6-trichloro-1,3,5-triazine (TCT, **18**) in methanol as the catalyst serving as the HCl source has been

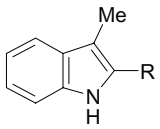
Scheme 7



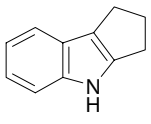
Examples of products



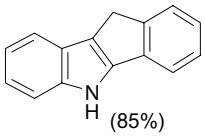
(95%)



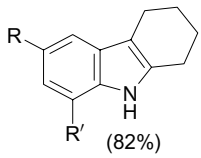
R = Et (82%),
CO_2Me (90%)



(76%)



(85%)



(82%)

R′ = H: R = Me (82%), CF_3 (86%);
R = H, R′ = Me (76%)

reported.[35] Since TCT is a very mild catalyst, this reaction can afford indoles with a high diversity of functional groups (Scheme 8), with ester, amide, sulfonyl and cyano groups being tolerant to the reaction conditions.

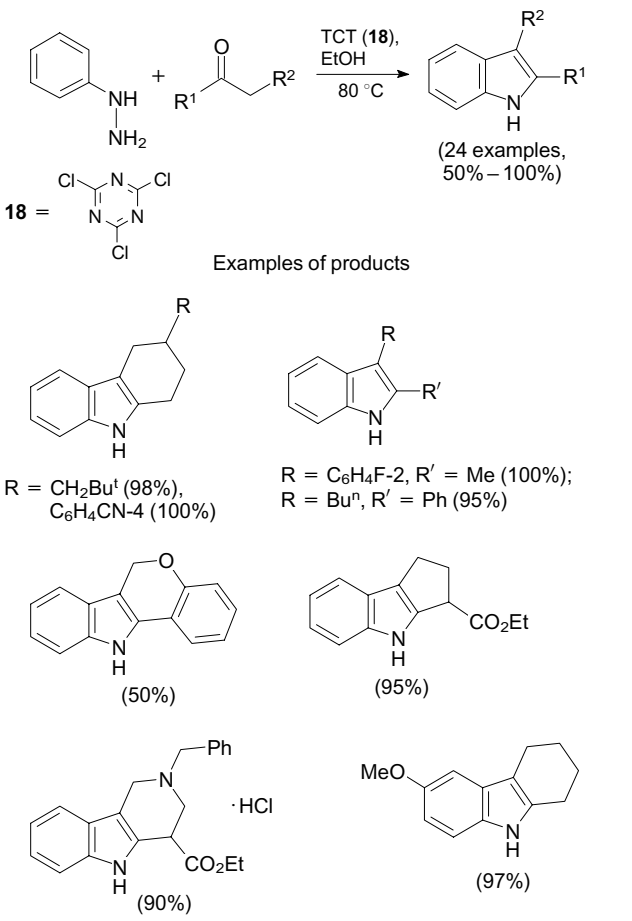
Although the classical Fischer indole synthesis is used rather widely, it still has some drawbacks. The synthesis is based on the use of arylhydrazines, which are obtained from anilines *via* diazonium salts or from aryl halides in the presence of expensive and toxic transition metal-based catalysts. These reactions require aniline precursors and toxic reagents (nitrous acid, tin chloride and so on) and involve unstable diazonium intermediates. Therefore, one trend of modification of the Fischer method is the development of original approaches to the synthesis of hydrazines, hydrazones and ene-hydrazines.

A version of the Fischer indole synthesis has been proposed in which the key intermediates, hydrazones and ene-hydrazines, are prepared by the reactions of stable diazonium salts with organozinc reagents **19** (Scheme 9).[36] The benefits of this method are the tolerance to a broad range of functional groups such as ester, cyano, nitro and keto groups, the accessibility of organozinc compounds and the ease of preparation of stable diazonium salts.

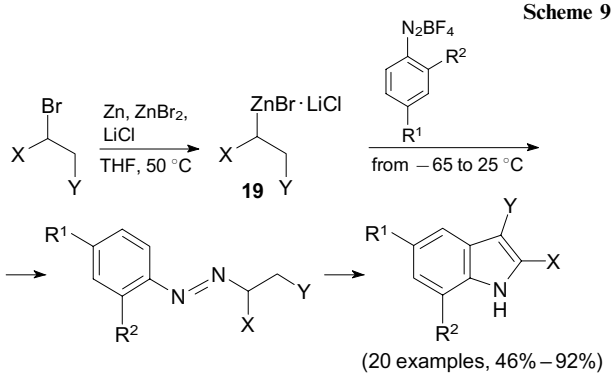
In a study of the same problem, a new version of the Fischer indole synthesis was proposed, which includes one-pot condensation of quinone monoketal with aliphatic hydrazines.[37] This is the first method for the Fischer type indole synthesis that uses aliphatic hydrazines as a source of nitrogen and quinone monoketals as a latent form of benzene (Scheme 10).

The development of an original approach to arylhydrazines gave rise to one more protocol for the Fischer indole synthesis (Scheme 11).[38] Arylhydrazines were prepared for the first time from readily available aryl iodides, which

Scheme 8



Scheme 9

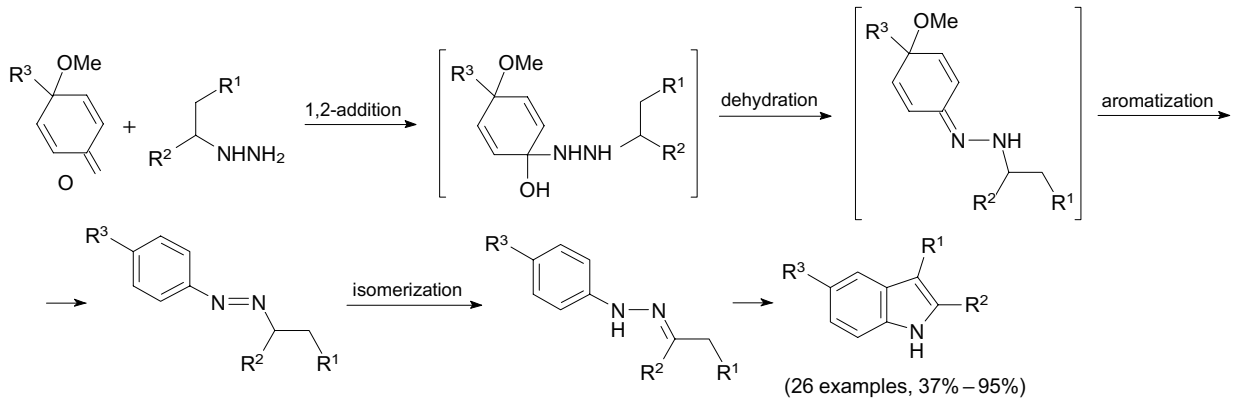


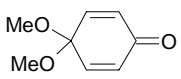
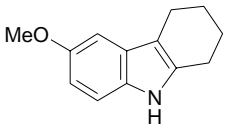
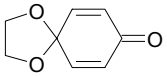
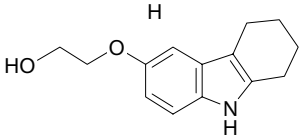
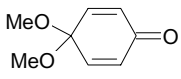
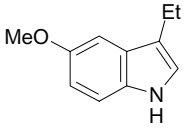
X	Y	R^1	R^2	Yield (%)
Me	CH_2CO_2Et	OMe	NO_2	69
Me	CH_2CO_2Et	Ac	H	73
Me	CH_2CO_2Et	OPiv	H	65
Me	Me	OMe	NO_2	81
Me	Me	CO_2Et	H	75
Me	Me	OPiv	H	78
Me	Me	OMe	H	84
Me	Me	Ac	H	81
Me	Me	I	H	85
Me	Me	CN	H	78
Ph	Me	OMe	NO_2	46

reacted with Grignard reagents according to the halogen – magnesium exchange pattern, and this was followed by the reaction with di-*tert*-butyl azodicarboxylate.

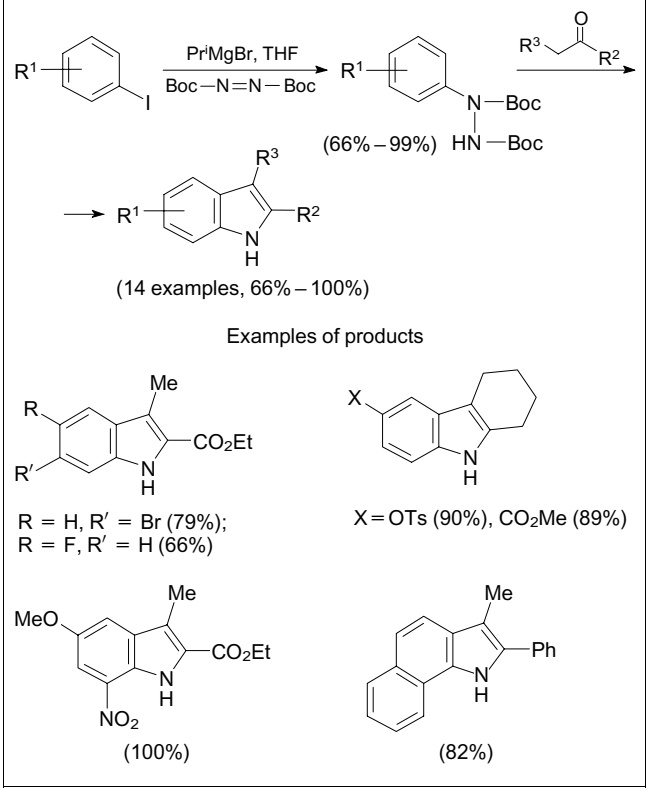
The arylation of *N*-tosylhydrazones with arynes (benzene derivative **20** serves as the aryne precursor) and

Scheme 10



Quinone monoketal	Hydrazine	Indole	Yield(%)
	$CyNHNH_2$		68
	$CyNHNH_2$		68
	Bu^nNHNH_2		37

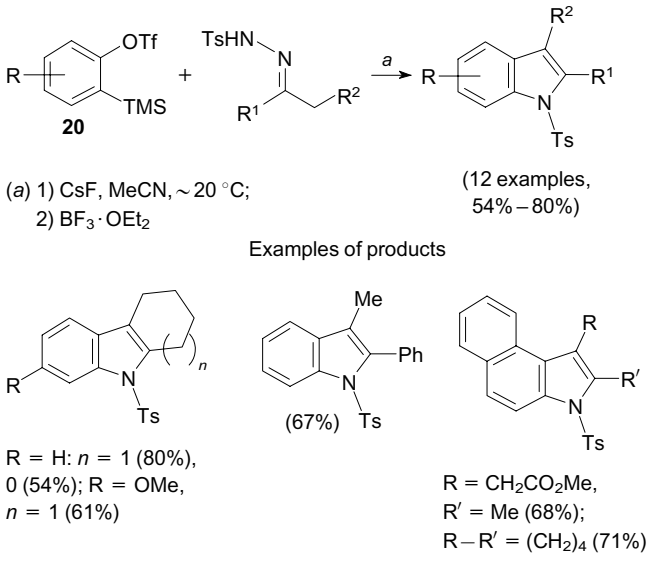
Scheme 11



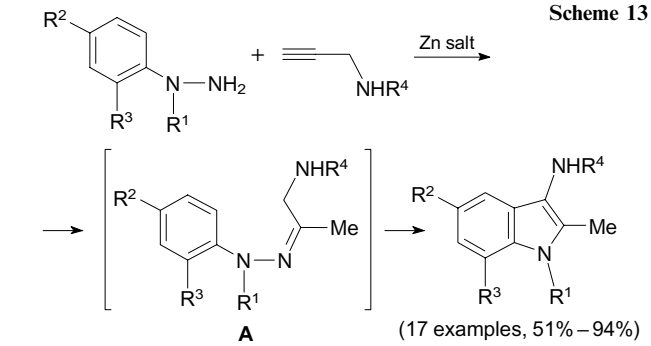
cyclization of the resulting arylhydrazones induced by Lewis acid, conducted as a one-pot reaction, affords indole derivatives in moderate to high yields (Scheme 12).[39]

An original approach to the synthesis of hydrazones needed as intermediates was accomplished using commercially available arylhydrazines and propargylamines (Scheme 13).[40] This gave a broad range of 3-aminoindoles as a result of a simple one-pot process catalyzed by zinc salts; this method is distinguished by high regioselectivity and yields of up to 94%. Presumably, the first step of the domino reaction is intermolecular hydroamination (hydrohydrazination) with the intermediate formation of hydrazones **A** followed by the standard cyclization. The benefits of the method include the lack of necessity for inert atmosphere and the tolerance to various functional groups.

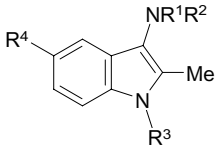
Scheme 12



Scheme 13



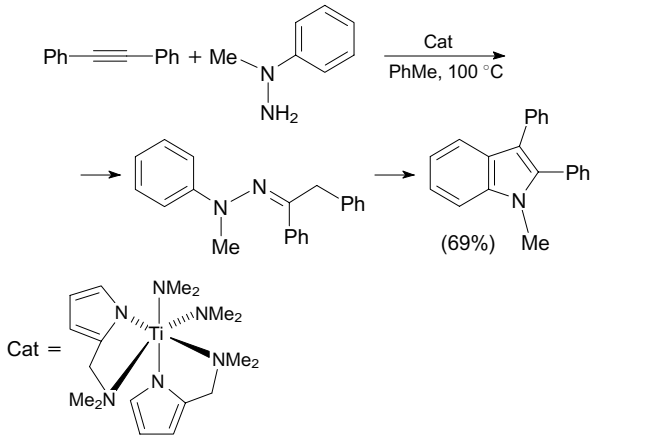
Examples of products



NR^1R^2	R^3	R^4	Yield (%)
NHAc	H	Br	78
NHAc	H	CN	80
NHAc	H	Pr^i	94
NHBz	H	Br	74
NHAc	Me	H	55
Phthalimido	H	Br	67
$NHSO_2$-3-benzothienyl	H	Br	51

The use of titanium-based catalysts also provides the formation of hydrazones (Scheme 14). The subsequent Fischer cyclization affords indoles in 42%–95% yields.[41]

Scheme 14

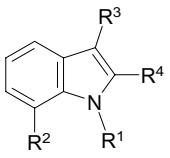


This method was used to synthesize a number of 1,2,3-trisubstituted indoles **21a–f**.

A three-component combination of acyl chlorides, diazonium salts **22** and alcohols or amines in the presence of pyridine was used to prepare hydrazonocarboxylic acid esters and amides **23**, which can be easily cyclized by the Fischer method (Scheme 15).[42]

The multicomponent cascade method for the synthesis of 2,2,2-trifluoroethyl-substituted indoles from accessible reagents such as unfunctionalized alkenes, diazonium salts **22** and sodium trifluoromethanesulfinate is based on

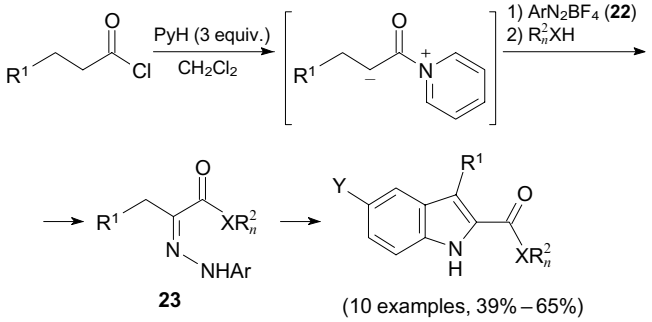
Structures 21



21a – f

Compound **21**	R^1	R^2	R^3	R^4	Yield (%)
a	Me	H	Pr^n	Me	56
b	Me	H	Ph	H	95
c	Me	H	Ph	Me	90
d	Ph	H	Ph	Ph	42
e	$(CH_2)_3$		Ph	Ph	73
f	$(CH_2)_2$		Ph	Me	66

Scheme 15



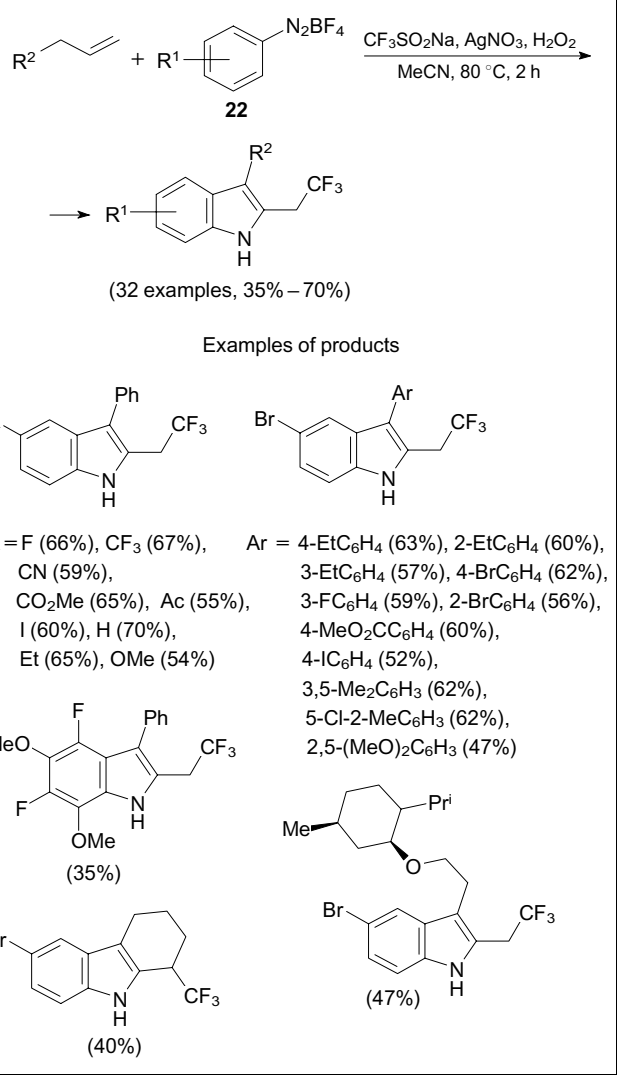
R^1 = Me, Ph; Y = F, Cl; XR^2_n = OMe, $OCH_2C_3H_5$-cyclo, OBn, $NAll_2$, NEt_2

radical trifluoromethylation of alkenes, which then react with diazonium salts and undergo the Fischer reaction *via* a number of tautomeric transformations (Scheme 16).[43]

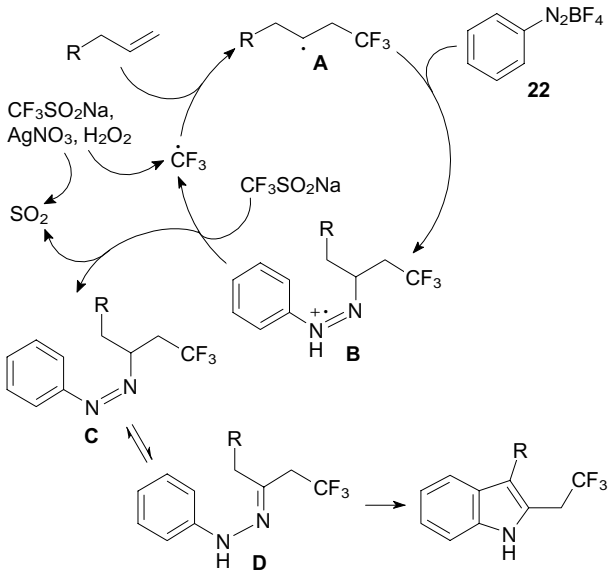
The mechanism proposed for this multicomponent process is depicted in Scheme 17. Presumably, the trifluoromethyl radical generated by a combination of CF_3SO_2Na, $AgNO_3$ and H_2O_2 adds to the terminal atom of the alkene to give radical intermediate **A**, which rapidly reacts with aryldiazonium salt **22** to give radical cation **B**. Intermediate **B** is then reduced to intermediate **C**, which isomerizes to hydrazone **D**; the latter is indolized according to the usual Fischer synthesis pathway. Thus, the described cascade of reactions forms a new, original approach to the synthesis of the starting arylhydrazones.[43]

The proposed one-pot cascade method for the preparation of substituted tryptamines (Schemes 18, 19, Table 1)[44] is also based on a new approach to the synthesis of arylhydrazones. As shown in Scheme 18, cyclic imines, for example imine **24**, can be activated with acyl chlorides in the presence of a mediator (pyridine). Pyridine or another mediator (for example, DMAP, *i.e.*, 4-dimethylaminopyridine) forms intermediates **25a**, **25b** and **25c**, which occur in equilibrium. There are two possible pathways to the target tryptamine **29a** from enamine **25a** or N-acylium ion **25c**. Under acidic conditions, intermediate **25a** can be hydrolyzed to give amino ketone **26**, which is the precursor of hydrazone **27**. Alternatively, the addition of phenylhydrazine to ion **25c** also leads to the formation of hydrazone **27**

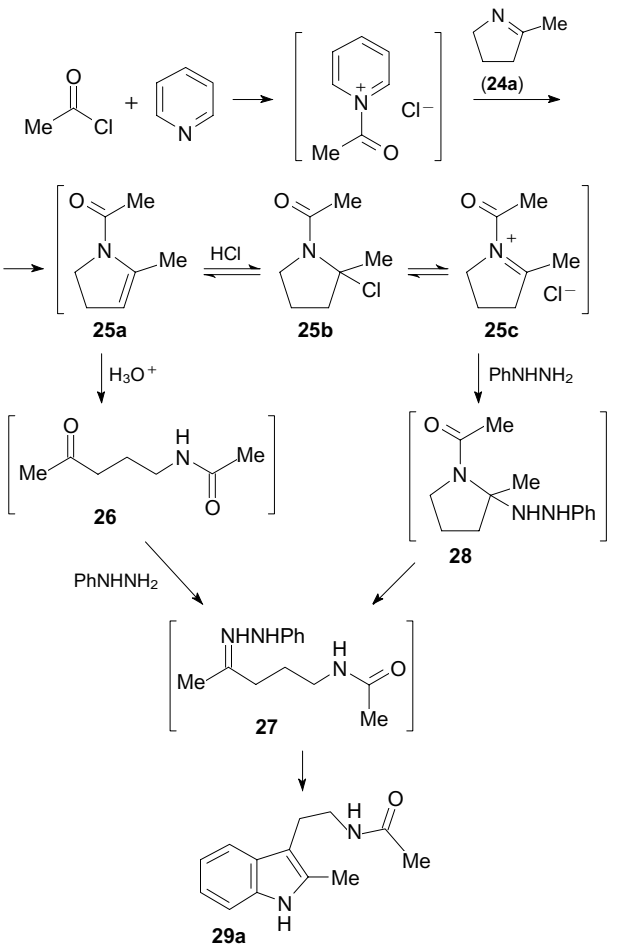
Scheme 16



Scheme 17

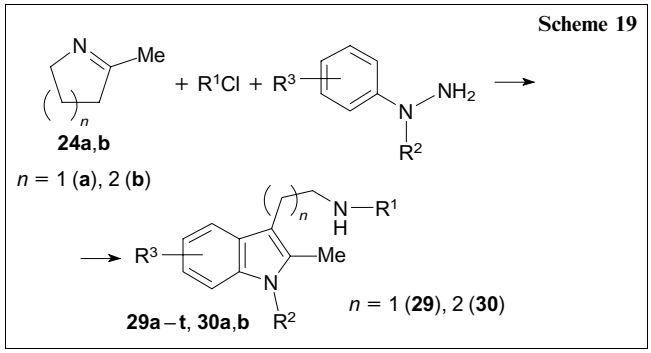


Scheme 18



via intermediate **28**. Since hydrazone **27** is a standard intermediate in the Fischer indole synthesis, it can easily cyclize in acid medium to give target tryptamine **29a**. Therefore, ketone **26** and/or intermediate **28** can be generated *in situ* from cyclic imine, and tryptamines can thus be obtained *via* the usual Fischer synthesis implemented as a one-pot procedure (see Scheme 19, Table 1).[44]

Scheme 19



The scope of the Fischer indole synthesis is also extended *via* development of the methods for the preparation of carbonyl components of the process. For example, nucleophilic substitution of the vinyl halogen atom by pyrrolydine to give α-trifluoromethyl-β-aryleneamines **31**, synthetic equivalents of benzyl trifluoromethyl ketones, is successfully used in the Fischer indole synthesis (Scheme 20).[45] The reaction of these enamines with arylhydrazines in acetic acid for 15 min gives high yields of hydrazones, which then undergo cyclization to the desired indoles.

The same strategy was implemented in the one-pot synthesis that combined the Heck isomerization to prepare the carbonyl component (ketone) and the microwave-assisted Fischer indolization (Scheme 21; the locants are given for the substrate).[46] Various 3-benzylindoles are formed in moderate to good yields.

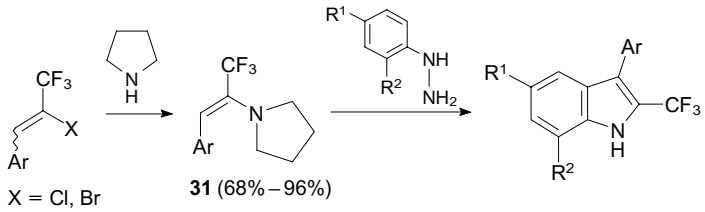
In a new version of Fischer indole synthesis, primary and secondary alcohols are catalytically oxidized in the presence of phenylhydrazine and protic or Lewis acids.[47] An original example of using *N*-Boc-phenylhydrazines (other than in the Fischer method) is the rhodium-catalyzed reaction with diazoketoesters, resulting in the formation of *N*-aminoindoles (the reaction is accompanied by elimination of the Boc group).[48]

Thus, this Section of the review clearly demonstrates good prospects and efficiency of the modern versions of the classical Fischer indole synthesis, which upgrade experimental techniques, increase their environmental safety and provide a larger variety of indole types.

Table 1. Synthesis of tryptamines and homotryptamines (see Scheme 19).[44]

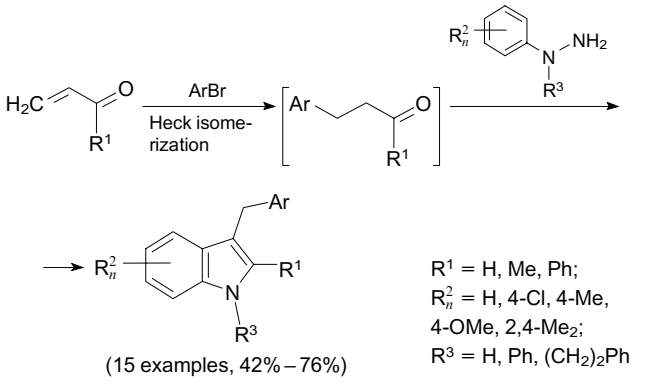
Compounds **29**, **30**	R^1	R^2	R^3	Yield (%)	Compounds **29**, **30**	R^1	R^2	R^3	Yield (%)
	Tryptamines **29**					*Tryptamines* **29**			
a	Ac	H	H	96	**m**	Ac	H	7-Cl	83
b	4-$FC_6H_4C(O)$	H	H	96	**n**	Ac	H	5-MeO	87
c	Ts	H	H	88	**o**	Ac	H	5-Br	71
d	Butyryl	H	H	85	**p**	Ac	All	5-MeO	96
e	MeOC(O)	H	H	82	**q**	Ts	3-$FC_6H_4CH_2$	5-MeO	73
f	Ms	H	H	83	**r**	Tf	Me	H	66
g	$CF_3C(O)$	H	H	92	**s**	4-$FC_6H_4C(O)$	Me	5-Br	90
h	Tf	H	H	92	**t**	$CF_3C(O)$	H	5-MeO	70
i	Ns	H	H	75					
j	Ac	Me	H	90		*Homotryptamines* **30**			
k	Ac	All	H	85	**a**	Ac	H	H	71
l	Ac	3-$FC_6H_4CH_2$	H	82	**b**	Ac	Me	H	70

Scheme 20

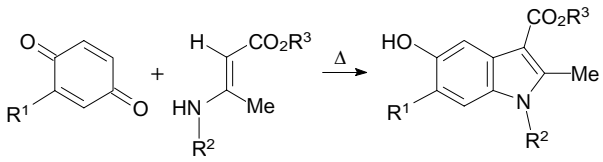


Ar	R^1	R^2	Yield (%)	Ar	R^1	R^2	Yield (%)
4-$O_2NC_6H_4$	H	H	88	4-ClC_6H_4	Cl	H	89
4-ClC_6H_4	H	H	68	4-ClC_6H_4	F	H	69
Ph	H	H	45	4-ClC_6H_4	CN	H	50
4-$MeOC_6H_4$	H	H	43	4-ClC_6H_4	Me	H	76
4-BrC_6H_4	H	H	70	4-ClC_6H_4	MeO	H	41
2-$O_2NC_6H_4$	H	H	45	4-ClC_6H_4	Cl	Cl	52
3-$O_2NC_6H_4$	H	H	70	4-ClC_6H_4	Me	Me	68

Scheme 21



Scheme 22



2.2. Nenitzescu reaction

The classical Nenitzescu synthesis of 5-hydroxyindoles comprises the condensation of *p*-benzoquinones with aminocrotonates (Scheme 22).[49]

This method still has not lost its significance, as indicated by the continuously appearing publications reporting its modification. In 2010, it was demonstrated that this method is applicable for the industrial production of 5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid (in 65 kg quantity) and 5-hydroxy-2-methyl-1*H*-indole (in 20 kg quantity).[50] The replacement of *p*-benzoquinone by quinoneimines **32**, which are readily obtained by the oxidation of the appropriate *p*-alkoxyanilines, and the subsequent condensation with hexafluoroacetylacetone (in the Nenitzescu synthesis, aminocrotonates are used) afford *o*-aminobenzyl diketone derivatives **33**, which readily undergo cyclization to 3-(trifluoroacetyl)indoles (Scheme 23, Table 2).[51] Thus, in this case, quinone imine serves as the source of indole nitrogen and phenyliodine(III) diacetate acts as the oxidant, and elimination of a water molecule is induced by trifluoroacetic acid.

This method has some substrate limitations. Thus it follows from Table 2 that in the presence of electron-withdrawing substituents in the benzene ring, indoles are rarely formed. An important practical application of the Nenit-

Scheme 23

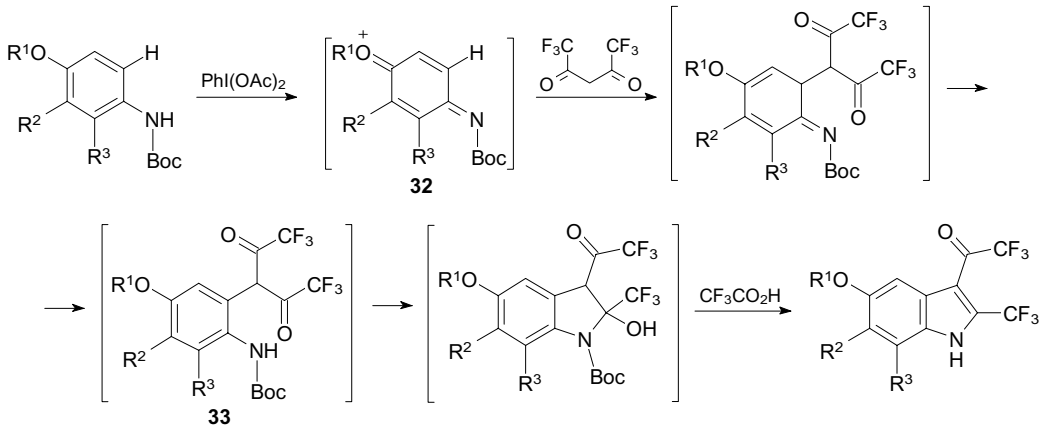
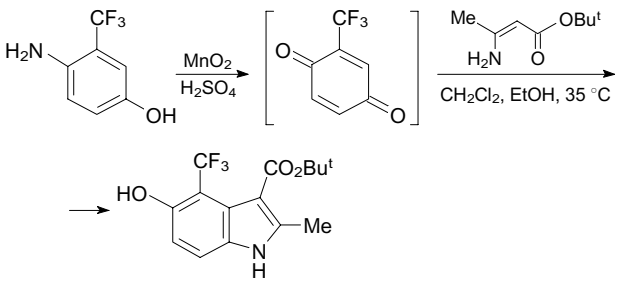


Table 2. Synthesis of 3-trifluoroacetyl-2-trifluoromethylindoles from aminophenols, which are oxidized to quinoneimines (see Scheme 23).[51]

R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
Me	H	Cl	64	Me	Cl	H	72
Me	H	Br	61	Me	Br	H	69
Me	H	H	90	Me	I	H	69
Me	H	Me	88	Me	Ph	H	81
Me	H	F	57	Me	CO_2Me	H	0
Me	H	I	37	Me	NO_2	H	0
Me	H	Ph	97	Me	OMe	H	0
Me	H	NO_2	0	Me	OCH_2CF_3	H	70
Me	H	OMe	8	Bn	H	H	99
Me	H	OCH_2CF_3	45	$CH_2CH{=}CH_2$	H	H	93
Me	Me	H	88	$CH_2C{\equiv}CH$	H	H	94
Me	F	H	68				

zescu reaction is the synthesis of *tert*-butyl 2-methyl-4-(trifluoromethyl)-1*H*-indole-3-carboxylate, a key intermediate in the synthesis of androgen receptor modulators. A convenient method has been developed for the synthesis of this indole from 4-amino-3-(trifluoromethyl)phenol and *tert*-butyl acetoacetate (Scheme 24). In 1968, Litell and Allen[52] showed that the Nenitzescu reaction of 2-trifluoromethyl-1,4-benzoquinone with 3-aminocrotonates leads to the selective formation of 4-substituted 5-hydroxyindoles. The regioselectivity is caused by the strong inductive effect of the trifluoromethyl group. Hence, the enamine addition occurs selectively at position 3 of benzoquinone.

Scheme 24

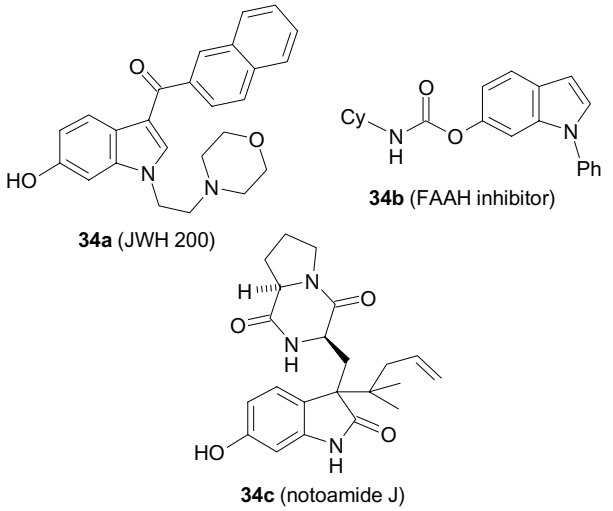


Unlike the synthesis of 5-hydroxyindoles, the preparation of 6-hydroxyindoles is faced with some obstacles. Meanwhile, compounds of this class have found practical use as inhibitors of target proteins, hair colourant, cannabinoid receptor agonists (JWH-200, **34a**) and fatty acid amide hydrolase (FAAH) inhibitors (**34b**); their fragments are encountered in indole alkaloid molecules (notoamide J, **34c**).[53 – 56]

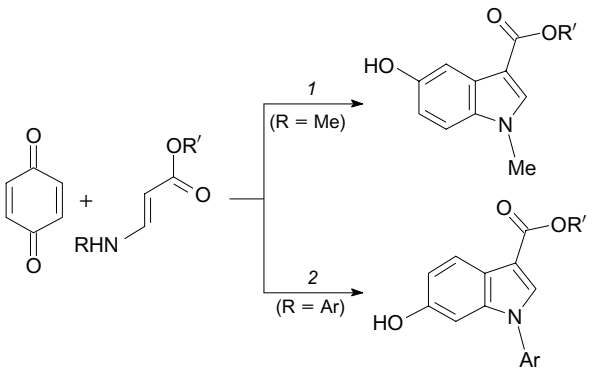
The Nenitzescu synthesis is usually employed to prepare 5-hydroxyindole derivatives by the reaction of 1,4-benzoquinones with aminocrotonates. The Nenitzescu reaction with reversed regioselectivity resulting in 6-hydroxyindoles is encountered very rarely. This reaction, which depends on the type of substituent in the aminoacrylate, was discovered by Grinev and co-workers,[57] who replaced the N-alkyl derivatives by N-aryl derivatives (Scheme 25).

In 2017, an alternative protocol was proposed for the Nenitzescu reaction with reversed regioselectivity to prepare a broad range of 6-hydroxyindole derivatives without the use of catalysts. This method is suitable for preparing not

Structures 34



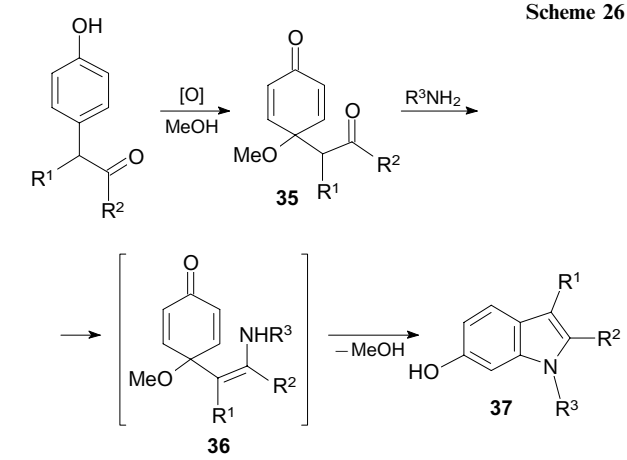
Scheme 25



(*1*) Nenitzescu reaction, (*2*) Nenitzescu reaction with reversed selectivity

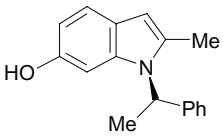
only *N*-aryl-, but also *N*-alkyl- and NH-6-hydroxyindoles (Scheme 26).[58] The method comprises the synthesis of 6-hydroxyindoles **37** by condensation of primary amines with cyclohexadienone **35** containing a β-carbonyl functional group in position 4. The reaction proceeds *via* the formation of enamine **36** followed by aza-Michael reaction and rearomatization. Substrate **35** was synthesized by

Scheme 26



R^3 = H, Alk, Ar

Examples of products (R^1 = H)



37i (76%, 99% *ee*)

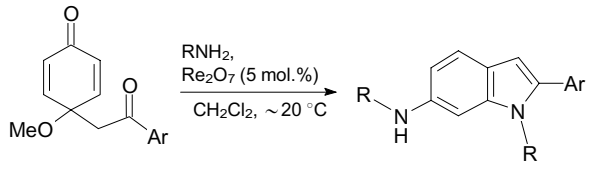
Compound **37**	R^2	R^3	Yield (%)
a	H	C_6H_4OMe-4	78
b	H	2-Py	78
c	H	H	92
d	H	cyclo-C_8H_{15}	87
e	H	Bn	80
f	H	Morpholino-methyl	40
g	Me	CH_2CO_2Et	47
h	Me	Bn	90

oxidation of the appropriate phenol with the Dess–Martin reagent.

Since the substituent at the nitrogen atom is not affected, this reaction was successfully applied to prepare 6-hydroxyindoles with a chiral substituent at nitrogen. For example, compound **37i** was obtained in 76% yield with 99% *ee*.

With a rhenium-based catalyst, this reaction affords 6-aminoindoles (Scheme 27).[58]

Scheme 27

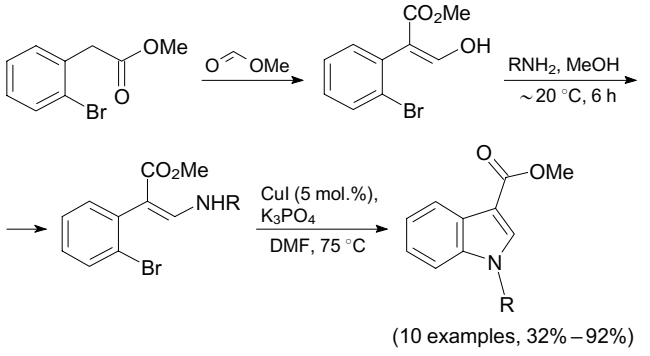


R	Ar	Yield (%)
Bn	Ph	60
Ph	Ph	82
2-(Cyclohex-2-enyl)ethyl	Ph	70
Bn	4-$MeOC_6H_4$	51
Ph(Me)CH	4-$MeOC_6H_4$	90

2.3. Ullmann reaction

N-Alkylated and N-arylated derivatives of methyl 1*H*-indole-3-carboxylate were synthesized for the first time by intramolecular Ullmann arylamination using CuI (Scheme 28).[59] This catalytic amination furnishes indole derivatives under mild reaction conditions in good to high yields. Under optimized conditions, this method was successfully used to prepare methyl 1*H*-indole-3-carboxylates with both aliphatic and aromatic substituents at the nitrogen atom (see Scheme 28). Attention is attracted by the possibility of preparing compounds with a chiral substituent at nitrogen, because the stereocentre of the chiral amine is not affected during the reaction.

Scheme 28

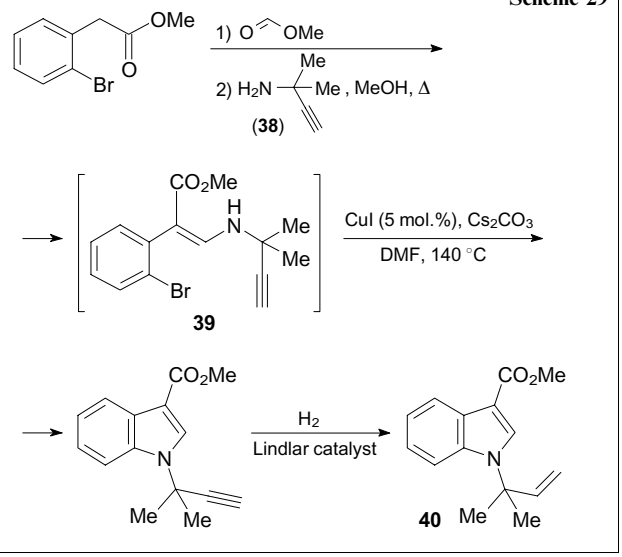


(10 examples, 32%–92%)

R	Yield (%)	R	Yield (%)
Bn	92	4-$MeOC_6H_4$	94
Cy	57	Mes	77
Bu^t	32		68
cyclo-C_3H_5	78		

This method was utilized for the synthesis of the simplest representative of *N*-isoprenylindole alkaloids, that is, methyl 1-(1,1-dimethylprop-2-en-1-yl)-1*H*-indole-3-carboxylate (**40**) (Scheme 29), isolated from *Aporpium caryae basidiomycetes fungus*.[60] This compound exhibits antifungal activity [61] and serves as the precursor for the synthesis of natural indole derivatives. Despite the seeming simplicity of structure **40**, its synthesis is a non-trivial task because the direct introduction of the isoprenyl moiety into position 1 of indole is impossible. Methods for indirect synthesis of these compounds consist of numerous steps and give products in low overall yields.[62–64] The proposed method[60] for the synthesis of this alkaloid using the modified Ullmann reaction includes three steps, is based on the accessible

Scheme 29

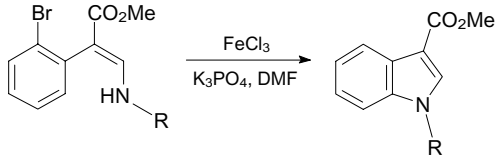


starting compounds and gives the product in an overall yield of 73%.

Commercially available 2-methylbut-3-yn-2-ylamine (**38**) was converted to enamine **39**, which was subjected to the Ullmann reaction without isolation to give alkynyl-substituted indole; the subsequent hydrogenation of the triple bond resulted in the target compound **40**.

In view of the achievements in the use of iron-based catalysts, the possibility of replacement of copper-containing catalysts by iron salts was studied. It was shown that iron chloride is an efficient catalyst for N-arylation; under optimized conditions, esters of indole-3-carboxylic acids with various substituents at nitrogen were obtained in high yields (75% – 78%) (Scheme 30).[65]

Scheme 30



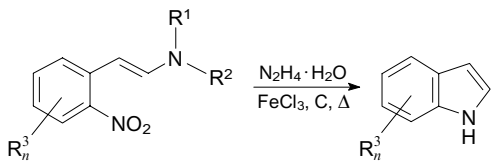
R = Bn (78%), 4-MeOC$_6$H$_4$ (75%), Me$_2$N (77%)

2.4. Leimgruber – Batcho indole synthesis

The reduction of enamines obtained by condensation of *o*-methylnitrobenzenes with DMF acetals is known as the Leimgruber – Batcho synthesis; it is normally used to prepare indoles with substituents in different positions of the benzene ring (see Chapter 2 in a book, Ref. 66). This reductive cyclization was previously performed using Pd/C-catalyzed hydrogenation, hydrazine in the presence of Pd or Raney nickel, various Ti^{III}, Fe^{II} or Sn^{II} derivatives or other reducing agents. These methods, however, suffer from a number of drawbacks. For example, the catalytic hydrogenation requires special equipment and, furthermore, precludes the presence of functional groups sensitive to the reaction conditions, such as OBn and Hal. When a Ni catalyst is used, nickel ions that get into the reaction medium considerably hamper the isolation and purification of indoles due to resinification.

The version of the method involving the use of hydrazine reduction in the presence of a complex catalyst based on ferric chloride and activated carbon for the reductive cyclization of β-dialkylamino-2-nitrostyrenes to various substituted indoles is free from these drawbacks (Scheme 31).[67] The reduction and cyclization of *o*-nitrophenylenamines is catalyzed by $FeCl_3 \cdot H_2O$ (5 mol.%) and high-dispersion activated carbon (20 mol.%); 10 moles of $N_2H_4 \cdot H_2O$ are required per mole of the substrate in propan-2-ol.

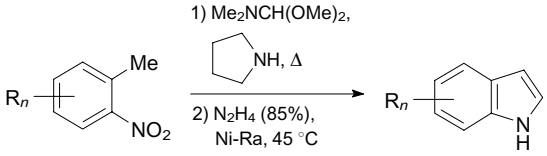
Scheme 31



(15 examples, 32% – 96%)

R^3_n	Yield (%)	R^3_n	Yield (%)
5-OMe	91	6-Cl	96
5-OCH$_2$CF$_2$H	72	4-Cl	32
6-Br	93	5,6-OCH$_2$O	80

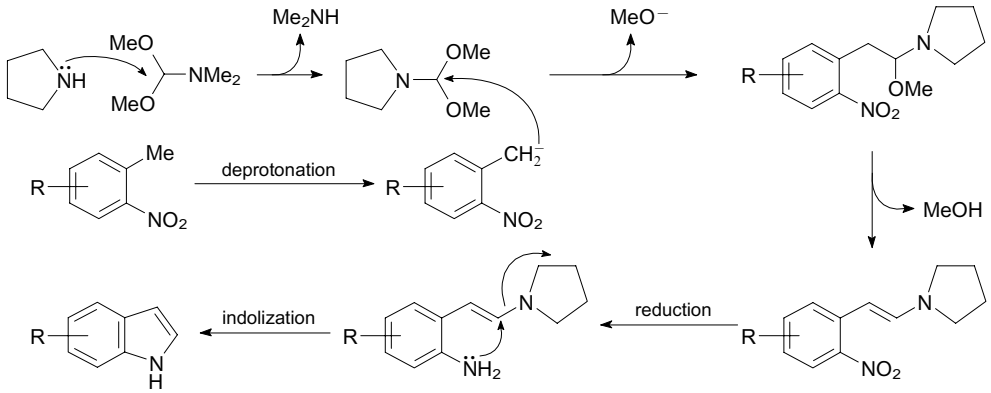
Scheme 32



R_n = H (71%), 6-Cl (90%, 30%*), 6-Br (82%, 37%*), 6-NH$_2$ (52%, 35%*), 5-Me (65%), 5-Cl (74%), 5-CN (71%), 5,6-Cl$_2$ (92%), 4-Cl (53%), 4-NH$_2$ (34%), 7-Cl (70%), 7-Me (53%); Ni-Ra is Raney nickel

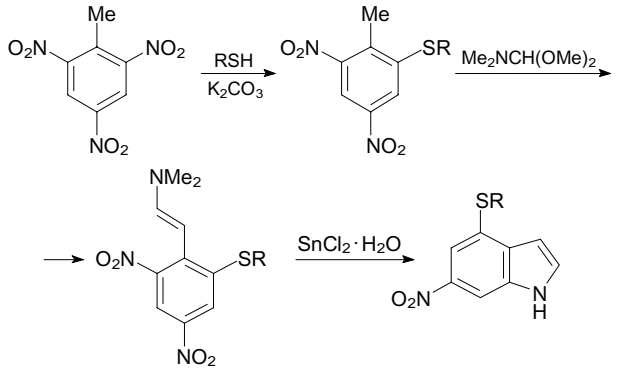
As compared with the classical Leimgruber – Batcho reaction, the one-pot process does not require the intermediate isolation of unstable enamines. Furthermore, the overall yield of the product upon the one-pot protocol is much (approximately two times) higher. Electron-withdrawing substituents in *o*-nitrotoluene increase the reactivity and the yields of indoles in comparison with those observed for electron-donating substituents. The presumptive mechanism of the reaction is depicted in Scheme 33.

Scheme 33



Indole derivatives can easily be prepared from commercially widely available 2,4,6-trinitrotoluene (TNT) (Scheme 34).[69] The first step is the nucleophilic substitution of the *ortho*-nitro group with a thiol to give the corresponding sulfide, which is then converted to enamine on treatment with dimethylformamide dimethylacetal. The enamine cyclizes to indole by the Leimgruber–Batcho method.

Scheme 34



R = Me (68%), Et (65%), Pr^n (69%), $(CH_2)_2OH$ (72%), $(CH_2)_2NHBoc$ (65%)

The formation of enamines **41** in the reaction of *o*-nitrophenylacetonitriles with the Vilsmeier reagent followed by the reduction with Zn in acetic acid affords various substituted 3-cyanoindoles **44** containing aryl, alkyl and aminoalkyl substituents in position 2 (Scheme 35, Table 3).[70] The Vilsmeier reagent is generated *in situ* before the reaction with nitroarene.[71] The reductive cyclization of cyanoenamines **41** affords 3-cyanoindoles **44**, which contain the substituent from the starting amide in position 2. In one case, apart from indole **44**, the reaction gave indole **45** with the dialkylamino group in position 2. Indole **45** can be formed only with unsubstituted cyanoenamine (generated from dimethylformamide) *via* elimination of water from intermediate **42** proceeding in parallel with elimination of the dialkylamino group. The intermediate hydroxylamine **42** with $R^2 \neq H$ cyclizes only with the loss of the dialkylamino group to give intermediate *N*-hydroxyindole **43**,

Scheme 35

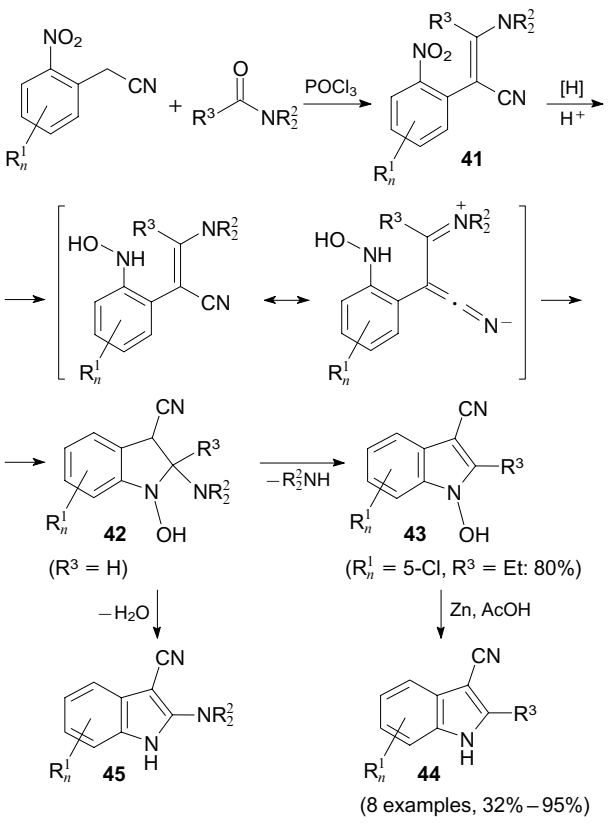
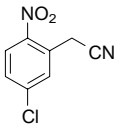
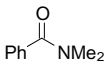
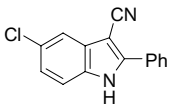
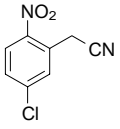
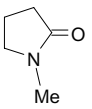
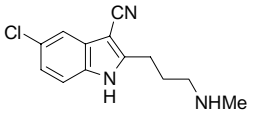
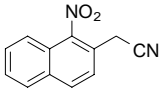
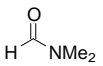
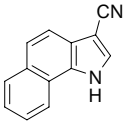
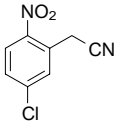
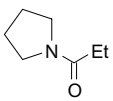
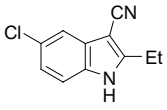
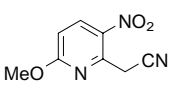
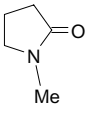
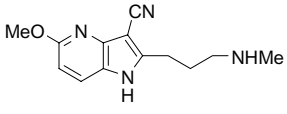


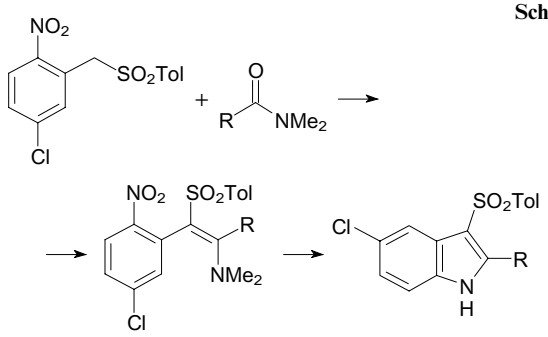
Table 3. Selected examples of the synthesis of 3-cyanoindoles (see Scheme 35).[70]

Nitroarene	Amide	Indole	Yield (%)
			83
			87
			41
			72
			32

which is then reduced to final indole **44**. When *N*-methylpyrrolidone is employed as the amide, this reaction is accompanied by five-membered ring opening to give 3-(indol-2-yl)propylmethylamines. However, the reaction can be stopped after the formation of 3-cyano-1-hydroxyindole **43** when it is conducted at room temperature. This result confirms the proposed reaction pathway, while the alternative pathway requiring complete reduction of the nitro group to the amino group before cyclization according to the addition–elimination mechanism can be ruled out. The method is also suitable for the synthesis of azaindoles.

The application of this method to appropriate *o*-nitrobenzyl sulfones can produce 3-(arylsulfonyl)indoles (Scheme 36).[70]

Scheme 36

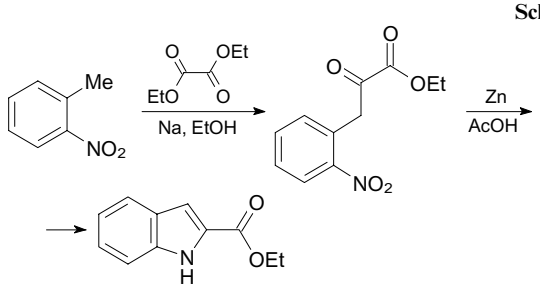


R = H (32%), Ph (33%)

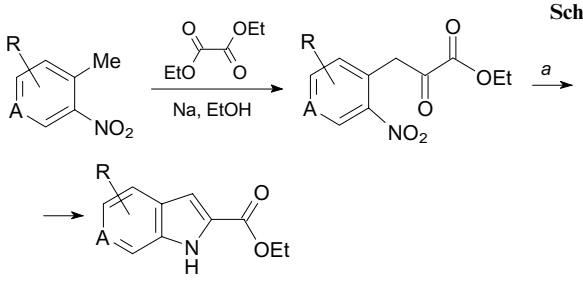
2.5. Reissert indole synthesis

The first step of the classical Reissert indole synthesis comprises the condensation of *o*-nitrotoluene with diethyl oxalate to give ethyl *o*-nitrophenylpyruvic acid (Scheme 37).[72] The subsequent reduction of the nitro group leads to spontaneous cyclization giving esters of indole-2-carboxylic acid.

Scheme 37



Scheme 38



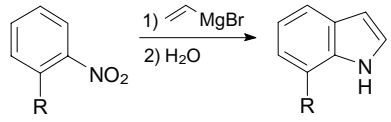
(*a*) H-Cube, Pd/C, H_2 (1–100 bar), AcOH–EtOH (1 : 1), 1–3 ml min^{-1}, 20–100 °C; A = CH: R = H (> 90%), 7-Me (88%), 6-OMe (88%), 5-CN (58%), 6-Cl (76%), 4-OBn (55%), 4-OH (> 90%), 7-OBn (> 90%); A = N , R = H (> 90%)

A modern version of the Reissert synthesis includes the catalytic hydrogenation in a continuous-flow reactor (H-Cube continuous-flow hydrogenation reactor) (Scheme 38, the yields are given according to the HPLC data with UV detection).[73] The best results were attained in the synthesis of 2-ethoxycarbonylindole (93% yield) at a hydrogen pressure of 1 bar in an ethyl acetate–ethanol mixture (1 : 1) at a flow rate of 1 ml min^{-1} and at 20 °C.

2.6. Bartoli indole synthesis

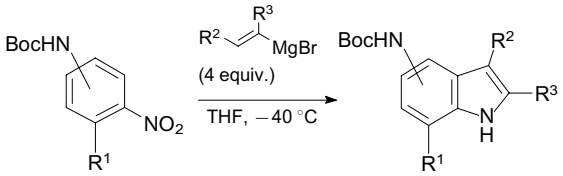
The classical Bartoli indole synthesis involves the preparation of 7-substituted indoles by the reaction of *ortho*-substituted nitroarenes with vinyl Grignard reagents (Scheme 39).[74]

Scheme 39



Substituted nitroanilines were used for the first time instead of nitrobenzenes for the Bartoli indole synthesis;[75] this resulted in the development of a new route to substituted aminoindoles, promising building blocks for fine organic and pharmaceutical chemistry (Scheme 40). However, this approach was applicable only to a rather narrow range of substrates and Grignard reagents.

Scheme 40



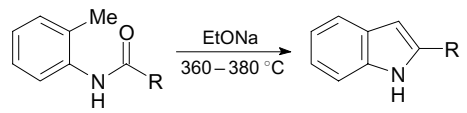
Method *a*: 57% Et_2O in THF; method *b*: 25% Et_2O in THF

NHBoc position in indole	R^1	R^2	R^3	Yield (%)	
				method *a*	method *b*
4	Br	H	H	64	41
4	Br	H	Me	44	43
4	Br	Me	H	0	22
4	Br	Me	Me	0	0
4	Me	H	H	0	0
5	Br	H	H	13	0
5	Br	H	Me	0	19
5	Br	Me	H	15	33
5	Br	Me	Me	0	22
5	Me	H	H	0	0
6	Br	H	H	0	0
6	Br	H	Me	0	0
6	Br	Me	H	0	0
6	Br	Me	Me	0	0
6	Me	H	H	22	27

2.7. Madelung synthesis

In 1912, Madelung [76] found for the first time that the *ortho*-alkyl-substituted anilides serve as appropriate substrates for the synthesis of α-substituted indoles (Scheme 41). The ready accessibility of the substrates accounts for the attraction of this method; however, the drastic reaction conditions impose some limitations. This has stimulated researchers to look, for many years, for procedural modifications.[77, 78] Despite the obvious success of this research, in the last decade, studies along this line have been continued and the methods have still been improved.

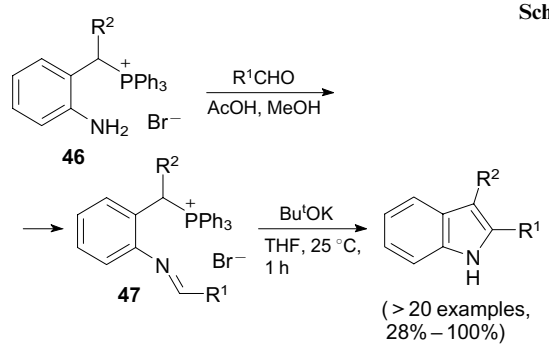
Scheme 41



R = Me (50%), Ph (60%)

The reaction of anilines **46** containing an activated *ortho*-benzyl group with aromatic or α,β-unsaturated aldehydes is an efficient synthetic route to 2,3-disubstituted indoles (Scheme 42).[79, 80] This is a modified Madelung reaction in which imines **47** are used instead of anilides.

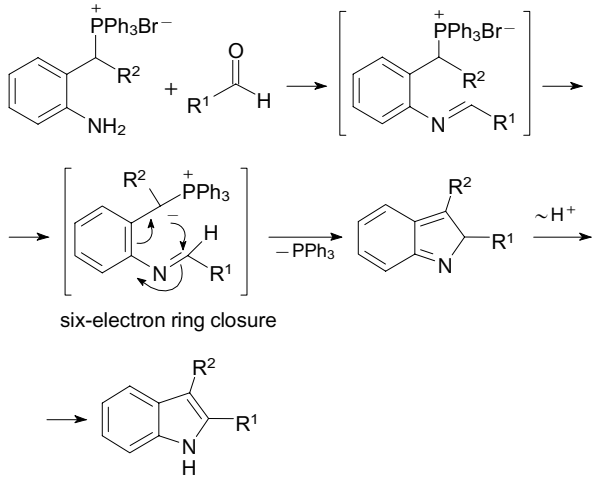
Scheme 42



R^2 = H: R^1 = Ph (95%), 2-Fu (86%), 3-Py (81%), PhCH=CH (100%), 4-BrC_6H_4 (95%), 2-MeC_6H_4 (81%), 2,6-$Me_2C_6H_3$ (28%);
R^2 = Ph: R^1 = Ph (93%), 4-FC_6H_4 (84%), 4-$MeOC_6H_4$ (100%), 4-$MeO_2CC_6H_4$ (45%), PhCH=CH (88%), *N*-methylpyrrol-2-yl (56%);
R^2 = Me: R^1 = Ph (97%), 2-Fu (78%), 2-Py (88%), *etc.*

In the authors' opinion, this cyclization involves the intermediate formation of imine followed by six-electron ring closure, giving rise to the target product (Scheme 43).

Scheme 43



The success of the reaction is determined by several factors: (1) the conjugation of the imine intermediate with the aromatic system provides high acidity; (2) the bulky triphenylphosphine substituent is a good leaving group and is easily eliminated.

2-Fluoroalkyl-substituted indoles were obtained in moderate to good yields in a one-pot process from 2-aminobenzyl alcohols. These starting compounds react with fluorinated carboxylic acids in the presence of triethylamine and halotriphenylphosphonium salts on refluxing in toluene to give indoles.[81] Halotriphenylphosphonium salts are generated *in situ* from triphenylphosphine and CX_4 (X is halogen) (Scheme 44, Table 4).

Probably, the excess of triphenylphosphine reacts with halide **48a** or **48b** to give phosphonium salt **A**, which then reacts with triethylamine to give ylide **B**. This is a reactive and unstable compound, which immediately cyclizes to indole. The presumptive mechanism of transformation of 2-aminobenzyl alcohols to indoles is shown in Scheme 44.

The synthesis of new types of highly functionalized benzofurans, benzothiophenes and indoles was implemented *via* the intramolecular Wittig reaction of the corresponding esters, thioesters or amides (Scheme 45).[82] The key intermediate, phosphonium ylide **49**, is formed upon the addition of Bu^n_3P to aldehydes followed by acylation and deprotonation.

This intramolecular Wittig reaction of the corresponding acid amides and chlorides in toluene at 80 °C was used to obtain indoles **50**. The reaction conditions are suitable

Scheme 44

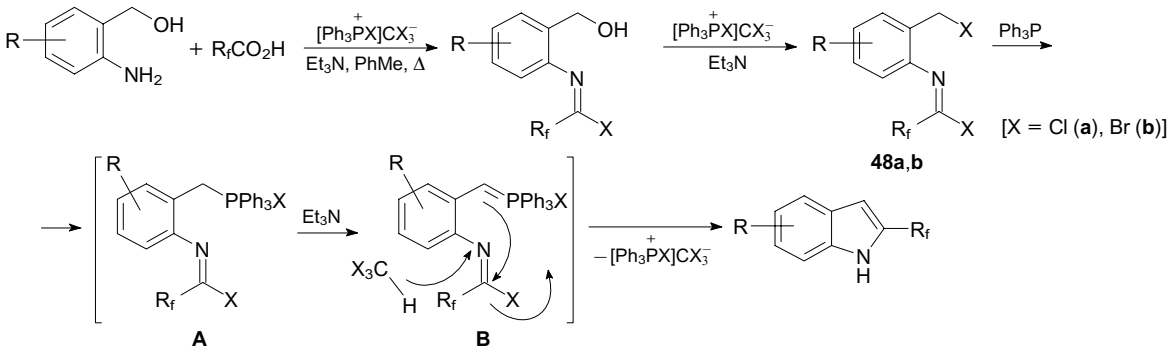
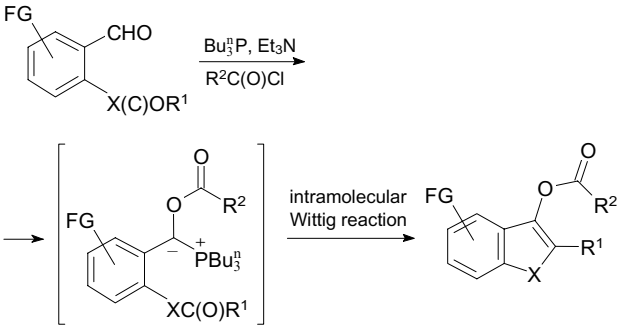


Table 4. Synthesis of 2-trifluoroalkylindoles by the modified Madelung reaction (see Scheme 44).[81]

R	R_f	Yield (%)	
		X = Cl	X = Br
H	CF_3	55	65
H	CF_2H	47	56
H	C_3F_7	62	72
4-OMe	CF_3	73	80
4-F	CF_3	55	64
4-Cl	CF_3	49	55
4-NO_2	CF_3	41	51
5-OMe	CF_3	66	77
5-OMe	C_3F_7	67	76

Scheme 45



49

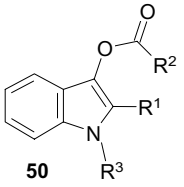
FG = H, 4-Cl, 4-Br, 4,6-Cl_2; R^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, Me, Pr^i, *etc.*; R^2 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, Me, Pr^i , *etc.*; X = O, S, NR^3 (R^3 = Bn, All, Me)

for not only benzyl (R^3 = Bn), but also allyl and methyl groups (R^3 = All, Me).[82]

A new method for indole synthesis employs isocyanide-substituted benzylphosphonium salts **51**, aldehydes and amines as reactants in a one-pot cascade combination of the three-component Ugi reaction and the Wittig reaction in the presence of phosphoric acid and potassium carbonate (Scheme 46, Table 5).[83] The Ugi reaction is used in this case to convert phenyl isocyanides to anilides **A**, which then undergo the intramolecular Wittig reaction to afford indole. The yields of indoles are 45% – 82%.

It can be seen from Table 5 that in the case of aromatic amines and aldehydes, indoles are formed in good yields

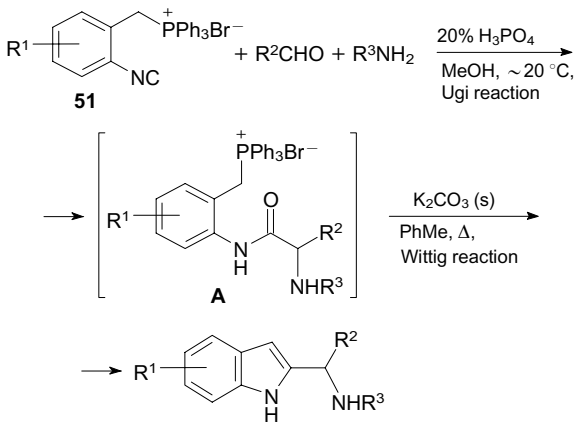
Structures 50



50

R^1	R^2	R^3	Yield (%)
Ph	Ph	Bn	75
Ph	4-ClC_6H_4	Bn	70
Ph	Me	Bn	65
4-$O_2NC_6H_4$	Ph	Bn	73
4-ClC_6H_4	Ph	Bn	71
4-$MeOC_6H_4$	Ph	Bn	65
Ph	Ph	All	70
Ph	Ph	Me	63

Scheme 46



51

A

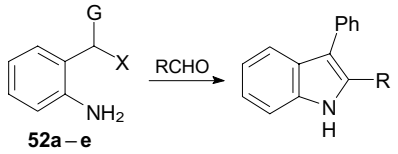
(70% – 82%); in the case of aromatic aldehydes and amines with *ortho*- or strong electron-donating substituents (MeO) (45% – 64%), the yields of indoles are moderate. The use of aliphatic aldehydes leads to good yields of indoles (77% – 81%); however, indoles with aliphatic primary and secondary amines are not formed at all.

Apart from the use of phosphonium ylides **46**, the carbon acidity of the *ortho*-alkyl substituent can be increased by an electron-withdrawing group present in the α-position of the substituent and activating the benzyl group. For example, the reaction was conducted for sub-

Table 5. Synthesis of indoles by tandem Ugi and Wittig reactions (see Scheme 46).[83]

R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
H	4-ClC_6H_4	3-MeC_6H_4	72	H	4-ClC_6H_4	2-MeC_6H_4	64
5-Me	4-ClC_6H_4	3-MeC_6H_4	73	H	4-MeC_6H_4	2-EtC_6H_4	46
H	4-ClC_6H_4	4-MeC_6H_4	74	H	4-$MeOC_6H_4$	4-ClC_6H_4	57
H	4-ClC_6H_4	4-ClC_6H_4	76	H	4-ClC_6H_4	4-$MeOC_6H_4$	45
H	4-$F_3CC_6H_4$	Ph	82	H	Et	4-ClC_6H_4	77
5-Me	3-BrC_6H_4	Ph	75	H	Pr	4-ClC_6H_4	81
H	4-MeC_6H_4	4-MeC_6H_4	71	H	4-$F_3CC_6H_4$	Bu^n	0
5-Me	Ph	Ph	74	H	4-ClC_6H_4	Et	0
H	Ph	4-MeC_6H_4	70	5-Cl	4-ClC_6H_4	4-ClC_6H_4	0
H	Ph	3-ClC_6H_4	73	4-F	4-$F_3CC_6H_4$	Ph	0

Scheme 47

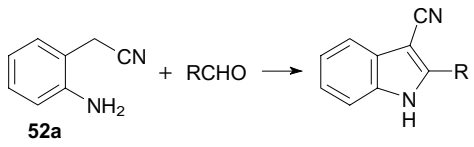


X = H: G = PPh_3 (**46**), CN (**52a**), $P(O)(OEt)_2$ (**52b**), SPh (**52c**);
X = G = SMe (**52d**); for X = Ph, G = SO_2Ph (**52e**):
R = Ph (85% yield), 4-ClC_6H_4 (81%),
3,4-$Me_2C_6H_3$ (71%), PhCH=CH (74%), indol-3-yl (68%)

strates **52a–e** with various benzyl group-activating substituents (Scheme 47).

An unexpected result was obtained in the reaction with 2-cyanomethylaniline **52a**, which gave 3-cyanoindoles in good yields under standard conditions (Scheme 48).[84] In this case, the cyano group is not eliminated, but base-induced condensation with the aldehyde and then cyclization and oxidation with oxygen take place to give 3-cyanoindole.

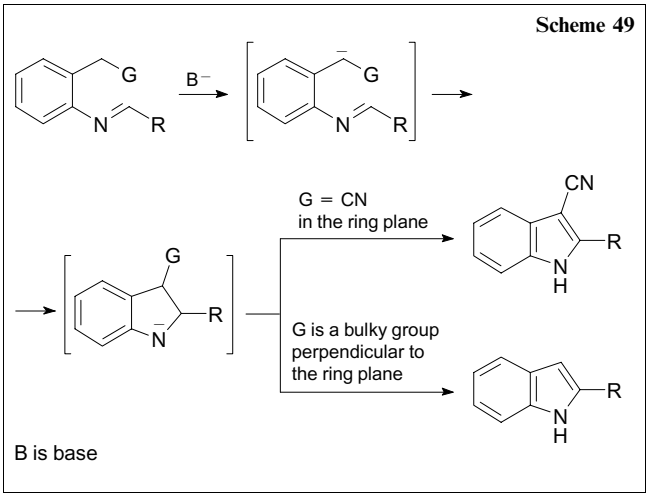
Scheme 48



R = Ph (97%), 4-$MeOC_6H_4$ (78%), 4-BrC_6H_4 (83%),
3-MeC_6H_4 (87%), PhCH=CH (74%), 4-$O_2NC_6H_4$ (85%)

Probably, the cyclization proceeds *via* the formation of imine followed by base-induced ring closure and hydride shift. The possibility of formation of two types of reaction products is shown in Scheme 49.

Scheme 49

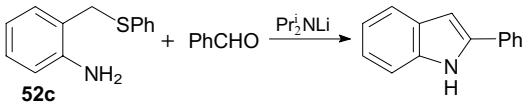


If G is a bulky group, it will be arranged, most likely, at right angle to the benzene ring. This group will be readily eliminated to give an intermediate in which a fast hydride shift takes place to form 3-unsubstituted indole. If G is a small group such as the CN group, it is likely to be coplanar. The acidic benzyl hydrogen atom adjacent to the cyano group will be easily eliminated and the oxidation will afford 3-cyanoindole.

The reaction of phosphonate **52b** [G = $PO(OEt)_2$, X = H] (see Scheme 47) with benzaldehyde yields the expected imine, which, however, does not cyclize.

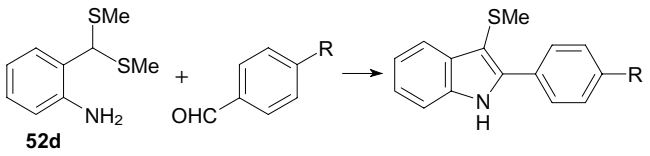
Sulfide **52c** (G = SPh, X = H) (Scheme 50) also gives the imine, which does not undergo any changes when treated with potassium *tert*-butoxide. However, if lithium diisopropylamide is used as the base, indole is formed with phenylthio group elimination.

Scheme 50



Thioacetal **52d** (G = X = SMe) (Scheme 51) reacts with benzaldehydes to give 2-aryl-3-methylthioindoles.

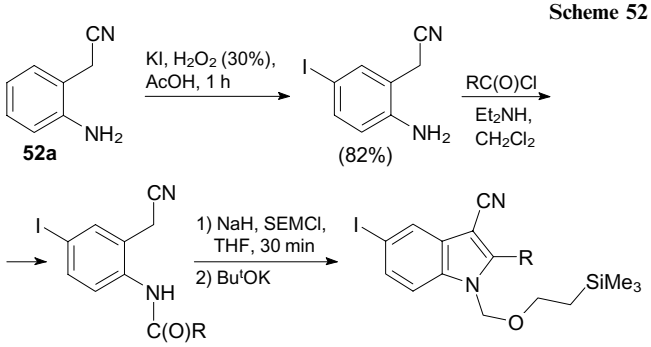
Scheme 51



R = H (42%), Br (78%)

An efficient synthesis of 2,5-disubstituted 3-cyanoindoles is based on selective iodination of 2-cyanomethylaniline **52a** according to the modified Madelung synthesis protocol using *o*-aminobenzyl cyanides (Scheme 52).[85]

Scheme 52



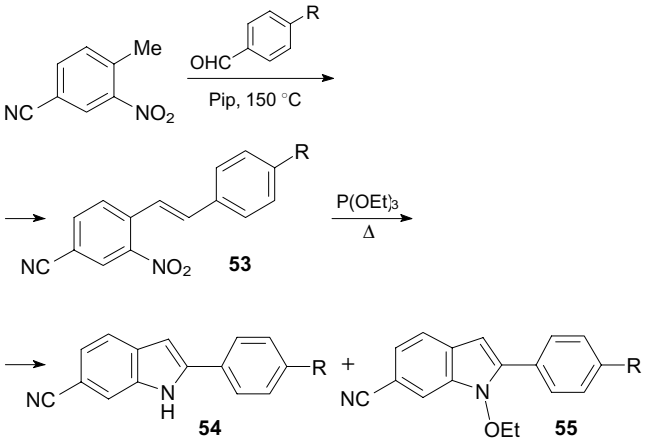
R = 4-Py (52%), 3-Py (33%), 4-$MeCO_2C_6H_4$ (43%), Me (47%),
Pr^i (26%), Bu^t (24%), Cy (4%); SEM = $CH_2OCH_2SiMe_3$

Palladium-catalyzed reaction of the same substrates with arylboronic acids follows the addition–cyclization tandem transformation pathway and gives 2-arylindoles.[86]

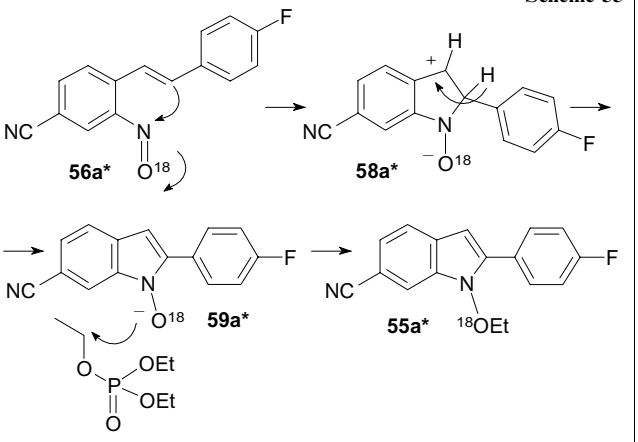
2.8. Cadogan–Sandberg reaction

The Cadogan–Sandberg reaction is a widely employed synthetic pathway from 2-nitrostilbenes **53** to 2-arylindoles **54** and 2-aryl-*N*-ethoxyindoles **55** induced by triethyl phosphite (Scheme 53) (see p. 585 in a book, Ref. 87).

Scheme 53



Scheme 55



In experiments with the use of ^{18}O isotope labels, it was found that the oxygen atom in *N*-ethoxyindole comes from the nitro group of the initial nitrostilbene rather than from triethyl phosphite.[88] The possible formation pathways of indoles and *N*-ethoxyindoles from labelled nitrostilbene **53*** are shown in Scheme 54.

All of the proposed mechanisms start with deoxygenation of the nitro derivative to 2-nitrosostilbene **56***. The subsequent electrocyclization leads to the key intermediate **57***, which is reduced by an additional amount of triethyl phosphite yielding 2-arylindole **54**. Alternatively, nitrosostilbene **56*** can be subjected to further deoxygenation to give nitrene, which can be inserted into the alkene C–H bond of stilbene to give indole **55**. It is assumed that *N*-hydroxyindole **57*** can be alkylated by triethyl phosphate generated *in situ* to give *N*-ethoxyindole **55***. The other possible mechanistic details include either the exchange of the hydroxy group in intermediate **57*** with the ethoxy group to give non-labelled *N*-ethoxyindoles **55** or the exchange of labelled ethoxy group in compound **55*** to give non-labelled indole **55**. Since the experiment with oxygen-labelled nitrostilbene **53*** affords labelled *N*-ethoxyindole, the mechanism can be depicted as shown in Scheme 55.

The electrocyclization of 2-nitrosostilbene intermediate **56a*** (obtained from substrate **53a***) to bicyclic compound **58a*** gives, after proton elimination, deprotonated *N*-hydroxyindole **59a***, which then serves as the substrate for alkylation with triethyl phosphate obtained upon deoxygenation of the nitro group. This alkylation yields oxygen-labelled *N*-ethoxyindole.

3. Transformations of other heterocycles

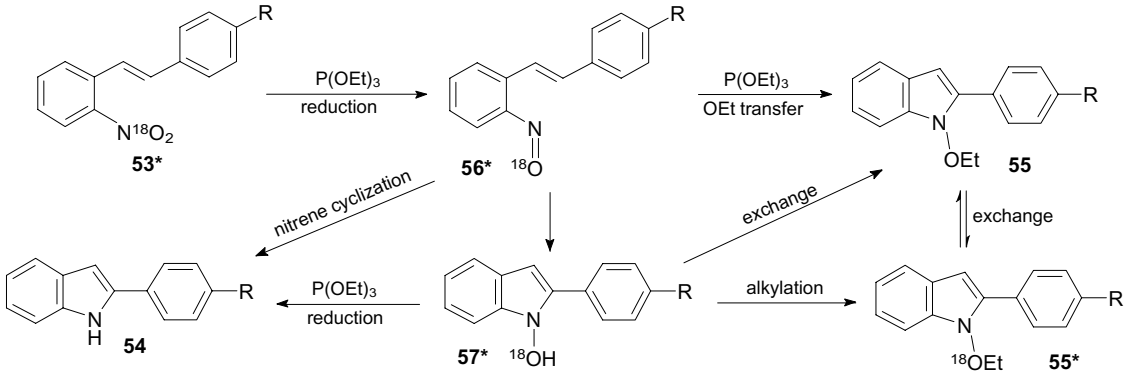
The strategy of transformation of one heterocycle into another is a potent and convenient means for the construction of a large diversity of heterocyclic structures.[89]

The low resonance energy of the furan ring determines the ease of ring transformation giving various carbo- and heterocycles.[90] Of particular interest is ring transformation of easily accessible furan derivatives to indoles. An enormous role in the development of studies on the conversion of furans into indoles belongs to Professor A.V.Butin and his colleagues and followers.

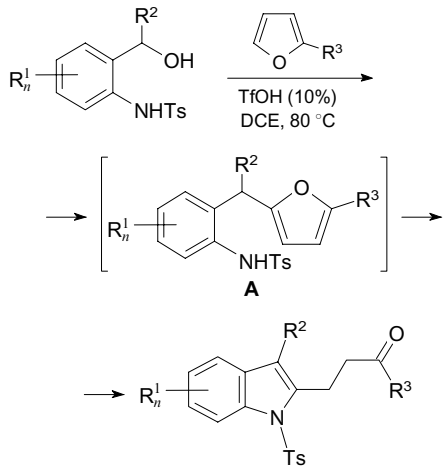
Thus, the acid-catalyzed one-pot synthesis of indoles from *o*-aminobenzyl alcohols and furans has been developed (Scheme 56).[91] The method includes the *in situ* formation of aminobenzylfurans **A** and the subsequent ring transformation to afford indole **60** containing an ethyl ketone group in position 2. The method is scalable and tolerates a broad range of substrates and more functional groups than the two-step method developed previously.[92]

The presence of this functional group in the indole bicyclic moiety implies the possibility of further transformations of indole into 2,3- and 1,2-fused indole derivatives and into indoles containing an α,β-unsaturated carbonyl moiety. The reduction of the carbonyl group of indole **60b** (R^1 = H, R^2 = R^3 = Ph) and the subsequent Friedel–Crafts cyclization give rise to tetracyclic indole **61**. The removal of the tosyl protecting group of indole **60a** (R^1 = H, R^2 = Ph, R^3 = Me) on treatment with sodium naphthalenide affords NH-indole **62**, which reacts with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to be

Scheme 54



Scheme 56



R^1_n = H, R^2 = Ph: R^3 = Me (**a**, 90%), 4-FC_6H_4 (83%), $EtO_2C(CH_2)_2$ (61%); R^1_n = H, R^2 = 2-Th, R^3 = Me (41%); R^1_n = 5,6-$(MeO)_2$, R^2 = Ph, R^3 = Me (60%); R^1_n = H, R^2 = Ph, $R^3C(O)CH_2$ is cyclohexanon-2-yl (70%), *etc.*

converted to unsaturated ketone **63**. Alternatively, after the reaction with excess Mg in methanol, the tosyl group in indole **60a** is efficiently removed with simultaneous reduction of the carbonyl group to the hydroxy group. Mesylation and the subsequent intramolecular alkylation of alcohol **64** gives dihydropyrroloindole **65**, which is an important structural moiety of potential medicinal agents and natural products (Scheme 57).[91] In addition, dihydropyrroloindoles can be prepared by cobalt-catalyzed intramolecular cyclization of 1-(but-3-enyl)-1*H*-indoles.[93]

Recently, an unusual domino reaction has been proposed in which the same α-carbon atom of furan reacts, first, as a nucleophile and then as an electrophile. In the presence of acids, *N*-tosylfurfurylamine (**66**) reacts with 2-(tosylamino)benzyl alcohol giving rise to 2-(acylvinyl)indoles **67a**–**n** (Scheme 58, Table 6).[94] The reaction proceeds as the Friedel–Crafts alkylation of furan position 2 followed by acid-catalyzed intramolecular attack by the *ortho*-amino group on the same atom.

The process optimization is mainly related to the choice of the acid. Three acidic agents, namely, AcOH–HCl (method *a*), CF_3CO_2H (method *b*) and $CuSO_4 \cdot 5H_2O$ (method *c*), were tested with a broad range of substrates.

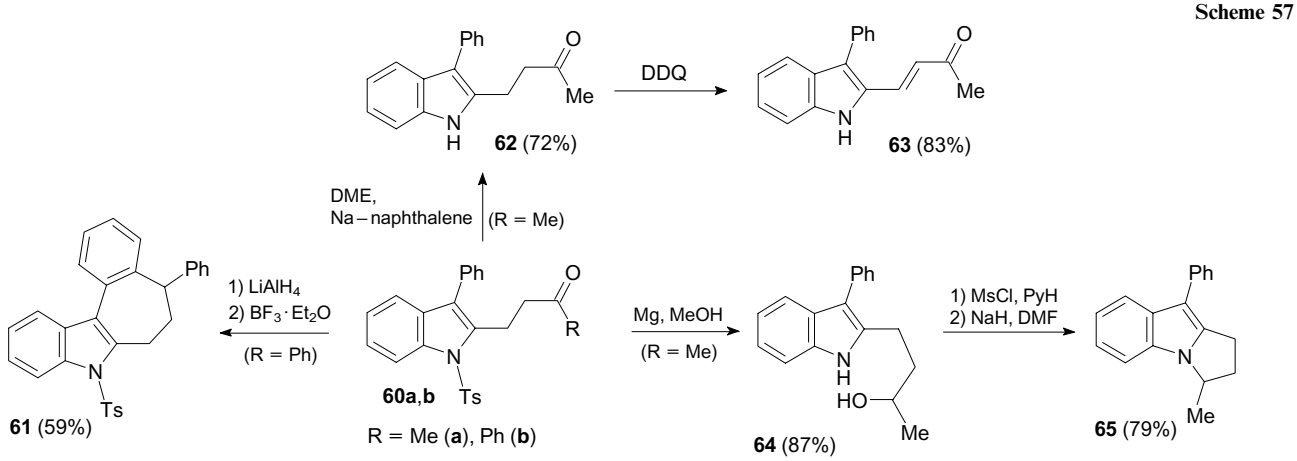
Method *a* resulted in the lowest yields of indoles **67e**,**f**,**l** . The use of primary benzyl alcohol gave a moderate yield of indole **67n**. This can be attributed to lower stability of primary carbocations, which leads to oligomerization and, as a consequence, to resinification of the reaction mixture. The presence of electron-withdrawing substituents in the benzene ring in the *para*-position relative to the amino group substantially decreases the yields of indoles (products **67i**,**j**).

The replacement of the leaving tosylamino group by the phthalimide group (furan **68**) permits the synthesis of indoles **69** of another type owing to the amphiphilic nature of the C(2) atom (Scheme 59).

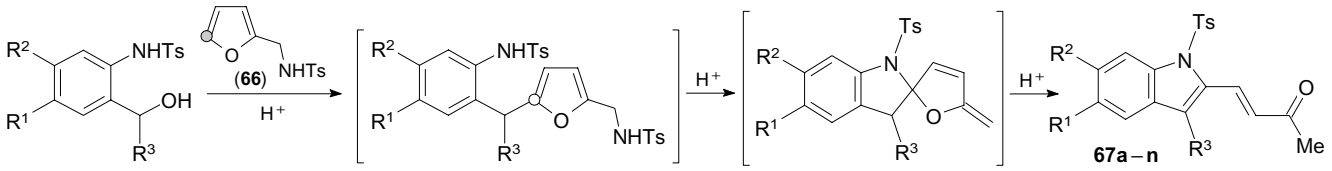
Indoles of both types (**67a** and **69a**–**c**) are formed upon the reaction of *N*-furfurylbenzamides (Scheme 60).[94]

The mechanism of formation of these indoles is depicted in Scheme 61. The results can be interpreted in terms of the competitive protonation of intermediate **70** either at the amide group or at the furan C(5) atom. The protonation at the amide group (pathway *a*) substantially increases its nucleofugality (cation **A**), which leads to the formation of cation **B** upon amide elimination. The nucleophilic attack by the 2-tosylamino group on the furan C(2) atom followed

Scheme 57



Scheme 58

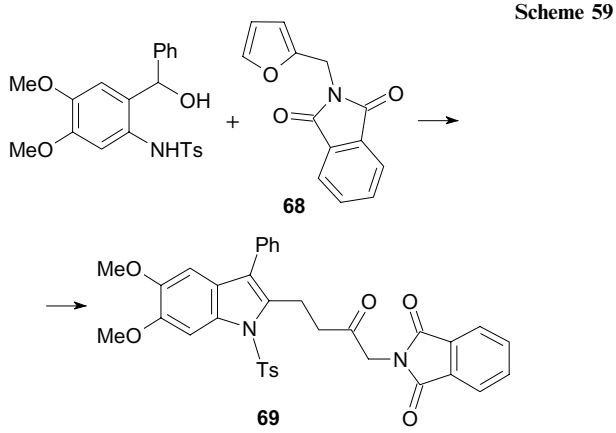


○ is nucleophile, ○ is electrophile

Table 6. Various benzyl alcohols in the domino reaction with *N*-tosylfurfurylamine (see Scheme 58).[94]

Compound **67**	R^1	R^2	R^3	Yield (%)		
				method *a*	method *b*	method *c*
a	OMe	OMe	Ph	64	68	69
b	OMe	OMe	4-MeC_6H_4	56	64	66
c	OMe	OMe	4-ClC_6H_4	70	67	61
d	OMe	OMe	4-BrC_6H_4	71	55	69
e	OMe	OMe	Me	32	62	64
f	H	H	Et	30	67	65
g	H	H	Ph	41	60	63
h	H	H	Me	–	17	–
i	Cl	H	Me	–	16	–
j	NO_2	H	Ph	–	12	–
k	OCH_2CH_2O		Ph	57	61	65
l	OCH_2CH_2O		Ph	33	59	62
m	OCH_2CH_2O		Et	31	52	56
n	OCH_2O		H	35	42	47

Scheme 59



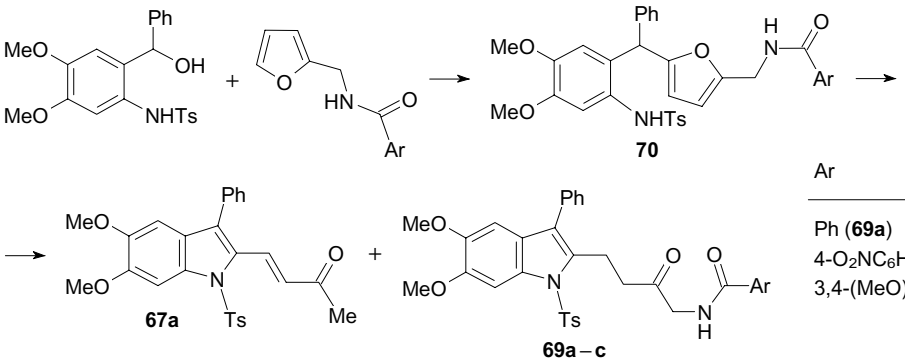
by opening of the spiro ring in intermediate **C** generates indole **67**. The protonation of the C(5) atom of furan (pathway *b*) affords cation **D** capable of generating spiro intermediate **E**, which is converted to intermediate **F** *via* tautomerization. It is noteworthy that in this case, too, the C(2) atom of furan demonstrates a dual reactivity, acting as a nucleophile in the step towards intermediate **70** and as an electrophile as the latter reacts with the 2-tosylamino group to yield intermediate **E**.

A simple and efficient synthesis of indoles **67** is based on thermolysis of 2-(2-azidobenzyl)furans with attack by the resulting nitrene on the *ipso*-position of the furan moiety (Scheme 62).[95] The cyclization is accompanied by furan ring opening and gives high yields of indoles with 2-acetylvinyl substituent at C(2), capable of further transformations.

Apparently, indole **67** is formed upon the electrophilic attack by the nitrene, generated *via* azide thermolysis, on furan position 2 to give spiro-zwitter-ion **A** (Scheme 63; shown for the substrate with R^1_n = H, R^2 = Ph, R^3 = Me).[95] Then the furan ring is opened, giving rise to 4-(3-phenyl-3*H*-indol-2-yl)but-3-en-2-one **71** and aromatization of the latter yields indole (*Z*)-**67a**, which isomerizes to the final indole (*E*)-**67a**.

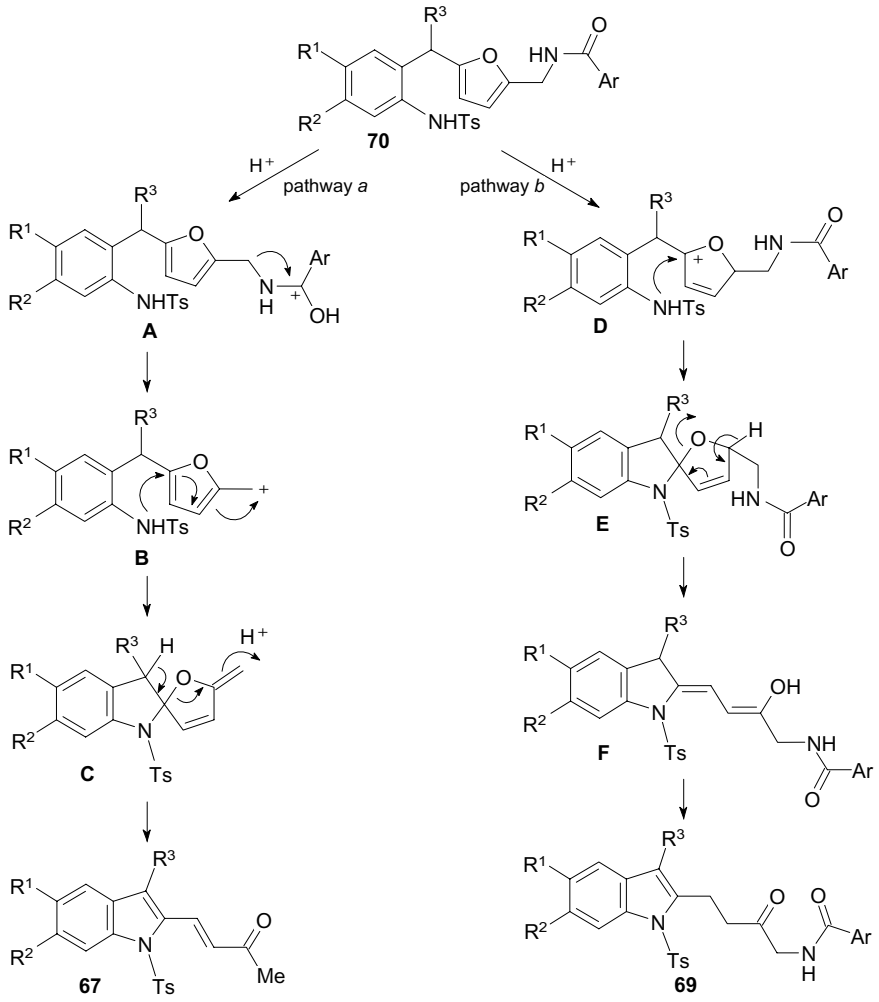
A convenient method for the synthesis of 3,4-disubstituted 5-hydroxyindoles, which are used in synthetic and biological studies, consists in the following one-pot cascade of reactions: microwave-initiated intramolecular [4 + 2]-cycloaddition of the alkynol group to furan, fragmentation and aromatization of the adduct and removal of the Boc protecting group.[96] The yields of indoles range from 15% to 74%; the presence of aromatic substituents provides higher yields. In earlier studies,[97] a sequence of reactions was developed, in which the 1,2-addition of lithiated derivative **72** to enone **73** affords allylic alcohol **74**; microwave irradiation of this product gives tricyclic Diels–Alder adduct **A**; successive elimination of a water molecule and the protecting group gives indoles **75** *via* intermediates **B** and **C** (Scheme 64). If alkynone is taken instead of enone, the reaction follows a different pathway: cleavage of the oxygen bridge in adduct **A** affords structure **D**, aromatization of which in an early step yields phenol **E**. Elimination of one water molecule from **E** with simultaneous deprotection furnishes the target indole **76**.

Scheme 60

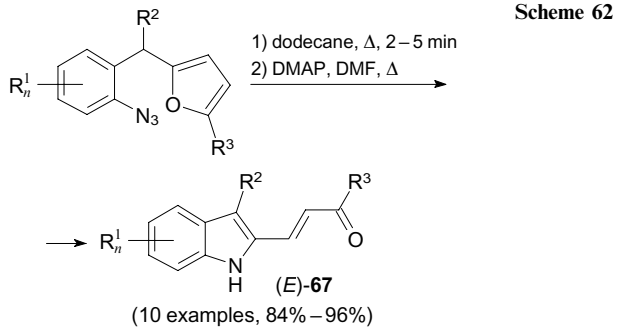


Ar	Yield of **67a** (%)	Yield of **69** (%)
Ph (**69a**)	12	62
4-$O_2NC_6H_4$ (**69b**)	6	63
3,4-$(MeO)_2C_6H_3$ (**69c**)	12	50

Scheme 61

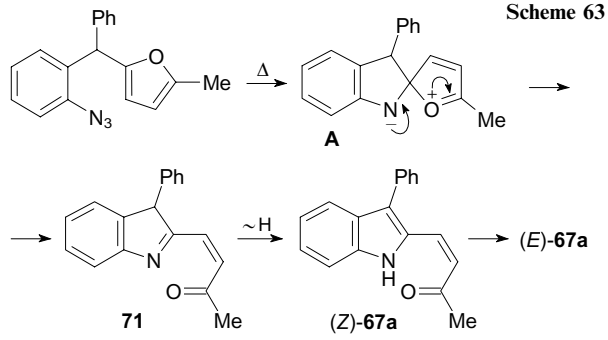


Scheme 62



R^3 = Me, R^2 is 5-methylfuran-2-yl: R^1_n = H (84%), 5-O_2N (96%);
R^3 = Me: R^1_n = H, R^2 = 4-FC_6H_4 (87%); R^1_n = 5,6-$(MeO)_2$,
R^2 = Ph (83%), *etc.*

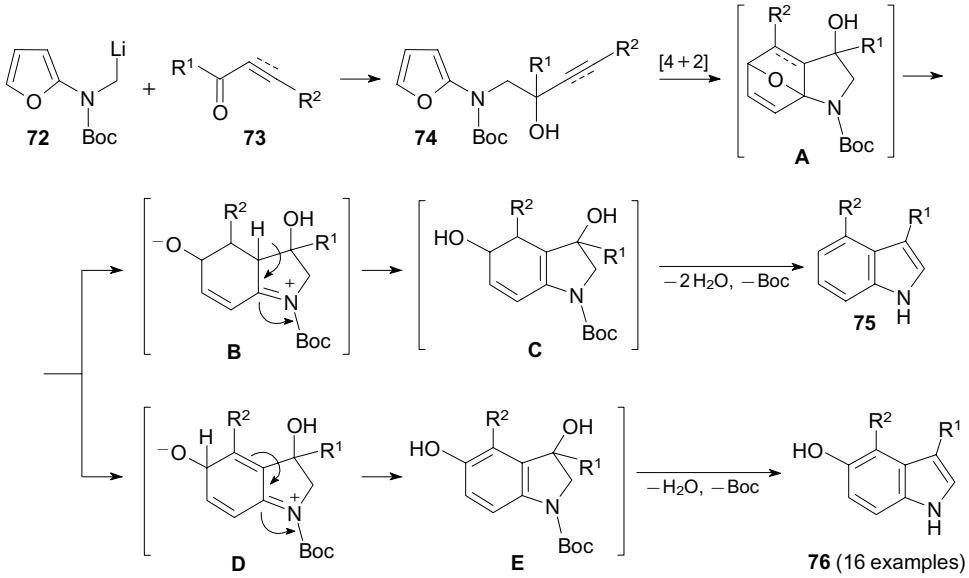
Scheme 63



Along with furans, relatively labile isoxazoles are convenient substrates for transformations of this type. For example, the reductive heterocycle–heterocycle transformation of nitrophenylisoxazoles allows the preparation of indoles (Scheme 65).[98] The reduction of substrate **77a** on treatment with Fe–AcOH produces indole **78a** in 46% yield, while the reduction of isoxazole **77b** gives only indole **78b** (60%). In both cases, the cyclization is chemoselective due to the attack by the NH_2 group of aniline on the imine carbon atom of the intermediate. Although the intermediate can exist in several tautomeric forms (**A**–**C**), which can easily be generated under the reaction conditions and can show different types of reactivity, complete chemoselectivity is observed.

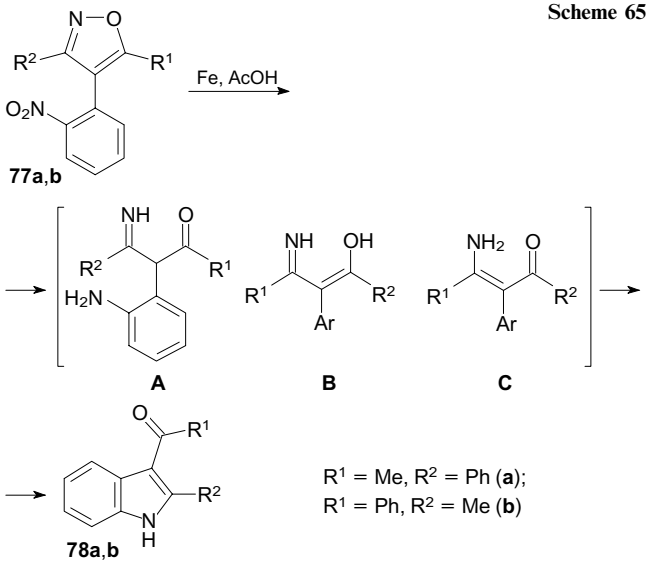
Although the prevailing tautomer of the intermediate is unknown, the authors consider cyclization of iminocarbonyl form **A** to be most probable. In order to establish the chemoselectivity limits, isoxazole **77c** was prepared (Scheme 66). Presumably, the electron-donating 2-methoxyphenyl substituent (R^2 in the imine) decreases the electrophilicity of the imine moiety. Treatment of isoxazole **77c** with Fe in AcOH at 120 °C results in the formation of two indoles (**78c**,**d**) in a total yield of 96% and in 60 : 40 ratio,

Scheme 64

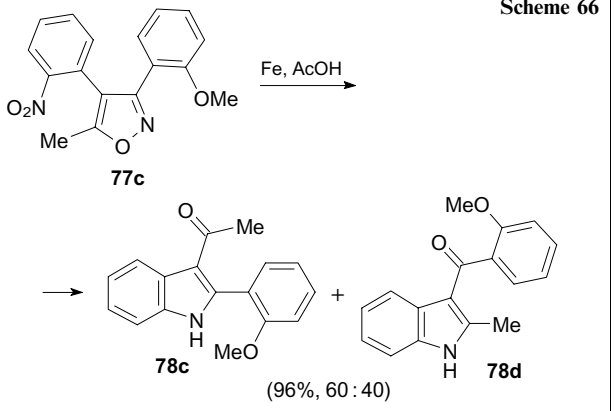


76: R^2 = Ph: R^1 = 2-Th (62%), Hex (38%), CH_2CH_2Ph (63%); R^1 = Cy, R^2 = Bu^n (36%), *etc*.

Scheme 65



Scheme 66



which attests to a low degree of competition of the two possible cyclization pathways.

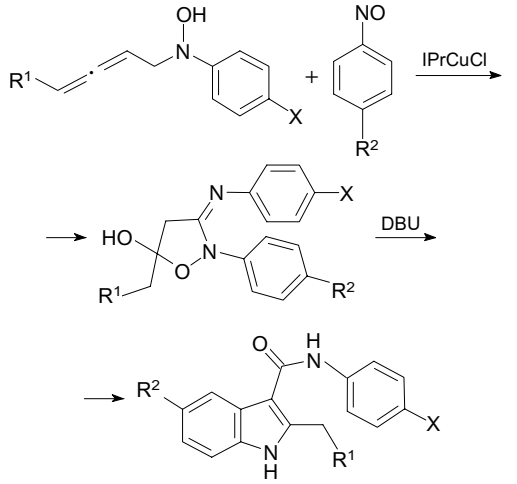
An interesting way of using a hydrogenated isoxazole analogue has been described.[99] First, attention is attracted by the preparation of substrates: in the presence of O_2 and IPrCuCl [IPr is 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (5 mol.%), [3 + 2]-cycloaddition of *N*-hydroxyallenylamines to nitrosobenzenes results in the desired 5-hydroxyisoxazolidines. Heating of this reaction mixture with DBU in toluene affords functionalized indoles (Scheme 67).

The mechanism of indole formation shown in Scheme 68 implies a key role of ketene imine intermediates: DBU promotes opening of the initial ketal to give intermediate **A**, which then undergoes catalytic rearrangement to the O-bonded isomer **C** *via* the intermediate formation of ketene imine species **B**. Unlike N-isomer **A**, intermediate **C** actively undergoes the 3,3-rearrangement to give 2-aryl-3-oxoamides **D** and **E**, which are finally converted to indoles.

An example of conversion of fused thiophene derivatives to indoles has been reported. The sulfone group in dibenzothiophene dioxides (*e.g.*, compound **79**), which are easily prepared by oxidation of dibenzothiophenes, undergoes, first, intermolecular and then intramolecular nucleophilic aromatic substitution with anilines, thus yielding carbazoles (Scheme 69).[100] This transformation of dibenzothiophenes to carbazoles does not require catalysis by heavy metals.

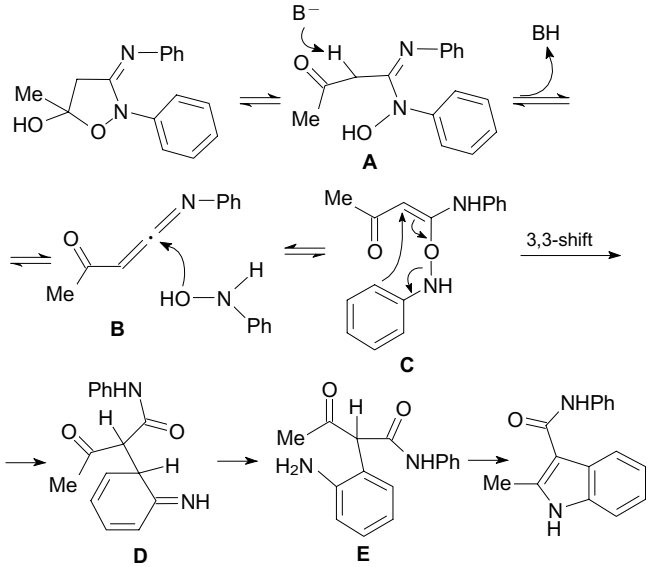
It is worth mentioning that the use of NaHMDS, instead of KHMDS, considerably decreases the product yield (for R_n = 4-Me, from 94% to 50%). The reaction proceeds equally smoothly for anilines with different types of substituents in the benzene ring and gives carbazoles in high yields. The reaction tolerates the vinyl group, although the corresponding carbazole is formed in a moderate yield. The TIPS group is partly hydrolyzed under the reaction conditions, resulting in a mixture of carbazoles with R_n = TIPSO and OH in 1 : 2.6 ratio. Unfortunately, unprotected *p*-aminophenol reacts to a low yield (26%).

Scheme 67

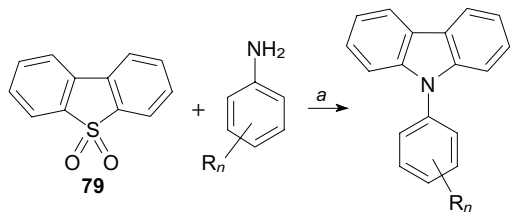


R^1	R^2	X	Yield (%)	R^1	R^2	X	Yield (%)
H	H	Cl	80	H	CO_2Et	H	87
H	H	Br	77	H	NO_2	H	75
H	H	Me	75	H	Me	H	82
H	H	Bu^t	76	H	OMe	H	76
H	Cl	H	82	Et	Cl	H	75
H	Br	H	80	Et	CO_2Et	H	65

Scheme 68

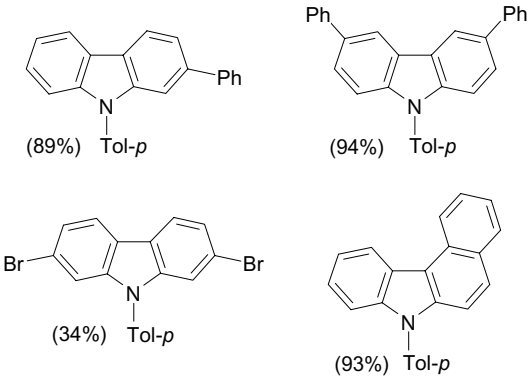


Scheme 69

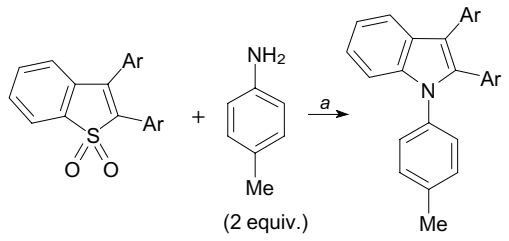


(*a*) KHMDS (3 equiv.), dioxane – toluene, 80 °C;
R_n = H (77%), 4-MeO (94%), 4-Bu^t (92%), 4-Me_2N (91%), 4-CH_2=CH (60%), 4-TIPSO (72%), 4-HO (26%), 3-MeO (70%), 3,5-Bu^t_2 (98%), 3,4-OCH_2O (65%), 2,4,6-Me_3 (67%), 4-Cl (51%), 4-F (30%)

Other product examples



Scheme 70



(*a*) KHMDS (3 equiv.), dioxane – toluene, 80 °C;
Ar = Ph (89%), *p*-Tol (90%), 1-Naph (97%)

The reaction was extended to the preparation of carbazoles substituted in the benzene rings and fused analogues (8 examples, 34% – 94% yields) (see Scheme 69).

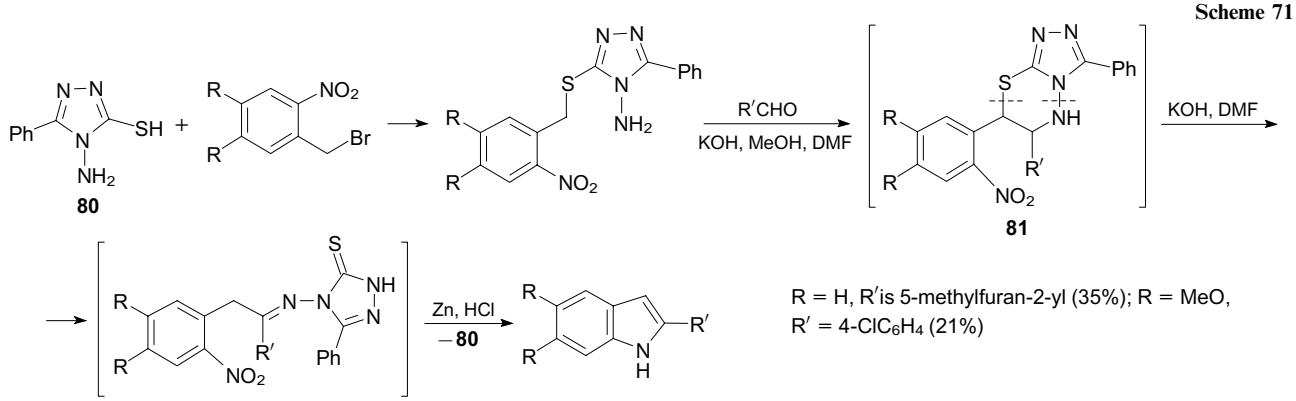
The developed conditions are also applicable to the synthesis of 2,3-diarylindoles from 2,3-diarylbenzothiophene dioxides (Scheme 70).

Among the five-membered heterocycles involved in the transformations to indoles, a special, rather peculiar, role is played by triazole derivatives (Scheme 71).[101] Formerly, the preparation of thiadiazine derivatives of type **81** from 4-amino-3-sulfanyl-4*H*-triazole (**80**) and subsequent transformation with C – S (Ref. 102) and N – N (Ref. 103) bond cleavage have been reported. While analyzing reactions of this type, the authors arrived to the conclusion that the C – S bond cleavage can be used to synthesize 2-arylindoles.

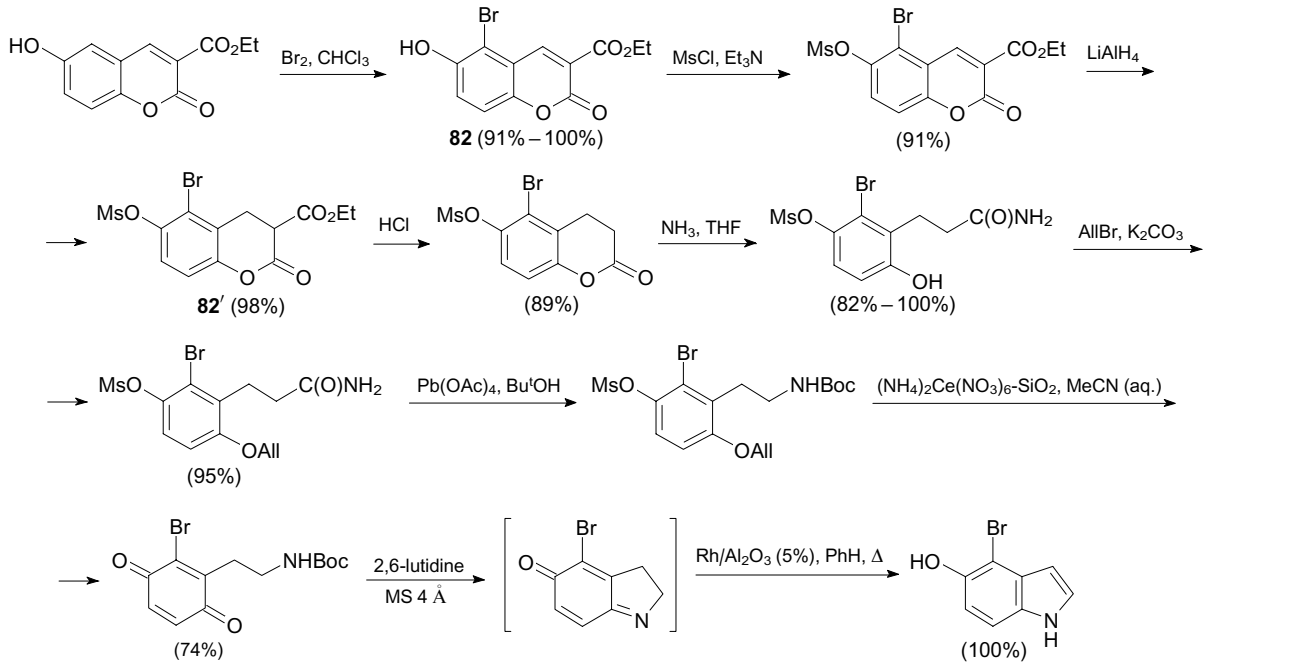
The developed method serves as an example of indole synthesis based on a heterocyclic matrix. 4-Amino-3-sulfanyltriazole **80** was used as the matrix that was later separated during the workup of the reaction mixture. The reaction can be implemented as a one-pot procedure. Although the product yields are low, this method has benefits such as ready accessibility of the starting compounds and a simple experimental procedure.

Over the last years, only one example of transformation of six-membered heterocycles into indoles has been reported.[104] Readily accessible 3-alkoxycarbonyl-5-halo-6-hydroxycoumarins **82** are converted to 4-halo-5-hydroxyindoles *via* a sequence of steps, in which the key step is the coumarin reduction to dihydrocoumarin **82′** (the presence

Scheme 71

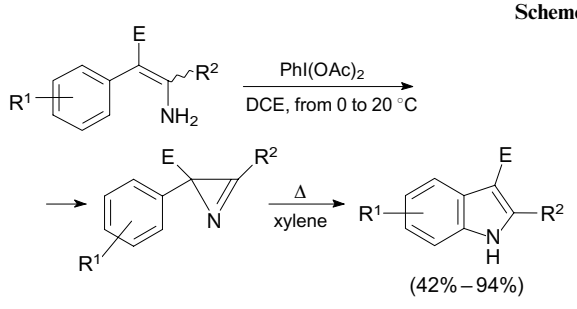


Scheme 72



of a halogen atom can interfere with the standard catalytic reduction). This is followed by decarboxylation, lactone ring opening with ammonia, protection of the phenolic hydroxyl, Hofmann rearrangement to *N*-Boc-ethylamine, quinone oxidation and deprotection of the nitrogen atom. β-Aminoethylquinone thus formed cyclizes to give a mixture of cyclic quinone imine and indole in which the imine easily tautomerizes to indole on treatment with rhodium on alumina (Scheme 72).

Scheme 73



E = CN, CO_2Et, $C(O)R^3$; R^1, R^2 = Ar, Me, Bn

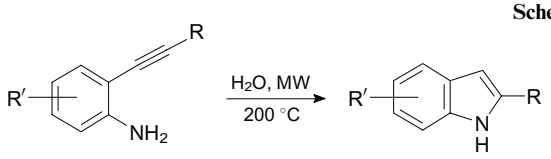
2*H*-Azirines obtained from enamines on treatment with phenyliodine(III) diacetate in a thermal reaction isomerize to 3-functionalized indoles (Scheme 73).[105]

4. Syntheses from *o*-alkynylanilines

The use of *o*-alkynylanilines is a part of a popular strategy for the synthesis of substituted indoles. *o*-Alkynylanilines are convenient substrates for annulation of a pyrrole ring to a benzene ring *via* intramolecular nucleophilic addition.[106] All methods of synthesis involving *o*-alkynylaniline derivatives can be split into several groups: (1) cyclization of ready *o*-alkynylaniline substrates under various conditions; (2) introduction of amine functions into the *ortho*-position of phenylacetylenes and their various uses; (3) utilization of the method to prepare functionalized indoles; (4) introduction of an ethynyl group into the *ortho*-position of the aniline molecule.

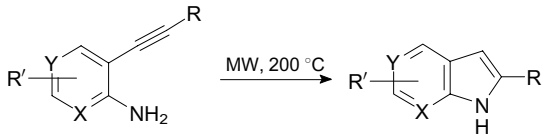
In the framework of the first group, a unique strategy has been developed for the preparation of substituted indoles by microwave-induced cycloisomerization of N-unsubstituted 2-alkynylanilines in water (Scheme 74).[107] The yields of the reaction products vary from moderate to

Scheme 74



R′	R	Yield (%)
H	H	23
H	Ph	46
H	4-$MeOC_6H_4$	79
H	4-ClC_6H_4	34
5-MeO	Ph	59
H	2,4-$(MeO)_2C_6H_3$	50
5-Cl	Ph	49
H	*p*-Tol	33
5-Me	Ph	46
5-Ac	Ph	20

Scheme 75



R′	X	Y	R	Yield (%)
H	CH	CH	Ph	85
H	CH	CH	4-$MeOC_6H_4$	79
H	CH	CH	4-ClC_6H_4	77
5-MeO	CH	CH	Ph	87
H	CH	CH	2,4-$(MeO)_2C_6H_3$	60
5-Cl	CH	CH	Ph	68
5-Ac	CH	CH	Ph	88
H	CH	CH	2-Py	96
H	CH	CH	2-Th	95
H	CH	N	Ph	99
H	N	CH	Ph	45
H	CH	CH	$HOCH_2$	53
H	CH	CH	Hex	60
H	CH	N	Hex	52

good. The reaction occurs without any additives, transition metal-based catalysts, acids or bases.

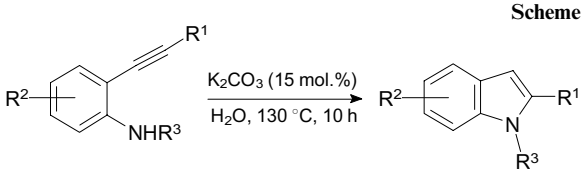
Using microwave radiation as an efficient activation method, one can obtain substituted indoles and azaindoles by the intramolecular cyclization of 2-alkynylanilines and alkynylpyridylamines (Scheme 75).[108] The cyclization proceeds with high yields and requires no transition metal-based catalysts.

The yields of reaction products virtually do not depend on the nature of substituent in the aromatic ring of alkynylamine. The highest yields were attained using 3-alkynyl-4-aminopyridine. The yields of indoles and azaindoles sharply decrease if mere heating is used instead of microwave irradiation.

In the synthesis of 1,2-disubstituted indoles from 2-alkynylanilines and alkylboronic acids, copper acetate serves as the catalyst.[109]

If the NH-acidity of the amine group is increased by introduction of an electron-withdrawing substituent to nitrogen, weak bases become suitable as catalysts for nucleophilic amination of the acetylene moiety. Thus, the cyclization of 2-ethynyl-*N*-sulfonylanilines to indoles smoothly proceeds in water in the presence of catalytic amounts of K_2CO_3 without transition metal catalysts to give products in high yields (Scheme 76, Table 7).[109] A possible reaction mechanism implies the K_2CO_3-induced formation of stabilized N-sulfonyl anion and nucleophilic addition of the anion to the triple bond.

Scheme 76

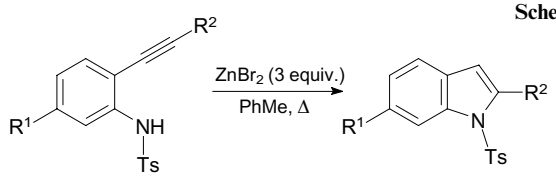


The desired cyclization can be accomplished with Lewis acid catalysis; this procedure involves the activation of the ethynyl moiety.[110] Thus, the reaction of *N*-tosyl-2-phenylethynylaniline with $ZnBr_2$ (3 equiv.) in refluxing toluene gives rise to *N*-tosyl-2-phenylindole in 93% yield. Treatment of 2-phenylethynylaniline with $ZnBr_2$ (1 equiv.) in refluxing toluene leads to 2-phenylindole in 91% yield. Zinc bromide in amount of 0.05 equiv. also efficiently catalyzes the reaction with 2-alkynylanilines giving 2-sub-

Table 7. Synthesis of indoles from *N*-sulfonyl-2-ethynylanilines in the presence of potassium carbonate (see Scheme 76).[109]

R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
4-$EtOC_6H_4$	H	Ts	99	Ph	4-F	Ts	99
4-$MeOC_6H_4$	H	Ts	99	Ph	4-Cl	Ts	100
4-EtC_6H_4	H	Ts	98	Ph	4-CF_3	Ts	95
4-MeC_6H_4	H	Ts	99	Ph	5-CF_3	Ts	99
Ph	H	Ts	98	H	H	Ts	100
4-ClC_6H_4	H	Ts	97	H	4-Me	Ts	99
4-BrC_6H_4	H	Ts	99	H	4-F	Ts	98
4-NCC_6H_4	H	Ts	100	H	4-Cl	Ts	100
Bu^n	H	Ts	100	H	5-CF_3	Ts	98
cyclo-C_3H_5	H	Ts	98	H	4-CF_3	Ts	97
Bu^t	H	Ts	95	H	H	$PhSO_2$	97
Ph	4-Me	Ts	92	H	H	Ns	98

Scheme 77

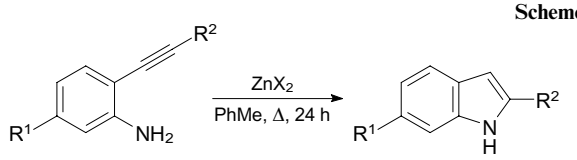


R^1	R^2	Reaction time /h	Yield (%)
H	Ph	16	93
OMe	Ph	48	88
H	Pr^n	33	90
H	n-C_5H_{11}	32	91

stituted indoles in high yields. Thus, zinc salt-catalyzed hydroamination of 2-alkynylanilines proceeding without Pd catalysts was developed.[110] The reactions of 2-alkynyl-*N*-tosylanilines with various *meta*-substituents in the aromatic ring were investigated under the optimized reaction conditions [$ZnBr_2$ (3 equiv.) in refluxing toluene]. In all cases, the expected indoles were obtained in high yields (Scheme 77).

The reaction of N-unprotected 2-alkynylanilines with catalytic amounts of zinc salts also gives NH-indoles in high yields (Scheme 78).[110]

Scheme 78



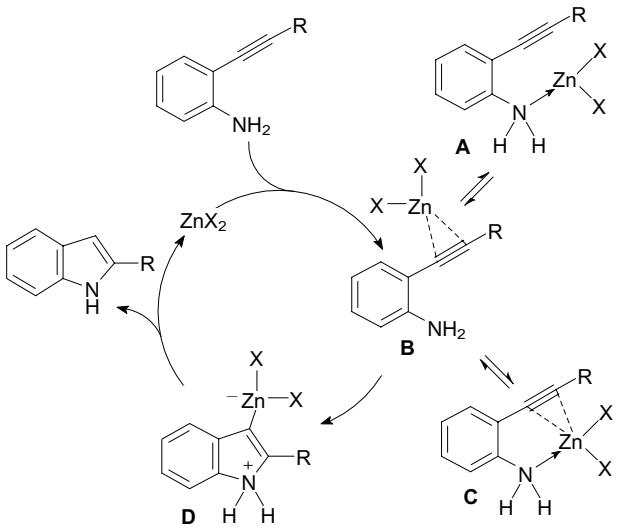
R^1	R^2	Catalyst (equiv.)	Yield (%)
OMe	Ph	$ZnBr_2$ (0.05)	92
H	Pr^n	$ZnBr_2$ (0.05)	90
H	Pr^n	ZnI_2 (0.01)	90
H	n-C_5H_{11}	$ZnBr_2$ (0.05)	91
H	n-C_5H_{11}	ZnI_2 (0.01)	91
Br	Ph	$ZnBr_2$ (0.05)	92
Cl	Ph	$ZnBr_2$ (0.05)	92

On the basis of calculations, the authors proposed a mechanism of intramolecular hydroamination of a model system, 2-(prop-1-ynyl)aniline, using ZnX_2, which gives 2-methylindole.[110] Structural optimization identifies four stable intermediates: N-coordinated complex **A**, π-coordinated complex **B**, N- and π-coordinated complex **C** and σ-complex **D**. The calculations confirm that complex **C** is the most stable one. Since the potential energy difference between complexes **B** and **C** is 16.8 kca mol^{-1}, the reaction can proceed in the following way: ZnX_2 reacts with 2-alkynylaniline to give complex **C**, which occurs in equilibrium with complex **B**, the latter cyclizes to afford σ-complex **D**, which is protodemetallated to yield indole and ZnX_2 (Scheme 79).

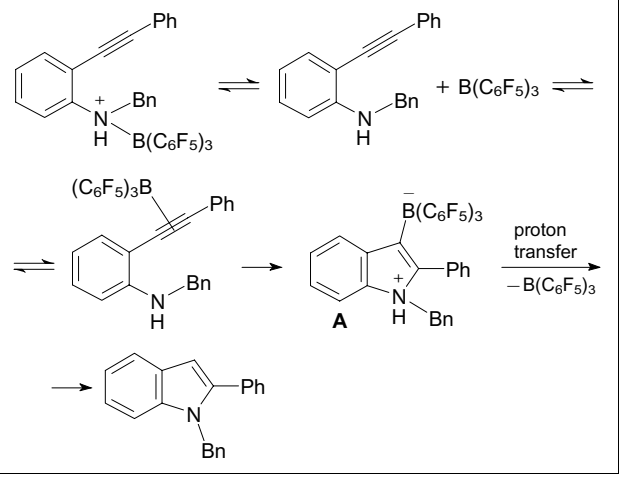
A simple and efficient synthesis of *N*-aryl-2-substituted indoles is based on the reaction of 2-alkynylanilines with diaryliodonium salts.[111]

The intramolecular cyclization of *o*-aminophenylacetylenes to indoles catalyzed by gold compounds[112] and $IrBr_3$[113] has been reported. The acetylene moiety can also

Scheme 79



Scheme 80

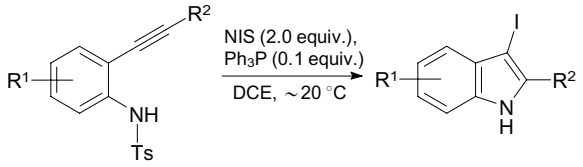


be activated by the $B(C_6F_5)_3$ catalyst.[114] The reaction of 2-alkynylanilines with $B(C_6F_5)_3$ (15 mol.%) affords 2-substituted indoles in good to high yields *via* intramolecular hydroamination. The reaction follows only the 5-*endo-dig*-cyclization pathway, the rate-limiting step of which is protodeboronation of intermediate **A** (Scheme 80).

The application of internal alkynes for indole synthesis by intramolecular hydroamination using FLP catalysis was demonstrated (FLP are frustrated Lewis pairs, that is, compounds containing both a Lewis acid and a Lewis base). The intramolecular hydroamination proceeds probably *via* the intermediate formation of a FLP-containing aniline derivative and borane followed by triple bond activation under the action of boron. The next step is 5-*endo-dig*-cyclization to the zwitter-ionic indole derivative **A** (see Scheme 80), which undergoes protodeboronation giving the target indole and regenerating the borane catalyst.

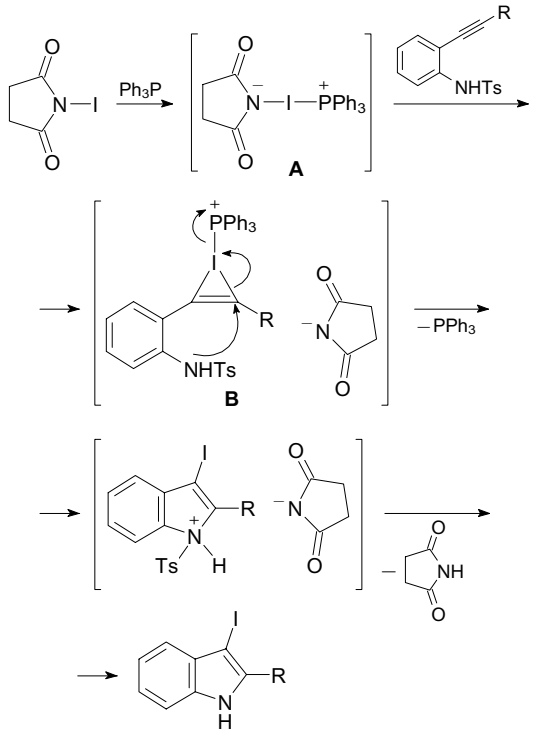
Molecular iodine catalyzes the cyclization of *N*-aryl-2-alkynylanilines to indoles, which includes cyclization coupled with iodination (iodocyclization) to give 3-iodoindole and subsequent protodeiodination at room temperature.[115]

Scheme 81



R^1	R^2	Time /h	Yield (%)
H	Ph	1.5	98
H	4-MeC_6H_4	1.5	97
H	3-MeC_6H_4	6	62
H	4-$MeOC_6H_4$	0.5	99
H	2-$MeOC_6H_4$	0.5	96
H	4-ClC_6H_4	5	92
H	4-FC_6H_4	18	87
H	4-$F_3CC_6H_4$	24	85
H	Bu^t	48	62
H	cyclo-C_3H_5	1	96
4-Me	Ph	2	88
4-MeO	Ph	2	92
4-Cl	Ph	2	94
4-Br	Ph	4	85
4-EtO_2C	Ph	48	60
4-EtO_2C	4-$MeOC_6H_4$	12	92
5-Me	Ph	12	76

Scheme 82



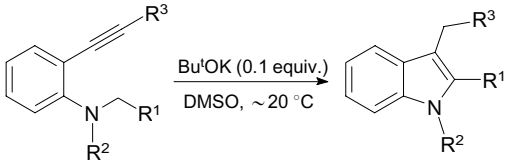
The acetylene moiety is also activated using *N*-iodosuccinimide (NIS).[116] A variety of 3-iodoindole derivatives were obtained in good to high yields from the corresponding 2-alkynylanilines by PPh_3-catalyzed iodocyclization in the presence of *N*-iodosuccinimide under mild conditions (Scheme 81).

The presumptive mechanism of the reaction is depicted in Scheme 82. It is assumed that initially the NIS iodine atom is activated by Lewis base (PPh_3) to give intermediate **A**. Then the electrophilic iodine atom adds to alkyne giving iodonium intermediate **B**, in which the intramolecular amination takes place to give the indole molecule.

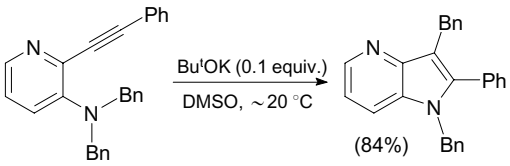
An untypical study is devoted to the use of basic catalysis (Bu^tOK) for the formation of the C–C bond (as opposed to all other reactions, which result in the C–N bond formation) in the radical synthesis of 2-arylindoles from *o*-alkynyl-*N*,*N*-dialkylanilines (Scheme 83, Table 8).[117]

The reaction was extended to the synthesis of the corresponding 4-azaindole (Scheme 84).

Scheme 83



Scheme 84

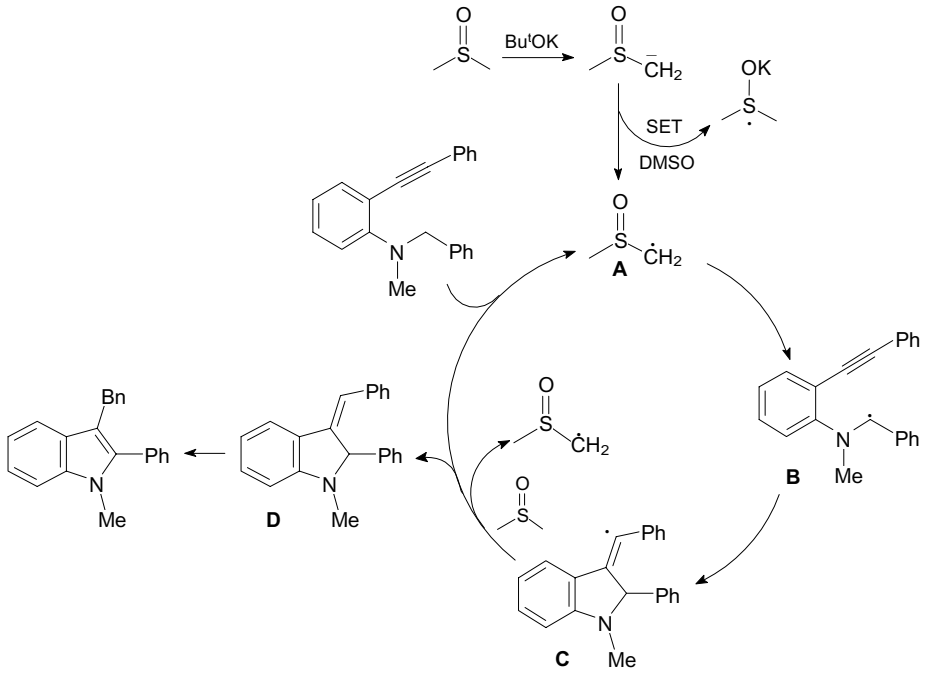


Substrates with electron-withdrawing groups (rows 2, 4–8 in Table 8) are converted to indoles in good yields. The introduction of 2- and 4-methoxy groups (rows 3 and 9 in Table 8) does not prevent efficient indole

Table 8. Synthesis of indoles from *o*-alkynyl-*N*,*N*-dialkylanilines (see Scheme 83).[115]

No.	R^1	R^2	R^3	Yield (%)	No.	R^1	R^2	R^3	Yield (%)
1	Ph	Me	Ph	94	11	2-Quinolyl	Me	Ph	94
2	2-ClC_6H_4	Me	Ph	91	12	Ph	Bn	Ph	88
3	2-$MeOC_6H_4$	Me	Ph	90	13	$(CH_2)_3$		Ph	0
4	3-ClC_6H_4	Me	Ph	92	14	Ph	Me	4-FC_6H_4	93
5	4-FC_6H_4	Me	Ph	95	15	Ph	Me	4-ClC_6H_4	89
6	4-ClC_6H_4	Me	Ph	88	16	Ph	Me	4-$MeOC_6H_4$	89
7	4-$F_3CC_6H_4$	Me	Ph	91	17	H	Me	Ph	0
8	4-NCC_6H_4	Me	Ph	86	18	Ph	Me	1-Naph	90
9	4-$MeOC_6H_4$	Me	Ph	92	19	Ph	Me	H	66
10	2-Naph	Me	Ph	95	20	Ph	Me	Bu^n	54

Scheme 85

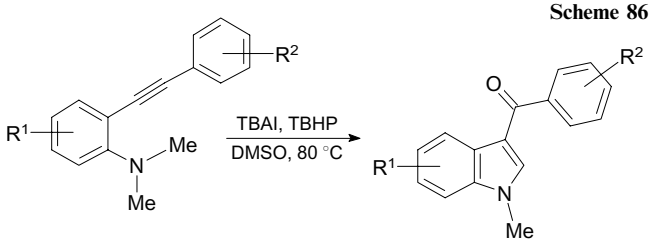


formation either; however, in this case, the use of 1.5 equiv. of Bu^{t}OK is required. The reactions with N-naphthyl and N-quinolyl substrates afford indoles in high yields (rows 10 and 11 in Table 8). In the case of pyrrolidine derivative, no indole is formed (row 13 in Table 8)

Additional experiments were undertaken to establish the reaction mechanism; it was found that the presence of TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] or oxygen completely inhibits the reaction. The authors assumed that DMSO is deprotonated on treatment with Bu^{t}OK to give the anion. This anion gives off the electron to another DMSO molecule to generate radical **A**. Hydrogen abstraction from the substrate affords α-aminoalkyl radical **B**. The subsequent intramolecular radical cyclization gives intermediate **C**. After hydrogen abstraction from DMSO, the primary reaction product **D** is formed; then it undergoes allylic rearrangement to give the target indole (Scheme 85).

A similar C–C bond formation is also observed with other *N*,*N*-dialkyl-*o*-alkynylanilines.[118] For example, a synthesis of 3-aroylindoles from *N*,*N*-dialkyl-*o*-alkynylanilines involves two C(sp^3)–H bond activations, with tetra-n-butylammonium iodide (TBAI) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 86).

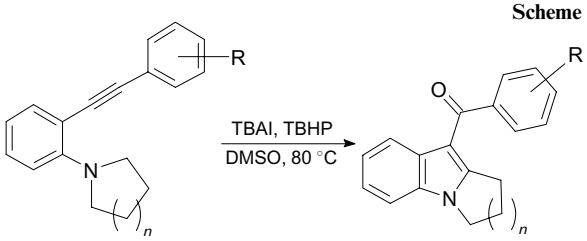
Scheme 86



(12 examples, 61%–77%)

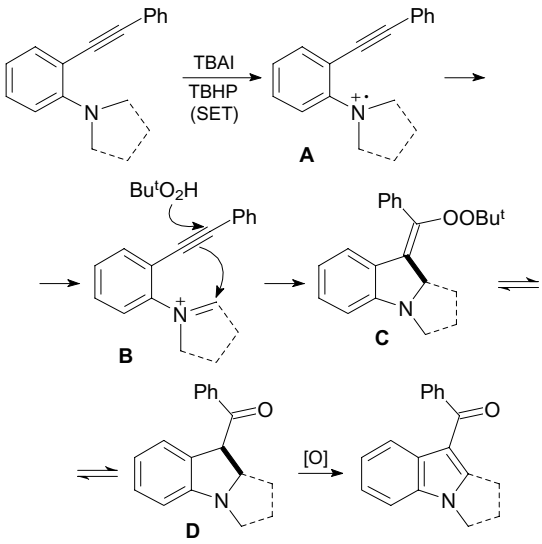
R^1 = H: R^2 = H (74%), 3-Me (76%), 4-Me (77%), 4-OMe (78%), 4-Br (69%), 4-F (67%); R^1 = 5-Me: R^2 = 4-OMe (81%), 3-F (69%); R^1 = 5-Cl, R^2 = 4-Me (67%), *etc.*

Scheme 87



n = 2: R = H (46%), 4-OMe (49%), 4-Br (41%);
n = 1: R = H (45%), 4-Me (49%)

Scheme 88



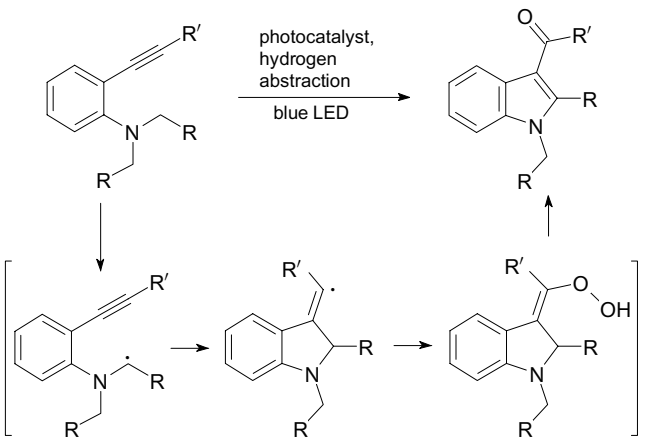
In the case of cyclic amine substituents in the substrates, fused indole derivatives are formed (Scheme 87).

The presumptive mechanism of the reaction is shown in Scheme 88. Probably, the aminyl radical cation **A** is formed

initially *via* the single-electron transfer from the nitrogen atom of *o*-alkynyl-*N*,*N*-dialkylaniline. The removal of a hydrogen atom leads to iminium intermediate **B**, which then cyclizes upon intramolecular nucleophilic attack by the alkynyl group on the iminium carbon atom with simultaneous attack by Bu^tO_2H on the ethylene carbon atom, resulting in the formation of structure **C**, which isomerizes to ketone **D**, and the latter is converted *via* oxidation to the target aroylindole (the newly formed C–C bond is marked).

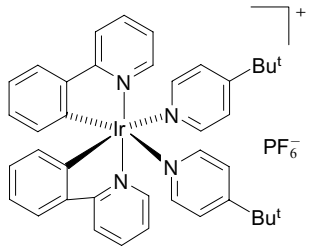
The photocatalytic synthesis of 3-acylindoles by intramolecular oxidative cyclization of *o*-alkynyl-N,N-disubstituted anilines induced by visible light was developed.[119] The reaction efficiently proceeds under mild conditions with atmospheric oxygen as the oxidant. The only side product in this case is water. The presumptive mechanism includes the addition of the aminoalkyl radical to alkyne and the subsequent C–O bond formation (Scheme 89).

Scheme 89



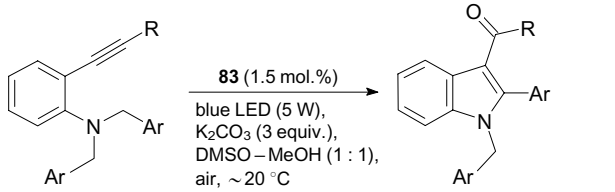
LED is light emitting diode

Structure 83



83

Scheme 90



(21 examples, 43%–80%)

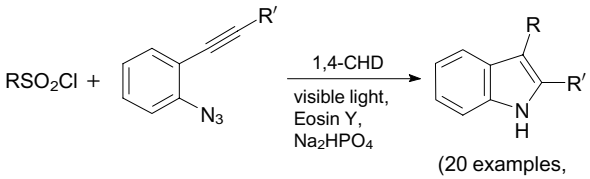
R = Ph: Ar = Ph (71%), *p*-Tol (65%), 4-$Bu^tC_6H_4$ (55%), 4-$F_3CC_6H_4$ (60%), 1-Naph (62%); Ar = Ph: R = 3-Th (63%), Pr^n (43%), 4-FC_6H_4 (79%), *etc.*

The complex $[Ir(ppy)_2dtbbpy]PF_6$ (**83**) proved to be the most efficient photocatalyst. In the presence of this complex, quite a number of 3-acylindoles were obtained in moderate to good yields (Scheme 90).[119]

The second trend in the studies of the use of nitrogen phenylacetylene derivatives is based on introduction of nitrogen-containing groups into the *ortho*-position, including the preparation and application in the indole synthesis. Thus, *o*-alkynylanilines can be replaced by azides. This is exemplified by the synthesis of 2,3-diarylindoles with various (mainly aryl) groups using sulfonyl chlorides and *o*-alkynylphenyl azides and visible light catalysis.[120]

This transformation is characterized by a very broad range of substrates and tolerance to various functional groups, and the use of cheap, commercially available eosin Y as the catalyst makes this method preparative (Scheme 91).[120]

Scheme 91



(20 examples, 31%–84%)

1,4-CHD is cyclohexa-1,4-diene

R	R′	Yield (%)	R	R′	Yield (%)
4-MeC_6H_4	Ph	74	2-Th	Ph	57
4-$MeOC_6H_4$	Ph	68	CF_3	Ph	31
4-FC_6H_4	Ph	71	Ph	4-$MeOC_6H_4$	84
4-ClC_6H_4	Ph	70	Ph	4-FC_6H_4	77
2-MeC_6H_4	Ph	62	Ph	2-Th	63
3-MeC_6H_4	Ph	68	Ph	1-Naph	69
1-Naph	Ph	64	Ph	Bu^t	0

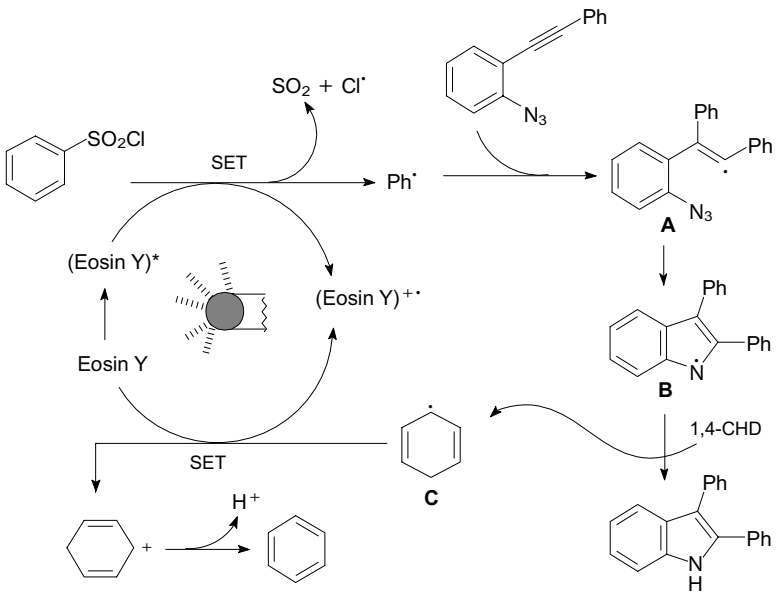
The putative mechanism of the process is shown in Scheme 92. Apparently, the photochemical excitation with visible light induces reduction of benzenesulfonyl chloride to give the phenyl radical and the eosin radical cation. The addition of the phenyl radical to the alkynyl group leads to alkenyl intermediate **A**, which immediately undergoes intramolecular cyclization with extrusion of a nitrogen molecule to give N-radical intermediate **B**. Hydrogen abstraction from cyclohexa-1,4-diene generates radical **C**, which completes the photoredox cycle *via* a single-electron transfer.

A similar synthetic pathway to 2-R-3-arylindoles was accomplished by Pd-catalyzed cyclization of *o*-azidophenylacetylenes in the presence of aryldiazonium salts.[121]

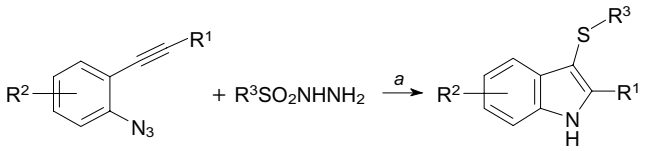
The highly efficient cascade of oxidative reactions of *o*-azidoarylalkynes as substrates and sulfonyl hydrazides as sulfenylating reagents catalyzed by Mn^{III} leads to polysubstituted indolyl thioethers (Scheme 93).[122] The tolerance of the reaction to functional groups in the reactants, together with the fact that nitrogen and water are the only by-products, make this method attractive.

The authors assumed that under catalytic oxidative conditions, sulfonyl hydrazide forms sulfenyl radical **A**, which adds to the carbon–carbon triple bond, thus facilitating the subsequent cyclization. The sharp decrease in the yield of the reaction product upon the addition of TEMPO

Scheme 92



Scheme 93



(29 examples, 36% – 88%)

(*a*) Mn^{III}, DMSO, 80 °C, 12 h

R^1	R^2	R^3	Yield (%)
p-Tol	H	Ph	85
2-Th	H	Ph	88
cyclo-C_5H_9	H	Ph	53
Ph	H	MeOCH=CHCH=CMe	86
Ph	H	4-FC_6H_4	75
Ph	H	4-ClC_6H_4	81
Ph	5-CF_3	Ph	53
Ph	5-CO_2Et	Ph	36

and BHT radical traps attests to a free radical mechanism. Considering these data, a mechanism was proposed for the reaction (Scheme 94).[122] Disulfide **A′** was detected as a by-product.

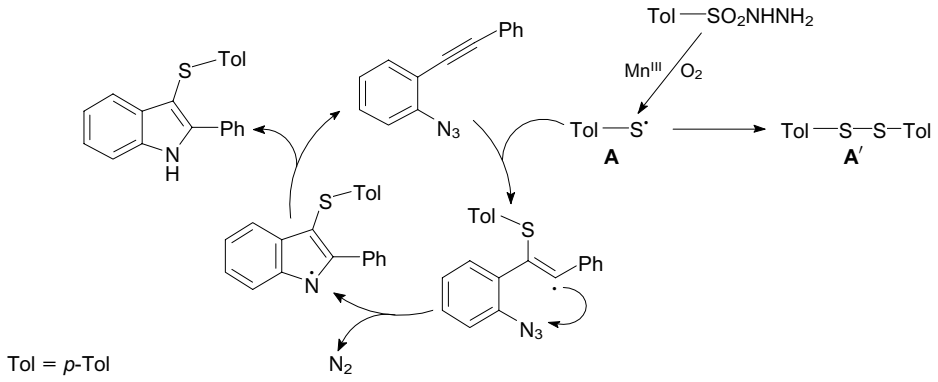
The reaction of *o*-azidoarylalkynes with sulfinic acids in the presence of *tert*-butyl hydroperoxide affords 3-sulfonylindoles.[123]

One more version of Pd-catalyzed cyclization to indoles involving the azide group includes *in situ* generation of iminophosphorane, which attacks the ethynyl group as a nucleophile.[124]

The *ortho*-amine substituent or its analogue can be generated *via* chemical transformation of another functional group. For example, the one-pot tandem reaction including the Hofmann rearrangement of *o*-alkynylcarbamoylbenzenes to the corresponding isocyanates and subsequent catalytic intramolecular cyclization gives indoles.[125] The Hofmann rearrangement yielding the reactive isocyanate intermediate **A** is induced by phenyliodine(III) diacetate (Scheme 95, Table 9).

The data in Table 9 indicate that the substituents in the aromatic ring do not influence the reaction efficiency; in the presence of either electron-withdrawing or electron-donating substituents, the yields of indoles are 82% – 91% (rows 1 – 3 in Table 9). The presence of the phenyl substituent in the acetylene moiety also leads to a high yield of indole (row 4 in Table 9); however, the tolyl group (row 5 in Table 9) results in some decrease in the yield (66%). The tosyloxy group tolerates well the reaction conditions, so that in the presence of this group, the corresponding indole is formed in a quantitative yield (row 6 in Table 9).

Scheme 94



Tol = *p*-Tol

Scheme 95

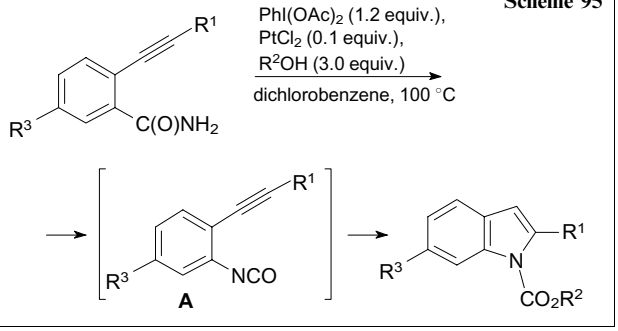


Table 9. Synthesis of indoles from *o*-alkynylamides (see Scheme 95).[125]

Í	R^1	R^2	R^3	Yield (%)
1	Bu^n	Et	F	84
2	Bu^n	Et	NO_2	91
3	Bu^n	Et	OMe	82
4	Ph	Et	H	84
5	*p*-Tol	Et	H	66
6	$(CH_2)_3OTs$	Et	H	100
7	H	Et	H	33
8	TMS	Et	H	0 [a]
9	Bu^n	Bn	H	90
10	Bu^n	Bu^t	H	34

[a] Desilylated indole was obtained in 66% yield.

Unfortunately, terminal alkynes are unsuitable for this reaction (row 7 in Table 9). This can be attributed to the known dimerization of terminal alkynes under the action of $PhI(OAc)_2$.[126]

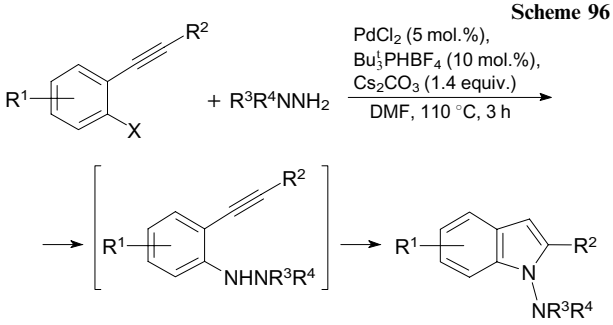
The *ortho*-isocyanate group was also used to synthesize 3-acylindoles by Pd-catalyzed insertion of this group into alkynes and its oxypalladation.[127, 128]

There are pathways for direct introduction of the amine group into the *ortho*-position relative to the alkynyl group in arylacetylene molecules, which can be catalyzed, in particular, by transition metal compounds.

A versatile and efficient method for the synthesis of diverse *N*-aminoindoles is based on Pd-catalyzed domino reactions of easily accessible 2-halophenylacetylenes with simple N,N-disubstituted hydrazines.[129] The reactions proceed in good to high yields, take several hours under mild conditions and are applicable to substrates with various functional groups (Scheme 96).

In another Pd-catalyzed process for introduction of the amino group into the aromatic ring, nitrogen comes from *tert*-butylsulfinamide (**84**),[130] which behaves as an equivalent of ammonia in the Pd-catalyzed amination of aryl bromides and chlorides. This reagent was used in the synthesis of indoles from 2-halophenols, with Pd-catalyzed cross-coupling of their triflates with acetylenes being the key step, followed by the replacement of the halogen atom by an amino group under the action of *tert*-butylsulfinamide (Scheme 97). The $Pd(OAc)_2$–Xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] system served as the catalyst in both steps. The method is applicable for the preparation of indoles with sensitive functional groups such as ester and cyano groups or halogen atoms. The sulfinamide group is eliminated under the reaction conditions to give the corresponding 2-aryl-NH-indoles in high yields.

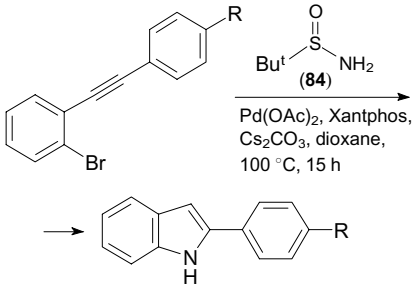
Scheme 96



X = Cl, Br (24 examples, 61%–99%)

R^1	R^2	R^3	R^4	Yield (%)
H	Ph	Ph	Boc	86
6-F	Ph	Ph	Boc	92
5-CF_3	Ph	Ph	Boc	90
6-OMe	Ph	Ph	Boc	99
H	2-Py	Ph	Boc	80
H	cyclo-C_3H_5	Ph	Boc	87
H	CH_2OBu^t	Ph	Boc	61
H	Ph	Ph	CO_2Et	72
H	Ph	$(CH_2)_5$		81
H	Ph	$(CH_2)_2O(CH_2)_2$		87
H	Ph	$(CH_2)_2NMe(CH_2)_2$		74

Scheme 97



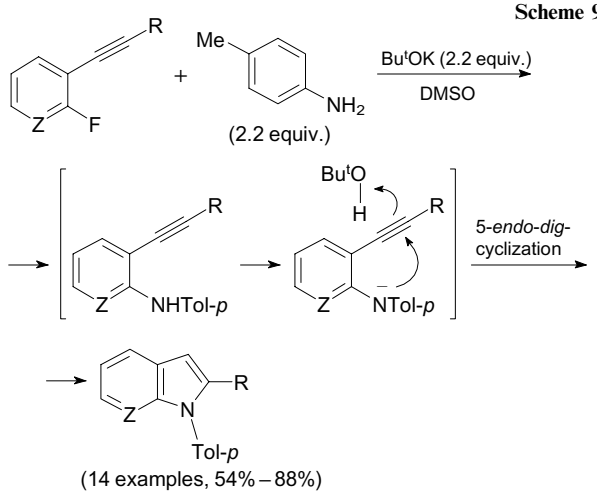
R = H (90%), OMe (88%), Bu^t (71%), F (86%), CN (86%), piperidino (72%), CO_2Me (80%), OCF_3 (86%), CO_2Et (83%)

The aromatic nucleophilic substitution of appropriate halogenated substrates can also be used to introduce the amino group into the *ortho*-position of arylacetylenes. For example, 2-substituted indoles and their aza analogues were obtained by the sequence of reactions including the aromatic nucleophilic substitution of a fluorine atom in *o*-alkynylfluorobenzene (-pyridine) by N-nucleophile (*p*-toluidine) and 5-*endo*-*dig*-cyclization with the *ortho*-acetylene moiety, which plays a dual role, that is, the electron-withdrawing substituent activating the substrate towards the S_NAr substitution and the C(1)–C(2) group for the five-membered ring formation (Scheme 98).[131] The method is suitable for the construction of Ar–N and N–C bonds in one synthetic step and gives indoles in moderate to good yields.

Original syntheses based on *o*-alkynylanilines are suitable for the direct preparation of unusual functionalized indoles.

It was found that the reaction of 2-phenylethynylaniline with acetone in the presence of $[IrCp^*Cl_2]_2$ affords *N*-isopropenylindole rather than N-unsubstituted indole, the

Scheme 98

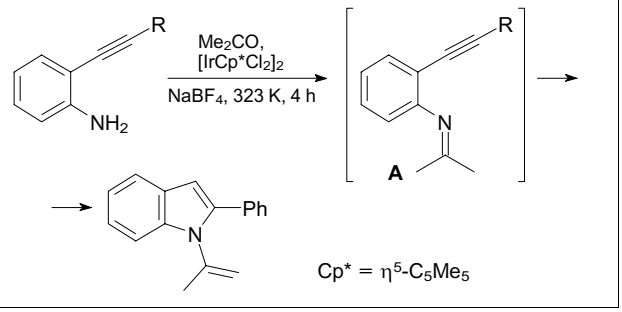


Z = CH: R = Ph (72%), *p*-Tol (69%), 3-Py (79%), *o*-Tol (68%), *m*-Tol (72%), 4-Bu^{t}C$_6$H$_4$ (61%), 4-F$_3$CC$_6$H$_4$ (81%), 4-NCC$_6$H$_4$ (80%), Bu^t (54%); Z = N: R = Bu^t (68%), H (51%), Ph (78%), 4-F$_3$CC$_6$H$_4$ (84%), 3-Py (88%)

formation of which upon hydroamination is to be expected (Scheme 99).[132] Experimental results, including isotope labeling experiments, product isolation and structure determination in the solid state, together with the density functional theory data (DFT) were used to determine the mechanism of formation of isopropenylindoles.[133] According to the mechanism, acetone plays an important role in some steps of the reaction pathway, including fragmentation of the binuclear Ir complex and formation of the catalyst active species, and suppresses the formation of the expected hydroamination product by being coordinated to the Ir catalyst. The coordinated acetone reacts with imine derivative **A**, which leads to the final indole *via* the acetone-catalyzed proton transfer. The proposed mechanism is in good agreement with experimental data.

One more way of synthesis of functionalized indoles is associated with the intermediate preparation of organozinc derivatives.[134] When organozinc compounds are formed with two acidic protons of N-protected *o*-ethynylaniline [NH and C(sp)H] at 120 °C, cyclization to 2,3-dizinc indole **A** takes place (Scheme 100). Since the formation of two C–Zn bonds is energetically favourable, the reaction proceeds smoothly and gives no by-products, although the reaction is actually endothermic for the free anionic form. The dizinc intermediate can be functionalized by one or two

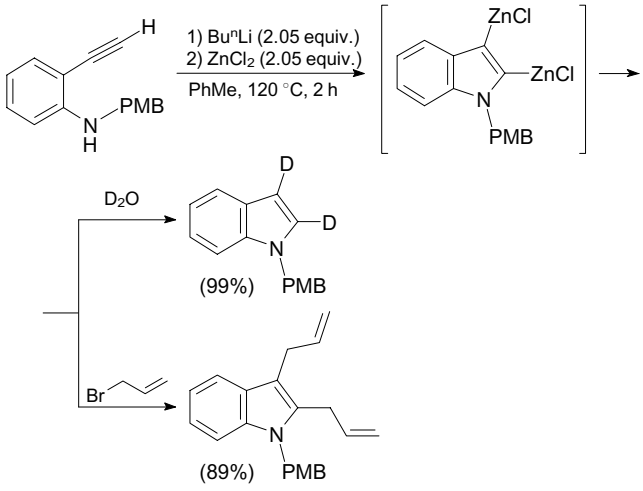
Scheme 99



different electrophiles *via* either inter- or intramolecular process involving positions 2 or 3, respectively, depending on the choice of the catalyst and the type of electrophile.

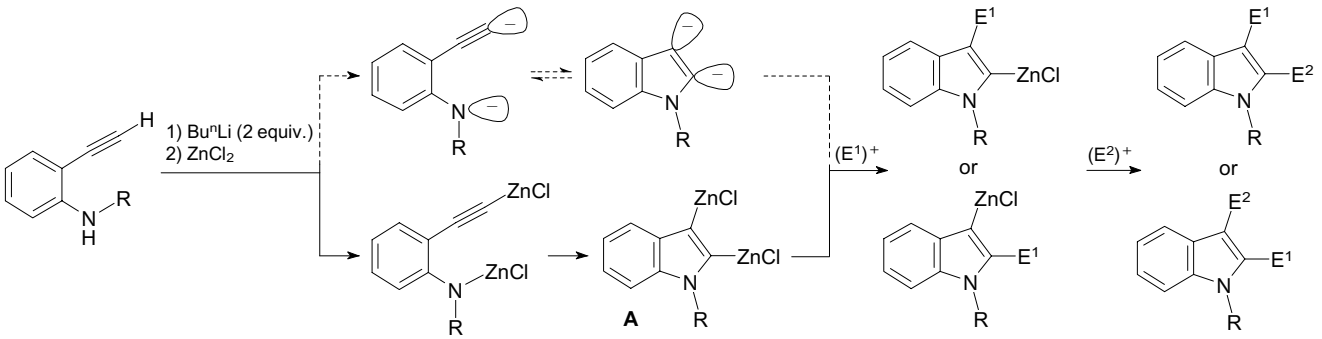
Twelve experiments were carried out with chemically different electrophiles and electrophile mixtures, resulting in the synthesis of 2,3-disubstituted indoles in 47% to 99% yields (examples are shown in Scheme 101).

Scheme 101



In the case of a mixture of electrophiles, the reaction gives a mixture of several indoles, in which one of the products predominates, depending on the nature and the ratio of electrophiles. For example, the reaction with I_2 (5 equiv.) in the presence of NH_4Cl (as the source of protons) furnishes a mixture of 2,3-diiodoindole (74%) and 3-iodoindole (7%), while in the case of MeI (1.2 equiv.) in the presence of D_2O, the reaction gives

Scheme 100

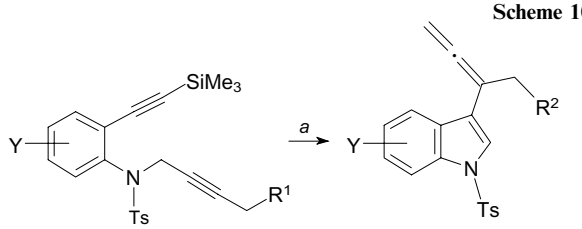


3-methyl-2-deuteroindole (74%), 2,3-dimethylindole (7%) and 2,3-dideuteroindole (6%).

The syntheses of functionalized indoles from *o*-aminophenylacetylenes are often associated with rearrangements and tandem or domino reactions. Indeed, in the case of NR^1R^2-*o*-alkynylanilines [R^1 = Me, Et, Bn; R^2 = $C(O)R^3$, CO_2R^3, $C(O)NHR^3$] and the $PdCl_2(MeCN)_2$ catalytic system, the functional substituent migrates to position 3 of the resulting indole.[135] A direct pathway to 2-aminoalkylindoles is the Cu-catalyzed three-component domino reaction of 2-ethynylaniline, secondary amines and aldehydes.[136] The direct $ZnEt_2$-catalyzed *anti*-azacarboxylation of 2-alkynylanilines on treatment with CO_2 yields indole-3-carboxylic acids.[137] The synthesis of indole-3-carboxamides from 2-ethynylanilines and isocyanates in the presence of a Rh catalyst proceeds as a cyclization–addition tandem reaction.[138,139] An efficient synthesis of 3-aroylindoles from (*o*-dimethylaminophenyl)phenylacetylene with the Cu catalyst proceeds *via* activation of the C–H bond of the N-methyl group, intramolecular nucleophilic addition and *tert*-butyl hydroperoxide oxidation.[140]

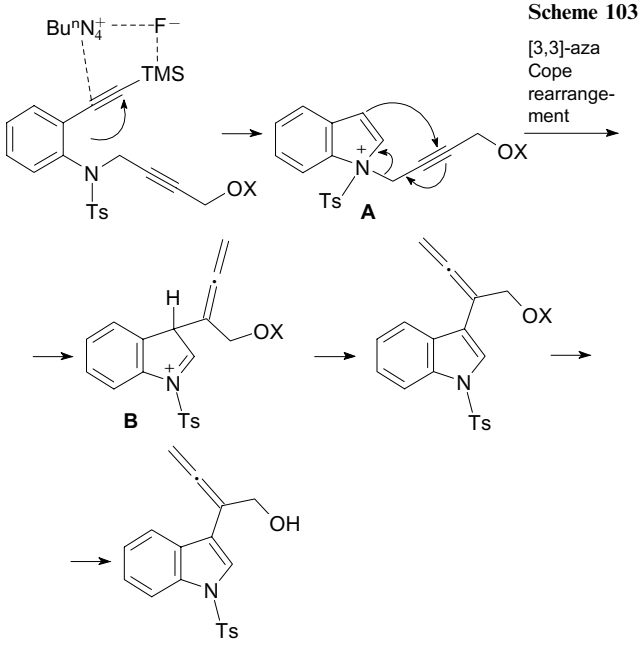
A selective synthesis of functionalized 3-allenyl-1*H*-indoles using tetra-n-butylammonium fluoride is a worthy alternative to the catalytic methods using noble metals (Scheme 102).[141] This approach, free from transition metal catalysts, is based on the efficiency of $Bu^n_4N^+$ and F^- ions in the reaction cascade including hydroamination of the carbon–carbon triple bond, elimination of the silyl protecting groups and site-selective sigmatropic [3,3]-aza Cope type rearrangement.

Scheme 102

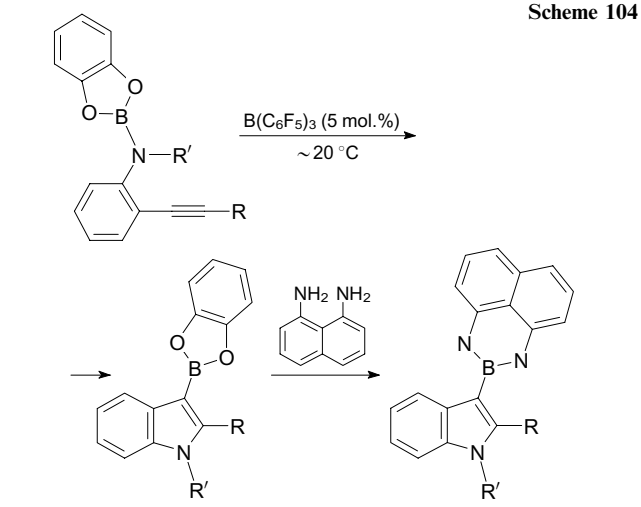


(*a*) TBAF·3H_2O (2 mol.%), THF, ~20 °C, 16 h; R^1 = OTBDMS, OBn, NHBn, CH_2OH; R^2 = OH: Y = 5-F (84%), 6-Cl (93%), 5-CF_3 (38%), 5-Me (86%), 4-Me (68%); Y = H: R^2 = OBn (70%), NHBn (45%), *etc.*

Scheme 103



Scheme 104



R′ = Me: R = Ph (45%), 4-$Bu^tC_6H_4$ (54%), 4-BrC_6H_4 (60%); R = Ph, R′ = Bn (50%), *etc.*

It is noteworthy that substrates with either electron-withdrawing (F, Cl, CF_3) or electron-donating substituents (Me) in various positions can serve as equally convenient starting compounds for the proposed synthesis. The putative mechanism of the reaction is depicted in Scheme 103 in relation to the trimethylsilyl derivative.

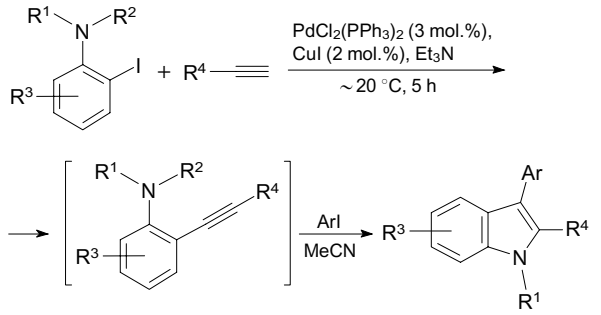
Initially, TBAF participates in hydroamination with simultaneous removal of the silyl protection ($Bu^n_4N^+$ ion is stabilized by the originating acetylene carbanion), resulting, after C(3) protonation, in the indolium intermediate **A**, which then undergoes sigmatropic [3,3]-aza Cope rearrangement to partially dearomatized intermediate **B**; proton migration leads to aromatization and the subsequent removal of the silyl protection gives the target indole.

The preparation of indole derivatives with a boron-containing substituent in position 3 from *o*-alkynylanilines has been reported.[142] This study describes a convenient synthesis of these indoles by $B(C_6F_5)_3$-catalyzed *trans*-aminoboronation of internal alkynes containing a borylated *ortho*-amino group at room temperature (Scheme 104). The reaction is accompanied by N–B bond cleavage and N–C and B–C bond formation, which gives, in one step, borylated indoles suitable for further functionalization.

A new method for the synthesis of 3-phosphinylindole derivatives is based on the Ag-catalyzed cycloaddition of 2-alkynyl-*N*-tosylanilines on treatment with H-phosphine oxides.[143]

The introduction of an ethynyl group into aniline molecules for the preparation of reaction substrates is encountered much more rarely (Scheme 105).[144] The developed microwave-assisted three-component one-pot catalytic synthesis of polysubstituted indoles starts with the Sonogashira cross-coupling of N-substituted or N,N-disubstituted 2-iodoanilines with terminal alkynes; the second step is the

Scheme 105



(24 examples, 33%–94%)

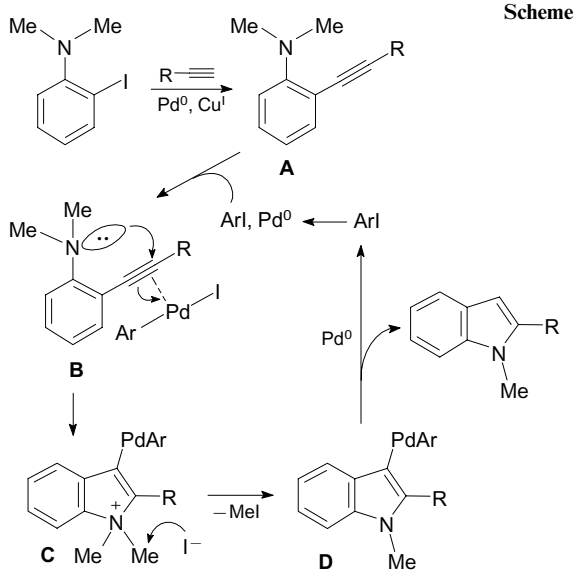
$R^1 = R^2$ = Me or R^1 = H, R^2 = C(O)CF_3

R^1	R^3	R^4	Ar	Yield (%)
Me	H	Ph	$C_6H_4CO_2Et$-4	86
Me	H	3-Th	$C_6H_4CO_2Et$-4	78
Me	H	$(CH_2)_3CN$	$C_6H_4NO_2$-4	72
Me	5-Me	$(CH_2)_2OH$	$C_6H_3(OMe)_2$-3,4	33
Me	5-Me	C_6H_4OH-4	C_6H_4Cl-4	94
H	H	C_6H_4OMe-4	$C_6H_4NO_2$-3	88

intramolecular cyclization induced by the addition of acetonitrile and aryl iodide. The method provides indoles in moderate to good yields and is tolerant to functional groups present in the substrates such as ester, nitro and cyano groups and halogen atoms.

The putative mechanism of the process is summarized in Scheme 106. The cross-coupling affords *N*,*N*-dialkyl-2-(1-alkynyl)aniline **A**. Aryl iodide is added after completion of the cross-coupling. The oxidative addition of aryl iodide to Pd^0 yields the electrophilic intermediate ArPdI, which activates the triple bond of structure **A** *via* coordination, thus giving palladium π-complex **B**. The latter immediately undergoes the intramolecular transamination according to the 5-*endo*-*dig*-cyclization pattern to afford indolium intermediate **C**, which eliminates the methyl group as a result of S_N2 substitution by the *in situ* generated iodide anion, thus yielding indole-containing Pd^{II} intermediate **D**.

Scheme 106



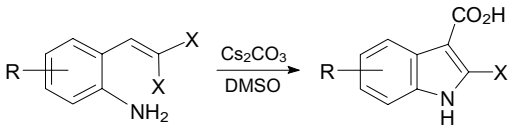
2,3-Disubstituted indole is generated upon the reductive elimination.

A convenient one-pot regioselective synthesis of 2,3-disubstituted indoles from 2-bromoanilines is based on successive Pd-catalyzed Sonogashira cross-coupling with alkylacetylenes, amidopalladation and reductive elimination.[145]

A rhodium-catalyzed introduction of an alkynyl group into the *ortho*-position of phenylhydrazines accompanied by *in situ* indole formation has been reported.[146]

In an interesting synthetic route to 2-haloindole-3-carboxylic acids, instead of the ethynyl group, the dihalovinyl group was employed as the ethynyl group precursor (Scheme 107).[147] The optimal conditions of synthesis of 2-halo-3-carboxyindoles from 2-(2,2-dihalovinyl)anilines include heating of the substrates in DMSO at 120 °C in the presence of caesium carbonate for several minutes. However, the reaction can successfully proceed over a broad temperature range in aqueous media and can be conducted using various combinations of a polar solvent and a carbonate base; the only limiting factor is the substrate solubility. Substituents present in 2-(2,2-dihalovinyl)anilines are, most often, tolerant to the reaction conditions and the product yields are usually high. The reaction mechanism includes the initial formation of the alkynyl bromide intermediate followed by cyclization and addition of carbon dioxide. Due to the nature of the intermediate, we attributed the cited publication to the Section devoted to the use of *o*-alkynylanilines in indole synthesis.

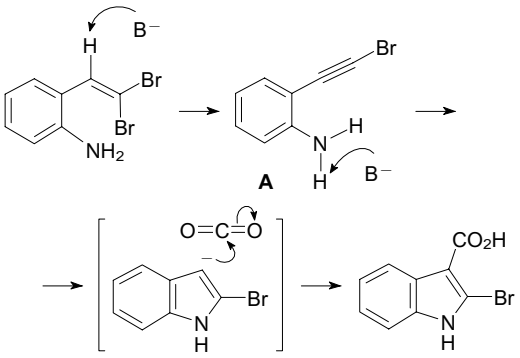
Scheme 107



X = Br: R = H (87%), 6-OMe (79%), 5-OMe (40%), 7-OMe (67%), 4-Cl (74%), 4-F (84%), 6-CO_2Me (73%), 5-CO_2Me (84%), 6-CN (85%), 5-CN (65%); X = Cl: R = H (95%), 6-Br (86%)

In order to elucidate the mechanism of indole formation, the authors started with the detection of intermediate **A**; this can be done by liquid chromatography–mass spectrometry (LC–MS) when the substrate (R = H, X = Br) is slowly converted at temperatures below 120 °C (Scheme 108). The mass of this intermediate corresponds to

Scheme 108



the mass of alkynyl bromide that can be generated upon elimination of the benzylic proton. Since it is known that these alkynyl bromides are formed from the corresponding 2,2-dihalovinyl compounds under basic conditions,[148] it is reasonable to assume that the formation of alkynyl bromide is the first step of the reaction. Indeed, this intermediate was detected using the LC–MS method and isolated in the reaction carried out under anhydrous conditions at 80 °C. Subsequently, the intermediate was converted, in 77% yield, to the final indole under standard conditions. The cyclization of alkynes to indoles is accompanied by the capture of CO_2, which was shown to be possible, for example, by carboxylation of heterocycles with CO_2 and Cs_2CO_3 in hot DMF.[149]

The reaction of 2-(2,2-difluorovinyl)aryl halides with anilines in the presence of a palladium catalyst and a base affords *N*-aryl-2-fluoroindoles.[150]

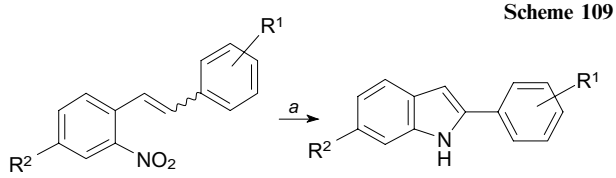
Dibromovinylanilines were also used to prepare 2-aminoindoles by the copper-catalyzed reaction with tosylamines[151] and to prepare 2-cyanoindoles by the Pd^0-catalyzed reaction in the presence of zinc cyanide;[152] the reaction of 2-(2,2-dibromovinyl)phenyl bromide with aldehydes and ammonia affords 3-cyanoindoles.[153]

5. Reductive cyclization of nitrobenzene derivatives

The strategy of application of stable and easily accessible nitroarene derivatives as aniline precursors in reductive cyclizations to indoles making use of the modern achievements of organic chemistry substantially extends the diversity of synthesized indole structures and simplifies the synthetic routes to previously known derivatives.

One version of such syntheses is the reduction of *o*-nitrostyrene derivatives. Often, new methods employ original reducing systems. For example, treatment of nitrostilbenes with carbon monoxide in the presence of elemental sulfur is accompanied by reductive cyclization, which smoothly leads to the corresponding indoles in moderate to good yields (Scheme 109).[154] The same method is used to convert 1-nitro-2-(prop-1-enyl)benzene to 2-methylindole in a yield of 38%.

Scheme 109



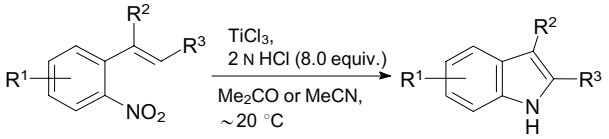
(*a*) CO, S, Et_3N, DMF, 150 °C, 24 h; R^2 = H: R^1 = 4-Me (86%), 3-Me (82%), 2-Me (60%), 4-OMe (85%), 4-Cl (90%), 4-CF_3 (82%); R^1 = H, R^2 = OMe (43%)

The corresponding uncyclized aminostilbene is formed as a by-product of the reaction. However, by optimizing the reaction conditions, the authors attained the predominant formation of target indoles in the reaction carried out in DMF at 150 °C in the presence of triethylamine.

The authors suggested that the generation of carbonyl sulfide in the reaction of sulfur with carbon monoxide in the presence of tertiary amine is the initial step of the reaction. The reaction apparently starts with deoxygenation of the nitro group under the action of thus generated SCO to give a short-lived nitrene or nitrenoid. The intramolecular attack by the nitrene on the vinyl double bond leads to indoles. The reductive cyclization of *o*-nitrostyrenes to indoles under the action of CO has also been reported.[155]

Treatment of *o*-nitrostyrenes with an aqueous solution of $TiCl_3$ at room temperature gives rise to indoles *via* the formal reductive amination of the $C(sp^2)$–H bond (Scheme 110).[156] Functional groups such as halogen atoms (Cl, Br), carbonyl groups (ester, carbamates) and cyano, hydroxy and amino groups are stable in this reaction. The process benefits are mild conditions, simple experimental procedure, the accessibility of reactants and good to high yields of products.

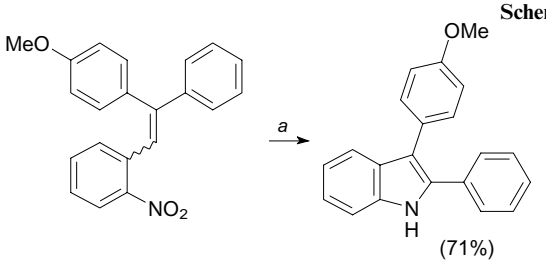
Scheme 110



R^1 = R^3 = H: R^2 = $(CH_2)_2Br$ (64%), $(CH_2)_2NMe_2$ (55%), $(CH_2)_2CN$ (52%); R^1 = H: R^2 = R^3 = Et (87%); R^2–R^3 = $(CH_2)_4$ (90%), $(CH_2)_5$ (94%), $(CH_2)_6$ (83%), $(CH_2)_2NCbz(CH_2)_2$ (70%); R^2–R^3 = $(CH_2)_4$: R^1 = 5-Cl (99%), 5-CO_2Me (90%), *etc.*

β,β-Disubstituted *o*-nitrostyrenes are converted to 2,3-disubstituted indoles *via* a domino reaction including reduction–cyclization–aryl group migration to position 3 of indole (Scheme 111).

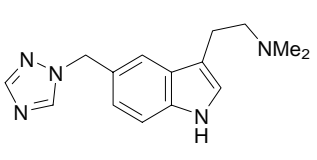
Scheme 111



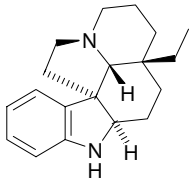
(*a*) $TiCl_3$, 2 N HCl (8.0 equiv.), MeCN, ~20 °C, 24 h

This strategy was used in the key step of the synthesis of the anti-migraine medication rizatriptan (**85**) and in the formal synthesis of the alkaloid aspidospermidine (**86**).

Structures 85, 86

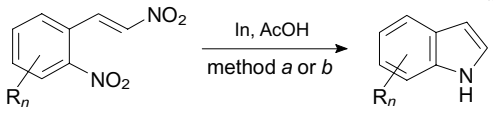


85 (rizatriptan)



86 (aspidospermidine)

Scheme 112

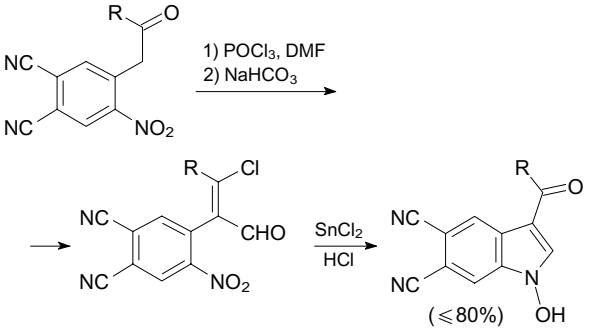


R	Yield (method *a*) (%)	Yield (method *b*) (%)
H	75	80
5,6-OCH_2O	71	65
7-MeO	84	90
5-Cl	80	89
4-Cl	74	69
6-Cl	69	69
7-Me	76	71
6-Me	78	65

The reductive cyclization of *o*,β-dinitrostyrenes induced by the indium–acetic acid system in benzene (method *a*) or toluene (method *b*) gives the corresponding indoles in good yields (Scheme 112).[157] In most cases, the outcome of method *b* is somewhat better. It is noteworthy that the presence of labile functional groups in the benzene ring does not interfere with the smooth proceeding of the reaction.

In some tandem methods, the reductive cyclization to indoles is preceded by the formation of a substituted vinyl group in the *ortho*-position to the nitro group. For example, the Vilsmeier–Haack formylation of 4-(2-aryl-2-oxoethyl)-5-nitrophthalonitriles followed by reduction gives rise to 3-acyl-1-hydroxy-1*H*-indole-5,6-dinitriles (Scheme 113).[158]

Scheme 113



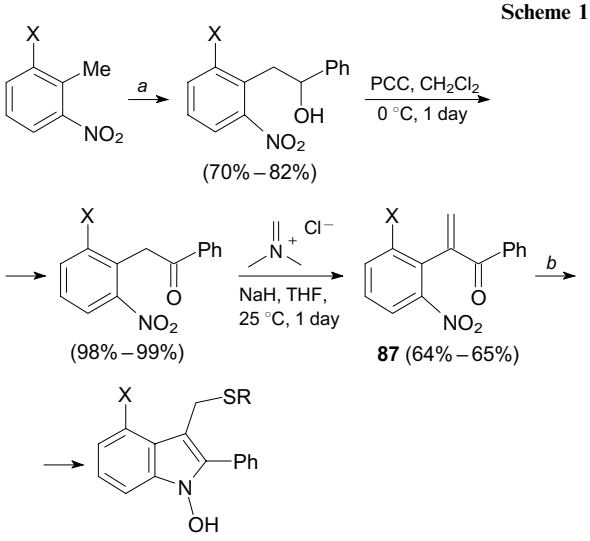
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

The interest in the methods of synthesis of *N*-hydroxyindoles is caused by their bactericidal and antitumour activities.[159, 160]

Apart from the vinyl group in the *ortho*-position to the nitro group, many other functional groups can also participate in the reductive cyclizations. This approach is also applied to prepare the above-described *N*-hydroxyindoles. New 3-alkylthiomethyl-1-hydroxy-2-phenylindoles are obtained from 2-(2-nitrophenyl-1-phenyl)propenones (Scheme 114, Table 10).[161] These substrates are prepared from *o*-nitrotoluenes by efficient three-step synthesis; then for the transformation into target indoles, they are treated with S-nucleophiles in the presence of $SnCl_2 \cdot 2H_2O$.

The authors deemed that indoles are mainly formed by pathway *a* consisting of reduction, condensation and subsequent 1,5-addition (Scheme 115). Good results obtained

Scheme 114



(*a*) PhCHO, DBU, DMSO, 25 °C, 3 days; (*b*) RSH, $SnCl_2 \cdot 2H_2O$; PCC is pyridinium chlorochromate

Table 10. Synthesis of 3-alkylthiomethyl-1-hydroxy-2-phenylindoles (see Scheme 114).[161]

X	R	Yield (%)	X	R	Yield (%)
H	Bn	84	Cl	Cy	40
H	Hex	68	Cl	Bu^t	46
H	Cy	68	Cl	Ph	47
H	Bu^t	61	Br	Bn	55
H	Ph	68	Br	Hex	58
Cl	Bn	54	Br	Cy	44
Cl	Hex	52	Br	Bu^t	54
			Br	Ph	51

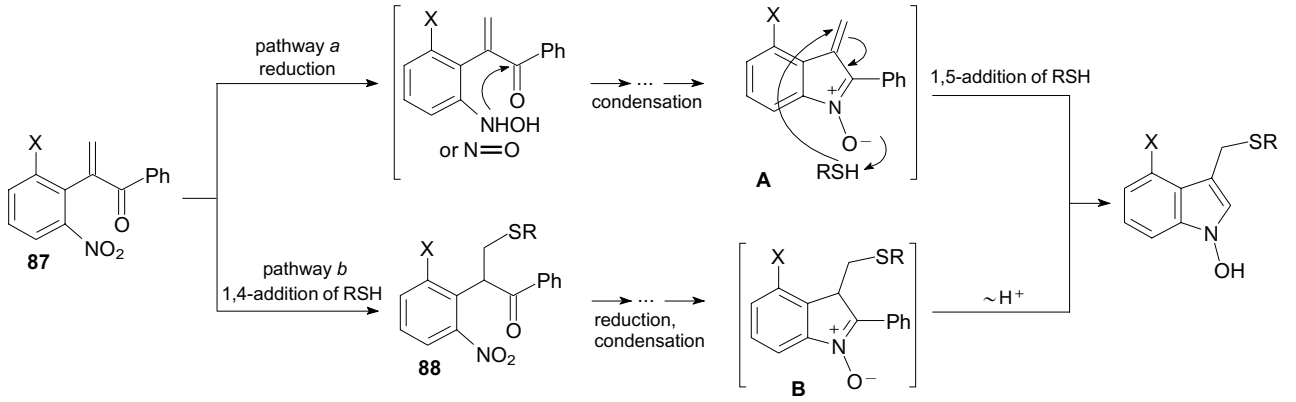
by the use of hindered secondary and tertiary thiols suggest that the intermediate (*e.g.*, conjugated nitrone **A**) has high electrophilicity. However, the authors were unable to experimentally prove the existence of intermediate **A**, probably, due to its high reactivity and low stability. Meanwhile, a different mechanism can also be proposed. Thus, pathway *b* is 1,4-addition to ketone **87**, reduction and cyclization of sulfide **88** and, finally, tautomerization of intermediate **B** to give the target 1-hydroxyindole.

Nitroso- rather than nitrobenzenes were also employed for the synthesis of N-hydroxy derivatives of this type (Scheme 116, Table 11, locants are shown for the substrate).[162] The thermal reaction between the nitrosoarenes and alkynes under the alkylation conditions leads to the formation of *N*-alkoxyindoles as the major products in moderate to high yields with high regioselectivity. In these multicomponent syntheses, the N–OH group is protected by various electrophilic alkylating and acylating agents. Thus, in the case of dimethyl sulfate, *N*-methoxyindoles are formed.

Other protecting groups were also used in the reactions with phenylacetylene (R = Ph) and methyl propiolate (R = CO_2Me)[162] (Scheme 117, Table 12).

N-Hydroxyindoles were obtained in up to 91% yields by the Rh^{III}-catalyzed reaction of arylnitrones with α-diazo ketones.[163]

Scheme 115



Scheme 116

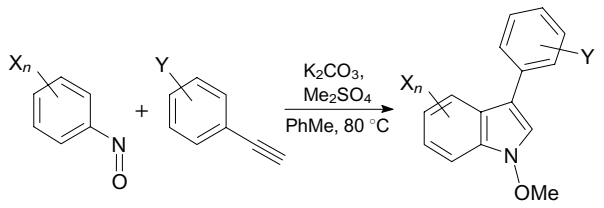
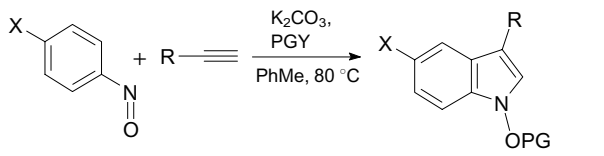


Table 11. Synthesis of *N*-hydroxyindoles from nitrosobenzene derivatives (see Scheme 116).[162]

X_n	Y	Yield (%)	X_n	Y	Yield (%)
4-NO_2	4-NO_2	91	4-CN	H	57
4-NO_2	4-CN	82	4-Br	H	47
4-NO_2	4-Br	77	2,5-$(CO_2Me)_2$	H	62
4-NO_2	4-Cl	67	H	4-NO_2	41
4-NO_2	2-NHAc	37	H	4-CN	39
4-NO_2	4-NHAc	55	H	4-Cl	29
4-NO_2	4-Me	48	H	4-Me	46
4-NO_2	4-OMe	76	H	4-OMe	35
			4-OMe	H	25

Scheme 117

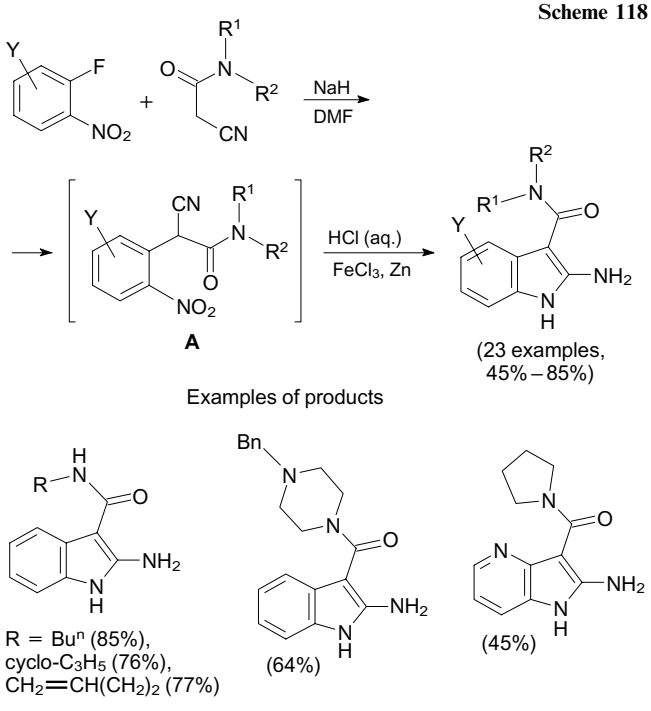


The presence of the side-chain nitrile group in the *ortho*-position to the nitro group provides a convenient reductive cyclization pathway to 2-aminoindoles. A two-step synthesis of 2-aminoindole-3-carboxamide from 2-nitroaryl halides and cyanoacetamides in solution has been developed (Scheme 118).[164] The reaction involves the primary formation of 2-cyano-2-(2-nitroaryl)acetamide **A** according to the aromatic nucleophilic substitution (S_{NAr}) pathway; then the addition of $FeCl_3$ in hydrochloric acid and a Zn powder induces reduction and cyclization involving the cyano group to give the target 2-aminoindoles. The method is also applicable for the synthesis of indole aza analogues — pyrrolopyridines.

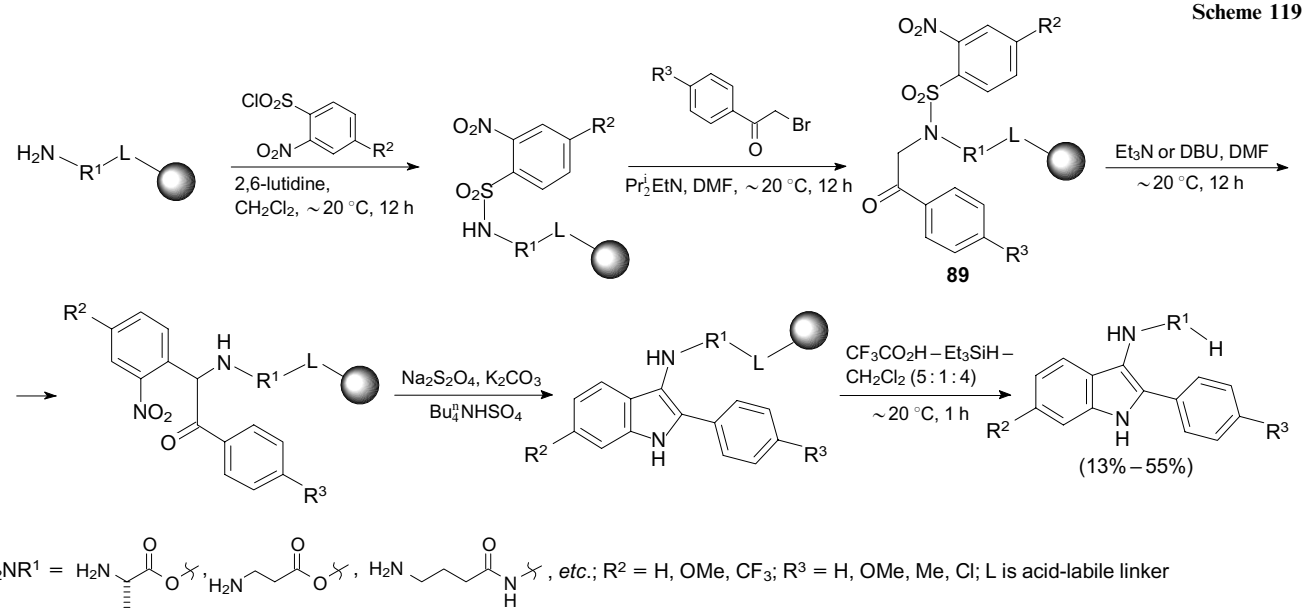
Table 12. Use of various protecting groups in the synthesis of *N*-hydroxyindoles from nitrosobenzenes (see Scheme 117).[162]

X	PGY	Yield (%)
	R = Ph	
4-NO_2	Boc_2O	65
4-NO_2	$PhCH_2Br$	77
4-NO_2	$ClCO_2Et$	61
4-NO_2	CbzCl	53
4-NO_2	$CH_2{=}CHCH_2Br$	86
4-NO_2	TsCl	32
4-CN	$CH_2{=}CHCH_2Br$	44
4-CN	PhCOCl	38
	R = CO_2Me	
4-NO_2	$ClCO_2Et$	73
4-NO_2	TsCl	57
4-NO_2	CbzCl	60
4-CN	Me_2SO_4	43
4-CN	PhC(O)Cl	56

Scheme 118



Scheme 119



The palladium acetate-catalyzed cascade synthesis of 2-arylindoles was also conducted using *o*-nitrocyanomethylbenzene combined with arylboronic acids.[165]

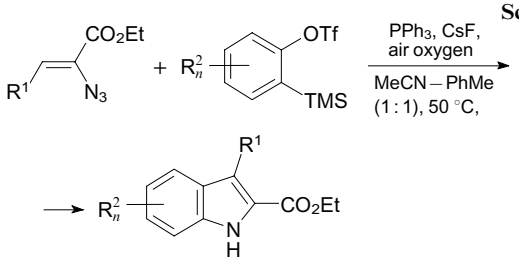
Polymer-supported 2-nitro-*N*-(2-oxo-2-arylethyl)benzenesulfonamides **89**, prepared from supported amines and substituted 2-nitrobenzenesulfonic chlorides followed by alkylation of α-bromoacetophenones, are convenient building blocks for the synthesis of nitrogen heterocycles.[166] A method has been developed for the combinatorial synthesis of 3-alkylamino-2-aryl-1*H*-indoles using base-induced C-arylation and the subsequent reduction of the C-arylated intermediate. The linear precursor for C-arylation was prepared by the solid-state synthesis from commercially available compounds. A number of polymer-supported amines react with substituted *o*-nitrobenzenesulfonyl chlorides in the presence of 2,6-lutidine, while the sulfonamide thus formed is alkylated by α-bromoacetophenones (Scheme 119). The reaction of acyl precursor **89** with a base leads to arylation of the methylene group activated by the neighbouring carbonyl group. Then the nitro group is reduced by the dithionite method.[167] The cyclization involves the side-chain carbonyl group. The target indole is detached from the polymeric resin by treatment with trifluoroacetic acid in dichloromethane containing triethylsilane for carbocation scavenging.[168]

6. Synthesis with the use of arynes

Extremely reactive arynes, which are easily generated *in situ*, are used in various types of indole synthesis. For example, 2-azidoacrylates react with arynes obtained in the presence of PPh_3 and CsF to give indoles in high yields (Scheme 120).[169] The process includes the formation of iminophosphoranes and arynes and the subsequent cascade reaction including double cyclization, hydrolysis and oxidation with air oxygen.

Presumably, the cycloaddition of arynes and iminophosphoranes should lead to the formation of indoles, as the nitrogen atom of iminophosphorane bears a partial negative charge and exhibits considerable nucleophilicity. The putative mechanism is shown in Scheme 121 for the substrate

Scheme 120



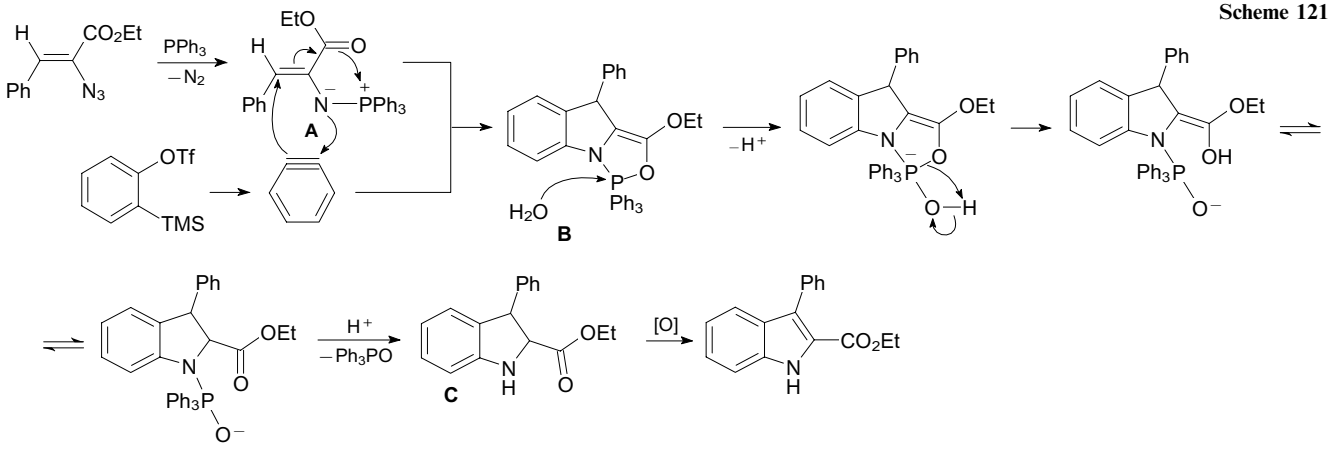
R^2_n = H: R¹ = Ph (81%), 4-MeC_6H_4 (79%), 4-ClC_6H_4 (84%), 4-BrC_6H_4 (82%), 4-$MeOC_6H_4$ (76%), 3-$O_2NC_6H_4$ (89%), 4-PhC_6H_4 (82%), 4-$PhCH_2OC_6H_4$ (74%), 2-Naph (80%), PhCH=CH (72%), 2-ClC_6H_4CH=CH (73%), 2-$MeOC_6H_4CH$=CH (70%), 2-$O_2NC_6H_4CH$=CH (76%); R^2_n = 5,6-Me_2: R¹ = Ph (80%), 3-$O_2NC_6H_4$ (88%); R¹ = Ph: R^2_n = 5,6-CH_2OCH_2 (78%), 6,7-benzo (80%), 7-MeO (64%), *etc.*

with R¹ = Ph, R^2_n = H. In the first step, the azide reacts with PPh_3 to give iminophosphorane **A** according to the Staudinger–Meyer reaction. Then phosphorane **A** reacts with dehydrobenzene generated *in situ*, giving rise to intermediate **B** as a result of two nucleophilic cyclizations. Compound **B** is easily hydrolyzed to give dihydroindole **C** with elimination of Ph_3PO (isolated) during the standard workup. Finally, indoline **C** is oxidized with air oxygen to indole.

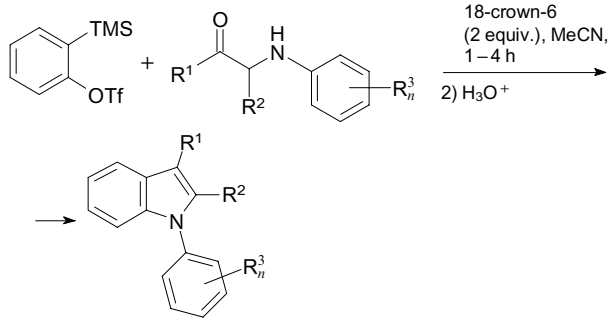
The use of azidoacrylates and arynes resulted in the synthesis of quite a few diverse indoles in good yields (see Scheme 120).

The amino group of α-amino ketone undergoes the nucleophilic addition reaction with aryne (N-arylation), and then nucleophilic addition of ketone takes place to give substituted indoline, which is also isolated in a high yield. Elimination of water under acidic conditions furnishes the target indole. This strategy was employed for the first regioselective one-step synthesis of *N*-aryl-2,3-dialkylindoles with various substituents at the C(2) and C(3)

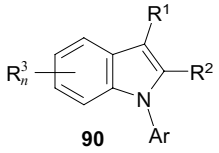
Scheme 121



Scheme 122



Structures 90



R^1	R^2	R^3_n	Ar	Yield (%)
Ph	Ph	5,6-Me_2	Ph	87
Ph	Ph	5,6-$(MeO)_2$	Ph	88
Ph	Ph	5,6-бензо	Ph	90
Ph	Ph	4-MeO	Ph	95
Me	Me	5,6-benzo	2,6-$Me_2C_6H_3$	65

atoms *via* simultaneous formation of the C(7a)–N(1) and C(3a)–C(3) bonds.

A simple one-step synthesis of *N*-arylindoles free from metal-based catalysts has been developed; the process includes coupling of *in situ* generated arynes with α-amino ketones (Scheme 122, Table 13).[170, 171]

The data in Table 13 attest to the minor influence of the nature of substituents in amino ketones on the course of the reaction and to tolerance of the reaction to diverse functional groups.

The use of substituted arynes extends the range of synthesized indoles (structures **90**).

N-Arylindoles represent an extensive class of compounds, the derivatives of which are successfully used in biology, pharmacology, agrochemistry and materials science.[172]

The developed method is the aryne-based version of the classical non-regioselective Bischler–Melau synthesis

Scheme 123

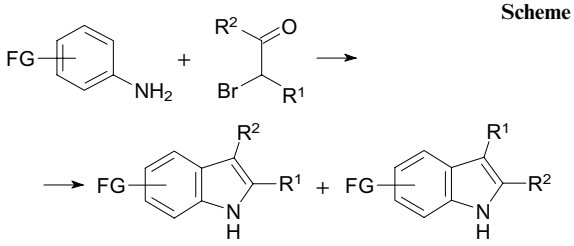


Table 13. Synthesis of indoles from dehydrobenzene and α-amino ketones (see Scheme 122).[170]

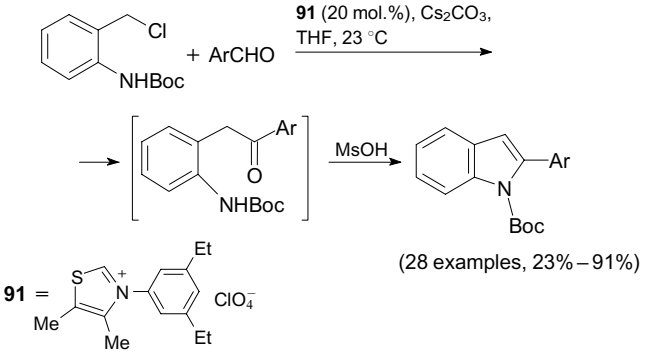
R^1	R^2	R^3_n	Yield (%)	R^1	R^2	R^3_n	Yield (%)
Ph	Ph	H	97	4-BrC_6H_4	4-BrC_6H_4	4-MeO	74
4-ClC_6H_4	4-ClC_6H_4	H	73	Ph	4-$F_3CC_6H_4$	H	88
4-BrC_6H_4	4-BrC_6H_4	H	74	3-$MeOC_6H_4$	3-BrC_6H_4	H	99
Ph	Ph	4-Cl	82	3-BrC_6H_4	2-$MeOC_6H_4$	H	99
4-BrC_6H_4	Ph	H	83	2-Fu	Ph	H	63
4-MeC_6H_4	4-MeC_6H_4	H	91	2-Fu	4-$MeOC_6H_4$	H	66
4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	85	4-ClC_6H_4	Me	H	72
4-MeC_6H_4	4-MeC_6H_4	4-MeO	93	Me	Et	H	51
Ph	Ph	4-Me	86	Ph	Ph	H	95
Ph	Ph	4-MeO	92	Me	Me	4-O_2N	21
Ph	4-$MeOC_6H_4$	H	89	Me	Me	2-Br	86
4-BrC_6H_4	4-$MeOC_6H_4$	H	88	Me	Me	2,6-Me_2	87
4-ClC_6H_4	4-ClC_6H_4	4-MeO	86	Ph	Pr^i	H	86
				Bn	Ph	H	83

resulting in the formation of two regioisomers (Scheme 123).[173]

7. Carbene catalysis

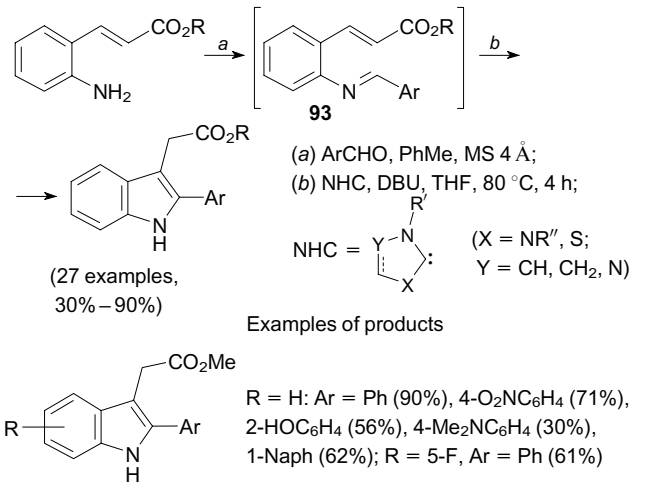
N-Heterocyclic carbenes (NHC) are widely used in the synthesis of N-heterocycles as organic catalysts, which are strong Lewis bases.[174–183] For example NHC are employed to prepare 2-arylindoles under mild conditions (Scheme 124).[184] The method is based on the reaction of *N*-Boc-*o*-chloromethylanilines with aromatic aldehydes catalyzed by NHC generated *in situ* from azolium salts under the action of bases. The catalytic reaction affords *o*-aminobenzyl ketone derivatives, which undergo spontaneous cyclization to 2-arylindoles. The optimal conditions are conducting the reaction in THF and using azolium salt **91** as the carbene source and Cs_2CO_3 as the base.

Scheme 124

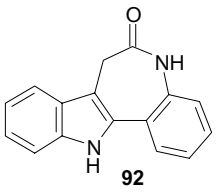


A new organocatalytic process has been developed for indole synthesis using the unique reactivity of N-heterocyclic carbenes (Scheme 125).[185] The NHC-catalyzed atom-economical synthesis can be used to prepare a broad range of 2-substituted methyl indole-3-ylacetates. This synthetic sequence was employed for the preparation of paullone — a cyclin-dependent kinase (CDK) inhibitor (structure **92**).

Scheme 125

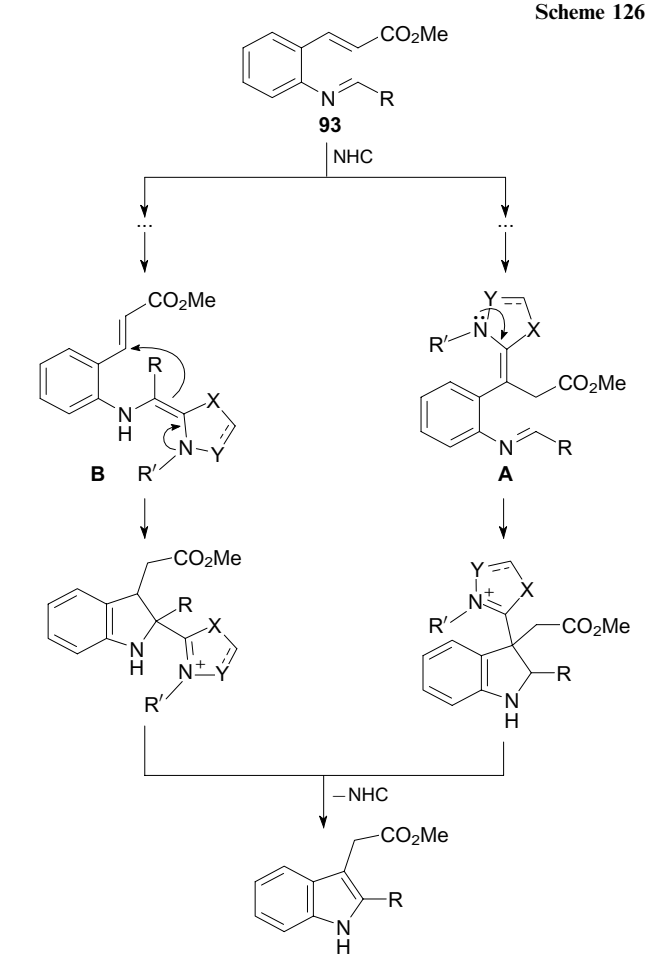


Structure 92



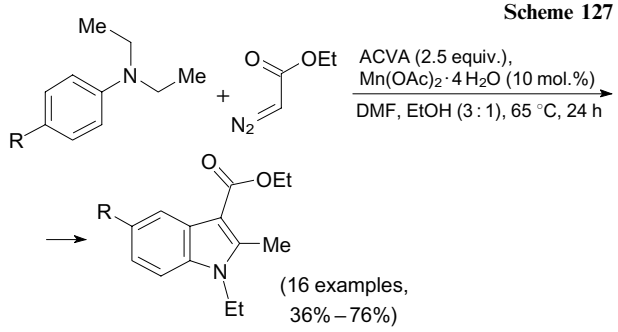
The authors suggested that NHC can invert the polarity of the electrophilic centres, both the β-carbon atom of α,β-unsaturated ester (*via* the deoxy Breslow intermediate **A**, Scheme 126) and the imine carbon atom (*via* the aza Breslow intermediate **B**, see Scheme 126)[186] of precursor **93**, which should become the nucleophilic centre (upon polarization inversion) and, hence, add to the remaining electrophilic centre; this should finally trigger the cyclization–aromatization cascade giving 2-substituted indolylacetic acid derivatives.[185]

Scheme 126



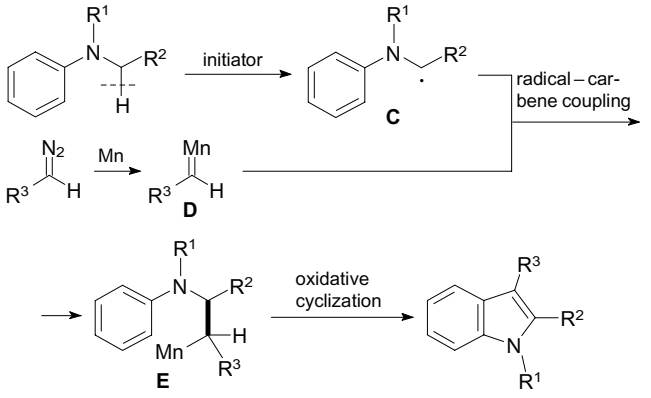
An unusual coupling of aromatic amines and diazo compounds has been found (Scheme 127).[187] The manganese-catalyzed reaction tandem is a new convenient approach to the formation of the indole core under mild conditions.

Scheme 127



R = Me (63%), Bu^t (67%), Pr^i (67%), OMe (41%), F (76%), Cl (56%), Br (48%), OBoc (58%), OCF_3 (45%) , *etc*; ACVA is 4,4′-azobis(4-cyanovaleric acid)

Scheme 128

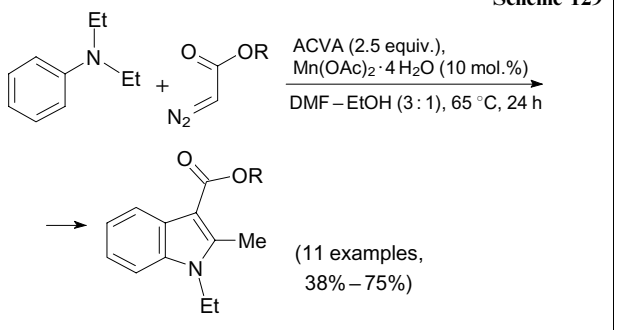


Initiator: ACVA

As shown in Scheme 128, the α-aminoalkyl radical **C** generated *in situ* from the aromatic amine is then coupled with manganese carbene **D** to afford intermediate **E** (the newly formed bond is marked), which undergoes the oxidative cyclization to give the target indole.

Using various diazo esters, indoles with various ester groups in position 3 were prepared (Scheme 129).

Scheme 129



R = Pr^i (64%), Bu^t (60%), $(CH_2)_2$TMS (64%), All (38%), C_6H_4R'-4 [R′ = H (73%), Me (75%), Cl (68%), CF_3 (57%)]

8. Miscellaneous syntheses

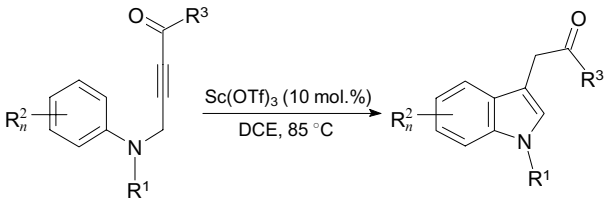
Quite a few original and interesting methods for indole synthesis that do not fit in any of the above groups can be found in the literature. These miscellaneous methods are classified in terms of the type of bond formed during the ring closure.

8.1. C–C bond formation

The methods reported in the literature imply, most often, some ways of C(3)–C(3a) bond formation and only some examples describe the formation of the C(2)–C(3) bond.

The ways of C(3)–C(3a) bond formation are rather diverse and include various types of chemical transformations. One approach is based on the modified Friedel–Crafts electrophilic substitution reaction. The $Sc(OTf)_3$-catalyzed formation of the C–C bond (intramolecular Friedel–Crafts alkenylation) was applied to obtain substituted aryl- and alkylindoles using 5-(arylamino)pent-3-yn-2-ones as substrates (Scheme 130).[188]

Scheme 130

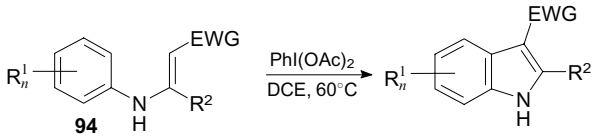


(19 examples, 30%–81%)

R^1 = Me, R^3 = Ph: R^2_n = 5-Cl (51%), 6,7-benzo (45%);
R^1 = Bn, R^2_n = H, R^3 = 4-ClC_6H_4 (50%), *etc*.

Functionalized indoles were synthesized by catalytic oxidative formation of the carbon–carbon bond (Scheme 131).[189] The benefits of this reaction are the easy preparation of the starting enamines **94**, tolerance to various functional groups, mild conditions and the absence of transition metal catalysis.

Scheme 131



(20 examples, 33%–91%)

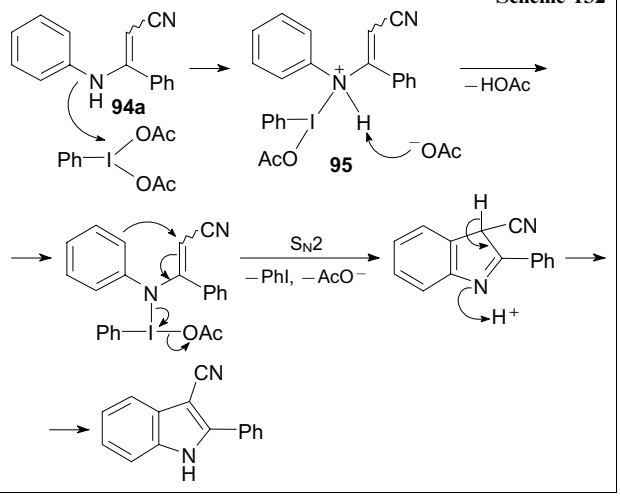
EWG	R^1_n	R^2	Yield (%)
CN	H	Ph	83
CN	5-Br	Ph	78
CN	5-OMe	Ph	51
CN	5,6-$(OMe)_2$	Ph	33
NO_2	H	Ph	62
CO_2Me	5-Me	Ph	71
CN	5-Me	Bu^t	85
Bz	5-Me	CO_2Et	51

The initial enamines — 3-aryl-3-arylaminoacrylonitriles **94** — are easily formed as mixtures of *cis*- and *trans*-isomers upon the acetic acid-catalyzed condensation of 3-aryl-3-oxopropionitriles with appropriate anilines. Due to high tolerance of the reaction to functional groups, the cyano

group in the substrate can be replaced by other electron-withdrawing substituents such as nitro and ester groups.

The mechanism of intramolecular S_N2 cyclization of substrate **94a** ($R_n^1 = R^2 = Ph$, EWG = CN) to indole is shown in Scheme 132. Intermediate **95** is formed upon the reaction of substrate **94a** with PIDA with the loss of one acetic acid molecule. The presence of EWG in the enamine β-position facilitates the formation of the intermediate; then the N–I bond is cleaved with simultaneous electrocyclic ring closure. The reaction ends with isomerization of 3*H*-indole to the target indole.

Scheme 132

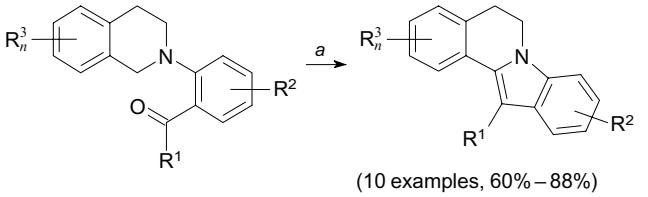


The cyclization of analogous α-iodo-enamines is induced by the action of $Pd(dba)_3$.[190]

Palladium-catalyzed cyclization of alkyl ketone *N*-arylimines leads to indoles *via* the oxidative formation of the C(3)–C(3a) bond with molecular oxygen as the only oxidant.[191]

A new synthesis of indole derivatives is based on intramolecular dehydrative coupling of tertiary amines with ketones catalyzed by the Bu^tOK–DMF superbasic system (Scheme 133).[192] A similar system for cyclization generating the C–N bond was employed to prepare esters of N-substituted 1*H*-indole-3-carboxylic acids.[193]

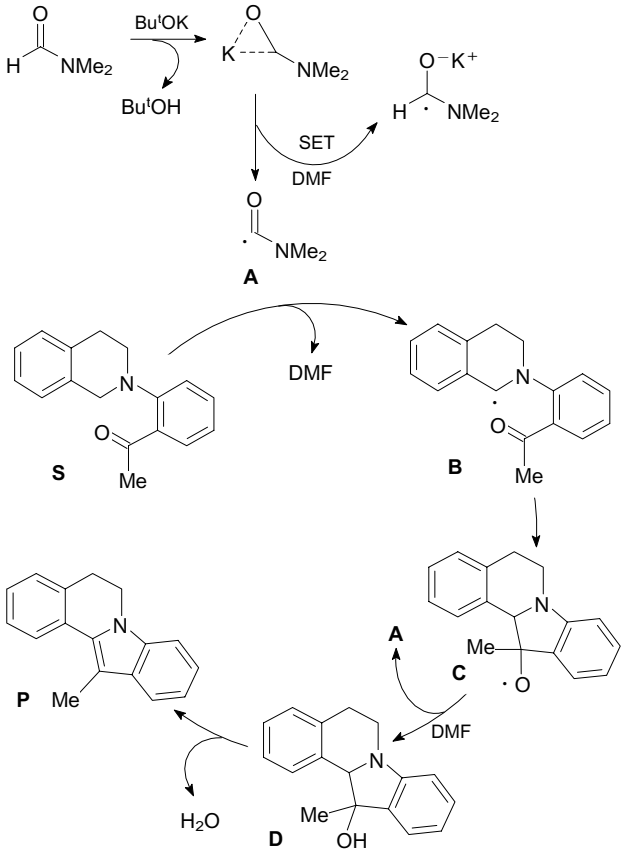
Scheme 133



(*a*) Bu^tOK (1.2 equiv.), DMF, 90 °C; $R^2 = R_n^3 = H$: $R^1 = Et$ (88%), Ph (75%), 4-$MeOC_6H_4$ (60%), 3,5-$Me_2C_6H_3$ (65%), *etc.*

Similar results were also obtained with acyclic tertiary amines. Probably, the reaction proceeds *via* the formation of the R-aminoalkyl radical. The putative mechanism of this reaction is depicted in Scheme 134. Carbamoyl radical **A** is generated upon deprotonation of DMF followed by single-electron transfer. Radical **A** eliminates the hydrogen atom from the C(1) atom of substrate **S** and the R-amino-

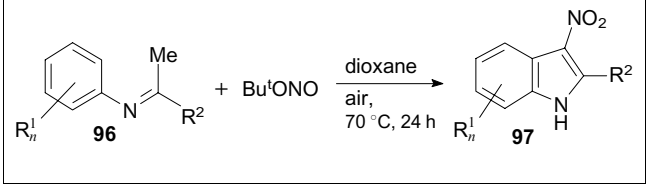
Scheme 134



alkyl radical **B** thus formed adds to the carbonyl group; intermediate **C** detaches a hydrogen atom from DMF. 3-Hydroxyindoline intermediate **D** is formed as the primary reaction product and radical **A** is recovered. The final reaction product **P** is formed upon dehydration of intermediate **D**.

A new synthesis of 3-nitroindoles **97**, free from metal catalysts, based on radical dehydrogenative cyclization of *N*-arylimines **96** induced by *tert*-butylnitrite includes the cascade cleavage of several C–H bonds, nitration, cyclization and isomerization reactions. The method has high compatibility with functional groups and high selectivity (Scheme 135, Table 14).[194]

Scheme 135



It follows from Table 14 that the reaction is tolerant to substituents of various natures, including MeO, MeS, Br and C(O)Me. For example, the *meta*-substituted substrate regioselectively forms indole **97b** in 62% yield. Substrates with electron-donating substituents also smoothly react to give indoles **97c–e** in moderate yields; the substrate with the electron-withdrawing Ac substituent behaves in a similar way, with indole **97g** being formed in 63% yield.

Table 14. Radical synthesis of 3-nitroindoles (see Scheme 135).[194]

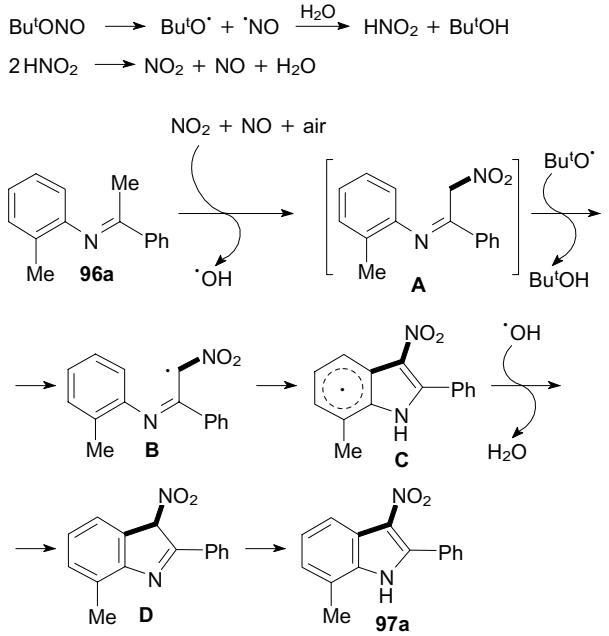
Indole **97**	R^1_n	R^2	Yield (%)
a	7-Me	Ph	60
b	6-Me	Ph	62
c	5-Me	Ph	50
d	5-MeO	Ph	55
e	5-MeS	Ph	50
f	5-Br	Ph	48
g	5-Ac	Ph	63
h	5,7-Me_2	Ph	50
i	5-MeO-7-Me	Ph	70
j	H	Ph	40
k	5-Me	4-$Pr^iC_6H_4$	67
l	5-Me	4-$MeOC_6H_4$	60
m	5-Me	4-ClC_6H_4	63
n	5-Me	4-NCC_6H_4	65
o	5-Me	4-$F_3CC_6H_4$	64
p	5-Me	3-$O_2NC_6H_4$	50
q	5-Me	2-$O_2NC_6H_4$	49
r	5-Me	2,4-$(MeO)_2C_6H_3$	62

The putative mechanism of formation of 3-nitroindoles is shown in Scheme 136 (the newly formed bonds are marked). Initially, Bu^tONO easily splits to the $Bu^tO^{\bullet}$ and $NO^{\bullet}$ radicals on heating.[195] The reaction of the $NO^{\bullet}$ radical with water affords HNO_2, which rapidly decomposes to NO_2, NO and H_2O. In the presence of NO_2, NO and air, the substrate (for example, **96a**) is converted to intermediate **A**, while the subsequent elimination of the hydrogen atom by the $Bu^tO^{\bullet}$ radical leads to the radical intermediate **B**, which undergoes cyclization to give a new cyclic radical intermediate **C**. Dehydrogenation and isomerization of **C** produces the target indole **97a**.

The microwave-assisted multicomponent domino reaction of enamines, aryl glyoxals and carboxylic acids gives indoles.[196]

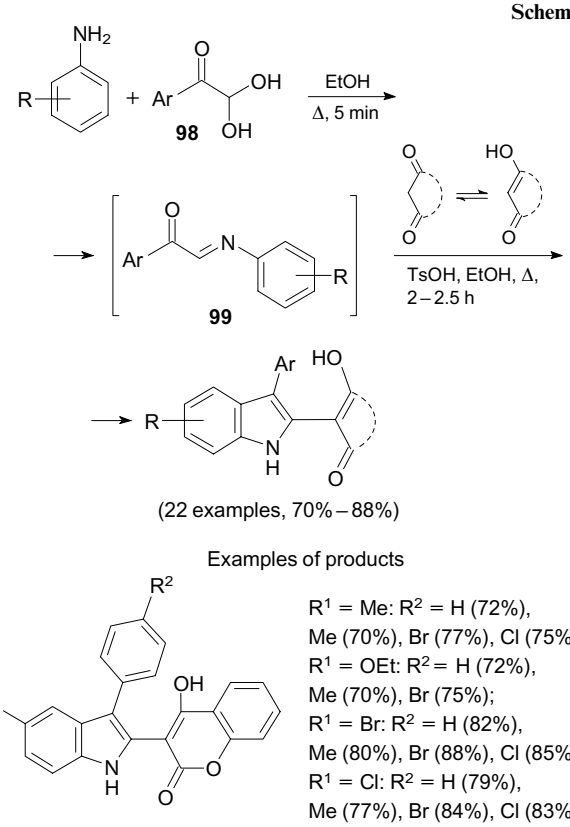
The simple and efficient synthesis of polyfunctionalized indoles, also involving C(3)–C(3a) bond formation,

Scheme 136



employs aryl glyoxal monohydrates **98**, which react with anilines to give α-ketoimines **99**.[197] The method represents a one-pot three-component reaction, including the primary reductive alkylation of these α-ketoimines with 1,3-dicarbonyl compounds and the subsequent TsOH-catalyzed cyclization (Scheme 137).

Scheme 137



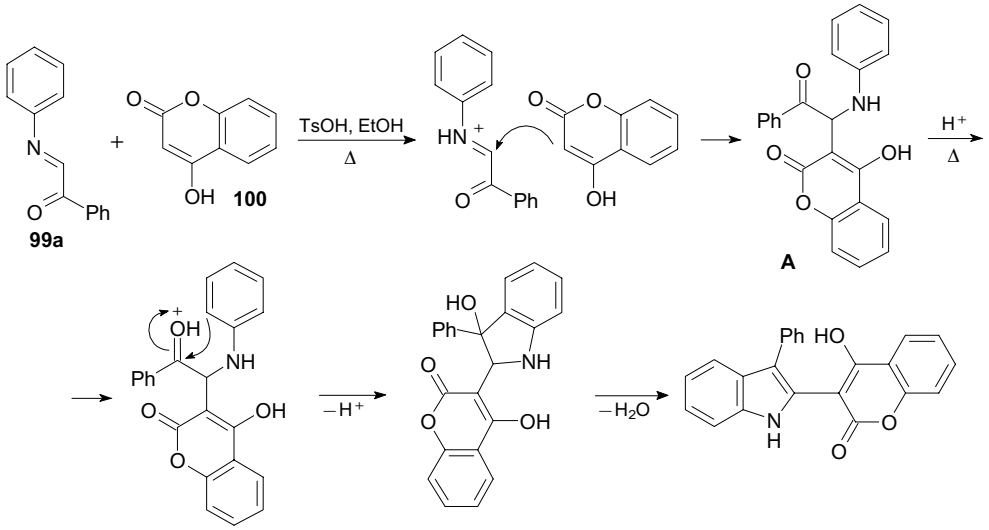
The reaction mechanism is presented in Scheme 138 in relation to formation of the indole with R = H, Ar = Ph using 4-hydroxycoumarin as the 1,3-dicarbonyl compound. First, imine **99a**, formed from aniline and phenyl glyoxal monohydrate, reacts with chromane-2,4-dione (4-hydroxycoumarin) (**100**) in the presence of TsOH giving rise to intermediate **A**. Then the acid-catalyzed intramolecular cyclization of intermediate **A** furnishes the final indole. This mechanism was confirmed by the step-by-step conduction of the reaction and isolation of intermediate **A**, which was then converted to indole.

A synthesis of polysubstituted indoles in 66%–90% yields by the copper-catalyzed domino reaction of 2-haloanilines with 1,3-dicarbonyl compounds has been reported.[198]

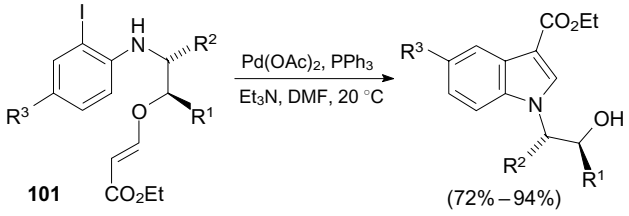
The intramolecular Heck reaction of NH-*o*-iodoanilines **101** containing an alkyl substituent at the N atom and a vinylogous carbonate group affords polyfunctionalized indoles (Scheme 139).[199]

A cascade reaction including the transformation of aromatic aldehydes to acyloins **102** on treatment with N-heterocyclic carbene (NHC) and subsequent reaction with anilines produces 2,3-diarylindoles. The process occurs without a solvent, and the method is distinguished by an easy experimental procedure, broad scope of application,

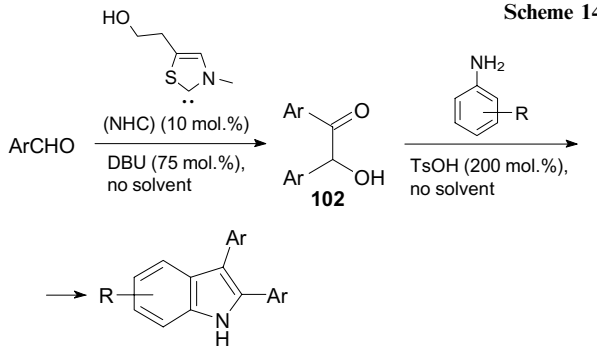
Scheme 138



Scheme 139



Scheme 140

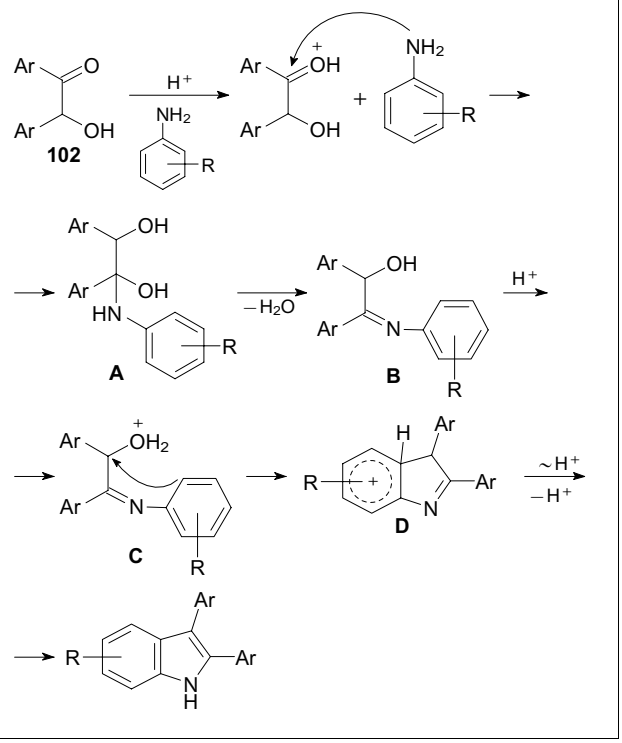


Ar	R (in the substrate)	Yield (%)
4-FC_6H_4	3-MeO	88
3-FC_6H_4	3-MeO	85
2-FC_6H_4	3-MeO	84
4-BrC_6H_4	3-MeO	65
4-ClC_6H_4	3-MeO	63
3-ClC_6H_4	3-MeO	78
3,4-$Cl_2C_6H_3$	3-MeO	71
3-$MeOC_6H_4$	3-MeO	74
2-Th	3-MeO	Traces
4-FC_6H_4	H	78
3-FC_6H_4	H	80
3,4-$Cl_2C_6H_3$	H	67
4-FC_6H_4	4-Cl	85
4-FC_6H_4	4-Me	83
4-FC_6H_4	4-MeO	80
Ph	H	78

high yields of products and environmental safety (Scheme 140).[200]

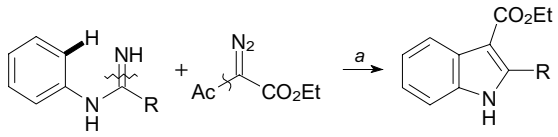
The putative mechanism of indole formation from acyloins and anilines (with C–C bond formation as the key point) is depicted in Scheme 141. The protonated acyloin reacts with anilines giving dihydroxy intermediate **A**, which loses water to give imine **B**. The protonated form of imine **C** undergoes intramolecular electrophilic attack to give 3*H*-indole **D**, which is aromatized by proton elimination to give the target indole.

Scheme 141



The synthesis of N-unsubstituted indoles proceeds *via* the Rh^{III}-catalyzed reaction of imide amides with α-diazo-β-ketoesters accompanied by C=N bond cleavage in the imide amide and the cleavage of the C–C(Acyl) bond of

Scheme 142



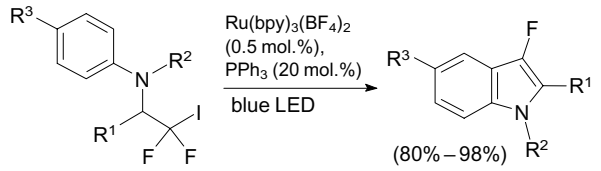
(*a*) $[RhCp^*Cl_2]_2$, CsOH, AcOH, DCE, $-AcNH_2$

diazo compounds (Scheme 142). The yields of the resulting 3-ethoxycarbonylindoles are in the range of 64%–93%.[201]

A similar outcome is attained in the reaction of α-diazo-β-ketoesters with *N*-nitrosoanilines.[202]

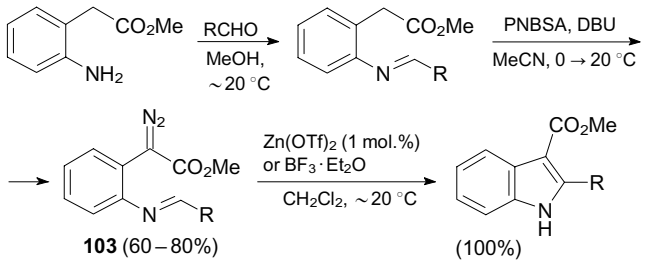
The photochemical synthesis of 3-fluoroindoles with the C(3)–C(3a) bond formation is carried out using *N*-alkylarylamines with the CF_2I group in the alkyl substituent at the nitrogen atom, a ruthenium catalyst, triphenylphosphine and irradiation with blue light (Scheme 143). The starting arylamines are easily formed upon iodofluorination of iminium salts.[203]

Scheme 143



An example of formation of the C(2)–C(3) bond is provided by the Lewis acid-catalyzed intramolecular cyclization of methyl phenyldiazoacetate **103** with the *ortho*-imino group, resulting in the formation of 2,3-disubstituted indoles in quantitative yields (Scheme 144).[204] The substrates are prepared from *o*-aminophenylacetate by the successive addition of aldehydes, *p*-nitrobenzenesulfonyl azide (PNBSA) and DBU.

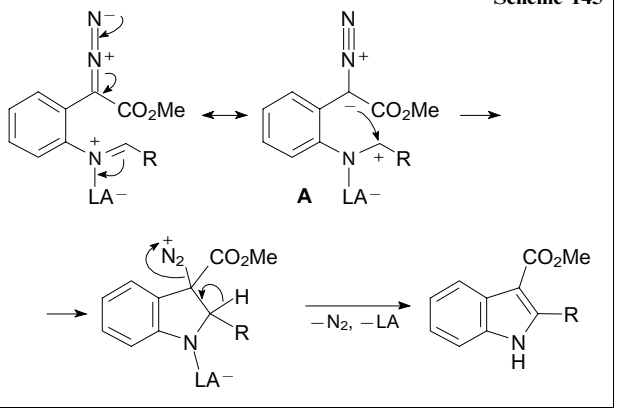
Scheme 144



R = Bu^t (here and below, the overall yield in relation to imine, 77%); PhCH=CH (71%), Ph (80%), 2,4-$(MeO)_2C_6H_3$ (73%), 4-MeC_6H_4 (78%), 4-ClC_6H_4 (65%), 2-Naph (70%), 2-Fu (60%)

The mechanism of cyclization consists of the imine activation with the Lewis acid towards the electrophilic attack by the carbon atom bonded to the diazo group to give the diazonium ionic intermediate **A** (Scheme 145). The extrusion of the nitrogen molecule and elimination of the Lewis acid give rise to indole. The driving force of this highly efficient catalytic process is the basicity difference between the imine and indole.

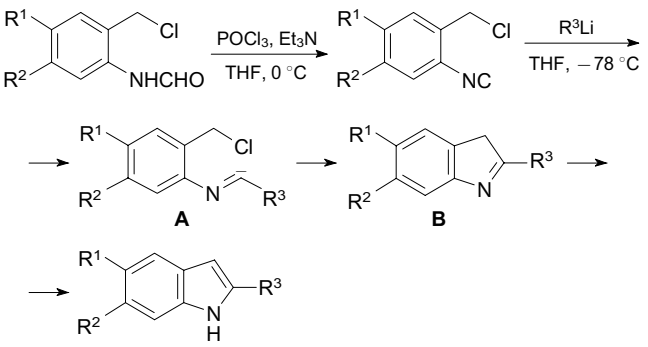
Scheme 145



Thus, a general efficient method was developed for the synthesis of functionalized indoles by Lewis acid-catalyzed intramolecular nucleophilic attack of phenyl diazoacetates by imines. The reaction proceeds under mild conditions and requires small amounts of commercially available, cheap Lewis acids. This approach can be useful for the preparation of the biologically active and natural indole derivatives.

One more example is the reaction of isonitriles, easily obtained from *N*-[2-(chloromethyl)phenyl]formamides, with organolithium compounds giving rise to 2-substituted indoles in satisfactory yields (Scheme 146).[205] It can be seen that the nature of substituents in the reactants has a slight influence on the efficiency of indole formation.

Scheme 146



R^1	R^2	R^3	Yield (%)
H	H	Ph	67
H	H	*p*-Tol	54
H	H	Bu^n	65
H	Cl	Ph	72
H	Cl	*o*-Tol	53
H	Cl	*m*-Tol	60
H	Cl	3-ClC_6H_4	63
H	Cl	4-ClC_6H_4	56
H	Cl	3-$MeOC_6H_4$	62
H	Cl	1-Naph	49
H	Cl	Bu^t	74
Me	H	Ph	57

The formation of 2-substituted indoles is induced of the attack of the organolithium reagent on the isonitrile carbon atom of 2-(chloromethyl)phenyl isocyanide; this affords intermediate imidoyl anion **A**. This intermediate is sub-

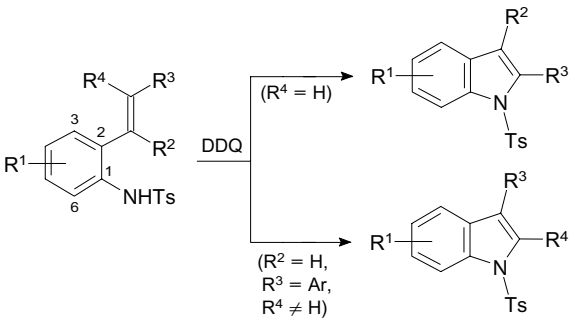
jected to the intramolecular S_N2 nucleophilic attack, being converted to indoline intermediate **B**, which isomerizes to indole during the workup of the reaction mixture or purification of the reaction products.

8.2. C – N bond formation

Most often, the C – N bond formation in the indole synthesis occurs with the participation of anilines with an appropriate functional group in the *ortho*-position to the amino group. An example of such groups is vinyl, which undergoes the C – H amination followed by oxidation to give a pyrrole ring.

Efficient intramolecular C – H amination in *N*-tosyl-2-alkenylanilines requiring no transition metal-based catalysts and using DDQ as the oxidant was utilized for the synthesis of a broad range of substituted indoles (Scheme 147).[206] The mechanism of this process includes the generation of a radical cation *via* single-electron transfer (SET) and migration steps in the intermediate phenonium ion. Apart from the absence of metal catalysts, benefits of the method include experimental simplicity and large diversity of suitable substrates.

Scheme 147

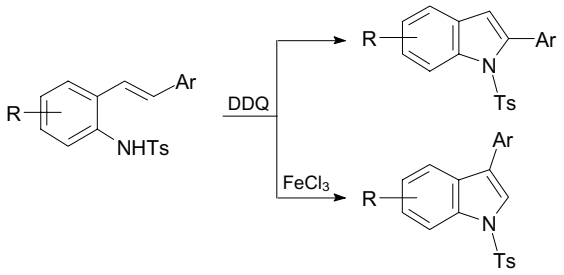


R^1 = H, Me, OMe, NO_2, Cl; R^2, R^3, R^4 = H, Alk, Ar, Het

The effect of substituents on the reaction efficiency was studied for quite a number of substrates with R^3 = H (Table 15). *N*-Tosylstyrylanilines (R^4 = Ar) are readily C – H-aminated yielding the corresponding indoles in good to high yields irrespective of the nature of the aryl substituent, with only minor electronic and/or steric requirements (rows 1 – 10 in Table 15). The *Z*-isomer also reacts to give the product in a yield of 76% (row 2). Alkenes with naphthyl and hetaryl substituents are also suitable for this reaction (rows 11, 12). It is noteworthy that the presence of the aryl substituent with the electron-donating 4-MeO group (row 6) results in a mixture of 2- and 3-substituted indoles in 5.6 : 1 ratio, which attests to occurrence of migration steps in the carbocation intermediate.

A highly regioselective synthesis of 3-arylindoles was performed starting from β-aryl-substituted 2-styrylanilines, with $FeCl_3$ and DDQ as the cheap and available catalyst and oxidant being used together (Scheme 148);[207] meanwhile the employment of DDQ alone resulted in the formation of isomeric 2-arylindoles.[163] Attention is attracted by the unusual joint effect of the components of this system on the 1,2-migration of the aryl group.

Scheme 148



The results of synthesis of 3-arylindoles by this strategy are summarized in Table 16. It can be seen that electron-withdrawing substituents in the aryl moiety (NO_2 and CF_3) completely suppress its migration from position 2 to 3. Conversely, the electronic properties of substituents in the indole benzene ring have virtually no effect on the regioselectivity of the reaction.

Two mechanisms, ionic and radical ones, were proposed for the oxidative cyclization.[207] According to the ionic mechanism (Scheme 149), intermediate **B** is generated upon deprotonation of compound **A**, which is formed initially upon Fe^{III} chelation by the sulfonamide and alkene groups of the substrate. This is followed by intramolecular formation of the C – N bond and intermolecular formation of the C – O bond between intermediate **B** and Fe^{III}-activated DDQ, thus giving intermediate **C**. The latter is likely

Table 15. Synthesis of indoles involving mono- and disubstituted alkenes [a] (see Scheme 147, R^4 = H).[206]

No.	R^1	R^2	R^3	Yield (%)	No.	R^1	R^2	R^3	Yield (%)
1	H	H	Ph	96	12	H	H	2-Th	86
2	H	H	Ph (*Z*)	76	13	H	H	H	50
3	H	H	4-MeC_6H_4	42	14	H	Ph	H	95
4	H	H	3-MeC_6H_4	84	15	5-OMe	H	Ph	57
5	H	H	2-MeC_6H_4	90	16	5-Me	H	Ph	6
6 [b]	H	H	4-$MeOC_6H_4$	99	17	5-Cl	H	Ph	87
7	H	H	3-$MeOC_6H_4$	74	18	5-NO_2	H	Ph	100
8	H	H	4-ClC_6H_4	86	19	4-OMe	H	Ph	100
9	H	H	4-$O_2NC_6H_4$	73	20	4-Me	H	Ph	20
10	H	H	3-$F_3CC_6H_4$	94	21	4-Cl	H	Ph	86
11	H	H	1-Naph	99	22	4-CF_3	H	Ph	99
					23	4-NO_2	H	Ph	96

[a] *E*-isomers were used ($MeCCl_3$ as the solvent), except for row 2, which refers to *Z*-isomer; [b] a mixture of 2- and 3-substituted indoles is formed.

Table 16. Regioselective synthesis of 3-arylindoles with the $FeCl_3$–DDQ system (DCE, 80 °C) (see Scheme 148).[207]

Ar	R	Yield (%) (see [a])
Ph	H	75 (89 : 11)
4-$MeOC_6H_4$	H	32 (100 : 0)
4-MeC_6H_4	H	57 (100 : 0)
3-MeC_6H_4	H	74 (89 : 11)
2-MeC_6H_4	H	97 (89 : 11)
1-Naph	H	59 (100 : 0)
4-$O_2NC_6H_4$	H	84 (0 : 100)
4-$F_3CC_6H_4$	H	92 (0 : 100)
4-MeC_6H_4	5-Me	48 (100 : 0)
2-MeC_6H_4	5-OMe	79 (96 : 4)
2-MeC_6H_4	5-Me	80 (91 : 9)
2-MeC_6H_4	5-Cl	91 (92 : 8)
2-MeC_6H_4	5-NO_2	100 (89 : 11)
2-MeC_6H_4	6-Me	67 (100 : 0)
2-MeC_6H_4	6-Cl	96 (91 : 9)
2-MeC_6H_4	6-NO_2	98 (90 : 10)
2-MeC_6H_4	7-OMe	67 (100 : 0)

[a] The value in parentheses is the ratio of 3- to 2-substituted indoles.

to undergo 1,2-aryl migration (pathway *a*) or to be converted *via* intermediate **D** (pathway *c*) to afford intermediate **E** and recover active Fe^{III} together with $DDQH^-$. The subsequent deprotonation of **E** induced by $DDQH^-$ affords the target 3-arylindole. 2-Arylindole may result from direct aromatization of intermediate **C** (pathway *b*) or be generated *via* intermediate **D** with the loss of a proton (pathway *c*). If the aryl substituent (Ar) is electron-deficient, one should expect suppression of the **C** → **E** conversion, resulting in the formation of only 2-substituted indoles in the presence of NO_2 or CF_3 groups in the aryl substituent.

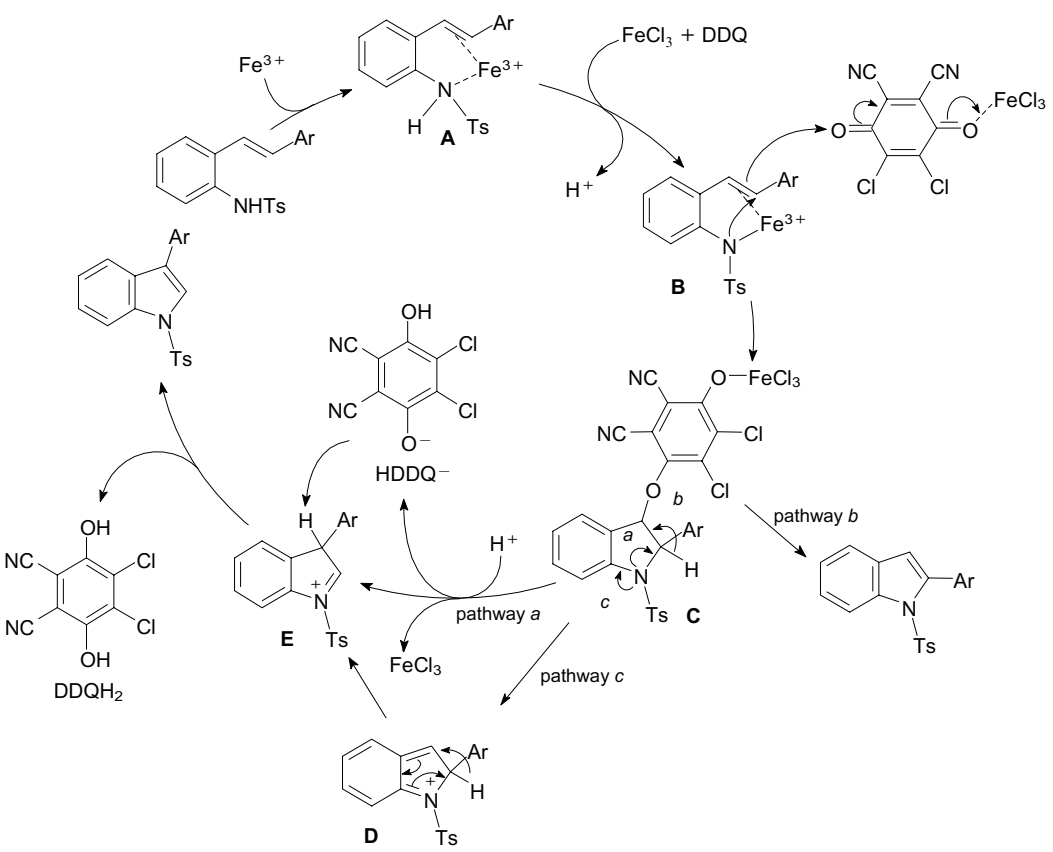
The alternative radical mechanism is presented in Scheme 150. Compound **A** is oxidized under the action of DDQ to give electrophilic Fe^{IV} species **F**, in which insertion into alkene takes place to generate structure **G**. The latter may undergo 1,2-migration of the aryl moiety (pathway *a*) or be converted *via* intermediate **D** (pathway *c*) to give intermediate **E** and Fe^{II}, the latter being oxidized again under the action of $HDDQ^{\bullet}$ to recover catalytically active Fe^{III}. As noted above, the subsequent deprotonation of intermediate **E** induced by $DDQH^-$ generates 3-substituted indole. In this pathway, $FeCl_3$ is involved in the single-electron transfer as the true reaction catalyst. However, the 1,2-migration of the aryl moiety in this oxidative cyclization can be catalyzed to some extent (less efficiently than by $FeCl_3$) by other Lewis acids [*e.g.*, $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, $ZnCl_2$ and $MgCl_2$], which cannot catalyze the oxidative coupling when exist in the higher oxidation state. Therefore, although strict proof for the mechanisms is missing, the ionic mechanism seems to be more general for the $FeCl_3$–DDQ system.

The palladium-catalyzed intramolecular formation of the C–N bond in *N*-[2-(1-arylvinyl)aryl]anilines affords 1,3-diarylindoles.[208]

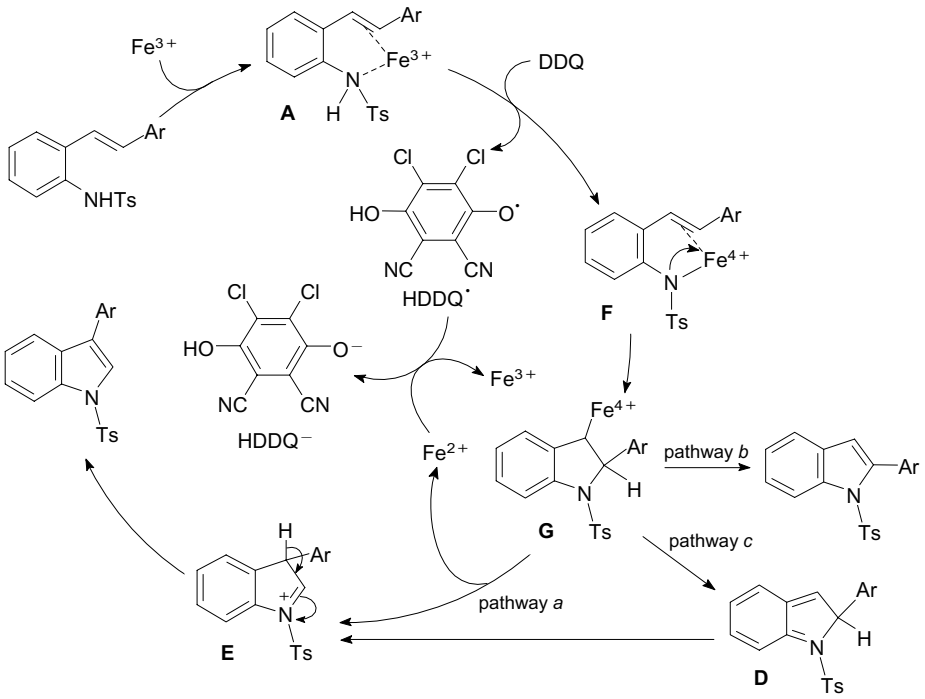
A new efficient synthesis of 2-substituted indoles from *N*-tosyl-2-vinylanilines involving the intramolecular amination of the C–H bond makes use of an organoselenium catalyst and *N*-fluorophenylsulfonimide (NFSI) as the oxidant (Scheme 151).[209] The reaction proceeds under mild conditions and the product yields reach 99%.

In the case of trisubstituted alkenes, the reaction proceeds in very high yields and is accompanied by migration

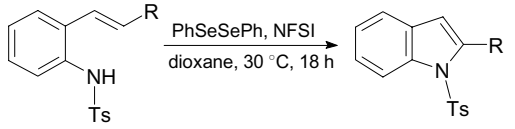
Scheme 149



Scheme 150



Scheme 151



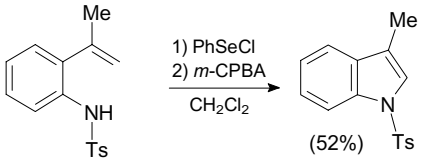
(14 examples, 31% – 99%)

R	Yield (%)	R	Yield (%)
Pr^n	70	C_6H_4F-4	99
$(CH_2)_2Ph$	84	C_6H_4OMe-4	97
$(CH_2)_4CN$	31	$C_6H_4NO_2$-4	98
CH_2OBz	64		

of substituents and formation of 2,3-disubstituted indoles; an example is presented in Scheme 152.[209]

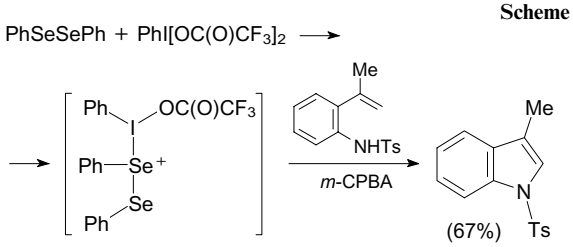
The reaction of phenylselenyl chloride with *N*-tosylisopropenylanilide with subsequent addition of *m*-chloroperbenzoic acid (*m*-CPBA) gives 3-methyl-*N*-tosylindole in a moderate yield (Scheme 153).[210]

Scheme 153

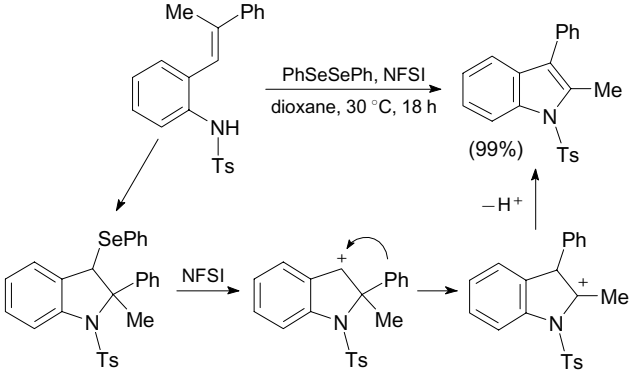


A similar intramolecular aminocyclization induced by diphenyl diselenide activated by the hypervalent iodine derivative $PhI[OC(O)CF_3]_2$ (PIFA) provides a somewhat higher yield of indole (67%); the indole synthesis occurs *via* selenoamination (Scheme 154).

Scheme 154



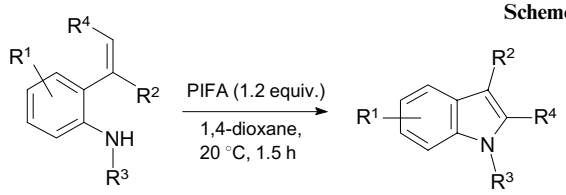
Scheme 152



The cyclization of 2-vinylanilines in the presence of PIFA provides indoles under mild conditions.[211] The target indoles are formed in moderate to good yields (Scheme 155).

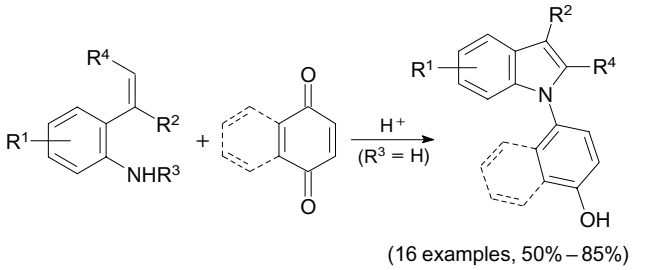
It can be seen that various substituents in the aromatic ring and at the nitrogen atom allow the preparation of the target indoles in 57% – 78% yields. Substrates with α,β-di- and α,α,β-trisubstituted alkenyl moieties do not form the expected indoles (the last two examples in Scheme 155).

Scheme 155



R^1	R^2	R^3	R^4	Yield (%)
H	Ph	H	H	78
Me	Ph	H	H	64
Pr^i	Ph	H	H	63
Bu^t	Ph	H	H	71
F	Ph	H	H	56
H	4-MeC_6H_4	H	H	73
H	Ph	Me	H	68
Br	4-FC_6H_4	H	H	63
Cl	4-ClC_6H_4	H	H	57
H	H	H	Ph	–
H	Ph	H	Me	Traces

Scheme 156



(16 examples, 50%–85%)

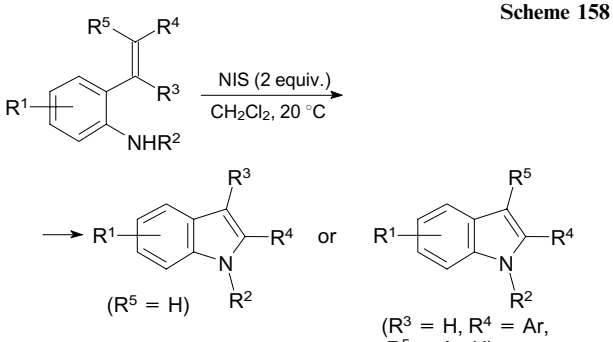
R^1	R^2	R^4	Yield (%)
	N-(4-hydroxyphenyl)indoles		
H	Me	H	50
6-Me	Ph	H	85
5-Bu^t	Ph	H	75
H	Ph	Me	76
	N-(8-hydroxynaphthyl)indole		
H	Ph	H	49

An attempt to perform this reaction of N-unsubstituted substrates (R^3 = H) using quinones as oxidants and trifluoroacetic acid [210] and other protic acids [212] as the catalysts resulted in the formation of indoles containing a *p*-hydroxyaryl substituent at the nitrogen atom (Scheme 156). The mechanism of these transformations is depicted in Scheme 157 in relation to the substrate with $R^1 = R^3 = R^4$ = H, R^2 = Ph.

First, 2-vinylaniline reacts with PIFA to give iodine-containing intermediate **A**; then intramolecular electrophilic cyclization takes place with the release of iodobenzene and trifluoroacetic acid, resulting in the formation of 3-phenylindole. Similarly, another process involves the reaction of the substrate with the protonated benzoquinone to give imine **B**. The intramolecular electrophilic addition in this imine generates intermediate **C**; the final reaction product, indole, is formed upon proton elimination.

A new simple and convenient synthesis of indoles from 2-alkenyl-*N*-tosylanilines is based on the cascade of reactions including the NIS-initiated C–N bond formation and aromatization (Scheme 158).[213] The method is character-

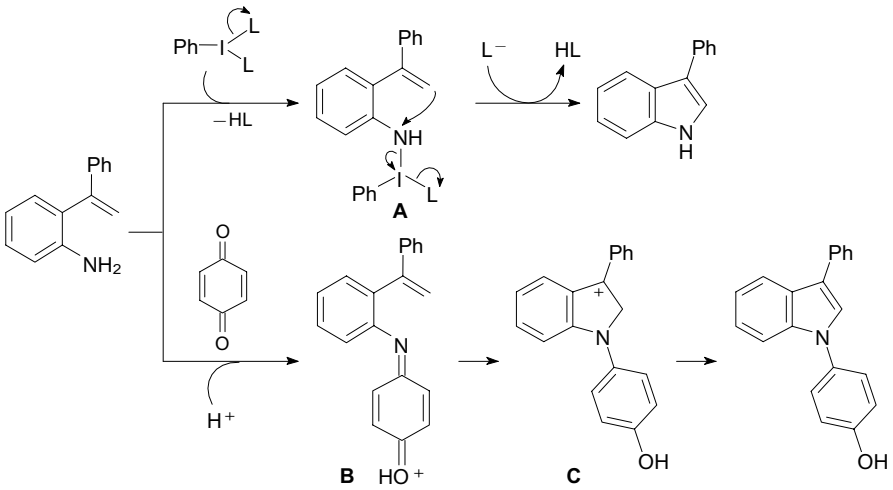
Scheme 158



R^2 = Ts, $R^3 = R^5$ = H

R^1	R^4	Yield (%)	R^1	R^4	Yield (%)
5-Me	Ph	92	5-Cl	Ph	86
6-Me	Ph	94	6-Cl	Ph	89
5-OMe	Ph	83	5-CF_3	Ph	78
5-F	Ph	82	5-CO_2Et	Ph	71
6-F	Ph	90	5-Me	4-MeC_6H_4	89
			5-CF_3	4-MeC_6H_4	95

Scheme 157



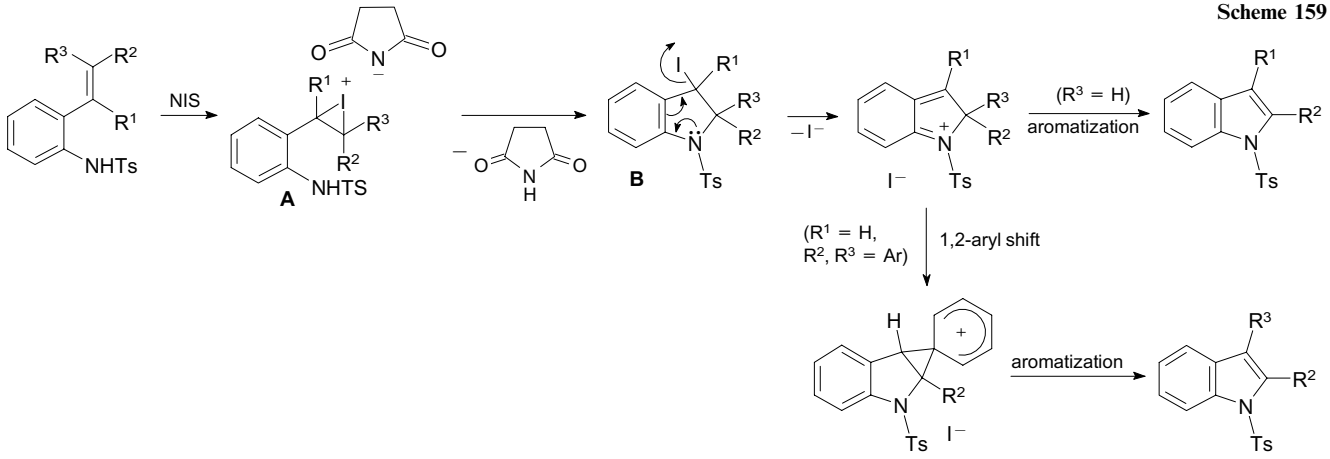
ized by ready accessibility of reactants, a simple experimental procedure, mild conditions, the absence of transition metal catalysts or any additives and applicability to a broad range of substrates; this allows the preparation of indoles with various substituents in both the benzene and pyrrole rings in high yields.

The putative mechanism of the NIS-initiated reaction cascade involves the formation of the C–N bond and aromatization. Initially, NIS reacts with alkene to give iodonium ion **A**, and the attack by the tosylamino group leads to generation of indoline **B** as a result of intramolecular amination (Scheme 159). The subsequent aromatization pathways depend on the substitution pattern in the alkenyl moiety. If $R^3 = H$, mere elimination of HI takes place; if $R^1 = H$ and R^2, $R^3 = Ar$, aromatization requires 1,2-aryl shift.

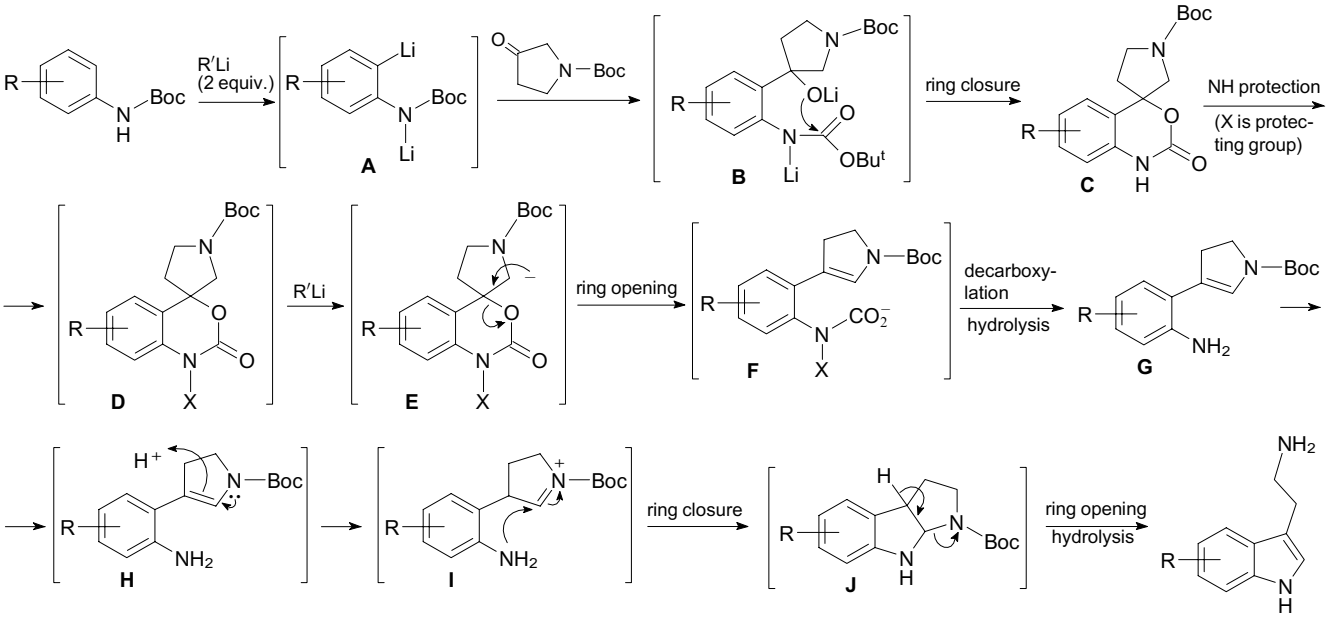
A convenient method developed for the synthesis of tryptamines from readily accessible *N*-Boc-anilines is based on the reaction cascade including the formation of spiro heterocycles, *ortho*-substituted anilines and, finally, tryptamines.[214] The complex cascade includes the C–N bond formation in a key step upon amination of the *ortho*-vinyl group (Scheme 160). *N*-Boc-aniline is converted to reactive dilithium intermediate **A**; the subsequent addition of *N*-Boc-pyrrolidin-3-one affords intermediate **B**, and the ring closure in **B** gives stable spirocyclic compound **C**. The introduction of an appropriate protecting group to the NH nitrogen atom enables the subsequent cascade of reactions initiated by regioselective deprotonation of intermediate **D** under the action of a strong base. Ring opening of deprotonated species **E** followed by hydrolysis and decarboxylation of intermediate **F** afford *ortho*-substituted anilines **G**, which are very promising, but insufficiently studied compounds. Finally, the third cascade initiated by acids gives tryptamines *via* intermediates **H**–**J**.

One example of application of *o*-allylanilines for indole synthesis is known from the literature. Thus, indolines and benzopyrrolizidinones are easily produced from *o*-allylphenyl azides and ethyl iodoacetate upon the radical addition–cyclization tandem reaction (Scheme 161).[215] The best results are obtained when triethylboron is used for initiation

Scheme 159

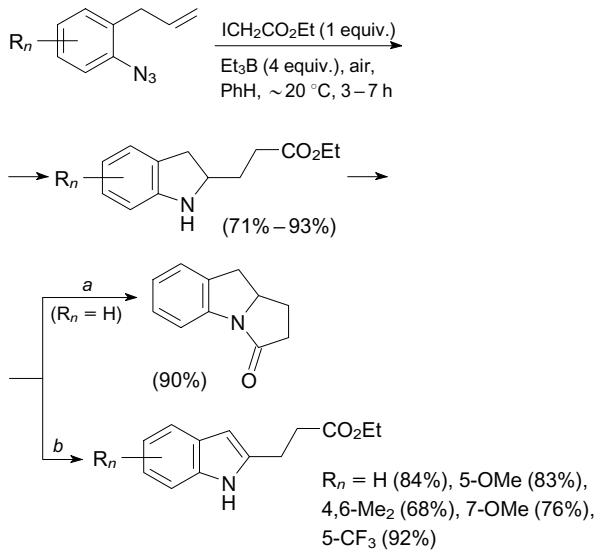


Scheme 160



R = H (76%), 4-OMe (84%), 5-Cl (80%), 5-F (71%), 5-Bu^t (66%), 5-CF_3 (68%), 6-CF_3 (77%), 5-Ph (87%) (10 examples, 41%–87%)

Scheme 161



(*a*) CSA (0.2 equiv.), PhMe, Δ; (*b*) MnO_2 (4 equiv), PhH, rt; CSA is camphorsulfonic acid

and maintenance of the process. Indolines are easily converted to indoles *via* oxidation with manganese dioxide.

The radical mechanism of this cascade is shown in Scheme 162.

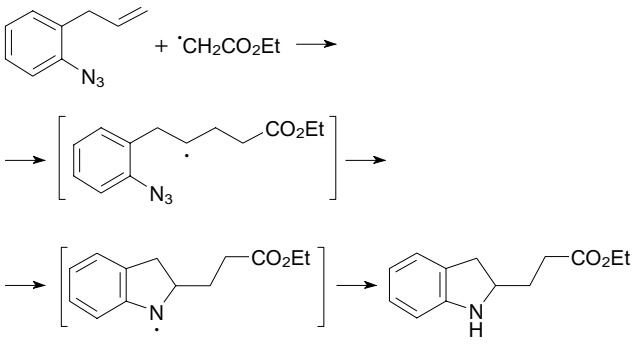
It is well known that *o*-aminobenzyl ketones spontaneously cyclize to indoles by any possible method for their preparation. An efficient method was developed for the synthesis of 3-substituted indoles from readily accessible nitrones and electron-deficient acetylenes;[216] the key step of the process was the formation of intermediate *o*-aminobenzyl ketones (Scheme 163). Study of the mechanism of 1,3-dipolar cycloaddition revealed an unusual (1 : 1) adduct **106**, formed upon the aza Cope rearrangement during the reaction between *N*-(9*H*-fluoren-9-ylidene)aniline oxide (**104**) and phenylbenzoylacetylene (**105a**).

The acid hydrolysis of imine **107** followed by *in situ* cyclization during the intramolecular condensation of amine with the carbonyl group leads to intermediate **109a** (*o*-aminobenzyl ketone). The reaction of compounds **104** and **105a** gives intermediate **107** in a good yield (64%) and isoxazoline **108** impurity (19%). Imine **107** is isolated from the reaction mixture by chromatography. On treatment with oxalic acid supported on silica gel, intermediate **107** undergoes hydrolysis and cyclization *in situ* to the final indole.

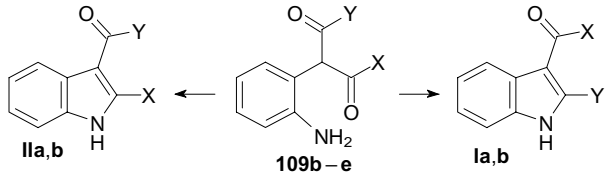
The general nature of the reaction was confirmed by using electron-deficient acetylenes **105b–e** (see Scheme 163). In all cases, indoles were formed in high yields. In the case of unsymmetrical intermediates **109b–e**, regioisomeric indoles should be formed (Scheme 164). The major reaction product can always be easily predicted considering the relative reactivities of the two carbonyl groups. For example, the reaction of nitrone **104** with acetylene **105c** yields indole **Ia** together with isoxazoline and fluorenone. In this case, the condensation of the more reactive acetyl group with the amine group predominates over the condensation of the less reactive benzoyl group. The reaction with acetylene **105e** proceeds in a similar way, with indole **Ib** being formed as the major reaction product. In the reaction of nitrone **104** with acetylenes **105b,d**, only indoles **IIa,b** are generated and no regioisomeric indoles are formed in detectable quantities. In the case of acetylenes **105a–c**, isoxazolines **108** are formed in minor quantities, while in the case of acetylenes **105d,e**, the corresponding indoles and fluorenone are the only isolable products.

The formation of the C(7a)–N bond is especially complicated, because it is associated with introduction of a

Scheme 162

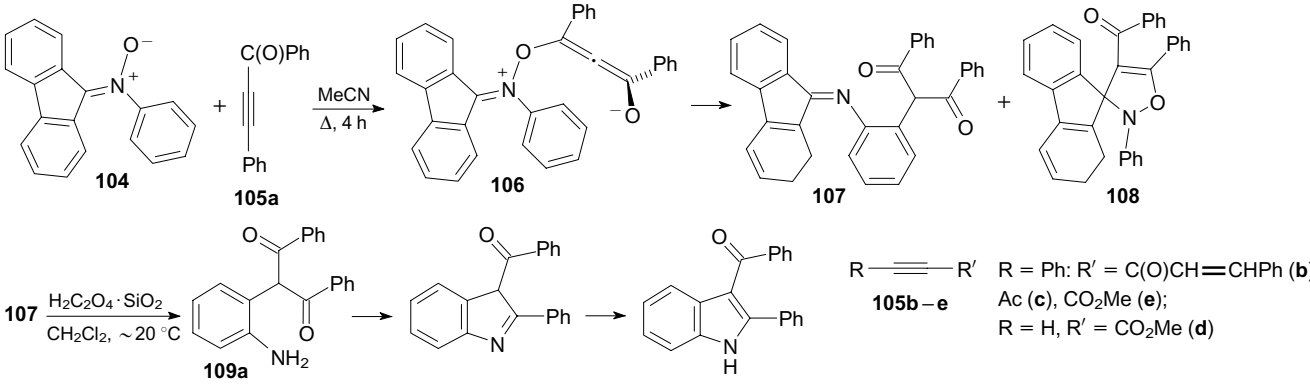


Scheme 164



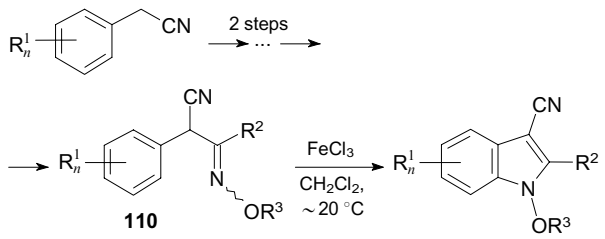
X = Ph, Y = CH=CHPh (**a**, 67%); X = Ph, Y = Me (**a**, 66%);
X = H, Y = OMe (**b**, 84%) X = Ph, Y = OH (**b**, 82%)

Scheme 163



nucleophilic nitrogen atom into the aromatic ring. In the past years, some approaches to solve this problem were reported in the literature. The functionalized derivatives of *N*-alkoxy-3-cyanoindoles are formed under very mild conditions in the $FeCl_3$-catalyzed intramolecular heterocyclization of 3-alkoxyimino-2-arylalkylnitriles **110** (Scheme 165).[217] The latter are prepared from benzyl cyanides in two steps representing reactions with $R^2C(O)OEt$ and R^3ONH_2. This method is suitable for the addition of the side chain N-function to the benzene ring in the final synthetic step, which enables functionalization of the benzene moiety in the early synthetic steps.

Scheme 165



$R^2 = R^3 = Me$: R^1_n = 4,6-Cl_2 (86%), 5,6-$(MeO)_2$ (74%), 4,5-benzo (72%); R^1_n = 6-Me, $R^2 = Pr^n$, R^3 = Me (60%), *etc.*

The putative mechanism of the process is shown in Scheme 166. The coordination of $FeCl_3$ to the cyano group followed by abstraction of the benzyl proton from intermediate **A** and then elimination of $FeCl_2$ from **B** should furnish stable N-radical **C**, which is stabilized by resonance with C-radical **D** and N-radical **E**. The second single-electron transfer catalyzed by $FeCl_3$ should convert N-radical **E** to nitrenium ion **F**. The electrophilic attack by the nitrenium ion on the benzene ring followed by the loss of proton may give the final indole (pathway *a*). Alternatively, the lone pair of nitrogen in resonance structure **G** can execute a nucleophilic attack on the cyclic carbocation, giving rise to intermediate **H**. Finally, aromatization of **H** as a result of proton abstraction should yield the final indole.

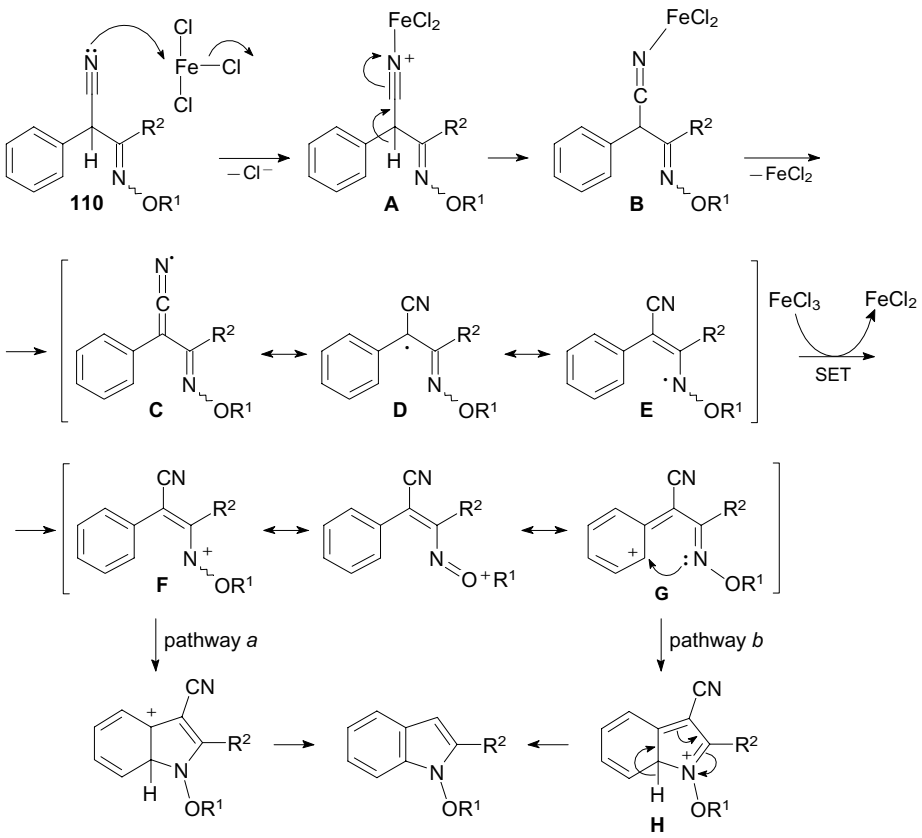
Unlike the described cyclodehydration of α-aryl ketone oximes to give indoles,[218] the proposed method converts oxime ethers to indoles without N–O bond cleavage.

One more version of C(7a)–N bond formation implies aromatization of the system in the final step after this bond has already formed. Using this strategy, 6-alkoxy-3-arylindoles were successfully synthesized from cyclohexane-1,3-dione enol ether **111** and β-nitrostyrenes (Scheme 167).[219] This strategy provides a convenient approach to various 6-alkoxyindoles.

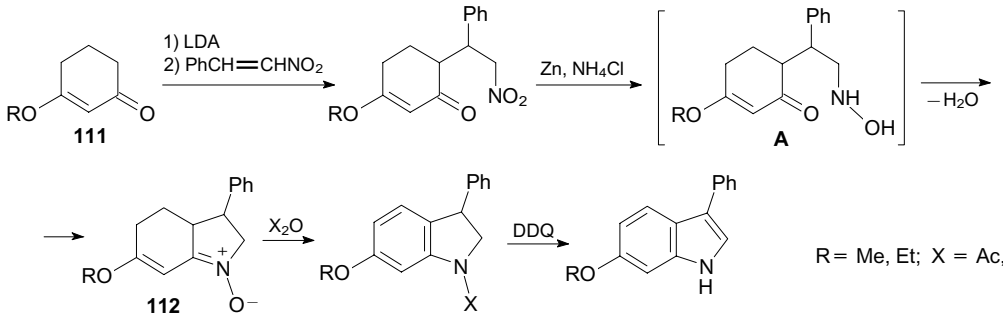
The aromatization step of nitrones to indolines is of particular interest. The aromatization of nitrone **112** is induced by dehydration under the action of acetic anhydride; the mechanism of nitrone conversion to the target indole is shown in Scheme 168.

Treatment of nitrone **112** with acetic anhydride induces N- and O-acylation of resonance form **112′**, which is accompanied by isomerization of the conjugated exocyclic azadiene **A** to endocyclic cyclohexadiene to give *N*-acylamine *N*-oxide *O*-acetate **B**. Intermediate **B** undergoes 1,4-elimination of AcOH, thus being converted to cross-

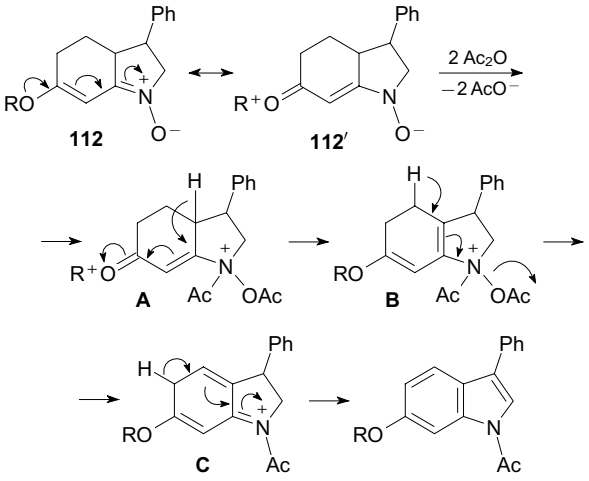
Scheme 166



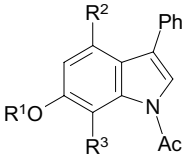
Scheme 167



Scheme 168



Structures 113



113a–d

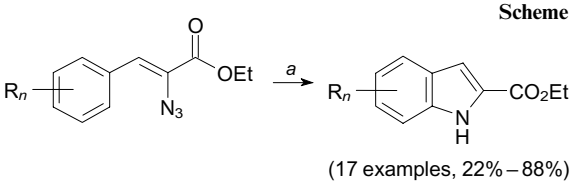
R^1 = Et, R^2 = Me, R^3 = H (**a**, 79%);
R^1 = Me: R^2 = Ph, R^3 = H (**b**, 82%),
R^2 = CO_2Me, R^3 = H (**c**, 72%),
R^2 = H, R^3 = Me (**d**, 75%)

conjugated acyliminium ion **C**, which immediately forms the aromatic ring of indole upon deprotonation.

This process was used to prepare a number of substituted 6-alkoxyindoles **113a–d** in good yields.

A reasonable pathway to the C(7a)–N bond formation is N-arylation of stabilized nitrenes (Scheme 169).[220] Cheap and commercially available zirconium(IV) chloride efficiently activates the formation of nitrenes from aryl azidoacrylates, and the subsequent cyclization results in the formation of substituted 2- alkoxycarbonylindoles in moderate yields. The reaction proceeds rapidly at low temperature and is applicable to a large number of diversified substrates.

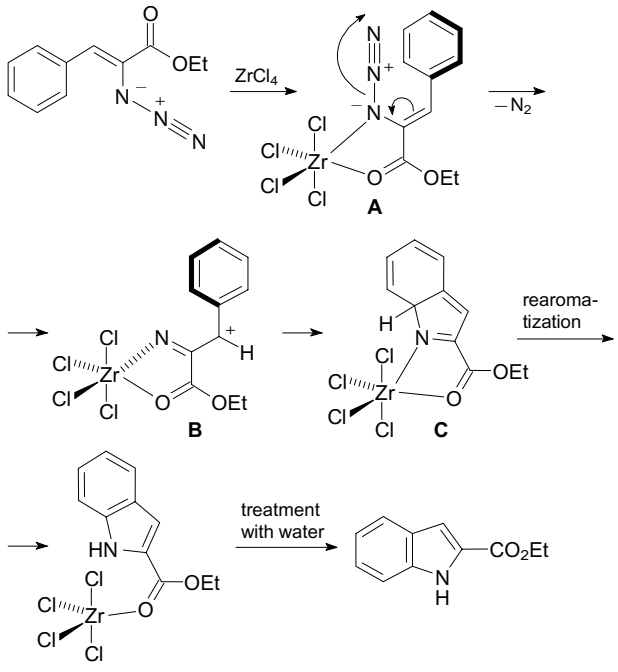
Scheme 169



(*a*) $ZrCl_4$ (4 equiv.), $AgNO_3$ (0.1 equiv.), DCE, 0 → 20 °C, 1–30 min; R_n = 4-Me (79%), 5,6-$(OMe)_2$ (88%), 6-Ph (44%), 6-NO_2 (22%), *etc.*

The putative mechanism of indole formation is depicted in Scheme 170. Owing to the high oxygen affinity, Zr^{IV} forms a stable metal–oxygen complex and is chelated by the nitrogen atom and the carbonyl group of the initial aryl azidoacrylate, thus forming, in the first step, six-coordinate zirconium complex **A**, which gives nitrene **B** upon extrusion of nitrogen. This is followed by intramolecular aromatic nucleophilic substitution, giving rise to cyclic intermediate **C**, which is aromatized and hydrolyzed to the desired indole on treatment with water.

Scheme 170

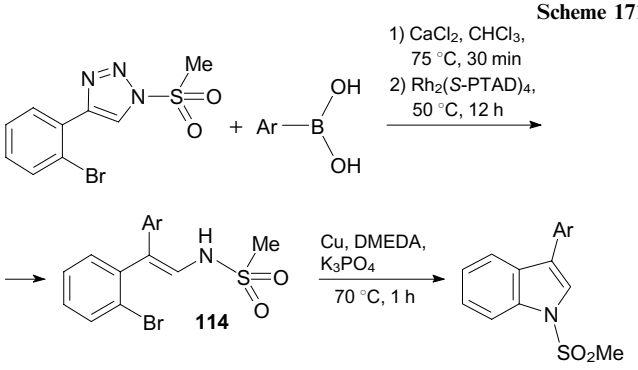


Iron(II) triflate was used as the catalyst in this process.[221]

The C(7a)–N bond is formed also in the copper-catalyzed intramolecular N-arylation of β-(2-bromophenyl)enamines **114**, which result from arylation of aza-vinyl carbenes generated *in situ* with arylboronic acids; the carbenes are generated from readily accessible 1-sulfonyl-1,2,3-triazoles with a Rh catalysis (Scheme 171).[222]

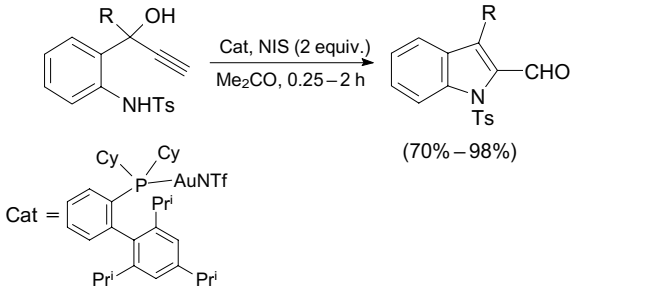
Another known method is the intramolecular cyclization of haloaryleneamines catalyzed by palladium in the presence of the RuPhos ligand {RuPhos is 2-[bis(2′,6′-diisopropoxybiphenyl)]dicyclohexylphosphine}[223] and ketene aminals.[224]

Scheme 171



Rh_2(*S*-PTAD)$_4$ is tetrakis[(*S*)-(+)-(1-adamantyl-1-phthalimidoacetato)-dirhodium(II), DMEDA is 1,2-dimethylethylenediamine

Scheme 172

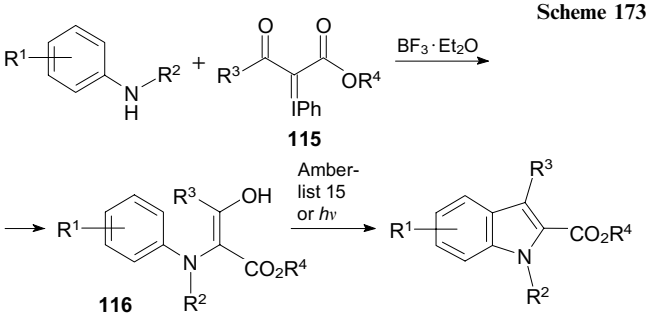


The synthesis of indole-2-carbaldehydes by gold-catalyzed cycloisomerization of 1-[(2-tosylamino)phenyl]prop-2-yn-1-ols with *N*-iodosuccinimide (NIS) has been reported (Scheme 172).[225]

8.3. Formation of both C–C and C–N bonds

Methods for indole synthesis with simultaneous formation of C–C and C–N bonds can be found in the literature (Scheme 173).[226] N-Substituted anilines react with phenyliodonium ylides **115** (obtained from 1,3-dicarbonyl compounds) in the presence of catalytic amounts of $BF_3 \cdot Et_2O$ to give the C–N bond in the coupling product **116**, which is the precursor of indoles. The C–C bond closure occurs in a one-pot thermal process according to the modified Bischler synthesis.[227]

Scheme 173

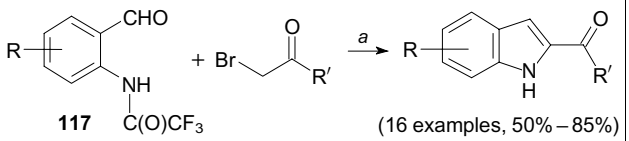


For thermal conditions:
$R^2 = R^3 = R^4 = Me$: R^1 = H (52%), 5-Cl (64%), 7-Cl (14%), 5-Br (75%), 5-Me (61%), 7-Me (19%); R^1 = 7-OMe, $R^2 = R^3$ = Me, R^4 = Et (14%); R^2 = Me, R^3 = Ph, R^4 = Et: R^1 = H (52%), 5-Cl (18%)
For photochemical conditions:
$R^2 = R^3 = R^4$ = Me: R^1 = H (94%), 5-Me (82%); $R^2 = R^4$ = Me, $R^3 = Pr^n$: R^1 = H (73%), 5-Me (64%); R^2 = Me, R^4 = Et: R^1 = 5-Cl, $R^3 = Pr^n$ (88%); R^1 = H, R^3 = Ph (80%); R^1 = 5-Cl, R^3 = Ph (88%)

Attention is attracted by the fact that the yields of indoles are much higher under photochemical conditions than under thermal conditions with the Amberlyst 15 catalyst.

A one-pot synthesis of functionalized 3-unsubstituted 2-aroylindoles is based on the reaction of readily accessible *N*-(2-formylphenyl)trifluoroacetamides **117** and α-bromoacetophenones or their heterocyclic analogues in the presence of K_2CO_3 and polyethylene glycol (PEG-400) as the solvent (Scheme 174).[228] The reaction results in the formation of C–N (alkylation of the nitrogen atom with α-bromoacetophenones) and C–C bonds (condensation at the formyl group).

Scheme 174

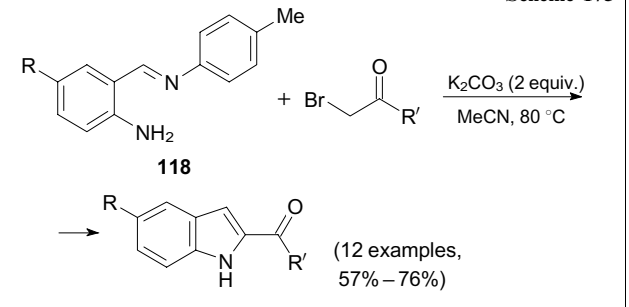


(*a*) K_2CO_3, PEG-400, 100 °C, 3 h;
R = H: R′ = 2-BrC_6H_4 (72%), 2-Fu (77%), 2-Th (85%), 4-$O_2NC_6H_4$ (50%), *etc.*

2-Aminobenzaldehydes were also used in another synthesis of functionalized indoles. Thus, they react with ethyl diazoacetate accompanied by [1,2]-aryl shift to give 3-ethoxycarbonylindoles.[229]

A synthesis of 3-unsubstituted 2-aroylindoles was developed using the reaction of α-bromo ketones with readily accessible *N*-(2-aminobenzylidene)-4-methylanilines **118**, which represent a stable cheap alternative to 2-aminobenzaldehydes (Scheme 175).[230] The reaction proceeds in a basic medium as a one-pot procedure and includes the cascade of the following reactions: N-alkylation (C–N bond formation), intramolecular nucleophilic cyclization (C–C bond formation) and elimination of toluidine (aromatization).

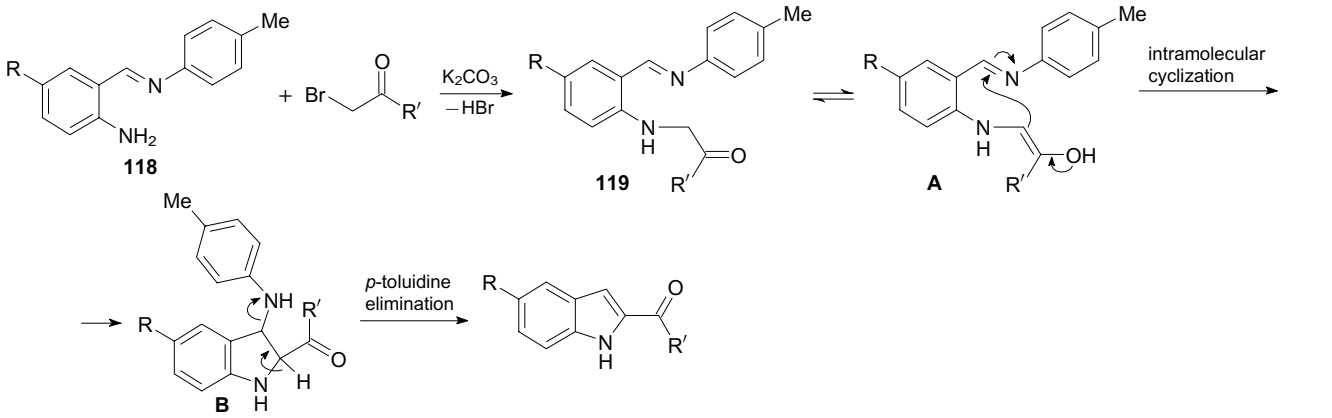
Scheme 175



R = H: R′ = Ph (74%), 4-MeC_6H_4 (70%), 4-$O_2NC_6H_4$ (60%), 3-Fu (69%); R = Br, R′ = 4-BrC_6H_4 (57%), *etc.*

The putative mechanism is shown in Scheme 176. The initial base-initiated alkylation of imine **118** with α-bromo ketone yields imine **119**, which undergoes intramolecular nucleophilic cyclization *via* enol form **A** to give intermediate **B**. The final elimination of *p*-toluidine from intermediate **B** occurs at room temperature. Elevated temperature is

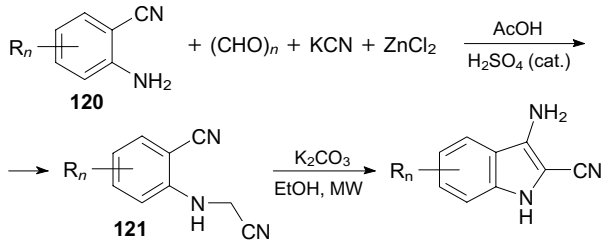
Scheme 176



needed in the cyclization step. Among the tested solvents, acetonitrile was found to be the solvent of choice owing to its aprotic polar nature, which favours the S_N2 reaction; the use of potassium carbonate, which is a weak base, facilitates the initial alkylation and the subsequent cyclization, thus promoting enolization.

Anthranilonitriles **120** react with paraformaldehyde, KCN and $ZnCl_2$ in acetic acid under acid catalysis (H_2SO_4) in a sealed tube at 55 °C to give the corresponding 2-(cyanomethylamino)benzonitriles **121**, which cyclize *via* the Thorpe–Ziegler reaction with K_2CO_3 in ethanol at room temperature, normal pressure and microwave irradiation in a sealed tube to give 3-aminoindole-2-carbonitriles (Scheme 177).[231]

Scheme 177

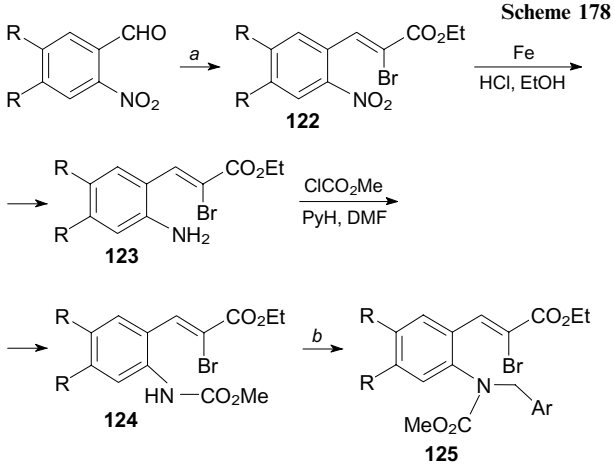


R_n = H (87%), 4,5-$(OMe)_2$ (88%), 5-NO_2 (87%)

Some substituted 2-cyanoindoles serve as important building blocks for the synthesis of heteroaromatic and biologically active compounds.[232, 233]

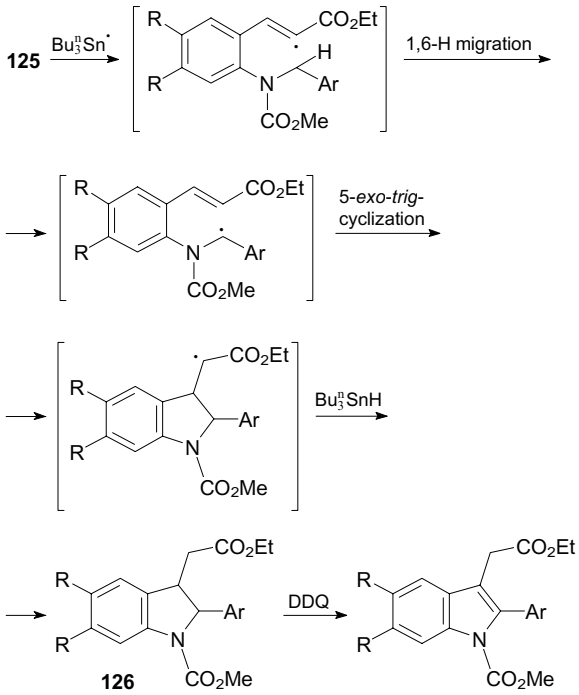
A direct method has been proposed for the synthesis of 2-(2-arylindol-3-yl)acetic acid derivatives and the corresponding indolines from 3-(2-aminophenyl)acrylates **123** using the tandem radical cyclization, involving 1,6-hydrogen atom transfer, and 5-*exo*-*trig*-cyclization (Schemes 178, 179).[234] This synthetic approach was first proposed by Parsons and co-workers.[235] Prediger *et al.*[234] used the following sequence of transformations for the synthesis of the target acrylates **123**. First, the Horner–Emmons reaction of accessible 2-nitrobenzaldehydes with *in situ* generated triethyl α-bromophosphonoacetate gives acrylates **122** in high yields. The subsequent reduction of acrylates **122** with iron powder in an acid affords anilines **123** (see Scheme 178). The attempts to protect the amino group of these anilines by the benzoyl or *tert*-butoxycarbonyl group were unsuccessful, whereas the introduction of the methoxycarbonyl protection (Moc) gave derivatives **124** in very high yields. The alkylation of these compounds with

Scheme 178



(*a*) $(EtO)_2P(O)CHBrCO_2Et$ (1.3 equiv.), NaH (1.4 equiv.), THF, 0 °C; (*b*) $ArCH_2Br$, LiOH, Bu^n_4NBr, DMF

Scheme 179



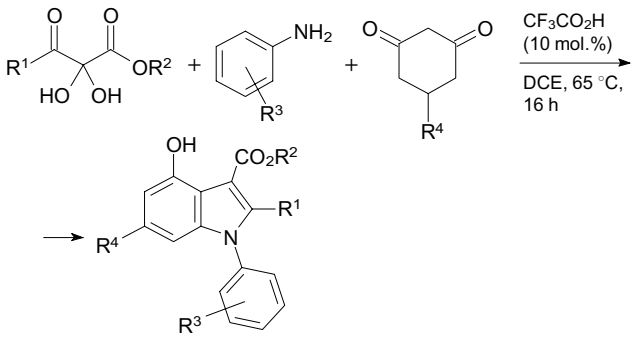
R = H: Ar = Ph (66%), 3-ClC_6H_4 (60%), 4-$MeOC_6H_4$ (61%), 3-$MeOC_6H_4$ (60%); 2-Naph (55%); R = MeO, Ar = Ph (69%)

$ArCH_2Br$ afforded substrates **125** required for preparing the target indoles.

Compounds **125** were subjected to the radical cyclization initiated by tri-n-butyltin hydride in a moderate concentration; the reaction was carried out under reflux in toluene (see Scheme 179). This gave indolines **126** in 25%–89% yields. Treating them with DDQ smoothly produced the target indoles in 55%–69% yields.

A three-component synthesis of substituted 4-hydroxyindoles from 2,3-diketoesters, anilines and cyclohexane-1,3-diones (Scheme 180),[236] also associated with C–C and C–N bond formation, has been developed. This atom-economical process has considerable benefits: it does not require the use of catalysts, it is suitable for the preparation of gram amounts and gives water as the only by-product.

Scheme 180



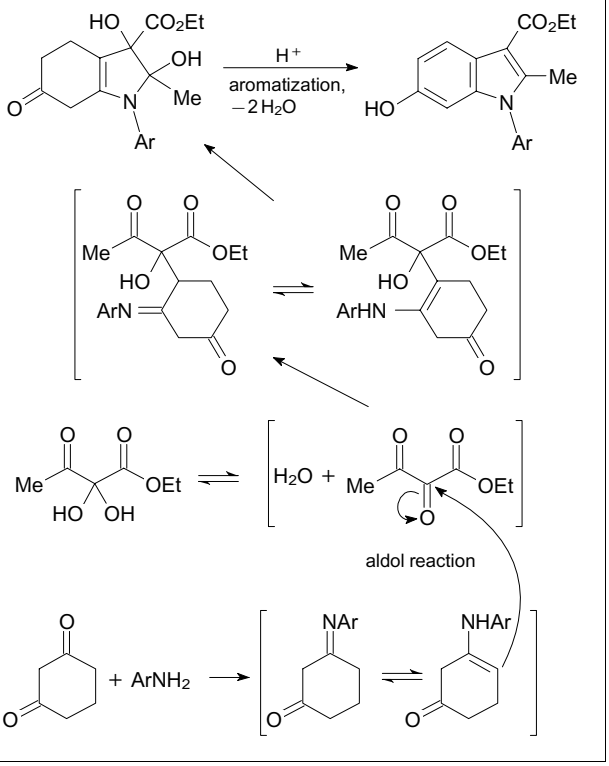
R^1	R^2	R^3	R^4	Yield (%)
Me	Bn	H	H	53
Ph	Et	H	H	58
Ph	Et	4-Br	H	71
Ph	Et	4-OMe	H	82
Ph	Et	4-CN	H	25
Ph	Bn	H	Ph	44

The cascade of reactions includes the formation of aldol from enamine generated *in situ* (C–C bond formation), cyclization (C–N bond formation) and aromatization (Scheme 181).

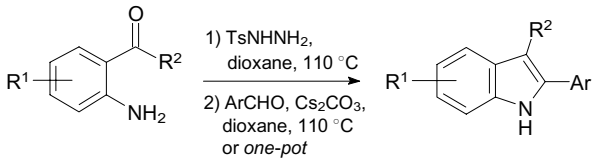
A simple and convenient cascade method has been developed for the synthesis of 2,3-disubstituted indoles from accessible reactants — 2-aminoaryl ketones, tosylhydrazine and aromatic aldehydes — under mild conditions using base catalysis (Scheme 182).[237]

The reaction mechanism includes the initial formation of 2-aminoaryl ketone tosylhydrazones, which are converted *in situ* to diazo intermediate **A** under the action of caesium carbonate (Scheme 183). The nucleophilic carbon atom of resonance structure **A′** attacks the electrophilic carbon atom of the carbonyl group to give intermediate **B** (formation of the C–C bond; marked in the scheme), which extrudes the N_2 molecule being converted to intermediate **C** (*o*-aminobenzyl ketone). The latter undergoes intramolecular cyclization to species **D** (C–N bond formation), which isomerizes to indole.

Scheme 181



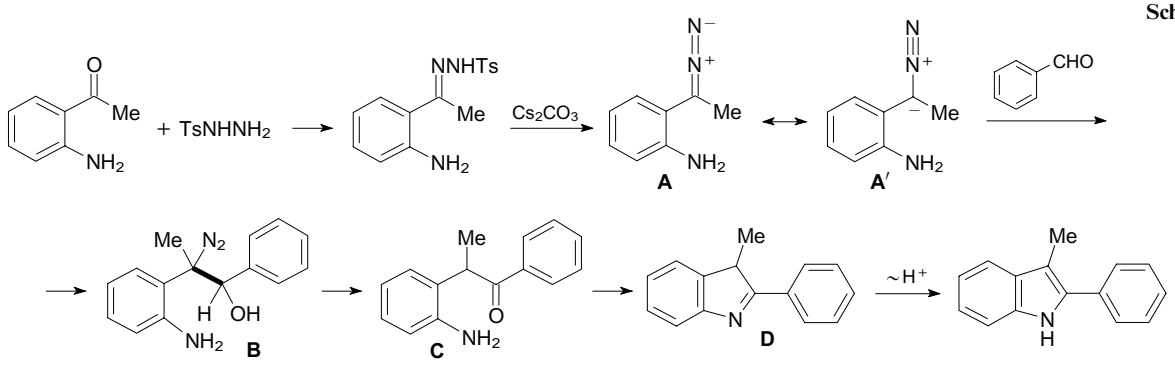
Scheme 182



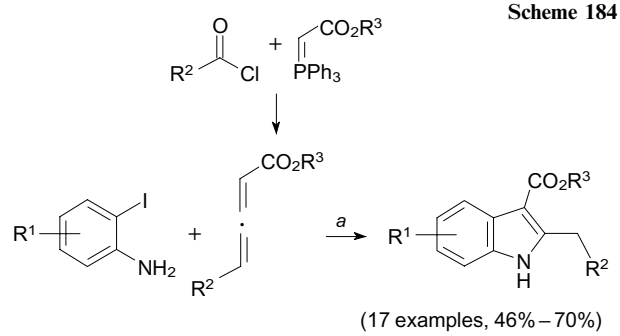
R^1 = H, R^2 = Me: Ar = Ph (45%), 4-MeC_6H_4 (50%), 4-$O_2NC_6H_4$ (60%); R^1 = R^2 = H, Ar = Ph (70%); R^2 = Me, Ar = Ph: R^1 = 5-Br (64%), 5-Ph (65%)

The one-pot reaction of acyl chlorides, Wittig reagents and *o*-iodoanilines includes the initial *in situ* formation of

Scheme 183



Scheme 184



(*a*) CuBr, L, K_2CO_3, dioxane–hexane, MS 4 Å, 120 °C;
L is 8-hydroxyquinoline

allenes, the Michael addition of iodoaniline, copper-catalyzed C–C coupling and tautomerization to indoles (Scheme 184).[238]

The reaction of 2-halobenzyl halides with α-aminonitriles catalyzed by Pd or Cu compounds results in the formation of 1,2-disubstituted indoles in moderate to high yields (up to 94%).[239] The oxidative intramolecular N-arylation of *N*-aryleneaminonitriles initiated by Pd and Cu or Pd and Ag catalytic systems affords *N*-aryl-2-substituted 3-cyanoindoles.[240]

Polysubstituted indoles can be synthesized in 60%–90% yields from aryl iodides and aminoacrylates by a Cu-catalyzed one-pot tandem process including the C–N bond formation upon the Ullmann reaction and intramolecular cross-coupling giving the C–C bond.[241]

3-Cyano-1*H*-indoles can be prepared by the reaction of 2-(2-bromophenyl)acetonitriles, aldehydes and aqueous ammonia. The process includes the aldol condensation, copper-catalyzed amination with ammonia as a mild source of nitrogen, cyclization and aromatization.[242] Regenerable solvents (ethyl acetate and 2-methyltetrahydrofuran) were proposed for the preparation of 2-ethoxycarbonylindoles from *o*-bromobenzaldehydes and *N*-acetylglycine ethyl ester in the presence of Cu catalysts.[243]

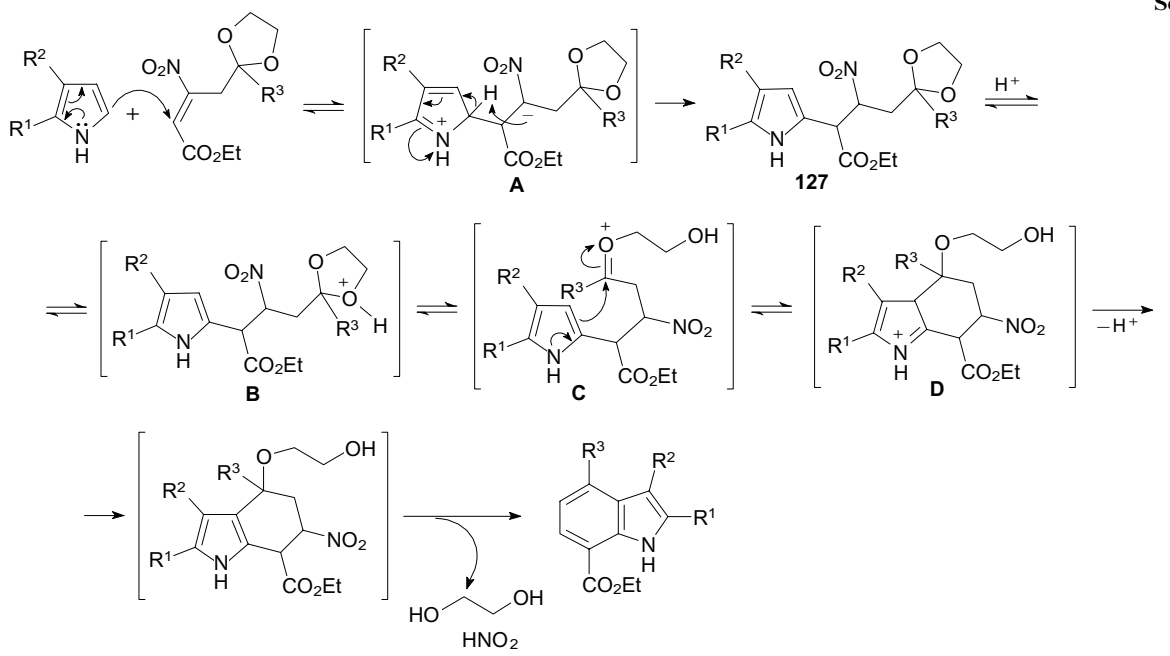
The reaction of π-deficient aryl 1,2-dihalides with geminal ene-diamines consists of two steps: aromatic nucleophilic substitution and Cu-catalyzed intramolecular N-arylation, ultimately yielding 2-aminoindole derivatives.[244]

9. Construction of the benzene ring

All the above-listed numerous methods for indole synthesis are based on annulation of a pyrrole ring to a benzene ring. The methods of benzene ring construction based on pyrrole derivatives are encountered much more rarely, probably, because of instability and poor accessibility of pyrrole derivatives. Nevertheless, new methods have appeared in the last decade. Most often, they are multistep processes including diverse chemical transformations.

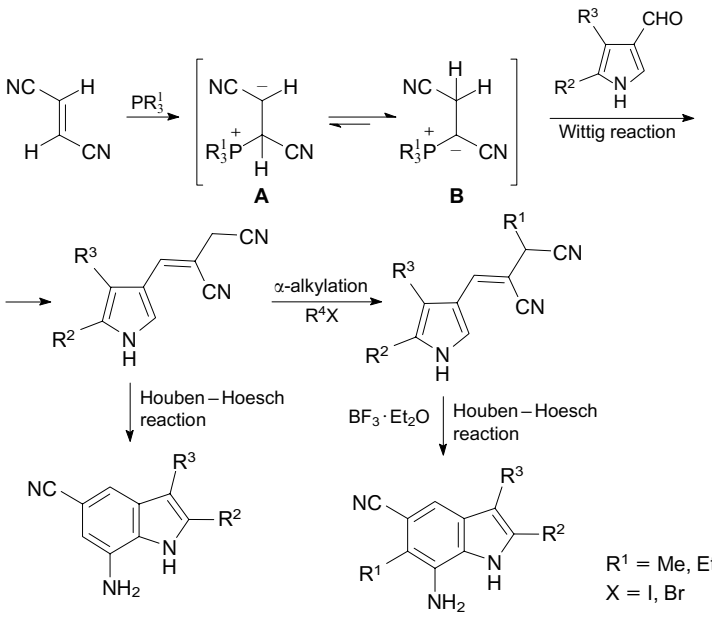
For example, the reaction of β-nitroacrylates with pyrroles without a solvents or a catalyst yields the Friedel–Crafts adduct, which gives polysubstituted indole *in situ*, in a one-pot process, on treatment with Amberlyst 15 in

Scheme 185



R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
Et	H	Me	60	H	H	H	68
H	H	Me	70	H	H	Ph	57
Et	H	Ph	59	H	H	$Ph(CH_2)_2$	74
$(CH_2)_4$		Et	61	H	4-NCC_6H_4	Me	58
$(CH_2)_4$		Ph	50	H	$Cl(CH_2)_4$	Me	53
H	H	Et	61				

Scheme 186



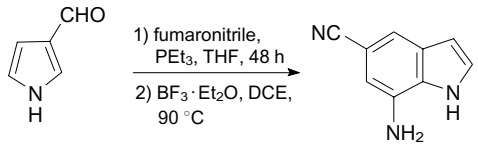
R^2	R^3	R^4	Yield (%)
H	H	H	91
Br	H	H	67
CO_2Et	H	H	62
Ph	H	H	87
H	Me	H	94
H	Et	H	92
H	Br	H	75
H	H	Me	88
H	H	Et	95
H	H	CH_2Ph	96
H	H	$CH_2CH{=}CH_2$	93
H	H	$CH_2C{\equiv}CH$	92
H	H	CH_2CO_2Et	72

2-propanol under reflux *via* annulation of the benzene ring.[245] The putative mechanism of indole formation is shown in Scheme 185. Initially, the Friedel – Crafts reaction between pyrrole and β-nitroacrylate gives adduct **127** *via* intermediate **A**. The subsequent *in situ* treatment of adduct **127** with Amberlyst 15 (cationic macromolecular ion exchange resin) affords protonated 1,3-dioxolane intermediate **B**, which is converted to the oxonium cation **C**. The subsequent Friedel – Crafts reaction generates bicyclic intermediate **D**, which loses ethylene glycol and nitrous acid molecules to be converted to the target indole.

A simple and efficient method has been developed for the transformation of pyrrole-2-carbaldehyde to 7-amino-5-cyanoindoles (Scheme 186).[246] The addition of phosphine to fumaronitrile is accompanied by prototropic rearrangement of the initially formed zwitter-ion **A** to thermodynamically more favourable phosphonium ylide **B**, which undergoes *in situ* Wittig olefination. The predominant *E*-alkene containing an allylic nitrile group readily undergoes the intramolecular Houben – Hoesch reaction in the presence of boron trifluoride etherate. The synthesis of 2,5- and 3,5-disubstituted 7-aminoindoles has been accomplished. In addition, the alkylation of the allylic nitrile group extends the range of synthesized models (preparation of various 6-R-indoles).

When the process is conducted as a one-pot procedure, the Wittig and Houben – Hoesch reactions can be combined; an example is presented in Scheme 187.[246]

Scheme 187



* * *

The review addresses the latest advances in the synthesis of indole derivatives. The presented strategies of the construction of the indole moiety are in line with the current level of development of organic chemistry and modern requirements imposed on new synthetic methods. The trend towards abandoning the use of toxic and expensive transition metals and organic ligands bound to them and switching to the green chemistry principles stimulates researchers to use new ways of activation of chemical processes, in particular, microwave radiation and visible light and to look for the ways to accomplish the reactions in aqueous media and to minimize the amounts of by-products. Undoubtedly, this attests to the rapid progress in the chemistry of a vitally important heterocycle such as indole. As applied to the classical methods for indole synthesis, their efficiency can be increased in accordance with modern requirements by switching to catalysis by iron salts and organocatalysis as opposed to platinum group transition metal and rare earth metal catalysis. In addition, considerable progress has been made in the development of atom-economical synthetic approaches to indole derivatives and in the use of continuous-flow reactors. All these achievements create real prospects for the design of new medicinal agents and materials in the series of indole derivatives.

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