REVIEW

Recent developments in indole ring synthesis—methodology and applications

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Received (in Cambridge, UK) 14th December 1999

Covering: 1994–1999. Previous review: *Contemp. Org. Synth.*, 1994, **1**, 145.

1 Introduction

Indole and its myriad derivatives continue to capture the attention of synthetic organic chemists, and a large number of original indole ring syntheses and applications of known methods to new problems in indole chemistry have been reported since the last review by this author in 1994.[1,2]

DOI: 10.1039/a909834h

Although most of the examples herein involve the indole ring system, a few novel syntheses of indolines, oxindoles,† isatins,† indoxyls,† carbazoles, and related ring systems are included in this review. The organization follows that adopted earlier,[1] albeit with the inclusion of several additional classifications. Unfortunately, space limitations preclude detailed discussions of these reactions.

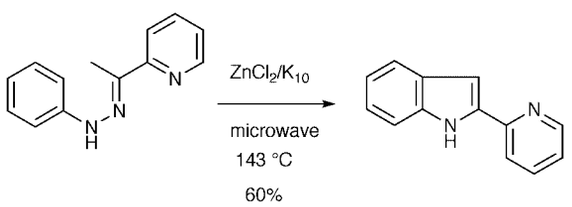
2 Sigmatropic rearrangements

2.1 Fischer indole synthesis

The venerable Fischer indole synthesis[3,4] has maintained its prominent role as a route to indoles, both new and old, and to the large-scale production of indole pharmaceutical intermediates. Furthermore, new methodologies have been developed and new mechanistic insights have been gleaned for the Fischer indole reaction since the last review.

2.1.1 Methodology

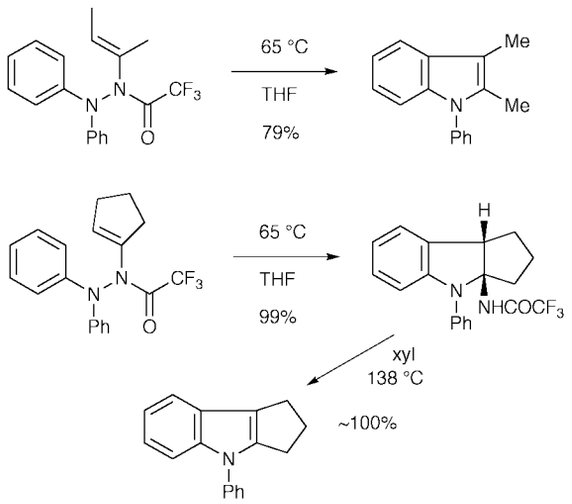
A one-pot synthesis of indoles from phenylhydrazine hydrochloride and ketones in acetic acid with microwave irradiation shows improvement in many cases (higher yields and reaction times of less than a minute) over the conventional thermal reaction conditions.[5,6] Microwave irradiation in a pressurized reactor with water as solvent (220 °C, 30 min) gives 2,3-dimethylindole in 67% yield from phenylhydrazine and butan-2-one.[7] The use of montmorillonite clay and $ZnCl_2$ under microwave conditions affords 2-(2-pyridyl)indoles at much lower temperatures and with solvent-free acid (Scheme 1).[8] The use of natural clays (bentonite) and infrared irradiation also furnishes indoles in high yield from phenylhydrazine and ketones.[9] For example, acetone affords 2-methylindole in 85% yield.



Scheme 1

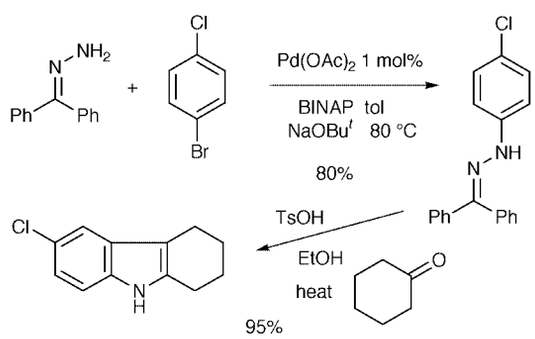
Zeolites in the Fischer indole synthesis are highly shape-selective catalysts and can reverse the normal regiochemistry seen with unsymmetrical ketones.[10,11] For example, 1-phenylbutan-2-one furnishes 2-benzyl-3-methylindole as the major isomer (83:17) in the presence of zeolite beta, whereas with no zeolite present this is the minor isomer and the major isomer is 2-ethyl-3-phenylindole (24:76).[10] The solid phase Fischer indole synthesis of spiroindolines using substituted arylhydrazines and polymer-bound piperidine-4-carbaldehyde has been reported.[12] This research group has described the preparation of 2-arylindoles on a solid support[13] and the synthesis of an indole combinatorial library using dendrimer supports.[14]

The thermal cyclization of *N*-trifluoroacetyl enehydrazines leads to indoles (or indolines) under relatively mild conditions (Scheme 2), apparently due to a lowering of the LUMO energy level of the trifluoroacetyl-substituted olefin that facilitates the [3,3]-sigmatropic rearrangement of the enehydrazine.[15] A new catalyst, diethylaluminium 2,2,6,6-tetramethylpiperidinide (DATMP), provides excellent regioselectivity in the Fischer indole synthesis of 2,3-dialkylindoles from unsymmetrical ketones *via* the isomeric (*Z*)- and (*E*)-hydrazones.[16] For example, (*E*)-*N*-methyl-*N*-phenylhydrazone of 5-methylheptan-3-one gives 3-*sec*-butyl-2-ethyl-1-methylindole as the only isolable product, and the *Z*-isomer yields 1,3-dimethyl-2-(2-methylbutyl)indole with high regioselectivity. The results are ascribed to regioselective enehydrazine formation by preferential proton abstraction by the hindered base DATMP.



Scheme 2

Buchwald and co-workers have utilized the palladium-catalyzed coupling of hydrazones with aryl bromides as an entry to *N*-arylhydrazones for use in the Fischer indolization.[17] Subsequent hydrolysis and trapping with a ketone under acidic conditions leads to indoles (Scheme 3).



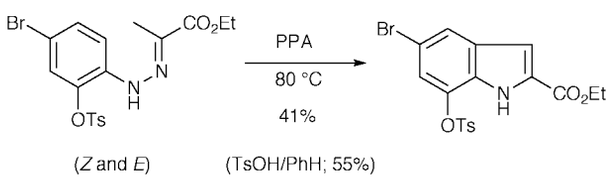
Scheme 3

2.1.2 Applications

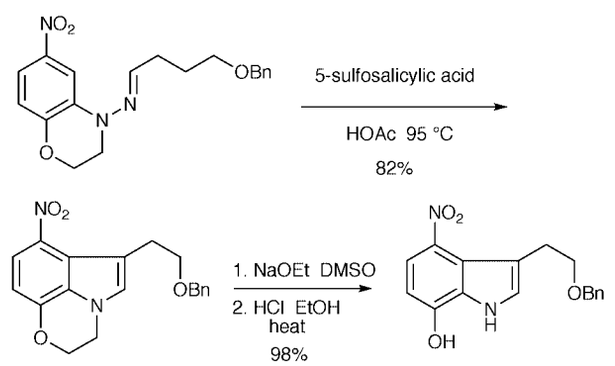
The Fischer indole synthesis was used extensively during the past five years to access a wide range of indoles and derivatives. Examples include 5-methoxy-2-phenylindole used in a photolysis study,[18] 2-ethoxycarbonyl-5-chloro-3-methylindole,[19] 2-ethoxycarbonyl-6-chloro-5-methoxy-3-methylindole,[19] and 2-ethoxycarbonyl-6-methoxy-3-methylindole[20] for use in indole alkaloid synthesis,[19,20] and 2-ethoxycarbonyl-7-methoxy-4-nitroindole,[21] 2-ethoxycarbonyl-7-methoxy-5-nitroindole,[21] 2-ethoxycarbonyl-4-methoxy-7-nitroindole,[21] and 2-ethoxycarbonyl-5-methoxy-7-nitroindole[22] for use in the synthesis of coenzyme PQQ (pyrroloquinoline quinone) analogs.[21,22] The last studies[19–22] utilize the Japp–Klingemann reaction of an aryl diazonium salt with α-substituted ethyl acetoacetate to obtain the requisite arylhydrazone. The Japp–Klingemann reaction was also used with malonates to prepare 2-alkoxycarbonyl-5-methoxyindoles on an industrial scale in high yields and with little waste.[23] The reaction of 1,5-di(*p*-tolyl)pentane-1,3,5-trione with 2 equivalents of phenylhydrazine gives rise to 3-[1-phenyl-5-(*p*-tolyl)pyrazol-3-yl]-2-(*p*-tolyl)indole,[24] and a bis-Fischer indolization of the bisphenylhydrazone of 2,5-dimethylcyclohexane-1,4-dione affords 5,11-dimethyl-6,12-dihydroindolo[3,2-*b*]carbazole in 80% yield.[25]

† The IUPAC name for oxindole is indolin-2-one, for indoxyl is indol-3-ol and for isatin is indoline-2,3-dione.

The synthesis of the marine alkaloid eudistomidin-A featured a Fischer indolization (Scheme 4); this paper describes the preparation of other 7-oxygenated indoles under conditions that preclude formation of the "abnormal" indole product.[26] Along these lines, Szczepankiewicz and Heathcock employed an oxygen bridge in a hydrazone to prevent the abnormal cyclization.[27] Subsequent elimination and hydrolysis to remove the oxyethylene bridge furnishes the desired 7-hydroxy-4-nitrotryptophanol derivative (Scheme 5). The loss of an *ortho*-oxygen substituent was encountered by White *et al.* in a synthesis of 6,7-dimethoxytryptophanol, to afford the abnormal product 4-methoxytryptophanol.[28]

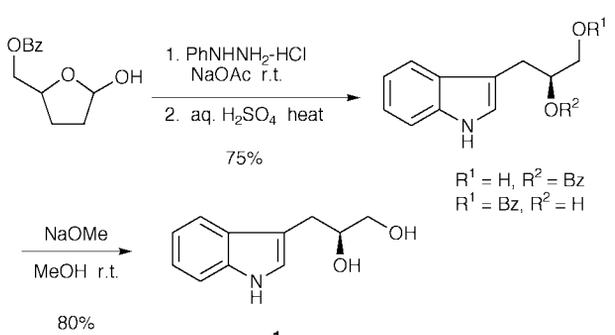


Scheme 4



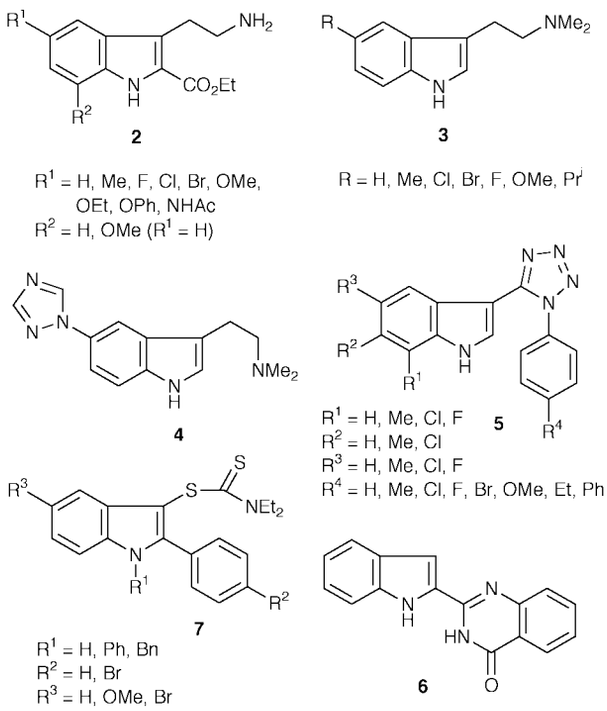
Scheme 5

The indole diol **1** was easily crafted from a 2,3-dideoxypentose as shown in Scheme 6.[29] The initial Fischer indole product was a mixture of two isomeric hydroxybenzoates resulting from benzoyl migration.



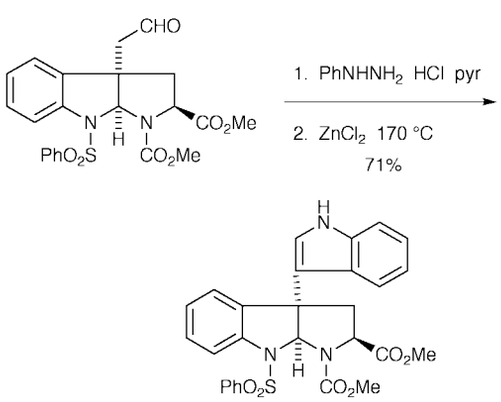
Scheme 6

Numerous tryptamine derivatives have been synthesized *via* the Fischer indole synthesis and some of these are listed below (**2**,[30] **3**,[31] **4**[32]). Other tryptamines have been prepared *via* Fischer indolization and studied as novel antagonists for the vascular 5-HT_{1B}-like receptors,[33,34] 5-HT_{1D} receptor agonists,[35] and melatonin analogs.[36] Several novel tetrazolylindoles **5** have also been prepared in this fashion,[37] and improvements in the Fischer indole step in the synthesis of the migraine treatment drug sumatriptan[38] and analogs[39] have been described. Both 2- and 3-indolylquinazolinones (*e.g.*, **6**) are readily prepared,[40] and the thiocarbamates **7** are available in good yields by a Fischer indolization.[41] An unexpected result in the Fischer indole protocol gives rise to 3-aminoindole-2-carboxylates,[42]



and phenylhydrazones of bulky ketones can lead to rearranged products.[43]

Several indole alkaloid studies feature a Fischer indole synthesis as a key step, including studies on uleine,[44] aspidospermidine,[45] and ibophyllidine alkaloids.[46] The core of the leptosin alkaloid family was nicely crafted by Crich *et al.* in this fashion (Scheme 7).[47]

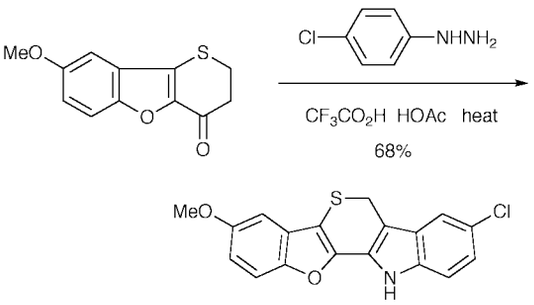


Scheme 7

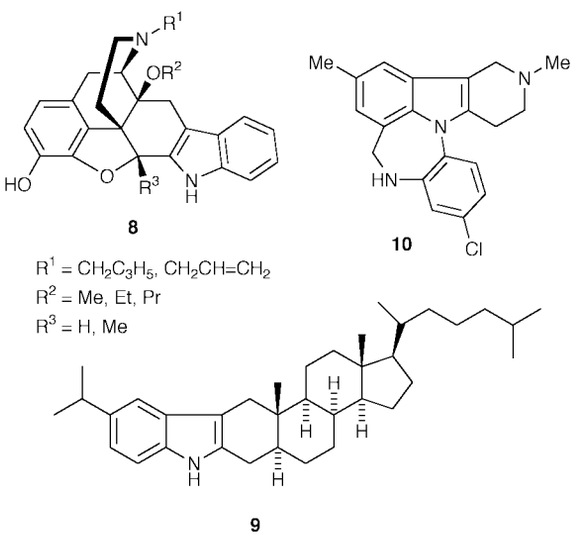
The Fischer indole synthesis has been used to construct numerous carbazoles including simple carbazole alkaloids,[48] rutaecarpine analogs,[49,50] biscarbazole alkaloids,[51] benzoindoloquinolines,[52] thiazolocarbazoles,[53] thienocarbazoles,[54] C-14 labelled benzocarbazole,[55] and other fused-indoles such as indolo[3,2-*d*]benzoazepinones.[56] Novel 14-alkoxyindolomorphinans (*e.g.*, **8**),[57] 4-hydroxy-3-methoxyindolomorphinans,[58] and indolinosteroids (*e.g.*, **9**)[59] are readily synthesized *via* Fischer indolization, as are pyridoindolobenzodiazepines (*e.g.*, **10**),[60] decal-1-one-derived indoles,[61] radiolabelled naltrindoles,[62] and 3-indolylcoumarins.[63]

A series of novel fused indoles has been synthesized using a Fischer indole strategy and one example is shown in Scheme 8.[64] Ketoindoles and ketobenzothiophenes were also employed in this reaction.

Spiroindolines and spiroindolenines are readily synthesized using the Fischer indolization and some examples include a crown-linked spiroindolenine used to make new signal transducers,[65] novel antipsychotics,[66] and MK-677, a growth



Scheme 8



8

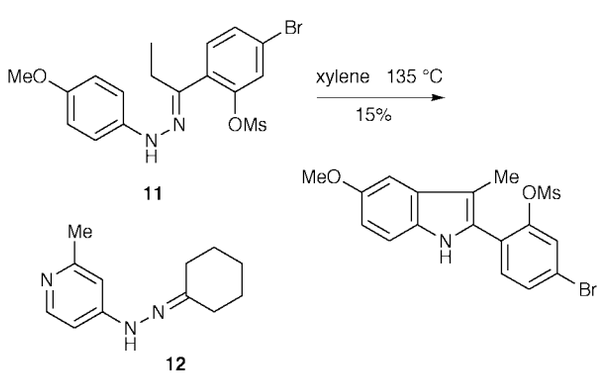
$R^1 = CH_2C_3H_5$, $CH_2CH{=}CH_2$
R^2 = Me, Et, Pr
R^3 = H, Me

10

9

hormone secretagogue.[67] The Fischer indole sequence has been used on an industrial scale in the manufacture of a pharmaceutical intermediate,[68] to prepare pyrrolo[2,3-*d*]pyrimidines as potential new thymidylate synthase inhibitors,[69,70] and to synthesize 7-bromo-2,3-bis(methoxycarbonyl)indole as a useful substrate for Pd-catalyzed cross coupling reactions leading to 7-substituted indoles.[71]

However, on rare occasions the Fischer indole synthesis proceeds poorly or even fails altogether. For example, hydrazone **11** afforded only 15% of the indole product, the major product (41%) being an indazole,[72] and hydrazone **12** failed to cyclize to an indole under all conditions tried[73] (Scheme 9), presumably because of the deactivating effect of the (protonated) pyridine ring.



11

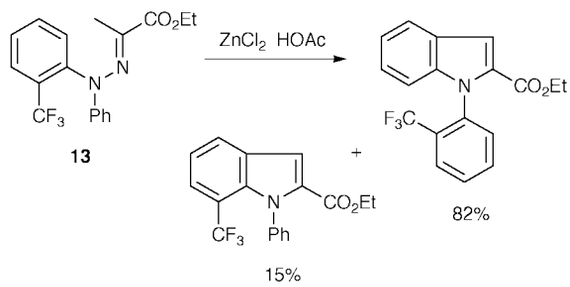
12

Scheme 9

2.1.3 Mechanism

An exhaustive study of the effects of acidity on the mechanism of the Fischer indole synthesis reveals that four different mechanistic variations can occur over the acidity range of $H_0 = +2$ to -8.[74] Thus, in strong acid the rate-determining step is deprotonation to form the enehydrazine, whereas under weakly acidic conditions tautomerization is sufficiently rapid that the [3,3]-sigmatropic rearrangement is rate determining. MNDO AM1 calculations have been performed on the conformations and sigmatropic rearrangement of the phenylhydrazones of ethyl pyruvate and acetaldehyde.[75,76]

Murakami and co-workers continue their investigations of the effects of *ortho*-substituents on the regiochemistry and rate of Fischer indole cyclizations,[77–79] and, as shown in Scheme 10, hydrazone **13** undergoes cyclization to the more electron-rich benzene ring.[77]



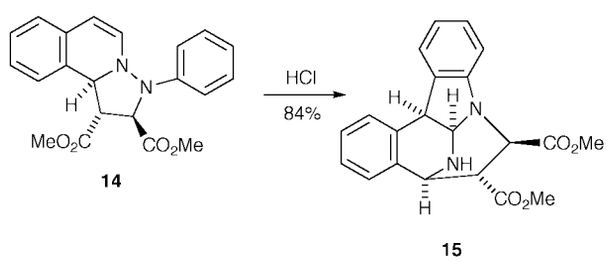
13

15%

82%

Scheme 10

A novel abnormal rearrangement has been uncovered in the Fischer indolization of the naltrexone *N*-methyl-*N*-(5,6,7,8-tetrahydro-1-naphthyl)hydrazone.[80] Huisgen and co-workers have found that under Fischer indole reaction conditions enehydrazine **14** stops at the 2-aminoindoline stage **15**, since indole formation is precluded by ring strain in the product (Scheme 11).[81,82]



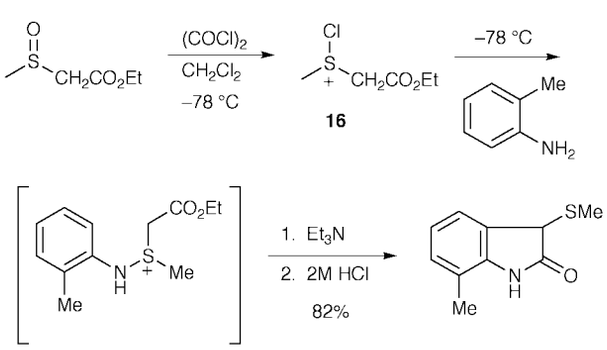
14

15

Scheme 11

2.2 Gassman indole synthesis

The beautiful Gassman indole-oxindole synthesis,[83–86] which features a [2,3]-sigmatropic rearrangement, has been used to prepare efficiently 6,7-dihydroxyoxindole, a subunit of the alkaloids paraherquamide A and marcfortine A.[87] Wright *et al.* have developed a modification of the Gassman synthesis that affords improved yields in many cases.[88] The key feature of the Wright modification is the facile formation of the chlorosulfonium salt **16**, which avoids elemental chlorine (Scheme 12).

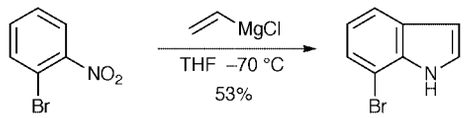


16

Scheme 12

2.3 Bartoli indole synthesis

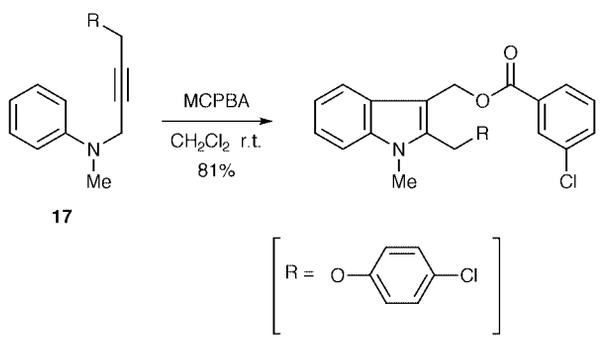
The fascinating Bartoli protocol,[89,90] which features a [3,3]-sigmatropic rearrangement analogous to the Fischer indolization step, has been used to prepare 7-bromo-4-ethylindole in a synthesis of (±)-*cis*-trikentrin A,[91] and 7-bromoindole (Scheme 13) in a synthesis of hippadine.[92]



Scheme 13

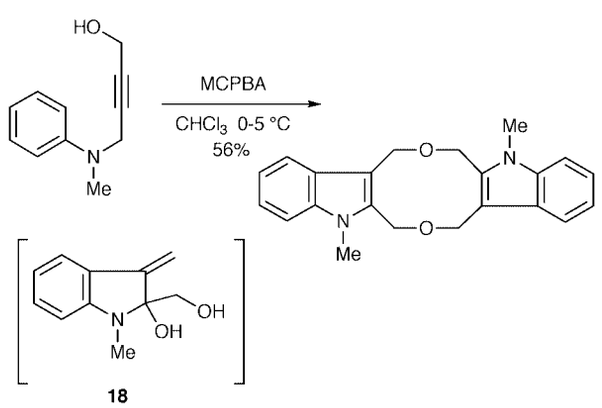
2.4 Thyagarajan indole synthesis

Thyagarajan and co-workers discovered a novel indole ring-forming reaction that involves sequential [2,3]- and [3,3]-sigmatropic rearrangements from the *N*-oxide of the aryl propynylamine **17** (Scheme 14).[93–95]



Scheme 14

In continuation of the original work, Majumdar *et al*. have extended this reaction to the preparation of cyclic bisethers containing two indole units (Scheme 15),[96,97] and to the synthesis of dihydro-1*H*-pyrano[3,2-*e*]indol-7-ones.[98] The mechanism is proposed to involve dimerization of 3-methyleneindoline **18**.

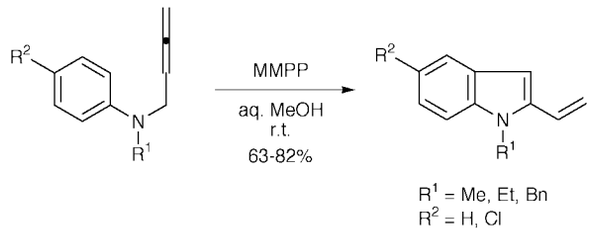


Scheme 15

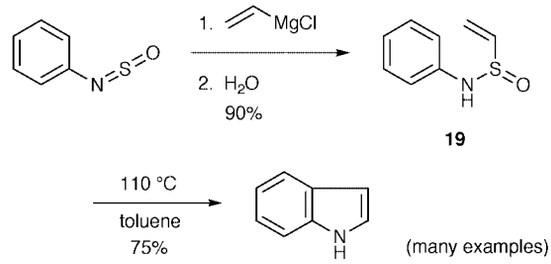
A related tandem [2,3]- and [3,3]-sigmatropic rearrangement sequence is suggested to explain the formation of *N*-alkyl-2-vinylindoles from *N*-alkyl-*N*-allenylmethylanilines upon exposure to MMPP (magnesium monoperoxyphthalate) (Scheme 16).[99]

2.5 Julia indole synthesis

Julia and co-workers have uncovered a novel indole ring synthesis involving the [3,3]-sigmatropic rearrangement of the readily available sulfinamides **19** (Scheme 17).[100] More recently, these workers have published a full account of their work including many examples of this clever reaction.[101]



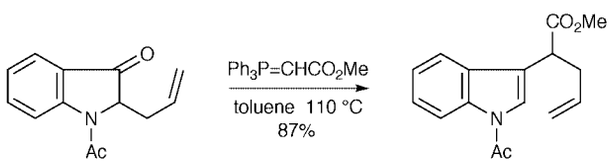
Scheme 16



Scheme 17

2.6 Miscellaneous sigmatropic rearrangements

A tandem Wittig–Cope reaction sequence converts a 2-allylindoxyl to the corresponding indole in excellent yield (Scheme 18).[102]



Scheme 18

3 Nucleophilic cyclization

3.1 Madelung indole synthesis

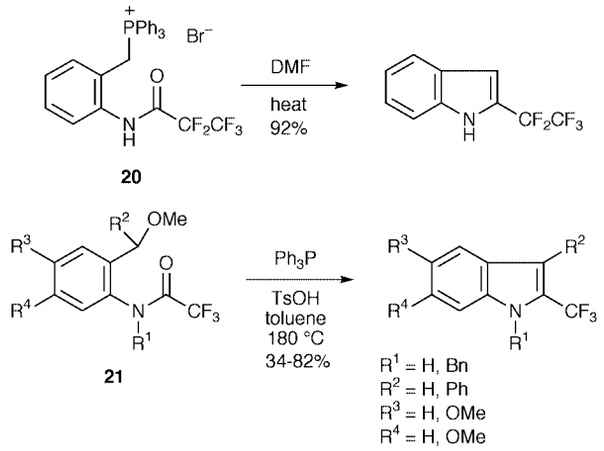
Although the classical Madelung synthesis is rarely employed nowadays, the excellent Houlihan modification,[103] which utilizes BuLi or LDA as bases under milder conditions than the original Madelung harsh conditions, has been extended in several ways. For example, benzylphosphonium salts such as **20** undergo facile cyclization to indoles under thermal conditions (Scheme 19).[104,105] The phosphonium salt can be generated *in situ* from the corresponding benzyl methyl ether **21**. The reaction is especially valuable for the synthesis of 2-perfluoroalkylindoles, although the yields are quite variable. The base-catalyzed version of this reaction has been adapted to solid phase synthesis.[106]

A Madelung–Houlihan variation in which an intermediate dianion derived from pyridine **22** is quenched with amides to yield azaindoles has been described (Scheme 20).[107] This reaction, which was first reported by Clark *et al.*,[108] has been utilized in a synthesis of novel pyrano[2,3-*e*]indoles as potential new dopaminergic agents.[109]

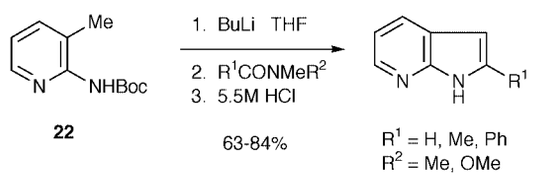
An aza-Wittig reaction of iminophosphoranes **23** with acyl cyanides leads to a novel indole synthesis (Scheme 21).[110] Moreover, quenching **23** with phenyl isocyanate yields carbodiimides which cyclize to 2-anilinoindoles with base.[110] These methods are excellent for the preparation of 2-aryl-3-(arylsulfonyl)indoles and 2-anilino-3-(arylsulfonyl)indoles.

Cyclization of phenylacetate imides such as **24** occurs readily under the influence of base (Scheme 22).[111]

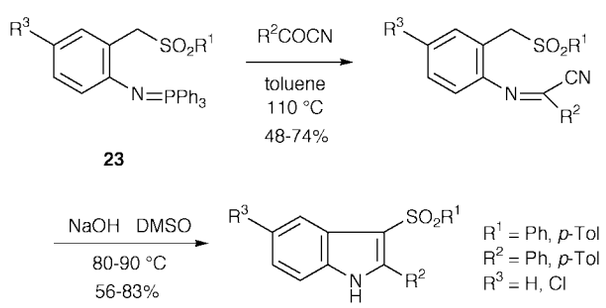
An interesting attempt to cyclize the imines derived from trifluoromethylaryl ketones and *o*-toluidines with lithium amides to indoles was not successful, yielding only amidines.[112]



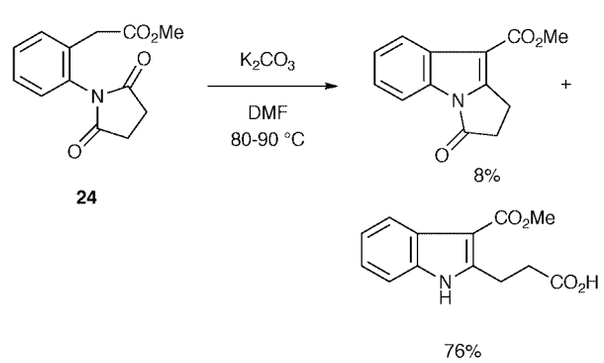
Scheme 19



Scheme 20



Scheme 21



Scheme 22

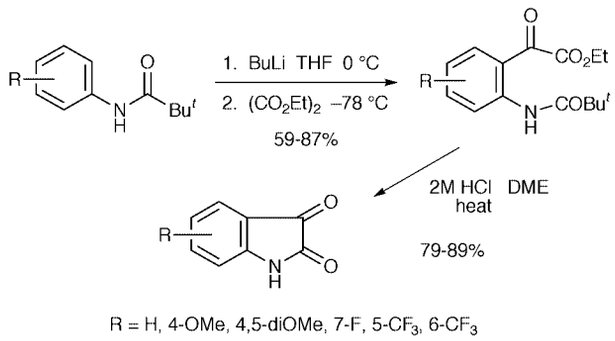
3.2 Schmid indole synthesis

No new examples were uncovered since the last review.

3.3 Wender indole synthesis

The Wender indole synthesis,[113] which involves the *ortho*-lithiation of *N*-phenylamides followed by reaction of the resulting dianion with α-haloketones and subsequent ring closure and dehydration, has been extended to a convenient synthesis of isatins by quenching with diethyl pyruvate (Scheme 23).[114]

A related isatin synthesis has been described by Smith and co-workers[115] that involves the carbonylation of the dianion derived from *N′*-(2-bromoaryl)-*N*,*N*-dimethylureas. The key



Scheme 23

intermediate is an acyllithium species which cyclizes onto the urea carbonyl group. This lithiation–carbonylation strategy was adapted to the synthesis of 3-hydroxyoxindoles by the lithiation of *N*-pivaloylanilines.[116] Smith and co-workers have also employed the original Wender indole synthesis to the synthesis of *N*-dimethylurea-protected indoles involving the dilithiation of *N′*-phenyl-*N*,*N*-dimethylurea.[117]

3.4 Couture indole synthesis

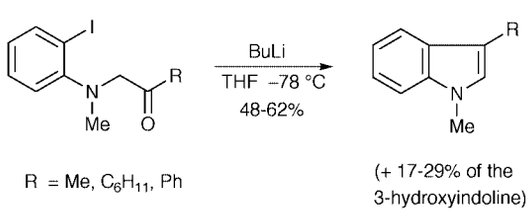
No new examples were reported since the last review.

3.5 Smith indole synthesis

The Smith indole synthesis,[118] which involves dilithiation of *N*-trimethylsilyl-*o*-toluidine and subsequent reaction with a non-enolizable ester to afford the 2-substituted indole, has been used to synthesize 2-trifluoromethylindole in 47% yield by quenching the above mentioned dianion with ethyl trifluoroacetate.[119]

3.6 Kihara indole synthesis

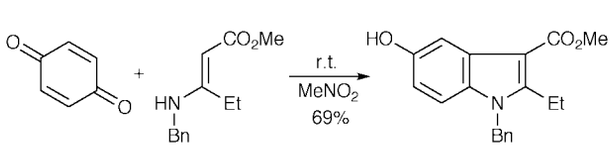
Kihara *et al*. have described an indole ring formation that involves an intramolecular Barbier reaction of phenyl and alkyl *N*-(2-iodophenyl)-*N*-methylaminomethyl ketones as summarized in Scheme 24.[120] The hydroxyindoline by-product, if obtained, can be converted to the indole with aqueous HCl.



Scheme 24

3.7 Nenitzescu indole synthesis

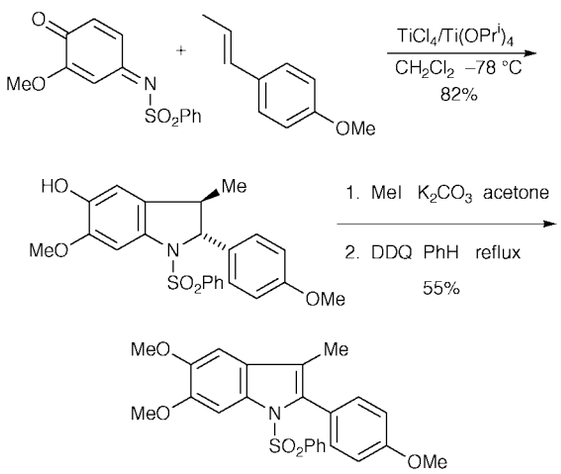
The past five years have seen a resurrection of the Nenitzescu indole synthesis and this classic sequence was used to construct methyl 5-hydroxy-2-methoxymethylindole-3-carboxylate, the key intermediate in a synthesis of the antitumor indolequinone EO 9.[121] This reaction has also been used to prepare a series of *N*-aryl-5-hydroxyindoles,[122] and it was utilized in the synthesis of a key indole (Scheme 25) used to prepare potent and selective s-PLA_2 inhibitors.[123]



Scheme 25

3.8 Engler indole synthesis

In a series of papers rich in detail, Engler and co-workers have described a new indole synthesis based on the Lewis acid-promoted reactions of enol ethers and styrenes with benzoquinone imines.[124–127] An example is shown in Scheme 26 and the reaction has obvious similarities to the Nenitzescu indole ring synthesis. Engler can manipulate the reaction to afford benzofurans instead of indoles by simply changing the Lewis acid.

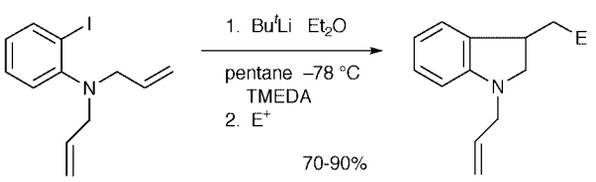


Scheme 26

Kita and colleagues have reported a synthesis of indoles closely related to the Engler synthesis.[128,129] Kita's variation involves the reaction of α-methylstyrene and phenyl vinyl sulfide with *p*-methoxy-*N*-tosylaniline under the influence of phenyliodonium bistrifluoroacetate, conditions that generate benzoquinone intermediates similar to the Engler intermediates.

3.9 Bailey–Liebeskind indole synthesis

Bailey and Liebeskind independently discovered the novel indole ring-forming reaction shown in Scheme 27 and involving anionic cyclization onto an *N*-allyl unit.[130,131] The resulting indoline anion can be further treated with an electrophile and then oxidized with chloranil‡ to the indole. The *N*-allylindole can be deprotected with Pd.[132] This new synthesis has been used to prepare a novel benzo[*f*]indole amino acid as a fluorescent probe,[133] and Bailey has extended the reaction to include the intermediacy of aryne intermediates in the sequence, the result being that the alkyllithium used to generate the aryne is incorporated into the cyclized indoline at the C-4 position.[134]

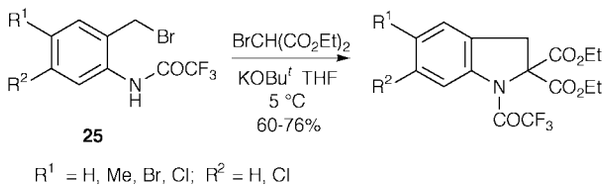


E = H, D, TMS, CHO, Br, Bu_3Sn, CH_2OH, CO_2Et

Scheme 27

3.10 Wright indoline synthesis

Wright and co-workers have developed an efficient synthesis of indoline-2,2-dicarboxylates by the tandem bis-alkylation of *o*-bromomethyltrifluoroacetanilides **25** (Scheme 28).[135] The



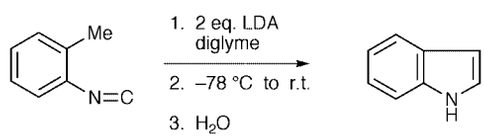
R1 = H, Me, Br, Cl; R2 = H, Cl

Scheme 28

indole nitrogen can be readily deprotected (Mg–MeOH) and further functionalized as desired (acylation, alkylation). Presumably, these indolines can be converted to indole-2-carboxylates by decarboxylation and oxidation.

3.11 Saegusa indole synthesis

The cyclization of *ortho*-lithiated *o*-tolylisocyanides is a powerful indole synthesis discovered by Saegusa and co-workers in 1977 (Scheme 29).[136,137] The reaction is very general and has been exploited by Makosza and co-workers in a synthesis of 5-allyloxy-3-(4-tolylsulfonyl)-1*H*-indole for use in 1,3,4,5-tetrahydrobenzo[*cd*]indole studies.[138] The requisite isocyanide precursor was synthesized by a vicarious nucleophilic substitution (VNS) reaction as developed by Makosza.[139,140]



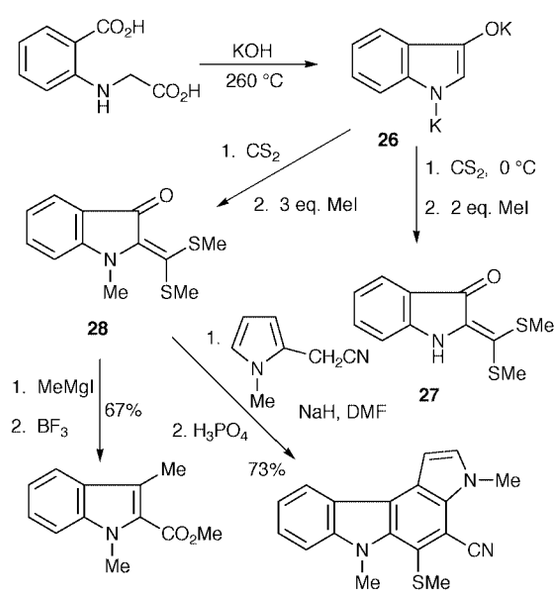
100%

Scheme 29

The elegant free-radical cyclization version of the Saegusa indole synthesis as developed by Fukuyama is presented in Section 7.1.

3.12 Miscellaneous nucleophilic cyclizations

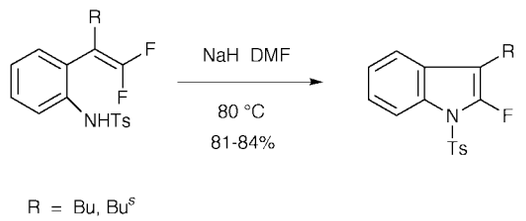
The known indoxyl dianion **26**, which is used to synthesize indigo, has now been successfully intercepted with carbon disulfide to furnish indoxyls and indoles (Scheme 30).[141] The trapped indoxyl ketene dithioacetals **27** and **28** can be used in cycloaromatization reactions to make carbazoles, *e.g.*, **29**.



Scheme 30

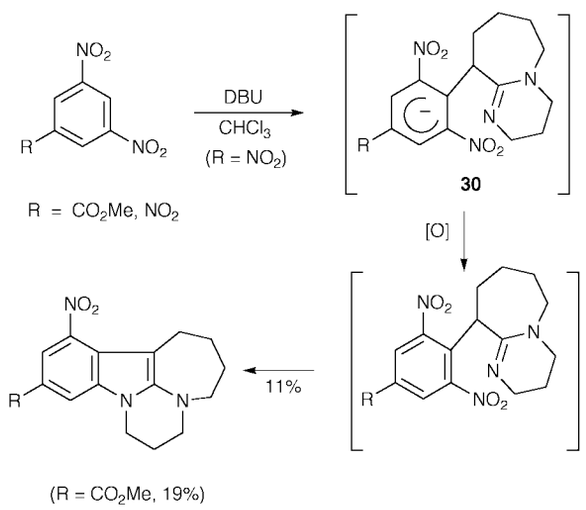
‡ Chloranil is 2,3,5,6-tetrachloro-*p*-benzoquinone.

Filler *et al.* have improved the synthesis of 4,5,6,7-tetrafluoroindole by the two-step reaction sequence of KF-induced cyclization of 2,3,4,5,6-pentafluorophenethylamine and DDQ oxidation of the resulting 4,5,6,7-tetrafluoroindoline.[142] Heating β,β-difluorostyrenes bearing *o*-tosylamido groups with NaH leads to the corresponding 2-fluoroindoles by a presumed disfavored 5-*endo-trig* cyclization (Scheme 31).[143]



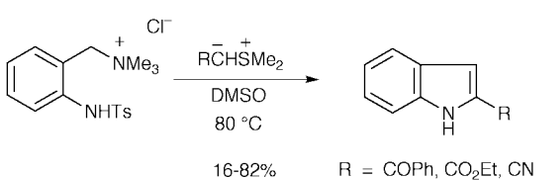
Scheme 31

Sutherland has uncovered a novel indole ring formation involving DBU nucleophilic addition to an electron-deficient benzene ring and elimination of a nitro group from an intermediate Meisenheimer complex **30** (Scheme 32).[144] In the case of methyl 3,5-dinitrobenzoate, an isoquinolone also forms depending on the initial site of attack by DBU.



Scheme 32

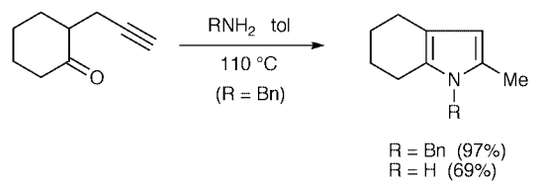
A novel use of sulfonium ylides has led to 2-substituted indoles (Scheme 33).[145] In the case of the non-stabilized ylide (R = H), only *N*-tosylindoline was isolated (76%).



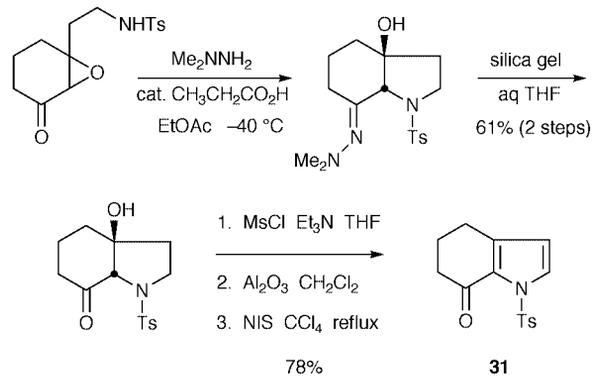
Scheme 33

Arcadi and Rossi have published a very simple synthesis of 4,5,6,7-tetrahydroindoles by the nucleophilic addition of benzylamine or ammonia to pent-4-ynones (Scheme 34).[146] This addition–elimination–cycloamination sequence was used to prepare a pyrrolosteroid from 17β-hydroxyandrost-4-en-3-one. As will be seen in Section 10, these tetrahydroindoles can usually be readily converted into indoles.

Kim and Fuchs have reported the reaction of cyclic epoxy ketones with *N*,*N*-dimethylhydrazine to afford bicyclic perhydroindoles. Subsequent manipulation gives tetrahydroindoles such as **31** (Scheme 35).[147]

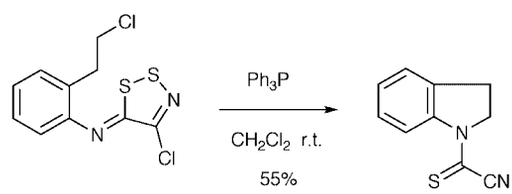


Scheme 34

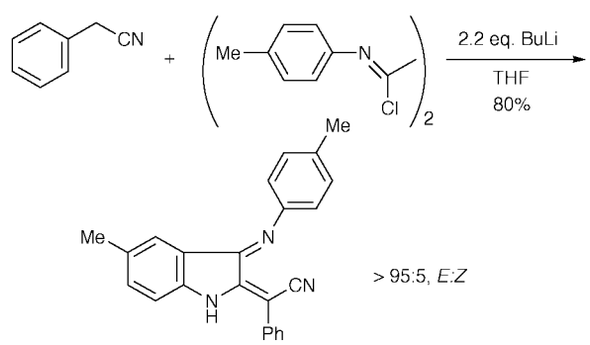


Scheme 35

A new indoline ring-forming reaction leads to the formation of *N*-(cyanoformyl)indoline (Scheme 36),[148] and the reaction between bislithiated substituted methylnitriles and methylsulfones with oxalimidoyl chlorides provides 3-iminoindoles in one step (Scheme 37).[149]



Scheme 36



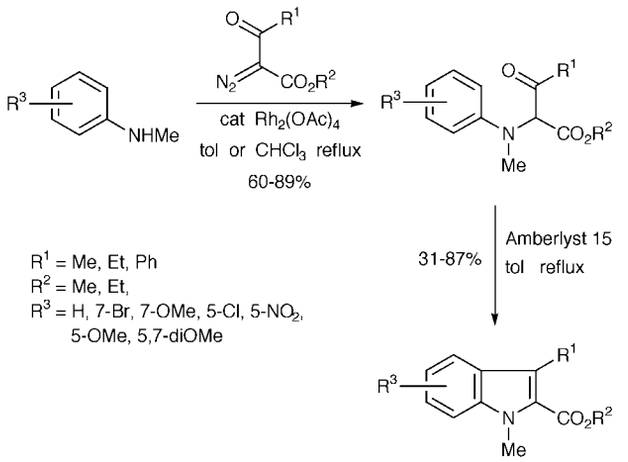
Scheme 37

4 Electrophilic cyclization

Several of the numerous electrophilic cyclization routes to indoles have been available to synthetic organic chemists for 100 years or more. Nevertheless, new examples and applications of this indole ring-forming strategy continue to appear in the literature.

4.1 Bischler indole synthesis

Moody and Swann have described a modification of the Bischler synthesis wherein the intermediate α-(*N*-arylamino)-ketones are prepared by a Rh-catalyzed insertion reaction.[150] Acid-catalyzed cyclization completes the synthesis (Scheme 38). Further examples of rhodium-catalyzed indole ring forming reactions are in Section 8.2.



Scheme 38

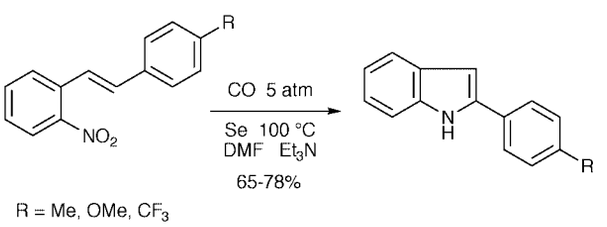
4.2 Nordlander indole synthesis

Although no new examples of this modification of the Bischler indole synthesis were found *per se*, Zard and co-workers have effected the Lewis acid induced cyclization of 2,2-dimethoxyarylacetanilides to 3-aryloxindoles.[151]

4.3 Nitrene cyclization

4.3.1 Cadogan–Sundberg indole synthesis

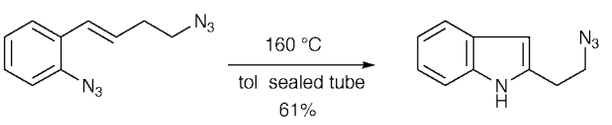
This powerful indole ring formation method involves the deoxygenation of *o*-nitrostyrenes or *o*-nitrostilbenes with triethyl phosphite and cyclization of the resulting nitrene to form an indole. Holzapfel and Dwyer have used this method to synthesize several carbazoles and norharman from the appropriate 2-nitrobiphenyls, and also several 2-methoxycarbonylindoles from methyl *o*-nitrocinnamates.[152] Another group has synthesized several 2,2′-biindolyls by the deoxygenation–cyclization of the appropriate 2-(*o*-nitrostyryl)indoles.[153] The presumed novel generation of nitrenes from *o*-nitrostilbenes using CO and Se leads to an efficient synthesis of 2-arylindoles (Scheme 39).[154] The authors propose the formation of carbonyl selenide (COSe) which is the deoxygenation agent. Both 2- and 3-methylindole can be synthesized in good yields (70%, 69%) from the corresponding *o*-nitrostyrenes, and indole is obtained in 55% yield.



Scheme 39

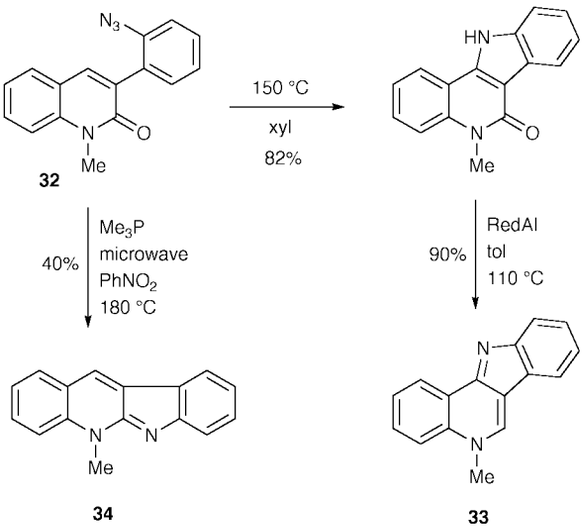
4.3.2 Sundberg indole synthesis

Molina *et al.* have employed the Sundberg indole synthesis, which involves the thermolysis of *o*-azidostyrenes and cyclization of the resulting nitrene to form indoles, to prepare 2-(2-azidoethyl)indole (Scheme 40).[155,156] The lack of reactivity of the aliphatic azido group is noteworthy.



Scheme 40

This research group has also used this methodology to synthesize the indole alkaloids cryptosanguinolentine (**33**) and cryptotackieine (**34**) from the common starting azide **32** (Scheme 41).[157] A very similar strategy to synthesize the alkaloids **33** and **34** was reported earlier by Timári *et al.*[158]

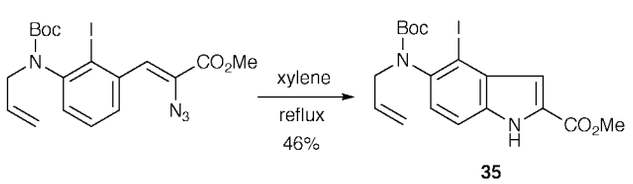


Scheme 41

Depending on the solvent, the photolysis of 2-amino-2′-azidobiphenyl yields small amounts of 4-aminocarbazole and 4,10-dihydroazepino[2,3-*b*]indole, amongst two non-indolic products.[159] Thermolysis of 1-benzylpyrazole affords α-carboline as the major product.[160] The reaction is proposed to involve a pyridylnitrene. We have used the Sundberg indole synthesis to synthesize the previously unknown 2-nitroindole from 2-(2-azidophenyl)nitroethylene in 54% yield.[161]

4.3.3 Hemetsberger indole synthesis

The Hemetsberger indole synthesis is related to the Sundberg indole synthesis except that the azido group is on the side chain (*i.e.*, α-azidocinnamate) rather than on the benzene ring. This indole synthesis has been used to prepare 2-methoxycarbonyl-6-cyanoindole[162] and 2-ethoxycarbonyl-3-methylindole.[163] The latter study includes a new preparation of the precursor α-azidocinnamates by azide ring opening of epoxides. The Hemetsberger protocol has been used to synthesize the ABC rings of nodulisporic acid,[164] the thieno[3,2-*g*]indole and thieno[3,2-*e*]indole ring systems,[165] and a precursor (**35**) to CC-1065 and related antitumor alkaloids (Scheme 42).[166]

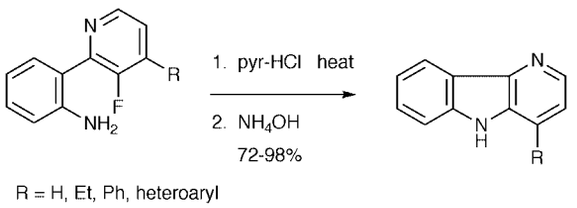


Scheme 42

Molina *et al.* have described a variation of the Hemetsberger synthesis involving the thermolysis of 2-alkyl- and 2-arylamino-3-(2-azidoethyl)quinolines to give the corresponding pyrrolo[2,3-*b*]quinolines in 39–70% yield.[167]

4.4 Quéguiner azacarbazole synthesis

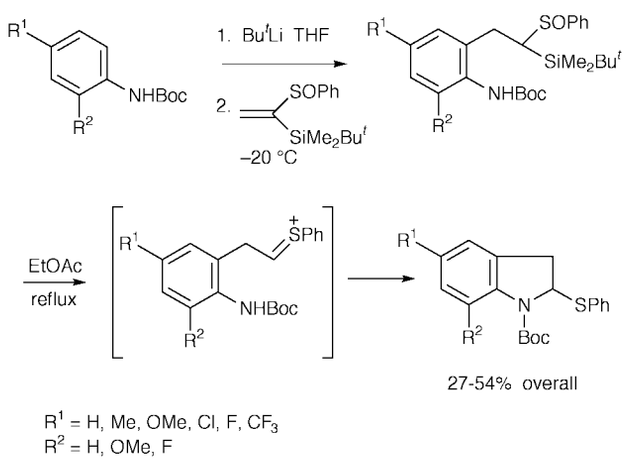
Quéguiner and co-workers have extended their short and efficient synthesis of azacarbazoles to the construction of α-substituted δ-carbolines (Scheme 43).[168]



Scheme 43

4.5 Iwao indole synthesis

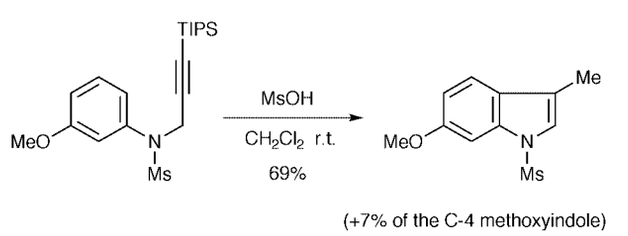
Iwao has published a new indole synthesis in which the ring-forming step is a thermal sila-Pummerer rearrangement (Scheme 44).[169] Oxidation of the 2-thioindolines with MCPBA furnishes the corresponding indoles ($R^1 = R^2 = H$, 100%). A related Pummerer rearrangement leading to an indole intermediate was used by Fukuyama and Chen in an elegant synthesis of (−)-hapalindole G.[170]



Scheme 44

4.6 Magnus indole synthesis

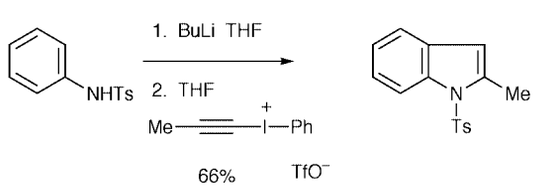
Magnus and Mitchell have discovered that terminal tri-isopropylsilylprop-2-ynylanilines afford 3-methylindoles upon treatment with methanesulfonic acid (Scheme 45).[171]



Scheme 45

4.7 Feldman indole synthesis

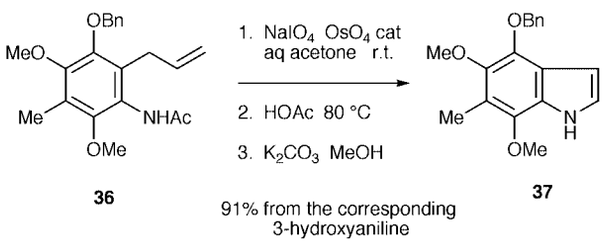
Feldman and co-workers have found that phenyl(propynyl)-iodonium triflate reacts with lithiated *N*-phenyl-*p*-toluenesulfonamide to afford indoles in one operation (Scheme 46).[172,173] The reaction is believed to involve a vinyl carbene which undergoes electrophilic cyclization to form an indole.



Scheme 46

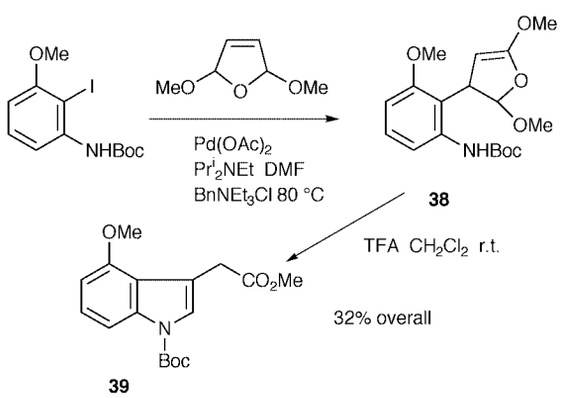
4.8 Miscellaneous electrophilic cyclizations

Several new routes to *o*-aminophenylacetaldehyde derivatives have provided new indole ring syntheses. Oxidative cleavage of the allyl side chain in aniline **36** affords indole **37**, used in a synthesis of (+)-desmethoxymitomycin A (Scheme 47),[174] and a similar osmium tetroxide oxidative cyclization yields 1-acetyl-5-methoxycarbonyl-7-chloro-4-methoxyindole (77%) from the corresponding *o*-allylacetanilide.[175] The use of 2-(2-amino-phenyl)acetaldehyde dimethyl acetal to synthesize a series of *N*-acylindoles by acid-catalyzed cyclization has been described.[176] The *N*-acylindoles can be converted into esters, amides, and aldehydes, but not ketones, by treatment with suitable nucleophiles.



Scheme 47

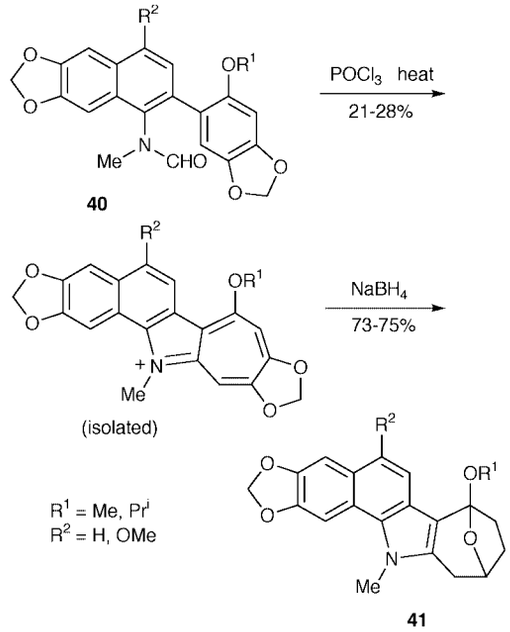
A synthesis of psilocin revealed the interesting indole synthesis shown in Scheme 48 wherein 2,3-dihydro-2,5-dimethoxyfuran **38**, prepared by Pd-catalyzed cross-coupling, is cyclized to indole **39**.[177] An unexpected rearrangement of 4-amino-2-methylbenzofurans to 4-hydroxy-2-methylindoles under strongly acidic conditions was recently reported.[178] The authors propose the generation of a vinyl carbocation by opening of the furan ring and then cyclization to the more stable indole ring system.



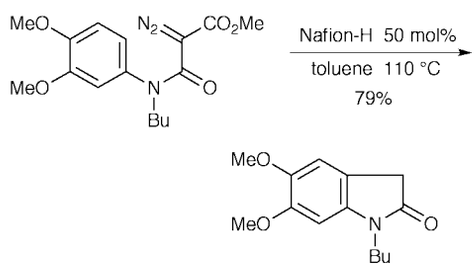
Scheme 48

Ishikawa and co-workers have uncovered a remarkable two-step rearrangement while studying the Bischler–Napieralski reaction of **40**, a double transformation that leads to **41** (Scheme 49),[179,180] and a "cume" question *par excellence*!

The mechanism of the previously known aromatization of cyclic *p*-quinomethanes to indoles has been investigated and extended to the synthesis of benzo[*e*]indoles.[181,182] Thus, the reaction of vinylmagnesium bromide with 2-benzylamino-naphtho-1,4-quinone followed by treatment with MsCl–Et_3N gives 5-mesyl-3-benzylbenzo[*e*]indole in 58% yield. The cyclization of diazoanilides to oxindoles, which is normally performed with rhodium (*cf.* Section 8.2), can also be accomplished with Nafion-H.[183] The authors propose an electrophilic mechanism by protonation of the diazo group and loss of N_2, presumably to a carbene intermediate. An example is shown in Scheme 50. Noteworthy is that the methoxycarbonyl group is invariably lost under these conditions, and the azetidin-2-ones



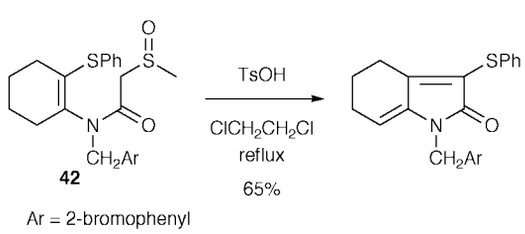
Scheme 49



Scheme 50

are minor products. Smith *et al*. have studied this cyclization to oxindoles as influenced by zeolite catalysts and they speculate that different carbenes are involved in the formation of oxindoles and azetidin-2-ones.[184]

The ancient Sandmeyer isatin synthesis, which involves the electrophilic cyclization of an α-isonitrosoacetanilide, has been employed in a synthesis of the marine natural product convolutamydine A *via* 4,6-dibromoisatin.[185] A new entry to 1,4,5,6-tetrahydro-2*H*-indol-2-ones involves 5-*endo*-*trig* cyclization of a sulfoxide amide **42** in a Pummerer rearrangement (Scheme 51).[186] Padwa *et al*. have developed elegant "domino Pummerer" cycloaddition[187] or cyclization[188] protocols to construct complex oxindoles.[189,190]



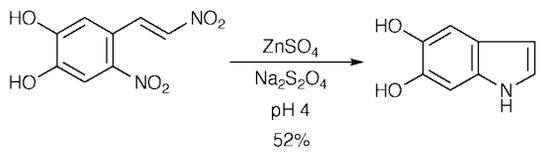
Scheme 51

5 Reductive cyclization

Like the Fischer indole synthesis, and the Madelung cyclization and its modifications, and the numerous variations of electrophilic cyclization to indoles, reductive cyclization of nitro aromatics is a powerful means of forming indoles, and several new developments have been described in recent years.

5.1 *o*,β-Dinitrostyrene reductive cyclization

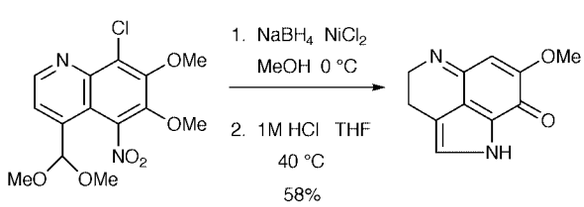
Corey and co-workers[191] have used the Borchardt modification (Fe–HOAc–silica gel–tol–reflux)[192] of the reductive cyclization of *o*,β-dinitrostyrenes to prepare 6,7-dimethoxyindole in a total synthesis of aspidophytine. This modification was employed in the preparation of 7-acetoxy-6-methoxyindole and 4-acetoxy-5-methoxyindole, which were used in syntheses of gastropod indolequinones.[193] Fukuyama and Chen have used this reductive cyclization to prepare a potential indole precursor to a synthesis of hapalindole G.[170] The synthesis of 5,6-methylenedioxyindole by the catalytic reduction of the corresponding *o*,β-dinitrostyrene proceeds in 94% yield.[194] The very labile 5,6-dihydroxyindole can be synthesized using the Zn-controlled conditions shown in Scheme 52.[195] All other conditions tried were unsatisfactory.



Scheme 52

5.2 Reissert indole synthesis

The classic Reissert indole synthesis, involving the reductive cyclization of *o*-nitrophenylpyruvic acid to indole-2-carboxylic acid, was used by Shin and co-workers to prepare a series of 2-ethoxycarbonyl-4-alkoxymethylindoles in a synthesis of fragment E of nosiheptide,[196] and by Sato *en route* to a series of tricyclic indole derivatives.[197] The modified Reissert reaction, involving the reductive cyclization of an *o*-nitrophenylacetaldehyde or *o*-nitrophenyl methyl ketone, has been adapted to solid-phase synthesis.[198] Kraus and Selvakumar have employed the reductive cyclization of a nitro aldehyde to synthesize a tricyclic indole related to the pyrroloiminoquinone marine natural products.[199] Related synthetic targets have been attacked by Joule and co-workers and a reductive cyclization step (Scheme 53) was used in a synthesis of several of these alkaloids.[200–202] Zard and co-workers have used formamidinesulfinic acid as a reducing agent in the reductive cyclization of nitroketones to pyrroles and a tetrahydroindole.[203] Rawal and Kozmin have utilized a Reissert reaction in a synthesis of tabersonine that features an elegant construction of the requisite nitro ketone **44** using the new reagent *o*-nitrophenylphenyliodonium fluoride (NPIF) to join the *o*-nitrophenyl unit to silyl enol ether **43** (Scheme 54).[204,205]

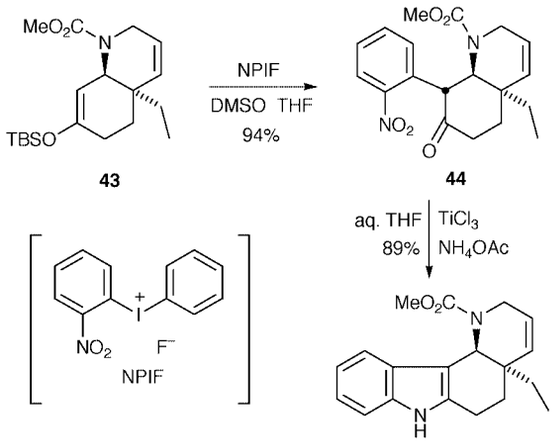


Scheme 53

The reductive cyclization of *o*-nitrophenylacetic acids or esters leading to oxindoles has been employed by Williams and co-workers to prepare 6-hydroxy-7-methoxyoxindole in a synthesis of (+)-paraherquamide B,[206] and a similar reduction sequence yielded several chlorinated oxindoles and isatins.[207]

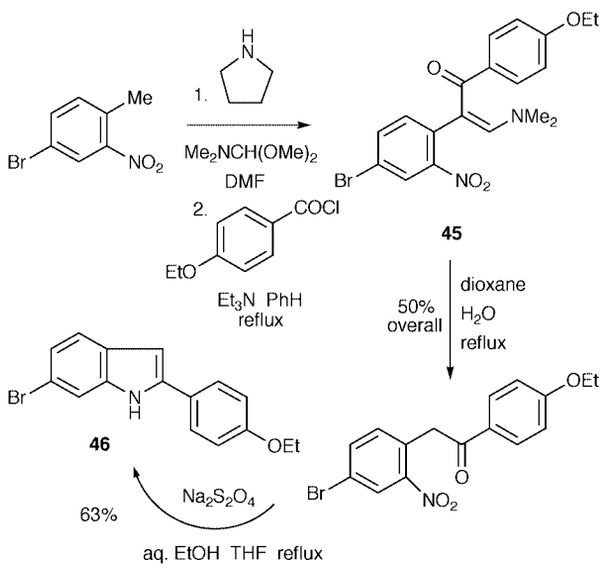
5.3 Leimgruber–Batcho indole synthesis

The Leimgruber–Batcho indole synthesis involves the conversion of an *o*-nitrotoluene to a β-dialkylamino-*o*-nitrostyrene with dimethylformamide acetal, followed by reductive cyclization to an indole. Ochi and co-workers have used this protocol to prepare 6-bromo-5-methoxyindole for use in the synthesis of



Scheme 54

marine bromoindoles,[208] and Showalter *et al.* synthesized 6-amino-5-ethoxycarbonylindole and 6-amino-7-ethoxycarbonylindole from the appropriate *o*-nitrotoluenes.[209] The Leimgruber–Batcho method has been used to make C-4 substituted indoles for elaboration to conformationally-restricted analogs of indolmycin,[210] and in a synthesis of arcyriacyanin A.[211] It has been used in a large-scale synthesis of 6-bromoindole.[212] An important extension of this indole ring synthesis is the functionalization of the intermediate β-dialkylamino-*o*-styrene. Thus, Clark and co-workers have acylated this intermediate enamine to yield **45** which was converted to indole **46** after reductive cyclization (Scheme 55).[213] Prashad and co-workers have also used this tactic to construct 3-methoxycarbonylindoles by exposing the Leimgruber–Batcho enamine to phosgene and then methanol, prior to reductive cyclization.[214] An enamine dimer was also identified in this study.

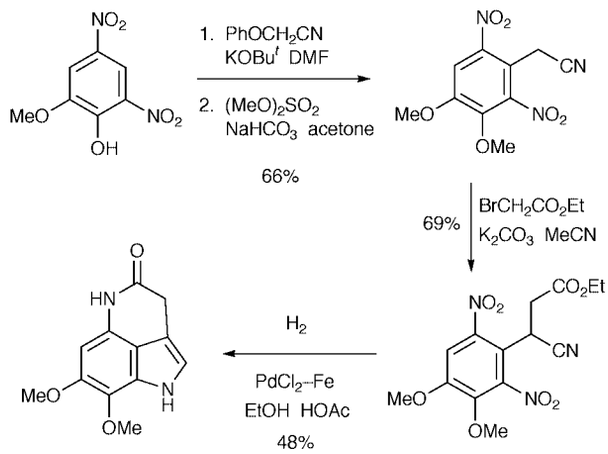


Scheme 55

Coe and co-workers have interrupted the Leimgruber–Batcho sequence by converting the intermediate enamine to an *o*-nitrophenylacetaldehyde acetal, which was reductively *N*-alkylated, and then cyclized with acid to give a series of 1-alkyl-6-methoxycarbonylindoles.[215]

5.4 Makosza indole synthesis

The essence of the Makosza indole synthesis is the vicarious nucleophilic substitution (VNS)[139,140] of hydrogen to install the requisite side chain (usually acetonitrile) for reductive cyclization onto a nitro group. Makosza has used this method to synthesize a series of *N*-hydroxyindoles and indoles,[216] and to prepare several pyrrolo[4,3,2-*de*]quinolines for use in the synthesis of the marine pyrroloiminoquinone alkaloids (Scheme 56).[217,218] The selectivity observed in the nitro group reduction is noteworthy; shorter reduction periods lead to the cyanoquinolone, indicating that the less hindered nitro group is reduced first.



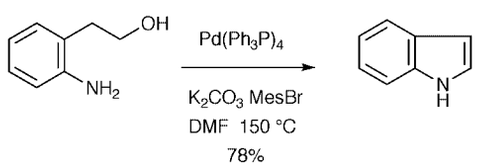
Scheme 56

Makosza has also described the condensation of *m*-nitroaniline with ketones under strongly basic conditions to form 4- and 6-nitroindoles.[219] Remarkably, imines are not involved in this reaction, but, rather, oxidative nucleophilic substitution of hydrogen by the ketone enolate occurs. Subsequent amine carbonyl condensation yields the indole. The similarity of this oxidative substitution of hydrogen to the VNS reaction is clear.

6 Oxidative cyclization

6.1 Watanabe indole synthesis

The Watanabe indole synthesis is the metal-catalyzed indole synthesis from anilines and glycols, or ethanolamines, and the related intramolecular cyclization of *o*-aminophenethyl alcohols to indoles. Watanabe, Shim, and co-workers have now extended this reaction to the synthesis of *N*-alkylindoles in yields up to 78% (*N*-methylindole) from the reaction of *N*-alkylanilines with triethanolamine and the catalyst $RuCl_2(PPh_3)_3$.[220,221] This oxidative cyclization has also been used to prepare a wide range of substituted indoles from ring-substituted (methyl, methoxy, chloro, isopropyl, dimethyl, dimethoxy) anilines.[222] Other catalysts have been studied in this reaction and $CdBr_2 \cdot 3KBr$ is particularly effective.[223,224] The intramolecular version of this reaction occurs with an aluminium orthophosphate–Pd system[225] and also with tetrakis(triphenylphosphine)palladium (Scheme 57).[226] This method also furnishes 4,5,6,7-tetrahydroindoles and pyrroles. A related electrolytic cyclization of *o*-nitrophenethylamines gives *N*-aminoalkylindoles.[227]

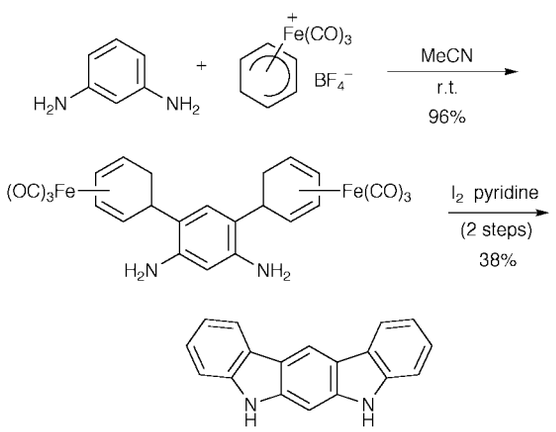


Scheme 57

6.2 Knölker indole-carbazole synthesis

Over the past several years Knölker and co-workers have parlayed the oxidative cyclization of tricarbonyliron–cyclohexadiene complexes into a remarkably versatile synthesis of

indoles and, especially, carbazoles. Recent synthetic successes in this arena include carazostatin,[228] carquinostatin A,[229] carbazomycins C and D,[230] G and H,[231] A and B,[232] carbazoquinocin C,[233] neocarazostatin B,[234] lavanduquinocin,[235] hyellazole,[236,237] 4a,9a-dihydro-9*H*-carbazoles,[238] indolo[2,3-*b*]-carbazole (Scheme 58),[239] and furostifolin.[240] The key oxidation cyclization step can usually also be accomplished with active manganese dioxide or ferricenium hexafluorophosphate–sodium carbonate, but in the case shown in Scheme 58 these reagents led to decomposition.



Scheme 58

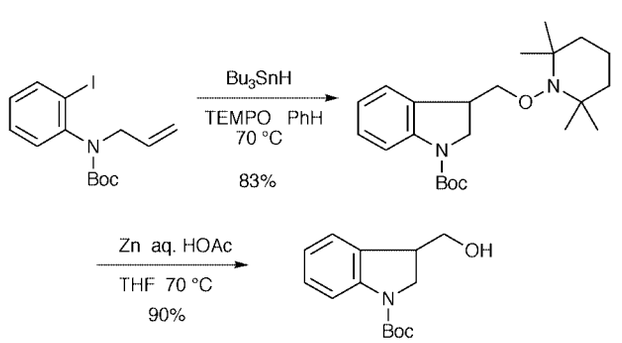
This oxidative cyclization sequence has been applied to the synthesis of the 2,3,3a,7a-tetrahydroindole nucleus by two groups, apparently independently.[241,242]

7 Radical cyclization

As was true in the earlier review,[1] radical cyclization routes to indoles and indolines are very popular amongst synthetic chemists, and several new such methodologies have been invented in recent years for the construction of indoles.

7.1 Tin-mediated cyclization

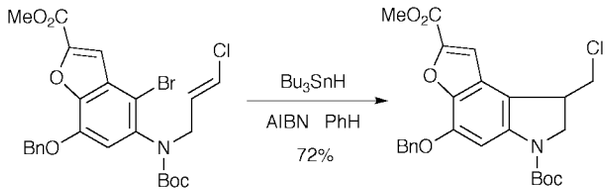
Boger has been one of the pioneers in the development of tin-mediated radical cyclization, notably in the area of CC-1065 and duocarmycin synthetic studies.[243–247] An example is depicted in Scheme 59.[245]



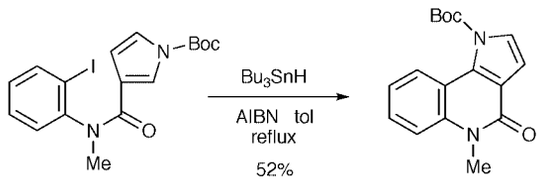
Scheme 59

Patel and co-workers have improved upon this method by effecting a similar 5-*exo-trig* cyclization onto a tethered vinyl chloride (Scheme 60).[248]

Jones and co-workers have reported a similar tin-mediated cyclization of *o*-bromoacryloylanilides leading to oxindoles, a method which employs *in situ N*-silylation to bias the requisite conformation for cyclization.[249] This group has also described the radical cyclization onto a pyrrole ring leading either to spirooxindoles or to the martinelline core (pyrrolo[3,2-*c*]-quinolone) (Scheme 61).[250,251] The tin-mediated cyclization



Scheme 60

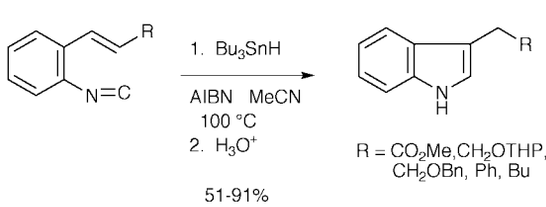


Scheme 61

onto a linked dihydropyrrole ring leads also to a spirooxindole and a pyrrolidinoquinolone in a 7 : 3 ratio.[252]

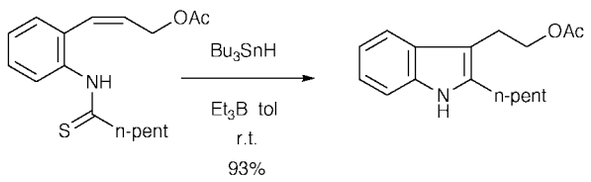
Curran and co-workers who also were pioneers in the development of tin-mediated 5-*exo-trig* cyclization to indolines,[253] have described the fluorous and the microwave-promoted fluorous versions of this reaction.[254,255] Other 5-*exo-trig* variations include the cyclization of 2-allyl thiocarbazones to hexahydroindoles, featuring a new source of nitrogen centered radicals,[256] the cyclization of *o*-bromo α-cyanoanilines to spiroindoxyls,[257] cyclization of *o*-haloaryl allenylmethyl amines to afford 3-ethenyl-2,3-dihydroindoles,[258] and cyclization of the *o*-bromo benzimidate of phenethylamine to *N*-benzoylindoline.[259] The Boger cyclization, which uses a TEMPO radical trap, has been used in concert with the Hemetsberger indole synthesis to prepare a duocarmycin model.[166] Murphy and co-workers have reported the tin-induced cyclization of an *ortho*-iodo tethered vinyl bromide leading, after loss of HBr, to a tetrahydrocarbazole.[260] Parsons and co-workers have presented a full account of his elegant tandem radical cyclization leading to lysergic acid derivatives[261] and to a pseudocopsinine model.[262]

An exciting development in the area of radical cyclization is Fukuyama's tin-mediated indole synthesis featuring the cyclization of *o*-isocyanostyrenes *via* an α-stannoimidoyl radical (Scheme 62).[263–265] This powerful methodology leads to 2-substituted indoles by a Stille palladium-cross coupling reaction of the intermediate 2-stannylindole,[263,264] and has been featured in syntheses of indolocarbazoles,[264] biindolyls,[264] and total syntheses of (±)-vincadifformine and (−)-tabersonine.[265] Others have used the Fukuyama synthesis to prepare 6-hydroxyindole-3-acetic acid[266] and 3-(trimethylsilyl)methylindoles.[267] The latter paper describes both the tin-mediated and a thiol-mediated cyclization of an *o*-isocyanophenyl trimethylsilyl alkyne to indoles.



Scheme 62

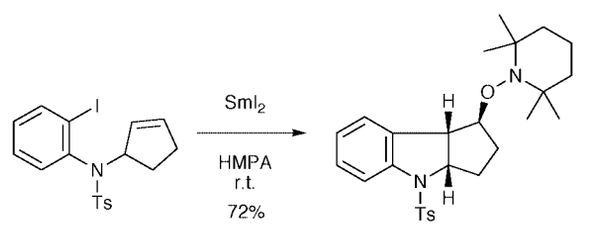
Fukuyama and co-workers have extended their indole radical cyclization chemistry to the use of *o*-alkenylthioanilides. These substrates furnish 2,3-disubstituted indoles in good to excellent yields (Scheme 63).[268] Fukuyama has also developed a phosphorus-initiated radical cyclization of thioanilides in the context of a synthesis of (±)-catharanthine.[269]



Scheme 63

7.2 Samarium-mediated cyclization

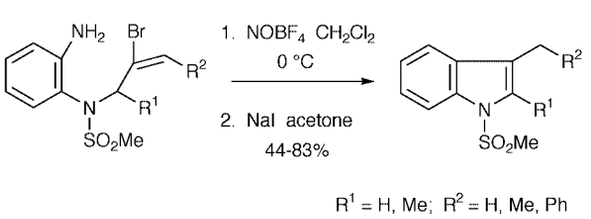
Samarium iodide has been used with *o*-iodoaniline derivatives to synthesize spirooxindoles,[270] and, with a TEMPO trap, indolines (Scheme 64).[271]



Scheme 64

7.3 Murphy indole-indoline synthesis

Murphy and co-workers have engineered an elegant new radical cyclization methodology involving "radical-polar crossover chemistry", which uses tetrathiafulvalene (TTF) or sodium iodide to mediate the 5-*exo*-*trig* cyclization to indolines or indoles.[260,272–275] A simple indole example is shown in Scheme 65,[260] but the method is particularly useful for the construction of the tetracyclic-indoline core of *Aspidosperma* alkaloids.[273,275] This methodology has been extended to the use of polymer-supported TTF reagents.[276]



Scheme 65

7.4 Miscellaneous radical cyclizations

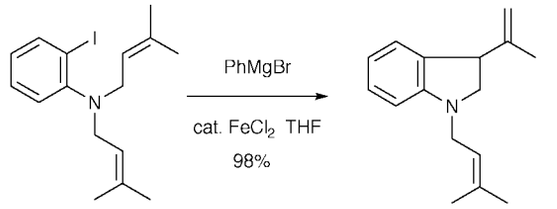
Several newer means to effect a radical cyclization leading to indoles or indolines have recently appeared in the literature. These include Mn(III) cyclization of α-thioamides,[277] the electrochemical-induced cyclization of *N*-allyl-2-chloroacetanilides,[278] the Grignard-induced cyclization of *N*,*N*-diprenyl-2-iodoaniline (Scheme 66),[279] the thermal radical cyclization of α,α,α-trichloroanilides to oxindoles,[280] the cyclization of α-xanthylanilides to oxindoles (Scheme 67),[281] the tris-(trimethylsilyl)silane-induced cyclization onto the nitrogen of an imidate ester,[259] the tris(trimethylsilyl)silane-induced cyclization onto an alkene and the radical so-formed onto an azide,[282] the NBS-triggered cyclization of lactam *m*-cyclophanes to yield tricyclic indoles (Scheme 68),[283] the Mn(II)-induced coupling of ethyl α-nitroacetate with 2-aminonaphthoquinones to furnish benzoindoloquinones,[284] and the thiol-triggered cyclization of *o*-alkynylanilines[285] and *o*-alkynylphenyl azides[286,287] to indoles.

These novel reactions would seem to offer enormous promise for future development and applications in synthesis.

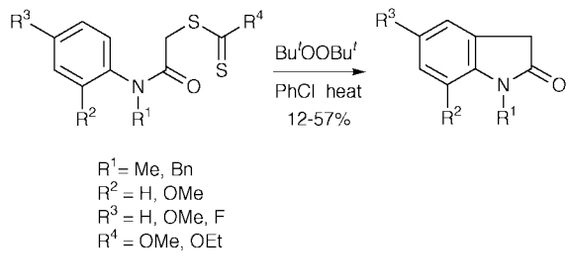
8 Metal-catalyzed indole synthesis

8.1 Palladium

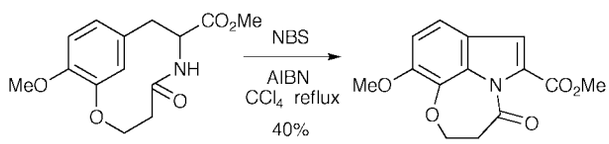
The use of palladium in indole and indoline ring synthesis has



Scheme 66



Scheme 67

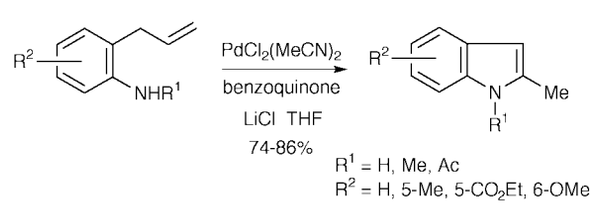


Scheme 68

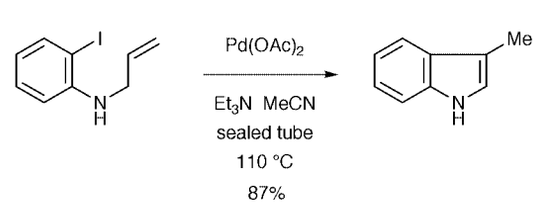
received such extraordinary attention that this section has been further subdivided from those divisions in the earlier review.[1] More importantly, proper credit (I hope!) has been given to the several discoverers of this chemistry.

8.1.1 Hegedus–Mori–Heck indole synthesis

The application of the intramolecular Heck reaction to the synthesis of indoles, oxindoles and indolines, depending on the cyclization substrate, was apparently discovered independently by Hegedus,[288–293] Mori[294,295] and Heck,[296] although Hegedus was the first in print. These workers found that Pd effects the cyclization of either *o*-allylanilines or *N*-allyl-*o*-haloanilines to indoles under standard Heck conditions.[297–300] Two of the original examples are shown in Scheme 69[288,289] and Scheme 70.[291] Hegedus was also the first to report the CO insertion version of this Pd-catalyzed cyclization reaction leading to indoline-2-acetic acid derivatives.[290]



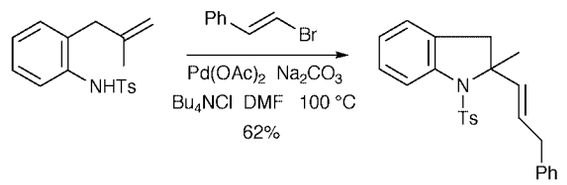
Scheme 69



Scheme 70

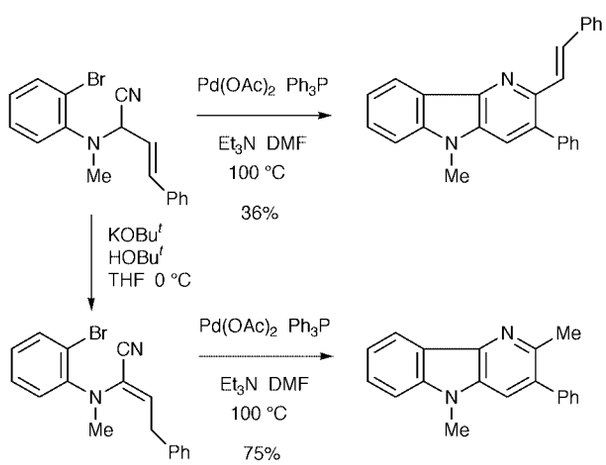
Larock and Babu have greatly improved upon the original Hegedus conditions for the cyclization of *N*-allyl-*o*-haloanilines and *N*-acryloyl-*o*-haloanilides,[301] such that, for example, the

reaction shown in Scheme 70 can be performed at lower temperature, with shorter reaction time and less catalyst to give 3-methylindole in 97% yield. Larock and co-workers have extended this Pd-mediated cyclization in other ways,[302–305] notably involving the cross-coupling of *o*-allylic and *o*-vinylic anilides with vinyl halides and triflates to produce 2-vinylindolines[303–305] (Scheme 71).[305] The related "Larock indole synthesis" is presented in Section 8.1.3.

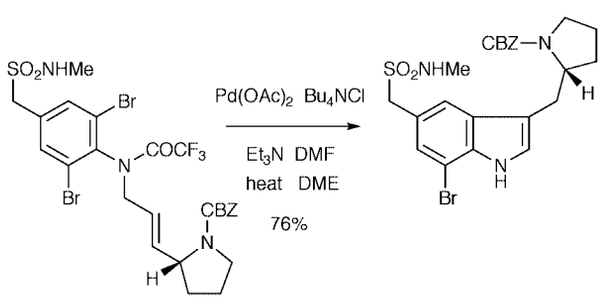


Scheme 71

Numerous examples of the Hegedus–Mori–Heck indole synthesis have been described, including applications to the synthesis of CC-1065 precursors,[306–308] 5-methyl- and 7-methylindole featuring a new *ortho*-vinylation of anilines with $SnCl_4$–Bu_3N,[309] indole-3-acetic acids,[310] indole-3-pyruvic acid oxime ethers,[311] 3-siloxyindoles,[312] δ-carbolines from the cyclization onto a cyano group (Scheme 72),[313] 7-bromoindoles related to sumatriptan (Scheme 73),[314] and a total synthesis of the alkaloid gelsemine.[315]

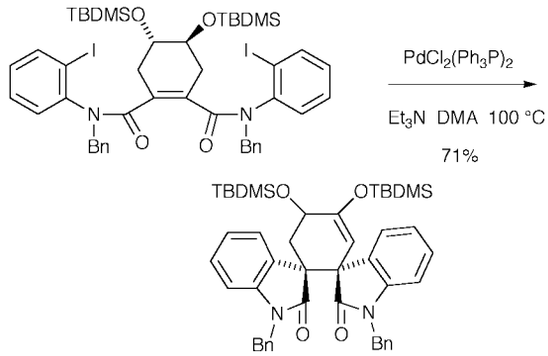


Scheme 72



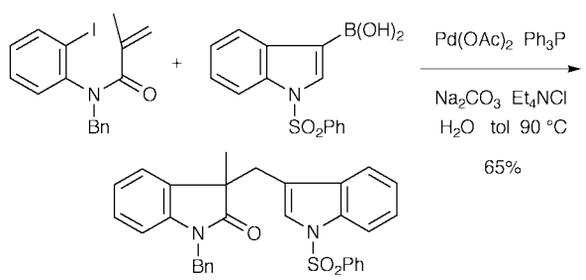
Scheme 73

The Pd-catalyzed synthesis of indoles[316,317] and oxindoles[318] has been adapted to the solid phase, and new fluorinated phosphine palladium complexes in supercritical carbon dioxide have been invented for these reactions.[319] Overman and co-workers have utilized the oxindole version of this reaction in the course of total syntheses of the Calabar bean alkaloids physostigmine and physovenine,[320] and, *via* a spectacular bis-Pd-catalyzed cyclization (Scheme 74), for total syntheses of chimonanthine and calycanthine.[321]



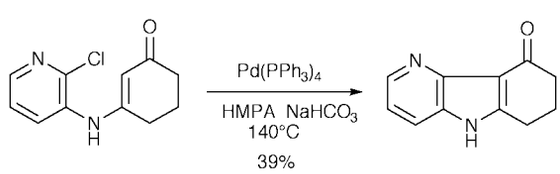
Scheme 74

Grigg and co-workers have described a series of Pd-catalyzed cyclizations leading to indoles, indolines, and oxindoles, including the reaction of *o*-haloanilines with vinyl halides or triflates and CO to produce 3-spiro-2-oxindoles,[322] cyclization protocols to yield 3-spiroindolines,[323,324] and cyclization–anion capture sequences to construct various indoles (Scheme 75).[325,326]

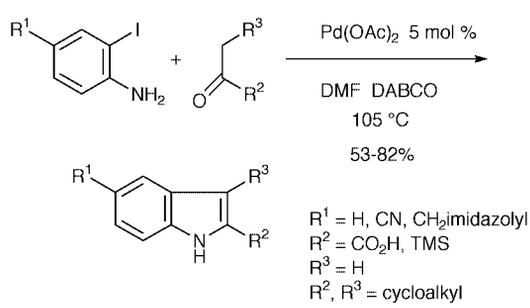


Scheme 75

Rawal and co-workers have reported that the Pd-catalyzed cyclization of *N*-(2-bromoallyl)anilines affords indoles, and they have used this to synthesize 4- and 6-hydroxyindoles.[327] Likewise, it has long been known that 2-(*o*-bromoanilino) enones undergo the intramolecular Heck reaction to form 3-acylindoles.[328] A recent example of this version of the Hegedus–Mori–Heck indole synthesis is shown in Scheme 76.[329] This cyclization has been applied to the synthesis of 3-ethoxycarbonyl-2-trifluoromethylindoles from the appropriate *o*-haloanilino vinylogous carbamates[330,331] and to 2-benzyloxycarbonyl-4-hydroxymethyl-3-methylindoles from a 2-(*o*-iodoanilino) unsaturated ester.[332] A nice variation on this theme utilizes the *in situ* preparation of *o*-iodoanilino enamines (Scheme 77).[333]

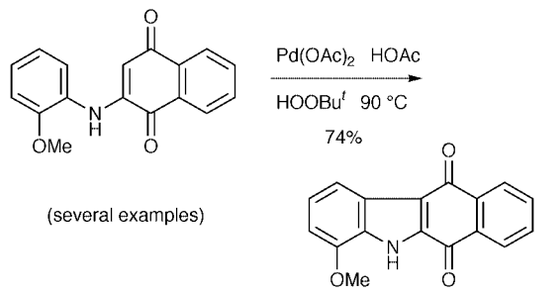


Scheme 76



Scheme 77

More than 20 years ago Åkermark and co-workers first reported that 2-anilino-*p*-benzoquinones are cyclized to carbazolequinones with $Pd(OAc)_2$.[334] Recently, this research group has extended this reaction to additional examples (Scheme 78).[335] This cyclization has been used in the synthesis of biscarbazoles,[51] kinamycin analogs,[336,337] carbazomycins G and H,[338] carbazoquinocin C,[339] (±)-carquinostatin A,[340] and 8,10-dimethoxyellipticine.[341] The final cyclization involves a diaryl amine precursor.

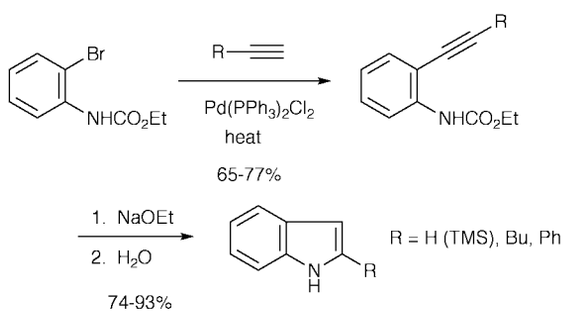


Scheme 78

8.1.2 Yamanaka–Sakamoto indole synthesis

Although the Yamanaka–Sakamoto indole synthesis does not necessarily involve Pd in the indole ring-forming step, it is included in this section in view of its close similarity to both the Hegedus–Mori–Heck and the Larock indole syntheses. This reaction is also related to the copper-promoted Castro indole synthesis (Section 8.5.1).

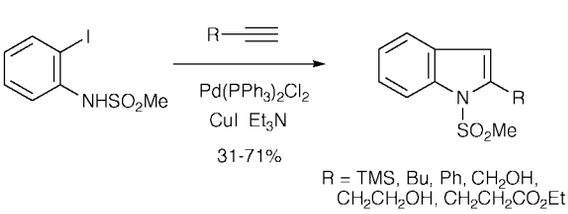
The Yamanaka–Sakamoto indole synthesis[298] features a Pd-catalyzed coupling of a terminal alkyne with an *o*-haloaniline to afford an *o*-alkynylaniline derivative which then readily cyclizes with base to yield an indole. The prototypical reaction is shown in Scheme 79.[342] The cyclization is either spontaneous or involves Pd mediation. This cyclization can also be effected with fluoride.[343]



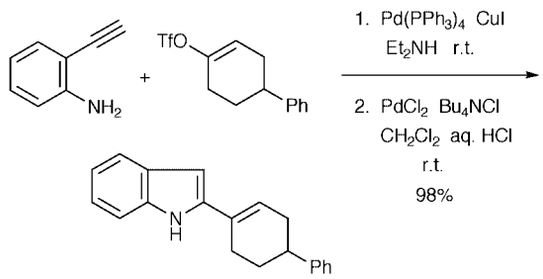
Scheme 79

In subsequent papers, these workers reported that copper is beneficial to the overall reaction (Scheme 80),[344] and this combination of catalysts has been used to effect a synthesis of 7-substituted indoles,[345] oxygenated indoles,[346] 3-methoxycarbonylindoles by CO carbonylation,[347] and 3-alkenylindoles by an *in situ* Heck reaction.[348]

The power of this indole ring synthesis has not gone unnoticed, and Cacchi and co-workers have made outstanding contributions in this general area of indole ring construction. For example, vinyl triflates react with *o*-aminophenylacetylene to afford 2-substituted indoles in excellent yield (Scheme 81).[349] A carbonylation variation provides 3-acylindoles,[350] and 3-aryl-2-unsubstituted indoles[351] and 3-allylindoles[352] are readily crafted using Pd-catalyzed coupling, followed by cyclization.

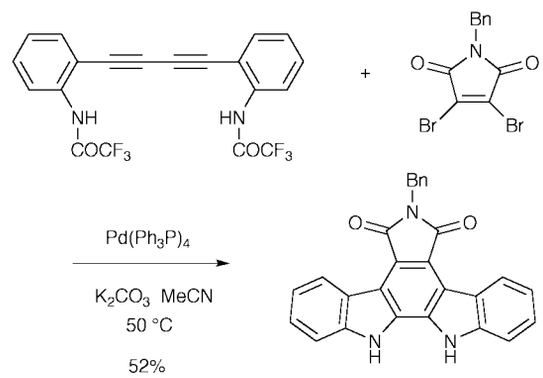


Scheme 80



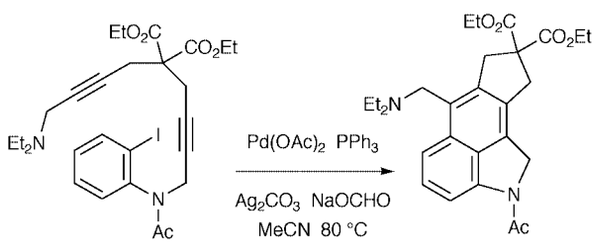
Scheme 81

The Yamanaka–Sakamoto indole synthesis has been used in a synthesis of carazostatin,[353] the solid-phase syntheses of 2-[354] and 3-substituted indoles[355] and 2,3-disubstituted indole-6-carboxylic acids,[356] 2-dienylindoles,[357] and biindolyls[358,359] (Scheme 82),[359] the latter of which utilizes the Cacchi variation.

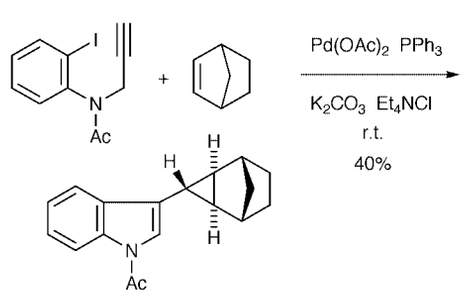


Scheme 82

Grigg and co-workers have extended this methodology to cyclization reactions of *o*-iodo-*N*-alkynylanilines leading to polycyclic indoles. Two examples of this cascade process are shown in Schemes 83[360] and 84.[361]



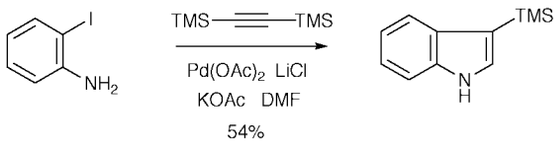
Scheme 83



Scheme 84

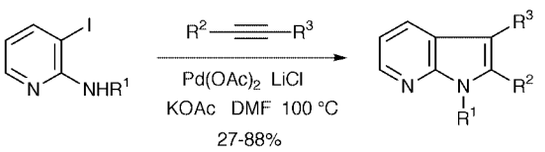
8.1.3 Larock indole synthesis

The Larock indole synthesis[362,363] refers to the intermolecular Pd-catalyzed reaction of *o*-haloanilines and alkynes (usually internal) to give indoles in one operation. Examples of allenes and alkenes functioning in this manner are also cited in this section. An example is shown in Scheme 85.[363]



Scheme 85

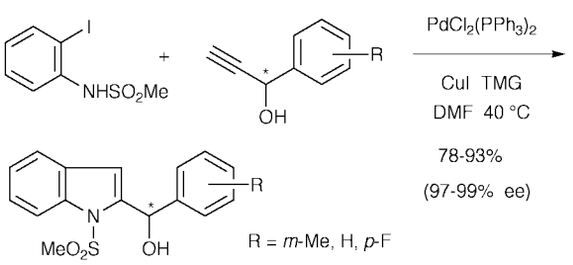
The Larock indole synthesis with internal alkynes has been used to synthesize 5-azaindoles,[364] 5-, 6-, and 7-azaindoles,[365] 7-azaindoles (Scheme 86),[366] pyrrolo[3,2-*c*]quinolines,[367] pyrrolo[3,2,1-*ij*]quinolines,[368*a*] isoindolo[2,1-*a*]indoles,[368*b*] 5-(triazolylmethyl)tryptamine analogs,[369] tetrahydroindoles,[370] and *N*-(2-pyridyl)indoles.[371]



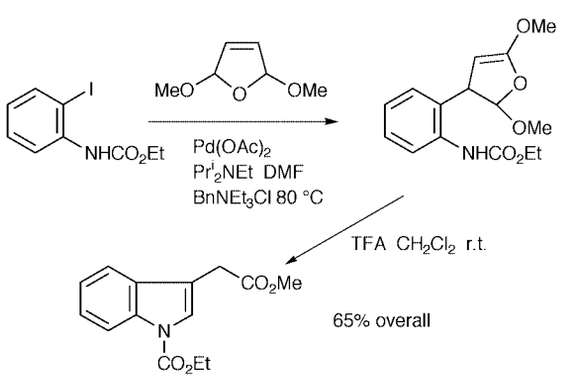
R^1 = Me, Bn, H, *p*-MeOBn
R^2 = TMS, Ph, Pr
R^3 = CH_2OH, CH_2CH_2OH, Me, Ph, Pr

Scheme 86

The Larock method has been applied to solid-phase synthesis,[372–374] terminal alkynes,[375,376] including chiral examples (Scheme 87),[376] and some alkenes.[377–379] For example, this last combination was used to synthesize indole-3-acetic acid (Scheme 88).[378]

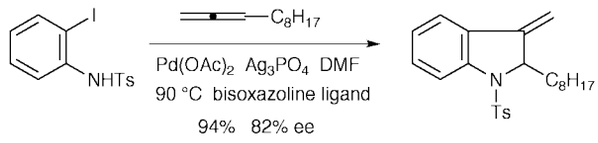


Scheme 87



Scheme 88

Larock has also utilized allenes to craft 3-methyleneindolines, including asymmetric synthesis (Scheme 89).[380,381] Allenes in this Pd-catalyzed indole synthesis variation lead to

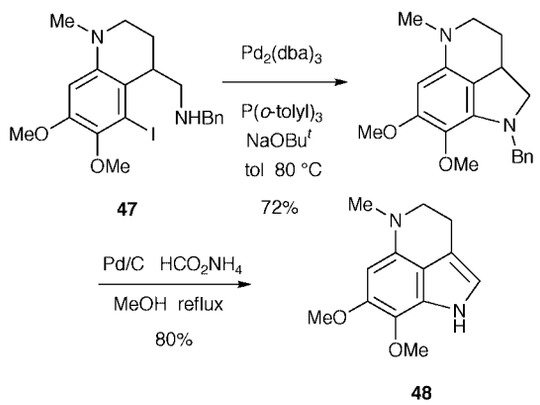


Scheme 89

7-azaindolinones following ozonolysis of the initially formed *exo*-methyleneindoline,[382] and 1-sulfonyl-1,3-dienes in the Larock methodology lead to 2-vinylindolines.[383] 1-Oxygenated dienes also work well.[384]

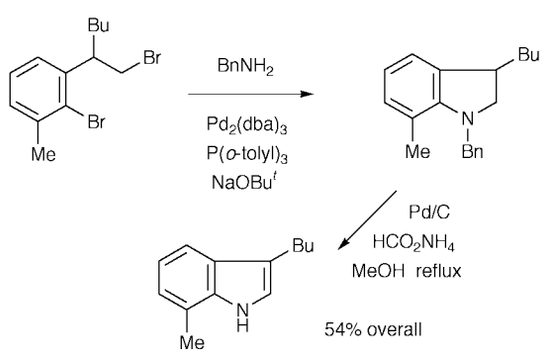
8.1.4 Buchwald indoline synthesis

Buchwald has parlayed a powerful aryl amination technology[385] into a simple and versatile indoline synthesis.[386] Indole **48**, which has been used in the total syntheses of the marine alkaloids makaluvamine C and damirones A and B, was readily synthesized using a Pd-mediated cyclization of **47** (Scheme 90).[387]



Scheme 90

This intramolecular Pd-catalyzed amination is applicable to the synthesis of *N*-substituted optically active indolines,[388] and *o*-bromobenzylic bromides can be employed in this indole ring synthesis (Scheme 91).[389] Recently, Yang and Buchwald have described improvements in this methodology.[390]

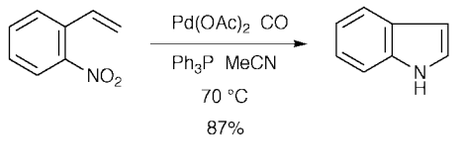


Scheme 91

8.1.5 Miscellaneous

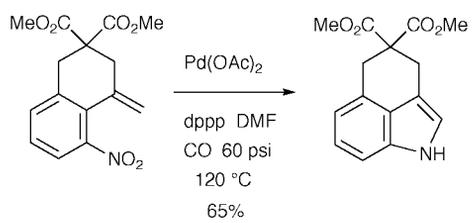
Several examples of Pd-mediated cyclization leading to indoles or indolines do not fit into the previous categories and are presented here.

The indole ring can be easily fashioned by the Pd-catalyzed cyclization of *o*-nitrostyrenes.[391,392] Söderberg and co-workers have developed this "reductive *N*-heteroannulation" reaction into a very attractive and general indole ring synthesis,[393,394] both for simple indoles (Scheme 92)[393] and fused indoles (Scheme 93).[394] A related cyclization of *o*-aminophenethyl alcohol was cited earlier.[226]



Also 4-OH, 4-OMe, 5-OMe, 6-OMe, 4-Br, 4-NO_2, 4-CO_2Me, 5-CO_2Me, 6-CO_2Me, 7-CO_2Me, 2-Ph, 2-Me, and others

Scheme 92

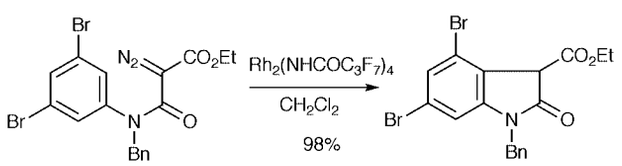


Scheme 93

Yang has reported the Pd-induced cyclization of an arylbromide to a pendant cyano group leading to γ-carbolines and related compounds.[395]

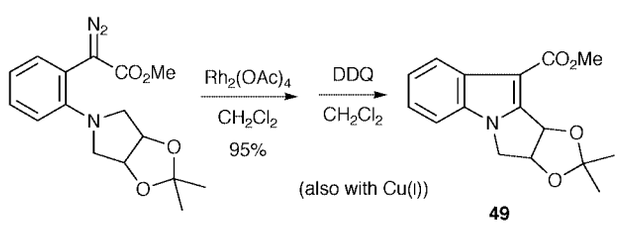
8.2 Rhodium and ruthenium

The rhodium(II)-catalyzed decomposition of α-diazocarbonyl compounds to yield oxindoles is an important synthetic operation, and Moody, Padwa, and co-workers have made several important contributions in this area.[396–399] Notably, the use of a perfluorinated carboxamide ligand on the rhodium catalyst decidedly promotes attack on the aromatic ring rather than leading to a β-lactam or other products. This reaction is a key step (Scheme 94) in a synthesis of the marine alkaloid convolutamydine C by Moody and co-workers.[398]



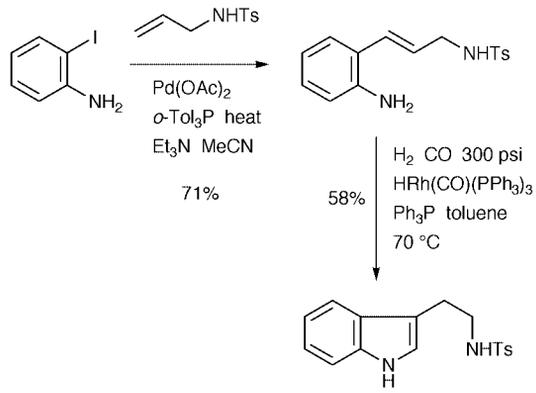
Scheme 94

The use of chiral α-diazocarbonyl compounds in this process preserves the optical activity in furnishing *N*-substituted oxindoles,[400] and Rh(II) also catalyzes the carbenoid insertion into a C–H bond of a pyrrolidine leading to 1,2-disubstituted mitosene **49** (Scheme 95).[401–403] This cyclization is also effected by chiral bis(oxazoline)copper(I) catalysts to give some enantioselectivity.



Scheme 95

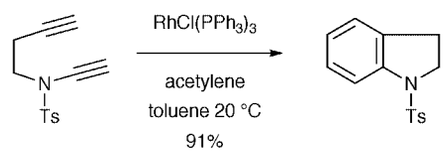
The Rh-catalyzed hydroformylation of functionalized anilines leads to tryptophanols and tryptamines (Scheme 96).[404] The Rh-catalyzed carbonylation of *o*-alkynylanilines yields oxindoles,[405] and a Rh-catalyzed process, using Wilkinson's catalyst, has been discovered that converts azobenzenes into *N*-anilinoindoles.[406,407] For example, under these conditions



Scheme 96

azobenzene reacts with diphenylacetylene to give *N*-anilino-2,3-diphenylindole in 90% yield.

Witulski has reported a very general Rh-catalyzed aromatic ring-forming reaction with alkynes leading to indolines (Scheme 97).[408] This [2+2+2] cycloaddition provides 4,5,6,7-tetrasubstituted indolines in good to excellent yields.



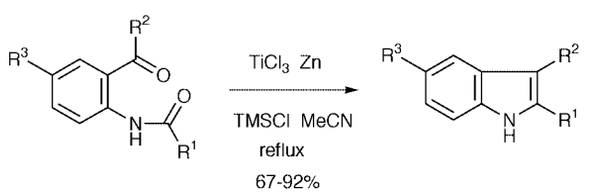
Scheme 97

A ruthenium catalyst converts *o*-alkylbenzonitriles to indoles,[409] and a 3-enylalkynylindole to a carbazole in low yield.[410]

8.3 Titanium

8.3.1 Fürstner indole synthesis

The Fürstner indole synthesis is the Ti-induced reductive cyclization of oxo amides leading to an indole ring.[411] Fürstner *et al.* have revealed the enormous power and versatility of this coupling reaction, illustrated by total syntheses of the indole alkaloids (+)-aristoteline,[412] camalexin,[413] flavopereirine and other indolo[2,3-*a*]quinolizine alkaloids,[413,414] and secofascaplysin.[414] The reaction is general for simple indoles (Scheme 98),[415] including highly strained examples (2,3-di-*tert*-butyl-1-methylindole[412]). It is also particularly useful for the preparation of 2-arylindoles.[416]



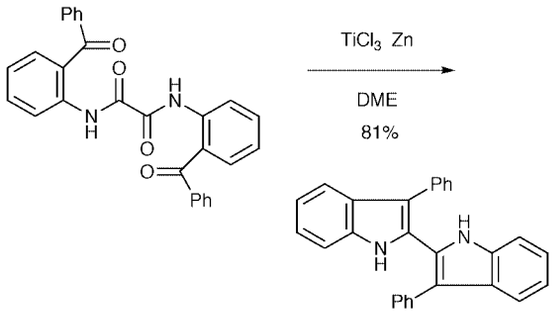
R^1 = Ph, CF_3, $CF_2CF_2CF_3$, CO_2Et, $(CH_2)_{15}CH_3$; R^2 = Me, Ph; R^3 = H, Cl

Scheme 98

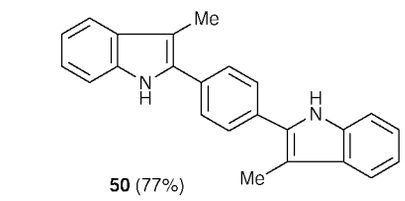
An improvement over the original procedure is the so-called "instant" method utilizing $TiCl_3$–Zn, and these newer conditions have been employed to synthesize a variety of bi-, ter-, and quaterindoles (Scheme 99).[417] For example, indoles **50** and **51** can be easily assembled using this Ti-induced "zipper reaction".

8.3.2 Miscellaneous

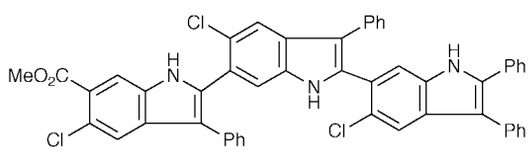
Mori and co-workers have continued their use of Ti–nitrogen



Scheme 99

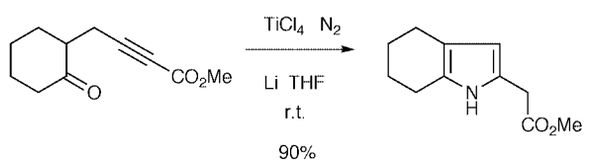


50 (77%)



51 (86%)

complexes (nitrogen fixation) in pyrrole ring formation leading to tetrahydroindoles (Scheme 100).[418,419]

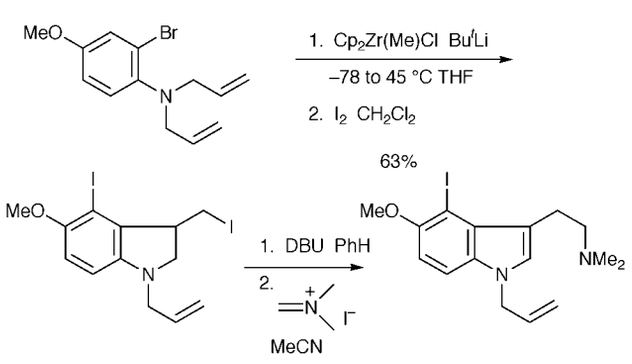


Scheme 100

The low-valent titanium reductive cyclization of aryl isothiocyanates to afford indole-2-carbothioamides has been described,[420] and Cha and co-workers have utilized an intramolecular Ti-coupling procedure to construct mitomycin indole analogs from *o*-imidostyrenes.[421]

8.4 Zirconium

The Buchwald indole-indoline ring synthesis, involving intramolecular alkene insertion into a zirconium-stabilized aryne complex and subsequent oxidation, has been used by Buchwald and co-workers to prepare 3,4-disubstituted indoles,[422] tryptophans and serotonin analogs (Scheme 101),[423] and dehydrobufotenine.[387]



Scheme 101

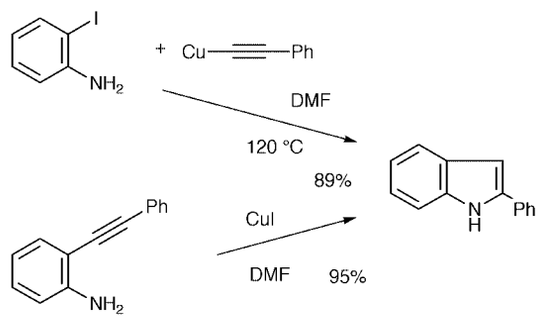
Tietze and Grote have employed this intramolecular insertion reaction of zirconocene-stabilized aryne complexes to synthesize the indoline portion of the CC-1065 pharmacophore.[306,307]

8.5 Copper

Although copper has played a role in earlier indole ring synthesis (*vide supra*), other indole ring-forming reactions prompted this separate section.

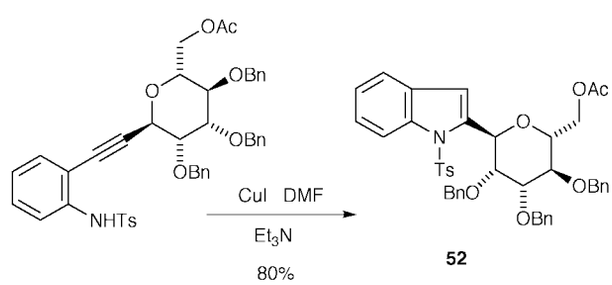
8.5.1 Castro indole synthesis

Castro *et al.* were the first to discover the metal-catalyzed cyclization of *o*-alkynylanilines to indoles using copper.[424–427] Their early contributions to this field are often overlooked, but Castro's discoveries include the copper acetylide coupling with *o*-iodoanilines and the CuI-induced cyclization of *o*-alkynylanilines to yield indoles, both of which are illustrated in Scheme 102.



Scheme 102

The Castro indole synthesis has been used to prepare 5-azaindoles,[364] a 2-(benzotriazolylmethyl)indole,[428] an indolo[7,6-*g*]indole,[429] a series of 5,7-disubstituted indoles and pyrroloindoles,[430] 5,7-difluoro- and 5,6,7-trifluoroindole,[431] 1,2-dialkyl-5-nitroindoles,[432] and α-*C*-mannosylindole **52** (Scheme 103).[433] In some cases the Castro cyclization of *o*-alkynylanilines succeeds where the Larock method of Pd-catalyzed coupling of *o*-iodoaniline with an alkyne fails.[428b] The reaction of *o*-ethynyltrifluoroacetanilide with $Cu(OAc)_2$ yields both indole and 2-alkynylindoles resulting from alkyne coupling and mono-cyclization.[359]



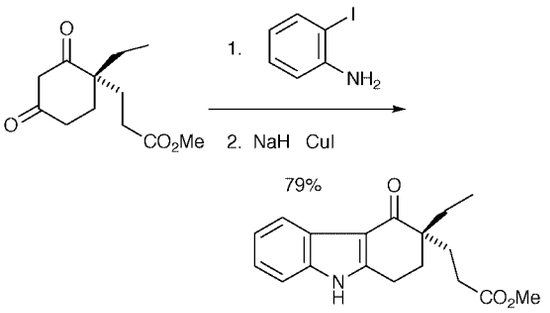
52

Scheme 103

8.5.2 Miscellaneous

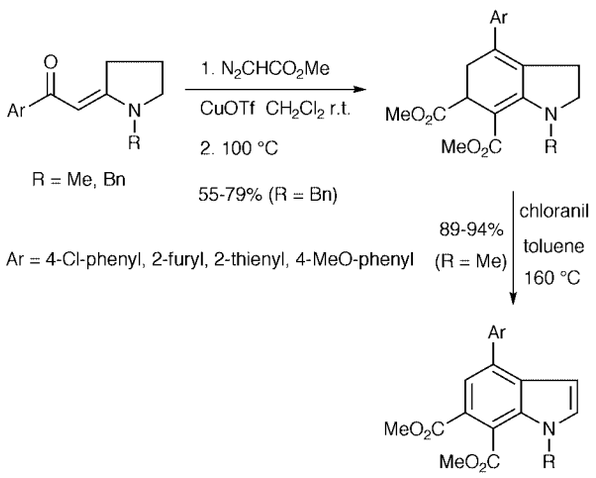
Early uses of copper(I) in combination with NaH to effect the cyclization of *o*-halogenated β-cyano- and β-oxoenamines to indoles were discovered by Kametani[434] and Suzuki.[435,436] More recently, this method has been used to make carbazoles (Scheme 104)[45] and carbazole quinone alkaloids.[437]

Copper(I) has been used in a modified intramolecular Goldberg amide arylation to forge several β-carbolines,[438] and we have already cited the use of CuOTf to promote the decomposition of α-diazo carbonyl compounds and C–H bond



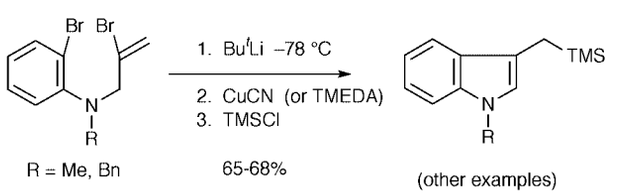
Scheme 104

insertion leading ultimately to tricyclic indoles.[401–403] A nice variation of this latter reaction leads to the indole ring directly from acylenamines and methyl diazoacetate (Scheme 105).[439]



Scheme 105

Barluenga *et al.* have reported a novel copper-promoted carbometalation of *o*-bromo-*N*-(2-bromoallyl)anilines leading to 2-substituted or 2,3-disubstituted indoles (Scheme 106).[440]



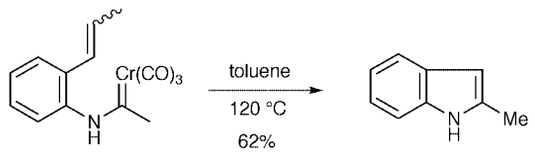
Scheme 106

8.6 Chromium

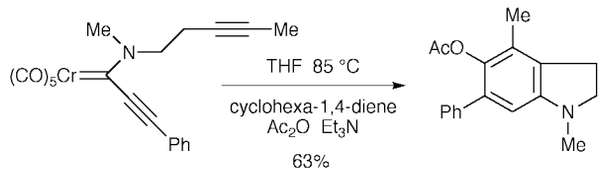
Chromium is a new entrée to the indole ring synthesis arena. Söderberg *et al.* have found that substituted indoles are formed from anilino-substituted Fischer chromium carbenes having *o*-alkenyl substituents on the benzene ring (Scheme 107).[441] The related cyclization of *o*-alkynylanilino chromium carbene complexes leads to indol-3-ylketene complexes by a tandem alkyne insertion–carbonylation sequence. Chromium removal and hydrolysis furnishes indole-3-acetic acids.[442] Benzocarbazoles and other fused indoles were prepared using this methodology.[442] Rahm and Wulff have described the Cr-induced cyclization of amine-tethered bisalkyne carbene complexes leading to 5-hydroxyindolines (Scheme 108).[443]

8.7 Molybdenum

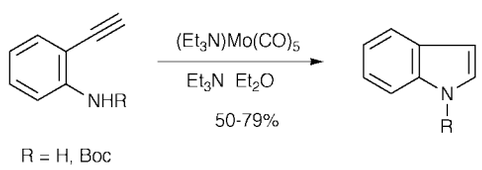
McDonald and Chatterjee have discovered the molybdenum-promoted cyclization of 2-ethynylanilines to indoles (Scheme 109).[444]



Scheme 107



Scheme 108

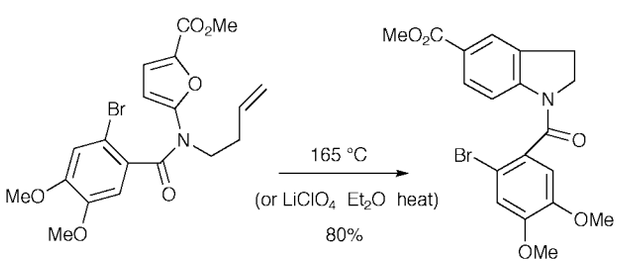


Scheme 109

9 Cycloaddition and electrocyclization

9.1 Diels–Alder cycloaddition

Padwa and co-workers have used inter- and intramolecular Diels–Alder reactions of 2-substituted aminofurans to effect the syntheses of indolines and indoles.[190,445–449] For example, indoline **53** was crafted in this fashion and then used to synthesize the alkaloid oxoassoanine (Scheme 110).[448]



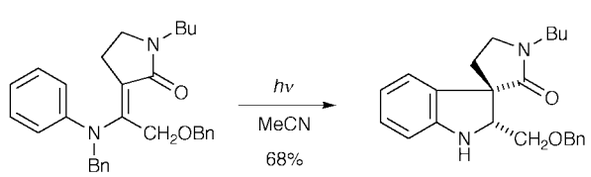
Scheme 110

Intramolecular Diels–Alder reactions of pyrazin-2(1*H*)-ones, with an *o*-alkynylanilino side chain, have been employed to access α- and β-carbolinones.[450]

9.2 Photocyclization

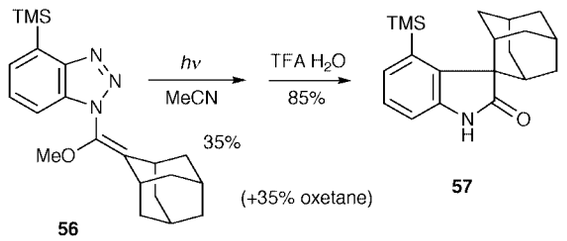
9.2.1 Chapman photocyclization

The well-established Chapman photocyclization of *N*-arylenamines to indolines[451] has been used in the synthesis of 8,10-dimethoxyellipticine,[341] fluorocarbazoles,[452] azatetrahydrocarbazolones,[329] and hexahydrocarbazolones.[453] Photocyclization routes to indoline spirolactones,[454] spiroimides,[455,456] and spirolactams[456] have also been developed. An example of the latter transformation is **54** to **55**.[456]



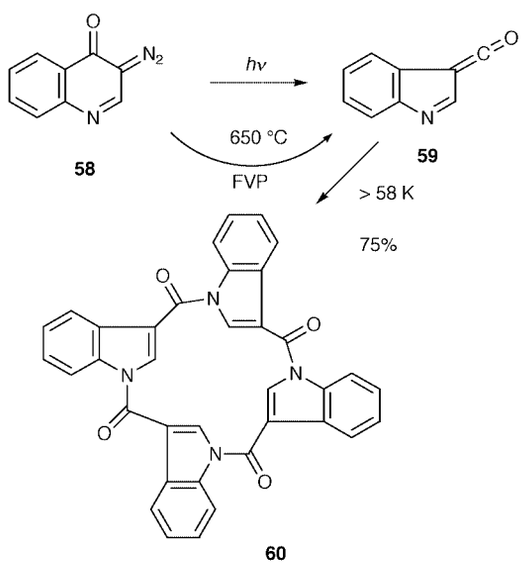
9.2.2 Miscellaneous photochemical reactions

The photolysis of *o*-alkynyltelluroimidates yields 3-acylindoles,[457] and the photolysis of the benzotriazolyladamantane **56** leads to oxindole **57** after hydrolysis (Scheme 111).[458,459] This reaction, which was first discovered by Wender and Cooper,[460] has been employed in a total synthesis of gelsemine.[461]



Scheme 111

Photolysis of α-diazo ketone **58** affords indolylketene **59** which is only stable below 58 K. Above this temperature tetrameric indole **60** forms in high yield (Scheme 112).[462,463]

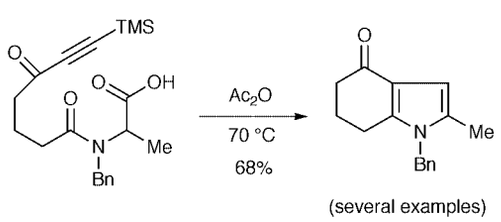


Scheme 112

Giese has observed that *o*-acylaniline derivatives undergo photocyclization to 3-hydroxyindolines.[464]

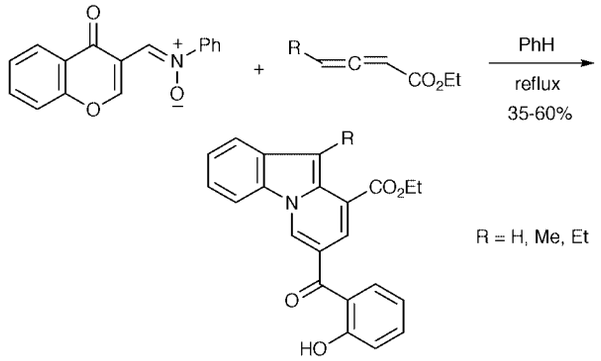
9.3 Dipolar cycloaddition

Vedejs and Monahan have reported the intramolecular 1,3-dipolar cycloaddition of an *N*-methyloxazolium species to an alkyne giving rise to indoloquinones.[465] A münchnone generation and intramolecular cycloaddition protocol by Martinelli and co-workers leads to 4-oxo-4,5,6,7-tetrahydroindoles (Scheme 113).[466,467]



Scheme 113

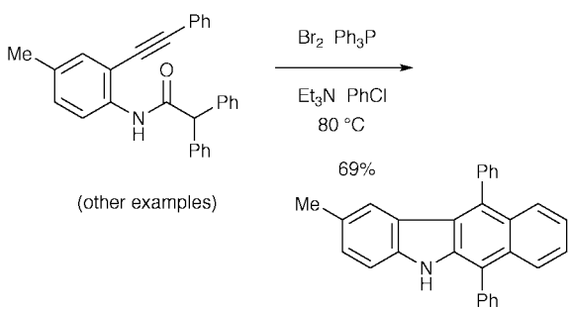
Ishar and Kumar have described 1,3-dipolar cycloadditions between allenic esters and nitrones to yield benzo[*b*]indolizines, the result of a novel sequence of molecular reorganizations (Scheme 114).[468]



Scheme 114

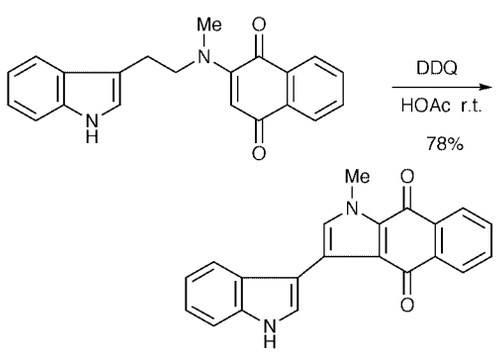
9.4 Miscellaneous

The biradical cyclization of enyne-ketenimines and enyne-carbodiimides is a powerful route to nitrogen heterocycles,[469–471] including fused indoles such as benzocarbazoles (Scheme 115)[470] and indolo[2,3-*b*]quinolines.[471] These reactions appear to involve a stepwise biradical alternative mechanism to the concerted Myers–Saito cycloaromatization pathway.



Scheme 115

Cava and co-workers discovered the surprising cyclization shown in Scheme 116 *en route* to the preparation of a wakayin model system.[472] The *N*-methyl group was necessary for a successful reaction, as the NH compound failed to undergo formation of the pyrrole ring.



Scheme 116

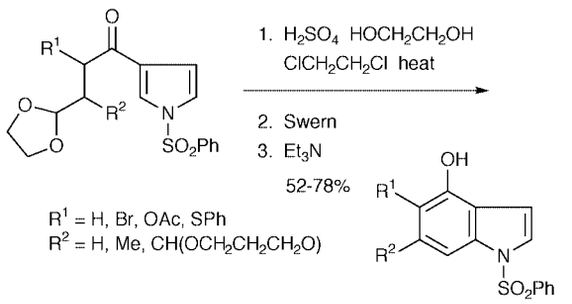
10 Indoles from pyrroles

10.1 Electrophilic cyclization

10.1.1 Natsume indole synthesis

Natsume and co-workers have adapted their indole synthesis to the preparation of herbindole and trikentrin model compounds,[473] as well as to the syntheses of several of these marine alkaloids.[474] This latter study established the absolute configuration of these indole alkaloids. This synthetic strategy, which involves electrophilic cyclization to C-2 or C-3 of a suitably tethered pyrrole substrate, has been used to construct the indole

ring in hapalindole O[475] and in mitosene analogs related to FR 900482 and FR 66979.[476] The method is particularly effective for the preparation of 4-hydroxyindoles (Scheme 117).[476]

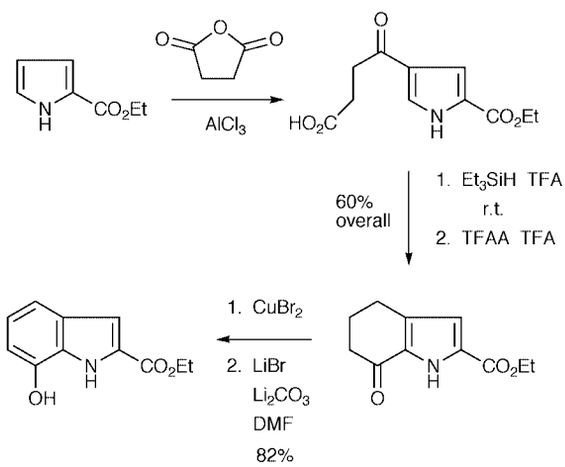


Scheme 117

The Natsume protocol has been used to synthesize (*S*)-(−)-pindolol and chuangxinmycin,[477] and Katritzky *et al.* have developed an alternative route to the Natsume cyclization substrates using the lithiation of 2-benzotriazolylmethylpyrroles followed by reaction with α,β-unsaturated aldehydes and ketones.[478–480] Recently, Natsume and co-workers have synthesized (+)-duocarmycin SA using his indole ring synthesis.[481]

10.1.2 Miscellaneous

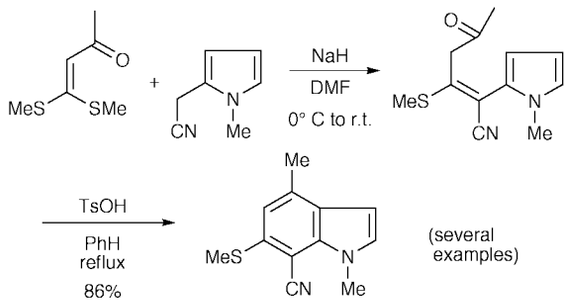
Murakami and co-workers have described an electrophilic cyclization route to 7-oxo-4,5,6,7-tetrahydroindole, initiated by the reaction of ethyl pyrrole-2-carboxylate and succinic anhydride (Scheme 118).[482] Another route to oxotetrahydroindoles involves the Friedel–Crafts acylation of *N*-methylpyrrole with lactones.[483] For example, the reaction of γ-valerolactone and *N*-methylpyrrole with $AlCl_3$ affords 1,4-dimethyl-7-oxo-4,5,6,7-tetrahydroindole in 65% yield.[483]



Scheme 118

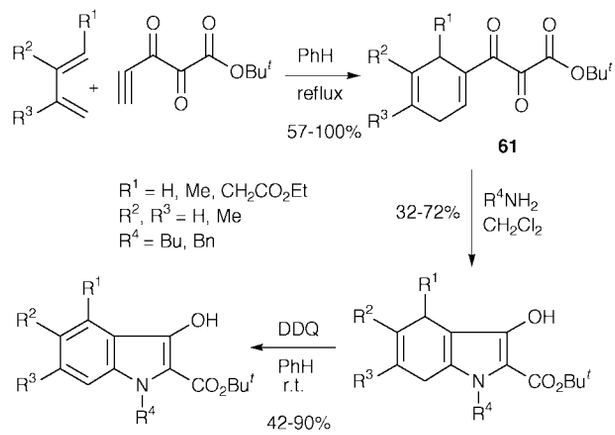
4-Oxotetrahydroindoles are important indole precursors and Edstrom and Yu have employed these intermediates in concise syntheses of 5-azaindole analogs[484] and 3-substituted 4-hydroxyindoles,[485,486] which were used to prepare indolequinones. Other routes to 4-oxo-4,5,6,7-tetrahydroindoles have been described, including the synthesis of 6-aminomethyl derivatives[487] and the enol triflate of *N*-tosyl-4-oxo-4,5,6,7-tetrahydroindole which was employed in Pd-catalyzed cross-coupling reactions.[488] Other electrophilic cyclization methodologies for converting pyrroles to indoles have been reported for the synthesis of 6-azaindoles,[489] novel fused indoles as potential dopamine receptor agonists,[490] 7-chloroindoles,[491] 4,5,6,7-tetrasubstituted and related indoles (Scheme 119),[492] and 1-benzyl-3-phenylindole and related indoles.[493]

Wasserman and Blum have reported a general synthesis of



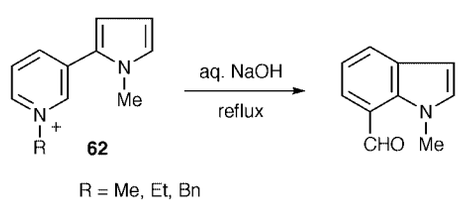
Scheme 119

2-alkoxycarbonyl-3-hydroxyindoles that involves a Diels–Alder cycloaddition, pyrrole ring formation from the tricarbonyl cycloadduct **61**, and DDQ oxidation (Scheme 120).[494]



Scheme 120

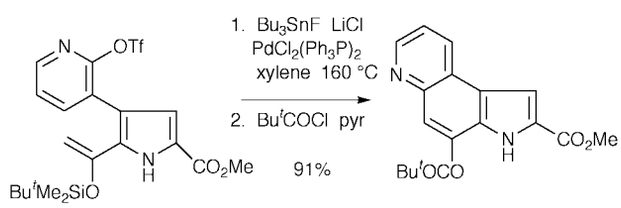
The interesting rearrangement of nicotine pyrrole **62** to 1-methylindole-7-carbaldehyde has been uncovered (Scheme 121),[495] and 7-azaindoles are fashioned in one-pot by the annulation of 2-aminopyrroles with the enolates of 3,3-dimethoxy-2-formylpropanenitrile and ethyl 3,3-diethoxy-2-formylpropanoate.[496]



Scheme 121

10.2 Palladium-catalyzed cyclization

Palladium has been employed in a synthesis of duocarmycin SA as illustrated in Scheme 122.[497,498]



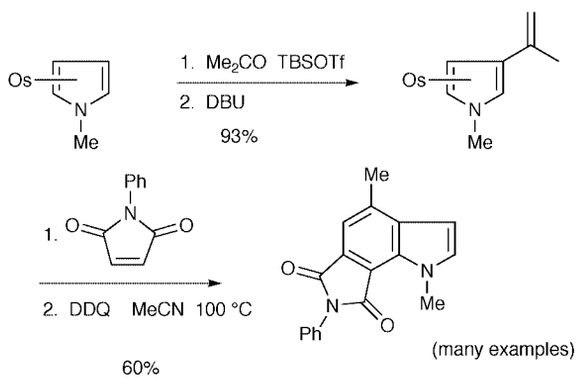
Scheme 122

10.3 Cycloaddition routes

10.3.1 From vinylpyrroles

The Diels–Alder cycloaddition of 2- and 3-vinylpyrroles is an attractive route to indoles, and several new examples of this

strategy have been reported in recent years. Ketcha and Xiao have synthesized 2- and 3-vinyl-1-(phenylsulfonyl)pyrroles and examined their Diels–Alder chemistry.[499] Domingo *et al*. have presented theoretical studies of the reactions of 1-methyl-2-vinylpyrroles with dimethyl acetylenedicarboxylate,[500,501] studies that suggest the existence of two competitive mechanisms depending on the solvent: an asynchronous concerted mechanism and a stepwise mechanism (Michael addition reaction). Harman and co-workers have developed an indole synthesis from Diels–Alder reactions of pentaammineosmium-pyrrole complexes (Scheme 123).[502,503]

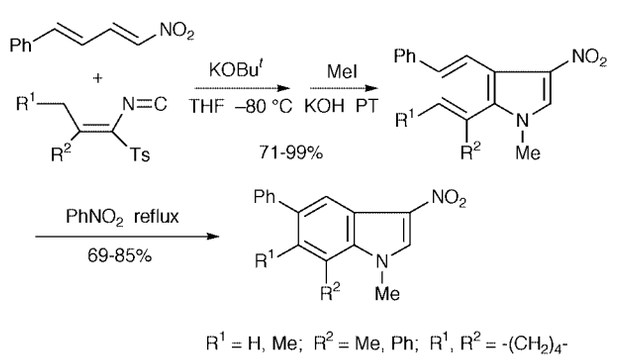


Scheme 123

An approach to the alkaloid martinelline utilizes an indium-catalyzed Diels–Alder reaction between aryl imines and *N*-acyl-2,3-dihydropyrroles.[504] Photolysis of 2-styrylpyrroles affords indoles,[505] and photolysis of thiobenzamide and 3-furylpropenal, which may involve a pyrrole intermediate, affords benzo[*g*]indoles.[506]

10.3.2 From pyrrole-2,3-quinodimethanes

The synthesis of 3-nitroindoles *via* the electrocyclization of nitropyrrole-2,3-quinodimethanes, reported in the last review, has been extended to a general synthesis of these compounds (Scheme 124).[507]

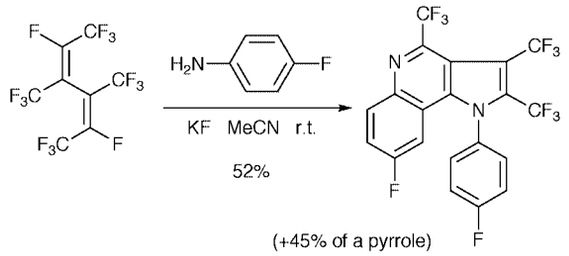


Scheme 124

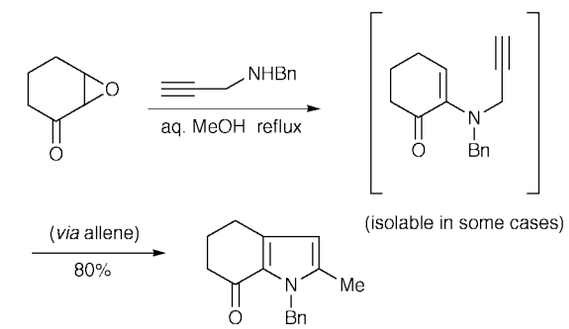
10.3.3 Miscellaneous

The sealed-tube reaction of 4,5-dicyanopyridazine with indole or *N*-methylindole affords the corresponding 2,3-dicyanocarbazoles in 59% and 53% yields, respectively.[508] However, a similar cycloaddition reaction with *N*-methylpyrrole gives 5,6-dicyano-1-methylindole in only 15–17% yield. Perfluoro-3,4-dimethylhexa-2,4-diene reacts with anilines in the presence of fluoride to yield pyrroloquinoline derivatives (Scheme 125).[509]

The thermolysis of *N*-alkyl-*N*-vinylprop-2-ynylamines provides 7-oxo-4,5,6,7-tetrahydroindoles in good yield (Scheme 126).[510]



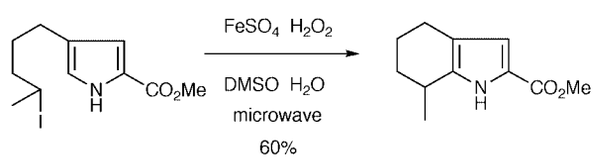
Scheme 125



Scheme 126

10.4 Radical cyclization

New routes to 4,5,6,7-tetrahydroindoles involving the radical cyclization of an iodoalkyl-tethered pyrrole (Scheme 127)[511] and a 2-alkenyl-tethered 3-iodopyrrole have been elaborated.[512]

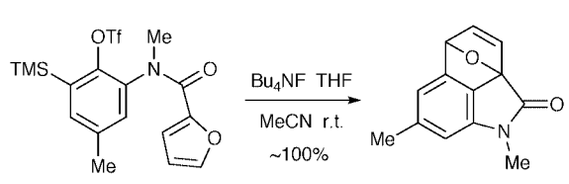


Scheme 127

11 Aryne intermediates

11.1 Aryne Diels–Alder cycloaddition

The ergot model **63** was obtained in essentially quantitative yield *via* the intramolecular aryne cycloaddition reaction shown in Scheme 128.[513]



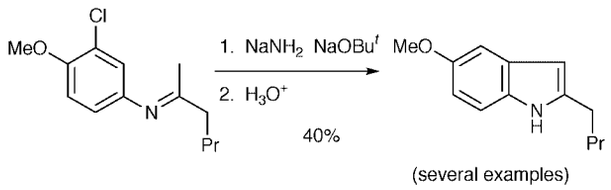
63

Scheme 128

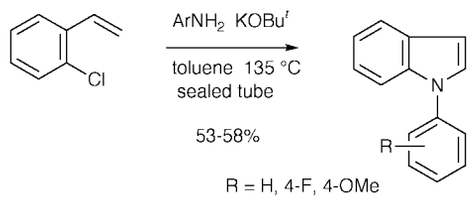
11.2 Nucleophilic cyclization of arynes

Caubère and co-workers have described in full their synthesis of tetrahydrocarbazoles and other indoles using the complex base $NaNH_2$–*t*-BuONa to generate the requisite arynes for cyclization.[514] More recently, this group has extended this methodology to an efficient synthesis of 2-substituted indoles by the arynic cyclization of halogenated aryl imines (Scheme 129).[515]

Beller *et al*. have discovered a novel "domino hydroamination aryne cyclization reaction" to give *N*-aryl indolines from *o*-chlorostyrenes in good yields (Scheme 130).[516] This method is superior to previous cyclizations of 2-(2-chlorophenyl)ethylamines.



Scheme 129



Scheme 130

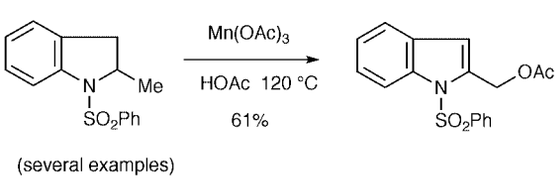
In chemistry similar to the Bailey–Liebeskind indole synthesis (Section 3.9), Barluenga and co-workers have found that the treatment of *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline with *tert*-butyllithium gives 1,3-dimethyl-4-lithioindole by intramolecular aryne cyclization. Quenching this intermediate with suitable electrophiles affords the 4-functionalized indoles.[517]

12 Miscellaneous indole syntheses

12.1 Oxidation of indolines

Although indolines (2,3-dihydroindoles) are an obvious vehicle for the synthesis of indoles, there has never been an efficient, general method for this oxidation reaction. However, a few new methods to address this problem have been described in recent years.

The use of catalytic tetra-*n*-propylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide is reported by Goti and Romani to oxidize indoline to indole in 73% yield.[518] The generality of this conversion remains to be seen. Carter and Van Vranken have observed the photooxidation of 2-indol-2-ylindolines to 2,2′-biindolyls,[519] and Giethlen and Schaus have investigated the mechanism of the oxidation of indolines with potassium nitrosodisulfonate (Frémy's salt) to furnish either indoles or 5-hydroxyindoles.[520] It was determined by isolation that an intermediate iminoquinone forms in this reaction. Ketcha *et al*. have utilized Mn(III) in the oxidation of 2-methyl-1-(phenylsulfonyl)indolines to the corresponding 2-acetoxymethylindoles (Scheme 131).[521]



Scheme 131

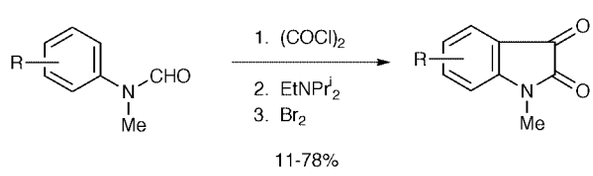
12.2 From oxindoles, isatins and indoxyls

Since we have included in this review the synthesis of oxindoles, isatins, and indoxyls, it seems appropriate to cite newer methods and applications for the conversion of these compounds to indoles.

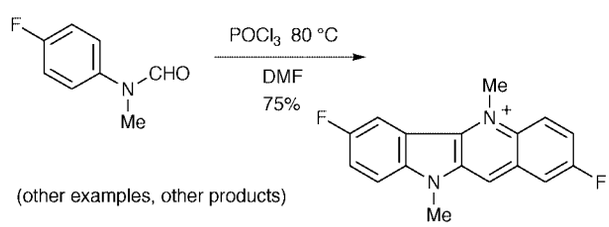
Williams and co-workers have employed the combination of $NaBH_4$ and $BF_3{\cdot}OEt_2$ to reduce an oxindole to an indole in their synthesis of (+)-paraherquamide B.[206] Other reduction methods were unsuccessful. Black and Rezaie have coupled oxindoles with benzofurans using triflic anhydride to give 2-indolylbenzofurans,[522] and Beccalli and Marchesini have synthesized 3-acyl-2-vinylindoles from chloroalkylidene oxindoles using a Stille reaction on the corresponding indolyl-2-triflates.[523] The chloroalkylidene oxindoles can also be easily transformed into 3-alkynylindoles.[524] The reduction of *N*-acylisatins to *N*-alkylindoles proceeds excellently with diborane,[525] and isatins are converted into oxindoles with hydrazine.[526] Merlic and co-workers have effected a Friedlander quinoline synthesis on an *N*-acylindoxyl to afford a quindoline, which was used to prepare the RNA-binding fluorochrome Fluoro Nissl Green.[527] As mentioned earlier (Section 2.6), Sakamoto and co-workers have used a tandem Wittig–Cope reaction sequence on 2-allylindoxyls to prepare 3-substituted indoles (Scheme 18).[102] Earlier work showed that Wittig reactions of indoxyls that cannot undergo a Cope reaction afford 3-substituted indoles.[528]

12.3 Miscellaneous

The thermolysis (900 °C) of *N*-(2-acetoxyethyl)acetanilide yields many products including some indole,[529] and flash vacuum pyrolysis of 1-phenyl-4-methoxycarbonyl-1,2,3-triazole affords a small amount of 3-methoxycarbonylindole *via* an imino carbene intermediate.[530] Treatment of *N*-(methyl)-anthranilic acids with the Vilsmeier reagent ($POCl_3$–DMF) leads to 3-chloroindole-2-carbaldehydes.[531] Meth-Cohn has uncovered interesting chemistry when Vilsmeier reagents are generated under basic conditions.[532–534] Thus, exposure of formanilides sequentially to oxalyl chloride, Hünig's base, and bromine affords, after hydrolysis, the corresponding isatin (Scheme 132).[532–534] Under slightly different conditions, *N*-alkylformanilides and $POCl_3$ yield the indolo[3,2-*b*]quinolines (Scheme 133).[534]

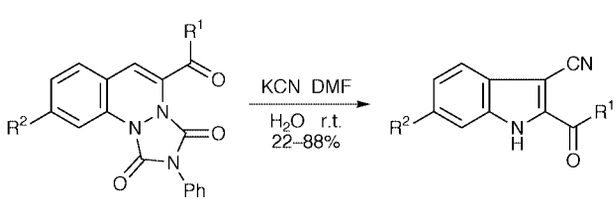


Scheme 132



Scheme 133

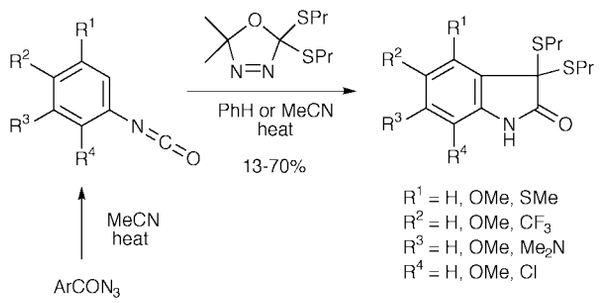
An unusual cyanide-induced skeletal rearrangement of 3-acyl- and 3-ethoxycarbonyl-1,2-dihydrocinnoline-1,2-dicarboximides leads to 2-acyl- and 2-ethoxycarbonyl-3-cyanoindoles (Scheme 134),[535] a reaction based on similar rearrangements discovered earlier.[536–538]



Scheme 134

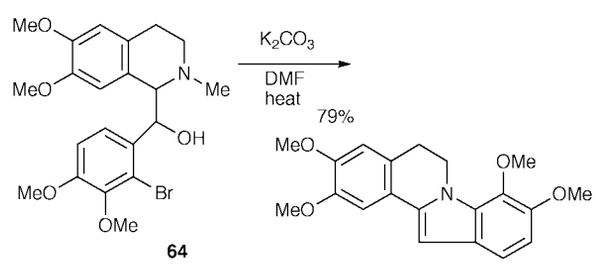
Ciufolini *et al*. have used the cyclization of 2-amino-2,3-dihydrobenzoquinone monoketals to obtain fused indolines after appropriate manipulation.[539] Studies by Paz and Hopkins

on the antitumor antibiotic agents FR66979, FR900482, and FK973, which are DNA crosslinkers similar to mitomycin C, indicate that cyclization to an indole is likely involved in the mode of action of these compounds.[540] Rigby and co-workers have developed several variations of the reaction between vinyl isocyanates and isocyanides or nucleophilic carbenes to afford functionalized oxindoles or isatins. Thus, these workers have prepared simple hydrooxindoles,[541–543] oxindoles (Scheme 135),[544] hydroisatins,[545–546] and the alkaloid degradation product (±)-α-lycorane.[547]



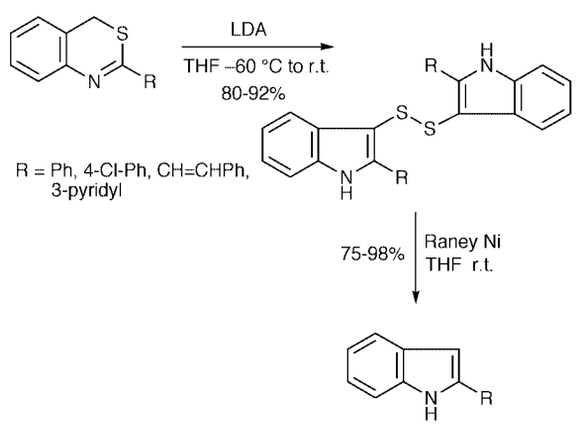
Scheme 135

An unusually facile cyclization of tetrahydroisoquinoline **64** leads to the indolo[2,1-*a*]isoquinoline ring system (Scheme 136).[548] Several examples of this reaction were reported.



Scheme 136

The reaction of diarylnitrones with trimethylsilylketene affords oxindoles,[549] and 1,4-naphthoquinone reacts with aza-*ortho*-xylylenes, which were generated from benzosultams, to give naphthoquinone spiroindolines.[550] Base-induced dimerization of 4*H*-3,1-benzothiazines gives 2-substituted indoles after reduction of the intermediate diindolyl disulfides (Scheme 137).[551]



Scheme 137

13 Acknowledgements

The author wishes to thank Professor Phil Crews and his colleagues and students at the University of California, Santa Cruz, for their hospitality during a sabbatical leave in 1999–2000 when this article was written. This paper is dedicated to the memory of Dr Pierre D. Lord, 1936–1999, fellow graduate student, indole chemist and friend.

14 References

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Review a909834h