Recent developments in indole ring synthesis—methodology and applications*

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Reviewing the literature published between 1990 and 1993

1 Introduction

Ever since the early studies, more than 100 years ago, by Baeyer[1] and others on the chemistry of indigo, isatin, and related compounds, indole and its myriad derivatives—both natural and unnatural—have captured the imagination of organic chemists, especially with regard to syntheses of the indole ring system.[2-7] Because the present review is restricted to coverage of the 1990–1993 literature, some excellent indole syntheses that were not utilized during this period are not covered herein (*e.g.*, those of Houlihan,[8] Saegusa,[9] and Smith[10]). Furthermore, with a few exceptions, syntheses of oxindoles, indolines, isatins, indoxyls, and related indole analogues, like carbazoles and carbolines, could not be included for reasons of space. This was unfortunate, since, for example, several excellent new oxindole syntheses have been reported during this period.[11-14] The organization of this review follows the type of reaction involved in the key step. In some cases, new or previously unnamed syntheses are named according to their discoverer(s) and/or developer(s).

2 Sigmatropic rearrangements

2.1 Fischer indole synthesis

Despite its myriad complications, rearrangements, and mechanistic mysteries, the Fischer indole synthesis, in which the key step is a [3,3]-sigmatropic rearrangement, remains the epitome of indole ring construction methods, and an exhaustive review is

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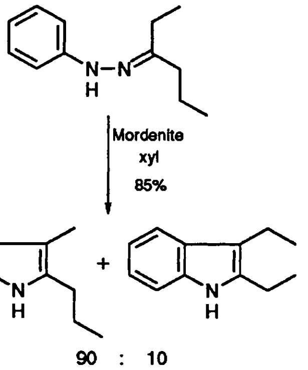
*Dedicated to the memory of Professor Manfred E. Mueller, San Francisco City College, 1911–1992.

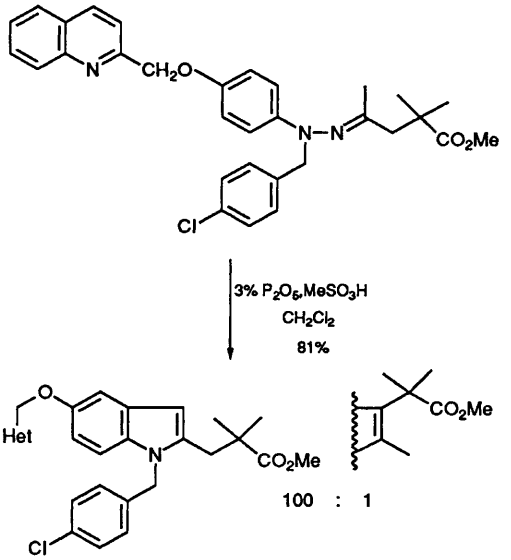
available.[15] Nevertheless, recent years have seen several improvements and novel applications of this classical reaction,[16,17] as well as new mechanistic surprises.

2.1.1 Methodology

The use of zeolites improves the regioselectivity in the Fischer indolization of phenylhydrazones from unsymmetrical ketones (**Scheme 1**),[18,19] and Eaton's reagent ($P_2O_5/MeSO_3H$) is highly regioselective in furnishing the 3-unsubstituted indole (**Scheme 2**).[20]

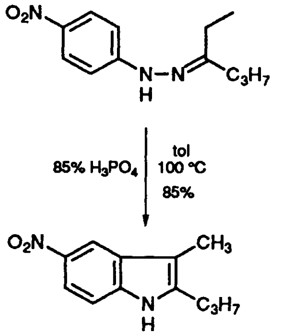


Scheme 1

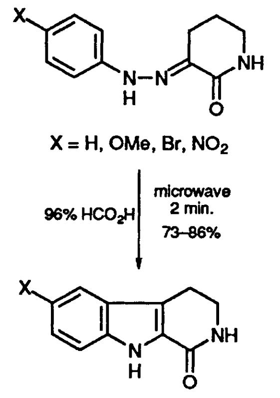


Scheme 2

Katritzky has found that the combination of (85% H_3PO_4)/toluene is crucial to a greatly improved preparation of nitroindoles (**Scheme 3**),[21] and Abramovitch used 96% HCO_2H and microwave irradiation to synthesize efficiently 1,2,3,4-tetrahydro-1-oxo-β-carbolines (**Scheme 4**).[22]



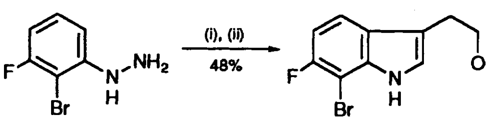
Scheme 3



Scheme 4

2.1.2 Applications

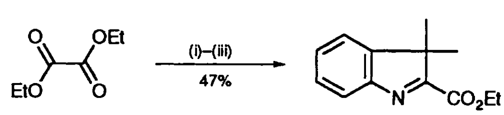
Thummel and his colleagues have made excellent use of the Fischer indole reaction in their syntheses of 'polyaza cavities' such as pyrido[3,2-*g*]indoles and higher condensed molecules.[23-25] Cook has reviewed his work on the Fischer indole construction of the 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]diindole ring system from 4-oxo-1,2,3,4-tetrahydro-β-carbolines.[26] Soll and his colleagues at Wyeth-Ayerst have made extensive use of the Fischer reaction with dihydrofuran to synthesize etodolac derivatives (**Scheme 5**),[27] and a Mexican group has developed a protocol that avoids pyrazole formation in the preparation of (β-oxo)indol-3-yl ketones.[28]



Reagents: (i) O, HCl, THF; (ii) $ZnCl_2$, $(HOCH_2)_2$ 170 °C

Scheme 5

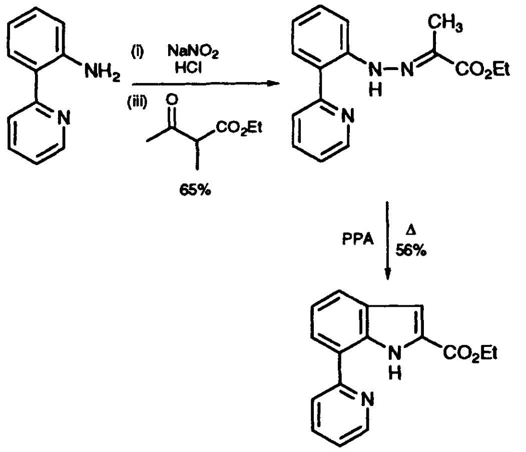
Likewise, an excellent new procedure for the synthesis of ethyl 3,3-dimethyl-3*H*-indole-2-carboxylate has been reported (**Scheme 6**).[29]



Reagents: (i) Pr^iMgCl; (ii) $PhNHNH_2$; (iii) HCl EtOH Δ

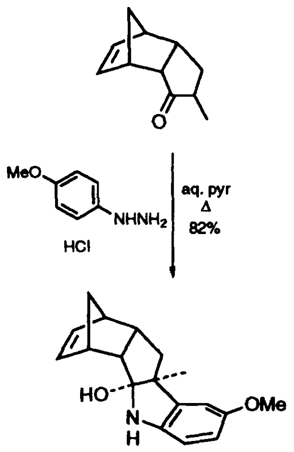
Scheme 6

Black and co-workers have used the Japp–Klingemann reaction as an entry to certain phenylhydrazones which were then converted into 7-substituted (heterocyclic) indoles (**Scheme 7**).[30]



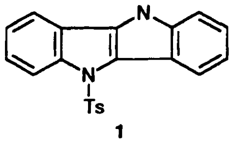
Scheme 7

Not surprisingly, the Fischer indole synthesis continues to find employment in the indole alkaloid field. In an elegant total synthesis of (−)-physovenine, an alkaloid of the calabar bean, Takano *et al.* utilized a non-acidic Fischer indolization as a key step in their sequence (**Scheme 8**).[31]



Scheme 8

This group used the same strategy in a synthesis of several cuparene sesquiterpenes.[32] Bosch and his colleagues have employed the Fischer indole synthesis in an approach to dasycarpidone,[33] and Hart has utilized this indolization in the context of gelsemine model studies.[34] Finally, the Fischer reaction was used to prepare fused indoles such as the indolo[3,2-*b*]indole ring system (*e.g.*, **1**[35]) and the 5,10-dihydroindeno[1,2-*b*]indole ring system (*e.g.*, **2**[36]).



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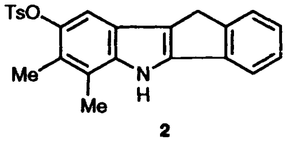

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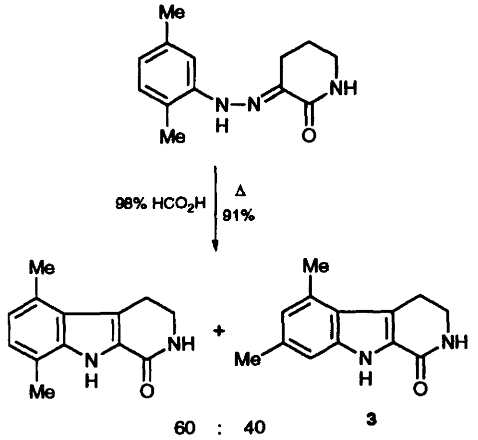
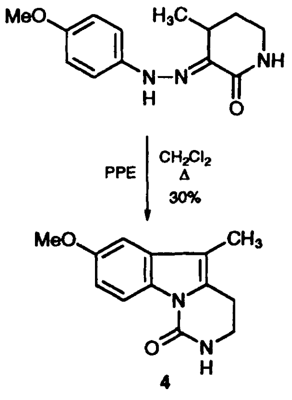
2.1.3 Mechanism

Since this review is primarily directed at the synthesis of indoles, the discussion of mechanistic abnormalities in the Fischer indolization will be brief. Luis and Burguete have discovered a large amount (up to 40%) of the 1,2-methyl migration product **3** during the course of a study (**Scheme 9**),[37] and a similar substrate was found by an Italian group to give the rearranged product **4** (**Scheme 10**).[38]

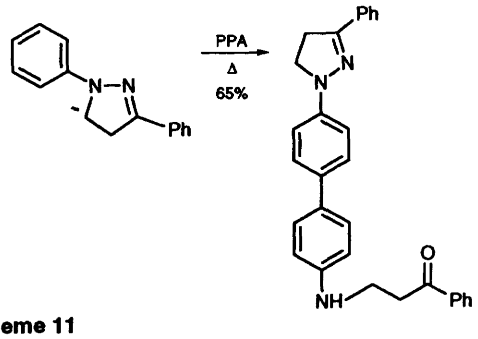


Scheme 9



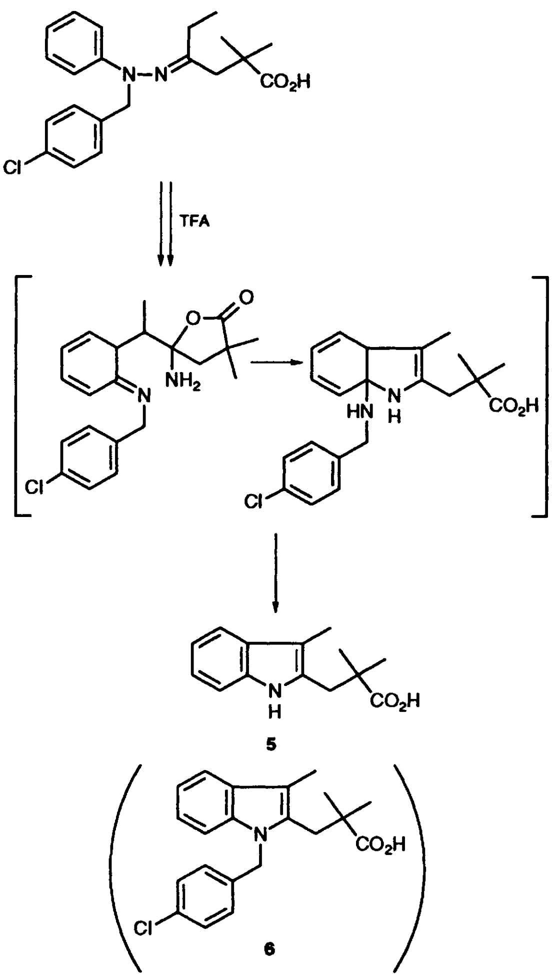
Scheme 10

Ishii and co-workers have extensively investigated the Fischer indolization reactions of the arylhydrazones of ethyl pyruvate, uncovering abnormal pathways and isolating multiple products from some substrates.[39–41] Likewise, in cyclic systems, one often encounters unusual reaction pathways (**Scheme 11**).[42]



Scheme 11

A detailed mechanistic study by Hughes and Zhao has revealed that in strong acid, such as $MeSO_3H$, the benzene ring of the phenylhydrazone can be protonated and that tautomerization of the hydrazone is rate limiting.[43] Another careful investigation provides evidence, including ^{15}N labelling experiments, for the interesting pathway shown in **Scheme 12**,[44] leading to the unexpected product **5**, which is formed in addition to the expected (major) product **6**.

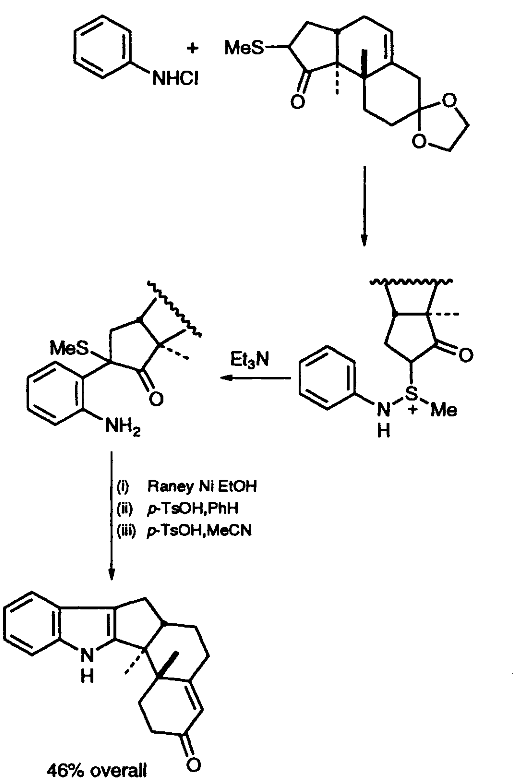


Scheme 12

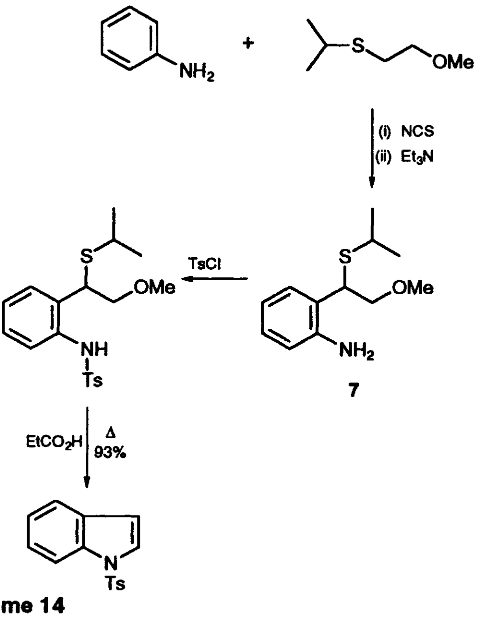
2.2 Gassman indole synthesis

The elegant Gassman indole synthesis,[45] which features a [2,3]-sigmatropic rearrangement, has been employed only sparingly in recent years. Smith has used this methodology in the first reported syntheses of the alkaloids (+)-paspalicine and (+)-paspalinine, the indole-forming step of which is depicted in **Scheme 13**.[46]

A Japanese group has extended the Gassman protocol in a clever way.[47] Following the preparation of the azasulfonium salt and its rearrangement to **7**, these workers found that acid treatment of the derived sulfonamides smoothly leads to indoles (**Scheme 14**), presumably *via* an episulfonium intermediate. A wide range of indoles were prepared in yields up to 95% (*e.g.*, 5-OMe, 5-Me, 5-Cl, 5-NO_2, 7-OMe, 7-Cl, and 7-Me).



Scheme 13

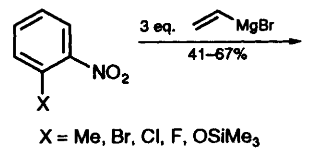


Scheme 14

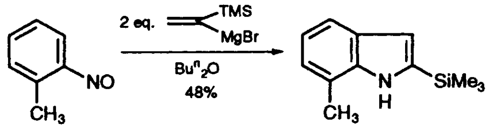
2.3 Bartoli indole synthesis

One of the most exciting recent developments in indole ring construction is the elegant discovery made by Bartoli and his co-workers that nitroarenes and nitrosoarenes react with vinyl Grignard reagents to afford indoles (**Schemes 15** and **16**).[48-50]

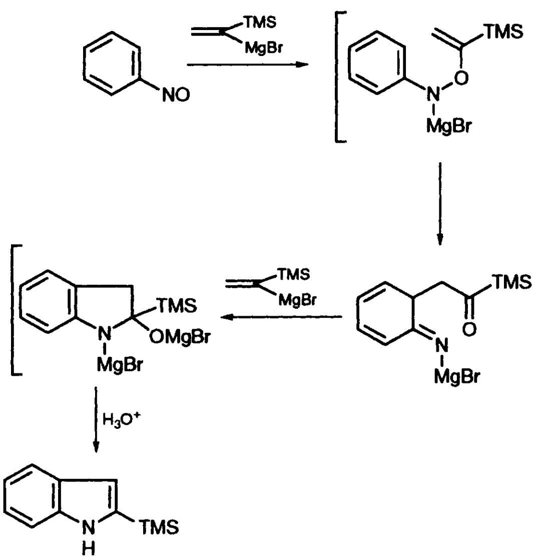
The scope, limitations, and mechanism of these reactions have been explored in substantial detail by Bartoli. The mechanism suggested by Bartoli for the nitrosoarene case is shown in **Scheme 17**.[49]



Scheme 15

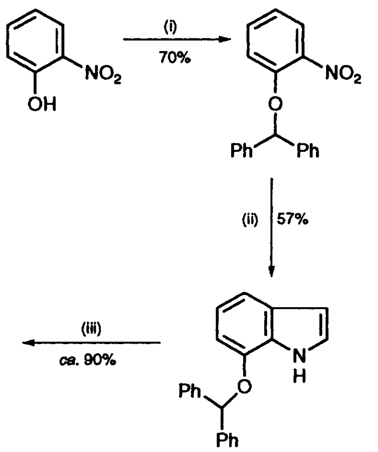


Scheme 16



Scheme 17

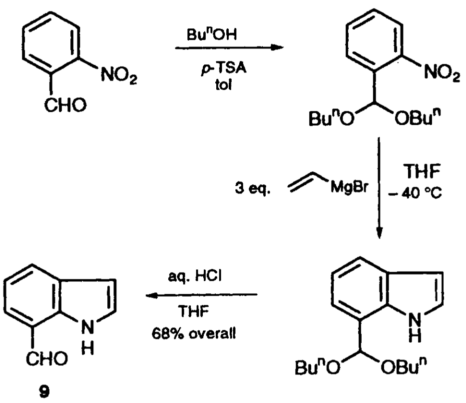
The Bartoli indole synthesis has been found to be far superior to the Gassman synthesis for the preparation of 7-hydroxyindole **8**, as shown in **Scheme 18**.[51] Noteworthy is the use of the benzhydryl protecting group which was preferable to benzyl in the Grignard step.



Reagents: (i) Ph_2CHBr, K_2CO_3, Acetone; (ii) 3 eq MgBr,THF; (iii) H_2, $Pd(OH)_2$, MeOH tol, 50 psi

Scheme 18

This same group of researchers adapted the Bartoli synthesis to an excellent preparation of 7-formylindole **9** (**Scheme 19**), in 68% overall yield on a 70-gram scale.[52]



Scheme 19

However, in a recent synthesis of the topoisomerase II inhibitor BE 10988, Moody found that the Bartoli indole synthesis did not provide the requisite 5,7-dioxygenated indole starting material.[53]

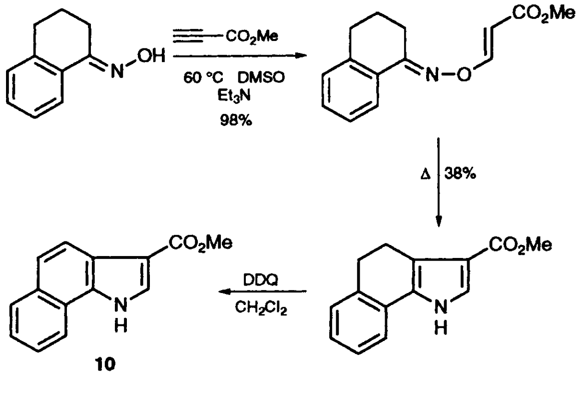
2.4 Miscellaneous sigmatropic rearrangements

A [3,3]-sigmatropic rearrangement is the crux of a short synthesis of the benz[*g*]indole **10** (**Scheme 20**),[54] and a [2,3]-sigmatropic rearrangement sets up the final indolization in the allene **11** (**Scheme 21**).[55]

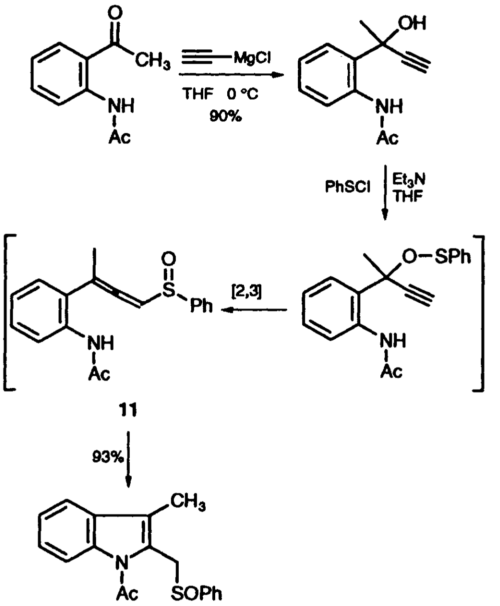
3 Nucleophilic cyclization

3.1 Madelung indole synthesis

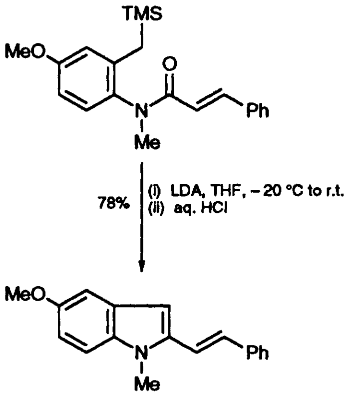
Like the Fischer and Bischler indole syntheses, the Madelung indole synthesis has had a long, rich history since its discovery some 80 years ago.[56] This cyclization method, involving the reaction of *ortho*-alkylanilides with strong base at high temperatures, has seen a number of improvements over the years. For example, Bartoli has reported the intramolecular Peterson olefination of *ortho*-trimethylsilylmethyl anilides under mild conditions (**Scheme 22**),[57] and, more recently, he extended this methodology to the synthesis of *N*-unsubstituted indoles (**Scheme 23**).[58]



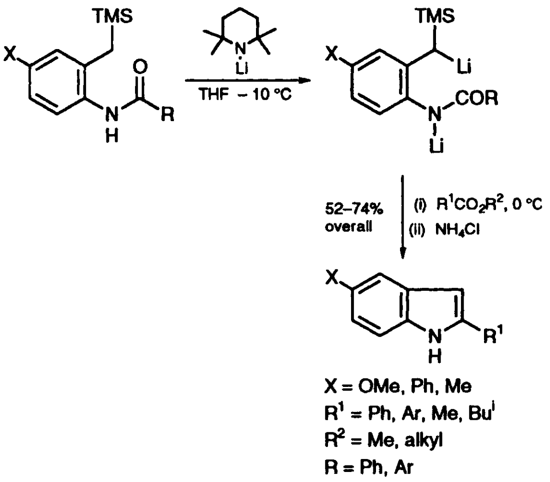
Scheme 20



Scheme 21

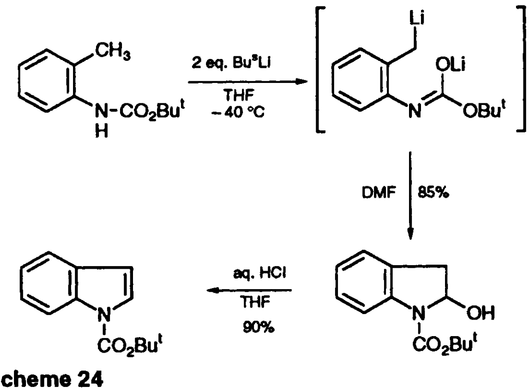


Scheme 22

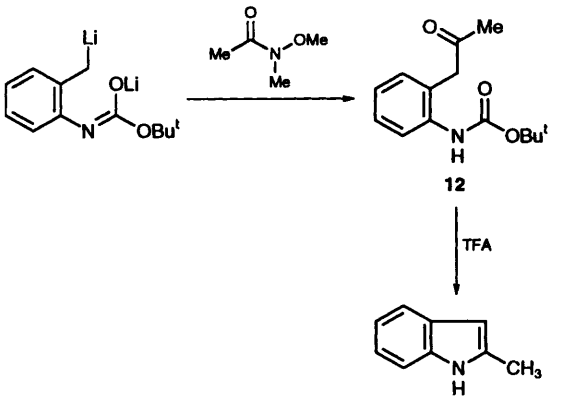


Scheme 23

Mild conditions also prevail in a directed-metalation route to Madelung-reaction type intermediates, as shown in **Scheme 24**.[59,60] Several substituted indoles were prepared in this study. Moreover, the employment of Weinreb's amides allowed for the construction of 2-substituted indoles by trifluoroacetic acid induced cyclization and deprotection of **12** (**Scheme 25**).[59,60]

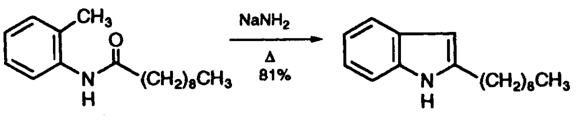


Scheme 24



Scheme 25

Despite these modernizations, the classic Madelung cyclization still finds use in indole ring construction. Thus, an Italian group found the Madelung indole synthesis to be the choice method for the preparation of the antithrombotic-drug-candidate precursor **13** (**Scheme 26**).[61]



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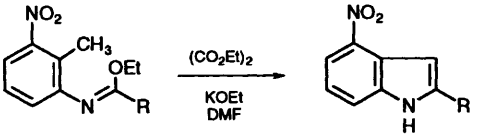
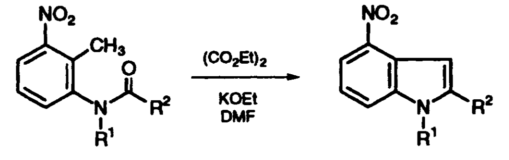
Scheme 26

Bergman has developed several variations of the Madelung rection to craft nitroindoles (**Schemes 27** and **28**);[62] many examples are described and the mechanism is discussed in this paper.[62]



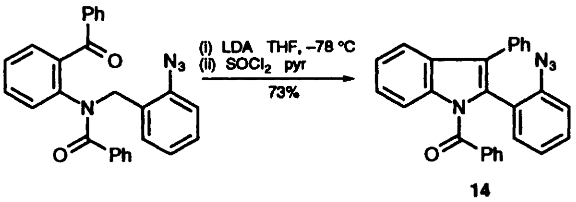
Scheme 27



Scheme 28

3.2 Schmid indole synthesis

In what might be construed as a 'reverse-Madelung' indole synthesis, Molina has utilized a reaction, which was originally discovered by Greuter and Schmid,[63] to prepare indolo[1,2-*c*]quinazoline precursors such as **14** (**Scheme 29**).[64]

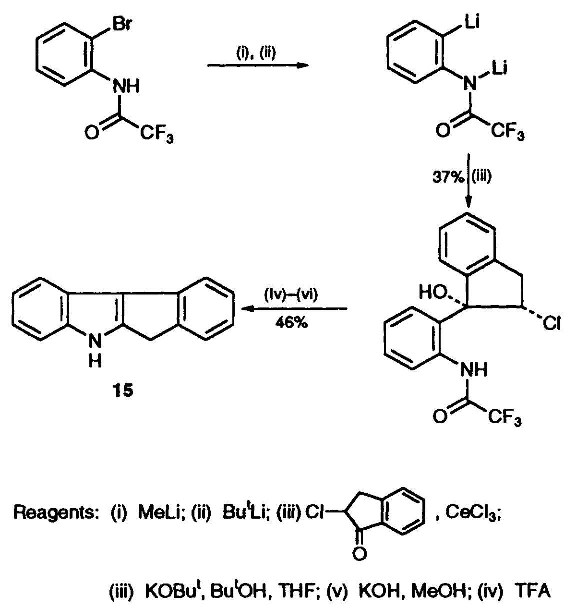


14

Scheme 29

3.3 Wender indole synthesis

The Wender indole synthesis involves the *ortho*-lithiation of *N*-phenylamides followed by reaction with α-haloketones and subsequent ring closure and dehydration.[65] Sainsbury and his co-workers have explored both the Bischler and Wender indole syntheses in order to prepare dihydroindenoindoles such as **15**, but only the latter method worked reasonably well.[66] They found that the addition of ceric chloride somewhat suppressed the enolate formation side-reaction (**Scheme 30**).



15

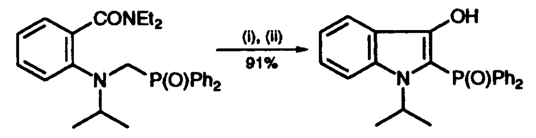
Reagents: (i) MeLi; (ii) Bu^{t}Li; (iii) Cl–, CeCl$_3$;

(iii) KOBu^t, Bu^{t}OH, THF; (v) KOH, MeOH; (iv) TFA

Scheme 30

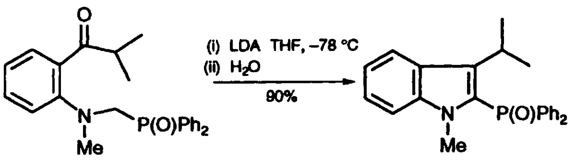
3.4 Couture indole synthesis

Couture and his group have described a simple indole synthesis based on the Wittig–Horner reaction.[67,68] The cyclization is extremely general and high-yielding, affording a variety of indole types (**Schemes 31–33**). The nature of the base dramatically affects the outcome of the reaction (*cf.*, **Schemes 32** and **33**).

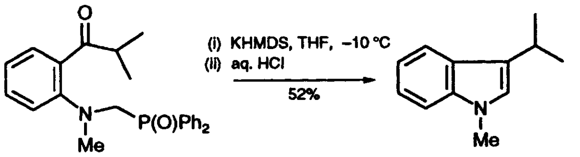


Reagents: (i) Bu^{n}Li, THF, – 78 °C; (ii) H_2O

Scheme 31



Scheme 32



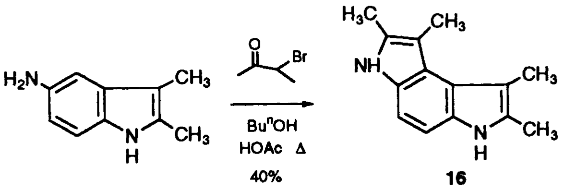
Scheme 33

4 Electrophilic cyclization

4.1 Bischler indole synthesis

The venerable Bischler indole synthesis[69,70] and its several variations involve the electrophilic cyclization of α-arylaminoketones or their synthetic equivalents.

In a study of indole-based conducting polymers and CC-1065 analogues, Dmitrienko and co-workers used the Bischler indole synthesis to prepare the two pyrroloindole ring systems **16** and **17** (**Schemes 34** and **35**).[71] The mode of cyclization in each case was correctly predicted by FMO analysis.



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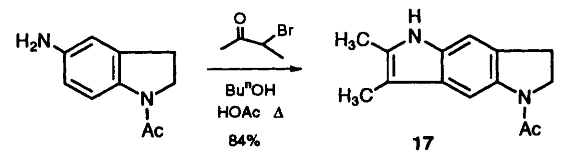
Scheme 34



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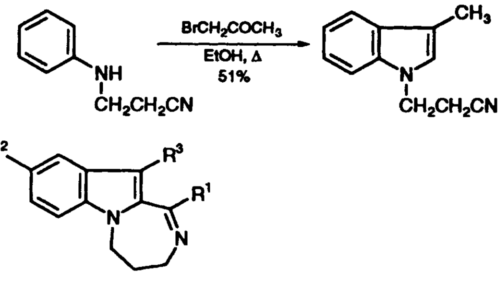
Scheme 35

Basanagoudar deployed the Bischler indole synthesis as the key step (**Scheme 36**) in the preparation of several diazepino[1,2-*a*]indoles **18**.[72]

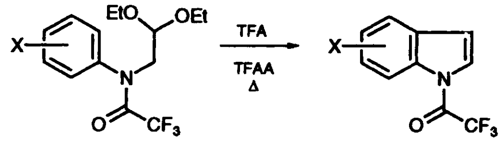


18 ($R^1 = CH_3$, Ph
R^2 = H, CH_3, OMe, OEt
$R^3 = CH_3$, Ph)

Scheme 36

4.2 Nordlander indole synthesis

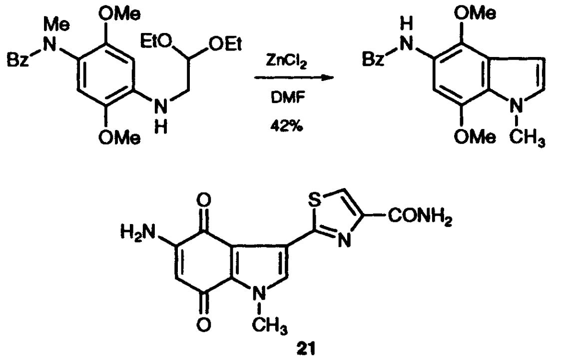
The Nordlander modification of the Bischler indole synthesis involves a combination of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) to effect cyclization of an *N*-trifluoroacetyl-2-anilino acetal (**19**) to the corresponding *N*-trifluoroacetylindole **20** (**Scheme 37**).[73]



19 **20**

Scheme 37

A slightly different version of the Nordlander's route used zinc chloride in a synthesis of the topoisomerase II inhibitor BE 10988 **21**, although the yield of the indole-ring forming step (**Scheme 38**) was only modest.[74]



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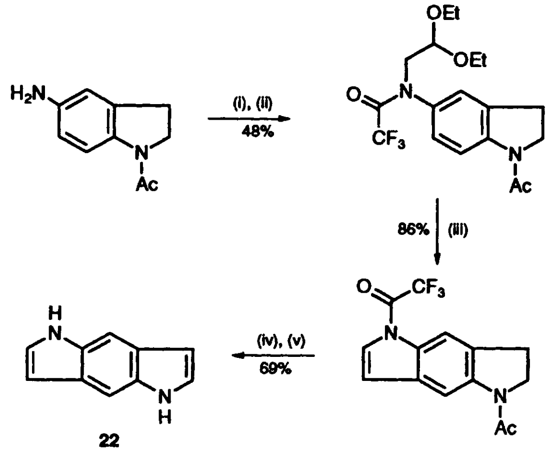
Scheme 38

The Nordlander cyclization was employed by Dmitrienko to fashion the pyrroloindole ring system **22** as shown in **Scheme 39**.[71]



22

Reagents: (i) $BrCH_2CH(OEt)_2$, Na_2CO_3, EtOH; (ii) TFAA, Et_3N; (iii) TFA, TFAA; (iv) DDQ, PhH, Δ; (v) KOH, MeOH

Scheme 39

Earlier, Sundberg developed an important modification of the Nordlander indole synthesis, which employs $TiCl_4$ in the cyclization of *N*-methylsulfonyl-2-anilino acetals.[75]

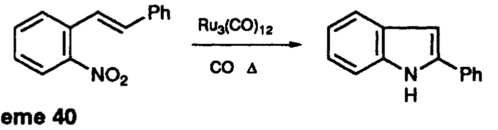
4.3 Nitrene cyclization

Several different approaches to the generation and cyclization of nitrenes to indoles have been explored over the years. As a result, this strategy has emerged as a powerful indole construction method.

4.3.1 Cadogan–Sundberg indole synthesis

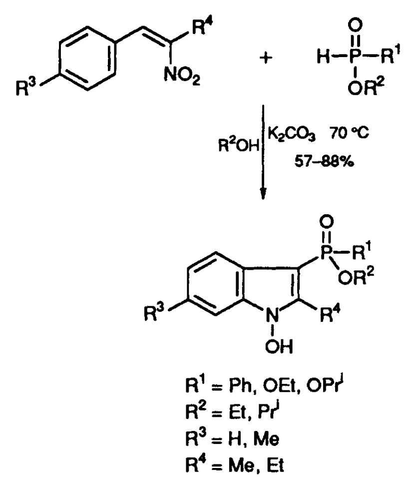
Cadogan[76] and Sundberg[77] discovered, independently, that *o*-nitrostilbenes and *o*-nitrostyrenes are deoxygenated by triethyl phosphite to a nitrene (or equivalent) which then cyclizes to form the indole ring. The cyclization of *α*-nitrostilbene was also reported.[76]

Several variations of this reaction have been described in recent years. Thus, *o*-nitrostilbene is deoxygenated and cyclized to 2-phenylindole with a ruthenium catalyst (**Scheme 40**),[78] and *β*-nitrostyrenes and dialkyl phosphites give rise to 3-dialkoxyphosphoryl-1-hydroxyindoles (**Scheme 41**).[79]

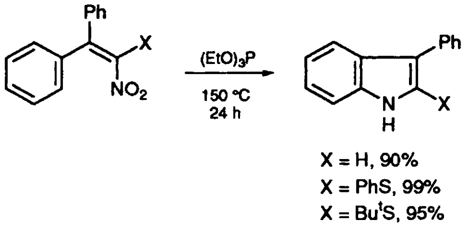


Scheme 40

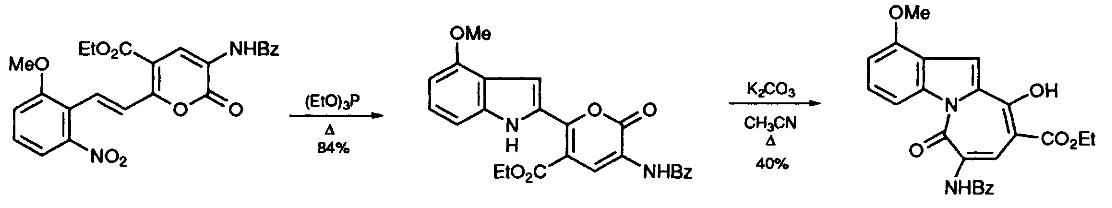
Russell and co-workers have reported the conversion of 2-nitro-1,1-diphenylethylene derivatives to 3-phenylindoles as shown (**Scheme 42**).[80] Likewise, Gelmi and his colleagues have employed this indole ring construction to prepare (unexpectedly) a series of azepino[1,2-*a*]indoles (*e.g.*, **25**) by rearrangement of the initially formed indolylpyranones **24** which were prepared from **23** (**Scheme 43**).[81]



Scheme 41



Scheme 42

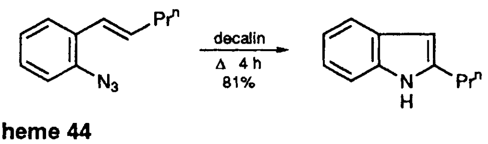


23 24 25

Scheme 43

4.3.2 Sundberg indole synthesis

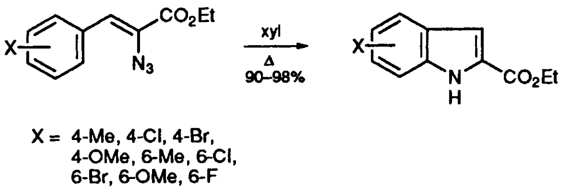
Although several groups, apparently simultaneously, discovered that *o*-azidostyrenes and *β*-azidostyrenes could be converted to indoles on pyrolysis,[82] Sundberg[83] and Hemetsberger (*vide infra*) developed these observations into useful indole construction methods. Thus, Sundberg reported that the thermolysis of *o*-azidostyrenes gives rise to indoles, apparently *via* nitrene formation and electrophilic cyclization (**Scheme 44**).[83] However, this reaction was not particularly successful in a bis-azide application.[84]



Scheme 44

4.3.3 Hemetsberger indole synthesis

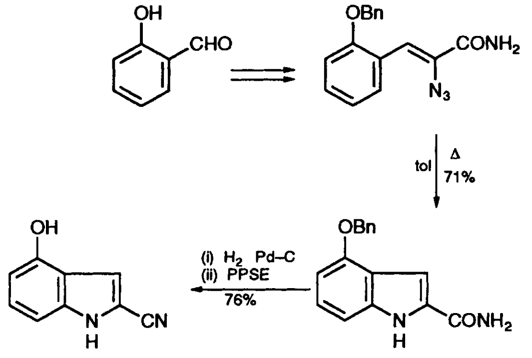
Although a relatively recent indole synthesis, the discovery by Hemetsberger that *α*-azidocinnamates undergo smooth thermolysis to afford indole-2-carboxylates has proven to be very useful in a number of instances. The reaction is exceptionally clean and the yields are high (**Scheme 45**).[85] Moreover, the *α*-azidocinnamates are readily prepared by base condensation of ethyl azidoacetate with the appropriate benzaldehyde.



Scheme 45

The Hemetsberger indole synthesis afforded an entry to 2-cyano-4-hydroxyindole **26** in 30% overall yield from salicylaldehyde (**Scheme 46**).[86] Indole **26** is useful in the preparation of cyanopindolol and other pharmaceuticals.

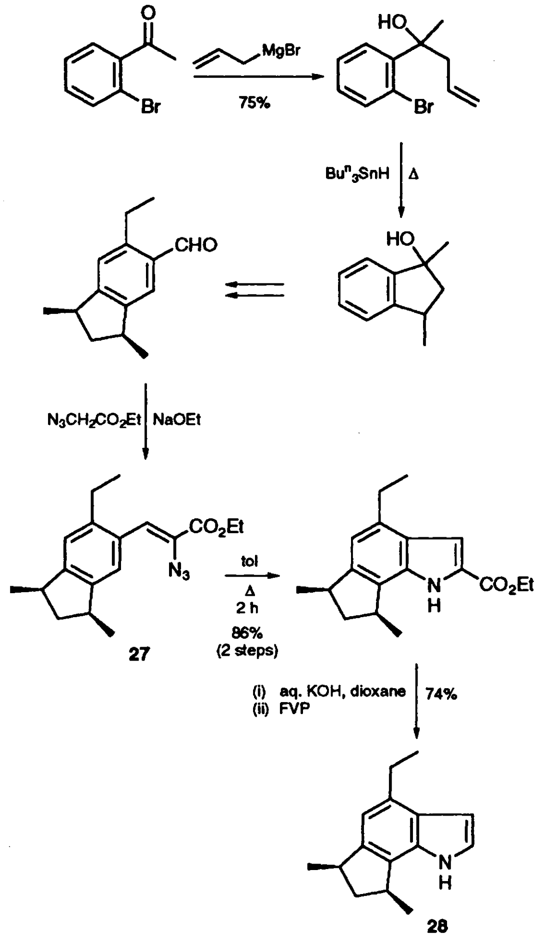
Thermolysis of **27** was the key manœuvre in the synthesis of the marine indoles (±)-*cis*- **28** and (±)-*trans*-trikentrin A, as summarized for the former in **Scheme 47**.[87] It is important to note that no isoquinoline ring formation, by insertion into the benzylic CH_2 group, was observed.



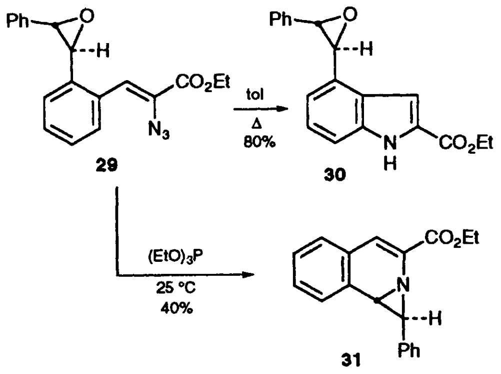
26

Scheme 46

In earlier work, it was found that thermolysis of azide **29** leads to indole **30** in high yield (**Scheme 48**).[88] However, on exposure to triethyl phosphite, **29** is converted into aziridine **31**, presumably *via* iminophosphorane formation and attack on the epoxide.



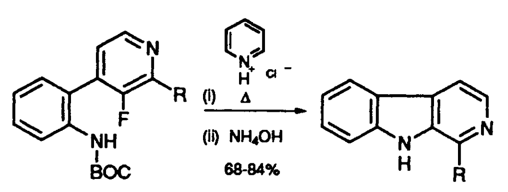
Scheme 47



Scheme 48

4.4 Queguiner azacarbazole synthesis

Queguiner and his colleagues have reported a remarkable cyclization to a pyridine (pyridinium) ring leading to an excellent β-carboline synthesis (**Scheme 49**).[89] This protocol has also been applied to azacarbazoles in general.[90] The biaryl substrates are neatly crafted using a combination of palladium-catalysed cross-coupling and directed-metalation technologies.

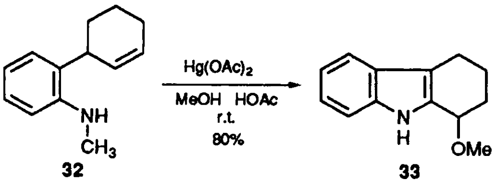


R = Ph, 2-pyr, 2-thienyl, Me, Et, CN

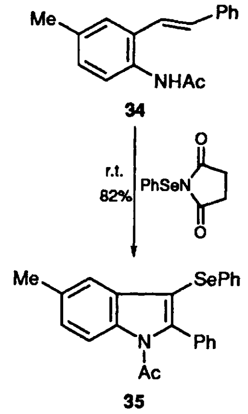
Scheme 49

4.5 Miscellaneous electrophilic cyclizations

Mercuric acetate smoothly transforms amine **32** into tetrahydrocarbazole **33** (**Scheme 50**).[91] The starting amino olefin was prepared *via* an amino Claisen rearrangement. A novel amidoselenation reaction was found to be very effective in the cyclization of amidostilbene **34** to indole **35** (**Scheme 51**).[92]

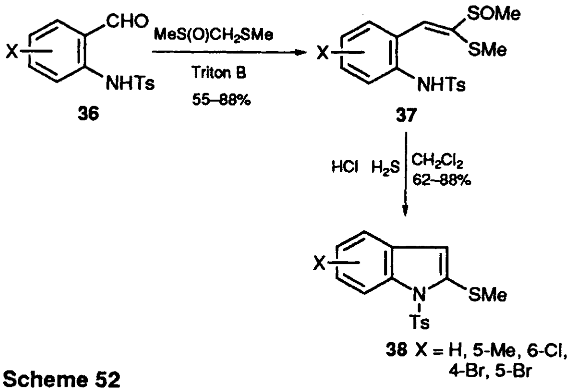


Scheme 50



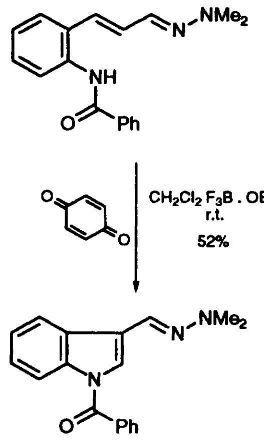
Scheme 51

The use of PhSeBr was less effective. An accidental discovery has led to a new indole ring synthesis (**Scheme 52**).[93] The starting materials **36** were prepared from substituted methyl anthranilates. In the key acid-promoted cyclization of **37** → **38**, it was found that H_2S prevents the formation of the 3-chloro derivatives.



Scheme 52

In a most unusual role for benzoquinone, Echavarren reported the novel indole synthesis shown in **Scheme 53**,[94] in which hydroquinone is isolated in 62% yield. A fascinating mechanism is proposed by Echavarren for this transformation.

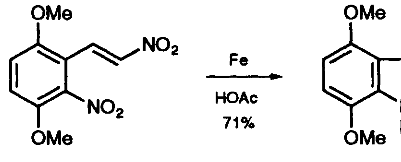


Scheme 53

5 Reductive cyclization

5.1 *o*,*β*-Dinitrostyrene reductive cyclization

The ancient reductive cyclization of *o*,*β*-dinitrostyrenes to indoles continues to enjoy popularity—both in application and methodological improvements. Three separate groups have utilized this indole ring construction to craft methoxyindoles. Both Fe/HOAc and $NaBH_4$/Pd/C are reported to furnish 4,7-dimethoxyindole **40** in good yield from the corresponding dinitro precursor **39** (**Scheme 54**).[95]



39 **40**

Scheme 54

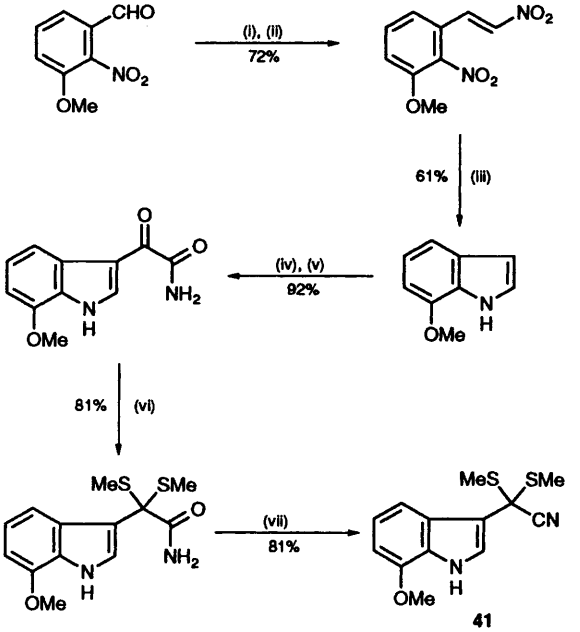
Indole **40** was also synthesized on an industrial scale, using catalytic hydrogenation in the key step.[96]

This latter method was employed in the first synthesis of the potent insect antifeedant dithyreanitrile **41** as summarized in **Scheme 55**.[97]

The use of $TiCl_3$ to cyclize *o*,*β*-dinitrostyrene to indole has been described,[98] and this cyclization has been accomplished using electrolysis, as has the conversion of 2-nitrophenylpyruvic acid to indole-2-carboxylic acid, in modest yields.[99]

5.2 Reissert indole synthesis

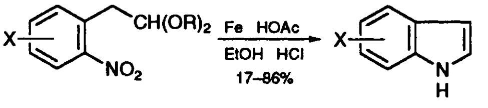
The classic Reissert indole synthesis, involving the reductive cyclization of *o*-nitrophenylpyruvic acid to indole-2-carboxylic acid, has been largely supplanted by newer methods, although a number of modifications and variations have been described in recent years. A series of substituted 2-nitrophenylacetaldehyde acetals, prepared from the corresponding styrenes, was cyclized to indoles (**Schemes 56**).[100] Castedo and colleagues published a new route to benzo[*b*]carbazoles and indeno[1,2-*b*]indoles using a simple reductive-cyclization protocol.[101] An example of each is shown in **Schemes 57** and **58**, respectively.



41

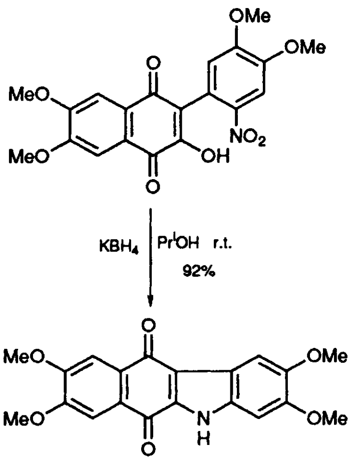
Reagents: (i) CH_3NO_2, NaOH, MeOH; (ii) Ac_2O, NaOAc, Δ;
(iii) H_2, 10% Pd–C, HOAc, EtOAc;
(iv) $(COCl)_2$ Et_2O, 0 °C; (v) NH_4OH, 0 °C;
(vi) TMS–SMe, $F_3B.OEt_2$, MeCN;
(vii) $POCl_3$, pyr, 0 °C

Scheme 55

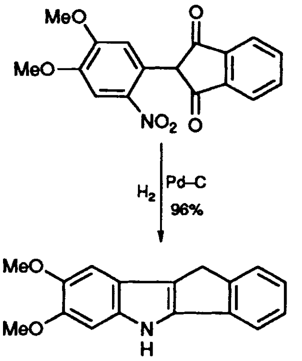


R = Me, Et, Bu^t, Bu^n
X = H, 4-OMe, 4-Me, 4-Cl,
5-OMe, 6-Me

Scheme 56

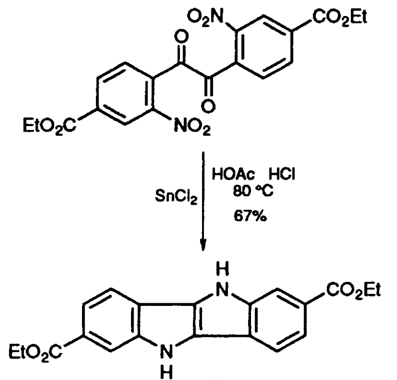


Scheme 57



Scheme 58

The use of a twin Reissert-like indole synthesis was employed to build the indolo[3,2-*b*]indole ring system **42** for use as a spin-containing unit for polaronic magnetic materials (**Scheme 59**).[84]

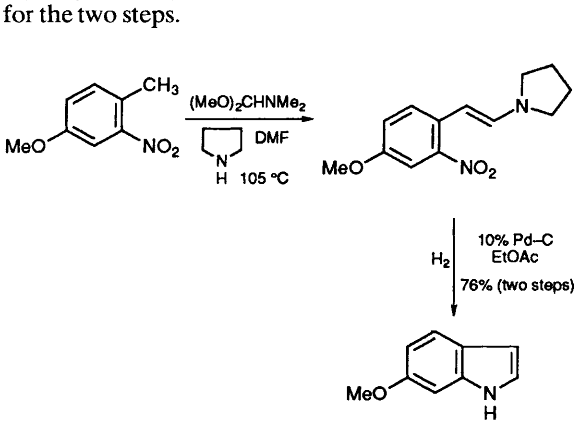


42

Scheme 59

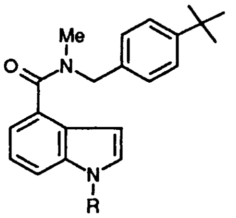
5.3 Leimgruber–Batcho indole synthesis

Since its inception some 20 years ago, the Leimgruber–Batcho indole synthesis has enjoyed great success in the preparation of benzene ring substituted indoles.[102-104] Modified versions now exist.[105] In the original synthesis, illustrated in **Scheme 60** for the preparation of 6-methoxyindole,[106] the appropriate nitrotoluene is condensed with DMF–acetal to afford the anticipated *β*-dialkylamino-2-nitrostyrene. Hydrogenation gives 6-methoxyindole in 76% yield for the two steps.

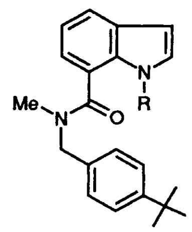


Scheme 60

Stanetty and Koller used the Leimgruber–Batcho protocol to synthesize indoles **43** and **45**. By performing the reductive cyclization at room temperature in THF, these workers could isolate *N*-hydroxyindoles **44** and **46**.[107]

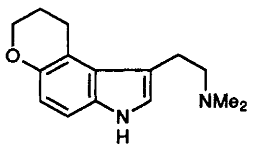


43 R = H
44 R = OH

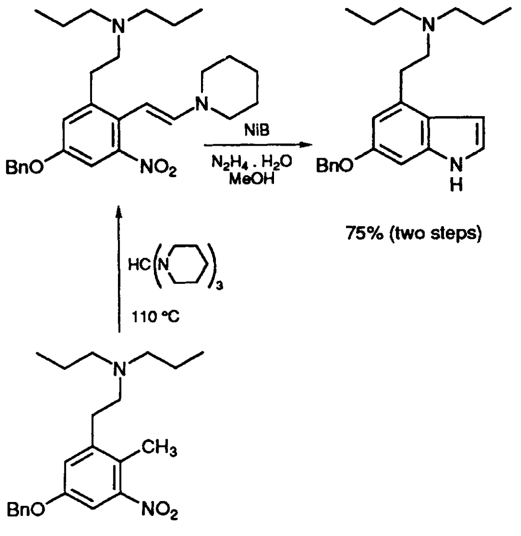


45 R = H
46 R = OH

Macor and his team at Pfizer have synthesized several rigid analogues of serotonin, such as **47**, using the Leimgruber–Batcho method.[108] Another group has utilized nickel boride in the reductive cyclization step (**Scheme 61**) in a synthesis of a metabolite of an ergoline derivative.[109]



47

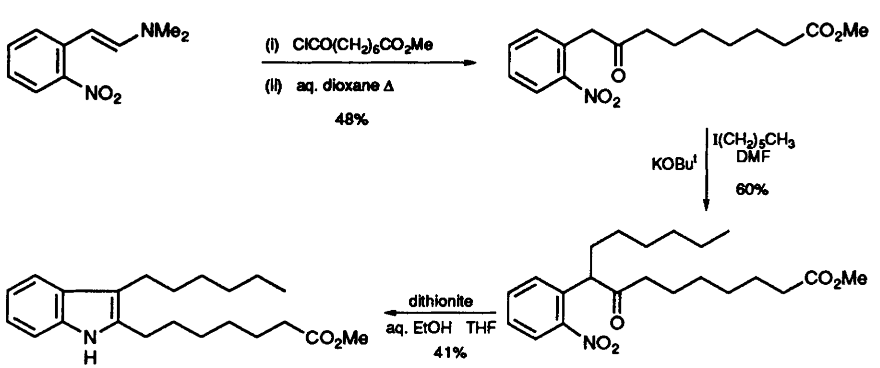


Scheme 61

In an important extension of the Leimgruber–Batcho methodology, an Italian group was able to prepare the 2,3-disubstituted indole **48** as shown in **Scheme 62**.[61]

5.4 Makosza indole synthesis

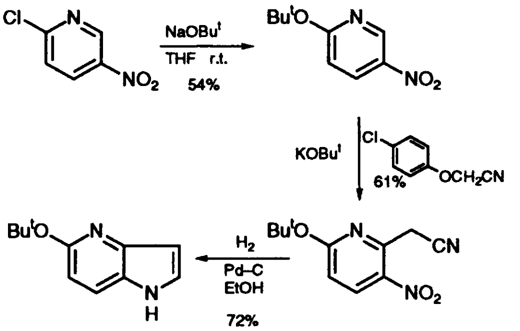
An excellent reductive cyclization protocol, which was developed by Makosza,[110] has been exploited extensively by Macor and his colleagues to synthesize both indoles and 4-azaindoles.[111,112] Two examples are



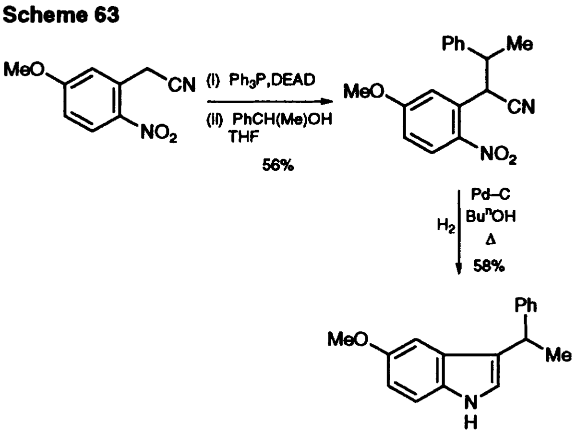
48

Scheme 62

listed in **Schemes 63** and **64**. A key feature of the first synthesis is the use of the Makosza 'Vicarious Nucleophilic Aromatic Substitution Reaction' (VNASR)[110,113] to install the acetonitrile side chain. Macor's second application featured the use of a carbon acid in the Mitsunobu reaction to lead eventually to 3-substituted indoles (**Scheme 64**).



Scheme 63

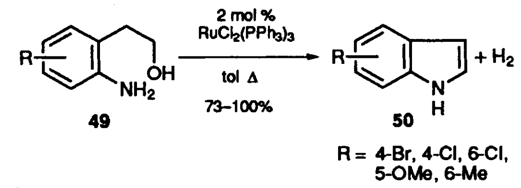


Scheme 64

6 Oxidative cyclization

6.1 Watanabe indole synthesis

In an extension of their earlier reported method of indole synthesis from anilines, glycols, and a ruthenium catalyst,[114,115] Watanabe and co-workers have described the intramolecular version of this reaction.[116] Thus, condensation of 2-nitrotoluenes with formaldehyde affords, after reduction, the requisite 2-aminophenethyl alcohols **49**. Exposure of the latter to a homogeneous ruthenium catalyst gave the corresponding indoles **50** in excellent yields (**Scheme 65**).



49 **50**

Scheme 65

A one-step version of this synthesis was also discovered. Thus, treatment of 2-nitrophenethyl alcohol with a mixture of Rh/C and $RuCl_2(PPh_3)_3$ in the presence of H_2 afforded indole in 96% yield.[116] Not surprisingly, indoline was oxidized to indole (100%) with $RuCl_2(PPh_3)_3$ in refluxing toluene.

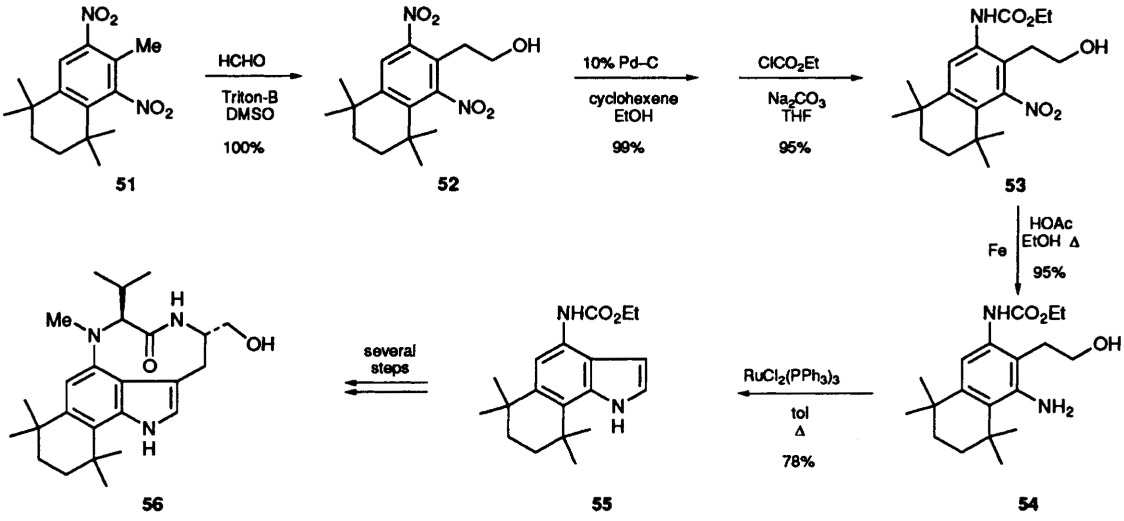
This Watanabe indole synthesis was used successfully in an elegant synthesis of the teleocidin analogue **56**, as outlined in **Scheme 66**.[117] Although attempts to apply the Leimgruber–Batcho indole ring synthesis to dinitro **51** failed, this compound was converted in excellent yield to amino alcohol **54** *via* **52** and **53**. A Watanabe oxidative cyclization afforded the desired indole **55** which was further transformed into the target molecule **56**.

6.2 Miscellaneous oxidative cyclizations

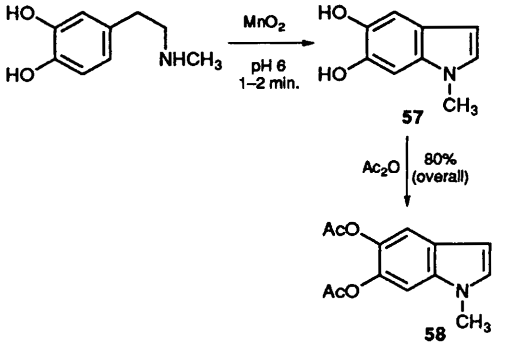
Although a relatively unexplored synthetic route to indoles, oxidative cyclization does play an important role in the biosynthesis of the melanin pigments. Carpender has developed carefully defined conditions for the synthesis of **58**, a stable protected form of *N*-methyl-5,6-dihydroxyindole **57**, which is a precursor to melanin polymers (**Scheme 67**).[118]

Manganese dioxide has also been used in the oxidative cyclization of tricarbonyliron-cyclohexadiene complexes, leading to carbazoles.[119,120] For example, Knölker applied this method to a synthesis of 4-deoxycarbazomycin B **59** (**Scheme 68**).[120]

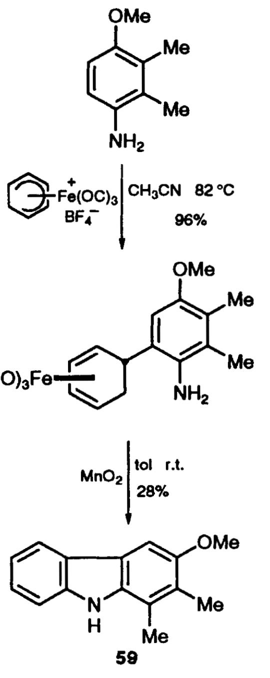
A Japanese group has discovered a very efficient oxidative cyclization route to 5-hydroxyindoles, involving the cyclization of aminoethyl-*p*-benzoquinones (**Scheme 69**).[121]



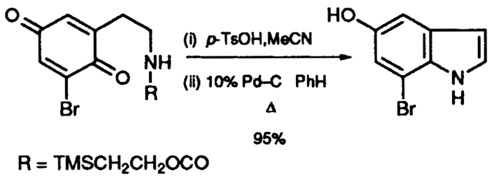
Scheme 66



Scheme 67



Scheme 68



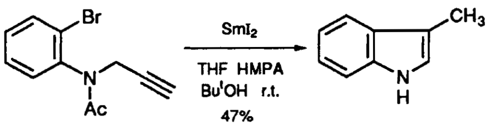
Scheme 69

The latter are prepared by oxidation of the appropriate 1,4-dioxygenated benzene with phenyliodine bis(trifluoroacetate).

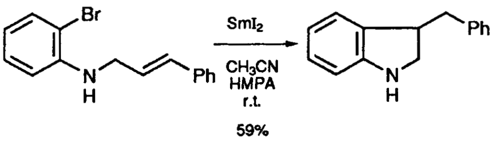
7 Radical cyclization

In recent times, radical cyclizations have pervaded all aspects of organic synthesis and the construction of the indole ring is no exception. Most of the pre-1990 work involved the synthesis of dihydroindoles,[122] and, even since then, only a few methods have been developed that provide indoles directly.

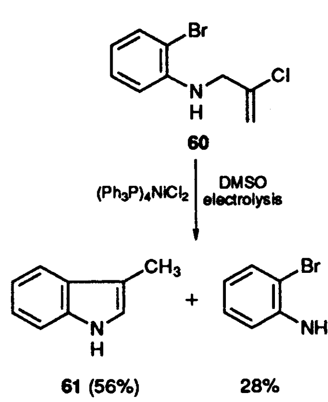
Samarium iodide is a useful reagent for effecting the radical cyclization of 2-bromoacetanilides (**Scheme 70**), conditions that also induce ring closure to dihydroindoles (**Scheme 71**).[123] A nickel catalyst in conjunction with electrolysis has been reported to convert bromoaniline **60** to 3-methylindole **61** (**Scheme 72**).[124]



Scheme 70

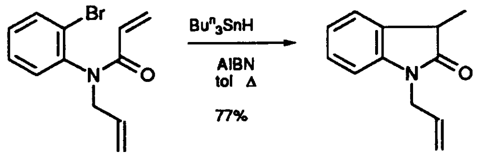


Scheme 71

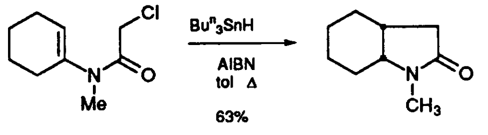


Scheme 72

Similarly, the following reactions lead to oxindoles or reduced versions thereof. It is worth noting that in **Scheme 73** there is no cyclization into the allyl unit (rationalized using conformational arguments),[125] and the first example of a 5-*endo-trig* radical cyclization is presented in **Scheme 74**.[126] The former research group has used this strategy in a synthesis of the alkaloid horsfiline.[127]

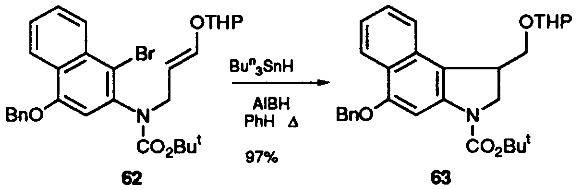


Scheme 73



Scheme 74

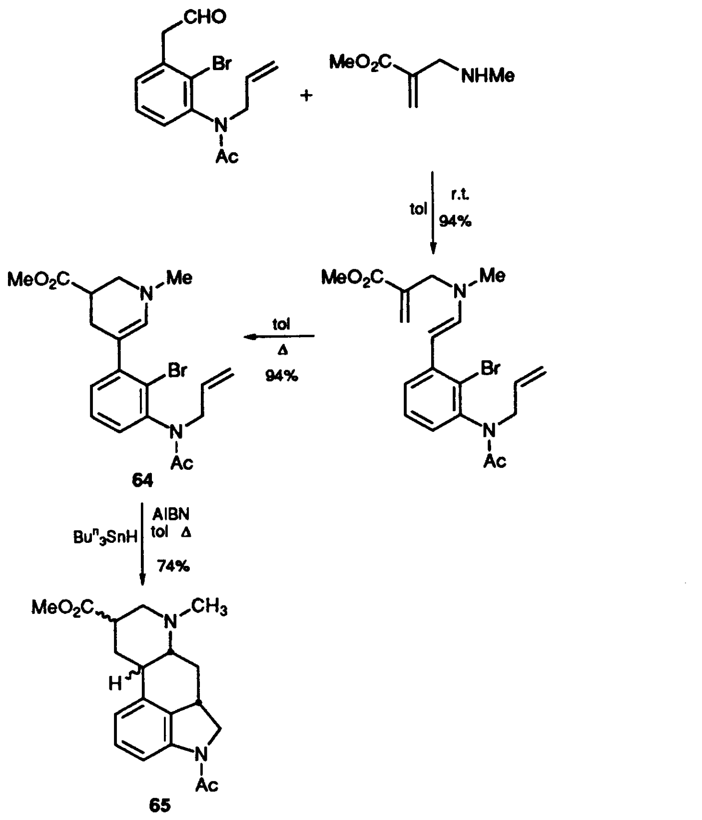
Boger and his colleagues have designed a 5-*exo-trig* radical cyclization in an improved synthesis of CBI, an analogue of a CC-1065 subunit.[128] Thus, the precursor **62** was rapidly assembled from 1,3-dihydroxynaphthalene and underwent closure to **63** in nearly quantitative yield (**Scheme 75**).



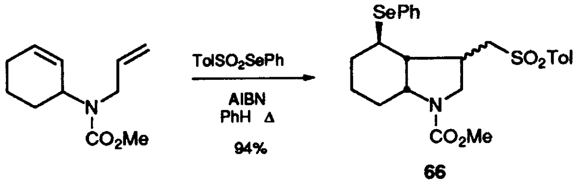
Scheme 75

Parsons *et al.* have presented an elegant tandem radical cyclization leading to lysergic acid derivatives.[129] The precursor **64** was fashioned as shown and then smoothly converted into a mixture of two diastereomers **65** (**Scheme 76**).

The use of *Se*-phenyl-*p*-tolueneselenosulfonate in a novel free radical selenosulfonylation cyclization to the perhydroindole ring system **66** has been described (**Scheme 77**).[130]



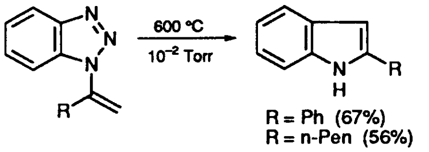
Scheme 76



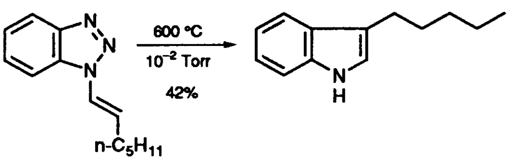
Scheme 77

An earlier indole synthesis developed by Katritzky[131] has been extended and improved by Barker and Storr.[132] Thus, flash vacuum pyrolysis (FVP) of *N*-vinylbenzotriazoles affords indoles (**Schemes 78** and **79**), although the reaction often leads to side products in other cases.

The same reaction as applied to *N*-arylbenzotriazoles to give carbazoles (the Graebe–Ullmann reaction) has



Scheme 78



Scheme 79

been recently extended to produce carbolines.[133,134] In a variation of this diradical generation and cyclization, Edstrom and Yuan have photolysed triazolyluracils to afford pyrrolo[2,3-*d*]pyrimidines.[135]

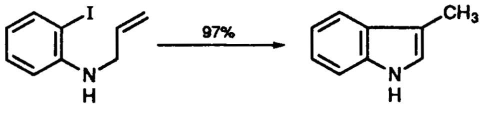
8 Metal-catalysed indole syntheses

8.1 Palladium

Applications of palladium in organic synthesis have assumed enormous proportions in the past ten years. For example, palladium-catalysed cross-coupling reactions provide facile syntheses of a variety of structures. Likewise, palladium has found important uses in indole synthesis, both in the indole-ring forming step and in the synthesis of precursor compounds.[136]

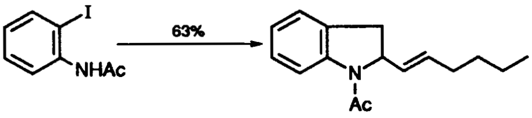
8.1.1 Larock indole–indoline synthesis

The pioneer in this area has been Larock, and, since his first paper (*e.g.*, **Scheme 80**),[137] he has described several applications to the synthesis of indolines and indoles (**Schemes 81–83**).[138–141] The reaction with unsymmetrical alkynes (*i.e.*, **Scheme 83**) gives predominantly the 2-substituted indole.



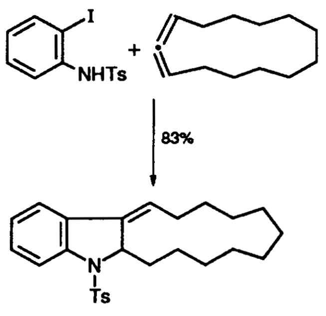
Reagents: 2 mol % Pd(OAc)$_2$, DMF, Na$_2$CO$_3$, Bu$^n_4$NCl, 25 °C

Scheme 80



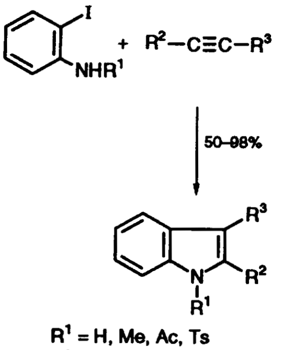
Reagents: Pd(OAc)$_2$, Na$_2$CO$_3$, Ph$_3$P, Bu$^n_4$NCl, DMF, 100 °C

Scheme 81



Reagents: Pd(OAc)$_2$, Ph$_3$P, Na$_2$CO$_3$, DMF, Bu$^n_4$NCl, 100 °C

Scheme 82

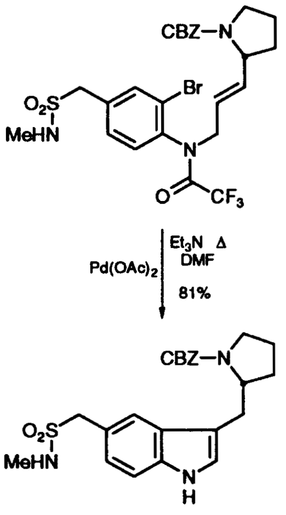


R^1 = H, Me, Ac, Ts
R^2 = Ph, n-Pr, t-Bu, TMS, CH$_2$OH
R^3 = Me, Et, Ph, n-Pr, CH$_2$OH

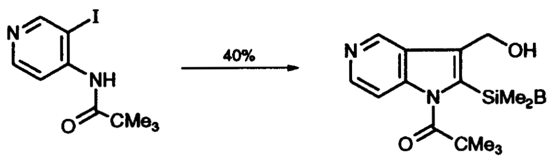
Reagents: Pd(OAc)$_2$, Bu$^n_4$NCl, DMF, K$_2$CO$_3$, 100 °C

Scheme 83

Other groups have exploited Larock's conditions to construct more complex indoles (**Schemes 84** and **85**).[142–144]



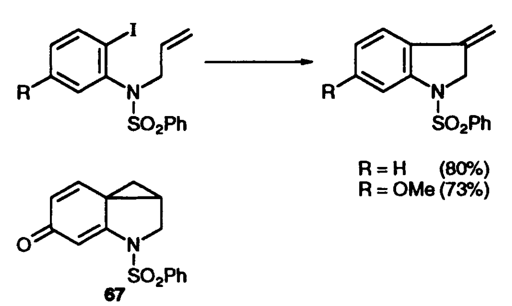
Scheme 84



Reagents: Me$_2$Bu^{t}SiC≡CCH$_2$OH, Pd(OAc)$_2$, Bu$^n_4$NCl, KOAc, 100 °C

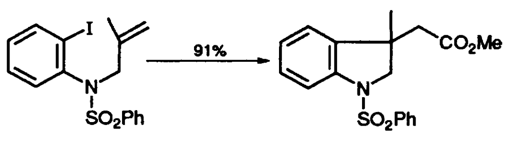
Scheme 85

In a synthesis of the CC-1065/duocarmycin pharmacophore **67**, Sakamoto and co-workers found that silver carbonate prevented tautomerism to the indole derivative (**Scheme 86**).[145]
Grigg has described a carbomethoxylation variation (**Scheme 87**),[146] and Genet has utilized the water-soluble palladium(0) catalyst prepared *in situ* from trisodium 3,3′,3″-phosphinetriyltribenzenesulfonate (TPPTS) and palladium(II) acetate.[147]



Reagents: $Pd(OAc)_2$, Ph_3P, DMF, Ag_2CO_3, r.t.

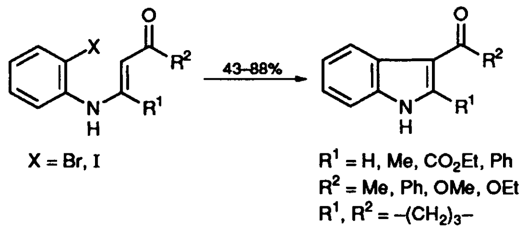
Scheme 86



Reagents: $PdCl_2(PPh_3)_2$, TlOAc, CO, MeOH

Scheme 87

Yamanaka and his colleagues studied exhaustively the palladium-catalysed cyclization of β-(2-halophenyl)amino substituted α,β-unsaturated ketones and esters to 2,3-disubstituted indoles (**Scheme 88**).[148]



X = Br, I

R^1 = H, Me, CO_2Et, Ph
R^2 = Me, Ph, OMe, OEt
R^1, R^2 = $-(CH_2)_3-$

Reagents: $Pd(OAc)_2$, Et_3N, $(o\text{-}Tol)_3P$, DMF, Δ

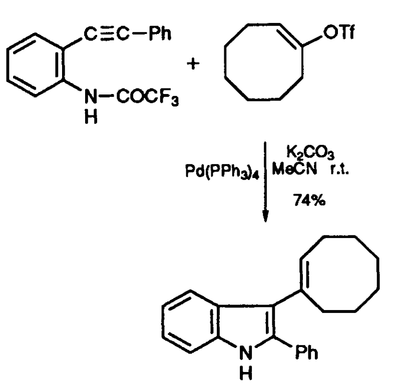
Scheme 88

8.1.2 Miscellaneous

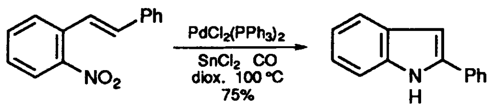
An interesting variation that leads to 3-vinyl- and 3-aryl-indoles has been reported by an Italian group (**Scheme 89**),[149] and the use of palladium in the reductive heterocyclization of *o*-nitrostyrenes has been discovered (**Scheme 90**).[150]

The palladium-catalysed cross-coupling of aryl bromides with organostannanes has led to an efficient indole synthesis (**Scheme 91**),[151] including a short synthesis of the pyrrolophenanthridine alkaloid hippadine **68**.[152]

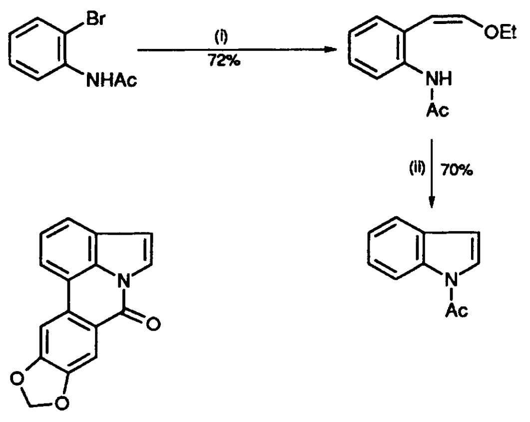
Bäckvall has devised a palladium-catalysed intramolecular 1,4-addition to cyclic 1,3-dienes (**Scheme 92**),[153] including the extension of this reaction to syntheses of α- and γ-lycorane.[154]



Scheme 89



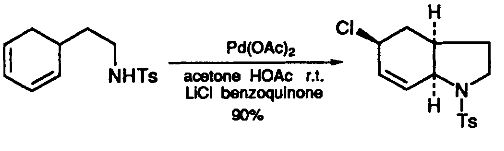
Scheme 90



68

Reagents: (i) $Bu^n{}_3SnCH{=}CHOEt$, $PdCl_2(PPh_3)_2$, DMF, Et_4NCl, 100 °C; (ii) *p*-TsOH, PhH

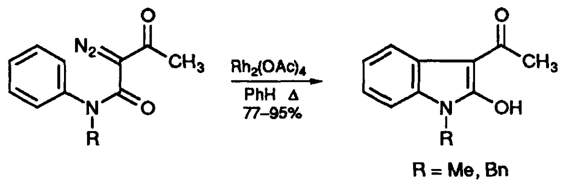
Scheme 91



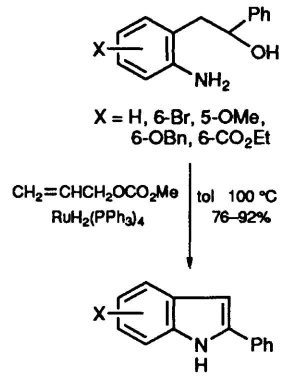
Scheme 92

8.2 Rhodium and ruthenium

Rhodium acetate smoothly converts diazo compounds into the corresponding 3-acylindoles (**Scheme 93**),[155] and a ruthenium catalyst was superior to palladium in the conversion of amino alcohols to 2-phenylindoles (**Scheme 94**),[156] in a variation of the Watanabe indole synthesis (*vide supra*).



Scheme 93

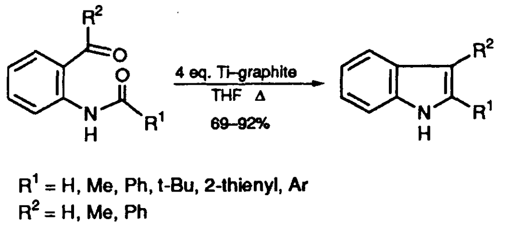


Scheme 94

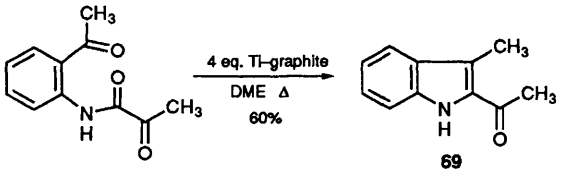
8.3 Titanium

8.3.1 Fürstner indole synthesis

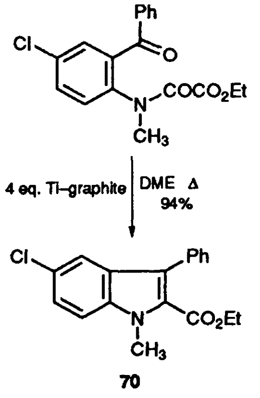
Fürstner forged a wide range of indoles using titanium/graphite in an intramolecular version of the McMurry coupling reaction (**Schemes 95–97**).[157–159]



Scheme 95



Scheme 96

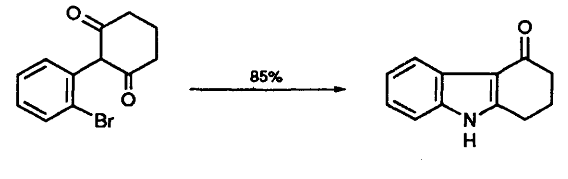


Scheme 97

The starting ketoamides are readily prepared by acylation of the corresponding aromatic amines. For example, the crowded 2-phenyl-3-t-butylindole was synthesized in 84% yield.[158] These researchers also prepared the Pakistan drug salvadoricine **69** (**Scheme 96**) and the diazepam precursor **70** (**Scheme 97**).[159]

8.3.2 Miscellaneous

A different use of titanium was reported by a Japanese group.[160] This involves the generation of a Ti-isocyanate complex and its reaction with a bromo ketone to effect indole formation (**Scheme 98**).

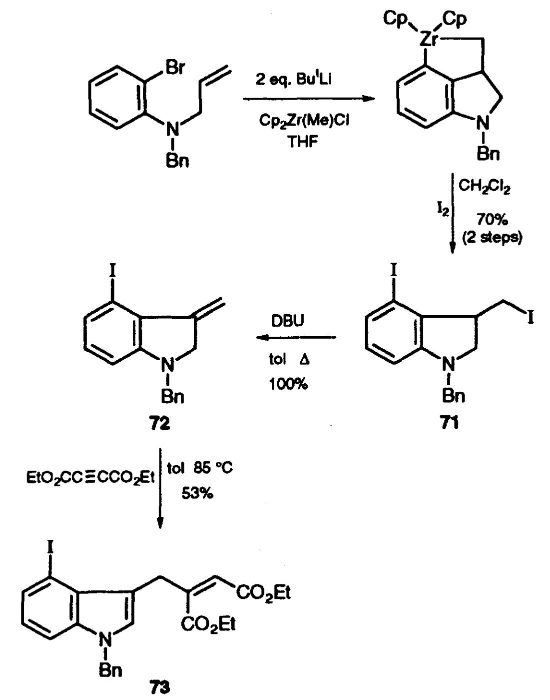


Reagents: TiCl$_3$, CO$_2$, N$_2$, Mg, Pd(PPh$_3$)$_4$,THF, NMP, 100 °C

Scheme 98

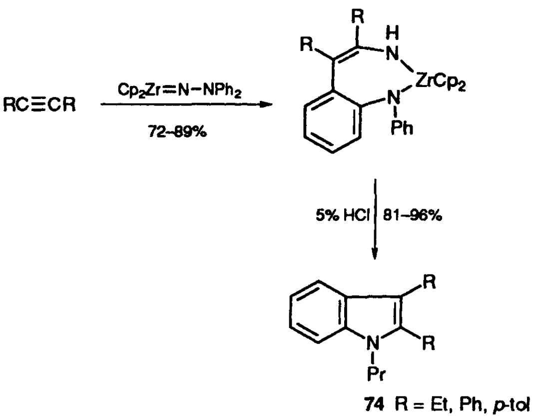
8.4 Zirconium

Buchwald has uncovered a novel indole ring construction involving sequential alkene insertion with a zirconium complex (**Scheme 99**).[161] Subsequent manipulation of **71** gave indole **73** *via* an ene reaction on the surprisingly stable indole tautomer **72**.



Scheme 99

Bergman discovered the remarkable set of transformations shown in **Scheme 100**, involving alkyne addition to a hydrazidozirconocene complex, leading eventually to indoles **74** in excellent yields.[162]

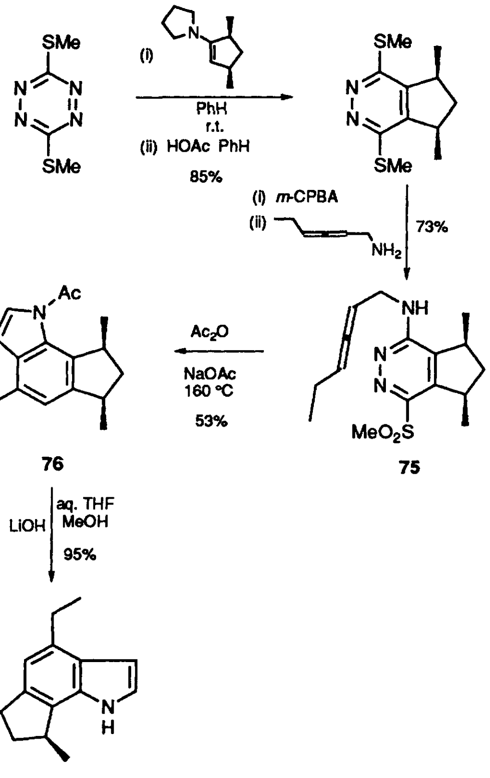


Scheme 100

9 Cycloaddition and electrocyclization

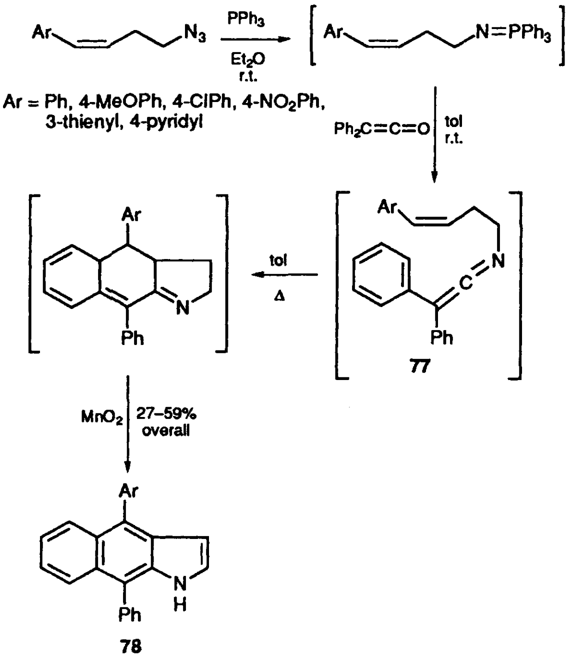
9.1 Diels–Alder cycloaddition

Boger has applied his earlier developed tetrazine cycloaddition methodology to a clever synthesis of the marine alkaloids *cis*-**28** and *trans*-trikentrin A (**Scheme 101**).[163] The indole-forming step is the intramolecular cycloaddition of allene pyridazine **75**→**76**.



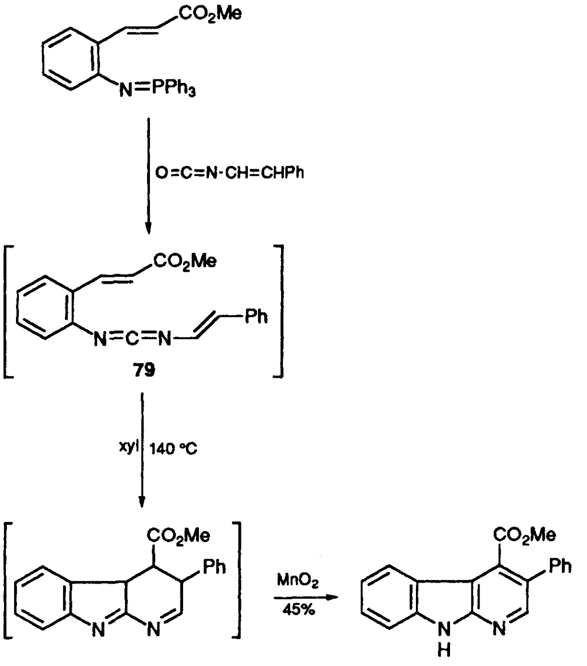
Scheme 101

The powerful intramolecular Diels–Alder cycloaddition of vinylketenimines developed by Ghosez[164] has been extended by two research groups. Molina discovered a one-pot synthesis of various fused indoles and carbolines.[165–168] For example, benz[*f*]indoles **78** are available from vinylketenimines **77**, which in turn are formed by the reaction between an iminophosphorane and an isocyanate (**Scheme 102**), in what is a consecutive Staudinger, aza-Wittig, intramolecular Diels–Alder sequence.[168]



Scheme 102

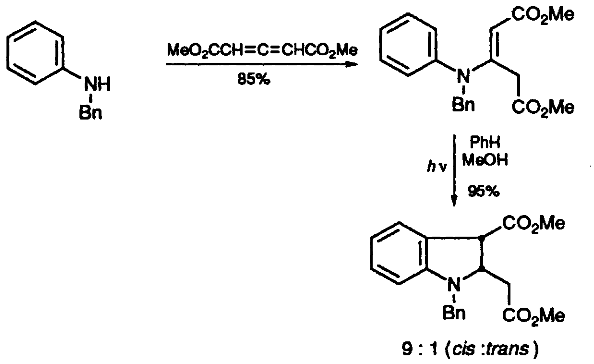
Similar chemistry was discovered independently by a Japanese group, leading to a one-pot synthesis of α-carbolines and pyridocarbolines (**Scheme 103**).[169] The intermediate carbodiimide **79** could be isolated.



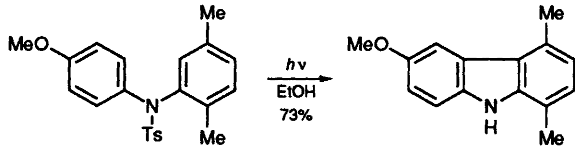
Scheme 103

9.2 Photoelectrocyclization

The well-known Chapman photocyclization of *N*-arylenamines to dihydroindoles[170] has been employed by a Barcelona group to construct *Aspidosperma* alkaloid intermediates (**Scheme 104**).[171] Similarly, a simple photochemical route to ellipticine-precursor carbazoles has been reported by a British group (**Scheme 105**).[172]



Scheme 104



Scheme 105

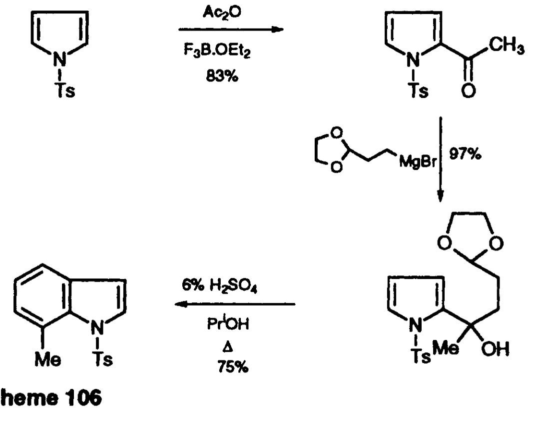
10 Indoles from pyrroles

The obvious close chemical relationship between pyrroles and indoles has made the former an attractive substrate for indole ring construction, and many examples have been reported recently.

10.1 Electrophilic cyclization

10.1.1 Natsume indole synthesis

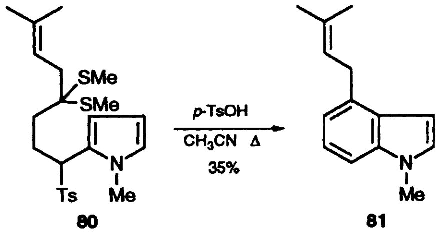
In a series of elegant papers, rich in chemical detail, Natsume and his colleagues have synthesized a number of different indoles and indole natural products, including a janthitrem G model system,[173] herbindoles A, B, and C,[174] (*S*)-pindolol,[175,176] pendolmycin,[177] trikentrins,[178,179] alkoxyindoles,[180] 4-substituted indoles,[181] and fused indoles.[182] As can be seen from the simple example in **Scheme 106**,[173] the key step is intramolecular electrophilic cyclization of C-2 of a pyrrole ring, followed by functionality manipulation and adjustment. The initial site of intermolecular electrophilic substitution (C-2 or C-3) is controlled by the nature of the Lewis acid.



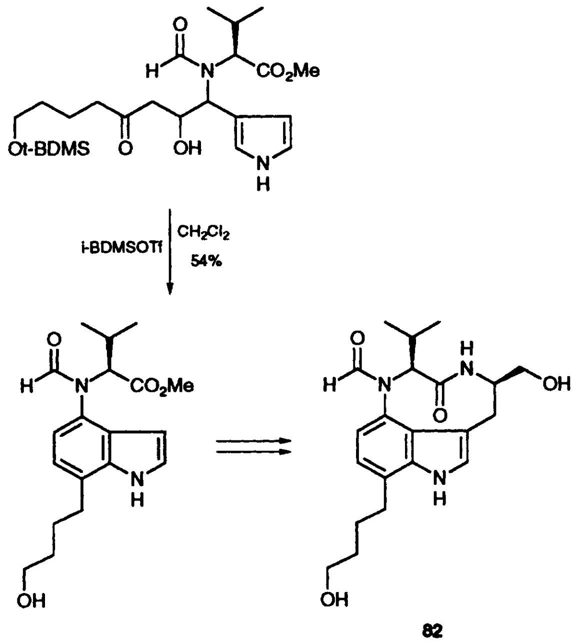
Scheme 106

10.1.2 Miscellaneous

Using chemistry similar to that of Natsume, Trost had previously reported the conversion of pyrrole thioketal **80** into indole **81** (**Scheme 107**),[183] and Kozikowski has synthesized several lyngbyatoxin A analogues (*e.g.*, **82**), utilizing a pyrrole cyclization strategy (**Scheme 108**).[184]



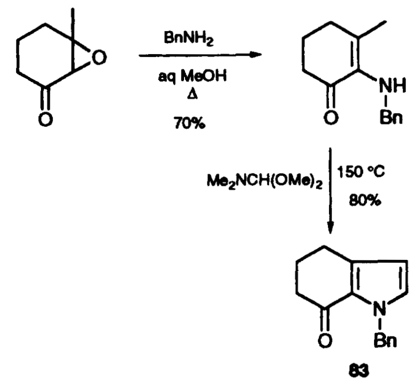
Scheme 107



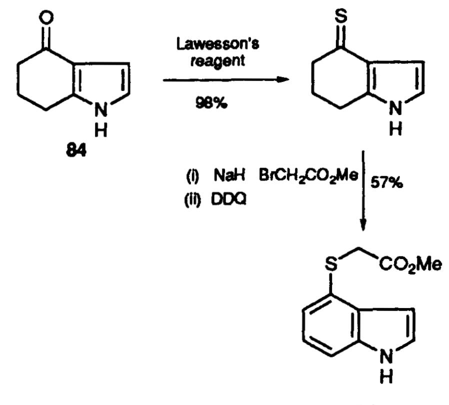
Scheme 108

As it has been over the years, the synthesis of 7- (and 4-) oxo-4,5,6,7-tetrahydroindoles as indole precursors continues to be an important route to indoles. For example, an Australian group has described a simple synthesis of *N*-benzyl-7-oxo-4,5,6,7-tetrahydroindole **83** (**Scheme 109**).[185]

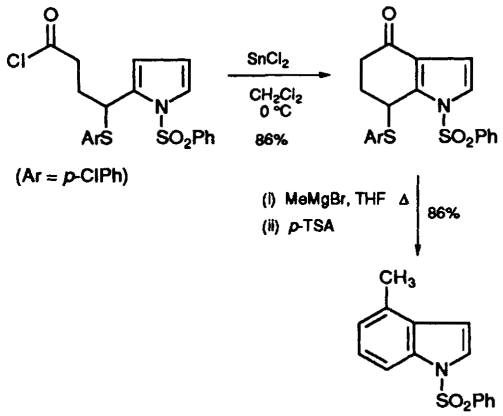
Tobinaga and co-workers used 4-oxo-4,5,6,7-tetrahydroindole **84** to fashion 4-alkylthioindoles (**Scheme 110**).[186] Ester **85** had previously been converted to chuangxinmycin. Ishibashi employed a Natsume-type protocol to synthesize 4-substituted indoles, including (*S*)-pindolol and (±)-chuangxinmycin.[187] An example is shown in **Scheme 111**.



Scheme 109



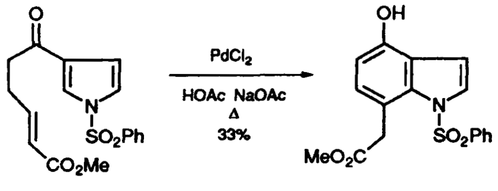
Scheme 110



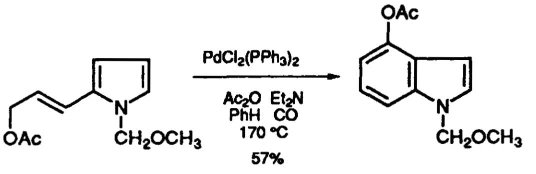
Scheme 111

10.2 Palladium-catalysed cyclization

Palladium has also been employed to spark the cyclization of a pyrrole to an indole (**Schemes 112** and **113**).[188,189] The latter study also included the synthesis of carbazoles from indolylallyl acetates by cyclocarbonylation.[189]



Scheme 112

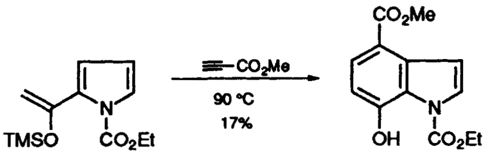


Scheme 113

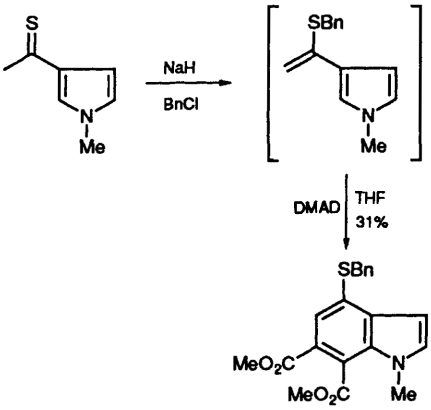
10.3 Cycloaddition routes

10.3.1 From vinylpyrroles

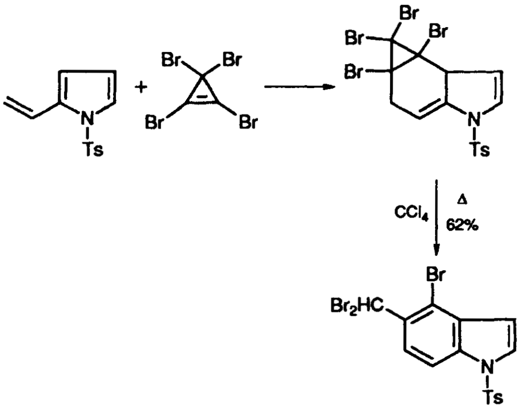
The Diels–Alder cycloaddition of vinyl heterocycles has long been a fascination to organic chemists. Not surprisingly, this motif is an important route to indoles from 2- and 3-vinyl-pyrroles. For an important and elegant earlier study leading to the synthesis of 4-acylindoles see Muchowski and Scheller.[190] Recent examples are summarized in **Schemes 114–116**.[191–194] Unfortunately, yields are low to modest, and there is clearly room for improvement in this approach to indoles.



Scheme 114



Scheme 115

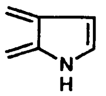


Scheme 116

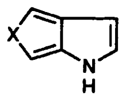
10.3.2 From pyrrole-2,3-quinodimethanes

The generation and Diels–Alder trapping of 2,3-dimethylene-2,3-dihydropyrrole (pyrrole-2,3-quinodimethane) **86**, or their synthetic analogues **87**, is a tantalizing route to indoles.

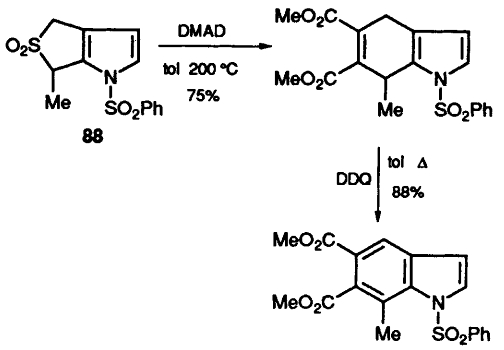
Chou and Chang have apparently generated derivatives of **86** during the pyrolysis and subsequent trapping of thieno[3,4-*b*]pyrrole-1,1-dioxides such as **88** (**Scheme 117**).[195]



86

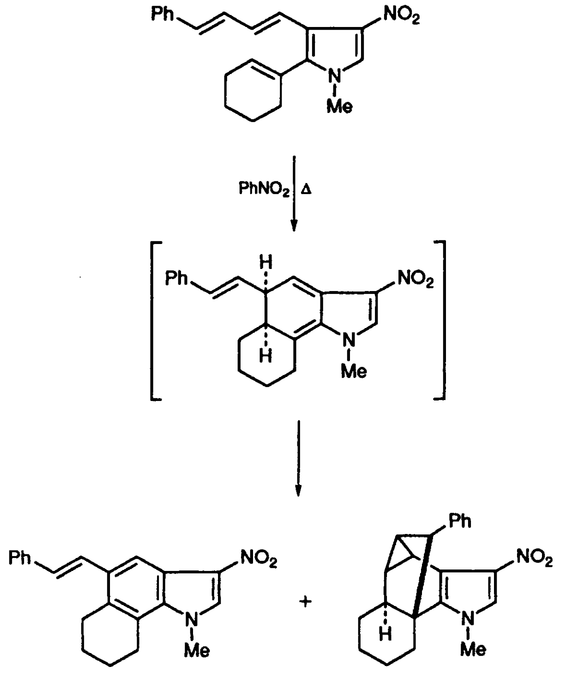


87



Scheme 117

Van Leusen has reported several approaches for the generation of pyrrole-2,3-quinomethanes, one of which is illustrated in **Scheme 118**; a reaction that leads to indole **89** and the novel compound **90**.[196]

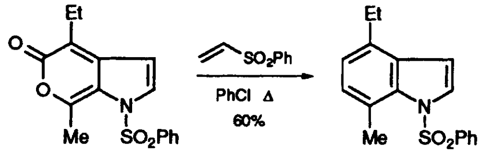


89 (21%)

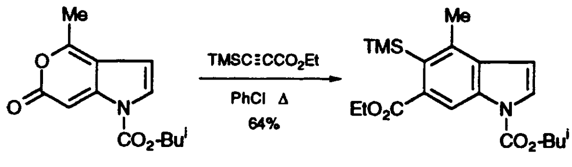
90 (50%)

Scheme 118

In a comprehensive set of papers, Moody *et al.* have elegantly illustrated the use of cycloaddition chemistry, involving both 1,5-dihydropyrano[3,4-*b*]pyrrol-5(1*H*)-ones and 1,6-dihydropyrano[4,3-*b*]pyrrol-6(1*H*)-ones in a new and powerful syntheses of indoles.[197–199] These synthetic analogues of pyrrole-2,3-quinodimethane **86** are readily prepared from the corresponding pyrroleacetic acids. Several examples are shown in **Schemes 119–121**.

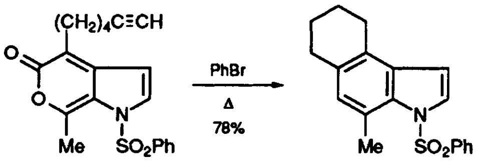


Scheme 119



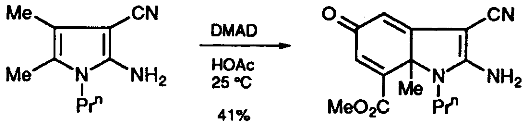
(isomer observed; >20:1)

Scheme 120



Scheme 121

Frey and Eger have uncovered a novel synthesis of 2-amino-3-cyanodihydroindol-5-ones *via* a cycloaddition of pyrroles such as **91** with dimethyl acetylenedicarboxylate (DMAD) (**Scheme 122**).[200]



91

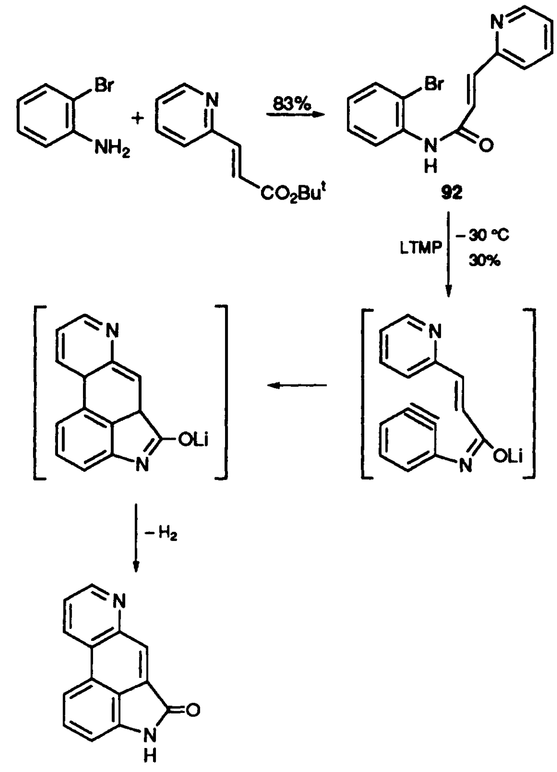
Scheme 122

11 Aryne intermediates

Given the enormous utility of benzyne and other arynes in organic synthesis, especially within the realm of cycloaddition chemistry, it is not surprising that these highly reactive intermediates have been exploited in indole ring construction.

11.1 Aryne Diels–Alder cycloaddition

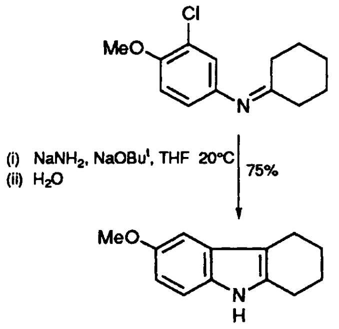
An intramolecular aryne cycloaddition has been devised to synthesize the ergot skeleton, as shown in **Scheme 123**.[201] Thus, the precursor **92** was crafted in high yield and then treated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) to give directly **93** in 30% yield.



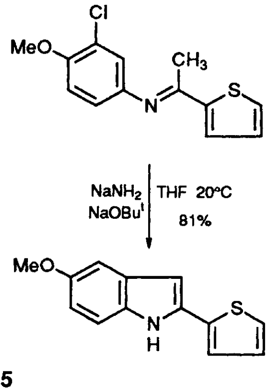
Scheme 123

11.2 Nucleophilic cyclization of arynes

In an extension of a reaction first reported in 1975 by the same group, a French team used the complex base $NaNH_2$-t-BuONa to synthesize several indoles *via* arynic cyclization, two of which are illustrated in **Schemes 124** and **125**.[202] Quenching with dimethylsulfate instead of water provides the corresponding *N*-methylindole.

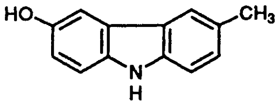


Scheme 124

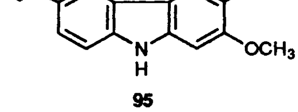


Scheme 125

Similarly, this arynic cyclization approach was used to prepare carbazoles, including the alkaloids glycozolinine **94** and glycozolidine **95**.[203]



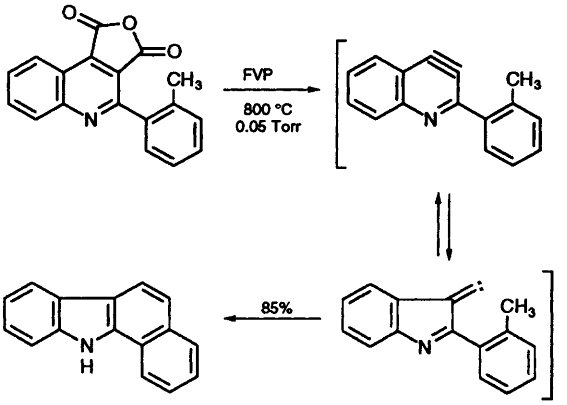
94



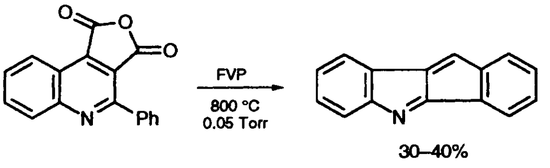
95

11.3 Miscellaneous aryne cyclizations

Flash vacuum pyrolysis of quinoline-3,4-dicarboxylic anhydrides at 800°C affords fused indole derivatives in variable yields.[204] The intermediacy and rearrangement of an aryne is postulated to account for these remarkable reactions in the two cases shown in **Schemes 126** and **127**.



Scheme 126

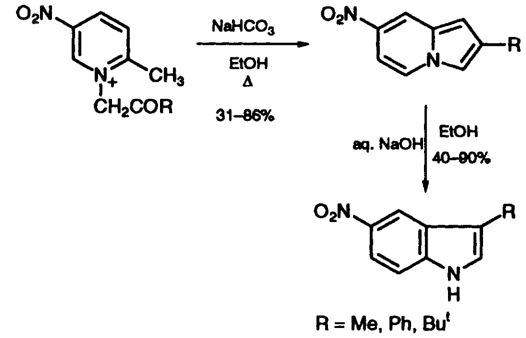


Scheme 127

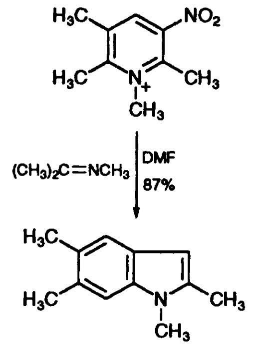
12 Miscellaneous indole syntheses

Fadda has described a remarkable synthesis of indoles from the consecutive rearrangement of *N*-alkylpyridinium salts to indolizines and then to indoles by ring opening and recyclization (**Scheme 128**).[205] This sequence is limited to nitroindoles thus far.

The mechanism of an earlier reported synthesis of indoles by the reaction of 3-nitropyridinium salts with *N*-alkylketimines (**Scheme 129**) has been discussed at length.[206] This remarkable transformation affords a powerful route to polyalkylindoles.

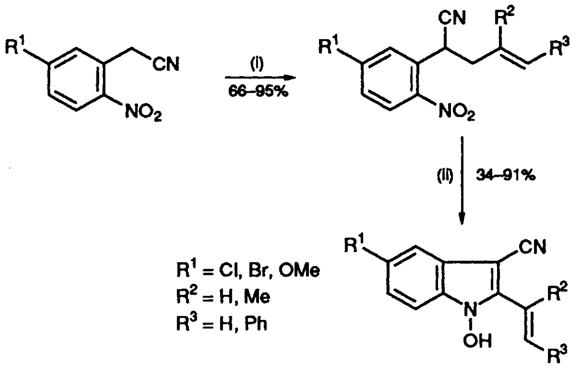


Scheme 128



Scheme 129

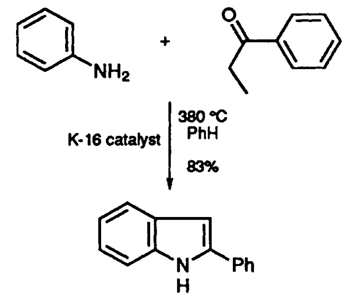
Makosza has discovered a facile synthesis of *N*-hydroxy-2-vinylindoles that involves a novel cyclization reaction (**Scheme 130**).[207] The requisite starting materials were prepared *via* cyanomethylation of nitroarenes in the vicarious nucleophilic substitution reaction,[113] followed by alkylation. The *N*-hydroxyindoles can be reduced to the corresponding indoles (Zn, HOAc, reflux).



Reagents: (i) $BrCH_2CHR^2{=}CHR^3$, K_2CO_3, Bu^n_4NI, CH_3CN; (ii) TMSCl, Et_3N, DMF, r.t.

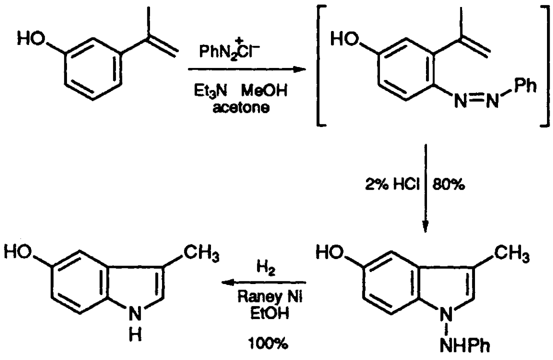
Scheme 130

A Russian research group has explored the use of metal oxides (Zn, Cr, Fe, Al) as catalysts in the high temperature conversion of ketimines to indoles (**Scheme 131**).[208] Interestingly, 3-methyl-2-phenylindole is an intermediate in the formation of 2-phenylindole.



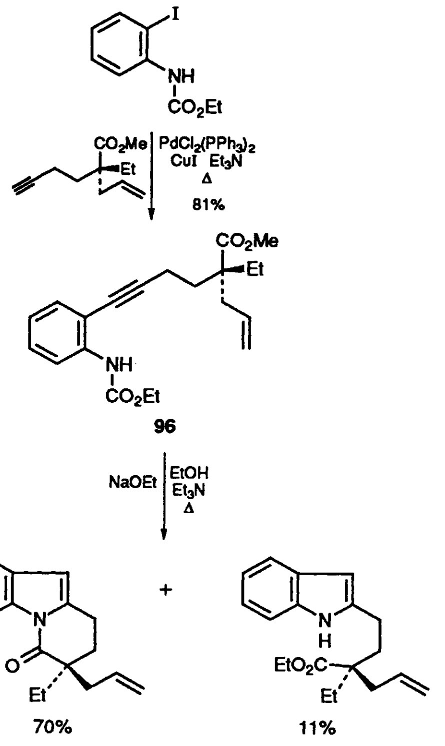
Scheme 131

Satomura reported an intriguing cyclization of *in situ* generated *o*-vinylazoarenes leading to *N*-amino-5-hydroxyindoles, which can be reduced to the corresponding 5-hydroxyindoles (**Scheme 132**).[209]



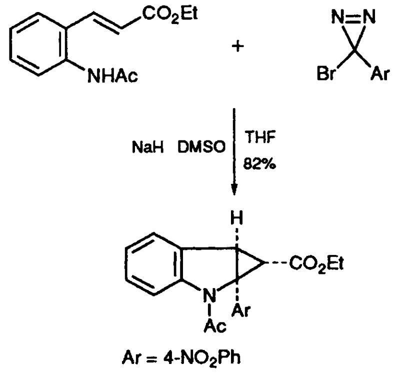
Scheme 132

Takano and co-workers have used a novel 5-*endo-dig* cyclization reaction, originally developed by Yamanaka,[210] to achieve a total synthesis of the alkaloid (−)-goniomitine.[211] The key precursor **96** was prepared *via* palladium-catalysed cross-coupling (**Scheme 133**).



Scheme 133

In a reaction thought to proceed *via* an α-aminocarbene intermediate, Li and Vasella have reported the synthesis of the cyclopropylindole shown in **Scheme 134**.[212]



Scheme 134

13 References

1 A. Baeyer, *Chem. Ber.*, 1880, **13**, 2254.
2 R.J. Sundberg, 'The Chemistry of Indoles', Academic Press, New York, 1970, Chapter III.
3 R.K. Brown, 'Indoles, The Chemistry of Heterocyclic Compounds', ed. W.J. Houlihan, Interscience, 1972, Vol. 25, part 1, Chapter II.
4 R.J. Sundberg, in 'Comprehensive Heterocyclic Chemistry', ed. A.R. Katritzky, C.W. Rees, C.W. Bird, and G.W.H. Cheeseman, Pergamon, Oxford, 1984, Vol. 4, pp. 313-376.
5 G.P. Ellis, in 'The Chemistry of Heterocyclic Compounds', Wiley, Chichester, 1992, Vol. 47, part 2.
6 M. Alvarez, M. Salas, and J.A. Joule, *Heterocycles*, 1991, **32**, 1391.
7 For ongoing reviews including indole ring syntheses, the reader is referred to (a) 'Progress in Heterocyclic Chemistry', ed. H. Suschitzky and E.F.V. Scriven, Pergamon Press, Oxford, Vols. 1-5; and (b) 'Annual Reports in Organic Synthesis', Academic Press, San Diego. For two excellent introductions to the synthesis of indoles, see (a) J.A. Joule and G.F. Smith, 'Heterocyclic Chemistry', 2nd edition, Van Nostrand Reinhold, London, 1979; (b) T.L. Gilchrist, 'Heterocyclic Chemistry', Longman, Essex, 1985.
8 W.J . Houlihan, V.A. Parrino, and Y. Uike, *J. Org. Chem.*, 1981, **46**, 4511.
9 Y. Ito, K. Kobayashi, and T. Saegusa, *J. Am. Chem. Soc.*, 1977, **99**, 3532.
10 A.B. Smith, III, M. Visnick, J.N. Haseltine, and P.A. Sprengeler, *Tetrahedron*, 1986, **42**, 2957.
11 K. Smith and G.J. Pritchard, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 282.
12 P.S. Almeida, S. Prabhakar, A.M. Lobo, and M.J. Marcelo-Curto, *Tetrahedon Lett.*, 1991, **32**, 2671.
13 B. Liu and A.G. Wee, *Heterocycles*, 1993, **36**, 445.
14 G.J. Quallich and P.M. Morrisey, *Synthesis*, 1993, 51.
15 B. Robinson, 'The Fischer Indole Synthesis', Wiley-Interscience, New York, 1982.
16 E. Fischer and F. Jourdan, *Chem. Ber.*, 1883, **16**, 2241.
17 E. Fischer and O. Hess, *Chem. Ber.*, 1884, **17**, 559.
18 M.P. Prochazka, L. Eklund, and R. Carlson, *Acta Chem. Scand.*, 1990, **44**, 610.
19 M.P. Prochazka and R. Carlson, *Acta Chem. Scand.*, 1990, **44**, 614.
20 D. Zhao, D.L. Hughes, D.R. Bender, A.M. De Marco, and P.J. Reider, *J. Org. Chem.*, 1991, **56**, 3001.
21 A.R. Katritzky, S. Rachwal, and S. Bayyuk, *Org. Prep. Proc. Int.*, 1991, **23**, 357.
22 R.A. Abramovitch and A. Bulman, *Synlett*, 1992, 795.
23 V. Hegde, P. Madhukar, J.D. Madura, and R.P. Thummel, *J. Am. Chem. Soc.*, 1990, **112**, 4549.
24 R.P. Thummel, *Tetrahedron*, 1991, **47**, 6851.
25 R.P. Thummel, *Synlett*, 1992, 1.
26 M.J. Martin, L.J. Dorn, and J.M. Cook, *Heterocycles*, 1993, **36**, 157.
27 B. McKittrick, A. Failli, R.J. Steffan, R.M. Soll, P. Hughes, J. Schmid, A.A. Asselin, C.C. Shaw, R. Noureldin, and G. Gavin, *J. Heterocycl. Chem.*, 1990, **27**, 2151.
28 L.G. Zepeda, M.S. Morales-Ríos, and P. Joseph-Nathan, *Synth. Commun.*, 1992, **22**, 3243.
29 C.W.G. Fishwick, A.D. Jones, and M.B. Mitchell, *Org. Prep. Proc. Int.*, 1990, **22**, 766.
30 D.St.C. Black, G.B. Deacon, and G.L. Edwards, *Aust. J. Chem.*, 1991, **44**, 1771.
31 S. Takano, M. Moriya, and K. Ogasawara, *J. Org. Chem.*, 1991, **56**, 5982.
32 S. Takano, M. Moriya, and K. Ogasawara, *Tetrahedron Lett.*, 1992, **33**, 329.
33 J. Bonjoch, N. Casamitjana, J. Gràcia, M.-C. Ubeda, and J. Bosch, *Tetrahedron Lett.*, 1990, **31**, 2449.
34 D.J. Hart and S.C. Wu, *Heterocycles*, 1993, **35**, 135.
35 J.-Y. Mérour and L. Savelon, *Heterocycles*, 1991, **32**, 849.
36 D.W. Brown, M.F. Mahon, A. Ninan, M. Sainsbury, and H.G. Shertzer, *Tetrahedron*, 1993, **49**, 8919.
37 S.V. Luis and M.I. Burguete, *Tetrahedron*, 1991, **47**, 1737.
38 A. Arnone, N. Cornaggia, C. Lorenzoni, and L. Merlini, *Gazz. Chim. Ital.*, 1991, **121**, 515.
39 H. Ishii, Y. Murakami, and T. Ishikawa, *Chem. Pharm. Bull.*, 1990, **38**, 597.
40 H. Ishii, T. Sugiura, Y. Akiyama, Y. Ichikawa, T. Watanabe, and Y. Murakami, *Chem. Pharm. Bull.*, 1990, **38**, 2118.
41 H. Ishii, T. Sugiura, K. Kogusuri, T. Watanabe, and Y. Murakami, *Chem. Pharm. Bull.*, 1991, **39**, 572.
42 T. Benincori, E. Brenna, and F. Sannicolò, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2139.
43 D.L. Hughes and D. Zhao, *J. Org. Chem.*, 1993, **58**, 228.
44 R.S. Eichen Conn, A.W. Douglas, S. Karady, E.G. Corley, A.V. Lovell, and I. Shinkai, *J. Org. Chem.*, 1990, **55**, 2908.
45 P.G. Gassman, T.J. van Bergen, D.P. Gilbert, and B.W. Cue, Jr., *J. Am. Chem. Soc.*, 1974, **96**, 5495.
46 A.B. Smith, T. Sunazuka, T.L. Leenay, and J. Kingery-Wood, *J. Am. Chem. Soc.*, 1990, **112**, 8197.
47 Y. Murai, S. Kobayashi, S. Inoue, and K. Sato, *Heterocycles*, 1992, **34**, 1017.
48 G. Bartoli, G. Palmieri, M. Bosco, and R. Dalpozzo, *Tetrahedron Lett.*, 1989, **30**, 2129.
49 G. Bartoli, M. Bosco, R. Dalpozzo, G. Palmieri, and E. Marcantoni, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2757.
50 M. Bosco, R. Dalpozzo, G. Bartoli, G. Palmieri, and M. Petrini, *J. Chem. Soc., Perkin Trans. 2*, 1991, 657.
51 D.P. Dobson, A. Todd, and J. Gilmore, *Synth. Commun.*, 1991, **21**, 611.
52 D.P. Dobson, J. Gilmore, and D.A. Long, *Synlett*, 1992, 79.
53 C.J. Moody and E. Swann, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2561.
54 G.A. Pinna, M.A. Pirisi, and G. Paglietti, *J. Chem. Res. (S)*, 1990, 360.
55 M. Gray, P.J. Parsons, and A.P. Neary, *Synlett*, 1993, 281.

56 W. Madelung, *Chem. Ber.*, 1912, **45**, 1128.

57 G. Bartoli, M. Bosco, R. Dalpozzo, and P.E. Todesco, *J. Chem. Soc., Chem. Commun.*, 1988, 807.

58 G. Bartoli, G. Palmieri, M. Petrini, M. Bosco, and R. Dalpozzo, *Tetrahedron*, 1990, **46**, 1379.

59 R.D. Clark, J.M. Muchowski, M. Souchet, and D.B. Repke, *Synlett*, 1990, 207.

60 R.D. Clark, J.M. Muchowski, L.E. Fisher, L.A. Flippin, D.B. Repke, and M. Souchet, *Synthesis*, 1991, 871.

61 M. Arcari, R. Aveta, A. Brandt, L. Cecchetelli, G.B. Corsi, and M. Di Rella, *Gazz. Chim. Ital.*, 1991, **121**, 499.

62 J. Bergman and P. Sand, *Tetrahedron*, 1990, **46**, 6085.

63 H. Greuter and H. Schmid, *Helv. Chim. Acta*, 1974, **57**, 281.

64 P. Molina, M. Alajarin, and A. Vidal, *Tetrahedron*, 1990, **46**, 1063.

65 P.A. Wender and A. W. White, *Tetrahedron*, 1983, **39**, 3767.

66 J. Graham, A. Ninan, K. Reza, M. Sainsbury, and H.G. Shertzer, *Tetrahedron*, 1992, **48**, 167.

67 A. Couture, E. Deniau, Y. Gimbert, and P. Grandclaudon, *Tetrahedron*, 1993, **49**, 1431.

68 A. Couture, E. Deniau, Y. Gimbert, and P. Grandclaudon, *J. Chem. Soc., Perkins Trans. 1*, 1993, 2463.

69 A. Bischler and H. Brion, *Chem. Ber.*, 1892, **25**, 2860.

70 A. Bischler and P. Firemann, *Chem. Ber.*, 1893, **26**, 1336.

71 G.K.B. Prasad, A. Burchat, G. Weeratunga, I. Watts, and G.I. Dmitrienko, *Tetrahedron Lett.*, 1991, **32**, 5035.

72 L.D. Basanagoudar, C.S. Mahajanshetti, and S.B. Dambal, *Ind. J. Chem., Sect. B*, 1991, **30**, 1018.

73 J.E. Nordlander, D.B. Catalane, K.D. Kotian, R.M. Stevens, and J.E. Haky, *J. Org. Chem.*, 1981, **46**, 778.

74 H. Suda, M. Ohkubo, K. Matsunaga, S. Yamamura, W. Shimomoto, N. Kimura, and Y. Shizuri, *Tetrahedron Lett.*, 1993, **34**, 3797.

75 R.J. Sundberg and J.P. Laurino, *J. Org. Chem.*, 1984, **49**, 249.

76 J.I.G. Cadogan, M. Cameron-Wood, R.K. Mackie, and R.J.G. Searle, *J. Chem. Soc.*, 1965, 4831.

77 R.J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604.

78 C. Crotti, S. Cenini, R. Todeschini, and S. Tollari, *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 2811.

79 R. Zhang, X. Liao, and Z. Gao, *Synthesis*, 1990, 801.

80 G.A. Russell, C.-F. Yao, H.I. Tashtoush, J.E. Russell, and D.F. Dedolph, *J. Org. Chem.*, 1991, **56**, 663.

81 M.L. Gelmi, D. Pocar, and F. Vago, *J. Chem. Soc., Perkin Trans. 1*, 1993, 969.

82 For example, see K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 1968, **19**, 3499.

83 R.J. Sundberg, H.F. Russell, W.V. Ligon, Jr., and L.-S. Lin, *J. Org. Chem.*, 1972, **37**, 719.

84 P. Kaszynski and D.A. Dougherty, *J. Org. Chem.*, 1993, **58**, 5209.

85 H. Hemetsberger, D. Knittel, and H. Weidmann, *Montash. Chem.*, 1970, **101**, 161.

86 R.E. Adams, J.B. Press, and E.G. Deegan, *Synth. Commun.*, 1991, **21**, 675.

87 J.K. MacLeod and L.C. Monahan, *Aust. J. Chem.*, 1990, **43**, 329.

88 D.M.B. Hickey, C.J. Moody, and C.W. Rees, *J. Chem. Soc., Chem. Commun.*, 1982, 1419.

89 P. Rocca, F. Marsais, A. Godard, and G. Queguiner, *Tetrahedron*, 1993, **49**, 3325.

90 P. Rocca, F. Marsais, A. Godard, and G. Queguiner, *Tetrahedron*, 1993, **49**, 49.

91 K.C. Majumdar, R.N. De, and S. Saha, *Tetrahedron Lett.*, 1990, **31**, 1207.

92 T. Izumi, M. Sugano, and T. Konno, *J. Heterocycl. Chem.*, 1992, **29**, 899.

93 A.T. Hewson, K. Hughes, S.K. Richardson, D.A. Sharpe, and A.H. Wadsworth, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1565.

94 A.M. Echavarren, *J. Org. Chem.*, 1990. **55**, 4255.

95 A.S. Ijaz, J. Parrick, and A. Yahya, *J. Chem. Res. (S)*, 1990, 116.

96 H.D.H. Showalter and G. Pohlmann, *Org. Prep. Proc. Int.*, 1992, **24**, 484.

97 E.K. Mantus and J. Clardy, *Tetrahedron Lett.*, 1993, **34**, 1085.

98 A.S. Ijaz and J. Parrick, *Sci. Int. (Lahore)*, 1989, **1**, 364; *Chem. Abstr.*, 1991, **114**, 6204.

99 S.C. Mishra and R.A. Mishra, *J. Electrochem. Soc. India*, 1990, **39**, 51.

100 T. Izumi, M. Soutome, and T. Miura, *J. Heterocycl. Chem.*, 1992, **29**, 1625.

101 J.C. Estévez, R.J. Estévez, and L. Castedo, *Tetrahedron Lett.*, 1993, **34**, 6479.

102 W. Leimgruber and A.D. Batcho, 'Third International Congress of Heterocyclic Chemistry', Tohuku University, Sendai, August, 1971.

103 A.D. Batcho and W. Leimgruber, *Org. Synth.*, 1984, **63**, 214.

104 For a review, see R.D. Clark and D.B. Repke, *Heterocycles*, 1984, **22**, 195.

105 D.H. Lloyd and D.E. Nichols, *Tetrahedron Lett.*, 1983, **24**, 4561.

106 P.L. Feldman and H. Rapoport, *Synthesis*, 1986, 735.

107 P. Stanetty and H. Koller, *Arch. Pharm. (Weinheim)*, 1992, **325**, 433.

108 J.E. Macor, K. Ryan, and M.E. Newman, *Tetrahedron*, 1992, **48**, 1039.

109 J.P. Mayer, J.M. Cassady, and D.E. Nichols, *Heterocycles*, 1990, **31**, 1035.

110 M. Makosza, W. Danikiewicz, and K. Wojciechowski, *Liebigs Ann. Chem.*, 1988, 203.

111 J.E. Macor and M.E. Newman, *Heterocycles*, 1990, **31**, 805.

112 J.E. Macor and J.M. Wehner, *Heterocycles*, 1993, **35**, 349.

113 M. Makosza and J. Winiarski, *Acc. Chem. Res.*, 1987, **20**, 282.

114 Y. Tsuji, K.T. Huh, and Y. Watanabe, *Tetrahedron Lett.*, 1986, **27**, 377.

115 Y. Tsuji, K.T. Huh, and Y. Watanabe, *J. Org. Chem.*, 1987, **52**, 1673.

116 Y. Tsuji, S. Kotachi, K. Huh, and Y. Watanabe, *J. Org. Chem.*, 1990, **55**, 580.

117 R.B. Webb, II, M.C. Venuti, and C. Eigenbrot, *J. Org. Chem.*, 1991, **56**, 4706.

118 J.F. Carpender, *J. Org. Chem.*, 1993, **58**, 1607.

119 H.-J. Knölker, M. Bauermeister, and J.-B. Pannek, *Chem. Ber.*, 1992, **125**, 2783.

120 H.-J. Knölker, M. Bauermeister, and J.-B. Pannek, *Tetrahedron*, 1993, **49**, 841.

121 Y. Kita, H. Tohma, M. Inagaki, and K. Hatanaka, *Heterocycles*, 1992, **33**, 503.

122 For example, see J.P. Dittami and H. Ramanathan, *Tetrahedron Lett.*, 1988, **29**, 45.

123 J. Inanaga, O. Ujikawa, and M. Yamaguchi, *Tetrahedron Lett.*, 1991 **32**, 1737.

124 M.A. Fox, D.A. Chandler, and C. Lee, *J. Org. Chem.*, 1991, **56**, 3246.

125 K. Jones and J.M.D. Storey, *J. Chem. Soc., Chem. Commun.*, 1992, 1766.

126 T. Sato, N. Nakamura, K. Ikeda, M. Okada, H. Ishibashi, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2399.

127. K. Jones and J. Wilkinson, *J. Chem. Soc., Chem. Commun.*, 1992, 1767.
128 D.L. Boger, W. Yun, and B.R. Teegarden, *J. Org. Chem.*, 1992, **57**, 2873.
129 (a) Y. Ozlu, D.E. Cladingboel, and P.J. Parsons, *Synlett*, 1993, 357; (b) D.E. Cladingboel and P.J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1990, 1543.
130 J.E. Brumwell, N.S. Simpkins, and N.K. Terrett, *Tetrahedron Lett.*, 1993, **34**, 1219.
131 A. Maquestiau, D. Beugnies, R. Flammang, A.R. Katritzky, M. Soleiman, T. Davis, and J.N. Lam, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1071.
132 S.J. Barker and R.C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 1990, 485.
133 L.K. Mehta, J. Parrick, and F. Payne, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1261.
134 A. Molina, J.J. Vaquero, J.L. García-Navio, and J. Alvarez-Builla, *Tetrahedron Lett.*, 1993, **34**, 2673.
135 E.D. Edstrom and W. Yuan, *Tetrahedron Lett.*, 1991, **32**, 323.
136 For reviews, see (a) L.S. Hegedus, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1113; (b) T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, **27**, 2225.
137 R.C. Larock and S. Babu, *Tetrahedron Lett.*, 1987, **28**, 5291.
138 R.C. Larock, N.G. Berrios-Peña, and K. Narayanan, *J. Org. Chem.*, 1990, **55**, 3447.
139 R.C. Larock, N.G. Berrios-Peña, and C.A. Fried, *J. Org. Chem.*, 1991, **56**, 2615.
140 R.C. Larock and E.K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689.
141 R.C. Larock and E.K. Yum, *Synlett*, 1990, 529.
142 J.E. Macor, D.H. Blank, R.J. Post, and K. Ryan, *Tetrahedron Lett.*, 1992, **33**, 8011.
143 D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, S. Gronowitz, and L.A. Cohen, *Tetrahedron Lett.*, 1993, **34**, 2823.
144 T. Jeschke, D. Wensbo, U. Annby, S. Gronowitz, and L.A. Cohen, *Tetrahedron Lett.*, 1993, **34**, 6471.
145 T. Sakamoto, Y. Kondo, M. Uchiyama, and H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1941.
146 R. Grigg, P. Kennewell, and A.J. Teasdale, *Tetrahedron Lett.*, 1992, **33**, 7789.
147 J.P. Genet, E. Blart, and M. Savignac, *Synlett*, 1992, 715.
148 T. Sakamoto, T. Nagano, Y. Kondo, and H. Yamanaka, *Synthesis*, 1990, 215.
149 A. Arcadi, S. Cacchi, and F. Marinelli, *Tetrahedron Lett.*, 1992, **33**, 3915.
150 M. Akazome, T. Kondo, and Y. Watanabe, *Chem. Lett.*, 1992, 769.
151 T. Sakamoto, Y. Kondo, A. Yasuhara, and H. Yamanaka, *Tetrahedron*, 1991, **47**, 1877.
152 T. Sakamoto, A. Yasuhara, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1993, **36**, 2597.
153 J.-E. Bäckvall and P.G. Andersson, *J. Am. Chem. Soc.*, 1990. **112**, 3683.
154 J.-E. Bäckvall, P.G. Andersson, G.B. Stone, and A. Gogoll, *J. Org. Chem.*, 1991, **56**, 2988.
155 N. Etkin, S.D. Babu, C.J. Fooks, and T. Durst, *J. Org. Chem.*, 1990, **55**, 1093.
156 T. Izumi and T. Yokota, *J. Heterocycl. Chem.*, 1992, **29**, 1085.
157 A. Fürstner, D.N. Jumbam, and H. Weidmann, *Tetrahedron Lett.*, 1991, **32**, 6695.
158 A. Fürstner and D.N. Jumbam, *Tetrahedron*, 1992, **48**, 5991.
159 A. Fürstner and D.N. Jumbam, *J. Chem. Soc., Chem. Commun.*, 1993, 211.
160 Y. Uozumi, M. Mori, and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*, 1991, 81.
161 J.H. Tidwell, D.R. Senn, and S.J. Buchwald, *J. Am. Chem. Soc.*, 1991, **113**, 4685.
162 P.J. Walsh, M.J. Carney, and R.G. Bergman, *J. Am. Chem. Soc.*, 1991, **113**, 6343.
163 D.L. Boger and M. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 4230.
164 E. Differding and L. Ghosez, *Tetrahedron Lett.*, 1985, **26**, 1647.
165 P. Molina, M. Alajarín, and A. Vidal, *J. Chem. Soc., Chem. Commun.*, 1990, 1277.
166 P. Molina, A. Arques, A. Alías, and M.V. Vinader, *Tetrahedron Lett.*, 1991, **32**, 4401.
167 P. Molina, M. Alajarín, A. Vidal, and P. Sánchez-Andrada, *J. Org. Chem.*, 1992, **57**, 929.
168 P. Molina and C. López-Leonardo, *Tetrahedron Lett.*, 1993, **34**, 2809.
169 T. Saito, H. Ohmori, E. Furuno, and S. Motoki, *J. Chem. Soc., Chem. Commun.*, 1992, 22.
170 O.L. Chapman, G.L. Eian, A. Bloom, and J. Clardy, *J. Am. Chem. Soc.*, 1971, **93**, 2918.
171 Y. Troin, M.-E. Sinibaldi, J.-C. Gramain, M. Rubiralta, and A. Diez, *Tetrahedron Lett.*, 1991, **32**, 6129.
172 A.-M. Oliveira-Campos, M.J.R.P. Queiroz, and P.V.R. Shannon, *Chem. Ind.*, 1991, 352.
173 H. Muratake and M. Natsume, *Heterocycles*, 1990, **31**, 683.
174 H. Muratake, A. Mikawa, and M. Natsume, *Tetrahedron Lett.*, 1992, **33**, 4595.
175 M. Fuji, M. Muratake, M. Akujama, and M. Natsume, *Chem. Pharm. Bull.*, 1992, **40**, 2353.
176 I. Utsunomiya, H. Muratake, and M. Natsume, *Chem. Pharm. Bull.*, 1992, **40**, 2358.
177 K. Okabe, H. Muratake, and M. Natsume, *Tetrahedron*, 1990, **46**, 5113.
178 H. Muratake, M. Watanabe, K. Goto, and M. Natsume, *Tetrahedron*, 1990, **46**, 4179.
179 H. Muratake, T. Seino, and M. Natsume, *Tetrahedron Lett.*, 1993, **34**, 4815.
180 M. Fuji, H. Muratake, and M. Natsume, *Chem. Pharm. Bull.*, 1992, **40**, 2344.
181 M. Fuji, H. Muratake, and M. Natsume, *Chem. Pharm. Bull.*, 1992, **40**, 2338.
182 H. Muratake and M. Natsume, *Heterocycles*, 1990, **31**, 691.
183 B.M. Trost, M. Reiffen, and M. Crimmin, *J. Am. Chem. Soc.*, 1979, **101**, 257.
184 A.P. Kozikowski, P.W. Shum, A. Basu, and J.S. Lazo, *J. Med. Chem.*, 1991, **34**, 2420.
185 B. Kasum, R.H. Prager, and C. Tsopelas, *Aust. J. Chem.*, 1990, **43**, 355.
186 M. Murase, T. Hosaka, and S. Tobinaga, *Heterocycles*, 1990, **30**, 905.
187 H. Ishibashi, T. Tabata, K. Hanaoka, H. Iriyama, S. Akamatsu, and M. Ikeda, *Tetrahedron Lett.*, 1993, **34**, 489.
188 Y. Yokoyama, H. Suzuki, S. Matsumoto, Y. Sunaga, M. Tani, and Y. Murakami, *Chem. Pharm. Bull.*, 1991, **39**, 2830.
189 M. Iwasaki, Y. Kobayashi, J.-P. Li, H. Matsuzaka, Y. Ishii, and M. Hidai, *J. Org. Chem.*, 1991, **56**, 1922.
190 J.M. Muchowski and M.E. Scheller, *Tetrahedron Lett.*, 1987, **28**, 3453.
191 M. Ohno, S. Shimizu, and S. Eguchi, *Tetrahedron Lett.*, 1990, **31**, 4613.
192 M. Ohno, S. Shimizu, and S. Eguchi, *Heterocycles*, 1991, **32**, 1199.
193 M. Murase, S. Yoshida, T. Hosaka, and S. Tobinaga, *Chem. Pharm. Bull.*, 1991, **39**, 489.
194 J.-M. Keil, T. Kämpchen, and G. Seitz, *Tetrahedron*

Lett., 1990, **31**, 4581.
195 T. Chou and R.-C. Chang, *J. Chem. Soc., Chem. Commun.*, 1992, 549.
196 F.R. Leusink, R. ten Have, K.J. van den Berg, and A.M. van Leusen, *J. Chem. Soc., Chem. Commun.*, 1992, 1401.
197 P.M. Jackson and C.J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2156.
198 P.M. Jackson and C.J. Moody, *Tetrahedron*, 1992, **48**, 7447.
199 J.F.P. Andrews, P.M. Jackson, and C.J. Moody, *Tetrahedron*, 1993, **49**, 7353.
200 M. Frey and K. Eger, *Arch. Pharm. (Weinheim)*, 1992, **325**, 545.
201 B. Gómez, E. Guitián, and L. Castedo, *Synlett*, 1992, 903.
202 C. Caubère, P. Caubère, P. Renard, J.-G. Bizot-Espiart, and B. Jamart-Grégoire, *Tetrahedron Lett.*, 1993, **34**, 6889.
203 M. Iwao, H. Takehara, S. Furukawa, and M. Watanabe, *Heterocycles*, 1993, **36**, 1483.
204 R.F.C. Brown, K.J. Coulston, F.W. Eastwood, and M.R. Moffat, *Tetrahedron*, 1992, **48**, 7763.
205 A.A. Fadda, *Ind. J. Chem., Sect. B*, 1990, **29**, 1017.
206 M.A. Yurovskaya, A.Z. Afanasyev, F.V. Maximova, and Y.G. Bundel, *Tetrahedron*, 1993, **49**, 4945.
207 Z. Wróbel and M. Makosza, *Synlett*, 1993, 597.
208 N.S. Prostakov, B.N. Anisimov, A.A. Obynochnyi, and A.V. Varlamov, *J. Org. Chem., USSR*, 1991, **27**, 541.
209 M. Satomura, *J. Org. Chem.*, 1993, **58**, 3757.
210 T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1986, **24**, 31.
211 S. Takano, T. Sato, K. Inomata, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1991, 462.
212 C. Li and A. Vasella, *Helv. Chim. Acta*, 1993, **76**, 197.