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Indole synthesis: a review and proposed classification

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1. Introduction

The indole alkaloids, ranging from lysergic acid to vincristine, have long inspired organic synthesis chemists. Interest in developing new methods for indole synthesis has burgeoned over the past few years. These new methods have been fragmented across the literature of organic chemistry. In this review, we present a framework for the classification of all indole syntheses.

As we approach the classification of routes for the preparation of indoles, we are mindful that the subject has occupied the minds of organic chemists for more than a century. There have been many reviews of indole synthesis.¹ We were also aware that much more could be said than we have written. We have only briefly covered the conversion of indolines into indoles, and the reduction of oxindoles to indoles. We have not covered the extensive literature on the modification of existing indoles. Throughout, our interest

has been to be illustrative, not exhaustively inclusive. It is apparent, however, that every indole synthesis must fit one or the other of the nine strategic approaches adumbrated here. The web of scientific citations unites and organizes the world-wide research effort. It is our intention that the system put forward here for classifying indole syntheses will be universally understood. As authors conceive of new approaches to the indole nucleus, they will be able to classify their approach, and so readily discover both the history and the current state of the art with that strategy for indole construction. In addition to avoiding duplication, it is also our hope that efforts will then be directed toward the very real challenges that remain to be overcome. It is noteworthy that, in the most recent year we have covered, 2009, significant new contributions were reported for each of these nine strategies. We have highlighted these at the end of each section.

There are four bonds in the five-membered indole ring. In classifying methods for synthesis (Fig. 1), we have focused on the last bond formed. We have also differentiated, in distinguishing Type 1 versus Type 2 and Type 3 versus Type 4, between forming

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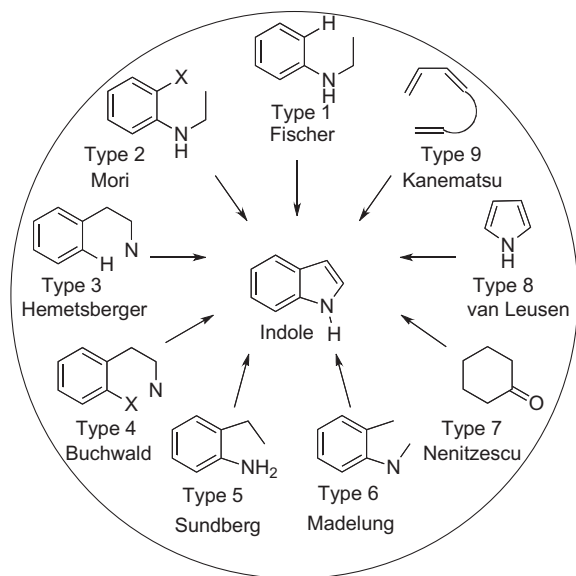


Fig. 1. The nine types of indole synthesis.

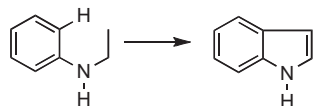
a bond to a functionalized aromatic carbon, and forming a bond to an aromatic carbon occupied only by an H. Type 5 has as the last step C–N bond formation, while with Type 6 the last step is C–C bond formation. In Type 7, the benzene ring has been derived from an existing cyclohexane, and in Type 8, the benzene ring has been built onto an existing pyrrole. Finally, in Type 9, both rings have been constructed.

There are several name reactions associated with indole synthesis. We have tried to note these in context, and to group examples of a particular name reaction together. For convenience, the ‘name reaction’ indole syntheses mentioned in this review are:

- Bartoli indole synthesis—Type 1
- Bischler indole synthesis—Type 5
- Fischer indole synthesis—Type 1
- Hemetsberger indole synthesis—Type 3
- Julia indole synthesis—Type 5
- Larock indole synthesis—Type 5
- Leimgruber–Batcho indole synthesis—Type 5
- Madelung indole synthesis—Type 6
- Nenitzescu indole synthesis—Type 7
- Reissert indole synthesis—Type 5
- Sundberg indole synthesis—Type 5

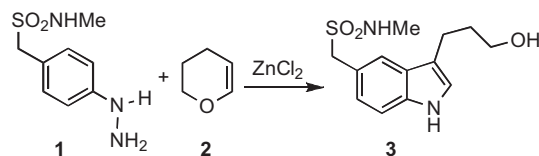
While it might be sufficient to merely label the nine strategies 1–9, for ease of recollection we have also associated each strategy with the name of an early or well-known practitioner. The division of strategies is strictly operational. Thus, the Fischer indole synthesis is classified as Type 1, Ar–H to C2, since that is the way it is carried out, even though the last bond formed, as the reaction proceeds, is in fact N to C1.

2. Type 1

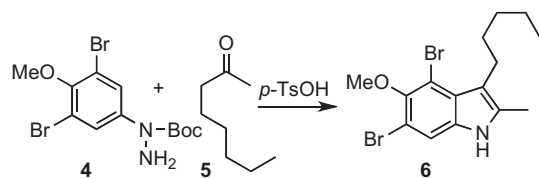


Fischer strategy

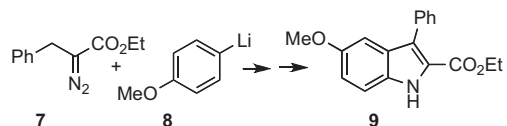
Type 1 synthesis (Scheme 1–17) involves aromatic C–H functionalization. Although C–H activation is thought of as a modern topic, the venerable Fischer indole synthesis (still under active development, Schemes 1–3) falls under this heading. Paul R. Brodfuehrer and Shaopeng Wang of Bristol-Myers Squibb described² the convenient (Scheme 1) reaction of an aryl hydrazine **1** with dihydropyran **2** to give the 3-hydroxypropylindole **3**. Stephen L. Buchwald of MIT developed³ an elegant (Scheme 2) amination of aryl iodides to give Boc-protected aryl hydrazines, such as **4**. Acid-mediated condensation of **4** with the ketone **5** delivered the indole **6**. The condensation of **4** and **5** proceeded with high regioselectivity. Norio Takamura of Musashino University, Tokyo presented⁴ a complementary approach (Scheme 3), the addition of an aryllithium **8** to an α -diazo ester **7**, followed by acid-mediated cyclization. The ester of **9** is easily manipulated, and can also be removed altogether. Several other useful variations on the Fischer indole synthesis have been reported.^{5–7}



Scheme 1.

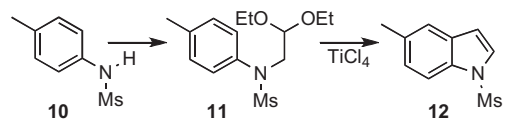


Scheme 2.

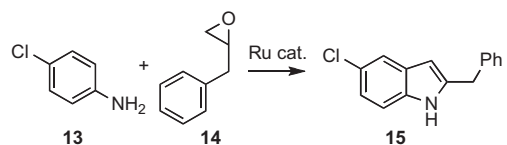


Scheme 3.

Indoles can also be formed by acid-mediated cyclization of aldehydes. Richard J. Sundberg of the University of Virginia described⁸ the preparation from **10** (Scheme 4) and cyclization of acetals, such as **11** to give the indole **12**. The Bischler indole synthesis^{9a,b} is a variation on this approach. Chan Sik Cho and Sang Chul Shim of Kyungpook National University, Taegu devised^{9c} a route to indoles (Scheme 5) based on Ru-mediated addition of an aniline **13** to an epoxide **14**. An interesting oxidation–reduction cascade led to the 2-alkyl indole **15**, probably via a Bischler-like tautomerization.

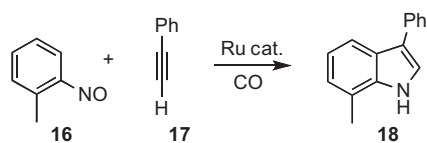


Scheme 4.

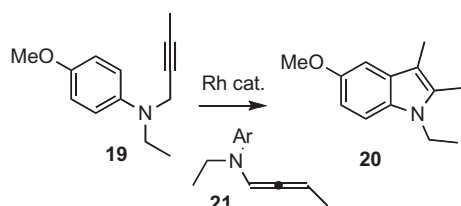


Scheme 5.

Other transition-metal-mediated protocols for indole synthesis have been developed. In a variant on the Bartoli indole synthesis, Kenneth M. Nicholas of the University of Oklahoma reported¹⁰ the Ru-catalyzed reductive coupling of a nitrosoaromatic, such as **16** (Scheme 6) with an alkyne **17** to give the indole **18**. Akio Saito and Yuji Hanzawa of Showa Pharmaceutical University described¹¹ the Rh-catalyzed cyclization of **19** (Scheme 7) to **20**. The reaction was thought to proceed via the allene **21**.

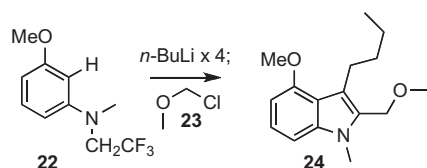


Scheme 6.

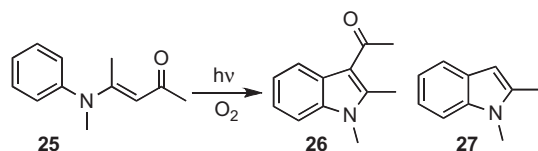


Scheme 7.

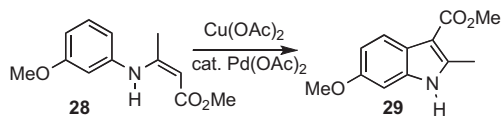
Several other Type 1 indole syntheses have been described. In the examples cited so far, only one regioisomeric aryl H could be substituted. In an *ortho*-metalation approach, Francis Johnson of SUNY Stony Brook showed¹² that (Scheme 8) the anion from cyclization of **22** could be alkylated with an electrophile, such as **23** to give the indole **24**. Darrell Watson and D.R. Dillin at the University of Mary Hardin-Baylor reported¹³ a photochemical route (Scheme 9) to indoles. Irradiation of **25** in an oxygen atmosphere led to **26**. When the photolysis was carried out under nitrogen, the product was **27**. Frank Glorius of the Universität Münster devised¹⁴ a related catalytic oxidation of enamines, such as **28** (Scheme 10) to the indole **29**. Just recently, Yan-Guang Wang of Zhejiang University, Hangzhou described¹⁵ the coupling (Scheme 11) of a wide range of anilides, such as **30** with ethyl diazoacetate **31** to give the indole **32**.



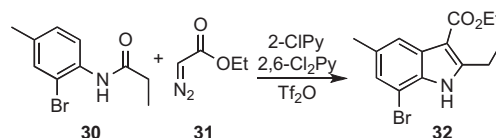
Scheme 8.



Scheme 9.

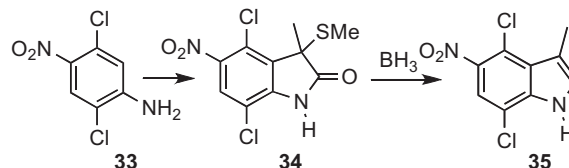


Scheme 10.



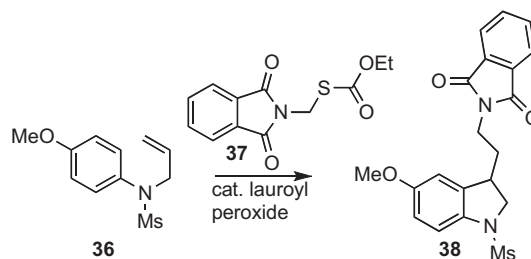
Scheme 11.

Indoles, such as **35** (Scheme 12) can also be prepared from oxindoles, such as **34**, prepared from **33**. Wendell Wierenga, then at Upjohn, optimized¹⁶ both the Gassman synthesis of oxindoles from anilines, and the subsequent reduction. This is a net Type 1 synthesis.



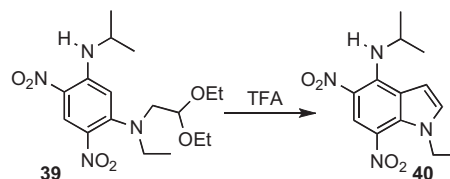
Scheme 12.

Samir Z. Zard of Ecole Polytechnique described¹⁷ the cyclization (Scheme 13) of allyl anilines, such as **36** to the indoline **38** using **37**. As indolines can be converted into indoles by oxidation¹⁸ or by base-mediated elimination of an *N*-sulfonyl group¹⁹ this is also a net Type 1 indole synthesis.



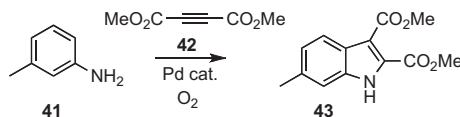
Scheme 13.

In 2009, four interesting new examples of Type 1 indole synthesis were described. It had been thought that the cyclization of an acetal (Scheme 4) to the indole would only work with electron-rich aromatic rings. Dali Yin of the Institute of Materia Medica, Beijing²⁰ observed that **39** (Scheme 14), readily prepared by sequential displacement on the corresponding difluorodinitrobenzene, smoothly cyclized to **40**.



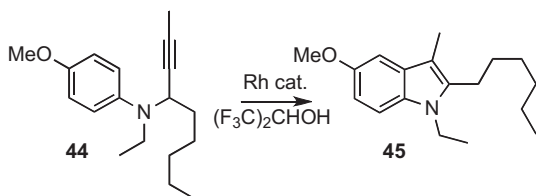
Scheme 14.

Following up on the work of Glorius (Scheme 10), Ning Jiao of Peking University found²¹ that, under oxidizing conditions, an aniline derivative, such as **41** (Scheme 15) could be condensed with the diester **42** to give the indole **43**. Note that the cyclization proceeded with high regioselectivity. The product was easily hydrolyzed and decarboxylated to give the 2,3-unsubstituted indole.



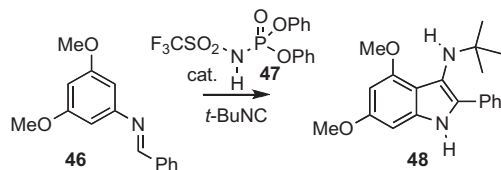
Scheme 15.

Akio Saito and Yuji Hanazawa of Showa Pharmaceutical University published²² a full account of the Rh-mediated cyclization of propargylaniline derivatives, such as **44** (Scheme 16) that they developed. This reaction is apparently proceeding via rearrangement to an intermediate *o*-allenylaniline, that then cyclizes to the product, **45**.



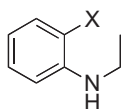
Scheme 16.

Erik J. Sorensen of Princeton University uncovered²³ a route to indoles (Scheme 17) based on an interrupted Ugi reaction, the combination of **46** and *tert*-butyl isocyanide to give the amino-indole **48**. The acid **47** was particularly effective at mediating this reaction.



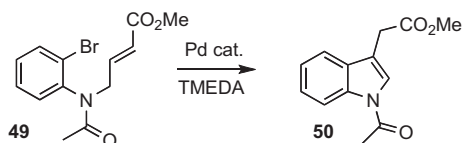
Scheme 17.

3. Type 2

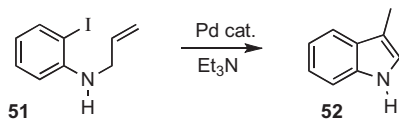


Mori strategy

In a landmark paper in 1977, Miwako Mori, working with Yoshio Ban at Hokkaido University, reported²⁴ the first intramolecular Heck cyclization, converting the 2-bromoaniline derivative **49** (Scheme 18) into the *N*-acetyl indole **50** with a Pd catalyst. In 1980, Louis S. Hegedus at Colorado State University showed²⁵ that iodides were superior to bromides for the cyclization, and that free amines, such as **51** (Scheme 19) were compatible with the reaction conditions, forming **52**.

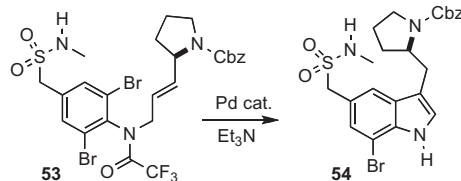


Scheme 18.

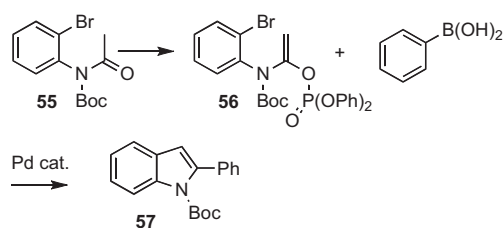


Scheme 19.

This approach has been extended in several directions. John E. Macor at Pfizer found²⁶ that cyclization of the dibromide **53** to **54** (Scheme 20) was more efficient than cyclization of the corresponding monobromide. Note that the potentially labile allylic carbamate survived the Pd reaction conditions. Haruhiko Fuwa and Makoto Sasaki of Tohoku University devised²⁷ the conversion of the *N*-acetyl aniline **55** (Scheme 21) into the enol phosphonate **56**. Consecutive Suzuki coupling followed by Heck cyclization delivered the indole **57**.

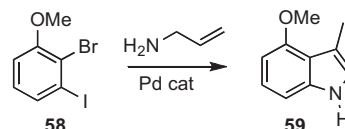


Scheme 20.

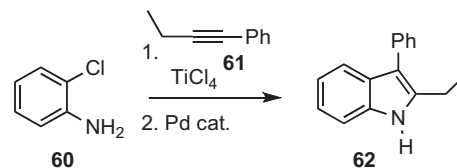


Scheme 21.

Morten Jørgensen of H. Lundbeck A/S, Denmark took advantage²⁸ of the more facile oxidative addition of aryl iodides compared to aryl bromides to accomplish sequential *N*-arylation and Heck cyclization, converting **58** (Scheme 22) into the indole **59**. Lutz Ackermann of the Ludwigs-Maximilian-Universität München effected²⁹ regioselective Ti-mediated hydroamination of the alkyne **61** (Scheme 23) with the aniline **60**. Pd-mediated cyclization of the nucleophilic enamine so formed gave the indole **62**.

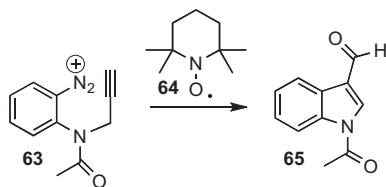


Scheme 22.

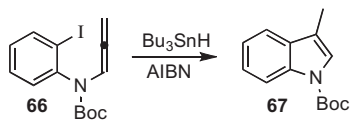


Scheme 23.

Indoles can also be prepared by free radical cyclization. Athelstan L. J. Beckwith of the University of Adelaide cleverly employed³⁰ the nitroxide **64** (Scheme 24) to effect first reduction, to facilitate loss of N_2 from the diazonium salt **63**, then radical cyclization, then radical-radical coupling with the nitroxide, followed by loss of the amine to give the indole aldehyde **65**. Richard P. Hsung, now at the University of Wisconsin, demonstrated³¹ that a more conventional reductive cyclization of the allenylaniline **66** to form **67** (Scheme 25) was also effective.

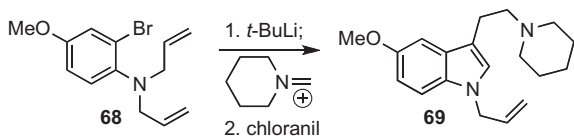


Scheme 24.

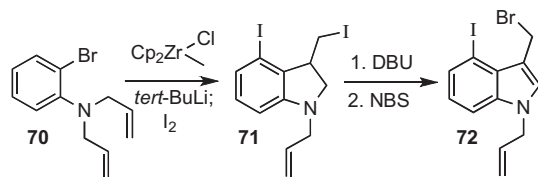


Scheme 25.

Lanny S. Liebeskind of Emory University showed³² that *ortho*-bromo allyl anilines, such as **68** (Scheme 26) could, on transmetalation, be induced to cyclize to the indoline anion. The anion could be trapped with a variety of electrophiles. The product indoline was readily oxidized to the indole **69**. Professor Buchwald generated³³ from **70** (Scheme 27) a zirconocene benzyne complex that inserted into the pendent alkene. Iodination delivered the indoline **71**, that via elimination and bromination was carried on to the indole **72**.

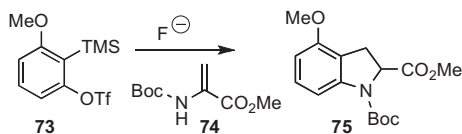


Scheme 26.



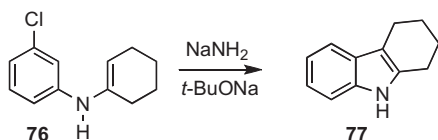
Scheme 27.

Brian M. Stoltz of Caltech added³⁴ the anion derived from **74** (Scheme 28) to the benzyne derived from **73** to give the indoline **75**. The authors did not oxidize **75** to the corresponding indole, but this should be straightforward.



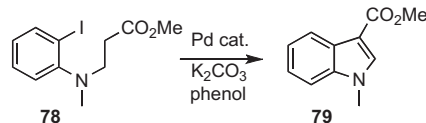
Scheme 28.

As described³⁵ by Brigitte Jamart-Grégoire of the Université de Nancy, a benzyne was also the intermediate in the cyclization of the anion derived from **76** (Scheme 29) to the indole **77**. Daniel Solé of the Universitat de Barcelona effected³⁶ the conceptual alternative,



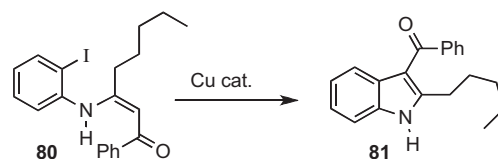
Scheme 29.

the Pd-mediated arylation of the anion derived from **78** (Scheme 30). Depending on the reaction conditions, the dominant product could be either the indoline, or the indole **79**.



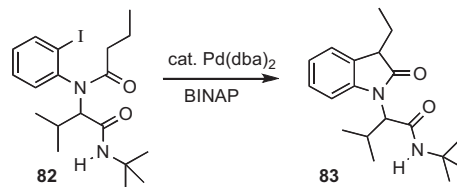
Scheme 30.

Among the several Type 2 indole syntheses reported in 2009, two were particularly interesting. Sandro Cacchi of the Università degli Studi 'La Sapienza', Roma, prepared³⁷ the enaminone **80** (Scheme 31) by condensation of the iodoaniline with the acetylenic ketone. On exposure to a Cu catalyst, **80** cyclized to the indole **81**.



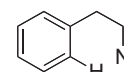
Scheme 31.

Luc Neuville and JZhu of CNRS Gif-sur-Yvette assembled³⁸ (Scheme 32) the amide **82** by a four-component coupling. With the proper choice of ligand, **82** could be cyclized to **83**. The conversion of an oxindole into the indole is described in the preceding section.



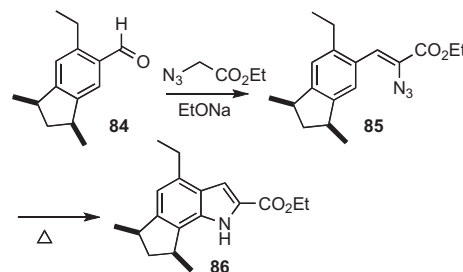
Scheme 32.

4. Type 3



Hemetsberger strategy

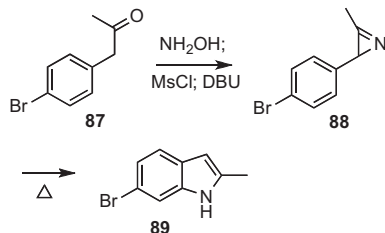
The lead Type 3 approach is the Hemetsberger³⁹ indole synthesis, as, for instance, employed⁴⁰ by John K. MacLeod of Australia National University in his synthesis (Scheme 33) of *cis*-trikentrin A. The aldehyde **84** was homologated to the azido ester **85**, that was then heated to convert it into the indole **86**.



Scheme 33.

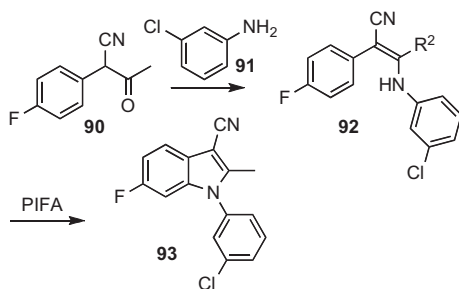
The thermal conversion of azido styrenes, such as **85** into the indole had been shown³⁹ to proceed by way of the azirine. We therefore developed⁴¹ a general method for the conversion of an α -

aryl ketone, such as **87** (Scheme 34) into the azirine **88**. Thermolysis of the azirine gave the indole **89**. Subsequently, Koichi Narasaka of the University of Tokyo demonstrated⁴² that Rh trifluoroacetate catalyzed the conversion of azirines, such as **88** into indoles at room temperature. Tom G. Driver of the University of Illinois, Chicago later found⁴³ that the same catalyst converted azido styrenes, such as **85** (Scheme 33) into the indole, also at room temperature.



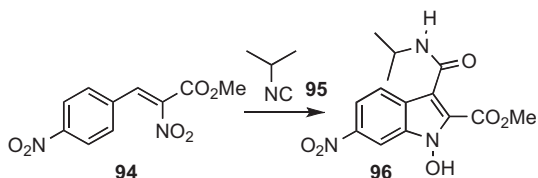
Scheme 34.

Kang Zhao of Tianjin University established⁴⁴ that PIFA oxidation of an enamine, such as **92** (Scheme 35), prepared from **90** and **91**, offered a convenient route to the *N*-aryl indole **93**. This cyclization may likely also be proceeding by way of the intermediate azirine.



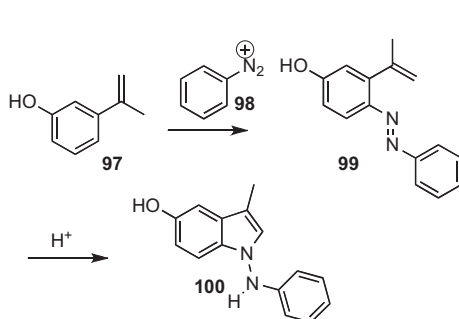
Scheme 35.

H. Person of the Université de Rennes found⁴⁵ that exposure of a β -nitro styrene **94** (Scheme 36) to an isonitrile **95** led to the *N*-hydroxy indole **96**. Glen A. Russell of Iowa State University reported⁴⁶ a related reductive cyclization of a β -nitro styrene with triethyl phosphite.



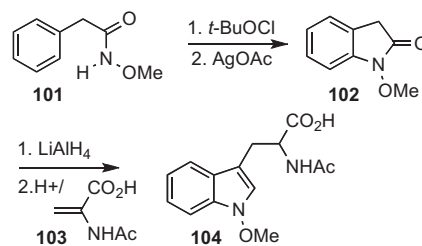
Scheme 36.

The coupling of a phenol **97** (Scheme 37) with a diazonium salt **98** is a well-known process. Masato Satomura of Fuji Photo Film Co. discovered⁴⁷ that exposure of the adduct **99** to mild acid led to cyclization to the indole **100**. The *N*-*N* bond was readily cleaved by Raney nickel to give the free amine.



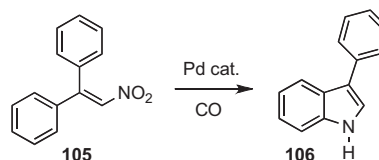
Scheme 37.

The cyclic heptadepsipeptide HUN-7293 contains the *N*-methoxy tryptophan **104** (Scheme 38). To prepare **104**, Dale L. Boger of Scripps/La Jolla took advantage⁴⁸ of the Kikugawa oxindole synthesis to convert **101** into **102**. Reduction followed by acid-catalyzed condensation with the enamide **103** then delivered **104**.

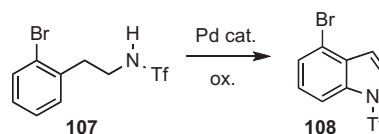


Scheme 38.

In 2009, Vy M. Dong of the University of Toronto found⁴⁹ that CO could serve (Scheme 39) as the reductant for the cyclization of a β -nitro styrene **105** to the indole **106**. Jin-Quan Yu, also of Scripps/La Jolla, developed⁵⁰ an oxidant that enabled the Pd-mediated cyclization of **107** (Scheme 40) to the indole **108**.

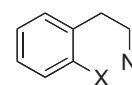


Scheme 39.



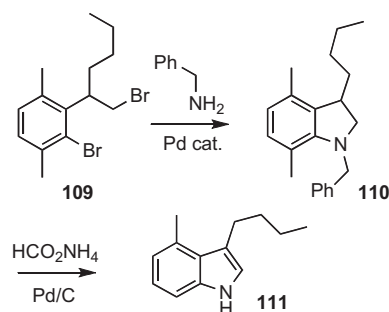
Scheme 40.

5. Type 4



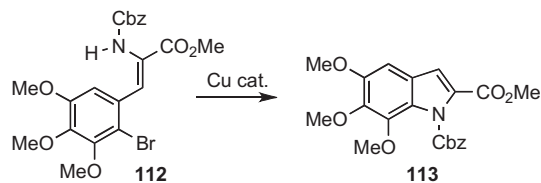
Buchwald strategy

The development of transition-metal-mediated aryl halide amination opened the way to Type 4 indole synthesis. In 1998, Stephen L. Buchwald of MIT reported⁵¹ that on exposure to benzylamine in the presence of a Pd catalyst, the dibromide **109** (Scheme 41) smoothly cyclized to the indoline **110**. Ammonium formate in the presence of Pd/C converted **110** into the indole **111**.



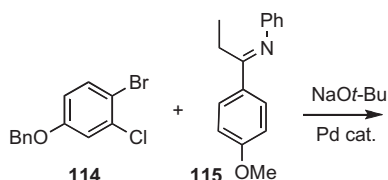
Scheme 41.

In the course of a synthesis of the duocarmycins, Tohru Fukuyama of the University of Tokyo employed⁵² a similar approach, cyclizing **112** (Scheme 42) to **113**. By that time, the Cu catalysts for aryl halide amination had been developed.



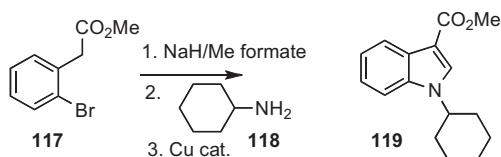
Scheme 42.

José Barluenga of the University of Oviedo took advantage⁵³ of the greater reactivity of an aryl bromide compared to the chloride as he developed the convergent coupling of **114** (Scheme 43) with **115** to give the indole **116**. For this coupling, a Pd catalyst was required.



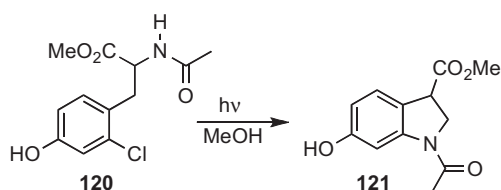
Scheme 43.

Alexander V. Karchava of Moscow State University devised⁵⁴ a route to indoles from *ortho*-bromophenylacetic acid esters, such as **117** (Scheme 44). Formylation followed by condensation with an amine **118** set the stage for the Cu-mediated intramolecular amination to give the indole **119**.



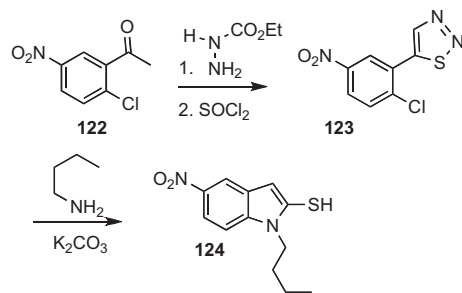
Scheme 44.

Phenols, under photolysis, can activate *meta*-substituted halides for nucleophilic displacement. Nien-chu C. Yang of the University of Chicago devised⁵⁵ an indoline synthesis based on this effect, irradiating **120** (Scheme 45) to give **121**.



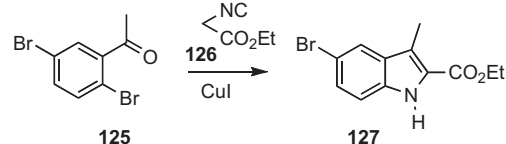
Scheme 45.

Similarly, nitro groups can activate *para*-substituted halides for nucleophilic displacement. Douglas C. Neckers of Bowling Green State University observed⁵⁶ that exposure to a primary amine converted the thiadiazole **123** (Scheme 46), prepared from **122**, into the indole-2-thiol **124**. The reaction is thought to be proceeding by way of the alkyne thiol.

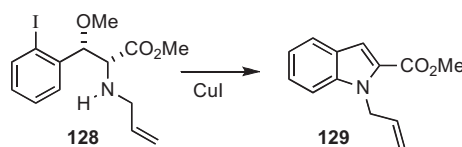


Scheme 46.

In 2009, Qian Cai and Ke Ding of the Institute of Biological Chemistry, Guangzhou described⁵⁷ (Scheme 47) the CuI-mediated condensation of the isocyano ester **126** with *o*-halo aromatic ketones and aldehydes, such as **125** to give directly the corresponding indole **127**. Stuart L. Schreiber of Harvard University took⁵⁸ a related approach, cyclizing **128** (Scheme 48), prepared via the corresponding aziridine, to the indole **129**.

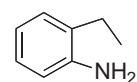


Scheme 47.



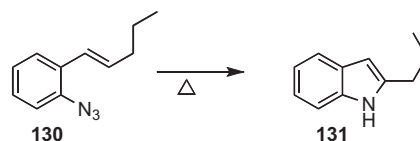
Scheme 48.

6. Type 5

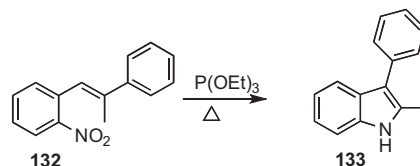


Sundberg strategy

In 1969, Richard J. Sundberg of the University of Virginia reported⁵⁹ that *ortho*-azido styrenes, such as **130** (Scheme 49) were converted on thermolysis into the corresponding indole **131**. He later found⁶⁰ that heating *ortho*-nitro styrenes, such as **132** (Scheme 50) with P(OEt)₃ also delivered the indole. Aryl migration dominated over alkyl migration, leading to **133**. Recently, Tom G. Driver of the University of Illinois, Chicago showed⁶¹ that the azide version of the Sundberg indole synthesis could be carried out at lower temperature with a Rh catalyst.

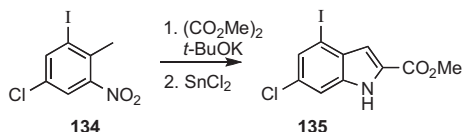


Scheme 49.

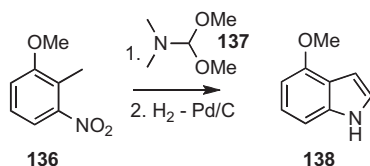


Scheme 50.

Benzylic methyl groups are acidic enough to be deprotonated, especially when there is an *ortho*-nitro group. This is the basis for the Reissert indole synthesis⁶² (**134** to **135**, Scheme 51) and the Leimgruber–Batcho indole synthesis⁶³ (**136** to **138**, Scheme 52).

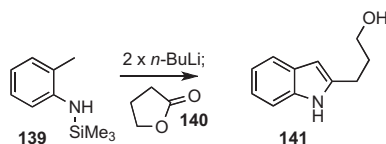


Scheme 51.



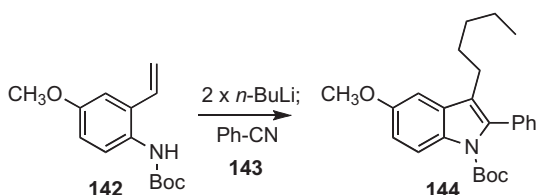
Scheme 52.

Amos B. Smith III of the University of Pennsylvania took advantage⁶⁴ of the acidity of **139** (Scheme 53). Double deprotonation followed by condensation with **140** delivered the indole **141**.



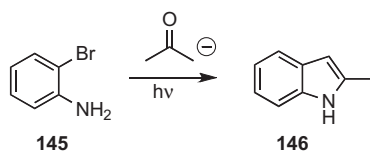
Scheme 53.

Donal F. O'Shea of University College Dublin demonstrated⁶⁵ that an alkyllithium first deprotonated **142** (Scheme 54), and then added to the pendent alkene. Benzonitrile **143** was added to the resulting carbanion to give the indole **144**.

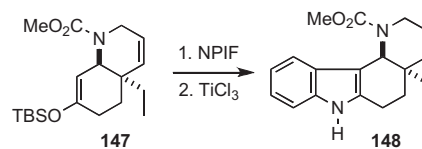


Scheme 54.

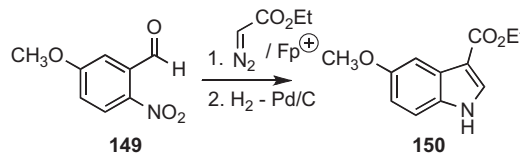
It is clear that any synthetic route to *ortho*-amino or *ortho*-nitro α -aryl ketones or aldehydes can be used to prepare indoles. Joseph F. Bunnett of the University of California, Santa Cruz observed⁶⁶ that, under S_{RN}1 conditions, acetone enolate displaced the bromide of **145** (Scheme 55), leading to the indole **146**. Viresh H. Rawal of the University of Chicago arylated⁶⁷ the silyl enol ether **147** (Scheme 56) with an *ortho*-nitrophenyl iodonium salt (NPIF) to give, after reduction, the indole **148**. M. Mahmoud Hossain of the University of Wisconsin, Milwaukee inserted⁶⁸ ethyl diazoacetate into the aldehyde **149** (Scheme 57), converting it, via reduction, into the indole **150**.



Scheme 55.

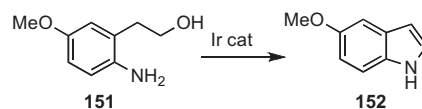


Scheme 56.



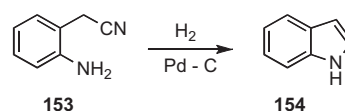
Scheme 57.

As demonstrated⁶⁹ by Ken-ichi Fujita and Ryohei Yamaguchi of Kyoto University, in situ oxidation of the alcohol **151** (Scheme 58) led to the indole **152**. With added 2-propanol, an alcohol with an *ortho*-nitro group was also converted into the indole.



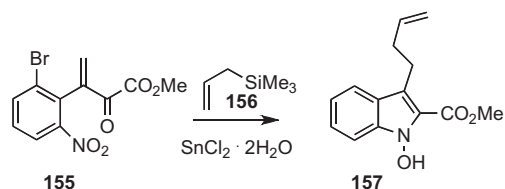
Scheme 58.

Hironao Sajiki and Kosaku Hirota of Gifu Pharmaceutical University showed⁷⁰ that reduction of an *ortho*-amino nitrile, such as **153** (Scheme 59) delivered the indole **154**, presumably by trapping of the intermediate imine. It may well be that an *ortho*-nitro substituent would work as well, but such a transformation was not included in this report.



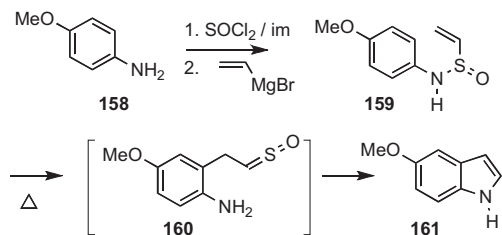
Scheme 59.

K. C. Nicolaou of Scripps/La Jolla prepared⁷¹ the enone **155** (Scheme 60) from the intermediate in the Bischler indole synthesis. Reduction of **155** gave an intermediate that reacted with mild nucleophiles, such as the allylsilane **156** to give the indole **157**.



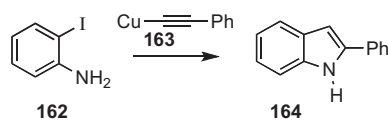
Scheme 60.

In 1986, Sylvestre A. Julia of the Ecole Normale Supérieure, Paris reported⁷² that sulfonamides, such as **159** (Scheme 61), readily prepared from the aniline **158**, were converted by heating into the indole **161** via **160**. It is striking that the Julia indole synthesis has been little used since it was reported.



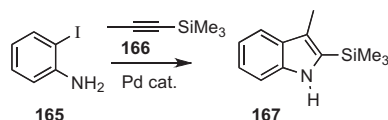
Scheme 61.

The preparation of indoles from *ortho*-haloanilines by condensation with an alkyne goes back at least to 1963, when C. E. Castro of the University of California, Riverside, observed⁷³ (Scheme 62) that coupling of **162** with **163** led not to the diaryl alkyne, but to the indole **164**.



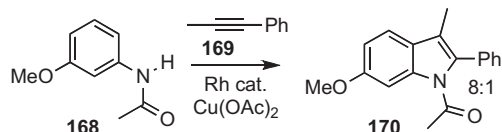
Scheme 62.

In 1985, Edward C. Taylor of Princeton University and Alexander McKillop of the University of East Anglia showed⁷⁴ that Pd was effective at cyclizing *ortho*-alkynylanilines to the corresponding indole. This led to the 1989 report⁷⁵ by J. K. Stille of Colorado State University that the two-step coupling described by Castro (Scheme 62) could be carried out at much lower temperature using Pd catalysis. With this precedent, in 1991 Richard C. Larock of Iowa State University disclosed⁷⁶ that, using Pd catalysis (Scheme 63), internal alkynes, such as **166** could be condensed with an *ortho*-iodoaniline **165** under Pd catalysis to give the 2,3-disubstituted indole **167** with high regiocontrol. One of the advantages of the Larock indole synthesis is the malleability of the 2-silyl substituent on the product indole.



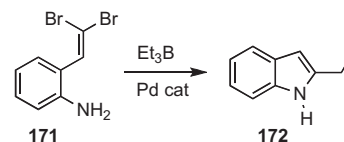
Scheme 63.

More recently, (the late) Keith Fagnou of the University of Ottawa demonstrated⁷⁷ that Rh catalysis could effect *ortho* functionalization of acetanilides, such as **168** (Scheme 64). Subsequent coupling with internal alkynes, such as **169** led to the indole **170** with high regiocontrol.

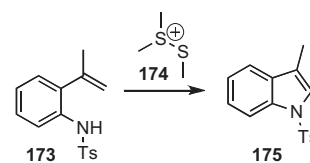


Scheme 64.

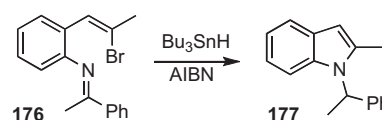
Several other flexible routes to indoles have been developed. Mark Lautens of the University of Toronto established⁷⁸ that *ortho* dihaloalkylidene anilines, such as **171** (Scheme 65) could be condensed with alkyl, alkenyl or aryl boranes or boronic acids to give the 2-substituted indole, in this case **172**. Kentaro Okuma of Fukuoka University found⁷⁹ that the sulfonium salt **174** (Scheme 66) effected cyclization of an *ortho* alkenyl aniline, such as **173** to the indole **175**. Jeffrey N. Johnston, now at Vanderbilt University, effected⁸⁰ free radical reductive cyclization of halides, such as **176** (Scheme 67), to give the indole **177**.



Scheme 65.

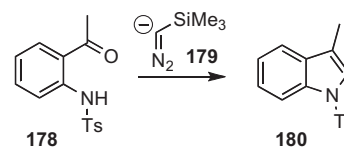


Scheme 66.

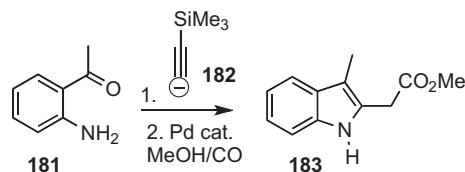


Scheme 67.

Toyohiko Aoyama of Nagoya City University reacted⁸¹ *ortho*-acylanilines, such as **178** (Scheme 68) with lithio TMS diazomethane **179** to give an alkylidene carbene, that inserted into the adjacent NH to give the indole **180**. Bartolo Gabriele of the Università della Calabria added⁸² acetylides, such as **182** (Scheme 69) to *ortho*-acylanilines, such as **181** to give alkynyl alcohols, that underwent carbonylative cyclization with Pd catalysis to give the indole **183**.

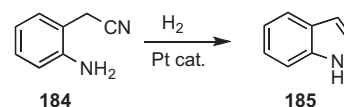


Scheme 68.

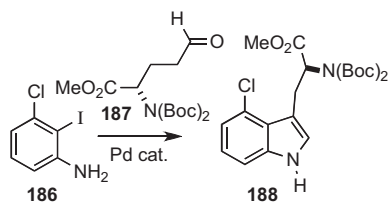


Scheme 69.

In 2009, Hideo Nagashima of Kyushu University reported⁸³ that an *o*-nitrophenyl acetonitrile **184** could indeed (Scheme 70) be reductively cyclized to the indole **185**. Yanxing Jia of Peking University prepared⁸⁴ **188**, a key intermediate in the synthesis of (–)-*cis*-clavicipitic acid, by selective condensation of the aldehyde **187** (Scheme 71) with the iodoaniline **186**.

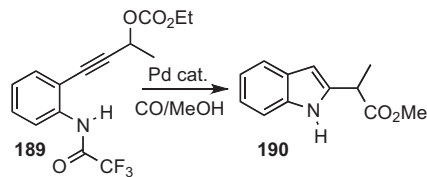


Scheme 70.



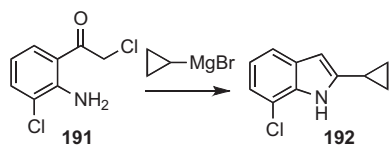
Scheme 71.

Sandro Cacchi of the Università 'La Sapienza', Rome, extended⁸⁵ the Gabriele approach, cyclizing (Scheme 72) the propargylic carbonate **189** to **190**. This transformation may be proceeding by way of the intermediate allene. Two related approaches to indole synthesis^{86,87} also appeared.



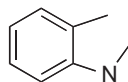
Scheme 72.

Tao Pei of Merck Rahway developed⁸⁸ a powerful new approach to substituted indoles, based on the addition (Scheme 73) of an organometallic to a chloro ketone **191**. The conversion into **192** proceeded by 1,2-migration of the arene with nucleophilic displacement of chloride.



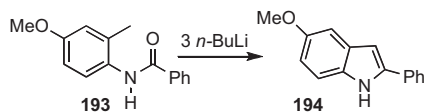
Scheme 73.

7. Type 6

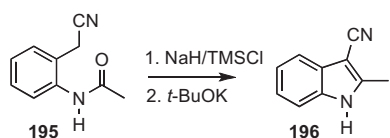


Madelung strategy

The Madelung indole synthesis, as exemplified by the cyclization (Scheme 74) of **193** to **194**, was originally carried out at elevated temperature with bases, such as NaNH_2 . William J. Houlihan of Sandoz, Inc. (now Novartis) showed⁸⁹ that, with BuLi , the cyclization of **193** to **194** was facile below room temperature. D. N. Reinhoudt of the University of Twente found⁹⁰ that phenylacetonitriles, such as **195** (Scheme 75) could be cyclized under even milder conditions, to form **196**.

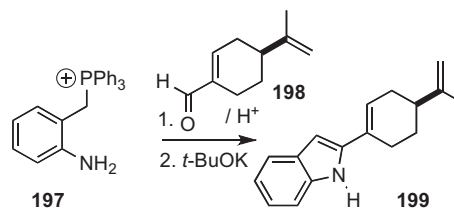


Scheme 74.

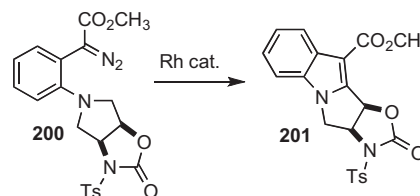


Scheme 75.

George A. Kraus of Iowa State University described⁹¹ a conceptually related cyclization (Scheme 76). Condensation of an aldehyde **198** with the aniline **197** gave the imine, that on exposure to strong base gave the indole **199**. Gary A. Sulikowski, now at Vanderbilt University, showed⁹² that cyclization of the carbene derived from **200** (Scheme 77) proceeded to give **201** with high regiocontrol.

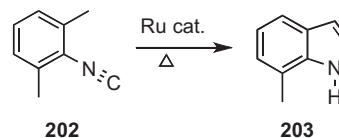


Scheme 76.



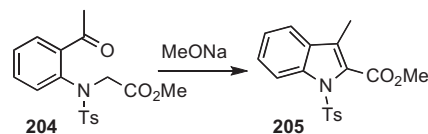
Scheme 77.

Bond formation in the opposite direction has also been developed. William D. Jones reported⁹³ that a Ru complex catalyzed the conversion of the isonitrile **202** (Scheme 78) into the indole **203**. This reaction may be proceeding by way of the Ru vinylidene complex.

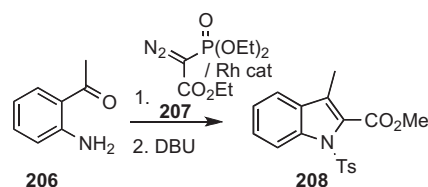


Scheme 78.

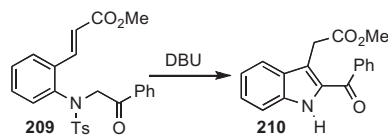
Charles D. Jones of Lilly described⁹⁴ an anionic cyclization in this direction, converting **204** (Scheme 79) into **205**. Yoshinori Nakamura of the Tanabe Seiyaku Co. contributed⁹⁵ the Rh-mediated coupling of the diazophosphonate **207** (Scheme 80) to an *ortho*-acylaniline, such as **206**, to give, after cyclization, the indole **208**. Note that, in the cyclization of **209** (Scheme 81) developed⁹⁶ by Rodney W. Stevens of Pfizer Nagoya, re-aromatization to the indole **210** was achieved by elimination of arenesulfonate.



Scheme 79.

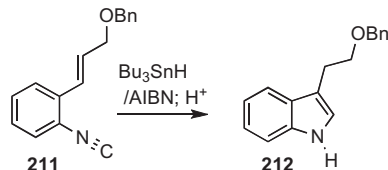


Scheme 80.



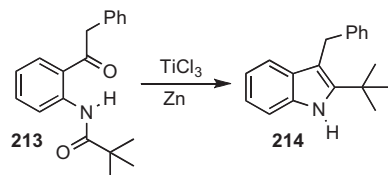
Scheme 81.

In 1994, Tohru Fukuyama, now at the University of Tokyo, disclosed^{97a} the cascade radical cyclization of the isonitrile **211** (Scheme 82) to the indole **212**. Later, he applied^{97b} a variant of this cyclization in the total synthesis of a complex indole alkaloid. Jon D. Rainier, now at the University of Utah, has explored^{97c} related radical cyclizations.



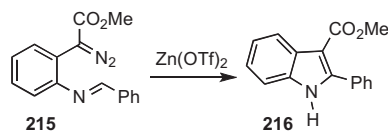
Scheme 82.

Alois Fürstner of the Max-Planck-Institute Mülheim developed^{98a,b} a reductive coupling of acyl anilides, such as **213** to give **214** (Scheme 83). In the presence of a silyl chloride, the reaction was catalytic in Ti. Bruce C. Lu of Boehringer Ingelheim employed^{98c} this reductive coupling in a combinatorial route to indoles.



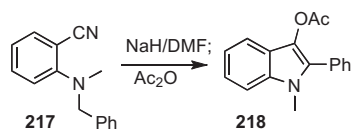
Scheme 83.

In 2009, Professor Doyle reported⁹⁹ an alternative (Scheme 84) diazo-based approach to indoles, Lewis acid-mediated cyclization of **215** to **216**.

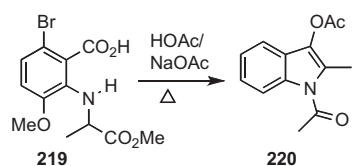


Scheme 84.

Churl Min Seong of the Korea Research Institute of Chemical Technology described¹⁰⁰ the facile cyclization (Scheme 85) of an *o*-cyano *N*-benzyl aniline **217** to the indole **218**. Andrew D. Hamilton employed¹⁰¹ a related protocol (Scheme 86), the cyclization of **219** to **220**.

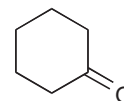


Scheme 85.



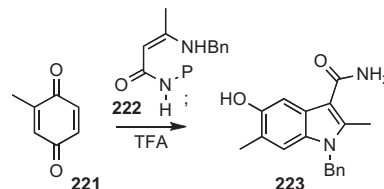
Scheme 86.

8. Type 7



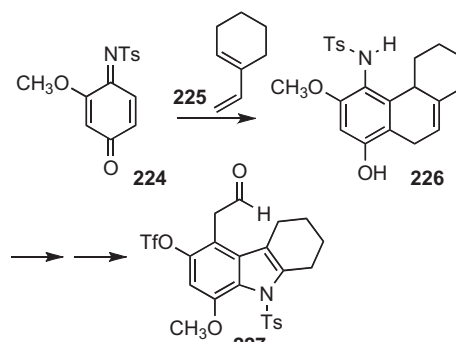
Nenitzescu strategy

Type 7 includes all routes to indoles from cycloalkane derivatives. The earliest such approach is the Nenitzescu indole synthesis, exemplified (Scheme 87) in a modern manifestation¹⁰² by Daniel M. Ketcha of Wright State University and Lawrence J. Wilson of Procter & Gamble. The combination of the benzoquinone **221** with the resin-bound enamine **222** gave, after release from the resin, the indole **223**.



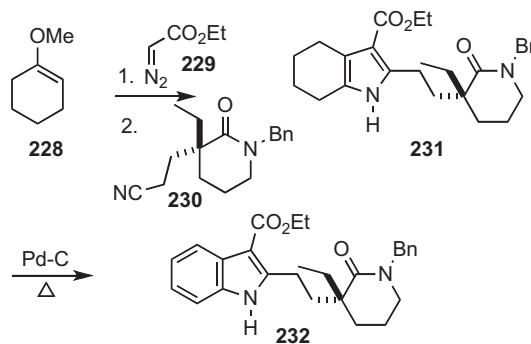
Scheme 87.

Michael A. Kerr of the University of Western Ontario developed¹⁰³ (Scheme 88) a complementary protocol for the conversion of a benzoquinone into the indole. Diels–Alder cycloaddition of the imine **224** to the diene **225** gave the adduct **226**. Protection followed by oxidative cleavage and condensation delivered the indole **227**.

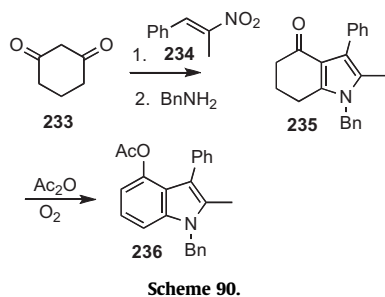


Scheme 88.

Fused pyrroles, such as **231** (Scheme 89) and **235** (Scheme 90) are readily aromatized. Brian L. Pagenkopf of the University of Western Ontario established¹⁰⁴ a pyrrole synthesis from cyclohexanone, by cyclopropanation of the enol ether **228** followed by condensation with the nitrile **230**. The aromatization of **231** to **232** was accomplished by heating with Pd/C in mesitylene.

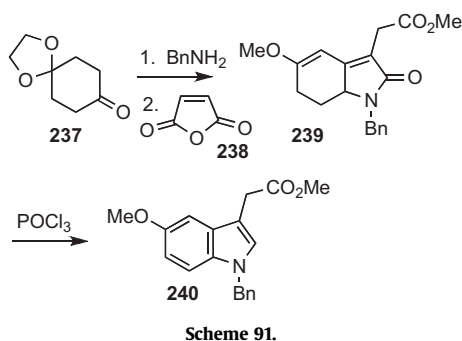


Scheme 89.

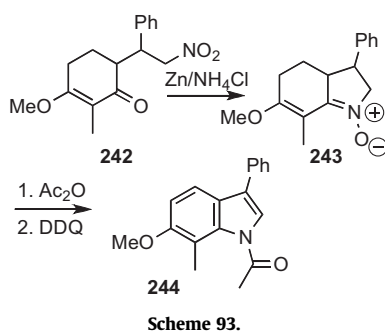
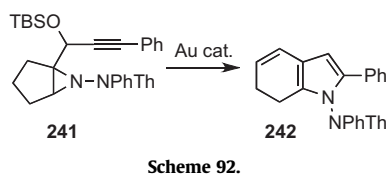


Teruhiko Ishikawa and Seiki Saito of Okayama University condensed¹⁰⁵ (Scheme 90) cyclohexane-1,3-dione **233** with the nitroalkene **234**, leading after exchange with benzylamine to the pyrrole **235**. Aromatization gave the 4-oxygenated indole **236**. Chihiro Kibiyashi of the Tokyo College of Pharmacy reported¹⁰⁶ a related approach to 4-oxygenated indoles.

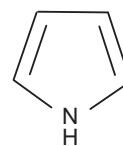
Michel Pfau of ESPCI Paris devised¹⁰⁷ an intriguing protocol for indole construction, starting with the benzyl imine of the monoprotected cyclohexane-1,4-dione **237** (Scheme 91). Metalation of the imine followed by condensation with maleic anhydride **238**, with methanol workup, delivered the lactam **239**. Exposure of **239** to POCl₃ effected aromatization to the 5-methoxyindole **240**.



In 2009, Yong-Qiang Tu of Lanzhou University described¹⁰⁸ the ring expansion (Scheme 92) of **241** to **242**. The aromatization of **242** to the indole should be facile. Tsutomu Inokuchi of Okayama University showed¹⁰⁹ that reduction (Scheme 93) of the Michael adduct **243** followed by aromatization delivered the indole **244**.

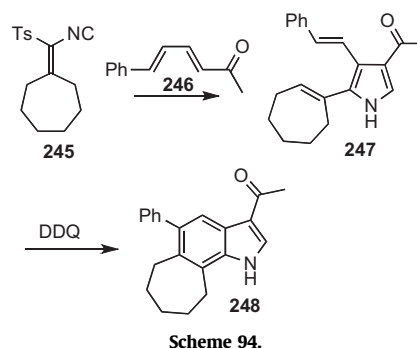


9. Type 8

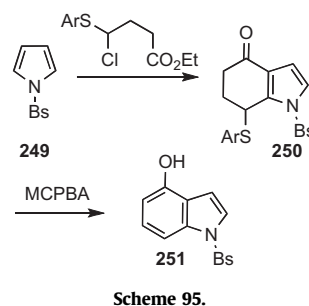


van Leusen strategy

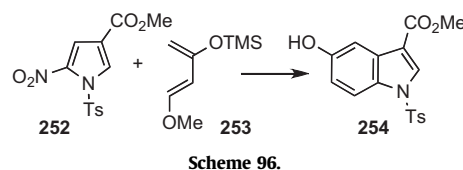
Type 8 indole syntheses include all those that proceed by way of the preformed *N*-containing five-membered ring. In 1986, Albert M. van Leusen of Groningen University established¹¹⁰ a route to highly substituted indoles, based on the condensation of isonitriles, such as **245** (Scheme 94) with unsaturated ketones, such as **246** to give the 2,3-bisalkenylpyrrole **247**. Heating followed by aromatization with DDQ completed the synthesis of the indole **248**.



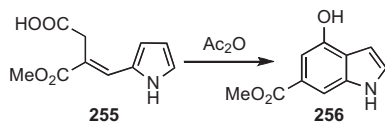
Hiroyuki Ishibashi of Kyoto Pharmaceutical University demonstrated¹¹¹ (Scheme 95) a route to 4-substituted indoles from pyrrole itself. Condensation of **249** with the chlorosulfide followed by saponification and intramolecular Friedel–Crafts acylation delivered the versatile intermediate **250**. Oxidation gave the indole **251**. The addition of nucleophiles to **250** followed by dehydration gave the 4-alkylindole (not illustrated).



Pedro Mancini of the Universidad Nacional de Litoral showed¹¹² that nitropyrroles, such as **252** (Scheme 96) were effective Diels–Alder dienophiles. Regiocontrol was poor with isoprene, whereas addition to the more activated diene **253** proceeded to give the 5-hydroxyindole **254** with complete regiocontrol.

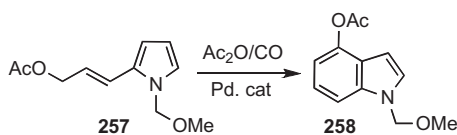


Edwin Vedejs of the University of Michigan optimized¹¹³ the acetic anhydride-mediated cyclization of the Stobbe condensation product **255** (Scheme 97) to the indole **256**. Although this cyclization had been reported earlier, Vedejs found that the conditions originally described also delivered substantial quantities of an indolizidine by-product.



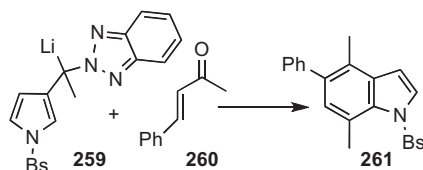
Scheme 97.

Masanobu Hidai of the University of Tokyo developed¹¹⁴ the Pd-catalyzed cyclocarbonylation of the allylic acetate **257** (Scheme 98) to the 4-acetoxyindole **258**. It seems likely that a more highly substituted version of **257** would cyclize with equal facility.



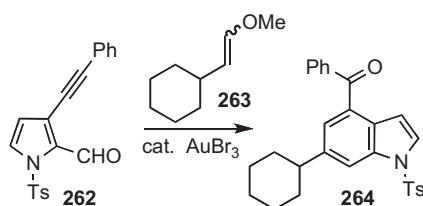
Scheme 98.

Alan R. Katrizky of the University of Florida devised¹¹⁵ an approach to indoles with more highly substituted benzene rings. Addition of the benzotriazolyl anion **259** (Scheme 99) to an enone, such as **260** followed by acid-catalyzed dehydrative cyclization delivered the indole **261**.



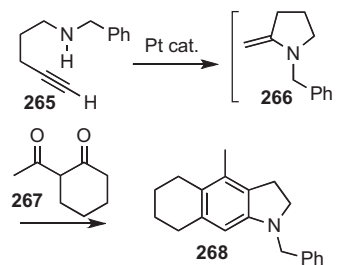
Scheme 99.

Naoki Asao of Tohoku University found¹¹⁶ that AuBr_3 was an effective catalyst for the cyclocondensation (Scheme 100) of **262** with **263** to give the indole **264**. F. Dean Toste of the University of California, Berkeley uncovered¹¹⁷ a related Au-catalyzed cyclization leading to indoles.



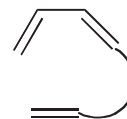
Scheme 100.

In 2009, Chi-Meng Che of the University of Hong Kong¹¹⁸ described (Scheme 101) the Pt-mediated intramolecular hydroamination of the alkyne **265**. Condensation of the cyclic enamine **266** so prepared with a β -diketone **267** proceeded with high regioselectivity to give the indoline **268**. For the aromatization of a similar *N*-benzyl indoline, see Scheme 41.



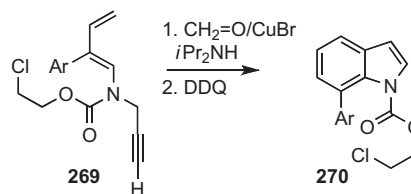
Scheme 101.

10. Type 9



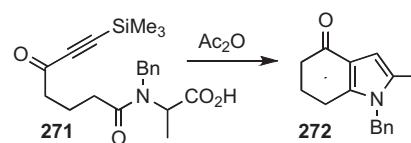
Kanematsu strategy

The least developed approach to indoles is Type 9, the simultaneous construction of both rings of the indole. This route was pioneered in 1986¹¹⁹ by Ken Kanematsu of Kyushu University. Homologation of **269** (Scheme 102) to the allene led to the intramolecular Diels–Alder cyclization product, that was readily aromatized to the indole **270**.

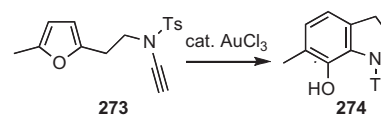


Scheme 102.

Three related approaches have been put forward since that time. Michael J. Martinelli, then at Lilly, established¹²⁰ that acetic anhydride-mediated decarboxylation of **271** (Scheme 103) led to a 1,3-dipole, that added in an intramolecular fashion to the alkyne, delivering the dihydro indole **272**. In a complementary approach, A. Stephen K. Hashmi of Ruprecht-Karls-Universität Heidelberg found¹²¹ that with catalytic AuBr_3 , **273** (Scheme 104) cyclized efficiently to **274**. As outlined earlier in this review, both **272** and **274** would be readily aromatized to the corresponding indoles.

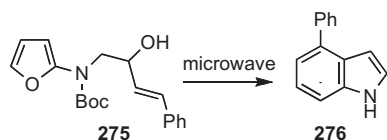


Scheme 103.



Scheme 104.

In 2009, Peter Wipf of the University of Pittsburgh described¹²² the intramolecular Diels–Alder cyclization (Scheme 105) of the allylic alcohol **275**. Microwave heating led directly to the doubly aromatized product **276**.



Scheme 105.

11. Conclusions

In this review, we have tried to be inclusive, but certainly not comprehensive. We hope that the scheme outlined here for the classification of synthetic routes to indoles will be useful to future practitioners of the art, and will stimulate new thinking in the field.

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