Practical Methodologies for the Synthesis of Indoles

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1. Introduction

The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents.[1] Substituted indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[2] For well over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.[3] Key factors, including starting material availability and functional group tolerance, often dictate which particular indole synthesis will be suitable. In some cases, specific substitution patterns remain difficult to obtain by standard indole-forming reactions; thus, new methodologies emerge.

The process chemist is primarily interested in mild synthetic methods that provide rapid assembly of the indole ring, tolerate a wide range of functional groups, and are atom economical. The implementation of practical, safe, and scalable methods for the large-scale preparation of indoles is of critical interest to synthetic chemists who design industrial or manufacturing syntheses, as well as researchers in academia. In this review, we will highlight practical methodologies which have either been successfully demonstrated or are potentially useful for the large-scale synthesis of indoles. Reactions and methodologies that have appeared in the scientific literature between 1995 and June 2005 will be discussed, and emphasis will be placed only on those reactions leading to the indole ring. The synthesis of oxindoles, indolines, carbazoles, azaindoles, and other similarly substituted analogous will not be presented in this review.[4,5] While it is recognized that many industrial preparations have only been reported as patents outlining the manufacturing route of a particular indole substrate, a thorough review of the patent literature, which is often difficult to interpret, is beyond the scope of this review.

2. Fischer Indole Synthesis

2.1. General Comments

For over 100 years, the Fischer indole reaction has remained an extremely useful and important method for the synthesis of a variety of indole intermediates and biologically active compounds.[6] The Fischer reaction often provides a simple, efficient method for the transformation of enolizable *N*-arylhydrazones into indoles. In many cases, the indolization reaction is carried out by simply heating the ketone or aldehyde and the arylhydrazine with the appropriate acid or

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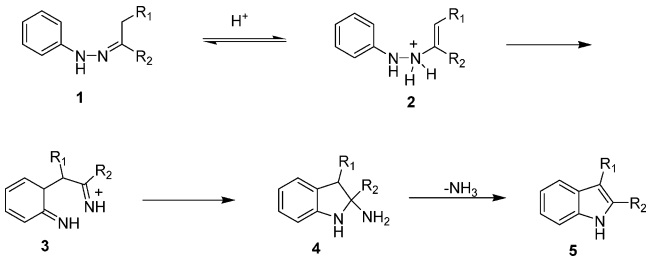
Jeff Kuethe was born in Cincinnati, OH in 1965. He studied chemistry at Middle Tennessee State University, where he received a Bachelor of Science degree in 1993. He then joined the group of Professor Albert Padwa at Emory University in Atlanta, GA, where he received a Ph.D. in 1998. He continued as a postdoctoral fellow in the group of Professor Daniel Comins at North Carolina State University before joining the Department of Process Research at Merck & Co., Inc., Rahway, NJ, in 2000. His research interests include process research, synthetic methodology, heterocyclic chemistry, alkaloid and natural product synthesis, and tandem transformations.

acid catalyst without isolation of the hydrazone intermediate. Advantages of the Fischer reaction include the acceptance of a wide range of compatible functional groups around the aromatic ring and lack of a requirement for a functional group to form the new C−C and C−N bonds. The *N*-arylhydrazones are frequently prepared via condensation of an arylhydrazine with an enolizable ketone. However, since few arylhydrazines are commercially available, they are generally prepared by reduction of aryl diazonium salts, which in turn are obtained from the appropriate aniline. Alternatively, aryl diazonium salts can be converted directly to hydrazones via the Japp−Klingemann reaction.[7] The Japp−Klingemann reaction involves treatment of the aryl diazonium salt with an active methylenyl or methinyl compound under acidic or basic conditions to form an azo derivative which under basic, acidic, or thermal conditions is converted to the hydrazone.

Scheme 1



Other, highly efficient, metal-catalyzed methods to access arylhydrazone intermediates useful in the Fischer cyclization have emerged over the last 5 years.

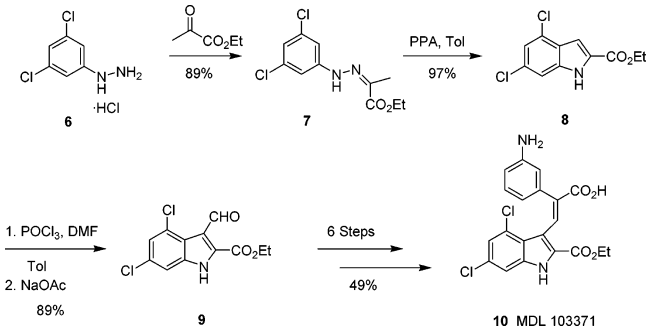
The mechanism of the Fischer indole cyclization is thought to involve a [3,3]-sigmatropic rearrangement of an ene-hydrazine tautomer **2** to a bis iminobenzylketone **3** (Scheme 1).[8,9] Cyclization and aromatization with loss of ammonia provides the indole product **5**. If the ketone is unsymmetrical, the tautomerization can occur at either α-position, resulting in the formation of a mixture of indole isomers.[10]

Developments in methodology and applications of the Fischer indole reaction have been recently reviewed.[1h,3a] A search of the literature over the last 10 years revealed over 700 references documenting the use of the Fischer reaction, mostly for the small-scale preparation of potentially interesting medicinal compounds. Several larger-scale applications of the Fischer reaction have been described over the same period, and these are highlighted in this section.

2.2. Via Aryl Hydrazines

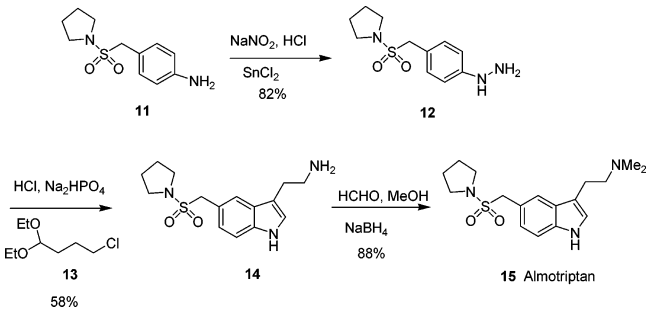
A large-scale preparation of MDL 103371 (**10**), an *N*-methyl-D-aspartate (NMDA)-type glycine receptor antagonist for the potential treatment of stroke, was required for clinical development purposes. As outlined in Scheme 2, Watson and co-workers developed a straightforward and efficient three-step synthesis based on Fischer indolization chemistry.[11] Starting from commercially available 3,5-dichlorophenylhydrazine hydrochloride (**6**), treatment with ethyl pyruvate in ethanol gave the hydrazone **7** as an *E*/*Z* mixture. Fischer cyclization using PPA (polyphosphoric acid) in toluene at 95−100 °C provided the indole ethylcarboxylate **8** in 97% yield as a crystalline solid. Finally, Vilsmeier−Haack formylation gave kilogram quantities of indole aldehyde **9** in 89% yield, which was subsequently converted in six steps to the active *E*-ene-acid **10** in 49% overall yield.

Scheme 2



A number of 5-HT_{1D} receptor agonists, containing a tryptamine nucleus with a sulfamoylmethyl group at the 5-position, have been synthesized using Fischer chemistry. Utilizing the Grandberg modification,[12] Bosch et al. con-

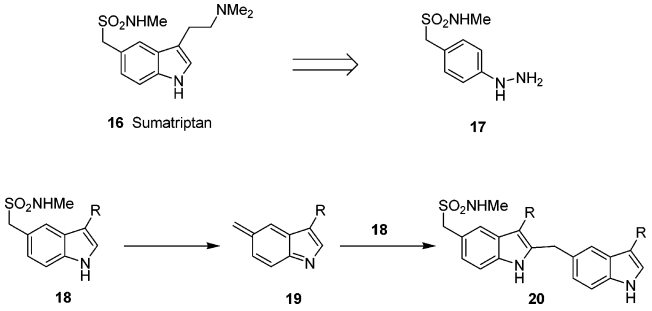
Scheme 3



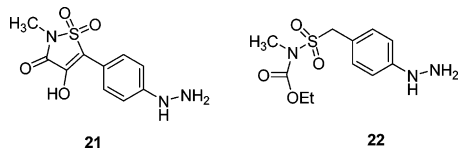
verted hydrazine **12** and acetal **13** to tryptamine **14** in a one-pot procedure (Scheme 3).[13] The sulfamoylphenylhydrazine **12** was prepared in 82% yield from aniline **11** by diazotization and reduction using $SnCl_2$. Treatment with 4-chlorobutyraldehyde diethyl acetal (**13**) in buffered HCl (buffered at pH 5 with Na_2HPO_4) gave the tryptamine **14** in 58% overall yield. Tryptamine **14** was dimethylated using formaldehyde−sodium borohydride to afford Almotriptan (**15**) in 88% yield.

Indoles substituted at C-5 with an *N*-methylaminosulfonylmethyl group such as Sumatriptan (**16**) and analogues are potent selective serotonin 5-HT_{1D} receptor agonists potentially useful for the treatment of migraines (Scheme 4).[14] Use of the Fischer indolization reaction to prepare indoles from the hydrazine **17** was shown to be problematic due to instability of the resultant indole product **18**. In many cases, bis-indoles (e.g. **20**) were obtained as difficult to remove byproducts, presumably via the Michael addition of product to the reactive imine **19**.[15,16]

Scheme 4

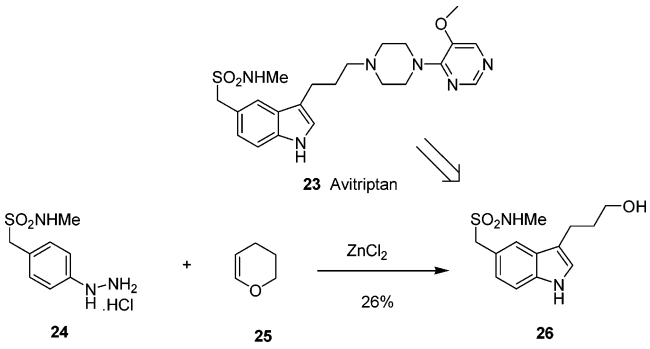


A number of methodologies have been developed in order to overcome this problem. Protection of the benzylic side chain as the 4-hydroxy-2-methyl-3-isothiazolone-1,1-dioxide **21** was described by Remuzon et al.,[15] and the *N*-ethoxycarbonyl derivative **22** was used by Péte and co-workers.[17,18] In both cases, the protecting groups prevented bis-indole formation and greatly aided product purification.



In other examples, careful control of the reaction parameters has proven successful in minimizing byproduct formation. Brodfuehrer et al. described the development of an efficient Fischer indole synthesis of avitriptan (**23**), a potent 5-HT_{1D} receptor agonist.[19] Previous work had shown that the key hydroxypropyl indole intermediate **26** could be

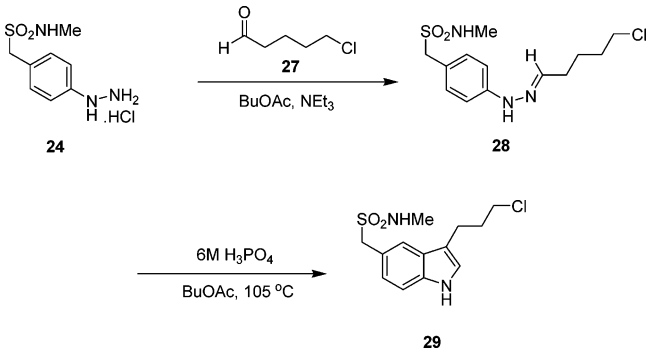
Scheme 5



prepared via a zinc chloride-catalyzed Fischer reaction between hydrazine **24** and dihydropyran **25** (Scheme 5).[20] However, the yield of the indolization step was only 26% and initial preparation of the drug on a multi-kilogram scale was carried out via a palladium-catalyzed heteroannulation reaction of an iodoaniline and an alkyne (see Scheme 47).

To develop an economical and scalable synthesis of avitriptan (**23**), the authors reinvestigated the Fischer approach and optimized the choice of aldehyde equivalent and reaction conditions (Scheme 6). A two-phase indolization procedure was developed which minimized the acid decomposition of the product and enabled the successful use of 5-chlorovaleraldehyde (**27**), providing a 65−70% yield of the chloroindole **29**. Namely, a solution of hydrazone **28** in butyl acetate was added to a two-phase mixture of 6 M phosphoric acid and butyl acetate at 105 °C, and after a simple workup, the product could be crystallized from butyl acetate without the need for chromatography.

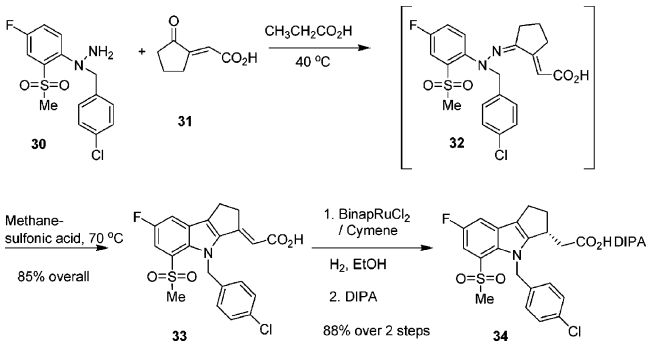
Scheme 6



A novel, highly convergent, asymmetric synthesis of the DP antagonist **34** was developed by the Merck process group (Scheme 7).[21] Reaction of benzylhydrazine **30** with unsaturated keto-acid **31** in propionic acid provided hydrazone **32**, which was cyclized in situ by addition of methanesulfonic acid to give exclusively the trans-unsaturated acid **33** in 85% yield. Subsequent asymmetric hydrogenation using binap-$RuCl_2$-cymene in ethanol gave the saturated acid **34** in >99% yield and 91−92% ee. Addition of diisopropylamine (DIPA) to the crude hydrogenation mixture resulted in the DIPA salt of **34** in 88% overall yield and enantiomeric purity upgrade to >99%. This synthesis was demonstrated successfully on a multi-kilogram scale.

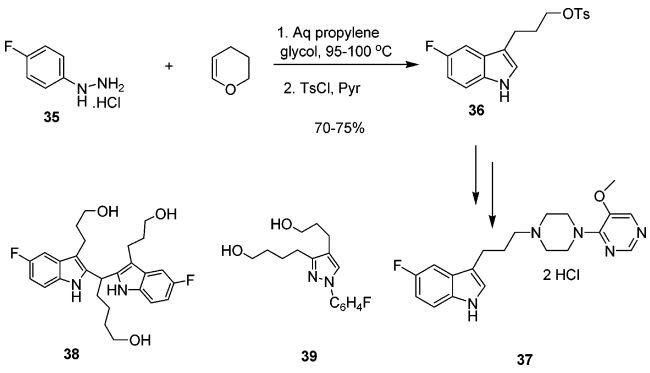
Fischer indole reactions of cyclic enol ethers have been utilized successfully by a number of groups to prepare substituted tryptophol intermediates. As detailed in Scheme 8, Anderson and co-workers explored and optimized the preparation of 5-fluorotryptophol derivative **36**.[22] The slow

Scheme 7



addition of dihydropyran (DHP) to a solution of hydrazine HCl salt **35** in aqueous propylene glycol was found to be critical to obtaining high yields of **36** and minimizing byproducts **38** and **39**. The tryptophol derivative **36** was subsequently converted to the 5-HT inhibitor **37** in approximately 50% yield.

Scheme 8



Campos et al. have recently reported an extension of this methodology to a general synthesis of substituted indoles from cyclic enol ethers and enol lactones (Scheme 9).[23] For the synthesis of substituted tryptophol derivatives **42**, addition of DHP to a mixture of hydrazine HCl salt **40** in 4% H_2SO_4/dimethylacetamide was found to provide good to excellent yields of isolated products. In addition, good to excellent yields of similarly substituted indole derivatives **48**−**52** were obtained from the corresponding enols **43**−**45** and enol lactones **46** and **47** (Table 1).

The methodology was also applied to the synthesis of Glaxo's antimigraine drug Sumatriptan (**16**) (Scheme 10) via a one-pot reaction of hydrazine **53** with dihydropyran to give the hydroxyindole **54**. Activation of the hydroxyl group as the mesylate followed by displacement with excess dimethylamine according to the method of Brodfuehrer[19] furnished Sumatriptan (**16**) in 45% overall yield.

The same paper described how Campos and co-workers extended this efficient approach to *N*-substituted indole acetic acids. Demonstration of the methodology was highlighted by a single-step synthesis of Merck's anti-inflammatory drug Indomethacin (**56**), from readily available starting materials (Scheme 11). Coupling of *N*-acylhydrazine **55**[24] with angelicalactone **47** using slightly modified conditions from those of the general procedure provided Indomethacin (**56**) in 65% yield.

Bentley and co-workers reported a short, practical synthesis of the 2,3,4-trisubstituted indole fragment **61** of the

Scheme 9

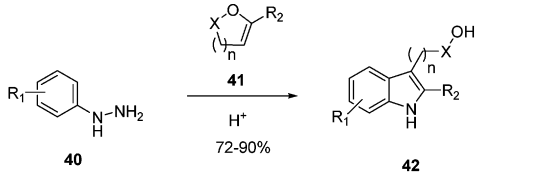
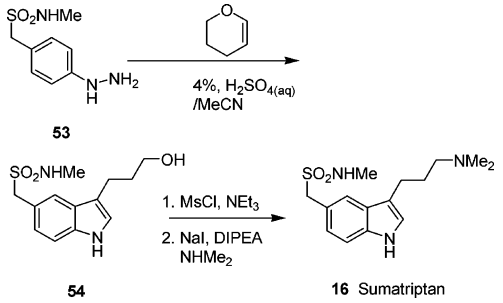


Table 1[a]

Entry	Enol	Indole
1	**43**	**48** 72%
2	**44**	**49** 83%
3	**45**	**50** 80%
4	**46**	**51** 75%
5	**47**	**52** 70%

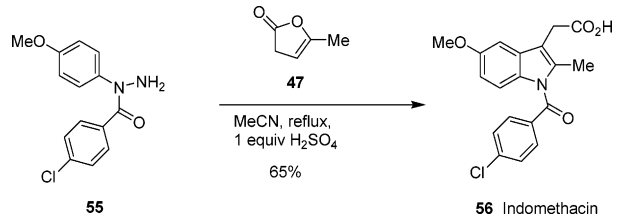
[a] Data taken from ref 23.

Scheme 10



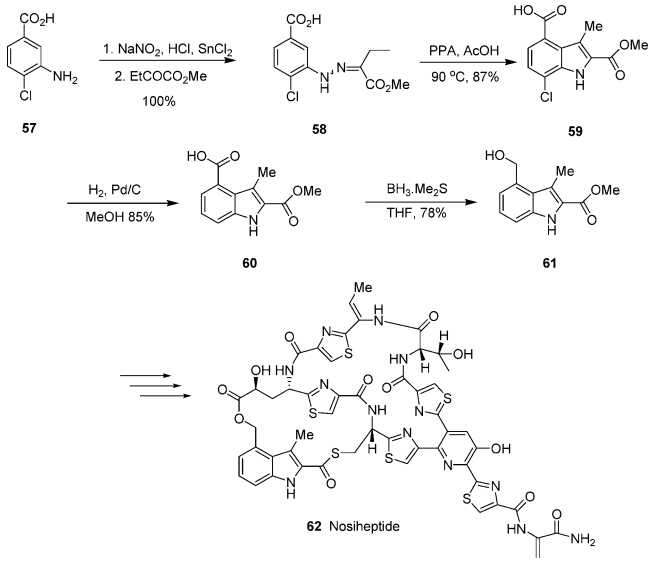
antibiotic nosiheptide **62** (Scheme 12).[25] Commercially available 3-amino-4-chlorobenzoic acid (**57**) was converted to the hydrazine and condensed in situ with methyl 2-oxobutanoate to give the hydrazone **58** in excellent yield as a crystalline solid. Subsequent Fischer indolization using PPA in AcOH provided the indole **59** in 87% isolated yield. Hydrogenolysis of the chlorine substituent, with Pd/C, gave the indole **60** in 85% yield. Reduction of the acid functional-

Scheme 11



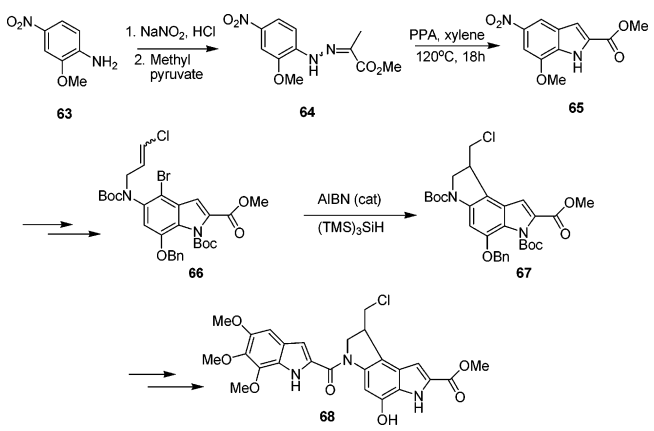
ity at C-4 provided the hydroxymethyl intermediate **61** in 78% yield.

Scheme 12



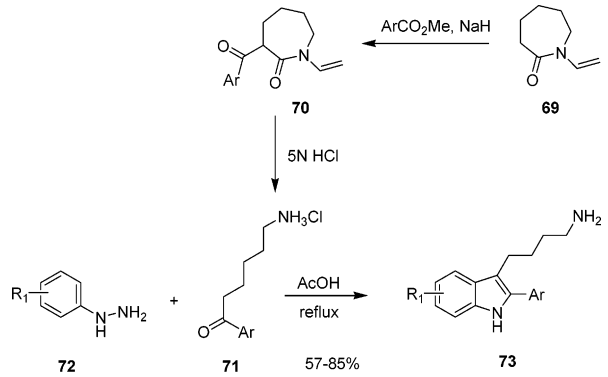
A concise and efficient synthesis of *seco*-duocarmycin SA (**68**) was reported by Tietze and co-workers in which the key indole **65** was constructed via Fischer cyclization and a radical 5-*exo*-trig cyclization was used to set up the tricyclic indole core **67** (Scheme 13).[26] Diazotization of commercially available 2-methoxy-4-nitroaniline (**63**) was followed by in situ reduction and condensation with methyl pyruvate cleanly to afford the crystalline hydrazone **64** in 69% overall yield. Fischer cyclization using PPA/xylene at 120 °C for 18 h furnished indole **65** in 64% yield. Protecting group manipulation, reduction of the nitro group, Boc protection, and bromination followed by alkylation with 1,3-dichloropropene resulted in the cyclization precursor **66** in 41% yield over the seven-step sequence. Cyclization using a catalytic amount of 2,2′-azobis(2-methylpropionitrile (AIBN) and tris(trimethylsilyl)silane gave the tricylic core **67** in 79% yield. Removal of the Boc group, *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide (EDC) coupling with trimethoxyindolecarboxylic acid, and debenzylation, under transfer hydrogenation conditions, gave *seco*-duocarmycin (**68**).

Scheme 13



Several convenient and potentially large-scale syntheses of melatonin analogues using Fischer indole cyclization chemistry have been reported. Nenajdenko disclosed the first examples of Fischer indolizations of aminocarbonyl compounds containing unprotected amino groups (Scheme 14).[27] The requisite hydrochloride salts of the amino-ketone compounds **71** were prepared via Claisen condensation of commercially available *N*-vinylcaprolactam **69** with aryl esters followed by acidic hydrolysis.[28] Condensation of the amino-ketones **71** with the aryl hydrazines **72** in acetic acid and warming to reflux, with or without the addition of gaseous HCl, provided the 2-substituted dihomotryptamines **73** in good to excellent yields. The products were obtained by crystallization after concentration of the acetic acid and addition of water.

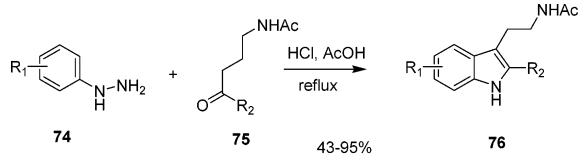
Scheme 14



72: R_1 = H, 4-Br, 4-OMe, 3,5-Me_2, 4-*n*-Bu
73: R_1 = H, 5-Br, 5-OMe, 4,6-Me_2, 5-*n*-Bu
Ar = Ph, 3-MeC_6H_4, 3-$MeOC_6H_5$, 4-ClC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$

The synthesis of a number of 2-aryl-*N*-acetylindolylalkylamines **76** was also reported recently by Nenajdenko and co-workers (Scheme 15).[29] *N*-Acylketones **75** were treated with arylhydrazines **74** in acetic acid with gaseous HCl as catalyst to provide the corresponding indolylalkylamides **76**. Good to excellent yields of products **76** were obtained from hydrazines bearing both electron-donating and -withdrawing groups.

Scheme 15



74: R_1 = H, 4-F, 4-Cl, 4-Br, 4-OMe, 2-Et
76: R_1 = H, 5-F, 5-Cl, 5-Br, 5-OMe, 7-Et
R_2 = Ph, 4-MeC_6H_4, 2,4-$MeOC_6H_3$, 2-thienyl, 2-furyl

Extension of this methodology to nonaryl ketones (**77a**−**c**) was explored with respect to regiochemistry in the indole product. Reaction of the benzyl ketone **77a** with phenylhydrazine afforded the 3-phenylindole **81a** in 93% yield, presumably via the more thermodynamically stable conju-

Scheme 16

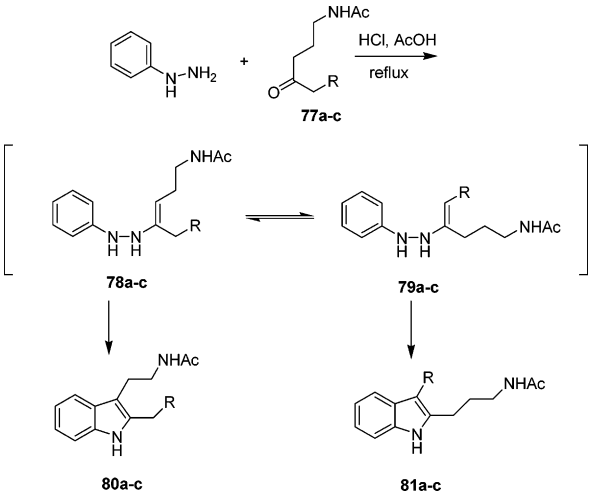


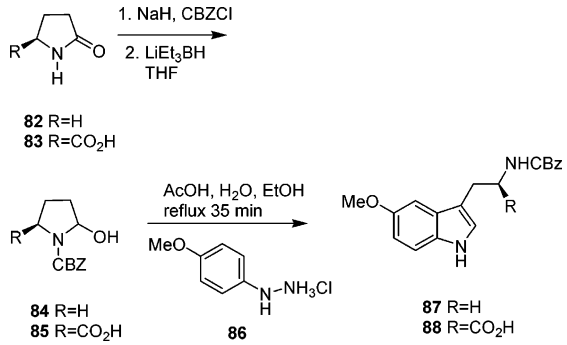
Table 2[a]

N-acetylindolylalkylamine	R	yield (%)
81a	Ph	93
80b	H	77
80c/**81c**	Pr	90

[a] Data taken from ref 29.

gated ene-hydrazine **79a**. On the other hand, the ketone **77b** gave the 2-methylindole compound **80b**. In this case, the internal ene-hydrazine **78b** was favored over the terminal ene-hydrazine **79b** (Scheme 16 and Table 2). The 4-oxooctyl-*N*-acetamide **77c** reacted with phenylhydrazine to yield a 1:2 ratio of the indole isomers **80c** and **81c**.

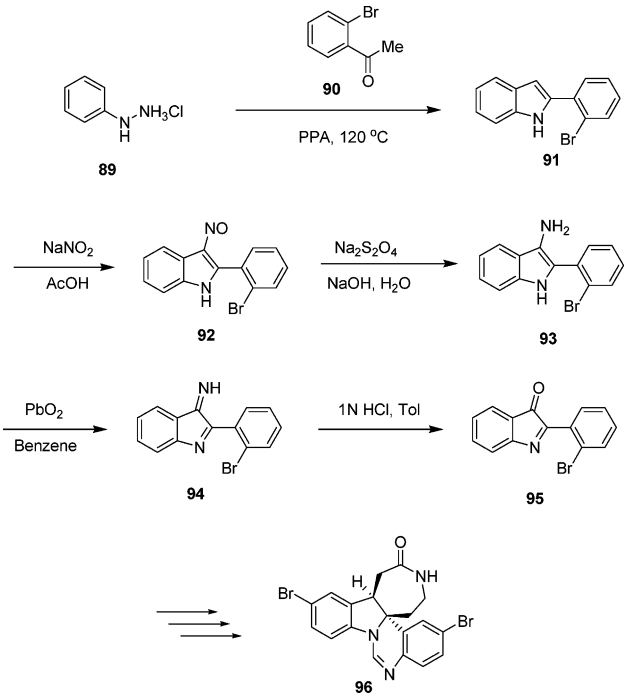
Scheme 17



Marais and Holzapfel described an interesting alternative approach to the melatonin and tryptophan nucleus from 2-hydroxypyrrolidine derivatives (Scheme 17).[30] Although this method was not carried out on a large scale, the simple procedures, high yields, and availability of pyrrolidinone **82** and pyroglutamic acid **83** as starting materials merit discussion of this work as a potential efficient, large-scale entry into these very important indole frameworks. The 2-hydroxypyrrolidine derivatives **84** and **85** were easily prepared from pyrrolidinone **82** and pyroglutamic acid (**83**), respectively. Protection of **82** and **83** as the CBZ derivatives and selective reduction of the ring carbonyl using lithium triethylborohydride provided the 2-hydroxy derivatives **84** and **85** in 84% and 91% yield, respectively. Fischer indole reaction with *p*-methoxyphenylhydrazine hydrochloride (**86**) in acetic acid/water/ethanol at reflux for 35 min gave the melatonin derivative **87** and the tryptophan derivative **88** in excellent yield (>95% in both cases).

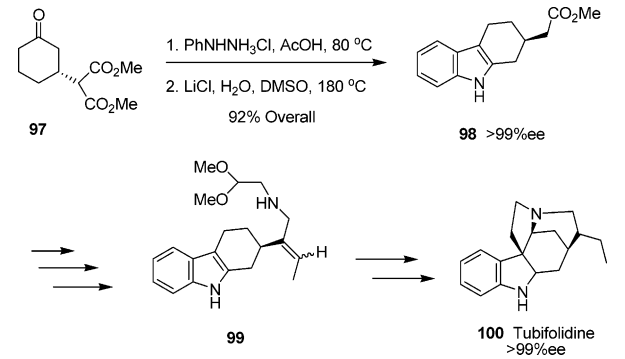
In the course of investigating approaches to the synthesis of 8-desbromohinckdentine A, Liu and McWhorter required a large-scale synthesis of the key indolenine **95** (Scheme 18).[31] Fischer indole reaction between phenylhydrazine hydrochloride (**89**) and 2-bromoacetophenone (**90**) using PPA at 120 °C[32] gave the indole **91** in 78% yield. Indole **91** was converted to indolenine **95** in high yield using a four-step sequence as shown.[33]

Scheme 18



An elegant asymmetric synthesis of the strychnos alkaloid Tubifolidine (**100**) relied on the chiral indole derivative **98** as a key intermediate to set the remaining asymmetric centers by substrate control (Scheme 19).[34] Indole **98** was assembled using a highly regioselective Fischer indolization between ketone **97**, available via asymmetric Michael reaction,[35] and phenylhydrazine hydrochloride in acetic acid at 80 °C. Standard decarboxylation gave indole **98** in very high yield and enantiomeric purity. Indole **98** was successfully converted to Tubifolidine (**100**) via a multistep synthesis with complete diastereocontrol.

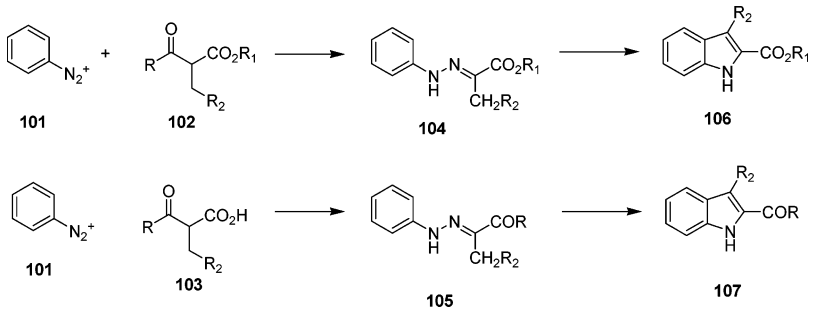
Scheme 19



2.3. Via Japp–Klingemann Reaction

The Japp−Klingemann reaction provides a very useful alternative route to a number of arylhydrazones employed in the Fischer indolization process (Scheme 20).[36] When

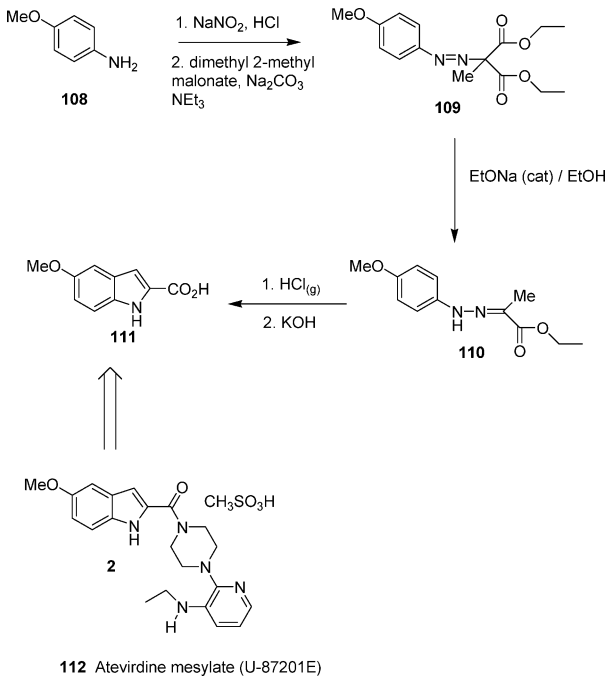
Scheme 20



aryldiazonium salts **101** are treated directly with β-ketoesters **102**, deacylation is followed by indole formation to give indole-2-carboxylate esters **106**.[37] Alternatively, if a β-ketoacid **103** is used, decarboxylation occurs and a 2-acylindole **107** is formed.[38] The Japp−Klingemann procedure avoids the formation and use of arylhydrazines, which can be difficult to prepare and handle in some cases.

Carboxylic acid **111** has been shown to be an extremely useful intermediate in the preparation of a wide range of pharmaceutical intermediates.[39] A production-scale synthesis of the non-nucleoside reverse transcriptase (RT) inhibitor Atevirdine mesylate (U-87201E; **112**) was described using indole **111** which was obtained from a commercial source.[40] Recently, Bessard described a new, efficient process for the preparation of **111** via Japp−Klingemann and Fischer indole chemistry using readily available malonate derivatives (Scheme 21).[41] Diazotization of *p*-anisidine **108** under classical conditions gave the diazonium salt, which was used directly as a solution in the next step. Successful reaction with dimethyl 2-methylmalonate was highly dependent on the choice of base. Best results were obtained using methanol/water as solvent and 1 equiv each of sodium carbonate and triethylamine. Using these conditions, the azo intermediate **109** was obtained in >90% conversion. Japp−Klingemann rearrangement of **109** was achieved using catalytic sodium ethoxide in ethanol at room temperature to afford hydrazone **110** in 90% assay yield. Fischer cyclization

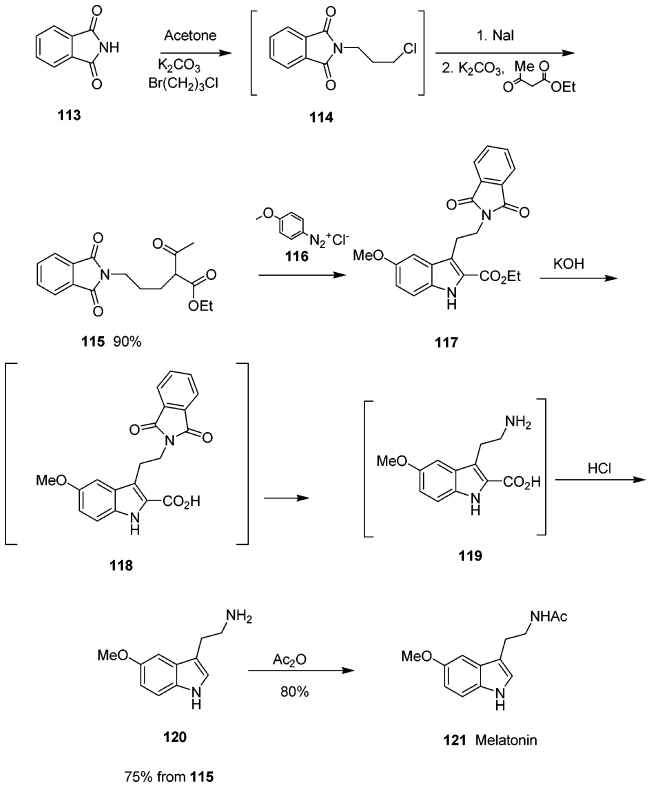
Scheme 21



by treatment of the crude hydrazone with gaseous HCl (3 equiv) in refluxing ethanol and subsequent hydrolysis provided the indole-2-carboxylic acid **111** in 64% overall yield from *p*-anisidine **109**.

An industrially viable synthesis of the hormone melatonin (**121**), based on Japp−Klingemann and Fischer cyclization chemistry, was recently described by Reddy and co-workers (Scheme 22).[42] Crystalline ethyl 2-acetyl-5-phthalimidopentanoate (**115**) was prepared in a simple, one-pot procedure from phthalimide **113** in 90% overall yield. Reaction of **115** with the diazonium salt of *p*-anisidine **116** gave the functionalized indole **117** in 80% yield (80 wt % pure) and contained intermediates **118**, **119**, and **120**. Hydrolysis of crude **117** using potassium hydroxide, followed by in situ treatment with 5% HCl gave **120** in 75% isolated yield from compound **115**. Acetylation provided melatonin (**121**) in 80% yield. This route was reportedly demonstrated at a 5−10 kilogram scale.

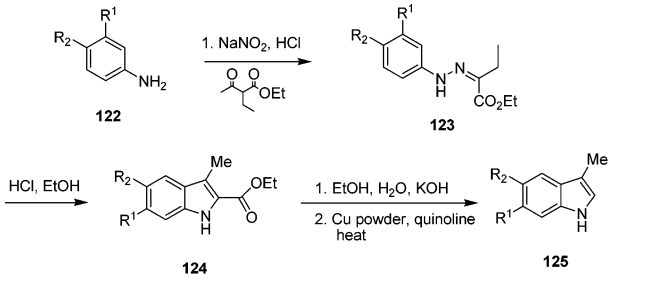
Scheme 22



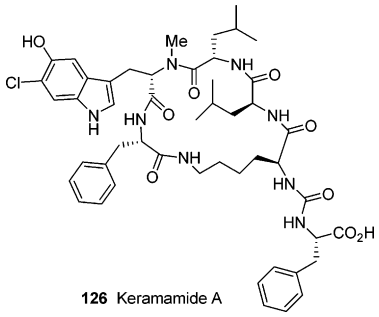
Cook et al.[43] reported the large-scale preparation of a series of 5-, 6-, and 5,6-disubstituted-3-methylindoles **125a**−**d** using the Japp−Klingemann/Fischer indole protocol of Heath-Brown and Philpott (Scheme 23).[44] For the synthesis

of indole **125a**, 3-chloroanisidine was diazotized under standard conditions and treated with ethyl α-ethylacetoacetate to provide hydrazone **123a**. Fischer cyclization using HCl in ethanol or PPA provided a 14:1 mixture of the regioisomeric indoles **124a** and the 4-chloro-5-methoxy regioisomer. The required product **124a** was isolated in pure form by simple crystallization from the crude reaction mixture. Hydrolysis with potassium hydroxide and decarboxylation under standard conditions gave indole **125a**.

Scheme 23



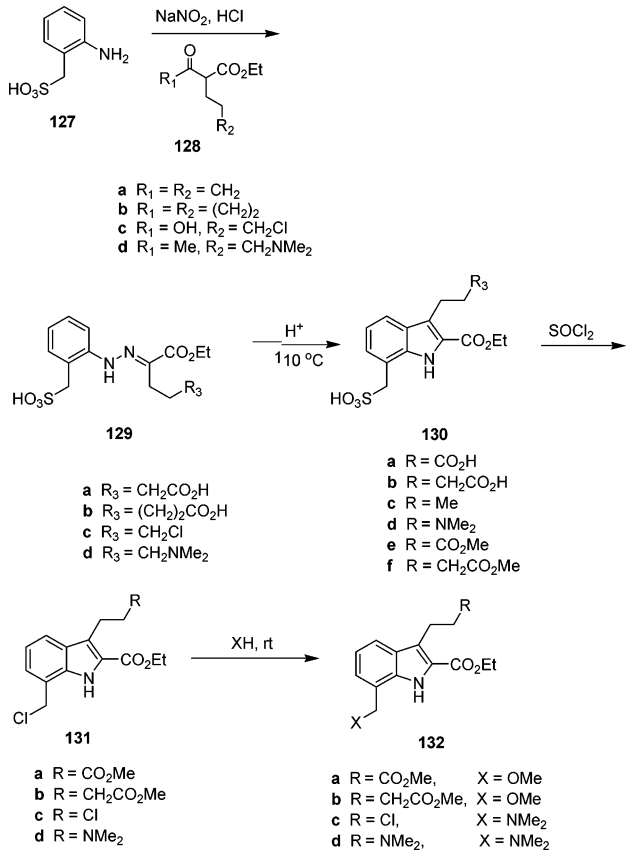
Indoles **125a**−**d** have been utilized in the synthesis of a wide range of interesting natural products. For example, indole **125a** was subsequently used to prepare the L(−)-6-chloro-5-hydroxytryptophan residue of the cyclic hexapeptide keramamide A (**126**).[45]



In a similar manner, indole **125b** was used for the total synthesis of a number of natural products including (+)-majvinine, (+)-10-methoxyaffinisine, (+)-*N*-methylsarpagine, and macralstonidine.[46] Indoles **125c** and **125d** were used in the enantiospecific total syntheses of Tryprostatin A[47] and the 2-bromotryptophan amino acid present in the cyclic peptide Jaspamide, respectively.[48]

Until recently, the regioselective synthesis of indoles containing benzylic substituents (e.g. CH_2X) was typically achieved via halogen−metal exchange[49] or directed lithiation chemistry[50] on a preformed indole nucleus. An interesting and potentially very useful regioselective synthesis of 7-chloromethylindoles **131** via the sulfonic acid derivative **130** was recently disclosed by Péte et al. (Scheme 24).[51] In this approach the sulfonyl group serves as a latent chloro substituent and subsequent reaction with nucleophiles such as alcohols or amines was extremely facile. Japp−Klingemann reaction of diazotized 2-aminophenylmethanesulfonic acid with the *β*-oxo-ester derivatives **128a**−**d** afforded hydrazones **129a**−**d**. Fischer indolization using formic acid for **129a**−**b** or acetic acid/HCl for **129c**−**d** followed by crystallization of the products from water provided the indole-7-methanesulfonic acids **130a**−**d** in 60−74% overall

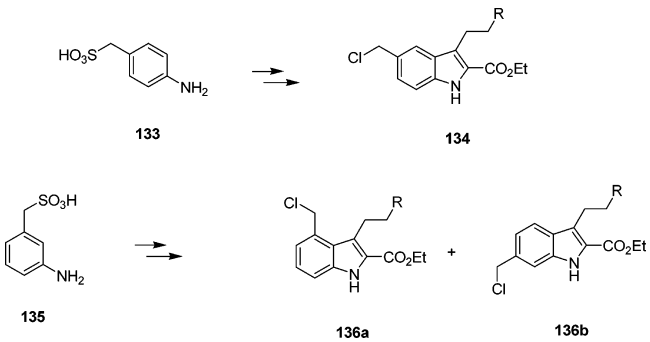
Scheme 24



yield. Treatment of the sulfonic acids **130a**−**b** and **130e**−**f** with thionyl chloride at room temperature gave the chloromethylindoles **131a**−**d** in essentially quantitative yield. The highly reactive chloromethylindoles were converted to useful substituted indoles **132** in high yield by treatment with various alcohols or amines (e.g. MeOH or $NHMe_2$).

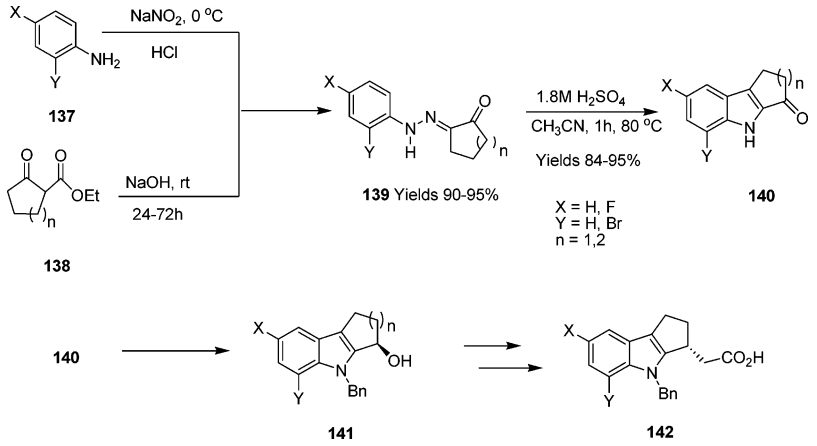
The same methodology was useful for the preparation of similar 5-substituted indoles **134** from *p*-methanesulfonic acids **133** whereas, as expected, mixtures of 4- and 6-substituted indoles **136a**−**b** were obtained from *m*-methanesulfonic acids **135** (Scheme 25).[52]

Scheme 25



A general, large-scale synthesis of cycloalkylindoles **140** was reported recently by Hillier et al. (Scheme 26).[53] Japp−Klingemann condensation of the diazonium salts of **137** with the hydrolyzed oxo-esters **138** following a modified literature procedure[36] gave the keto-hydrazones **139** in excellent yield by simple crystallization from the reaction mixture. Fisher indolization using 1.8 M H_2SO_4 in acetonitrile at 80 °C for 1 h provided indoles **140** in good to excellent yields.

Scheme 26



Reduction of the tricyclic ketoindoles **140** using (*S*)-oxazaborolidine (OAB) and borane−dimethylsulfide complex (BH_3·DMS) gave the chiral alcohols **141**. Displacement under Mitsunobu conditions with an enolate equivalent provided a novel access to the indole acetic acid derivatives **142**, which were useful as prostaglandin-D (DP) receptor antagonists.

2.4. Via Metal-Catalyzed Arylation of Benzophenone Hydrazone or *tert*-Butylcarbazate

One of the limitations of the Fischer indole reaction is the availability of certain substituted aryl hydrazine or arylhydrazone intermediates. As mentioned in the introduction to this section, the most common methods for the preparation of *N*-aryl hydrazones are the direct condensation of the *N*-aryl hydrazine with a carbonyl compound or the Japp−Klingemann reaction of aryl diazonium halides. Both methods involve formation of aryl diazonium salts which are either reduced to hydrazines or reacted directly in the Japp−Klingemann reaction. In an attempt to overcome this limitation, Buchwald and co-workers reported a palladium-catalyzed coupling strategy for the preparation of *N*-aryl benzophenone hydrazones **145** from commercially available, inexpensive benzophenone hydrazone **143** and aryl bromides **144** (Scheme 27).[54] The stable, often crystalline, nonenolizable benzophenone hydrazones **145** are not capable of undergoing Fischer indolization; however, on treatment with acid in the presence of various ketones, enolizable hydrazones are formed which undergo smooth Fischer reaction to provide indoles **146** in good yields. In general, *p*-toluenesulfonic acid was found to be the optimum acid catalyst for the Fischer reaction in most cases, and only a small excess (1.5 equiv) of the ketone was required. This methodology was proven to be quite general and applicable to a wide range of aryl bromide and ketone substrates, giving indoles, in most cases, in good to excellent yields (Table 3).

In subsequent work by the same group, Xantphos [9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene] was found to be far superior to 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) as a catalyst for the cross-coupling reaction to provide the aryl hydrazones. The methodology was extended to include *N*-alkylation of the *N*-aryl hydrazones **161** and subsequent in situ Fischer reaction to provide *N*-alkyl (R^2= Bn, Pr, Me, allyl, $CH_2CH(OH)Me$, $CH_2CH(OH)^nBu$) indoles **162** in good yields (Scheme 28).[55]

Buchwald and co-workers have also demonstrated that *N*-arylindoles could be prepared from benzophenone hydra-

Scheme 27

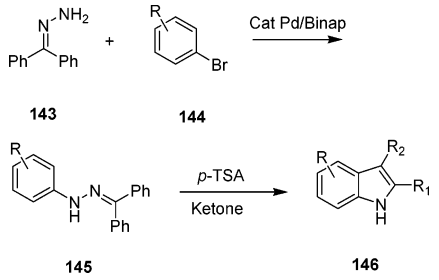
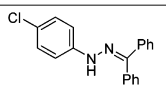
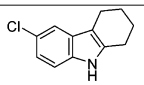
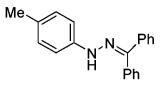
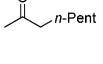
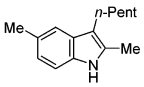
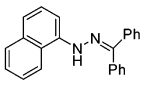
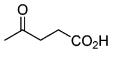
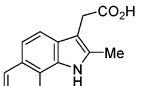
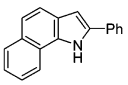
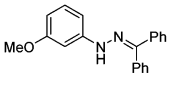
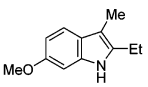
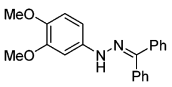
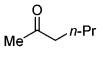
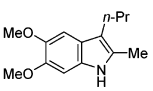
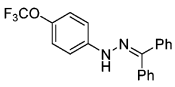
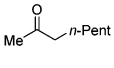
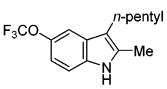
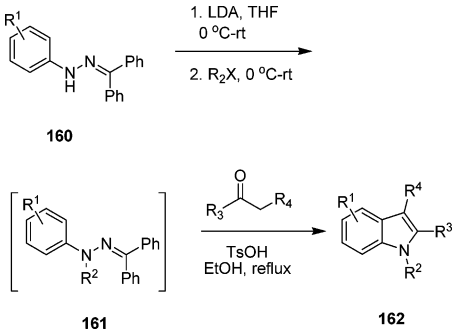


Table 3[a]

Entry	Hydrazone	Ketone	Indole
1	 **147** 80%		 **153** 95%
2	 **148** 97%		 **154** 83%
3	 **149** 91%		 **155** 90%
4	**149**		 **156** 85%
5	 **150** 95%		 **157** 74%
6	 **151** 85%		 **158** 74%
7	 **152** 83%		 **159** >5%

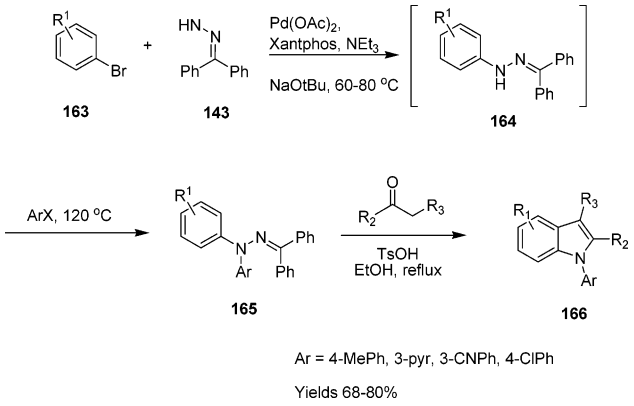
[a] Data taken from ref 54.

Scheme 28



zone **143** and an arylbromide **163** via a one-pot sequential palladium-catalyzed coupling (Scheme 29). Treatment of intermediate hydrazone **164** with a second mole of aryl halide in a one-pot procedure provided *N*,*N*-diarylhydrazones **165**. Treatment of **165** with a variety of ketones in the presence of TsOH in refluxing ethanol furnished indoles **166** in good to excellent overall yield. Interestingly, when unsymmetrical *N*,*N*-diarylhydrazones were employed, the Fischer cyclization occurred predominately on the more electron-rich arene.[56]

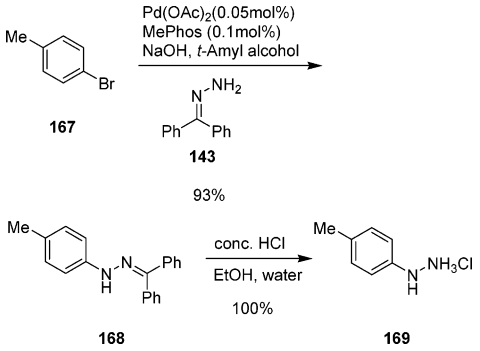
Scheme 29



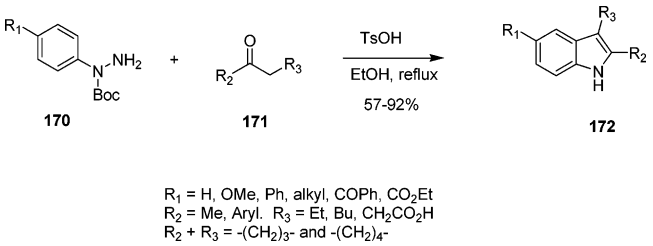
While highly useful for the small-scale rapid preparation of many structurally diverse *N*-H, *N*-alkyl, and *N*-aryl indoles, from a practical standpoint the separation of the benzophenone byproduct from either the indole (one-pot reaction) or the arylhydrazine is a key issue. In a recent publication, Mauger and Mignani described the successful optimization and safe scale-up of the Buchwald palladium-catalyzed hydrazonation chemistry for the preparation of hydrazine hydrochloride **169** from *p*-bromotoluene **167** (Scheme 30).[57] In this case, benzophenone hydrazone **168** was obtained in 93% isolated yield as a crystalline solid. Hydrolysis using concentrated hydrochloric acid in ethanol provided the hydrazine hydrochloride **169** in essentially quantitative yield containing only traces of benzophenone.

In related work, an expedient synthesis of indoles from *N*-Boc arylhydrazines was described by Lim and Cho (Scheme 31).[58] Reaction of *N*-Boc arylhydrazines **170** with ketones **171** in the presence of TsOH provided good to excellent yields of the Fischer indole products **172**. The reaction was demonstrated with a number of substituted hydrazines and a variety of acyclic and cyclic ketones. Unlike the benzophenone hydrazone chemistry, this methodology does not generate potentially difficult to remove byproducts. The products were isolated in essentially pure form by simple water workup. *N*-Boc arylhydrazides **170** were available via palladium or copper catalysis as described by Skerlj[59] and

Scheme 30



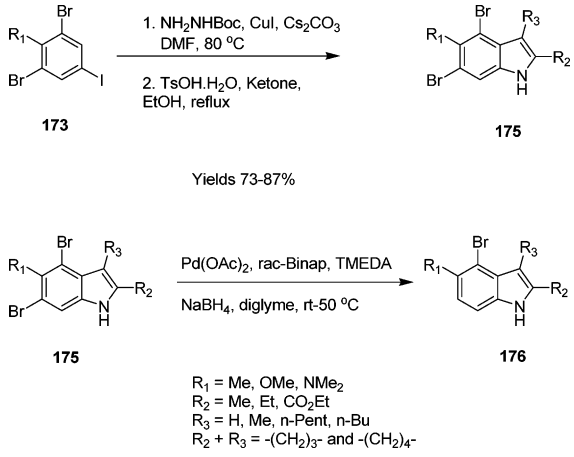
Scheme 31



Buchwald,[60] respectively. Thus, para-substituted electron-deficient aryl bromides were coupled in good yield using *tert*-butylcarbazate (2.0 equiv), $Pd_2(dba)_3$ (1 mol %), DPPF (3 mol %), and Cs_2CO_3 (1.0 equiv) in toluene at 100 °C.[48] Alternatively, both electron-rich and electron-deficient hydrazides were prepared by the copper-catalyzed coupling of *tert*-butylcarbazate with aryl iodides using 1,10-phenanthroline as ligand.[49] One limitation of this reaction was the poor yields obtained from ortho-substituted *N*-Boc arylhydrazines.

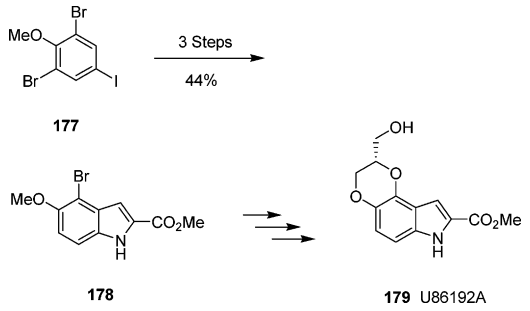
An interesting extension of this methodology for the selective synthesis of 4-bromoindoles was reported by Chae and Buchwald.[61] Chemoselective, copper-catalyzed hydrazonation of symmetrical 3,5-dibromoiodoarenes **173**, followed by Fischer indolization, gave a variety of 4,6-dibromo-5-substituted indoles **175** (Scheme 32). Selective hydrodebromination at the less hindered 6-position, using the catalytic system $Pd(OAc)_2$/*rac*-BINAP/$NaBH_4$ in THF/diglyme, provided the 4-bromoindoles **176** in high regioselectivity.

Scheme 32



This methodology was successfully applied to the efficient synthesis of 4-bromo-5-methoxyindole ester **178**. Indole **178** was used as a key intermediate in the enantioselective

Scheme 33

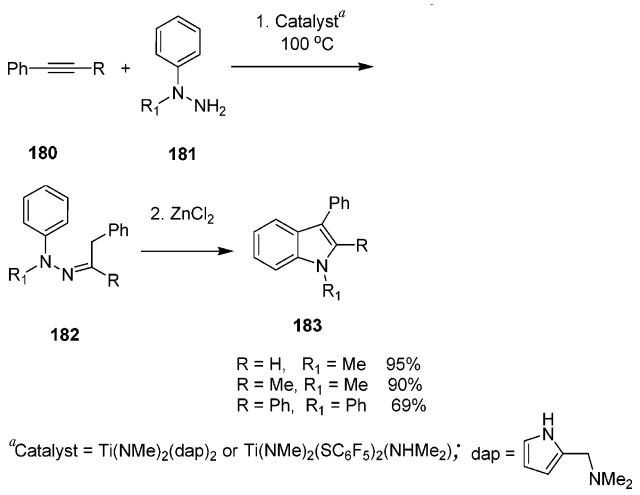


synthesis of the antihypertensive agent Indolodioxane (U86192A; **179**) (Scheme 33).

2.5. Via Metal-Catalyzed Hydroamination of Alkynes

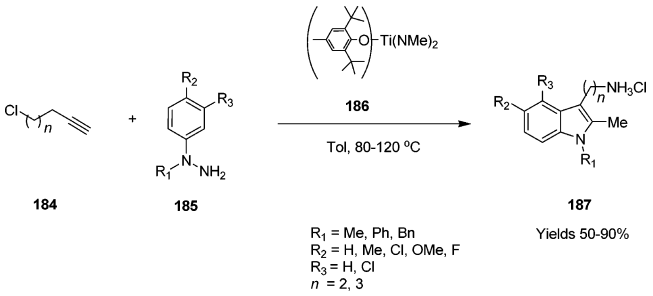
Despite the incredible range of substrates tolerated and the versatility of the Fischer indolization process, the reaction of hydrazines with unprotected aldehydes often proceeds in low yields and can generate unwanted side-products.[62] A number of strategies, including protection as acetals, aminals, enol ethers, or bisulfite adducts, have been used to overcome this problem, some of which are described in earlier sections of this review. Very recently, the titanium-catalyzed intermolecular hydroamination of alkynes with hydrazines to give hydrazones directly was described by Odom and co-workers (Scheme 34).[63] In the case of arylhydrazines **181**, the product hydrazones **182** underwent a one-pot Fischer indole reaction by addition of $ZnCl_2$ to provide *N*-alkyl and *N*-aryl indoles **183** in high yield on a multigram scale. This methodology represents a novel entry into hydrazone synthesis via alkynes **180** and has been extended by several other groups.

Scheme 34



As a part of a general study on the hydroamination of alkynes, Bellar investigated the regioselectivity of arylhydrazine addition to various alkynes using 2.5−10 mol % the cyclopentadienyl titanium catalyst $[(\eta^5\text{-Cp})_2\text{Ti}(\eta^2\text{-Me}_3\text{SiC}_2\text{-SiMe}_3)]$.[64] The work was extended to provide an efficient one-pot synthesis of tryptamine and tryptamine homologues by a titanium-catalyzed hydroamination of chloroalkynes (Scheme 35).[65] The titanium catalyst **186** was readily prepared from commercially available 2,6-di-*tert*-butyl-4-methylphenol and $Ti(NMe_2)_4$ in 72% yield via a published procedure.[66] The simple, one-pot indolization involved

Scheme 35



heating the chloroalkyne and hydrazine with 2.5−5 mol % catalyst in toluene at 80−120 °C for 1−24 h. The mechanism involved an initial highly selective, titanium-catalyzed, Markovnikov hydroamination of the alkyne **184** to provide the *N*-aryl-*N*-chloro-alkylhydrazones. In situ Fischer reaction and nucleophilic substitution of the alkyl chloride by the liberated ammonia afforded the tryptamine derivatives **187** in good to excellent yields. When R_3 = Cl, mixtures of the two regioisomeric indoles were obtained.

A similar catalyst system was used by the same authors in a new, very efficient synthesis of tryptophols and tryptophol homologues by hydroamination of alkynyl alcohols followed by in situ Fischer indole reaction (Scheme 36).[67] For example, TBS-protected pentyne **188** was reacted with *N*-methyl-*N*-phenylhydrazine **189** in the presence of 5 mol % catalyst **190** to afford the hydrazone **192** as the major product. Treatment of the reaction mixture with $ZnCl_2$ gave the silyl-protected tryptophol **193** in 75% yield (Scheme 36). The highly selective Markovnikov addition[68] to afford hydrazone **192** was explained by the intermediacy of the titanaazacyclobutene derivative **191**.

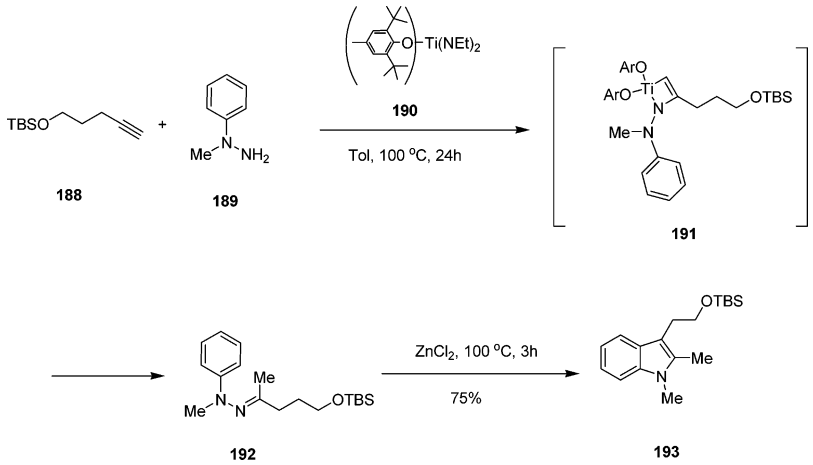
In this work, the catalyst was conveniently formed in situ from commercially available 2,6-di-*tert*-butyl-4-methylphenol and $Ti(NEt_2)_4$. The one-pot synthesis of a number of functionalized tryptophols **196** from TBS-protected pentynol **188a** and hexynol **188b** was carried out in high yield (Scheme 37). Although high yields of 2,3-disubstituted indoles **195** were obtained in most cases, application of this methodology to the synthesis of indoles unsubstituted at the 2-position has not been reported. The use of a combination of $TiCl_4$ and *t*-$BuNH_2$ as the sole catalyst for the tandem hydroamination/Fischer indolization was also reported by Ackermann and Born.[69]

2.6. Via Metal-Catalyzed Hydroformylation of Alkenes

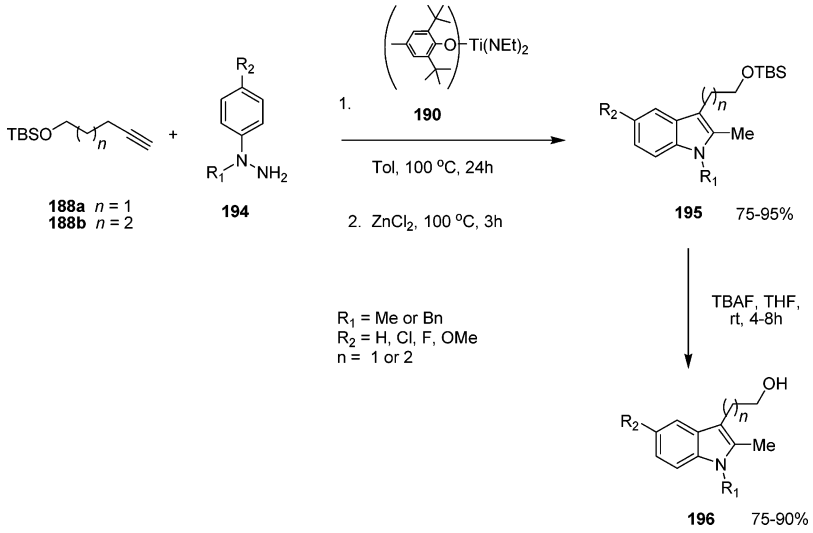
The preparation of aldehydes, useful for the Fischer indole process, via hydroformylation of alkenes is well-known.[70] Originally reported by Eilbracht and co-workers, the tandem hydroformylation/Fischer indole reaction has evolved into a powerful and efficient method for the one-pot construction of complex indoles (Scheme 38).[71] The general reaction pathway involves in situ generation of the aldehyde intermediate **198**, condensation with an aryl hydrazine to give hydrazone intermediate **199**, and finally [3,3]-sigmatropic rearrangement to provide the indole product **200**.

Beller and co-workers have reported an extension of this methodology to a general synthesis of hydrazones from olefins using Iphos **204** as catalyst (Scheme 39).[72] A number of simple and functionalized alkenes **201** were reacted with aryl hydrazines **202** using $Rh(CO)_2$acac (0.1 mol %), Iphos

Scheme 36



Scheme 37

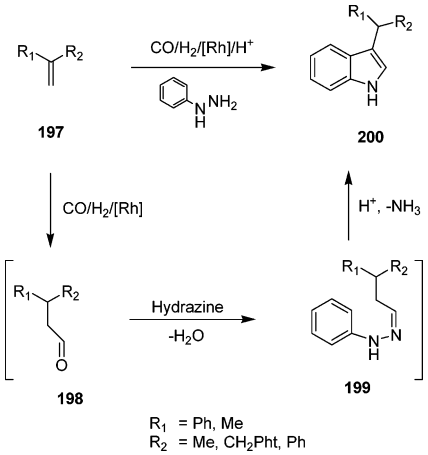


204 (0.2 mol %), and 10 bar of CO/H_2 in toluene to provide the hydrazones **203** in very high yield and selectivity. Addition of $ZnCl_2$ to selected hydrazones **203** gave the indole products **205** in high overall yields.

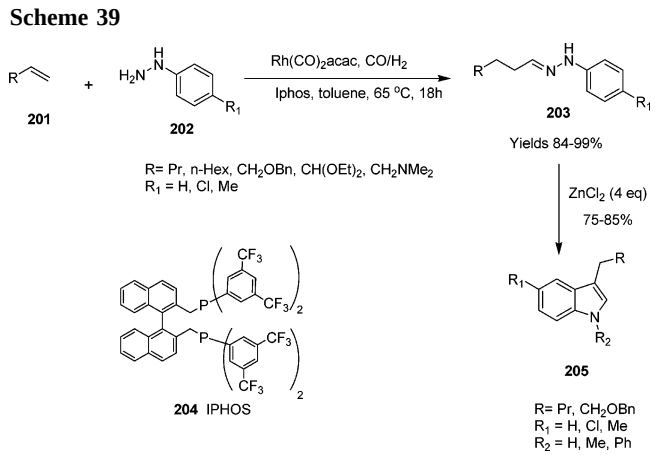
The use of the tandem hydroformylation/Fischer indolization protocol for the synthesis of pharmacologically interesting indoles bearing amino-alkyl side chains was recently reported by Eilbracht and Schmidt (Scheme 40).[73,74] Excellent yields of substituted tryptamines **208** were obtained from various allylamines **206** and hydrazines **207** using Xantphos as the ligand. The Rh/Xantphos system provided completely regioselective hydroformylation of the allylamines such that no products from the isomeric aldehydes were detected.

The procedure involved hydroformylation in the presence of the hydrazine in THF to provide the intermediate hydrazones. The hydrazone was then heated to 100 °C in 4 wt % aqueous H_2SO_4 for 2 h to complete the Fischer reaction. The stability of the carbamate protecting group of **208e** and **208f** to the Fischer indolization conditions is especially

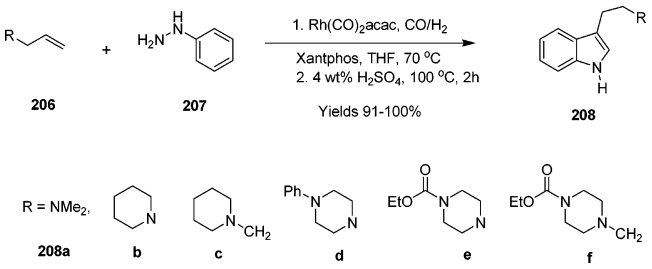
Scheme 38



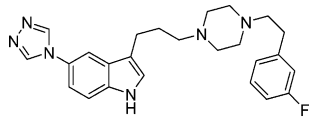
Scheme 39



Scheme 40



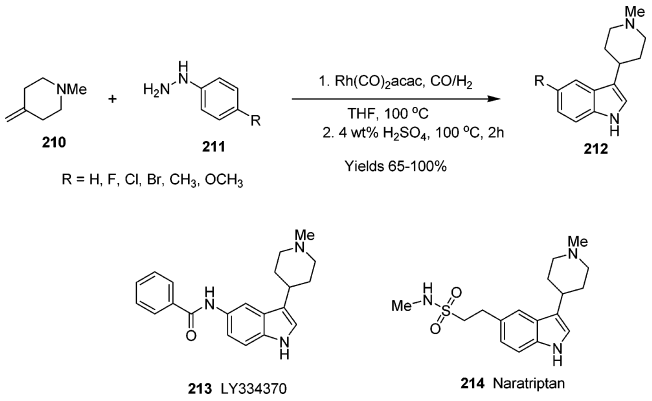
noteworthy since it provides a handle for derivatization to more complex potential targets such as L-775606 (**209**).



209 L-775606

The same methodology was extended to branched tryptamines and homotryptamines (Scheme 41). For example,

Scheme 41



piperidine alkene **210** gave good to quantitative yields of the 3-(*N*-methylpiperidyl)indoles **212**, which are important structural elements of clinical candidates such as the antimigraine compound LY334370 (**213**) and Naratriptan (**214**).

The procedure was subsequently improved to carry out the hydroformylation/Fischer reaction in a single operation without the need for a solvent switch; use of the water soluble ligands **216** and **217** allowed the whole reaction to be performed in aqueous sulfuric acid. Simple basification of the crude reaction mixture, extraction, and crystallization afforded the desired indoles **215** and **219** in good to excellent yield (Scheme 42).

The methodology was compatible with *N*-Boc hydrazines synthesized via the Goldberg reaction, and several one-pot syntheses of antimigraine drug candidates have been demonstrated. For example, LY334370 (**221**) was prepared from piperidine (**210**) and *N*-Boc arylhydrazine **220** in 95% overall yield (Scheme 43).

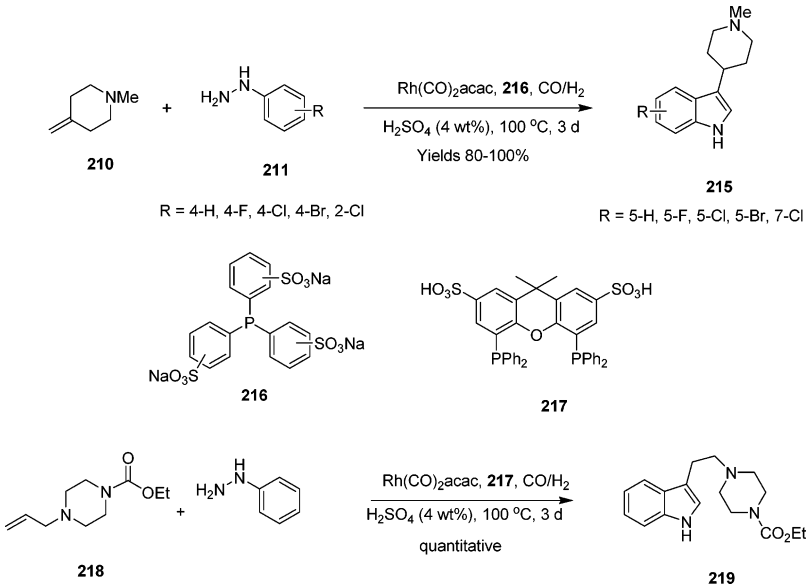
The hydroamination/Fischer indolization chemistry clearly has tremendous potential for the rapid synthesis of indole libraries. The relatively mild reaction conditions, low catalyst loadings, environmentally benign solvent systems, and general overall atom efficiency are also very attractive from a large-scale preparative viewpoint.

3. Heteroannulations and Cyclization of 2-Alkynylanilines

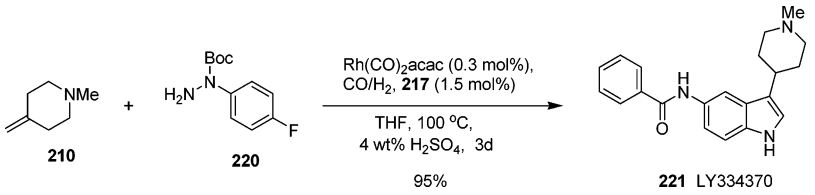
3.1. General Comments

Efficient methods for the construction of functionalized indoles have involved the reaction of 2-haloanilines and 2-aminophenols with either terminal or internal alkynes. These starting materials are often commercially available or readily accessible through proven synthetic techniques. The application of these attractive starting materials for the large-scale preparation of both 2-substituted and 2,3-disubstituted indoles has emerged in recent years as an important and effective means of preparing the indole ring system. The one-pot preparation of indoles from 2-haloanilines has been achieved by a number of transition-metal-catalyzed processes. In addition, the cyclization of 2-alkynylanilines, often obtained from 2-haloanilines or activated 2-aminophenols, has been mediated by strong bases or catalyzed by either palladium complexes or Lewis acids such as copper(I) and copper(II) salts. Furthermore, the preparation of indoles via

Scheme 42



Scheme 43

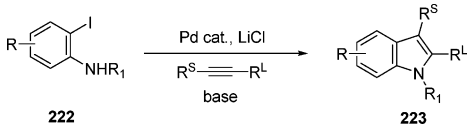


an in situ amination/cyclization of an aromatic *ortho*-haloalkyne that proceeded through an intermediate 2-alkynylaniline has been described. The heteroannulation of *o*-haloanilines with internal alkynes (Larock heteroannulation) and the cyclization of 2-alkynylanilines are both versatile and practical methods for the construction of the indole ring. These reactions will be highlighted in this section.

3.2. Indole Synthesis via the Larock Heteroannulation

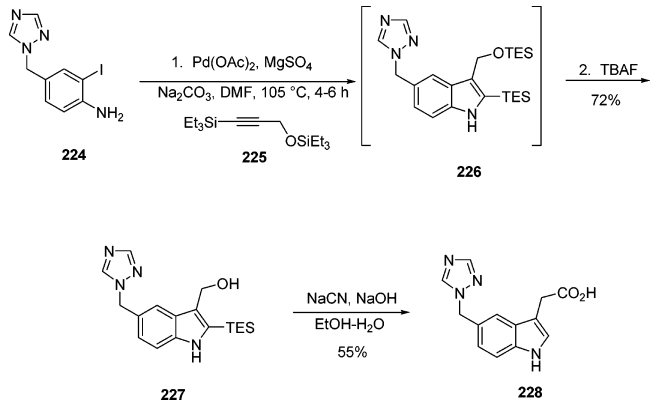
The palladium-catalyzed reaction between *o*-iodoaniline derivatives **222** and internal alkynes for the preparation of 2,3-disubstituted indoles **223** is referred to as the Larock heteroannulation reaction (Scheme 44).[75] The Larock heteroannulation is an extremely attractive method for the formation of complex indoles in a single operation. The reaction generally provides a means of preparing complex indole targets in a highly convergent manner, since both starting materials (i.e. *o*-iodoaniline and internal alkyne) can possess considerable functionality. The heteroannulation reaction is regioselective and almost always gives 2,3-disubstituted indoles, where the more sterically hindered group (R^L) of the alkyne occupies the 2-position of the indole ring. In particular, silylated alkynes have been extensively employed in the annulation process, which proceeded with excellent regiocontrol, giving almost exclusively 3-substituted 2-silylindoles. The resulting silylindoles can be protodesilylated to the corresponding 3-substituted indoles or serve as a useful handle for further manipulation. In addition, substituents on the nitrogen moiety are also tolerated, leading to *N*-substituted indoles. Therefore, it is not surprising that this important reaction has received considerable attention for the large-scale preparation of indoles.

Scheme 44



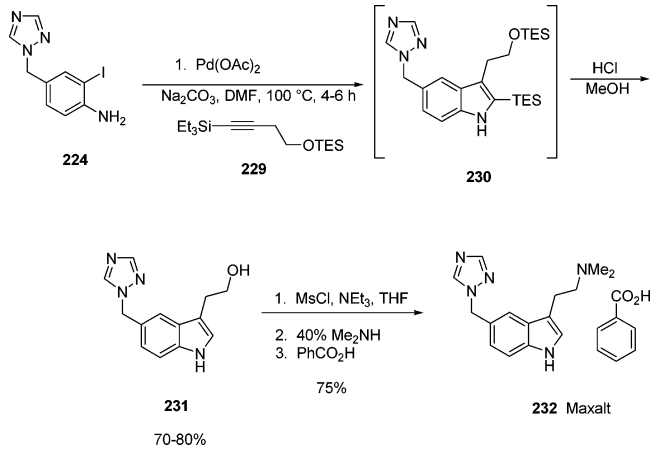
Chen and co-workers utilized the Larock heteroannulation for the preparation of indole **227**. Further elaboration of **227** gave indole **228**, which was required for activity screening and safety assessment studies (Scheme 45).[76] Coupling of iodoaniline **224** with bis-TES-propargyl alcohol **225** in the presence of $Pd(OAc)_2$ in DMF with 5 equiv of Na_2CO_3 provided a mixture of **226** and **227** in a 96:4 ratio. Due to the high water solubility of **227**, addition of 1.5 equiv of $MgSO_4$ minimized the desilylation of **226** to **227** and increased the overall yield of the reaction. Selective *O*-desilylation of **226** with tetrabutylammonium fluoride gave the desired mono-TES-indole **227**, which was crystallized from the one-pot reaction mixture in 72% isolated yield. Reaction of **227** with NaCN and NaOH in ethanol/water resulted in cyanide exchange, hydrolysis of the cyano group, and desilylation. Indole **228** was precipitated from the crude reaction mixture in excellent purity and 55% overall yield.

Scheme 45



Chen and co-workers also utilized the above methodology for the synthesis of Maxalt (**232**) (Scheme 46).[77]

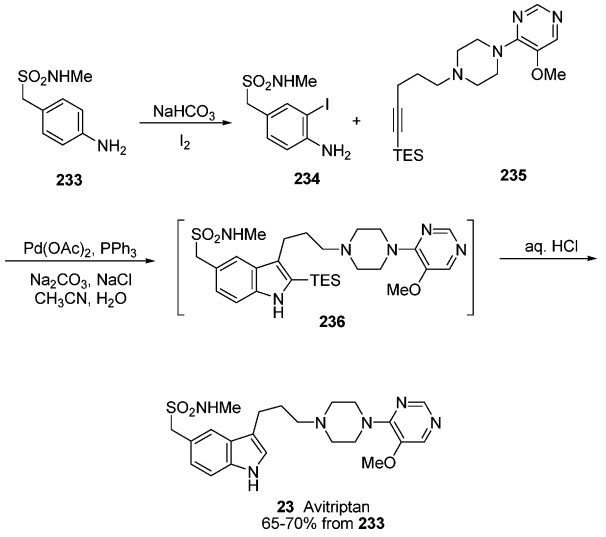
Scheme 46



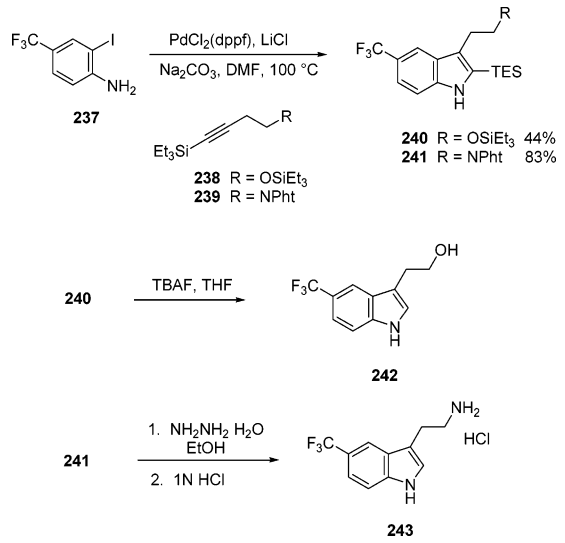
Brodfuehrer and Wang et al. in their paper on the Fischer indole cyclization synthesis of Avitriptan (**23**) (Schemes 5 and 6) briefly reported that the Larock heteroannulation had been used to prepare multikilogram quantities of Avitriptan (**23**) (Scheme 47).[19,78] The key transformation involved the palladium-catalyzed heteroannulation of iodoaniline **234** and acetylene **235**, which provided indole **236**. Subsequent acid hydrolysis of the silyl group furnished Avitriptan (**23**) in 65−70% overall yield from aniline **233**.

Goldstein et al. reported a practical synthesis of (5-trifluoromethyl)tryptophol and tryptamines via the Larock heteroannulation (Scheme 48).[79] Reaction of (trifluoromethyl)iodoaniline **237** with (triethylsilyl)acetylene **238** in the presence of $PdCl_2(dppf)$, 2 equiv of Na_2CO_3, and 1 equiv of LiCl in DMF at 100 °C gave tryptophol **240** in 44% yield.

Scheme 47



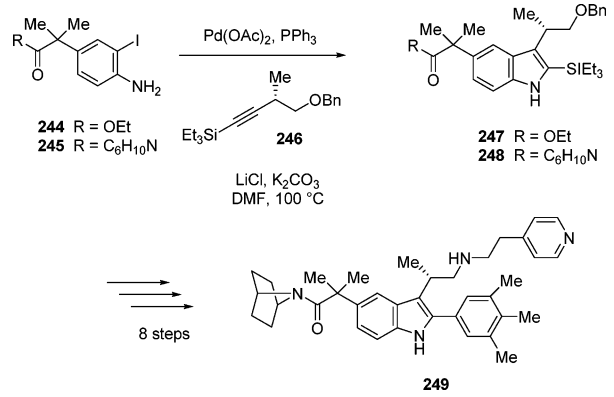
Scheme 48



On the other hand, reaction of **237** with acetylene **239** under the identical reaction conditions afforded tryptamine **241** in 83% isolated yield. Desilylation of **240** with TBAF gave indole **242** in 82% yield. Treatment of **241** with hydrazine hydrate followed by the addition of 1 N HCl gave the deprotected tryptamine derivative **243** in 87% yield after the direct crystallization of the HCl salt from the crude reaction mixture.

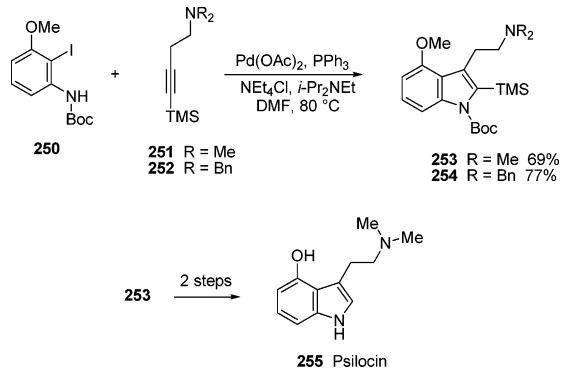
Walsh and co-workers reported the preparation of indoles **247** and **248**, which were utilized in the synthesis of the gonadotropin releasing hormone antagonist **249** (Scheme 49).[80] The key transformation in their synthesis involved the Larock heteroannulation of *o*-iodoanilines **244** and **245** with chiral alkynylsilane **246**. Reaction of **244** with **246** in the presence of $Pd(OAc)_2$ and PPh_3 with 1 equiv of LiCl and 2.5 equiv of K_2CO_3 in DMF at 100 °C gave indole **247** in 89% yield. Subjection of *o*-iodoaniline **245** to reaction with **246** under the identical reaction conditions yielded indole **248** in 72% yield. Although the reaction of **245** with **246** occurred in lower isolated yield, it was pointed out that the convergence afforded by incorporating the desired amide earlier in the synthesis justified the use of this transformation. The preparation of **249** was accomplished in an additional eight synthetic steps from indole **248**.

Scheme 49



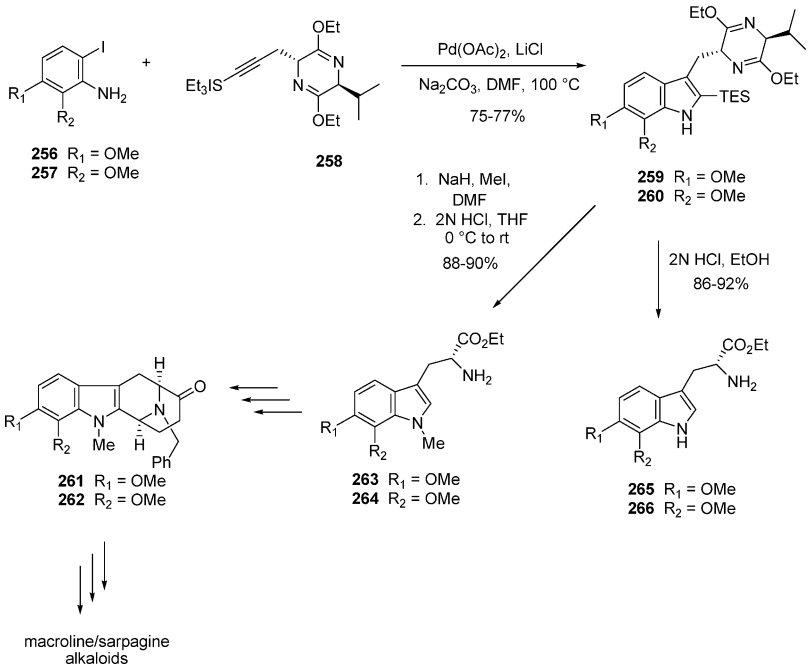
Gathergood and Scammells have extended the Larock heteroannulation to the preparation of *N*,*N*-disubstituted tryptamines **253** and **254**, which were used in a practical and versatile synthesis of the natural product psilocin **255** (Scheme 50).[81] Reaction of *N*-Boc-2-iodo-3-methoxyaniline **250** with acetylene **251** in the presence of $Pd(OAc)_2$, PPh_3, tetraethylammonium chloride, and Hünigs base in DMF at 80 °C for 48 h afforded tryptamine **253** in 69% yield. Reaction of **250** with acetylene **252** under the identical reaction conditions gave tryptamine **254** in 77% isolated yield. Two additional steps were required for the completion of the synthesis of psilocin **255** from indole **253**.

Scheme 50



In an elegant approach to optically active tryptophans, Cook et al. have utilized the Larock heteroannulation for the large-scale synthesis of D-tryptophans **263** and **264** which can be further elaborated to tetracyclic ketones **261** and **262** (Scheme 51).[82,83] These intermediates have proven to be valuable building blocks which were applied for highly functionalized macroline and sarpagine indole syntheses. The key indole-forming step involved reaction between iodoanilines **256** or **257** and the propargyl-substituted Schöllkopf chiral auxiliary **258**, which is readily derived from L-valine and glycine.[84] The Larock heteroannulation between **256** and **258** in the presence of $Pd(OAc)_2$, Na_2CO_3, and LiCl in DMF at 100 °C provided indole **259** in 77% isolated yield. In a similar fashion, reaction between **257** and **258** under the identical reaction conditions employing K_2CO_3 as the base afforded indole **260** in 75% isolated yield. Hydrolysis of **259** or **260** with 2 N HCl in ethanol resulted in cleavage of the Schöllkopf chiral auxiliary and concomitant loss of the indole-2-silyl group to give D-tryptophane ethyl esters **265** and **266** in 86 and 92% yields, respectively. Methylation of **259** and **260** with MeI and NaH followed by hydrolysis gave *N*-methyl methoxy-substituted D-tryptophan ethyl esters **263**

Scheme 51



(88%) and **264** (90%). Tryptophans **263** and **264** were subsequently converted in a highly optimized three-step procedure to ketones **261** and **262**, which have been carried on to highly functionalized macroline and sarpagine alkaloids. Cook and co-workers have also demonstrated the synthetic utility of this approach for the preparation of other substituted tryptophans.[85]

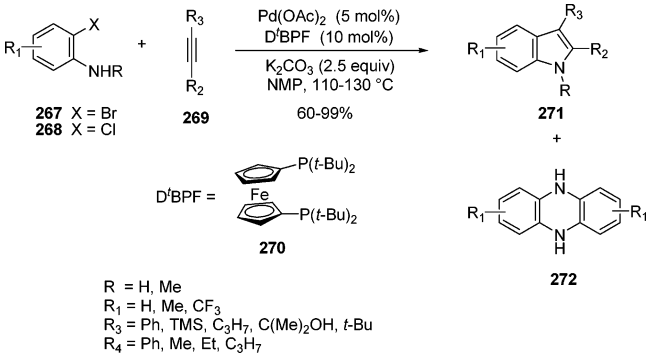
One of the major limitations of the Larock heteroannulation is that the reaction fails to give indole products in useful synthetic yields when 2-bromo- or 2-chloroanilines are employed and requires the use of iodoanilines which are often not commercially available. Recently, Lu and Senanayake reported the first regioselective palladium-catalyzed indolization of 2-bromo- or 2-chloroanilines with internal alkynes, which greatly extended the scope and utility of the Larock heteroannulation (Scheme 52).[86] In this work it has been rightfully emphasized that the use of cheaper 2-bromo- or 2-chloroaniline derivatives should provide significant practical and economical value. Reaction of a variety of either 2-bromo- or 2-chloroanilines (**267** or **268**) with various internal alkynes **269** in the presence of K_2CO_3 and $Pd(OAc)_2$ employing 1,1′-bis(di-*tert*-butylphosphino)ferrocene (**270**) as the ligand in NMP at 110−130 °C provided 2,3-disubstituted indoles **271** in yields ranging from 60 to 99% and with excellent regioselectivity. The major byproducts observed under these conditions were dihydrophenazines **272**; however, when the reaction was conducted at lower concentrations, the formation of these byproducts was greatly minimized.

3.3. Cyclization of 2-Alkynylaniline Derivatives

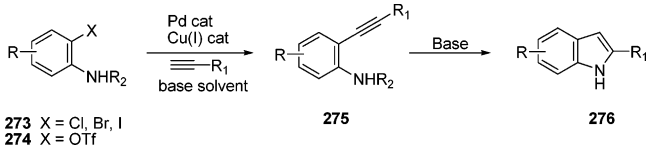
3.3.1. Metal Alkoxide-Mediated Reactions

The alkoxide-mediated cyclization of 2-alkynylanilines has long been exploited as a valuable synthetic method for the construction of 2,3-unsubstituted and 2-substituted indoles (Scheme 53).[87−89] The overall sequence usually involves a two-step process: (1) Sonogashira cross-coupling of 2-haloanilines **273** or 2-carboxamidoaryl triflates **274** affords 2-alkynylanilines **275**; and (2) alkoxide-mediated cyclization gives the corresponding indole **276**. Most noteable success has been achieved by heating the appropriate 2-alkynylaniline with either NaOEt or KO*t*-Bu in a protic solvent, usually the corresponding alcohol. Initial investigations involved reactions with *N*-substituted anilines, usually carbamates (methyl, ethyl, Boc, trifluoro); however, the unsubstituted anilines can also be utilized in the reaction. When carbamates were employed in the reaction, cyclization to the indole with concurrent deacylation occurred, giving *N*-unsubstituted indoles of type **276**.

Scheme 52

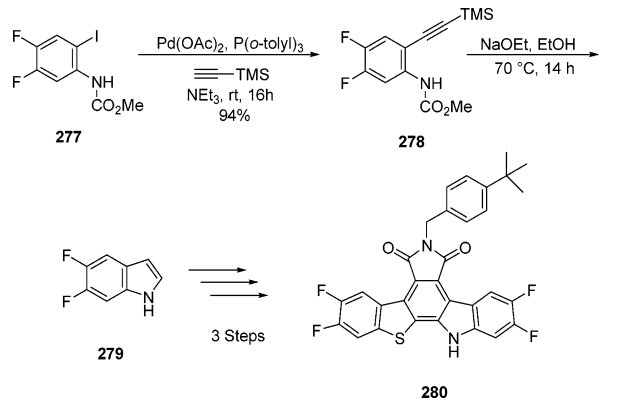


Scheme 53



Wang and co-workers utilized an alkoxide-mediated cyclization of 2-alkynylaniline **278** for the synthesis of 5,6-difluoroindole **279**, which was needed in large quantities as an intermediate in the preparation of the rebeccamycin analogue **280** (Scheme 54).[90] Palladium-catalyzed coupling of carbamate **277** with trimethylsilylacetylene in the presence

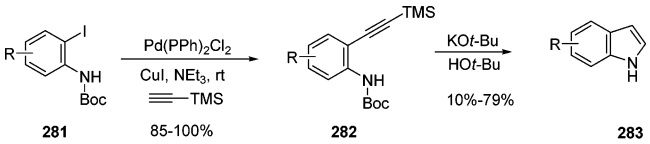
Scheme 54



of $Pd(OAc)_2$ and $P(o\text{-tolyl})_3$ in NEt_3 afforded acetylenide **278** in 94% yield. Treatment of **278** with NaOEt in EtOH at 70 °C for 14 h resulted in cyclization, desilylation, and deacylation to provide 5,6-difluoroindole **279** in 82% isolated yield. Further elaboration of this indole to **280** was completed in three additional steps.

Indole derivatives containing oxygen-bearing substituents such as hydroxyl, alkoxy, or acetoxy groups are known to be important medicinal agents and are present in a number of physiologically active substances and natural products. Kondo and Sakamoto have demonstrated the synthetic utility of the alkoxide-mediated cyclization of 2-alkynylanilines for the preparation of a number of these important compounds (Scheme 55).[91] For example, Sonogashira cross-coupling of iodoanilides **281** with (trimethylsilyl)acetylene in the presence of $Pd(PPh)_2Cl_2$ and copper(I) iodide in triethylamine gave the (trimethylsilyl)ethynyl phenylcarbamates **282** in yields of 85−100%. Cyclization of **282** in the presence of KO*t*Bu in *tert*-butyl alcohol afforded methoxy- and isopropylsiloxyindoles **283** in 10−79% yields.

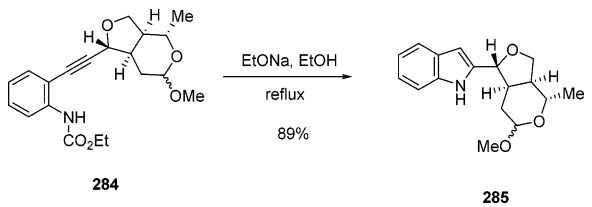
Scheme 55



281, 282: R = 3-OMe, 4-OMe,6-OMe, 4-OTIPS, 5-OTIPS, 6-OTIPS
283: R = 4-OMe, 5-OMe, 7-OMe, 5-OTIPS, 6-OTIPS, 7-OTIPS

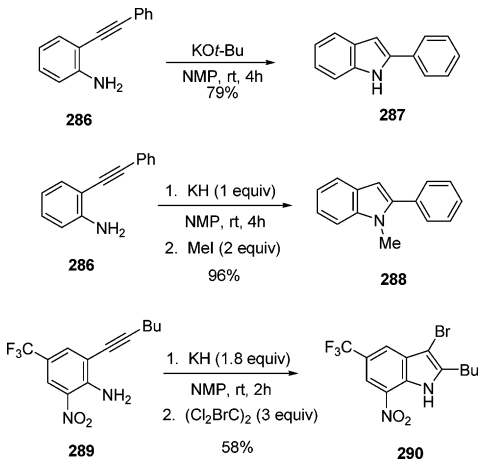
Ogasawara and co-workers utilized an alkoxide-mediated cyclization of the highly functionalized indole precursor **284** to give indole **285**, which was used in the total synthesis of 19-oxygenated pentacyclic *Strychnos* alkaloids (Scheme 56).[92] The 2-alkynylaniline **284** was prepared in reasonable yield in a limited number of steps. Treatment of **284** with NaOEt in refluxing EtOH provided indole **285** in 85% isolated yield.

Scheme 56



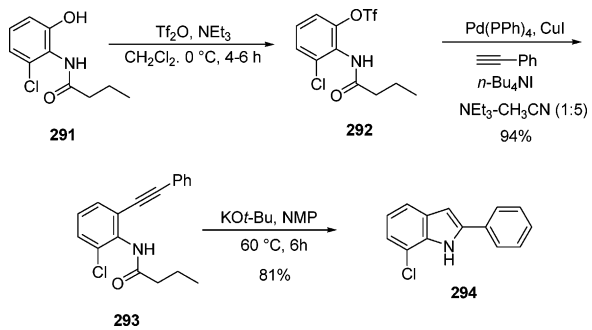
Recently, Knochel reported an extremely mild procedure for the alkoxide-mediated cyclization of 2-alkynylanilines to indoles which relied on the use of NMP as the reaction solvent (Scheme 57).[93] The use of NMP enables solubilization of potassium and cesium alkoxides such as KO*t*-Bu, CsO*t*-Bu, and KH and leads to increased reaction rates and lower reaction temperatures. These mild conditions allow using various functionalities which may not survive in more forcing cyclization conditions and allowed for the preparation of a range of polyfunctional indoles. For example, reaction of **286** with KO*t*-Bu in NMP for 4 h at room temperature afforded 2-phenylindole **287** in 79% yield. An interesting extension of this methodology involved the one-pot preparation of indole **288**. Reaction of **286** first with potassium hydride in NMP for 2 h followed by the direct addition of methyl iodide gave *N*-methyl-2-phenylindole **288** in 96% yield. The one-pot functionalization of the C-3 position of the indole ring was also possible. For example, reaction of **289** with potassium hydride in NMP for 2 h followed by the direct addition of dibromotetrachloroethane furnished the highly substituted indole **290** in 58% yield by a one-pot transformation.

Scheme 57

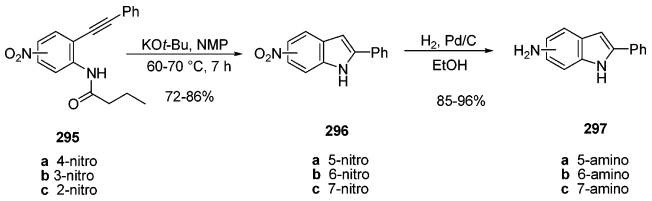


Dai and co-workers have reported a practical indole synthesis starting from commercially available 2-aminophenols (Scheme 58).[94] For example, reaction of acylated 2-aminophenol **291** with Tf_2O in the presence of NEt_3 furnished aryl triflate **292**. Sonogashira cross-coupling with phenylacetylene was reported to be remarkably enhanced when conducted in the presence of tetrabutylammonium iodide (n-Bu_4NI) and gave the 2-alkynylanilide **293** in 94% yield. Reaction of **293** with KO*t*-Bu in NMP at 60 °C provided indole **294** in 81% isolated yield where deacylation occurred under the reaction conditions. Several

Scheme 58



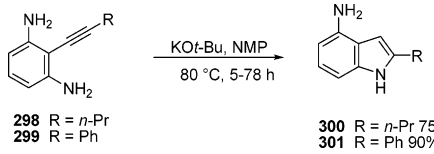
Scheme 59



additional examples of this transformation were also reported.

This methodology has also been utilized for the preparation of 5-, 6-, and 7-aminoindoles **297a**−**c** (Scheme 59).[95] The key step involved reaction of 2-alkynylanilines **295a**−**c** with KO*t*-Bu in NMP at 60−70 °C, providing the corresponding nitroindoles **296a**−**c** in 72−86% yield. Hydrogenation of the nitro group over Pd/C in EtOH furnished the aminoindoles **297a**−**c** in 85−96% yield. In the same paper, 4-aminoindoles **300** and **301** were obtained by reaction of **298** or **299** with KO*t*-Bu in NMP at 80 °C, which directly gave the desired 4-aminoindoles **300** and **301** in 75 and 90% yields, respectively (Scheme 60).

Scheme 60

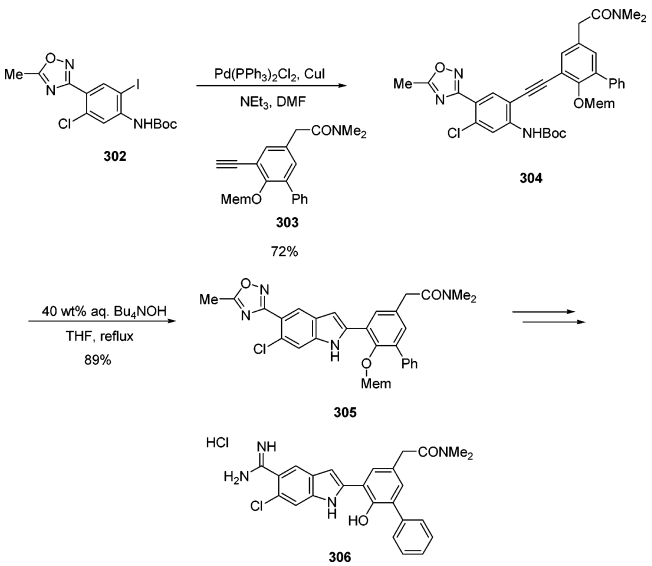


Sendzik and Hui have reported the aqueous tetrabutylammonium hydroxide (Bu_4NOH)-mediated cyclization of 2-alkynylaniline **304** to give indole **305**, which is the direct precursor of the uPA inhibitor **306** (Scheme 61).[96] Sonogashira coupling of *N*-Boc-aniline **302** with arylacetylene **303** provided 2-alkynylaniline **304** in 72% yield. Treatment of **304** with 40 wt % aqueous Bu_4NOH in refluxing THF resulted in cyclization with concomitant loss of the Boc group to give indole **305** in 89% yield. Indole **305** was converted to **306** in two additional steps.

3.3.2. Castro Indole Synthesis

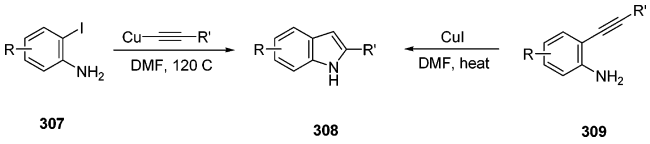
The Castro indole synthesis formally involves cyclization of either *o*-iodoaniline derivatives with cuprous acetylides

Scheme 61



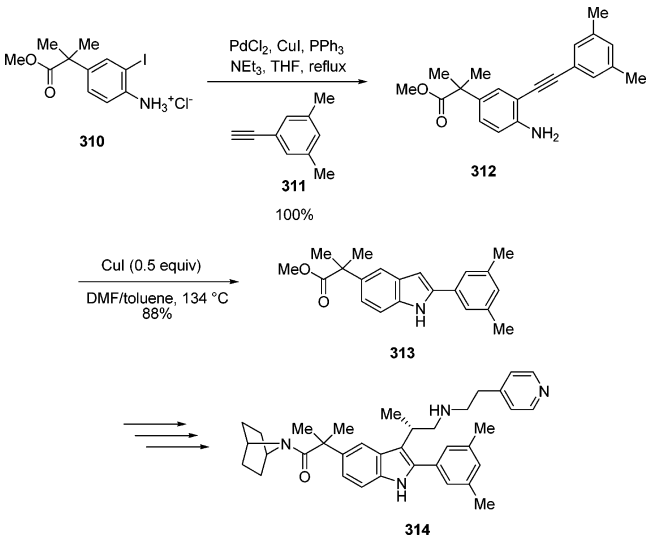
or 2-alkynylanilines with copper(I) salts, usually copper(I) iodide (Scheme 62).[97] While reactions employing cuprous acetylides are rare and not amenable to scale up, copper-promoted cyclizations of 2-alkynylanilines **309** have received considerable attention as an attractive method for the construction of indoles. In most cases, copper(I) iodide is used in excess;[98] however, cases using substoichiometric amounts (<1.0 equiv) and even catalytic reactions employing both Cu(I) and Cu(II) salts have recently surfaced (vida infra). For the process chemist, the Castro indole synthesis is particularly attractive since it affords free *N*-H indoles without requiring the use of cumbersome nitrogen protecting groups, utilizes economically attractive copper as the metal source, and succeeds where other methods often fail.

Scheme 62



Farr and co-workers reported the multi-kilogram-scale preparation of indole **313** using a modification of the procedure originally reported by Castro (Scheme 63).[99] Indole **313** was an intermediate utilized in the synthesis of the gonanotropin releasing hormone antagonist **314**. The required 2-alkynylaniline **312** was prepared in quantitative yield by coupling of acetylene **311** and iodoaniline hydrochloride **310**. Reaction of crude **312** with 0.5 equiv of copper(I) iodide in DMF at 134 °C for 3 h afforded **313**, which was isolated by crystallization in 88% yield. Indole **313** was converted to **314** in four to five additional steps via two separate reaction pathways.

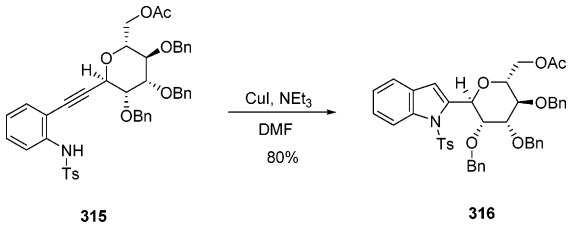
Scheme 63



Isobe has described the synthesis of α-*C*-mannosylindole **316** via the Castro indole synthesis of *N*-tosylalkynylaniline **315** (Scheme 64).[100] While no experimental details were provided, treatment of **315** with CuI and NEt_3 in DMF allowed for the preparation of gram quantities of indole **316** in 80% yield.

Cook et al. employed a Castro indole synthesis for the preparation of L-isotryptophan (**321**) (Scheme 65).[101] Palladium-catalyzed cross-coupling of 2-iodoaniline (**317**) with alkyne **318** gave 2-alkynylaniline **319** in 95% yield. When

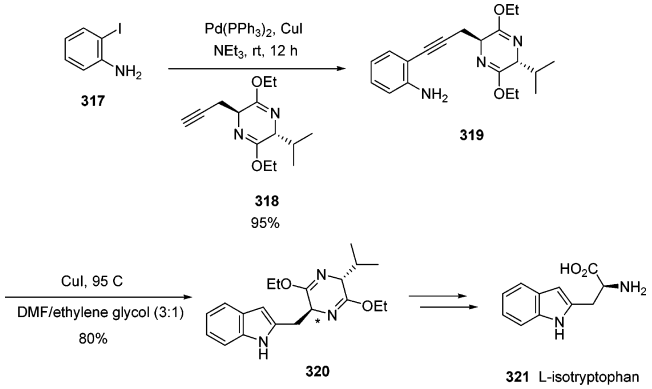
Scheme 64



315 316

treated with CuI in DMF at 95 °C, cyclization to indole **320** occurred; however, under these reaction conditions significant epimerization of the stereogenic center (*) was observed. This problem was alleviated through the use of ethylene glycol, which served as a proton source and suppressed the epimerization to less than 6%, and indole **320** was isolated in 80% yield. The desired L-isotryptophan (**321**) was obtained in two additional steps in 72% yield.

Scheme 65

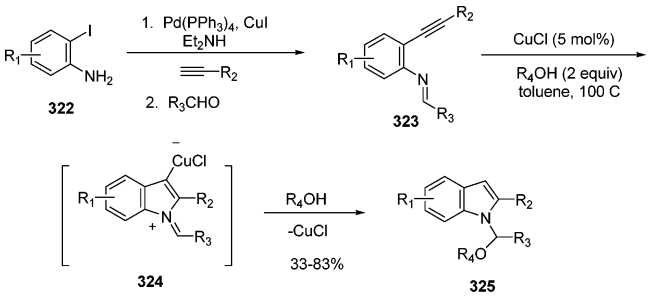


The development of a catalytic variant of the Castro indole synthesis has been stimulated by an increased interest in copper-catalyzed reactions, which provide economical attractiveness and potential applications for the large-scale synthesis of indoles. Villemin and Goussu[102] demonstrated in 1989 that cyclization of 2-aminodiphenylacetylene could be conducted with a catalytic amount of copper(I) iodide (5.8 mol %) in refluxing DMF to give 2-phenylindole in 99% yield; however, the application of these harsh reaction conditions for the general synthesis of other indole substrates has not surfaced.

Yamamoto and co-workers have reported the CuCl-catalyzed cyclization of 2-alkynyl-*N*-arylideneanilines **323** in the presence of various alcohols as a practical means of synthesizing *N*-(alkoxybenzyl)indoles **325** (Scheme 66).[103] The starting imines **323** were prepared in two steps by Sonogashira coupling of 2-iodoanilines **322** with terminal alkynes followed by condensation with an aldehyde. Treatment of **323** with 5 mol % CuCl and 2 equiv of a number of different alcohols in toluene at 100 °C for 1−24 h provided indoles **325** in modest to good yields. Presumably, copper-mediated cyclization gives the zwitterionic intermediate **324**, which is attacked by alcohol to give indole **325**.

The cyclization of 2-alkynylanilines employing catalytic copper(II) salts was recently demonstrated by Hiroya et al. (Scheme 67).[104,105] This reaction could be applied to sulfonamide and primary and secondary aniline derivatives where the catalysts of choice were either $Cu(OAc)_2$ for *N*-substituted 2-alkynylanilines or $Cu(OCOCF_3)_2$ hydrate for unsubstituted 2-alkynylanilines; however, it should be pointed out that other copper(II) salts, such as $Cu(OTf)_2$, could also

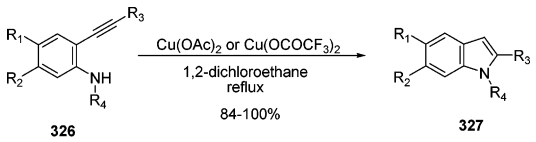
Scheme 66



R_1 = H, OMe, CN
R_2 = H, Pr, Cyclohexyl, Ph, *p*-OMe-C_6H_4, *p*-CO_2Me-C_6H_4, Me_3SiC_2
R_3 = *p*-Me, OMe, SMe, NO_2, Cl, Br-C_6H_4, *o*-Me-C_6H_4, *m*-Me-C_6H_4, *trans*-CH=CHPh
R_4 = Me, *n*-Pr, *i*-Pr, CF_3CH_2, Bn, *p*-MeO-C_6H_4, Ph, CH_2=$CHCH_2$, $Me_3Si(CH_2)_2$

be used. The reactions were typically conducted in refluxing 1,2-dichloroethane for 2−48 h, giving the desired indoles **327** in good to excellent yield. Several representative examples are depicted in Scheme 67. The yields of the indoles were dependent on the bulkiness of the substituents on the acetylene terminus.

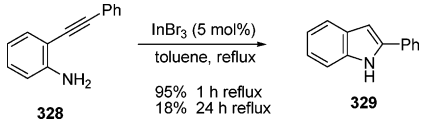
Scheme 67



R_1 = H, Me
R_2 = H, OMe, CN
R_3 = H, Ph, $(CH_2)_4$OTBS
R_4 = H, Ms, PMB, *i*-Pr
PMB = *p*-methoxybenzyl

The same research group also reported that attempted cyclization of *N*-substituted 2-alkynylanilines **326** employing other Lewis acids such as BF_3·OEt_2, $TiCl_4$, $TiCl_2(Oi\text{-}Pr)_2$, $AlCl_3$, $ZnCl_2$, and $Sn(OTf)_2$ failed to give any synthetically useful yields of the corresponding indoles. On the other hand, Sakai, Annaka, and Konakahara have demonstrated that the intramolecular cyclization of 2-alkynylaniline **328** could be catalyzed by indium tribromide (Scheme 68).[106] Reaction of **328** with 1 equiv of $InBr_3$ in refluxing toluene gave 2-phenylindole **329** in less than 10 min and in quantitative yield. When the reaction was conducted with only 5 mol % $InBr_3$, 2-phenylindole was isolated in nearly quantitative yield after only 1 h of reflux. Prolonged heating does, however, lead to a dramatic decrease in yield of **329**; the authors did not comment any further on this observation.

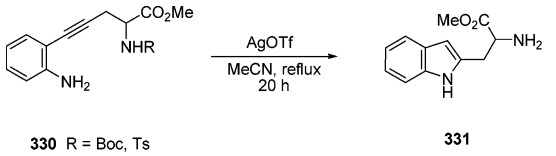
Scheme 68



328 329

Rutjes el al. have utilized a silver triflate (AgOTf)-catalyzed cyclization of 2-alkynylanilines **330** for the preparation of isotryptophan **331** (Scheme 69).[107] The key transformation involved refluxing Boc-protected amino acid **330** in the presence of 10 mol % AgOTf to provide a slow but clean conversion to chiral isotryptophan derivative **331**, which was isolated in 75% yield. Treatment of the racemic *N*-tosyl derivative under the identical reaction conditions gave racemic **331** in 86% yield. In both cases, cyclization to the indole was accompanied by cleavage of the amino-protecting group.

Scheme 69



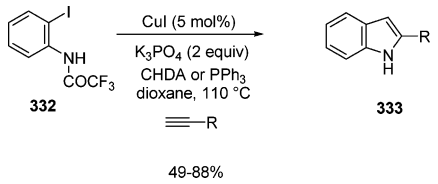
330 R = Boc, Ts

331

(*S*) isotryptophan 75%
racemic tryptophan 86%

Cacchi and co-workers have reported that reaction of 2-(phenylethynyl)aniline in the presence of 5% CuI and 2 equiv of K_3PO_4, in dioxane at 110 °C for 24 h, gave only trace amounts of 2-phenylindole (Scheme 70).[108] The addition of the chelating ligand (±)-1,2-*trans*-cyclohexanediamine (CHDA) improved the yield to 50%. Speculating that a more acidic *N*-H bond may favor cyclization to the indole, they turned their attention to reactions of the trifluoroacetamido derivative **332**. Reactions of **332** with 5 mol % CuI in the presence of either CHDA or PPh_3 gave 2-substituted indoles **333** in 49−88% yields.

Scheme 70



332

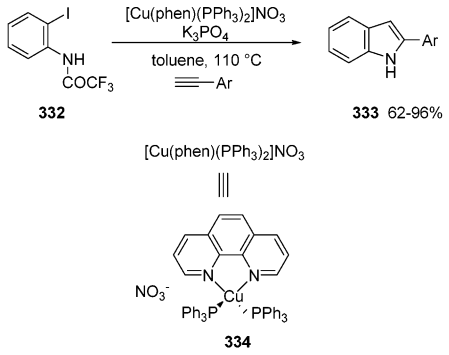
333

49-88%

R = Ph, CH_2NHCO_2Et, *p*-$NO_2C_6H_4$, *o*-Br-C_6H_4, *n*-C_5H_{11}

In the same paper, it was shown that the copper complex **334** ([Cu(phen)$(PPh_3)_2$]-NO_3)[109] can serve as an efficient catalyst for the preparation of 2-aryl- and 2-heteroarylindoles from 2-iodotrifluoroacetanilide **332** and 1-alkynes (Scheme 71). Reaction of **332** with various arylacetylenes in the presence of 10 mol % **334** in refluxing toluene afforded indoles **333** in good to excellent yield (62−96%). In addition, phenylacetylene bearing both electron-donating and electron-withdrawing groups furnished the desired indoles. However, reaction with 1-hexyne under these conditions gave 2-butylindole in only 11% yield.

Scheme 71



332

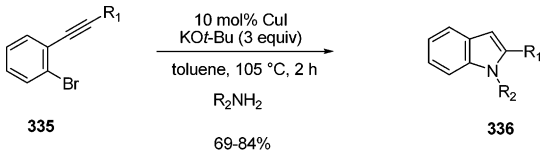
333 62-96%

334

Ar = *p*-$MeCOC_6H_4$, *p*-ClC_6H_4, *p*-$MeCONHC_6H_4$, *p*-$OMeC_6H_4$, *m*-$OMeC_6H_4$, *o*-$OMeC_6H_4$, 3,5-Me_2-C_6H_3, *p*-MeOOC-C_6H_4, *p*-OHC-C_6H_4, *p*-NO_2-C_6H_4, 2-pyridyl, 3-quinoline

Ackermann has reported a general and efficient indole synthesis based on a catalytic one-pot [Ullman−Goldberg/Castro (or alkoxide-mediated)] indole synthesis (Scheme 72).[110] Treatment of 2-alkynylbromobenzenes **335** with 10 mol % CuI and 3 equiv of KO*t*-Bu in toluene containing an

Scheme 72



335

336

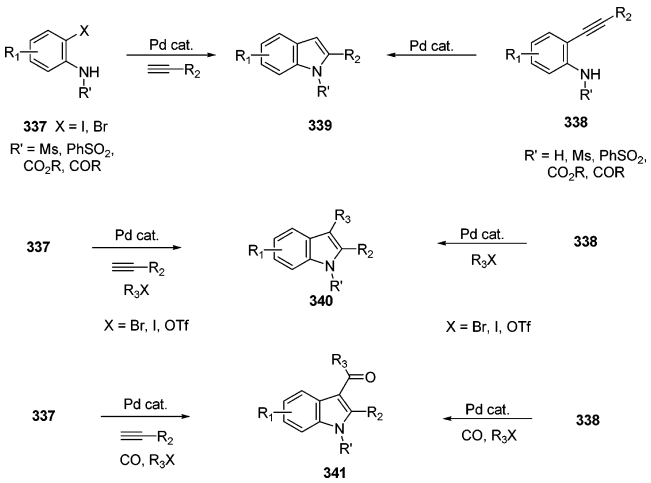
R_1 = *n*-hexyl, *n*-butyl
R_2 = Ph, *p*-Tol, *p*-ClC_6H_4, *o*-$MeOC_6H_4$

appropriately substituted aniline furnished indoles **336** in 67−84% isolated yield for the one-pot transformation. In this work it was pointed out that the intermolecular Ullmann coupling, or hydroamination, was followed by intramolecular cyclization to give the indole products.

3.3.3. Palladium-Mediated Processes

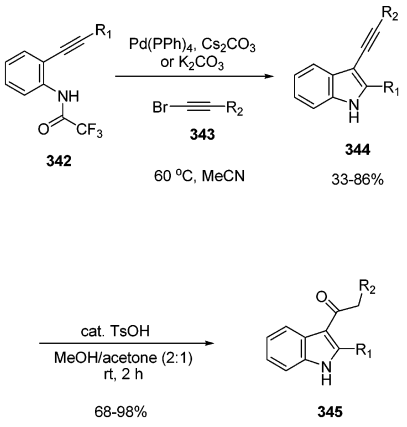
The palladium-catalyzed cyclization of 2-alkynylanilines and the one-pot annulation of 2-haloanilines with terminal alkynes have received considerable attention as useful methods for the construction of indoles (Scheme 73). For example, both 2-substituted indoles **339** and 2,3-disubstituted indoles **340** and **341** can be obtained from either 2-alkynylanilines **338** or 2-haloanilines **337** in modest to excellent yields. Reaction of 2-haloanilines with terminal acetylenes likely involves 2-alkynylanilines **338** as synthetic intermediates which further react with the palladium catalyst, leading to the desired indoles. The preparation of 2,3-disubstituted indoles **340** and **341** from both **337** and **338** requires reductive elimination of either an indolylpalladium intermediate, leading to substituted indoles of type **340**, or an acylindolylpalladium species, giving acylindoles of type **341**. While these methods have not yet been reported for the large-scale preparation of indoles, they deserve mention as potentially scalable processes. Since these reactions were recently reviewed in detail, they will not be discussed here.[111] Instead, only the most recently reported examples will be highlighted.

Scheme 73



Cacchi has disclosed a rapid approach to 3-alkynylindoles **344** and 2-substituted 3-acylindoles **345** which involved the palladium-catalyzed reaction of *o*-alkynyltrifluoroacetanilide **342** with 1-bromoalkynes **343** (Scheme 74).[112] For example, reaction of **342** with 1.2 equiv of **343** in the presence of 5 mol % $Pd(PPh)_4$ and 3 equiv of Cs_2CO_3 or K_2CO_3 in MeCN furnished the corresponding 3-alkynylindoles **344** in modest to good yield. Higher yields were obtained when 1-bro-

Scheme 74

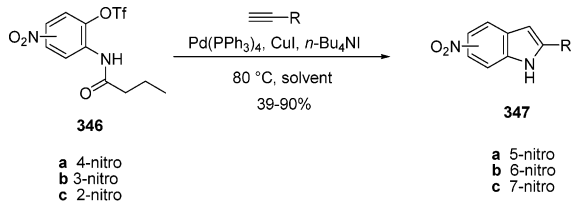


R_1 = Ph, *p*-$MeOC_6H_4$, CH_2OTHP
R_2 = Ph, *p*-$MeOC_6H_5$, *p*-$NO_2C_6H_5$, *m*-$NO_2C_6H_5$, *n*-C_8H_{17}, $Me_2C(OH)$, $Ph(CH_2)_2$, 2-,3-quinoline

moarylacetylenes were used; however, 1-bromoalkylacetylenes could also be employed. Reaction of indoles **344** with a catalytic amount of *p*-TsOH in a 2:1 mixture of MeOH/acetone gave 2-substituted 3-acylindoles **345** in good to excellent yield.

The one-pot cross-coupling and heteroannulation of trifloxyanilides **346a**−**c** with various terminal alkynes for the preparation of 2-substituted 5-, 6-, and 7-nitroindoles was reported by Dai and co-workers (Scheme 75).[113] The one-pot reactions for **346a** and **346b** were carried out in the presence of 10 mol % $Pd(PPh)_4$, 30 mol % CuI, and 150 mol % *n*-Bu_4NI in a solvent combination of either 5:1 DMF/NEt_3 or CH_3CN/NEt_3. A variety of functional groups were tolerated in the reaction, and protection of the OH was not required. Formation of the C-7 nitroindole **347c** was problematic and required the use of $Pd(PPh_3)Cl_2$ as the catalyst along with the stronger base tetramethylguanidine (TMG) at 100 °C. It was suggested that the *ortho*-nitro group of **347c** may form a hydrogen bond with the amido moiety and interfere with the indole ring closure reaction; however, no comment was made regarding the isolation of any intermediates prior to cyclization to indole **347c**.

Scheme 75



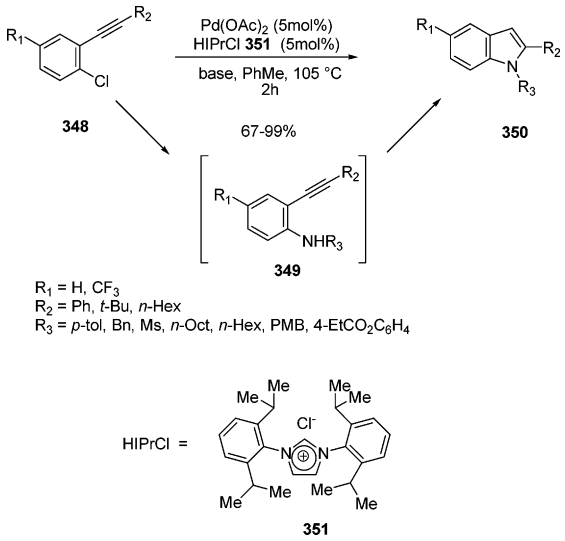
R = Ph, *n*-Pr, $(CH_2)_2OH$, $(CH_2)_3CN$, $(CH_2)_3Cl$

346a and **346b** Solvent = DMF-NEt_3 (5:1) or CH_3CN-NEt_3 (5:1) or

346c Solvent = DMF-TMG (5:1), catalyst = $Pd(PPh_3)_2Cl_2$

Ackermann has reported a highly efficient, regioselective indole synthesis based on a palladium-catalyzed amination/cyclization protocol of 2-alkynyl-1-chlorobenzenes **348** (Scheme 76).[114] The starting 2-alkynyl-1-chlorobenzenes **348** were prepared with excellent selectivity and isolated yields (73−96%) by Sonogashira coupling of the corresponding *o*-dihalobenzenes using $Pd(PPh_3)_2Cl_2$ and CuI. Reaction of chloroalkynes **348** with the palladium complex generated from the commercially available imidazolium carbene salt **351** (HIPrCl) and $Pd(OAc)_2$ in the presence of KO*t*-Bu in toluene at 105 °C for 2 h afforded good to excellent yields

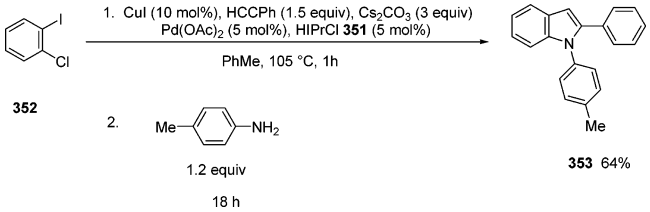
Scheme 76



of the indole products **350** for the single-step transformation. A variety of *N*-protecting groups, such as benzyl or *p*-methoxybenzyl (PMB), could be introduced via the corresponding amine, which allows the further manipulation of the resulting indoles. In addition, the reaction could be carried out with mild bases such as Cs_2CO_3 or the less expensive K_3PO_4. When these bases were employed, longer reaction times and incomplete cyclization of the amination intermediate **349** were observed. However, the addition of CuI (5 mol %) was found to accelerate these reactions and quantitative conversion to the indole occurred.

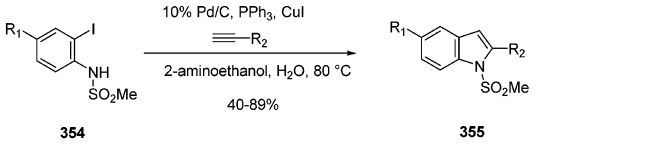
In the same paper, this methodology was expanded to the multicatalytic one-pot synthesis of indole **353** starting from 1-chloro-2-iodobenzene (**352**) (Scheme 77). This particularly remarkable transformation consisted of a Sonogashira coupling reaction, amination, and intramolecular cyclization to the corresponding indole. Treatment of **32** first with a combination of 10 mol % CuI, 1.5 equiv of phenylacetylene, 3 equiv of Cs_2CO_3, 5 mol % $Pd(OAc)_2$, and 5 mol % HIPrCl **351** in toluene at 105 °C for 1 h followed by the direct addition of *p*-toluidine to the reaction mixture gave quantitative conversion to indole **353**, which was isolated in 64% yield.

Scheme 77



Pal and co-workers have disclosed a straightforward one-pot procedure catalyzed by Pd/C in water/2-aminoethanol for the preparation of 2-substituted *N*-methanesulfonyl indoles **355** beginning with *N*-(2-iodophenyl)methanesulfonamides **354** (Scheme 78).[115] Reaction of **354** with a variety of acetylenes in the presence of 10% Pd/C (3 mol %), PPh_3 (10 mol %), CuI (6 mol %), and 2-aminoethanol (3 equiv) in water provided good to excellent yields of the corresponding *N*-methanesulfonyl indoles **355**. Since this water-based synthesis is safe and inexpensive, the authors point out that the methodology is efficient, simple to perform, does not

Scheme 78



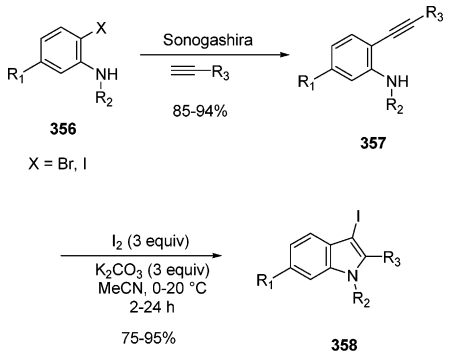
R_1 = Cl, Me
R_2 = Ph, $C(CH_3)_2OH$, CH_2OH, $(CH_2)_2OH$, $(CH_2)_5Me$, CH(OH)Me, $CH(OH)CH_2Me$, $CH(OH)C_6H_5$

involve the use of expensive reagents or catalysts, and is amenable for the large-scale preparation of 2-substituted indoles.

3.3.4. Iodine-Promoted Electrophilic Cyclizations

The electrophilic cyclization of appropriately functionalized aromatic acetylenes promoted by iodine has been utilized for the preparation of a number of heterocyclic compounds.[116] The application of this strategy for the construction of 3-iodoindoles from 2-alkynylanilines was recently investigated as a practical method for the preparation of these versatile synthetic intermediates.[117] Although the implementation of these strategies for the large-scale synthesis of 3-iodoindoles has not yet been reported, the relatively mild reaction conditions and generality of these processes necessitate their inclusion in this section. For example, Amjad and Knight reported a simple two-step method for the construction of *N*-tosyl- or *N*-Boc-protected indoles **358** from 2-haloanilines **356** (Scheme 79).[118] The first step involved Sonogashira coupling of 2-haloanilines **356** to give the 2-alkynylanilines **357** in excellent yields (85−94%). Exposure of **357** with 3 equiv of iodine and anhydrous K_2CO_3 in MeCN at 0 °C followed by warming to room temperature gave the desired 3-iodoindoles **358** in good to excellent overall yield.

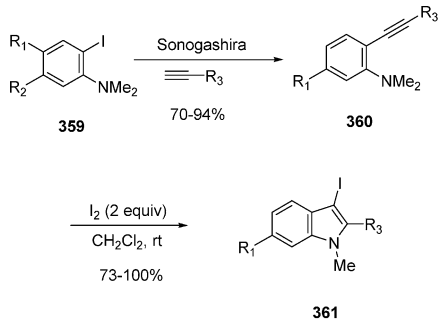
Scheme 79



R_1 = H, NO_2
R_2 = Ts, Boc
R_3 = Ph, Bu, TMS, CH_2OTBS

Yue and Larock have also developed a two-step synthesis of *N*-methyl-3-iodoindoles **361** beginning with *N*,*N*-dimethyl-2-iodoanilines **359** (Scheme 80).[119] Sonogashira coupling of **359** with various alkynes provided the 2-alkynyldimethylanilines **360** in good yield. Treatment of **360** with 2 equiv of molecular iodine in CH_2Cl_2 at room temperature afforded the 3-iodoindoles **361**, in nearly quantitative yield for most examples. Workup of these reactions required the addition of aqueous $Na_2S_2O_3$, which spontaneously decomposed trace amounts of indolium triodide salts and effectively removed any excess of iodine.

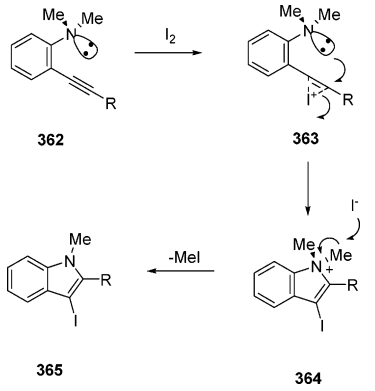
Scheme 80



R_1 = H, OMe
R_2 = H, NO_2
R_3 = Ph, *t*-Bu, $(CH_2)_3CN$, $(CH_2)_3Cl$, *n*-C_6H_{13}, C_6H_9 (Cyclohexenyl)

The overall success of the above reaction was attributed to a number of factors. The enhanced nucleophilicity of the dimethylaniline nitrogen also orientates the nitrogen lone pair of electrons pointing toward the triple bond (Scheme 81). Subsequent cyclization was followed by removal of the methyl group by the highly nucleophilic iodide ion. The use of CH_2Cl_2 as the solvent increases the solubility of the indolium salt **364** and facilitates the dealkylation step.

Scheme 81



4. Reductive Cyclizations

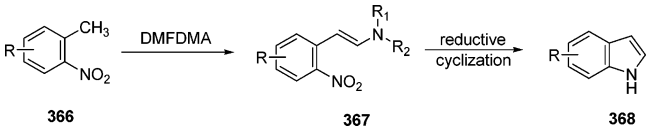
4.1. General Comments

The reductive cyclization of aromatic nitro compounds is an extremely powerful method for the preparation of the indole ring and has been reviewed.[120,121] Due to a significant array of both commercially available and readily accessible *o*-nitrotoluenes, researchers in both academia and industry have come to rely on reductive cyclization techniques for the large-scale preparation of indoles. Reductive cyclization is usually accomplished by catalytic hydrogenation over Pd/C, Pt/C, or a combination of Raney nickel and hydrazine. Other suitable reductants that have also been employed include sodium dithionite, nickel boride/hydrazine, iron or zinc in acetic acid, stannous chloride, $TiCl_2$−HCl, and $TiCl_3$. For the large-scale preparation of indoles, reactions which are robust and are able to tolerate a large range of functional groups have received the most attention. The Leimgruber−Batcho indole synthesis and the reductive cyclization of *o*-nitrobenzylcarbonyl compounds (including the Reissert indole synthesis), *o*-dinitrostyrenes, *o*-nitrostyrenes, and *o*-nitrophenylacetonitriles have proven to be practical and scalable methods for the construction of the indole ring.

4.2. Leimgruber–Batcho Indole Synthesis

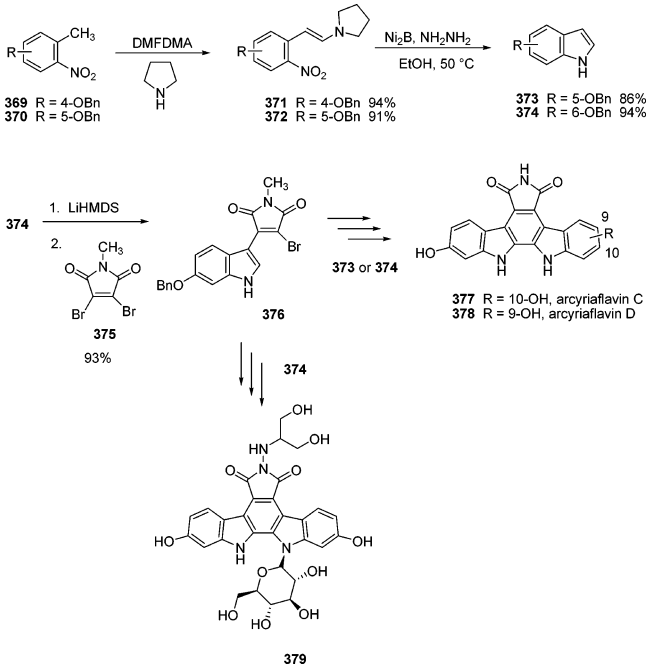
One of the most important and commonly used methods for the preparation of 2,3-unsubstituted indoles is the Leimgruber−Batcho indole synthesis.[122] The classical Leimgruber−Batcho indole synthesis involves the condensation of an appropriately substituted *o*-nitrotoluene **366** with dimethylformamide dimethyl acetal (DMFDMA) to give intermediate *β*-(dimethylamino)-2-nitrostyrene (**367**). Reductive cyclization leads to substituted indoles **368** (Scheme 82). The increased acidity of the methyl group of the *o*-nitrotoluene allows the facile preparation of the remarkably stable intermediate **367**. In an improved procedure, the formation of **367** is conducted in the presence of an excess of pyrrolidine, which exchanges with the dimethylamino substituent.[123] The reaction is capable of tolerating a large range of ring substituents and has been used extensively for the construction of both natural products and pharmaceutically important compounds.

Scheme 82



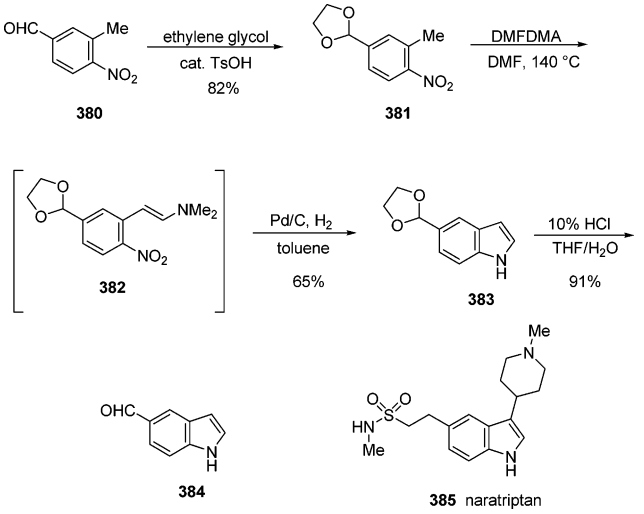
Ohkubo and co-workers reported the large-scale preparation of both 5- and 6-benzyloxyindole (**373**/**374**), which were utilized in the preparation of intermediate **376**. Indole **376** was further elaborated to the indolopyrrolocarbazole alkaloids acryriaflavins **377** and **378** (Scheme 83).[124] Reaction of **369** or **370** with DMFDMA in the presence of pyrrolidine was followed by the direct crystallization of **371** (94%) or **372** (91%) from the crude reaction mixture by addition of ethanol. Reductive cyclization with nickel boride/hydrazine monohydrate gave the desired indoles **373** and **374** in 86% and 94% yields, respectively. Indole **374** has also been employed in the multi-kilogram synthesis of the potent DNA topoisomerase I inhibitor **379**.[125]

Scheme 83



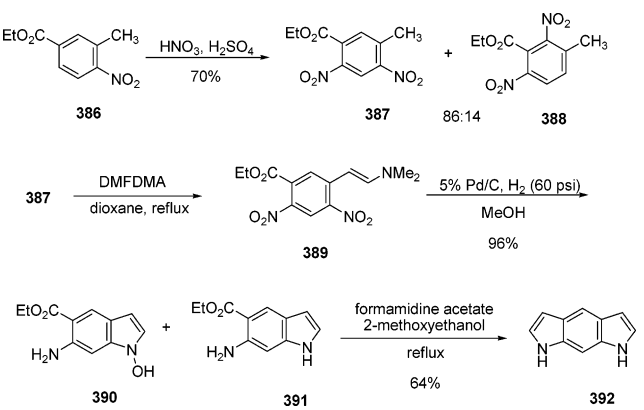
Simig and co-workers have demonstrated a new and practical synthesis of 5-formylindole **384** for the elaboration of a new manufacturing route to the antimigraine drug naratriptan (**385**) (Scheme 84).[126] The synthesis began by reaction of 3-methyl-4-nitrobenzaldehyde (**380**) with ethylene glycol in the presence of a catalytic amount of TsOH to give acetal **381** in 82% yield. Treatment of **381** with DMFDMA in DMF at 140 °C and subsequent catalytic hydrogenation of the nitro group with Pd/C afforded indole **383** in 65% yield. Hydrolysis of **383** with aqueous HCl furnished 5-formylindole **384** in 91% yield. According to the authors, the overall yield of 49% represents the best synthetic route currently available for the preparation of 5-formylindole.

Scheme 84

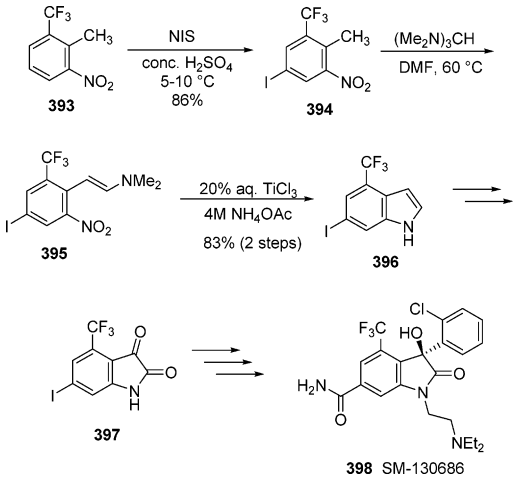


Showalter et al. reported an efficient route to indole **391** which was used for the preparation of the novel 1*H*-pyrrolo-[3,2-*g*]quinazoline ring system **392** (Scheme 85).[127] Nitration of ethyl 3-methyl-4-nitrobenzoate (**386**) gave a mixture (86:14) of regioisomers **387**/**388** where the desired regioisomer **387** was obtained in 70% yield by crystallization from 2-propanol. Condensation of **387** with DMF dimethylacetal in refluxing 1,4-dioxane gave intermediate **389**, which was not isolated but directly underwent cylization via catalytic hydrogenation with 5% Pd/C to afford indole **391** in 96% yield for the two steps. Indole **391** was reported to be contaminated with 4−10% of 1-hydroxyindole **390** but could be obtained in pure form by crystallization from aqueous MeOH. Subsequent reaction with formamidine acetate in refluxing 2-methoxyethanol provided the target compound **392**.

Scheme 85



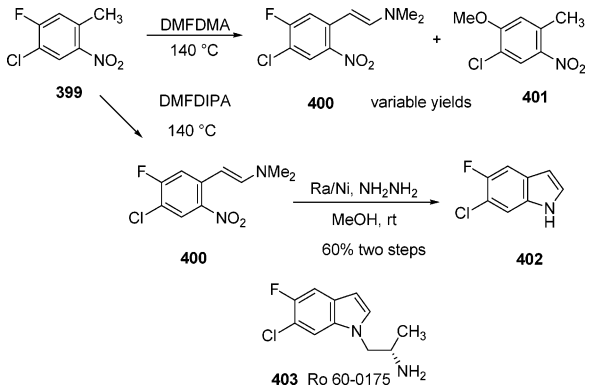
Scheme 86



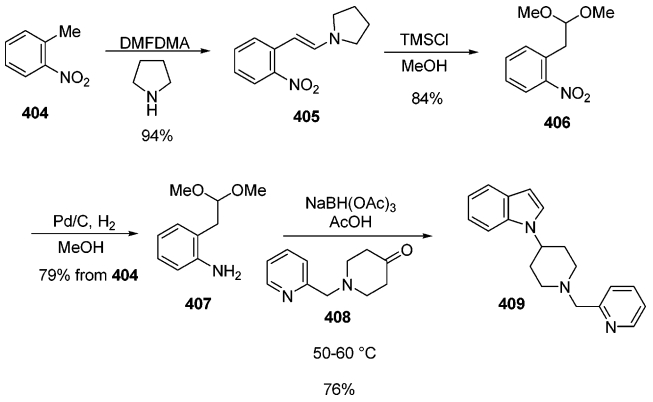
Nagata and co-workers required large quantities of 6-iodo-4-trimethylisatin **397**, which was the key intermediate in the synthesis of SM-130686 (**398**) (Scheme 86).[128] One of the preparative synthetic routes described in their paper utilized indole **396**, which was derived from commercially available 2-methyl-3-nitrobenzotrifluoride (**393**). Reaction of **393** with *N*-iodosuccinimide in 96% sulfuric acid gave **394** in 86% yield. Condensation of **394** with tris(dimethylamino)-methane[129] in DMF yielded enamine **395**, which was used directly in the reductive cyclization step. Reduction of the nitro group using buffered aqueous titanium(III) chloride was accompanied by simultaneous hydrolysis of the enamine and cyclization[130] to indole **396**, which occurred in 83% yield from nitrotoluene **393**. Indole **396** was converted in two synthetic steps to the required isatin **397** in 65% overall yield.

Duncton has reported the large-scale preparation of 6-chloro-5-fluoroindole (**402**) via a modified Leimgruber−Batcho reaction (Scheme 87).[131] Indole **402** is the heterocyclic core of the potent and selective 5-HT_{2c} receptor agonist Ro 60-0175 (**403**). Reaction of nitrotoluene **399** with DMF dimethylacetal at 140 °C under standard conditions afforded varying amounts of the methoxy-substituted side product **401** in addition to the desired enamine **400**. Reductive cyclization of this mixture with Raney nickel and hydrazine in methanol afforded indole **402**, which could not be separated from **401** without resorting to careful chromatographic separation. These problems were solved by simply condensing **399** with *N*,*N*-dimethylformamide diisopropylacetal (DMFDIPA); these conditions cleanly gave enamine **400** as the sole product. Subsequent reductive cyclization with Raney nickel/hydrazine yielded indole **402** in 60% overall yield from nitrotoluene **399**.

Scheme 87



Scheme 88

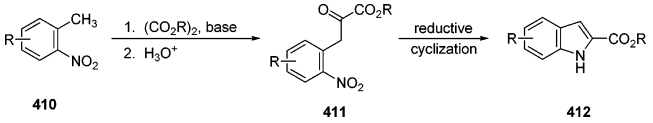


Faul and co-workers reported the large-scale preparation of *N*-(azacycloalkyl) indole **409** via the modified Leimgruber−Batcho synthesis originally described by Coe et al.[132] (Scheme 88).[133] Condensation of **404** with DMFDMA in the presence of pyrrolidine at 60 °C for 5 h gave the pyrrolidine enamine **405** in 94% yield. Methanolysis of **405** with trimethylsilyl chloride in MeOH afforded **406** in 84% yield. Catalytic hydrogenation of **406** with 5% Pd/C in MeOH furnished **407** in quantitative yield. The reductive amination of **407** was performed by addition of **408** to a solution of $NaBH(OAc)_3$ in AcOH at room temperature followed by heating to 50−60 °C for 24−48 h to effect the cyclization to indole **409**, that was isolated in 76% yield by crystallization from the crude reaction mixture after aqueous workup.

4.3. Reductive Cyclization of *o*-Nitrobenzylcarbonyl Compounds

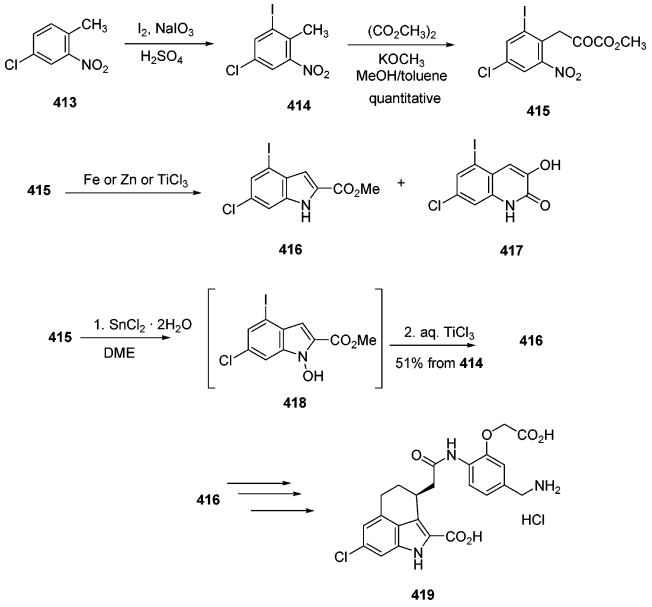
One of the oldest methods for the construction of indoles is reductive cyclization of *o*-nitrobenzylcarbonyl compounds.[134] The classic Reissert indole synthesis involves condensation of an *o*-nitrotoluene **410** with an oxalic ester to give *o*-nitrophenylpyruvate derivative **411** followed by reductive cyclization to indole-2-carboxylic acid derivatives **412** (Scheme 89).[11,135] While the Reissert indole synthesis has been utilized for the small-scale synthesis of a wide range of both natural and unnatural products, the general application of the Reissert indole synthesis for the large-scale synthesis of indoles has received limited attention.

Scheme 89



A modified Reissert procedure for the large-scale preparation of indole **416** was recently reported which was used in the preparation of the potent NMDA/glycine antagonist **419** (Scheme 90).[136] Chloronitrotoluene **413** was iodinated to provide iodide **414**. Treatment of **414** with dimethyl oxalate in the presence of potassium methoxide gave keto ester **415** in quantitative yield. Reduction of **415** with iron, zinc, or aqueous titanium trichloride yielded varying amounts of the desired indole **416** together with hydroxyquinolinone **417** as a significant byproduct (>20%). When tin(II) chloride dihydrate was employed as the reductant, *N*-hydroxyindole **418** was obtained exclusively. Conversion of **418** to indole **416** was effected in quantitative yield by reaction with

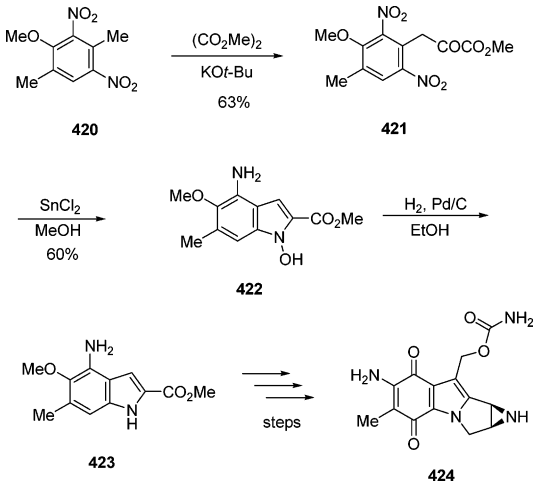
Scheme 90



aqueous $TiCl_3$. A one-pot procedure was adapted whereby reduction of **415** with tin(II) chloride dihydrate was followed by the addition of aqueous $TiCl_3$ to give indole **416** in 51% overall yield from **414**. Conversion to **419** was completed in 10 additional steps.

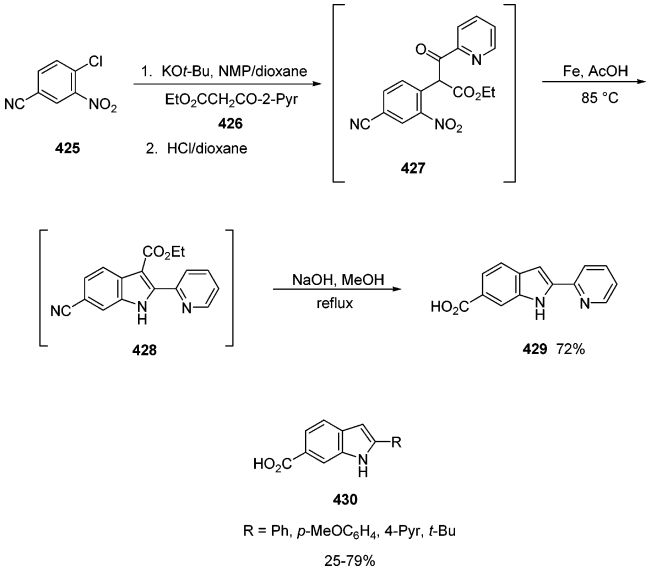
Jimenez and co-workers have reported the multigram preparation of indole **423** via a Reissert reaction and its use in the synthesis of the mitomycin derivative **424** (Scheme 91).[137] Reaction of 3,6-dimethyl-2,4-dinitroanisole (**420**) with dimethyl oxalate in the presence of KO*t*-Bu gave keto ester **421**, which was crystallized in 63% yield. Reductive cyclization of **421** with stannous chloride in MeOH gave exclusively *N*-hydroxyindole **422** in 60% yield where none of the regioisomeric indole resulting from cyclization of the *o*-nitrogroup was detected. This suggested that the least sterically hindered *p*-nitro group underwent reduction/cyclization prior to reduction of the more sterically hindered *o*-nitro group. Catalytic hydrogenation of **422** furnished indole **423** in quantitative yield, which was further elaborated to the target compound **424**.

Scheme 91



Gallou has disclosed an efficient and practical synthesis of 2-arylindole-6-carboxylic acid derivatives **430** via a modified Reissert indole synthesis.[138] The key transformation

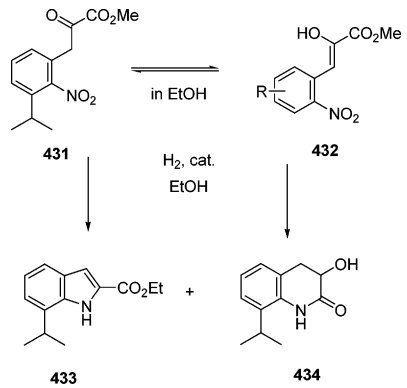
Scheme 92



involved an aromatic nucleophilic substitution (S_NAr) of aryl nitro chlorides with β-keto esters followed by a one-pot reductive cyclization/decarboxylation. As shown in Scheme 92, treatment of **425** first with β-keto ester **426** in the presence of KO-*t*Bu in NMP and quenching into HCl in dioxane furnished intermediate **427**, which was not isolated. Reductive cyclization of **427** by the direct addition of Fe/AcOH to the reaction mixture and heating to 85 °C for 4 h gave indole intermediate **428**. The crude ester was then subjected to decarboxylation (NaOH, MeOH, reflux) and concomitant hydrolysis of the cyano group to give indole **429** in 72% overall yield. The sequence was accomplished without any isolation of intermediates or chromatography. The methodology was also applied to the preparation of other indoles **430** with overall yields ranging from 25 to 79%. The authors also comment that, considering the operational simplicity and cost-effectiveness of the protocol, this method would be useful in the large-scale preparation of this class of indoles.

Murakami et al. examined the Reissert indole synthesis and discovered that reduction of 2-nitrophenylpyruvate esters **432** with either Pd/C in EtOH or PtO_2 in either EtOH or AcOH gave varying amounts of both the expected indole product **433** and 3-hydroxy-1,2,3,4-tetrahydro-2-quinolones **434** (Scheme 93).[139] They concluded that hydrogenation of

Scheme 93

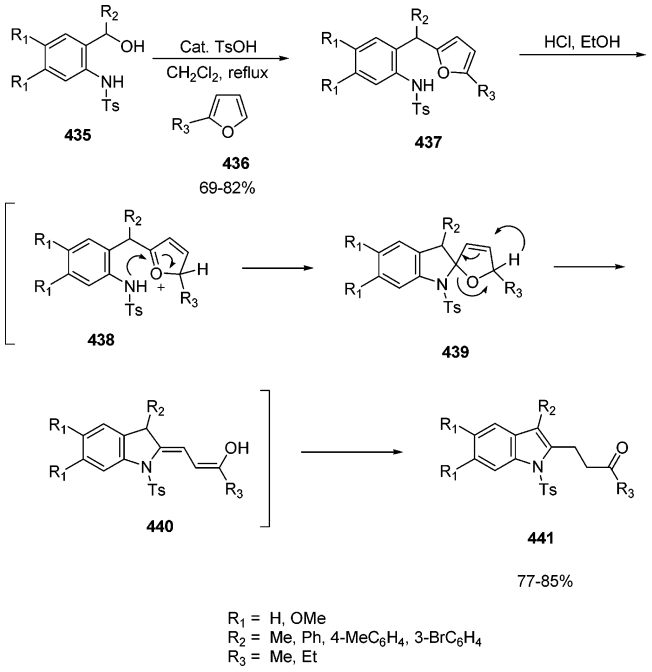


cat. = Pd/C	ratio **433**:**434**	Yield
5% Pd/C	90:10	81%
PtO_2	7:93	88%

2-nitrophenylpyruvate esters with 5% Pd/C in EtOH was the best conditions for the preparation of indoles by the Reissert indole synthesis. However, up to 10% of quinolone byproducts **435** was observed, as shown in the reduction of the sterically hindered 2-nitrophenylpyruvate **431**. Hydrogenation of the same substrate with PtO_2 gave a reversal in this selectivity, and quinolone **434** was obtained as the major product. It was proposed that reduction of the enol tautomer **432** was competitive under catalytic hydrogenation conditions, and the judicious choice of hydrogenation catalyst was crucial for control of the product distribution.

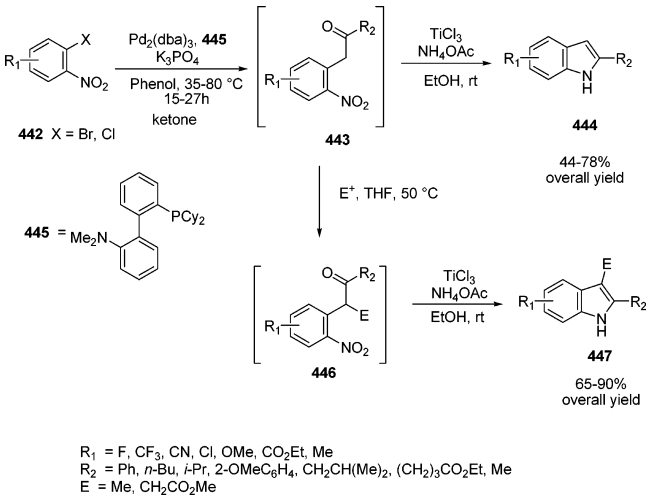
An extremely interesting acid-mediated indole ring closure of readily available *o*-tosylaminobenzylfurans **437** via a modified Reissert reaction (Scheme 94) has been demonstrated by Butin and co-workers.[140] Alkylation of either 2-methyl- or 2-ethylfuran **436** with *o*-tosylaminobenzyl alcohols **435** was conducted in the presence of a catalytic amount of *p*-TsOH in refluxing CH_2Cl_2 to provide the benzylfurans **437** in high yields. The products were obtained directly by crystallization from the crude reaction mixtures. When compounds **437** were heated in ethanolic HCl, protonation, cyclization, rearrangement, and tautomerization led to indoles **441** in good to excellent yields. The indole products were also isolated by direct crystallization from the crude reaction.

Scheme 94



The reductive cyclization of *o*-nitrobenzyl ketones for the synthesis of 2- or 2,3-substituted indoles has long been known to be a valuable method for the construction of indoles. However, this method has been severely limited by available methods for the synthesis of the prerequisite *o*-nitrobenzyl ketones. While there have been advances which give ready access to these starting materials,[141,142,143] the practical implementation of these methods for the large-scale preparation of indoles has not yet been realized. However, recent reports have surfaced for the preparation of *o*-nitrobenzyl ketones which should allow for the large-scale construction of highly substituted indoles from relatively simple precursors.

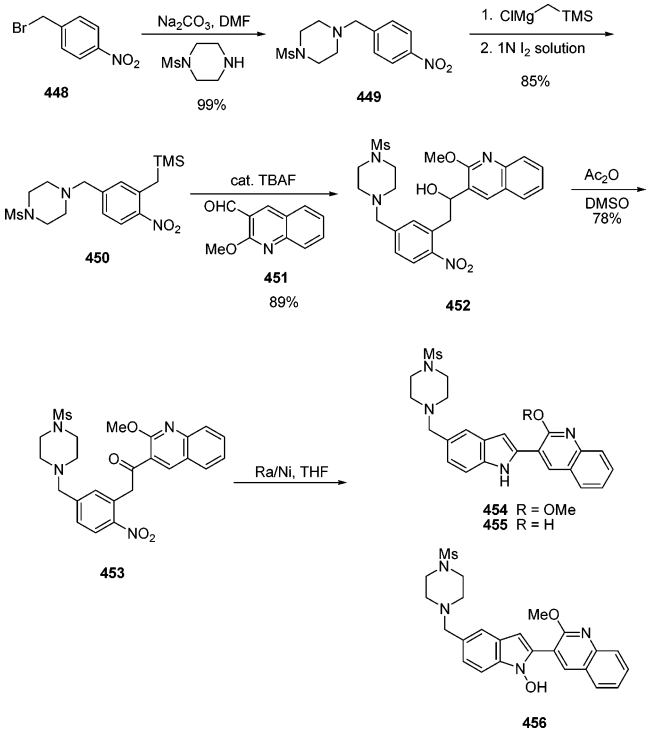
Scheme 95



Buchwald has developed an outstanding approach for the synthesis of both 2-substituted indoles **444** and 2,3-disubstituted indoles **447** starting from readily available 2-halonitrobenzenes **442** and methyl or cyclic ketones (Scheme 95).[144] Arylation of either 2-bromo- or 2-chloro-substituted benzenes **442** with a number of methyl and cyclic ketones in the presence of 1 mol % $Pd_2(dba)_3$, 4 mol % ligand **445**, 2.5 equiv of K_3PO_4, and 20 mol % phenol (or 4-methoxyphenol) in toluene at 35−50 °C for 15−27 h gave the intermediate *o*-nitrobenzyl ketones **443**. The use of a phenol additive in combination with the phosphine ligand was found to be crucial for the successful preparation of the *o*-nitrobenzyl ketone intermediates. In the absence of any phenol additive, low conversion to product was observed. Following an aqueous workup, reductive cyclization of **443** to the 2-substituted indole products **444** was accomplished with aqueous $TiCl_3$ in the presence of NH_4OAc in EtOH to furnish the indole products in moderate to excellent overall yields. It was also reported that direct addition of an electrophile such as MeI or methyl bromoacetate to the reaction mixture upon completion of the ketone arylation, followed by heating to 50 °C, yielded the alkylated ketone intermediates **446**. Reductive cyclization of crude **446** with aqueous $TiCl_3/NH_4$-OAc in EtOH gave access to 2,3-disubstituted indoles **447** in modest to excellent yields.

Another practical and attractive method for the reductive cyclization of ketone **453** to give the protected 1*H*-indol-2-yl-1*H*-quinolin-2-one ring system **454** of the potent KDR kinase inhibitor **455** has been described by Wong and coworkers (Scheme 96).[145] Reaction of silyl-nitro compound **450**, prepared in two steps from commercially available 4-nitrobenzyl bromide **448**, with aldehyde **451** in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) furnished alcohol **452** in 89% yield. Oxidation of **452** with Ac_2O/DMSO gave ketone **453**, which could be crystallized from the crude reaction mixture in 78% yield. The reductive cyclization of **453** was accomplished under highly optimized conditions employing hydrogenation over Raney nickel in order to minimize the formation of *N*-hydroxyindole **456**. Under these conditions, indole **454** was obtained in 90% isolated yield by crystallization from the crude reaction mixture. When Pd/C or Pt/C was employed as the reductant, *N*-hydroxyindole **456** became the major product. Acid hydrolysis of **454** provided the target compound **455** in near quantitative yield.

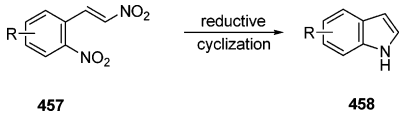
Scheme 96



4.4. Dinitrostyrene Reductive Cyclizations

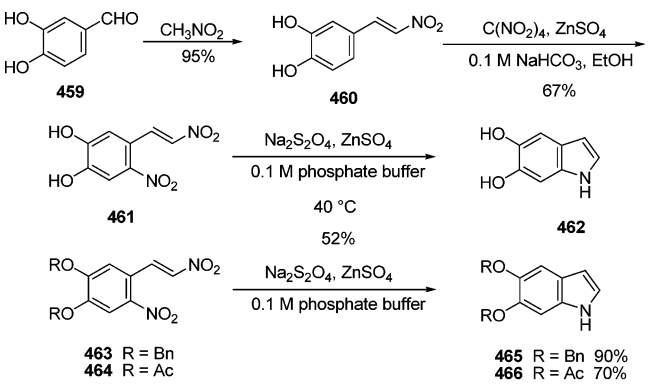
The reductive cyclization of *ortho*-β-nitrostyrenes **457** is known to be an effective and proven method for the construction of indoles where other methods have failed (Scheme 97). Related to the Leimgruber−Batcho indole synthesis, the prerequisite ortho-β-nitrostyrenes **457** are often prepared by condensation of an *o*-nitrobenzaldehyde with a nitroalkane or nitration of a benzaldehyde precursor. Reductive cyclization has usually been carried out under the standard reductive methods listed above.

Scheme 97



Prota and co-workers reported an expedient synthesis of 5,6-dihydroxyindole **462** which required no protecting groups or chromatographic purifications and took advantage of the reductive cyclization of *o*-β-nitrostyrene **461** (Scheme 98).[146]

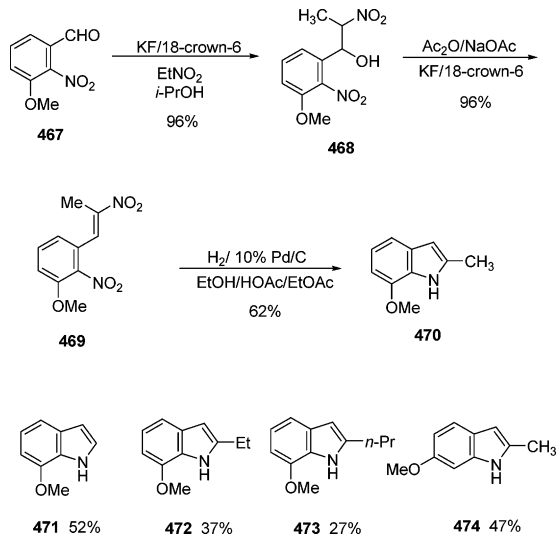
Scheme 98



The required precursor **461** was prepared in two steps from 3,4-dihydroxybenzaldehyde **459** in 67% overall yield. Treatment of **461** with sodium dithionite in a phosphate buffer (pH 4) at 40 °C in the presence of $ZnSO_4$ afforded the desired indole **462** in 52% yield. The use of $Na_2S_2O_4$ in the presence of Zn(II) ions was critical for the success of the reaction and reproducibly provided **462** in high purity, despite its pronounced instability. In a similar fashion, reaction of the protected precursors **463** and **464** under the identical reaction conditions gave indoles **465** and **466** in 90% and 70% yields, respectively.

Chen and Leftheris et al. reported a general, large-scale synthesis of 2-methyl-7-methoxyindole **470**, a common structural unit found in a number of biologically active compounds, by the reductive cyclization of β-methyl-3-methoxy-2,β-dinitrostyrene (**469**) (Scheme 99).[147] Attempts to prepare **469** by the direct condensation of commercially available 3-methoxy-2-nitrobenzaldehyde (**467**) with nitroethane, in the presence of either ammonium acetate or methylamine hydrochloride, gave low yields of **469** (<45%). The poor yields were presumably due to oligomerization or polymerization, and a stepwise preparation of **469** was developed. Treatment of **467** with nitroethane in the presence of potassium fluoride and 18-crown-6 at room temperature in 2-propanol gave the hydroxydinitro product **468** in 96% isolated yield. Subsequent reaction of **468** with acetic anhydride and sodium acetate in the presence of potassium fluoride and 18-crown-6 furnished **469** in 96% yield. The reductive cyclization was carried out by hydrogenation of **469** with 10% Pd/C in a solvent combination of EtOAc, acetic acid, and EtOH to afford 2-methyl-7-methoxyindole (**470**) in 62% yield. Intermediates **468** and **469** and indole **470** were isolated in a straightforward manner by direct crystallization from the crude reaction mixtures. The synthesis of indoles **471**−**474** via the same synthetic strategy was also described.

Scheme 99

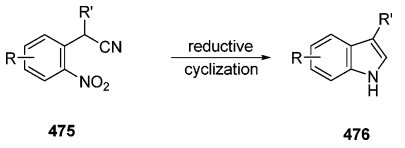


4.5. Reductive Cyclization of *o*-Nitrophenylacetonitriles

The reductive cyclization of *o*-nitrophenylacetonitriles **475** for the preparation of indoles is also a useful method for the construction of both 2,3-unsubstituted and 3-substituted indoles **476** (Scheme 100).[148−150]

Recently, Walkington and co-workers utilized this process for the preparation of >100 kg of 6-(trifluoromethyl)indole

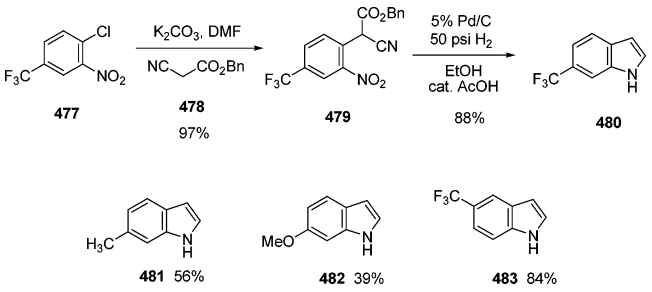
Scheme 100



475 476

480 (Scheme 101).[151] Nucleophilic aromatic substitution of 4-chloro-3-nitrobenzotrifluoride (**477**) with benzyl cyanoacetate (**478**) in a suspension of K_2CO_3 in DMF gave compound **479** in 97% yield after precipitation of the product from the crude reaction mixture by the addition of water. The wet cake was used directly in the reductive cyclization step. Hydrogenation of crude **479** with 5% Pd/C in EtOH involved a sequence of several transformations (i.e. reduction of the nitro group, hydrogenolysis of the benzyl ester, decarboxylation, cyclization, and elimination of ammonia) and gave indole **480** in 88% isolated yield. The authors commented that the exact order of these events for this remarkable transformation remained unclear. The synthesis of indoles **481**−**483** via the same synthetic strategy was also described in the paper.

Scheme 101



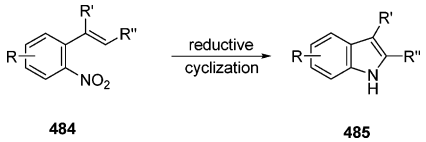
477 478 97% 479 88% 480

481 56% 482 39% 483 84%

4.6. Reductive Cyclization of *o*-Nitrostyrenes

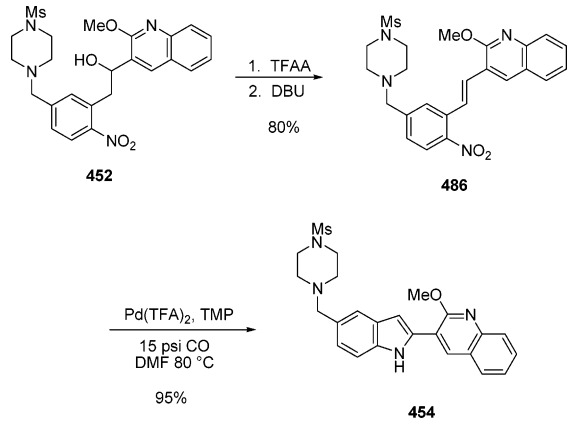
The reductive cyclization of nitrostyrene compounds **484** (Scheme 102) for the formation of substituted indoles has received considerable attention since the pioneering work of Cadogan[152] and Sundberg[153] first described the formation of indoles by the deoxygenation of aromatic nitro compounds with trivalent phosphorus compounds (typically triethyl phosphite). While this reaction is broad in scope, the extreme reaction conditions (>150 °C), formation of both *N*-hydroxy- and *N*-ethoxyindole byproducts, and generation of large amounts of phosphorus waste render this transformation impractical for the process chemist. The transition metal-catalyzed reductive cyclization of aromatic nitro compounds employing carbon monoxide as the stoichiometric reductant has emerged in recent years as a highly versatile method for the construction of indoles.[154−157] Due to the harsh reaction conditions of many of these approaches which employ high pressures of CO, high reaction temperatures, or high catalyst/ligand loadings, these methods have remained only academic. However, recent developments have now surfaced which make this extremely efficient transformation a reality for the large-scale preparation of indoles.

Scheme 102



484 485

Scheme 103

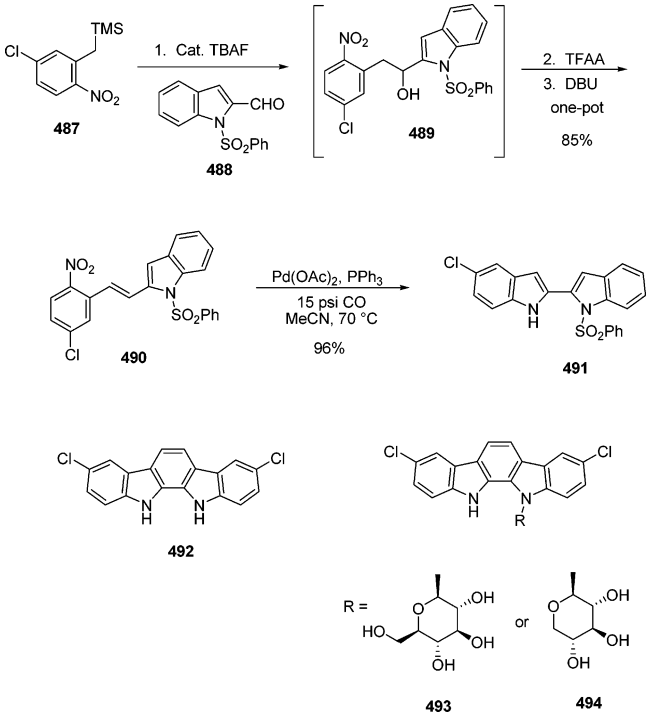


452 486 454

Kuethe and co-workers described the preparation of the highly functionalized indole **454,** which was subsequently deprotected to give the potent and selective KDR kinase inhibitor **455** (Scheme 103).[158] Treatment of the crude alcohol **452** (Scheme 96) with trifluoroacetic anhydride (TFAA) followed by elimination of the resulting trifluoroacetate with DBU at 60 °C in a one-pot operation afforded exclusively the *trans*-nitrostyrene **486**. The product was isolated in 80% yield by direct crystallization from the crude reaction mixture. Under optimized reaction conditions which employed 0.1 mol % $Pd(TFA)_2$, 0.7 mol % 3,4,7,8-tetramethylphenanthroline (TMP) in DMF, at 80 °C, and 15 psi of CO, indole **454** was isolated by crystallization from the crude reaction mixture in analytically pure form and in 95% isolated yield.

The same group has also utilized this methodology for the preparation of a number of 2,2′- and 2,3′-bisindoles **491**, which were subsequently used in the synthesis of indolocarbazole aglycon **492** and glycosides **493** and **494** (Scheme 104).[159] For example, reaction of TMS-nitro compound **487** and indole 2-carboxaldehyde **488** with a catalytic amount of TBAF afforded intermediate alcohol **489**. Direct addition of TFAA to the reaction mixture followed by elimination of

Scheme 104



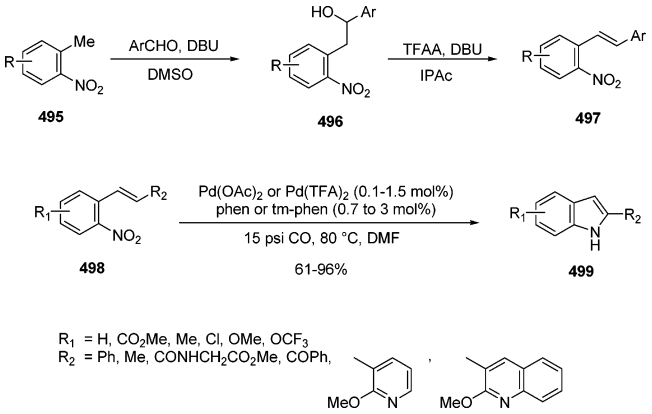
487 488 489 85%

490 96% 491

492

493 494

Scheme 105



the corresponding trifluoroacetate with DBU at 60 °C, in a one-pot procedure, afforded exclusively the *trans*-nitrostyrene **490** in 85% overall yield. Reductive cyclization of **490** utilizing $Pd(OAc)_2$, PPh_3 in MeCN at 70 °C, and 15 psi CO furnished the unsymmetrical 2,2′-bisindole **491** in 96% yield.

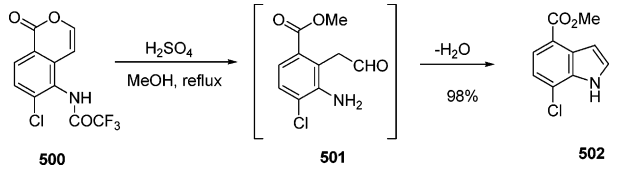
Davies and Smitrovich et al. have reported the application of the highly active catalyst system utilized in Schemes 103 and 104 for the reductive cyclization of other *ortho*-nitrostyrenes under mild conditions.[160] The required *ortho*-nitrostyrenes used in this study either were commercially available or were prepared by the synthetic sequences outlined in Schemes 103 and 104, or by a DBU-mediated addition of an *ortho*-nitrotoluene to benzaldehydes (Scheme 105). Optimization of the reaction parameters for the reductive cyclization of *ortho*-nitrostyrenes **497** was accomplished in an extremely rapid fashion employing a parallel pressure reactor (PPR).[161] Reductive cyclization of **498** in the presence of 0.1−1.5 mol % $Pd(OAc)_2$ or $Pd(TFA)_2$, 0.7−3 mol % 1,10-phenanthroline (phen), or 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen), at 15 psi CO at 80 °C for 16 h in DMF, afforded good to excellent yields of the corresponding indoles **499**. The indole products could be obtained by simply filtering the crude reaction mixture and crystallization of the product. Since the only byproduct of the reaction is CO_2, the reductive cyclization of *o*-nitrostyrenes under these conditions offers significant economic and environmental advantages.

5. Miscellaneous Processes

5.1. Cyclization of 2-Aminophenethyl Aldehydes

Alper and Nguyen required several hundred grams of methyl 7-chloroindole-4-carboxylate **502** and devised an elegant, chromatography-free synthesis which was based on the intramolecular cyclization of a masked 2-aminophenethyl alcohol (Scheme 106).[162] Trifluoroacetamide **500** was prepared in four synthetic steps, in 23% yield, from readily available starting materials. The key indolization reaction involved treatment of **500** with H_2SO_4 in refluxing methanol, which afforded the desired indole **502** in nearly quantitative

Scheme 106



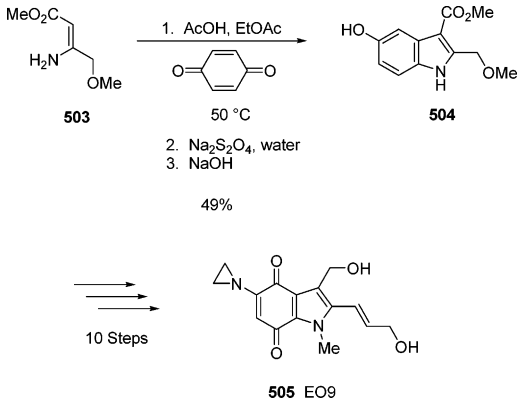
yield after aqueous workup. Presumably, methanolysis of the isocoumarin functionality was followed by rapid tautomerization to **501** and cyclization to the corresponding indole. This reaction closely resembles the Watanabe indole synthesis involving the oxidative cyclization of 2-aminophenethyl alcohols.[163]

5.2. Nenitzescu Indole Synthesis

The classical Nenitzescu indole synthesis involves the condensation of *p*-benzoquinones with β-aminocrotonic esters and is a highly regioselective method for the formation 1,2,3-trisubstituted-5-hydroxyindoles.[164,165,166] While this method provides a rapid means of preparing functionalized 5-hydroxindoles from simple, readily accessible starting materials, isolated yields are typically low, presumably due to an elaborate mechanism which provides numerous possibilities for side reactions. Despite this limitation, applications of the Nenitzescu indole synthesis for the large-scale production of indole substrates continue to be reported.

Kasai et al. reported the large-scale preparation of indole **504**, which was further elaborated to the antitumor indolequinone EO9 (**505**) (Scheme 107).[167] Reaction of **503**, prepared from 4-methoxyacetoacetate and ammonia, with 3 equiv of benzoquinone, in EtOAc at 50 °C containing 3.5 equiv of AcOH, for 16 h was followed by the addition of $Na_2S_2O_4$ and adjustment of the pH to 7.5 using aqueous NaOH. The resulting sodium salts of hydroquinone were filtered off, and indole **504** was obtained in 49% yield after recrystallization. Indole **504** was then converted to EO9 in 10 additional steps.

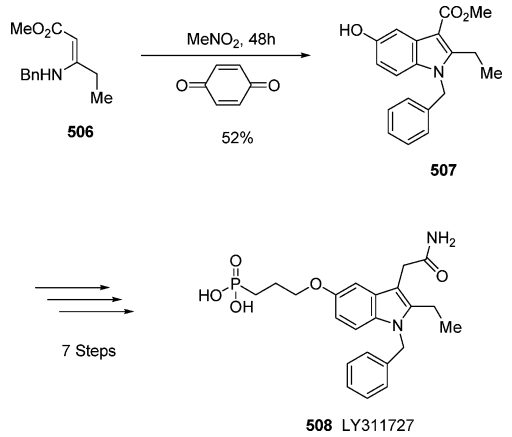
Scheme 107



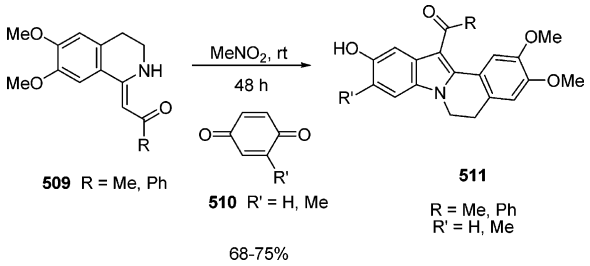
Martinelli and co-workers utilized a Nenitzescu-based approach for the large-scale synthesis of LY311727 (**508**), a potent and selective s-PLA_2 inhibitor (Scheme 108).[168] Treatment of crude **506**, prepared by condensation of methyl propionyl acetate and benzylamine, with 1.4 equiv of benzoquinone in nitromethane for 48 h furnished indole **507**, which precipitated from the crude reaction mixture in 69% yield. The crude product was slurried in hot 1,2-dichloroethane to give pure **507** in 52% overall yield. The preparation of **508** was accomplished in seven additional steps.

Ila and Junjappa and co-workers have reported the preparation of the indolo[2,1-*a*]isoquinolines **511** employing a convergent Nenitzescu reaction between tetrahydroisoquinoline-derived enaminones **509** and benzoquinones **510** (Scheme 109).[169] Reaction of equimolar amounts of **509** with benzoquinones **510** in nitromethane for 2 days gave exclusively the desired indolo[2,1-*a*]isoquinolines **511** in 68−75% yield.

Scheme 108

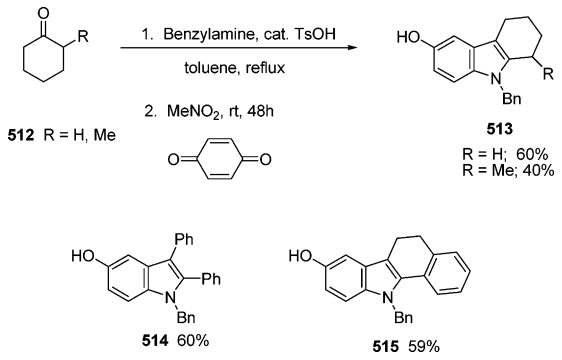


Scheme 109



Lewis and co-workers recently disclosed the extension of the Nenitzescu reaction to the benzylimines of simple ketones, thus proving that a stabilized enamine tautomeric form of a β-dicarbonyl system is not a structural prerequisite for the Nenitzescu reaction (Scheme 110).[170] For example, preparation and reaction of the benzylimines of cyclohexanone and 2-methylcyclohexanone (**512**) in essentially a one-pot procedure with benzoquinone afforded indole derivatives **513** in 60% and 40% yields, respectively. In a similar fashion, reaction of deoxybenzoin benzylamine gave indole **514** in 60%, and reaction of the benzylimine of α-tetralone furnished indole **515** in 59% yields.

Scheme 110

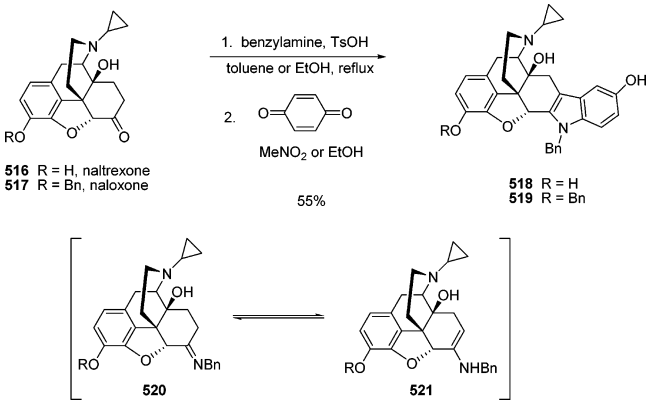


In the same paper, Lewis and co-workers utilized this approach for the preparation of the potent and selective δ-opioid receptor antagonists **518** and **519** (Scheme 111). For example, treatment of naltrexone (**516**) or naloxone (**517**) with benzylamine in the presence of TsOH followed by reaction with benzoquinone in either nitromethane or EtOH afforded indoles **518** and **519** in 55% yield.

5.3. Hydroformylation of Anilines

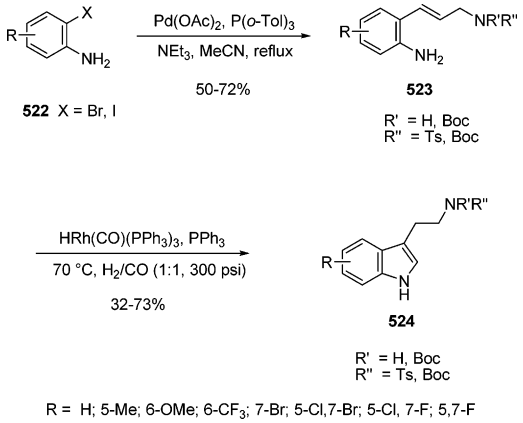
Dong and Busacca have developed a two-step synthesis of tryptamines and tryptophols from 2-haloanilines **522**

Scheme 111



involving a palladium-catalyzed Heck reaction followed by a rhodium-catalyzed hydroformylation/cyclization/dehydration sequence (Scheme 112).[171] Reaction of a variety of haloanilines with either *N*-tosylallylamine or *N*,*N*-di-Boc-allylamine under standard Heck conditions (5 mol % $Pd(OAc)_2$, 10 mol % $(o\text{-Tol})_3P$, NEt_3, MeCN, reflux) afforded the corresponding Heck adducts **523** in modest to good yields. The hydroformylation/cyclization/dehydration of functionalized anilines **523** was accomplished by reaction with 5 mol % $HRh(CO)(PPh_3)_3$ and PPh_3, at 70 °C for 70 h in the presence of H_2/CO (1:1, 300 psi) to give the tryptamines in modest to good yield. When the sequence was carried out using allyl alcohol, tryptophol was produced.

Scheme 112



5.4. Intramolecular Heck Cyclizations

The intramolecular Heck reaction has found much use in the synthesis of carbazoles, indoles, oxindoles, and indo-

Scheme 113

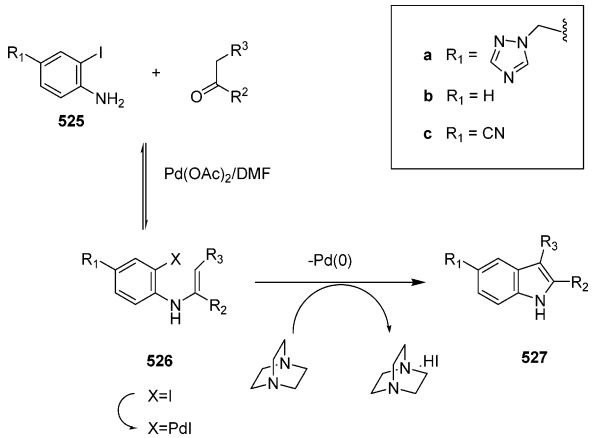
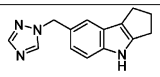
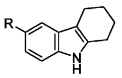
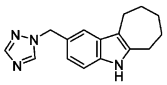
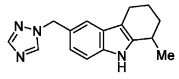
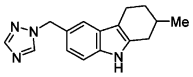
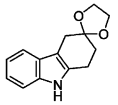
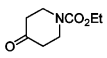
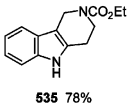
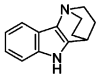
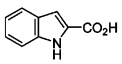
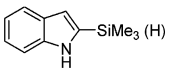


Table 4[a]

Entry	Iodoaniline	Ketone	Indole
1	**525a**		 **528** 53%
2	**525b** **525c**		 **529** R = H, 77% **530** R = CN, 61%
3	**525a**		 **531** 72%
4	**525a**		 **532** 68%
5	**525a**		 **533** 65%, 8% regioisomer
6	**525b**		 **534** 55%
7	**525b**		 **535** 78%
8	**525b**		 **536** 55%
9	**525b**	Pyruvic acid	 **537** 82%
10	**525b**		 **538** 64%

[a] Data taken from ref 173.

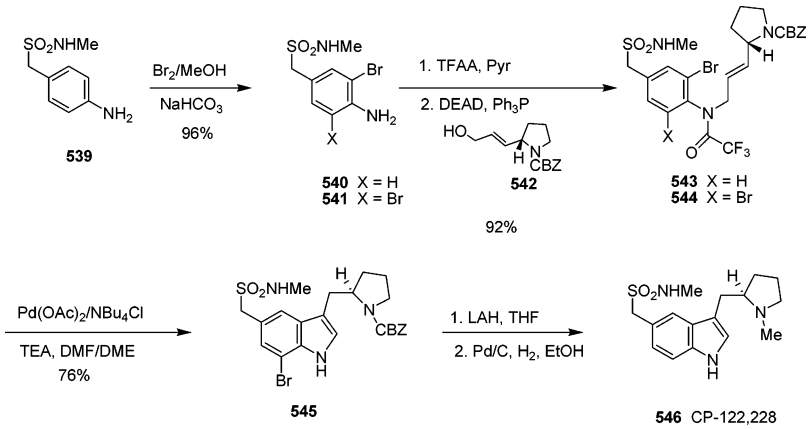
lines.[172] However, relatively few reports of large-scale indole syntheses utilizing the intramolecular Heck reaction were found in the literature over the last 10 years. The first example of a very straightforward and direct coupling of *o*-iodoanilines with ketones via palladium catalysis to provide indoles was described by Chen and co-workers (Scheme 113).[173] The reaction pathway was assumed to be formation of enamines **526** followed by an intramolecular Heck reaction to provide the indoles **527**. The choices of base and solvent were found to be critical to the success of the reaction and to minimize byproduct formation. When a nonoxidizable amine base such as DABCO was used in DMF as solvent, good yields of the intramolecular Heck cyclized products were obtained.

The reaction was generally tolerant of substitution on the aniline ring with a number of cyclic ketones, pyruvic acid, and acetylsilane (Table 4). Addition of magnesium sulfate (1.5 equiv) was found to promote the annulation in some cases (entries 1, 2b, 4, 8, and 10), presumably aiding enamine formation via removal of water. While this method was very effective for the Heck cyclization employing aryl iodides, the use of aryl bromides was not discussed.

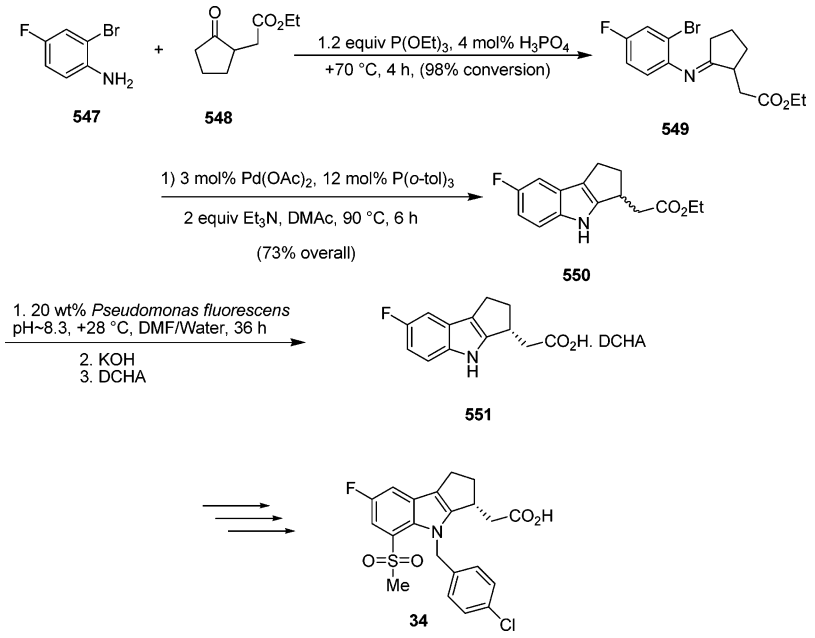
Macor and co-workers required a large-scale synthesis of the anti-migraine agent CP-122,288 (**546**) (Scheme 114).[174] In their original synthesis, Heck cyclization of a monobromoaniline **540** gave the intermediate **543** in good yield. The problematic and low yielding formation of monobromoaniline **540** led the authors to investigate the Heck reaction on the more easily prepared dibromide **541**. Thus, dibromination of the aniline **539** using Br_2/MeOH/$NaHCO_3$ gave dibromide **541** in 96% yield. Trifluoroacetylation and Mitsunobu coupling with the allylic alcohol **542** gave the Heck substrate **544** in 92% yield. Intramolecular Heck cyclization using $Pd(OAc)_2$ and NBu_4Cl in the presence of triethylamine gave the highly substituted indole **545** (X = Br) in a very respectable 76% yield.[175] Reduction of the CBZ moiety and hydrogenolysis of the bromine at the 7-position provided CP-122,228 (**546**). It was noted that this highly efficient Heck cyclization of dibromoanilines may provide a general synthesis of 7-bromoindole derivatives and, via further transformation, of more complex 7-substituted indoles not easily accessed via other methods.

The large-scale synthesis of a key intermediate useful for the preparation of DP antagonist **34** was recently described by Shafiee et al. (Scheme 115).[176] The approach involved the enzymatic hydrolysis of racemic indole ester **550** and subsequent functionalization of the chiral indole acid **551**. The synthesis of **550** was carried out by condensation of 2-bromo-4-fluoroaniline (**547**) with the keto ester **548** using $P(OEt)_3$ as the dehydrating agent to afford the relatively hydrolytically stable imine **549** in >98% yield. Intramo-

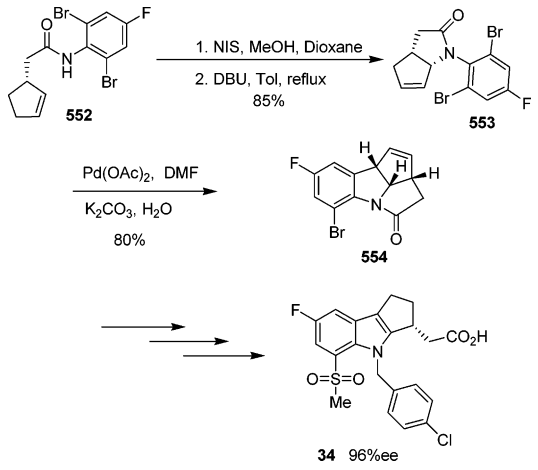
Scheme 114



Scheme 115



Scheme 116



lecular Heck cyclization using $Pd(OAc)_2$ and P(*o*-tol)$_3$ in DMAc provided indole ester **550** in 76% yield. Efficient enzymatic hydrolysis of **550** with *Pseudomonas fluorescens* and removal of the (*S*)-acid by basic workup was followed by basic hydrolysis to give the (*R*)-indole acid **551**, which was isolated as the dicyclohexylamine (DCHA) salt in 45% overall yield (Scheme 2).[176] Introduction of the methyl sulfone and benzyl moieties provided the DP antagonist **34**, in 65% overall yield from **551**, where the whole sequence was carried out on a 25−50 kg scale.

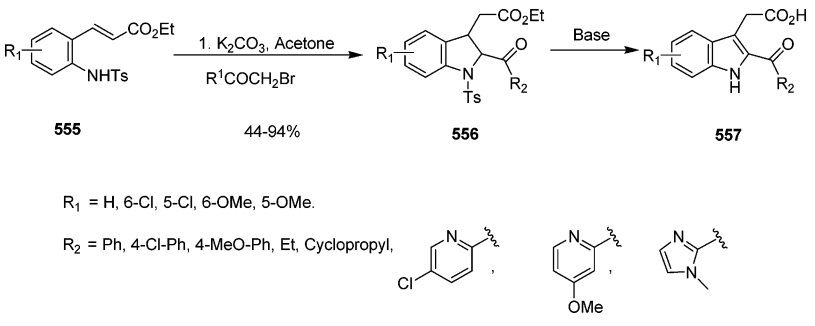
A very elegant asymmetric synthesis of the same DP antagonist **34** using an intramolecular Heck reaction to construct the tricyclic core was described by Campos et al. (Scheme 116).[177] Although not fully developed for large-scale use, the key indole-forming sequence is worthy of note. The amide **552**, prepared via Trost[178] asymmetric allylic alkylation of cyclopentenyl acetate and subsequent amidation with dibromofluoroaniline, was subjected to iodolactamization and elimination to provide the bicyclic lactam Heck precursor **553** in 85% yield over two steps. Palladium-catalyzed Heck reaction under a number of conditions reported in the literature gave incomplete conversion to **554**.[171,179] Complete conversion to **554** was obtained when the intramolecular Heck reaction was carried out employing ligand-free conditions using $Pd(OAc)_2$. Tetracycle **554** was converted to **34** in six steps with retention of optical purity.

5.5. Intramolecular Michael Addition/Elimination

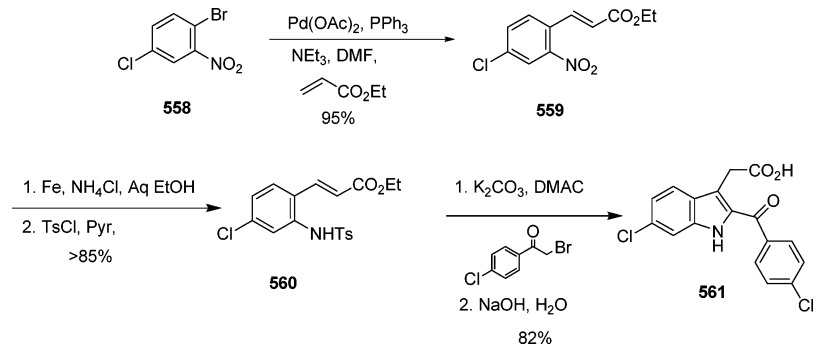
A practical, one-pot 2-acylindole-3-acetic acid synthesis via an intramolecular Michael addition was described by Stevens and co-workers (Scheme 117).[180] Treatment of sulfonamides **555** with bromoacetophenones and potassium carbonate generated the indolines **556**. Subsequent addition of a stronger base such as DBU or Cs_2CO_3 promoted elimination of toluenesulfinic acid and aromatization to afford the indoles **557** in excellent yields.

This methodology was applied to the very simple and highly efficient, large-scale synthesis of the selective cy-

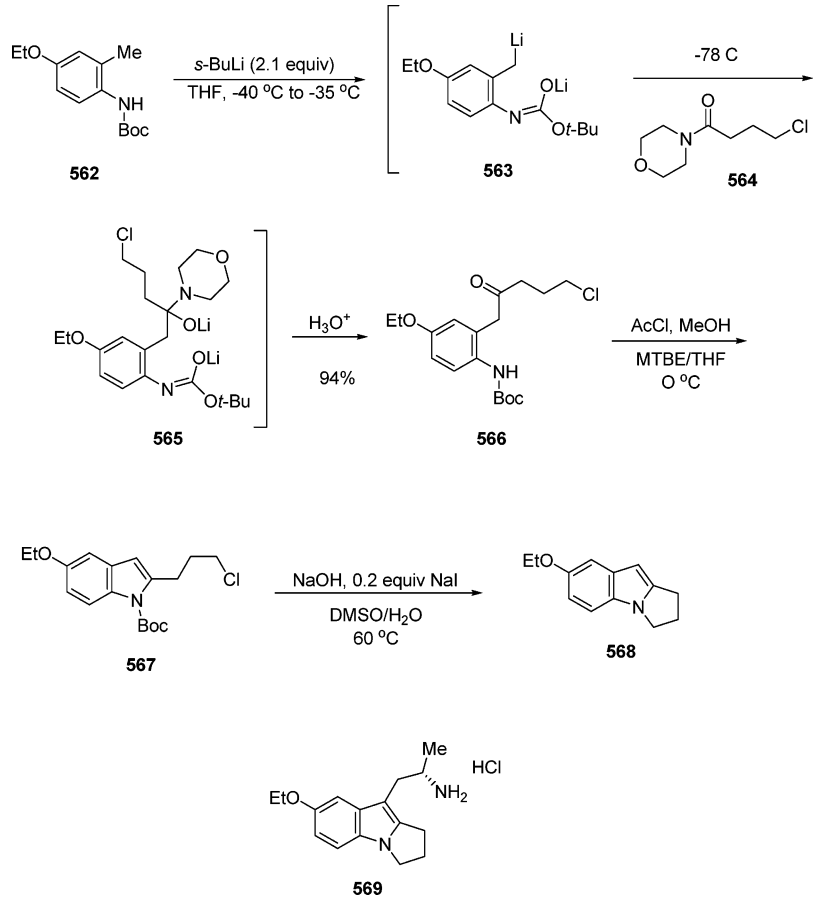
Scheme 117



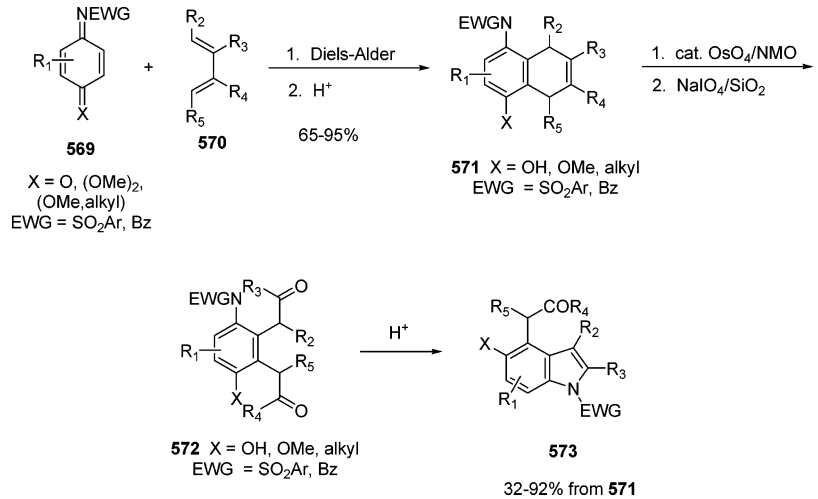
Scheme 118



Scheme 119



Scheme 120



clooxygenase-2 (COX-2) inhibitor **561** as described by Caron et al. (Scheme 118).[181] Thus, Heck reaction of 2-bromo-5-chloronitrobenzene (**558**) with ethyl acrylate gave the cinnamate **559** in 95% yield. Reduction and protection of the resultant aniline furnished sulfonamide **560**. Alkylation of **560** with α-bromoacetophenone using K_2CO_3 in DMAC afforded the dihydroindole intermediate. Addition of sodium hydroxide to the same pot promoted both the elimination of the toluenesulfinic acid and hydrolysis of the ester to provide acid **561** in 82% overall yield.

5.6. Madelung–Houlihan Indole Synthesis

Although the Madelung−Houlihan indole synthesis[182] has seldom been utilized for the large-scale preparation of indoles, a recent application deserves mention (Scheme 119).[183] A large-scale route to tricyclic indole **568**, which is the synthetic precursor to the 5-HT_{2C} receptor agonist **569**, was developed where the key step in the process involved the Madelung−Houlihan indole synthesis between aniline **562** and morpholine amide **564**. Treatment of **562** with *sec*-butyllithium at −40 °C afforded the dilithiated intermediate **563**. Cooling to −78 °C and reaction with amide **564** gave the tetrahedral intermediate lithium *N*,*O*-semiacetal **565**, which upon acidic workup afforded ketone **566** in 94% yield. Cyclization to indole **567** was accomplished by treating ketone **566** with in situ generated HCl in MeOH. Reaction of **567** with NaOH/NaI in DMSO/H_2O resulted in cleavage of the *N*-Boc group and cyclization to give the target compound **568** in 92% isolated yield from ketone **566**. The overall sequence did not require any chromatographic purifications and gave **568** in excellent overall yield.

5.7. Plieninger Indole Synthesis

The Plieninger indole synthesis involves the conversion of a 2-aminodihydronaphthalene to a 4-substituted indole. The lack of available synthetic methods for the preparation of the starting materials has severely limited the utility of this reaction.[184] Recently, Kerr and co-workers extended the synthetic utility of the Plieninger indole reaction and applied the method toward the synthesis of 5-hydroxy-, alkoxy-, and alkyl-4-alkylindoles **573** (Scheme 120).[185] Diels−Alder cycloaddition of quinoid imine derivatives **569** with various butadienes **570** provided the cycloadducts **571** in good to excellent yield. Oxidative cleavage of the resulting double bond yielded a dicarbonyl intermediate **572**, which upon treatment with anhydrous acid cyclized to give highly functionalized indoles **573**. The overall sequence only required two purifications and represents an expedient method for the construction of indoles of type **573**.

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