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A review on indole synthesis from nitroarenes: classical to modern approaches

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Indoles are highly privileged and versatile heterocyclic pharmacophores that play a crucial role in natural product synthesis, drug discovery, pharmaceuticals, and medicinal chemistry. This review provides a comprehensive analysis of various synthetic approaches to indoles with a particular emphasis on nitroarenes as key precursors. Although indoles and their derivatives have been extensively explored for their bioactivity in natural and pharmacological contexts, several classical synthetic methodologies remain underutilized. Traditionally, indole synthesis from *ortho*-substituted nitroarenes has been achieved through methods such as Bartoli, Reissert, Cadogan, and Leimgruber–Batcho approaches. However, recent advancements have introduced novel one-pot and tandem strategies that effectively integrate redox and hydrogenation reactions to streamline indole formation. Emerging photochemical and electrochemical techniques have also enabled the selective conversion of nitroarenes into indoles bearing well-defined functional groups. Beyond their intrinsic biological activity, indoles serve as valuable intermediates for further derivatization into compounds such as isatins and oxindoles, expanding their synthetic potential. These advancements continue to enhance the synthetic toolkit for constructing biologically active indoles, with far-reaching applications in pharmaceuticals, agrochemicals, and advanced materials.

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1. Introduction

The exploration, development, and synthesis of heterocyclic frameworks have long been captivating due to their remarkable biological and pharmacological properties.[1–6] Heterocycles play a vital role in everyday life, offering various applications across various fields. Nitrogen-bearing heterocycles have long been a key focus in diverse fields due to their remarkable biological activities.[7,8] Over the past several decades, *N*-based heterocycles have garnered significant attention from synthetic chemists and chemical biologists due to their unique ability to bind with various receptors and their presence in numerous natural products and medicinally important compounds.[9–12] Five-membered nitrogen-containing heterocyclic systems are widely distributed in nature and play a significant role in medicinal chemistry, pharmaceuticals, agrochemicals, dyes, chemosensors, and materials. Additionally, they serve as essential intermediates in organic synthesis.[7,13–21] Among these scaffolds, indole is a privileged pharmacophore, serving as a core structure in many biologically active molecules.[22–35]

Indole units are key structural motifs in natural products and synthetic macrocycles with distinct biological activities. Moreover, indoles interact with enzymes and receptors through non-covalent interactions and contribute to treatments for cancer, neurological disorders, and cardiovascular diseases.[26,36–43] They serve as versatile building blocks in heterocycle synthesis and are present in alkaloids, hormones, and therapeutic agents. Indoles exhibit potent anticancer, antimicrobial, and anti-inflammatory properties.[44–47] Structurally, they form the core of serotonin, a critical neurotransmitter.[48,49] Their broad pharmacological relevance includes antiviral applications, such as SARS-CoV-2 3CL protease inhibition. Representative biologically active indole scaffolds are shown in Fig. 1.[50–53] In recent years, there has been growing interest in developing macrocyclic frameworks with heteroaryl systems.[54–57] Notably, indole-based macrocyclic scaffolds are widely prevalent in biologically significant molecules, highlighting their central role in modern drug discovery and development.[58–69] Indole-based drugs approved by the FDA play various roles in medical treatments (Fig. 1).[22,28,70–79] Numerous strategies have been developed and widely employed for constructing indoles and their macrocycles.[80]

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To date, limited reactions have been reported for easily accessible greener protocols with efficient yields.[81] Herein, we report some of the important and well-established classical named reactions for indole synthesis, such as the Kanematsu indole synthesis,[82] Mori indole synthesis,[83] Buchwald indole synthesis, Bartoli indole synthesis, Bischler indole synthesis, Fischer indole synthesis, Hemetsberger indole synthesis, Julia indole synthesis, Larock indole synthesis, Leimgruber indole synthesis, Madelung indole synthesis, Nenitzescu indole synthesis, Reissert indole synthesis, Fukuyama indole synthesis, Gassman indole synthesis, Sundberg indole synthesis, *etc*.[84] Among these, various protocols lead to the formation of indoles in one-pot and multistep operations (Fig. 2).[85] However, the various classical approaches are well known for the synthesis of indoles *via* single-step as well as multistep reactions. Among these, some of the reaction conditions afford high yields of challenging indole derivatives. However, in addition to classical reactions, transition metal-catalyzed protocols have also been developed for indole synthesis, including those performed under microwave-assisted conditions.[85a,e] In this review, we have attempted to cover the most significant approaches for the synthesis of indoles from nitroarenes and their analogues. The report encompasses one-pot, multi-step, and multicomponent reactions. Additionally, we have included the synthesis of *N*-hydroxyindoles, owing to their facile transformation into indoles. All these methodologies proceed with intramolecular annulation, where the five-membered ring is newly generated *via* an intramolecular as well as a coupling reaction, followed by intermolecular annulation.

2. Diverse approaches for the synthesis of indoles from nitroarenes

2.1. Vicarious nucleophilic substitution (VNS) approach for indole synthesis *via ortho*-functionalization of nitroarenes

In this synthetic process, nitrobenzene is converted into 2-nitrophenylacetonitrile and 4-nitrophenylacetonitrile (10 : 1 ratio) with the aid of 2-chloroacetonitrile as a base. This category belongs to VNS reaction, where the nucleophilic displacement of hydrogen of nitroarenes with carbanion produces *ortho*- and *para*-substituted products. Herein, it involved in the synthesis of indoles *via* VNS approach followed by an annulation reaction, which is commonly denoted as Mąkosza indole synthesis, *cf*. Scheme 1.[86a,86b] The reductive annulation of indole synthesis using 2-nitrobenzonitrile intermediates is also known as the Pschorr–Hoppe indole synthesis.[87] Furthermore, the isolated crude mixture was employed for a hydrogenation reaction using 10% Pd/C in ethyl acetate. The *ortho*-reduced nitro group undergoes annulation with the nitrile group and then eliminates ammonia *via* a reductive elimination process and produces an indole derivative with an overall two-step reaction yield of 24%.

The following heterocycles are highly important synthons for the synthesis of medicines,[88] natural products, perfumes, agrochemicals, *etc*.[89–94] The synthesis of 6-(pentafluorosulfanyl)-1*H*-indole from pentafluoro(3-nitrophenyl)-λ^6-sulfane was a chaotic protocol due to the four-step synthesis and cost-ineffective method (Scheme 2a). Hence, a modified methodology has been accomplished for the synthesis of indoles

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Dr Ajeet Chandra has completed his doctoral degree in oxidative transformation using hypervalent iodine(v) reagents. He completed his BSc and MSc programs from TDPG College, Jaunpur, in affiliation with VBSPU Jaunpur, and the University of Allahabad, Prayagraj, Uttar Pradesh (UP), respectively. In pursuit of his research interests, he enrolled in a doctoral program at IIT Delhi. Due to his interest in pure organic synthesis, he moved to IIT Kanpur and completed his doctoral program under the supervision of Prof. J. N. Moorthy. Later, he joined as an institute postdoctoral fellow at IIT Bombay and explored sulfonyl phthalides and asymmetric amines. Presently, Dr Chandra is a Research Professor in the Department of Information Display at Kyung Hee University (KHU), Seoul, South Korea. With his interest in organic synthesis, he is exploring organic materials for device applications in the orientation of commercialization purposes for real-world display applications.

Suresh C. Yadav

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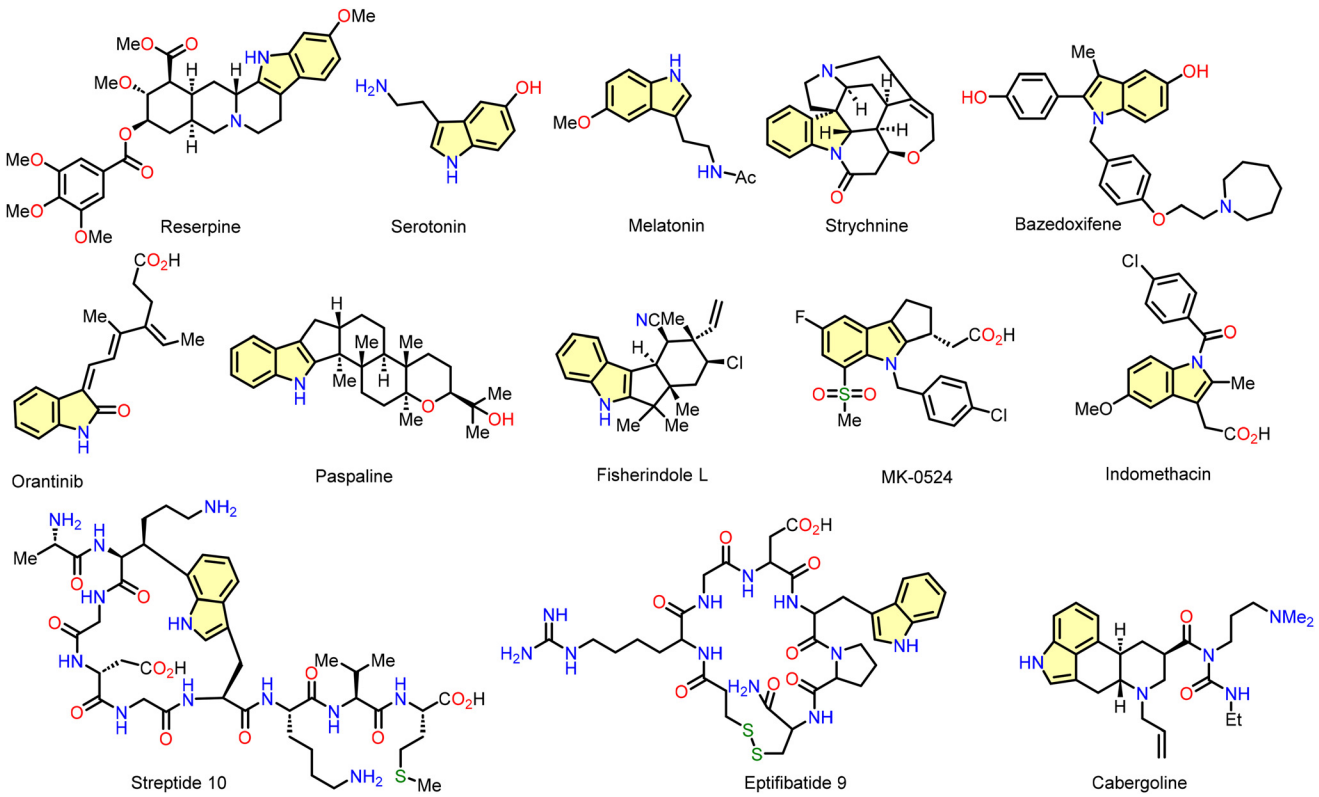


Fig. 1 Biologically relevant indole-based heterocycles.

Subba Rao Cheekatla

Dr Subba Rao Cheekatla, born in Bobbillanka village, Andhra Pradesh, India, earned his master's degree in organic chemistry from Andhra University. He completed his PhD in synthetic organic chemistry at IIT Bombay, Mumbai, under Prof. Sambasivarao Kotha. Subba worked as a research associate at IIT Palakkad before joining Korea University College of Medicine as a postdoctoral fellow under the supervision of Prof. Jun-Seok Lee. His research focuses on diverse heterocycles, cage hydrocarbons, aryl/heteroaryl fused macrocycles, and designing fluorescent probes for chemical proteomics and biological applications.

Abhijeet Kumar

Dr Abhijeet Kumar obtained his B.Sc. (Hons.) and M.Sc. from Banaras Hindu University (BHU), India. Later he moved to R&D (API) division to get industrial experience at Dr Reddy's Laboratory, Hyderabad. After obtaining industrial exposure and experience, he moved to IIT Kanpur to purse his Ph.D. under the supervision of Prof. M. L. N. Rao. There, he developed various efficient metal-catalysed protocols for cross-coupling reactions to synthesize important heterocyclic molecules. Furthermore, he joined a faculty position for a short tenure at the National Institute of Technology, Raipur, and then joined to the Department of Chemistry, Mahatma Gandhi Central University, in 2016 as an Assistant Professor. Presently, he is involved in both teaching and research. Currently, he is teaching common chemistry and green chemistry as elective papers. He has published various research and review articles in reputed national and international journals.

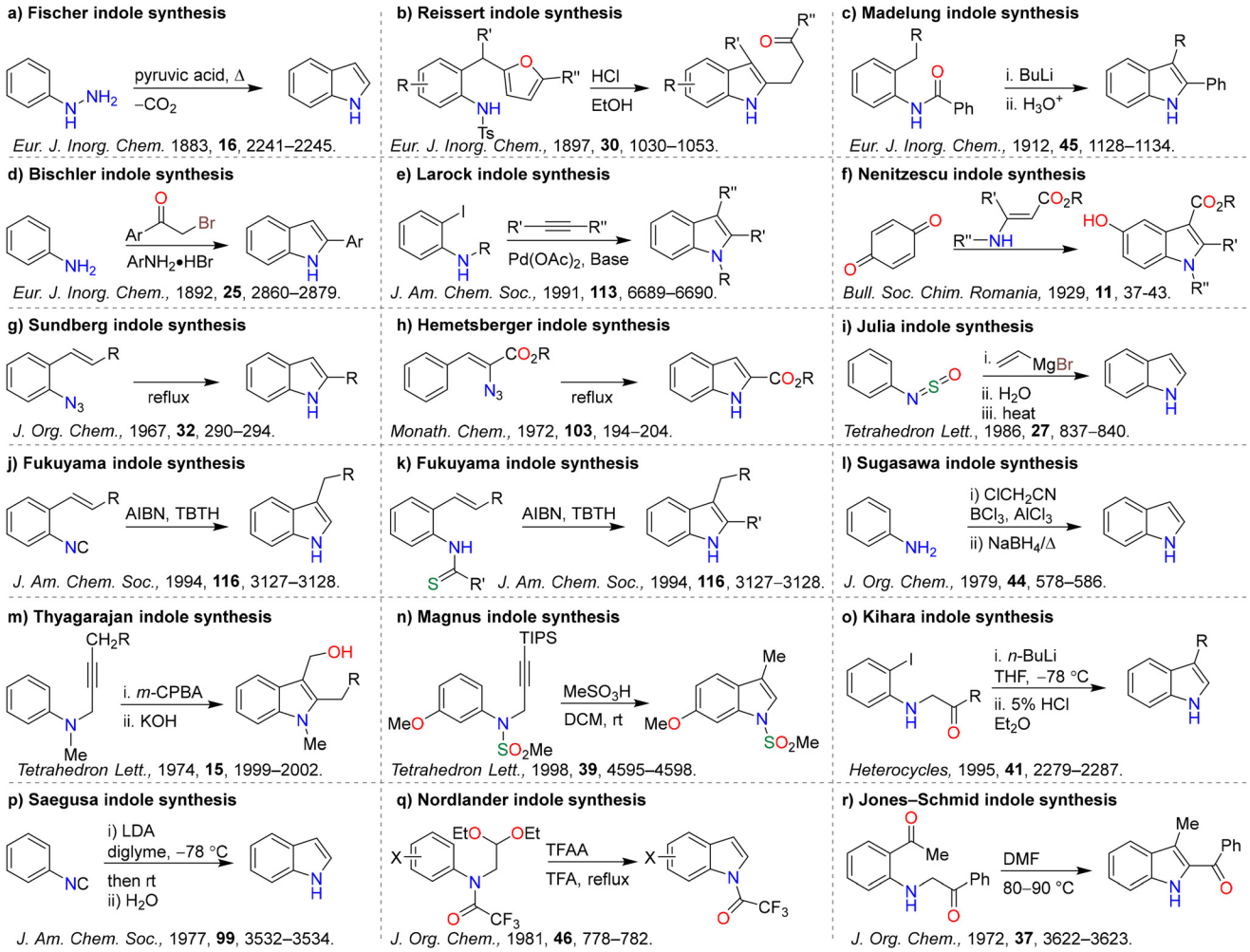
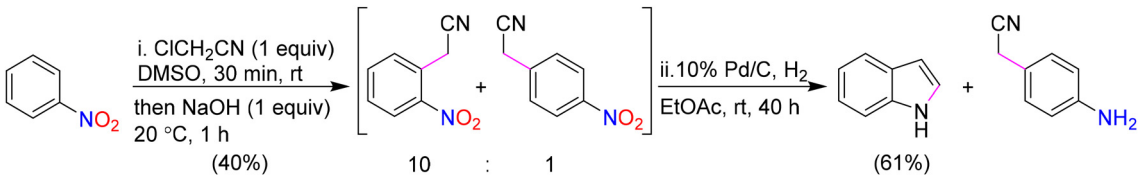


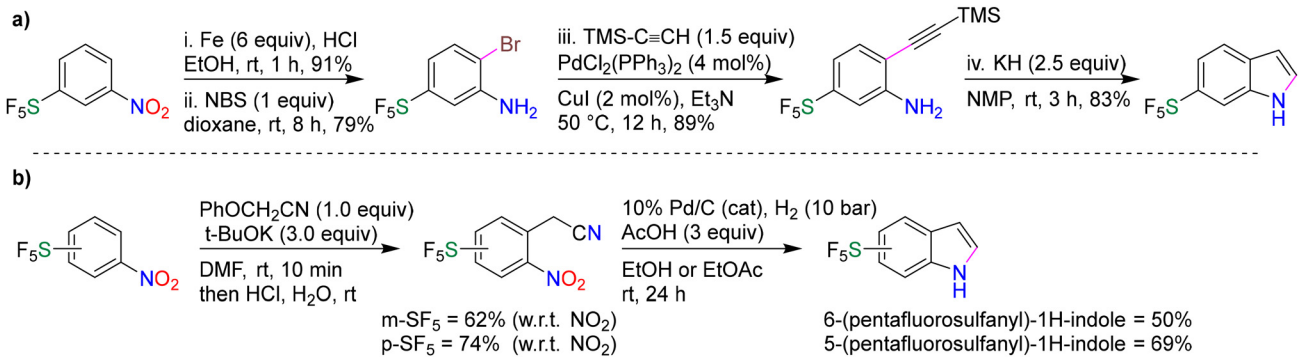
Fig. 2 Classical approaches for the synthesis of indoles.



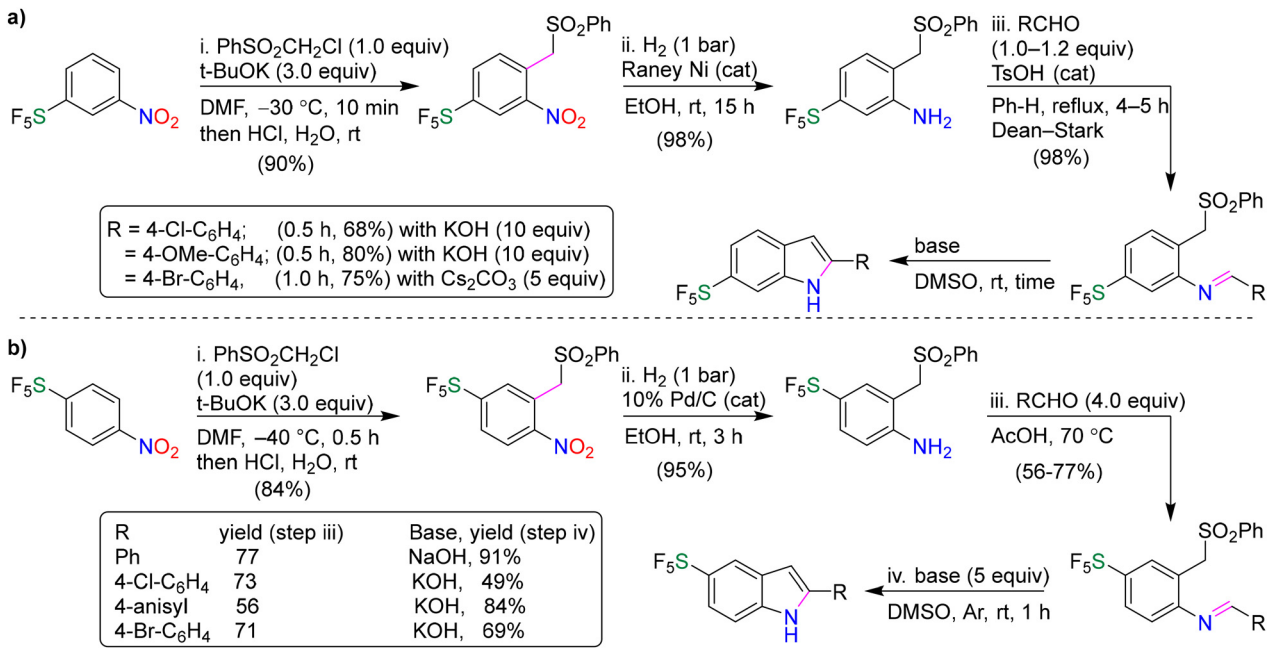
Scheme 1 VNS reaction using chloroacetonitrile followed by hydrogenation.

from pentafluoro(4/3-nitrophenyl)-λ^6-sulfane within two steps with the help of 2-phenoxyacetonitrile in a basic medium and hydrogenation with hydrogen gas and Pd/C (Scheme 2b).[95] Although the overall yield was lower than that of the previous method, this approach remains attractive due to its simplicity, reduced reaction time, and cost-effectiveness.[96] The reaction of pentafluoro(3-nitrophenyl)-λ^6-sulfane with 2-phenoxy acetonitrile affords VNS products as a mixture of both *ortho*- and *para*-derivatives in a ratio of 85 : 15; 73%, whereas the reaction of pentafluoro(4-nitrophenyl)-λ^6-sulfane ends up with only the *ortho*-VNS product with a high yield of 74%. Among these, the conversion of pentafluoro(4-nitrophenyl)-λ^6-sulfane to 5-(pentafluorosulfanyl)-1*H*-indole leads to a high reaction yield due to the good to excellent yield of each step, *cf.* Scheme 2.

An alternative strategy for synthesizing 2-aryl 5/6-(pentafluorosulfanyl)indoles[96,97] has been explored by using the reagent chloromethyl phenyl sulfone instead of 2-phenoxyacetonitrile (Scheme 2b) in a basic medium (Scheme 3).[95] This approach involves a reduction with Raney® Ni or Pd/C catalysed hydrogenation, followed by imine formation with an aldehyde and an annulation reaction leading to the formation of indole analogues. The choice of base plays a crucial role in determining product yields. Herein, the high stoichiometric amounts of KOH or Cs_2CO_3 mediated annulation in the last



Scheme 2 VNS reaction using 2-phenoxyacetonitrile followed by hydrogenation.



R	yield (step iii)	Base, yield (step iv)
Ph	77	NaOH, 91%
4-Cl-C_6H_4	73	KOH, 49%
4-anisyl	56	KOH, 84%
4-Br-C_6H_4	71	KOH, 69%

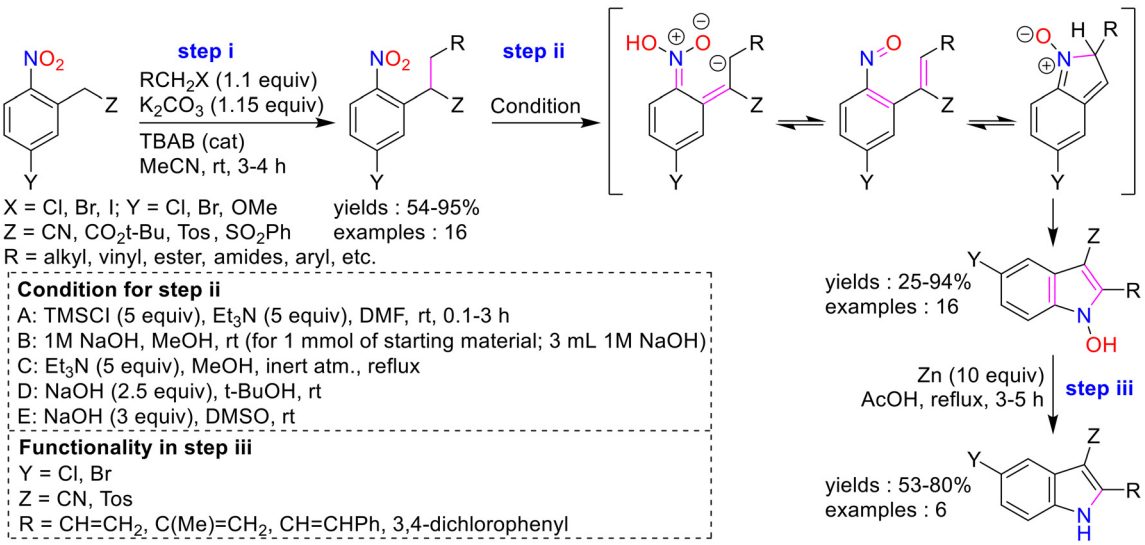
Scheme 3 VNS reaction using chloromethyl phenylsulfone as the key step for indole synthesis.

step, resulting in indole yields of 68–80%, and indole formation depends on the involvement of the aryl group during the annulation and aromatization reaction (Scheme 3a).

Notably, the synthesis involving 4-nitro(pentafluorosulfanyl)benzene, with annulation in the fourth step under inert conditions with KOH, resulted in a significantly higher yield than that of reactions conducted under aerial conditions. Similarly, when benzaldehyde was subjected to annulation using NaOH, product yields of 77% and 91% were observed under aerobic and inert conditions, respectively (Scheme 3b). These findings underscore the impact of reaction conditions on efficiency and selectivity in the synthesis of pentafluorosulfanyl-substituted indoles.

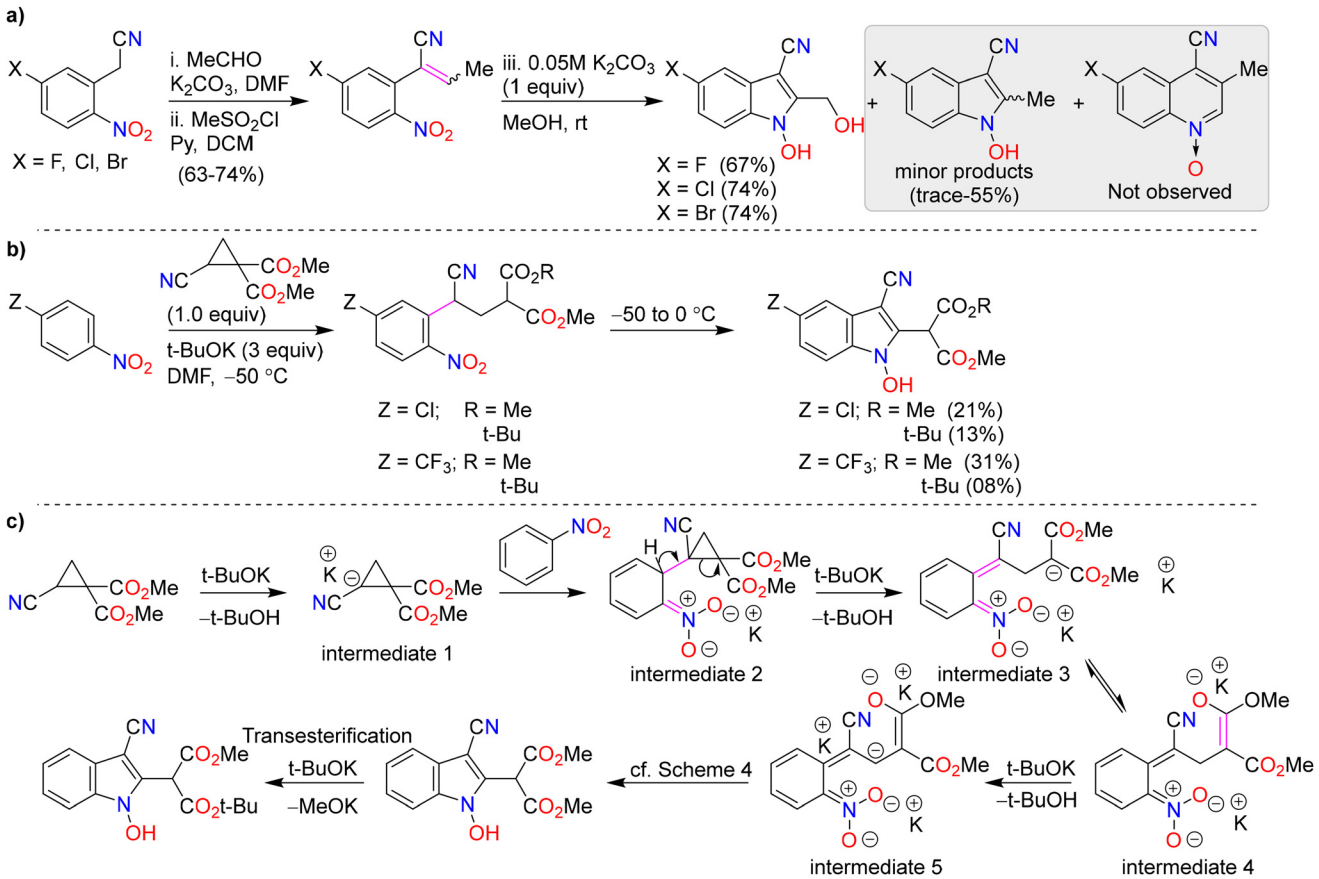
Later on, the VNS has been fixed by the previous reaction protocol[86] and it was subjected to an alkylation reaction in step i[98] to achieve the highly 2-substituted *N*-hydroxyindoles as the end products of step ii, and this process was utilized by Wróbel and Mąkosza in 1997.[99] During the exploration of step ii, various basic conditions were employed for the annulation reaction and NaOH was found to be better than that using the ester functionality. Finally, the hydroxyindole was subjected to a deoxygenation reaction using the Zn/AcOH protocol under reflux conditions, offering moderate to excellent yields (Scheme 4).[99,100]

The following examples also proceeded with a VNS reaction as a key step, which was explored for the synthesis of *N*-hydroxyindoles as the end products. Wróbel and Mąkosza reported that 4-halo-nitrobenzene underwent a VNS reaction with chloroacetonitrile followed by condensation with ethanal which afforded 2-(5-halo-2-nitrophenyl)but-2-enenitrile.[101] Annulations in a strongly basic medium (5 M NaOH) in methanol led to the formation of quinoline *N*-oxide derivatives as



Scheme 4 Higher indole synthesis *via* the cascade of benzyl functionalization, intramolecular annulation and deoxygenation reactions.

products, and when lowering the concentration of the base (0.1 M NaOH) and using the mixed solvent system MeOH : DMSO, the major product was the 5-halo-*N*-hydroxy-2-(hydroxymethyl)-indole-3-carbonitrile derivative. Furthermore, they have made a successful attempt to get the desired product, 5-halo-*N*-hydroxy-2-methyl-indole-3-carbonitrile, with the help of potassium carbonate in methanol at room temperature (Scheme 5a). The tuning of indole derivatives bearing



Scheme 5 Various approaches for the synthesis of 2,3-disubstituted indoles.

electron-deficient substituents at the C-2 position has been explored through reactions involving dimethyl 2-cyanocyclopropane-1,1-dicarboxylate under mild basic conditions at very low temperatures, followed by gradual warming up to 0 °C.[102] The limitation of the reactions was found to be the formation of the transesterification products (methoxyl exchanged with the *t*-butoxyl group) along with the desired products (Scheme 5b). Mechanistically, after the deprotonation of an acidic proton from the cyclopropane ring *ortho*-addition with nitrobenzene occurs and it offers the sequence of intermediates 1 to 5, which further leads to the formation of *N*-hydroxyindole derivatives as shown in step ii of Scheme 4. Due to the excess base and butanol, the transesterification products were also formed (Scheme 5c). Furthermore, the hydroxyindoles can easily be converted into indoles as shown in step iii of Scheme 4.

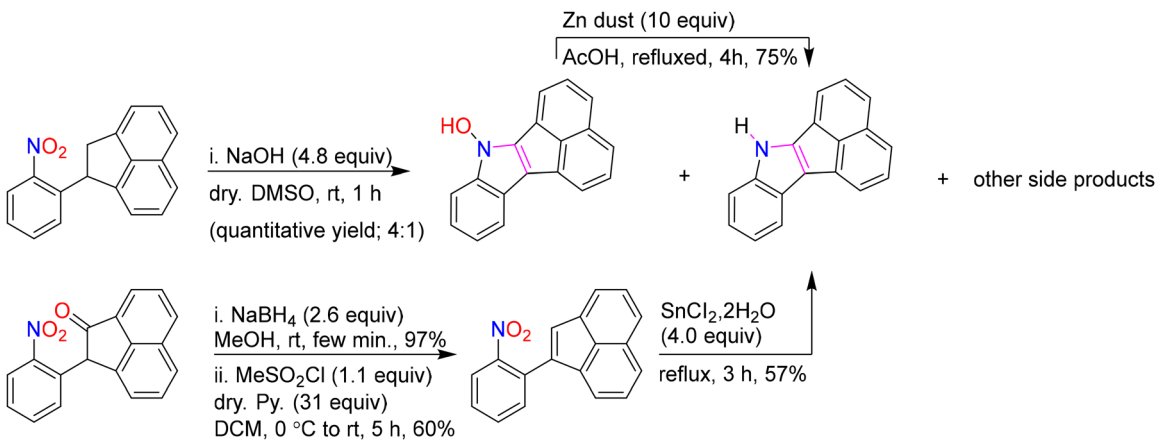
Wróbel and Mąkosza explored a challenging approach for the synthesis of 7*H*-acenaphtho[1,2-*b*]indole from 1-(2-nitrophenyl)-1,2-dihydroacenaphthylene using NaOH at ambient temperature.[100] During the reaction, they observed the formation of major products in a 4 : 1 ratio of 7*H*-acenaphtho[1,2-*b*]indol-7-ol to 7*H*-acenaphtho[1,2-*b*]indole, along with minor side products. To enhance the yield, they treated the reaction mixture with zinc dust and successfully increased the yield of the desired product to 75%. To simplify this process, an alternative route was developed starting from 2-(2-nitrophenyl) acenaphthylen-1(2*H*)-one, which underwent carbonyl reduction and dehydration to yield the key intermediate 1-(2-nitrophenyl)acenaphthylene.[99] Subsequent treatment with stannous chloride dihydrate resulted in the formation of 7*H*-acenaphtho[1,2-*b*]indole with a 57% yield (Scheme 6).

Mąkosza and coworkers reported a novel approach for the synthesis of indole derivatives to mimic the naturally occurring nitrogen-containing alkaloids batzellines, isobatzellines, damirones, discorhabdins, *etc*.[103,104] They accomplished the synthesis of the indole ring starting from the synthesized 4,6-dinitroguaiacol with the help of 2-phenoxy acetonitrile *via* the VNS approach and a methylation reaction followed by methylene functionalization upon sequential treatment with dimethyl sulfate and ethyl bromoacetate under basic conditions. Furthermore, the hydrogenation of the achieved product with a palladium chloride/iron reagent system and hydrogen gas in the presence of a polar mixed-solvent system afforded an indole derivative with a yield of 48% (Scheme 7). Similarly, two distinct intermediate products were isolated under identical reaction conditions but at different temperatures: intermediate I (at 0 °C, 7 h) and intermediate II (at 30 °C, 7 h), with good yield.

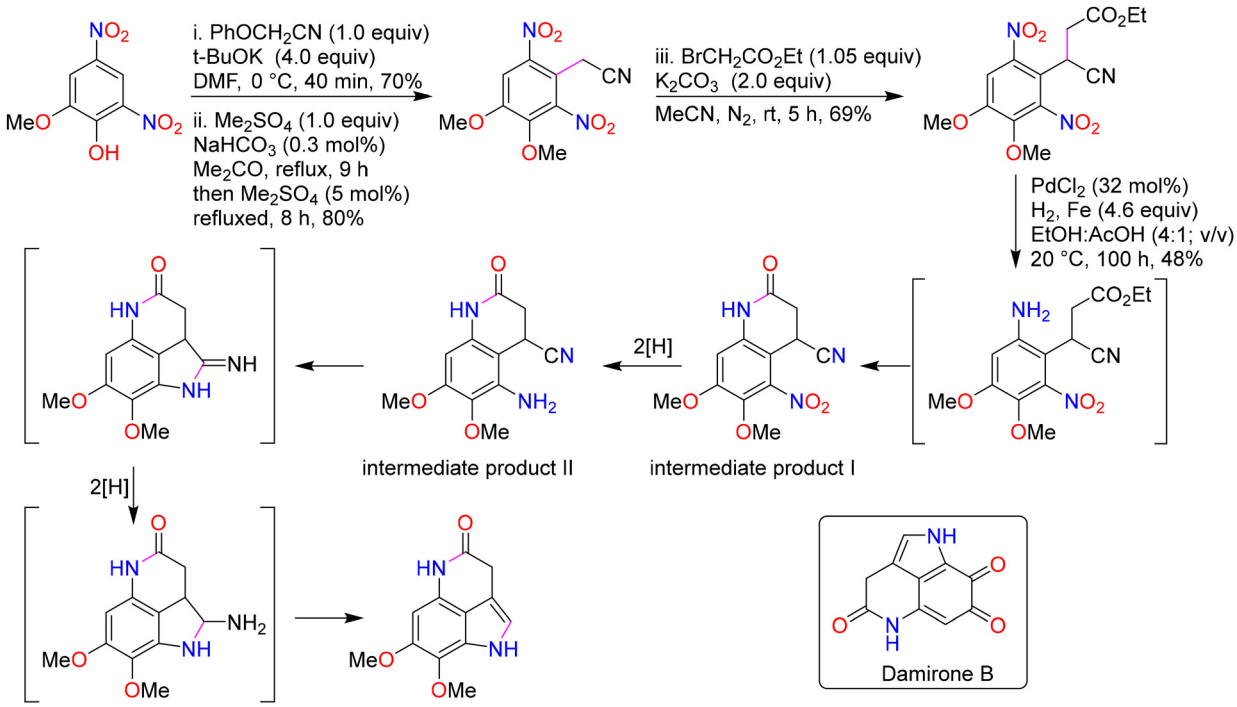
Wojciechowski *et al.* have developed a novel protocol for the synthesis of indoles from the commercially available compound dinitrobenzene.[105] Interestingly, they prepared hydroxyindoles through the VNS reaction with α-chloroketones in basic media followed by a reduction process using stannous chloride. For the deoxygenation of *N*-hydroxyindoles, lots of reducing reagents are well established. The smartness of the following deoxygenation is that it was reported with α-bromoacetophenone in the presence of triethylamine (TEA) as a mild protocol with excellent yields of 83–99% (Scheme 8a). They have proposed the mechanism that the nitro-hydroxyindoles undergo protection with α-bromoacetophenone and then fragmentation of it produces desired indole products and phenylglyoxal as the side product (Scheme 8b).

In 1997, Sutherland reported the unusual behavior of DBU with methyl 3,5-dinitrobenzoate and trinitrobenzene in chloroform as well as in ethyl acetate at room temperature after two days.[106] It has been reported that, first, both the starting materials form Meisenheimer complexes as intermediates I and II, which can be observed by the change of the deep red color of the reaction mixtures. In the next step, these mixtures were oxidized to form intermediates III and IV, which later underwent annulation reactions *via* the *ipso*-displacement, offering indole analogues. Simultaneously, the intermediate also forms a six-membered isoquinolone product upon cyclization with the ester group (Scheme 9).

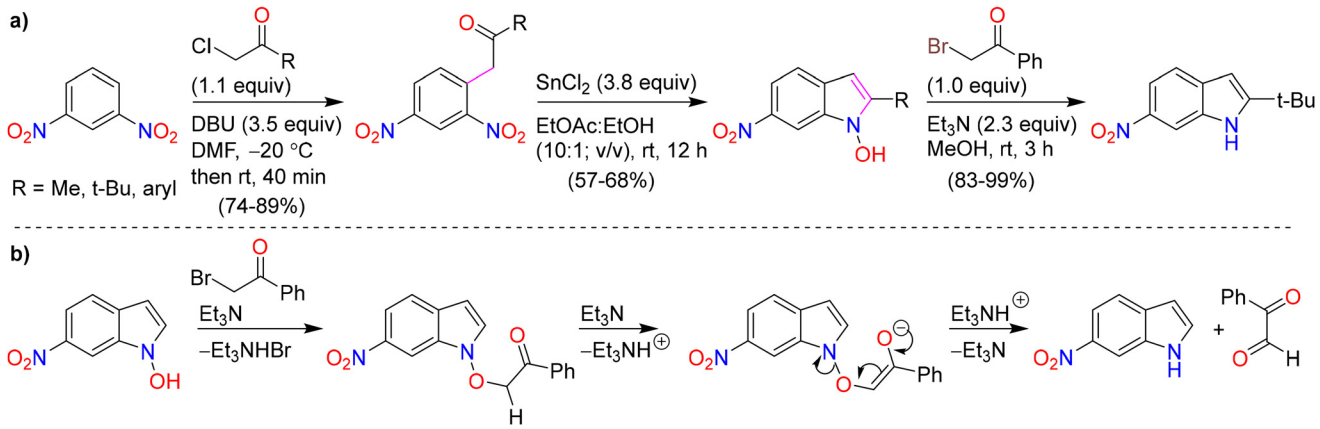
In 2001, Chen and coworkers reported the synthesis of 2-methyl-7-methoxyindole starting from 3-methoxy-2-nitroben-



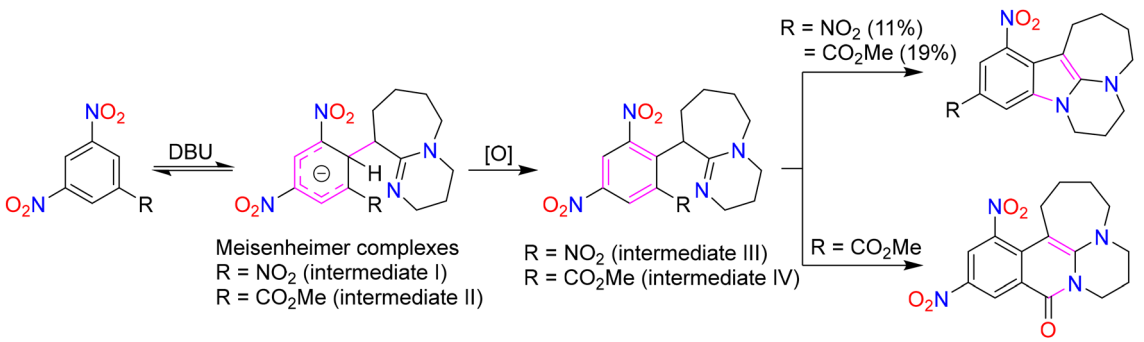
Scheme 6 Synthesis of fused indoles.



Scheme 7 VNS reaction involved in the synthesis of compounds mimicking alkaloids.



Scheme 8 VNS reaction using α-chloroketone and reductive annulation followed by deoxygenation for the synthesis of *ortho*-substituted indoles.



Scheme 9 DBU participating in indole synthesis *via* the VNS reaction as the key step.

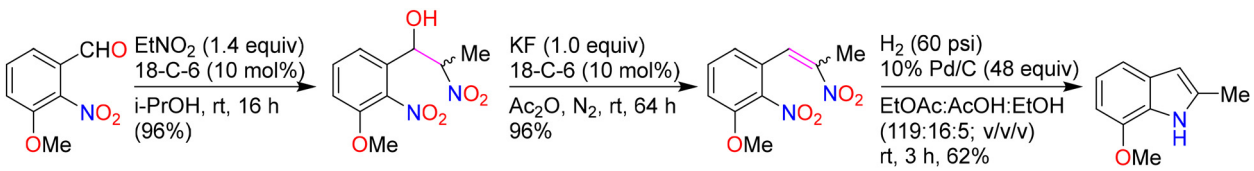
zaldehyde.[107] The reaction involved a cascade sequence of reactions (Henry reaction, condensation reaction, reductive annulation, and deaminative aromatization). This reaction has also been employed for the synthesis of 6,7-dimethoxy-2-methyl-1*H*-indole and 7-methoxy-2-methyl-1*H*-pyrrolo[2,3-*c*]pyridine from 3,4-dimethoxy-2-nitrobenzaldehyde and 2-methoxy-3-nitroisonicotinaldehyde, respectively (Scheme 10).

Hossain *et al.* developed a straightforward two-step strategy for the synthesis of indoles. Each step of the reaction was convenient and associated with high yields.[108] In the first step of the reaction, 2-(2-nitroaryl)-3-hydroxypropenoic acid esters were synthesized upon treatment of 2-nitrobenzaldehydes and ethyl diazoacetate in the presence of a Lewis acid or Brønsted-Lowry acid, and the product formed by molecular rearrangement. In the final step, indole was achieved *via* reductive-annulation process with the aid Pd/C at hydrogen atmosphere for 24 h (Scheme 11).

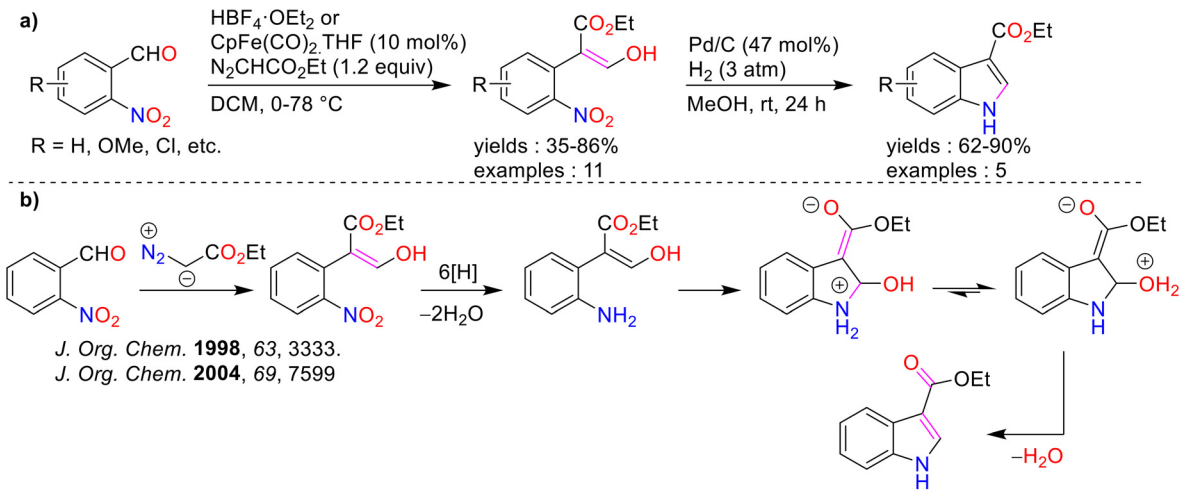
Söderberg *et al.* reported the synthesis of alkyl 2-(2-nitrophenyl)but-2-enoate by accomplishing the Kosugi–Migita–Stille coupling and Barluenga coupling reactions, and the intermediate product was subjected to indole synthesis in a basic medium at 0 °C in butanol.[109] The reaction conditions were well tolerated, and a library of compounds was explored using this method and some of the approaches are shown in Scheme 12a. Alternatively, the intermediate product ethyl 2-(2-nitrophenyl)but-2-enoate was also synthesized by the reaction between methyl 2-(2-nitrophenyl)acetate and acetaldehyde in a basic medium. During the mechanistic investigation, they found that the mono-substituted double bond must have a methyl group, which undergoes a fragmentation reaction that produces the potassium salt of 3-(methoxycarbonyl)-indol-1-olate, and then the alkylation produces methyl 1-methoxy-1*H*-indole-3-carboxylate upon treatment with methyl iodide, *cf.* Scheme 12b. However, when the methyl of the vinyl group was substituted with the propyl group, the reaction conditions were unable to produce the desired product, indole.

In 2021, Tsukamoto *et al.* reported a stepwise synthesis of indoles from a 2-nitrobenzaldehyde derivative.[107,110] They carried out the transformation through a three-step sequence involving a Henry reaction, dehydration, and amino-reductive annulation (Scheme 13a). The final step resembles a Fischer-type indole formation, where a diamine derivative facilitates the synthesis of five-membered heterocycles.[111] Later on, the Henry reaction was also employed for the synthesis of dihydroxy nitrostyrene from the corresponding aldehyde, which was employed for the nitration reaction with the help of tetranitromethane (TNM) under Zn(II)-assisted conditions.[112] In the next step, an effective approach was employed for the synthesis of an indole derivative with the help of a Zn-controlled reduction process, which led to the formation of the product with a good yield (Scheme 13b).[113–116]

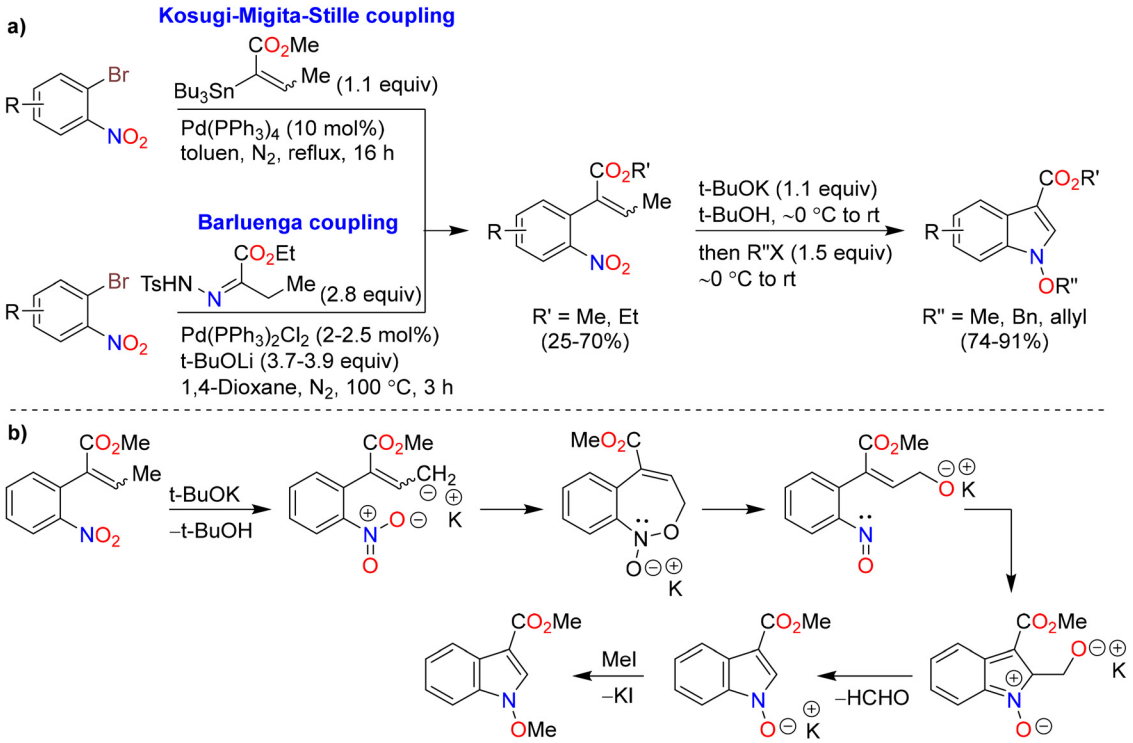
Bartoli and Palmieri (1989) developed a facile and alternative substitute for Gassman indole synthesis.[117] In this process, nitroarenes can be directly converted into indole derivatives in a single step with the aid of vinyl magnesium bromide derivatives.[118,119] This method not only reduces the



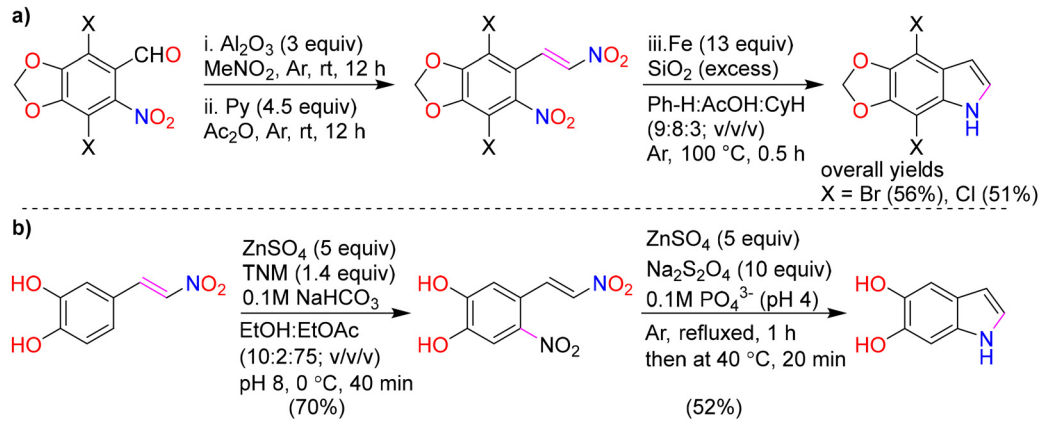
Scheme 10 Synthesis of indoles *via* Henry condensation followed by a hydrogenation reaction.



Scheme 11 Tandem approach for the synthesis of indoles from 2-nitrobenzaldehydes.



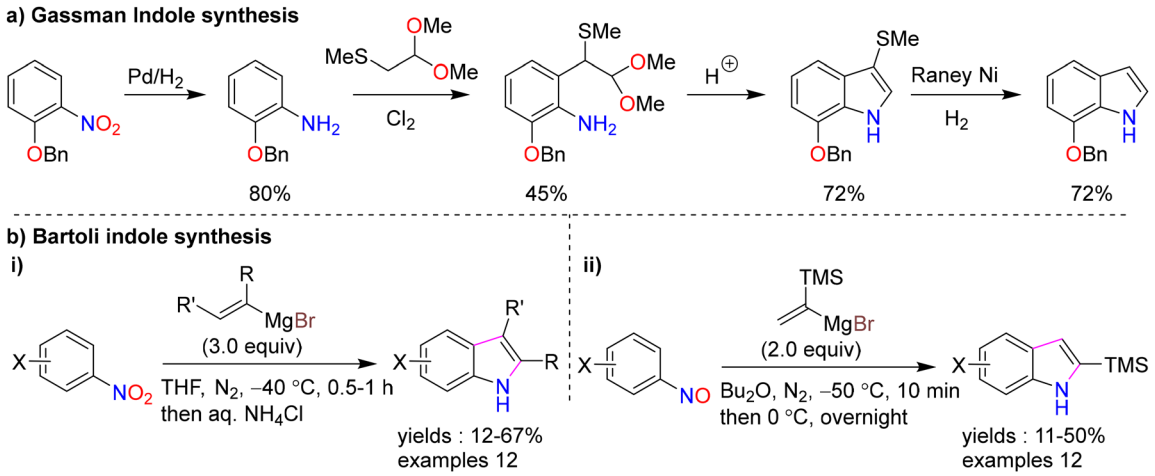
Scheme 12 Synthesis of *N*-hydroxy/alkoxyindoles.



Scheme 13 Alternative approach for indole synthesis *via* Henry condensation followed by a hydrogenation reaction.

reaction time and solvent usage while simplifying the protocol but also delivers excellent yields.[120,121] In the following cases, an example of Gassman indole synthesis is shown with a multistep path (Scheme 14a).[122,123] Herein, each step afforded a good to excellent yield, and the total yield of the reaction was found to be 19%. Indoles were efficiently synthesized *via* this method, employing for diversely substituted nitrobenzene substrates with three equivalents of vinyl Grignard reagents under mild conditions, generating products in 12–67% yield across twelve examples (Scheme 14b(i)). In their exploration, they found that the *ortho*-substituted nitroarene offers a higher yield than the *meta*- and *para*-substituted nitroarenes. Although the yields were generally low, the reaction protocols are still preferred due to their simplicity and cost-effectiveness compared to the Gassman indole synthesis. Furthermore, Bartoli and coworkers also explored the synthesis of indole derivatives by employing the same reagent system with nitrosoarenes and reported moderate yields. The substrates also worked well with a broad range of cyclic and acyclic salts of olefinic magnesium bromides (Scheme 14b(ii)).

To illustrate the mechanism of indole synthesis, 2-nitrotoluene and vinylmagnesium bromide were selected as representative precursors. In the reaction, the first mole of vinyl magnesium bromide reacts with the nitro group to transform it to



Scheme 14 The overall comparative yields of Gassman and Bartoli indole synthesis from nitroarenes.

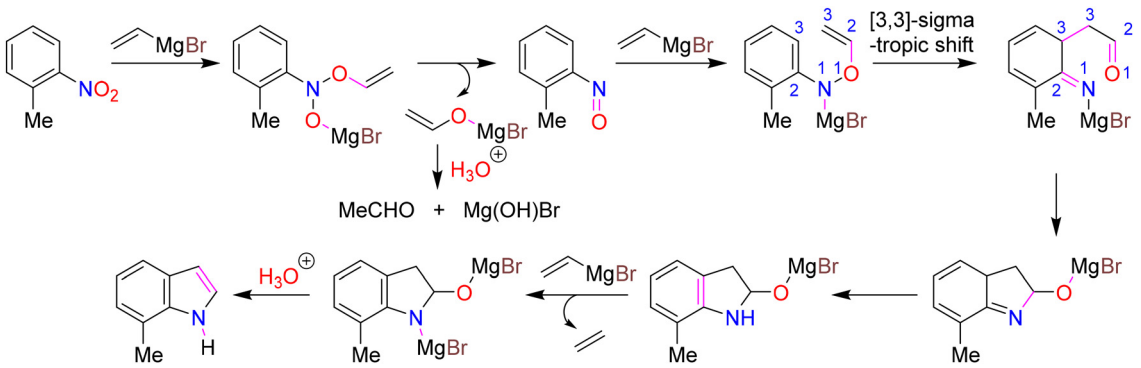
the reduced functional group nitrosobenzene, and then the second mole of vinyl magnesium bromide reacts with the nitroso group to form magnesium *o*-tolyl(vinyloxy)amide bromide followed by a [3,3]-sigmatropic shift and an intramolecular annulation reaction to offer magnesium 7-methylindolin-2-olate bromide. Finally, this intermediate reacts with the third mole of vinyl magnesium bromide to furnish magnesium 7-methyl-2-oxidoindolin-1-ide dibromide by the loss of an ethylene group, and then acid hydrolysis of the di-magnesium bromide salt produces the desired products, such as 7-methyl indoles (Scheme 15).

Independently, the Bartoli indole and Barton–Zard reactions of 9-nitrophenanthrene offer two different types of isomeric products, namely, 1*H*-dibenzo[*e*,*g*]indole and 2*H*-dibenzo[*e*,*g*]isoindole, *cf.* Scheme 16a. Also, the reaction mechanism of the Barton–Zard reaction is depicted in Scheme 16b.[124–127]

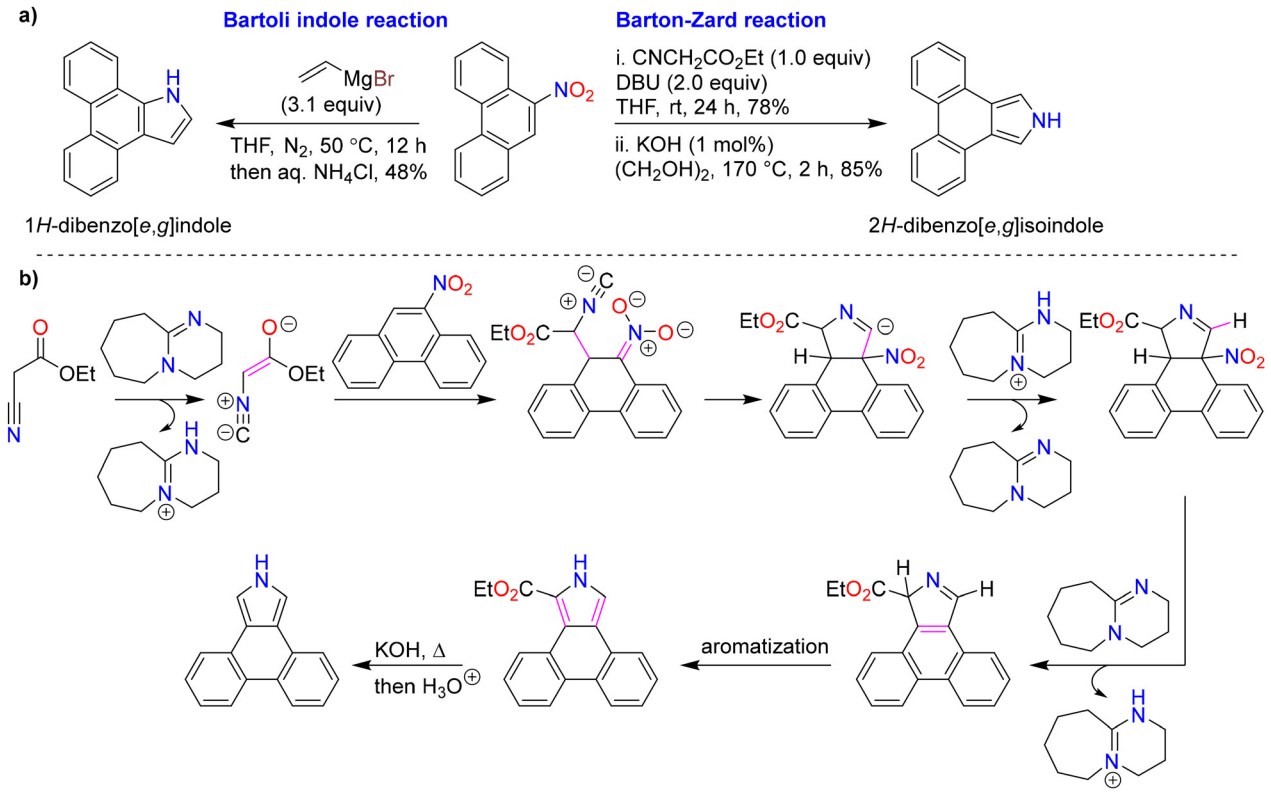
In 2003, Knochel and his co-workers introduced a novel approach for the synthesis of indole analogues from β-aryl *o*-nitrostyrenes *via* reaction with a Grignard reagent.[128] This transformation is recognized as the Knochel indole synthesis, an extension of the Bartoli indole reaction, and offers key advantages. Unlike the Bartoli reaction, this approach requires a lower stoichiometric amount of the Grignard reagent due to intramolecular annulation, making it more efficient. Beyond facilitating indole synthesis, this methodology also enables the construction of benzimidazoles when selecting appropriate starting materials as both reactions proceed *via* a similar mechanism. In this process, two equivalents of phenyl magnesium chloride are sufficient: the first generates β-aryl *o*-nitrosostyrene, while the second reduces it to form a nitrene intermediate. The resulting nitrene undergoes annulation, and subsequent aromatization generates either indoles or benzimidazoles as the final cyclized heterocyclic products (Scheme 17). This innovative approach broadens the synthetic access to structurally diverse nitrogen-containing heterocycles.

2.2. Involvement of an *ortho*-group in the synthesis of indoles from nitroarenes

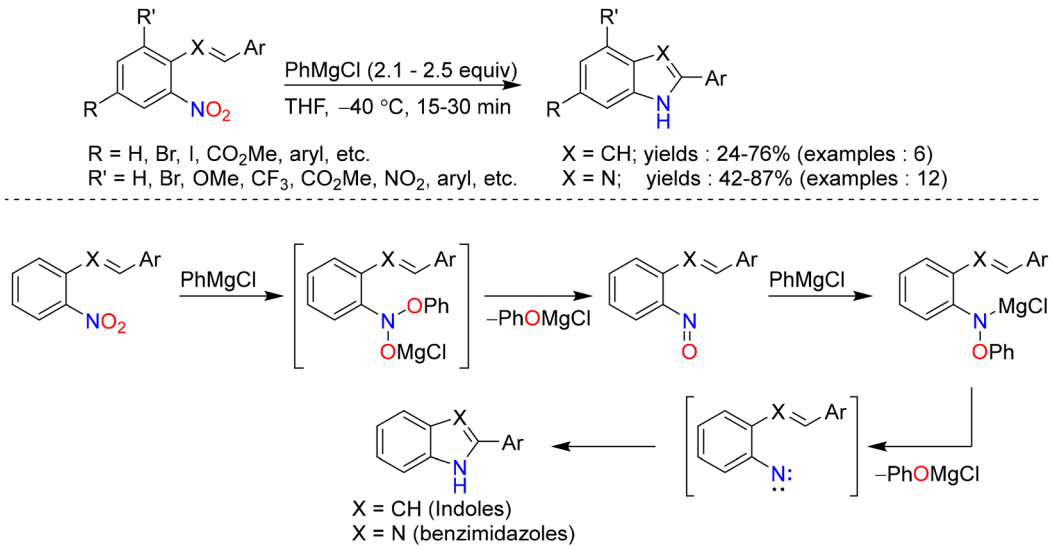
Batcho and Leimgruber have discovered a novel approach for the synthesis of indoles[129] and their analogues from the corresponding 2-nitrotoluenes *via* the condensation of *N*,*N*-dimethylformamide dimethyl acetal in DMF at high temperature



Scheme 15 Mechanism of the Bartoli indole synthesis.



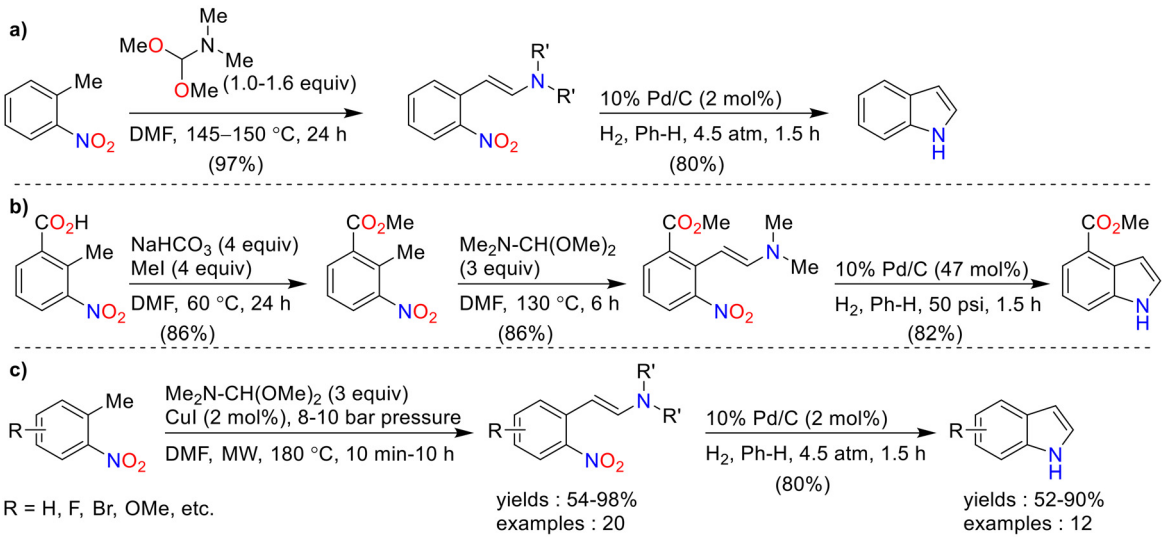
Scheme 16 Synthesis of dibenzo[*e*,*g*]indole/isoindole from 9-nitrophenanthrene and the mechanistic details of the Barton–Zard reaction.



Scheme 17 Knochel indole reactions for the synthesis of indoles and benzimidazoles.

followed by hydrogenation with the aid of Pd/C in benzene *via* a reductive-annulation reaction (Scheme 18a).[130]

However, they also varied the secondary amines of formamide dimethyl acetal and found good to excellent yields of indoles. The other hydrogenation protocol was also explored with Fe/AcOH and sodium dithionite, which afforded a poorer yield than Pd/C. After the successful establishment of these reactions, various substrates were explored using this method. Hence, the reaction became more popular as the Batcho–Leimgruber indole reaction for indole synthesis. Similarly, Ponticello and Baldwin have reported a common synthon, methyl indole-4-carboxylate, for the synthesis of alkaloids starting from 2-methyl-3-nitrobenzoic acid with an excellent yield in each step (Scheme 18b). Recently, Ley *et al.* enhanced



Scheme 18 Batcho–Leimgruber indole synthesis from 2-nitrotoluenes.

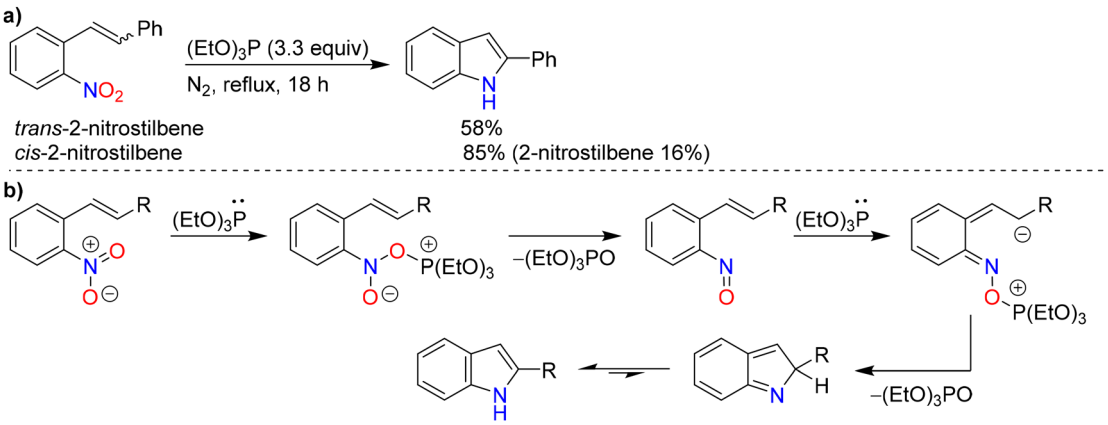
the Leimgruber–Batcho enamine synthesis by employing microwave conditions, and then used it for indole synthesis.[131] This reaction protocol is a superior protocol to the previous protocol with regard to the reaction time and yields of the indoles (Scheme 18c).[132]

Cadogan–Sundberg indole synthesis. Cadogan and Sundberg developed the progress of direct indole synthesis with the reaction of nitrostyrene with triethyl phosphite or triphenylphosphine (Scheme 19a). Herein, the triethyl phosphite behaves as a deoxygenating reagent and transforms it into the nitroso derivative that undergoes a 6-electron thermal ring closure reaction and provides the aromatized indoles (Scheme 19b).[133–137]

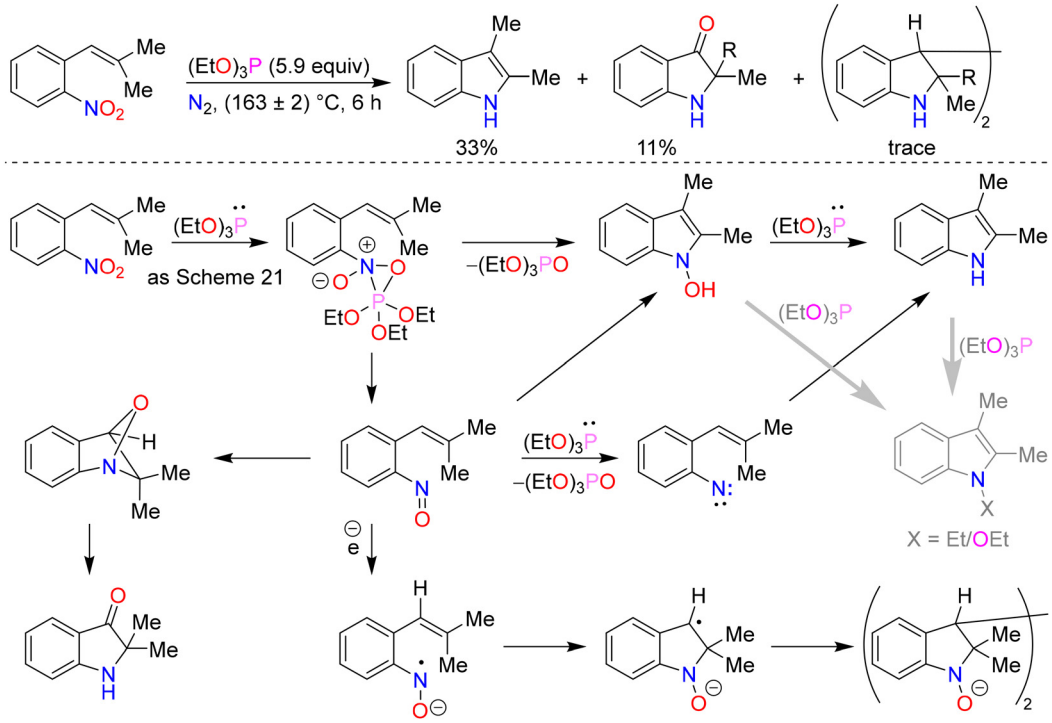
Simultaneously, Sundberg *et al.* also reported the deoxygenation-based annulation of *ortho*-nitrostyrenes to the corresponding indoles. Furthermore, they also studied the conversion of terminal disubstituted 2-nitrostyrenes to the corresponding indoles and proposed the formation of various types of side products along with the major product (Scheme 20).[138–140]

The above combined reaction is known as the Cadogan–Sundberg indole synthesis. Additionally, Peet *et al.* have reported that the reaction of 2-nitrostilbenes with triethyl phosphite leads to the formation of two types of major products, such as 2-arylindoles and the corresponding 2-aryl-*N*-ethoxyindoles.[141] They also explored the mechanistic deoxidative investigation to deeply understand the formation of *N*-alkoxyindoles by using isotopically labeled '^{18}O' in the nitrostyrenes and found that the reactions proceed through two mechanistic paths as shown in Scheme 21.

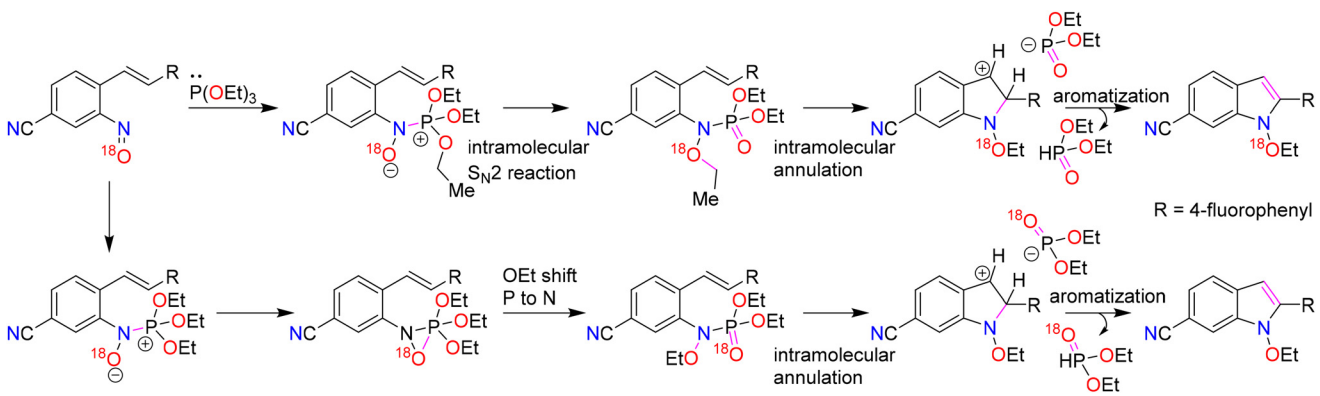
Interestingly, Söderberg and coworkers have utilized a variety of palladium catalysts in combination with organic phosphines and nitrogenous organic ligands and developed modified approaches[142] for the synthesis of indoles in the



Scheme 19 Reactions and the mechanism reported by Cadogan and co-workers.



Scheme 20 Sundberg analysis of the formation of indole products and side-products.

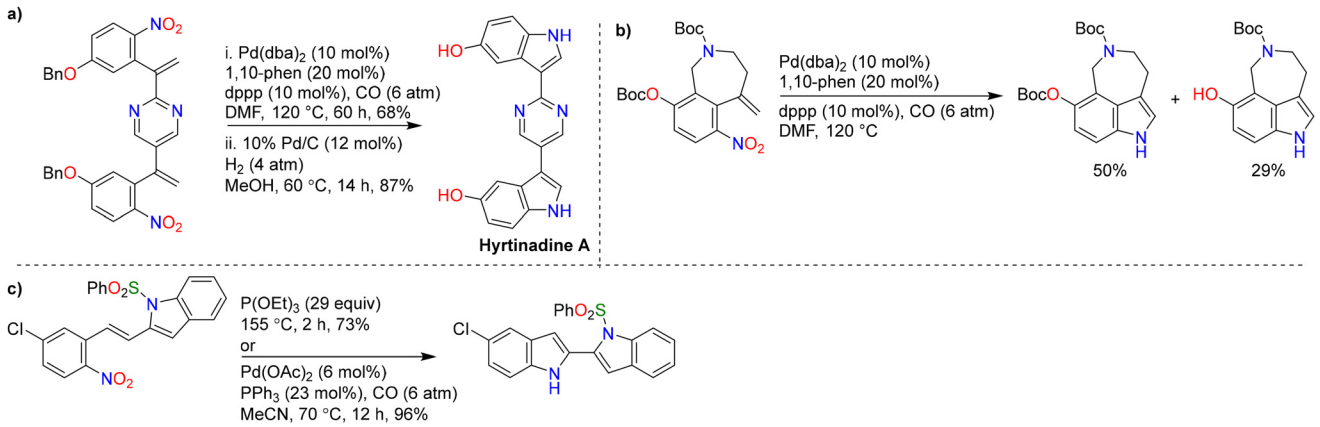


Scheme 21 The analysis of the Cadogan–Sundberg indole reaction for the information on the formation of *N*-alkoxyindoles.

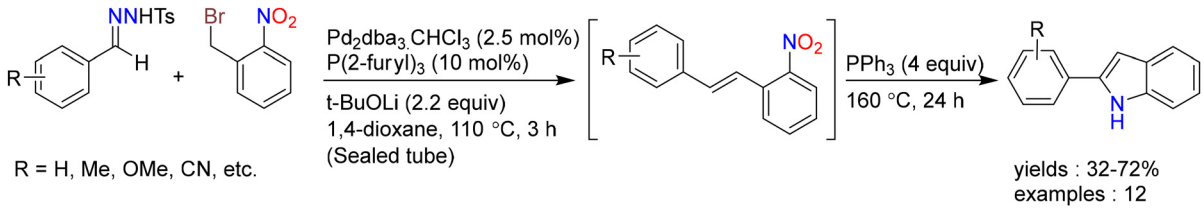
presence of CO (6 atm.). Herein, two important examples of indole alkaloids noted as hyrtinadine A and fargesine were reported by Söderberg's group (Scheme 22a and b).[143,144] In 2003, Kuethe and coworkers reported the synthesis of indoles from nitrostyrenes in the presence of triethyl phosphite (TEP) at very high temperatures during the exploration of the total synthesis of tjipanazoles B, D, E, and I.[145] Instantaneously, they also explored the same target by modifying the protocol using the $Pd(OAc)_2/PPh_3$ reagent in a carbon monoxide environment at 6 atm under reflux conditions. The latter approach of indole synthesis afforded a superior yield with higher purity than that using TEP (Scheme 22c).[146] The limitation of the CO atmosphere supported protocol offering the CO insertion product is that it leads to the formation of amide or lactam derivatives instead of the desired indole products. As a result, the yield of the product is below the expected yield.

In the following successful attempt, Hamze *et al.* developed an excellent synthesis route for 2-arylindoles by treating equal stoichiometric amounts of *N*-tosylhydrazones and 2-nitrobenzyl bromide using $Pd_2(dba)_3{\cdot}CHCl_3$ in a basic medium with P(2-furyl)$_3$ generating the *ortho*-nitrostilbene intermediate followed by Cadogan annulation in the presence of an excess of phosphine (Scheme 23).[147]

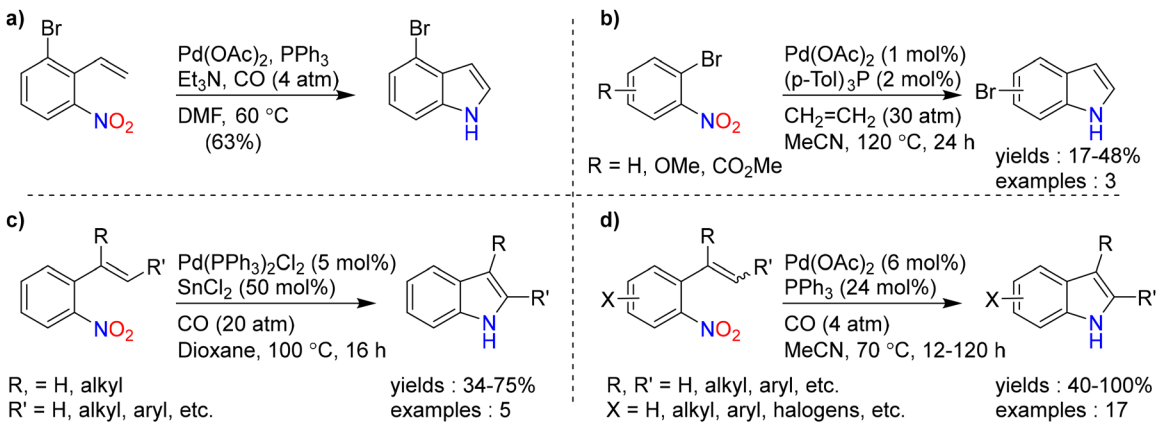
In the following serendipitous examples, the synthesis of indoles was explored using Pd(II) catalysts with good to excellent yields. In Scheme 24a,[148] the reaction was attempted for a methoxycarbonylation reaction, but it offered cyclized indole products. Similarly, as shown in Scheme 24b, the strategy fully



Scheme 22 Modified approach of the Cadogan–Sundberg cyclization for the synthesis of indoles.



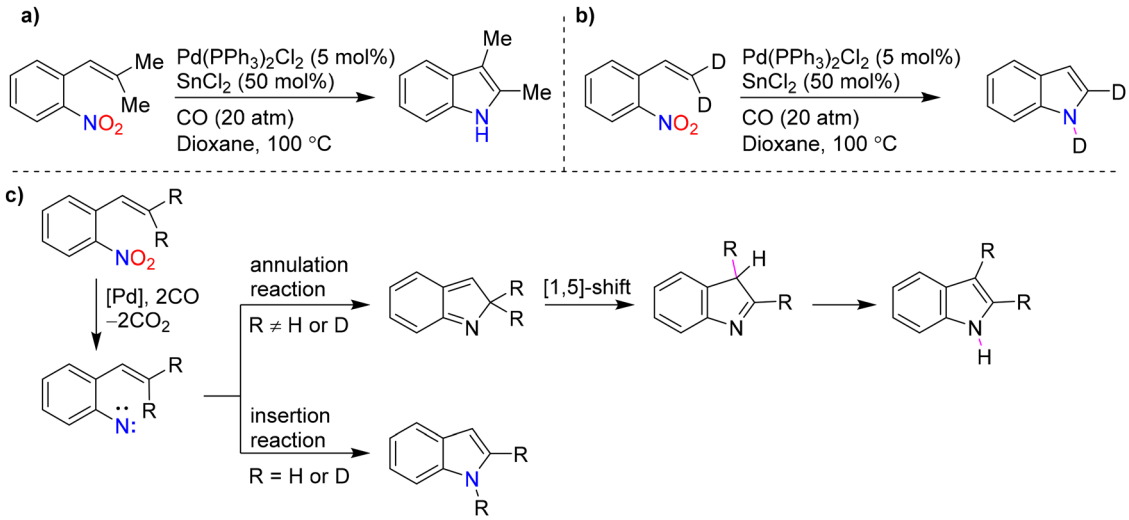
Scheme 23 The synthesis of 2-arylindoles from *N*-tosylhydrazones and 2-nitrobenzyl.



Scheme 24 The synthetic approach for indoles using Pd(II) reagents and additives from 2-nitroarenes.

employed Heck reactions to synthesize nitrostyrene analogues. However, this protocol was not efficient for the synthesis of indoles, but it worked within a limited scope. Next, the Stille reaction was also attempted for the synthesis of carbonylated products, but the reaction led to the formation of indole derivatives.[149] Along similar lines, the general reaction mechanism of this Pd(II)-catalyzed reaction is proved with cross experiments as depicted in Scheme 25. Additionally, the reactions shown in Scheme 24c and d were directly employed for the synthesis of indoles with good to excellent yields without any base.[150–152]

During the mechanistic investigations, it was found that terminally disubstituted and unsubstituted *o*-nitrostyrenes, when subjected to the above Pd(II) protocol form nitrene intermediates.[151] Noticeably, terminally disubstituted olefins undergo an annulation reaction that furnishes 2,3-disubstituted indoles *via* a cascade of steps such as a [1,5]-sigmatropic shift and an aromatization reaction. However, *o*-nitrostyrene undergoes an insertion reaction *via* rearrangement, leading to the formation of indoles. Furthermore, the experiment was confirmed by deuterium labelling experiments (Scheme 25).

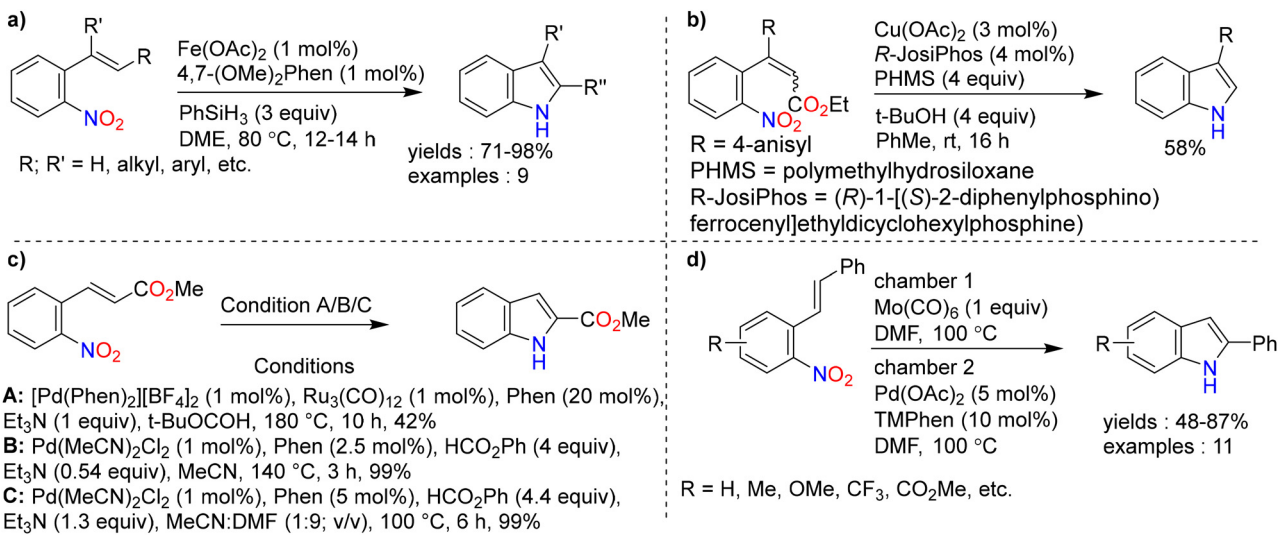


Scheme 25 Cross experiments and the mechanism of formation of indoles.

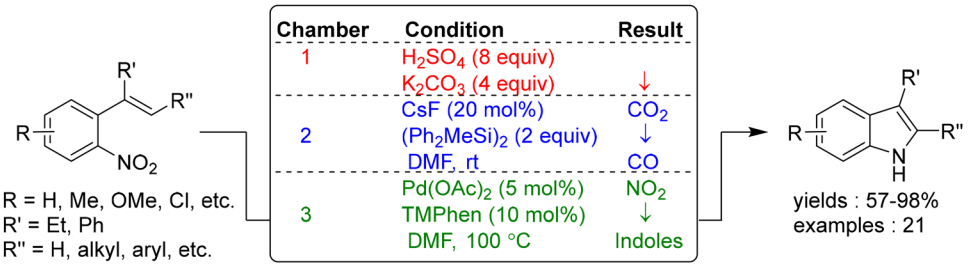
In the following examples, the Cadogan–Sundberg strategy was successfully used for indole formation with the help of catalytic mol% of transition metals such as Fe(II), Cu(II), and Pd(II), *etc.*[143,153,154] by the combination of organic nitrogenous heterocyclic ligands and reducing silane reagents or surrogate equivalents of CO.[155,156] The combination of the approaches afforded excellent yield of the product in all cases (Scheme 26a–d).[157] However, some other carbonylation catalysts such as $Fe(CO)_5$, $Ru_3(CO)_{12}$, and $Rh_6(CO)_{16}$ are also well-known for indole synthesis from nitrostyrenes, but they led to the formation of amines and other incredible products.[158] Thus, these procedures are used less frequently for the synthesis of indoles.

In 2019, Driver and coworkers developed a multi-chambered reduction process for reductive transformation of *ortho*-nitrostyrenes to indoles. The reaction conditions are slightly chaotic with a tedious protocol.[159] However, the reaction conditions are well tolerated by most of the functional groups, and chemoselectively the nitro group, after the reduction process, forms the heterocyclic indole compounds with excellent yields (Scheme 27).

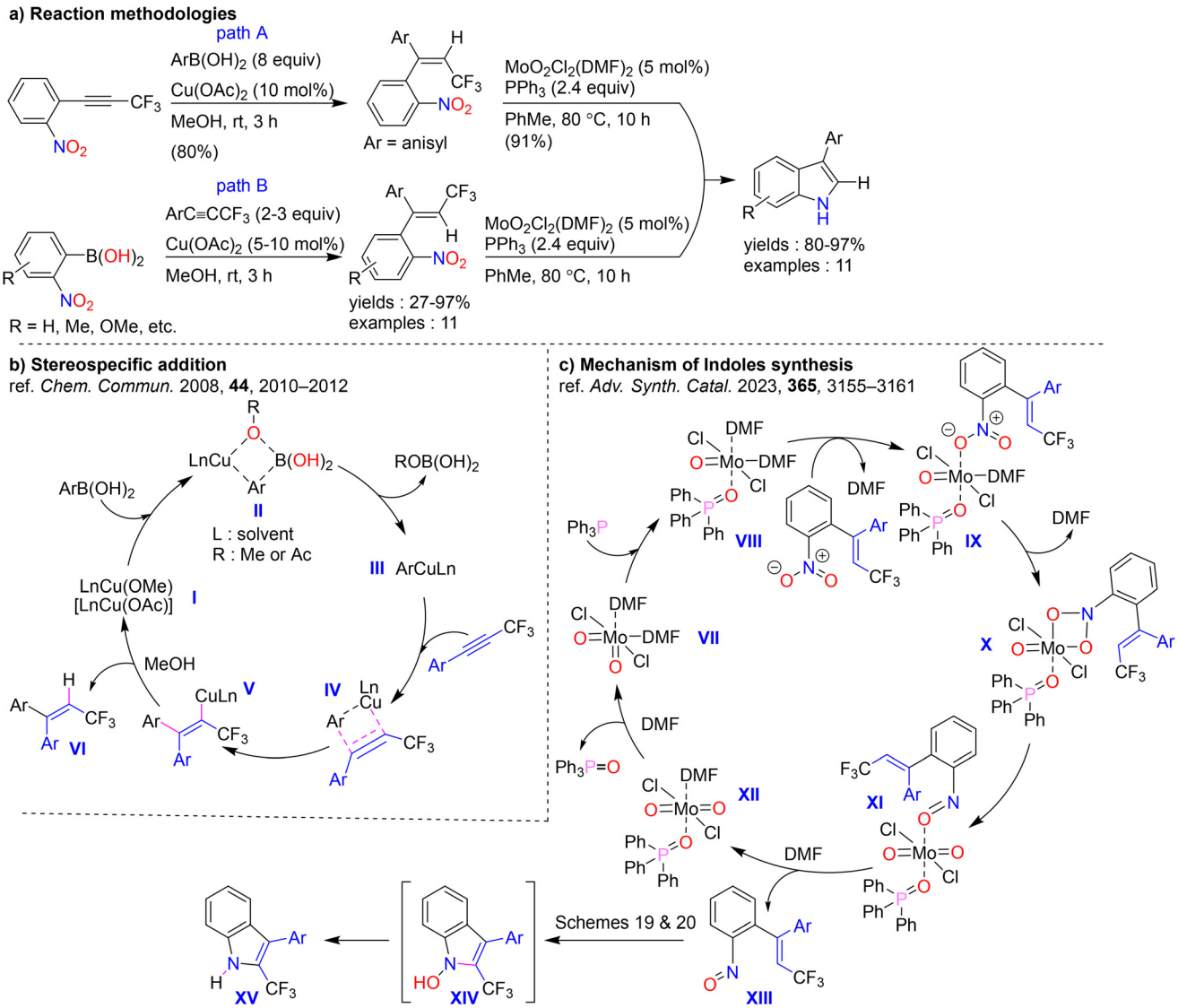
In further approaches, the replacement of TEP used in the oldest mode of the Cadogan annulation approach with triphenylphosphine under mild to severe conditions was also explored.[160a–163] However, many other approaches were reported for the improvement of indole synthesis in the presence of additives such as salts/complexes of transition metals, *etc.*, with PPh_3. Herein, the indoles were synthesized in two steps, such as hydroarylation and Mo-catalyzed Cadogan annulation. In both of the approaches, the indoles were synthesized with good to excellent yields (Scheme 28a).[160a,134] Herein, a stereospecific *syn*-addition approach similar to the hydroboration reaction as established by Yamamoto *et al.* was followed (Scheme 28b).[160b] The reaction proceeds in the presence of a



Scheme 26 Indole synthesis with the help of reducing reagents or CO-surrogate reagents.



Scheme 27 Single-pot three-chambered reductive annulation of *ortho*-nitrostyrenes to indoles.



Scheme 28 Molybdenum catalyst-assisted indole synthesis.

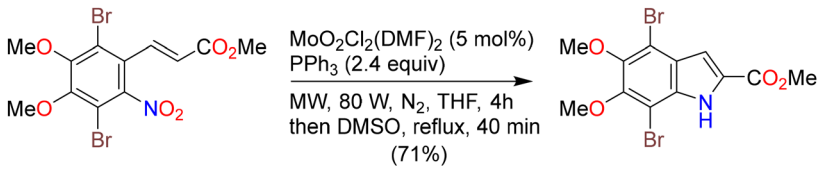
copper catalyst and an exchange reaction occurs to form complex I. This is followed by coordination with an aryl boronic acid to form complex III *via* intermediate complex II. Subsequently, a stereospecific *syn*-addition with an alkyne yields compound V. Rapid regeneration of the catalytic complex occurs in the presence of methanol, affording the major product VI. In the subsequent sequence (Scheme 28c),[160c] $MoO_2Cl_2(DMF)_2$ undergoes an exchange reaction with PPh_3, followed by coordination with a nitrostyrene analogue through intermediates VII and VIII, to yield

complex IX. The nitro group facilitates the formation of a strained four-membered intermediate X by displacing *N*,*N*-dimethylformamide (DMF). This intermediate is then transformed into complex XI, which subsequently generates the catalyst precursor XII and finally the active catalytic species VII. Throughout this sequence, the formation of a nitro-reduced product XIII is observed, arising *via* a cascade of exchange reactions involving DMF and complexes XI and XII. Ultimately, these transformations conclude in an intramolecular annulation reaction to furnish the corresponding indole derivatives, consistent with earlier transformations described in Schemes 19 and 20.

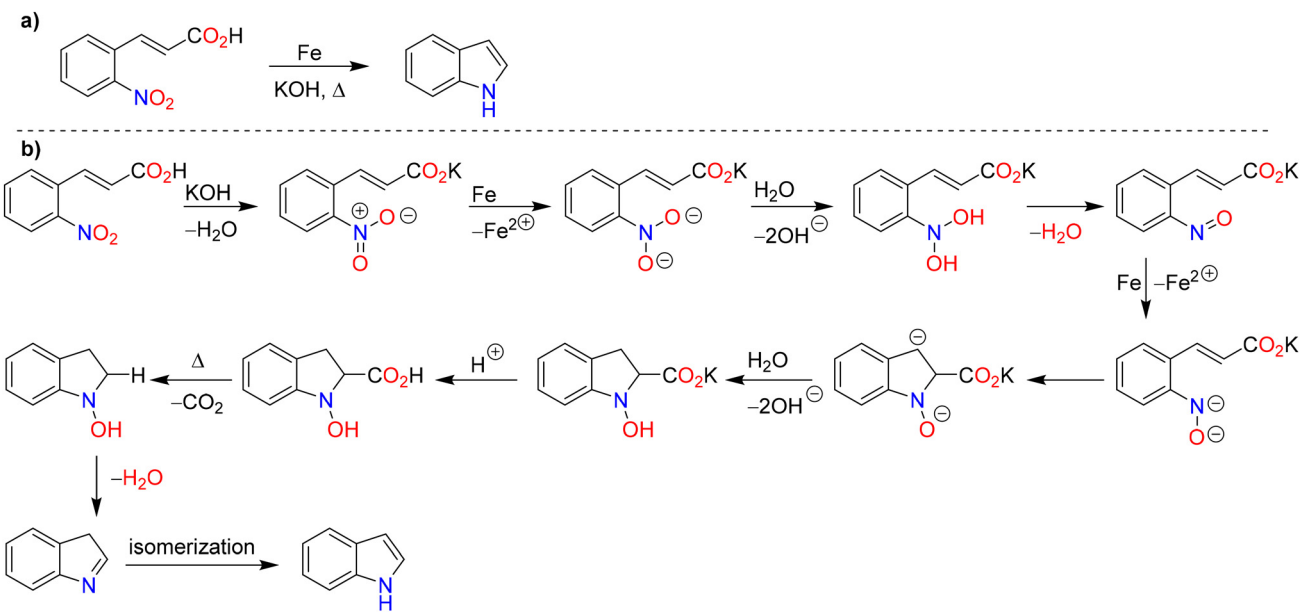
In 2015, Nelson and coworkers modified the Cadogan–Sundberg annulation with the help of a stoichiometric amount of triphenyl phosphine and catalytic mol% of molybdenum dichloride dioxide bis(*N*,*N*-dimethylformamide) [$MoO_2Cl_2(DMF)_2$] under microwave (MW) conditions during the exploration of the synthesis of the eumelanin-inspired polymer from vanillin.[164,165] The reported reaction offered a good yield (Scheme 29).[166,167] The mechanistic pathway of the reaction is similar to that shown in Scheme 28c, and the applied microwave conditions reduce the time of the reaction with improved yield of the desired product.

In 1869, Baeyer and Emmerling reported a novel approach for indole synthesis using iron metal from *ortho*-nitrocinnamic acid under strongly alkaline conditions, as illustrated in Scheme 30a.[168] The reaction proceeds *via* reductive annulation, followed by a decarboxylation process, which is commonly known as Baeyer–Emmerling indole synthesis.[169] During the exploration of the reaction, the nitro functionality is converted into the corresponding nitroso group, which plays a crucial role in the formation of the five-membered ring (Scheme 30b).[170]

In the 19th century, Arnold Reiesert developed a two-step indole synthesis from *ortho*-nitrotoluenes, and it was a hot topic for chemists. In this procedure, various types of *ortho*-nitrotoluenes are subjected to indole synthesis with the help of diethyl oxalate in the presence of sodium metal followed by reduction with zinc/acetic acid, which leads to the formation of an amino-phenylpyruvic acid intermediate. Furthermore, this intermediate undergoes a cyclization reaction followed by a decarboxylation process that produces an indole carboxylic



Scheme 29 Microwave-assisted Cadogan–Sundberg cyclization.

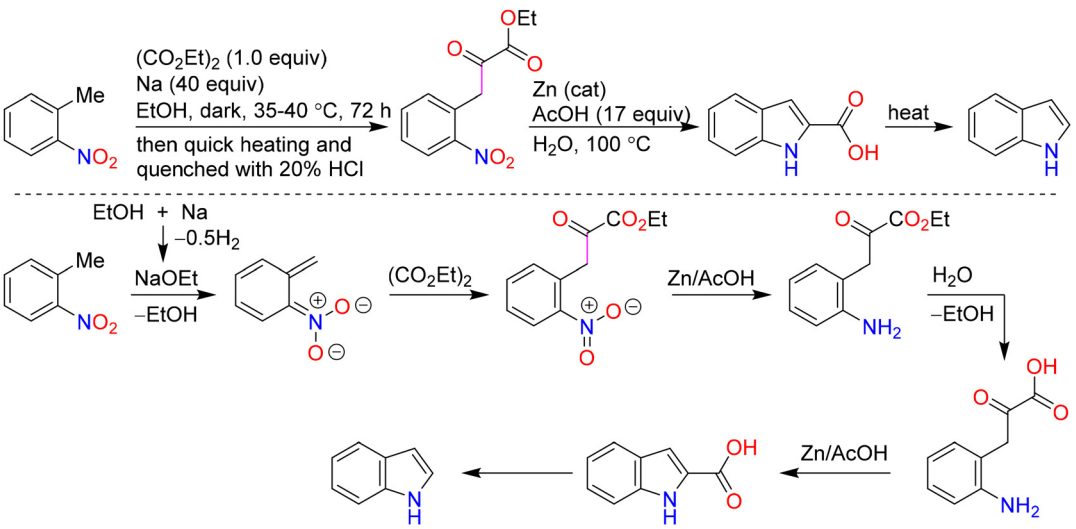


Scheme 30 Synthesis of indoles from 2-nitrocinnamic acid.

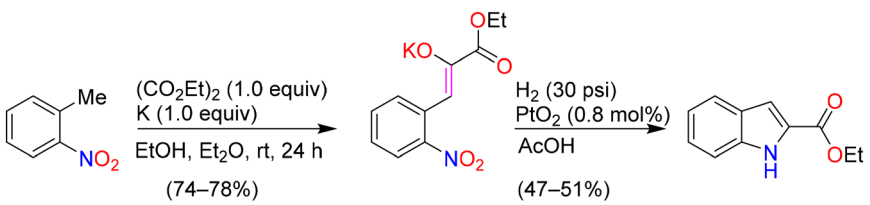
acid derivative. This procedure afforded good to excellent yields of the indole products, and this procedure is commonly known as the Reissert indole synthesis.[171–174] The other alternative method for the hydrogenation of the nitrophenylpyruvic acid intermediate was also explored with the help of ferrous sulphate/ammonium hydroxide, stannous chloride/dehydrate, and Pd/C, which also gives the desired indole products. The mechanistic pathway of these reactions is also shown in Scheme 31.[175,176]

In the following examples, potassium metal was dissolved in absolute ethanol (without stirring) to prepare the potassium ethoxide base, and then it was mixed with a solution of diethyl oxalate under an inert atmosphere at room temperature. Furthermore, nitrotoluene was also added for the synthesis of the potassium salt of ethyl *o*-nitrophenylpyruvate, which was later subjected to a hydrogenation reaction at high pressure using hydrogen gas in the presence of a catalytic amount of platinum(IV) oxide in acetic acid. The yield of the product varied based on the purification methods through several washes. The synthesis of indoles *via* the Arnold Reiesert method is a challenging and hectic procedure; thus, it was replaced by many other alternative synthetic methods (Scheme 32).[172]

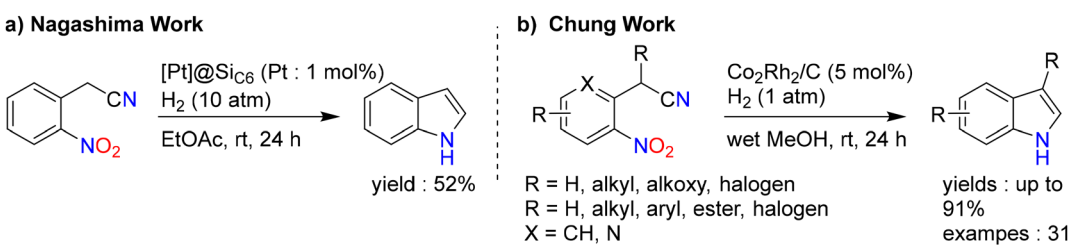
Independently, the Nagashima group and the Chung group reported indole synthesis *via* a hydrogenation reaction of 2-(2-nitrophenyl)acetonitrile using [Pt]@SiC_6 and Co–Rh heterobimetallic nanoparticles under 10 atm and 1 atm pressures of hydrogen in ethyl acetate and wet methanol, respectively (Scheme 33).[177–179]



Scheme 31 Synthesis of indoles *via* Reissert indole synthesis.



Scheme 32 Synthesis of indoles *via* modified Reissert indole synthesis.



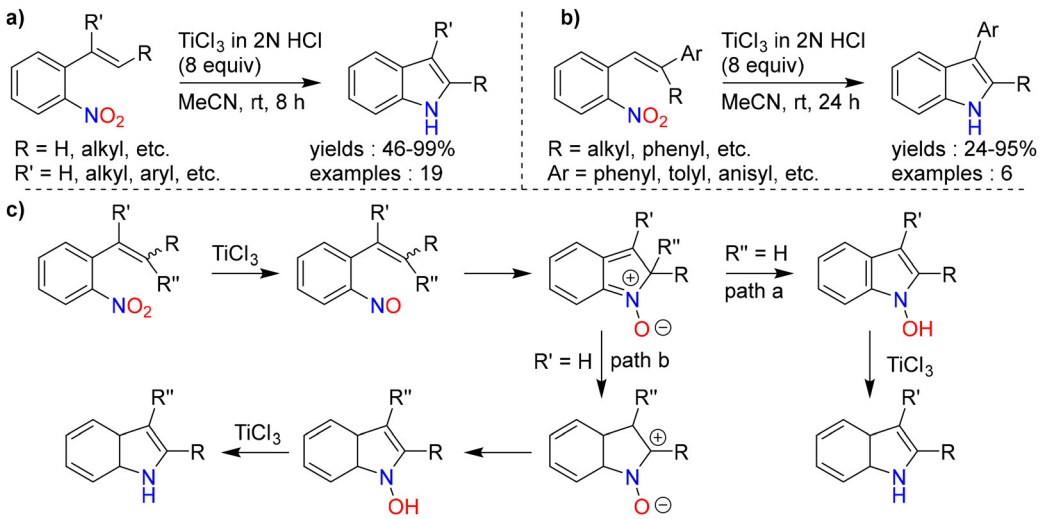
Scheme 33 Nitrile hydrogenations for indole synthesis.

In the next reaction, low-valent titanium(III) chloride was used to synthesize *ortho*-nitrostyrene analogues. Herein, the titanium acts as a reducing reagent for the nitro group and transforms it into the corresponding nitroso derivative.[180] As illustrated below, the cyclization proceeds through the formation of a hydroxyindole intermediate (path a), which is then reduced to the final indole product due to the presence of excess trivalent titanium chloride (Scheme 34a). However, the trisubstituted olefins of *ortho*-nitrostyrene analogues also proceed in the same mode as path a and undergo a 1,2-shift *via* path b, and further undergo rearrangement, followed by aromatization and deoxygenation reactions that furnish 2,3-disubstituted indoles as the major products (Scheme 34b). The detailed mechanistic information is shown in Scheme 34c.

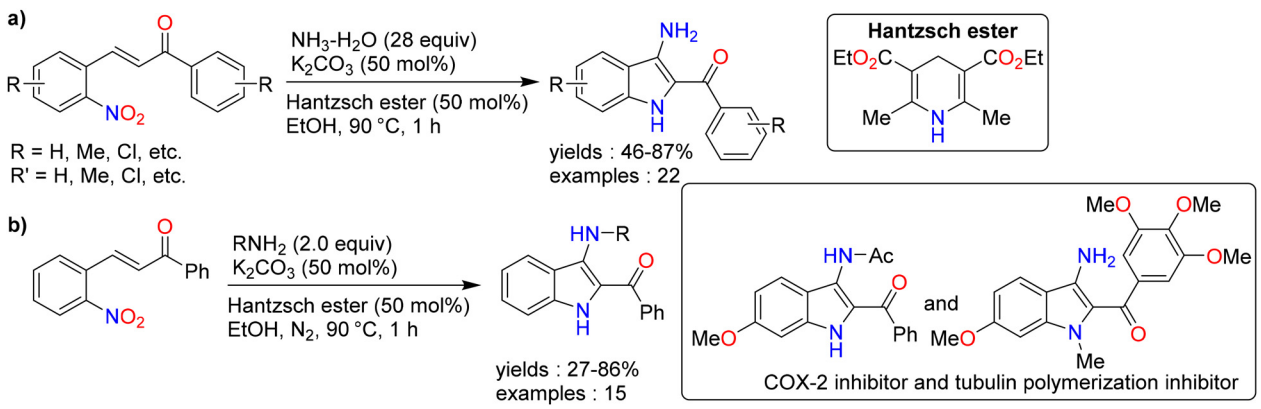
In 2019, Song *et al.* established the development of 3-amino/aminoalkyl-2-keto-indole analogs from *ortho*-nitrochalcones.[181] They treated the corresponding chalcones with ammonia and a Hantzsch ester in a basic medium, leading to the formation of 3-amino-indoles (Scheme 35a). Interestingly, the methodology was also employed for the synthesis of COX-2 and tubulin polymerization inhibitors. Furthermore, the ammonia was substituted by primary amines to perform the successful synthesis of 3-aminoalkyl-indoles with yields of 27–86% (Scheme 35b).

According to recent studies, it is reported that stannous chloride is utilized to reduce 3-(2-nitrophenyl)acrylic acid to the alkyl 3-(2-nitrosophenyl)acrylate intermediate, which further undergoes annulation with the double bond of acrylate, followed by an aromatization process that produces alkyl 1-hydroxyindole carboxylate as the major product. At the same time, annulation of the lone pair of nitro with the carbonyl of the ester gives a 2-hydroxyquinoline derivative as the side product (Scheme 36).[182]

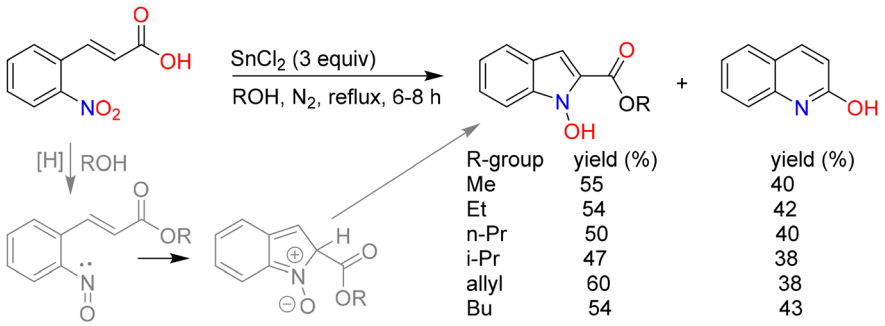
Song *et al.* reported a novel approach for the synthesis of indoles from 3-(2-nitrophenyl)acrylic acids and stilbenes with the help of bis(pinacolato)diboron (B_2Pin_2) and KF in an ethanolic solution (Scheme 37a and b).[183] Here, the Bis(pinacolato)diboron acts as a deoxygenating agent, converting the



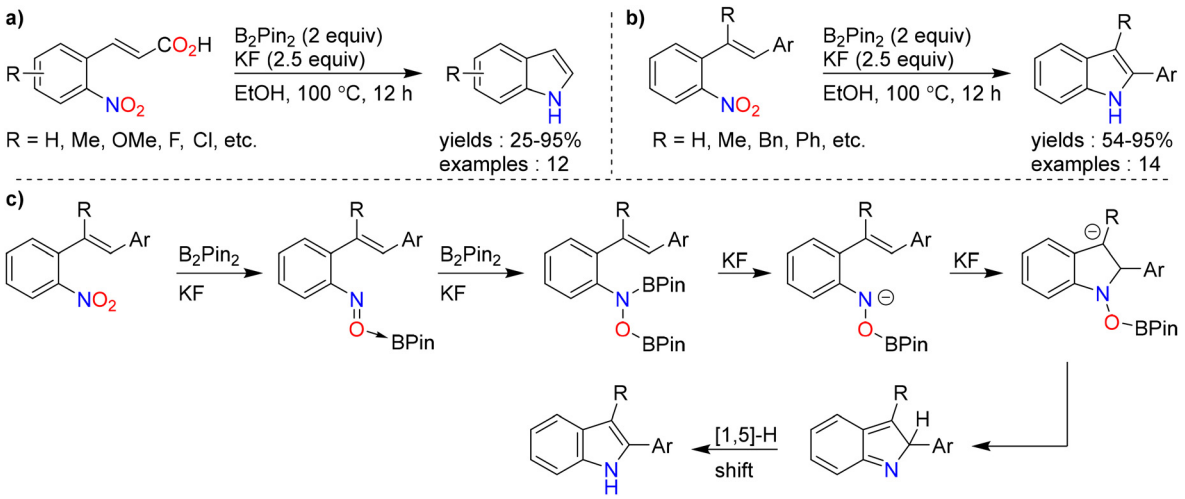
Scheme 34 Titanium(III)-supported intramolecular reductive annulation for indole synthesis.



Scheme 35 Synthesis of indoles from chalcones.



Scheme 36 Synthesis of *N*-hydroxyindoles from 3-(2-nitrophenyl)acrylic acid.



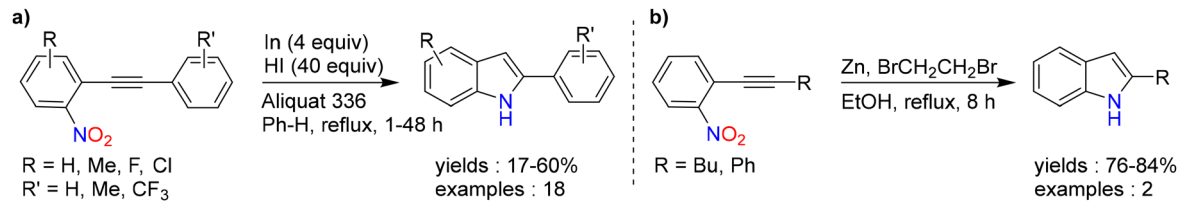
Scheme 37 Reductive annulation of nitrostyrenes to indoles using B_2Pin_2 and KF reagents.

nitro group into a nitroso intermediate. Further, it reacts with another mole of bis(pinacolato)diboron, and then undergoes annulation followed by a [1,5]-sigmatropic shift affording the indoles (Scheme 37c).

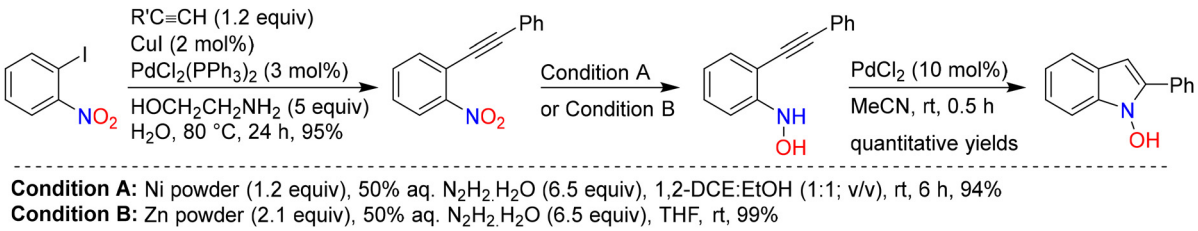
Alkynes can easily be prepared by the most frequent reaction, *i.e.*, Sonogashira coupling, and then the obtained starting materials were further treated with the metals In and Zn upon activation with additives HI/Aliquat and dibromoethane.[184] Remarkably, both metals are known for the reduction of selective functionalities *via* the electron transfer mechanism. Herein, the nitro group is reduced by the metals, and the salts are formed during these reactions, activating the triple bond for the annulation reaction, which leads to the formation of the heterocyclic indole compounds (Scheme 38).[185]

Oh and Shin have reported a tandem reaction for the synthesis of 1-hydroxyindoles from *ortho*-iodonitrobenzene.[186] Herein, these reactions were performed *via* a cascade of reactions, *i.e.*, Sonogashira coupling, selective partial reduction, followed by a Pd(II)-catalyzed electrophilic annulation reaction, affording the hydroxyindoles with overall moderate to good yields (Scheme 39).[187]

In 2021, Ying *et al.* vastly developed a novel approach for the synthesis of 1-aroyl-2-arylindoles through a coupling reaction between disubstituted *ortho*-nitroaryl acetylene and iodoarenes in the presence of $Zn/ZnI_2/Co_2(CO)_8$ and a catalytic amount of



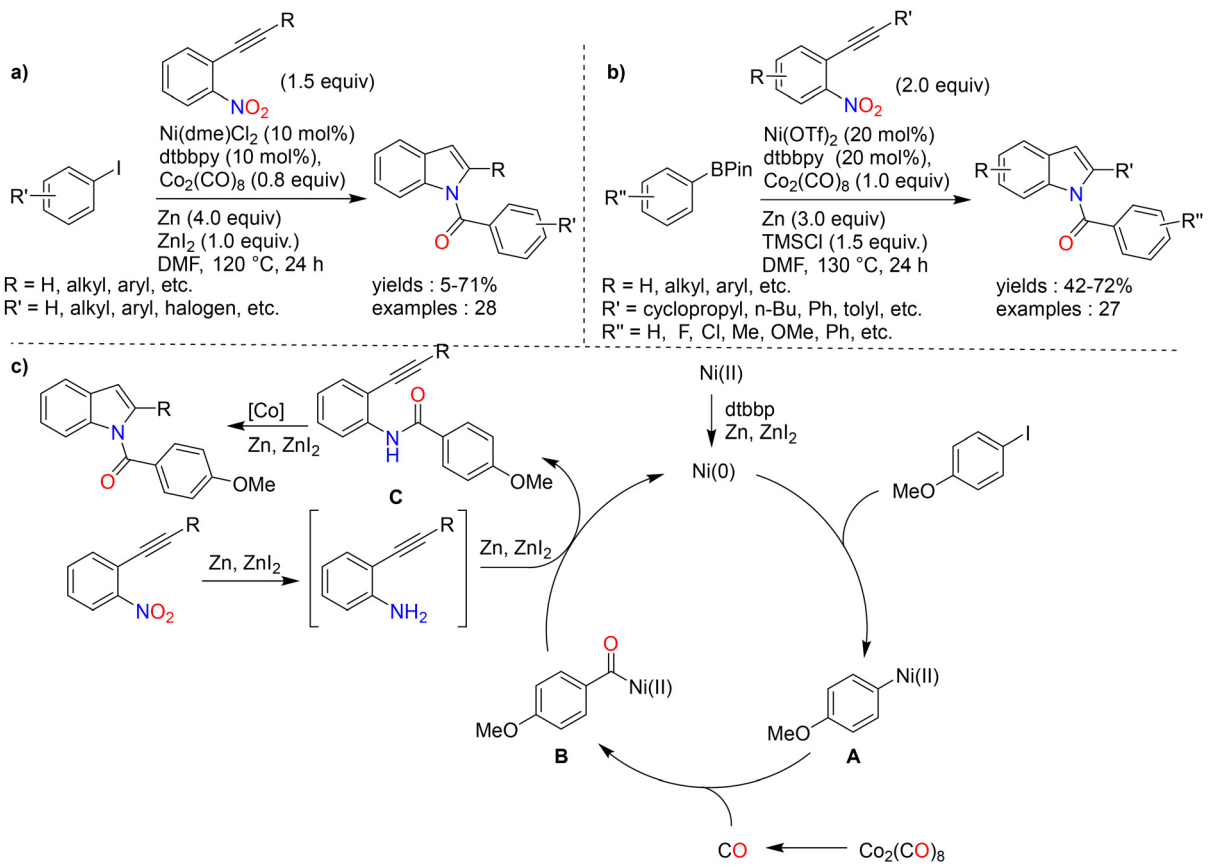
Scheme 38 Synthesis of indoles using In and Zn metals *via* an intramolecular reductive-annulation reaction.



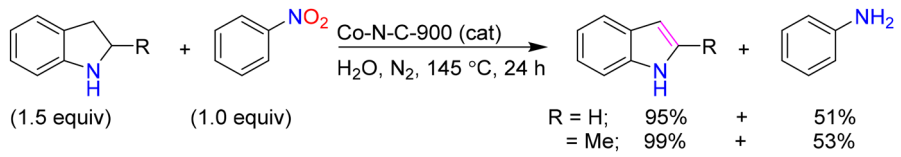
Scheme 39 Synthesis of *N*-hydroxyindoles *via* a Pd(II)-catalyzed intramolecular annulation reaction.

Ni(II) salt and the 4,4′-di-tert-butyl-2,2′-dipyridyl (dtbbpy) ligand in DMF at 120 °C (Scheme 40a).[188] In 2022, the same group modified the previous protocol by replacing the iodoarenes, ZnI_2, and $Ni(dme)Cl_2$ with aryl boronate esters, TMSCl, and $Ni(OTf)_2$ and by changing their corresponding stoichiometric amounts and elevating the temperature, respectively (Scheme 40b).[189] The later improved protocol afforded better yields of the indoles than the previous one, and both reactions were well tolerated by a variety of functionalities of the substrates. The proposed mechanism for this coupling reaction involves the reduction of the Ni(II) catalyst to a catalytically active Ni(0) species, facilitated by dtbbpy and a Zn/ZnI_2 reducing system. Next, the Ni(0) species undergoes oxidative insertion with iodoarene, followed by carbonylation *via* the *in situ*-generated $Co_2(CO)_8$ reagent that transforms active species A to B. At the same time, chemoselective reduction of the nitroalkyne generates the aniline derivative due to the presence of the reducing agent Zn/ZnI_2 and then it immediately reacts with *in situ* generated reactive species B, generating the intermediate product C. Finally, it undergoes an annulation reaction that produces the corresponding *N*-aroyl indole with the aid of $Co_2(CO)_8$, zinc powder, and ZnI_2 (Scheme 40c).[188]

The cobalt nitrogen-doped carbon catalyst (Co–N–C-900) was employed to facilitate an *in-situ* hydrogen transfer reaction. This transformation proceeds *via* a redox process, where dihydroindoles are generated through the reduction of nitroarenes[190a] (Scheme 41). The reaction likely involves a Skraup-type mechanism, consistent with quinoline synthesis.[190b]



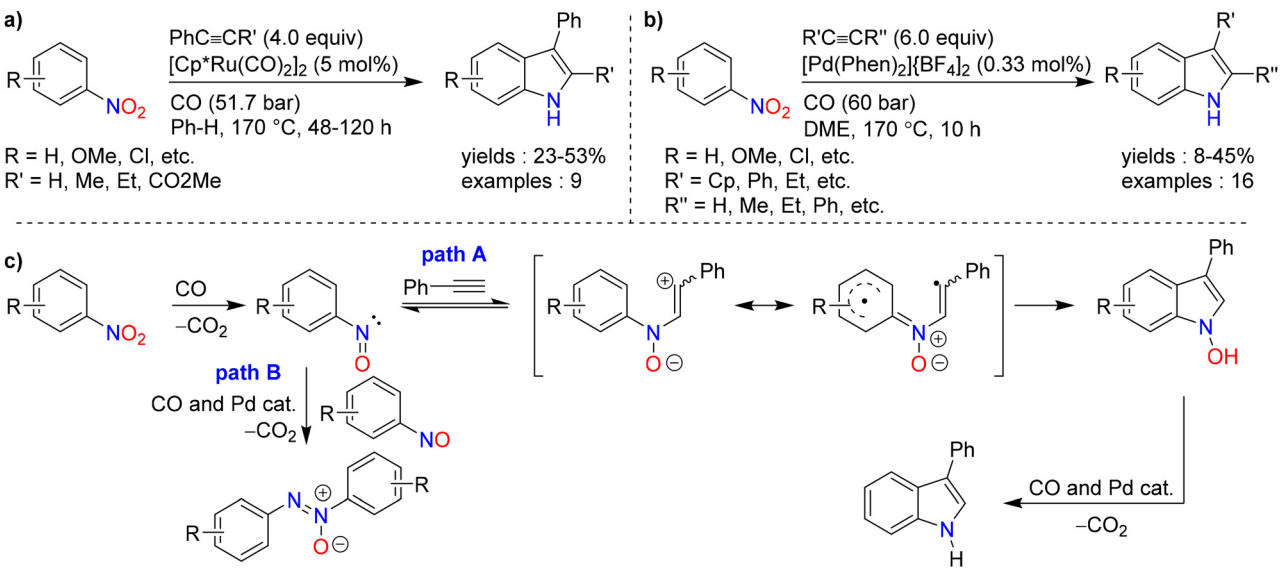
Scheme 40 Ni(II) catalyzed synthesis of *N*-aroylindoles from 2-nitroalkynes.



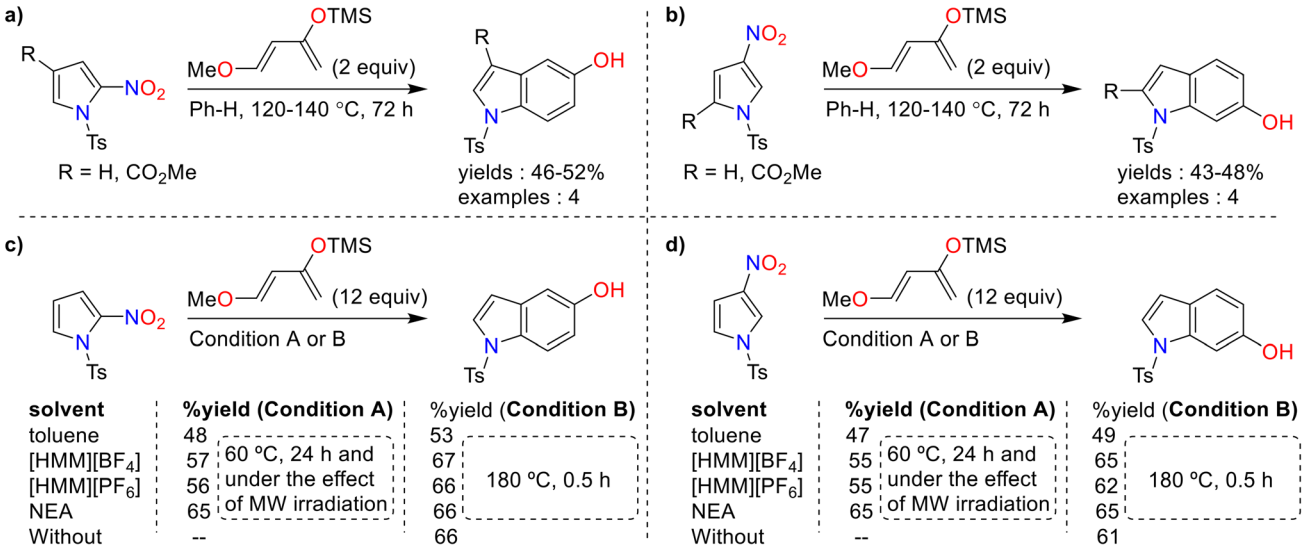
Scheme 41 Oxidation of dihydroindoles with nitrobenzene.

Cycloaddition approach. In 2002, K. M. Nicholas and his group developed a novel approach for indole synthesis through reaction of nitroarenes and alkenes in the presence of $[Cp^*Ru(CO)_2]_2$ and a carbon monoxide atmosphere at 750 psi (Scheme 42a).[191] This developed procedure also had some limitations, such as regioselectivity and solvent selection, which resulted in inferior yields. At the same time, his group also performed mechanistic investigation by additionally adding the corresponding nitrosoarene in the same reaction mixture and reported a superior yield of the indole. Later, they explored indole synthesis from nitrosoarenes and alkynes and found that the current synthesis procedure gives higher yields than the previous one.[192] Ragaini *et al.* utilized palladium–phenanthroline complexes to get the indole derivative similarly at 60 bar pressure and synthesized a library of compounds with yields of 8–45% (Scheme 42b).[193a] However, the exact mechanism is unclear. In mechanistic studies, it was also found that the nitro group converted into the nitroso derivative and then underwent an addition reaction with alkynes to furnish the indoles as the major products. During the controlled experiment, they observed that the absence of either catalyst or carbon monoxide does not favour the reaction in the forward direction. Based on their controlled experiments, they also assumed that the interaction between the nitrosoarene (it might be generated from the reduction of nitroarene with CO) and the alkyne takes place outside the metal's coordination sphere, as suggested by Nicholas and co-workers (Scheme 42c).[191,192] The regioselective addition of alkenes to nitrosoarenes generates dipolar α-styryl cation intermediates, as supported by theoretical studies.[193b] Additionally, the formation of α-styryl radicals has been confirmed by EPR spectroscopy.[193c] Furthermore, it affords the indoles *via* intramolecular annulation followed by carbon monoxide deoxygenation (Scheme 42c, path A). At the same time an alternative path was also found that leads to the formation of azoxyarenes *via* self-dimerization in the presence of carbon monoxide. We assume that this can be an insightful and selective synthetic approach for indole analogues.

Mancini *et al.* introduced a route different from the previous reports for the synthesis of indoles *via* the cycloaddition approach without any kind of metal catalysts.[194] In this work, they elaborated on the reactions between different types of 1-tosyl-nitropyrroles (electrophilic dienophiles) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (nucleophilic Danishefsky's diene) in non-polar benzene at 120–140 °C (Scheme 43a and b). Here, the 1-tosyl-2-nitropyrroles upon cycloaddition with Danishefsky's diene, followed by nitrous acid elimination and desilylation, produced the corresponding 5-hydroxyindoles. In contrast, 6-hydroxyindoles were obtained from 1-tosyl-3-nitropyrroles, likely due to electronic effects influencing the regioselectivity of the cycloaddition.[195] However, this work was performed with isoprene and *N*-(buta-1,3-dien-1-yl)-*N*-propylaceta-



Scheme 42 Cycloaddition approach for indole synthesis.



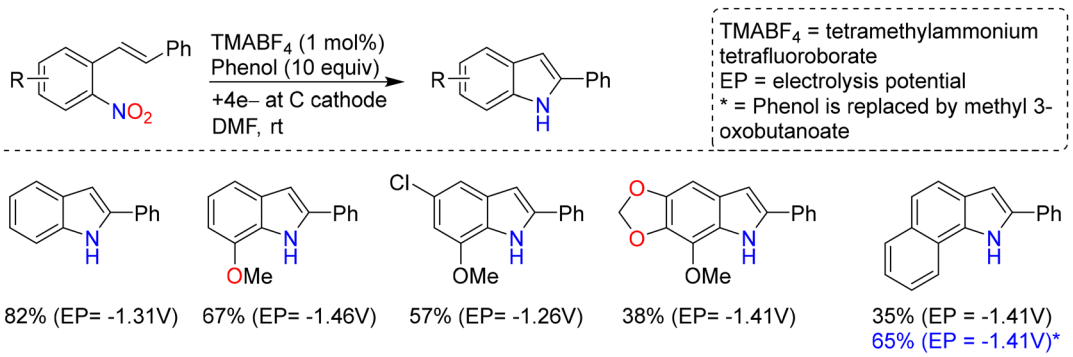
Scheme 43 Synthesis of indoles from electrophilic dienophiles with Danishefsky's dienes.

mide, which also produces the annulation product with poor yield. Furthermore, the reaction was explored by the same group for indole products under microwave-assisted conditions with and without solvent, where they found a higher yield than that of the previous reaction protocols (Scheme 43c and d). Similarly, the reactions were also performed with two more nucleophilic dienes, such as isoprene and 1-trimethylsilyl-1,3-butadiene, which also afforded poor yields of *N*-tosylindoles (The solvents [HMIM][BF_4], [HMIM][PF_6], and [NEA] have been prepared according to the previously reported methods).[196]

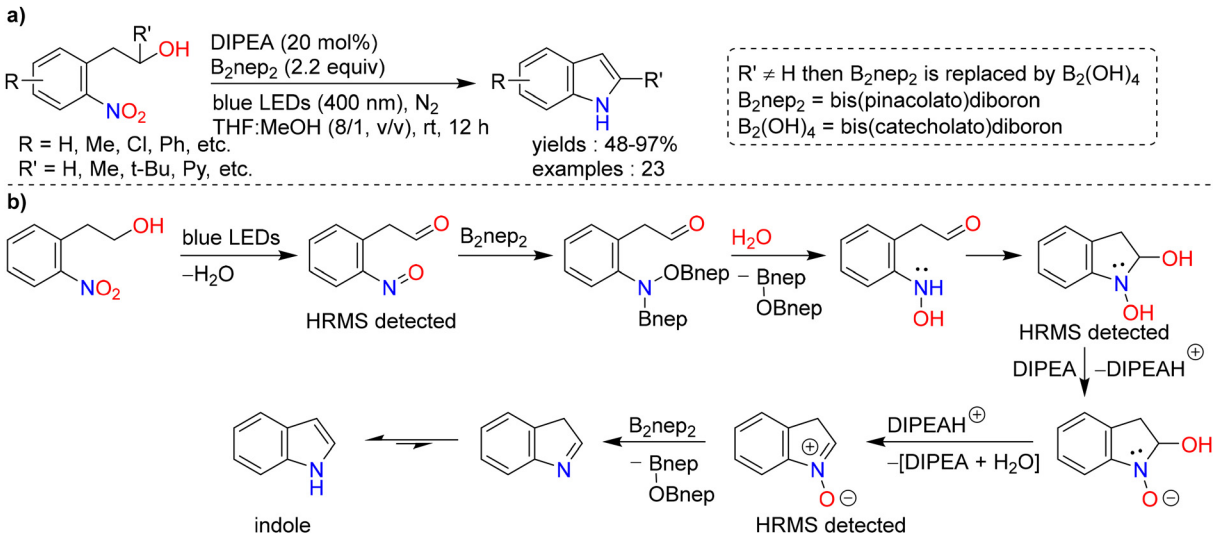
Electrochemical approach. Peters and his coworkers reported an electrochemical reductive approach[197] for indole synthesis at carbon cathodes in deoxygenated *N*,*N*-dimethylformamide using tetramethylammonium tetrafluoroborate as an electrolyte and an excess amount of a proton donor source such as phenol or methyl 3-oxobutanoate at room temperature with yields of 35–82% (Scheme 44).[198] For the justification of the indole synthesis, it was believed that the reaction proceeded with the nitrene intermediate as formed in the case of the Soderberg approach. In the following reaction, the synthesis of 2-phenyl benzoindole phenol offered a poor yield of 35%. Hence, it was replaced by the same equivalent of a strong acidic proton source such as methyl 3-oxobutanoate which furnished a superior yield of 65% compared to the prior protocol.[199]

Photochemical approach. Wang *et al.* performed the synthesis of indoles from *ortho*-nitrohomobenzyl alcohols by employing diborane and DIPEA under 400 nm blue LEDs (Scheme 45a). Herein, the nitro- and hydroxyl-groups underwent intramolecular redox reactions in the presence of blue LEDs to form 2-(2-nitrosophenyl)acetaldehyde, which is then reduced with the diborane derivative to form 2-(2-(hydroxyamino)phenyl)acetaldehyde.[200] Furthermore, it cyclized to form the indoline-1,2-diol intermediate, which later underwent base-mediated dehydration and diborane-mediated deoxygenation and aromatization reactions giving the indole (Scheme 45b).[201]

Waheed and his coworkers successfully attempted the photoinduced synthesis of indoles from nitrostyrenes with



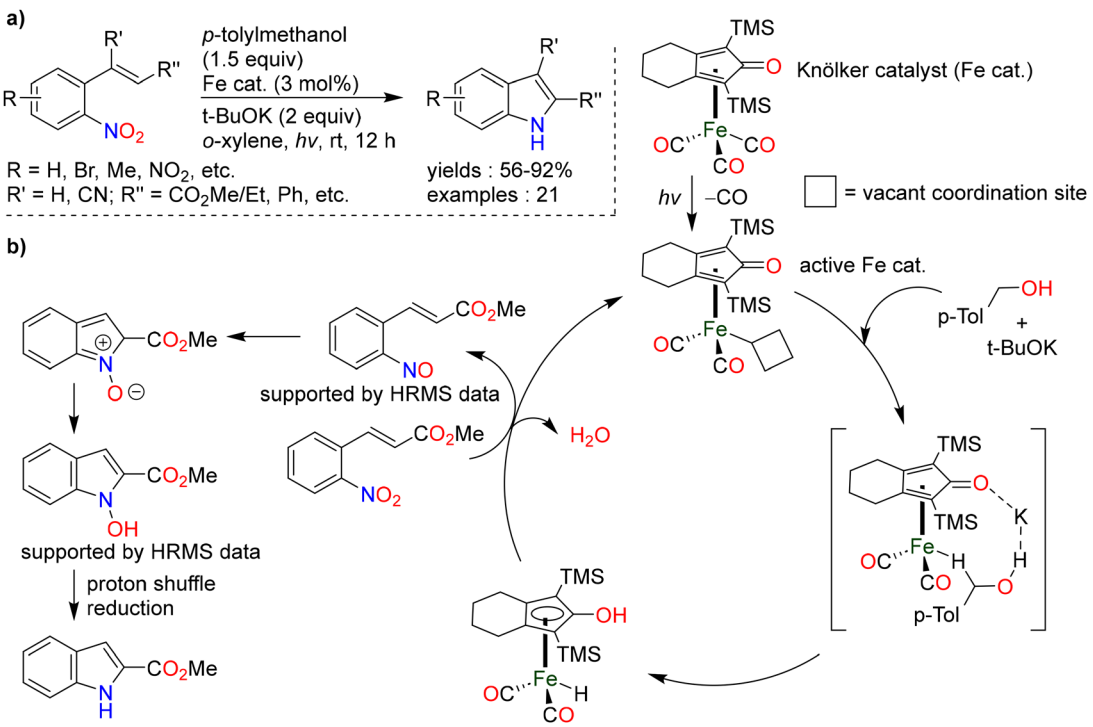
Scheme 44 Electrochemical approach for the synthesis of indoles.



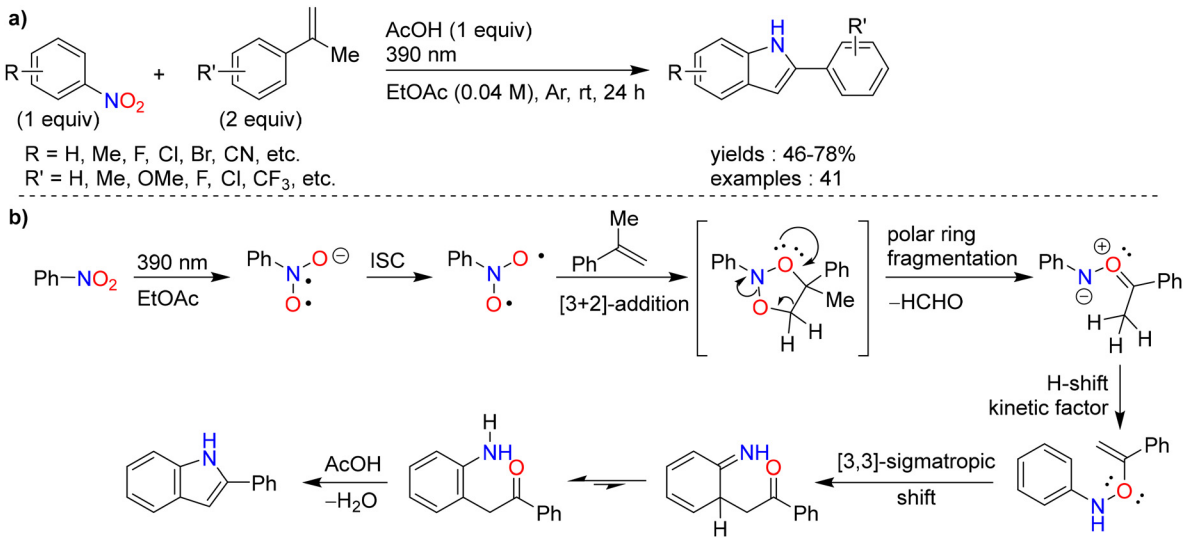
Scheme 45 Synthesis of indoles from *ortho*-nitrohomobenzyl alcohols.

the help of the Knölker catalyst and 4-tolylmethanol in a basic medium at rt.[202,203] This synthetic procedure was employed for the exploration of the synthesis of a variety of indoles in good to excellent yields (Scheme 46a). They have proposed a mechanism of reaction, where the Knölker catalyst plays a significant role in the reduction of the nitro group to nitroso and then hydroxyindoles to indole derivatives. Here, 4-tolylmethanol acts as a reducing agent of the Knölker catalyst. The formation of the intermediate nitroso and hydroxyindoles was confirmed by HRMS data analysis (Scheme 46b).

Dayong Shi and coworkers explored a novel photochemical approach of Bartoli indole synthesis by the reaction between nitroarenes and *gem*-methylstyrene in a mild acidic medium under an inert atmosphere[204] by applying 390 nm light in ethyl acetate. The reaction worked well for a wide range of substrates having halogens, nitriles, acids, esters, *etc.* (Scheme 47a). They have proposed a mechanism in which the



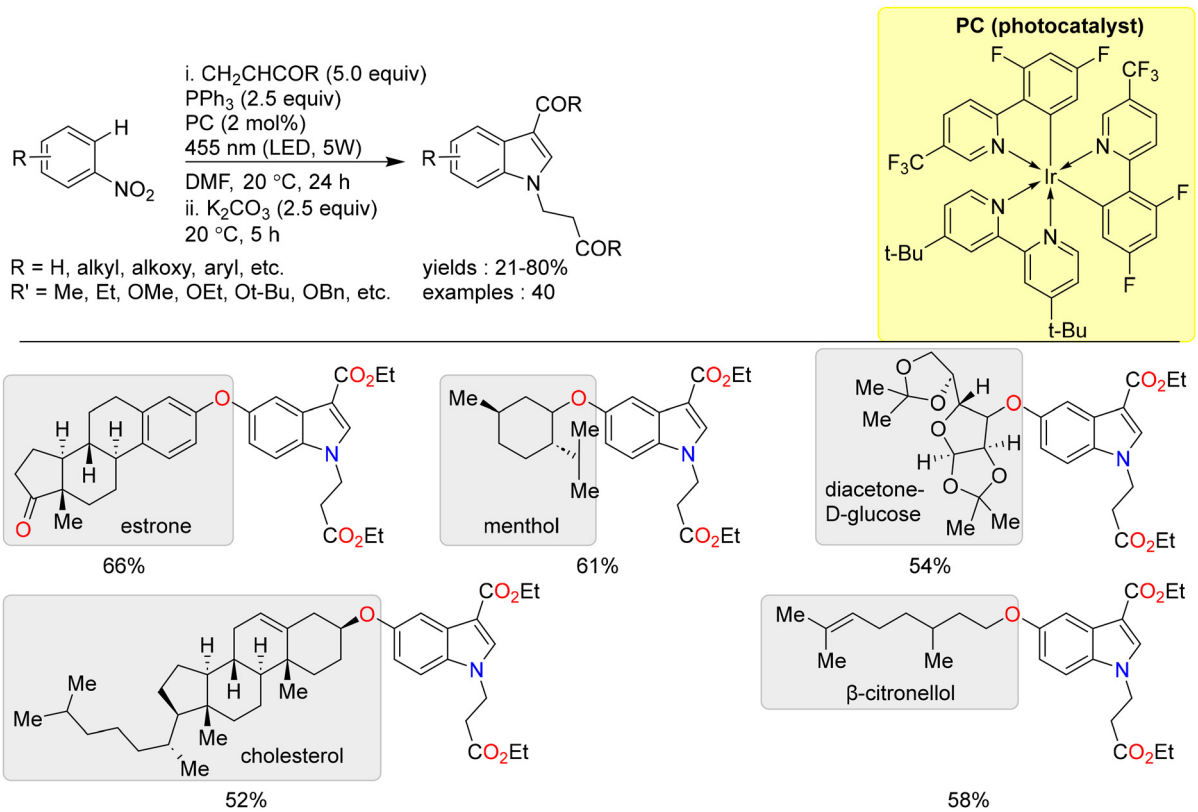
Scheme 46 Photochemical synthesis of indoles from nitrostyrenes using the Knölker catalyst.



Scheme 47 Photoinduced Bartoli indole synthesis.

nitroarene produces diradical species *via* the ISC process when employing light of 390 nm wavelength, which forms a [3 + 2]-cycloadduct with methylstyrene, and then it produces a dipolar intermediate *via* a favoured polar ring fragmentation reaction. Next, this dipolar species forms the 2-(2-aminophenyl)acetophenone intermediate *via* the cascade of hydride and [3,3]-sigmatropic shifts. Finally, 2-(2-aminophenyl)acetophenone forms the desired product by a dehydration reaction in the presence of acetic acid (Scheme 47b).

In 2024, Studer and his group developed an excellent approach for the synthesis of *N*-alkylated indoles *via* a photochemical [3 + 2]-cycloaddition reaction.[205] To demonstrate [3 +



Scheme 48 Photocatalyst-induced reaction of nitroarenes with vinylketones/esters for indole synthesis.

2]-annulation, they chose nitroarenes and vinyl ketones/esters as the 3- and 2-skeleton constituents, respectively. The nitroarenes are activated in combination with vinyl ketones/esters using an iridium-based photocatalyst (PC) to initiate a chain reaction of the radical annulation process while maintaining light irradiation of 455 nm with the help of a 5-watt light-emitting diode (LED) at the ambient temperature. The developed reaction conditions were well tolerated for the synthesis of a myriad of indoles and afforded moderate to good yields of 21 to 80%. In some cases, the reaction suffered from regiochemical annulation, which reduced the formation of the desired products. This work also had good enough novelty in the direct synthesis of pharmacophores and natural product components with a combination of indoles such as estrone, L-(−)-menthol, diacetone-D-glucose, cholesterol, and β-citronellol with yields of 52–66% (Scheme 48).

3. Conclusions

This review describes the classical to modern approaches for indole synthesis using nitroarenes and through their precursor routes. Chemists are showing interest in indole synthesis due to the high bioactivity potential of indoles. Importantly, various synthons were utilized with commercial nitroarenes for the VNS reaction, which were treated as precursor intermediates of indoles. Also, synthetic approaches of hydroxyindoles are described, as they can be further transformed into the desired indoles by easily accessible reduction methods. In the classical approaches, most of the indole analogues were synthesized from *ortho*-substituted nitroarenes, such as Cadogan, Bartoli, Knochel, Batcho–Leimgruber, *etc*., and also without *ortho*-substituted arenes such as in Bartoli indole synthesis. Furthermore, several other recent approaches have been developed, where the indole syntheses are conducted using transition metal catalysts such as palladium, molybdenum, nickel, zinc, *etc*. in diverse modified advanced protocols with convenient and easily available sources to develop cost-effective synthesis. Furthermore, the novel photochemical and electrochemical approaches are also promising for the progression of indole synthesis. We assume that this study can provide a better understanding of the synthesis of indole-derived natural products, drugs, and complex heterocyclic molecules. Thus, our study can play a significant role in both academics and research.

3.1. Future aspects

Herein, various approaches based on cascade, tandem, and multistep reactions have been studied. We assume that this study can provide ample knowledge for the construction of indoles and can provide a better platform for its development.

1. Additionally, the VNS approach has been described to develop the precursors of indoles, which can play an important role in the synthesis of the desired substituted indole derivatives.

2. The synthesis of *N*-hydroxyindoles is also included to provide an alternative way, as they can easily be transformed into indoles *via* selective reduction methods, such as Zn/AcOH, PPh_3, $TiCl_3$, *etc*.

3. Despite the vast progress in indole chemistry, the chiral approach remains underexplored, highlighting the need for the development of catalytic as well as enantioselective methods.

4. These methods will not only allow the synthesis of indoles, but can also provide a platform for the easy synthesis of indole derivatives like carbazoles, indolocarbazoles, diphenyl indoles, 1,2-disubstituted indoles, *etc*.

5. This study provides the approaches of one-pot, single-step as well as multistep reactions and tandem synthetic approaches for various indoles.

6. This study affords the direct and sustainable routes from nitroarenes/*ortho*-substituted nitroarenes to indoles by leveraging photochemical, electrochemical, and metal-free catalysis. Additionally, expanding the substrate scope to electron-deficient and sterically hindered nitroarenes, improving the step economy, and integrating continuous flow processes may address current limitations and establish nitroarene-based approaches as mainstream strategies for indole synthesis.

7. The photochemical strategies can be an insightful approach for the direct access to indoles from nitroarenes, often bypassing the intermediate aniline, and by focusing on such emerging methodologies, a critical comparison with traditional multistep routes can be adopted simply. At this time, the advancements have introduced one-pot, tandem, and photochemical strategies enabling more direct access, often bypassing the aniline intermediate.

8. The nitroarenes/*ortho*-substituted nitroarenes have moderate to excellent tolerance against acid as well as base in the synthesis of target molecules. Hence, these methodologies can provide a great base for the development of several bioactive indoles in the pharma and chemical industries in the future.

Data availability

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review.

Conflicts of interest

All the authors declared that there are no conflicts to declare.

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