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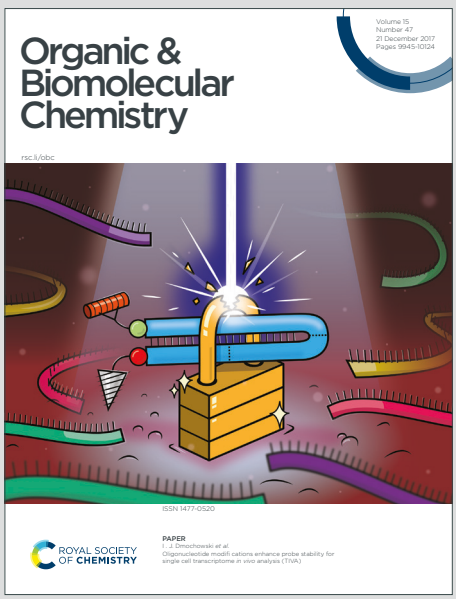

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REVIEW

A Review on Indoles Synthesis from Nitroarenes: Classical to Modern Approaches

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Indole is a highly privileged and versatile heterocyclic pharmacophore that plays a crucial role in natural product synthesis, drug discovery, pharmaceuticals, and medicinal chemistry. This review provides a comprehensive analysis of various synthetic approaches to indole 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, etc. 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.

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 for their unique ability to bind 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 heterocyclic 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 Figure 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 and 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 (Figure 1).[22, 28, 70-79] . Numerous strategies have been developed and widely employed for constructing indoles and their macrocycles.[80]

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DOI: 10.1039/x0xx00000x

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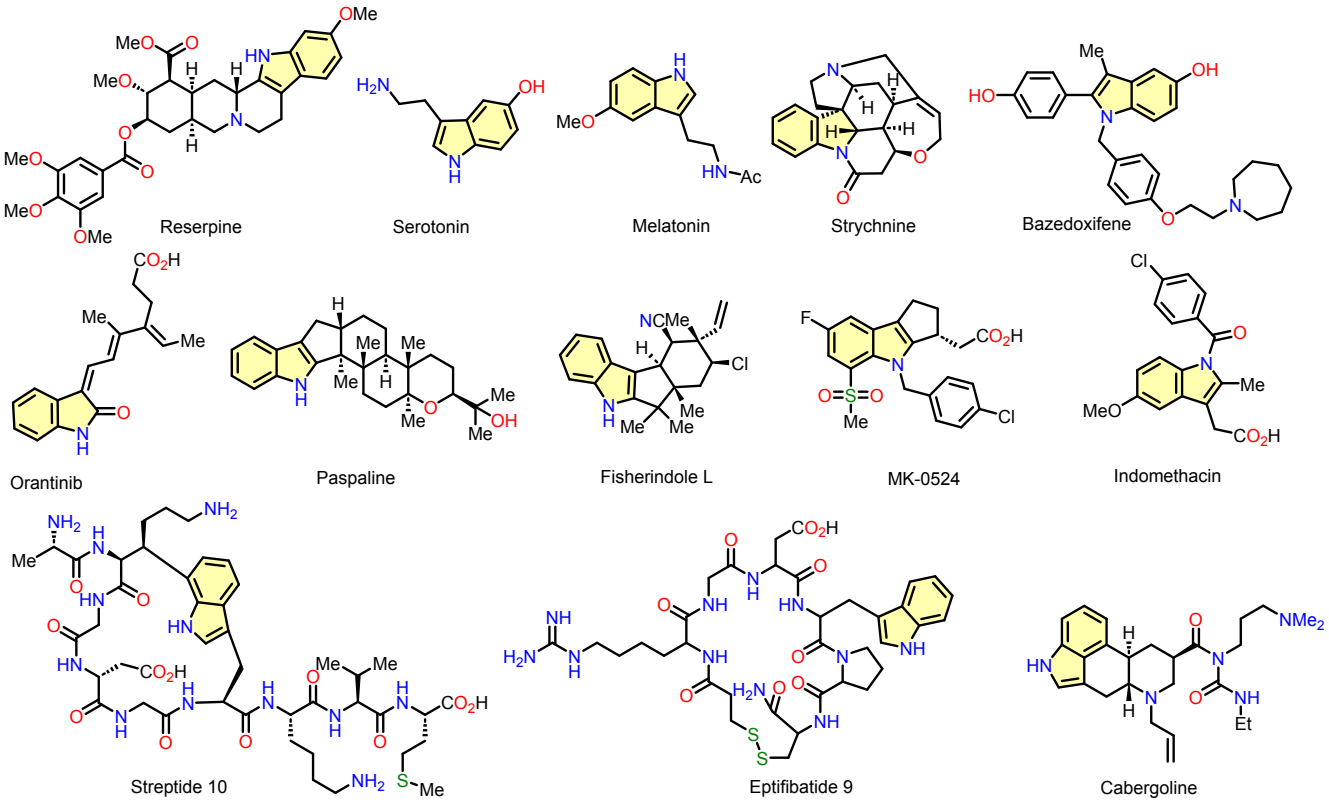

Figure 1. Biologically relevant indole-based heterocycles.

To date, limited reactions have been reported to have easily accessible greener protocols with the formation of efficient yields.[81] Herein, some of the important well-established classical name reactions for its 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, and Sundberg indole synthesis, etc.[84]. Among these, various protocols lead to the formation of indoles in single-pot and multistep operations (Figure 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 the 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 single-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 the intramolecular annulation, where the five-membered ring is newly generated via the intramolecular as well as the coupling reaction, followed by intermolecular annulation.

2. Diverse Synthetic Approach of the Indoles from the Nitroarenes

2.1. Vicarious Nucleophilic Substitution Approach for Indoles Synthesis *via ortho*-Functionalization of Nitroarenes. In this synthetic process, the nitrobenzene was converted into 2-nitrophenylacetonitrile and 4-nitrophenylacetonitrile (10:1 ratio) with the aid of 2-chloroacetonitrile as a base. This is also called vicarious nucleophilic substitution (VNS) and is involved in the synthesis of indoles *via* the VNS followed by an annulation reaction commonly assigned as Mąkosza Indole synthesis, cf..

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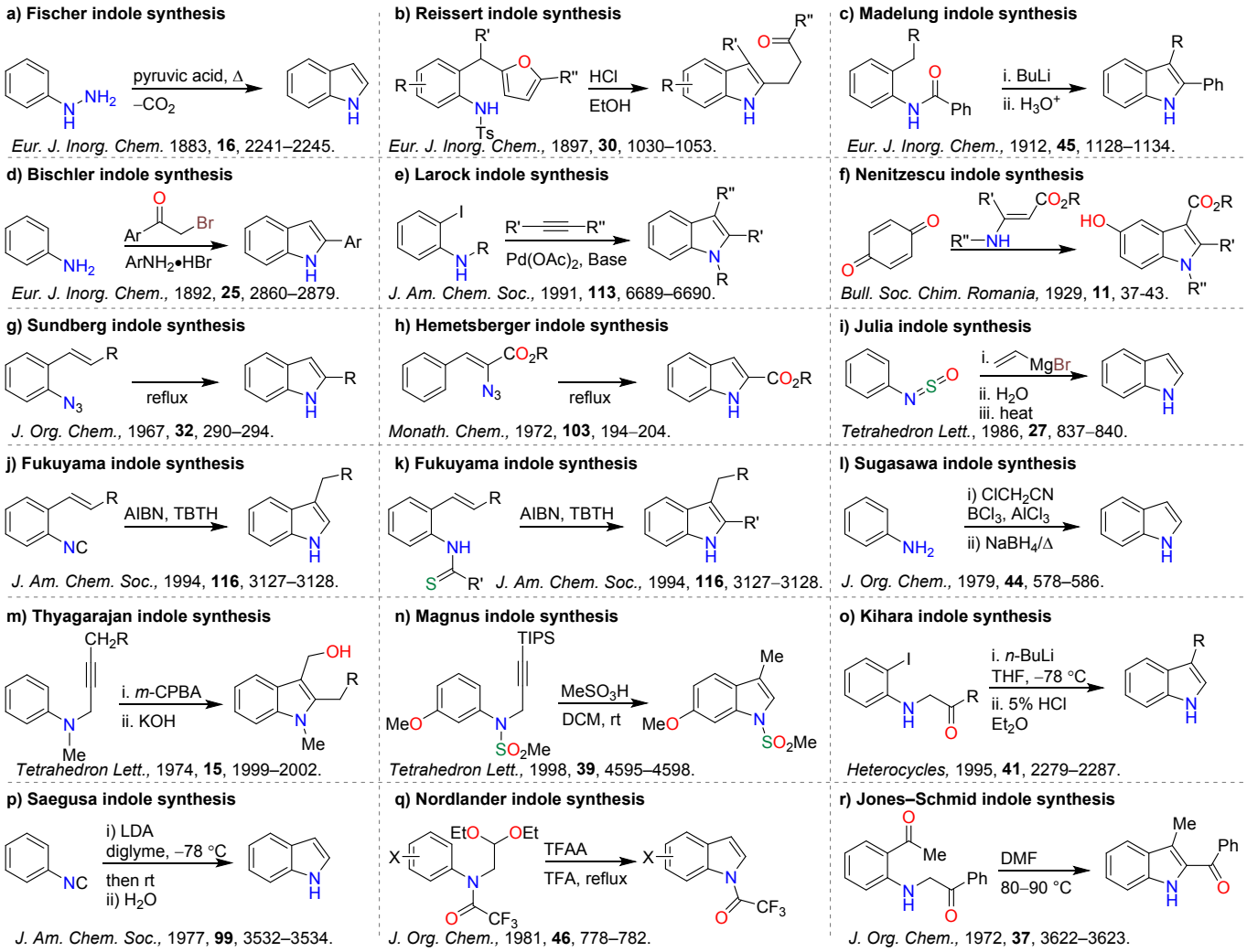

Figure 2. Classical Approaches for the Synthesis of Indoles.

Scheme 1.[86] However, the reductive annulation of the indole's synthesis with the corresponding intermediate 2-nitrobenzonitriles is called as Pschorr–Hoppe indole synthesis.[87] Furthermore, the isolated crude mixture was employed for the hydrogenation reaction using 10% Pd/C in ethyl acetate. The *ortho*-reduced nitro group undergoes annulation with the nitrile group and then abolishes ammonia *via* the 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 the 6-(pentafluorosulfanyl)-1*H*-indole from the pentafluoro(3-nitrophenyl)-λ⁶-sulfane was a chaotic protocol due to the four-step synthesis and cost-ineffective method (Scheme 2a). Herein, a modified methodology has been accomplished for the synthesis of indoles from the pentafluoro(4/3-nitrophenyl)-λ⁶-sulfane within two steps with the help of 2-phenoxy acetonitrile in a basic medium and hydrogenation with the hydrogen gas and Pd/C (Scheme 2b).[95]Although the overall yield was lower compared to the previous method but this approach remains attractive due to its simplicity, reduced reaction time, and cost-effectiveness.[96] The reaction of pentafluoro(3-nitrophenyl)-λ⁶-sulfane with 2-phenoxy acetonitrile affords VNS products as the mixture of both *ortho*- and *para*-derivatives in the ratio of (85:15; 73%), whereas the pentafluoro(4-nitrophenyl)-λ⁶-sulfane ends up with only the *ortho*-VNS product with the high

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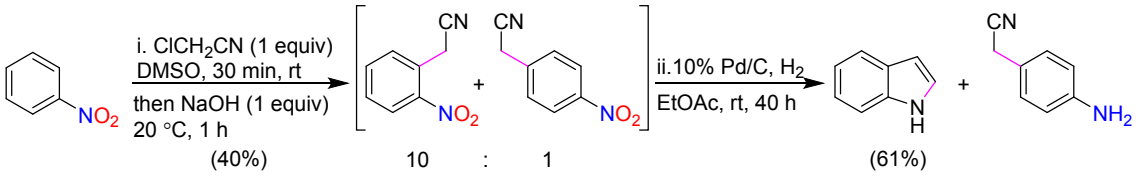
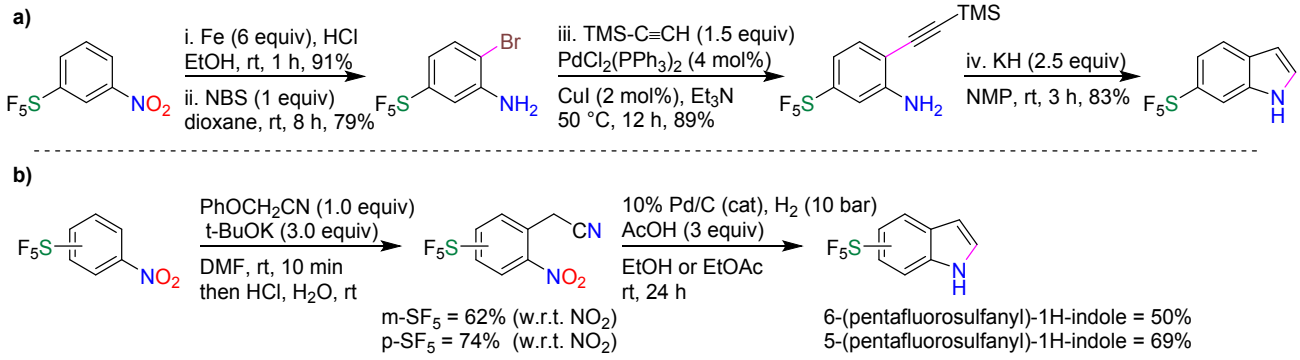
yield of 74%. Among these, pentafluoro(4-nitrophenyl)-λ^6-sulfane to 5-(pentafluorosulfanyl)-1*H*-indole leads to a high reaction yield due to the good to excellent yield of each step, cf. Scheme 2.

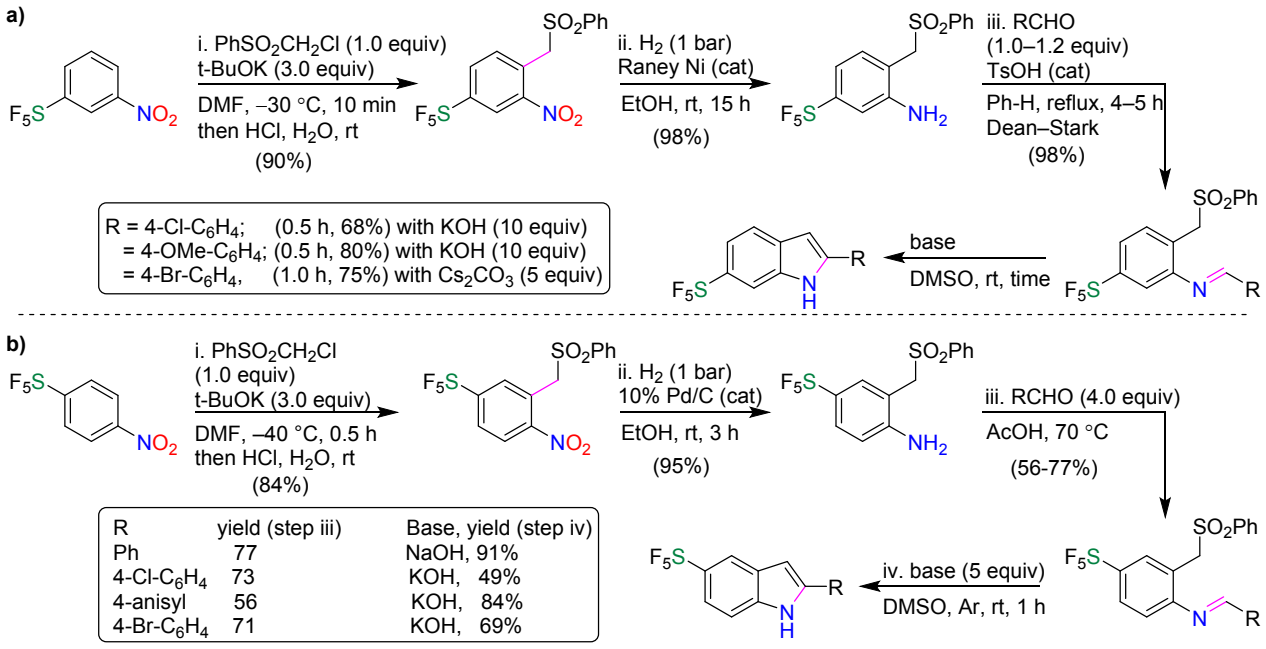
An alternative strategy for synthesizing 2-aryl 5/6-(pentafluorosulfanyl)indoles[96, 97] has been explored by replacing the reagent chloromethyl phenyl sulfone instead of 2-phenoxy acetonitrile (Scheme 2b) under a basic medium (Scheme 3).[95] This approach involves a reduction with Raney Ni or Pd/C catalysed hydrogenation, followed by imine formation with an aldehyde and annulation reaction leading to the formation of the 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 step, resulting in the indole yields of 68-80%, and its formation depends on the involvement of the aryl group during the annulation and aromatization reaction (Scheme 3a).



Scheme 1. VNS Reaction Using Chloroacetonitrile Followed by Hydrogenation Approach.



Scheme 2. VNS Reaction Using 2-Phenoxyacetonitrile Followed by Hydrogenation Approach.



Scheme 3. VNS Reaction Using Chloromethyl Phenylsulfone as the Key Step for Indoles Synthesis.

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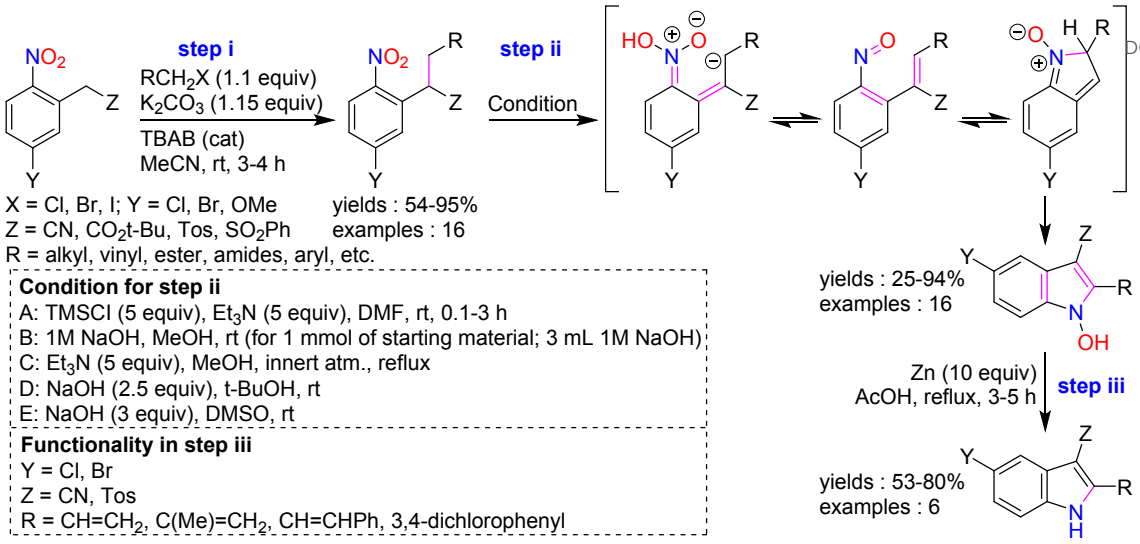

Scheme 4. Higher Indoles Synthesis via the Cascade of Benzyl Fictionalization, Intramolecular Annulation and Deoxygenation Reactions.

Notably, the synthesis involving 4-nitro(pentafluorosulfanyl)benzene, annulation in the fourth step under inert conditions with KOH, resulted in a significantly higher yield compared to reactions conducted under aerial conditions. Similarly, when benzaldehyde was subjected to annulation using NaOH, the 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.

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

The following examples also proceeded with a key step of VNS reactions, which was explored for the synthesis of *N*-hydroxyindoles as the end products. Wróbe and Mąkosza reported that the 4-halo-nitrobenzene on VNS reaction with chloroacetonitrile followed by condensation with ethanal afforded 2-(5-halo-2-nitrophenyl)but-2-enenitrile.[101] The annulations in the strong basic media (5M NaOH) in the methanol lead to the formation of the product quinoline N-oxide derivatives, and to lowering the concentration of the base (0.1M NaOH) by using the mixture of solvent systemMeOH: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). Next, the approach of indoles of the tuning of similar indoles with the electron-deficient substituents as constructed at the position-2 of indoles product has been explored in the reaction of dimethyl 2-cyanocyclopropane-1,1-dicarboxylate in the mild basic condition at very low temperature, followed by 0 °C.[102] The limitation of the reactions was found in 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 undergoes *ortho*-addition with nitrobenzene and it offers the sequence of intermediates 1 to 5, which further leads to the formation of *N*-hydroxyindoles derivatives as shown in step ii (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 the indoles as shown in step iii (Scheme 4).

Wróbel and Mąkosza explored a challenging approach for the synthesis of 7*H*-acenaphtho[1,2-*b*]indole from the 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).

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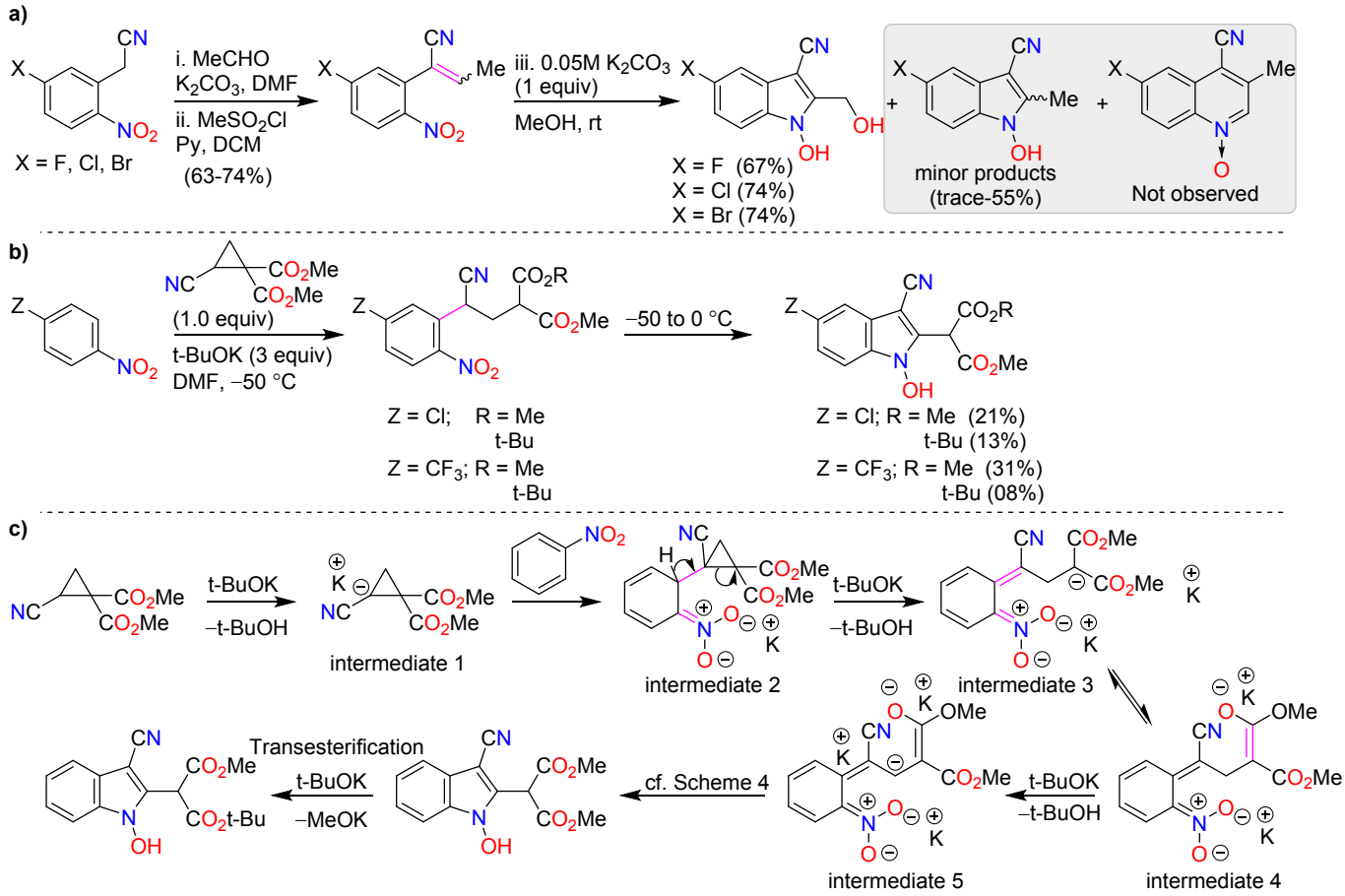
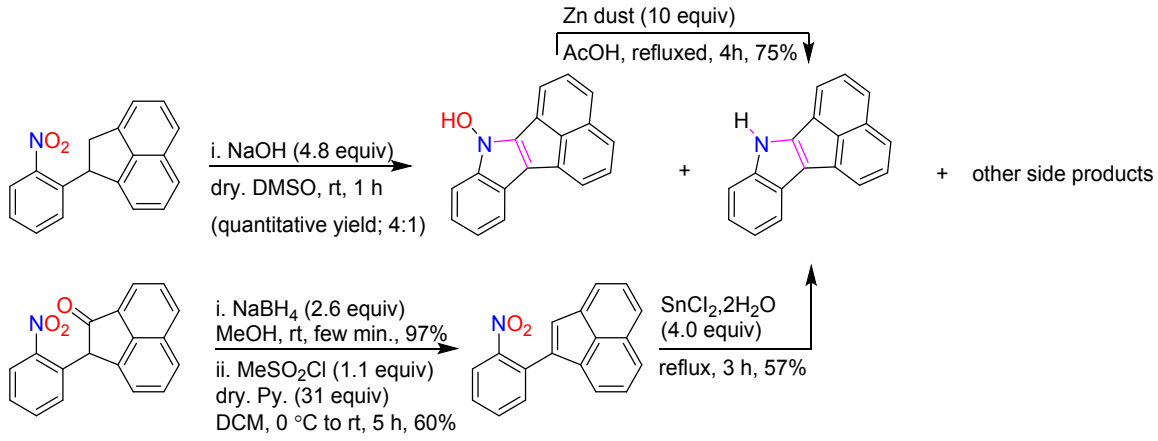


Scheme 5. Various Approaches for the Synthesis of 2,3-Disubstituted Indoles.



Scheme 6. Synthesis of Fused Indoles.

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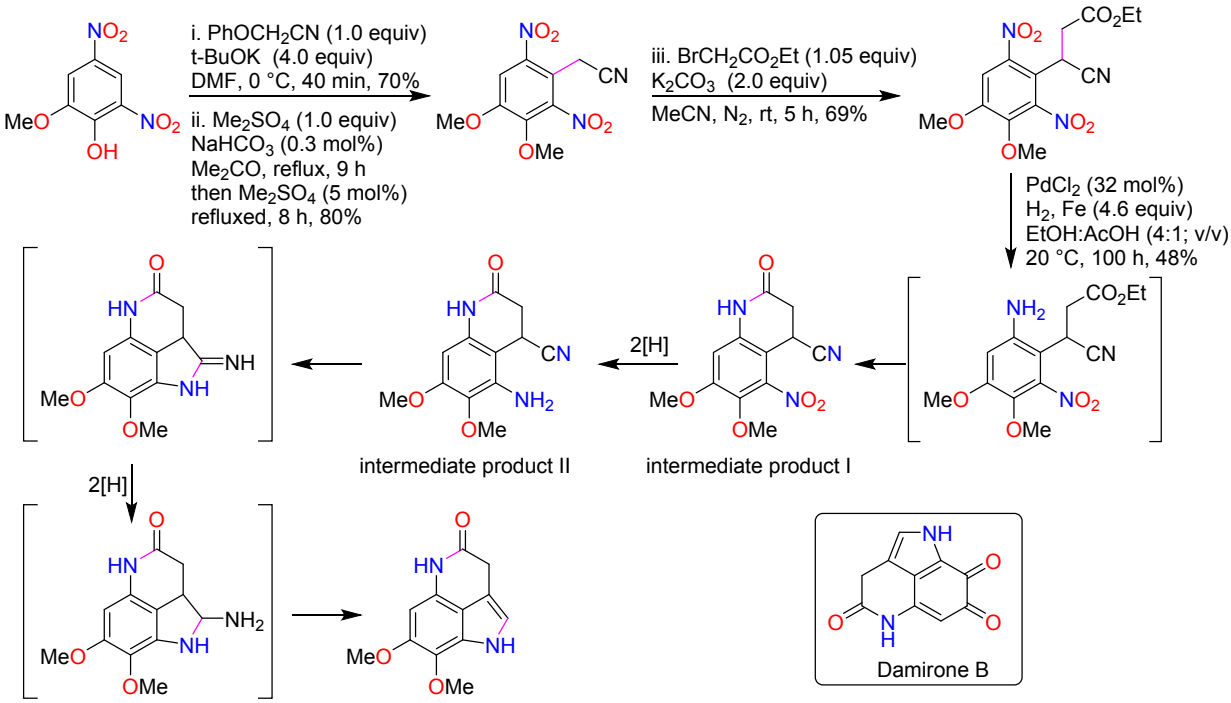
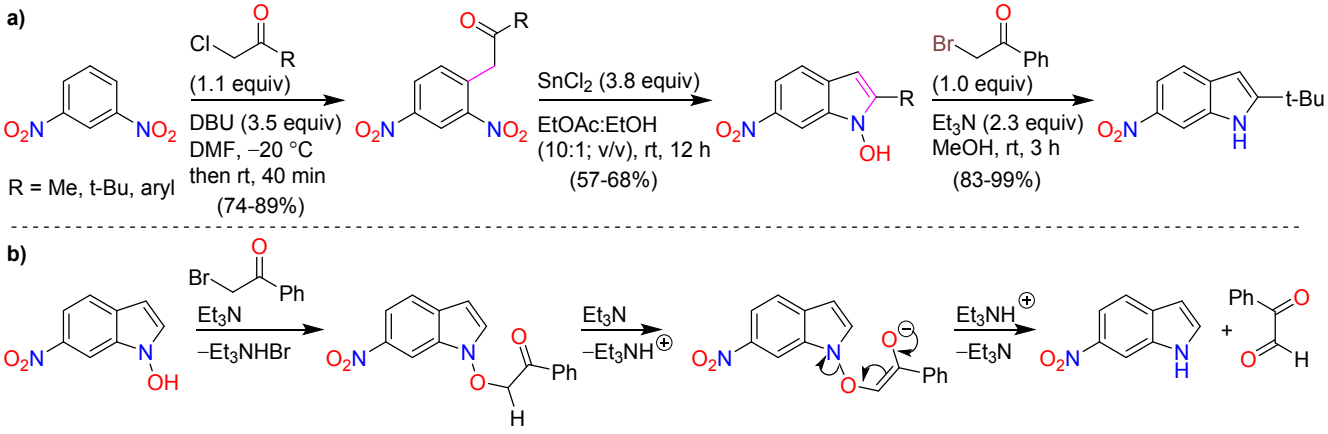


Scheme 7. VNS Reaction Involved in the Mimicking of Alkaloids.



Scheme 8. VNS Reaction using α-Chloroketone and Reductive-Annulation Followed by Deoxygenation for the *ortho*-Substituted Indoles.

Mąkosza and coworkers (1957) 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 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 the methylene functionalization on sequential treatment with dimethyl sulfate and ethyl bromoacetate in basic conditions. Furthermore, the hydrogenation of the achieved product with the palladium chloride/iron reagent system and hydrogen gas in the presence of polar mixed-solvent systems afforded an indole derivative with a yield of 48% (Scheme 7). However, the same reaction condition based on the temperature deviations of two different intermediate products isolated, i.e.,

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intermediate I (0 °C, 7 h) and intermediate II (30 °C, 7 h), was reported with the yield (88%).

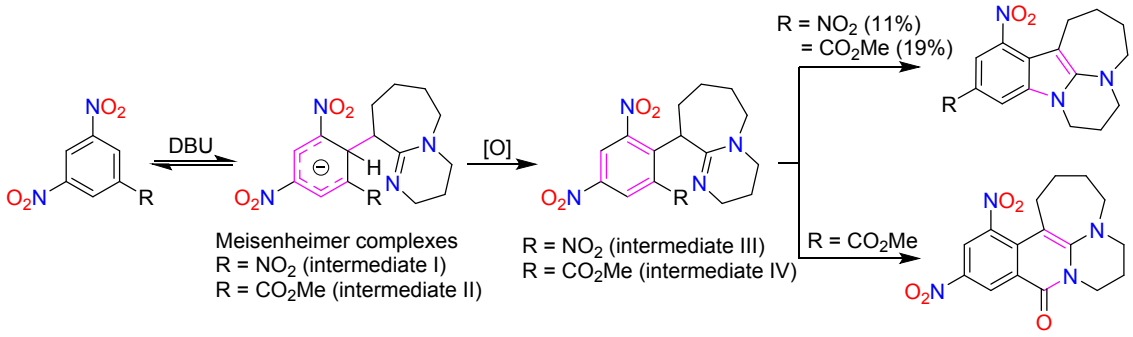
Wojciechowski et al. have developed a novel protocol for the synthesis of indoles from the commercially available compound dinitrobenzene.[105] Interestingly, they prepared the hydroxyindoles by the VNS reaction with α-chloroketones in basic media followed by a reduction process using stannous chloride. 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 the triethylamine (TEA) base as the mild protocol with excellent yields of 83-99% (Scheme 8a). Mechanistically, the nitro-hydroxyindoles undergo protection with α-bromoacetophenone and then further fragment into the desired product indoles and side products as the phenylglyoxal (Scheme 8b).

In 1997, Sutherland reported the unusual behavior of the 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, firstly, both the starting materials form Meisenheimer complexes as the intermediates I and II, which can be observed by the change of the deep red color of reaction mixtures. In the next step, these mixtures oxidized to form intermediates III and IV, which later undergo annulation reactions *via* the *ipso*-displacement offering indole analogues. Simultaneously, the intermediate also undergoes a six-membered isoquinolone product on cyclization with the ester group (Scheme 9).

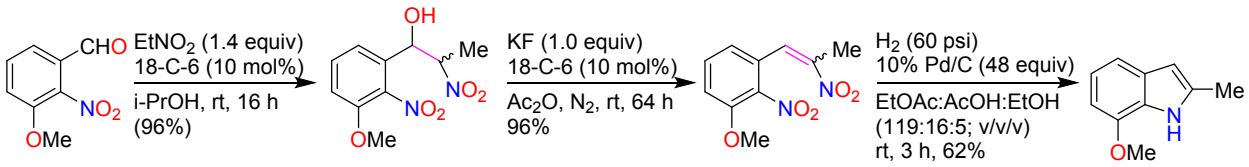
In 2001, Chen and coworkers reported the synthesis of 2-methyl-7-methoxyindole starting from 3-methoxy-2-nitrobenzaldehyde.[107] The reaction involved a cascade sequence of reactions (Henry reaction, condensation reaction, reductive annulation, and deaminative aromatization). This reaction has also been 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 the 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 on treatment with 2-nitrobenzaldehydes and ethyl diazoacetate in the presence of Lewis acid or Brønsted-Lowry acid, and the product formed by molecular rearrangement. In the final step, indole was achieved as the product after the hydrogenation of the first step associated with the reductive-annulation process (Scheme 11).

Soderberg et al. reported the synthesis of alkyl 2-(2-nitrophenyl)but-2-enoate by succeeding the Kosugi-Migita-Stille coupling and Barluenga coupling reactions, and the intermediate product was subjected to indole synthesis in the basic medium at 0 °C in butanol.[109] The reaction condition was well tolerated, and the library of the compounds was explored by this method and some of the approaches 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*-



Scheme 9. DBU Participating in the Indoles Synthesis *via* VNS Reaction as the Key Step.



Scheme 10. Synthesis of Indoles *via* Henry Condensation Followed by Hydrogenation Reaction.

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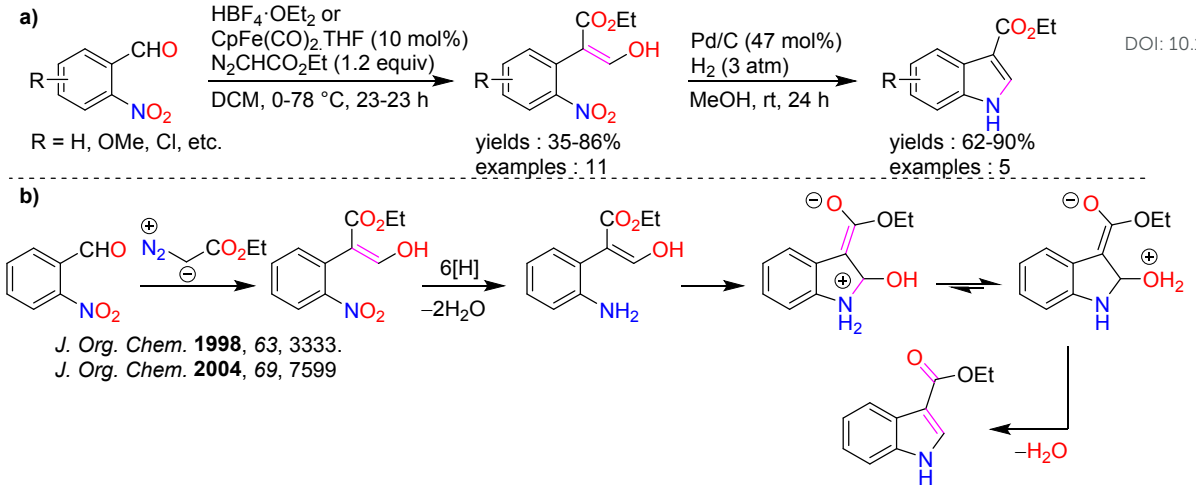
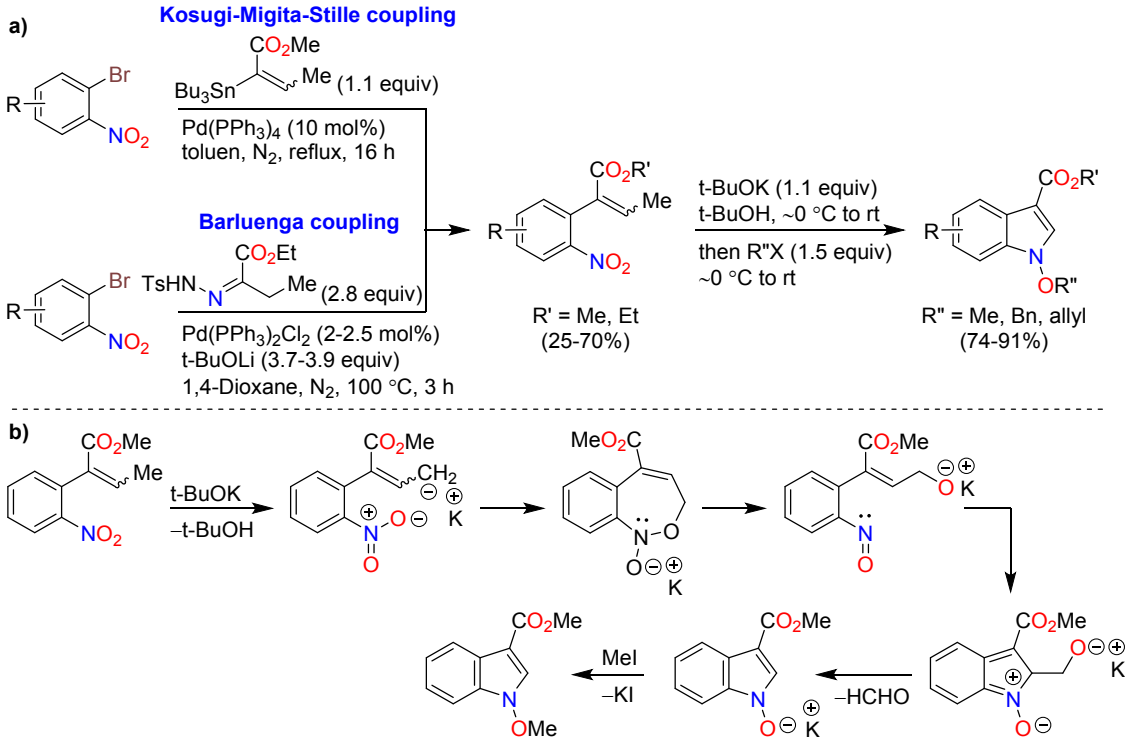


Scheme 11. Tandem Approach for the Synthesis of Indoles from the 2-nitrobenzaldehydes.



Scheme 12. Synthesis of *N*-Hydroxy/Alkoxyindoles.

indole-3-carboxylate on treatment with methyl iodide, cf. Scheme 12b. However, when the methyl of the vinyl group was substituted with the propyl group, the reaction condition was unable to produce the desired product, indole.

In 2021, Tsukamoto et al. reported the stepwise synthesis of indoles from the 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 of the reaction can have the resemblance of the diamine derivative as the Fischer-Indole intermediates, which leads to the formation of the five-membered heterocyclic compounds.[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 tetra-nitromethane (TNM) with the Zn(II)-assisted condition.[112] In the next step, an effective approach was employed for the synthesis of the indole derivative with the help of the Zn-controlled reduction process, which led to the formation of the product with a good yield (Scheme 13b).[113-116]

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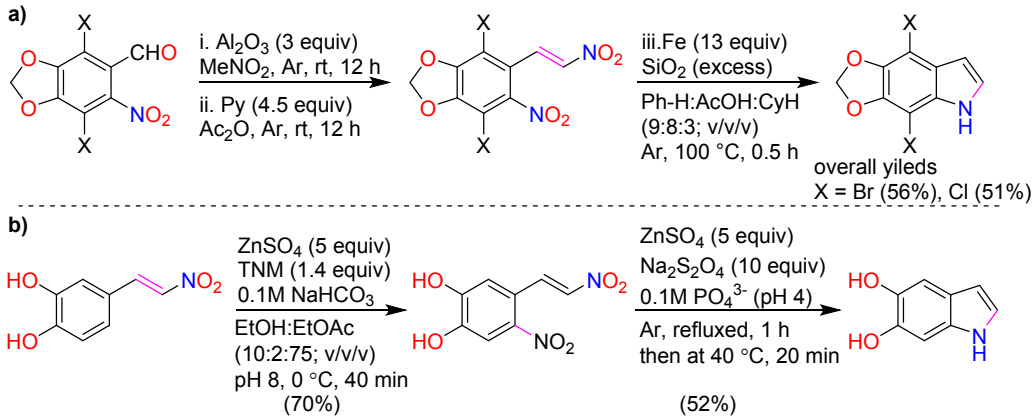
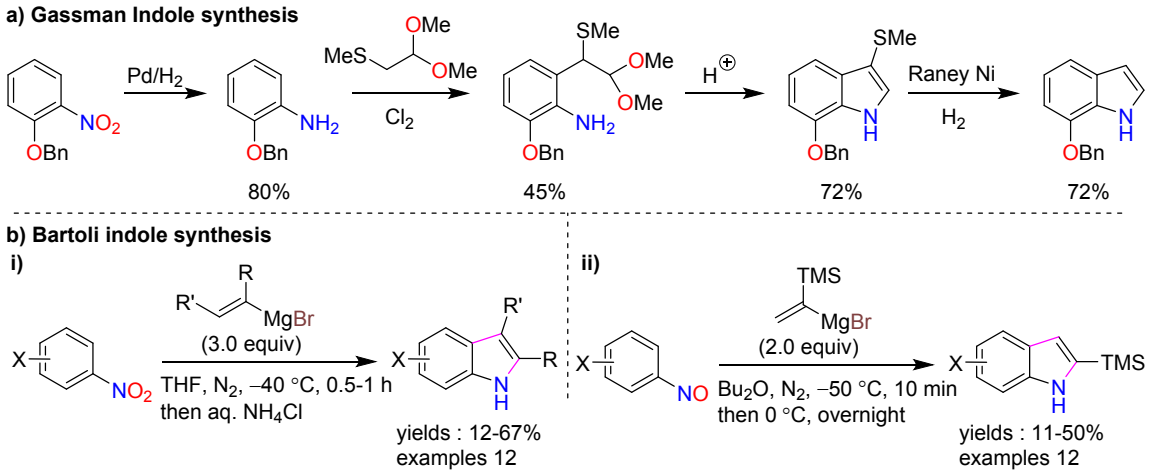


Scheme 13. Alternative Approach of Indoles *via* Henry Condensation Followed by Hydrogenation Reaction.



Scheme 14. The Overall Comparative Yields of Gassman and Bartoli Indoles Synthesis from Nitroarenes.

Bartoli and Palmieri (1989) developed a facile and alternative substitute for Gassman indole synthesis.[117] In this process, the nitroarenes can be directly converted into the indole derivative in a single step with the aid of vinyl magnesium bromide derivatives.[118, 119] This method not only reduces 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 was shown with a multistep path (Scheme 14a).[122, 123] Herein, each step afforded a good to excellent yield of the reaction, and the total yield of the reaction was found to be 19%. However, the indole syntheses using 2/3/4-nitrobenzene with 3 moles of vinyl magnesium bromide derivatives (Grignard reagents) offered up to be good (Scheme 14b(i)). In their exploration, they found that the *ortho*-substituted offers a higher yield than the meta- and *para*-substituted nitroarenes. Although they achieved a poor yield of the reactions in most of the cases, the reaction procedures are preferred due to the poor convenience and cheap protocol rather than 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 of the reactions. The substrates also worked well with the broad range of cyclic and acyclic salts of the olefinic magnesium bromides (Scheme 14b(ii)).

To illustrate the mechanism of indole synthesis, 2-nitrotoluene and vinylmagnesium bromide were selected as representative precursors. In which the first mol of vinyl magnesium bromide reacts with the nitro group to transform it to the reduced functional group nitrosobenzene, and then the second mol 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 intramolecular annulation reaction to

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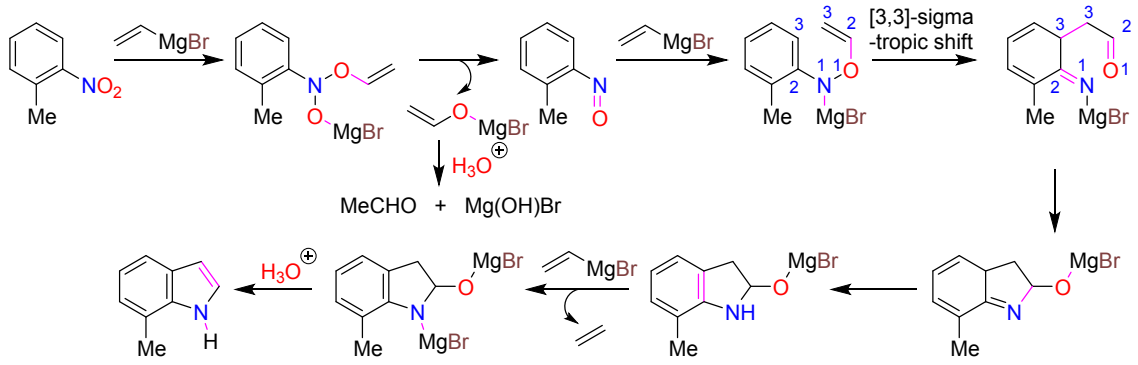
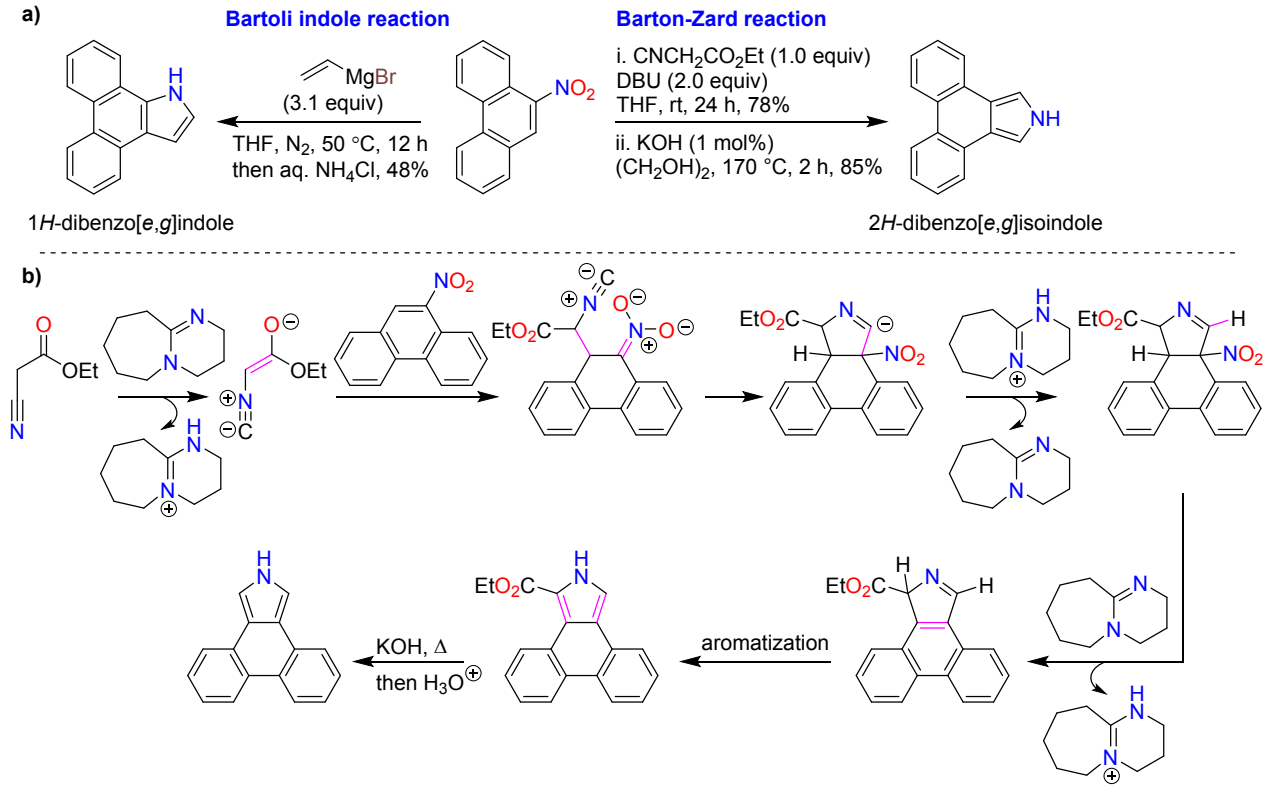
offer magnesium 7-methylindolin-2-olate bromide. Finally, this intermediate reacts with the third mol of vinyl magnesium bromide to furnish magnesium 7-methyl-2-oxidoindolin-1-ide dibromide by the loss of an ethylene group, and then acidic hydrolysis of the di-magnesium bromide salt produces the desired product, 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, such as 1*H*-dibenzo[*e*,*g*]indole and 2*H*-dibenzo[*e*,*g*]isoindole, cf. Scheme 16a. The reaction and mechanism of the Barton-Zard reaction are depicted in the Schemes 16b.[124-127]

In 2003, Knochel and his co-workers introduced a novel approach to the synthesis of indole analogues from the 6-aryl *o*-nitrostyrenes *via* reaction with the 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 Grignard reagent due to intramolecular annulation, making it more efficient. Beyond facilitating indole synthesis, this methodology also enables the construction of benzimidazoles by selecting appropriatestarting materials as both reactions proceed *via* a similar mechanism. In this process, two equivalents of phenyl magnesium chloride are



Scheme 15. Mechanism of the Bartoli Indole Synthesis.



Scheme 16. Synthesis of Dibenzo[e,g]indole/isoindole from the 9-Nitrophenanthrene and the Mechanistic Details of Barton-Zard Reaction.

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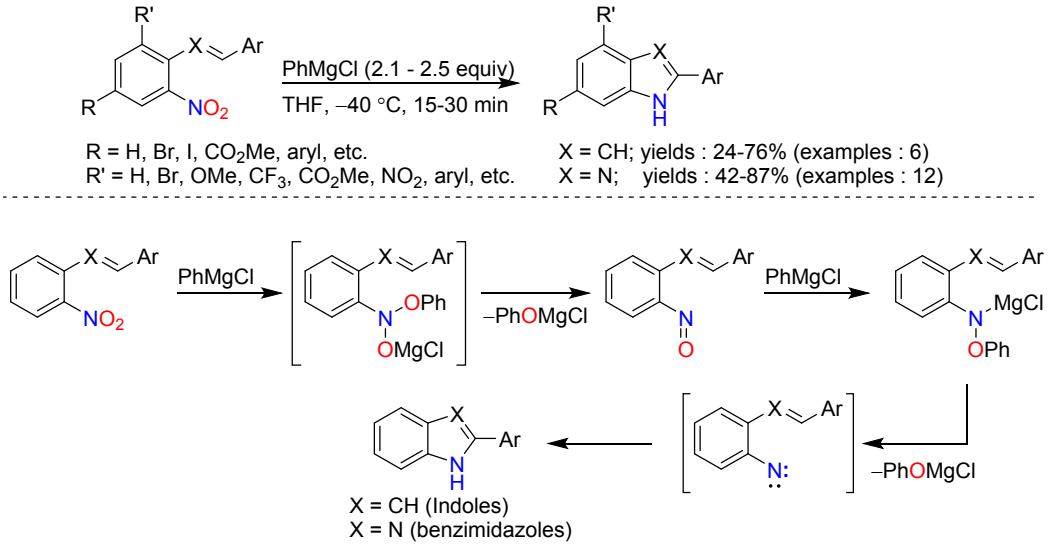


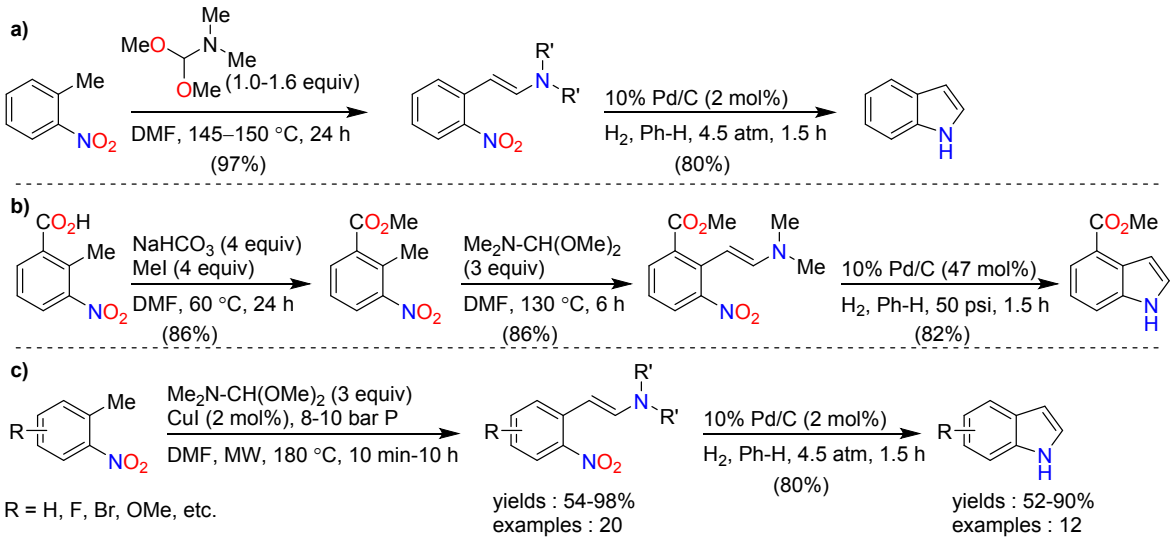
Scheme 17. Knochel-Indole Reactions in the Synthesis of Indoles and Benzimidazoles.

sufficient: the first generates the 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 synthetic access to structurally numerous nitrogen-containing heterocycles.

2.2. Involvement of an *Ortho*-Group in the Synthesis of Nitroarenes to Indoles.

Batcho and Leimgruber have discovered a novel approach for the synthesis of indole[129] and their analogues from the corresponding 2-nitrotoluenes *via* the condensation of *N*,*N*-dimethylformamide dimethyl acetal in DMF at high temperature followed by hydrogenation with the aid of Pd/C in benzene *via* 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 the Fe/AcOH and sodium dithionite, which afforded a poorer yield than the Pd/C. After the successful establishment of these reactions, various substrate scopes were explored in using this method. Hence, the reaction becomes more popular as the Batcho-Leimgruber indole reaction for the indole synthesis. Similarly, Ponticello and Baldwin have reported a common synthon, such as methyl indole-4-carboxylate, for the synthesis of alkaloids starting from the 2-methyl-3-nitrobenzoic acid in excellent yields of each step (Scheme 18b). Recently, Ley et al. modified the Leimgruber-Batcho enamine intermediate product synthesis by employing the microwave condition, and then they were subjected to the indole synthesis.[131] This reaction protocol is a superior protocol to the previous in regards to the time and yields of the indoles (Scheme 18c).[132]



Scheme 18. Batcho–Leimgruber Indoles Synthesis from 2-Nitrotoluenes.

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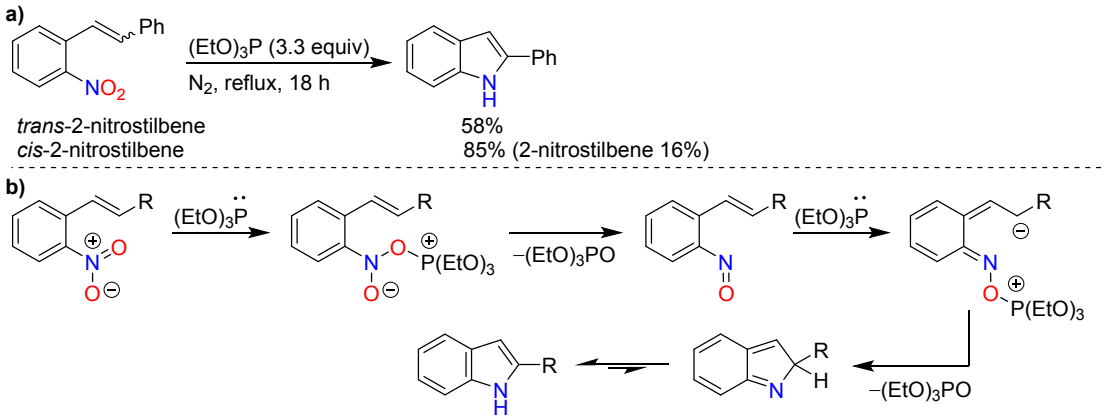
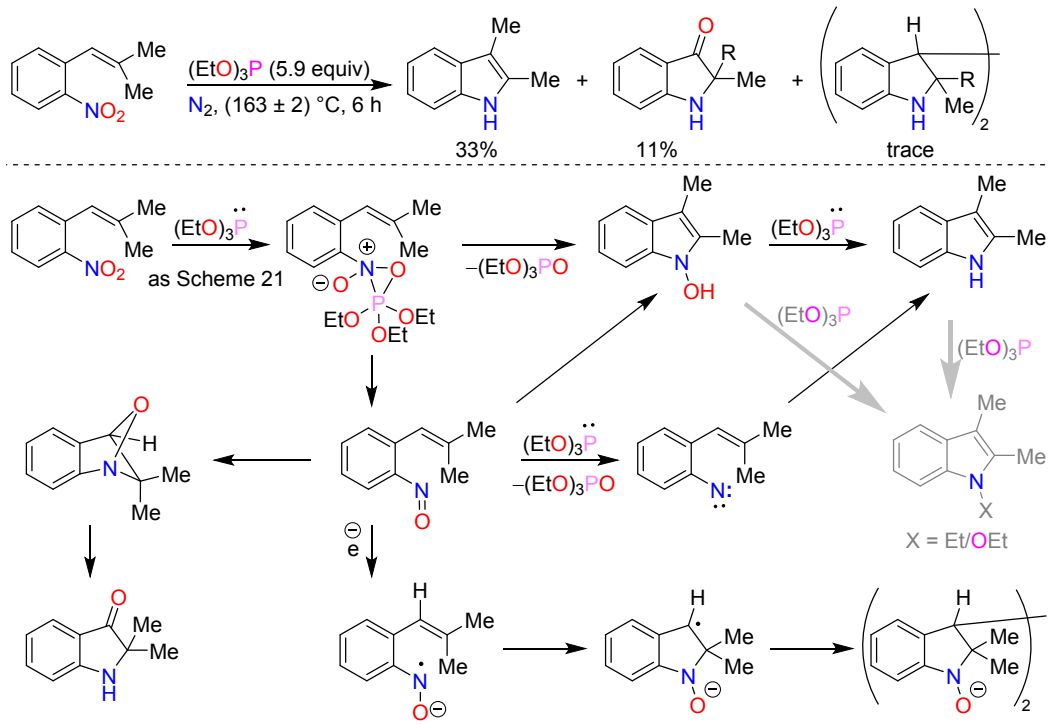
Cadogan-Sundberg indole synthesis. Cadogan and Sundberg developed the progress of the direct indole synthesis with the reaction of nitrostyrene with triethyl phosphite or triphenylphosphine (Scheme 19a). Herein, the triethyl phosphite behaves as a deoxygenating reagent and transforms it into the nitroso 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 corresponding indoles. Furthermore, they also studied the terminal disubstituted 2-nitrostyrenes to corresponding indoles and proposed the various types of side products along with the major product (Scheme 20).[138-140]



Scheme 19. Reactions and Mechanism by the Cadogan and Coworkers.



Scheme 20. Sundberg Analysis in the Formation of Indoles Products and Side-Products.

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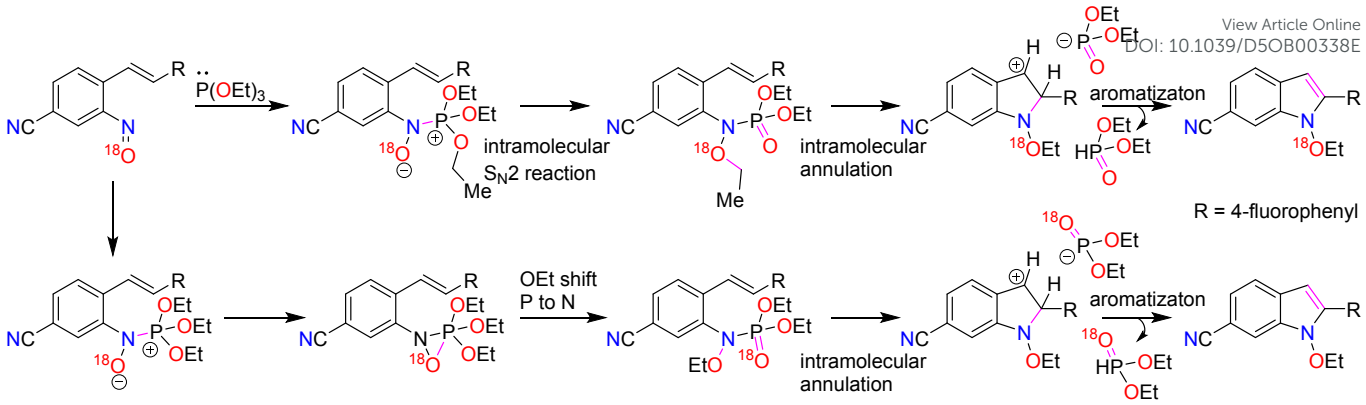
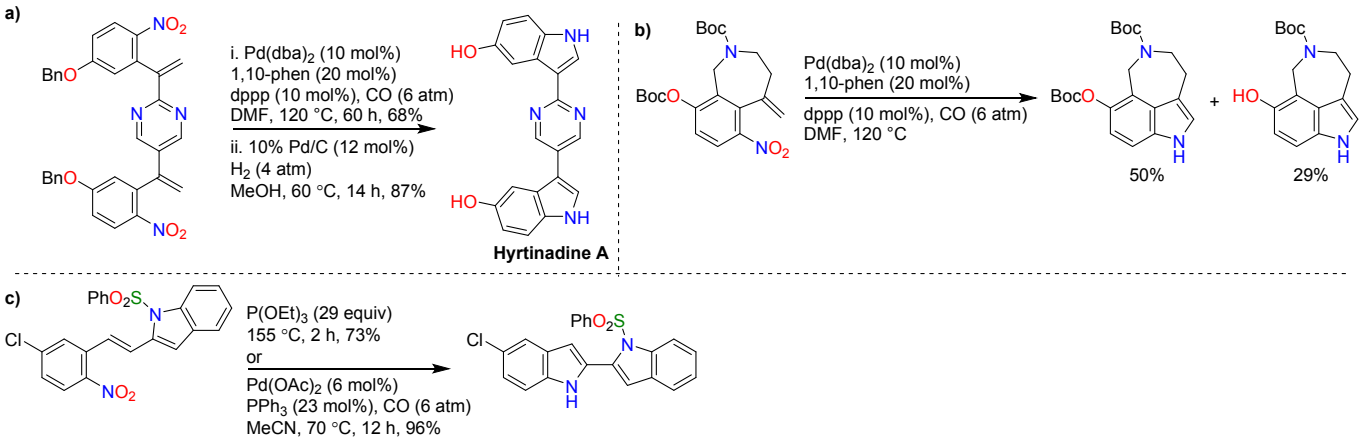


Scheme 21. The Analysis of the Cadogan-Sundberg Indoles Reaction for the Information of *N*-Alkoxyindles.

The combined reaction above is known as the Cadogan-Sundberg indole synthesis. Additionally, Peet et al. have studied 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' of the nitrostyrenes and found that the reactions are proceeding with the adopting of both the 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 presence of CO (6 atm.). Herein, two important examples of the indole alkaloids noted as Hyrtinadine A and Fargesine were reported by the Söderbergs' group (Scheme 22a-b).[143, 144] In 2003, Kuethe and coworkers reported the synthesis of indoles from the nitrosyrenes 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 $Pd(OAc)_2/PPh_3$ reagent conditions in a carbon monoxide environment at 6 atm in a refluxed condition. The latter approach of indoles afforded a superior yield with higher purity than the TEP condition (Scheme 22c).[146] The limitations of the CO atmosphere supported protocol offering the CO insertion product that leads to the formation of amides or lactams derivatives instead of the desired product as indoles. As a result, the yield of the product is dropping below than the expected yield of the indoles.

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



Scheme 22. Modified Approach of Cadogan-Sundgberg Cyclization for the Syntheses of Indoles.

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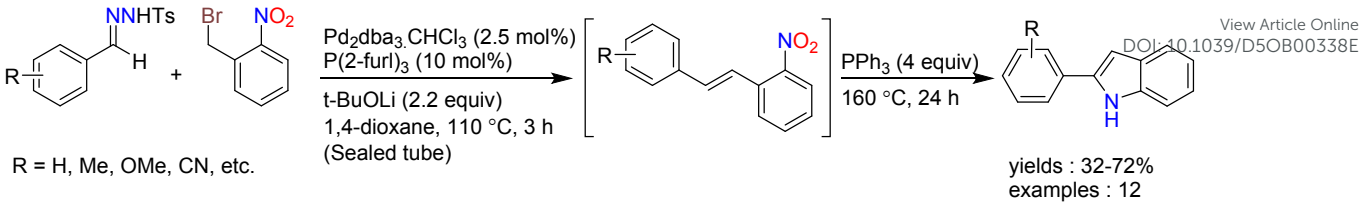
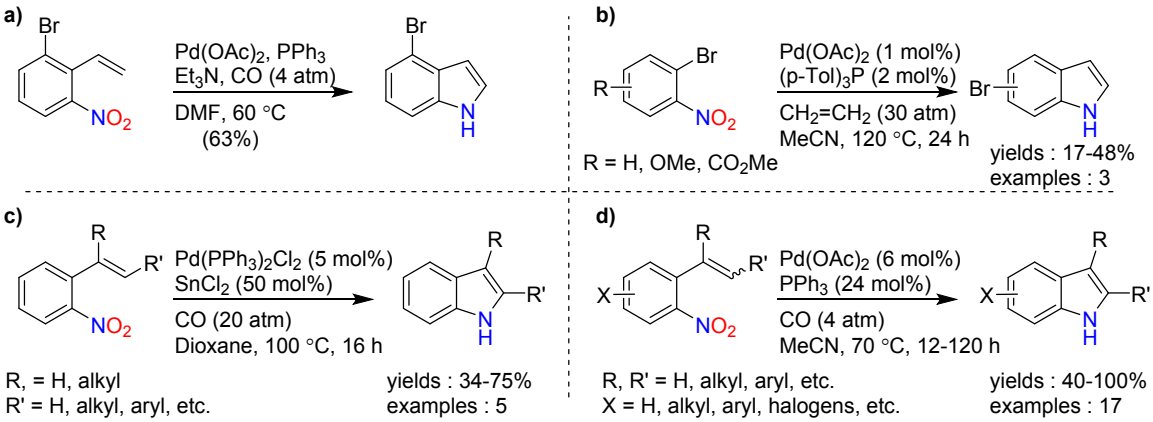


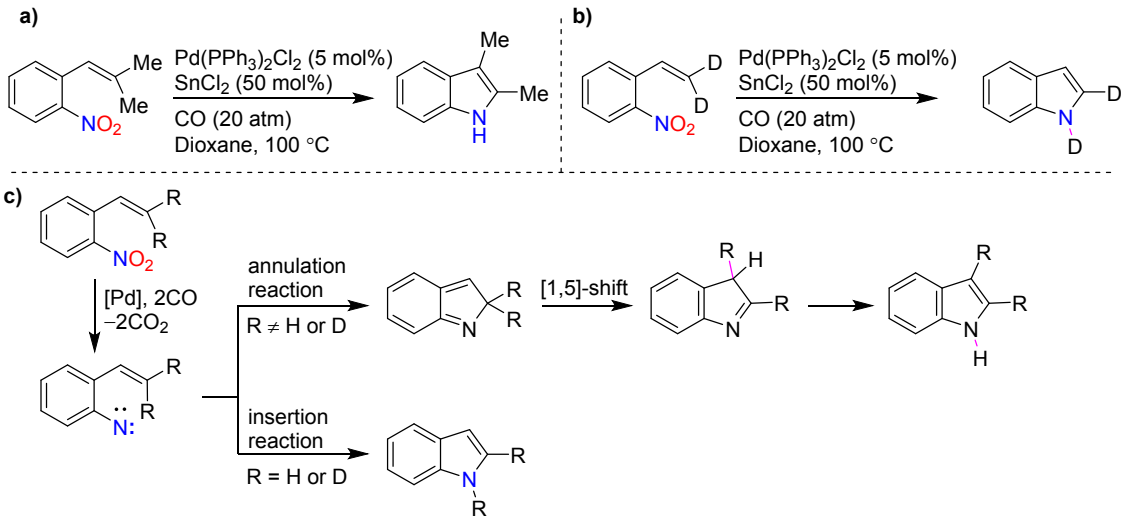
Scheme 23. The Synthesis of 2-Arylindoles from *N*-tosylhydrazones and 2-Nitrobenzyl.



Scheme 24. The Synthetic Approach of Indoles Using Pd(II) Reagents and Additives from 2-Nitroarenes.

In the following serendipitous examples, the indoles were explored using the Pd(II) catalysts with good to excellent yields. In Scheme 24a,[148] the reaction was attempted for the methoxycarbonylation reaction, but it offered the cyclized product indoles. Similarly, Scheme 24b was fully employed for Heck reactions to synthesize nitrostyrene analogues. However, this protocol was not efficient for the synthesis of indoles, but it worked within some of the limited scopes. Next, the Stille reaction was also attempted for the synthesis of carbonylated products, but the reaction led to the formation of indole derivatives.[149] A general reaction and mechanism of the Pd(II)-catalyzed reaction is shown with the cross experiments in Scheme 25. Similarly, Scheme 24c and Scheme 24d were directly employed for the indoles with good to excellent yields of the reactions without any base.[150-152]

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



Scheme 25. Cross Experiments and Mechanism of the Formation of the Indoles.

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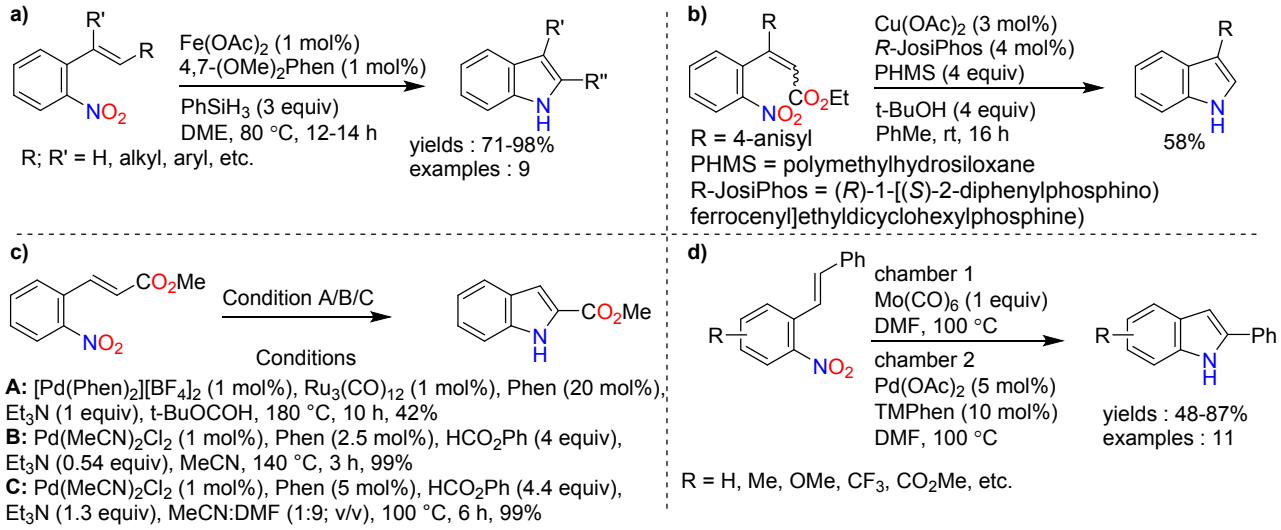
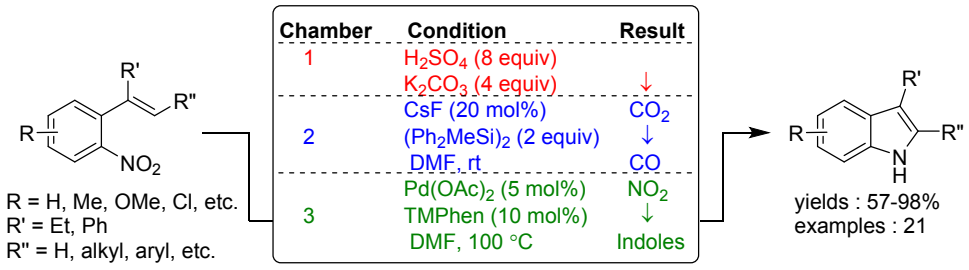
In the following examples, the Cadogan–Sundberg strategy was successfully transformed into indoles with the help of catalytic mol% of the transition metals of Fe(II), Cu(II), and Pd(II), etc.[143, 153, 154] by the combination of organic nitrogenous heterocyclic ligands and reducing silane reagents or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

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



Scheme 26. Indoles Synthesis with the Help of Reducing Reagents or CO-Surrogating Reagents.



Scheme 27. Single-Pot Thee-Chambered Reductive-Annulation of *ortho*-Nitrostyrenes to Indoles.

In further approaches, the oldest mode of the Cadogan annulation approach using TEP was replaced by triphenylphosphine at mild to severe conditions also explored.[160a-163] However, many other approaches were reported for the improvement of the indoles in the presence of the additive of the salts/complexes of the transition metals, etc., with the 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, we followed a stereospecific *syn*-addition approach similar to the hydroboration reaction as established by Yamamoto et al. (Scheme 28b).[160b] The reaction proceeds in the presence of a copper catalyst and undergoes an exchange

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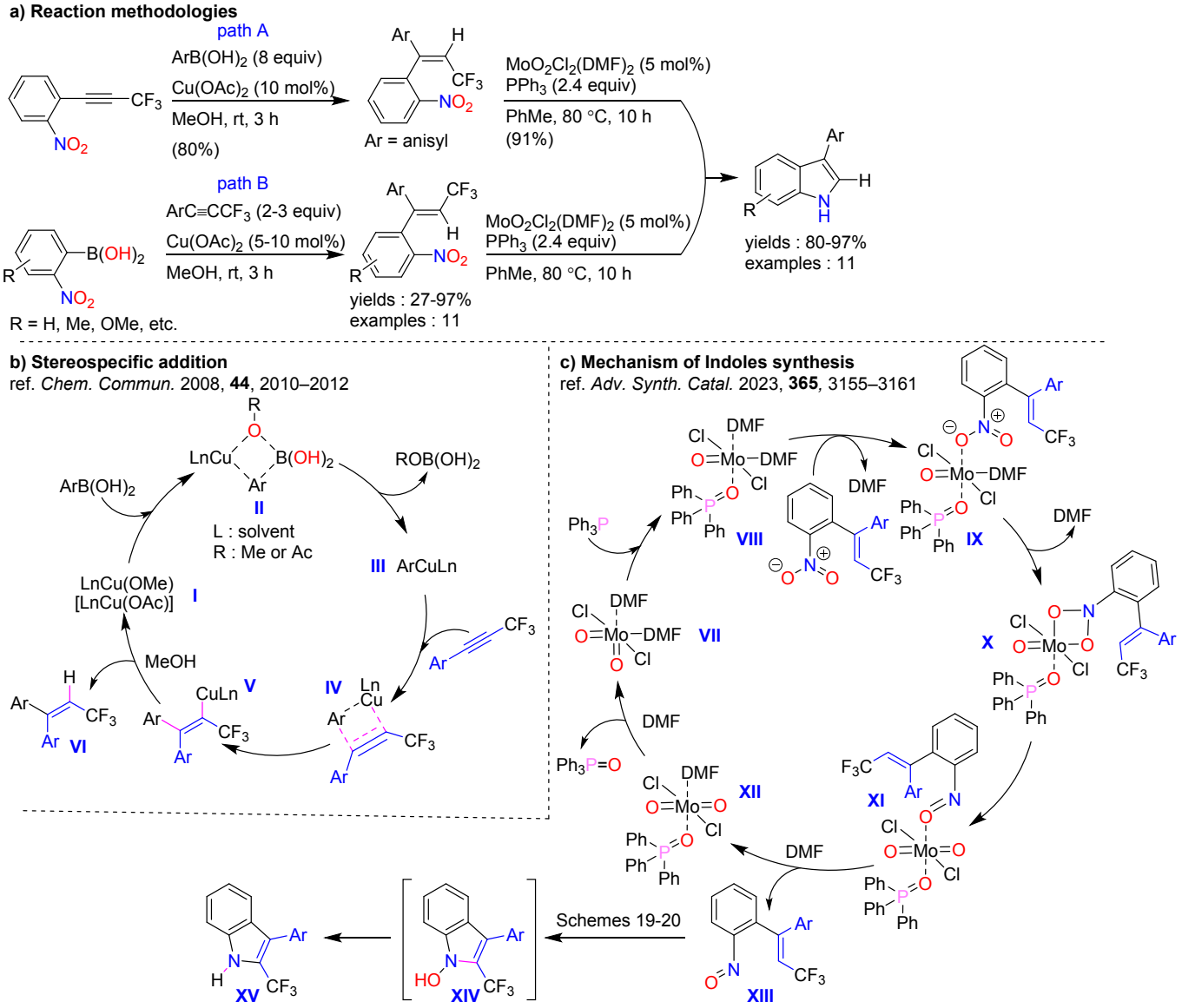
reaction to form complex I. This is followed by coordination with an aryl boronic acid to form complex III via intermediate complex II. Subsequently, a stereospecific *syn*-addition with the alkyne yields compound V. Rapid regeneration of the catalytic complex occurs in the presence of methanol, affording 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 19–20.

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



Scheme 28. Molybdenum Catalysts-Assisted Indoles Synthesis.

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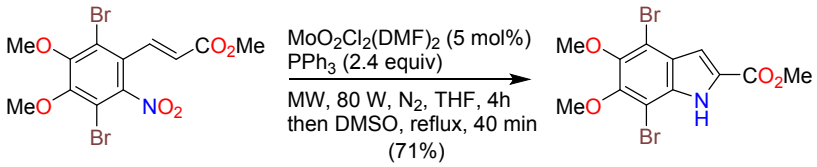
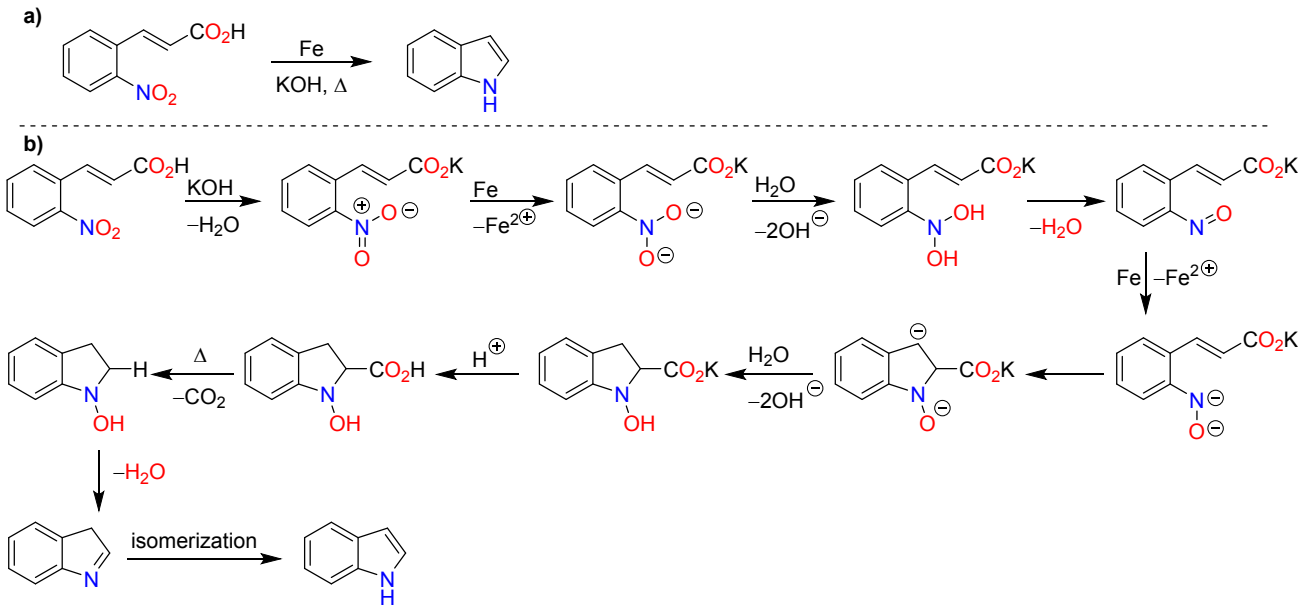


Scheme 29. Microwave-Assisted Cadogan–Sundberg Cyclization.

In 1869, Baeyer and Emmerling reported a novel approach for indole synthesis using iron metal from *ortho*-nitrocinnamic acid in strongly alkaline conditions, illustrated in Scheme 30a.[168] The reaction proceeds *via* the reductive annulation, followed by the decarboxylation process 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 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 syntheses with the help of diethyl oxalate in the presence of sodium metal followed by reduction with Zinc/Acetic acid leads to the formation of an amino-phenylpyruvic acid intermediate. Furthermore, this intermediate undergoes a cyclization reaction followed by the decarboxylation process that produces an indole carboxylic acid derivative. This procedure afforded a good to excellent yield of the indole product, and this procedure is commonly known as the Reissert indole synthesis.[171-174] The other alternative method for the hydrogenation methods of the nitrophenylpyruvic acid intermediate was also explored with the help of ferrous sulphate/ammonium hydroxide, stannous chloride/dehydrate, and Pd/C that also gives the desired product as indoles. The mechanistic approach of these reactions is also shown in Scheme 31.[175, 176]

In the following examples, the potassium metal was dissolved into the absolute ethanol (without stirring) to prepare the potassium ethoxide base, and then it was mixed with the solution of diethyl oxalate in the inert atmosphere at room temperature. Further, the nitrotoluene was also added for the synthesis of the potassium salt of ethyl *o*-nitrophenylpyruvate, which was later subjected to the hydrogenation reaction at high pressure using hydrogen gas in the presence of the 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]



Scheme 30. Synthesis of Indoles from the 2-Nitrocinnamic Acid.

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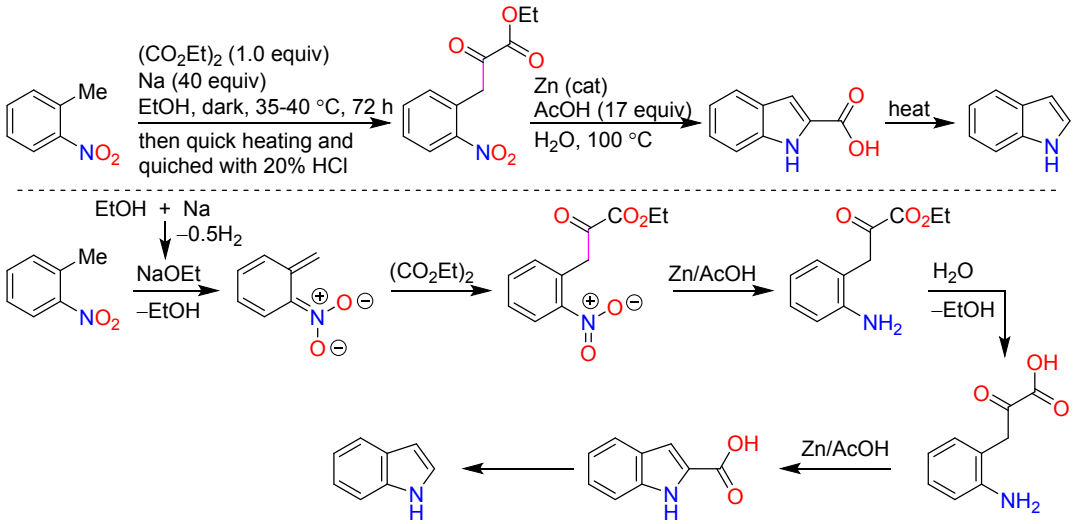
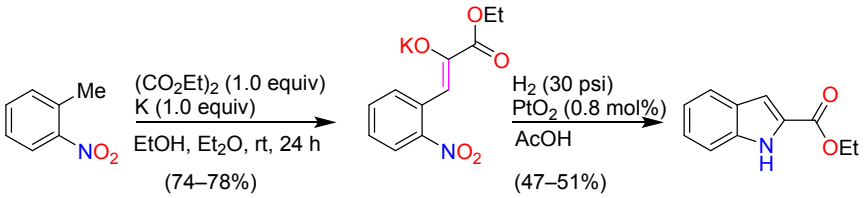


Scheme 31. Synthesis of Indole *via* Reissert Indole Synthesis.

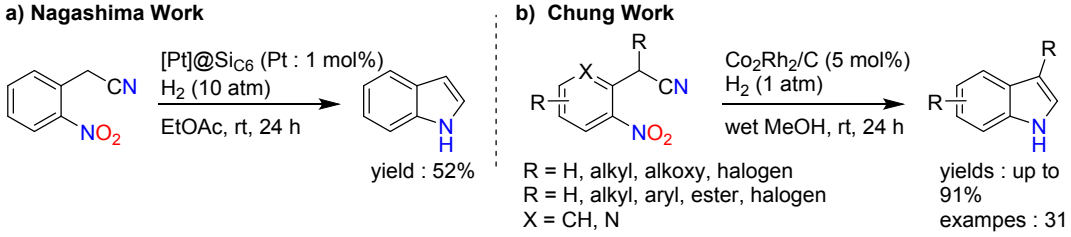


Scheme 32. Modified Synthesis of Indole *via* Reissert Indole Synthesis.

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

In the next reaction, low-valent titanium(III) chloride was used to look into *ortho*-nitrostyrene analogues. Herein, the titanium acts as a reducing reagent for the nitro group and transforms it into the corresponding nitroso derivatives.[180] Further, it cyclized into the corresponding product hydroxyindoles *via* path a, and later it reduced to indole derivatives due to the presence of an excessive amount of valent titanium(III) chloride (Scheme 34a). However, the trisubstituted olefins of *ortho*-nitrostyrene analogues also proceed with the same mode as path a and the 1,2-shift *via* path b, which further undergo rearrangement followed by aromatization and deoxygenation reactions that finish 2,3-disubstituted indoles as the major product (Scheme 34b). The mechanistic detailed 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 chalconeswith ammonia and Hantzsch ester in the basic medium leading to the formation of the 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 amine s to perform the successful synthesis of 3-aminoalkyl-indoles with a yield of 27-86% (Scheme 35b).



Scheme 33. Nitrile Hydrogenations in Indoles Synthesis.

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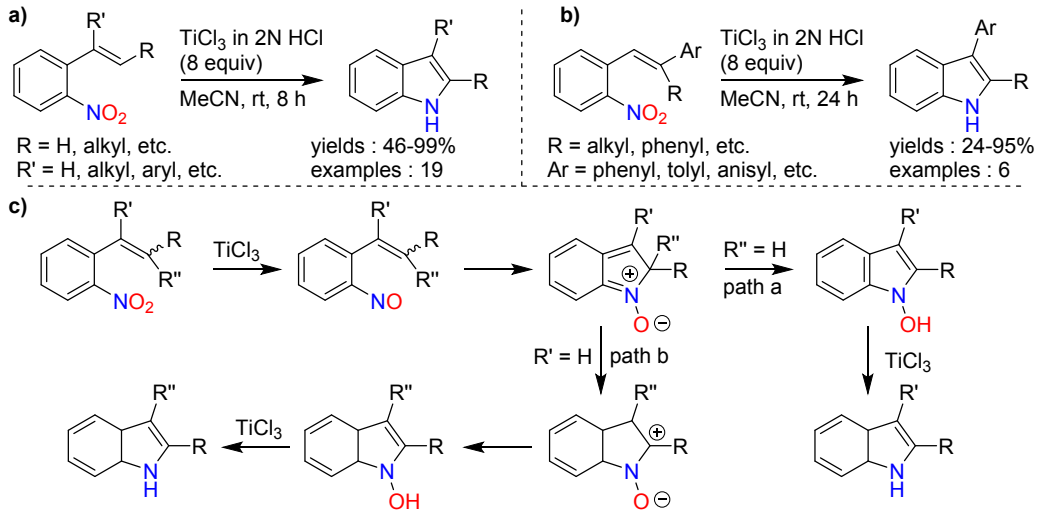
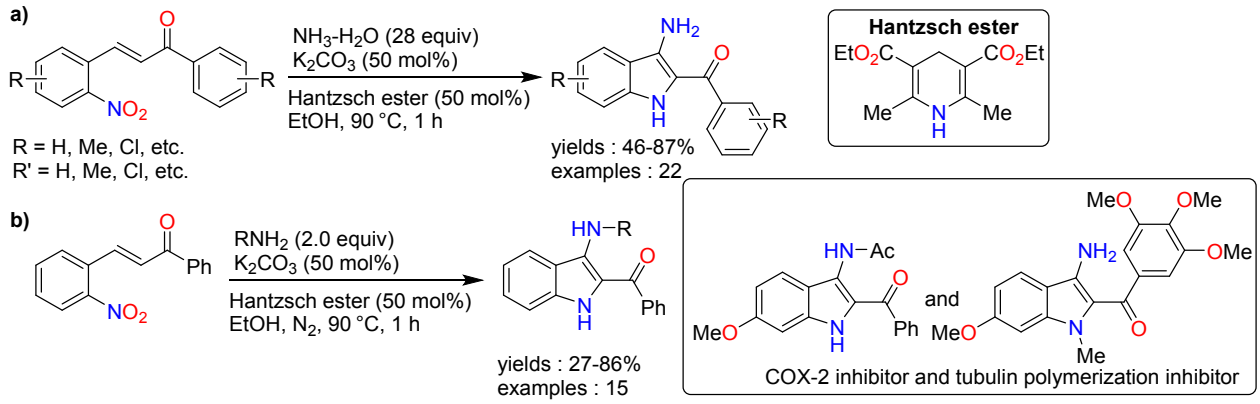
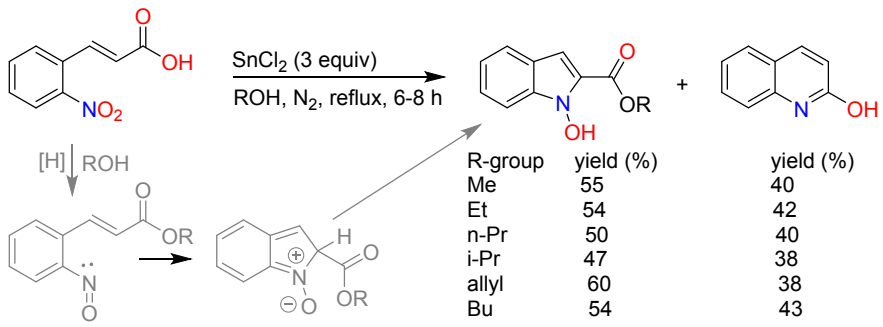


Scheme 34. Titanium(III)-Supported Intramolecular Reductive-Annulation of Indoles Synthesis.



Scheme 35. Synthesis of Indoles from the Chalcones.



Scheme 36. Synthesis of *N*-Hydroxyindoles form 3-(2-Nitrophenyl)acrylic Acid.

According to recent studies, it was reported that stannous chloride was utilized to reduce the 3-(2-nitrophenyl)acrylic acid to 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 carboxylates as the major product. At the same time, annulation with the lone pair of nitro with the carbonyls 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-b).[183] Virtually, the bis(pinacolato)diboron reagent does the deoxygenation of nitro-group and shows it in the form of a nitroso derivative. Later, it again reacts with another mole of bis(pinacolato)diboron, and then annulation followed by the [1,5]-sigmatropic shift affording the indoles (Scheme 37c).

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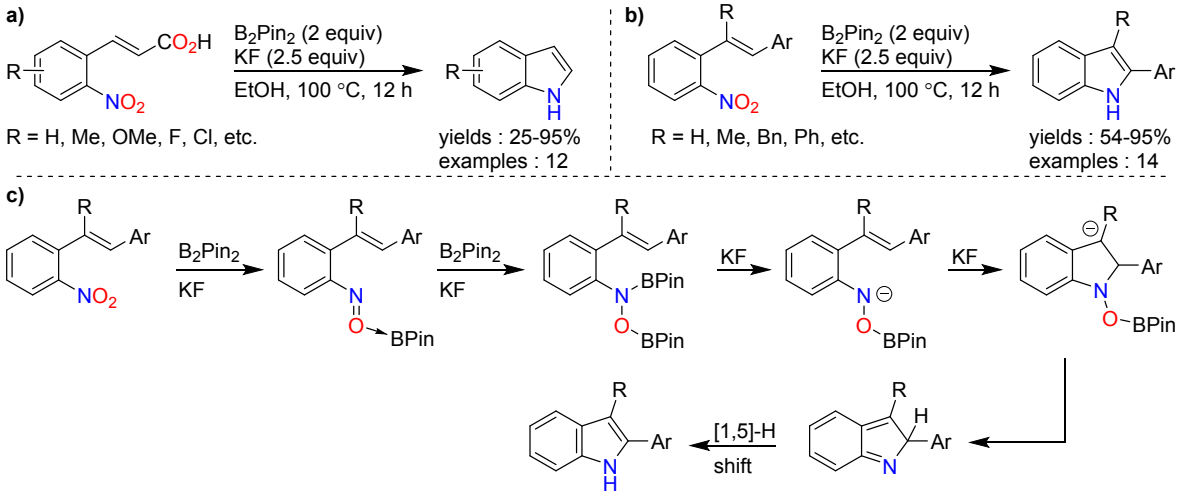
The following alkynes can easily be prepared by the most frequent reaction, i.e., Sonogashira coupling, and then the obtained starting materials were further treated with the metals (In and Zn) in activation with the additives of HI/Aliquat, dibromoethane.[184] Remarkably, both metals were known for the reduction of the selective functionality *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 compound indoles (Scheme 38).[185]

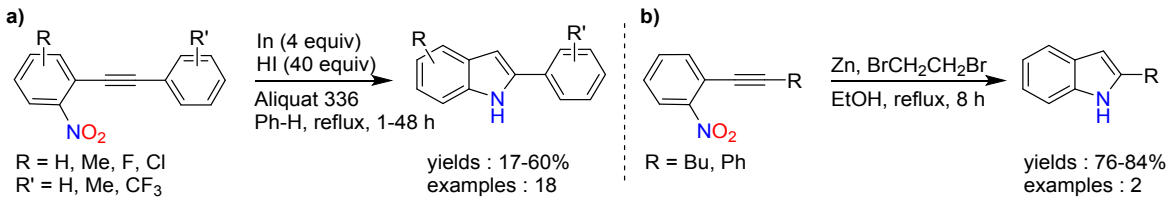
Oh and Shin have reported a tandem reaction for the synthesis of 1-hydroxyindoles from the *ortho*-iodonitrobenzene.[186] Herein, these reactions were performed *via* a cascade of reactions, i.e., Sonogashira coupling, selective partial reduction, followed by the Pd(II)-catalyzed electrophilic annulation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

In 2021, Ying et al. have vastly developed a novel approach for the 1-aroyl-2-arylindoles through the coupling reaction between disubstituted *ortho*-nitroaryl acetylene with iodoarenes in the presence of $Zn/ZnI_2/Co_2(CO)_8$ and the catalytic amount of Ni(II) salt and 4,4′-Di-tert-butyl-2,2′-dipyridyl (dtbbpy) ligand into the 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 $Ni(OTf)_2$ 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 for the variety of the functionality of the substrates. They have proposed the mechanism of this coupling process by using a Ni(II) catalyst by generating the Ni(0) species by using dtbbp and Zn/ZnI_2. Next, the Ni(0) species undergo oxidative insertion with iodoarene, followed by carbonylation *via* in situ-generated $Co_2(CO)_8$ reagent that forms active species A to B. At the same time, chemoselective reduction of the nitroalkynes generates the aniline derivative due to the presence reducing agent Zn/ZnI_2 and then immediately reacts with in situ generated reactive species B and generating an 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]

Herein, the cobalt nitrogen-doped carbon-900 (Co-N-C-900) catalyst was accompanied for the in situ hydrogen transfer reaction.[190] The set of reactions proceeds with the redox process, in which the dihydroindoles are reduced with the nitro group as the reactions are involved in the Skraup reaction during the quinoline synthesis depicted in Scheme 41.



Scheme 37. Reductive Annulation of Nitrostyrenes to Indoles using B_2Pin_2 and KF Reagents.



Scheme 38. Synthesis of Indoles Using In and Zn metals for Intramolecular Reductive-Annulation Reaction.

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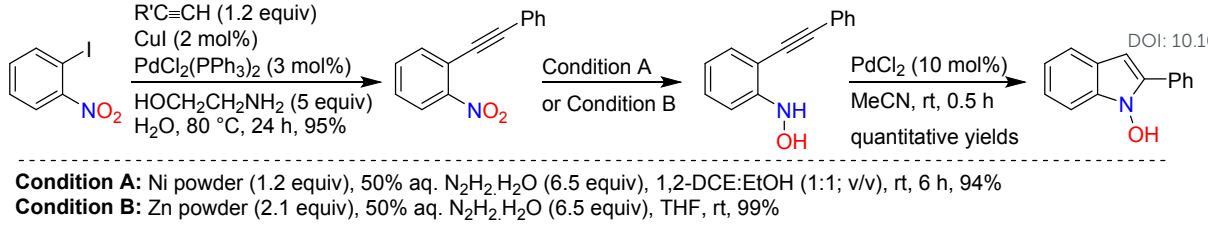
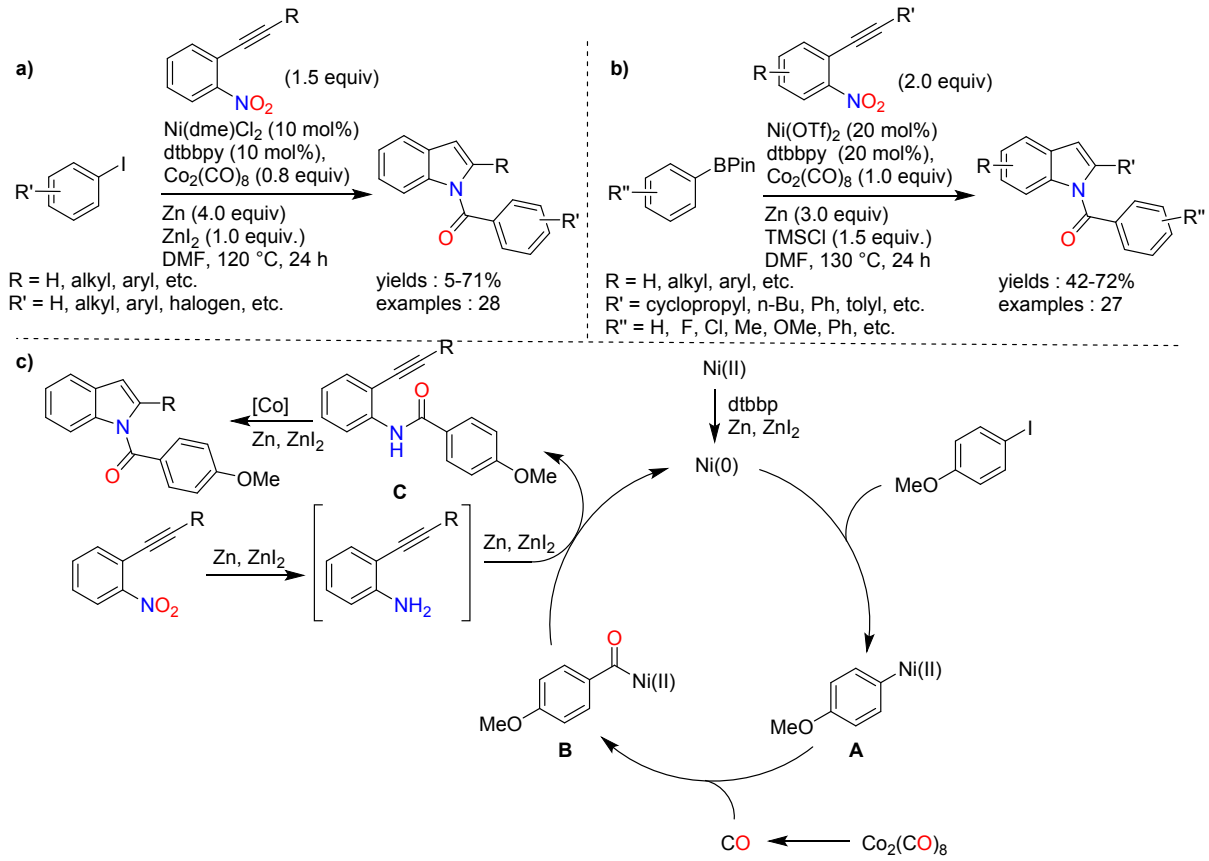
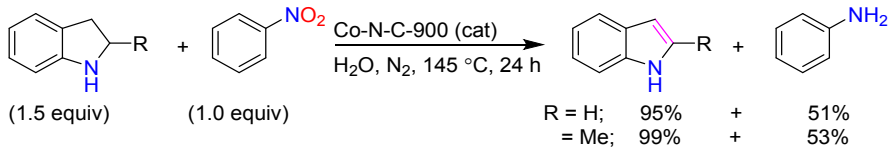


Scheme 39. Synthesis of *N*-Hydroxyindoles *via* Pd(II)-Catalyzed Intramolecular Annulation Reaction.



Scheme 40. Ni(II) Catalyzed Synthesis of *N*-Aroylindoles from the 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 in reaction with nitroarenes and alkenes in the presence of $[Cp^*Ru(CO)_2]_2$ and carbon monoxide atm. 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 did the mechanistic investigation by additionally adding the corresponding nitrosoarene in the same reaction mixture and reported a superior yield of the indole. Later, they explored indoles from nitrosoarenes with alkynes and found that the current procedure of the synthesis gives higher yields than the previous one.[192] Ragaini et al. utilized the palladium-phenanthroline complexes to get the indole derivative similarly at 60 bar pressure and synthesized the library of the compounds with a yield of 8-45% (Scheme 42b).[193a] However, the exact mechanism is unclear. While mechanistic studies were being attempted, it was also found that the nitro group converted into the nitroso derivative and then underwent an addition reaction

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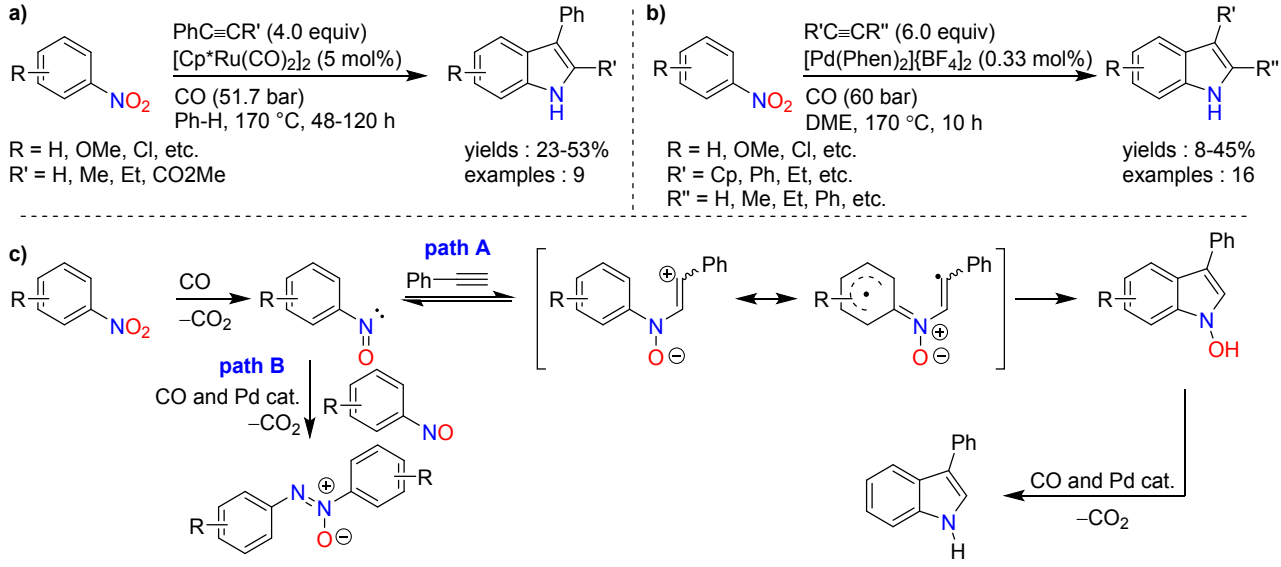
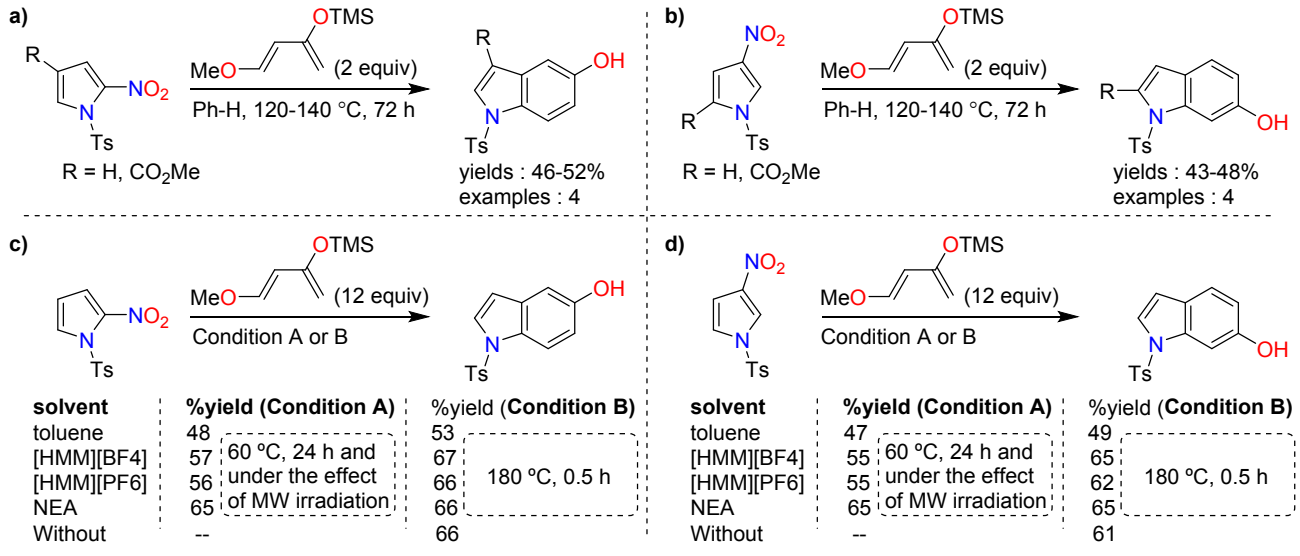
with alkynes to furnish the indoles as the major products. During the controlled experiment, they were observed that the absence of either catalyst or carbon monoxide does not favour the reaction in the forward direction. Based on their controlled experiments, they also assumed that the interaction between 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 found with alkenes and nitrosoarenes and generating dipolar α-styryl cations (theoretical support[193b]), which also can generate the α-styryl radicals (EPR-support[139c]). Further, it affords the indoles via intramolecular annulation followed by carbon monoxide deoxygenation (Scheme 42c, path A). At the same 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 the indole analogues.

Mancini et al. introduce a different route for the synthesis of indoles *via* the cycloaddition approach than the previous reports without any kind of metal catalysts.[194] In this work, they elaborated on the reactions between the different types of 1-tosyl-nitropyrrole (electrophilic dienophile) with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (nucleophilic Danishefsky's diene) in the non-polar benzene at 120-140 °C (Schemes 43a-b). Noticeably, the 1-tosyl-2-nitropyrroles on cycloaddition with Danishefsky's diene, followed by the nitrous acid elimination



Scheme 42. Cycloaddition Approach for the Indoles Synthesis.



Scheme 43. Synthesis of Indoles from Electrophilic Dienophiles with Danishefsky's Dienes

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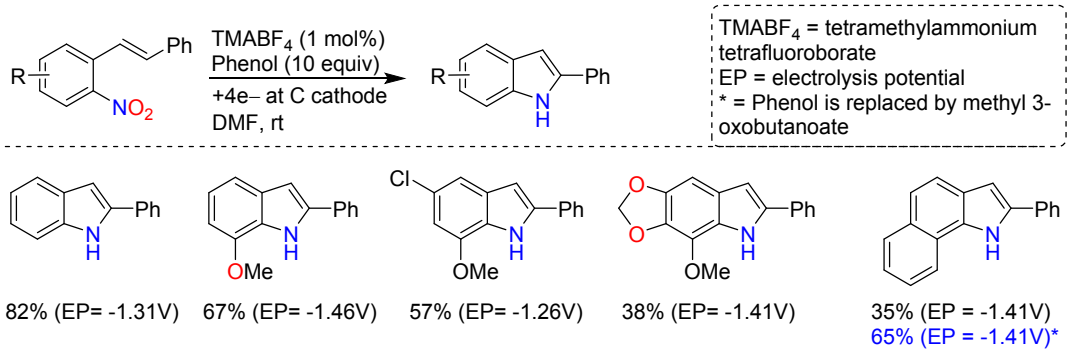
and desilylation, produced corresponding 5-hydroxyindoles, whereas 6-hydroxyindoles were formed by the 1-tosyl-3-nitropyrroles due to the cycloaddition of the electron-demanding rules.[195] However, this work was performed with the isoprene and *N*-(buta-1,3-dien-1-yl)-*N*-propylacetamide, which also produces the annulation product with poor yields. Furthermore, the reaction was explored by the same group as indole products in microwave-assisted with and without solvent conditions, where they found a higher yield than the previous reaction protocols (Scheme 43c-d). Similarly, the reactions were also performed with two more types of nucleophilic dienes, such as isoprene and 1-trimethylsilyl-1,3-butadiene, which also afforded poor yields of *N*-tosylindoles (for the preparation of the [HMIM][BF_4], [HMIM][PF_6], and [NEA] solvents according to the previously reported methods.[196]

Peters and his coworkers reported an electrochemical reductive approach[197] for indole synthesis at carbon cathodes in deoxygenated *N*, *N*-dimethylformamide using electrolyte as tetramethylammonium tetrafluoroborate and an excessive amount of proton donor source as phenol or methyl 3-oxobutanoate at room temperature with yields of 35-82% (Scheme 44).[198] For the justification of the indoles, 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 equivalents of a strong acidic proton source as methyl 3-oxobutanoate then it furnishing a superior yield of 65% than the prior protocol.[199]

Electrochemical Approach.



Scheme 44. Electrochemical Approach for the Synthesis of Indoles

Photochemical Approach.

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

Waheed and his coworkers successfully attempted the photoinduced synthesis of indoles from nitrostyrenes with the help of the Knölker catalyst and the 4-tolylmethanol in a basic medium at rt.[202, 203] This synthetic procedure was employed for the exploration of the variety of indoles in good to excellent yields (Scheme 46a). They have proposed the 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. During these reactions, 4-tolylmethanol acts as a reducing agent of the Knölker catalyst during the complete set of reactions. The formation of the intermediate nitroso and hydroxyindoles was confirmed by the HRMS data analysis (Scheme 46b).

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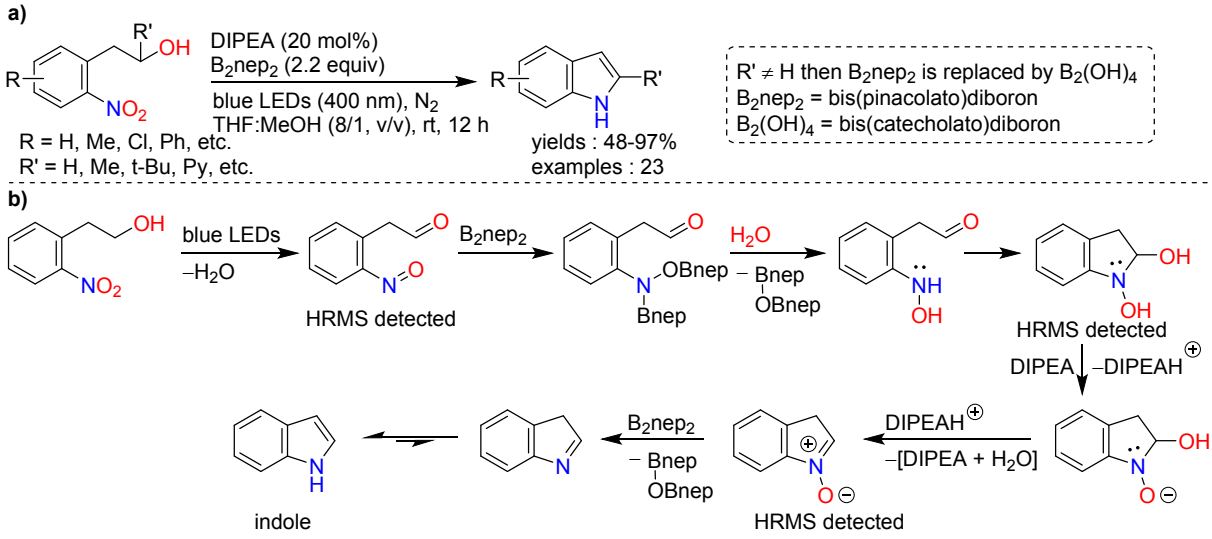
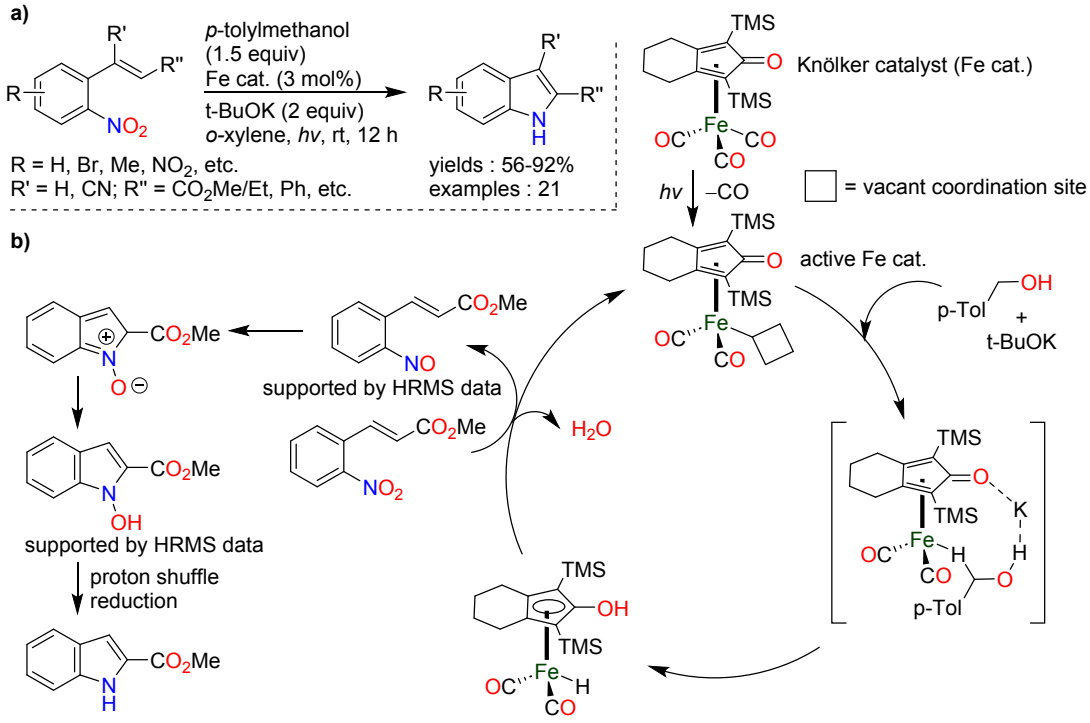


Scheme 45. Synthesis of Indoles from *ortho*-Nitrohomobenzyl Alcohols.



Scheme 46. Photochemical Synthesis of Indoles from Nitrostyrenes Using Knölker Catalyst.

Dayong Shi and coworkers explored the novel photochemical approach of Bartoli-Indole synthesis on the reaction between nitroarenes with gem-methylstyrene in the mild acidic medium with inert atm.[204] by applying 390 nm of the intensity of 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 the mechanism that the nitroarene produces diradical species *via* the ISC process employing the

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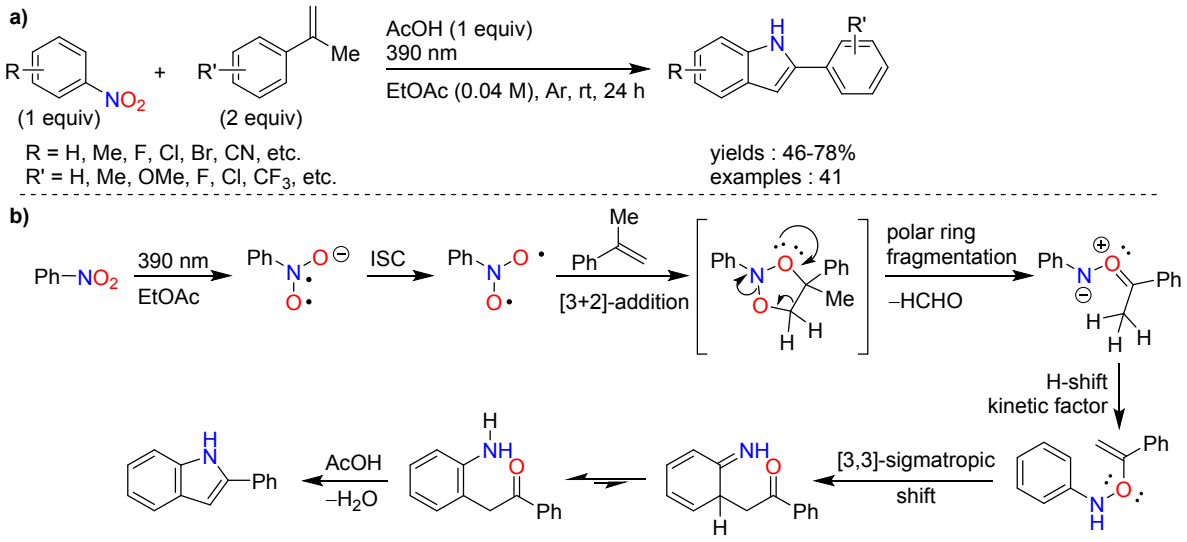
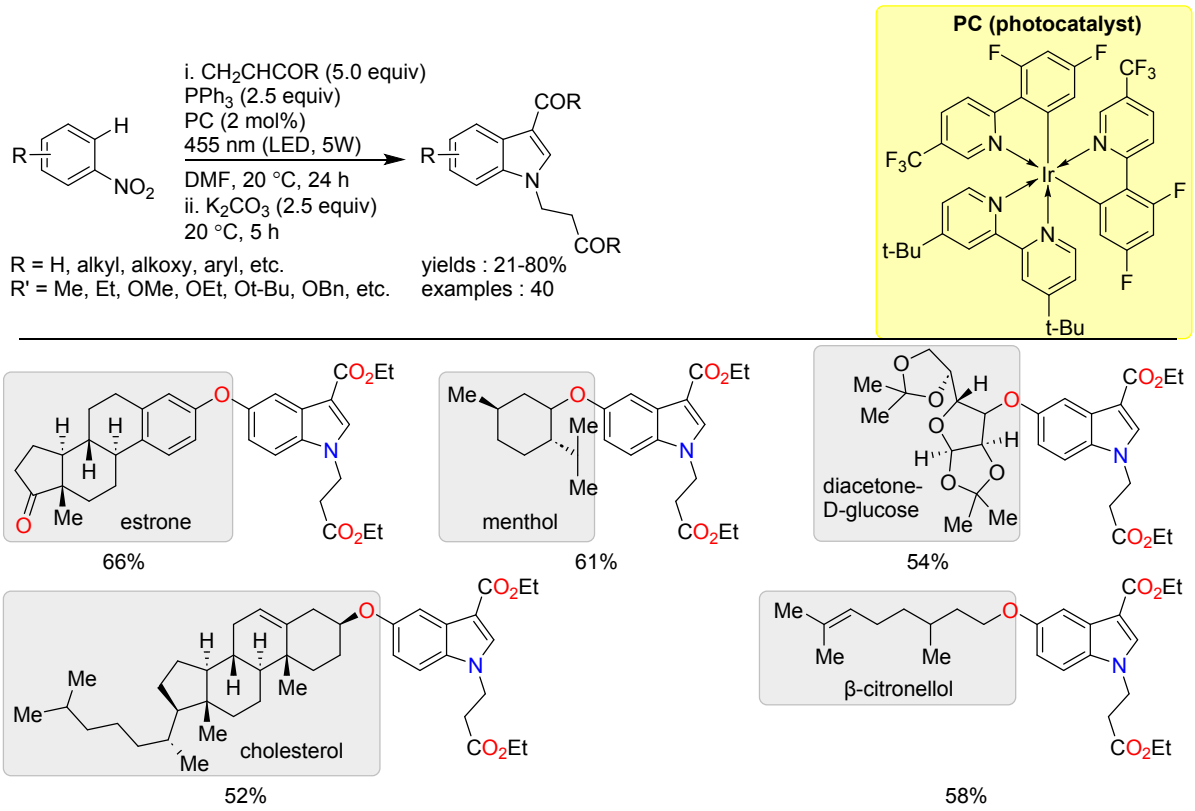
390 nm wavelength of light, which forms a [3+2]-cycloadduct with methylstyrene, and then it produces a dipolar intermediate *via* a favoured polar ring fragmentation reaction. Next, this dipolar species forms the 2-(2-aminophenyl)acetophenone intermediate *via* the cascade of hydride and [3,3]-sigmatropic shifts. Finally, 2-(2-aminophenyl)acetophenone forms the desired product on the 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* photochemical [3+2]-cycloaddition reaction.[205] To demonstrate [3+2]-annulation, they were chosen as the nitroarenes and vinyl ketones/esters as the 3- and 2-skeleton constituents, respectively. The nitroarenes are activated in combination with vinyl ketones/esters using the iridium-based photocatalyst (PC) to initiate a chain reaction of the radical annulation process while



Scheme 47. Photoinduced Bartoli-Indoles Synthesis.



Scheme 48. Photocatalyst-Induced Reaction of Nitroarenes with Vinylketones/esters Indoles Synthesis.

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retaining the light intensity of 455 nm with the help of a 5-watt light-emitting diode (LED) at the ambient temperature. The developed reaction condition was well tolerated for the synthesis of myriads of indoles and afforded moderate to good yields of 21 to 80%. In some cases, the reaction suffered from regiochemical annulation, which dropped the formation of desired outcomes. 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).

Conclusions

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

Future Aspects. Herein, various approaches based on the 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 in its development.

1. Additionally, the VNS approach has been added to develop the precursor of the indoles, which can play an important role in the synthesis substituted desired indole derivatives.
2. The N-hydroxyindoles are also added to get an alternative way, which can easily be helpful in its via selective reduction methods. In contrast, classical indole syntheses such as the Fischer, Bartoli, or Gassman approaches offer more predictable regioselectivity and often proceed in fewer steps, albeit sometimes with less functional group tolerance.
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 creation of indoles, but can also provide the 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 single-pot one-shot 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. Recent advancements of photochemical strategies enabling more direct access to indoles from nitroarenes, often bypassing the intermediate aniline and focusing on such emerging methodologies to provide a critical comparison with traditional multistep routes. Recent 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 the acid as well as base during the synthesis of target molecules. Hence, these methodologies can provide a great baseline in the development of several bioactive indoles in pharma and chemical industries in future aspects.

Conflicts of interest

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

Acknowledgments

Individually, we all appreciate and thank our respective departments of the current institutions for giving us the great

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opportunity as the funding and infrastructures to work as the higher post to explore the field of education and research.

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Data availability statement

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

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