

Cite this: *Org. Biomol. Chem.*, 2025, **23**, 6853

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

Ajeet Chandra,^a Suresh C. Yadav,^{†b} Subba Rao Cheekatla^{†c} and Abhijeet Kumar^d

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.

Received 26th February 2025,
Accepted 29th May 2025

DOI: 10.1039/d5ob00338e

rsc.li/obc

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

^aDepartment of Information Display, Kyung Hee University, Seoul 02447, Republic of Korea. E-mail: ajeet12300@gmail.com^bDepartment of Chemistry, Satish Chandra College, Ballia, Uttar Pradesh 277001, India^cDepartment of Pharmacology, Korea University (KU), Seoul 02841, South Korea^dDepartment of Chemistry, Mahatma Gandhi Central University, Motihari, Bihar, 845401, India

† Both authors contributed equally.



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 Małosza 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)-λ⁶-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



Ajeet Chandra

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

Dr Suresh C. Yadav is working as an assistant professor in the Department of Chemistry at Satish Chandra College, Ballia, India. He did his master's and doctoral programs at the Department of Chemistry, TDPG College, Jaunpur, and the University of Allahabad, respectively. He defended his thesis in the area of oxidative reaction kinetics and synthetic transformations with the help of transition metals and an excess amount of

oxidizing reagents under the supervision of Prof. PK Tandon. Dr Yadav is highly dedicated to teaching and research education and has carried out reaction kinetics as well as mechanistic investigations of transition metal-catalysed reactions.



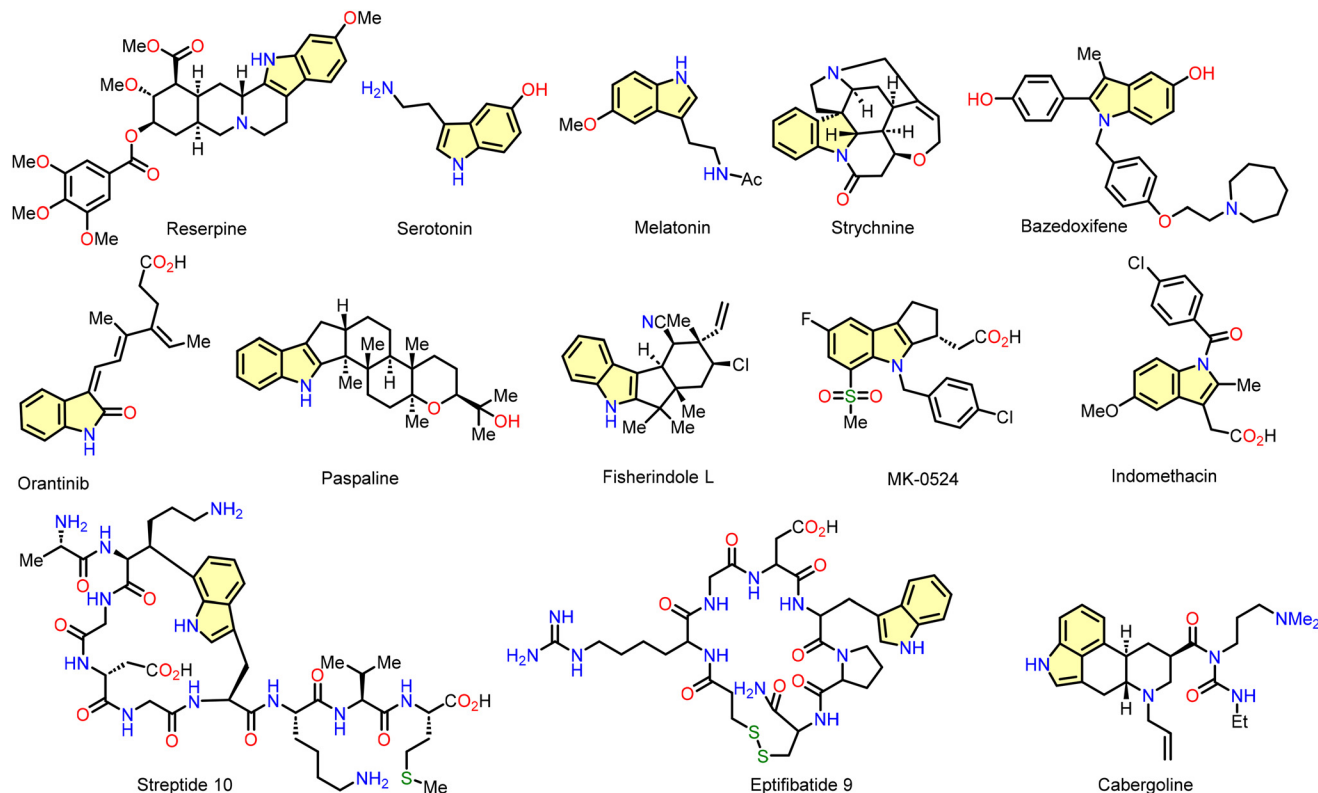


Fig. 1 Biologically relevant indole-based heterocycles.



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 pursue 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.



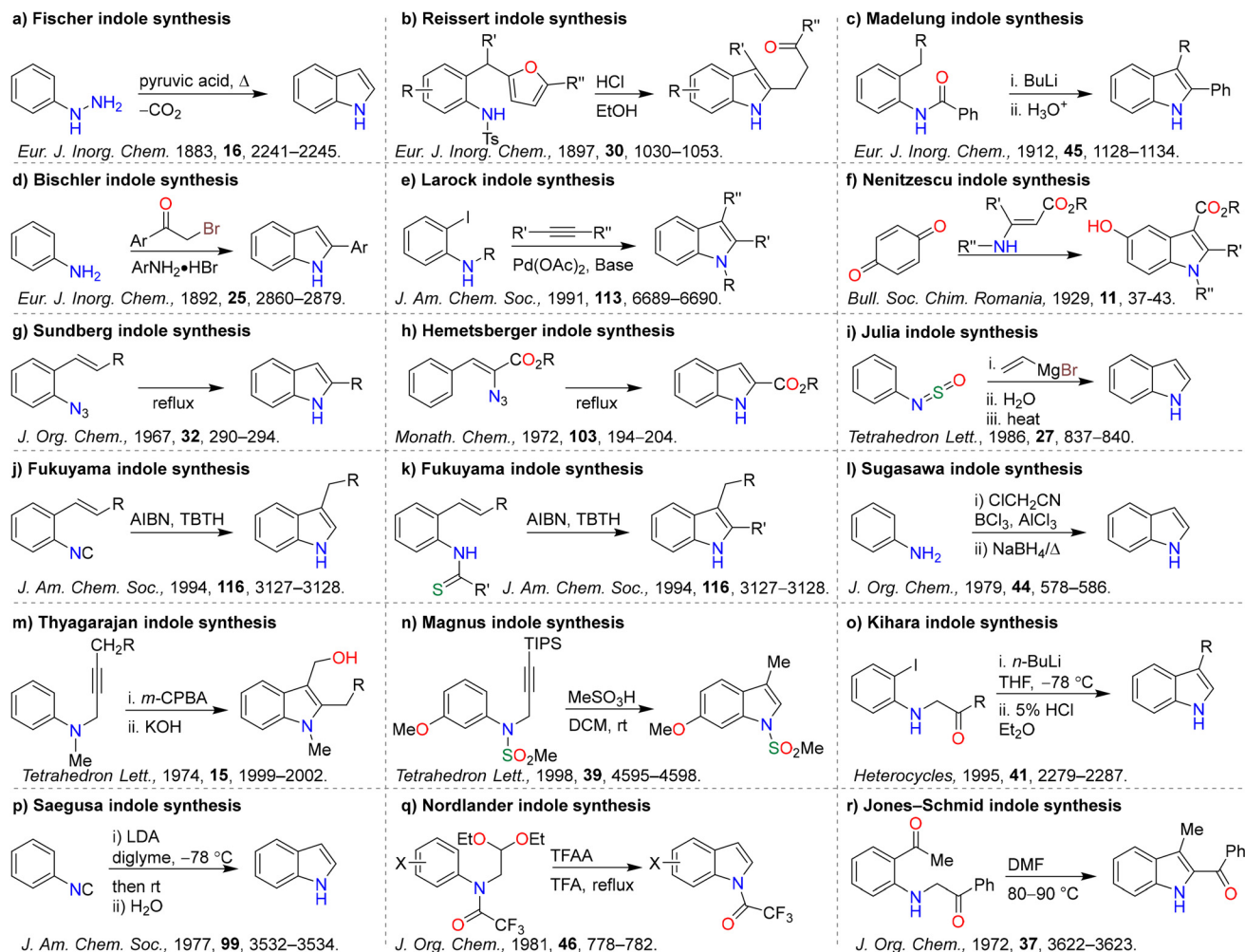
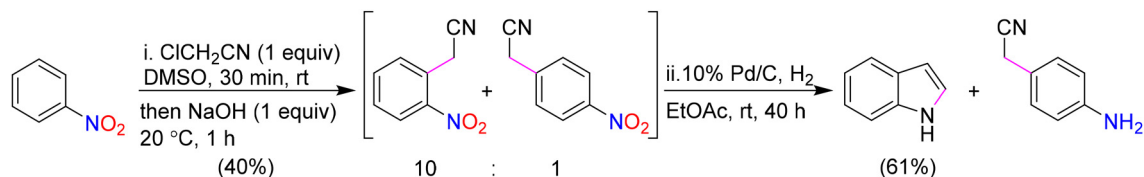


Fig. 2 Classical approaches for the synthesis of indoles.



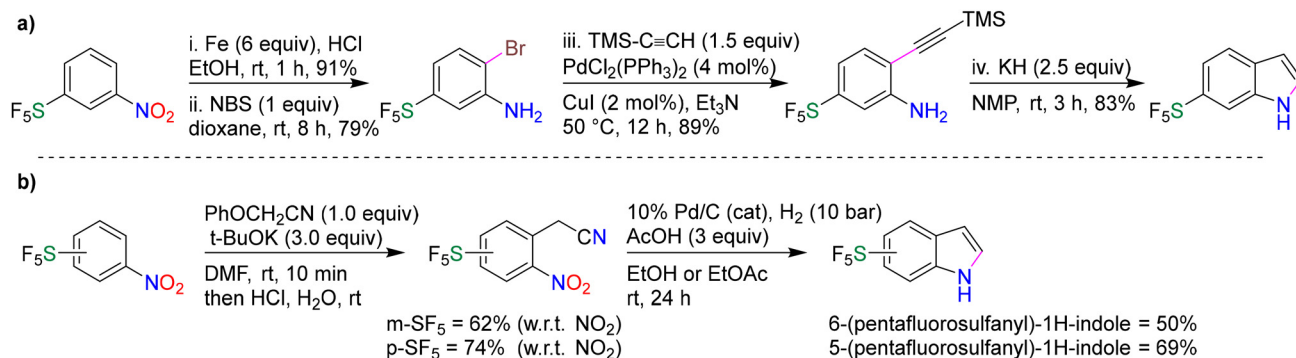
Scheme 1 VNS reaction using chloroacetonitrile followed by hydrogenation.

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-(pen-

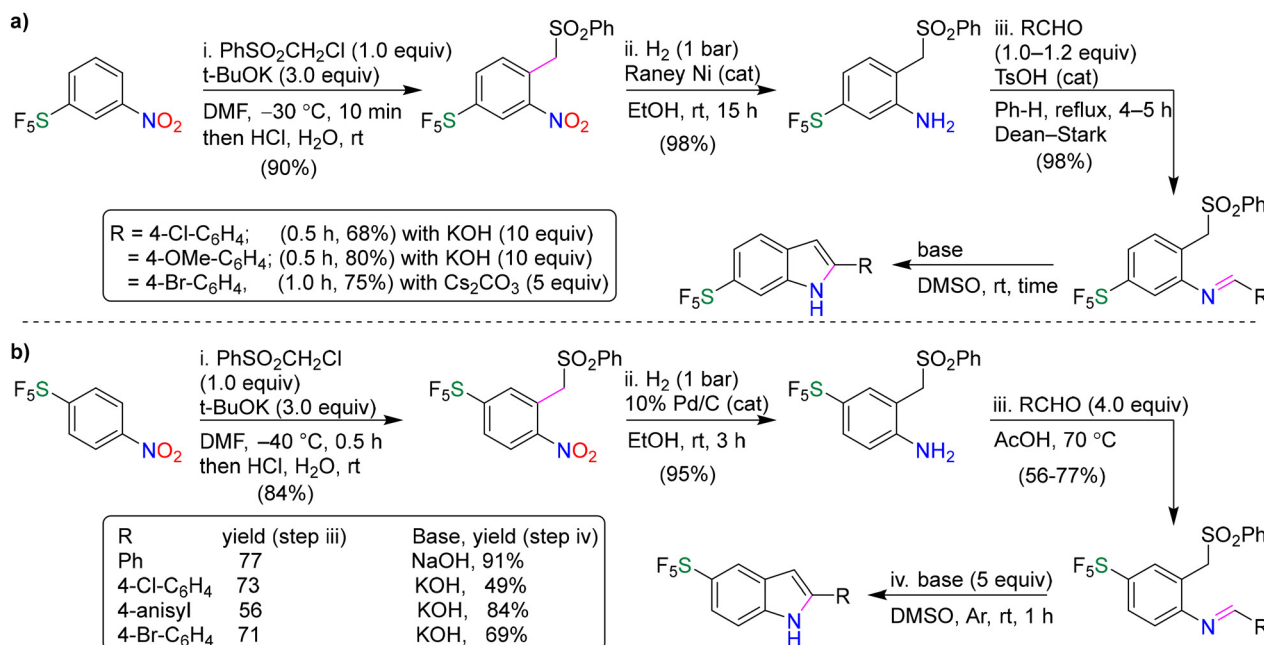
tafluorosulfanyl)-1*H*-indole leads to a high reaction yield due to the good to excellent yield of each step, *cf.* Scheme 2.

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 Cs₂CO₃ mediated annulation in the last





Scheme 2 VNS reaction using 2-phenoxyacetone nitrile followed by hydrogenation.



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).

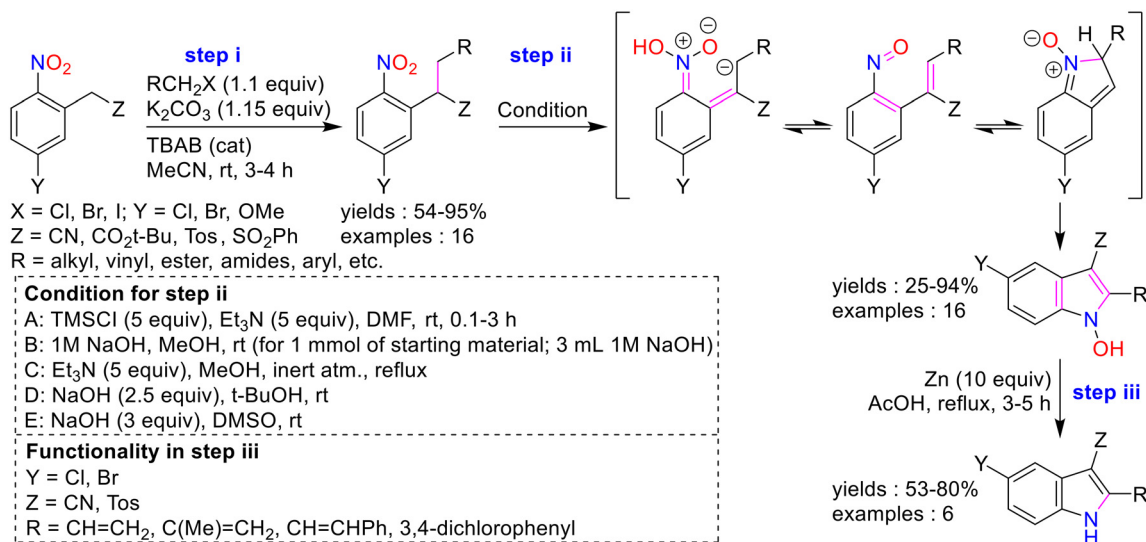
Notably, the synthesis involving 4-nitro(pentafluorosulfonyl)benzene, with annulation in the fourth step under inert conditions with KOH, resulted in a significantly higher yield than that of reactions conducted under aerobic conditions. Similarly, when benzaldehyde was subjected to annulation using 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 pentafluorosulfonyl-substituted indoles.

Later on, the VNS has been fixed by the previous reaction protocol⁸⁶ and it was subjected to an alkylation reaction in step i⁹⁸ 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

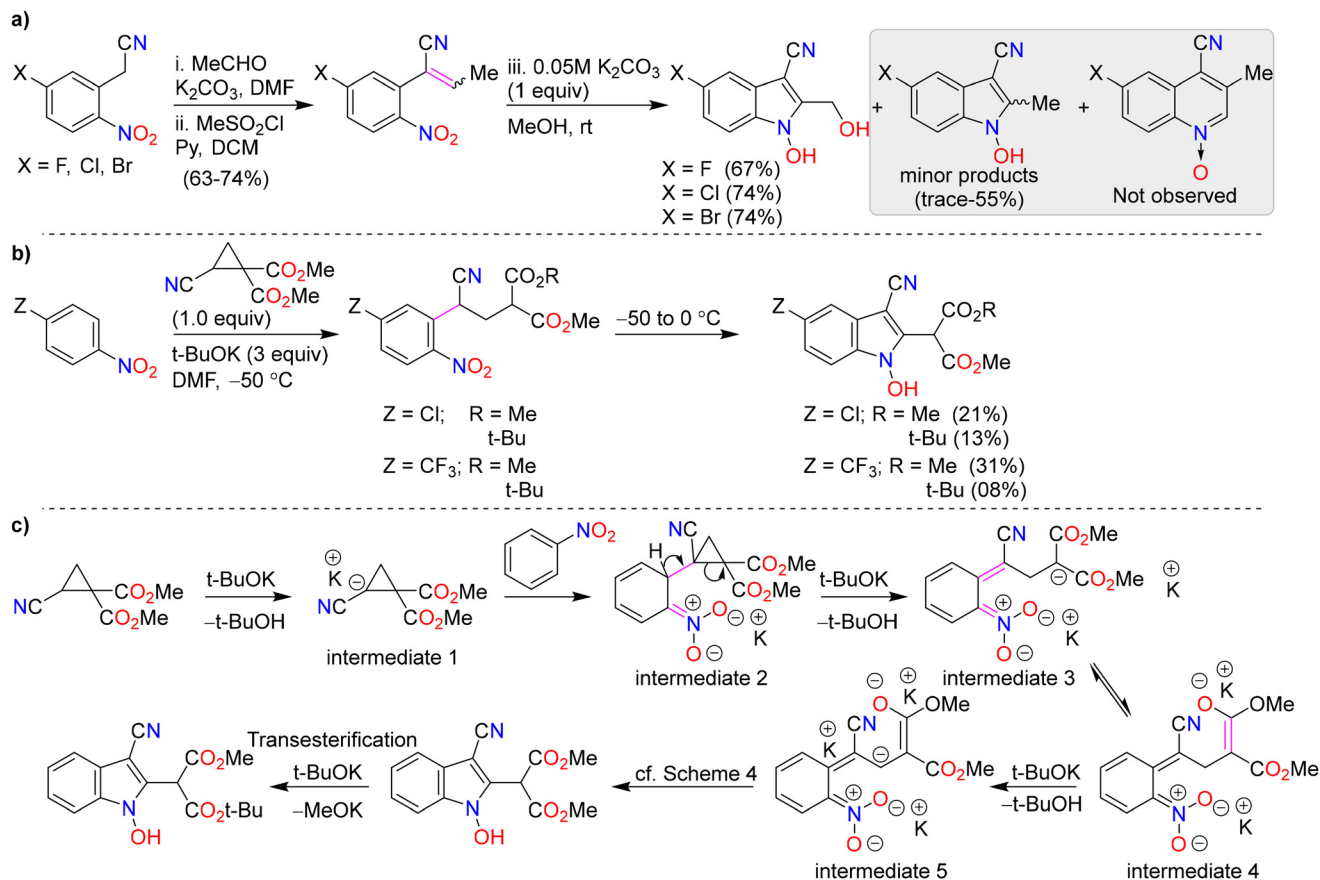




Scheme 4 Higher indole synthesis via the cascade of benzyl functionalization, intramolecular annulation and deoxygenation reactions.

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 Małosza 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).

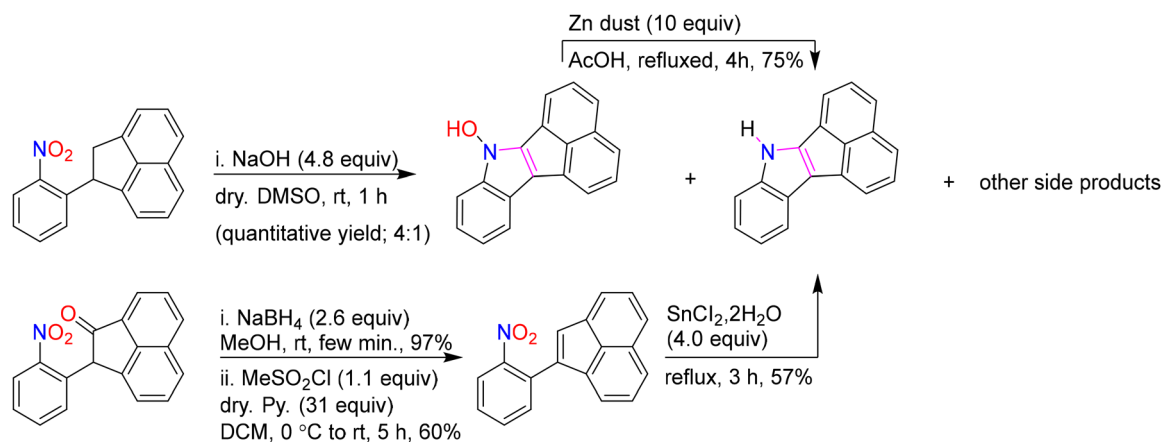
Małosza and coworkers reported a novel approach for the synthesis of indole derivatives to mimic the naturally occurring nitrogen-containing alkaloids batzellines, isobatzellines, damirones, discorhabdins, *etc.*^{103,104} They accomplished the synthesis of the indole ring starting from the synthesized 4,6-dinitroguaiacol with the help of 2-phenoxy acetonitrile *via* the VNS approach and a methylation reaction followed by methylene functionali-

zation 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 -chloro ketones 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).

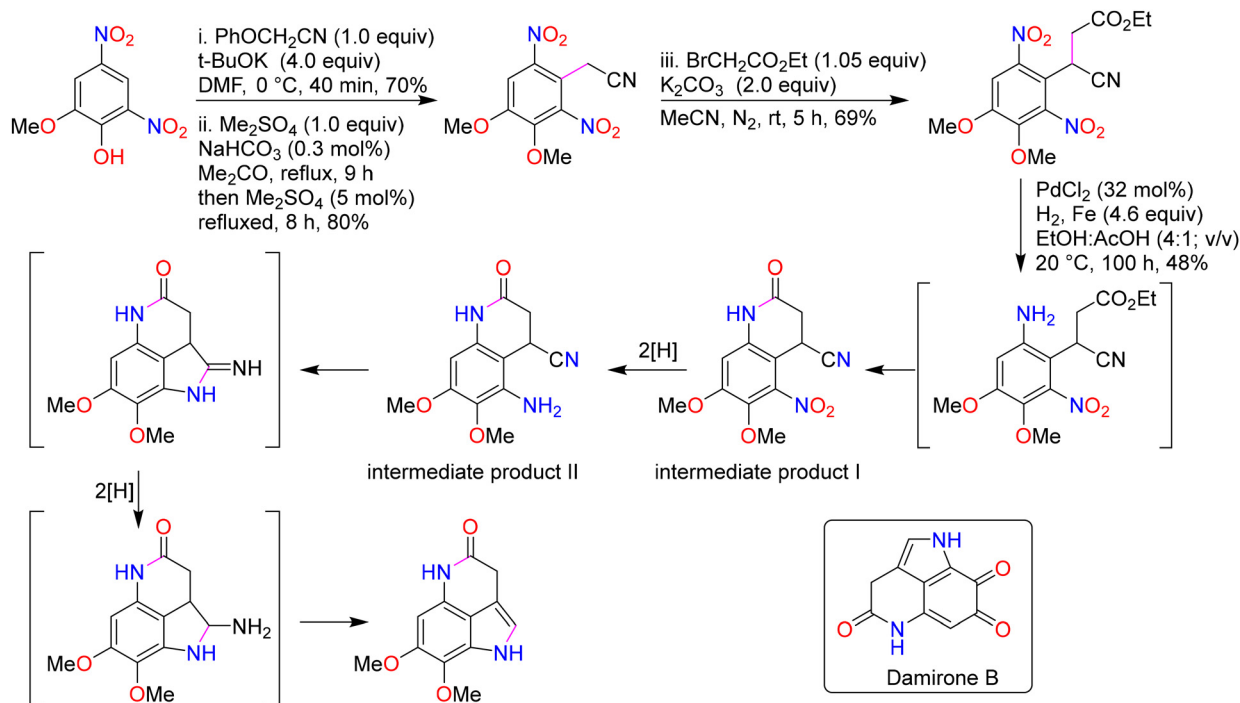
In 1997, Sutherland reported the unusual behavior of DBU with methyl 3,5-dinitrobenzoate and trinitrobenzene in chloroform as well as in ethyl acetate at room temperature after two days.¹⁰⁶ It has been reported that, first, both the starting materials form Meisenheimer complexes as intermediates I and 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-

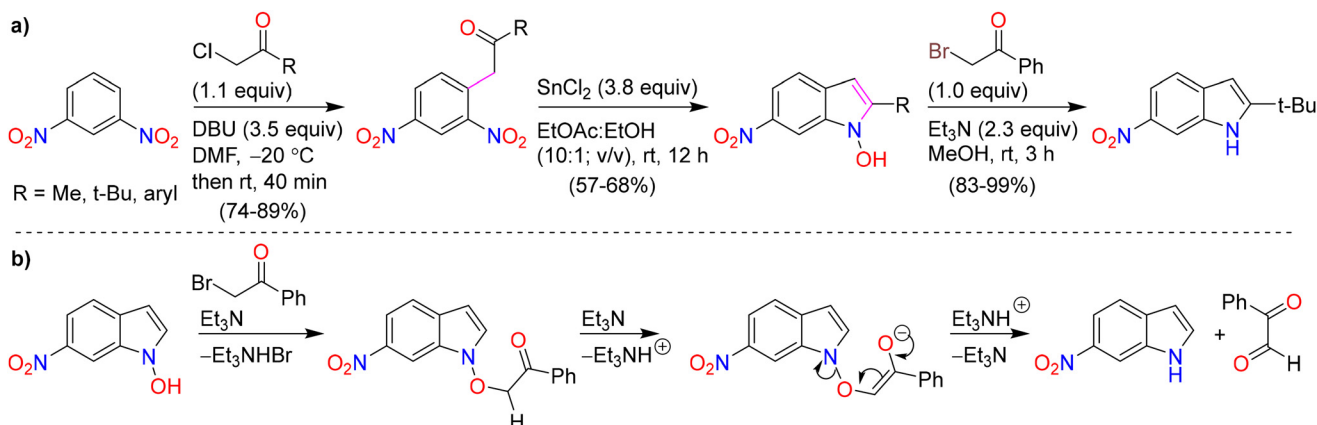
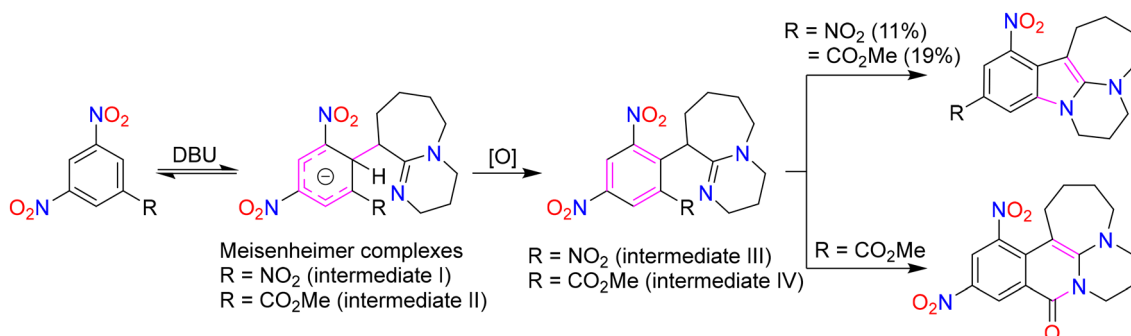


Scheme 6 Synthesis of fused indoles.





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-nitroisocotinaldehyde, respectively (Scheme 10).

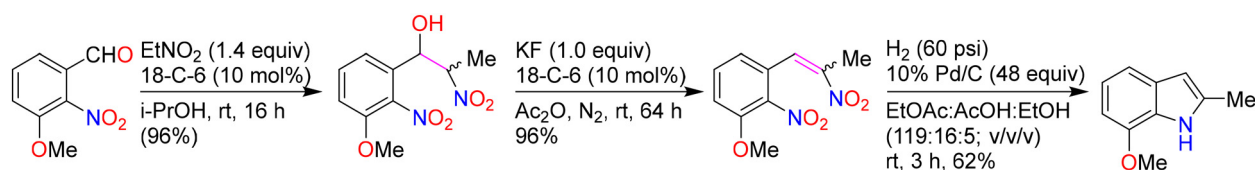
Hossain *et al.* developed a straightforward two-step strategy for the synthesis of indoles. Each step of the reaction was convenient and associated with high yields.¹⁰⁸ In the first step of the reaction, 2-(2-nitroaryl)-3-hydroxypropenoic acid esters were synthesized upon treatment of 2-nitrobenzaldehydes 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

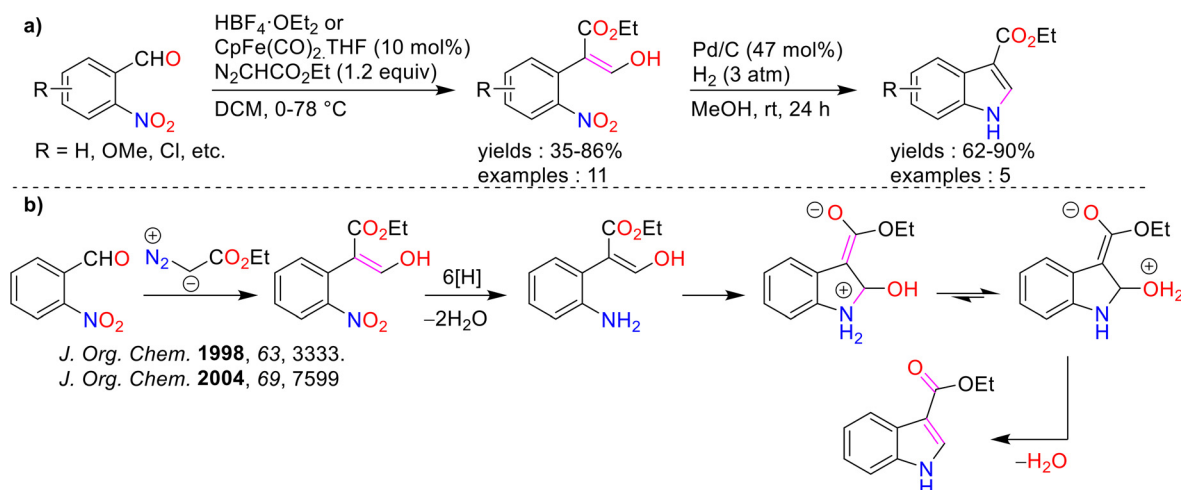
found that the mono-substituted double bond must have a methyl group, which undergoes a fragmentation reaction that produces the potassium salt of 3-(methoxycarbonyl)-indol-1-olate, and then the alkylation produces methyl 1-methoxy-1*H*-indole-3-carboxylate upon treatment with methyl iodide, *cf.* Scheme 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

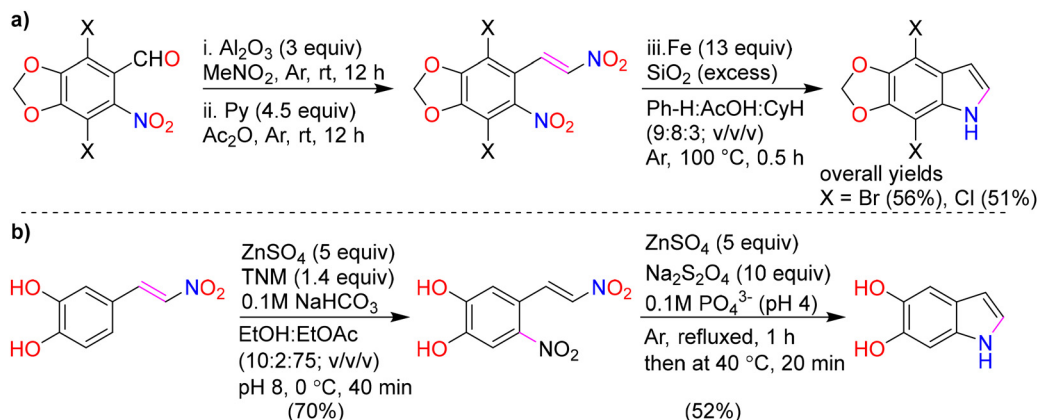
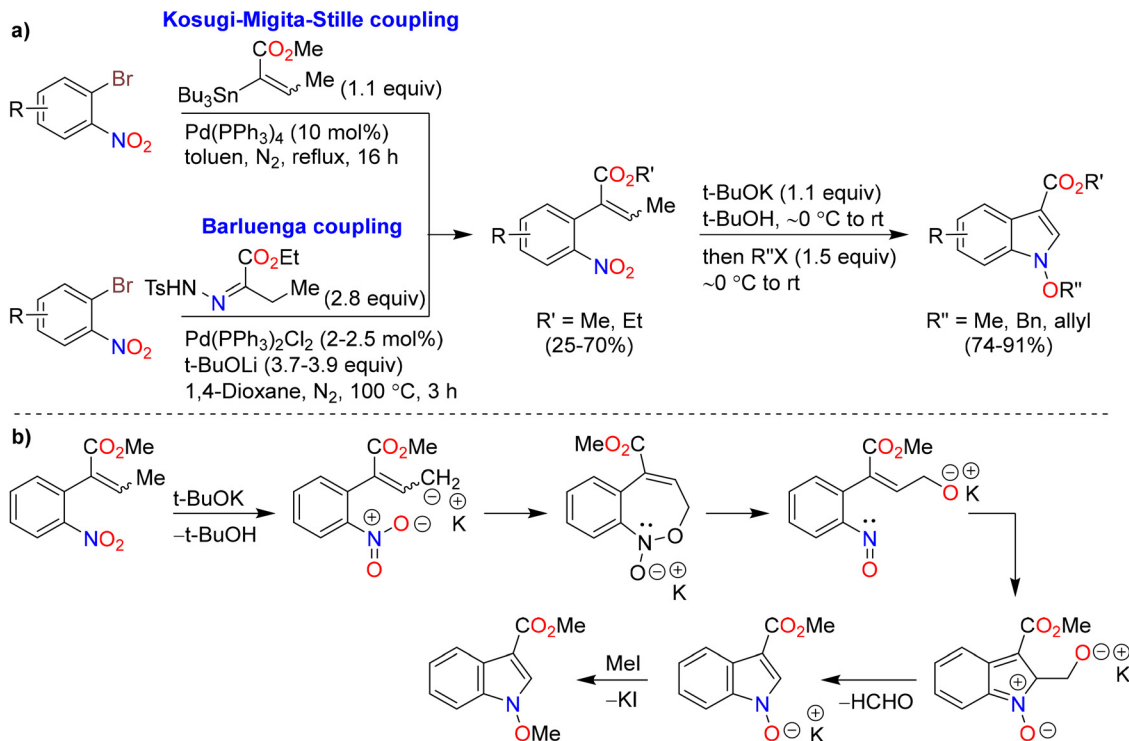


Scheme 10 Synthesis of indoles *via* Henry condensation followed by a hydrogenation reaction.



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



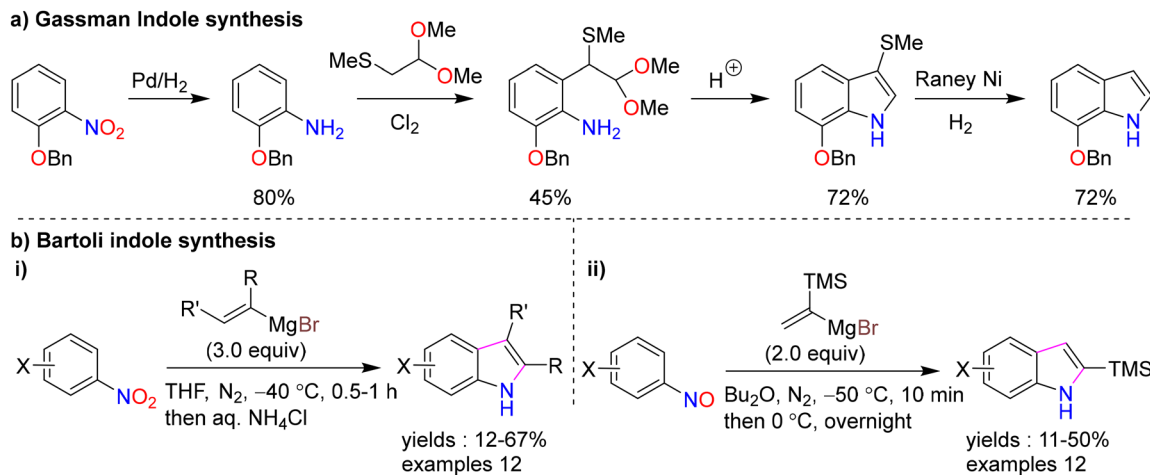


reaction time and solvent usage while simplifying the protocol but also delivers excellent yields.^{120,121} In the following cases, an example of Gassman indole synthesis is shown with a multistep path (Scheme 14a).^{122,123} Herein, each step afforded a good to excellent yield, and the total yield 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 nitroarenes 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-oxindolin-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).

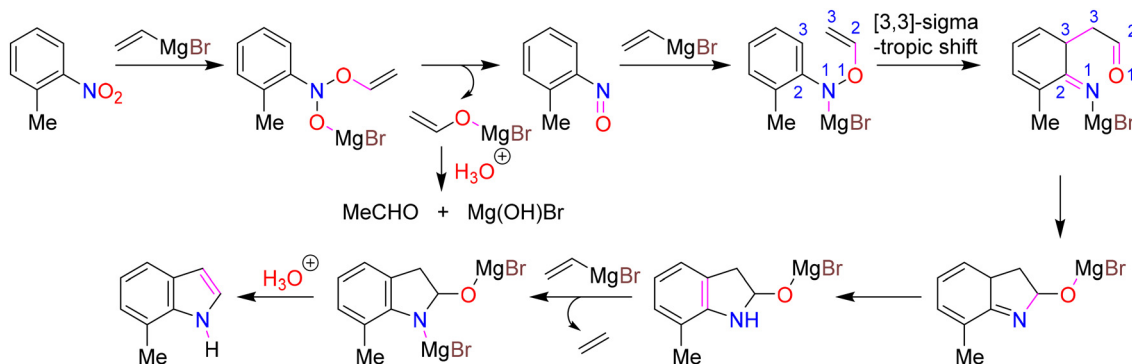
Independently, the Bartoli indole and Barton-Zard reactions of 9-nitrophenanthrene offer two different types of isomeric products, namely, 1*H*-dibenzo[*e,g*]indole and 2*H*-dibenzo[*e,g*]isoindole, *cf.* Scheme 16a. Also, the reaction mechanism of the Barton-Zard reaction is depicted in Scheme 16b.¹²⁴⁻¹²⁷

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*-nitrostyrene, 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.

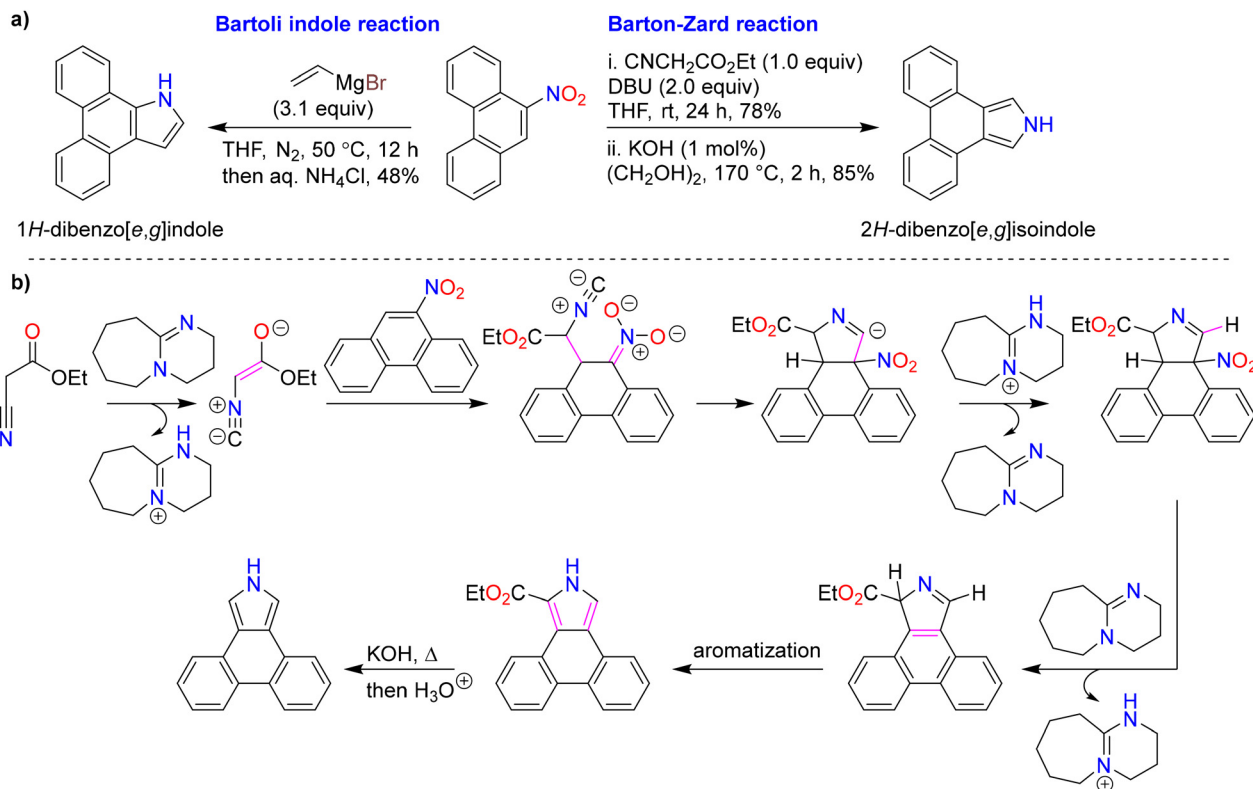
2.2. Involvement of an *ortho*-group in the synthesis of indoles from nitroarenes

Batcho and Leimgruber have discovered a novel approach for the synthesis of indoles¹²⁹ and their analogues from the corresponding 2-nitrotoluenes *via* the condensation of *N,N*-dimethylformamide dimethyl acetal in DMF at high temperature

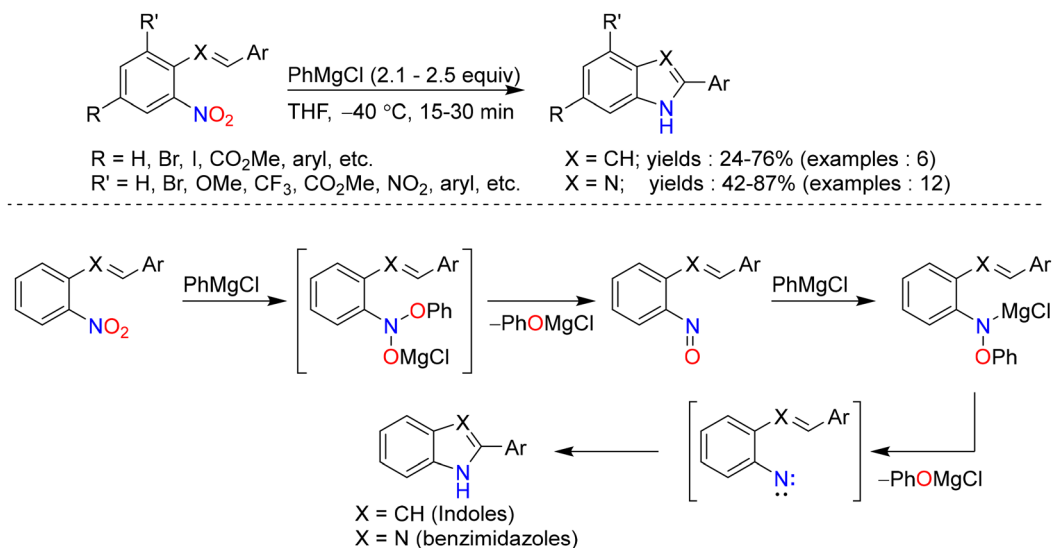


Scheme 15 Mechanism of the Bartoli indole synthesis.





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



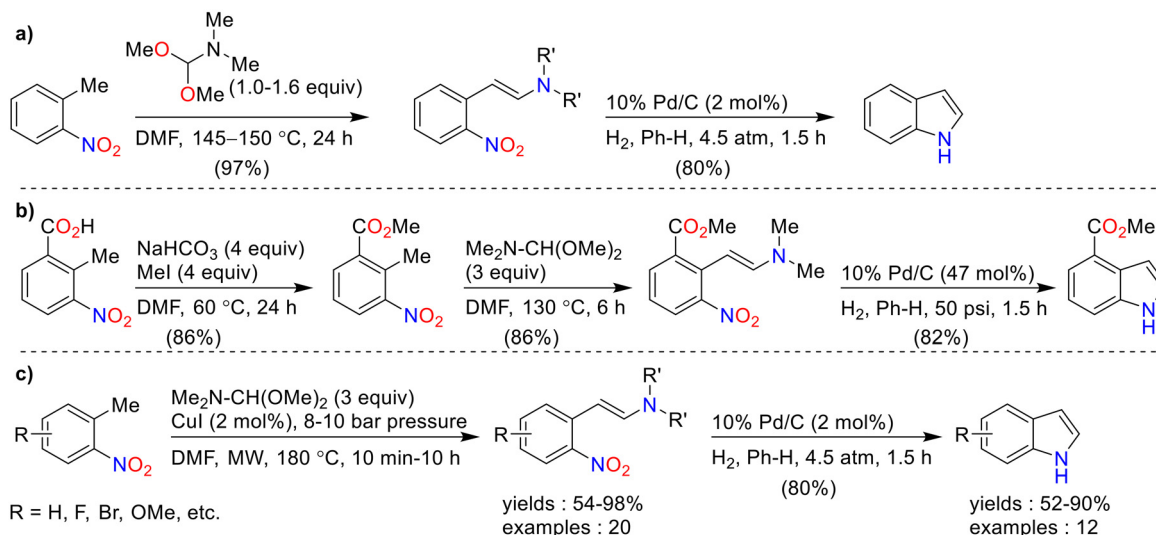
Scheme 17 Knochel indole reactions for the synthesis of indoles and benzimidazoles.

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

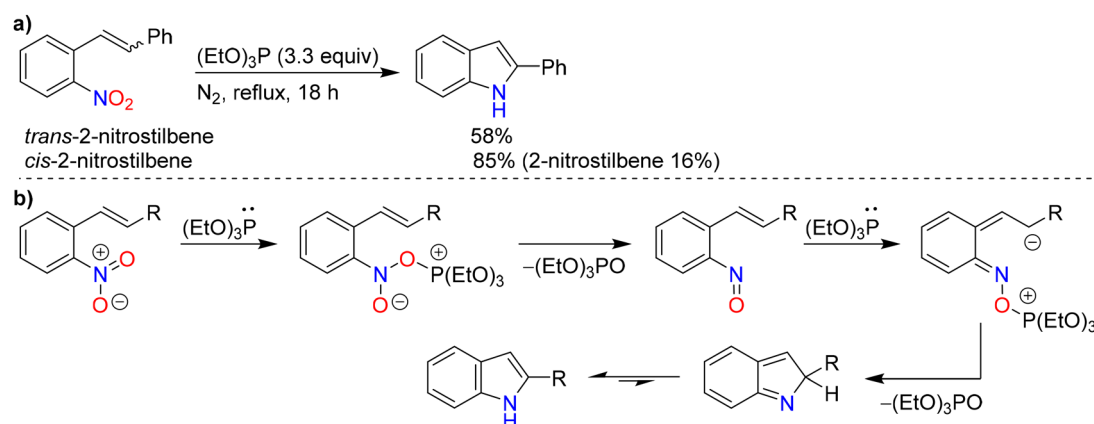
Cadogan–Sundberg indole synthesis. Cadogan and Sundberg developed the progress of direct indole synthesis with the reaction of nitrostyrene with triethyl phosphite or triphenylphosphine (Scheme 19a). Herein, the triethyl phosphite behaves as a deoxygenating reagent and transforms it into the nitroso 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 corres-

ponding indoles and proposed the formation of various types of side products along with the major product (Scheme 20).^{138–140}

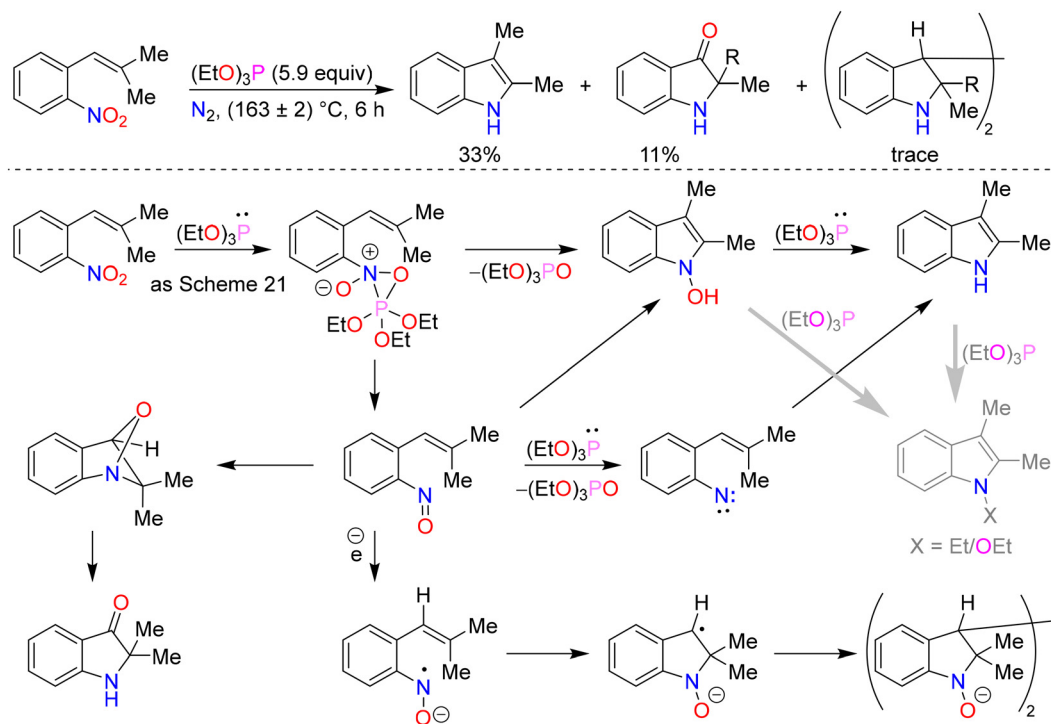
The above combined reaction is known as the Cadogan–Sundberg indole synthesis. Additionally, Peet *et al.* have reported that the reaction of 2-nitrostilbenes with triethyl phosphite leads to the formation of two types of major products, such as 2-arylindoles and the corresponding 2-aryl-*N*-ethoxyindoles.¹⁴¹ They also explored the mechanistic deoxidative investigation to deeply understand the formation of *N*-alkoxyindoles by using isotopically labeled ¹⁸O 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 approaches¹⁴² for the synthesis of indoles in the

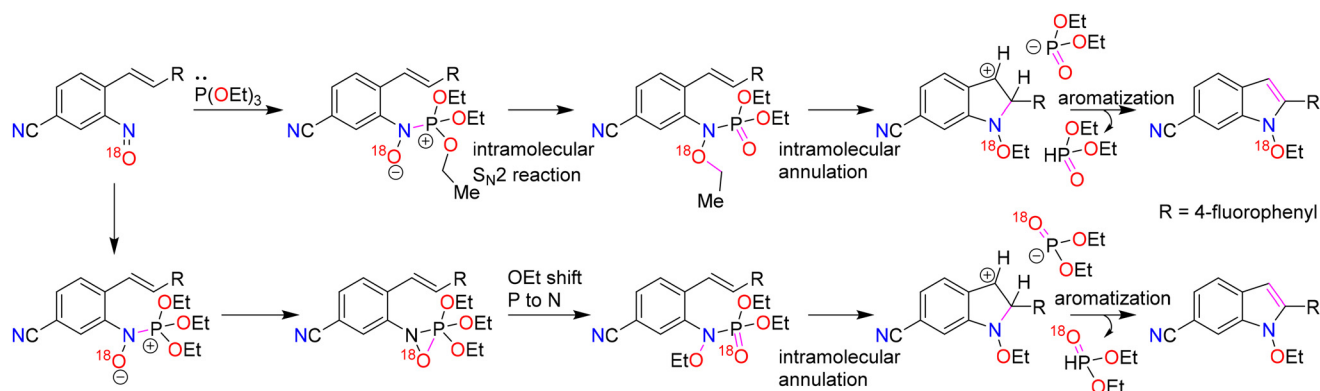


Scheme 19 Reactions and the mechanism reported by Cadogan and co-workers.





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.

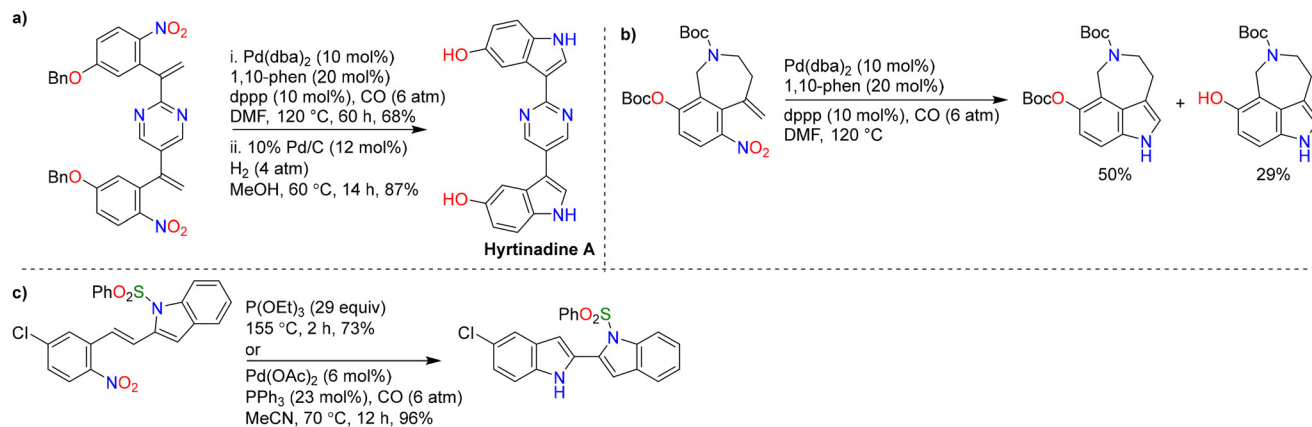
presence of CO (6 atm.). Herein, two important examples of indole alkaloids noted as hyrtinadine A and fargesine were reported by Söderberg's group (Scheme 22a and b).^{143,144} In 2003, Kueth and coworkers reported the synthesis of indoles from nitrostyrenes in the presence of triethyl phosphite (TEP) at very high temperatures during the exploration of the total synthesis of tjianazoles B, D, E, and I.¹⁴⁵ Instantaneously, they also explored the same target by modifying the protocol using the Pd(OAc)₂/PPh₃ 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.

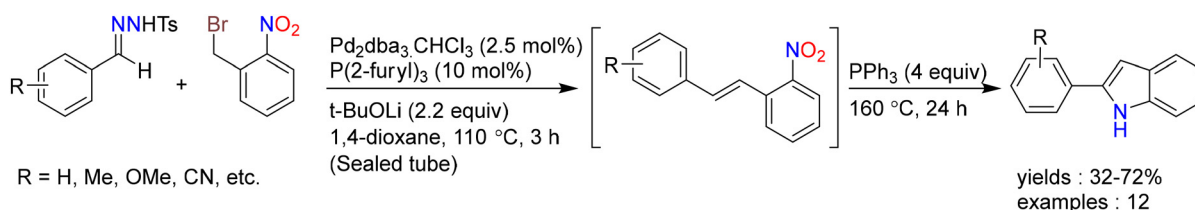
In the following successful attempt, Hamze *et al.* developed an excellent synthesis route for 2-arylindoles by treating equal stoichiometric amounts of *N*-tosylhydrazones and 2-nitrobenzyl bromide using Pd₂(dba)₃·CHCl₃ in a basic medium with P(2-furyl)₃ generating the *ortho*-nitrostilbene intermediate 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

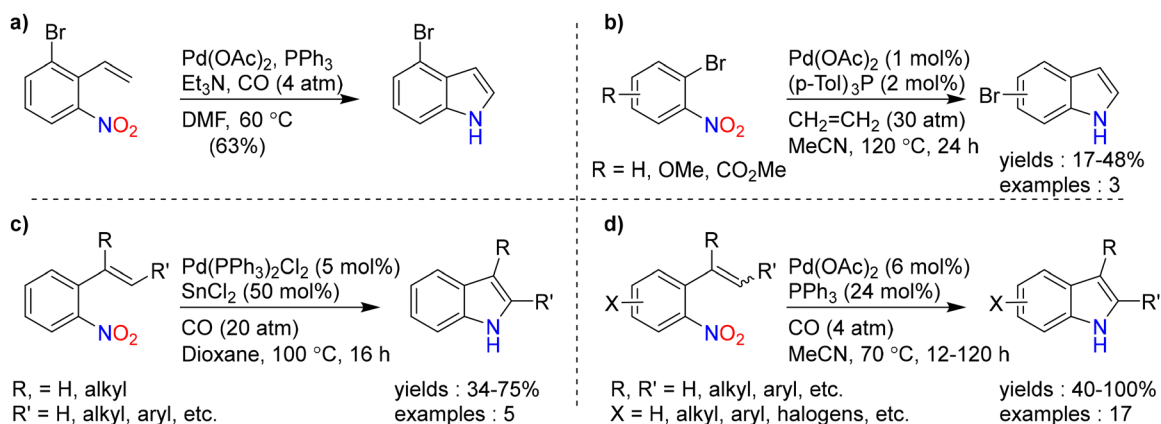




Scheme 22 Modified approach of the Cadogan–Sundberg cyclization for the synthesis of indoles.



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

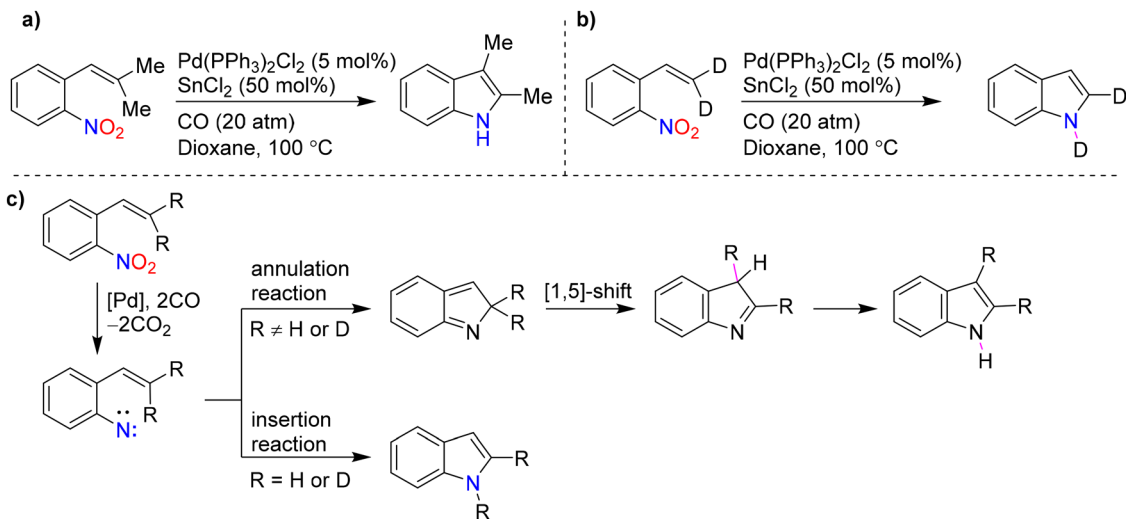


Scheme 24 The synthetic approach for indoles using Pd(II) reagents and additives from 2-nitroarenes.

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).





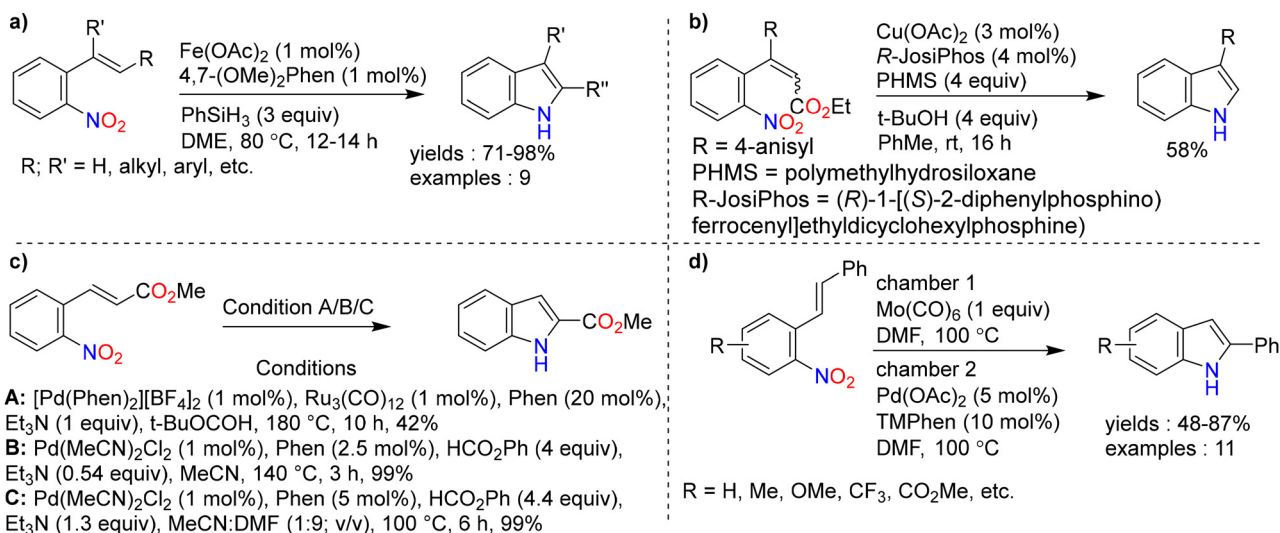
Scheme 25 Cross experiments and the mechanism of formation of indoles.

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, Ru₃(CO)₁₂, and Rh₆(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 con-

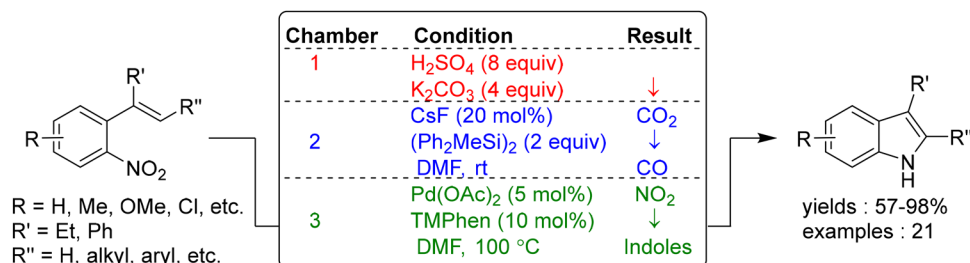
ditions are well tolerated by most of the functional groups, and chemoselectively the nitro group, after the reduction process, forms the heterocyclic indole compounds with excellent yields (Scheme 27).

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 PPh₃. 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

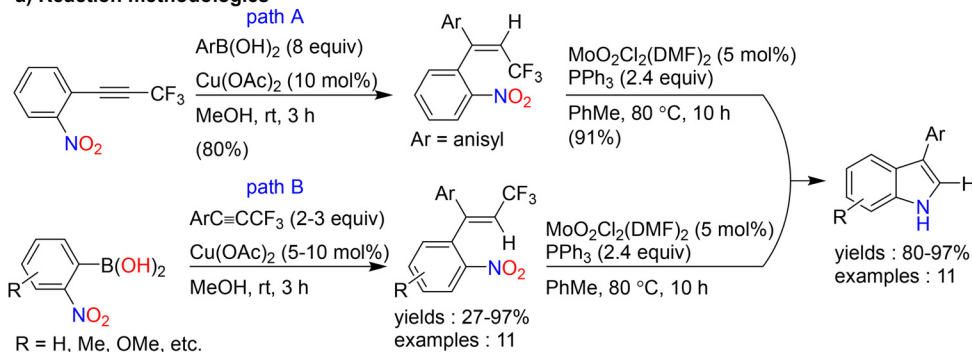


Scheme 26 Indole synthesis with the help of reducing reagents or CO-surrogate reagents.

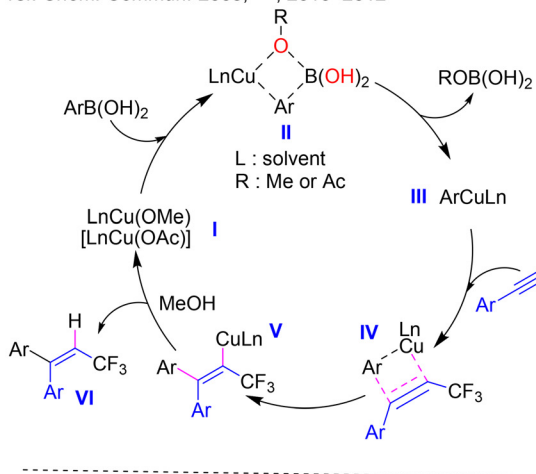


Scheme 27 Single-pot three-chambered reductive annulation of *ortho*-nitrostyrenes to indoles.

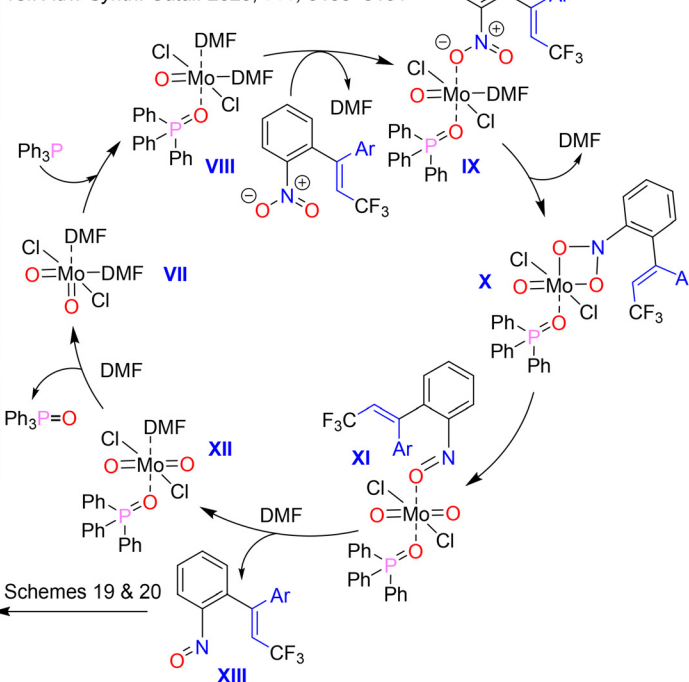
a) Reaction methodologies



b) Stereospecific addition

ref. *Chem. Commun.* 2008, **44**, 2010–2012

c) Mechanism of indoles synthesis

ref. *Adv. Synth. Catal.* 2023, **365**, 3155–3161

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} MoO₂Cl₂(DMF)₂ undergoes an exchange reaction with PPh₃, followed by coordination with a nitro-styrene analogue through intermediates VII and VIII, to yield



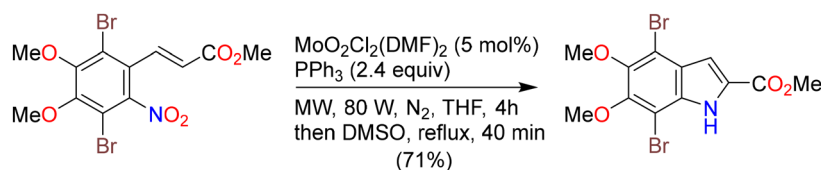
complex IX. The nitro group facilitates the formation of a strained four-membered intermediate X by displacing *N,N*-dimethylformamide (DMF). This intermediate is then transformed into complex XI, which subsequently generates the catalyst precursor XII and finally the active catalytic species VII. Throughout 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) [MoO₂Cl₂(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

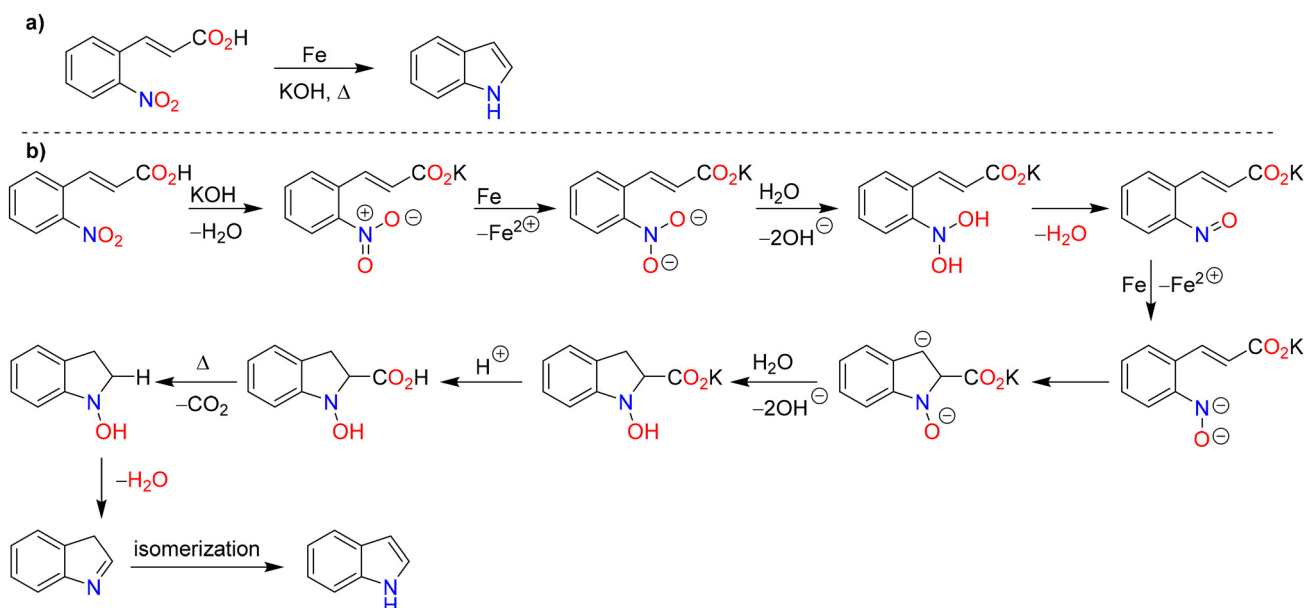
applied microwave conditions reduce the time of the reaction with improved yield of the desired product.

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.

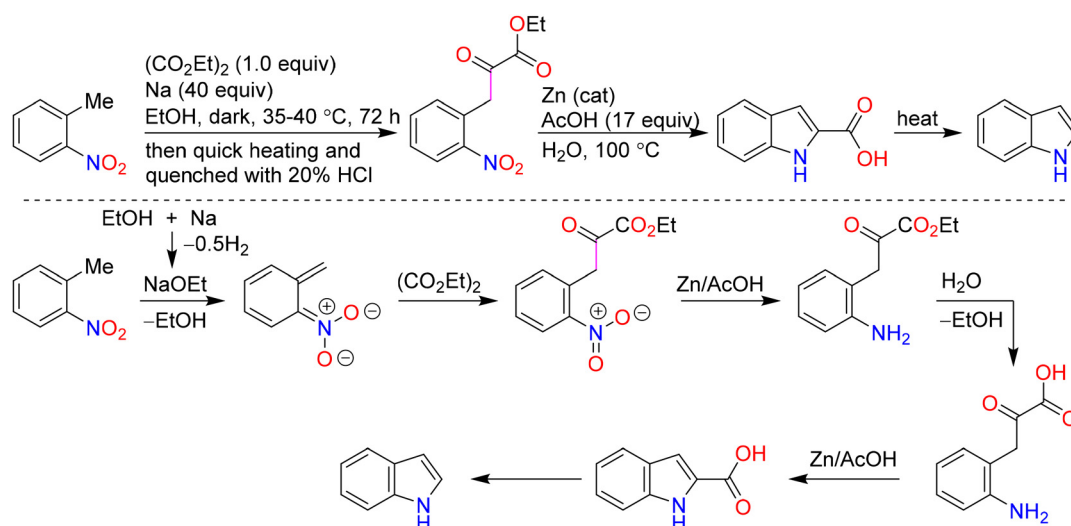


acid derivative. This procedure afforded good to excellent yields of the indole products, and this procedure is commonly known as the Reissert indole synthesis.^{171–174} The other alternative method for the hydrogenation of the nitrophenylpyruvic acid intermediate was also explored with the help of 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}

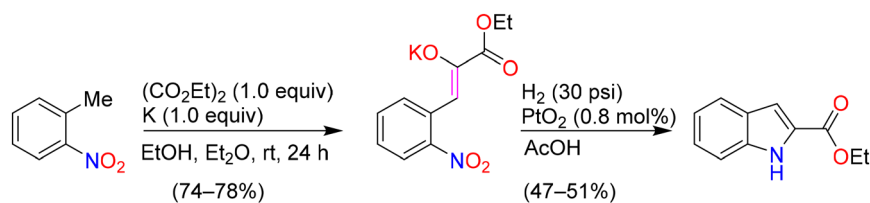
In the following examples, potassium metal was dissolved in absolute ethanol (without stirring) to prepare the potassium ethoxide base, and then it was mixed with a solution of diethyl oxalate under an inert atmosphere at room temperature. Furthermore, nitrotoluene was also added for the synthesis of

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]@SiC₆ 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}

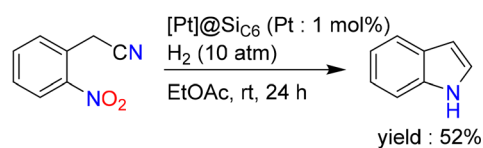


Scheme 31 Synthesis of indoles *via* Reissert indole synthesis.

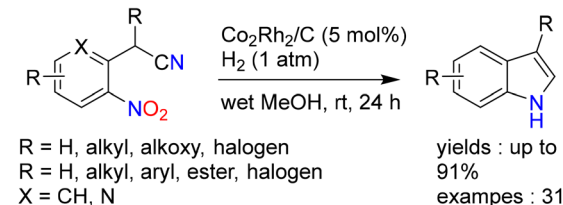


Scheme 32 Synthesis of indoles *via* modified Reissert indole synthesis.

a) Nagashima Work



b) Chung Work



Scheme 33 Nitrile hydrogenations for indole synthesis.



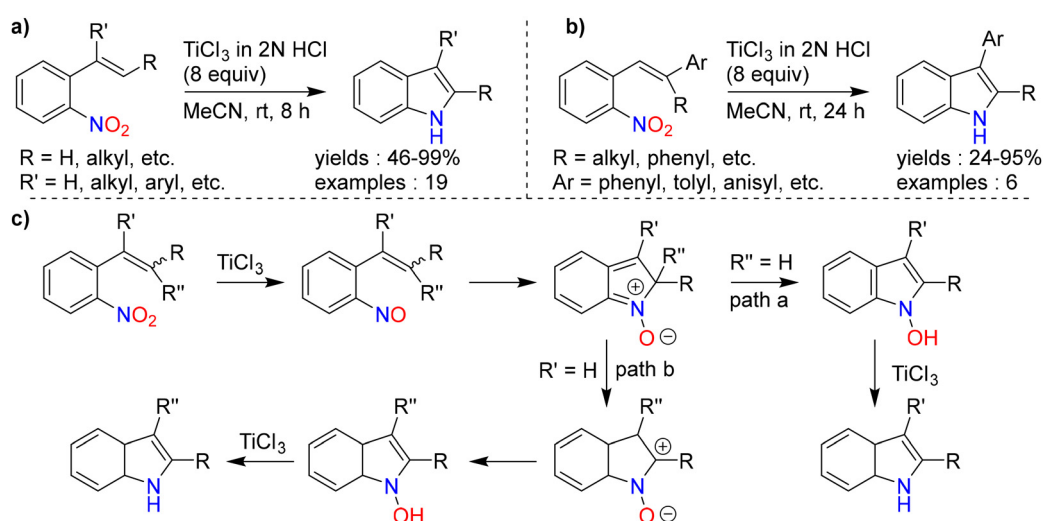
In the next reaction, low-valent titanium(III) chloride was used to synthesize *ortho*-nitrostyrene analogues. Herein, the titanium acts as a reducing reagent for the nitro group and transforms it into the corresponding nitroso derivative.¹⁸⁰ As illustrated below, the cyclization proceeds through the 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,

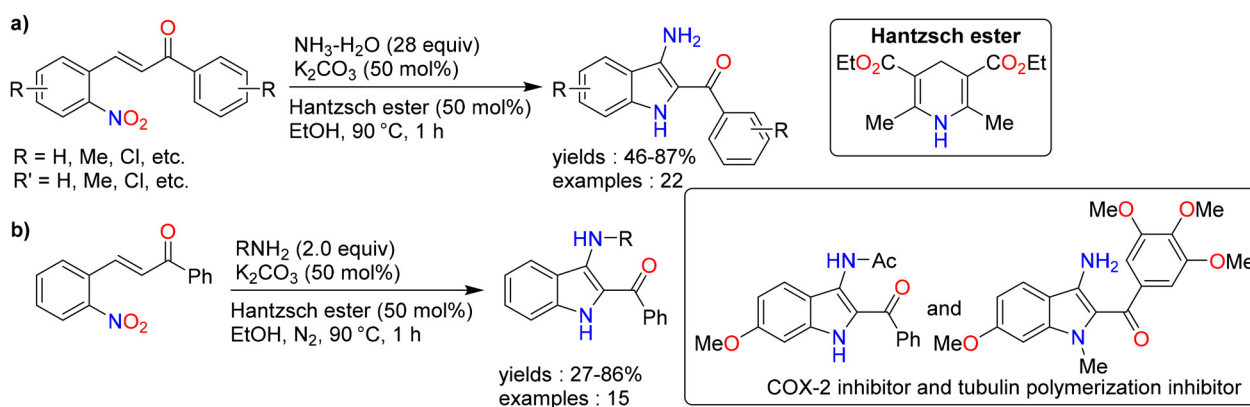
the methodology was also employed for the synthesis of COX-2 and tubulin polymerization inhibitors. Furthermore, the ammonia was substituted by primary amines to perform the successful synthesis of 3-aminoalkyl-indoles with yields of 27–86% (Scheme 35b).

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

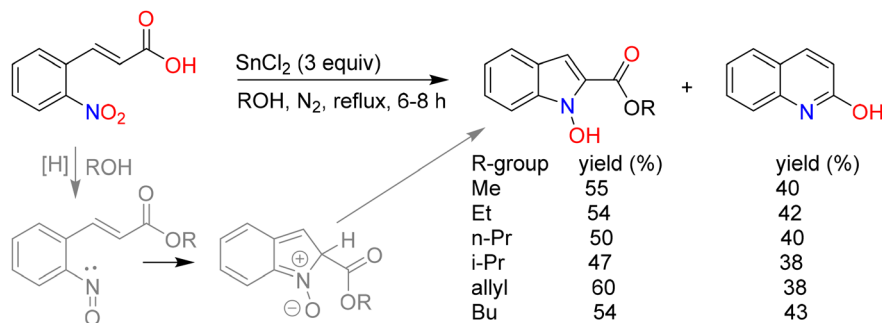


Scheme 34 Titanium(III)-supported intramolecular reductive annulation for indole synthesis.

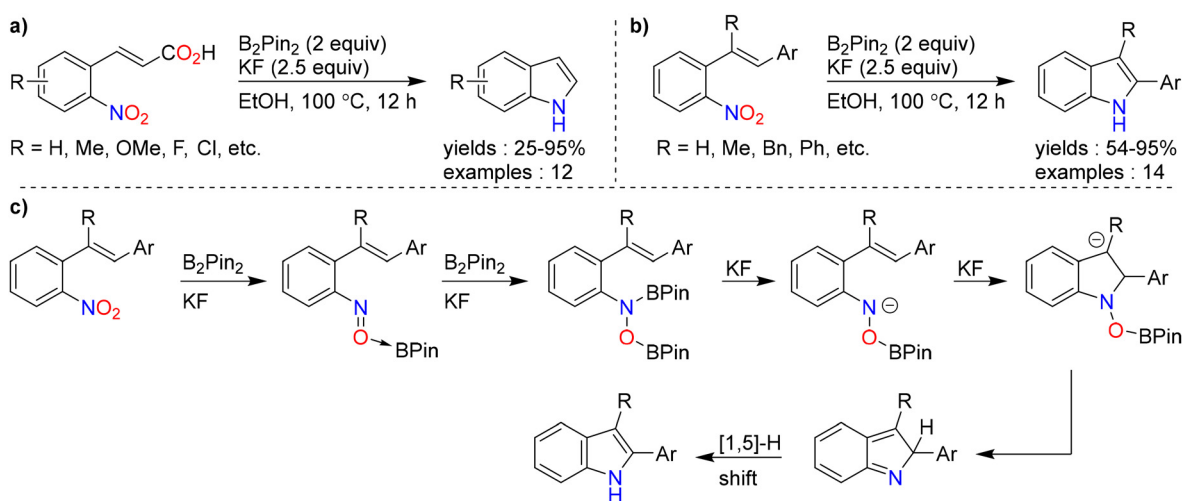


Scheme 35 Synthesis of indoles from chalcones.





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.

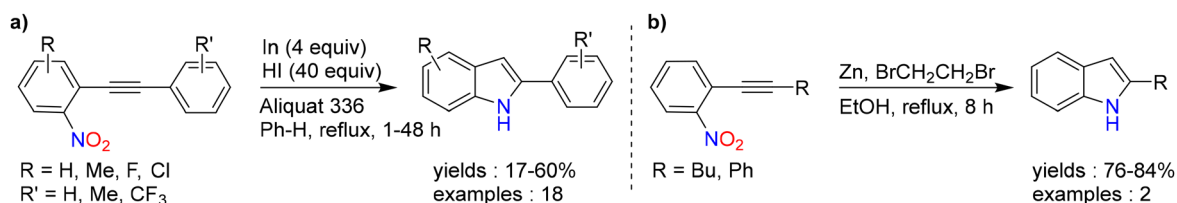
nitro group into a nitroso intermediate. Further, it reacts with another mole of bis(pinacolato)diboron, and then undergoes annulation followed by a [1,5]-sigmatropic shift affording the indoles (Scheme 37c).

Alkynes can easily be prepared by the most frequent reactions, *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

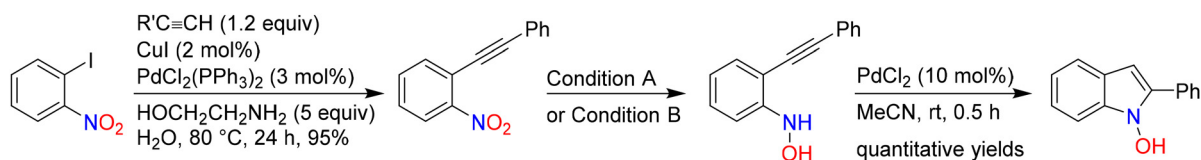
Oh and Shin have reported a tandem reaction for the synthesis of 1-hydroxyindoles from *ortho*-iodonitrobenzene.¹⁸⁶ Herein, these reactions were performed *via* a cascade of reactions, *i.e.*, Sonogashira coupling, selective partial reduction, followed by a Pd(II)-catalyzed electrophilic annulation reaction, 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-aryl-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.





Condition A: Ni powder (1.2 equiv), 50% aq. $\text{N}_2\text{H}_2\cdot\text{H}_2\text{O}$ (6.5 equiv), 1,2-DCE:EtOH (1:1; v/v), rt, 6 h, 94%

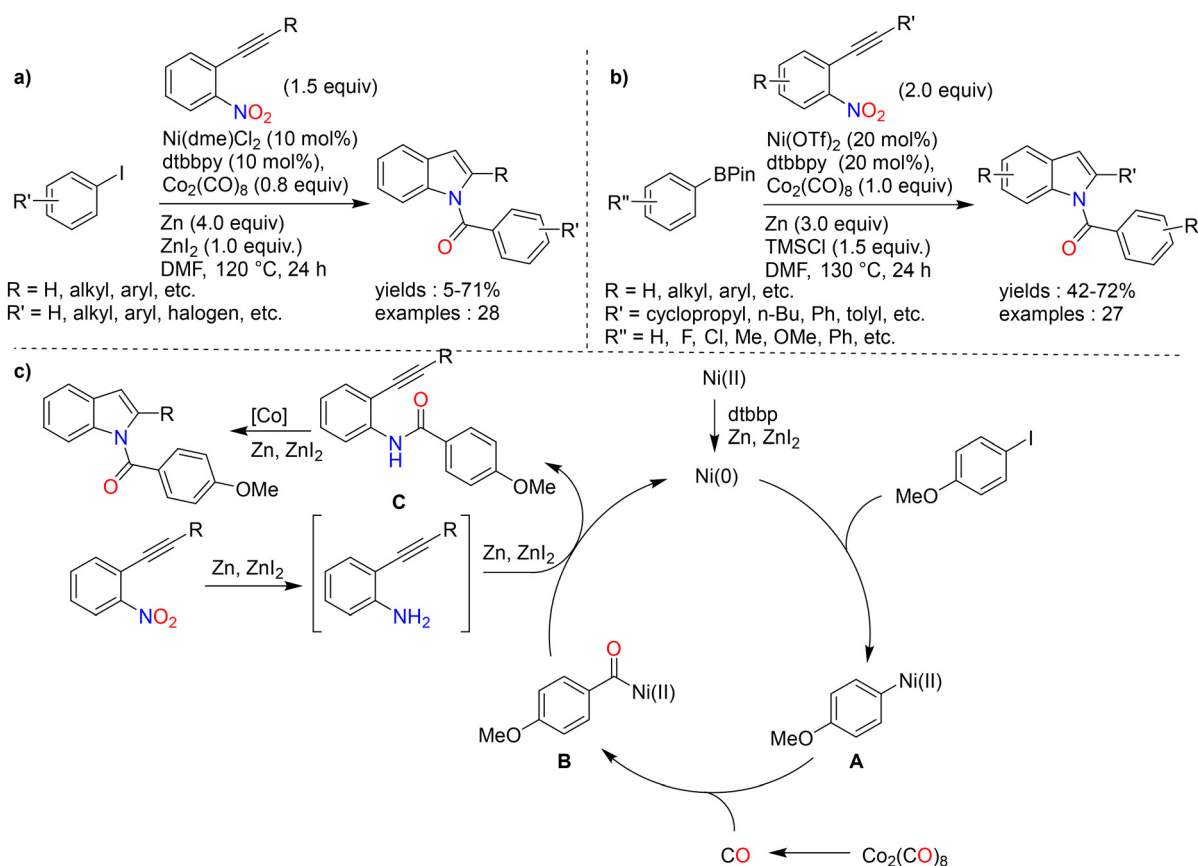
Condition B: Zn powder (2.1 equiv), 50% aq. $\text{N}_2\text{H}_2\cdot\text{H}_2\text{O}$ (6.5 equiv), THF, rt, 99%

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 $\text{Ni}(\text{dme})\text{Cl}_2$ with aryl boronate esters, TMSCl, and $\text{Ni}(\text{OTf})_2$ 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/ZnI₂ reducing system. Next, the Ni(0) species undergoes oxidative insertion with iodoarene, followed by carbonylation *via* the *in situ*-gener-

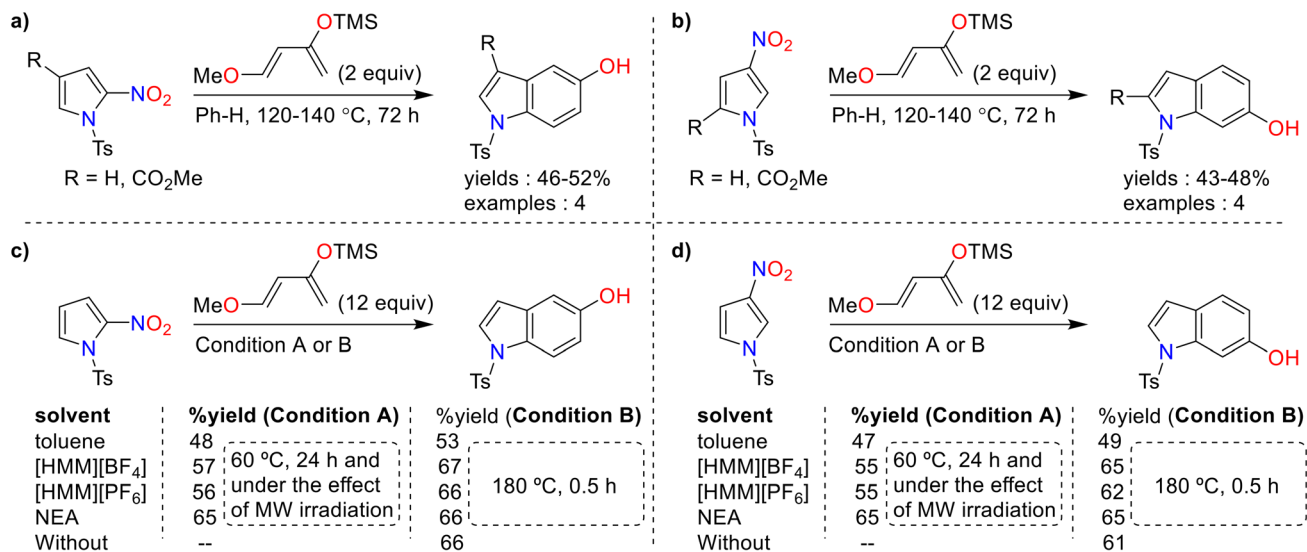
ated $\text{Co}_2(\text{CO})_8$ reagent that transforms active species A to B. At the same time, chemoselective reduction of the nitroalkyne generates the aniline derivative due to the presence of the reducing agent Zn/ZnI₂ and then it immediately reacts with *in situ* generated reactive species B, generating the intermediate product C. Finally, it undergoes an annulation reaction that produces the corresponding *N*-aryl indole with the aid of $\text{Co}_2(\text{CO})_8$, 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*-aryloindoles from 2-nitroalkynes.





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

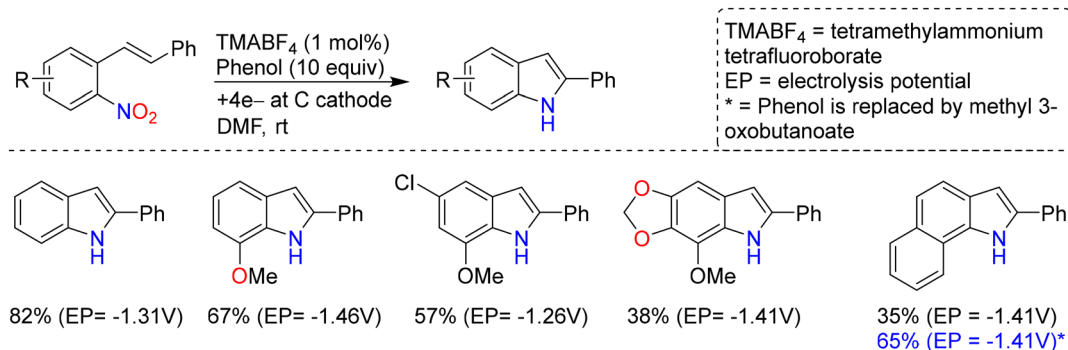
amide, which also produces the annulation product with poor yield. Furthermore, the reaction was explored by the same group for indole products under microwave-assisted conditions with and without solvent, where they found a higher yield than that of the previous reaction protocols (Scheme 43c and d). 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][BF₄], [HMIM][PF₆], and [NEA] have been prepared according to the previously reported methods).¹⁹⁶

Electrochemical approach. Peters and his coworkers reported an electrochemical reductive approach¹⁹⁷ 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

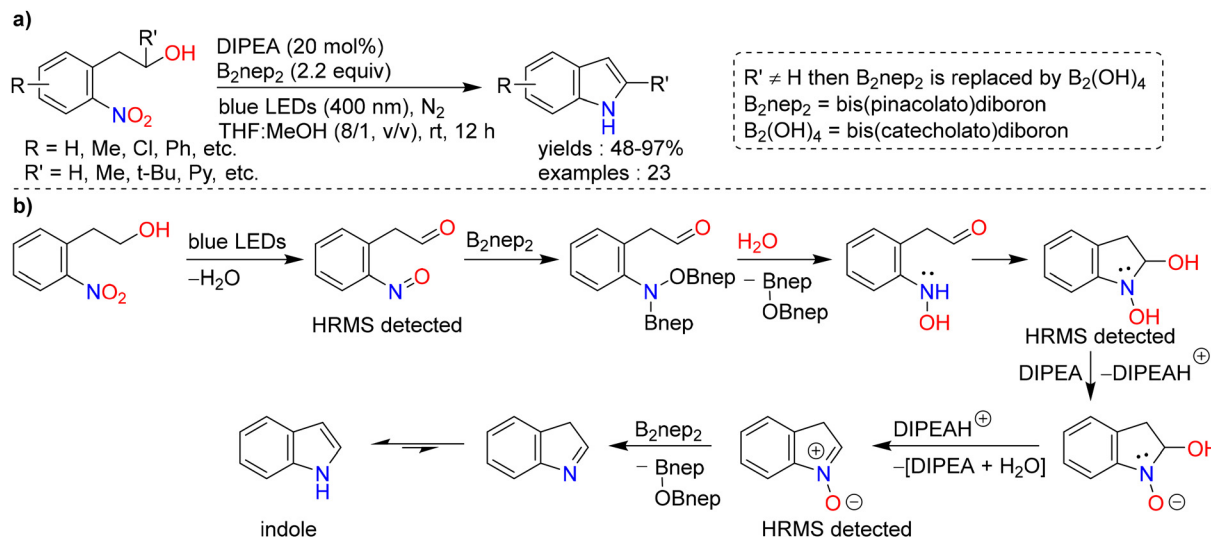
Photochemical approach. Wang *et al.* performed the synthesis of indoles from *ortho*-nitrohomobenzyl alcohols by employing diborane and DIPEA under 400 nm blue LEDs (Scheme 45a). Herein, the nitro- and hydroxyl-groups underwent intramolecular redox reactions in the presence of blue LEDs to form 2-(2-nitrosophenyl)acetaldehyde, 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.



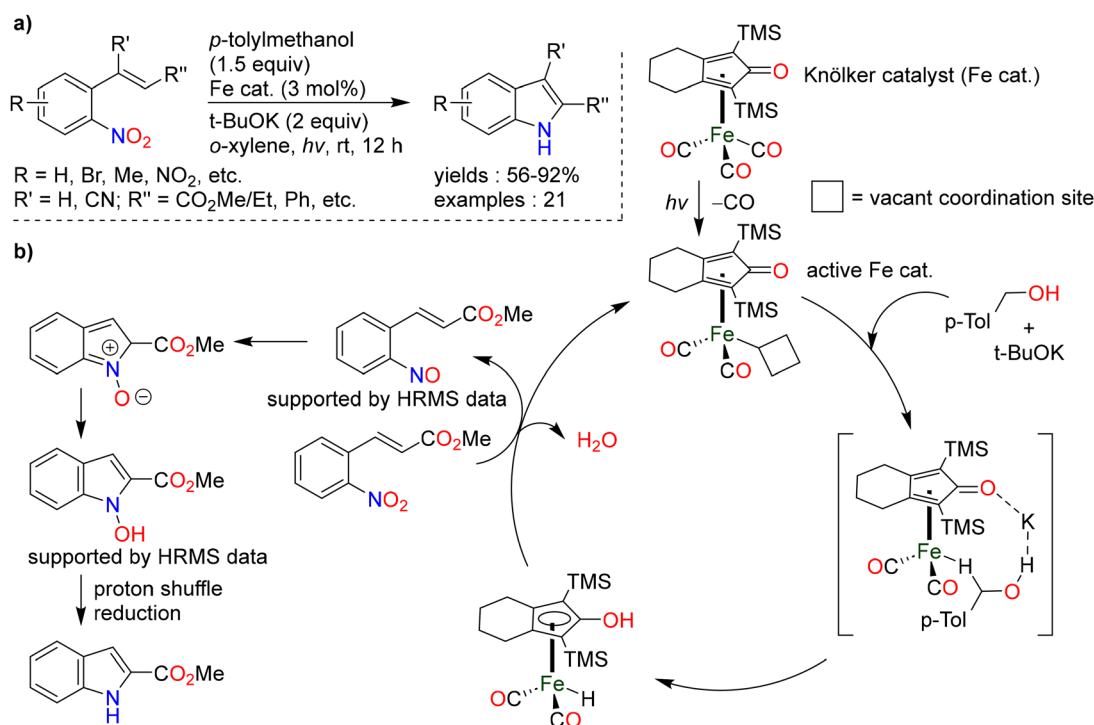


Scheme 45 Synthesis of indoles from *ortho*-nitrohomobenzyl alcohols.

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

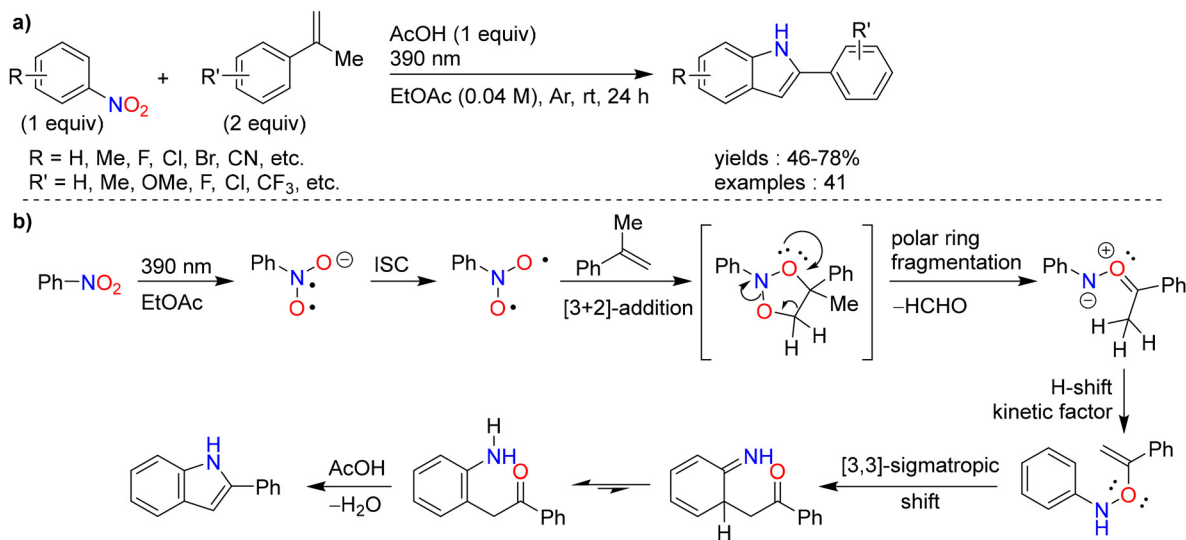
and hydroxyindoles was confirmed by HRMS data analysis (Scheme 46b).

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 atmosphere²⁰⁴ 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.



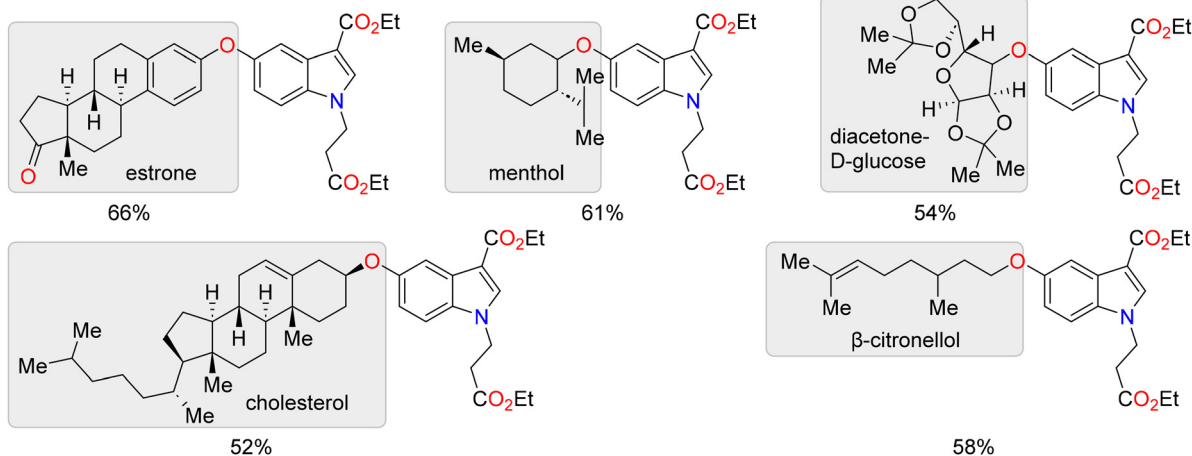
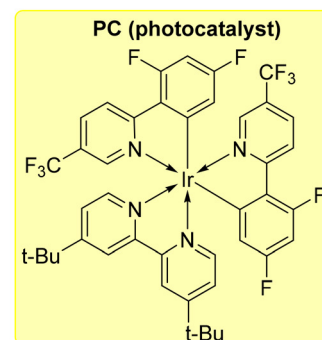
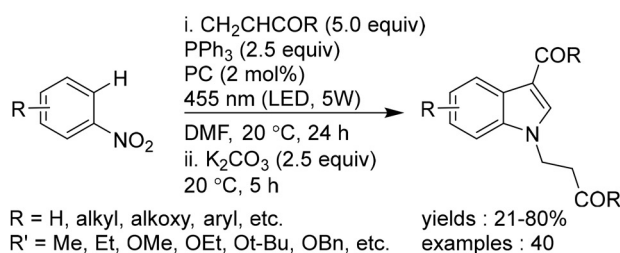


Scheme 47 Photoinduced Bartoli indole synthesis.

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, PPh₃, TiCl₃, *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.

Acknowledgements

Dr Chandra is thankful to the KHU Seoul, South Korea, for the research professor position and also for the excellent funding and infrastructure for the exploration of education and



science. Dr Suresh C. Yadav, Dr Subba Rao Cheekatla, and Dr Abhijeet Kumar are thankful for their affiliations with Satish Chandra College, Ballia; Korea University, Seoul; and Mahatma Gandhi Central University, respectively, for the funding and infrastructure.

References

- E. Kabir and M. Uzzaman, A review on biological and medicinal impact of heterocyclic compounds, *Results Chem.*, 2022, **4**, 100606.
- B. Yu and X. Yang, Why are heterocycles so special in medicinal chemistry?, *Chem. Biol. Drug Des.*, 2022, **100**, 763–764.
- I. Pibiri, Recent Advances: Heterocycles in Drugs and Drug Discovery, *Int. J. Mol. Sci.*, 2024, **25**, 9503.
- P. H. M. Zabiulla and S. A. Khanum, An Overview of the Synthetic Routes and Pharmacological Aspects of Pyridine, Isoxazole, Thiazole, and Indole Derivatives, *Polycyclic Aromat. Compd.*, 2024, **44**, 7168–7196.
- S. Kotha and S. R. Cheekatla, Design and synthesis of pentacycloundecane cage compound containing oxazole moiety, *Heterocycles*, 2020, **100**, 1623–1632.
- S. Kotha and S. R. Cheekatla, Synthesis of Bisoxazole and Bromo-substituted Aryloxazoles, *Molbank*, 2022, **2022**, M1440, DOI: [10.3390/M1440](https://doi.org/10.3390/M1440).
- É. Frank and G. Szöllösi, Nitrogen-Containing Heterocycles as Significant Molecular Scaffolds for Medicinal and Other Applications, *Molecules*, 2021, **26**, 4617.
- S. Kotha, M. Salman and S. R. Cheekatla, Synthesis of Indenoindole Derivatives under Deep Eutectic Solvent Conditions, *ChemistrySelect*, 2024, **9**, e202402530.
- D. Monica, N-heterocycles: Recent Advances in Biological Applications, *Mini-Rev. Org. Chem.*, 2023, **20**, 735–747.
- C. Prandi and E. G. Occhiato, From synthetic control to natural products: a focus on N-heterocycles, *Pest Manage. Sci.*, 2019, **75**, 2385–2402.
- N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications, *Molecules*, 2020, **25**, 1909.
- A. Amin, T. Qadir, P. K. Sharma, I. Jeelani and H. Abe, A Review on The Medicinal And Industrial Applications of N-Containing Heterocycles, *Open J. Med. Chem.*, 2022, **16**, e187410452209010.
- A. Rusu, I.-M. Moga, L. Uncu and G. Hancu, The Role of Five-Membered Heterocycles in the Molecular Structure of Antibacterial Drugs Used in Therapy, *Pharmaceutics*, 2023, **15**, 2554.
- S. Pramod, S. Jitendra, J. P. Geeta and S. M. R. Mohan, 2-Pyrazolines as Biologically Active and Fluorescent Agents, An Overview, *Anticancer Agents Med. Chem.*, 2018, **18**, 1366–1385.
- Y.-J. Wu, in *Prog. Heterocycl. Chem*, ed. G. W. Gribble and J. A. Joule, Elsevier, 2021, vol. 33, pp. 277–292.
- M. M. Heravi and V. Zadsirjan, Prescribed drugs containing nitrogen heterocycles: an overview, *RSC Adv.*, 2020, **10**, 44247–44311.
- A. Ansari, A. Ali, M. Asif and Shamsuzzaman, Review: biologically active pyrazole derivatives, *New J. Chem.*, 2017, **41**, 16–41, DOI: [10.1039/C6NJ03181A](https://doi.org/10.1039/C6NJ03181A).
- R. Khajuria, S. Dham and K. K. Kapoor, Active methylenes in the synthesis of a pyrrole motif: an imperative structural unit of pharmaceuticals, natural products and optoelectronic materials, *RSC Adv.*, 2016, **6**, 37039–37066.
- P. K. Sharma, A. Amin and M. Kumar, A Review: Medicinally Important Nitrogen Sulphur Containing Heterocycles, *Open J. Med. Chem.*, 2020, **14**, 49–64.
- E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- S. Rao Cheekatla, D. P. Murale, L. Gopala and J.-S. Lee, Sensing and Imaging Agents for Cyclooxygenase Enzyme, *ChemMedChem*, 2024, **2024**, e202400636.
- J. Dhuguru and R. Skouta, Role of Indole Scaffolds as Pharmacophores in the Development of Anti-Lung Cancer Agents, *Molecules*, 2020, **25**, 1615.
- J. N. Marcelo and K. L. Hannah, Indole and Indoline Scaffolds in Antimicrobials: Overview, Synthesis and Recent Advances in Antimicrobial Research, *Curr. Med. Chem.*, 2021, **28**, 4828–4844.
- Y. Wan, Y. Li, C. Yan, M. Yan and Z. Tang, Indole: A privileged scaffold for the design of anti-cancer agents, *Eur. J. Med. Chem.*, 2019, **183**, 111691.
- A. Kumari and R. K. Singh, Medicinal chemistry of indole derivatives: Current to future therapeutic perspectives, *Bioorg. Chem.*, 2019, **89**, 103021.
- S. Dadashpour and S. Emami, Indole in the target-based design of anticancer agents: A versatile scaffold with diverse mechanisms, *Eur. J. Med. Chem.*, 2018, **150**, 9–29.
- T. V. Sravanthi and S. L. Manju, Indoles—A promising scaffold for drug development, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10.
- A. Singh, C. Bhutani, P. Khanna, S. Talwar, S. K. Singh and L. Khanna, Recent report on indoles as a privileged anti-viral scaffold in drug discovery, *Eur. J. Med. Chem.*, 2025, **281**, 117017.
- E. Barresi, E. Baglini, V. Poggetti, J. Castagnoli, D. Giorgini, S. Salerno, S. Taliani and F. Da Settimo, Indole-Based Compounds in the Development of Anti-Neurodegenerative Agents, *Molecules*, 2024, **29**, 2127.
- T. Nishith, A. Khushbu, M. P. Tarun, P. Archita, P. Samir, S. Umang, S. Shaileshkumar, R. Khushman and P. Krupa, A Review of the Therapeutic Importance of Indole Scaffold in Drug Discovery, *Curr. Drug Discovery Technol.*, 2023, **20**, 9–37.
- F. R. S. Alves, E. J. Barreiro and C. A. M. Fraga, From Nature to Drug Discovery: The Indole Scaffold as a 'Privileged Structure', *Mini-Rev. Med. Chem.*, 2009, **9**, 782–793, DOI: [10.2174/138955709788452649](https://doi.org/10.2174/138955709788452649).



- 32 R. Pino-Rios and M. Solà, The Relative Stability of Indole Isomers Is a Consequence of the Glidewell-Lloyd Rule, *J. Phys. Chem. A*, 2021, **125**, 230–234.
- 33 M. Bandini, Electrophilicity: the “dark-side” of indole chemistry, *Org. Biomol. Chem.*, 2013, **11**, 5206–5212.
- 34 C. C. J. Loh and D. Enders, Exploiting the Electrophilic Properties of Indole Intermediates: New Options in Designing Asymmetric Reactions, *Angew. Chem., Int. Ed.*, 2012, **51**, 46–48.
- 35 C. T. Walsh, Biological Matching of Chemical Reactivity: Pairing Indole Nucleophilicity with Electrophilic Isoprenoids, *ACS Chem. Biol.*, 2014, **9**, 2718–2728.
- 36 A. M. Janeiro and C. S. Marques, Biological Profile of Synthetic and Natural Indole Derivatives: Paving New Paths in Cancer Treatment, *Drugs Drug-Candidates*, 2024, **3**, 488–511.
- 37 S. Kumar and Ritika, A brief review of the biological potential of indole derivatives, *Future J. Pharm. Sci.*, 2020, **6**, 121, DOI: [10.1186/s43094-020-00141-y](https://doi.org/10.1186/s43094-020-00141-y).
- 38 L. Tianze and X. Hui, Recent Progress of Bioactivities, Mechanisms of Action, Total Synthesis, Structural Modifications and Structure-activity Relationships of Indole Derivatives: A Review, *Mini-Rev. Med. Chem.*, 2022, **22**, 2702–2725.
- 39 P. V. Thanikachalam, R. K. Maurya, V. Garg and V. Monga, An insight into the medicinal perspective of synthetic analogs of indole: A review, *Eur. J. Med. Chem.*, 2019, **180**, 562–612.
- 40 J. W. Huffman, in *The Cannabinoid Receptors*, ed. P. H. Reggio, Humana Press, Totowa, NJ, 2009, pp. 49–94. DOI: [10.1007/978-1-59745-503-9_3](https://doi.org/10.1007/978-1-59745-503-9_3).
- 41 Z. Dvořák, K. Poulíková and S. Mani, Indole scaffolds as a promising class of the aryl hydrocarbon receptor ligands, *Eur. J. Med. Chem.*, 2021, **215**, 113231.
- 42 C. T. Walsh, S. Garneau-Tsodikova and A. R. Howard-Jones, Biological formation of pyrroles: Nature’s logic and enzymatic machinery, *Nat. Prod. Rep.*, 2006, **23**, 517–531.
- 43 S. Taliani, F. Da Settimo, C. Martini, S. Laneri, E. Novellino and G. Greco, Exploiting the Indole Scaffold to Design Compounds Binding to Different Pharmacological Targets, *Molecules*, 2020, **25**, 2331.
- 44 K. Himani, T. Abhishek and T. Varsha, Indole Derivatives: Versatile Scaffolds in Drug Development and Cancer Therapeutics, *Lett. Org. Chem.*, 2025, **22**, 1–39.
- 45 N. J. Pravin, R. S. Kavalapure, S. G. Alegaon, S. Garge and S. D. Ranade, Indoles as promising Therapeutics: A review of recent drug discovery efforts, *Bioorg. Chem.*, 2025, **154**, 108092.
- 46 D. Paul and J. John, Recent Advances towards the Synthesis and Material Applications of Indoloindoles, *Chem. – Asian J.*, 2022, **17**, e202200460.
- 47 O. Younis, M. Sayed, A. A. K. Mohammed, M. S. Tolba, R. Hassanien, A. M. K. El-Dean, O. Tsutsumi and M. Ahmed, Solid-State Luminescent Materials Containing Both Indole and Pyrimidine Moieties: Design, Synthesis, and Density Functional Theory Calculations, *ACS Omega*, 2022, **7**, 15016–15026.
- 48 A. V. Terry, J. J. Buccafusco and C. Wilson, Cognitive dysfunction in neuropsychiatric disorders: Selected serotonin receptor subtypes as therapeutic targets, *Behav. Brain Res.*, 2008, **195**, 30–38.
- 49 C. Kriegebaum, L. Gutknecht, A. Schmitt, K.-P. Lesch and A. Reif, Serotonin Compact – Part 1; Neurobiological and developmental genetic foundations Serotonin Now: Part 1 Neurobiology and Developmental Genetics, *Fortschr. Neurol., Psychiatr.*, 2010, **78**, 319–331, DOI: [10.1055/s-0029-1245240](https://doi.org/10.1055/s-0029-1245240).
- 50 B. Alka and S. Shalu, Serotonergic 5-HT₆ Receptor Antagonists: Heterocyclic Chemistry and Potential Therapeutic Significance, *Curr. Top. Med. Chem.*, 2015, **15**, 1643–1662.
- 51 X. Li and A. Polter, Glycogen Synthase Kinase-3 is an Intermediate Modulator of Serotonin Neurotransmission, *Front. Mol. Neurosci.*, 2011, **4**, 1–14.
- 52 J. Opacka-Juffry, The role of serotonin as a neurotransmitter in health and illness: A review, *Br. J. Neurosci. Nurs.*, 2008, **4**, 272–277.
- 53 A. S. Girgis, S. S. Panda, B. M. Kariuki, M. S. Bekheit, R. F. Barghash and D. R. Aboshouk, Indole-Based Compounds as Potential Drug Candidates for SARS-CoV-2, *Molecules*, 2023, **28**, 6603.
- 54 H. S. Soor, S. D. Appavoo and A. K. Yudin, Heterocycles: Versatile control elements in bioactive macrocycles, *Bioorg. Med. Chem.*, 2018, **26**, 2774–2779.
- 55 D. G. Jimenez, V. Poongavanam and J. Kihlberg, Macrocycles in Drug Discovery—Learning from the Past for the Future, *J. Med. Chem.*, 2023, **66**, 5377–5396, DOI: [10.1021/acs.jmedchem.3c0013](https://doi.org/10.1021/acs.jmedchem.3c0013).
- 56 S. R. Cheekatla, D. Barik, G. Anand, M. K. M. Rakhi and M. Porel, Indole-Based Macrocyclization by Metal-Catalyzed Approaches, *Organics*, 2023, **4**, 333–363, DOI: [10.3390/org4030026](https://doi.org/10.3390/org4030026).
- 57 S. R. Cheekatla, L. Thurakkal, A. Jose, D. Barik and M. Porel, Aza-Oxa-Triazole Based Macrocycles with Tunable Properties: Design, Synthesis, and Bioactivity, *Molecules*, 2022, **27**, 3409.
- 58 M. D. Cummings and S. Sekharan, Structure-Based Macrocycle Design in Small-Molecule Drug Discovery and Simple Metrics To Identify Opportunities for Macrocyclization of Small-Molecule Ligands, *J. Med. Chem.*, 2019, **62**, 6843–6853.
- 59 S. A. Patil, S. A. Patil and R. Patil, Medicinal applications of (benz)imidazole- and indole-based macrocycles, *Chem. Biol. Drug Des.*, 2017, **89**, 639–649.
- 60 C. G. Neochoritis, M. K. Miraki, E. M. M. Abdelraheem, E. Surmiak, T. Zarganes-Tzitzikas, B. Łabuzek, T. A. Holak and A. Dömling, Design of indole- and MCR-based macrocycles as p53-MDM2 antagonists, *Beilstein J. Org. Chem.*, 2019, **15**, 513–520, DOI: [10.3762/bjoc.15.45](https://doi.org/10.3762/bjoc.15.45).
- 61 R. N. Das, M. Andréasson, R. Kumar and E. Chorell, Macrocyclization of bis-indole quinolines for selective stabilization of G-quadruplex DNA structures, *Chem. Sci.*, 2020, **11**, 10529–10537.



- 62 K. Devendra, S. Sahil, K. Sourav, S. Gurpreet, M. Vikramdeep and K. Bhupinder, Medicinal Perspective of Indole Derivatives: Recent Developments and Structure-Activity Relationship Studies, *Curr. Drug Targets*, 2020, **21**, 864–891.
- 63 Y. Chen, H. Li, J. Liu, R. Zhong, H. Li, S. Fang, S. Liu and S. Lin, Synthesis and biological evaluation of indole-based peptidomimetics as antibacterial agents against Gram-positive bacteria, *Eur. J. Med. Chem.*, 2021, **226**, 113813.
- 64 M. Tsuda, Y. Takahashi, J. Fromont, Y. Mikami and J. i. Kobayashi, Dendridine A, a Bis-indole Alkaloid from a Marine Sponge Dictyodendrilla Species, *J. Nat. Prod.*, 2005, **68**, 1277–1278.
- 65 X. Mo, D. P. Rao, K. Kaur, R. Hassan, A. S. Abdel-Samea, S. M. Farhan, S. Bräse and H. Hashem, Indole Derivatives: A Versatile Scaffold in Modern Drug Discovery—An Updated Review on Their Multifaceted Therapeutic Applications (2020–2024), *Molecules*, 2024, **29**, 4770.
- 66 D. R. Aboshouk, M. A. Youssef, M. S. Bekheit, A. R. Hamed and A. S. Girgis, Antineoplastic indole-containing compounds with potential VEGFR inhibitory properties, *RSC Adv.*, 2024, **14**, 5690–5728.
- 67 N. Chadha and O. Silakari, Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view, *Eur. J. Med. Chem.*, 2017, **134**, 159–184.
- 68 P. A. Kumar, Md Iftekhar, S. Singh, M. R. F. Pratam and A. K. Mishra, Recent advancements on biological activity of indole and their derivatives: A review, *Thai J. Pharm. Sci.*, 2022, **46**, 233–250.
- 69 L. Ferrer, M. Mindt, V. F. Wendisch and K. Cankar, Indoles and the advances in their biotechnological production for industrial applications, *Syst. Microbiol. Biomanuf.*, 2024, **4**, 511–527.
- 70 S. M. Hassan, A. Farid, S. S. Panda, M. S. Bekheit, H. Dinkins, W. Fayad and A. S. Girgis, Indole Compounds in Oncology: Therapeutic Potential and Mechanistic Insights, *Pharmaceuticals*, 2024, **17**, 922.
- 71 L. K. Golightly, Pindolol: A Review of Its Pharmacology, Pharmacokinetics, Clinical Uses, and Adverse Effects, *Pharmacotherapy*, 1982, **2**, 134–147.
- 72 R. R. Ruffolo and G. Z. Feuerstein, Pharmacology of Carvedilol: Rationale for Use in Hypertension, Coronary Artery Disease, and Congestive Heart Failure, *Cardiovasc. Drugs Ther.*, 1997, **11**, 247–256.
- 73 K. A. Shaw, J. Turner and C. Del Mar, Tryptophan and 5-Hydroxytryptophan for depression, *Cochrane Database Syst. Rev.*, 2002, (1), CD003198, DOI: [10.1002/14651858.CD003198](https://doi.org/10.1002/14651858.CD003198).
- 74 M. D. Ferrari and P. R. S. Saxena, Clinical effects and mechanism of action of sumatriptan in migraine, *Clin. Neurol. Neurosurg.*, 1992, **94**, 73–77.
- 75 H. D. Langtry and S. P. Clissold, Pergolide, *Drugs*, 1990, **39**, 491–506.
- 76 C. P. Rains, H. M. Bryson and A. Fitton, Cabergoline, *Drugs*, 1995, **49**, 255–279.
- 77 M. P. Yavropoulou, P. Makras and A. D. Anastasilakis, Bazedoxifene for the treatment of osteoporosis, *Expert Opin. Pharmacother.*, 2019, **20**, 1201–1210.
- 78 S. Nalamachu and R. Wortmann, Role of Indomethacin in Acute Pain and Inflammation Management: A Review of the Literature, *Postgrad. Med.*, 2014, **126**, 92–97.
- 79 P. G. Casali, C. R. Garrett, M. E. Blackstein, M. Shah, J. Verweij, G. McArthur, I. Judson, J. Li, C. M. Baum and G. D. Demetri, Updated results from a phase III trial of sunitinib in GIST patients (pts) for whom imatinib (IM) therapy has failed due to resistance or intolerance, *J. Clin. Oncol.*, 2006, **24**, 9513–9513.
- 80 S. Kotha, S. R. Cheekatla, A. K. Chinnam and T. Jain, Design and synthesis of polycyclic bisindoles via Fischer indolization and ring-closing metathesis as key steps, *Tetrahedron Lett.*, 2016, **57**, 5605–5607.
- 81 S. Kotha and C. Chakkapalli, Application of Fischer Indolization under Green Conditions using Deep Eutectic Solvents, *Chem. Rec.*, 2017, **17**, 1039–1058.
- 82 K. Hayakawa, T. Yasukouchi and K. Kanematsu, A new approach to the efficient indole synthesis by allene intramolecular cycloaddition, *Tetrahedron Lett.*, 1986, **27**, 1837–1840.
- 83 J. J. Li, in *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, ed. J. J. Li, Springer International Publishing, Cham, 5th edn, 2014, pp. 415–416. DOI: [10.1007/978-3-319-03979-4_182](https://doi.org/10.1007/978-3-319-03979-4_182).
- 84 (a) A. Porwal, A. Rajendiran, P. Alam, H. Singh, K. Singh and A. Dubey, Indole Moiety in Organic Synthesis: A Comprehensive Review of Methods and Mechanisms, *Int. J. Pharm. Invest.*, 2024, **14**, 1052–1060; (b) D. I. Bugaenko, A. V. Karchava and M. A. Yurovskaya, Synthesis of indoles: recent advances, *Russ. Chem. Rev.*, 2019, **88**, 99.
- 85 (a) D. F. Taber and P. K. Tirunahari, Indole Synthesis: A Review and Proposed Classification, *Tetrahedron*, 2011, **67**, 7195–7210; (b) R. Vicente, Recent Advances in Indole Syntheses: New Routes for a Classic Target, *Org. Biomol. Chem.*, 2011, **9**, 6469–6480; (c) J. S. S. Neto and G. Zeni, Recent Advances in the Synthesis of Indoles from Alkynes And Nitrogen Sources, *Org. Chem. Front.*, 2020, **7**, 155–210; (d) B. S. Mathada and N. G. Yernale, Current Advances in Transition Metal-Free Access to Indoles, *Org. Prep. Proced. Int.*, 2023, **55**, 299–316; (e) F. A. Almalki and A. O. Baryyan, Recent advances in the green synthesis of indole and its derivatives using microwave irradiation and the role of indole moiety in cancer, *Green Chem. Lett. Rev.*, 2024, **17**, 2362925, DOI: [10.1080/17518253.2024.2362925](https://doi.org/10.1080/17518253.2024.2362925); (f) G. W. Gribble, *Indole Ring Synthesis: From Natural Products to Drug Discovery*, John Wiley & Sons Ltd, 2016. DOI: [10.1002/9781118695692](https://doi.org/10.1002/9781118695692).
- 86 (a) M. Makosza and J. Winiarski, Vicarious nucleophilic substitution of hydrogen, *Acc. Chem. Res.*, 1987, **20**, 282–289; (b) M. Małosza, Synthesis of heterocyclic compounds via vicarious nucleophilic substitution of hydrogen, *Pure Appl. Chem.*, 1997, **69**, 559–564, DOI: [10.1351/pac199769030559](https://doi.org/10.1351/pac199769030559).



- 87 G. W. Gribble, in *Indole Ring Synthesis*, 2016, pp. 349–353. DOI: [10.1002/9781118695692.ch42](https://doi.org/10.1002/9781118695692.ch42).
- 88 A. Frischmuth, A. Unsinn, K. Groll, H. Stadtmüller and P. Knochel, Preparations and Reactions of SF₅-Substituted Aryl and Heteroaryl Derivatives via Mg and Zn Organometallics, *Chem. – Eur. J.*, 2012, **18**, 10234–10238.
- 89 T. Eicher, Hauptmann, Siegfried, in *The Chemistry of Heterocycles*, 2003, pp. 52–121, DOI: [10.1002/352760183X.ch5a](https://doi.org/10.1002/352760183X.ch5a).
- 90 L. Marion, Heterocyclic Compounds with Indole and Carbazole Systems. The Chemistry of Heterocyclic Compounds, *J. Am. Chem. Soc.*, 1955, **77**, 2917–2917.
- 91 S. Cacchi and G. Fabrizi, Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions, *Chem. Rev.*, 2005, **105**, 2873–2920.
- 92 M. Bandini and A. Eichholzer, Catalytic Functionalization of Indoles in a New Dimension, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608–9644.
- 93 V. Sharma, P. Kumar and D. Pathak, Biological importance of the indole nucleus in recent years: A comprehensive review, *J. Heterocycl. Chem.*, 2010, **47**, 491–502.
- 94 T. Kawasaki and K. Higuchi, Simple indole alkaloids and those with a nonrearranged monoterpenoid unit, *Nat. Prod. Rep.*, 2005, **22**, 761–793.
- 95 P. Beier, T. Pastýříková and G. Iakobson, Preparation of SF₅ Aromatics by Vicarious Nucleophilic Substitution Reactions of Nitro(pentafluorosulfonyl)benzenes with Carbanions, *J. Org. Chem.*, 2011, **76**, 4781–4786.
- 96 G. Iakobson, M. Pošta and P. Beier, Synthesis of Pentafluorosulfonyl-Containing Indoles and Oxindoles, *Synlett*, 2013, 855–859.
- 97 G. D. Heffernan, R. D. Coghlan, E. S. Manas, R. E. McDevitt, Y. Li, P. E. Mahaney, A. J. Robichaud, C. Huselton, P. Alfinito, J. A. Bray, S. A. Cosmi, G. H. Johnston, T. Kenney, E. Koury, R. C. Winneker, D. C. Deecher and E. J. Trybulski, Dual acting norepinephrine reuptake inhibitors and 5-HT_{2A} receptor antagonists: Identification, synthesis and activity of novel 4-aminoethyl-3-(phenylsulfonyl)-1H-indoles, *Bioorg. Med. Chem.*, 2009, **17**, 7802–7815.
- 98 M. Makosza and A. Tyrala, Alkylation and the Knoevenagel Condensation of Nitrobenzyl Sulfones and Nitriles.1, *Synth. Commun.*, 1986, **16**, 419–423.
- 99 Z. Wróbel and M. Małosza, Synthesis of 1-hydroxyindoles and indoles from *ortho*-nitroarylethanes, *Tetrahedron*, 1997, **53**, 5501–5514.
- 100 Z. Wróbel and M. Małosza, New Simple Synthesis of N-Hydroxy 2-Vinylindoles, *Synlett*, 1993, 597–598.
- 101 Z. Wróbel and M. Małosza, Transformations of *o*-nitroarylallyl carbanions. Synthesis of quinoline N-oxides and N-hydroxyindoles, *Tetrahedron*, 1993, **49**, 5315–5326.
- 102 J. Stalewski, The vicarious nucleophilic substitution of hydrogen proceeding via a cyclopropane ring-opening, *Tetrahedron Lett.*, 1998, **39**, 9523–9526.
- 103 M. Małosza, J. Stalewski and O. S. Maslennikova, Synthesis of 7,8-Dimethoxy-2-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline: A Key Intermediate en Route to Makaluvamines, Discorhabdin C and Other Marine Alkaloids of this Group via Vicarious Nucleophilic Substitution of Hydrogen, *Synthesis*, 1997, 1131–1133.
- 104 J. P. Hénichart, S. Chackal, F. Dudouit and R. Houssin, On the synthesis of two dimethoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline regioisomers, *Heterocycles*, 2003, **60**, 615–622.
- 105 R. Bujok, Z. Wróbel and K. Wojciechowski, Expedient Synthesis of 1-Hydroxy-4- and 1-Hydroxy-6-nitroindoles, *Synlett*, 2012, 1315–1320.
- 106 J. K. Sutherland, Reaction of 1,8-diazabicyclo[5.4.0]undec-8-ene with methyl 3,5-dinitrobenzoate and 1,3,5-trinitrobenzene, *Chem. Commun.*, 1997, 325–326, DOI: [10.1039/A607723D](https://doi.org/10.1039/A607723D).
- 107 B.-C. Chen, J. Hynes, C. R. Pandit, R. Zhao, A. P. Skoumbourdis, H. Wu, J. E. Sundeen and K. Leftheris, A General Large Scale Synthesis Of 2-Alkyl-7-Methoxyindoles, *Heterocycles*, 2001, **55**, 951–960, DOI: [10.3987/COM-01-9162](https://doi.org/10.3987/COM-01-9162).
- 108 M. S. Islam, C. Brennan, Q. Wang and M. M. Hossain, Convenient Method of Synthesizing 3-Ethoxycarbonyl Indoles, *J. Org. Chem.*, 2006, **71**, 4675–4677.
- 109 B. T. McClay, K. E. Lambson, S. R. Banini, T. N. Akhmedov and B. C. G. Söderberg, A base-mediated synthesis of N-hydroxy- and N-alkoxyindoles from 2-nitrostyrenes, *Tetrahedron*, 2023, **144**, 133578.
- 110 Y. Maeyama, Y. Nakashima, H. Kato, Y. Hitora, K. Maki, N. Inada, S. Murakami, T. Inazumi, Y. Ise, Y. Sugimoto, H. Ishikawa and S. Tsukamoto, Amakusamine from a Psammocinia sp. Sponge: Isolation, Synthesis, and SAR Study on the Inhibition of RANKL-Induced Formation of Multinuclear Osteoclasts, *J. Nat. Prod.*, 2021, **84**, 2738–2743.
- 111 G. W. Gribble, in *Indole Ring Synthesis*, 2016, pp. 41–115, DOI: [10.1002/9781118695692.ch2](https://doi.org/10.1002/9781118695692.ch2).
- 112 L. Novellino, M. d'Ischia and G. Prota, Expedient Synthesis of 5,6-Dihydroxyindole and Derivatives via an Improved Zn(II)-Assisted 2,β-Dinitrostyrene Approach, *Synthesis*, 1999, 793–796.
- 113 F. He, Y. Bo, J. D. Altom and E. J. Corey, Enantioselective Total Synthesis of Aspidophytine, *J. Am. Chem. Soc.*, 1999, **121**, 6771–6772.
- 114 A. K. Sinhababu and R. T. Borchardt, Silica gel assisted reductive cyclization of alkoxy-2, beta.-dinitrostyrenes to alkoxyindoles, *J. Org. Chem.*, 1983, **48**, 3347–3349.
- 115 Y. Fukuyama, C. Iwatsuki, M. Kodama, M. Ochi, K. Kataoka and K. Shibata, Antimicrobial indolequinones from the mid-intestinal gland of the muricid gastropod *Drupella fragum*, *Tetrahedron*, 1998, **54**, 10007–10016.
- 116 L.-M. Yang, C.-F. Chen and K.-H. Lee, Synthesis of rutaecarpine and cytotoxic analogues, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 465–468.
- 117 G. W. Gribble, in *Indole Ring Synthesis*, 2016, pp. 121–130, DOI: [10.1002/9781118695692.ch4](https://doi.org/10.1002/9781118695692.ch4).
- 118 G. Bartoli, G. Palmieri, M. Bosco and R. Dalpozzo, The reaction of vinyl grignard reagents with 2-substituted



- nitroarenes: A new approach to the synthesis of 7-substituted indoles, *Tetrahedron Lett.*, 1989, **30**, 2129–2132.
- 119 G. Bartoli, M. Bosco, R. Dalpozzo, G. Palmieri and E. Marcantoni, Reactivity of nitro- and nitroso-arenes with vinyl grignard reagents: synthesis of 2-(trimethylsilyl) indoles, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2757–2761, DOI: [10.1039/P19910002757](https://doi.org/10.1039/P19910002757).
- 120 D. Dobson, A. Todd and J. Gilmore, The Synthesis of 7-Alkoxyindoles, *Synth. Commun.*, 1991, **21**, 611–617.
- 121 K. R. Buszek, N. Brown and D. Luo, Concise Total Synthesis of (±)-cis-Trikertrin A and (±)-Herbindole A via Intermolecular Indole Aryne Cycloaddition, *Org. Lett.*, 2009, **11**, 201–204.
- 122 J. J. Li, in *Gassman indole synthesis; Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, ed. J. J. Li, Springer International Publishing, Cham, 5th edn, 2014, pp. 276–277. DOI: [10.1007/978-3-319-03979-4_116](https://doi.org/10.1007/978-3-319-03979-4_116).
- 123 P. G. Gassman, T. J. Van Bergen, D. P. Gilbert and B. W. Cue Jr., General method for the synthesis of indoles, *J. Am. Chem. Soc.*, 1974, **96**, 5495–5508.
- 124 T. D. Lash, C. Wijesinghe, A. T. Osuma and J. R. Patel, Synthesis of novel porphyrin chromophores from nitroarenes: Further applications of the Barton-Zard pyrrole condensation, *Tetrahedron Lett.*, 1997, **38**, 2031–2034.
- 125 H.-J. Xu, Z. Shen, T. Okujima, N. Ono and X.-Z. You, Synthesis and spectroscopic characterization of meso-tetraarylporphyrins with fused phenanthrene rings, *Tetrahedron Lett.*, 2006, **47**, 931–934.
- 126 C. S. B. Gomes, P. T. Gomes, M. T. Duarte, R. E. Di Paolo, A. L. Maçanita and M. J. Calhorda, Synthesis, Structure, and Photophysical Characterization of Blue-Green Luminescent Zinc Complexes Containing 2-Iminophenanthrolyl Ligands, *Inorg. Chem.*, 2009, **48**, 11176–11186.
- 127 S. Sahoo, M. H. Mahadavaiah, D. Usharani and H. Rath, NIR Absorbing Aromatic E-Ethylene Bridged Hexaphyrins (2.1.1.2.1.1): Synthesis, Characterization, and Protonation Studies, *Org. Lett.*, 2023, **25**, 1491–1496.
- 128 W. Dohle, A. Staubitz and P. Knochel, Mild Synthesis of Polyfunctional Benzimidazoles and Indoles by the Reduction of Functionalized Nitroarenes with Phenylmagnesium Chloride, *Chem. – Eur. J.*, 2003, **9**, 5323–5331.
- 129 R. D. Clark and D. B. Repke, The Leimgruber–Batcho Indole Synthesis, *Heterocycles*, 1984, **22**, 195–221.
- 130 A. D. Batcho and W. Leimgruber, Indoles from 2-methylnitrobenzenes by condensation with formamide acetals followed by reduction: 4-benzyloxyindole, *Org. Synth.*, 2003, **63**, 214–220, DOI: [10.1002/0471264180.os063.28](https://doi.org/10.1002/0471264180.os063.28).
- 131 J. Siu, I. R. Baxendale and S. V. Ley, Microwave assisted Leimgruber–Batcho reaction for the preparation of indoles, azaindoles and pyrrolylquinolines, *Org. Biomol. Chem.*, 2004, **2**, 160–167.
- 132 A. P. Kozikowski, H. Ishida and Y.-Y. Chen, New synthesis and some selected reactions of the potential ergot alkaloid precursor indole-4-carboxaldehyde, *J. Org. Chem.*, 1980, **45**, 3350–3352.
- 133 G. W. Gribble, in *Indole Ring Synthesis*, 2016, pp. 266–277. DOI: [10.1002/9781118695692.ch26](https://doi.org/10.1002/9781118695692.ch26).
- 134 J. I. G. Cadogan and R. K. Mackie, Tervalent phosphorus compounds in organic synthesis, *Chem. Soc. Rev.*, 1974, **3**, 87–137.
- 135 J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie and R. J. G. Searle, 896. The reactivity of organophosphorus compounds. Part XIX. Reduction of nitro-compounds by triethyl phosphite: a convenient new route to carbazoles, indoles, indazoles, triazoles, and related compounds, *J. Chem. Soc. (Resumed)*, 1965, 4831–4837, DOI: [10.1039/JR9650004831](https://doi.org/10.1039/JR9650004831).
- 136 Z. Qu, X. Chen, S. Zhong, G.-J. Deng and H. Huang, NaI/PPh₃-Mediated Photochemical Reduction and Amination of Nitroarenes, *Org. Lett.*, 2021, **23**, 5349–5353.
- 137 J. I. G. Cadogan, B. S. Tait and N. J. Tweddle, Formation of carbazoles by photolytic extrusion of dimethyl phenylphosphonate from oxazaphosphoranes. A phosphorus analogue of the Graebe–Ullmann reaction, *J. Chem. Soc., Chem. Commun.*, 1975, 847–848, DOI: [10.1039/C39750000847](https://doi.org/10.1039/C39750000847).
- 138 R. J. Sundberg, Deoxygenation of Nitro Groups by Trivalent Phosphorus. Indoles from *o*-Nitrostyrenes, *J. Org. Chem.*, 1965, **30**, 3604–3610.
- 139 R. J. Sundberg, A Study of the Deoxygenation of Some *o*-Alkylnitro- and *o*-Alkylnitrosobenzenes in Triethyl Phosphite, *J. Am. Chem. Soc.*, 1966, **88**, 3781–3789.
- 140 R. J. Sundberg and T. Yamazaki, Rearrangements and ring expansions during the deoxygenation of .beta.,.beta.-disubstituted *o*-nitrostyrenes, *J. Org. Chem.*, 1967, **32**, 290–294.
- 141 H. Majgier-Baranowska, J. D. Williams, B. Li and N. P. Peet, Studies on the mechanism of the Cadogan–Sundberg indole synthesis, *Tetrahedron Lett.*, 2012, **53**, 4785–4788.
- 142 N. H. Ansari and B. C. G. Söderberg, Short syntheses of the indole alkaloids alocaasin A, scalaridine A, and hyrtinadine A-B, *Tetrahedron*, 2016, **72**, 4214–4221.
- 143 F. Ferretti, D. R. Ramadan and F. Ragaini, Transition Metal Catalyzed Reductive Cyclization Reactions of Nitroarenes and Nitroalkenes, *ChemCatChem*, 2019, **11**, 4450–4488.
- 144 G. Ghimire and B. C. G. Söderberg, Short syntheses of the tricyclic indole alkaloids cimitrypazepine and fargesine, *Tetrahedron Lett.*, 2016, **57**, 3873–3876.
- 145 J. T. Kuethe, A. Wong and I. W. Davies, Effective Strategy for the Preparation of Indolocarbazole Aglycons and Glycosides: Total Synthesis of Tjipanazoles B, D, E, and I, *Org. Lett.*, 2003, **5**, 3721–3723.
- 146 R. W. Clawson, C. A. Dacko, R. E. Deavers, N. G. Akhmedov and B. C. G. Söderberg, Attempted synthesis of 3-hydroxy-2-octadecylindole. Proposed structural revision of previously prepared 3-hydroxy-2-octadecylindole and a proposed structure of fistulosin, *Tetrahedron*, 2009, **65**, 8786–8793.



- 147 T. Bzeih, K. Zhang, A. Khalaf, A. Hachem, M. Alami and A. Hamze, One-Pot Reaction between N-Tosylhydrazones and 2-Nitrobenzyl Bromide: Route to NH-Free C2-Arylindoles, *J. Org. Chem.*, 2019, **84**, 228–238.
- 148 A. Kasahara, T. Izumi, S. Murakami, K. Miyamoto and T. Hino, A regiocontrolled synthesis of substituted indoles by palladium-catalyzed coupling of 2-bromonitrobenzenes and 2-bromoacetanilides, *J. Heterocycl. Chem.*, 1989, **26**, 1405–1413.
- 149 M. Akazome, T. Kondo and Y. Watanabe, Novel Synthesis of Indoles via Palladium-Catalyzed Reductive N-Heterocyclization of *o*-Nitrostyrene Derivatives, *Chem. Lett.*, 1992, **21**, 769–772.
- 150 M. Akazome, T. Kondo and Y. Watanabe, Palladium complex-catalysed reductive N-heterocyclization of N-(2-nitrobenzylidene)amines into 2H-indazole derivatives, *J. Chem. Soc., Chem. Commun.*, 1991, 1466–1467, DOI: [10.1039/C39910001466](https://doi.org/10.1039/C39910001466).
- 151 M. Akazome, T. Kondo and Y. Watanabe, Palladium Complex-Catalyzed Reductive N-Heterocyclization of Nitroarenes: Novel Synthesis of Indole and 2H-Indazole Derivatives, *J. Org. Chem.*, 1994, **59**, 3375–3380.
- 152 B. C. Söderberg and J. A. Shriver, Palladium-Catalyzed Synthesis of Indoles by Reductive N-Heteroannulation of 2-Nitrostyrenes, *J. Org. Chem.*, 1997, **62**, 5838–5845.
- 153 M. Shevlin, X. Guan and T. G. Driver, Iron-Catalyzed Reductive Cyclization of *o*-Nitrostyrenes Using Phenylsilane as the Terminal Reductant, *ACS Catal.*, 2017, **7**, 5518–5522.
- 154 J. G. Taylor and C. R. D. Correia, Stereoselective Synthesis of Unsymmetrical β,β -Diarylacrylates by a Heck–Matsuda Reaction: Versatile Building Blocks for Asymmetric Synthesis of β,β -Diphenylpropanoates, 3-Aryl-indole, and 4-Aryl-3,4-dihydro-quinolin-2-one and Formal Synthesis of (–)-Indatraline, *J. Org. Chem.*, 2011, **76**, 857–869.
- 155 F. Ragaini, F. Ferretti and M. A. Fouad, Phenyl Formate as a CO Surrogate for the Reductive Cyclization of Organic Nitro Compounds to Yield Different N-Heterocycles: No Need for Autoclaves and Pressurized Carbon Monoxide, *Catalysis*, 2023, **13**, 224, DOI: [10.3390/catal13020224](https://doi.org/10.3390/catal13020224).
- 156 F. Zhou, D.-S. Wang and T. G. Driver, Palladium-Catalyzed Formation of N-Heteroarenes from Nitroarenes using Molybdenum Hexacarbonyl as the Source of Carbon Monoxide, *Adv. Synth. Catal.*, 2015, **357**, 3463–3468.
- 157 Y. Dong, X. Wang, M. Cal, M. Kaiser and J. L. Vennerstrom, Activity of diimidazoline amides against African trypanosomiasis, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 944–948.
- 158 C. Crotti, S. Cenini, B. Rindone, S. Tollari and F. Demartin, Deoxygenation reactions of *ortho*-nitrostyrenes with carbon monoxide catalysed by metal carbonyls: a new route to indoles, *J. Chem. Soc., Chem. Commun.*, 1986, 784–786, DOI: [10.1039/C39860000784](https://doi.org/10.1039/C39860000784).
- 159 X. Guan, H. Zhu, Y. Zhao and T. G. Driver, Pd-Catalyzed Reductive Cyclization of Nitroarenes with CO₂ as the CO Source, *Eur. J. Org. Chem.*, 2020, 57–60.
- 160 (a) Y. Yamamoto, E. Ohkubo and M. Shibuya, Synthesis of 3-Aryl-2-(trifluoromethyl)indoles via Copper-Catalyzed Hydroarylation and Subsequent Cadogan Cyclization, *Adv. Synth. Catal.*, 2017, **359**, 1747–1751; (b) Y. Yamamoto, N. Kirai and Y. Harada, Cu-catalyzed stereoselective conjugate addition of arylboronic acids to alkynoates, *Chem. Commun.*, 2008, **44**, 2010–2012, DOI: [10.1039/B802231C](https://doi.org/10.1039/B802231C); (c) X. Liu, O. Provot, R. Franco, P. Retailleau, M. Alami, V. Gandon, C. Tran and A. Hamze, Synthesis of Aza-Heterocyclic Compounds with N-Tosylhydrazones: Formation of Bi-Indoles via Reductive Molybdenum Catalysis, *Adv. Synth. Catal.*, 2023, **365**, 3155–3161, DOI: [10.1002/adsc.202300613](https://doi.org/10.1002/adsc.202300613).
- 161 J. I. G. Cadogan, Phosphite-Reduction of Aromatic Nitro-Compounds as a Route to Heterocycles, *Synthesis*, 1969, 11–17.
- 162 I. W. Davies, V. A. Guner and K. N. Houk, Theoretical Evidence for Oxygenated Intermediates in the Reductive Cyclization of Nitrobenzenes, *Org. Lett.*, 2004, **6**, 743–746.
- 163 A. W. Freeman, M. Urvoy and M. E. Criswell, Triphenylphosphine-Mediated Reductive Cyclization of 2-Nitrobiphenyls: A Practical and Convenient Synthesis of Carbazoles, *J. Org. Chem.*, 2005, **70**, 5014–5019.
- 164 S. Selvaraju, K. A. Niradha Sachintheni, R. A. Hopson, F. M. McFarland, S. Guo, A. L. Rheingold and T. L. Nelson, Eumelanin-inspired core derived from vanillin: a new building block for organic semiconductors, *Chem. Commun.*, 2015, **51**, 2957–2959.
- 165 R. Sanz, J. Escribano, M. R. Pedrosa, R. Aguado and F. J. Arnáiz, Dioxomolybdenum(VI)-Catalyzed Reductive Cyclization of Nitroaromatics. Synthesis of Carbazoles and Indoles, *Adv. Synth. Catal.*, 2007, **349**, 713–718.
- 166 H. Gao, Q.-L. Xu, M. Yousufuddin, D. H. Ess and L. Kürti, Rapid Synthesis of Fused N-Heterocycles by Transition-Metal-Free Electrophilic Amination of Arene C-H Bonds, *Angew. Chem., Int. Ed.*, 2014, **53**, 2701–2705.
- 167 T. N. Poudel and Y. R. Lee, Construction of highly functionalized carbazoles via condensation of an enolate to a nitro group, *Chem. Sci.*, 2015, **6**, 7028–7033.
- 168 A. Baeyer and A. Emmerling, Synthese des Indols, *Ber. Dtsch. Chem. Ges.*, 1869, **2**, 679–682.
- 169 B. Robinson, The Fischer Indole Synthesis, *Chem. Rev.*, 1963, **63**, 373–401.
- 170 H. E. R, Indigo and its Artificial Production, *Nature*, 1881, **24**, 227–231.
- 171 A. Reissert, Einwirkung von Oxalester und Natriumäthylat auf Nitrotoluole. Synthese nitrirter Phenylbrenztraubensäuren, *Ber. Dtsch. Chem. Ges.*, 1897, **30**, 1030–1053.
- 172 W. E. Noland and F. J. Baude, Ethyl indole-2-carboxylate, *Org. Synth.*, 1963, **43**, 40, DOI: [10.15227/orgsyn.043.0040](https://doi.org/10.15227/orgsyn.043.0040).
- 173 J. R. Johnson, R. B. Hasbrouck, J. D. Dutcher and W. F. Bruce, Gliotoxin. V. The Structure of Certain Indole Derivatives Related to Gliotoxin_{1,2}, *J. Am. Chem. Soc.*, 1945, **67**, 423–430.
- 174 S. Katayama, N. Ae and R. Nagata, Synthesis of Tricyclic Indole-2-carboxylic Acids as Potent NMDA-Glycine Antagonists, *J. Org. Chem.*, 2001, **66**, 3474–3483.



- 175 A. V. Butin, T. y. A. Stroganova, I. V. Lodina and G. D. Krapivin, Furan ring opening—indole ring closure: a new modification of the Reissert reaction for indole synthesis, *Tetrahedron Lett.*, 2001, **42**, 2031–2033.
- 176 G. W. Gribble, in *Indole Ring Synthesis*, 2016, pp. 332–337. DOI: [10.1002/9781118695692.ch40](https://doi.org/10.1002/9781118695692.ch40).
- 177 Y. Motoyama, K. Kamo and H. Nagashima, Catalysis in Polysiloxane Gels: Platinum-Catalyzed Hydrosilylation of Polymethylhydrosiloxane Leading to Reusable Catalysts for Reduction of Nitroarenes, *Org. Lett.*, 2009, **11**, 1345–1348.
- 178 I. Choi, H. Chung, J. W. Park and Y. K. Chung, Active and Recyclable Catalytic Synthesis of Indoles by Reductive Cyclization of 2-(2-Nitroaryl)acetonitriles in the Presence of Co–Rh Heterobimetallic Nanoparticles with Atmospheric Hydrogen under Mild Conditions, *Org. Lett.*, 2016, **18**, 5508–5511.
- 179 E. Ucciani and A. Bonfand, Catalytic synthesis of 3-substituted indoles using CO as building block and supported rhodium as catalyst, *J. Chem. Soc., Chem. Commun.*, 1981, 82–83, DOI: [10.1039/C3981000082](https://doi.org/10.1039/C3981000082).
- 180 S. Tong, Z. Xu, M. Mamboury, Q. Wang and J. Zhu, Aqueous Titanium Trichloride Promoted Reductive Cyclization of *o*-Nitrostyrenes to Indoles: Development and Application to the Synthesis of Rizatriptan and Aspidospermidine, *Angew. Chem., Int. Ed.*, 2015, **54**, 11809–11812.
- 181 G. Zhang, L. Lin, K. Yang, S. Wang, Q. Feng, J. Zhu and Q. Song, 3-Aminoindole Synthesis from 2-Nitrochalcones and Ammonia or Primary Amines, *Adv. Synth. Catal.*, 2019, **361**, 3718–3722.
- 182 Y. Hakmaoui, A. Eşme, R. E. Ajlaoui, M. E. Belghiti, A. Zeroual and E. M. Rakib, Efficient One-Pot Synthesis of Indolhydroxy Derivatives Catalyzed by SnCl₂, DFT Calculations and Docking Study, *Chem. Afr.*, 2022, **5**, 827–839.
- 183 K. Yang, F. Zhou, Z. Kuang, G. Gao, T. G. Driver and Q. Song, Diborane-Mediated Deoxygenation of *o*-Nitrostyrenes To Form Indoles, *Org. Lett.*, 2016, **18**, 4088–4091.
- 184 J. S. Kim, J. H. Han, J. J. Lee, Y. M. Jun, B. M. Lee and B. H. Kim, Indium-HI-mediated one-pot reaction of 1-(2-arylethynyl)-2-nitroarenes to 2-arylindoles, *Tetrahedron Lett.*, 2008, **49**, 3733–3738.
- 185 K. Okuma, J.-i. Seto, K.-i. Sakaguchi, S. Ozaki, N. Nagahora and K. Shioji, Palladium-free zinc-mediated hydroamination of alkynes: efficient synthesis of indoles from 2-alkynylaniline derivatives, *Tetrahedron Lett.*, 2009, **50**, 2943–2945.
- 186 S. M. Oh and S. Shin, Synthesis of α -Hydroxyindole Derivatives via Pd-Catalyzed Electrophilic Cyclization, *Bull. Korean Chem. Soc.*, 2021, **42**, 925–928.
- 187 M. S. Lokolkar, P. A. Mane, S. Dey and B. M. Bhanage, Synthesis of 2-Substituted Indoles by Pd-Catalyzed Reductive Cyclization of 1-Halo-2-nitrobenzene with Alkynes, *Eur. J. Org. Chem.*, 2022, e202101505.
- 188 L. Yao, J. Ying and X.-F. Wu, Nickel-catalyzed cascade carbonylative synthesis of *N*-benzoyl indoles from 2-nitroalkynes and aryl iodides, *Org. Chem. Front.*, 2021, **8**, 6541–6545.
- 189 L. Yao, P. Wei, J. Ying and X.-F. Wu, Nickel-catalyzed carbonylative domino cyclization of arylboronic acid pinacol esters with 2-alkynyl nitroarenes toward *N*-aroyl indoles, *Org. Chem. Front.*, 2022, **9**, 2685–2689.
- 190 (a) D. Xu, R. Liu, J. Li, H. Zhao, J. Ma and Z. Dong, Atomically dispersed Co-N₄ sites anchored on N-doped carbon for aqueous phase transfer hydrogenation between nitroarenes and saturated N-heterocycles, *Appl. Catal., B*, 2021, **299**, 120681; (b) D. S. AlMarzouq and N. M. H. Elnagdi, Green Catalyst and Technique for Synthesis of Polyfunctionally Substituted Heteroaromatics and Anilines, *Molecules*, 2019, **24**, 1806, DOI: [10.3390/molecules24091806](https://doi.org/10.3390/molecules24091806).
- 191 A. Penoni and K. M. Nicholas, A novel and direct synthesis of indoles via catalytic reductive annulation of nitroaromatics with alkynes, *Chem. Commun.*, 2002, 484–485, DOI: [10.1039/B110370A](https://doi.org/10.1039/B110370A).
- 192 A. Penoni, J. Volkmann and K. M. Nicholas, Regioselective Synthesis of Indoles via Reductive Annulation of Nitrosoaromatics with Alkynes, *Org. Lett.*, 2002, **4**, 699–701.
- 193 (a) F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli and S. Cenini, Synthesis of Indoles by Intermolecular Cyclization of Unfunctionalized Nitroarenes and Alkynes, Catalyzed by Palladium–Phenanthroline Complexes, *J. Org. Chem.*, 2006, **71**, 3748–3753; (b) C. Galli, P. Gentili, A. Guarnieri, S. Kobayashi and Z. Rappoport, Competition of Mechanisms in the Photochemical Cleavage of the C–X Bond of Aryl-Substituted Vinyl Halides, *J. Org. Chem.*, 1998, **63**, 9292–9299; (c) B. Brocklehurst, J. S. Robinson and D. N. Tawn, The fluorescence spectrum of the α -styryl radical, C₆H₅CH₂, *Chem. Phys. Lett.*, 1972, **12**, 610–611, DOI: [10.1016/0009-2614\(72\)80019-8](https://doi.org/10.1016/0009-2614(72)80019-8).
- 194 C. D. Rosa, M. Kneeteman and P. Mancini, Comparison of the reactivity between 2- and 3-nitropyrroles in cycloaddition reactions. A simple indole synthesis, *Tetrahedron Lett.*, 2007, **48**, 1435–1438, DOI: [10.1016/j.tetlet.2006.12.097](https://doi.org/10.1016/j.tetlet.2006.12.097).
- 195 P. M. E. Mancini, M. N. Kneeteman, M. Cainelli, C. M. Ormachea and L. R. Domingo, Nitropyrroles, Diels–Alder reactions assisted by microwave irradiation and solvent effect. An experimental and theoretical study, *J. Mol. Struct.*, 2017, **1147**, 155–160.
- 196 P. Geerlings, F. De Proft and W. Langenaeker, Conceptual Density Functional Theory, *Chem. Rev.*, 2003, **103**, 1793–1874.
- 197 P. Du, J. L. Brosmer and D. G. Peters, Electrosynthesis of Substituted 1H-Indoles from *o*-Nitrostyrenes, *Org. Lett.*, 2011, **13**, 4072–4075.
- 198 T. Wirtanen, E. Rodrigo and S. R. Waldvogel, Recent Advances in the Electrochemical Reduction of Substrates



- Involving N–O Bonds, *Adv. Synth. Catal.*, 2020, **362**, 2088–2101.
- 199 C. G. S. Bjorn, Synthesis of Heterocycles via Intramolecular Annulation of Nitrene Intermediates, *Curr. Org. Chem.*, 2000, **4**, 727–764.
- 200 B. Wang, H. Ren, H.-J. Cao, C. Lu and H. Yan, A switchable redox annulation of 2-nitroarylethanol affording N-heterocycles: photoexcited nitro as a multifunctional handle, *Chem. Sci.*, 2022, **13**, 11074–11082.
- 201 K. Teng, Q. Liu, J. Lv and T. Li, The application of nitroarenes in catalyst-free photo-driven reactions, *ChemPhotoChem*, 2024, **8**, e202300236.
- 202 M. Waheed, M. A. Alsharif, M. I. Alahmdi, S. Mukhtar and H. Parveen, Iron-catalyzed intramolecular reductive cyclization of *o*-nitroarenes to indoles under visible light irradiation, *Tetrahedron Lett.*, 2023, **123**, 154543.
- 203 A. Berkessel, S. Reichau, A. von der Höh, N. Leconte and J.-M. Neudörfl, Light-Induced Enantioselective Hydrogenation Using Chiral Derivatives of Casey's Iron–Cyclopentadienone Catalyst, *Organometallics*, 2011, **30**, 3880–3887.
- 204 H. Qin, R. Liu, Z. Wang, F. Xu, X. Li, C. Shi, J. Chen, W. Shan, C. Liu, P. Xing, J. Zhu, X. Li and D. Shi, Photoinduced Bartoli Indole Synthesis by the Oxidative Cleavage of Alkenes with Nitro(hetero)arenes, *Angew. Chem.*, 2025, **64**, e202416923.
- 205 J. Zhang, C. Mück-Lichtenfeld, M.-A. Wiethoff and A. Studer, Photocatalytic PPh₃-Mediated Synthesis of C3-Functionalized Indoles via Radical Annulation of Nitroarenes and Alkenes, *Angew. Chem., Int. Ed.*, 2024, **63**, e202416726.

