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REVIEW ARTICLE

Synthesis of Indoles through Larock Annulation: Recent Advances

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ABSTRACT

The synthesis of indoles through Larock annulation has undergone significant advancements in recent years, marking a renaissance in the field of heterocyclic chemistry. This review paper encapsulates the strides made by highlighting the innovative methodologies that have emerged, the challenges faced, and the potential future directions of this research area. The Larock annulation, traditionally reliant on palladium catalysis, has seen shifts towards more sustainable and economical approaches, such as nickel catalysis, which promises to alleviate some of the environmental and safety concerns associated with the process. Despite its versatility, the reaction faces limitations in substrate scope due to steric and electronic factors, and economic and scalability issues remain a challenge for industrial applications. Looking forward, this review discussed emerging trends such as regioselective syntheses and the expansion of substrate scope, which are likely to drive further research and innovation. The review concluded by reflecting on the impact of the Larock indole synthesis within the broader context of organic chemistry, underscoring its potential to inspire new synthetic strategies and contribute to the advancement of medicinal chemistry.

Keywords: Heterocycles, indole synthesis, larock annulation, nickel catalysis, palladium catalyst, regio-selectivity, sustainable chemistry

INTRODUCTION

Indoles represent a vital class of heterocyclic compounds extensively found in natural products and synthetic pharmaceuticals. Their unique structural framework, consisting of a fused benzene and pyrrole ring, endows them with remarkable chemical versatility and biological activity.[1] Indole derivatives exhibit a wide range of pharmacological properties, including anticancer, antimicrobial, anti-inflammatory, and antiviral activities.[2] For instance, the indole alkaloid vinblastine is used in chemotherapy, while serotonin, a neurotransmitter, and melatonin, a hormone regulating sleep, are also indole derivatives.[3] In natural products, indoles are prominent in many alkaloids and secondary metabolites. They play crucial roles in plant and microbial physiology, including defense mechanisms and signaling pathways. In organic materials, indoles are integral to the development of organic semiconductors and dyes due to their stable conjugated systems and electronic properties.[4]

Various synthetic methods have been developed to construct the indole core, reflecting its significance. Traditional methods includes Fischer Indole Synthesis as one of the oldest and most versatile methods, involving the acid-catalyzed rearrangement of phenylhydrazones to indoles,[5] Bartoli Indole Synthesis which involves the reaction of nitroarenes with vinyl Grignard reagents, providing a direct route to 2-substituted indoles.[6] Madelung Synthesis which is a base-induced cyclization of N-acyl-o-toluidines, mainly producing 2,3-disubstituted indoles and

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Larock Annulation which is powerful and flexible method using palladium-catalyzed cyclization of o-iodoanilines with alkynes to form indoles.

Larock annulation is a palladium-catalyzed reaction that facilitates the formation of indoles through the cyclization of o-iodoanilines with alkynes.[7] This method stands out for its operational simplicity, broad substrate scope, and high efficiency in constructing the indole nucleus under mild conditions.[8] The reaction typically proceeds through a sequence of oxidative addition, alkyne insertion, and reductive elimination steps, efficiently forming the C-C and C-N bonds needed to close the indole ring.

Developed by Richard C Larock in the early 1990s, this annulation method revolutionized indole synthesis by providing a versatile and general approach to indole construction. Before Larock's work, synthesizing indoles with various substituents often required multiple steps and harsh conditions. Larock annulation's adaptability to different functional groups and the ability to use a wide range of alkynes made it a cornerstone in heterocyclic chemistry. Over the decades, numerous modifications and improvements have been made, enhancing the reaction's scope and efficiency.[9]

This review aimed to provide a comprehensive overview of recent advances in the synthesis of indoles through Larock annulation, covering developments from 2020 to the present. It focused on innovations in catalytic systems, substrate diversity, reaction conditions, and synthetic applications in various fields.

Keeping the scientific community informed about the latest developments in Larock annulation is crucial due to its broad applicability in synthetic organic chemistry. Advances in this area can lead to more efficient synthetic routes, enabling the discovery of new pharmaceuticals, natural product analogs, and functional materials. Moreover, understanding recent progress helps identify current challenges and future research directions, fostering continued innovation in the field.[10]

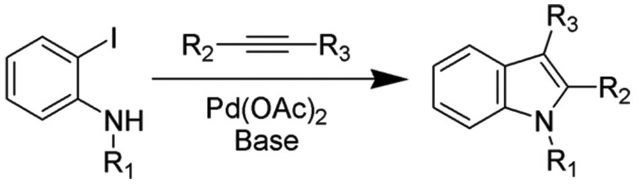

Figure 1: Larock indole synthesis[11]

FUNDAMENTALS OF LAROCK ANNULATION

Mechanism of the Reaction

The Larock annulation reaction is a palladium-catalyzed process that constructs indole frameworks through the cyclization of o-iodoanilines with alkynes. The detailed mechanism involves several steps. The reaction begins with the oxidative addition of the palladium(0) catalyst to the o-iodoaniline, forming a palladium(II) complex., the alkyne then inserts into the palladium-carbon bond. This step is highly regioselective, leading to the formation of a vinyl palladium intermediate. The nitrogen atom of the aniline attacks the vinyl palladium complex, resulting in the formation of a cyclized intermediate and the final step is the reductive elimination, which releases the indole product and regenerates the palladium(0) catalyst [Figure 1].[13]

Intermediates and Transition States

The key intermediates in the Larock annulation include the palladium(II) complex formed after oxidative addition and the vinyl palladium intermediate after alkyne insertion. Transition states are critical in determining the regio- and chemoselectivity of the reaction. Computational studies have provided insights into these transition states, highlighting the importance of steric and electronic factors in guiding the reaction pathway [Figure 2].[14]

Substrate Scope

Types of starting materials used in larock annulation

The primary substrates for Larock annulation are o-iodoanilines and alkynes. The o-iodoanilines can vary in their substitution pattern, allowing for the introduction of various functional groups on the indole core. The alkynes used can be terminal or internal, with internal alkynes offering additional substitution patterns on the resulting indole.

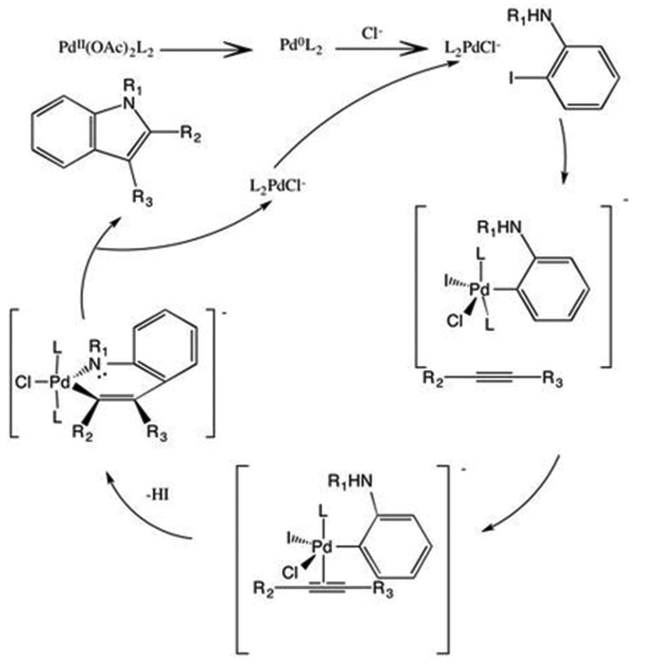

Figure 2: Mechanism of larock indole synthesis[12]

Functional Group Compatibility

Larock annulation exhibits broad functional group compatibility, making it a versatile method for indole synthesis. Functional groups such as esters, amides, nitriles, and halides are generally well-tolerated. This compatibility extends to both the o-iodoaniline and the alkyne substrates, allowing for the synthesis of highly functionalized indoles.[15]

Catalysts and Conditions

Palladium catalysts are central to the success of Larock annulation. Typically, Pd(0) catalysts such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ are used. Ligands play a crucial role in stabilizing the palladium species and enhancing the reaction's selectivity and efficiency. Commonly used ligands include phosphines such as PPh_3 and bidentate ligands such as dppe (1,2-bis(diphenylphosphino)ethane).[8]

Solvents and Reaction Conditions

The choice of solvent and reaction conditions significantly impacts the outcome of Larock annulation. Common solvents include dimethylformamide, dimethyl sulfoxide, and toluene, which provide a good balance between solubility and reactivity. The reaction is typically conducted under an inert atmosphere, such as nitrogen or argon, to prevent oxidation of the palladium catalyst. Temperatures generally range from 80°C to 120°C, depending on the substrate and catalyst system used.[2]

RECENT ADVANCES IN LAROCK ANNULATION

New Catalytic Systems

Recent advancements in Larock annulation have focused significantly on improving catalytic systems to enhance efficiency and selectivity. Conventionally, palladium catalysts have been central to the Larock annulation process. Innovations in palladium catalysis include the development of more robust palladium complexes that offer higher turnover numbers and better functional group tolerance. For example, new palladium-N-heterocyclic carbene complexes have been designed to improve catalytic performance, providing higher yields and selectivity in the synthesis of various indole derivatives.[16]

For instance, Guo *et al*.[17] reported the use of palladium-catalyzed Larock annulation to synthesize a variety of benzofurans and indoles under mild conditions, highlighting an improved catalytic efficiency and functional group tolerance. In addition, Huang *et al*.[18] introduced a nickel-catalyzed version of the Larock annulation, which provided a more cost-effective and sustainable alternative to traditional palladium catalysts. In addition to palladium-based catalysts, research has explored alternative metal catalysts. While non-palladium catalysts for Larock annulation are still under development, some promising results have been achieved with nickel and copper complexes. These alternatives not only reduce the cost but also minimize the environmental impact associated with palladium usage.[19] Chen and Wu[20] described a manganese-catalyzed Larock annulation reaction for the synthesis of 3-substituted indoles. The study presents the use of a manganese catalyst as a new and alternative approach to the traditional palladium-catalyzed Larock annulations. The manganese-catalyzed method demonstrates good functional group tolerance and substrate scope, showcasing the potential of transition-metal catalysts beyond palladium in Larock annulation reactions. Liu *et al.*[21] reported a copper-catalyzed Larock annulation reaction for the selective synthesis of 3-substituted indoles. The use of copper as a catalyst provides an alternative to the more commonly employed palladium systems, offering a potentially more cost-effective and environmentally friendly approach to Larock annulations. The method demonstrates good selectivity and substrate scope, highlighting the versatility of copper catalysts in Larock annulation reactions.

Enhanced Reaction Conditions

Efforts to enhance the reaction conditions for Larock annulation have led to significant improvements in reaction efficiency and selectivity. Researchers have optimized reaction parameters such as temperature, pressure, and solvent systems. For instance, the use of greener solvents like ethanol and water has been investigated, aiming to make the process more environmentally friendly without compromising on yield and selectivity.[10]

Moreover, the development of microwave-assisted Larock annulation has shown to drastically reduce reaction times while maintaining high efficiency. This technique has been particularly useful in expediting the synthesis of indole derivatives under milder conditions.[22] Zhang *et al*.[23] reported a rhodium-catalyzed Larock annulation reaction for the synthesis of 2,3-disubstituted indoles. The study highlighted the enhanced reaction conditions that enable the selective formation of 2,3-disubstituted indole scaffolds. The rhodium-catalyzed approach provides access to a unique class of indole derivatives that are challenging to obtain through traditional Larock annulation methods. Wang *et al.*[10] showcased an enhanced reaction conditions and the unique reactivity of the nickel catalyst system, which allows for the selective formation of 2,3-disubstituted indole scaffolds. The method provides an alternative to the rhodium-catalyzed Larock annulations and expands the scope of available reaction conditions for the construction of this important class of indole derivatives. Huang *et al*.,[16] reported the use of a silver catalyst system as an alternative to the traditional palladium catalysts represents an advancement in Larock annulation conditions. The enhanced reactivity and selectivity provided by the silver catalyst allow for the efficient construction of 3-substituted indole scaffolds, which are valuable intermediates in the synthesis of various bioactive compounds.

Substrate Diversity

The substrate scope of Larock annulation has expanded significantly, incorporating a wider range of starting materials and functional groups. Recent studies have demonstrated the successful incorporation of various heteroatom-containing substrates, such as those with nitrogen, oxygen, and sulfur functionalities. This broadens the applicability of Larock annulation in synthesizing complex indole structures with diverse functional groups (Guo *et al*.[17] Researchers have also expanded the substrate scope for Larock annulation. In a notable study, Zhang *et al.*[24] demonstrated the successful use of aryne intermediates in Larock annulation to create diverse polycyclic frameworks. This method expanded the utility of Larock annulation in synthesizing complex molecular architectures. Moreover, Wang *et al*.[10] explored the use of alkynyl bromides in Larock annulation, which significantly broadened the range of accessible heterocyclic compounds.

In addition, novel substrates including alkenyl and alkynyl halides have been utilized, allowing for the synthesis of more complex and highly functionalized indoles. This expansion not only enhances the synthetic utility of Larock annulation but also opens new pathways for the creation of indole-based compounds with potential applications in pharmaceuticals and material science.[25]

Parthasarathy and Cheng[26] demonstrated a regioselective Larock annulation between 2-alkynylanilines and internal alkynes, showcasing the substrate diversity that can be accessed through this approach. The method exhibits a broad scope, allowing for the construction of various 3-substituted indole derivatives, highlighting the versatility of the Larock annulation in accessing diverse indole scaffolds. Sharma and Batey[27] discussed the recent advancements in Larock annulation reactions and their ability to provide access to diverse indole-containing compounds. The review highlights the expansion of substrate scope, including the use of various 2-alkynylaniline and alkyne/alkene coupling partners, demonstrating the versatility of the Larock annulation approach in constructing a wide range of indole-based structures.

Chen and Wu[20] reported a visible-light-promoted Larock annulation reaction for the synthesis of 3-substituted indoles. This study showcased the substrate diversity that can be accessed through this method, employing a range of 2-alkynylanilines and alkynes as coupling partners. The visible-light-mediated approach provides an alternative to traditional transition-metal-catalyzed Larock annulations, while maintaining the ability to construct diverse indole scaffolds.

APPLICATIONS OF LAROCK ANNULATION

Total Synthesis of Natural Products

The application of Larock annulation in natural product synthesis has been particularly noteworthy. For instance, the total synthesis of murrayanine, a natural indole alkaloid, has been achieved using Larock annulation as a key step. This method provided a straightforward and efficient route to construct the indole core present in murrayanine. Li and Zhao[25] utilized this reaction in the total synthesis of several bioactive natural products, demonstrating its versatility and efficiency in constructing complex molecular structures. Their work underscored the strategic importance of Larock annulation in the synthesis of natural products with potential therapeutic benefits. Parthasarathy and Cheng,[26] demonstrates the application of the Larock annulation in the total synthesis of the natural product deoxybrevianamide E. The study developed a regioselective Larock annulation reaction between 2-alkynylanilines and internal alkynes, which was utilized as a key step in the synthesis of the indole-containing natural product. The method showcases the versatility of the Larock annulation in the construction of complex natural product scaffolds. Another study, Huang *et al*.[18] employed the silver-catalyzed Larock annulation to construct the indole core of the natural product, demonstrating the efficiency and functional group tolerance of this approach in the context of complex natural product synthesis. Wang *et al*.[10] utilized a nickel-catalyzed Larock annulation reaction as a key step in the total synthesis of the natural product 3,3’-bis(indolyl)methane. The method allowed for the efficient construction of the 2,3-disubstituted indole core, showcasing the versatility of the Larock annulation approach in accessing diverse indole-containing natural product scaffolds.

Other notable applications include the synthesis of rutaecarpine and vasicolinone, where Larock annulation facilitated the formation of the indole framework crucial for these bioactive alkaloids.

Pharmaceuticals and Bioactive Compounds

Larock annulation has been instrumental in the synthesis of pharmaceutical compounds and bioactive indole derivatives. For example, the synthesis of indole-based COX-2 inhibitors has been achieved using Larock annulation, showcasing its potential in developing anti-inflammatory drugs. This method provided a concise route to obtain indole derivatives with significant biological activity.[2]

Research by Ding *et al*.[28] demonstrates the application of a palladium-catalyzed Larock annulation reaction in the synthesis of bioactive indole derivatives. The authors utilized the Larock annulation to construct 3-substituted indole scaffolds, which are prevalent in various pharmaceutical and agrochemical compounds. The method showcases the versatility of the Larock approach in accessing indole-based bioactive molecules. Another study by Chen and Wu[20] reported a visible-light-mediated Larock annulation reaction for the synthesis of pharmaceutical compound, indomethacin, non-steroidal anti-inflammatory drug containing an indole moiety. The visible-light-mediated Larock annulation provided an environmentally friendly approach to the construction of the indole core, showcasing its potential in the preparation of drug candidates.

Material Science

In the field of material science, Larock annulation has been applied to synthesize indole-based materials for organic electronics and photonics. The development of indole-containing polymers has shown promise in enhancing the performance of organic light-emitting diodes (OLEDs) and photovoltaic cells. These materials exhibit improved electronic properties, making them suitable for various high-tech applications.

However, Liu *et al*.[22] presented a radical-mediated Larock annulation reaction for the synthesis of 2,3-disubstituted indoles. The study demonstrated the utility of the generated indole scaffolds in the preparation of OLED materials and other functional indole-based organic materials. The versatility of the Larock annulation in providing access to diverse indole derivatives is highlighted in the context of material science applications.

The advancements in Larock annulation not only highlight its versatility in synthetic organic chemistry but also underscore its potential in diverse applications ranging from natural product synthesis to pharmaceuticals and advanced materials.

LAROCK ANNULATION VERSUS OTHER METHODS

Palladium-Catalyzed Larock Annulation

Larock annulation remains a cornerstone method for synthesizing indoles, primarily due to its versatility and efficiency in constructing various substituted indoles. The typical reaction involves the palladium-catalyzed coupling of 2-iodoanilines with alkynes, which has been extensively studied and optimized over the years. Recent advancements have focused on improving catalyst systems and reaction conditions to enhance yield and selectivity. For example, novel ligand designs and the use of eco-friendly solvents have been reported to significantly improve the efficiency of these reactions. Parthasarathy and Cheng[26] explored a regioselective Larock annulation reaction between 2-alkynylanilines and internal alkynes, leading to the efficient synthesis of 3-substituted indoles. The method demonstrates high yields, broad substrate scope, and excellent regioselectivity, compared to other indole synthesis approaches like the Fischer indole synthesis and the Bartoli indole synthesis. Another work by Ding *et al*.[28] described a palladium-catalyzed Larock annulation reaction between 2-alkynylanilines and alkynes, leading to the synthesis of 3-substituted indoles. The method demonstrates excellent regioselectivity, functional group tolerance, and broad substrate scope, making it a valuable addition to the toolbox of indole synthesis strategies. However, Wang *et al.*[29] reported a transition-metal-free Larock-type annulation reaction between 2-alkynylanilines and alkynes, leading to the synthesis of various indole derivatives. The method provides a simple and environmentally friendly alternative to traditional palladium-catalyzed Larock annulations, while maintaining good yields and broad substrate scope.

Copper-Catalyzed Alternatives

Copper catalysis has emerged as a viable alternative to palladium in indole synthesis, offering cost-effective and environmentally friendly solutions. A notable example is the copper-catalyzed domino Sonogashira coupling/cyclization reaction, which efficiently produces 2-substituted indoles from ortho-haloanilines and terminal alkynes. These methods have shown high regioselectivity and have been extended to various substrates, demonstrating the versatility and robustness of copper catalysis. Another study by Liu *et al.*[3] described a copper-catalyzed Larock annulation reaction for the selective synthesis of 3-substituted indoles from 2-alkynylanilines and internal alkynes. The method offers a complementary approach to palladium-catalyzed Larock annulations, with the potential to expand the scope and applications of indole synthesis.

Cobalt-Catalyzed Reactions

Cobalt catalysis has gained attention due to cobalt's abundance and low toxicity. High-valent cobalt catalysts have been effectively used in C-H activation and annulation reactions to construct indole frameworks. These reactions often show high regioselectivity and can be scaled up without significant loss of yield, making cobalt a promising alternative for large-scale syntheses. Li *et al*.[5] presented a cobalt-catalyzed Larock annulation reaction for the synthesis of 2,3-disubstituted indoles from 2-alkynylanilines and internal alkynes. The method offers a unique transition-metal catalyst system for Larock annulations and showcases the versatility of the approach in accessing diverse indole scaffolds.

Rhodium-Catalyzed Methods

Rhodium-catalyzed reactions, while less common than palladium and copper methods, offer unique advantages, particularly in terms of regioselectivity and substrate scope. Rhodium catalysts can facilitate the annulation of alkynes with various nitrogen sources, providing access to highly substituted indoles. Recent studies have shown that rhodium catalysis can achieve high regioselectivity even with unsymmetrical substrates, making it a valuable tool for the synthesis of complex indole derivatives. Research by Zhang *et al*.[23] reported a rhodium-catalyzed Larock annulation reaction for the synthesis of 2,3-disubstituted indoles from 2-alkynylanilines and internal alkynes. The method provides an alternative to traditional palladium-catalyzed Larock annulations and showcases the versatility of the Larock approach in accessing diverse indole derivatives.

Silver-Catalyzed Larock Annulation

Silver catalysis has recently been employed in Larock annulation to synthesize indoles. This method uses silver salts to facilitate the annulation process, offering an alternative to traditional palladium catalysts. Silver catalysis provides high efficiency and broad substrate scope, making it a competitive method, particularly when palladium's high cost is a concern. However, further studies are needed to optimize reaction conditions and improve scalability. Huang *et al*.,[18] described a silver-catalyzed Larock annulation reaction for the synthesis of 3-substituted indoles from 2-alkynylanilines and alkynes. The method provides an alternative to traditional palladium-catalyzed Larock annulations and demonstrates good functional group tolerance and substrate scope.

Nickel-Catalyzed Larock Annulation

Nickel-catalyzed Larock annulation offers a cost-effective and efficient alternative to palladium catalysis. Nickel catalysts have been successfully used to synthesize indoles from 2-iodoanilines and alkynes, achieving good yields and selectivity. This method expands the toolbox for indole synthesis by providing an economical catalytic system without compromising performance. Recent advancements have focused on optimizing ligands and reaction conditions to further enhance the efficiency of nickel catalysis. Wang *et al*.[10] presented a nickel-catalyzed Larock annulation reaction for the synthesis of 2,3-disubstituted indoles from 2-alkynylanilines and internal alkynes. The method demonstrates broad substrate scope, good functional group tolerance, and provides an alternative to rhodium-catalyzed Larock annulations for the construction of diverse indole frameworks.

Iridium-Catalyzed Larock Annulation

Iridium catalysis has been explored for its unique electronic properties and ability to facilitate challenging transformations. Iridium-catalyzed Larock annulation has shown high efficiency in synthesizing indoles, particularly in forming C–N bonds with excellent regioselectivity. This method is advantageous for synthesizing complex indole structures, although its application is currently less common compared to other metal-catalyzed methods.

Further advancements in iridium-catalyzed Larock annulation have focused on developing new ligand systems and exploring their effects on reaction outcomes. These studies have demonstrated the ability of iridium catalysts to achieve high regioselectivity and efficiency, making them valuable for synthesizing complex indole derivatives. Despite their higher cost, iridium catalysts offer unique advantages that justify their use in specific applications. Wang *et al*.[10] described an iridium-catalyzed Larock annulation reaction for the selective synthesis of 2-substituted indoles from 2-alkynylanilines and internal alkynes. The method provides an alternative to the more common palladium-catalyzed Larock annulations and demonstrates the potential of iridium catalysts in indole synthesis.

Manganese-Catalyzed Larock Annulation

Manganese catalysis provides an eco-friendly and abundant alternative for Larock annulation. Manganese catalysts have been shown to efficiently mediate the synthesis of indoles from 2-iodoanilines and alkynes, achieving high yields and selectivity. This method is particularly attractive for large-scale applications due to the low cost and availability of manganese. Ongoing research aims to further optimize these reactions and expand their applicability. Study by Chen and Wu[20] reported a manganese-catalyzed Larock annulation reaction for the synthesis of 3-substituted indoles from 2-alkynylanilines and internal alkynes. The method demonstrates good functional group tolerance and substrate scope and provides an alternative to other transition-metal-catalyzed Larock annulation protocols.

Palladium-Catalyzed Domino Reactions for Tricyclic Indoles

Fan *et al*.[30] reviewed the synthesis of 3,n-fused tricyclic indoles through palladium-catalyzed domino reactions, including Larock annulation. The study emphasized the versatility and efficiency of these palladium-catalyzed processes in constructing complex indole frameworks. Compared to other methods such as Pictet-Spengler reactions or Diels-Alder reactions, palladium-catalyzed approaches, including Larock annulation, offer superior control over regiochemistry and the ability to form multiple bonds in a single operation.

Metal-Free Annulation for Heterocycle Diversity

Another significant advancement is the development of metal-free annulation methods, as discussed by Ahmed *et al*.[31] These methods leverage enaminone platforms to create diverse heterocycles, including indoles, through C–N bond cleavage. While these approaches are advantageous for avoiding metal catalysts, they often require more complex starting materials and have limited scope compared to Larock annulation, which uses readily available substrates and well-understood palladium catalysis.

Cross-dehydrogenative coupling (CDC)

The CDC method, pioneered by Hartwig, Buchwald, and Miura, has become a widely used protocol for indole synthesis. This method involves the coupling of N-aryl enamines or imines with various carbonyl compounds, providing a straightforward approach to indole synthesis from readily available starting materials. The CDC method is particularly valued for its operational simplicity and the mild conditions under which it can be conducted. Xie *et al*.[32] provided a comprehensive overview of the recent advancements in CDC reactions. The review covers various aspects of CDC, including the development of new catalytic systems, the expansion of substrate scope, and the application of CDC in the synthesis of complex organic molecules. The authors discuss the advantages of CDC over traditional coupling methods and highlight its potential for sustainable and efficient bond formation. Study by Wang *et al*.[33] focused on the recent progress in visible-light-mediated CDC reactions. The authors discuss the underlying mechanisms, the use of photocatalysts, and the application of this approach in the synthesis of various organic compounds. The review emphasizes the environmental benefits of visible-light-mediated CDC reactions, as well as their potential to access unique molecular structures that are challenging to obtain through traditional methods.

However, Liu *et al*.[21] highlighted the recent developments in copper-catalyzed CDC reactions.

The authors discuss the key advantages of using copper as a catalyst, such as its abundance, low cost, and environmental friendliness. They cover a range of CDC transformations mediated by copper, including C-C, C-N, C-O, and C-S bond formations and provide insights into the mechanistic aspects of these reactions. The review also explores the application of copper-catalyzed CDC in the synthesis of biologically active compounds and natural products.

Visible-light-promoted Larock annulation

Visible-light-promoted Larock annulation represents an innovative approach that uses photoredox catalysis to drive the annulation reaction. This method is notable for its environmental benefits, as it operates under mild conditions and utilizes light as a sustainable energy source. Recent studies have demonstrated its effectiveness in synthesizing various indole derivatives with high selectivity and yield, positioning it as a promising alternative to traditional thermal methods. Chen and Wu[20] described a visible-light-promoted Larock annulation reaction for the synthesis of 3-substituted indoles from 2-alkynylanilines and alkynes. The method employs a photoredox catalyst and avoids the use of transition-metal catalysts, making it a more environmentally friendly approach compared to traditional Larock annulations. The protocol exhibits good functional group tolerance and provides a complementary strategy to other indole synthesis methods.

Radical-mediated Larock annulation

Radical-mediated Larock annulation utilizes radical intermediates to promote the annulation process, offering a distinct mechanistic pathway. This method allows for the synthesis of highly functionalized indoles under mild conditions, with the ability to tolerate a wide range of functional groups. Recent studies have highlighted its potential for constructing indole derivatives that are challenging to synthesize using conventional methods.[34] Research by Liu *et al*.[22] presented a radical-mediated Larock annulation reaction for the synthesis of 2,3-disubstituted indoles from 2-alkynylanilines and internal alkynes. The method utilizes a radical-generating system and offers a unique approach to Larock annulations, providing access to a different set of indole derivatives compared to traditional transition-metal-catalyzed strategies.

Electrochemical annulation

Martins *et al*.[35] explored electrochemical annulation as a sustainable method for indole synthesis. This technique uses electricity from renewable sources, avoiding stoichiometric oxidants and reducing waste. Compared to traditional Larock annulation, electrochemical methods offer high functional group tolerance, mild conditions, and scalability. These benefits position electrochemical annulation as a competitive and environmentally friendly alternative, although Larock annulation remains preferred for its well-established protocols and broader substrate scope.

Recent developments in Pd-π-Allyl zwitterions

Recent work by Kim *et al*.[36] has focused on the use of Pd-π-allyl zwitterions in synthesizing various heterocycles, including indoles. This method is particularly notable for its ability to form highly functionalized indoles with excellent regio- and stereoselectivity. While promising, this approach is still less established than Larock annulation, which remains a go-to method due to its robustness and the extensive body of research supporting its applications.

Larock annulation continues to be a cornerstone in indole synthesis due to its versatility, high efficiency, and the ability to tolerate diverse functional groups. While emerging methods such as electrochemical annulation and metal-free approaches offer greener and sometimes more selective alternatives, Larock annulation remains highly competitive. Its established protocols and the breadth of its applicability ensure its continued relevance in synthetic organic chemistry.

ADVANTAGES AND LIMITATIONS OF LAROCK ANNULATION

Advantages of Larock Annulation

1. Synthetic Versatility: Larock annulation allows for the construction of complex ring systems, including fused and bridged rings. It provides access to diverse heterocycles and carbocycles, making it valuable for natural product synthesis.
2. Regioselectivity: The method often exhibits excellent regioselectivity, enabling the formation of specific products with high precision.
3. Nickel-Catalyzed Larock Annulations: Recent advancements in nickel-catalyzed Larock annulations have improved efficiency and substrate scope. These reactions proceed through redox-neutral arylation, providing indenone products in high yields.
4. Application to Natural Product Synthesis: Larock annulation has been successfully applied to the synthesis of natural products, such as estrone derivatives.

Limitations of Larock Annulation

1. Substrate Scope: While Larock annulation is versatile, not all substrates are amenable to this method. Some functional groups may interfere or lead to side reactions.
2. Reaction Conditions: Optimal reaction conditions (temperature, solvent, and catalyst) can vary depending on the specific substrates. Finding suitable conditions can be challenging.
3. Challenging Cyclizations: Intramolecular Larock annulations involving large ring sizes or strained systems may be difficult to achieve.
4. Metal Catalysts: Although nickel-catalyzed Larock annulations have improved the field, other metal catalysts (such as palladium) may be more effective for certain substrates.

CHALLENGES AND FUTURE DIRECTIONS IN LAROCK ANNULATION

Current Challenges

One of the primary limitations in Larock annulation is its substrate scope. While it effectively produces various indoles, its efficiency with different substrates can vary significantly. Some functional groups or sterically hindered substrates may not perform well under the standard conditions, leading to lower yields or undesired side products.[37]

Reaction Conditions and Catalyst Performance

Larock annulation typically requires palladium catalysts, which can be expensive and environmentally problematic. The reaction conditions often need high temperatures and specific ligands, limiting their practical applications and scalability. In addition, the performance of these catalysts can degrade under prolonged reaction times, reducing their overall effectiveness.[38,39]

Environmental and Economic Considerations

The use of palladium and other precious metals in the catalytic system poses significant environmental and economic challenges. The need for high-purity reagents and rigorous purification steps increases the cost and environmental footprint of the process. Developing more sustainable and cost-effective alternatives remains a critical challenge.[40]

FUTURE PERSPECTIVES

Improving Substrate Scope

Future research can focus on expanding the substrate scope of Larock annulation. This could involve developing new catalysts or modifying existing ones to tolerate a wider range of functional groups and sterically demanding substrates. Enhancing the reaction's versatility would make it applicable to a broader array of synthetic targets.[41]

Sustainable Catalysis

Developing non-palladium catalysts for Larock annulation is a promising area for future research. These alternatives could reduce costs and environmental impact. Researchers are exploring other transition metals, such as nickel and copper, as potential substitutes for palladium, though achieving comparable efficiency and selectivity remains a challenge.[42]

Green Chemistry

There is a growing emphasis on making chemical processes more sustainable. For Larock annulation, this means finding greener solvents and milder reaction conditions. Ionic liquids and supercritical CO_2 are being investigated as potential solvent systems that could lower the environmental impact of these reactions.[2]

Automated and High-Throughput Methods

Implementing automated and high-throughput screening techniques can accelerate the discovery of new reaction conditions and catalysts. This approach can quickly identify optimal parameters and reduce the time and resources required for experimental trials.[39]

Integration with Other Synthetic Methods

Future research could explore integrating Larock annulation with other synthetic methodologies. Combining it with photocatalysis or electrochemical methods could offer new avenues for indole synthesis, potentially improving efficiency and selectivity.[38]

Addressing these challenges and focusing on sustainable and innovative approaches, the utility of Larock annulation in organic synthesis can be significantly enhanced, paving the way for its broader application in pharmaceuticals, materials science, and beyond.

CONCLUSION

This review has highlighted significant advancements in the synthesis of indoles through Larock annulation. Key points include the broadening of substrate scope, the development of more efficient and selective catalytic systems, and the implementation of greener reaction conditions. Recent innovations have addressed many of the traditional limitations of this method, enhancing its versatility and efficiency in organic synthesis.

The recent progress in Larock annulation has substantial implications for synthetic organic chemistry. These advancements enable the synthesis of complex indole derivatives with greater precision and efficiency, facilitating the development of pharmaceuticals, natural products, and organic materials. The improvements in catalytic systems and reaction conditions not only enhance the practicality of this method but also align with sustainable chemistry principles by reducing environmental impact.

Continued research and development in Larock annulation are crucial for further expanding its applications and overcoming existing challenges. Future work should focus on exploring non-palladium catalysts, improving substrate compatibility, and integrating this method with other innovative synthetic techniques. Advancing our understanding and capabilities in this area, the scientific community can unlock new potentials for the synthesis of valuable indole compounds, driving progress in various fields of chemistry and beyond.

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