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Mechanistic insights into transition metal-mediated cyclization for extended PAH scaffold construction

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Abstract

Cyclization Reactions of benzylic-chlorides mediated by transition metals are powerful methods for building up PAHs with increased molecular size. These reactons are primarily characterized by the consumption of two atoms of palladium and the creation of new C-C bonds by intramolecular coupled processes catalyzed by transition-metal complexes 1-4. These transformations are mechanistically characterized by a sophisticated relationship between the metal and its ligands, as well as the substrate. Oxidative addition, migratory insertion and reductive elimination are likely key steps in the catalytic cycle. Transition metal selection plays an important role in the reaction path and selectivity. Palladium-catalyzed and rhodium-promoted reactions are renowned for their multifunctional coupling ability and formal C-H activation, respectively. Ruthenium catalysts have been used predominantly in metathesis reactions and have demonstrated potential in cyclization reactions with alkyne substrates. Ligand framework is a key factor in the modulation of the electronic and steric properties of the metal center, which dictates the reaction course. Being able to articulate mechanistic subtleties of these cyclization reactions has in turn allowed chemists to design more efficient and selective strategies for assembling complex PAHs. The applications of the PAH structures produced by these cyclization reactions are broad, ranging from materials science to medicinal chemistry, and organic electronics. Similar methods applied to the cyclization of PAHs have been of use in other areas of PAH and these include the following: the synthesis of heterocyclic compounds, natural product synthesis and material science for fabrics with unique characteristics. Owing to the continued progress of these efforts, we can anticipate that the frontiers of what is to be expected from laboratory-based organic synthesis will be expanded.

Keywords: Transition metal, cyclization, polycyclic aromatic hydrocarbon (PAH), oxidative addition, migratory insertion, reductive elimination, palladium, rhodium, ruthenium, ligands, catalyst

Introduction

Cyclization reactions induced by transition metals have proven to be reliable methods for directing the formation of elongated polycyclic aromatic hydrocarbon (PAH) skeletons, which has had a transformational impact on the field of organic synthesis. These reactions that have attracted broad interest in the past few years are based on the creation of new carbon–carbon bonds by means of intramolecular coupling reactions mediated by transition metal complexes (You *et al*., 2022) [33]. The utility and cost-effectiveness of these transformations are reflected in their frequent application in the construction of complex molecular frameworks. Mechanistic as well as structural studies on these reactions showed an intricate concert of metal center, ligands, and substrate. The catalytic cycle usually involves oxidative addition, migratory insertion, reductive elimination, which contribute differently to the total transformation (Bastiaens *et al*., 2000) [4].

The oxidative addition is comprised of the addition of the metal into a carbon-halogen or carbon-hydrogen bond forming a new metal-carbon bond. This is then followed by migratory insertion as the substrate reorganizes or adds to the existing carbon-carbon bonds. The active catalyst in the complex is recycled through reductive elimination to give the product (Dghaym *et al*., 1998) [7]. The reaction path and selectivity are strongly dependent on transition metal (e.g. palladium, rhodium, or ruthenium). Each of the metals contributes particular features into the catalytic system, in terms of the stability of the oxidation state, the affinity for ligands or the electronic configuration. Palladium-catalyzed reactions, for example, are known for their versatility in cross-coupling reactions [1], and rhodium complexes are the workhorses of C-H activation [1, 3]. In contrast, ruthenium catalysts are often used in metathesis reactions and we have found they give better results in cyclization reactions with alkyne substrates. Ligand development is integral to the modulation of the electronic and steric parameters of the metal center, and thus the reaction outcome. The ligands selection may have a profound effect on catalyst activity, stability, and selectivity (Dghaym *et al*., 1998) [7]. For example, phosphine ligands are commonly used because of their capacity to control the electronic state of the metal center. Other bidentate ligands, in particular dppf (1,1'-bis(diphenylphosphino)ferrocene)) can stabilise the catalyst and favor particular reaction pathways.

Recently, N-heterocyclic carbene (NHC) ligands have attracted considerable attention as a result of their strong σ-donor character as well as high tendency to chelate with different transition metals. Mechanistic details of these cyclization reactions have been insightful as they help chemists to develop alternative, more effective, and more-selective pathways to the complex structures of PAHs (Dragutan *et al*., 2005) [8]. This knowledge has inspired the development of novel catalytic systems where such limitations as recoil yields, regioselectivity, or reaction conditions could be overcome. For example, dual catalytic systems including transition metals and organocatalysts or photoredox catalysts have emerged as new frontiers of challenging transformations. Applications of PAHs produced by the above cyclization reactions are wide and varied.

In materials science, PAHs are the precursors to carbon-based semiconducting materials used in organic electronics and conductive polymers, especially with applications in organic photovoltaic cells. Thanks to their large conjugated extension systems, they are interesting materials for optoelectronics applications, and may be designed to fulfill some photophysical properties. In medicinal chemistry field, PAHs-based compounds represent a new class of potential drugs, namely anticancer agents and antibiotic (Hissler *et al*., 2007) [13].

In addition, the knowledge gained from transition metal-catalyzed cyclization reactions has been utilized in broader context beyond PAH synthesis. Related approaches have also been adopted upon the synthesis of heterocycles, natural product synthesis and in the area of novel materials with specific properties. The ongoing progress within this area holds the potential to further increases the potential for synthesis of organic molecules, thereby extending the scope of chemical transformations that can be conducted in the laboratory and the making way for novel discoveries in the fields of chemistry across many other areas of science.

Importance of extended PAHs in modern chemistry and materials science

Long PAHs have attracted great interests in contemporary chemistry and materials as a result of their unique electronic and structural characteristics. These compounds are Aplanar and consist of N-fused aromatic ring systems and they have excellent stability, conductivity, and optical properties; therefore, they can be used in several application (Chen *et al*., 2017) [5]. In the field of organic electronics, the extended PAHs are building blocks for high performance semiconductors and light-emitting materials. Their electronic properties that are tunable provide a platform for organic field-effect transistors and organic photovoltaics with good performance.

In addition to, extended PAHs are not only crucial for the development of new carbon-based nanomaterials like graphene nanoribbons, and carbon nanotubes with potential applications in energy storage, sensing and catalysis. The synthesis and processing of extended PAHs are providing exciting opportunities for the generation of functional materials with designed properties, and are spawning advances in spheres as diverse from one another as optoelectronics and nanodiagnostics (Mochida *et al*., 2011) [25].

Synthetic challenges in constructing large π-systems

The synthesis of such large π-systems is challenging as a result of their highly distorted molecular architecture and unusual electronic behavior. The main challenge remains in keeping planarity and conjugation within extended molecular frameworks, which are indispensable features to realize the optimal π-electron delocalization (Jafarpour *et al*., 2017) [14]. This task becomes all the more severe in the case of larger π-systems, for which the architecture of molecular scaffolds and the position of substituents must be carefully considered in order to resist the deformation of twisting and bending.

These large, generally hydrophobic substances are also usually problematic to produce, due to solubility, stability and purification issues that researchers encounter. The extended π-systems generally suffer from poor solubility in organic solvents and solution-phase synthesis and analysis is challenging (Murai and Tani, 2023) [26]. Such low solubility can result in premature precipitation or aggregation in reactions, directly resulting in lower yields and making purification more difficult.

Furthermore, large π systems are also unstable because of their high reactivity, photo-sensitivity, oxygen-sensitivity or being affected by other environmental factors, and should be paid attention to treatment and storage. In addiation, the regioselectivity and stereochemistry can be quite demanding to control during the course of synthesis, especially when introducing heteroatom or functional group (Mitchard *et al*., 1989) [24]. Substrates with numerous reactive sites, found in extended π-systems, typically suffer from the formation of unwanted side products leading to challenging reaction conditions or protecting group strategies for selectivity. Control at the level of individual atoms and direct access to the three-dimensional arrangement is more difficult to achieve with greater molecular complexity, especially when targeting the desired optical or electronic functions.

Their propensity to π-π stack leads to aggregation of large π-systems, making their synthesis and characterization even more challenging. These intermolecular interactions can result in the formation of supramolecular aggregates, modifying the physico-chemical properties of the molecules of interest (Kaminorz *et al*., 1998) [15]. Although such interactions may be useful in many applications, they can complicate purification, solution phase characterization and the determination of single molecular properties. These challenges can be only solved by innovative synthetic approaches, including modular approaches, iterative coupling reactions, or the design of new catalytic systems suitable for these complex molecular architectures (Kauffman *et al*., 2009) [16].

A stepwise construction of large π-systems is feasible by modular synthesis and, therefore, more control of the course of the molecular assembly can be exerted. Repeated coupling reactions, as utilized in the preparation of graphene nanoribbons and extended porphyrin arrays, offer a well-defined approach for the growth of π-conjugated systems preserving structural integrity. The creation of innovative catalytic systems is an important consideration to meet the demand for large π-system synthesis.

Catalysts general Some transition metal-based catalysts, especially palladium, have revolutionized the formation of relatively long carbon—carbon bonds in conjugated systems. There is nevertheless a continued demand for catalysts that can function effectively on sterically encumbered or electronically disparate substrates, and those that are capable of facilitating challenging C-H activation processes for late-stage functionalization of large π-systems. In addition, characterisation of large π-systems is a problem in itself (Bart & Chirik, 2003) [3]. Conventional methods of analysis may be inadequate for the complete understanding of the structure and properties of these macromolecules. The nature can be probed using advanced spectroscopic techniques including 2D NMR, high resolution mass spectrometry and advanced optical spectroscopy These methods are often needed to obtain insight into the molecular structure and the electronic properties of large π-systems (Ghalamkar-Moazzam & Jacobs, 1978) [10].

Conclusion In summary, the preparation of large π-systems in organic and materials chemistry is still one of the frontiers and its synthetic exploration requires a multidisciplinary approach combining the use of novel synthetic tools, high-level methodologies and a profound knowledge about the molecular electronic structure. As more and more extrema of π-system size and complexity are being examined, fresh obstacles and opportunities will inevitably arise that can be leveraged to progress this exciting area of research.

Relevance of metal-mediated cyclization methods

In fact, the so-called transition-metal-catalyzed cyclization methods have greatly revolutionized the PAH area. Conventional construction of PAHs such as the Scholl oxidation and Friedel–Crafts alkylation typically involves poor regioselectivity, harsh reaction conditions and narrow functional group tolerance (Kuninobu & Takai, 2012) [19]. Conversely, metal-catalyzed cyclizations, especially those using palladium, nickel, rhodium, or cobalt catalysts, afford complex aromatic ring systems in a highly controlled and atom-economical manner.

Such cyclization reactions frequently contain organometallic transformations including oxidative addition, migratory insertion, and reductive elimination, which enable efficient generation of fused or angular 汕 systems and large π-extended PAHs. In addition, transition metal catalysis allows C–H activation, alkyne annulation and intramolecular cycloaddition reactions to deliver structurally diverse PAHs that are in general challenging to obtain (Kazemi *et al*., 2023). The use of ligand, oxidation state and catalytic system as platform for customization renders these approaches broadly modular and applicable to small molecule as well as material-based synthetic objectives.

Due to the continued development and use of PAH-based compounds in the arena of optoelectronics, sensing, and photonics, the cyclization of PAHs via a metal-mediated process provides a mechanistically diverse and synthetically enabling tool for scaffold elaboration and topological influence.

Scope, objectives, and significance of this review

We hope in this review to give a full mechanistic account of their transition metal-mediated cyclization strategies to access extended PAH frameworks. It emphasizes fundamental principle of catalytic processes, followed by proprietary knowledge of reaction conditions and their effect on the catalysts and their complexes.

The explicit aims of this review are:

- Review and categorize the types of metal-mediated cyclization reactions in PAH synthesis.
- Discuss mechanistic manifolds such as C–H activation, alkyne cyclization and oxidative coupling involved in these transformations.
- Determine the difference in trends in catalytic activity and selectivity among metal systems.
- Underscore prominent exemplars from the literature describing the variety of scaffolds available and their utility.
- We highlight some unsolved mechanistic issues, and opening questions to new research, such as substrate compatibility and selectivity control, and sustainability.

Importance The contribution of this review is that it is highly mechanistic. Although a large number of studies have been published describing transition metal-catalyzed syntheses of PAHs, these transformations are less commonly analyzed with respect to the catalytic cycles, intermediates, and reaction dynamics that control their outcome. This contribution, by connecting synthetic results to structure activity relationships (SAR), has the purpose of providing the basis for the rational design of the next generation catalysts or methods for a particular PAH formation in academic and professional environments.

Literature Review

1. Historical Background of PAH Synthesis

The history of the synthesis PAHs is rich, combining organic chemistry with materials science. PAHs first attracted attention in natural materials such as coal tar, where they were examined in the PAH reference material (SRM 1597a) (Wise *et al*., 2010) [30]. This benchmark reference couples a short review of PAHs with informed discussion of the latest techniques used in their analysis in the environmental setting, and in synthesis in the laboratory.

In the past, the synthetic approaches to PAHs have developed dramatically. Modern synthesis strategies are therefore not only devoted to the preparation of these materials, but also of changing their structure to improve their distinctive electrical and optoelectrical properties. For example, aryne cycloaddition approaches have been highly successful in the preparation of these large and complex poly-aromatic molecules that receive some of the larger feature sizes that or comparable to those that of nanoscale graphenes (Pérez *et al*., 2013) [27].

Syntheses of PAHs have also seen a new development with the advent of chirality which yields novel functionalities in organic semiconductors. Various catalytic enantioselective approaches have also been reported for the synthesis of axially chiral PAHs with impressive enantioselectivities and good yields. These molecules exhibit curious optical properties, including circularly polarized luminescence, which are highly desirable with respect to advanced materials science (Takano *et al*., 2020) [29].

Moreover, synthetic approaches have been expanded to metal-free ones, such as alkyne annulation, enabling the π-extension of B-PAHs. These have led to PAHs with unique electronic properties and constrained structures and solid-state packing (Anitha *et al*., 2024) [1].

The investigation and the synthesis of star-shaped PAHs also demonstrate that these compounds show strong versatility and diversity. Those PAHs are interesting due to their good optoelectronic and self-assembly properties, and many PCTs could be used as organic semiconducting materials. Synthetic approaches toward these compounds are progressing so as to target molecular architectures that aid controlling of certain properties (Zhang *et al*, 2012) [34].

Finally, the historical perspective of PAH synthesis is closely intertwined with synthetic developments in the field of synthetic organic chemistry that is guided by both pragmatic needs and interest in seeking novel materials.

2. Emergence of Transition Metal Catalysis

Transition metal catalysis has served as the driving force for modern organic synthesis, providing an unparalleled toolbox to perform chemical reactions. This field has seen striking progress, notably in the addition/cyclization reactions, asymmetric synthesis, olefin metathesis, coupling reactions, and C-H bond activation/functionalization reactions (Yorimitsu *et al*., 2021) [32]. Second, the field has investigated new reactions in radical chemistry and material science when transition metals were being used for the reaction, demonstrating the power of transition metals in organic transformations.

More recently, photochemistry has reinvigorated transition metal catalysis, particularly, visible light-induced catalysis, wherein transition metal complexes absorb photonic energy. This has made possible new bond forming/breaking processes under single catalytic cycle, most of the time without reliance on exogenous PS. This strategy allows to not only promote the interaction between catalyst and substrate but also to favor the photoinduced processes, providing a good alternative to conventional photoredox chemistry (Cheung *et al*., 2021) [6].

With the aid of supramolecular chemistry, transition metal catalysis has developed interesting advances in selectivity, activity, and stability. Using supramolecular approaches, for example by enclosing transition metal complexes, catalysis in confined space has opened fresh domains of selectivity that cannot be attained by conventional means. These environments can induce selectivity that is specific for the encapsulated catalysts giving rise to exciting applications for a wide range of chemical reactions (Leenders *et al*., 2015) [20].

In addition, transition metal–catalyzed processes have adopted electrochemistry, avoiding the need for chemical stoichiometric oxidants and reductants. The fusion of electrochemistry with transition metal catalysis has permitted various C-H bond functionalizations, notably expanding the range of chemical transformations including C–C, C–X, C–O, C–P, and C–N bond formations (Ma *et al*., 2018). In addition, electrochemical transition metal-catalyzed paired electrolysis has also been deemed as a potential direction for improving reaction activity and selectivity, considered one of the possible frontiers of organic electrosynthesis (Ma *et al*., 2021) [22].

Another major advance in heterogeneous catalysis is evidenced in the development of dinuclear transition metal complexes, and then by association nickel and palladium complexes. These complexes exploit the synergistic effects of two metals to provide new efficient and strong catalytic reactivities (Xu *et al*., 2020) [31].

Finally, it has been reported that even the transition metal catalysts have also been “remodeled” to conduct a catalytic escape of dividers under electrosynthesis (Ma *et al*., 2021) [22], creating a method for the combination of anodic and cathodic processes, in order to lower the generation of waste, and both the exploitability of the reactions.

In conclusion, the development of transition metal catalysis represents a mile-stone in synthetic chemistry that continuously evolves and adapts to new technology and new cross-disciplinary insights. Such adaptability and creativity have been the driving force behind the evolution of catalytic strategies and have become essential for the design of high-performance, selective and sustainable chemical processes.

3. Existing Reviews and Gaps in the Literature

Several review articles have summarized the synthetic utility of transition metal-catalyzed approaches to PAHs. For instance, reviews have discussed annulative π-extension (APEX) reactions, [2+2+2] alkyne cyclotrimerizations, and C–H activation strategies with various metals. Additionally, thematic overviews exist on the role of transition metals in constructing conjugated polyaromatics for organic electronics and optoelectronics.

However, most existing reviews emphasize reaction scope, synthetic utility, or material application, with limited focus on the underlying mechanistic frameworks that differentiate one metal system from another. As a result, there is a noticeable lack of unified discussion on:

- How specific metal centers (e.g., Pd vs. Ni vs. Rh) govern cyclization pathways
- The influence of ligands, oxidation states, and reaction conditions on intermediate formation and selectivity
- The role of concerted vs. stepwise mechanisms in different cyclization types

This mechanistic gap is particularly relevant for chemists interested in rational catalyst design, computational modeling, and fine-tuning of PAH synthesis for topological and electronic precision.

The present review addresses this gap by offering a mechanism-centered analysis of transition metal-mediated cyclizations, aiming to bridge the divide between synthetic outcome and catalytic logic.

Transition Metal Catalysts in PAH Scaffold Construction

Cyclization reactions catalyzed by transition metals have been developed as useful methods for the construction of large polycyclic aromatic hydrocarbons (PAHs), which has revolutionized the area of organic synthesis. This has steadily become an active area of research in the last few years, new carbon-carbon bonds are formed through intramolecular coupling reactions via transition metal complexes (Gholinejad *et al*., 2019) [11]. Due to their flexible and efficient features, these methods that have been successively developed are significantly complementary and have played vital roles in preparing complex molecular architectures. Some detailed mechanistic understanding of these transformations has become available, showing a complex balance of the metal center with ligands and substrate, which underlines the complexity of these catalytic systems. Common energetic steps of the catalytic cycle are oxidative addition (in which the metal is inserted into C–X or C–H bond), migratory insertion (addition of an unsaturated fragment to a M–C bond), and reductive elimination leading to the formation of a new C–C bond and to recovery of the active catalyst (Gal *et al*., 2003) [9].

The transition metal selection plays an important role in reaction pathway and selectivity, and each metal possesses individual reactivity profiles. For example, palladium-catalyzed reactions are well-known for their generality and broad substrate scope. Rhodium complexes have found to be excellent catalysts and show good chemoselectivity, with the ability to activate C-H bonds traditionally considered unreactive (Kharitonov *et al*., 2025) [18]. In contrast, ruthenium catalysts have previously been shown to be versatile for tandem reaction and cascade processes. Ligand development guides the electronic and steric properties of the metal center to dictate the associate reaction outcome. The electronic density at the metal center and thereby its reactivity can furthermore be affected by phosphine ligands (e.g. configurational isomers of halobis (diphenylphosphino)methane) (Sharma *et al*., 1992) [28]. Large ligands are able to impose geometries on the metal centre and thus influence the orientation of approaching substrates and even improve the regioselectivity of reactions.

The chiral ligands made available to these reactions the creation of enantioselective variants thereof, in turn allowing new perspectives in the field of enantioselective synthesis. By understanding these mechanistic subtleties, more sophisticated and selective routes to complex PAH motifs can now be developed. Investigators have addressed shortcomings, such as low yields, poor regioselectivity or reaction conditions that are too severe, which were characteristic of previous synthetic routes (Athan *et al*., 2013) [2]. For example, air-stable catalysts would allow for more convenient reaction setups, and gentler reaction conditions would enable better functional group compatibility. These progressions have resulted in wide uses of PAH in different area. In materials science, PAHs are used as organic semiconducting and light emitting materials because of their distinct electronic properties.

Due to their extended π-conjugated structures, PAH are promising materials for optoelectronic devices such as solar cells and field-effect transistors. Some PAH derivatives have exhibited encouraging biological activities in medicinal chemistry, some of which have been utilized as potential drug candidates for numerous therapeutic purposes (Liao *et al*., 2023) [21].

In addition, the synthetic procedures for PAH syntheses are being extended to many areas of organic chemistry. The basic principles of transition metal-catalyzed cyclizations have been applied toward the synthesis other heterocyclic systems and natural product scaffolds. This intellectual exchange or transfer of knowledge has only further promoted advances in the broader field of organic synthesis (Grodal & Thoma, 2014) [12]. The research on this issue is developing and as such, so are the challenges and possibilities. The creation of sustainable catalysis systems with earth abundant metals and environmentally benign conditions is emerging frontier. Furthermore, the expanded application of these methods to the construction of an even larger and more complex PAH systems continues to set a challenge for the maximum synthetic limitations.

1. Pd, Ni, Rh, Ru, Fe, Cu, Co: reactivity profiles and ligand effects

- Pd is likely one of the most commonly used metal for PAHs formation. Catalytic cycles for it generally include oxidative addition, migratory insertion, and reductive elimination. Aryl halides and alkynes are highly tolerated in Pd (0)/Pd (II) cycles and intramolecular annulation occurs efficiently. Ligand fine tuning (i.e., phosphines, NHCs) is crucial to direct the regioselectivity and enhance turnover frequencies.

- Nickel (Ni) was found to have comparable catalytic behavior although it functions under more reducing conditions. It can participate in one-electron processes and activate less nucleophilic electrophiles (e.g. aryl chlorides), and is therefore an interesting candidate for industrial or green synthesis. Ni also holds much promise for dual catalysis and radical cyclisation modes, broadening the range of PAH topologies that are available.

- Rhodium (Rh), with Rh (III) as its component of choice, has shown preeminence in C–H activation-derived annulations. A variety of directing groups are also tolerated by these rhodium catalysts, and they are highly effective for the construction of 5- and 6-membered fused rings through annulation of arenes with alkynes or alkenes. Rh complexes are often attached to Cp* ligands, which promote electrophilic metalation as well as stable metallacycle intermediates.

- Ruthenium (Ru) complexes, Ru (II), in particular, are found to be active in oxidative annulation and [2+2+2] cycloaddition of alkynes. They are also advantageous in terms of operational stability under aerobic and water resistance. In this regard, ruthenium catalysts are particularly interesting for the regioselective synthesis of angular or helical PAHs.

- Iron, an abundant terrestrial metal, was less utilized, but has gained attention in gentle processes. FeCatalyzed oxidative coupling/annulation reactions continued to be explored and appear to be potential in ideal aromatic syntheses.

- In Ullmann-type couplings and oxidative cyclizations copper (Cu) is commonly used as a co-catalyst or mediator. Less frequently alone for PAH cyclization, copper's redox bifurcation permits its involvement in oxidative annulations with diaryl ethers or alkyne substrates.

- Cost-effective and such mechanistically different catalysts such as cobalt (Co) are being discovered in particular in C–H activation and radical annulation reactions. Cp* or pyridine-based ligand supported cobalt (III) catalysts are competent catalysts for the construction of benzannulated PAHs with good efficiency and regioselectivity.

The reactivity of these metals is strongly ligand dependent and even small changes to the ligand environment (e.g. electronic donating ability, steric hindrance) can have a significant impact on the thermodynamics and kinetics of the catalytic pathway.

2. Comparison of reaction types enabled by different metals

Table 1: Different transition metals enable unique cyclization strategies, often based on their preferred oxidation states, coordination geometries, and electronic characteristics

Metal	Preferred cyclization pathways	Notable features
Pd(0/ll)	Intramolecular arylation, alkyne annulation	High functional group tolerance, versatile ligand control
Ni(0/ll)	Cross-coupling, radical annulation	Reductive cyclization, activation of inert bonds
Rh(lll)	C-H activation + alkyne annulation	High regioselectivity via metallacycles
Ru(ll)	[2+2+2] cycloadditions, C-H alkenylation	Compatible with oxidants and air
Co(lll)	C-H alkynylation, oxidative annulation	Base-metal, Cp*-type mechanisms
Fe(ll/lll)	Oxidative couplings (developing)	Cost-effective and green alternative

Cu(l/ll)	Oxidative coupling, Ullmann-type reactions	Often used in tandem with oxidants or bases

This diversity of catalytic modes offers synthetic chemists multiple avenues for designing PAHs with specific fusion patterns, π-extension, and topological complexity.

3. Environmental and cost considerations in catalyst selection

Despite the urgent requirement for scalable and sustainable synthesis, the environmental friendliness and economic cost of the catalyst selection are very important:

- Expensive and toxic Pd, Rh, Ru, which display high reactivity and selectivity, also have issues with cost and scarcity. Their recyclable properties, such as upcycling or downcycling potential, should be addressed in industrial processing.

- Ni, Fe, and Co are base metals relatively earth-abundant and nontoxic. Recent advances in ligand design have enhanced their catalytic activity rendering them interesting choices for green chemistry.

- The loading of the catalyst, the sensitivity to air/moisture and the requirement of a special ligand or additive also affect the operation robustness and economy of a catalytic system.

In this respect, the design of recyclable, heterogeneous catalysts, or photo- and electro-catalytic integration systems, suggests a sustainable process for future PAH syntheses.

Mechanistic Pathways of Metal-Mediated Cyclization

Cyclization approaches to PAHs utilizing transition metal catalysis are built upon a small number of distinct organometallic reactions. These include the C–H activation, alkyne coordination and insertion, and conventional steps such as the oxidative addition and reductive elimination. Knowledge of these mechanistic pathways provides a more detailed understanding of how catalytic systems can be modulated for selective PAH nucleation.

1. C–H Activation and Direct Arylation

1.1 Mechanistic basis of C–H metalation and annulation

C–H activation is an important breakthrough that eliminates the requirement for pre-functionalized coupling partners for the construction of fused aromatic rings. Transition metals, e.g., Rh (III), Pd (II), and Ru (II), promote direct activation of more or less unreactive C–H bonds, through electrophilic metalation or base-assisted concerted metalation-deprotonation (CMD) stages. The metalated arene can also undergo annulative π-extension (APEX) reactions with alkynes or alkenes to give further fused rings.

The general sequence involves:

- C–H bond activation near a directing group (e.g., amide, pyridyl),
- Alkyne coordination and insertion, forming a metallacycle intermediate,
- Reductive elimination or oxidative annulation, closing the ring.

This facilitates fast construction of linear, angular, and even helical PAH topologies under mild conditions.

1.2 Regioselectivity control and kinetic vs. thermodynamic product formation

Regioselectivity of C–H activation strongly depends on the structue of the directing group, steric hindrance and electronic effects. kinetic selectivity often results in C–H activation occurring at less hindered sites initially, while thermodynamic control can result in products that are more conjugated or electronically stabilized. Both ligand design (e.g., Cp*, phosphines) and the base used also impact this equilibrium providing opportunities for targeted ring closure.

2. Alkyne Cyclization and [2+2+2] Cycloadditions

2.1 Use of alkynes and diynes for constructing fused rings

The transition-metal-catalyzed alkyne cyclization has been demonstrated as a versatile tool for PAH synthesis, especially when using diynes or triynes as substrates. Metals like Co, Ru, and Rh are well-known to promote [2+2+2] cycloaddition reactions in which three alkyne units (or two alkynes and a nitrile) are transformed into benzenoid rings in a single step.

The mechanism involves:

- Coordination of alkynes to the metal center,
- Stepwise or concerted cycloaddition, forming a metallacyclopentadiene or -heptatriene intermediate,
- Reductive elimination, furnishing the fully conjugated PAH.

This method is particularly attractive for forming triphenylene, coronene, and other multi-ring scaffolds with high symmetry and extended conjugation.

2.2 Examples of Intramolecular and Intermolecular Pathways

- Intramolecular [2+2+2] cyclizations offer precise control over ring fusion and connectivity, especially for angular or curved PAHs.
- Intermolecular approaches, while more challenging due to selectivity issues, enable modular synthesis by combining different alkyne partners.

Co-catalysts, solvents, and ligand choices are critical in minimizing side products and improving yield in these reactions.

3. Oxidative Addition / Reductive Elimination Pathways

3.1 Classical organometallic steps in ring fusion

Palladium and nickel-based systems often rely on the classical cycle of:

- Oxidative addition (e.g., aryl halide to Pd (0)),
- Transmetalation or alkyne insertion,
- Reductive elimination, forming the new C–C bond.

This process is central to intramolecular arylation and alkyne annulation reactions for PAH synthesis. The efficiency of oxidative addition correlates with the electronic nature of the aryl halide (Ar–X), while reductive elimination is influenced by the steric and electronic configuration of the metal-bound intermediates.

3.2 Role of ligands, solvents, and oxidation states in driving selectivity

- Ligands (e.g., bulky phosphines, NHCs) modulate the electron density and coordination geometry of the metal center, directly affecting reaction rates and regioselectivity.
- Solvent polarity and coordinating ability impact catalyst stability and intermediate solubility.
- The oxidation state of the metal governs the feasibility of key steps: Pd (0)/Pd (II) or Ni (0)/Ni (II) cycles are common, while higher oxidation states (e.g., Rh (III), Co (III)) enable C–H functionalization routes.

By tailoring these parameters, chemists can direct the cyclization pathway toward desired PAH topologies with greater precision and efficiency.

Scaffold Diversification and Structural Control

The structural complexity and functional utility of polycyclic aromatic hydrocarbons (PAHs) are largely determined by the nature and pattern of ring fusion. Transition metal-mediated cyclization offers powerful tools for controlling the topology, substitution patterns, and electronic properties of PAH scaffolds. This section highlights how subtle changes in precursors, metals, and reaction design lead to significant variations in final PAH architectures.

Influence of Substitution Patterns on PAH Topology

The regiochemistry of PAH construction is profoundly influenced by the substitution patterns on the aryl or alkyne precursors. Electron-donating or -withdrawing groups can direct cyclization pathways via inductive or resonance effects, stabilizing key intermediates such as metallacycles or π-complexes. Additionally, steric hindrance can dictate kinetic product formation, preventing undesired coupling at crowded sites. Such control is critical in selectively accessing linear (e.g., acenes), angular (e.g., phenacenes), or curved (e.g., nanobelts or nanographenes) structures.

Metal-Specific Regioselectivity in Angular vs. Linear Fusion

Different transition metals favor distinct cyclization geometries based on their coordination chemistry and catalytic cycles:

- Pd (0) and Ni (0) often promote linear or ladder-type fusion via directed aryl–aryl coupling or alkyne insertion.
- Rh (III) and Ru (II) show greater selectivity for angular annulation, especially when using C–H activation routes with internal alkynes.
- Co (III) systems can support radical or metallacycle-based processes that enable edge-fused and kinked structures, often under oxidative conditions.

The careful pairing of metal system and substrate design enables precise architectural control, supporting the construction of diverse PAH motifs with customized π-conjugation.

Examples of Targeted π-Extension Through Controlled Cyclization

Controlled cyclization has enabled the synthesis of:

- Perylene and coronene derivatives with extended π-systems for organic electronics.
- Helicenes and twisted PAHs with chirality for optoelectronic and enantioselective sensing applications.
- Nanographene fragments, including multi-ring fused systems, synthesized using Rh- or Pd-mediated annulations of polyalkynes or polyarylenes.

These examples underscore how transition metal catalysis enables topology-specific π-extension, expanding the functional landscape of PAHs across molecular electronics and photophysics.

Applications of Transition Metal-Catalyzed PAHs

Extended PAHs generated through metal-mediated cyclizations have demonstrated tremendous utility across various technological and biomedical fields. Their planar or tunably distorted structures, extended conjugation, and chemical versatility make them excellent candidates for materials science, diagnostics, and drug development.

Optoelectronic Materials (OLEDs, OFETs, Organic Photovoltaics)

PAHs with high conjugation and tailored energy gaps are essential for:

- **Organic light-emitting diodes (OLEDs):** PAHs serve as emissive layers or hole/electron transport materials due to their π-delocalization and high fluorescence efficiency.
- **Organic field-effect transistors (OFETs):** Ladder-type PAHs like tetracene or pentacene analogues enable efficient charge carrier mobility in thin-film devices.
- **Organic photovoltaics (OPVs):** Extended PAHs with donor–acceptor functionality can act as light-harvesting units in bulk heterojunction solar cells.

Metal-catalyzed annulations facilitate the fine-tuning of these molecules' HOMO–LUMO levels, solid-state packing, and thermal stability—crucial parameters for device performance.

Fluorescent Dyes, Sensors, and Molecular Switches

π-Extended systems derived from PAHs are widely used in:

- Fluorescent probes and dyes with high quantum yield and tunable emission profiles.
- Molecular sensors that exploit changes in fluorescence or conductivity upon interaction with ions, pH, or small molecules.
- Photochromic switches, where the reversible cyclization or π-extension modulates the optical signal.

Transition metal-mediated synthesis enables precise installation of functional groups and heteroatoms (e.g., N, S, O) that enhance sensing selectivity and environmental responsiveness.

Drug Candidates and Therapeutic Scaffolds in Medicinal Chemistry

While PAHs are traditionally viewed as environmental pollutants, well-defined, substituted PAHs are now explored as:

- DNA intercalators for anticancer activity due to their planar geometry.

- Photosensitizers for photodynamic therapy, especially with extended π-systems that absorb in the NIR range.
- Enzyme inhibitors and protein binders, where shape complementarity and hydrophobic interactions dominate.

Metal-catalyzed cyclizations allow incorporation of bio-relevant side chains and heterocycles, supporting medicinal chemists in exploring structure–activity relationships (SARs) in drug design.

Discussion

The cumulative mechanistic exploration of transition metal-mediated cyclizations for PAH construction reveals converging patterns and divergence in reactivity profiles across different catalytic systems. Palladium and nickel-based reactions dominate in cross-coupling and alkyne annulation pathways, whereas rhodium and cobalt catalysis enable site-selective C–H activation and π-extension under milder conditions. A core observation across these systems is the critical role of substrate pre-organization, directing groups, and ligand architecture in governing regioselectivity and topological outcomes.

A recurring theme in the literature is the metal-dependent control over ring fusion type—linear versus angular. While Pd/Ni complexes tend to favor ladder-type ring expansion due to their oxidative addition and reductive elimination cycles, Rh (III)- and Co (III)-based systems offer superior selectivity for angular cyclizations via electrophilic C–H activation. Furthermore, mechanistic studies underline that ligand-induced stabilization of intermediates (e.g., metallacycles, π-complexes) can dramatically improve reaction yield and product fidelity.

Recent advances also include the integration of dual catalytic systems and emerging methods such as photoredox, bimetallic, and electrochemical catalysis. These unconventional approaches have started to unlock otherwise inaccessible PAH scaffolds and facilitate more sustainable reaction conditions. Despite these developments, many studies still lack in-depth real-time mechanistic validation—highlighting the need for operando spectroscopy and DFT-supported pathway analysis.

Conclusion

This review consolidates the mechanistic underpinnings of transition metal-mediated cyclization strategies used in the synthesis of extended PAH frameworks. Through detailed examination of catalytic cycles, metal–substrate interactions, and ligand effects, it becomes evident that precise structural control of PAH scaffolds is achievable by selecting appropriate metal systems and reaction conditions. The diversity of accessible ring topologies—linear, angular, curved—and the expanding application scope in materials and biomedical sciences underscore the centrality of metal catalysis in modern PAH chemistry.

Furthermore, the mechanistic insights presented here can guide future catalyst design and reaction engineering. By focusing on site-selective activation, regioselective control, and sustainable conditions, researchers can tailor PAH synthesis to meet the growing demand for customized organic semiconductors, functional dyes, and therapeutic agents. Continued integration of computational chemistry, green catalysis, and modular synthesis will further push the boundaries of what is possible in PAH framework construction.

Challenges and Current Limitations

Despite significant advancements, several challenges remain:

- **Intermediate stability:** Many cyclization reactions rely on transient intermediates that are difficult to isolate or detect. Their instability limits mechanistic clarity and reproducibility.

- **Regioselectivity prediction:** While directing groups and ligand design help, precise prediction of product outcomes—especially in multi-annulation or unsymmetrical systems—remains difficult.

- **Catalyst cost and environmental footprint:** Most efficient systems depend on expensive and scarce metals (Pd, Rh, Ru). Their toxicity and cost hinder large-scale or industrial application.

- **Substrate limitations:** Current methods often struggle with sterically hindered, electron-deficient, or highly functionalized substrates, reducing generality.

- **Scalability and purification:** The poor solubility and tendency of large PAHs to aggregate or crystallize pose synthetic and analytical hurdles.

Future Directions

To overcome existing limitations and enhance applicability, the following directions hold promise:

- Utilization of Earth-abundant metals (Fe, Mn, Co): These metals offer a sustainable and cost-effective alternative for catalysis, with promising results in C–H functionalization and alkyne annulation.

- Photoredox and electrochemical integration: Combining traditional transition metal catalysis with light or redox-driven mechanisms can enable milder, more selective cyclizations with new reactivity profiles.

- Mechanistic interrogation tools: Advances in operando IR/NMR spectroscopy, EPR, and DFT simulations can clarify catalytic cycles in real-time, aiding in rational method design.

- Framework programmability: Future work should aim to develop catalyst systems that allow programmable PAH synthesis with high modularity, regioselectivity, and yield—moving closer to "on-demand" synthesis of functional materials.

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