

# Metal–Organic Frameworks (MOFs) as Green Catalysts in Pharmaceutical Synthesis

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## ABSTRACT

Metal–Organic Frameworks (MOFs) have garnered significant attention as next-generation green catalysts due to their unique structural and physicochemical properties, offering transformative potential in pharmaceutical synthesis. These crystalline porous materials, constructed from metal ions or clusters interconnected by organic linkers, exhibit exceptionally high surface areas, tunable pore architectures, and chemically tailorable functionalities. Such characteristics enable precise modulation of catalytic sites, thereby enhancing activity, selectivity, and substrate specificity in complex organic transformations.

From a green chemistry perspective, MOFs present a compelling alternative to conventional catalytic systems by enabling reactions under mild conditions, reducing energy input, and minimizing waste generation. Their heterogeneous nature facilitates easy separation and recyclability, addressing key limitations associated with homogeneous catalysts. Moreover, the ability to incorporate catalytically active sites—such as Lewis acids, Brønsted acids, and redox-active centers—within the MOF framework allows for the design of multifunctional catalysts capable of promoting cascade and tandem reactions, which are highly desirable in the synthesis of active pharmaceutical ingredients (APIs).

Recent advances have further expanded the applicability of MOFs through the development of engineered systems, including defect-engineered MOFs, metal nanoparticle-encapsulated frameworks, and enzyme–MOF biocomposites. These innovations have demonstrated remarkable efficiency in key pharmaceutical reactions such as C–C and C–N bond formation, selective oxidation, and asymmetric synthesis, often achieving superior performance compared to traditional catalysts. Additionally, the integration of MOFs into continuous flow systems highlights their potential for scalable and industrially viable green processes.

However, challenges related to long-term stability, moisture sensitivity, metal leaching, and large-scale production remain critical barriers to commercialization. Ongoing research efforts are focused on enhancing structural robustness and developing cost-effective synthesis strategies. Overall, MOFs represent a promising frontier in sustainable catalysis, with the potential to significantly advance environmentally benign pharmaceutical manufacturing.

**Keywords:** Metal–Organic Frameworks (MOFs); Green Catalysis; Pharmaceutical Synthesis; Sustainable Chemistry; Heterogeneous Catalysis; Porous Crystalline Materials; Active Pharmaceutical Ingredients (APIs); Catalyst Design; Reusability; Eco-efficient Processes

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### 1. Introduction

The contemporary pharmaceutical industry is undergoing a paradigm shift toward sustainability, driven by stringent environmental regulations, rising production costs, and the global imperative to minimize ecological footprints (1). Conventional synthetic routes for active pharmaceutical ingredients (APIs) are frequently associated with low atom economy, extensive solvent usage, multi-step reaction pathways, and the generation of hazardous waste. These challenges underscore the urgent need for catalytic systems that align with the principles of green chemistry, particularly in enhancing reaction efficiency, reducing energy consumption, and enabling cleaner production processes.

Catalysis remains central to pharmaceutical manufacturing, yet traditional catalytic systems present inherent limitations. Homogeneous catalysts, while offering superior activity and selectivity, are often plagued by issues related to separation, recyclability, and metal contamination in final products—an especially critical concern in pharmaceutical applications (2). Conversely, conventional heterogeneous catalysts provide operational advantages in terms of recovery and reuse but frequently lack the structural precision and tunability required for complex, stereoselective transformations (3). Bridging this gap necessitates the development of advanced catalytic materials that integrate the benefits of both systems without compromising sustainability.

Metal–Organic Frameworks (MOFs) have emerged as a transformative class of crystalline porous materials that address these limitations through their unique structural and functional attributes (4). Constructed from metal ions or clusters interconnected by organic linkers, MOFs exhibit exceptionally high surface areas, uniform and tunable pore architectures, and remarkable chemical versatility. This modularity enables the rational design of catalytic sites at the molecular level, allowing precise control over reaction environments, diffusion pathways, and substrate–catalyst interactions.

A defining advantage of MOFs in pharmaceutical catalysis lies in their ability to incorporate diverse active functionalities within a single framework. Metal nodes can act as Lewis acidic centers, while functionalized organic linkers can introduce Brønsted acidity, chirality, or redox activity (5). Furthermore, post-synthetic modification and defect engineering strategies have enabled the creation of hierarchical and multifunctional catalytic systems capable of promoting complex transformations, including C–C and C–N bond formation, asymmetric synthesis, selective oxidation, and multicomponent reactions (6). Such capabilities are particularly valuable in the synthesis of structurally intricate drug molecules, where efficiency and selectivity are paramount.

From a green chemistry standpoint, MOFs offer several compelling advantages. Their heterogeneous nature facilitates straightforward separation and recyclability, significantly reducing downstream processing requirements. The well-defined pore environments enhance mass transfer and substrate accessibility, often enabling reactions to proceed under mild conditions with high selectivity and minimal by-product formation (7). Additionally, the integration of MOFs into continuous flow systems represents a significant advancement toward process intensification, enabling scalable and energy-efficient pharmaceutical production.

Recent research has further expanded the functional scope of MOFs through the development of hybrid and composite systems, including metal nanoparticle@MOF catalysts and enzyme–MOF bioconjugates. These engineered materials combine the robustness of inorganic frameworks with the high catalytic efficiency of nanoparticles or the exquisite selectivity of enzymes, thereby offering synergistic enhancements in catalytic performance. Such innovations have demonstrated considerable promise in the synthesis of key pharmaceutical intermediates and APIs, reinforcing the potential of MOFs as next-generation green catalysts.

Despite these advancements, several critical challenges remain. The long-term structural stability of MOFs under reaction conditions, particularly in the

presence of moisture or acidic/basic environments, continues to be a major concern (8). Metal leaching, which may compromise both catalyst integrity and product purity, must be carefully addressed. Furthermore, the scalability and economic viability of MOF synthesis are essential considerations for industrial implementation. Ongoing efforts are focused on developing robust, cost-effective, and environmentally benign synthesis routes, as well as enhancing the durability and reusability of MOF-based catalysts.

In this context, the present study aims to critically evaluate the role of Metal–Organic Frameworks as green catalysts in pharmaceutical synthesis. It provides a comprehensive analysis of their structural characteristics, catalytic mechanisms, and recent technological advancements, while also addressing current limitations and future research directions. By integrating advanced materials engineering with sustainable chemistry principles, MOFs hold significant promise in redefining catalytic strategies for environmentally responsible pharmaceutical manufacturing.

### 1. Fundamentals of Metal–Organic Frameworks (MOFs)

#### 1.1 Structural Design and Coordination Chemistry

Metal–Organic Frameworks (MOFs) represent a highly ordered class of crystalline porous materials constructed via the coordination-driven self-assembly of metal ions or polynuclear metal clusters—commonly referred to as secondary building units (SBUs)—with multidentate organic linkers (9). The structural architecture of MOFs is fundamentally dictated by coordination chemistry principles, including metal ion geometry, preferred coordination number, ligand denticity, and bonding directionality. Transition metals (e.g.,  $Zn^{2+}$ ,  $Cu^{2+}$ ,  $Fe^{3+}$ ) and high-valent metal clusters (e.g.,  $Zr_6O_4(OH)_4$ ,  $Ti_8O_8$ ) are frequently employed due to their ability to form robust and geometrically predictable coordination environments with oxygen- and nitrogen-donor ligands such as carboxylates, azolates, and pyridyl derivatives.

The conceptual framework of reticular chemistry underpins the rational design of MOFs, enabling the systematic construction of extended networks with predetermined topologies. By judicious selection of SBUs and organic linkers, it is possible to engineer

frameworks with precise control over pore size, connectivity, and chemical functionality (10). Strategies such as isoreticular expansion (IRMOF series), mixed-linker incorporation, and post-synthetic modification (PSM) further extend the tunability of MOFs. Of particular relevance to catalysis is the generation of coordinatively unsaturated metal sites (open metal sites), which serve as accessible and highly active catalytic centers. Additionally, defect engineering has emerged as a powerful tool to introduce structural heterogeneity and enhance catalytic performance through the creation of additional active sites.

#### 1.2 Classification and Types of MOFs

MOFs can be systematically classified based on their metal composition, structural topology, and functional attributes. From a compositional perspective, MOFs are often categorized according to the nature of their metal nodes. For instance, zirconium-based frameworks (e.g., UiO-type MOFs) are distinguished by their exceptional thermal and hydrolytic stability, attributable to strong Zr–O bonds, whereas copper-based frameworks (e.g., HKUST-1) exhibit prominent Lewis acidity and catalytic activity due to accessible  $Cu^{2+}$  centers. Similarly, zeolitic imidazolate frameworks (ZIFs), constructed from tetrahedrally coordinated metal ions and imidazolate linkers, exhibit zeolite-like topologies and enhanced chemical stability.

Structurally, MOFs are classified according to pore dimensions and topology, including microporous (<2 nm), mesoporous (2–50 nm), and hierarchical frameworks that integrate multiple pore regimes to facilitate improved mass transport. Functional classification distinguishes between pristine MOFs, post-synthetically modified (PSM) MOFs, and composite or hybrid systems. These include metal nanoparticle@MOF architectures, core–shell structures, and enzyme–MOF biocomposites, which are specifically engineered to enhance catalytic efficiency, selectivity, and durability.

Application-oriented classification further identifies catalytic MOFs, gas storage/separation MOFs, sensing MOFs, and biomedical MOFs. Catalytic MOFs, in particular, are designed to incorporate active sites either intrinsically within the framework (via metal nodes or functionalized linkers) or extrinsically through encapsulation or immobilization

of catalytic species, rendering them highly suitable for complex pharmaceutical transformations.

### 1.3 Physicochemical Properties Relevant to Catalysis

The catalytic efficacy of MOFs arises from a synergistic interplay of their unique physicochemical properties. A defining feature is their exceptionally high specific surface area—often exceeding 1000–7000 m<sup>2</sup> g<sup>-1</sup>—which provides a high density of accessible active sites. The presence of uniform and tunable pore systems enables size- and shape-selective catalysis, facilitating controlled diffusion of reactants and products and minimizing undesired side reactions.

Chemical tunability is another critical attribute, allowing the incorporation of functional groups that impart Lewis acidity, Brønsted acidity, redox activity, or chirality. This enables the rational design of catalysts tailored for specific transformations, including enantioselective reactions that are of paramount importance in pharmaceutical synthesis. Furthermore, the spatial isolation of active sites within the framework reduces catalyst deactivation and enhances selectivity.

The stability of MOFs under operational conditions is a key determinant of their practical applicability. Advanced frameworks, particularly those based on high-valent metals such as Zr<sup>4+</sup>, Ti<sup>4+</sup>, and Al<sup>3+</sup>, exhibit superior thermal, chemical, and hydrolytic stability. Additionally, the heterogeneous nature of MOFs facilitates facile separation and recyclability, aligning with the principles of green chemistry.

A distinctive advantage of MOFs is their ability to act as host matrices for encapsulating catalytically active species, including metal nanoparticles, organocatalysts, and enzymes. The confinement effect within their well-defined pore environments can significantly alter reaction kinetics and pathways, often leading to enhanced activity and selectivity (11). Moreover, hierarchical porosity and defect sites can further improve mass transport and catalytic accessibility.

Collectively, these attributes position MOFs as highly versatile and tunable catalytic platforms, capable of addressing the complex demands of sustainable pharmaceutical synthesis while offering opportunities for innovation in catalyst design and process intensification.

## 2. Principles of Green Chemistry in Pharmaceutical Synthesis

### 2.1 Overview of Green Chemistry Principles

Green chemistry provides a rigorous and systematic framework for the design of environmentally benign chemical processes, and its application is particularly critical in pharmaceutical synthesis, where molecular complexity often necessitates multistep transformations with significant material and energy inputs (12). The twelve principles articulated by Paul Anastas and John Warner emphasize waste prevention, atom economy, safer solvents and auxiliaries, energy efficiency, use of renewable feedstocks, and the design of inherently safer chemicals and processes.

In pharmaceutical manufacturing, the implementation of these principles is quantitatively assessed using green metrics such as the E-factor and Process Mass Intensity (PMI), both of which highlight the disproportionate waste generation characteristic of fine chemical and pharmaceutical industries (13). The extensive use of organic solvents, protecting groups, and stoichiometric reagents contributes significantly to this inefficiency. Consequently, there is a growing emphasis on reaction pathway optimization, solvent minimization, and the adoption of alternative media such as water, ionic liquids, and bio-derived solvents. Process intensification strategies—including one-pot, tandem, and cascade reactions—have emerged as effective approaches to enhance atom economy and reduce intermediate handling. Furthermore, the shift toward continuous flow chemistry has enabled improved heat and mass transfer, enhanced safety profiles, and reduced environmental impact. Collectively, these strategies underscore the transition from traditional yield-centric approaches to holistic sustainability-driven process design in pharmaceutical synthesis.

### 2.2 Role of Catalysis in Sustainable Drug Manufacturing

Catalysis constitutes the cornerstone of green pharmaceutical synthesis, enabling the transformation of raw materials into high-value products with maximal efficiency and minimal environmental burden. By providing alternative reaction pathways with lower activation energies, catalysts significantly reduce energy consumption and improve reaction kinetics. More critically, catalytic systems enable high levels of chemo-, regio-

, and enantioselectivity—attributes that are indispensable in the synthesis of structurally complex and stereochemically defined active pharmaceutical ingredients (APIs).

The replacement of stoichiometric reagents with catalytic systems markedly enhances atom economy and reduces waste generation. In particular, heterogeneous catalysts offer distinct advantages in terms of facile separation, operational stability, and recyclability, thereby aligning with industrial sustainability requirements (14). Additionally, the development of multifunctional catalytic systems capable of promoting sequential or tandem transformations has enabled substantial reductions in process steps, solvent usage, and purification requirements.

Emerging paradigms such as biocatalysis, photocatalysis, and electrocatalysis further expand the scope of sustainable drug manufacturing. These approaches often operate under mild conditions and utilize renewable energy inputs, thereby minimizing environmental impact. Within this evolving landscape, advanced materials such as Metal–Organic Frameworks (MOFs) have attracted considerable attention due to their ability to integrate multiple catalytic functionalities within a single, structurally well-defined platform, offering unprecedented opportunities for process optimization and sustainability.

### 2.3 Limitations of Conventional Catalytic Systems

Despite their central role in chemical synthesis, conventional catalytic systems exhibit intrinsic limitations that impede their full alignment with green chemistry objectives. Homogeneous catalysts, typically comprising transition metal complexes or organocatalysts, are characterized by high activity and selectivity but suffer from critical drawbacks, including challenges in catalyst separation, limited recyclability, and the risk of residual metal contamination in pharmaceutical products (15). Such contamination is tightly regulated due to its potential impact on drug safety and efficacy, necessitating additional purification steps that increase process complexity and waste generation.

Conversely, traditional heterogeneous catalysts—such as supported metals, metal oxides, and zeolites—offer advantages in terms of ease of separation and reuse. However, these systems often lack the structural uniformity and tunability required

for precise control over catalytic environments. Limitations such as diffusion constraints, non-uniform active sites, catalyst deactivation (e.g., sintering, coking), and reduced selectivity in complex transformations restrict their applicability in advanced pharmaceutical synthesis.

Moreover, many conventional catalytic processes rely on harsh reaction conditions, including elevated temperatures, high pressures, and the use of toxic or non-renewable solvents. The synthesis and regeneration of these catalysts may also involve energy-intensive and environmentally detrimental procedures, further diminishing their sustainability profile.

These challenges collectively highlight the need for next-generation catalytic platforms that combine molecular-level precision, structural tunability, operational stability, and environmental compatibility. In this context, Metal–Organic Frameworks (MOFs) offer a compelling solution, bridging the gap between homogeneous and heterogeneous catalysis while adhering to the principles of green chemistry and advancing the sustainability of pharmaceutical manufacturing.

## 3. Catalytic Mechanisms of Metal–Organic Frameworks (MOFs)

### 3.1 Lewis and Brønsted Acid Catalysis

MOFs provide a uniquely addressable platform for engineering both Lewis and Brønsted acidity with molecular-level precision. Lewis acid sites predominantly originate from coordinatively unsaturated metal centers (open metal sites, OMS) generated either intrinsically during framework construction or via post-synthetic activation. High-valent nodes such as  $Zr^{4+}$ ,  $Ti^{4+}$ , and  $Al^{3+}$  exhibit strong Lewis acidity, enabling efficient polarization of substrates (e.g., carbonyls, epoxides) and facilitating key transformations such as acylation, cyclization, and C–C bond formation (16). The periodic arrangement and site isolation of these OMS within the crystalline lattice minimize site heterogeneity and suppress undesired side reactions.

Brønsted acidity is typically introduced through functionalized linkers (e.g.,  $-SO_3H$ ,  $-COOH$ ,  $-PO_3H_2$ ) or via post-synthetic grafting, enabling proton-mediated activation pathways relevant to esterification, hydrolysis, and multicomponent condensations. Importantly, MOFs can be designed to co-localize Lewis and Brønsted sites within confined

domains, enabling cooperative or bifunctional catalysis. Such synergistic interactions can lower activation barriers, stabilize intermediates, and enhance chemo- and regioselectivity—attributes that are critical for complex pharmaceutical transformations.

### 3.2 Redox-Active MOFs

Redox-active MOFs constitute a versatile class of catalysts wherein either the metal nodes, the organic linkers, or both participate in reversible electron-transfer processes. Transition metal centers such as Fe, Cu, Co, Mn, and V are frequently employed due to their accessible redox couples, enabling catalytic cycles for oxidation and reduction reactions central to pharmaceutical synthesis (e.g., alcohol oxidation, olefin epoxidation, oxidative coupling, and hydrogenation) (17).

Mechanistically, redox catalysis in MOFs benefits from the stabilization of reactive intermediates within the framework's confined environment, which can suppress over-oxidation and improve selectivity. Additionally, redox-active linkers—such as quinone-, porphyrin-, or bipyridine-based systems—can serve as electron reservoirs, facilitating charge transfer and expanding the catalytic repertoire beyond metal-centered pathways.

Recent advances have integrated photoactive and electroactive functionalities into MOFs, giving rise to photocatalytic and electrocatalytic systems that harness light or electrical energy to drive redox transformations under mild conditions (18). These approaches align strongly with sustainable chemistry paradigms by reducing reliance on thermal energy inputs and enabling the use of renewable energy sources.

### 3.3 Structure–Activity Relationships

Elucidating structure–activity relationships (SAR) in MOFs is essential for the rational design of high-performance catalytic systems. Catalytic behavior is intricately governed by the interplay between metal node identity, linker functionality, pore architecture, topology, and defect density. Variations in these parameters modulate the electronic environment, accessibility, and spatial distribution of active sites.

The choice of metal node dictates the intrinsic catalytic modality (acidic, basic, or redox), while functionalized linkers can fine-tune electronic properties or introduce secondary catalytic functionalities, including chirality for

enantioselective synthesis. Pore size and geometry exert a decisive influence on substrate diffusion and shape selectivity, enabling discrimination between reactants based on steric constraints—an effect analogous to enzyme active sites (19).

Defect engineering has emerged as a powerful strategy to enhance catalytic performance by generating additional active sites (e.g., missing-linker or missing-cluster defects) and improving mass transport. However, the introduction of defects must be carefully controlled, as excessive disorder can compromise framework integrity and long-term stability. Advanced characterization techniques and computational modeling are increasingly employed to correlate structural parameters with catalytic outcomes, thereby enabling predictive catalyst design.

### 3.4 Diffusion and Confinement Effects

The well-defined porous architecture of MOFs imparts distinctive diffusion and confinement effects that are central to their catalytic performance. Molecular transport within MOF channels is governed by pore size, connectivity, and surface functionality, which collectively influence reaction kinetics and selectivity. In microporous systems, diffusion limitations may arise for bulky substrates; however, the development of hierarchical MOFs with integrated micro- and mesoporosity has effectively mitigated such constraints, enhancing accessibility to active sites.

Confinement effects within MOF cavities can profoundly alter reaction pathways by stabilizing transition states and reactive intermediates through non-covalent interactions (e.g., van der Waals forces, hydrogen bonding,  $\pi$ – $\pi$  interactions). This microenvironment can lead to enhanced regio-, chemo-, and stereoselectivity, closely mimicking enzymatic catalysis. Furthermore, spatial confinement can prevent aggregation or sintering of encapsulated catalytic species (e.g., metal nanoparticles), thereby preserving catalytic activity and prolonging catalyst lifetime.

Site isolation within the framework also reduces the likelihood of bimolecular deactivation pathways, contributing to improved catalyst robustness. In pharmaceutical synthesis, where precision and selectivity are paramount, these confinement-driven effects provide a decisive advantage over conventional catalytic systems.

### 4. Applications of Metal–Organic Frameworks (MOFs) in Pharmaceutical Synthesis

#### 4.1 C–C and C–N Bond Formation Reactions

The formation of carbon–carbon (C–C) and carbon–nitrogen (C–N) bonds constitutes the backbone of pharmaceutical synthesis, underpinning the construction of complex molecular architectures. MOFs have emerged as highly efficient heterogeneous catalysts for these transformations, particularly in transition metal-catalyzed cross-coupling reactions. Frameworks incorporating catalytically active metals such as Pd, Cu, Ni, and Fe—either as intrinsic nodes or as encapsulated nanoparticles—have demonstrated excellent performance in Suzuki–Miyaura, Heck, Sonogashira, and Buchwald–Hartwig coupling reactions.

The periodic arrangement of active sites within MOFs ensures uniform catalytic environments, which enhances reproducibility and selectivity. Furthermore, the confinement of metal species within the porous matrix mitigates nanoparticle aggregation and suppresses metal leaching—two critical limitations in conventional catalytic systems. For C–N bond formation, MOFs have shown high efficiency in Ullmann-type amination and amide bond formation, which are pivotal steps in the synthesis of numerous active pharmaceutical ingredients (APIs) (20). The tunable pore architecture also enables size- and shape-selective catalysis, offering an additional level of control in complex reaction systems.

#### 4.2 Oxidation and Reduction Processes

Selective oxidation and reduction reactions are indispensable in the functionalization of pharmaceutical intermediates. MOFs, particularly those incorporating redox-active metal centers (e.g., Fe, Cu, Mn, Co, and V), have demonstrated exceptional catalytic performance in these transformations. The well-defined coordination environment of metal nodes facilitates controlled electron transfer processes, enabling high selectivity in oxidation reactions such as alcohol-to-aldehyde/ketone conversion, alkene epoxidation, and oxidative coupling.

In reduction chemistry, MOF-based catalysts have been effectively employed in hydrogenation and transfer hydrogenation reactions, including the reduction of nitroarenes to anilines—key intermediates in drug synthesis. The confined

microenvironment within MOF pores plays a crucial role in stabilizing reactive intermediates and preventing over-reduction, thereby enhancing chemoselectivity.

Recent advancements in photoactive and electroactive MOFs have further expanded their applicability, enabling redox transformations under mild and energy-efficient conditions. These systems utilize visible light or electrical potential to drive catalytic cycles, significantly reducing dependence on hazardous reagents and aligning with sustainable manufacturing paradigms.

#### 4.3 Multicomponent and Cascade Reactions

Multicomponent reactions (MCRs) and cascade (tandem) processes represent powerful synthetic strategies for constructing complex pharmaceutical scaffolds with high atom economy and operational simplicity. MOFs are particularly well-suited for these applications due to their ability to integrate multiple catalytic functionalities within a single, spatially organized framework.

The coexistence of Lewis and Brønsted acid sites, along with redox-active centers, enables MOFs to catalyze sequential transformations in a one-pot manner without the need for intermediate isolation (21). This significantly reduces solvent consumption, purification steps, and overall process time. MOF-catalyzed MCRs, such as Biginelli, Hantzsch, and Strecker reactions, have been extensively explored for the synthesis of biologically relevant heterocycles. The confinement effect within MOF pores further enhances cascade catalysis by stabilizing intermediates and directing reaction pathways toward desired products. Additionally, the spatial proximity of different active sites facilitates efficient substrate channeling, mimicking enzymatic systems and improving overall catalytic efficiency. Such features are highly advantageous in pharmaceutical synthesis, where process intensification and selectivity are critical.

#### 4.4 Asymmetric Synthesis of Active Pharmaceutical Ingredients (APIs)

The synthesis of enantiomerically pure compounds is of paramount importance in pharmaceutical chemistry, as the biological activity, efficacy, and safety of drugs are often enantioselective. MOFs provide a robust platform for asymmetric catalysis through the incorporation of chiral elements within their framework, either via enantiopure organic

linkers or through post-synthetic functionalization with chiral ligands and organocatalysts (22).

Chiral MOFs create well-defined asymmetric microenvironments that enable precise substrate orientation and selective transition state stabilization, resulting in high enantioselectivity. These systems have been successfully applied in a variety of asymmetric transformations, including hydrogenation, epoxidation, aldol reactions, and Michael additions.

A key advantage of MOF-based asymmetric catalysts lies in their heterogeneous nature, which allows for facile separation and reuse without significant loss of activity or selectivity. Furthermore, the integration of chiral functionalities with other catalytic features—such as Lewis acidity or redox activity—enables the development of multifunctional catalysts capable of performing complex, stereoselective transformations in a single framework.

### 5. Advanced MOF-Based Catalytic Systems

#### 5.1 Functionalized and Defect-Engineered MOFs

The progression of MOFs into high-performance catalytic platforms has been significantly advanced through deliberate structural engineering, particularly via functionalization and defect modulation. Functionalized MOFs are synthesized either through pre-designed linker modification or post-synthetic modification (PSM), enabling the incorporation of catalytically active moieties such as Brønsted acidic ( $-\text{SO}_3\text{H}$ ), basic ( $-\text{NH}_2$ ), redox-active, or chiral functionalities (23). This level of molecular precision allows fine-tuning of the electronic environment, steric accessibility, and spatial distribution of active sites, thereby optimizing catalytic performance for specific pharmaceutical transformations.

Defect engineering has emerged as a complementary strategy to enhance catalytic efficiency by introducing controlled structural imperfections, such as missing-linker or missing-cluster defects. These defects generate additional coordinatively unsaturated metal sites and can create hierarchical porosity, improving mass transport and substrate accessibility. Importantly, defect-induced heterogeneity can enhance catalytic turnover frequencies without sacrificing selectivity when carefully controlled. However, excessive defect density may compromise crystallinity and framework stability; thus, rational defect incorporation, supported by advanced characterization and

computational modeling, is essential for balancing activity and durability.

#### 5.2 Metal Nanoparticle@MOF Composites

Metal nanoparticle@MOF composites represent a synergistic integration of homogeneous-like activity with heterogeneous stability. In these systems, catalytically active nanoparticles (e.g., Pd, Pt, Au, Ru) are either encapsulated within MOF cavities or anchored to internal surfaces, leveraging the framework as a spatially confined host matrix. This confinement effect effectively suppresses nanoparticle aggregation, sintering, and leaching—key limitations in conventional nanoparticle catalysis. Beyond physical stabilization, the MOF environment can modulate the electronic properties of embedded nanoparticles through metal–support interactions, thereby influencing catalytic activity and selectivity. The well-defined pore architecture further enables size- and shape-selective substrate diffusion, enhancing reaction specificity in complex pharmaceutical systems. These composites have demonstrated exceptional performance in hydrogenation, oxidation, and cross-coupling reactions, often under mild and environmentally benign conditions.

From a sustainability perspective, nanoparticle@MOF systems offer improved catalyst longevity, reduced metal loading, and enhanced recyclability. Their structural versatility also allows for the rational design of multifunctional catalytic systems, where both the MOF matrix and the encapsulated nanoparticles contribute to catalytic activity in a cooperative manner.

#### 5.3 Enzyme–MOF Hybrid Catalysts

Enzyme–MOF hybrid systems represent a frontier in catalytic science, integrating the unparalleled selectivity of biocatalysts with the robustness and tunability of inorganic frameworks (24). Enzymes can be immobilized within MOFs via in situ encapsulation, covalent attachment, or adsorption, resulting in hybrid materials that retain high catalytic specificity while exhibiting enhanced resistance to thermal, chemical, and mechanical degradation.

The confined microenvironment of MOFs provides a protective matrix that preserves enzyme conformation and activity, even under conditions that would typically lead to denaturation. Simultaneously, the porous architecture facilitates efficient substrate diffusion and product release. These systems are

particularly advantageous for stereoselective transformations, including asymmetric reductions and hydrolytic processes, which are critical in the synthesis of enantiomerically pure pharmaceutical compounds.

Moreover, the integration of multiple enzymes within a single MOF framework enables the design of cascade biocatalytic systems, mimicking natural metabolic pathways. Such systems facilitate sequential transformations in a single reaction vessel, significantly improving process efficiency, reducing intermediate handling, and minimizing waste generation. This convergence of biocatalysis and materials engineering represents a powerful approach toward sustainable pharmaceutical synthesis.

### 5.4 MOFs in Continuous Flow Systems

The incorporation of MOF-based catalysts into continuous flow systems represents a transformative advancement toward industrial-scale, sustainable pharmaceutical manufacturing. Continuous flow processing offers distinct advantages over conventional batch operations, including enhanced heat and mass transfer, improved reaction control, increased safety, and seamless scalability.

MOFs are particularly well-suited for flow applications due to their high surface area, structural uniformity, and mechanical stability. When immobilized in fixed-bed reactors, monolithic structures, or microfluidic devices, MOFs enable continuous catalytic operation with high efficiency and minimal deactivation (25). Their tunable porosity ensures optimal contact between reactants and active sites, while their heterogeneous nature facilitates catalyst recovery and reuse.

The integration of MOFs into flow systems also enables process intensification, allowing multiple reaction steps to be combined into a single, continuous operation. This reduces solvent consumption, energy input, and waste generation, aligning closely with green chemistry principles. Furthermore, the compatibility of MOFs with emerging technologies such as photochemical and electrochemical flow systems expands their applicability in sustainable pharmaceutical synthesis.

## 6. Challenges and Limitations

### 6.1 Stability under Reaction Conditions

Notwithstanding the rapid advancement in MOF chemistry, framework stability under realistic catalytic environments remains a critical bottleneck

for their industrial deployment. Many MOFs constructed from relatively labile metal–ligand coordination bonds—particularly those based on divalent metals such as  $Zn^{2+}$  and  $Cu^{2+}$ —exhibit susceptibility to hydrolysis, ligand displacement, or structural collapse under conditions involving moisture, protic solvents, or extreme pH. Such degradation leads to loss of crystallinity, pore integrity, and ultimately catalytic activity.

Although frameworks incorporating high-valent metal clusters (e.g.,  $Zr^{4+}$ ,  $Ti^{4+}$ ,  $Al^{3+}$ ) demonstrate enhanced thermal and hydrolytic robustness due to stronger metal–oxygen bonds, maintaining long-term structural integrity under continuous catalytic operation remains non-trivial. Dynamic processes such as framework breathing, defect evolution, and pore blockage can further compromise performance over repeated cycles. Therefore, the rational design of ultra-stable MOFs—through ligand engineering, hydrophobic surface modification, and topology optimization—remains a priority for ensuring durability under industrially relevant conditions.

### 6.2 Metal Leaching and Toxicity Concerns

Metal leaching constitutes a significant challenge in MOF-based catalysis, particularly in pharmaceutical contexts where stringent regulatory limits are imposed on trace metal impurities in active pharmaceutical ingredients (APIs). The partial dissociation of metal nodes or migration of catalytically active species during reaction cycles can lead to contamination, thereby undermining both catalyst integrity and product safety.

Leaching is often exacerbated under harsh reaction conditions or in the presence of coordinating substrates and solvents that can destabilize metal–ligand interactions. Furthermore, the use of potentially toxic metals (e.g., Cr, Cd, or even residual Pd in coupling reactions) raises additional environmental and toxicological concerns. From a mechanistic standpoint, distinguishing between true heterogeneous catalysis and leached homogeneous species remains a critical issue, necessitating rigorous catalytic testing protocols (e.g., hot filtration tests, ICP analysis).

Current mitigation strategies include the use of strongly bound high-valent metal clusters, encapsulation of active species within robust frameworks, and surface passivation techniques. However, achieving complete suppression of

leaching while preserving catalytic accessibility and activity remains an ongoing challenge.

### 6.3 Scalability and Cost-Effectiveness

The translation of MOFs from laboratory-scale materials to industrial catalysts is significantly constrained by challenges associated with scalable and economically viable synthesis. Conventional solvothermal and hydrothermal methods often involve dilute reaction conditions, expensive organic linkers, high energy input, and the use of toxic or non-recyclable solvents. These factors collectively limit production throughput and increase material costs.

Moreover, maintaining batch-to-batch reproducibility in terms of crystallinity, particle size distribution, defect density, and surface functionality is inherently challenging at scale. Variations in these parameters can lead to inconsistencies in catalytic performance, which is unacceptable in pharmaceutical manufacturing.

Emerging synthesis strategies—including mechanochemical methods, microwave-assisted synthesis, continuous flow MOF production, and solvent-free routes—offer promising alternatives for reducing cost and environmental impact. However, these methods require further optimization and standardization to ensure scalability without compromising structural and functional integrity. Additionally, lifecycle considerations, including catalyst longevity and regeneration efficiency, are essential for establishing the economic competitiveness of MOF-based systems relative to conventional catalysts.

### 6.4 Industrial Applicability Constraints

Beyond intrinsic material limitations, several engineering and regulatory challenges hinder the integration of MOFs into industrial pharmaceutical processes. One major issue is the physical form of MOFs; they are typically synthesized as fine powders, which are not directly compatible with industrial reactor configurations due to issues related to pressure drop, mechanical attrition, and handling. Shaping strategies such as pelletization, extrusion, or incorporation into structured supports must be carefully designed to preserve porosity and catalytic activity.

Mass transport limitations also present a significant challenge, particularly for reactions involving bulky pharmaceutical intermediates. While hierarchical and mesoporous MOFs can alleviate diffusion

constraints, achieving optimal pore architecture without compromising structural stability remains complex.

Catalyst deactivation mechanisms—including fouling, pore blockage, and structural degradation—can further impact long-term performance under continuous operation. Additionally, integration into existing process infrastructure (e.g., fixed-bed or flow reactors) requires careful consideration of hydrodynamics, heat transfer, and catalyst packing. From a regulatory standpoint, the adoption of MOF-based catalysts in pharmaceutical manufacturing necessitates rigorous validation to ensure compliance with Good Manufacturing Practices (GMP), reproducibility, and product safety. The absence of standardized protocols for MOF synthesis, characterization, and catalytic evaluation further complicates their industrial acceptance.

## 7. Future Perspectives and Emerging Trends

### 7.1 AI and Machine Learning in MOF Design

The application of artificial intelligence (AI) and machine learning (ML) is redefining the landscape of MOF discovery and catalytic optimization by enabling data-driven, predictive materials design. The immense combinatorial diversity of MOFs—arising from the multitude of possible metal nodes, organic linkers, and topologies—renders conventional empirical approaches inefficient. In this context, ML models trained on experimental datasets and high-throughput computational outputs (e.g., density functional theory, DFT) are increasingly employed to predict structure–property relationships, including stability, adsorption behavior, catalytic activity, and selectivity.

Advanced methodologies, such as graph neural networks, generative adversarial networks, and inverse design frameworks, are facilitating the rational design of MOFs with targeted functionalities. These approaches enable rapid virtual screening of candidate structures, significantly reducing experimental workload and accelerating discovery cycles. Importantly, AI-assisted design can be leveraged to optimize key parameters relevant to pharmaceutical catalysis, such as minimizing metal leaching, enhancing enantioselectivity, and improving resistance to hydrolytic degradation. As curated databases and interoperable data infrastructures expand, AI-driven strategies are

expected to become integral to next-generation catalyst development.

### 7.2 Green and Sustainable Synthesis Routes for MOFs

While MOFs are widely recognized for their role in green catalysis, the sustainability of their own synthesis is an equally critical consideration. Traditional solvothermal routes often involve high temperatures, long reaction times, dilute conditions, and the use of toxic organic solvents, thereby diminishing the overall environmental benefits of MOF-based systems. Consequently, there is a strong impetus toward developing greener, energy-efficient, and scalable synthetic methodologies.

Emerging approaches such as mechanochemical (solvent-free) synthesis, microwave-assisted synthesis, electrochemical methods, and aqueous-phase synthesis offer significant reductions in energy consumption, solvent usage, and reaction time. The utilization of renewable or waste-derived organic linkers, as well as low-cost and earth-abundant metal precursors, further aligns MOF production with circular economy principles. Continuous flow synthesis of MOFs is also gaining traction as a means to achieve high reproducibility, scalability, and process control.

A critical challenge lies in ensuring that these green synthesis routes do not compromise structural integrity, crystallinity, or catalytic performance. Future research must therefore focus on optimizing these methods to achieve a balance between sustainability, scalability, and functional performance.

### 7.3 Integration with Industrial Processes and Technologies

The successful translation of MOF-based catalysts into pharmaceutical manufacturing requires their seamless integration into industrial process architectures. Advances in materials engineering—such as pelletization, extrusion, 3D printing, and the development of MOF-based monoliths and membranes—are enabling improved mechanical stability and compatibility with industrial reactor systems, including fixed-bed, packed-bed, and microreactor configurations.

The convergence of MOF catalysis with continuous flow processing represents a particularly promising avenue for process intensification. Continuous flow systems offer superior heat and mass transfer,

enhanced safety, and precise control over reaction parameters, making them highly suitable for pharmaceutical production. MOFs, with their high surface area and tunable porosity, are well-positioned to function as immobilized catalysts in such systems, enabling long-term, stable operation.

Furthermore, the integration of MOFs with hybrid catalytic platforms—combining thermal, photochemical, and electrochemical processes—opens new possibilities for energy-efficient and multifunctional reaction systems. The incorporation of digital technologies, including real-time monitoring, process automation, and feedback control, will further enhance the reliability and scalability of MOF-based processes.

### 7.4 Outlook for Sustainable Pharmaceutical Manufacturing

Looking forward, MOFs are poised to play a transformative role in advancing sustainable pharmaceutical manufacturing. Their unparalleled structural tunability, capacity for multifunctional catalysis, and compatibility with green chemistry principles position them as key enablers of next-generation catalytic processes. The development of ultra-stable, defect-engineered, and hierarchically porous MOFs capable of operating under industrially relevant conditions will be critical for their widespread adoption.

Future research is expected to focus on the design of integrated catalytic systems capable of performing multi-step transformations within a single framework, thereby enabling true process intensification. The synergy between MOF chemistry and emerging technologies—such as AI-driven materials discovery, biocatalysis, and renewable energy-based catalysis—will further expand their functional scope and efficiency.

Importantly, comprehensive lifecycle assessment (LCA) and techno-economic analysis (TEA) will be essential to evaluate the sustainability and commercial viability of MOF-based processes across the entire production chain. Collaborative efforts among academia, industry, and regulatory agencies will be crucial in establishing standardized protocols, ensuring reproducibility, and facilitating regulatory acceptance.

In conclusion, while challenges related to stability, scalability, and integration persist, the future trajectory of MOFs in pharmaceutical synthesis is

highly promising. Continued interdisciplinary innovation is expected to unlock their full potential, enabling the development of efficient, selective, and environmentally benign catalytic systems that can redefine the paradigm of pharmaceutical manufacturing.

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