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Perspective

Opportunities and Challenges of Metal–Organic Framework Micro/Nano Reactors for Cascade Reactions

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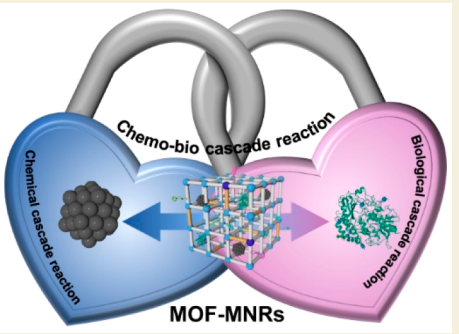
ABSTRACT: Building bridges among different types of catalysts to construct cascades is a highly worthwhile pursuit, such as chemo-, bio-, and chemo–bio cascade reactions. Cascade reactions can improve the reaction efficiency and selectivity while reducing steps of separation and purification, thereby promoting the development of "green chemistry". However, compatibility issues in cascade reactions pose significant constraints on the development of this field, particularly concerning the compatibility of diverse catalyst types, reaction conditions, and reaction rates. Metal–organic framework micro/nano reactors (MOF-MNRs) are porous crystalline materials formed by the self-assembly coordination of metal sites and organic ligands, possessing a periodic network structure. Due to the uniform pore size with the capability of controlling selective transfer of substances as well as protecting active substances and the organic–inorganic parts providing reactive microenvironment, MOF-MNRs have attracted significant attention in cascade reactions in recent years. In this Perspective, we first discuss how to address compatibility issues in cascade reactions using MOF-MNRs, including structural design and synthetic strategies. Then we summarize the research progress on MOF-MNRs in various cascade reactions. Finally, we analyze the challenges facing MOF-MNRs and potential breakthrough directions and opportunities for the future.



KEYWORDS: *Metal–organic framework, micro/nano reactor, biocatalysis, chemo-catalysis, cascade reaction*

1. INTRODUCTION

Catalysis technology is a fundamental pillar of the chemical and energy industries. Most chemical reactions that are industrially significant rely on catalysts to boost reaction rates and enhance selectivity and efficiency. Similarly in living organisms, metabolic processes depend on the catalytic activity of enzymes or organisms to achieve the desired transformations. Currently, more than 90% of chemical production is facilitated by catalysts. In recent decades, the concept of "green chemistry" has gained popularity and captured attention for energy conservation and clean product generation. Meanwhile, avoiding or eliminating environmental pollution has become a key development direction for catalytic technology.[1−3]

Cascade reactions refer to reaction systems where multiple chemical reactions occur sequentially or simultaneously within a single reaction system.[4,5] Cascade reactions reduce the separation and purification steps in traditional multistep reactions, which can increase the utilization of raw materials, reduce the generation of byproducts and waste, lower energy consumption, and avoid environmental pollution. Additionally, the synergistic effect of multiple catalysts can effectively prevent unfavorable reaction equilibria and overcome problems such as unstable or difficult-to-handle intermediates, leading to improved reaction activity and selectivity (Scheme 1).[6,7] Hence, cascade reactions are considered a promising research area in green chemistry with wide-ranging applications and huge potential for innovation. Depending on the catalysts involved, they can be classified into chemical, biological, and chemo–bio cascade reactions, which have been successfully applied in traditional thermal catalysis, photocatalysis, and electrocatalysis.[8−10] During the reaction, multiple catalysts may complement each other. This advantage inspires researchers to design novel pathways and prepare high-value-added products more efficiently.[11] For example, as an important intermediate for synthesizing various resins and dye molecules, glycerol dehydration is used in the industrial production of glycerol and gluconic acid from glucose. Traditionally in a chemical method, zinc sulfate is used as the catalyst at 215 °C under harsh conditions, often leading to limited product yields.[12] While in a chemo–bio cascade reaction, glucose can be

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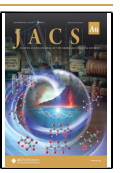

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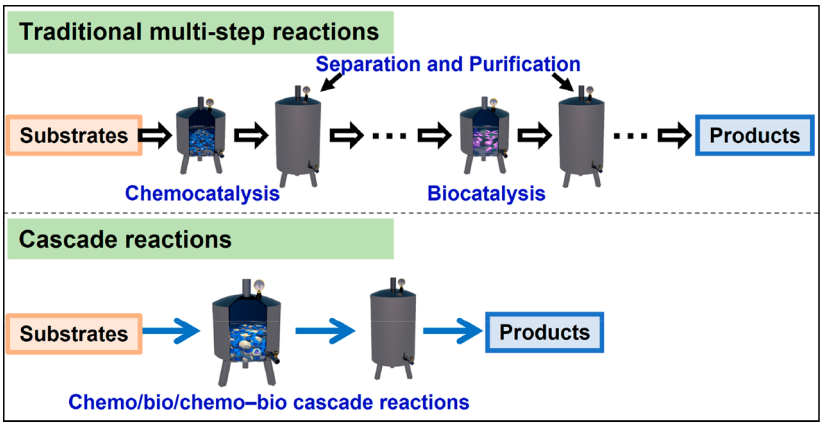
Scheme 1. Schematic Comparison between Traditional Multi-step Reactions and Cascade Reactions



converted to furanose using oxidoreductase enzymes, which produce hydrogen peroxide under mild conditions. This hydrogen peroxide then serves as an oxidant for the titanium metal catalyst to catalyze the oxidation of allyl alcohol and produce glycerol, achieving byproduct recycling.[13]

However, a major challenge facing cascade catalysis is the compatibility issues among different reaction steps.[14−16] The incompatibility of cascade reactions can be divided into several aspects. (1) Catalyst deactivation: some chemo-catalysts or enzymes may lose activity during the cascade reaction, leading to decreased efficiency or stoppage. This is a common phenomenon in enzyme catalysis mainly due to inhibitors (such as chemo catalysts, metal ions, and organic molecules) in the reaction environment. (2) Reaction condition mismatch: different reaction steps in cascade reactions may require different conditions, such as varying temperatures, pH values, and solvents. These conditions are difficult to satisfy simultaneously in one system, which can affect the reaction progress. Biocatalysts generally work under mild conditions with aqueous solvents, while chemical catalysts need harsher conditions like high temperatures, high pressures, strong acids or bases, and multiple organic phases. This makes it difficult for chemical reactions catalyzed by chemical catalysts to occur in the presence of mild biocatalysts, whereas many biocatalysts can lose activity under the demanding reaction conditions of chemical catalysts, resulting in failed chemical−enzyme catalyzed reactions. (3) Reaction rate mismatch: different reaction steps in cascade reactions may have different reaction rates which can cause imbalance, byproduct generation, or reduced yield if the rate is too fast or slow. For example, temperature is one of the important factors affecting the reaction rate and catalyst activity. In cascade reactions, the reaction conditions are often balanced. Endeavors to increase the temperature for certain chemical catalyst reactions may be accompanied by decreased biocatalyst activity or even deactivation, rendering it ineffective and resulting in increased production costs. Conversely, maintaining biocatalyst activity by conducting reactions at lower temperatures can result in slower reaction rates or no reaction at all, limiting the range of chemical reactions and the selection of chemical catalysts.

In recent years, significant efforts have been devoted to tailoring and optimizing catalysts for coexisting multiple types of catalytic functions in cascade reactions.[17−20] Inspired by biological systems, compartmentalized units with functionalities such as selective substance transport control, active species protection, substrate exchange facilitation, and microenvironment provision have garnered considerable attention in the field of cascade catalysis. The biological system is a coordinated and integrated entity where each unit possesses its unique structure and function, collaborating with others to achieve complex life activities. Rational separation can establish independent internal microenvironments while preventing interference from external substances. Identification and transmission enable cells to safeguard their internal environment and facilitate energy transfer. Communication can establish material connections between individual cells, thereby constructing a cohesive network for cellular interactions.[21,22] The micro/nano reactors (MNRs) are miniaturized chemical reactors designed at the micro- or nanoscale based on the principles of compartmentalized units. They possess the capability to create internal microenvironments and regulate substance transport at the micro/nano scale. They are considered crucial materials for expanding the range and possibilities of cascade reactions. MNRs spatially isolate multiple catalysts by immobilizing one type of catalyst on a carrier and confining it within the carrier's pores, while simultaneously restricting its contact with other catalysts.[18] This allows for precise control over reactant and product transport, preventing any potential incompatibilities.

Typically, the design and synthesis of MNRs adhere to several principles: (1) possessing a large specific surface area and ample space for catalyst accommodation; (2) exhibiting high stability to prevent structural collapse or side reactions while maintaining catalyst activity and stability, particularly for delicate biological catalysts; and (3) being recyclable with a straightforward and cost-effective preparation process. MNRs are typically novel composite catalyst materials with cell-like structures that are self-organized from molecules such as liposomes, polymer particles, and colloids. These reactors possess relatively independent internal spaces that promote catalysis. The shell structure can isolate different types of catalysts, providing separation and protection, while the semipermeable shell characteristics facilitate reactant and product diffusion transport.[19,23−25]

Metal−organic frameworks (MOFs) represent a highly promising class of materials that can satisfy the design requirements for MNRs (Scheme 2). MOFs are porous crystalline solids with a periodic network structure resulting from the self-assembly coordination between metal sites (metal ions or clusters) and organic ligands. The tunability of both metal sites and organic ligands enables precise optimization and regulation of the pore size and microenvironment of

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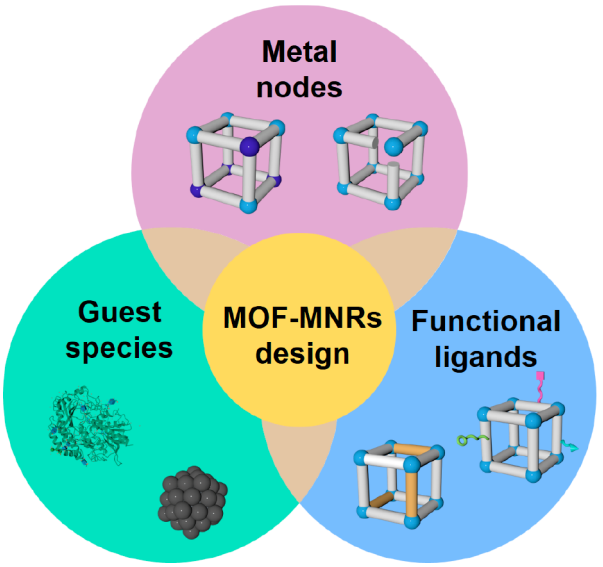
Scheme 2. Schematic Illustration of the Active Site Design of MOFs Employed for MNRs



MOFs to suit specific application scenarios. The periodic network structure endows MOFs with uniform pore size, which provides unique structural advantages in selective catalysis and separation.[26] Among them, in the field of catalysis, MOFs not only provide highly dense metal sites and modifiable ligand molecules that can be used as catalytic active sites but also offer the possibility of combining guest functional species into its framework to achieve more effective composite construction.[27,28] Therefore, utilizing MOFs to construct MNRs has significant benefits in reactant separation and protection as well as material transport control.

Currently, extensive studies have been conducted to develop diverse MOF micro/nano reactors (MOF-MNRs) that have found widespread applications in cascade catalysis, drug delivery, sensing, dye degradation, and other fields.[29,30] These reactors enable controlled transport of reactant molecules and ensure stable overall catalytic activity in cascade reactions. Compared to other types of MNRs such as liposomes, hollow silica nanoparticles, capsules, and polymer vesicles, the internal cavities of MOF-MNRs can overcome pore size limitations and provide distinct catalytic reaction spaces for various substances, including enzymes, biomolecules, metal catalysts, and organic molecules. On the other hand, the uniform pores of the external MOF layer not only provide protection and stability for the catalyst but also offer an alternative loading site for catalysts that can segregate and safeguard incompatible catalysts while regulating reactant transport to ensure the seamless progress of catalytic reactions at different locations, thereby enabling cascade reactions. Therefore, MOF-MNRs possess unique structural characteristics that render effective encapsulation, controlled transport, and separation, as well as intercommunication. These features provide significant advantages and broad prospects for addressing compatibility challenges in cascade reactions.

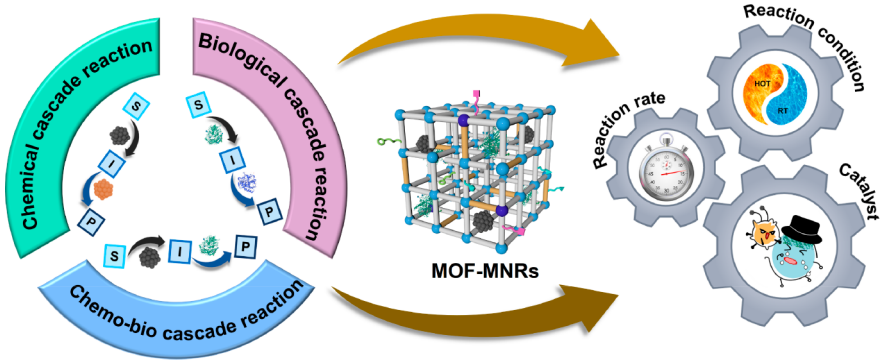
In this Perspective, we initially provide a summary of the types and methods used to synthesize MOF-MNRs. Various synthetic strategies have been employed to construct MOF MNRs with multiple active sites for catalysis. Subsequently, this Perspective emphasizes the potential of MOF-MNRs in addressing challenges posed by incompatible multistep chemical cascade reactions, biological cascade reactions, and chemo−bio cascade reactions. Finally, the current challenges faced by MOF-MNRs and potential breakthrough directions are discussed (Scheme 3).

2. CONSTRUCTION STRATEGY OF MOF-MNRS

The field of MOF-MNRs has undergone rapid development in recent years, which can be attributed to the unique properties of MOFs. These include highly dense metal sites and easily modifiable ligand molecules that can serve as catalytically active sites. Additionally, the tunable pore size and uniform porous structure of MOFs enable the efficient incorporation of guest functional molecules such as metal nanoparticles (MNPs), enzymes, organometallic complexes, and heteropoly acids.[31−33] By incorporating guest functional molecules into the MOF structure, the pore architecture will provide confinement effects that protect functional materials from aggregation and leaching, while simultaneously facilitating reactant and product transfer in catalytic reactions. Several reviews have already been published concerning the preparation strategies for MOF composite materials.[27,34,35] In this section, we summarize the preparation strategies for MOF-MNRs with multiple active centers for cascade reactions, focusing specifically on the spatial separation design of various catalytic sites within these reactors and the key points involved in their synthesis and preparation process.

To achieve cascade reactions, the active sites of MOF-MNRs with multifunctional sites can be mainly classified into four categories: (1) ligands with multiple active sites; (2) functional

Scheme 3. Schematic Illustration of the Construction Strategy for MOF-MNRs with Multiple Active Sites and Their Application in Different Types of Cascade Reactions



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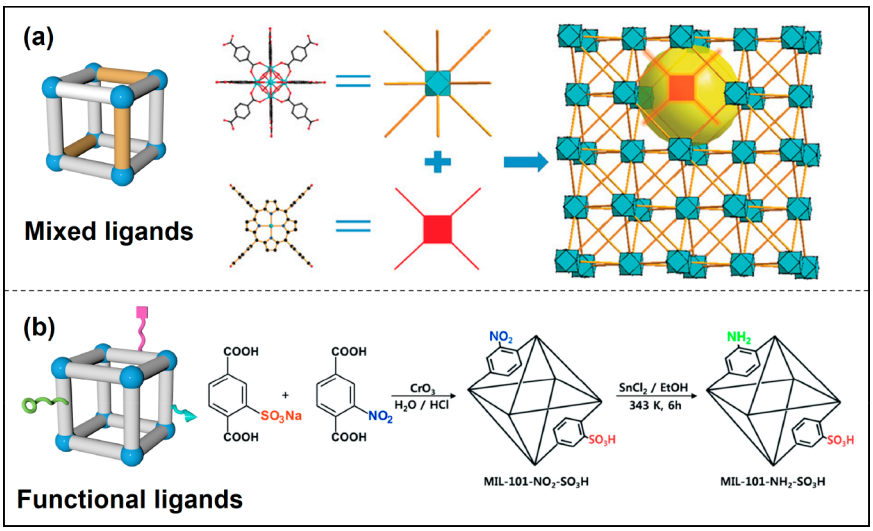

Figure 1. Design and synthesis of MOF-MNRs with organic ligands as active sites. (a) Schematic illustration of UiO-66 incorporating TCPP as well as the usual Zr_6 clusters. Adapted with permission from ref 41. Copyright 2016 John Wiley and Sons. (b) Preparation of the site-isolated acid−base bifunctional catalyst, MIL-101−NH_2−SO_3H. Adapted with permission from ref 44. Copyright 2014 Royal Society of Chemistry.

ligands and metal nodes; (3) various guest functional molecules; and (4) coassembled guest functional molecules with MOF functional sites. Similar to the preparation strategies of single-component MOFs, the synthetic strategies for MOFs nanoreactors are mainly divided into in situ and post-modification methods. The types and synthetic methods of MOF-MNRs are introduced in detail in the following parts.

2.1. Design of MOF-MNRs with Organic Ligands and Metal Clusters as Active Sites

Since MOF-MNRs can be precisely synthesized by selecting the desired building blocks, a variety of functions can be enabled. Until now, different combinations of multi-ligands and multi-metal sites/clusters in MOF-MNRs have been achieved to promote cascade reactions.[36−40] First, the diverse selection of ligands endows them with various unique characteristics. For instance, Zhou et al. reported a facile one-pot method for synthesizing Zr-MOF (Figure 1a).[41] In this method, tetratopic tetrakis(4-carboxyphenyl) porphyrin (TCPP) ligands were successfully integrated into UiO-66 while maintaining the crystal structure, morphology, and ultrahigh chemical stability of UiO-66. This strategy provides a straightforward approach to introducing multiple functional ligands into stable Zr-MOFs. The incorporation of diverse ligands can expand the potential for designing active sites in MOF-MNRs. For instance, BDC ligands may be functionalized with hydroxy group, amino group, and sulfonic group, while TCPP ligands can serve as one of the active sites by coordinating with various metals (Ni, Fe, Cu, Mn, and Co). Compared to UiO-66, UiO-66 with FeTCPPCl exhibited superior catalytic activity in the oxidation of 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS). However, when employing a mixed ligand strategy, it is crucial to take into account the coordination structure of MOFs to ensure that the ligands possess similar geometry and connectivity, thereby avoiding the formation of mixed phases.[42] This limitation significantly impacts the development and design of multi-ligand MOFs.

Another approach involves functionalizing different active centers on the original ligands in MOF-MNRs to create a multi-site reaction platform for cascade reactions.[43] Due to the unique structure of MOFs, incompatible functional groups can still be incorporated and assembled within the single MOF-MNR. For instance, Ahn et al. synthesized a multi-ligand MIL-101(Cr)−NO_2−SO_3H incorporating monosodium 2-sulfoterephthalate (H_2BDC−SO_3Na) and 2-nitrobenzene−1,4-dicarboxylic acid (H_2BDC−NO_2). Subsequently, they reduced the NO_2 groups in the product to NH_2 groups using $SnCl_2$, leading to the formation of MIL-101−NH_2−SO_3H (Figure 1b).[44] This material, serving as a dual-function Brønsted acid−base catalyst, was employed in a one-pot cascade deacetalization−nitroaldol reaction. The coexistence of acid and base sites in the MOFs, which is challenging to achieve in homogeneous catalysts, makes them promising catalysts for cascade reactions.

The distinct properties inherent to metal sites in different MOFs often exhibit specific catalytic activity and selectivity in various catalytic reactions. In the process of synthesizing MOFs, the selection of metal sites can encompass almost all metallic elements in the periodic table, enabling researchers to tailor suitable MOF catalysts for specific reactions.[45−48] The design of metal sites/clusters as active centers in MOF-MNRs can be classified into two strategies: (1) the formation of unsaturated coordination sites, which can also be regarded as the introduction of structural defects; (2) the incorporation of multiple metallic sites into the structure.

In studies aimed at regulating the number of defects in MOF-MNRs, a commonly employed strategy for inducing structural defects is to incorporate modulators such as monocarboxylic acid ligands (e.g., acetic and formic acids) during MOF synthesis.[49] Modulators serve two primary functions in the MOF-MNRs synthesis. First, a small quantity of modulators can decrease the nucleation and growth rate of MOF crystals, resulting in high-quality crystals. Second, a higher concentration of modulators is involved in the coordination process of MOFs, competing with the original ligand for coordination and promoting rapid nucleation and crystal growth while also leading to defects.[50] For example, Lillerud et al. investigated the impact of various modulators on defects in UiO-66 structure and found that Brønsted acidity plays a significant role in regulating the number of defects (Figure 2a).[51] Trifluoroacetic acid, with its lower pK_a value,

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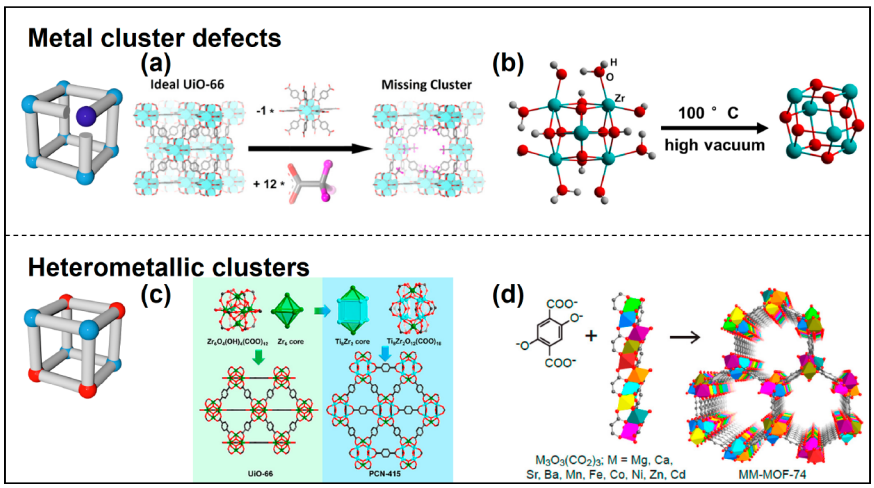

Figure 2. Design and synthesis of MOF-MNRs with metal clusters as active sites. (a) Schematic illustration of the structural and compositional differences between the ideal UiO-66 unit cell and those with missing cluster/missing linker defects. Adapted with permission from ref 51. Copyright 2016 American Chemical Society. (b) Structural changes of the secondary building units of NU-1000. Adapted with permission from ref 52. Copyright 2018 American Chemical Society. (c) Combination of two metals into a bimetallic cluster to synthesize bimetallic PCN-415 (Zr/Ti). Adapted with permission from ref 53. Copyright 2018 American Chemical Society. (d) Combination of ten metal ions to synthesize heterometallic MOF-74. Adapted with permission from ref 54. Copyright 2018 American Chemical Society.

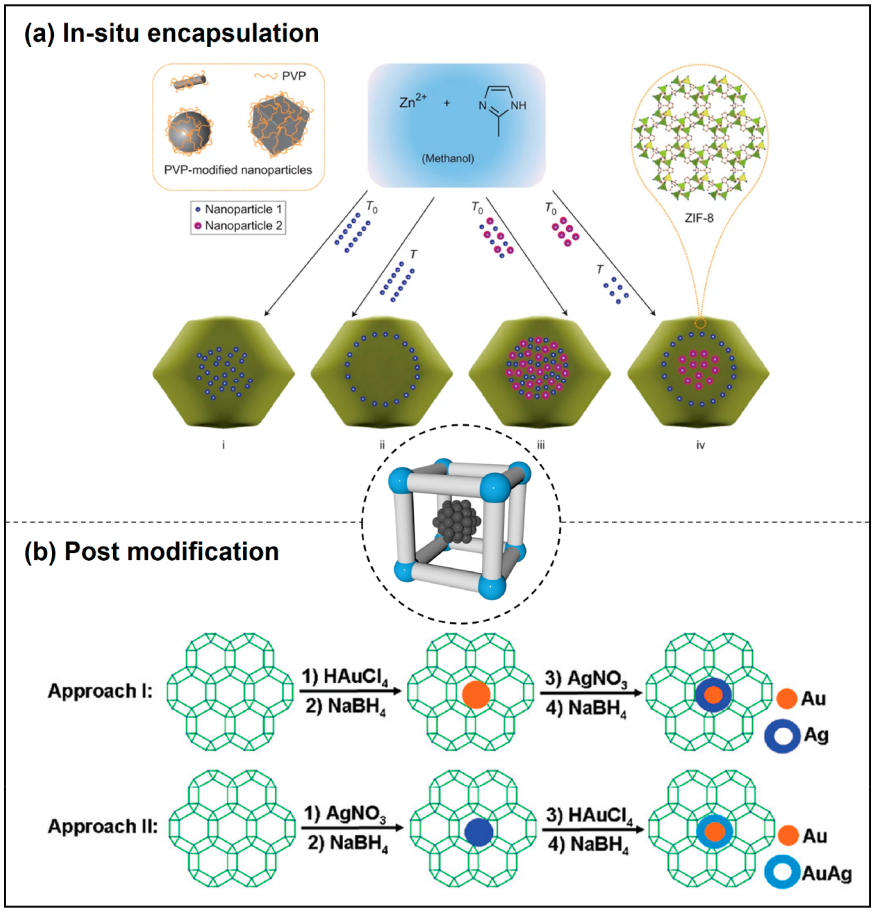

Figure 3. Preparation strategies for incorporating multiple types of MNPs. (a) Schematic illustration of the controlled encapsulation of nanoparticles in ZIF-8 crystals. Adapted with permission from ref 59. Copyright 2012 Springer Nature. (b) Preparation of Au@Ag core−shell NPs on the ZIF-8 support. Adapted with permission from ref 64. Copyright 2011 American Chemical Society.

produced more defects during synthesis and resulted in a material with a higher reactivity. In addition, the utilization of poor solvents and extreme activation procedures, particularly high temperature, during the postprocessing of MOFs can generate a significant number of defects. For example, Mircea Dincă et al. found that NU-1000 can be activated to expose stronger Lewis acid sites by removing coordinated H_2O and hydroxyl groups under high temperature and vacuum treat-

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ment (Figure 2b).[52] The incorporation of multiple metallic sites into the MOF-MNRs' structure is a viable strategy for regulating the properties of metal sites as active sites. Different metal ion salts are primarily used as precursors to interact with ligands and form MOF structures. Zhou et al. synthesized a bimetallic MOF, PCN-415 (Zr/Ti). In this structure, Zr metal clusters provide anchoring sites for Ti metal ions and maintain framework stability, while Ti metal sites serve as active sites participating in photocatalytic reactions, thereby enhancing the catalytic activity of the MOF (Figure 2c).[53] Yaghi et al. utilized MOF-74 to synthesize multi-component MOFs containing up to ten different metals (Figure 2d).[54] The introduction of additional metal sites can modulate the electronic properties of active sites, thus improving the reaction activity. However, this approach necessitates precise control of reaction conditions and a strict selection of metal salts, that is, different metal salts with similar binding strength and kinetics with the ligands, or otherwise, single-metal MOFs may form instead of bimetallic MOFs, even polycrystalline MOFs. The preparation strategies for these MOFs with active sites provide a foundation for the integration with guest functional molecules.

2.2. Design of MOF-MNRs with Multi Guest Species as Active Sites

In addition to the self-structural adjustment of MOFs as active sites in cascade reactions, the introduction of guest molecules into the MOF structure plays a central role in the development of this field. Importantly, the introduction of various types of guest molecules expands the potential applications of MOF-MNRs in diverse cascade reactions. Compared to incorporating a single guest molecule, introducing multiple types requires careful consideration of their existence states within MOFs and their interactions with each other.[55,56] In this section, we primarily discuss the preparation strategies and challenges involved in incorporating multiple types of MNPs and/or enzymes into MOFs. The synergistic interactions between single guest molecules and MOF active sites for cascade reactions will be explored in dedicated sections.

2.2.1. MOF-MNRs with Multi MNPs as Active Sites. At present, strategies for in situ synthesis of MNPs in MOFs mainly comprise coprecipitation, seed-mediated growth, colloidal methods, and mechanical grinding.[34,57,58] The fundamental concept behind this approach is to presynthesize nanoparticles or metal clusters and combine them with metal sites or ligands through designed binding sites during the nucleation and growth process of MOFs, resulting in the in situ formation of MNPs/MOF composites. The advantages of this approach lie in the ability to control nanoparticle growth conditions, which can overcome limitations in the MOF particle size and enable the production of MNPs with varying compositions, sizes, and morphologies. Additionally, the positioning of MNPs within the MOFs is relatively controllable, allowing for complete encapsulation within the MOF structure. For instance, Huo et al. utilized an in situ encapsulation strategy to confine diverse nanomaterials within MOFs (Figure 3a).[59] Initially, nanoparticles with varying sizes, compositions, and morphologies were presynthesized with the participation of a surfactant, polyvinylpyrrolidone (PVP). These nanoparticles were surface-coated with PVP, which served as the nucleation sites for ZIF-8. This allowed the adsorption of Zn ions and 2-methylimidazole ligands on the nanoparticle surfaces for coordination. As a result, complete encapsulation of the nanoparticles within the MOFs was achieved through the growth of ZIF-8 around them. Furthermore, this approach facilitated the regulation of the addition timing of nanoparticles to the MOF synthesis solution, thereby controlling the spatial distribution of nanoparticles within MOFs. The findings indicated a correlation between the nanoparticle distribution and addition time. Generally, early addition of nanoparticles resulted in their primary distribution within the innermost structure of ZIF-8 particles, whereas intermediate addition led to their distribution in the outer space of the ZIF-8 particles. This approach facilitated encapsulation of Pt NPs, CdTe NPs, Fe_3O_4 NPs, La-doped $NaYF_4$ NPs, Ag nanocubes, polystyrene microspheres, β-FeOOH nanorods, and La-doped $NaYF_4$ nanorods within ZIF-8 for diverse guest molecule introduction.

The strategies for postmodification of MNPs loading primarily encompass ion exchange, impregnation, double-solvent method, and vapor deposition. Essentially, this approach employs MOFs as templates to facilitate the formation of MNPs within the pores or cavities via reduction or insertion methods. Vapor deposition is initially utilized for synthesizing MNP/MOF composites due to the high volatility of most organometallic precursors, which can easily sublime at elevated temperatures and infiltrate into the exposed cavities and pores of activated MOFs. Subsequently, the generated MNPs are encapsulated within the MOF framework via high temperature, chemical treatment, ultraviolet (UV) irradiation, or reductive gas treatment.[60,61] The advantage of this method lies in the absence of solvent involvement, which enhances the loading capacity of MNPs in MOFs. Fischer's research group conducted systematic studies on this method. They successfully prepared MNPs/MOF-5 composites. During the preparation process, metal precursors were dispersed within the MOF-5 framework via vapor deposition. Subsequently, hydrogenation of these precursors resulted in uniform dispersion of nanoparticles throughout MOF-5. Fe, Pt, Pd, Au, Cu, Zn, and Sn NPs were successfully incorporated into the pores of MOF-5 to form MNPs/MOF composites.[62,63] Solution impregnation is a widely employed and straightforward method for synthesizing MOF-based composites, similar to the preparation of traditionally supported heterogeneous catalysts. In this approach, metal precursors are added to a solution containing MOFs, and capillary action drives them into the internal voids of MOFs with sufficient kinetic energy for uniform dispersion throughout the entire structure. Following that, the metal precursors undergo reduction to form MNPs, and the size and morphology of in situ-generated MNPs are primarily determined by the cavity structure of MOFs. Xu et al. first developed a double-solvent impregnation method for synthesizing Au@Ag/ZIF-8 composites with bimetallic nanoparticles (Figure 3b).[64] In this synthetic method, they initially introduced Au precursors into the ZIF-8 structure and then reduced. Utilizing the obtained Au NPs, Ag NPs were introduced as a second noble metal precursor via the same impregnation method, resulting in core−shell structured Au@Ag NPs confined within the MOF cavities.

2.2.2. MOF-MNRs with Multi Enzymes as Active Sites. In addition to loading chemical catalysts, the encapsulation of biocatalysts, such as enzymes within MOFs is crucial for utilizing MOF-MNRs in multi-enzyme cascade reactions and chemo−bio cascade reactions. There are several strategies for fabricating enzymes/MOFs MNRs such as coprecipitation, surface immobilization, infiltration, and MOF-assembled capsules.[65−67] In contrast to the loading of MNPs, enzyme

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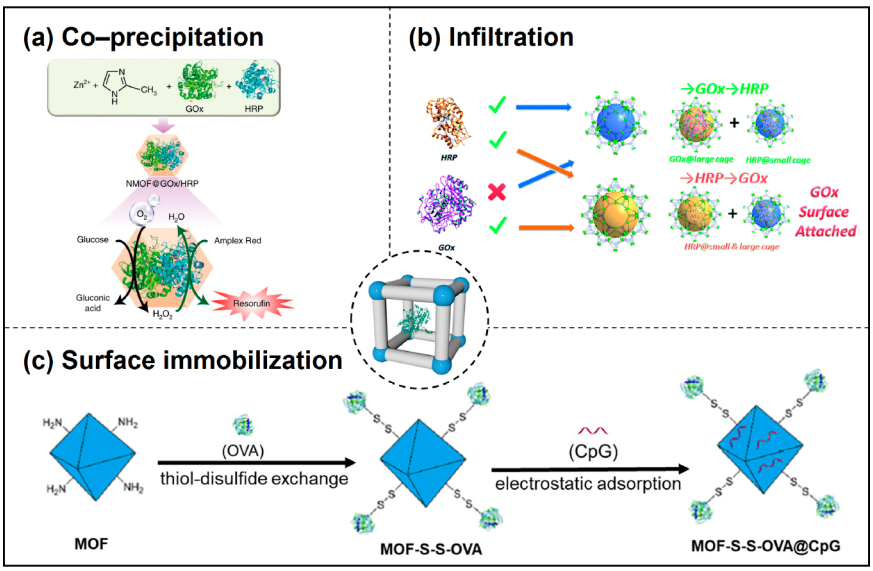

Figure 4. Preparation strategies for incorporating multiple types of enzymes. (a) Fabrication of the dual enzyme-functionalized ZIF-8 MNRs. Adapted with permission from ref 72. Copyright 2018 Springer Nature. (b) Stepwise encapsulation of GOx and HRP following different orders through an infiltration method. Adapted with permission from ref 73. Copyright 2016 Royal Society of Chemistry. (c) Schematic illustration of the preparation of a MOF-based antigen delivery system. Adapted with permission from ref 76. Copyright 2018 American Chemical Society.

loading is typically conducted under mild conditions such as aqueous solution, close to ambient temperature, atmospheric pressure, and neutral pH.[68,69]

2.2.2.1. Coprecipitation. The coprecipitation strategy facilitates the simultaneous growth of MOFs and the immobilization of enzymes within a one-step reaction system. The synthesis involves mixing MOF precursors together, including metal salts and organic ligands, enzymes, reaction solvents, and sometimes surface modifiers such as PVP.[70,71] Enzymes act as nucleation sites for MOFs growth, facilitating the simultaneous formation of MOFs and the confinement of enzymes. This approach effectively addresses the issue of the size disparity between enzymes and MOF pores. An illustrative instance of this approach was devised by Willner et al., in which ZIF-8 served as nanoreactors for the encapsulation of two or three enzymes, leading to enhanced activity and stability of cascade reactions. Ge et al. reported the coencapsulation of lactate oxidase and horseradish peroxidase (HRP) in amorphous MOFs, forming multi-enzyme MOF-MNRs that exhibit high activity and selectivity for the intracellular detection of the important metabolite lactate (Figure 4a).[72] The utilization of surfactants can facilitate the dispersion and stabilization of enzymes in solution as well as provide additional heterogeneous nucleation sites for MOF growth. For instance, Liu et al. presented a typical demonstration of enzyme encapsulation through coprecipitation with PVP. A mixture containing both cytochrome (CytC) and PVP was introduced into a methanol solution comprising zinc nitrate hexahydrate and 2-methylimidazole, followed by stirring at room temperature to obtain ZIF-8 crystals embedded with CytC. In situ synthetic strategies are typically conducted in liquid phase conditions. However, the synthesis of MOFs in a liquid phase often involves strong acids or organic solvents, which can result in enzyme deactivation and significantly limit the selection of enzymes and MOFs. Therefore, most studies prefer to use the ZIF series MOFs as carriers since they can be synthesized in biocompatible aqueous environments without requiring high temperatures. However, certain ligands present in ZIFs, such as 2-methylimidazole, have the potential to undergo protonation and create an alkaline environment within the aqueous phase. This may result in structural damage to enzymes.

2.2.2.2. Infiltration. With the aid of tunable porous structures and high surface area inherent in MOF architectures, enzymes can be immobilized within MOFs via postmodification techniques. In cases where the dimensions of these enzymes are smaller than those of the pores in MOFs, direct encapsulation of these enzymes into their porous frameworks is possible. For example, Zhou et al. have developed a hierarchical mesoporous PCN-888 with three distinct cavity sizes, where the large and medium-sized cavities exhibit selective binding toward target enzymes while the small-sized cavities serve as a diffusion channel.[73] In the postmodification process, specific sequential encapsulation is identified as the key step for effectively encapsulating both glucose oxidase (GOx) and horseradish peroxidase (HRP) enzymes into MOF cavities. GOx ($6.0 \times 5.2 \times 7.7$ nm^3) can only fit into the largest cages (6.2 nm), while HRP ($4.0 \times 4.4 \times 6.8$ nm^3) can be accommodated into both the large and medium pores (5.0 nm). Therefore, a stepwise encapsulation is necessary to control the distribution of two enzymes in the large and medium pores, respectively. GOx was initially incorporated into the larger pores, followed by the immobilization of HRP into the medium pores. When added in reverse order, HRP occupied both large and medium pores of MOFs while GOx only attached to the surface of MOFs, resulting in significantly compromised loading efficiency (Figure 4b). This approach for fabricating multi-enzyme@MOF composites was further advanced through the design and synthesis of various hierarchically porous MOFs.

2.2.2.3. Surface Immobilization. Compared to the infiltration method that is restricted by material pore size, surface immobilization exhibits greater applicability due to the lower structural design requirements for MOFs. Enzymes can be immobilized on the MOF surfaces through physical adsorption and chemical bonding. Physical adsorption is the

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most straightforward method for synthesizing enzyme/MOFs composites. The enzymes combine on the surface of MOFs via adsorption which mainly relies on van der Waals forces, hydrophobic interactions, $\pi-\pi$ interactions and electrostatics.[74,75] However, physical adsorption alone may not provide sufficient strength to prevent enzyme desorption from MOFs. To enhance the binding strength of enzymes, chemical bonding was developed for enzyme immobilization. The unsaturated metal sites and functional groups on ligands, such as amino and carboxylic groups, can serve as bonding sites to immobilize enzymes. It should be emphasized that the interface between enzymes and MOFs is complex and usually contains various types of binding forces. For instance, Liu et al. utilized MIL-101-Fe-NH_2 as a substrate to immobilize the antigen model ovalbumin (OVA) and an immune adjuvant, unmethylated cytosine−phosphate−guanine (CpG) oligonucleotide (Figure 4c).[76] The antigen model of the OVA was immobilized on the surface of MOFs via a disulfide bond grafted onto the ligand through chemical modification. Meanwhile, electronegative CpG was loaded onto positively charged MOF nanoparticles through electrostatic adsorption. However, several issues persist in the immobilization of enzymes within the MOF particles. For example, the size mismatch between the enzyme and MOF pores limits the selection of both the MOF and enzyme types. Additionally, enzymes loaded onto the surface of MOFs cannot guarantee cyclic stability during catalytic reactions. To enhance the binding affinity between enzymes and the MOF surface, more intricate chemical modifications or cross-linking methods are demanded.

2.2.2.4. MOF Assembled Capsules. Besides porous MOF nanoparticles as nanoreactors, MOF nanoparticles can self-assemble into capsules acting as microreactors for the encapsulation of guest species. On the one hand, the internal cavities of MOF microreactors can overcome the size limitations of pores, allowing for the confinement of different species such as enzymes, biomacromolecules, metal catalysts, and organic molecules, providing individual catalytic reaction spaces for these substances. On the other hand, the uniform pores of the external MOF shell offer additional loading sites for catalysts, facilitating the separation and protection of incompatible catalysts, while regulating reactant transport to ensure smooth implementation of cascade reactions. MOF capsules are typically prepared via Pickering emulsion assembly,[77] wherein MOF nanoparticles serve as building blocks that are dispersed in either the water or oil phase. The assembled units then stabilize the oil-in-water or water-in-oil emulsion to form the MOF capsules. By introduction of guest functional molecules, such as enzymes usually found in the aqueous phase, into their corresponding phases, they can be encapsulated within the cavities of MOF capsules to create highly efficient MNRs. Wang et al. reported the rapid self-assembly of Fe_3O_4@NH_2−UiO-66 (Fe-UiO) nanoparticles into Fe_3O_4@NH_2−UiO-66 capsules using the Pickering emulsion method (Figure 5a).[78] The factors influencing the morphological evolution of MOF capsules based on Pickering emulsion formation theory were systematically investigated, including shearing speed, shearing time, and particle content. To improve the stability of capsules, Bradshaw proposed to construct MOF capsule structures by assembling presynthesized MOF nanoparticles onto Pickering emulsion surfaces and then fixing them onto polystyrene membranes. Subsequently, a layer of ZIF-8 was regrown on the capsule surface to obtain multi-level porous MOF capsules for size-selective biocatalysis (Figure 5b).[79] Recently, Yang et al. further developed the Pickering emulsion method for the fabrication of multi-compartment MOF microreactors (Figure 5c).[80] Importantly, a single MOF microreactor can achieve simultaneous encapsulation of incompatible functionalities, such as hydrophilic enzymes (Candida antarctica lipase B (CALB), GOx) and hydrophobic molecular catalysts (Grubb' catalyst, Fe-porphyrin), for the operation of chemo-enzymatic cascade reactions.

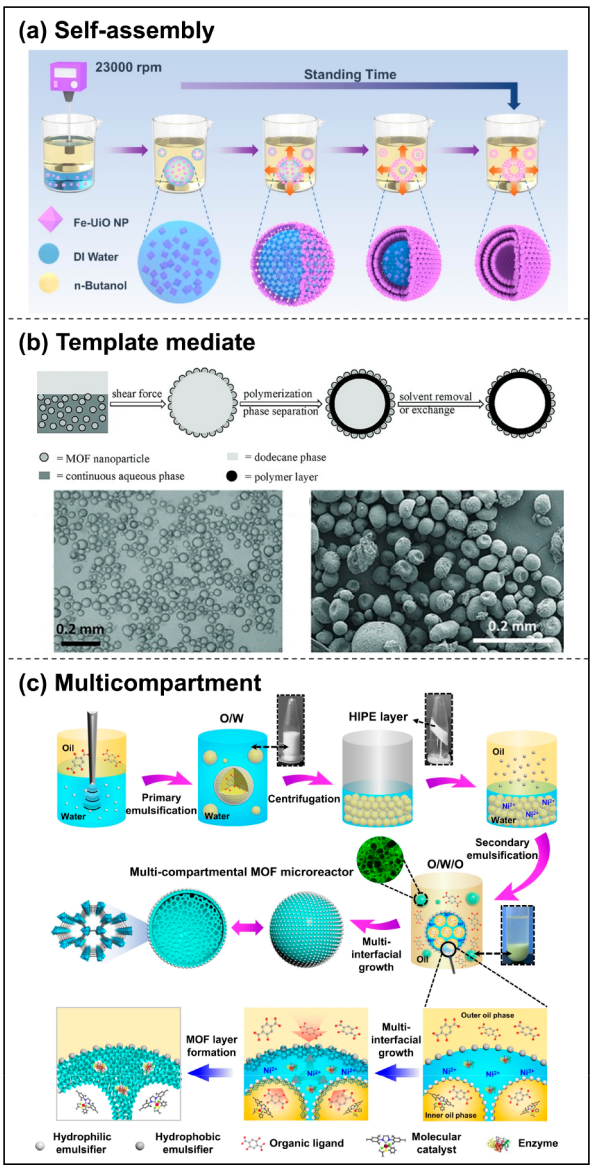

Figure 5. Schematic illustration of the formation of MOF-MNRs by Pickering emulsion assembly. (a) Preparation of Fe-UiO capsules through the transient self-assembly Picking emulsion method. Adapted with permission from ref 78. Copyright 2022 John Wiley and Sons. (b) Template-mediated formation of MOF-polymer composite capsules. Adapted with permission from ref 79. Copyright 2013 John Wiley and Sons. (c) Preparation of multi-compartmental MOF microreactors. Adapted with permission from ref 80. Copyright 2023 Springer Nature.

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Table 1. Summary of Multi-functional MOF-MNRs Used in Chemical Cascade Reactions

MOF-MNRs	Active sites	Cascade reactions	Ref
Zr-MOF-NH_2	Zr^{4+} (Lewis acid), $-NH_2$ (Lewis base)	Oxidation−Knoevenagel condensation	85
UiO-66-NH_2	Zr^{4+} (Lewis acid), $-NH_2$ (Lewis base)	Cross-aldol condensations	86
MIL-101(Al)-NH_2	Al^{3+}(Lewis acid), $-NH_2$ (Lewis base)	deacetalization−Knoevenagel condensation	87
MIL-101(Fe)-NH_2	Fe^{3+} (Lewis acid), $-NH_2$ (Lewis base)	photooxidation−Knoevenagel condensation	88
$In_{0.28}Ga_{0.72}PF$	In^{3+}, Ga^{3+} (Lewis acid), Bridging O atoms (Lewis base)	Strecker reaction	89
MIL-100($Sc_{60}Fe_{40}$)	Sc^{3+} (Lewis acid), Fe^{3+} (redox site)	Friedel−Crafts addition−oxidation	90
MIL-101−NH_2−SO_3H	$-SO_3H$ (Brønsted acid), $-NH_2$ (Brønsted base)	Deacetalization−nitroaldol reaction	91
IRMOF-9-Irdcppy-NH_2	$-NH_2$ (Lewis base), Ir(I) sites	Knoevenagel condensation−allylic N-alkylation	92
PAF-NProRh	Lewis base, [Rh] sites	Knoevenagel condensation−hydrogenation	93
LIFM-80(Cu)	$-NH_2$ (base), Cu(I) sites	Oxidation−click reaction−Knoevenagel condensation	94
1-OTf-Ir	Al−OTf (Lewis acid), $[Ir(ppy)_2(dcbpy)]^+$ (photoredox site)	Reductive cross-coupling reaction	95
CuMnCr-MTV-MOF	Metallosalen-based linkers	Asymmetric epoxidation−ring-opening reactions	96
Pd@IRMOF-3	$-NH_2$(Lewis base), Pd NPs	Knoevenagel condensation/hydrogenation	58
Au@MIL-53-NH_2	$-NH_2$ (Lewis base), Au NPs	Oxidation−Knoevenagel condensation	57
Pd@UiO-66-NH_2	Zr^{4+} (Lewis acid), Pd NPs	Oxidation−acetalization	97
PtPd/MIL-53(Al)	$AlO_4(OH)_2$ sites, PtPd NPs	Oxidant-free dehydrogenation	98
Pd_2Ag_1@MIL-101	Cr^{3+} (Lewis acid), PdAg NPs	Hydrogenation−amination−hydrogenation	99

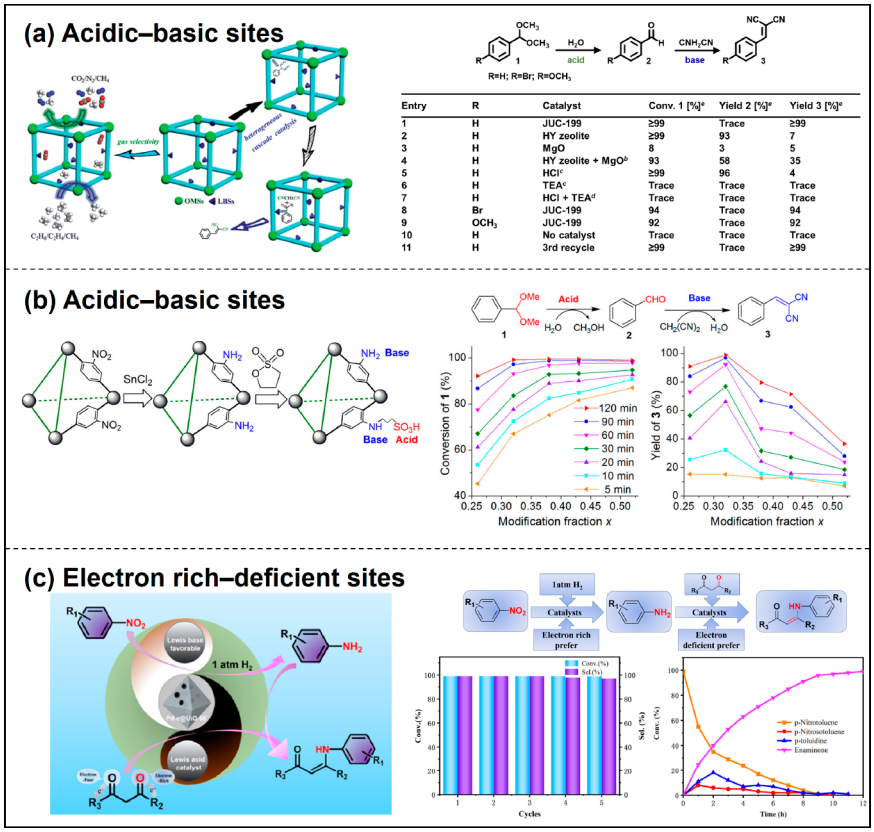

Figure 6. Design strategies and applications of MOF-MNRs with incompatible active sites. (a) Schematic illustration of bifunctional MOF-MNRs for selective gas adsorption and one-pot DK condensation reactions. Adapted with permission from ref 100. Copyright 2016 Royal Society of Chemistry. (b) Schematic illustration of the bifunctional MOF-MNRs through ligand modification for DK condensation reactions. Adapted with permission from ref 101. Copyright 2016 American Chemical Society. (c) The fabrication of Pd-e@UiO-66 for the template reaction of p-nitrotoluene with acetylacetone. Adapted with permission from ref 102. Copyright 2022 American Chemical Society.

3. CHEMICAL CASCADE REACTIONS

In the cascade reactions, catalysts with multiple active sites are required, where each site is responsible for a specific reaction step.[28,81,82] For example, reforming catalysts typically contain both metal and acidic components; the former facilitates dehydrogenation, while the latter promotes isomerization. The adjustment of the reforming catalyst is a crucial step in ensuring the catalytic activity. If the metal function is too strong, excessive dehydrogenation can occur, accelerating coke deposition and leading to catalyst deactivation and decreased stability. Conversely, if the acidic function is too strong, it can promote alkane cracking reactions, reducing selectivity and catalyst stability.[3,83,84] Therefore, the development of new catalysts to overcome incompatibility in cascade reactions is a crucial direction for their advancement. MOF-MNRs as

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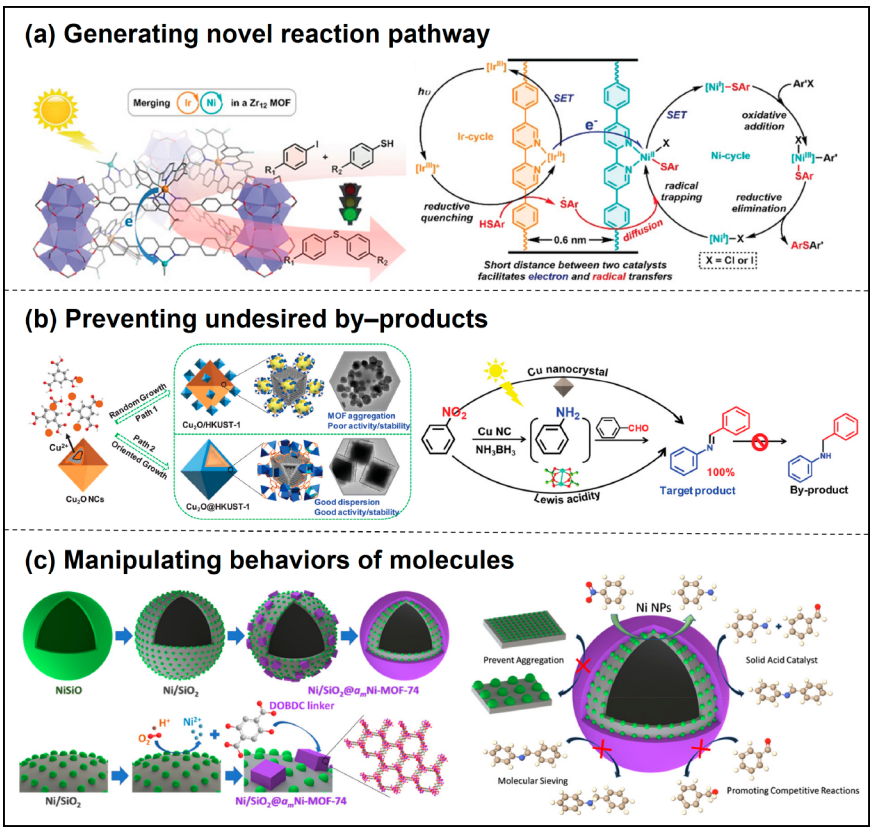

Figure 7. Application strategy of MOFs-MNRs in the chemical cascade catalysis of reaction rate and condition mismatch. (a) Schematic illustration of multi-functional MOF nanoreactors that incorporate Ir^{III} and Ni^{II} sites for cross-coupling reactions. Adapted with permission from ref 104. Copyright 2018 John Wiley and Sons. (b) Schematic illustration of the oriented growth of Cu_2O@HKUST-1 and random growth of Cu_2O/HKUST-1 composites for one-pot cascades. Adapted with permission from ref 106. Copyright 2021 John Wiley and Sons. (c) Schematic illustration of the fabrication process for bifunctional Ni/SiO_2@Ni-MOF-74 nanoreactors designed for the imination of nitrobenzene with benzaldehyde. Adapted with permission from ref 110. Copyright 2019 American Chemical Society.

catalysts have the advantages of providing abundant active sites, compartment separation, confinement effect, and controllable substance transport, thereby presenting more opportunities for addressing various challenges in cascade reactions including reforming reactions. Table 1 provides a summary of the multi-functional MOF-MNRs used in chemical cascade reactions. This section primarily focuses on discussing the potential opportunities presented by micro/nano reactors made from multi-functional MOFs to address incompatible chemical cascade reactions.

3.1. Incompatibility of Multi Active Sites

The compatibility issues arising from acidic−basic sites often impede the development of chemical cascade reactions due to rapid neutralization between these sites. However, MOF-MNRs offer unique opportunities for incorporating acidity and basicity into their structures with precise control over the locations of different active sites. In general, coordinatively unsaturated metal sites in MOF-MNRs can serve as typical Lewis acidic sites. Additionally, functional species such as chelating sites and thioether groups can be grafted onto MOFs to act as Lewis acids, as well. In contrast, functional ligands containing different types of basic site groups (e.g., NH_2, pyridine) can be rationally designed to construct MOF-MNR structures that accommodate basic sites.[75−87] The challenges to be addressed in this process include the selection and immobilization of acid−base sites within the structure of MOF-MNRs, as well as ensuring rapid mass transfer through rigid porous structures and the cyclic stability of cascade catalysts. One representative cascade reaction used to identify the catalytic activity of MOFs accommodating both acidic and basic sites is deacetalization−Knoevenagel (DK) condensation reactions. For example, Zhu et al. demonstrated the bifunctionality of JUC-199, a MOF-MNR with coordinatively unsaturated Zn^{2+} sites and $-NH_2$ functional groups acting as Lewis acidic and basic sites, respectively, assembled via binuclear Zn-based metal nodes and benzidine ligands.[100] The synergistic effect between Zn^{2+} Lewis acid sites and $-NH_2$ Lewis base sites in JUC-199 resulted in a high reaction activity for DK condensation reactions (Figure 6a). Moreover, control experiments were conducted using homogeneous catalysts HCl and triethanolamine. The instantaneous neutralization between them caused no reaction activity for cascade reactions. Additionally, ligands with different acid−base sites can be assembled to form bifunctional MOF-MNRs for DK condensation reactions. Gao et al. synthesized MIL-101−SO_3H−NH_2, in which amino and sulfo groups are simultaneously present in the structures attached to the organic linker.[101] The acid and base sites in the MOFs are responsible for deacetalization and condensation, respectively. The modified MOFs greatly promote DK condensation reactions, whereas monofunctionalized MIL-101−SO_3H and MIL-101−NH_2 exhibit poor reaction activity (Figure 6b). In addition, MOF-MNRs offer opportunities for the development of cascade reactions that require both electron-rich and

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electron-deficient catalysts. For instance, in the cascade synthesis of β-ketoenamines via nitro reduction, a hydrogenation reaction of nitro compounds necessitates an electron-rich catalyst, while condensation between amine compounds and β-dicarbonyl compounds often requires an electron-deficient environment. Simply mixing the two catalysts will result in a less selectivity reaction. Sun et al. demonstrated that Pd-e@UiO-66 can be applied to the catalytic hydrogenation of nitroarene coupled condensation with β-diketone to afford β-ketoenamines.[102] The Pd NPs act as an electron-rich catalyst, while unsaturated Zr^{4+} sites serve as electron-deficient sites within this MOF-MNRs nanoreactor, which exhibits excellent selectivity and activity. Furthermore, these catalysts maintain their performance for more than five cycles (Figure 6c).

3.2. Incompatibility of Reaction Rate and Condition

MOF-MNRs have the ability to create novel reaction pathways that offer opportunities for cascade reactions that are both thermodynamically and kinetically incompatible. For example, the sluggishness of cross-coupling reactions involving alkyl boronic acids and their derivatives with traditional catalysts can be ascribed to the lower reaction rates of oxidative addition and transmetalation of an organometallic nucleophile to an electrophile, which typically involve harsh reaction conditions.[103] To address this issue, Lin et al. have developed multifunctional MOF nanoreactors (Zr_{12}−Ir−Ni) that incorporate Ir^{III} and Ni^{II} sites as photoredox and cross-coupling catalysts, respectively, enabling efficient C−S cross-coupling reactions under mild reaction condition between various aryl iodides and thiols (Figure 7a).[104] They suggested that the proximity of catalysts enforced by MOF nanoreactors significantly accelerates electron transfer and thiyl radical transfer steps, resulting in a nearly 10-fold improvement in turnover number compared to homogeneous conditions. Additionally, they designed Hf_{12}−Ir−Ni 2D MOF-MNRs which exhibit high activity in catalytic C−S, C−O, and C−C cross-coupling by exploiting the proximity between photosensitizing bridging ligands and Ni catalysts on metal nodes of MOFs.[105] These works demonstrate the potential of MOF-MNRs in generating novel reaction pathways by integrating multiple active sites to overcome the incompatibility of the reaction rate challenges encountered in cascade reactions.

In many cases, the intermediates of the catalytic reaction usually undergo secondary side reactions under catalytic conditions, reducing the reaction selectivity of the target product. MOF-MNRs offer opportunities to address the incompatibility of reaction kinetics among each step in the cascade reaction through the design of the active sites and structures, thereby preventing the formation of undesired byproducts to enhance the selectivity of target products. For instance, aromatic imines serve as crucial chemical intermediates in various industrial sectors, promoting the production of diverse types of fine chemicals. However, the imine intermediates are easily overreduced to generate undesired secondary arylamines, resulting in the impurity of the target products. Jiang et al. synthesized multi-functional MOF-MNRs, Cu_2O@HKUST-1, which combined the properties of Cu_2O and the advantages of MOFs that exhibit cocatalytic promoted activity and selectivity under mild conditions involving visible light irradiation for one-pot cascades (Figure 7b).[106] The excellent performance is attributed to the plasma photothermal effect of Cu_2O, while the HKUST-1 shell provides Lewis acid sites, substrate, and H_2 enrichment. Importantly, the stabilization of the Cu core plays a crucial role in effectively suppressing the over-reduction of imines resulting from its inactivity toward the hydrogenation of unsaturated C=N.

Furthermore, to solve the challenge of incompatibility of reaction kinetics in chemical cascade reactions, the confinement effect within the pore channels of MOF-MNRs provides a unique opportunity to manipulate and direct the adsorption and diffusion behaviors of molecules on active sites.[107] By selectively loading these sites in specific positions, one can induce reactions that align with the desired outcomes. This approach enables precise control over chemical processes occurring within MOF channels, resulting in more efficient prevention of side reactions during cascade reactions.[108,109] Benzylideneaniline is the desired product in the cascade reaction of nitrobenzene and benzaldehyde as it serves as a valuable intermediate in many chemical syntheses. However, due to the multi-step nature of this reaction and the complexity of its reactants, several side reactions may occur. For example, overhydrogenation of imine to amine can take place because the catalyst used for hydrogenating nitrobenzene may also promote the hydrogenation of imine. Zeng et al. reported that Ni/SiO_2@Ni-MOF-74 nanoreactors were assembled from the amorphous Ni-MOF-74 shell and the hollow silica sphere.[110] The Ni NPs are firmly fixed at the interface of the structure. This hollow nanoreactor has demonstrated efficient control over the nitrobenzene imination with benzaldehyde, resulting in desired selectivity for both nitrobenzene hydrogenation to aniline and subsequent aniline condensation with benzaldehyde toward an imine (Figure 7c). The MOF-MNRs' shell plays a crucial role in the reaction by preventing leaching and segregation of active Ni NPs, while also acting as an acid catalyst. The narrow pore size is crucial in preventing potential adsorption between the C=N bond and Ni NPs, which overcoming the challenge for deep hydrogenation of the desired product. Moreover, the confinement effect of MOF-MNRs can significantly enhance both catalyst activity and stability. For example, extensive researches have been conducted on the synergistic effect between guest functional molecules and MOF structures, as well as pore confinement for preventing the sintering agglomeration of MNPs.[30,111]

4. BIOLOGICAL CASCADE REACTIONS

Enzymes are complex biological macromolecules produced by living cells composed of linear chains of amino acids that fold into precise tertiary structures.[112,113] They exhibit specific activity and selectivity, allowing them to perform various chemical reactions with high regioselectivity and stereoselectivity. As a result, enzymes have found widespread use in industrial biocatalytic processes, offering cost- and time-saving advantages compared to single-step reactions. One approach to enhance their efficiency is the utilization of multi-enzyme cascades, which integrate multiple catalytic steps into a single reaction vessel.[114−116] Nevertheless, the design and construction of multi-enzyme catalytic systems often encounter the following challenges. The first one is negative external factors, such as protease and toxic chemicals, which have the potential to denature enzymes and terminate cascade reactions.[117] Additionally, the incompatibilities with reaction rate and reaction conditions in a multi-enzyme system can cause the inactivation of one enzyme catalyst during cascade reactions, thereby impacting the overall efficiency of the process. For instance, intermediates produced in the first step

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Table 2. Summary of MOF-MNRs Used in Multi-enzyme Cascade Reactions

MOF-MNRs	Enzymes	Cascade reactions	Ref
MIL-101(Al)-NH_2	*Aspergillus saitoi* protease and GOx	Glucose oxidation	124
ZIF-8	CytC	The convert ABTS to $ABTS^+$	125
UiO-66	Lipase, GOx and CAT	Catalytic hydrolysis and chiral resolution	126
PCN-333(Al)	Tyrosinase	Tyrosinase oxidation catalyzed	127
ZIF-8	GOx and HRP	Catalyzed oxidation reaction	128
PCN-88	GOx and HRP	Catalyzed oxidation reaction	129
MIL-101(Cr) and HKUST-1	Carbonic anhydrase, formaldehyde dehydrogenase, and glutamate dehydrogenase	Conversion of CO_2 to formate	130
ZIF-90	Catalase and protease	Peroxide decomposing	131
ZIF-8	GOx and HRP; β-Gal, GOx and HRP; alcohol dehydrogenase, NAD^+−polymer and lactate dehydrogenase	β-Gal hydrolysis−glucose oxidation−Amplex Red oxidation	72
HP-DUT-5	GOx and HRP; GOx and uricase	Glucose and uric acid biosensor	132
ZIF-L	GOx and HRP	Glucose oxidation	133
ZIF-8 and ZIF-67	GOx and HRP; Pro and ADH/NAD	Catalytic hydrolysis and chiral resolution	134
UiO-66-NH_2	Protease and GOx	Glucose oxidation	135
ZIF-8	Imultaneously carbonic anhydrase, formate dehydrogenase, NADH, and glutamate dehydrogenases	Conversion of CO_2 to formate	136
NH_2-MIL-101(qNM)	Single enzyme (GOx) or two enzymes (β-Gal and GOx)	Catalyzed ABTS oxidation	137
ZIF-8	CAT, GOx and HRP	Glucose oxidation	120

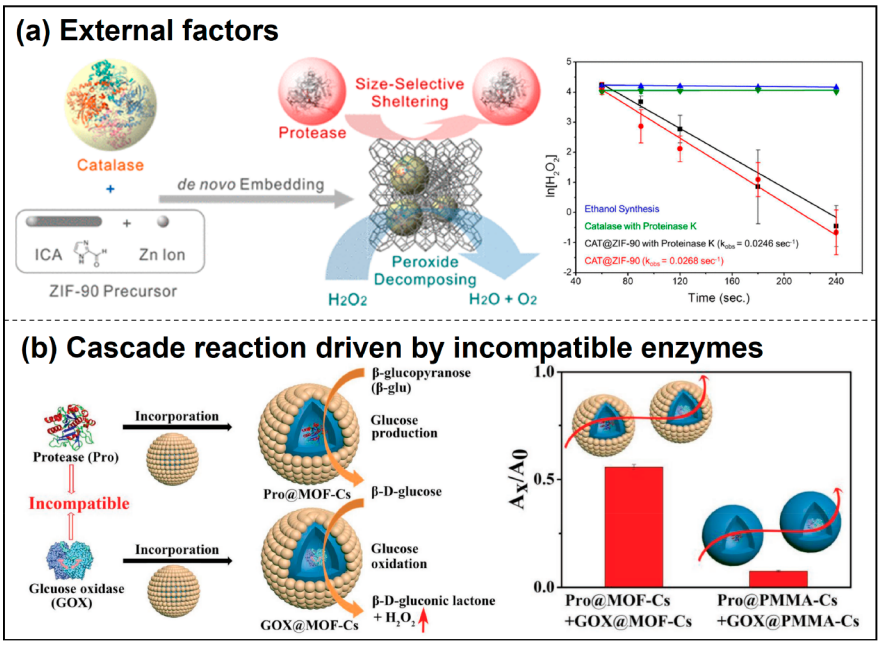

Figure 8. Application strategy of MOFs-MNRs in the cascade catalysis of negative external factors and incompatible enzymes. (a) Water-based synthesis of ZIF-90 with the encapsulated catalase enzyme and its kinetics of degradation of H_2O_2. Adapted with permission from ref 131. Copyright 2015 American Chemical Society. (b) Scheme image of the communication between separate incorporation of two incompatible enzymes (GOx and Pro) inside MOF-Cs for cascade reaction and UV−vis absorption of ABTS (an indicator of H_2O_2) in the cascade reaction of hydrolysis and oxidation by the mixture of GOx@MOF-Cs with Pro@MOF-Cs or the mixture of GOx@PMMA-Cs with Pro@PMMA-Cs. Adapted with permission from ref 135. Copyright 2018 John Wiley and Sons.

of the reaction may diffuse back into the bulk environment, hindering their enrichment around the second enzyme and reducing activity.[118] Accordingly, the ideal multi-enzymes cascade should be able to inhibit the negative external attack and facilitate the intermediates transfer between neighboring enzymes. To address this, substrates with compartmentalized protection and material transport capabilities have been developed. Recently, MOF-MNRs have emerged as one of the most promising matrices for enzymes immobilization due to their ability to protect enzymes from harsh external environments (such as high temperatures or proteolytic environments) while also facilitating selective transport of substrates to active site through ordered and customizable pore network.[119−123] The relevant research findings of MOF-MNRs for enzyme cascade reactions are summarized in Table 2. In the following section, the potential opportunities presented by MOF-MNRs for addressing compatibility issues in multi-enzyme cascade reactions will be discussed.

4.1. Incompatibility of Reaction Conditions

To fully utilize the high catalytic activity and selectivity of enzymes, it is crucial to overcome their inherent fragility under complex conditions. Compared with the pure enzyme, MOFs immobilized enzymes exhibit significantly enhanced stability

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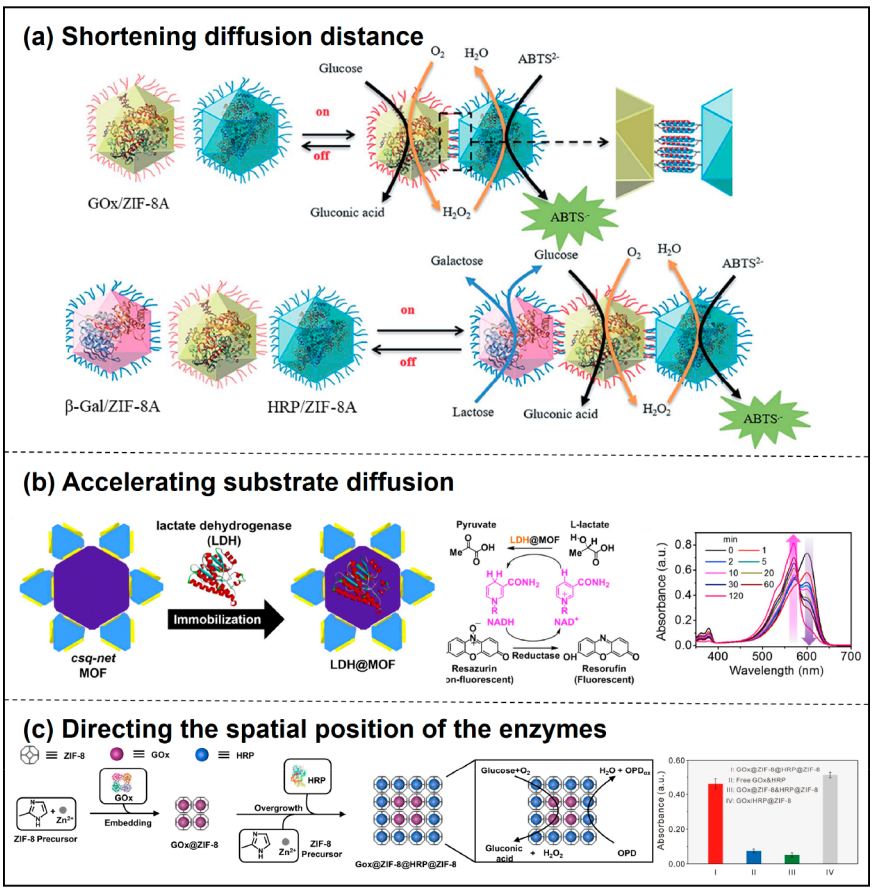

Figure 9. Application strategy of MOFs-MNRs in the cascade catalysis of reaction rate mismatch. (a) Schematic illustration of peptide-induced compartmentalization of bienzyme and three-enzyme superassembly and dissembled by protease. Adapted with permission from ref 138. Copyright 2019 Royal Society of Chemistry. (b) Hierarchically encapsulating enzymes with MOFs for enzyme cascade reactions. Adapted with permission from ref 55. Copyright 2018 Elsevier. (c) Enzyme cascade reaction driven by compatible enzymes (GOx and HRP) and catalytic efficiencies in GOx@ZIF-8@HRP@ZIF-8, free GOx and HRP, GOx@ZIF-8 and HRP@ZIF-8, and GOx/HRP@ZIF-8 systems. Adapted with permission from ref 134. Copyright 2022 Springer Nature.

under harsh reaction conditions such as high temperature, extreme pH and organic solvent.[79,129] In addition, MOFs can also act as a barrier against proteases, thereby protecting the coated enzyme from proteolytic degradation. For example, Tsung and co-workers embedded catalase (CAT) in ZIF-90 in an aqueous solution to obtain CAT/ZIF-90 catalyst, which showed high activity even in the presence of proteinase K.[131] Furthermore, the catalytic activity and thermal tolerance stability of CAT/ZIF-90 are higher than those of free enzymes (Figure 8a). In addition, the obtained composites maintain their biological activity when hydrogen peroxide is decomposed in 6 M urea at 80 °C, while free CAT loses its biological functions. Furthermore, MOF-MNRs formed by the assembly of MOF capsules (MOF-Cs) provide more opportunities for coating and protecting multiple enzymes. For instance, Huo et al. used MOF nanoparticles to self-assemble into multifunctional MOF-Cs to protect enzymes from the external environment. It was found that GOx@MOF-Cs retain more than 96% of their initial activity after protease (Pro) digestion, while the activities of free GOx and GOx@PMMA-Cs significantly reduce. This encapsulation strategy could also be extended to other classes of enzymes, such as HRP or both enzymes together, providing MOF-MNRs with greater flexibility and designability. Moreover, our group encapsulated two incompatible enzymes (GOx and Pro) into the MOF-Cs for cascade reaction (Figure 8b). The internal cavity of MOF-MNRs not only confines biomolecules but also provides a distinct reaction space for them. Additionally, the uniform pores of the outer MOFs layer regulate molecular transport while separating and safeguarding incompatible enzymes to maintain their original catalytic activity without external interference. This approach prevents the hydrolysis of GOx by Pro and allows Pro to catalyze the hydrolysis reactions. Such cascade reaction cannot be achieved using Pro@PMMA-Cs, GOx@PMMA-Cs or the mixture of Pro with GOx.[135] Therefore, MOF-Cs have good compartmentalizing effects and communication ability, which can convert chemical incompatibility (Pro and GOx) into chemical affinity. Compared with the free-enzymes-induced cascade catalysis, the immobilized enzymes-induced cascade systems exhibit excellent performances, including high store stability, recyclability, antijamming ability, and cascade catalytic efficiency. However, challenges such as reduced catalytic activity after immobilization, complex micro/nano environments, and low loading amounts still need to be addressed.

4.2. Incompatibility of Reaction Rates

In the process of a multi-enzymes cascade reaction, the activity may decrease due to kinetic mismatches between different enzymes. This rate mismatch can result in various effects on the reaction system, such as decreased reaction rate, restricted

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Table 3. Summary of Multi-functional MOF-MNRs Used in Chemo−Bio Cascade Reactions

MOF-MNRs	Chemical catalysts	Enzymes	Cascade reactions	Ref
NKMOF-101-M	Zn, Mn, Co, Ni	CytC; lipase	Remove superoxide and Hydrogen peroxide; Catalytic hydrolysis	142
UiO-66	Photoactive organosilica	GluDH; GlyDH	Photobiocatalysis under aerobic conditions	143
MIL-125 (Ti)	TiO_2	CytC	Formation of H_2O_2 by photocatalysis	8
MOF-545(Fe)	MOF-545(Fe)	GOx	The oxidation of glucose	144
NU-1006	Cp*Rh(2,2′-bipyridyl-5,5′-dicarboxylic acid)Cl_2 complex	FDH	Bioelectrocatalytic reduction of CO_2	145
NU-1006	Cp*Rh(2,2′-bipyridyl-5,5′-dicarboxylic acid)Cl	FDH	Light-driven CO_2 reduction	146
PCN-222(Fe)	PCN-222(Fe)	GOx	The convert ABTS to $ABTS^+$	147
MIL-88B(Fe)-NH_2	MIL-88B(Fe)-NH_2	Glutamate oxidase	Detection of glutamate	148
TCPP/ZIF-8	Cp*Rh(bpy)Cl	FateDH and FaldDH	Conversion of CO_2 to HCHO	149
DP-ZIF67	Pd NCs	CALA	Catalytic nitroaldol reaction	150
UiO-66-NH_2	Pd NPs	CALB	Formation of benzyl hexanoate from benzaldehyde and ethyl hexanoate	151
UiO-66-NH_2	$Pt[(C_6H_5)_3P]_4$	AlcDH/NAD^+	Conversion of formate to CO_2	152

reaction flux, substrate wastage, altered reaction equilibrium and increased risk of enzyme inactivation.[55] These consequences can hinder the efficiency, yield, and controllability of the reaction. To overcome this problem, the spatial organization of enzymes in confined structures provides a general method for designing enzyme cascade reactions, particularly through the coimmobilization of multi enzymes. This approach shortens the diffusion path of the substrate and intermediate to improve transfer efficiency and enhance the cascade reaction rate of multiple enzymes. Willner and co-workers demonstrated effective enzyme cascade reactions by encapsulating two or three enzymes or enzyme/cofactor components in ZIF-8 NPs.[72,129] Compared with free enzymes in a homogeneous buffer solution, the catalytic cascade activity of the integrated two-enzyme system (GOx and HRP) or three-enzyme system (β-Gal, GOx, and HRP) in the MOF-MNRs are 7.5-fold and 5.3-fold higher, respectively. This improvement is attributed to the close proximity of the two enzymes, which induces more complete and immediate consumption of intermediates in the multi-enzyme-containing MOF-MNRs.

Similarly, Liang and co-workers developed a smart and stimulus-responsive approach to locate discrete enzymes@MOF-MNRs through complementary peptide interactions (Figure 9a).[138] Surface-functionalized MOF-MNRs with a single enzyme are modified with complementary peptides, inducing superassembly through self-assembled peptide coiled-coil structures. This brings different enzyme-containing MOF-MNRs together to trigger cascade reactions. Compared with the unassembled MOF nanoparticles, the cascade catalytic activity of multi-enzymes in the superassembled MOF-MNRs shows remarkable 7.3-fold and 4.4-fold higher in two and three enzyme cascade reactions, respectively. This enhancement can be ascribed to the interparticle organization induced by peptides, bringing the discrete enzyme/ZIF-8A MNRs into close proximity and facilitating the addition of high local concentrations of products generated by one enzyme into the subsequent biocatalyst.

Within the hierarchical structure of MOF-MNRs, Li and co-workers found that the size of the triangular channels and bridging windows are crucial for the diffusion and accessibility of large coenzymes such as NAD^+ and NADH.[55] The inherent expansion properties of channels and windows can overcome the barriers of small reactants and coenzyme diffusion, providing enough space for enzyme-coenzyme recognition in the confined MOF structures. As a result, lactate dehydrogenase (LDH)@NU-100x (x = 5, 6, 7) and free diaphorase catalyze NAD^+ and NADH regeneration at a rate 1.5−3 times higher than that of free enzymes, probably due to the substrate channeling effect when coimmobilizing multiple enzymes for cascade reactions (Figure 9b). In addition, the problem of kinetic mismatches in multi-enzyme cascade reactions can be accurately controlled by spatially positioning and orientating enzymes at the nanoscale, in which close positioning of enzyme-1-loaded and enzyme-2-loaded shells along the inner-to-outer shells could effectively facilitate mass transportation and promote efficient enzyme cascade reaction (Figure 9c).[134] The GOx@ZIF-8@HRP@ZIF-8 exhibits ∼5.8-fold and ∼9.1-fold increase in catalytic activity than the homogeneous diffusional mixture of free enzymes (free GOx and HRP) and unassembled single-enzyme-loaded ZIF-8 (GOx@ZIF-8 and HRP@ZIF-8), respectively. This is because the intermediates that follow the specified diffusion pathway are constrained by the pore channels, resulting in a longer residence time and increased local concentration of the intermediates near the HRP site. To sum up, multi-enzymes within MOF-MNRs provide an isolated interspace with specific circumstances for different enzymes, which offer benefits for regulating multi-enzyme reactions and enhancing their cascade reaction rates.

5. CHEMO−BIO CASCADE REACTIONS

To date, most cascade processes involve chemical cascade reactions, multi-enzyme cascade reactions, or pure biotechnological processes. One-pot cascade reactions that combine both bio- and chemo-catalysts are more challenging due to the radically different environments in which these two catalysts typically operate.[139] Thus, chemical catalysts should be biocompatible and active enough to cooperate effectively with biocatalysts for successful cross-class reactions. Taking inspiration from nature, researchers have designed several approaches (such as biphasic systems, supramolecular hosts, artificial metalloenzymes, and spatial separation by flow chemistry) to address the aforementioned challenges and achieve chemo−bio cascade reactions.[15,140,141] MOFs are classified as porous hybrid inorganic−organic materials with architecture. They have gained attention to be applied as

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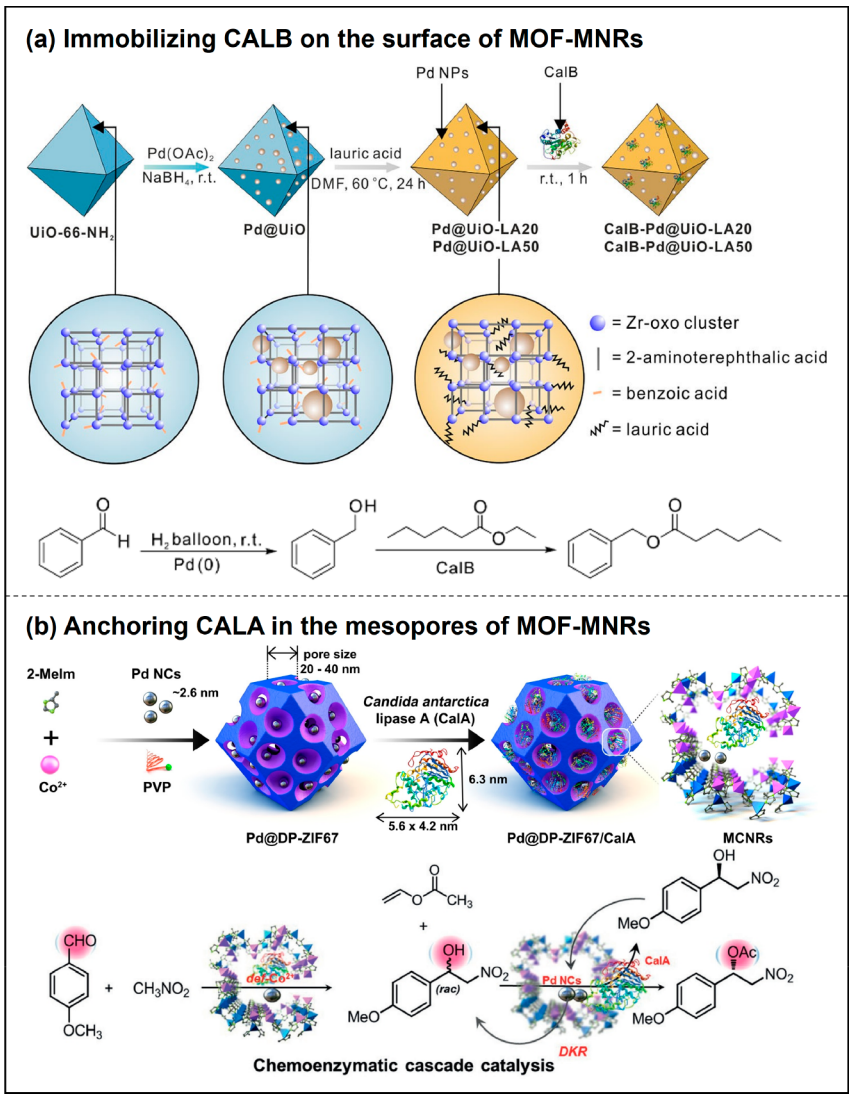

Figure 10. Schematic illustration of strategies to prevent mutual inactivation of chemo-biocatalysts. (a) Co-immobilization of Pd NPs and lipase CALB into UiO-66-NH_2. Adapted with permission from ref 157. Copyright 2019 John Wiley and Sons. (b) Synthetic strategy toward MOF-MNRs containing coordinately unsaturated Co^{2+}, Pd NCs and CALA inside DP-ZIF-67, and the cascade reaction catalyzed by Pd@DP-ZIF-67/CALA. Adapted with permission from ref 158. Copyright 2020 John Wiley and Sons.

suitable matrices for enzymes and/or chemo-catalysts immobilization. In the following section, Table 3 provides a summary of multi-functional MOF-MNRs used in chemo−bio cascade reactions. Subsequently, the potential opportunities of MOF-MNRs in addressing the incompatibility challenges in chemo−bio cascade reactions, such as mutual inactivation, incompatible reaction conditions, and mismatched kinetics, are discussed with relevant examples.

5.1. Mutual Inactivation of Chemo−Biocatalysts

The cascade of biological and chemical catalysts, including enzymes and metal catalysts (Pd,[153,154] Ni,[155] and Cu[156]), has been extensively employed in the industry. However, when these catalysts are utilized in a one-pot reaction, a typical challenge occurs: the mutual inactivation between enzymes and metal catalysts. Co-immobilization of enzymes and MNPs on the solid matrix is a commonly employed approach to spatially separate the two catalysts, thereby addressing the mutual inactivation issues encountered in chemo−bio cascade reactions. For example, Wang and co-workers reported MOF-based biohybrids in which the small-sized Pd NPs are encapsulated within the inner pores of MOF-MNRs, whereas CALB is immobilized on the MOF-MNRs surface (Figure 10a).[157] In this work, MOFs are utilized as support carriers to compartmentalize chemo- and biocatalysts in different locations, thereby preventing their mutual inactivation. By catalyzing the cascade reaction with CALB-Pd@UiO-LA50 instead of a physical mixture of Pd@UiO-LA50 and free CALB, a higher yield of the final product can be achieved. Another example is the multi-functional nanoreactor designed by Lee and co-workers, which is based on a mesoporous DP-ZIF-67. This nanoreactor incorporates Pd nanoclusters (NCs) and stably anchored Candida antarctica lipase A (CALA) in the mesopores, along with coordinately unsaturated cationic metal nodes of MOF-MNRs (Figure 10b).[158] Compared with physically mixed Pd NCs and CALA (20% ee), Pd@DP-ZIF-67 and CALA@DP-ZIF-67 (ca. 38%), Pd@DP-ZIF-67 and free CALA (24% ee), Pd@DPZIF-67/CALA has excellent yield (>99%) and enantioselectivity (>99% ee). This strategy not only avoids the deactivation of the chemo- and biocatalysts

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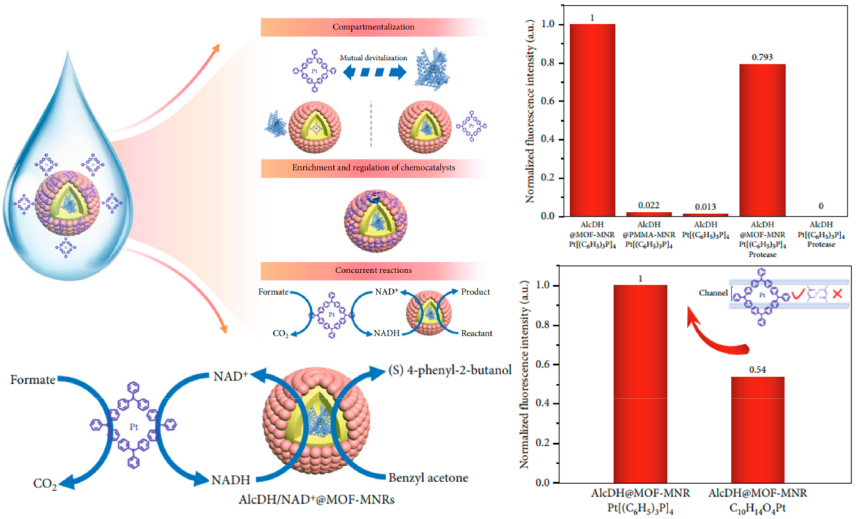

Figure 11. Schematic illustration of the reduction of pyruvic acid to lactic acid by the concurrent chemobioreaction of $Pt[(C_6H_5)_3P]_4$–AlcDH/NAD^+@MOF-MNRs. Adapted with permission from ref 160. Copyright 2019 Amer. Assoc. Advancement Science.

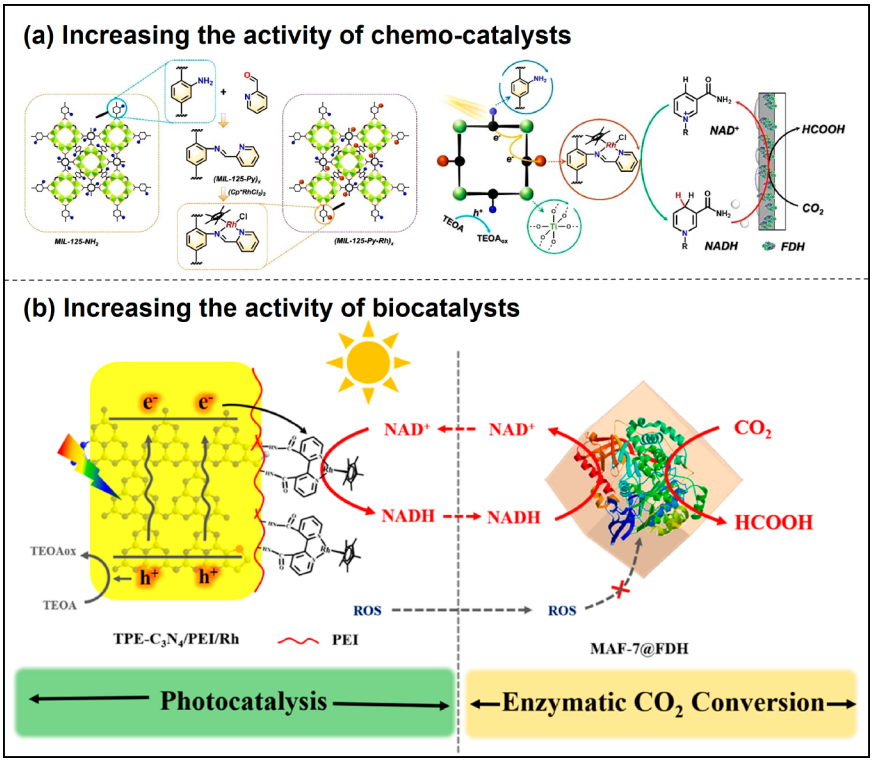

Figure 12. Schematic illustration of strategies to address kinetics mismatch issues in biochemo cascade reactions. (a) Synthetic pathways for covalent functionalization and metalation of unsaturated metal nodes in MIL-125-NH_2, and the reaction mechanism for light-harvesting and electron-transfer in MIL-125-NH_2 MNRs during NADH-dependent formic acid production using immobilized FDH. Adapted with permission from ref 163. Copyright 2022 John Wiley and Sons. (b) Mechanism of TPE-C_3N_4 using light to photoexcite electrons for NADH cofactor regeneration in CO_2 conversion. Adapted with permission from ref 164. Copyright 2020 American Chemical Society.

but also realizes the cooperative and synergistic catalysis within a single MOF-MNRs nanoplatform.

5.2. Incompatibility of Reaction Conditions

In addition to the mutual inactivation between the different catalysts, the compatibility of their respective reaction conditions is another key requirement for a successful cascade. Biocatalysts typically operate under mild conditions, with water being the primary reaction solvent, while chemical catalysts often require harsh conditions, such as high temperatures, high pressures, strong acids or bases, and various organic phase reactions. It is challenging for chemically catalyzed reactions to occur in the presence of mild biocatalysts, as many biocatalysts are prone to direct inactivation under the conditions required by chemical catalysts. Therefore, the combination of biocatalysts and chemical catalysts necessitates compatibility of conditions wherein both catalysts exhibit reasonable activity levels. A popular strategy is to immobilize enzymes with MOF-MNRs to improve their catalytic activity under incompatible

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reaction conditions.[159] In a recent work, we have developed a convenient strategy (Figure 11) to construct versatile functional MOF-MNRs, which have a good encapsulation and protection effect on alcohol dehydrogenase (AlcDH), enabling them to maintain catalytic efficiency in organic environment.[160] In addition, in the presence of protease and a metal catalyst, AlcDH/NAD^+@UiO-66-NH_2-MNRs still maintain the initial activity of AlcDH, while free enzymes lose their biological functions.

The designed MOF-MNRs not only protect enzymes from the deactivation of metal catalysts but also guarantee simultaneous chemo−bio cascade catalysis in more complex reaction systems. Importantly, the MOF shell of the MOF-MNRs exerts a controllable regulatory effect on the activity and stability of the chemical catalysts, making them compatible with biocatalysts in the same reaction environment. This strategy of constructing MOF-MNRs offers a distinctive platform for bridging the "two worlds" of chemocatalysis and biocatalysis, presenting an exquisite approach to catalytic research.

5.3. Incompatibility of Reaction Rates

Electron transport plays a crucial role in driving both chemical and enzymatic reactions, such as the alteration of electron state at the active site and the replenishment of redox equivalents nicotinamide adenine dinucleotide cofactors [NAD(P)H].[161] The primary reason for the incompatibility of reaction rates within chemo−bio cascades is the kinetic mismatch between electron production and transport rates in these two types of reactions.[162] Great efforts have been made to accelerate the regeneration of NAD(P)H to meet the reaction rate requirements. Photodriven chemo-enzymatic cascade reaction has received special attention due to the combination of the advantages of photocatalysis and enzyme catalysis, exhibiting high efficiency and specificity of enzyme catalysis as well as a high conversion rate of NAD(P)H. Several strategies have been proposed to enclose catalytically active organometallic complexes/enzymes within MOFs for photo chemo−bio cascade reactions. For example, Liu and co-workers precisely anchored a Rh complex onto the unsaturated metal nodes of MIL-125-NH_2 (Figure 12a).[163] The $-NH_2$ group of MIL-125-NH_2 on the linkers could be readily converted to iminopyridine through Schiff-base condensation, which provides a suitable docking site for the Rh complex. This design facilitates the coupling between the light-harvesting iminopyridine unit and electron-transferring Rh-complex enabling photoinduced electron transfer for NADH regeneration with a yield of 66.4% in 60 min for 5 cycles. The subsequent enzymatic reaction involving formate dehydrogenase results in an enhanced formic acid yield of 9.5 mM in 24 h coupled with the in situ regenerated NADH.

In photocatalytic and enzymatic reactions, different media are typically used. To improve the catalytic efficiency of enzymes under incompatible conditions, enzymes are usually wrapped in MOFs to enhance their activity and stability. Song and co-workers encapsulated FDH in MAF-7 to protect FDH and enhance electron transfer of NADH cofactor regeneration using TPE-C_3N_4 (Figure 12b).[164] After 9 h of continuous photocatalysis, the formic acid of ∼16.75 mM is produced in the system, which is 3.24-times higher than that of the homogeneous reaction product (5.17 mM). Similarly, Schmuki and co-workers have delineated the strategy employed for the in situ fabrication of MIL-125 MNRs featuring a hierarchically porous structure that accommodates enzymes within TiO_2 nanochannels.[8] In this work, the encapsulation of CytC molecules in MOF-MNRs can enhance the coupling interaction between the $\pi-\pi^*$ transition of heme and nearby aromatic amino acids, thereby improving the catalytic activity of the enzyme. At the same time, anchoring Au NPs on the surface of MOF-MNRs effectively enhances the photocatalytic activity of MIL-125/TiO_2 in the visible range. In the photoenzyme cascade catalytic system, MOF-MNRs can be used as both a photocatalyst and a protective shell for enzymes, which improves the catalytic activity and stability of the catalyst. However, due to the harsh synthetic conditions of many photoactive MOF-MNRs, they do not meet the packaging conditions of enzymes, limiting their application in photoenzyme cascade catalysis.

6. SUMMARY AND OUTLOOK

Inspired by biological systems, the development of MNRs with functionalities such as controlled substance selectivity, active species protection, intercommunication between substances, and provision of microenvironments represents a crucial direction in the advancement of catalysts for cascade reactions. MOFs, with their uniformly connected porous microenvironments and abundant tunable chemical functionalities, have emerged as highly researched nanomaterials in recent years. In this Perspective, we provide an overview of the design and fabrication strategies for various types of MOF-MNRs. These reactors, incorporating MOFs with diverse active sites, have found extensive applications in a wide range of chemical, enzymatic, and chemical−enzymatic cascade reactions, demonstrating exceptional catalytic performance. It is worth noting that compatibility issues remain a major challenge in the development of cascade reactions. We focus on discussing strategies that utilize MOF-MNRs to address compatibility issues in various cascade reactions. Precise loading of active sites within the spatial location of MOF-MNRs can effectively prevent catalyst deactivation caused by contact deactivation. Additionally, significant progress has been made in addressing compatibility issues such as catalyst stability and reaction rate through the microenvironments provided by MOF-MNRs. Despite the potential of MOF-MNRs in cascade reactions, their application still faces several challenges.

6.1. Design and Fabrication of MOF-MNRs

The development of novel design strategies and advanced fabrication methods for multi-site immobilization systems may lead to new application scenarios and broader applicability of cascade reactions. For instance, potential areas for improvement include the optimization of MOF-MNRs synthesis and assembly processes, refinement of Picking emulsion preparation techniques, and precise separation of active sites. Furthermore, although the preparation of catalysts with single active sites for chemical catalysis and enzyme immobilization has reached a mature stage, attention should be given to the development and fabrication of large-scale cascade catalysts suitable for industrial production, including scaling up MOF-MNRs production, catalyst shaping techniques, and practical industrial catalysis.

6.2. Compatibility of Reaction Condition

MOF-MNRs need to withstand the specific cascade reaction conditions, including temperature, pH, solvents, and reactants. Developing MOF-MNRs that are stable and active under the reaction conditions is crucial for their successful application in

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cascade reactions. One important direction in biocatalysis is the modification of enzymes and other biocatalysts to adapt them to harsh conditions. For chemical catalysts, there has been an increasing emphasis on exploring novel catalytic pathways. One strategy involves the development of catalytic reactions in aqueous or solvent-free systems to promote green chemistry. Numerous metal and organic catalytic reactions have been demonstrated to occur in aqueous solutions or solvent-free conditions, providing a benchmark for cascade reactions that are enzyme-catalyzed. Moreover, novel reaction pathways can replace the harsh conditions required for traditional reactions. For example, CuRu bimetallic nanoclusters supported on a carrier can facilitate the production of 1,4-cyclohexanedimethanol from dimethyl terephthalate under mild conditions, whereas traditional industrial methods require harsh conditions involving high temperature and pressure (493 K, 4.0 MPa).[165] Exploring novel chemical reaction pathways not only broadens the scope of chemical cascade reactions but also presents new opportunities for cascading between chemical catalysts and enzymes.

6.3. Compatibility of Reaction Rate

The integration of MOF-MNRs with other functional materials presents an opportunity to explore alternative reaction pathways to address the reaction rate compatibility challenges in cascade catalysis. One such example is the incorporation of photothermal effects, which have been shown to be efficient but limited in their action range. Due to the small size and volume of nanoparticles, when heated, it is limited by the thermal diffusion effect and heat loss effect. The generated heat cannot be distributed to the surrounding environment quickly and usually can only be controlled to heat on its surface and inside. Therefore, the overall reaction temperature of the reaction system containing the nanoheater will not change greatly, which can ensure the improvement of chemical catalyst activity while maintaining the stability of the biocatalyst. Therefore, the integration of nanoscale heaters with photothermal effects into microreactors presents a promising avenue for addressing temperature compatibility issues among different catalysts. Furthermore, the exploration of responsive materials that can be triggered by electricity, magnetism, pH, and other stimuli to regulate the reaction microenvironment within MOF-MNRs holds great potential for resolving incompatibilities between multiple active sites.

6.4. Compatibility of Multi Catalysts

For the MOF-MNRs substrate, the dissolution of metal ions and organic ligands during the cascade reaction usually acts as an inhibitor of enzymes or MNPs. Therefore, the design and development of MOF-MNRs with varying compartmentalization to accommodate different types of catalysts in distinct spatial locations, ensuring both activity and stability while facilitating the mutual exchange of reactive substances, will advance the MNRs' ability to address challenges related to catalyst compatibility. In addition, novel assembly forms of MNRs such as biomimetic cell structures are still required to maintain the optimal state of catalysts. As such, there is a pressing need for continued research and development in this area to fully unlock the potential of MNRs as powerful tools for cascade reactions.

6.5. Develop New Types of Cascade Reactions

Enzyme and chemical catalysts are typically chosen and optimized for specific reactions or substrates. When two catalysts are utilized, it is crucial to consider their respective characteristics and limitations, making appropriate selections and optimizations to ensure the efficiency and selectivity of the cascade reaction. Machine learning has the capability to discover novel catalysts and reactions by mining and analyzing vast amounts of chemical and biological data. Machine learning models can identify new catalyst structures, reaction pathways, and reaction conditions, driving the development and innovation of cascade reactions.

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Author Contributions

[§]P.W. and Y.Z. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Peng Wu** conceptualization, writing-original draft; **Yanhua Zhao** writing-original draft; **Xinglong Zhang** conceptualization, writing-review & editing; **Yun Fan** writing-review & editing; **Suoying Zhang** writing-review & editing; **Weina Zhang** conceptualization, funding acquisition, supervision, writing-review & editing; **Fengwei Huo** conceptualization, funding acquisition, supervision, writing-review & editing.

Notes

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