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Towards hybrid MOF@COF and COF@MOF platforms for next-generation biocatalysis

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Enzyme immobilization is central to advancing sustainable biocatalysis, yet conventional supports often fail to simultaneously provide structural protection, mass transport, and chemical tunability. Traditional support materials often lack the optimal combination of porosity, stability, and surface functionality needed to preserve enzyme activity. Metal–organic frameworks (MOFs) and covalent organic frameworks (COFs) have emerged as promising hosts due to their high surface area, tunable porosity, and chemical versatility. Recent developments in hybrid architectures MOF@COF and COF@MOF offer a synergistic platform that integrates the structural flexibility and catalytic tunability of MOFs with the robustness and stability of COFs. This review highlights the design principles, immobilization strategies, and catalytic behavior of enzyme@MOF@COF and enzyme@COF@MOF systems. We discuss advances *in situ* encapsulation, covalent binding, and adsorption-based immobilization, emphasizing how hybrid frameworks enhance enzyme protection, substrate diffusion, and cascade catalysis. Key challenges including scalability, enzyme leaching, and synthesis reproducibility are also critically examined. Finally, we outline future opportunities for rational design of hybrid frameworks that enable precise enzyme spatial organization and multi-enzyme systems, paving the way for next-generation, sustainable biocatalytic technologies.

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1. Introduction

While industrial development and technological progress have greatly improved modern life, they have also introduced significant environmental challenges. In response, industries are increasingly turning towards cleaner and more sustainable production approaches to reduce their environmental footprint.[1–3] These efforts reflect the principles of green chemistry, which focus on designing and optimizing catalytic systems for efficient and environmentally friendly processes.[4–6] A good catalyst not only improves product yield and simplifies synthesis but also lowers energy use and waste generation.[7,8] Among the different types of catalysts, biocatalysts have received special attention because of their high activity, selectivity, and compatibility with green processes.[9–13]

Enzymes are versatile, highly efficient, and environmentally benign biocatalysts widely applied across diverse chemical processes.[14–16] However, their three-dimensional structures are mainly stabilized by weak non-covalent interactions, making them sensitive to external factors such as temperature, pH, and certain chemical agents.[17–19] These conditions can easily alter or even deactivate their biological function. To overcome these challenges, several approaches have been explored, including genetic engineering, chemical modification, enzyme immobilization, and adjustment of the reaction medium.[20–23] Among these strategies, enzyme immobilization stands out as an effective and practical method. By confining enzymes on solid supports, immobilization enhances their operational stability and maintains catalytic activity, allowing reactions to proceed even in media that would otherwise be biologically incompatible.[24–26] Moreover, immobilized enzymes can often be recovered and reused, improving process efficiency.[27,28] A key challenge, however, lies in selecting or designing support materials that minimize structural damage and preserve enzyme activity.[29] Hence, identifying suitable carriers remains crucial for advancing the performance of immobilized biocatalysts.

Over the years, a variety of porous materials have been explored as supports to enhance enzyme stability and usability in catalysis. Materials such as mesoporous silica, hydrogels, sol–gel matrices, MOFs, and COFs have all shown potential.[30–33] However, conventional supports often face practical limitations. For example, tailoring the pore structure of mesoporous silica or preventing enzyme leaching can be difficult, while hydrogels and organic microparticles tend to swell or degrade, leading to enzyme loss and reduced mass transfer.[34,35] Sol–gel matrices can restrict the diffusion of larger molecules, and enzymes encapsulated within them may partially denature during synthesis.[36] Altogether, challenges such as low enzyme

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loading, leakage, and conformational instability have limited the effectiveness of these materials.[14,27] This has led to growing interest in developing more versatile carriers with tunable pore sizes, chemical stability, and environments that can preserve enzyme structure and activity under diverse reaction conditions.

To overcome these limitations, recent advances in reticular chemistry have led to remarkable progress in the design of MOFs and COFs.[16,18] These materials can be precisely engineered at the atomic level, allowing fine control over their composition, structure, pore size, and surface functionality.[37,38] Their combination of large surface areas, high porosity, and structural tunability provides an exceptional platform for enzyme immobilization.[39–41] The modular nature of MOFs built from metal nodes and organic linkers enables flexible architectures and the introduction of catalytic metal centers, while COFs, composed entirely of organic units connected through strong covalent bonds, offer outstanding thermal and chemical stability.[42,43] These features collectively make MOFs and COFs ideal hosts for enzymes of various sizes, addressing many of the limitations observed in traditional porous supports. Nevertheless, both frameworks also have their weaknesses: MOFs can be susceptible to hydrolysis, and COFs may suffer from limited pore accessibility and lower enzyme loading.[18,19] Recognizing their complementary characteristics has motivated growing interest in hybrid MOF–COF systems, which aim to merge the advantages of both materials to achieve enhanced enzyme immobilization and stability.

In such composites, the structural flexibility and catalytic tunability of MOFs can be combined with the robustness and chemical stability of COFs, resulting in materials with hierarchical porosity, enhanced mass transport, and improved environmental tolerance. These hybrid MOF–COF architectures can provide optimized microenvironments for enzyme immobilization, facilitating better substrate diffusion, stronger enzyme–support interactions, and higher catalytic efficiency. The synergy between MOF and COF components thus opens a new direction for the design of advanced biocatalytic materials.

This review aims to highlight the potential of enzyme@MOF@COF systems, emphasizing their structural and functional advantages, and to outline future research directions toward sustainable, high-performance enzyme-based catalysis. Recent reviews have extensively covered enzyme immobilization in MOFs and COFs, focusing on synthesis methods, structural properties, and catalytic applications. However, these studies largely treat MOFs and COFs as independent systems and do not systematically address how hybrid MOF@COF architectures influence enzyme behavior at the interface. In contrast, this work provides a comparative and mechanistic review, emphasizing how the integration of these frameworks creates synergistic effects that govern enzyme stability, diffusion, and catalytic performance.

2. Framework properties

2.1 High porosity, tunability, and functionality

MOF@COF hybrids combine ultrahigh surface area and metal coordination sites (typical of MOFs) with the chemical stability and modular functionality of COFs. This synergy provides multiple anchoring chemistries and adjustable microenvironments (hydrophobic pockets, polar domains, metal coordination centers), enabling optimization of enzyme–support interactions and substrate accessibility. Reviews demonstrating how tailoring pore size and surface chemistry is crucial to maintain enzyme structure and enhance catalytic performance have been presented in literature.[44,45]

2.2 Structural diversity (MOFs *vs.* COFs)

MOFs offer diverse metal nodes (Zr, Fe, Cu, *etc.*) and labile coordination chemistry that can provide Lewis-acidic or metal-coordinating environments beneficial for some enzymes or

Table 1 Comparative analysis of MOF-only, COF-only, and MOF@COF hybrid systems for enzyme immobilization

Parameter	MOF-only systems	COF-only systems	MOF@COF hybrid systems
Structural stability	Generally high (especially Zr-based MOFs); can suffer under harsh aqueous/biological conditions	Moderate; often limited hydrolytic stability depending on linkage chemistry	Enhanced stability due to synergistic framework integration and protective shell effects
Enzyme loading capacity	Moderate to high; governed by pore size and surface area	High; tunable pore structures and high surface area facilitate loading	High; hierarchical porosity enables improved enzyme encapsulation and distribution
Catalytic performance	Good; may be limited by diffusion constraints and enzyme leaching	Variable; improved accessibility but sometimes lower structural robustness	Enhanced; improved mass transfer, reduced leaching, and better enzyme stabilization
Enzyme leaching	Possible, especially with adsorption-based immobilization	Moderate; depends on interaction strength	Reduced due to combined confinement and interfacial interactions
Scalability	Moderate to high (some industrial translation exists)	Limited large-scale production	Currently limited; scale-up remains a key challenge
Key advantages	High crystallinity, tunable chemistry, well-studied systems	Tunable functionality, high surface area	Synergistic properties: stability, tunability, improved catalytic efficiency
Limitations	Enzyme leaching, pore blockage, stability in water	Stability issues, fewer established protocols	Synthetic complexity, cost, scalability challenges

catalytic cascades. COFs contribute rigid, covalent linkages (imine, keto–enamine, triazine frameworks) and extended π-systems that improve chemical stability, reduce metal leaching concerns, and provide tailored surface chemistries for covalent enzyme attachment. The hybrid architecture thus allows selection of the "best of both" material properties for specific enzymes and processes.

2.3 Enzyme-compatible microenvironments

Successful immobilization balances confinement (to retain enzyme) against steric restriction (which can limit turnover). The pore sizes, channel connectivity, and local polarity of hybrids can be engineered to match enzyme dimensions and to stabilize active conformations *via* hydrogen bonding or hydrophobic packing, strategies that are repeatedly highlighted as central to preserving activity in MOF- and COF-based biocomposites.[46]

To provide a clearer and more critical comparison of the key features of different immobilization platforms, the main differences between MOF-only, COF-only, and hybrid MOF@COF systems are summarized in Table 1.

3. Strategies for enzyme immobilization in hybrid systems

The combination of MOFs and COFs in MOF@COF and COF@MOF hybrid architectures offers versatile platforms for enzyme immobilization, merging MOFs' rich coordination chemistry and high surface areas with COFs' covalent robustness and tunable pore/chemical environments.[47] Recent studies have explored different ways to combine MOFs and COFs into hybrid materials suitable for enzyme immobilization. One common method is core–shell growth, where a MOF core is coated with a COF layer to form a MOF@COF structure.[44,48] This design takes advantage of the high surface area and tunable pores of MOFs while adding the chemical stability and selective permeability of COFs. In some cases, the MOF template is later removed, leaving behind a COF capsule that still contains the enzyme.[49] These approaches allow researchers to control the shell thickness and adjust how easily small molecules move through the material.

COF-based systems have also shown promise for improving enzyme stability. Reviews highlight that COF capsules can protect enzymes from harsh solvents, temperature changes, and protease attack. The porous and ordered structure of COFs also supports the co-immobilization of multiple enzymes, enabling efficient multi-enzyme cascade reactions.[50,51] On the other hand, studies on MOF-based immobilization emphasize the role of metal coordination, pore structure, and buffer conditions in enzyme loading and activity.[45] Combining MOFs and COFs into one hybrid system can therefore bring the best of both worlds, that is, the strong interactions and high loading capacity of MOFs with the robustness and chemical flexibility of COFs. As a result, MOF@COF and COF@MOF hybrids are emerging as versatile platforms for advanced biocatalysis.

3.1 Immobilization mechanisms in hybrid systems

Enzymes can be tied into hybrid materials (such as enzyme@MOF@COF or enzyme@COF@MOF systems) by different mechanistic strategies, each of which affects loading efficiency, catalytic activity retention, and stability under operation. The main approaches are: *in situ* encapsulation, post-synthetic loading or covalent attachment, surface adsorption (including electrostatic interactions), and multi-enzyme cascade designs.

3.1.1 *In situ* encapsulation during hybrid formation. In this approach the enzyme is present right when the framework (or hybrid framework) is being formed, so that the porous matrix grows around the biomolecule, entrapping it in a protective pore environment. The benefit is strong physical confinement and often enhanced stability (for example against protease digestion or harsh solvents). MOFs have been widely used for *in situ* encapsulation of enzymes.[52–54] One example is the study where ZIF-8 MOF was grown around horseradish peroxidase on magnetic particles and the enzyme was shown to greatly increase stability.[55] Also, COF studies describe direct enzyme encapsulation during COF growth, achieving high loading and minimal leaching.[2,50,56] In a hybrid context, a templated route (enzyme@MOF followed by COF shell) is analogous to this mechanism, the enzyme becomes part of the host during growth of the shell and core.[49,57,58] This method offers high protection and minimal enzyme leakage, but requires synthesis conditions compatible with enzyme survival.

Li *et al*[49] developed an elegant *in situ* encapsulation strategy in which enzymes and other biomacromolecules were immobilized during the formation of MOF-templated COF capsules. In their approach, a MOF core first served as a sacrificial scaffold onto which a COF shell was grown under mild, enzyme-compatible conditions. The enzyme molecules (*e.g.*, cytochrome c) became physically confined within the growing COF shell, producing stable enzyme@COF capsules after the MOF template was removed. This process ensured uniform coating, preserved enzyme activity, and allowed precise control over capsule thickness and permeability. The work demonstrated that *in situ* growth of a COF layer around an enzyme@MOF composite provides an efficient route to create protective hybrid microenvironments for biocatalysts. The synthetic procedure for the enzyme@MOF/COF composite is shown in Fig. 1.

A refined *in situ* route for constructing enzyme@COF nanoreactors using a MOF@COF hybrid strategy was also demonstrated by Zhong *et al.*[57] In their approach, glucose oxidase (GOx) was first encapsulated within a ZIF-90 framework through coordination between Zn^{2+} ions and imidazolate linkers. The enzyme-loaded MOF core then served as a structural and reactive template for the *in situ* growth of a COF-42-B shell *via* Schiff-base condensation between terephthalaldehyde and 1,3,5-tris(4-aminophenyl)benzene. Subsequent removal of the ZIF-90 core yielded hollow COF capsules that retained the enzyme inside a stable, porous microenvironment as shown in Fig. 2. The resulting GOx@COF capsules exhibited enhanced catalytic activity, high substrate accessibility, and superior stability compared to free enzymes or single-component supports.

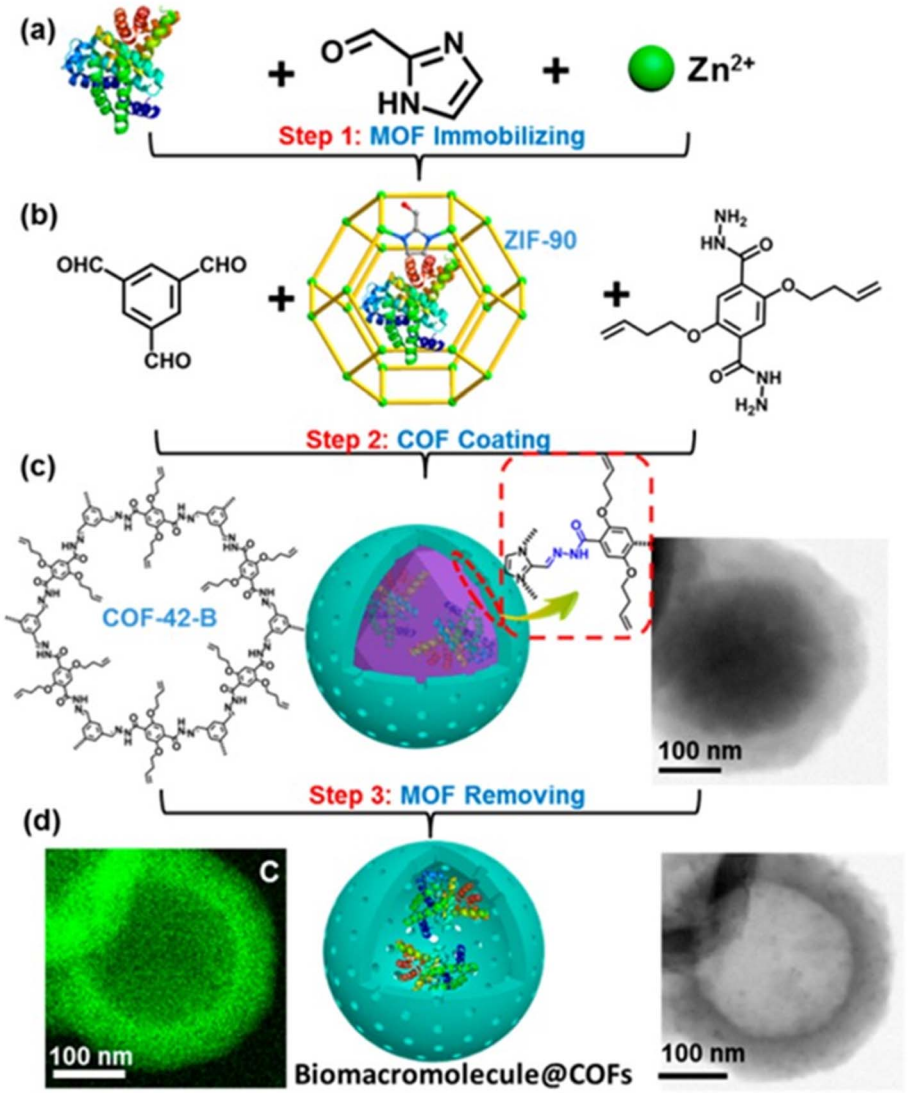

Fig. 1 Schematic illustration of the stepwise synthesis of biomacromolecule@COF hybrid capsules through an *in situ* MOF@COF templating strategy. (a) Enzyme immobilization within ZIF-90. (b) *In situ* growth of a COF-42-B shell on the enzyme@ZIF-90 composite (c) removal of the MOF template to yield hollow COF capsules with enzymes confined inside (biomacromolecule@COFs). (d) TEM and EDX images confirm the hollow structure and carbon-rich COF shell.[49] Reproduced with permission from ref. 49. Copyright © 2020, American Chemical Society.

Furthermore, this strategy enabled precise spatial organization of multiple enzymes within COF capsules, facilitating the construction of efficient cascade systems. Glucose oxidase (GOx) and cytochrome c (Cyt c) were co-encapsulated in the COF shell to form a Gox-Cyt c cascade complex. The integrated hybrid exhibited approximately 1.6-times higher catalytic activity compared with the free enzymes, and the resulting GOx-Cyt c@COF nanoreactor was effectively applied for sensitive glucose detection in serum. This study highlighted a promising pathway for developing COF-based platforms for advanced enzyme immobilization and biocatalysis. This strategy exemplifies how *in situ* encapsulation can combine the ordered porosity and mild coordination chemistry of MOFs with the chemical robustness and tunable permeability of COFs creating multifunctional platforms for cascade catalysis and biosensing applications.

3.1.2 Post-synthetic loading or covalent attachment. Post-synthetic loading of enzymes means that, after the hybrid material has been synthesized, the enzyme can be introduced either by diffusion into the framework pores or through covalent attachment to functional groups such as amine, carboxyl, aldehyde, or epoxy linkers present on the framework surface. This strategy gives control over enzyme orientation and loading amount. For example, reviews of MOF-enzyme immobilization discuss how covalent linking helps avoid enzyme leaching and enhances operational stability.[60,61] In hybrid materials, one might first build a MOF@COF structure with surface functional groups (–NH_2, –CHO) and then attach the enzyme, or embed the enzyme in the COF shell by covalent binding. This method is good for controlled enzyme positioning and strong retention, but may require more modification steps and risk affecting enzyme activity if the binding is too rigid.

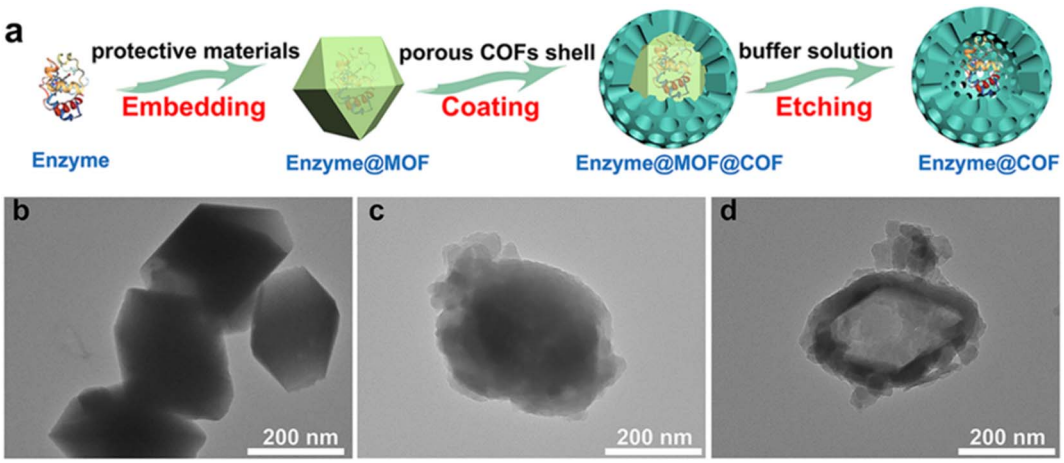

Fig. 2 Schematic illustration of the *in situ* synthesis of biomacromolecule@COF hybrid capsules. Step 1: enzyme immobilization within ZIF-90 (MOF) *via* metal ions and linker coordination. Step 2: growth of a COF shell on the enzyme@MOF template through Schiff-base condensation. Step 3: selective removal of the MOF core using buffer solution to yield a hollow COF capsule encapsulating the enzyme. TEM images for Cyt c@ZPF-1 (b), Cyt c@ZPF-1@COF (c), and Cyt c@COF (d).[57] Reproduced with permission from ref. 57. Copyright © 2023, American Chemical Society.

Experimental studies to date most often employ the templated approach for encapsulating enzymes within MOFs and then growing COF shells around the enzyme@MOF composite or etching the MOF to yield COF capsules. This is done to achieve protection, tunable shell thickness, and cascade capabilities.[49,57,58] In contrast, post-synthetic covalent immobilization of enzymes onto pre-formed MOF@COF hybrids using the hybrid's surface functional groups appears rare in the literature, representing an important experimental gap and a promising direction for future work.

3.1.3 Surface adsorption and electrostatic interactions. Surface adsorption is one of the most straightforward and mild strategies for enzyme immobilization in porous frameworks, including MOF–COF hybrid systems. In this approach, enzymes interact non-covalently with the framework surface through weak forces such as hydrogen bonding, electrostatic attraction, hydrophobic interactions, and π–π stacking. The method preserves the native enzyme conformation, avoids harsh chemical modification, and allows reversible immobilization, making it ideal for biosensing and catalytic applications.[61] However, limited binding strength may cause enzyme leaching during continuous operation. The concept of adsorptive enzyme confinement was demonstrated by Li *et al.*[49] who designed MOF@COF core–shell nanostructures where the COF shell provided an accessible, functionalized surface for enzyme. Even though originally *in situ* synthesis was used to immobilize the enzymes in the MOF frameworks, their study demonstrated that surface hydroxyl and imine sites on the COF shell could effectively anchor enzymes, enhancing catalytic stability compared to bare MOFs. Similarly, Zhong *et al.*[57] constructed MOF-templated COF capsules capable of hosting enzymes *via* both *in situ* encapsulation and post-synthetic adsorption. The enzyme molecules were physically adsorbed onto the inner COF surfaces through electrostatic and hydrogen-bonding interactions, forming nanoreactors with enhanced activity and diffusion efficiency.

Hybrid MOF@COF nanozyme studies,[62,63] further illustrate how core–shell microenvironments and surface chemistry can be tuned to favor adsorption/entrapment and modulate catalytic outcomes. While pure post-synthetic adsorption onto pristine MOF@COF surfaces (no template, no electrode modifiers) is still less common, the templated capsule and hybrid-electrode literature together provide clear experimental evidence that adsorption is a feasible and practical immobilization route in hybrid systems. Collectively, these studies highlight that adsorption-based immobilization in MOF–COF hybrid systems combine the advantages of high surface area, tunable pore environments, and chemical functionality from both frameworks.

3.1.4 Multi-enzyme cascade designs. Multi-enzyme cascade reactions, where the product of enzyme A is the substrate for enzyme B, are central to natural metabolism and highly attractive for synthetic biocatalysis because they reduce intermediate handling, improve overall conversion, and can shift unfavorable equilibria.[64] MOF/COF hybrid platforms are particularly well suited to host cascade systems because their hierarchical porosity and modular chemistry allow spatial organization, controlled substrate diffusion, and stable microenvironments for each enzyme. Two complementary hybrid design concepts have emerged experimentally: (i) layered/hierarchical architectures (multi-shelled MOFs or core–shell MOF@COF) that place enzymes in sequence across compartments,[49,64] and (ii) templated hollow COF capsules derived from enzyme@MOF templates that co-localize two or more enzymes inside a protective shell.[57] Both strategies aim to promote substrate channeling (short diffusion paths between active sites) and to protect sensitive enzymes from denaturation or proteolysis. However, when compared with established industrial cascade systems such as co-immobilized enzymes on polymer resins,[65] silica supports,[34] or cross-linked enzyme aggregates (CLEAs),[66] these hybrid systems remain largely at the

proof-of-concept stage, with challenges in scalability, reproducibility, and long-term operational stability still limiting their practical deployment.

3.1.4.1 Layered/hierarchical MOF architectures. Multi-shelled MOFs and related hierarchical MOF constructs allow stepwise positioning of enzymes in concentric shells or layers. Man *et al.*,[60] used multi-shelled ZIF-8 structures to place enzymes at defined radial positions, demonstrating that such spatial ordering significantly increased tandem biocatalytic efficiency relative to mixed, unconfined enzymes. Their work shows that compartmentalized shells can both concentrate intermediates near the next catalytic site and protect intermediate-sensitive enzymes in inner compartments. Key factors for success were control over shell number/thickness, pore connectivity between shells, and retention of enzyme activity during assembly.[49]

3.1.4.2 Templated COF capsules for co-localization. An alternative, experimentally validated route uses a MOF as a sacrificial or structural template: enzymes are first loaded into a MOF, a COF shell is grown around the enzyme@MOF composite, and the MOF core can be retained or selectively removed to yield a hollow COF capsule that contains the enzymes. Li *et al.*[49] established this templated approach and showed precise control of shell thickness and permeability, enabling protective, enzyme-containing COF capsules. Zhong *et al.*[57] applied this strategy to co-encapsulate GOx and Cyt c; the resulting GOx-Cyt c@COF cascade showed ~1.6× higher cascade activity than the free enzymes and was used as a sensitive nanoreactor for glucose detection in serum as shown in Fig. 3. Meng *et al.*[58] extended templated COF capsules to a lactate synthesis cascade, demonstrating good activity and reusability. These studies illustrate that templated COF capsules are versatile platforms for co-immobilizing cascade partners with tunable mass transport properties.

3.1.4.3 Mechanistic considerations for multienzyme cascade reactions. By positioning enzymes close to one another (within nanometre–micrometre scale domains), hybrid hosts reduce the diffusional distance of intermediates and increase their effective local concentration at the downstream enzyme. This substrate channeling reduces intermediate loss to bulk solution and can accelerate overall cascade rates or shift equilibria. Reports comparing co-localized *vs.* freely mixed enzyme systems consistently find improved apparent turnover and product yields for the co-localized versions in hierarchical hosts.[64]

Experimental evidence highlights several tunable parameters that determine cascade performance in hybrid systems, including the following: (1) compartment size and shell thickness, where thicker shells increase protection but can impede substrate flux, whereas thin, porous shells favor higher rates but less shielding. Templated studies emphasize tailoring shell thickness to balance protection and diffusion.[49] (2) Pore connectivity and selectivity. Channel networks that allow fast diffusion of desired intermediates while blocking inhibitors or proteases improve cascade robustness.[64] (3) Enzyme loading and stoichiometry. Optimal enzyme ratios minimize bottlenecks; many studies report tuning loadings to match kinetic demands of each cascade step.[58] (4) Synthesis conditions (mildness). Enzyme activity is sensitive to pH, solvent, and temperature. Successful templated or layered approaches adopt mild, enzyme-compatible growth conditions (room temperature/near-neutral pH, short exposure to reagents).[49,57]

MOF/COF hybrids, particularly templated COF capsules and layered MOF@COF architectures, offer a flexible toolbox for constructing cascade nanoreactors combining high loading, selective permeability, and spatial organization. Future directions likely to accelerate practical application include: rational pore engineering for selective intermediate channeling; incorporation of cofactor regeneration systems; scalable, mild syntheses for consistent enzyme placement; and head-to-head comparisons of layered *vs.* templated capsule designs across representative cascade pairs to extract general design rules. Given the early, positive experimental results by scientists,[49,57,58,62] hybrid cascade platforms are positioned to bridge

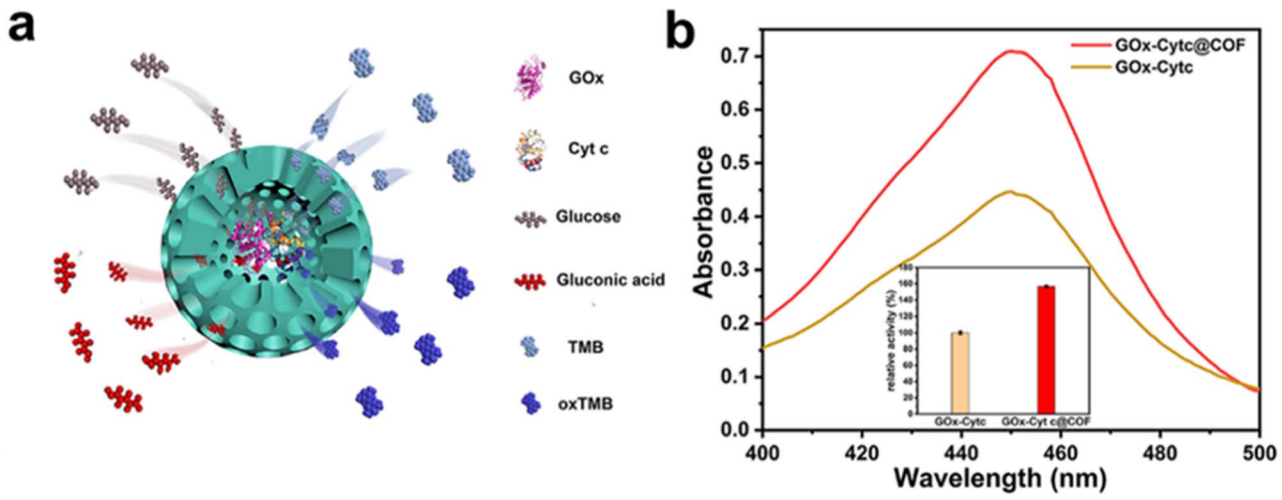

Fig. 3 (a) Representation of the multienzyme cascade reaction in a COF capsule, (b) the activity of the cascade GOx-Cyt c@COF capsule compared to free GOx-Cyt c.[57] Reproduced with permission from ref. 57. Copyright© 2023, American Chemical Society.

lab-scale demonstrations and application-focused biocatalytic processes.

4. Enzyme immobilization in hybrid MOF@COF and COF@MOF

Several MOFs have been successfully used to date for enzyme immobilization. Zirconium based MOFs, for example UiO-66, has shown great promise due to its exceptional hydrolytic stability and modifiable linkers (–NH_2, –OH) that permit covalent crosslinking and strong hydrogen-bonding interactions with enzyme residues. It has been widely used for single and multi-enzyme systems.[67–69] MIL-101 has also been used due to the large mesoporous cages that enable high enzyme loading and facile mass transport.[68,69] MIL-88 due to framework flexibility can adapt to guest dimensions,[70,71] sometimes improving accommodation of larger proteins.[68] NU-1000 has hierarchical pore architecture and exposed metal sites have been exploited in enzyme stabilization and hybrid constructs.[72,73]

Different COF linkages bring distinct advantages for enzyme immobilization. Imine-linked COFs are synthetically versatile and easily functionalized, making them convenient for mild, *in*

Table 2 Key properties and examples of enzyme systems suitable for the COF types

COF type	Key properties	Suitable enzyme systems	Ref.
Imine-linked COFs	Easy to synthesize from aldehyde + amine monomers; highly tunable pore size and surface functionalization (Schiff-base chemistry allows post-synthetic modification). Good for mild, *in situ* immobilization and covalent linking *via* Schiff-base routes	Horseradish peroxidase (HRP) and glucose oxidase (GOx) immobilized on imine-COFs for colorimetric sensing of H_2O_2 and glucose	76 and 77
β-Ketoenamine COFs	Exceptional chemical and hydrolytic stability (acid/base resistance), good crystallinity; suitable for operations in harsher pH/solvent conditions. Ideal when robust support is required	Enzymes requiring robust support: *e.g.*, lipase immobilized in β-ketoenamine COF capsules, operating in aqueous/organic solvent mixtures	78
Triazine COFs	Nitrogen-rich, polar surfaces that promote hydrogen bonding/electrostatic adsorption; strong π-conjugation (useful for redox enzymes and electron transfer). Synthesis can be more forcing (thermal/polycondensation) but yields highly stable networks	Redox enzymes (*e.g.*, dehydrogenases, oxidases) or multi-enzyme systems where electron transfer and polar surface interactions matter; for instance, COFs used for enzyme immobilization under mild *in situ* conditions	50

Table 3 Examples of some MOF@COF hybrids used for enzyme immobilization, method of immobilization and key findings

Hybrid type	Immobilization method	Enzyme(s)	Key findings	Ref.
MOF-templated COF capsule	*In situ* encapsulation during COF shell formation (MOF core sacrificially etched)	Catalase (CAT), cytochrome c (Cyt c)	Enzymes encapsulated within COF capsules retained >90% activity; improved solvent and temperature stability	49
COF capsule nanoreactor (MOF-templated)	Co-encapsulation within COF capsule using ZIF-8 as template	Glucose oxidase (GOx), cytochrome c	Built cascade biocatalytic system for glucose detection; exhibited higher signal response and durability	57
MOF → COF capsule (bioactive)	Stepwise biomineralization + COF shell growth	L-Lactate dehydrogenase (LDH), formate dehydrogenase (FDH)	Created enzyme-loaded COF capsules; showed enhanced cascade efficiency in lactate synthesis; reusability up to 10 cycles	58
MOF@COF nanozyme hybrid	Electrostatic adsorption (model system for enzyme mimicry)	Nanozyme used to mimic oxidase/peroxidase	Demonstrated controllable microenvironments for catalytic reactions; informs design for real enzyme encapsulation	59

situ immobilization or for further covalent modification *via* Schiff-base chemistry.[51] β-Ketoenamine COFs combine ordered porosity with superior chemical and hydrolytic stability, which favors immobilization for reactions performed in harsher pH or organic co-solvent conditions.[74] Triazine-based COFs (CTFs) are nitrogen-rich and polar, promoting hydrogen-bonding and electrostatic interactions that can be advantageous for redox enzymes and for electrode-coupled biosensing applications.[75] Recent experimental work also shows that introducing hierarchical porosity (*e.g.*, COF foams) expands the range of enzymes that can be accommodated and improves recyclability and stability in multi-enzyme tandem catalysis.[74] Key properties including examples of suitable enzyme systems of the COFs are shown in Table 2.

Recent studies report that COFs alone, or when integrated with MOFs, forming COF@MOF or MOF@COF hybrids, with their modular design enables control over pore environment, hydrophilicity, and surface functionality. These are the key factors that determine enzyme orientation and activity within hybrid biocatalytic systems. Table 3 shows some examples of COF@MOF hybrids used in enzyme immobilization, including the key findings.

5. Strategies to explore in future research

The use of hybrid MOF@COF and COF@MOF architectures for enzyme immobilization remains largely unexplored, despite extensive studies on MOFs and COFs as individual carriers. To advance this emerging field, researchers must tailor synthetic approaches, material design, computational modeling, experimental assessment, and device integration to the specific requirements of fragile biocatalysts. Developing these elements in a systematic manner could transform enzyme@MOF@COF assemblies from a theoretical concept into robust and practical catalytic platforms.

A major challenge in constructing enzyme@MOF@COF hybrids lies in developing synthetic routes compatible with enzyme stability. Conventional COF syntheses generally require high temperatures (120–180 °C), organic solvents such as dioxane or mesitylene, and prolonged reaction times, all of which disrupt protein tertiary structures.[79] Similarly, early MOF syntheses often relied on solvothermal methods that denature biomolecules, limiting their direct use in biocatalysis.

Recent studies, however, demonstrate that crystalline frameworks can be obtained under mild and bio-friendly conditions. For example, imine-linked COFs have been synthesized in water at room temperature, while scalable approaches such as ultrasonication-assisted nucleation and liquid-crystal-templated aqueous synthesis yield highly ordered COFs without harsh solvents or heating. These advances create opportunities for directly growing a COF shell around enzyme-loaded MOFs while retaining enzymatic activity. On the MOF side, Zr-based frameworks such as UiO-66 can now be synthesized in aqueous media using benign modulators like acetic acid, with crystallization times reduced to minutes. Moreover, biomimetic mineralization enables enzymes to be encapsulated during MOF formation, producing composites where the enzyme remains both protected and catalytically accessible. Future work should optimize COF shell growth kinetics under mild conditions, potentially through Lewis acid catalysis in water or template-directed crystallization.[19]

5.1 Bio-friendly linkers and solvents

The design of linkers, solvents, and additives is central to maintaining enzyme stability during immobilization. In COFs, hydrophilic, zwitterionic, or PEG-functionalized linkers enhance enzyme affinity, retention, and dispersion, while in MOFs, harsh mineral acids have been replaced by mild modulators such as acetic or formic acid to allow controlled crystal growth under gentle conditions. Strategies such as dynamic exchange enable post-synthetic immobilization through ligand substitution, avoiding exposure to solvothermal environments. Notably, functionalization with photoactive ligands has expanded functionality; for example, incorporation of tetra(4-carboxyphenyl) porphine (TCPP) into UiO-66 enhanced catalytic activity and photoelectric performance, enabling semi-artificial photosynthetic systems capable of NADH regeneration and FDH immobilization.

For MOF@COF hybrids, interface engineering offers unique opportunities. Surface modification of MOFs with –OH or –COOH groups can promote COF nucleation while stabilizing enzymes, and solvent systems such as buffers, glycerol–water mixtures, or deep eutectic solvents further preserve protein structure. Beyond stabilization, integrating photoactive components allows multifunctional platforms where MOF metal centers and COF photoactive linkers cooperate to support photoenzymatic cascades (*e.g.*, NADH regeneration, radical initiation). Compared with conventional immobilization strategies (surface attachment, covalent bonding, mesopore encapsulation, co-precipitation), which often suffer from stability and mass-transfer limitations, these bio-friendly and multifunctional approaches are more versatile. Recent work, including dynamic exchange strategy, demonstrates how enzymes can act as macro-ligands to generate stabilizing defects, improving immobilization in practical systems such as PGA. Likewise, imine-linked COFs formed from multitopic aldehydes and amines offer tailored pore chemistry, customizable surfaces, and robust non-metal frameworks, making them ideal supports for future enzyme immobilization studies.[80,81]

5.2 Computational modeling to predict enzyme compatibility

Experimental investigation of enzyme@MOF@COF systems will be highly resource-intensive, making computational modeling a decisive tool for guiding design. Methods such as molecular docking and molecular dynamics (MD) simulations at both all-atom and coarse-grained levels have already been applied to enzyme–MOF systems, providing insights into how confinement influences enzyme orientation, stability, and catalytic efficiency. Metrics such as root mean square deviation (RMSD), solvent-accessible surface area (SASA), and hydrogen-bonding

networks serve as reliable indicators of compatibility, while docking and MD can also predict enantioselectivity, catalytic deactivation, or substrate affinity arising from enzyme–substrate–solvent interactions. For MOF@COF hybrids, tailored computational workflows could include docking enzymes into MOF pores or at MOF@COF interfaces to map contact residues, performing long-timescale MD in explicit solvent to monitor conformational stability, and applying umbrella sampling or steered MD to probe substrate diffusion through hierarchical pores. Additionally, QM/MM approaches can quantify changes in catalytic turnover under confinement. Such predictive frameworks not only reduce trial-and-error in material selection but also accelerate discovery by identifying optimal MOF/COF combinations prior to synthesis. Looking ahead, machine learning integrated with simulation and experimental datasets could further refine predictions of enzyme compatibility, stability, and efficiency in complex hybrid architectures.[82,83]

5.3 Experimental platforms for activity, leaching, and recyclability

Once synthesized, enzyme@MOF@COF systems must be benchmarked against free enzymes and single-component supports to validate their advantages. Free enzymes typically suffer from poor stability, leaching, and limited reusability, making systematic testing essential. Standard evaluation protocols include: (i) measuring initial specific activity relative to free enzyme to confirm that immobilization does not excessively compromise performance; (ii) conducting leaching tests using Bradford assay, SDS-PAGE, or supernatant activity analysis; (iii) assessing recyclability by monitoring activity retention across multiple recovery reuse cycles; (iv) determining operational stability under prolonged reaction or continuous-flow conditions; and (v) verifying structural integrity *via* PXRD, TEM, FTIR, and nitrogen sorption before and after catalysis. Recent work on MOF-immobilized enzymes has already shown high stability in flow reactors and minimal leaching, while dynamic exchange methods demonstrated strong binding with excellent activity retention across cycles. For hybrid enzyme@MOF@COF systems, hierarchical design could further enhance performance by combining size-selective confinement within MOF pores and stabilization from COF shells against solvent leaching. Future comparative studies should directly test whether these hybrids provide measurable improvements over conventional MOF- or COF-based supports.

5.4 Integration into photoreactors and microfluidic continuous flow

The ultimate evaluation of enzyme@MOF@COF hybrids lies in their integration into practical catalytic devices. Continuous-flow reactors and photo(bio)catalytic systems represent particularly promising applications. Recent studies have shown that pore-size matching between immobilized enzymes and substrates in flow reactors enhances conversion and extends operational lifetimes. Similarly, microfluidic platforms provide precise control over residence time, reduce reagent consumption, and improve mass transfer.[84] MOF-hosted enzymes have already demonstrated sustained activity in packed-bed reactors under aqueous conditions, establishing a precedent for hybrid systems. However, most reported systems remain at laboratory scale, whereas industrial biocatalysis typically relies on immobilized enzymes on robust polymer beads or silica supports operated in large fixed-bed or stirred tank reactors, which are easier to manufacture, regenerate, and scale.[84] Building on this, enzyme@MOF@COF composites could be fabricated as monodisperse particles or membranes suitable for incorporation into microreactors, tubular flow systems, or photoreactors. Embedding these hybrids into such devices would enable new operational modes, effectively bridging the gap between laboratory-scale synthesis and industrial biocatalysis.[85] In practice, successful implementation will depend on controlling pressure drop in packed systems, maintaining mechanical integrity of hybrid particles, and ensuring long-term resistance to fouling and enzyme deactivation under continuous operation.[84]

The strategies discussed provide a roadmap for transforming enzyme@MOF@COF hybrids from conceptual frameworks into functional, application-ready systems. Mild synthetic methods and bio-friendly catalysis ensure the protection of fragile enzymes during assembly, while computational modeling offers predictive guidance on enzyme–host interactions. Nevertheless, translation to industrial deployment will require standardized fabrication protocols, long-term operational benchmarking, and techno-economic assessments comparing hybrid systems with existing immobilization technologies. Rigorous experimental evaluation validates performance gains, and integration into continuous-flow and photo(bio)catalytic devices will test their practical utility. By combining advances in materials chemistry, computational design, and biochemical engineering, the next decade could see the emergence of robust, reusable, and multifunctional hybrid catalysts. These systems hold significant potential to advance CO_2 utilization, fine chemical synthesis, and bioenergy conversion, positioning MOF@COF and COF@MOF platforms as central components in the future of sustainable biocatalysis.

6. Conclusion and outlook

The integration of enzymes within hybrid MOF@COF and COF@MOF architectures represents a transformative step toward next-generation biocatalytic systems. By merging the high tunability, metal coordination chemistry, and flexible architectures of MOFs with the robustness, chemical stability, and extended conjugation of COFs, these hybrid frameworks overcome many of the challenges that have historically limited enzyme immobilization, such as leaching, denaturation, and poor recyclability. The resulting materials offer unprecedented control over enzyme spatial organization, pore environment, and substrate transport crucial parameters for improving catalytic efficiency and operational stability.

Current studies demonstrate that templated synthesis and core–shell assembly strategies can achieve precise enzyme encapsulation, multi-enzyme cascade integration, and enhanced protection against harsh reaction conditions.

However, several challenges remain before these hybrid materials can transition from laboratory prototypes to practical industrial biocatalysts. These include the need for scalable and reproducible synthesis routes, improved control of interfacial compatibility between MOF and COF domains, and a deeper mechanistic understanding of enzyme–framework interactions at the molecular level.

Future research should focus on rational framework design guided by computational modeling and advanced characterization to tailor pore chemistry and spatial confinement for specific enzymatic reactions. In particular, techniques such as solid-state NMR spectroscopy can provide insight into enzyme–framework bonding environments and conformational stability, while cryo-electron microscopy (cryo-EM) can elucidate enzyme spatial distribution and confinement within hybrid architectures. X-ray absorption spectroscopy (XAS) and *in situ* FTIR spectroscopy can further reveal local coordination environments and dynamic interactions during catalysis, whereas fluorescence and confocal microscopy can be used to track enzyme localization and distribution within porous matrices. Incorporating cofactor regeneration systems, designing stimuli-responsive or self-healing hybrid supports, and coupling these frameworks with photocatalytic or electrocatalytic modules could further expand their functionality. Moreover, developing green, aqueous synthetic routes will be essential for aligning these materials with the principles of sustainable chemistry.

Author contributions

Mercy Chaparadza – conceptualisation, writing, original draft preparation; Linia Gedi Marazani – writing, original draft preparation; Johannes Hungwe – reviewing and editing; Lendly Moyo – reviewing and original draft preparation; Evernice Chikukwa – reviewing and original draft preparation, Piwai Tshuma – reviewing and editing, Gift Mehlana-supervision, reviewing and editing.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this pespective

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