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Metal Organic Framework Catalysis: *Quo vadis*?

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ABSTRACT: In this perspective, we highlight the main opportunities of metal organic frameworks (MOFs) as heterogeneous catalysts. Along with our personal view on the most promising catalytic applications, the most important issues that still need to be addressed before commercial implementation of MOF catalysis are discussed.

KEYWORDS: *metal organic frameworks, heterogeneous catalysis, perspective, multifunctional catalysis, catalyst testing*

1. INTRODUCTION

Synthetic crystalline porous materials are applied every day in many different fields, such as catalysis, adsorption/separation/storage, electronics, health, semiconductors, the food industry or in detergents.[1] Several unique aspects of these materials are responsible for their success: they have a very high and tunable adsorption capacity; active sites of different strengths can be generated in the frameworks; the uniform size of their channels and cavities falls within the range of that of many molecules of interest; and many materials present excellent ion exchange capabilities and exciting electronic properties, ranging from insulators to conductors and semiconductors.[2,3] In addition, because of their periodic nature, these materials are excellent playgrounds for scientists, since macroscopic events may be explained on the basis of interactions occurring at the molecular level.

Among the different classes, metal organic frameworks (MOFs) bridge micro- and mesoporous materials and present unprecedented topological richness. MOFs or, more widely speaking, coordination polymers have been known since the late 1950s[4] and early 1960s,[5−9] although it was not until the end of the last century when the field was relaunched, thanks to the efforts of, among others, Robson and co-workers[10,11] Kitagawa et al.,[12,13] Yaghi and co-workers,[14] Lee and Moore,[15] and Férey et al.[16] Metal organic frameworks are crystalline compounds consisting of infinite lattices built up of the inorganic secondary building unit (SBU, metal ions or clusters) and organic linkers, connected by coordination bonds of moderate strength. Distinct from traditional inorganic materials, MOFs can be synthesized from well-defined molecular building blocks, thanks to both the reliability of molecular synthesis and the hierarchical organization via crystal engineering. MOFs can therefore be understood as molecules arranged in a crystalline lattice.[17] Even within such a relatively short time span, the field has rapidly evolved from an early stage, mostly focused on the discovery of new structures, to a more mature phase in which several applications are being explored. High adsorption capacities and easy tunability have spurred applications in gas storage, separation, and molecular sensing.[18−22] Biocompatible scaffolds hold promise for a bright future for medical applications.[23−26] Magnetic, semiconductor, and proton-conducting MOFs will certainly find their way toward advanced applications in several research fields.[27] The easy compatibilization of MOFs with either organic or inorganic materials may result in composites with applications varying from (opto)electronic devices to food packaging materials and membrane separation.[28−31] Finally, their tunable adsorption properties, high dispersion of components, and pore size and topology, along with their intrinsic hybrid nature, all point at applications in heterogeneous catalysis.[32,33,30]

It was, indeed, only a matter of time until the first catalytic applications of MOFs were explored.[34] First reports consisted of merely proofs of concept, with mediocre performances and concerns on stability. With the discovery of more robust structures and a deeper knowledge of their limitations, the performance of MOF catalysts has been shown to be, in a few cases, already comparable or even superior to state-of-the-art catalysts. At the same time, probably because of the fact that MOFs are at the interface of several scientific disciplines, many publications dealing with MOF catalysis still overlook

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fundamental aspects of heterogeneous catalysis. Because of the latter, it is not overly controversial to acknowledge that interpretation of catalytic data in many publications is questionable.

In this perspective, we do not intend to review the state-of-the-art MOF catalysis; for this, we recommend several recent reviews on the topic.[32,35−38] In contrast, we will first critically evaluate MOF catalysis on the basis of their main advantages and weaknesses, and we will highlight common pitfalls in catalytic performance evaluation. Finally, we will share our personal view on the most promising niches for application of MOFs in catalysis and on the most important issues that still need to be addressed before massive application can become reality.

2. STRENGTHS AND WEAKNESSES OF MOFS AS HETEROGENEOUS CATALYSTS

The main strategies for the inclusion of catalytic activity into a MOF scaffold are summarized in Figure 1. In addition to the fact that MOFs are among the materials with the highest porosity, their pore size, shape, dimensionality, and chemical environment can be finely tuned. This is in contrast to other crystalline porous solids, for which the diversity of framework types is significantly limited due to the use of a rather reduced number of building units (e.g., only [SiO_4] and [AlO_4] tetrahedral units are used in zeolites, whereas AlO_4 and PO_4 units are used in aluminophosphates).

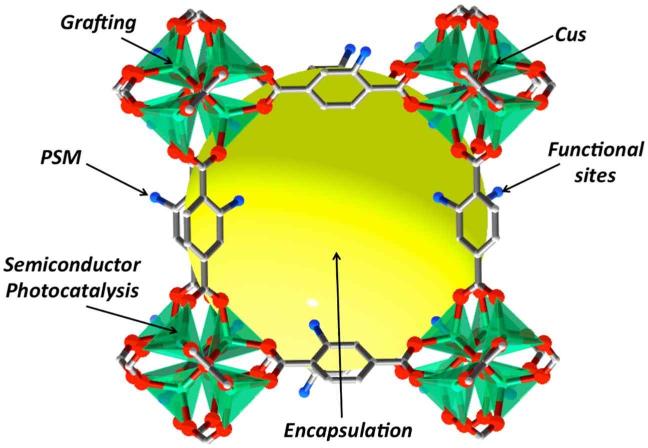


Figure 1. Different strategies for the inclusion of catalytic moieties into a MOF scaffold.

This high versatility of MOF design provides clear advantages for catalysis, since in principle, it should be possible to rationally design not only the active site but also its environment with an unprecedented degree of precision.[39] The catalytic function can be implemented at the organic[40] or at the inorganic[41] component, and this can be done by direct synthesis of the envisaged scaffold or by postsynthetic modification (PSM).[42−45] Alternatively, the pore system of the MOF can also serve as the physical space in which a catalytic species (e.g., metal or metal oxide nanoparticle, metal coordination complex, or other discrete molecular species) is encapsulated[46,47] or as the confined space where a chemical reaction is taking place. In these cases, the MOF may act as a simple spectator or passive medium for dispersing the catalytic species, but it can also participate in the catalytic reaction, by stabilizing transition states, orienting molecules, or introducing additional active sites. Moreover, the pore dimensions of many MOFs may change without breaking chemical bonds within the framework. This results in special properties such as the breathing effect[48,49] and the gate phenomenon,[50,51] in which pores contract or open during molecule adsorption. Although this property has been hardly explored in catalysis, outstanding results in selective gas separation have already been reported.[52−54]

Knowing the limitations of MOFs is of the utmost importance to propose feasible catalytic applications. Particularly relevant in this sense are the relatively low thermal and chemical stability of MOFs, especially when compared with inorganic porous solids. Although a handful of remarkably robust compounds have been prepared,[55−57] other MOFs are highly sensitive to moisture and unstable in the open air, undergoing hydrolysis, amorphization, or phase transformations, even at room temperature.[58,59]

The thermal stability of a MOF is frequently established by thermogravimetric (TGA) or by thermodiffraction analysis, usually carried out in a flow of air or inert gas (N_2 or He) or in vacuum while raising progressively the temperature up to the complete destruction of the framework (typically up to 850−1000 K). Under these conditions, several MOFs are found to be thermally stable at temperatures higher than 573 K. This temperature in principle would be sufficiently high to envisage the applicability of the material in many liquid-phase reactions, which are typically performed at temperatures below 473 K. However, these thermogravimetric data have to be taken with caution because structures that are stable over 573 K for the limited time of the TGA measurement may undergo extensive damage when exposed to lower temperature for much longer times. In addition, degradation and framework dissolution in certain solvents, in acidic or basic media, or in the presence of certain functional groups are often drawbacks that can severely delimit the scope of MOFs as heterogeneous catalysts. In general, it is very difficult to anticipate the stability of a given MOF under certain reaction conditions, even when its thermal stability is very high. For this reason, it is always necessary to check if the crystalline structure of the MOF is preserved after the catalytic reaction. Common tests for assessing MOF stability include the comparison of the X-ray powder diffraction pattern, specific surface area, pore volume, and elemental analysis of the fresh MOF and the solid recovered after the catalytic reaction by filtration or centrifugation and analysis of the reaction solution.[60,61]

It is also necessary to stress here that upon repeated use under reaction conditions, a solid catalyst may become gradually deactivated as a result of the strong adsorption of reaction products or byproducts. This is even more so for reactions that are accompanied by formation of coke or heavier residual products. In robust heterogeneous catalysts, such as zeolites, the problem of coke formation or irreversible adsorption is commonly addressed by calcination after a certain time on-stream or a given number of catalytic cycles. It is evident that catalyst regeneration by combustion is not possible for MOFs; therefore, other alternative means of regenerating the spent MOF, compatible with the preservation of the crystallinity (such as, e.g., solvent extractions at low temperature), should be specifically developed. Otherwise, the use of MOFs will be restricted to reactions in where very high turnover numbers (TONs) are attained.

Another important issue that can delimit the stability (and thus, the potential application) of MOFs is their mechanical resistance. Some MOFs are known to collapse when submitted to mechanical compression beyond a certain pressure, thus losing their crystallinity and specific surface area. For instance, Montoro et al.[62] reported that two of the most extensively studied MOFs, namely, Cr-MIL-101 and HKUST-1, lose most of their crystallinity and specific surface area when pressed at 200 MPa. As discussed later, mechanical stability of the MOF is relevant for those (catalytic) applications requiring compressing or molding the material into pellets.

3. GENERAL CONSIDERATIONS ABOUT HETEROGENEOUS CATALYSTS TESTING

As mentioned before, the MOF catalysis literature is plagued with examples of poor catalyst testing practices. In this section, we outline the main considerations that need to be addressed when exploring the catalytic performance of a porous solid, with special emphasis on liquid phase reactions, the most likely niche for application niche of MOF catalysts, and at the laboratory scale. For more details on proper practices in heterogeneous catalysis, we recommend the reader see the dedicated literature on the topic.[63,64]

Catalytic reactors can roughly be classified on the basis of their mode of operation, as indicated in Figure 2. Steady-state operation of especially packed-bed reactors is most widely used in heterogeneous catalyst testing, predominantly because of the ease of operation and low costs. Transient operation is less common and has some disadvantages for the mere goal of catalyst testing. In batchwise operation, most widely reported in MOF catalysis, the possible deactivation during the extent of the experiment cannot be established, except afterward by repeating the experiment for verification.

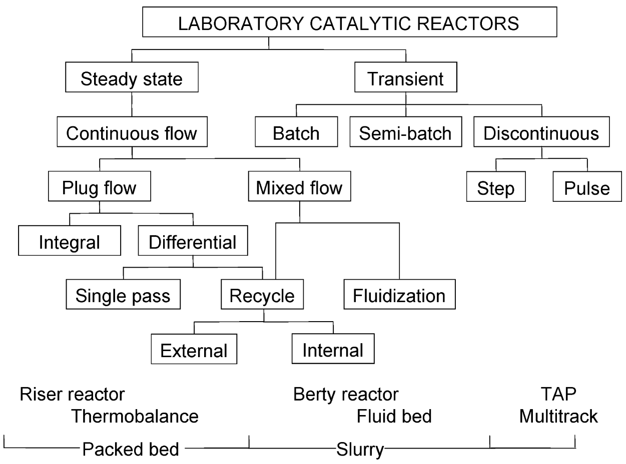


Figure 2. Classification of laboratory reactors according to mode of operation.

With the goal of obtaining intrinsic catalyst properties (reaction kinetics and selectivities) from experimental data without being disguised by noncatalytic phenomena, the following conditions should be fulfilled:

- effective contact between reactants and catalyst;
- absence of mass and heat transport limitations inside and outside the catalyst particles;
- good description of reactor characteristics, with well-defined residence time distributions under isothermal conditions (ideal reaction systems).

Therefore, the following guidelines should be applied:

i. Adhere to criteria
  - ideal reactor behavior: plug flow (PFR) or continuous stirred tank reactor (CSTR)
  - isothermal conditions
  - absence of limitations: verify observables in diagnostic tests

ii. In continuously operated reactor systems (e.g., PFR), catalysts should be compared at low conversions to get insight into real activity differences and to compare intrinsic deactivation rates

iii. Compare selectivities at the same conversion level

iv. In the case of batch experiments, kinetic curves (evolution of conversion and selectivity with time) and repetition of experiments are of the utmost importance

v. When developing new catalysts, comparisons with at least a standard catalyst (if possible, commercially available) in terms of turnover frequency (*TOF*) and total number of turnovers (*TON*) should be reported

3.1. Transport Control of the Reaction. Transport limitations and deactivation phenomena affect not only catalyst activity, but also reaction selectivities and should therefore be avoided and studied (another common negligence in MOF catalysis literature). Apart from the criteria based on the observable quantities derived in classical reaction engineering,[65] experimental tests exist to verify the presence or absence of transport limitations. To check whether external diffusion limitations are present during catalyst testing under continuous operation, we can either vary the flow rate and amount of catalyst simultaneously while keeping the space-time W/F_i^0 constant in fixed-bed experiments or vary the stirring rate in the case of CSTR reactors. Because the mass-transfer coefficient, k_f, depends on the fluid velocity around the catalyst, external limitations then show by a change in conversion. This not only is of concern in heterogeneous catalysis, but also is important in homogeneous and phase transfer catalytic applications.[66] If no external limitations exist, the resulting conversions should be the same. Two caveats should be mentioned, however: if temperature effects also interfere, these might (over-)compensate for concentration gradients or faster stirring when using small particles may not have the desired effect of better mass transfer because the particles may go with the flow and experience a stagnant fluid. So this method requires a careful analysis.

More attention should be paid to internal diffusion limitations. Under strongly limited conditions, the observed rate becomes particle-size-dependent, $\propto 1/L$. Variation of the particle size, for example, by crushing and sieving the catalyst, and performing the tests under identical conditions, should give a proper answer to whether diffusion interferes. In the case of MOFs, this might be tricky, because particle crushing might result in structural collapse. At small particle sizes, the reaction is chemically controlled and independent of the particle size. Only for larger particles would a decrease in the observed rate occur. One should be aware of the fact that extraparticle limitations also induce a particle size dependency. The flow rate through a packed bed should not have any effect. Also in this case, temperature effects should be avoided.

Under kinetic control, selectivities may depend strongly on the conversion level, as exemplified in Figure 3 for two irreversible consecutive reactions, $A \rightarrow R \rightarrow S$, where the intermediate, R, is the desired product. In this case, different apparent selectivities are obtained at different space-times

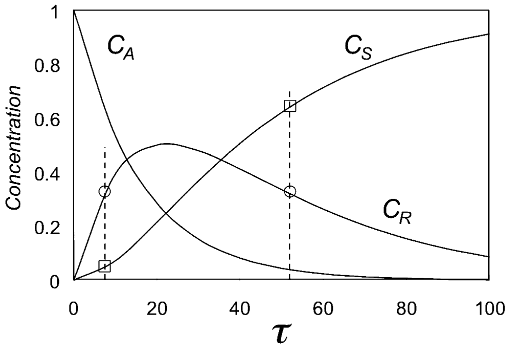


Figure 3. Product distribution for a consecutive irreversible first-order reaction A → R → S as a function of space−time.

(corresponding to different conversion levels). A more active catalyst may therefore appear to be less selective, which is not necessarily true. For catalyst selection, it is of great importance to have a good model of the reaction network. This determines the selectivity performance of a catalyst and exemplifies the importance of kinetic curves to judge the intrinsic properties of a catalyst. In other words, reporting tables with conversions and yields after a number of hours, the main practice in MOF catalysis, gives little information on the intrinsic catalytic performance.

3.2. Comparison with Reference Catalysts.

Performance comparison between new MOF catalysts and commercial standards or literature data under similar reaction conditions is also very important and hardly reported in literature. It is very surprising to discover that only a few[67−71] out of the hundreds of publications on MOF catalysis report turnover numbers and turnover frequencies for a given reaction and comparisons with other catalysts from literature.

3.3. Leaching Issues.

When performing a reaction catalyzed by a MOF, the possible occurrence of leaching of the active metal (or organic components) to the reaction medium must be verified. This is of paramount importance, since it is necessary to know the true origin of the catalytic process. Extensive metal (or organic linker) leaching of a MOF during a catalytic reaction is easily detected by a simple chemical analysis of the filtrate of the reaction medium or by hot filtration testing. Note that, for certain organic reactions, only a few parts per million of metal in solution can be sufficient to act as excellent catalyst. Moreover, cocatalysts such as carbonates in solution can certainly affect MOF stability. For instance, some of us recently published the catalytic performance of Pd containing MIL-101(Cr) in different Suzuki−Miyaura cross couplings.[72] We observed that the use of solvents such as water or alcohols resulted in the complete dissolution of both the base cocatalysts (potassium carbonate) and the MOF catalyst, probably as a result of complexation of the metal nodes by the carbonate in solution. Experiments performed with other carboxylate-based MOFs under similar conditions also resulted in a complete dissolution of the framework. These results shed serious doubts on the heterogeneous catalytic character of some recently published works in which different carboxylate-based MOFs have been used as Pd supports and claimed to be stable under Suzuki−Miyaura conditions using potassium carbonate as the base in the presence of water or alcohols.[73,74]

3.4. Catalyst Reusability.

In addition, recyclability is a must for heterogeneous catalysts. In the case of MOFs, where most publications deal with batch operation under vigorous stirring, catalyst attrition is a very important problem that has hardly been studied in the literature.

4. DESIGNING MOFS FOR CATALYTIC APPLICATIONS

MOFs contain three well-differentiated parts where the catalytic function can be allocated: the metallic component, the organic linker, and the pore space. Unfortunately, the MOFs that can be directly used as catalysts in the as-synthesized form represent only a small part of the whole family of MOFs. Indeed, metal carboxylates are not known for their outstanding catalytic performance. In most cases, it has been necessary to develop specific strategies to modify the starting material before it can be used in a catalytic reaction.

Some MOFs contain metal ions that can directly coordinate to the substrates to catalyze a chemical transformation, and these are what we refer to as *as-synthesized active MOFs*. Coordination of the substrate to the metal requires either an expansion of the coordination sphere of the metal ion or a displacement of one of the ligands forming the MOF originally coordinated to the metal site. In either case, the crystalline network of the MOF has to be highly adaptable to prevent the collapse of the structure as a consequence of the local distortions produced upon substrate coordination.

Some of us have recently found that both copper imidazolate, $[Cu(im)_2]$ (im = imidazolate),[75] and copper pyrimidinolate, $[Cu(2\text{-pymo})_2]$ (2-pymo = 2-hydroxypyrimidinolate)[76] feature highly adaptable networks that can readily accommodate changes in the coordination sphere of copper upon substrate binding while preserving the structure integrity. This property makes the two materials active catalysts for a number of reactions, including oxidation of activated alkanes;[77] 1,3-dipolar cycloaddition of azides to terminal alkynes;[78] or three-component coupling (A^3) of aldehydes, alkynes, and amines.[79] DFT calculations on model clusters demonstrate that both MOFs can coordinate a hydroperoxide molecule (HOOR) directly onto the copper center to form an adsorption complex of the type $[Cu^{2+}\text{-HOOR}]$.[77] A similar ligand displacement and recoordination cycle has been demonstrated to occur in a series of zinc(II) benzoate coordination polymers during transesterification reactions.[80]

The use of MOFs with coordinatively unsaturated sites (cus) is probably the most widely explored application. In this case, one of the coordination positions of the metal centers is occupied by a weakly coordinated ligand (i.e., water), which can be removed without causing the collapse of the crystalline structure. Relevant examples of this type of MOFs are the copper trimesate HKUST-1,[81] the chromium terephthalate MIL-101,[55] and related materials. Upon creation of a coordination vacancy by removal of such a ligand, the resulting metal center will act as a Lewis acid; it will be available to accept electron density from any donor molecule that can be present in the medium. A lot of examples describing the use of cus-containing MOFs have been published, with applications in cyanosilylation of carbonyl compounds,[61,82,83] Mukaiyama-aldol condensation,[82] Friedel−Crafts benzylation,[84] isomerization of α-pinene oxide, and conversion of citronellal into isopulegol,[85−87] as well as catalysts for the oxidation of alcohols,[88] sulfides,[89] olefins, paraffins,[90] or CO.[91] In addition, another strategy for introducing a catalytic center in the MOF consists of using these cus as anchoring points for grafting of additional functionalities.[92−94]

When metal oxide nanoclusters whose electronic configuration correspond to that of a semiconductor (i.e., with a band structure containing a completely filled valence band and an empty conduction band separated by a relatively small energy gap) are used as metal SBU, it has been demonstrated that these materials may display semiconducting properties.[95,96] Upon light excitation, charge separation occurs with creation of electron−hole pairs. The resulting electrons and holes are long-lived species that decay to the ground state in the microsecond time scale.[95] Therefore, the lifetime of the charge separated state is long enough to allow interaction with suitable electron donors or acceptors, making photocatalytic processes possible.[95−98]

When it comes to catalysis at the organic linker, MOFs might behave as solid organocatalysts. It is evident that the linkers that form this type of MOFs need to contain two different types of organic functional groups: (i) coordinative functional groups that coordinate to the metal sites to hold the crystalline framework and (ii) reactive functional groups, which remain uncoordinated and will be responsible for the catalytic properties of the material. A prototypic example of MOFs having two types of functional groups are those containing the ligand 2-aminoterephthalate, such as IRMOF-3, NH_2-UiO-66, NH_2-MIL-53(M) or NH_2-MIL-101(M) (M = Cr^{3+}, Fe^{3+}, Al^{3+}, V^{3+}). These amino groups can confer basic properties to the material.[69,86] Another historic example of ligand containing two types of functional groups that have been used for preparing a MOF is 1,3,5-benzene tricarboxylic acid tris[*N*-(4-pyridyl)-amide].[40] This molecule coordinates to the metal ions through the pyridyl N atom while the amide groups remain free and can be used as active sites for base catalysis. A more recent example has been reported by Hupp and co-workers. These authors prepared the material NU-601, containing 2D layers of Zn paddlewheel dimers connected to a urea ligand and pillared with 4,4′-bipyridine. NU-601 was found to be an active hydrogen-bond-donor catalyst for Friedel−Crafts reactions between pyrroles and nitroalkenes.[99]

However, it is not straightforward to prepare MOFs with free reactive functional groups and accessible to substrates, given the large tendency of the metal ions to coordinate to all the available functional groups of the ligand. To overcome this drawback, several strategies have been proposed in the literature: (i) use of protecting groups,[100,101] (ii) (postsynthesis) ligand exchange,[102−104] and (iii) use of mixed-linkers (MIXMOFs)[105−107] are among the most widely applied approaches.

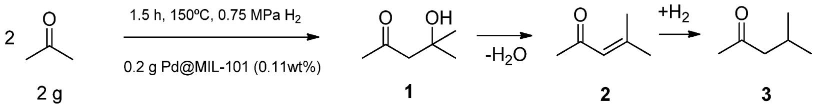
Another very interesting approach related to catalysis at the linker consists of the use of metallo-ligands. In most existing MOFs, the structural metal sites have no coordination positions available to substrates; neither can these vacancies be created by removal of labile ligand molecules. On the contrary, the metal sites are completely blocked by tightly coordinative linkers forming the crystalline network. A possible alternative to introduce metal active sites in a MOF is by binding the metal ion to a suitable organic molecule to form a metal coordination complex (a metallo ligand). Then, this metallo-ligand is used as a linker to form the MOF. This strategy offers several interesting advantages because oxidation state, electronic properties, and coordination environment (including chiral environments) can be finely tuned.

Kitagawa and co-workers[108,109] prepared a MOF containing $Cu(2,4\text{-pydca})_2$ metallo-ligands (2,4-pydca = pyridine-2,4-dicarboxylate) coordinated to Zn^{2+} cations through one of the carboxylate groups to form a 3D structure. In this material, Zn^{2+} acted as a mere structural element, while Cu^{2+} ions were accessible for guest coordination. Similarly, the same group[110] prepared a series of materials containing metal Schiff base complexes, $M(H_2salphdc)$ (M = Cu^{2+}, Ni^{2+}, or Co^{2+}, salphdc = *N*,*N*′-phenylenebis(salicylideneimine)dicarboxylate), with Zn^{2+} cations at the nodes. Lin and co-workers[111] have prepared a homochiral MOF containing Cd^{2+} ions and the chiral ligand (*R*)-6,6′-dichloro-2,2′-dihydroxy-1,1′-binaphthyl-4,4′-bipyridine as the organic building unit. The ligand coordinates to Cd^{2+} through chlorine and the pyridine nitrogen, while the two hydroxyl groups of the binaphthyl moiety remain uncoordinated and pointing to the channels. Postsynthesis modification of this material by adding titanium isopropoxide yielded a titanium-containing material, with titanium diisopropoxide grafted to the walls of the MOF through the dihydroxy groups. Szeto et al. prepared bimetallic materials containing Gd[112] or Yb[113] ions at the nodes, and Pt^{2+} ions four-coordinated by two Cl and by two N atoms of 2,2′-bipyridine-4,4′-dicarboxylate, which could act as potential catalytic sites. Similarly, instead of directly preparing the metallo-ligand, a MOF containing noncoordinated organic sites can be used as chelating agent. In this way, some of us described the preparation of Au(III)-IRMOF-3.[114] The resulting MOF-containing Schiff base Au(III) complexes decorating the organic ligands was found to be an active catalyst for the selective hydrogenation of butadiene and for the synthesis of indoles through a three-component coupling of amines, aldehydes, and alkynes, followed by intramolecular cyclization.

Last, the high porosity of MOFs can be used as reaction environment and for the encapsulation of active molecules. When active species are encapsulated in the pores of a support, the active moieties cannot leave the support, but their main properties (catalytic, opto-electronic, ...) can be exploited and even enhanced by confinement effects in the resulting composite. To satisfy the condition of encapsulation in a porous matrix, the entrapped species must be small enough to fit the pores of the support material and at the same time larger than the openings that give access to these pores. Because the active species is larger than the pore openings of the support, techniques such as impregnation cannot be used. Having said this, two synthetic approaches can be followed: (i) assembling the active species within the pores of the support, known as a "*ship in bottle*" approach, and (ii) assembling the support around the active species, also known as a "*bottle around ship*" or "*templated synthesis*" approach.

The route used for the encapsulation is dictated by the chemistry of the support and the system to be encapsulated. If the targeted species is to be assembled within the pores of the support, then the support needs to be stable under the reaction conditions used. If the support is assembled around the active species, then this active species needs to be stable under the synthesis conditions of that support. Hence, if the active species can be made easily in a small number of steps, then assembly within the pores is preferred. If the active species is hard to synthesize but is intrinsically stable, then the assembly of the support around the active species is preferred. The use of MOFs as encapsulation matrices has been widely explored in the literature, and main examples of encapsulated moieties are[32] metal nanoparticles,[7,55,115−120] polyoxometalates,[67,68,121−124] and porphyrins and metallo-porphyrins.[121,125−128]

Scheme 1



5. UNIQUE APPLICATION NICHES FOR MOF CATALYSIS

The high tunability of structures and composition of MOFs, together with the possibility to introduce catalytic active sites at the metallic nodes at the ligands or inside the pores, offers unique and unprecedented possibilities of engineering MOFs for catalytic applications. However, as the field of MOF catalysis matures and the number of available examples of materials and catalytic reactions increases, it becomes clear that MOFs will hardly replace other more conventional catalysts (such as mineral acids and bases, metal salts and complexes, or zeolites) for the synthesis of bulk chemicals. This is especially true for processes that do not require highly specific transformations to be carried out. These alternative catalysts are usually cheaper (even after including the costs of waste neutralization and disposal) and more stable than MOFs and will certainly be the choice of industry. Circumstantial evidence of this is that nowadays, there is not yet a single industrial application of MOFs in catalysis; therefore, if MOFs are to have a future in catalysis, the efforts should be directed toward applying these materials in reactions where their superior tunability can be exploited without being hampered by stability issues and where other catalysts may find severe limitations. For instance, it is relatively easy to introduce chiral centers in MOFs, either during synthesis or a posteriori by postsynthesis modification. Conversely, attempts to prepare chiral zeolites have found only limited success, with a few chiral zeolites being known so far (SU-32,[129] ITQ-37[130] or goosecreekite[131]). Thus, MOFs could become preferred over zeolites and other catalysts for the synthesis of (chiral) drugs and other high added value fine chemicals. The syntheses of these complex substances will usually require the use of highly efficient and (enantio)selective catalysts; and the requirements of the catalysts are even more demanding when polyfunctional substrates are involved, which is the case of most fine chemicals.

Then, also the chemo- and regioselectivity of the catalyst becomes an important issue; that is, the catalyst must be able to transform selectively a given functional group in the presence of other functionalities that are susceptible to react under the same conditions, thus triggering unwanted side reactions that decrease the overall yield of the target compound, increase the production of wastes, and complicate isolation and purification steps. On the other hand, the use of MOFs in one-pot multicomponent coupling reactions (MCRs)[132] and sequential (tandem or cascade) reactions[133] allows process simplification, avoiding costly time- and energy-consuming isolation and purification of intermediate products. However, the design of multistep sequential transformations requires the simultaneous presence in the same reaction vessel (i.e., in one pot) of two or more types of active centers, which can mutually interfere or even be incompatible and neutralize if they are not properly immobilized onto suitable supports.[134] Therefore, the use of one-pot tandem procedures can never be taken for granted and requires a strict control over the type, concentration, and distance among the different catalytic active sites and their interplay with the support. Again, the high tunability of MOFs can largely facilitate the preparation of multifunctional catalysts for sequential one-pot transformations as well as the tailoring of electronic and coordination properties of the metal ions that participate in metal-catalyzed MCRs.

The high added value of fine chemical products on one hand and the design of more economic processes based on one-pot procedures on the other hand could largely compensate for the possible higher costs of MOFs as compared to other catalysts. We therefore believe that, in the next few years, MOFs will find unique application niches in (i) asymmetric catalysis, (ii) one-pot multicomponent coupling reactions, (iii) multifunctional MOFs for one-pot tandem reactions, or (iv) a combination of them.[135] These, together with light harvesting applications (i.e., photocatalysis), are probably the scenarios in which MOFs can outperform other alternative catalysts, even those that are less expensive or more robust than MOFs but less selective or not amenable to process intensification. There are already a number of excellent reviews dedicated to the use of chiral MOFs for heterogeneous asymmetric catalysis,[135−137] so we will not discuss this topic herein. We will rather focus our attention to present the recent developments in the preparation of multifunctional MOFs for one-pot tandem reactions and MCRs, a largely overlooked topic.

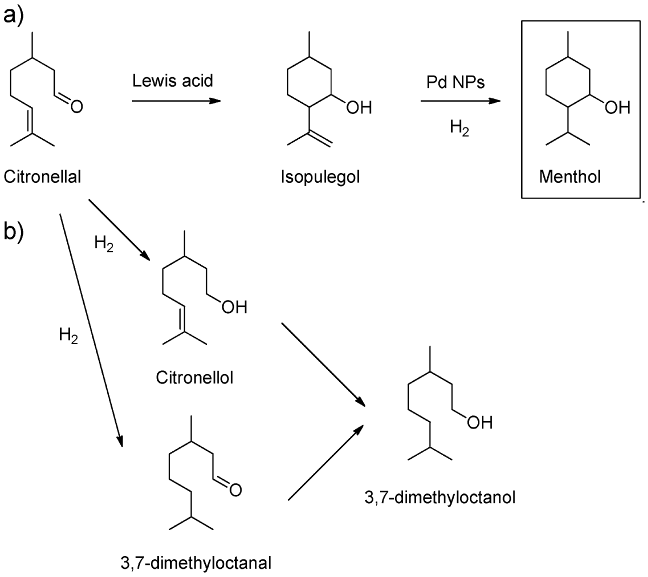
5.1. Bifunctional Acid−Metal Systems. Pan et al.[138] described the one-pot synthesis of methyl isobutyl ketone (MIBK) from acetone and H_2 using MIL-101(Cr^{3+}) containing palladium nanoparticles (NPs) as a bifunctional Lewis acid/hydrogenation catalyst. This reaction proceeds through condensation and dehydration catalyzed by the Lewis acid sites (coordinatively unsaturated Cr^{3+} centers of the MOF), while Pd NPs catalyzed the final hydrogenation step (see Scheme 1). The parent MIL-101 MOF afforded 60.1% acetone conversion with 74.9% selectivity to product **2** (45% yield). Meanwhile, the addition of Pd significantly promoted the hydrogenation of **2** and, thus, enhanced the conversion of acetone and selectivity to the desired product **3**.

Interestingly, the authors argued that as the concentration of Pd increased beyond a certain optimal limit, more and more Pd NPs are deposited on the external surface of the MOF crystals, far from the Cr^{3+}acid sites located mainly inside the pores, resulting in an "egg−shell" system. Therefore, production of isopropyl alcohol, coming from the reduction of the carbonyl group of acetone and requiring only hydrogenation centers, becomes preferred over the formation of the desired MIBK product **3**, in which both Lewis and hydrogenation sites in close proximity are necessary. This example clearly illustrates that if we want to design an efficient multifunctional catalyst, it is not enough to introduce all the required types of functionalities in a solid, but a delicate interplay must exist between them concerning concentration, location, and distance, in good agreement with more recent reports.[139]

We have recently used a similar Pd@MIL-101 system as bifunctional catalyst for the sequential conversion of citronellal into isopulegol and hydrogenation to menthol, according to Scheme 2a.

We found that when the parent MIL-101(Cr^{3+}) was used as catalyst, citronellal was quantitatively converted in 18 h at

Scheme 2



80 °C, with full selectivity to cyclization products and with a disatereoselectivity of 74% to the most industrially relevant isopulegol isomer. When Pd@MIL-101 was used as catalyst, we noticed an increase in the reaction rate (full conversion after 12h) without affecting the selectivity or diastereoselectivity. These results were in line with previous reports on Ir-containing H-beta zeolite catalysts,[140] although they were far from the performance described for Sn-beta.[141] In a second step, isopulegol was quantitatively hydrogenated over Pd@MIL-101 after an additional 6 h, producing menthol with an overall 86% selectivity and 81% diastereoselectivity. However, an important limitation of our Pd−MOF system with respect to the previously reported Ir-containing zeolites is that when we attempted to perform the tandem citronellal−isopulegol−menthol reaction in one step (i.e., introducing H_2 from the beginning of the reaction), the final menthol yield was very low. The reason for this is that citronellal cyclization competes with hydrogenation of C=O and C=C double bonds, leading to the formation of byproducts as shown in Scheme 2b.

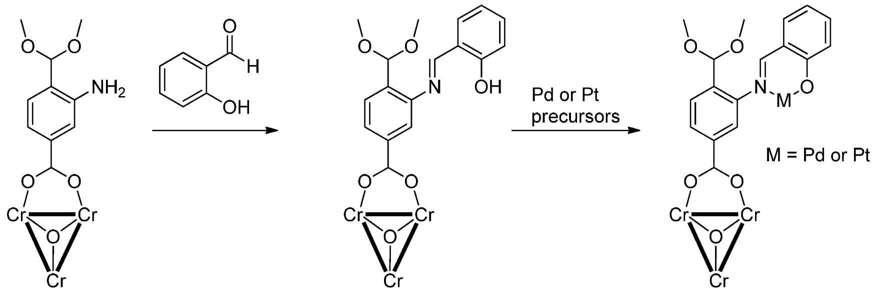
We later extended the preparation of bifunctional acid-hydrogenation systems based on MIL-101(Cr^{3+}) to materials containing Pd or Pt,[142] either in the form of encapsulated metal nanoparticles (Pd@MIL-101 and Pt@MIL-101) or in the form of isolated transition metal Schiff base complexes (MIL-101-SI-Pd and MIL-101-SI-Pt) prepared according to Scheme 3.

The Pd- and Pt-containing MOFs were used as bifunctional catalysts for the one-pot synthesis of secondary arylamines through hydrogenation of nitroarene compounds, followed by reductive amination of aldehydes and ketones, according to the general scheme 4. Various carbonyl compounds (benzaldehyde, acetophenone, and cyclohexanone)[142] were combined with nitrobenzene to yield the corresponding secondary amines with excellent results. The MOFs were found to reduce the nitro groups chemoselectively in the presence of the carbonyl compounds, leading to a low concentration of the corresponding alcohol side products (below 10% in all cases). Unfortunately, it was not possible to isolate the intermediate imines in good yields due to a lack of chemoselectivity of the MOFs, unlike other highly chemoselective catalysts previously reported, such as Au/TiO_2.[143]

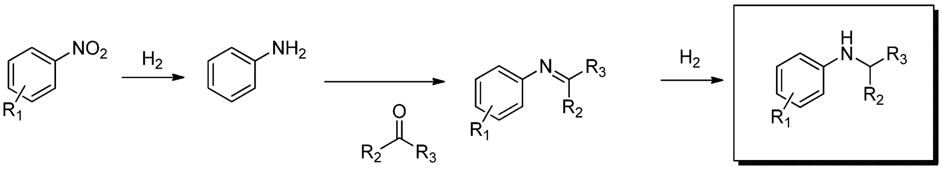
The tandem process leading to secondary amines was also applied to the synthesis of N-containing heterocycles of interest, such as (tetrahydro)quinolines (Scheme 5a), while the coupling of nitroarene reduction with Paal—-Knorr condensation or Michael addition of suitable substrates led to the formation of pyrrole (Scheme 5b) or 3-arylpyrrolidine and N-substituted 3-arylpyrrolidine (Scheme 5c), respectively. In these reactions catalyzed by bifunctional MOFs, we demonstrated the beneficial interplay between Lewis acid sites of the MOF and the hydrogenation properties of the metal species. As a result, the MOFs surpassed the performance of commercially available Pd/C, Pt/C, Pd/Al_2O_3, and Pt/Al_2O_3 catalysts under the same conditions. These commercial catalysts, having only marginal acidity of the respective supports (carbon or Al_2O_3), cannot perform as well as the MIL-101 materials, which feature highly active Cr^{3+} Lewis acid sites.

This was especially clear for the synthesis of pyrrole and pyrrolidines, for which the limitation of the commercial catalysts was evident. Unlike the tandem conversion of citronellal to menthol commented before, in all the above reactions with nitroarene compounds, we have been able to find convenient reaction conditions to perform all the sequential transformations in just one step; that is, introducing H_2 from the beginning of the reaction. The sole exception was the tandem process leading to 3-arylpyrrolidines (Scheme 5c). In this case, it is important to avoid the presence of H_2 during the first step, that is, the Michael addition. The reason for this is that the presence of H_2 at the beginning of the process resulted in the reduction of β-nitrostyrene to β-aminostyrene (or 2-phenylethanamine), which did not produce the Michael addition product. Therefore, it was necessary to carry out the Michael addition in N_2 atmosphere until complete conversion of β-nitrostyrene and to supply H_2 only afterward to allow the reduction of the nitro group and the imines formed. In other

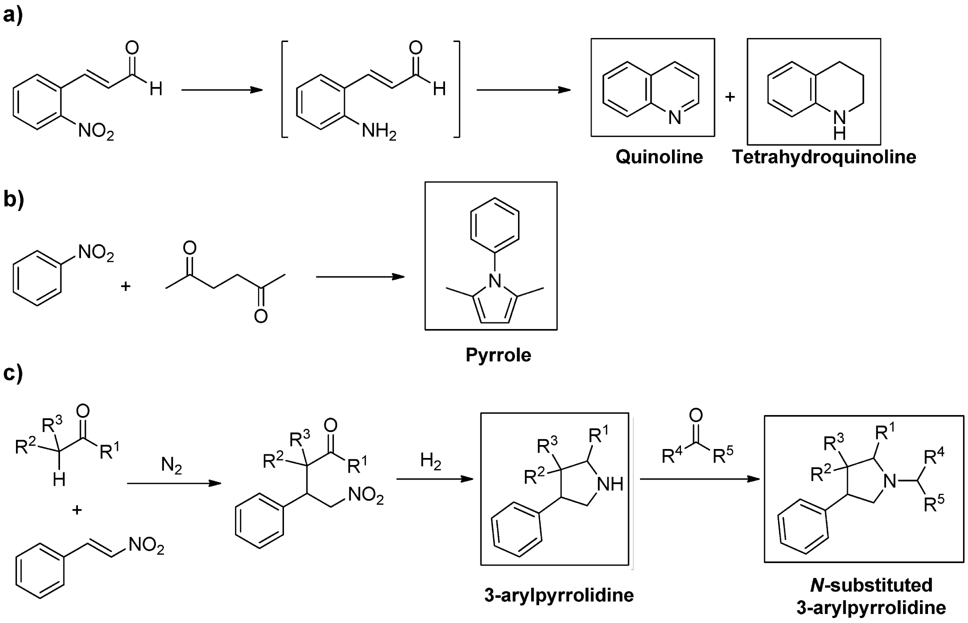
Scheme 3



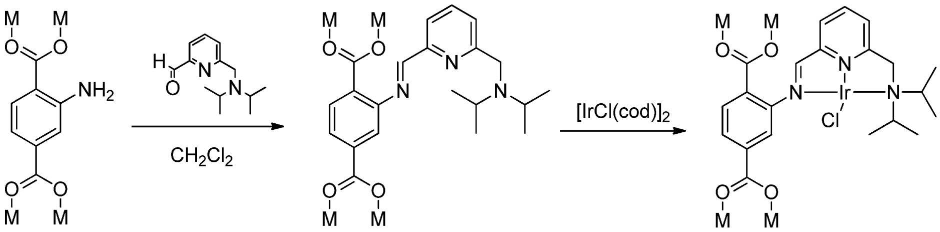
Scheme 4



Scheme 5



Scheme 6



words, the synthesis of arylpyrrolidines was a one-pot, two-step reaction process.

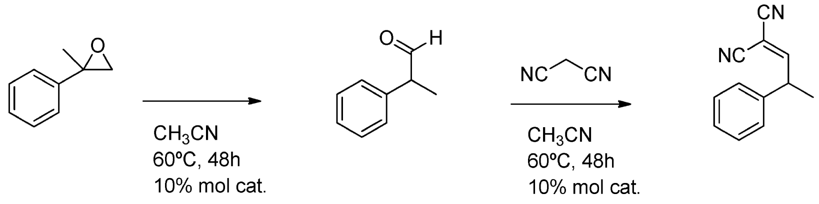
Nitroarene reduction followed by reductive amination using an Ir-containing bifunctional MOF was also reported very recently by Pintado-Sierra.[144] These authors used amino-containing UiO-66-NH_2 (or IRMOF-3) MOFs as supports and introduced the iridium imino-pincer complex shown in Scheme 6 by postsynthesis modification as hydrogenation function. The scope of the reaction with this catalyst was demonstrated for various benzaldehydes and nitrobenzences.

5.2. Bifunctional Acid–Base Systems. De Vos and co-workers were among the first to describe a bifunctional acid–base MOF catalyst.[145] The authors used zirconium amino-terephthalate UiO-66-NH_2, and they concluded that controlled thermal treatment under vacuum produced the reversible dehydroxylation of the $[Zr_6O_4(OH)_4]^{12+}$ clusters to $[Zr_6O_6]^{12+}$ at temperatures between 373 and 523 K, thus leaving coordinatively unsaturated positions in the triangular faces of the cluster (shared by 3 Zr centers) in close proximity to the amino groups of the organic linkers. Moreover, of the 12 linkers surrounding each Zr cluster in the ideal structure, approximately 3 were found to be systematically missing for the real materials. Such linker deficiency allows coordinatively unsaturated sites on Zr to be identified as the active sites. According to the authors, the resulting dehydroxylated material acted as a bifunctional acid base catalyst, as demonstrated for the cross aldol condensation reaction between benzaldehyde and heptanal.

Kim and co-workers have reported on the use of Al^{3+}-MIL-101-NH_2 as a bifunctional Lewis acid (coordinatively unsaturated Al^{3+} sites) and Brønsted base (−NH_2 groups) catalyst for the tandem Meinwald rearrangement of epoxides and Knoevenagel condensation of the resulting aldehyde with activated methylene groups,[146] according to Scheme 7.

Reaction of the epoxide **4** and malononitrile in the presence of 10 mol % Al^{3+}-MIL-101-NH_2 resulted in the tandem epoxide ring-opening to **5**, followed by condensation and subsequent dehydration to **6** with and overall 70% yield. Although this reaction certainly demonstrates the bifunctional character of the Al^{3+}-MIL-101-NH_2, the scope of the reaction was somewhat limited: Meinwald rearrangement failed when aliphatic epoxides, styrene oxide, or *trans*-stilbene oxide where used as

Scheme 7

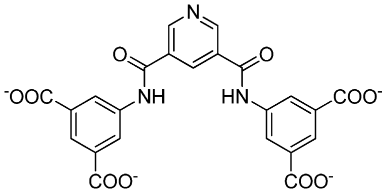


(4) (5) (6)

substrates. Meanwhile, only a highly activated methylene compound, malononitrile, was tested for the Knoevenagel condensation. It would be interesting to test the reactivity with more demanding methylenic compounds, such as ethyl acetoacetate or diethylmalonate.

A similar acid−base tandem process consisting of a sequential deacetalization followed by Knoevenagel condensation catalyzed by PCN-124 was reported by Zhou and co-workers.[147] This MOF contains weakly acidic coordinatively unsaturated Cu^{2+} and basic pyridine and amide groups provided by the ligand 5,5′-((pyridine-3,5-dicarbonyl)bis(azanediyl))diisophthalate (7, Scheme 8).

Scheme 8



(7)

The first step of the tandem reaction studied consisted in the acid-catalyzed deacetalization of dimethoxymethylbenzene to give benzaldehyde. The second step produced benzylidene malononitrile through the Knoevenagel reaction between benzaldehyde and malononitrile. Control experiments proved that both open Cu^{2+} sites and amide groups are essential for the tandem reaction, and they work cooperatively.

We have recently drawn attention to an intriguing point.[148] Sometimes we might deal with a bifunctional catalyst without being aware of it. We demonstrated that this could be the case of the zinc aminoterephthalate IRMOF-3. In the "ideal" structure of the MOF, the amino groups of the linkers are the only catalytic function because the Zn^{2+} ions are completely blocked by the ligands, and in principle, they are not accessible to catalysis. However, we found that in the "real" MOF, and depending critically on the synthesis conditions, a nonnegligible concentration of framework defects can be present, along with zinc oxide and hydroxide nanoparticles that may be formed during the MOF synthesis. These defect species, which, in principle, should not be present in the MOF, can contribute with Lewis acidity and, together with the amino groups of the linkers, lead to an unexpected bifunctional acid−base catalyst. Although the introduction of a (defective) second catalytic functionality to the material may seem advantageous for certain reactions, as we showed for the Knoevenagel condensation reaction, we must take this into account when working with substrates that can further react in the presence of Lewis acid sites through unwanted side reactions. In this latter case, preparation procedures and manipulation of the MOFs have to be carefully considered to generate or to avoid this second type of site.

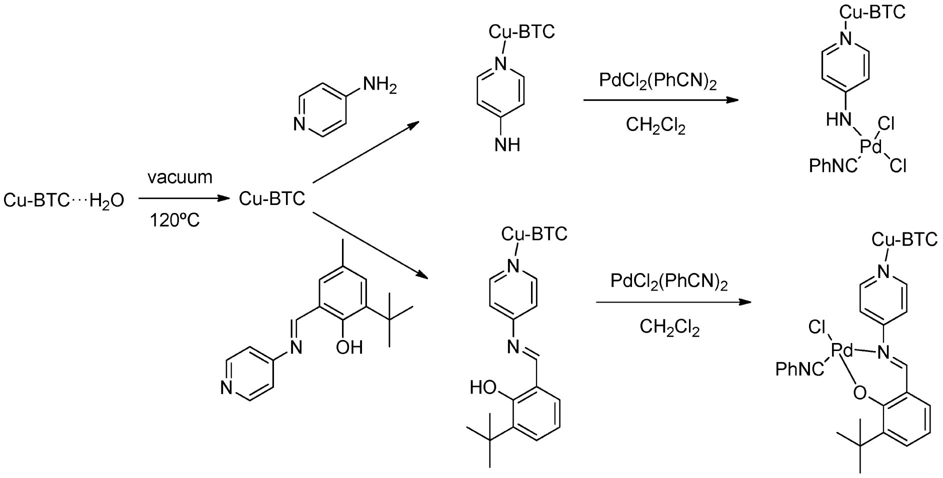
5.3. Bifunctional Metal−Metal Systems. We recently demonstrated that various copper-containing MOFs can catalyze the 1,3-dipolar cycloaddition reaction of alkynes to azides (known as the "click" reaction), yielding the corresponding 1,4-disubstituted 1,2,3-triazoles with activities and selectivities as high as when using homogeneous catalysts.[72,149] The Cu-MOF tested were also able to form in situ the azide needed for the "click" reaction starting from the corresponding brominated compound and sodium azide, NaN_3. As a continuation to this work, we later described how this azide−alkyne coupling reaction can be successfully incorporated into a sequential Sonogashira/"click" process after properly designing the multifunctional MOF-based catalyst required for this transformation. Thus, we have used the coordinatively unsaturated Cu^{2+} sites of CuBTC as anchoring points for introducing either 4-aminopyridine or a pyridine-terminated Schiff base complex, followed by palladium coordination, as shown in Scheme 9.[94]

The resulting bimetallic Cu−Pd MOF catalyzes the tandem Sonogashira/click reaction starting from 2-iodobenzyl bromide, sodium azide, and different alkynes, leading to the one-pot synthesis a series of triazolo[5,1-*a*]isoindoles (Scheme 10).

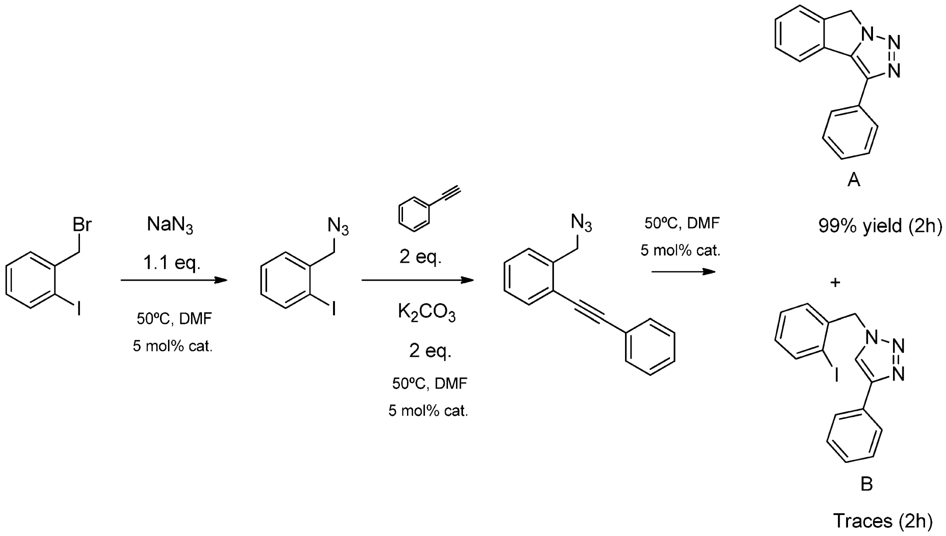
Lin and co-workers[150] reported on the preparation of a bifunctional MOF containing tetranuclear Zn clusters as Lewis acid centers and a chiral Mn−salen metallo ligand. With this material, the authors studied the formation of a chiral epoxide directly from achiral substrates catalyzed by the Mn−salen complex, followed by the acid-catalyzed ring-opening with trimethylsilyl azide (see Scheme 11). Yields of the final ring-open product of up to 60% with enantioselectivities of up to 81% were obtained. Moreover, the ring-opening step was highly regioselective, with only one pair of enantiomers of the four possible pairs being formed.

5.4. Other Multifunctional MOFs. *Photoactive Chiral MOFs.* Very recently, Wu et al. have reported an interesting example in which chiral organocatalytic centers (namely, L- or D-proline) were combined with triphenylamine photoactive units into a single MOF scaffold, leading to a rare example of a heterogeneous asymmetric photocatalyst (see Scheme 12).[151] These materials were found to be active for the α-alkylation of aliphatic aldehydes with diethyl 2-bromomalonate, affording up to 92% ee in certain cases. As suggested by the authors, upon irradiation of the MOF at 350 nm, a photoinduced electron transfer occurs from the MOF to diethyl 2-bromomalonate, thus facilitating the light-induced alkylation of the aldehyde. Indeed, control experiments in the dark yielded negligible amounts of α-alkylation products, evidencing the necessity of light for this reaction. A size-exclusion effect was also evidenced by the lack of reaction when a bulky aliphatic aldehyde was used, suggesting that the alkylation reaction occurs inside the pores and not at the external surface of the MOF.

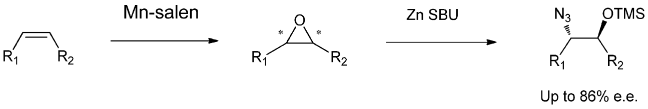
Scheme 9



Scheme 10



Scheme 11



Shi and co-workers[152] recently presented the first example of an organo-bifunctional catalyst in which a MIL-101 type MOF was simultaneously functionalized with amino groups anchored to the Cr^{3+} coordinatively unsaturated metal sites and sulfonic groups on the organic linker, following the process depicted in Scheme 13. This organobifunctional acid−base catalyst showed a superior performance for the tandem acetal hydrolysis−Henry reaction than the monofunctionalized MOFs. Meanwhile, a homogeneous mixture of free acid and base showed no activity due to neutralization of the catalytic species. This clearly evidence the high impact of having immobilized acid−base pairs in the MOF structure to avoid mutual inactivation.

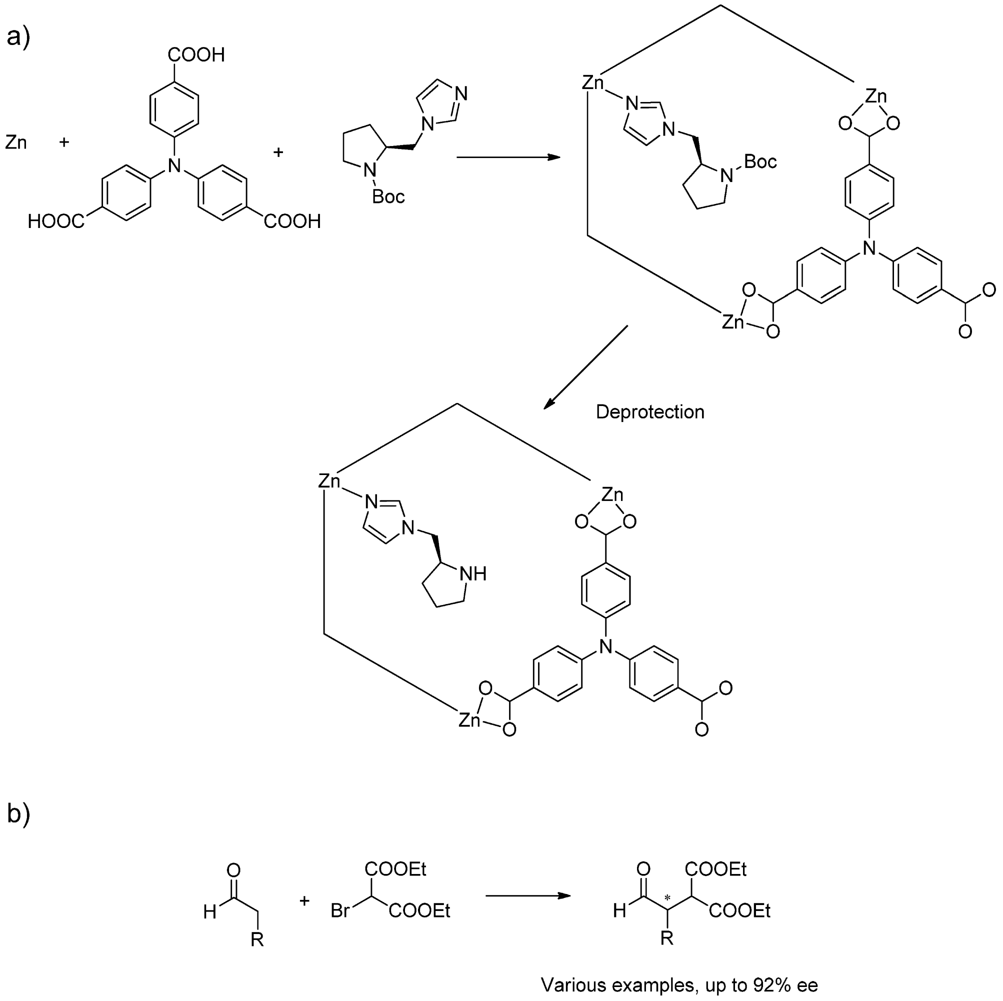
5.5. MOFs for Multicomponent Coupling Reactions.

Multicomponent coupling reactions (MCRs) are also reactions occurring in one reaction vessel and involve more than two starting reagents that form a single product that contains the essential parts of the starting materials. MCR procedures are powerful tools in modern drug discovery processes, providing an important source of molecular diversity by systematically using variants of each of the components involved in the reaction. Moreover, the simple experimental procedures and its one-pot character make MCRs highly suitable for automated and high-throughput generation of organic compounds.

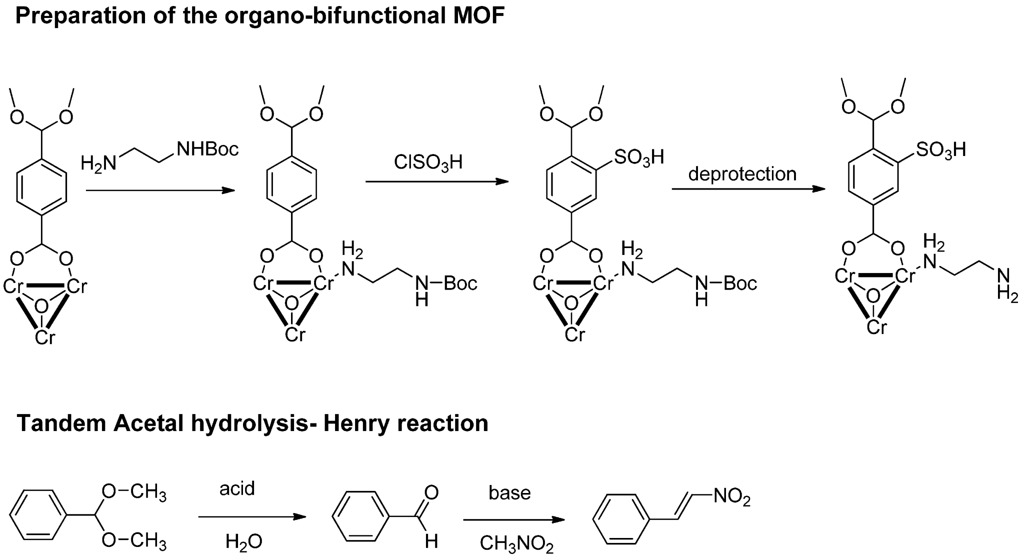
MOFs could become very interesting catalysts for MCRs due to the possibility to add shape and/or transition state selectivity and the fine-tuning of the electronic properties and (chiral) environments of the metal sites. This provides unprecedented privileged systems in which the flexibility of design of metal coordination complexes is combined with the advantages of heterogeneous catalysts. In this section, we will revise some of the successful examples on the use of MOFs as catalysts for MCRs described so far.

Propargylamines are present in many products of interest for the pharmaceutical industry, such as the drugs shown in Scheme 14a. Traditional synthesis of propargylamines relies on the reaction between lithium acetylides or Grignard reagents with imines. Alternatively, propargylamines can also be prepared by the three-component coupling of amines, alkynes, and aldehydes (the so-called A^3 reaction) (Scheme 14b). Moreover, by properly selecting the substrates of this reaction, these

Scheme 12

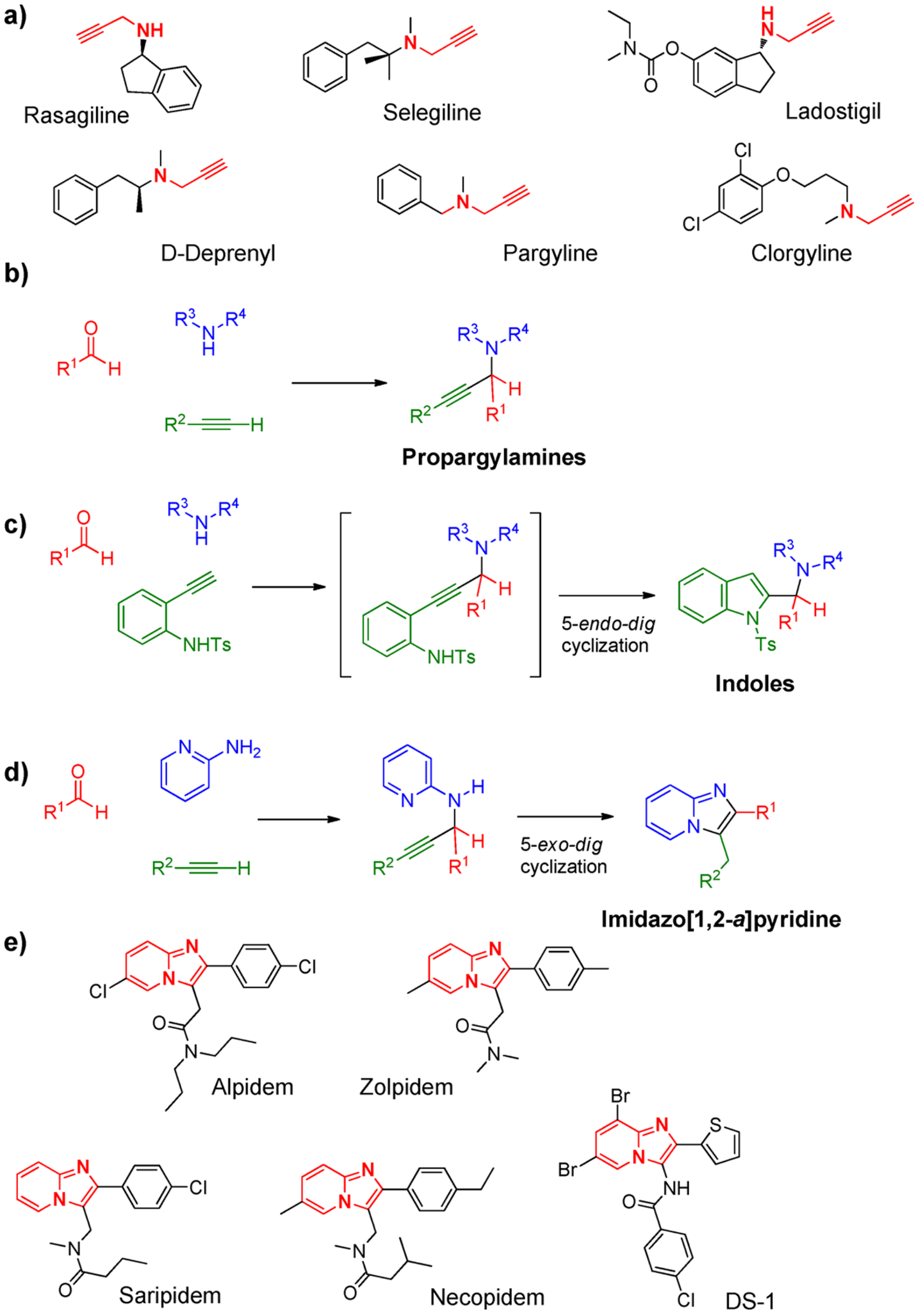


Scheme 13



propargylamines can be further converted into other interesting fine chemicals, such as indoles (Scheme 14c) and imidazo[1,2-*a*]pyridines (Scheme 14d), which are also found in certain anxiolytic drugs (Scheme 14d) . We have reported that this MCR is successfully catalyzed by various MOFs. First, we demonstrated the use of a MOF containing a Au^{3+}-Schiff base complex for the synthesis of indoles through an A^3 reaction.[114] We found that the Schiff base complex was very effective in stabilizing cationic gold species, avoiding their spontaneous reduction to metallic Au^0 and the corresponding loss of activity.

Scheme 14



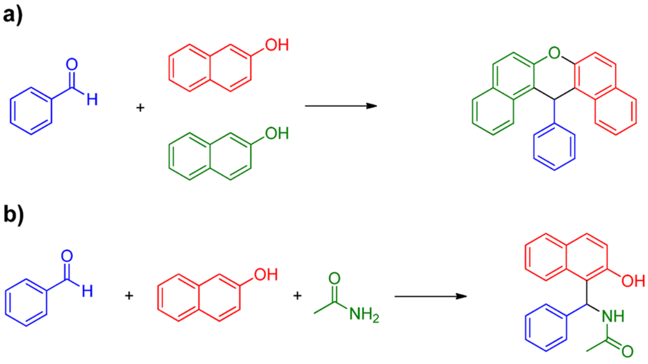
Therefore, the Au-MOF was found to be very effective for the A^3 reaction.

We later extended our study to various Cu^{2+}-containing MOFs for the synthesis of propargylamines, indoles, and imidazopyridines.[79] Particularly good results for the synthesis of imidazopyridines with the lamellar [Cu(BDC)] MOF were found, surpassing the results obtained with other homogeneous catalysts while allowing the reusability of the catalyst. When working with homogeneous copper catalysts, it is usually necessary to work under an inert atmosphere to avoid the Glaser coupling reaction between two terminal alkynes, which is a side reaction that can compete with the formation of the propargylamine; however, we found that the Cu-MOFs studied did not catalyze the Glaser coupling, and therefore, the use of an inert atmosphere was not required. This is a further advantage of the Cu-MOFs with respect to homogeneous catalysts.

Later, other studies on MOF-catalyzed A^3 coupling reactions were reported by Jayaramulu et al.,[153] Yang et al.,[154] Liu et al.,[155] and Juan-Alcañiz et al.[72] Bromberg et al.[156] have recently reported on the use of MIL-101 containing encapsulated phosphotungstic acid (PTA) as catalyst under microwave irradiation for various three-component coupling reactions leading to bioactive drug intermediates: synthesis of dibenzoxanthene by condensation of benzaldehyde and two molecules of 2-naphtol (Scheme 15a) and synthesis of 1-amidoalkyl-2-naphthol by coupling of benzaldehyde, 2-naphthol and acetamide (Scheme 15b).

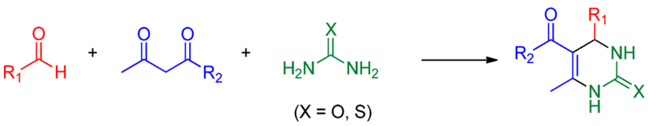
Li et al.[157] have reported the use of two isostructural Zn^{2+} and Cd^{2+} MOFs prepared with the ligands 1,2-bis(4-pyridyl)ethylene

Scheme 15



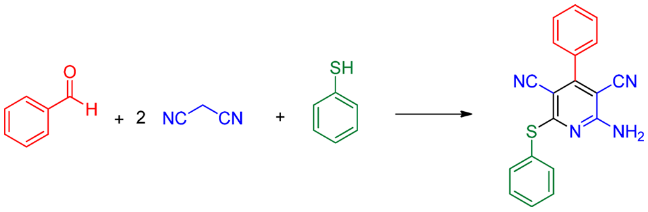
and 1,3-benzenedisulfonic acid for the synthesis of dihydropyrimidinone derivatives through the Biginelli three-component coupling reaction (Scheme 16).

Scheme 16



One year later, the same group also reported the use of these two MOFs as catalysts for the three component coupling reaction of aldehydes, malononitrile, and thiophenols leading to the one-pot synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines (scheme 17).[158]

Scheme 17



Although this is only the beginning, we are witnessing an increasing interest in developing new catalytic applications of MOFs, focusing the interest in the synthesis of high added value products and designing new, more efficient, one-pot synthesis procedures. In this sense, it is evident that the use of MOFs as multifunctional catalysts and in MCRs will certainly trigger a thrilling research. The current challenge not yet addressed is to combine the most evident advantages of MOFs with respect to other catalysts to design efficient asymmetric cascade transformations or MCR leading to complex enantiopure compounds in one pot.

6. CATALYST FORMULATION FOR FINAL APPLICATION

One of the most important challenges to be addressed by the MOF community is the efficient shaping of MOFs for final application. This is important not only for catalysis, but also for other applications, such as adsorptive separation. Most industrial porous materials are used in the form of tablets, rings, spheres, extrudates, or lumps that are prepared under relatively high pressures.[159] In the case of catalysis, as discussed before, to secure a high activity per unit volume and to avoid diffusion limitations, catalysts need to be prepared in a very fine state of subdivision: crystallites from 5 to 500 Å diameter are common in industrial catalysts. On the other hand, these crystals must be in contact with the reagent gas or liquid and then separated from the product while producing a minimum pressure drop in fixed-bed reactors and avoid catalyst attrition in slurry operation. For these reasons, crystallites are usually aggregated into bigger particles (50 μm to 10 mm) that must be porous to allow diffusional traffic of reagents and products.[160] Surprisingly, outside of the vast patent literature, there is little publicly available information on the formulation of industrial heterogeneous catalysts.[161]

When it comes to metal organic frameworks, the compaction of powders into the desired shape by pressing might result in a considerable decrease in surface area due to destruction of the crystalline structure. At this point, the mechanical behavior of the MOF, the way a given framework behaves under pressure, becomes very important, and information on mechanical properties of MOFs is crucial.[162−168] Also for MOFs, outside patent literature,[169−172] there is little publicly available information on formulation.[173−175] CuBTC bodies prepared according to this patent[128] were later tested by Rodrigues and co-workers[176] in the separation of propane/propylene mixtures. Results demonstrate that even in case of such a fragile MOF as CuBTC, pellets with adsorptive behavior similar to that of the parent material can be manufactured. Whether this method can be extended to other MOF topologies with different mechanical properties is still to be unraveled.

A very elegant way to avoid serendipity and possible framework collapse during catalyst formulation is the use of structured reactors or supports: a structured reactor contains a structured interior that can be made out of ceramics, metals, or carbon, situated inside a reactor. It can be considered as an intensified form of a randomly packed bed reactor. A monolith is an example of a structured reactor; in fact, the borderline between catalyst and reactor vanishes for this application. Immobilization of MOFs into supports can offer several advantages over the use of self-supported pellets, especially when one considers that the most promising MOF catalytic applications involve reactions in the liquid phase and slurry operation, where catalyst pellets are not only more likely to collapse but also more likely to induce diffusion limitations. In contrast, when using a coated catalyst, because of the short diffusion distances, the catalytically active material can be utilized more efficiently.[178−181] Once more, the moderate thermal stability of MOFs does not allow for common immobilization techniques applied for structured reactors, namely, washcoating followed by thermal compaction.[182] Therefore, alternative preparation routes are needed.

The immobilization of MOFs into different structured supports, mostly for application in gas separation, has been extensively studied during the past few years.[28] Although MOF membrane literature is already quite extensive,[183−192] to the best of our knowledge, only a few works report on the use of immobilized MOFs in catalytic applications.[177,193,194] We were among the first[177] reporting the synthesis, via secondary growth, of MOF monoliths (figure 4). The resulting structured MIL-101(Cr) was applied in a stirring monolithic reactor configuration in the oxidation of tetralin. The catalysts could be recovered and reused for tens of times, experiencing neither catalyst attrition nor leaching. In the same spirit, Aguado and co-workers have reported the immobilization of the so-called

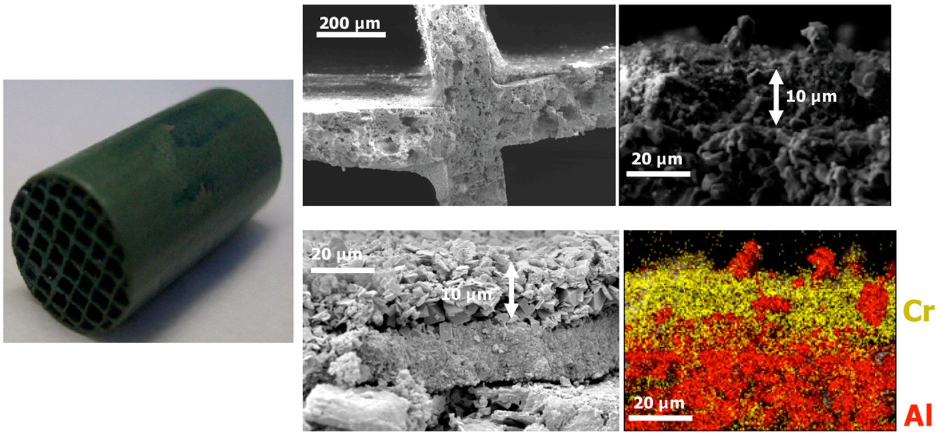


Figure 4. A MIL-101(Cr)-coated monolith. Figures adapted from ref 177.

SIM-1 (a porous zinc carboxylimidazolate) by direct hydrothermal treatment in both monolithic supports and Al_2O_3 beads and the application of the resulting structured support in ketone transfer hydrogenations and Knoevenagel condensations (see Figure 5).[193,194] Even when using the Al_2O_3 beads under vigorous magnetic stirring (400 rpm), no notable weathering was observed and once the beads could easily be separated from the reaction mixture by removing the solution.

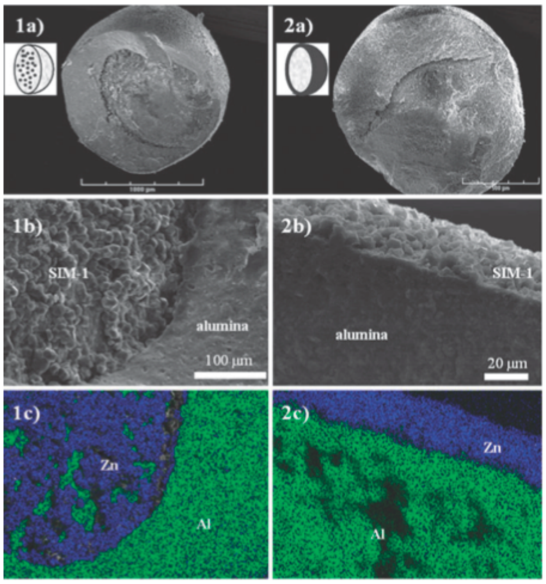


Figure 5. SIM-1 supported on γ- (1) and α-alumina beads (2). (a) SEM image of the bead, view of the cross-section. (b) SEM image and (c) EDXS mapping of the core (1) or surface (2) (color code: blue, Zn; green, Al).[193] Figure reproduced with permission from Royal Society of Chemistry.

Alternatively to the channel type monolithic structures, mesomacroporous monolithic bodies can be used in continuous flow operation, as demonstrated for the Friedländer coupling over Cu-BTC coated on such a system.[195]

The examples above demonstrate that several strategies can be successfully applied to the immobilization and shaping of MOFs. However, there is no general method, and selection and optimization of the most adequate protocol should be performed for every different MOF.

7. CONCLUSIONS AND OUTLOOK

The most recent two decades have witnessed the development of MOFs into a mature class of nanostructured crystalline materials. Although the takeoff of MOF catalysis advanced at a slower pace, already, hundreds of publications demonstrate not only the potential but also the limitations of these materials. The latter is very important, since knowing the limitations certainly defines the scope of application.

Catalyst testing and interpretation of catalytic data deserve special attention when it comes to MOF catalysis. In this paper, we have briefly discussed the case of several carboxylate MOFs dissolving in the presence of carbonates and protic solvents, seeding serious doubts over a number of scientific publications. Furthermore, we believe that catalyst testing needs to be taken more seriously. Here, we have emphasized the most important aspects of catalyst testing. These guidelines should be implemented and known to the community active in catalytic application of MOFs. Finally, to fully assess the potential of MOF catalysts, we should be aware of possible competitors and report fair comparisons, as we tried to do when evaluating literature reports on multifunctional MOFs.

The hybrid nature of MOFs, their high tunability and large porosity, the fact that MOFs are made of molecules arranged in a crystalline lattice, along with their largely discussed chemical, thermal and physical limitations, all point at catalysis under mild conditions and most probably in the liquid phase and with the objective of forming high-added-value products. Despite initial concerns, this limitation is also an opportunity: there is a great lack of heterogeneous catalysts for application under such conditions and for the efficient synthesis of, for example, pharmaceuticals, fragrances, and other high-added-value products. We have summarized most of the efforts toward the development of multifunctional MOFs for one-pot multicomponent coupling reactions and sequential (tandem or cascade) reactions. We strongly believe that MOFs are not only an excellent playground for the development of such complex heterogeneous catalytic systems but also an excellent tool to understand multifunctional catalysis and the ideal bridge between homo- and heterogeneous catalysis. Even in the worst-case scenario, in which such developments would not lead to direct industrial implementation, the acquired knowledge in terms of reaction mechanism and influence of active site proximity will certainly pay back all the efforts devoted to multifunctional MOFs.

Because of the scope of this article and to the excellent reviews that are already published on MOF photocatalysis and MOF chiral catalysis, we hardly touched upon these certainly promising catalytic applications of MOFs. Charge transfer in MOFs and light absorption in the visible region have already been reported to be straightforward for many MOF structures.[196−200] Now it is time to devote more effort to active site engineering. Homogeneous photo- and electrocatalysts should be the source of inspiration. In this sense, new methods for the encapsulation of well-defined nanoparticles, such as those developed by Hupp and co-workers,[201] will be of great help. MOFs have been shown to offer unprecedented possibilities for the immobilization of stereoselective catalysts.[135,137] We are sure that in the future, more and more examples will appear on this topic.

Finally, regarding active site engineering, a rational control over the framework flexibility of the material may also have a large impact on its final catalytic properties. Although framework flexibility has been largely overlooked when designing catalytic applications of MOFs, it can be expected that this property will be considered in future developments. Taking enzymes as source of inspiration, the objective has to be the preparation of materials capable of adapting their pore space by conformational changes of their building units.

Before large-scale application is a reality, we will need to face not only the scale-up of synthesis, a topic already many pioneering researchers are busy with, but also the shaping of MOFs into the appropriate shape for application. Looking at the mechanical properties of most MOFs, it is clear that traditional methods involving high-pressure shaping will not be an option. Therefore, either coatings or other methods toward self-supported agglomerates, such as spray drying[202] or electrochemical coatings,[203] will need to be further explored.

Summarizing, it has been a long but fast journey, and there is yet a long road ahead, but now the chances of MOFs in catalysis are higher, and the directions to follow in terms of application have been better identified than a few years ago. We have no doubt that research into MOF catalysis will certainly contribute to a much better understanding of heterogeneous catalysis.

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Notes

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