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ARTICLE

The post-synthesis modification (PSM) of MOFs for catalysis

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While there are myriad ways to construct metal-organic framework (MOF) based catalysts, the introduction of catalytic functionality via covalent post-synthesis functionalization (PSM) offers multiple advantages: i) a wide range of different catalyst types are generated from a handful of well-known parent MOFs, ii) MOF catalyst properties can be systematiclly tuned while changing few variables, and iii) catalytically active functional groups that would otherwise interefere with MOF assembly can be introduced faciley. This last is particulary crucial for our quest to generate MOF active sites that are decorated with multiple functional groups that are capaple of cooperative activity, analogus to enzyme acive sites.

Introduction

An oft-touted attribute of metal-organic framework (MOF) materials is their resemblance to enzyme active sites,[1] largely because MOF-based catalysts transform reactants within the confines of their pores, much in the way that biochemical reactions are frequently restricted within enzyme cavities. However, said confinement is often where the similarity between MOF catalysts and enzymes ends since, besides their constrained size and shape, enzyme active sites are also characterised by their decoration with multiple amino acid side chains. These multiple functional groups promote reactions depending on their chemical properties: e.g., acidity, basicity, hydrophobicity, nucleophilicity, flexibility etc. They not only define the confines of the active site, but they influence both the activity and selectivity of the enzymatic reaction by any combination of reacting covalently with substrates, stabilizing transition states, and perturbing, via non-covalent interactions, the physical properties of reacting species and/or other functional groups present in the cavity.

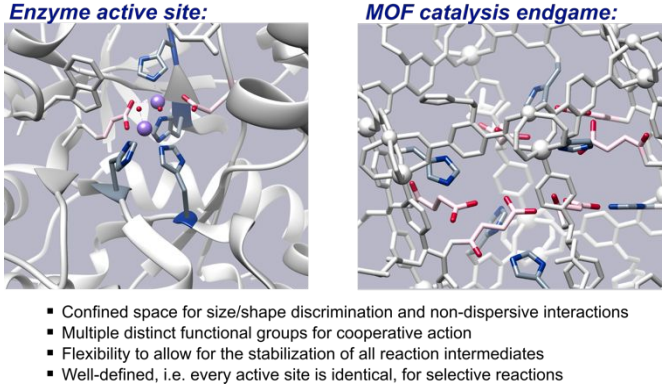

Figure 1. Properties of enzyme active sites which multifunctional MOF-based catalysts aspire to.

Thus, to more adequately mimic enzyme sites, thereby attaining more of their efficiency, the pores of MOF-based catalysts need to be decorated with multiple functional groups that can cooperatively orient and/or activate substrates and intermediates. Additional requirements for achieving more enzyme-like activity are that the cavities should be flexible and identically functionalised. Flexibility allows for dynamic binding, in which small adjustments of the cavity ensure favorable interactions for all species along the reaction pathway, while the uniformity of the of the functional groups present in each cavity is imperative for selective transformation. The difficulty arises in the requirement that the many of the functional groups should be capable of supramolecular interactions such as hydrogen bonding and electrostatic interactions, or capable of nucleophilic reactivity. The generation of MOFs in which such functionalities are present free and uncoordinated within the pore is challenging as these types of functional groups often coordinate to the metal building blocks, becoming a part of the framework vertices,[2,3] e.g. –OH in MOF-74[4] and –COOH in HKUST-1.[5]

Despite the difficulty of assembling MOFs bearing the desired functional groups as free substituents, there are several examples of generating such MOFs via traditional synthesis methods. We must note, however, that the functional groups in such frameworks are attached directly to the framework linkers, which are generally aromatic,[6–9,2] rigid,[10,11] or otherwise so sterically encumbered as to preclude their coordination to metal species during MOF assembly.[12] This necessarily limits the ability of these functional groups to reorient themselves in the pores for dynamic binding. Unfortunately, the assembly of MOFs with linkers in which these ligating substituents are tethered to the linkers via aliphatic chains or other attachments that afford them conformational flexibility is more likely to yield structures in which those groups are coordinated to the metal vertices. Thus, the most reliable strategy for obtaining MOFs in which the desired functional groups are uncoordinated and available

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for synergistic catalysis is to introduce them into the pores after framework assembly.

Post-synthesis modification of MOFs

The post-synthesis modification (PSM) of MOFs spans a wide range of transformations, including the exchange of monotopic ligands at unsaturated metal clusters, transmetalation, linker exchange and insertion, etc.[13] While multiple functionalities can be introduced using linker exchange/insertion and coordination at metal corners, in this article we focus on "traditional" PSM in which organic linkers are transformed via the breaking and/or forming of covalent bonds. This is because we are interested in catalytic MOFs that are well-defined and where there is a low risk of catalyst leaching under a variety of reaction conditions. In covalent PSM, a parent MOF with linkers bearing reactive substituents such as amines, hydroxyls, azides, terminal alkynes and alkenes, etc., are reacted with the corresponding substrate to yield a new MOF. Thus, a single parent MOF can be systematically modified to generate several mono- and multifunctionalised daughter MOFs using strategies such as single, tandem, and multi-step functionalization (Figure 2). Perusal of the PSM literature reveals myriad examples of the covalent modification of MOF to introduce functional groups that have supramolecular and/or nucleophilic capabilities that would otherwise interfere with MOF assembly. Of particular interest, are reports in which the resulting daughter MOFs are applied to catalysed reactions.[14]

The PSM of MOFs for catalysis

The first report of covalent PSM of a MOF was the alkylation of free pyridine groups in a homochiral MOF transesterification catalyst. It is worth mentioning that, while the parent framework demonstrated the first example of enantioselective catalysis by a MOF,[6] the resulting methylpyridinium iodide MOF was itself not catalytically active. The next example of enantioselective catalysis was by a framework obtained by metalating a homochiral BINOL-based MOF. It should be noted that the construction of a large number of MOF catalysts involves this type of dative modification of frameworks assembled using "privileged" organic ligands, which highlights the importance of PSM in generating catalytic MOFs.[18]

Though fewer, the examples of MOF catalysts produced via covalent modification demonstrate the breadth of catalysts that can be produced from a single material. Just considering IRMOF-3, the archetypal modifiable MOF, we find that its $-NH_2$ groups have been elaborated with numerous organic moieties that can be applied to an assortment of catalysed reactions. Many of these PSM-derived MOF catalysts have been metalated Schiff bases which are applied to a host of reactions (Figure 2B).[16,19] Eventually, catalysts were synthesised via the elaboration of other common $-NH_2$ bearing MOFs such as UMCM-1-NH_2 which has larger pores,[20] and MIL-53(Al)-NH_2 and UiO-66-NH_2 which are chemically more stable.[21,22] The framework structures of these MOFs and some representative PSM reactions are shown in Figure 3.

There are far fewer examples of MOF catalysts that have been generated via the PSM of non-amine reactive handles such as nitrogen heterocycles,[6,23–26] aldehydes,[27–29] acid anhydrides, etc.[30] The advantage of non-amine reactive tags in the post-synthesis generation of catalysts is exemplified by "clickable" MOFs. Frameworks bearing either alkynes or azides can undergo the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC, Figure 4A),[31–37] a selective reaction, occurring exclusively between azides and terminal alkynes regardless of other functional groups present. Other "click" reactions performed on MOFs include the tetrazine-alkene ligation and the sulfur(VI) fluoride exchange (SuFEx) reactions (Figure 4B-C).[38,39] These reactions allow for the introduction of functional groups that are more nucleophilic than $-NH_2$,[31,35,40] without requiring extra protection-deprotection steps, e.g. biologically relevant functionalities. Thus, the ability to functionalise MOFs with good nucleophiles is especially important when attempting to synthesise biomimetic MOF-based catalysts.

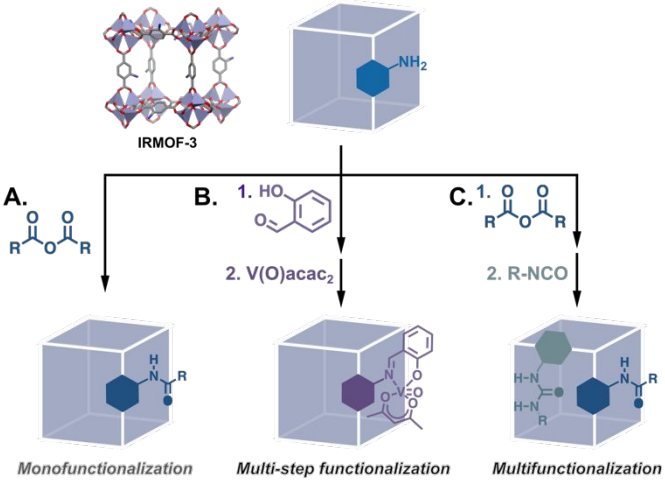


Figure 2. PSM of a parent MOF can yield monofunctionalised daughter MOFs via A) a single reaction[15] and B) a tandem process,[16] or C. multifunctionalised MOFs by reaction with multiple reactants.[17]

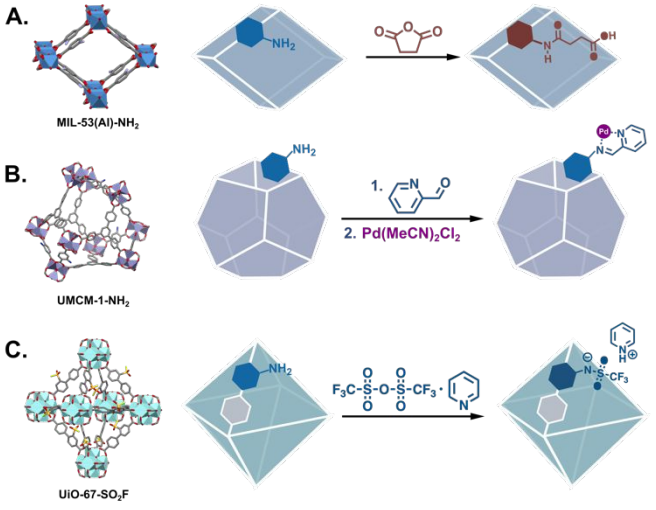


Figure 3. Other common amine-tagged MOFs demonstrating PSM via nucleophilic substitution A) MIL-53(Al)-NH_2,[41] B) UMCM-1-NH_2,[42] and C. UiO-67-NH_2.[43]

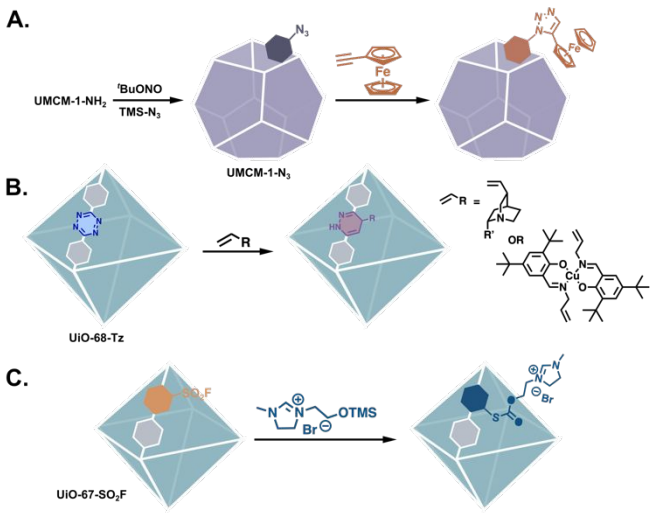


Figure 4. MOFs tagged with non-amine functionalities for introduction of complex functionality via A) CuAAC,[44] B) tetrazine-alkene ligation,[39] and C) SuFEx "click" reactions.[38]

Given the premise that PSM is an ideal way to generate enzyme-inspired environments in MOFs, the daughter MOFs of greatest interest are those that have been modified to bear functional groups that are reminiscent of amino acid side chains. Amino acid substituents possess any of several properties to tailor the chemical environments of enzyme cavities: acidity, basicity, nucleophilicity, hydrophobicity, etc. And, as the cavities are frequently decorated by several different side chains, multiple of these features are present simultaneously in enzyme active sites.[42] Many enzymatic reactions depend on side chains with different properties acting synergistically to effect catalytic transformation (Figure 1).[45] For example, a common catalytic motif in enzymes is the catalytic triad consisting of an acidic, basic, and nucleophilic side chain.[46] Promisingly, there are multiple examples of covalent MOF modification to introduce functionalities that have similar attributes.[47]

PSM to introduce nucleophilic catalysts

Nucleophilic side chains in enzymes partake in covalent catalysis via formation of covalent bonds with substrates.[48] While several amino acid residues can be nucleophilic, cysteine, serine, and threonine are the predominant nucleophiles.[49] Though the amine of proline is not available for covalent catalysis as it forms the peptide backbone in enzymes, PSM has also been used to introduce analogues of this potent nucleophile into MOFs as an accessible catalyst. In most examples, the modification has involved the deprotection of MOFs assembled from linkers bearing protected prolines or pyrrolidines (Figure 5A).[50–56] However, the use of orthogonal reactions such as the CuAAC has allowed the direct functionalization of alkyne and/or azide-tagged MOFs with unprotected proline analogues (Figure 5B).[31,35] Regardless of the PSM strategy employed for synthesizing MOFs decorated with proline analogues, these materials have been successfully applied to asymmetric aldol reactions, with some affording respectable enantioselectivities.[31,53]

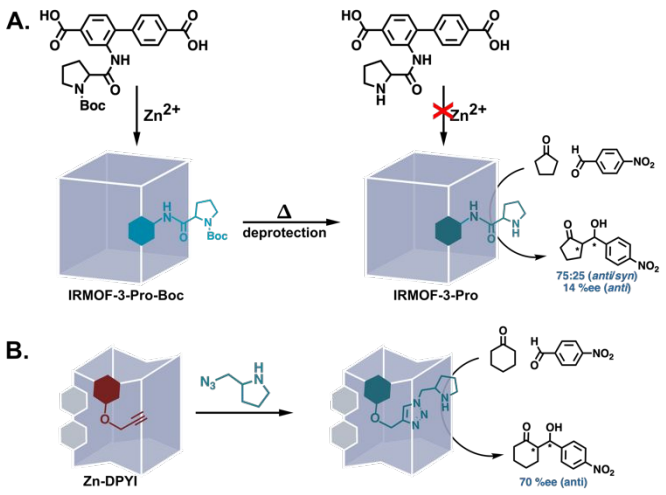


Figure 5. Introduction of unprotected proline analogues into MOFs via PSM for the catalysis of aldol reactions. A) The deprotection of a Boc-protected proline substituent.[51] B) CuAAC between an alkyne-tagged MOF and an azide-functionalised pyrrolidine.[31]

PSM to introduce acid-base catalysts

Another important mechanism in enzymatic reactions is acid-base catalysis, in which the reactions are promoted by the transfer of protons. MOF catalysts emulate these mechanisms by incorporating acidic functional groups (Figure 6), basic substituents (Figure 7), or hydrogen-bond donors (Figure 8). Aspartic and glutamic acids primarily play an acidic role, though they can also be H-bond donor-acceptors, or nucleophiles in their deprotonated form. Aspartic and glutamic acids analogues have been grafted into MOF pores via the facile nucleophilic ring opening of cyclic anhydrides (Figure 6A),[17,57,58] as well as by the CuAAC reaction.[59] In a demonstration of the efficiency of PSM, Garibay et al.

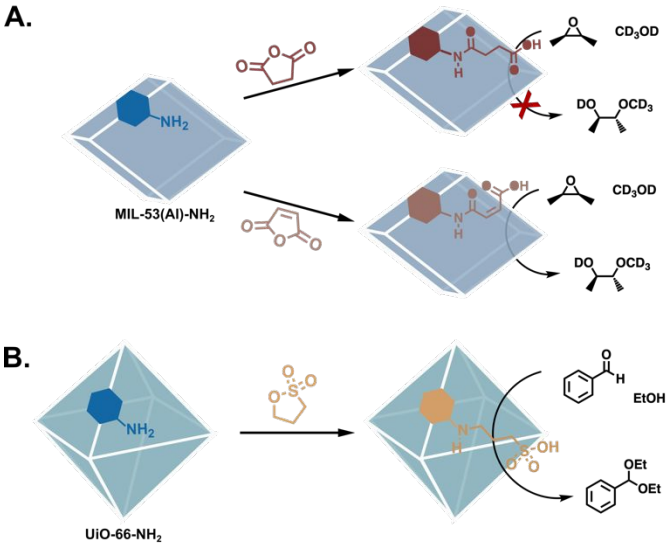
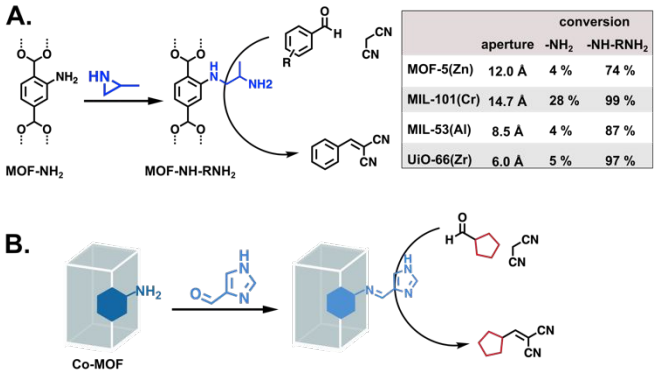


Figure 6. PSM to functionalise MOFs with Brønsted acid catalysts. A) Altering the stereoelectronic properties of the carboxylic acid substituents results in significantly different conversions in the methanolysis of epoxides.[41] B) A sulfonic acid-functionalised MOF is efficient in aldehyde acetalization.[60]



	aperture	conversion -NH$_2$	conversion -NH-RNH$_2$
MOF-5(Zn)	12.0 Å	4 %	74 %
MIL-101(Cr)	14.7 Å	28 %	99 %
MIL-53(Al)	8.5 Å	4 %	87 %
UiO-66(Zr)	6.0 Å	5 %	97 %

Figure 7. Functionalization of MOFs with bases for the Knoevenagel reaction. A) Ring-opening of aziridine by different –NH_2-tagged MOFs to afford aliphatic primary amine MOF catalysts.[61] B) Imine condensation to introduce imidazole functionality.[62]

synthesised several aliphatic carboxylic acid-bearing MOFs by reacting MIL-53(Al)-NH_2 with different cyclic anhydrides. Via this facile modulation they determined that the *cis*-maleic acid-based catalyst was the most effective in the methanolysis of several epoxides.[41] Sulphonic acids have also been grafted onto MOFs post-synthetically,[63] and their aptitude for catalysis has also been demonstrated in aldehyde acetalization, acid-catalysed epoxide ring-opening, and Morita–Baylis–Hillman reactions (Figure 6B).[60,64,65]

The primarily basic enzyme side chains belong to amino acids lysine, histidine, and arginine. Lysine-adjacent functionalities have been introduced as a variety of amines, and have catalysed reactions such as transesterifications, Knoevenagel condensations, and Henry reactions.[61,66,67] The report by Luan et al. highlighted the importance of the MOF scaffold, showing improved Knoevenagel reaction conversions with increasing MOF pore size (Figure 7A). The analogue of histidine that is widely used in MOFs is imidazole, though it typically appears as part of the underlying framework rather than as a free substituent. Imidazole is an excellent coordinator of metals, with a large family of MOFs based on imidazolate SBUs,[68] so, PSM is required to obtain free imidazoles.[62,69,70] In the report by Liu et al., the imidazole functionalised MOF was successfully applied to the Knoevenagel reaction of furfural (Figure 7B).[62]

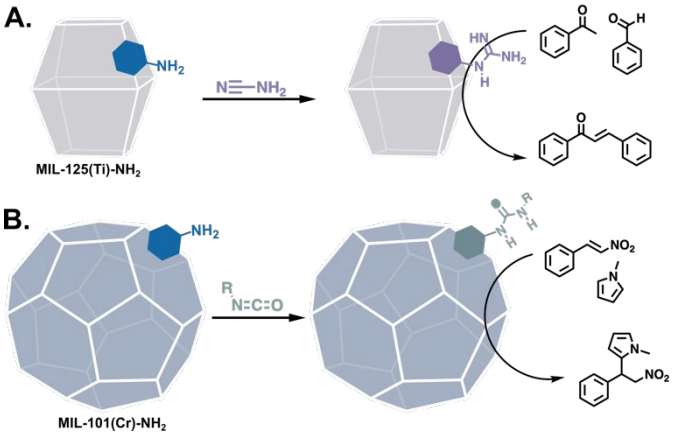


Figure 8. PSM of to afford MOF with arginine-adjacent functionalities: A) guanidine for Claisen-Schmidt condensation catalysis,[71] and B) a series of ureas for Friedel-Crafts alkylation.[72]

Arginine, the final primarily basic amino acid, bears a guanidine group that can be a base when neutral, and a 2-point H-bond donor when protonated. Thus, MOFs have been elaborated with arginine-adjacent functionalities in the form of guanidine groups for Claisen-Schmidt condensation (Figure 8A)[71] and CO_2 fixation.[73,74] Ureas and thioureas, the ubiquitous 2-point H-bonding organocatalysts, have also been generated in MOFs post-assembly,[75] and applied to Morita-Baylis-Hillman and Friedel-Crafts alkylation reactions (Figure 8B).[72,76]

PSM for the hydrohphobization of MOF catalysts

The final class of amino acids are those that are hydrophobic. The hydrophobicity of enzyme cavities is crucial for the binding of hydrophobic substrates in an aqueous environment,[77,78] as well as for perturbing the pK_as of residues involved in acid-base catalysis. A large percentage of MOF PSM reactions involve the introduction of hydrophobic groups, aliphatic and aromatic, by a variety of reactions. In catalysis, hydrophobicity chiefly plays a stabilizing role, repelling water from moisture-sensitive frameworks.[79,80] However, there are examples of hydrophobic groups accelerating condensation reactions by expelling water from MOF pores.[81] For example, upon grafting dodecylamine onto an aldehyde-tagged framework, Canivet et al. observed a greater than ten-fold increase in the initial rate of a Knoevenagel condensation (Figure 9).

PSM of MOFs with amino acids

Aside from modifications with functional groups that resemble amino acids, MOFs have also been elaborated with actual amino acids for catalysis. In 2011, Bonnefoy et al. reported the peptide coupling of amino acids to (In) MIL-68-NH_2,[50] and followed up with the grafting of oligopeptides (mono- to tetra-) on –NH_2 bearing MOFs (Figure 10A).[82] The proline-terminated mono- and dipeptide MOFs catalysed an asymmetric aldol reaction, giving 18% and 25% enantiomeric excess (ee), respectively. Using a different approach, Fracaroli et al. produced tripeptide-bearing MOF catalysts via a seven step sequence of peptide couplings and deprotections (Figure 10B).[83] The resulting MOF catalysts selectively cleaved a bond in an oligopeptide while the solution phase tripeptide showed no such reactivity. Additionally, when functionalised with a proline-terminated tripeptide, the MOF catalyst achieved significantly higher ee than molecular proline (20% vs 2%) in the α-chlorination of butyraldehyde. The authors postulated that the increased activity and selectivity were due to stereochemical constraints in the functionalised MOF pores.

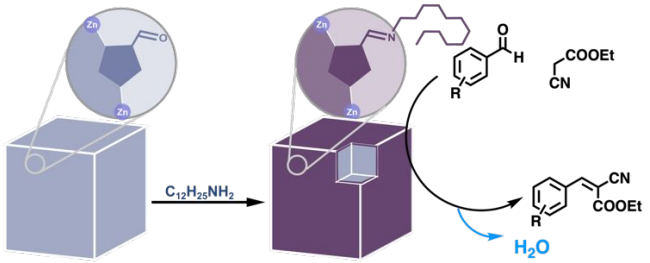


Figure 9. Surface hydrophobization of a catalytic MOF to accelerate the Knoevenagel condensation.[81]

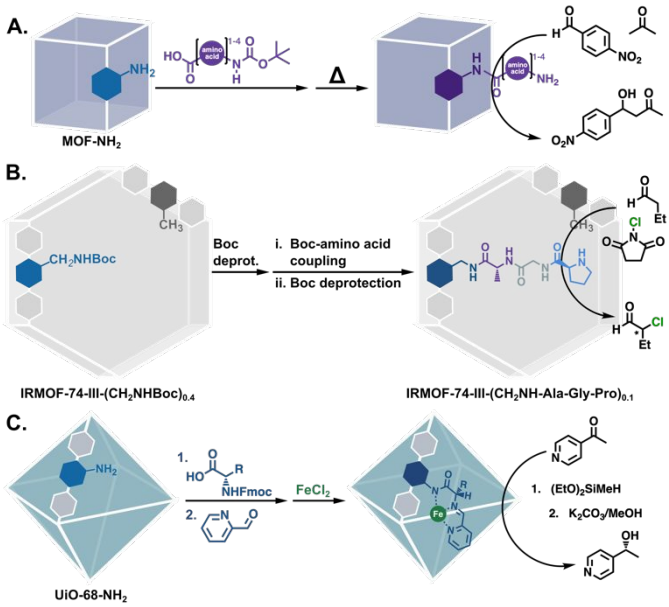


Figure 10. PSM to functionalise MOFs with amino acids: A) a series of mono-, di-, tri-, and tetra peptides for the asymmetric aldol reaction.[82] B) Seven PSM steps to yield a tripeptide functionalised MOF for asymmetric α-chlorination.[83] C) Elaborated and metalated amino acid for the hydrofunctionalization of carbonyls.[84]

More recently, Manna and co-workers also functionalised their MOFs with amino acids, but they went a few steps further by elaborating the amino acids themselves to introduce additional functionality. Protected amino acids were coupled to UiO-68-NH_2 and subsequently deprotected. The free amino acid was then condensed with 2-formylpyridine to form a bidentate pyridyl-imine moiety that was finally metalated with iron (II) (Figure 10C).[84] The resulting catalysts were active and selective in the hydrosilylation and hydroboration of carbonyls, with the valine-based catalyst, in particular, achieving excellent conversions and enantioselectivities (>95 %) for most of the substrates.

Multifunctional MOF catalysts via PSM

Given the extensive list of functional groups that emulate amino acid side chains that have already been grafted into MOFs, one would suppose that the introduction of multiple such groups into the confined spaces of MOF cavities would be a straightforward strategy for synthesizing enzyme inspired catalysts. Indeed, some of the PSM reports mentioned above have resulted in, or involved, multifunctional catalysts. While most have been applied to tandem reactions in which each of the functional groups catalyses a different reaction,[85,86] a few have demonstrated the promotion of reactions via the cooperative action of multiple groups. Such catalysis is most commonly seen in ionic MOFs where anionic counterions work synergistically with ammoniums,[87] pyridiniums,[23] phosphoniums,[88] imidazoliums,[89,90] triazoliums,[36] guanadiniums,[74] etc., primarily for CO_2 fixation (Figure 11).

Other examples of multifunctional, PSM-derived MOF catalysts involve a catalytically active functionality together with one or more functionalities that tailor the pore environment for

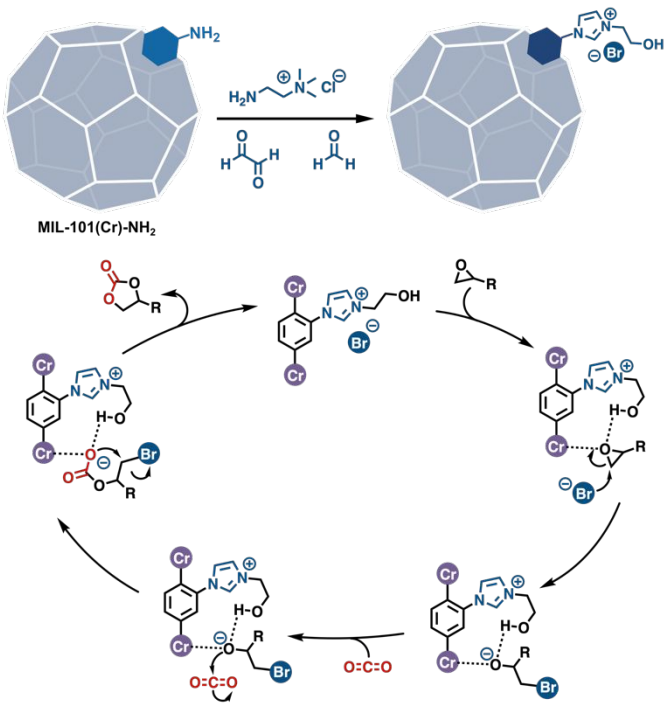


Figure 11. A multifunctional MOF catalyst achieved by PSM. The Lewis acidic metal corner, the cationic imidazolium, and bromide work cooperatively for the fixation of CO_2.[90]

selectivity or further reaction acceleration. For example, via a 2-step diazotransfer/"click" reaction sequence, Savonnet et al. bifunctionalised an $-NH_2$ bearing MOF with a basic trialkyl amine and a hydrophobic phenyl group (Figure 12A).[91] They found that, while the MOF solely functionalised by the trialkyl amine was active in the transesterification of ethyldecanoate with methanol, the hydrophobicised catalyst was significantly more active. The monofunctionalised (40% trialkyl amine) catalyst afforded 48% conversion after 20 h, while the bifunctional (30% trialkyl amine; 30% phenyl) catalyst had a conversion of 84%.

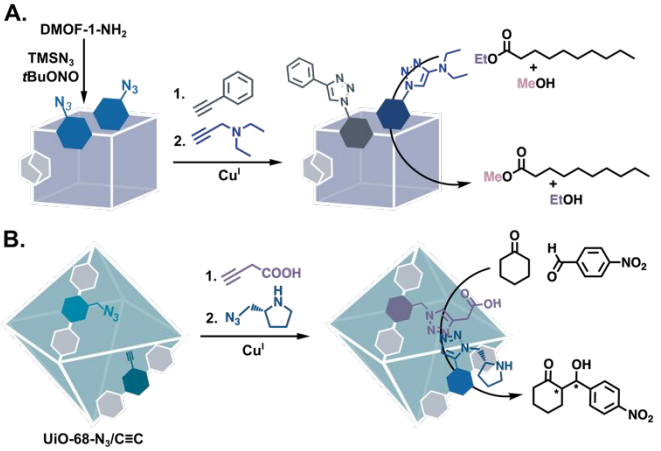


Figure 12. Post synthetic multifunctionalization of MOFs to generate bifunctional catalysts: A) addition of amine base and hydrophobic substituent for transesterification.[91] B) addition of proline covalent catalyst and acid/base co-factor for the aldol reaction.[35]

The benefits of multifunctional MOF catalysts in which the different groups are reminiscent of amino acid side chains is demonstrated in the PSM-derived, bifunctional MOFs reported by Zhang et al.[35] The team synthesised a multivariate MIL-68 analogue in which the triphenyl linkers have azide or alkyne substituents (Figure 12B). Following sequential CuAAC reactions to functionalise the MOF with both proline and carboxylic acid groups, the bifunctional MOF yielded 95 % product in a proline-catalyzed aldol reaction. The bifunctional proline/carboxylic acid MOF produced four aldol products with a 35:65 syn/anti ratio, and a 26 % ee for the anti product. As evidence of the benefit of the secondary carboxylic functionality, when -COOH was replaced by -COOMe or -C≡CH, yields of only 32 % and 13 %, respectively, were obtained.

Outlook

While the last example demonstrated the benefits that can be obtained by having multiple distinct functional groups working cooperatively to turnover a reaction, there are drawbacks to the use of PSM to generate multifunctional MOFs for catalysis. Namely, i) the non-uniformity of the composition of the MOF pores and ii) the reduction of pore size due to functionalization. To the first point, the blocking of the MOF pores by additional functionality leads to reduced mass-transport though the frameworks, resulting in lower apparent activity or no access to the interior active sites at all. Common strategies to circumvent such pore blockage include the use of mesoporous MOFs,[83] the of use macroporous–microporous hierarchical MOFs, and/or partial functionalization by, for example, synthesizing multivariate MOFs in which only a fraction of the linkers contain reactive groups (Figure 10B).[83,92] The previous example, however, leads to the second concern with multifunctionalized catalytic MOFs: non-uniformity due to the methods employed to introduce multiple functional groups into the active site. Two of the more prominent strategies are schematically represented in Figure 13. In the first route, a MOF with a single reactive tag reacts with multiple reactants resulting in a random distribution of the moieties (Figure 13A). Alternately, one can start with a MOF decorated with multiple

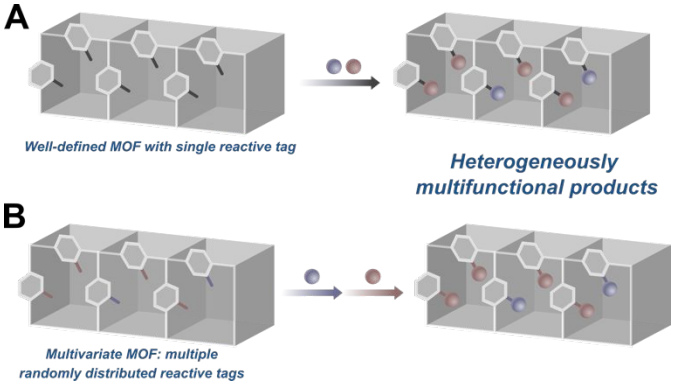


Figure 13. Common strategies for the post synthetic multifunctionalization of MOFs: A) A well-defined MOF functionalized with two different moieties. B) A multivariate MOF in which two different tags react independently with two different moieties. Both strategies result in multivariate MOF.

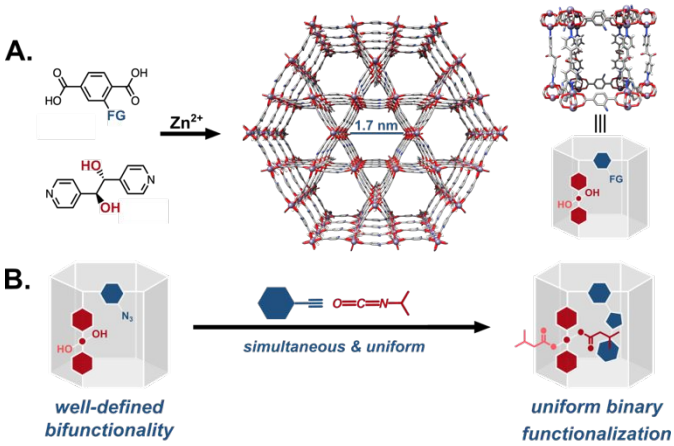


Figure 14. Uniform post synthetic multifunctionalization of MOFs: A) Well-defined, large-pore, pillared MOFs are constructed with two different linkers, each with independently reactive tags. For example, B) A framework with orthogonally reactive tags yields uniformly bifunctionalized MOF even in simultaneous reactions.[93]

reactive handles that can be independently functionalized with different reactants (Figure 13B). In most examples of this strategy, however, the reactive tags in the parent MOF are also randomly distributed resulting in similarly multivariate daughter MOFs. This heterogeneity is difficult to characterize, requiring herculean efforts to map the distribution of the functional groups in the MOF. More importantly, in the context of catalysis, the heterogeneity of the MOF active sites likely leads to poor selectivities and sub-optimal activities. As a case in point, while the bifunctionalization of the proline MOF shown in Figure 12B greatly improved the system's activity, the stereoselectivity was much lower compared to other proline MOFs performing the same reaction.[31,53]We speculate that that the construction of more homogeneously functionalised MOFs will deliver better selectivities for reactions that rely on the cooperative action of multiple functional groups. To this end, our group has spent the last few years developing strategies for the uniform covalent bifunctionalization of well-defined, mixed-linker MOFs with large pores and two disparate reactive functionalities (Figure 14A).[58,93,94] Taking advantage of the different reactivities of the tags, we have independently and quantitatively decorated MOFs with two different moieties, generating uniformly bifunctionalised MOF pores (Figure 14B).

Conclusions

The myriad ways, discussed herein, of post-synthetically introducing catalytic functionality into MOFs, coupled with the availability of strategies for uniform multifunctionalization, portend the construction of well-defined, confined, multifunctional MOF catalysts in the foreseeable future. Specifically, uniform, MOF based catalysts in which the disparate functionalities are capable of cooperative action; thereby bringing us closer to our goal of synthesizing catalysts that possess the most salient features of enzymes.

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Table 1. Summary of post-synthesis modification (PSM)-derived MOF catalysts.

Ref	Reactive tag	MOF(s)	PSM	New functionality	Catalysis
16	$-NH_2$	IRMOF-3	imine condensation followed by metalation	V(O) salicylidene	cyclohexene oxidation
23	pyridine	UiO-66-Py UiO-67-Bpy	*N*-alkylation	*N*-methyl iodide and *N*-methyl *p*-toluenesulfonate	CO_2 fixation with epoxide
24	pyridine	Pyridyl-MOF-1	*N*-alkylation	*N*-methyl bromide	CO_2 fixation with epoxide
25	imidazolium	Im-UiO-66	*N*-alkylation	*N*-methyl iodide	CO_2 fixation with epoxide
26	pyridine	1-Eu	*N*-alkylation	*N*-methyl halides	CO_2 fixation with epoxide
27	–CHO	UiO-67-CHO	imine condensation /reductive alkylation	Alkyl amine	Knoevenagel condensation
28	–CHO	ZIF-90	imine condensation with aminopyridinium iodide	imino pyridinium iodide	CO_2 fixation with epoxide
29	–CHO	UiO-67-CHO UiO-68-CHO	imine condensation followed by metalation	Fe-metalated l-valinol	hydrofunctionalization
30	–COOH/ anhydride	MIL-121	Decarboxylation/conden-sation then metalation	$Pt(NH_3)_4(OH)_2$	oxygen reduction reaction (ORR)
31	–C≡CH	Zn-DPYI	Cu-catalysed azide-alkyne cycloaddition (CuAAC)	D or L pyrrolidine	asymmetric aldol reaction
32	$-N_3$	UiO-67–N_3	CuAAC	alkyl amine	Knoevenagel reaction
33	$-N_3$	MIL-101(Cr)	CuAAC then metalation	terpyridyl($RuCl_3$)	alcohol oxidation
35	–C≡CH/–N_3	UiO-68-azide/alkyne	CuAAC	R-pyrrolidine with carboxylic acid or methyl ester.	aldol addition
36	$-N_3$	MIL-101-N_3	CuAAC then *N*-alkylation	3- triazolium bromide	CO_2 fixation with epoxide
37	–C≡CH	UiO-66-alkyne	metalation	Ni acetylide	Knoevenagel condensation
38	$-SO_2F$	UiO-67-SO_2F	sulfur(VI) fluoride exchange (SuFEx)	1H-imidazolium bromide	benzoin condensation
41	$-NH_2$	MIL-53-(Al)-NH_2	nucleophilic acyl substitution	maleic acid	epoxide methanolysis
60	$-NH_2$	UiO-66-NH_2	propanesultone ring opening	sulfonic acid	benzaldehyde acetalization
61	$-NH_2$	UiO-66-NH_2 Cr-MIL-101-NH_2	aziridine ring opening	alkyl amine	Knoevenagel reaction
62	$-NH_2$	Co-MOF	imine condensation	imidazole	Knoevenagel reaction
64	$-NH_2$	UiO-66-NH_2	nucleophilic acyl substitution	sulfonic acid	acetalization and Morita–Baylis–Hillman reaction
65	$-NH_2$	NH2-MIL-88-B (Fe)	propanesultone ring opening	sulfonic acid	epoxide ring-opening
66	$-NH_2$	MIL-53(Al)-NH_2	nucleophilic substitution	dimethyl amine	transesterification
71	$-NH_2$	NH_2-MIL-125	guanylation	guanidyl	Claisen-Schmidt condensation
72	$-NH_2$	Cr-MIL-101-NH_2	nucleophilic addition to isocyanates	urea	Friedel–Crafts alkylation
76	$-NH_2$	IRMOF-3	nucleophilic addition to isocyanates	urea	Morita–Baylis–Hillman reaction & acetalization
81	–CHO	SIM-1	imine condensation	dodecylamine (exterior)	Knoevenagel condensation

82	$-NH_2$	Al-MIL-101-NH_2 In-MIL-68-NH_2 Zr-UiO-66-NH_2	peptide coupling	mono-, di-, tri-, and tetrapeptides	asymmetric aldol reaction
83	$-CH_2NHBoc$	MTV-IRMOF-74-III-$(CH3)_{0.6}(CH_2NHBoc)_{0.4}$	sequential peptide coupling	tripeptides	transesterification and α-chlorination
84	$-NH_2$	UiO-68-NH_2	peptide coupling then imine condensation and metalation	amino acid pyridylimine(Fe)	asymmetric hydrosilylation
85	$-NO_2$ and $-SO_3H$	MIL-101-NO_2-SO_3H	NO_2 reduction	amine and sulfonic acid	tandem deacetalization–nitroaldol reaction
86	$-NO_2$	MIL-101-NO_2	NO_2 reduction then partial propanesultone ring opening	amine and sulfonic acid	tandem deacetalization–Knoevenagel reaction
87	$-NH_2$	IRMOF-3	*N*-alkylation of amine	methylammonium iodide	CO_2 fixation with epoxide
88	$-NH_2$	Cr-MIL-101-NH_2	nucleophilic substitution	triphenylalkylphosphonium bromide	CO_2 fixation with epoxide
89	−Br	MIL-101-Br	nucleophilic substitution by imidazole	imidazolium bromide	CO_2 fixation with epoxide
90	$-NH_2$	MIL-101-NH_2	Debus–Radziszewski reaction	ethanol imidazolium	CO_2 fixation with epoxide
91	$-NH_2$	DMOF-NH_2	diazoransfer then CuAAC	alkyl amine and phenyl	transesterification

Author Contributions

T.G.: Conceptualization (lead); writing – original draft (lead); writing – review and editing (equal). P.M.: Writing – review and editing (equal).

Conflicts of interest

There are no conflicts to declare.

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