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ARTICLE TYPE

Proline-Functionalized Metal-Organic Frameworks and their Use in Asymmetric Catalysis: Pitfalls in the MOFs Rush

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Post-functionalisation of Metal-Organic Frameworks is a very efficient and elegant method for designing tailor-made chiral solids for selective asymmetric catalysis. However, erroneous data and misinterpretation can be easily done. We report some best of practices in amino acid grafting and use.

RSC Advances recently published a puzzling research article by Liu *et al*. entitled "Catalysis by metal–organic frameworks: proline and gold functionalized MOFs for the aldol and three-component coupling reactions".[1] Several key points of this article caught our attention. The authors claim to have successfully performed a post-synthetic peptide coupling (Fig. 1) and to have obtained with their post-modified MOF one of the highest activity and selectivity reported for a heterogeneous catalyst in the asymmetric aldol reaction. The reported method for post-synthetic modification as well as the catalysis data are not supported by adequate scientific evidences and are in contradiction with those previously by our group [2, 3] and others.[4-10]

First, the synthetic procedure described by Lilli *et al.* consists in simply mixing the IRMOF-3 and proline in ethanol overnight, followed by the evaporation of the solvent to obtained their IRMOF-3-Pr(PM).

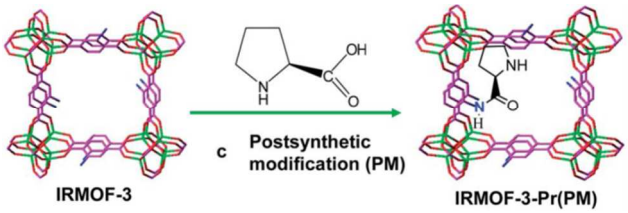

Fig. 1. Synthesis of IRMOF-3–Pr(PM). Reprinted with permission from ref. 1

The authors claimed that this IRMOF-3-Pr(PM) is a post-modified IRMOF-3 containing prolinamide-functionalized terephthalate linkers (Fig. 1). However, one can easily understand that without purification this material obviously contain components from the reaction mixture such as, at least, remaining free proline in the pores, which can be responsible for catalytic activity discussed later. It can also possibly contain degradation products from the MOF in ethanol. Beyond the apparent simplicity of this coupling methodology, we have to point out that, to the best of our knowledge, the amide formation between the amino groups at the MOF walls and an amino acid will never occur under these conditions. Indeed, we extensively studied the solid-phase peptide coupling applied in MOFs and we published in 2011 the first report on amino-acid functionalized Metal-Organic Frameworks through covalent post-synthetic modification.[2] In this study, we demonstrate that, as described and comprehensively studied by B. Merrifield on resins,[11-13] the solid-phase peptide synthesis in MOFs requires the activation of the carboxylic acid functions of the amino acid using a so-called coupling agent.[14-17] This is even more crucial taking into account that the amino groups on the MOF are much less nucleophilic than their homogenous counterpart due to the coordination of 2-aminoterephthalate to metal nodes. This low reactivity was also highlighted by S. Cohen in his early work on post-synthetic modification (PSM) when he used acyl chloride or acid anhydride to react with amino group in amino-MOFs such as IRMOF-3 and MIL-53.[5, 18]

Beyond strong doubts on the actual synthesis achievement, key characterization data are missing while reported data do not support the achievement of this IRMOF-3-Pr(PM). In all reference reports on covalent PSM,[19-22] liquid ^{1}H NMR of the digested MOF is used in order to assess the functionalization of the organic ligand and also to determine the ratio of modified linkers. Moreover N_2 adsorption isotherms (or at least surface area measurements) are always carried out for measuring the porosity remaining after the PSM process. These two key characterizations, ^{1}H NMR and N_2 adsorption data, are missing in the article by Liu *et al*. As a result, the grafting yield cannot be determined and thus cannot be used to define the catalyst loading in the catalytic application described later. Without porous characterization, we can assume that the proline obstructs the pore of the IRMOF-3-Pr(PM).

Other data are also inconsistent about the characterization of IRMOF-3-Pr(PM). The powder X-ray diffraction pattern shows a major loss of crystallinity with disappearance and broadening of the main peaks corresponding to the IRMOF-3 structure whereas the authors only note a slight change.

The authors also present puzzling infrared spectra of these materials. When they argue for the disappearance of bands at 3473 and 3356 cm^{-1} attributed to N-H stretching band of primary amine, one can see on the published figure only large broadening of the signal due to O-H stretching band of water with two shoulder remaining at 3473 and 3356 cm^{-1} (Figure 2). Moreover, one would expect the appearance of only one band at 3100-3500 cm^{-1} corresponding to the (CO)N-H stretching band of the

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secondary amide, stronger than those of amine, which cannot be observed here. Analyzing carefully the data given by Liu *et al.*, no conclusions can be made about a hypothetical organic transformation of the linkers between the pristine IRMOF-3 and the IRMOF-3-Pr(PM) according to infrared study.

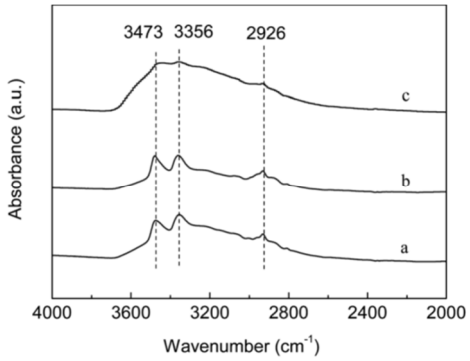

Fig. 2. Infrared spectra of IRMOF-3 (a) and IRMOF-3-Pr(PM) (c) samples. Reprinted with permission from ref. 1

As last spectroscopic evidence, the authors used ^{13}C solid state NMR to characterize their IRMOF-3-Pr(PM). Again, interpretation of data is here hazardous. Indeed, proline-functionalized MIL-68 MOF was studied using solid state NMR.[3] SinceMIL-68-NH_2 and the IRMOF-3 are both made from 2-aminoterephthalate linker, their proline-functionalized analogues present the same NMR spectra of their organic components. We agree with the reported attribution of ^{13}C NMR peaks in the aromatic region corresponding to the terephthalate linker (115-150 ppm). However, we showed that the C=O signal of the amide bond in proline-functionalized MOF has a shift similar to those of carboxylate at 170-175 ppm, supported by 2D correlation experiments.[3] We think that Liu *et al.* wrongly attributed the very intense peak at around 180 ppm to the C=O of the amide, when it should be attributed to the COOH of free proline encapsulated inside the MOF. Indeed, Berendt *et al.* reported that, depending on packing, the carboxylic group of crystallized proline can present a shift in ^{13}C solid state NMR spectrum which varies from 175 to 178 ppm.[23]

From the reported data and experience in the domain, we think that most of the proline is encapsulated in the MOF cavity in IRMOF-3-Pr(PM). No data support unambiguously that proline is grafted covalently through amide bond as claimed by the authors.

Finaly, the very high enantiomeric excess (e.e) reported are very questionable. The HPLC traces used to determine the e.e. are very ambiguous (Fig. 3). Indeed, it is difficult to extrapolate enantiomers ratio without a clear separation of their corresponding peaks in the chromatogram. In addition, it is very intriguing that the same aldol compounds, namely the 4-hydroxy-4-phenylbutan-2-one, analyzed under the same conditions (column, temperature, eluent and flow rate) show a so big difference in retention time, reaching one minute for enantiomer 2 (10.45 min in case A and 9.416 min. in case B), when the benzaldehyde has the same retention time from one analysis to another (7.86 min.). These data cannot support the conclusion of superior selectivity of the IRMOF-3-Pr(PM) which is highly overestimated. Prolinamides, which can be considered as homogeneous counterparts of proline-functionalized MOFs such as IRMOF-3-Pr(PM), are reported to catalyze the asymmetric aldol reaction with relatively modest e.e. values of 55-60%.[8, 10] Moreover, the selectivity of 33% e.e. obtained at 40°C with IRMOF-3-Pr(PM) is similar to that reported by S. Telfer using the self-assembled IRMOF-Pro (29% e.e.).[4]

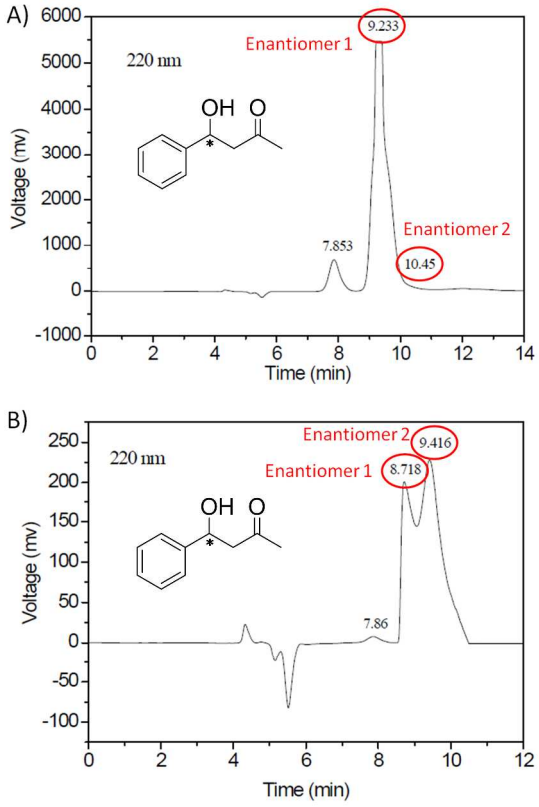

Fig. 3. HPLC trace of IRMOF-3-Pr(PM)-catalyzed aldol reaction products (A) when catalysis is performed at room temperature showing 93% e.e. and (B) when catalysis is performed at 40°C showing 33% e.e. Both chromatograms are recorded for the same aldol compounds under the same analytical conditions. Reprinted with permission from ref. 1

Conclusions

The post-synthetic anchoring of functionalities inside MOFs, especially using amino acids and derivatives for high value added applications, is a very subtle chemistry that requires skills in material science as well as in organic synthesis. The characterizations of such sophisticated hybrid solids must at least combine routine analyses of both organics and materials such as liquid phase ^1H NMR (or, in the best case, high resolution solid-state NMR) for the ratio of functional organic linkers and also structural and porosity analysis. Concerning applications such as catalysis, appropriate analytical techniques and testing conditions shall also be used. We believe that these recommendations will help the authors and reviewers to avoid the pitfalls of a MOF chemistry which is increasingly sophisticated.

Notes and references

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