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Amino Acid Functionalized Metal-Organic Framework by Soft Coupling-Deprotection Sequence

Jerome Canivet,* Sonia Aguado, Gerard Bergeret and David Farrusseng

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Covalent post-synthetic modification of a MOF, (In) MIL-68-NH₂, is carried out in a novel fashion to immobilize amino acids within the structure. Solid-phase peptide coupling methodology opens new perspectives for anchoring chiral bio- and catalytically active species. This could facilitate the immobilization of highly active and/or coordinating moieties inside MOF cavities.

Metal-organic frameworks (MOFs) are a class of microporous inorganic-organic hybrid materials whose structural features and porous nature make them good candidates for heterogeneous catalysis.¹ Recently, new breakthroughs have been made toward the development of biocompatible MOFs for biomedical applications² such as drug delivery³ or imaging.⁴ Chiral metal-organic frameworks are of great interest for enantioselective catalysis,⁵ molecular recognition⁶ or nonlinear optical devices.⁷ This sophisticated subclass of materials presents enzyme-like biological architectures by incorporating a nucleotide base, such as adeninate (BioMOF),⁸ intrinsically chiral amino acids, such as L-valine⁹ or serine derivatives,^{5e} or peptide (metal-peptide frameworks)¹⁰ as linkers.

Covalent post-modification, which has been comprehensively reviewed by Cohen and coworkers,¹¹ is a powerful tool for obtaining highly sophisticated functionalized structures from amino-containing frameworks by condensation with an aldehyde to generate an imine,¹² by coupling with an anhydride to give an amide¹³ or through click chemistry to form a triazolyl group.¹⁴ Very recently, Telfer reported the thermal post-synthetic deprotection of a proline-functionalized MOF.¹⁵ In his study, the functionalized linker was first synthesized via several organic steps in order to graft the protected proline, the framework was then obtained by self-assembly and finally the protecting group was removed by heating the MOF at 165°C in a solvent.

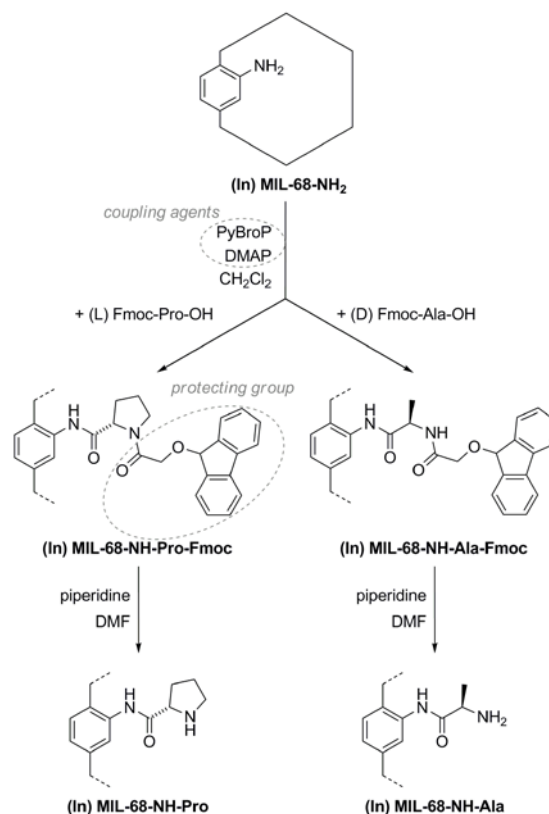
We report here, for the first time, the application of solid-phase peptide coupling strategy to an amino-functionalized MOF in order to immobilize amino acids within the framework under mild conditions.

Solid-phase peptide synthesis,¹⁶ is currently the most common of the methods used by synthetic chemists to prepare sequenced oligopeptides. The principle is as follows: the free N-terminal amine of an amino acid, immobilized on a small solid (polymer resin), is coupled to another N-protected amino acid unit in order to provide the corresponding N-protected amide. This unit is then deprotected, revealing a new N-terminal amine. Moreover, the peptide coupling often requires the activation of the carboxylic acid moiety using an activator or a coupling agent.

In order to apply the peptide coupling methodology to MOF structures, several constraints must be taken into account. It requires (i) the use of solvent-soluble coupling agent in order to be able to purify the functionalized solid MOF by simple washings and (ii) the use of amino acid protecting group which can be removed under conditions compatible with the thermal and pH sensitivity of the MOF framework.

Among the coupling agents, the N,N'-dicyclohexylcarbodiimide (DCC) is frequently used in homogeneous organic synthesis, but it leads to the formation of N,N'-dicyclohexylurea (DCU), which is an insoluble solid. This is a serious drawback in our case, since it is impossible to separate the DCU from the parent MOF. As an alternative, we chose the bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBroP), a very efficient homogeneous coupling agent,¹⁷ combined with 4-(dimethylamino)pyridine (DMAP) as base additive.

This system, based on the combination PyBroP-DMAP, is applied to (In) MIL-68-NH₂,¹⁸ also called IHM-2 (Scheme 1).



Scheme. 1 Two-step MOF functionalization through peptide coupling.

This MOF is isostructural to MIL-68^{14c, 19} and has a one-dimensional rod-shaped structure, formed by indium octahedra and 2-aminoterephthalates (BDC-NH₂) as bridging linkers. It is composed by hexahedral and triangular 1D-channels with an aperture of 16 and 6 Å respectively. MIL-68-NH₂ sample comes in microcrystalline powder form with crystallites sizes of about 200nm. Considering the acid and thermal sensitivity of MOFs in general and of (In) MIL-68-NH₂ in particular, the Boc protecting group (Boc = *tert*-butyloxycarbonyl) was not applicable because its removal takes place into acidic media or at high temperature. Consequently, we based our coupling strategy on the fluorenylmethyloxycarbonyl group (Fmoc), a base-label protecting group for amines which can be removed under mild conditions. Under standard peptide coupling conditions (Supporting Information), Fmoc-protected enantiopure amino acids, such as L-proline (Pro-OH) and D-alanine (Ala-OH), react successfully with (In) MIL-68-NH₂ to give the two amino acid-functionalized MOFs designated (In) MIL-68-NH-Pro-Fmoc and (In) MIL-68-NH-Ala-Fmoc, respectively (Scheme 1).

The post-modification yields are measured from ¹H NMR spectra after sample digestion in DCI/D₂O/dmsO-d₆. The couplings proceed with 10% yield for the proline and alanine derivatives (Figure 1 and Supporting Information). The presence in the NMR spectra of new typical aromatic signals at 7.7, 8.0 and 9.1 ppm indicates the efficient functionalization of the BDC aromatic ring, in line with the data already reported by Cohen in the case of amidations.^{13a, 20} The integrations of these aromatic signals fit with those of the Fmoc-protected amino acid moiety and allow the determination of the functionalization yield by comparison with those of the unmodified BDC-NH₂. The low yields likely arise from the large sizes of the PyBroP and Fmoc groups with respect to the micropore network, only one protected amino acid may be contained into the 2D hexagonal window. A non-negligible amount of DMAP also remains blocked within the framework even after several washing/soaking procedures, as indicated by the signals at 3.2, 6.9 and 8.2 ppm.

Without further purification, the DMAP-filled samples are then directly involved in the chemically-assisted deprotection step using piperidine in dimethylformamide (DMF), as typically described for peptide synthesis.²¹ The deprotection, *i.e.*, the removal of the Fmoc, and the DMAP displacement proceed simultaneously (Figure 1 and Supporting Information). The NMR spectra clearly show the disappearance of the Fmoc signals in the aromatic part and at ~4.2 ppm combined with the loss of those of the DMAP. The amino acid-functionalized (In) MIL-68-NH-Pro and (In) MIL-68-NH-Ala are thus quantitatively obtained from their protected precursors, the residual piperidine being removed by washing/soaking the materials in water. It is worth noting that the deprotection step is solvent-dependent, the Fmoc being quantitatively removed in DMF but left intact in dichloromethane. Although the yields are relatively low, the functionalization cannot be limited only to the external surface of the crystallites. Considering that all the grafted moieties are pointed toward the hexagonal aperture of the framework, the functionalization ratio is statistically two amino acid units for three successive hexagonal windows. The efficiency of the coupling-deprotection procedure is also confirmed by mass spectroscopy of the dissolved samples under acidic conditions.

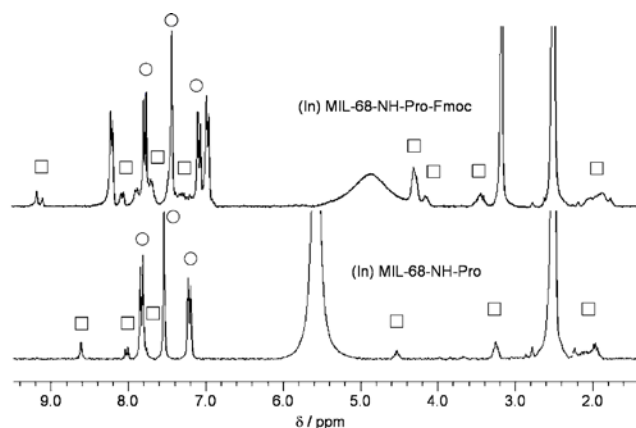


Fig. 1 ¹H NMR spectra of digested proline-functionalized (In) MIL-68 sample (ca. 10% modified). Unmodified BDC-NH₂ and functionalized linker are indicated by circles and squares respectively.

According to the N₂ adsorption isotherms, the post-modification is accompanied by a decrease of the BET surface, from 1260 m².g⁻¹ for (In) MIL-68-NH₂ to 768 m².g⁻¹ for (In) MIL-68-NH-Pro and 825 m².g⁻¹ for (In) MIL-68-NH-Ala.

Furthermore, PXRD analyses show that the structural integrity of the materials remains for the both two functionalized MOFs throughout the coupling and deprotection steps (Figure 2 and Supporting Information). According to the appearance of new peaks in the PRXD patterns of the functionalized materials, new unit cell parameters were calculated. It showed that the amino acids grafting did occur into the MIL-68-NH₂ cavity on defined sites, no new phase was created, and that the original MIL-68 framework was kept intact (Supporting Information).

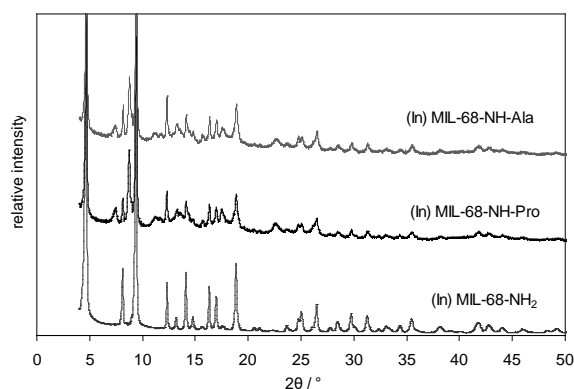


Fig. 2 PXRD patterns of (In) MIL-68-NH₂ (bottom), (In) MIL-68-NH-Pro (middle) and (In) MIL-68-NH-Ala (top).

Thermogravimetric analysis performed for (In) MIL-68-NH-Pro shows its thermal stability up to 120-150°C. As expected, the optical rotation angles measured using the digested samples show that no racemization of the grafted chiral amino acids occurs during the coupling and deprotection steps in each case.

In summary, we have developed a novel procedure for the post-synthetic functionalization of a metal-organic framework. The soft reaction conditions shall allow its application to a wide range of amino-functionalized MOFs. In addition, the repetition of coupling and deprotection cycles will enable the generation of sequenced oligopeptide-functionalized frameworks. This study is another example of MOF post-functionalization using the

protection-deprotection technique, which is among the most suitable for engineering MOFs with highly reactive centers.^{14a, 22}

Peptide coupling methodology applied to MOFs offers new perspectives for anchoring chiral functional groups into/onto the framework in order to obtain confined, highly catalytically active and/or metal-coordinating moieties.^{15, 23} This opens a new route to the synthesis of single-site chiral catalysts inside MOF cavities.

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Notes and references

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† Electronic Supplementary Information (ESI) available: synthesis and characterisations: NMR, XRD, gas sorption, mass spectra.

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Graphical Abstract

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