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

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

Covalent post-synthetic modification of a MOF, (In) MIL-68-NH<sub>2</sub>, is carried out in a novel fashion to immobilize amino acids within the structure. Solid-phase peptide coupling methodology <sup>10</sup> 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 <sup>15</sup> inorganic-organic hybrid materials whose structural features and porous nature make them good candidates for heterogeneous catalysis.<sup>1</sup> Recently, new breakthroughs have been made toward the development of biocompatible MOFs for biomedical applications<sup>2</sup> such as drug delivery<sup>3</sup> or <sup>20</sup> imaging.<sup>4</sup> Chiral metal-organic frameworks are of great

- interest for enantioselective catalysis,<sup>5</sup> molecular recognition<sup>6</sup> or nonlinear optical devices.<sup>7</sup> This sophisticated subclass of materials presents enzyme-like biological architectures by incorporating a nucleotide base, such as adeninate <sup>25</sup> (BioMOF),<sup>8</sup> intrinsically chiral amino acids, such as L-valine<sup>9</sup>
- or serine derivatives,<sup>5e</sup> or peptide (metal-peptide frameworks)<sup>10</sup> as linkers.

Covalent post-modification, which has been comprehensively reviewed by Cohen and coworkers,<sup>11</sup> is a powerful tool for <sup>30</sup> obtaining highly sophisticated functionalized structures from amino-containing frameworks by condensation with an aldehyde to generate an imine,<sup>12</sup> by coupling with an anhydride to give an amide<sup>13</sup> or through click chemistry to form a triazolyl group.<sup>14</sup> Very recently, Telfer reported the thermal post-synthetic

- <sup>35</sup> deprotection of a proline-functionalized MOF.<sup>15</sup> 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.
- <sup>40</sup> We report here, for the first time, the application of solidphase peptide coupling strategy to an amino-functionalized MOF in order to immobilize amino acids within the framework under mild conditions.
- Solid-phase peptide synthesis,<sup>16</sup> is currently the most 45 common of the methods used by synthetic chemists to prepare sequenced oligopeptides. The principle is as follows: the free Nterminal 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.
- <sup>50</sup> 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 <sup>55</sup> 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 N.N'agents, the 60 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 65 separate the DCU from the parent MOF. As an alternative, we chose the bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBroP), a very efficient homogeneous coupling agent,<sup>17</sup> combined with 4-(dimethylamino)pyridine (DMAP) as base additive.
- <sup>0</sup> This system, based on the combination PyBroP-DMAP, is applied to (In) MIL-68-NH<sub>2</sub>,<sup>18</sup> also called IHM-2 (Scheme 1).



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

This MOF is isostructural to MIL-68 <sup>14c, 19</sup> and has a onedimensional rod-shaped structure, formed by indium octahedra and 2-aminoterephthalates (BDC-NH<sub>2</sub>) as bridging linkers. It is composed by hexahedral and triangular 1D-channels with an s aperture of 16 and 6 Å respectively. MIL-68-NH<sub>2</sub> 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-NH<sub>2</sub> in particular, the Boc protecting group (Boc = *tert*-butyloxycarbonyl) was not applicable because
- <sup>10</sup> 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
- <sup>15</sup> (Supporting Information), Fmoc-protected enantiopure amino acids, such as L-proline (Pro-OH) and D-alanine (Ala-OH), react successfully with (In) MIL-68-NH<sub>2</sub> to give the two amino acidfunctionalized MOFs designated (In) MIL-68-NH-Pro-Fmoc and (In) MIL-68-NH-Ala-Fmoc, respectively (Scheme 1).
- <sup>20</sup> The post-modification yields are measured from <sup>1</sup>H NMR spectra after sample digestion in DCl/D<sub>2</sub>O/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
- <sup>25</sup> 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.<sup>13a, 20</sup> 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
- <sup>30</sup> comparison with those of the unmodified BDC-NH<sub>2</sub>. 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 <sup>35</sup> 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

- <sup>40</sup> described for peptide synthesis.<sup>21</sup> 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
- <sup>45</sup> 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
- <sup>50</sup> 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
- 55 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 <sup>1</sup>H NMR spectra of digested proline-functionalized (In) MIL-68 sample (ca. 10% modified). Unmodified BDC-NH<sub>2</sub> and functionalized linker are indicated by circles and squares respectively.

According to the N<sub>2</sub> adsorption isotherms, the postmodification is accompanied by a decrease of the BET surface, <sup>65</sup> from 1260 m<sup>2</sup>.g<sup>-1</sup> for (In) MIL-68-NH<sub>2</sub> to 768 m<sup>2</sup>.g<sup>-1</sup> for (In) MIL-68-NH-Pro and 825 m<sup>2</sup>.g<sup>-1</sup> 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 70 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-NH<sub>2</sub> cavity on defined sites, no new phase was created, and that the original 75 MIL-68 framework was kept intact (Supporting Information).



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

Thermogravimetric analysis performed for (In) MIL-68-NH-<sup>80</sup> 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 so 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 so another example of MOF post-functionalization using the protection-deprotection technique, which is among the most suitable for engineering MOFs with highly reactive centers.<sup>14a, 22</sup>

Peptide coupling methodology applied to MOFs offers new perspectives for anchoring chiral functional groups into/onto the

5 framework in order to obtain confined, highly catalytically active and/or metal-coordinating moieties.<sup>15, 23</sup> 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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#### **Graphical Abstract**

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	NH2 NH2 NH2	PEPTIDE COUPLING	AA HAA DEPROTECTI	W NAA NAA
10	MOF	AA = amino acid	protecting group	MOF -