

Enantiopure Peptide-Functionalized Metal-Organic Frameworks

Jonathan Bonnefoy, Alexandre Legrand, Elsje Alessandra Quadrelli, Jérôme Canivet and David Farrusseng*

Supporting Information

| | |
|--|-----|
| 1. General remarks | S1 |
| 2. Peptide coupling | S1 |
| 2.1 Conventional heating | S1 |
| 2.2 Microwave irradiations | S3 |
| 3. Deprotection – Boc removal..... | S5 |
| 3.1 Proline (MOF-NH-Pro) | S6 |
| 3.2 Glycine-Proline (MOF-NH-Gly-Pro)..... | S8 |
| 4. Coupling-Deprotection sequence applied to other peptides..... | S11 |
| 5. HPLC analysis of (D)- and (L)-Al-MIL-101-Gly-Pro..... | S14 |
| 6. Solid-state characterizations | S15 |
| 6.1 X-ray diffraction (PXRD)..... | S15 |
| 6.2 N ₂ sorption analysis | S17 |
| 7. Aldol reaction | S21 |
| 8. References | S24 |

1. General remarks

All reactions are carried out in anhydrous solvents. The Al-MIL-101-NH₂,^[1] In-MIL-68-NH₂^[2] and Zr-Uio-66-NH₂^[3] are synthesized and activated according to previously reported procedures. (L)-Boc-Pro-OH and (D)-Boc-Pro-Gly-OH are purchased from Sigma-Aldrich. (L)-Boc-Pro-Gly-OH, (L)-Boc-Ala-Gly-Sar-OH, (L)-Boc-Ala-Gly-Gly-Gly-OH and (L)-Boc-Gly-Gly-Phe-Gly-OH are purchased from Bachem AG. Without indication, the enantiomer used is in the L form. All others reactants are commercially available (Sigma-Aldrich) and are used without further purification.

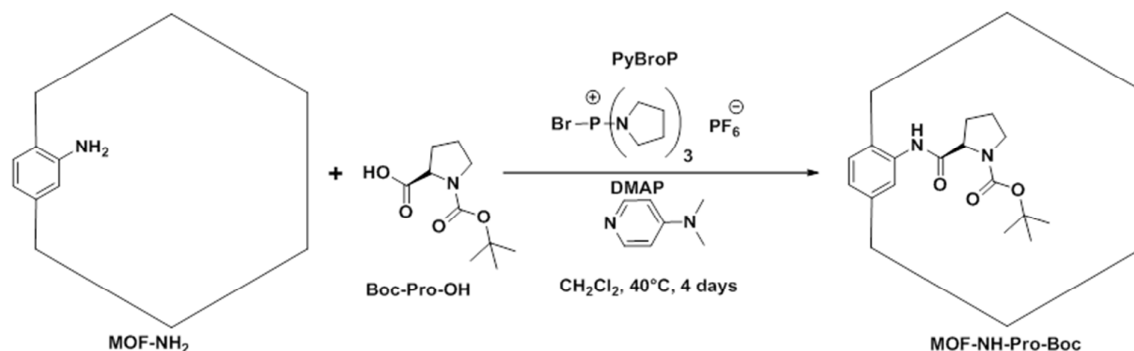
Liquid-state NMR spectra are recorded on a Bruker 250MHz spectrometer. Chemical shifts are reported in parts per million (ppm) referenced to the appropriate solvent peak. Prior to NMR analysis, MOF samples are dissolved in a HF-H₂O/dmsO d6 solution (MIL-101 and UiO), a DCl-D₂O/dmsO d6 solution (MIL-68) or NaOD-D₂O solution (di- to tetrapeptides in MIL-101).

N₂ isotherms at 77K are performed using a BELSORP-mini apparatus (BEL Japan).

2. Peptide coupling

2.1 Conventional heating

2.1.1 Proline (Boc-L-Pro-OH)



In a 7 mL glass vial, 0.60 mmol of PyBroP (300 mg), 1.2 mmol of DMAP (156 mg) and 0.60 mmol of the Boc-L-Pro-OH (130 mg) are dissolved in 6 mL of anhydrous dichloromethane. The solution is stirred at 25°C for one hour. After a desorption of one hour under vacuum at 100°C, the desired amount of MOF-NH₂ (ca. 0.3 mmol -NH₂) is added and the suspension is allowed to react under vigorous stirring for four days at 40°C. The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give the desired product as a fine yellow powder after drying under vacuum at room temperature. The solid is finally characterized by powder X-ray diffraction, ¹H NMR and N₂ sorption analysis.

According to ¹H NMR analysis, no unreacted amino acid remains inside the MOF. NMR spectra show DMAP signals at around 8.20, 6.96 and 3.18 ppm which remain even after several washings.

Following this procedure, the samples Al-MIL-101-NH-Pro-Boc and In-MIL-68-NH-Pro-Boc contain 10% of their linkers grafted with proline. The coupling does not seem to occur in UiO-66 framework.

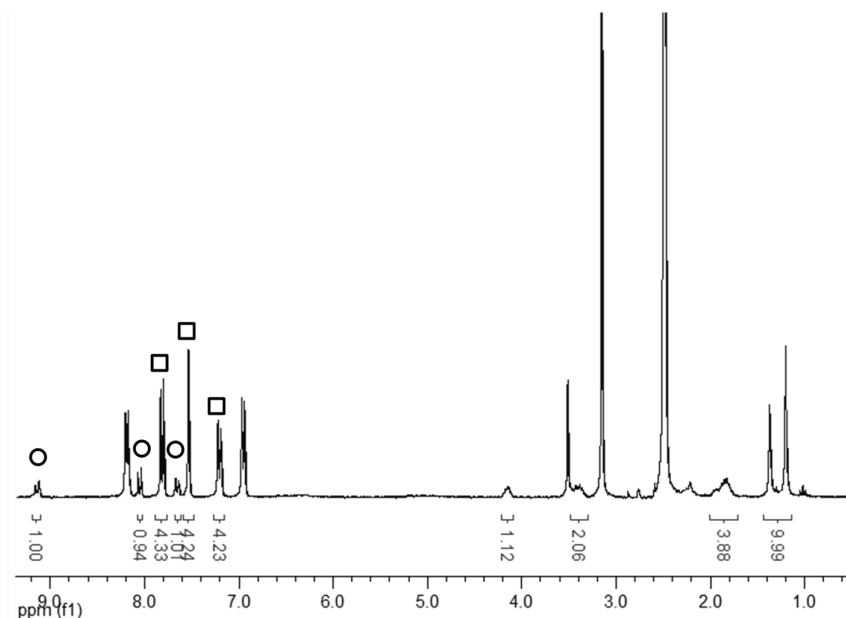
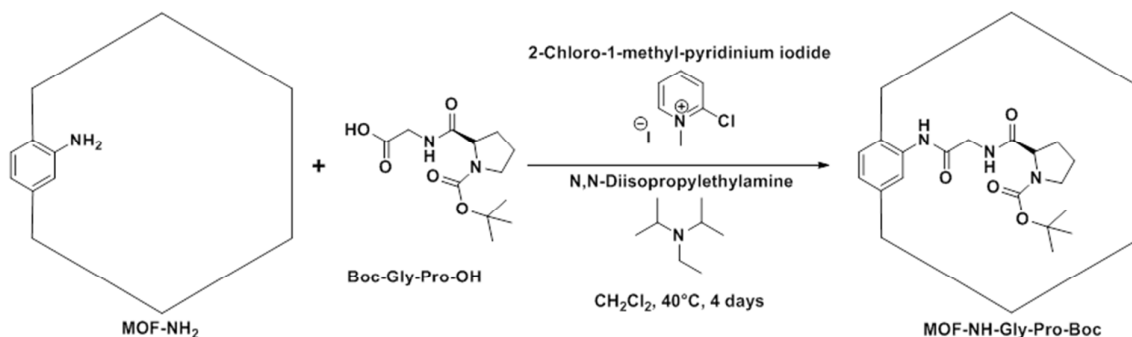


Fig. S1. Representative ^1H NMR spectrum of In-MIL-68-NH-Pro-Boc dissolved in $\text{DCl-D}_2\text{O/dmsO d}_6$ solution (ca. 10% modified). Unmodified BDC-NH₂ and functionalized linker are indicated by circles and squares, respectively.

2.1.2 Glycine-Proline (Boc-D-Pro-Gly-OH)



In a 7 mL glass vial, 0.60 mmol of 2-Chloro-1-methyl-pyridinium iodide (164 mg), 0.6 mmol of EtN^iPr_2 (112 μL) and 0.60 mmol of Boc-D-Pro-Gly-OH (164 mg) are dissolved in 6 mL of anhydrous dichloromethane. The solution is stirred at 25°C for one hour. After a desorption of one hour under vacuum at 100°C, the desired amount of MOF-NH₂ (ca. 0.3 mmol -NH₂) is added and the suspension is allowed to react under vigorous stirring for seven days at 40°C. The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give the desired product as a fine yellow powder after drying under vacuum. The solid is finally characterized by powder X-ray diffraction, ^1H NMR and N_2 sorption analysis.

NMR spectra show traces 2-Chloro-1-methyl-pyridinium iodide signals at around 9.05, 8.50 and 4.39 ppm which remain even after washings.

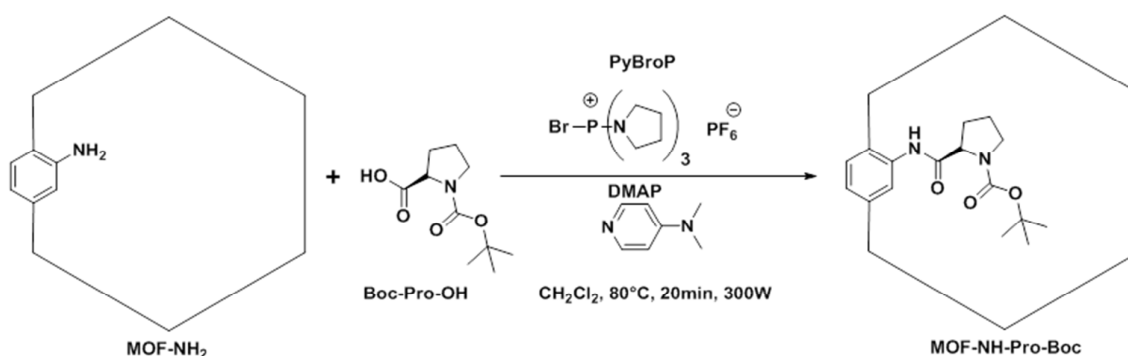
Following this procedure, around 50 % of the amino groups are converted into the corresponding amide in Al-MIL-101-NH-Gly-Pro-Boc and 10% in In-MIL-68-NH-Gly-Pro-Boc. The coupling does not seem to occur in UiO-66 framework.

2.2 Microwave irradiations

Table S1. Coupling conditions screening under microwave irradiation at 80°C for 20 minutes.

| Target MOF | Solvent | Coupling agent | Base | Grafting yield [%] |
|------------------------------|-----------------------|-----------------|------|--------------------|
| Al-MIL-101-NH-Gly-Pro | <i>n</i> -hexane | Mukaiyama agent | DIEA | 20 |
| | dichloromethane | Mukaiyama agent | DIEA | 60 |
| | ethyl acetate | Mukaiyama agent | DIEA | 35 |
| | acetonitrile | Mukaiyama agent | DIEA | 40 |
| | N,N-dimethylformamide | Mukaiyama agent | DIEA | 30 |
| | N,N-dimethylsulfoxide | Mukaiyama agent | DIEA | 5 |
| | dichloromethane | PyBrOP | DMAP | 10 |
| | dichloromethane | PyBrOP | DIEA | 45 |
| | dichloromethane | PyClOP | DMAP | 15 |
| | dichloromethane | PyClOP | DIEA | 35 |
| | | | | |
| Al-MIL-101-NH-Pro | dichloromethane | Mukaiyama agent | DIEA | 15 |
| | dichloromethane | PyBrOP | DMAP | 15 |

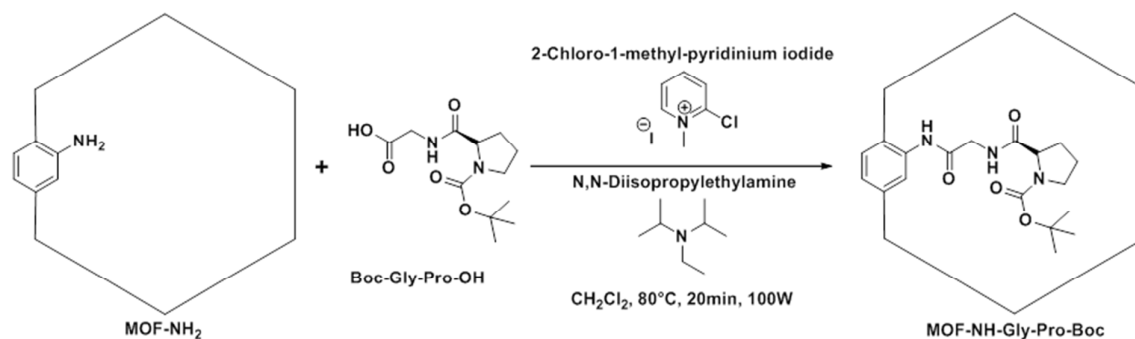
2.2.1 Proline (Boc-Pro-OH)



In a 10 mL microwave glass vial, 0.15 mmol of PyBrOP (75 mg), 0.3 mmol of DMAP (39 mg) and 0.15 mmol of the Boc-Pro-OH (32.5 mg) and the desired amount of MOF-NH₂ (ca. 0.225 mmol -NH₂) are suspended in 5 mL of anhydrous dichloromethane. The resulting suspension is allowed to react under microwave irradiations for 20 minutes at 80°C (300 watts) under air cooling. The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give the desired product as a fine yellow powder after drying under vacuum at room temperature. The solid is finally characterized by powder X-ray diffraction, ¹H NMR and N₂ sorption analysis.

Following this procedure, around 15 % of the amino groups are converted into the corresponding amide in Al-MIL-101-NH-Gly-Pro-Boc, 11% in In-MIL-68-NH-Gly-Pro-Boc and 10% in Zr-UiO-66-NH-Pro-Boc.

2.2.2 Glycine-Proline (Boc-Pro-Gly-OH)



In a 10 mL microwave glass vial, 0.50 mmol of 2-Chloro-1-methyl-pyridinium iodide (Mukaiyama agent, 124 mg), 1.2 mmol of EtNⁱPr₂ (DIEA, 112 μ L) and 0.50 mmol of the Boc-Pro-Gly-OH (123 mg) and the desired amount of MOF-NH₂ (ca. 0.225 mmol -NH₂) are suspended in 5 mL of anhydrous dichloromethane. The resulting suspension is allowed to react under microwave irradiations for 20 minutes at 80°C (300 watts) under air cooling. The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give a fine yellow powder after drying under vacuum at room temperature. The solid is finally characterized by powder X-ray diffraction, ¹H NMR and N₂ sorption analysis.

Following this procedure, around 60 % of the amino groups are converted into the corresponding amide in Al-MIL-101-NH-Gly-Pro-Boc and 5% in In-MIL-68-NH-Gly-Pro-Boc when the coupling does not seem to occur in UiO-66 framework.

3. Deprotection – Boc removal

Several attempts of Boc protecting group removal, including heating at 110-150°C under conventional heating in solvent or the use of trifluoroacetic acid, lead in every cases other than the microwave route and whatever the MOF used to a drastic loss of crystallinity and a loss of porosity.

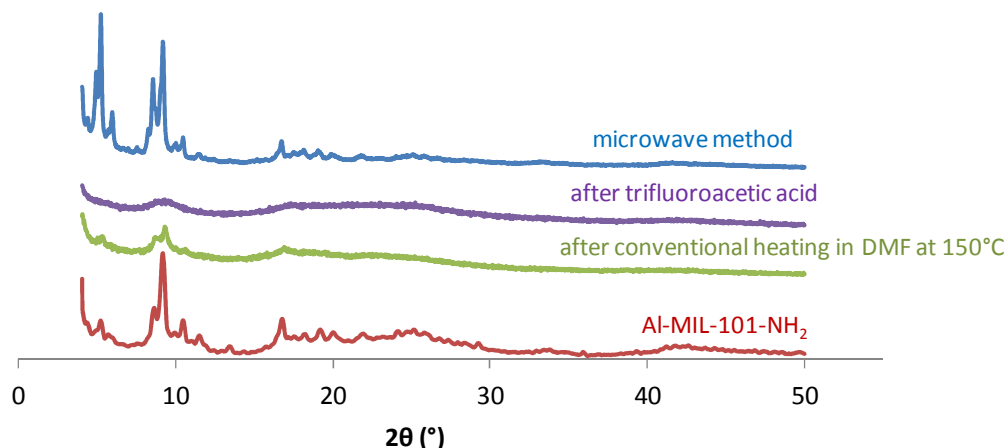


Fig. S2. From bottom to top PXRD patterns of Al-MIL-101-NH_2 , $\text{Al-MIL-101-NH-Gly-Pro-Boc}$ after deprotection at 150°C in DMF under conventional heating, $\text{Al-MIL-101-NH-Gly-Pro-Boc}$ after deprotection using trifluoroacetic acid in dichloromethane and $\text{Al-MIL-101-NH-Gly-Pro-Boc}$ after microwave-assisted deprotection.

For stability test, 10 mg of Al-MIL-101-NH_2 (0.045 mmol of ligand) are suspended in 5 mL DMF d_7 and heated at 150°C either under microwave irradiation (300W) for 10 minutes or under conventional heating (oven) for 8 hours. The leaching of ligand is determined by ^1H NMR using 0.5 mL of the supernatant. Under these conditions 1.5 mol% of ligand are released under microwave irradiations and 20 mol% under conventional heating.

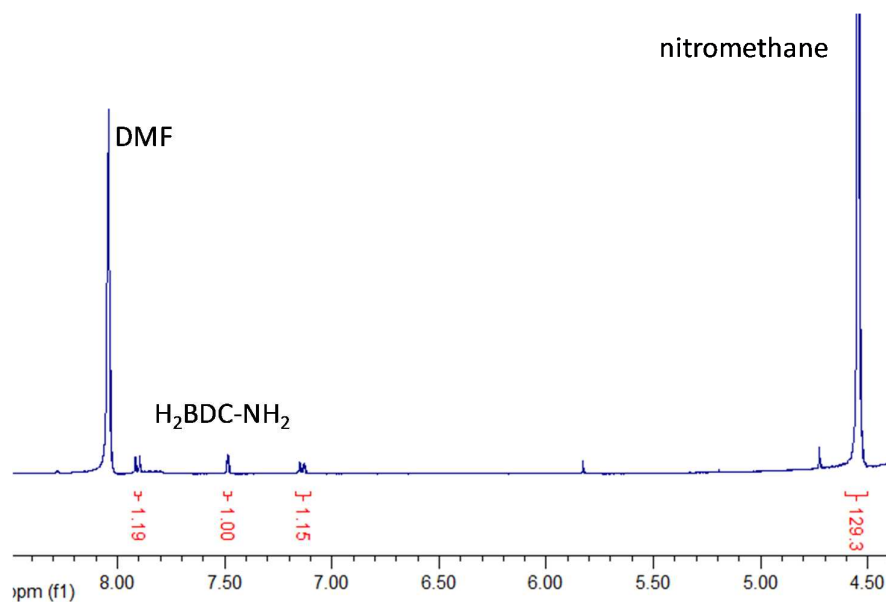


Fig. S3. ^1H NMR spectrum of supernatant after heating Al-MIL-101-NH_2 at 150°C for 8 hours in DMF d_7 under conventional heating. Nitromethane (0.046 mmol) is used as standard.

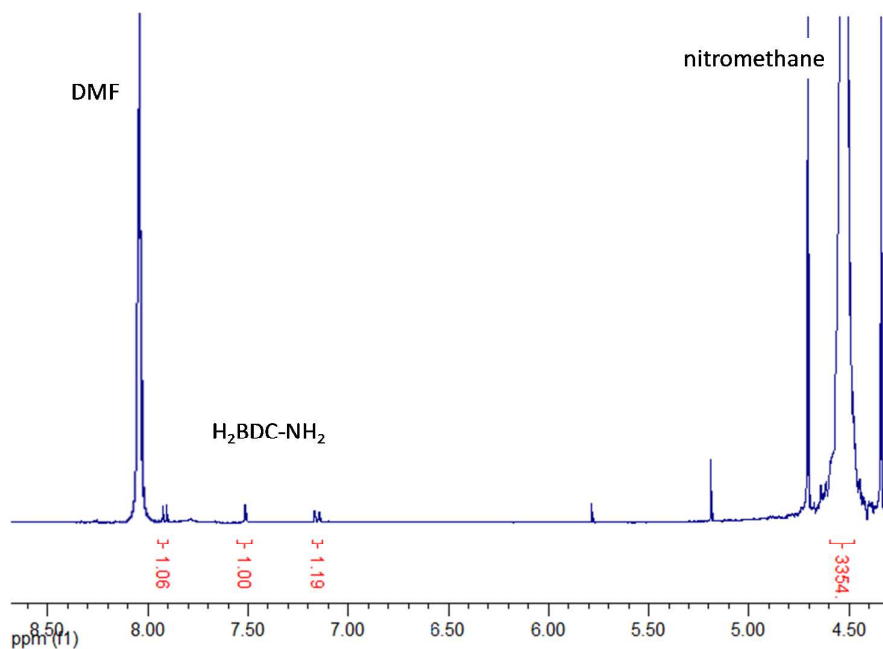
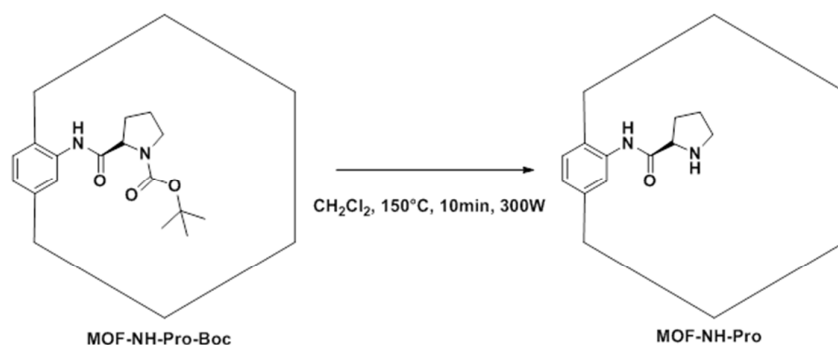


Fig. S4. ^1H NMR spectrum of supernatant after heating Al-MIL-101- NH_2 at 150°C for 10 minutes in DMF d_7 under microwave irradiations. Nitromethane (0.046 mmol) is used as standard.

The use of microwave irradiation to perform thermal deprotection is thus privileged.

3.1 Proline (MOF-NH-Pro)



In a 10 mL microwave glass vial, the desired MOF-NH-Pro-Boc is suspended in 5 mL of anhydrous dichloromethane. The resulting suspension is allowed to react under microwave irradiation for 10 minutes at 150°C (300 watts). The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give the desired product as a fine yellow powder after drying under vacuum at room temperature.

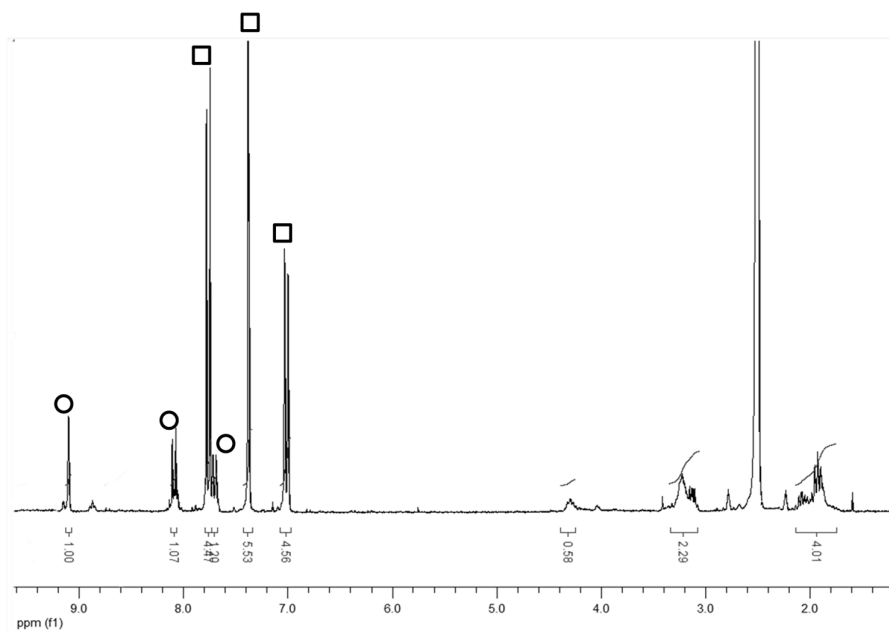


Fig. S5. ^1H NMR spectrum of Al-MIL-101-NH-Pro dissolved in HF-H₂O/dmsO d₆ solution (ca. 15% modified). Unmodified BDC-NH₂ and functionalized linker are indicated by squares and circles, respectively.

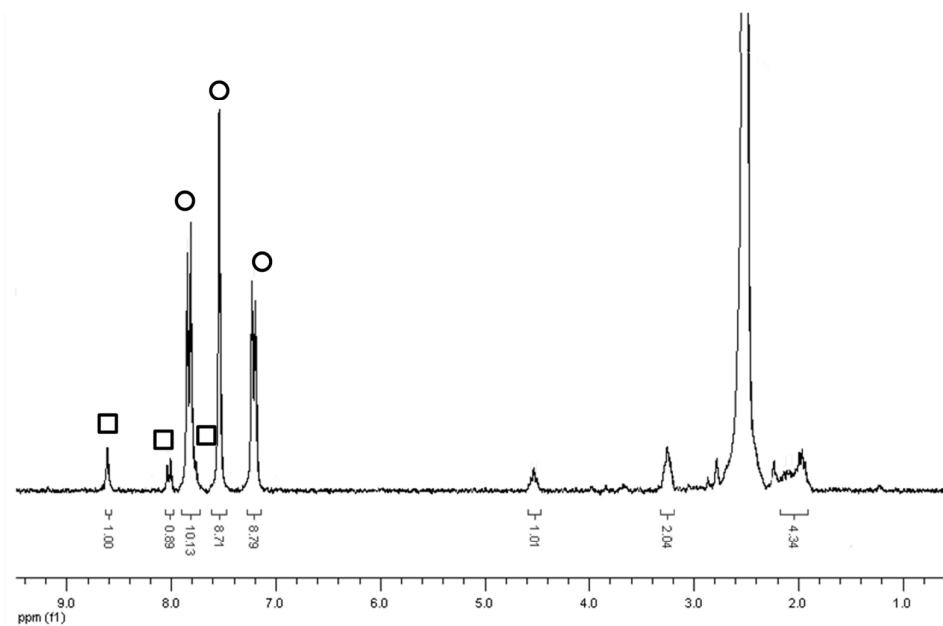
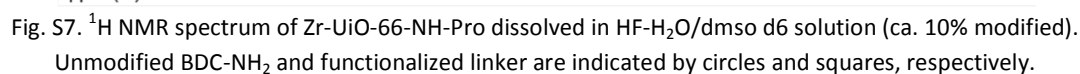


Fig. S6. ^1H NMR spectrum of In-MIL-68-NH-Pro dissolved in DCl-D₂O/dmsO d₆ solution (ca. 11% modified). Unmodified BDC-NH₂ and functionalized linker are indicated by circles and squares, respectively.



MOF-NH-Glv-Pro-Boc

CH₂Cl₂, 150°C, 10min, 300W

MOF-NH-Glv-Pro

S8

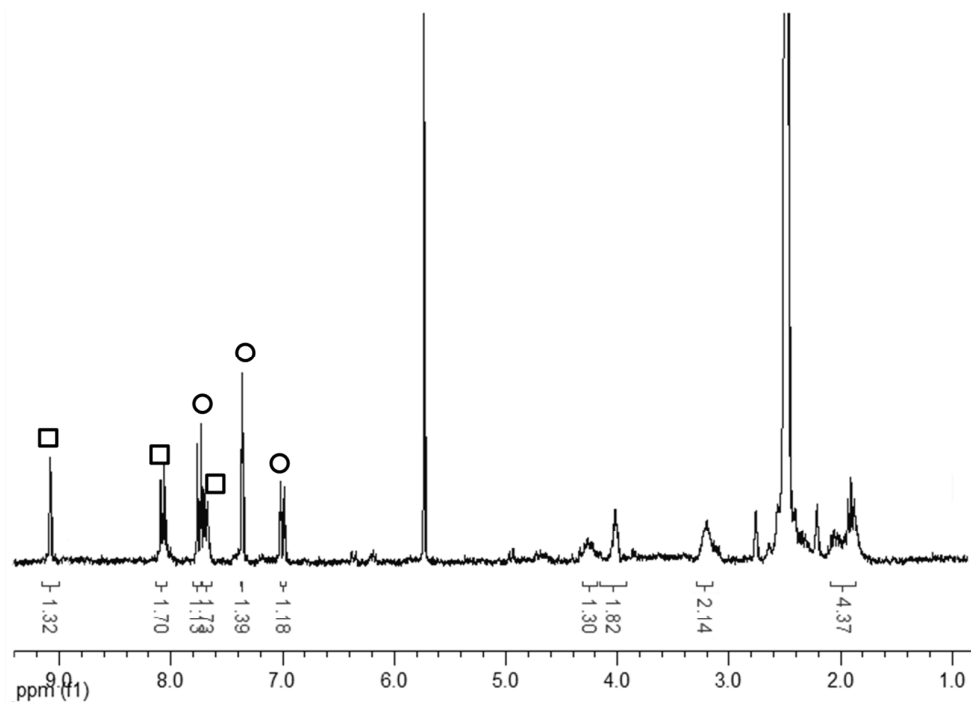


Fig. S8. ^1H NMR spectrum of Al-MIL-101-NH-Gly-Pro dissolved in HF- H_2O /dmso d6 solution (ca. 60% modified). Unmodified BDC- NH_2 and functionalized linker are indicated by circles and squares, respectively.

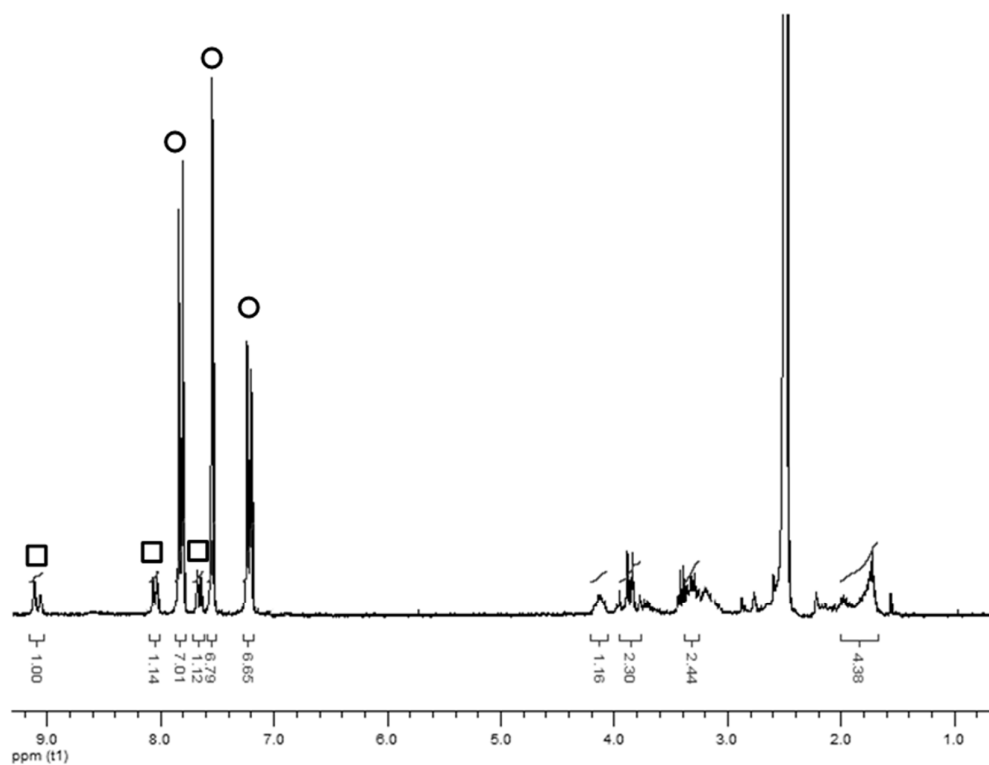
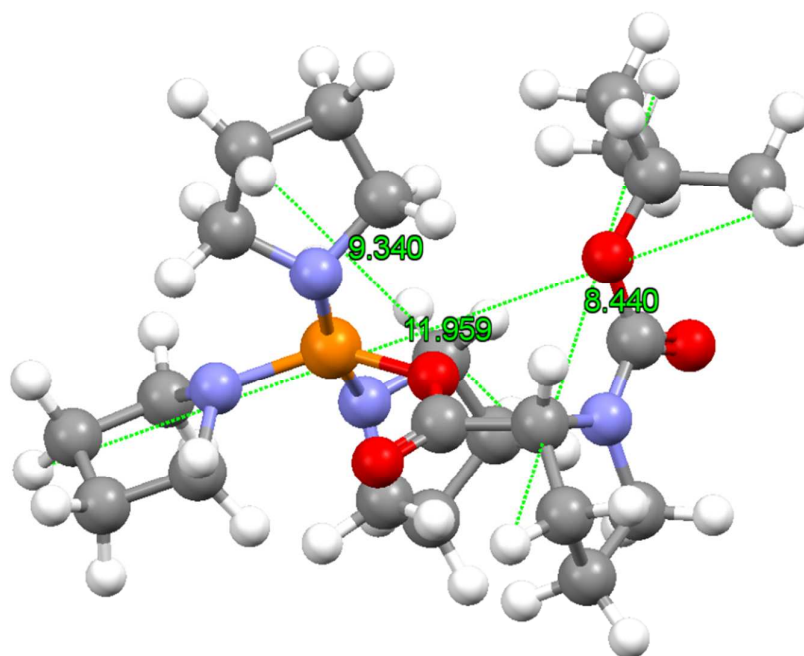


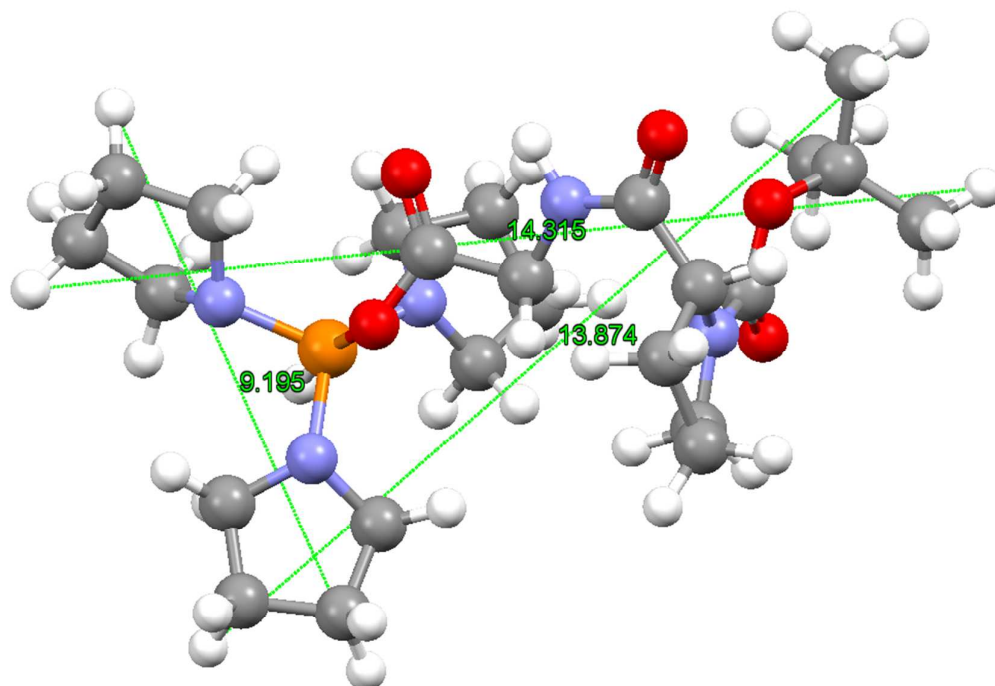
Fig. S9. ^1H NMR spectrum of In-MIL-68-NH-Gly-Pro dissolved in DCl- D_2O /dmso d6 solution (ca. 15% modified). Unmodified BDC- NH_2 and functionalized linker are indicated by circles and squares, respectively.

Following the described procedures, the Boc removal is complete and leads to MOF samples grafted with unprotected proline and glycine-proline moieties.

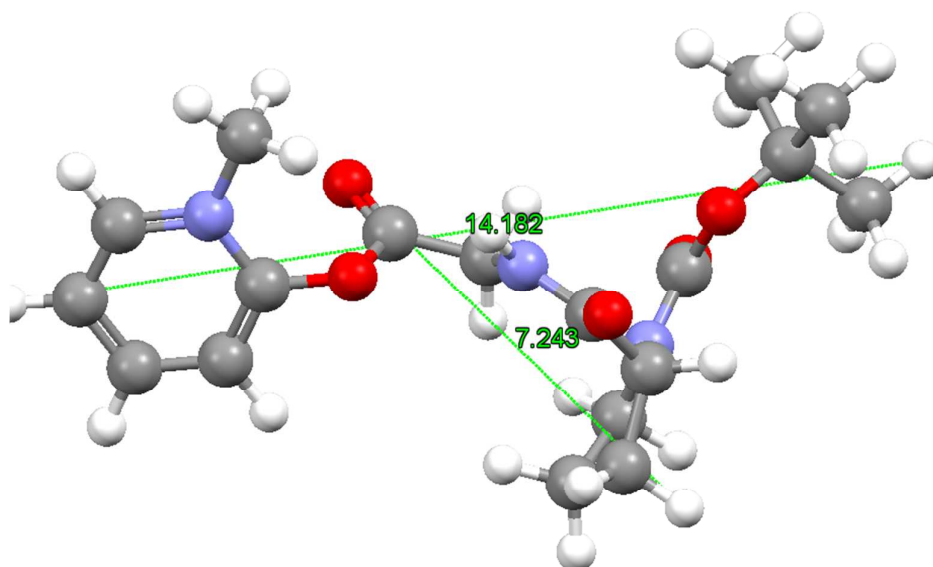
The sizes of PyBrop- and Mukaiyama-activated Boc-protected Proline and Glycine-Proline below are estimated according to calculation made using ChemOffice 2008 (Cambridgesoft) and Mercury (CCDC):



Sketch of Boc-Pro-OP(Py)₃ with relevant sizes given in Å



Sketch of Boc-Pro-Gly-OP(Py)₃ with relevant sizes given in Å



Sketch of Boc-Pro-Gly-O(*o*-Me-Pyridinium) with relevant sizes given in Å

Taking into account these estimated lengths and additional flexibility of both organics and MOF structures in solution, the activated Boc-Gly-Pro seems not able to easily access Zr-Uio-66-NH₂ cavity (windows size 6 Å) as found experimentally in contrast to Al-MIL-101-NH₂ (window size 12 Å) and In-MIL-68-NH₂ (window size 16 Å).

4. Coupling-Deprotection sequence applied to other peptides

In a 10 mL microwave glass vial, 0.50 mmol of 2-Chloro-1-methyl-pyridinium iodide (Mukaiyama agent, 124 mg), 1.2 mmol of EtNⁱPr₂ (DIEA, 112 µL) and 0.30 mmol of the Boc-protected peptide and 50 mg of Al-MIL-101-NH₂ (0.225 mmol -NH₂) are suspended in 5 mL of anhydrous dichloromethane. The resulting suspension is allowed to react under microwave irradiations for 20 minutes at 80°C (300 watts) under air cooling. The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give the desired product as a fine yellow powder after drying under vacuum at room temperature.

Then, in a 10 mL microwave glass vial, the solid is suspended in 5 mL of anhydrous dichloromethane. The resulting suspension is allowed to react under microwave irradiation for 10 minutes at 150°C (300 watts). The resulting suspension is centrifuged and the solid washed with dichloromethane (3 x 5 mL) to give the desired product as a fine yellow powder after drying under vacuum at room temperature.

The solid is finally characterized by powder X-ray diffraction, ¹H NMR and N₂ sorption analysis.

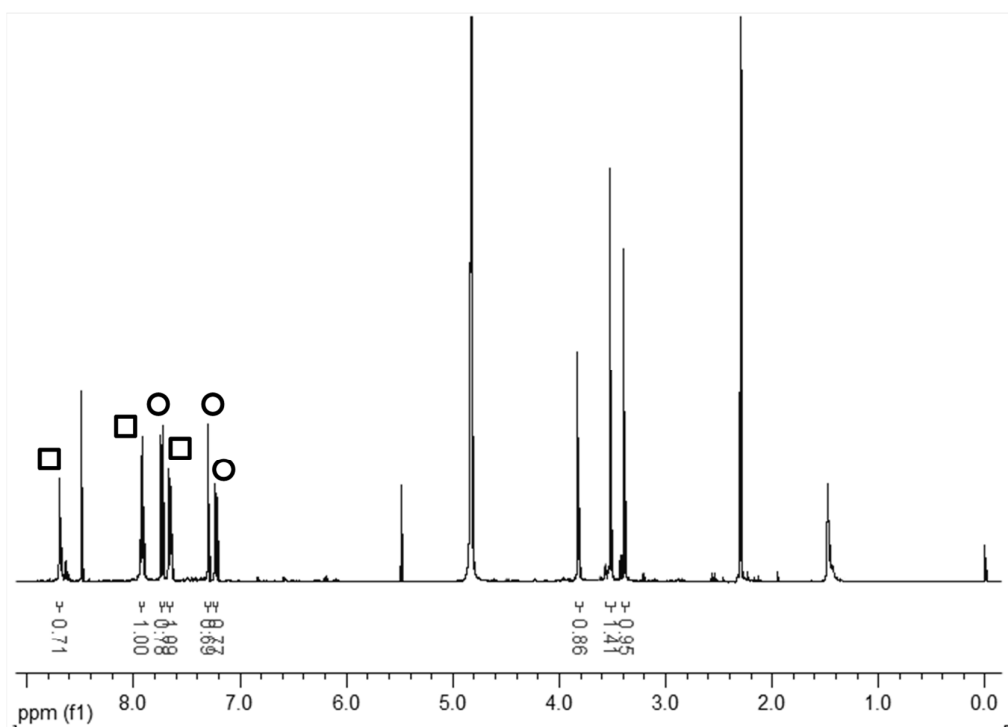


Fig.S10. ^1H NMR spectrum of Al-MIL-101-NH-Gly-Gly dissolved in NaOD-D₂O solution (ca. 55% modified). Unmodified BDC-NH₂ and functionalized linker are indicated by circles and squares, respectively.

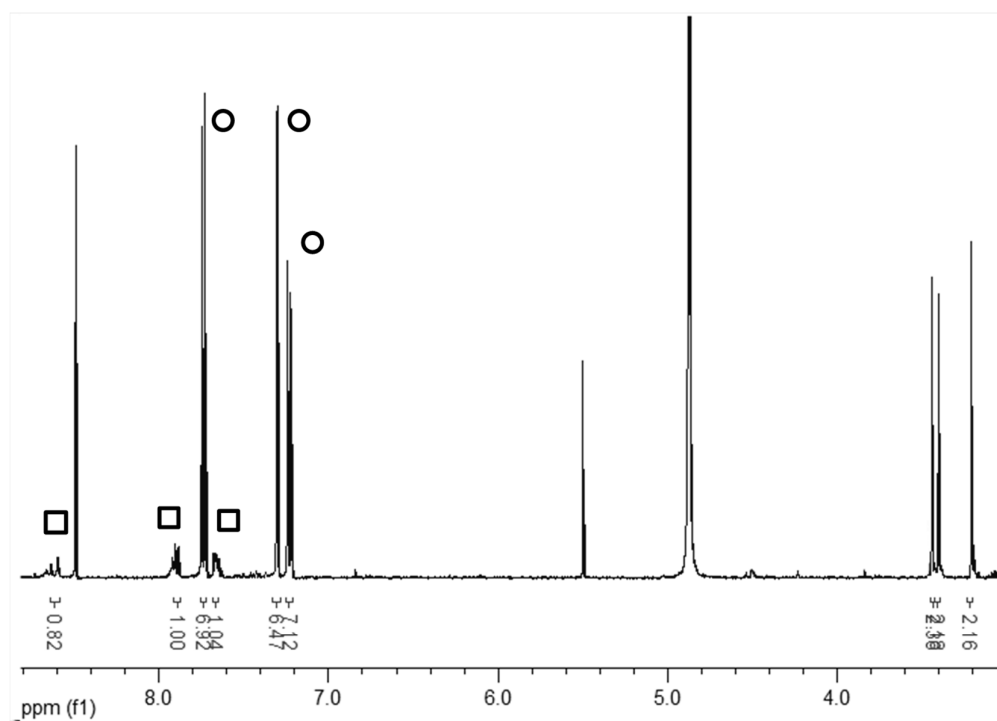


Fig.S11. ^1H NMR spectrum of Al-MIL-101-NH-Gly-Gly-Gly dissolved in NaOD-D₂O solution (ca. 15% modified). Unmodified BDC-NH₂ and functionalized linker are indicated by circles and squares, respectively.

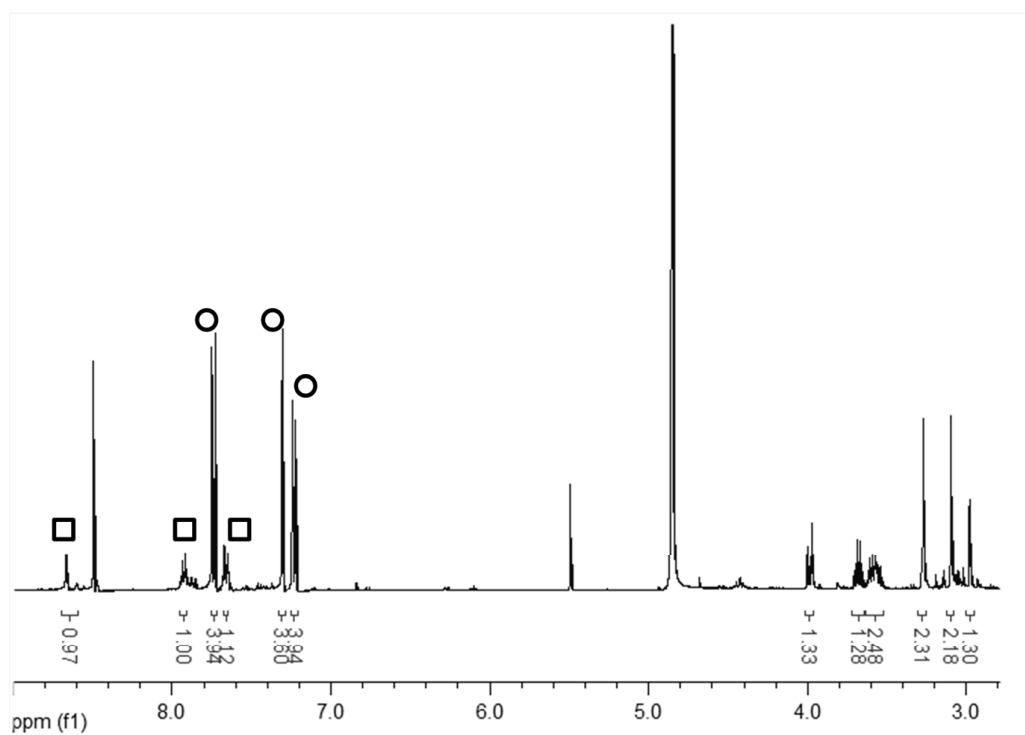


Fig.S12. ^1H NMR spectrum of Al-MIL-101-NH-Sar-Gly-Ala dissolved in NaOD- D_2O solution (ca. 20% modified). Unmodified BDC- NH_2 and functionalized linker are indicated by circles and squares, respectively.

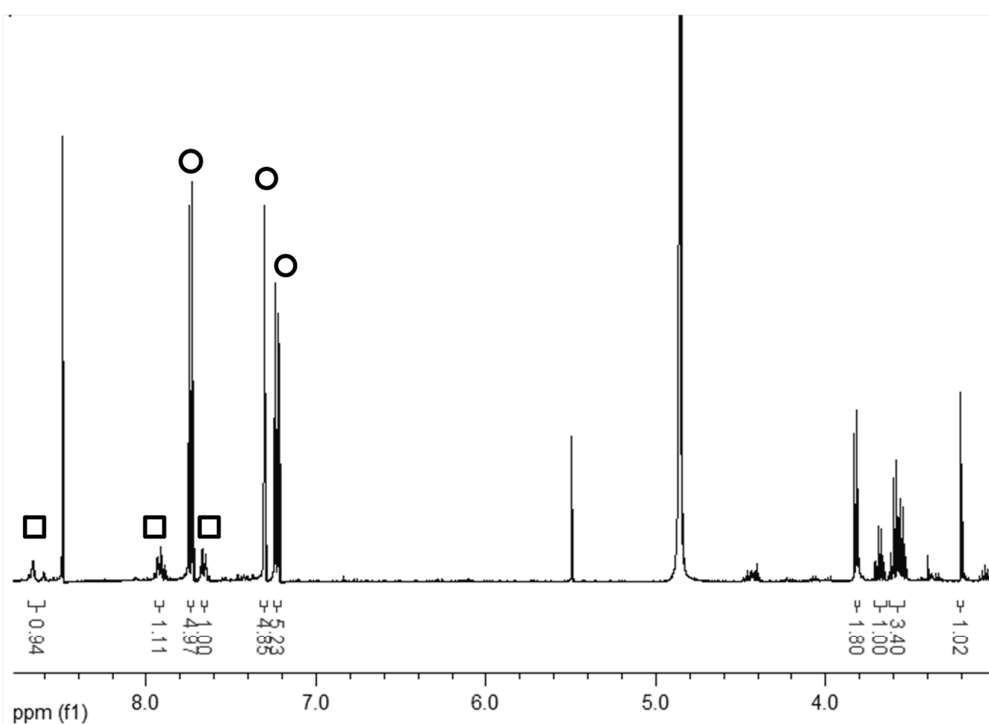


Fig.S13. ^1H NMR spectrum of Al-MIL-101-NH-Gly-Gly-Gly-Ala dissolved in NaOD- D_2O solution (ca. 20% modified). Unmodified BDC- NH_2 and functionalized linker are indicated by circles and squares, respectively.

5. HPLC analysis of (*D*)- and (*L*)-Al-MIL-101-Gly-Pro

Al-MIL-101-Gly-Pro was prepared using either (*D*)-Boc-Pro-Gly-OH (Sigma-Aldrich) or (*L*)-Boc-Pro-Gly-OH (Bachem AG) following the procedure described above to give respectively (*D*)-Al-MIL-101-Gly-Pro and (*L*)-Al-MIL-101-Gly-Pro with the same grafting yield (ca. 60%).

Prior to analysis, a sample of 10mg of each solid is dissolved in 5mL of a solution of MeOH:H₂O:TFA = 50:49:1. A portion of this solution is then analysed by HPLC using a CHIRALPAK IA column (H₂O:MeOH = 65:35 with 0.05%vol TFA, 0.2 mL.min⁻¹, detector at 254 nm).

| sample | retention time (min) | ligand | area | e.e. (%) |
|---------------------------------|----------------------|--|---------|----------|
| (<i>D</i>)-Al-MIL-101-Gly-Pro | 25.06 | (<i>D</i>)-H ₂ BDC-NH-Gly-Pro | 5158895 | n.d. |
| | 77.15 | H ₂ BDC-NH ₂ | 3109664 | |
| (<i>L</i>)-Al-MIL-101-Gly-Pro | 25.06 | (<i>D</i>)-H ₂ BDC-NH-Gly-Pro | 73533 | 97% |
| | 27.00 | (<i>L</i>)-H ₂ BDC-NH-Gly-Pro | 4552542 | |
| | 77.15 | H ₂ BDC-NH ₂ | 2987055 | |

6. Solid-state characterizations

6.1 X-ray diffraction (PXRD)

The XRD measurements on the materials were carried out by powder X-Ray diffraction (PXRD) using a Brüker D8 advance diffractometer equipped with a Lynx-Eye detector (CuK α radiation, wavelengths λ = 0.154178nm). The XRD studies were performed at room temperature.

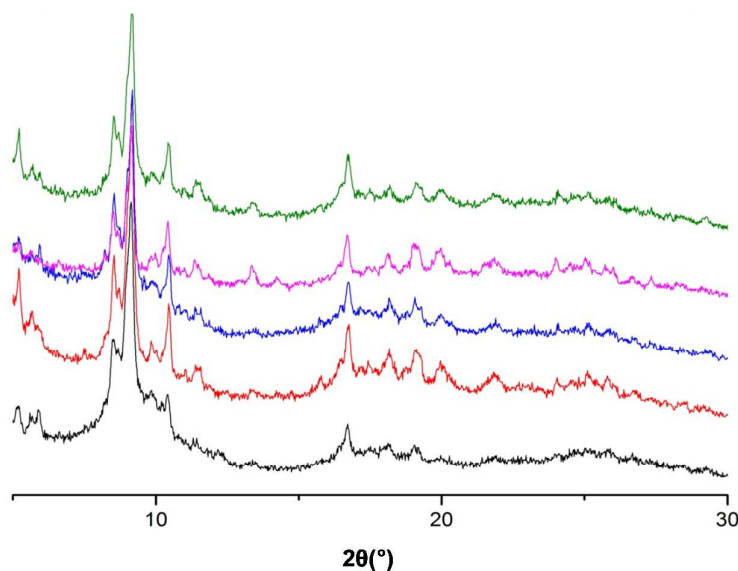


Fig. S14. PXRD patterns of Al-MIL-101 samples obtained through various coupling procedures but with common microwave-assisted deprotection. From bottom to top: Al-MIL-101-NH₂, Al-MIL-101-NH-Pro (conventional heating), Al-MIL-101-NH-Pro (microwave), Al-MIL-101-NH-Gly-Pro (conventional heating), Al-MIL-101-NH-Gly-Pro (microwave).

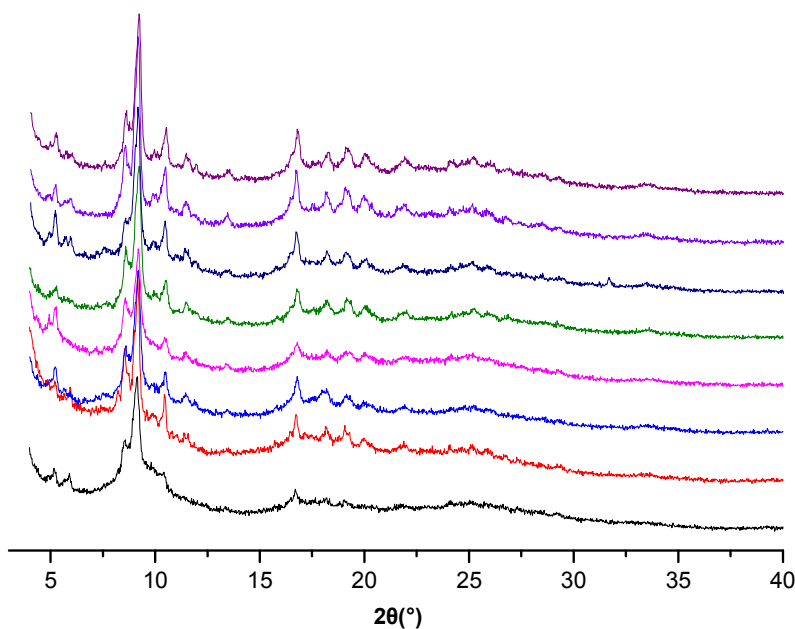


Fig. S15. From bottom to top, PXRD patterns of Al-MIL-101-NH₂, Al-MIL-101-NH-Pro, Al-MIL-101-NH-Gly-Pro, Al-MIL-101-NH-Gly-Gly, Al-MIL-101-Gly-Gly-Gly, Al-MIL-101-Sar-Gly-Ala, Al-MIL-101-Gly-Gly-Gly-Ala, Al-MIL-101-Gly-Phe-Gly-Gly prepared under microwave irradiation including microwave-assisted deprotection.

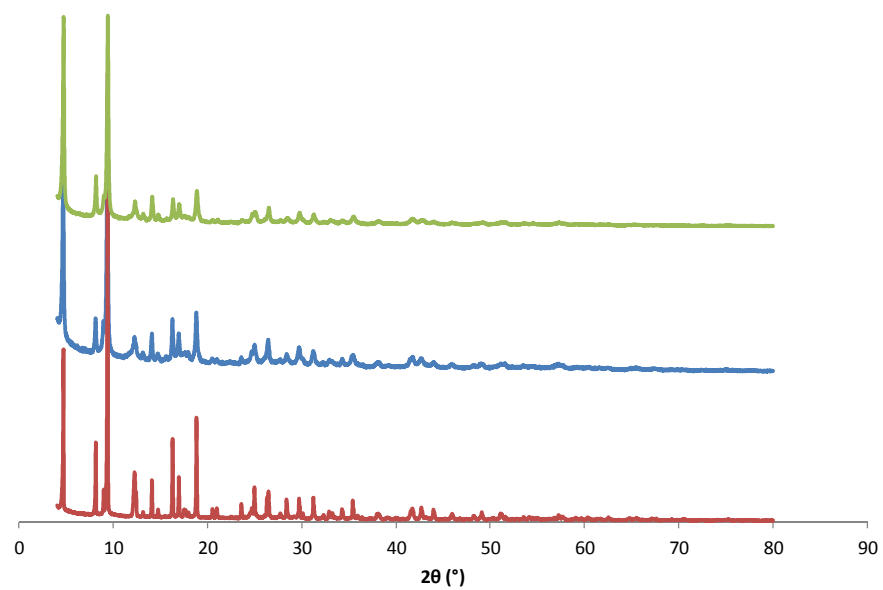


Fig. S16. PXRD patterns of In-MIL-68-NH₂ (bottom), In-MIL-68-NH-Pro (middle) and In-MIL-68-NH-Gly-Pro(top).

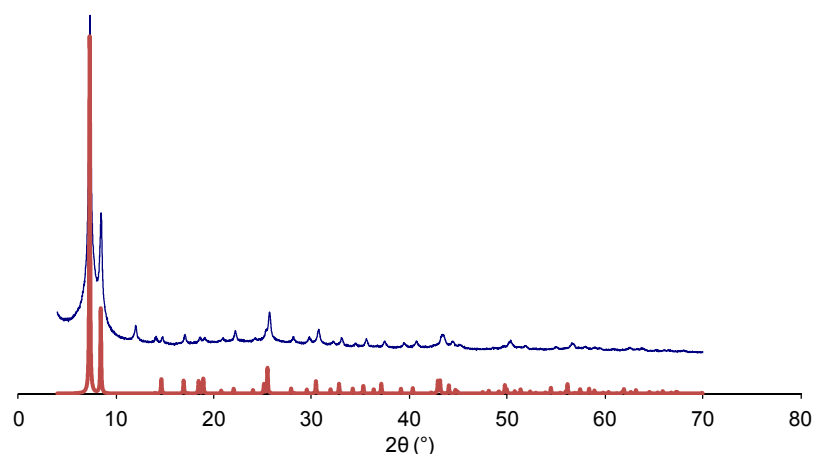


Fig. S17. PXRD patterns of Zr-UiO-66-NH₂ (bottom) and Zr-UiO-66-NH-Pro (top).

6.2 N₂ sorption analysis

The N₂ adsorption/desorption isotherms at 77K were measured on a BELSORP-Mini. The samples were out gassed under vacuum ($\approx 10^{-4}$ mbar) at room temperature for 12h before start the measurement. The specific surface was determined by BET method.

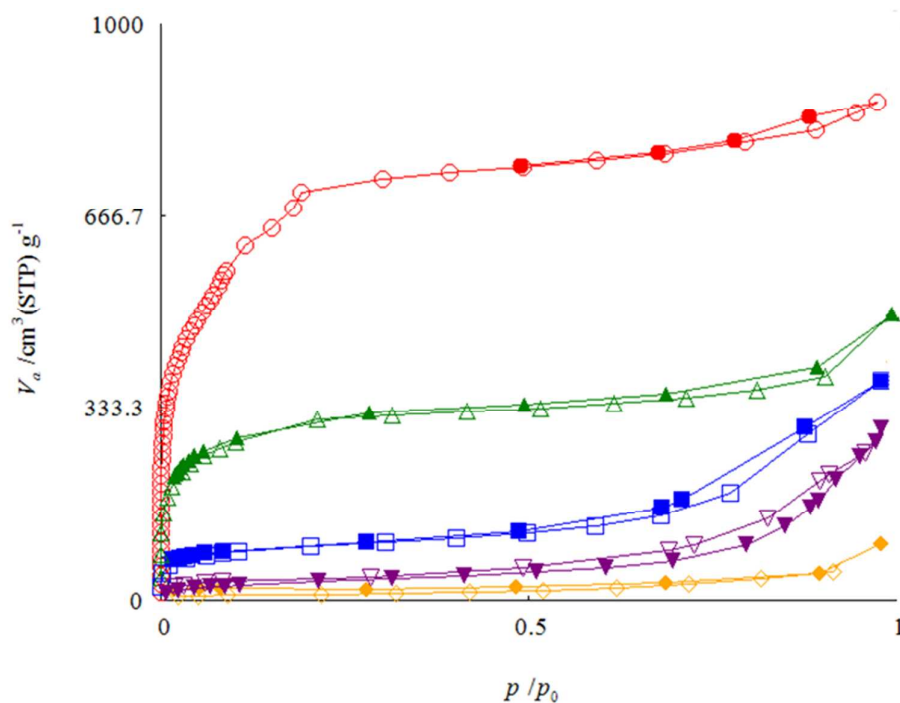


Fig. S18. Nitrogen isotherms (77K) represented as linear-linear diagrams for Al-MIL-101-NH₂ (●), Al-MIL-101-NH-Gly-Pro (Conventional procedure) (◆), Al-MIL-101-NH-Pro (Conventional procedure) (▼), Al-MIL-101-NH-Pro (Microwave Procedure) (■), Al-MIL-101-NH-Gly-Pro (Microwave Procedure) (▲). Close and open symbols correspond to adsorption and desorption data, respectively.

| MOF | BET surface area (m ² /g) | Pore volume (cm ³ /g) |
|----------------------------|--------------------------------------|----------------------------------|
| Al-MIL-101-NH ₂ | 3000 | 1.32 |
| Al-MIL -101-NH-Pro (CH) | 115 | 0.46 |
| Al-MIL-101-NH-Gly-Pro(CH) | 30 | 0.27 |
| Al-MIL-101-NH-Pro (MW) | 330 | 0.59 |
| Al-MIL-101-NH-Gly-Pro (MW) | 800 | 0.72 |

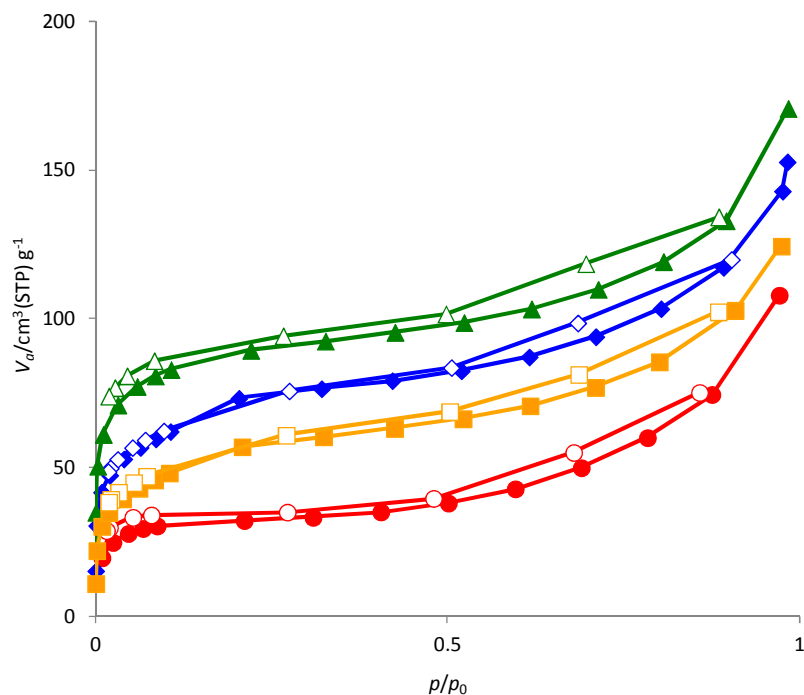


Fig. S19. Nitrogen isotherms (77K) represented as linear-linear diagrams for Al-MIL-101-NH-Gly-Gly (●), Al-MIL-101-NH-Gly-Gly-Gly (◆), Al-MIL-101-NH-Sar-Gly-Ala (▲), Al-MIL-101-NH-Gly-Phe-Gly-Gly (Microwave Procedure) (■). Close and open symbols correspond to adsorption and desorption data, respectively.

| MOF | BET surface area (m ² /g) | Pore volume (cm ³ /g) |
|--------------------------------|---|-------------------------------------|
| Al-MIL -101-NH-Gly-Pro | 800 | 0.72 |
| Al-MIL -101-NH-Gly-Gly | 130 | 0.152 |
| Al-MIL -101-NH-Gly-Gly-Gly | 260 | 0.236 |
| Al-MIL -101-NH-Sar-Gly-Ala | 330 | 0.264 |
| Al-MIL -101-NH-Gly-Gly-Gly-Ala | 200 | 0.192 |
| Al-MIL -101-NH-Gly-Phe-Gly-Gly | 280 | 0.109 |

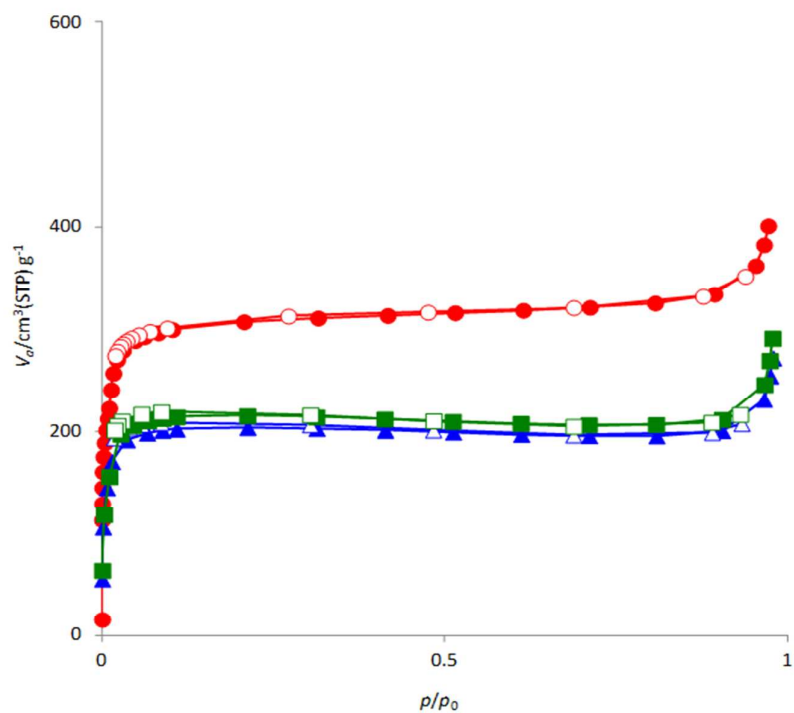


Fig. S20. Nitrogen isotherms (77K) represented as linear-linear diagrams for In-MIL-68-NH₂ (●), In-MIL-68-NH-Pro (■) and In-MIL-68-NH-Gly-Pro (▲). Close and open symbols correspond to adsorption and desorption data, respectively.

| MOF | BET surface area (m ² /g) | Pore volume (cm ³ /g) |
|---------------------------|---|-------------------------------------|
| In-MIL-68-NH ₂ | 1200 | 0.620 |
| In-MIL-68-NH-Pro | 850 | 0.450 |
| In-MIL-68-NH-Gly-Pro | 800 | 0.420 |

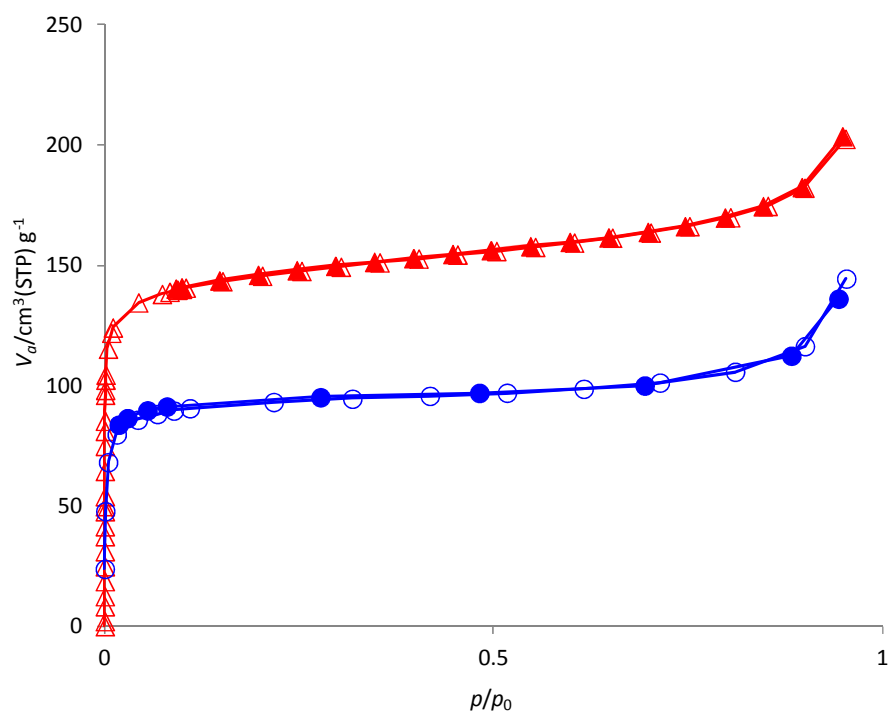
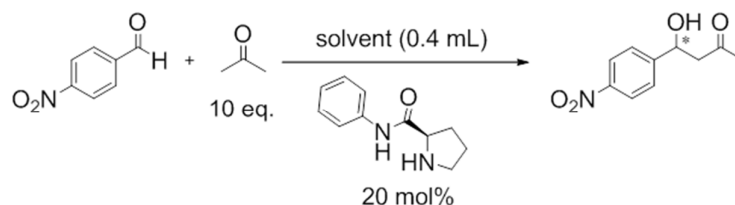


Fig. S21. Nitrogen isotherms (77K) represented as linear-linear diagrams for Zr-UiO-66-NH₂ (▲) and Zr-UiO-66-NH-Pro (●). Close and open symbols correspond to adsorption and desorption data, respectively.

| MOF | BET surface area (m ² /g) | Pore volume (cm ³ /g) |
|---------------------------|---|-------------------------------------|
| Zr-UiO-66-NH ₂ | 553 | 0.50 |
| Zr-UiO-66-NH-Pro | 355 | 0.36 |

7. Aldol reaction

Homogeneous system



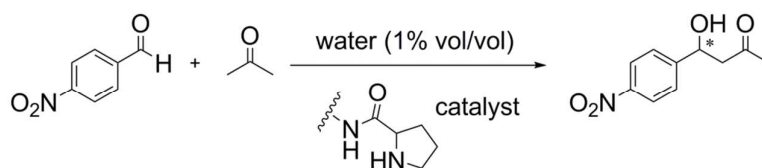
In a typical catalytic run, 5 mg of (*R*)-*N*-phenylpyrrolidine-2-carboxamide (0.027 mmol; 20mol% catalyst) are suspended in a solution of *p*-nitro-benzaldehyde (20 mg, 0.135 mmol) in a solvent (0.4mL) with acetone (0.5 mL). The solution is allowed to react at 22°C for 72 hours. Then the solution is quenched with an aqueous ammonium chloride solution and the organic products are extracted using diethyl ether. The organic solution is analyzed by HPLC (AS-H column, hexane:isopropanol = 70:30, 1mL/min, 254 nm) to determine yield and enantiomeric excess (e.e.)

Table S2. Observed yields and enantiomeric excess in asymmetric aldol reactions:^[a]

| solvent | additive | yield (%) | ee (%) |
|-----------------|----------------|-----------|--------|
| isopropanol | none | 38 | 21 |
| isopropanol | water (4% vol) | 95 | 17 |
| NMP | none | 5 | n.d. |
| NMP | water (4% vol) | 95 | 28 |
| DMF | none | 18 | 22 |
| DMF | water (4% vol) | 95 | 35 |
| acetonitrile | none | 21 | 42 |
| acetonitrile | water (4% vol) | 95 | 29 |
| DMSO | none | 5 | n.d. |
| DMSO | water (4% vol) | 19 | 22 |
| dioxane | none | 95 | 40 |
| dioxane | water (4% vol) | 95 | 38 |
| THF | none | 95 | 35 |
| THF | water (4% vol) | 95 | 28 |
| dichloromethane | none | 50 | 35 |
| dichloromethane | water (4% vol) | 64 | 29 |
| acetone | none | 67 | 41 |
| acetone | water (1% vol) | 95 | 44 |
| acetone | water (4% vol) | 95 | 37 |

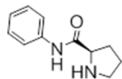
[a] Reaction performed using 20 mol% of (*R*)-*N*-phenylpyrrolidine-2-carboxamide catalyst at room temperature for 72 hours. NMP = *N*-methylpyrrolidinone, DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran, n.d. = not determined.

MOF system



In a typical catalytic run, 60 mg of Al-MIL-101-NH-Pro (10% functionalized with proline) or 10 mg of Al-MIL-101-NH-Gly-Pro (60% functionalized with glycine-proline) which correspond to 0.030 mmol of proline moiety, are suspended in a solution of *p*-nitro-benzaldehyde (30 mg, 0.200 mmol) in acetone (1 mL) in the presence of water (50 μ L). The suspension is allowed to react at 22°C for seven days in analogy to the previously reported experimental procedure for MOF catalyzed asymmetric aldol reaction.^[4] Then, after centrifugation, the solution is quenched with an aqueous ammonium chloride solution and the organic products are extracted using diethyl ether. In parallel, the solid catalyst is washed twice with diethyl ether. The organic phases are combined, dried using magnesium sulphate and analyzed by HPLC (AS-H column, hexane:isopropanol = 70:30, 1mL/min, 254 nm) to obtain conversion and enantiomeric excess (e.e.)

Table S3. Observed yields and enantiomeric excess in asymmetric aldol reactions.^[a]

| catalyst | yield [%] ^[b] | e.e. [%] ^[b] |
|---|--------------------------|-------------------------|
| Al-MIL-101-NH ₂ | < 5 | < 2 |
| Al-MIL-101-NH-Pro | 18 | 18 |
| Al-MIL-101-NH-Gly-Pro | 26 | 25 |
| Al-MIL-101-NH-Gly-Pro | 80 ^[c] | 27 |
| Al-MIL-101-NH-Gly-Pro | > 95 ^[d] | 17 |
| In-MIL-68-NH ₂ | 83 | 0 |
| In-MIL-68-NH-Pro | 14 | 0 |
| In-MIL-68-NH-Gly-Pro | < 5 | n.d. |
| Zr-UiO-66-NH ₂ | < 5 | n.d. |
| In-MIL-68-NH ₂ | < 5 | n.d. |
|  | > 95 | 35 |

[a] Reaction performed using 15 mol% of catalytic species (0.03 mmol of proline derivative either in MOF or as pure organic), *p*-nitro-benzaldehyde (0.2 mmol), water (50 μ L) in acetone (5 mL) at room temperature for seven days. [b] Determined by HPLC using Chiralpak AS-H column. [c] Result obtained using 100 mol% of Pro according to ref. [4a]. [d] Reaction performed at 45°C.

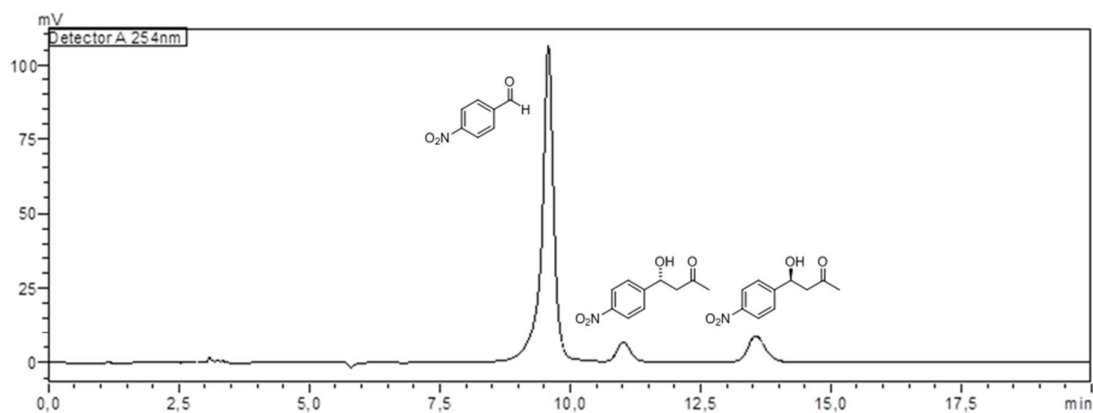


Figure S22. Typical HPLC trace for the aldol reaction catalyzed by Al-MIL-101-Gly-Pro (acetone/water, 26% yield, 25% e.e.)

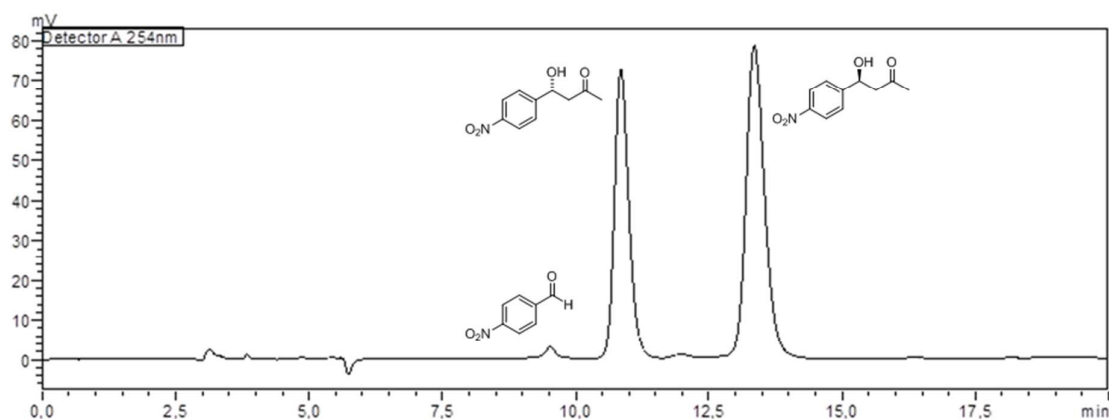


Figure S23. Typical HPLC trace for the aldol reaction catalyzed by Al-MIL-101-Gly-Pro (acetone/water at 45°C, 95% yield, 17% e.e.)

Leaching test

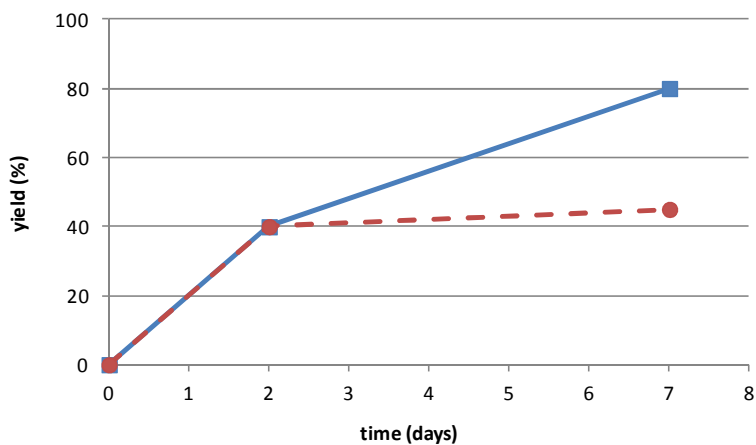


Figure S24. Evolution of aldol product yield in the case of 100 mol% Al-MIL-101-NH-Gly-Pro catalyst at room temperature (plain line: classical catalytic run, dashed line: filtration and removal of the MOF catalyst after 2 days).

8. References

- [1] a) M. Hartmann, M. Fischer, *Microporous Mesoporous Mater.* **2012**, *164*, 38-43; b) P. Serra-Crespo, E. V. Ramos-Fernandez, J. Gascon, F. Kapteijn, *Chem. Mater.* **2011**, *23*, 2565-2572.
- [2] a) M. Savonnet, D. Farrusseng, *PCT Appl. WO2011048284*, **2011**; b) J. Canivet, S. Aguado, G. Bergeret, D. Farrusseng, *Chem. Commun.* **2011**, *47*, 11650-11652.
- [3] M. Kandiah, M. H. Nilsen, S. Usseglio, S. Jakobsen, U. Olsbye, M. Tilset, C. Larabi, E. A. Quadrelli, F. Bonino, K. P. Lillerud, *Chem. Mater.* **2010**, *22*, 6632-6640.
- [4] a) D. J. Lun, G. I. N. Waterhouse, S. G. Telfer, *J. Am. Chem. Soc.* **2011**, *133*, 5806-5809; b) W. Zhu, C. He, P. Wu, X. Wu, C. Duan, *Dalton Trans.* **2012**, *41*, 3072-3077.