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Supporting Information

Postsynthetic modification of an amino-tagged MOF using peptide coupling reagents: a comparative study

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1. Materials

Acetic acid (p.A.), acetylsalicylic acid (≥ 99 %, Sigma), aluminium chloride hexahydrate (≥ 99 %, Fluka), 2-aminoterephthalic acid (99 %, Aldrich), Boc-Gly-OH[i] (≥ 99 %, Aldrich), 1,1'-carbonyldiimidazole (reagent grade, Aldrich), caesium fluoride (≥ 98.0 %, Aldrich), chlorambucil (Sigma), chloroform anhydrous (≥ 99 %, Sigma-Aldrich), deuterium oxide (99.9 %, Eurisotop), dichloromethane anhydrous (≥ 99.9 %, Carl Roth), dimethylsulfoxide-d_6 (99.8 %, Eurisotop), ethanol (p.A.), HBTU[ii] (≥ 99 %, Carl Roth), *N*,*N'*-diisopropylcarbodiimide (99 %, Aldrich), *N*,*N'*-diisopropylethylamine (≥ 99 %, Sigma-Aldrich), *N*,*N*-dimethylformamide anhydrous (synthesis grade, Fisher Scientific), PyBroP®[iii] (> 98.5 %, Carl Roth).

2. Characterization

XRD: The *STOE Stadi MP* diffractometer with Cu$K_{\alpha 1}$-radiation (λ= 1.54060 Å) and Ge(111) single crystal monochromator was used for wide angle X-ray diffraction in transition mode. The diffractometer was equipped with a *DECTRIS* solid state strip detector *MYTHEN 1K*. X-ray diffraction patterns of the samples were collected with an omega-2-theta scan using a step size of 4.71° and a counting time of 60 s per step.

Nitrogen sorption was measured at 77 K with a *Quantachrome NOVA 4000e* station after degasing the sample at 150 °C for at least 12 h in vacuum. Scientific evaluation of sorption data was carried out with the software suite *NovaWin*, Version 10.0 (*Quantachrome Instruments 2007*). BET surface areas of the samples were calculated employing the linearized form of the BET equation with 6 data points (p/p_0 = 0.050, 0.075, 0.100, 0.125, 0.150 and 0.200) in range from p/p_0 0.05 to 0.2. For all samples the correlation coefficient was higher than 0.999. Adsorption isotherms were used to calculate the pore size distribution by employing NLDFT (N_2 at 77 K on silica,

[i] *N*-(*tert*-butoxycarbonyl)glycine
[ii] *N*,*N*,*N'*,*N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
[iii] bromotripyrrolidinophosphonium hexafluorophosphate

cylindrical/spherical pore adsorption model). Total pore volume was calculated at p/p_0 0.30.

MS: Electrospray ionization (ESI) mass spectrometry was carried out with a *Thermo Finnigan LTQ FT* with *Finnigan IonMax* ion source. For these measurements a water/acetonitrile mixture with a flow rate of 100 µL/min was used.

NMR was performed on a JEOL ECX-400. Detailed measurement parameter for ^{1}H measurements can be found in Table S1. For the deuterium lock DMSO-d_6 was used as an internal reference.

Table S1: *Measurement parameter for ^{1}H-NMR measurements.*

Spektrometer frequency	400 MHz
Decoupling	-
Temperature	25 °C
Pulse angle	45°
Acquisition time	3.64 s
Relaxation delay	2 s
Spectral width	18 ppm
Acquired size	32768 (32 k)
Number of scans	16
Processing: line broadening	-
Processing: zero filling	64 k
Processing: phase correction	Manual
Processing: baseline correction	Automatic, polynomial order 3

3. Experimental section

All peptide coupling reactions were performed under nitrogen atmosphere using standard Schlenk technique and dry solvents (DMF, dichloromethane or chloroform). All samples were stored under nitrogen. Samples were dispersed by shaking at 100 min^{-1} (orbital shaker *GFL 3017*), with mixing (*neoLab vortex mixer*) or with ultrasound (*Bandelin SONOREX RK510H*).

3.1 Synthesis of MIL-101(Al)-NH_2

MIL-101(Al)-NH_2 was synthesized following a slightly modified procedure of *Hartmann* and co-workers:[1] In a 250 mL glass flask and 2-aminoterephthalic acid (0.68 g, 3.75 mmol) was dissolved in DMF (150 mL) and heated up to 110 °C in an oil bath. Then aluminium chloride hexahydrate (1.81 g, 7.5 mmol) was added in 7 equal portions (258 mg) with a time delay of 15 min between each two additions. Subsequently, the temperature was kept for another 3 h under stirring at 110 °C. Then the flask was tightly sealed and placed in an oven at 110 °C for 16 h without stirring. After cooling down to r.t. the yellow precipitate was filtered off and washed with ethanol. Subsequently, the powder was purified by Soxhlet extraction with ethanol for 24 h. Finally, the sample was dried in an oven at 110 °C for 24 h and then stored under nitrogen. Typically, yield was around 0.8 g for the activated product.

3.2 Digestion of MIL-101(Al)-NH_2 samples

For digestion of MIL-101(Al)-NH_2 samples about 3 mg sample was added to a solution of 24 mg caesium fluoride in 450 µL DMSO-d_6 and 250 µL D_2O. After vortex mixing the suspension was sonicated for 5 min. After repeating this procedure once again the solution was transferred in a NMR tube. For determination of postfunctionalization yield integral of peak A of postfunctionalized 2-aminoterephthalic acid was divided by the sum of integral A and integral A´ of 2-aminoterephthalic acid (see Fig. S9 for proton

denotation). If necessary, the digestion was also used for mass spectrometry after NMR measurement.

3.3 Determination of reaction parameters for peptide coupling reagents

In a 25 mL Schlenk flask dichloromethane (15 mL) was cooled down in an ice bath. Then acetic acid (46 µL, 0.800 mmol), Hünig's base (140 µL, 0.80 mmol; or 410 µL, 2.4 mmol) and PyBroP® (373 mg, 0.800 mmol) were added. After 2 min stirring MIL-101(Al)-NH_2 (101 mg, contains approximately 0.4 mmol NH_2-functions) was added. Samples of 2 mL volume were taken after 0.5 h, 1 h, 5 h, 24 h and 48 h stirring at r.t which were filtered immediately and washed three times with acetone.

3.4 Performance screening of peptide coupling reagents

Peptide coupling reactions of 4 peptide coupling reagents DIC, PyBroP®, HBTU and CDI were carried out each at following 5 different synthesis conditions (DMF r.t. 2d, DMF 50 °C 7h, dichloromethane r.t. 2d, dichloromethane reflux 7 h, chloroform reflux 7 h. All reactions were repeated once again (in total: 40 reactions).

DIC coupling procedure

In a 25 mL Schlenk flask solvent (6 mL) was cooled down in an ice bath. Then acetic acid (29 µL, 0.500 mmol) and DIC (81 µL, 0.520 mmol) were added and the mixture was stirred for 5 min. Then MIL-101(Al)-NH_2 (29 mg, contains approximately 0.1 mmol NH_2-functions) was given to the mixture. After stirring for a certain time at certain temperature (see above) the sample was filtered and washed three times with acetone. Samples which were synthesized in dichloromethane at r.t. were purified by Soxhlet extraction in ethanol for 8 h.

PyBroP® coupling procedure

In a 25 mL Schlenk flask solvent (6 mL) was cooled down in an ice bath. Then acetic acid (17 µL, 0.300 mmol), Hünig's base (140 µL, 0.80 mmol) and PyBroP® (140 mg, 0.30 mmol) were added. After 2 min stirring MIL-101(Al)-NH_2 (29 mg, contains approximately 0.1 mmol NH_2-functions) was given to the mixture. After stirring for a certain time at certain temperature (see above) the sample was filtered and washed three times with acetone.

HBTU coupling procedure

In a 25 mL Schlenk flask solvent (6 mL), acetic acid (17 µL, 0.300 mmol), Hünig's base (140 µL, 0.80 mmol) and HBTU (114 mg, 0.30 mmol) were stirred for 2 min. Then MIL-101(Al)-NH_2 (29 mg, contains approximately 0.1 mmol NH_2-functions) was given to the mixture. After stirring for a certain time at certain temperature (see above) the sample was filtered and washed three times with acetone.

CDI coupling procedure

In a 25 mL Schlenk flask solvent (6 mL), acetic acid (17 µL, 0.300 mmol) and CDI (49 mg, 0.30 mmol) were stirred for 30 min. Then MIL-101(Al)-NH_2 (29 mg, contains approximately 0.1 mmol NH_2-functions) was given to the mixture. After stirring for a certain time at certain temperature (see above) the sample was filtered and washed three times with acetone.

3.5. PSM with Boc-Gly-OH, acetylsalicylic acid and chlorambucil

DIC coupling procedure with Boc-Gly-OH

In a 25 mL Schlenk flask dichloromethane (20 mL) was cooled down in an ice bath. Then Boc-Gly-OH (289 mg, 1.650 mmol) and DIC (261 µL, 1.686 mmol) were added and the mixture was stirred for 5 min. Then MIL-101(Al)-NH_2 (96 mg, contains approximately 0.33 mmol NH_2-functions) was given to the mixture. After stirring for 2d

at r.t. the sample was filtered and washed three times with acetone. Subsequently, the yellow powder was purified by Soxhlet extraction in ethanol for 8 h.

DIC coupling procedure with acetylsalicylic acid

In a 25 mL Schlenk flask dichloromethane (20 mL) was cooled down in an ice bath. Then acetylsalicylic acid (297 mg, 1.650 mmol) and DIC (261 µL, 1.686 mmol) were added and the mixture was stirred for 5 min. Then MIL-101(Al)-NH_2 (96 mg, contains approximately 0.33 mmol NH_2-functions) was given to the mixture. After stirring for 2d at r.t. the sample was filtered and washed three times with acetone. Subsequently, the yellow powder was purified by Soxhlet extraction in ethanol for 8 h.

DIC coupling procedure with chlorambucil

In a 25 mL Schlenk flask dichloromethane (20 mL) was cooled down in an ice bath. Then chorambucil (201 mg, 0.660 mmol) and DIC (110 µL, 0.69 mmol) were added and the mixture was stirred for 5 min. Then MIL-101(Al)-NH_2 (96 mg, contains approximately 0.33 mmol NH_2-functions) was given to the mixture. After stirring for 2d at r.t. the sample was filtered and washed three times with acetone. Subsequently, the yellow powder was purified by Soxhlet extraction in ethanol for 8 h.

3.6 Calculation of the number of linker per cage in MIL-101(Al)-NH_2

The MIL-101 structure contains large cages build up by 42 linker and small cages build up by 30 linker.[2] Every linker is shared by 3 cages.[2] Therefore, large cages contain 14 linker and small cages 10 linker. Large cages and small cages are distributed in a 1:2 ratio in this structure.[2] Thus, one large cage and two small cages contain 34 linker. If statistically one linker per cage is postfunctionalized a postfunctionalization yield of 3/34 (about 9 %) is expected.

3.7 Calculation of the external MOF surface

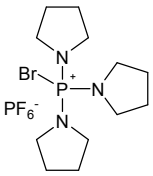
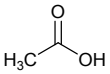
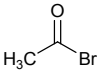
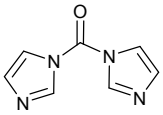
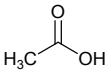
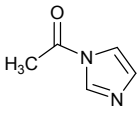
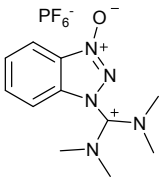
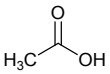
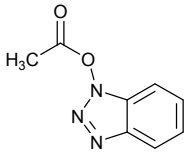
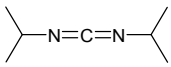
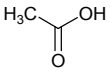
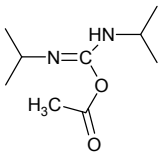
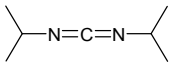
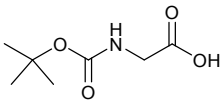
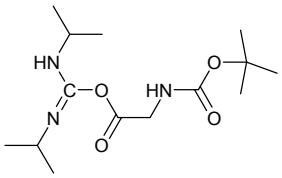
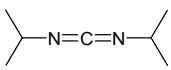
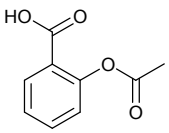
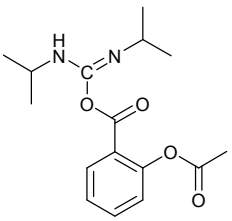
For filtration of MIL-101(Al)-NH_2 Satorius filter paper with 1 µm pore size was used. If all particles are assumed to have a spherical shape with 0.5 µm radius ($3.14*10^{-12}$ m^2 external surface and $5.24*10^{-19}$ m^3 volume), than 1 g MOF with a density of 0.3 g/mL would contain $6.4*10^{12}$ particles with 20 m^2 external surface in total. BET surface area of the MOF batch used for the PSM with chlorambucil was 2059 m^2/g. If all amino functions of 2-aminoterephthalic acid are distributed equally over the surface of this material than the postfunctionalization yield would be about 1 % for only external postfunctionalization. Notable feature of this calculation is that the particles of MIL-101(Al)-NH_2 are probably larger and with this the external surface area smaller than the calculated one. Hence, we calculated the highest external surface area that this material could have.

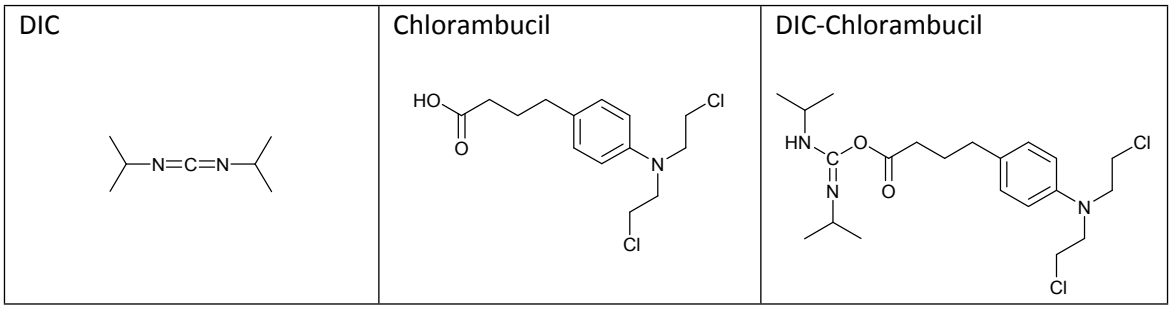
3.8 Calculation of projection diameters of molecules

Calculator Plugins were used for structure property prediction and calculation, *Marvin 6.1.0, 2013, ChemAxon* (http://www.chemaxon.com). Calculation was carried out for the molecular conformation with lowest energy based on van der Waals radii of the atoms (projection optimization enabled, optimization limit: very strict).

4. Figures and tables

Table S2: *Molecular structures of peptide coupling reagents, acids and activated acids.*

Peptide coupling reagent	Acid	Activated acid
PyBroP® 	AcOH (acetic acid) 	PyBroP®-AcOH 
CDI 	AcOH 	CDI-AcOH 
HBTU 	AcOH 	HBTU-AcOH 
DIC 	AcOH 	DIC-AcOH 
DIC 	Boc-Gly-OH 	DIC-Boc-Gly-OH 
DIC 	Acetylsalicylic acid 	DIC-Acetylsalicylic acid 



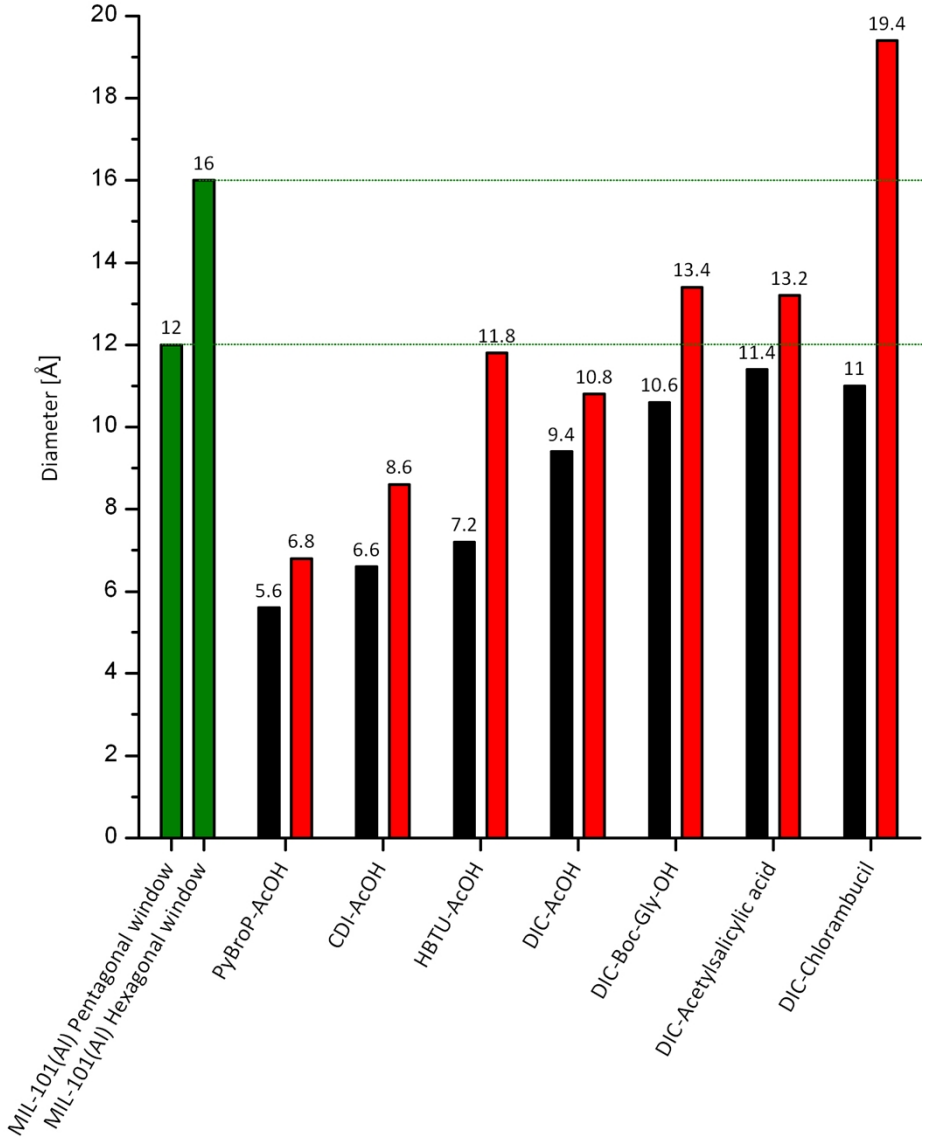


Fig. S1: *Calculated minimum and maximum projection diameter of the activated acids of acetic acid coupled with PyBroP®, CDI, HBTU or DIC as well as Boc-Gly-OH, acetylsalicylic acid or chlorambucil coupled with DIC compared to sizes of pentagonal and hexagonal windows of MIL-101(Al)-NH_2.[3] MOF dimensions are depicted from literature.[2]*

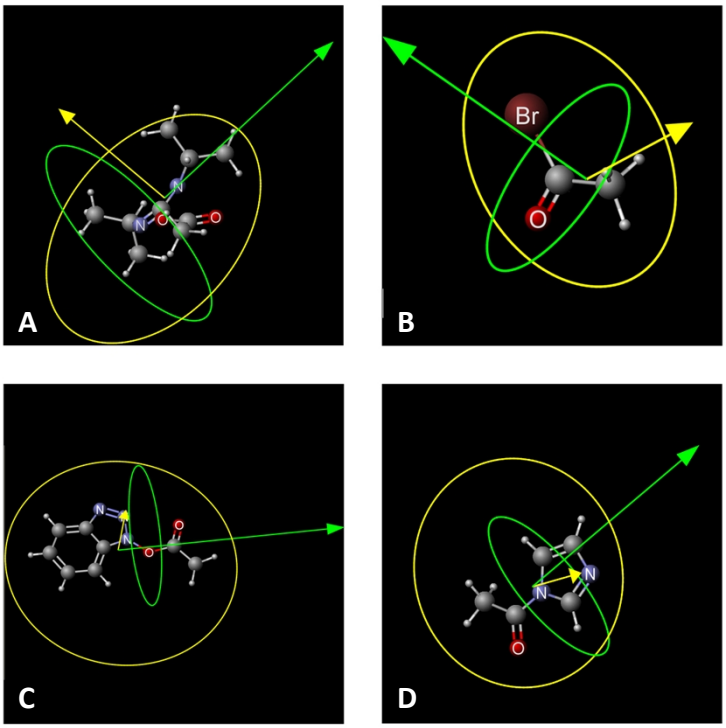


Fig. S2: *Calculated and visualized minimum (**green**) and maximum (**yellow**) projection diameter of activated acids of acetic acid coupled with DIC (**A**), PyBroP® (**B**), HBTU (**C**) or CDI (**D**).[3] Arrows represent the orthogonal directions on the projection planes*

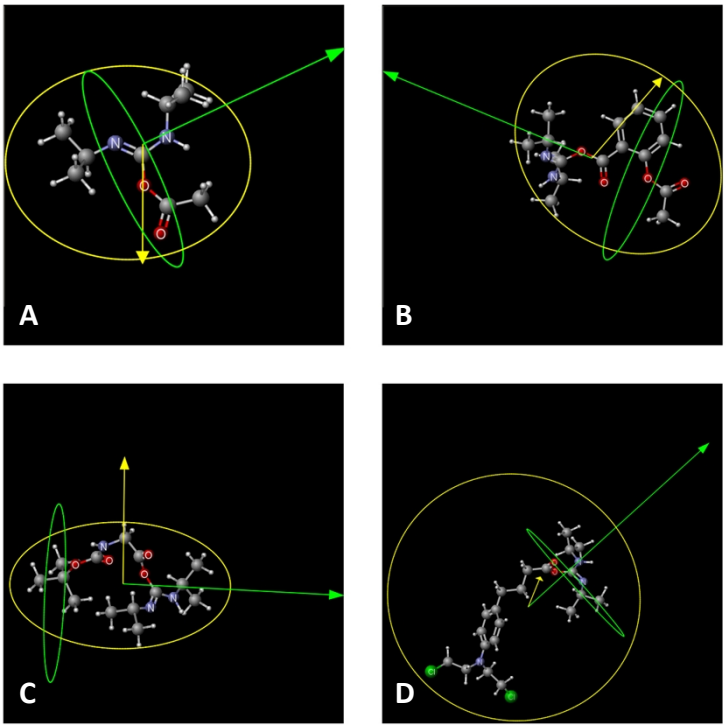


Fig. S3: *Calculated and visualized minimum (**green**) and maximum (**yellow**) projection diameter of activated acids of acetic acid (**A**), acetylsalicylic acid (**B**) Boc-Gly-OH (**C**), or chlorambucil (**D**) coupled with DIC.[3] Arrows represent the orthogonal directions on the projection planes.*

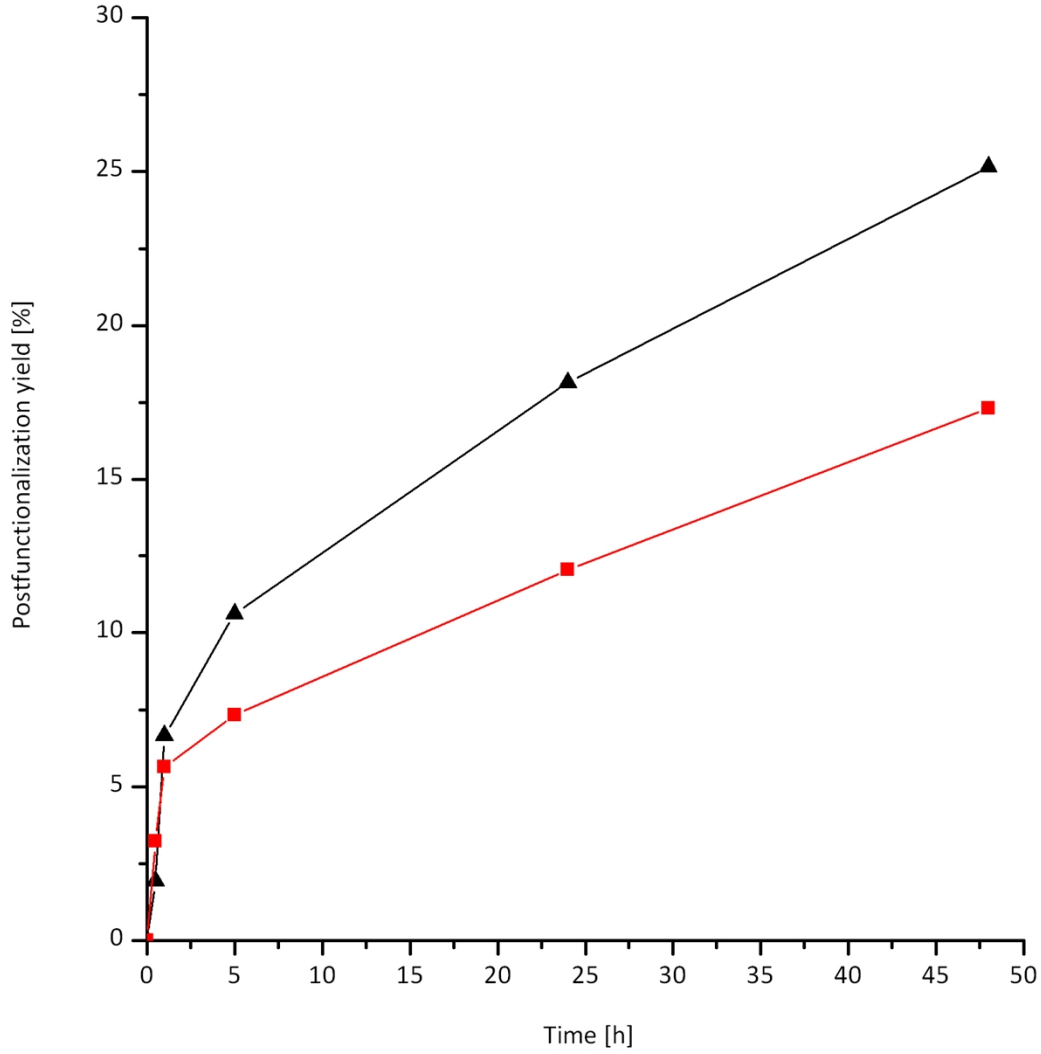


Fig. S4: *Postfunctionalization yield of MIL-101(Al)-NH_2 (1 eq.) functionalized with acetic acid (2 eq.) employing peptide coupling reagent PyBroP® (2 eq.) as well as 6 eq. (**black**) or 2 eq. Hünig's base (**red**) in dichloromethane for 0.5 h, 1 h, 5 h, 24 h and 48 h.*

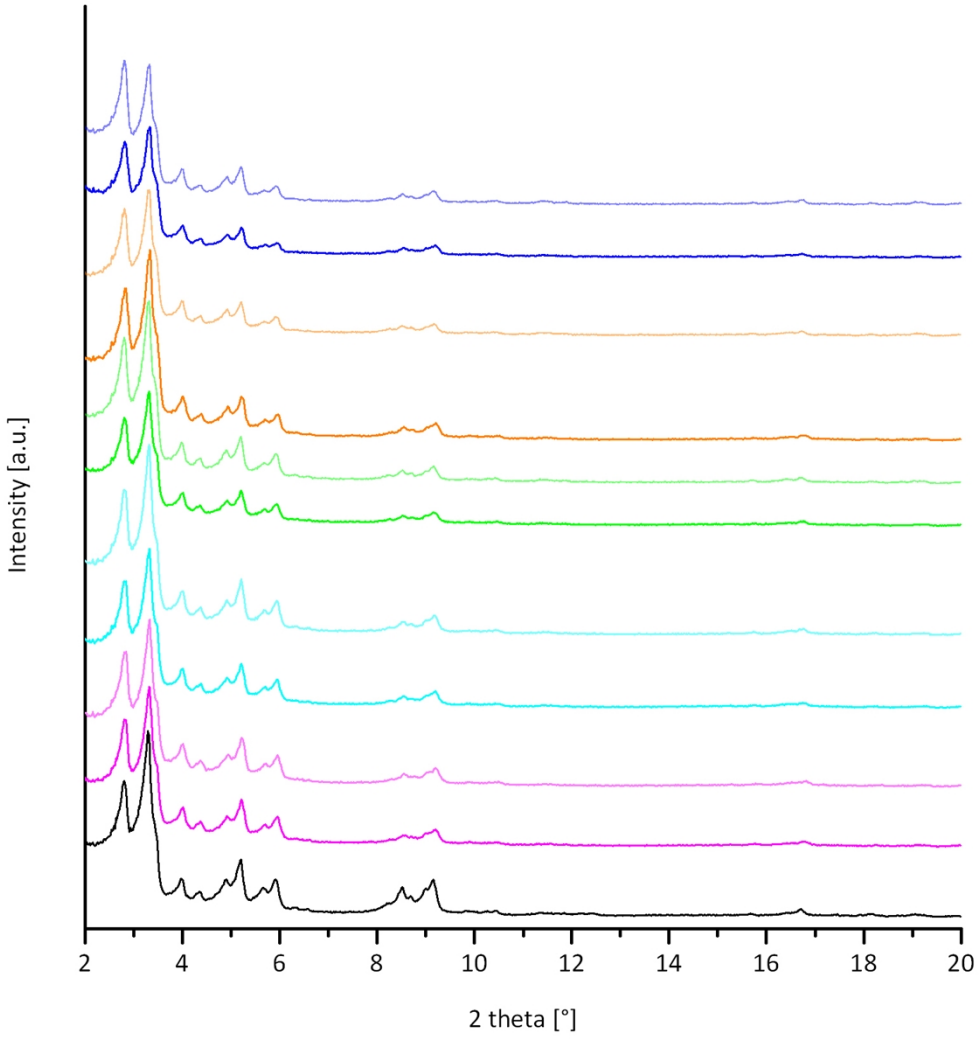


Fig. S5: *X-ray powder diffraction patterns of MIL-101(Al)-NH_2 (**black**) as well as postsynthetically modified MIL-101(Al)-NH_2 (1 eq.) with acetic acid (2 eq.) employing PyBroP® (2 eq.) as well as 6 eq. (**dark colours**) or 2 eq Hünig's base (**light colours**) in dichloromethane for 30 min (**magenta**), 60 min (**cyan**), 5 h (**green**), 24 h (**orange**) and 48 h (**blue**).*

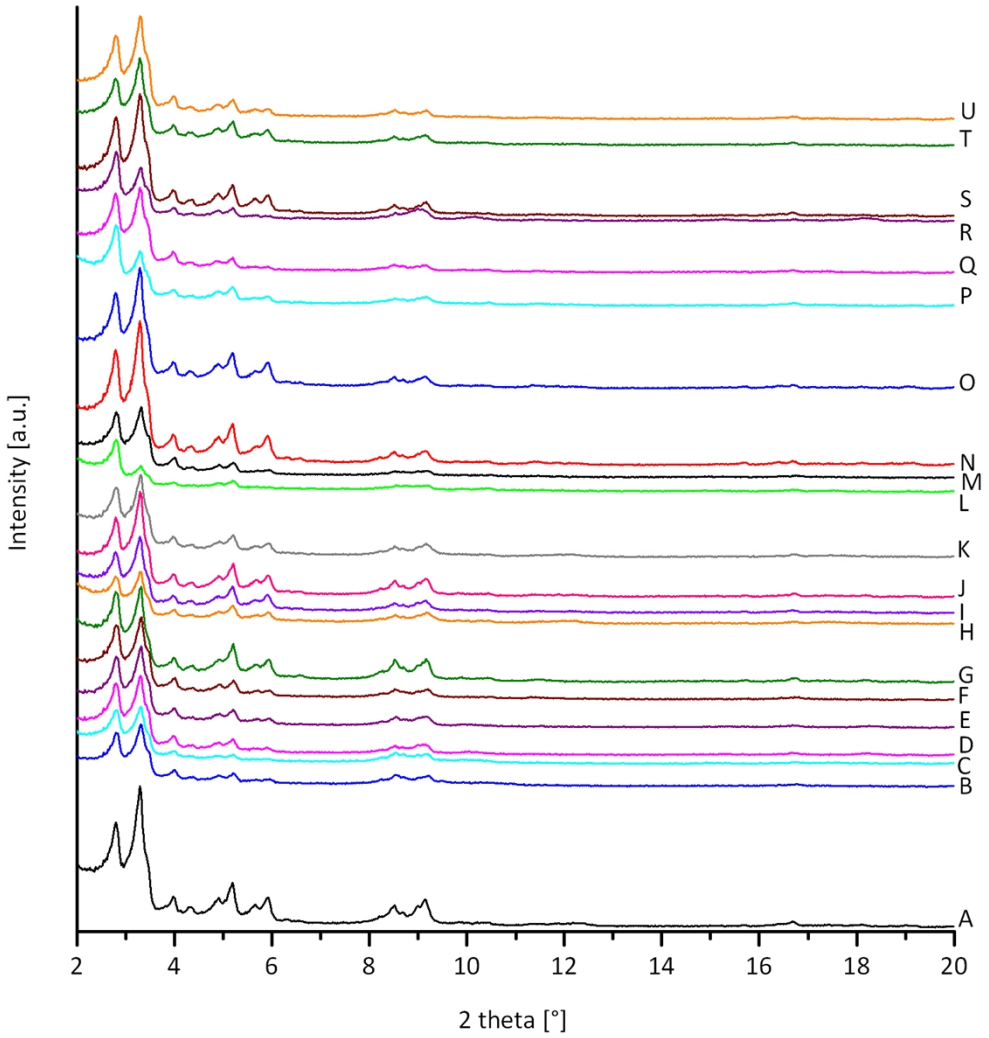


Fig. S6: *X-ray powder diffraction patterns of MIL-101(Al)-NH_2 (**A**) as well as postsynthetically modified MIL-101(Al)-NH_2 with DIC in dichloromethane 2 d at r.t. (**B**), DIC in dichloromethane 7 h reflux (**C**), DIC in DMF 2 d at r.t. (**D**), DIC in DMF 7 h at 50 °C (**E**), DIC in chloroform 7 h reflux (**F**), CDI in dichloromethane 2 d at r.t. (**G**), CDI in dichloromethane 7 h reflux (**H**), CDI in DMF 2 d at r.t. (**I**), CDI in DMF 7 h at 50 °C (**J**), CDI in chloroform 7 h reflux (**K**), PyBroP® in dichloromethane 2 d at r.t. (**L**), PyBroP® in dichloromethane 7 h reflux (**M**), PyBroP® in DMF 2 d at r.t. (**N**), PyBroP® in DMF 7 h at 50 °C (**O**), PyBroP® in chloroform 7 h reflux (**P**), HBTU in dichloromethane 2 d at r.t. (**Q**), HBTU in dichloromethane 7 h reflux (**R**), HBTU in DMF 2 d at r.t. (**S**), HBTU in DMF 7 h at 50 °C (**T**), HBTU in chloroform 7 h reflux (**U**).*

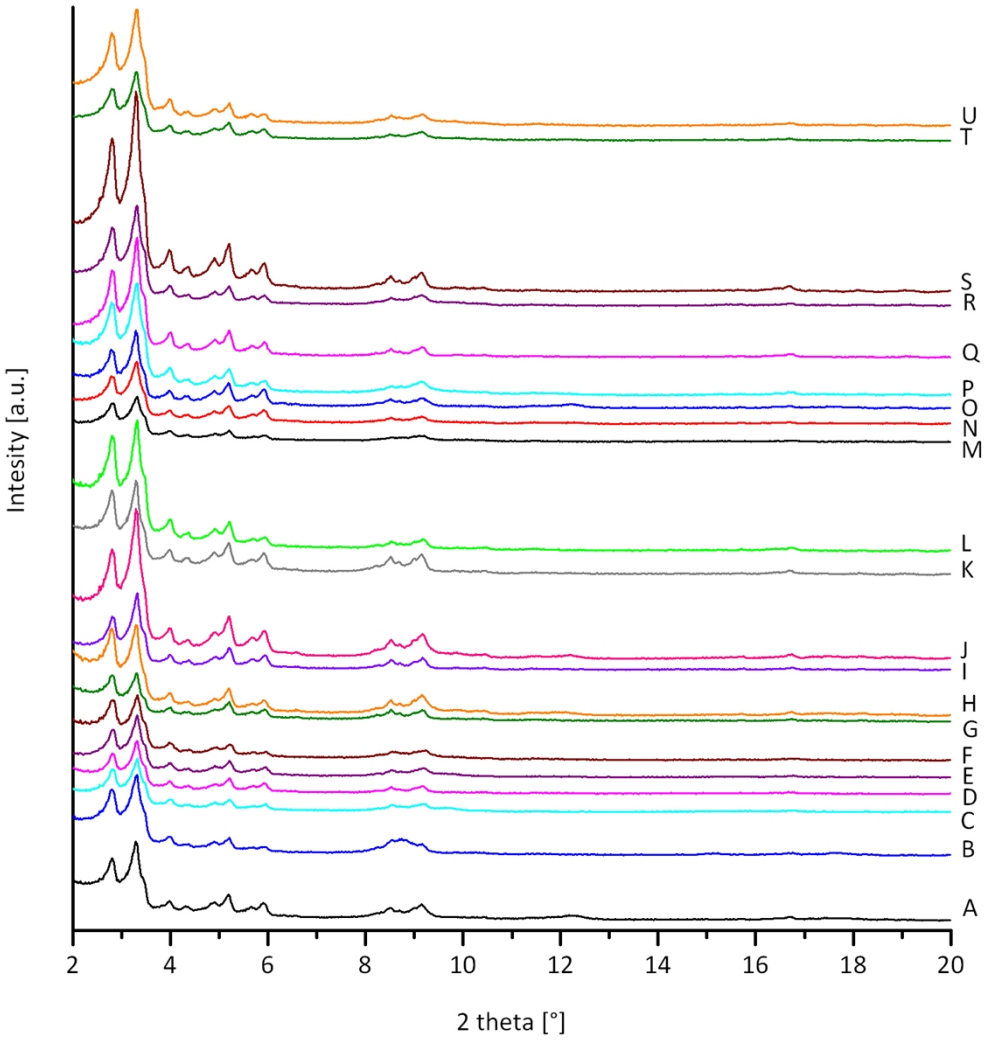


Fig. S7: *Repetition: X-ray powder diffraction patterns of MIL-101(Al)-NH_2 (**A**) as well as postsynthetically modified MIL-101(Al)-NH_2 with DIC in dichloromethane 2 d at r.t. (**B**), DIC in dichloromethane 7 h reflux (**C**), DIC in DMF 2 d at r.t. (**D**), DIC in DMF 7 h at 50 °C (**E**), DIC in chloroform 7 h reflux (**F**), CDI in dichloromethane 2 d at r.t. (**G**), CDI in dichloromethane 7 h reflux (**H**), CDI in DMF 2 d at r.t. (**I**), CDI in DMF 7 h at 50 °C (**J**), CDI in chloroform 7 h reflux (**K**), PyBroP® in dichloromethane 2 d at r.t. (**L**), PyBroP® in dichloromethane 7 h reflux (**M**), PyBroP® in DMF 2 d at r.t. (**N**), PyBroP® in DMF 7 h at 50 °C (**O**), PyBroP® in chloroform 7 h reflux (**P**), HBTU in dichloromethane 2 d at r.t. (**Q**), HBTU in dichloromethane 7 h reflux (**R**), HBTU in DMF 2 d at r.t. (**S**), HBTU in DMF 7 h at 50 °C (**T**), HBTU in chloroform 7 h reflux (**U**).*

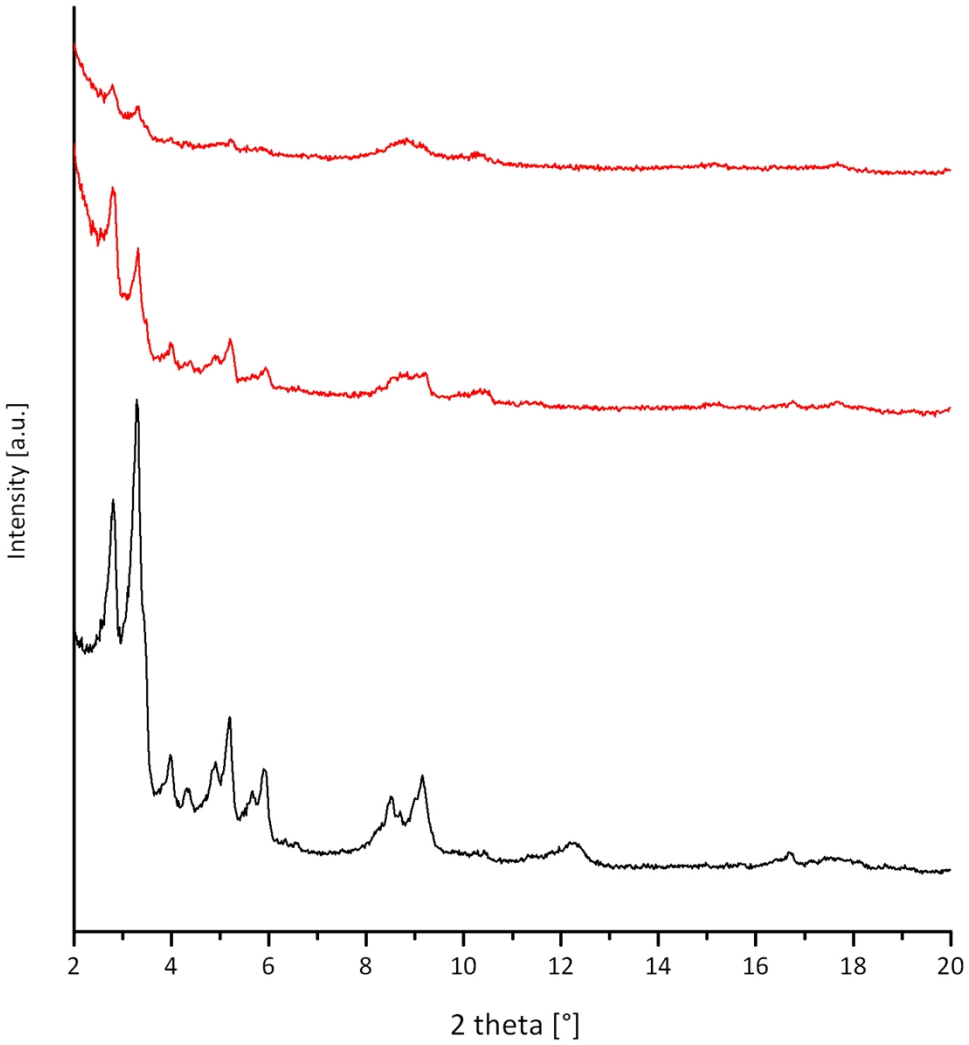


Fig. S8: *X-ray powder diffraction patterns of MIL-101(Al)-NH_2 (**black**) as well as 2 samples of MIL-101(Al)-NH_2 (1 eq.) incubated with acetic acid (5 eq.) in dichloromethane without coupling reagent for 2 d at r.t. (**red**).*

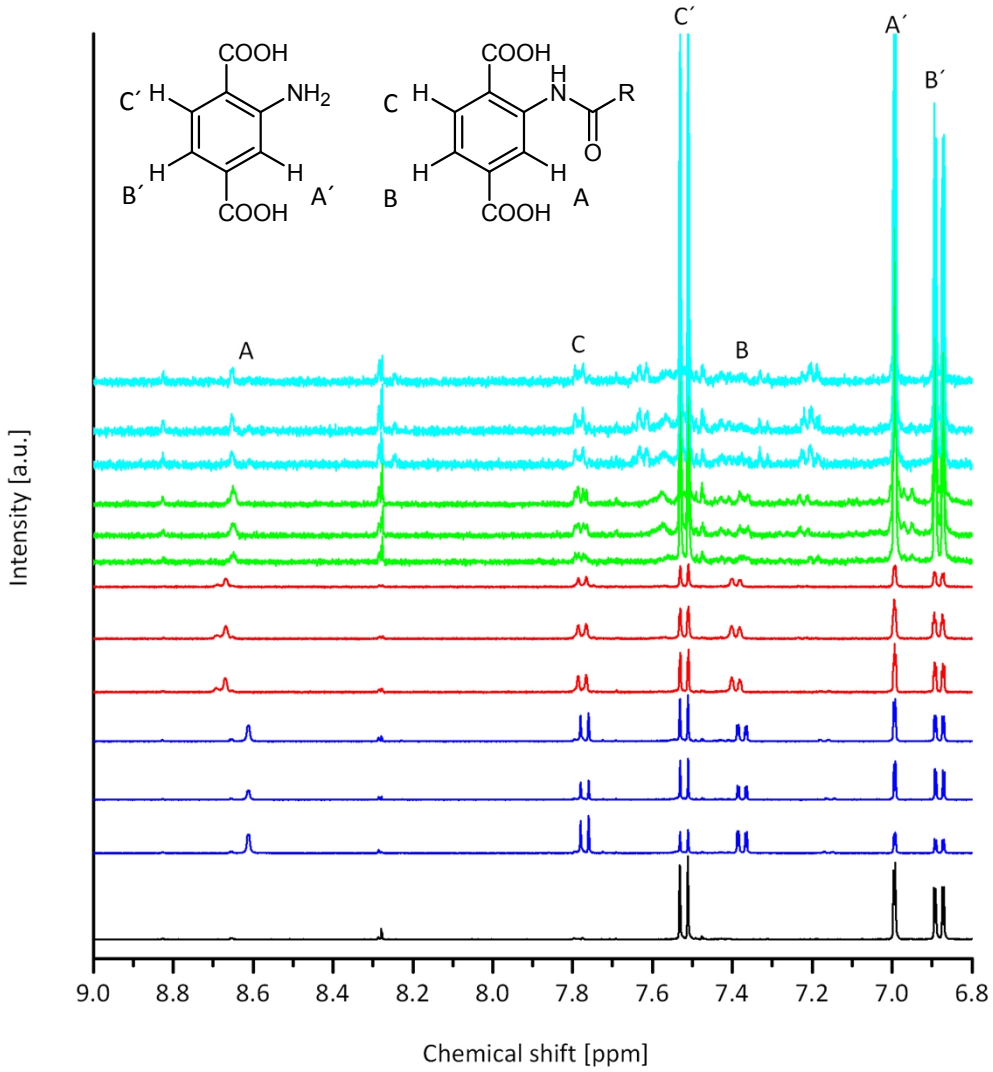


Fig. S9**:** *NMR spectra (6.8 – 9.0 ppm) of MIL-101(Al)-NH_2 (**black**) and MIL-101(Al)-NH_2 postfunctionalized with acetic acid (**blue**), Boc-Gly-OH (**red**), acetylsalicylic acid (**green**) or chlorambucil (**cyan**) employing DIC after purification by Soxhlet extraction (three repetitions each). Not labelled peaks belong to slight impurities in the MOF-structure already reported for an amino functionalized MOF synthesized in DMF at elevated temperature.* [4]

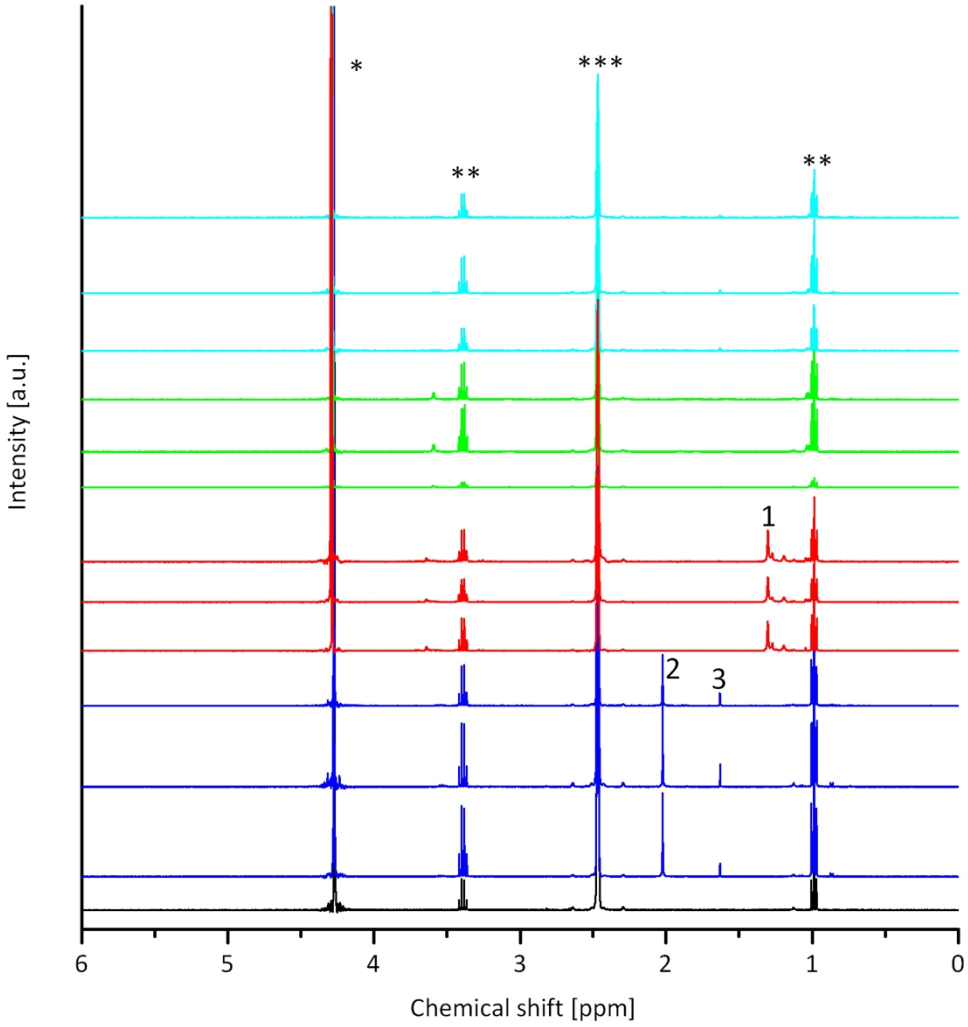


Fig. S10: *NMR spectra (0 – 6 ppm) of MIL-101(Al)-NH_2 (**black**) and MIL-101(Al)-NH_2 postfunctionalized with acetic acid (**blue**), Boc-Gly-OH (**red**), acetylsalicylic acid (**green**) or chlorambucil (**cyan**) employing DIC after purification by Soxhlet extraction (three samples each). Marked signals are: *water, **ethanol, ***solvent residual peak DMSO-d_6, 1: tert-butyl group of 2-aminoterphthalic acid postfunctionalized with Boc-Gly-OH, 2: methyl group of 2-amino-terphthalic acid postfunctionalized with acetic acid, 3: acetic acid.*

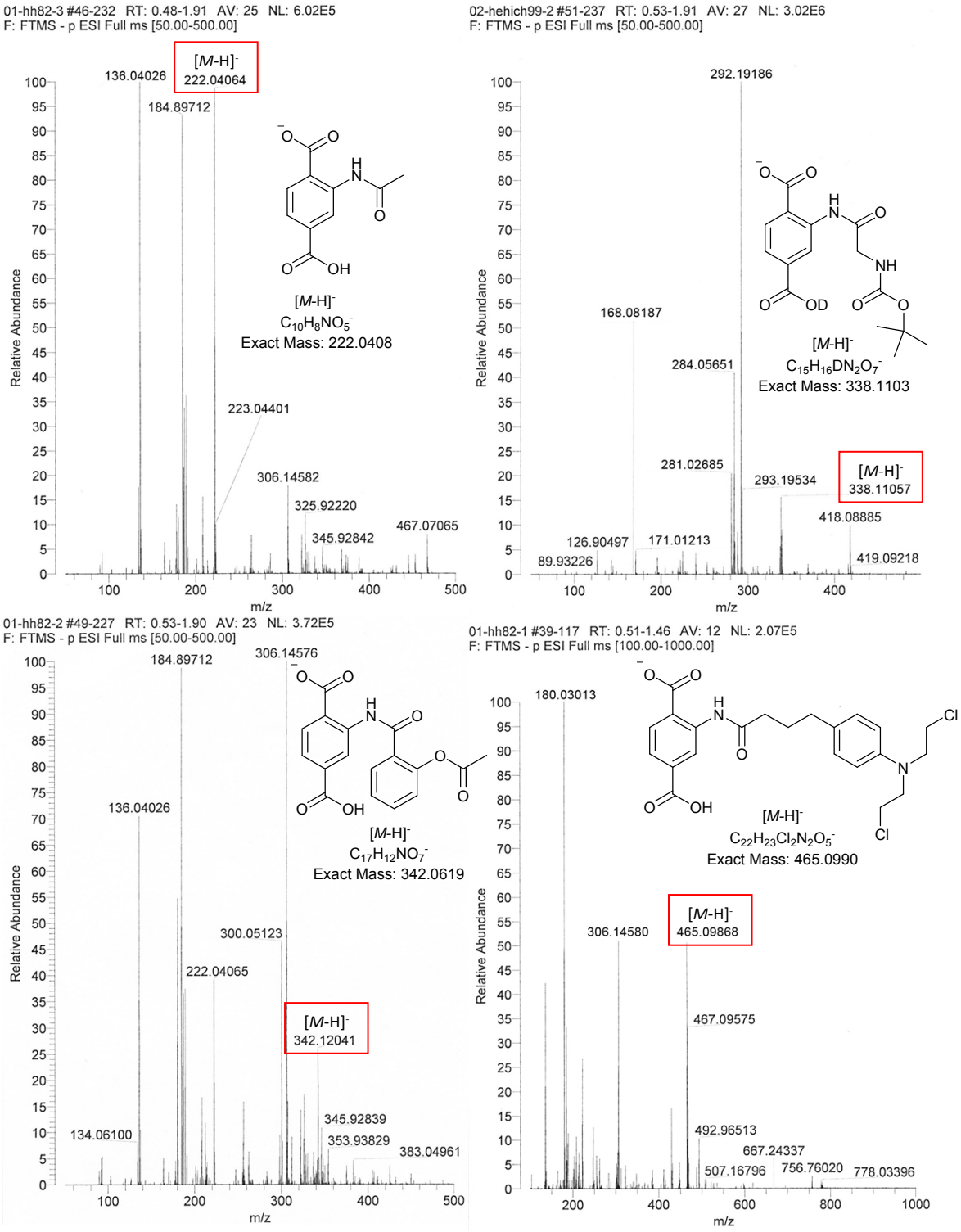


Fig. S11: *Mass spectrometric analysis (ESI, negative mode) of digested MIL-101(Al)-NH_2 samples postfunctionalized with acetic acid (**top, left**), BocGlyOH (**top, right**), acetylsalicylic acid (**bottom, left**) or chlorambucil (**bottom, right**) employing DIC.*

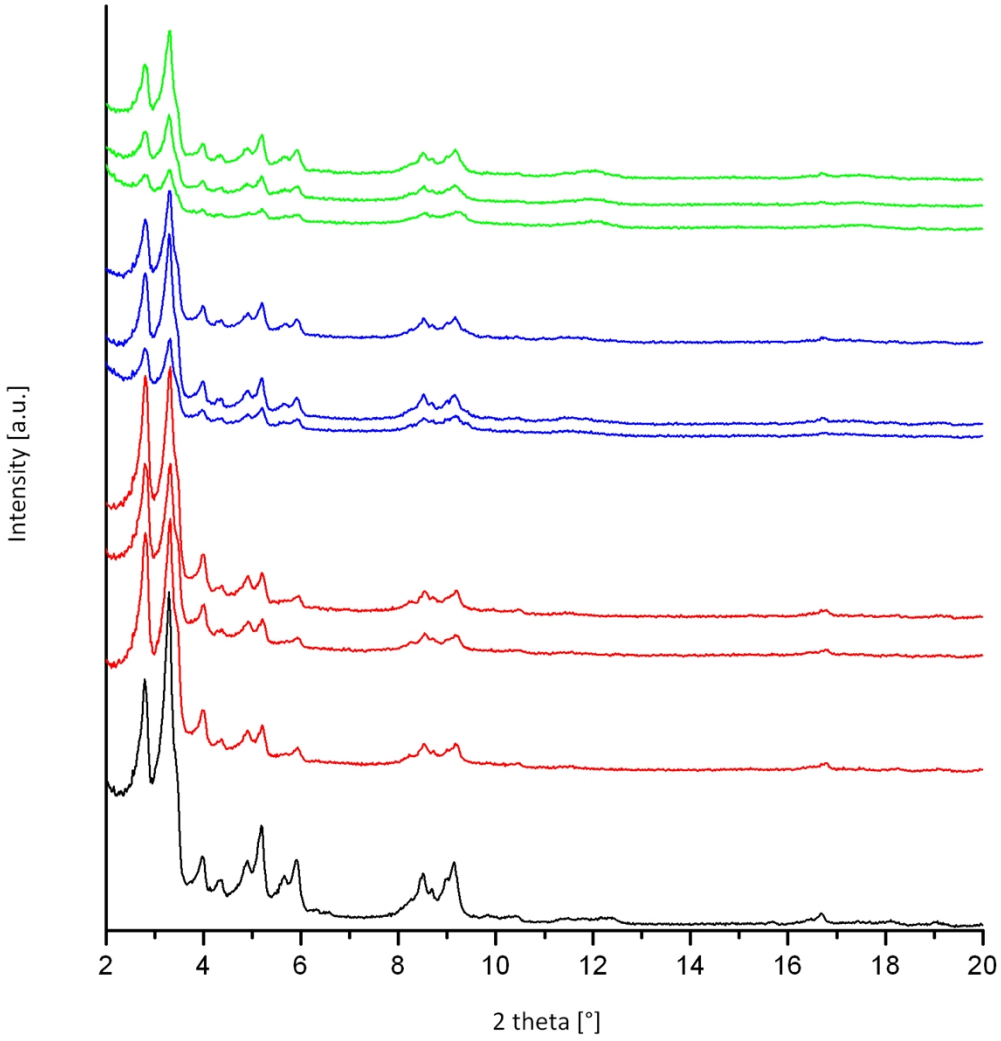


Fig. S12: *X-ray powder diffraction patterns of MIL-101(Al)-NH_2 (**black**) as well as postsynthetically modified MIL-101(Al)-NH_2 employing DIC in dichloromethane at r.t. for 2 d with Boc-Gly-OH (**red**), acetylsalicylic acid (**blue**) or chlorambucil (**green**) after purification by Soxhlet extraction. Postsynthetic modifications were carried out 3 times for every carbonic acid with the same MOF-batch.*

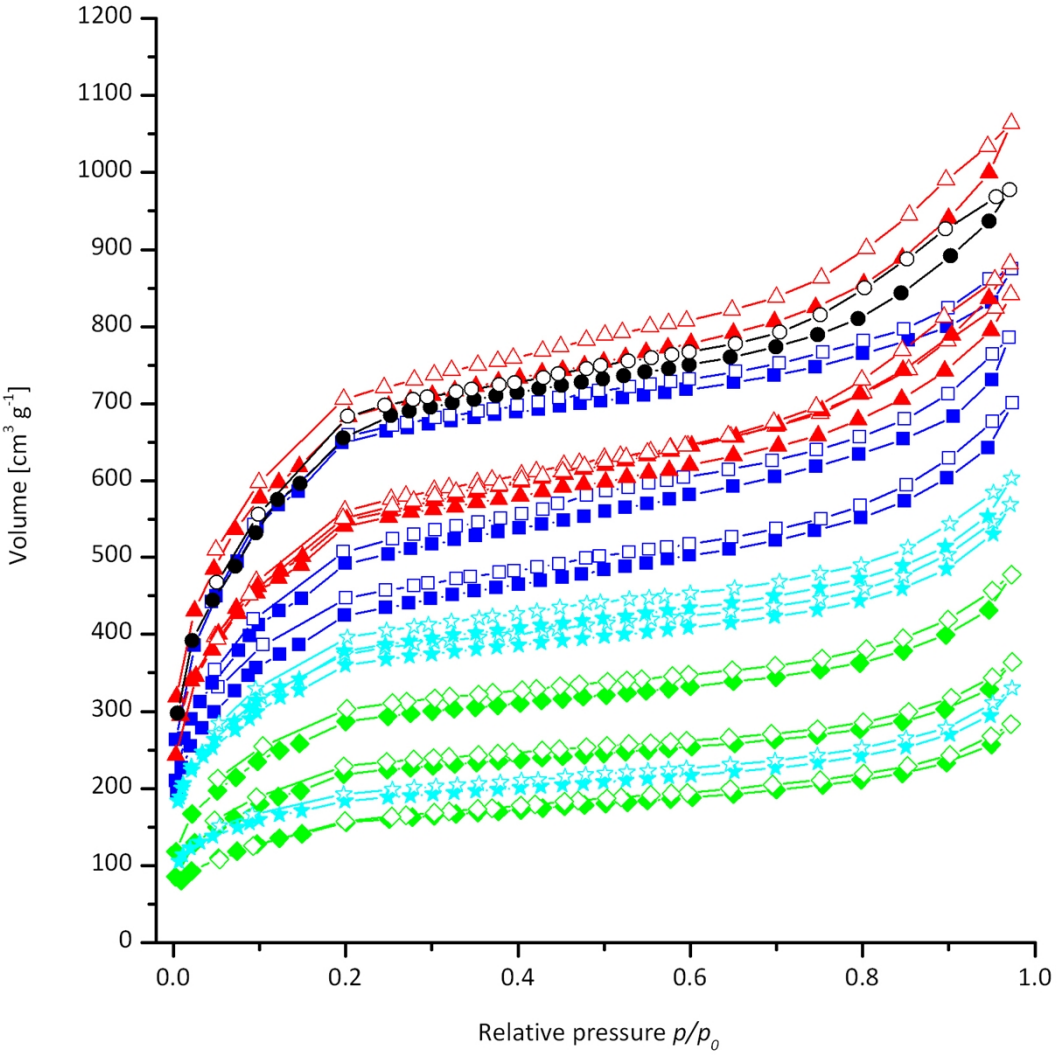


Fig. S13: *Nitrogen sorption isotherms at 77 K of MIL-101(Al)-NH_2 (□,□) as well as postsynthetically modified MIL-101(Al)-NH_2 employing DIC in dichloromethane at r.t. for 2 d with acetic acid (□,□), Boc-Gly-OH (□,□), acetylsalicylic acid (□,□) and chlorambucil (□,□) after purification by Soxhlet extraction. Filled symbols represent adsorption isotherms, empty symbols represent desorption isotherms.*

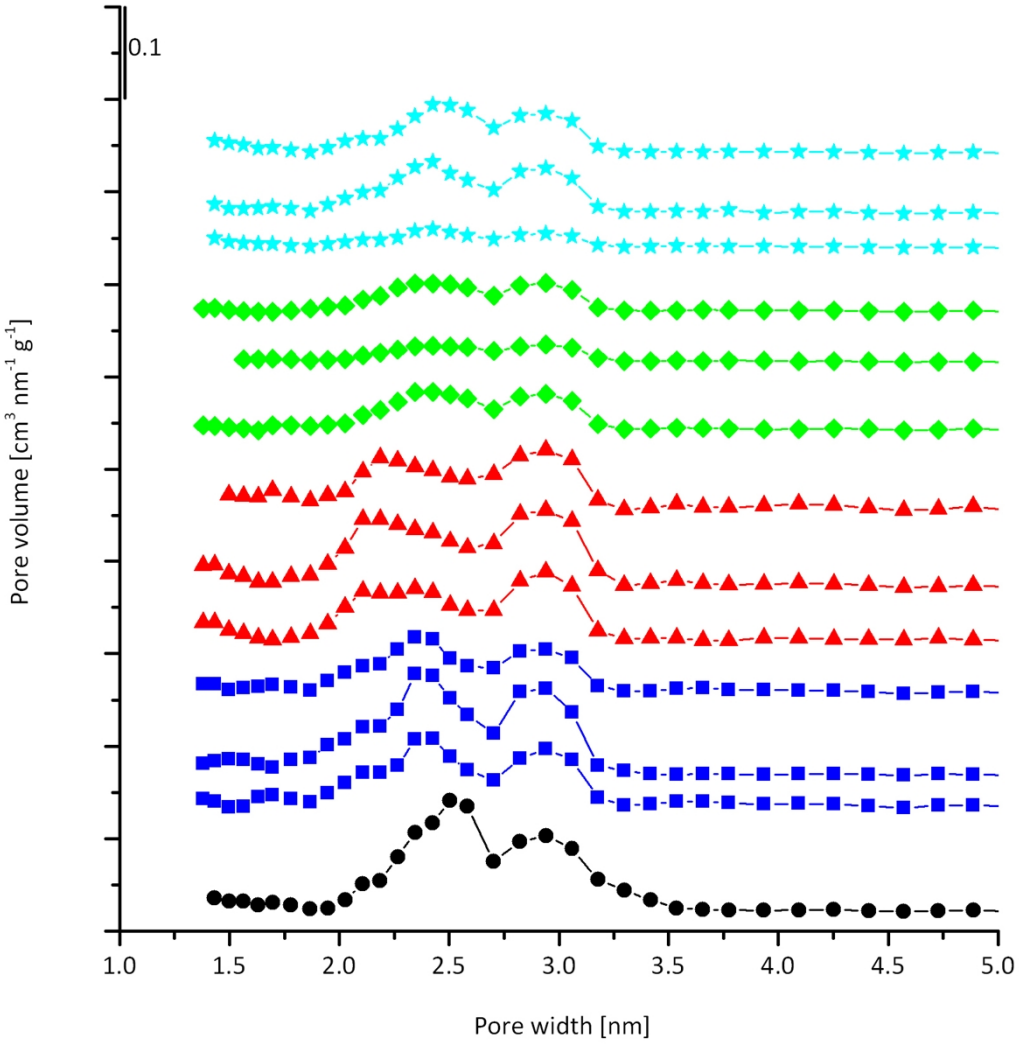


Fig. S14: *NLDFT pore size distribution of MIL-101(Al)-NH_2 (□) as well as postsynthetically modified MIL-101(Al)-NH_2 employing DIC in dichloromethane at r.t. for 2 d with acetic acid (□), Boc-Gly-OH (□), acetylsalicylic acid (□) and chlorambucil (□) after purification by Soxhlet extraction. Measurements were carried out three times for every carbonic acid functionalized employing the same MOF-batch (Boc-Gly-OH, acetylsalicylic acid, chlorambucil) or different MOF batches (acetic acid).*

Table S3: *BET surface areas and total pore volumes measured at p/p_0 0.30 of MIL-101(Al)-NH_2 samples functionalized with acetic acid, Boc-Gly-OH, acetylsalicylic acid and chlorambucil employing DIC. T.p.v stands for total pore volume.*

Reagent	T.p.v before PSM [cm^3/g]	T.p.v after PSM [cm^3/g]	BET before PSM [m^2/g]	BET after PSM [m^2/g]	Ratio after / before PSM [%]
1 Acetic acid	0.79	0.69	1781	1553	87
2 Acetic acid	1.24	1.04	2792	2410	86
3 Acetic acid	0.91	0.80	2059	1806	88
1 Acetylsalicylic acid		0.46		1065	52
2 Acetylsalicylic acid		0.25		573	28
3 Acetylsalicylic acid		0.35		815	40
1 Chlorambucil		0.30		659	32
2 Chlorambucil		0.61		1389	67
3 Chlorambucil		0.58		1315	64
1 Boc-Gly-OH	1.08	1.10	2442	2466	101
2 Boc-Gly-OH		0.89		1984	81
3 Boc-Gly-OH		0.87		1961	80

5. Notes and references

1 M. Hartmann and M. Fischer, *Microporous Mesoporous Mater.*, 2012, **164**, 38.

2 G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé and I. Margiolaki, *Science*, 2005, **309**, 2040.

3 Calculator Plugins were used for structure property prediction and calculation, Marvin 6.1.0, 2013, ChemAxon (*http://www.chemaxon.com*). Calculation was carried out for the molecular conformation with lowest energy based on van der Waals radii of the atoms.

4 S. J. Garibay and S. M. Cohen, *Chem. Commun.*, 2010, **46**, 7700.