Supporting Information

Vectorial Catalysis in Surface-Anchored Nanometer-Sized Metal–Organic Frameworks-Based Microfluidic Devices

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Supporting Information

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1. Analytical Techniques, Calculation, and Characterization Techniques

**Dynamic Light Scattering (DLS)**

For Dynamic Light Scattering, stock solutions of the MOFs were prepared by immersing 2 mg NMOF in 2 mL ethanol and sonicated for 5 min. Afterwards, 100 µL of the stock solution were mixed with 2 mL ethanol and transferred to a DLS cuvette. The measurement was performed on a Zetasizer Nano by Malvern Instruments and the data was analyzed and evaluated with the Zetasizer Software 7.11 by Malvern Instruments. The shown distributions are the number distributions calculated by the program and plotted with python.

**Gas chromatography (GC).**

GC is performed with an Agilent Technologies 7890B GC with a flame ionization detector (FID). The substance separation occurs via a capillary column HP-5 (length 30 m, inside diameter 0.32 mm, film 0.25 µm, stationary phase (5% phenyl) methylpolysiloxane)). Samples are prepared by taking ~50 µL aliquot from the reaction mixture, adding 1.45 mL of the respective solvent, filtering through a syringe filter in order to remove the MOF catalyst.

**Gas chromatography calibration.**

To evaluate the amount of benzaldehyde dimethyl acetal (BADMA), benzaldehyde (BA), 2-phenyl-2-((trimethylsilyl)oxy)acetonitrile (BAOTMS) and 2-benzylidene malononitrile (BACN) calibration curves were measured. Therefore, several solutions with 0, 0.5, 1, 2.5, 5, 10, 20 µmol/L of these compounds were prepared and measured by GC. Afterwards, the regression lines are calculated for each compound.

\[
y(BADMA) = 96.5 \cdot x + 6.9 \quad (R^2 = 0.9996) \\
y(BA) = 59.8 \cdot x + 3.4 \quad (R^2 = 0.9997) \\
y(BAOTMSCN) = 108.3 \cdot x - 1.4 \quad (R^2 = 0.9997) \\
y(BACN) = 95.4 \cdot x + 6.1 \quad (R^2 = 0.9985)
\]

For the GC calibration, BADMA, BA, and malononitrile (MAN) were purchased from commercial vendors, and BACN and BAOTMSCN were synthesized according to literature procedures (see chapter S2).

**Inductively coupled plasma mass spectrometry (ICP-MS).**

To obtain an accurate quantification of Zr and Cr amount anchored to PDMS and silicon wafers, ICP-MS for zirconium is conducted on an Agilent Technologies 7900 ICP-MS. The respective samples are immersed in concentrated 7.5 mL nitric acid and 2.5 mL H₂O₂ (30 w% in H₂O) (v%) and treated in the microwave at 150 °C for 5 min. Subsequently, 0.5 mL of each solution was diluted 1/20 and 1/200 times, respectively, with ultra-pure water containing 1.65 % (v%) HCl. Each solvent used is extra pure and contains no traces of zirconium. Ninety two (92) Zr and fifty two (52) Cr were used as target masses for the analyte and eleven (115) In for the internal standard. Zr/Cr quantification was carried out in He CCT-mode to avoid isobaric and polyatomic interferences. The detection limit for Zr was 2.997 ng L⁻¹ (0.15 ng). Calibration was performed in the range of 0 ng L⁻¹ to 20 µg L⁻¹ Zr (0 ng to 1 µg Zr) and 50-500 ppt for Cr. Measurements were carried out
three times for each sample by Dominik Huber, M.Sc. from the research group Analytical Chemistry (Technical University of Munich) lead by Prof. Schuster.

**Nitrogen adsorption measurements**

Adsorption measurements with N$_2$ (99.999 vol%) at 77 K were carried out on a 3Flex Physisorption from Micromeritics Instrument Corp., which uses a manometric method to determine the amount adsorbed under equilibrated gas pressure. Adsorption data was processed using the 3Flex Software Version 5.01 by Micromeritics Instrument Corp. and plotted with Python. Activated samples (3h, 150°C) were transferred under dry Ar atmosphere into preweighed sample tubes and capped with Micromeritics CheckSeals. Samples were subsequently activated again at 150°C for 3 h under a dynamic vacuum of ~ 10$^{-3}$ mbar using a SmartVac Prep by Micromeritics Instrument Corp. to ensure the absence of unwanted adsorbates and identical pre-measurement states of all samples. The mass of the adsorbent was then recorded, generally in the range of 25 mg. Free space of the sample tube is determined prior to measuring each adsorption isotherm using helium (99.999 vol%). A liquid nitrogen bath is used for measurements at 77 K. The apparent surface area of the samples was derived using the Brunauer-Emmett-Teller (BET) model, is hence given as the ‘BET area’ and based on N$_2$ isotherms measured at 77 K. To determine this value for microporous materials, care was taken to adhere to the Rouquerol criteria.

**Nuclear Magnetic Resonance (NMR)**

NMR spectra are recorded by a Bruker Ultrashield DRX400 (1$^1$H: 400.13 MHz, 13$^C$: 100.62 MHz) at ambient temperature (298 K). The 1$^1$H NMR spectroscopic chemical shifts δ are reported in ppm relative to tetramethylsilane. 1$^1$H spectra are calibrated against the residual proton and natural abundance carbon resonances of the respective deuterated solvent as an internal standard (CDCl$_3$: δ (1$^1$H) = 7.26 ppm).

The following abbreviations are used to describe signal multiplicities: s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet.

**Powder X-Ray Diffraction (PXRD)**

PXRD measurements are performed on a silicon single-crystal wafer cut in [510] direction using Bragg-Brentano geometry in a PANalytical Empyrean diffractometer equipped with a PANalytical PIXcel 1D detector.

X-ray Cu Kα radiation is used and Kβ radiation is removed by a Ni-filter. Voltage and intensity are 45 kV and 40 mA, respectively. The measurement range is from 5.0° to 50.0° (2θ) with a scan speed of 0.015 degrees per second.

**Scanning Electron Microscopy (SEM)**

SEM images are obtained with a Jeol JSM-7500F field emission scanning electron microscope with the Gentle Beam mode. SEM measurements were performed at room temperature with a JEOL Ltd. JAMP-9500F system. SEM spectra were acquired with a primary beam of 2 keV.

**Surface preparation**

(a) **Silicon substrates.**
The silicon wafers purchased from Sigert Wafers (100) were cut into 1.0 cm x 1.0 cm pieces. Prior to reaction, the silicon surfaces were cleaned by sonication in acetone, ethanol, and DCM for 5 min each. Afterwards, they were dried under argon.

**Activation of Si.**

In order to enhance the hydrophilicity of the substrates and clean the surface from organic impurities, the surfaces are activated by piranha acid. For the activation in piranha acid, the substrates are treated with H$_2$SO$_4$ (96 w% in H$_2$O)/H$_2$O$_2$ (30 w% H$_2$O$_2$(aq)) (7:3 v%) (Caution: Piranha is a very strong oxidizer and can react explosively with organic compounds) at room temperature for 30 min. Afterwards, the substrates are thoroughly washed with deionized water and ethanol and blow-dried for further use.

**Curing of PDMS.**

15 g Sylgard 184 silicone elastomer base and 1.5 g (10:1 w%) Sylgard 184 silicone elastomer curing agent are thoroughly mixed for three minutes. Afterwards, the mixture is poured into a petri dish and degassed in a desiccator under a moderate vacuum. For the curing procedure, the dish is placed in an oven for one hour at 70 °C. If needed the PDMS was cut into 1 cm x 1 cm pieces after cooling down to room temperature.

**Activation of PDMS.**

For the surface activation prior to the functionalization and cleaning, the PDMS samples were treated with H$_2$O/H$_2$O$_2$ (30 w% H$_2$O$_2$(aq))/HCl (37 w% HCl(aq)) (5:1:1 v%) for 30 min at room temperature. The surfaces are rinsed with deionized water, ethanol and dried with pressurized air.

**Turnover Frequency Calculations**

The following formulas were used to calculate the TOFs of the catalysts, whereby the turnover frequency (1) is defined by the initial reaction rate ($r'$) (2) divided by the amount of catalyst ($n$ catalyst). The initial reaction rate itself is defined as the difference between the concentration of BADMA at the beginning of the reaction ($t_0$) and the end of the microfluidic device ($t_1$) divided by the difference between $t_1$ and $t_0$.

$$TOF = \frac{r'[\text{nmol}]}{n_{\text{catalyst}}[\text{nmol}]}$$

$$r' = \frac{c(BADMA)_{t_1} - c(BADMA)_{t_0}}{t_1 - t_0}$$

The following assumptions were made for the various parameters:

For the $n_{\text{catalyst}}$ per area (in cm$^2$) we use:

$n_{\text{catalyst/area}}$ (MIL-101-NH$_2$) = 0.67 ± 0.12 nmol/cm$^2$ (see ICP-MS);

$n_{\text{catalyst/area}}$ (MIL-101) = 1.60 ± 0.17 nmol/cm$^2$ (see ICP-MS)

We assume that the catalytically active centre for the acetal hydrolysis is the protonated NH$_2$ or SO$_3$H group. As we cannot determine the linker itself by ICPMS, we assume that the linker and metal are in a 1:1 ratio, as it is in the molecular formula of the MOF unit: $(\text{Cr}_3\text{O(OH)}_2(\text{H}_2\text{O})(\text{bdc-NH}_2)_3)/ (\text{Cr}_3\text{O(OH)}_2(\text{H}_2\text{O})(\text{bdc-SO}_3\text{H})_3)$. Similarly, we assume that the Knoevenagel condensation is catalyzed by the basic ligands (OH-, H$_2$O) coordinating to the metal centre, for which also a 1:1 ratio of Cr:L is assumed. Additionally, we assumed that the ~1 cm$^2$ SA-NMOF PDMS substrates possess an actual area of 2 cm$^2$, as the PDMS substrates
show functionalized top and bottom sites. Therefore, the amount of accessible catalyst is divided by a factor of 2. (see equation 4,5)

For the area of the channel surface that is covered with the respective catalyst we applied the following calculations.

\[ A_{\text{catalyst}} (\text{MIL-101-NH}_2) = 30 \text{ mm}^2; \quad A_{\text{catalyst}} (\text{MIL-101}) = 30 \text{ mm}^2; \]

The accessible area of the SA-NMOFs is determined by the dimensions of the channels (\( A = 9 \mu\text{L}/0.15 \text{ mm} \) (V/height)=60 mm²), where half of the area is covered with MIL-101-NH₂ and the other half with MIL-101.

The following equation (3) can be used to calculate \( n_{\text{catalyst}} \) for the TOF calculations:

\[
 n_{\text{catalyst}} [\text{nmol}] = n_{\text{catalyst}/\text{Area}} [\text{nmol/cm}^2] \cdot A [\text{cm}^2] \quad (3)
\]

\[
 n_{\text{catalyst}} (\text{MIL} - 101 - \text{NH}_2) [\text{nmol}] = \frac{0.67 \text{ nmol}}{2} \cdot 0.30 \text{ cm}^2 = 0.10 \text{ nmol} \quad (4)
\]

\[
 n_{\text{catalyst}} (\text{MIL} - 101) [\text{nmol}] = \frac{1.60 \text{ nmol}}{2} \cdot 0.30 \text{ cm}^2 = 0.24 \text{ nmol} \quad (5)
\]

At the start of the reaction, the amount of BADMA in the channel was:

\[ n_{0h} = 1120 \text{ nmol} \] (in 9 µL)

The material quantity of BADMA at the beginning of the experiment was determined for 9 µL as this is the volume of the microfluidic reactor with dimensions of 14 coils (13 mm x 0.3 mm x 0.15 mm; 9 µL) (further details about the reactor see Figure S1). Subsequently, the relative quantity of BADMA, BA, and BACN at the end of the reactor was determined by GC/MS. To calculate the amount of BA, we added the amount of BACN as this was formed from BA.

Yield \( 30s \) (BA) = 12.8 %

Yield \( 30s \) (BACN) = 72.3 %

\[
 n_{30s}(\text{BADMA}) = \frac{100 - Y_1 - Y_2}{100} \cdot c_0 = \frac{100 - 12.8 - 72.3}{100} \cdot 1120 \text{nmol} = 167 \text{ nmol}
\]

\[
 n_{30s}(\text{BA}) = \frac{Y(\text{BA}) + Y(\text{BACN})}{100} \cdot c_0 = \frac{12.8 + 72.3}{100} \cdot 1120 \text{nmol} = 953 \text{ nmol}
\]

\[
 n_{30s}(\text{BACN}) = \frac{Y}{100} \cdot c_0 = \frac{72.3}{100} \cdot 1120 \text{nmol} = 810 \text{ nmol}
\]

Then we determined the initial reaction rates, with the measured mean retention times of the solution in the microfluidic reactor.

\[
 r'(\text{BA}) \left[ \frac{\text{nmol}}{\text{h}} \right] = \frac{953 \text{ nmol}}{0.00833h} = 1.14 \cdot 10^5 \text{ nmol/h}
\]

\[
 r'(\text{BACN}) \left[ \frac{\text{nmol}}{\text{h}} \right] = \frac{810 \text{ nmol}}{0.00833h} = 9.72 \cdot 10^4 \text{ nmol/h}
\]
For the calculation of the TOF values, we assumed that acetal hydrolysis is exclusively catalyzed by MIL-101-NH$_2$, and the Knoevenagel condensation is exclusively catalyzed by MIL-101, which is not entirely correct, but a reasonable approximation as judged from our control experiment displayed in Figure 2d.

\[
TOF(c{\text{at}}}1) = \frac{1.14 \cdot 10^5 \text{nmol}}{0.10 \text{nmol}} \cdot \frac{1}{h} = 1.13 \cdot 10^6 \frac{1}{h}
\]

\[
TOF(c{\text{at}}}2) = \frac{9.72 \cdot 10^4 \text{nmol}}{0.24 \text{nmol}} \cdot \frac{1}{h} = 4.05 \cdot 10^5 \frac{1}{h}
\]

\[
\Delta TOF(c{\text{at}}}1) = \left( \frac{\Delta n}{n} \right) \cdot TOF = \left( \frac{0.12 \text{nmol}}{0.67 \text{nmol}} \right) \cdot 1.13 \cdot 10^6 \frac{1}{h} = 0.20 \cdot 10^6 \frac{1}{h}
\]

\[
\Delta TOF(c{\text{at}}}2) = \left( \frac{\Delta n}{n} \right) \cdot TOF = \left( \frac{0.17 \text{nmol}}{1.60 \text{nmol}} \right) \cdot 4.05 \cdot 10^5 \frac{1}{h} = 0.43 \cdot 10^5 \frac{1}{h}
\]

The values were calculated for the various samples and are summed up in Table S4.
Calculation of the diffusion length

With this point source one-dimensional diffusion equation based on the random-walk equation (6) can be used to calculate the average displacement of particles in a 1-D process <x> within a given time t in a solvent with the concentration c and the diffusion constant D:\(^5,^6\)

\[ x > 2 \sqrt{\frac{Dt}{\pi}} \quad (6) \]

The average particle displacement <x> can give an insight if the substrate can move from one side of the microfluidic channel to the other to the other to supply the immobilized SA-NMOFs with new substrates.

First, we need to calculate the diffusion coefficient which can be done with the Einstein-Stokes Equation (7):

\[ D = \frac{kT}{6\pi\eta a} \quad (7) \]

\[ D = \frac{1.38 \cdot 10^{-23} \text{Kg}^2 \text{m}^{-2} \text{s}^{-1} \text{K}^{-1} \cdot 298 \text{K}}{6\pi \cdot 0.82 \cdot 10^{-3} \text{Kg}^{-1} \text{m}^{-1} \text{s}^{-1} \cdot 0.78 \cdot 10^{-9} \text{m}^{-1}} = 3.41 \cdot 10^{-10} \text{m}^2 \text{s}^{-1} \]

Whereby \( k \) is the Boltzmann constant \( (1.38 \cdot 10^{-23} \text{Kg}^2 \text{m}^{-2} \text{s}^{-1} \text{K}^{-1} ) \), \( T \) is the temperature 298 K, \( \eta \) is the viscosity of the solvent \( (\eta(\text{acetonitrile/H}_2\text{O (1:1 v/v)}) = 0.82 \cdot 10^{-3} \text{Kg}^{-1} \text{m}^{-1} \text{s}^{-1} ) \) and the diameter of the substrate is \( 0.78 \cdot 10^{-9} \text{m} \) determined by molecular mechanics simulations (MM2) with Chem3D. Finally resulting in the diffusion coefficient of \( 3.41 \cdot 10^{-10} \text{m}^2 \text{s}^{-1} \).

Together with the retention time, these values can then be used to calculate the diffusion length <x> as 114 µm.

\[ x > 2 \sqrt{\frac{3.41 \cdot 10^{-10} \text{m}^2 \text{s}^{-1} \cdot 30 \text{s}}{\pi}} \]

\[ x > 114 \mu \text{m} \]

This calculated average particle displacement is 1.5 times higher than the radius of the microfluidic device (75 µm), therefore the diffusion of the substrate from the solution to the SA-NMOFs not expected to be a limiting factor.
2. Synthetical Procedures, Microfluidic Device Manufacturing

2.1. NMOFs

**MIL-101(Cr)**\(^{[7]}\) 740.4 mg Cr(NO\(_3\))\(_3\)·9 H\(_2\)O (1.85 mmol, 1.0 equiv.) and 307.4 mg benzene dicarboxylic acid (1.85 mmol, 1.0 equiv.) were dispersed in 10 mL deionized water in a 50 mL microwave tube. After 10 min of stirring at room temperature, the reaction solution was heated with maximum power to a set temperature of 200 °C. After about 7 min the temperature reached 190 °C and was kept at that temperature for 1 min. After the reaction mixture was cooled down to room temperature, it was filtered over a Schott filter No. 2 to filter off unreacted benzene dicarboxylic acid. The colloidal green solution was centrifuged and the solution was replaced three times with fresh water (20 mL each) and three times with fresh ethanol (20 mL each).

**MIL-101-\(\text{SO}_3\text{H}(\text{Cr})\)**\(^{[8]}\) 0.376 g CrO\(_3\) (3.75 mmol, 1 equiv.) and 1 g monosodium-2,5-dicarboxybenzenesulfonate (H\(_2\)bdc-\(\text{SO}_3\text{Na}\)) (3.75 mmol, 1 equiv.) were dissolved in 15 mL H\(_2\)O and mixed with 230 µL 37 w% HCl\(_{\text{aq}}\) (0.273 g, 2.7 mmol, 0.75 equiv.). The reaction mixture was heated in a 20 mL autoclave to 180 °C for 6 days. After cooling to room temperature, the turquoise product was separated from the reaction mixture by centrifugation and washed with water and ethanol over a couple of days three times each. Afterwards, for the activation, the powder is placed at 150 °C for 12 h under an oil pump vacuum. Then, the powders were handled under inert conditions.

**MIL-101-\(\text{NH}_2\text{(Cr})\)**\(^{[9]}\) 1.25 g Cr(NO\(_3\))\(_3\)·9 H\(_2\)O (3.13 mmol, 1 equiv.) and 0.58 g 2-amino-terephthalic acid (H\(_2\)bdc-\(\text{NH}_2\)) (3.15 mmol, 1 equiv.) were dissolved in 17.5 mL H\(_2\)O. The reaction mixture was initially stirred for 3 h at room temperature and then heated in a 50 mL autoclave to 130 °C for 24 h. After cooling to room temperature, the yellow-green product was separated from the reaction mixture by centrifugation and washed with water and ethanol over a couple of days three times each. For the activation, the powder is placed at 150 °C for 12 h under an oil pump vacuum. Then, the powders were handled under inert conditions.

**Uio-66(Zr)**\(^{[10]}\) 21 mg zirconium oxychloride octahydrate (0.066 mmol, 1,0 equiv.) and 50 mg benzene dicarboxylic acid (0.30 mmol, 4.5 equiv.) were dissolved by sonication in 3 mL and 1 mL dimethylformamide (DMF). Then, both solutions were mixed, and 0.35 mL acetic acid (6.11 mmol, 20.4 equiv.) was added. Afterwards, the reaction mixture was kept at 90 °C for 12 h. The synthesis yields a white, colloidal solution. The solvent of the solution is exchanged by centrifugation three times with 4 mL of fresh DMF and three times with 4 mL ethanol each.
2.2. Surface Functionalization and NMOF Anchoring

For general surface preparation techniques, see chapter S1.

**Functionalization of PDMS substrates.**[^4] Amino terminated surfaces were fabricated by immersion of activated PDMS substrates in neat (3-aminopropyl)-triethoxysilane for 30 min at room temperature. Afterwards, the samples are washed with copious amounts of ethanol and deionized water and place in deionized water overnight. Alkyne terminated substrates were synthesized in a 2-step procedure, creating a chlorine terminated surface in the first step and replacing the chlorine in a second step by an alkyne group. In the first step, after activation (described in chapter S1), the PDMS substrates are immersed in neat (3-chloropropyl)triethoxysilane for 30 min at room temperature, followed by a thorough rinse of the substrate with ethanol and deionized water. In the second step, the chlorine functionalized substrates are immersed in an 18w% slurry of sodium acetylide in xylene/mineral oil for 5 h at 150 °C. The cooled substrates are washed with a mixture of tetrahydrofuran (THF) and Methanol (MeOH) and sonicated in MeOH for 10 min.

**Functionalization of silicon/glass substrates.**[^11][^12] (1) Amino-terminated surfaces were fabricated by immersion of piranha acid-activated silicon substrates into a 10 wt.% (3-aminopropyl)-triethoxysilane solution in ethanol for 4 h at room temperature. Afterwards, the samples are washed with copious amounts of deionized water and place in deionized water overnight. Alkyne terminated substrates (2) were synthesized in a 2-step procedure, creating a chlorine terminated surface in the first step and replacing the chlorine in a second step by an alkyne group. In the first step, the piranha acid-activated Si substrates were immersed in a 10 w% (3-chloropropyl)triethoxysilane solution in ethanol for 4 h at room temperature, followed by a thorough rinse of the substrate with deionized water. In the second step, the chlorine functionalized substrates are immersed in an 18 w% slurry of sodium acetylene in xylene/mineral oil for 5 h at 150 °C. The cooled substrates are washed with a mixture of tetrahydrofuran (THF) and methanol (MeOH) and sonicated in MeOH for 10 min.

**Surface anchoring of the NMOFs@substrate (Si, PDMS).**[^13][^14][^15] For the amide bond formation amine-terminated substrates (PDMS or silicon) were placed in a reaction mixture consisting of 12 mg of the respective MOF in 4 mL EtOH, 22.3 μL N,N'-diisopropyl carbodiimide (18 mg, 0.14 mmol), and catalytic amounts of N-hydroxysuccinimide for 24 h at room temperature. Prior to the addition of the substrate, the mixture is sonicated for 5 min. Afterwards, the substrates were washed thoroughly with EtOH and were sonicated for 5 min in EtOH.
2.3. Microfluidic Device Manufacturing

**Microfluidic device manufacturing.**[16–19]
Cured PDMS with the microfluidic channel structure was obtained by pouring PDMS onto a suitable mold (see Figure S10). The PDMS curing procedure is described in chapter S1.

**Microfluidic device substrate functionalization.**[13–15]
The successful approach to obtain NMOFs anchored inside a microfluidic device is modifying the glass slide or PDMS substrate serving as a reactor base via the experimental procedure described in chapter S1 to yield amino-functionalized glass or PDMS. Then, the glass or PDMS substrate is immersed in UiO-66(Zr), MIL-101-NH$_2$ (Cr), MIL-101-SO$_3$H (Cr), MIL-101 (Cr) NMOF suspended in absolute ethanol (9 mL, ca. 27 mg NMOF) and additional absolute ethanol is added for full submersion (roughly 15 mL). Additionally, 89.6 µL N,N'-diisopropylcarbodiimide (DIC) (72.0 mg, 574 µmol) and catalytic amounts of N-hydroxysulfosuccinimide (NHS) are weighed in. Then the reaction mixture reacted for 12 h, followed by thorough washing with absolute ethanol and drying with compressed air.

For the selectively functionalized microfluidic devices, identical reaction conditions are chosen, however, half of the amino-functionalized PDMS/glass slide is immersed in the UiO-66(Zr)/MIL-101-NH$_2$ (Cr)/MIL-101-SO$_3$H (Cr) solution. Subsequently, the other side is immersed in freshly synthesized MIL-101-SO$_3$H (Cr)/MIL-101(Cr) suspended in absolute ethanol (5 mL, ca. 25 mg NMOF). The remaining reagents and quantities for the amide bond formation described above are kept identical.

**Microfluidic device sealing.**[16–19]
To seal the molded PDMS sample to the modified glass slide/ PDMS substrate is kept in an oven at 100 °C for 24 hours, weighed down by an autoclave to ensure tight sealing.
2.4. Organic Synthesis

2-benzylidene malononitrile$^{[20]}$ as a reactant for GC calibration

![Chemical structure diagram]

1.01 mL BA (10 mmol, 1 equiv.), 660 mg MAN (10 mmol, 1 equiv.) were mixed with 3 g Al$_2$O$_3$ and stirred at 100 °C for 15 min. Afterwards, the product was extracted with DCM, and Al$_2$O$_3$ was filtered off. After DCM was removed, the product was characterized by $^1$H NMR.

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 8.11 (s, 1H, H-C=CCN), 7.98–7.90 (m, 2H, C-H arom.), 7.72–7.63 (m, 1H, C-H arom.), 7.62–7.55 (m, 2H, C-H arom.).

2-phenyl-2-((trimethylsilyl)oxy)-acetonitrile$^{[21]}$ as reactant for GC calibration

![Chemical structure diagram]

10.0 g CaF$_2$ (128 mmol), 2 mL BA (20 mmol, 1 equiv.), 3 mL TMSCN (22 mmol, 1.1 equiv.) were dissolved in 80 mL DCM and stirred at 0 °C for 4 h. Afterwards, CaF$_2$ is filtered off and DCM is removed to yield the product. (Caution: remove the solvent as fast as possible at low temperatures otherwise the product decomposes.) 3.83 g BAOTMSCN (18.7 mmol, 94.3%) was obtained as a yellowish oil.

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 7.54–7.34 (m, 5H, C-H arom.), 5.52 (s, 1H C-H), 0.23 (s, 9H Si-CH$_3$).

$^{13}$C NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ 136.5 (C-H arom.), 129.3 (C-H arom.), 128.9, (C-H arom.), 126.4 (C-H arom.), 119.3 (C-N), 63.6 (q, C-H), 0.7 (TMS).
2.5. Catalysis

Reaction sequence optimization in batch: benzaldehyde dimethyl acetal (BADMA) to benzaldehyde (BA) and finally to 2-benzylidene malononitrile (BACN).²²–²⁵

To transfer the reaction sequence to vectorial catalysis in a microfluidic device, we optimized the parameters for each reaction in batch, and applied these optimal reaction conditions for the reaction sequence.

Therefore, we started optimizing the reaction conditions for the hydrolysis of BADMA to BA. The liquid phase catalysis was conducted under atmospheric pressure. Prior to their use as catalysts, the MOF powders were activated according to the procedures described in chapter 2.2. In a typical experiment, 75 µL BADMA (0.50 mmol, 1 equiv.) was dissolved in 4 mL of solvent (acetonitrile (MeCN), tetrahydrofuran, dioxane, propylene carbonate, or dimethylformamide) and 0-125 equiv. H₂O, and finally 5 mg of activated catalyst powder (MIL-101 (Cr), MIL-101-NH₂ (Cr), MIL-101-SO₃H (Cr), UIO-66, and CoBTC) were added and stirred in a 20 mL screw cap vial at various temperatures (25 °C, 50 °C). After certain time intervals, an aliquot of 100 µL is taken, diluted with the solvent (1.4 mL), filtered with a syringe filter, and finally analyzed by GC. For the blind reactions (-), the same reaction conditions were applied, but the catalyst was omitted.

For the second reaction of the reaction sequence, the Knoevenagel reaction of BA and MAN yielding BACN; the MOF catalyzed reaction conditions were optimized. The liquid phase catalysis was conducted under atmospheric pressure. Prior to their use as catalysts, the MOF powders were activated according to the procedures described in chapter 2.2. In a typical experiment, 50 µL BA (0.49 mmol, 1 equiv.) and 1-10 equiv. malononitrile were dissolved in 4 mL of solvent (MeCN, tetrahydrofuran, dioxane, propylene carbonate, or dimethylformamide) and 0-125 equiv. H₂O and finally 5 mg of activated catalyst powder (MIL-101 (Cr), MIL-101-NH₂ (Cr), MIL-101-SO₃H (Cr), UIO-66, and CoBTC) were stirred in a 20 mL screw cap vial at various temperatures (25 °C, 50 °C). After the certain time intervals, an aliquot of 100 µL is taken diluted with the solvent (1.4 mL) and analyzed by GC. For the blind reactions (-), the same reaction conditions were applied, but the catalyst was omitted.
Benzaldehyde dimethylacetal hydrolysis and subsequent Knoevenagel condensation using MIL-101-SO$_3$H(Cr) or MIL-101-NH$_2$(Cr) and MIL-101(Cr) in a microfluidic reactor.\textsuperscript{[26]}

The liquid phase vectorial catalysis was conducted in microfluidic devices, which were assembled as described above. The flow catalysis was conducted in liquid phase and under ambient conditions. Prior to their use as reactors, the microfluidic devices containing the SA-NMOFs were activated at atmospheric pressure in an oven at 100 °C for 30 min.

Simultaneously, a solution of 75 µL benzaldehyde dimethylacetal (79 mg, 490 µmol, 1.0 equiv.), 66 or 330 mg malononitrile (980 µmol, 2.0 equiv.; 4900 µmol, 10.0 equiv.) in 4 mL acetonitrile/water (1:1 v%) is prepared and stirred in a 20 mL screw cap vial for 1 min at room temperature for homogeneity. 50 µL of this solution is applied to the microfluidic device, at the outlet of the reactor a syringe is used to apply a vacuum, inducing the flow of the solution through the reactor. The typical retention time for the acetonitrile/water (1:1 v%) based solution in a 9 µL microfluidic device (14 coils á 13 mm x 0.3 mm x 0.15 mm) was 30s. The mean retention time was determined by dividing the total time by the total applied volume and multiplying it with the reactor volume (9 µL). The syringe is additionally used to collect the aliquot, which is diluted with MeCN (1.4 mL) and analyzed via GC.
Cyanosilylation of benzaldehyde with TMSCN and subsequential hydrolysis of BAOTMSCN using UiO-66(Zr) and MIL-101-SO₃H(Cr) in a microfluidic reactor.

The liquid phase vectorial catalysis was conducted in microfluidic devices, which were assembled as described above. The flow catalysis was conducted in liquid phase and under ambient conditions. Prior to their use as reactors, the microfluidic devices containing the SA-NMOFs were activated under atmospheric pressure in an oven at 100 °C for 30 min.

Simultaneously, a solution of 25 µL benzaldehyde (26 mg, 245 µmol, 1.0 equiv.), 60 or 300 µL trimethylsilyl cyanide (48 mg, 490 µmol, 10.0 equiv.; 238 mg, 2450 µmol, 10.0 equiv.) in 1 mL DMF is prepared and stirred in a 5 mL screw cap vial for 1 min at room temperature for homogeneity. 50 µL of this solution is applied to the microfluidic device, at the outlet of the reactor a syringe is used to apply a vacuum, inducing the flow of the solution through the reactor. The typical retention time for the DMF-based solution in a 9 µL microfluidic device (14 coils á 13 mm x 0.3 mm x 0.15 mm) was 60 s. The mean retention time was determined by dividing the total time by the total applied volume and multiplying it with the reactor volume (9 µL). The syringe is additionally used to collect the aliquot, which is partly diluted with DMF (1.4 mL) and analyzed via GC, the other half of the solution is diluted with CDCl₃ (0.4 mL) and analyzed via ¹H-NMR.
Application of HCl.

In order to test the vectorial principle for the second reaction sequence, we used HCl as a second catalyst instead of a SA-NMOF based one.

Another reactor design (see below) enables the addition of 1 equiv. of HCl halfway through the reactor. The reactor design includes in total 28 coils and 3 inlets (front, after 14 coils, end). Each coil is 13 mm long, 0.3 mm wide, and 0.15 mm high. The experiment was conducted under ambient conditions. Prior to their use, the reactors were activated under atmospheric pressure in an oven at 100 °C for 30 min.

In a typical procedure, 25 µL benzaldehyde (26 mg, 245 µmol, 1.0 equiv.) and 60 or 300 µL trimethylsilyl cyanide (48 mg, 490 µmol, 10.0 equiv.; 238 mg, 2450 µmol, 10.0 equiv.) were dissolved in 1 mL DMF and stirred in a 5 mL screw cap vial for 1 min at room temperature for homogeneity. A second solution was prepared by dissolving 19.7 µL HCl(aq) (37 w%, 23.4 mg, 245 µmol, 1.0 equiv.) in 1 mL DMF. 25 µL of the first solution was applied to the front inlet and 25 µL of the second solution was applied to the middle inlet (after 14 coils) of the microfluidic device. At the outlet of the reactor, a syringe was used to apply a vacuum, inducing the flow of the solution through the reactor. The typical retention time for the DMF/H₂O-based solution in an 18 µL microfluidic device (28 coils à 13 mm x 0.3 mm x 0.15 mm) was 120s. The mean retention time was determined by dividing the total time by the total applied volume and multiplying it with the reactor volume (18 µL). The syringe is additionally used to collect the aliquot, which is partly diluted with DMF (1.4 mL) and analyzed via GC, the other half of the solution is diluted with CDCl₃ (0.4 mL) and analyzed via ¹H-NMR.
3. Supporting Figures

Figure S1. PXRD (a,c,e,g) and DLS (b,d,f,h) of MIL-101-SO$_3$H (a,f), MIL-101 (b,d), MIL-101-NH$_2$ (e,f), and UiO-66 (e,f). The reference patterns were calculated using the cif files for MIL-101 (CCDC 605510) and UiO-66 (CCDC 733458).
Figure S2. SEM images and histograms of the primary particle size of MIL-101-SO₃H (a,b), MIL-101 (c,d), MIL-101-NH₂ (e,f), UiO-66 (g,h).
Figure S3. Nitrogen adsorption measurements were recorded from activated MIL-101-NH$_2$, MIL-101(Cr), MIL-101-SO$_3$H as well as UiO-66. Adsorption and desorption are visualized by full and empty symbols, respectively. BET surface areas were determined as 1714 ± 7 m$^2$/g (MIL-101-NH$_2$), 1856 ± 16 m$^2$/g (MIL-101 (Cr)), 1072 ± 6 m$^2$/g (MIL-101-SO$_3$H) und 1051 ± 9 m$^2$/g (UiO-66).
Figure S4. Optimization of the reaction conditions: catalysts (a), water content (b), the solvent (c) and temperature (d) on the hydrolysis of BADMA to BA. The blind conversions which were obtained without any added catalysts are displayed in hatched. Experimental details: (a) solvent: MeCN; water: 125 equiv. (1.10 mL); m_{catalysts}: 5 mg, t: 6 h (left of dotted line) or 1 min (right of the dotted line), T: 50 °C. (b) solvent: MeCN, catalyst: MIL-101-SO_3H, blank (behind the dotted line), m_{catalysts}: 5 mg, t: 13 h, T: 50 °C. (c) water: 125 equiv. (1.10 mL), catalyst: MIL-101-SO_3H, m_{catalysts}: 5 mg, t: 6 h (left of dotted line) or 1 h (right of the dotted line), T: 50 °C. (d) solvent: MeCN, water: 125 equiv. (1.10 mL), catalyst: MIL-101-SO_3H, m (catalysts): 5 mg, t: 6 h.
Figure S5. Optimization of the reaction conditions: catalysts (a), water content (b), the solvent (c), MAN content (d), and temperature (e) on the Knoevenagel reaction of BA and MAN to BACN. The blind conversions which were obtained without any added catalysts are displayed in hatched. Experimental details: (a) solvent: MeCN, water: 125 equiv. (1.10 mL), MAN: 2 equiv., m\text{catalysts}: 5 mg, t: 1 h, T: 50 °C; (b) solvent: MeCN, MAN: 2 equiv., catalyst: MIL-101, m\text{catalyst}: 5 mg, t: 1 h, T: 50 °C; (c) water: 125 equiv. (1.10 mL), MAN: 2 equiv., catalyst: MIL-101, m\text{catalysts}: 5 mg, t: 1 h, T: 50 °C; (d) solvent: MeCN, water: 125 equiv. (1.10 mL), catalyst: MIL-101, m\text{catalyst}: 5 mg, t: 1 h, T: 50 °C; (e) solvent: MeCN, water: 125 equiv. (1.10 mL), MAN: 2 equiv., m\text{catalysts}: 5 mg, t: 1 h, T: 25 °C.
**Figure S6.** SEM images and histograms of surface anchored MIL-101-SO$_3$H (a-c), MIL-101 (d-f), MIL-101-NH$_2$ (g-i), and UiO-66 (j-l) immobilized on (3-aminopropyl)triethoxysilane functionalized silicon substrates.
Figure S7. Schematic representation of the manufacturing process of a microfluidic device. 
(a) Silicon master mold manufactured by microLIQUID by photolithography. (b) PDMS was molded on top of the Si master mold. (c) Cured PDMS stamp after the molding process removed from the master mold, yielding a hollowed-out pathway. (d) Subsequently, the PDMS stamp is sealed to a substrate such as glass or PDMS, which is functionalized with SA-NMOFs prior. (e) Complete microfluidic device after assembly and functionalization.
Figure S8. Schematic representation of the stepwise process of anchoring two different NMOFs onto the bottom substrate of a microfluidic device by DIC/NHS catalysed amide bond formation (a,c) resulting in the formation of a substrate with two separately NMOF anchored areas (d).
**Figure S9.** Silicon wafer master mold with the respective channel structure used for the fabrication of PDMS based microfluidic devices. Purchased from *microLIQUID S.L.* under communication of design needs. The dimensions are 14 coils (13 mm x 0.3 mm x 0.15 mm; 9 µL) for the small reactors and 28 coils (13 mm x 0.3 mm x 0.15 mm; 18 µL) for the larger microfluidic reactors.
4. Supporting Tables

**Table S1**: Crystalline domain sizes (CDS), primary particle sizes, and hydrodynamic radii determined by PXRD, SEM, and DLS, respectively, of MIL-101-SO$_3$H, MIL-101, MIL-101-NH$_2$ and UiO-66.

| MOF          | CDS/nm    | Primary Particle Size/nm | Hydrodynamic radius/nm |
|--------------|-----------|--------------------------|------------------------|
| MIL-101-SO$_3$H | 25.8 ± 4.4 | 157 ± 39                  | 1019 ± 188              |
| MIL-101      | 12.4 ± 2.8 | 26.7 ± 3.9                | 79 ± 33                 |
| MIL-101-NH$_2$ | 14.9 ± 1.5 | 25.9 ± 5.8                | 128 ± 59                |
| UiO-66       | 17.7 ± 2.1 | 21.0 ± 3.3                | 164 ± 24                |
Table S2. Amount of Chromium and Zirconium determined by ICP-MS for the surface anchored NMOFs.

| Name       | Metal | Substrate | Mass (m) [ng] | Sample area (A) [cm²] | Metal Mass (m*) [ng/cm²] | Catalyst amount [nmol per cm²] |
|------------|-------|-----------|---------------|------------------------|---------------------------|-------------------------------|
| MIL-101-SO₃H Cr PDMS 296.29 ± 8.20 1.07 ± 0.10 276.15 ± 26.85 | 5.31 ± 0.52 |
| MIL-101-SO₃H Cr Si 236.35 ± 7.01 1.00 ± 0.10 236.35 ± 24.64 | 4.55 ± 0.47 |
| MIL-101-NH₂ Cr PDMS 40.10 ± 6.21 1.15 ± 0.10 34.83 ± 6.19 | 0.67 ± 0.12 |
| MIL-101-NH₂ Cr Si 34.42 ± 3.98 1.00 ± 0.10 34.42 ± 5.26 | 0.66 ± 0.10 |
| MIL-101 Cr PDMS 89.72 ± 4.90 1.08 ± 0.10 83.44 ± 9.00 | 1.60 ± 0.17 |
| MIL-101 Cr Si 33.00 ±6.48 1.00 ± 0.10 33.00 ± 7.27 | 0.63 ± 0.14 |
| Blank Cr PDMS 29.22 ± 8.74 1.10 ± 0.10 29.22 ± 8.74 | 0.51 ± 0.1 |
| Blank Cr Si 17.42 ± 10.90 1.00 ± 0.10 17.42 ± 11.04 | 0.34 ± 0.21 |
| Uio-66 Zr PDMS 369.00 ± 11.28 1.00 ± 0.10 369 ± 48 | 4.05 ± 0.53 |
| Uio-66 Zr Si 58.41 ±2.14 1.00 ± 0.10 58.4 ± 8.0 | 6.40·10⁻¹ ± 8.8·10⁻² |
| Blank Zr PDMS 4.28 ± 1.11 1.05 ± 0.10 4.08 ± 1.50 | 4.46·10⁻² ± 1.58·10⁻² |
| Blank Zr Si 5.04 ± 2.49 1.00 ± 0.10 5.04 ± 2.99 | 5.52·10⁻² ± 3.28·10⁻² |

¹Calculated with the molar mass of Cr=51.996 g·mol⁻¹ and Zr=91.224 g·mol⁻¹

*Metal
**Table S3.** Conversion of BADMA, and yields of BA, and BACN after vectorial catalysis (acetal hydrolysis followed by a Knoevenagel reaction) performed in microfluidic devices. The reactant concentrations were 125 μM BADMA and 1.25 mM (10 equiv.) MAN in 1:1 (v %) acetonitrile/water at room temperature.

![Diagram of microfluidic devices](image_url)

| No | catalyst 1 | catalyst 2 | equiv. MAN | substrate | amounts | % BADMA | % BA | % BACN |
|----|------------|------------|-----------|-----------|---------|---------|------|--------|
| 1  | -          | -          | 10        | -         | -       | 90.1    | 9.9  | 0.0    |
| 2  | -          | -          | 2         | -         | -       | 93.6    | 6.4  | 0.0    |
| 3  | -          | -          | 10        | PDMS      |         | 100.0   | 0.0  | 0.0    |
| 4  | MIL-101-NH₂ | MIL-101-NH₂ | 10        | PDMS      |         | 41.0    | 59.0 | 0.0    |
| 5  | MIL-101-SO₂H | MIL-101-SO₂H | 10        | PDMS      |         | 58.7    | 41.3 | 0.0    |
| 6  | MIL-101     | MIL-101    | 10        | PDMS      |         | 84.5    | 15.5 | 0.0    |
| 7  | MIL-101-NH₂ | MIL-101    | 10        | PDMS      |         | 14.9    | 12.8 | 72.3   |
| 8  | MIL-101-NH₂ | MIL-101    | c4        | 10        | PDMS    | 0.0     | 18.9 | 81.1   |
| 9  | MIL-101-NH₂ | MIL-101    | 2nd       | 10        | PDMS    | 51.2    | 32.8 | 16.0   |
| 10 | MIL-101-NH₂ | MIL-101    | *         | 10        | PDMS    | 73.5    | 26.5 | 0.0    |
| 11 | MIL-101-NH₂ | MIL-101    | 2         | 2         | PDMS    | 91.3    | 8.7  | 0.0    |
| 12 | MIL-101-NH₂ | MIL-101    |          | 10        | glass   | 48.6    | 51.4 | 0.0    |
| 13 | MIL-101-SO₂H | MIL-101  | 10        | PDMS      |         | 9.7     | 7.9  | 82.4   |
| 14 | MIL-101-SO₂H | MIL-101  | 2nd       | 10        | PDMS    | 52.5    | 12.2 | 35.3   |
| 15 | MIL-101-SO₂H | MIL-101  | 2         | 2         | PDMS    | 100.0   | 0.0  | 0.0    |
| 16 | MIL-101     | MIL-101-SO₂H | 10        | PDMS      |         | 74.5    | 25.5 | 0.0    |

*Notes:* c4*: the reactant solution was cycles four times through the reactor. * dioxane/H₂O was used as a solvent
Table S4. Turnover frequencies calculated for the different catalysts applied in vectorial catalysis of acetal hydrolysis followed up by a Knoevenagel reaction performed in microfluidic reactors with a PDMS substrate and 10 equiv. of MAN used for the reaction.

| No | Catalyst 1 | Catalyst 2 | TOF/h⁻¹ Catalyst I | TOF/h⁻¹ Catalyst II |
|----|------------|------------|---------------------|---------------------|
| 1  | MIL-101-NH₂ | MIL-101-NH₂ | (3.96 ± 1.40)∙10⁵  | -                   |
| 2  | MIL-101-SO₃H | MIL-101-SO₃H | (3.50 ± 0.68)∙10⁴  | -                   |
| 3  | MIL-101   | MIL-101   | (4.34 ± 0.46)∙10⁴  | -                   |
| 4  | MIL-101-NH₂ | MIL-101   | (1.13 ± 0.20)∙10⁵  | (4.05 ± 0.43)∙10⁵  |
| 5  | MIL-101-NH₂ | MIL-101   | (1.13 ± 0.20)∙10⁵  | (4.05 ± 0.43)∙10⁵  |
| 6  | MIL-101-SO₃H | MIL-101   | (6.55 ± 0.12)∙10⁵  | (8.97 ± 0.87)∙10⁵  |
| 7  | MIL-101-SO₃H | MIL-101   | (1.53 ± 0.15)∙10⁵  | (4.62 ± 0.50)∙10⁵  |
| 8  | MIL-101-SO₃H | MIL-101   | (8.04 ± 0.78)∙10⁴  | (1.97 ± 0.19)∙10⁵  |

c4: cycle solution four times through the reactor; 2nd: recycle the reactor for the next reaction
Table S5. Comparison of TOFs obtained from vectorial catalysis in microfluidic reactors for the reaction sequence consisting of hydrolysis of BADMA to BA, and Knoevenagel condensation to BACN with the tandem catalysis of the same reaction sequence catalyzed by bifunctional catalysts. The TOFs were not given by the authors but calculated with the information given in the publications, which are listed in the table.

| catalyst                      | solvent          | T/°C | t/h | %cat/mol | %BA | %BAC | TOF/h | TOF/h<sup>-1</sup> | ref       |
|-------------------------------|------------------|------|-----|----------|-----|------|-------|---------------------|-----------|
| MIL-101-NH<sub>2</sub> (Cr)   | MeCN, H<sub>2</sub>O | RT   | 8   | 0.00     | 0.00| 12.8 | 72.3  | 1.13·10<sup>6</sup> | -         |
| MIL-101 (Cr)                  | MeCN, H<sub>2</sub>O | RT   | 8   | 0.00     | 0.02| 12.8 | 72.3  | -                   | 4.05·10<sup>5</sup> | +         |
| PCN-124 (Cu)                  | DMSO             | 50   | 12  | 43       | 6   | 94   | 0.76  | 0.74                | [23]      |
| MIL-101-NH<sub>2</sub> (Al)   | dioxane          | 90   | 3   | 6        | 94  | 2.8  | 2.7   | 2.7                 | [22]      |
| UiO-67(-NH<sub>2</sub>)<sub>2</sub> | ethanol          | 60   | 10  | 3.6      | 1   | 98   | 2.3   | 2.3                 | [27]      |
| MIL-101(Cr)<sub>2</sub> @ citosan | MeCN            | 80   | 12  | 3.6      | 0   | 99   | 2.3   | 2.3                 | [28]      |
| Cr-MIL-101-AB-x               | DMF              | 90   | 0.08| 4.0      | 17  | 180  | 51    |                     | [29]      |
| Yb-bdc-NH<sub>2</sub>         | DMSO             | 50   | 24  | 2.0      | 0   | 97   | 2.0   | 2.0                 | [30]      |
| Zn-MOF 1                      | DMF              | 80   | 0.5 | 1.0      | 16  | 10   | 52    | 20                  | [31]      |
| Zn-MOF 2                      | DMF              | 80   | 0.5 | 1.0      | 27  | 5    | 64    | 10                  | [31]      |
| Cd-MOF 1                      | DMF              | 90   | 5   | 0.56     | 0   | 84   | 30    | 30                  | [32]      |
| Cd-MOF 2                      | DMF              | 90   | 5   | 0.56     | 0   | 95   | 34    | 34                  | [32]      |
| PCN-905(Eu)-SO<sub>2</sub>-SO<sub>3</sub>H | toluene, H<sub>2</sub>O | 90   | 1   | 4.5      | 95.5| 10   | 9.6   |                     | [33]      |

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