Supplementary Information (SI)

Synthesis of the biocompatible and highly stable MIL-127(Fe): from large scale synthesis to particle size control

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I. Characterization techniques

A small amount of solid was analyzed by a Thermo Nicolet spectrometer (Thermo, USA). The spectrum was recorded from 4000-400 cm⁻¹.

 N_2 isotherms were obtained at 77 K using a Belsorp Mini (Bel, Japan). Prior to the analysis, approximately 40-60 mg of activated samples were evacuated for 16 h at 200°C under primary vacuum. BET surface and micropore volume were estimated at a relative pressure lower than 0.25.

Approximately 5-10 mg of the sample were used for the thermogravimetric analysis (TGA). Samples were analyzed under an oxygen flow (20 mL·min⁻¹) using a Perkin Elmer Diamond TGA/DTA STA 6000 running from room temperature to 600 °C with a scan rate of 2 °C·min⁻¹.

Particle size was monitored by Dynamic Light Scattering (DLS) on a Zetasizer Nano (Malvern Instruments). Samples were prepared by dispersing at $0.1 \text{ mg} \cdot \text{mL}^{-1}$ of nanoparticles (NPs) at RT in the ethanol by using an ultrasound tip (30% amplitude for 1 min; Digital Sonifer 450, Branson).

Field emission gun scanning electron microspopy (FEG-SEM) images of the crystals were carried out using a microspope JEOL JAMP 9500F.

II. Synthesis of 3,3',5,5'-azobenzenetetracarboxylic acid¹

In a 1 L 3-neck round bottomed flask containing 250 mL of distilled water, 19 g of 5nitroisophthalic acid were added and then, slowly, 50 g of sodium hydroxide NaOH, followed by heating at 50-60 °C under magnetic stirring. A pink slurry was formed.



Figure S1: Chemical structure of the 3,3',5,5'-azobenzenetetracarboxylic acid

100 g of glucose dissolved in 150 mL of water were slowly added to the previously obtained pink slurry. The solution turned from yellow to orange and then brown. The heating was stopped, and air was bubbled through the solution overnight at room temperature. The mixture was cooled down with an ice-bath in order to optimize the amount of precipitate, before recovering the disodium salt by filtration. The filtrate was then redissolved in 200 mL of distilled water and then this solution was acidified to pH = 1 using 37% HCl. This yielded to a bright orange precipitate, recovered by filtration, washed with ethanol and dried at 70°C.

NMR ¹H (d₆-DMSO): 12-13 (broad, 2H), 8.03 (d, $J_1 = 8.1$ Hz, 4H), 8.03 (d, $J_2 = 1.5$ Hz, 4H) ; 7.97 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz, 4H). NMR ¹³C (d₆-DMSO): 166.2, 153.1, 134.1, 132.7, 131.9, 124.0, 122.1.

III. Water stability tests

30 mg of activated MIL-127(DMF) were introduced in a 10 mL round bottom flask containing 3 mL of distilled water (pH = 4.2). The mixture was placed under stirring either at room temperature (RT) or under reflux for 16 h. Stability experiments were performed in basic media (pH = 8 and 12) by adding sodium hydroxide NaOH and in acid media (pH= 2 or 3) by adding hydrochloric acid HCl.

The resulting solids have been characterized by powder X-ray diffraction.



Figure S2: X-ray powder diffraction patterns of MIL-127(DMF) before (black) and after the treatment at RT at pH=2, pH=8 and pH=12 as well as under reflux pH=2, pH= 6.5 and pH=8.



Figure S3: Nitrogen sorption isotherms at 77K of MIL-127(DMF) before (black) and after the treatment at RT (on the top) pH=2, pH=7, pH=8 and pH=12 as well as under reflux (on the bottom) pH=2, pH=7, pH=8 and pH=12.

IV. Characterization of MIL-127(DMF/HF)



Figure S4: Comparison between the PXRD patterns of the indium(III) *soc* MOF (black line) and MIL-127(DMF/HF) (red line). X-ray powder diffraction (XRPD) patterns were recorded on a Siemens D5000 ($\lambda_{Cu_{\alpha 1}} = 1.54056$ Å, $\lambda_{Cu_{\alpha 2}} = 1.54439$ Å) at room temperature over the angular range 4-50° 20 with a step of 0.02°.

PXRD pattern of MIL-127(DMF/HF) was first compared with the simulated XRD pattern of indium(III) *soc* MOF and a strong similarity between them could be observed despite a small shift of XRD peaks of MIL-127(DMF/HF) towards higher 2θ (°) (Figure S4).

In order to confirm the structure of MIL-127(DMF/HF), the X-ray diffraction pattern was indexed on 15 Bragg reflections using Dicvol06, giving a cubic structure with a *a* cell parameter of 21.8527 Å. Then, the cell parameter and space group were refined and determined, respectively, by performing a Lebail refinement on WinPlotR² of the FullProf Suite.³ Thus the structure is cubic with a *a* cell parameter of 21.897(3) Å. The space group P-43n, is identical to that of the indium(III) *soc* MOF (Rp= 4.27, Rwp= 5.45, Chi2= 1.34) (Figure S5).



Figure S5: Lebail refinement of MIL-127(DMF/HF) using WinPlotR.² Cubic, space group P-43n, a= 21.897(3) Å (Rp= 4.27, Rwp= 5.45, Chi2= 1.34). The PXRD pattern was recorded on a Siemens D5000 ($\lambda_{Cu_{-}\alpha_{1}} = 1.54056$ Å, $\lambda_{Cu_{-}\alpha_{2}} = 1.54439$ Å) at room temperature over the angular range 5-50 20 with a step of 0.02°.



Figure S6: TGA of activated MIL-127(DMF/HF).



Figure S7: IR spectrum of activated MIL-127(DMF/HF).



Figure S8: Nitrogen sorption isotherm measurement at 77K of activated MIL-127(DMF/HF). The BET surface area is estimated to 1400 m².g⁻¹.

V. Characterization of MIL-127(DMF)



Figure S9: Lebail refinement of MIL-127(DMF) using WinPlotR.² Cubic, space group P-43n, a= 21.969(3) Å (Rp= 10.3, Rwp= 13.4, Chi2= 1.39). The PXRD pattern was recorded on a Siemens D5000 ($\lambda_{Cu_{\alpha}1} = 1.54056$ Å, $\lambda_{Cu_{\alpha}2} = 1.54439$ Å) at room temperature over the angular range 2-50 20 with a step of 0.03°. The Lebail refinement confirms a cubic structure, with a space group P-43n, and a cell parameter a= 21.969(3) Å, as found for MIL-127(DMF/HF).



Figure S10: TGA of activated MIL-127(DMF).



Figure S11: FTIR spectrum of activated MIL-127(DMF).



Figure S12: N_2 sorption isotherm at 77K of the activated MIL-127(DMF). The BET surface area is estimated to 1310 m².g⁻¹.

VI. Characterization of MIL-127(Prop)



Figure S13: Lebail refinement of MIL-127(Prop) using WinPlotR.² Cubic, space group P-43n, a= 21.972(1) Å (Rp= 7.9, Rwp= 10.6, Chi2= 2.21). The PXRD pattern was recorded on a Siemens D5000 ($\lambda_{Cu_{\alpha}1} = 1.54056$ Å, $\lambda_{Cu_{\alpha}2} = 1.54439$ Å) at room temperature over the angular range 4-60° 20 with a step of 0.02°. The Lebail refinement confirms a cubic structure, with a space group P-43n, and a cell parameter a= 21.972(1) Å, as found for MIL-127(DMF/HF) and MIL-127(DMF).



Figure S14: TGA of activated MIL-127(Prop).



Figure S15: IR spectrum of activated MIL-127(Prop)



Figure S16: Nitrogen sorption isotherm of MIL-127(Prop) at T = 77 K. BET surface area of $1350 \text{ m}^2.\text{g}^{-1}$

VII. Time-resolved *in situ* energy-dispersive X-ray diffraction (EDXRD) study of the solvothermal crystallization of MIL-127(DMF) and (Prop)

1. Theory

The d-spacing (Å) of a Bragg peak is calculated from the recorded energy (KeV) as follows:

$$d = \frac{6,19921}{E * \sin(\theta)}$$

 θ being the incident beam source angle.

Data can be normalized either using the fluorescence or the synchrotron radiation current provided within the recorded instrumental data. As the solid are based on iron, no fluorescence was observed and the second approach applied. The profiles of Bragg peaks were fitted with a Gaussian function, implement in the F3tool software developed by Rotkirch *et al.* (DESY, Hambourg, Germany) and their surface area integrated.

The extent of crystallisation $\alpha(t)$ was obtained as the ratio of the integrated intensities I(t) at the different times to the maximum integrated intensity Imax at the end of the reaction:

$$\alpha(t) = \frac{I(t)}{Imax}$$

The first approach applied is the Avrami-Erofe'ev (AE) model, which is the most frequently used for the kinetics study of hybrid materials:^{4, 5}

$$\alpha(t) = 1 - e^{-(k(t-t_0)^n)}$$

Where k is an overall rate constant; t_0 the induction time; n, the Avrami-exponent.

The AE model can used through the approach of Sharp and Hancock, that consists in a linear regression of the AE equation:⁶

$$\ln[-\ln(1-\alpha)] = n\ln(k) + n\ln(t-t_0)$$

The activation energy of the reaction process could thus be determined by calculation of the overal constant k at each temperature and by the use of the Arrhenius equation:

$$k = A e^{-E_a/_{RT}}$$

A, the pre-exponential factor; $R = 8.314 \text{ J.mol}^{-1}$. K⁻¹.

The Gualtieri model consists in a 2-terms function that separates nucleation and growth processes in the following equation, where the first term is related to the nucleation:

$$\alpha(t) = \frac{1}{1 + e^{-(t-a)/b}} \left[1 - e^{-(k_g t)^n} \right]$$

 k_g , the rate constant of the growth; n, the dimension of the growth thus n= 3 (three-dimensional growth) as the crystals are cubic (See SEM-FEG images).

From the Gualtieri model, and more precisely from the a and b parameters, the dimensionless probability of nucleation (a Gaussian function) can be calculated by:

$$P_N = \exp(\frac{-(t-a)^2}{2b^2})$$

a and b, being the position of the peak and the variance of the Gaussian distribution, respectively. The rate constant of nucleation is calculated by:

$$x_n = 1/a$$

2. Experimental

Solvothermal reactions were performed in sealed borosilicate glass tubes Schott® (H*diam. 100 * 12 mm) with an inner diameter of 9 mm and a volume of 7 mL. 0.66 mmol of iron(III) chloride hydrated (180 mg) and 0.33 mmol of H₄-TazBz (118 mg) were dissolved into 2 mL of DMF. The tube was placed under magnetic stirring in an oven preheated to the desired temperature (170, 175, 190 and 200°C) using a circulating oil heater and equipped with a magnetic stirring device.

Bragg peaks integration was performed using "calf3" (software offered and available for free at beamline F3, private copy by A. Rothkirch/DESY).



Figure S17: Time resolved in situ EDXRD data measured during the crystallization of MIL-127(DMF) at different temperatures (170, 175, 190 and 200°C).

Figure and S18 show time-resolved EDXRD data recorded at intervals of 60 s during the crystallization of MIL-127(DMF) and MIL-127(Prop), respectively, at four different temperatures. The hkl Bragg reflection (002) of MIL-127(DMF) and MIL-127(Prop), as well as the (022) reflection for MIL-127(DMF), observed after a temperature-dependent induction time t_0 (*i.e.* t_0 decreases with temperature), increase in intensity with time, reaching a maximum intensity at the end of the reaction. The product is presumably a pure MIL-127 as no other crystalline phases can be detected, neither as intermediate phases nor as by-products. After integration of the most intense Bragg reflection (002) and normalization of the

integrated intensities to the corresponding synchrotron radiation current and the integrated maximum intensities, the crystallization curves (extent of crystallization $\alpha(t)$ versus time)) (Figure 2 in the main text) can be plotted.



Figure S18: Time resolved in situ EDXRD data measured during the crystallization of MIL-127(Prop) at 75, 80, 85 and 90°C

i. <u>Avrami – Erofe'ev</u>

Then, the curves have been linearized using the Sharp and Hancock approach, allowing the extraction of the Avrami exponent n and the rate constant. (Figure S20and Table 1)



Figure S19: Sharp and Hancock linear regression of the Avrami-Eroféev nucleation-growth crystallization model for MIL-127(DMF) and MIL-127(Prop)

The activation energy Ea for the crystallization of MIL-127(DMF) and MIL-127(Prop) of respectively 102(10) and 92(24) kJ.mol⁻¹ can be calculated by using the Arrhenius equation (Figure S209)



Figure S20: Determination of the Arrhenius activation energies of the synthesis of MIL-127(DMF) and MIL-127(Prop).

For MIL-127(DMF), an Avrami exponent close to 0.6 was obtained, which indicates a diffusion controlled crystal growth mechanism and a high concentration of nucleation sites. Nevertheless, as it will be shown by the use of the Gualtieri model, both nucleation and growth processes occur simultaneously but the crystallization process is kinetically controlled by the growth step.

For MIL-127(Prop), rate constants are significantly higher than those of MIL-127(DMF), which means that the physico-chemical conditions of the MIL-127(Prop) synthesis induces a faster crystallization process compared to that of MIL-127(DMF). A large induction time is observed at 75°C which may be imparted by the low solubility of the ligand at that temperature.

Table S1 : Induction time t_0 , overall rate constant k, Avrami exponent n, pre-exponential factor A and activation energy obtained from the Sharp and Hancock fit as a function of the temperature.

S	Solvent	T (° C)	t ₀ (s)	n _{SH}	k_{SH} (s ⁻¹).10 ⁻³	$A(s^{-1})$	$E_a (kJ.mol^{-1})$	
	F)	170	720	0.66	2.82			
	MIL- 127(DM	175	360	0.61	$\begin{array}{c} 4.96 \\ 8.07 \end{array} \qquad 3.6 \ 10^9 \end{array}$		102(10)	
		190	300	0.6			102(10)	
		200 240		0.61	20.05			
	MIL- 127(Prop)	75	1500	1.6	0.35		·	
		80	720	1.0	0.81	0 0 10 ⁹	02(24)	
		85	540	1.4	0.7	0.0 10	92(24)	
		90	360	0.9	1.6			

ii. Gualtieri model

Figure S21 and S22 shows the fit of the extent of crystallisation $\alpha(t)$ by the Gualtieri model and the corresponding probability curve of nucleation P_N .



Figure S21: Extent of crystallization of MIL-127(DMF) at 170, 175, 190 and 200°C vs. time (pink squares, green circles, red triangles, violet rhombus, respectively) and corresponding non-linear least-squares fits with the Gualtieri equation (curve) as well as probability curve of nucleation P_N (blue circles).



Figure S22: Extent of crystallization of MIL-127(Prop) at 75, 80, 85 and 90°C vs. time (pink squares, green circles, red triangles, violet rhombus, respectively) and corresponding non-linear least-squares fits with the Gualtieri equation (line) as well as the probability curves of nucleation P_N (blue circles).

The activation energies and pre-exponential factor for the nucleation and the growth are extracted from the fits of the extent of crystallization using the Gualtieri equations as shown in Table S2.

Table S2: Kinetic parameters (a, b, k_g and k_n), activation energy Ea and pre-exponential factor A for the nucleation and for the growth using the Gualtieri model.

Solvent	T (° C)	a (min)	b (min)	$k_{g} (s^{-1}).10^{-3}$	$k_n (s^{-1}).10^{-3}$	$A_g(s^{-1})$	$E_{a,g}\left(kJ.mol^{\text{-}1}\right)$	$A_n(s^{-1})$	$E_{a,n} (kJ.mol^{-1})$	
$\hat{}$	170	10.8(9)	9.5(1)	71.1(4)	91.7(4)		55(17)	5.3 10 ¹²		
I NH	175	3.7(6)	6.8(4)	133.7(3)	265.7(4)	2.4 10 ⁵			116(28)	
DNI DN	190	2.5(7)	4.6(7)	162.3(5)	388.2(6)					
H	200	1.0(5)	2.6(5)	217.4(7)	952.0(6)					
ol	75	59.0(1)	20.2(3)	24.0(1)	16.9(3)		106(20)	1.3 10 ¹²	02(24)	
Prop n-2-	80	26.3(2)	14.9(3)	57.0(3)	37.9(4)	3.2 10 ¹⁴				
IM 1)72 (I)	85	28.1(1)	9.9(1)	63.7(4)	35.5(4)				92(24)	
Pr 1	90	13.4(1)	9.1(2)	126.5(8)	74.5(6)					

In agreement with the AE model, it can be observed that k_n is higher than k_g , indicating that the growth step is rate-limiting.

VIII. High throughput tests

In order to investigate the effect of the solvent, several syntheses in different solvents and different pHs have been performed using a high-throughput system of 48 Teflon vessels of 200 μ L. 24 of them have been used to perform the synthesis listed in Table S3. Then, the vessels have been introduced in a metallic grid then sealed between 2 metallic blocks with a pressure of 1 bar. Teflon sheets have been used between the vessel and the metallic block in order to improve permeability of the system, then the system has been placed in an oven at 120°C during 24 h.

Nb	Ratio	Metal			TazBz		0.1		Base/acide		
		Metal	mmol	mg	mmol	mg	Solvent		quoi	mmol	μL
1	3:1	FeCl ₃	0.1	27	0.03	11.9	H ₂ O 200 μl		-	-	-
2	3:1	FeCl ₃	0.1	27	0.03	11.9	H ₂ O	200 µl	HCl pur	0.1	8.3
3	3:1	FeCl ₃	0.1	27	0.03	11.9	H ₂ O	200 µl	NaOH(5M)	0.1	20
4	3:1	FeCl ₃	0.1	27	0.03	11.9	Ethanol	200 µl	-	-	-
5	3:1	FeCl ₃	0.1	27	0.03	11.9	Ethanol	200 µl	HCl pur	0.1	8.3
6	3:1	FeCl ₃	0.1	27	0.03	11.9	Ethanol 200 µl		NaOH(5M)	0.1	20
7	3:1	FeCl ₃	0.1	27	0.03	11.9	Methanol 200 µl		-	-	-
8	3:1	FeCl ₃	0.1	27	0.03	11.9	Methanol 200 µl		HCl pur	0.1	8.3
9	3:1	FeCl ₃	0.1	27	0.03	11.9	Methanol 200 µl		NaOH(5M)	0.1	20
10	3:1	FeCl ₃	0.1	27	0.03	11.9	Toluene	200 µl	-	-	-
11	3:1	FeCl ₃	0.1	27	0.03	11.9	Toluene	200 µl	HCl pur	0.1	8.3
12	3:1	FeCl ₃	0.1	27	0.03	11.9	Toluene	200 µl	NaOH(5M)	0.1	20
13	3:1	FeCl ₃	0.1	27	0.03	11.9	cyclohexane	200 µl	-	-	-
14	3:1	FeCl ₃	0.1	27	0.03	11.9	cyclohexane	200 µl	HCl pur	0.1	8.3
15	3:1	FeCl ₃	0.1	27	0.03	11.9	cyclohexane 200 µl		NaOH(5M)	0.1	20
16	3:1	FeCl ₃	0.1	27	0.03	11.9	acetonitrile 200 µl		-	-	-
17	3:1	FeCl ₃	0.1	27	0.03	11.9	acetonitrile 200 µl		HCl pur	0.1	8.3
18	3:1	FeCl ₃	0.1	27	0.03	11.9	acetonitrile	200 µl	NaOH(5M)	0.1	20
19	3:1	FeCl ₃	0.1	27	0.03	11.9	isopropanol	200 µl	-	-	-
20	3:1	FeCl ₃	0.1	27	0.03	11.9	isopropanol	200 µl	HCl pur	0.1	8.3
21	3:1	FeCl ₃	0.1	27	0.03	11.9	isopropanol	200 µl	NaOH(5M)	0.1	20
22	3:1	FeCl ₃	0.1	27	0.03	11.9	cyclohexanol	200 µl	-	-	-
23	3:1	FeCl ₃	0.1	27	0.03	11.9	cyclohexanol	200 µl	HCl pur	0.1	8.3
24	3:1	FeCl ₃	0.1	27	0.03	11.9	cyclohexanol	200 µl	NaOH(5M)	0.1	20

Table S3: Synthesis conditions of MIL-127 in different solvents.

Then the 24 vessels have been filtered on a filter block before being characterized by X-ray diffraction. The determination of the compounds is given in figure S23.





Figure S23: Results of the X-ray powder diffraction on the 24 syntheses of Table S3.

IX. Characterization of MIL-127 nanoparticles (MIL-127_NPs1 and MIL-127_NPs2)



Figure S24: PXRD patterns of MIL-127_NPs1 and MIL-127_NPs2 in comparison with the MIL-127(DMF).



Figure S25: TGA of activated MIL-127_NPs1 and MIL-127_NPs2



Figure S26: IR spectrum of activated MIL-127_NPs1 and MIL-127_NPs2.



Figure S27: N_2 sorption isotherm at 77 K of activated MIL-127_NP1 and MIL-127_NP2 (previously outgassed at 200°C for 8 h under primary vacuum). BET surface area was 1390 and 1360 m².g⁻¹, respectively.

References

- 1 A. Dhakshinamoorthy, M. Alvaro, H. Chevreau, P. Horcajada, T. Devic, C. Serre and H. Garcia, *Catalysis Science & Technology*, 2012, **2**, 324-330.
- 2 T. Roisnel and J. Rodríguez-Carvajal, *Materials Science Forum, Proceedings of the* Seventh European Powder Diffraction Conference (EPDIC 7), 2000, 118-123.
- 3 J. Rodríguez-Carvajal and T. Roisne, *International Union for Crystallography*, *Newletter N°20 (May-August)*, Summer 1998.
- 4 M. J. Avrami, J. Chem. Phys., 1941, 9.
- 5 B. V. Erofe'ev, Compt. Rend. Acad. Sci. USRR, 1946, 52.
- 6 J. D. Hancock and J. H. Sharp, J. Am. Ceram. Soc., 1972, 55, 74-77.