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## Supplementary information

Nucleation kinetics for primary, secondary and ultrasound-induced paracetamol crystallization

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## S1 Two-sample Kolmogorov Smirnov test

The two-sample Kolmogorov Smirnov test is used to determine whether two independent samples arise from the same underlying distribution. <sup>1</sup> The  $H_0$  hypothesis is that the cumulative probability function  $(P_{\rm n}(t))$  with m measurements is identical to the cumulative probability function  $(P_{\rm m}(t))$  with n measurements.

$$H_0: P_m(t) = P_n(t)$$
 for  $0 < t < \infty$   
 $H_1: H_0$  is not true

The largest difference between two cumulative distribution functions for the two samples can be calculated as shown in eq. S1.  $^1$ 

$$D_{mn} = \sup_{0 < t < \infty} |P_m(t) - P_n(t)| \qquad (S1)$$

The  $H_0$  hypothesis (that the two samples are from the same underlying distribution) is rejected when  $D_{mn}$  is large.<sup>1</sup>

$$\left(\frac{mn}{m+n}\right)^{\frac{1}{2}}D_{mn} \ge c \tag{S2}$$

If a level of significance of 0.05 is chosen, then the constant c is 1.358.  $^{\rm 1}$ 

The two-sample Kolmogorov-Smirnov test is applied by Little et al. to determine whether variances in experimental cumulative probability functions are due to statistical noise or due to the fact that the samples are from different underlying probabilities functions (and therefore there is a difference in the nucleation). <sup>2</sup>

#### S1.1 US as a replacement for agitation

The two-sample Kolmogorov-Smirnov test is used here to check whether a change in the agitation rate has significantly affected the nucleation rate in sonicated microvials. If the nucleation rate is significantly affected, we will have to reject the  $H_0$  hypothesis 95% of the time.

Calculating  $D_{mn}$  for the cumulative probability functions for sonicated samples cooled to 20°C at 0 RPM and at 1250 RPM results in eq. S3.

$$D_{mn} = 0.16$$
 (S3)

Eq S2 is invalid, as is shown in S4.

$$0.72 < 1.358$$
 (S4)

Thus, we cannot reject the  $H_0$  hypothesis. It is therefore unlikely that changing the agitation rate has significantly affected the nucleation rate in the sonicated microvials.

#### S1.2 Impact of UP50H maintenance

The two-sample Kolmogorov-Smirnov test is also applied to determine whether the UP50H maintenance significantly affected the results.

Calculating  $D_{mn}$  for the cumulative probability functions for sonicated samples cooled to 20°C before and after maintenance of the ultrasonic processor results in eq. S5.

$$D_{mn} = 0.11$$
 (S5)

Eq S2 is invalid, as is shown in S6.

$$0.50 < 1.358$$
 (S6)

Thus, also here we cannot reject the  $H_0$  hypothesis. It can be concluded that it is unlikely that sonication with the UP50H before and after maintenance has significantly affected the nucleation behaviour.

## S2 Temperature measurements

## S2.1 Heat transfer in the microvials

To evaluate the heat transfer in the agitated (1250 RPM) microvials, the temperature is measured in the

silent and sonicated microvials (as explained in *3. Materials and Methods* in the manuscript). The microvials are filled with 1.4 mL of distilled water. The results are shown in Fig. S1 For the sonicated samples a steady-state temperature is obtained regardless of the starting temperature (as is shown in Fig. S2). The microvials are sonicated with the UP50H (MS1 sonotrode, continuous sonication, 20% amplitude). For the silent samples, the steady-state temperature is very close to the well temperature.



**Fig. S1** Temperature measurements in the microvial for varying well temperatures (10, 15, 20, 25°C), with a starting temperature of 42°C. Sonicated microvials (MS1, amplitude=20%, continuous sonication) are shown in red, silent microvials are shown in black. The agitation rate is fixed at 1250 RPM.



Fig. S2 Temperature measurements in the sonicated microvial (MS1, amplitude=20%, continuous sonication) for a well temperature of 10°C and 25°C, with a starting temperature of 42°C and respectively 10°C and 25°C.

#### S2.2 Calorimetric power

Fig. S2 can be used to determine the calorimetric power that is supplied to the system. The calorimetric power can be calculated using eq. S7, with m the mass of water in the microvial (1.4g) and  $c_p$  the specific heat capacity.

$$P_{\rm cal} = mc_p \frac{dT}{dt} \tag{S7}$$

As the calorimetric experiments are performed with distilled water,  $c_p$ =4186 J/kg·K. For the UP50H processor with the MS1 sonotrode (continuous sonication, 20% amplitude, MS1) a value of approximately 0.34 is obtained for the temperature derivative. Which leads to a value of 1.99 W for the calorimetric power.

## S3 Fitted values

Tables S1, S2, S3, S4, S5, S6, and S7 give the nucleation rate and CI95% obtained from fitting for varying well temperatures and varying nucleation mechanisms. The coefficient of determination is also given in these tables. Tables S9, S10, S11, S12, S13, and S14 give the growth times and CI95% obtained from fitting for varying well temperatures and varying nucleation mechanisms.

## S3.1 Nucleation rates and coefficients of determination

Table S1 Nucleation rates for primary (filtered) nucleation (T\_{start}=42°C) for varying well temperatures and the coefficient of determination for the fitting.

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
5	21410	± 2390	0.8317
10	14600	± 1090	0.9325
15	8948	<u>+</u> 591	0.9445
20	9348	<u>±</u> 443	0.9739
25	6049	± 257	0.9819
30	922.3	± 56.8	0.9723

Table S2 Nucleation rates for primary (unfiltered) nucleation ( $T_{start}$ =42°C) for varying well temperatures and the coefficients of determination for the fitting.

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
5	31960	± 2960	0.8702
10	28190	± 2940	0.8394
15	21560	± 2160	0.8519
20	9348	± 880	0.9697
25	7257	± 400	0.9656
30	987.9	± 70.6	0.9686

Table S3 Nucleation rates for primary (cage) nucleation ( $T_{start}=42$  °C) for varying well temperatures and the coefficients of determination for the fitting.

т	Nucleation rate	CI95%	<b>R</b> <sup>2</sup>
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
10	37490	± 4330	0.9296
15	22470	± 2090	0.9627
20	25250	± 2640	0.9448
25	16970	± 1660	0.9501
30	8027	<u>+</u> 530	0.9781

Table S4 Nucleation rates for primary (probe) nucleation ( $T_{start}$ =42°C) for varying well temperatures and the coefficients of determination for the fitting.

т	Nucleation rate	CI95%	<b>R</b> <sup>2</sup>
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
10	45100	± 4150	0.9536
15	36700	<u>+</u> 4190	0.9346
20	35460	<u>+</u> 3930	0.9395
25	24470	<u>+</u> 1450	0.9847
30	11400	± 580	0.9896

 $\label{eq:table_$ 

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
10	50810	± 8970	0.7658
15	65960	± 8400	0.8973
20	31260	<u>+</u> 4550	0.8512
25	31260	<u>+</u> 3530	0.9249
30	21500	<u>+</u> 2840	0.8926

Table S6 Nucleation rates for US-induced nucleation for varying well temperatures ( $T_{start}$ =42°C) and the coefficients of determination for the fitting.

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
15.6	109000	± 10200	0.9491
20.2	56290	± 6600	0.9156
25.6	44430	± 4990	0.9227
29.4	27490	± 2060	0.9709

Table S7 Nucleation rate values for US-induced secondary nucleation for varying well temperatures ( $T_{start}$ =42°C) and the coefficients of determination for the fitting.

T IºCI	Nucleation rate	CI95%	<b>R</b> <sup>2</sup>
1[0]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
15.6	73290	± 9200	0.8915
20.2	63130	± 5920	0.9446
25.6	49540	± 4600	0.9514
29.4	29020	± 4610	0.8317

## S3.2 Growth times

Table S8 Growth times for primary (filtered) nucleation ( $T_{start}$ =42°C) for varying well temperatures.

T [°C]	Growth time [s]	CI95% [s]
5	57.82	± 2.19
10	51.7	± 1.96
15	63.14	± 2.81
20	81.42	<u>+</u> 1.85
25	102.7	± 2.50
30	35.46	± 20.86

Table S9 Growth times for primary (unfiltered) nucleation ( $T_{start}$ =42°C) for varying well temperatures.

T [°C]	Growth time [s]	CI95% [s]
5	56.94	± 1.20
10	68.89	<u>+</u> 1.57
15	68.33	<u>±</u> 1.94
20	81.42	<u>+</u> 1.57
25	101.9	<u>+</u> 2.80
30	31.62	± 23.39

Table S10 Growth time values for primary (cage) nucleation (T\_{start}=42°C) for varying well temperatures.

T [°C]	Growth time [s]	CI95% [s]
10	41.91	± 1.23
15	64.97	± 1.33
20	73.35	<u>±</u> 1.57
25	87.19	± 2.16
30	132.8	± 3.00

Table S11 Growth times for primary (probe) nucleation ( $T_{start}$ =42°C) for varying well temperatures.

T [°C]	Growth time [s]	CI95% [s]
10	43.83	± 0.80
15	55.9	± 1.20
20	67.5	± 1.19
25	89.39	<u>±</u> 0.87
30	121.1	<u>±</u> 1.50

Table S12 Growth times for secondary nucleation ( $T_{\text{start}}\!\!=\!\!42^{\circ}C)$  for varying well temperatures.

т [°С]	Growth time [s]	CI95% [s]
10	38.96	± 1.58
15	46.54	$\pm 0.81$
20	68.33	± 2.06
25	68.33	± 1.42
30	101.7	± 2.50

Table S13 Growth times for US-induced nucleation ( $T_{start}$ =42°C) for varying well temperatures.

т [°С]	Growth time [s]	Cl95% [s]
15.6	30.40	± 0.35
20.2	35.05	± 0.86
25.6	43.84	± 1.02
29.4	60.15	$\pm 1.01$

Table S14 Growth times for US-induced secondary nucleation (T\_{start}=42°C) for varying well temperatures.

Growth time [s]	CI95% [s]	
17.50	± 0.72	
18.18	± 0.58	
19.91	± 0.73	
31.29	± 2.35	
	Growth time [s] 17.50 18.18 19.91 31.29	Growth time [s]      CI95% [s]        17.50      ± 0.72        18.18      ± 0.58        19.91      ± 0.73        31.29      ± 2.35

## **S4 Interfacial tension**

The theoretical interfacial tension is calculated using the equation proposed by Mersmann (eq. S9 in the manuscript) <sup>3</sup>, but is dependent on the equilibrium solubility. In this work, the solubility equation proposed

by Fujiwara et al. has been used, (eq S8) <sup>4</sup>, with  $x_{PCM}$  the equilibrium solubility in mole fraction. The solubility of PCM in a variety of compounds has also been investigated by Granberg and Rasmuson for 26 solvents. <sup>5</sup> Grant et al. have proposed an equation for the PCM in water solubility. <sup>6</sup> Table S15 shows theoretical interfacial values ( $\gamma$ ) for PCM-water for various temperatures (T), assuming different PCM-water solubilities.

 $\ln(x_{\rm PCM}) = 5193.11 \frac{1}{T} + 27.12 \cdot \ln(T) - 178.28 \,(S8)$ 

$$\ln(x_{\text{PCM}}) = 12.200 \frac{1}{T} + 49.69 \cdot \ln(T) - 330.3$$
(S9)

 $\label{eq:table_transformation} \textbf{Table $15$} \ \textbf{Theoretically calculated interfacial tensions for PCM in water,} for different solubilities.$ 

TRO	γ [mJ/m²]	γ [mJ/m²]	γ [mJ/m²]
ΠCJ	[Fujiwara] <sup>4</sup>	[Granberg] <sup>5</sup>	[Grant] <sup>6</sup>
5	25.08	24.91	24.62
10	24.76	24.66	24.51
15	24.41	24.34	24.33
20	24.01	23.98	24.07
25	23.57	23.58	23.73
30	23.10	23.16	23.32

The critical nucleus radius can be found using eq. S10 (assuming spherical nuclei). The critical radius ( $r_{\rm crit}$ ) is almost unaffected by the variances in the interfacial tensions due to the differences in equilibrium solubilities.

$$r_{\rm crit} = 2\gamma \nu_0 \cdot \frac{\ln(S)}{kT} \tag{S10}$$

The number of molecules in a critical nucleus  $(n^{\ast})$  can then be found using eq. S11.  $^{\rm 8}$ 

$$n^* = \frac{\frac{4}{3}r_{\rm crit}^3}{\nu_0} \tag{S11}$$

The critical nucleus radius and number of molecules are plotted as a function of supersaturation in Fig. S3. As expected the radius calculated from the theoretical interfacial tension is significantly higher than the one calculated from the experimentally determined effective interfacial tension. The experimentally determined number of molecules are also shown in Table 9 in the manuscript. Eq. S10 can be generalised for all particles, by using a shape factor. Hendriksen and Grant have shown that the number of molecules was not affected for parallelepiped nuclei, compared to spherical nuclei. <sup>7</sup>



**Fig. S3** [top graph] The critical radius as a function of supersaturation, calculated from the theoretical interfacial tension (assuming equilibrium solubility as determined by Fujiwara et al.) and effective interfacial tension for primary (filtered) and secondary nucleation. [bottom graphs] The number of molecules as a function of supersaturation, calculated from the critical radii in the top graph.

# S5 Effect of the starting temperature on the results

To evaluate the effect of heat transfer not being completed on the results discussed in the manuscript, the worst case is studied here. The time before heat transfer is completed is increased by starting from a microvials heated to 80°C. Apart from a different starting temperature, the experimental methodology is completely similar, as discussed in the manuscript. It is observed that even with significant heat transfer problems, the same trends are observed as in the main manuscript (with a starting temperature of 42°C, very close to the saturation temperature).

## **S5.1** Mean induction times

The mean induction times are reported in Tables S16 and S17.

Table S16 Mean induction time for primary (filtered) and primary (cage), and secondary nucleation ( $T_{start}$ =80°C).

T [°C]	S [-]		mean induction time $\pm$ CI95% [s]
		Primary (filtered)	176.36± 13.27
5	3.09	Primary (cage)	129.78 ± 12.16
		Secondary	73.78 <u>+</u> 3.99
		Primary (filtered)	$146.28 \pm 8.37$
10 2.65	2.65	Primary (cage)	$146.83 \pm 11.26$
		Secondary	81.45 ± 4.25
		Primary (filtered)	339.9 <u>+</u> 87.41
15	1.94	Primary (cage)	230.58 ± 35.08
		Secondary	$113.23 \pm 11.06$
		Primary (filtered)	723.25 ± 278.77
20	1.64	Primary (cage)	375.08 ± 87.12
		Secondary	162.45 ± 27.82

 $\label{eq:table_$ 

т [°C] S [-]			mean induction
			time $\pm$ Cl95% [s]
0.0	2.67	US-induced	82.40 ± 2.97
9.8	2.67	US-induced secondary	60.05 <u>+</u> 2.60
15.6	2 22	US-induced	93.00 ± 2.95
15.0	2.22	US-induced secondary	68.20 ± 2.83
20.2	1 02	US-induced	114.28 <u>+</u> 4.21
20.2 1.92		US-induced secondary	79.83 ± 4.76
25.6	1.61	US-induced	148.00 ± 7.44
		US-induced secondary	93.28 <u>+</u> 5.52

#### **S5.2** Nucleation rate parameters

The nucleation rate parameters can be obtained from fitting the nucleation rate equation, as discussed in the main manuscript. Fig. S4 and Table S18 show the obtained results.



Fig. S4 Fitting of the nucleation rate equation for US-induced, and USinduced secondary nucleation (MS1, amplitude=20%, continuous sonication).

Table S18 A,B parameters (T<sub>start</sub>=80°C).

26
.21
075
.12
.01

## S5.3 Effect of the sonotrode

Apart from the MS1 (1 mm diameter, 125 W/cm<sup>2</sup>) probe that is used in this article, also a new MS2 (2 mm diameter, 600 W/cm<sup>2</sup>) and a worn-out MS2 (here called MS2 [old]) have been used to study the effect of changing sonotrodes on the mean induction time and the nucleation rate parameters. In Table S19 the steady-state temperatures for the different conditions and probes are summarized. The mean induction times for the different sonotrodes for different temperatures are shown in Table S20. The results are plotted in Fig. S5.

As mentioned earlier, titanium particles might come off the sonotrode's surface. With the worn-out MS2 probe in some cases so many particles went into the solution that the solution turned turbid and detection of the onset of nucleation became impossible. These measurements were discarded.

Table S19Steady-state temperatures for various well temperatures insonicated microvials for MS1 (amplitude=20%, continuous sonication),MS2 (amplitude=20%, continuous sonication), and MS2 (amplitude=20%,pulsed sonication).

T <sub>well</sub> [°C]	MS1 (A=20%)	MS2 (A=20%)	MS2 (A=20%,C=0.5)
5	9.8	10.9	7.4
10	15.6	15.6	12.8
15	20.2	20.7	17.7
20	25.6	26.5	22.9

**Table S20** Mean induction times for US-induced nucleation varying well temperatures for two different sonotrodes (MS1, MS2, and MS2 [old]; operated at amplitude: 20%, cycle: 1). It is assumed that the old MS2 and new MS2 sonotrode have the same calorimetric power.

T [°C]	Sonotrode [-]	mean induction time + 95%CI [s]		
9.8	MS1	82.40 ± 2.97		
10.0	MS2	$89.10 \pm 2.87$		
10.9	MS2 [old]	73.65 <u>+</u> 5.26		
15.6	MS1	93.00 ± 2.95		
15.0	MS2	99.68 ± 4.57		
15.9	MS2 [old]	83.13 ± 2.15		
20.2	MS1	<b>MS1</b> 114.28 ± 4.21		
20.7	MS2	$118.85 \pm 4.47$		
20.7	MS2 [old]	94.03 ± 2.66		
25.6	25.6 <b>MS1</b> 148.00 ± 7.44			
26.5	MS2	150.85 ± 6.52		
	MS2 [old]	112.73 ± 3.41		



**Fig. S5** Fitting of the nucleation rate equation for primary (filtered), and US-induced nucleation (MS1, amplitude=20%, continuous sonication; MS2, amplitude=20%, continuous sonication; MS2 [old], amplitude=20%, continuous sonication (C=1); MS2 [old], amplitude=20%, pulsed sonication C=0.5)).

## S5.4 Nucleation rates and coefficients of determination

Tables S21, S22, S23, S24, and S25 give the nucleation rate and CI95% obtained from fitting for varying well temperatures and varying nucleation mechanisms (with starting temperature of 80°C). The coefficient of determination is also given in these tables. Tables S26, S27, S28, and S29 give the growth times and CI95% obtained from fitting for varying well temperatures and varying nucleation mechanisms. Table S21 Nucleation rate values for primary filtered nucleation ( $T_{start}$ =80°C). for varying well temperatures.

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
5	1.155·10 <sup>4</sup>	± 1050	0.9019
10	7.84·10 <sup>3</sup>	± 584	0.9745
20	4.46·10 <sup>3</sup>	<u>±</u> 344	0.9791
25	2.46·10 <sup>3</sup>	± 213	0.9768

Table S22 Nucleation rate values for primary (cage) nucleation ( $T_{start}{=}80^{\circ}C$ ). for varying well temperatures.

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
5	1.186·10 <sup>4</sup>	± 1180	0.9448
10	1.221·10 <sup>4</sup>	± 2450	0.9423
20	7.032·10 <sup>3</sup>	± 644	0.9569
25	3.398·10 <sup>3</sup>	± 184	0.9879

Table S23 Nucleation rate values for secondary nucleation ( $T_{start}$ =80°C). for varying well temperatures.

т	Nucleation rate	CI95%	<b>R</b> <sup>2</sup>
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
5	2.496·10 <sup>4</sup>	± 4070	0.8288
10	3.474·10 <sup>4</sup>	<u>+</u> 3790	0.9349
20	2.109·10 <sup>4</sup>	± 1840	0.9690
25	1.266·10 <sup>4</sup>	± 750	0.9879

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
9.8	4.956·10 <sup>4</sup>	± 4220	0.9623
15.6	5.048·10 <sup>4</sup>	± 4130	0.9651
20.2	3.264·10 <sup>4</sup>	± 2860	0.9572
25.6	2.092·10 <sup>4</sup>	± 2580	0.9163

Table S25 Nucleation rate values for US-induced secondary nucleation (MS1, amplitude=20%, continuous sonication) ( $T_{start}$ =80°C). for varying well temperatures.

т	Nucleation rate	CI95%	$R^2$
[°C]	[m <sup>-3</sup> s <sup>-1</sup> ]	[m <sup>-3</sup> s <sup>-1</sup> ]	[-]
9.8	5.309·10 <sup>4</sup>	± 4800	0.9552
15.6	5.302·10 <sup>4</sup>	± 4900	0.9592
20.2	2.587·10 <sup>4</sup>	± 3530	0.8918
25.6	2.981·10 <sup>4</sup>	± 2430	0.9658

## S5.5 Growth times

Table S26 Growth times for primary (filtered) nucleation (T\_{start}=80°C) for varying well temperatures.

T [°C]	Growth time [s]	CI95% [s]
5	117.9	± 3.1
10	111.9	<u>+</u> 3.5
20	129.8	± 5.8
25	185.9	<u>+</u> 11.4

Table S27 Growth times for primary (unfiltered) nucleation (T\_{start}=80  $^{\circ}\text{C})$  for varying well temperatures.

т [°С]	Growth time [s]	CI95% [s]
5	76.79	± 3.25
10	95.87	<u>+</u> 3.18
20	127.3	± 4.9
25	135.0	± 5.5

Table S28 Growth times for secondary nucleation ( $T_{\text{start}}\!\!=\!\!80^\circ\text{C})$  for varying well temperatures.

T [°C]	Growth time [s]	CI95% [s]
5	50.11	± 2.79
10	62.83	<u>+</u> 1.25
20	77.18	<u>+</u> 1.48
25	90.42	<u>+</u> 1.58

 $\label{eq:table_$ 

T [°C]	Growth time [s]	CI95% [s]
	69.14	± 0.66
	69.31	± 0.62
	94.91	± 1.04
	117.4	± 2.3

Table S30 Growth times for US-induced secondary nucleation (MS1, amplitude=20%, continuous sonication) ( $T_{\rm start}{=}80^\circ C$ ) for varying well temperatures.

т [°С]	Growth time [s]	CI95% [s]
	47.87	± 0.67
	47.88	± 0.68
	58.35	<u>+</u> 2.12
	70.69	± 1.06

## S6 Product crystals

The product crystals are analyzed using optical microscopy (Nikon SMZ1500 Stereoscopic Zoom Microscope with a Nikon DS-2M digital camera) after filtration on a filter (Merck, MF-Millipore Membrane, 0.22  $\mu$ m pore size) connected to a vacuum pump (VP 100 C vacuubrand for VWR). All the crystals produced in the Crystal16 exhibit a monoclinic shape. After removal of the solution, large agglomerates where formed. The results are shown in Fig. S6 and Fig. S7.



Fig. S6 Product crystals inspected using optical microscopy immediately after detection in the Crystal16 with a well temperature at 20°C, for : (a,e) filtered solution; (b,f) solution with the empty cage submerged; (c,g) solution with the cage and crystal submerged; (d,h) solution continuously sonicated (MS1, amplitude 20%)



**Fig. S7** Product crystals inspected using optical microscopy immediately after detection in the Crystal16 with a well temperature at 20°C, for : (i,m) filtered solution; (j,n) solution with the empty cage submerged; (k,o) solution with the cage and crystal submerged; (l,p) solution continuously sonicated (MS1, amplitude 20%)

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