Supporting Information

Continuous Production of Iron Oxide Nanoparticles *via* Fast and Economical High Temperature Synthesis

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SI 1: LIST OF CHEMICALS USED

All chemicals used for this work are listed in Table S1.

Table S1: Details of chemicals used

Compound	Purchased from	Manufacturer	Lot Nr.	Purity
Ferric acetylacetonate	Sigma Aldrich UK	Aldrich(517003)	MKBT5618V	97%
Oleylamine	Sigma Aldrich UK	Aldrich (O7805)	STBG8339	Technical grade, 70%
1-Octadecene	Sigma Aldrich UK	Aldrich (O806)	SHBJ3034	Technical grade, 90%
Isopropyl alcohol	Sigma Aldrich UK	Fischer Scientific (P/7500)	1849784	Certified AR for analysis, >95%

SI 2: REACTOR FOR CONTINUOUS THERMAL DECOMPOSITION SYNTHESIS

SI 2.1: Details of reactor set-up

Pictures of the reactor system used are shown in Figure S1. A picture of the flow meter in its customised heater is shown in Figure S2a. In order to calibrate the flow meter heated to 50 °C, 1-octadecene was pumped though the flow meter using a syringe pump (Legato210 KD Scientific, USA) at different flow rates while recording the flow meter readout. The set and measured flow rates, as well as the obtained calibration curve are shown in Figure 2b.
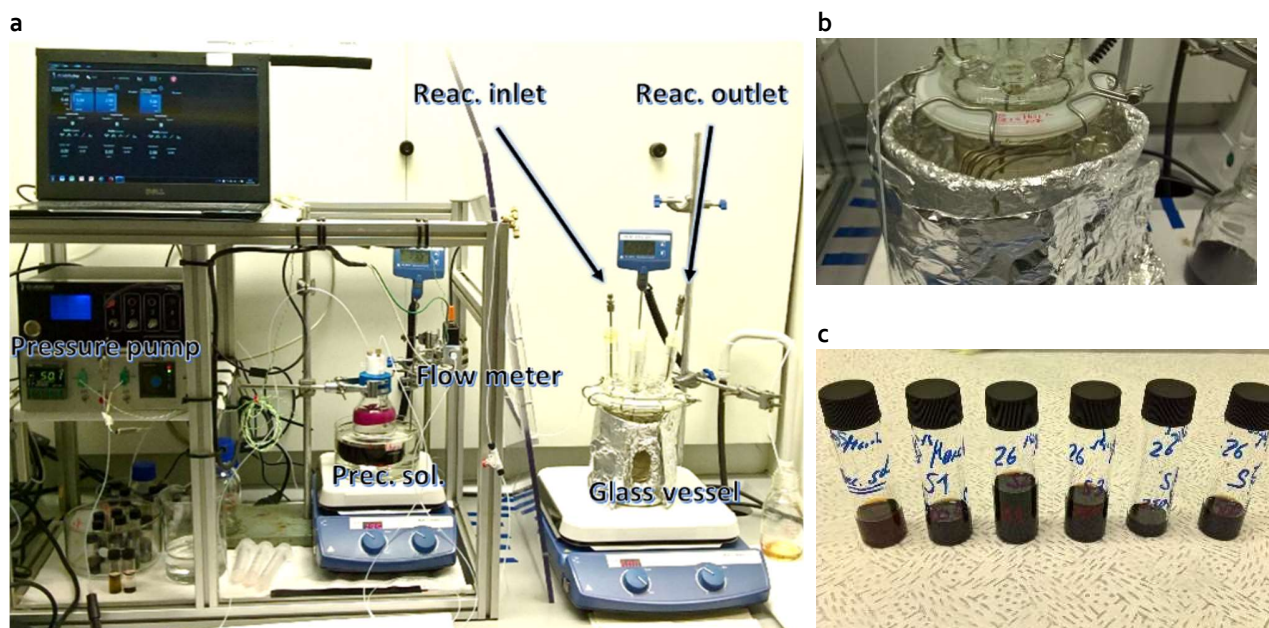

Figure S1: Pictures of the reactor set-up used for continuous synthesis of IONPs by thermal decomposition. (**a**) Overview; (**b**) Tubular reactor in the heated glass vessel with insulation; (**c**) Collected samples after synthesis at 250 °C.
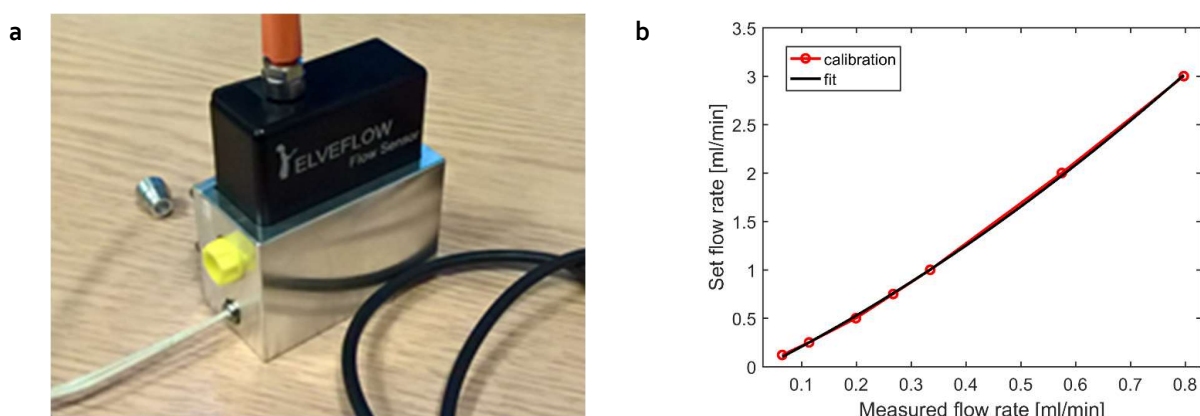

Figure S2: (**a**) Customised heater for flow meter, *i.e.*, aluminium frame heated *via* cartridge heater. (**b**) Set and measured flow rates of 1-octadecene with the flow meter heated to 50 °C used for calibration.

SI 2.2: Feed stability study

In order to study if the feed solution remains stable during the process (*i.e.*, no precipitation in the connection between the heated precursor solution reservoir and the heated tubular reactor, and no fluctuations in feed precursor concentration), samples

were collected over a period of 1.5 h just before the precursor solution entered the reactor. These samples were then analysed *via* UV-Vis spectroscopy, as described in the Materials and Methods section. These results, as well as the pressure profile during this study are shown in Figure S3. Figure S4 shows the collected samples.
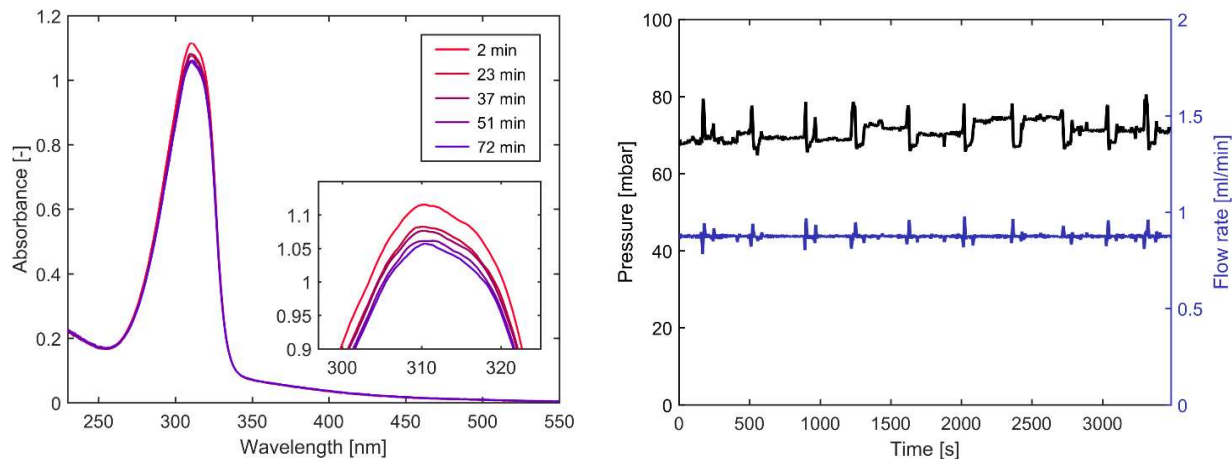

Figure S3: (*left*) Absorption spectra of feed samples collected before entering the reactor at various operation times. (*right*) pressure pump readout (applied pressure and measured flow rate) when setting the flow rate to 0.85 ml/min. The fluctuations in pressure approx. every 5 min originate from sampling, *i.e.*, lifting the tube connected to the reactor outlet to collect sample in vials. The pressure remained very low during this study demonstrating absence of precipitation in the connection tubing.
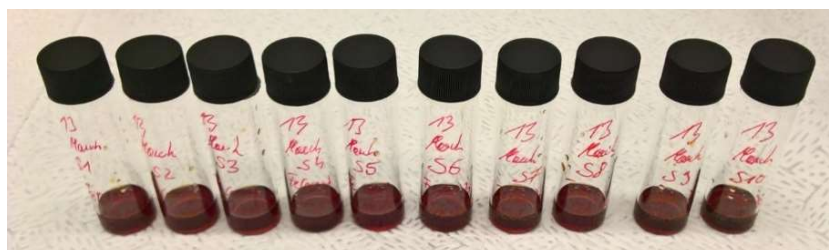

Figure S4: Samples collected during the feed stability study

SI 2.3: Reactor cleaning studies

After each operation, the tubular reactor was cleaned simply by pushing air through it with a syringe connected to the inlet. Once cooled to room temperature, the reactor was flushed with a nonpolar solvent first (twice with 1-octadecene) and then with isopropyl alcohol. This was followed by a rinse with DI water, always ~20 ml each, and purging with air. Afterwards, the reactor was rinsed with a HCl solution (~15%) to dissolve possible ferrous residuals. The effluent of the 1st 1-octadecene cleaning after operation was always brownish. This is because this effluent contained IONP solution residuals that remained in the reactor after terminating the operation and purging the reactor with air. The described purging with air after each operation was not enough to completely remove the processed solution from the reactor. Therefore, the cleaning procedure (after the reactor reached room temperature) started with the 1-octadecene rinses. However, iron containing residuals adhering to the reactor wall would not have been removed during this or the following flushing(s), but dissolved when rinsing the reactor with the HCl solution and coloured the effluent. The collection of this HCl solution (*i.e.*, all HCl solution that was passed through the reactor), did not show any change in colour (see Figure S5), indicating the absence of iron containing residuals growing on the reactor wall. It is worth mentioning that the effluent of the HCl flushing was brownish when testing the reactor for other high temperature synthesis of IONPs using different solvents (results not shown here).

Effluent of 1st 1-octadecene cleaning after operation at 290 °C

Effluent of 2nd 1-octadecene cleaning after operation at 290 °C
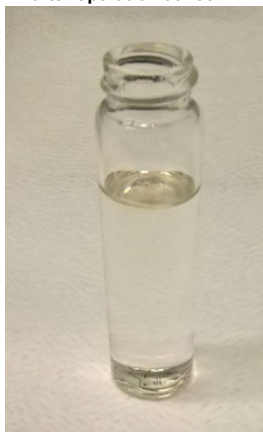
Effluent of isopropyl alcohol cleaning after operation at 290 °C

Effluent of HCl cleaning after operation at 250 °C

Effluent of HCl cleaning after operation at 270 °C

Effluent of HCl cleaning after operation at 290 °C

Figure S5: Effluent of the cleaning, *i.e.*, solutions collected after rinsing the reactor. The first row corresponds to the cleaning chronology which was followed by a HCl rinse. The effluent of the HCl cleaning step after operating at the different temperatures are shown in the bottom row.

SI 3: SAXS STUDIES

For the background correction of SAXS curves, a spectrum of 1-octadecene recorded using an identical capillary was used as background. The background was subtracted from each sample spectra after merging the spectra (background and sample) for scattering vectors of $q > 2\ nm^{-1}$. The radius of gyration R_g was determined via the Guinier approximation for globular particles (equation S1) by a straight-line fit (equation S2) within a q range of $q^2 = 0.06 - 0.45\ nm^{-2}$ for all spectra.

$$I(q) = I(0) \cdot \exp\left(-q^2 \cdot R_g{}^2/3\right) \qquad \text{S1}$$

$$\ln\bigl(I(q)\bigr) = \ln\bigl(I(0)\bigr) - q^2 \cdot \left(R_g{}^2/3\right) \qquad \text{S2}$$

The particle diameter obtained *via* SAXS analysis was determined assuming spherical particles, *i.e.*, using the definition of the radius of gyration of a sphere with the radius R_{sphe} , (equation S3).

S3

$$D_{sphere}(SAXS) \equiv 2 \cdot R_{sphere} = 2 \cdot \sqrt{5/3} \cdot R_g$$

The analysis was executed in ATSAS version 2.8 (Franke, D., et al*., J. Appl. Cryst.* 50, 1212-1225).

SI 4: UV-VIS STUDIES

Due to the strong absorbance of Fe(acac)$_3$, the precursor solution (0.0073 g/ml) had to be diluted to maintain the linearity according to the Beer-Lambert law, *i.e.*, allowing for precursor concentration determination from absorbance measurements. To determine for which Fe(acac)$_3$ concentrations linearity is maintained, UV-Vis spectra of IPA solutions with decreasing Fe(acac)$_3$ concentrations were recorded. Based on these results (see top of Figure S6), a 1/750 dilution with IPA was chosen for the Fe(acac)$_3$ concentration determination.

A picture of the precursor solution and its 1/750 dilution achieved by adding 0.08 ml to 60 ml IPA is shown in Figure S7. The UV-Vis spectrum of the precursor solution after heating (see bottom of Figure S6) was different than the spectra of the initially prepared Fe(acac)$_3$ IPA solutions. Still, the maximum absorbance values were similar, showing that the linear regime is still maintained. For all studied precursor and IONP solutions, the wavelength of the maximum absorption used to obtain the conversion was between 310 and 315 nm.
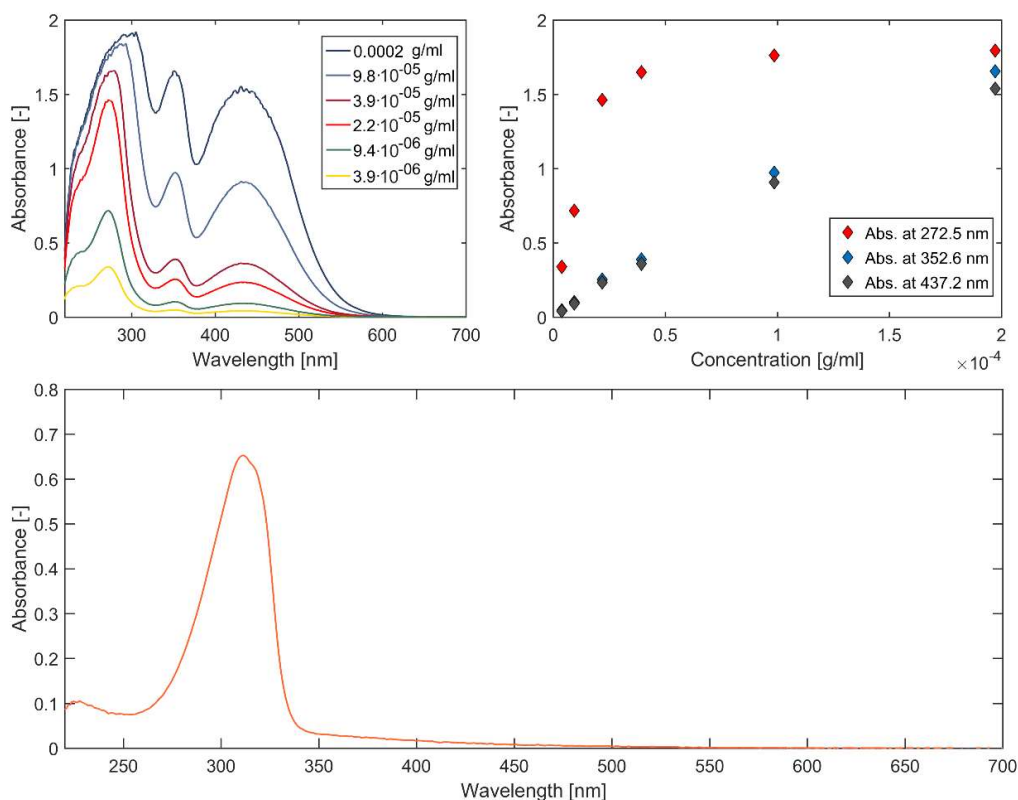
Figure S6: Absorption spectra of (top, *left*) Fe(acac)$_3$ (as received) dissolved in IPA, (top, *right*) absorbance of the three characteristic peaks vs. Fe(acac)$_3$ concentration, (bottom) absorption spectra of precursor solution after heating to 120 °C for > 30 min 1/750 diluted with IPA.

Figure S7: Sample of precursor solution (*left*) and 1/750 diluted precursor solution (0.08 ml precursor solution added to 60 ml IPA) as used for UV-Vis studies (*right*).

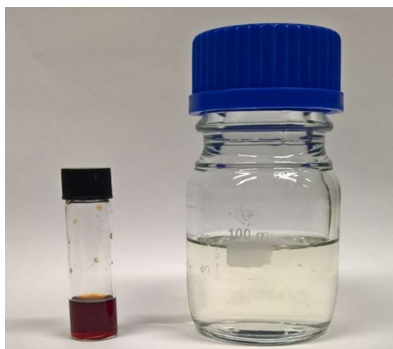## SI 5: TEM STUDIES

As part of the TEM analysis electron diffraction profiles of the samples shown in Figure 5 and Figure 8 were recorded (see Figure S8a). Radially averaging the diffraction profiles confirmed that the synthesised IONPs were of the inverse spinel structure of magnetite (see Figure S8b). The particle size histograms of the samples in Figure 5 and Figure 8 are shown in Figure S9 and Figure S10.
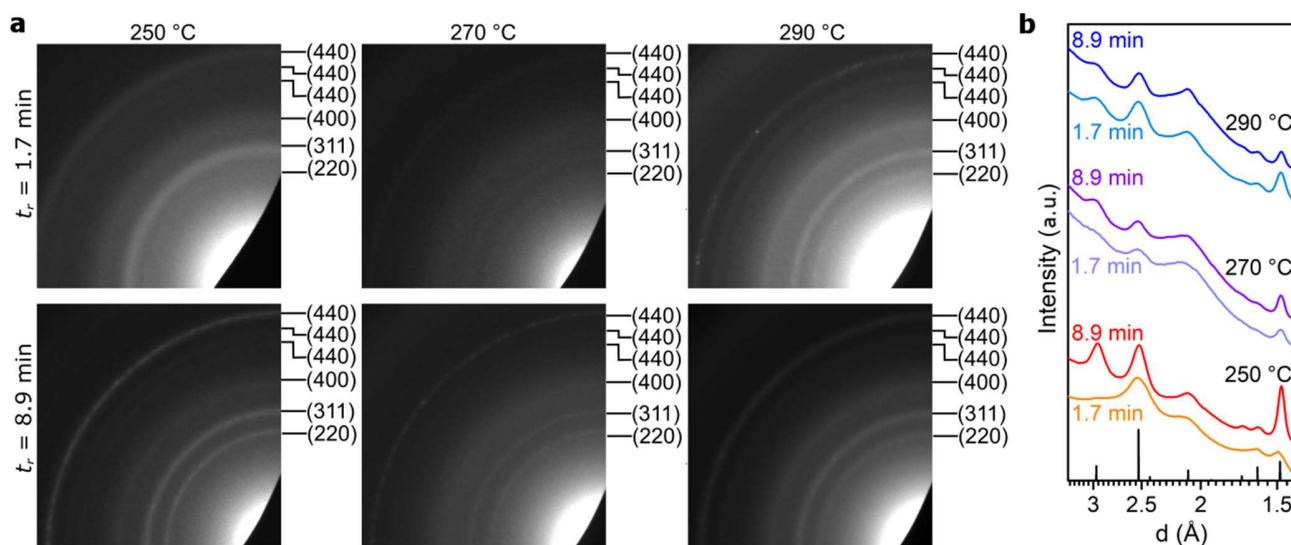
Figure S8: (a) Electron diffraction patterns recorded *via* TEM for samples synthesised at 250 °C, 270 °C and 290 °C using the shortest and longest residence time, *i.e.*, t_r = 1.7 min and t_r = 8.9 min, with indexing of the *hkl* values corresponding to magnetite. (**b**) Radially averaged diffraction profiles and the corresponding pattern for magnetite shown by the black bars at the bottom (magnetite PDF ref. 03-065-3107).

Figure S9: Histograms (*bars*) of particle sizes obtained from TEM images of IONPs synthesised at 250 °C (see Figure 5) and the normal distributions (*solid line*) generated using the mean particle size and the particle size standard deviation.

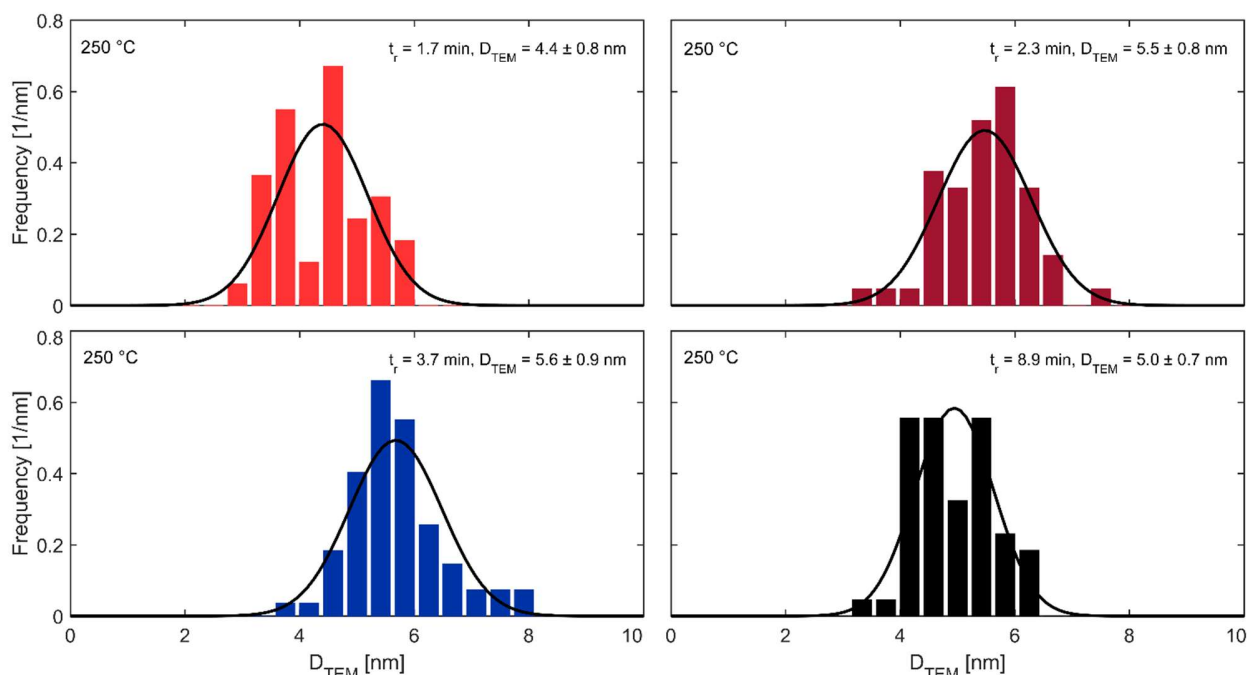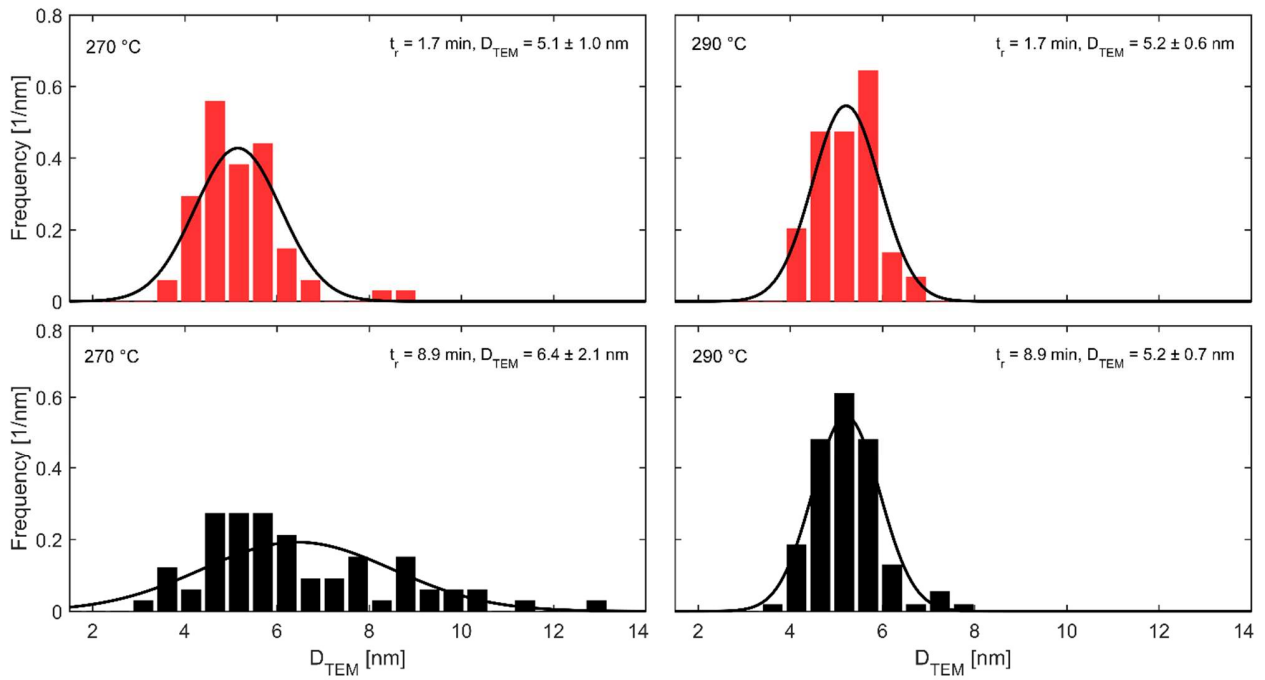**Figure S10:** Histograms (*bars*) of particle sizes obtained from TEM images of IONPs synthesised at 270 °C and 290 °C (see Figure 8) and the normal distributions (*solid line*) generated using the mean particle size and the particle size standard deviation.

SI 6: BATCH STUDY

The IONP batch synthesis was performed using a 50 ml round bottom flask connected to a Schlenk line system. Similar to the reaction conditions of the flow reactor, 6.6 ml of oleylamine and 13.3 ml of 1-octadecene were used as solvent (20 ml in total) and 146 mg of $Fe(acac)_3$ (0.41 mmol) were added to the solution. This precursor solution was heated in a round bottom flask to 120 °C under N_2 flow and left for 30 min at this temperature. Subsequently the solution was heated up at 270 °C and left at this temperature for 10 min. Aliquots were taken from the solution at different stages of reaction: at 120 °C (precursor solution) and at 270 °C after 5 and 10 min at this temperature. The solution was cooled to room temperature by removing the heating mantle. After each experiment the glassware was rinsed with *aqua regia* (HCl: HNO_3 mixture) to remove any residuals and was washed with abundant water to rinse away the *aqua regia*. The absorption spectra of samples (recorded as described in the Materials and Methods section) withdrawn before (= precursor sol), during (= 5 and 10 min) and after the batch (= final) synthesis are shown in Figure S11.
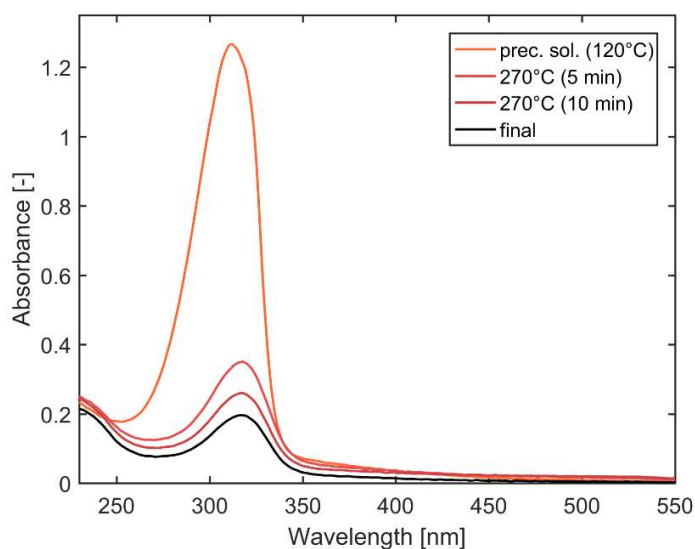
Figure S11: Absorption spectra of IONP solutions synthesised at 270 °C in a batch process.

Based on the absorption spectra of samples withdrawn from the batch reactor it was confirmed that the reaction did not need long operating times. Most of the precursor was converted before reaching the final reaction temperature (*i.e.*, at undefined temperatures) based on a comparison of the spectra of the precursor solution and the 5 min sample. However, a slight increase of conversion at the final reaction temperature is indicated by a decrease in characteristic absorbance peak between 310 and 315 nm comparing the samples withdrawn after 5 and 10 min, and after the batch synthesis. From the maximum absorbance of the final sample a conversion of 80% was obtained for the batch synthesis.

SI 7: PRESSURE PUMP RECORDINGS

The pressure and flow rate measured during the operation at 250 °C is shown in Figure 2. The pressure and flow rate measured during operations at 270 °C and 290 °C are shown in Figure S12 and Figure S13.

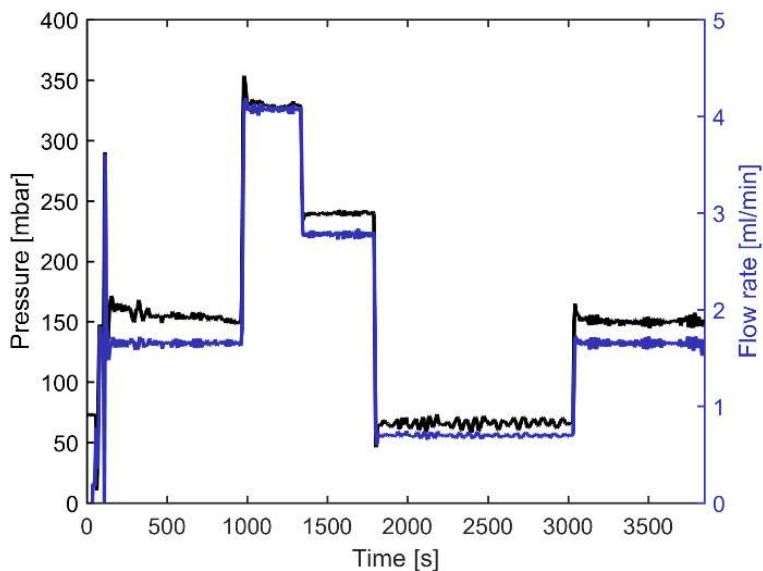**Figure S12:** Measured pressure and flow rate during the flow experiment at 270 °C, while changing flow rates.
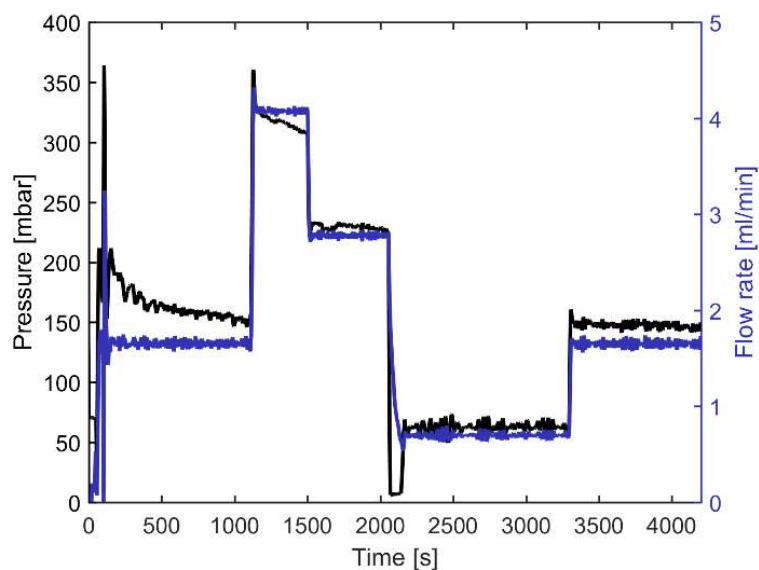

Figure S13: Measured pressure and flow rate during the flow experiment at 290 °C, while changing flow rates.

SI 8: COST ANALYSIS

SI 8.1: Chemicals

Table S2: Price list of the chemicals used to calculate costs for production in the batch and flow system (prices obtained August 2019).

Compound	Identified supplier	Quantity	Info	Price
Ferric acetylacetonate	Fisher Scientific	1 kg	99%	208 GBP
Oleylamine	Fisher Scientific	5 l	Technical grade 96%	523 GBP
Octadecene	Fisher Scientific	2.5 l	Technical grade 90%	64 GBP
Isopropyl alcohol	Sigma-Aldrich	8 kg	Used in the cleaning phase	96 GBP
Hydrochloric acid	Fisher Scientific	25 l	37%, used in the cleaning phase	290 GBP
Acetone	Alfa Aesar	2.5 l	Used in the cleaning phase	21 GBP
Nitric acid	Sigma-Aldrich	1 l	Used in the cleaning phase	24 GBP

Table S3: Breakdown of costs for chemicals for the production of 60 ml IONP solution in batch.

Compound	Quantity/60 ml	Price/unit	Price/60 ml	Total
Ferric acetylacetonate	0.44 g	0.21 GBP/g	0.09 GBP	
Oleylamine	20.00 ml	0.10 GBP/ml	2.09 GBP	
Octadecene	40.00 ml	0.03 GBP/ml	1.02 GBP	
Hydrochloric acid	112.50 ml	0.01 GBP/ml	1.31 GBP	8.23 GBP
Nitric acid	37.50 ml	0.02 GBP/ml	0.89 GBP	
Water	270.00 ml	1.77×10^{-05} GBP/ml	4.77×10^{-03} GBP	
DI water	270.00 ml	2.00×10^{-03} GBP/ml	0.54 GBP	
Acetone	270.00 ml	0.01 GBP/ml	2.28 GBP	

Note 1: The values per 60 ml might not match exactly the listed quantity and price due to round-off errors
Note 2: For the cleaning of the glassware including the flask a quantity of 150 ml of *aqua regia* (assuming a quantity of 50 ml for each of the three 20 ml batches to produce 60 ml IONP solution) was assumed together with 150 ml of DI water and acetone.

Table S4: Breakdown of costs for chemicals for the production of 60 ml IONP solution using the flow reactor (operated at 0.7 ml/min).

Compound	Quantity/60 ml	Price/unit	Price/60 ml	Total
Ferric acetylacetonate	0.44 g	0.21 GBP/g	0.09 GBP	
Oleylamine	20.00 ml	0.10 GBP/ml	2.09 GBP	
Octadecene	40.00 ml	0.03 GBP/ml	1.02 GBP	
Octadecene (cleaning)	1.27 ml	0.03 GBP/ml	0.04 GBP	3.28 GBP
Isopropyl alcohol	1.27 ml	0.02 GBP/ml	0.02 GBP	
DI water	1.27 ml	2.00×10^{-03} GBP/ml	2.00×10^{-03} GBP	
Hydrochloric acid	1.27 ml	0.01 GBP/ml	0.01 GBP	

Note: The values per 60 ml might not match exactly the listed quantity and price due to round-off errors

SI 8.2: Reactor equipment

Table S5: Price list of the equipment (including heat transfer fluid) used to calculate costs for production in the batch and flow system.

Reactor equipment	Quantity	Price	Assumed lifetime
Oil bath vessel	1 unit	70 GBP	2 years
Heat transfer fluid	1 l	6 GBP	4 months
Glassware	10 units	30 GBP	3 years
Coated metal tubing	2 m	300 GBP	1 year
Stirring hotplate (500 W)	1 unit	500 GBP	5 years
Stirring hotplate (1500 W)	1 unit	800 GBP	5 years
Pressure pump and flow meter	1 unit	3500 GBP	2 years
Schlenk line system	1 unit	1500 GBP	10 years

Note: Prices are representative values for the required type of equipment.

Table S6: Breakdown of costs for reactor equipment for the production of 60 ml IONP solution in batch.

Element	Quantity/60 ml	Price/unit	Price/60 ml	Total
Heat transfer fluid	17.31 mL	6.00×10^{-03} GBP/ml	0.10 GBP	
Oil bath vessel	2.02×10^{-03} unit	70.00 GBP/unit	0.14 GBP	
Glassware	4.03×10^{-03} unit	2.98 GBP/unit	0.01 GBP	2.01 GBP
Stirring hotplate	0.002 unit	714.00 GBP/unit	1.15 GBP	
Schlenk line system	4.03×10^{-04} unit	1500.00 GBP/unit	0.60 GBP	

Note 1: The values per 60 ml might not match exactly the listed quantity and price due to round-off errors
Note 2: Costs for the equipment were estimated based on the assumed lifetime of each element and the assumed annual working days, *i.e.*, 248 days (8 h working time each). An example for the price per unit estimation is shown at the end of this section.

Table S7: Breakdown of costs for reactor equipment for the production of 60 ml IONP solution using the flow reactor (operated at 0.7 ml/min).

Component	Quantity/60 ml	Price/unit	Price/60 ml	Total
Heat transfer fluid	3.53 ml	6.00E-03 GBP/ml	0.02 GMP	
Oil bath vessel	8.23×10^{-04} unit	70.00 GBP/l	0.06 GMP	
Glassware	5.49×10^{-04} unit	2.98 GBP/unit	0.002 GMP	1.95 GBP
Coated metal tubing	8.23×10^{-04} unit	293.30 GBP/unit	0.24 GMP	
Stirring hotplate	3.29×10^{-04} unit	1300.00 GBP/unit	0.20 GMP	
Pressure pump and flow meter	4.11×10^{-04} unit	3500.00 GBP/unit	1.43 GMP	

Note: The values per 60 ml might not match exactly the listed quantity and price due to round-off errors

Example price per unit estimation: For the batch system, we use one oil bath vessel with a lifetime of 2 years. Therefore, its daily usage is: 1 unit for 2 × 248 days, giving 2.02×10^{-03} unit/d (= 2.02×10^{-03} per 60 ml which was the assumed production volume for one day). For the flow system two oil bath vessels were used, each with a lifetime of 2 years: 2 units for 2 × 248 days, giving 4.03×10^{-03} unit/d. As the flow system produced 294 ml/d, the 4.03×10^{-03} unit/d were scaled to match the production of 60 ml by multiplying with 60/294 ml/ml giving 8.23×10^{-04} per 60 ml produced in flow.

SI 8.3: Energy and labour

Table S8: Energy and labour for the production of 60 ml IONP solution in batch.

		Quantity/60 ml	Price/unit	Price/60 ml (= Total)
Energy	Heating	4.90 kWh	0.11 GBP/unit	0.54 GMP
Labour	Technician	8 h	30.38 GBP/h	243.00 GMP

Note: The values per 60 ml might not match exactly the listed quantity and price due to round-off errors

Table S9: Energy and labour costs for the production of 60 ml IONP using the flow reactor (operated at 0.7 ml/min).

		Quantity/60 ml	Price/unit	Price/60 ml (= Total)
Energy	Heating	4.01 kWh	0.11 GBP/kWh	0.44 GMP
Labour	Technician	1.63 h	30.38 GBP/h	49.59 GMP

Note 1: The values per 60 ml might not match exactly the listed quantity and price due to round-off errors
Note 2: The required hours of the technician to produce 60 ml were calculated based on the 294 ml produced per day, *i.e.*, during an 8 h shift.
Note 3: Energy costs assigned to pumping where estimated to be 3.00×10^{-03} GBP (for 60 ml), hence negligible.