



OPEN

SUBJECT AREAS:

METAL-ORGANIC  
FRAMEWORKS

SYNTHESIS AND PROCESSING

Received  
14 April 2014Accepted  
6 June 2014Published  
25 June 2014

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# Versatile, High Quality and Scalable Continuous Flow Production of Metal-Organic Frameworks

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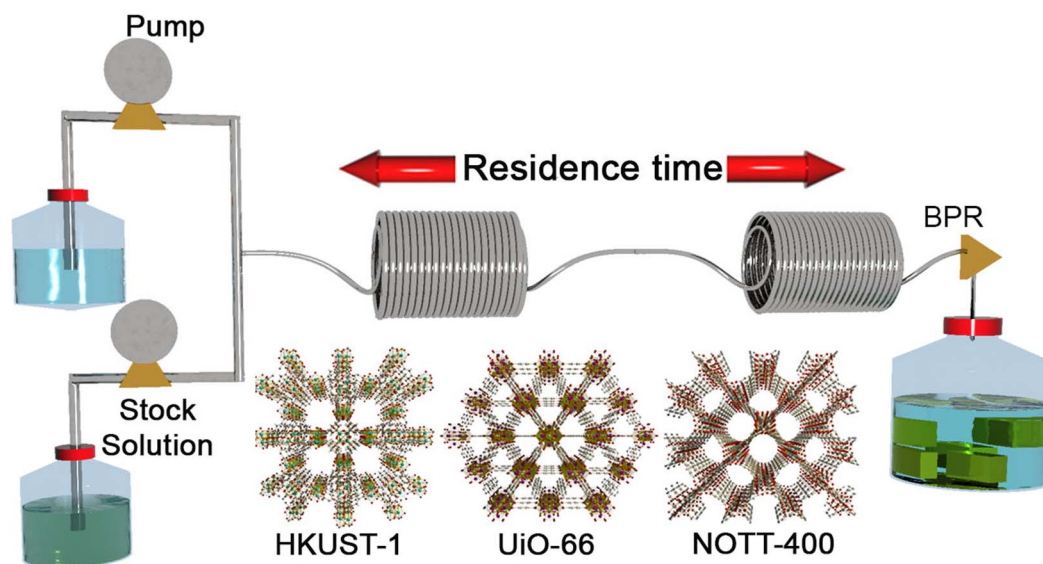
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**Further deployment of Metal-Organic Frameworks in applied settings requires their ready preparation at scale. Expansion of typical batch processes can lead to unsuccessful or low quality synthesis for some systems. Here we report how continuous flow chemistry can be adapted as a versatile route to a range of MOFs, by emulating conditions of lab-scale batch synthesis. This delivers ready synthesis of three different MOFs, with surface areas that closely match theoretical maxima, with production rates of 60 g/h at extremely high space-time yields.**

The last two decades of research into metal-organic frameworks (MOFs) have uncovered a multitude of potential industrial applications. Derived from organic linkers bound periodically by metal coordination centres, MOFs have unprecedented internal surface areas and uniform pore sizes<sup>1,2</sup>. Amongst others, they have been shown to be prospective materials for the storage<sup>3,4</sup>, separation<sup>5,6</sup> and triggered release of gases<sup>7,8</sup>, drug molecules<sup>9,10</sup> or toxins<sup>11</sup>. Underpinning all of these potential applications is the ability to routinely synthesise the MOFs in large quantities at high efficiency. One of the barriers to scaled-up MOF synthesis is that commonly, MOFs nucleate at a reaction surface<sup>12</sup>, meaning that the size of the reaction vessel becomes a significant parameter in the synthesis conditions. Consequently, reactions that proceed in small lab scale conditions are not always successful when scaled up into larger vessels, limiting scaled up MOF chemistry to a small number of MOFs that are robust in their preparation, each requiring bespoke equipment<sup>13,14</sup>. Therefore a method to conveniently expand the scale of reaction whilst maintaining the reaction vessel size is extremely attractive to applied MOF chemistry, offering a versatile route to production. Continuous flow chemistry is renowned as a paradigm shifting approach to chemical synthesis, offering an impressive surface to volume ratio. The improved heat and mass transfer available leads to speedy and reaction syntheses, new synthetic pathways, and broader green chemistry implications<sup>15</sup>.

Recently, some early reports have indicated that it is possible for MOFs to be produced by continuous processes. Walton *et al.*<sup>15</sup> showed that counter-current mixing at the high temperature of 300°C can lead to MOFs. It was also shown that small amounts of MOFs, within oil droplets, can be made in microfluidic reactors<sup>16,17</sup>. In 2013 Chang *et al.* reported a proof of concept mesoscale flow production of HKUST-1, albeit with moderate surface area at low scale<sup>18</sup>. All of these early reports are promising steps towards production of MOFs at scale, however, in order for this to be viable, pure MOFs must be readily attainable without a loss in product quality. Given the wide array of MOFs known, and the likelihood of a large range of applications each requiring different MOFs in the future, a versatile fabrication technique is crucial. Here, we have devised an optimal continuous flow chemistry concept for the production of MOFs. We show that it is applicable to a number of MOFs, each with different reaction conditions. It is demonstrated that the results can be extended 30-fold in scale, capable of more than a kilogram per day production. Our optimisation revealed that all this was possible without a loss in yield or surface area in the material.

Firstly, the emulation of typical lab conditions inside small vials makes this a versatile approach to a number of MOFs, removing the need for bespoke equipment for each synthesis. Secondly, parametric analysis reveals the key factors influencing product quality, and by optimising and exploiting these it has been demonstrated that fast synthesis can be achieved without a loss in product quality, and moreover with a control over particle size. Finally,



**Figure 1** | Schematic representation showing the general flow reactor setup for the production of MOFs. The precursor solutions are pumped continuously, mixed via a static-mixer (T-piece) and enter the coiled reactor tubes at temperature (T). A backpressure regulator (BPR) situated after the reactor coil is used to maintain a constant liquid pressure. The residence time can be varied by changing the length of the reactor or pumping rates.

we have scaled up this process into larger reactors, demonstrating the production of quantities approaching those required for widespread application.

## Results and Discussion

To demonstrate the effectiveness and the versatility of this approach, we chose to synthesize three different MOFs: the copper trimesate HKUST-1<sup>19</sup>, the zirconium terephthalate UiO-66<sup>20</sup> and the scandium biphenyl-tetracarboxylate NOTT-400<sup>21</sup>. These three MOFs represent some of the most interesting materials for potential applications in gas storage and catalysis besides being thermally and chemically stable crystals<sup>22</sup>.

Our method is based on the simultaneous pumping of the separate precursor solutions of the organic ligand and the metallic salt into a T-micro mixer via HPLC pumps using a commercially available flow chemistry synthesis platform (see Figure 1 and S1). The mixed solvent streams were combined and directed into coiled flow reactors consisting of one to four 1.0 mm ID perfluoroalkoxy polymer (PFA) coil modules connected in series. Each reactor coil has a volume of 10 mL and its temperature is regulated to be constant and homogeneous throughout the reaction, eliminating the possible temperature gradients often observed in batch reactors. The synthesis of HKUST-1 was performed in a total volume of 20 mL at 80 °C and at total flow rates of 2, 10 and 20 mL·min<sup>-1</sup>, which resulted in a residence time of 10, 5 and 1 min respectively. UiO-66 was also successfully synthesized using the same set-up but at 130 °C in 10 min and using a flow rate of 2 mL·min<sup>-1</sup> and NOTT-400 at 85 °C in 15 min, at 2 mL·min<sup>-1</sup>, using a total volume of 30 mL. These reaction times are a dramatic improvement over conventional batch synthesis, which requires between 24 h for the production of HKUST-1 and UiO-66 and 72 h for NOTT-400. These short reaction times are made possible by the high surface-area-to-volume ratio in the reactor which is much higher than that of a typical bottom flask used in solvothermal synthesis. The dimensions of the flow reactor (1 mm ID) ensure an excellent heat and mass transfer showing a narrow residence time distribution and a near plug-flow like profile<sup>23</sup>. To evaluate the impact of our chemical flow approach on larger scale production we calculate the hourly rate of MOF production of the synthesis. In Table 1 our values are reported and compared to other candidates for larger scale production of MOFs and

commercially produced HKUST-1. To our best knowledge the values obtained by a flow chemistry approach are many multiples higher than any other values reported in the literature<sup>25</sup>. This fact underlines the great potential of continuous flow processing for industrial production of MOF materials, especially bearing in mind that the setup allows to continuously produce material for extended periods of time without observable blocking of the reactor coil or back-pressure regulator.

To demonstrate the scale-up capabilities of our approach we repeated the synthesis of HKUST-1 in a setup that was ten times larger scale than the Vapourtec reactor, i.e. a 108 mL reactor volume and a total flow rate of 90 mL·min<sup>-1</sup> (see Figure S2). Using exactly the same temperature and precursor concentrations we were able to produce 61.2 g of product in 1 hour. The resulting space-time yield (STY) of the process, which is given as Kg of MOFs product per m<sup>3</sup> of reaction mixture per day of synthesis, was estimated to 4533 Kg·m<sup>-3</sup>·day<sup>-1</sup> (see Figure S5). Remarkably, the STY value of HKUST-1 is sufficiently high for the mass production, considering that is twenty times that of the commercial analogue Basolite

**Table 1** | Comparisons of the reaction time between MOFs synthesized by convectional batch and by flow chemistry. BET surface areas, grams of MOF produced per 1 hour using flow chemistry and STY. Full adsorption isotherms are provided in the supplement information

MOF	Reaction time	SA <sub>BET</sub> (m <sup>2</sup> g <sup>-1</sup> )	g·h <sup>-1</sup>	STY (Kg m <sup>-3</sup> d <sup>-1</sup> )
HKUST-1 <sup>a</sup>	10 min	1852	1.48	592
HKUST-1 <sup>b</sup>	1.2 min	1805	61.2	4533
HKUST-1 <sup>c</sup>	5 min	1673	2.04	n/a
Basolite C300 <sup>d</sup>	150 min	1820	n/a	225
UiO-66 <sup>a</sup>	10 min	1186	1.68	672
UiO-66 <sup>e</sup>	24 h	1147	n/a	n/a
NOTT-400 <sup>a</sup>	15 min	1078	2.78	741
NOTT-400 <sup>f</sup>	72 h	1350	n/a	n/a

<sup>a</sup>Vapourtec Flow chemistry reactor (Mesoscale).

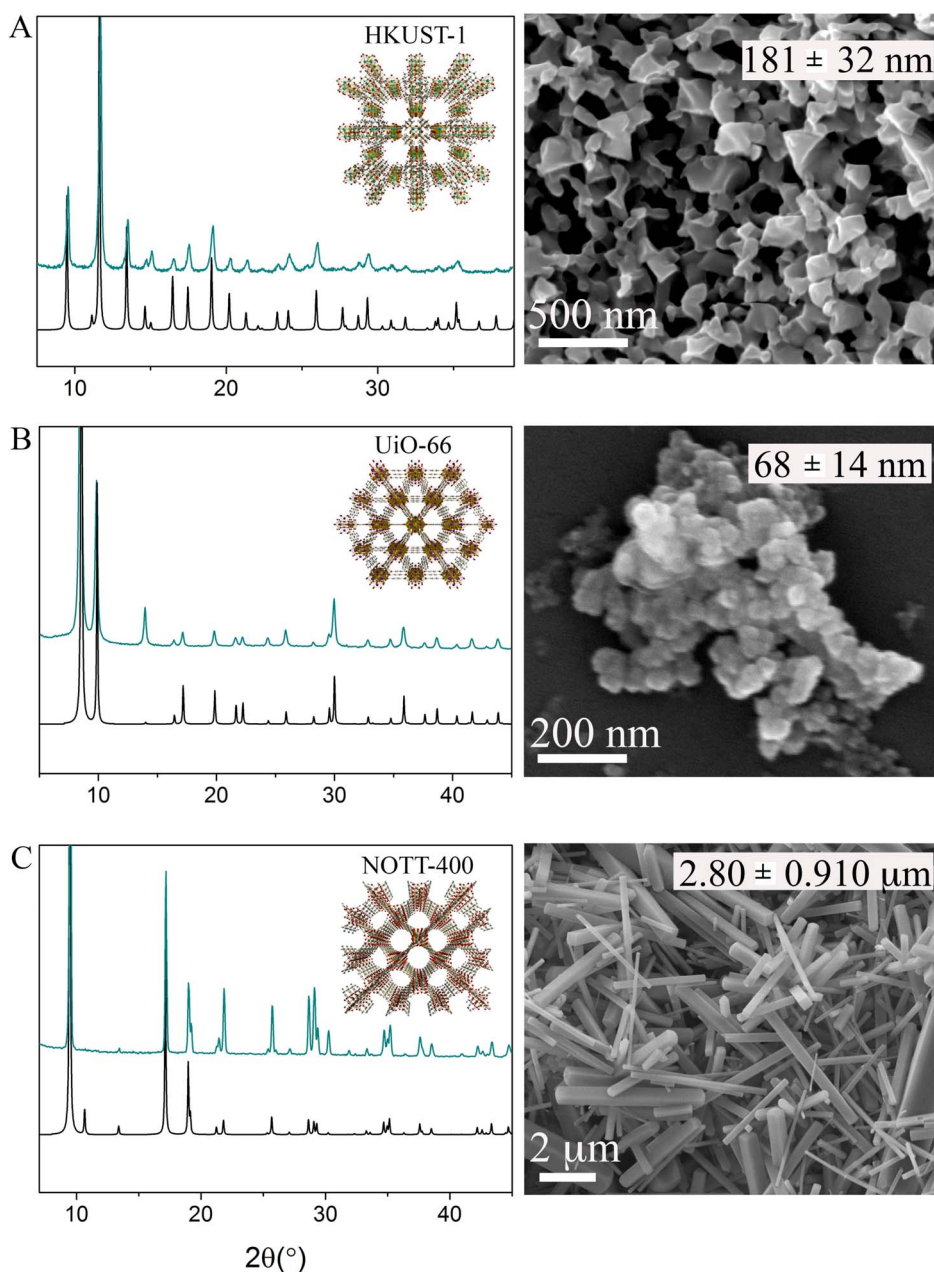
<sup>b</sup>Salamander flow chemistry results (Macroscale).

<sup>c</sup>Data from ref. 16.

<sup>d</sup>Data from ref. 24.

<sup>e</sup>Data from ref. 20.

<sup>f</sup>Data from ref. 21. Space-time yields given in this table based on the volume of the reaction mixture in 8 hours. Calculation based on ref. 13, see S5.



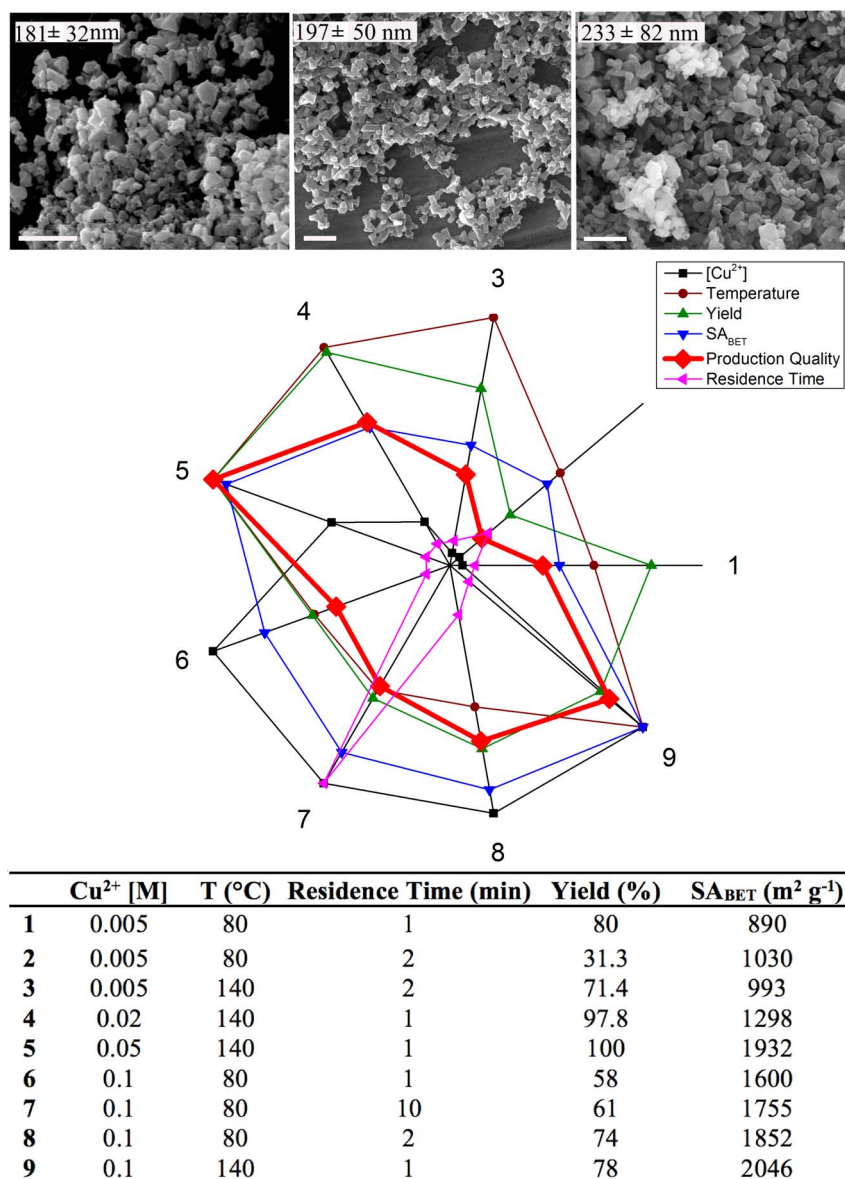
**Figure 2** | Characterization of a) HKUST-1, b) UiO-66 and c) NOTT-400 crystals obtained by flow chemistry using a total flow rate of  $2 \text{ mL} \cdot \text{min}^{-1}$  respectively. Comparisons of the XRPD patterns obtained by flow (green) with simulated structures (black). SEM images of the crystals obtained by flow chemistry.

C300<sup>24</sup>. This success clearly underlines the feasibility and potential of chemical flow synthesis for larger scale production of MOFs, which could meet future industrial and commercial requirements.

The overall quality of our HKUST-1, UiO-66 and NOTT-400 crystals was confirmed using X-Ray powder diffraction (XRPD). The diffraction patterns shown in Figure 2 confirm that the purity of the crystals obtained by flow chemistry is identical to the crystals synthesized by conventional solvothermal methods. The thermogravimetric analysis (TGA) curves show a continuous weight loss over the temperatures ranges 50 to  $100^\circ\text{C}$  due to the solvent loss, with small differences due to the type of solvent used in the purification processes (see Fig. S7). The size and morphology of the crystals were corroborated by scanning electron microscopy (SEM), as shown in Figure 2. The typical octahedral HKUST-1 crystals are obtained using different residence times and temperatures, where lower flow rates yielded more ideal crystal shapes (see Figure 3). For UiO-66,

small crystals under 100 nm are obtained, while for NOTT-400 rectangular crystals below  $10 \mu\text{m}$  are obtained. These crystal sizes, as with other faster synthetic methodologies like microwaves, are smaller than the crystals obtained under standard solvothermal conditions. This effect is attributed to the rapid crystallization kinetics induced by the flow chemistry approach<sup>26</sup>. Standard  $\text{N}_2$  and  $\text{H}_2$  adsorption measurements proved the porous character of the MOFs and yielded BET surface areas that are similar to values obtained by conventional methods, some mesoporosity was witnessed in UiO-66 due to inter-particle packing between the nano-sized crystallites.

The continuous flow chemistry set-up employed in the present case is amenable to precise control over reaction parameters. Taking advantage of this, a detailed investigation of different reaction conditions was undertaken to elucidate to what point facile and commercially attractive conditions (i.e. low temperatures, high



**Figure 3** | Representative SEM images of the HKUST-1 crystals synthesized by flow chemistry at 80 °C after 1, 2 and 10 minute residence times showing control over particle size (top). Scale bar: 500 nm. Overview diagram of the influence of reaction parameters on product synthesised based on data presented in the table (bottom). Production quality is defined as the product of BET surface area and percentage yield. Data have been normalised such that the maximum value for each parameter is set to unity.

concentrations, short residence times) could be employed prior to a loss of production quality, which in Figure 3 is defined as the result of yield multiplied by surface area, normalised to a value between zero and one. Control of particle size is also attractive for tailoring MOF production to a specific application, without the need for bespoke equipment. For example, use in mixed matrix membranes requires nanoparticulate materials, whereas bulk applications such as gas storage are better suited to macroscale particles that are not flocculent. The results indicate (Figure 3) that reaction temperature is the key factor affecting product quality, with both yield and surface area correlated in this case. Higher copper concentrations moderate the yield, but surface areas were largely unaffected. Encouragingly, reducing residence time appeared to improve surface areas without diminishing yields. In this case, the increase in surface area could be accounted for by a corresponding decrease in particle size (Figure 3, top). This type of control over particle size distribution from 100 nm to 1  $\mu\text{m}$  is of paramount importance for many applications, such as adsorption and catalysis<sup>27,28</sup>.

## Conclusions

To conclude, in the preceding, three key breakthroughs regarding the future directions for MOF synthesis at scale have been reported. Firstly, versatility within the one reaction apparatus led to the rapid production of three separate MOFs, namely HKUST-1, UiO-66 and NOTT-400. Secondly, this can be achieved without loss in product quality, with process optimisation leading to unprecedented production efficiency as measured by space-time yields, and control over particle size without a loss of surface area or yield. Finally, the proof-of-concept continuous flow production was expanded to a macroscale reactor where synthesis also proved facile, with a drastic increase in production rates from 2 to 60 g/h attained.

## Methods

**Synthesis of HKUST-1 using Vapourtec R4/R2+ reactor.** The general procedure described S1.a. was employed. In a typical reaction, solutions of 0.1 M  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  and 0.24 M benzene-1,3,5-tricarboxylic acid (BTC) both in ethanol, were pumped into the flow reactor (PFA tubing, 20 mL). The synthesis was



conducted at 80°C using three total flow rates of 2, 10 and 20 mL·min<sup>-1</sup> giving a residence time of 10, 5 and 1 min respectively and at 140°C using a flow rate of 20 mL·min<sup>-1</sup>. The material was washed twice with ethanol and dried under vacuum for 8 hours at 40°C. Yield: 74% for 2 mL·min<sup>-1</sup> at 80°C; 61% for 10 mL·min<sup>-1</sup> at 80°C; 58% for 20 mL·min<sup>-1</sup> at 80°C; 89% for 20 mL·min<sup>-1</sup> at 140°C.

**Synthesis of HKUST-1 using Salamander Plug Flow reactor.** The general procedure described S1.b. was employed. In a typical reaction, solutions of 0.1 M Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O and 0.24 M benzene-1,3,5-tricarboxylic acid (BTC) also in ethanol were mixed under continuous flow conditions and heated in a tubular reactor. The synthesis was conducted at 140°C using a total flow rate of 90 mL·min<sup>-1</sup>, giving a total residence time of 1.2 min. The material was washed twice with ethanol and dried under vacuum for 8 hours at 40°C. Yield: 100%.

**Synthesis of UiO-66 using Vapourtec R4/R2+ reactor.** The general procedure described S1.a. was employed. In a typical reaction, the two reactants were 0.1 M ZrCl<sub>4</sub> and 0.1 M 1,4-tricarboxylic acid (BDC), both of them prepared in dimethylformamide (DMF). The total volume was 20 mL. The synthesis was conducted at 130°C and with a combined flow rate of 2 mL·min<sup>-1</sup> yielding a residence time of 10 min. The material was washed once with DMF and immersed in methanol bath for 2 days. The final product was dried under vacuum for 8 hours at 40°C. Yield: 67%.

**Synthesis of NOTT-400 using Vapourtec R4/R2+ reactor.** The general procedure described S1.a. was employed. In a typical reaction, 0.04 M Sc(SO<sub>3</sub>CF<sub>3</sub>)<sub>3</sub> and 0.08 M Biphenyl-3,3',5,5'-tetracarboxylic acid (H<sub>4</sub>BPTC) were prepared in a mixture of DMF, tetrahydrofuran (THF) and water (3:4:1, respectively) and were pumped continuously into the flow reactor. The total reactor volume was 30 mL. The synthesis was conducted at 85°C and with an individual flow rate of 1 mL·min<sup>-1</sup> giving a residence time of 15 min. The material was washed once with DMF and immersed in acetone bath for 1 day. The final product was dried under vacuum for 8 hours at 40°C. Yield: 61%.

**Characterisation.** The scanning electron microscopy (SEM) images were collected on a Quanta 400 FEG ESEM (FEI) at acceleration voltage of 0.2–30 kV. Copper was used as support. The X-ray powder diffraction (XRPD) measurements were performed with an X'Pert Pro MPD diffractometer (Panalytical) over a 2θ range of 5° to 45°. The thermogravimetric analysis (TGA) was performed on a Perkin-Elmer STA-600 under a constant flow of N<sub>2</sub> at a temperature increase rate of 5°C/min. Gas adsorption isotherms for pressures in the range 0–120 kPa were measured by a volumetric approach using a Micrometrics ASAP 2420 instrument. All the samples were transferred to pre-dried and weighed analysis tubes and sealed with Transcal stoppers. HKUST-1, UiO-66 and NOTT-400 were evacuated and activated under dynamic vacuum at 10<sup>-6</sup> Torr at 140°C for 8 hours, 120°C for 12 hours and 170°C for 12 hours respectively. Ultra-high purity N<sub>2</sub> and H<sub>2</sub> gases were used for the experiments. N<sub>2</sub> and H<sub>2</sub> adsorption and desorption measurements were conducted at 77 K. Surface area measurements were performed on N<sub>2</sub> isotherms at 77 K using the Brunauer-Emmer-Teller (BET) model with adsorption values increasing range of 0.005 to 0.2 relative pressures. In order to estimate the particle size of the MOFs a statistical study was done based on five different SEM images of each MOFs.

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## Author contributions

M.R.M., M.B., A.P., J.I.M. and M.R.H. designed the experiments and the flow chemistry set-up. M.R.M. and M.B. carried out the experiments. M.R.M. and K.C. characterized the samples. M.R.H. and S.K.L. conceived the project. M.R.H. and M.R.M. drafted the manuscript. All authors discussed the results and commented on the manuscript.

## Additional information

Supplementary information accompanies this paper at <http://www.nature.com/scientificreports>

**Competing financial interests:** The authors declare no competing financial interests.

**How to cite this article:** Rubio-Martinez, M. *et al.* Versatile, High Quality and Scalable Continuous Flow Production of Metal–Organic Frameworks. *Sci. Rep.* **4**, 5443; DOI:10.1038/srep05443 (2014).



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