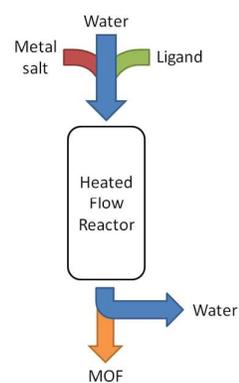


**Synthesis of Metal-Organic Frameworks by Continuous Flow**

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**Table of Contents Graphic**

Continuous flow synthesis of MIL-53(Al) can be achieved *via* continuous flow reaction in only 5-6 minutes with a space time yield of  $1300 \text{ kg m}^{-3} \text{ d}^{-1}$ . In addition, an effective method for the extraction of terephthalic acid from within the pores of MIL-53(Al) using supercritical ethanol has been developed, representing a methodology for the activation and removal of substrates from within porous hosts.



## Synthesis of Metal-Organic Frameworks by Continuous Flow

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### Keywords

Continuous process, flow chemistry, metal-organic framework, high temperature water, green chemistry, MIL-53, HKUST-1.

**Abstract**

A continuous flow process for the synthesis of a metal-organic framework using only water as the reaction medium and requiring only short residence times is described. This affords a new route to scale-up of materials incorporating many of the principles of green chemistry. The process is demonstrated by the synthesis MIL-53(Al) *via* continuous flow reaction requiring only 5-6 minutes with a space time yield of  $1300 \text{ kg m}^{-3} \text{ d}^{-1}$ . We have demonstrated the synthesis of 500 g of MIL-53(Al) using this process, which can be scaled-up further by simply feeding further solutions of metal salt and ligand through the reactor. The product has a higher surface area and a better colour than a commercially produced sample of this MOF. In addition, a new and effective method for the extraction of terephthalic acid from within the pores of MIL-53(Al) using supercritical ethanol has been developed, representing a new methodology for activation and removal of substrates from porous hosts.

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**Introduction**

Metal-organic frameworks (MOFs) are currently the focus of intense scientific interest due to their wide range of potential applications in gas storage<sup>1,2</sup> and separation,<sup>3</sup> catalysis,<sup>4,5</sup> drug delivery,<sup>6-8</sup> and as thermo-active,<sup>9</sup> conducting<sup>10,11</sup> and electronic<sup>12,13</sup> materials. Of particular interest to us is the potential of MOFs to store and purify fuel and exhaust gases.<sup>14</sup> For industrial scale applications, MOFs must not only possess the desired functionality and properties, but their synthesis and processing must be scalable at low cost to give products in high yield and purity. Increasing environmental awareness and commercial constraints mean that synthetic processes must be as green as possible, and water is thus an attractive solvent for the synthesis of MOFs.<sup>15,16</sup>

The most common methods for MOF synthesis are solvothermal batch reactions in Teflon-lined stainless steel bombs or glass pressure tubes.<sup>17-19</sup> Long reactions times of several days are commonly used with slow heating and cooling rates using solvents such as N,N'-dimethylformamide (DMF), which is a toxic mutagen and environmentally hazardous.<sup>20,21</sup> Slow hydrothermal syntheses are typically carried out at temperatures up to 220 °C, while microwave,<sup>22,23</sup> sonication and mechanochemical<sup>24,25</sup> syntheses involve shorter reaction times in some cases. However, for microwave and alternative methods of synthesis to be cost effective for scale-up, they need to have clear benefits over conventional heating routes.<sup>26,27</sup> Continuous flow synthesis of MOFs has been demonstrated previously in elegant studies

using interfacial synthesis to produce hollow MOF capsules on a small scale,<sup>28</sup> and utilising rapid solvent mixing.<sup>29,30</sup> Significantly, however, these methods still make use of organic solvents such as 1-octanol,<sup>28</sup> DMF<sup>29</sup> and EtOH.<sup>30</sup> One of our objectives is to completely eliminate the use of toxic/organic solvents by using high temperature water (HTW). In previous reports water has been successfully used as the reaction solvent for the synthesis of MOF materials.<sup>15,16,31</sup> Herein we confirm that HTW can be used to reduce the reaction times from days to minutes in order to prepare porous materials rapidly and cleanly with excellent potential for scale-up, particularly under continuous flow. We demonstrate this methodology by using HTW to produce MIL-53(Al), a benchmark MOF that combines thermal stability with porosity<sup>32</sup> and adsorption selectivity.<sup>33</sup> We combine this with a new strategy for removal of guest molecule in MIL-53(Al) using supercritical EtOH.

## Results and discussion

We have previously reported the use of HTW for the batch synthesis of MOFs, but the reaction generally required 48 hr for completion.<sup>15</sup> We have now developed this further such that the *batch* reaction of  $\text{Al}(\text{NO}_3)_3$  with terephthalic acid ( $\text{H}_2\text{L}^1$ ) in HTW at 250 °C yielded porous MIL-53(Al) in 10 min. A molar ratio for  $\text{Al}(\text{NO}_3)_3$ :  $\text{H}_2\text{L}^1$  of 2:3 was used with concentrations of 0.04 mol dm<sup>-3</sup> and 0.06 mol dm<sup>-3</sup>, respectively. The identity and composition of the MIL-53(Al) produced by this method was confirmed by powder X-ray diffraction (PXRD) and characterised further by thermal gravimetric analysis (TGA) and gas adsorption isotherms. Given that this represents a reduction in reaction time from 3 days to 10 min.,<sup>34</sup> we reasoned that this new approach could be developed further towards scale-up via *continuous* processing. However,  $\text{H}_2\text{L}^1$  is insoluble in cold water and is thus difficult to use in a continuous flow process using water. Thus, a trial batch reaction was carried out using disodium terephthalate ( $\text{Na}_2\text{L}^1$ ), which is water-soluble. This yielded MIL-53(Al) identical to the experiments using  $\text{H}_2\text{L}^1$  (Scheme 1). Reactions in batch were then carried out to establish whether the reaction temperature could be reduced whilst still using reaction times of 10 minutes. Batch reactions at 200 °C afforded product that is less crystalline as confirmed by PXRD which shows significant peak broadening, while reactions at 150 °C afforded almost no MOF product and much of the  $\text{H}_2\text{L}^1$  could be isolated as unreacted starting material.

A schematic of our apparatus developed for the continuous reaction is shown in (Figure 1). Aqueous solutions of  $\text{Al}(\text{NO}_3)_3$  and  $\text{Na}_2\text{L}^1$  are pumped by means of HPLC pumps (Gilson 306, 10 ml pump heads), and these solutions are mixed with another stream of water preheated to 300 °C before entering the tubular reactor (ID 0.370", volume 20.8 ml). The

temperature of the reactor is kept constant using resistance heaters and a temperature controller (Eurotherm 2216L), and downstream, the mixture is cooled by a heat exchanger. The solid product is recovered by a Tee filter (0.5  $\mu\text{m}$ ) and after filtration the liquid by-product stream enters a Back Pressure Regulator (BPR). The use of filtration enables the product to be recovered dry, and minimises the chance of BPR malfunctions. Two sets of filters and BPRs are installed in parallel to facilitate continuous operation of the system.

Reaction of  $\text{Al}(\text{NO}_3)_3$  with  $\text{Na}_2\text{L}^1$  in the continuous reactor in a 1:1 ratio at  $0.05 \text{ mol dm}^{-3}$  concentration gave high quality MIL-53(Al), and running the reaction for 20 minutes gave 0.5 g of product as a white powder (yield: 86% crude, 59% after removal of terephthalic acid from pores, based on Al utilisation and product  $[\text{AlOH}(\text{L}^1)]_n$ ). Both the as-synthesised batch and continuous flow products are microcrystalline and match known MIL-53(Al) phases. MIL-53(Al) is known to exhibit a breathing effect and phase transitions induced by heating or by uptake and removal of guest species.<sup>34-38</sup> Furthermore, the as-synthesised phase, MIL-53(Al)*ta*, contains uncoordinated  $\text{H}_2\text{L}^1$  trapped within the pores and this requires removal to maximise its porosity. Usually removal of trapped  $\text{H}_2\text{L}^1$  is achieved *via* calcination involving heating at 330 °C for 3 days<sup>34</sup> or washing with DMF.<sup>35,36</sup> In order to remove this uncoordinated ligand we developed a new procedure involving extraction of the product with supercritical ethanol (scEtOH) at 250 °C and 100 bar for 2 hr. This method effectively removes the uncoordinated  $\text{H}_2\text{L}^1$  from within the pores without decomposing the material. The extraction rig (Figure 2) used liquid ethanol at a flow rate of  $0.5 \text{ ml min}^{-1}$ , a back pressure of 100 bar with the first batch reactor held at 250 °C for 2 h. Removal of in-pore  $\text{H}_2\text{L}^1$  could be readily monitored by PXRD (Figure S3), TGA (Figure S14) and ATR-FTIR (Figure S16).

The removal of  $\text{H}_2\text{L}^1$  causes a phase change to a more open structure, MIL-53(Al)*op*, and this converts to the hydrated form, MIL-53(Al)*hy*, upon adsorption of water. The major phase using HTW in batch reaction is MIL-53(Al)*ta*. In continuous flow, the same phase is isolated but MIL-53(Al)*hy* is also present in the product (Figure 3a). PXRD analysis of products obtained from batch and by continuous flow reactions shows no peaks for  $\gamma\text{-AlO}(\text{OH})$ ,  $\text{H}_2\text{L}^1$  or other MOF phases. High resolution PXRD were recorded for a desolvated sample in which  $\text{H}_2\text{L}^1$  had been removed, and the recorded pattern matches very well with the MIL-53(Al)*op* phase (Figure 3b). Refinement of the PXRD patterns confirms the bulk purity of the sample (Figures S7 and S8). TGA demonstrates that the as-synthesised batch product MIL-53(Al)*ta* has thermal stability up to 540 °C and contains 0.8 equivalents of free  $\text{H}_2\text{L}^1$  (Figure 4). This is consistent with the thermal behaviour reported by Loiseau *et*

*al.*<sup>34</sup> where 0.7 equivalents of free H<sub>2</sub>L<sup>1</sup> was observed in the material. The product formed by continuous process shows similar thermal stability and contains 0.41 equivalents of free H<sub>2</sub>L<sup>1</sup> as determined by TGA.

MIL-53(Al) prepared at 250 °C using batch and continuous flow processes was treated with scEtOH to remove free H<sub>2</sub>L<sup>1</sup> from the pores (see ESI for details). This was followed by activation of the sample at 125 °C under vacuum overnight, and the N<sub>2</sub> adsorption was recorded for samples. The isotherms are type I as expected for this microporous material and the maximum uptakes (at 0.95 P/P<sub>0</sub>) for the batch and continuous flow samples were 289 cm<sup>3</sup> g<sup>-1</sup> and 296 cm<sup>3</sup> g<sup>-1</sup>, respectively (Figure 5). BET surface areas for the batch and continuous flow samples were 1097 m<sup>2</sup> g<sup>-1</sup> and 919 m<sup>2</sup> g<sup>-1</sup>, respectively, consistent with previously reported values for MIL-53(Al) of between 1270 m<sup>2</sup> g<sup>-1</sup> and 933 m<sup>2</sup> g<sup>-1</sup>.<sup>32,34,39</sup> A significant feature of MIL-53 materials is their framework flexibility upon gas loading. Importantly, the desolvated MIL-53(Al) sample produced *via* continuous flow in HTW exhibits the same expected framework phase transition upon CO<sub>2</sub> adsorption (Figure S17). Therefore, this HTW method does not alter the nature of the MOF material produced suggesting wider applicability of continuous flow to produce other MOFs. However, it is important to select the right reaction conditions to produce a highly porous material. The effect of temperature on the surface area and gas uptake of the material produced was investigated by performing the reactions between 200 and 300 °C. These results, summarised in Table 1, confirm that the optimum temperature for this system is 250 °C.

The real test of any 'green' process is whether it can be scaled up to produce commercially useful quantities of product. Therefore in collaboration with an industrial partner we have tested our synthesis of MIL-53(Al) using a larger scale reactor. With a flow rate for Na<sub>2</sub>L<sup>1</sup> of 400 ml min<sup>-1</sup> mixed with a heated flow of Al(NO<sub>3</sub>)<sub>3</sub> at 200 ml min<sup>-1</sup>, more than 500 g of MIL-53(Al) were produced as an aqueous slurry in 4 hr. After drying of the material, the resulting MOF powder is pure white in appearance (Figure 6) and after removal by calcination of H<sub>2</sub>L<sup>1</sup> from the pores the material has a surface area of 1010 m<sup>2</sup> g<sup>-1</sup> similar to that of the lab-scale sample and nearly double the 553 m<sup>2</sup> g<sup>-1</sup> of a commercially supplied sample of the same MOF (see ESI).<sup>40</sup> This scale of reaction corresponds to approximately 1 metric tonne per annum. The waste from this process include salts such as NaNO<sub>3</sub> but these can be readily removed from the effluent.<sup>41,42</sup> Another possibility to be explored is the use of a terephthalic acid saturator after the preheater to avoid the generation of sodium salts or by the substitution of Al(NO<sub>3</sub>)<sub>3</sub> by Al(OAc)<sub>3</sub> as acetate waste would be less hazardous.

However at the current scale of MOF manufacturing, disposal of these wastes does not pose a significant problem.

In order to demonstrate further the scope of the above methods, the MOF material HKUST-1 was synthesised in high temperature ethanol as the reaction solvent, first in batch and then using the continuous process. HKUST-1 has been synthesised previously in continuous flow,<sup>28,29,43</sup> and using ethanol in batch.<sup>44</sup> The process reported here combines the use of the green solvent ethanol and a continuous process, and PXRD of the isolated materials from this process confirms the formation of HKUST-1 (Figure 7). As both the trimesic acid ligand ( $H_3L^2$ ) and  $Cu(NO_3)_2$  are soluble in ethanol the use of ligand salts was not required in this case. No free ligand was recovered with the MOF material and so a second purification step was not necessary. The material produced by continuous process had a surface area of  $1554\text{ m}^2\text{ g}^{-1}$ , a maximum  $N_2$  uptake of  $417\text{ cm}^3\text{ g}^{-1}$  (0.95 P/P<sub>0</sub>), and a pore volume of  $0.62\text{ cm}^3\text{ g}^{-1}$  (Figure S15). The space time yield of HKUST-1 in this process was  $730\text{ kg m}^{-3}\text{ d}^{-1}$ .

## Conclusions

In summary, a rapid and green method for the synthesis of MIL-53(Al) with an excellent potential for scale-up has been developed in which HTW is used in continuous flow. We have thus far produced MIL-53(Al) in up to 500 g scale via continuous flow, and the utilisation of a green solvent combined with abundant, low-cost metal and ligand enhance this potential to form multi-kg quantities. A green synthesis for  $H_2L^1$  using HTW is already established<sup>45-47</sup> and so a complete process from the synthesis of the ligand to final MOF product can be envisaged using HTW. Although some MOFs including MIL-53(Al) are commercially available, their current price is too high for them to be used in most applications. MIL-53(Al) is currently sold at £2440-3455 for 500 g.<sup>40</sup> To reduce this cost, more productive processes are required, and the space time yield, defining the mass of product produced per unit volume per unit time, is an important parameter for comparing processes. Reported values for commercially-available MOFs correspond to space time yields of between 20 and  $>300\text{ kg m}^{-3}\text{ d}^{-1}$  with MIL-53(Al) at  $160\text{ kg m}^{-3}\text{ d}^{-1}$ .<sup>49-51</sup> The space time yield for our continuous flow process for MIL-53(Al) reported here is significantly higher at  $1300\text{ kg m}^{-3}\text{ d}^{-1}$ . Thus, the rapid synthesis of MOFs in HTW represents a greener method with potential for further investigation and possible commercialisation.

## Experimental

All reagents and solvents were used as received from commercial suppliers without further purification for both the batch and the continuous reactions.

### *Synthesis of MIL-53(Al)*

*Batch Synthesis:* The synthesis of  $\{[\text{AlOH}(\text{L}^1)] \cdot 0.8 \text{H}_2\text{L}^1\}_n$ , MIL-53(Al) in water was carried out in a high-pressure stainless steel batch reactor (10 ml of internal volume). The reactor was located in an aluminium heating block surrounded by an electric band heater (1 kW) with a cooling jacket for rapid cooling. Details of the device have been previously reported.<sup>48</sup>  $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  (112.9 mg, 0.301 mmol),  $\text{H}_2\text{L}^1$  (75.0 mg, 0.451 mmol) and water (5.0 ml) were transferred into the reactor, and the reaction mixture rapidly heated by preheating the aluminium block 20 °C higher than the desired temperature. The time required to reach the target reaction temperature is *ca* 5 min, and the system was kept at the target reaction temperature for 10 min and rapidly quenched using the cooling jacket. The product was recovered by filtration, washed with water and acetone, and dried in air. The reaction gave a white powder with a yield of 54 mg (91%) and a purified yield after *sc*EtOH extraction of 39 mg (66%).

*Continuous Process:* General conditions involved a flow rate of 1.0 ml min<sup>-1</sup> to give a total flow rate of 3.0 ml min<sup>-1</sup> of water. The pressure of the system (230 bar), and the temperature of the preheater and the reactor (300 °C and 250 °C, respectively) were set to the desired values. Once the temperatures were stable, the streams were changed to metal salt and ligand solutions and the flows passed through Filter 1 for 20 min. The three way valve was then switched to Filter 2 and next batch of product collected for 20 min, while product in Filter 1 was collected and a new filter inserted. After 20 min, the three way valve was switched back to Filter 1, new reaction conditions set and while the product in Filter 2 was collected and the filter, further product was collected in Filter 1. This process can be repeated for as long as sufficient metal salt and carboxylate ligand can be supplied.

### *Synthesis of HKUST-1*

The same procedure was used for the synthesis of HKUST-1 but ethanol instead of water was used (see Supplementary Details). For the synthesis of HKUST-1, the pressure of the system, temperature of the preheater and the reactor set were to 75 bar, 300 °C and 200 °C respectively, resulting in a 5.1 min residence time. Feed concentrations of 0.15 mol dm<sup>-3</sup> and 0.10 mol dm<sup>-3</sup> were used for the  $\text{Cu}(\text{NO}_3)_2$  and trimesic acid ( $\text{H}_3\text{L}^2$ ), and

the concentration in the reactor was  $0.05 \text{ mol dm}^{-3}$  and  $0.03 \text{ mol dm}^{-3}$ , respectively. After 15 minutes the reaction yielded 0.536 g of HKUST-1 as a blue powder. The powder contained 31.3% solvent as determined by TGA and so the yield of dry MOF was 63% with the product defined as  $[\text{Cu}_3(\text{C}_6\text{H}_3(\text{CO}_2)_3)_n]$ .

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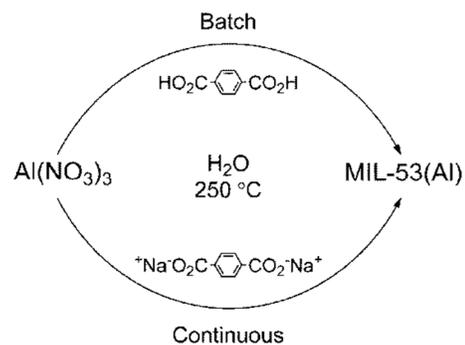
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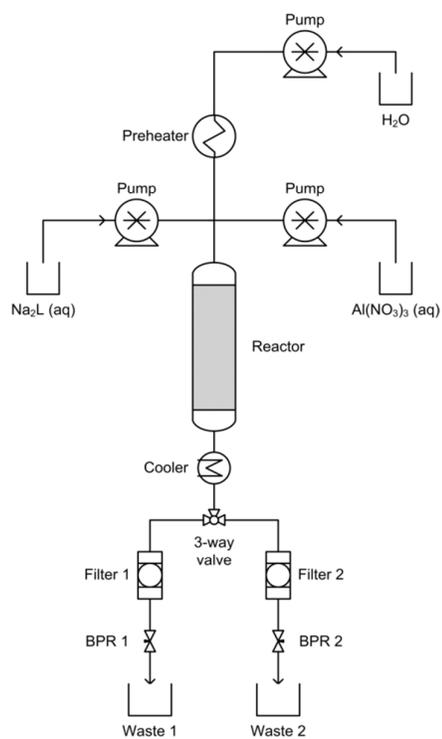
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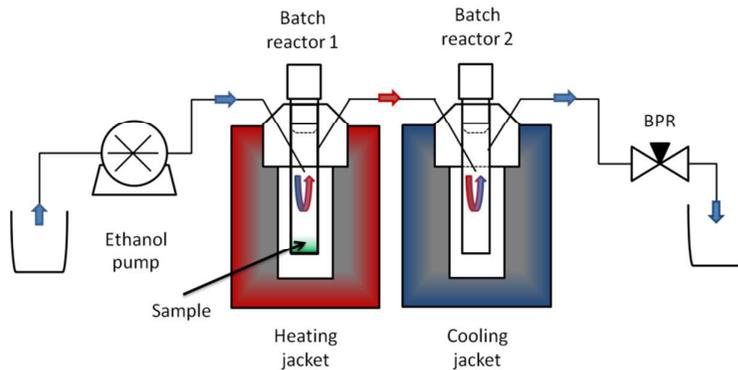
## Figure and Legends



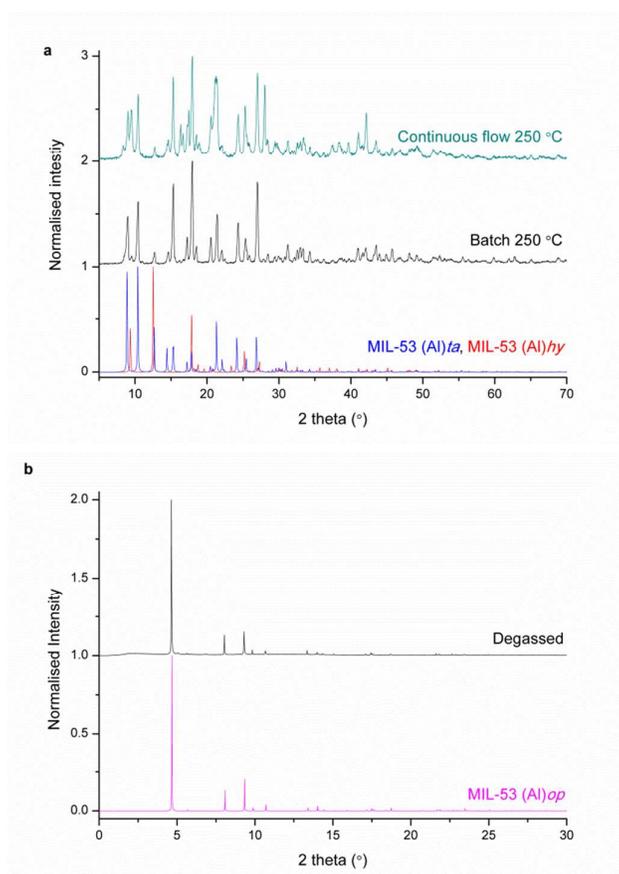
**Scheme 1** Reaction scheme for batch reaction and continuous flow processes for the synthesis of MIL-53(Al).



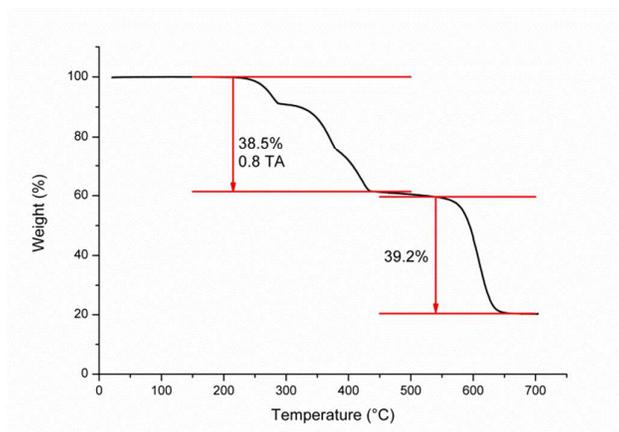
**Figure 1** Schematic of the continuous process rig. The grey section represents the heated section of the reactor.



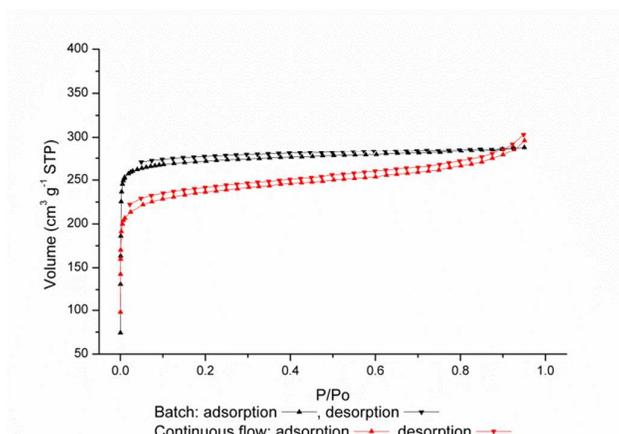
**Figure 2** Diagram of extraction rig comprising of a pump, two batch reactors in series (1<sup>st</sup> heated, 2<sup>nd</sup> cooled) and a back pressure regulator. Arrows indicate the flow direction; red and blue highlight heated and cold areas, respectively.



**Figure 3** (a) PXRD patterns of as-synthesised MIL-53(Al) produced in batch (black) and continuous flow (green) at 250 °C, and simulated pattern for MIL-53(Al)*ta* (blue) and MIL-53(Al)*hy* (red). (b) High resolution PXRD ( $\lambda = 0.827107 \text{ \AA}$ ) of desolvated MIL-53(Al) produced in batch at 250 °C and treated with scEtOH (black) and simulated pattern for MIL-53(Al)*op* (pink).



**Figure 4** TGA of as-synthesised MIL-53(Al) material prepared by batch reaction (250 °C) at a heating rate of 5 °C min<sup>-1</sup>. The first step of 38.5% between 215 °C and 440 °C is the loss of in-pore H<sub>2</sub>L<sup>1</sup> and the second step of 39.2% between 500 °C to 690 °C is loss of coordinated ligand and decomposition of the material.



**Figure 5** Comparison of N<sub>2</sub> isotherms at 77K for activated MIL-53(Al) prepared by batch (black) and continuous flow (red).

**Table 1** Summary of surface areas and N<sub>2</sub> uptake at 77K for MIL-53(Al) produced by continuous flow at temperatures between 225 and 300 °C.

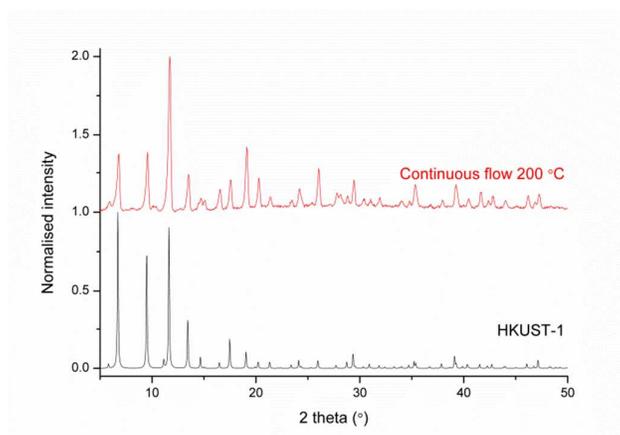
| Synthesis temperature (°C) | BET surface area (m <sup>2</sup> g <sup>-1</sup> ) | Uptake at p/p <sub>0</sub> = 0.95 (cm <sup>3</sup> g <sup>-1</sup> ) |
|----------------------------|--|--|
| 225                        | 459  | 223.5  |
| 250                        | 919  | 296.4  |
| 275                        | 804  | 258.7  |
| 300                        | 566  | 204.5  |



**Figure 6** Photograph of the barrel containing a suspension of MIL-53(Al) formed by continuous flow in our scaled-up reaction (centre), together with a commercial sample (bottom left) and dried MIL-53(Al) from the barrel (bottom right). A fifty pence piece is shown for scale (bottom centre).



**Figure 7** Photograph of a commercial sample of MIL-53(Al) (left), and our scaled-up material prepared by continuous flow (right).



**Figure 7** Comparison of PXRD for as-synthesised HKUST-1 material produced by continuous flow reaction at 200 °C (red), and the simulated pattern of HKUST-1 (black).