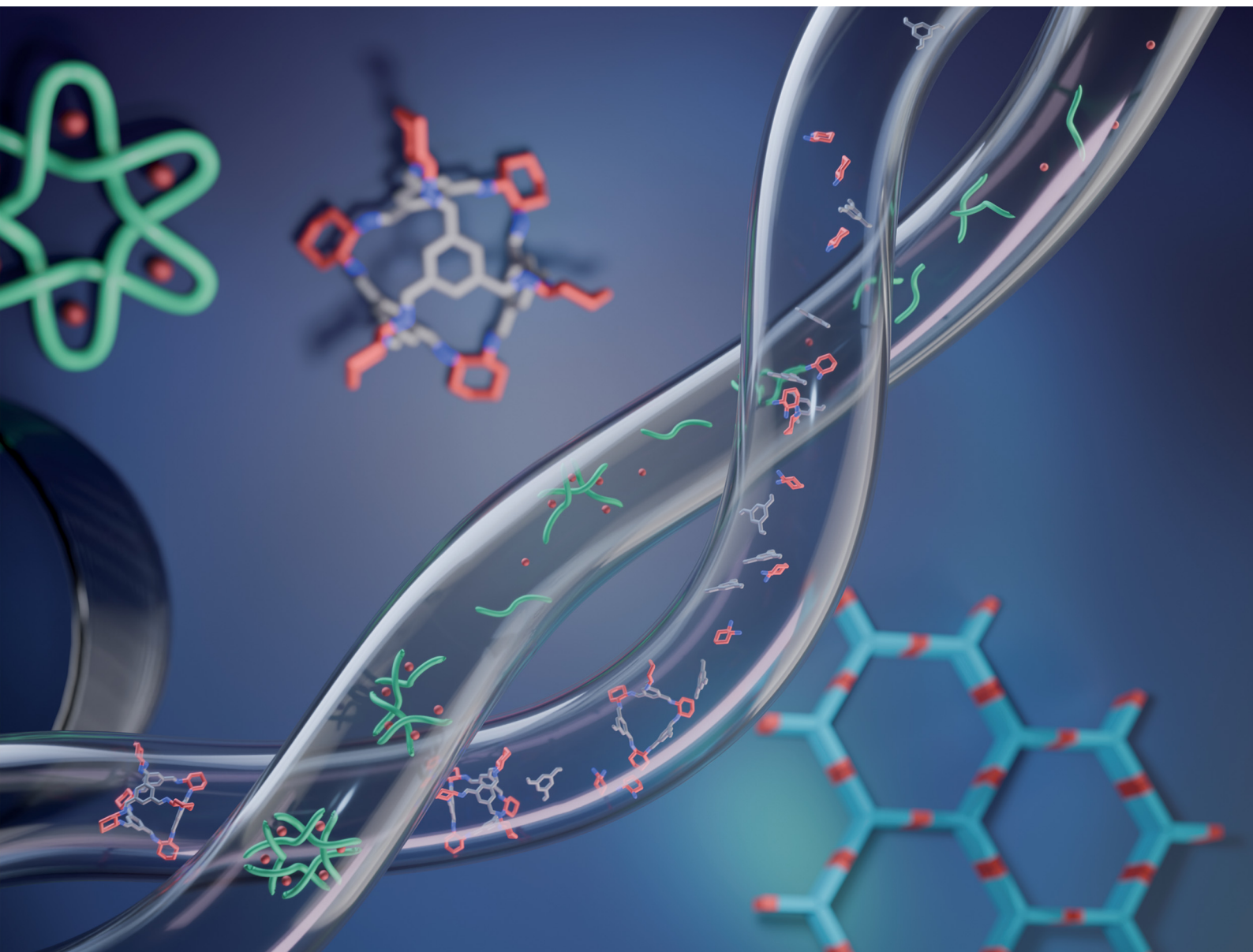


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## Self-assembly under continuous flow conditions

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Self-assembly plays a crucial role in the formation of hierarchical supramolecular structures and functional materials. The use of flow chemistry for self-assembly processes has garnered significant attention due to its enhanced ability to control the formation of complex molecular and nanoscale architectures. Compared to conventional batch processes, flow-based systems offer improved regulation of key reaction parameters, such as mixing dynamics, temperature gradients, and residence time, facilitating continuous and scalable synthesis. This review examines recent advances in self-assembly under flow conditions, highlighting advantages in four domains: scalable production, opportunities to control selectivity, improved product crystallinity, and precise regulation of size and morphology in particle formation. Selected case studies from the literature, including our work in this field, will be discussed to demonstrate that flow-based technology is valuable for the fabrication of supramolecular structures and represents a promising approach for advanced materials science.

### 1. Introduction

Self-assembled structures form from individual building blocks that collectively organise over time into the most thermodynamically favoured configuration, driven by non-covalent interactions such as hydrogen bonding, electrostatic interactions,  $\pi$ - $\pi$  stacking, metal-ligand coordination, and van der Waals forces.<sup>1,2</sup> By leveraging these interactions, small molecules can assemble into larger supramolecular architectures whose combined properties and behaviours differ significantly from that of their individual precursor building blocks.<sup>3,4</sup>

Governed by the principles of reversibility and ‘error-correction’, self-assembly presents a powerful strategy to achieve long-range order and/or hierarchical structures that are extremely difficult to obtain *via* stepwise synthesis.<sup>5-7</sup> As such, the principles of error-correction and assembly driven by overall thermodynamic stability have also been used to form multicomponent molecular species using reversible covalent bonds,<sup>8</sup> and, through crystallisation processes, porous crystalline materials.<sup>9</sup>

The range of such supramolecular systems is vast, including materials such as metal-organic frameworks (MOFs),<sup>10-13</sup> covalent organic frameworks (COFs)<sup>14-16</sup> and coordination polymers (CPs),<sup>17-20</sup> porous organic cages (POCs),<sup>21,22</sup> metal organic cages (MOCs),<sup>23-25</sup> molecular knots,<sup>26-28</sup> macrocycles,<sup>29,30</sup> and hydrogels.<sup>31,32</sup> Collectively,

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these materials exhibit significant potential for various applications, including host–guest chemistry for molecular storage, separation, and recognition,<sup>33–35</sup> drug delivery,<sup>34,36–38</sup> catalysis,<sup>39</sup> sensing,<sup>37,38</sup> and beyond. However, to achieve this potential, the reliable, sustainable, and scalable production of such structures is required: a remaining challenge for the field.<sup>40,41</sup>

Traditionally, self-assembly processes are carried out in batch reactors, which present several limitations including poor reproducibility, inefficient mixing, and challenges in scalable production due to inconsistent reaction conditions.<sup>42</sup> Furthermore, self-assembly often requires high-dilution conditions to avoid formation of kinetic by-products (*e.g.*, polymeric *vs.* discrete species), or relies on templating approaches, meaning that substantial solvent and waste would be generated upon scale-up of supramolecular syntheses for industrial applications.<sup>43,44</sup>

To address these challenges, flow reactors have emerged as a powerful alternative to batch due to their unique capabilities: precisely controlled reaction parameters, enhanced mass and heat transfer, and continuous operation.<sup>45,46</sup> The well-defined reaction environment in flow systems can afford a better control over nucleation and growth processes in self-assembly, which can result in improved uniformity, higher yields, enhanced reproducibility, and improved crystallinity in solid-state materials.<sup>47–52</sup> The ability to modulate parameters such as flow rate and temperature allows the formation of tuneable size and shape controlled self-assemblies, enabling the development of process-structure–function relationships.<sup>53–55</sup> Controlling selectivity *via* defined flow pathways and parameters rather than using high-dilution approaches also opens opportunities to increase concentration and throughput, minimising solvent use and waste.<sup>56</sup>

Compared to conventional batch processes, continuous flow systems offer precise control over key reaction parameters, enhancing reaction efficiency, selectivity, sustainability, and reproducibility, as summarised in recent reviews.<sup>45,46,51,57–59</sup> Two advantages that are particularly relevant to the examples in this review are (a) reproducible mixing and (b) improved temperature control.

Efficient mixing is essential for homogeneous reaction environments and consistent product quality. In batch systems,



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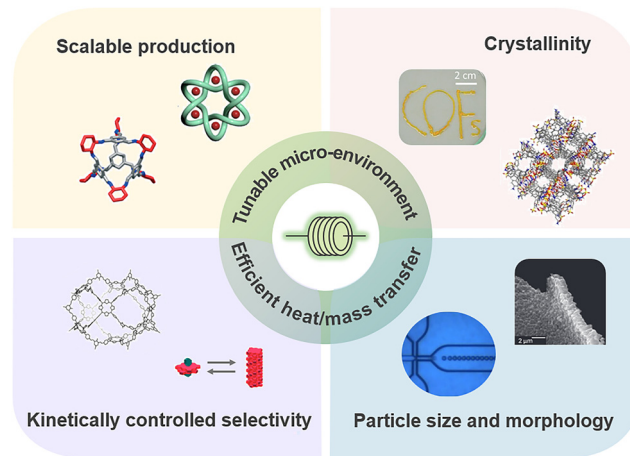


Fig. 1 Schematic representation of the advantages and enhancements offered by flow-based technology in the formation of self-assembled supramolecules.

mixing can be impacted by slow diffusion and/or variable shear forces, leading to concentration gradients and reduced selectivity—especially during scale-up. Flow chemistry can help to overcome these limitations by allowing improved control over shear rate through adjustments in flow rate, residence time, and channel geometry.<sup>46</sup>

Temperature is a key determinant of both the kinetics and selectivity of chemical reactions. The high surface area-to-volume ratios of flow reactors provide rapid and uniform heat transfer, enabling tight control over thermal conditions.<sup>45,50</sup> In combination with the use of back-pressure regulators which allow solvents to be heated to elevated temperatures compared with reactors under ambient pressure, this capability allows researchers to access reaction regimes that are difficult or unsafe to achieve in batch processes.

In this review, we summarise recent progress in the synthesis of self-assembled structures using flow reactors, highlighting the advantages of flow chemistry in four areas: (a) routes to scalable production, (b) opportunities to control selectivity of kinetic *vs.* thermodynamic products, (c) enhanced crystallinity, and (d) improved size/morphology control compared to batch processes (Fig. 1). As such, we aim to highlight opportunities for supramolecular chemists to benefit from the technique, as well as future directions for technological development in this interdisciplinary area.

## 2. Advantages of flow compared to batch

### 2.1 Routes to scalable production

Scalable production remains a major challenge for supramolecular materials, primarily due to the lack of uniform reaction conditions in batch reactors. Most supramolecular compounds are synthesized on a limited scale (mg to g) and typically require prolonged reaction times (days), resulting in low production rates. Translation of a mg g<sup>-1</sup>-scale synthesis to kg and



beyond typically requires re-optimisation even for well-understood batchwise reactions, as demonstrated in pharmaceutical process chemistry;<sup>60</sup> this is exacerbated for processes involving weak, non-covalent interactions or reversible covalent bonds due to increased sensitivity to reaction conditions. It has been demonstrated that a move to flow can significantly reduce re-optimisation requirements on scale-up of active pharmaceutical ingredients,<sup>61</sup> due to easier replication of desired mass-transport and heat-transfer requirements across length scales,<sup>62</sup> although this is not universal and depends on the reaction and reactor in use.<sup>63,64</sup> Such advantages are beginning to be used for supramolecular chemistry: the use of flow-based devices to improve throughput, and hence scalability, while reducing reagent and solvent consumption has been exemplified in the synthesis of MOFs,<sup>65–76</sup> COFs,<sup>77–80</sup> POCs,<sup>81–84</sup> and other supramolecular assemblies, such as polymers<sup>85–87</sup> and hydrogels.<sup>55,88–90</sup> Although many of these studies remain on the g scale, improving throughput from  $\text{mg h}^{-1}$  to  $\text{g h}^{-1}$  is important to demonstrate scalability in principle, allowing assessment of the requirements of a pilot-scale process to begin without excessive use of resources.

**MOFs.** Scaling up a flow reactor is the most direct approach to increasing production rates, and this can be achieved through three main strategies: numbering up (parallelisation of reactors), increasing the channel length, or increasing the channel diameter.<sup>91</sup> A notable example is the pilot-scale synthesis of aluminium fumarate MOF reported by Rubio-Martinez and co-workers in 2016. By scaling up the reactor volume from 10 mL to 1394 mL through an increase in tubing diameter, they achieved an exceptional space-time yield (STY) of  $97\,159\text{ kg m}^{-3}\text{ day}^{-1}$  ( $5.6\text{ kg h}^{-1}$ ), demonstrating the potential for commercial-scale MOF production (Fig. 2A).<sup>74</sup> Compared to batch processes, scaling up in a flow reactor provides a safer and more sustainable approach, particularly for MOF synthesis, which often requires prolonged high temperatures in sealed environments followed by cooling. Additionally, flow systems minimize exposure to hazardous solvents like *N,N'*-dimethylformamide, a toxic mutagen with environmental risks.<sup>92</sup> To date, multiple studies have reported the successful scale-up of MOFs in flow, including MIL-53 (Al),<sup>92</sup> UIO-66,<sup>66,71,76</sup> HKUST-1,<sup>67,70,76,93</sup> ZIF-8,<sup>68,73</sup> MOF-5<sup>75</sup> and zirconium MOFs.<sup>65,69</sup>

**Cages.** In 2015, we reported the first continuous-flow synthesis of imine-based porous organic cages, CC1 and CC3 (Fig. 2(B)).<sup>82</sup> For the latter, solutions of 1,3,5-triformylbenzene and *R,R'*-1,2-cyclohexanediamine in dichloromethane (DCM) were mixed at a combined flow rate of  $1\text{ mL min}^{-1}$  and heated to  $100\text{ }^\circ\text{C}$ , attainable due to intrinsic pressure conditions within the flow reactor. The transition from batch to continuous-flow synthesis significantly improved production efficiency, achieving throughput of  $0.35\text{ g h}^{-1}$  for CC1 and  $0.50\text{ g h}^{-1}$  for CC3, compared to the 3–5 days required in batch. In the same year, Doonan's group reported the continuous-flow synthesis of a three-fold homo-coupled cage molecule ( $\text{C}_{110}\text{H}_{56}\text{Br}_2$ ) using Breslow-modified Glaser–Eglinton coupling. While batch reactions required highly dilute conditions and excess copper reagent, yielding only 20%, the flow-based approach significantly reduced the copper ratio from 71% to 32%, while maintaining a

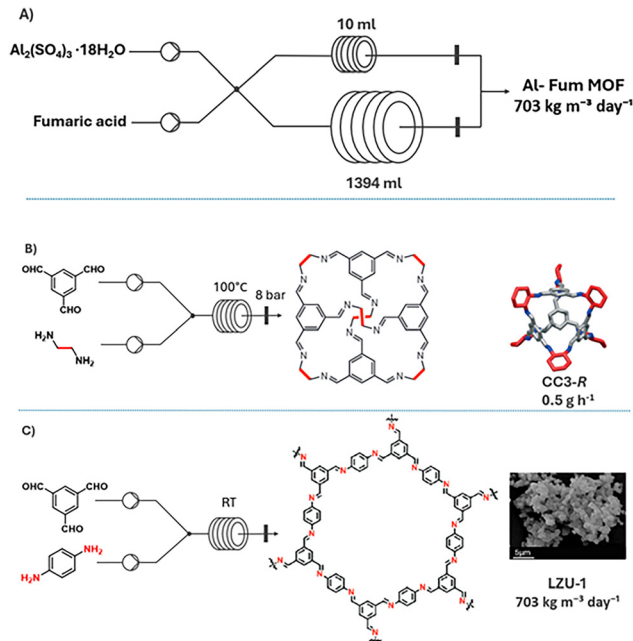


Fig. 2 Schematic representation of the formation of (A) Al-Fum MOF; (B) CC3-R and (C) LZU-1 in a flow reactor. Adapted with permission from ref. 74 (copyright 2016 Wiley-VCH), ref. 82 (copyright 2015 Royal Society of Chemistry) and ref. 78 (copyright 2015 American Chemical Society).

comparable yield of 21% within a 33.3-minute residence time with a STY of  $104.6\text{ g m}^{-3}\text{ day}^{-1}$ .<sup>56,81</sup>

**COFs.** In 2015, Zhao and co-workers also reported the first continuous-flow synthesis of an imine-based COF, COF-LZU1, at room temperature, achieving an exceptionally high STY of  $703\text{ kg m}^{-3}\text{ day}^{-1}$  (Fig. 2(C)).<sup>78</sup> Later, Puigmartí-Luis and co-workers reported the flow synthesis of MF-COF-1 with a production rate of  $2\text{ mg min}^{-1}$ , while COF-LZU1 was obtained at  $0.7\text{ mg min}^{-1}$  under similar conditions; the primary difference between these syntheses was the reactor length and the required residence time.<sup>80,94</sup> Traxler and co-workers recently demonstrated the continuous production of crystalline COFs, specifically CF-TAPB-DMPDA and CF-TAPPy-PDA, as single crystals with a residence time of just 5 seconds and a throughput exceeding  $16.7\text{ mg min}^{-1}$ .<sup>79</sup> Compared to the highest-yielding batch synthesis conditions for 2D COF single crystals, the flow synthesis approach achieved a 2–3-fold increase in framework production rate. Furthermore, the versatility of the flow system was exemplified in a post-synthetic single-crystal-to-single-crystal transformation under flow conditions, where CF-TAPB-DMPDA underwent demethylation upon reaction with boron tribromide, yielding CF-TAPB-DHPDA with a residence time of only 6 minutes. These studies demonstrate the potential for industrial-scale production of COFs for commercial applications.

**Knots.** The scalability of molecular knots and metal self-assemblies has long been a significant challenge in batch synthesis due to their intricate topologies and multiple potential assembly products. Traditional batch processes typically yield less than 500 mg of the desired product and require reaction times exceeding 24 hours, making it challenging to obtain



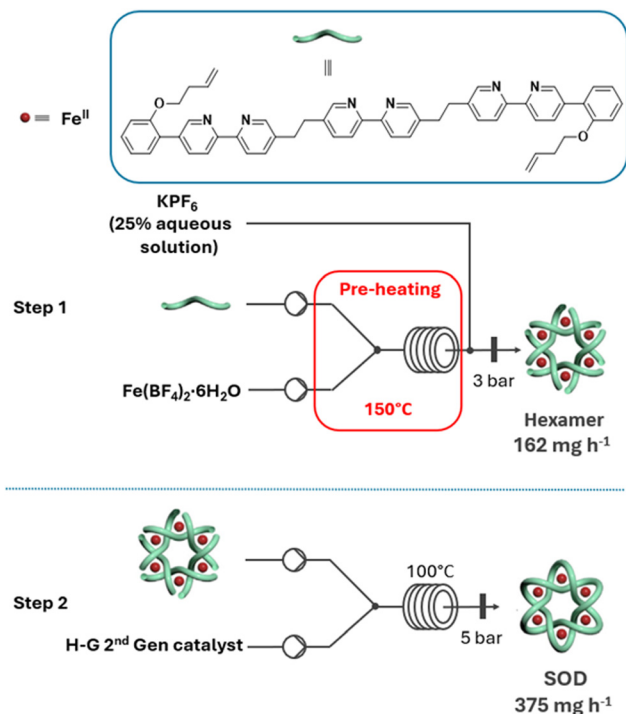


Fig. 3 Schematic representation of the formation of hexamer and SOD in a flow reactor. Adapted with permission from ref. 95 (copyright 2024 Elsevier).

enough material to rigorously test the properties and potential applications of such structures. In 2024, we reported a two-step continuous-flow synthesis of two prototypical interlocked molecules in collaboration with the Zhang group: the Star of David catenane (SOD) and the pentafoil knot (Fig. 3).<sup>95</sup> In this study, key optimisations such as preheating the starting materials prior to mixing and inline quenching with 25% KPF<sub>6</sub> significantly enhanced both the purity and throughput of the final products. The production rates of the intermediate coordination complexes were markedly improved with respect to batch syntheses (hexamer: 162 mg h<sup>-1</sup> vs. 2.3 mg h<sup>-1</sup>; pentamer: 282 mg h<sup>-1</sup> vs. 7.9 mg h<sup>-1</sup>), as were the final molecular knots (SOD: 375 mg h<sup>-1</sup> vs. 1 mg h<sup>-1</sup>; pentafoil knot: 121 mg h<sup>-1</sup> vs. 2 mg h<sup>-1</sup>). In contrast, conventional batch synthesis led to higher amounts of byproducts, such as trimeric linear helicates and pentameric circular helicates; in flow, the main components in the reaction mixture were the desired product and starting material, which could be recovered and reused.

**Alternative approaches.** In most reported flow reactions, reagent solutions are introduced as continuous streams through a mixer before entering the reactor; however, solvent-free methods are also possible. An especially noteworthy advancement is the solvent-free continuous synthesis of MOFs and POCs *via* twin-screw extrusion, which significantly reduces or eliminates solvent usage within the reactor. This approach has led to a remarkable ~20- to 300-fold enhancement STY for the synthesis of various prototypical MOFs and cage structures.<sup>83,96,97</sup> It is also not necessary to include a full flow pathway to achieve improvements compared to batchwise mixing; for example, vortex flow mixing has been recently employed to enable the continuous

synthesis of liposomes and nanojunction photocatalysts for hydrogen evolution.<sup>98,99</sup>

The above breakthroughs highlight the potential and diversity of flow-based methodologies for the scalable synthesis of supramolecular materials, paving the way for their expanded applications. However, multiple possible products can arise from self-assembly, and it is also advantageous to be able to identify, scale up, and test the properties of minor products, such as kinetically trapped species, which may have superior properties to the most thermodynamically stable structure. Here, flow can offer routes to alter selectivity and access novel structures that may not be scalable or even obtainable in batch.

## 2.2 Kinetically controlled self-assembly in flow

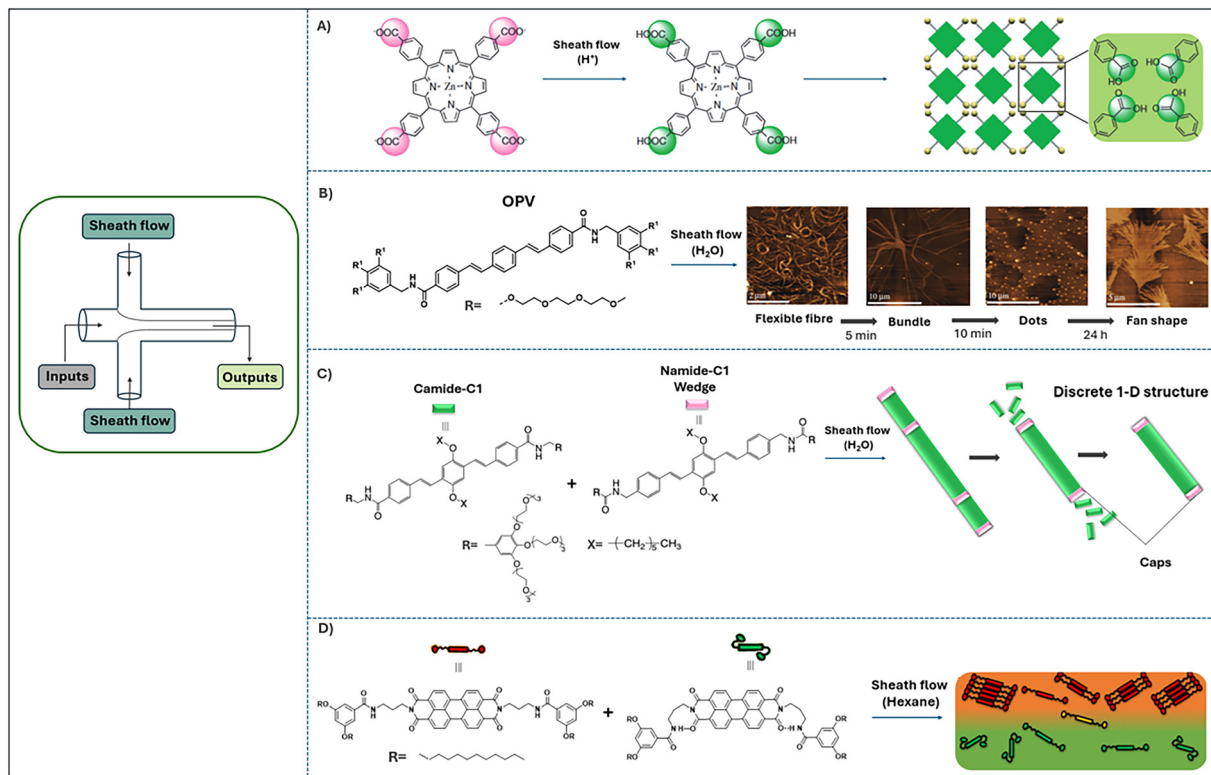
The synthesis of supramolecular assemblies with well-defined structures typically requires the careful design of building blocks and precise regulation of their behaviour during the assembly process. In conventional batch reactions, supramolecular assembly often requires low concentrations and prolonged reaction times, with product formation predominantly governed by thermodynamic control. This reliance on thermodynamic equilibrium presents a significant challenge in obtaining kinetically controlled assemblies.<sup>43,100</sup> A direct approach to modulating the assembly process is to alter the microenvironment surrounding the self-assembling molecules, an advantage readily accessible in flowing solutions within microchannels.<sup>101</sup> Flow chemistry enables precise control over key parameters such as temperature, reactant ratios, and residence time along with inline analytical techniques, which can detect short-lived intermediates and provide real-time reaction feedback. Furthermore, efficient heat transfer and pressurised reactors open opportunities to achieve rapid and extreme temperature swings, alongside telescoping with inline quenching to stabilise and isolate kinetically trapped products. As such, the selectivity of kinetic *vs.* thermodynamic assembly products can be controlled with improved accuracy.<sup>102</sup>

**Supramolecular polymers *via* non-covalent interactions.** In 2013, Meijer and co-workers reported the cooperative self-assembly of (*S*)-Zn-porphyrin in the presence of pyridine, forming helical stacks *via* strong hydrogen bonding (Fig. 4).<sup>103</sup> However, pyridine coordination led to a competing side reaction, producing capped dimers that hindered stack formation. To investigate the impact of flow conditions on self-assembly, an equilibrium mixture of stacks and dimers was eluted against methylcyclohexane (MCH) in a microfluidic H-cell at varying flow rates. Inline UV-Vis spectroscopy revealed different stack-to-dimer (S/D) ratios in the residual and extraction streams, demonstrating the ability of microfluidic systems to modulate the thermodynamic state of self-assemblies—an effect not achievable in batch reactions.

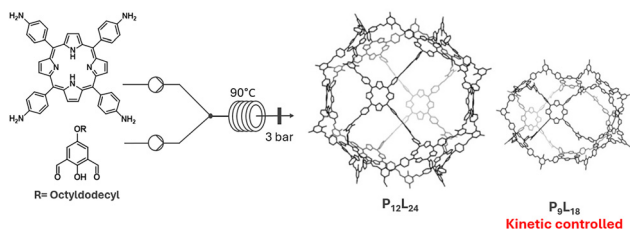
In the same year, Kozawa and colleagues reported the formation of kinetically trapped guanosine 5'-monophosphate (GMP) fibres through stepwise activation of hydrogen bonding and  $\pi$ - $\pi$  stacking within a microfluidic channel (Fig. 5).<sup>104</sup> This metastable configuration was sustained exclusively under continuous-flow conditions. Introducing a linker into these trapped nanofibers facilitated the formation of micron-sized fibrous aggregates,



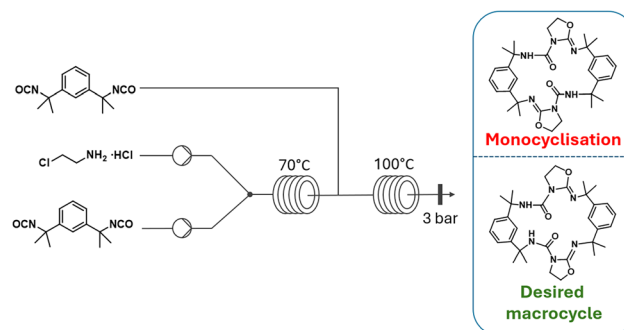




**Fig. 6** Schematic representation of the formation of (A) porphyrin-based self-assembly; (B) OPV-based amphiphilic self-assembled fibres, (C) Namide-C1-capped Camide-C1 nanofibres and (D) PBI-based polymers under sheath flow based microfluidic conditions. Adapted with permission from ref. 105 (copyright 2015 Chemical Society of Japan), ref. 106 (copyright 2015 Royal Society of Chemistry) ref. 107 (copyright 2015 American Chemical Society) and 101 (copyright 2017 Wiley-VCH).



**Fig. 7** Schematic representation of the formation of kinetically trapped  $P_{9L_{18}}$  and zinc(II) pentameric circular helicate under continuous flow conditions. Adapted with permission from ref. 84 (copyright 2023 Wiley-VCH).



**Fig. 8** Schematic representation of the two-step formation of clamp-like macrocycle under continuous flow conditions. Adapted with permission from ref. 108 (copyright 2021 American Chemical Society).

leading to the expansion of the aggregate or crystal. Here, flow can offer advantages of improved crystallinity and control over particle size and morphology.

### 2.3 Improved crystallinity

Crystallinity plays a crucial role in defining the mechanical, optical, and electronic properties of self-assembled materials. Amorphous structures can exhibit distinct physicochemical properties compared to their crystalline counterparts, such as differences in solubility.<sup>54,109</sup> However, traditional batch synthesis often leads to inconsistencies in crystallisation due to uncontrolled concentration fluctuations, temperature gradients,

and limited mass transfer, which can introduce defects in crystal structures. In contrast, flow reactors enable continuous processing under precisely controlled conditions, including regulated supersaturation levels, uniform temperature distribution, and homogeneous reactant dispersion within the flow system. These factors facilitate well-defined nucleation events and can significantly enhance crystallinity.<sup>110,111</sup> Moreover, flow reactors minimize polydispersity, which can result in morphological variations, by fine-tuning parameters such as flow rate, residence time, and shear forces. This level of control promotes ordered



molecular packing and yields superior crystalline quality,<sup>43</sup> although care must be taken to avoid fouling and blockages.

**COFs.** In 2016, Puigmarti-Luis and co-workers reported the first instance of imine-based MF-COF-1 crystallisation under microfluidic conditions in the presence of acetic acid (Fig. 9).<sup>80</sup> By mixing 1,3,5-tris(4-aminophenyl)benzene (TAPB) and 1,3,5-benzenetricarbaldehyde (BTCA) through microfluidic tubing with an acidic sheath flow, they achieved precise control over mixing, leading to the successful formation of highly crystalline COF fibres. In contrast, the conventional batch process yielded only sub-micron COF particles. Furthermore, the flexible fibres collected from the microfluidic chip outlet could be readily manipulated into diverse structural forms, demonstrating the potential of microfluidic platforms as a versatile printing tool for the fabrication of 2D and 3D COF architectures on surfaces.

**Porous salts.** The versatility of how flow chemistry affects the crystallinity of supramolecules has been demonstrated in multiple studies. In 2023, we reported the flow synthesis of a crystalline porous organic salt, CPOS-7, which exhibits promising performance in water and CO<sub>2</sub> capture.<sup>52</sup> CPOS-7 does not form using standard solvents typically employed for CPOS synthesis; instead, a hydrated intermediate phase, Hydrate-2920, is initially obtained. The addition of acetic acid facilitates the transformation of Hydrate-2920 into CPOS-7, thereby improving both yield and selectivity. However, this reconstruction process is only reliably reproducible at small scales, up to 150 mg. By transferring the reaction to a flow system, the crystallisation time was significantly reduced to just 35 seconds, enabling the direct formation of CPOS-7 at a throughput of 45 mg h<sup>-1</sup> (Fig. 10). In contrast, achieving the same quantity in batch would require more than twice the processing time. Additionally, the flow-synthesised CPOS-7 exhibited a higher degree of crystallinity compared to its batch-prepared counterpart, underscoring the advantages of flow chemistry in enhancing both efficiency and structural control in porous organic salt synthesis.

**Coordination polymers.** Crystal growth of organometallic polymers has long been a challenging task. In 2015, Cao and co-workers achieved a breakthrough by reporting the first determination of the single-crystal structure of silver phenylacetylide (Fig. 11).<sup>85</sup> This was accomplished by flowing metal

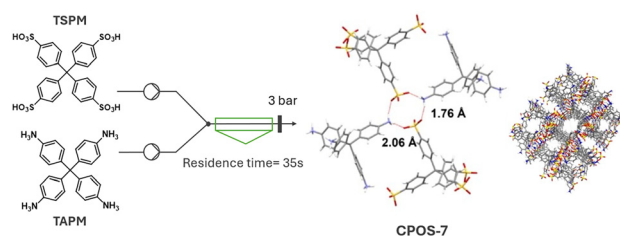


Fig. 10 Schematic representation of the crystallisation of CPOS-7 under flow conditions. Adapted with permission from ref. 52 (copyright 2023 Wiley-VCH).

salts and ligands from opposite directions through a long microfluidic channel, enabling controlled nucleation and crystallisation. Additionally, controlled crystallisation of silver acetylide at specific locations on a planar surface was achieved by modifying the reagent diffusion. This approach provided a novel strategy for obtaining high-quality single crystals, which is often difficult to achieve through conventional batch synthesis due to uncontrolled growth conditions and rapid precipitation.

**Defect-induced MOFs.** Beyond enhancing crystallinity, microfluidic techniques can also be used to reduce crystallinity in specific materials, leading to functional benefits. In 2020, Ge and co-workers synthesised a three-component enzyme-metal-organic framework (enzyme-MOF) using a microfluidic laminar flow channel.<sup>112</sup> Interestingly, by continuously varying the concentrations of MOF precursors in the gradient mixing process of microfluidic flow synthesis, the resulting MOFs exhibited lower crystallinity compared to those synthesized in batch reactions. This controlled reduction in crystallinity improved the biological activity of encapsulated enzymes by increasing substrate accessibility while maintaining a protective environment. The study highlights how microfluidic systems can fine-tune crystallinity to optimise material functionality.

Two other aspects that can control behaviour in application are particle size and morphology, which can both significantly influence material performance. Flow dynamics can also play a crucial role in shaping these properties, affecting the way particles aggregate, disperse, or interact within a given system.

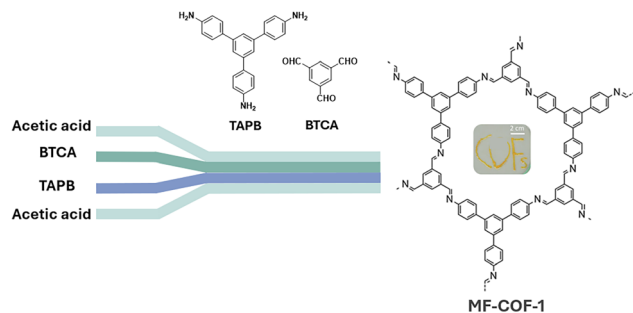


Fig. 9 Schematic representation of the synthesis of MF-COF-1 under sheath flow based microfluidic conditions. Adapted with permission from ref. 80 (copyright 2016 Royal Society of Chemistry).

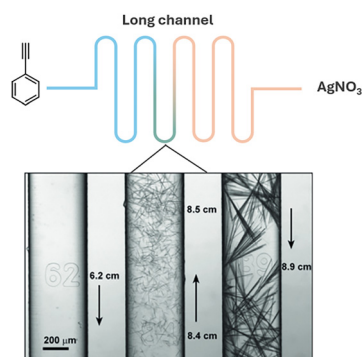


Fig. 11 Schematic representation of the microfluidic device for synthesis of silver acetylides and microphotographs of distribution and morphology of crystals formed along the microchannel. Adapted with permission from ref. 85 (copyright 2015 Wiley-VCH).



## 2.4 Control of particle size and morphology in self-assembled structures

Precise control over the size and morphology of self-assemblies remains a significant challenge due to kinetic (nucleation rates, diffusion limitations, and reaction times) and thermodynamic factors (intermolecular interactions, solvent effects, and temperature). Balancing these factors is essential for achieving well-defined, reproducible structures with tailored properties. Flow chemistry, with its ability to finely tune reaction conditions such as concentration gradients, mixing efficiency, and residence time, offers a promising approach to overcoming these limitations. Unlike conventional batch methods, the laminar flow regime in microfluidic channels establishes well-defined reaction interfaces, facilitating precise control over nucleation and growth processes. This approach allows for the tailored synthesis of self-assemblies with desired sizes and properties, overcoming limitations inherent in traditional synthesis techniques.<sup>109,113–115</sup> Here, reactor design is frequently used to control particle nucleation and growth, using sheath flow, droplet flow, or flow cells to generate solvent–solvent interfaces and influence mixing regimes.

### Sheath flow-based microfluidics for production of materials.

In 2010, Puigmartí-Luis and co-workers reported a structure-controlled self-assembly of tetrathiafulvalene (TTF), a crucial molecular building block widely employed in the fabrication of conductive materials.<sup>113</sup> Using a microfluidic device, they demonstrated that shear force present at the interfaces of the co-flowing streams and the width of the laminar streams containing the reactants can be modulated by varying the flow rate ratio (FRR) between sheath flows and reagent flows, enabling the determined morphology of formed TTF-Au nanostructures (Fig. 12). A sheath flow-based microfluidic chip was also used for the shape-controlled crystallisation of coordination polymers by Rubio-Martinez and co-workers in 2016.<sup>87</sup> Compared to the conventional batch process, which exclusively produced square plate-like crystals, microfluidic conditions enabled the formation of diverse crystalline phases, ranging from needle-like and hollow-frame structures to plate-like morphologies.

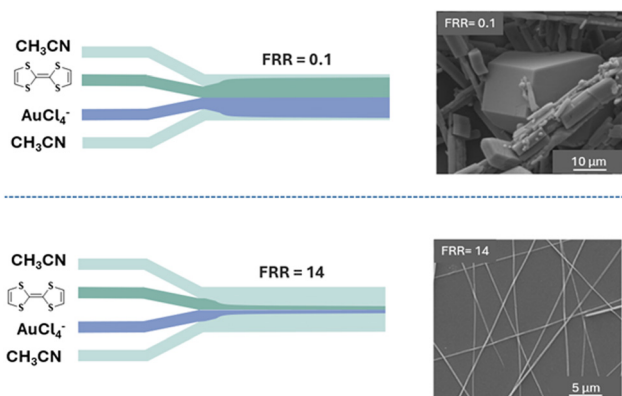


Fig. 12 Schematic representation of the formation of TTF assembly and prepared hybrid ribbons at varied flow-rate ratios under microfluidic conditions. Adapted with permission from ref. 113 (copyright 2010 Wiley-VCH).

Microfluidic systems can also provide deeper insights into reaction mechanisms. In 2016 Knowles, Gazit, and co-workers reported the controllable distribution of nanotube lengths by adjusting the molecular ratio of diphenylalanine and its end-capped analogue (Fig. 13).<sup>116</sup> Using a microfluidic chip with micron-scale pillars, they successfully tuned the length of individual peptide nanotubes formed from diphenylalanine (FF) building blocks. These nanotubes were subsequently exposed to monomer solutions of varying concentrations, allowing real-time visualisation and analysis of their growth or shrinkage through electron microscopy—an approach that would be challenging in batch reactions due to uncontrolled aggregation.

In 2014, a 3D hydrodynamic focusing device was developed by Huang and co-workers to protect the channel wall from the precursors to avoid precipitation (Fig. 14).<sup>117</sup> Using Dean vortices in curved channels, it vertically focused solutions of TTF and H<sub>2</sub>AuCl<sub>4</sub>, optimising spatial control during self-assembly. This innovation facilitated the selective formation of diverse morphologies, such as branched and hexagonal structures.

In 2014, Nair and co-workers synthesised ZIF-8 MOF membranes with exceptional separation performance, achieving H<sub>2</sub>/C<sub>3</sub>H<sub>8</sub> and C<sub>3</sub>H<sub>6</sub>/C<sub>3</sub>H<sub>8</sub> separation factors of 370 and 12 respectively, by changing flow parameters to tune the membrane thickness (Fig. 15).<sup>118</sup> Using a microfluidic device with polymeric hollow fibre supports, they introduced Zn<sup>2+</sup> and methylimidazole ligand solutions into separate layers to achieve controlled membrane production.

### Droplet-based microfluidics for production of materials.

Beyond continuous flow processes, droplet generation within microchannels has been widely adopted for the synthesis of various materials. The generated small reaction volume micro-environment with high surface-area-to-volume ratio, efficient mixing and heat transfer, makes droplet-based microfluidics particularly advantageous for synthesizing solid particles, facilitating precipitation, and enabling sol-gel techniques.<sup>88,119</sup> This approach not only achieves precise control over particle size but also mitigates the risk of channel clogging, offering significant advantages over conventional batch methods.<sup>71,120</sup>

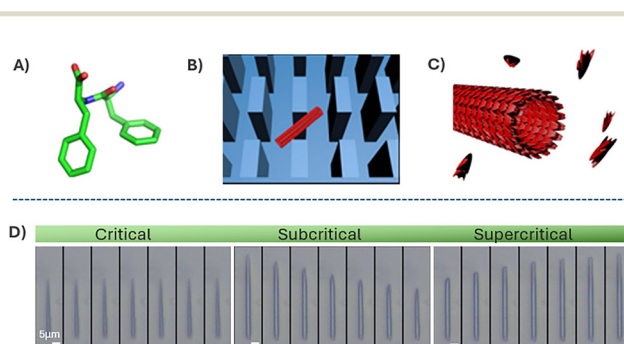
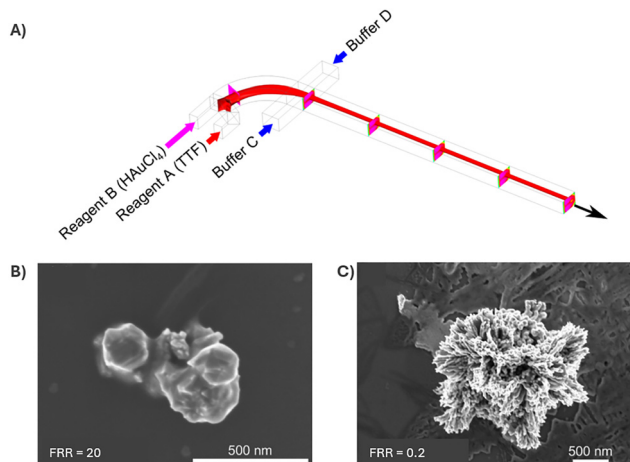


Fig. 13 (A) Chemical structure of FF. (B) Schematic illustration of a single FF nanotube trapped between the micro-scale pillars. (C) Illustration of the FF tube growth. (D) Imaging of FF nanotubes at different times under critical (2.43 mM, 60 s interval), subcritical (1.6 mM, 10 s interval), and supercritical (3.20 mM, 100 s interval) concentration conditions. Adapted with permission from ref. 116 (copyright 2016 Springer Nature).



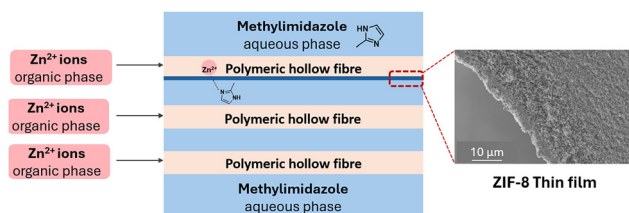


**Fig. 14** (A) Schematic representation of the formation of 3D hydrodynamic flow focusing device used for the shape control synthesis of TTF-Au structures under microfluidic conditions and SEM images of the structures collected at a FRR of (B) 20 and (C) 0.2, respectively. Adapted with permission from ref. 117 (copyright 2014 American Chemical Society).

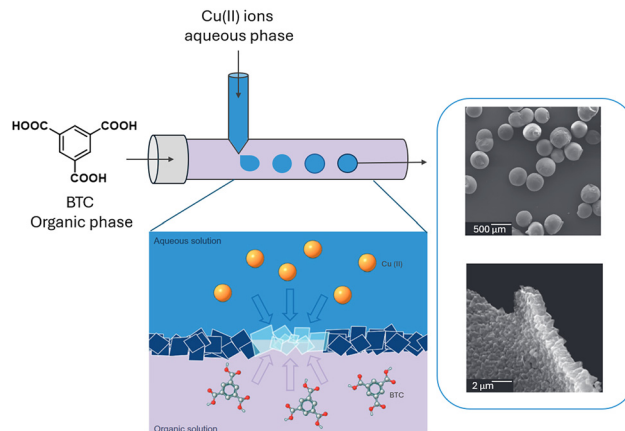
To date, numerous studies have explored droplet-based flow synthesis for the fabrication of MOFs, demonstrating its effectiveness in controlling particle size, morphology, and crystallisation kinetics.

MOF film growth in batch processes typically relies on a supported liquid interface, where undesired nucleation or overgrowth on preformed crystals often occurs, resulting in uneven membrane thickness. In 2011, De Vos and co-workers synthesised the MOF HKUST-1 by introducing a Cu(II) solution dropwise into a 1,3,5-benzenetricarboxylic acid (BTC) ligand solution under continuous flow, restricting the reaction to the phase interface (Fig. 16).<sup>121,122</sup> The diffusion of MOF precursors occurs more rapidly at remaining defects than through the already-formed layer, leading to the preferential formation of new crystallites at these defect sites, effectively sealing the gaps, resulting in the formation of a uniformly thick film. Moreover, by adjusting the ratio of flow rates, size tuneable crystalline capsules are achievable.

Similarly, in 2013, Kim and co-workers reported the biphasic droplet-based microfluidic synthesis of size- and morphology-controlled MOFs, including HKUST-1, MOF-5, IRMOF-3, and UiO-66.<sup>120</sup> Notably, MOF crystals were assembled within minutes under microfluidic conditions, whereas conventional



**Fig. 15** Schematic representation of the formation of thickness controlled ZIF-8 MOF membranes under microfluidic conditions. Adapted with permission from ref. 118 (copyright 2014 The American Association for the Advancement of Science).



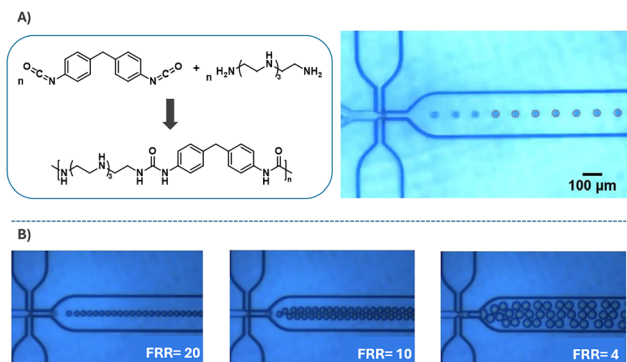
**Fig. 16** Schematic representation of the formation of size-controlled MOF HKUST-1, under droplets-based microfluidic conditions. Adapted with permission from ref. 121 (copyright 2011 Springer Nature).

batch synthesis required several hours to days to achieve comparable results.<sup>54</sup> In the same year, Coronas and co-workers reported synthesis of three dicarboxylate based MOFs (Fe-MIL-88B-NH<sub>2</sub>, Fe-MIL-88B, and Fe-MIL-88B-Br) by using droplet-based microfluidics, allowing control of the crystal size of MOFs in the range of 90–900 nm.<sup>123</sup> In 2015, Falcaro and co-workers synthesised bio-MOF MIL-88A hollow spheres with controlled sizes using a droplet-based microfluidic system.<sup>124</sup> By adjusting the FRR of the two phases and the reaction tube diameter, MIL-88A hollow spheres ranging from 35 to 2000 µm in size were successfully obtained. In 2019, Sun and co-workers reported a continuous synthetic process for MOF capsules with a hierarchical pore structure using a droplet-based microfluidic strategy.<sup>125</sup> By precisely tuning the flow rates of the organic and aqueous phases, they were able to control the size distribution of the microcapsules with high precision. These studies highlight the significant advantages of microfluidic droplet-based systems in accelerating MOF crystallisation while ensuring precise control over particle characteristics, although scalability can be challenging in such systems.

The application of droplet-based microfluidics extends beyond MOFs to hydrogel and polymer microcapsule synthesis. In 2009, Shen and co-workers fabricated supramolecular hydrogel microspheres *via* hydrogen bonding between 1,2,4,5-benzene tetracarboxylic acid and 4-hydroxy pyridine, achieving precise size control by regulating flow rates.<sup>88</sup> In 2019, we developed a continuous synthesis of polyurea microcapsules (Fig. 17).<sup>119</sup> Using a flow system with a droplet sizing method based on video recording and Python-based analysis, precise control over microcapsule diameters was achieved (27–35 µm) with narrow size distributions ( $\pm 2$  µm).

**Flow cell-based microfluidics for production of materials.** Reactor design and the inclusion of flow cells offers further opportunities to control self-assembly and structure formation in flow. In 2016, Dichtel and co-workers achieved thickness-controlled synthesis of 2D COF thin films using a flow cell reactor incorporating a quartz crystal microbalance as substrate, and modulating flow rates (Fig. 18).<sup>126</sup> In 2022, Börjesson and



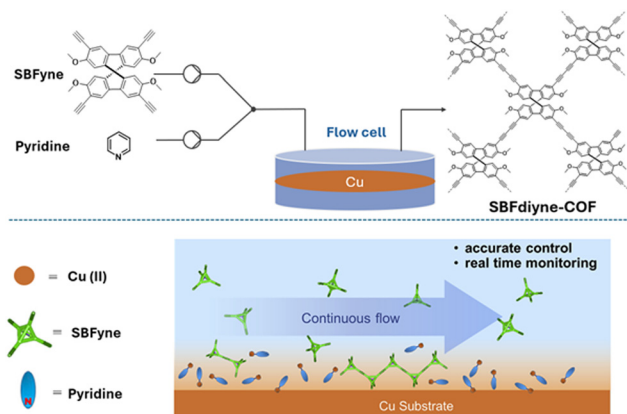


**Fig. 17** Size control of limonene droplets produced in a microfluidic chip (A) Synthesis of the polyurea microcapsules and an example of still from microscope video that has undergone processing to detect and measure droplet diameter via Python code. (B) Optical microscope images of o/w emulsions produced at varied FRR. Adapted with permission from ref. 119 (copyright 2019 Springer Nature).

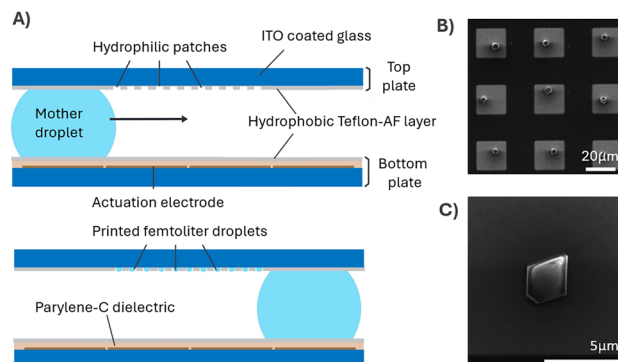
co-workers further advanced supramolecular film control using a Cu-based cell as both a substrate holder and catalyst for 3D COF film formation.<sup>127</sup> These flow-based approaches enabled uniform thickness and enhanced structural integrity, highlighting its potential for the fabrication of semiconductor/COF hybrid materials.

Other microfluidic techniques have also been employed for the controlled synthesis of self-assembled structures with precise size and morphology. In 2012, Witters and co-workers developed a high-throughput digital microfluidic method for synthesising single MOF crystals (Fig. 19).<sup>128</sup> Using a modular two-plate device with an electronically controlled bottom plate and a hydrophilic-patterned top plate, they achieved precise spatial control over HKUST-1 crystal formation. Crystal size was finely tuned by adjusting the hydrophilic micro-patch dimensions, offering a scalable and efficient approach for tailored MOF synthesis.

As these examples demonstrate, flow reactors offer significant advantages over traditional batch processes in the control of size and morphology during self-assembly. The ability to



**Fig. 18** Schematic representation of the formation of thickness-controlled 3D COF films under cell-based flow conditions. Adapted with permission from ref. 126 (copyright 2016 American Chemical Society).



**Fig. 19** (A) Schematic representation of the formation of MOF crystals under a digital microfluidic chip. (B) By transporting mother droplets over arrays of hydrophilic-in-hydrophobic micropatches, large arrays of femtoliter droplets are printed due to the selective wettability of the hydrophilic micropatches. (C) And crystals are formed from these droplets upon evaporation. Adapted with permission from ref. 128 (copyright 2012 Wiley-VCH).

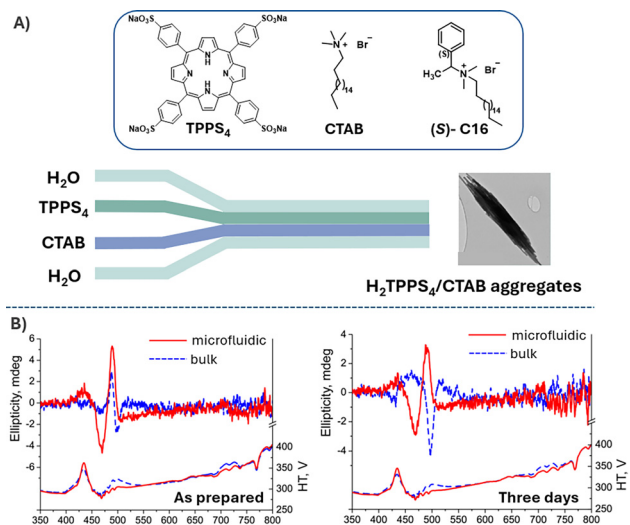
precisely regulate flow rates, temperature, and concentration gradients in a flow reactor enables more uniform and reproducible formation of self-assembled structures. This level of control minimizes the variability in particle size and shape, which is often a challenge in batch processes due to the uncontrolled nature of solvent evaporation and mixing. Furthermore, the ability to fine-tune the micro-environment in flow systems extends beyond size and morphology control, offering broader opportunities for tailoring the structural and functional properties of self-assembled materials.

## 2.5 Other improved properties

**Chirality.** Beyond the enhancements discussed, certain strategies in flow chemistry further refine additional properties of self-assemblies. In 2016, Puigmartí-Luis and co-workers demonstrated how reagent mixing impacts product chirality.<sup>129</sup> Using a microfluidic device to control diffusion, a porphyrin derivative ( $\text{H}_2\text{TPPS}_4$ ) and cetyltrimethylammonium bromide (CTAB) were combined in the presence of the chiral amphiphile (*S*)-C16 as an inducer (Fig. 20). Remarkably, only 20 milliseconds of residence time in the laminar microfluidic system were sufficient to achieve chirality control, and the chirality induction did not change with time. In contrast, batch conditions exhibited a changing signal in the Circular Dichroism (CD) spectrum over several days.

**Luminescence.** Most recently, Xu and co-workers synthesised a chiral metal cage-based framework as a circularly polarized luminescence (CPL)-active material, which shows potential applications in chiral separation, 3-D displays and photocatalysis. Precise control over luminescence is crucial for optimizing performance in practical applications, as luminescence properties—such as intensity, emission wavelength, and dissymmetry factors—directly affect the efficiency and functionality of CPL-active materials.<sup>130</sup> Co-assembling the chiral donor metal cage ( $\Delta 4/\Lambda 4$ -Zn4A4) with the achiral acceptor Nile red enabled efficient energy and chirality transfer, enhancing the luminescence dissymmetry factor ( $|g_{\text{lum}}|$ ), which quantifies the difference in luminescence intensity between left- and





**Fig. 20** (A) Schematic representation of the formation of chirality biased  $H_2TPPS_4$  porphyrin. (B) CD showing the effect of microfluidic versus flask-based mixing on the chirality of the formed  $H_2TPPS_4/CTAB$  heteroaggregates. Adapted with permission from ref. 129 (copyright 2016 American Chemical Society).

right-handed circularly polarised light. However, achieving controlled distribution of luminescent moieties during film formation remains challenging due to inconsistencies in their spatial arrangement. By employing a microfluidic system with steady laminar flow, low Reynolds numbers, and minimal shear forces, solute diffusion and molecular interactions were precisely regulated, restricting vibrational and rotational freedom. This approach significantly improved  $|g_{lum}|$  values, achieving a 2.7-fold ( $\Delta 4-Zn4A4$ ) and 1.9-fold ( $\Delta 4-Zn4A4/NiR$ ) enhancement compared to batch synthesis.

## 2.6 Summarised comparison of different methodology

In summary, the selected cases presented in this review underscore the versatility of flow chemistry in both the investigation and scalable production of self-assembled materials. A range of flow techniques has been introduced, each offering unique advantages tailored to specific stages of research and development—from fundamental mechanistic studies to pilot-scale synthesis (Fig. 21).

**Batch reactors.** Batch reactors are the most commonly employed platforms for laboratory-scale self-assembly studies due to their operational simplicity and flexibility. They allow for straightforward adjustment of key parameters such as concentration, temperature, and reaction time, making them ideal for preliminary mechanistic investigations. However, limitations in mixing efficiency and heat transfer—both critical to self-assembly processes—compromise reproducibility and hinder scalable production. As a result, most batch-based self-assembly syntheses remain restricted to the gram-scale or lower.

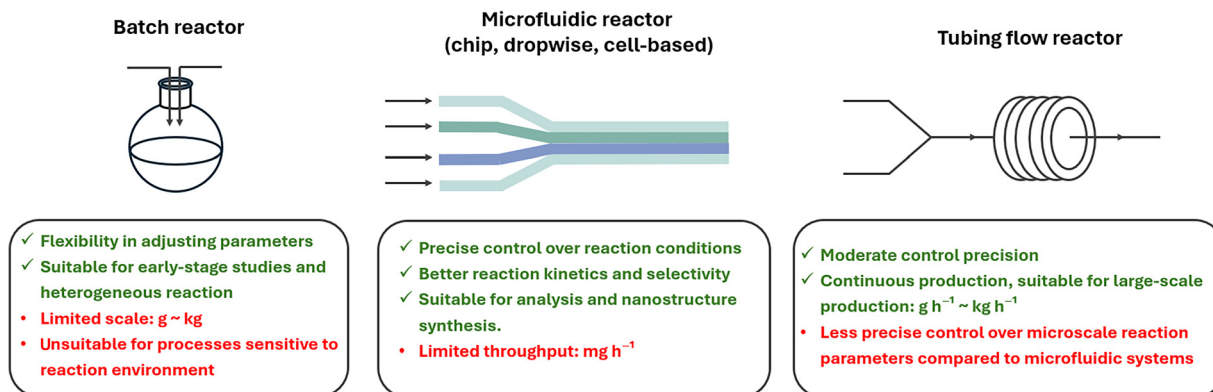
**Microfluidic chip reactors.** Microfluidic reactors, with channel dimensions in the tens to hundreds of micrometres, offer exceptional control over reaction environments, making them highly suitable for studying the pathways and synthesis of kinetically sensitive self-assemblies,<sup>103–105,107</sup> microcapsule formation under droplet-based conditions,<sup>119,121</sup> and the fabrication of thickness-controlled films using cell reactors.<sup>126</sup> Their integration with high-throughput screening capabilities enables systematic exploration of assembly conditions. However, due to their limited throughput, microfluidic systems are generally unsuitable for large-scale production. Parallelisation is preferred over channel scaling to enhance productivity.<sup>48</sup>

**Tubing flow reactors.** Tubing-based flow reactors, which use tubing with millimetre- to centimetre-scale inner diameters, provide higher flow rates and greater scalability. These systems support throughput ranging from  $mg\ h^{-1}$  to  $g\ h^{-1}$ ,<sup>52,78,82,95</sup> and, in certain MOF syntheses, up to  $kg\ h^{-1}$ .<sup>74</sup> While they may offer reduced environmental precision in comparison to microfluidic systems, their practicality and compatibility with continuous manufacturing make them a compelling bridge between laboratory-scale innovation and industrial-scale production of self-assembled materials.

## 2.7 The challenges faced in self-assembly under continuous flow conditions

Despite the growing interest in integrating flow chemistry with self-assembling systems, several critical challenges remain that warrant focused future research.

**Scalable production of self-assembled structures.** Currently, most of the supramolecular processes which have been carried



**Fig. 21** A comparative overview of batch reactors, microfluidic systems, and general tubing flow reactors.



out on the  $\text{g h}^{-1}$  scale and above are those which involve reversible covalent bonding, metal–ligand interactions, or crystallisation processes, rather than non-covalent assembly. Bridging the gap between microfluidic control and typically millifluidic scalability is required to combine the benefits of control, reproducibility, and scale for structures formed *via* non-covalent interactions. Additionally, as self-assembled architectures often rely on delicate non-covalent interactions, even slight deviations in mixing, temperature, or flow rate during scale-up can lead to undesired morphologies or incomplete assembly. A major target in the future is the development of scalable flow protocols that can reliably support the precise conditions needed for self-assembly without compromising structural fidelity.

**Solids as starting material or products.** One of the major challenges in applying continuous flow processing to chemical synthesis is the handling of solids—either as starting materials or as products.<sup>131</sup> Solid reagents often require pre-treatment (*e.g.*, dissolution or suspension), and their presence can lead to issues such as clogging, pressure build-up, and inconsistent flow. Although the synthesis of self-assembled structures is typically carried out under high dilution conditions to prevent the formation of kinetically trapped species, the *in situ* generation of solid products—such as crystalline particles or gels—can lead to reactor fouling and significantly disrupt flow dynamics. Selection of appropriate reactors and components, *e.g.*, CSTRs, wider-bore mixing pieces, *in situ* sonication, or the use of carrier fluids can mitigate these issues, and enable the study of processes which produce or require solid materials.<sup>132–134</sup> However, the development of accurate process models is essential to take full advantage of such solutions, which is typically outside the expertise of chemists.<sup>135</sup>

**Multistep self-assembly processes.** Self-assembly involving sequential steps, or the telescoping of synthesis and self-assembly, are both exciting prospects that would take full advantage of the spatial resolution and real-time analysis possible in flow. However, each step adds complexity which can be challenging to automate, optimise, and reproduce. Developing modular flow platforms capable of handling such complexity, while enabling fine control over intermediate structures, is a promising yet underexplored direction. Ultimately, such flow platforms will be underpinned by methodical method development of each step, and be realised *via* collaboration between multiple disciplines, including chemistry, chemical engineering, reactor design, automation, and analytical science.

### 3. Conclusions and prospects

In this review, we have highlighted how the unique conditions provided by flow reactors can be effectively leveraged to optimize the synthesis of various self-assembled structures compared to conventional batch methods. Key advantages include: (1) scalable production with reduced solvent and reagent consumption, enabling large-scale production while maintaining uniformity and reproducibility; (2) the ability to tune selectivity of kinetically

trapped species *vs.* thermodynamically controlled structures; (3) improved crystallinity and (4) precise control over crystal size and morphology by modulating key reaction parameters such as flow rate, reagent concentration, and temperature. These studies demonstrate that flow chemistry serves as a powerful toolbox for uncovering, studying, and designing self-assembly mechanisms that are inaccessible in batch reactors, thereby facilitating the development of novel functional materials.

Although there are few examples of hierarchical or far-from-equilibrium self-assembly demonstrated in flow, the methods described above, such as controlled and sequential mixing in telescoped reactions, may be particularly suited to control and scale such processes. As previously noted, most non-covalent-based self-assemblies are constrained to production scales in the  $\text{g h}^{-1}$  range. To assist in bridging the gap between microfluidic control and typically millifluidic scalability, flow chemistry combined with inline analysis offers opportunities for real-time characterization of self-assembly processes, helping to optimise reactions<sup>136</sup> or, for example, control particle size.<sup>137</sup> Combining continuous flow processes with high-throughput platforms could greatly accelerate discovery and optimisation in materials science by enabling large-scale parallel synthesis and characterization,<sup>98,138</sup> and would help provide the missing datasets that are needed to effectively use approaches such as machine learning. However, developments in analytical technology, high-throughput data handling, and methods for interrogating complex data will be essential to elucidate the complex mixtures of products often present during self-assembly processes. Further research should also focus on developing novel reactor designs that maximize efficiency while minimizing energy consumption and waste.

By bridging fundamental principles with engineering innovations, self-assembly under flow conditions holds significant potential for applications ranging from fundamental understanding of nanomaterials synthesis to advanced manufacturing. We anticipate that such approaches will find use in ever-broader classes of supramolecular systems, reflecting the diversity and breadth of the field and lowering the barriers to translation and industrial use of functional supramolecular architectures.

### Author contributions

Conceptualization: Liqun Guo, Qiang Zhu, Anna Slater; writing – original draft: Liqun Guo; writing – review and editing: Liqun Guo, Anna Slater; supervision: Anna Slater; funding acquisition: Anna Slater.

### Data availability

This Feature Article titled “Self-assembly under continuous flow conditions” is a review summarizing recent developments in the field of self-assembly under continuous flow conditions, and no original experimental data were generated or analysed during the preparation of this manuscript. As such, there are no data sets associated with this work.



## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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