# Microfluidic Synthesis of Metal-Organic and Covalent Organic Frameworks: Techniques and Benefits

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**Abstract.** Microfluidic technology represents a significant advancement in the synthesis of metal-organic frameworks (MOFs) and covalent organic frameworks (COFs), offering rapid and continuous production with precise control over reaction conditions. Traditional methods for synthesizing these materials, such as hydrothermal and solvothermal techniques, often require several hours or days and can result in inconsistent particle sizes and crystallinity. In contrast, microfluidic approaches could enable faster synthesis, enhance crystallinity, and make particle size uniform within minutes. This technology could prevent channel clogging and improve mas, and heat transfer efficiency enabled the successful production of hierarchical structures and core-shell composites with superior stability and catalytic properties. Examples like the synthesis of HKUST-1, MOF-5, IRMOF-3, UiO-66, and advanced COF fibers demonstrate the versatility and scalability of microfluidic systems. These advancements suggest that microfluidic synthesis not only streamlines the production process but also opens new possibilities for scalable industrial applications, paving the way for innovative uses in catalysis, gas storage, and sensing.

**Keywords:** Microfluidics, Covalent Organic Frameworks, Metal-Organic Frameworks.

## 1. Introduction

Microfluidics is a multidisciplinary field that manipulates small volumes of fluids (ranging from $10^{-9}$ to $10^{-18}$ liters) using channels with dimensions on the order of tens to hundreds of micrometers [1]. Emerging in the early 1980s, microfluidics integrates principles from molecular analysis, molecular biology, and microelectronics to create systems capable of processing low volumes of fluids with high precision [2]. This technology has revolutionized the design of systems for multiplexing, automation, and high-throughput screening, finding applications in inkjet printheads, DNA chips, lab-on-a-chip technology, micro-propulsion, and micro-thermal technologies. Microfluidic systems are typically characterized by their small size, low energy consumption, and the ability to facilitate complex fluidic manipulations such as transport, mixing, and separation [3].

Metal-Organic Frameworks (MOFs) and Covalent Organic Frameworks (COFs) are two classes of porous materials that have attracted significant attention due to their unique properties and wide range of applications. MOFs consist of metal clusters, also known as Secondary Building Units (SBUs), coordinated to organic ligands to form one-, two-, or three-dimensional topology structures. These materials are known for their high porosity, stability, and crystallinity, making them suitable for applications in gas storage, gas separation, catalysis, and so on [4]. Traditional methods for synthesizing MOFs include solution synthesis, solvothermal synthesis, and electrochemical synthesis, but each of which has its own set of challenges such as long reaction times, high energy consumption, and difficulties in controlling the crystallinity and purity of the final product.

COFs, as crystalline porous polymers, were formed through the covalent bonding of organic precursors, resulting in highly stable and ordered two- or three-dimensional structures. These materials are composed entirely of light elements such as hydrogen, boron, carbon, nitrogen, and oxygen. COFs exhibit exceptional stability in various solvents and conditions, and their pore sizes and structures can be precisely controlled through the careful selection of building blocks and synthetic conditions[5]. Traditional synthesis methods for COFs include solution-based synthesis and solvothermal methods, which similarly face issues such as long reaction times and challenges in achieving high crystallinity and purity.

## 2. Microfluidics-based synthesis of MOF and COF materials

### 2.1. Conventional methods for synthesizing MOF and COF materials

Traditionally, MOFs are synthesized using solvothermal or hydrothermal methods. These methods involve dissolving metal salts and organic linkers in a solvent and heating the mixture in a sealed vessel (e.g., an autoclave) at elevated temperatures (typically 80-220°C) for several hours to days. The steps include mixing the precursors, transferring the solution to a reaction vessel, sealing the vessel, heating it under specific conditions, and finally cooling, washing, and drying the resulting MOF crystals. The main drawbacks of these traditional methods are the long reaction times, high energy consumption, and the need for high-pressure equipment [6]. Additionally, scale-up is challenging due to the batch nature of the synthesis, and there is often a lack of control over crystal size and morphology.

COFs are typically synthesized through solvothermal methods as well. This involves mixing organic monomers with solvents and catalysts in a sealed vessel, followed by heating at high temperatures (e.g., 80-120°C) under negative pressure atmosphere for extended periods (up to several days). The process includes dissolving monomers, sealing the reaction mixture, heating, and post-synthesis washing and drying [7]. The primary disadvantages of these methods are the harsh reaction conditions, long synthesis times, and the potential need for post-synthetic modifications to introduce desired functionalities. These factors make large-scale production difficult and resource-intensive, and the resulting COFs may exhibit lower crystallinity and porosity compared to those synthesized by more controlled methods.

### 2.2. Synthesis of MOF and COF materials using microfluidic technology

The microfluidic approach to MOF synthesis involves the use of microdroplets or continuous flow systems to confine the reactants. The process typically starts with the preparation of precursor solutions containing metal salts and organic ligand. These solutions are pumped into a microfluidic device where they form microdroplets within a carrier fluid (such as oil) or are mixed continuously in a microchannel. The reaction occurs rapidly within these confined spaces due to enhanced mixing and heat transfer. The droplets or continuous flow pass through a heated microreactor, where crystallization of MOFs takes place within minutes. The resulting MOF crystals are then collected, washed, and dried. The key steps include preparing precursors, generating and transporting microdroplets or continuous flow, carrying out the reaction under controlled temperature, and collecting and processing the product [8]. Similar to MOFs, COFs can be synthesized using microfluidic systems to enhance reaction efficiency. The process involves dissolving organic monomers and catalysts in suitable solvents and introducing these solutions into a microfluidic device. The monomers are encapsulated in microdroplets or mixed continuously in microchannels (Figure 1). The reaction can be assisted by heating the microreactor, typically at lower temperatures compared to traditional solvothermal methods. The confined environment and efficient mixing lead to rapid formation of COFs, often within minutes. After the reaction, the COF materials are collected, washed, and dried. The steps include preparing monomer solutions, generating and transporting microdroplets or continuous flow, maintaining reaction conditions, and collecting and processing the product [9].

Microfluidic techniques offer several advantages over traditional synthesis methods for MOFs and COFs. Firstly, the reaction times are significantly reduced from hours or days to minutes, owing to enhanced mixing and heat transfer within the microdroplets or microchannels. This leads to faster crystallization and higher throughput. Secondly, the confined reaction environment in microfluidic systems allows for precise control over reaction conditions, resulting in uniform particle sizes and improved crystallinity. Thirdly, the continuous flow nature of microfluidic systems facilitates scalability and continuous production, overcoming the limitations of batch processes. Additionally, microfluidic systems minimize the risk of channel clogging and allow for real-time monitoring and optimization of reaction parameters. Overall, the microfluidic approach not only enhances efficiency and product quality but also provides a scalable and environmentally friendly alternative to traditional methods.

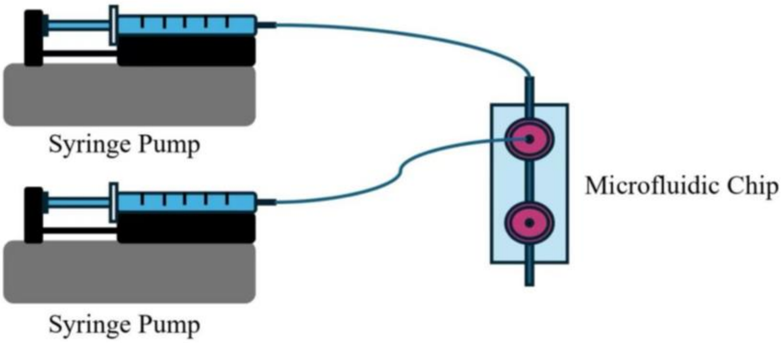

**Figure 1.** Schematic diagram of microfluidic device synthesis

## 3. Rapid and Continuous Microfluidic Synthesis of MOF Crystals and Heterostructures

Faustini and coworkers introduce a novel microfluidic method for the rapid and continuous synthesis of metal-organic frameworks (MOFs) and their heterostructures. By confining reactants within nanoliter droplets, the researchers achieved significant improvements in reaction kinetics, allowing for the synthesis of high-quality MOF crystals within minutes. Representative MOF structures, including HKUST-1, MOF-5, IRMOF-3, and UiO-66, were synthesized using this technique, demonstrating its versatility and efficiency compared to traditional batch methods that typically require hours or days. The microfluidic system also successfully synthesized Ru3BTC2 under high-pressure hydrothermal conditions, highlighting its capability to handle more demanding synthesis environments. Furthermore, the study extended the microfluidic approach to create core-shell MOF composites, such as $Co_3BTC_2@Ni_3BTC_2$, MOF-5@di$CH_3$-MOF-5, and $Fe_3O_4$@ZIF-8, through a two-step integrated microfluidic process. These heterostructured MOFs exhibited unique properties, including enhanced structural stability and improved catalytic performance. The synthesized MOF crystals and composites were characterized using techniques like X-ray diffraction, scanning electron microscopy, and BET surface area measurements, confirming their structural integrity and quality [10]. The microfluidic strategy offers a time-efficient and scalable alternative to traditional MOF synthesis methods, enabling continuous production and precise control over the morphology of the resulting crystals. This approach has significant potential for industrial applications, particularly in the area of requiring high-throughput and high-quality MOF materials.

## 4. High-Throughput Printing of Single MOF Crystals Using Digital Microfluidics

Witters and coworkers introduces a novel digital microfluidic approach for high-throughput and flexible printing of single metal-organic framework (MOF) crystals. MOFs, known for their large porosity and diverse applications in gas storage, catalysis, and sensing, traditionally involve complex synthesis and integration processes. The proposed method leverages a digital microfluidic platform that manipulates femtoliter droplets using software-controlled electrical signals, enabling precise deposition of monodisperse MOF crystals on a planar surface. The microfluidic device consists of a modular two-plate system where the bottom plate handles the transport of 'mother droplets', and the top plate features hydrophilic-in-hydrophobic micropatches for printing femtoliter droplets. This configuration ensures selective wettability and high control over the crystal formation area. By adjusting the software-controlled actuation sequence, different patterns of single MOF crystals can be achieved. The research demonstrated the effectiveness of this method by printing arrays of HKUST-1 crystals. The resulting crystals showed high uniformity in size and well-defined octahedral shapes. The flexibility of the system was further highlighted by varying micropatch dimensions to control crystal size and by printing different MOF materials in various patterns [11]. This digital microfluidic approach offers several advantages over traditional methods, including higher throughput, improved spatial control, and reduced equipment costs. The ability to print large arrays of monodisperse MOF crystals quickly and efficiently makes this technique a promising alternative for future MOF applications and studies at the single-crystal level.

## 5. Rapid Synthesis of MIL-88B MOFs Using Segmented Microfluidics

Paseta and coworkers explores the use of segmented microfluidics for the ultrafast synthesis of MIL-88B type metal-organic frameworks (MOFs), specifically Fe-MIL-88B-NH2, Fe-MIL-88B, and Fe-MIL-88B-Br. The research focuses on the effects of temperature, residence time, and slug volume on the size and distribution of MOF crystals. By employing a microfluidic system, the researchers achieved significant acceleration in the synthesis process, with crystal growth occurring in as little as 20 seconds. The segmented flow technique promotes efficient internal circulation within the microdroplets, leading to uniform nanoparticle sizes and preventing reactor clogging. The study found that different MOF types and synthesis conditions resulted in varying crystal sizes, ranging from 90 to 900 nm, with relatively narrow size distributions. For example, Fe-MIL-88B-NH2 was successfully synthesized with an average size of 180 nm within just 20 seconds, while Fe-MIL-88B and Fe-MIL-88B-Br required longer times (4 and 6 minutes, respectively) and resulted in larger crystal sizes. The microfluidic approach not only reduced synthesis time but also allowed precise control over particle size and distribution. Characterization techniques such as X-ray diffraction (XRD), transmission electron microscopy (TEM), and thermogravimetric analysis (TGA) confirmed the structural integrity and thermal stability of the synthesized MOFs. The study demonstrated that the microfluidic method could be a powerful tool for the controlled synthesis of MOFs with high reproducibility and potential applications in various fields, including catalysis, adsorption, and biomedical applications [12].

## 6. Microfluidic Synthesis of Crystalline COF Fibers with Enhanced Structural Order

Rodríguez-San-Miguel’s group presents a novel microfluidic approach for synthesizing high-quality crystalline fibers of covalent organic frameworks (COFs). The research focuses on the reaction between 1,3,5-tris(4-aminophenyl) benzene (TAPB) and 1,3,5-benzenetricarbaldehyde (BTCA) in acetic acid under continuous microfluidic flow conditions. This method results in the formation of a highly crystalline and porous COF, referred to as MF-COF-1, which exhibits fibrillar microstructures with mechanical stability suitable for direct drawing on surfaces. The microfluidic chip used in this study is made of polydimethylsiloxane (PDMS) and includes four input channels leading to a main microfluidic channel where the reaction occurs. The flow rates of the reagent-laden and sheath flows are controlled to optimize the reaction conditions and avoid clogging. The presence of acetic acid is crucial as it catalyzes both the condensation reaction and the hydrolysis of imine groups, ensuring reversibility and high crystallinity of the resulting COF. Characterization of MF-COF-1 through various techniques such as FT-IR spectroscopy, solid-state $^{13}$C CP-MAS NMR, and elemental analysis confirmed the formation of the COF structure. Notably, the powder X-ray diffraction (PXRD) patterns revealed a higher crystallinity for MF-COF-1 compared to similar COFs synthesized through bulk methods. Electron microscopy studies showed that MF-COF-1 consists of interconnected fibers forming a macroporous sponge-like structure, a unique morphology not observed in bulk-synthesized COFs. Additionally, nitrogen adsorption isotherms demonstrated the microporous nature of MF-COF-1, with significant surface area and pore volume. The study also highlights the potential of using the microfluidic chip as a printing tool to create complex two- or three-dimensional COF structures on various surfaces, opening up new possibilities for advanced material applications [13]. This microfluidic synthesis method offers precise control over the formation of COFs, leading to high-quality materials with unique structural properties, and paves the way for scalable production and innovative applications in fields such as catalysis, sensing, and energy storage.

## 7. Continuous Flow Microdroplet Technique for Rapid Synthesis and Modification of COFs

Singh's group introduces a continuous flow microdroplet (CFM) technique for the rapid synthesis and post-synthetic modification of covalent organic frameworks (COFs). COFs are known for their diverse applications due to their porous and crystalline nature, but their traditional synthesis methods are often time-consuming and require harsh conditions. The CFM technique addresses these limitations by confining organic building units (OBUs) in moving microdroplets within a transparent capillary, significantly accelerating the synthesis process. The researchers synthesized three β-ketoenamine-linked COFs (TpPa-H, TpPa-Me, and TpPa-$NO_2$) under microfluidic solvothermal conditions. The OBUs were partially dissolved in a mixture of dimethylacetamide (DMA) and water, then merged with silicone oil at a T-junction to form microdroplets. These droplets moved through a coiled capillary heated to 80~100°C, completing the reaction in just 15 minutes. The resulting COFs showed high crystallinity and stability, confirmed by techniques such as PXRD, ATR-IR, and solid-state NMR spectroscopy. Additionally, the study demonstrated a one-step post-synthetic modification of COFs. TpPa-NO2 was successfully reduced to TpPa-$NH_2$ by merging droplets containing TpPa-NO2 with a solution of SnCl2 in DMA/ethanol at a second T-junction, followed by heating. This modification was completed in a fraction of the time required by traditional methods, without the need for extensive separation and purification steps [14]. The continuous flow approach not only enhances the efficiency and scalability of COF synthesis but also allows for the integration of post-synthetic modifications. This technique opens new possibilities for the mass production of functionalized COFs, facilitating their application in various fields such as catalysis, gas adsorption, and sensing. The study's findings suggest that the CFM technique could be a powerful tool for developing novel COFs with unique properties.

## 8. Microfluidic Synthesis of Hierarchical Porous Covalent Organic Polymer Monoliths

Zhao and coworkers explore the continuous synthesis of hierarchical porous covalent organic polymer (COP) monoliths using a droplet microfluidic system. The research demonstrates how altering the flow rate ratio between the continuous and dispersed phases can control the shape of the COP monoliths, producing either spherical or rod-like structures. Key parameters such as catalyst concentration, retention time, and flow rate were systematically investigated to optimize the synthesis conditions. The COP monoliths were synthesized via Schiff-base chemistry within microdroplets, which provided a controlled environment for the reaction. The interconnected macropores (up to 130 nm) were formed by the condensation of COP particles within the confined droplets. The study showed that the concentration of reactants significantly impacts the morphology and size distribution of the COP particles, with higher concentrations leading to more homogeneous and smaller particles [15]. The optimized microfluidic system achieved a high space-time yield of 413 $kg \cdot m^{-3} \cdot day^{-1}$ for spherical COP monoliths. This high yield highlights the potential of microfluidic systems for scalable production of hierarchical porous materials. The synthesized COP monoliths exhibited enhanced properties suitable for industrial applications, such as heterogeneous catalysis, due to their improved diffusion efficiency and reduced pressure drop. This method offers a promising approach for the large-scale production of COP monoliths with tunable shapes and sizes, providing a significant advantage over traditional batch synthesis methods. The ability to control the morphology and porosity of COPs through microfluidic techniques opens new avenues for their application in various fields, including catalysis and material science.

## 9. Conclusion

Microfluidic techniques have demonstrated substantial improvements in synthesis speed, control over reaction conditions, and the quality of the resulting materials. Microfluidic systems confine reactants into nanoliter or picoliter droplets, which are then transported through microchannels. This setup allows for exceptional control over the reaction environment, including temperature, flow rate, and reactant concentration. Such precise control leads to the formation of uniformly sized particles and highly crystalline structures within a fraction of the time required by conventional methods. For example, MOF crystals like HKUST-1, MOF-5, IRMOF-3, and UiO-66 have been synthesized in just a few minutes, compared to the hours or days needed for traditional solvothermal or hydrothermal methods. One of the key advantages of microfluidic synthesis is the prevention of channel clogging, a common issue in continuous flow systems. The droplets act as individual microreactors, isolating the reaction from the channel walls and thereby avoiding blockages. This isolation also enhances mass and heat transfer within the droplets, leading to faster reaction rates and higher yields. For instance, studies have shown that the production rate of HKUST-1 via microfluidics can be significantly higher than that achieved through batch processes.

Moreover, microfluidic techniques facilitate the synthesis of hierarchical structures and core-shell composites, which are challenging to produce with traditional methods. For example, the synthesis of $Co_3BTC_2@Ni_3BTC_2$ core-shell MOFs and $Fe_3O_4$@ZIF-8 magnetic composites using a two-step serial microfluidic approach has been successfully demonstrated. The structures of these complexes exhibit enhanced stability and catalytic properties, highlighting the potential of microfluidic systems to create advanced materials with tailored functionalities. The studies also illustrate the versatility of microfluidic synthesis for COF materials. The continuous flow of microdroplets has been used to produce highly crystalline COF fibers with unique morphologies and improved properties. The ability to control the mixing of reagents dynamically within the microchannels leads to materials that are not easily achievable through bulk synthesis.

In summary, microfluidic technology offers a superior alternative to traditional synthesis methods for MOFs and COFs. Its ability to rapidly produce high-quality, uniform materials with precise control over reaction conditions makes it a promising approach for both research and industrial applications. The scalability and efficiency of microfluidic systems could revolutionize the production of these advanced materials, paving the way for new applications in catalysis, gas storage, sensing, and beyond.

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