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Perspective

Advanced In-Line Purification Technologies in Multistep Continuous Flow Pharmaceutical Synthesis

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ABSTRACT: Continuous flow synthesis is a widely used method for synthesizing fine chemicals due to its benefits such as process intensification, improved reproducibility, and the ability to perform otherwise impossible transformations. Multistep continuous flow synthesis (MCFS) simplifies the synthesis of complex molecules by telescoping multiple steps into a streamlined and potentially automated process, reducing human efforts and time. Despite these advantages, challenges such as solid formation, solvent and reagent incompatibilities, and intermediate purification difficulties limit the development of MCFS. Overcoming these challenges will accelerate the innovative development of MCFS, thereby leading to enhanced multistep synthesis. This Perspective highlights representative examples of complex molecule production enabled by MCFS, where various in-line purification technologies were utilized during the flow processes.

KEYWORDS: *continuous flow synthesis, multistep synthesis, in-line purification technology, liquid−liquid phase separation, solid-phase synthesis, in-line solvent switch*

To date, organic synthesis remains a bottleneck in the pharmaceutical industry, with reactions traditionally performed in round-bottom flasks (RBFs) in laboratories or reaction tanks in industrial plants. However, the use of continuous flow reactors, an emerging synthesis platform, has provided chemists with great opportunities to render organic synthesis safer, faster, more efficient, and reproducible, with the potential for full automation.[1]

In continuous flow chemistry, reactions are performed in a continuous manner in specialized miniaturized reactors, such as tubular reactors or packed-bed reactors. The reaction mixture is pumped through a tubular reactor where various reaction conditions, such as heat, irradiation, or immobilized reagents, are applied. The small volume of these reactors enhances safety and allows for precise control over temperature and pressure. The high surface-area-to-volume ratio of tubular reactors improves phase mixing and heat transfer efficiency, making flow chemistry particularly suitable for multiphasic reactions. Additionally, flow chemistry benefits from great reproducibility with minimal human intervention and can be easily scaled up through continuous production, the numbering-up strategy, or more practical approaches such as sizing-up and smart dimensioning, which have gained increasing attention.[1−6] Moreover, the unique attributes of flow chemistry allow for access to reactivities unattainable in batch mode, particularly the ability to capture extremely short-lived intermediates by precise control over residence time (flash chemistry).[7,8] Meanwhile, flow chemistry has progressively become prevalent in chemical industry, aligning with the concept of continuous manufacturing (CM) that integrates reaction, workup, crystallization, drying, and blending into a seamless and continuous process. This approach to pharmaceutical manufacturing is believed to offer advantages in terms of cost, efficiency, flexibility, and quality assurance compared to "campaignlike" manufacturing in batch mode.[9]

Aside from tubular or packed-bed reactors, continuous flow chemistry can also be conducted in a cascade of miniaturized reactors based on continuous stirred-tank reactors (CSTRs). A CSTR is another type of chemical reactor designed for continuous operation and is capable of handling solid materials in the reaction mixture. A cascade of CSTRs results in a narrower residence time distribution (RTD) and behavior closer to a plug flow reactor with adjustable residence time. The miniaturized jacketed CSTR cascades were developed to address solid incompatibilities in continuous flow chemistry while maintaining efficient heat transfer due to the small reactor size.[10]

A platform for multistep continuous flow synthesis (MCFS) can be assembled by connecting multiple flow reactors with appropriate in-line purification modules along with proper substrate feeds. MCFS without intermediate purification is desirable due to its operational simplicity and minimal waste generation, leading to a sustainable process. However, this ideal MCFS faces challenges such as solid formation, reagent/solvent incompatibilities, and inconsistent flow rates between different reaction modules (Figure 1).[11−14] The development of intermediate handling technologies, such as in-line phase

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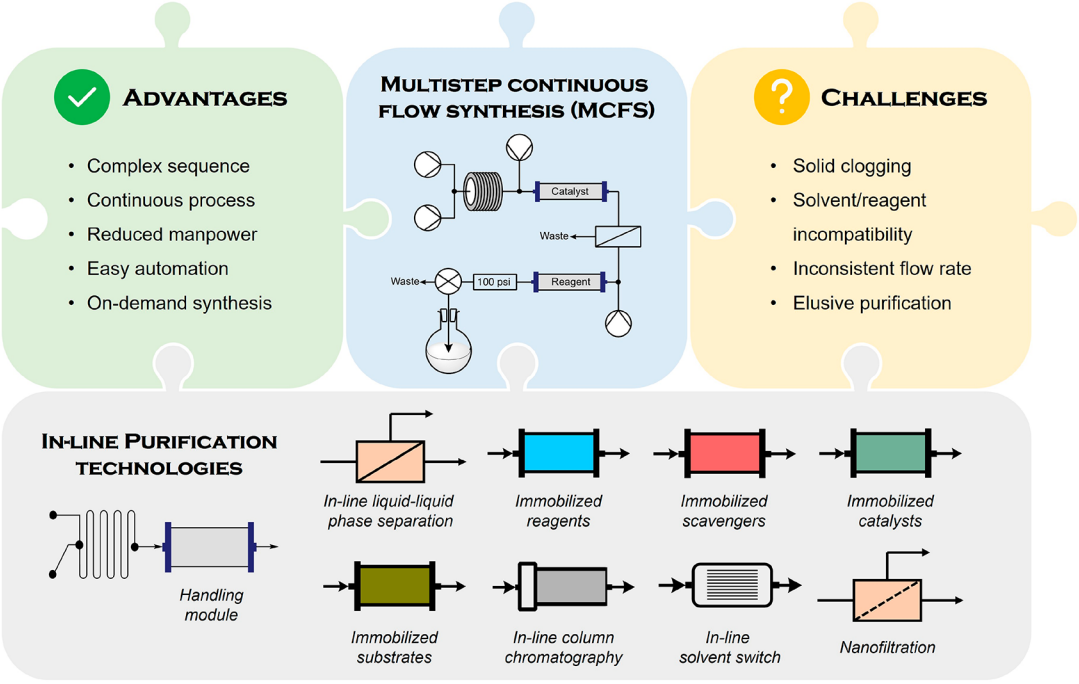

Figure 1. Multistep continuous flow synthesis: advantages, challenges, and contemporary in-line purification technologies.

separation, solvent switching, and immobilized reagents, has greatly enhanced the compatibility of end-to-end flow reaction modules, making more diverse synthetic routes feasible.[15] By integrating the advantages of flow chemistry into multistep synthesis, the production of complex molecules is expected to be achieved with reduced time, effort, and instrument footprint and has the potential for full automation.[16−18]

In this Perspective, we aim to present a series of examples of complex organic synthesis by MCFS. From a chemist's viewpoint, a carefully designed and intensively optimized route free of in-line purification would be ideal. Nonetheless, compromising with these technologies enables a more versatile multistep flow sequence with less development effort. Although there are comprehensive reviews on MCFS,[13−15,19−26] the applied in-line purification technologies are rarely discussed in detail. In this Perspective, examples of MCFS-enabled complex synthesis will be highlighted in different sections based on the in-line purification technologies involved as follows:

- Telescoped MCFS: rapid process without intermediate purification
- In-line workup: liquid−liquid phase separation
- Immobilized reagents: in-line transformation and impurity removal
- Flow catalysis: in-line immobilized catalysts
- Solid-phase synthesis in flow: in-line immobilized substrates
- Future: emerging in-line purification technologies.

Through comparison between these in-line purification technologies, we hope to illustrate how they have improved MCFS.

TELESCOPED MCFS: RAPID PROCESS WITHOUT INTERMEDIATE PURIFICATION

Through intensive optimization of reaction conditions and resolution of all the solvent and byproduct incompatibility issues, certain MCFS sequences can be performed in a telescoped fashion without the need for in-line purification technologies.

In 2007, Yoshida et al. reported an MCFS-based sequential difunctionalization of 1,2-dibromobenzene using *n*-butyllithium.[27] This study demonstrated the remarkable tolerance of *o*-bromophenyllithium, a highly unstable intermediate, in flow chemistry without the formation of benzyne (Figure 2A). The success of this sensitive difunctionalization was attributed to the short residence time achieved by the flow reactor through immediate quenching of the unstable intermediate upon its formation with electrophiles.

In 2009, McQuade et al. reported a three-step end-to-end continuous flow synthesis of ibuprofen without intermediate purification.[28] The synthesis involved a cascade of Friedel−Crafts acylation, oxidative 1,2-aryl migration, and ester hydrolysis, which was conducted in a continuous flow system with a total residence time of 10 min and a 9 mg/min throughput (Figure 2B). The results of this work highlighted the benefits of precise temperature control in flow systems.

In 2017, the Jamison group developed a rapid MCFS of ciprofloxacin that involved a linear synthetic route consisting of five end-to-end connected flow reactors and was completed within 9 min (Figure 2C).[29] The resulting sodium salt of ciprofloxacin was transformed into ciprofloxacin hydrochloride through an off-line acidification and filtration in 60% overall yield, which is comparable to the batch synthesis but with a greatly reduced time frame. Despite the need for an extra step to remove the generated dimethylamine by addition of acetyl chloride, this complex reaction sequence demonstrated the potential of well-designed and optimized MCFS in complex organic synthesis.

Numerous other successful examples of complex molecule synthesis enabled by end-to-end MCFS have been reported.[30−43] Despite these achievements, the development of MCFS has been hindered by challenges including the need for intensive process design and optimization as well as practical

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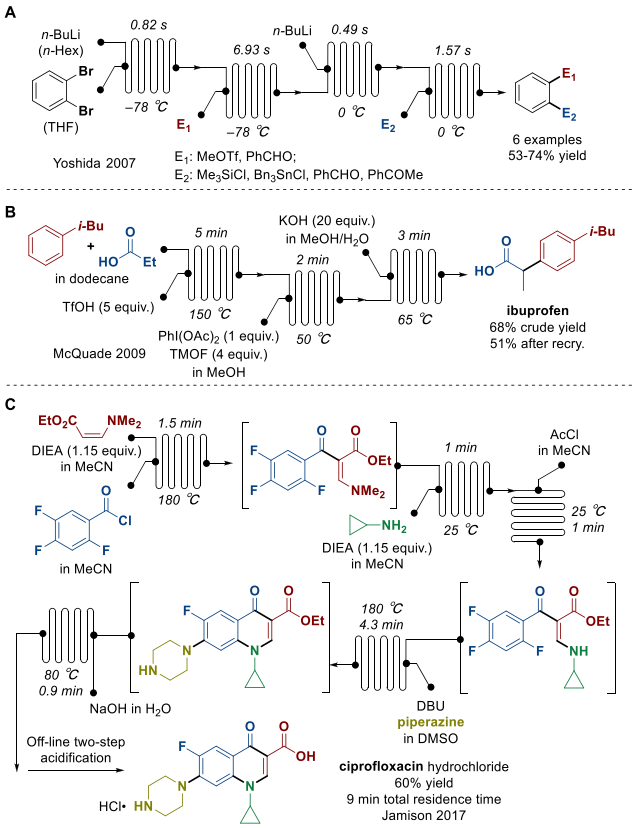

Figure 2. (A) Sequential difunctionalization of 1,2-dibromobenzene through *o*-bromophenyllithium without benzyne formation. (B) Three-step MCFS of ibuprofen from simple substrates. (C) Seven-step rapid total synthesis of ciprofloxacin.

issues such as incompatibility of solvent/reagents, mismatched flow rates between reaction modules, and formation of solids during reaction. However, the advent of in-line purification technologies has provided solutions to these problems, thereby enhancing the versatility of MCFS.

IN-LINE WORKUP: LIQUID–LIQUID PHASE SEPARATION

The use of highly reactive reagents, such as strong acids/bases and strong electrophiles/nucleophiles, is a common practice in organic laboratories. These reactive species are often quenched by appropriate aqueous reagents prior to purification. Incorporating this workup process into the flow process can improve the reagent compatibility between reaction modules. Meanwhile, the downstream organic/aqueous phase separation can be achieved by in-line liquid–liquid phase separation technology.

In 2007, Jensen et al. developed an integrated in-line liquid–liquid extraction device consisting of an extractor and a porous hydrophobic polymer membrane-based phase separator (Figure 3A, left).[44] The hydrophobic nature of the polymer membrane is responsible for the selective surface wetting by nonaqueous solvents, and the high micropore density contributes to efficient separation. With a precise pressure control unit, accurate permeation of the organic phase along with rejection of the aqueous phase is achieved. The apparent advantages of in-line liquid–liquid separation in flow chemistry have led to the commercialization of various standard in-line separators (Figure 3A, right).[45,46] Using this in-line phase separation technology, the Jensen group reported an MCFS of a series of carbamates in the same year (Figure 3B).[47] The carbamates were synthesized through an azidation of acyl chlorides followed by a Curtius rearrangement and a nucleophilic addition by alcohols. The in-line liquid–liquid separation technology facilitated handling of the aqueous/toluene biphasic reaction mixture and removal of aqueous waste downstream from the azidation reaction, providing a net solution of acyl azides in toluene as the input for the subsequent rearrangement.

In 2011, Jensen, Buchwald, and co-workers reported an MCFS of biaryls using Suzuki–Miyaura cross-coupling starting from substituted phenols, which were first transformed to aryl triflates as suitable coupling partners (Figure 3C).[48] The process began with treating the phenol with triflic anhydride in toluene, followed by the introduction of aqueous HCl to remove triethylamine and other salts from the reaction mixture. The aqueous waste was subsequently removed by an in-line liquid–liquid phase separator, yielding a net organic phase containing pure aryl triflate for the final Suzuki–Miyaura coupling with arylboronic acid via palladium catalysis.

In 2015, Seeberger et al. established a chemical assembly system with five different interchangeable flow reaction modules that provides access to various target chemicals through divergent MCFS (Figure 3D).[49] An in-line liquid–liquid phase separator was integrated in four of the reaction modules to separate the aqueous waste from the biphasic reaction mixture or the mixture after aqueous quenching. The modular reaction systems consisted of an alcohol oxidation, an HWE olefination of aldehydes, a Michael addition by nitromethane, an ester hydrolysis, and a catalytic hydrogenation module that did not require a phase separator. By varying substrates, reagent choices, and the sequence of reaction modules, MCFSs of five different APIs with distinctive structural motifs (γ-amino acid and γ-lactam) and two β-amino acids were achieved in good overall yields.

In 2016, Jensen, Jamison, Myerson, and co-workers developed a reconfigurable flow chemistry system for on-demand and continuous APIs manufacturing (Figure 3E).[16] An in-line liquid–liquid phase separator was a crucial enabling technology in the upstream synthesis. Aside from membrane-based phase separators, gravity-based liquid–liquid separators were also employed in this platform. The capability of this system was showcased by the highly efficient on-demand MCFS of four APIs, including the three-step synthesis of fluoxetine hydrochloride with three membrane-based separators.

In-line liquid–liquid separation technology has played a crucial role in the adaptation of traditional batch synthesis procedures to continuous flow systems. The frequent use of aqueous quenching and multiphasic reactions in organic synthesis makes this technology desirable. Although alternative routes or further optimization of the reaction conditions may be used to bypass the need for in-line purification, the use of in-line liquid–liquid separator offers simplicity and practicality. The current widespread availability and ease of operation of this technology make it a preferred choice for many MCFS processes.

Despite their widespread use, in-line membrane-based phase separators are not without limitations. The selective face wetting and precise pressure control mechanisms become unreliable or ineffective in situations where multiphasic mixtures form emulsions or have small differences in surface

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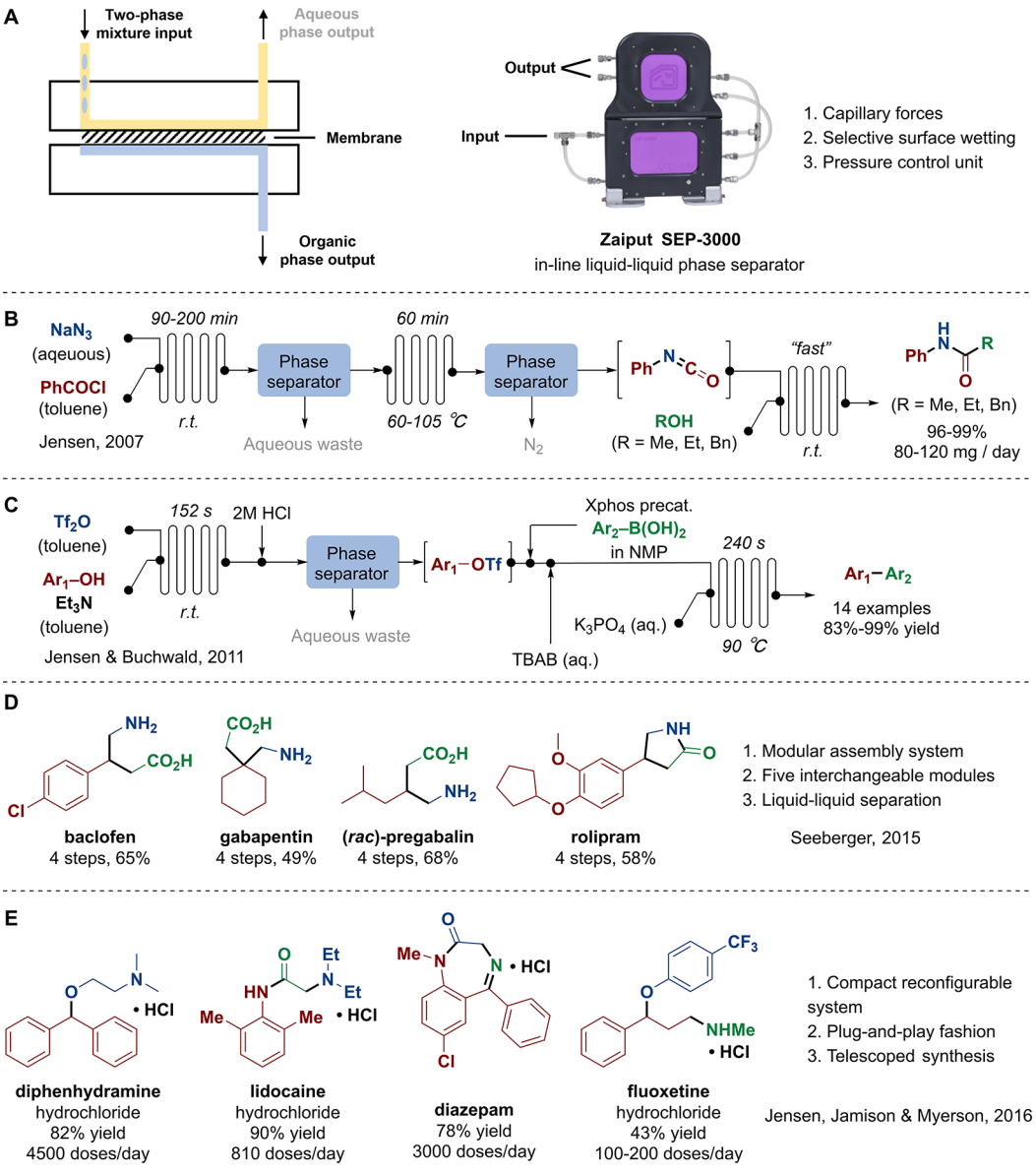

Figure 3. (A) In-line liquid−liquid phase separation technology. (B) MCFS of carbamates enabled by in-line liquid−liquid separation. (C) MCFS of biaryls through Suzuki−Miyaura coupling enabled by in-line liquid−liquid separation. (D) Chemical assembly system featuring in-line liquid−liquid separation for an MCFS of APIs. (E) On-demand MCFS-based production of APIs enabled by in-line liquid−liquid separation.

tension. Additionally, the nonideal partitioning of products or impurities between the phases can pose challenges for effective separation.

IMMOBILIZED REAGENTS: IN-LINE TRANSFORMATION AND IMPURITY REMOVAL

Using heterogeneous reagents in organic synthesis provides the benefit of straightforward separation by simple filtration. In flow chemistry, these reagents can be immobilized in packed-bed reactors rather than flowing along with the reaction mixture. Similarly, an in-line heterogeneous scavenger module can be installed downstream of flow reactors to effectively remove impurities from the output mixture (Figure 4A).

In 2006, Ley et al. made an important contribution to the use of immobilized reagents and scavengers in flow synthesis. They reported a seven-step MCFS of the natural product (±)-oxomaritidine, with five of the reactions utilizing column reactors packed with immobilized reagents, each performing a unique transformation (Figure 4B).[50] Despite its complex structure, (±)-oxomaritidine was produced from two simple starting materials in 40% overall yield with over 90% purity without any off-line purification. This work showcased the benefits of integrating immobilized reagents in flow chemistry, where the separation process was greatly simplified.

In 2014, the Ley group reported the total synthesis of a spirocyclic polyketide natural product using a combination of batch and flow synthesis (Figure 4C).[51] Multiple immobilized reagents and a scavenger were employed in the system, including a phosphorus ylide for HWE olefination, a sulfonic acid for acetal formation, and a thiosulfate as a scavenger for oxidative impurities. While not fully continuous, this lengthy and complex total synthesis demonstrates the advantages of incorporating flow chemistry to accelerate the synthetic process.

An MCFS of triazole derivatives was reported by the Ley group in 2009, featuring multiple in-line scavenger modules

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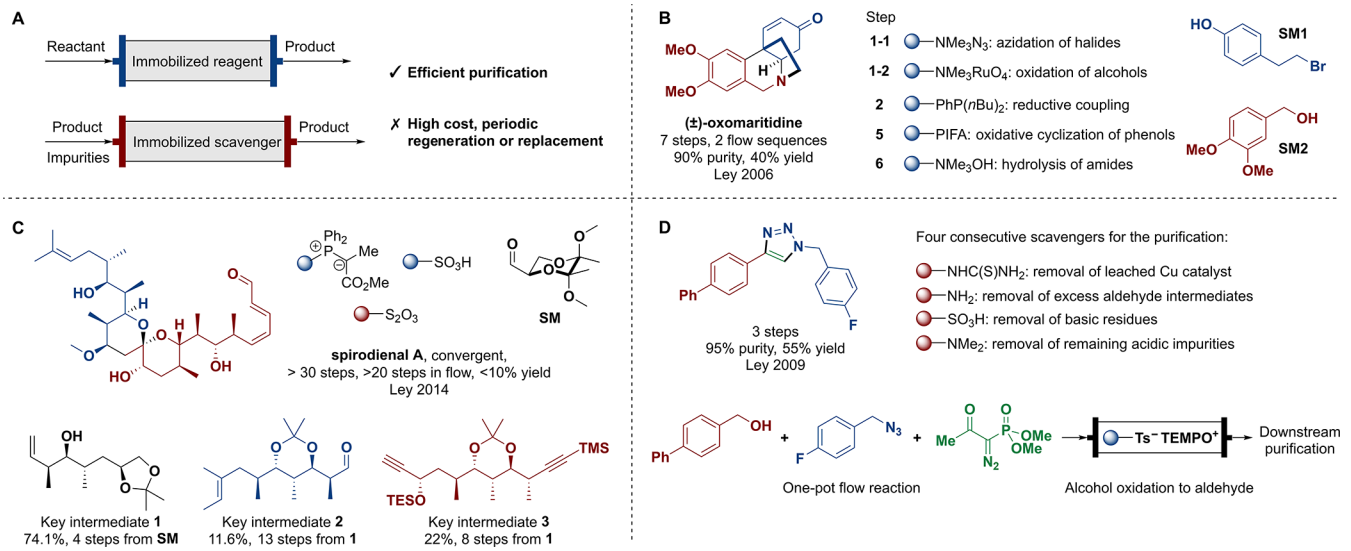

Figure 4. (A) Immobilized reagents and scavengers used in flow chemistry. (B) MCFS of oxomaritidine, an alkaloid natural product, enabled by solid-supported reagents. (C) Spirocyclic polyketide total synthesis via a batch and flow hybrid system with solid-supported reagents and scavengers. (D) MCFS of triazoles with multiple consecutive solid-supported scavengers.

(Figure 4D).[52] The process began with the oxidation of a substituted benzyl alcohol using immobilized TsO-TEMPO, followed by treatment with Bestmann−Ohira reagent to yield phenylacetylene. The intermediate was then reacted with azide in a CuI-immobilized packed-bed reactor to yield the corresponding triazole product through a CuAAC reaction. After purification using four consecutive scavenger cartridges, a solution containing the desired triazole product with 95% purity in 55% overall yield was obtained. This work highlighted the effectiveness of using in-line immobilized scavengers for purifying intermediates in continuous flow processes.

Immobilized reagents and scavengers are highly efficient in flow chemistry due to their heterogeneous nature, allowing for traceless treatment of the reaction mixture. However, their use in flow chemistry also presents some complications such as (i) limited flow rate caused by the compressed flow path and increased risk of clogging; (ii) the need for periodic regeneration and eventually replacement of the supported materials due to consumption, deterioration, or leaching; (iii) sometimes inadequate differentiation between product and impurities; (iv) potential contamination from leaching of the immobilized chemicals.

FLOW CATALYSIS: IN-LINE IMMOBILIZED CATALYSTS

Using optimized immobilized catalysts in flow chemistry (Figure 5A) does not require regular regeneration or replacement and in principle is an ideal way to facilitate catalytic reactions in flow synthesis. Effective and stable immobilized catalysts are ideal for long-term continuous operation of catalytic reactions.

Early efforts devoted to the development of immobilized catalysts in flow chemistry involved polystyrene resin-bound piperidine for catalytic Knoevenagel reaction[53] and toluenesulfonic acid for catalytic benzaldehyde acetal formation.[54] To date, a wide variety of immobilized catalysts have been employed in flow chemistry, including chiral catalysts for enantioselective transformations.[55−59]

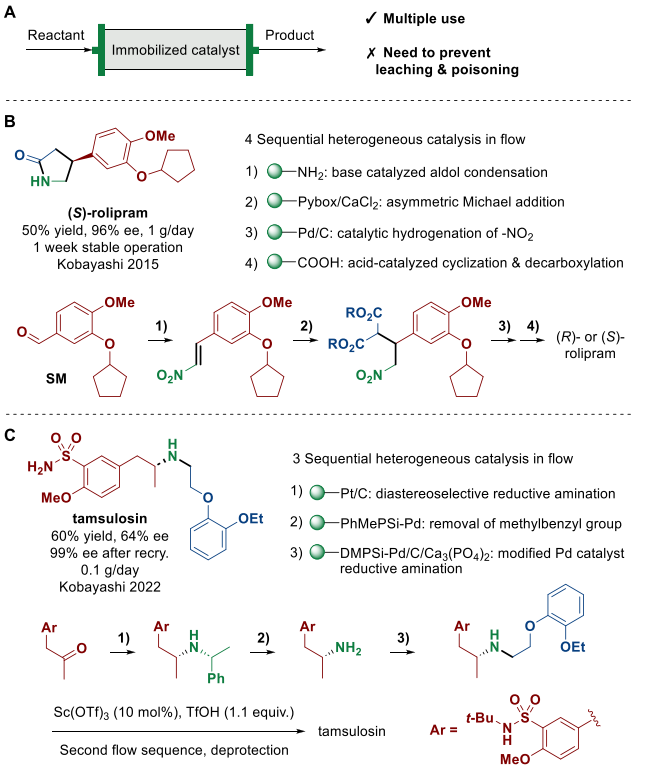

Figure 5. (A) Immobilized catalysts in flow chemistry. (B) MCFS of an API featuring consecutive in-line immobilized catalysts. (C) MCFS of an API using optimized heterogeneous catalysts.

The Kobayashi group has made significant advancements in the utilization of in-line immobilized catalysts in MCFS. In 2015, they reported an enantioselective MCFS of the anti-inflammatory drug (*S*)- or (*R*)-rolipram using only column reactors packed with heterogeneous catalysts (Figure 5B).[57] The system consisted of four cartridges with immobilized catalysts connected in an end-to-end fashion, two scavenger modules packed with 4 Å molecular sieves (MS) and Celite, respectively, and another module to separate hydrogen gas

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from the reaction mixture. Starting from a substituted benzaldehyde, (*S*)- and (*R*)-rolipram were both obtained in 50% yield with 96% ee by altering the chirality of the Pybox ligand in the second catalysis module. The consecutive immobilized catalysts flow system showed great long-term stability with 1 week continuous operation.

In 2022, the same group reported an MCFS of tamsulosin utilizing a series of in-line immobilized catalysts (Figure 5C).[60] The synthesis began with a Pt/C-catalyzed diastereoselective reductive amination of a substituted phenylacetone with phenylethylamine, followed by hydrogenative debenzylation catalyzed by a polysilane-modified Pd catalyst (PdMePSi-Pd/SiO_2) to afford a primary amine, and concluded with a catalytic reductive coupling between the primary amine and a nitrile compound facilitated by another polysilane-modified Pd catalyst (DMPSi-Pd/C/$Ca_3(PO_4)_2$). The desired (*R*)-tamsulosin was obtained in 60% yield with 64% ee. This work highlighted the significance of catalyst design and optimization in the effective application of immobilized catalysts in MCFS.

In 2017, the Kobayashi group reported an MCFS of the precursor of (±)-pregabalin enabled by in-line immobilized catalysts (Figure 6A).[61] The synthesis started with the

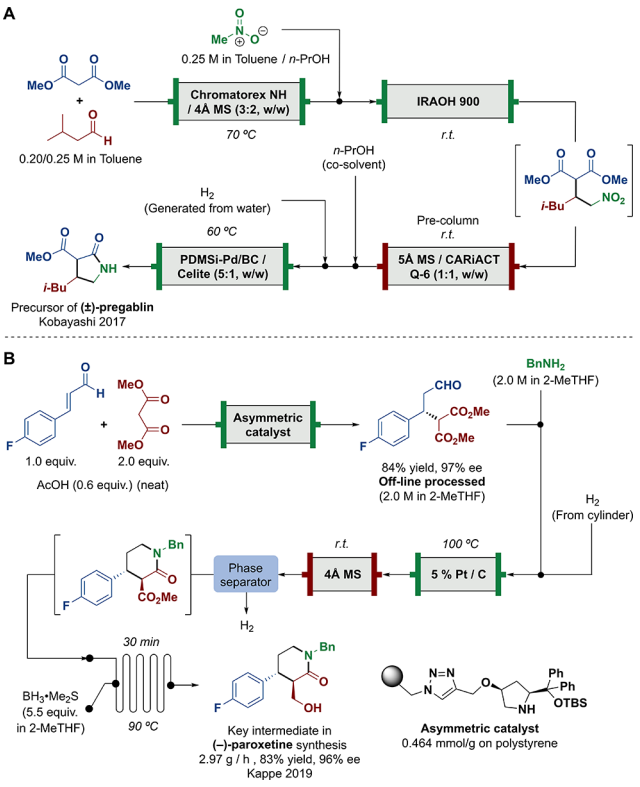

Figure 6. Continuous flow syntheses enabled by multiple in-line immobilized catalysts of (A) the precursor of (±)-pregabalin and (B) a key intermediate in the synthesis of (−)-paroxetine.

condensation of dimethyl malonate with 3-methylbutanal catalyzed by Chromatorex NH, a primary-amine-functionalized silica, along with 4 Å MS to remove the water generated. The resulting α,β-unsaturated ester was then reacted with nitromethane catalyzed by IRAOH 900, a strongly basic resin. After treatment with a precolumn packed with 5 Å MS and silica gel, the nitro compound was hydrogenated using a previously developed immobilized palladium catalyst. The resulting amine readily underwent cyclization to form the γ-lactam product, which was then converted to (±)-pregabalin off-line in 67% yield in two steps.

In 2019, Kappe et al. reported an MCFS of a crucial chiral intermediate in (−)-paroxetine synthesis using an in-line immobilized chiral organocatalyst (Figure 6B).[62] The asymmetric conjugate addition of dimethyl malonate to 4-fluorocinnamaldehyde was facilitated by a polystyrene-supported chiral *cis*-4-hydroxydiphenylprolinol TBS ether catalyst. The aldehyde was then mixed with benzylamine and underwent a reductive amination in a Pd/C-catalyst-packed reactor. After removal of water and hydrogen gas by a molecular sieve scavenger and a phase separator, the product underwent reduction by borane to yield the key intermediate, a primary alcohol, in 83% yield with 96% ee.

Heterogeneous catalysts, such as Pt/C or Pd/C, can be straightforwardly adopted in flow chemistry and have found wide application in continuous flow catalytic hydrogenation (as demonstrated by the commercialized H-Cube reactor).[63] On the other hand, transforming homogeneous catalysts, especially most organocatalysts, into immobilized heterogeneous catalysts for use in flow synthesis presents significant challenges. These challenges include catalyst loading, reduced reactivity or selectivity upon immobilization, the choice of a suitable solid support, long-term stability, and catalytic activity.[56,64,65] The feasibility of transforming a catalyst into its solid-supported form needs to be assessed carefully before implementation. Additionally, clogging and regeneration issues, like those faced by in-line immobilized reagents, must be addressed in the use of immobilized catalysts.

SOLID-PHASE SYNTHESIS IN FLOW: IN-LINE IMMOBILIZED SUBSTRATES

Efficient purification of products has always been a major concern among organic chemists. Immobilized reagents and catalysts represent efficient ways of separating product from other components. However, purification becomes increasingly important in multistep synthesis, as impurities can potentially disrupt subsequent reactions. In this context, solid-phase synthesis (SPS), which was introduced in the 1960s,[66] has received significant interest from researchers due to its ease of post-reaction purification through simple filtration. Unlike conventional chemistry, SPS involves immobilizing the starting material on a solid support and transforming it step-by-step. After each reaction, the immobilized product is separated from other materials by simple filtration, and at the end the desired product is obtained by chemical cleavage from the solid support. By incorporating SPS into flow chemistry, compatibility issues between solvents and reagents as well as mismatched flow rates in MCFS can be overcome, as reagents and solvents are pumped sequentially through the same reactor packed with the immobilized substrate (Figure 7A). Additionally, one of the major advantages of this approach is the ease of automation, as the reaction sequence can be controlled by pumps and valves. However, it should be noted that unlike typical flow chemistry, the SPS−flow strategy results in batchwise production.

In 2017, Pentelute et al. developed a fully automated platform for rapid solid-phase peptide synthesis enabled by flow technology, showcasing the merits of combining SPS and flow chemistry (Figure 7B).[67] By utilizing flow-based preactivation of the Fmoc-protected amino acid with a condensation reagent such as HATU, this robust platform enables instant amide bond formation in just 7 s and an overall

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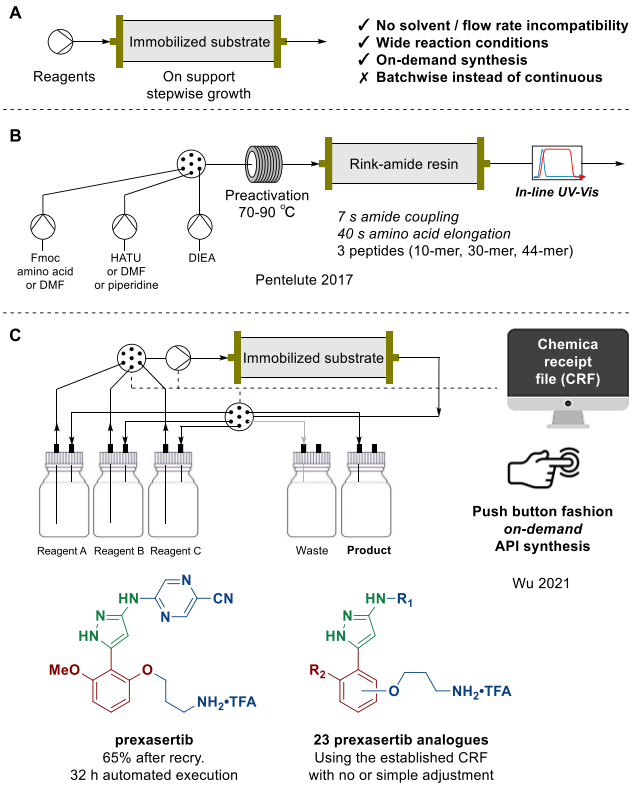

Figure 7. (A) SPS−flow synthesis. (B) Automated peptide synthesis enabled by SPS−flow technology. (C) Automated MCFS of an API enabled by SPS−flow technology.

40 s chain elongation per amino acid. The significant boost in efficiency compared to the batch SPS method was exemplified by the rapid syntheses of three different peptides (10-mer, 30-mer, 44-mer) using this platform. Additionally, through meticulous condition optimization, the platform was able to achieve even higher efficiency in chain elongation and enabled the rapid syntheses of single-domain proteins with up to 164 amino acid residues within hours.[68]

The combination of the SPS strategy and flow chemistry has advanced the intelligent synthesis of more complicated active pharmaceutical ingredients (APIs). In 2021, Wu et al. reported a fully automated synthesis platform enabled by SPS−flow and demonstrated its practicality through the streamlined six-step synthesis of prexasertib (Figure 7C).[18] Directed by an optimized chemical recipe file (CRF), this automated platform produced 635 mg of prexasertib in 65% yield over 32 h of continuous operation using 1 g of solid support resin. With minimal to no modifications, the CRF was used to produce 23 derivatives of prexasertib in yields ranging from 13% to 70% within 22 to 36 h of operation time. The SPS−flow technology is particularly advantageous for API synthesis due to its ability to tolerate a wide range of reagents and solvents, which is essential to accommodate the diverse reaction conditions required for API synthesis. Moreover, compared to traditional end-to-end MCFS platforms, the SPS−flow platform has a simpler and more compact hardware structure, which enables the execution of multiple synthetic routes without physical reconfiguration of the instrument.

Despite the great advances in the application of solid-phase synthesis (immobilized substrates) in flow chemistry, such as the recent breakthroughs in API synthesis enabled by SPS−flow technology, there are still major challenges that need to be addressed. These challenges include issues with the resin loading and cost, solvent-dependent swelling of the resin, and utilization of excess solvents.

FUTURE: EMERGING IN-LINE PURIFICATION TECHNOLOGIES

The integration of other advanced in-line purification technologies such as organic solvent nanofiltration, in-line evaporation, and in-line column chromatography in flow chemistry is also gaining momentum. Considerable effort has been devoted to expanding the toolkits of in-line technologies for flow synthesis. However, there are still major challenges to overcome, including the lack of a widely accepted general operational protocol and issues with integrating these techniques into standard flow chemistry setups.

The introduction of organic solvent nanofiltration has provided MCFS with another powerful tool for the purification of intermediates.[69,70] From simple particle filtration to micro- and ultrafiltration and finally to nanofiltration, the separation techniques have progressed from targeting heterogeneous suspensions to homogeneous solutions containing molecules of different sizes. Nanofiltration leverages the semipermeability of specialized membranes with nanosized pores to achieve "molecular sieving" by distinguishing molecules of different molecular weights and different sizes (Figure 8A). For direct downstream nanofiltration in flow, a solvent-resistant membrane can be employed.

In 2019, Livingston et al. reported an efficient sequence-defined polyether synthesis facilitated by an in-line membrane-based nanofiltration device.[71] A three-armed starlike "hub" was used as the molecular weight enlargement unit, to which the substrate was attached and elongated over reaction cycles (Figure 8A). The nanofiltration process efficiently separated the hub−product complex from the smaller monomers (pentagol, an oligomer with five glycolyl units) through molecular sieving. The retained product was then fed to a deprotection−extraction−substitution sequence for chain elongation. Optimal separation was achieved using multiple end-to-end-connected nanofiltration modules. The high efficiency of this system was demonstrated by the synthesis of two different sequence-defined six-mer polyether "stars" in overall yields of 88% and 79%, respectively, after a 12-step synthesis. The final polyether product was obtained by cleavage from the supporting hub with BCl_3, a Lewis acid. Although this multistep synthesis was not conducted in a streamlined end-to-end flow chemistry fashion, we can envision that the integration of continuous nanofiltration in MCFS has great potential for advancement in this field.

Nevertheless, one of the major challenges for application of nanofiltration in MCFS is the solvent compatibility of the membrane. For this reason, the development of organic-solvent-resistant membranes with high throughput and selectivity is crucial.[70,72] Meanwhile, molecular weight enlargement is usually required to distinguish the product from impurities during nanofiltration.

Solvent incompatibility has been a long-standing issue in end-to-end MCFS. The solvent dependence in certain organic reactions limits the choice of synthetic routes in MCFS. While it is possible to switch solvents by evaporation followed by redissolution in another solvent, an in-line solvent switch is preferable due to its continuous nature.

In this context, a microfluidic distillation device based on differences in volatility was introduced by Jensen et al. in 2009,

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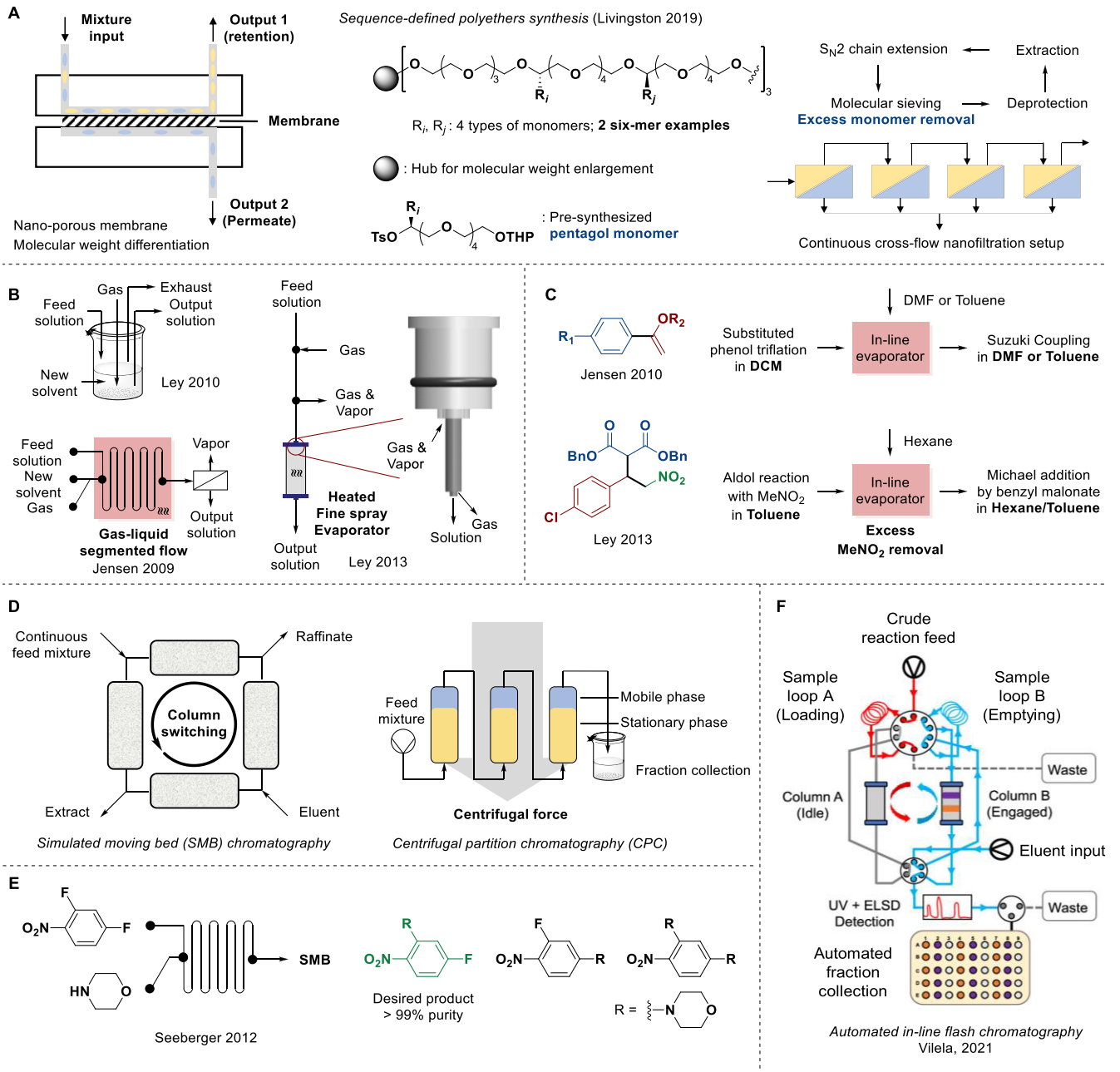

Figure 8. In-line purification technologies. (A) Membrane-based nanofiltration. (B) Solvent switch (reproduced from the Supporting Information of ref 76). (C) Flow synthesis involving solvent switch. (D) Chromatography. (E) Flow synthesis involving in-line chromatography. (F) Automated in-line flash chromatography (reproduced from ref 80, copyright 2021 American Chemical Society.

where the switch from a volatile solvent to a solvent with higher boiling point (b.p.) was realized in a continuous manner (Figure 8B, bottom).[73] The system consists of a heated gas−liquid segmented flow module fed with a binary mixture of two solvents with different volatilities and nitrogen gas. As the mixture passes through the heated reactor, the volatile solvent is vaporized and gradually saturates the gaseous phase. Subsequently, a downstream membrane-based separator is used to remove the gaseous phase, leaving the solution with the less volatile solvent to be fed into the next reaction module. The feasibility of this strategy in MCFS was demonstrated by the multistep synthesis of a series of substituted styrenes that involved a solvent switch from DCM, in which the triflation of phenol was conducted, to DMF for the high-temperature Suzuki−Miyaura coupling reaction (Figure 8C, top).[74]

In 2010, Ley et al. reported an MCFS of imatinib that involved a solvent switch from DCM to DMF. The switch was accomplished by transferring the reaction mixture in DCM into a container charged with DMF and then evaporating the highly volatile DCM through nitrogen bubbling at 50 °C before performing the subsequent transformation (Figure 8B, top).[75]

In 2013, the Ley group developed an in-line evaporator for solvent removal that allows concentration of the feed for both batch and flow chemical processes (Figure 8B, right).[76] The solvent evaporation was realized by exposing a fine spray of solution to a desolvation gas (N_2) in a heated evaporation chamber while constantly exhausting the desolvation gas and solvent vapor, affording a concentrated solution at the bottom of the evaporation chamber. The flow of liquid and gas in and

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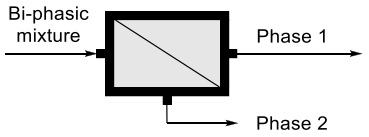
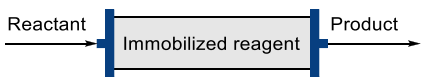
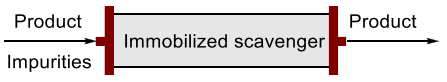
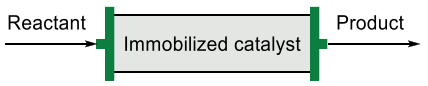
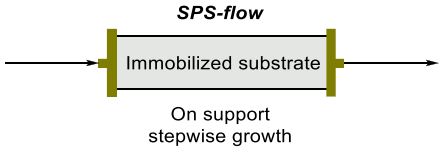
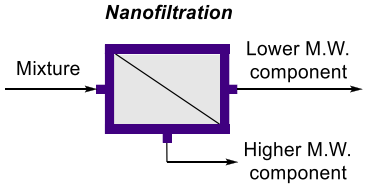
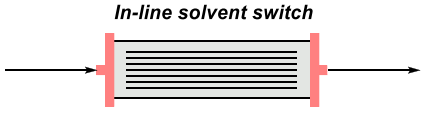
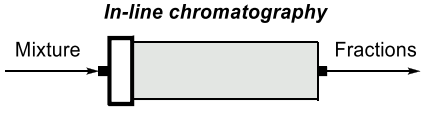
Table 1. In-Line Purification Technologies and Their Benefits, Limitations, and Potential Future Developments

In-line purification technologies	Benefits	Limitations	Potential future developments
Liquid-liquid separation 	In-line continuous separation of liquid-liquid biphasic mixtures.	Inefficiency with multi-phasic mixtures that have small differences in surface tension.	Improved membrane materials for more effective and robust separation.
In-line transformation 	Traceless transformation of reactants to products.	Need for regular regeneration or replacement. Leaching problem. Solid incompatibility.	Resins with less cost, higher loading, and recyclability.
In-line impurity removal 	Traceless removal of impurities from reaction mixtures.		
Flow catalysis 	Traceless transformation of reactants to products. Less frequent need for regeneration or replacement.	Reduced reactivity upon immobilization. Effort needed for adapting a catalyst into its immobilized form. Solid incompatibility.	
SPS-flow 	Straightforward separation of product in multistep synthesis. Compatibility with wide variety of reaction conditions.	Large solvent consumption. Solid incompatibility; Solvent-dependent swelling of resins.	Resins with less cost, higher loading, and better swelling properties in various solvents.
Nanofiltration 	Separation of components with different MW in homogeneous mixture.	The availability of solvent-resistant membrane with great selectivity.	Improved membrane materials for practical nanofiltration.
In-line solvent switch 	Continuous solvent switching.	Ineffectiveness when switching from less volatile solvent to a more volatile one.	Improved engineering design. Better mechanism for solvent removal other than evaporation.
In-line chromatography 	Continuous precise separation of components based on their different affinity to materials.	Difficulty in handling dilute solution input; Excess solvent consumption.	More effective system that can isolate all components.

out of the chamber was regulated through a three-layer tubing system (Figure 8B, right). The concentrate could be pumped out from the chamber continuously and transported to the subsequent reactor after the introduction of a new solvent. This device is capable of removing not only low-b.p. solvents but also high-b.p. solvents. For example 56% DMF can be removed upon 80 °C heating. It is notable that the removed solvent can be easily recovered by condensing the exhausted vapor.

The practicality of this in-line evaporator was demonstrated by a two-step synthesis that required the removal of excess nonvolatile reagent in a continuous flow fashion (Figure 8C, bottom). The synthesis involved a condensation of 4-chlorobenzaldehyde with excess nitromethane followed by a

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Michael addition using benzyl malonate. The in-line evaporator was used to remove the excess nitromethane (b.p. 101 °C) at 20 °C as an azeotropic mixture with hexanes.

The current in-line solvent switch technologies have advanced MCFS by efficiently switching low-b.p. solvents to higher-b.p. solvents but are limited in the reverse direction. Moreover, the in-line evaporation process can lead to unstable flow rates and even pose safety risks associated with buildup of pressure by vaporization of solvents.

Chromatography—a method that enables the separation of mixtures containing multiple components into different fractions of the pure compounds—is one of the most widely used purification techniques in organic synthetic laboratories. However, its usage in flow chemistry is limited by factors including operational complexity, high solvent consumption, strong reliance on human intervention, and empirically determined operation parameters. Additionally, the difficulty in handling dilute mixture feeds and the potential impact of incoming solvent on partition efficiency make it challenging to implement this method in a continuous manner. Despite these challenges, a few in-line chromatography-based purification devices have been designed and employed in flow synthesis.

Simulated moving bed (SMB) chromatography is a well-established continuous purification technology in the petrochemical industry.[77] It functions by periodically changing the connections of the system, which simulates the moving of the stationary phase counter to the eluent. This action causes the extract and raffinate to move in different directions, thereby allowing for separation of compounds (Figure 8D, left). Inspired by this purification technique, Seeberger et al. designed and built an in-line SMB chromatography module that connected to a flow reactor to directly isolate the desired product downstream.[78] The utility of this system was demonstrated by the downstream separation of the desired ortho product from the mixture of three regioisomers resulting from an aromatic nucleophilic substitution reaction with >99% purity (Figure 8E).

In addition, centrifugal partition chromatography (CPC) is another technology worth mentioning. CPC involves a liquid stationary phase that is "fixed" by centrifugal force and another liquid acting as mobile phase that passes through this stationary phase, partitioning the compounds and eventually collecting pure compounds as fractions at the outlet (Figure 8D, right). Utilizing this technique, Greiner et al. developed a downstream in-line CPC purification module for their two-step flow reaction system, which involved an aromatic nucleophilic substitution of 2,4-difluoronitrobenzene by morpholine followed by hydrogenation of the nitro group.[79] The CPC module was used to purify the desired product, 4-fluoro-2-morpholinoaniline, to >99.9% purity.

More recently, even common column chromatography using silica gel has been introduced in continuous flow chemistry as a downstream purification module. In 2021, Vilela et al. reported an in-line column chromatography system based on an automated flash chromatography instrument (Figure 8F).[80] The utility of this system was showcased by the purification of the crude mixtures from three diverse reactions.

Although the adaptation of chromatography in continuous flow chemistry presents various challenges, the recent advancements show great potential in advancing the field of MCFS by providing high-purity products in a continuous manner, which is critical for streamlining and optimizing MCFS. By improving the purification efficiency, these technologies could significantly enhance the performance and versatility of MCFS, enabling the rapid and efficient synthesis of complex molecules.

PERSPECTIVE AND OUTLOOK

In summary, we have discussed several examples of telescoped MCFS categorized by in-line purification technologies utilized in the process. Other promising in-line technologies that could be used in MCFS have also been briefly mentioned. These examples illustrate how in-line purification technologies have made MCFS more compatible with various reaction conditions, thus making the synthesis of diversified complex molecules more feasible.[74,81−87] The advantages, limitations, and potential future developments of these in-line purification technologies are briefly summarized in Table 1.

The standardization of apparatus will drive the development of in-line purification technologies. Flow chemical synthesis has been increasingly adopted into organic chemistry laboratories in recent decades, largely due to the standardization and commercialization of flow chemistry equipment.[6] Extending these aspects to in-line purification technologies will facilitate the purchase and assembly of common in-line purification modules into continuous flow platforms to enable a wide variety of synthetic routes, which is crucial for MCFS to become a widespread method for the synthesis of complex molecules.

Scaling up MCFS is critical for its practical applications in the chemical industry, where production on a large scale is necessary. In this context, long-term stability of the modules involved is essential to ensure that the system can be used continuously over an extended period of time. The development of robust and durable in-line postsynthetic technologies is crucial to enable the adoption of MCFS as a widespread method for the synthesis of complex molecules on a large scale.

Chemical process automation is becoming increasingly popular among the synthetic community and is a major future direction for fine chemical production.[18,68,88−94] Flow chemistry, particularly MCFS, can further advance process automation due to its continuously operating nature, making it easier for machines to handle compared to batch chemistry. Currently, most flow chemistry syntheses are already using computer-controlled instruments, such as pumps and multiway valves,[1] unless off-line batchwise purification or separation is involved. Therefore, well-established in-line purification technologies offer the potential for fully automated implementation of complex MCFS sequences by eliminating the need for off-line purification.

Aside from production of fine chemicals such as APIs in an efficient and automated manner through an optimized synthetic route, flow chemistry also offers benefits in reaction optimization. Traditional optimization is often performed in batch mode through a manual trial-and-error method that involves repetitive experimentation. Flow chemistry simplifies this process by enabling easy adjustment of the reaction conditions, such as flow rate and reaction temperature, and continuous monitoring of the output, especially when coupled with in-line monitoring techniques such as IR, NMR, UV−vis, and LC-MS, to establish the optimal conditions. Additionally, microscale reactions are more viable in flow chemistry, which can largely reduce the reaction time and accelerate the optimization process. With the help of artificial intelligence and data routing, the optimization process can be entirely automated as well.[95−98] Although contemporary automated

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reaction optimizations are mainly for one-step processes, when a multistep flow synthesis sequence is coupled with sufficient in-line monitoring modules, global optimization of reaction parameters in different steps within the sequence can potentially be achieved.[99,100]

Currently, the development of advanced in-line purification technologies is crucial in realizing the great potential of MCFS for producing complex molecules, especially APIs. It is our hope that with the emergence of standard, advanced, and versatile in-line purification technologies, MCFS will become routine in not just common organic chemistry laboratories but also industrial settings and will eventually pave the way for full automation in chemical synthesis.

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Notes

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ABBREVIATIONS

AA, amino acid; Ac, acetyl; API, active pharmaceutical ingredient; b.p., boiling point; CPC, centrifugal partition chromatography; CRF, chemical receipt file; CuAAC, copper-catalyzed azide−alkyne cycloaddition; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; DCM, dichloromethane; DIEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; ee, enantiomeric excess; equiv, equivalent; Fmoc, fluorenylmethoxycarbonyl; HATU, 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate; HWE, Horner−Wadsworth−Emmons; IR, infrared; LC-MS, liquid chromatography−mass spectrometry; MCFS, multistep continuous flow synthesis; MeCN, acetonitrile; MS, molecular sieve; *n*-BuLi, *n*-butyllithium; *n*-Hex, *n*-hexane; *n*-PrOH, *n*-propanol; NMP, *N*-methyl-2-pyrrolidone; NMR, nuclear magnetic resonance; PIFA, phenyliodine bis(trifluoroacetate); Ph, phenyl; Pybox, pyridine-linked bis-(oxazaline); RBF, round-bottom flask; r.t., room temperature; SM, starting material; SMB, simulated moving bed; SPS, solid-phase synthesis; TBAB, tetrabutylammonium bromide; TBS, *tert*-butyldimethylsilyl; TEMPO, 2,2,6,6-tetramethylpiperidin-1-oxyl; TfOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TMOF, trimethyl orthoformate; Ts, toluenesulfonyl; UV−vis, ultraviolet−visible; XPhos, dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane

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