Integrated Flow Processing — Challenges in Continuous Multistep Synthesis

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The way organic multistep synthesis is performed is changing due to the adoption of flow chemical techniques, which has enabled the development of improved methods to make complex molecules. The modular nature of the technique provides not only access to target molecules via linear flow approaches but also for the targeting of structural cores with single systems. This perspective article summarizes the state of the art of continuous multistep synthesis and discusses the main challenges and opportunities in this area.

Keywords: Flow chemistry, continuous multistep synthesis, chemical assembly systems, active pharmaceutical ingredients

1. Introduction

In the past century, chemists have made immense advances concerning the types of transformations that can be accomplished, as well as the methods used to analyze and interrogate chemistry. Key achievements of synthetic organic chemistry have been illustrated by the total syntheses of complex natural products or valuable molecules such as active pharmaceutical ingredients (APIs) and agrochemicals from simple natural sources. These syntheses were accomplished using targeted approaches consisting of a sequential series of steps. Due to the myriad of potential synthetic transformations, this linear approach is versatile [1], and the continued development of new and more selective methodologies further pushes the field, producing shorter – as well as more efficient and sustainable – routes to target compounds. Conversely, the techniques and equipment that chemists use to perform reactions experimentally have not changed significantly in more than one hundred years.

A consequence of this lack of technological advancement is the limitation of the chemist's potential, as a range of chemical transformations is either inefficient or impossible with conditions achievable in flasks and vessels, and such ineffective processes may bear safety risks for some transformations. To overcome these limitations and in order to access the full potential of organic chemistry, the synthetic community needs to adopt and develop alternative technologies. An increasingly popular approach to advance the means of chemical synthesis is to switch from using flasks to continuous-flow chemical equipment. Flow chemistry [2] represents the "philosophical umpolung" to traditional batch processes, bearing its own set of advantages and disadvantages as a method to perform chemical transformations. At its most basic, a batch process is a vessel which contains reagents and solvents to which conditions are applied. The contents can be stirred, heated, cooled, irradiated, sonicated, or pressurized. Once the reaction has completed, these conditions are removed and the transformed reagents are then available for further steps. Alternatively, a flow process is a vessel held at a stable set of conditions through which a solution is passed. This ostensibly subtle difference – conditioning a reactor versus reacting to conditions – provides an increased level of control, that is advantageous for reactions such as gas–liquid transformations, fast reactions, unsafe reactions (toxic/explosive), those with short-lived reactive intermediates, and photochemistry [2].

In addition to enabling or facilitating single transformations, flow chemistry offers advantages in multistep syntheses via the direct connection of multiple reaction modules for the streamlined synthesis of small molecules [3–8]. With traditional multistep syntheses, intermediates are usually isolated prior to the next manipulation, resulting in long overall process times and the generation of unnecessary chemical waste. Certain inherent advantages of flow chemistry allow for processes to be designed where sequential reaction steps can be directly coupled, providing an uninterrupted single process. Inline purification techniques can be used to telescope transformations where side products that may interfere with the downstream processes are generated. The quality of material can be determined at any of the intermediate stages of the streamlined sequence using in- or online process analytical techniques (PATs).

Organic multistep synthesis is about to be transformed through the embracement of technological improvements, allowing for the development of improved ways to make molecules. The modular nature of flow chemical techniques not only facilitates the linear synthesis of target molecules but also allows for targeting of structural classes of molecules, where multiple products are synthesized with single systems. There are opportunities for further improvement of this approach to synthesis, with several hurdles and issues needing to be addressed to fully open the door for broader applicability. The focus of this article is integrated flow processing as a tool for multistep synthesis in academia. The underlying concepts are initially introduced, followed by a brief summary of state-of-the-art applications. Thereafter, the remaining challenges of this enabling technology are discussed. Industrial applications and challenges are largely omitted as this topic is discussed in detail elsewhere in this special issue.

2. Concepts in Continuous Multistep Synthesis

Flow chemistry is a toolbox for synthetic chemists, where individual components are brought together to create modules for synthetic transformations, which can be combined for multistep syntheses. A typical continuous-flow module is broken down into eight basic zones: fluid and reagent delivery, mixing, reactor, quenching, pressure regulation, collection (or connection to the next module), analysis, and purification (Figure 1).

Precise control over the movement of fluids through a module by dedicated pumps or mass flow controllers is important for a continuous-flow process; it regulates not only the residence time but also the stoichiometry if two or more reagent streams are combined in a subsequent mixing unit. The latter can be a simple T- or Y-shaped connection unit, or a gas permeable membrane in the case of gas–liquid chemistries. If fast mixing is crucial, as in reactions involving highly reactive species, more specialized

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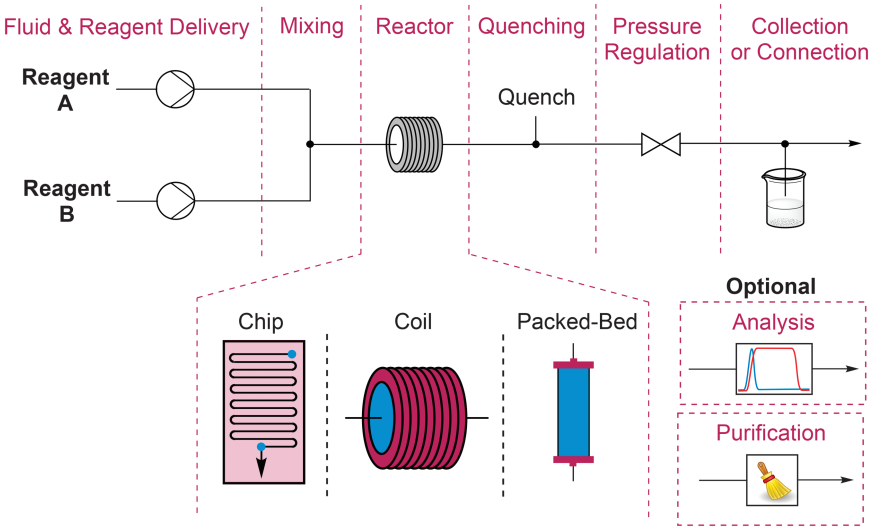


Figure 1. Reaction zones of a continuous-flow module. Adapted from Ref [2]

micromixing units are required to reduce the mixing time [9]. The core of every flow module is the reactor unit – generally a (micro)chip, coil, or packed-bed – to which the respective reaction conditions (heating, cooling, irradiation, etc.) are applied. For accurate control of the residence time, a quenching procedure appropriate to the chemical transformation is often necessary. A back pressure regulator (BPR) is installed immediately preceding the collection/connection unit for processes above the boiling point of the reaction medium or when gases are utilized or generated. These individual parts can be arranged interchangeably, resulting in a near infinite number of possible modifications to access almost every chemical transformation in a continuous manner.

To date, most modules are specifically developed for carrying out a certain reaction type (oxidation, reduction, hydrolysis, etc.). However, they can also be developed for the on-demand production – and direct utilization – of hazardous and highly reactive species. These specialized modules, called "generators," are one of the strengths of flow chemistry, allowing for safe access to reagents which are usually avoided or even deemed "forbidden" such as diazomethane [10], chlorine [11, 12], singlet oxygen [13–16], ozone [17–20], phosgene [21], carbon monoxide [22–24], or hydrogen [25]. These generators are often integrated into multistep syntheses, opening up otherwise inaccessible synthetic routes.

2.1. Linear Approaches versus Chemical Assembly Systems. While modules can be linked together for consecutive transformations, it is first worthwhile to examine the philosophical approach chemists use in the development of multistep flow syntheses. Linear strategies start with a compound and make stepwise, sequential transformations to generate a target compound in a continuous or semi-continuous process (Figure 2 (a)) [3–8]. This approach takes advantage of a myriad of potential reactions, making it incredibly versatile. This synthesis strategy is limited mostly by its focus — the target structure. Synthetic routes are designed, reactions are optimized, and transformations are created to yield a given compound in the highest overall yield and lowest number of steps. When the next compound is targeted, this process is repeated, with a focus on differentiation from previous processes. However, a large number of desirable compounds – for example, biologically active molecules – share similar core structures. Based on this, a synthetic approach called the "Chemical Assembly System (CAS)" which targets core structures was developed [26–28]. An assembly system is made up of flow reaction modules, each performing a chemoselective transformation which produces minimal or aqueous soluble waste and is designed to be flexible

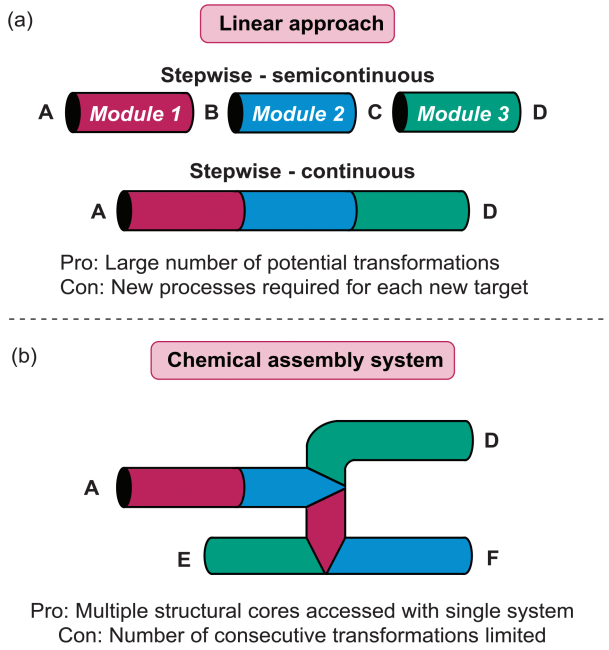


Figure 2. Continuous-flow multistep synthesis using (a) a linear or (b) an assembly line approach

in its reaction conditions. By coupling these reaction modules in a non-iterative way, it is possible that a multistep process can be created which targets multiple structural cores independent of pendant functionalities (Figure 2 (b)).

Chemical assembly systems expand the potential of a chemical synthesis in three ways [26]. The first level relates to the starting materials, which when exchanged within a given set of modules yield the same structural core with different pendant groups. The target core structure can be modified with the modular order and reagents utilized. For the former, as the reaction modules are not dependent on the preceding or succeeding reactions, they can be interchanged or additional units utilized as long as the necessary functionality is present. By using different versions of a given reagent, additional functionalities can be added or different structural classes accessed using a fixed module sequence.

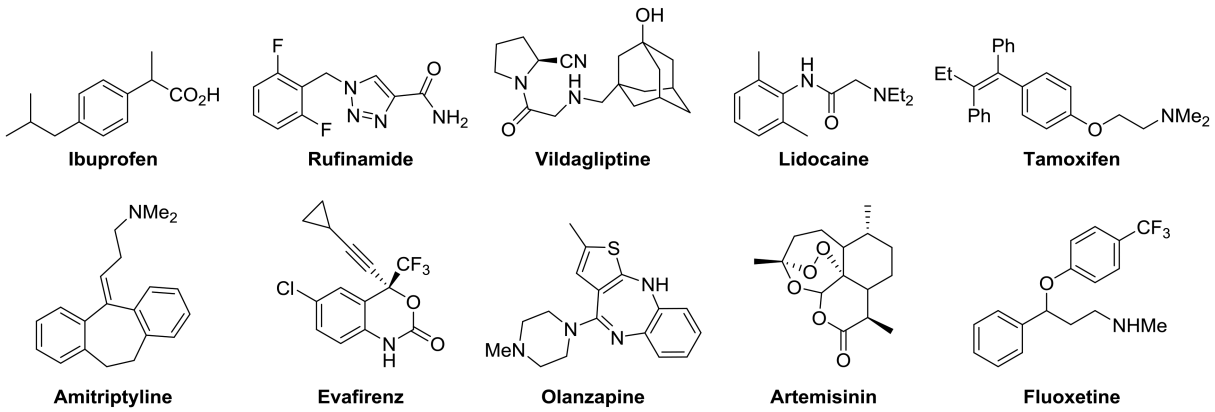
3. State-of-the-Art: A Comparison of Approaches

The modular nature of a continuous multistep synthesis was already conceived of in a 1995 patent by Prof. Allen J. Bard on

"Integrated chemical synthesizers" [29]. Bard described a "modular multi-component system with interchangeable microreactors, that can be used in tandem, series or individually" which was applicable to thermal, photochemical, electrochemical, biocatalytic, and metal catalyzed transformations with integrated analytical techniques and inline purification tools. More than two decades later, this visionary idea has matured and became a highly active research area with a plethora of APIs that have been successfully synthesized by continuous multistep synthesis, mainly following linear approaches (Scheme 1) [3–8].

The synthesis of the γ-lactam Rolipram offers an excellent opportunity to contrast recent advances in the approaches towards continuous multistep synthesis. Kobayashi and coworkers recently presented a rather unique example of a linear process [30], where enantiomerically pure Rolipram was prepared using exclusively heterogeneously catalyzed steps (Figure 3 (a)). The four-step system begins with a base-catalyzed nitroaldol reaction of the respective aldehyde and nitromethane, carried out using a silica-supported amine catalyst. The resulting nitroalkene was mixed with malonate and passed through two consecutive packed-bed reactors containing a chiral calcium catalyst for the asymmetric Michael-type addition. Subsequent hydrogenation of the nitro group over a palladium catalyst supported on carbon and polysilane resulted in the respective γ-lactam, which was finally converted into (S)-Rolipram via hydrolysis and decarboxylation using a silica-supported carboxylic acid catalyst. Overall, 50% (productivity of ~1 g/day) of the target compound was isolated by preparative TLC in high enantiomeric excess and the system was operated for 1 week to showcase its scalability. One of the strengths of this packed-bed strategy is that virtually no inline purification was necessary except for the removal of excess H_2 after the hydrogenation step, realized by the connection of the hydrogenation module with the final hydrolysis module in a semi-continuous fashion.

At the same time, a chemical assembly system to synthesize γ-lactams (including racemic Rolipram), β-amino acids, and γ-amino acids (including Phenibut, Pregabalin, Gabapentin, and Baclofen; (Figure 3 (b)) was reported [26]. The divergent synthetic strategy was developed using five modules (oxidation, olefination, Michael addition, hydrogenation, and saponification). The methodology starts with two sequential modules that are necessary for the synthesis of all product classes from alcohol starting materials: oxidation to the corresponding carbonyl compound followed by olefination. The latter module provides the first point of divergence, where reagent control (cyanoacetate vs. ylide) provides access to either β- or γ-amino acid derivatives. The synthesis of β-amino acids is achieved via connecting hydrogenation and saponification modules following olefination using cyanoacetate. Alternatively, the ylide gives the di-substituted α,β-unsaturated ester which is transformed using a module for Michael additions into the respective γ-nitroesters. These intermediates can then either be transferred into the hydrogenation module to synthesize γ-lactams – providing racemic Rolipram in 58% yield over the four steps – or subjected to saponification followed by hydrogenation to result in γ-amino acids (including four



Scheme 1. Selected examples of active pharmaceutical ingredients synthesized via continuous multistep synthesis

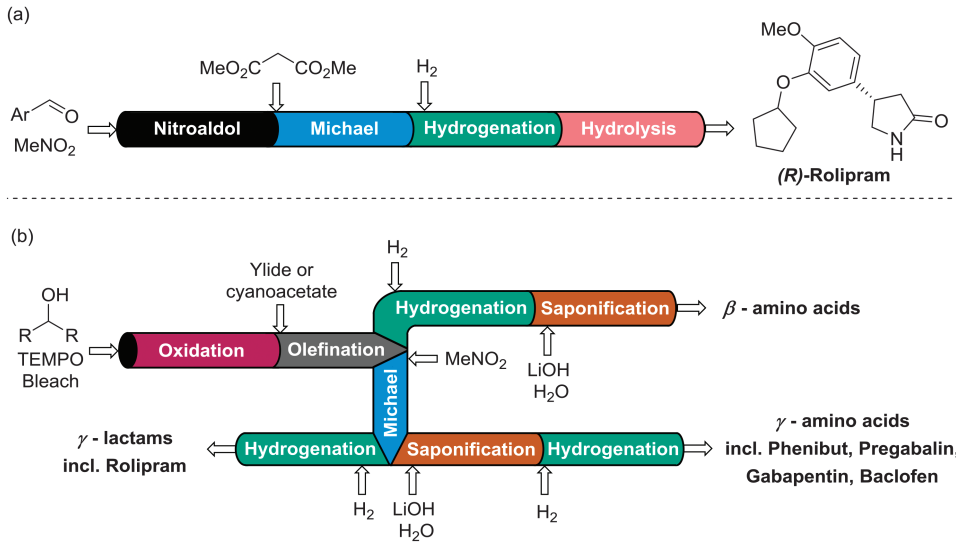


Figure 3. (a) Kobayashi's Rolipram synthesis following a continuous linear multistep approach and (b) synthesis of γ-lactams (including racemic Rolipram), β-amino acids, and γ-amino acids (including Phenibut, Pregabalin, Gabapentin and Baclofen) using the CAS concept

APIs). Compared to the previously described linear approach, only one of the CAS modules consisted of a heterogeneous catalyst (hydrogenation), which necessitated the implementation of inline work-up (liquid–liquid extraction) in all other modules to remove by- and side products.

The decision whether to follow a linear or a CAS approach depends on the goal of the respective research project and has to be made on a case by case basis. The two Rolipram examples clearly showcase that modules in linear flow multistep synthesis can often have a simpler, more straightforward design than CAS approaches; however, the latter offers a significantly higher versatility and synthetic potential. The divergent CAS approach was recently also applied for the synthesis of substituted pyrazoles and pyrazolines by Britton and Jamison [28]. In addition, the concept was further used in a convergent manner for the continuous production of β-amino alcohols from two different classes of starting materials [27].

4. Challenges and Opportunities

Continuous multistep synthesis has a potential to improve the construction of small organic compounds, whether it is the lower space–time demand for the production or for the straightforward and automated assembly of complex molecules and compound libraries. The opportunities inherent to this technique continue to motivate its rapid evolution. However, the field is still far away from being a cure-all for multistep synthesis. Several challenges exist – ranging from reaction modules, connectivity, analytics, and education – that have to be met in order for the greater synthetic community to fully benefit from this enabling technology.

4.1. Reaction Modules. For single-step transformations, the applicability of a flow approach is determined by whether the advantages of this technology align with the obstacles presented by the respective chemical transformation in a batch process (selectivity, safety, etc.) [2]. This is not necessarily true in the case of multistep transformations, as additional overall process benefits in continuous systems (e.g., automation, scalability) exist. As such, flow modules which result neither in higher yields nor faster reactions than the respective batch process can sometimes be justified when used in conjunction with additional steps.

An analysis of continuous multistep transformations in the literature reveals that the modules utilized can be divided into two categories based on their physical and conceptual differences: coil/chip and packed-bed systems. Chip- and coil-based systems can be universally applied for reactions involving monophasic (liquid) or biphasic (liquid–liquid or gas–liquid) systems. More advanced versions of these reactors are often utilized when gases are employed, in particular membrane-based reactor setups such as the tube-in-tube reactor [31]. Here, a homogeneous (saturated) solution of the respective gas in the reaction medium is obtained when the gas passes through the membrane into the solution. This means of addition is an advantageous approach for coupled modules, as dissolved gas facilitates subsequent downstream processes compared to biphasic conditions. The technique is often applied for the on-demand generation of reactive and toxic gases, especially if the generation and utilization occur in different liquid phases [32].

In general, heating and cooling of chip and coil reactor units can be achieved either by conventional means – such as submersion of the reactor unit in a dedicated cooling/heating bath – or by using specialized technologies such as cryogenic cooling units, microwave irradiation, or inductive heating techniques [33]. Photochemical applications require a light transparent reactor material and a dedicated light source [34].

If heterogeneous catalysts are required in a continuous chemical transformation (solid–liquid or gas–liquid–solid), typically packed-bed reactors are utilized. These units consist of a volume of solid material(s) embedded between filter units through which the reaction solution is passed. This reactor type has several advantages for heterogeneous catalysis in comparison to a batch reactor. First, a packed-bed reactor affords a significantly higher effective molarity of the catalyst/reagent, decreasing reaction times. Secondly, as the catalyst/reagent is contained by the frit, there is no subsequent step to separate the reaction mixture from the catalyst, which often spares inline purification when modules are connected.

Copper catalysis is a special field within continuous chemistry involving solids. Copper coils can serve as reactor and catalyst, for example, catalyzing Huisgen 1,3-dipolar cycloadditions — the key step in Jamison's continuous multistep synthesis of rufinamide [35]. However, continuous heterogeneous catalysis in a packed-bed reactor is not always trivial. In particular for immobilized transition-metal catalysis, leaching of the catalytic material can occur, resulting in contamination of the product and column deactivation [36]. In these situations, the selection of a homogeneous precatalyst may be more appropriate, as their reactivity and selectivity can be more easily modulated.

Apart from heterogeneous catalysis, the handling of solids in continuous flow is the major remaining challenge facing flow chemistry. While solid reagents can be utilized by filling them into packed-bed reactors, they are consumed during the course of the experiment, necessitating the periodic reactivation or refilling/exchange of the packed-bed unit. Solids can be fed into coil reactors as suspensions [37], but this is a non-trivial task as a sufficiently stable dispersion must be found for every solid material. There are also a number of issues which lead to fouling and clogging – such as nucleation, precipitation, and deposition of solid reagents – which need to be considered

While these issues can be minimized, employing tricks such as liquid–liquid or gas–liquid flow patterns to reduce particle–wall interactions or ultrasonication [38, 39], more specialized reactors such as the agitated cell reactor are sometimes necessary [40]. Even if a solid is passed through the reactor, clogging can occur at the BPR, requiring an additional solvent to dissolve the precipitate after the reactor unit or the use of a Parr bomb collection vessel, the latter hindering downstream processing [41, 42]. To date, no generally applicable solution to handle solid reagents has been presented, and a versatile, robust, and user-friendly dosing device that can deliver any dispersion needs to be developed to achieve reliable continuous addition of solids into flow systems.

4.2. Connecting Modules and Integrating Inline Work-up and Purification. Another crucial factor in the design and optimization of a multistep flow process is the connectivity of individual modules. Multistep flow processes suffer the limitation that subsequent steps always have either identical or faster flow rates than the previous steps. As such, when subsequent reactions require longer residence times than the reactor volume allows at a given flow rate, two modules cannot be directly connected. In these situations, the reaction stream can be collected in a reservoir flask which serves as feed for the next step (semi-continuous processing). This reservoir method is also used to remove excess gas from biphasic systems.

Even with a judicious reactor design, many reactions require a work-up to quench the reaction or remove byproducts. While the integration of work-up zones into modules is a logistical challenge for multistep systems, it is worthwhile as it helps to avoid processing problems such as unwanted consumption of downstream reagents and it facilitates purification of the final product. The most common technique currently used in the field is liquid–liquid extraction using membrane-based separation techniques [43]. The working principle of such a continuous extraction is straightforward (Figure 4). Initially, the extraction

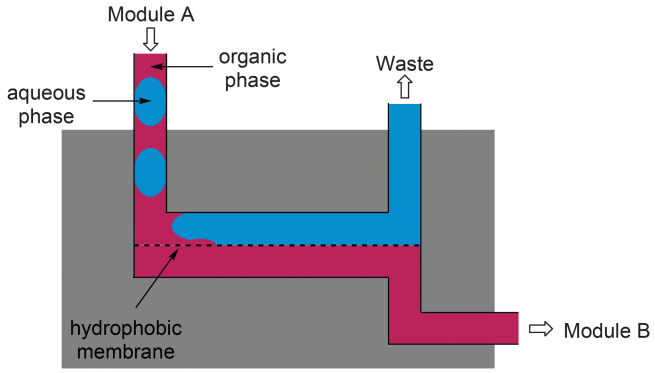


Figure 4. Continuous liquid–liquid separation using a hydrophobic membrane

solvent has to be added to the reaction stream via a mixing unit and the resultant biphasic mixture reagent stream is then passed through a residence time unit for extraction. The mixture then enters the membrane separation unit that usually consists of a PTFE membrane sandwiched between two flow channels. The organic phase is able to pass the hydrophobic membrane, controlled by the pressure across the membrane, and both phases can be accessed for subsequent reaction modules.

If gases are generated, or a gas–liquid reaction is used in the initial stage of a reaction, membrane technologies can also be used for separation. The tube-in-tube gas addition device can be simply converted into a gas separator by connecting it to a vacuum line; one example is the successful removal of the ethylene generated during olefin metathesis reactions [44].

Another effective and common technique for inline purification at a laboratory scale is the use of scavenger cartridges to remove impurities [45]. Such scavenger cartridges are, in principle, packed-bed reactors filled with a suitably reactive material (acidic, basic, etc.) and can be installed at any position in the flow path. These scavenger cartridges have the same limitations as packed-bed reagents; once these scavenger cartridges have reached their maximum capacity, they need to be exchanged or reactivated, making them impractical for large scale syntheses [45].

Another major challenge in flow multistep synthesis is the continuous switching of solvents. The solvent often plays a key role in modulating and facilitating organic transformations, and while flow reactions also take into account solubility in solvent screenings, reactions are optimized in isolation to maximize product yield. As a result, the majority of synthetic pathways utilize different solvents for distinct steps.

In selected cases where water-miscible organic solvents are used, the addition of water and a new, immiscible organic solvent, followed by a membrane separator, has been utilized to switch solvents [46]. Large multistep syntheses, however, usually require the addition of a plethora of reagents and catalysts over the course of the system, which results in an increasing dilution of the initial flow stream throughout the entire process. While a potential solution is inline distillation, there are limited examples using home-built microdistillation systems and these techniques have not found many applications to date [47, 48]. A robust and efficient inline distillation tool could potentially tackle both dilution and solvent exchange but is challenging enough without tackling high-boiling solvents.

With respect to purification, there are a number of techniques which are used sparingly to terminate a continuous process. These methods generally require advanced training and equipment. For purification of final compounds, simulated moving-bed chromatography (SMB) uses a counter-current flow to continuously separate compounds over a stationary phase based on their polarity [49] and has been used following the synthesis of small molecules [50] and medicines [51]. More recently, Greiner and coworkers presented the utilization of centrifugal partition chromatography (CPC) for the continuous purification of multistep synthesis products as an alternative purification concept [52]. Continuous crystallization(s) have also been used in isolate, in combination with other continuous chromatographic methods [51], or as part of more complex multi-step purifications [53, 54].

The implementation of recycling strategies for solvents, homogeneous catalysts, and unreacted reagents and additives is a big opportunity for the future of continuous multistep synthesis. So far, the majority of literature examples focus on the isolation of final compounds — proper recycling strategies in an attempt to minimize chemical waste are generally not explored. In this arena, membrane-based separation strategies are also promising and can be potentially implemented for recycling solvents, gases, and homogeneous catalysts [55].

4.3. Integrating Analytical Techniques and Automation. The implementation of process analytical techniques for continuous monitoring of parameters and product/intermediate purities is important for, e.g., scaling out experiments in order to produce high quantities of the respective target structures. Monitoring of process conditions (flow rate, pressure, temperature, etc.) is carried out by dedicated sensors which are often integrated in pumps, BPRs, and thermostatic units and are therefore routinely applied. The analysis of the chemical composition of reaction mixtures is less trivial and has become an actively studied topic in flow chemistry laboratories.

In recent years, almost all standard analytical techniques have been integrated into flow processes to monitoring the progress and quality of chemical transformations [2]. Online analytical tools (high-performance liquid chromatography [HPLC], gas chromatography [GC], mass spectroscopy, fluorescence spectroscopy, x-ray spectroscopy) [56–59] analyze the chemical composition of the stream by sampling aliquots and transferring them to the respective analytical device. These are powerful techniques utilized for automated reaction optimization and kinetic studies of single step transformations and for determining the purity of final products after continuous purification. They are less valuable for the development of continuous multistep syntheses, however, as the sampling and analysis times are relatively long. When such systems are integrated between two modules, the feedback delay would postpone adjustments of reaction parameters in case of malfunctions.

On the other hand, analytical methods which are nondestructive and allow “real-time analysis” such as Fourier transform infrared (FTIR), Raman, ultraviolet–visible (UV–vis), and nuclear magnetic resonance (NMR) spectroscopy can be integrated in the flow process via an analytical flow-through cell (inline) [56–59]. Consequently, such analytical tools allow to quickly adapt certain conditions such as flow rates of downstream modules “on the fly” via manual control or feedback algorithms (Figure 5). This is important to, e.g., tune the stoichiometry in case of concentration changes in a preceding reaction module which can result from dispersion phenomena [60]. Undoubtedly, continuous innovations and advancements in analytical chemistry and the integration of those instruments into flow modules will have an increasing impact on the field.

4.4. Novel Concepts: Reaction Screenings and Search Engines. Linear, as well as CAS flow processes, are designed in order to obtain target compounds or core functionalities via carefully selected synthetic routes. Both methodologies are powerful strategies to produce high-value molecules in large quantities but are not suitable for automatically discovering and evaluating synthetic routes or systematically exploring the chemical space via combinatorial screenings. Automated continuous-flow platforms utilizing feedback optimization can easily vary and optimize reaction parameters (temperature, reaction time, stoichiometry, and concentration), and recently,

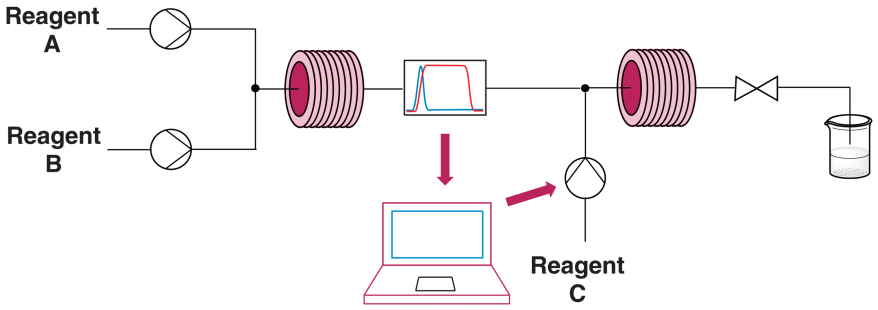


Figure 5. Controlling the addition of reagents in consecutive modules via feedback algorithms using inline analytics

several research groups have developed flow platforms to optimize discrete parameters (solvents, catalysts, ligands, etc.) [2]. Merging efforts in this area with continuous multistep synthesis could potentially facilitate how medicinal chemistry libraries are made in the future as well as in the discovery of new reactions and reactivities.

Along those lines, Jensen and coworkers recently reported a segmented flow platform that enables reaction screening for lead optimization [61]. In the automated droplet-based flow apparatus, reagents were withdrawn by liquid handler and injected as droplets into an argon stream. The reactions were carried out in an oscillatory flow reactor, subsequently quenched and collected. Online analysis (HPLC/mass spectrometry [MS]/evaporative light scattering detector [ELSD]) was implemented for reaction analysis and quantification. The authors could demonstrate that the system can be also used for multistep synthesis; after an initial optimization of phosphine ligands and precatalysts for a Buchwald-Hartwig amination, the resulting product was subjected into the same system to carry out an ester hydrolysis.

Simultaneously, Cronin and colleagues reported on a continuous-flow search engine for assessing the highest chemical reactivity within a network of 64 possible reaction combinations via a reaction selection index-based algorithm (Figure 6) [62]. The system consists of three consecutive modules (Diels-Alder, reductive amination, amide formation) which are connected to attenuated total reflection infrared (ATR-IR) spectroscopy and electrospray ionization (ESI)–MS analysis, all controlled by LabVIEW software. The approach uses a reaction selection index (RSI) to direct the reaction network to the most reactive pathway without any work-up and purification steps. The fully automated system initially runs several Diels–Alder reactions under identical conditions. The cycloadduct resulting from the most reactive substrate–reagent combination is subsequently subjected to the next module where a set of amines is tested for their reactivity in a reductive amination step. Finally, the most reactive combination is forwarded into the last module where four reagents are screened for the final amide synthesis.

These alternative approaches allow for the rapid screening of distinct chemical spaces and represents early examples of automated approaches which could be used to supplement the creativity of a chemist in reaction design and development.

4.5. Education: Thinking outside the (Batch) Box. Regardless of the impressive achievements of the field and its potential, if the chemistry community in general does not understand and accept flow chemistry as a useful technique, its growth will be slow, its techniques under-utilized, and its future will remain ever distant. Through its adolescence, the field was isolated to the bulk chemical processing and chemical

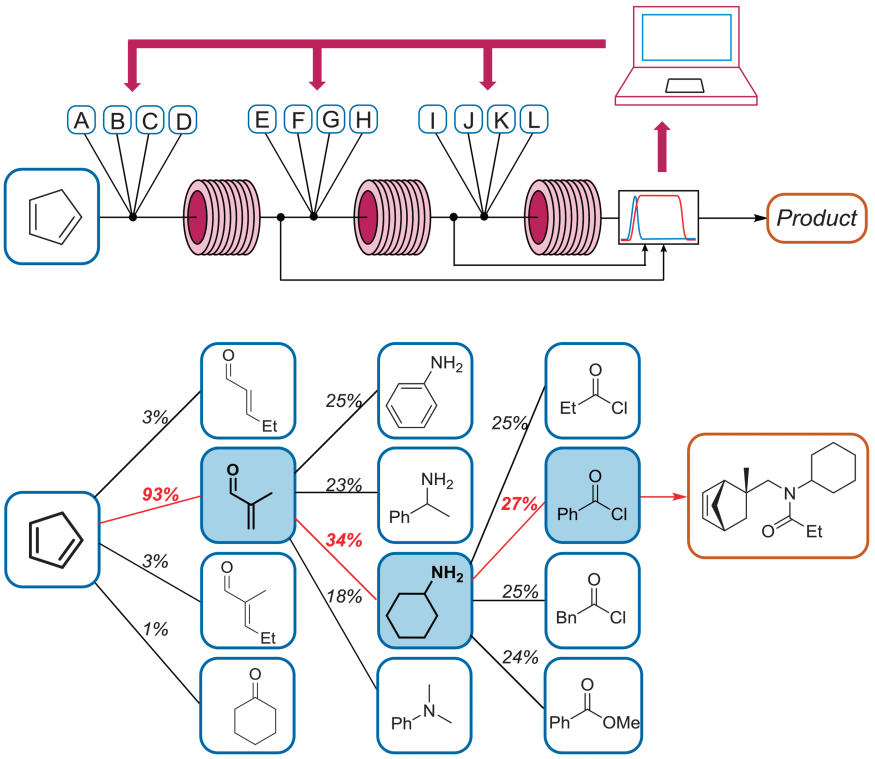


Figure 6. Schematic description of the continuous-flow search engine for assessing the highest chemical reactivity within a network of 64 possible reaction combinations via a reaction selection index-based algorithm

engineering communities due to its significant degree of complexity as compared to the round bottom flask. While in recent years, the number of organic research groups exploring and exploiting this technology – in general and as a valuable tool for multistep synthesis – has significantly increased [2], a lack of experience combined with organic chemists' innate fear of technology has limited its broader inclusion of the field.

Early exposure in chemical education to the principles and practices of flow chemistry is critical for the advancement of future scientists for the following reasons:

- They would not know that there is a "traditional" way. When entering into their undergraduate studies, both classes and laboratories, the majority of students have no idea how chemistry is actually performed. Through the introduction of philosophical concepts regarding single and multistep synthesis – approaches, methodologies, concepts, etc. – students will gain firmer grasps on the themes being explored and will not develop biases or knowledge gaps regarding experimental practices.
- Options are always better. One of the greatest strengths (or limitations in its absence) of a chemist is his/her creativity. As chemists move from the classroom into a research setting, the more techniques they have been exposed to, the greater their toolbox will be to facilitate problem solving. Researchers need to be aware that other equipment and strategies exist, whose advantages may precisely coincide with the challenges of their research.
- It builds cross-disciplinary thinking. Increasingly, chemical research is not performed in an isolated or "pure" form, but in bridging the gap between itself and physics, biology, materials, engineering, and others. This not only allows for greater scientific problems to be tackled but also strengthens the individual researchers by expanding their expertise and conceptual approaches. Flow chemistry, and especially continuous multistep synthesis, is an excellent example where the best of both chemistry and engineering come together to achieve what either cannot alone.
- Expanded potentials. While not suited for everything, a number of transformations cannot be performed – either efficiently or at all – outside of flow chemistry. This provides the opportunity for a new generation of synthetic chemists to reevaluate existing total synthesis protocols and implement such reactions in order to provide shorter, more efficient or highly sustainable protocols.

Currently, only a limited number of universities have teaching courses in flow chemistry and students are exposed to the field only if they join dedicated research groups. The topic has matured to the point where those without engineering backgrounds can easily adopt the technique, making it an established and recognized subfield of chemistry. The next step is to increase the exposure of current and future researchers to the strengths and weaknesses of flow, which will hopefully allow them to pursue greater and more challenging research in the future.

5. Conclusion

Organic chemists have always prided themselves on showcasing the power and versatility of their synthetic transformations with the construction of complex molecules. These syntheses, whether they are three or fifty steps, all follow the same basic approach: develop and optimize a step, purify the compound, and move on to the next step. This occurs in a linear fashion until the target is obtained. With the adoption of flow chemistry, the last 20 years has seen chemists gain an increased control over their reactions, allowing for the expansion of what kinds of reactions are possible and – importantly – synthetically useful.

One major advantage (and admittedly challenge) of flow chemistry is its modularity. In the context of multistep synthesis, this modularity allows for multiple units to be linked together via the incorporation of inline processes like extraction, separation, and analysis. It also allows for the conceptual relaxing of "target" molecules and the focus of reaction development, such that multistep systems can be designed to access variants of core functionalities as opposed to single molecules, expanding the potential and scope of multistep synthesis. While the field continues to advance, there remain a number of technical challenges which limit its applicability. These will only be overcome with combined efforts of interdisciplinary teams, by attracting new talented researchers to the field through increased education/training, and, of course, with a little luck.

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