Continuous Flow Chemistry for Molecular Synthesis

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Abstract

Continuous flow techniques have become important tools for molecular synthesis, both in academia and across the fine chemicals industry. The success of these methods has been in part due to their interdisciplinary nature, bringing together chemists and engineers to design and construct creative solutions for the novel synthesis and scale-up of molecules, with applications in pharmaceuticals, agrochemistry, materials chemistry, and crystallisation. The advantages of flow chemistry include the high surface area-to-volume ratio of narrow tubing, which improves temperature control, and the ability to scale by increasing reaction time rather than vessel volume. Further, the use of flow enables improved safety protocols, reduces waste, and has the potential to telescope down-stream work-up processes. Perceptions of flow chemistry as a field with a high barrier to entry remain, and these techniques have not yet become a standard option for most chemists due to the lack of exposure in academic settings. To help reduce this barrier, this Primer introduces the field, covering the fundamental considerations of assembling a lab-scale flow experiment, using literature examples to illustrate their practical application. We conclude with an outlook for the field, highlighting opportunities for potential and existing users of the technique alike.

[H1] Introduction

Continuous flow chemistry is a research discipline at the boundaries of molecular synthesis and chemical engineering and covers a group of methods for carrying out a chemical reaction in a continuous stream. Flow chemistry is typically carried out in liquid phase through tubing or microfluidic reactors, although recent applications to a broad range of problems have expanded flow chemistry to include both gas and solid phase

reactors.[1–4] Continuous flow methods have inspired those involved in molecular synthesis to reimagine processes for chemical production, in some cases giving access to conditions or products not achievable with more traditional batch-type processing. Similarly, continuous processing offers tighter control on operating parameters, safety, and scalability, compared to bulk batch conditions which are key advantages for industrial chemists. As such, continuous flow chemistry is being explored as a tool in many fine chemical companies at the research, process, and manufacturing scales to serve a variety of purposes, including reaction screening, reaction optimisation, library synthesis, molecule discovery, and the synthesis of kilograms of materials.[5–10]

Flow chemistry optimizes parameters that are familiar in conventional batch chemistry, including time, temperature, and scale. However, the switch to continuous processing brings fundamental conceptual differences. Flow chemistry allows an evolving reaction mixture to be separated by space rather than time, known as spatiotemporal control. By running reactions in continuous mode, scale becomes proportional to overall process time rather than the total reaction vessel capacity. The switch to continuous chemistry also brings specific advantages. Narrow tubular reactors with ~ 1 mm inner diameter offer improved surface area-to-volume ratios compared to batch vessels, enabling more efficient mixing and greater control of reaction temperature due to improved heat-transfer. The ability to better manage exotherms allows flow reactions to be run at room temperature when a comparable batch reaction would require active cooling (Figure 1A).[11] Additionally, improved selectivity can be achieved for temperature-sensitive reactions through precise temperature control. For example, a method for selectively functionalising iodophenyl carbamates at the ortho position was described in a microfluidic reactor at cryogenic temperatures.[12] Efficient mixing and precise cooling to -70 °C prevented the unwanted Fries rearrangement to give the desired products in up to 91% yield.

Another driver for the adoption of flow chemistry is the ability to streamline processes that might be labour or time intensive. For example, Ley and co-workers compared the use of continuous flow processing to batch for the polymer-supported synthesis of (±)-oxomaritidine.[13] In the batch process, reagents and reactants were separated by immobilising one on polymeric beads with the other in solution; when the reaction step was completed, the pure product was isolated via filtration.[14] This process must be repeated to build up a natural product, involving many manual handling steps and requiring days to complete. By packing the polymeric beads into cartridges and transferring the process into flow, the beads are essentially in a permanent state of filtration. The seven synthetic steps were combined into one flow process, resulting in the synthesis of the target natural product in a matter of hours (Figure 1B).

When initially considering translating a process from batch methods to flow conditions, it is important to consider the goals of the project as flow chemistry has different advantages in discovery and process chemistry. In discovery, flow processing can provide advantages through enabling the safe use of hazardous reagents and in accessing reaction conditions that are difficult to attain in batch processing, such as high pressures and temperatures. For gathering the large data sets needed for reaction discovery, microreactors fitted with in-line analysis can compete with 96 well plates. For

process chemistry, if a reaction already works well in batch, it may not be worth the investment of time and money for translation into flow. However, where there are problems with reproducibility, yield, selectivity or scaling, many reactions perform more reproducibly in a flow configuration. This is particularly pronounced for reactions where mixing and heat transfer are significant factors for reaction outcome. We recommend using the flow chart from ref[11] to help decide whether to 'go with the flow' and use a flow chemistry set-up for a given reaction.

Complex flow pathways are possible and the modular nature of flow chemistry gives access to diverse and advanced capability and functionality. However, continuous processing can also be achieved with simple, low-cost, and readily available components. Knowing which component to use and when is one of the first barriers the new user encounters. In the experimentation section, we therefore aim to guide the new user of flow chemistry in navigating the set-up and running of their experiments. The results section features examples from the literature that illustrate the experimental considerations in the context of fundamental synthesis reactions. Although we include literature exemplars to assist in this, this Primer is not intended to be a comprehensive review of flow chemistry and we recommend consulting the many excellent flow chemistry reviews for this purpose.[15–26] The applications section highlights cutting-edge examples from academia, industry, and materials chemistry. Finally, the Primer concludes with sections on reproducibility, data deposition, limitations of the technique, and future outlook. We hope to demonstrate the versatility and flexibility of flow systems and provide a source of inspiration for the chemical synthesis community to consider how flow chemistry could impact their own research.

[H1] Experimentation

In this section, we introduce the fundamental components of a flow reactor and considerations for its setup, including references to papers that discuss each aspect in more detail. We cover the basic information and knowledge needed to design a flow system as a foundation for the worked examples in the subsequent sections.

The basic components of a simple flow setup are a pump, tubing, nuts, ferrules **[G]**, and unions **[G]**. Additional components can be added for specific capabilities to the system (Figure 2A). For example, mixers can be used to combine more than one pumping stream. Tubes can be coiled into a disc shape forming a 'reactor' section with a known volume that can be heated (by an oil bath or by convection heating) or cooled (by immersion into a cold bath or by convection cooling). Installation of an appropriate pressure regulator enables heating of flowing reaction mixtures beyond their atmospheric boiling points without evaporation of the solvent and minimises bubble formation: this 'superheating' can dramatically increase reaction rates. Flow chemistry is particularly suited to automation and a continuous flow apparatus can be plugged into AI optimisation algorithms and coupled with robotic devices to increase data production, reproducibility and integrity in both academic and industry settings.[27]

[H2] Continuous or segmented flow

Continuous flow refers to pumping directly from stock solutions containing reagents for a prolonged period. Another approach, segmented flow **[G],** uses loading loops and injection valves to allow the introduction of a small segment of reagents into a carrying solvent stream that then pushes the segment **[G]** along the flow system. It should be noted that for a segmented approach, the injected segment of reagents will begin to dilute owing to dispersion at the front and back ends of the segment where it is in contact with the carrying solvent. This can be especially pronounced with longer flow circuits or slower flow rates (Figure 2C),[28] leading to variable concentration along the segment and sections that should be discarded as outside the 'steady state'. One workaround to reduce the dispersion of segments is to use gaseous spacers.

Both segmented and continuous flow are widely used in the field. Continuous flow is best for producing large quantities of product, whereas segmented flow has the advantage of using less substrate and taking less time. One might first optimise a process (by varying concentrations, flow rates, reactor temperatures, or pressure set-points) using segmented flow mode and then demonstrate the longevity of operation via continuous flow.

Liquids in flowing tubes typically exhibit either laminar flow **[G]** or turbulent flow **[G],** with the latter a result of lateral mixing in addition to forward flow. In lab scale flow reactors for chemical synthesis, such as the examples described later in the Primer, most devices will exhibit laminar flow. This behaviour can be seen in both continuous and segmented flow setups. With laminar flow, the liquid materials in contact with the tubing walls experience interactions and travel slower than the bulk liquid leading to a distribution of residence times.

[H2] Pumps

There are many pump types available; for research-scale flow applications, the most common are high-performance liquid chromatography (HPLC), syringe, and peristaltic pumps.[15] HPLC pumps are piston driven, typically featuring single or double-pistons. Pistons force material out when moving in one direction and draw material in (aspirates) when moving in the other direction. In dual piston systems, pistons move in tandem to deliver a smoother flow. HPLC pumps are excellent for dealing with high pressure. Syringe pumps are a simpler type of piston pump, familiar to many chemists, that work by emptying a syringe at a set flow rate. Some models are also able to draw fluid, meaning it is possible to use two in tandem with one syringe injecting material into the flow system while the other is being refilled. Flipping a valve then allows the syringes to swap, providing a continuous infusion of material into the flow system. Peristaltic pumps use positive displacement to move a liquid through the tubing. This is carried out by rollers which press the flexible tubing along the wall of the pump creating a pressure differential. It is particularly important to consider chemical compatibility for peristaltic pumps as the tubing experiences wear through the motion of the rollers which can be worsened by chemical degradation.

When selecting a pump, one must consider the types of solutions to be pumped, the chance of solid formation, and the compatibility of the reactants and solvent with the chosen pump. It is also essential to consider the intended pressure for operating the flow

system, and the targeted flow rates. Finally, the choice of continuous or segmented flow will affect the choice of pump. HPLC pumps are good for continuous or segmented flow mode as they can operate at high pressures and generally have a broad chemical compatibility. Syringe pumps are useful for segmented or shorter-run continuous processes (although longer continuous operation can be achieved with syringe pumps operating in pairs), and can have good chemical compatibility depending on the material of fabrication.[18] Of the three types, syringe pumps afford the most accurate delivery at lower flow rates (such as < 0.1 mL/min), but rarely operate well at medium-to-high pressures (over 100 psi). Peristaltic pumps are useful for continuous or segmented flow, and can handle slurries, but typically only operate at low pressures (up to 10 bar) and can introduce pulsing **[G]**.[29] Depending on the pump tubing selected, a broad range of chemical compatibility is possible. Manufacturers will advise on pump capability and suitability for a given application; many flow labs will have access to multiple pump types to cover a broad range of applications. It is important to calibrate pumps of any type regularly by measuring the amount of material delivered over a given timeframe at a fixed flow rate and either correcting the hardware or manually altering the flow rate to achieve the desired value. For a more in-depth discussion of choosing an appropriate pump, we direct readers to the "hitchhiker's guide to flow chemistry".[15]

[H2] Tubing and Connectors

Tubing, nuts, ferrules and unions form the circuitry of a flow setup. Choice of material and construction is typically based on the pressure required of the system. Tubing is used to connect the different parts of the flow device, as well as for loading loops and reactor coils. For synthesis research labs, polytetrafluoroethylene (PTFE) or perfluoroalkoxy alkane (PFA) tubing with an inner diameter of 0.8 mm (1/32'') is commonly used and can be purchased in 1000 m reels. PTFE tubing is particularly useful because it allows visualisation of the contents of the flow circuit, allowing blockages to be monitored. Tubing kits can be purchased for fixed volumes with the connectors already installed on either end of the tube, but we would recommend installing connectors to the tubing manually to gain hands-on understanding (Figure 2D). The simplest way to set up a flow system, such as that shown in Figure 1, is to make the volumes of the tubing connecting the loading loops of stream A and stream B to the mixing point identical so that the segments of these reagents meet each other at the mixing point simultaneously. For higher pressure applications or chemistry where control of temperature is very important, such as in high-pressure hydrogenation reactions,[2,30,31] using stainless-steel tubing and fittings is preferred as these materials have a higher-pressure rating and better heat transfer than PTFE.

[H2] Mixing

Proper mixing of flow streams is important. Mixing, also referred to as mass transfer, is particularly important for rapid reactions, where the rate of the reaction can be mass-transfer limited **[G]**.[32] Mixing can be categorised as active or passive. Active mixing is characterised by the input of additional energy to bring about efficient mixing, such as in stirred tanks, inline impellers, or vibrational membranes. Conversely, passive mixing does not require additional energy input, and its dynamics are solely governed by flow rates, fluid properties, and flow reactor dimensions. In cases where the reaction rate is slow and the phases to be combined are the same (for example, both liquid and in the

same solvent) then a simple T-shaped or Y-shaped mixer is sufficient for passive mixing. In these mixers, the angle of confluence does affect mixing efficiency.[33] For mixed phase reactions, such as with mixed solvents or gas and liquid reactions, the general mixing strategy relies on increasing the interfacial contact area between the two phases by split-and-recombine-shaped mixers **[G]**. These mixers work by splitting the reaction down into smaller streams, thus increasing the surface-area-to-volume ratio between the components and decreasing diffusion distances, ultimately enhancing mass transfer before recombining the streams. There is a wealth of literature and examples on this topic.[1,15,34–40] For the new user, it is important to understand the mixing requirements of the reaction studied, and to appreciate that passive mixing, such as that achieved using a T-piece in a flow system based on 1 mm inner diameter tubing, might be insufficient for reactions that are rapid or influenced by concentration gradients.

[H2] DIY or commercial systems

Flow chemistry systems can be built in the lab or purchased commercially. Building a flow setup from scratch can be relatively straightforward and there might be more to learn by building a personal setup and validating ideas prior to expenditure. It is technically challenging to connect a pressure sensor to a DIY setup, which is an important consideration as a spike or drop in pressure could indicate that the flow setup has encountered a blockage or a tubing rupture. Using affordable Arduino microflow controllers along with a wealth of freely available python scripts can be used to enhance the control of DIY flow reactors.[41] However, there are commercially available intelligent flow systems with pressure sensor feedback to the pumps capable of automatically detecting pressure changes and shutting down pump operation.

There are many exciting, commercially available, 'out-of-the-box' pieces for lab scale flow chemistry, but they come at a financial cost. **[Au: I suggest referencing a few of the commonly used commercial pieces at the end of this sentence. Understanding the common equipment is important for a newcomer and some general suggestions can be provided without sounding like an advertisement. You could either cite another article that highlights common equipment, or you could link to a few common pieces. Please note, we cannot have standalone URLs in the reference list: links are instead formatted in a "Related Links" section at the end of the manuscript.]** Intelligent commercial systems are capable of predicting dispersion of segments, automate the injection of loading loops, control reactor temperature and automate collection (and even loading) from a range of input samples. Calculating dispersion for simple set-ups can be done manually, however it becomes increasingly difficult with more complex multi-step setups. Whether choosing a DIY or commercial approach, flow chemistry should be considered modular in design and further capabilities can often be added at a later date.[18,42,43]

[H2] Packed beds

Another reactor module that can be added to a flow system is a column pre-packed with solid materials, particularly suitable if the process requires a solid reagent that cannot be solubilised. Such a solid could be a catalyst, reagent, reactant, or downstream scavenger for purification purposes.[44–50] Typically these packed beds are made from an empty HPLC column or an Omnifit™ glass column. Packed-bed reactors often operate at

higher than ambient pressures to force solution through compact solids; with the smaller the solid particles to be packed, the greater pressure increase needed. A workaround to this pressure increase is to pack the bed with an additional inert solid with larger particles (such as glass beads or sand) to reduce the pressure increase. If a solid bed is not packed efficiently or is under too much pressure then cracks or channels can appear in the bed, leading to broader residence time **[G]** distributions, where some reactants bypass interacting with the solid altogether – a particularly important limitation for catalytically active packed beds. Each solid will have different optimal packing conditions and it is best to experiment until efficient packing is achieved. In each case, the pre-packed bed should be weighed empty and full of solvent to determine the reactor volume. The pre-packed bed should also be characterised to establish the impact of the solid on the residence time distribution, or how interactions of the solid with the segment lead to variations in the residence time of each part of the segment travelling through it, similar to column chromatography. The wear of packed beds is an important consideration, as in some cases the volume can change over time as the solid phase is abraded, leached, or consumed, leading to changes in residence time if not accounted for. When using catalysts in packed beds minor catalyst poisoning or leaching can occur over extended use leading to a substantial loss of activity over time.

[H2] Telescoping and downstream processes

Although used somewhat interchangeably, telescoping refers to combining multiple chemical reactions in sequence along a flow reactor, while downstream processes integrate work-up or purification into the flow system.[50] Multiple downstream processes themselves can either be telescoped or separated into a continuous multistep system.

Following the initial reaction, it is possible to introduce another stream by connecting an additional pump and T-piece at the outlet of the first reactor.[51–54] Such a stream can deliver another reagent or reactant at an appropriate flow rate and concentration, to commence a second reaction or a quench material (such as water, acid or base). The incorporation of such designs has been effectively used for multi-step syntheses, the generation and use of reactive intermediates, the quenching of excess hazardous intermediates, as well as for inline purification. From a practical perspective, we suggest to optimising the first process prior to adding additional steps to the flow process. An additional consideration for multistep or telescoped processes is the cumulative flow rate of all of the contributing channels. Fast flow rates must be compensated for by using very large reactor volumes. For example, if the system has five pumps, each running at 1 mL/min, and require a 10-minute residence time, then a reactor volume of 50 mL would be required. Sometimes ‘resetting’ the flow rate by collecting in a reservoir is necessary for complex multi-step operations. When telescoping it is important to consider solvent compatibility of subsequent processes to decide if telescoping is appropriate. Solvent-switching and using continuous phase separation techniques, such as membrane separators or centrifugation, can ensure downstream solvent compatibility.

[H2] Inline analysis and process analytical technology (PAT)

The performance of a flow reaction can be monitored in real-time by incorporation of a flow-cell for a range of analytical techniques such as IR, Raman, UV-Vis, or NMR spectroscopies. Here, the flowing material passes directly through an appropriate piece of analytical equipment for inline analysis .[55,56] These methods of monitoring reactions

(usually referred to as process analytical technology or PAT) give valuable information for optimising a flow process and also serve to monitor the performance of optimised systems that are running continuously without losing material. At manufacturing scales, PAT is invaluable for continuous quality control. When issues arise, the flow can be automatically diverted until the process has been corrected which minimizes waste. Online and at-line analysis is also possible and requires a manual or automated sampling system of the flowing stream. While online and at-line analysis give useful information, inline monitoring is the preferred method owing to the real-time data acquisition of performance.

[H2] Flow photochemistry and electrochemistry

Continuous flow offers a great opportunity for scaling photochemical reactions[57–60] as the surface-area-to-volume ratio of flow channels enable greater efficiency of light penetration compared to batch. A review of photochemistry in the pharmaceutical industry in 2024 found that the majority (54%) of photochemical processes were scaled up using flow.[61] Such a flow reactor setup would consist of a coiled tube (often wound around a reflective core) or plate design, with an external light source uniformly irradiating the reactor coil. Filters can be placed between the light source and the coil and the temperature of the device can be readily managed. Continuous flow also offers a good option for scaling electrochemical processes.[62,63] Critical here is the ability to have a narrow inter-electrode gap, which reduces the quantity of electrolyte required and can increase efficiencies. There are many electrochemical reactor designs in this space, many iterations of which focus on optimizing the potential delivered so that it achieves desired reaction while minimizing over-potential and undesired reactions.[62,63]

[H2] Practical considerations for the first experiment

When commencing a project in flow conditions, there are many parameters to consider, such as reaction concentration, residence time, yield, stoichiometry, and reactions pre- and post-flow (such as reactions in the feed reservoir or collection flask). We discuss these parameters below.

[H3] Concentration As for batch processing, is important to select the correct concentration for the desired focus: screening, optimisation, or scale-up. In flow, there is a tension against having the highest concentration possible, maximising throughput, and avoiding blockages due to precipitation and fouling of tubes and connectors.[22,64] It is advised to start at lower concentrations and gradually increase with successive runs to find the maximum concentration while minimising blockages and clean-down requirements (if at all).

[H3] Yield There are many ways to calculate yield under flow conditions, and the choice of method will largely depend on the mode of operation. Any method used to determine the yield of a flow process will be proportional to the concentration and volume of the collection. In segmented mode, the smaller the reacting segment is, the less accurate the yield will be when collecting the full segment of material due to dispersion within tubular reactors. As the size of the injected segment increases, the error relating to dispersion decreases, and the yield value tends towards the yield for continuous operation. One way to more accurately find a representation of a continuous yield from a

segmented-flow experiment is to take a short steady state collection of the segment. This can be achieved by heart-cutting, which involves collecting a middle section of the output flow where the product yield concentration is at a plateau and variations are minimal (essentially in a steady state) and avoiding the dispersed front and back ends. To achieve heart-cutting, calculate (or better, detect using inline analysis) the expected start and end times for elution of the segment; collect the flow for 1 minute in the middle of this timeframe; and correlate the yield for this collection to the input flow rates and concentrations to calculate an accurate continuous yield. Process consistency can be measured by doing this repeatedly throughout a segment. To ensure yield is accurate, the possibility of pre-flow or post-flow reactions must be considered. For example, if the reaction rate is sufficient at RT to proceed within the reagent flask, it is important to address this, such as by splitting the reagents into two bottles to ensure that $t = 0$ is at the point of mixing in the flow reactor. Likewise, if inline monitoring is not available, the output of the reactor can be collected directly into a quench solution to ensure accurate measurement. This is particularly important when benchmarking flow conditions against batch conditions.

[H3] Productivity As flow is a continuous process, evaluating productivity in addition to yield is beneficial. Productivity is a measure of the amount of material produced within the working period, expressed as g h^{-1} (sometimes mmol h^{-1}).[65] Although productivity can be extrapolated from the yield and flow rate of a system, running a reaction for a longer period (such as up to a full day) can stress test the flow set up, providing more accurate productivity data and ensuring true longevity of operation.

When scaling up a process one may also want to consider the productivity in relation to both the time and space required for the process to run. Space time yield (STY) measures the total amount of product formed within a given time and reactor volume reported in g dm^{-3} day^{-1} (sometime mmol dm^{-3} day^{-1}). This metric is particularly useful at large scale when comparing different types of reactors for industrial use.[66]

[H3] Stoichiometry In flow, reagent stoichiometry can be changed through changing the input concentration or relative flow rate. For example, if both A and B have concentration X and flow rate Y (mL/min,) then A and B will be automatically matched at a 1:1 ratio. If a 2:1 ratio of A:B is desired, concentrations can be fixed at X and the flow rate of A doubled to 2Y, or the concentration of A can be changed to 2X while maintaining a flow rate of Y.

[H3] Scaling-up Lab-scale flow chemistry generally scales up more reliably than lab-scale batch synthesis with minimal reduction in reaction performance.[8,67,68] There are two broad strategies for scaling up flow reactions: numbering up and sizing up.[16,69] A numbering up approach uses a parallel arrangement of identical channels or reactors, allowing the hydrodynamics and transfer characteristics of the original flow system to be replicated. Achieving identical conditions across many reaction units to fulfil the demands of industrial production can be a challenge; the use of flow distributors is the most common and resource-efficient way of addressing this.[69] A sizing up approach increases the size of the channel, avoiding the need for flow distributors by operating using a single stream. However, by changing the diameter of the channel, hydrodynamic and transfer properties will also be altered, requiring further optimisation of the process.

Noël *et al* provide an overview of applying these strategies to scaling up micro- and milli-reactors.[69]

[H1] Results

Here, literature examples will demonstrate how the flow components described in the Experimentation section have been applied to a range of fundamental reactions. Beginning with an example using a relatively simple flow set-up, different flow conditions and components will be introduced through case studies of different reaction types with increasing complexity.

[H2] Nucleophilic aromatic substitution

An archetypal transformation that has acted as a model for understanding translation into flow processing is nucleophilic aromatic substitution (S_NAr). Continuous flow S_NAr reaction development has resulted in several advantages over traditional batch processes, including enhanced reaction rates, precise control over reaction conditions, scalability, safety, and consistent product formation. Several classes of products have been efficiently generated from flow S_NAr reactions including anilines, aryl ethers, and aryl sulfides, as well as heterocyclic compounds.[70] Wilson and coworkers at *Boehringer Ingelheim* explored the development of a continuous flow microwave reactor for S_NAr chemistry.[71] Inserting a flow cell into a microwave cavity permitted them to continuously pump reactants through the flow cell and back into a reservoir in a recirculating flow circuit (Figure 3A). After 5 hours of processing at 120 °C (flow rate of 1 mL/min and reactor volume of 4 mL) an 81% yield (9.3 grams) was obtained. Notably, the same reaction at room temperature returned no product and heating the reaction to 100 °C for 18 hours afforded 20% conversion demonstrating the necessity of the higher temperatures achievable through microwave flow. Wiles and Watts reported a microscale flow setup for an S_NAr preparation of diaryl ethers.[72] The system consisted of a 10 μL reactor chip with a serpentine-type reactor channel (Figure 3B). The electrophile and nucleophile were delivered by one syringe pump while the base, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) was delivered by another syringe pump. With a chip temperature of 195 °C and syringe pump flow rates of 5 μL/min each, collection for 100 minutes afforded the diaryl ether product in 99.7% yield (90.4 mg).

A recent example of this approach is exemplified by Ulven, where aryldimethylamines were prepared by S_NAr of aryl or heteroaryl halides with dimethylamine.[73] Key to this protocol was the *in-situ* generation of dimethylamine from the thermal decomposition of *N,N*-dimethylformamide (DMF). To achieve this reaction, a two-step procedure was developed where the generation of dimethylamine and the nucleophilic substitution were performed in separate reactors, allowing for independent control of temperatures and reaction times (Figure 3C). Aqueous ammonia in DMF (1:9 v/v) was pumped at a flow rate of 0.250 mL/min through a stainless-steel reactor at 240 °C (residence time: 40 min) to form dimethylamine. This was then mixed with a solution of the electrophile (0.25 or 0.50 M) in DMF. The resulting mixture was passed through a polymer tubing reactor (PFA) at 30–50 °C (residence time: 20 min), where the substitution occurred; generally, 30 °C was sufficient to complete the substitution reaction. To demonstrate the advantages of flow chemistry for scale-up, a solution of 4-chloro-6-methylpyrimidin-2-amine (0.50 M in

DMF, 135 mL) was used to produce 8.8 g (83% yield) of N^4,N^4,6-trimethylpyrimidine-2,4-diamine, corresponding to a space-time yield of 65 g h^{-1} L^{-1}, without re-optimization of the developed protocol.

[H2] Heterocycle formation

The formation of heterocycles has also provided a rich playground for exploring the application of continuous flow chemistry, with an emphasis on developing systems that can be applied to a range of substrates and then toward the scale-up of a particular analogue. Kappe and coworkers reported a continuous flow system capable of delivering a benzimidazole or pyrazole product.[74] By making the connection between microwave and continuous flow reactors to heat reactions beyond atmospheric boiling points under pressurised conditions, it was recognised that a significant reduction in reaction time could be afforded by increasing reaction temperature. Using a straightforward setup of a single piston pump, stainless steel reactor coil and back pressure regulator (BPR) through a commercial X-Cube instrument, it was possible to heat reactions up to 200 °C at 130 bar back-pressure (Figure 3D). At this temperature, 2-methylbenzimidazole was produced from a single input stream of *o*-phenylenediamine dissolved in acetic acid. Processing a 1M solution for 50 minutes afforded 50.7 grams of the heterocycle product in 94% isolated yield. Using the same setup, but with a reduced reaction temperature of 180 °C, a mixture of phenyl hydrazine, acetoacetate, and concentrated HCl in ethanol gave 225.8 grams of 3,5-dimethyl-1-phenylpyrazole (97%) in approximately 56 minutes.

[H2] Organometallic reagents

Owing to improved temperature control/heat transfer (through increased surface area to volume ratios in flow tubing), the manipulation, generation and use of organometallic reagents under continuous flow conditions is a useful combination. By way of example, Ley and coworkers demonstrated a lithium-halogen exchange process using n-butyllithium (n-BuLi) and a boron electrophile to generate a series of aryl boronic esters. The flow setup consisted of a cryogenic cooling system (the Polar Bear reactor™) with pre-cooling loops and a cooled-coil reactor, the use of two piston pumps and two loading loops (and corresponding 6-port 2-position switching valves) (Figure 3E). Typically, most organometallic chemistry is conducted at -78 °C, yet in flow systems a higher temperature can often be used;[75] in this case -60 °C was employed. By bypassing the loading loop system and running directly from the n-BuLi reagent bottle, the system was run continuously for 5 hours, affording 12.87 grams of boronic ester product. Many researchers have reported the ability to run organometallic reactions in flow conditions higher than - 60 °C,[8,76] including 0 °C, room temperature or higher, and non-cryogenic temperatures reduce the carbon footprint of these reactions by removing the requirement for cryogenic consumables[77]. **[Au: Could you cite example studies for these specific temperatures? Presumably, the cost of heating impacts the carbon footprint. Could you comment on this?]** Yoshida et al. recognised that extremely fast organometallic reactions can benefit from being manipulated under flow conditions and deliver products and protocols not achievable by traditional techniques.[32] This work pioneered the area of flash chemistry **[G]** where extremely fast reactions are conducted with precise control to produce the desired compounds with high selectivity, and this field has developed alongside the success of micro flow reactors.

[H2] Gases in flow conditions

Working with gases under continuous flow conditions has sparked creativity in reactor design and synthetic applications. There are essentially two ways to achieve mixing between a liquid and a gas: biphasic and single phase. A biphasic approach looks to maximise the interfacial surface area between a liquid and gas, which can be achieved by a series of alternating gas and liquid segments, blowing an appropriate gas into a liquid vortex, or creating a falling film of liquid that is exposed to gas. Alternatively, if the mixture of a flowing gas and liquid is pressurised (by use of an appropriate back pressure regulator), then the system will become a single-phase and will no longer be mass-transfer limited.

A pump for gases is called a mass flow controller (MFC) **[G]**. Noël *et al*. used an MFC to meter oxygen into a photochemical process for the C-H oxidation of hydrocarbons. The system established a series of biphasic segments, consisting of gas and liquid. Tetrabutylammonium decatungstate was used as hydrogen atom transfer catalyst allowing for the selective C-H oxidation of industrially relevant scaffolds which overcame limitations observed in batch such as low conversion resulting from insufficient light penetration.[78]

An alternative approach for introducing gases into continuous flow processes features the use of a tube-in-tube design, whereby the inner tube is permeable to small molecules. In this manner, if a pressure differential is applied across the two tubes, it is possible to sparge gas from one layer and enrich the flowing liquid stream. For continuous flow processing, the Ley group identified Teflon AF-2400 as a key material for the fabrication of the inner tubing. Teflon AF-2400 is permeable to small molecules and has good chemical resistivity.[79] In one example application, Grignard reagents were flowed through a tube-in-tube reactor exposed to carbon dioxide (Figure 3F).[3] The system was under back pressure regulation, resulting in CO_2 passing through the Teflon AF-2400 membrane and into a single-phase liquid flow where it intercepted the Grignard reagent as electrophile to afford carboxylic acid products. The use of inline gas scrubbers can facilitate and improve the safety profile of using hazardous gases which is otherwise extremely difficult under batch conditions. For example, using a polydimethylsiloxane membrane, diazomethane was able to be generated in situ and separated from the aqueous saline phase for immediate use in oxidative heck cross couplings.[80] A one step synthesis of the antifungal medication flucytosine demonstrated the safe use of fluorine gas for direct fluorination in flow. The use of a gas scrubber for the unreacted F_2 was essential for the safe use of fluorine gas in this reaction process.[81]

[H2] Polymeric and solid-supported materials

The use of solid catalyst packed beds is commonplace for the large-scale continuous preparation of commodity chemicals. A convenient method to downscale and explore such capabilities in the context of assembling more complex molecules was a transformative step in the capabilities of continuous flow synthesis. Here, such packed beds can feature materials that host reagents, sequester byproducts or trace impurities, catalyse reactions[67,81] or ligands that coordinate to metals.[13,46,48,50,66,82] The use of polymer resins or beads (such as kind used for solid-phase peptide synthesis) has also sparked much creativity. For example, in the Grignard and CO_2 case described above, polymeric

reagents were used to facilitate the purification of the reaction process (Figure 3F). Following addition of a Grignard reagent to CO_2, the resulting carboxylate passed through a cartridge packed with a polymer-bound sulfonic acid resin where the carboxylate was protonated to the carboxylic acid and quenched any remaining Grignard reagent. The resulting materials then passed to a second cartridge packed with a polymer-bound amine resin, where the carboxylic acid proton was transferred to the amine functionality resulting in the formation of an ammonium/carboxylate ion pairing that caught and immobilised the product.[3] In this manner, any impurities (such as a quenched Grignard) passed through the system and were collected in the waste stream. In a subsequent process, the amine cartridge (hosting the product as an ion pair) was flushed with formic acid to protonate and release the desired carboxylic acid product, with the only impurities being formic acid and the reaction solvent. This catch-and-release **[G]** protocol is a powerful strategy for both purification and library synthesis. For example, a polymer-assisted flow catch-react-and-release approach was demonstrated for the alkylation of thiourea and thiol pharmacophore motifs (Figure 3G).[83] In this instance, a thiourea or thiol motif was immobilised onto a polymer supported-triazabicyclodecene resin housed in a packed bed. Changing the input feed to deliver a sub-stoichiometric quantity of an alkylating agent permitted partial reaction of the immobilised motif and thus release of the alkylated product. Through this approach, it was possible to subject the immobilised pharmacophore material to a sequence of 11 different alkylating agents — leading to 11 different products in good yields and high purities. Remaining on the packed bed was the protonated resin with a halide counterion which could be regenerated by flushing with a base. This catch-react-and-release design was mediated and executed by an automated system complete with a fraction collector, auto-injection unit and computer operating program.

[H1] Applications

Reactions employing hazardous chemicals and reactive intermediates stand out as a prime area where flow techniques are frequently used to improve safety, efficiency, and productivity. Several dedicated reviews have discussed this important field including applications where flow chemistry permits the safe performance of reactions that are not feasible under analogous conditions in batch.[84–87] Here we focus on selected recent examples to further exemplify this application of continuous processing.

[H2] Recent examples in organic synthesis

Dinitrogen trioxide (N_2O_3) has potential as an efficient nitrosating agent benefiting from excellent atom economy. Unfortunately, unreliable preparation protocols and the unstable nature of N_2O_3 have so far prevented its wider use. Monbaliu and co-workers recently presented a powerful flow approach to produce anhydrous N_2O_3 solutions on demand.[88] Flow technology helped to enhance the stability and accuracy of the N_2O_3 concentration through synchronisation of the gas flows and the elimination of reactor headspace. This was successfully applied to over 30 nitrosation reactions affording sydnones and benzotriazoles in high yields (Figure 4A).[88,89] Similarly, the on-demand production of phosgene from chloroform and oxygen gas has been reported in flow mode by Tsuda.[90] This exploited photochemical conditions for the safe in situ generation of

phosgene and its immediate consumption to yield valuable acid chlorides and carbonates from alcohols (Figure 4B).

Persulfuric acid is an oxidant often used in industry, but it also displays an unfortunate tendency toward explosive decomposition that greatly limits its use in organic synthesis. Flow chemistry excels at handling hazardous species as the comparatively small reactor volume minimises the amount of hazardous reagent being processed at any one time, as shown by Kappe and Otvos.[91] Generating persulfuric acid in situ from sulfuric acid and H_2O_2 allowed for the telescoped synthesis of a library of esters from aldehydes in yields up to 97% which included the synthesis of an intermediate towards paroxetine produced on a multigram-scale in under an hour (Figure 4C). Other related case studies include the scaled three-step synthesis of indazoles via diazonium and azide intermediates performed by a team at Novartis[67] as well as the safe and scalable preparation and use of *tert*-butyl nitrite towards versatile nitro olefins.[92]

A further important research area concerns lithiation reactions in flow mode.[77] Lithiation reactions are widespread and very useful but require unfavourable cryogenic conditions. The lithiation of azetidines opens a door towards a variety of biologically active compounds but suffers from self-quenching and scalability issues. Luisi provided a solution harnessing a flow procedure that generates the lithiated species in 82 ms prior to reaction with an electrophile (yields: 41-91%, productivity: 4.5 g/h, Figure 4D). Although this procedure required temperatures of -50 °C, a variation could be run at 0 °C that gave a productivity of 6.3 g/h. The process permits lithiation and functionalisation at either C2 or C3. Both of these procedures took less than 12 seconds and were highly reproducible, a feat that would be very difficult to replicate through batch processing.[93] Moreover, the same group reported on the flow-based generation of chloroiodomethyl lithium and its use in reactions with ketones to generate α-halo carbonyls thus further highlighting the power of flow processing for modern lithiation reactions.[94]

[H2] Examples in photochemistry and electrochemistry

Applications of photochemistry in flow have highlighted many advantages such as rate acceleration due to short pathlengths of light and uniform irradiation under high spatio-temporal control. [57–60] This has been exploited in recent chemical reactions exploiting gaseous reactants[95] as well as brominations that can be performed at kilo-scale. [96] The latter was demonstrated by a team at Merck Sharp & Dohme (MSD) employing 1,3-dibromo-5,5-dimethylhydantoin as the brominating agent under irradiation at 450 nm. The desired product, which is an intermediate towards the drug belzutifan, was obtained in excellent yield (91%) in only 3 minutes, allowing the production of approximately 100 kg/day. Moreover, continuous processing of photochemical reactions has also enabled their application in reaction sequences involving thermal transformations[97] as well as new continuously stirred tank reactor (CSTR) **[G]** approaches that enable the use of stoichiometric solids in scaled photochemical transformations.[98]

Similarly to photochemistry, electrochemistry can be performed in a highly controlled and scalable manner using flow technology. [62,63] This can be seen in a recent application by Xu reporting the selective C-H hydroxylation of arenes under operationally simple conditions.[99] A large substrate scope showed that the method was broadly applicable

with good yields and most substrates giving a single regioisomer. A scale-out was performed resulting in a productivity of 204 g/day. Related electrochemical examples from the same group address scalability, reaction efficiency, and safety for oxidation to benzylic alcohols (Figure 4E),[100] as well as asymmetric C-S and C-C bond forming reactions rendering chiral building blocks with high stereoselectivity.[101]

[H2] Recent industrial examples

The ability to safely and effectively deliver potentially hazardous chemistry using continuous flow techniques is well recognized by the fine chemicals industry.

An interesting and challenging example is provided by Roche and collaborators for the formation of 1,5-tetrazoles via azide cycloaddition (Figure 5A).[102] Adopting a flow chemistry setup here is beneficial due to the small reactive inventory and absence of a reactor headspace, as well as the control to manage the formation of an azido-tetrazole impurity. This example demonstrates how a flow process effectively addresses several critical safety issues in chemical manufacturing. In this reaction, it is important to avoid the generation of hydrazoic acid, a highly toxic and explosive compound that can accumulate in the headspace of reactions due to its volatility. Flow processing eliminates headspace avoiding HN_3 accumulation and allows for better control over the reaction environment, reducing the likelihood of its formation. Flow is also effective for hazardous reagent handling; the use of hazardous reagents, such as azides, is safer in flow processing than batch conditions, due to the reduced volumes involved and the ability to rapidly quench reactions, preventing the accumulation of dangerous intermediates. For reactions requiring careful pressure control, flow systems can be designed with integrated safety features, such as pressure sensors that trigger shutdowns in the event of blockages or leaks, thus preventing potential explosions or the release of hazardous material from the system. The use of continuous extraction and quenching methods can help to immediately separate products from hazardous reaction environments, thus maintaining safety during the work-up stages. Consistent temperature control in flow throughout a reaction minimizes the risk of temperature spikes that could lead to dangerous situations in batch reactors. By controlling reaction conditions more effectively, flow processes help reduce formation of impurities that can pose safety risks during handling and storage. When the fully optimized set up and maximised flow rates were applied, the Roche team achieved an 88% yield of the target chlorotetrazole, with a mean residence time of 22.5 min through the CSTR work-up cascade. The overall final productivity reached roughly 10 g/h and a high space–time yield of 1.16 kg L^{-1} h^{-1}, due to the high concentration and short residence time deployed.

A further industrial example where flow chemistry provides the appropriate solutions to handle difficult chemistries was reported by Syngenta Crop Protection and collaborators to generate 3-bromoisoxazolines, via a telescoped multistep continuous process for the preparation of dibromoformaldoxime (DBFO) as a pivotal, yet highly hazardous precursor towards the target scaffold.[103,104] The team devised a process for the generation and on demand consumption of highly hazardous materials as well as inline work-ups and purification (Figure 5B).

Many other examples of flow processes have been reported by large industrial companies. For example, MSD have reported on the elegant development of an organometallic reaction for Verubecestat at pilot-plant scale of >100kg, featuring the addition of an organolitium to a chiral ketimine.[76] Similarly, Eli Lilly have reported a process for the kilogram-scale flow synthesis of prexasertib monolactate monohydrate under cGMP conditions. The authors use a multistep approach yielding 24 kilograms of prexasertib monolactate monohydrate. The process comprises eight continuous unit operations, to produce the target amount using small footprint continuous reactors, evaporators, extractors, crystallizers, and filters in a laboratory environment.[105] AstraZeneca demonstrated the development of a large-scale continuous flow Curtius rearrangement process towards AZD7648, highlighting the powerful approach in generating kilogram scale material with unsafe chemistries.[106] Researchers at Novartis have recently published a very useful article focused on their experience of scaling-up organolithium-mediated transformations by flow.[64] In their work, the authors disclose a new method to avoid reactor fouling for pilot plant operations.[64]

The reproducibility of flow reactions between laboratory and plant scale processing also makes it an attractive technology for the chemical industry. Merck reported the use of continuous flow to scale the synthesis of an aldol product,[68] a key intermediate towards the synthesis of doravirine,[107] an important active pharmaceutical ingredient. The yield and purity on the pilot plant scale were comparable to laboratory data, confirming the reproducibility of the process. In another report, a team of researchers from Boehringer Ingelheim carried out a Curtius rearrangement in flow to obtain a CCR1 antagonist at up to 40 kg scale.[108] A team from Jansen described the synthesis of a Grignard reagent in continuous flow using a magnesium-packed column, where reproducibility was confirmed by titration experiments every 30 mins and found to be sufficient for the desired production quantity. A drop in concentration of the organometallic solution was observed on consumption of 60-70 % of the magnesium packed into the column, which was readily corrected by replenishing the column.[44] These examples demonstrate the increasing integration of flow chemistry into global chemical supply chain.

[H2] Recent applications in Materials Synthesis

Flow chemistry has found extensive use in organic synthesis and has shown promise as a powerful technique for materials chemists. For example, in recent years there has been renewed focus on the tailoring of porous materials, such as metal organic frameworks (MOFs), covalent organic frameworks (COFs), polymer frameworks, and molecular materials, to achieve desirable surface area and pore size for specific applications.[109] Such materials can be readily modified and have a wide range of applications including catalysis,[110–112] gas storage,[113–116] chemical separations,[115,117,118] molecular recognition,[114] energy storage,[119] and wastewater treatment.[120] However, such tuneability brings synthesis challenges: current approaches towards the synthesis of most of these materials require either harsh solvothermal[121,122] or high dilution[123–125] conditions, and often suffer from poor reproducibility or scalability.[126] Flow synthesis, displaying effective reaction control,[5] spatio-temporal resolution, and efficient heat-mass transfer[11,15,127] has proven beneficial for optimising and scaling up[17,128]of novel materials with a much lower environmental impact than batch processes,[129] offering a promising route to overcome these challenges.

To give a specific example, optoelectronics or energy storage devices based on polymeric COFs require the fabrication of a uniform thin film of the material to maintain performance.[130,131] Poor control over polymerisation in batch often leads to non-uniformity in the films alongside contamination with microcrystalline COF powders. Bisbey *et al.* used a continuous flow process to form thin films of COFs,[128] in which a flow reactor was paired with a quartz crystal microbalance to monitor the mass and thickness of the growing films and elucidate the impact of varying residence time. Offline microscopy indicated that flow gave uniform film growth and greatly reduced contamination compared to batch synthesis. Blockages due to precipitation of material within the flow cell or tubing were avoided by keeping the residence time lower than the time for of COF formation, in this case 2 minutes at 90 °C, overcoming a key challenge of material synthesis in flow.

Continuous flow approaches have proven advantageous for the synthesis of a range of molecular materials including cages,[132,133] macrocycles,[134,135] polymer frameworks,[136,137] MOFs[138] and nanoparticles ,[139–143] catering to the specific demands for the production and scale up of such materials and targeting improvements in selectivity, yield, sustainability, efficiency, or throughput. For example, Kitchin *et al.* reported the first flow synthesis of an organic cage (Figure 6A).[132] The process was markedly improved in flow compared to a batch; by reducing the reaction time from 6 hours to 33.3 minutes a space time yield of 104.6 g m^{-3} day^{-1} was achieved. The copper catalyst loading was also substantially lowered, while maintaining comparable conversion to batch conditions (21 % vs 20 %). Soon after this study was published, Cooper *et al.* demonstrated the flow synthesis of porous organic cages via reversible imine condensation, telescoping flow synthesis with precipitation of a crystalline porous material.[133] Reaction temperatures of 100 °C were achieved despite the requirement for dichloromethane as solvent, reducing the reaction time from days in batch to minutes in flow while maintaining purity and yield (Figure 6B).

Any material to be used by industry must be scalable, ideally in an environmentally and economically sustainable manner. In this vein, the production of MOFs has also benefited from a continuous flow approach. Bagi *et al.* applied a flow process to synthesise the widely used Zr-MOF, MOF-808; the optimised conditions reduced the use of DMF by ~84% and formic acid by ~67%, using a residence time of 5 minutes (as compared to 48 hours in batch).[133,144] The overall productivity was thereby increased by ~300 fold with corresponding space time yields of 335.5 kg m^{-3} day^{-1} in batch to 95,155 kg m^{-3} day^{-1} in flow. Interestingly, varying the residence time altered the measured surface area of the material produced: a residence time of 15 mins produced a material with high surface area, ~2000 m^2 g^{-1}, with reduced productivity: 31,730 kg m^{-3} day^{-1}. A trade-off in productivity and surface area was observed: lowering of residence time to 5 mins lowered the surface area to ~1600 m^2 g^{-1} while improving the productivity. Thus, continuous processing gives an added advantage of fine-tuning the properties of material to cater to specific needs of on-demand synthesis.

Aside from producing known materials, flow has been used both to discover new materials via screening[145] and to produce sufficient amounts of material for testing,

particularly for materials where typical lab experiments suffer from very poor scalability and/or reproducibility. For example, flow chemistry was recently used to scale up production of a crystalline porous organic salt[146] that had been identified via high-throughput screening but which proved challenging to scale in batch. Likewise, the self-assembly and ring-closing metathesis of molecular knots was transferred to flow to scale the synthesis of these intriguing structures, providing sufficient material to investigate the potential applications of such entangled materials. [147]

[H2] Reproducibility and data reposition

In this section, we focus on achieving reproducible, repeatable flow experiments to benefit the wider field. As discussed earlier, a typical continuous flow process consists of multiple components, including pumps, reactors, mixing pieces, tubing, temperature controller, check valves, a back pressure regulator, flow cells and in- or at-line analysis.[18] Each of these components is essential to control and study a given reaction; all contribute to the overall reproducibility of the process, and all can generate data and metadata that could and should be recorded. For results to be repeatable, detailed information of the flow setup including all components must therefore be included in manuscripts.

There are various factors contributing to consistent results. Like any other protocol, one should ensure the system is clean and not contaminated from any previous runs. As a good practice, it is advised to store the system under appropriate solvents as well as prime and calibrate the system at the beginning of each experiment. As discussed, it is particularly important to check the calibration of pumps. Since the flow process needs time to acquire equilibrium, steady state should be ensured before reporting results, ideally by using analytical measurements to confirm the predicted time when steady state should occur. Ideally, how these practices have been observed should be recorded alongside the experimental parameters in the experimental section of publications.

Many authors prefer to attach photographs of the complete flow process; this is particularly important when using custom-built platforms but is still illustrative when commercial equipment is used. Unlike single crystal XRD data, for example,[148] there is no specifically dedicated data repository for reporting continuous flow synthesis, although it is possible to search existing reaction databases such as Reaxys[149] and SciFinder[150] for reactions that have been annotated with keywords such as “flow”.[151]

Like any other synthesis, repeats should be carried out to establish reproducibility. In the case of flow, this could take the form of establishing steady state by sampling at time intervals, running the process for an extended time, re-running the entire process, or ideally, all three. Understanding the variation of yields is helpful for benchmarking between batch and flow, but also for identifying opportunities to improve the process. For example, Pijper *et al*. studied the reproducibility of a photo flow reaction over 96 experiments. The initial flow protocol showed a standard deviation in yield of 2.7% with variation of 7.2% over time.[152] The decrease was traced to degradation of the reagent stock solution over an extended period – showing how important it is to take account of pre-flow reactions. The use of two separate stock solutions avoided this problem and

decreased the variation in analytical yield to 2.5% with standard deviation of 1.6 %. In another study, during the synthesis of gold nanoparticles, the standard deviation in the size of particles was found to be ~2% in flow as compared to ~5% in batch, confirming the benefit of moving to flow.[142]

The advantages of improved reproducibility and reduction in economic cost have attracted many chemical industries to transition processes from batch to continuous flow. Here, it is important to establish whether processes are scalable without reducing yield and purity, and capable of sustained production over the required time.

[H1] Limitations and Optimisations

Flow chemistry offers several advantages over traditional batch methods, however it is important to acknowledge its limitations. Perhaps the most important consideration relates to challenges associated with the processing of precipitates and particulates that lead to blockages of the tubes or mixers and pump fouling.[15] Blocking and fouling of flow systems will affect reproducibility due to inconsistent or mis-recorded flow rates and residence times. Depending on the location, blockages can reduce the lifetime of the pump and risk overall failure of the system due to overpressurisation.[15,54,153] Blockages can occur for several reasons, including fouling of channel surfaces due to precipitation of reagents, intermediates, or products from the reaction stream; deposition and accumulation of solids from a heterogenous reaction mixture onto the channel surfaces; reactions of reagents or products of the reaction stream with the channel surfaces leading to particulate formation and deposition; and corrosion of the channel surfaces.[154]

Several workarounds for blockages exist, although some are more involved than others. The interaction of stream with the channel surfaces and corrosion can generally be overcome by judicious selection of reagents and equipment, ensuring channel surfaces are inert to the components of the flow reaction.[154] With this in mind, commercial suppliers of flow equipment generally supply solvent compatibility tables for both the tubing and pump check valves to expedite this process. It is, however, a factor to consider when translating a potentially well-optimised batch process to flow. Fouling of the channel surfaces due to crystallisation and solid accumulation require more creative work arounds. Several groups have employed ultrasonication of either particularly vulnerable unions or even whole reactor assemblies.[155–158] Droplet based microfluidic regimes can limit the fouling of reactor surfaces[159] and biphasic flow regimes can also assist in dislodging particulates immiscible in one of the solvents of the flow regime.[82] Additionally, complex hydrodynamic-focussing mixing regimes can limit the interactions of the active flow stream with the channel surfaces and thus prevent the deposition of solids on or reaction with the channel surface.[160–162] Depending on the particle size and morphology, simple interventions can assist in avoiding blockages for short run time flow processes such as avoiding pinch-points and abrupt changes of direction, increasing tubing size, or using peristaltic pumps in reverse as active BPRs instead of standard BPRs, which contain very narrow diameter tubes and are particularly susceptible to blockage.

Another limitation of flow chemistry is the relatively high cost of entry. The largest contributor to costs is the pumps; commercial pumping modules or repurposed HPLC pumps can require large capital investments (typically several thousand USD). A cost-effective entry point might be syringe pumps to offer a cheaper 'one-shot' delivery of solvent to begin initial experimentation. However, syringe pumps are restricted to working with relatively small volumes and low system pressure tolerance.[15] In addition, repurposed pumps and bespoke flow setups might lack the ability to detect sudden rises or falls in system pressure, meaning system failures and leaks may pass undetected, presenting safety risk if hazardous reagents are being employed.[15]

Should a pump malfunction be identified, the repairing of the failed pump modules can impose long delays on the progress of a flow project. Due to the strong dependence of flow systems to reagent residence times, stoichiometry, and pump-derived hydrodynamic flow regimes, pump idiosyncrasies could impact the reproducibility of the system.[15,153] Routine calibration of the pumps can forestall this somewhat.[153] Alternatively, peristaltic pumps are generally more immune to failure by fouling, as sometimes observed in piston pumps, and can prove to be a good option if performing chemistry where pump failures may be a concern. However, peristaltic pump systems operate at low system pressures below ~10 bar,[15] limiting experimental conditions that can be addressed.

In addition to the pumping modules, the cost of commercially available reactors designed to leverage the inherent advantages of flow such as photoreactors, electrochemical reactors, and heating or cryogenic elements can impose additional cost hurdles to fully exploiting the advantages of flow chemistry. However, with the increasing accessibility and decreasing cost of 3D printing, laser cutting, and other fine manufacturing technologies, there is ample opportunity for collaboration with engineering expertise to deliver custom reactors at a cost lower than comparable commercial products and perfectly suited to a particular purpose.[153,163] It is essential to thoroughly report these custom setups to ensure the replicability of the process.[153,164,165]

A final consideration regarding the implementation of flow chemistry is the lack of graduate students' familiarity with these setups, when compared to traditional batch synthetic techniques.[54] Typically, students are not exposed to theory and practical application of flow chemistry at an undergraduate level. To address this, extensive step-by-step flow tutorials and videos have been published in the literature.[18] Additionally, flow chemistry vendors offer teaching modules for undergraduate students that introduce practical and theoretical considerations of flow alongside walk-up flow systems designed to be 'plug-and-play'; with more researchers receiving their training in flow-orientated environments, this will likely not be a significant issue in the near future.

[H1] Outlook

The field of flow chemistry is undergoing rapid development in terms of both technological capability and applications. Barriers such as training and access to equipment are lessening, and collaborations across disciplines are resulting in new approaches. In the last 10 years, flow chemistry initiatives have already demonstrated

the ability to synthesise and formulate bio-active molecules in a piece of equipment occupying a similar volume to a large home fridge-freezer unit.[166] The field has also demonstrated the use of robotics and automation to design and assemble flow reactor hardware modules from a hardware library, perform the appropriate synthesis and then automatically reconfigure the device, robotically, for an alternative molecular synthesis process.[27]

Similarly, applications that take advantage of the temporally resolved nature of flow, such as inline analysis, real-time feedback loops, and the trapping of transiently stable intermediates, are well-placed to benefit from digital approaches capable of handling the resultant large datasets. This is exemplified by recent advances in transient kinetic experiments, where very large volumes of data can be obtained with efficient use of materials and time by using flow combined with process analytical tools to continuously sweep through residence times and output kinetic profiles.[167–172] For example the recently described "switch off" method in photo-flow is a powerful tool allowing the collection of kinetic data for all irradiation times up to the maximum in a single experiment.[173]

Through interfacing inline analysis with optimisation algorithms, self-optimising flow systems have been used for multi-factor optimisation, process chemistry, photochemical transformations, and more.[174] The use of flow complements related high throughput screening strategies, offering advantages such as routes to scalability, ease of inline analysis, and access to larger process space (e.g., large temperature ranges).

The enabling aspect of flow chemistry and its natural amenability to automation will necessarily play a role in positioning flow chemistry as an essential technology to accelerate process optimisation. Recently, multi-task Bayesian optimization, which equips optimisation algorithms with prior knowledge from previous optimization campaigns, has been used to improve efficiency for flow chemistry processes like in, medicinal chemistry workflows.[175,176] [164]The integration of computer-aided synthetic planning tools with modular flow hardware to optimize the multi-step synthesis of the active pharmaceutical ingredient, sonidegib, showcases the potential for autonomous process chemistry platforms, although the authors highlight that human input was still critical. The use of a "radial flow" system for automated synthesis has been demonstrated for both linear and convergent syntheses.[177] While we have seen an increase in the number of groups working on this topic and an exponential number of publications around the topic of self-optimisation platforms, more is needed to make such "islands of innovation" an everyday approach to how we bring value to process chemistry. Current barriers for adoption are flexibility (especially of analytical techniques), the robustness of setups, and unfavourable benefit-to-effort ratios. If barriers exist to the use of flow chemistry, further barriers are undoubtedly present for the development and use of complex automated flow systems. As the numbers of examples in the literature increase, the use of FAIR data, the publishing of negative results, and detailed descriptions of hardware, code, experimental detail, and metadata will be essential for these methods to find more widespread adoption.

Continuous processing offers opportunities for the sustainable development of chemical processes and reactions, by reducing energy usage and waste, improving

safety and increasing productivity. Both electrochemistry and photochemistry have benefits from being conducted under continuous flow conditions. However, to reduce issues with fouling and clogging of reactors, flow reactions in general operate at lower concentrations than typical batch processes which may result in increased solvent usage. Appropriate use of Bayesian optimization and machine learning approaches may help to address this by finding conditions using more environmentally benign solvents and higher throughputs (or higher concentrations). On a related theme, the development of aqueous-based biocatalytic methods by continuous conditions is a rich seam of potential for minimising the use of environmentally harmful solvents.[178,179] Opportunities and challenges here include immobilisation of enzymes into packed-beds, recycling of cofactors, efficient gas-liquid mixing, and improving productivity.

In parallel to the development of solution-based flow, in recent years, the technique of solvent-minimised continuous reactive extrusion has emerged as a useful technique for the synthesis of materials, and many organic transformations, including palladium-catalysed and nickel-catalysed reaction processes.[4,180–183] In the absence of a reaction solvent, productivities typically become several orders of magnitude higher than traditional methods, with obvious benefits in reducing solvent waste and increasing productivity. Key opportunities and challenges with this technique include reducing solvent usage for purification and understanding the translation to extrusion from either smaller scale ball-mills or from solvent-based processes.

To conclude, flow chemistry is highly versatile and proven as a useful technology for molecular synthesis of all kinds. Critically, its utility is recognised by the fine-chemicals industry, which will drive adoption and investment. Moving forward, the most exciting opportunities for flow chemistry are as a central synthesis platform in conjunction with self-optimising capabilities to expedite the discovery to process development pipeline, and the fields that will benefit as new adopters of the technique provide diverse challenges that flow can address. New reactor technologies are likely to emerge which lead to the development of new organic methodologies and chemistries as it has done before with solid phase peptide synthesis, flash chemistry, and tube-in-tube reactors. As flow chemistry becomes more commonplace, it will aid the development of scalable processes, especially in electro and photo chemistry, where scaling up in flow has considerable advantages.

Author contributions

Introduction: D.L.B. and S.R-B.; Experimentation: D.L.B. and S.R-B.; Results: D.L.B., A.P., and S.R-B.; Applications: C.B., M.B., J.D., P.G., and A.G.S.; Reproducibility and data deposition: P.G. and A.G.S.; Limitations and optimizations: D.L.B and A.P.; Outlook: D.L.B., C.B., M.B., P.G., S.R-B., and A.G.S.

Competing interests

The authors declare no competing interests.

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Figure Captions:

Figure 1. Comparisons between batch and flow chemistry. A) The surface area-to-volume ratio of tubular reactors are an order of magnitude greater than for a batch reaction vessel. B) An early demonstration of the potential of flow chemistry for molecular synthesis applied a series of polymer-supported reagents, hosted in cartridges, to the synthesis of (±) oxomartidine.[8]

Figure 2. Various fundamentals of flow reactors. A) Anatomy of a simple flow reactor. B) Reaction evolution along a flowing stream is spatially resolved. C) Output of a flow reactor with input from a reagent reservoir vs a loading loop. D) Guide for installing a connector to a piece of tubing for a common connector type.

Figure 3. Examples of flow setups described in the experimentation section with relevant apparatuses. A) A flow microwave approach for S_NAr;[71] B) A microfluidic chip flow setup for S_NAr chemistry;[72] C) A flow approach for the in situ generation and use of dimethylamine for S_NAr;[73] D) High pressure and temperature flow chemistry for the synthesis of heterocycles;[74] E) A continuous flow process for the lithiation and borylation of aromatics;[75] F) Use of a tube-in-tube flow device for the introduction of gaseous reagents and downstream purification with polymer support reagents in packed-beds;[3] G) Early examples of the use of catch & release on polymer support and process automation.[83]

Figure 4. Recent examples of flow setups demonstrating capabilities in organic synthesis. A) The introduction of NO and O_2 gas using mass flow controllers for the generation and use of N_2O_3;[88] B) The generation and use of phosgene in flow for the synthesis of carbonates and polymers;[90] C) The generation and use of persulfuric acid in flow for the conversion of aldehydes to esters;[91] D) Controlled lithiation of azetidines in flow to deliver either azetidine or dihydroazete products;[93] E) Continuous flow electrochemical C-H oxidation.[99,100] Abbreviations used; back pressure regulator (BPR), mass flow controller (MFC), dichloromethane (DCM), dimethylformamide (DMF), trifluoroacetic anhydride (TFAA), lithium diisopropylamide (LDA) cyclopentyl methyl ether (CPME), trifluoroacetic acid (TFA).

Figure 5. Recent examples of flow setups demonstrating capabilities in industrial applications. A) A continuous flow setup designed for the preparation of a chlorotetrazole material, designed to minimise the formation of hazardous azidotetrazole byproduct.[102] B) A telescoped continuous process for the synthesis of 3-bromoisoxazolines.[103] Abbreviations used: continuous stirred tank reactor (CSTR), dibromoformaldoxime (DBFO).

Figure 6. Recent examples of flow setups demonstrating capabilities in materials applications. A) Flow synthesis of cage C2 via a three-fold Eglinton homocoupling;[132] B) Flow synthesis of organic cages via imine condensation.[133] Abbreviations used: dichloromethane (DCM).

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Glossary:

Ferrules: Small ring or cap shaped components which allow the formation of secure leak free joins between tubes and other reactor components. **[Au: This definition says *what* ferrules do, but doesn't explain what they physically are first. Please rewrite this definition, using the definition for unions below as an example.]**

Union: A fitting with thread on the inside that allows it to join tubing and other components of the flow reactor by screwing on to nuts.

Segmented flow: A technique where reactions are run in discrete sections carried along in a carrier fluid.

Segment: The discrete sections in segmented flow are referred to as segments, slugs or plugs.

Laminar flow: A type of flow where the fluid moves along in smooth parallel layers.

Turbulent flow: A type of flow characterised by chaotic changes in pressure and flow velocity leading to the fluid moving in a swirling pattern instead of parallel layers.

Pulsing: Changes in flow pressure fluctuating around a non-zero mean value.

Mass-transfer limited: A reaction where the rate is primarily limited by the movement of the reagent to the reaction site, meaning mixing or diffusion becomes the limiting factor.

Split-and-recombine-shaped mixers: This shape of mixer works by splitting the reaction down into smaller streams, increasing the surface area to volume ratio between reagents. The smaller streams are then recombined back into one tube.

Residence time: The average time a reagent molecule spends in the reactor, calculated from the flow rate and the reactor volume.

Flash chemistry: Extremely fast chemical reactions enabled by the high degree of control over reaction parameters possible in flow reactors.

Mass flow controller (MFC): A device which precisely controls the flow rate of a fluid.

Catch-and-release: A technique where a molecule is temporarily adhered to a solid support (caught), allowing impurities to be washed away. The desired molecule is then released allowing further derivatisation or work up.

Continuous stirred tank reactor (CSTR): Also known as a vat or back mix reactors, CSTRs are large tanks with inlet and outlets connected to the flow system. The material in the tank is continuously stirred by an agitator as the reaction mixture flows through. They allow the use of stoichiometric solids in the flow system by confining them to the stirred reactor tank.