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Flow Chemistry

Overcoming the Hurdles and Challenges Associated with Developing Continuous Industrial Processes

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Abstract: Continuous flow chemistry is often viewed as a very simple concept on paper, however scientists with significant flow chemistry experience will highlight a number of challenges that need to be overcome. Critical for the successful development of any flow process is a high level of understanding of potential pitfalls that may be encountered. A collaborative and multi-disciplinary team of chemists and chemical engineers is essential in the development of a process from lab scale through to production. This Minireview will identify and highlight relevant risks and their subsequent mitigation strategies to ensure successful flow processing.

1. Introduction

The adoption of continuous chemistry within the chemical and pharmaceutical industries continues to increase with the number of commercially relevant examples on the rise.[1] Translation from batch to flow is often viewed as an extremely simple concept whereby reagents are continuously pumped, mixed together before passing through a narrow channel or coil where they react before quenching and collecting the product (Figure 1). In principle, this is the case however, the reality is that the development of a continuous process can be complex with a number of hurdles to overcome not traditionally faced in batch.

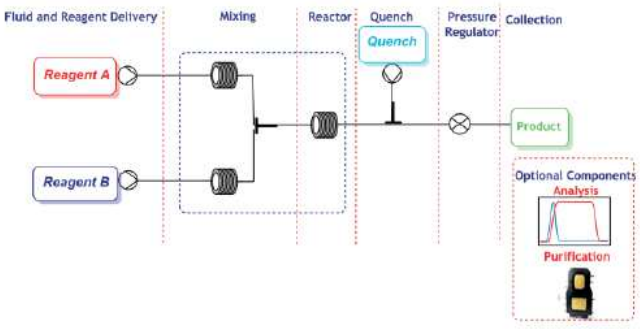

Figure 1. The anatomy of a continuous flow set-up.

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One of the main drivers for implementation of continuous flow includes enhanced safety, with flow considered beneficial over batch for handling of hazardous/toxic intermediates in situ,[2] use of hazardous gases at higher pressures,[3] exothermic reactions, and circumvention of any build-up of vapor headspace.[4] These attributes are of importance to many in industry, who seek new process design resulting in a competitive edge.

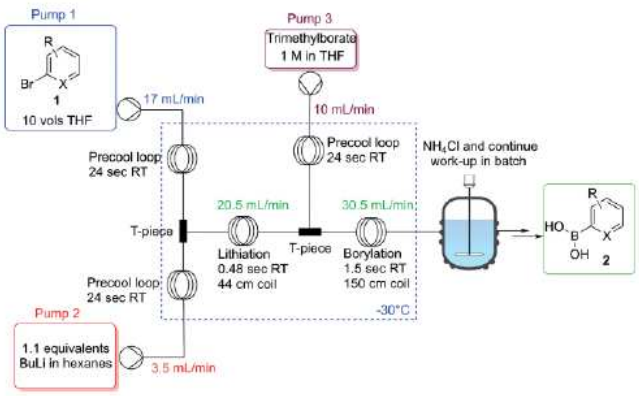
This Minireview article aims to highlight some of the pitfalls associated with the development of a continuous process, focussing on translating the process from batch lab scale to industrially relevant quantities using flow. The focus will be on reaction classes which are inherently difficult to perform at industrial scale, including lithiation/borylation reactions as well as outlining how to overcome handling solids in a continuous flow set-up.

2. Identifying the Pitfalls in Flow Chemistry

2.1 Lithiation/Borylations

Organometallic reagents are typically used in batch at cryogenic temperatures (−78 °C). Organolithiations access a number of key synthetic utilities and reactions involving these species are often extremely exothermic and proceed very quickly. This makes them difficult to control under batch processing conditions and the cryogenic reaction temperatures are required to avoid decomposition of the highly unstable lithiated species prior to electrophilic quench. Under continuous flow due to the better dissipation of heat, reactions often can be run at much higher temperatures, even up to ambient. The fast reactions along with inline quenching with an electrophile facilitates very short residence times and consequently, high throughputs (kg/day) can be achieved with even lab-scale flow rigs. With many Pharmaceutical and Contract Development Manufacturing Organisations (CDMO's) limited by cryogenic vessel size, the use of continuous flow as an enabling technology to address the supply of chemicals via these synthetic strategies is sought.

Boronic acids are synthetically useful as a precursor for Suzuki cross-coupling reactions.[5] The work of Sedelmeier et al.[6] reports the benefits and critically the limitations of a simple flow set-up (Scheme 1) for the handling of organolithium chemistry for multi-gram delivery. The very short residence times (<1 s) and highly efficient mixing at non-cryogenic reaction temperatures are indicative of Flash Chemistry.[7] This chemistry avoids decomposition of the unstable aryllithium species through rapid trapping with an appropriate electrophile. One of the limitations from an industrial perspective with the development of this type of chemistry is the large quantity of material that is processed in short periods of time during development work. For example, for a reaction such as this with <1 s residence time, the magnitude of material processed is in the order of 10's to 100's of grams per hour due to the high flow rates which are required for such chemistries. In order to ensure sufficient mixing the flow rate is critical independent of residence time selection. The availability of sufficient quantities of material for early phase projects can be troublesome and limit the amount of process development that can occur prior to scale up. The authors demonstrate and discuss the construction of a continuous flow rig using commercially available T-pieces and PFA tubing which allows flexibility in terms of reactor size and ease of replacement should blocking occur. Organolithiation can result in reactor clogging due to fouling as a result of the precipitation of lithium salt by-products. A critical advantage from an industrial perspective surrounding the use of simple, modular custom-built flow rigs is the ability to rapidly replace the reactor should any fouling occur on lab scale. More often on industrial scale reactor fouling is circumvented with periodic flush out of the system based on Process



Scheme 1. Continuous flow set-up for conversion of aryl bromides to boronic acids.

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Dr. Megan Smyth is a Senior Chemist within Almac Sciences. Megan graduated from Queen's University Belfast with 1st Class Hons. Chemistry (MSci) in 2012 before returning to obtain a PhD graduating in 2016. Megan is responsible for the development of flow capabilities and delivery of projects for customers. Additional experience includes bioprocessing, technology transfer and process scale-up.

Dr. Scott Wharry is Custom and Flow Chemistry Manager at Almac Sciences. Scott completed his studies at Queen's University Belfast graduating in both 1994 (BSc) and 1998 (Ph.D. Organic Chemistry). Scott is responsible for continuous processes at Almac. He has over twenty years of experience managing multi-disciplinary teams across process development, technology transfer, and multi-kg GMP manufacturing. Additional expertise includes GMP manufacture and bioprocessing.

Dr. Marcus Baumann is Assistant Professor for Continuous Flow Chemistry at University College Dublin where his research group focusses on developing new continuous flow technologies for sustainable chemical synthesis including reaction scale-up, photochemistry, and biocatalysis. Marcus graduated from Philipps-University Marburg (2007) and received his Ph.D. from the University of Cambridge (2011) before doing postdoctoral research at the University of California Irvine (2011–2013) and Durham University (2013–2017). He currently holds a prestigious SFI Industry Fellowship intensifying research links with chemical companies specifically in modern continuous flow biocatalysis.

Analytical Technology (PAT) collected on pressure rise or on the experience of the chemistry being performed. Solvent predrying strategies can also be useful risk mitigation to prevent reactor fouling in organolithiations.[7c]

Development of the organolithiation reaction involved consideration of;

• The use of commercially available *n*BuLi (1.6 M in hexanes – note for scale-up the use of hexanes would be an important consideration due to the associated safety concerns) as no predilution is required and the reagent can be added directly from the bottle/cylinder,

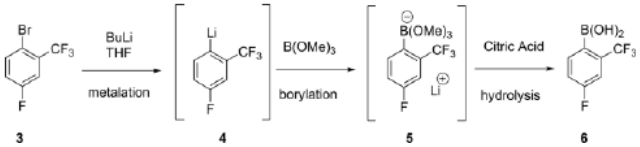
• Aryl bromide concentration was set at 0.3 M. The concentration was used without any problems with clogging and provides a good starting point for most reaction feasibility assessments,

• Jacket temperature (JT) was set to –30 °C as this is readily available using standard cooling devices.

A total flow rate of 20.5 mL/min was used as it was not only applicable to both electron-rich and poor substrates ensuring full conversion but was considered a good compromise between throughput (up to 60 g/h), consumption of starting material, and total flow rates achievable for common laboratory pumps.

Interestingly, for mixing-dependent chemistries such as this, the residence time is not the critical parameter to develop. As a result, process development is best undertaken assessing the conversion and yield as a function of the total flow rate. A useful paper from Röder et al.[8] reports a methodology to allow adequate selection of commercially available mixing devices to ensure suitability for chemical reactions which are known to be mixing sensitive. The authors investigated and determined the range of flow rates at which each of the selected micromixers (T-piece, y-mixers, etc.) must be operated to ensure the intensity of mixing is sufficient. It is a useful resource for industrial chemists in the design process of a suitable flow rig for scale-up.

Sedelmeier et al.[9] followed up their preliminary work with a further publication discussing the key factors and corresponding practical assessments undertaken to ensure a streamlined and seamless scale up from lab to higher throughput and productivity (Scheme 2). It is essential that redevelopment upon scale-up is minimal and in batch processing, differing vessel geometries, the cooling capacity of the reactor, and deviations in holding or dosing times can all change the reaction outcome.



Scheme 2. Metalation/borylation sequence for the synthesis of boronic acid **6**.

Flowability is the assessment of solubility of all starting materials, intermediates, and products under the processing conditions and considers the stability of feedstocks over the reaction timeframe. To ensure no reactor clogging occurs, feasibility must be demonstrated over extended time periods. The work was performed using the aryl bromides as shown in Scheme 1 with batch experiments demonstrating low yields (21 %) at cryogenic temperatures (JT = –78 °C) due to the rapid decomposition of the lithiated species. In flow, the reaction can be performed at –30 °C with 90 % yield (HPLC peak area) and a number of conclusions can be drawn;

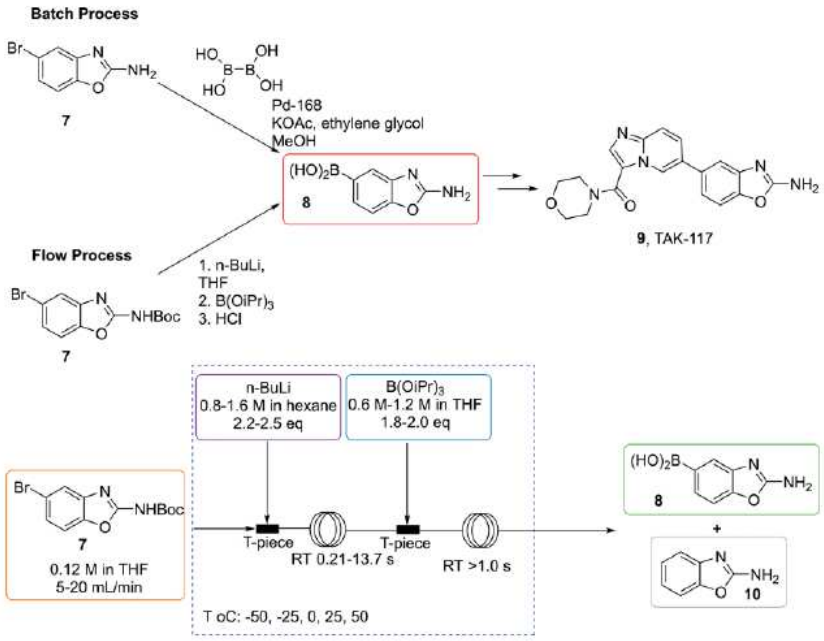
•Reaction feasibility in flow was demonstrated with no observed pressure build-up. Development experiments confirmed the solubility of all reaction partners and intermediates at the applied concentrations,

• The reaction was superior in flow compared with batch as higher yields were achieved at higher temperatures. Critically, the temperature employed is industrially relevant and achievable without the requirement for specialist cooling,

• Both metalation and borylation were confirmed to be very fast with residence times of 0.5 secs required for both steps and as such the benefits of continuous flow arise from the combination of short residence time control and fast mixing together (i.e. no time for the molecules to degrade, even at higher temperatures, before electrophilic quench).

The temperature profile was also considered to ensure not only the robustness but to guarantee the safety of the reaction over a broad temperature range. This was investigated using the early development set-up described above and robustness was demonstrated from –30 to +2 °C with a drop in yield from 90.5 % to 86.3 % observed. The main by-product was identified as the des-brominated compound which can be attributed to the presence of trace water in the system. In terms of mixing for scale-up, static mixer units were employed. Commercially available PTFE static mixer elements (4.8 mm length) were fitted within PFA tubing (ID = 5.0 mm, OD = 6.0 mm) as mixers, and the length of the reactor adjusted to give 0.5 s residence time. The feeds were connected with Swagelock® T-pieces orientated so that the stream with the higher flow rate entered at a 90° angle to prevent premixing within the T-piece, alleviate back mixing effects of the different flow rates to ensure the majority of the mixing and consequently reaction occurs within the static mixer element. In terms of PAT, the authors utilized inline thermocouples to measure the adiabatic temperature increase and monitor steady-state of the flow system. The synthesis of the boronic acid was successfully demonstrated with annular gear pumps capable of delivery of flow rates up to 288 mL/min and each stream was controlled by a Coriolis mass flow controller. The scale-up system demonstrated throughputs of ca. 370 g/h which equated to 8.9 kg/day.

Further demonstration of a lithiation-borylation was reported by Cork et al.[10] utilizing flow flash chemistry. The aryl boronic acid was a key starting material for the synthesis of TAK-117, a selective PI3Kα inhibitor (Scheme 3). Here the use of continuous flow offers a number of additional advantages over the batch process including the avoidance of using a costly metal catalyst thus reducing overall cost contribution to the process from raw materials. In addition, the use of bis-boronic acid (BBA), a potential source of genotoxic impurities, was circumvented which was important given the close proximity to the final API. However, the necessity for Boc protection meant

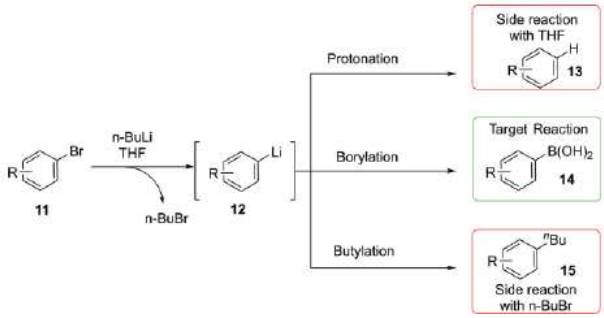


Scheme 3. Batch Miyaura borylation and flow chemistry lithiation-borylation routes for the synthesis of a key aryl boronic acid (**8**).

the Miyaura borylation raw material costs were higher than for the batch process. Attempts to perform the lithiation-borylation under batch conditions resulted in no desired product formation being observed.

The general lab-scale set up consisted of syringe pumps with stainless steel (SS ID = 1 mm) tubing. The residence time employed for the lithiation was 0.25 s and 1 s was found to be sufficient for the borylation with longer residence times shown to not have a detrimental effect. The product was quenched offline followed by a deprotection which was carried out in batch to yield the product as white to off-white crystals in 98.9 % purity and a yield of 79 %. In this instance, as shown in Scheme 3, the starting aryl bromide was reacted at a 0.12 M concentration as preliminary feasibility studies using the free amine indicated significant reactor clogging at this concentration despite a solvent screen which included toluene and 1,2-dimethoxyethane. Consequently, the lithiation was investigated using a Coflore® agitated cell reactor which can handle slurries and immiscible liquids through the use of wider channels with dynamic mixing suspension of solids being achieved.[11] To compensate for the wider channels and consequential larger reaction volume, reactions were performed at –20 °C, however with no successful product formation when the free amine substrate was used due to the proton transfer from the free amine to the intermediate aryllithium. Conversely, Boc protected starting material was found to afford 82 % lithium–halogen exchange yet alternative protecting groups (acetyl, trifluoroacetyl, and carboxybenzyl) did not afford the product. With Proof of Concept (PoC) demonstrated, the experimental conditions were scaled up to facilitate the delivery of 1.23 kg of material after batch work-up in 70 % yield and 97.7 % purity.

Further work by Cork[12] reported the use of continuous flow to prevent the lithiated intermediates from undergoing competing side reactions such a butylation as shown in Scheme 4. With longer residence times the unstable lithiated intermediate was more likely to form the undesired side products.



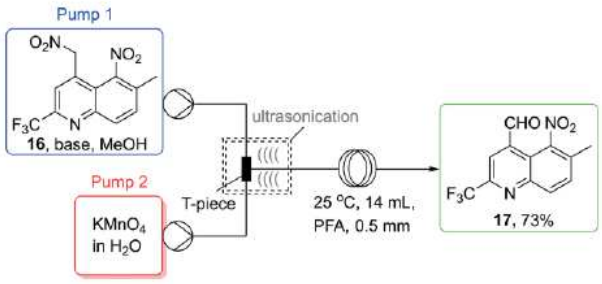
Scheme 4. Sequence of bromine-lithium exchange followed by the desired reaction and side reactions.

2.3. Handling Solids in Flow

Continuous flow is widely recognized as a powerful synthesis technology applicable to solution phase transformations.[13] The requirement for homogeneity is highlighted in most flow applications as a prerequisite to prevent fouling within reactor components (mixing elements, connectors, reactors, Back Pressure Regulator (BPR)) which leads to inaccurate flow rates and eventually complete blockages.[14] There is no one size fits all solution to handling solids in flow and it should be reviewed on a case by case basis.

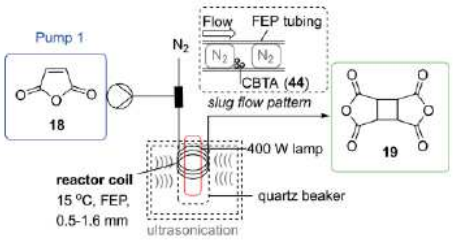
A $KMnO_4$-mediated oxidation of alcohols, aldehydes, and nitroalkanes (Scheme 5)[15] highlights how the insoluble MnO_2 by-product presented an issue that led to blockage at the

T-piece mixer. To prevent finely powdered MnO_2 from accumulating in the small-bore T-piece or the adjacent section of tubing this was submerged in a standard laboratory sonication bath. The application of either pulsed or continuous sonication prevented sedimentation and subsequent reactor fouling. The resulting flow process was maintained for extended periods of time (3.3 h, 50 mmol scale) with the product solution separated from the MnO_2 by-product by final filtration.



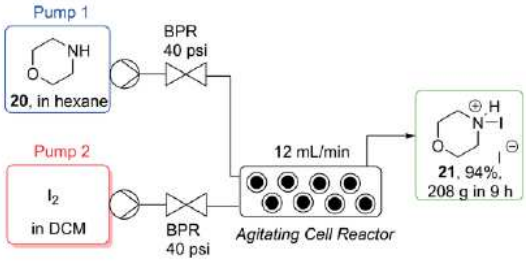
Scheme 5. Exemplary Nef oxidation reaction with sonication in flow mode.

A further demonstration of the value of ultrasonication was reported for a photodimerization reaction of maleic anhydride (**18**, MA) to generate cyclobutene tetracarboxylic dianhydride (**19**, CBTA) which is an important monomer for the generation of polyimides[16] (Scheme 6). As CBTA is sparsely soluble in common organic solvents, a modified flow process was required to prevent reactor fouling due to adhesion and sedimentation of the solid product. To resolve this problem a microreactor was constructed from FEP tubing wound around a quartz beaker. A high-pressure Hg-lamp was placed in the center of the beaker and the entire unit was placed in an ultrasound bath. Importantly, a liquid/gas slug flow regime was exploited by interspersing the liquid phase (MA in EtOAc, delivered via a plunger pump) with nitrogen gas which ensured that the solid product would not sediment and adhere to the tubing wall where eventual fouling would be inevitable. Alternating slugs of solution and gas were therefore generated continuously and processed through the irradiated reactor coil held at reduced temperature (<15 °C) before collection in a vessel. For longer runs, this slug flow regime was complemented with ultrasonication of the reactor unit to ensure reliable processing with all solid exiting the reactor. This allowed operation of this system over 16 h without any clogging issues.



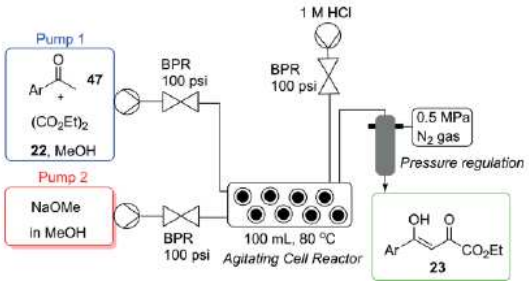
Scheme 6. Flow photodimerization exploiting slug flow and ultrasonication.

The importance of applying effective agitation to continuous slurry-based processes was demonstrated using the Coflore® reactor system. This unit is based on a layered reactor block comprising of individual cells, interconnecting channels, and different agitators that are placed within the cells (Scheme 7). By applying a rapidly reversing transverse movement, the reaction mixture is continuously agitated, and insoluble components are kept in motion thus avoiding sedimentation and clogging of the unit. The type of agitator inserts (springs, cylinders, etc.), the agitation speed (frequency) as well as the temperature of the reactor block can be adjusted allowing for enhanced flexibility. This renders a dynamically agitated system in which the interconnected cells are comparable to a sequence of continuously stirred tank reactors (CSTRs). The utility of this system was initially demonstrated for a salt-forming reaction yielding morpholinium iodide **21** reaching a productivity of over 200 g in 9 h of continuous processing.[17]



Scheme 7. Coflore® system for the generation of morpholinium iodide.

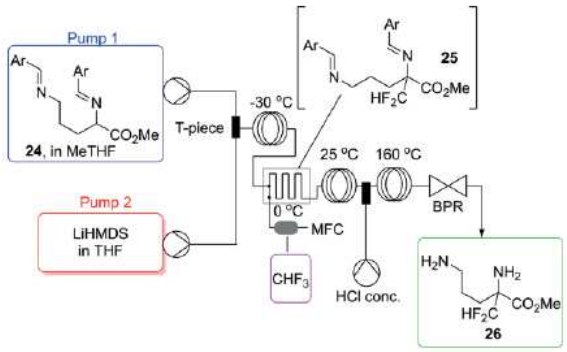
Whilst the previous example outlined the application of continuously agitated slurry-forming reactions at ambient temperature, flow chemistry is often applied under superheated conditions. As conventional BPRs would not tolerate particulate matter due to small-bore components, a bespoke pressure chamber with a volume up to 1 L was developed for slurry-forming reactions in flow mode (Scheme 8).[18] In this case an aldol reaction between acetophenone and diethyl oxalate was performed under basic conditions at elevated temperatures using the Coflore® unit. Under these conditions, the reaction reached completion within 25 min and was quenched at the outlet of the agitated reactor using a stream of aqueous hydrochloric acid delivering a suspension of the crystalline aldol product **23**. This was connected via wide-bore tubing that introduced the slurry into a nitrogen gas-filled pressure chamber. The stainless steel and PTFE lined chamber offer chemical compatibility across different applications. A nitrogen gas supply of 0.5 MPa provided sufficient positive pressure to allow for periodic emptying of the suspension into a collection vessel. Importantly, this design outlines how slurry forming reactions can be per-



Scheme 8. Coflore®-based slurry forming reaction with bespoke pressure chamber.

formed continuously under superheated conditions without issues due to blockages in either the reactor or the BPR. The value of this technology has since been demonstrated in other scaled multi-step processes including reaction quench and work-up processes.[19]

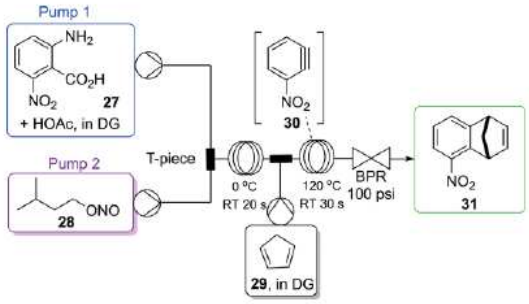
The necessity for appropriate BPRs was furthermore highlighted in the flow synthesis of eflornithine (**26**).[20] Eflornithine is a difluoromethylated derivative of the amino acid ornithine and can be generated by the reaction of a suitably protected ornithine species (**24**) with gaseous fluoroform under basic conditions (e.g. using LiHMDS, Scheme 9).



Scheme 9. Continuous flow synthesis of eflornithine **26**.

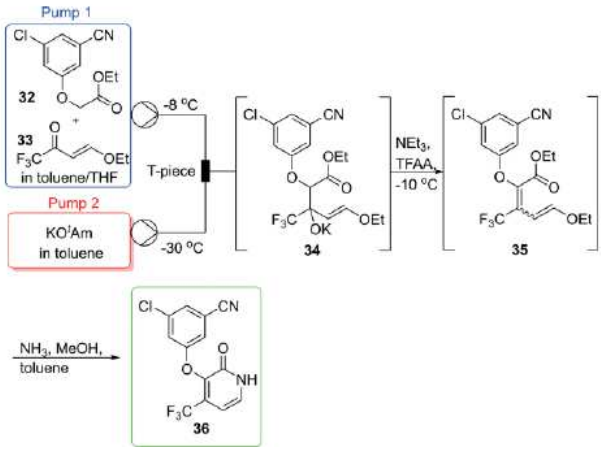
To safely handle fluoroform and generate the lithiated ornithine derivative, an improved continuous flow approach was developed. Earlier studies[20] had demonstrated that a continuous flow approach enabled the effective generation of lithiated intermediates that subsequently reacted with fluoroform gas delivered via a mass flow controller (MFC). Whilst the flow set-up allowed control of the reactor temperature at different stages and cleanly form the desired eflornithine precursor, the precipitation of inorganic salts (mainly LiF) posed a major challenge due to recurring clogging of the BPR. To rectify this problem different BPRs were investigated. A solution was found when using a Zaiput BPR, which is based on an internal chamber filled with a gas pressing against a membrane. This adjustable system allowed for minimal pressure fluctuation (± 0.1 bar) and smooth flow without issues due to clogging and highlights the value of investigating suitable reactor components.[20c] The telescoped flow synthesis of eflornithine was subsequently realized after performing a final deprotection step rendering 19.5 g of the desired API after a 4 h process.

In a recent example,[21] the choice of solvent was vital in a scaled flow process converting 6-nitroanthranilic acid **27** into a sparsely soluble diazonium salt, an intermediate towards the generation and use of nitrobenzyne **30** (Scheme 10). It was crucial to retain the diazonium intermediate in solution as this species is shock sensitive in the solid form. As benzynes are known to react with several solvents including DMSO and DMF, alternative polar aprotic solvents led to the use of diethylene glycol dimethyl ether (diglyme, DG). Upon mixing of isoamyl nitrite (**28**, generated in situ) with 6-nitroanthranilic acid dissolved in DG with acetic acid (1 equiv.), a homogeneous solution of the diazonium salt was formed at low temperature. This was then combined with a stream of cyclopentadiene (3 equiv. in DG) prior to entering a heated flow reactor where both the benzyne formation and the subsequent Diels-Alder reaction between nitrobenzyne and cyclopentadiene occurred. The desired cycloadduct **31** was obtained after passing through a BPR which offered control over the release of gaseous by-products (N_2 and CO_2). Crucially, this multi-step flow process (Scheme 10) accomplished the synthesis of the desired product without clogging issues and highlights the importance of early-stage solvent consideration (3 steps: 250 s residence time, 242 g isolated yield, purity 99 %).



Scheme 10. Multistep flow synthesis where solvent optimisation prevented precipitation.

The previous examples demonstrated that ethereal solvents can enhance solubility of intermediates. A related observation was reported in a scale-up campaign for an API intermediate by researchers from Merck.[22] The process involved an aldol condensation rendering an enone species (**35**) which subsequently underwent cyclisation to a pyrimidone (**36**) in the presence of ammonia (Scheme 11).

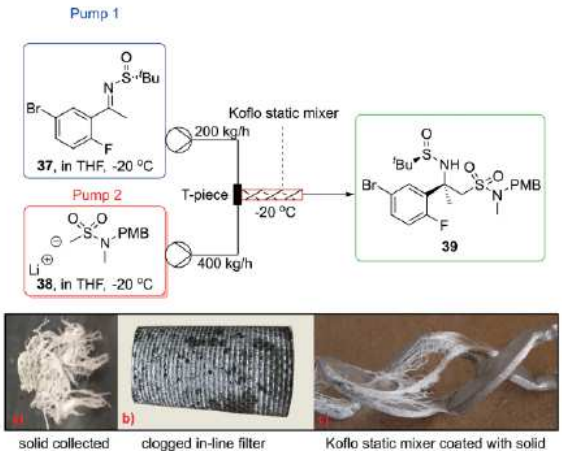


Scheme 11. Synthetic strategy to produce pyrimidone **58**.

The aldol reaction required low-temperature flow processing. It had been established that KO^{t}Am was a suitable base in the aldol process using toluene as solvent to provide homogeneous conditions. The initial set-up, therefore, combined a stream containing both substrates (0.6 M, ester **32** and enone **33,** in toluene) with a stream of commercially available KO^{t}Am (1.7 M, in toluene) using stainless steel tubing. As the substrate solution was close to saturation, precooling was limited to –8 °C, whereas the base solution was precooled to –30 °C prior to mixing in a T-mixer. The resulting aldolate solution was then

charged in a semi-continuous manner into a receiving vessel (at –10 °C) containing NEt_3 and trifluoroacetic anhydride (TFAA) to afford the diene product. This set-up effectively provided the desired product in a short residence time (15 s, 11.2 mL/min) on batches of 25 g ester substrate **32**. The transfer to a continuous pilot plant resulted in several challenges including the formation of a thick gel-like mixture that was attributed to the ingress of water to the base feed. The resulting KOH was not soluble in toluene and thus led to fouling along the reactor walls and at the heat exchanger of the KO^{t}Am stream. To overcome these issues, THF was evaluated as a co-solvent and satisfactory results were obtained when using 10 % of THF in toluene. Additionally, solids that formed over time in the KO^{t}Am source vessel were removed via decanting and in-line filters were employed to avoid solids entering the flow system. Subsequently, a modular flow reactor skid was fabricated processing 200 kg of starting material at a throughput of 1.6 L/min.

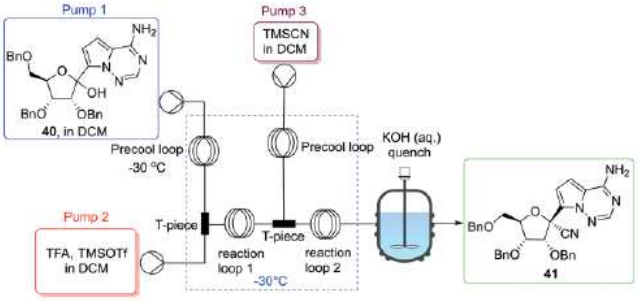
Whilst solvents like THF can overcome clogging related issues in continuous flow processes through increased solubilization, solvent contaminants can also be the root cause of reactor fouling and clogging. An example was recently reported by researchers at Merck during a scale-up campaign towards Verubecestat (Scheme 12).[23] When developing the synthesis of a key intermediate it was found that flow processing provided a 20 % increase in yield for a Mannich reaction between a chiral Ellman sulfinyl ketimine (**37**) and a methyl sulfonamide anion (**38**) due to the suppression of unproductive proton transfer as observed in batch mode. Flow processing was thereby employed in both the deprotonation step (using *n*-HexLi, 2.3 M, THF, –20 °C) and the subsequent Mannich reaction.



Scheme 12. Reactor fouling attributed to the presence of poly-THF. Reprinted with permission from N. R. Rivera, B. Kassim, P. Grigorov, H. Wang, M. Armenante, X. B. A. Lekhal, N. Variankaval *Org. Process Res. Dev.* **2020**, *24*, 2556–2561. Copyright (2020) American Chemical Society.

The study reports that a pronounced reduction in flow rate (from 800 kg/h to ca. 50 kg/h) was observed when lowering the temperature from 0 °C to –20 °C. Initial investigations after warming the set-up and disassembling its components did not identify any issues relating to water ingress or other contaminants in the system. However, when disconnecting the components whilst still cold, a white fibrous solid was observed both on the inline filters and the static mixer. The analysis identified the material as poly(THF) present in small amounts in a particular lot of THF. Despite the low concentration of this contaminant, the high shear environment of the static mixer is believed to have caused the gradual deposition of poly(THF) at low temperatures through hydrodynamic cavitation.

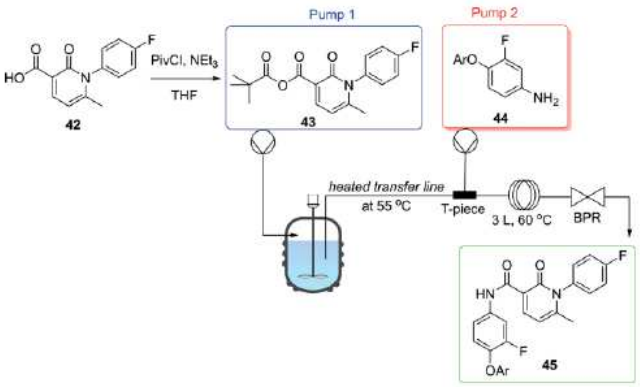
Low temperatures of precooled stock solutions or reactor sections can have a profound effect on continuous processing due to increased viscosity or reduced solubility of components as exemplified by Gilead during the development of a continuous cyanation reaction for the antiviral Remdesivir as shown in Scheme 13.[24] Continuous flow delivered the desired product (**41**) in high yield and diastereoselectivity whilst providing increased safety in view of the HCN gas being generated. Brönsted acid (TFA, 1 equiv.) in combination with TMSOTf yielded reproducibly high stereoselectivity when coupled with low temperature (–20 °C to –40 °C). At –40 °C, an increase in backpressure was observed that eventually plugged the reactor. This was due to the partial crystallization of TFA (melting point –15.4 °C) in the reaction mixture (TFA/TMSOTf, DCM). The resolution to the problem was to increase the temperature to –30 °C. This small adjustment allowed for a stable flow process and provided satisfactory results when performing the cyanation reaction repeatedly on lab-scale (2.75 kg substrate) and subsequently at plant scale (up to 250 kg substrate).



Scheme 13. Continuous flow approach towards the synthesis of Remdesivir intermediate.

The necessity to carefully control the temperature of the reactor zone was additionally highlighted in a publication by Eli Lilly for the synthesis of Merestinib (Scheme 14).[25] One of the steps features an amide formation between two advanced reaction partners. Mixed anhydride formation of the acid substrate **42** with PivCl/NEt_3 led to excellent reactivity with the aniline partner (**44**). The mixed anhydride was prepared in batch mode and the by-product (NEt_3·HCl salt) was removed by filtration prior to use in the coupling step.

Peristaltic pumps delivered the mixed anhydride and the aniline into a CSTRs (4 min residence time), prior to transfer into a PFR maintained at 60 °C and 1.7 bar backpressure. Crucially the chosen concentration of the amide mixture was close to the saturation point to benefit from faster kinetics and lower process mass intensity (PMI) of the process. Reactor fouling triggered by product precipitation below 35 °C could be prevented by using a heated transfer line (55 °C) into a surge vessel. However, partial blockage of the anhydride feed was observed after



Scheme 14. Synthetic route towards Merestinib.

55 h of operation. This was monitored by inline HPLC which recorded an 80-fold increase of residual aniline. It was subsequently established that incomplete anhydride formation caused accumulation of further NEt_3·HCl salt in the anhydride feed after the initial filtration. Detailed knowledge on maximum solubility of product mixtures coupled with suitable PAT for detecting developing process instabilities is essential to mitigate the potential of reactor fouling.

2.4. PAT for Flow Chemistry

Manufacturing campaigns can be supported through the use of in-line analytical methods to prevent and resolve clogging issues and to ensure that the material produced conforms to quality requirements. For high-throughput commercial manufacture, the introduction of PAT can ensure non-conforming material is diverted to waste at a point prior to product collection thus protecting the quality of material already produced within specifications. PAT facilitates in-line, real-time monitoring of a flow process.[26] PAT can be an additional, expensive investment although significant reductions in cost have been observed in recent years with further development of bench-top devices and flow-through cells. Often the choice of in-line analytical technique will be IR, Raman, or UV/Vis.[27] For many reactions, sample preparation can often be required, thereby offline monitoring via GC or HPLC using existing analytical instrumentation often proves more than sufficient for lab development of flow processes. It is important to consider the time between sampling and analysis and critically evaluate all results obtained to ensure data is representative of reaction performance. The use of real-time analysis will lead to reliable and faster process development compared with offline analysis, however, the majority of processes discussed within this article have not availed of PAT. Instead, the authors report the use of offline sampling including HPLC, IR, ^{1}H NMR, or LCMS. In terms of real-time monitoring of flow reactions, temperature fluctuations are often recorded using inline thermocouples or using thermal mass flow meters (ref.[7,10]). Ref.[20] also used integrated FTIR which allowed for effective scale-up with minimal impact from insoluble degradants. One example with inline HPLC reported is ref.[23].

2.5. Troubleshooting Flow Process

The flow chemistry community would most likely be in agreement with the authors that the development of flow processes is by no means trivial and a "one-size-fits-all" approach is certainly not viable for troubleshooting. This article has highlighted some specific examples where elegant solutions were used to circumvent some of the common pitfalls associated with flow processes and Table 1 serves as a basis for consideration when issues are encountered.

Table 1. Highlighted problem statements and solutions.

Problem Statement	Solutions
Limitations around cryogenic batch capabilities for Pharmaceutical and CDMO	Considerations for development of organolithiations include; *Use of commercially available n-BuLi* – circumvents the requirement for pre-dilution and allows flow process to be designed to charge reagent directly from cylinder. *Substrate concentration* –Critical for development to fine-tune process robustness and demonstrate concentration whereby all reagents remain in solution but maximise throughput. *Reaction temperature* - Under continuous flow higher temperatures can often be used (even up to ambient) than for the associated batch process. However, starting at -30 °C gives best chance of success as going straight to higher temperatures may cause lead to instability of reaction components. It is better to begin flow development at a lower temperature where you may not achieve reaction completion but can account for mass balance- something which is difficult if observing degradation. *Observation of undesired side reactions* – butylation/proton quench of lithiated species from *n*-BuBr or wet solvent can be prevented by short residence times to ensure effective electrophilic quench. *Mixing importance* – Lithiation chemistry is typically fast and if experiencing difficulties it is important to consider the flow rates/geometry which determine the mixing efficiency.[17]
Solid precipitations can cause reactor fouling/ clogging	If source of precipitation is; *Reaction mixture is a slurry* – For lab scale consider sonication to prevent sedimentation and subsequent reactor fouling. Larger scale flow processes may require agitation with commercially available equipment (Coflore® from AMT or HANU reactor from Creaflow). *Insolubles formed as by-products in reaction* – consider dilution of reaction stream solvent choice and/or reaction temperature. *Unknown solids accumulating* – potentially could be a result of reagent quality. Employ risk mitigation strategies to assess suitability eg. polyTHF can be present in certain lots of THF.

3. Conclusions and Future Outlook

The benefits of flow chemistry over batch are well documented, however, the uptake of the technology in commercial produc-

tion can be slow. Flow chemistry usage is multifaceted and fundamental hurdles include the lack of expertise, equipment availability, and often an internal drive to make flow processes a reality. Increasing publications of commercially relevant examples showcasing success along with the necessary risk mitigation strategies to ensure successful delivery and alliance of academic/industrial partners are driving knowledge transfer. An understanding of the root cause of potential failure of a flow process must be evaluated on lab scale in order to put in place the necessary risk mitigation for scale-up. This includes careful consideration of hardware utilized including material of construction, flow path geometries, and dosing line design with stability assessments of reagents/products imperative. The expectation for continuous flow capabilities at Pharmaceutical and CDMO site(s) is increasing and as a "one-size-fits-all" approach is not viable for continuous flow, the development of modular, flexible equipment trains applicable for a range of chemistries, combined with the development of in-house expertise is critical. The increasing maturity of the technology allows commercial providers to develop in-house platforms accessing a wide range of chemistries often increasing the volume of supply within competitive timelines for their clients.

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Keywords: Borylation · Flow chemistry · Industrial Chemistry · Lithiation · Reaction scale-up

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Flow Chemistry

Flow chemistry, on paper, is a straightforward concept with most chemists from academia and industry now well versed in the associated advantages. This Minireview highlights some of the common pitfalls and considers solutions to successfully navigate implementation of cryogenic flow processes or those whereby solid handling is required. This should accelerate the development of similar processes and help chemists to avoid the pitfalls!

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