A Perspective on Continuous Flow Chemistry in the Pharmaceutical Industry

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ABSTRACT Continuous flow manufacture is an innovative technology platform which is gaining momentum within the pharmaceutical industry. The key advantages of continuous flow includes faster and safer reactions which can be more environmentally friendly, smaller footprint, better quality product and critically, the ability to perform chemistry that is difficult or impossible to do in batch mode. Globally, significant efforts have been made to develop the manufacturing flexibility and robustness of processes used to produce chemicals in a continuous way, yet, despite these scientific developments, a major challenge for industry is the established application of flow technology to commercially relevant examples. The identification of opportunities to apply flow solutions to current processes is also critical to the success of this new technology for pharmaceutical and fine chemical companies. This review highlights industrial hurdles, the

importance of education and showcases recent (2018-2019) and relevant industrial examples where utilisation of flow technology has been successfully performed.

KEY WORDS Flow chemistry, continuous manufacture, industrial perspective, sustainable, green manufacturing, electrochemistry, biocatalysis, Active Pharmaceutical Ingredient (API)

Introduction

Continuous flow simply is the performance of chemical reactions in a pipe or tube rather than in a traditional batch stirred vessel, or as a cascade using continuous stirred tank reactors (CSTR). Moving from batch to continuous chemical processing is now an important goal for the pharmaceutical, speciality chemical and flavour and fragrance (F&F) industries.[1,2] Continuous flow chemistry describes the performance of a reaction in a continuous manner within narrow channels exploiting these intrinsic properties resulting in strictly controlled reaction conditions.[3] The production of advanced intermediates for fine chemicals and Active Pharmaceutical Ingredients (APIs) has primarily relied on traditional batch processing. The use of simple batch reactors arises from the fact that the synthesis of these intermediates often involves a wide variety of reactions and simple stirred tank reactors offer a great deal of versatility and flexibility. However, such batch reactors also have some important limitations. One driving force behind the need for adoption of continuous manufacturing as a technical innovation is the accessibility to reactions which are more difficult to perform in batch mode.

Continuous flow processing has been coined to be inherently safer due to a myriad of reasons including lower reaction volumes, better temperature control and ability to accommodate higher

pressures without risk. Flow processing offers better selectivity, can be more environmentally friendly, has a smaller footprint and can offer an accelerated scale-up route from proof of concept studies to large scale manufacture (Figure 1). The improved selectivity, and often yield, are attributed to more efficient heat-transfer[4] and mixing efficiency[5,6] which is achievable in the flow system. The smaller-scale architectures present in the flow system offer higher surface area to volume when compared with traditional batch vessels.[7,8] These advantages can address a number of key priority areas including sustainable chemistry to lead to cleaner, more efficient, less consumptive and safer chemical processes, as well as the area of novel and efficient chemical synthesis. It is also well accepted that future industrial systems using continuous flow will lead to increased automation in manufacturing operations thereby lowering Operating Expenditure (OPEX).

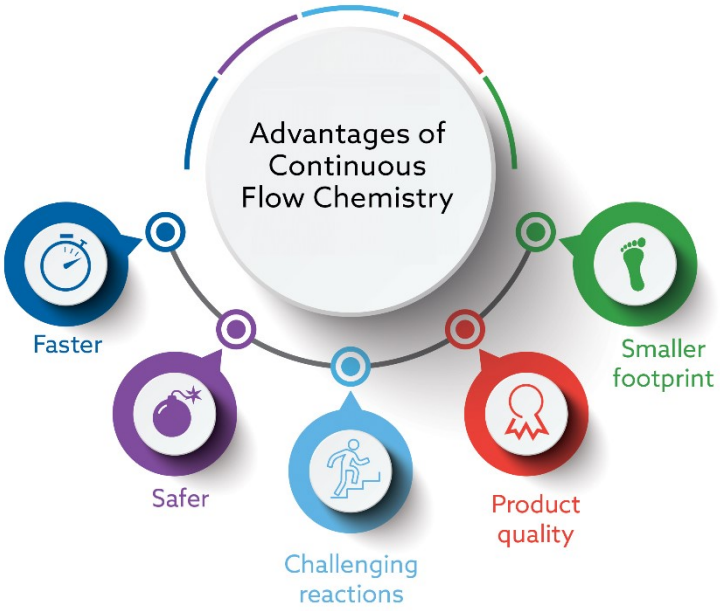


Figure 1: Strategic drivers for the adoption of continuous flow approaches for the synthesis of chemicals.

Industrial Hurdles

There are a multitude of continuous flow publications over the last decade and the number of publications from a recent SciFinder search for the topic 'continuous flow chemistry' shows a steady increase, however, the vast majority of these have come from within the academic sphere (Figure 2).

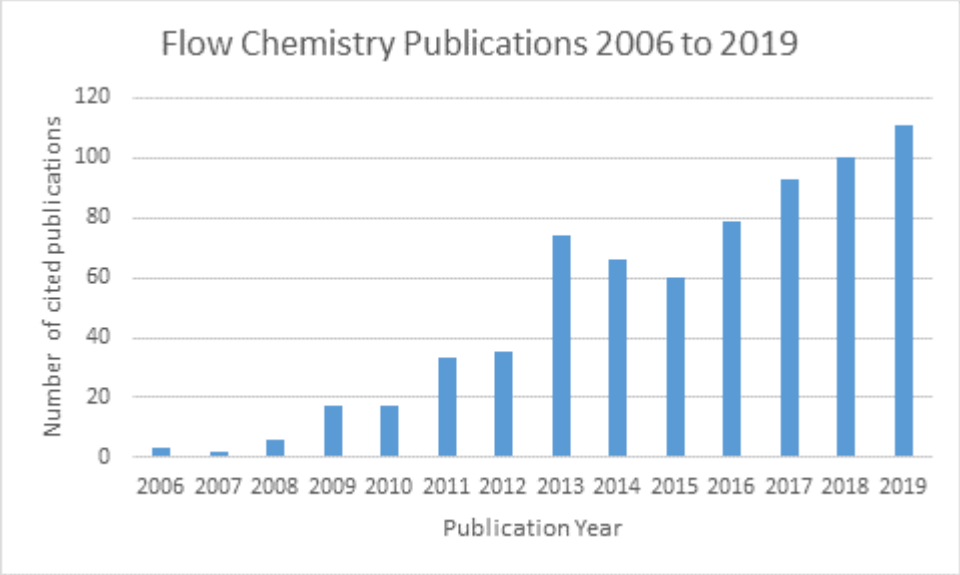


Figure 2: Flow chemistry publications from 2006 to 2019.

There are several identified factors which to date have slowed the mainstream adoption of continuous manufacture within the chemical industries and are outlined in points A to C:

A. **Cultural change**: The adoption of continuous flow as an armoury in the chemical tool kit for process chemists is often restricted due to the ambitious timeline deliveries set by the industry. In many cases, there is no time to consider or even redesign the chemical batch process into flow. Moving from a typical batch process to flow methodology, a critical evaluation of the chemistry is needed to determine if there is an advantage (cost analysis/suitability of process in flow). In addition, the redevelopment requires and relies heavily in many cases on chemical engineering input[9,10,11,12] to redesign a suitable flow

architecture. The chemical industry's prerequisite for adoption for any new technology is demonstration of the significant economics to lower the cost of production compared to batch. They require an understanding of speed to delivery and off-the-shelf ready to use systems to minimise timelines of implementation.

B. **Management support**: As continuous manufacture becomes more mainstream within the industry, it will be expected that continuous platform offerings are available at innovator and supplier sites. It is time now to build business cases to invest before falling behind industrial trends. The adoption of flow processes over batch could result in lowered Capital Expenditure (CAPEX) investments and OPEX costs. In addition, flow offers the ability to perform more hazardous and batch-inaccessible chemistries thereby unlocking access to products that would have been difficult to be competitive in. Changing culture and technology can be an expensive transition, but must be embraced, business cases developed, scrutinized, and driven to completion before falling behind the competition. The era of companies having and using large batch reactors and equipment trains is changing and flow offers value generation including production cost savings, minimised safety issues, environmental advantages and access to novel functional group interchanges. In the pharmaceutical industry, drug identification and treatment is getting more sophisticated and the medicines being identified are highly effective meaning smaller volumes of API are needed. This paradigm shift makes the business case for major investments even more challenging.[2]

C. **Education**: Lack of trained personnel has slowed the growth of the continuous manufacture industry. Critical to the success of continuous flow acceptance is training of the next generation of scientists which will deliver chemists, chemical engineers, QA and

regulatory personnel with the knowledge and expertise necessary to support implementation. More recently there has been a surge in interest in continuous manufacture with the FDA supportive of the adoption of continuous manufacturing for API synthesis due to the improved quality control. Dr Janet Woodcock, FDA CDER director, has said the 'US FDA continue to support innovation' recommending 'pharma manufacturers and contract manufacturing organisations (CMO's) should begin to consider the switch as in the long run it will end up saving companies time, money and space'.[13]

Importance of Education

Continuous flow chemistry is not a new concept, in fact continuous processing at bulk scale has been used for the production of chemicals in the petrochemical industries for 100's of years.[14] However, its adoption into the pharmaceutical industry has been much slower. Considering the advantages of flow chemistry, and its increasing relevance for pharmaceutical and speciality chemical industries, it is imperative that continuous flow education is increased to ensure the adequate training of future staff.[15] Engaging with industry to tailor programmes and ensure continuous flow is an integral and core discipline in undergraduate courses will help accelerate the cultural change and understanding of why one would transition from batch to flow processing. Undergraduate chemistry degrees focus on the fundamental aspects of chemistry and chemical reactions. Flow chemistry in comparison with traditional batch chemistry is a much closer discipline to chemical engineering and so inclusion of such in an undergraduate programme will be advantageous for the chemists of the future. Teaching laboratories are typically equipped with cheap, easy to use equipment designed for educating on the basic principles of chemical reactions. Inclusion of continuous flow at this stage in a chemist's career is critical in training to circumvent and address the above reasons of cultural change which are deemed hurdles to the implementation.

From an academic perspective it can be stated that currently only very few universities offer tailored courses on continuous flow chemistry and process engineering that are typically delivered to final year undergraduate students through chemistry or chemical engineering departments respectively. It is even more unlikely that such courses are complemented by suitable laboratory classes due to constraints in the curriculum and the availability of appropriate tools or flow chemistry set-ups that would necessitate redesigning labs and investment in new flow-related equipment and consumables. There is, however, a noticeable trend that, one by one, chemistry departments are incorporating modern synthesis technologies into their teaching curricula to showcase undergraduate and sometimes postgraduate students the value and relevance of continuous flow technology in both academic and industrial settings. In addition, students may get exposure to flow chemistry through research projects (undergraduate and postgraduate level), internships, dedicated workshops that are jointly run by academics and industrial partners, or at later stages in their studies with participation at scientific meetings.

It has often been stated that students must be exposed to new synthesis technologies that are revolutionising the way we perform chemical reactions much earlier in their studies. To achieve this, it will be paramount to identify suitable means to incorporate the performance of continuous reactions into undergraduate laboratories at an affordable price. In view of this, modern 3D-printing technology[16] may play a key role as it can cheaply provide simple flow reactor components (mixers, micro-reactors) that can be coupled with plug-flow reactors which are cheap and easily assembled from coiled PTFE tubing and suitable connectors. The concept of building custom flow rigs is beneficial training for chemists in order to develop flow chemistry philosophy whereby the chemist has enough knowledge to adapt the technology to the chemistry rather than vice versa. A remaining issue will concern the availability of affordable yet robust pumps, be it

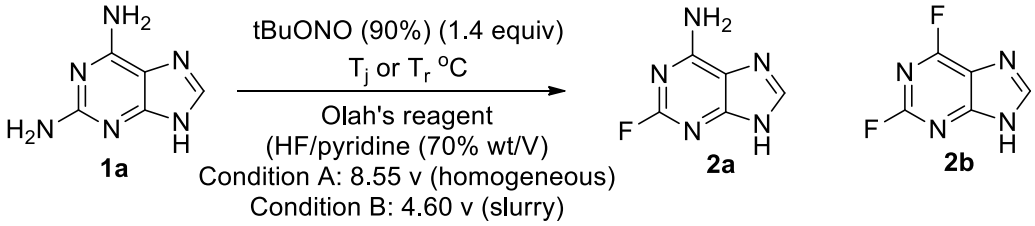
syringe, piston or peristaltic pumps or alternatively the assembly of home-built systems. In this scenario, it can be expected that the students will not only gain a better understanding of the different components, but moreover will take ownership of their set-up and will be encouraged to make adjustments based on a thorough understanding of its assembly. Pleasingly, several academic groups have started to publish research papers including detailed accounts for sourcing vital components and with short videos demonstrating the assembly of home-built flow systems.[17]

Funding initiatives supported by government agencies, industrial partners and equipment vendors will likely play a significant role in supporting these endeavours. Equally, collaborations between industrial partners and academics are imperative in order to fast track the dissemination of key flow chemistry techniques already embedded within universities and will be a key driver towards the successful education of chemists in the industrial environment.

Overcoming the challenges

There have been an increasing number of industrial examples reported in the literature on multi-kg scale and this narrative will highlight such examples. A recent paper from Merck, highlights a one-step diazotization synthesis of 2-fluoroadenine using Olah′s reagent (hydrogen fluoride pyridine complex) under continuous flow.[18] The goal was to improve the yield and purity of the intermediate through a robust flow process. The selective introduction of fluorine atoms in biologically active molecules is driven by the similarity in size of fluorine and hydrogen atoms with organofluorine compounds typically demonstrating higher biological and chemical stability.[19] Specifically, the interest in 2-fluoroadenine nucleosides is increasing[20] and although many efficient synthetic strategies[21] are reported, these encounter difficulties due to the high polarity and lack of solubility in organic solvents. Existing methods are long, require protecting group

manipulations or employ expensive starting materials. Marzijarani *et al.* present the synthesis of 2-fluoroadenine in continuous flow where a thorough understanding of heat transfer and process development resulted in an efficient synthesis in high yields and selectivity. Initial process understanding of the batch mode was carried out (Scheme 1) with scaling up showing the increasing formation of the difluoro impurity. Investigations discovered that the reaction was rapid, highly exothermic and sensitive to temperature rise. The lack of robustness toward even minor changes in operating conditions led the authors to explore the use of continuous flow to exploit the better heat transfer achievable.



Scheme 1: Synthesis of 2-fluoroadenine.

The authors report the single step synthesis of 2-fluoroadenine from commercially available and inexpensive 2,6-diaminopurine through diazonium chemistry without prefunctionalisation (Figure 3). The reaction is extremely exothermic and rapid with poor batch selectivities and low conversions attributed to the difficulties in controlling the temperature. Critical to process improvement was an understanding of the impact of temperature control, heat transfer and residence time. The process using continuous flow required less equivalents of *t*BuONO and resulted in improved selectivity which translated to yield increases of approximately 10 % higher than batch mode (82.4 % isolated yield). With a higher selectivity of 2-fluoroadenine being produced from the flow process, the isolated product material had >98% purity with a single crystallisation circumventing chromatographic purification.

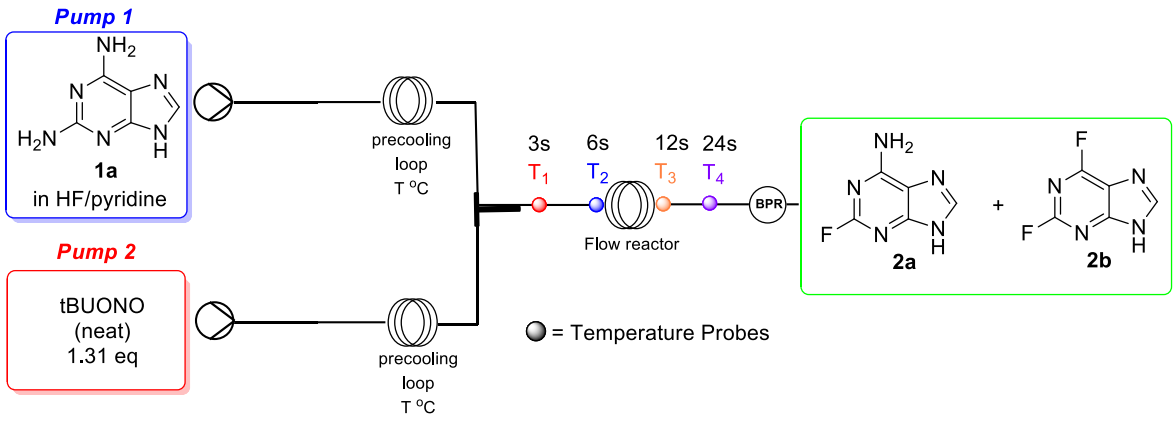


Figure 3: Flow mediated diazotization synthesis of 2-Fluoroadenine using Olah's reagent with thermocouples for understanding of reaction temperature profile.

In order to better understand the reaction exotherm and the impact this had on the selectivity of the reaction under continuous flow operation, the reaction kinetics were modelled. The evidence of a large exotherm indicated the slow addition of the nitrite could be advantageous, however the active species had shown a short lifetime as evidenced by low conversion in a semi-batch process. To generate a reaction temperature profile, thermocouples were inserted into the reactor tubing to measure the temperature at various positions. This allowed understanding of the temperature rise immediately after mixing (3 secs) and as the reaction stream continued to react (6, 12 and 24 seconds respectively). The temperature was recorded for two tubing diameters (0.063inch and 0.03inch id) with a notable difference between the two noted. In thinner tubing the temperature never rose above 12 °C, however in larger tubing the maximum temperature observed was 27 °C and it remained above 0 °C for a longer period of time resulting in the decomposition of the nitrite source and consequently lower conversions and selectivity obtained.

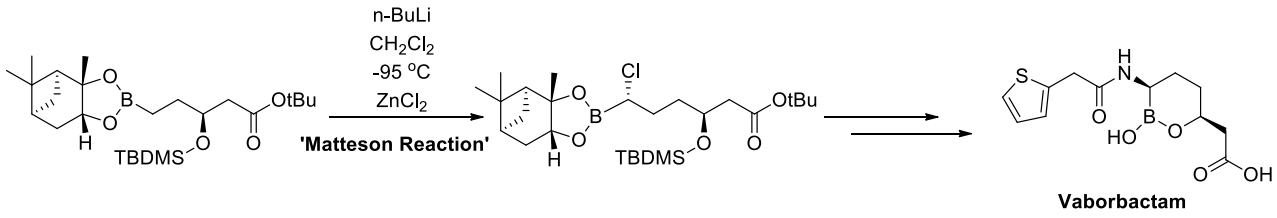
As a strategy to scale up, the bath temperature was lowered to -8 °C when utilising the thicker tubing and this was found to achieve similar results in control of exotherm comparable with the thinner tubing. This confirmed the importance of the internal temperature on the ability to further

scale the reaction, however running at lower temperatures risked freezing of *t*BuONO and reactor clogging. An alternative strategy employing a first reactor coil with narrow diameter to improve heat transfer in the mixing phase was then coupled to a wider bore tubing to facilitate an acceptable residence time to allow reaction completion. This provided efficient heat transfer for the critical early stages of the reaction and a greater volume for the reaction to reach completion in a larger diameter tubing reducing the pressure drop. This approach was demonstrated with success with both a 2 and 10 mL/min flow rate. Further advancements were made to allow a 20 mL/min flow rate by splitting the addition of *t*BuONO into multiple portions to decrease the energy released into the reaction stream at any one time. A multiport system with four nitrite streams was demonstrated in 0.063inch tubing with this approach deemed scalable as the number of sequential addition points of *t*BuONO is dependent on the heat removal rates at the desired reactor scale.

The process developed and the methodology applied highlights the key considerations which require focus for designing a continuous process for highly exothermic reactions. The platform allows chemists to execute hazardous chemistry with increased safety and reliability. The safer process developed synthesised an important intermediate for a low-dose pharmaceutical drug by controlling heat formation in the reaction and using an automated platform to circumvent exposure of the operator to the reaction stream.

The design, development and scale-up of a continuous process for a Matteson reaction has been described by Schuster *et al.* to produce a key intermediate in a pathway towards the β-lactamase inhibitor Vaborbactam.[22] In this synthesis of Vaborbactam there are a number of opportunities where continuous manufacture has been demonstrated to improve on efficiency and scalability. A key step is the Matteson reaction[23] which is performed at very low temperatures (-95 to -100 °C). The ability to regulate tight temperature control is very difficult to maintain in batch mode without

specialised equipment. Scheme 2 shows the Matteson reaction which involves a diastereoselective chain elongation of boronic ester to an α-chloroboronic ester. The reaction involves generation of (dichloromethyl)lithium in the presence of zinc chloride necessary to achieve high diastereoselectivity.[24] The use of (dichloromethyl)lithium requires very low temperatures as it is a labile species prone to carbene formation through α-elimination of LiCl.[25] Cryogenic reactions are particularly difficult to scale in batch mode due to the difficulties in dissipating the heat and control of exotherm. Mixing is critical to control any potential hot spots and ensure correct stoichiometry at point of contact. Continuous flow is often used as an approach to circumvent such issues, and this is the case with the Matteson chemistry. One additional challenge for flow is the ability to avoid precipitates (salts) or to handle them freely ensuring a robust scalable process without blockage. The successful use of (dichloromethyl)lithium under continuous flow conditions has been reported elsewhere by Novartis.[26]



Scheme 2: Matteson reaction used in the synthesis of Vaborbactam API.

Reaction feasibility was initially assessed using a set-up analogous to the reported Novartis protocol, using stainless steel T-pieces and reaction coils, controlled by four HPLC pumps and a cooling bath for reactors 1-3 with reactor 4 run at ambient, as shown in Figure 4. In the initial experiments a diastereomeric ratio of only 89:11 was obtained. Further improvements were made with application of a larger excess of zinc chloride giving a diastereomeric ratio of >95:5, however under flow conditions this resulted in precipitation and consequently reactor clogging. The flow set-up was modified to have the process stream leaving the flow reactor to be quenched in a batch

vessel containing precooled zinc chloride solution. Slight excess of n-BuLi at -80 °C and increased residence time gave near full conversion and a diastereomeric ratio of 97.7:2.3.

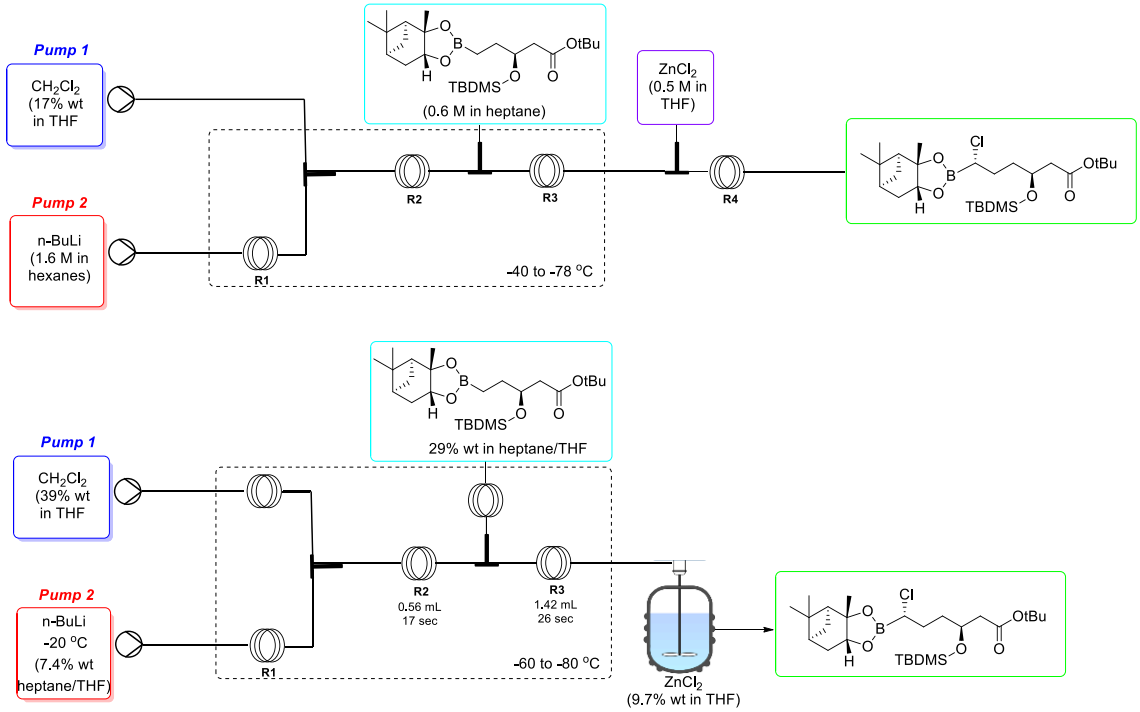


Figure 4: Flow set up for reaction feasibility experiments and improved flow set-up utilising a batch vessel.

The modified lab scale reactor set-up was transferred to pilot scale capable of 40 kg output of Matteson product. With a scaled-up flow reactor built, further fine tuning was carried out to define the equivalents of n-BuLi, residence times and reaction temperatures all whilst demonstrating the flow reactor could be run over a long period of time to provide α-chloroboronic ester in high yield (>90%) and high selectivity (>95:5) with pilot plant runs in the scale of 15-25 kg. Further scale to commercial manufacture involved process validation including defining of reaction start-up and shutdown. The registration campaign produced several hundred kg of material in high yield and purity followed by a process validation campaign generating several metric tons of the Matteson product. The product, process and equipment passed an FDA audit in 2017.

The batch quench with $ZnCl_2$ quickly became a bottleneck for increasing the throughput of the process. In a move towards a fully continuous process, two concepts as shown in Figure 5 were devised. The customised loop reactor system for the rearrangement with the Lewis acid was developed and scaled to production scale. The continuous loop quench was comparable to the batch process, highly pressure resistant and offered a safe mode of operation. It had low construction costs (simply a tube, pump and heat exchanger) and was easily scalable as the volume circulated in high flow is significantly higher than the reaction mixture entering and exiting the loop. The continuous stirred tank on the other hand requires a Hastelloy® vessel to be pressure resistant incurring high costs and the risk of hot spot formation.

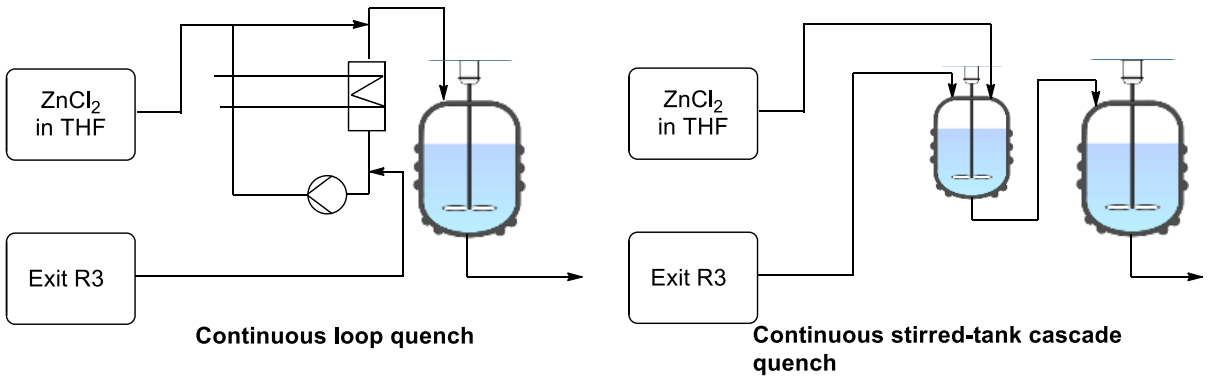


Figure 5: Approaches to move to a fully continuous process for the Matteson reaction.

Continuous flow took an unscalable batch process for the Matteson reaction to an operable manufacturing process delivering product in high quality and high yields. The demonstration of lab to commercial manufacture within the timelines of a pharmaceutical development process gives good merit for industrial engagement in similar circumstances. The new process allowed for industrial scale production with improved economics and a reduced ecological footprint.

Recently, Kappe and co-workers reported a safe and scalable methodology for the Wolff-Kishner reduction under continuous flow.[27] The Wolff-Kishner reaction involves the use of

hydrazine in the presence of a strong base for the conversion of the carbonyl functionality present in aldehydes and ketones into the reduced methylene moiety.[28] The use of low cost hydrazine as the reducing agent in combination with caustic base yields an atom efficient, environmentally friendly method for the deoxygenation of aldehydes and ketones to alkanes. The reaction requires harsh and corrosive reaction conditions (200 °C and 50 bar) so encounters problems with traditional production scale reactor materials such as stainless steel, glass and/or any other type of polymer coatings. As well, the use of hydrazine hydrate at production scale has a variety of concerns surrounding its usage including high toxicity, potential carcinogenic properties, high corrosive nature and in particular accumulation can result in explosions if the volatile build up in the head space of a batch vessel occurs.[29] The use of corrosion resistant silicon carbide unlocks the possibility to perform the Wolff-Kishner reaction at production scale with continuous flow offering improved handling, lower excess requirements and improved safety of the hydrazine reagents by eliminating gaseous headspace and reducing exposure risk to the operator.[30] The flow step is shown in Figure 6 and involves two set-ups including (i) a single feed protocol for substrates not prone to fast hydrazone formation and (ii) a two feed protocol allowing preformation of the hydrazone before addition of base.

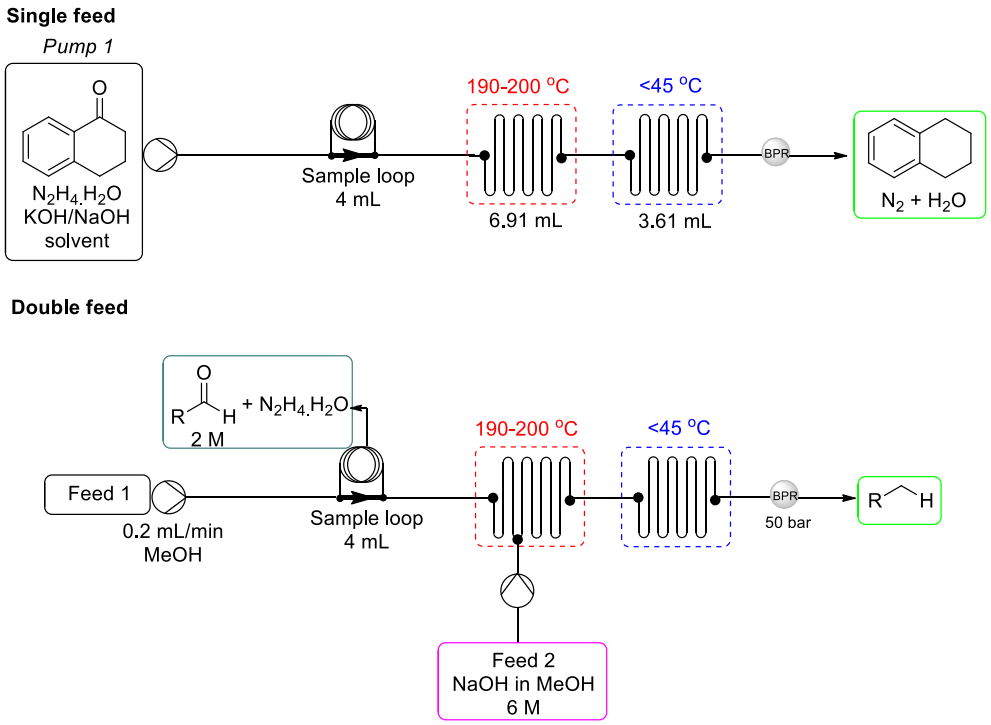
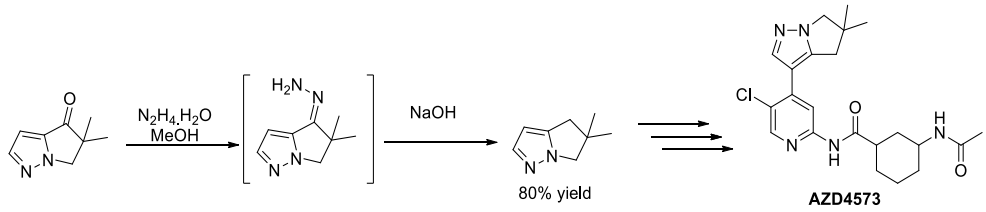


Figure 6: (i) Single feed and (ii) double addition flow protocols.

The developed methodology was applied to an API synthesis for AstraZeneca for an intermediate in the pathway to **AZD4573** which has been demonstrated to be a potent CDK9 inhibitor as shown in *Scheme 3*. The two feed approach was used and the overall reaction time decreased to less than 20 minutes with the hydrazine loading reduced to 1.5 equivalents compared to 5 in the batch process. The batch process in diethylene glycol suffered from poor yields. Under continuous flow the desired intermediate was achieved in 80% yield with >99 % purity after a simple extraction with water and ether.

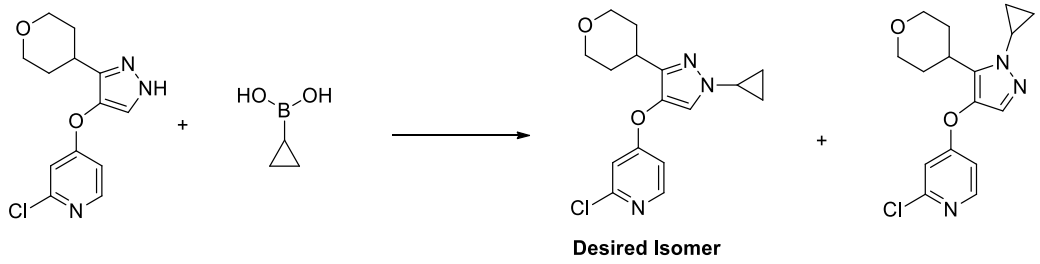


Scheme 3: Wolff-Kishner reaction used in the synthesis of a key intermediate en route to AZD4573.

The reaction was demonstrated over a longer run time using α-tetralone as a model reaction. A total of 96 mL of reaction mixture was processed to give 12.1 g of material (81 % yield) of 1,2,3,4-tetrahydronaphthalene after workup which corresponded to a productivity of 1.6 g h^{-1} and a space time yield of 152 g L^{-1} h^{-1}. This took advantage of the Protrix reactor from Chemtrix which allowed processes to be developed on lab scale and directly transferred to a production scale reaction maintaining the thermal control and corrosion resistance.[31] The major advantage of this technology is that the performance of the reactor remains unchanged as scale increases as 'smart dimensioning' maintains the heat and mass transfer parameters.[32] Under this principle up to 13.7 kg of material per day could be synthesised to fully exploit the potential of such an atom-economical reduction process.

Safety concerns and poor selectivity from aerobic oxidations mean that despite the benefits of high atom economy and low cost, there are limited examples in the synthesis of API's. The development and scale-up of a continuous aerobic oxidative Chan-Lam coupling has been recently reported to produce the penultimate precursor of a pyrazole-derived API.[33] The identification of robust homogeneous conditions for the oxidative C-N coupling of interest and the use of diluted air allowed for the continuous process to be implemented at manufacturing scale with improved safety and selectivity using a vertical 'pipes-in-series' reactor. Oxidations are important transformations as they increase chemical complexity within a molecule and in particular molecular oxygen (O_2) is the ideal oxidant for such transformations as it is low in cost, highly abundant and aligns with green chemistry principles.[34] Reactions involving gases are difficult to scale due to safety concerns and mixing issues (gas solubility vs temperature/pressure/contact surface area) however use of gas in stoichiometric amounts is atom efficient. Continuous flow

reactors are safer and more practical in an approach for manufacturing using gas phase.[35] Copper-mediated coupling of N-nucleophiles with boronic acids was first reported by Chan and Lam[36] in 1998 with more recent reports of mild conditions using catalytic copper and O_2 as the terminal oxidant. Eli Lilly had identified a Chan-Lam coupling of a pyrazole and cyclopropylboronic acid as shown in *Scheme 4*.[37] The process was demonstrated as a multi-kg GMP campaign.



Scheme 4: Cu-catalysed Chan-Lam coupling to perform the penultimate step to API.

The flow reactor design consisted of vertical 'pipes-in-series' reactor using both bubble flow and segmented flow regimes with oxygen mixed into a moving stream of starting material solution at the beginning. The reactor design was safely and successfully scaled maintaining high vapour/liquid mass transfer rates. Kinetics were unaffected by reactor volume and by-product formation was effectively minimised with starting material visibly diminished after ~2 hours. The reaction was shown to be nearly independent of oxygen pressure and steady state profile for 2 L reactor shows reliable performance over 50 hours. As the reaction is slow, long residence times and large reactor volumes are required for full scale up manufacturing. Steady-state performance (process robustness) and safety wrt O_2/N_2 and high pressure (290 psig) were main drivers for flow development. The key to a safe, scalable execution of an aerobic oxidation reaction was the use of diluted air as the oxygen source and identification of homogeneous reaction conditions. This facilitated the reaction in continuous vapour-liquid 'pipes-in series' reactor. A 75 kg GMP campaign demonstrated a 3.5 order of magnitude of scale up from lab scale with no further

development work or changes to reaction conditions necessary to accommodate the change in scale.

Continuous flow is an appropriate technology for the handling of energetic and potentially explosive substances such as sodium azide. A recent paper from UCB reports the amination of a mesylated cyclobutanol compound.[38] The continuous process involved an azidation followed by a Staudinger reduction which avoids the handling and isolation of a hazardous alkyl azide compound. The reaction proceeds with complete stereochemical inversion to produce multigram quantities of the target cyclobutyl species as shown in Figure 7. An integrated micromixer was utilised to preheat the feeds prior to mixing and the azidation step was carried out in PTFE setup in series with the [1-(5-bromopyrimidin-2-yl)-3-cyano-3-methyl-cyclobutyl] methane-sulfonate compound isolated in 59% yield and with complete stereochemical inversion (stereochemistry was confirmed by X-ray analysis). The flow set-up offered process safety improvements not possible in batch.

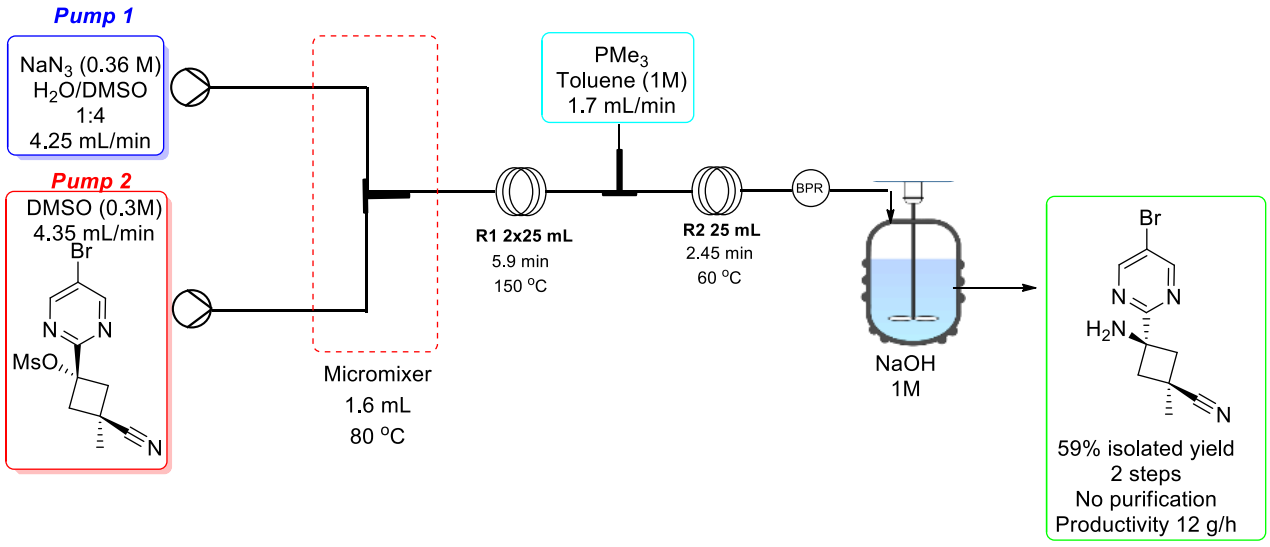
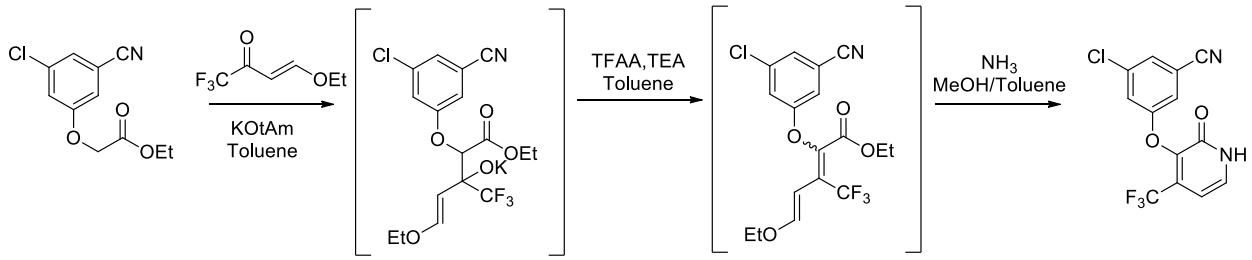


Figure 7: Flow set-up for azidation/Staudinger reduction process.

Further work from Merck[39] highlighted the transfer of a continuous flow process from lab to pilot plant scale. A continuous flow process for the aldol formation of a key intermediate in the synthesis of doravirine[40] was reported with lab development ensuring the delivery of a robust, transferable flow process to commercialisation (Scheme 5).

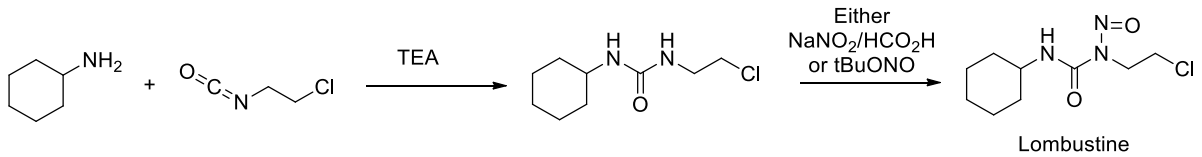


Scheme 5: Aldol chemistry of ethyl ester and enone to form aldolate with subsequent elimination and cyclisation.

The process utilised THF as a co-solvent which improved the solubility of reagent degradants thus preventing accumulation or reactor fouling. The understanding of the impact of mixing, residence time and solvent composition on reaction performance were all critical aspects considered for process development with the flow regime understood through the Reynolds number to determine suitable scaling parameters. A modular flow reactor skid was commissioned and built to integrate the flow chemistry steps within existing batch equipment with 200 kg of starting material processed at flow rates of 1.6 L/min for production scale delivery with 68 % yield. Inclusion of inline PAT provided additional information and key learnings during pilot plant campaigns, with FTIR utilised to ensure steady state. Steady state was reached within 6 mins of a 6-8 hour run time which showed that the transient start-up and shutdown would not impact on product quality. Scale-up principles and processing guidelines are important and particularly relevant for mixing sensitive reactions, which operate at high flow rates, to ensure the reaction

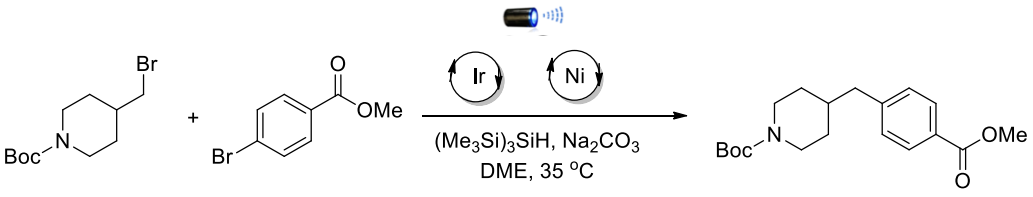
behaves as intended. Without such protocols in place, a significant portion of a batch may be processed before it becomes apparent that the reaction is not proceeding as expected.

Lombustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-urea), an important agent for the treatment of brain tumours and Hodgkin's lymphoma, has been prepared under continuous flow exploiting desorption electrospray ionisation mass spectrometry (DESI-MS) to rapidly screen reaction conditions to define parameters for a scalable process.[41,42] Two reactions were telescoped without any isolation of the reaction intermediate, an approach which reduces production costs radically by facilitating the use of a simple reactor set-up and cheap raw materials (Scheme 6) DESI-MS was used to evaluate the impact of solvent, concentration and nitrosation reagent choice on the efficiency of Lombustine production. Analysis of the information generated led to the development of a flow process telescoping with a total residence time of 9 minutes, producing a 63 % yield which was superior to batch conditions which took over 2 hours and generated a lower yield.[43] The process was initially run on small scale in glass microreactors before moving to fluorinated ethylene propylene (FEP) tubing for scaling up with single inline work-up. As before with Merck, a mixed solvent system was used to prevent reactor clogging due to the low solubility of the intermediate formed. *tert*-Butyl nitrite was chosen as the nitrosation reagent as milder conditions were required and Lombustine could be isolated through simple extraction, filtration and washing. Overall the flow process was faster and more environmentally friendly circumventing chromatographic purification and reducing waste production.



Scheme 6: Continuous flow synthetic route to Lombustine.

Synthetic organic photochemistry is considered a powerful tool to obtain highly reactive intermediates which give way to compounds with valuable structural complexity that would otherwise be difficult to access.[44] One of the fundamental advantages of photochemistry under continuous processing is the ability to scale up easily using parallel multi-reactors by numbering up.[45,46,47] Poor light penetration (Beer Lambert law) often hinders large scale photochemical transformations in batch mode however this can be overcome in flow.[48] GSK report a continuous stirred-tank reactor (CSTR) cascade capable of handling solid-containing photochemical reactions facilitating performance of heterogeneous photoredox reactions under mild conditions.[49] This follows the work of Abbvie where a single stage laser-driven photo-CSTR was developed capable of multi-kg productivity through fine tuning of light attenuation, reactor geometry and catalyst concentration for a homogenous system.[50] Photoredox reactions play an increasing strategic role in the selective late-stage functionalisation of complex pharmaceutically relevant complexes.[51] A CSTR cascade, comprised of five individual chambers was designed and built using a slurry pump to controllably deliver reaction mixture to the CSTR. Residence time distribution experiments facilitated an understanding of the mixing characteristics in the CSTR and photon flux was characterised by chemical actinometry. The newly developed solid feeding technique within the heterogeneous photoredox platform offers a simple translation from batch to flow. The handling of insoluble starting material in a silyl radical-mediated metalla-photoredox cross-electrophile coupling reaction (Scheme 7) demonstrated the robustness of the flow platform with gram scale synthesis achieved (58% yield, 99% conversion, 80 mg/hr productivity).



Scheme 7: Continuous silyl radical mediated metalla-photoredox cross-electrophile coupling.

Another area where continuous flow is offering advantages over batch is within the field of electrochemistry.[52] Electrosynthesis is considered a green and environmentally friendly approach as it circumvents the use of toxic or dangerous oxidants or reducing agents through the use of electrons as traceless reagents. GSK report the development and scale-up of continuous electrocatalytic hydrogenation of functionalised nitro arenes, nitriles and unsaturated aldehydes.[53] Electrochemical reduction of aromatic nitro groups is not reported often, however the reactor geometry and catalysts developed are scalable and tuneable to achieve robust processes delivering high selectivities and high rates with increased safety (necessity for high pressure hydrogen can be circumvented). The work demonstrated that suitable catalyst choice can confer regioselectivity and halt interference with other chemical moieties.

Biocatalysts or enzymes are essential tools in chemical synthesis for, highly regio-, chemo- and enantioselective synthesis of complex achiral and chiral compounds. The use of continuous flow in biotransformations offers a number of advantages including reduced enzyme inhibition as a result of removal of the substrates and or products and simplified downstream processing due to application of immobilized catalysts. Recent reviews[54] extensively cover the use of continuous flow for biocatalysis, highlighting that benefits including improved reactions rates, better mixing and control, improved enzyme stability and lifetime. More recently, the application of an efficient flow system for a chemo-enzymatic Baeyer-Villiger oxidation resulted in high yields of the product per reactor capacity and eliminated the need to handle unstable peracids.[55] The process was carried out in the presence of *Candida antarctica* lipase B immobilised *via* simple physical adsorption on multi-walled carbon nanotubes. The nanocatalyst generated peracid *in situ* from

ethyl acetate and 30% wt aq. hydrogen peroxide as the primary oxidant. A high product yield (87%) and selectivity (>99%) was achieved for the Baeyer-Villiger oxidation of 2-methylcyclohexanone to 6-methyl-ε-caprolactone in 8 hours at 40 °C (Figure 8). Ethyl acetate as both the solvent and peracid precursor is an environmentally favourable choice. The first report of the application of a nanobiocatalyst for the chemoenzymatic transformation offered process improvements both with an increase in yield when compared with the batch process and with demonstration of a shorter reaction time under mild conditions.

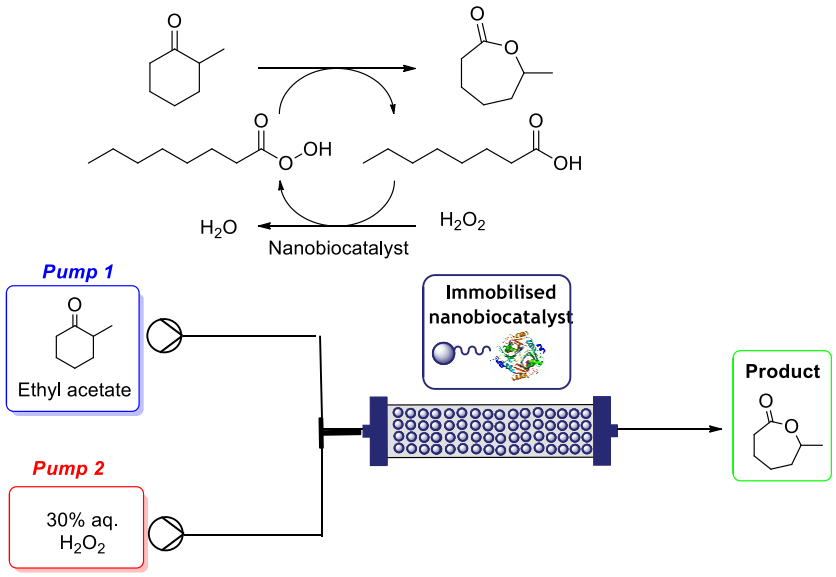


Figure 8: Continuous flow set up for Baeyer-Villiger Oxidation using CALB/H_2O_2.

Future Perspective and Opportunities

The purpose of any flow chemistry platform is to provide superior solutions for the chemical industry, utilising the best available technology to meet demanding processing needs today, tomorrow and in the future. The development of new technologies that enable the competitive and environmentally friendly chemical manufacture of intermediates, building blocks, drug substances and active ingredients *via* continuous flow are imperative for the continued growth of

manufacturing industries and for advancing academia alike. For industry, an initial focus to expedite development is the target of chemistries which are not typically accessible or scalable in batch processing. Almac's **F**low **A**ssisted **S**ynthesis **T**echnology (**FAST**) platform endeavours to facilitate manufacture of new and highly valuable functional group interchanges using high energy, high pressure, oxidation and photochemical transformations in a safe and scalable manner. As more flow processes are brought online, it further demonstrates the robustness and maturity of this exciting, enabling technology. It is envisaged that the age old 'nothing succeeds like success' will come to fruition.

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REFERENCES

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[1] Review on flow processing for pharmaceutical industry: a) B. Gutmann, D. Cantillo and C. O. Kappe, Continuous-flow technology—a tool for the safe manufacturing of active pharmaceutical ingredients, Angew. Chem. Int. Ed., 2015, 54, 6688. b) M. Baumann, I.R. Baxendale, The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry, Beilstein J. Org. Chem., 2015, 11, 1194-1219, c) R. Porta, M. Benaglia, A. Puglisi, Flow chemistry: recent developments in the synthesis of pharmaceutical products, Org. Process Res. Dev., 2016, 20, 2-25.

[2] C. Badman, C. L. Cooney, A. Florence, K. Konstantinov, M. Krumme, S. Mascia, M. Nasr, B. L. Trout, Why We Need Continuous Pharmaceutical Manufacturing and How to Make It Happen, Journal of Pharmaceutical Sciences, 2019, 3521-3523.

[3] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, The hitchhiker's guide to flow chemistry, Chem. Rev., 2017, 117, 11796-11893.

[4] S. Schwolow, A. Neumuller, L. Abahmane, N. Kockmann, T. Roder, Design and application of a millistructured heat exchanger reactor for an energy-efficient process, Chem. Eng. Process, 2016, 108, 109-116.

[5] S. Schwolow, J. Hollmann, B. Schenkel, T. Roder, Application-oriented analysis of mixing performance in microreactors, Org. Process Res. Dev., 2012, 16, 1513-1522.

[6] J. M. Reckamp, A. Bindels, S. Duffield, Y. C. Liu, E. Bradford, E. Ricci, F. Susanne, A. Rutter, Mixing Performance Evaluation for Commercially Available Micromixers Using Villermaux–Dushman Reaction Scheme with the Interaction by Exchange with the Mean Model, Org. Process Res. Dev., 2017, 21, 816-820.

[7] P. Plouffe, A. Macchi, D. M. Roberge, From Batch to Continuous Chemical Synthesis: A Toolbox Approach, Org. Process Res. Dev., 18, 1286-1294.

[8] B. Martin, H.Lehmann, H. Yang, L. Chen, X. Tian, J. Polenk, B. Schenkel, Continuous manufacturing as an enabling tool with green credentials in early-phase pharmaceutical chemistry, Current Opinion in Green and Sustainable Chemistry, 2018, 11, 27-33.

[9] S. R. L. Gobert, S. Kuhn, L. Braeken, L. C. J. Thomassen, Characterization of milli-and microflow reactors: mixing efficiency and residence time distribution, Org. Process Res. Dev., 2017, 21, 531-542.

[10] J. Britton, C. L. Raston, Multi-step continuous-flow synthesis, Chem. Soc. Rev., 2017, 46, 1250-1271.

[11] C. A. Shukla, A. A. Kulkarni, Automating multistep flow synthesis: approach and challenges in integrating chemistry, machines and logic, Beilstein J. Org. Chem., 2017, 13, 960-987.

[12] R. L. Hartman, J. P. McMullen, K. F. Jensen., Deciding whether to go with the flow: evaluating the merits of flow reactors for synthesis, Angew. Chem. Int. Ed., 2011, 50 (33), 7502-7519.

[13] https://www.in-pharmatechnologist.com/Article/2015/05/01/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production

[14] J. Harmsen, Process intensification in the petrochemicals industry: drivers and hurdles for commercial implementation, J. Chemical Engineering and Processing: Process Intensification, 49, 1, 2010, 70-73

[15] D. Blanco-Ania and F. P. J. T. Rutjes, Continuous-flow chemistry in chemical education, J. Flow. Chem., 2017, 7(3-4), 157-158.

[16] a) B. Gutmann, M. Köckinger, G. Glotz, T. Ciaglia, E. Slama, M. Zadravec, S. Pfanner, M. C. Maier, H. Gruber-Wölfler and C. O. Kappe, Design and 3D printing of a stainless steel reactor for continuous difluoromethylations using fluoroform, React. Chem. Eng., 2017, 2, 919-927, b) E. Peris, O. Okafor, E. Kulcinskaja, R. Goodridge, S. V. Luis, E. Garcia-Verdugo, E. O'Reilly and V. Sans, Tuneable 3D printed bioreactors for transaminations under continuous-flow, Green

Chem., 2017, 19, 5345-5349, c) S. Rossi, A. Puglisi and M. Benagalia, Additive Manufacturing Technologies: 3D Printing in Organic Synthesis, ChemCatChem, 2017, 10 (7), 1512-1525, d) C. Parra-Cabrera, C. Achille, S. Kuhn and R. Ameloot, 3D printing in chemical engineering and catalytic technology: structured catalysts, mixers and reactors, Chem. Soc. Rev., 2018, 47(1), 209-230.

[17] a) F. A. Leibfarth, M. G. Russell, D. M. Langley, H. Seo, L. P. Kelly, D. W. Carney, J. K. Sello and T. F. Jamison, Continuous-Flow Chemistry in Undergraduate Education: Sustainable Conversion of Reclaimed Vegetable Oil into Biodiesel, J. Chem. Educ., 2018, 95, 8, 1371-1375, b) J. Britton and T. F. Jamison, The assembly and use of continuous flow systems for chemical synthesis, Nat. Prot., 2017, 12, 2423, c) B. König, P. Kreitmeier, P. Hilgers and T. Wirth, Flow chemistry in undergraduate organic chemistry education, J. Chem. Educ., 2013, 90, 7, 934-936.

[18] N. S. Marzijarani, D. R. Snead, J. P. McMullen, F. Levesque, M. Weisel, R. J. Varsolona, Y. Lam, Z. Liu and J. R. Naber, One-Step Synthesis of 2-Fluoroadenine Using Hydrogen Fluoride Pyridine in a Continuous Flow Operation, Org. Process Res. Dev., 2019, 23, 1522-1528.

[19] a) P. Liu, A. Sharon, C. K. Chu, Fluorinated nucleosides: synthesis and biological implication, J. Fluorine Chem., 2008, 129, 9, 743-766, b) J. A. Wilkinson, Recent advances in the selective formation of the carbon-fluorine bond, Chem. Rev., 92, 4, 505-519.

[20] (a) M. J. Robins, B. Uznanski, Nucleic acid related compounds. 34. Non-aqueous diazotization with *tert*-butyl nitrite. Introduction of fluorine, chlorine, and bromine at C-2 of purine nucleosides, Can. J. Chem., 1981, 59, 17, 2608-2611, (b) H. P. Baer, G. I. Drummond, E. L. Duncan, Formation and deamination of adenosine by cardiac muscle enzymes, Mol. Pharmacol., 1966, 2, 1, 67-76.

[21] (a) K. Yamamoto, J. Li, J. A. O. Garber, J. D. Rolfes, G. B. Boursalian, J. C. Borghs, C. Genicot, J. Jacq, M. van Gastel, F. Neese, T. Ritter, Palladium-catalysed electrophilic aromatic C–H fluorination, Nature, 2018, 554, 511, (b) M. G. Campbell, T. Ritter, Modern carbon–fluorine bond forming reactions for aryl fluoride synthesis, Chem. Rev., 2015, 115, 2, 612-633, (c) Y. Zhang, C. Wen, J. Li, C5-Regioselective C–H fluorination of 8-aminoquinoline amides and sulfonamides with Selectfluor under metal-free conditions, Org. Biomol. Chem., 2018, 16, 11, 1912-1920, (d) A. Lin, C. B. Huehls, J. Yang, Recent advances in C–H fluorination, Org. Chem. Front, 2014, 1, 4, 434-438, (e) V. V. Grushin, The organometallic fluorine chemistry of palladium and rhodium: studies toward aromatic fluorination, Acc. Chem. Res., 2010, 43, 1, 160-171, (f) X.-Q, Ning, S. J. Lou, Y. J. Mao, Z. Y. Xu, D. Q. Xu, Nitrate-promoted Selective C–H Fluorination of Benzamides and Benzeneacetamides, Org. Lett., 2018, 20, 8, 2445-2448.

[22] C. Stueckler, P. Hermsen, B. Ritzen, M. Vasiloiu, P. Poechlauer, S. Steinhofer, A. Pelz, C. Zinganell, U. Felfer, S. Boyer, M. Goldbach, A. de Vries, T. Pabst, G. Winkler, V. LaVopa, S. Hecker and C. Schuster, Development of a Continuous Flow Process for a Matteson Reaction: From Lab Scale to Full-Scale Production of a Pharmaceutical Intermediate, Org. Process Res. Dev., 2019, 23, 1069-1077.

[23] a) D. S. Matteson, D. Majumdar, Homologation of boronic esters to .alpha.-chloro boronic esters, Organometallics, 1983, 2, 1529, b) D. S. Matteson, Stereodirected Synthesis with Organoboranes, Springer Verlag: Berlin, 1995, Chapter 5, c) D. S. Matteson, Boronic Esters in Asymmetric Synthesis, J. Org. Chem., 2013, 78, 10009-10023.

[24] D. S. Matteson, E. Erdik, Epimerization of .alpha.-chloroboronic esters by lithium and zinc chlorides, Organometallics, 1983, 2, 1083-1088.

[25] a) G. Köbrich, K. Flory, W. Drischel, Angew. Chem. Int. Ed. Engl., 1964, 3, 513, b) G. Köbrich, A. Akhtar, F. Ansari, W. E. Breckoff, H. Büttner, W. Drischel, R. H. Fisher, K. Flory, H. Fröhlich, W. Goyert, H. Heinemann, I. Hornke, H. R. Merkle, H. Trapp, W. Zündorf, Chemistry of Stable α-Halogenoorganolithium Compounds and the Mechanism of Carbenoid Reactions, Angew. Chem. Int. Ed. Engl., 1967, 6, 41-52, c) G. Köbrich, The Chemistry of Carbenoids and Other Thermolabile Organolithium Compounds, Angew. Chem. Int. Ed. Engl., 1972, 11, 473-485.

[26] A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel and J. Sedelmeier, Dichloromethyllithium: Synthesis and Application in Continuous Flow Mode, Org. Lett., 2017, 19, 4, 786-789.

[27] D. Znidar, A. O'Kearney-McMullan, R. Munday, C. Wiles, P. Poechlauer, C. Schmoelzer, D. Dallinger and C. O. Kappe, Scalable Wolff−Kishner Reductions in Extreme Process Windows Using a Silicon Carbide Flow Reactor, Org. Process Res. Dev., 2019, 23, 11, 2445-2455.

[28] a) L. Wolff, Justus Liebigs Ann. Chem., 1912, 394, 86-108, b) N. J. Kishner, J. Russ. Chem. Soc., 1911, 43, 582-595, c) J. W. Burton, Comprehensive Organic Synthesis II, Elsevier, Oxford, UK, 2014, Vol 8., 446-478, d) D. Todd, Org. React., 1948, 4, 378-391, e) Z. Wang., Comprehensive Organic Name Reactions, John Wiley & Sons, 2010, 3084-3089.

[29] J. K. Niemeier, D. P. Kjell, Hydrazine and Aqueous Hydrazine Solutions: Evaluating Safety in Chemical Processes, Org. Process Res. Dev., 2013, 17, 1580-1590.

[30] a) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, Taming hazardous chemistry by continuous flow technology, Chem. Soc. Rev., 2016, 45, 4892-4928 b) N. Kockmann, P. Thenée, C. Fleischer-Trebes, G. Laudadio, T. Nöel, Safety assessment

in development and operation of modular continuous-flow processes, React. Chem. Eng., 2017, 2, 258-280.

[31] a) S. Schwolow, B. Heikenwälder, L. Abahmane, N. Kockmann, T. Röder, Kinetic and Scale-up Investigations of a Michael Addition in Microreactors, Org. Process Res. Dev., 2014, 18, 1535-1544, b) F. Meschke, G. Riebler, V. Hessel, J. Schurer, T. Baier, Hermetic Gas-tight Ceramic Microreactors, Chem. Eng. Technol., 2005, 28, 465-473.

[32] a) P. Plouffe, A. Macchi, D. Roberge, Flow Chemistry, Volume 1: Fundamentals; F. Darvas, V. Hessel, G. Dorman, Eds. De Gruyter: Berlin, 2014, pp139, b) I. Dencic, V. Hessel, Microreactors in Organic Synthesis and Catalysis, 2nd Edition; T. Wirth, Ed.; Wiley-VCH: Weinheim Germany, 2013, pp373, c) N. G. Anderson, Using Continuous Processes to Increase Production, Org. Process Res. Dev., 2012, 16, 852-869.

[33] A. Campbell Brewer, P. C. Hoffman, J. R. Martinelli, M. E. Kobierski, N. Mullane and D. Robbins, Development and Scale-Up of a Continuous Aerobic Oxidative Chan–Lam Coupling, Org. Process Res. Dev., 2019, 23, 1484-1498.

[34] a) P. T. Anastas, J. C. Warner, Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, b) D. J. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, Key green chemistry research areas—a perspective from pharmaceutical manufacturers, Green. Chem., 2007, 9, 411-420.

[35] a) C. J. Mallia and I. R. Baxendale, The Use of Gases in Flow Synthesis, Org. Process Res. Dev. 2016, 20, 2, 327-360; b) M. Brzozowski, M. O'Brien, S. V. Ley and A. Polyzos, Flow

Chemistry: Intelligent Processing of Gas–Liquid Transformations Using a Tube-in-Tube Reactor, Acc. Chem. Res. 2015, 48, 2, 349-362

[36] Recent reviews: a) J. X. Qiao, P. Y. S. Lam, Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives, Synthesis, 2011, 829-856, b) K. S. Rao, T. – S., Wu, Chan-Lam coupling reactions: Synthesis of heterocycles, Tetrahedron, 2012, 68, 7735-7754.

[37] a) T. Tsuritani, N. A. Strotman, Y. Yamamoto, M. Kawasaki, N. Yasuda, T. Mase, *N*-Cyclopropylation of Indoles and Cyclic Amides with Copper(II) Reagent, Org. Lett. 2008, 10, 1653-1655, b) S. Benad, L. Neuville, J. Zhu, Copper-Mediated *N*-Cyclopropylation of Azoles, Amides, and Sulfonamides by Cyclopropylboronic Acid, J. Org. Chem., 2008, 73, 6441-6444, c) S. Benard, L. Neuville, J. Zhu, Copper-promoted *N*-cyclopropylation of anilines and amines by cyclopropylboronic acid, Chem. Commun., 2010, 46, 3393-3395, d) E. Racine, F. Monnier, J.-P. Vors, M. Taillefer, Direct *N*-cyclopropylation of secondary acyclic amides promoted by copper, Chem. Commun., 2013, 49, 7412.

[38] M. Tissot, J. Jacq and P. Pasau, Stereospecific Amination of Mesylated Cyclobutanol in Continuous Flow, Org. Process Res. Dev., 2019, Ahead of Print.

[39] J. P. McMullen, C. H. Marton, B. D. Sherry, G. Spencer, J. Kukura and N. S. Eyke, Development and Scale-Up of a Continuous Reaction for Production of an Active Pharmaceutical Ingredient Intermediate, Org. Process Res. Dev., 2018, 22, 1208-1213.

[40] D. R. Gauthier, B. D. Sherry, Y. Cao, M. Journet, G. Humphrey, T. Itoh, I. Mangion, D. M. Tschaen, Highly efficient synthesis of HIV NNRTI doravirine, Org. Lett., 2015, 17, 6, 1353-1356.

[41] Z. Jaman, T. J. P. Sobreira, A. Mufti, C. R. Ferreira, R. G. Cooks, D. H. Thompson, Rapid On-Demand Synthesis of Lomustine under Continuous Flow Conditions Org. Process Res. Dev., 2019, 23, 334-341.

[42] M. Wleklinski, B. P. Loren, C. R. Ferreira, Z. Jaman, L. Avramova, T. J. P. Sobreira, D. H. Thompson, R. G. Cooks, High throughput reaction screening using desorption electrospray ionization mass spectrometry, Chem. Sci., 2018, 9, 1647-1653.

[43] a) T. P. Johnson, G. S. McCaleb, J. A. Montgomery, Synthesis of chlorozotocin, the 2-chloroethyl analog of the anticancer antibiotic streptozotocin, J. Med. Chem., 1975,18, 104-106, b) I. Baracu, I. Niculescu-Duvaz, Potential anticancer agents. XXVIII[†]. Synthesis of Some Cyclohexanone Derived N-Nitrosoureas, J. Prakt. Chem., 1985, 327, 675-681, c) L. Dirikolu, T. Chakkath, T. Fan, N. R. Mente, Synthesis of trans- and cis-4'-hydroxylomustine and development of validated analytical method for lomustine and trans- and cis-4'-hydroxylomustine in canine plasma, J. Anal. Toxicol., 2009, 33, 595-603, d) J. W. Lown, S. M. S. Chauhan, Synthesis of specifically nitrogen-15- and carbon-13-labeled antitumor (2-haloethyl)nitrosoureas. The study of their conformations in solution by nitrogen-15 and carbon-13 nuclear magnetic resonance electronic control in their aqueous decomposition, J. Org. Chem., 1981, 46, 5309-5321.

[44] F. Politano, G. Oksdath-Mansilla, Light on the Horizon: Current Research and Future Perspectives in Flow Photochemistry, Org. Process Res. Dev., 2018, 22, 9, 1045-1062.

[45] Y. Su, K. Kuijpers, V. Hessel, T. A. Noel, A convenient numbering-up strategy for the scale-up of gas–liquid photoredox catalysis in flow, React. Chem. Eng., 2016, 1, 73-81.

[46] K. P. L. Kuijpers, M. A. H. van Dijk, Q. G. Rumeur, V. Hessel, Y. Su, T. A. Noel, A sensitivity analysis of a numbered-up photomicroreactor system, React. Chem. Eng., 2017, 2, 109-115.

[47] F. Zhao, D. Cambie, J. Janse, E. W. Wieland, K. P. L. Kuijpers, V. Hessel, M. G. Debije, T. Noel, Scale-up of a Luminescent Solar Concentrator-Based Photomicroreactor via Numbering-up, Sustainable Chem. Eng. 2018, 6, 422-429.

[48] J. P. Knowles, L. D. Elliot, K. I. Brooker-Milburn, Flow photochemistry: Old light through new windows, Beilstein J. Org. Chem., 2012, 8, 2025-2052.

[49] A. Pomberger, Y. Mo, K. Y. Nandiwale, V. L. Schultz, R. Duvadie, R. I. Robinson, E. I. Altinoglu and K. F. Jensen, A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions, Org. Process Res. Dev., 2019, Ahead of Print.

[50] K. C. Harper, E. G. Moschetta, S. V. Bordawekar, S. J. A. Wittenberger, A Laser Driven Flow Chemistry Platform for Scaling Photochemical Reactions with Visible Light, ACS Cent. Sci, 2019, 5, 109-115.

[51] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis, Chem. Rev., 2013, 113, 5322-5363.

[52] a) A. A. Folgueiras-Amador and T. Wirth, Perpectives in Flow Electrochemistry, J. Flow Chem., 2017, 7(3-4), 94-95, b) T. Nöel, Y. Cao and G. Laudadio, The fundamentals behind the use of flow reactors in electrochemistry, Acc. Chem. Res. 2019, 52, 2858-2869.

[53] J. D. Egbert, E. C. Thomsen, S. A. O'Neill-Slawecki, D. M. Mans, D. C. Leitch, L. J. Edwards, C. E. Wade, R. S. Weber, Development and Scale-up of Continuous Electrocatalytic Hydrogenation of Functionalized Nitro Arenes, Nitriles, and Unsaturated Aldehydes, Org. Process Res. Dev., 2019, 23, 1803-1812.

[54] a) J. Britton, S. Majumdar, G. A. Weiss, Continuous Flow Biocatalysis, Chem. Soc. Rev., 2018, 47, 5891-5918, b) M. P. Thompson, I. Peñafiel, S. C. Cosgrove and N. J. Turner, Biocatalysis using immobilized enzymes in continuous flow for the synthesis of fine chemicals, Org. Process Res. Dev., 2019, 23, 9-18.

[55] A. Szelwicka, P. Zawadzki, M. Sitko, S. Boncel, W. Czardybon, A. Chrobok, Continuous Flow Chemo-Enzymatic Baeyer–Villiger Oxidation with Superactive and Extra-Stable Enzyme/Carbon Nanotube Catalyst: An Efficient Upgrade from Batch to Flow, Org. Process Res. Dev., 2019, 23, 1386-1395.