ASSESSMENT OF THE IMPACT OF CONTINOUS FLOW CHEMISTRY ON MODERN HETEROCYCLIC CHEMISTRY

DOI: http://dx.medra.org/10.17374/targets.2022.25.281

Cormac Bracken, Marcus Baumann*

UCD School of Chemistry, Science Centre South, University College Dublin, Belfield, Dublin 4, Ireland
(e-mail: cormac.bracken@ucdconnect.ie, marcus.baumann@ucd.ie)

Abstract. *Over the last 20 years, continuous flow synthesis has left a distinct mark on modern synthetic chemistry where it is now commonly used in academia and industry alike. Advantages of flow processing arise from reactor miniaturization, which in turn leads to improved heat and mass transfer, while reaction containment increases process safety and facilitates scale-up and scale-out of continuous reactions. Heterocyclic synthesis remains at the forefront of industrially relevant applications of organic chemistry and as this chapter will highlight, the synthesis and functionalization of heterocyclic targets frequently benefits from continuous flow approaches. This chapter will highlight a selection of relevant case studies from the last 5 years that demonstrate the positive impact of modern flow chemistry on the field of heterocyclic chemistry.*

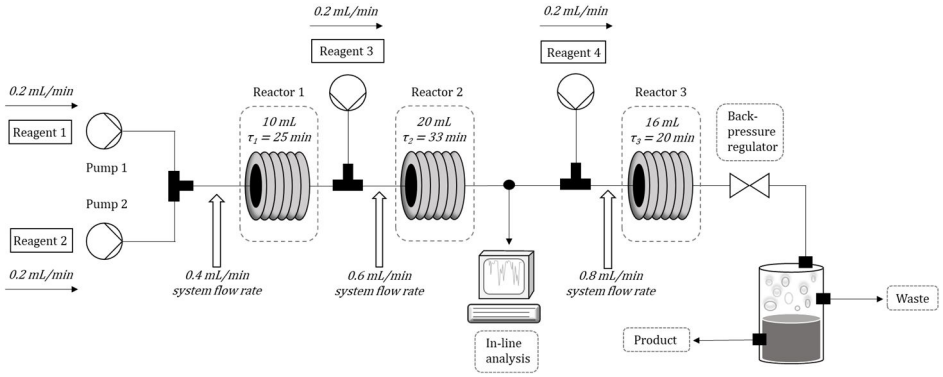
Contents

1. Introduction to flow chemistry

This section will discuss the synthesis of heterocyclic compounds performed using continuous flow technology. Flow chemistry is typically associated with the development of a continuous chemical transformation using miniaturized reactor components such as microchannels or polymer tubing. This process can involve a single or multi-step reaction. The transition of a process from batch to flow introduces benefits to the synthesis such as improved selectivity, effective scale-up and increased safety, usually leading to an increase in reaction efficiency, lower handling/maintenance costs, and reduced environmental footprint.[1,2] The recent shift from batch mode to continuous flow processing for the synthesis of many fine chemicals has been particularly prominent in the area of pharmaceuticals, agrochemicals, small-volume compounds, and the 'flavour and fragrance' sectors.[3] The batch-to-flow evolution in both academia and industry has been associated with rapid development of novel continuous flow enabling technologies, especially micro-engineered apparatus.

Heterocycles are fundamental structural components of many organic molecules that are produced in large volumes *via* classical procedures. In view of sustainability and increased efficiency there is a strong interest in devising improved procedures by which such targets can be synthesized through more chemically economic means.[4] With the intention of utilizing continuous flow systems to increase reaction performance, a primary consideration is the choice of flow equipment that will be used to facilitate the chemical reaction(s). This can be based on commercial or home-built flow reactor units. Flow systems exploit pumps, which can be a simple syringe pump, a HPLC pump, or a peristaltic pump contained within specialized flow reactor set-ups (Scheme 1).[5] With the assistance of the pump, the reaction solution is delivered to reactors which can vary widely in their composition. Reactors can be composed of polymer tubing (PFA, PEEK, PTFE), or metals such as copper, stainless steel or Hastelloy, for example. These reactors can vary greatly in their size and physical arrangement, and they may be acquired commercially or through bespoke design realized through novel means such as 3D-printing. The choice of reactor coil is dependent on the nature of the ensuing chemical reaction within the tubing, where chemical compatibility and reactor stability (*e.g.* temperature and pressure) are the key determining factors.[6] Other important factors to be considered in the

design of the reactor coil include internal diameter (i.d.) and tubing length. Tubing volume is important as it is a key factor in calculating the residence time (r.t.=τ=tube volume/flow rate),[7] which is the amount of time spent by the reaction mixture within the reactor before it moves into the next step.



Scheme 1. Representation of a typical multi-step flow process.

Once a decision is made regarding the delivery arrangement for directing the reaction media through a flow system, attention subsequently turns to the chemical reactions themselves which occur at each step of a flow process. A possible step may involve the simple delivery of a reagent to a reactor coil *via* a pump connected through a T-piece mixer, or a reactor where the reaction solution becomes exposed to a particular energy source, catalyst, enzyme *etc.* Depending on the targeted reaction scale, different types of flow reactor components are available and can be assembled in a modular fashion to complete the desired flow module. These may include heated coils,[8] light sources,[9] immobilized catalysts and enzymes,[10] static mixers, quenching units, back pressure regulators (BPR) and in-line analysis devices.[11,12]

2. Flow chemistry and its applications in heterocycle synthesis

In the context of heterocyclic chemistry, continuous flow applications may be divided into three groups: (a) synthesis of heterocycles from acyclic precursors, (b) heterocycle transposition reactions, and (c) heterocycle functionalization and derivatization processes. This chapter will discuss the practical aspects of making and working with heterocycles in continuous flow, with the intention of illustrating the practicalities of performing these transformations. What these examples all provide is precedent for how continuous flow can improve heterocycle formation in terms of product yield, product scope, reaction time, and easy scale-up for bulk production, all made possible through some key synthetic benefits afforded by flow technology (Table 1).

The recent evolution of flow-based technology for performing chemical reactions has afforded the opportunity for its application in the efficient and reliable synthesis of heterocycles. Heterocycles are key structural scaffolds of many compounds with 85% of biologically active chemical species containing at least one heterocyclic moiety,[13] hence investigations into heterocyclic synthesis garners considerable interest in academia and industry. This in turn has provided an opportunity for the implementation of novel synthetic methodologies to explore and expand our ability to effectively generate heterocyclic targets.

Most heterocyclic syntheses performed in continuous flow are performed as such because the parameters of a particular reaction in batch are inefficient and in need of improvement to augment reaction efficiency leading to a heterocyclic target. Key parameters such as micro-mixing, facile scale-up, improved mass and heat transfer, and a better safety profile grant the ideal platform to transition from unreliable batch procedures towards improved continuous processes rendering heterocyclic targets more reliably.

If a chemist is considering employing flow chemistry to access a heterocyclic compound, it can benefit the synthesis by way of increased reaction efficiency on a micro-fluidic scale. As previously mentioned, a continuous flow system can accommodate all reaction conditions, including for example: thermal, photochemical, redox, radical, and coupling reactions.[14]

Table 1. Potential advantages and disadvantages of flow chemistry.

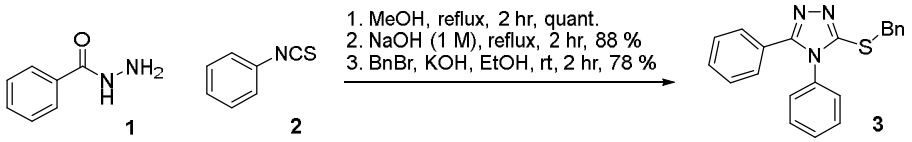
Continuous Flow Chemistry	
Advantages	*Disadvantages*
Improved heat transfer (i.e. heat dissipation)	Up-front cost for new equipment to replace existing batch equipment
Improved mass transfer (i.e. mixing profile)	Challenges towards heterogeneous mixtures
Increased safety through containment	Perceived lack of relevant published case studies
Ability to integrate process automation	Lack of familiarity and training of operators
Ability to telescope multi-step sequences	
In-line purification/scavenging *etc.*	
Safe handling of pressurised gases	
Reliable reaction scale-up and scale-out	
Less chemical waste/energy consumption	

Herein, we will illustrate how flow technology has been used for synthesizing heterocycles by discussing selected examples from the recent literature. This section will touch on how continuous flow has offered an improvement on many problematic syntheses, and attempt to highlight why the authors of these examples undertook a continuous flow approach for constructing heterocycles.

2.1. De novo synthesis of heterocycles

To begin, we will discuss the flow synthesis of some important 5-membered heterocycles. The volume of research attributed to 5-membered ring systems containing one or more heteroatoms is vast owing to their usefulness as biological isosteres with appropriate hydrogen-bonding features. This is particularly prominent in the field of pharmaceuticals where reliable access to a multitude of heterocyclic targets is strongly desired.[15,16] Pastre *et al.* provided an interesting example of a telescoped flow procedure for the synthesis of a library of functionalized 3-thio-1,2,4-triazoles. Telescoping steps in a continuous process is applicable in industry, as moving from one step to the next without the need for laborious and wasteful isolation allows for a more streamlined synthesis.[17]

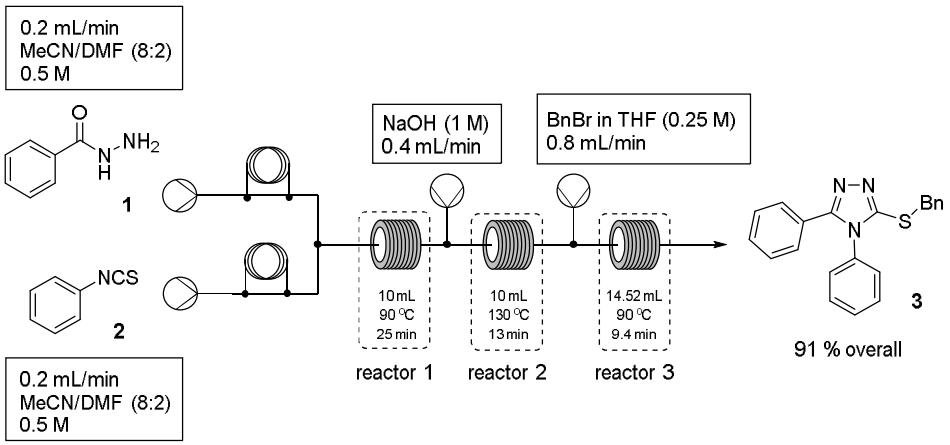
In the beginning 3-thio-1,2,4-triazoles were synthesized in batch. Compound **3** was synthesized in three steps in six hours to give a 69% overall yield from benzhydrazide **1** and phenyl isocyanate **2** (Scheme 2). The formation of a precipitate in this method rendered the original literature methodology impractical in a flow set-up. To maintain the solubility of all substances, a variety of solvents were screened, with the authors arriving at MeCN/DMF (8:2) as the ideal choice. These steps were then applied in a flow-based approach aimed at reducing the time taken to complete the reaction, improving the yield, and avoiding tedious work-up and purifications.



Scheme 2. Original three step batch procedure towards **3**.

Optimization of the reaction conditions was based on using a 10 mL coil reactor and sample loops for both the reagents. It was established that a temperature of 90 °C and a 5-minute residence time were appropriate to obtain quantitative conversion of the substrates. The heating of the solvent above its boiling point without evaporation is referred to as 'super-heating',[18] and allows for faster reactions at higher temperature without evaporation aided by back pressure regulators (BPRs). The subsequent cyclization step proved cumbersome in batch and hence was integrated with the first step, using two tandem flow reactors (Vapourtec R2+R4, and Uniqsis FlowSyn). The exiting stream of the first reactor containing the intermediate thiosemicarbazide was mixed with NaOH (1 M, aq.) *via* a T-piece. NaOH (1 M, aq.) was then

fed into the reaction stream at a flow rate of 0.4 mL/min under optimized conditions. In the reactor (130 °C) this equated to a 38-minute residence time giving a yield of 85% for the desired heterocyclic intermediate. Benzyl bromide in THF was fed into the stream for the third step to affect an S-alkylation and the final product **3** was isolated by column chromatography (Scheme 3). In this final step, an excess of the alkylating agent was found to be necessary, and after optimization a 48-minute residence time at 90 °C afforded **3** in 91% overall yield. Throughout the multi-step telescoped integration, the super-heating of the solvents allowed by microflow tubing proved to be critical to attaining high yields. The high yield of the final product was achieved in only 48 minutes and is a drastic improvement on the 6 hours taken in batch to obtain a yield of 66%.



Scheme 3. Telescoped flow process for the synthesis of **3**.

Next, the scope of the reaction was studied, varying alkyl/aryl hydrazides, isothiocyanates and alkyl as well as benzyl halides for this flow methodology. Alkyl halides and benzyl halides bearing electron withdrawing and electron donating groups were well tolerated and furnished products in yields ranging 40-94%. Various aromatic isothiocyantes were also trialled, resulting in a series of products which differed in their respective *N*-aryl substitution pattern. These products were furnished in 65-91% yields, again containing a diverse range of aliphatic and aromatic moieties. While this telescoped multi-step flow process afforded further diversified 1,2,4-triazole products, certain products did require slight modification of the reaction steps to achieve higher conversion and thus circumvent issues which arose from reactivity and steric influences. Notably, yields were lower when other alkyl/aryl hydrazides were used. These hydrazides contained a variety of heterocyclic, aliphatic and aryl substituents, with substituents of aliphatic or electron withdrawing character showing particularly reduced yields.

A final scale-up experiment for the entire telescoped flow process using 0.3 M reagent solutions and a temperature of 100 °C (in reactor 1) allowed for processing of 3.6 mmol of material per hour. The result was that over three hours a 93% yield (10.8 mmol, 3.5 grams) was obtained following purification. Overall, the multi-step telescoped flow procedure proved a viable alternative for delivering a diverse range of 5-membered heterocycles. The desired 3-thio-1,2,4-triazoles were synthesized in a rapid and efficient manner, where super-heated solvents greatly reduced the time taken to provide the desired products. Time-consuming intermediate isolation was avoided, leading to higher yields in a streamlined process with a noted reduction in energy consumption and waste generation.

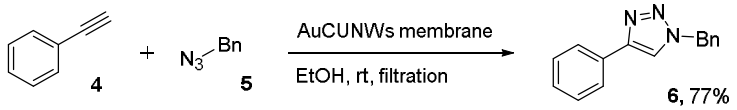
As previously discussed, the synthesis of 5-membered heterocycles is of high importance, and chemists explore numerous means for their generation. This includes searching for new transition metal catalyzed processes which allow for more efficient reactions in terms of yield and scope.

CuAAC catalysis (Cu-mediated alkyne-azide cycloaddition) is an example of a click reaction which yields triazole products under mild reaction conditions. However, a limitation of the reaction is that the

triazole product and the catalyst are often difficult to separate, and the reaction is challenging to scale up due to the use of hazardous azide species.

Wen *et al.* described a process whereby a catalytically active membrane was produced by depositing *in situ* generated AuCu nanowires onto a filter.[19] The porous membrane allowed for a high surface area-contact ratio and was also more stable to oxidation and leaching and opened the possibility for introducing the catalyst in a low-pressure reaction flow stream. The physical features of the AuCu wires were key to the integration of this membrane in a flow system. The porous nature and high surface area-contact ratio are critical aspects of many similar catalysts, and this is exacerbated in a flow process where the flowing reaction solution will spend a limited amount of time in contact with the catalyst. This means that highly active catalysts are needed to maximize turnover numbers and frequency within the short contact time.

The effectiveness of this catalytic membrane in a flow system was initially tested with phenylacetylene **4** and benzyl azide **5** at <1 bar and at room temperature. A solution containing phenylacetylene **4** (0.25 mmol) and benyzl azide **5** (0.5 mmol) in ethanol was circulated through the AuCu reactor ten times at a flow rate of 5 mL/min to yield 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **6** (Scheme 4). To assess the reusability of this membrane-bound catalyst the same catalyst was reused under optimized conditions with different reactants in each cycle, where activity decreased slightly to 89% although overall activity nonetheless did remain high throughout. Only minute amounts of Cu (7.8 ppm) were detected in the product mixture using inductively coupled plasma mass spectrometry (ICP-MS), showing the high stability of the catalyst to reuse in multiple cycles. Leached Cu(I) in solution was found to not have catalytic activity.



4 5 **6**, 77%

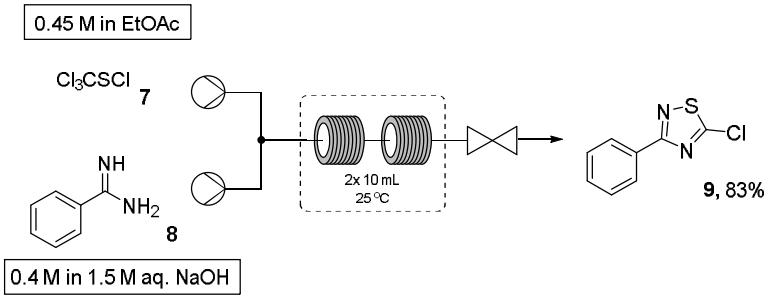
Scheme 4. Synthesis of triazole product **6**.

The CuAAC flow approach was then applied to a range of alkynes and azides to assess the scope of the procedure. The heterocyclic products were produced in yields ranging 75-96%, and contained a range of electron withdrawing, electron donating, and aliphatic groups. Triazoles are components of α-glucosidase inhibitors, and as such a scale-up experiment was performed to assess the viability of this methodology in a scaled production. This yielded 1.81 g of **6** (77%) and corresponded to a high turnover number (TON) of 5133. This experiment combined the use of TM catalysts and organic flow synthesis, providing a unique and effective method for accessing 1,2,3-triazoles. The absence of significant catalyst leaching makes this example particularly interesting because such characteristics are highly sought after in large-scale bulk synthesis using metal catalysts.

Flow chemistry is often employed in reactions that deal with hazardous reagents, and this will be encountered many times throughout this section. When using hazardous reagents in flow, containment within a sealed tube prevents the release of toxic/harmful reagents, and the conditions promote efficacious heat and mass transfer leading to controlled chemical interactions. In the synthesis of 1,2,4-thiadiazoles, Baxendale *et al*. demonstrated how hazardous trichloromethane sulfenylchloride can be used and quenched in flow to prevent the formation of obnoxious and corrosive by-products such as HCl and SO_2.[20]

Thiadiazoles are five-membered heterocycles, where the incorporation of one sulfur and two nitrogen atoms leads to increased membrane permeability and a potential to behave as H-bond acceptors. The 1,2,4-thiadiazole is thus an important scaffold as it resembles pyrimidine, a useful biological moiety,[21] and a convenient method for its synthesis that allows for further derivatization is *via* reacting various amidines with trichloromethane sulfenylchloride (Cl_3CSO_2Cl) **7**. This liquid reagent is a notoriously corrosive and fetid substance and is therefore impractical for large-scale synthetic applications in batch mode. The trichloromethane sulfenylchloride approach with its tendency to form malodorous and corrosive by-products accordingly represented an opportunity to implement flow technology to augment the safe handling of a precarious reagent. In early experiments, Cl_3CSO_2Cl (0.45 M, EtOAc) and hydrated benzamidine hydrochloride salt **8** (0.4 M, in 1.5 M NaOH, aq.) stock solutions were prepared and pumped through a Vapourtec R-series reactor (Scheme 5). PTFE sample loops (2-5 mL each) delivered the solutions to a

T-piece mixer which resulted in an emulsion. The emulsion then was pumped into two coiled reactors (PTFE, 2 x 10 mL, rt, no active cooling) in a one-step flow process which also included a 75 psi BPR prior to the product solution being collected in a flask. The ability to quickly screen reactions allowed the authors to determine that a residence time of 5 min was sufficient to obtain a yield of 80% of the desired product. Effective heat transfer in flow was credited to minimize the formation of the undesired side-products while maintaining the viability of the chemical transformation and realizing good overall yields.



Scheme 5. Telescoped flow reaction for generating target **9** using multiple reactors.

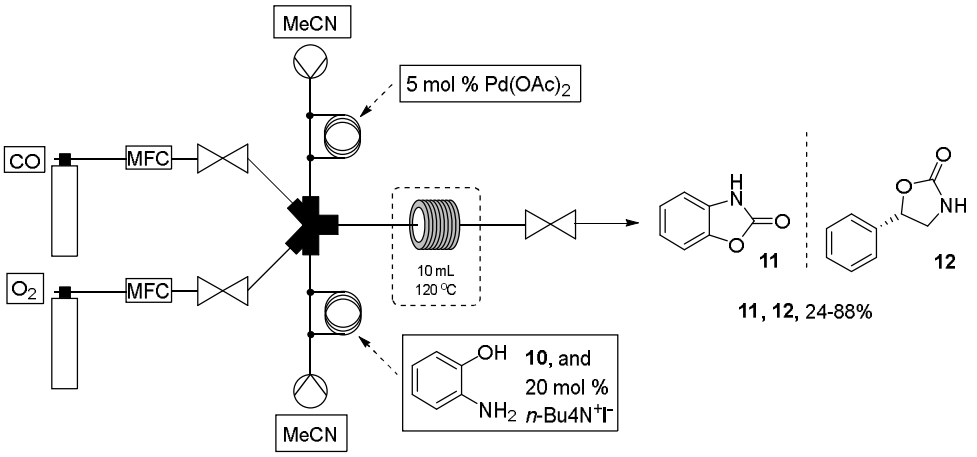
A 30 min residence time was used in further experimentation to complete the consumption of Cl_3CSO_2Cl and the subsequent quench of relevant by-products in aqueous NaOH. The biphasic solvent system thereby resulted in species **9** residing in the organic phase where it avoided hydrolysis, a feature that is described as difficult to achieve under similar batch procedures. This was then applied in a scale-up experiment, where 20 mmol of starting material was processed. The product solution was extracted and filtered over a pad of silica to provide 3.25 g of thiadiazole **9** (83%). This is a good demonstration for how easily flow can lead to a higher yielding, safer and more scalable organic transformation, where the product was very easily isolated following the reaction. Heterocyclic building block **9** was subsequently derivatized by reacting this material with an amine nucleophile (1.1 equiv.) in CH_2Cl_2 (1.0 mmol, 2.5 M) and Et_3N (1.1 equiv.). These reactions were stirred for 2-8 hrs and purified by flash chromatography. This resulted in a series of novel products bearing aromatic, cyclic and aliphatic amine appendages in yields ranging 73-87%, demonstrating the attractive scope and various functional groups that the flow process allowed for. Furthermore, sulfur-linked products were also realized, and moreover, 5-phenoxy-substituted 1,2,4-thiadiazoles were synthesized by reacting **9** (0.5 M, THF) at room temperature with bromophenol and polymer-substituted BEMP acting as a base. In a further increase to the reaction scope, samples bearing bromo substituents on the aryl moiety of the product were derivatized *via* metal mediated amination or cross-coupling reactions.

This methodology for efficiently synthesizing 1,2,4-thiadiazoles in a one-step manner granted increased yield, product scope and safety. The products were sequentially diversified using simple substitution reactions, and the substrates themselves could also be expanded upon thus resulting in a library of biologically interesting molecules.

Reactive gases are important inputs in chemical reactions and their use in combination with flow technology can significantly improve both efficiency and safety of resulting processes. In 2017, Kappe *et al.* demonstrated a use of gaseous reagents in a flow procedure whereby benzoxazolone **11** and 2-oxazolidinone **12** products were synthesized *via* a continuous flow palladium-catalyzed oxidative carbonylation (Scheme 6).[22] Pd-catalyzed carbonylation reactions are an important type of coupling reactions that insert carbonyl moieties into organic frameworks. In the case of a Pd-catalyzed oxidative carbonylation, the Pd(0) ensuing from the carbonylation process is reoxidized to Pd(II) by an external oxidant.[23] Here, precise control of CO and O_2 gas concentration fed into the reaction stream using a mass flow controller (MFC) allowed for a significant improvement in safety, reaction time as well as providing the desired heterocyclic products in generally high yields (24-88%).

Stainless-steel capillary tubes allowed for the use of high temperature and pressure, which was crucial to maintaining the concentration of CO and O_2 at 4 and 8 equivalents respectively (*vs* 127 and 13 equiv. in

batch). The ability to use lower amounts of these gases is important as CO and O_2 are known to form explosive mixtures in a large range of compositions. In addition, the stainless-steel tubing was easily cleaned of Pd residues after the reaction using 20% HNO_3 at 70 °C.



Scheme 6. Flow approach for synthesizing benzoxazolone **11** and 2-oxazolidinone **12** from gaseous reagents.

Following a series of optimization studies the authors determined that a pressure range of 15-20 bar and flow rate for the gaseous feed streams of 4.4 mL/min were ideal for achieving high yields of the desired products. Although Pd catalyst loading was quite high (5 mol%), the possibility for it to be recycled within the catalytic system drastically improved the efficiency of this reaction in a batch *vs* flow comparison (24 h *vs* 24 min). The reaction scope was also studied, with the procedure shown to be viable for a variety of aromatic and aliphatic substrates. However, it should also be noted at this point that, under batch conditions and with a different palladium catalyst, benzoxazolone **11** and oxazolidinones (including **12**) had been previously obtained with TONs as high as 4750 mol product/mol Pd.[24]

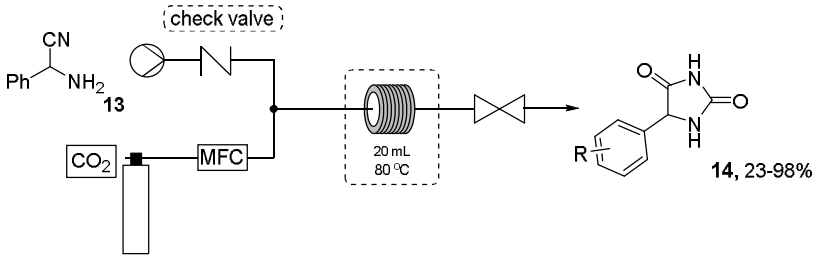
Overall, the flow reaction demonstrated great potential for enabling efficient, safe, and reliable synthesis of valuable heterocyclic targets in a continuous manner. Gaseous reagents were used in a safe and highly controlled manner, with the benzoxazolone products showing high efficacy as anticancer, antimycobacterial, and anticonvulsant therapeutics, and 2-oxazolidinone a valuable organic molecule used as Evans chiral auxiliaries.

Hydantoins (*e.g.* **14**, Scheme 7) are heterocyclic molecules which are of interest in pharmaceuticals,[23] agrochemicals, and also useful as synthetic intermediates. Normal batch-based procedures for synthesizing these interesting heterocycles involve multiple steps and require access to non-commercially available substrates. Vukelić *et al.* described a flow procedure for the synthesis of hydantoins starting from simple amine substrates through consecutive gas-liquid transformations.[24]

The classic approach to synthesizing these target molecules proceeds *via* the Bucherer-Bergs reaction. While this approach allows the chemist to exploit a range of substituted starting materials and has the possibility for further derivatization of hydantoin product, it suffers from poor solubility of starting materials in the appropriate solvents and the use of ammonium carbonate at elevated temperatures causing loss of CO_2 which is required for the final step involving the intermediate. With CO_2 loss being an issue, it is possible to negate this by supplying excess gas from a feed stream source. A further issue is related to the long reaction time (23-41 h) of the Lewis-acid catalysed one-pot procedure making this impractical on large scale.

Here continuous flow chemistry offered the advantage of improved gas-liquid reactions. Increased interfacial areas and better mixing on the microscale combined with facile implementation of high pressure to increase gas solubility are well explored features of continuous procedures.[25] Previous literature has shown that primary and secondary amine photooxidation with singlet oxygen ($^1O_2$) may form an imine

species which can be trapped with cyanide. The authors wanted to couple this amine oxidation with a second gas-liquid CO_2 trapping reaction in the hope it could tolerate a wider range of solvents and therefore a wider range of substrates to produce a more diverse array of hydantoin products. The α-amino nitrile substrates (*e.g.* **13**) were initially synthesized from benzylamine and alkylamine substrates in batch before being subjected to the flow process. α-Amino nitrile **13** (0.1 M in MeOH) was then chosen as the test substrate, and DIPEA (3 equiv.) as the base. The solution was pumped (1 mL/min) into a flow reactor composed of PTFE tubing. Optimized conditions were found to include a CO_2 flow rate of 6 mL/min, temperature of 80 °C, a 20-minute residence time, and pressure of 6 bar for the one-step flow procedure (Scheme 7).



Scheme 7. Flow setup with gaseous reagents for synthesizing hydantoins **14**.

Using these conditions, the scope of the chemical transformation was explored, testing a range of various α-amino nitriles. These reactions provided the substituted hydantoin products in yields ranging 23-98%. Substituents with strong electron withdrawing character provided better yields than those with strong donating character, and aliphatic substrates were limited due to steric hindrance at the α-position. The photooxidation and cyanide trapping of the nitrile intermediate can be performed in THF, however hydantoins are known to have poor solubility in THF. To bypass this issue, the product entering the reactor was mixed with a methanol/DIPEA solution. Using this new input method involving a 420 nm LED to initiate photooxidation, a 20-minute residence time, CO_2 (3.3 equiv.) flowing at 8 mL/min, pressure of 6 bar, and a temperature of 90 °C gave high conversion to the heterocyclic target. Switching the solvent to 2-MeTHF then gave a product which was easier to crystallize following an aqueous wash, while also having the added benefit of using a bioderived solvent in the procedure. Aromatic and aliphatic hydantoins were subsequently synthesized in yields ranging 52-84% without the need for chromatographic purification.

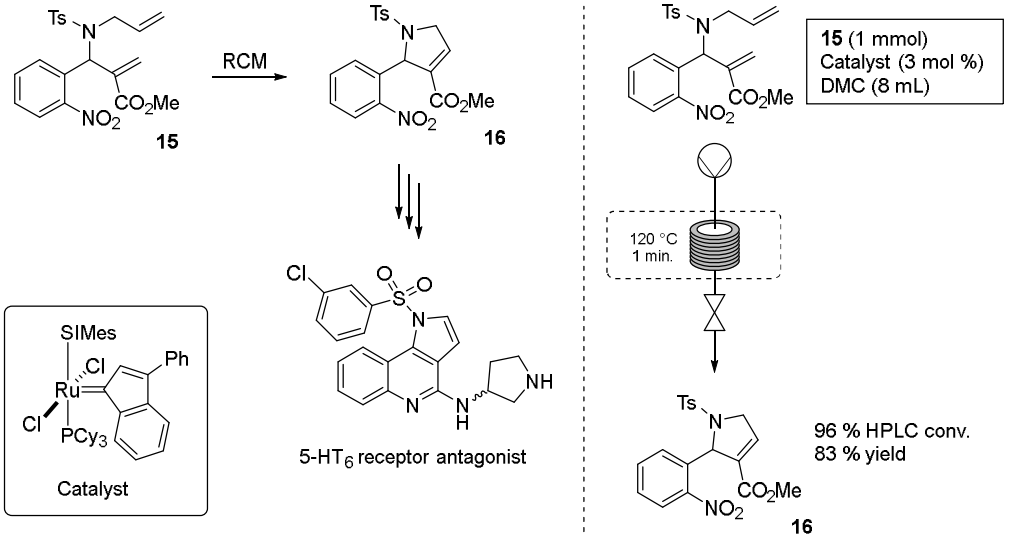
This example is an excellent demonstration of how flow chemistry can provide improvements on reactions involving gas-liquid mixtures that are often difficult to use. The possibility to integrate UV-light sources to initiate photooxidation, and the use of a more environmentally friendly solvent were two aspects that make this flow process appealing. Elevated pressure and temperature within the reactor tubing granted increased solubility of the gaseous input to the reaction mixture, enabling a far more efficient synthesis of an important heterocyclic target whereby excess CO_2 was easily removed from the reaction stream after passing the BPR.

Olefin metathesis is a popular reaction type in the synthesis of APIs, arising from the desire to efficiently generate carbon-carbon double bonds. Its popularity derives from its high atom economy giving a reliable reaction outcome, which leads to fewer by-products and a decrease in hazardous waste. One of the most well-demonstrated applications of olefin metathesis in continuous flow was published by Drop *et al.* who employed the ring-closing metathesis (RCM) reaction in a low-waste synthesis of heterocyclic 2,5-dihydro-1*H*-pyrrole-3-carboxylates (*e.g.* **16**).[26]

Recent literature had shown that **16** was a versatile building block en route towards pyrroloquinolines, a class of bioactive molecules which mimic 5-HT_6 receptor antagonists (Scheme 8). Current examples of pharmaceutical drugs that include similar moieties within their framework include Tamiflu® and Ciluprevir®. Previous attempts by the authors in converting **15** into **16** were performed using microwaves to initiate RCM of **15**, however the use of microwaves for such a purpose meant this method lacked feasibility for application on an industrial scale. In re-imagining their approach, the authors decided to employ flow chemistry with the intention of performing the ring-closing metathesis in miniaturized apparatus to alleviate

potential issues with safety and scalability. Microflow systems afforded the possibility to precisely control reaction conditions such as super-heating solvents, shortening reaction times, and the safe handling of potentially hazardous catalysts. Super-heating the solvent would prove to be particularly useful in this incidence, as elevated temperature is seen as a crucial parameter in achieving high yielding RCM reactions.[27]

The reactor system chosen to perform the RCM step for the flow synthesis of pyrroloquinolines was the FlowSyn® reactor. Reactions were initially screened using the desired substrate and a range of solvents including dimethyl carbonate (DMC), CH_2Cl_2 and EtOAc. DMC was found to be the best solvent which was then super-heated within the reactor (PTFE, 5 mL). Having settled upon a choice of solvent for the flow process, the authors next investigated a range of parameters including temperatures ranging from 90-130 °C and residence times of 5-30 min, while concurrently studying the effectiveness of a range of commercially available second-generation Ru catalysts for the purpose of this olefin metathesis. Eventually the authors settled upon the indenylidene species depicted in Scheme 8 as the preferred catalyst (3 mol%) as it gave 96% conversion of substrate **15** in a very short residence time (1 min), a temperature of 120 °C, and 100 psi pressure while fully solubilizing the catalyst ensuring a homogenous catalytic reaction mixture.



Scheme 8. Synthetic approach to a 5-HT_6 receptor antagonist involving RCM. Flow chemistry in performing RCM to provide **16**.

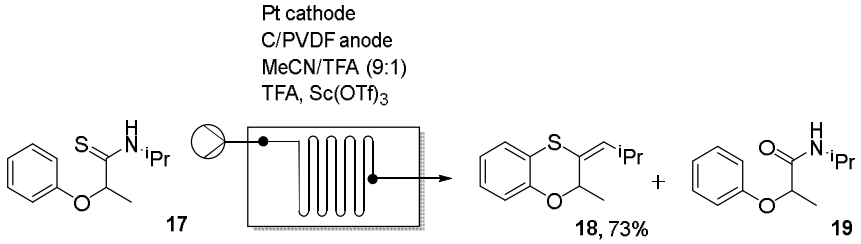
Ensuring a homogenous mixture in such incidences is crucial, as a solution containing small solid particles tends to result in reactor fouling and clogging. To nullify the potential for catalyst decomposition through mixing it in a single vial with the substrate, a two-pump system for separate solutions was also studied. This phenomenon is known in the literature and results in the formation of a Ru-methylidene species.[28] Employing the optimized conditions with a 2.5 mL/min flow rate, an 83% yield was obtained following flash chromatography. This was interesting as the yield was lower than the one-pump system, despite deciding to feed the substrate and catalyst into the reactor system in separate solutions. Reverting to the one-pump system, the scope of this in-flow metathesis was further investigated by employing a range of substrates, which bore a variety of electron donating and withdrawing substituents on the aryl ring. These reactions gave yields ranging 79-92% (5 min, 110 °C) and 52-91% (1 min, 120 °C). Finally, a scale-up reaction was also attempted, successfully producing 10 g (91%) of **16** in 37 min; an excellent demonstration of how the flow system in this case was adapted to manipulate a super-heated solvent and a catalytic process greatly increasing the speed for the synthesis of an important heterocyclic target. This is a significant improvement upon the batch process for similar substrates, which provide similar quantities of product, however, reactions are in the order of hours and yields typically range from 50-70%.[29]

In demonstrating the wide-ranging applications of various flow approaches, chemists will often push the boundaries of what is possible to explore how flow chemistry may be applied in organic synthesis. As we have previously discussed in this chapter, sulfur-containing heterocycles are a target in many organic syntheses, and new methods for their synthesis are constantly in development. A novel flow-based approach was also detailed by Xu *et al*. who employed a flow regime to an electrochemical synthesis of benzofused sulfur-containing heterocycles in good yields, short reaction times and with the potential for a scale-up process.[30]

Dehydrogenative cross-coupling is an appealing method for making new C-C and C-heteroatom bonds in organic chemistry.[31] However, there is currently a lack of viable C-S coupling methods, owing to the tendency of sulfur nucleophiles to form irreversible complexes with TM catalysts and oxidative side-reactions, hence most methods for synthesizing C-S bonds rely on aryl-halide redox-neutral cross-coupling reactions. While organic electrochemistry for intramolecular reactions has been studied, to date the intermolecular dehydrogenative cross-coupling of electron-rich arenes with thiophenols has been relatively unexplored.

Organic electrochemistry has experienced an uptick in popularity, due to its feasibility as a green process for synthesis through passive H_2 generation, and in this incidence the authors envisaged de-hydrogenative cross-coupling reactions initiated through electrochemical means. Electrosynthesis when applied in flow, may avail of the benefits of high surface area/reactor volume, improved mass transfer and reagent mixing, and facile scale-up present the ideal opportunity for flow technology to be applied to a difficult organic transformation. Having previously employed flow chemistry in the synthesis of benzothiazoles under catalyst- and electrolyte-free conditions, the authors decided to implement a similar hypothesis for the dehydrogenative cross coupling of benzofused *S*-heterocycles through electrochemistry (Scheme 9).

Electrosynthesis was performed in an electrolytic flow cell housing a Pt cathode (1x1 cm) and an anode (1x1 cm) made of carbon filled polyvinylidene fluoride (C/PVDF). Optimization studies showed that a 73% yield of the desired heterocyclic product **18** was attainable using continuous-flow electrolysis in a mixed solvent of MeCN/TFA (9:1) in the presence of $Sc(OTf)_3$ (0.3 equiv.), without observing the desulfurized amide species **19**. The presence of acid was found to be crucial to the feasibility of this reaction. The reactor had a 10 cm^2 surface area supplying a current of 35 mA. A flow rate of 0.3 mL/min at room temperature conditions was also necessary to achieve the previously mentioned yield of 73% determined by ^{1}H-NMR.



Scheme 9. Simplified schematic of electrosynthetic flow chemistry in the preparation of **18**.

In studying the scope of this reaction, the methodology was found to be applicable for a range of substrates containing electron withdrawing and electron donating groups. The α-position and the ^{i}Pr group of the thioamide were also successfully diversified without having a drastic effect on yields (54-81%). The synthesis could also be expanded to include 1,4-benzothiazines. The *N*-phenyl ring, *N*-substituents, and the α-substituents all tolerated variation and afforded the corresponding products in high yield (48-80%).

Regarding the design of the flow electrolysis cell, the platinum cathode allowed for high electrochemical stability and low overpotential for proton reduction, preventing the occurrence of side reactions. In forming the desired product, the thioketone was oxidized to the free radical intermediate before rapidly undergoing cross-coupling with the neighbouring aromatic ring to afford the product. To alleviate the worry of expensive Pt cathodes, Pt-plated cathodes were prepared using an inexpensive base on a

stainless-steel plate. This new plated cathode was used in a 24 hour scale-up experiment, which produced 1.91 g (67%) of **18**. Some final cyclic voltammetry studies also revealed how the oxidative potential of **17** was reduced in the presence of $Sc(OTf)_3$ and TFA, however, the oxidative potential of the product is higher. This study demonstrated how these additives were important for initiating the dehydrogenative cross coupling of the product but had a negligible possibility to over-oxidize the product.

Throughout this chapter, we have discussed several reactions forming heteroaromatic rings. However, something that is underexplored are dearomatizing processes for converting aromatic compounds into saturated heterocyclic compounds, and it is a popular topic in modern organic chemistry.[32] Another approach yielding saturated heteroaromatic targets is based on reacting ylides as dipoles with dipolarophiles *via* dipolar cycloaddition chemistry. A recent related example described in literature shows a flow-based approach to promote 3-cyanoindoles to behave as C=C dipolarophiles to undergo dearomative [3+2] cycloaddition.[33]

To begin, the authors studied cyanoindole **20** (Scheme 10) containing a tosylate group as protecting group on the nitrogen atom. Reacting **20** with 9 equiv. of **21** and catalytic amounts of TFA over 30 min at 0 °C resulted in 84% conversion (58% yield) towards cycloadduct **22**. To increase conversion, different nitrogen protecting groups were investigated, with triflouromethylsulfonyl (Tf) proving to give full conversion and a 78% overall yield. Further optimization resulted in 6 equiv. of ylide precursor **21** being used and completion of the reaction upon full dropwise addition of the catalyst giving an 88% yield of the desired product. Of particular interest in this example was the integration of infrared (IR) in-line analysis techniques to determine the composition of the product solution as the reaction progressed. This was done by analysing the formation of bands at 1406 cm^{-1} and 1200 cm^{-1} which corresponded to the desired product, and in this case once all the TFA had been added the intensity of the previously discussed bands reached a maximum.

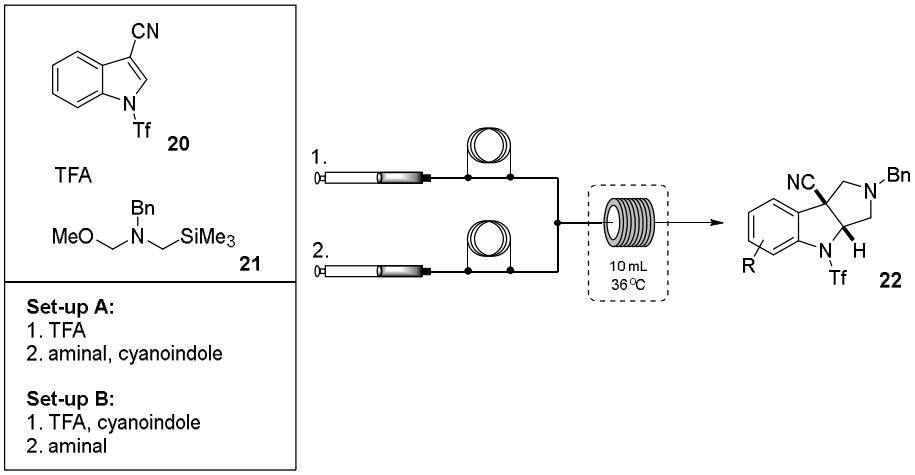
Scheme 10. Dearomatization of 3-cyanoindoles performed in batch.

Applying this method to a range of aromatic substrates bearing electron withdrawing/donating, heteroaromatic and electron-poor substituents furnished a series of products in 73-97% yield demonstrating a wide scope for this cycloaddition. The reaction also showed good tolerance and no competing reactivity between these various substrates and the intended dearomatizing dipolar cycloaddition process.

The large excess of dipole precursor **21** and slow addition of TFA to prevent self-condensation is a tedious process also suffering from potential ylide consumption as the TFA concentration increases. Here, the ability of microflow reactors allowing for precise control over reaction times and the ability to form and trap reactive intermediates made this an obvious candidate to improve the overall efficiency. Ley *et al.* described a procedure whereby 3-nitropyrrolidines were synthesized in flow from an analogous ylide formed *in situ* and nitroalkenes behaving as dipolarophiles.[34] This flow set-up consisted of two inlets which fed the reaction solutions into a 10 mL coil reactor at 20 °C at a rate of 2 mL/min. Initial test results gave a promising result of 97% conversion (determined by ^{1}H-NMR) in 5 minutes. Increasing the flow rate to 20 mL/min to enhance a turbulent mode of flow in the reaction solution resulted in almost complete conversion (τ=30 sec). Further optimization to study the effects of reduced TFA concentration showed that conditions of 36 °C with 3 equiv. of substrate and 0.24 equiv. of TFA gave full conversion. For comparison, these conditions utilised in batch gave a 44% conversion.

This flow set-up was subsequently applied to the same substrates which were investigated in batch and yields for the products synthesized in flow ranged from 75-97% (Scheme 11). These products represent a molecular scaffold with the potential for further derivatization to increase their complexity and their potential biological application. As such, the authors successfully performed a Suzuki-coupling reaction with a substrate bearing an arylbromide substituent, and successfully reduced the nitrile group to its

corresponding amine with $LiAlH_4$. These substituted indoline derivatives have displayed potential use as biomolecules, organocatalysts, and as ligands. Being able to synthesize such products in a rapid (30 s res. time) and highly controlled manner is appealing in academia and industry.



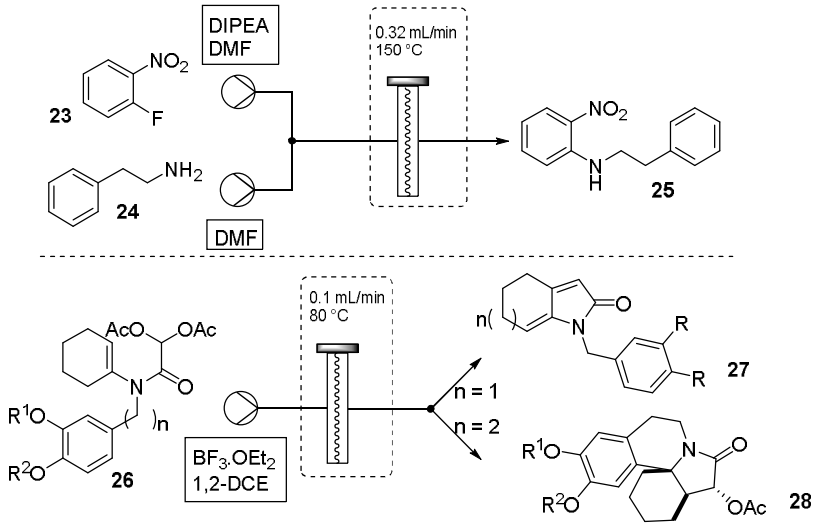
Scheme 11. Set-ups studied for the continuous dearomatization of 3-cyanoindoles.

Having access to conceptual prototype reactors with which to perform continuous flow reactions has been expedited by the advancements made in 3D printing technology. 3D printing allows for unique and specially designed reactor components to be realized quickly and at a low cost. One example where this was included in a synthetic procedure was by Rao *et al.* who incorporated a polypropylene (PP) reactor in the Lews acid-mediated synthesis of heterocycles.[35]

The authors initially investigated the utility and solvent-resistance of the PP 3D-printed reactor for an S_NAr reaction produce substituted aniline derivatives (*e.g.* **25**). The 3D-printed PP reactor was coupled with a Uniqis FlowSyn system. The central column of the printed reactor was thereby in direct contact with the heated reactor of the FlowSyn set-up. The flow path of the solvent for the reactor was designed to move as an internal spiral, thus maximizing contact of the solution with the outside hot surface of the column positioned within the heating block of the FlowSyn system to initiate chemical reactions. Internal coil diameter was 2 mm and internal reactor volume was 1.6 mL. A high material flow rate in the 3D-printing process ensured complete fusion of joints and a contiguous sealed surface in the printed reactor. Finally, a screw head was tapped out to provide a fitting for PEEK tubing (Scheme 12). In this example, 1-flouro-2-nitrobenzene **23** and phenylethylamine **24** were the model substrates for the flow synthesis of 2-nitro-*N*-phenethylaniline **25**.

S_NAr reactions were trialled to test the durability of these printed reactors towards high temperatures and a variety of solvents as these reaction types typically employ harsh conditions. Setting both pumps to a flow rate of 0.16 mL/min and a temperature of 150 °C, a 66% conversion (63% isolated yield) to the desired product was observed. Using these conditions, a range of substituted aniline derivatives were prepared in yields ranging 24-100%. Following this success, the authors tested this new PEEK reactor column to synthesize compounds that would structurally mimic the naturally occurring erythrina alkaloids, such as lycorane. Tertiary amide **26** containing alkyl chains of varying length (n=1/2) was heated under the optimised microwave flow conditions providing a series of bicyclic **27** and tetracyclic **28** alkaloid products. The authors had previously described a procedure to access these bicyclic and tetracyclic cores using microwaves.[36,37] In the previously optimized conditions, the precursors were treated with BF_3 acting as the Lewis acid at 65 °C using microwaves for 15 minutes. For the flow process, the solution was heated at 80 °C at a flow rate of 0.1 mL/min equating to a 16-minute residence time, therefore replicating the microwave conditions. These conditions allowed for the flow synthesis of a range of bicyclic structures in 34-77%

yields (Scheme 12). These yields were comparable with those that were obtained when the same reaction was performed in batch, albeit at a slightly elevated temperature. For the tetracyclic structures related to the erythrina family, the tetracyclic precursor was subjected to the same conditions as that of the bicyclic reaction. This Lewis acid mediated domino cyclization process facilitates the formation of a single diastereoisomer. The flow reaction in the PP reactor provided the racemic products in excellent yields, comparable to those of the microwave reaction.



Scheme 12. Integration of a 3D printed PEEK reactor in synthesizing a range of heterocyclic products.

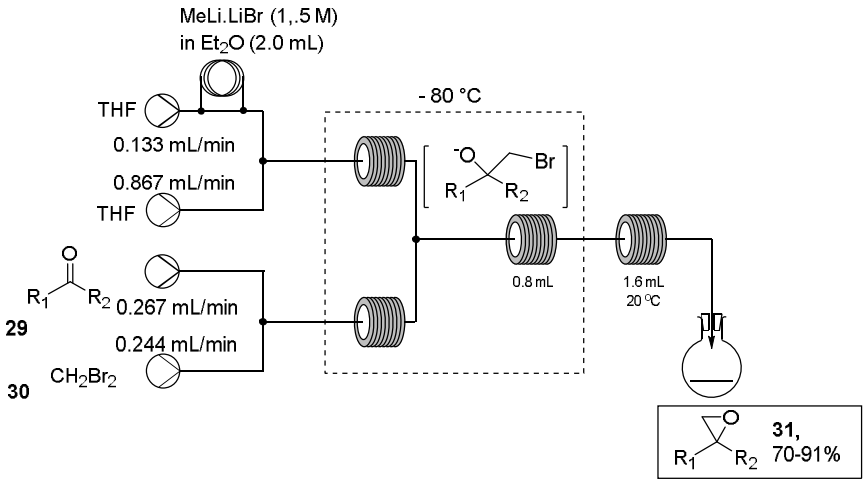
The ability to transition batch-based microwave reactions to readily scalable continuous flow reactions with equivalent yields is an attractive feature of this example. Microwave energy is impractical to use in large-scale batch syntheses, particularly in an industrial setting for scale-up purposes. Thus, realizing a process whereby microwaves are no longer required, and the process may be performed under more gentle heating in a microflow system is desirable. Furthermore, the demonstration with which 3D-printing can be used as a complement to flow chemistry in the form of unique and specially designed reactor components shows how flow chemistry may be further integrated with many forms of commercially available enabling technologies with a view towards synthetic augmentation.

Ring sizes of heterocycles vary greatly in nature. One common small heterocycle is the epoxide moiety, and it is a highly desirable synthetic target owing to its high degree of ring strain and hence potential for nucleophilic ring opening leading to β-substituted alcohols.[38] While typically generated from the oxidation of alkenes, it is also possible to prepare 2,2-disubstituted epoxides using halomethyl lithium reagents. (Bromomethyl)lithium is attractive for this purpose as it is easily prepared from inexpensive CH_2Br_2 and MeLi, however, it suffers from drawbacks such as thermal instability and the need to generate it *in situ*. Additionally, the lithium base must be added slowly, rendering the process unfeasible on large scale. These issues to generate desirable disubstituted epoxides were overcame by von Keutz *et al.* who described a continuous flow procedure for their synthesis.[39]

The authors proposed that the *in situ* generation of $LiCH_2Br$ using microflow technology would allow for the synthesis of epoxides from disubstituted ketones in a controlled and efficient manner. (Bromomethyl)lithium generation was initially studied in batch, *via* lithium-halogen exchange using CH_2Br_2 prior to reaction with acetophenone. Lithium bases such as LDA and LHMDS gave low selectivity of the desired product, while MeLi and BuLi both gave high conversion and selectivity, with the MeLi·LiBr complex providing even better results after investigations. It is suspected here that the LiBr salt stabilized the

bromolithium complex thus increasing its half-life in solution, and this would prove key in applying the *in situ* generation of the reagent.

For the flow procedure (Scheme 13), syringe pumps delivered the reagent solutions into PFA tubing with the feed streams connected *via* T-piece mixers. The MeLi·LiBr complex was insoluble at a concentration of 1.5 M below 0 °C, and so a feed stream with surplus THF was introduced to dilute the mixture and prevent clogging of the reactor. Pre-cooling loops ensured the reagent solution was cooled before entering the reactor where it mixed with a selected ketone **29** and dibromomethane **30**. The reaction mixture was maintained at –80 °C with a 30 second residence time employed before being warmed to 20 °C in a second reactor where the cyclization step occurred before being quenched with water. The substrate scope was then studied, with good yields obtained for all products. Electron donating substituents on the substrate molecule gave higher yields than those containing electron withdrawing groups. High selectivity was observed in all cases enabling the integration of a simple liquid-liquid extraction followed by evaporation to provide the desired epoxide products **31** without further purification.



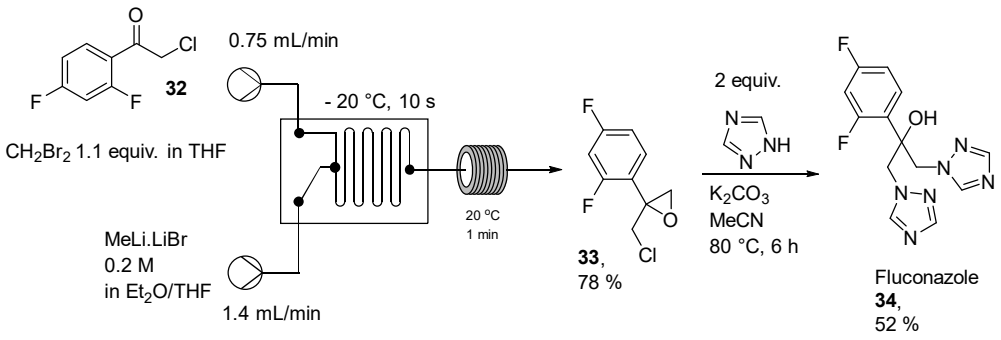
Scheme 13. Flow set-up for producing 2,2-disubstituted epoxides **31**.

To demonstrate the industrial feasibility of this continuous (bromomethyl)lithium generation process, the methodology was applied to the synthesis of the API fluconazole, a drug used to treat fungal infections and on the WHO list of '100 essential medicines'. This was generated from 2-chloro-1-(2,4-difluorophenyl)ethan-1-one **32** starting material and the reaction was performed using a Lonza FlowPlate reactor, which afforded better heat transfer and mixing of the reagent solutions, thus alleviating the need for cryogenic temperatures, a phenomenon well-noted in modern flow literature. With the key epoxide accessed at –20 °C in this case, a scale-up experiment over a 3-hour period also successfully processed 34 mmol of starting material with constant conversion and selectivity. The residence time was 10 seconds, and 1 minute for the following cyclization step, which was performed in a capillary reactor. This epoxide **33** was subsequently treated with 2.0 equiv. of 1,2,4-triazole to provide the fluconazole product **34** in 5.4 g (52% yield, Scheme 14).

In this example, flow synthesis was successfully applied to the synthesis of a highly desirable 2,2-disubstituted epoxide product with excellent yields. The short reactions times and simple work-up allowed for a short process to access these products, and the scope was wide ranging in that the method could be applied to prepare an in-demand API on multi-gram scale.

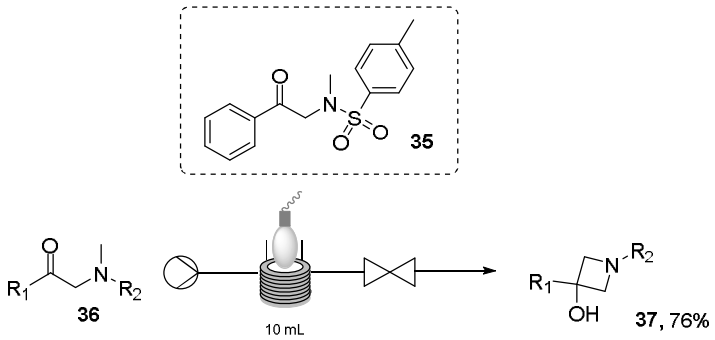
Keeping with small heterocyclic molecules as synthetic targets, azetidines are saturated 4-membered rings containing a single nitrogen atom. The organic structure mimics the ring system in β-lactam antibiotics,[40] and can be widely used as chemical analogs for structural targets. One method for their preparation is *via* the Norrish-Yang reaction which yields a 3-hydroxyazetidine system. The reaction

proceeds photochemically, and as we will discuss in this section it is therefore prone to certain synthetic limitations which commonly arise when performing photochemical reactions in batch mode. Ruggeri *et al.* recently described a flow synthesis of these desirable synthetic targets, where the flow set-up provided an attractive platform to overcome the drawbacks of the typical batch procedure.[41]



Scheme 14. Flow synthesis of fluconazole **34**.

Solutions of the starting material were subjected to UV irradiation within the photoreactor of a Vapourtec E-series flow module which contains a medium-pressure Hg-lamp (150 W at 100% power) as depicted in Scheme 15. Solutions were delivered from a peristaltic pump at 1.0 mL/min which equated a 10-minute residence time. Initial studies revealed that substrate **35** gave 99% conversion resulting in 76% isolated yield of the desired product **37** following flash chromatography. Other lamps such as a low-pressure Hg-lamp (7.8 W, 59% conversion) were trialled but failed to improve the reaction, as did various photocatalysts such as methylene blue and benzophenone. Various solvents were also trialled, with MeCN proving the best candidate in terms of product yield, solubility, and reduced capacity to undergo potential radical side reactions.



Scheme 15. Flow photosynthesis of azetidines **37** *via* Norrish-Yang approach.

In studying the scope of the reaction, various substrates were prepared in a similar process to that of **36**. Aromatic rings bearing *para* and *meta*-chloride and bromide substituents proceeded well, however, *ortho*-substituted rings gave more decomposition of the starting material when subjected to the photoflow process. *Ortho*-fluoro substitution on the aryl ring (R_1) did proceed well and this was attributed to the small size of the fluorine atom not interfering sterically with the reaction intermediate transition state. Electron donating and withdrawing groups were also included in these studies, and notably electron donating groups gave far lower yields of the desired product. These limitations for electron donating substituents were overcome through varying some parameters, including a reduced flow rate (0.7 mL/min), lower lamp power (90%), and a higher temperature (70 °C, normally 20 °C). These studies revealed the nature of the aryl ring

as a determining factor in the success of achieving high yielding reactions for this photoflow process. Good yields were almost always achieved when there was a good match between the substrate absorbance and the lamp emission. Heteroaromatic rings were well-tolerated (60-69% yields) but aliphatic substrates bound to the azetidine product ring gave diminished yields (30-47%). Modification of the sulfonamide component of the starting material was also feasible for the photochemical flow reaction giving yields ~60%. N-Boc protected substrates were also investigated but required an alteration of flow conditions whereby MeOH as solvent, 40 °C and 0.8 mL/min flow rate was sufficient to give 71-89% yields in another series of *N*-substituted azetidine products.

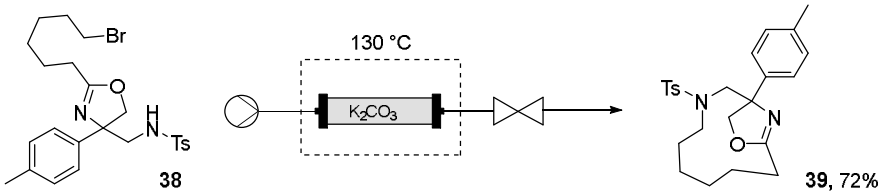
A final scale-up reaction processing 100 mmol of starting material in a single run over 11.5 hours gave a 60% yield of the desired hydroxy-azetidine following column chromatography, effectively demonstrating the ability to synthesize a desirable azetidine target on multigram scale. Appropriate optimization and studying of the reaction scope delivered a viable, efficient continuous flow process, yielding valuable molecular targets.

In an interesting follow-up project concerning the flow synthesis of hydroxy-azetidines, the same authors recently provided an interesting extension of their work whereby the 3-hydroxy-azetidine products underwent a flow-based Ritter reaction cascade to provide highly substituted 2-oxazolines.[42] Oxazolines are valuable molecular scaffolds and occur in several natural products and drug molecules. As with the previous example, the scope of the reaction was diverse with the products further derivatized to provide a series of macrocycles *via* intramolecular cyclization.

The initial idea was to replace the tertiary benzylic alcohol of the 3-hydroxy-azetidine with an amide group through a Ritter reaction using MeCN as reagent. The substrate was refluxed in CH_2Cl_2 with H_2SO_4 (1.0 equiv.) and excess MeCN, but surprisingly gave a 90% isolated yield of a 2-oxazoline species as confirmed by X-ray crystallography. The authors proposed that this reaction proceeded *via* a Ritter reaction cascade. The initially formed amide thereby underwent rearrangement where the amide carbonyl attacks and ring opens the azetidine, with the driving force of the reaction being the release of ring strain.

Various acid additives were trialled, yet H_2SO_4 was found to give the best results. Sub-stoichiometric quantities of acid could be used, however, this required greatly extended residence time to maintain the high conversion, and ultimately led to more decomposition and a reduced yield. H_2SO_4 in this case proved a superior choice in terms of yield, cost, safety, and availability. The nitrile reagents and azetidine substrates were varied to study the scope of the reaction, with a range of possible substituents in both cases providing high yields in short reaction time (~10 minutes).

During initial studies, it was shown that a bromide appendage could be attached to the nitrogen atom of the starting material *via* a nucleophilic addition reaction which displaced the tosyl moiety. This opened the possibility for including alkyl halide chains in the products generated from the Ritter reaction cascade (*e.g.* **38**, Scheme 16).



Scheme 16. Flow synthesis of macrocycle **39** *via* a K_2CO_3 packed-bed reactor.

This was subsequently applied to a series of products that were treated with K_2CO_3 at reflux for 36 hours to provide a series of macrocyclic oxazoline products (*e.g.* **39**). These novel macrocyclic products are particularly interesting due to their unexplored applications to date, and hence a continuous flow process was developed to scale their synthesis for biological investigations. The same ring-closing cyclization reaction was performed in flow because the flow parameters would allow for more effective heating of the reagent solution to produce the target molecules. A Vapourtec E-series reactor equipped with a packed-bed column filled with solid K_2CO_3 was used successfully. A BPR (100 psi) maintained pressure and consistent flow

rates of the heated reaction solution (>100 °C in MeCN). The stock solution was pumped through the column at 0.4 mL/min and hugely cut the reaction time to produce the macrocyclic target molecules from 36 hours to 1.5 hours. Gram quantities of the desired products were synthesized with throughputs of ~800 mg/h.

This novel process provided a series of previously unseen reaction cascade products, with the potential to diversify the reaction downstream to further provide more diverse products in the form of macrocyclic oxazolines. The wide-ranging reaction scope, and short reaction times and scale-up potential arising from its translation to continuous flow gave a process that has high applicability in an industrial setting for bulk synthesis.

Macrocycles are of considerable interest to chemists owing to their prominent use as antibiotics and in the fragrance industry.[43] Recently, Kirschning *et al.* devised a continuous flow process for their production starting from simple cyclic ketones and triperoxides. This approach took advantage of flow chemistry to deliver macrolactones continuously through the safe use of hazardous reagents.[44]

As early as 1970 an analogous batch approach to access macrocyclic lactones was reported in which the target molecules were synthesized *via* triperoxides (*e.g.* **41**, Figure 1). These were obtained through trimerization of small cyclic ketones.[45] In this batch method, heating the ketones in concentrated H_2O_2 rendered the process unfeasible on large scale, and this is where the authors proposed that flow chemistry could provide a suitable alternative to turn this synthesis into a viable route. In flow, only small amounts of H_2O_2 and triperoxide would experience heating at any one time, greatly improving the safety aspect of the reaction for scale-up purposes.

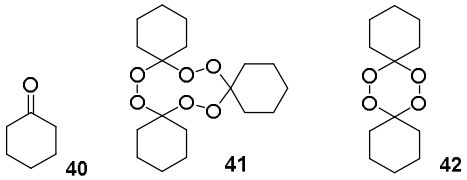
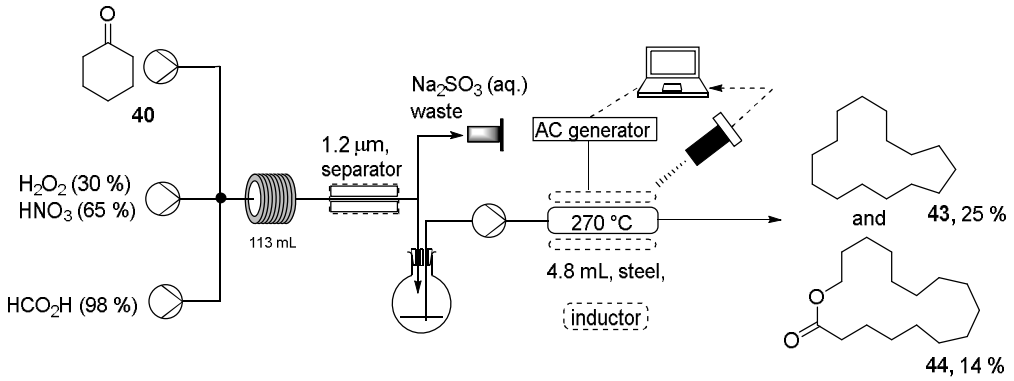


Figure 1. Structures of compounds **40**, **41** and **42**.

To begin, a series of triperoxides were synthesized in batch. Compound **41** was chosen as the model substrate and was heated in flow using an inductive heating method previously employed by the authors, where an oscillating electromagnetic field (medium frequency: 15-100 MHz, or high frequency: 100-800 MHz) induces heat in metal-based flow reactors. Ketone **40** was dissolved in dodecane and added to a sample loop containing excess dodecane before being pumped into the reactor (4.8 mL volume). The computer-controlled reactor was equipped with an in-line IR pyrometer for initial reaction analysis. Design of Experiment (DoE) software was used in determining that stainless steel was ideal for the reactor loop material as copper reactors led to lower yields and oligomeric side-products. Highest yields were obtained at 300 °C at a 5-minute residence time. Macrocyclic lactone targets and hydrocarbon products were both synthesized in these cases, but successfully separated using gas chromatography (Scheme 17). The synthesis of cyclohexanone triperoxide **41** was then optimized under flow conditions. Three reservoirs containing cyclohexanone triperoxide, 98% formic acid, and 30% hydrogen peroxide with 65% HNO_3 were set up with inert PTFE chosen as the reactor tubing to prevent peroxide-metal interactions. The three feed streams mixed after being pumped through HPLC columns; pump 1-cyclohexanone **40** in dodecane, pump 2-98% formic acid, pump 3-peroxide mixture delivered the solutions to the 50 mL PTFE reactor *via* a mixing piece. Higher temperatures resulted in increased side-product formation, and the formation of cyclohexanone diperoxide **42** was proven to be unavoidable after considerable optimization studies.

The next stage involved the telescoping of both optimized steps to form a continuous multi-step flow process. To do this, a separation membrane between the first and second step was required. This was because H_2O_2 had to be removed from the product phase of reactor 1 to prevent the dangers associated with its pyrolysis in reactor 2. The phase separator consisted of two stainless steel plates containing a hydrophobic PTFE membrane with a 1.2 μm pore size and could be operated at a flow rate of 5 mL/min. The reaction mixture exiting reactor 1 (93 min.) was collected in a flask before being pumped by a HPLC pump directly into the second reactor to undergo pyrolysis. The pyrolysis step was inductively heated to 270 °C,

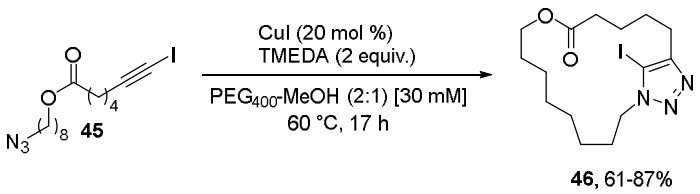
and the initial oxidation in PTFE tubing was performed at room temperature (12 min.). One interesting detail was that although the flow process was unique in terms of safety, scale-up potential, and its continuous nature, the yields were not entirely different from those obtained in batch (**43**, 14%; **44**, 23%). This flow process allowed for the continuous flow synthesis of nine macrolactone species of varying sizes between 14-20 carbons, and nine corresponding hydrocarbon products which were separated by gas chromatography.



Scheme 17. Telescoped flow synthesis of macrocyclic lactone **44**.

Normal batch macrocycle syntheses require high dilution and high catalyst loading and have a tendency for oligomer formation, rendering their synthesis impractical on large scale despite their relevance to the pharmaceutical industry.[46] Even though examples in literature using continuous flow chemistry to synthesize these targets are scarce, some early examples employed copper catalysts to initiate cycloaddition and form the drug-like macrocyclic target molecule.[47] In recent years, the Collins group has explored macrocycle synthesis through various click reactions and a 'phase-separation' strategy *via* copper-catalyzed azide-iodoalkyne cycloaddition (CuAiAC) chemistry. After initial encouraging results in the CuAiAC method, the authors of this example developed a high concentration CuAiAAC method which was expanded to include a copper catalyzed azide alkyne cycloaddition (CuAAC) continuous flow protocol with an extensive substrate scope.[48]

Initial studies began with a batch-optimized macrocyclization of an azide **45** (Scheme 18) The reaction proceeded well, but the reaction efficiency suffered as it proceeded due to the reaction mixture becoming increasingly heterogenous. The ligand was then replaced by TMEDA, and although no conversion to the desired product **46** was observed, this was improved to 50% once the ratio of PEG_{400}-MeOH was adjusted.



Scheme 18. Batch optimization of macrolactone synthesis for **46**.

The flow procedure exploited a Vapourtec R-series reactor housing four in-line 10 mL PFA coil reactors. Using phase separation at high concentration, a 0.1 and 0.4 mL/min flow rate (400 min.) at 80 °C maintained the homogeneous character in the reaction solution and managed to provide the desired macrolactone product in 83% yield following column chromatography. Furthermore, the concentration could be increased to 50 mM and in a scale-up reaction an 81% yield was achieved after purification. Using their optimized conditions, the authors expanded the scope of the reaction to synthesize a series of macrocyclic lactones containing a variety of phenolic, and amino substituents (isoleucine, phenylalanine) in 76-90%

yields. The scope was further broadened when the optimized conditions were applied to a CuAAC click reaction. This product series comprised of macrolactones with fused aryl esters, naphthalene and aryl esters containing various electron donating groups and halide substituents in 61-87% yields.

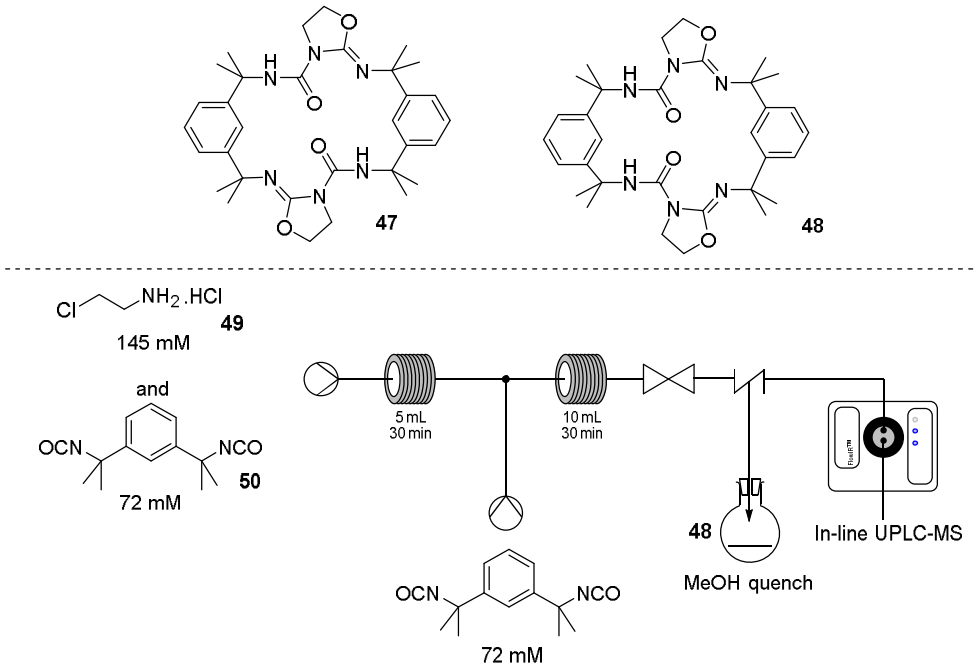
This efficient method for generating macrocyclic triazoles in flow provided a series of interesting products in high yield with potential for future applications in medicinal chemistry. The flow-based phase separation strategy allowed the homogenous reaction to be performed at high temperatures and with higher-than-normal substrate loading in the reaction solution.

Large heterocyclic macrocycles have pertinent application in chemistry as discussed in this section. Their applications are wide-ranging, with use in the pharmaceutical and fragrance industries. One prominent developing area in chemistry is the idea of 'molecular machines', molecules which produce mechanical movement in response to an external stimulus.[49] In 2021, Jones *et al.* described a continuous flow process leading to the bulk production of a heterocyclic molecular hinge, with clamp-like open and close conformations.[50] The synthesis was high yielding with facile scale-up potential from readily-available starting materials.

Molecular machines are comprised of modular components linked through covalent or mechanical bonds, that change shape reversibly in a predictable manner. Hinged macrocycles may function as clips or tweezers, where the closing mechanism maximizes interaction between chemical species within the encapsulating structure. Most hinges close *via* a dihedral rotation of bonding character, however their ineffectiveness when fully closing to encapsulate a reactive species may impart inadequate functionality relative to their purpose. Therefore, the hinge must be able to function aptly to an external stimulus without disturbing supramolecular structure or chemical reactivity, while being chemically stable, readily accessible, and crucially avoiding host-guest interactions. To date, many examples which display all these requirements suffer from poor solubility, high reactivity, and expensive/complicated assembly. Synthesizing macrocyclic molecular hinges also requires the use of protecting groups, supramolecular templates, and high-dilution conditions, meaning their synthesis on large scale is not practical. Here, continuous flow may provide a solution, where process automation, in-line monitoring and better heat and mass transfer through micro-mixing grant chemists the opportunity to screen and optimise molecular machine synthesis reactions at greater speed. If these products could be made in flow, then there is the potential to quickly optimize the synthesis in terms of the thermodynamics and kinetics involved in the intermediate and product forming steps.

In this example, macrocyclic molecular hinges **47** and **48** were prepared *via* a one-pot cyclization process (Scheme 19). Both macrocycle transitions were isolated as separate concomitant individual crystals for analysis. Macrocycles **47** and **48** are insoluble in water but soluble in $CHCl_3$ and CH_2Cl_2 and sparingly in MeOH and DMSO and are isolable *via* column chromatography with further purification *via* recrystallization. Selective production of **48** would eliminate wasteful separation, but the synthesis requires stepwise addition of isocyanate, is slow by nature and at higher temperatures is prone to side-reactions. By adapting the process to flow the yield, scale-up potential and efficiency can be improved. Transitioning the synthesis to a continuous process in a Vapourtec R-series reactor with twin heated reactor PFA coils ensured high mixing and automated reagent addition at ideal points in the synthetic route. A dynamic BPR allowed the reaction temperature to be safely increased to 100 °C, which in combination with the microtubing maintained the $CHCl_3$ solvent in liquid state. A switching valve also allowed for analysis of the exiting compounds by UPLC-MS. An extra equivalent of isocyanate was added into reactor 2 to minimize premature macrocycle formation in the first step, thus maintaining solubility in the reaction solution. Products exiting the reaction stream were immediately quenched with MeOH. The use of higher temperatures (~70 °C) when compared to the batch process also did not detrimentally affect the reaction but increased the yield of the desired product formed in reactor 1. Elevated temperature (~90 °C) in reactor 2 increased cyclization selectivity up to 90% while concurrently increasing the yield to 70-74%.

The transitioning to a flow process resulted in an overall production rate of 0.25g/hr. The total effects of the flow process allowed for the yield to triple while also offering a better safety profile and a reliable scale-up method. Overall conversion was measured at 85-93% with 80% selectivity for the single isomer **48** starting from 2-chloroethan-1-amine hydrochloride **49** and 1,3-bis(2-isocyanatopropan-2-yl)benzene **50**.

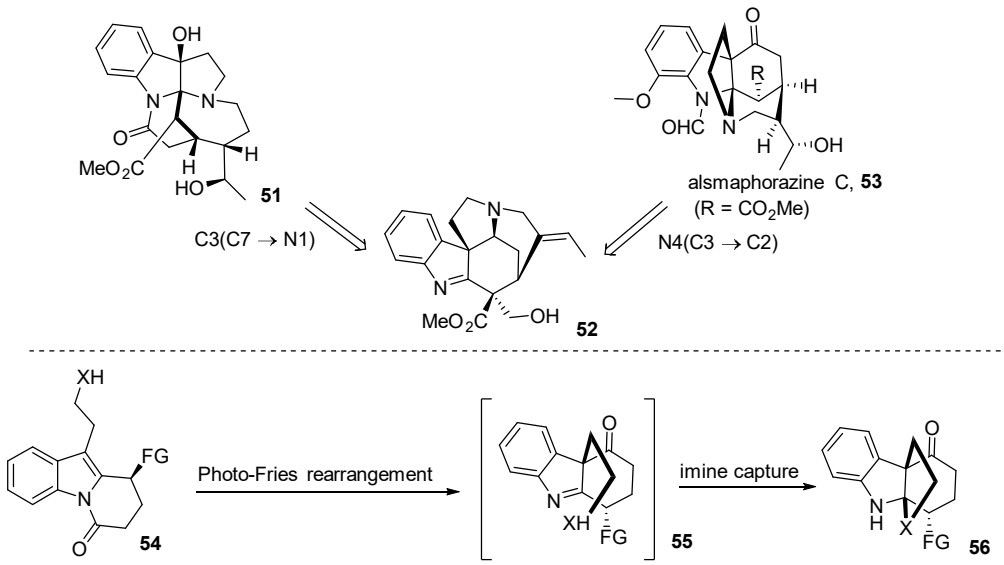


Scheme 19. Structures of macrocycles **47** and **48** and continuous flow set-up for synthesizing **48**.

2.2. Heterocycle transposition reactions

Normally, under batch conditions, photochemistry is difficult to perform effectively and suffers from a series of limitations. These limitations are mainly centred around the Beer-Lambert law (A=εcl), which details that the light absorption of a given compound in solution is dependent upon concentration and path length of the light. In batch photochemistry, the light source is normally submerged in a well containing the substrate solution and this process suffers greatly from poor light penetration, resulting in lower yields, inefficient reactions, long reaction times and excess side-products. However, these issues may be by-passed by implementing a flow photochemistry approach. Flow photochemistry has become popular in recent years as the micro conditions provide a shorter path length, allowing for total and uniform light penetration of the reaction solution. To this effect, Ding *et al.* recently exploited the advantages of performing photochemical reactions in flow to report a photoflow total synthesis of the alkaloid (+)-alsmaphorazine C **53** and a formal synthesis of (+)-strictamine **52** *via* the photo-Fries reaction (Scheme 20).[51] This photochemical transposition reaction typically converts a phenolic ester to a hydroxy aryl ketone by catalysis of Lewis acids. Target **52** is typically prepared *via* an oxidative treatment of congener alsmaphorazine **51**.

Strychnos and *akuammiline* alkaloids possess a common core structure, the 2,7-heterocycle-fused tetrahydrocarbazole skeleton, which contains two adjacent quaternary stereocenters. However, despite the high demand placed on attaining these biomolecules, there is limited information available on cascade reactions for their syntheses. Usually, these molecular skeletons are formed from oxidative skeletal rearrangements, where CO attaches at C7 and N1. Migration of CO from C7 to N1 is a normal synthetic procedure, yet it is theoretically possible for the migration to go in the opposite direction and still retrieve the same product. The authors postulated that synthesizing the same molecule may be possible if the inverse C3(N1→C7) reaction was performed on dihydropyrido[1,2-a]indolone **54** (DHPI) under photo-Fries conditions. Capturing the imine product as an indolenine intermediate **55** in a cascade would allow for the "*akuammiline* ketone" **56** to be obtained in a short reaction sequence (Scheme 20). Furthermore, having a pre-installed chiral centre may work to control the diastereoselectivity within the molecule early, and alleviate the worry of terminal functionalization which would be a lengthy process.



Scheme 20. Retrosynthetic approach taken towards alsmaphorazine C (top). Photo-Fries approach to synthesize alsmaphorazine C and a strictamine precursor substrate (bottom).

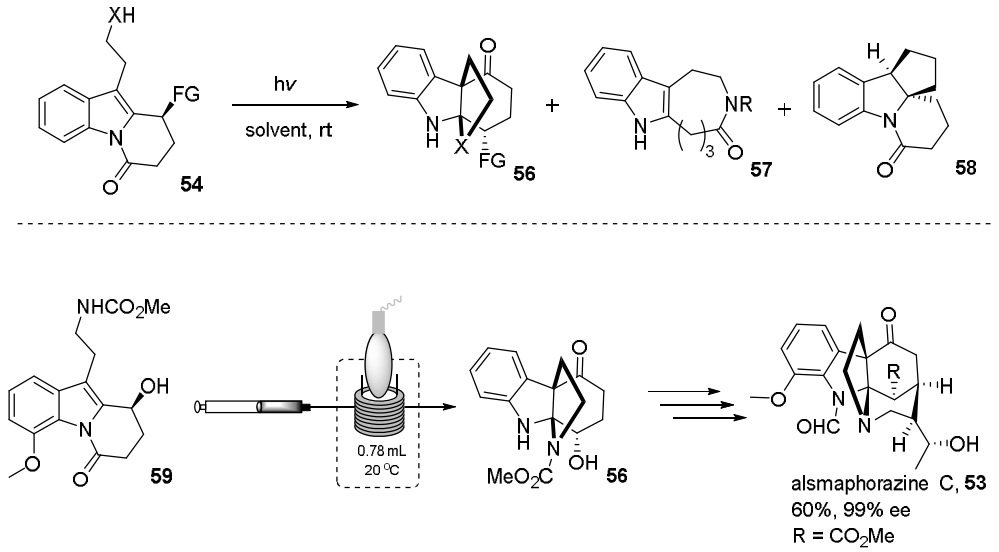
Studies commenced with a series of DHPIs dissolved in MeOH/Et_2O which bore various *N*-protecting groups. An electron withdrawing group on the alkyl amine was found to be crucial in circumventing undesired side reactions, as otherwise only the side-products **57** and **58** were formed (Scheme 21). Exploiting the 300 W high-power mercury lamp in a continuous flow protocol related to that described by Booker-Milburn *et al*.[52] afforded the desired compound **56** in 77% yield. The substrate **54** (0.5 mmol 0.1 M) was thereby dissolved in ^{t}BuOH and irradiated at room temperature for 20 minutes in flow.

The scope of this photo-flow reaction was then investigated, with different DHPIs bearing various steric and electronic modifications being investigated. The desired products were obtained in yields ranging 40-81%. These encouraging yields prompted the authors into using their methodology for the total synthesis of (+)-alsmaphorazine C. Irradiating a solution of **59** afforded tetracyclic ketone **56** (>99% ee) and its C2,C7-diepimer (99% ee) as a 3.7:1 mixture with an overall yield of 70%. A scale-up experiment was conducted while employing a flow rate of 0.75 mL/min and resulted in circa. 1 g of the desired product every hour. This clearly was advantageous and showed the easy scale-up possible with flow chemistry, as under normal batch conditions scale-up experiments for large quantities of substrate are almost unfathomable. Conveniently, treatment of **57** with $BF_3{\cdot}Et_2O$ allowed for this product to be recycled back to **56** in 85% overall yield, opening the potential for higher yields *via* product recycling and subsequent conversion. The overall total synthesis is lengthy, and hence unsuitable to be fully accounted for in this piece, but the desired (+)-alsmaphorazine C **53** product was isolatable in 60% yield after the 11-step total synthesis (Scheme 21).

In displaying the highly applicability of the photo-Fries imine capture cascade, the authors also synthesized *akuammiline* alkaloid (+)-strictamine. The molecular structure contains a methanoquinolizidine cage (6/6/6 ring system), with four stereocenters. Using their method, the authors were able to synthesize and isolate the intermediate product **56** in 52% yield (99% ee), which was progressed in five steps to afford (+)-strictamine.

This unique photoflow approach showcased another facet of chemistry within which flow technology may provide the ideal platform for by-passing issues which are normally major synthetic drawbacks. In this case, microflow provided the ideal situation for total light penetration of a solution in a photochemical reaction. This photo-Fries reaction provided an alternative pathway to a highly desirable range of alkaloid natural products and was progressed to the first total synthesis of (+)-alsmaphorazine C and formal synthesis

of (+)-strictamine. Also included was a scale-up experiment, which is challenging under batch conditions but very feasible in flow, in this circumstance providing the desired photo product on a scale of ca. 1 gram/hour.



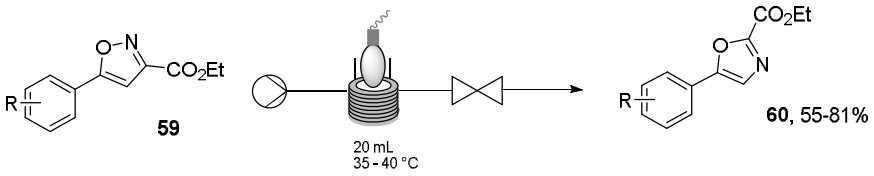
Scheme 21. Possible side-products formed from irradiation of **54**. Photo-flow approach in the steps taken to provide alsmaphorazine C (bottom section).

Oxazoles and isoxazoles are common structural targets in organic chemistry and these biologically active heterocyclic moieties appear in many natural products and drug molecules.[53] While methods are in place for synthesizing both structures from acyclic precursors, there are currently only few examples which discuss directly converting isoxazoles **59** into oxazoles **60** (Scheme 22), and as such methods for performing this transposition in an effective manner are of value. Thermal and photochemical methods are both possible, with the batch-based photochemical strategy in particular suffering from classical photochemical limitations such as the need for specialized reaction glassware, limited scalability, and poor light penetration. Many of these limitations were overcome in a recent publication which took advantage of flow chemistry to deliver a high yielding heterocyclic photoisomerization approach to a diverse range of oxazole products.[54]

To begin, a series of Claisen adducts were synthesized before being converted into a range of isoxazoles which differed in the nature of the substitution pattern on the aryl ring. The substrates (*e.g.* **59**, Scheme 22) were then pumped through the UV150 reactor of a Vapourtec E-series flow system which housed a medium-pressure mercury lamp. At a flow rate of 0.5 mL/min which equated to a 20-minute residence time, various solvents were trialled, with MeCN (0.1 mM) providing the highest yields in optimization studies. This 20-minute residence time is a significant improvement upon the photochemical transformation in batch which required 4-8 hours. The additional use of a low-pass filter ensured the exclusion of irrelevant wavelengths >400 nm and maintained the temperature at 35-40 °C thus minimizing the occurrence of side-products.

With optimized conditions in hand, a scale-up reaction was performed where ethyl 5-(4-methoxyphenyl)isoxazole-3-carboxylate **59** (R=4-OMe) was converted into its isomeric oxazole target **60** in 1.5 g yield over a 12 hour period thus demonstrating the utility of the photochemical transposition for potential gram-scale syntheses. After succeeding in scale-up experiments to generate gram quantities of oxazole product, the study turned to investigating the scope of the photochemical isomerization process. The aryl appendage was varied to include a diverse range of electron-withdrawing and electron-donating substituents as well as several heteroaryl groups. While studying the scope of this reaction, it became apparent that a clear trend was emerging in terms of product yield. It was observed that isoxazole substrates

bearing electron withdrawing substituents had lower λ_{max} values with their absorbance being less of a match-up with the emission of the medium-pressure Hg-lamp, compared to those of the isoxazole substrates containing electron donating substituents. This resulted in a pattern whereby electron deficient substrates resulted in lower yields of the oxazole products. Overall, the single step photo-flow procedure did provide an appealing access to producing desirable aryl oxazole products in generally high yields and fast reaction times.



Scheme 22. One-step photochemical flow isomerization of isoxazoles **59** to oxazoles **60**.

2.3. Heterocycle functionalization processes

Carbon-hydrogen bond functionalization (C-H activation) is a powerful tool in molecular synthesis, resulting in a functionalized molecule which can be further reacted en route towards a more complex product.[55,56] Typical procedures involve the use of a transition metal (TM) catalyst, and this was successfully performed in continuous flow by Ackermann *et al*. who demonstrated the first flow-based Mn-catalysed C-H activation for chemoselective hydroarylations *via* a novel synergistic Brønsted acid/Mn(I)-catalysis.[57]

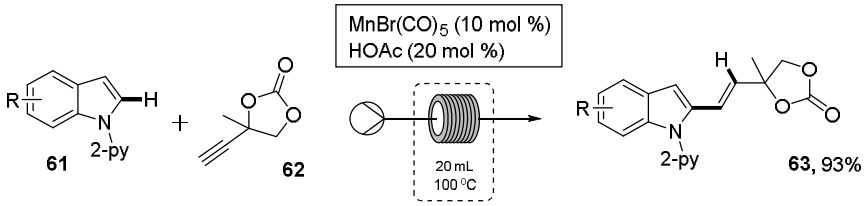
In recent years, substitutive C-H functionalizations through hydroarylations with simultaneous β-O elimination has become a popular synthetic strategy. However, a signifcant drawback of this method has been that manganese-catalyzed hydroarylations with leaving groups near the unsaturated bonds can result in β-heteroatom eliminations. To alleviate this potential worry, the authors stipulated that a synergistic Brønsted acid-mediated approach may limit the potential for β-heteroatomic elimination. The study began by investigating the hydroarylation of compound **61** with 4-ethynyl-4-methyl-1,3-dioxolan-2-one **62** (Scheme 23). Synergistic Brønsted acid/Mn(I) homogenous catalysis was initially studied after base additives proved ineffective in increasing the yield. An optimization study showed that Brønsted acid in the form of HOAc, 1,4-dioxane as solvent, and a flow rate of 0.5 mL/min afforded the desired product **63** in a 95% yield while crucially also fully solubilizing the manganese catalyst at 100 °C.

In this example, the *cis* nature of the alkene geometry of the indole substrate allowed for the slightly more acidic alpha proton to be selectively functionalized to react with the incoming alkyne. In this way, the homogenous Mn(I) catalyst was successfully applied to a range of electrophilic functional groups, including ether, halogen, carboxylic acid, and ester motifs. High regioselectivity at the α-position also allowed for a range of indoles, thiophenes, pyrroles, tryptophan species, and pyridones to be used in the flow procedure without any risk of isomerization. The short residence time and improved mass and heat transfer arising from the microflow conditions also limited the potential for unwanted thermal side reactions.

The reaction was also performed in batch for comparative purposes. At a temperature of 60 °C the reaction afforded the same products in 16 hours reaction time, and markedly there were some products whose yields were higher in batch than the same product synthesized in flow. In this incidence, flow chemistry through its benefits greatly shortened the reaction time, however, comparable yields were also achieved in batch showing flow chemistry as a complement as well as a solution to some batch procedures. Superb chemoselectivity was also demonstrated by the flow protocol, in that efficient transformation of substituted propargylic alkynes was achieved while avoiding the occurrence of any competing β-O elimination reactions. Mechanistic studies using deuterated acetic acid shone light on the chemoselectivity criteria of the catalytic process, showing that an allene forms from β-O elimination when no Brønsted acid is present in solution.

In a scale-up experiment the desired product **63** was delivered in a 93% yield (2.24 g). The authors devised a column containing immobilized nitrilodiacetic acid as a scavenger to recover the catalyst after the thermal reaction cycle. This illustrated the high practicality of performing flow-base C-H functionalization, as normally such catalysts would be lost to work-up/ silica chromatography purification steps. Overall, the

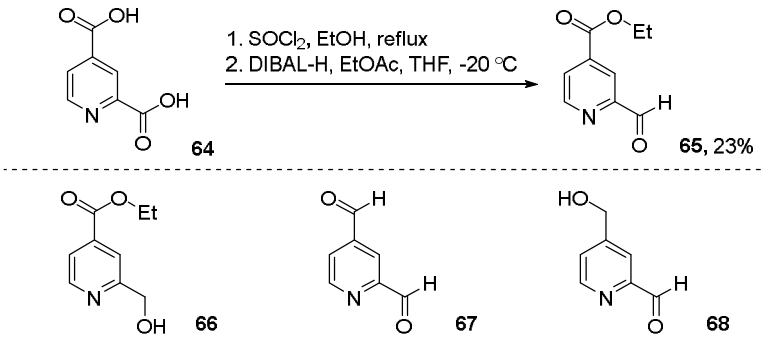
synergistic Brønsted acid/Mn(I)-catalyzed C-H activation offered the possibility for highly chemo- and regioselective hydroarylations in a relatively short sequence (20 min). Unwanted β-O elimination paths were avoided affording allylic carbonates with the potential to be further derivatized in downstream reactions. Being able to perform the process without inert conditions with high yields and the potential for catalyst recovery from what is typically a sensitive reaction is an adequate demonstration for how flow chemistry is currently finding uses not only in many organic syntheses but also some organometallic procedures.



Scheme 23. C-H activation chemistry performed in flow in the presence of a Mn-catalyst.

Demonstrating the ease with which microflow chemistry can be translated from laboratory to industrial scale is a key selling-point of the technological practicality of using continuous synthesis platforms. Recently, Uhlig *et al.* reported a selective DIBAL-H mediated reduction of a heterocyclic diester to the corresponding monoaldehyde, employing continuous flow chemistry to gain precise control over the reaction temperature and time in the process. The high utility of this flow-based reduction was then extrapolated to kilogram scale to demonstrate the effectiveness with which it may be performed in an industrial setting.[58]

Reduction of carbonyl compounds is prominent in both academia and industry, yet few large-scale examples exist which detail the transformation of esters to aldehydes. Diisobutylaluminum hydride (DIBAL-H) is a commonly used reagent to perform this reduction,[59] but its strongly exothermic reactivity, the cost and the likely generation of side-products conventionally reduce the feasibility of using DIBAL-H in a large-scale industrial setting to regio- and chemo-selectively transform diesters into their monoaldehyde counterparts. Compound **64** (Scheme 24) is a heterocyclic precursor in the synthesis of a bioactive compound, formed *via* ester formation followed by selective monoreduction of the ester in the 4-position to yield the monoaldehyde species **65**.

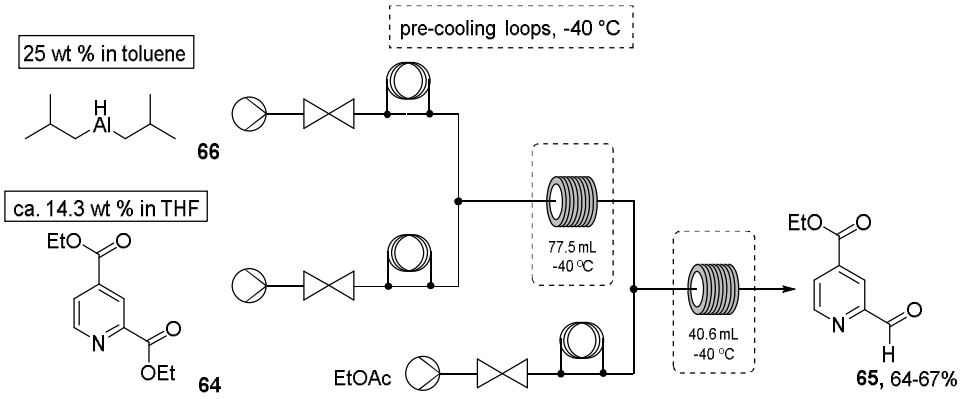


Scheme 24. Batch synthesis of desired monoaldehyde product **65** and possible side-products.

When the synthesis of **65** was attempted in batch on 18 kg scale at –20 °C the formation of side-products **66**, **67**, and **68** was observed complicating downstream purification and leading to reduced yields of the desired monoaldehyde product **65** (22%). The authors initially set out to determine how higher control of reaction enthalpy and stoichiometry may lead to increased reaction selectivity and subsequently higher yields. The interaction between DIBAL-H and the diester substrate chelated by the pyridinyl nitrogen forms a pentacyclic intermediate that was observed to be significantly more stable at lower temperatures (–20 °C *vs* –78 °C), whereby lower temperatures are shown to be key in preventing the formation of

impurity **66**. In a likewise manner, impurities **67** and **68** are formed from over-reduction of the desired product owing to untimely collapse of the chelated intermediate.

Typically, large-scale batch reactors are unattractive for cryogenic-type reactions as temperatures are difficult to maintain below –20 °C. Moreover, control over such an 18 kg reduction was therefore limited to slow addition of DIBAL-H to the reaction mixture over a >6 hr period, with even 1.2 equiv. of DIBAL-H still resulting in the generation of significant quantities of side-products. Here, it was postulated that switching from batch to flow synthesis would offer the benefits of highly controlled reaction times and improved temperature control and mass transfer. The authors employed a Vapourtec R-series flow reactor that delivered DIBAL-H, diester substrate, and EtOAc from three separate stock solutions through a network of PFA tubing connected *via* T-piece mixers. The flow system contained various heating and cooling segments, controlled *via* an output from the Vapourtec flow reactor that provided precise control over the reaction temperature(s) within individual reactor coils. Flow-based optimization of the reduction showed that the reaction was highly sensitive to temperature. Following optimization, a residence time of 75 s, a temperature of –40 °C and 1.5 equiv. of DIBAL-H resulted in an 82% yield of **65**. In a first attempt to demonstrate the effectiveness of this flow-based selective reduction in a scale-up reaction, extending the process time to ~4 h converted 500 g of **64** (2.24 mol) to **65**. An in-line work-up was also implemented, composed of a quench of the remaining DIBAL-H using EtOAc followed by solubilization and removal of Al-salts in a second quenching loop delivering aq. potassium sodium tartrate (Scheme 25). Aqueous and brine washes of the organic layer following filtration through silica allowed for pure **65** (yields 64-67%) to be utilized further downstream for additional chemical reactions.



Scheme 25. Multi-step flow approach of the synthetic route to monoaldehyde **65**.

In this example, an effective scale-up of regioselective DIBAL-H reduction of a pyridinyl diester to its corresponding monoaldehyde was achieved by translating the reaction from batch to a continuous flow process. Flow chemistry offered a major improvement to the yield outcome by allowing for precise control over the temperature and time of a mixing sensitive reaction to provide a desired product regioselectively and in high yields.

3. Conclusion

In this chapter, we have explored how flow chemistry is becoming an increasingly popular method in the synthesis of heterocyclic compounds. In these examples, flow technology enabled improved heterocyclic syntheses which previously suffered from limitations that could not be overcome through normal batch operations. This chapter highlighted the benefits that microflow synthesis offers, such as improved mixing and heat transfer, reliable scale-up and increased safety, and we discussed how those benefits were exploited in these syntheses to improve the product output of otherwise inefficient or difficult batch processes.

Nonetheless, it should be noted that flow chemistry is not a panacea. Although microflow technology is highly beneficial and has the potential to greatly improve upon a wide range of organic reaction types, it

should not be viewed and a solution to replace batch chemistry, but more of a complement.[60] Indeed, many hybrid examples where reaction stages in batch are combined with flow processing exist and are oftentimes favored to make use of the best of both technologies. To identify cases where flow processing can be superior joint efforts from synthetic chemists and chemical engineers are vital to resolve bottlenecks that prevent the effective synthesis of heterocyclic targets. In this vein, the training of tomorrow's chemists in modern flow technology is vital and efforts are underway for bespoke courses and laboratory classes in most universities.

It is our hope that the reader has gained an appreciation of the enterprise of a flow synthesis and why it is becoming increasingly applied in organic chemistry for targeting heterocycles. Many modern target structures contain heterocycles, and the desire to access them through effective and sustainable means is extensive. This has presented the opportunity for chemists of all disciplines to delve into this fast-expanding field which offers some of the latest technologies available. It can thus be expected that future developments will result in further advances and industrial applications detailing the modern synthesis of heterocyclic targets, be it in pharmaceuticals, organic materials, fragrances, or agrochemicals.

Acknowledgements

This work was supported by Science Foundation Ireland under the SFI Industry Fellowship programme for the project entitled "Development of Continuous Biocatalysed Processes-Continuous Biocatalysed Chemicals (CATCH)" (19/IFA/7420, to MB) as well as the Royal Society of Chemistry for a Research Enablement Grant (E20-2998, to MB). CB thanks the School of Chemistry at UCD for a Research Demonstratorship.

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