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TUTORIAL REVIEW

Continuous flow reactors: a perspective

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With aspects of continuous processing featuring heavily in efforts towards increasing the 'green' prospects of pharmaceutical and fine chemical manufacturing, this article focuses on the developments made into the application of continuous flow reactors for sustainable chemical research and production.

Introduction

The chemical sector has long been viewed by wider society as being 'dirty'; however, in the past two decades significant amounts of research have been conducted into the development of 'green' techniques for chemical synthesis, with the goal being to reduce the waste generated by the chemical industry.[1]

In 2007, the Green Chemistry Institute (GCI), part of the American Chemical Society (ACS), set up a roundtable in conjunction with a series of global pharmaceutical companies. The roundtable listed several key areas where research was required to facilitate the development of sustainable manufacturing, the details of which can be found in a recent publication by Jiménez-González *et al.*[2] The importance of continuous processing was acknowledged, with the panel ranking continuous processing as the primary key area for research activities.

With the pharmaceutical industry in particular still dominated by flexible batch processes and segmented unit operations, there is a lot to be learnt from the petrochemical and food industries where continuous processing features widely as a means of keeping productivity high and costs low. With these factors in mind, there has been renewed interest in the development of sustainable processes, with many of the 'big pharma' looking towards new techniques for both research and production.[3,4] For this to be a success however, techniques are required that compliment the way that early stage researchers and process chemists work, therefore advantages associated with its use must span both disciplines; continuous flow technology has the potential to do this.

Unlike batch reactor technology, which has changed little over the past Century, continuous flow reactors form part of a rapidly growing research area which has the opportunity to change the way synthetic chemistry is performed both at a research and industrial level.[5] Compared to stirred tank reactors, flow reactors have significant processing advantages including improved thermal management, mixing control and the application of extreme reaction conditions.[6] Consequently, synthetic processes can be intensified by reducing the volume of solvent employed whilst maintaining control of reaction temperature.[7] With this in mind, this article focuses on identifying which of the twelve principles of green chemistry, as outlined by Anastas *et al.*,[8] have the potential to benefit from flow reactor technology (*discussed herein);

1. *Prevention*: It is better to prevent waste than to treat or clean up after creation.*
2. *Atom economy*: Synthetic methods should be designed to maximise the incorporation of all materials into the final product.*
3. *Less hazardous chemical syntheses*: Synthetic methods should be designed to use and generate substances that possess little or no toxicity to humans and the environment.
4. *Designing safer chemicals*: Chemical products should be designed to effect their desired function while minimizing their toxicity.
5. *Safer solvents and auxiliaries*: The use of auxiliary substances should be avoided and where necessary be innocuous.*
6. *Design for energy efficiency*: Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised.*
7. *Use of renewable feedstocks*: A raw material or feedstock should be renewable whenever technically and economically practical.*
8. *Reduce derivatives*: Unnecessary derivatisation should be avoided because such steps can generate waste.*
9. *Catalysis*: Catalytic processes (as selective as possible) are superior to stoichiometric reagents.*
10. *Design for degradation*: Chemical products should be designed so that at the end of their function they break down into innocuous products that do not persist in the environment.
11. *Real-time analysis for pollution prevention*: In-process monitoring and control to minimise the formation of hazardous substances.*
12. *Inherently safer chemistry for accident prevention*: Substances used in a chemical process should be chosen to minimise

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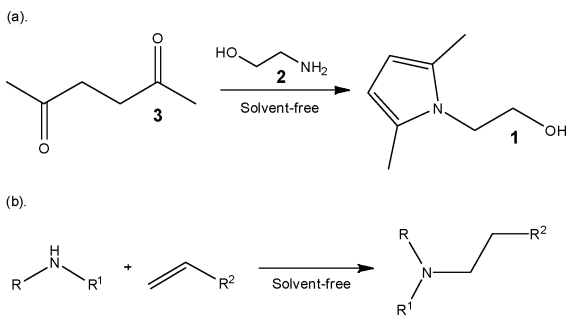
the potential for chemical accidents, such as releases, explosions, and fires.*

Principle 1. Prevention of waste

Historically, the focus of reaction development has been on increasing the production yield of high value target compounds. More recently, due to changes in legislation and rising material costs, objectives have changed to also consider the green profile of a reaction/process.[9] This can be seen in Principle 1 which focuses on the development of synthetic methods that prevent waste generation; rather than treating or cleaning-up the waste once it has been created.

Solvent-free. With reaction solvents contributing greatly towards the waste generated by a synthetic process, considerable research has been undertaken to identify if more conventional solvents can be substituted with environmentally benign or recyclable analogues (see Principle 5, for a detailed discussion of published examples utilising safer solvents and auxiliaries under flow conditions). Whilst the use of 'green solvents' can be viewed as a step in the right direction, the most desirable approach remains to perform reactions in the absence of a solvent. In batch, this is undesirable as it can lead to uncontrollable reaction exotherms due to insufficient thermal management of reactor vessels; consequently, relatively few solvent-free reactions are employed on a production scale.[10] In comparison, the excellent thermal management obtained within continuous flow reactors, and in particular microstructured reactors, means that it is now possible to safely and efficiently manage such reactions in the absence of a diluting solvent. Two early examples of this mode of operation were the Paal–Knorr and Michael addition reactions reported by Schwalbe *et al.*[11] (Scheme 1a) and Hessel *et al.*[12] (Scheme 1b) respectively.



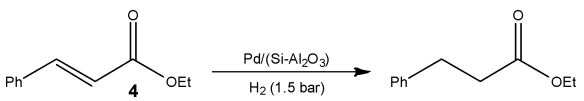
Scheme 1 Illustration of solvent-free reactions performed under continuous flow conditions.

In the former case, the synthesis of 2-(2,5-dimethylpyrrol-1-yl)ethanol **1** was used as a model reaction, enabling Schwalbe and co-workers[11] to demonstrate the ability to dramatically reduce the reaction time required for the Paal–Knorr reaction by efficiently controlling the reactor temperature. Using a stainless steel microstructured reactor, the authors were able to increase thermal control of the reaction identifying a reaction time of 5.1 min and a reactor temperature of 65 °C as being optimal for the target pyrrole **1** (91% yield); obtaining a throughput of 260 g h^{-1}. Compared to batch, the main time saving was achieved *via* the ability to constantly add neat ethanolamine **2** to acetonylacetone **3** whilst controlling the reactor temperature.

In the second example, Löwe and co-workers[12] performed the addition of secondary amines to α,β-unsaturated compounds whereby reaction times of 17 to 25 h were typically required in order to maintain thermal control over the batch process. Utilising a micro mixer with dimensions of 40 μm (wide) × 200 μm (deep) and a tube reactor, the authors were able to access reaction times in the range of 0.8 to 5.0 ms, without the need for additional cooling; owing to the high heat transfer capacity of the microstructured device (4000 W $(m^2K)^{-1}$).

A niche product area that has the potential to benefit from solvent-free continuous processing is that of ionic liquid synthesis, whereby conventional synthetic procedures rely on lengthy purification steps in order to access these solvents in sufficient purities. Batch techniques are limited due to the rapid and exothermic nature of the reactions, which give rise to impurities-characterised by a yellow colouration. Renken *et al.*[13] investigated the use of a microstructured reactor as a means of increasing reaction control and product purity. Using the synthesis of [EMIM][$EtSO_4$] as a model reaction, the authors investigated the solvent-free alkylation under flow conditions. Using a catepillar static mixer, the authors were able to increase the production efficiency by three orders of magnitude obtaining the ionic liquid at a throughput of 0.5 kg h^{-1}.

Employing a polysilane-supported palladium/alumina hybrid catalyst, Kobayashi and co-workers[14] recently reported the development of a gas-liquid-solid reactor suitable for the hydrogenation of unsaturated C–C bonds **4** and deprotection of carbobenzyloxy functional groups under solvent-free conditions. Using this approach, the authors were able to perform selective hydrogenations without the need for dilute substrate concentrations, affording high turnover numbers (8700) and no Pd-leaching (ICP-MS analysis) (Scheme 2). In the case of solid substrates, small quantities of solvent were required however substrate concentrations in the range of 0.33 to 1.0 M were typically employed.



Scheme 2 Hydrogenation of ethylcinnamate **4** under solvent-free conditions.

When considering the removal of a reaction solvent for use under flow conditions, it is essential that the reactants and products remain in the liquid phase, under the processing conditions employed, otherwise fouling of the reactor will result. It is for this reason that continuous flow reactions are more often performed at higher concentrations than their batch counterparts, but few allow the complete exclusion of solvent. To overcome this issue, additional research is required into improving post reaction separation of solvents in order to further develop solvent recyclers for use with continuous flow reactors.

Minimal reagent consumption. In further efforts towards minimising waste formation, micro reactors have a key role to play in reaction screening and optimisation. When performed in batch, scouting experiments can be conducted on small scales utilising typically mg of reactants and ml of solvents;

with the number of reactions performed dependant on reaction time and available material. In flow, ten's to hundred's of reactions can be performed using these quantities of materials, leading to reduced reagent consumption and waste production. In addition, the ability to rapidly change reaction conditions enables reactions to be probed in a more detailed way, increasing user understanding ahead of scaling reactions to prepare and isolate target compounds. This approach was demonstrated in a recent publication by van Hest, Rutjes and co-workers[15] whereby the Moffatt-Swern oxidation was evaluated using an automated reaction platform.

Using a borosilicate glass micro reactor (Channel dimensions = 120 μm (wide) × 55 μm (deep) × 0.26 or 13.20 cm (long); Volume = 0.14 or 7.02 μl) the authors were able to conduct a detailed optimisation study which enabled a 32 s mixing time and a reaction temperature of 70 °C to be identified as being the best conditions for obtaining the target compound whilst minimising competing side reactions. By employing a flow reactor, many more reaction conditions could be evaluated than would be practical in batch whilst having the added advantage that minimal reagent volumes are consumed and higher reactor temperatures can be readily evaluated. Once identified, the optimised reaction conditions were used to produce the oxidation product, which was obtained in 96% yield.

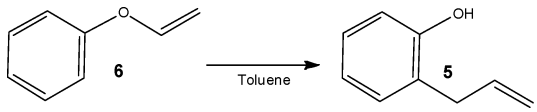
In the same year, Buchwald and Jensen[16] reported the combination of micro reactors and feedback control for the development of a self-optimising platform. Using the Heck reaction as a model, the authors were able to rapidly optimise the process using minimal quantities of reagent and then scale those optimised conditions by a factor of fifty to produce the coupling product in comparable yield. The ability to tune a reaction using small quantities of reactants therefore not only minimises the waste generated during early stage reaction screening, but also has the potential to simplify downstream processing and hence decrease the volume of waste generated at the clean-up step(s). Further waste prevention can also come about through the use of catalysts in place of stoichiometric reagents, for examples of the use of catalysts under flow, please refer to Principle 9.

Principle 2. Atom economy

The atom economy of a reaction is a measure of the percentage of the mass of reactants that are incorporated into the product and is often used as a measure of waste generation.[17] Whilst this approach describes the theoretical economy of a synthetic route, reactions can still be low yielding and require purification to isolate the target compound. When looking towards continuous flow reactors, researchers have shown that by stringently controlling reaction conditions, the purity profile of reaction products can be improved, therefore reducing the complexity of subsequent purification steps or even removing the need for them altogether. Focussing on those reactions conventionally termed atom economic, the following section describes the additional synthetic advantages that can be accessed by their performance under flow conditions.

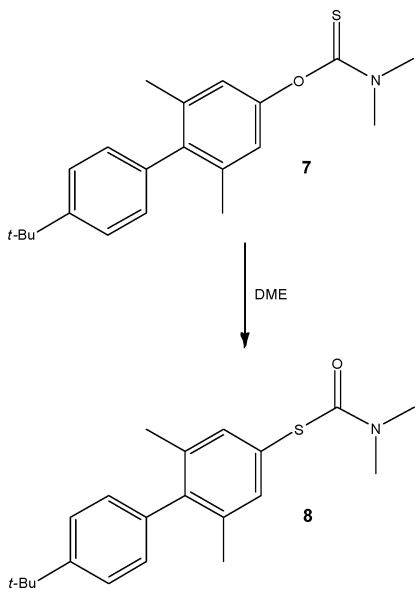
Re-arrangement reactions. When looking at employing atom economic reactions, intramolecular re-arrangements represent some of the most synthetically useful; reaction conditions required to promote them can however be viewed as extreme. To address this, Kappe and co-workers[18] evaluated the use of a high temperature and pressure tubular reactor to enable access to Claisen re-arrangement products without the need for long reaction times.

Examining the synthesis of 2-allylphenol **5** from allyl phenyl ether **6** (Scheme 3), the authors employed toluene as the reaction solvent and examined the effect of reactor temperature and pressure on the reaction. Focussing on the use of a stainless steel reactor (volume = 4 ml), the authors identified that a reactor temperature of 240 °C and system pressure of 100 bar afforded the target phenol **5** in 95% yield, with a reaction time of 4 min. Using inductive heating, Kirschning *et al.*[19] have also demonstrated the Claisen re-arrangement where increases in product yield (~23%) were obtained when utilising a flow reactor.



Scheme 3 Illustration of a Claisen re-arrangement reaction performed under high temperature and pressure flow conditions.

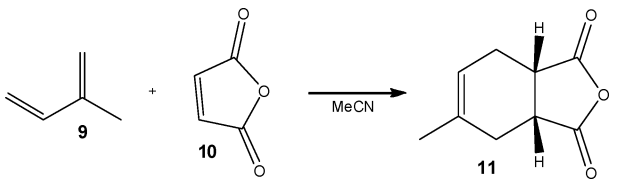
Exploiting the ability to access extreme combinations of temperature and pressure, researchers at Lilly also demonstrated the use of a re-arrangement reaction as a key synthetic step in the preparation of a thiol required for an early stage development project.[20] Employing a Newman-Kwart re-arrangement (Scheme 4), the authors were able to screen the effect of temperature (250–320 °C) on the reaction, reporting the conversion of *O*-thiocarbamate **7** to the respective *S*-thiocarbamate **8** in high yield and purity. Optimal thermal conditions were found to be 300 °C, affording the target product **8** in 99.1% conversion and 93% isolated yield after recrystallisation.



Scheme 4 Conversion of an *O*-thiocarbamate **7** to an *S*-thiocarbamate **8** under high temperature flow conditions.

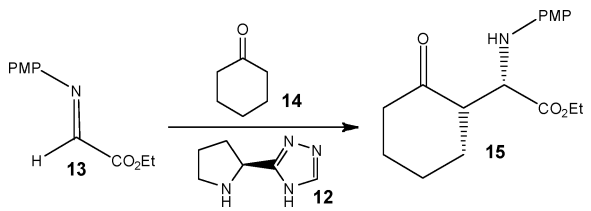
Addition reactions. Several researchers have investigated the Diels–Alder cycloaddition under continuous flow using stainless steel reactors.[21,22] Using a polymeric microflow disk reactor,

containing eight parallel channels (~200 μm i.d.), Hallmark and co-workers[23] reported the reaction of isoprene **9** with maleic anhydride **10** to afford 3α,5,7α-trimethyl-3α,4,7,7α-tetrahydroisobenzofuran-1,3-dione **11** (Scheme 5). Immersing the reactor in an oil bath, the reaction was investigated at 60 °C, whereby the authors obtained isolated yields of 85 to 98% depending on the residence time employed (28 to 113 min). Under optimal reaction conditions, the authors were able to produce the pharmaceutically relevant core-motif at a throughput of 1.05 kg day^{-1}.



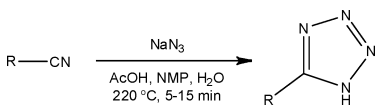
Scheme 5 A Diels–Alder reaction performed under flow conditions within a MFD reactor.

Using a chiral organocatalyst **12**, Odedra and Seeberger[24] reported the performance of the Mannich reaction in a glass micro reactor. Employing DMSO as the reaction solvent, the reaction of α-iminoglyoxylate **13** and cyclohexanone **14** was investigated to afford β-aminoketone **15** (Scheme 6). Using 5 mol% of catalyst **12** and a reactor temperature of 60 °C, the authors obtained the target compound in 91% yield (>95% *de*).



Scheme 6 Continuous flow Mannich reaction performed using an organocatalyst **12**.

Looking to capitalise on the growing synthetic interest in the synthesis of substituted tetrazoles from medicinal, coordination and materials chemists, Roberge and Kappe[25] recently disclosed details of a continuous flow process for the atom efficient synthesis of tetrazoles. Using the addition of hydrazoic acid to organic nitriles, the authors were able to exploit the increased process safety associated with flow reactors to efficiently synthesise a series of 5-substituted 1*H*-tetrazoles (Scheme 7).



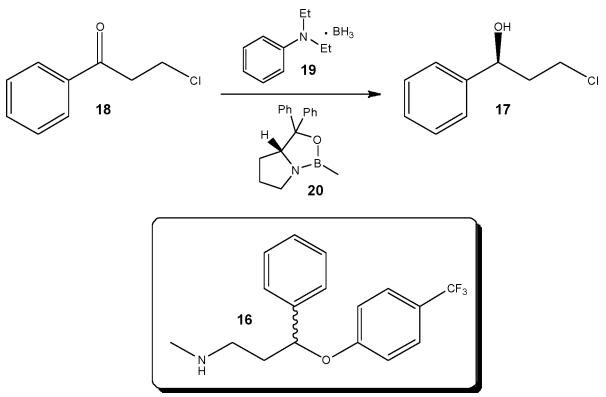
Scheme 7 General schematic illustrating the conditions used for the continuous synthesis of 5-substituted 1*H*-tetrazoles.

Employing a two feed Sulfinert tube reactor, the authors reacted a solution of nitrile in NMP/AcOH with a solution of aqueous sodium azide (2.5 eq.). Heating the system to 220 °C, the authors were able to safely generate HN_3 *in situ*, obtaining the target tetrazoles in isolated yields ranging from 75 to 98% with reaction times of 5 to 15 min. Compared to analogous batch reactions, the authors comment that flow reactors provide a significantly safer method for the large scale synthesis of tetrazoles as the liquid filled reactor has no headspace. In one example, 18.9 g of a tetrazole (89% yield) was synthesised in a 1 h continuous experiment. The authors have subsequently utilised a flow reactor to investigate the decomposition of 5-benzhydryl-1*H*-tetrazole to diphenylmethane, employing a reaction temperature of 220 °C and a residence time of 10 min.[26] Jensen and Zaborenko[27] concurrently reported the use of a silicon micro mixer (volume = 4.1 μl) for the two-step synthesis of the highly energetic sodium nitrotetrazole, gaining access to the material at an impressive throughput of 4.4 g h^{-1}.

Improved atom economy has also been demonstrated for polymer synthesis in flow. Using a process of reversible addition-fragmentation chain transfer, Hornung and co-workers[28] demonstrated the ability to perform the controlled radical polymerisation of a series of monomers including *n*-isopropylacrylamide and *n*-butyl acrylate. Performing the reactions under flow conditions, the authors were able to obtain narrow molecular weight distributions, when compared to batch techniques, representing a more efficient incorporation of precursors into the target products. To obtain high conversions (80–100%), the authors found it necessary to minimise the proportion of oxygen in the solvent system and reactor, thus preventing quenching of the radicals generated. The reaction sensitivity to O_2 was also highlighted when a gas permeable PFA tube reactor was compared with a steel system, resulting in significantly lower product conversions.

Asymmetric synthesis. Another way of increasing the efficiency of a synthetic process is to increase the enantiomeric excess of the target compound thus reducing the proportion of substrate that is consumed in the formation of the undesirable enantiomer.

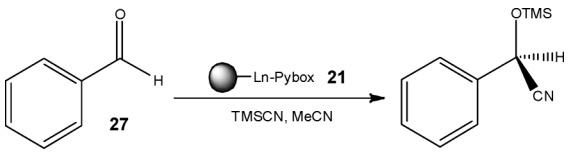
Forming part of a continuous strategy for the synthesis of (±)-fluoxetine **16** Sanderson and Ahmed-Omer[29] reported the development of an enantioselective reduction, used for the preparation of a key (*S*)-alcohol **17** (Scheme 8). Employing Corey–Bakshi–Shibata conditions, the authors investigated the reduction of ketone **18** with borane-*N*,*N*-diethylaniline **19** in the presence of a chiral oxazaborolidine catalyst **20**. Performing the reaction at 0.24–0.40 M, no reaction was observed; however, increasing the concentration to 0.70 M resulted in



Scheme 8 Enantioselective synthesis of a secondary alcohol **17** used in the synthesis of (±)-fluoxetine **16**.

quantitative reduction to afford (*S*)-3-chloro-1-phenyl-propanol **17** in 72% *ee*. Reducing the reactor temperature to −7 °C afforded the desired increase in *ee*, delivering the alcohol **17** in 88% yield and 92% *ee*. The alcohol **17** was subsequently converted to the iodo derivative in batch, followed by amination under biphasic flow conditions. The final step, a Mitsunobu reaction, enabled the nucleophilic substitution of alcohol **17** with 4-hydroxybenzotrifluoride to afford (±)-fluoxetine **16**; at a throughput of 4.8 mmol h^{-1}.

To further increase the efficiency of asymmetric syntheses, Moberg and co-workers[30] developed a solid-supported Lewis acid catalyst, affording a means of efficiently recycling the catalyst and simultaneously simplifying the post reaction processing required to isolate the target compounds. Using the enantioselective synthesis of TMS-cyanohydrins (Scheme 9), the authors evaluated the Lanthanide-Pybox catalyst **21** illustrating ease of reaction screening compared to batch techniques.



Scheme 9 Use of a solid-supported catalyst **21** for the enantioselective synthesis of TMS-cyanohydrins.

Hodge *et al.*[31] demonstrated the use of a polymer-supported cinchonidine derivative **22** (Fig. 1) and evaluated it towards the enantioselective Michael addition depicted in Scheme 10. Employing a glass tubular reactor containing 15 g of PS-cinchonidine **22**, the authors investigated the addition reaction between 1-oxoindan-2-carboxylate **23** and methyl vinyl ketone **24** to afford the Michael adduct as the (*S*)-enantiomer **25**. Using 1.06 eq. of MVK **24** and toluene as the reaction solvent the reaction mixture was pumped through the reactor which was maintained at 50 °C. Under the aforementioned conditions, the authors obtained the Michael adduct in 97% yield and 52% *ee* at a throughput of 10 g day^{-1}, using a simple reaction set-up.

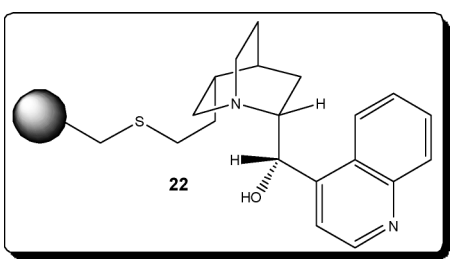
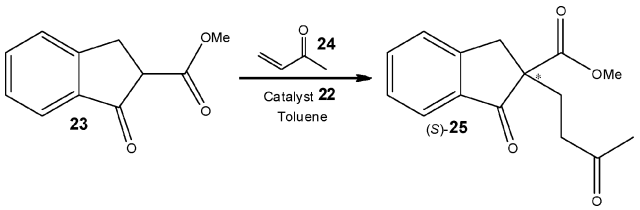


Fig. 1 Polymer-supported cinchonidine derivative **22** shown to promote enantioselective addition reactions.

Principle 5. Safer solvents and auxilliaries

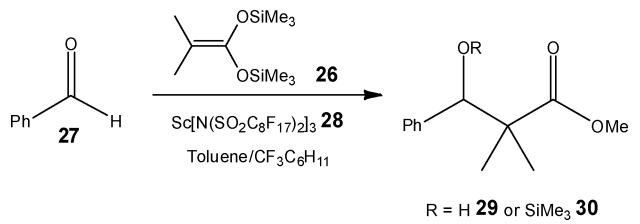
When looking to improve the environmental performance of a chemical process, solvents play a large role in the defining process costs and safety; consequently, the use and definition of 'green solvents' has attracted significant interest.[32]

Employing a biphasic solvent system comprising of co-flowing perfluoromethylcyclohexane/toluene, Mikami *et al.*[33] demonstrated the ability to readily recycle a Lewis acid catalyst



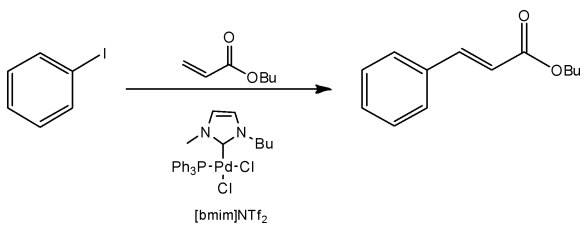
Scheme 10 Illustration of a polymer-supported cinchonidine derivative **22** used to promote the enantioselective Michael addition in a packed-bed reactor.

for use in the aldol reaction. As Scheme 11 illustrates, the model reaction involved the reaction of a silyl derivative **26** and aldehyde **27** (2 : 1) in the presence of scandium bis(perfluorooctanesulfonyl)amide **28** (0.06 mol%); with quantification performed offline using GC-FID analysis of the toluene phase. Applying a reaction time of 10.8 s, the authors obtained 92% conversion of the silyl enol ether **26** (1.5 : 1 **29**:**30**) compared to 11% in a stirred batch reactor (2 h); an observation that is attributed to the high interfacial area obtained in the micro reactor. Under the aforementioned conditions, the catalyst **28** remained in the perfluorinated solvent and the authors isolated the reaction products from the toluene phase; enabling the catalyst solution to be re-used without the need for post reaction processing.



Scheme 11 Illustration of the aldol reaction used to demonstrate the advantages of fluorous solvents in flow reactors.

In addition to fluorinated solvents, ionic liquids have also been employed as a reaction media for flow reactions. Using 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, Ryu *et al.*[34] evaluated the continuous flow Heck reaction (Scheme 12) and subsequent recycling of the reaction solvent.

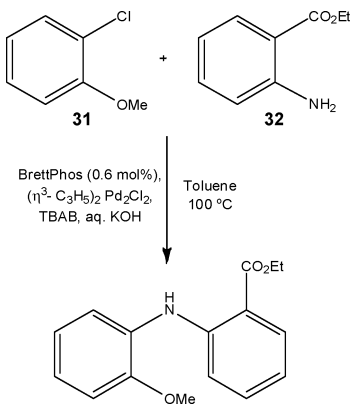


Scheme 12 Illustration of the Heck reaction performed in a recyclable ionic liquid.

Biphasic reactions. Biphasic reaction conditions represent a largely under utilised area of synthetic chemistry, namely because of the poor mixing that occurs between the two liquid phases; particularly when reactions are performed at scale. When such transformations are conducted in micro flow reactors, be they etched channel networks or microbore tubes, the high interfacial surface area that results can have a dramatic increase in reaction rate compared to flask based reactions.[35,36] A recent

example exploiting this phenomenon was a biphasic Wittig reaction reported by Krajnc and Šinkovec.[37] Using a simple FEP tube reactor (0.25 μm i.d. × 90 cm or 17 m), the authors investigated the reaction of benzyltriphenyl-phosphonium salt and methoxybenzaldehyde in DCM, with an aqueous solution of sodium hydroxide as the base. In this case, the advantages of a biphasic system were two-fold, firstly the slug flow regime obtained in a tube reactor afforded a reproducible method for increasing the interfacial area between the two phases, resulting in an increase in reaction rate and secondly, the presence of H_2O prevented the precipitation of Ph_3PO within the small reaction channels. For additional examples of precipitate manipulation under flow conditions, please see McQuade *et al.*,[38] Dolman *et al.*[39] and Jensen *et al.*[40,41]

Whilst authors have demonstrated rate acceleration as a result of utilising segmented flow,[42] Buchwald and Nager[43] recently reported the need for additional mixing of the immiscible toluene : water phases when performing a C–N cross coupling reaction (Scheme 13). Packing an FEP tube reactor with stainless steel spheres (60–125 μm), the authors observed 60% conversion of 2-chloroanisole **31** to ethyl 2-((2-methoxyphenyl)amino)benzoate **32** compared with 10% in an open tube reactor; rising to 98% conversion at a residence time of 6 min. Evaluating the effect of packed-bed size, the authors observed increased substrate conversion with increasing bed size, concluding that the higher fluid velocity resulted in increased mixing efficiency.



Scheme 13 Model reaction used to demonstrate the C–N cross coupling under flow conditions.

Supercritical solvents. By developing customised reactor solutions, it is now possible for the research chemist to access reaction conditions previously termed 'extreme' within conventional synthetic laboratories, opening up new opportunities for the synthetic chemist. Using this approach, Kappe and co-workers[22] have reported the utility of supercritical solvents for the catalyst free esterification and transesterification of simple carboxylic acids. In a second example, the dramatic rate accelerations possible when performing reactions in flow under high temperature and pressure was also reported by Kawanami and Sato[44] who demonstrated the $PdCl_2$ catalysed Sonogashira coupling with reaction times of the order of 0.1 to 4.0 s. Employing the rapid collision of super-heated reagents and water, the authors were able to access unprecedented turnover frequencies of 4.3×10^6 h^{-1} for the coupling of iodobenzene and phenylacetylene performed in the environmentally benign solvent-water. Product isolation was also easy, with the precipitated Pd^0 filtered under vacuum and the product isolated *via* phase separation from the aqueous reaction solvent.

An interesting area that has received attention from researchers is the development of continuous methodology for the preparation of well defined semiconductor materials. Applying continuous flow processing to the synthesis of quantum dots, Jensen *et al.*[45] reported the development and use of a high temperature and high pressure micro reactor suitable for the synthesis of nanocrystalline quantum dots. In addition to demonstrating an increase in the optical characteristics of the CdSe quantum dots, the authors were also able to replace conventional solvents such as squalane and octadecane with reduced toxicity solvents such as hexane, toluene and octane.

Principle 3: Less hazardous chemical syntheses

Whilst the toxicity and hazards associated with a specific final product do not alter with the production method employed, the fact that flow reactor technology has routinely been shown to generate products in higher yield and selectivities, it can be envisaged that the implementation of this technology at a production level has the potential to reduce the number and type of by-products generated and hence reduce the generation of hazardous products realised *via* side reactions.

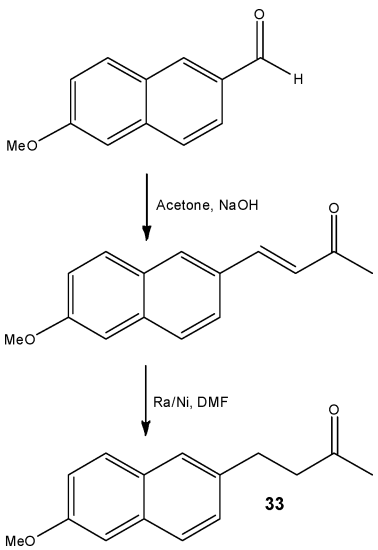
Principle 6: Design for energy efficiency

Over the past decade it has become widely accepted in academic circles that flow reactors offer the user the potential to intensify processes and thus reduce the energy impact of transformations employed at a production scale; with industrial researchers more recently reporting its application.

In an early disclosure by industry, researchers at Degussa AG described the ability to boost production capacity of an existing tubular reactor plant by installing a wall-coated microstructured reactor upfront.[46] Focussing on the synthesis of acrolein *via* a gas-phase partial oxidation reaction, the authors determined that the process would afford a temperature rise of 133 °C when performed in a 10 mm (i.d.) tubular reactor, reducing to only 1.3 °C in a 1 mm tube. With this in mind, a wall-coated microstructured device was fabricated where the increased process control led to a reduction in operational costs previously associated with thermal management. Using this approach, the researchers calculated that for a highly exothermic reaction the use of such a system would enable a 20% increase in production capacity by exploiting micro process technology for the modification of existing plant infrastructure.

Microwave heating. The coupling between continuous flow and microwave heating has received a significant amount of interest as a means of efficiently producing synthetically interesting chemicals at the small scale. In a critical assessment, Moseley and Kappe[47] however appraised the energy efficiency of microwave assisted organic synthesis, concluding that on a small scale (1 to 50 ml) any energy savings made are due to the reduction in reaction time, accessed through the use of sealed vessels, and not because microwave irradiation is a more energy efficient

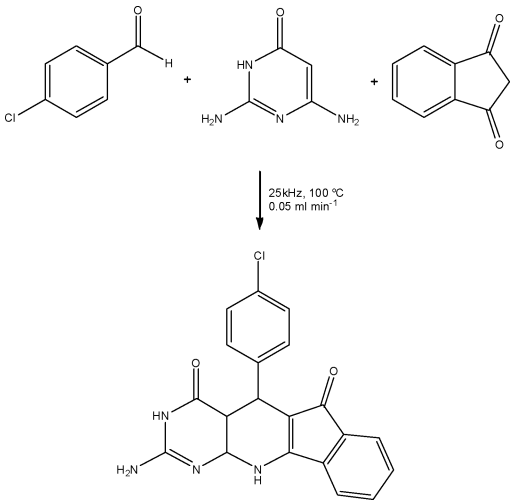
method of heating. When considering large scale reactors, multi-mode microwave reactors have been found to be more energy efficient than small single mode systems, but not more efficient than conventional heating; due to minimal penetration depth.[48] Coupled with the fact that microwave heating is 8 times more expensive than conventional heating,[49] techniques for efficient heat transfer are required if costs are to be reduced, particularly at the production level. One way of achieving this is to use small volume continuous flow reactors, with the authors demonstrating a reduction in energy usage mol^{-1}. Kappe has also shown that heating to the same temperature in a flow reactor by conventional means affords the same product therefore flow reactors have the ability to scale reactions screened in microwave reactors without a loss in performance with an increase in heating efficiency.[50] Scheme 14 illustrates a scalable two-step process developed for the continuous synthesis of Nabumetone **33** capable of producing the target compound in 75% yield at a throughput of 0.35 kg h^{-1}.[51]



Scheme 14 Two-step synthesis of Nabumetone **33** developed using microwave reactors and scaled using flow reactors.

Radiofrequency heating. Using tube reactors filled with functionalised superparamagnetic nanoparticles or steel beads, Kirschning *et al.*[52] demonstrated the ability to efficiently heat continuous flow reagent streams by placing the reactor in an electromagnetic field; affording the temperatures of 350 °C to be achieved. With this technique in hand, the authors compared the use of an oil bath, microwave and inductive heating for a Claisen re-arrangement, reporting 17% for the oil bath, 38% for the microwave and 39% for the inductively heated system. Based on these results, the authors have subsequently explored the utility of this technique reporting a range of transformations including condensations, hydrogenations, oxidations and multi-component reactions. Scheme 15 illustrates an example of a multi-component reaction whereby the target compound was obtained in 87% yield representing a 17% increase compared to the batch process.

Photochemistry. Whilst the synthetic power of photochemistry is widely recognised as a means of preparing structurally



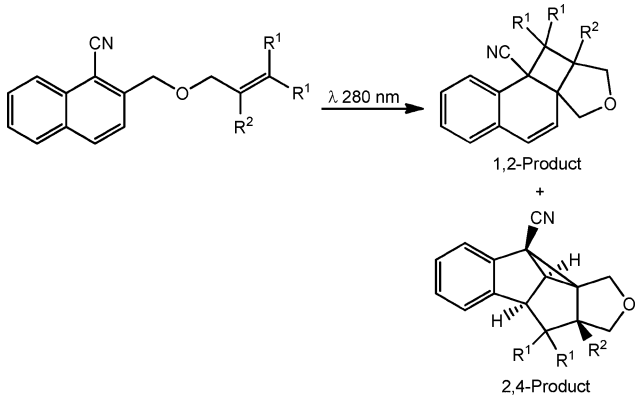
Scheme 15 Illustration of a multi-component flow reaction promoted using inductive heating.

complex architectures from relatively simple precursors, the lack of commercially available equipment and the stigma of being a difficult technique to scale means that photochemical routes are often not even considered. If we think that micro reactors, generally speaking, have a small liquid depth, it stands to reason that increases in reaction efficiency and selectivity could be possible due to homogeneous light penetration. With photochemical routes including isomerisations, cycloadditions, bond cleavages reported, this is something that researchers in the flow community hope to exploit by the development of reactors that could make high volume photochemical syntheses a reality.

An early example of photochemistry under flow was reported by Lu, Schmidt and Jensen,[53] whereby the conversion of benzophenone to benzopinacol under UV irradiation (λ = 366 nm) was investigated in a silicon/quartz micro reactor (Channel dimensions = 500 μm^2).

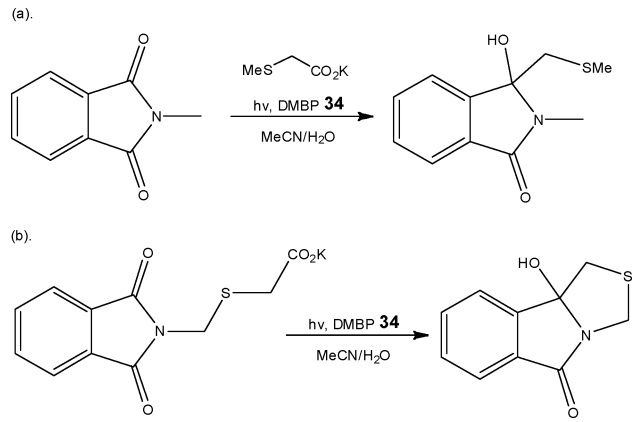
Maeda *et al.*[54] subsequently investigated the intramolecular [2+2] and [2+3] photocycloaddition of 2-(2-alkenyloxymethyl)-naphthalene-1-carbonitriles, comparing the efficiency of reactions performed under standard and flow conditions (Channel dimensions = 2.5 mm (wide) × 60 mm (long)); employing a Xenon lamp (500 W, λ = 280 nm) (Scheme 16). Performing the reaction under flow conditions the authors were able to uniformly irradiate the reaction mixture, which not only reduced the irradiation time from 240 min to 1 min, but also minimised the proportion of photocycloreversion observed. Using this approach, the authors were able to selectively perform the desired [2+2] photocycloaddition, affording the 1,2-adduct in excellent selectivity (96%); demonstrating that when fast reversible reactions and slow irreversible reactions co-exist, micro reactors offer an efficient method for the synthesis of materials *via* the former reaction pathway. The generality of the technique developed was then investigated for a series of substituted carbonitriles whereby excellent selectivities were obtained when benchmarked against comparable photochemical batch reactions.

Shvydkiv, Nolan and Oelgemöller,[55] recently described the development of 4,4′-dimethoxybenzophenone **34** mediated microphotochemical transformations of phthalimides. Employing a Foturan™ micro reactor (Volume = 1.6 ml) and five 8 W UVA



Scheme 16 Illustration of the intramolecular [2+2] and [2+3] photocycloaddition reactions of 2-(2-alkenyloxymethyl)-naphthalene-1-carbonitriles performed under flow conditions.

lamps (λ = 350 nm) as a light source, the authors investigated a series of photodecarboxylation addition (Scheme 17a) and cyclisation reactions (Scheme 17b).



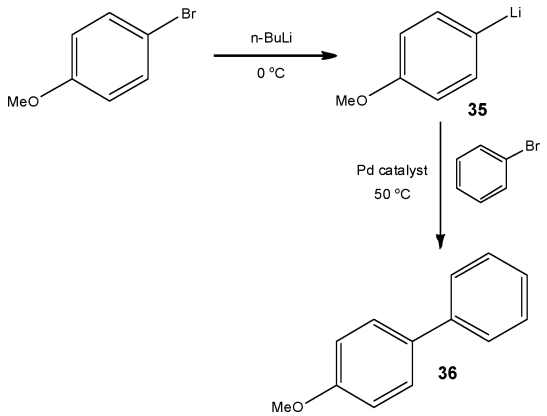
Scheme 17 Illustration of photochemical (a) addition and (b) cyclisation reactions performed using a Foturan™ flow reactor.

Compared to conventional cylindrical Schlenk apparatus, the authors calculated that the irradiated area of the micro reactor was 5 to 8 times larger than a 50–100 ml batch vessel and demonstrated larger energy efficiencies. Furthermore, decomposition processes were also avoided through the use of a flow reactor as 'over-irradiation' could be minimised. With these observations in mind, the researchers are currently exploring the development of a solid-supported mediator to aid with product purification.

Devices for the photochemical degradation of waste materials have also been developed as a means of reducing the impact of chemical production and waste treatment.[56]

Active cooling. In addition to increasing the efficiency with which energy can be put into reactions, the excellent thermal management within micro reactors means that cryogenic conditions are often no longer required. An observation initially made by Schwalbe *et al.*[57] for the halogen-lithium exchange reaction between an organolithium derivative and 3-bromoanisole.

In recent years Yoshida and co-workers[58] have extensively explored this area of flow chemistry, concluding that a series of short living organolithium intermediates can be readily generated and reacted under flow conditions at temperatures greater than those conventionally required in batch. In an extension to this investigation, the authors have also demonstrated an additional advantage of flow reactors over batch vessels, that being the ability to readily perform reaction steps for precise times at different temperatures (Scheme 18).[59]



Scheme 18 Sequential lithiation and Murashasi couplings performed at different temperatures under flow conditions.

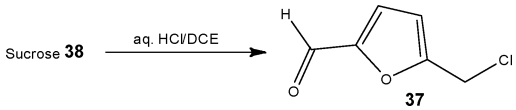
Under batch conditions, the authors formed the organolithium intermediate **35** at –78 °C, warming the reaction mixture to 30 °C to perform the Murahasi coupling, affording 53% 4-methoxybiphenyl **36**, 7% 4-butylmethoxybenzene and 3% butylbenzene. In comparison, generation of the organolithium intermediate at 0 °C (Residence time = 2.6 s) in a flow reactor, followed by the coupling reaction at 30 °C (Residence time = 16 s) the authors were able to increase the yield of 4-methoxybiphenyl **36** to 80%. Further increasing the second reactor temperature to 50 °C enabled isolation of the biphenyl derivative **36** in 93% yield at a semi-preparative throughput of 15.6 g h^{-1}. In other work the authors have also demonstrated the safe manipulation of *sec*-BuLi at –48 °C, representing a 30 °C increase compared to batch[60] and the homocoupling of aryl halides using $FeCl_3$.[61] The manipulation of moisture sensitive reagents and their introduction into flow reactors can prove challenging, refer to 'Challenges of flow reactor technology' for details.

In addition to lithiations, other transformations have been shown to benefit from increased reactor temperature include the Swern-Moffatt oxidation[15] (see Principle 1. Prevention of waste). In some cases reactor temperatures have been increased by 80 °C whilst having no detrimental effect on the reaction yield and product selectivity-giving access to a wide range of chemistries that may otherwise not be employed at a production-scale due to the need for cryogenic conditions. Looking towards production environments, this approach has potential to substantially reduce energy requirements and simultaneously the costs associated with the use of such synthetic pathways.

Principle 7. Use of renewable feedstocks

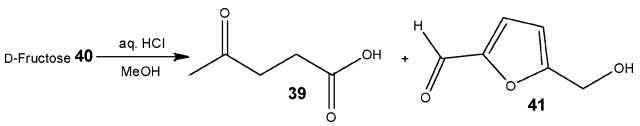
The use of renewable feedstocks in synthetic research is a relatively new area, examples of their application under flow conditions are however starting to appear in the literature. Using biphasic flow, Brasholz and Tsanaktsidis[62] demonstrated the ability to synthesise value-added furan derivatives, such as

5-(chloromethyl)furfural **37** from renewable feedstocks (Scheme 19). Employing aqueous HCl at 130 °C, the authors reported the efficient dehydration of sucrose **38** to 5-(chloromethyl)furfural **37** at a throughput of 18.0 g min^{-1}.



Scheme 19 Use of renewable feedstocks for the synthesis of value-added furan derivatives.

As an extension, the authors also reported the ability to synthesise levulinic acid **39** from D-fructose **40** using 2.0 M HCl and MeOH as the reaction solvent. Employing a reactor temperature of 140 °C for 80 min, the target compound was obtained in 72% yield with 11% 5-(hydroxymethyl)furfural **41** (Scheme 20).



Scheme 20 Synthesis of levulinic acid **39** from D-fructose **40** under flow conditions.

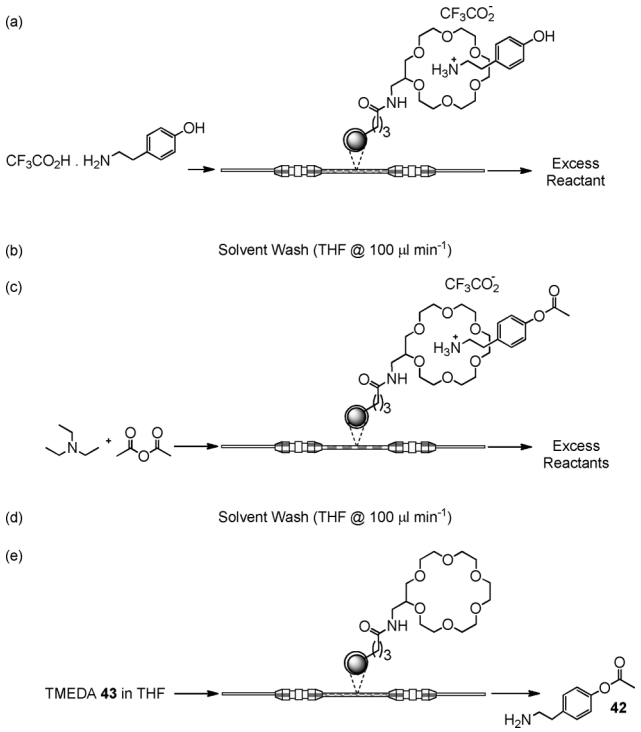
Looking towards the renewability of feedstocks, the generation of hydrogen from water and its subsequent use in hydrogenation reactions represent an area that has received significant interest from the flow chemistry community; see Principle 12 for examples using water as the H_2 source.

Principle 8. Reduce derivatives

One approach to reducing the environmental burden of synthetic chemistry is to develop methodology that requires minimal or no protecting group steps.

Whilst protecting group chemistry is by its very nature not atom efficient, Wild and co-workers[63] were able to develop a novel, re-usable non-covalent *N*-protecting group strategy; which coupled with continuous flow enabled the synthesis of *O*-tyramine acetate **42** in high yield and selectivity. In comparison, when the reaction was performed in the absence of the protecting group, a mixture of tyramine acetate **42** (23%), tyramine *N*-acetate (12%), tyramine diacetate (20%) and residual starting material (45%) was obtained.

With a strategy based on the non-covalent *N*-protection *via* an immobilised crown ether, the authors were able to *N*-protect bifunctional compounds, which upon reaction could be released to afford the derivatised amine. Using the *O*-acetylation of tyramine **42** as a model reaction, the authors evaluated the synthetic strategy outlined in Scheme 21, obtaining the target compound **42** in quantitative yield and selectivity. In addition, using an organic base **43** as a releasing agent left the crown ether cavity free for subsequent use. Whilst the solid-supported reagent could be utilised in a stirred vessel, mechanical degradation occurs making efficient recovery after each step problematic. In addition, large volumes of solvent and reagents are required in order to perform each step when compared to the use of a packed-bed reactor. Whilst at a



Scheme 21 Schematic illustrating the reaction protocol used for the non-covelent protection of amines under flow conditions.

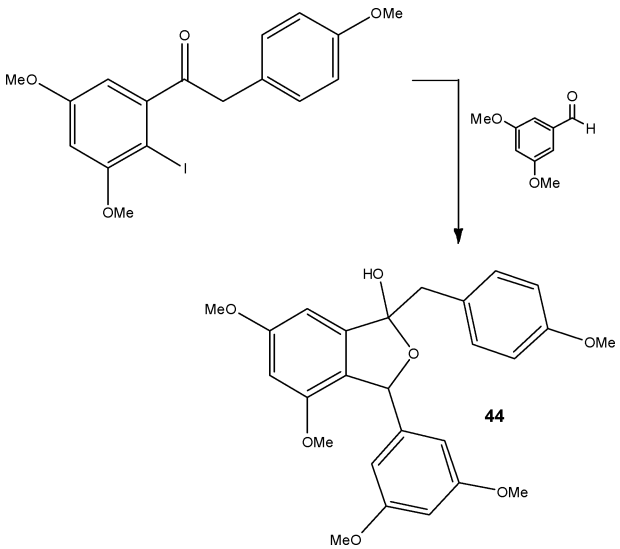
research level techniques such as 'catch and release' are shown to afford facile access to high purity materials, at a production level the procedures used to prepare and regenerate the solid-supported material must also be considered when assessing the environmental impact of a process.

More recently, Kim, Nagaki and Yoshida[64] reported a flow reactor approach for the protecting group free synthesis and reaction of organolithium derivatives (Scheme 22). In conventional batch reactors, treatment of a ketone with an organolithium reagent would result in reaction. By carefully controlling the reaction time in a micro mixer (<0.003 s), the authors found it possible to generate aryllithium intermediates from substrates possessing a ketonic moiety without the need for formal protection; which was not possible using a stirred reactor. The synthetic utility of the methodology developed was subsequently demonstrated for the preparation of derivative **44**, an intermediate used in the synthesis of the natural product Pauciflorol F **45** (Fig. 2). Using the micro reaction strategy described, the authors were able to synthesise compound **45** in 81% yield at a throughput of 12.7 g h^{-1}.

The increased control micro reactors afford enables the user to exploit subtle differences in reaction rate in order to select the desired synthetic pathway over a competing one. This approach therefore has great potential for the modern synthetic chemist, enabling the realisation of protecting group free synthesis.

Principle 9. Catalysis

Catalysis is a powerful synthetic tool used to increase the efficiency and selectivity of reactions; however identification of suitable reaction conditions, catalyst loadings and type can be both laborious and consume significant quantities of



Scheme 22 Illustration of the protecting group free synthesis of derivative **44**, a key component in the synthesis of Pauciflorol F **45**.

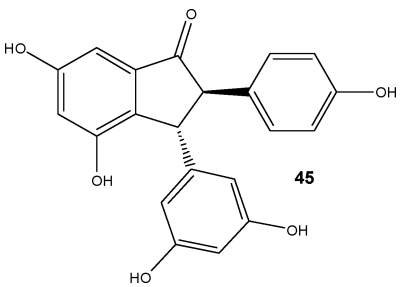
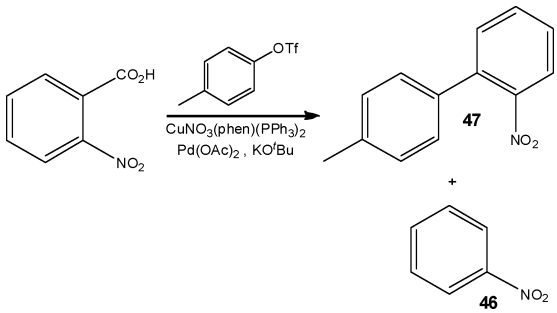


Fig. 2 Natural product Pauciflorol F **45**.

precious material. With this in mind, micro flow reactors are advantageous as they enable rapid screening of catalysts towards and array of substrates whilst minimising the volume of catalysts required. Strategic examples are selected to illustrate the advantages associated with performing catalysed processes conducted under flow conditions.

Utilising a Cu/Pd catalyst system, Underwood and Gooßen[65] described the development of a new synthetic strategy for the decarboxylative biaryl synthesis performed under flow conditions (Scheme 23). When attempted under batch conditions, minimal C–C bond formation was observed (6%), with protodecarboxylation dominating to afford nitrobenzene **46** as the major product (Scheme 23). In comparison, when the reaction was performed under the same reaction conditions in a tubular flow reactor 4′-methyl-2-nitro-1,1′-biphenyl **47** was isolated in 71% yield, with no nitrobenzene **46** formation observed. The origin of this impressive C–C selectivity is currently the subject of further investigations by the authors.

In addition to employing homogeneous catalysts, several authors have described the used of heterogeneous catalysts within flow reactors as a means of increasing the ease and efficiency of catalyst recovery and recycle. Several methods have been employed to incorporate the catalyst into the reactors including packed-beds,[65] monoliths[66,67] and wall-coated systems (Au-films,[68] polymer brushes,[69] zeolites[70] and Pd nanoparticles[71]) to exploit the high surface to volume areas obtained in micro



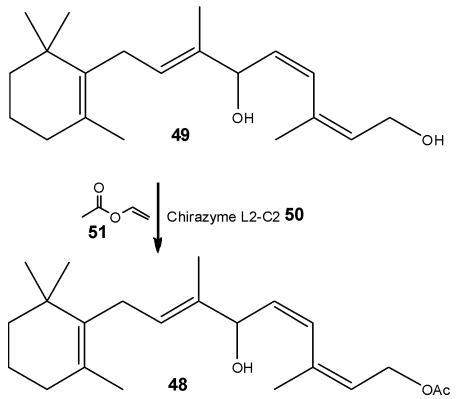
Scheme 23 Decarboxylative biaryl synthesis and the accompanying protodecarboxylation by-product **46**.

channel devices, opening up the possibility to design and evaluate novel, selective catalyst types. For additional examples please see the tutorial review by Frost and Mutton[72] and the references cited therein.

Biocatalysis. Whilst biocatalysts are extremely efficient, particularly with regards to stereoselective reactions, the costs associated with their use have somewhat limited industrial uptake. Researchers have however shown that by employing continuous flow reactors, small quantities of precious biocatalytic material[73] can be used to obtained detailed information regarding reaction kinetics, substrate specificity and operational stability. Furthermore, researchers have demonstrated the screening of biocatalytic flow processes at the bench-scale allows facile translation of synthetic methodology to production-scale.

Using previously developed polymer brushes as a surface for functionalisation, Vancso and Verboom[74] demonstrated the ability to efficiently incorporate a lipase biocatalyst (*Candidia Rugosa* type VII) onto the walls of silicon-glass micro reactors. Assessment of the devices using the BCA assay confirmed the immobilisation of 3.25–4.25 $\times$ 10^{-8} μg μm^{-2} of biocatalyst, depending on the coating time used and the thickness of the resulting catalytic layer; as with all immobilised biocatalysts, reduction in activity was observed compared to the free biocatalyst. Using the modified micro channel reactor, the authors were able to determine that the hydrolysis of nitrophenyl acetate was first order and extracted a rate constant of 22 $\times$ 10^{-3} s^{-1}. More recently He, Greenway and Haswell[75] combined biphasic flow with an immobilised lipase (*C. antarctica* lipase A) demonstrating the ability to biocatalytically hydrolyse 4-nitrophenyl butyrate at 80 °C without loss of activity over 480 h.

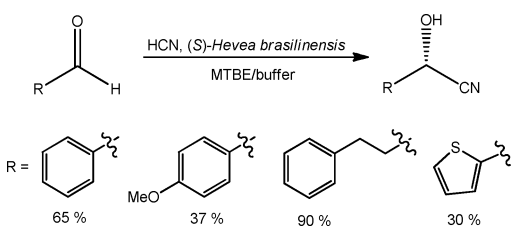
An early example of scaling a biocatalytic flow process was the lipase catalysed synthesis of (*E*)-retinyl acetate **48**, an intermediate in the preparation of Vitamin A (Scheme 24), reported by Orsat, Wirz and Bischof.[76] Starting from a 1,6-diol **49**, the authors employed an immobilised *Chirazyme L2-C2* **50** as the biocatalyst and vinyl acetate **51** in acetone as the acylating agent. Employing a small packed-bed reactor, containing 5.0 g of *Chirazyme L2-C2* **50**, the authors were able to synthesise (*E*)-retinyl acetate **48** in 99% yield and >97% selectivity affording a throughput of 49 g day^{-1}. Scaling the technique to the mini-plant, the authors employed 120 g of biocatalyst **50** and evaluated the reactor for long-term stability. After a few days they observed a decrease in production efficiency, identifying deactivation as a result of feedstock impurities. Adding a protective pre-column,



Scheme 24 Biocatalytic synthesis of a key intermediate of Vitamin A.

it was possible to operate the system at a throughput of 10 g min^{-1} (1.6 kg day^{-1}) over a period of 100 days without needing to replace the pre-column. Isolation of the target product **48** was achieved *via* distillation of acetaldehyde and rectification of residual vinyl acetate **51** allowed re-use.

Whilst considerable research has been performed into the development of chiral organocatalysts, biocatalysts afford the ultimate atom efficient route enantiomerically pure products. Using crude enzyme lysates, containing hydroxynitrile lysate, Rutjes *et al.*[77] evaluated the synthesis of a series of (*S*)-cyanohydrins in a glass microstructured reactor. Employing an organic phase containing the aldehyde (plus internal standard) and an aqueous solution containing potassium cyanide and the enzyme lysate, the effect of a fixed reaction time (12.5 min) on substrate reactivity was investigated under biphasic laminar flow. Using this approach, the authors obtained the target (*S*)-cyanohydrins in moderate to high yields, as illustrated in Scheme 25, with > 95% *ee* for aromatic substrates and ~85% for aliphatic aldehydes. Employing (*R*)-*P. amygdalus*, the authors also investigated the synthesis of (*R*)-cyanohydrins using an automated screening platform to reduce biocatalyst consumption, an important consideration when selecting an appropriate biocatalyst for a specific transformation.



Scheme 25 Biocatalytic synthesis of cyanohydrins, developed under biphasic flow conditions.

Principle 11. Real time analysis for pollution prevention

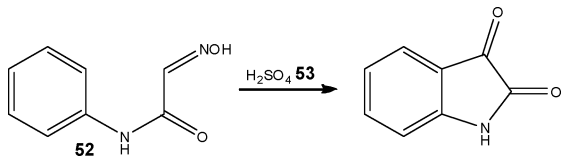
A key element of a production process is validation of product quality. Should part of a process deviate from the set condition *i.e.* dosing rate, temperature, it is imperative that the change be picked up and the effect on the process as a whole known. With this in mind, process analytics offer the ability to monitor a process in real-time, readily identifying deviations from the production target-allowing operators to more rapidly resolve issues and divert out of specification process streams before significant batches of material are spoiled. In addition to offering product quality management, process analytical tools (PAT) are also an important safety measure within the production environment. Whilst PAT such as on-line Raman and IR spectrometry find frequent application in the monitoring of industrial processes, the techniques are not yet widely exploited in synthetic research laboratories; however they have the potential to greatly increase the understanding of process at the research level.

Raman spectrsocopy. To demonstrate the synthetic utility of the Raman spectroscopy, Nordon and Mozharov[78] coupled a micro reactor to a Raman spectrometer as a means of gathering real-time reaction information from which they were able to determine reaction order and rate. Using the base-catalysed Knoevenagel condensation reaction between ethylcyanoacetate and benzaldehyde **27** as a model reaction, the authors were able to readily determine the observed reaction rate k = 0.24 $mol^{-0.1}dm^{0.3}s^{-1}$ was obtained at 40 °C.

Infra-red spectroscopy. Jensen and co-workers[79] reported an early example of online FTIR by mounting a micro reactor into the sample holder of a standard bench-top instrument. More recently online flow cells have been reported, with researchers coupling them to the outlet of continuous flow reactors to perform real-time analysis of process streams. The ReactIR™ (Mettler Toledo) system has been widely employed in the labs of Baxendale for the monitoring of short-lived reactive intermediates; illustrating in one example the instruments use in the synthesis of butane-2,3-tartrates.[80]

Mass spectrometry. Coupling a micro reactor directly to the spray capillary of a mass spectrometer, Santos and co-workers[81] were able to identify and characterise intermediates of the Sandmeyer reaction; confirming the mechanism of this controversial reaction (Scheme 26). Reacting isonitroacetanilide **52** with sulfuric acid **53** in a T-mixer, connected directly with the ESI-MS instruments source, the authors were able to sample the reactor effluent allowing samples to be analysed < 2.0 s. Under these conditions, the authors confirmed that the reaction proceeded through a previously unidentified cationic species.

In addition to analytical instrumentation, examples of specialised sensors have been reported within flow reactors as a means of monitoring changing in conduction which can be related to chemical conversion.[82] Due to the specific nature of these sensors, they are relatively inexpensive and therefore demonstrate great potential for the monitoring of continuous flow processes.



Scheme 26 Model reaction used to demonstrate the identification of short-lived intermediates using online ESI-MS detection.

For those that are interested in additional reading on this subject, an excellent review summarising the application of

in-line monitoring within continuous flow process was recently published by McMullen and Jensen.[83]

Principle 12. Inherently safer chemistry for accident prevention

One of the potentially most interesting aspects of flow chemistry is ability to increase the safety profile of synthetic transformations through reactor engineering.

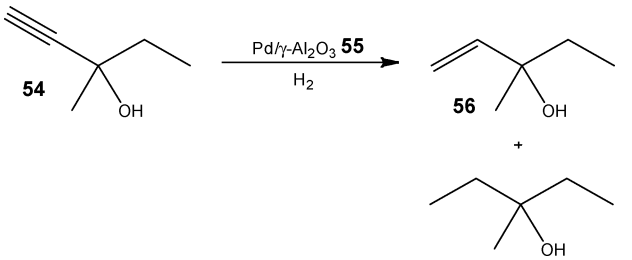
Ebrahimi *et al.*[84] investigated the production of unstable percarboxylic acids which find application as oxidisers in bleaches and disinfectants; comparing the safety rating with a batch process. In addition, the authors explored the possibility of developing micro processing systems to enable customers to generate the compounds at the point of use, concluding that this mode of operation would reduce the hazards, costs and environmental burden associated with transportation of these unstable materials.

In addition to speciality chemical production, a niche area that has benefited from increased process safety is that of gas-liquid reactions, for which access has previously been limited in the everyday synthetic laboratory.

Hydrogenation. Whilst hydrogenations represent one of the most synthetically useful transformations, the hazards associated with the manipulation of H_2 gas, and the need to employ pressure in order to drive reactions, means that stringent safety precautions are required. To address this, researchers at the University of Cambridge[85] developed a prototype 'tube in tube' reactor which employs a gas-permeable Teflon AF-2400 tube housed within a PTFE tube. Using this approach, the authors are able to deliver H_2 through the outer tube, making efficient contact with the fluid flowing through the inner tube. Using Crabtree's catalyst or Pd–C, the authors were able to demonstrate the technique for both homogeneous and heterogeneous hydrogenations, with the former taking typically 160 s *cf*. 110–250 min for the latter.

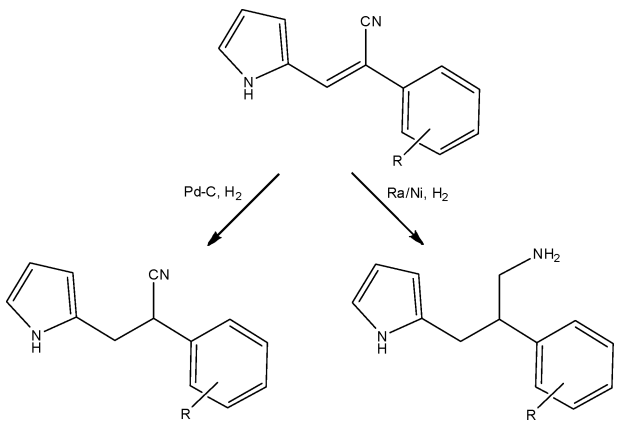
Again employing a capillary based system, this time derived from a GC column, Kreutzer and co-workers[86] demonstrated the ability to eliminate axial dispersion, utilising gas-liquid segmented flow to gain access to product selectivities currently unobtainable using conventional techniques. Investigating the hydrogenation of 3-methyl-1-penten-3-ol **54**, the authors employed a Pd impregnated γ-Al_2O_3 **55** wall-coating as the catalyst (tunable Pd contents of 0.02–5.7 wt% Pd) and evaluated the effect of reaction time on the product distribution. Over the course of 1 day, the authors were able to optimise their system to attain a maximum yield of 78 ± 2% **56**, which is in line with previous kinetic modelling studies (Scheme 27).[87] In a subsequent experiment, the technique was applied to the hydrogenation of aliphatic azides, due to the pharmaceutical relevance of the resulting amines.

When commercially available flow chemistry equipment is discussed, more often than not the piece of equipment that comes to mind is the H-cube™ (Thalesnano, Hungary), the primary reason for this being that it is an engineered solution to a long-standing laboratory problem. With laboratory safety being at the forefront of the modern researchers mind, the development of a dedicated piece of equipment capable of performing hydrogenations *via* the *in situ* generation of hydrogen from water was inspired, removing the need for H_2 cylinders



Scheme 27 Illustration of the over-oxidation product obtained for the hydrogenation of 3-methyl-1-penten-3-ol **54** in batch.

within the laboratory, further increasing operator safety.[88] Over the past 5 years, the equipment has been used for an array of gas-liquid-solid reductions such as nitro, alkene, alkyne, oxime and nitrile, along with debenzylations and deuterations. These examples have served to demonstrate not only increased process safety but also dramatic reductions in reaction time, enhanced catalytic lifetimes and increased product selectivity accessible through flow.[89] Scheme 28 illustrates a recent example utilising the H-cube™ in the synthesis of 2-phenyl-3-(1*H*-pyrrol-2-yl)propan-1-amines by Tarleton and McCluskey.[90] For a discussion of recent advances in this area of flow chemistry, please refer to the review article of Kappe and co-workers.[91]

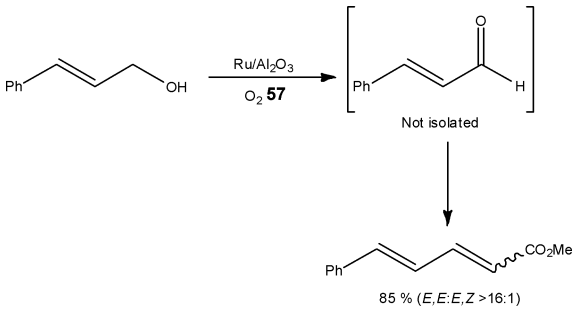


Scheme 28 Illustration of the key hydrogenation steps employed under flow conditions for the preparation of synthetically interesting pyrroles.

Oxidations. Due to safety concerns associated with the use of gases such as oxygen on a production scale, the chemical industry have in the past missed the opportunity to implement direct oxidation routes for the preparation of pharmaceutically interesting materials. By applying the use of flow reactor technology, researchers are beginning to demonstrate the industrial advantages associated with this new way of thinking.

Using a commercially available tube reactor, Hii *et al.*[92] evaluated the Ru-catalysed oxidation of benzylic and allylic alcohols to aldehydes (and ketones) with >99% selectivity. Using air (15 bar) as the oxidant in place of O_2 **57**, the authors demonstrated no change in reaction selectivity; illustrating a tolerance to halides and heteroatoms (S and N). In an extended application, the authors developed a tandem oxidation (90 °C, 1 h) and olefination (3 h) which could be performed without a solvent switch (Scheme 29).

Concurrently, Johnson, Yates and Stahl[93] reported the development of a continuous flow process for the aerobic oxidation

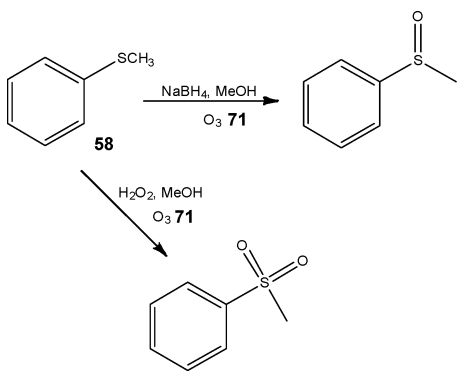


Scheme 29 An example of a tandem oxidation and olefination reaction performed in toluene.

of alcohols using a dilute oxygen source (8% O_2 **57** in N_2), taking inspiration from the commodity chemicals industry where selective oxidations are performed on large scales. A further advantage of the technique developed was that the authors operated outside the explosive regime which meant that decomposition of the Pd catalyst, to Pd metal, was avoided giving rise to potential recycle of the catalyst.

Ozonolysis. Another underutilised synthetic transformation is that of ozonolysis whereby alkenes are readily converted into aldehydes or carboxylic acids. The central reason for this is the hazards associated with both the handling and disposal of ozone, discouraging researchers from widely adopting this green oxidant.

As observed with hydrogenations, laboratory flow equipment is also commercially available for ozonolyses, with the ozonolysis of 1-decene to nonanal at −10 °C demonstrated by Gavriilidis *et al.*[94] Glasnov *et al.*[95] recently demonstrated the high yielding ozonolysis of styrenes and thioanisole, whereby the methods developed were suitable for the preparation of up to 10 g of oxidised material per day (Scheme 30).

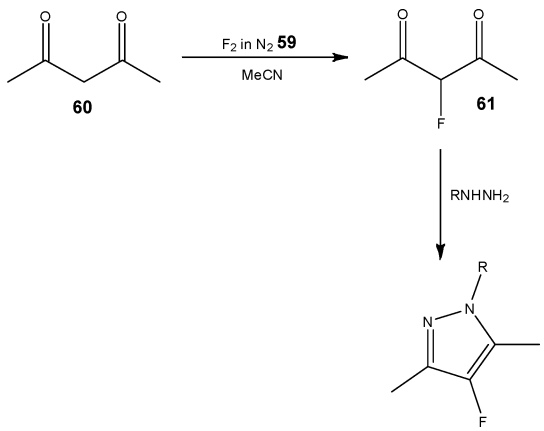


Scheme 30 Illustration of the selective ozonolysis of thioanisole **58** achieved under flow conditions.

By performing such reactions under controlled gas handling and with a suitable quench agent such as triphenyl phosphine, ozonolyses have the potential to become another routine addition to the synthetic chemists toolbox. See section 2.0 for an example of an ozonloysis performed at the tonne scale.

Fluorinations. Due to the hazards associated with the use of fluorine gas, the direct fluorination of small organic molecules is not routinely performed in the research lab. Over the past 15 years however, the research group at Durham University have developed a series of microstructured flow reactors in which they are able to safely and efficiently perform direct fluorinations using F_2.[96]

In a recent example, Sandford *et al.*[97] reported for the first time the ability to combine gas-liquid and liquid–liquid reaction steps in the synthesis of 4-fluoropyrazole derivatives (Scheme 31). Employing a stream of F_2 in N_2 **59** (10%), the first step of the reaction was performed in a nickel micro reactor, enabling the selective fluorination of 2,4-pentanedione **60** to afford 3-fluoropentane-2,4-dione **61** in quantitative conversion. The output of the nickel reactor was then connected to a T-piece where a solution of hydrazine derivative (1.5 eq.) in MeCN, EtOH or H_2O was mixed and the cyclisation reaction performed in a PTFE tube reactor. Using this approach, the authors were able to obtain the 4-fluoropyrazole derivatives in moderate to high yields (66–83%), with product purities determined using offline ^{19}F NMR spectroscopic analysis.



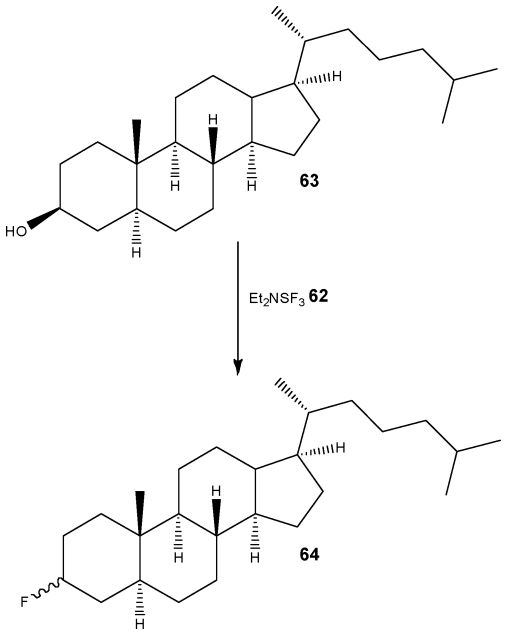
Scheme 31 Illustration of the selective fluorination step used to synthesise 4-fluoropyrazoles.

In addition to gas-liquid fluorinations, several authors have also reported the successful performance of liquid–liquid fluorinations employing reagents such as DAST (diethylaminosulfur trifluoride) **62**. The details of a comprehensive study was reported by Seeberger and co-workers[98] who identified that fluorinations could be performed in a simple PTFE tubular reactor (volume = 16 ml) by mixing the substrate with DAST **62** at a T-mixer, followed by quenching using $NaHCO_3$. Scheme 32 illustrates an example of the transformation performed on a complex alcohol **63** whereby the target fluorinated analogue **64** was obtained in 61% yield as a 6 : 1 mixture of diastereomers.

Whilst from the examples provided it can be seen that there are some obvious benefits associated with increasing the ease with which flammable gases are generated and manipulated, the safety profile of liquid–liquid phase reactions has also been shown to be increased through the use of flow reactor technology. The following section includes several a examples of the techniques applied to the large-scale production of fine chemicals and pharmaceuticals.

Production-scale processes

From the examples provided it is clear that flow processing has the advantage of providing the researcher access to a series of



Scheme 32 Fluorination of alcohols using DAST **62** under flow conditions.

previously forbidden transformations using either homemade or commercially available platforms. When it comes to production, reactor safety is key and with the foundations of the technology being the facile up-scaling of bench process to production, it comes as no surprise that a series of large-scale examples have been reported by the fine chemical and pharmaceutical industries, with system engineers reporting the fabrication of both dedicated and flexible installations.[99]

Liquid–liquid phase

In an early example of micro reaction engineering, Kirschneck and Tekautz,[100] reported the installation of a StarLam 3000 static micro mixer and tube reactor for the performance of a two-stage industrial reaction. Conventionally performed in a 10 m^3 batch reactor at a throughput of 1800 kg h^{-1}, with a reaction time of 4 h, the authors were able to double the system productivity to 3600 kg h^{-1} employing a reaction time of 60 s and demonstrating significant energy savings. At the point of reporting, the system had been installed for 18 months and had been operated with no operational problems reported. After ten months in use, the mixer was dismantled from the system and inspection revealed no corrosion; demonstrating the applicability of micro-structured reactors to fine chemical production.

de Mello and co-workers[101] illustrated at the bench-scale, the potential of micro reactors for the continuous flow synthesis of azo-dyes, highlighting that operator safety was increased as a result of performing the diazotisation *in situ*. The technique was subsequently exploited for the transformation of anilines to aryl chlorides under continuous flow conditions using the Sandmeyer reaction.[102] Building on this initial work, Wille *et al.*[103] employed a three-stage pilot plant for the synthesis of an undisclosed azo-dye capable of operating at a throughput of 30 L h^{-1}. Pennemann and co-workers[104] subsequently described improvements in pigment quality as a result of employing flow

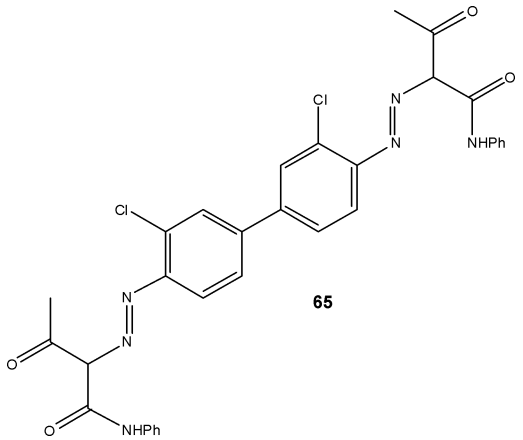


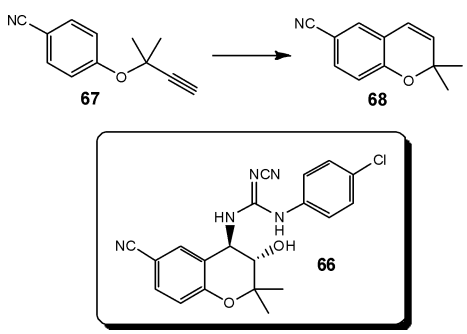
Fig. 3 Illustration of Yellow-12 **65** an azo-dye produced under flow conditions.

processing for the production of Yellow-12 **65** (Fig. 3); with improved particle size distribution, glossiness and transparency among the metrics reported.

Looking towards the production of highly energetic materials, Loebbecke *et al.*[105] described the construction of a micro reaction plant for the synthesis and downstream processing of nitrate esters. Owing to the thermallability of the materials, a remote controlled reactor was constructed and the optimisation of an undisclosed material performed; enabling the evaluation of process parameters that would have previously remained uninvestigated. Once identified, the optimal processing conditions were transferred an automated multi-purpose plant where continuous synthesis of the explosive materials was performed; incorporating downstream processes such as washing and extraction. Using this approach the authors were able to synthesise materials such as trinitroglycerin at a pharmaceutical grade with throughputs of 9 kg h^{-1}.

Experiencing significant temperature rises (180 to 445 °C) during a key synthetic step in the preparation of a drug candidate **66**, researchers at Bristol Myers Squibb proposed a safe process could be developed through the application of continuous flow.

Employing a stainless steel tube reactor, heated to 220 °C, the authors investigated the effect of reaction time (3.5–17.7 min) Claisen re-arrangement of propargyl ether **67** to 6-cyano-2,2-dimethylchromene **68**; observing >96% conversion under all conditions explored (Scheme 33).[106]

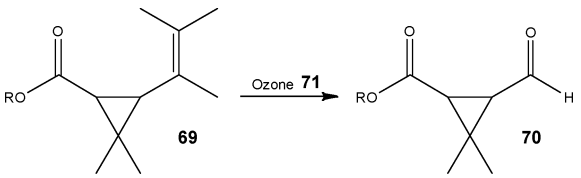


Scheme 33 Illustration of the Claisen re-arrangement which forms a key step in the synthesis of the benzopyran-based potassium channel activator **66** of BMS.

Increasing the reactor volume, the authors readily scaled the process to afford the benzopyran **68** derivative in 91% yield at a throughput of 7 kg h^{-1}. By controlling the exothermicity of the reaction, the authors were also able to increase the quality of the product generated, with purities > 96% obtained over four 40 g batches.

Gas-liquid phase

In addition to the laboratory scale examples of ozonolysis reactions, Roberge and Nobis[107] recently published details of a tonne-scale ozonolysis reaction performed under flow conditions. Looking to the conversion of chrysanthemic ester **69**, as illustrated in Scheme 34, the authors were able to develop a safe method of synthesising the corresponding aldehyde **70**-a key intermediate of an insecticide. Utilising a 450 L loop reactor, the ester was safely reacted with ozone **71** in a process that was optimised to a production scale of 0.5 tonne day^{-1}; with Lonza demonstrating the manufacture of commercial quantities of the material.

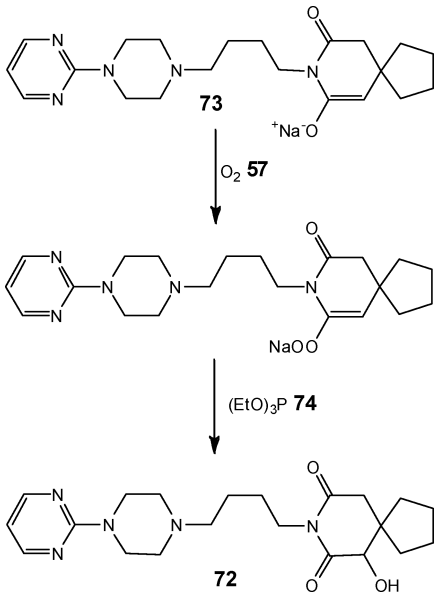


Scheme 34 Oxidation of chrysanthemic ester **69** to the aldehyde **70** which is a key intermediate in the synthesis of an insecticide.

With a view to reducing scaling issues associated with a key oxidation step, which required 16–24 h at –70 °C in batch, LaPorte and co-workers[108] developed a three-stage continuous flow process for the synthesis of 6-hydroxybuspirone **72** (Scheme 35). Utilising a pre-formed enolate **73**, the authors investigated its reaction with oxygen **57** at a reactor temperature of –10 °C and addition of triethylphosphite **74** afforded the target product **72** in 65–70% conversion; which was readily increased to 85–92% by the addition of a second stream of O_2 **57**; affording a throughput of 300 g day^{-1}. Compared to the previous process, reaction times were reduced to 5 min and large cost savings harnessed by increasing the reactor temperature by 60 °C for the oxidation step.

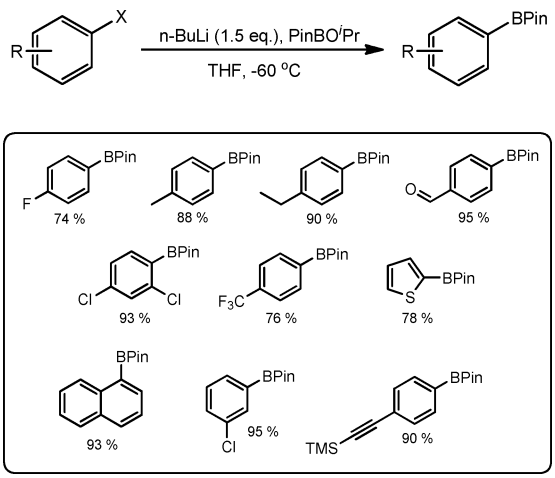
Challenges of flow reactor technology

Whilst it can be seen from the examples provided that flow reactor technology is an emerging technique that will benefit many synthetic researchers over the years to come, a recent publication by Ley and co-workers[109] succinctly combines a practical description of the advantages and disadvantages of continuous flow processing.[22] In this report, the authors highlight on one hand the processing advantages associated with the performance of reactions under cryogenic conditions; without the need for liquid N_2 or solid CO_2 baths. On the other hand, the authors detail the challenges associated with the manipulation of highly corrosive reagents and the foresight required in order to prevent precipitation of intermediates and products within the reactor coil itself. Once time is spent to overcome these technical challenges, the result is a segmented



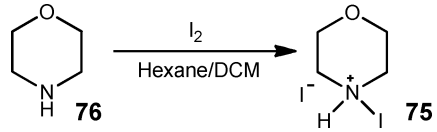
Scheme 35 Illustration of the synthetic route developed for the continuous processing of 6-hydroxybuspirone **72**.

flow process capable of rapidly preparing pinacol boronate esters at a maximum product concentration of 0.2 M in moderate to high yield and > 95% purity; after an offline aqueous extraction (Scheme 36).



Scheme 36 Illustration of the synthetic route to pinacol boronate esters under segmented flow conditions.

Another significant aspect of flow reactor research that is often over-looked by those new to the field is the importance of selecting the correct reactor for the process under investigation. Of the wide number of reactors available, it is imperative that the user select the correct one for the task at hand, this can include (but not exhaustively) wetted material type, pumping mechanism, reactor size and mixer type. This is illustrated in an example by Browne *et al.*[110] where the manipulation of slurries would be unsuitable in a tube reactor however the hydroiodide salt of *N*-iodomorpholine **75** (Scheme 37) is efficiently prepared at a throughput of 3.9 kg $week^{-1}$; even in this case however it must be noted that homogeneous solutions were required to dose the reagents due to the pumping technology employed.



Scheme 37 Iodination of morpholine **76** in an agitated cell reactor to afford the hydroiodide salt of *N*-iodomorpholine **75**.

Summary

For the chemical industry to realise its potential in developing sustainable processes, it is imperative that the link between research chemists and process engineers continues to strengthen. Going forward, the focus of the chemical sector therefore needs to centre on the development of practices which continue to reduce waste and increase sustainability, whilst maintaining high production qualities.

Through improvements in process control, continuous flow methodology has the ability to play an integral role in revolutionising the chemical sector, not only from an environmental standpoint but also from a quality, safety and economic perspective. Further work is required to address the challenges associated with the manipulation of slurries and the recovery of solvents and catalysts in order to expand the reaction types that can benefit from flow processing.

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