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FULL-LENGTH PAPER

The flow synthesis of heterocycles for natural product and medicinal chemistry applications

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Abstract This article represents an overview of recent research from the Innovative Technology Centre in the field of flow chemistry which was presented at the FROST2 meeting in Budapest in October 2009. After a short introduction of this rapidly expanding field, we discuss some of our results with a main focus on the synthesis of heterocyclic compounds which we use in various natural product and medicinal chemistry programmes.

Keywords Flow synthesis · Micro-reactor · Meso-reactor · Solid-supported reagents · Heterocycles · Automated synthesis

Within the last century, the chemical community has seen tremendous progress in terms of new chemical reactions which have not only aided our fundamental understanding but also importantly enabled chemists to devise chemical synthesis routes to almost any conceivable structure. Although our knowledge has improved immeasurably and our ability to construct these new chemical entities is impressive, the efficiency by which we carry out the necessary synthetic transformations is arguably much less well developed. We still produce significant quantities of waste material, have an excessively high carbon foot-print, and we need to employ a highly skilled and trained workforce although sometimes their tasks can be very menial, time consuming and repetitive [1]. Similarly, optimisation, purification and analysis of reactions can be very tedious. A significant contributing factor to this wastage is the relatively conservative nature of the chemical community. Unlike many other sciences synthetic methodology and laboratory practices have remained relatively unchanged for a long period of time. A chemist of 50 years past would still recognise much of the general apparatus, tools and equipment in use within a chemical laboratory today. Our reliance on batch processes has shackled us and engrained a dependence on round bottomed flasks, separating funnels and other traditional glass manifolds. As a result, although incremental changes in design and application of the standard laboratory formats have been achieved; these have led to only relatively minor improvements in productivity [2–5]. In reality, we have not fundamentally tackled the true problems or bottlenecks of synthesis and consequently many limitations still remain. However, there has been a growing recognition and acceptance that these problems do exist and need addressing. The resulting solutions have become referred to as "enabling technologies" [6]. This term indicates new thinking and concepts that are typically interdisciplinary in nature. The acceptance and implementation of these enabling tools should immediately broaden the scope and allow easier access to key synthetic transformations that were previously difficult or even impossible owing to restrictions imposed by safety, time or cost. In recent times such tools have included combinatorial chemistry approaches to increase the number of lead compounds generated and bioinformatics to improve the target and lead evaluation, others such as high throughput screening and focused microwave heating have also been introduced to address a variety of specific problems. The use of microwave radiation to accelerate chemical reactions is possibly the best described example creating whole new opportunities for chemical synthesis with thousands of applications and publications having been reported [7–9]. Indeed, today one can find microwave reactors in almost every chemical and materials research facility around the world. Microwave reactors have not only helped by conveniently performing single transformations but also

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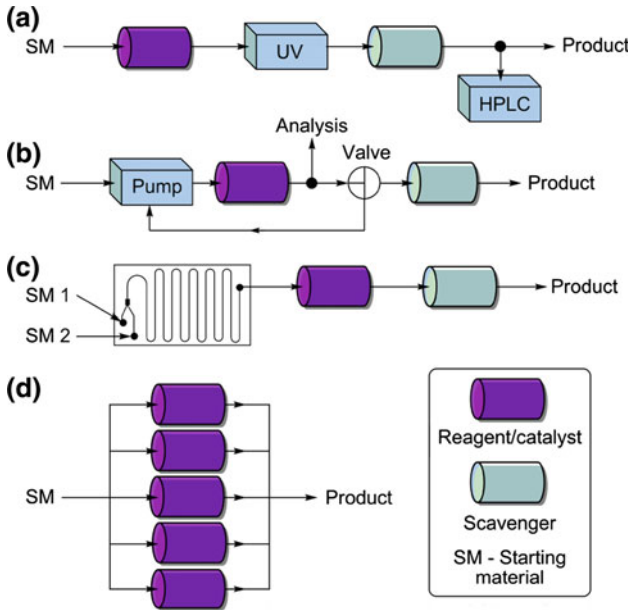
changed the way we consider running multiple reaction optimisations. The possibility to run a sequence of reactions within the containment of independent small glass vials in an automated and computer controlled manner has highlighted the benefits of changing working practices and embracing more time-efficient chemical research [10].

Nevertheless, chemical synthesis still faces many problems, for example, when the existing technology repertoire fails to deliver the large number of compounds required within a short timeframe necessary in many pharmaceutical research programs. In addition, even with large arrays of compounds available for high throughput screening the synthetic chemist is often frustrated by failure of compounds in late stage biological trials rendering all the synthesis chemistry redundant [11,12]. In order to minimise such occurrences and offset the associated loss of time and money, the trend is to frontload or leverage the risk of compound failure by speeding up the entire candidate selection process [13–15]. However, this can only be sensibly accomplished when compounds can be prepared very quickly as needed in a flexible manner. This concept, also known as closed-loop lead-optimisation paradigm [16], therefore, requires the closer collaboration between synthetic, medicinal, analytical chemists and biologists in designing small better quality libraries of potential drug candidates. Once a compound has been prepared and purified, the biological evaluation needs to follow immediately to provide crucial feedback to aid the design program. The iterative cycle is repeated several times until a potent compound with good DMPK properties (drug metabolism and pharmacokinetics) is identified. It is obvious, therefore, that one of the main bottlenecks in today's drug discovery programmes is the rapid supply of structurally diverse chemical entities [17–19].

An emerging technology to address these goals can be found in flow chemistry devices [20–22]. With this equipment, continuous processing can be accomplished using a small foot-print, computer controlled flow reactor. Furthermore, there is the possibility to run reactions over 24 h 7 days a week in a reproducible and fully automated fashion giving the chemist the extra time to make decisions, plan syntheses and design assays. This approach accelerates the initial hit to lead process by considerably reducing time delays within the target choice/synthesis/biological evaluation loop. Once a lead compound has been identified, flow reactors additionally allow for the preparation of larger quantities of material for extended evaluation. It is, however, pertinent to point out that although these flow reactors can speed up the overall synthesis process; they do not replace the need for skilled chemists whose input informs and directs the synthesis routes.

In order to achieve reactions in a flow-based manner, one can envision a variety of simple experimental set-ups depending on the type and parameters of the reactions under investigation. For instance, in its simplest configuration, two



Scheme 1 Typical set-ups for flow chemistry [29]

reagent streams can be combined via a static mixing T-piece or a serpentine-channelled glass chip (commonly referred to as microfluidic chips) before being directed into a reactor device. This can be subjected to various physical interactions such as heating/cooling, ultrasonication or microwave radiation to initiate the desired transformations (Scheme 1c). It is also advantageous to gather real-time data on the composition of the reaction stream using in-line monitoring such as UV, Raman or IR-detector [23–25] (Scheme 1a). Other coupled diagnostic tools including integrated LC-MS systems are also very informative in recording and analysing product formation and thereby permitting feed-back mechanisms to enable fast serial processing and optimisation of the reaction conditions [26] (Scheme 1b). Moreover, the use of immobilised reagents and scavengers packed in columns and cartridges is also of great benefit to provide in-line purification of the flow stream [2]. The increasing availability of many high quality commercial sources of immobilised reagents that possess synthetically useful functional groups has driven the application of solid-supported species under flow conditions [27,28]. In addition, these resins can be packed into various glass tubes to allow for parallel processing and thereby enabling the preparation of larger quantities of material by scaling out of the process (Scheme 1d).

Over the last 10 years, these concepts have found wide applications in organic Synthesis. Some recent examples include the generation of small compound libraries of thioethers [30] or *N*-alkylated sulfonamides [31] using polymer-supported TBD acting as both a base and an alkylating agent. These reactions used stoichiometric amounts of the immobilised species which could be regenerated.

Further examples using ion-exchange monoliths (prepared by precipitation polymerisation) have been used to perform a variety of transformations [32] including ether syntheses, reductive aminations, oxidations and Horner–Wadsworth–Emmons olefinations [33] in flow mode. In addition, these monolith cartridges have also been loaded with metal salts of palladium and nickel which, upon reduction, form polymer-embedded nanoparticulate species that can be used as catalysts. The Pd-monoliths, for example, have been extensively used for various reductions and Heck reactions and can therefore be considered as complementary devices to metal-coated capillaries or the more sophisticated purpose built equipment such as the H-Cube system [34] for hydrogenation reactions. Alternatively, polymer-encapsulated palladium systems have been shown to be highly effective for performing Suzuki and Sonogashira reactions in flow with very low levels of associated metal leaching [35]. Other types of immobilised catalysts have been prepared by employing a tetherable chelation site for metal ions linked to a polymerisable monomer backbone. This approach has been a very popular method to immobilise various chiral ligand systems and thereby enabled asymmetric reactions to be performed in flow mode in some cases [36–40]. These reactions include kinetic resolution processes (with Co-salen complexes), asymmetric Diels-Alder reactions (with Ti-taddolates) and cyclopropanation reactions (with Ru-PyBox). An excellent early example of a multi-step β-lactam synthesis starting from acid chlorides employing immobilised catalysts is a flow trickle reactor and was reported by Lectka in 2001 [41].

Some of the most impressive applications of flow chemistry reported more recently have employed multi-step preparation of biologically active substances. These examples are particularly noteworthy when compared with their batch-mode counterparts. For example, Lectka's synthesis of BMS-275291 (Rebimastat, [42]) again using simple gravity fed columns nicely illustrates these flow concepts. The preparation of di- and tripeptides [43], pharmaceutical products [44–46] and natural products like Grossamide [26] and Oxomaritidine [47] by our group also demonstrate clear advantages especially in overall reaction and processing times when compared to batch-mode preparation.

In order to perform the very wide range of different transformations available to the organic chemist, different flow reactor configurations are needed to address specific problems. Simple syringe pumps or HPLC have been widely used in bespoke devices. However, with drive from the community requiring flow chemistry equipment, many new devices have become commercially available. The H-Cube system mentioned earlier for flow hydrogenations as well as the AFRICA flow system [48] and more recently the Uniqsis FlowSyn reactor [49], the Advion Nanotec reactor [50] and the Vapourtec R2+R4 system [51] have all entered the area by providing commercially available flow platforms. Other systems such as the Microreactor Explorer from Aldrich [52], the LabTRIX system [53], the Future Chemistry system [54] and the X-cube [34] are also useful devices. These more sophisticated systems not only allow the user to conveniently run a variety of flow reactions but also facilitate the scheduling, documentation and optimisation of experiments by means of dedicated software. The addition of front- and back-end liquid handlers as well as in-line UV-detectors and other analysis tools also helps to maximise reaction performance and product outcomes (Fig. 1).

Having introduced flow chemistry as a promising and very powerful enabling method to facilitate and accelerate chemical synthesis, we report below some of our recent research applications of the technology. However, before we do this we need to consider some specific ambitions. New developments in science are often misused and applied to the wrong problems. Consequently, in our view it is not sufficient to simply use a new device to reproduce relatively trivial chemistry which already works well under automated batch conditions. We therefore set out to identify a number of more strategically important chemical transformations which despite their obvious usefulness are considered difficult as a result of certain safety concerns. In addition, we believe that the high quality of the product obtained from a flow process is important as this minimises issues of work-up and down-stream processing. Our approach is therefore to develop processes that are reliable and robust giving the desired product in purities above 95% without the need for conventional work-up and product isolation steps.

The heterocyclic ring is the most prominent structural feature in the vast majority of pharmaceutical compounds since this facilitates tuneable interactions with the biological target whilst conferring a degree of structural and metabolic stability. Furthermore, these structures can be conveniently assembled with a large variety of substitution patterns, which are not readily accessed using simple carbocyclic counterparts. In order, therefore, to investigate heterocyclic compound syntheses, we began by preparing a collection of structurally interesting oxazole derivatives using a combination of readily available or easily prepared isocyanides and acid chlorides [55]. Since both these starting materials posses corrosive and malodorous properties, which make them difficult to handle in batch-mode syntheses, the flow approach was thought to be more convenient. Owing to the contained environment of a flow reactor, we can readily manipulate the ethyl isocyanoacetate starting material and add it to the electrophilic acid chloride. Cyclisation can then be achieved using an immobilised phosphazene P1 base. In this study, the polymer-supported base PS-BEMP was found to be far superior to any other base investigated, either immobilised or solution phase and gave the highest conversions and cleanest products. Using automated test and optimisation experiments conditions to

Fig. 1 Some commercially available flow chemistry systems. **(a)** Uniqsis FlowSyn reactor *(top left)*; **(b)** Advion Nanotec reactor *(top second)*; **(c)** LabTRIX system *(top third)*; **(d)** X-Cube *(middle left)*; **(e)** AFRICA flow system *(middle centre)*; **(f)** Vapourtec R2+R4 system *(bottom left)*; **(g)** FutureChemistry system *(bottom centre)*; **(h)** Microreactor Explorer kit *(bottom right)*

produce a small selection of 4,5-disubstituted oxazoles in very good yields were soon realised. In order to ensure complete conversion in these reactions, a slight excess of the acid chloride component (10–20 mol%) was used which was removed by later scavenging using an immobilised benzyl amine resin (QP-BZA, [56]). We also demonstrated that a similar reactor set-up can be successfully used to generate 10–25 g quantities of the desired oxazoles by simply scaling up the immobilised species and extending the reaction processing times (Fig. 2).

Encouraged by these results, we then wished to increase the molecular diversity of the products by exploring isothiocyanates as alternative electrophilic inputs thereby hopefully generating the corresponding thiazole products in flow [57]. Interestingly, whilst profiling the reactions under typical flow conditions, the anticipated heterocyclic products were only recovered in moderate yield. Upon further examination of the product outputs, however, and by rationalisation of the mechanism, we determined that an initial vinylic thiolate was being formed as expected, but that this species could ring-close via the amine nitrogen or the thiolate sulfur atom to give two different products. Under our initial reaction conditions, a proportion of the thiolate anion was clearly being trapped by the BEMP resin as opposed to undergoing rapid ring-closure to the thiazole product. We were able to exploit this inter-

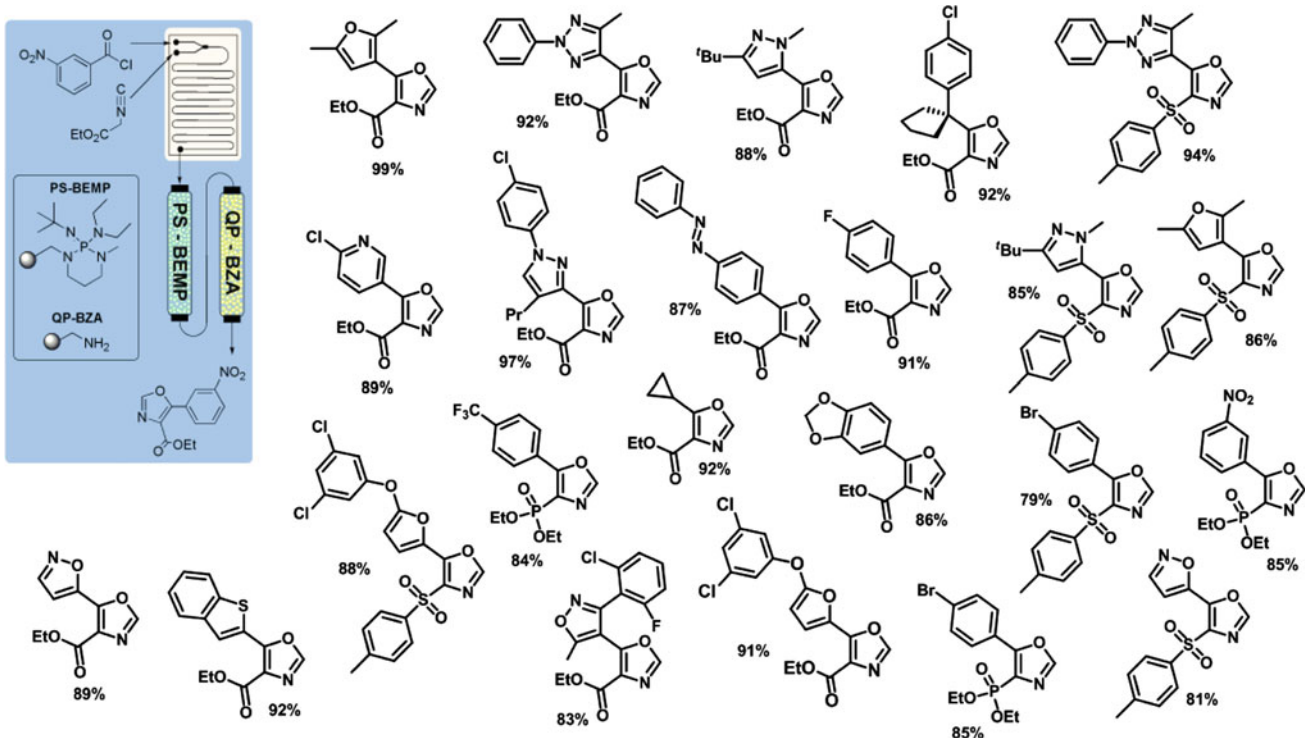
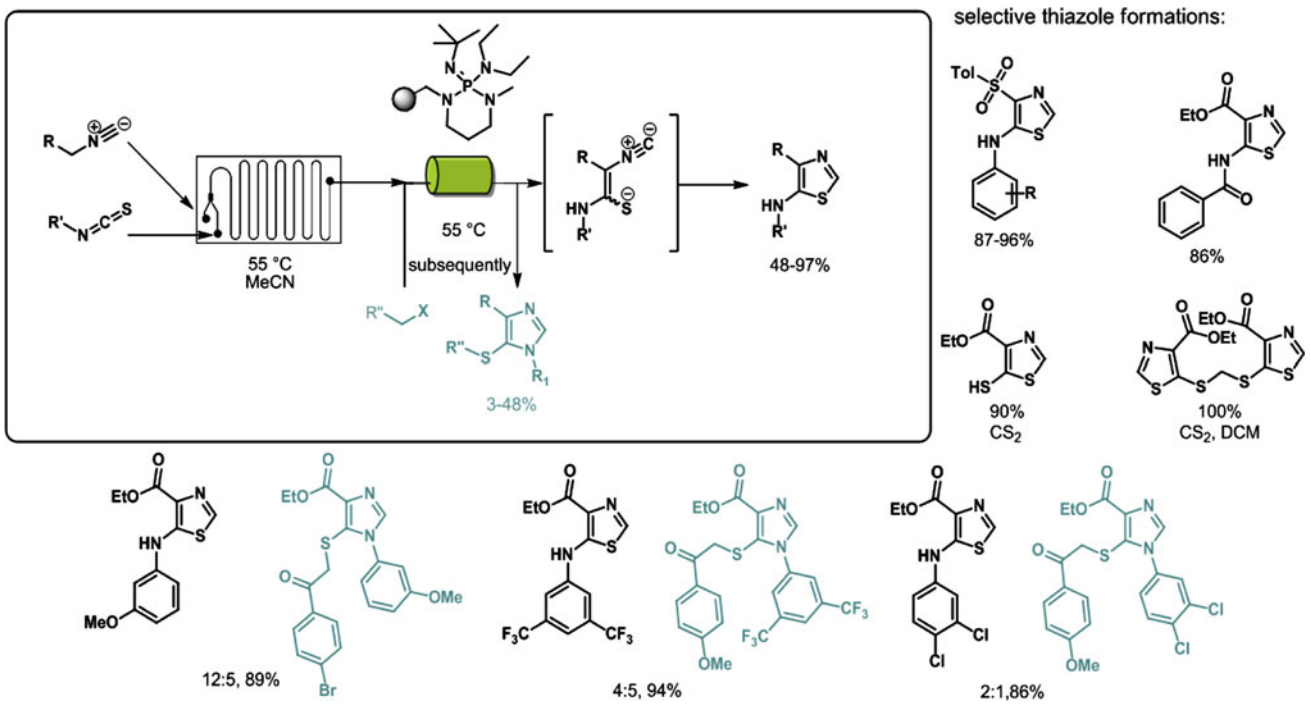


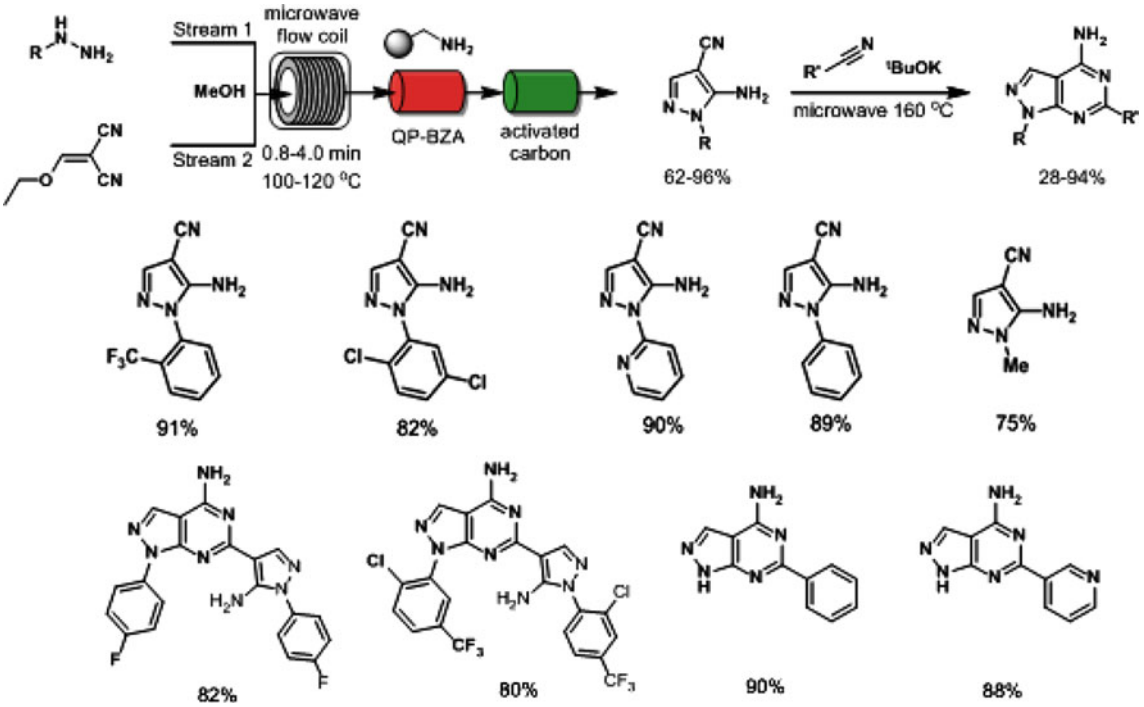
Fig. 2 Flow synthesis of 4,5-disubstituted oxazoles

esting opportunity by introducing a second electrophile to divert material to an imidazole as the final product (Scheme 2).

By carefully tailoring the reaction conditions and tuning the reactivities of the starting materials, we could generate a new series of compounds where either both



Scheme 2 Bifurcated pathway to thiazoles and imidazoles



Scheme 3 Aminopyrazoles and pyrazolopyrimidines prepared using microwave radiation

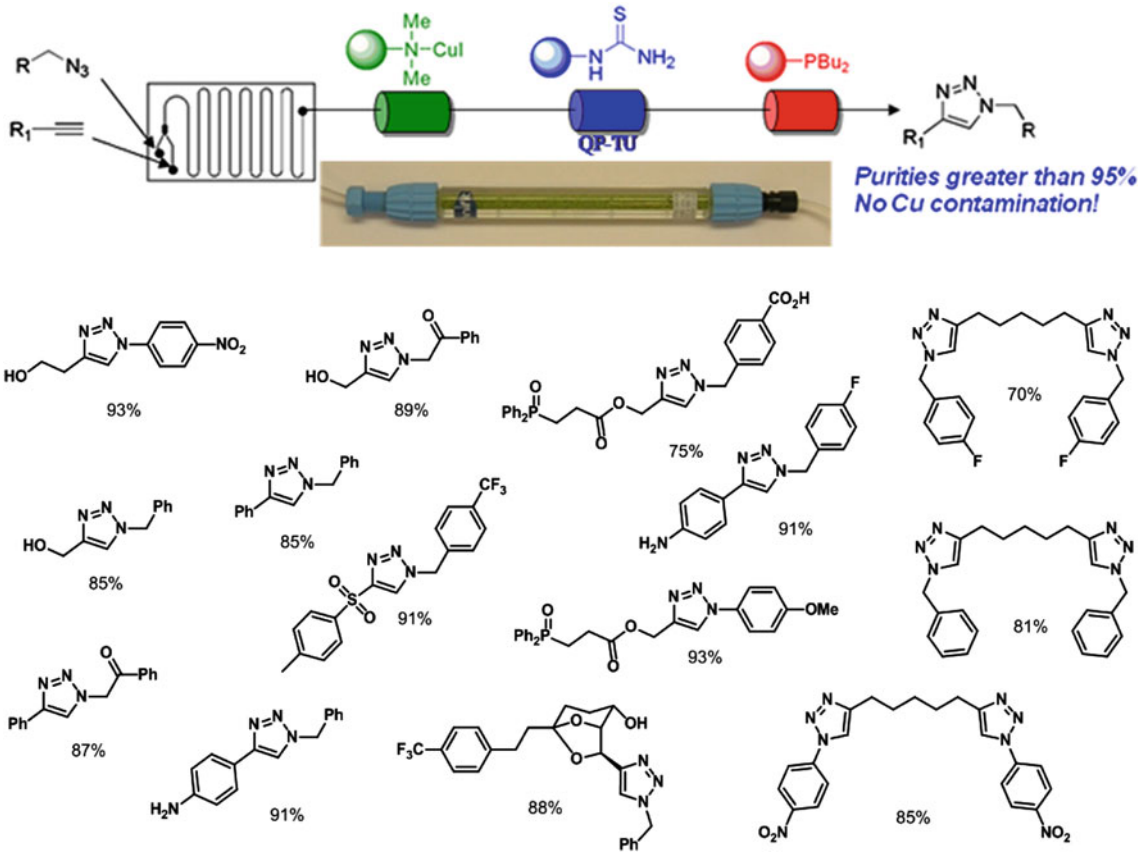
heterocyclic structures could be prepared sequentially or the thiazole could be obtained as the sole product.

Pyrazoles and triazoles represent two other interesting five-membered heterocycles which have found extensive applications in medicinal chemistry particularly as building blocks for various drug substances. Based on earlier studies from our group where we had converted nitriles to aminopyrimidines via a trimerisation process [58], we expected that a similar condensation sequence between hydrazines and ethyl ethoxymethylene malononitrile would give rise to a complementary series of aminopyrazoles [59]. Therefore, mixing stock solutions of the starting materials and subsequently passing the combined flow stream through a newly developed microwave chemistry flow device that effectively mimicked a standard 20-mL microwave vial, we could furnish the desired product using elevated temperatures (0.8–4.0 min, 100–120 °C). A high purity of the product was maintained by in-line sequestration in flow of any excess ethoxymethylene malononitrile using glass tubes filled with a benzylamine scavenger and activated carbon. Accordingly, we prepared a series of aminopyrazoles on scale (up to 250 g) using this new combined flow microwave set-up [60–63]. We demonstrated further that the aminocyano pyrazole products could be condensed with a nitrile under standard batch microwave conditions to provide a set of novel pyrazolopyrimidine compounds (Scheme 3). More generally, we have found microwave heating, immobilised reagents and flow chemistry to be a particularly powerful combination which is especially attractive when applied to metal-catalysed processes [64–66].

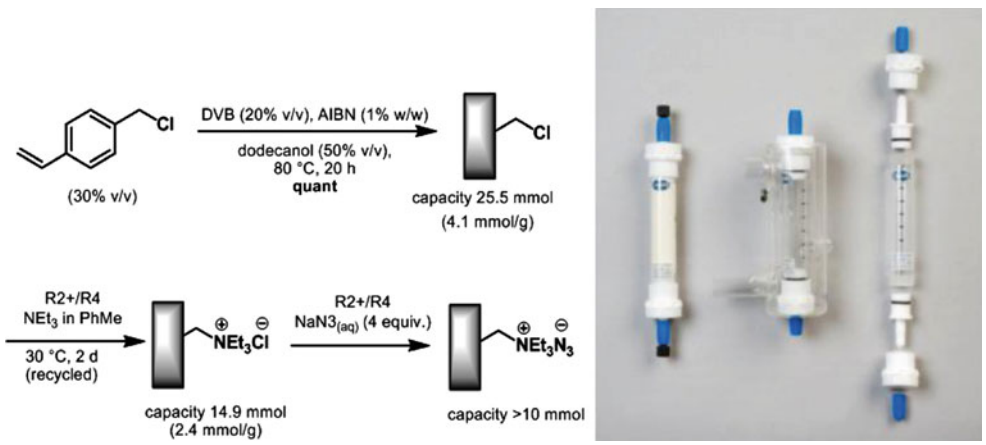
Since 1,2,3-triazoles have become very popular structures owing to the ease by which these heterocycles can be made via a mild copper-catalysed Huisgen cycloaddition reaction, we decided to develop a flow chemistry version of this important process [67]. In order to introduce the necessary copper catalyst at the appropriate stage, we prepared copper(I) iodide supported on an Amberlyst 21 dimethylamine resin by vortexing the two components in acetonitrile overnight to generate a light green-coloured catalyst which was easily loaded into an Omnifit column [68] to act as an in-line flow reactor cartridge (Scheme 4).

The starting materials (azide and acetylene) were then reacted by passage through the glass column packed with the tethered copper(I) species. However, some leaching of the copper species was observed although this could be readily sequestered using a column of QP-TU (an immobilised thiourea species, [56]). In addition, we incorporated a flow tube packed with an immobilised phosphine to scavenge any residual azide contaminant. Using this procedure, we were able to prepare a variety of triazoles in good yields and excellent purities after solvent removal. The thiourea scavenger furthermore proved very efficient as no detectable copper contamination was observed, despite the triazole structures being very effective ligating materials.

A major limitation of conducting this type of "click" chemistry is due to the restricted commercial availability



Scheme 4 Flow synthesis of 1,2,3-triazoles



Scheme 5 Preparation of azide ion-exchange monoliths

of potentially hazardous azide and alkyne coupling components. In order to therefore address this supply issue, we investigated new ways to prepare these starting materials using flow chemistry procedures. As organic azides are most commonly obtained by substitution reactions using sodium azide, we required a way of immobilising the azide anion onto a solid support yet be compatible with the flow system. This was finally achieved by preparing a high-loading ion-exchange monolith resin [69,70], which was prepared by precipitation polymerisation then functionalised via an ion-exchange process using aqueous sodium azide followed by conditioning of the column with an organic solvent (Scheme 5).

These azide monoliths show a high functional loading in excess of 10 mmol (column size: 10-cm length, 10-mm bore) and can be regenerated many times using a recycling

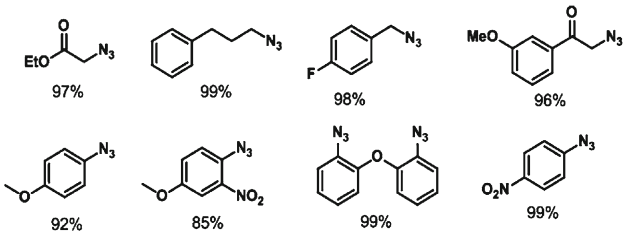


Fig. 3 Azides prepared using a monolith in flow

sequence. When solutions of alkyl and benzyl halides were passed through monolith columns, a variety of organic azides were obtained in excellent yields and purities (Fig. 3).

Then in order to generate the necessary alkyne coupling partners in flow, we used the Bestmann–Ohira modification of the Seyferth–Gilbert reaction [71] as this is a very mild method to homologate aldehydes to the corresponding alkynes [72]. Accordingly, the Bestmann–Ohira reagent was treated with a base to cause it to fragment to a diazomethyl phosphonate which then condensed with the aldehyde starting material to give the desired alkyne following elimination of the phosphonate and a subsequent 1,2-migration. This flow chemistry approach also allows for the incorporation of scavengers to remove unreacted aldehyde as well as the phosphonate by-product and inorganic species generated during this somewhat wasteful process (Scheme 6).

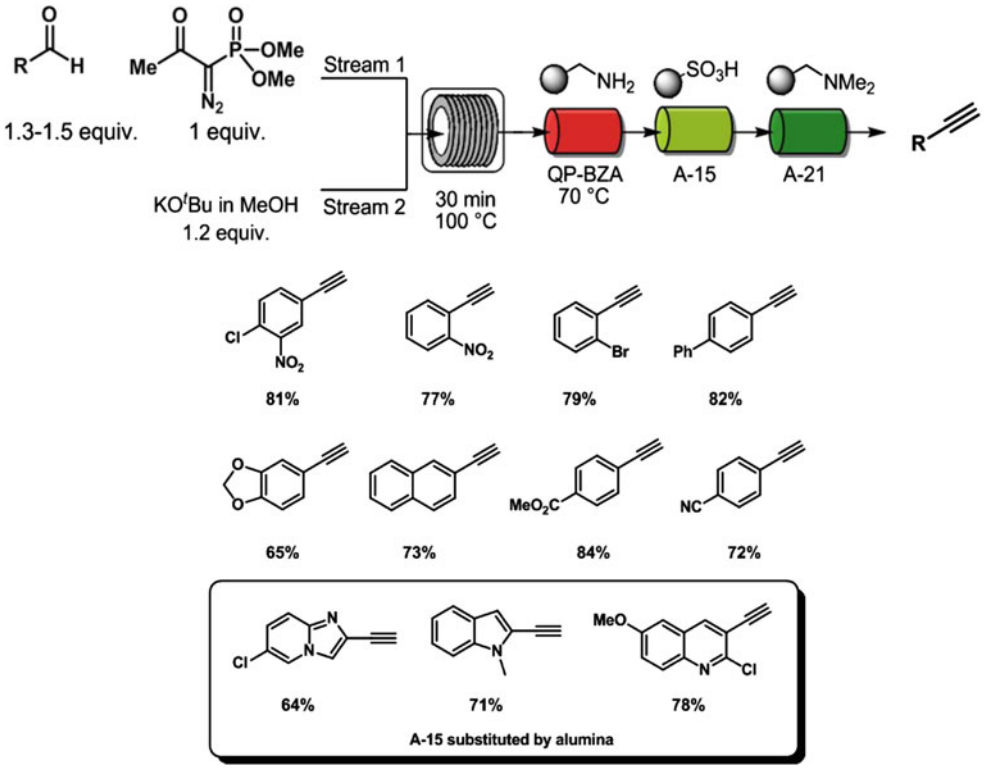
Using a combined reaction time of 30 min at elevated temperatures (>100 °C), a small collection of pure non-commercial alkynes was prepared in good yield. Then, we demonstrated the ability to telescope these processes together to provide an overall multi-step synthesis of 1,2,3-triazoles in an efficient fashion. As a proof of concept, we began from an alcohol starting material which was oxidised in situ to the corresponding aldehyde using immobilised TEMPO followed by conversion to the alkyne (Scheme 7). Using this arrangement, we obtained the alkynes in high yield and purity after passage through a number of coordinated scavenging columns. Then, we devised an extended multi-step sequence starting with the homologation of the aldehyde to the alkyne followed by the cycloaddition process in flow. The resulting triazoles were obtained as crystalline materials in good yields and purities after the usual in-line scavenging of by-products (Scheme 8). It is evident, therefore, that this type of extended multi-step sequence will be very powerful for delivering progressively more complex architectures whilst minimising the user intervention owing to the machine-assisted nature of the approach.

We also wanted to extend this idea by creating even more functionalised alkynes through a series of acylation reactions using catalytic amounts of palladium acetate [73]. Although this is a well-established procedure in batch, the reaction suffers from a number of issues such as the stoichiometry of the acid chloride and the excess of base that is necessary also causes high levels of residual palladium contamination in the final product. With these issues in mind, we constructed a flow sequence with integrated scavenging and reaction clean-up that delivered yne-one derivatives in high yield and purities and avoided any traditional work-up procedures (Scheme 9).

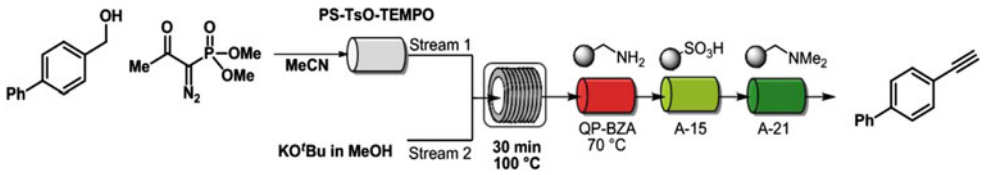
In order to demonstrate the further synthetic utility of these yne-one products, the output flow stream was partitioned into four separate channels which were individually mixed with a set of different nucleophiles to provide access to a new set of heterocyclic compounds. To achieve this, four small HPLC pumps were used in-line to combine the nucleophiles with the yne-one stream and then direct the reaction mixture into parallel heated flow coils to promote the heterocycle ring formation. This approach, therefore, nicely highlights how flow chemistry can be used to prepare useful building blocks in an automated manner, but can subsequently deliver medicinally interesting compounds by further chemical transformations (Scheme 10).

Substituted pyrrolidines also represent another group of interesting heterocyclic compounds which are prevalent in many natural products as well as in many drug substances. The preparation of functionalised pyrrolidines, therefore, is important and can be accomplished either by intramolecular nucleophilic substitutions of δ-halobutylamines or via a more adaptable fashion by dipolar cycloaddition using unstabilised azomethine ylids [74,75]. Although synthetically very useful the azomethine ylids are extremely carcinogenic and potentially explosive when used at scale. We, therefore, concluded that this process would be an ideal candidate for a sealed flow reactor. We selected nitro-olefins as suitable starting materials and combined these with the commercially available *N*-(methoxymethyl)-*N*-(trimethylsilyl) benzylamine using stoichiometric quantities of TFA to form the dipole in situ (Scheme 11). Although we were able to generate the desired compounds in reasonable yields using a benzylamine scavenger for clean-up of the reaction stream (QP-BZA) we considered this process to be sub-optimal. A better procedure was, therefore, developed which used a monolithic fluoride source to provide the dipole which proved highly effective giving cleaner conversions and higher yields under milder reaction conditions. Using the fluoride monolith approach, we were able to rapidly expand on the initial work and introduced other synthetically useful substituents such as phosphonates, sulfonates and esters in the coupling process.

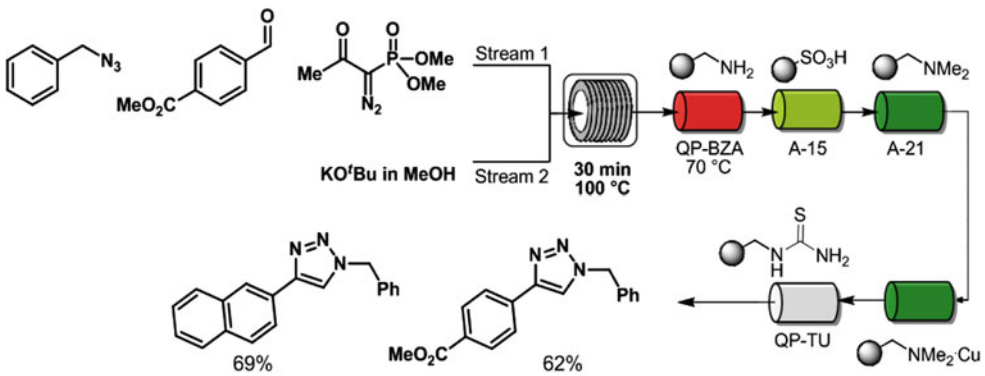
It was also possible to conduct a quantitative chemoselective reduction of the pendant nitro group in the addition products using Raney Nickel in flow using an H-Cube to yield the corresponding 3-amino pyrrolidines. Alternatively, employing palladium on carbon as a catalyst enabled simultaneous debenzylation and reduction of the nitro group. In either case, the desired products were obtained in high yield and purity and with full stereochemical integrity (Fig. 4).



Scheme 6 Bestmann–Ohira modification of the Seyferth–Gilbert homologation in flow

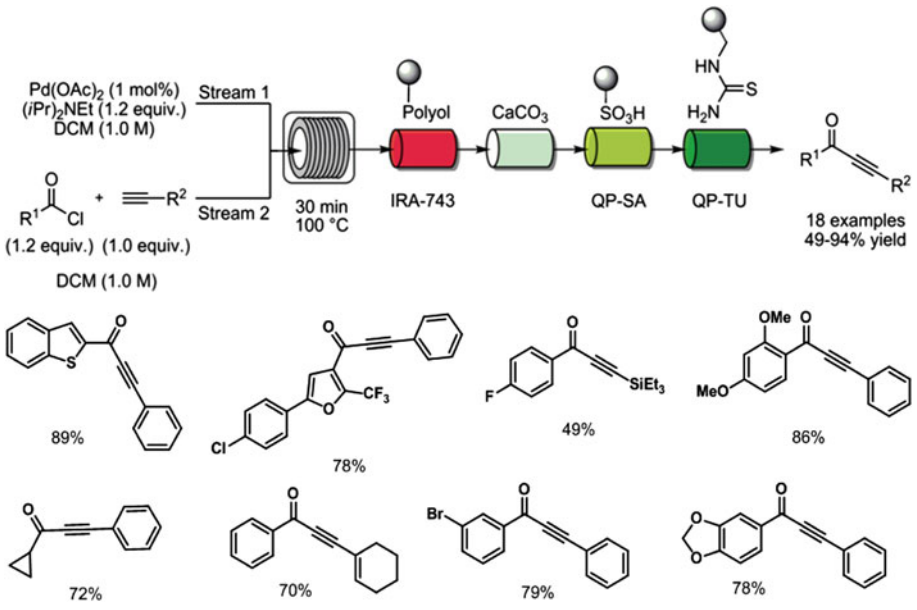


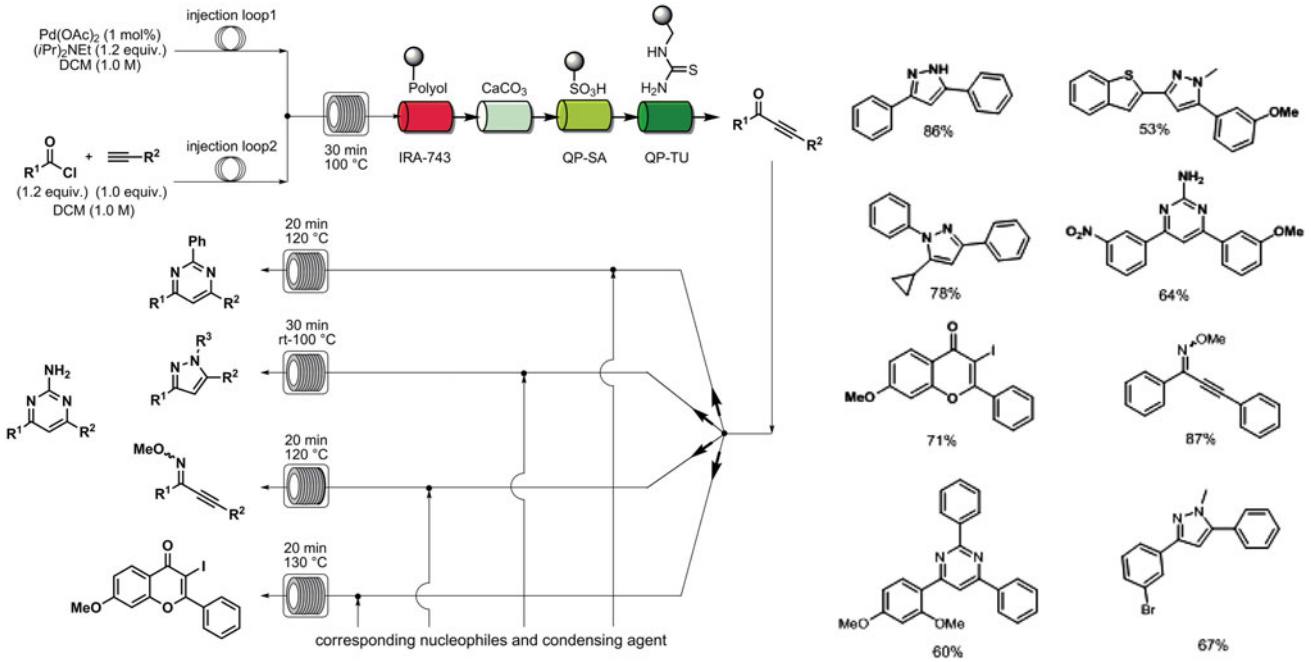
Scheme 7 Multi-step oxidation–homologation towards alkynes



Scheme 8 Multi-step formation of triazoles in flow

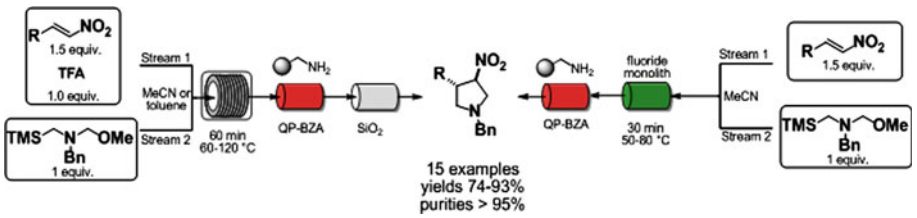
Scheme 9 Sonogashira reactions in flow highlighting a few selected products





Scheme 10 Yne-one synthesis followed by 4-way splitting towards heterocyclic compounds

Scheme 11 Flow synthesis of substituted pyrrolidines via dipolar cycloadditions



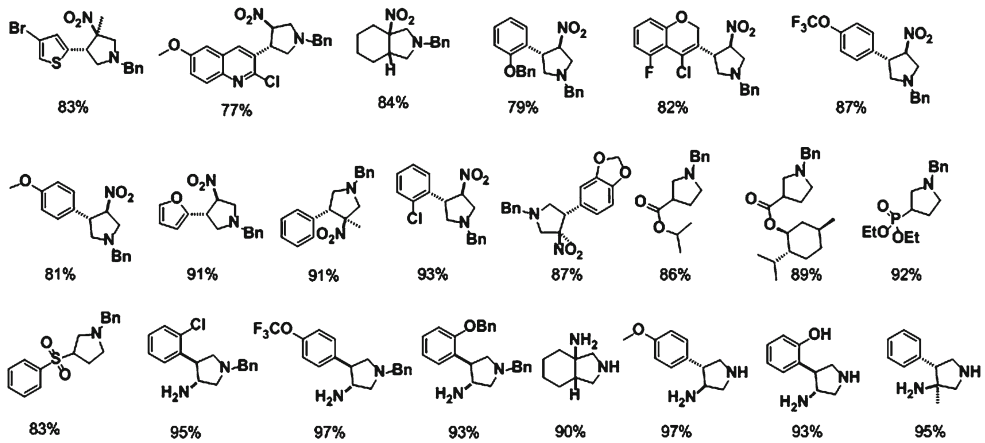


Fig. 4 3-Nitropyrrolidines and related structures prepared in flow

Now, we have firmly established the versatility of the flow chemistry reactors and their ability to deliver both aromatic and non-aromatic heterocycles we needed to expand on these concepts. To this end, we chose to study the handling of very hazardous reagents or reactive intermediates in the flow process. As part of an ongoing research programme, we needed oxazolines for both a natural product project and PyBox-type ligands for the preparation of some new asymmetric catalysts. The formation of these heterocycles is best performed by a cyclodehydrating reaction of β-hydroxy amides using diethylamino sulfurtrifluoride (DAST). This reagent is also useful as a nucleophilic fluorinating agent [76]. In first experiments with this reagent, we combined stock solutions of DAST and the substrate in dry DCM using a standard mixing T-piece and directed the reaction mixture into a heated flow coil maintained at 50–70 °C to promote the ring formation. In order to quench the reaction and ensure, the output stream was free from any fluoride contamination that was passed through a glass column filled with a plug of powdered calcium carbonate followed by a similar plug of silica gel. This simple but effective purification method was reliable as no inorganic fluoride contaminants could be detected using a commercial test kit (Macherey-Nagel GmbH & Co, Dueren, Germany). The method also ensured any baseline-coloured impurities generated during the reaction were trapped on passage through the silica gel plug (right hand side in Fig. 5).

As shown in Fig. 5, cyclodehydration towards the desired oxazoline was accomplished in high yield either forming one or in some cases two heterocycles simultaneously. In addition, the cyclodehydration event may be combined with fluorination of adjacent hydroxyl functionalities. We have also demonstrated that DAST can be used to facilitate a number of fluorination reactions of alcohols, aldehydes and ketones by employing a similar flow set-up. Clean formation of a variety of *mono*- and *bis*-fluoromethylene compounds was achieved in excellent yields (Fig. 6) [77]. This procedure also gave the products by superheating of the DCM solvent typically at temperatures in excess of 60 °C yet still displaying very good functional group tolerance during the reaction.

The introduction of fluorine into pharmaceutical and agrochemical compounds is increasingly important since this feature can modulate metabolism or could regulate pharmokinetic properties. Consequently, flow methods for the incorporation of fluorine units into new building blocks were investigated. The use of the commercially available electrophilic fluorinating agent Selectfluor [78] is a good example as the ionic nature of this crystalline starting material imposes certain solubility issues. It was found that

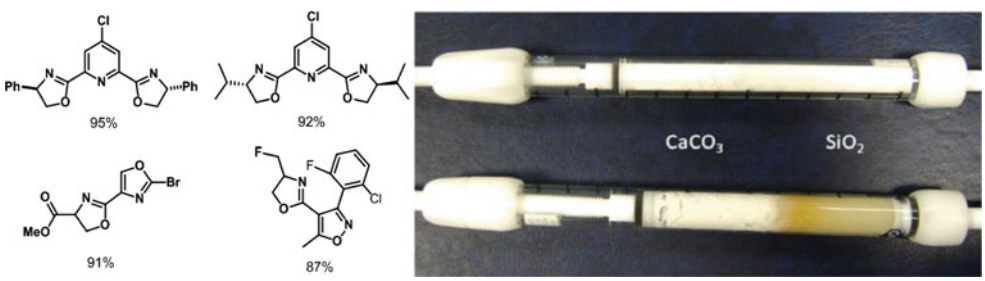


Fig. 5 Oxazolines prepared in flow using a $CaCO_3$-based scavenging and purification system

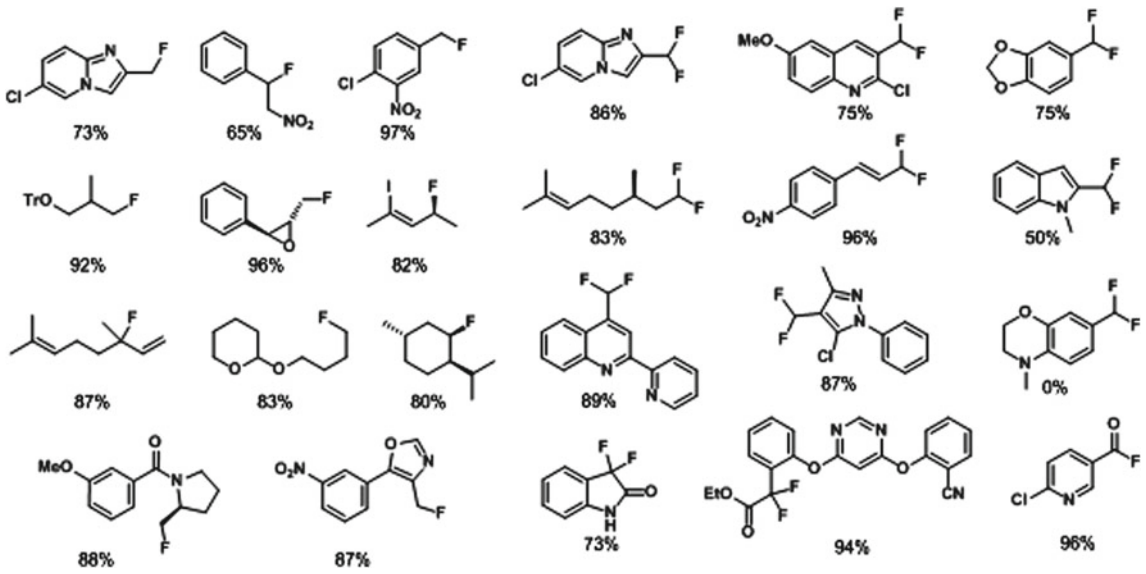


Fig. 6 Fluorination products using DAST in flow

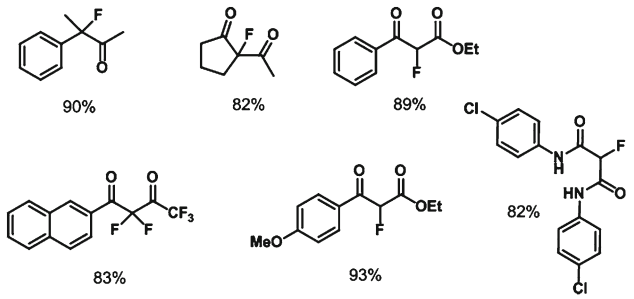


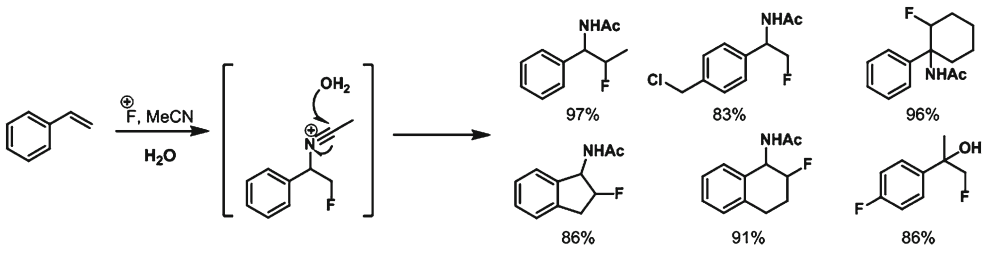
Fig. 7 α-Fluorination using Selectfluor in flow

acetonitrile as the solvent was beneficial and enabled a number of activated carbonyl compounds to be fluorinated in the α-position. Only relatively short heating times at 120 °C in a flow coil were required to generate the fluorinated carbonyl compounds in high yields. The subsequent removal of the spent reagent as well as the scavenging of any residual starting material was achieved by directing the reaction mixture through a mixed bed of QP-SA (sulfonic acid resin [56]) and QP-DMA (dimethyl amine resin [56]) packed in a glass column and positioned in-line (Fig. 7).

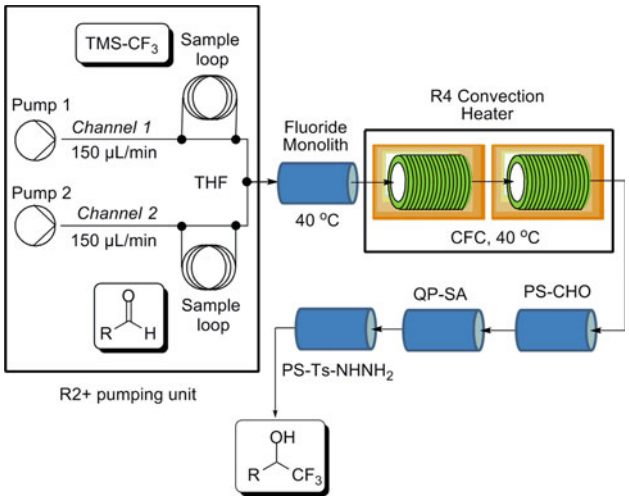
Selectfluor was also used to perform a version of the fluoro-Ritter reaction converting simple electron-rich styrenes into the β-fluoro-α-acetamidophenylethylene derivatives. This simultaneous introduction of fluorine and an oxygen or nitrogen can be accomplished by quenching the intermediate benzylic cation with acetonitrile in the presence of wet acetic acid (Scheme 12).

Based on earlier precedent from our group, we also investigated a flow method for the introduction of trifluoromethyl groups using the Ruppert reagent (trimethylsilyl trifluoromethane) [79]. The straightforward flow set-up as shown in Scheme 13, where aldehyde inputs react with the Ruppert reagent (both as THF solutions) upon passage through a fluoride monolith to promote the formation of the required trifluoromethyl anion yielded the trifluoromethyl alcohol products. As in other procedures, the purification of the reaction stream was accomplished using a series of in-line immobilised scavengers.

The resulting trifluoromethyl alcohols are themselves very valuable building blocks and can be converted into the corresponding trifluoroacetyl groups by MnO_2-mediated flow oxidation or the tetrafluoroalkyl group via nucleophilic



Scheme 12 Fluoro-Ritter reaction using Selectfluor in flow



Scheme 13 Flow set-up for trifluoromethylation reactions

fluorination using the above mentioned DAST-mediated procedure. In all cases, the desired compounds were obtained in high yields and purities without the need for further purification (Fig. 8).

Azides are recognised to be very useful but potentially hazardous building blocks. By way of illustration, the Curtius rearrangement which converts a carboxylic acid functionality via an acyl azide intermediate into an amine is a good example. Many safety concerns relating to the use of toxic and explosive starting materials and the generation of hazardous intermediates during this reaction make it an ideal candidate for development of a convenient flow process. Our first approach was based on the use of diphenylphosphoryl azide (DPPA) to in situ convert the carboxylic acids to the acyl azides which then underwent rearrangement in a heated flow coil to the corresponding isocyanates [80]. A variety of different nucleophiles could be premixed into the stock solutions to intercept the isocyanates once formed and deliver the final amine products (Fig. 9).

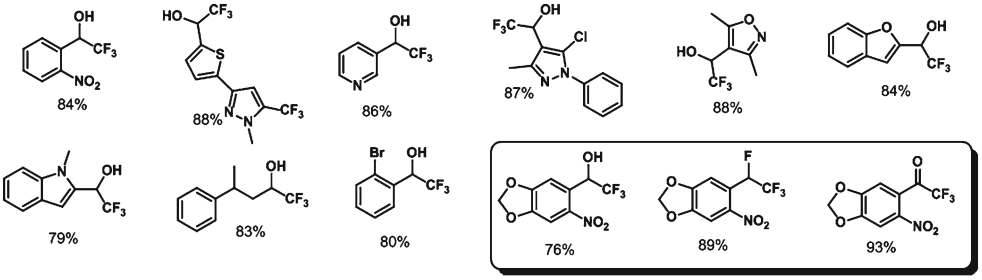


Fig. 8 Flow synthesis and derivatisation of trifluoromethyl alcohols

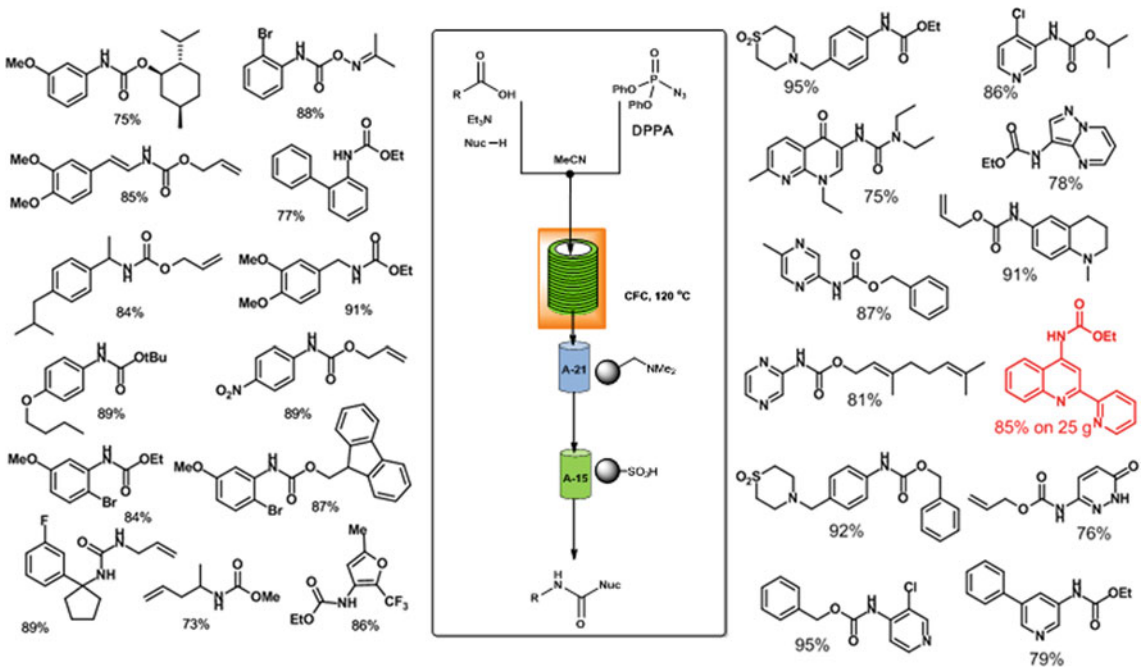
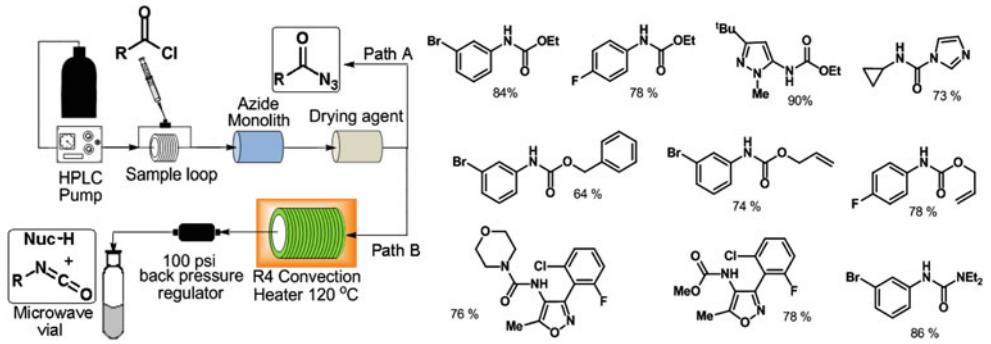


Fig. 9 Curtius rearrangement using DPPA in flow



Scheme 14 Curtius rearrangement using azide monoliths in flow

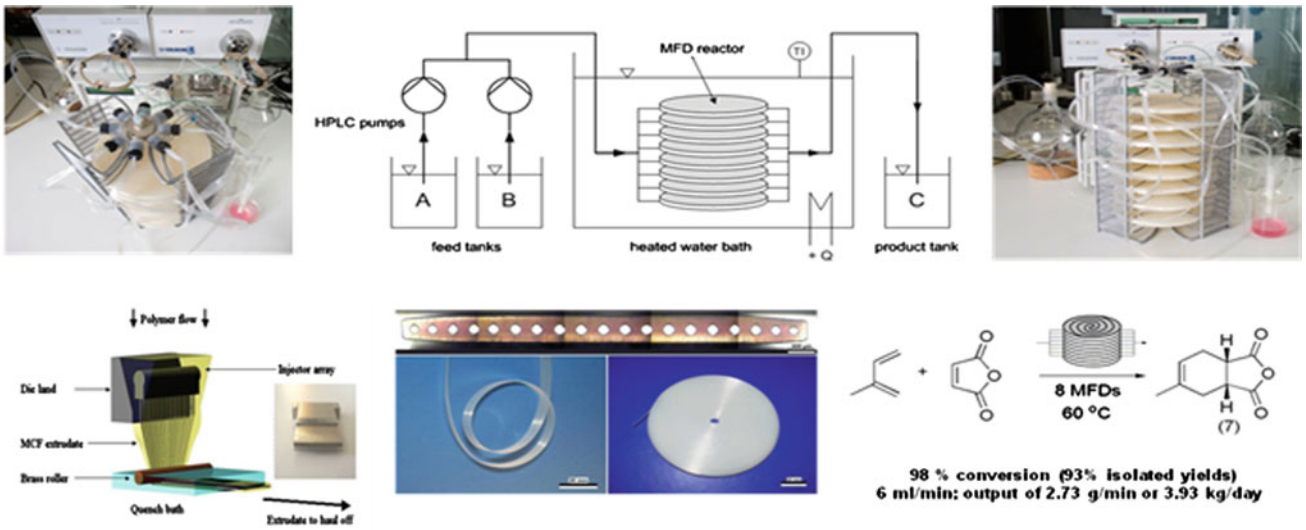


Fig. 10 Microcapillary flow discs

Any excess of the carboxylic acid starting material as well as the diphenylphosphonate and added triethylamine base were removed using a mixed bed of Amberlyst 15 and 21 resins packed into an in-line glass column thereby yielding the desired products in purities typically above 95%. In cases where substrates possessed a basic functionality, the Curtius rearrangement products were alternatively purified by a catch and release protocol. This variation was accomplished by trapping the excess acid starting material as well as the diphenylphosphonate onto A21 resin allowing the rearrangement product to be trapped within a separate A15 resin containing column. After elution of any impurities using a wash sequence, the desired product was released from the immobilising support using a solution of ammonia in methanol. The catch and release protocol used in this sequence were also applied successfully in one example on a greater than 25 g scale.

As an alternative protocol to using DPPA as the azide source, we evaluated the use of an azide monolith to affect the same transformation [81]. In these Curtius rearrangements, the acid chloride starting material was passed through a heated azide monolith to form the acyl azide which underwent spontaneous migration to the isocyanate in a subsequent flow coil at elevated temperatures. The resulting isocyanates may be isolated or treated with a series of nucleophiles to yield various carbamates, ureas as the final products (Scheme 14).

In both of the approaches, we found the flow process to be superior to the batch synthesis allowing us to safely perform these rearrangement reactions at various scales in less than 60- min reaction time under superheated solvent conditions. The nitrogen gas liberated during the reaction was safely contained within the pressurised system and was securely vented upon exit from the reactor.

A key aspect of our study is to improve upon or provide alternative reactor devices. As part of this effort, we have investigated the use of novel microcapillary flow discs comprising of an array of up to uniform 19 parallel capillaries

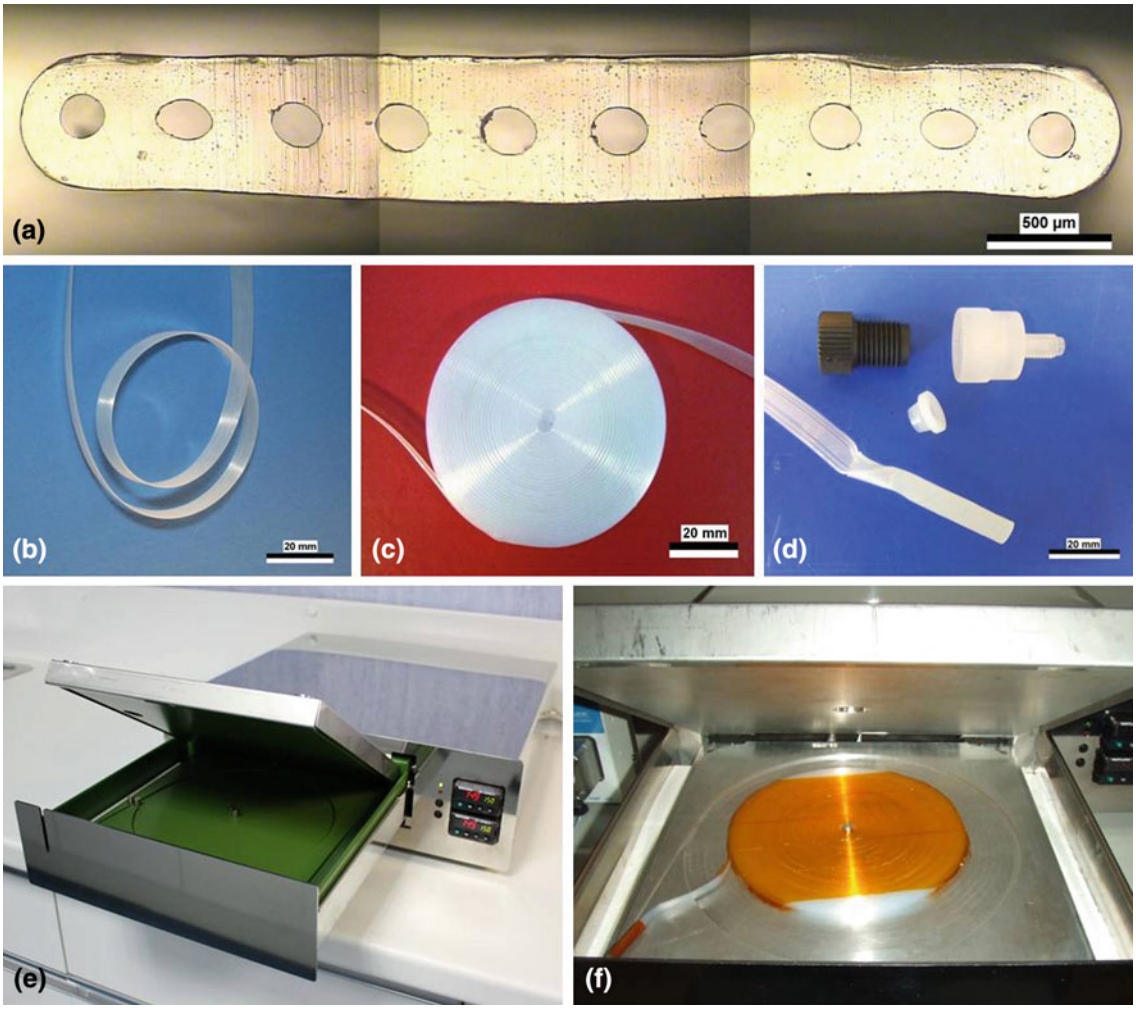
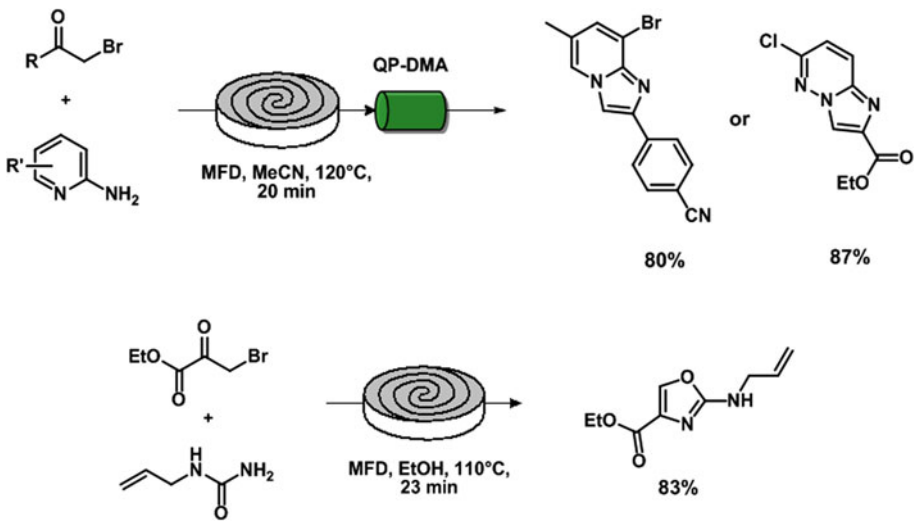


Fig. 11 Cambridge disc microreactor

(150–400 − µm diameters) embedded within a polymer film which is prepared by an extrusion process from any molten polymer matrix [82]. These films are then wound to produce discs with individual capillary lengths up to 40 m. The discs may be connected in a serial or parallel fashion to a pumping unit and used to perform various flow reactions (Fig. 10).

For example, using a stack of 8 linked MCF discs connected via a distribution feed line in a regulated heating bath,

Scheme 15 Reactions performed in the Cambridge disc Microreactor



we were able to produce Diels-Alder products on scales of 4 kg per day. In order to provide a more flexible reactor set-up, we have recently developed the Cambridge Disc Microreactor which allows for the convenient application of microcapillary flow discs [83] (Fig. 11).

To validate the design of this equipment, we tested the system at higher reaction temperatures (up to 150 °C) to induce a number of well-documented and characterised transformations including heterocycle formations and electrophilic fluorination chemistries (Scheme 15).

In all these experiments, we obtained the desired reaction products rapidly with high yields and purities.

From our research in the area of flow chemistry over the past 10 years, we can conclude that running reaction sequences in a contained and continuously operating system are a very effective way of performing chemical synthesis. The use of various in-line monitoring techniques adds to the success of such flow procedures as the real-time information thus obtained can be used for quality control and immediate optimisation. In addition, the use of immobilised reagents, scavengers and phase switch techniques enables the chemist to perform multi-step syntheses yielding high quality products without the need for further purification.

Consequently, an increasing number of excellent publications [84–98] in this rapidly expanding area both from academic and industrial research groups have appeared in the literature showing a growing acceptance of flow chemistry as a powerful enabling technology with many more applications to come.

References

1. Anastas PT, Warner JC (1998) Green chemistry: theory and practice. Oxford University Press, New York 30
2. Seeberger PH (2009) Scavengers in full flow. Nat Chem 1:258–260. doi:10.1038/nchem.267
3. Lombardino JG, Lowe JAIII (2004) A guide to drug discovery: the role of the medicinal chemist in drug discovery—then and now. Nat Rev Drug Discov 3:853–862. doi:10.1038/nrd1523
4. Ley SV, Baxendale IR (2008) The changing face of organic synthesis. Chimia 62:162–168. doi:10.2533/chimia.2008.162
5. Seeberger PH, Blume T (2007) New avenues to efficient chemical synthesis—emerging technologies. Springer, Berlin, Heidelberg, New York
6. Dar YL (2004) High-throughput experimentation: a powerful enabling technology for the chemicals and materials industry. Macromol Rapid Commun 25:34–47. doi:10.1002/marc.200300166
7. Tierney JP, Lidström P (2005) Microwave assisted organic synthesis. Blackwell Publishing, Oxford. ISBN 1-4051-1560-2
8. Kappe OC, Stadler A (2005) Microwaves in organic and medicinal chemistry. Wiley-VCH, Weinheim
9. Shipe WD, Wolkenberg SE, Lindsley CW (2005) Accelerating lead development by microwave-enhanced medicinal chemistry. Drug Discov Today Technol 2:155–161. doi:10.1016/j.ddtec.2005.05.002
10. Gedye R, Smith F, Westaway K, Ali H, Baldisera L, Laberge L, Rousell J (1986) The use of microwave ovens for rapid organic synthesis. Tetrahedron Lett 3:279–282. doi:10.1016/S0040-4039(00)83996-9
11. Bonander N, Bill RM (2009) Relieving the first bottleneck in the drug discovery pipeline: using array technologies to rationalize membrane protein production. Expert Rev Proteomics 6:501–505. doi:10.1586/epr.09.65
12. Congreve M, Murray CW (2003) In: Hillisch A, Hilgenfeld R (eds) Modern methods of drug discovery. Series: experientia supplementum, vol 93. Birkhauser Verlag, Berlin
13. Ojima I, Thurston DE (2009) Welcome to future medicinal chemistry. Future Med Chem 1:1–2. doi:10.4155/FMC.09.14
14. Grabowski M, Chruszcz M, Zimmermann MD, Kirillova O, Mino W (2009) Benefits of structural genomics for drug discovery research. Infect Disord Drug Targets 9:459–474. doi:10.2174/187152609789105704
15. Congreve M, Murray CW, Blundell TL (2005) Structural biology and drug discovery. Drug Discov Today 10:895–907. doi:10.1016/S1359-6446(05)03484-7
16. Kennedy JP, Williams L, Bridges TM, Daniels RN, Weaver D, Lindsley CW (2008) Application of combinatorial chemistry science on modern drug discovery. J Comb Chem 10:345–354. doi:10.1021/cc700187t
17. Murray CW, Rees DC (2009) The rise of fragment based drug discovery. Nat Chem 1:187–192. doi:10.1038/nchem.217
18. Verdonk ML, Rees DC (2008) Group efficiency—a guideline for hits-to leads chemistry. ChemMedChem 3:1179–1180. doi:10.1002/cmdc.200800132
19. Tickle I, Sharff A, Vinkovic M, Yon J, Jhoti H (2004) High throughput protein crystallography and drug discovery. Chem Soc Rev 33:558–565. doi:10.1039/B314510G
20. Ley SV, Baxendale IR (2008) New tools for molecule makers: emerging technologies. In: Proceedings of Bozen Symposium, systems chemistry, p 65–85. ISBN 978-8325-2188-2
21. Ceylan S, Kirschning A (2009) Organic synthesis in mini flow reactors using immobilised catalysts. In: Benaglia M (ed) Recoverable and recyclable catalysts. John Wiley & Sons, New York, pp 379–410
22. Hessel V, Knobloch C, Löwe H (2008) Review on patents in microreactor and microprocess engineering. Recent Pat Chem Eng 1:1–16
23. Carter CF, Baxendale IR, O'Brien M, Pavey JBJ, Ley SV (2009) Synthesis of acetal protected building blocks using flow chemistry and flow I.R. methods: preparation of butane-2,3-diacetal tartrates. Org Biomol Chem 7:4594–4597. doi:10.1039/b917289k
24. Carter CF, Baxendale IR, Pavey JBJ, Ley SV (2010) The continuous flow synthesis of butane-2,3-diacetal protected building blocks using microreactors. Org Biomol Chem 8:1588–1595. doi:10.1039/b924309g
25. Carter CF, Lange H, Ley SV, Baxendale IR, Wittkamp B, Goode JG, Gaunt NL (2010) ReactIR flow cell: a new analytical tool for continuous flow chemical processing. Org Process Res Dev 14:393–404. doi:10.1021/op900305v
26. Baxendale IR, Griffiths-Jones CM, Ley SV, Tranmer GK (2006) Preparation of the neolignan natural product Grossamide by a continous-flow process. Synlett 3:427–430. doi:10.1055/s-2006-926244
27. Ley SV, Baxendale IR, Bream RN, Jackson PS, Leach AG, Longbottom DA, Nesi M, Scott JS, Storer RI, Taylor SJ (2000) Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation. J Chem Soc Perkin Trans 9:3815–4196. doi:10.1039/B006588I
28. Kirschning A, Solodenko W, Mennecke K (2006) Comining enabling techniques in organic synthesis—continuous flow pro-

cesses with heterogenized catalysts. Chem Eur J 12:5972–5990. doi:10.1002/chem.200600236
29. Baxendale IR, Hayward JJ, Lanners S, Ley SV, Smith CD (2008) Microreactors in organic synthesis and catalysis. In: Wirth T (ed) Organic chemistry in microreactors: heterogeneous reactions, chapter 4.2. Wiley-VCH, Weinheim pp 84–122
30. Jönsson D, Warrington BH, Ladlow M (2004) Automated flow-through synthesis of heterocyclic thioethers. J Comb Chem 6:584–595. doi:10.1021/cc0499486
31. Griffiths-Jones CM, Hopkin MD, Jonsson D, Ley SV, Tapolczay DJ, Vickerstaffe E, Ladlow M (2007) A fully automated flow-through synthesis of secondary sulphonamides in a binary reactor system. J Comb Chem 9:422–430. doi:10.1021/cc060152b
32. Kirschning A, Altwickler C, Dräger G, Harders J, Hoffmann N, Hoffmann U, Schönfeld H, Solodenko W, Kunz U (2001) PASS-flow syntheses using functionalized monolithic polymer/glass composites in flow-through microreactors. Angew Chem Int Ed 40:3995–3998. doi:10.1002/1521-3773(20011105)
33. Solodenko W, Kunz U, Jas G, Kirschning A (2002) polymer-assisted Horner-Emmons olefination using pass-flow reactors: pure products without purification. Bioorg Med Chem Lett 12:1833–1835. doi:10.1016/S0960-894X(02)00265-2
34. The H-Cube hydrogenation system and the X-Cube system are commercially available from ThalesNano. Website: http://www.thalesnano.com; Saaby S, Knudsen KR, Ladlow M, Ley SV (2005) The Use of a Continuous Flow-Reactor Employing a Mixed Hydrogen-Liquid Flow Stream for the Efficient Reduction of Imines to Amines. J Chem Soc, Chem Commun 23:2909-2911. doi:10.1039/b504854k
35. Baxendale IR, Griffiths-Jones CM, Ley SV, Tranmer GK (2006) Microwave-assisted Suzuki coupling reactions with encapsulated palladium catalyst for batch and continuous-flow transformations. Chem Eur J 12:4407–4416. doi:10.1002/chem.200501400
36. Solodenko W, Jas G, Kunz U, Kirschning A (2007) Continuous enantioselective kinetic resolution of terminal epoxides using immobilized chiral cobalt-salen complexes. Synthesis 5:583–589. doi:10.1055/s-2007-965877
37. Kamahori K, Ito K, Itsuno S (1996) Asymmetric Diels-Alder reaction of methacrolein with cyclopentadiene using polymer-supported catalysts: design of highly enantioselective polymeric catalysts. J Org Chem 61:8321–8324. doi:10.1021/jo960518e
38. Mandoli A, Orlandi S, Pini D, Salvadori P (2004) Insoluble polystyrene-bound bis(oxazoline): batch and continuous-flow heterogeneous enantioselective glyoxylate-ene reaction. Tetrahedron Asymmetry 15:3233–3244. doi:10.1016/j.tetasy.2004.08.015
39. Bonfils F, Cazaux I, Hodge P, Caze C (2006) Michael reactions carried out using a bench-top flow system. Org Biomol Chem 4:493–497. doi:10.1039/B515241K
40. Burguete MI, Cornejo A, Garcia-Verdugo E, Gil MJ, Luis SV, Mayoral JA, Martinez-Merino V, Sokolova M (2007) Pybox monolithic miniflow reactors for continuous asymmetric cyclopropanation reaction under conventional and supercritical conditions. J Org Chem 72:4344–4350. doi:10.1021/jo070119r
41. Hafez AM, Taggi AE, Dudding T, Lectka T (2001) Asymmetric catalysis on sequentially-linked columns. J Am Chem Soc 123:10853–10859. doi:10.1021/ja016556j
42. France S, Bernstein D, Weatherwax A, Lectka T (2005) Performing the synthesis of a complex molecule on sequentially linked columns: toward the development of a "synthesis machine". Org Lett 7:3009–3012. doi:10.1021/ol050980y
43. Baxendale IR, Ley SV, Smith CD, Tranmer GK (2006) A flow reactor for the synthesis of peptides utilizing immobilised reagents, scavengers and catch and release protocols. Chem Commun 46:4835–4837. doi:10.1039/b612197g
44. Hopkin MD, Baxendale IR, Ley SV (2010) An automated flow-based synthesis of imatinib: the API of Gleevec. Chem Commun 46:2450–2452. doi:10.1039/c001550d
45. Qian Z, Baxendale IR, Ley SV (2010) A flow process using microreactors for the preparation of a quinolone derivative as a potent $5HT_{1B}$ Antagonist. Synlett 4:505–508. doi:10.1055/s-0029-1219358
46. Venturoni F, Nikbin N, Ley SV, Baxendale IR (2010) Application of flow chemistry microreactors in the preparation of casein kinase I inhibitors. Org Biomol Chem 8:1798–1806. doi:10.1039/b925327k
47. Baxendale IR, Deeley J, Griffiths-Jones CM, Ley SV, Saaby S, Tranmer GK (2006) A flow process for the multi-step synthesis of the alkaloid natural product oxomaritidine: a new paradigm for molecular assembly. Chem Commun 24:2566–2568. doi:10.1039/b600382f
48. The AFRICA flow system is commercially available from Syrris. Website: http://www.syrris.com
49. The UniqsisFlowSyn system is commercially available from Uniqsis. Website: http://www.uniqsis.com
50. The Advion NanoTek system is commercially available from Advion. Website: http://www.advion.com
51. The Vapourtec R2+/R4 flow system is commercially available from Vapourtec. Website: http://www.vapourtec.com
52. The Microreactor Explorer kit is commercially available from Aldrich. Website: http://www.sigmaaldrich.com/chemistry/chemical-synthesis/technology-spotlights/microreactor-explorer-kit.html
53. The Labtrix system is commercially available from Chemtrix. Website: http://www.chemtrix.com/web/4/1/product.html
54. The Future Chemistry is commercially available from Future Chemistry. Website: http://www.futurechemistry.com
55. Baumann M, Baxendale IR, Ley SV, Smith CD, Tranmer GK (2006) Fully automated continuous flow synthesis of 4,5-disubstituted oxazoles. Org Lett 8:5231–5234. doi:10.1021/ol061975c
56. Quadrapure Benzylamine (QP-BZA), Quadrapure Sulfonic Acid (QP-SA), Quadrapure Dimethylamine (QP-DMA) and Quadrapure Thiourea (QP-TU) are high-loading scavengers commercially available from Johnson Matthey. Website: http://www.reaxa.com
57. Baxendale IR, Ley SV, Smith CD, Tamborini L, Voica A-F (2008) A bifurcated pathway to thiazioles and imidazoles using a modular flow microreactor. J Comb Chem 10:851–857. doi:10.1021/cc800070a
58. Baxendale IR, Ley SV (2005) Formation of 4-aminopyrimidines via trimerisation of nitriles using focused microwave heating. J Comb Chem 7:483–489. doi:10.1021/cc049826d
59. Smith CJ, Iglesias-Sigüenza FJ, Baxendale IR, Ley IR (2007) Flow and batch mode focused microwave synthesis of 5-amino-4-cyanopyrazoles and their further conversion to 4-aminopyrazolopyrimidines. Org Biomol Chem 5:2758–2761. doi:10.1039/b709043a
60. Baxendale IR, Hayward JJ, Ley SV (2007) Microwave reactions under continuous flow conditions. Comb Chem High Throughput Screen 35:802–836. doi:10.2174/138620707783220374
61. Baxendale IR, Pitts MR (2006) Microwave flow chemistry: the next evolutionary step in synthetic chemistry? Chim Oggi Chem Today 24:41–45 ISSN: 0392-839X
62. Dressen MHCL, van de Kruijs BHP, Meuldijk J, Vekemans JAJM, Hulshof LA (2010) Flow processing of microwave-assisted (heterogeneous) organic reactions. Org Process Res Dev 14:351–361. doi:10.1021/op900257f
63. Glasnov TN, Kappe CO (2007) Microwave-assisted synthesis under continuous flow conditions. Macromol Rapid Commun 28:395–410. doi:10.1002/marc.200600665
64. Baxendale IR, Griffiths-Jones CM, Ley SV, Tranmer GK (2006) Microwave-assisted Suzuki coupling reactions with an

encapsulated palladium catalyst for batch and continuous-flow transformations. Chem Eur J 12:4407–4416. doi:10.1002/chem.200501400
65. Saaby S, Baxendale IR, Ley SV (2005) Non-metal-catalysed intramolecular alkyne cyclotrimerisation reactions promoted by focused microwave heating in batch and flow modes. Org Biomol Chem 3:3365–3368. doi:10.1002/chem.200501400
66. Sedelmeier J, Ley SV, Lange H, Baxendale IR (2009) Pd-EnCAT^{TM} TPP30 as a catalyst for the generation of functionalised aryl- and alkyl-substituted acetylenes via microwave-assisted Sonogashira type reactions. Eur J Org Chem 26:4412–4420. doi:10.1002/ejoc.200900344
67. Smith CD, Baxendale IR, Lanners S, Hayward JJ, Smith SC, Ley SV (2007) [3+2] Cycloaddition of acetylenes with azides to give 1,4-disubstituted 1,2,3-triazoles in a modular flow reactor. Org Biomol Chem 5:1559–1561. doi:10.1039/b702995k
68. Commercially available Omnifit glass columns with adjustable hight-end pieces (plunger) Typically, the solid-supported reagent is placed in an appropriately sized Omnifit column, usually 10- mm bore by 150- mm length, or shorter and the plungers are adjusted to relevant bed heights and the polymer swelled/washed with solvent. Website: http://www.omnifit.com
69. Smith CJ, Baxendale IR, Nikbin N, Ley SV, Smith CD (2010) manuscript submitted
70. Nikbin N, Ladlow M, Ley SV (2007) Continuous flow ligand-free Heck reactions using monolithic Pd[0] nanoparticles. Org Process Res Dev 11:458–462. doi:10.1021/op7000436
71. Baxendale IR, Ley SV, Mansfield AC, Smith CD (2009) Multistep synthesis using modular flow reactors: Bestmann-Ohira Reagent for the formation of alkynes and triazoles. Angew Chem Int Ed 48:4017–4021. doi:10.1002/anie.200900970
72. Roth GJ, Liepold B, Müller SG, Bestmann HJ (2004) Further improvements of the synthesis of alkynes from aldehydes. Synthesis 1:59–62. doi:10.1055/s-2003-44346
73. Baxendale IR, Schou SC, Sedelmeier J, Ley SV (2010) Multi-step synthesis by using modular flow reactors: the preparation of ynones and their use in heterocycle synthesis. Chem Eur J 16:89–94. doi:10.1002/chem.200902906
74. Baumann M, Baxendale IR, Ley SV (2010) Synthesis of 3-nitropyrrolidines via dipolar cycloaddition reactions using a modular flow reactor. Synlett 5:749–752. doi:10.1055/s-0029-1219344
75. Baumann M, Baxendale IR, Kirschning A, Ley SV, Wegner J (2010) Synthesis of highly substituted nitropyrrolidines, nitropyrrolizines and nitropyrroles via multicomponent-multistep sequences within a flow-reactor. Heterocycles (in print). doi:10.3987/COM-10-S(E)77
76. Singh RP, Meshri DT, Shreeve JM (2006) DAST and Deoxofluor mediated nucleophilic fluorination reactions of organic compounds. Adv Org Synth 2:291–326. ISSN: 1574-0900
77. Baumann M, Baxendale IR, Ley SV (2008) The use of diethylaminosulfur trifluoride (DAST) for fluorination in a continuous-flow microreactor. Synlett 14:2111–2114. doi:10.1055/s-2008-1078026
78. Baumann M, Baxendale IR, Martin LJ, Ley SV (2009) Development of fluorination methods using continuous-flow microreactors. Tetrahedron 65:6611–6625. doi:10.1016/j.tet.2009.05.083
79. Prakash GKS, Yudin AK (1997) Perfluoroalkylation with organosilicon reagents. Chem Rev 97:757–786. doi:10.1021/cr9408991
80. Baumann M, Baxendale IR, Ley SV, Nikbin N, Smith CD, Tierney JP (2008) A modular flow reactor for performing Curtius rearrangements as a continuous flow process. Org Biomol Chem 6:1577–1586. doi:10.1039/b801631n
81. Baumann M, Baxendale IR, Ley SV, Nikbin N, Smith CD (2008) Azide monoliths as convenient flow reactors for efficient Curtius rearrangement reactions. Org Biomol Chem 6:1587–1593. doi:10.1039/b801634h
82. Hornung CH, Mackley MR, Baxendale IR, Ley SV (2007) A microcapillary flow disc reactor for organic synthesis. Org Process Res Dev 11(3):399–405. doi:10.1021/op700015f
83. Hornung CH, Hallmark B, Baumann M, Baxendale IR, Ley SV, Hester P, Clayton P, Mackley MR (2010) A multiple microcapillary reactor for organic synthesis. Ind Eng Chem Res 49:4576–4582. doi:10.1021/ie901674h
84. Jun-ichi Y, Nagaki A, Yamada T (2008) Flash chemistry: fast chemical synthesis by using microreactors. Chem Eur J 14:7450–7459. doi:10.1002/chem.200800582
85. Goto S, Verlder J, Sheikh SE, Sakamoto Y, Mitani M, Elmas S, Adler A, Becker A, Neudörfl JM, Lex J, Schmalz H-G (2008) Butyllithium-mediated coupling of aryl bromides with ketones under in-situ-quench (ISQ) conditions: an efficient one-step protocol applicable to microreactor technology. Synlett 9:1361–1365. doi:10.1055/s-2008-1072771
86. Gustafsson T, Gilmour R, Seeberger PH (2008) Fluorination reactions in microreactors. Chem Commun 26:3022–3024. doi:10.1039/B803695K
87. Csajági C, Szatzker G, Tőke ER, Ürge L, Darvas F, Poppe L (2008) Enantiomer selective acylation of racemic alcohols by lipases in continuous-flow bioreactors. Tetrahedron Asymmetry 19:237–246. doi:10.1016/j.tetasy.2008.01.002
88. Gustafsson T, Pontén F, Seeberger PH (2008) Trimethylaluminium mediated amide bond formation in a continuous flow microreactor as key to the synthesis of rimonabant and efaproxial. Chem Commun 9:1100–1102. doi:10.1039/B719603B
89. Kralj JG, Sahoo HR, Jensen KF (2007) Integrated continuous microfluidic liquid-liquid extraction. Lab Chip 7:256–263. doi:10.1039/B610888A
90. Murphy ER, Martinelli JR, Zaborenko N, Buchwald SL, Jensen KF (2007) Accelerating reactions with microreactors at elevated temperatures and pressures: profiling aminocarbonylation reactions. Angew Chem Int Ed 46:1734–1737. doi:10.1002/anie.200604175
91. Brandt JC, Wirth T (2009) Controlling hazardous chemicals in microreactors: synthesis with iodine azide. Beilstein J Org Chem 5(30) doi:10.3762/bjoc.5.30
92. Grant D, Dahl R, Cosford NDP (2008) Rapid multistep synthesis of 1,2,4-oxadiazoles in a single continuous microreactor sequence. J Org Chem 73:7219–7223. doi:10.1021/jo801152c
93. Kulkami AA, Kalyani VS, Joshi RA, Joshi RR (2009) Continuous flow nitration of benzaldehyde. Org Process Res Dev 13:999–1002. doi:10.1021/op900129w
94. Hübner S, Bentrup U, Budde U, Lovis K, Dietrich T, Freitag A, Küpper L, Jähnisch K (2009) An ozonolysis-reduction sequence for the synthesis of pharmaceutical intermediates in microstructured devices. Org Process Res Dev 13:952–960. doi:10.1021/op9000669
95. Damm M, Glasnov TN, Kappe CO (2010) Translating high-temperature microwave chemistry to scalable continuous flow processes. Org Process Res Dev 14:215–224. doi:10.1021/op900297e
96. Sedelmeier J, Ley SV, Baxendale IR, Baumann M (2010) $KMnO_4$ mediated oxidation as a continuous flow process. Org Lett 12:2618–2621. doi:10.1021/ol101345z
97. Hornung CH, Hallmark B, Mackley MR, Baxendale IR, Ley SV (2010) A palladium wall coated microcapillary reactor for use in continuous flow transfer hydrogenation. Adv Synth Catal 352:1736–1745. doi:10.1002/adsc.201000139
98. Malet-Sanz L, Madrazak J, Ley SV, Baxendale IR (2010) Preparation of arylsulfonyl Chlorides by Chlorosulfonylation of in situ generated diazonium salts using a continuous flow reactor. Org Biomol Chem. doi:10.1039/c0ob00450b