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Review

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Flow chemistry approaches directed at improving chemical synthesis

Abstract: Flow synthesis offers many advantages when applied to the processing of difficult or dangerous chemical transformations. Furthermore, continuous production allows for rapid scale up of reactions without significant redevelopment of the routes. Importantly, it can also provide a versatile platform from which to build integrated multi-step transformations, delivering more advanced chemical architectures. The construction of multi-purpose micro and meso flow systems, that utilize in-line purification and diagnostic capabilities, creates a scenario of seamless connectivity between sequential steps of a longer chemical sequence. In this mini perspective, we will discuss our experience of target orientated multi-step synthesis as presented at the recent inaugural meeting of LEGOMEDIC at Namar University, Belgium.

Keywords: automation; flow; meso/micro reactor; solid-supported reagents; synthesis.

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1 Introduction

The discovery process for small biologically active molecules is changing rapidly, generating an inherent need to conduct synthesis in a more efficient and timely manner [1–5]. As the global emphasis towards achieving higher safety standards and more sustainable practices unfolds, it is becoming necessary to re-evaluate how chemical synthesis is conducted [6]. Accelerated discovery cycle times have also placed increasing pressures on the reliability and timeliness of preparative processes. There is, therefore, a requirement for new chemical processing techniques that can conduct industrially relevant chemical syntheses, faster and in a more directly scalable fashion. Consequently, these chemical processing techniques need to adopt greater levels of automation to facilitate continuous scale-up, whilst being coupled with integrated diagnostic capabilities that ensure the highest standards of quality control for the processes. Downstream post reaction clean-up is also a critical development area requiring more effective quenching, extraction and work-up methods to facilitate a truly seamless continuous product supply chain.

In this context, microreactor flow technologies have several potential advantages for chemical production. Firstly, the high heat and mass transfer rates possible within mesofluidic systems, allow reactions to be performed under a more extensive range of conditions than can be achieved with conventional reactors (including expanded ΔT and ΔP). Hence, new reaction pathways, deemed too difficult or dangerous to operate in conventional batch equipment, can be pursued [7]. Furthermore, the inherent safety characteristics of the technology, also allow for production scale systems comprising of multiple connected reactors giving distributed point-of-use synthesis of chemicals without storage and shipping limitations. This neatly avoids many issues associated with worker contact and the use or generation of highly reactive and/or toxic intermediates. In addition, scale-up to production levels by replication of the same microreactor conditions used in the laboratory, can eliminate costly redesign and pilot plant experiments, thereby shortening the development time from laboratory to final production levels.

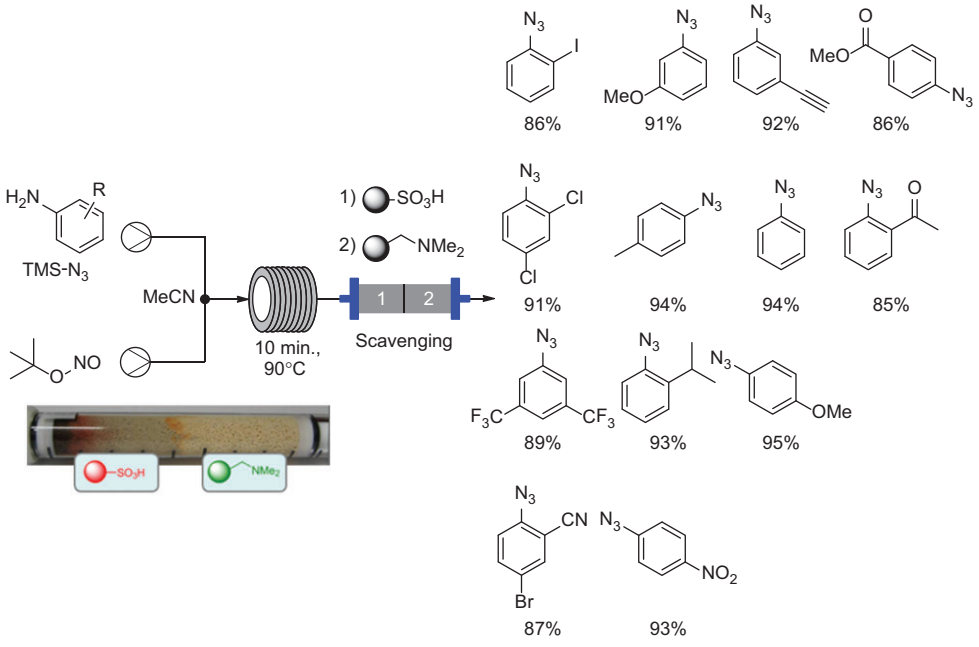
2 Building block synthesis

To rapidly assemble novel bioactive molecules requires the implementation of well-planned routes using robust, reliable and functional group tolerant chemistries. However, a common bottle neck, that limits even well designed routes, is the availability and diversity of individual starting materials and advanced building blocks. Therefore, a process for rapid on-demand and in-house manufacture of these potentially proprietary components is optimum. Here, flow chemistry can provide a solution.

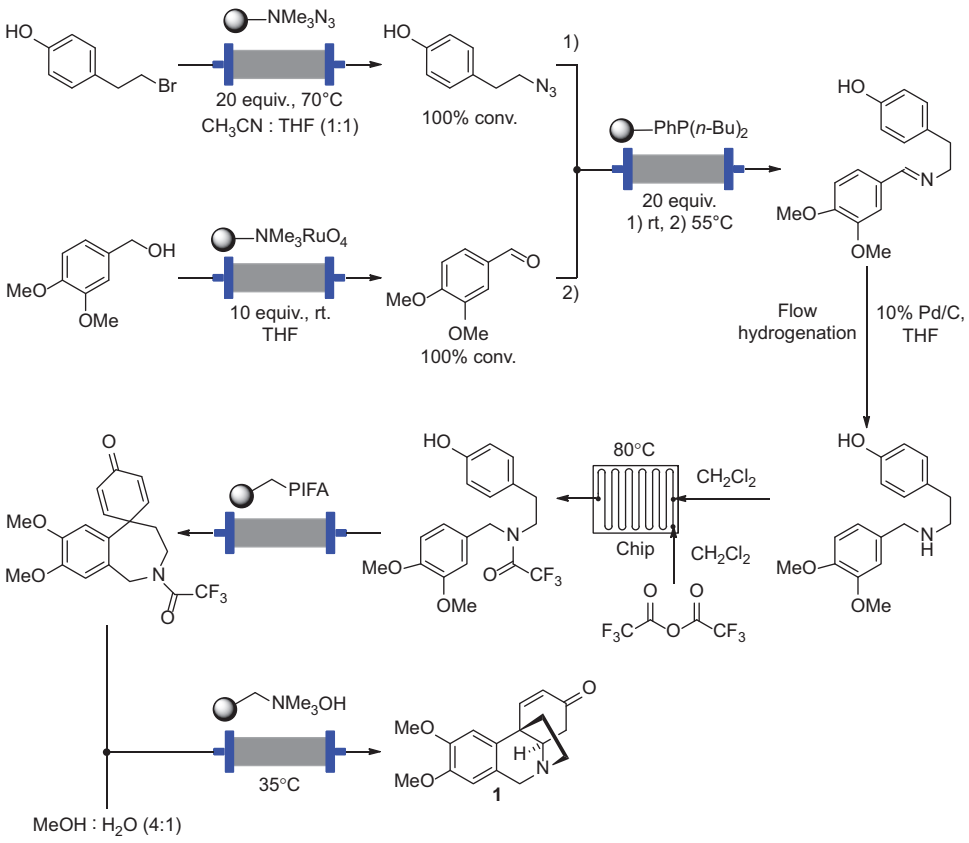
A good example of a high yielding transformation, which can in practice be problematic to employ, is the Huisgen azide-alkyne copper catalyzed cycloaddition reaction. This reaction represents one of the most facile reactions in the modern cited "click chemistry" grouping. However, although this reaction reliably yields excellent conversions of the triazole adducts, the availability of the alkyne and azide precursors is often limited. Both of the reactive functional groups, azide and alkyne have the propensity to be explosive, unless attached to large molecular weight units, meaning transport and storage is often an issue. Therefore, to make effective use of such coupling chemistry, flexible methods of preparing the necessary starting materials, on demand and in sufficient quantities, are required.

We and others have shown that it is possible to synthesize a wide range of azide building blocks in flow using various substitution chemistries [8–15]. For example, readily available aniline starting materials can be transformed into their aryl azide counterparts via an intermediate diazonium species prepared by reaction with *tert*-butyl nitrate. Substitution of the intermediate diazo group using an azide nucleophile generated *in situ* from trimethylsilyl azide, rapidly furnishes the desired azide product through loss of nitrogen gas [16]. In our flow process, we further utilized a combination of immobilized reagents to perform in-line quenching and scavenging of by-products (Scheme 1) [17–34]. A cartridge containing a packed bed of a sulfonic acid resin followed by a trialkyl amine base was attached prior to the outlet of the reactor. The sulfonic acid resin acted to sequester in its ionic form any residual aniline starting material from the flow stream. Additionally it functioned to degrade and protonate any trimethylsilyl azide forming hydrazoic acid. This latter by-product, which is a potentially highly explosive component, was scavenged quantitatively by the presence of the amine base (inorganic azide contamination of the out flow was colorimetrically tested for). Consequently, a purified flow stream of the organic azide was produced which could be directed as a stream of starting material into other transformations [8, 35]. We have also used alternative strategies which make use of azide ion exchange polymers to substitute more reactive alkyl halide groups in flow. Simply taking a column of the appropriately loaded azide resin and passing a flow stream of the substrate through under heated reaction conditions, can be used to yield the azide product. This approach has been used to great effect in our total synthesis in flow of the natural product oxomaritidine (**1**) where substitution of an alkyl bromide was conducted to prepare the corresponding azide for use in a key Staudinger aza-Wittig coupling reaction (Scheme 2) [36].

We have also used flow chemistry for the preparation of acetylenes in flow via the Seyferth-Gilbert homologation of an aldehyde using the Bestmann-Ohira reagent (Scheme 3) [37]. A flow stream of the corresponding aldehyde along with the Bestmann-Ohira reagent were combined with a secondary stream containing the base, potassium *tert*-butoxide, and progressed into a heated flow



Scheme 1 Flow aryl azide preparation including scavenger purification.

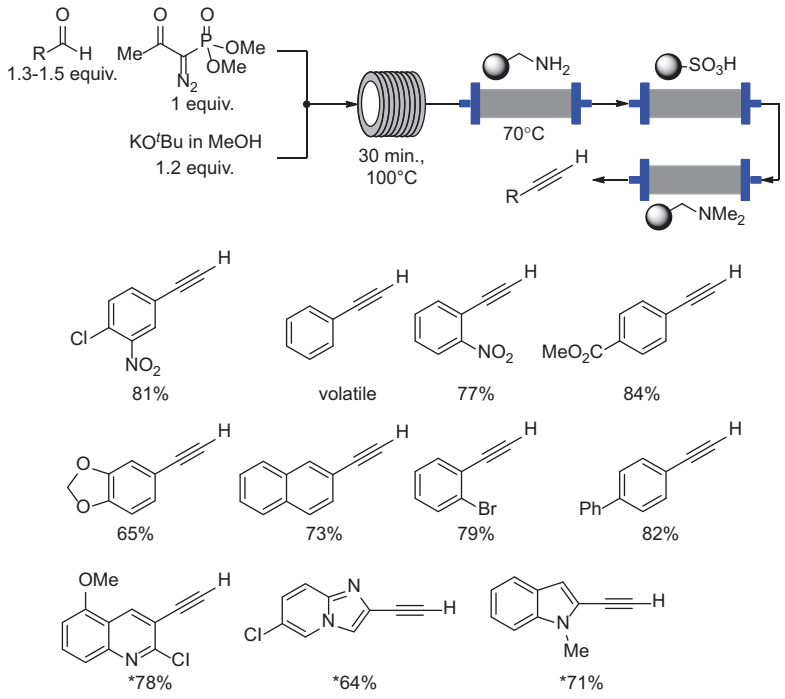


Scheme 2 Synthesis of the natural product oxomaritidine.

coil. The flow stream upon exiting the reactor coil was then directed into a cartridge of immobilized benzylamine to remove excess aldehyde, followed by a sulfonic acid resin to quench the base and protonate any phosphoric residues. Finally, a dimethylamine resin column was used to remove the acidic impurities. The resulting acetylene product could then be collected in high yield and purity for further use. It should be noted that a small modification to the sequence was necessary for nitrogen-containing starting materials, where the sulfonic acid resin was substituted for an alumina packed cartridge to avoid capture of the newly formed product during the work-up.

Another advantage of flow chemistry is that once a targeted sequence has been exemplified, it is possible to take the individual step and incorporate it with other sequential steps into more elaborate and integrated processes. In this way, multi-step reactions can be run in a planned and automated fashion. For example, the fully functional triazole can be assembled by plugging together the individual steps as discussed above (Scheme 4) [37]. This scheme also involves an additional TEMPO oxidation of the benzylic alcohol to generate the aldehyde as part of the flow process. This is conducted in the presence of the other reaction components, giving a superior overall yield when compared to the stepwise process.

Furthermore, adopting these approaches allows archived protocols to be quickly reloaded and transposed into other reaction sequences, to create new classes of building blocks. This can be aptly demonstrated by the utilization of the previously described aryl azide reaction (Scheme 1), where the product can be reproduced and the flow stream routed into a new amino triazole forming reaction (Scheme 5) [8, 35]. In this way, it is possible to establish a library of reactor configurations and parameters which can be readily applied for repetition of existing reactions, or insertion into new reaction arrangements. A significant benefit of this approach to working is that the devised chemistry is less reliant on human experimental recording and interpretation. The majority of the reaction parameters (e.g., ΔT, ΔP, time) can be captured and monitored by the reactor platform which can then repeat the exact sequence including heating ramp rates and injection times with absolute precision. This increase in automation enhances accuracy and reduces user variation and human error. It should, however, be implicitly highlighted that this does not negate the need for a

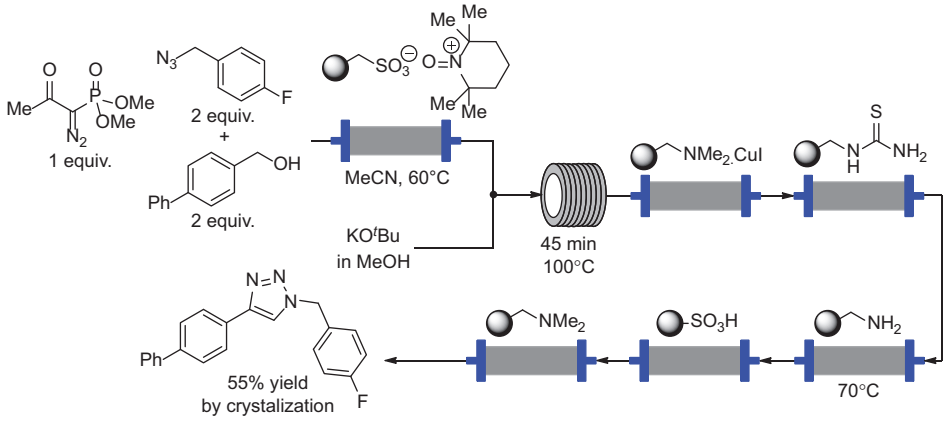


Scheme 3 Seyferth-Gilbert homologation.
*Required alternative procedure as described in the main body text.

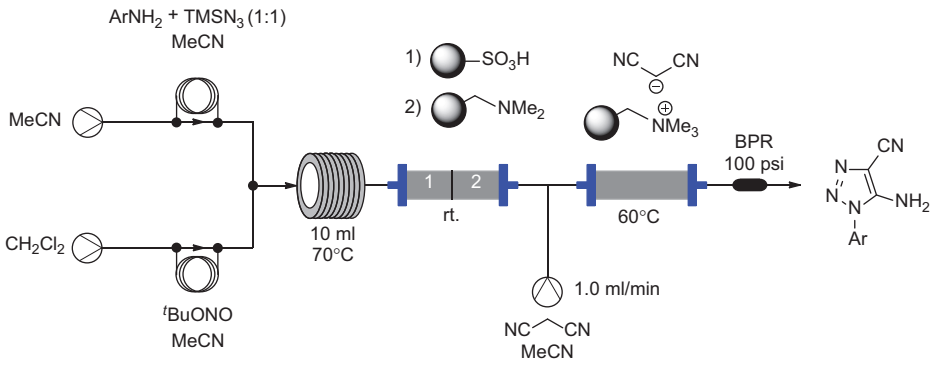
well-trained chemist as part of the process, but instead frees up valuable time for creative thinking and advanced experimentation, as opposed to conducting repetitive and labor intensive manual operations.

3 Reactive intermediates

Another aspect where flow chemistry offers a major advantage is in the area of reactive and dangerous intermediate production, especially as part of a telescoped production pathway. Often, when conducting batch chemistry a particular chemical step or occurrence of an intermediate along the planned synthetic route will necessitate either a work-around or the devising of a new route, to avoid issues of potential toxicity and/or explosive or extreme exothermic behavior [38, 39]. As well as this being less than optimum in terms of chemical strategy and efficiency, it can also represent a significant time and cost implication for reworking the route. Obviously, obviating the inherent danger associated with such chemistry by decreasing



Scheme 4 Multi-step triazole synthesis using an integrated flow reactor.



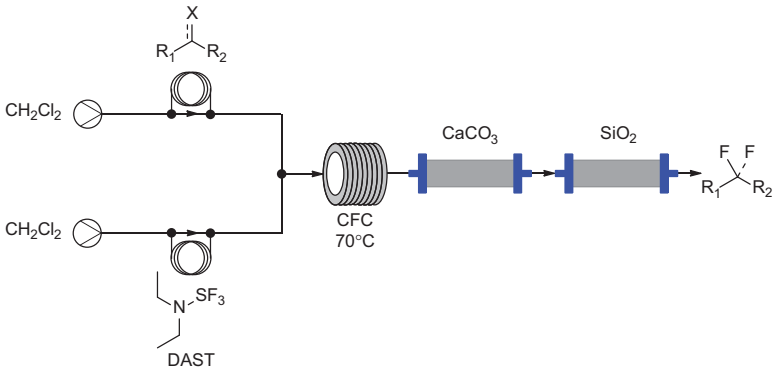
Scheme 5 Concerted formation of amino triazole products in flow.

the associated risks is a far better solution, thus allowing the chemistry to be safely progressed. Microreactor technology has been shown to very effectively address many of the safety concerns associated with high risk chemistries, mainly through reduction in reactive volumes (small reactor volumes) and increased containment (sealed reactor systems) [40–47]. Additionally, the manufacturing concept of "make-and-use" where the potentially problematic chemical is generated and then immediately consumed in a subsequent step, thereby furnishing a more stable and easily handled product, further directly increases the safety profile of the process.

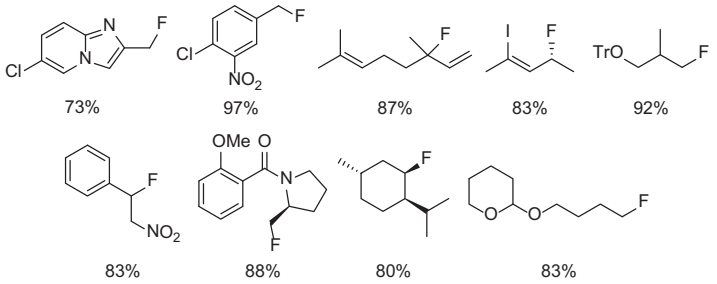
We have conducted several examples of reactions which fall under this general categorization of classically problematic to run, or previously thought of as "forbidden chemistries", when considered as batch based procedures [7]. As an illustration, fluorination chemistry with a reagent such as diethylamino sulfur trifluoride (DAST) provides rapid access to many chemical structures with modified pharmacokinetic profiles, by replacement of alcohols or carbonyls units with mono or *gem* difluoro groups, respectively. Whilst this reagent is extremely effective, it has a number of drawbacks, such as it is volatile, reacts violently with water and readily undergoes dismutation to SF_4 and $(Et_2N)_2SF_2$ when heated to temperatures in excess of 90°C [48]. Another issue that arises is that the products are formed with concurrent release of hazardous hydrofluoric acid. Fortunately, in flow, it is possible to incorporate a direct in-line work-up, to facilitate a flow scheme where inorganic fluoride and excess starting material and by-products are systematically extracted from the liquid stream and sequestered onto a solid matrix (Scheme 6) [49–51]. Such a scavenger process does not need to be highly complex to enhance the processing capabilities, as illustrated in the above chemistry by the expedient application of a calcium carbonate packed hydrofluoric acid (HF) quenching column, immediately followed by a small silica gel plug to trap inorganic salts. This simple, yet very effective modification immediately renders the flow output free from HF and other inorganic fluoride contamination. This eliminates high risk user exposure for this versatile, but previously potentially dangerous reaction sequence, thereby expanding the scope of chemistry available to the bench chemist. Taking advantage of this increased safety and extending its scope, DAST has also been used to promote cyclodehydration of amido alcohols to furnish oxazoline structures in flow (Scheme 7) [52, 53]. This has been used to synthesize both natural products and as part of a sequence leading to chiral ligands for use in catalysis.

Alternatively, the electrophilic fluorinating species 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (Selectfluor) can be used to induce α-fluorination (Scheme 8) of an activated carbonyl or nitrile [49–51]. It has also been used to promote a fluoro-Ritter reaction of a series of olefinic substrates (Scheme 9). This demonstrates the practicality and versatility of using flow reactors which can allow the running of different chemistries on the same reactor platform, with only minor modifications.

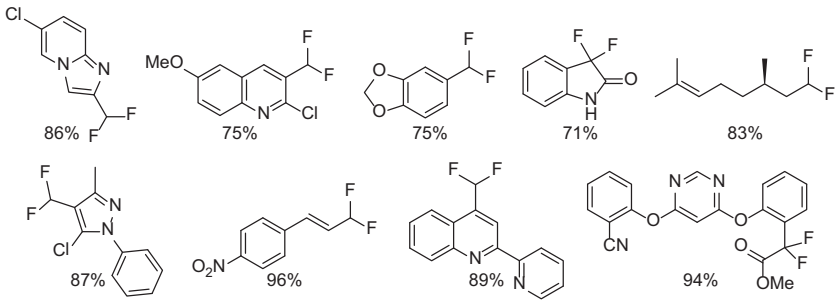
Acyl azides are another class of useful, but potentially high risk intermediates. They have found particular utility in the Curtius rearrangement, which converts a carboxylic acid moiety into the corresponding amino group. Classically, an acid chloride would be treated with an azide source [12, 54, 55] to effect this transformation, but improved reagents such as diphenylphosphoryl azide (DPPA) are able to convert the parent carboxylic acid directly to a protected amine [13]. This chemistry has been shown to be highly amenable to flow synthesis, allowing us to prepare a wide range of materials using immobilized reagents, to facilitate the work-up of the product stream (Scheme 10). Following rearrangement, the intermediate generated isocyanate in our procedure was immediately intercepted by an *in situ* nucleophile (an alcohol or



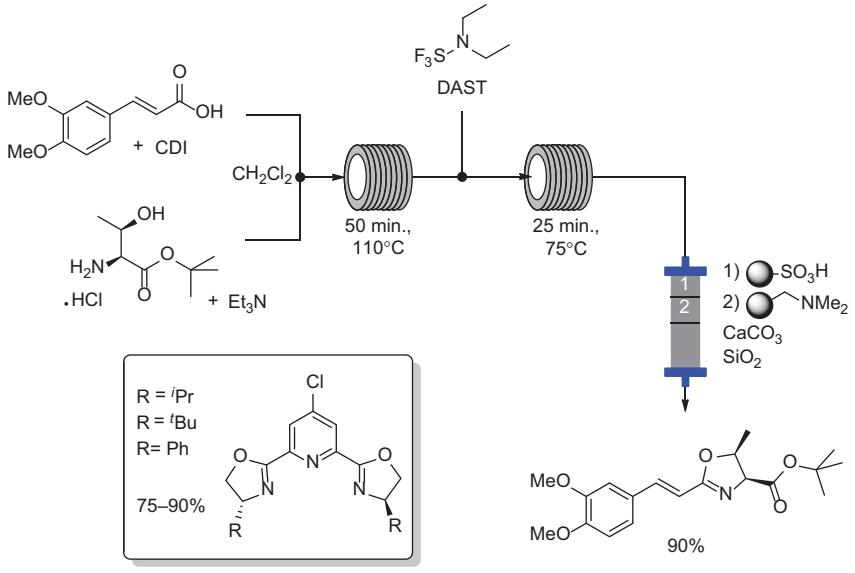
Fluorination products derived from alcohols



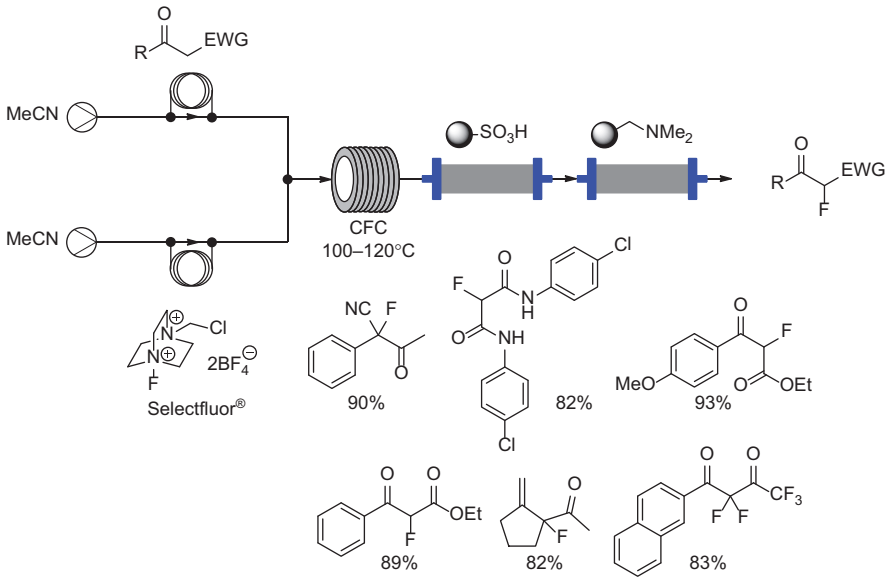
Fluorination products derived from carbonyls



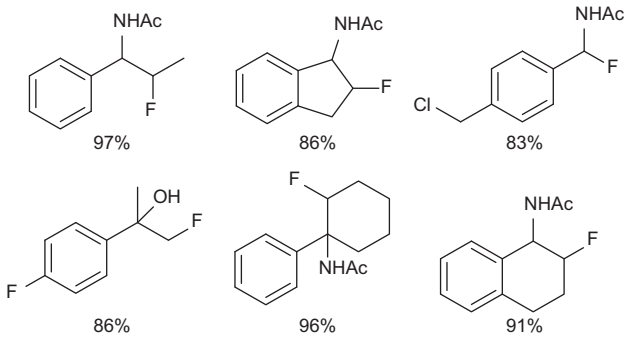
Scheme 6 Fluorination chemistry performed using diethylamino sulfur trifluoride (DAST) in flow.



Scheme 7 Activation and cyclization of β-amino alcohols to form oxazoles.



Scheme 8 Electrophilic α-fluorination using Selectfluor in flow.

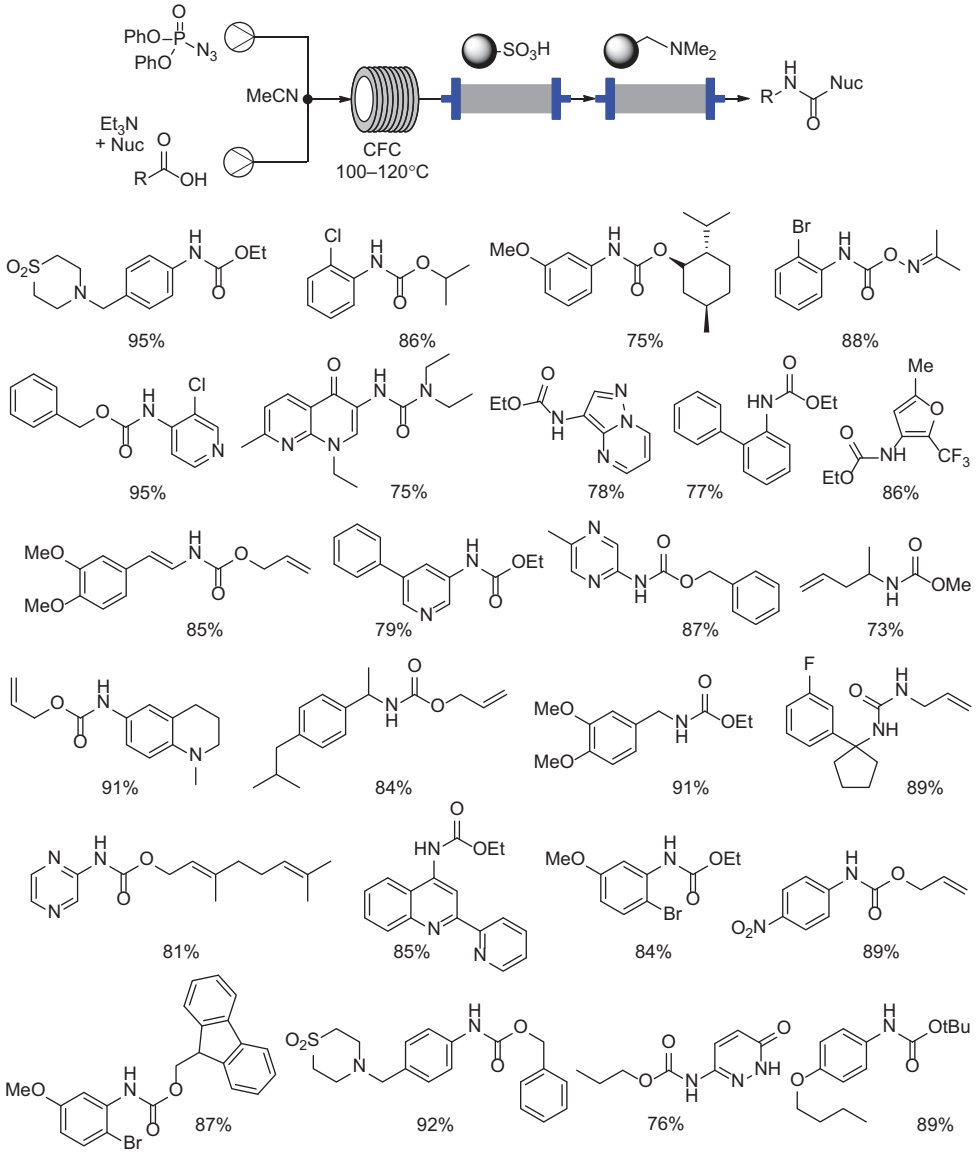


Scheme 9 Product prepared via a Fluoro-Ritter reaction in flow.

amine), to furnish carbonates or carbamates as the final products. It is worth highlighting that in this sequence, the final product could be isolated without recourse to any further purification. This demonstrates the synergistic effect of employing flow synthesis in combination with immobilized reagents, for improved product output. In this way, by extending and integrating additional steps that each generate clean product flows, it is possible to prepare more complex molecular architectures through multi-step transformations.

4 Synthesis of drug substances

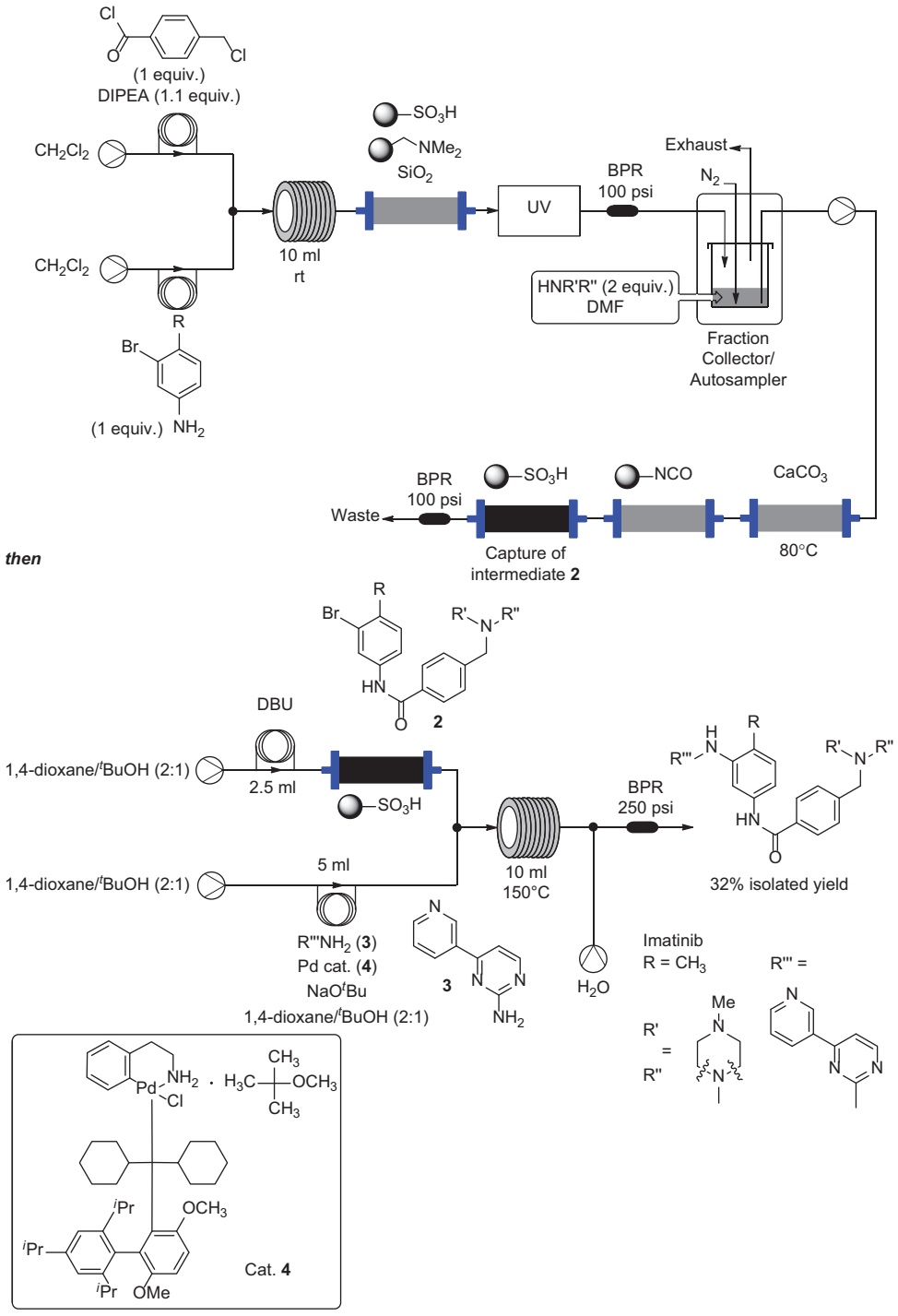
The true potential of flow chemistry as an enabling technology can really only be fully appreciated when seen in the context of a target driven multi-step synthesis, aimed at the delivery of advanced chemical structures such as active pharmaceutical ingredients (APIs) [56–66]. As most pharmaceutical syntheses typically require between 8 and 10 chemical transformations (this is often somewhat reduced to 5/6 steps when analogue/library syntheses are being conducted), excluding protecting group manipulations, to realize the target molecule, this is a good foundation from which to explore the advantages of flow chemistry. We have generated a flow protocol for the synthesis of imatinib, the API of the Novartis block buster anticancer therapeutic Gleevec (imatinib mesylate), including a series of analogues (Scheme 11) [67]. This molecule also highlights a difference in planning and thinking between the original batch based routes [68, 69] and the flow based synthesis. The batch preparative routes had been originally optimized to provide intermediates of low solubility, which facilitate isolation and purification through sequences of precipitation, crystallization and filtration. However, this is inherently counterproductive for a flow approach where solubility is a prerequisite. Furthermore, we aimed to create a route which would allow each of the three main fragments to be exchanged to address maximum variation in subsequent analogue synthesis. This requires additional planning to build flexibility into the sequence where this desired diversity can be easily introduced. Again, prior consideration of the generated intermediates, and any potential by-products that may arise, is critical and should be addressed prior to embarking on the synthesis. Consequently, the extensive profiling



Scheme 10 Curtius rearrangement using diphenylphosphoryl azide (DPPA) in flow.

of the reaction in terms of its purity profile is more closely analogous to process chemistry than traditional Medicinal Chemistry, even at the development stage. So, although more time consuming in the planning stage, having a greater understanding of the chemistry, does then enable a smoother up scaling and more rapid optimization of the route.

The continuous flow synthesis of imatinib commences with a coupling between an acid chloride and an aniline component, each of which can be easily varied (Scheme 11). The resulting amide product stream was worked up by elution through a mixed bed column containing both an acidic and basic resin, followed by a short plug of silica. The purified output stream was then directly collected into a pre-charged vial containing a dimethylformamide (DMF) solution of *N*- methylpiperazine (other secondary amines could be used) by an automatic fraction collector triggered by a UV detector. This collection process facilitated an automated solvent exchange from the highly volatile dichloromethane (DCM) used for the first step to the more polar DMF required for further processing. A simple heating plate was used to raise the temperature of the vial of collected solution to 50°C and a purge flow of nitrogen gas was used to encourage evaporation of the volatile DCM. After a predetermined time, the resulting DMF solution was automatically re-injected into the second stage reactor. The stream was passed through a column of calcium carbonate maintained at 80°C, then scavenged with immobilized



Scheme 11 Flow route used to prepare imatinib related analogues.

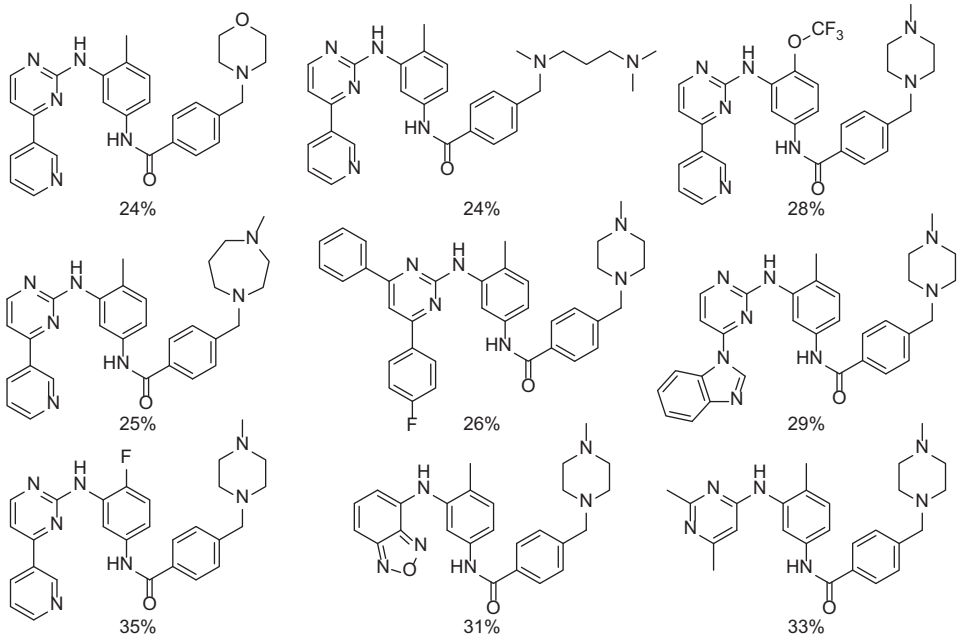
isocyanate to remove the excess *N*-methylpiperazine. The flow was then directed into a further column containing silica-immobilized sulfonic acid, to conduct a catch-and-release purification (capture of **2**). The intermediate **2** was then released from the silica supported sulfonic acid by elution with a 1,8-diazabicycloundec-7-ene/sodium tert-butoxide (DBU)/(^{t}BuONa) solution directly into a subsequent Buchwald-Hartwig coupling with heterocyclic material **3,** using the BrettPhos Pd precatalyst (**4**), at an elevated temperature of 150°C. A water stream was combined towards the exit of the reactor, which aided dissolution of sodium bromide precipitate formed during the coupling. Finally, the reactor output was concentrated *in vacuo* and loaded onto a silica Samplet cartridge for automated flash

chromatography, to give the desired product in 32% yield in better than 95% purity.

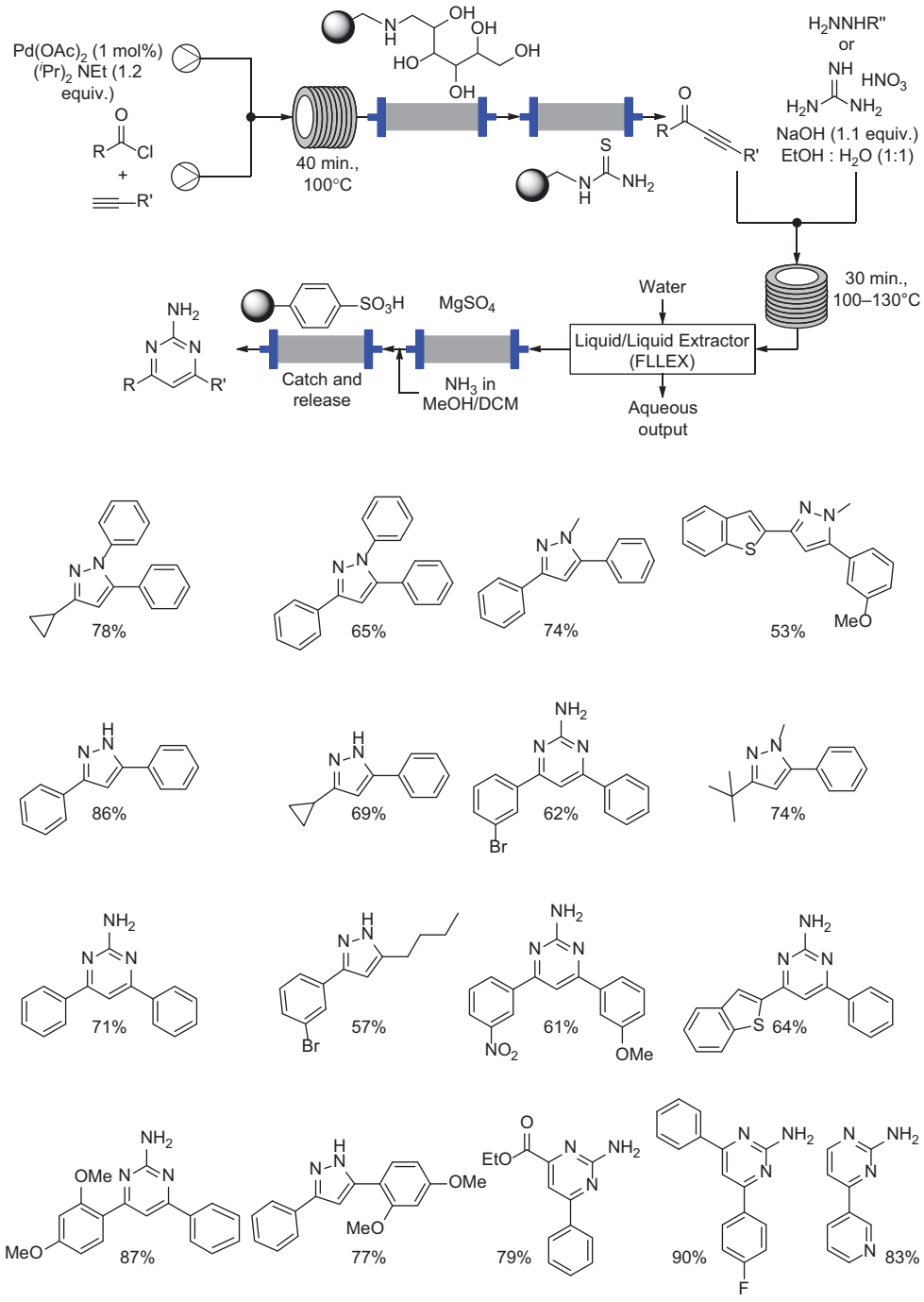
Also, by modification of the input fragments, we were able to demonstrate that a small derivative library could be synthesized, in which a new unique structure could be prepared every approximately 12 h under automated control (Scheme 12). In addition to supplying commercial fragment sets to the system, we were also able to supplement the structural diversity by incorporating heterocyclic scaffolds prepared in a convergent manner on a second flow platform. This involved the synthesis and further condensation reaction of ynone intermediates to generate the corresponding pyrimidines (Scheme 13).

Using palladium catalysis, an acid chloride and acetylene (which can be made as described earlier) are induced to undergo a Sonogashira coupling to yield the unified ynones (Scheme 13) [70]. To generate a flow process, a solution of the acid chloride and acetylene were combined with a stream containing a catalytic amount of palladium (II) acetate and Hünig's ($^{i}Pr_2NEt$) base. The united flow was heated at 100°C for 30 min in a tubular coil reactor and the output purified by passage through a series of four different solid reagents and scavengers. First, a polyol resin was used to remove the excess acid chloride (1.2 equiv. used) then a column of calcium carbonate trapped the hydrochloric acid formed during the reaction and deprotonated the ammonium salts. The resultant Hünig's free base was trapped on a sulfonic acid resin and finally a column of immobilized thiourea removed the palladium salts. The freshly prepared ynone products could be isolated in moderate to high yield (41–95%) and excellent purity, following only evaporation of the solvent. However, without intermediate isolation, they could be further elaborated by combination with an additional input stream containing a nucleophile, such as a hydrazine or guanidine derivative. By uniting the flow streams and heating the resultant mixture, the corresponding heterocycles could be directly prepared as a single linked flow sequence. This also allowed us to exemplify another attractive feature of this mode of processing, which was the ability to split the main product stream with each of these new flow tributaries being directed towards different product outcomes by varying the subsequently introduced condensation agents (Scheme 14).

With the growing number of reported syntheses, flow chemistry is slowly gaining acceptance as a very versatile tool for performing many different types of chemistry [71]. Even within our own laboratory, we have already demonstrated it can be used to prepare a wide range of chemical structures including quite complex natural products (Scheme 15) [72–83]. However, in order to utilize the full capacity of flow chemistry, it is imperative that we gain better insights into the active chemical transformation occurring within the reactors, in real-time, so as to make immediate informed modifications to reaction parameters enhancing and accelerating optimization and increasing process quality control.



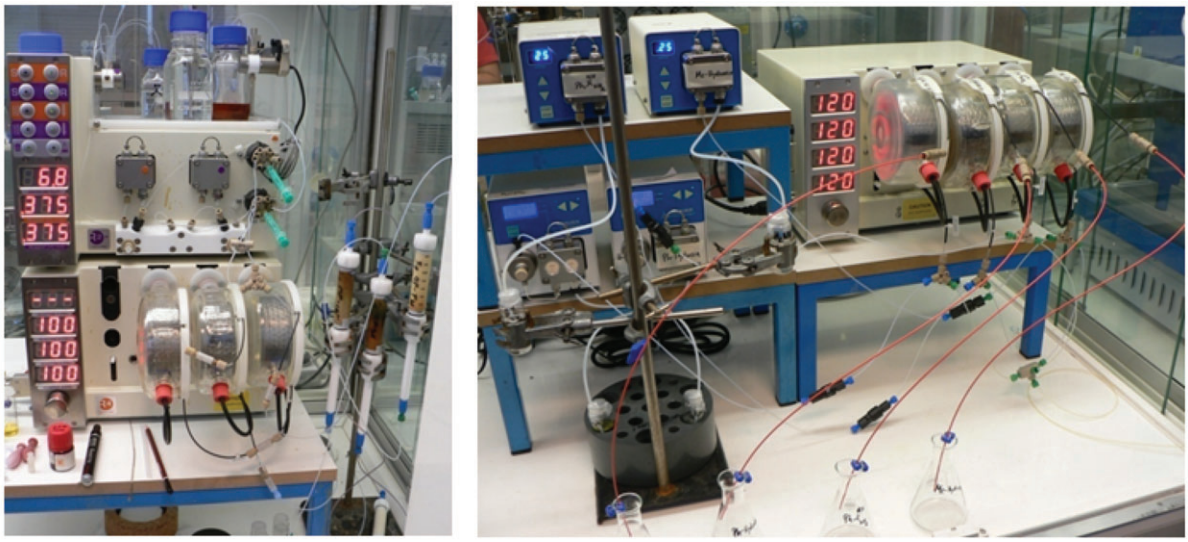
Scheme 12 Examples of imatinib analogues prepared in flow.

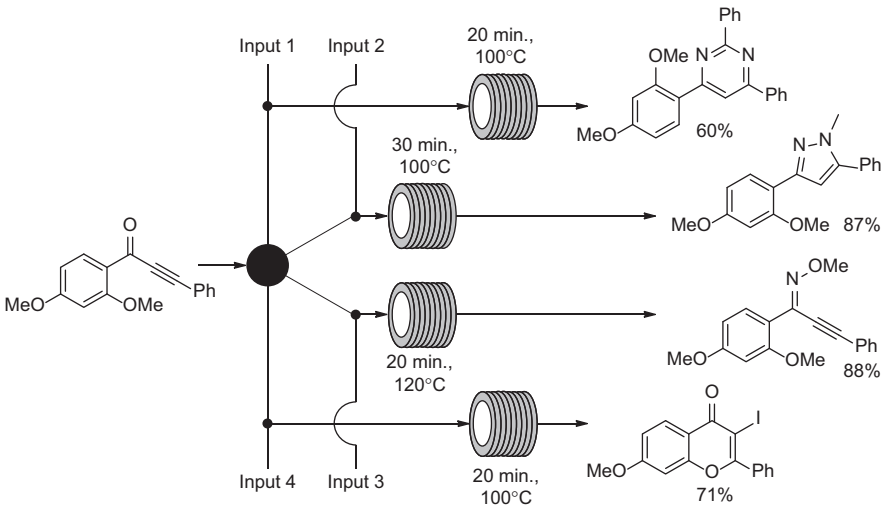


Scheme 13 Preparation of ynones and elaboration to their heterocyclic derivatives.

5 Reaction monitoring with in-line diagnostics

Working within a flow domain is not directly comparable to conducting the same reaction in batch. Many additional factors contribute to the altered reaction environment, such as the increased governance of surface phenomenon over bulk solution characteristics (high surface to volume reactor ratio) and improved mixing coefficients. As a continuous flow process is by definition a dynamic environment, it is possible to effect rapid changes in reaction parameters leading to immediate downstream changes in the reactor output. Therefore, utilizing real-time analysis of flow processes allows the rapid harvesting of large amounts of data regarding multiple reaction parameters

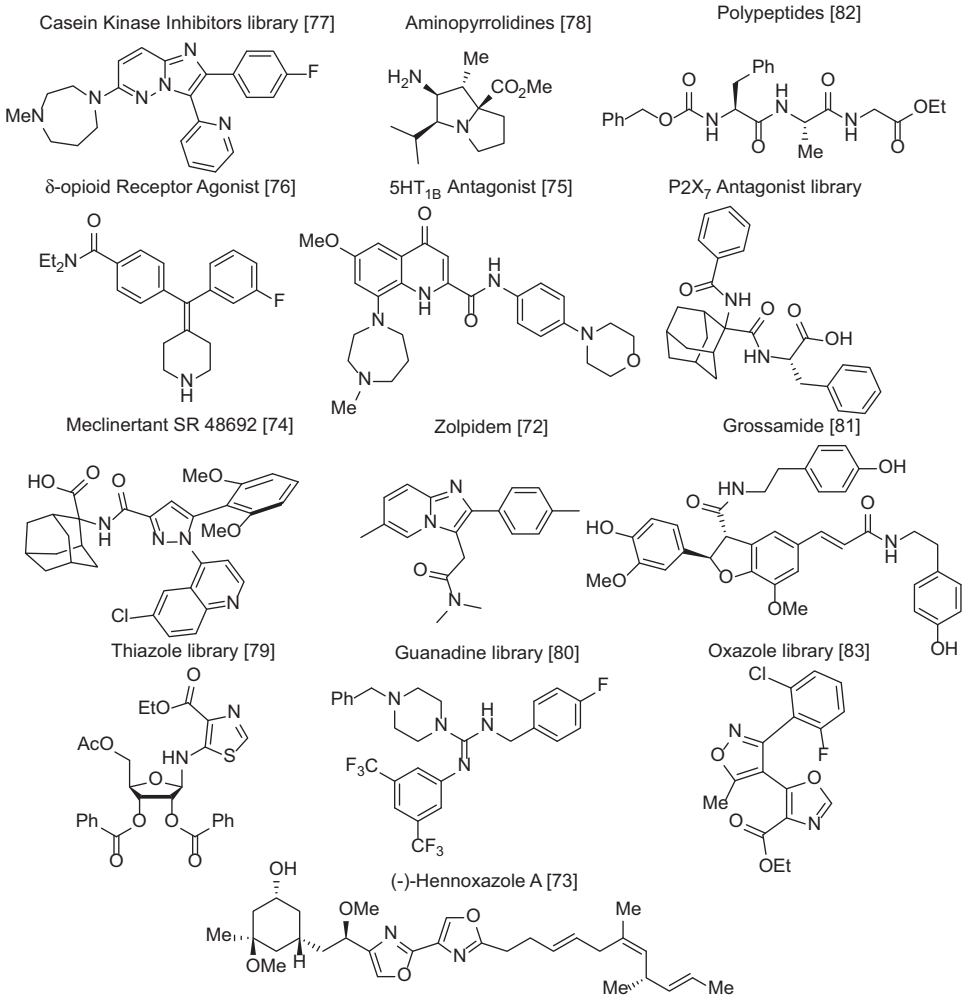




Scheme 14 Divergent chemical synthesis by stream splitting.

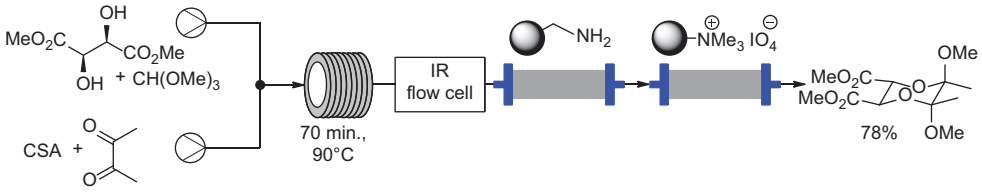
that can then be usefully employed to optimize the transformation [84–87]. Qualitative spectral data can be easily acquired using adjustable wavelength photodiode detectors (or similar spectrometers) placed as in-line analysis cells. Other diagnostic devices can also be used to report on reaction progress, e.g., impedance measurements, Raman spectroscopy, near or React IR, fluorescence measurements and various in-line bioassays. Alternatively, or in addition, automated sampling techniques can be used to divert aliquots of reaction media into auxiliary monitoring equipment, allowing standard LCMS or GCMS to be assimilated into the system.

One device we have found particularly useful has been a ReactIR flow cell which can be easily positioned at any point throughout the reactor to interrogate a flow stream in real-time, including monitoring for the presence of transient or reactive intermediates [88, 89]. We have used this diagnostic tool to help evolve a flow route to various butane-2,3-diacetals (BDAs) which are key polyol fragments used in the synthesis of numerous natural products [90, 91]. The developed flow approach allowed the BDA units to be prepared generally in much higher yields and with greater reproducibility than the equivalent batch processes. Specifically, the BDA protected tartrate was generated in multigram quantities from a mixed stream of dimethyl-L-tartrate, trimethyl orthoformate and butane-2,3-dione under acid catalysis using catalytic camphorsulfonic acid (CSA) (Scheme 16). It was discovered that when the dimethyl-L-tartrate and trimethyl orthoformate were premixed, rapid formation of an intermediate diacetal occurred, which was observed using the ReactIR flow cell (Scheme 17). This proved to be an important observation and optimization of

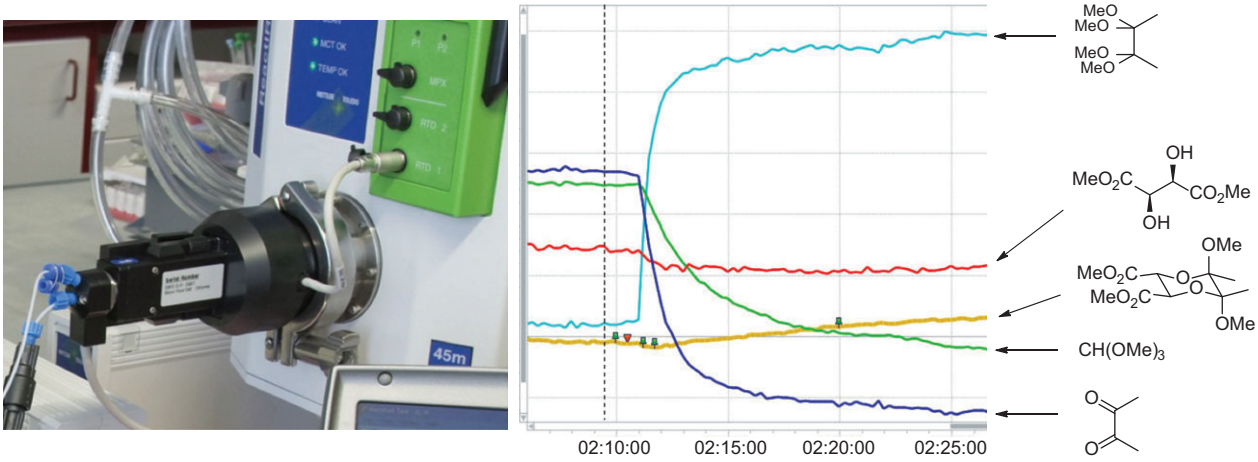


Scheme 15 A range of other targeted structures achieved using multi-step flow synthesis.

the breakdown of this reactive relay species increased the yield of the protected diol. In this sequence, the product stream was again conveniently purified using a sequence of immobilized scavengers to remove any remaining butanedione and CSA catalyst, a process which could also be confirmed using the ReactIR flow cell to monitor for disappearance of these materials. A periodate resin was then employed to perform a rapid glycol cleavage of the residual tartrate ester, to generate volatile by-products that could then be easily removed. As a result, only evaporation of the volatiles was required in order to isolate the product in a crystalline form. This newly synthesized BDA-protected tartrate was further modified in a two-step transformation, first to furnish an unsaturated system by treatment with a strong base lithium diisopropylamide (LDA) in the presence of iodine, then through a selective hydrogenation using the H-cube Midi system (Rh on alumina catalyst) to yield the corresponding *meso* reduced form in quantitative conversion (Scheme 18). Here again, application of the ReactIR proved valuable in optimizing the process.



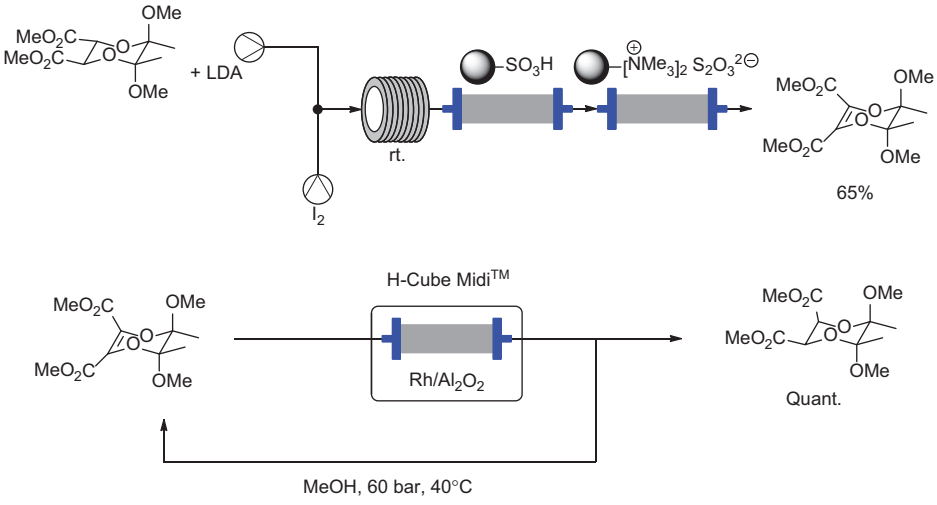
Scheme 16 Flow synthesis of butane-2,3-diacetal (BDA) protected tartrate.



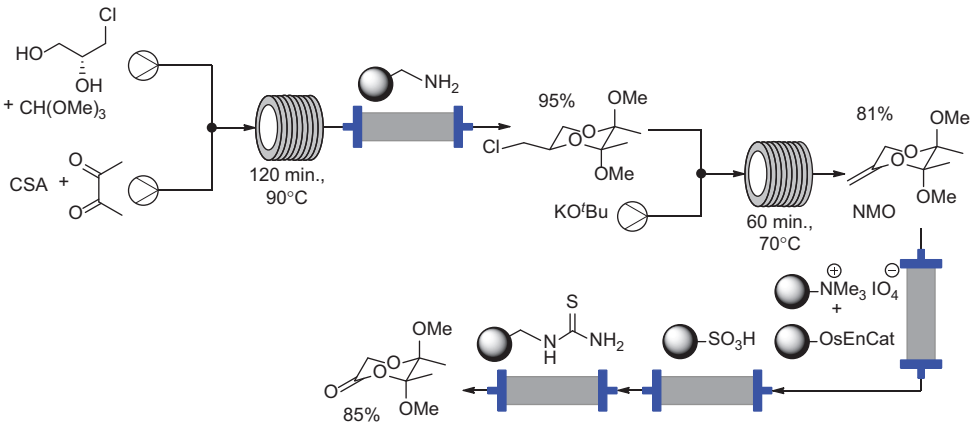
Scheme 17 Mettler Toledo ReactIR Flow Cell and processed output.

A more challenging sequence, based upon this same general protection strategy, was investigated involving the preparation of a BDA protected glycolate (Scheme 19). Utilizing conditions similar to those used to protect the tartrate above (Scheme 16), enantiomerically pure chloropropanediol was first converted to the *bis*-acetal without racemization. The resulting primary chloride substituted product was then treated with a strong base (KO^{t}Bu) to promote elimination to the exo-alkene. It was gratifying to discover that this new flow procedure consistently produced a high quality product, in an improved ratio of 24:1, exo:endo, compared to variable ratios of between 15:1 and 5:1 as achieved in batch. The final oxidative cleavage of the double bond was conducted with a combination of Osmium EnCat and immobilized periodate in the presence of morpholine *N*-oxide as a solution-phase reoxidant yielding the lactone. Reaction clean-up was then affected by passage of the flow stream through a sulfonic acid resin, to scavenge the morpholine then an immobilized thiourea matrix to sequester any leached osmium. Finally, isolation of the pure lactone product involved only solvent evaporation.

These examples clearly indicate that flow approaches assisted by in-line purification and real-time reaction monitoring can significantly improve existing processes. However, they can also help to automate and regulate new sequences. We recently required an approach to repeatedly prepare quantities of various coumarin-8-carbaldehydes as selective IRE1-binders for investigations of mRNA splicing [92, 93]. Having ready access to the freshly prepared substrate was very beneficial for biological investigations, as this aldehyde tended to undergo auto oxidation upon



Scheme 18 Flow derivatization of a butane-2,3-diacetal (BDA)-protected tartrate.

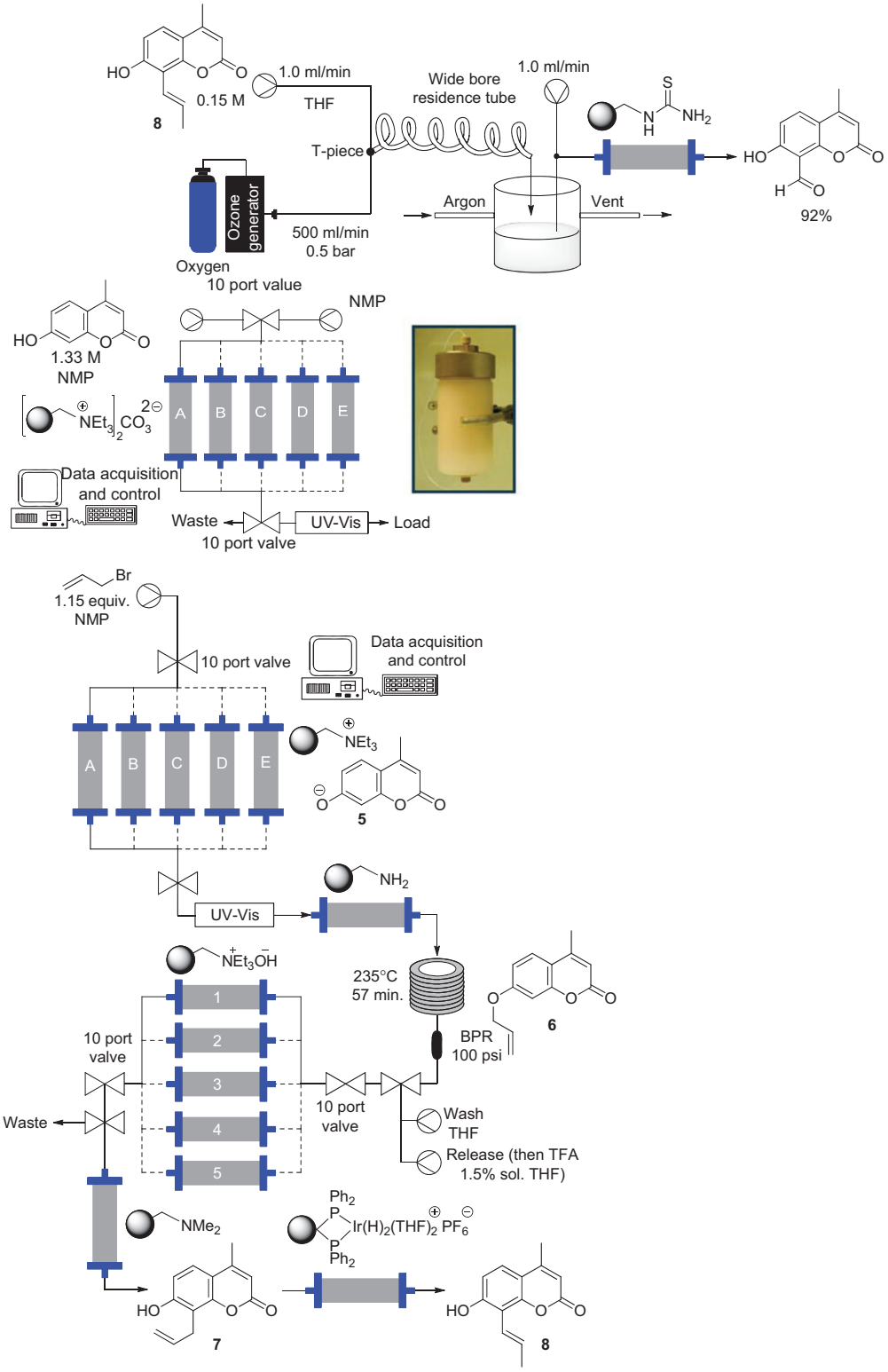


Scheme 19 Synthesis of butane-2,3-diacetal (BDA) protected glycolate.

storage. One particular route to this molecule is depicted in Scheme 20 below. The synthesis provides clean, easily isolated material, and can be reproducibly run. Furthermore, the operation of the reactor can be performed by numerous people, as much of the sequence is automated. This significantly increases access times to these compounds when scheduling time allocation in a busy synthesis laboratory.

The selected route is based upon a key Claisen rearrangement reaction, which in high regioselectivity forms the required carbon functionality at position 8. As a starting point, we elected to utilize readily available 7-hydroxycoumarin, as isolation of this material was readily achieved at scale from our previous acetic acid flow procedure by direct induced precipitation by dilution of the output stream with water [93]. The first step of the sequence involved the allylation of the phenolic group with allyl bromide, which was conducted in *N*-methyl-2-pyrrolidone (NMP) in the presence of an immobilized carbonate base. To conduct this reaction, a bulk solution of the 7-hydroxycoumarin in NMP was eluted through a series of capture cartridges (each was 40 mm internal diameter (id.) 75 mm depth, containing ~200 mmol loadable carbonate base). A high concentration and flow rate were used for this rapid and efficient ion exchange process, where the phenolic component **5** was trapped upon the resin following deprotonation. An automated valve network was set up to exchange between the different columns, as the resin became saturated by the substrate. Breakthrough of the coumarin was easily monitored for by an in-line UV/Vis detector using a threshold based voltage to trigger switching to the next column for loading. During this loading phase, a second HPLC pump (pure NMP solvent delivery) enabled sequential washing of the newly loaded column, thereby eluting any non-bound starting material which could be recycled. The entire loading procedure could be run in an automated manner using Gilson Unipoint control software.

Once each column had been fully loaded and cleaned (10 in total), a modified set-up was used for the *O*-allylation and linked Claisen rearrangement process. The feed line for the coumarin loaded columns was switched to deliver a solution of allyl bromide in NMP. Upon allylation, the coumarin material was released from the solid phase and passed through a scavenging step (an amine resin) to sequester any co-eluting allyl bromide. Real-time monitoring of the reaction stream using the UV/Vis device enables automatic succession to a new phenoxide cartridge, when the signal intensity received by the detector falls below a pre-prescribed absorption threshold (also triggering simultaneous exchange of the amine scavenger column). This allows an automatic and essentially seamless transition between the different reactor cartridges. The reaction flow stream containing intermediate **6** was next relayed into a stainless steel flow reactor and heated at 235°C, promoting the Claisen sigmatropic rearrangement. At this stage, the Claisen product **7** is recaptured onto a second ion exchange resin, supported tetraalkylammonium hydroxide. This simplifies the isolation of the alkylated coumarin product from the high boiling point NMP solvent, as well as enabling its separation from any residual non-Claisen rearranged intermediate (2.5–4%). Following washing of the column with tetrahydrofuran (THF) (flushing all the NMP solvent away), release from the resin could be affected by passing a 1.5% (v/v) trifluoroacetic acid (TFA) in THF solution through the column. The released material could be isolated directly by solvent evaporation in a pure form. Alternatively, the isomerization of the double bond leading to the conjugated analogue **8** could be achieved using an immobilized



Scheme 20 Synthetic flow route to coumarin-8-carbaldehyde.

version of Felkin's iridium catalyst at 60°C, although a long residence time was required [90, 91].

Having had previous experience performing ozonolysis reactions in flow [94, 95] we quickly established a simple set-up to perform the cleavage step of the alkene **8** using an immobilized thiourea as a solid ozonide quenching agent. A flow stream of the substrate was pumped to mix with a continuous gas flow (O_2/O_3) at a

T-piece and directed into a plastic tubular reactor with a residence time of ~75 s. The reactor output, which was comprised of a droplet spray, was collected into a nitrogen blanketed purge vessel where the excess ozone was eliminated by passing a constant flow of nitrogen through the chamber. The expunged solution was continuously pumped from the chamber as it collected passing through a packed bed cartridge containing an excess of the polymer-supported thiourea. This gave the desired aldehydes in quantitative conversion and 92% isolated yield after solvent removal.

In total, this four step sequence involving allylation, Claisen rearrangement, isomerization and ozonolysis, could be used to deliver the desired product in 51% overall yield after crystallization (used to remove the minor regioisomer by-product derived from the alternative sigmatropic rearrangement). The limiting step of the route was the iridium catalyzed isomerization, although this could conceivably be performed using parallel reactor cartridges, thereby increasing the throughput. Despite this restriction, it was still possible to preform multi-gram preparations (5–20 g).

This and the other examples highlighted starts to clearly demonstrate the value of flow chemistry as a development tool in research and scale-up

6 Conclusion: the future of flow chemistry in discovery research

The complete flow solution tool box is still a future dream for chemists, but significant process is being made to expand the available chemistry and improve reactor designs. Some key areas of developments covering aspects such as improving downstream processing, better gas delivery, enhanced pressure regulation (current back pressure regulators are limiting due to their potential for fouling) and the expansion of self-interrogating Design of Experiment software packages, are still required. In addition, for translation to larger scale applications, it will be necessary to devise better methods of performing aqueous quenching and extraction. Solid supported reagents, although extremely valuable and cost effective for laboratory based use, do have limitations regarding volume and scaling (pressure effects and reactor volumes), especially when used as stoichiometric reagents or scavengers at scale. So, although they remain an effective alternative for catalytic processes or for the removal of low level contaminants, their viability as reagents or excess sequestering agents generally falls off with up scaling. Consequently, classical aqueous extractions must be re-evaluated and modified to fit continuous processing frameworks. Although several concept designs using semi-permeable membranes and counter-current extraction methods have been reported, these still need substantial improvements to reach the levels and processing capacity currently available from existing reactors, thereby avoiding the creation of an artificial bottleneck.

Another aspect of flow which has attracted significant attention is the ability to instantly evaluate newly prepared compounds, flowing directly from a reactor straight into a bioassay [96, 97]. Linking synthesis sequentially with property assays (physical, chemical or biological) will allow for a fully closed loop discovery and optimization process at a much reduced cost and much higher speed (greater throughput) than currently achievable. This ability to specifically explore chemistry and biology in an integrated manner, offers tremendous advantages for pharmaceutical and agrochemical research, especially at the early stage of hit-to-lead discovery. As indicated in the introduction, cycle times to new compounds need to be as short as possible, therefore, being able to screen a compound to give an early indicator of its biological potency could save valuable time. This would be particularly beneficial when preparing new discovery libraries, by giving rapid evidence to guide the selection of the next suitable compound to be prepared. As a result, a faster and more comprehensive structure-activity relationship (SAR) picture could be systematically constructed, which would lead to a higher degree of success. This would be even more profitable if, as well as basic potency evaluation, additional tests relating to ADME and toxicology could be run in parallel by splitting the synthesized compound flow stream. This approach to combined synthesis and screening could revolutionize the pharmaceutical and agrochemical research discovery pipelines. With the exponential growth in this area, it is anticipated that this will be a plausible alternative way of working within the next 5 years.

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