Chemistry in a changing world

Steven V. Ley, Rebecca M. Myers and Daniel E. Fitzpatrick

This article constitutes a summary of the lecture given by Steven V. Ley as the recipient of the SCF Franco-Britannique Prize at the University of Montpellier on the 4th June 2014.

Abstract This article summarises the opportunities that arise through the use of flow chemistry to bring about multi-step telescoped reaction sequences. This holistic systems approach harnessing various aspects of chemistry, engineering and informatics provides a unifying platform for all available enabling technologies.

Keywords **Flow chemistry, continuous processing, flow reactor, multi-step, tamoxifen, imatanib.**

Résumé **La chimie dans un monde en changement**

Cet article fait la synthèse des apports de la chimie en flux continu et de ses opportunités, notamment la concaténation de séquences réactionnelles multi-étapes. Cette approche globale alternative fait le lien entre divers aspects de la chimie, de l'ingénierie et de l'informatique fournissant une plate-forme unifiée pour toute technologie innovante.

Mots-clés **Chimie et procédés en flux continu, multi-étapes, tamoxifène, imatanib.**

In our rapidly changing world, organic synthesis plays a key role in providing society's functional materials. While synthesis serves society in this way, it also comes at a cost in terms of the planet's resources. Increasingly today we recognise the need for greater sustainability and lower environmental impact of our chemistries while also recognising that wasting the human resource on trivial, repetitive and routine scale-up tasks is equally unacceptable [1].

Our laboratories and our attitudes need to change in order to transform the way we work. We need to employ a holistic understanding of processes: a synthesis systems approach to our chemistry whereby better integration of *all* the underpinning elements are evaluated, be they related to the chemistry and specific experimental details, or to the engineering and equipment needs or to the IT components and overall knowledge management of the processes involved. In any complex multi-step assembly of a functional product any individual part can influence the whole. This is precisely why the often overlooked and less glamorous downstream reaction work-up protocols play such a defining role in decision-making at all levels of a chemical synthesis.

To date organic synthesis programmes are usually conducted by a highly trained, expensive and skilled workforce and are commonly operated in batch mode. The process is very labour intensive often requiring extensive reaction optimisation, repetitive tasks and routine reaction work-up skills often below or inappropriate to the high ability of the experimental chemist. Much of this activity we would argue is best relegated to machines.

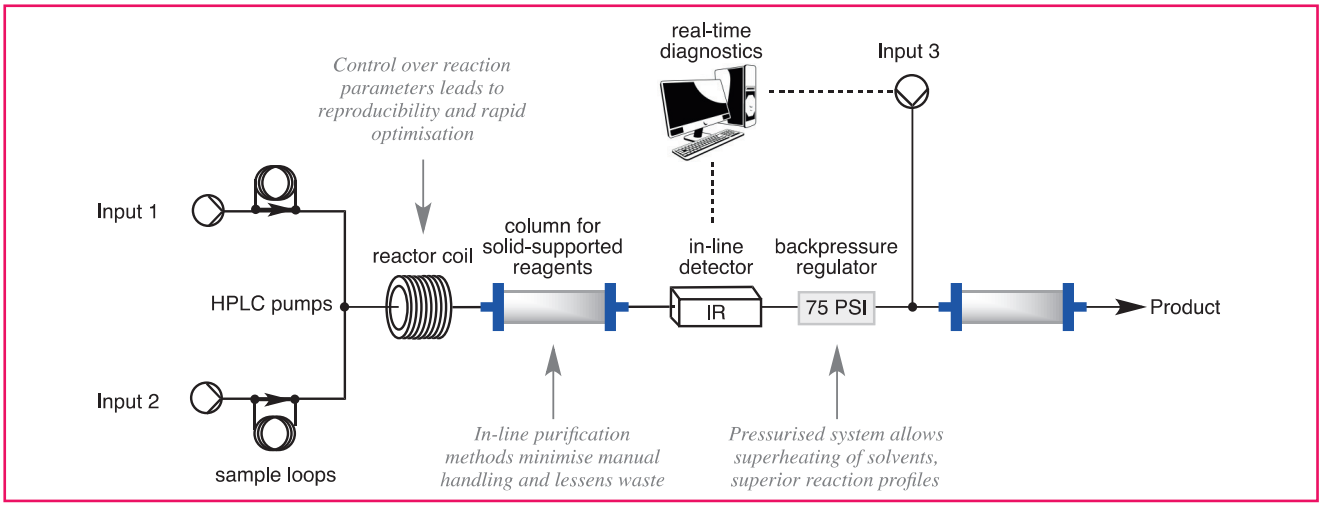
Today, more and more enabling tools are becoming available to accelerate the discovery process and particularly organic synthesis programmes [2].

We began our efforts in this area in the mid-1990s with the specific desire to conduct multi-step synthesis routes without the need for traditional and wasteful work-up methods such as chromatography, distillation, crystallisation and water washes common to conventional approaches. This was accomplished with a suite of immobilised reagents and scavengers acting in concert to deliver a range of biologically relevant products [3]. We also clearly pointed out at the time the advantages of these concepts that would accrue when moving from batch to flow mode using cartridges and packed tube flow reactors to achieve fully telescoped multi-step sequences of reactions [4].

Over the years these ideas have evolved whereby all the modular elements from the initial chemical inputs, ideas, synthetic planning, safety, availability of reagents etc. through to the equipment capabilities, sequencing, monitoring, feedback control, and on to the informatics generated, can be evaluated with all components contributing to defining "the system".

By way of a diagram we can delineate the individual modules of a complicated flow reactor arrangement that can ultimately lead to scale-up or achieve multi-step syntheses of complex target molecules (*scheme 1*). Owing to the closed nature of the equipment, hazardous or malodorous substances can be accommodated leading to increased process safety and extended working regimes. Controllable pumps and sample loops introduce building blocks and solvents into the reactor which are rapidly mixed and reacted through reactor coils made of inert materials. Further control and reproducibility arises by varying tube dimensions and accurate temperature measurement of the system. Immobilised reagents packed into flow tubes can be used as a method to scavenge by-products and achieve in-line purification. Monitoring of the flow streams at any point is possible, for example, using in-line IR. This provides information to computer systems that are able to effectively self-regulate the system and control further equipment such as pumps to achieve multi-step operations [5]. In-line back pressure regulators facilitate alternative reaction profiles allowing superheating of solvents for example.

Being modular in design affords maximum flexibility such that the system can operate in a variety of modes to produce



Scheme 1 - Scaling up and multi-step synthesis.

Figure 1 - Vapourtec R2 + R4 flow reactor.

compound collections, pilot and discover new reactions and optimise processes or scale-up existing chemistries.

Very many reactor configurations are now known and much of the equipment is commercially available. A typical flow laboratory illustrates how the equipment can be organised, providing ready access to any individual component over a small footprint (*figure 1*). In our laboratories we also like to include an overview webcam to provide further levels of safety monitoring.

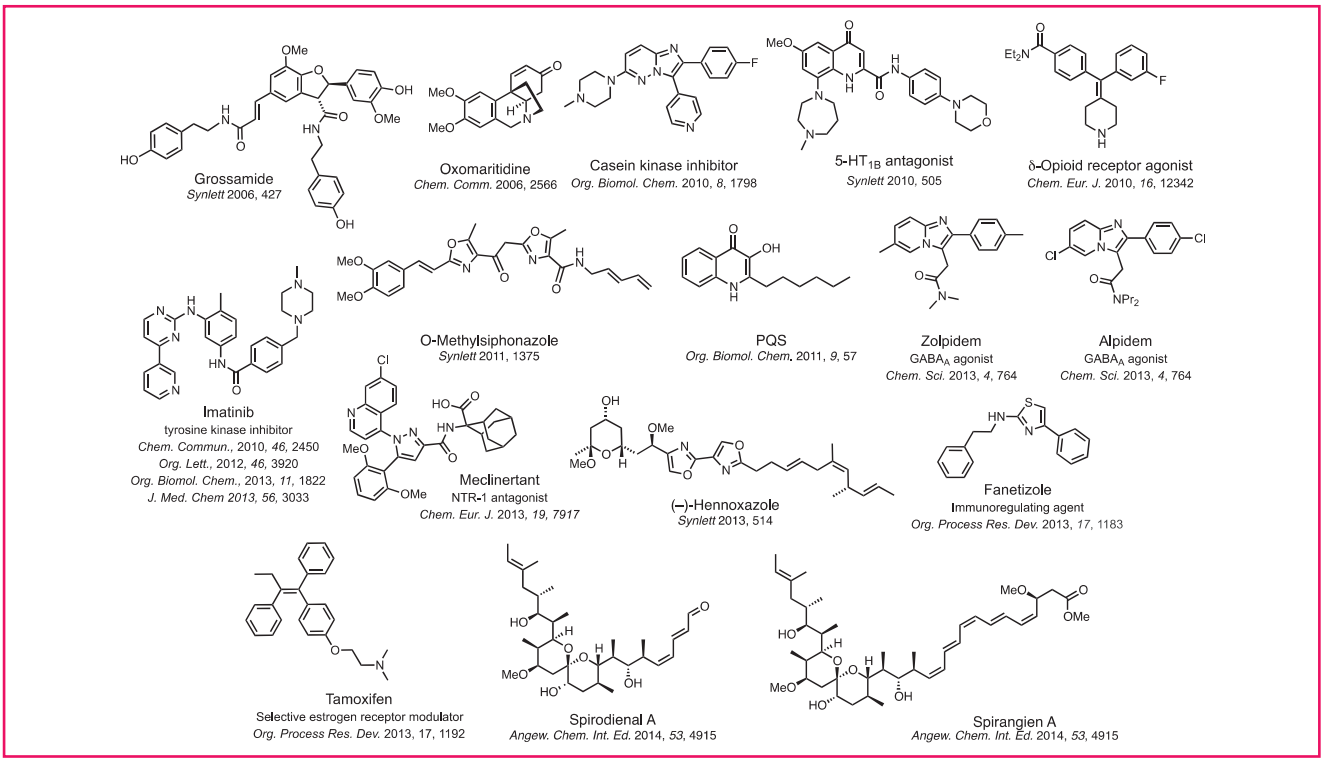
In thinking about how we might change the way we work, a lab of the future will go well beyond where we are today. The beginnings of this revolution are already underway. We firmly believe this machine assisted synthesis approach using all the enabling methods and modern technologies makes both scientific and economic sense.

Integrating modelling with synthesis saves time and resource. The ability to achieve superfast reaction optimisation using, for example, microfluidic methods is possible and when combined with other configurations facilitates new reaction discovery. Combining calorimetry with flow experiments provides a further level of understanding of reaction and process kinetics. The “smart” fume cupboard which can be rapidly reconfigured (on wheels) is with us today. It can be operated in energy saving modes or be used to collect and port information to remote sites or insert entries directly in electronic lab notebooks. It is even possible to use facial recognition software to determine organisation and structure within a hood. Related to this is the greater use of webcams and the exploitation of readily available open source software to provide support for the monitoring and control of equipment; all of which release research personnel to conduct more meaningful experiments and provide the opportunity for extended working regimes [6].

Advanced techniques such as high-speed thermal imagery can go beyond the human eye, providing additional valuable information useful for the design of synthesis pathways. Taken together with the power that comes from wireless networking, tablets, cell phones and lab apps, it is clear that the laboratory is evolving rapidly.

Further advancement can occur when our synthesised materials are subjected to integrated functional evaluation. For example, in our laboratories, we can link Frontal Affinity Chromatography (FAC) using immobilised proteins to biologically interrogate freshly synthesised compounds using our flow chemistry platforms [7].

We are also making headway with the incorporation of cheap micro-processing circuitry, such as the Arduino and Raspberry Pi, in reaction platforms to aid with the control of equipment from multiple manufacturers [8]. This has enabled advanced in-line processing techniques such as evaporation, filtration and solvent switching [9]. All of this actively enhances our ability to link reactors and provides numerous opportunities for multi-tasking. Indeed, the coordination and sharing of information between instruments at levels sufficient for autonomous operation (possibly through the use of artificial neural networking) is very much a part of the thinking behind the Internet of Things [10]. Advances in equipment are similarly moving at an extremely rapid pace. The recent availability of mini mass spectrometry and bench-top NMR are beginning to impact how our laboratories are configured [11]. It is expected that the processing power found in the



Scheme 2 - Ley group flow synthesis of pharmaceutical agents and natural products.

Cloud will be used for interpreting and managing the sheer volume of data acquired using these new technologies.

The 3D printing of laboratory equipment such as reactor prototypes is with us today [12], yet they are currently under exploited in the synthesis research laboratory environment. Similarly visual representation of reactions and molecular structures through virtual reality methods is gaining an interest as a design and teaching tool [13]. It is easy to see that the introduction of “head-up” display technology such as Google Glass could instigate a new approach in laboratory safety and information management where reaction data can be accessed instantly from any location in the world.

Although as research synthesis chemists we would normally consult a variety of search engines to look for similarities, prior art, novelty or operating protocols on any new synthesis scheme prior to beginning a reaction, we seem to hesitate when it comes to using reaction evaluation and decision tools. This is largely owing to an impression that these are considered to be less developed or even naïve when compared to the ideas generated by the experienced chemist. Yet through the use of these tools it is possible to bring together techniques that the traditional research chemist would not consider, nor would be able to envisage without the aid of machine support. Extremely useful information which has the potential to affect reaction parameters and results can be obtained when incorporating computational analysis at early planning stages. *In-silico* simulations of electron distributions, likely transition states, relative reactivities and probable sites of reaction can enable researchers to better understand changes that are occurring at a molecular level, shaping and guiding the synthesis route that may be taken.

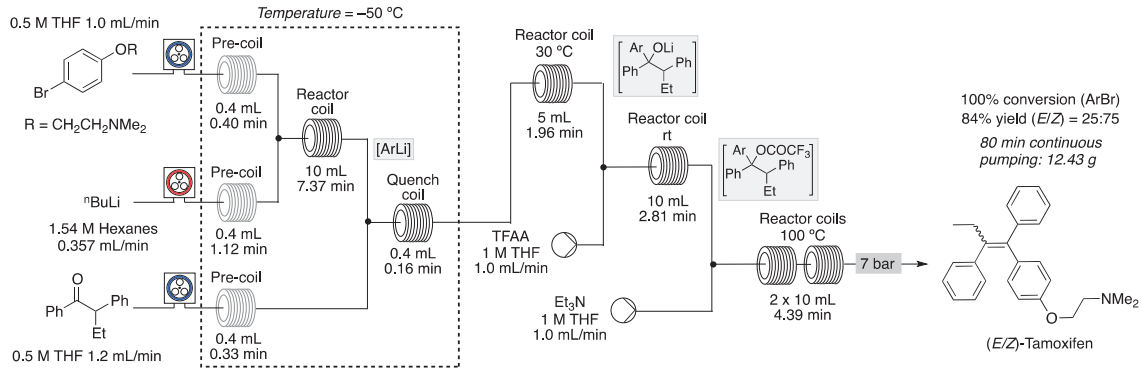
Armed with these new tools, we can expect that the synthesis process can be greatly accelerated and, with the aid of the flow chemistry technologies, help minimise the labour intensive practices common to conventional methods.

As an overview of what we have achieved using flow chemistry to prepare pharmaceutical agents and complex natural products (*scheme 2*) [14], we can see a broad range of chemical architectures are possible. These include those containing multiple stereogenic centres such as those in (-)-hennoxazole and the spirangiens, normally considered to be the domain of dedicated natural product synthesis groups. While space here precludes a detailed discussion of all these synthesis targets, one can conclude that all benefited to a significant extent from the use of flow methods. These advantages include improved heat/mass transfer, reduced solvent usage, better control of exotherms, containment of hazardous reagents and enzymes and provision of accurate temperature control between -80 and +350 °C.

In more detail, if one were to consider the synthesis of tamoxifen (a front line product for the treatment of breast cancer), a short route can be devised which exploits the use of organometallic species [15]. These reagents of course are well known as being pyrophoric and sensitive to moisture, bringing significant reagent handling constraints especially when moving upscale in batch mode.

Nevertheless, through the use of new flow reactor technology (Vapourtec E-series), a coordinated suite of pumps can deliver organometallic agents to various precooling and reactor coils and *in-situ* quenching to eventually deliver tamoxifen at a rate of 12.43 g over 80 mins (*scheme 3*). This would equate to 223 grams per day, or approximately 20,000 doses of the drug substance on a daily basis! All this being achieved using a small-footprint reactor occupying less than one standard fume cupboard (*figure 2*).

A similar opportunity arises during the handling of reactive or potentially hazardous gases in the research environment. Normally researchers would require expensive pressure vessels and have to follow appropriate venting procedures to remove excess gases at the end of each



Scheme 3 - Telescoped synthesis of E/Z tamoxifen.

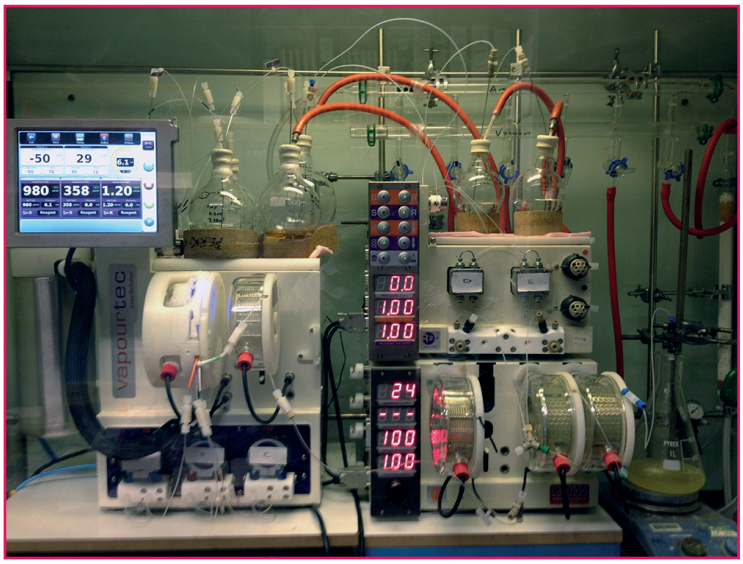


Figure 2 - Equipment set-up for the telescoped synthesis of E/Z tamoxifen.

synthesis step. However, moving to flow mode we have invented the use of a tube-in-tube device whereby a semi-permeable Teflon tube (AF2400), contained within a second PTFE tube, permits the passage of gas while inhibiting liquid flow [16]. Using this equipment we can minimise the use of gas to safely deliver enriched reaction streams for a whole variety of gases. Again we have published extensively in this area so restrict ourselves here to just a couple of interesting applications.

The first of these shows the use of a triple gas combination (ethylene, hydrogen and carbon monoxide) to form two new carbon-carbon bonds leading from an initial aromatic iodide as the chemical input to a branched aldehyde as the product (*scheme 4*) [17]. The process involves an initial Heck coupling of the ethylene gas to deliver a styrene, which after brief venting, is further hydroformylated to the final product.

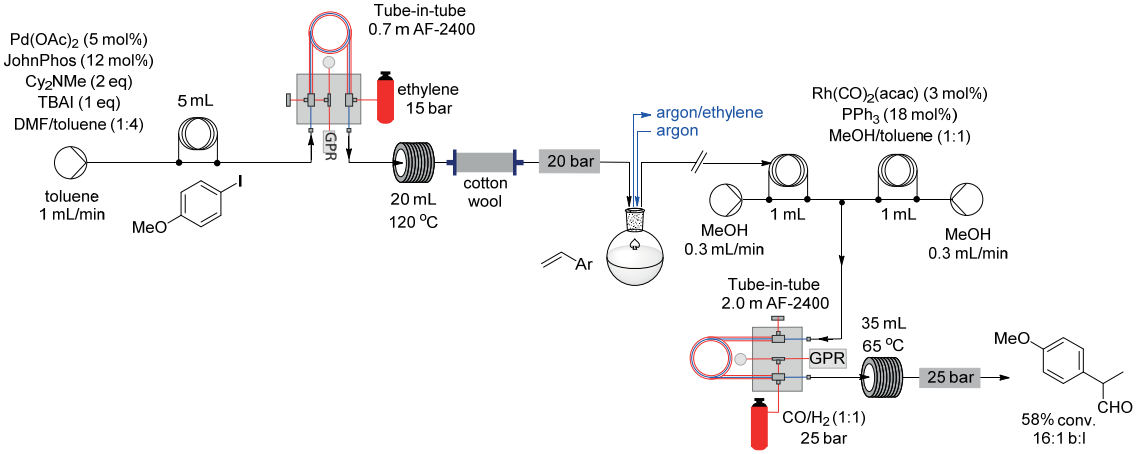
This idea of using multiple gases is attractive and brings a new dimension to general synthetic planning since many different combinations of reactive gases can be envisioned.

Finally, we can consider moving these concepts forward to consider more advanced multi-step telescoped sequences. The flow synthesis of casein kinase inhibitors nicely showcases these opportunities that arise (*scheme 5*) [18].

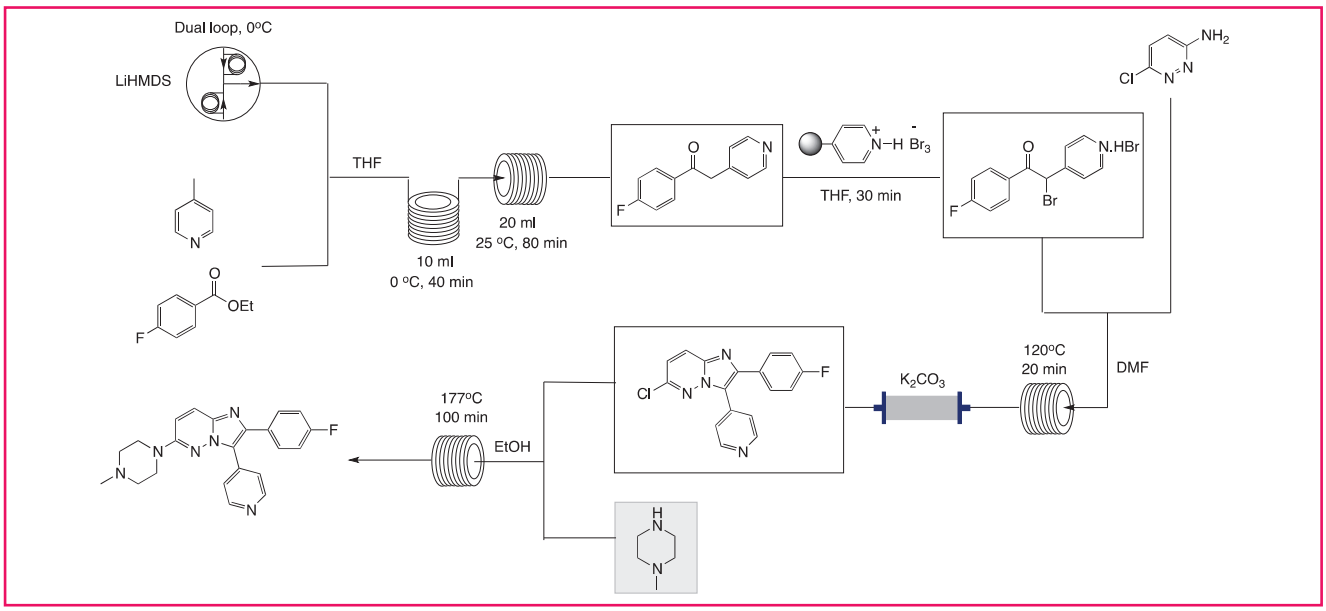
Here the imidazo[1,2-*b*]pyridazine core can be rapidly assembled through the coupling of various components using flow coils, immobilised reagents, scavengers and high pressure reactors following a logical sequence of reactions. It should be noted however that attempting similar reactions to the deprotonation of methyl pyridines and unimolecular coupling with esters or the later monobromination of highly active benzylic ketones can be problematic in batch mode operation.

A final more advanced sequence involves the flow synthesis of imatanib mesylate (Gleevec®), the important Novartis drug for the treatment of chronic myeloid leukemia (*scheme 6*) [19].

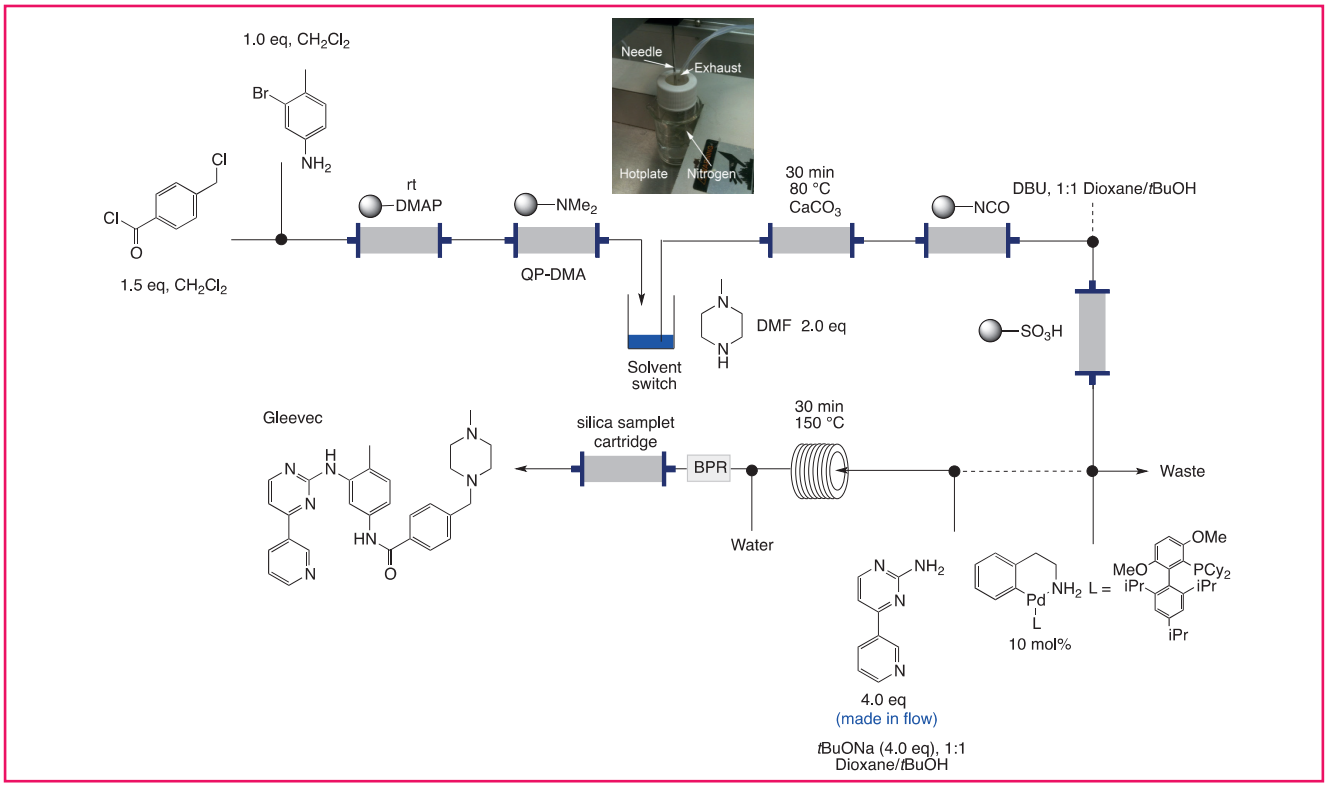
In this work, several interesting features of flow chemistry are harnessed to afford the final active pharmaceutical



Scheme 4 - C-C bond formation in flow.



Scheme 5 - Flow synthesis of casein kinase I inhibitors.



Scheme 6 - Flow synthesis of if imatanib mesylate (Gleevec®).

ingredient (API). Most notably the use of immobilised reagents and scavengers, the use of an in-line solvent switch, a catch and release step and a crucial Buchwald coupling using the Bret-Phos precatalyst to effect formation of the drug substance.

In summary, therefore, we believe that by taking a more holistic systems approach to synthesis particularly using flow chemistry methods, many advantages can be realised especially when linked to all the enabling technologies a modern laboratory can offer. The area is expanding rapidly and most encouragingly is helping to deliver on the green chemistry agenda.

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