NEW TOOLS FOR MOLECULE MAKERS: EMERGING TECHNOLOGIES

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INTRODUCTION

If one reflects for a moment about the current practices used by a skilled synthesis chemist, we must be impressed by the sheer complexity of what can be achieved. Moreover, the impact on society is staggering, given the array of healing drugs, compounds that protect and guarantee our food supply to the colours and materials of our modern society. All the sciences benefit to some degree from our ability to assemble novel molecular architectures that display function and beneficial properties. The synthesis chemist's ability to understand and create these selective features at a molecular level from simple building blocks is truly awe-inspiring; especially given that a combination of only a small selection of nine different elements of the periodic table and a molecular weight limit of 500 Daltons can, in principle, generate a difficult to comprehend number of 10^{63} different molecules! Despite the obvious achievements of chemical synthesis, it is not without its problems. These relate to its current sustainability as a discipline, where we see issues of poor atom and step economy.

The rising costs, waste production and excessive use of solvents are equally unacceptable. However, over recent years many new tools have become available to molecule makers to aid them in their task [1 – 4]. These maybe biochemical in nature, such as gene shuffling techniques whereby proteins are expressed to assemble complex natural products or we could use a multitude of enzymes *via* directed evolution methods. The whole area of synthetic biology is also poised to have a significant impact. There are also synthesis techniques becoming available that allow us to work at lower scales such as the use of microarrays, mini-reactor wells and microfluidics, which we will discuss later. In addition to these, there is a range of computational methods and databases along with ReactArray reaction optimising software for design of experiments (DOE) and principal component analysis (PCA) [5 – 7]. Chemical tools for parallel synthesis or fast serial processing such

as microwave methods have also become popular [8 – 12]. In our work we have concentrated on the use of immobilised reagents and scavenging methods for multi-step molecular synthesis and shown how powerful these concepts can be in the construction of pharmaceutical agents [13, 14] and natural products [15 – 20]. Indeed, it is this holistic systems chemistry approach that differentiates this from more conventional synthesis planning. In this lecture we discuss how these immobilisation methods for reagents, scavengers and catch-and-release techniques [21, 22] can be combined with phase switching and controlled release techniques to achieve chemical synthesis by continuous processing in the flow mode [23 – 25]. This will necessitate the development of suitable microreactors, packed flow tubes, flow coils, microfluidic reactor chips and appropriate reaction engineering. In order to maintain flexibility and reconfiguration of the equipment, modular units will be preferred. User-friendly interfaces and ease of operation are also important components, and although we recognise that this will represent a change in technology, it will constitute a massive change in synthesis philosophy.

GENERAL ASPECTS OF FLOW BASED CHEMISTRY

In our work, we will focus on the *quality* of the synthesis product with the aim of progressing to a multi-step operation without intermediate product isolation. While the pumping devices and reactors are clearly important, they purely assist the synthesis, and it is the processes and the quality of the product outcome that will justify their use. There is no point in simply replacing the versatile batch mode round-bottomed flasks with new tools unless clear productivity gains can be seen. Indeed, with this in mind, we can quickly list some of the anticipated synthesis opportunities and advantages of moving to flow mode. We can expect enhanced reactivity in the microfluidic channels, but also because we are working in a contained environment, high pressures and temperatures can be readily achieved. Likewise, the use of toxic, odorous or hazardous reagents would be less problematic, as would the incorporation of gases, enzymes and novel catalysts as these would be readily accommodated by the new concepts. Exothermic processes and reactive intermediates are also both readily assimilated by the devices. We can anticipate lower solvent usage and less waste-product generation leading to overall safer working practices. The machinery and processes are clearly automatable and can be easily adapted for rapid optimisation. The idea of on-demand synthesis being able to make material in the quantity and quality required at the time it is needed is also an attractive concept. Moreover, the equipment is capable of working over a 24/7 time framework, thereby extending the use and efficiency of expensive real estate. Into the future, one can imagine many further advances by using segmented flow processing for reaction and reagent profiling. Also, the idea that the machine itself, through some smart information software *via in silico* avatars, may be able to evaluate opportunities through interrogation of available literature and databases, a concept which we believe is entirely realistic. Eventually, we can anticipate linkage of several of the flow reactors, controlled by computers, to generate long synthesis sequences whereby all the modern drugs and even complex natural products will come within reach of the technology.

MICROFLUIDIC REACTORS USED IN FLOW CHEMISTRY

To begin the process of achieving flow chemistry we first describe the consequences of moving down in scale to microfluidic reactor chips which consist of serpent like channels fabricated in glass to provide the robustness required for repeated use and reuse, and to be inert to the chemistry and solvents planned in any synthesis scheme. These chips can be heated, cooled or irradiated depending on the reaction needs. Various chemical inputs can be introduced via connection ports and the reaction products can be monitored by infared or LCMS techniques in the usual way (Scheme 1).
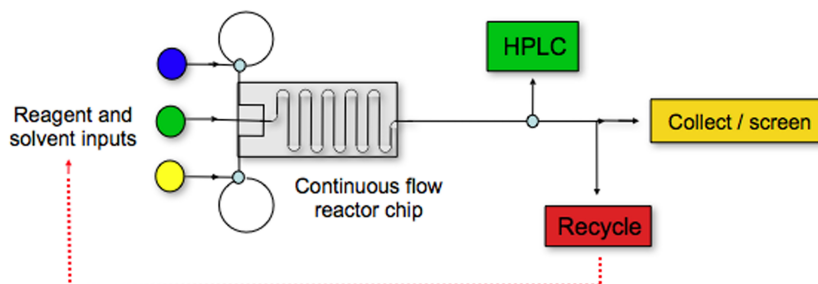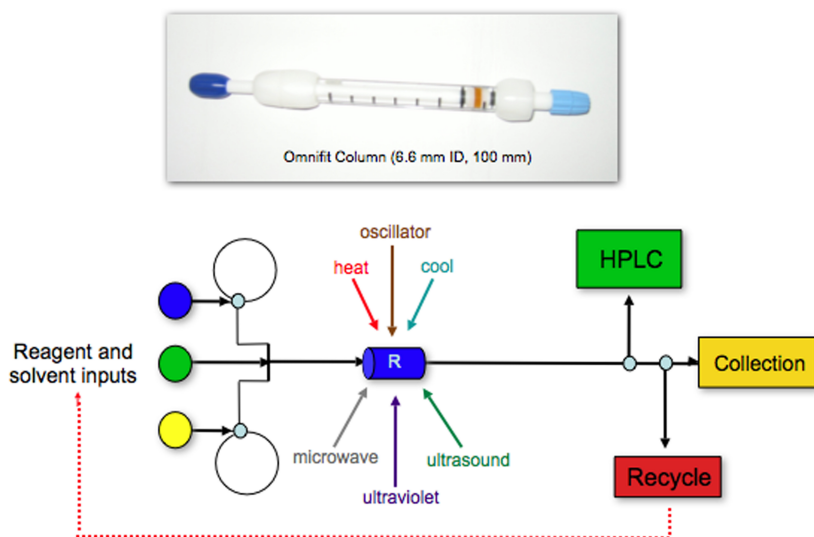

Scheme 1. Typical Flow Reactor Configuration

Recycle pathways are also possible to vary or optimise the reaction and product collection *via* preparative mass directed LC can be easily incorporated into the system. Also, importantly, small scavenger or clean-up cartridges can be linked in-line to the output stream to aid the product purity profile. In this configuration, especially with very fine channels, reactions can be very fast (seconds) when compared to similar batch mode processes (hours). When scale-up is required, it is useful to *scale-out* using multiple chips to achieve the output volumes required. A particularly important aspect of these microfluidic arrangements is that the exiting flow stream can be rapidly evaluated and the data collected can be used by intelligent feedback algorithms to iterate and improve the compound design (the closed loop concept). Especially attractive here is the ability to collect biological screening data using similar microfluidic devices immediately the compounds have been synthesised (make and screen concept). This ability to collect and assimilate data rapidly also creates wonderful synthetic opportunities for reaction, reagent or catalyst prospecting. Given that very clean products can be prepared very rapidly on this type of equipment, excellent applications to translational medicine through, for example, positron emission tomography (PET) present themselves.

As organic chemists, we expect these flow reactors to be capable of synthesis not only on a research scale, but hopefully onto full scale as well, thereby providing better continuity in the synthesis process. The equipment needs to be able to deliver pure material and avoid, where possible, high skill techniques such as chromatography, crystallisation or distillation,

which are common to batch processing. In order to design systems that would fit these criteria, we devised the use of pre-packed reagent (or scavenging) tubes. These are commercially available, through Omnifit, and come in a variety of sizes, including adjustable end units, which can add further flexibility to the systems. The internal packing consists of commercially available reagents and scavengers generally supplied in bead formats. We have, however, become attracted to the use of monolithic materials prepared *in situ* as these give noticeably improved properties and loadings, and are discussed later in this article. The flow tube arrangement (Scheme 2) is versatile and can be connected and pumped in series or in parallel. Furthermore, it is possible to physically interact with the reagent through heating, cooling, oscillation, microwave, sonication and irradiation.

Scheme 2. Typical Flow Reactor Configuration

Recycling, reagent regeneration and reverse pumping techniques are readily accommodated. Real-time in-line analysis allows for appropriate checkpoints and valve switching so as to address complex reaction schemes, catalyst or reaction screening protocols. By way of example Scheme 3 illustrates a typical combination of chemical inputs coming together *via* an assembly of packed tubes, flow coils, chips and immobilised reagents, scavengers and catch-and-release techniques to affect the desired coupling reactions, and deal with any impurities and by-products on route to the fully constructed target molecule.
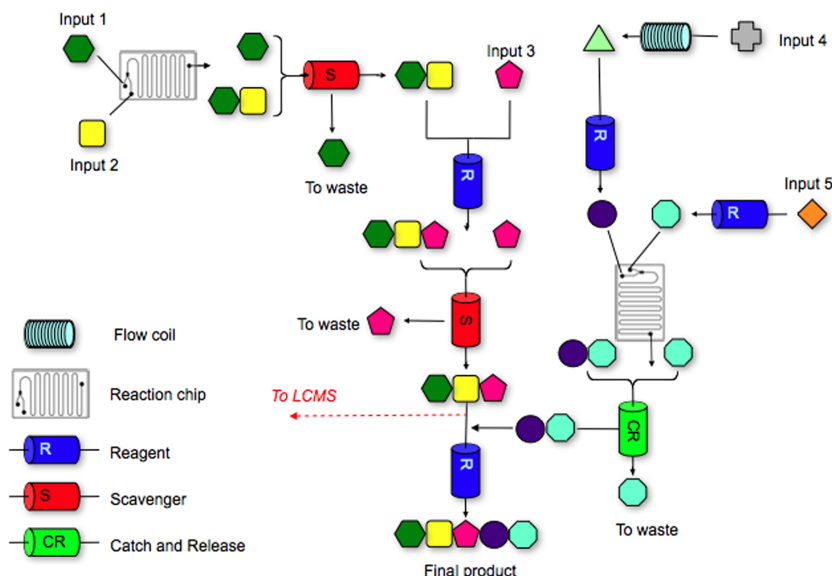
Scheme 3. Typical Flow Reactor Configuration – More Advanced Systems

FLOW SYNTHESIS EQUIPMENT

At this point it is pertinent to comment in more detail on the peripheral equipment needed to conduct these flow chemistry sequences. In its simplest form, syringe or cheap HPLC pumps can be used to drive the systems. We chose, however, to use these in combination with commercially available units from a variety of sources (see http://leyitc.ch.cam.ac.uk/) since this gives us flexibility, ease of modular assembly and effective clean-up and analysis. Also, the equipment can be tailored for specific applications such as gas reactions, microwave, chemical library synthesis, or reaction screening and profiling. While the equipment is generally used in the continuous flow mode, it should be recognised that segmental (or plug) flow operation creates additional versatility and opportunity. Although space here does not allow us to describe all of our systems in detail we would like to comment on specific items that are generally applicable. More details can be found in our publications [26 – 31] not all of which are discussed below.

The Vapourtec R4+R2 combination (Figure 1) consists of a two-pump unit, which can be controlled either manually or by computer, delivering solvent and reagents from a storage tray through various control valves to the R4 block. This is an independently temperature controlled four channel convection heater block that can be rapidly modified to use either packed reagent or scavenger flow tubes or connected to a variable length polymer or steel flow coil adaptor. These set ups can conduct syntheses ranging from milligrams potentially

through to kilograms of material. Additional scavenger tubes can be added externally in-line, should the products require further purification. Units can be linked together and computer controlled to achieve multi-step mode of operation.

Figure 1. The Flow Coil Reactor System

Figure 2. The Uniqsis Reactor Unit

Figure 3. Flow Synthesis Equipment Configurations

The Uniqsis FlowSyn System is an attractive alternative commercially available flow chemistry reactor (Figure 2). This employs a similar two-pump arrangement, solvent store and delivery valves with touch pad control. The primary reactor consists of a heatable steel or Peek variable length flow coil. Temperatures can be varied up to 250 °C in a covered thermal transfer heater arrangement. The exiting samples cool rapidly and can be channelled additionally through a further tube device, reaction, or scavenging as required. Alternatively, custom-built devices (Figure 3) can be assembled from a mixture of commercially available HPLC pumps, Syrris reaction chips, liquid handlers, Rheodyne valves, flow columns, detectors and product collection equipment. These flow reactors are particularly versatile and also permit intermediate sample purification through mass directed preparative chromatography, should this be deemed necessary.

APPLICATIONS OF FLOW CHEMISTRY

By way of application in this developing area of science, the Curtius reaction represents a particularly instructive example (Scheme 4). This strategically important, but hazardous to implement process converts acids through intermediate acyl azides, which rearrange at high temperature (120 °C), to useful isocyanates and their derivatives. The first sequence combines diphenylphosphoryl azide (DPPA) with a mixed stream of acid, triethylamine and a nucleophile for subsequent *in situ* trapping of the final isocyanate [30].
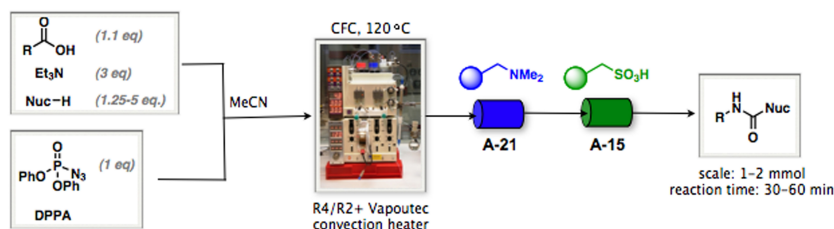

Scheme 4. Curtius Rearrangements in Flow

Passage in acetonitrile of the flow solvent through a convection-heated flow coil at 120 °C, mounted on the R4 reaction block gave a product stream that was quenched through a mixed bed of Amberlyst 21 and 15 scavengers. Alternatively, for more basic polar products, the final acidic Amberlyst 15 could be used as a "catching" device, where clean products are subsequently released by NH_3 in methanol pumped through the column. In a further modification of the Curtius process, we have shown that the intermediates acyl azides could be formed by reaction of acid chlorides flowed through an azide loaded monolith reactor [33] (Scheme 5).
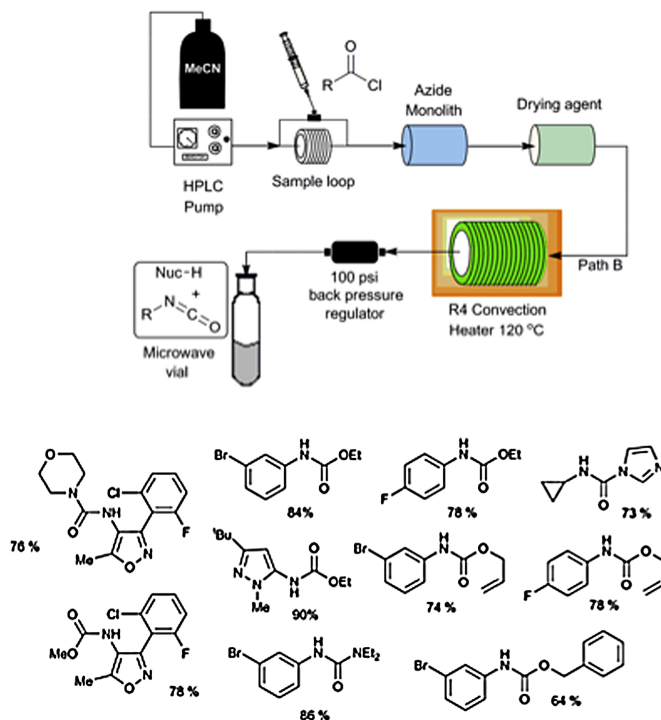
Scheme 5. Curtius Rearrangements in Flow using Azide Monoliths

In other work, owing to the thermal hazards of using azides and, to some extent, acetylenes, we have shown that the cycloaddition can be achieved smoothly by passage through a glass serpent reactor chip and onto a CuI.dimethylamino resin. Following reaction stream clean up through commercially available Quadrapure thiourea QP-TU and dibutylphosphine scavengers excellent yields and purity of the corresponding triazoles are obtained [34] (Scheme 6).
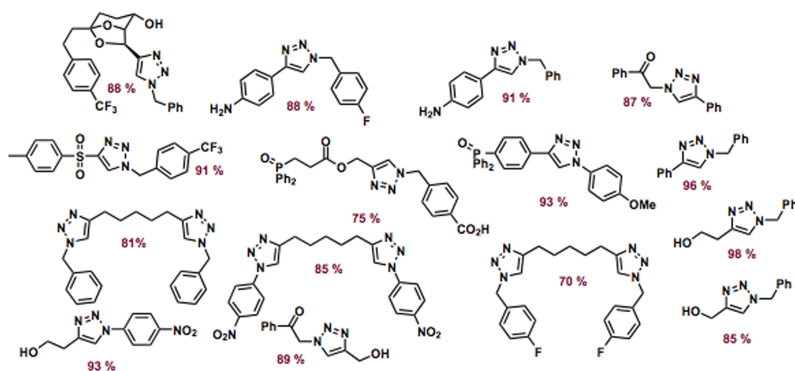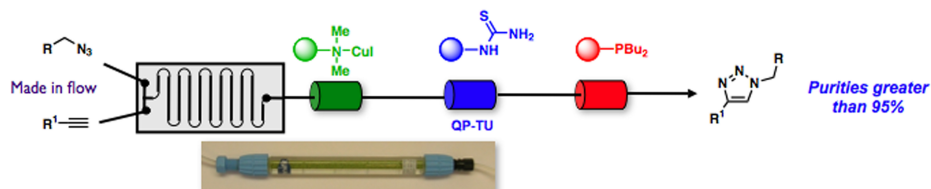
Scheme 6. Azide Couplings in Flow

By way of extending this theme of using flow reactions to control other potentially hazardous processes, we have also investigated the use of diethylaminosulfurtrifluoride (DAST) in the R4 reactor coil to achieve fluorination (Scheme 7). Several useful transformations were affected in good yield and purity, providing appropriate scavenging and product clean-up, using a plug of $CaCO_3$ and silica gel was incorporated into the flow sequence [35].
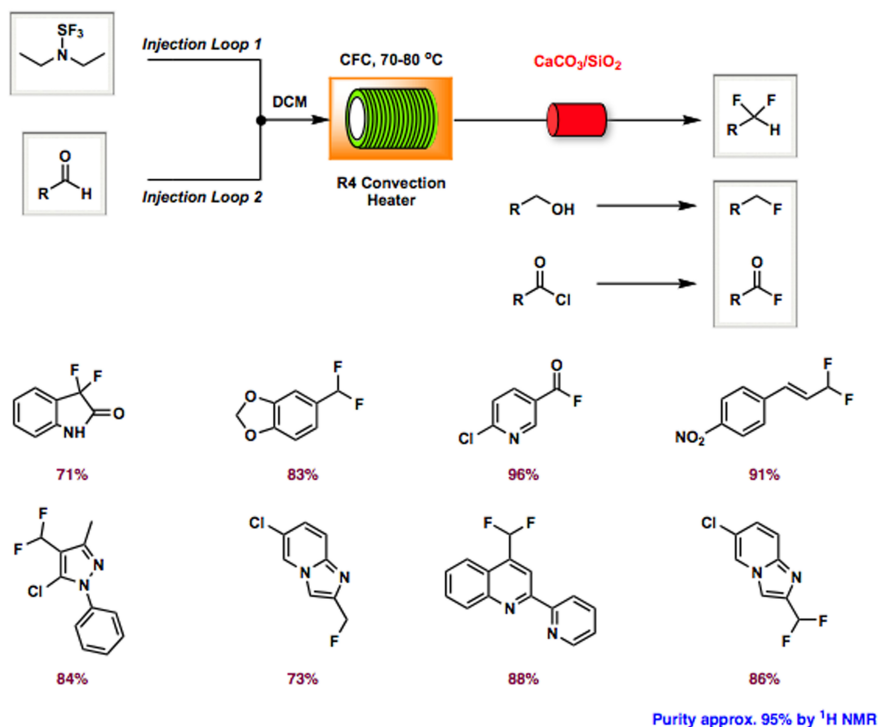
Scheme 7. Fluorination Reactions in Flow

We had mentioned earlier the improvements that accrue using monolithic polymer material to support reagents for flow chemistry. Given the importance of palladium in mediating chemical reactions, we have also shown that we can produce highly defined nanoparticles in Omnifit flow tubes [36]. These reactors are then highly efficient at achieving Heck reactions with outstanding conversion, yields and quality of product following Quadrapure scavenging (QP-TU) (Scheme 8). Clearly these metal particle reactors could be applied to a vast range of related reactions, and studies to are underway to exploit these aspects and opportunities.

Aryl Halide	Alkene	Product	Conv. / %	Purity	Yield / %
			100	>99	86
			100	>95	87
			100	>95	88
			100	>95	88
			100	>85	88
			100	>99	79
			100	>99	85
			100	>99	78
			100	>99	73
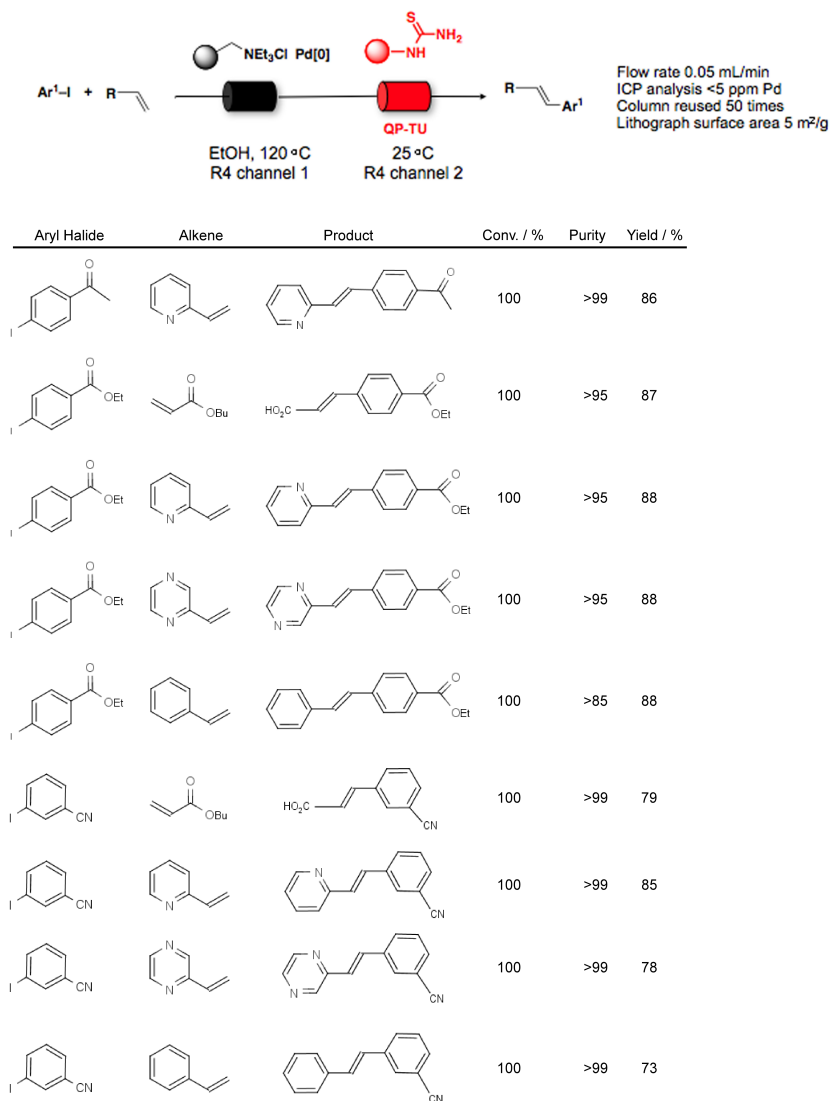
Scheme 8. Nanoparticular Monolith Pd in Heck Reactions

NATURAL PRODUCT SYNTHESIS IN FLOW REACTORS

In other work we have reported on multi-channelled micro capillary flow tubes and shown these to be useful for several key reaction types [37]. These included Diels-Alder reactions, where we demonstrated that by scaling out to eight flow discs equivalent to 11.2 kilometres of channel, quantities of product in the order of 4 kg per day were realised. Other applica-

tions to heterocyclic synthesis [38] using flow reactor microwave methods are also possible. These methods have been effective in the generation of peptides [39] and various natural products. Two of these are reported here, since they demonstrate further interesting aspects of flow chemistry.

The first of these is the short synthesis of the neolignan natural product grossamide [40] (Scheme 9). This involved the initial coupling of an appropriately functionalised carboxylic acid, ferulic acid, by activation and trapping onto a hydroxybenzotriazole supported polymer within an Omnifit flow tube and subsequent reactions with tryptamine to give the corresponding amide. Next, after considerable experimentation with a wide range of oxidants, we found that the desired oxidative dimerisation to give grossamide in 91% yield was best accomplished using an immobilised enzyme, horseradish peroxidase, in flow mode. This last, difficult, reaction is particularly interesting in that it does not work well in batch mode due to competitive further oxidative transformations. However, by adjusting flow rates, clean chemoselective transformation occurs as the first formed grossamide product is swept through the flow tube into a benign environment where no further oxidative processes can occur. The use of immobilised enzymes in this way when combined with other chemical coupling reactions, is an attractive process for achieving molecular complexity. Considerable other opportunities arise when directed evolution techniques are used to give a novel range of enzymes for specific organic transformations. The flow equipment is ideally suited for screening and evaluation of these biotransformations.
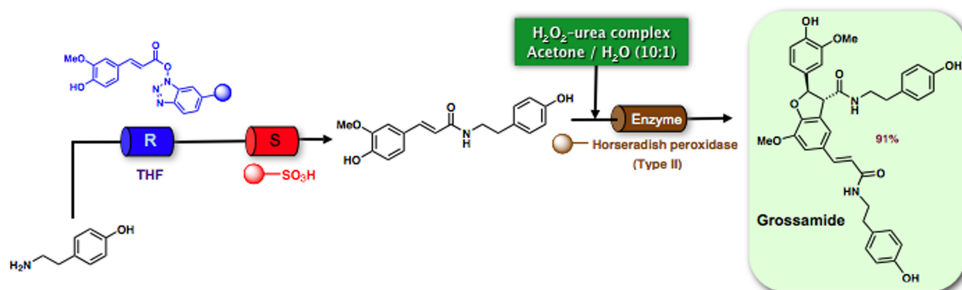
Scheme 9. Flow Synthesis of Grossamide using Immobilised Enzymes

The last synthesis describes the coupling of no less than seven chemical reactions to prepare the alkaloid natural product oxomaritidine in flow (Scheme 10) [41]. In one flow stream, a phenolic ethyl bromide was displaced by an azide delivered from an alkylammonium resin. The azide was not isolated, but simply flows to the next immobilised phosphonium reagent, where it becomes trapped as an iminophosphorane. In a second flow process, the requisite aldehyde was prepared by passage of an alcohol through an immobilised perruthenate resin [42].

The aldehyde then joins the prepared iminophosphorane, where it undergoes coupling at 55 °C to give the corresponding imine. This flow stream is then introduced to a flow hydrogenation reactor, the Thales Nano H-Cube, where reduction takes place to give an amine [43]. Solvent was then removed using a Vapourtec V10 evaporator and replaced with methylene chloride to continue the flow synthesis. Next, trifluoroacetylation of the secondary amine was achieved by mixing with trifluoroacetic anhydride and passage through a microfluidic reactor chip. Flow through a packed column containing an immobilised hypervalent iodine reagent [44] affects oxidative spirocyclization to a spirodienone. Finally, the synthesis was completed by deprotection of the trifluoroacetate, which causes spontaneous intramolecular conjugate addition of the amine to the enone to deliver the natural product. What is remarkable about this synthesis is that the whole process takes only a few hours to complete, which should be contrasted with the conventional batch mode preparation, which takes some 4 days of synthesis time! Clearly, the important message from this work is that the whole process can be automated to produce quality material competitively with more conventional methods, and as a result releases skilled operator time for more complex tasks such as compound and route design.
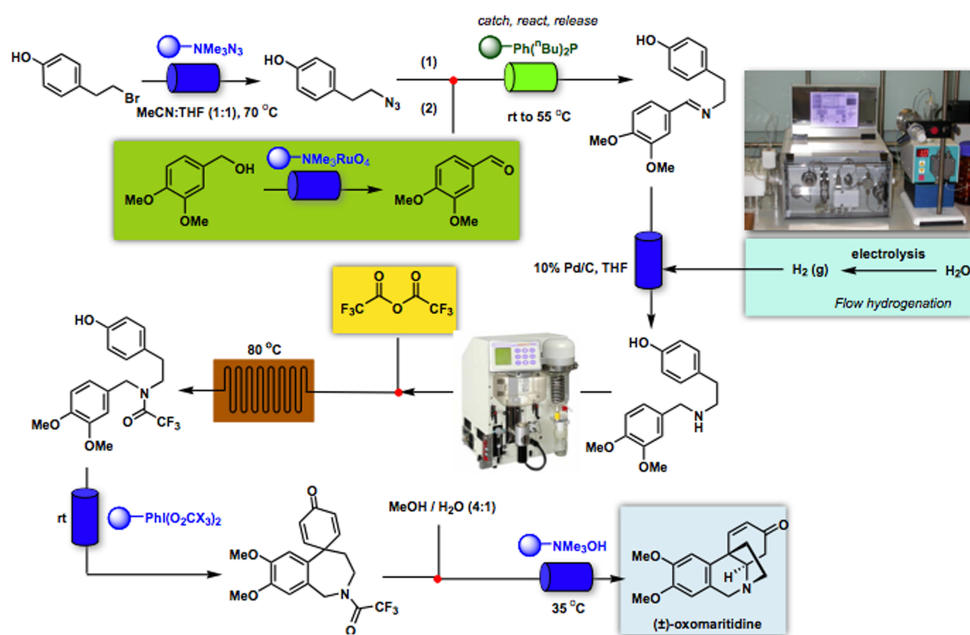
Scheme 10. Convergent Flow Synthesis of Oxomaritidine

CONCLUSION

We conclude this article by suggesting that the use of flow chemistry equipment, when combined with supported reagents, scavengers and phase switch techniques, provides a powerful platform and enabling technology for future automation of synthesis. We are not alone in this area and there is a growing user community as judged from the number of outstanding papers appearing in the literature [45 – 67]. This is, however, a disruptive technology and, as such, we cannot only expect further advances, but we can also expect resistance to adopt these new ideas. It takes time to learn the new procedures, and an open mind is essential in order to reap the eventual rewards. We have worked for over ten years with multi-step immobilised systems, including flow chemistry, and there is still much to learn. Nevertheless, it is the people that drive the changes, and the machines are only as good as the operators.

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